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Investigating Diagnostic Capability of Acetylcholine Polymers for Detecting Alzheimer's Disease By Lina Moammar

Abstract

Acetylcholine (ACh) is an essential neurotransmitter in various physiological processes, including muscle contraction, memory, and learning. Previous research has shown that a hallmark of Alzheimer's disease is a deficiency of ACh at the synapse. A lack of ACh contributes to learning impairments which is a primary indicator of early-onset Alzheimer's disease.[1] Itaconic acid, acrylamide, and methacrylamide are all compounds that contain amide groups, which are nitrogen-containing chemical groups that can act as proton acceptors. ACh is also a compound that contains an amide group, which makes it capable of forming hydrogen bonds with other amide-containing compounds. Due to the presence of these amide groups, in silico simulations revealed that itaconic acid, acrylamide, and methacrylamide have an unusually energetically favorable tendency to form a complex with ACh.[2] The strong binding affinity of ACh for these compounds is most likely due to the formation of multiple hydrogen bonds between the amide groups, resulting in a stable complex. The ability of itaconic acid, acrylamide, and methacrylamide to bind strongly to ACh makes them ideal candidates for use as biosensors. The formation of the complex between these compounds and ACh can be easily detected best using optical biosensor techniques such as fluorescence[3] or mass spectrometry[4], allowing for highly sensitive and specific detection of ACh synapses and biological samples such as a spinal tap that can be used to diagnose Alzheimer's disease.

Introduction

Alzheimer's disease is a neurodegenerative disease that affects millions upon millions worldwide.[5] One of the clinical signs of this disease is a deficiency of acetylcholine (ACh) at the synapse, which leads to impairments in learning and memory[6]. In addition, ACh is a neurotransmitter involved in various physiological processes such as muscle contraction[7], informational processing[8], and attention.[9] Its role in learning and memory is well established[10][11][12][13], and a lack of ACh has been linked to early onset Alzheimer's[14]. Moreover, the loss of cholinergic, or activity of the ACh neurotransmitters activity has been shown to significantly contribute to cognitive decline in Alzheimer's patients.[15] The known ACh deficiency at the synapse makes ACh an ideal target for early Alzheimer's diagnosis.[16]

Recent research has revealed that certain chemical compounds, such as itaconic acid, acrylamide, and methacrylamide, have an exceedingly energetically favorable tendency to form a complex with ACh.[17] The formation of multiple hydrogen bonds between the two amide groups, resulting in a stable complex[18], is most likely responsible for ACh's strong binding affinity for these compounds. Due to these properties, these compounds are ideal for biosensors detecting ACh in biological samples, such as postmortem brain biopsies, and spinal taps. This review paper aims to discuss the various methods for using itaconic acid, acrylamide, and

methacrylamide as biosensors to detect the amount of ACh in the brain to help diagnose Alzheimer's disease

Chemical makeup of itaconic acid, acrylamide, and methacrylamide in relation to ACh

It is critical to consider the chemical composition of the polymers. Acrylamide and methacrylamide are organic compounds that contain amide groups, nitrogen-containing chemical groups that can act as proton acceptors.[19] ACh is an organic compound with an amide group that can form hydrogen bonds with other amide-containing compounds. On the contrary, itaconic acid (Figure 1) has two carboxylic acid groups allowing it to form hydrogen bonds with ACh. The formation of hydrogen bonds is an essential concept in organic chemistry due to the electrostatic attraction between a hydrogen atom and a highly electronegative atom, such as oxygen, nitrogen, or fluorine.[20] The formation of hydrogen bonds between the amide groups of ACh and the three polymers is responsible for their strong binding affinity. Notably, acrylamide (Figure 2a) and methacrylamide (Figure 2b) have chemical structures similar to ACh, with acrylamide having a vinyl group (CH2=CH-) and methacrylamide having a methyl group (-CH3). Both polymers have an amide group at the end (-CONH$_2$) that can form stable complexes with ACh (-CO). Since itaconic acid has two carboxylic acid groups (-COOH), it can similarly form hydrogen bonds with ACh. The multiple hydrogen bonds formed between ACh and these compounds result in a stable complex with high energy stabilization. Furthermore, an amide group in both ACh and two of the three polymers indicates that they share structural similarities, making them suitable for binding. Due to this compatibility, these three polymers are ideal for use as biosensors for detecting the amount of ACh in the brain through mass spectrometry (MS) and fluorescence labeling.

Figure 1: Itaconic acid and carboxylic groups pictured
Figure created with BioRender.com

(a)   *(b)*

Figure 2: Acylamide (a) and Methacrylamide (b) Amide groups picture Figure
created with BioRender.com

Biosensors and polymer methodology–Liquid chromatography-mass spectrometry (LC-MS)

      A promising method for measuring itaconic acid, acrylamide, and methacrylamide concerning detecting ACh in the brain, would be using liquid chromatography-mass spectrometry (LC-MS). LC-MS is a powerful tool for detecting and quantifying small molecules like ACh.[21] Its process involves separating ACh molecules in the eluent using a liquid chromatography column and then introducing the separated ACh molecules into the mass spectrometer.[22] In the mass spectrometer, the ACh molecules are ionized and fragmented into smaller ions. The mass-to-charge (m/z) ratios of the ions are then determined. Next, the ACh molecules are identified based on their mass.[23] Itaconic acid, acrylamide, and methacrylamide polymers could be injected into the biological sample to bind to the ACh to detect ACh using the LC-MS biosensor. The resulting polymer-ACh complex would have a different configuration and weight than ACh alone. This is because the hydrogen bonds formed between the polymers and ACh change the electron density distribution in the molecule, which can alter its configuration. As the molecule binds to the polymers, the electronic environment around the amide groups of ACh changes, resulting in a new configuration. The LC-MS instrument would detect this change in configuration and weight because it separates the complex and ACh based on their mass-to-charge ratios.[24] On the LC-MS spectrum, the complex and ACh would appear as distinct peaks, allowing for accurate detection and quantification of ACh.[25] The amount of bound polymer would be determined by the quantity of ACh in the sample. The LC-MS spectrum would show distinct peak intensities for ACh and the ACh-polymer complex. Based on the peaks in the reading, if the peaks of the complex and ACh are significantly lower than the usual readings of a healthy brain, it could be concluded diagnostically that the individual has Alzheimer's disease.

Fluorescence biosensors

      Fluorescence biosensors are a type of biosensor that utilize a fluorophore, a molecule that absorbs light of a specific wavelength and re-emits light at a longer wavelength, to detect the

binding of a target molecule to a sensor molecule.[26][27] In the case of an ACh biosensor, the sensor molecule is a modified polymer containing acrylamide, or methacrylamide with a covalently attached fluorophore. While itaconic acid could be used, it would yield more accurate results when acrylamide and methacrylamide are used because of their amide groups which can act as proton acceptors, making them highly sensitive to small changes in the local environment, which can also be exploited to enhance the sensitivity of the biosensor. In continuation, the amide containing polymers containing the covalently attached fluorophore is immobilized on a substrate, such as a glass slide or a microplate well. When a fluorophore-containing polymer is excited by light of a specific wavelength in the fluorescent cage, it absorbs the energy and becomes excited to a higher energy state.[28] The excited fluorophore then relaxes back to its ground state by emitting light at a longer wavelength, and the emitted light can be measured.[29] The fluorescence intensity of the biosensor will be proportional to the concentration of ACh present in the sample.

In terms of how this could be used practically for diagnostic purposes, cerebral spinal fluid (CSF) could be collected using a lumbar puncture (spinal tap)[30] of a suspecting patient with early Alzheimer's to apply the fluorescence process to. By comparing the ACh level in the CSF sample to a reference range of ACh levels in healthy individuals, the fluorescence biosensor could potentially aid in the diagnosis of Alzheimer's disease.[31]

Conclusion

The potential of using acrylamide, methacrylamide, and itaconic acid as biosensors for determining the quantity of ACh in the brain to assist in the early diagnosis of Alzheimer's disease has not been investigated in the lab. However, based on the gathered evidence, these polymers are excellent candidates for use as biosensors due to their chemical composition, particularly the presence of amide groups that can form hydrogen bonds with ACh. For example, the polymer-ACh complex providing a distinct peak on the LC-MS spectrum, the liquid chromatography-mass spectrometry (LC-MS) method has been suggested as a promising method for detecting and quantifying ACh in biological samples. The use of these polymers as ACh biosensors could lead to earlier and more accurate Alzheimer's disease diagnoses, ultimately improving diagnostic capabilities. This approach has the potential to improve diagnostic accuracy and early detection of Alzheimer's disease, and also calls for further investigation in the lab. If proven effective, this approach has the potential to revolutionize current Alzheimer's disease diagnostic approaches and have a significant impact on patients and families affected by the disease.

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***Tár*, a Film of Cancel Culture and Power, Told Through Classical Music By Kaiyan Guan**

  The 2022 film, *Tár*, directed by Todd Field and starring Cate Blanchett, tells the story of a world-renowned female conductor's downfall as she was allegedly exposed of grooming other female musicians and, consequently, canceled. Some of the readings of this film are blunt — they argue that the thesis is simply "Put a woman in power, and she'll be as sexually inappropriate and badly behaved as any man", and Marin Alsop also argues that "the premise that women would fall into the traps laid by traditional power structures was 'premature'" (Woolfe). If one is eager to draw a straightforward conclusion or to decide whether to applaud or condemn the film, one can also easily find Todd Field saying in his interview that "whoever holds power, it's going to corrupt them" (Gross). However, while the story of cancel culture can be told through other lenses, it is crucial and brilliant that it chooses classical music as its setting. It is a medium where the complexity of cancel culture and power imbalance could be discussed. Because classical music has an emphasis on professionalism, there is more of a separation between the art and the artist. However, the advent of a younger generation challenges this separation, placing the artists under scrutiny. Moreover, the structure of the orchestra represents a strict hierarchy, in which the story of power is even more fitting.

  Classical music is treated more as a profession and associated more with a high level of artistic excellence; conversely, it is less like the entertainment industry. During the 19th century, musicians gathered and formed musicians' unions, the mission was to "elevate and safeguard the intellectual and material interests and thus the social position of the musical profession". On the one hand they "safeguard the intellectual and material interests", dealing with issues like copyright in order to make a living, and on the other hand, they aim to "elevate" their "social positions". Therefore, it was also "a process of self-civilizing intended to upgrade within society a profession whose members still mostly came from modest backgrounds," as quoted in Rempe, 131[1]. This is a paradigm that continues in the present. For example, as Anna Bull points out many white middle-class families in the UK enroll their children in classical music training as a way of "boundary drawing around their protected spaces and of reproducing their privilege through education, both of which are camouflaged by the ideology of 'autonomous art' that classical music carries" (Bull xxii).

  Though classical musicians uphold professionalism, one may argue that classical music canons are very much "personal", even similar to modern pop music etiquette. Indeed, the culture of "diva worship" in the opera world, particularly during the 19th century when the construct of classical music was emerging, was built around fans who worshiped famous singers like the Swedish Nightingale and P. T. Barnum. However, it was in the opera world where there is a strong focus on the artist's persona, and by contrast, symphonic music is removed mainly from the persona of the composers. This allows for more space between the artist and the art. In fact, classical music is a space that allows Tár to construct a different identity, hiding the innate identities that she is not so proud of. The opening scene of *Tár* is an introduction given by Adam

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[1] 'Statut des Allg. Deutschen Musiker-Verbandes', DMZ no. 40, 5 October 1873, 313 f.

Gopnik during the New Yorker interview, from which the viewers grasp for the first time her tremendous accomplishments (5:54-9:10), adding immense ethos to Tár. It is a much later scene where she visits her childhood home that we have a glimpse of her background and her upbringing– she has a brother, her real name is Linda Tarr, and her family is not upper-class (2:23:38-2:27:40).

In this film, Tár represents the self-ideology of professionalism and self-discipline. With this mentality, it is unsurprising that Tár commented, "If you want to dance the mask, you must service the composer" (35:35-35:46). She represents the 'self-talk' from musicians who uphold the highest standards of their craft by putting the art in front of the artist. According to Tár, since the ultimate goal is to "service the composer", a performer's value lies in their ability to produce good music but not in their identities; therefore, the "yourself", "your ego", and "your identity" simply does not matter.

However, Gen Z is now bringing different expectations of classical music to the forefront that are challenging these long-standing assumptions and the professionalization of classical music. The character Max is constructed by Todd Field as a mouthpiece to represent Gen Z's perspective. Through Max, the film segues into showing that classical music is starting to reckon with some of its longstanding inequalities and exclusions in the creative process and the discourse musicians built around it.

Both Max and Tár can agree that the performance of music is a conversation with the composer and with oneself: the musician will need to read into the composer's intent and draw on their own experience. In discussing Anna Thorvaldsdottir's music, Max explains that from Anna's masterclass, he learns that she is often influenced by the "form and structure of the landscapes and nature she grew up within", and Max adds his own observation that "[he is] not sure if she is interested per se, in describing those actual sounds" (28:00). Tár then follows that Anna's description of her music is indeed very vague; therefore, "now is the time to conduct music that actually requires something from you". Till this point of the conversation, Max and Tár still stand on common ground. It seems self-evident that the art of music is for a composer to express and for a musician to receive, and re-expressive with an unique interpretation.

However, their opinions start to diverge when examining exactly what experience one could draw on to create a unique interpretation. This is where the clashing values of Gen Z and older generations emerge. In their book *The Art of Living in a Digital Age*, authors Linda Katz, Roberta Ogilvie, Sarah Shaw, and Linda Woodhead explain that in Gen Z's lives, "identity is intimately tied to the notion of authenticity" (Katz, Roberta R., et al. 80). This idea is expressed in Max's standpoint when he explains that he cannot enjoy Bach's music because he cannot identify with Bach's misogyny and whiteness. Tár interprets from Max's "allergy" (31:10) that he cannot cast aside personal feelings nor sublimate his identities to serve the composer; by contrast, Max is conveying that his ability to create music that is true to himself lies in expressing his authentic identities, and suppressing his gender and sexuality is against his "notion of authenticity"(Katz, Roberta R., et al. 80).

From a cinematographic point of view, this 10-minute continuous, unbroken take of high tension contributes further to how Tar's words leave no ground for compromise or understanding. The camera discretely follows Tar's steady yet propelling pace, and it manages to play out Todd Field's intention: "Keep in mind, it's the first time we've seen her stand, other than backstage, it's the first time we've seen her move, so it was important she had control over the time" (Screendaily). Throughout this long sequence of inquiries, Tar is firing questions at Max, firmly establishing her position of power which leaves no space for Max. Along with this cinematic choice, the camera is almost like a character that reinforces Tar's argument that music like Bach's is superior because it is "music that actually requires something from you" (29:00), leaving Max isolated on stage, viewing him with condescension from the elevated stairs Tar is standing from.

Gen Z is also increasingly starting to closely inspect the work as well as the artist, which can be seen in the contrast between Tar and her mentor's conversation and Tar and Olga's conversation (1:24:27). In the conversation between Tar and her mentor, they discussed Schopenhauer (55:20):

ANDRIS. Schopenhauer measured a person's intelligence against their sensitivity to noise.

TÁR. Didn't he also famously throw a woman down a flight of stairs who later sued him?

ANDRIS. Yes, though it's unclear that this private and personal failing is at all relevant to his work. (Field 33)

Both music and philosophy are direct expressions of the mind, making them a privileged language. This language then created a facade that stands between the art and the artist and the professional and the personal. However, Gen Z challenges this by suggesting that art should be championed by the artist and that the artists' identities are an important factor when determining whether we should support their work. Though Clara Zetkin is not an artist, but the way Olga views her identity along with her work contrasts Tár's way of thinking (1:24:27).

TÁR (CONT'D). At some point everyone from Napoleon to Beethoven tucked into a meal at one of these tables.

OLGA. Yes, and Clara Zetkin. (looks around) ... I wonder which one.

TÁR. Who's that? A musician?

OLGA. No. She helped found social-democratic women's movement in Germany. And KPD until Hitler came to power and she was exiled to Soviet Union.

TÁR. Clara Zetkin?

OLGA. Yes. Every March eighth we place flowers at her plaque in Kremlin Wall Necropolis.

TÁR. Her birthday.

OLGA. (As if to a child) No, International Women's Day.

Tár feeling outclassed by a long-dead woman, and out-educated by the one seated across from
 her. (Field 50)

This exchange demonstrates that Olga, representing Gen Z, is not only commemorating work Zetkin through the work she has done, but Olga also commemorates her identity as a woman and an activist. Todd Field describes in the screenplay that Tar is "feeling outclassed by a long-dead woman, and out-educated by the one seated across from her" (Field 50). This remark demonstrates the way Tar thinks — A "long-dead woman" and "the one seated across from her" are merely labels, without significance, like artists, when we are simply examining their work. Therefore, it appears striking to Tar that Gen Z, in particular, perceives the significance of viewing the artist through recognizing the intrinsic values and identities the artist embodies. She now feels challenged — "outclassed" and "out-educated".

Moreover, a lot of the scenes from this film are mediated by technology and social media, another characteristic brought forth by Gen Z that clashes with the idea of separation between the art and the artist. Whether it's from the opening scene where the film shows someone texting over the Live function of Tiktok with Tar sleeping in the background or the edited video with clips to slander Tar, Tar's more intimate spaces are closely inspected. Moreover, Tar succumbed to the appeal of maintaining her image online despite the musician's self-talk of being focused on the expressions of the art and totally uninterested in everyday concerns. Instead, though Tar claims that she does not read reviews, she cuts out pieces of them from the newspaper and collects them. She also attempts to edit her own Wikipedia page when she finds the description bothering her.

While Tar is challenged by the contrasting values brought forth by Gen Z, Todd Field further creates events of ambiguity to challenge the notion that artists and art are distinguishable, also challenging Tar's ideology.

First, Todd Field obscures any potentially incriminating evidence that points to Tar's misconduct. making it ambiguous whether Tar has actually taken sexual advantage of young female musicians. As William Cheng points out, music can hurt others when a victim's cry for justice is not heard because of our personal connection with the music that we love (Cheng 5). Therefore, in Tar, it is important to recognize that Krista Taylor's suicide can well be the result of Tar's grooming, Tar's ruining of her career, and her protest being left unheard. However, direct evidence is scarce. A piece of more concrete evidence shows Tar sending emails to other orchestra's conductors to urge them to not hire the young girl. Less direct clues come in the form of dreams and anonymity— in the opening montage where Tar is arranging records on the floor, another foot creeps into the frame barely to caress Tar's foot (6:15); Tar's dreams show her mingled with Krista along with the presence of Franchesca, her wife, and an unknown man (1:51:14); and finally, a few barely noticeable shots of the apparition of a Krista (56:09). Todd

Field creates an illusion that deliberately appeals to the audience's emotions and convinces the audience that Tar had been indeed inappropriate. It is the emotional fallouts that prompted the audience to believe in Tar's affair.

Second, Todd Field creates more ambiguity by highlighting the humane side of Tar, highlighting that a seemingly "high above all" conductor is not exempt from dealing with the mundane. Consequently, Field argues that art, something that transcends morality, cannot be distinctly separated from the artist, who ultimately is a carnal entity. Todd then emphasizes this human side of Tar by putting Tar in situations where she has to face morality and the vicissitude of life.

For example, the seemingly irrelevant scene where Tar is requested by her neighbor Eleanor to help her move her mother is actually such a life-or-death situation that compels Tar and the audience to remember that she is ultimately human. This scene starts with Eleanor pounding on the door, disrupting Tar's still dreamy state of mind from just waking up. While most of the film is shot with still frames, even panning and tilting are rare, this scene is one of the few that is handheld. The shakiness of the camera and the dissonance from the two-tone warning of the "smart caregiver" box contributed to Todd's portrayal of the disruption of the internal rhythm that Tar has when she is in control of the situation. In the opening scene's interview, Tar essentially establishes herself as "time" and that "you cannot start without me"; by contrast, this room is described to be "frozen in time" in the screenplay (Field 66), suggesting that Tar is stepping out of her comfort zone— Field explains in an interview that "there is such a primal for in her neighbor that [Lydia] must obey", reminding Tar and the audience that she is after all human (Screendaily). When Tar returns to her apartment, she takes all her clothes off, throws them into the trashcan, and scrubs herself by the kitchen sink. The camera observes her from afar with only the middle of the frame illuminated with the blue backlighting from the window. Without being close up on Tar, the camera creates a separation between the audience and Tar, rendering Tar alone against her vulnerability. Cate Blanchett, furthermore, brings more humanity into the character of Lydia Tar. In fact, the original plan was a shower scene, but on the day of shooting, Cate thought that having Tar scrubbing herself by the sink was more compelling because "Here, she's so vulnerable; she's throwing her nightgown into the garbage, not really thinking about it too much" (Screendaily).

Another more direct invitation for the audience to view Tar with humanity and sympathy is the scene where she returns to her childhood home. As viewers, we have a rare glimpse into her vulnerability, her memories, her fears, and her aspirations. While other scenes often have cooler tones like grey and blue, this scene has a warmer color, making it less mechanical but more welcoming. Moreover, this scene breaks the rhythmic pace set by the rest of the film. To show Tar is very in control of her situation, Hildur Guonadottir reveals that she has Cate Blanchett wear an earpiece playing 120 bpm so she could follow this pattern while walking (Pitchfork). She also explains that "The film works on such a delicate level—it manages to be very dry and slow, but also unsettling and eerie and exciting, without you really understanding why." However, this scene is dominated by silence and not the emphatic rhythm of her footsteps.

Upon her return to her home, Tar is no longer dressed briskly, instead, she is completely tired out. Just like Eleanor's mother's bedroom, hers is also frozen in time. Not necessarily deserted to neglect, but it is a place where she desperately tried to run away from, albeit the start of her dream. The camera keeps a medium close-up shot of Tar's face as "she studies this place like an anthropologist looking for clues about the person who once occupied this place," described by Todd Field. Though the script has only one line to describe this shot — "Close on Tar, remembering the effect this first had on her" (Field 87), Cate Blanchet is able to expand the magnitude of this scene through her acting. She embodies Tar's vulnerability with a smile of nostalgia and overflowing tears, adding to Tar's humanity.

This is a pivotal scene because it paints a fuller character of Tar. Without this scene, we only see Tar as someone who is corrupted by power, but this scene invites the audience to an intimate space where they can understand Tar from another dimension— her past. We are able to know that behind the things she had done for classical music, good or bad, she was driven by the love of music and the escape it brings her. We ultimately see the human behind her art.

Thirdly, the soundtrack produced by Hildur Guonadottir also paints Tar with a fuller persona, emphasizing her love for her daughter. Hildur composed two versions of For Petra, dedicated to her daughter. The vocal version is a monophonic female voice with impassioned, disjunct melodic motion ("Guðnadóttir: For Petra (Vocal Version)"). This piece is composed of clear phrases, shorter rhythms, and extended notes on the dissonance, creating a sense of tension. As the movement goes forward, the melody gets higher, creating an arch to the piece. Finally, the music goes back to the central motif, creating a sense of homecoming. Composed in the style of a lullaby, For Petra is apparently not soothing but indicative of uncertainty and unsettledness. However, the voice is pure without any over-exaggerating polishing, suggesting that Tar giving love to Petra might not be the easiest gesture but a pure and truthful one. The orchestral version adds another dimension to Tar's or Hildur's composition ("Guðnadóttir: For Petra (Recording Session)"). It begins with a bed of strings playing dissonance, which is resolved by another dissonance in a quiet dynamic. Phrases are transitory, which fade into meaningful pauses. At 1:03, woodwinds enter imperceptively, increasing a sense of friction and tension, and with the introduction of an English horn, which propels the motif of melancholy. Around 2:02, lower strings are added to create a greater spacial depth, accompanied by glissandos, adding a larger sense of dissonance and tension. Contrastingly, at 6:36, the English Horn returns, partially resolved, which fulfills the listeners' expectation in the state of becoming. Finally, at 7:00 the orchestra unanimously starts to crescendo, as if, spacially, the music is coming towards the listeners, and suddenly the tension is gone followed by a downward glissando. This piece ends with the tension being removed, yet it leaves the listeners shaken and reminiscent of its tension and magnitude. Without these compositions, we would never know that Tar's love is full of complexity and magnitudes, and we can now see that whether her love encompasses struggle or determination, Tar is human and the embodiment of human emotions.

Moreover, the credit section also makes a statement that the art and the artists should be viewed as a whole, opposing what Tar stands for. The credit section of the movie is at the

beginning of the film. The audience, not knowing all the names on the screen, will have to sit for three minutes until Tar shows up. This bold choice sets a tone for the film, emphasizing the people who made it, not just the film itself.

Oftentimes, Tár's humanness is brought forth not by herself but by the director and composer of the film — Tar does not see the innate humanness in herself, and, therefore, one of the main reasons for her downfall is that by separating the art and the artist, she renders the relationship she has with others unimportant. To begin with, she is unable to recognize the power she wields. The orchestra also presents a strict hierarchy, which is an excellent medium to talk about the power structure. The Berlin Philharmonic, founded in the late 18th century, is epitomized as one of the most significant institutions. It represents "serious music" where musicians adhere to a high degree of professionalism. Deutsche Grammophon, a recording company, represents the utmost technology and recording precision. Together, they are two powerful institutions that contribute to the stature of Tar. In a scene where Tar is conducting the Berlin Philharmonic, Todd Field describes in the screenplay that "this is where we see the why and how of who she is. The art of the particular. The discipline. The only real reason that people put up with her" (Field 34). Field emphasized the "art" and the "discipline", again, demonstrating the degree of professionalism. However, she does not recognize what it means to wield this power. Instead, her power seamlessly extends to non-rehearsal scenarios. She has the power to grant a new member of the orchestra the seat of the soloist when the section leader has the right to do so. She fires a member of the orchestra to "rotate" him because he is old so she can have a new cellist that she favors (1:17:45).

By abusing her power, Tar paves the road for her downfall because the transactional relationship she has with the orchestra prompts her to believe that forming bonds with humans is irrelevant to her love for music when the support from the orchestra members is what keeps her in power. Tar ignores that her fellow musicians are humans, who have aspirations, dreams, and the reality of needing to earn money. In his book *The Art of Conducting*, John Mauceri points out that "Within an orchestra, there are many conflicting forces, including job security, the future of the institution, fear, pride, a desire for inspired leadership, and in some cases, cynicism" (Mauceri 109). These are all human emotions, and though not particularly emphasized in the movie, they are indeed a part of a musician's life. The relationship a conductor has with the orchestra is also important— "Conducting is inevitably about partnership" (Mauceri 106). If the Berlin Philharmonic can be seen as a character, Tar doesn't seem like she's in a partnership with it but more of an autocracy. Mauceri points out further that "every conductor is always auditioning, even if we appear to be the unquestioned leader of all that is in front of us" — it is like a partnership that needs frequent maintenance, yet Tar attempts to single-handedly mold this relationship to her liking to keep herself in power.

Tar is more than a genre film. Besides its main focus on cancel culture and power, it encompasses other themes like gender and sexuality and classical music, and with its attention to detail, it portrays Tar as an ambiguous and complex character through contrasting scenes, musical compositions, and dynamic cinematography. The film makes a great choice by making a

conductor of the Berlin Philharmonic as its lens through which we examine cancel culture and power structure. Classical music on the one hand allows more separation between the art and the artist, but on the other hand, Gen Z brought forth a different set of values that clashes with the exclusive traditions of classical music, placing Tar in a difficult position where she has to re-examine her belief that she could get away with her personal failings. Director Todd Field seems to be in agreement with Gen Z in this film as he places an emphasis on the vulnerability of Tar, demonstrating that her power is maintained by the human relationships she has formed. When she creates a distance between her work and her behaviors, she naturally overlooks the human nature of her occupation, leading to her broken relationship with her fellow musicians and music. William Cheng says in his book *Loving Music Till it Hurts*, "Love music and love people. If ever in doubt—or if forced to choose— choose people" (5). Tar perhaps should have chosen "people", and then she could continue to love music.

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A Comprehensive Analysis of the Behavior of Rubber Bands by Sai Pranav Parvathaneni

Abstract

　　Rubber bands are the most widely used elastomers in daily life. While Hooke's law models the elasticity of metals, no single model of elasticity explains all properties of rubber bands. In this study, we conducted experiments that tested rubber bands' response to external forces and deformations by exploring concepts from thermodynamics and harmonic motion. We then proposed several qualitative explanations for the behavior of rubber bands by observing trends in the data. We first tested the influence of physical parameters like color and size on the behavior of rubber bands and proposed an explanation based on particle agglomeration and viscous forces. Then, we tested rubber bands under different constraints such as torsion and coupling, and we proposed explanations based on shear stresses and force transmission. Next, we recorded the response of rubber bands to different sources of heat and proposed a hypothesis for the unpredictable results. Finally, we studied oscillatory systems involving rubber bands and used the data to support or weaken our previous hypotheses. The results of this research provide us with valuable insights into the material properties of rubber bands and enable the creation of more resilient rubber bands in the future.

Introduction

　　The ability of an elastomer to stretch is widely desired in several applications, making rubber bands a common sighting in our surroundings. They are the most used and most versatile elastomers employed daily. Physicists, chemists, and material engineers have worked extensively to aid the development of polymer science. While researchers have proposed several models to better understand and quantify phenomena associated with polymers, more can be done on an experimental basis to explore the behavior of elastomers in different conditions.

　　It is easy to understand the elasticity of a metal rod. When a metal rod is deformed by applying a force longitudinally at one end, a restoring force is developed due to the elongation. However, the extent of restoration produced by this force depends on the cross-sectional area of the rod: a 1N force would favor restoration in a thinner rod as each point in the lattice experiences, on average, a larger share of it. Also, it is futile to speak of elongations in non-relative terms: a 1cm elongation in a rod as tall as the Everest would be trivial, but the same in a 10cm rod would be significant. It is thus meaningful to say for a metal rod that the restoring stress(the restoring force per unit cross-sectional area) is directly proportional to the strain(the fraction of original length deformed) produced, a relation known as Hooke's law ("Mechanical Properties" 234).

$$\frac{F}{A} = Y\frac{\Delta L}{L} \qquad\qquad \text{……Eq. (1)}$$

　　In Equation (1), *F* denotes the restoring force in the rod(which is generally equal to the externally applied force), *A* denotes its cross-sectional area, *Y* denotes Young's modulus which is the constant of proportionality, *ΔL* denotes the change in length of the rod and *L* denotes the

length of the rod. The Young's modulus of a material is a measure of its stiffness: the greater the Young's modulus, the greater the force required to produce a given strain.

But why does this happen? In metals, elasticity has a very straightforward explanation. Metals have a lattice structure with metal atoms at the lattice points in a stable equilibrium. When an external force is applied, the displacement of these atoms from their respective lattice points in the direction of the force causes an interatomic restoring force, which tends to drive them back to their original position. A famous analogy is to imagine atoms in the lattice connected by atomic-scale springs ("Mechanical Properties" 232).

This analogy doesn't apply to elastomers, however. A key feature of Hooke's law is that it is valid for homogeneous, lattice-like structures (Feynman, "Elasticity"). However, elastomers are neither a lattice nor homogeneous. They are quite the opposite of a lattice: a randomly coiled-up, entangled mess of molecular chains. Thus, the idea of interatomic springs breaks down, and molecular phenomena predominate.

2 Elastomers: Theory and Terminology

2.1 Structure of Rubber

Rubber bands are mostly made of natural(vulcanized) rubber, which is derived from the milky sap of the rubber tree *Hevea Brasiliensis* called latex. Chemically known as polyisoprene, it is a linear polymer of cis-1,4-isoprene repeating units(Fig 2.1). These chains are extremely long and massive, having molecular weights of around 500 kg/mol (Vijayaram 28).

Figure 2.1: Chemical structure of natural rubber.

However, natural rubber is prone to aerial oxidation. Also, its molecular chains begin to flow like a fluid when stress is applied, which isn't desirable. Thus, vulcanization is performed, most commonly using sulfur, to add cross-links to the molecular chains. The cross-links improve the elastic properties, resistance to oxidation, ductility, and viscosity of rubber.

Viscoelasticity

A particularly useful model in analyzing the movement of polymer chains is viscoelasticity. In fluids, viscous forces oppose relative motion between the composite layers. This idea can be extended to elastomers in the sense that the relative sliding of molecular chains is opposed by internal viscous forces. Viscoelasticity is thus a superposition of entropic and viscous forces. Viscoelastic models explain hysteresis particularly well since it is known that even in fluids, viscous drag causes energy losses. A hysteresis loop is thus characteristic of any viscoelastic material. In viscoelastic polymers, the tension is proportional to the *strain rate* rather than the strain itself (Dunn 2).

Rubber molecules exist in a large number of conformations due to free rotation around the C-C single bonds in the connecting units. The molecules show a high tendency to coil up and form an entangled network, which increases the disorder of the system. Furthermore, due to the thermal agitation of the atoms, the chains are in a state of continuous wriggling (Bunn 95-96). Thus, rubber bands naturally rest in a high entropy state. Hence, when an external force is applied, stress is developed due to entropic forces which drive the molecular chains back to the high entropy state.

Elastic Hysteresis

The stress-strain curve of a Hookean spring shows linear behavior throughout. When the loads are removed slowly and the restoration process is monitored, the curve is retraced back along the deformation path. For elastomers, however, the restoration curve lies below the deformation curve and the path can't be retraced(Figure 4.2, Section 4). The area enclosed between the deformation and restoration curves represents hysteresis energy- that is, the energy lost to the surroundings as heat during the cycle. This arises due to the difference in the work done by the external force during deformation and the work done by the elastomer during restoration.

Experimentation

3.1 Research Objectives

The goal of this project is to qualitatively explain the behavior of rubber bands under different settings and their responses to different tests using molecular phenomena. The project was divided into 4 major parts: the physical, mechanical, thermal, and oscillatory properties of rubber bands. The objectives of each section are as follows:

- Section 4, **Physical Properties**: To study the effect of parameters such as the color and the size of the rubber band on its behavior.
- Section 5, **Mechanical Properties**: To study the effect of torsion of rubber bands both individually and taken together on the behavior of rubber bands.
- Section 6, **Thermal Properties**: To study the responses of rubber bands to external heating via household heat sources such as candles and hairdryers.
- Section 7, **Oscillatory Properties:** To study the time period and energy variations in oscillatory systems involving rubber bands and compare the data with predicted values to test the validity of some equations.

Method of Experimentation

All experiments were performed in a closed room at temperatures near $30℃$. A 1m ruler with a least count of 1mm and a 15cm caliper with a least count of 1mm were used to measure the lengths and thicknesses of the rubber bands respectively. The ruler was clamped to a rod hoisted on a table. Two S-shaped hooks were used to suspend the rubber bands from the clamp and the weight holder from the rubber band respectively. A 67g box and a 100g crate were used

as weight holders depending on the size and stiffness of the rubber bands. As most daily processes involving rubber bands are quick, 15 weights of 50g each were placed in the weight holders at 40-second intervals unless otherwise mentioned. New rubber bands of the same pack were used for each experiment. All the data were recorded using Google Sheets and the graphs were plotted using Jupyter Notebook. Throughout the paper, the weights were calculated using the value of the gravitational constant g = 9.8 ms^{-2}. All the integrals were approximated using Simpson's method.

Figure 3.1(a)(Left): The figure shows the ruler attached to the clamp. The rubber band is suspended from the clamp with 2 S-hooks. **Figure 3.1(b)(Top Right):** The fifteen 50g weights used to load the rubber bands. **Figure 3.1(c)(Bottom Right):** The 100g weight holder (shown on the left) and the 50g weight holder (shown on the right).

Physical Properties

4.1 Colour

Historically, particulate fillers such as carbon black and silica have been added to polymers to reinforce them and improve their properties- namely tensile strength, elasticity, abrasive resistance, and viscosity. These fillers form clusters of particles, which get dispersed throughout the polymer network (Roland 2). These clusters have a hydrodynamic effect on the elasticity of rubber: because they are inextensible, they strain the surrounding polymer chains instead (Roland 4). Sometimes, the dyes and pigments added to rubber bands may act as filler particles. If the molecules have a chemically reactive site, they may even bond to the polymer

chains. These pigment particles, if not dispersed properly in the network, might weaken some of the properties of rubber bands. Agglomerated particles in particular cause increased hysteresis (Roland 2; Marzec). The extent of dispersion thus depends on the reactivity and size of the pigment being used.

Figure 4.1: The rubber bands used for the 1st trial

To study the effect of color on the behavior of rubber bands, 3 trials each were performed for red, yellow, and green colored rubber bands(Figure 4.1) of the same size(natural length around 8.2 cm on average). These unconstrained trials also give us a general idea of the behavior of rubber bands. A 33g S-hook and a 67g weight holder were suspended from the rubber bands to remove the slack. After the slack was removed, their natural length was measured, with respect to which all the strains were calculated. The rubber bands were loaded at 40-second time intervals, except for the last load for which a resting time of 5 minutes was provided to allow the rubber band to fully creep before the unloading began.

Figure 4.2: The graph shows the force due to the weights and the average corresponding strains produced in the rubber bands. Note that most of the restoration takes place in 3-4 steps.

Because the cross-sectional area of the rubber band keeps changing throughout the loading-unloading cycle, it was difficult to monitor the stress of the rubber band; thus, only the forces due to the weights were recorded and used in the subsequent graphs. However, initial and final thicknesses were measured. All data shown are averages of the 3 trials.

From the Force vs. Strain graph(Figure 4.2), it is clear that rubber bands have a linear portion for small strains, indicating that the idea of Young's Modulus is valid for elastomers. After crossing a threshold of 25% strain, the graph curves and seems to have passed the linear proportionality limit. The slope of the graph decreases continuously, which represents a loss in stiffness. Interestingly, after 3.92N tension, the graph takes a roughly linear form again, attaining a 2nd constant value of stiffness.

On a molecular scale, before the weights are added, the polymer chains are heavily entangled. Adding the weights causes the chains to try to slide past one another, so the chains begin to uncoil, which is represented by the first 3 weights. Not only does uncoiling decrease the number of conformations available to the chains, but it also causes them to arrange themselves linearly in the direction of the applied force, which kickstarts the entropic forces. As the molecular chains straighten out, they have a greater tendency to slide past one another, which is reflected in the decrease in stiffness. This response to longitudinal loading in polymers is called strain-induced crystallization because stretched polymer chains assume a roughly crystalline structure (Geethamma 221). However, the chains do not begin to flow, because of the cross-links and filler particles.

Figure 4.3: The effective spring constant (stiffness) of rubber bands as a function of strain. Note that the stiffness steadily decreases, assumes a nearly constant value, and increases during the restoration before decreasing again.

During the restoration, it was observed that the stiffness was extremely high for tensions between 7.35N and 3.92N(Figure 4.3). Between tensions of 3.92N and 1.96N, almost 300% strain was restored in a region of low stiffness. We hypothesize that somewhere in the 2nd linear portion of the deformation curve, the cross-links between a few of the polymer chains started breaking due to increased stress. Thus, the entropy of the system partially increases as there are a

greater number of entities. Simultaneously, as the thickness of the band decreases with loading, molecular movement and wriggling become more and more restricted. This makes it harder for the chains to extend, effectively increasing the viscosity of the rubber band. These effects seem to cancel out each other during the deformation process, resulting in an approximately linear graph between 200% and 400% strains.

While unloading, however, restricted molecular movement predominates, making it extremely hard for uncrosslinked molecular chains to get restored to their natural state. Entropic forces are diminished since the overall entropy of the system is slightly greater. The weight of the load, despite producing less stress, is sufficient to maintain the induced crystalline structure. After a certain strain is restored, however, the molecular chains break free and the rubber band rapidly restores its length. The stiffness is very low in this unstable intermediate state of the rubber bands due to the sheer number of molecules trying to get back to their natural state. Effect of color

Figure 4.4: The area of the hysteresis loop for different colors of rubber bands.

It was observed that green rubber bands achieved higher strains than yellow and red rubber bands. Throughout this study, green rubber bands, whenever tested, showed higher strains on average(~17%). The difference between yellow and red rubber bands(7%) can be trivial, as they showed only slightly different behavior in other trials. The amount of energy lost to hysteresis was also the least for green rubber bands(Figure 4.4). This might be an indication that green pigment particles are dispersed more evenly through the polymer network and do not agglomerate as much. The more dispersed the particles are, the less likely they are to form inter-particle bonds, and less is the energy lost in breaking and forming those bonds. Interestingly, the order of increasing hysteresis area is exactly opposite of that of increasing maximum strain, indicating that the difference between red and yellow rubber bands might not be trivial after all.

4.2 Size

The size of a rubber band determines its strain for a given elongation. Testing different sizes of rubber bands thus allows us to study their behavior over a wide range of strains. For instance, a smaller rubber band gives us insights into response to extremely high strains whereas

a larger rubber band can allow us to study smaller strains in greater detail. Three different sizes of rubber bands were subjected to the same process over 2 trials and the mean strains were recorded. Red bands were used to eliminate the effect of color on the rubber bands. The smaller rubber bands had an average cross-sectional area of 0.78 mm^2 at their natural length, whereas medium-sized and larger ones had areas of 2.50 mm^2 and 8.70 mm^2 respectively. For the larger rubber band, the 100g weight holder was used to remove the slack.

Figure 4.5(a): Spring Constant as a Function of Strain for different sizes of Rubber Bands, **Figure 4.5(b):** Area of hysteresis loop for different sizes of rubber bands.

Figure 4.5(a) demonstrates that the stiffness of the rubber bands increased with their size. Larger rubber bands(17.8 cm) showed linear behavior for a wider range of weights compared to smaller bands(Figure 4.6). At maximum tension, the larger bands didn't enter another linear region yet. Their restoration curves were radically different, for they followed a roughly similar path backward. The backward entropic forces were thus very strong, an indication that the strains were neither large enough to induce crystallization nor break the cross-links. As a result, viscous forces had little impact and only a tiny amount of energy was lost to hysteresis(Figure 4.5(b)).

Small rubber bands(3.45 cm), on the other hand, showed barely any linearity for the first few loads. They appeared to have undergone crystallization rather quickly and showed approximately linear behavior between tensions of 1.47N and 2.94N. However, their stiffness increased very quickly after 400% strain, and elongations were comparable to those of the large(17.8 cm) band at similar weights. The concavity of the curve also changed in this region.

Figure 4.6: Force-strain curves for different sizes of red rubber bands. Note that the smaller rubber band loses linearity due to heavily restricted molecular movement.

We hypothesize that at very large strains, the polymer chains are no longer entangled, and the rubber band is almost purely crystalline. Thus, the relative motion of the chains is the major contributor to strain, and viscous forces dominate. Because the rubber band becomes extremely thin(close to half of the initial thickness), this relative motion is restricted and the system is analogous to a highly viscous fluid. Thus, small rubber bands lost about the same amount of energy to hysteresis as their medium-sized counterparts. For most of the restoration process, small rubber bands remain elongated(>500% strains). Forces as small as 1.47N are sufficient to hold them in their crystalline structure. This can again be attributed to the existence of a higher number of entities in the system after the breakage of cross-links. In this case, the intermediate state(between 100% and 500% strains) is even more short-lived.

5 Mechanical Properties: Torsion

Elastomers have significantly less resistance to torsion compared to metals. It is quite common for rubber bands to be twisted in daily use. When a rubber band is twisted along its axis, the path that the molecular chains have to take during deformation becomes more complex, and as a result, the effect of viscous forces increases. Thus, as the number of twists increases, the bands are expected to become stiffer.

Individual Rubber Bands

Individual yellow rubber bands were twisted 6, 12, 18, 24, and 30 times about the axis of loading and transferred to an S-hook. The hooks were secured in a contraption to prevent untwisting(Figure 3.2(a)). The contraption was ensured to be free to move to minimize any frictional energy losses. Depending on the degree of twisting, weights were added to the weight holder before measuring the initial length to remove slack.

No major deviations were observed for rubber bands with 6 and 12 twists apart from a slight decrease in stiffness and a corresponding increase in the final strain. We hypothesize that the initial entropy of the system partially decreased since the molecules became aligned in the direction of twisting. As the weights were added, it became easier for the rubber band to undergo strain-induced crystallization. Thus, the rubber bands seemed to have skipped some or most of the initial linear region that regular rubber bands had to go past. The hysteresis energy was also less for these rubber bands(Figure 5.2). The path complications didn't seem to kick in yet, resulting in pretty standard viscous forces.

Figure 5.1: Force-strain curves for twisted rubber bands. Note that highly twisted bands, during restoration, resembled the behavior of small rubber bands from Fig. 4.6.

However, the curves for bands with 18 twists and higher had a sharp deviation to the left. They had significantly lower strains(~120%) and also showed extreme resistance to restoration, resembling small rubber bands(Section 4.2) in the latter aspect. This, again, might be due to the complicated path they take. Thus, the restriction of molecular movement appears to become a major constraint during both deformation and restoration after 12 twists.

Another possible explanation is that somewhere between 12 twists and 18 twists, the shear stress developed due to torsion inside the rubber bands reached a critical value after which the restoring forces were strong enough to break the cross-links and possibly even the molecular chains, which increased the initial entropy of the rubber band. As the rubber band was loaded, there were on average a higher number of molecules trying to get back to their natural state, making the rubber band stiffer. This hypothesis differs from that proposed for smaller bands in the sense that here, the rubber bands started with a greater number of entities on average, whereas in small rubber bands, the chains started breaking after a certain strain.

Figure 5.2: Area of hysteresis loops of twisted rubber bands.

     There is also an interesting trend in the energy lost to hysteresis: the area of the hysteresis loop decreased steadily until 18 twists and increased thereafter. A possible explanation is that up to 18 twists, the twisting allowed the rubber bands to start in a partially uncoiled state. The more uncoiled they were in their initial state, the less energy is lost in further uncoiling them. After 18 twists, the stronger viscous forces could've played a part in the higher energy dissipation.

Coupling and Twisting

     In a subsequent trial, two yellow rubber bands were placed adjacent(parallel combination) to each other and were twisted along the axis of loading to form a single supercoiled structure. It will be interesting to see, in this case, whether restricted molecular movement becomes even more of a constraint.

     This time, there was a clear decrease in the stiffness of the rubber bands and a corresponding increase in the final strain as the number of twists increased from 10 to 30. Thereafter, the trend reversed and the final strain decreased. Here, the critical shear stress might have occurred somewhere between 30 and 40 twists, which is consistent with the prediction from the twisting of individual bands; two rubber bands were used instead of one, and about twice the shear stress was required to start breaking the crosslinks.

Figure 5.3: Force-strain curves for supercoiled rubber bands(coupled and twisted).

Interestingly, the restoration curves for 30 or more twists had the opposite concavity(concave up) to those for 10 and 20 twists(concave down). From Section 4.2, we know that a concave down restoration curve, as seen in large rubber bands, is an indication of the band *not* being crystallized to a great extent. Medium-sized rubber bands had a concave up restoration curve, which means they have undergone some degree of crystallization. This is further in support of the hypothesis that twisted rubber bands bypass the initial stages of uncoiling. However, the extent of this effect seems to be greater in coupled bands under torsion compared to individual bands in torsion. Another interesting observation is the rubber bands reaching abysmally low maximum strains. Linear behavior is completely lost after the initial few loads, and the curves themselves are different from the previous cases.

As for the hysteresis energy of coupled bands under torsion, bands with greater twists generally lost more energy(Figure 5.4). As the thickness of the supercoiled band is twice as large in this case, the diameter of each twist is also twice as large. Thus, the path that the molecular chains follow is even more complicated, and due to greater viscous forces, more energy is lost. The initial alignment of molecules due to twisting had a negligible effect compared to the viscous forces. The final decrease in hysteresis energy when moving from 40 bands to 50 might be due to the initial load being 150g as opposed to 50g. As the bands were highly twisted, greater loads were required to remove the slack in them. Thus, a full graph couldn't be obtained, which is reflected in the decrease in area.

Figure 5.4: Area of Hysteresis Loops for supercoiled rubber bands.

Thermal Properties

When an elastomer is stretched, there is a net decrease in entropy, and as part of that process, the molecular chains lose some of their kinetic and vibrational freedom. This energy is lost as heat; that is the reason why a rubber band stretched quickly appears warm to the touch for a short duration. It is thus sensible that when a rubber band is heated, it contracts. The heat directly goes into the wriggling of molecular chains, which drives them back to their entangled state (Geethamma 218-221; Feynman, "The Laws of Thermodynamics"). This phenomenon is known as the Gough-Joule effect.

A radiation heat source is ideal for observing this phenomenon as it is a direct mode of heat transfer ("Thermal Properties" 290): no medium is required, and if the source is large enough, the heat is uniformly distributed. A daily example is the shrinkage of rubber slippers and crocs when placed in sunlight. However, heat transfer via convection from sources like a candle flame placed in the vicinity of the rubber band might yield interesting results.

When a candle flame is directly placed on a stretched rubber band, the band contracts abruptly due to a high amount of heat supplied at a particular location. At high enough strains, the contraction is so rapid that the rubber band snaps. When the flame is close enough to heat the rubber band but not too close enough that it snaps, however, convection kicks in. First, the air around the rubber band is heated. When the air molecules come in thermal contact with the surface of the rubber band, heat flows from the air onto the surface. From here, the heat is transferred to the rest of the band via conduction. There are two problems with the method: firstly, it is an indirect mode of heat transfer, as the air acts as a medium. Therefore, high efficiency can't be expected. Secondly, even in the case that air as a medium is efficient, the

thermal conductivity of rubber is awfully low (~0.25 Wm⁻¹K⁻¹) (Burtscher 4), which means that the part of the band exposed to heat *will remain* at higher temperatures than the rest of the band for long durations.

To better test this phenomenon, a small candle flame was used to heat rubber bands (8.2 cm) of different colors at different strains. First, rubber bands of each color were taken and their initial dimensions were measured. The rubber bands were then loaded with three weights at 20s intervals. After the 3rd weight, a resting time of 120 seconds was given to allow the bands to fully creep, and the extension at this instant was measured. A candle flame was placed within 2 inches of the rubber bands. After another 120 seconds, the candle was removed and the length of the rubber band was measured. This was repeated 4 times (until all the 15 weights were used). The whole experiment was repeated twice, first without a heat source and then with a hair drye to measure the natural creep and creep due to more uniform heating respectively.

Figure 6.1: The additional percentage of strain crept for heated rubber bands compared to unheated bands at different tensions. Percentage strain creep denotes the percentage change in the strain of the rubber bands when they are heated.

In the experiments, virtually no shrinkage was observed, and in most cases, the bands elongated more than normal (Figure 6.1). In general, the rubber bands heated with a hair dryer crept a higher percentage of their strains compared to those heated with a candle. Also, the relative extension was higher at lower tensions (observer's bias might account for this, as this effect isn't observed among absolute extensions). The physical reason for this is the positive

coefficient of thermal expansion of rubber at low strains. This coefficient eventually becomes negative as the strain increases, a phenomenon known as thermoelastic inversion (Geethamma 219).

In metals, the thermal expansion is calculated with respect to the original dimensions because the subsequent change in the dimensions is negligible. In materials like elastomers, however, where large strains are observed, it is better to calculate the thermal expansion with respect to the instantaneous dimensions, and in this case, the instantaneous strain (see *true strain* in Section 8). All references to creep hereafter refer to the percentage of strain crept.

Figure 6.2: The creep-strain curves for **(a)** green rubber bands, **(b)** yellow rubber bands, **(c)** red rubber bands, and **(d)** large rubber bands under different modes of heating.

The variance of creep with strain for regular-sized bands (Figure 6.2(a),(b),(c)) shows a regular decrease in creep as strain increases. This suggests that there might be a threshold value of strain at which the curves cross the x-axis and the band starts shrinking - a thermoelastic inversion point under these conditions. Also, at the same strains, the stronger and more uniform heat source(hair dryer) resulted in larger creep. It is possible that until the hypothetical inversion

point(the x-intercept of the curve), the supplied heat is used to overcome the viscous forces between the molecular chains.

There are several possible reasons why the Gough-Joule effect wasn't observed. Firstly, convection can be an unreliable source of heating as previously explained. The bands thus might not have received sufficient heat to shrink, and the heat might have been redirected to support extension. On a molecular level, it might be possible that the heat does cause the chains to vibrate but not at large enough amplitudes to entangle. This might even be counterproductive, as the heat can be used to break the crosslinks at the location of heating. The poor conductivity of rubber can also play a part, as any entangling at the location of heating can be undone by the extension of the other parts of the molecular chain. An observation in favor of shrinkage, however, is that as soon as the heat source was removed, the rubber bands extended slightly (0.5 to 1cm), indicating that heating might indeed have been holding back the rubber bands from elongation: a thermal "hindrance" to expansion.

An interesting observation while heating with a hair dryer was that at certain strains, the fluid force exerted by the hair dryer matched the resonant frequency of the rubber bands. Though the rubber bands vibrated at large amplitudes, these vibrations happened in short-lived bursts. To better test whether this caused the higher creeps in the bands heated with the hair dryer, the experiment was repeated with larger rubber bands so that the force acts on a larger surface area on average (Figure 6.2(d)). It was observed that in the case of larger rubber bands, not only were the absolute values of the creep (not the percentage) greater but also the maximum strain achieved by the rubber bands(70% higher). It is possible that the vibration allowed the chains to uncoil faster, making crystallization easier. This implies that resonance not only affects the rubber band during vibration but also has an aftereffect on their subsequent deformations.

Oscillatory Properties

A vertical simple harmonic oscillator comprises a mass suspended from a string fixed at one end to a rigid wall. When the mass is pulled down slowly and released at t=0, it performs simple harmonic motion defined by the equation

$$y = Acos\omega t$$

, where y is the displacement from the mean position and ω is the angular frequency of the oscillator ("Oscillations" 261). The time period of such an oscillator is given by

$$T = 2\pi\sqrt{\frac{m}{k}} \qquad\qquad ....Eq. (2)$$

("Oscillations" 262), where k is the stiffness of the spring. If we replace the spring with a rubber band, we can obtain the time period of oscillations as we know the stiffness from the data. Table 7.1 shows the observed(average) and calculated time periods for rubber band simple harmonic oscillators at different loads.

Load	T(Calculated)	T(Observed)

200g	0.467s	0.526s
350g	0.759s	0.926s
450g	0.813s	1.13s

Table 7.1: Time periods of simple harmonic oscillations at different weights

The time period increases as predicted with increasing mass. However, the deviation from the calculated time period is greater at higher tensions, possibly due to viscous effects unaccounted for by Equation 5. The equation seems to be good enough to give us an approximate, hinting towards variable stiffnesses. In simple harmonic motion, the potential energy stored in the oscillator at any displacement y is given by ("Oscillations 268):

$$U = \frac{1}{2}ky^2$$

Thus, the maximum energy in the oscillator in one oscillation is:

$$U = \frac{1}{2}kA^2$$

The energy varies with the square of the amplitude of oscillations. Studying the amplitude decay will roughly model the energy decay in the oscillator. For a rubber band, defining a mean position is difficult because the equilibrium position the band is in after the oscillations stop is different from the initial equilibrium position. Hence, in all calculations, the distance between successive extremes is taken, assuming it to be twice the amplitude.

Figure 7.1: The ratio of the square of distance between successive extremes of the oscillations to the square of the distance between the first two extremes for different loads.

The energy in the oscillator quickly decayed to 25% of the initial(Figure 7.1). Up to the 7th extreme, oscillators with higher loads decayed faster. In general, the energy(and the amplitude) appears to approach zero asymptotically, but the oscillations are still observed, a sign

of underdamped oscillations. When the rubber bands were equipped with loads greater than 450g, however, the oscillations ceased, and the band returned to equilibrium very slowly, a sign of overdamped oscillations(as there were no oscillations, graphs could not be obtained). This transition from 450g to 550g, we hypothesize, caused the bands to become reluctant to restoration, similar to the high stiffness during restoration observed in Section 4. The strains in this range(450g-550g) are approximately 300% to 350%. Thus, after these strains, restoration becomes no longer favorable and the band doesn't oscillate anymore. This could be due to several factors, one of them being the molecular chains becoming almost fully unentangled- the molecules have been sufficiently crystallized for the structure to be maintained by the load during restoration.

> **Underdamped, Critically Damped, and Overdamped Oscillations**
> An oscillator is said to be damped if it continuously loses energy- as a result, the oscillations die out after some time. In **underdamped** oscillations, the amplitude decays exponentially but the system does oscillate until all energy is lost ("Under, Over"; "Damped Oscillations"). In **critically damped** and **overdamped** oscillations, the damping is so strong that the system doesn't oscillate- the difference being that in the former, the system returns to equilibrium much quicker than the latter, and sometimes almost instantly ("Damped Oscillations").

Conclusions

8.1 Implications

- When dying rubber bands, manufacturers who want stretchier rubber bands should pick the dye with the most effective dispersal of pigment particles as it does cause a marginal improvement in their maximum strain.
- Manufacturers can exploit the resistance of smaller rubber bands, used as orthodontic elastics, and to hold pens together, during restoration.
- Rubber bands employed in scenarios where they would be subjected to extremely high strains(>400%) can operate over a large range of stresses while maintaining roughly the same strain.
- When subjecting rubber bands to loading-unloading cycles in industrial works, larger rubber bands that are strained to a small extent(<200%) should be preferred as they result in the smallest energy loss to hysteresis.
- Wherever high stiffness is desired, rubber bands can be highly twisted(as long as it is beyond the critical shear stress), resulting in similar resistance to restoration at higher strains.
- Wherever desired, shrinkage of rubber can be obtained by using a radiation heat source. Convection can practically be ignored when considering the effects of small periods of heat exposure on rubbers.
- The Young's modulus of an elastomer at low strains can be roughly approximated by calculating it through the observed time period.

8.2 Potential Flaws

Throughout the study, the stress and strain values were measured with respect to the original dimensions. However, more accurate results can be obtained by plotting true stress against true strain, two quantities that take into account the instantaneous dimensions of the body (Hurlston). All the experiments were performed at home, and parallax errors were not taken into account while measuring the dimensions. In the torsion experiment(Section 5), there could have been frictional energy losses which can be minimized by setting up a near frictionless contraption in their laboratory. In the Simple Harmonic Oscillator experiment(Section 7), the amplitude was estimated with the human eye from a slow-motion video. More accurate results can be obtained by using a motion sensor. All the results were discussed using basic models of elasticity, thermodynamics, and harmonic motion, and most, if not all, of the hypotheses were made on a qualitative basis. More quantitative results can be obtained by dealing with parameters and equations beyond the scope of my knowledge and by considering phenomena such as the Payne effect and the Mullins effect.

8.3 Future Work

The agglomeration of pigment particles and its effects on the elasticity of rubber can be further studied. The coupling and torsion experiments can be performed in better-equipped labs and with more accurate measurements. The effects of resonance can be quantified using better apparatus, and further studies can reveal its potential long-term effect on the rubber band. A possible experiment to measure the Young's modulus of rubber bands differently is to measure the speed of propagation of sound via a rubber band at different strains and compare it with the calculated value, provided we know the density of the rubber band ("Waves" 371). Throughout this study, the data from rubber bands showing anomalous behavior were discarded and the experiments were repeated with other rubber bands. The anomalous rubber bands either had slightly different dimensions, were slightly more translucent, or had a lot of specks in them. Thus, considering the implications of chaos theory- the study of systems that are highly sensitive to initial conditions- on rubber bands can be beneficial. Since rubber bands consist of randomly entangled polymer chains and dispersed fillers, more quantitative and mathematically supported results can be obtained by employing statistical mechanics. Also, miscellaneous topics such as elasticity in biomolecules(DNA and elastin), rubber band heat engines, and viscoelasticity can be studied in detail using statistical mechanics, and the results of this study, although qualitative, can be considered in their context.

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The Effect of Supreme Court Decisions on Contract Regulations and Intellectual Property on Stock Prices By Will Sanders

Abstract

In this paper, I study how Supreme Court rulings on contract and intellectual property cases affect stock prices using a linear regression event study model. I study *AT&T vs. Concepcion* (2011), *Sony vs. Universal* (1984), and *Myriad Genetics vs. Association for Molecular Pathology* (2013). I predict that investors believe strong contract and intellectual property protections increase a company's stock price, which will in turn affect the stock market valuation of the company's sector and the overall market index. Furthermore, I predict that, following SCOTUS decisions strengthening intellectual property and contract protections, the stock price of the affected company will increase. Overall, I find that stronger intellectual property and contract protections do raise the stock prices of the companies benefiting from the decisions. The SCOTUS decisions generally do affect the participating companies' sectors but not the S&P 500, with mixed statistical significance. The results imply that investors could profit off investing in the companies and sectors who might benefit from SCOTUS decisions when the Supreme Court strengthens intellectual property and patent protections.

Intro/Background

There have been various prior studies which had a similar focus to my research. Prior research has used the linear regression event study model to study the impact of hundreds of cases over 15 years finding that 37% of cases have an abnormal return following Supreme Court decisions .[2] Interestingly, they found that in response to the Myriad Genetics vs. Association for Molecular Pathology ruling, one case that I analyzed, Myriad Genetics experienced an initial positive effect on their stock price but then a significant negative effect due to false reporting of the results. Using linear regression, a study found that the stock prices of both companies involved rise after writ of certiorari, when a case is accepted by the Supreme Court, but that in response to SCOTUS cases, the winner's stock price rises and the loser's stock price falls.[3] A different study that used a linear regression model found that antitrust supreme court rulings against entertainment companies hurt participating and non-participating companies in the film industry.[4] Another study used linear regression to determine that a typical high court decision broadening copyright protections created a 13-105 basis point increase in the affected company's

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[2] Daniel Martin Katz et al., "Law on the Market? Abnormal Stock Returns and Supreme Court Decision-Making," *ARXIV*, accessed August 9, 2023, https://arxiv.org/abs/1508.05751.

[3] Daniel Martin Katz et al., "Law on the Market? Abnormal Stock Returns and Supreme Court Decision-Making," *ARXIV*, accessed August 9, 2023, https://arxiv.org/abs/1508.05751.

[4] Arthur De Vany and Henry McMillan, "Was the Antitrust Action that Broke Up the Movie Studios Good for the Movies?," *American Law and Economics Review*, [Page #], https://dpl6hyzg28thp.cloudfront.net/media/antitrust.pdf.

stock price.[5] In my paper I will study how three SCOTUS decisions, in the categories of intellectual property and contract regulations, affect the stock market using linear regression.

Contracts

AT&T

In 2006 Liza and Vincent Conception sued ATT, a telecom company, for deceptive advertising. That year the Conceptions bought a wireless plan from AT&T which they advertised to include a complementary phone. However, after purchasing the wireless plan the Conceptions were charged an additional thirty dollar sales tax for the phone. The lawsuit filed by the Conceptions gained traction with other AT&T customer**s** and it evolved into a class action suit. However, the Conceptions and all the other members of the class action were contractually obligated to settle any disputes with AT&T through individual arbitration. Individual arbitration is a mediation substitute for court in which parties individually settle disputes through a third party. This would be bad for the Conceptions because it would allow AT&T to sidestep the class action suit which would be much more damaging than individual arbitrations. AT&T sought to compel individual arbitration by petitioning the Southern District Court of California.

The district court ruled against AT&T because it claimed that California's State Law preempted arbitration in cases where it was unconscionable (unfairly extrapolates one party for wrongdoing or would not have been agreed to by a reasonable person). AT&T appealed the district court's decision to the Ninth Circuit Court of Appeals.

The Supreme Court heard arguments beginning on November 9, 2010. They answered whether the FAA preempts states from constraining the enforcement of arbitration under state law. The Supreme Court reversed the decision of the district court and court of appeals stating that the FAA supersedes state law that prevents arbitration agreements from achieving their purpose. In this case the purpose of the arbitration clause was to require individual arbitration, and California State Law prevented that from happening. Basically, the strength of arbitration clauses were strengthened and the authority of the state was weakened. Immediately following this decision, many large businesses, including Microsoft and Sony, added arbitration clauses with class action waivers, making contracts less consumer friendly, to avoid burdensome litigation.

Intellectual Property

Myriad Genetics

The Association for Molecular Pathology sued Myriad genetics, a research and development (R and D) biotech company, for their gene and methods patents. In 1994, Myriad Genetics isolated, sequenced, and patented the BRCA 1 and BRCA 2 genes which were associated with heightened risk of ovarian and breast cancer. In 1996, Myriad launched their

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[5] Matthew Baker and Brendan Cunningham, "Court Decisions and Equity Markets: Estimating the Value of Copyright Protection," *Chicago Journals*, [Page #], https://www.journals.uchicago.edu/doi/abs/10.1086/505372.

patented BRACAAnalysis test to detect mutations of the BRCA1 and BRCA2 genes in customers. The Association for Molecular Pathology sued Myriad because their parents provided the company with exclusive rights for further research on their patented genes and exclusive rights to sell the BRACAnalysis tests. They claimed the patents limited scientific progress and violated the Patent Act because the genes were products of nature.

On March 29, 2012, The United States District Court for the Southern District of New York invalidated the patents in a summary judgment (a judgment made without going to trial). The district court reasoned that isolating a gene does not alter its fundamental qualities which makes it a product of nature. The United States Court of Appeals for the Federal Circuit overturned the part of the lower court's decision that methods for screening cancer therapeutics were not patent eligible. However, they affirmed that the patents on the DNA sequences are ineligible because the isolated sequences were not chemically different from their natural state. They cited Diamond v. Chakrabarty, which set a precedent requiring genetically modified organisms to be markedly different from those found in nature in order to be patent eligible. In 2012, the Supreme Court vacated the ruling and sent it back to the federal Circuit Court. On August 16, 2012, the federal circuit court ruled the same way they did originally and the Supreme Court granted certiorari.

On June 13, 2013, Judge Clarence Thomas delivered the majority opinion. The Supreme Court answered the question of whether individual genes could be patented. The opinion of the court was that isolated DNA sequences and their derivative products were patent ineligible because they were only a discovery of natural products. However, the creation of cDNA (complementary DNA) or a new product in a lab could be patented. This decision was widely regarded as a compromise.

Intellectual Property

Sony

In 1976 Universal Studios sued Sony, an electronics company, in the U.S. District Court of the Central District of California over the Betamax. In the 1970s Sony created the Betamax, a video tape recording device. At the same time, Universal City Studios was broadcasting copyrighted television programs on public airways. Universal was worried that Betamax would be used by consumers to commit copyright infringement of their broadcasts on public airways. Universal wanted an injunction on the production of Betamax, equitable part of the profits, and monterey damages. Additionally, the lawsuit accused Sony of liability for all copyright infringement committed by consumers using Betamax: known as contributory copyright infringement.

The District Court rejected all claims made by Universal ruling that the device was fair use. The court argued that non-commercial home recordings of public airways was fair use of copyrighted works. Furthermore, if the use of Betamax to record broadcasts on public airways was copyright infringement, Sony could not be held liable. However upon appeal, the 9th Circuit Court ruled that Sony was liable for contributory copyright infringement.

The Supreme Court answered whether Sony could be held liable for copyright infringement committed by consumers using Betamax to record copyrighted public broadcasts and whether Betamax was allowed to be sold. The Supreme Court sided with Sony deciding that the device was fair use. The Supreme Court reasoned that Universal did not show that recording public broadcast to watch at different times would cause substantial harm to the market for copyrighted works. They argued that the sale of Betamax does not cause contributory infringement because the product is mainly used for legitimate purposes. In short, companies selling products that do not have a primary purpose of copyright infringement can not be held liable for contributory copyright infringement. This ruling created a safe haven for video recording technology, adding to its growth in the subsequent years.

Methods and Data

I chose the cases mentioned above to focus on Supreme Court rulings on contracts and intellectual property cases involving major public companies for which I have publicly-available stock price data. I focus on contracts and intellectual property because these are two major areas that are likely to affect corporate profits and therefore stock prices.

I performed an event study using linear regression to determine if Supreme Court cases affect the stock prices of involved companies within 1-day, 7-day, and 30-day windows. An event study determines whether an event (in this case, a SCOTUS decision) affected a dependent variable (stock price) by comparing the change in the value of the dependent variable before and after the event. The statistical significance computed by the linear regression model determines whether we can rule out that the change in the dependent variable was due to random chance with less than 5% probability.

First, I chose the cases that I wanted to study by looking for landmark cases in categories, intellectual property and contracts, which were likely to affect the stock market because they could have large effects on the value of companies. Then, I compiled data of each company involved in a case that was publicly traded during the year of the decision in a google spreadsheet. For each company, I compiled data from their stock price, sector via exchange traded funds, and the S&P 500 for the year of the decision using Market Watch and Yahoo Finance.

Note, however, the linear regression model only gives us the statistical relationship between time (before vs. after the SCOTUS ruling) and involved companies' stock prices. This can help us determine whether a statistically significant abnormal stock return occurred at the time of the ruling, but even if we find such an effect, this does not necessarily mean that the ruling was the cause of the change in stock price. Other events could have occurred at the same time to change the stock price. A key assumption of the event study model is that the only thing that affected the stock price during the specified time window is the Supreme Court ruling. However, if this assumption is not true, then the statistical relationship between stock price and time may have been driven by an event other than the Supreme Court ruling.

Results

        I find SCOTUS rulings that strengthen contract protections increase the stock prices of the companies whose contracts are strengthened and sometimes also boost the stock prices of other companies in the same market.

AT&T

        AT&T won their SCOTUS decision which strengthened contract protections and resulted in a stock price increase for AT&T, Telecom sector, and the S&P 500.

        I find that the AT&T vs. Concepcion (2011) decision, which strengthened contract protections, increased AT&T's stock price by 2.4% over a 1-day interval.[6] Over the 7-day interval, AT&T's stock price increased 3.7% compared to its average stock price over the seven days before the ruling (p =0.00%). Over a 30-day window, AT&T's stock price increased 5% relative to the average stock price over the preceding 30 days (p =0.00%). To put these results in perspective, in 2010 AT&T's annual stock price growth was 10%.

        At the sector level, I found that over the 1-day interval, the telecommunications sector's stock price increased 1.7% relative to the day before the ruling. Over the seven-day interval, the stock price rose 2.1% (p=0.00). Over the 30-day interval, the stock price increased 4.8% (p=0.00). These results suggest that the SCOTUS ruling affected the telecom sector as a whole, which has many companies who all use contracts, and those contracts have considerable implication for their value, meaning a broader effect from the SCOTUS decision can be expected.

        Finally, I tested whether the ruling affected the stock market more broadly, beyond the telecommunications sector. To measure this, I used the value of S&P 500, which is a weighted average of the stock price of the 500 largest American companies, as my dependent variable. I found that over the 1-day interval after the ruling, the S&P 500 price increased by 1.3%. There was a 2.4% increase in stock price over the seven day interval (p=0.00%). Over the 30-day interval there was a 1.4% increase in stock price (p=0.02%). This suggests that all of the companies in the S&P 500 might experience higher profits as a result of stronger contract protections, and that companies' contracts have sizable implications on their value.

        The statistical significance of the results on stock price for the seven-day and 30-day intervals suggests that these changes in stock price are not driven by simple random chance. The statistical significance of a regression coefficient depends on two key factors: the number of observations and the standard deviation of the data. First, if our dataset were too small to capture the broader trends in the stock price before and after the ruling, our results would not be statistically significant because the change in stock price might simply represent short-term fluctuations. Second, if the standard deviation of the stock price in our data were high, it would be difficult to distinguish between a genuine increase in the stock price and the usual large fluctuations in the stock price (over any given amount of time). As a result, the fact that our

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[6] We cannot compute the statistical significance of the 1one-day regression because we cannot compute a standard deviation over one data point.

results are statistically significant suggests that they are not driven either by the short-term features of our selected time intervals or by usual large fluctuations in the stock price. Put another way, the results suggest that AT&T's stock price genuinely increased on the given day due to some event.

To conclude that the driving event is the SCOTUS ruling, however, we must assume that the only event during our time intervals that would have caused a substantial change in the stock price is the SCOTUS decision. This assumption is required for our model to be capturing a causal effect, rather than simply a statistical correlation. This seems likely, since events with major impact on companies' profitabilities like SCOTUS rulings happen only rarely.

Myriad Genetics

Myriad Genetics lost their SCOTUS decision which weakened intellectual property protections and resulted in a stock price decrease for Myriad and the Biotechnology sector but not the S&P 500.

I found that over the 1-day interval before and after the ruling, Myriad Genetics experienced an enormous 11.6 % decrease in its stock price. The 7-day interval yielded a massive 16.8% decrease in stock price (p = 0.00%) and the 30-day interval showed an 8.3% decrease in stock price (p =0.00%), suggesting that Myriad's stock price partially recovered within the next month, but remained far below its pre-ruling level.

Interestingly, the results of the Myriad case were initially misreported as a a favorable compromise for Myriad, causing an initial stock bump in the hours following the decision. However, as the actual results matriculated into the public eye in the afternoon of the decision day, the stock price plummeted.[7] This highlights that the stock market is a function of public opinion which is often controlled by information (true or untrue) rather than the merit of the company. Clearly, this case had an adverse effect on Myriad which is predictable because their entire business model was based on being the sole provider of their gene test. But does this decision have a broader effect on other biotech companies?

Evidently, this decision was bad for Myriad, but I would expect that the effect on the biotech sector as a whole would not be as severe because of the diversity of products. Over the 1-day interval, I found that the biosector experienced a 1.5% decrease in its stock price. Over the 7-day interval, the sector experienced a 1.9% (p=0.136%) decrease in stock price, and over the 30-day (p=0.041) interval it experienced a 2.2% increase in stock price. It appears that the news initially hurt the biotech sector, but overall it remained fairly unscathed. This underscores the diversity of the biotech industry, which for the most part, keeps any one product from controlling too much of the value in the sector systemically.

It does seem like this ruling was broad enough to reach most biotech companies but did it affect the entire market? Since there was only a small effect on the biotech sector, I would guess that the ripples of the decision would not reach the broader market. Over the one day interval the stock price increased 0.3%. Over the 7 day interval the stock price decreased 0.5% (p=0.442).

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[7] Katz et al., "Law on the Market?," 1.

During the 30 day interval the stock price increased 0.5% (p=0.292). The results show that, over the three intervals, the stock increased and decreased a small amount. There does not appear to be any abnormal behavior because the weighted average deviated slightly from the mean over the time periods and did not move in a consistent pattern. The 7 day and 30 day variables were not statistically significant, supporting the fact that the changes were likely due to random chance.

Sony

Sony won their SCOTUS decision which strengthened patent protections and resulted in a stock price increase for Sony and the S&P 500.

For the Sony case, again, I looked for an individual effect on Sony. For larger market implications, some electronics companies even sold VCRs in the 1980s so there may be some breadth. For major companies like Sony, the VCR is only a faction of their company so I would expect some effect but nothing detrimental.

For the one day interval I found a 1.9% increase in stock price. For the seven day interval I observed a 1.8% increase in stock price (p = 0.005%). The thirty day interval showed a 0.7% increase in stock price (p =0.00%). It seems like the changes in Sony stock price were small compared to the prior examples, but not statistically insignificant. I find these results plausible because Sony is a massive corporation with a diversity of products. The Betamax was a new product which had contributed very little to their cumulative value limiting the positive effect of the decision.

The Sony decision did have a minimal effect on Sony's stock. Sadly, there were no ETFs in 1984 so we can not measure the effect of the ruling on the electronics sector, but we can measure the effect of the ruling on the S&P 500. For the 1-day interval I found that there was a 0.5% decrease. For the 7-day interval I found that there was a 1.1% increase in stock price (p=0.005). For thirty days I found that there was a 4.4% increase in stock price (p=0.00%). The S&P 500 price slowly increased, with the largest increase materializing by the 30 day interval. All three variables were statistically significant, suggesting that over this period, the S&P500 experienced unusual price gains, although we cannot prove that they were driven by the Supreme Court ruling .

It is hard to ignore a 4.4% increase in stock price given that in 1984 the annual growth of the S&P 500 was 11.14%. The broader safe haven for VCR recorders, which was a most prominent dispute in the public eye, could have been perceived negatively by the market leading to an initial negative reaction. Then, once the public realized that the decision strengthened protections for businesses from contributory patent infringement, a rise materialized within 30 days. The slow public reaction could be due to the news not being as accessible in 1984.While the statistical significance does tell us something caused these results it could have been another reason altogether.

Conclusion

Overall, I find that SCOTUS decisions affect the stock prices of the affected companies and often their broader sectors. The stock market generally responds positively to Supreme Court decisions that strengthen contract and intellectual property protections. Two principles seem to govern the effect of a SCOTUS ruling on sector-level and market-level valuations: breadth and value. For example, the AT&-T case had breadth over the entire stock market because every company has contracts. Contracts are essential to companies creating high value. However, the Myriad Genetics decision had a more isolated effect. While gene patents have some breadth in the biotech industry, the sector relies on a diverse set of products and services, so one product does not account for much value creation in the biotech sector as a whole, although it accounts for a substantial portion of a single company's profits. This explains why this case had the most isolated effect. The Sony decision had breadth in the electronics sector although the sector was much more diverse than VCR recorders. However, increasing protections from contributory patent infringement is highly broad, reaching all companies who make products. It has reasonable value too, not as much as contracts, because it can protect companies from lawsuits and increase their manufacturing freedoms. These results provide an idea of the perspective of investors and highlight that at the end of the day the stock market is largely a function of public opinion. My results suggest that, if a stock investor had a strong belief that the Supreme Court would issue a ruling protecting companies' contracts or intellectual property, she could profit off this belief if she turned out to be correct by investing in the stock of the company who she expected to benefit from the ruling.

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The Role of Protein S Deficiency in the Development of Pulmonary Embolism in Children
By Yutong Chen

Abstract

Pulmonary embolism is a type of blood clot that often originates from deep venous thrombosis and travels to the lung. Pediatric pulmonary embolism is rare but dangerous. Compared with adult patients, children have a lower risk of forming blood clots and developing pulmonary embolism. Furthermore, pediatric pulmonary embolism is often overlooked because of its non-specific traits and the imprecise diagnostic testing. This overlook often leads to the delay of treatment. Despite the lower risk, the high mortality rate among pediatric patients is still unignorable and it has raised awareness among researchers. Past studies have shown that the presence of pediatric pulmonary embolism is usually related to risk factors. Among these risk factors, protein S deficiency has an evident effect on the development of pulmonary embolism. Protein S deficiency is a rare disorder that causes abnormal coagulation, increasing the chance of forming blood clots in the body and impacts how the treatment is given to pulmonary embolism patients. By having accurate evaluations of protein S deficiency, the patients will be given more suitable treatments. This research aimed to conclude the past studies on pediatric pulmonary embolism patients with protein S deficiency. It will be presented in several aspects including traits, diagnostic testings, and treatments.

Introduction

Pulmonary embolism (PE) is a dangerous complication of deep venous thrombosis (DVT). DVT is a blood clot that forms in the legs. The formation of these blood clots can result from external factors, such as immobilization or inherited reasons, including protein S deficiency and protein C deficiency. PE is a dangerous complication of DVT, where a patient's pulmonary artery is blocked by thrombus that travels to the lungs. This leads to a more serious result than usual venous thromboembolism, such as a higher mortality rate. In patients with shock and cardiac arrest at presentation, the mortality rates are 30% and 65%, respectively. This increasing risk of PE is also related to a higher chance of recurrences (Rajpurkar et. al, 2017). It is estimated that PE presents in 5-7 per 10,000 people annually. Also, in a study consisting of 5451 DVT patients, instead of gender and age, proximal localization is highly associated with the presence of PE (Rossi et. al, 2008).

Despite a lower frequency in children, PE is still a fatal disease among pediatric patients. The annual incidence of getting PE is 7-14 per 1,000,000 children (Rossi et. al, 2008). However, this number is still increasing as the diagnostic technology improves, since pediatric patients with PE are often under-recognized (Rossi et. al, 2008). This conclusion is demonstrated by the data that diagnoses of 87% of pediatric PE were established through autopsy. Facing the high risk of death and low chance to be diagnosed, increasing awareness of PE among children is important.

There are many causes that can contribute to the presence of PE, including the lack of protein S, a condition known as protein S deficiency (PSD). Protein S is a vitamin K-dependent

protein which plays an essential role in controlling the body's coagulation and preventing excessive formation of thrombus. PSD is usually inherited. Although inherited thrombophilia is common among DVT patients with a frequency of 30% appearances among all patients, PSD is rarely found within those patients (Klostermeier et. al, 2015). PSD is often a heterozygous deficiency, segregating as a dominant trait. If homozygous deficiency is presented, the patient will likely present early thrombotic incidence during infancy period (Martinez Licha et. al, 2020). The presence of PSD will greatly increase the risk of people at any age to get PE, so it should be given more attention. Also, special awareness should be given to those people who have a family history of PSD. In this population, the risk of PE will increase. The goal of this paper is to analyze the existing research on PE in pediatric patients with PSD.

Methods

For this project, a search was conducted from the database PubMed on July 29, 2023. The searching terms are (("pulmonary embolism"[Title/Abstract]) AND (children OR pediatric)) AND "protein S ". 41 articles were found using the searching terms. After reading each article's title and abstract, those that only focus on PE in adults, lack an emphasis on protein S deficiency, and focus on the specific mutation without including clinical information are being excluded from this research. In total, eight articles are generated. Within the eight chosen articles, information on PE's traits, diagnosis, and treatment are explicitly valued.

Traits

In adult patients, traits of PE are well studied with a reliable amount of research. According to the study on acute PE done by Licha's group, 81% of patients have dyspnea, 70% of them have tachycardia and 50% are presented with hypoxia. Other traits such as chest pain and hypotension are also included as symptoms of PE (Martinez Licha et. al, 2020). However, the study on children's PE traits is still lacking, and the limited research illustrates a difference of PE traits between the pediatric population and the adult population.

The traits of PE in pediatric patients vary between individuals. In the four case reports which include information of PE traits, chest pain, cough, respiratory distress, trauma of ankle, progressive dyspnea, tachycardia, and skin necrosis have been reported (Kosch et. al, 2022; Martinelli et. al, 2013; Wei et. al, 2022; Degan, 1994). In these traits, cough has occurred the most times with a frequency of 50% among the studied patients. However, other traits have been only reported once. This result indicates a lack of consistent and identifiable traits of PE, which raises concern of hindering the accurate diagnosis of PE for pediatric patients.

The non-specific traits of PE often lead to the misjudgments of disease in pediatric PE patients. There were three cases that reported wrong judgments depending on the occurring non-specific traits. One patient who was previously determined to have long standing bronchitis later found to have PE that was formed due to ankle pain. Another PE patient who has chest pain was initially thought to have *Mycoplasma pneumoniae* pneumonia. In another case, dyspnea

from a PE patient is wrongly seen as a symptom of asthma. The result shows a necessity of treating non-specific traits more carefully with a consideration of having PE in children.

Diagnostic Testing

There are various methods for diagnosing PE in pediatric patients. Although there are a great variety of diagnosis methods, pediatric PE may be very complicated under most circumstances, and some methods used in adult patients are not translatable to children. In the five case reports that only focused on pediatric PE patients, three of them reported delayed diagnosis of PE (Kosch et. al, 2022; Martinelli et. al, 2013; Wei et. al, 2022; Degan, 1994; Michiels et. al, 1987). The symptoms of PE were previously determined as long standing bronchitis, *Mycoplasma pneumoniae* pneumonia, and asthma, in 3 delayed diagnoses respectively.

In the four case studies reviewed, imaging methods were used to diagnose PE including: computed tomography with pulmonary angiography (CTPA), ventilation-perfusion (VQ) scans, phlebography, compression Doppler ultrasonography, and chest x-ray examination. The review articles noted that the most prevalent diagnostic method used is CTPA. In the systematic review done by Biss' group in 2017, CTPA was performed in 74% of patients while VQ scans was performed in 49% (Rajpurkar et. al, 2017).

D-dimer is an indicator of coagulation in PE diagnosis. If the level of D-dimer increases in the blood, this shows the patient is at higher risk of having PE. Using D-dimer as an indicator of PE diagnosis was variable between research articles. In this study, only 1 of the 5 case reports provided the detection of D-dimer's level as an indicator of PE. Results from several other studies indicate the result of D-dimer evaluation to be non-discriminatory despite a rise of D-dimer in most pediatric patients with PE. In the study done by Biss' group, which consisted of 50 children with PE and 25 children without PE, there were 27 patients with PE and 12 patients without PE having higher D-dimer value (Rajpurkar et. al, 2017). Thus, the utility of D-dimer in PE diagnosis was low, demonstrating its weakness in diagnostic usage in children. In a separate study from the same group, another 58% pediatric patients were performed with D-dimer, but among these tested patients, the result is still found to be non-discriminatory.

The two most commonly used risk calculators used in PE diagnosis are Pulmonary Embolism Rule-Out Criteria（PERC) and Wells criteria. PERC is a series of eight clinical questions that helps to exclude PE in low risk patients. Wells criteria is a score that incorporates a patient's signs and symptoms to determine the risk of PE. PERC has a sensitivity of 100% compared to 86% in Wells criteria. However, PERC's specificity was 36% lower than Wells criteria (Rajpurkar et. al, 2017). Medical records further showed that PERC that is used in adults faced difficulties diagnosing PE in 84% of pediatric patients. This result indicates extra care is essential in detection and evaluation of PE in children.

Treatment

Several types of anticoagulants are used in clinical practices of PE patients (summarized in Table 1). This study has looked at five studies containing descriptions of PE treatment (Kosch et. al, 2022; Martinelli et. al, 2013; Wei et. al, 2022; Degan, 1994; Michiels et. al, 1987). Among these studies, heparin is used most frequently, as it was taken by the patients in 4 out of 5 studies. It works by activating antithrombin III, a factor that prevents the formation of blood clots. Furthermore, as opposed to taking it individually, heparin is often taken along with other anticoagulants, which happened in three out of four cases with heparin. The general usage of heparin shows its reliability and effectiveness in the treatment of pediatric PE patients. Despite the wide application of heparin, rivaroxaban is used in two cases while coumadin in three cases; Recombinant tissue plasminogen activator (rt-PA), urokinase, and enoxaparin appeared once. Overall, although all the PE patients were treated with anticoagulants, there is still a large variety of anticoagulants that can be used and exert promising clinical effects on treating the disease.

Table 1. Different anticoagulants in PE treatment

Emergency Treatment	Short Term Treatment	Long Term Treatment
rt-PA	heparin	rivaroxaban
Urokinase		warfarin

The choice of anticoagulant used by pediatric PE patients is affected by the presence of PSD. In a case, a female PE patient with homozygous protein S deficiency developed skin necrosis. Firstly, she took coumadin to treat her thrombus, but coumadin didn't work as expected. As a result, she increased the dose of coumadin, but the skin necrosis was not being successfully prevented until rivaroxaban was given. This case shows that despite the general usefulness and effectiveness of coumadin, coumadin is not a suitable choice for patients with PSD. This is because coumadin works by non-specifically blocking all types of proteins, including the targeted protein that promotes the formation of blood clots and protein S that works as a natural anticoagulant. However, after blocking the beneficial protein, protein S, the patient's body will lack the ability to decrease the blood clots. Especially in this case, after taking coumadin, the girl with PSD is still incapable of stopping the excessive coagulation. Opposed to coumadin, rivaroxaban can successfully deal with a patient's PE since rivaroxaban only blocks factor X instead of all the proteins. Factor X helps with clotting, thus blocking it can efficiently cure the thrombus (Kosch et. al, 2022). This difference in choices of anticoagulants demonstrated that PSD, as a thrombophilia, will significantly impact how treatment will be done.

Different types of anticoagulants are also taken at different times during a pediatric PE patient's treatment. Among the five studies, all the cases in which patients used rt-PA and heparin were taken by patients immediately after the diagnosis. Conversely, rivaroxaban was always taken at the late stage of treatment. This difference indicates that the time to take an anticoagulant varied depending on the type of anticoagulant. For rt-PA and urokinase, they are

the strongest anticoagulants that can only be used when the situation is in an emergency. Patients have to take them as a medication to quickly dissolve their clots. This urgent need for strong medication usually happens when PE was first diagnosed, so it is often used immediately. Heparin is also used widely at the first stage, but for a different reason. Preventing the body from regenerating clots, heparin can reach the effective stage sooner than other anticoagulants. Its immediacy makes it a preferable choice at the first stage of treatment. Also, because heparin is well studied, patients, especially those with high risk, prefer to have it at the beginning as a safe choice. In contrast, rivaroxaban is always taken by patients later. This is because rivaroxaban is a relatively new medicine, which makes the risk of taking it higher than other anticoagulants. However, Its convenience and ideal clinical effect are still suitable for patients to take it long-term. In conclusion, the difference in time of taking anticoagulants depends on the patient's condition and the mechanisms of the anticoagulants.

Discussion

This paper reviewed the existing studies on pediatric PE patients with PSD. It provides helpful information on the traits, diagnostic testing, and treatment of pediatric PE. Also, it talks about how PSD affects the patient's ideal treatment. There is indeed a lack of research on pediatric PE compared with PE in the adult population, because PE is rarely present in children. However, pediatric PE's severity, fatalness, and under-recognition make it an unignorable health risk.

Traits of PE vary a lot among children, and they differ from traits of adult patients. This results in a disability to directly adapt experiences from adults to children. Pediatric PE symptoms are non-specific, which leads to significant difficulty accurately diagnosing PE. Diagnosis of PE is usually complicated in children, which often results in delayed diagnosis. Although a variety of diagnostic methods have been used, many of these diagnostic methods lack specificity or sensitivity. For example D-dimer testing has a high false positive rate. The traits and diagnostic methods of PE do not seem to be affected by the presence of PSD in patients.

There are many anticoagulants available in the treatment of pediatric PE patients. Each anticoagulant has its own unique usage depending on the patient's condition and its mechanism. For example, warfarin may not be a suitable treatment for PE patients with PSD. This is because warfarin blocks many proteins, including those like protein S that are helpful for anticoagulation. Giving the suitable anticoagulant at the accurate time is important for a PE patient's treatment. There are some anticoagulants that are used only in an emergency, for example rt-PA and urokinase. Other anticoagulants are used in short and long term treatment. For example, heparin is usually used in the short term, and rivaroxaban is usually used in the long term. This is because the orally taken anticoagulant, rivaroxaban, is more convenient compared with heparin that is taken through injection.

Raising awareness of pediatric PE is important, because it is often under-recognized and can be very dangerous. Future research on the risk factors and symptoms of PE will be important in improving recognition of PE in pediatric patients. Although the presence of PE is rare in

children, the presence of genetic clotting disorders is relatively common in children with PE. This makes the detection of PSD in pediatric PE patients essential since the presence of PSD will greatly affect how and when the anticoagulants are given. In the future, improving detection of genetic clotting disorders including PSD will be important.

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Blue Light and Health: A Review of Blue Light and its Structural and Functional Effects on Children's Brains and Neural Development By Pranauv Dev Muneeswaran

Abstract

Light is essential to all life and is pivotal to humans' visual perception abilities. Without light, biological functioning would not be possible. Blue light, a higher-energy light with a shorter wavelength, makes up almost one-third of all visible light and is particularly known for its positive effects on cognitive function, mood regulation, and the body's circadian rhythms. Recently, blue light has also been recognized as detrimental to the body's health and there has been increased concern about the long-term effects of exposure to blue light during specific time periods in the day. These effects may include a loss of hormone secretion, retinal damage, disturbances in the body's circadian rhythms, and more. Here, these impacts will be discussed in three distinct sections: circadian rhythms/melatonin secretion, retinal cells and visual perception, and other ramifications on human health. This paper will additionally address the advantages and disadvantages of blue light and specific physiological and psychological effects on the brain. This review will focus predominantly on children and their neural development. Structural and possible functional effects that blue light has on the brain will also be mentioned with a particular emphasis on children. The objective of this paper is to recognize these effects and possibly find a correlation between such exposure and the development of specific health issues later in children's lives. Using evidence from multiple studies and attributable data, this paper will provide an objective analysis that expands on current findings and provides insight into the lesser-known effects of blue light. Finally, possible recommendations and preventative measures that may arise due to these effects will also be discussed.

Understanding blue light

Blue light is part of the visible light spectrum, meaning is perceivable to the human eye. Composed of one-third of all visible light, blue light vibrates within the 400-500 nanometer range and is characterized by its high energy level and short wavelength. Blue light is just one of the different spectral components of any given light (Leid, 2019). Blue light is emitted through many sources, including sunlight (most prominent), digital screens, light-emitting diodes (LEDs), and fluorescent lighting (Coats et al., 2020). Scientists have been interested in the effects of blue light for decades and have found many positive effects that this part of the visible light spectrum provides. Such positive effects include an active role in melatonin suppression, circadian rhythm entertainment, alertness, cognitive performance, overall well-being, and additional benefits (Cajochen et al., 2011; Engelhardt et al., 2019). However, there has been growing evidence suggesting that blue light may have more negative effects than positive. These negative effects include implications on overall sleep quality, retinal damage, and even disruptions in circadian phase and cycle durations (Engelhardt et al., 2019). Additionally, it has been shown that blue light may even have detrimental effects on the cardiovascular system, and

can increase the risk for mental disorders including psychiatric illnesses as well (Engelhardt et al., 2019).

In terms of the brain and neural development, there have been multiple contrasting studies in regard to the effect of blue light. Some have suggested that brain activation in certain regions increases when exposed to blue light thus changing the course of its neural development as well. Alkozei and colleagues (2016) have found that the prefrontal cortex is one of these regions. The prefrontal cortex functions to regulate our thoughts, actions, and emotions by forming connections with other regions in the brain. Other scientific studies have suggested that some neural areas are silenced or have no effect from blue light exposure. More research is necessary to come to a more complete understanding of these regions. This paper will address the profound effects of blue light on the human body as well as its implications on neural development/progression.

Blue light on health–*Impact on circadian rhythms and melatonin suppression*

Circadian rhythms are the 24-hour cycles that are part of the body's internal clock. The circadian rhythm serves to carry out necessary biological processes in the body. For background, melatonin is secreted by the pineal gland and helps regulate circadian rhythm (i.e., cycles of alertness and sleepiness) and synchronize the sleep-wake cycle. Blue light, as a result of its short wavelength, is considered the strongest regulator of the circadian system (Wahl et al., 2019). It is important to understand that this does not mean that excess blue light correlates to a healthier amount of sleep. In fact, sometimes it conveys the exact opposite. The timing of blue-light exposure and level of intensity play a vital part in the amount of melatonin suppressed and the number of sleep-wake disruptions that result because of the disturbed sleep (**Figure 1**). To be more specific, blue light inhibits the amount of melatonin suppressed by the brain, which encourages wakefulness and can be disruptive to the sleep-wake cycle (Wahl et al., 2019). This is precisely the reason why chronic exposure to blue-enriched light directly before bedtime may have serious implications on sleep quality, circadian phase, and cycle durations (Wahl et al., 2019). Conversely, undergoing blue light exposure during the day suppresses melatonin secretion, and leads to less sleepiness (i.e., more wakefulness) during the day.

(a) Blue light exposure at morning

Blue light exposure from sunlight, LED lights, fluorescent lighting, etc. → Melatonin is suppressed leading to effects in circadian rhythm. → Positive effect. Body feels awake and alert with cognitive performance.

(b) Blue light exposure at night

Blue light exposure mainly from tech devices before sleeping. → Melatonin is suppressed leading to effects in circadian rhythm. → Negative effect. Body feels awake leading to implications in sleep quality.

Figure 1. Blue light exposure and its effect on melatonin suppression depending on the time of day. (a) Blue light exposure in the morning and (b) blue light exposure at night.Information derived from Wahl et and colleagues (2019).

Impact on retinal cells and visual perception

Blue light can be harmful to eye tissue because of its high energy level and short wavelength characteristics. More specifically, high energy short wave blue light between 415-455 nanometers is the most harmful (Zhou et al., 2018). Due to the increasing popularity and use of technological devices, the effects of blue light are becoming more prominent in humans becoming a prevalent concern. Blue light causes detrimental effects on many structures in the eyes. This includes the cornea, lens, and retina (**Figure 2**). The cornea is the first structure that light encounters when passing through the eye, so it is afflicted first. Niwano and colleagues (2014) found that blue light exposure to developing corneal epithelial cells is detrimental, and can lead to dry eyes and loss of stability/stability of the tear film, which is the thin fluid layer that protects outer mucosal surfaces of the eye. Blue light also has a negative effect on the lens and has been implicated in the development of cataracts (Zhou et al., 2018). Multiple studies have shown that blue light may induce the production of reactive oxygen species (ROS) in the mitochondria of lens epithelial cells, which may increase the development of cataracts (Zhao et al., 2018). Indeed, the lens does function as a structural boundary in limiting the transmission of blue light to the retina, but this protective effect can also lead to a decrease in transparency or color change of the lens, leading to cataract formation as well (Zhao et al., 2018). In the case that the lens does not block blue light transmission appropriately, the blue light can contact the retina and cause retinal photochemical damage.

Currently, the effects of blue light on the retina and possible negative effects are still being studied and reviewed but there is reason to state that blue light causes adverse effects on retinal cells in people of all ages and can lead to age-related macular degeneration. Moreover, these alterations can cause the onset of many eye disorders such as the development of dry eye disease, glaucoma, and keratitis (Ouyang et al., 2020). Accordingly, there have been many preventative measures for eye-related effects of blue light which will be stated later in the paper.

Figure 2. Basic anatomy of the human eye. Image adapted from Eye Health Nepal (2021) and created with Biorender.

Blue light and other ramifications on human health

Most attribute blue light to disruptions in the circadian rhythm cycle and problems related to the eye, but there are considerably more ramifications on human health that are still being researched and reviewed today. In fact, there have been studies that have shown that ultraviolet light can decrease overall blood pressure by releasing nitric oxide from the skin (Stern et al., 2018). Stern and colleagues (2020) conducted an experiment in which healthy male subjects were exposed (i.e., through lighting) to monochromatic blue light or blue light with a filter foil for approximately 30 minutes. Along with other benefits, the blue light exposure significantly decreased systolic blood pressure and increased heart rate compared to the control individuals. The blue light exposure also significantly increased forearm blood flow, and flow-mediated dilation while also decreasing pulse wave velocity and forearm vascular resistance. This suggests that blue light therapy may be promising for those with vascular issues or diseases. As seen, we can observe possible advancements in cardiac research and therapy. This is still a growing body of work and more research is needed to reach a more thorough understanding of these alternate effects of blue light on the body. There have additionally been significant increases in alertness, information processing, and cognitive performance in those who are exposed to blue light as opposed to those who are not; this can be attributed to blue light's impact on circadian rhythm and its effect of "waking up" the exposed individuals (**Figure 1**). Overall, these ramifications need to be studied in a more detailed manner in order to come to a more compelling conclusion.

Impact on children's brains and future implications in neural development–*Brain maturation and mental health*

Excessive amounts of blue-enriched light can have disruptive effects on the circadian rhythm of humans at night (Cajochen et al., 2011). These effects can lead to a lack of sleep ultimately causing unnecessary effects on behavior and mental health (Engelhardt et al., 2019). Kocevska and colleagues (2016) conducted a prospective cohort study that assessed the association between childhood sleep disturbances and brain morphology at various ages (2 months, 1.5, 2, 3, and 6 years old). The results revealed that sleep disturbances from age two onwards are associated with smaller gray matter volumes in the brain. This reveals that sleep disturbance trajectories in children may interfere with children's neural development and brain maturation. Specifically, this means that sleep disturbances can interfere with – and potentially delay – the maturational processes of the brain, and a thinner prefrontal cortex (Kocevska et al., 2017). Ultimately, these effects can also translate to mental health difficulties. Insufficient and poor-quality sleep is associated with worse mood and emotion regulation, as well as an increased likelihood of developing a mood or anxiety disorder, and a heightened risk of suicidal ideation in children and adolescents (Short et al., 2019). It is important to note that these early years of life are foundational in neural development and pave the way for future developmental changes, so disruptions can lead to a lack of brain maturation and neural development (Short et al., 2019). It is also worth mentioning that more research on the consequences of sleep loss on mental health has been conducted in adults, so more studies of children specifically are needed in this area.

Learning problems and disorders

The disruption of the circadian rhythm cycle can also have implications on children's ability to learn and may even lead to learning problems and disorders (Javary et al., 2020). These correlations could be positive or negative depending on the nature of the sleep schedule (Curcio et al., 2006). Nonetheless, prior research has manipulated sleep in individuals to observe neurocognitive and behavioral consequences such as learning and overall school performance. One such study has suggested that sleep loss is frequently associated with poor declarative and procedural learning in students and that restricted sleep, mainly meaning less than recommended, can lead to a worsening in neurocognitive and academic performance (Curcio et al., 2006). Importantly, sleep modifications such as sleeping during different parts of the day, or less/more amounts of sleep per day than is ideal (i.e., 8-10 hours per night) can have mixed effects over the course of the child's life. Javary and colleagues (2020) conducted a related study that analyzed sleep pattern modifications (i.e., 45-minute reduction in sleep) on learning basic concepts such as mathematical operations/applications in elementary children. The results of this study indicated that sleep pattern modification can reduce students' math-learning disorder. That is, children saw an increase in academic performance and a reduction of learning disorder from the manipulation (dependent on each student) of sleep. This increase in performance may prove to be promising enough to examine and modify the sleep pattern (optimal range of sleeping hours differed between various students in the study) of students with a math learning disorder so as to mitigate learning problems in the school setting. Ultimately, sleep patterns are vital in children and can drastically affect their academic performance as well.

Blue light recommendations and preventative measures

As discussed in previous sections, blue light has various effects on the human body. These effects can be categorized as positive or negative depending on the time of exposure during the day (Wahl et al., 2019; **Figure 1**). This is a growing concern, especially with the rise of technological usage in adults and children. In order to protect the human body from the possible negative effects of blue light exposure, there are specific recommendations and preventative measures that may be utilized to decrease exposure to excessive blue light. One such product is blue-light blocking glasses, which can block from 20% to 100% of blue light from reaching the eyes depending on the type of lenses used. Esaki and colleagues (2016) conducted a study that measured the effect of blue-light-blocking amber glasses on subjects with delayed sleep disorder (DSPD), which is when individuals experience sleep patterns that are two or more hours delayed from a typical sleep pattern. Dim-light melatonin onset was measured after sleep cycles and it was concluded that the blue-light blocking glasses advanced circadian rhythms in the patients with delayed sleep phase disorder. This means blue-light blocking glasses enhanced individuals' ability to sleep, which therefore affected circadian rhythm in a positive manner (Figure. 1). These findings have also been similar with patients that do not have DSPD. Burkhart and Phelps (2009) conducted a randomized study that measured the effect of blue-light-blocking amber glasses and UV-light-blocking yellow-tinted glasses for three hours

prior to sleep. The results indicated that sleep quality in the blue-blocking amber lens group experienced significant improvement in sleep quality relative to those who wore glasses that only blocked ultraviolet light. In addition, those who wore the blue-blocking glasses also experienced an improvement in mood. As seen, these blue-light-blocking amber glasses may show promise.

Another device that can show promise is blue-light filtering intraocular lenses (IOLs), which are tiny surgically implanted lenses designed to filter short-wave (blue) light from reaching the eye. Davison and colleagues (2011) evaluated the potential risks and benefits of these intraocular lenses. It was found that these blue-light filtering IOLs allowed individuals to experience an overall better quality of vision, reduced glare disability, and protection from retinal phototoxicity and its potential risk of age-related macular degeneration. These possible preventative measures should be leveraged in addition to basic lifestyle habits that promote healthy sleep. These habits include avoiding short wavelength (i.e., blue-enriched) light, typically from a smart device, before sleep and having a regular nighttime routine. Avoiding these blue-enriched emissions for a certain period before sleep can enhance sleep quality and mood.

Conclusion

As shown through the research presented in this review, many studies have been conducted that demonstrate the various effects that blue light has on the human body. At this point, it is known that excessive blue light exposure can have negative effects on the circadian rhythm, retinal components of the eye, brain maturation, and a few other ramifications. It is important to understand that more research is necessary to understand the specific relationships between blue light and other aspects of human health. More research is also needed to understand blue light's impact on children and how blue light may impact brain maturation and development in particular. Disruptions in children's brain maturation and cognitive development can have effects even decades after childhood and can lead to a prominent issue later in life.

Furthermore, it is important to note that the preventative measures discussed in this review such as the blue-light blocking glasses and the intraocular lenses (IOLs) are best leveraged after other measures have been taken to adjust sleep schedule and other lifestyle factors. Changing such lifestyle factors can have a higher impact in blocking blue light compared to external devices, which is why it is advisable to adjust these lifestyle factors first. External devices may be utilized afterward if sleep schedule is still an issue.

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Factors About and a Proposed Method to Harvest Acoustic Energy By Hanyuan Liu

Abstract

Scientists have tested many different ways to generate electrical energy from other forms of energy, including nuclear, potential, kinetic, solar, and thermal energy. However, acoustic energy has not been as rigorously studied. We are constantly surrounded by sound to the point it may even be considered pollution. There are noises almost everywhere: in karaoke rooms, factories, airports, and highways, to name a few sources. These huge amounts of energy (for example, there is 1 megaWatts amount of power when the sound intensity is 60dB) can be used if we are able to find an effective way to convert acoustic energy to electrical energy, not only to reduce "noise pollution", but also to relieve the energy problem in our world. In this research we propose and partially test a potential method to harvest acoustic energy. A speaker/microphone can be used to convert pressure into electrical signals. The efficiency and cost of the system will be evaluated. In addition, future work could use resonance to create a vibration in a small piece of metal and induce electricity using a changing magnetic field. Throughout the research, it is found the proposed diode-capacitor rectifier could convert an AC input (representing an acoustic input) to a DC output (usable electrical energy). These results show a way to generate electricity from noise. Moreover, the proposed device could be used to measure or monitor the intensities of sounds using an LED as a power threshold indicator. Using resonance, which is highly frequency selective, frequency measurements could be obtained of various acoustic sources.

Introduction

Finding ways to generate energy has been an enduring issue throughout human history. From burning fossil fuels to utilizing solar energy, the evolution in energy sources influences human development. However, most energy comes at a cost: Burning fossil fuels releases carbon dioxide which adds to the greenhouse effect; solar and wind energy depend on the weather; nuclear fission has the potential to become unmanageable, leading to genetic alterations and even fatalities. It is important to find more efficient and cleaner ways to generate electrical energy, and acoustic energy, which many people have ignored, might be a good option.

Many metropolitan areas, where energy is required for life, have high levels of sound. As a result, finding an efficient way to convert acoustic energy into electrical energy may relieve the global energy crisis. Additionally, this technology can absorb the "annoying" noise and convert it to electrical energy which can be directly used.

Section 1: Definitions and Literature Review

In order to convert acoustic energy into electrical energy, a microphone/speaker is needed as a transducer; the key difference between a microphone and a speaker is that a speaker converts electrical energy to acoustic energy, requiring some input electrical power, whereas a microphone converts acoustic energy to electrical energy. However, the construction of both devices is very similar. The main physical law governing the conversion of acoustic energy to

electrical energy is Faraday's Law [1]: a magnetic field will interact with an electric circuit to produce an electromotive force. After collecting the acoustic energy, a transformer can be used to amplify either the current or voltage harvested from the acoustic input. A transformer can increase the voltage if it has more turns of wires on the secondary winding. Another technique to convert acoustic to electrical energy is to use resonance. To convert the AC output from the transformer to a DC value, which can be stored on a capacitor, a Schottky diode [2] is used. Additionally, a Schottky diode does not consume much power from the circuit so there will be enough voltage and energy across the capacitor.

To further increase the gain of the harvester (at the cost of acoustic bandwidth) resonance can be used. Resonance is the phenomenon of increased amplitude that occurs when the frequency of an applied periodic force/signal is equal or close to a natural frequency of the system on which it acts. Research has already identified the two main methods of converting acoustic energy to electrical energy. The first method uses piezoelectric materials to generate electricity. The amount of electrical energy that can be harvested is directly affected by the volume of the substance and the density of it.[3] All previous designs on piezoelectric materials can output 30,000 uHz power at maximum, which is still a small number. Another method will use a Helmholtz resonator to harvest acoustic energy. Previous experiment found that the coil produces more power at 98 Hz when Sound Pressure Level (SPL) is less than 105 dB, but it outputs more power at 140 Hz when SPL is larger than 105 dB.[4]

Section 2: Overview/Methodology

The proposed harvester will use a microphone, a power transformer, wires, LED (as an indicator), a multimeter, a Schottky diode and a capacitor to create a method of converting acoustic energy into electrical energy. The output voltage of this harvester at different frequencies is investigated.

The microphone collects acoustic energy from the environment. A transformer with a high turn ratio is used to connect 2 circuits together and amplify the voltage output from the microphone. A Schottky diode limits current flow to one direction, acting as a rectifier. The capacitor serves to store the electrical energy harvested by the microphone. The multimeter is used to measure the amount of voltage and current in different components of the circuit. The breadboard connects the wires and components together. Finally, if desired, an LED can be used to indicate whether the capacitor voltage exceeds a certain threshold.

To test the system, a computer speaker will be used as a sound source and it can provide sound in the same frequency range, which keeps one variable fixed.

Table of components and proposed Schematic:

Table 1: Components

Component	Part Number (from digikey)	Unit Price
microphone	931-SPKM.50.8.A-ND	$2.88
LED	1080-1064-ND	$0.36
Power Transformer	237-1577-ND	$5.13
Jumper wires	1568-1511-ND	$2.10
Breadboard	1528-2143-ND	$5.95
Multimeter	1568-TOL-18340-ND	$18.25
Schottky diode	1655-1922-1-ND - Cut Tape (CT)	$0.60
Capacitor	732-8851-1-ND - Cut Tape (CT)	$0.10
Signal generator	1HZ-500KHZ DDS	$29.99

Diagram 1: the Circuit in Stimulation

Section 3: Simulation Results

The harvester was stimulated in Circuitlab [5] and different input voltages were applied to the circuit which correspond to the different amounts of acoustic energy the microphone receives. **For each diagram, the blue curve is the amount of input voltage; the orange one is the output voltage from the transformer; the yellow one is the voltage across the capacitor.** The actual forward voltage of the Schottky diode used is 350mV. The transformer turns ratio used in simulation matches that of the transformer purchased, which is 1:19.

Diagram 2: (10mV input voltage with 20mV diode forward voltage)

Diagram 3: (1V input voltage with 2V diode forward voltage)

Diagram 4: (3V input voltage with 6V diode forward voltage)

Section 4: Measurement Results

Diagram 5:The diagram of the circuit which the experiment used

Due to limited acoustic energy produced by standard computer speakers, a signal generator [6] is used to emulate what would be the transformer output. The signal generator output is set to 10Vpp and the input frequency was swept from 20Hz to 20000Hz. This frequency range approximately matches the audible range [5]. The DC voltage across the capacitor(s) is measured using the multimeter.

Table 2: Frequency vs Voltage across Single 1uF Capacitor

	Frequency	Capacitor Voltage (DC)
1	20 Hz	0.045 V
2	100 Hz	0.045 V
3	500 Hz	1.99 V
4	1000 Hz	3.7 V
5	1500 Hz	4.63 V
6	2500 Hz	5.64 V
7	3500 Hz	6.19 V

8	7000 Hz	6.95 V
9	13000 Hz	7.28 V
10	20000 Hz	7.42 V

Diagram 6: Voltage over different frequencies

$R^2=0.9914$

Table 3: Frequency vs Voltage across Two 1uF Capacitors

	Frequency	Capacitor Voltage (DC)
1	20 Hz	0.044 V
2	100 Hz	0.059 V
3	500 Hz	3.81 V
4	1000 Hz	5.36 V
5	1500 Hz	6.09 V
6	2500 Hz	6.81 V
7	3500 Hz	7.13 V
8	7000 Hz	7.48 V
9	13000 Hz	7.58 V
10	20000 Hz	7.61 V

Diagram 7: graph of data from Table B

Section 5: Discussion of Results

The result above shows that as the input frequency increases, the amount of voltage across the capacitor increases. Both curves are hyperbolic and have a horizontal asymptote. Every capacitor has an inherent leakage which causes the capacitor to discharge slowly. As the input frequency increases, the capacitor charges up more often, which leads to a higher average voltage. The highest voltage that can be harvested, in the frequency range tested, is around 7.5 V for single capacitor and 7.7 V for double capacitor. We find that as the input frequency increases, the output voltage monotonically increases. For both a 1uF and 2uF storage capacitor, the slope between from 100 to 500 Hz is the greatest. Adding capacitance leads to an increase of voltage across the capacitor, and increasing the input frequency has the same trend. The slope levels off at approximately 7 kHz for a 1uF storage capacitor and about 3.5kHz for a 2uF storage capacitor. At these frequencies the capacitors have more than 90% of their maximum voltage. While this input across all frequencies had the same input magnitude (10Vpp).

Section 6: Conclusion

We have proposed a method where acoustic energy can be harvested by the speaker and be stored in a circuit after being transformed. While limited sound levels prevented testing full systems, the rectifier circuit consisting of the diode and capacitor was characterized and shows promise of operating in an acoustic harvester. Based on the data, the DC voltage across the capacitor increases as frequency or the amount of storage capacitance increases. Although this is only a small amount of energy, it could come from otherwise un-utilized acoustic energy. Even these small amounts of energy can add up in the long run and prove to be useful as power for electronics. This circuit can be referenced in the future experiment on harvesting acoustic energy, which converts acoustic signal to electrical energy. In the future, this experiment can be implemented by adding the factor of a transformer and using a more sensitive speaker to collect the sound.

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How AI will Revolutionize Digital Marketing By Dhanush Tella

Abstract

Marketing is a crucial component of modern businesses today. Most of marketing however, has been digital due to its superior return on investment. There are four stages of digital marketing. Awareness, the first stage, is the process of making a demographic aware of a company and its services. Consideration, the second stage, is the stage to solidify the need by a person for a company's services. Conversion, the third stage, is the stage to convert people into customers. Loyalty, the last stage, is the stage to retain customers. AI is also an extremely applicable tool that is growing fast in many industries. In all these stages, AI can enhance the efficiency, effectiveness of marketers by eliminating repetitive tasks, harnessing large datasets and creating tangible demographics to market to, personalizing advertisements effectively, and much more. In conclusion, AI is a growing tool that will continue to find new applications and change the process of digital marketing.

Intro

Marketing in modern times is a critical component for the basic functionality of any successful business today. Marketing controls how our economy moves and interacts; it is the most dominant factor that helps build a formidable customer base. Strong marketing is a dynamic process that attends to the customers needs while benefiting the business. Marketing allows businesses to target groups differently based on demographics. In general, the steps of marketing are: awareness, consideration, conversion, and loyalty.

Recently, a great deal of marketing has been digital, because of its profitable return where "60% of marketers across various industries have already shifted their efforts toward digital marketing"(Arma and Elma). For example, PPC (pay per click) returns $2 for every $1 spent, resulting in a 200% ROI (return on investment) (Marino). However, no matter how effective digital marketing can be, one thing that will always affect the campaign or ads's efficiency is the quality of the marketer's work. Logically, if a marketer had more campaigns, assuming that the time is fixed, then the overall quality of those campaigns goes down. This means that the total ROI would be less. Subsequently, if one would like to increase the ROI from marketing campaigns, one would have to invest to increase a marketer's efficiency.

This is where artificial intelligence (AI) becomes an attractive approach in modern marketing. AI is a great tool that compiles, observes and learns from data to better suit its programmed goal. AI dynamically learns to act on data without context and uses algorithms to come up with an outcome to then repeat this cycle to refine and find the most accurate answer. This cycle, although visually intense, happens quickly and efficiently. However, a question may arise: How is AI good for digital marketing? Given that AI is useful for almost any task and uses digital data like a marketer, it can easily impact specific stages of digital marketing. As a reminder, the steps are: awareness, consideration, conversion, and retention. AI is not meant to replace marketers, but rather to be used as a tool to aid marketers and improve efficiency. If AI

increases efficiency, marketers have more time to plan, create, and deploy campaigns with more quality for increased ROI. Overall, to improve digital marketing, AI must improve the marketer's efficiency. We hypothesize that AI will improve the efficiency and effectiveness of digital marketers. In this research paper, we review how AI will impact marketers with the four steps of marketing.

Awareness

Awareness is, in simple terms, the process of informing people of a business's product or service. Awareness is crucial because it is the process that starts the digital marketing cycle. The "awareness" stage typically looks something like this: A business places an advertisement and hopes that a person who needs the product at that specific time clicks on or acts upon the advertisement. A marketer's job in this is to create advertisements based on a specific or general demographic. The more data the marketer has, the less personalized an advertisement is and the less the marketer can do. However, the less personalized the advertisement is, the less likely customers are to click on it. In the example of mail, "Compared to unpersonalized mailings, personalized promotional mailings have 41% higher unique click rates"(Vrountas). This means the business is actually losing money that it could have if the marketers were more efficient. With AI, ads can be personalized in two ways, through segmentation and individualization marketing.

Segmentation marketing targets groups of people that have been grouped together based on their demographics. For example, if a large technology company wants to hire qualified candidates for their vacant software engineer roles, they wouldn't individually market for every candidate, they would place a general advertisement for a group of software engineers. Not only is this technique quick and efficient, it is also very effective for general products or services. Segmentation is meant for products that are generally in demand by a group that wants it. However, generally in segmentation marketing, the group is not actively looking for it. In other words, segmentation marketing aims to make customers realize their interests and buy the business's product or service. Unfortunately, this is still time-consuming for the marketer because marketers still have to go through a big dataset, identify their target groups, and create the advertisement. This is where AI can be beneficial. AI is an excellent data compiler and learner that can act upon large datasets much more efficiently and accurately than marketers can. With AI the business can take this grouping process and group people much more efficiently. When given a target demographic AI can find matches to that group based on behaviors, timings, or demographics. In this way, AI will help marketers save time for more important things, improving their total efficiency. Finally, AI can create content for marketers from related ideas and interests with generative AI which is a tool that can turn ideas into tangible content. AI can also give marketers insights or demographic statistics to make more detailed advertisements. This helps to prove the hypothesis because AI in segmentation marketing increases any digital marketer's efficiency and helps them do more things in general.

The individualization is much more personalized than segmentation. It is focused on each person, in a distinct way, to build a strong connection through personalization. It is notable that advertisements are not human interactions, making it hard to make a personal connection. Unlike segmentation, this type of personalization, however, makes up for lack of personalization by making an artificial connection with the customer almost instantaneously . "64% of customers want to shop with companies that can meet their needs in real-time" (Salesforce). Individualization, however, is an arduous process that requires identifying customers based on demographics, behaviors, and locations, followed by content creation. This is another area where AI can be useful. AI can help marketers find individual customers who are most likely to buy or click, by identifying target customers, matching and learning based on the customer's demographics. In other words, the process works like this: there are 1000 people, and each of them have certain interests. The goal is to find what the people individually like to sell an associated product accordingly. A part of this process is predicting if a person is willing to click on an ad. Once again, AI can predict who is more likely to click on an ad and output a better database to decrease budget but increase ROI. To prove this, the researcher built an AI model using a Random Forests Classifier. This model takes in account daily internet usage, area income, daily related site usage, and age. This model returns an answer with 95-97% accuracy. This proves many things. First, that these "AI" models can be made right now. Next, even with only a few variables, people can still be used to build a more reliable database for future use and profit.

The previous models, however, need the campaign to search for customers. However, if the customer is looking for products themselves, the previous strategies do not work. In addition, these customers can be a gold mine for businesses because these customers are almost guaranteed to be buyers and are also good for retention. A gold mine like this can be harnessed by search engine optimization (SEO). "More than half of shoppers surveyed say they use Google to discover or find a new brand" (Google). When a highly interested customer searches for their desired service, they turn to a search engine. They most likely look and click the top few links and the rest of the links below are ignored. AI, unexpectedly, is important here too. By analyzing the keywords most relevant to the business's product, AI can find the cheapest and most effective optimization to make the business's product stand out and increase the amount of traffic. This increase means an increase of total people buying products. Additionally, AI, using generative AI, can create an original heading or page name to better emphasize uniqueness and to differentiate the business from its competitors.

What all of these digital marketing strategies have in common is the fact that they require defined content. Whether segmented attractive advertisements or individualized marketing, advertisers need tangible content, be it a picture, video, or any other form of content to visually attract potential customers. Content creation is also a very time consuming endeavor, and AI can once again be useful in this context. AI can first analyze which modes of advertising are most effective in marketing. Second, it can analyze the brand's style and how it is expressed towards

its customers and then tell the marketer to offer products along these lines. AI can also help the marketer identify more relevant terms, which, in turn, can increase the marketers' creativity. AI can use relevant terms to research, analyze and identify the proper demographics and customers to target. Another helpful tool is Generative AI. Generative AI is, in simple terms, an AI that can generate content. An example of this is ChatGPT. With tools like ChatGPT, projects like scripts can be created in a particular style or format that is desired. Therefore, TV commercials or written advertisements are quite easily generated. Finally, AI can use NLP (natural language processor) to voice the actual advertisement if needed.

Finally, AI can easily market to social media with the content creation from ChatGPT and target demographics and find an active customer base. Since the demographics of users on social media are very documented, on social media, a marketer can use the individualization marketing strategy with AI to gather a large interested user base, increasing the number of potential customers. This is because social media marketing individually tailors ads into the user's experience. This process leads to great returns. For example, "The average ROI for social media ad campaigns is around 250%" (Gitnux).

Consideration

An important part of digital marketing is to make sure that potential customers do not forget about the business. Consideration solves this because it is the reminder and persuasion to buy a product. Consideration is also the continuation of customer experience through reminders. Consideration affects people who are considered potential customers of a product. This step often needs a sign, email, or number to contact the potential customer. Without consideration, customers will not remember the business and a customer that doesn't remember that a specific business exists cannot buy from that business.

One of the largest techniques of consideration is email marketing, where "59% of respondents said that marketing emails influence their purchase decisions, while just over 50% buy from marketing emails at least once a month" (Charlton). Email marketing uses a database of users, sorted as groups, who are all sent emails that are often quite generic. This is often done by marketers and is very time-consuming. AI, however, can address this problem. AI, with some help from RPA (Robotic Process Automation), can fully automate this process. First, we can start by identifying each customer individually. Then, using AI, we can curate the emails created by a generative AI application like ChatGPT towards each person. This in turn creates a more personalized touch that can influence purchase decisions. Finally, an unattended robot can send these messages to finish the process. Similarly, mobile marketing uses the same principles but uses phone numbers and texting instead of emails. This can be a large time saver for marketers because they don't have to waste time writing emails.

The last great technique of consideration is deals. Businesses want to make profit faster and more efficiently. Sometimes, the customer knows about the business's product and does not buy from the business based on price or an outside factor. An example of an outside factor would be someone telling a could-be buyer that a certain product is bad. This is where deals come in,

with labels like "personal deal" or " special deal" people will be more persuaded to purchase a product. In addition, if these deals are done during times like the Christmas season or a public holiday, they can be labeled as "personal holiday deals" or something similar to add more persuasion by creating a persuasive atmosphere. For example, overall retail spending will rise 4.5% to $1.328 trillion for the 2023 holiday season (Lipsman). In addition, "81% of Americans say finding a great offer or discount is on their mind throughout the entire purchase journey"(Retailmenot). "Nearly all consumers (94%) search for a deal or offer when shopping online" (Retailmenot). As stated before, a simpler experience is a better experience so why not bring something that the possible future customer is looking for straight to them so they can buy exclusively from the business itself. AI ties into this by analyzing probabilities and datasets of to-be customers and selectively choosing a customer that could be the most profitable of a deal. For example, if a customer had a history of buying from coupons or deals, the AI would most likely give them a deal. After finding the customer, AI can give a deal that would still persuade the customer to buy, but also give the business the most money. This especially saves lots of time for marketers because not only do they not have to analyze datasets, they don't have to waste time to curate deals.

Conversion

The next and probably the most important step in digital marketing is "conversion", or turning people into buyers. Conversion is customer experience before a person buys. Conversion usually looks something like this: *After a person navigates to a website from SEO, Ads, Email Marketing, etcetera, a person buys a product in mind of the customer experience*. First the data is updated with the interactions, history, and other actions of the user. Then, using data the feed or information on the website can automatically be configured by AI for the certain user. Next, chatbots can also be pre configured to help the user easily navigate through the pages. Chatbots as themselves aren't made by AI and are just made by keyword triggers. However, with the implementation of conversational AI, chatbots can be developed and optimized to simulate a conversation also with the help of NLP. With the human component of conversational AI and NLP, the chatbot increases the amount of personal and human connection towards possible customers. This personalization of the customer experience increases revenue. For example, "personalized language that promotes an emotional connection boosts revenue by up to 55% across multiple campaigns" ("Ameya Dusane"). Finally, AI can also stimulate personalized deals for certain people based on their interests and create a more personal touch and build up customer loyalty over time.

The interesting part is that this somewhat complex personalization is already happening. Geico, an insurance company, is a prime example of this. On their landing page, first we can observe a chatbot. This chatbot takes in the customer's basic details like name, email, and state. Based on this information, the chatbot personalizes the chat experience with the user using Conversational AI and gives them options to proceed. Not only is this chatbot tailoring towards the customer but it is learning while talking which makes it even more personalized. In addition,

the geico webpage takes in extra details like zip code and insurance type to make an even more personalized experience inside and outside the login page. For example, if a customer wanted certain insurance, it would take in conditions of the zip code and many other things and either send the customer to a partner site for an even more personalized experience in the form of insurance or give a personalized quote. These quotes are calculated based on an AI model that trains on previous data and outputs the best amount for the new user. This helps marketers because personalization in general relieves the amount of stress on advertisements. Without it, marketers would be forced to spend more time creating higher quality advertisements which severely hurts their efficiency.

Product recommendations can also improve conversion. The reason why this is so important is because if a person is looking for a product, the business is basically giving a good product for their needs right in front of them, which simplifies the entire processes of research, search, and review. The simpler the process, the more convincing and easier it is for the customers to buy into it. AI, with its skills with data compiling, can read customer demographics, and identify what the possible customer wants based on past searches, ad recommendations and their overall behavior and demographics. AI can also use these data management skills to analyze the most popular item or the most searched item to improve and make better data-driven decisions. A prime example of this is Amazon. Amazon's product recommendation system is one of, if not the best, recommendation systems in the world. The amazon AI recommendation system takes in purchased items, owned items, ratings, and activity of other customers with similar interests. It returns a full menu of curated, high quality recommendations that will benefit the customer. In fact, "Personalized product recommendations are estimated to account for more than 35% of purchases on Amazon"(clerk.io). Product recommendations are fundamental because it persuades the customer to buy things that they already need which means that they are much more likely to buy it. Without AI in this instance, marketers would be forced to spend more time creating higher quality advertisements and emailing customers which would severely hurt their output.

Loyalty

Now, we have the final step: loyalty, or customer retention. This step is meant to fight against the churn of the customer or the conversion of the customer to a different business. The most valuable quality of a customer at this point is brand trust and connection.

The second is that because customers are unique, businesses must make them feel valuable through personal connection made with personalization. Since this consumer has already interacted with business, there is more data on them. This means that personalization will be more accurate. This personalization at such a late stage builds brand trust and connection. This means that less effort needs to be done to retain the customer. The third is that since they are returning customers, deals can be more exclusive to each customer. This "exclusivity" creates a more personal touch and builds brand trust. AI can easily facilitate this by looking at the data and

deciding an appropriate amount of discount that would still make profit and create a better customer experience/behavior.

Finally, the last thing that AI can do is to monitor churn. By using algorithms and neural networks, AI can predict the customers most likely to churn or leave the business for other services and give the business a chance to recover the customer, which is not possible without AI. To prove this, the researcher built an AI churn prediction model with Random Forests that takes in account the customer's balance, age, tenure, credit score, credit card, activity, and salary. The model trained on a churn dataset and returned a model with 84% accuracy. This shows many things. First, it proves that churn, something that a human could never predict, can be predicted by AI at a high accuracy with only a few variables. Second, it shows that AI can be easily implemented into loyalty right now. When the customer is about to churn, the business can be even more exclusive to the customer and do the methods listed above in greater measure to recover the customer. This cannot be done by AI but it can be done by the marketers who use AI. This is the most important part of the loyalty phase because if a customer is gone, then the business cannot profit again. This helps the marker's efficiency and effectiveness because if a customer is gone, there will be no one to market to in the first place and these measures prevent this.

Conclusion

In conclusion, digital marketing is one of the most impactful events in the modern day business world. It is the deciding factor for customers for a certain business and its competitor. It shapes our economy every day by using our data and drives success in business. However, what really determines a campaign's, or an ad's, legitimacy are the marketers who create it. AI is a perfect match because it increases a marketer's efficiency, thus giving more time back to the marketers to focus on more important things like brainstorming or increasing the quality of ads. Moreover, AI can help the business grow itself and its customer base to have a more personal, trustworthy, and monetized connection. With the help of AI, groups of similar people can be almost instantly created from datasets even too big for marketers to compile. These groups are then used in effective marketing strategies like segmentation, social media, etc. to increase general personalization, ROI, and the overall customer experience. In addition, AI can also cater individually creating a more personal connection between customer and business in addition to the benefits generated by grouping. AI does not stop there, however, as using generative AI, can write full scripts making things like loyalty, consideration, awareness, much more unique and human-like. Additionally, conversational AI can make conversations more human-like or conversational, thus automatically making things like chatbots or customer service much more viable and efficient with the additional help of NLP (natural language process). This is crucial as regular AI cannot be human-like, but with the help of these new and upcoming technologies, humans can be simulated. This is fundamental as Chris Melnore says, "A new survey with a panel of 2,000 adults revealed that, compared with AI, more people still prefer to use a real person when creating an account or making a purchase". The exciting part about this is that AI

has a relatively small market right now at 95.6 billion USD, and it is expected to reach 1.84758 trillion USD which is almost twentyfold (Contrive Datum Insights). Overall, throughout this paper, it is proven that a digital marketer's efficiency and effectiveness will be greatly affected by the applications of AI.

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The Role of Cell Signaling in Lung Cancer By Samuel Yin

Introduction

To begin with, cells are the smallest living units in the world that make up our bodies. Cells of the same type make up tissues, which in turn make up organs which in turn are part of an organ system, and an organism is made up of different organ systems. Our body has billions, if not trillions of cells that help it maintain stability and keep our bodies functioning. There are different types of cells in our body and they each have specific functions whether it be white blood cells helping fight off foreign intruders in our bodies or sperm cells being involved in reproduction [1]. Cells are so plentiful and unique that they require communication to get certain functions done within the body. This communication is known today as cell signaling. Cells within the body communicate by sending signals to each other to start or stop a variety of cellular processes [2].

Cell Division

Cell division refers to the process of one cell producing two or more cells. It plays several roles in living organisms including growth, repair, and reproduction. Cell division begins with the phase known as interphase and then proceeds to either mitosis or meiosis. Mitosis is for creating two identical daughter cells while meiosis creates four different gametes (reproductive cells). The stages though are still the same. A cell spends most of its life in the interphase, which contains three different parts. The G1 phase, the S phase, and the G2 phase. During the G1 phase, the cell grows and duplicates its organelles. Then during the S phase the cell begins to prepare for division by replicating its DNA, where the two copies are called sister chromatids and they remain attached together, particularly at a region called centromere. Finally, for the G2 phase, the cell completes its final preparations for mitosis. It is then during mitosis that the cell begins to divide. Just like in interphase where there are different phases, mitosis has the same concept. It consists of prophase, prometaphase, metaphase, anaphase, and telophase/cytokinesis. In prophase, the DNA condenses into chromosomes with two sister chromatids held together by protein complexes called cohesins. Then in the prometaphase, the centrosome from each pole sends its microtubules to attach to the kinetochores of the chromosomes, which are protein complexes located at the centromere. In metaphase, the chromosomes line up in the middle of the cell. In anaphase, the chromosomes are separated into chromatids and one sister chromatid (now called a daughter chromosome) is pulled to one side while the other daughter chromosome is pulled to the opposite side. Then during telophase/cytokinesis, the nuclear envelope starts developing around the chromosomes, which in turn start to decondense, while the spindle fibers begin to depolymerize and the cell proceeds to elongate and separate into two with the help of the microtubules. This creates a cleavage furrow and then the cell separates creating two identical daughter cells [3]. It is also important to note that cell division has multiple checkpoints throughout the cycle. There is a G1 checkpoint, a G2 checkpoint, and an M checkpoint. The G1 checkpoint checks to see if the DNA is damaged or not and determines whether or not the cell

can proceed to the S phase. During the G2 checkpoint DNA damage and DNA replication completion are checked to make sure that there are no problems [4]. One of the major factors that allows the cell to pass the G2 checkpoint is the adequate amount of MPF, the maturation promoting factor, which is a complex made of cyclin and cyclin-dependent kinase (CDK). The M checkpoint is another checkpoint that checks if all the sister chromatids are correctly attached to the spindle microtubules and are aligned correctly. These checkpoints all help regulate cell division and make sure that cell division goes smoothly and in proper conditions to make sure that no irregular cells are replicated [5].

Cell Signaling

Cell signaling comes with three basic steps—reception, transduction, and response. Reception happens when a signal molecule attaches to a receptor that is located either on the cell membrane, or inside the cell, depending on the type of the signaling molecule. After the signaling molecule (ligand) binds to the receptor, there is a change within the intracellular portion of the cell, which causes the transduction pathway to activate. Where a group of molecules relays a signal as if in a relay race, this then results in the activation of a cellular response [6]. In this article, we are going to be focusing on the cell division as a possible cellular response.

Cell division starts with the activation of specific genes that start the signaling process. A normal cell has these specific genes called proto-oncogenes. Usually, these genes are inactive in the body and help with cell division only when necessary, or help produce proteins that allow the cell to pass the cell cycle checkpoints [7]. However, in certain cases, the proto-oncogenes can get activated and turn into oncogenes. There are multiple ways for the proto-oncogenes to get activated into oncogenes. The first one is regarding gene mutation. In this case, when the cell duplicates its DNA, there can be errors during DNA replication resulting in a gene mutation such as altering, adding, or removing nucleotides within the DNA molecule. This can cause the proto-oncogenes to turn into oncogenes, which increase the rate of cell division. In other cases, people are born with proto-oncogenes activated all the time and so there already is a high rate of cell division. These are pathogenic variants and the change within the DNA sequence causes diseases such as cancer within the human body. Another case can occur as a result of chromosome translocations. When the cell divides, chromosomes exchange segments, which sometimes causes a gene that normally has a high level of expression to relocate next to a proto-oncogene, resulting in an elevated level of gene expression of the proto-oncogene, turning it into an oncogene. Another case can be regarding gene duplication. In some cells, the proto-oncogenes are duplicated too many times and this can cause the cell to express too much of the gene product, leading to an increased cell division rate [8]. Now, the purpose of understanding this process is that activated proto-oncogenes, which are now called oncogenes, can lead to cancer and that is why this particular group of genes has great significance in cancer development. In the body, there is a different group of genes called tumor suppressor genes. These genes help produce proteins in the cell that restrict cell division or even signal cells to

undergo apoptosis (programmed cell death) if necessary. For example, the tumor suppressor genes code for a protein called p53 which helps cell division stay under control. This gene is very useful for the body because it stops cells from over-multiplying [9]. This gene is commonly compared to the brakes on a car, which can bring the car to a stop. However, if there are mutations in tumor suppressor genes, it is as if the brakes are not working properly and the car can not be stopped. The oncogenes can code for the continued production of proteins which in turn causes continued cell division. This can ultimately result in cancer with the formation of a tumor. Thus it is important prior to the cell division process to make sure that DNA is not damaged or else, some proto-oncogenes might be activated, or some tumor suppressor proteins may be dysfunctional, leading to constant and uncontrolled cell division.

Cancer

As I have explained previously cancer is when situations go wrong that lead to uncontrolled cell division. When cells start to divide at an uncontrolled rate, these cells can form either a benign tumor or a malignant one. As these cells continue to multiply they usually start to form a mass and create a tumor, which can be seen as a lump on or inside the human body. At the cellular level, a tumor is a mass of cancer cells lumped together. In some situations, cancer cells can go through a process called metastasis [10]. This is when a few cancer cells detach from the primary tumor and move throughout the body, eventually nesting at a different location in the body and multiplying, forming secondary tumors. Cancer cells start off as normal cells but when there is alteration in the genome, including mutations, a series of events occur which lead to the cell cycle getting out of control. First, these cells become hyperplasia cells. This is the initial stage in the development of cancer as a tissue or organ starts to enlarge due to the rapid reproduction of cells. Next, it moves on towards dysplasia when the cells are actually abnormal in shape and function within the tissue or organ. This usually signals cancer, however, it does not always lead to cancer. An example would be a mole on the skin. Then from here, it is the start of cancer as abnormal cells start to rapidly multiply and cause tumor growth [11][12]. Benign tumors are more easily manageable as there are target treatments just for those tumors. Treatments include radiation therapy, surgical removal, or chemotherapy. However, in case of malignant tumors, since these cells have moved and spread throughout the body using pathways such as the bloodstream or the lymphatic system, they are more difficult to treat and control. This type of cancer is most deadly as over time without diagnosis and treatment the patient has a lower survival rate, especially if the cancer has spread all throughout the body. Treatments for malignant tumors include surgery, radiation therapy, chemotherapy, bone marrow transplant, immunotherapy, etc.[13]

Types Of Cancer

Cancer is not one disease. It comes in different forms, affecting different types of cells and organs and tissues. Following is a brief list of cancer types, organs and tissues affected, and some examples for each [14]:

- Carcinomas- Start in cells that cover external and internal organs or glands.
  - Prostate Cancer
  - Breast Cancer
  - Lung Cancer
  - Colorectal Cancer
- Sarcomas- Start in cells of supporting tissues.
  - Bone Cancer
  - Muscle Cancer
  - Liposarcoma(fat cell cancer)
  - Nerve Cancer
- Lymphomas- Starts in lymph nodes and tissues of the immune system.
  - non-Hodgkin Lymphoma
  - Hodgkin Lymphoma
- Leukemias- Start in the newly developed white blood cells in the bone marrow.
  - Blood cancer

Lung Cancer

Now getting into the lung cancer portion we will first start off with some simple statistics. According to the National Center for Health Statistics, there were 1,918,030 new cancer cases and 609,360 cancer deaths projected to occur in the United States with approximately 350 deaths per day being due to lung cancer which is still the leading cause of cancer death. It is important to note as well that over 80% of lung cancer cases in the United States have been identified as cigarette smoking causes [15]. For worldwide statistics, it is estimated 2 million diagnoses and 1.8 million deaths. The average diagnosis is 70 years old and men are twice as likely to be diagnosed with lung cancer. In the United States, American men are at the highest risk of lung cancer. [16]

Lung cancer has some specific symptoms that let people identify if they have cancer before it is too late. The main unexplained symptoms will usually be a cough, feeling of fatigue, shortness of breath, chest pain, weight loss, and appetite loss. These are the more common and significant symptoms of lung cancer that show that there is a problem within the body due to the cancer cells using up the body's natural resources. For people aged 40 and over there is a need for an urgent chest X-ray to see if they have persistent or recurrent chest infection, finger clubbing, supraclavicular lymphadenopathy, persistent cervical lymphadenopathy, chest signs consistent with lung cancer, or thrombocytosis. Early states of lung cancer usually don't show symptoms and over time when the cancer develops symptoms start to show [17]. The most common later stages of lung cancer are cough and dyspnea, but the most specific symptom is hemoptysis. Dyspnea is difficulty breathing which is a major sign of lung cancer because the lung is being taken over and so it isn't able to take in as much oxygen to be able to breathe properly. Hemoptysis is coughing up blood. These symptoms are very serious and require an

urgent meeting with a doctor because they are the major signs leading to lung cancer. However, early screening even if symptoms are not present is still recommended because they can catch the cancer before it is even allowed to multiply over time and reveal any symptoms [18].

Cell signaling plays an important role in the start and spread of lung cancer. An example can be starting from an RTK signaling cascade. Receptor tyrosine kinases' normal activity in resting cells is closely regulated but if mutations arise they may function as potent oncogenes. Ligands such as EGF, VEGF, and HGF bind to the homo and heterodimer kinase domain which causes activation and receptor transphosphorylation. The result of this creates docking sites for the adaptor proteins, Grb2 and SZos which recruit Ras and phosphatidylinositol 3-kinase which creates the formation of two major signaling pathway branches: Ras/MAPK, PI3K/AKT and PLC-PKC pathways. The PI3K-AKT signaling phosphorylates and inhibits several apoptosis-inducing genes. The activation of the RTK pathway can have effects on angiogenesis, evasion of apoptosis, and cell growth.

Another possible cell signaling pathway gone wrong is the integrin-mediated signaling cascade. Integrins are cell adhesion receptors that allow a cell to interact with the extracellular matrix in the local environment. This affinity with which integrins bind to ligands is dynamically regulated. Engagement and cross-linking integrins can possibly stimulate multiple intracellular signaling pathways including those mediated by Ras phosphoinositide 3-kinase which relates to what we talked about earlier. This cascade can promote cell growth and mitogenesis [19].

It is also important to note the crucial role of matrix metalloproteinases, MMPs, in the metastasizing process of lung cancer cells. MMPs are zinc-dependent endopeptidases that regulate the turnover of extracellular matrix components. It basically starts with the degradation of the ECM that leads to the invasion of tumor cells that allow metastasis. MMPs help in the degradation of the ECM, but also expose some binding sites to other receptors and release biologically active molecules. Cancer cells form specialized F-actin-based protrusions of the plasma membrane called invadopodia which helps to clear the path by the ECM degradation. Invadopodia are found in cancer cells with high metastatic potential. Trans-membrane-type 1 MMP(MT1-MMP), MMP-14 accumulates in the invadopodia and facilitates the degradation of the ECM. MT4-MMP regulates invadopodia formation and cell movement and exchange cell migration and invasion. MT1-MMP is also involved in the activation of pro-MMP-2, which can possibly lead to tumor growth [20].

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Common Electromagnetic Motor Configurations and Changes In Those Configurations Exploiting Permanent Magnet By Gibson D. Hochhauser

Abstract

Current electromagnetic motors are vital to our modern era. These motors use electricity to charge electromagnets which then interact with permanent magnets to create rotary or linear motion. Electromagnetic motors are extremely common and are utilized for a plethora of applications. Ranging from industrial machines to child toys, electromagnetic motors are heavily exploited for their immense versatility. The commonplace electromagnetic motors require energy to operate. In the current environment, energy is in short supply with energy supply issues around the globe and electromagnetic motors being one of the major draws of energy due to the fact that these motor types are in high demand and in constant use. This paper explores possible solutions and aids that can be added on, or used with current electromagnetic motor platforms, to increase efficiency and lower energy draw. In this paper, the three most common electromagnetic motors are examined and defined: Alternating Current (AC) motor, Direct Current (DC) motor, and Linear motor. Once these technologies are clearly defined, this paper describes and deconstructs these motors with permanent magnet configurations. These permanent magnet configurations are then discussed in their viability to be utilized in the world. This paper also discusses the configurations in relation to each other and in relation to their base configuration counterparts that do not exploit permanent magnets. This paper evaluates these configurations on a broader scale, including their problems and benefits.

Electromagnetic Principales

Alternating Current, Direct Current, and Linear Motors are able to operate due to several electromagnetic principles. The most important of which are Faraday's law of electromagnetic induction and Coulomb's law. To understand, those laws of electromagnetics first electromagnetic fields must be defined as well as how these fields are created and manipulated to generate force/motion. Electrical fields are produced by electrical currents flowing arcing from positive charges toward corresponding negative charges.Magnetic fields originate from this same process, however, with a closed loop current. Coulomb's Law then quantifies the force of these charges in an electrical field. Coulomb's Law states that "attraction or repulsion varies inversely with the square of the distance between the charges." For the purposes of this paper, Coulomb's Law is what tells us that the closer magnets are to each other, the greater their repel or attraction forces are onto another. Faraday's First Law of electromagnetic induction is also crucial for the processes of these electromagnetic motors. Faraday's First Law states that "Whenever a conductor is placed in a varying magnetic field, an electromotive force is induced. If the conductor circuit is closed, a current is induced, which is called induced current." For the purposes of this paper, this law is telling us when a non-constant magnetic field passes through an area it will produce energy - voltage or power and energy. The key concepts and laws are

crucial in how these and all other electromagnetic motors operate and a small understanding of them is necessary for understanding the operation of these motors. (*18.3*, 2016; *Magnetism*, n.d.)

Common Electromagnetic motors: AC, DC, and Linear–Alternating Current Motor

Within the context of this paper common AC, DC, and linear motors will be what is addressed and used as the standard and base platforms. The AC motor configuration (Figure 1) consists of a stator and a rotor. The stator and stator core in its most generic form consists of a hollow core with stator windings - constantly spaced slots of insulated wire coils. When in operation, the windings are connected to a power source which turns each of the coils along with the core itself into an electromagnet. A squirrel cage rotor configuration is the most common rotor configuration in AC motors and will be what is defined and used as the AC motor rotor configuration for all purposes in this evaluation. The squirrel cage rotor configuration consists of a cylindrical central component fixed to two permanent shafts on either side. The central configuration is created by layering thin steel laminations on top of one another while leaving slots between stackings. These slots are filled with conductor bars that are diecast into the central configuration. Then, once the conductor bars are cast into the central piece of the rotor, they are connected - electrically and mechanically - to the end rings. In its entirety, the stator and squirrel cage rotor together form the common AC motor design and the norm for AC motor configurations. (*AC Motor - Definition, Working, AC Motor Parts, Applications*, n.d.; *The Basics of AC Motors and Their Applications - Power Electronic Tips*, n.d.)

Figure 1: Diagram of AC Motor ((*AC Motor - Definition, Working, AC Motor Parts, Applications*, n.d.; *The Basics of AC Motors and Their Applications - Power Electronic Tips*, n.d.))

Direct Current Motor

The DC motor (Figure 2) consists of a more complex rotor and frame. The rotor of a DC motor consists of insulated magnetic laminations that are perpendicular from the rotors center and completely wrap the rotors circumference: armature windings. In the center of the rotor, insulated stacks of carbon wrap the axis of the rotor which serve to provide electrical current to the farther out interior armature winding. The DC motor frame, where the rotor sits, consists of

field coils and bushings. The field coils are stationary electromagnets that sit adjacent to one another on opposing sides of the rotor. There is key space between the rotor and the field coils allowing for magnetic fields to properly form. Importantly, the field coils have slopes from end to end to match and curve with the rotor, providing an even distance from field coil to rotor. The bushings conduct electricity from an outside source to the interior rotating electromagnetic commutators. Once electricity is provided, the copper windings become electromagnets and as current travels through the positive north field coil then through the air gaps and rotor to the negative south field coil, a magnetic field is created in the air between the rotor and field coils. This process converts electric and magnetic fields and their interaction into rotary motion.(*DC Motor: What Is It? How Does It Work? Types, Uses*, n.d.; *DC Motor - Definition, Working, Types, and FAQs*, n.d.; MACFOS, 2023)

Figure 2: Diagram of DC Motor(*DC Motor: What Is It? How Does It Work? Types, Uses*, n.d.; *DC Motor - Definition, Working, Types, and FAQs*, n.d.; MACFOS, 2023)

Linear Induction Motor

The linear induction motor (Figure 3) consists of two main parts: primary and secondary. The primary is created from the stacking of steel lamination on top of each other and three phased copper coils or windings. The secondary, or reaction plate, is a plate that sits slightly above the primary plate. The secondary is equal length of the primary plate and has a copper, steel or aluminum backing. Then most often a ball bearing system will ensure there is a constant air gap between the primary and the plate. The primary, when energized, will magnetize the secondary, creating a field of currents which interact back to the primary itself causing forward linear motion. The linear induction motor can also have a second primary above the reaction plate to allow for greater movement possibilities. This is what forms and makes up the original linear induction motor and what will be used when a linear induction motor is mentioned any

further in this paper. (*Linear Induction Motor: How It Works - H2W Technologies*, n.d.; *Linear Induction Motor*, 2020; *The Advantages of High Performance Linear Motors*, 2022)

Figure 3: Diagram of Linear Induction Motor (*Linear Induction Motor: How It Works - H2W Technologies*, n.d.; *Linear Induction Motor*, 2020; *The Advantages of High Performance Linear Motors*, 2022)

Differing Configurations–Permanent Magnet Alternating Current

This concept has seen utilization in AC motor configuration. In the AC motor permanent magnet configuration instead of having the squirrel cage lined with conductor bars it is lined with rare earth metals that operate as permanent magnets (Figure 4). This is a permanent magnet alternating current (PMAC) motor, or synchronous AC motor, rather than the normal AC motor which is an electrically commutated motor. In this motor form, rotation is created using the magnetic field that is created from the permanent magnets rather than a magnetic field that is created by energizing the copper wire. This configuration also utilizes the power or permanent magnets to help conserve energy with the AC motor. (Dillard, 2014; *The Basics of AC Motors and Their Applications - Power Electronic Tips*, n.d.)

Figure 4: Diagram of How PMAC Motor Works (Dillard, 2014; *The Basics of AC Motors and Their Applications - Power Electronic Tips*, n.d.)

Permanent Magnet Direct Current

      A variant form of a DC motor configuration is very interesting in operation as it addresses issues with DC motors. However, it has drawbacks as well. This configuration as shown in Figure 4 is labeled permanent magnet direct current (PMDC) motors which stands for permanent magnet DC motor (Figure 5). In a PMDC motor the stator is a permanent magnet creating the magnetic field in which the DC motor can operate. This design has been utilized for applications that require very little precision, like a childrens toy where it is used. This configuration of DC motor - PMDC - allows for energy draw to be reduced significantly as it requires less input. DC motors are effective and efficient; they still do draw energy and permanent magnets can be exploited to lower their energy draw. (*Permanent Magnet DC Motor (PMDC Motor) – How Do They Work?*, 2020)

Figure 5: Diagram of PMDC Motor (*Permanent Magnet DC Motor (PMDC Motor) – How Do They Work?*, 2020)

Permanent Magnet Linear Synchronous Motors

      With linear induction motors, permanent magnets have found utilization in a configuration labeled permanent magnet linear synchronous motors (PMLSM). This configuration differs from the original configuration as the secondary or reaction plate consists of permanent magnets which alters field direction from one another. The purpose of this secondary plate is that the secondary is now a permanent magnet and has a magnetic field, not energized by the primary. The PMLSM motor is different from the other permanent magnet configurations - PMDC and PMAC - as this magnetic configuration does not increase energy efficiency. This is due to the fact that the secondary plate is not replacing an energized part therefore not taking down the energy input needed for operation. Instead the secondary plate or permanent magnet will help the motor with speed, power, and precision. (*Linear Induction Motor: How It Works - H2W Technologies*, n.d.)

Table 1: Summary table of application for different types of motors:

Metric	AC	PMAC	DC	PMDC	LIM	PMLSM
Common Applications	appliances, compressors, drive systems, conveyor systems	Many Automotive applications	Sewing machine, power tools Elevators Cranes	Windshield wiper starter motor Toys Wheelchairs	Automatic doors Propulsion (Trains) Conveyor belt Pumping of liquid materials	Aircraft carrier launch system (USS Gerald R. Ford aircraft carrier) amusement park rides

Conclusion

In all of these configurations there are applications that are more or less suited for (Table 1) for a permanent magnet utility and permanent magnet configuration (PMAC,PMDC, and PMLSM). Permanent magnets may in effect increase efficiency, speed or control, vital for certain applications. Also with permanent magnets supply may have strong negative effects, which questions their utility in the market. looking purely at how these configuration variations affect energy draw and not at the process it requires to make them the results are mostly beneficial. This is because the permanent magnet direct current motor (PMDC) and the permanent magnet alternating current motor (PMAC) switch out a piece in the motor that is an electromagnet and therefore energized and drawing energy - either the stator or rotor - to a piece that is permanent and does not draw energy. Then permanent magnet linear synchronous motors (PMLSM) in this configuration that utilizes permanent magnets, the magnets do not replace an electromagnet and it just improves the reaction plate. With this the PMLSM are not a beneficially motor over the normal configuration unlike the PMAC and the PMDC.

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Mental Health Equity Post-Covid in Youth By Aditi Avinash and Cindy Zhang

Abstract

As mental health issues are more widely discussed, their prevalence within adolescents is becoming more apparent. Early intervention and treatment are vital because many mental health conditions take root from an early age. These are the years when children are learning where and how they might fit into the wider world, and need access to resources to support them. With the development of world issues such as Covid-19, these struggles with mental health have only soared. With a concentration on youth, mental health has taken a toll on the health of local communities. This paper aims to define what mental health problems exist pre-pandemic and post-pandemic among adolescent teens.

Mental Health and Heightened Stressors

Mental Health is our ability to solve problems, maintain social connections, and our overall mental well-being. Mental illnesses are factors that affect someone's mental health, specifically, how people feel and interact with each other. Mental illnesses include anxiety, mood, impulse and control, addiction, and personality disorders (Centers for Disease Control and Prevention, 2023). Often, these mental illnesses have catastrophic effects. Suicide is the leading cause of death among high school students in Colorado. 24.3% of High School students stopped doing their usual activities because they felt sad or hopeless (Colorado Health Institute 2015). One of the biggest problems includes access to mental health resources and targeting problems at the start. For example, "It is becoming more difficult to get a mental health appointment. In 2015, 34.0 percent of Coloradans who didn't get needed care said they had trouble getting an appointment, up from 30.5 percent in 2013 (Colorado Health Institute 2015)" A few years prior in 2019, before the intensity of the COVID-19 pandemic began, a student at Rock Canyon conducted an extensive survey analyzing mental health among students in Rock Canyon. The results of the study indicated that of 286 RCHS students. "The three top stressors students identified included academics (68.5%), college-related pressures (51.7%), and money (29.4%). Students who reported high levels of stress also reported symptoms of anxiety (62.1%), insomnia (58.2%), and bad mood swings (52.5%) occurring multiple times a week" (Titensor, 2020). In our own community, there was a high level of stress, anxiety, and other mental disorders before the pandemic. The goal of this paper is to better understand how these stressors and the mental health of high school students may have changed after the pandemic. The information collected from the literature review can not only be used to provide RCHS staff with data about stressors among students but also within the district and other schools within the state when evaluating equity and mental health among high school students.

Social Media and Mental Health

Social media has greatly impacted mental health and how it is talked about. In adolescents, the young mind is very malleable, and social media is a large region behind its shift.

There was a heightened use of social media during the pandemic, and that still carries on. Displaying this, 37.1% of U.S. high school students reported poor mental health during the COVID-19 pandemic (Anderson 2021). In the research conducted through the previous Rock Canyon survey, participants noted their struggles with social media feeling all-consuming. This data was taken pre-pandemic, and if trends follow, the data post-pandemic should mark an increase in this feeling. However, while historically social media has been deemed a negative influence on mental health, it can actually add unforeseen benefits. Some forms of social media may positively impact mental health, such as memes. Humorous memes play a role in coping mechanisms and cognitive reappraisal (Rahman 2021). The humor of the meme must be intertwined with the ability to make individuals feel both included and understood in order to have a positive benefit. Memes help users voice their opinions and feel heard.

Communication on Mental Health

There is no doubt that the pandemic has created a vast divide in how we interact with others. While some students indicate that they feel more comfortable interacting with others online, most students indicate that the pandemic has made them suffer severely from social restrictions (Holm-Hadulla 2021). Another issue greatly affecting mental health is the way that it is discussed. It is a taboo topic and thus changes the conversation and the conversation rate. This has led to the idea that mental health has no roots, and appears out of seemingly nothing. "Drug and alcohol abuse in the home, neglect, physical and verbal abuse, sexual abuse, poverty, job loss ... These are just some of the precipitating factors, which combine to lead to homelessness, as well as the mental health crises that often accompany it. In almost all cases, poor mental health doesn't "just happen" (Toronto Star Digital 2023). The lack of conversation around the topics that create these mental health issues has led the youth to feel unseen and therefore alone. "How mental health issues are diagnosed, managed and treated, and how the community responds to mental health conditions, are highly complex concerns" (Age 2019). Increasing the conversation around these difficult subjects will increase feelings of support, and decrease the negative emotions that students inhabit due to isolation.

Conclusion

The effect of COVID-19 on the Mental Health of students is an extremely nuanced issue that is still being studied by social scientists today. The pandemic effectively changed social communication. The heavy reliance on technology and social media for communication impacted the mental health of students. Preliminary research has shown that the heavy reliance on technology had mainly negative effects on students by creating a device that teenagers are quick to become addicted to, however, social media may encourage creative and individualist expression with platforms to show humor and create art in a more accessible manner during a national lockdown. This heavy reliance and extended relationship between social media and students over the several months of lockdown has made students more vulnerable to the threats and addictive nature of social media. More research is needed to determine the lasting effects of

the pandemic on the mental health of students. For now, increasing conversation about the isolation and addiction to technology students felt during the pandemic is vital to continue learning more about the effects of the pandemic, and creating resources to help students navigate the post-pandemic world.

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How Was the Universe Formed and What Played a Part in Its Creation? By Ryan Verrette

Abstract

Throughout history, cosmologists have constructed theories that are, essentially, the building blocks of the universe. Over this paper, I will describe the theory of inflation and the problems that were solved by its creation. I will also dive into the cosmic microwave background (CMB) and its history, as well as what it tells us about the formation of the early universe and how we know it today. Using python, I also generated and examined simulated data to tell us more about the distribution of the universe and factors that affect its analysis.

Introduction

In the world of cosmology, the great majority of cosmologists support the theory of the Big Bang – the idea that the universe underwent exponentially large expansion within a split second. Despite the research studies conducted in recent years surrounding the Big Bang, cosmologists are still searching for ways to prove the theory. Such proofs have been analyzed through observations created around the cosmic microwave background – background radiation leftover from the Big Bang – that didn't take shape until the last couple of decades. Through the development of new technologies such as the COBE satellite[1] to analyze this background radiation, cosmologists are a step closer to proving the Big Bang theory and now have a deep understanding of how the universe was formed and what initial conditions impacted its creation, such as the theory of inflation.

Inflation

In modern cosmology, three main problems have persisted across decades in the search for theorizing the creation of the universe: the flatness problem, the monopole problem, and the horizon problem. However, the theory of inflation is one that aims to solve these three governing problems. Coined by cosmologist Alan Guth in 1981[2] , inflation is defined as a period of time between 10^-33 and 10^-32 seconds after the Big Bang singularity, or the initial "creation" of the universe where the universe underwent very rapid exponential expansion. This expansion saw the length of the universe expanding at a linear factor of at least 10^26, with the volume – the amount of space in the universe – expanding at a factor of at least 10^78. This inflationary epoch, as it is described, is a theory that is becoming increasingly popular among cosmologists due to its properties that can theoretically resolve these three governing problems.

The Flatness Problem

The flatness problem, also known as one of Dicke's coincidences, was proposed by American astronomer and physicist Robert Dicke in 1969. The problem surrounds the understanding of the Friedmann equations, a set of equations in cosmology by cosmologist Alexander Friedmann that relates the scale factor of expansion of the universe, its density, and its curvature[3].

According to the Friedmann equations, the universe is theorized to be almost perfectly flat in the present day, but this would propose that the universe would have to be even flatter in the past due to the idea of expansion. This flatness has to do with the density of matter in the universe and its relation to its "critical density". Critical density describes the average density of 43matter required for the universe to be at its limit to eventually prevent any further expansion, and when at this critical density the universe is said to be flat[4]. The Friedmann equations follow the formula $\rho_c = \frac{3H^2}{8\pi G}$, where ρ_c is the critical density required for a flat universe, H is the Hubble Constant, and G is the gravitational constant[5]. Since the values of H and G are constants, the value of ρ_c is derived to be equal to approximately 10^-26 km m^-3[6]. When incorporating the actual density of the universe into this equation, the equation then follows that $\frac{\rho}{\rho_c} = \frac{3H^2}{8\pi G}$, where $\frac{\rho}{\rho_c}$ – the ratio of the actual density over the critical density – can be represented by the greek letter Ω[5].

Friedmann theorized that if $\Omega < 1$, then the universe would be "open" and infinitely expand, following a negative curvature (like the shape of a saddle). If $\Omega > 1$, Friedmann theorized that the universe would be "closed" and eventually collapse in on itself, following positive curvature (like the shape of a sphere). In reality, the value of Ω is almost exactly the value of 1, meaning that the universe is almost exactly flat[7]. The flatness problem, however, arises when comparing the current value of Ω to the value of Ω when the universe was initially expanding.

At the beginning of the universe's creation immediately after the Big Bang, it can be theorized that the shape of the universe could have been any shape, but the rapid exponential expansion from the inflationary period flattened it out suddenly, thus solving the flatness problem. The period of inflation made this Ω value so close to 1 that the universe is almost perfectly flat, despite it being inferred to be a different value from Ω in the past when it was initially formed.

The Horizon Problem

The second issue that arises with the Big Bang model is the horizon problem. This discrepancy centers around the temperature of the universe when involving the Cosmic Microwave Background (CMB). The CMB can be described as the background microwave radiation left over from the Big Bang, and this radiation is a consistent 2.7 Kelvin throughout, achieving an equilibrium[8]. However, according to the Big Bang model, since some regions in the universe today are so far apart from each other, CMB photons can't make contact with each other. This means that this temperature equilibrium shouldn't theoretically be achieved as it is in our modern model of the universe; the distance between these regions in lightyears is so great that it exceeds the actual age of the universe.

When viewing the CMB, the distance between the farthest objects in the universe is around 46 billion light years apart, but the age of the universe is only around 13.8 billion years old; for these two objects in space to reach an equilibrium with each other would be impossible[9]. Essentially, the time it takes for the CMB to transfer from one side of the universe to another is impossible as light cannot move faster, meaning that both regions couldn't have made contact, and thus couldn't reach the same equilibrium temperature of 2.7 Kelvin.

According to the inflationary model, the universe was initially extremely small and then it suddenly expanded during the inflationary epoch period. The regions of the universe that seem ever so distant apart today would have been in contact with each other in the early universe, and during inflation these regions grew exponentially far from each other; solving the suspicion that this equilibrium would have never been achieved.

The Monopole Problem

The final issue associated with the Big Bang model was the monopole problem that is based upon the Grand Unified Theory. The Grand Unified Theory (GUT) is a model that describes the four fundamental forces: strong, weak, electromagnetic, and gravity forces. Three of these four fundamental forces – strong, weak, and electromagnetic – can be categorized as one unifying theoretical framework, known as the GUT scale[10]. This is because during the early existence of the universe when it was small and compact, it was extremely hot and dense, causing all three of these forces to be detected as one unifying force. As time went on and the universe cooled down, this drastic difference in temperature caused the GUT forces to divide throughout the universe in the form of magnetic monopoles. Magnetic monopoles are hypothetical particles with a magnetic charge with only one isolated magnetic pole, causing them to have different magnetic forces than other traditional magnetic particles. However, these monopoles have never been directly observed due to their small density, leading to the rise of the monopole problem[11].

The issue of detecting these monopoles can be solved with the theory of inflation, ultimately describing how the inflationary period made these monopoles diluted. As inflation occurred and the universe suddenly expanded, this expansion decreased the presence of magnetic monopoles in the universe, making them increasingly harder to observe. The density of them in the universe is so small because of inflation, making it not surprising that they are difficult to see.

The Cosmic Microwave Background

The Cosmic Microwave Background (CMB) is the background microwave radiation in the universe. After the Big Bang, the universe underwent massive inflation, expansion, and cooling. In essence, the CMB is able to allow astronomers and cosmologists alike to gather and analyze data on the primordial universe, or specifically around 13.7 billion years ago. At the time of the formation of the universe with the Big Bang, the temperature release was initially drastic, being estimated at around 1000 trillion degrees Celsius right after its occurrence. However, after

around 380,000 years after the Big Bang, the universe had cooled to around 3000 Kelvin, or 2700 degrees Celsius[12]. According to cosmologists, This recombination occurred because the universe had cooled to a point where electrons were able to combine with protons to form hydrogen atoms; the temperature was too low for them to separate again. Paired with a phenomena called decoupling – a period where different particles fall out of equilibrium with each other – radiation was released into the universe, and such radiation is what we experience today with the radiation of the CMB[13]. Although the CMB's formation was such a long time ago, its radiation still floats through space, but instead at a temperature of around 2.7 Kelvin, or -270 degrees Celsius. This temperature is so low that it can't be detected by the naked eye, but advancements in cosmology as of recent have made this detection possible.

Discovered in June 1963 by Robert Wilson and Arno Penzias in Holmdel, New Jersey, the CMB was first detected as a "noise", like static, that interrupted their observations at their previous organization Bells Telephone Laboratories. After initial confusion as to what could have caused the interruption, Wilson and Penzias looked into it further. Around the same time of their discovery of the "noise", other notable physicist Robert Dicke of Princeton University theorized that if the Big Bang theory was the reason for the creation of the universe, then a background radiation of around 3 degrees Kelvin must exist in the universe[14].

Wilson and Penzias took this information for what they could and began to look for any evidence that could support Dicke's theory. After later analyzing in their laboratory, Wilson and Penzias consolidated their findings with Dicke to establish that there was a low-background radiation in the universe present at around 3 degrees Kelvin, just as Dicke theorized. Shortly after discovering this enigma, the physicists officially published their findings – that there was indeed a radiation signal present in space that they named the cosmic microwave background. They declared that the CMB would be able to provide proof of the preexisting but vaguely supported Big Bang Theory, a theory that describes how the universe was created with an extremely outwards explosion of energy that expanded and grew from a single point.

With this newly found information, they were then able to send out more research expeditions and projects to further explore the CMB to hopefully gather information about it and its importance to the universe. Of which was the CMB's impact on proving the theory of inflation. Scientists were able to hypothesize that slight fluctuations were visible in the radiation of the CMB, and that these fluctuations were created as a result of the inflationary period. Essentially, if there were fluctuations in the CMB, then something must have caused these fluctuations – the CMB.

COBE Discoveries

A number of these research expeditions were conducted by NASA's Cosmic Microwave Background Explorer (COBE) satellite, of which Wilson, Penzias, and Dicke collaborated with in order to gather further evidence on the CMB. COBE was initially launched on November 18, 1989 and, according to NASA: "carried three instruments, a Far Infrared Absolute Spectrophotometer (FIRAS) to compare the spectrum of the cosmic microwave background

radiation with a precise blackbody, a Differential Microwave Radiometer (DMR) to map the cosmic radiation precisely, and a Diffuse Infrared Background Experiment (DIRBE) to search for the cosmic infrared background radiation"[1]. These instruments, however, were terminated in December 23, 1993 and the operation of the COBE satellite was replaced and continued by the NASA WMAP, or the Wilkinson Microwave Anisotropy Probe, mission from 2001-2010 that also worked to conduct information on the CMB[15]. The WMAP was also later replaced by the European Space Agency's Planck satellite that also worked to achieve gathering information on the CMB. Because of the efforts of satellites such as the COBE, WMAP, and Planck, astronomers and cosmologists have gained extensive knowledge on the start of the universe and the factors that contributed to its formation. During the time that the COBE satellite was in commission, it had made two key discoveries that supported the theory of the Big Bang and the CMB.

Black-body Spectrum

First, it declared that the CMB had a near-perfect blackbody spectrum, or a spectrum with frequencies measured from thermal electromagnetic radiation within a surrounding body in thermodynamic equilibrium that is emitted by a black body, or an idealized physical body that absorbs all incident electromagnetic radiation. Essentially, this is radiation at thermal equilibrium that can be used to measure the relationship between an object's temperature and the wavelength of the electromagnetic radiation that it emits. When displayed on a spectrum, this blackbody radiation is continuous, meaning that it gives off some light at all wavelengths, and also peaks at a specific wavelength. In terms of the CMB, this means that its blackbody spectrum is nearly perfect and that it would absorb almost all the radiation that falls on it; it would not reflect or transmit any radiation[16].

Temperature Anisotropies

Second, the COBE declared that the CMB has faint anisotropies, or small fluctuations in temperature from the blackbody radiation left over from the Big Bang. As measured by the COBE, these temperature fluctuations were also around 2.725 Kelvin, the approximate temperature of the CMB. Astronomers were able to analyze these anisotropic fluctuations in order to reveal components of the universe that initially remained hidden in the past. They concluded that in the cooler areas of the anisotropies there were presence of galaxy clusters, and in the warmer areas there were no clusters present[17]. These anisotropies can also be classified into two categories based on the circumstances on which they occurred: primary anisotropies and secondary anisotropies.

Primary anisotropies can be described as fluctuations that have occurred before or during the recombination event. On the other hand, secondary anisotropies are fluctuations that have occurred after the recombination period where photons and other interactions like background radiation, hot gasses, or gravitational potentials have influenced the fluctuations[18]. Ultimately, astronomers were able to use these temperature fluctuations of the CMB to determine the

approximate location of preexisting galaxy clusters, leading to greater understanding of how the universe is arranged.

Polarization Anisotropies

Polarization is a term that surrounds the properties of light and how it is oriented. When CMB photons in the early stages of the universe were reflected off each other and other particles perpendicular to the direction of propagation these photons and light waves became polarized[19]. The CMB polarizes in two different spectrums called E-modes and B-modes. These polar spectrums are able to support the theory of inflation when further analyzed. E-modes – an analogy for electric field (E-field) – are waves that were polarized at 90 degrees to propagation, while B-modes – an analogy for magnetic field (B-field) were polarized at 45 degrees to propagation.

In particular, cosmologists have used B-modes specifically in order to provide evidence for the theory of inflation. B-modes can be created by two main mechanisms: the gravitational lensing of E-modes and the generation of gravitational waves arising from inflation[20]. As a result, cosmologists have predicted there to be a presence of two types of B-modes, those generated during the inflationary period, and those generated by gravitational lensing later in the universe's existence. The theory of inflation, being initially difficult to approve its existence, was able to be supported with the detection of B-modes. Although hard to detect and have never been observed, cosmologists concluded that inflation would have released massive gravitational waves that polarized waves from the CMB and created B-modes. Hence, if B-modes are observed, then the theory of inflation can be confirmed.

Power Spectrum

These anisotropies that cosmologists discovered can be displayed on a series of graphs after applying different equations. Data can be plotted on a graph with with the x-axis showing different angular scales from a viewer – in this case the Planck satellite – going from 90 to 0 degrees, and the y-axis showing the temperature fluctuations of the anisotropies, or essentially the power signal of the CMB, thus capturing the spatial wavelength of fluctuations in temperature of the CMB across the universe. Also plotted on the x-axis are the multiple moment values, ℓ, that are inversely proportion values to the angular scale. To find the multipole moment, one is able to use the equation $\ell = 180/\theta$. The red plot points on the spectrum in Figure 1 capture these fluctuations, showing a range of fluctuations at a particular angular scale/multipole moment. A green line of best fit can also be then generated through it, capturing the most widely accepted portrayal of the estimation of these fluctuations. Essentially, one can see the relative strength of temperature fluctuations at different angular measurements in the universe.

As seen in the power spectrum, the most fluctuations occur in the one degree to 0.07 degree range. In the 90 degree to one degree range, there are less fluctuations in temperature, as there is only a measured around 1000 micro-Kelvin. The temperatures then "peak" at the one degree value, reaching a temperature with a high of around 5500-5600 micro-Kelvin. After this

one degree measurement, the temperature then steeply decreases and fluctuates more leading up to the 0.07 degree value, with two more major peaks happening between these values.

By analyzing the trends in the power spectrum, one can make out key themes in the universe's history. It is theorized that the first "peak" in the power spectrum was caused by sound waves in the early universe compressing and creating great amounts of temperature. This compression was caused by the period of inflation, as during its occurrence the universe expanded and all matter was greatly affected[21]. This is also the period of time where photons were polarized into E-modes and these anisotropies were created. This peak also is also able to illustrate a general idea of the geometry of the universe. After analyzing WMAP data, scientists were able to determine that at this peak at multiple moment ℓ=100, the critical density of the universe is remarkably close to zero, meaning that it is flat; this too supports the flatness problem mentioned earlier. After this large first peak, there are smaller corresponding peaks along the power spectrum that capture periods in the universe where soundwaves had compressed similarly, but not to the same extreme. The CMB power spectrum is able to give a holistic idea of how the temperature of the universe is structured and distributed in space.

Figure 1: CMB Temperature Power Spectrum[22]

Similar to temperature anisotropies, a power spectra can also be generated for E-mode and B-mode anisotropies, as featured in Figure 2. The E-modes power spectra is constructed similarly to the temperature power spectra in that the x-axis and y-axis are representative of the same measurements and units. The x-axis follows with the monopole moment, and the y-axis shows E-mode fluctuations.

The spectrum is closely related to the temperature power spectra, as where in the regions where there are dips in the E-mode spectra, there is a "peak" in temperature. Compared to the temperature power spectra, the peaks on this spectra correlate to the dips in the E-mode power spectra. Both of the power spectrums show structure formation and are complementary to each other; where there are trends in fluctuations in one, there are correlating fluctuations in the other. Also visualized on the B-modes power spectra on the same graph, the fluctuations appear in different arrangements than E-modes. In the universe, B-modes are formed from inflationary waves, and the fluctuations created by these waves in B-modes are also represented.

Furthermore, there are different "r" values represented throughout the spectrum. This "r" value is represented as the tensor to scalar ratio, and on the spectrum finds itself at a value of r=0.3 and r=0.01, with them representing the B-mode power spectrums at two different tensor to scalar ratio values. By analyzing these different "r" values, astronomers get a general idea of how to scale inflation as well as different amplitudes of B-mode power signals.

Figure 2: CMB E-mode and B-mode Anisotropy Power Spectrum[23]

Data Analysis

Using code and data compiled from an online github resource centered around CMB analysis, I used a theoretical CMB temperature power spectrum to generate a map of the CMB[24]. I first used simulated data to generate a temperature anisotropy heat map in python that highlights fluctuation in temperature throughout the CMB. I then used a similar methodology that shows a point source map of the CMB to realize noise from the galaxy. I then generated full sky maps that emphasize noise fluctuations from the instrument that impact raw measurements of the CMB. It is crucial to simulate CMB measurements with noise as a way to enhance analysis techniques for removing systematic noise such as point sources from the galaxy and detector

noise from the telescope (like the Atacama Cosmology Telescope), and atmospheric noise that skews our measurements of the CMB.

Heat Map

For instance using this data, an angular power spectra can be generated that shows temperature anisotropies in the CMB, as shown in Figure 3. Similar to the temperature power spectra mentioned earlier, this spectra shows temperature fluctuations in the CMB as measured by the telescopes but displays them on a heat map. The heat map presents the common multipole moment ℓ at varying values across the space in the universe and displays the temperature as it appears at such differing multipoles. As portrayed in the map, the temperature fluctuates between -400 micro-Kelvin and 400 micro-Kelvin, but shows an almost equal balance between temperatures greater than 0 or less than 0. This represents the variations that the CMB has when analyzing different angles of it through instruments; it is not uniform throughout, but shows fluctuations between large temperature values.

Figure 3: CMB Temperature Anisotropy Heat Map

Point Source Map

Using a similar methodology as the heat source map generated from simulated CMB values taken, a point source map can also be created. Point sources in the CMB essentially come from astrophysical objects in the universe such as Active Galactic Nuclei (AGN) or Dust Star Forming Galaxies (DSFGs). When put on a map, DSFGs grow brighter due to their higher frequencies, while AGNs are the opposite. Using both a poisson and exponential distribution for

the pre-registered data values, a sky map can be generated that presents the point sources of such formations in the universe at different angles, as shown in Figure 4. Although very hard to see initially, the "specks" in the map represent clusters with varying temperatures and locations at different angles.

Figure 3: CMB Point Source Map

The Sunyaev-Zel'dovich effect, or SZ effect for short, is a distortion that occurs when CMB photons collide with high-energy cluster electrons and receive an energy boost, allowing easier detection of disturbances in density in the sky. Compiling the SZ effect with pre-registered data from the telescopes from before, a new point source map can then be generated. Points on the map, similar to the other point source map, capture clusters of formations and galaxies. The effect makes it easier to view these galaxies than before, as well as trace their masses. The SZ map follows in Figure 5.

Figure 5: CMB Sunyaev-Zel'dovich Effect Point Source Map

Full Sky Map

       Compiling the CMB anisotropy map, the point source map, and the SZ map, a new map can be generated that captures the full sky at different angles and temperatures using a gaussian distribution.. Similar to the original CMB map with simulated data, the map is fairly balanced and uniform, seen in Figure 6.

Figure 6: CMB Full Sky Map

       This map, however, is one that doesn't account for noise that would naturally occur in an astronomical instrument. This noise is composed of white noise that is created from a typical gaussian distribution, atmospheric noise that occurs at large angular scales, and 1/f noise – noise that is created from a signal such that the energy of the map is inversely proportional to the frequency of the signal. Depending on how much noise is present in detectors in ground instruments, the heat map may appear to be less or more cohesive. For instance when there is no 1/f noise but there is both white noise and atmospheric noise present, the heat map will be generated as follows in Figure 7. This map is much more distorted and difficult to analyze than the original full sky map with no noise.

Figure 7: CMB Full Sky Map with White Noise and Atmospheric Noise

On the other hand, you can "whiten" or reduce this noise by using a high pass filter or square filter. By using python, you can manipulate the data to portray the effects that the filter has on the sky map. For instance, when setting a value N that is set to "mask" the sky is lower, then there is less noise, and vice versa for when the value is larger. As seen in Figure 8 and 9, a lower N value would result in a clearer image, but a higher N value would result in a more blurry image.

Figure 8: CMB Full Sky Map with Low N   Figure 9: CMB Full Sky Map with High N

This data representation is extremely helpful to visualize how small obstacles – like noise in instruments – in the data collection process can make a huge impact on the overall readings and analyzing of data.

Conclusion

The theories surrounding the creation of the universe are ideas that are still being proven and disproven today. The Big Bang theory and the theory of inflation are two governing ideas that cosmologists have developed in recent decades to prove the formation of the universe as we know it. Different components analyzed from the CMB have played a part in our understanding, such as anisotropies, polarization, and E-modes and B-modes. Upon running further analysis on data gathered from telescopes that analyzed the CMB, one can see how each component of the CMB plays a part in presenting information about the formation of our universe and how it came to be. With the use of data collected from the cosmic microwave background, the Big bang theory and inflation have become ever so close to becoming the basis for our understanding.

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How Machine Learning Affects Research in Brain Diseases By Faheem Hossain

Abstract

It is estimated that about one billion people globally suffer from neurological disorders . These disorders can be neuromuscular or neurodegenerative. Common neurological disorders can leave individuals greatly disabled with a significantly diminished quality of life. The nervous system is a challenging area in medical science to study due to the complexities of the brain and the intricate relations between bodily components. Additionally, the human brain is markedly personalized. While traditional methods of studying the brain and nervous system have demonstrated notable progress, they are limited in understanding the intricacies of our behavior. Machine learning models have been rapidly advancing since their inception, demonstrating a heightened ability to problem-solve and recognize patterns in vast amounts of data by simulating human intelligence and adaptability to new information. The advancements of machine learning models could help the field of neurology identify and predict neurological disorders early, classify these disorders accurately, and develop treatments or cures to pre-existing neurological disorders. This literature review compiles research of machine learning in neurology to illustrate how machine learning has affected the field. Specifically, this paper shows the advancements made in neurology due to machine learning and compares it to previous methods and techniques.

Introduction

Artificial Intelligence (AI) is an ever growing field in computer science that refers to the simulation of human intelligence in machines. The goal of AI is to program machines to problem-solve and have decision-making capabilities similar to the human brain, namely, possessing the ability to perceive, interact, reason, and adapt in isolated situations [1]. Systems that utilize AI work by training a machine using a vast amount of data in order for the machine to understand how to perform a desired task. AI does this by finding connections between its inputs and outputs. Once the system is properly trained, the aim is to analyze an unknown input and draw a correct output using what the system previously learned. The greatest advantage of AI is that it is able to process large sets of data efficiently.

There are two main forms of AI, narrow (weak) and general (strong). Narrow AIs are what we have today and are programmed to be able to perform a specific structured task(s), such as an AI to play chess or a facial recognition system. The narrow AI can beat the best chess player in the world nearly every time or detect every face accurately, but won't be able to understand how to play another game like Tic Tac Toe or be able to identify an animal. Narrow AI pools all its information from a specific data set that is given to it, which is why it can't perform functions not outlined in the data set. This type of AI is not conscious nor sentient as it can only work inside a predefined and determined range. This type of AI can't think for itself like humans can. That being said, narrow AI is a great benefit as it increases productivity and efficiency by being able to outperform an expert doing the same task [2]. Even narrow AI is able to process and interpret patterns faster than humans, leading to more desirable decisions [2].

General AI is at the moment a theoretical idea where the AI is able to reason and think similar to a human [3]. General AI would have cognitive functions of humans by being able to gather new information on its own and learn from prior experiences to better tackle a multitude of tasks [3]. It would be able to simulate the basic principles of consciousness [3]. The main benefit of general AI is so an AI can learn to solve multiple problems without having to be programmed for every nuance. The AI would be able to adapt to various situations and problems on its own using information from a range of topics [3].

Machine learning (ML) is a subset of AI that focuses on improving computers without having to explicitly program them. The field of machine learning exists to find more sophisticated ways for computers to interpret vast amounts of information to make better conclusions and to adapt to new experiences [1]. This is done by creating mathematical algorithms that are able to interpret given data by finding connections and recognizing patterns. The algorithms help identify how certain inputs lead to certain outputs, and thus given new unseen data, could be able to conclude a reasonable output. There are three main types of machine learning: supervised learning algorithms (SLAs), reinforcement learning algorithms (RLAs), and unsupervised learning algorithms (ULAs). SLAs are used for classification purposes and are trained using clearly labeled data where each input has a clear output. The algorithm learns to identify connections between the data and their labels. Thus, when given unseen data, it can find similar characteristics from known labeled data and make an inference of the output as well as its label. RLAs are primarily used in regression models and are trained by interacting with an environment (i.e. simulation),either rewarded or penalized based on if the algorithm came closer or further from the desired objective. Here algorithms are given certain actions in relation to certain data. The algorithm is designed to run through all available actions using a trial-error method in order to reach a desired goal. The actions aren't clearly labeled; instead, the machine has a function that gets rewarded if its action brings it closer to a desired goal or penalized if it gets further away from the goal. Similar to a point system, every step closer to the goal is +1 but every step further is -1 with the program trying to reach the maximum number of points possible (meets the objective). ULAs are important for clustering purposes by using unlabeled data where the algorithm may find similarities among the data samples and cluster them into groups, with each group having distinct characteristics. These groups can be later tested to see if the algorithm detected a meaningful difference or similarity and can provide valuable information.

Both AI and ML take heavy inspiration from the nervous system [4]. Neuroscience is the scientific field that investigates the structure and functions of the nervous system, which includes the brain, neurons, and the spinal cord. To be more precise, neuroscience studies these components to understand our cognition, behavior, emotions, and actions. The field combines various disciplines such as mathematics, physiology, cytology, anatomy, chemistry, psychology, physics, medicine, and even computer science to comprehend how the brain works and develop treatments or cures to neurological disorders [5]. From decades of research of the brain and nervous systems, it has been discovered that our brain works in systems of neural networks that

underlie all our human systems [4]. We have also come to understand neuroplasticity, essentially our ability as humans to change connections in our brains to adapt and reason about new information [6].

There is an overlap between ML and neurology with ML models developing in relation to how the human brain functions [7]. Understanding the mechanisms by which the human brain functions can allow ML models to create simulations of neural processes that are better equipped to problem-solve which in turn can produce localized intelligence at a specific task [7].

With all this information in mind, the remainder of this literature review analyzes the effects ML has had on neurology by describing the progress we've made in neurology directly caused by our progress in ML. With ML being capable of associating the similarities and differences in vast data sets to identify patterns, ML models have proven to be useful in imaging, detection, identification, prediction, classification, and in the development of assistive technologies that allow users to regain healthy bodily functions.

Objective

As mentioned earlier, the study of the brain and nervous system has been ongoing for decades. For each section, the paper will discuss previous and current practices followed by the advancements made with the introduction of ML.

This paper addresses the following questions in depth:
- How was neurology conducted before the addition of AI and ML and what were the limitations of those methods?
- How did AI and ML advance the field of neurology?
- What are the actual applications of AI and ML currently in neurology?
- How significant of a role does AI and ML play in the advancement in neurology?

Terminology

Conventional AI models can be described as rule-based systems which are already coded with a predefined set of instructions [7]. Anything outside of those instructions that hasn't been explicitly coded would break these systems, resulting in a limited capacity of solving more obscure tasks. Such as classification or identification where neurology hasn't fully understood the complexities of the human brain to be able to code the classifiers or identification markers directly. ML networks on the other hand, can adapt to new data to constantly improve their performance. Using ML techniques instead to train networks on labeled data, as well as taking inspiration from the neurons in human brains, allows software engineers to develop artificial neural networks (ANNs), a system that is able to outperform conventional AI models [8].

ANNs are made up of an input layer, hidden (possibly multiple) layer(s), and an output layer. The layers are made up of nodes and are connected via synapses, inspired loosely by how the human brain works. Each synapse contains a certain weight and each hidden node contains a certain bias, both of which are modified during the learning process. The modifications are updated via optimization algorithms. Optimization algorithms used in ANNs primarily stem from

gradient descent, which is used to minimize the loss function by altering the weights and biases in the direction of the steepest descent down the loss function. The loss functions are used in ML to describe mathematically the discrepancy between the values outputted by a model versus the actual values of the training data. They are used to evaluate how accurate a model is, with algorithms aiming to reduce the loss function as much as possible.

Combining the anatomy of the structures of the human brain with gradient descent allowed for the creation of perceptron, a mathematical algorithm utilized in simple ANNs where binary inputs produce desired binary outputs [9]. When given binary inputs, the input layer forwards the information using the synapses to nodes in the hidden layer. In the hidden nodes, each input value is multiplied by the weight of its synapse. Afterwards, all the multiplied weights are added together. Following that, the constant bias of the particular hidden node is added. If the weighted sums are equal to or less than the threshold, an output value of 0 is given while if the weighted sums are greater than the threshold, an output value of 1 is given. However, commonly, miniscule changes can suddenly lead to one node going from a 0 to a 1 and vice versa. To add more room for nuance, a loss function (commonly a sigmoid or tanh function) is added to non-binary inputs which allows the inputs to be assigned a continuous value ranging from 0 to 1.

Multilayer Perceptron (MLP) describes the perceptron algorithm but with more than one hidden layer and multiple nodes stacked together [9]. Essentially, the output values of one hidden layer become the input values of the following hidden layer. The process is achieved using backpropagation, a process in neural networks that calculates the gradient of a loss function by propagating the errors backward from the output layer to the input layer, layer by layer, by using the chain rule of calculus. The percent error between the actual and expected output is calculated and the gradients indicate how much each weight and bias contributes to the overall prediction error and tells the algorithm how to update the parameters.

Convolutional neural networks (CNNs) build on the concept of ANNs by specializing in image recognition and analysis through the detection of patterns in an image [10]. This specialization can be found in the convolutional layers, hidden layers that are unique to CNNs, and separate them from MLPs. CNNs are built using a convolution block and a fully connected block. The convolution block consists of both the convolution and pooling layers which function together for feature-extraction. During the convolution layer, small matrices of weights (filters) are added to the original image. These filters, typically sizes of 3 x 3 or 5 x 5 colvolve the original image, performing element-wise multiplication and summation operations. This allows the network to detect patterns and features at different spatial locations. Different filters learn to identify a unique aspect of the image, such as edges, shapes, and textures. The implementation of multiple filters allows CNNs to detect more complex patterns at a greater degree of accuracy and detail. During the pooling layer, inputs are sectioned out into smaller non-overlapping regions and then summarized by taking a particular value from the set of values. Often the maximum or average of all the values is extracted. The pooling layer is added periodically between successive convolutional blocks as the process helps reduce spatial dimensions of the inputs while retaining the important information. Spatial dimensions being reduced helps with computational

efficiency. The fully connected block consists of a basic neural network structure that serves the function of classification based on the inputs given from the convolutional block. The neural network contains a number of hidden layers in addition to an output layer using regression or classification. These types of neural networks make up a bulk of the ML that is used in neurology today.

Ai for the Development of Neuroscience

AI is generally used to analyze and interpret highly sophisticated and nuanced data through the detection and implementation of hidden patterns. The complexity of our brains is ineffable, but ML has enabled the effective translation of our neural activity into useful applications that would be unattainable completely manually. Advanced AI systems have already been developed to create simulations of the human brain that can be used to test hypotheses of the human brain without going directly to animal or human testing. Innovations like the IBM Blue Gene, a supercomputer built with 8×10^6 neurons in addition to 6300 synapses per neuron [11] facilitates the development of technology with a greater degree of intelligence and utility, especially in the field of neurology. Furthermore, these simulations can help improve the following applications.

Brain-Computer Interfaces

One of the greatest developments made in neurology credited to ML is the brain-computer interface (BCI)---sophisticated assistive technologies that can help those currently suffering from neurological disorders that prevent normal daily functions [12]. BCIs describe a range of computer-based systems designed to establish a link between neural activity in the brain in relation to an external device with no interference from the peripheral nerves and muscles. BCIs work by gathering signals in the brain, analyzing them for distinct patterns of activity, and then deciphering them so they can be used as commands for an external device. Currently electroencephalograms (EEGs) are used as the primary method to gather brain signals as it is a non-invasive procedure that works by placing multiple electrodes on the scalp. The electrodes detect electrical signals traveling across neurons known as action potentials or spikes. Each electrode records the difference in electrical potential between the brain tissue underneath it and a reference electrode placed elsewhere on the scalp. The electrodes are able to capture rapid changes in brain activity. Patterns of electrical activity (brainwaves) suggest a significant group of neurons working in a synchronized manner. Each brainwave produces its own frequency, with higher frequency being associated with greater levels of cognitive abilities being performed [13]. There are many types of EEG signals we are able to track, but for BCIs, the most commonly used are sensorimotor rhythms (SMRs), slow cortical potentials (SCPs), P300 event-related potentials (ERPs), and steady-state visually evoked potentials (SSVEPs) [14]. Based on the literature, P300 and SSVEP have demonstrated a greater capability to transfer signals [15]. BCIs are used for a multitude of neurological conditions which inhibit one's ability to use their regular bodily functions despite the fact they exhibit healthy cognitive abilities [16]. Effective BCIs

should be able to relay neural activity in the brain and translate it in real time for a patient to use an external device, such as a prosthetic limb or exoskeleton. Thus allowing users to be able to perform basic and more complex tasks without the assistance of a caretaker or simplifying traditional methods of self sufficiency. BCIs would serve as a huge relief particularly to those suffering from neuromuscular disorders. Neuromuscular disorders can occur from the progression of diseases, such as in the cases of amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), and primary lateral sclerosis (PLS) that involve the deterioration of motor neurons which leads to the brain losing its ability to control muscles. Or they can occur from injuries, such as ones sustained to the spinal cord that often lead to partial or full paralysis, or worse, injuries to the brain like stroke where 80% of patients experience hemiparesis or hemiplegia [17]. Depending on the state of anyone experiencing these disorders, it can leave patients with little to no voluntary control over their muscles. And with life-support technology advancing, it leaves millions of patients able to live long lives but with poorer qualities of life.

Research and development of BCIs began back in the 1960s. Scientists at the time primarily focused on developing basic techniques for detecting brain signals and using them to control simple tasks. Of the limited research at the time on detecting brain signals, there were two notable figures, Manfred Clynes and Grey Walter. Clynes was an Australian physiologist and musician, but was notable because he proposed the concept of "sentics" [18]. In essence, he explored the relationship between emotions and bodily responses. While not directly related to BCIs, his work touched on the idea of interpreting emotional states through physiological signals, which is a relevant aspect of BCI research nowadays. Walter on the other hand was a British neurophysiologist and cybernetician that conducted research on brainwave patterns and their relation to consciousness and behavior. He developed the "Lateral Inhibition" theory which led to the understanding of brain oscillations [19]. Lateral Inhibition theory states that neighboring neurons inhibit each other's activity to enhance contrast and sharpen perception. The process would explain how the brain differentiates between sensory inputs and make sense of various forms of stimuli. Again, his work isn't directly connected to BCIs, but his findings into how the brain functions were influential to future research. There were also a couple of noteworthy tests that showed the early stages of practical BCIs. Lawrence Pinneo, a researcher at Stanford University, explored the use of brainwave patterns to control external devices. He demonstrated a simple BCI system in which subjects could control the movement of a cursor on a computer screen using their brainwave signals [20]. However, the movement was erratic and unreliable for any practical applications. But, the term "brain-computer interface" was coined by Professor Jacques Vidal of the University of California. Vidal provided some of the earliest notable research for BCIs with experiments performed on animals to establish a neural link with an external device in his paper titled "Toward Direct Brain-Computer Communication" [21]. In the paper, he outlined the great potential of BCIs if the technology is better studied.

In the 1970s, research was conducted using non-invasive communication via EEGs. Dr. Lawrence Pinneo again conducted experiments in which he demonstrated that individuals could generate specific ERPs by focusing their attention on specific visual stimuli [22]. The concept

was used to develop a simple EEG-based communication system, allowing individuals to select letters on a computer screen by attending to specific visual cues. Another notable was German neuroscientist, Dr. Niels Birbaumer. Dr. Birbaumer conducted research on "biofeedback" and supported the idea that individuals could learn to control their brainwave patterns voluntarily [23]. The research at the time would pave the way for mental control mechanisms in recent times. While noteworthy feats, one of the greatest breakthroughs of the time came from physiologist Eberhard Fetz who demonstrated the direct control of a computer cursor on a screen using neural signals from a monkey, which would pave the way for brain-controlled devices [24]. Later, in 1979, researchers Farwell and Donchin introduced the P300 Speller, a system that allowed users to spell words on a computer screen by selecting characters using their attention to specific flashing characters [25]. A P300 is a positive ERP occurring around 300 milliseconds after a stimulus, for brainwave-based communication. These breakthroughs in the 1970s laid the groundwork for demonstrating the potential of BCIs for direct neural control of devices and communication using brainwave patterns. However, the technology was still in its infancy and faced limitations in terms of speed and accuracy.

The 1980s built on these findings, specifically the P300 Speller concept with researchers continuing to refine and develop brainwave-based communication paradigms using ERPs [26]. The developments laid the foundation for the evolution of non-invasive BCIs that allow users to communicate using their brainwave patterns. Along with that, there were significant advancements in neural signal processing and decoding algorithms. Researchers developed methods to extract meaningful information from neural signals, allowing for more accurate interpretation of user intentions and commands [27]. The advancements were crucial for enhancing the performance and usability of BCIs, making them more reliable for real-world applications. They can also be considered early forms of ML. For example, ERPs analysis involves detecting and analyzing specific brainwave patterns associated with different tasks or events. While not as sophisticated as modern ML techniques, the process can be seen as a rudimentary form of pattern recognition, where the system learns to identify characteristic EEG patterns linked to certain cognitive states or intentions. Spatial filtering techniques, such as average reference, Laplacian filtering, principal component analysis (PCA), and independent component analysis (ICA) aim to maximize the variance between different classes of EEG signals, such as different emotions. This involves a form of feature extraction that can be identified as an early form of dimensionality reduction and pattern separation, which are central concepts in ML. Pattern recognition and classification techniques like linear discriminant analysis (LDA) and Bayes classifiers are forms of SML. These methods involve training a model on labeled data to learn decision boundaries that separate different classes of data (e.g. different intentions or cognitive states). There were also adaptive algorithms that are a precursor to modern adaptive ML algorithms. These algorithms adjust their parameters based on the evolving user's neural patterns, which aligns with the concept of adapting models to changing data distributions, a common principle in ML. These advancements led to the development of weaker BCIs for humans. In 1989, researchers Philip Kennedy and Roy Bakay implanted electrodes into

the brain of a paralyzed individual [28]. The device, known as the "Thought-Translation Device," utilized neural signals to detect the user's intentions and translate them into cursor movements on a computer screen. The device allowed the patient to control a computer cursor and communicate using nothing but their thoughts which marked one of the earliest instances of invasive BCIs enabling communication and control for individuals with severe motor disabilities. The 1980s marked a period of continued progress in BCIs, with researchers making strides in both invasive and non-invasive technologies using principles of ML. The development of the Thought-Translation Device and the refinement of brainwave-based communication paradigms were particularly significant in demonstrating the potential of BCIs for communication and control, especially for individuals with severe disabilities.

During the 1990s, however, researchers really began to bring these findings to practical devices for humans in both non-invasive and invasive measures. Researchers continued to explore non-invasive BCIs using EEG signals. Advances in signal processing and ML allowed for better decoding of motor intentions and cognitive states. Improvements in signal processing included more sophisticated feature extraction techniques (specific frequency bands, time-domain characteristics, or statistical measures that captured the neural activity patterns associated with different intentions or cognitive states), pattern recognition algorithms (linear discriminant analysis (LDA) and support vector machines (SVM)), integration of multiple signals, adaptive algorithms, and real-time processing. Limited research also for the first time utilized neural networks, although the technology was very primitive in comparison to what we use today. A study conducted in 1996 by researchers like Christoph Guger and Gert Pfurtscheller explored the use of neural networks to classify EEG patterns related to motor imagery tasks [29]. The team trained neural networks to differentiate between EEG patterns recorded during left and right hand motor imagery tasks. The team demonstrated the potential of neural networks in decoding different motor intentions from EEG signals, contributing to the development of motor imagery-based BCIs. However, most studies during this time focused heavily on improving the speed and accuracy of EEG-based communication and control systems. In 1991, researchers at Duke University led by Miguel Nicolelis demonstrated that monkeys could control the movement of a computer cursor using neural signals recorded from the motor cortex, building upon Eberhard Fetz's experiment from the 1960s [30]. In 1997 a landmark study from the University of California, San Francisco showcased a person with severe paralysis communicating directly with a computer using brain signals that was achieved by putting electrodes in the motor cortex, and the participant learned to control a cursor on a computer screen, spelling out words using a point-and-click interface [31]. The study highlighted the potential of BCIs for communication and assistive technology. Overall, the 1990s were a foundational period for BCI technology. While ML was applied in a relatively limited capacity, it still showed that ML would be key to improving BCIs for practical use.

These early applications set the stage for the more sophisticated integration of ML techniques in the 2000s, when BCI research skyrocketed. In 2000, researchers explored P300-based BCIs, where users spell words by selecting characters displayed on a screen using

their thoughts [32]. The P300 ERP interpreted the commands from the users that allowed the patients to select characters on screen. And in 2004, researchers demonstrated the typing of individual letters using a virtual keyboard interface driven by neural signals [33]. Users could select letters on the virtual keyboard using motor imagery or other cognitive tasks. Once again in 2005, research at Brown University allowed participants to control a computer cursor directly using neural signals [34]. The study involved participants with implanted electrode arrays who moved a cursor on a screen and clicked on targets. The approaches demonstrated the potential of non-invasive BCIs for communication. But, research was also heavily exploring the possibility for control mechanisms for means other than communication. In 2006, researchers explored BCIs for enabling individuals with paralysis to control robotic limbs or computer cursors [35]. Followed in 2008, a study showcased a mind-controlled exoskeleton that enabled a paralyzed individual to take steps [36]. Neural signals were decoded to control the exoskeleton's movements, demonstrating the potential of BCIs for enabling mobility. These studies highlighted the potential of BCIs for restoring motor function and enhancing quality of life. In summary, the breakthroughs in the 2000s highlighted the expanding range of applications for BCIs, from communication and control to mobility restoration, and can be credited to advancements in ML.

During the 2010s, the shift from traditional methods to more ML based methods became more evident. For example in signal processing, traditional methods of manually interpreting brain signals was time-consuming and unreliable. The introduction of CNNs helped in a number of ways. As discussed before, CNNs are particularly well-suited for spatial hierarchies. Recording EEG signals from multiple areas of the brain creates a spatial grid. CNNs can learn to capture spatial patterns in the data by applying convolutional filters that scan across the grid, as shown in [37]. This process also allows for feature learning where CNNs automatically learn hierarchical features directly from the raw EEG signal without human intervention, leading to more adaptability and discovery of previously unknown patterns. The ability of analyzing spatial hierarchies also facilitates translation invariance. Essentially, CNNs can interpret data no matter the spatial location. Oftentimes, when an individual is performing a task or experiencing an event, it is observed that different parts of the brain work from person to person [37]. CNNs being able to still interpret EEG data allows for the BCI technology to be used in a wider range of tasks and experiences while also being able to be designed for the general population. To further expand the uses for BCIs, the introduction of support vector machines (SVMs) have given better dimensionality reduction techniques– a needed component to help filter out noise that could make it harder for BCIs to interpret brain signals correctly. There are many types of SVMs, but the most common one used in BCIs are margin-based classification (MBC). BCI developers first use kernels to map the original input data into a higher-dimensional space. A kernel function is a mathematical function that calculates the similarity or inner product between pairs of data points in the original space. Common kernel functions used in BCIs include the linear kernel, polynomial kernel, radial basis function kernel, and sigmoid kernel. The choice of kernel function depends on the nature of the data and the specific BCI task. The radial basis function kernel is often a popular choice because of its ability to capture complex non-linear

relationships in the data. In MBC, succeeding the calculation of differences among different classes of data, MBC creates a hyperplane. The hyperplane works in the feature space between separate labeled data. The goal is to maximize the distance between the hyperplane and the nearest data points in order to have clearly defined classes of data. For BCIs, classification is necessary to determine the wishes of the user. For example, a BCI needs to know when a user wants to run versus when a user wants to walk. Making as many differences in the EEG data is critical for any practical purposes. SVM being incorporated into BCI has allowed for the technologies to outperform previous versions, such as the P300 Speller as seen in [38].

Overall, what we can observe is ML being utilized throughout the decades to greatly improve our understanding of the brain which allows us to make effective assistive technologies.

Single and Multi Review Learning

Within the past few decades we have observed a surge in technological advancement in both sequencing and imaging that have allowed for an abundance of data that wasn't available before [39]. With this came our ability to share medical data safely with researchers globally, which could be used to fuel independent studies. This would transform the field of neurology where clinical trials could be limited due to there being sufficient data being easily accessible. For neurology particularly, we see there exist vast amounts of multimodal data (genetic, genomic, behavioral, neuroimaging, and clinical data). The multimodal data could subsequently be used to provide insights into how different structures of the brain translate to different diseases and disabilities. Even the National Institute of Mental Health has shifted focus from clinical research and trials to data-driven understanding of the biological mechanisms and causal models of mental illnesses [40]. With the large sums of data out there, it opens the door for ML to identify correlations to better predict the development of intellectual or developmental disabilities and diseases. In ML, there is single-view (SVML) and multi-view learning (MVML). SVML is used in scenarios where there is only one source of data available for training the model, meaning the model can only learn from a single perspective and representation of the data. This type of learning is effective in scenarios where the available data is highly accurate and informative as is. SVML is used in neurology in three ways, neurological imaging, clinical data, and multi-omics data. However, in scenarios where the data may be insufficient, MVML is optimal. In contrast to SVML, MVML training models have access to multiple sources of data. Multiple sources of data allows the model to draw more broad perspectives and representations of the information. In each view of the data, a different conclusion could be deemed based on what information is considered most valuable. However, over time these models could improve their performance, given more data and certain parameters.

Neurological Imaging

Imaging in neurology is crucial as it allows doctors to visualize the structure and cognitive functions of the brain and be able to detect illnesses. Imaging of the brain can either be structural or functional. Structural imaging studies the brain's structure and is used to identify

tumors or injuries while functional imaging studies brain activity. Radiologists use both types of images to identify abnormalities, namely neurodegenerative diseases. These diseases develop due to the progressive degradation of neurons which can be caused by genetic mutations, accumulation of abnormal proteins, inflammation, or oxidative stress. The process is highly complex, with neurologists still researching to find better treatments. Currently, the most common scans done on the brain are computed tomography (CT), magnetic resonance imaging (MRI), and positive emission tomography (PET) [12]. These scans have the ability to identify structural abnormalities caused by tumors, lesions, and hemorrhages and to visualize brain atrophy and general changes in neural activity. While these types of scans are able to provide detailed depictions of the brain, they still have their fair share of flaws.

An often overlooked part of neuroimaging is radiation and contrast agent exposure to the patient. In MRIs, gadolinium-based contrast agents (GBCAs) are part of the standard procedure to enhance images. While considered safe by the Food & Drug Administration (FDA), GBCAs are to be used in the lowest doses necessary as GCBAs have been linked to nephrogenic systemic fibrosis (NSF) and allergic reactions. Research on the link between GBCAs and any other long term effects are ongoing. With NSF being a potentially life-threatening illness, it is a legitimate worry for patients who are recommended to obtain frequent neuroimaging. While these risks are avoidable by greatly limiting the use of GBCAs, it results in images taken from MRIs to be insufficient for proper analysis.

Research using deep ML methods based on an encoder-decoder CNN has been used to obtain high contrast quality MRI images using much lower dosages of GBCAs. The study performed by Gong et al. [41] was tested on 60 patients who had various brain anomalies. The patients received only 10% of the normal dosage of GBCAs. The MRI images taken of the low-dosage patients were given to the network as inputs and were compared to MRI images of full-dose patients. The network during training learned effective denoising techniques to identify and extract relevant signals in the noisy, low-contrast images to reconstruct an image of a full-dose patient. The results were assessed by two board-certified neurologists that deemed the low-dose images satisfactory for analysis and detection. A similar study involved researchers training generative adversarial networks (GANs), which are deep learning–based models, to synthesize MRI scans that were similar in appearance to full-dose contrast-enhanced MRI scans [42]. GANs are made up of two networks, the generator and the discriminator. The generator adds noise to images while the discriminator is trained to interpret the noisy images accurately. Essentially, the GAN was inputted with full-dose MRI images, was generated to be noisier, and then discriminated to predict what a full-dose image would look like. When the results were assessed by two radiologists, the radiologists struggled to identify the actual full-dose MRI versus the GAN generated MRI. Research on this matter points in the direction that in the near future, we can expect ML networks to be able to reliably reconstruct high contrast MRI images from low-dosage images, allowing for safer and more frequent neuroimaging.

MRI images can also suffer from unwanted, random variations in MRI signals that hinder the visibility of the image, otherwise known as noise [35]. The presence of metallic objects or

simply motions and body heat from the patient can result in scans being of lower quality due to alterations in the magnetic field. Lower quality scans make it harder for radiologists to segment the brain and identify any differences between images. Traditional methods of denoising included bilateral filtering, non-local means, and block-matching 3D filtering.

Bilateral filtering (BF) involves smoothing images to be more clear while preserving distinct shapes by applying a low-pass kernel. The kernel works by analyzing each pixel by their color intensity relative to nearby pixels in order to create a weighted average for all pixels in certain areas of the image. This process allows to smooth out outlier pixels that can be assumed to be noise while preserving relevant edges. While this process is useful, BF can oftentimes lead to a loss of fine details in an image as seen in [43]. Additionally, BF can also struggle to denoise images when the parameters used to evaluate relevant features aren't clearly defined [43]. Non-local means (NLM) is similar to BF as it also analyzes pixels, however, the pixels are grouped into rectangular regions or patches. The patches contain key information using weighted averages of the pixels in it while being able to ignore random details that are insignificant, which would be the noise. This technique suffers from the same limitations of BF; plus it is more computationally intensive, leading to inefficiency either in time or quality.

Block-matching 3D filtering (BM3D) is an advanced denoising algorithm that works by exploiting the similarities between different patches or blocks within an image [44]. The algorithm starts by dividing the image into overlapping blocks. It then searches for similar blocks within a certain window around each block. The search is based on a similarity measure, such as the average squared difference between the blocks. Once these blocks are established, the algorithm groups blocks based on common structures and characteristics. Following that, the algorithm applies a collaborative filtering to each group of similar blocks. The collaborative filtering involves averaging the values of corresponding pixels across similar blocks. The process helps to reduce the noise and enhance the underlying structures of the image. Next, the algorithm applies a filter such as a 2D Discrete Cosine Transform (DCT) to transform the blocks which helps separate the image into different frequency components. Following the transformation, the algorithm applies a threshold operation to each frequency component. This helps to further suppress noise by discarding coefficients that are below a threshold that determines significance. Finally, an inverse transform is used to produce the denoised image. BM3D is commonly favored to BF and NLM in scenarios where the noise is highly complex and has a non-Gaussian distribution. However, BM3D has shown to struggle with certain types of noise---namely impulse and high-frequency noise because it primarily relies on the assumption of signal sparsity. Impulse noise, which consists of sudden and random intensity spikes, goes against this assumption. Similarly, high-frequency noise can disrupt the block matching process by throwing off the estimated significant threshold.

CNNs have demonstrated the ability to accelerate data acquisition by being able to construct higher-quality images from noisy and undersampled data. The various CNNs are trained on large, clean available data sets to learn the underlying patterns and structures. Then during the reconstruction process, the trained CNNs can effectively identify what a clean image

is meant to look like and remove the extra noise. One of the most exemplary examples are denoising convolutional neural networks (DnCNNs). DnCNNs were introduced by [45] which utilizes a supervised learning model. The network consists of multiple hidden layers. First the network takes an input of a noisy image. The inputs would then move through convolutional layers with each filter applying a filter to extract key features. But where DnCNNs differ from standard CNNs that make it preferable for denoising is through residual learning and skip connections. Residual learning involves training the network to predict the residual between the noisy inputs to a clean image. Instead of directly estimating the denoised image like BF, NLM, and BM3D, residual learning allows the network to focus on learning the difference between the noisy and clean images. Skip connections, on the other hand, help preserve important details and gradients. These connections allow information from earlier layers to be passed directly to later layers. By doing so, the network can access both low and high level features at various depths of the network, allowing the network to better handle noise at different scales and preserve fine details in the output. The output is optimized through standard backpropagation. Research has demonstrated that DnCNNs have outperformed BM3D as shown in [45]. Specifically, the DnCNNs evaluated showed to be capable of recovering sharp edges and fine details while being able to reconstruct a more visually pleasant image.

All of the tasks that go into the analysis of images make the process a laborious, time-consuming, and mentally draining task for radiologists. As is, we simply don't have an adequate number of radiologists to interpret all the imaging data out there. As radiologists are pressured to work greater workloads at a higher rate with less time, it is to be expected that errors become more frequent as shown by [46], making it crucial to develop better ML models that can be applied on a large scale.

Data

While it is easy to assume physicians are constantly working with patients and running tests, much of the time is actually spent organizing electronic health records (EHRs) [46]. EHRs contain comprehensive patient information that can be easily communicated for reasons of care or for research purposes. In neurology, EHRs play a crucial role in managing and monitoring chronic neurological conditions, tracking disease progression, and facilitating collaborative care among specialists. Editing EHRs are manual and require complex information about the patient but also have to be updated to regulatory standards. Not to mention the customization of different EHRs and consistent security checks which slow the process even more.

Recently, ML models have been developed that are able to predict whether a patient is likely to have an illness. A recent example that highlights the process of establishing accurate predictive models can be seen from a 2021 study that took the EHRs of 1.7 million patients in the USA and developed a ML model that could detect for the presence of Fragile X syndrome (FXS) [47]. During the preprocessing step, the International Classification of Diseases (ICD) codes for FXS were taken. Patients were chosen only if the researchers could identify the code occurring twice in the patient's EHR. From there, all the EHRs were separated into two classes,

those with and those without FXS. This is to follow a supervised learning approach where the model is trained on labeled data first to find connections. Lastly, a random forest classifier was used to find characteristics that make a patient likely to have FXS. The study concluded that their ML models had an accuracy of 80%. While this accuracy alone isn't enough to rely completely on, in addition to familial and genetic data, this process can be improved significantly. ML models that specialize in predictive analysis operate in a similar fashion using a supervised learning model that needs data to be properly trained and a type of classifier to actually classify if a patient has an illness or not [47].

Optice Data

ANN has also helped advance the field of neurology through the deep analysis of neurons. Neurodegenerative diseases are caused due to the loss of neurons over time. However, if we were able to study the gene expressions of neurons we could identify root causes for these diseases. Furthermore, we could also link specific abnormalities to exact diseases. In recent years, ANNs have been used to analyze neurons at the genetic level by leveraging ML algorithms. Methods like data clustering, dimensionality reduction, and correlation analysis work to study large genomic datasets to pinpoint patterns in the gene expression data. The models help uncover key genes and regulatory mechanisms involved in neuronal development, function, and disease. For instance, ANNs assists in analyzing single-cell RNA sequencing data to identify druggable cancer-associated protein targets and potential blood-based biomarkers for the early diagnosis of Alzheimer's disease (AD). This is supported by a meta-analysis which compiled research of various ML models to identify specific genetic factors that can predict one's likelihood of developing AD [48]. Another group of researchers at the Francis Crick Institute and UCL Queen Square Institute of Neurology were successful in creating a CNN model that was able to detect Parkinson's disease and classify the disease into a subtype with a great degree of accuracy by discovering the role that the mitochondria and lysosomes had [49]. Research has also been performed on other neurodegenerative diseases, however the research is limited largely due to the diseases being more niche, resulting in less public training data basis for ML models.

Integrating Using Machine Learning

MVML builds off of SVML by integrating these three subjects with multimodal data. Most research previously on ML for treating neurological conditions were trained primarily on unimodal data [50]. This trend however has been changing as newer research has been moving in the direction of integration as it helps identify unknowns and allows for the correction of human error [50]. The process of interaction allows ML applications to take into consideration data from various sources. For example, taking into account a patient's genetic information, familial history, and lab tests can all work together to help make a more accurate diagnosis. Integration is especially effective in situations where there is incomplete data in one area, so the missing information is compensated with information from other areas. Speaking broadly, MVML

functions in four logical steps: data cleaning and preprocessing, feature extraction, model training, and model evaluation.

When dealing with heterogeneous data, the integration process can be of three different levels, depending on the scenario [51]. The first level is considered early fusion (EF), where features are gathered from various datasets and are concatenated into a single, unified feature representation matrix before analysis in a single model. The way EF works is through methods like pooling, which was previously mentioned in reference to CNNs. EF's goal is to join different types of data into one single entity. When dealing with different types of data, conversions will also be necessary. All the data will first need to be preprocessed before features can be extracted. For example, preprocessing textual data may undergo tokenization or be converted into numerical vectors. For images or numerical data, the data may be resized or have an augmentation technique applied for standardization purposes. Following preprocessing comes feature extraction, a phase which was discussed heavily in the previous sections. Following feature extraction is concatenation where all the different data types have successfully been converted into a suitable format. The concatenation can be given to an ANN or other ML models as training data. EF is commonly used when the different types of data are roughly similar and the views of the data are considered equally important as this puts less strain on the model to reduce dimensionality and make large sums of data easier to comprehend. But the more unique the data types, structures, or formats, the less effective EF becomes. This is where intermediate and late fusion show their superiority, especially in neurology.

In intermediate fusion (IF), there are multiple models being trained in a stepwise fashion. Similar to EF, multimodal data is preprocessed before being extracted for features. But in IF, instead of going straight to concatenation of the raw feature vectors, the models create intermediate representations for each view. The intermediate representations of each view is what gets concatenated during IF into a single model. As a result, a single intermediate representation is created that captures critical information from all the different views with a higher level of abstraction. This type of integration allows for sharing of information among different types of data which can help discover useful relationships. Plus, IF often ends up with lower-dimensional representations compared to both early and late fusion, which in turn means more efficient computational functionality. The major drawback is this integration type requires the level of abstraction to be clearly defined and fine-tuning the preprocessing and feature extraction stages. In addition, determining the quality of the IF is tricky as you would need to analyze the components that went into the multiple intermediate representations.

Late fusion (LF) on the other hand combines decisions produced by different models. In LF, ideally each type of data is given its own unique model to be trained to give a decision or prediction. The results from all the different models are then fused to another singular model that outputs a final result. The benefits of this type of integration is that it allows for parallel processing which can cut down on computational time. It also allows for a greater degree of diversity and flexibility compared to the other two levels, which is especially useful in cases where there may be missing information. With that being said, this type of integration requires a

higher degree of sophistication than EF or IF as the models would need to be calibrated to be looking for a certain outcome and then deciding how to combine them into a single model (such as the significance of each model). This process can also be very computationally expensive. LF also doesn't facilitate the sharing of information like early and intermediate learning that could be used to discover relationships between multiple forms of data.

Integrating Using Neurological Imaging

MVML has improved neuroimaging in a multitude of ways. For imaging in particular, MVML is used to fuse different modalities of neuroimaging together. An example of EF at work can be seen in research of AD [52]. In AD research, EF combines structural MRI and PET data by concatenating the voxel-wise intensity values from both modalities into a single feature vector for each patient. The combined feature vector is then used for disease classification, where ML models predict whether a patient has AD or is healthy based on the fused data. This approach has improved the overall understanding of brain structure and functioning by helping to identify the relationship between brain anatomy and functional connectivity patterns, enhancing the characterization of AD. This is further supported in [53] where the integration of multimodal data in a cost-effective experimental model achieved state-of-the-art testing performance and was more stable than traditional SVML models. A later study by [54] also took into account multiple biomarkers for AD and found better results in classification than the trails of just one biomarker. Meanwhile IF can be used to analyze the brain connectivity of stroke patients. IF is applied by extracting functional connectivity matrices from resting-state fMRI and structural connectivity information from diffusion MRI. These intermediate representations are then fused using graph-based techniques to identify disrupted brain networks and predict functional outcomes in stroke survivors. As found in [55], the researchers were able to predict sensorimotor behaviors of stroke or other brain injuries with a high degree of accuracy. Showing that behavior could be better explained if multiple factors are taken into account. LF is used to a limited capacity in neurodegenerative diseases, such as autism spectrum disorder (ASD) [56]. Specifically for ASD, LF works by training separate models on different neuroimaging modalities, most commonly functional MRI (fMRI) and diffusion tensor imaging (DTI). Each model predicts specific aspects of ASD, such as social behavior or language deficits. The individual model predictions are combined using weighted voting to make an overall assessment of ASD severity. In [57], by combining predictions from separate models trained on these modalities, the researchers were able to enhance their ability to classify and understand ASD. LF approaches like this help address the heterogeneity of ASD and improve the reliability of diagnostic and predictive models.

Integrating Multi-Omics Data

Multi-omics is already a collection of multiple forms of data, some data being numerical values, some being images, and some being text (such as descriptions or predictions). A lot of this data has to do with genetics as identifying gene-loci/SNPs as well as knowing their

relationship to structures and functionality in the brain makes the process of prediction much simpler. To discover the relationships between the two, it would be reasonable to integrate genetic data with neuroimaging data discussed in the previous section. The integration of the two have allowed for numerous feats. Such as in, [58] where researchers were able to successfully correlate dynamic gene expression patterns with fMRI images to identify molecular mechanisms in memory encoding. Memory encoding is the process by which information is transformed into a format that can be stored and retrieved from memory. It involves changes in the strength and connectivity of synapses (structural and functional plasticity) within neural circuits. Over time, memories are consolidated, which means they become more stable and less dependent on the continuous activity of specific brain regions. Gene expression refers to the process by which genetic information encoded in DNA is transcribed into messenger RNA (mRNA) and translated into proteins. It plays a fundamental role in the functioning and plasticity of neurons, including changes in synaptic strength that underlie memory encoding and consolidation. To uncover the correlation between memory encoding and dynamic gene expression patterns, the researchers have employed various techniques and approaches in addition to neuroimaging, namely transcriptomics and epigenomics. Transcriptomics uses RNA sequencing (RNA-seq) to profile the entire transcriptome of neurons or brain regions at different time points during memory formation. This allows them to identify which genes are upregulated or downregulated during memory encoding and consolidation. On the other hand, epigenomics refers to changes in gene expression or cellular phenotype that do not involve alterations to the underlying DNA sequence. Instead, these changes are brought about by modifications to DNA itself or to the proteins associated with DNA, such as histones. Once all the genetic and neuroimaging data had been gathered, the researchers fed models using a combination of the EF, IF, and LF processes to ensure the reliability of the connections. By uncovering these connections, targeted drugs can be developed to treat neurodegenerative disorders that impact memory, or even identify predispositions of hindered cognitive function of people from an earlier age. As further supported by [59], who developed a transcriptome-connectome correlation analysis method that was able to integrate transcriptome data with fMRI connectome data found age-specific cortex developmental gene signatures, which are highly associated with brain disorders.

Conclusion

After centuries of studying the human brain, the field of neurology remains an enigmatic and obscure field of science. The complexity of the human brain is unfathomable, and trying to aid its processes is a daunting task. Through traditional methods in various aspects of neurology we have undeniably made impressive breakthroughs. However, the breakthroughs are limited in their capacity and still leave billions of people globally who suffer from several neurological illnesses that affect their quality of life. To better understand the human brain and develop improved technologies requires the deep analysis of large sums of data. This issue led to the integration of machine learning to help perform analysis of the data. Machine learning and its components have furthered our understanding of the brain in both its structure and functionality.

Over a couple of decades, we have seen machine learning be used to advance methods of imaging, classification, detection, and analysis of both clinical and multi-omics data. These advancements have facilitated the development of assistive technologies that are capable of being used in a practical setting.

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India's Transition from Fossil Fuel to Renewables: Social & Environmental Implications
By Satyam Gupta

Abstract

This article explores the profound social and environmental consequences of transitioning from fossil fuels to renewable energy sources in India. Apart from highlighting the harmful impacts of fossil fuels, such as greenhouse gas emissions, air, and water pollution etc., it also emphasizes the urgency of shifting to renewable energy sources to combat climate change and ensure sustainability. The article attempts to outline India's significant efforts in harnessing its renewable sources (solar, wind, hydropower, biomass, geothermal, ocean, hydrogen, and biogas energy) to meet its growing energy demands by being mindful of reducing the carbon footprint. The influence of climate change on renewable energies is also discussed, noting how changing weather patterns, extreme events, and temperature fluctuations can affect the performance and reliability of renewable energy systems. Adaptation measures and resilient technologies are proposed to address these challenges. While underscoring the urgency of India's transition from fossil fuels to renewable energy sources, emphasizing this shift's compelling social and environmental benefits, the article presents a comprehensive overview of the renewable energy landscape, including the types available in India, their costs, economic impacts, and strategies to address climate-related challenges.

Keywords: greenhouse gas emissions, geothermal energy, renewable resources, climate change, solar energy, biomass, fossil fuels

Introduction

Fossil fuels have a keen impact on society, contributing to a range of social issues, including health problems, energy access disparities, and geopolitical conflicts[1]. While these fuels have played a pivotal role in economic development, they come at the cost of volatility and energy security concerns. Despite the need for a transition, fossil fuels still dominate the global energy landscape, accounting for over 80% of the world's energy supply[2]. Regrettably, the production and consumption of fossil fuels are responsible for a staggering 89% of greenhouse gas emissions and harmful pollutants[3]. This has made fossil fuels a primary driver of climate change, resulting in global warming, pollution, habitat destruction, and resource depletion. Consequently, the imperative for renewable energy resources is undeniable[4].

Renewable energy resources are indispensable due to their numerous benefits. They offer a sustainable and environmentally friendly alternative, addressing the dire need for reduced carbon emissions[5]. Renewable energy sources are abundant, non-depleting, and offer enhanced energy security. They also hold the potential to stimulate economic growth and job creation while improving public health through reduced air pollution[3]. Moreover, renewable energy diversifies energy sources, enhances energy access in underserved regions, drives technological innovation, and fosters global cooperation in combating climate change. Projections indicate that

the share of renewable energy in global energy production will surge from 14% in 2018 to an estimated 74% by 2050[6], [7]. This transition promises to lower both economic costs and environmental impacts, steering us toward a more sustainable and resilient energy future.

Environmental effect of Fossil fuels

Fossil fuels, which include coal, oil, and natural gas, have significant environmental effects throughout their lifecycle, from extraction and production to combustion and disposal[8], [9]. These effects contribute to environmental problems and can have far-reaching consequences such as climatic changes due to greenhouse gas emissions, air and water pollution, land degradation, impact on human health, etc. and are discussed below[7],[10].

The burning of fossil fuels releases carbon dioxide (CO_2)[11], methane (CH_4), and other greenhouse gases into the atmosphere[12]. These gases trap heat, leading to global warming and climate change. This has consequences like rising global temperatures, sea-level rise, extreme weather events, and ecosystem disruptions. The combustion of fossil fuels releases particulate matter (PM) and other air pollutants into the atmosphere, leading to poor air quality[13]. PM can harm respiratory health and contribute to various respiratory diseases. Pollutants like sulphur dioxide (SO_2) and nitrogen oxides (NO_x) can lead to acid rain, which harms ecosystems, forests, and aquatic life. They can also contribute to the formation of ground-level ozone, a component of smog, which can harm human health. Accidental oil spills during fossil fuel extraction, transportation, and refining can devastate marine ecosystems and wildlife. The process of hydraulic fracturing (fracking) for natural gas can produce wastewater with toxic chemicals and heavy metals, posing risks to water quality if not properly managed. Coal mining, particularly, can result in habitat destruction, deforestation, and landscape alterations. This can disrupt ecosystems and harm biodiversity. The infrastructure and activities associated with oil and gas exploration can lead to habitat fragmentation and disruption of wildlife. The extraction of fossil fuels often involves destructive practices, like mountaintop removal, mining for coal or drilling in sensitive ecosystems. This can lead to habitat loss and ecosystem disruption. The extraction of fossil fuels often requires significant water resources, which can lead to water scarcity in regions with high extraction levels. Air pollution from fossil fuel combustion is associated with various health issues, including respiratory problems, cardiovascular diseases, and premature deaths. People living near fossil fuel extraction and processing sites may be exposed to toxic chemicals and pollutants that can harm their health. Increased CO_2 levels in the atmosphere can lead to ocean acidification, negatively affecting marine ecosystems, including coral reefs and shellfish populations. The construction and operation of fossil fuel infrastructure can lead to habitat destruction and displacement of wildlife.

To mitigate these environmental effects, there is a global effort to transition away from fossil fuels toward cleaner and more sustainable energy sources, such as renewable energy (solar, wind, hydro, geothermal) and improved energy efficiency measures. These transitions are critical for reducing the impact of fossil fuels on the environment and mitigating climate change.

The need for renewable energy

  Renewable energy is important for various reasons, and its adoption is crucial for addressing several pressing global challenges. Perhaps the most critical reason for adopting renewable energy is its role in mitigating climate change. Burning fossil fuels for energy releases greenhouse gases like CO_2 into the atmosphere, which trap heat and lead to global warming[11]. Renewable energy sources, such as solar, wind, and hydropower, generate electricity with little to no direct greenhouse gas emissions, helping to reduce the carbon footprint of energy production. Unlike fossil fuels, renewable energy sources do not produce harmful air pollutants like sulfur dioxide, nitrogen oxides, or particulate matter. This improves air quality and public health by reducing respiratory illnesses and other health problems associated with air pollution. Renewable energy sources are often domestic and decentralized, reducing a country's dependence on imported fossil fuels. This enhances energy security and reduces vulnerability to energy supply disruptions due to geopolitical conflicts or market fluctuations. Fossil fuels are finite resources that will eventually run out, while renewable energy sources are continually replenished by natural processes. Investing in renewables helps ensure a sustainable and long-term energy supply. The renewable energy sector has been a significant driver of job creation. Renewable energy infrastructure design, construction, and maintenance, such as wind farms and solar installations, create employment opportunities in various regions. Renewable energy investments can stimulate economic growth. This includes manufacturing research and development in the renewable energy industry and cost savings associated with reduced air pollution and healthcare expenditures. A shift to renewable energy sources can reduce a country's reliance on imported fossil fuels, enhancing energy independence and reducing exposure to volatile international energy markets. The development and deployment of renewable energy technologies drive innovation and technological advancements in energy production, storage, and distribution. These innovations can have spillover effects, helping other sectors as well. Many renewable energy projects are designed to impact ecosystems and biodiversity less than fossil fuel extraction and infrastructure. This can help protect natural habitats and wildlife. Renewable energy projects, such as wind farms or solar installations, often involve partnerships with local communities and landowners. These projects can provide additional income for rural areas, supporting local economies. Distributed renewable energy sources, like rooftop solar panels, can enhance grid resilience by providing backup power during outages and reducing strain on centralized power infrastructure. Renewable energy is a key component of sustainable development goals, helping countries meet their energy needs while reducing environmental impacts and advancing social and economic equity.

  Overall, the adoption of renewable energy is essential for achieving a more sustainable, resilient, and environmentally friendly energy system that addresses climate change, improves public health, and supports economic growth and energy security.

Types of renewable energies

Renewable energy comes from sources that are naturally replenished and can be used without depleting them[14]. India is actively developing and harnessing various renewable energy sources to meet its growing energy demand while reducing greenhouse gas emissions and dependence on fossil fuels[15]. There are several types of renewable energy sources, each with its own unique characteristics and applications. The cost of implementing renewable energy projects can vary widely depending on several factors, including the type of renewable energy source, the scale of the project, the location, technological advancements, and local market conditions[16]. Generally, the cost of renewable energy has been decreasing over the years, making it increasingly competitive with fossil fuels[17]. Here are main types of renewable energy:

1.1 **Solar Energy**

Solar panels convert sunlight directly into electricity. They are commonly used on rooftops and in solar farms. India has vast solar potential, and solar PV technology is widely deployed. Rooftop solar installations, solar farms, and solar power purchase agreements (PPAs) are common[18]. This technology uses sunlight to heat a fluid that can be used for electricity generation or space heating and cooling[19]. Concentrated solar power (CSP) plants are also being explored, which use mirrors or lenses to concentrate sunlight and produce high-temperature heat for electricity generation[20]. The cost of solar PV has seen significant reductions due to improvements in technology and economies of scale. As of the last knowledge update in September 2021, the levelized cost of electricity (LCOE) for utility-scale solar PV projects in many regions was competitive with or lower than fossil fuels[21]. In some areas, the cost of rooftop solar installations for homes and businesses was also relatively affordable.

1.2 **Wind Energy**

Wind turbines harness the kinetic energy of wind to generate electricity[22]. Wind farms consist of multiple turbines and are often located in areas with strong, consistent winds. Wind energy is a major contributor to India's renewable energy capacity[23]. Wind farms are located in several states, with the states of Tamil Nadu, Karnataka, and Gujarat having significant wind power installations[24]. Wind energy costs have also declined, making it one of the most cost-competitive sources of renewable energy[21]. Large-scale wind farms benefit from favourable economies of scale[20].

1.3 **Hydropower (Hydroelectric Power)**

The energy of flowing water is used to turn turbines and generate electricity in hydroelectric dams. India has a substantial number of hydropower projects, both large and small, located in various regions[25]. Projects like the Bhakra Nangal Dam and Tehri Dam are notable examples. Smaller-scale hydropower systems can be installed in rivers or streams to generate electricity without large dams. Small hydropower plants are also prevalent, especially in hilly

and remote areas. The cost of building and maintaining large hydroelectric dams can be substantial, but these projects often have long lifespans and low operating costs, making them cost-effective over the long term. Small hydropower projects can be more cost-effective and suitable for decentralized energy generation.

1.4 Biomass Energy

Biomass, such as wood, crop residues, and organic waste, can be burned directly for heat and electricity or converted into biofuels like biodiesel and ethanol[26]. Biomass power plants use agricultural residues, organic waste, and dedicated energy crops to generate electricity and provide heat for industrial processes. India has numerous biomass power projects. The cost of biomass energy can vary depending on the type of feedstock used, transportation costs, and technology[14]. Biomass projects can be competitive in regions with abundant biomass resources.

1.5 Geothermal Energy

Geothermal energy harnesses heat from the Earth's interior to generate electricity. Geothermal power plants are often found in regions with geothermal activity. India has some potential for geothermal energy in regions with geothermal activity. However, it is not as widely developed as other renewable sources. The cost of geothermal projects can be influenced by the depth and temperature of geothermal resources. In areas with suitable conditions, geothermal energy can be cost-competitive.

1.6 Ocean Energy

Tidal power uses the gravitational forces of the moon and the sun to generate electricity from the rise and fall of tides. Wave energy devices capture the kinetic energy of ocean waves and convert it into electricity. India is exploring tidal and wave energy projects along its coastline, particularly in the Gulf of Kutch and the Gulf of Cambay. Ocean Thermal Energy Conversion (OTEC) systems use the temperature difference between warm surface water and cold deep water to produce electricity. Ocean energy technologies are still in the development phase, and costs can be relatively high. However, advancements may lead to cost reductions in the future.

1.7 Hydrogen Energy

Hydrogen can be produced through various renewable methods, such as electrolysis, using renewable electricity to split water into hydrogen and oxygen. India is exploring hydrogen production through renewable methods, including electrolysis powered by renewable energy sources. Hydrogen can be stored and used as a clean energy carrier for various applications, including transportation and industrial processes. The cost of hydrogen production from renewable sources like electrolysis depends on the cost of electricity and the efficiency of the

electrolysis process. As renewable energy costs decrease, so does the cost of renewable hydrogen production.

1.8 Biogas Energy

Organic matter, such as agricultural waste and sewage, can be converted into biogas through anaerobic digestion, which can be used for heat and electricity production. Biogas plants that use organic waste from agriculture and municipal sources for biogas production are common in India.

1.9 Waste-to-Energy

Some waste-to-energy facilities burn municipal solid waste to generate heat and electricity, reducing landfill waste. Waste-to-energy projects, such as municipal solid waste incineration, are being developed in some Indian cities[27]. Each of these renewable energy sources has its own advantages and limitations, making them suitable for different applications and geographic locations[28]. The choice of renewable energy type depends on factors such as resource availability, cost, environmental impact, and local energy needs. Many regions use a combination of these renewable energy sources to diversify their energy supply and reduce greenhouse gas emissions. India has set ambitious renewable energy targets as part of its efforts to combat climate change and improve energy security. The country's National Solar Mission, National Wind Mission, and various state-level policies and incentives have played a crucial role in promoting renewable energy adoption. India's renewable energy sector continues to grow, attracting investment and contributing to its sustainable energy future[29]. The cost of waste-to-energy projects can vary depending on technology and waste management practices. These projects can be cost-effective in areas with limited landfill space. It is important to note that the cost of renewable energy technologies continues to evolve, and they have become more competitive in comparison to fossil fuels in many regions. Government incentives, subsidies, and policies can also influence the cost-effectiveness of renewable energy projects. Additionally, the concept of the levelized cost of electricity (LCOE) is often used to compare the lifetime costs of different energy sources. LCOE takes into account factors like capital costs, operating and maintenance costs, and the expected lifetime of the equipment. As technology advances and economies of scale continue to play a role, the cost of implementing renewable energy is expected to further decrease, making it an increasingly attractive option for addressing energy needs while reducing environmental impacts.

2. Economic impact of renewable energy

Renewable energy can have significant economic impacts, both at the macroeconomic and microeconomic levels, contributing to economic growth and stability[30]. These impacts are generally positive and encompass various aspects of the economy.

The renewable energy sector is a major source of employment. Jobs are created across the value chain, from manufacturing and installation to maintenance and operation of renewable

energy systems[31]. This job growth stimulates economic activity and reduces unemployment rates. The development of renewable energy projects attracts significant investment, including foreign direct investment. This infusion of capital can boost economic development in regions with renewable energy installations. Renewable energy projects, such as wind farms and solar installations, often involve partnerships with local communities and landowners. These projects can provide additional income to farmers and landowners through lease agreements and create new revenue streams for local governments through taxes and royalties[32]. Over the long term, renewable energy can help stabilize and reduce energy costs for consumers, businesses, and industries. This can lead to increased disposable income for households and improved competitiveness for businesses. Investing in renewable energy helps diversify a country's energy sources, reducing its vulnerability to energy supply disruptions and price fluctuations in fossil fuel markets[33]. This energy security can have positive economic implications. Countries that develop expertise in renewable energy technologies can become exporters of these technologies and services. This can lead to trade surpluses and economic growth. By reducing reliance on imported fossil fuels, a country can reduce its trade deficit and decrease the outflow of funds to foreign energy suppliers[34]. While there may be initial capital investments in renewable energy infrastructure, the long-term operational and maintenance costs are often lower than those of fossil fuel-based energy systems. This can result in cost savings over the lifespan of renewable energy projects. Renewable energy reduces the environmental and health costs associated with fossil fuel use. Lower air pollution and reduced healthcare expenditures can result in economic savings. The development of renewable energy technologies fosters innovation and can drive economic growth in related industries. For example, advances in battery technology for energy storage have applications beyond the energy sector. Transitioning to renewable energy can help mitigate the economic costs associated with climate change, such as damage from extreme weather events and disruptions to agriculture and supply chains. Investing in renewable energy can help countries meet their international commitments to reduce greenhouse gas emissions, which can have trade and diplomatic benefits.

It is important to note that the economic impact of renewable energy can vary depending on factors such as government policies, the scale and maturity of the renewable energy market, the availability of resources, and the overall energy mix of a country. However, on a global scale, the transition to renewable energy is increasingly seen as an engine for economic growth, job creation, and sustainability.

3. Impact of climate change on renewable energies

Climate change can have both direct and indirect impacts on renewable energies, affecting their performance, reliability, and efficiency. While renewable energy sources themselves do not contribute to climate change, they can be influenced by changes in weather patterns, temperature, and other climate-related factors[35]. Here are some of the key impacts of climate change on renewable energies:

Climate change can alter cloud cover and solar radiation patterns. Extended periods of cloudiness or changes in sunlight intensity can affect the output of solar photovoltaic (PV) systems. Changes in wind patterns and wind speeds can impact the generation potential of wind turbines. Some regions may experience decreased wind speeds, affecting wind energy production. Climate change can affect precipitation patterns and snowmelt timing, which, in turn, can impact river flow and reservoir levels crucial for hydropower generation[36]. Droughts and reduced water availability can limit hydropower production. Severe weather events, such as hurricanes and floods, can damage renewable energy infrastructure, including wind turbines, solar panels, and hydropower dams. These events may lead to disruptions in energy generation and require costly repairs. Extreme temperatures, especially extreme heat, can affect the efficiency and lifespan of solar panels and wind turbine components[37]. High temperatures can reduce the efficiency of PV cells and increase maintenance requirements for wind turbines. Climate change can affect geothermal reservoirs by altering underground temperature gradients and impacting the long-term sustainability of geothermal power plants. Many renewable energy projects, such as offshore wind farms and tidal energy installations, are located in coastal areas[38]. Rising sea levels and increased storm surges can threaten the integrity of these installations. Climate policies and regulations aimed at reducing greenhouse gas emissions can impact the growth and development of renewable energy markets. Stronger climate policies may accelerate the adoption of renewables, while weaker policies may hinder progress. Climate change can introduce greater uncertainty into the availability of renewable energy resources, making it more challenging to plan and manage energy systems effectively.

Despite these challenges, it is worth noting that renewable energy sources often exhibit more resilience to certain climate-related factors compared to fossil fuel infrastructure[4]. For example, renewable energy systems do not rely on fuel supply chains vulnerable to disruptions caused by extreme weather events, and they produce no direct greenhouse gas emissions[39]. To address the impacts of climate change on renewable energies, adaptation measures such as improved weather forecasting, changes in system design, and the development of more resilient technologies are being explored[28]. Additionally, the integration of diverse renewable energy sources and energy storage systems can enhance the overall reliability and resilience of renewable energy systems in the face of changing climate conditions.

Conclusion

It is important to note that the transition to renewables is not without challenges. The intermittent nature of some renewable sources can pose grid stability issues, and the manufacturing of renewable technologies can have environmental impacts, particularly in terms of resource extraction and production. Additionally, there may be social and environmental concerns associated with land acquisition and displacement for large-scale renewable projects. A successful transition requires comprehensive policies that address these concerns, promote sustainability, and ensure a just and equitable transition for all. Public awareness, stakeholder

engagement, and international cooperation are essential to navigating the complex social and environmental landscape of transitioning to renewable energy in India.

Acknowledgement

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Should Companies Implement Wellness Programs? By Jungmin Im

Abstract

The goal of this study is to figure out whether companies should impose wellness programs for their employees. A survey was done to find out people's current situation by asking multiple questions regarding their working conditions and other aspects to prove that some factors do cause mental/physical illness to workers. The participants were tech company workers in the US aged 30~60. The results showed that working remotely and having family history had substantially higher chances of having mental diseases. Moreover, companies that had health-care programs implemented saw more than 50% increase in workers' benefits (satisfaction, stress level, absenteeism, etc). Even though there are some limits such as the sample being too specific, I suggest that wellness programs are still quite effective and should be recommended to companies, especially tech companies, for their employees expeditiously.

Introduction

The world is changing extremely fast. As almost everyone in the planet knows, Covid-19 has been a massive problem among all aspects of life such as, education, health, and economy ETC. Although those are all very important to sustain a well balanced life, mental health that is related to working in different conditions is definitely one of the most major concerns. I have, for that reason, recently constructed an idea: due to the changing environments of workspaces, many individuals have seized mental illnesses.

With the curiosity to figure out if my suspicions were true, I have conducted a global survey in 2021 through opportunity sampling of people that are currently working in companies. If my theory is correct, companies around the world can decide whether they should offer wellness programs to their employees and improve productivity.I found prior research done in Malaysia by Dayang Nailul Munna Abg Abdullah(2012). This study found that employees who took part in wellness programs reported higher job satisfaction, lower stress levels, and lower absenteeism compared to those who did not attend such programs. The study illustrates the importance of corporate wellness managers in promoting employee health and suggests the need to integrate these programs into the organizational culture for a more positive impact.

Literature Review

For more information about my hypothesis from past papers, I've done a literature review on similar/corresponding documents and the following are the contents. Rietveld(2014) found out that self-employed people don't actually get healthier. Rather, it is the healthy people that choose to be self-employed as the study suggests. In fact, self-employment has a negative impact on health for most individuals. Ewers(2023) states that while remote work offers mostly advantages, it has been a varied experience. Those juggling work-from-home with childcare faced significant adjustments, and while some enjoyed flexibility, others struggled with technology-related stress. This shift in work dynamics and living spaces challenges traditional

views of labor inequality. To understand these changes, a survey of 1,172 remote workers in the US during the pandemic examined how remote work affected autonomy, technostress, and life disruptions. The results highlighted disparities in work experiences and outcomes, especially concerning race, age, and the number of dependents, revealing both existing and emerging forms of inequality.

Data/Variables

The survey data I used has approximately 324 total values for mental health problems, and a comprehensive set of features that describe which kind of participants were selected. The respondents are males and females between the age of 30-60 because most workers are affiliated to that age. I only aggregated values from people who go to technology companies in the United States because America has the most typical tech companies in the world for independence and controlling selection bias. All the data are aggregated as binary. The survey asked people about their mental consequences, family history, working conditions, company's treatment programs, and finally, the benefits from the treatments if they have any. Mental consequence means that the subjects have had at least one type of mental illness. Family history clarifies whether the participant's family have had any sort of mental diseases in the past or present. Working conditions ask if the subjects work remotely (telecommute). Treatments ask if the company provided mental health-care programs and benefits question whether the participant received advantages after getting treated.

Methodology

First, a linear regression model is used for the model. it is generally used to analyze the marginal effects for explanatory variables on a response variable. However, in dealing with binary variables, it is better to use a logistic model or probit model for treating issues related to the linear model with binary variables. For this reason, the paper applies all models mentioned above(Linear probability model/ Logistic model/Probit model) to analyze the effects.

Each dependent variable(having mental health) and independent variable(remote work/ family history) are binary variables, having only two values Y = {0,1}, which means that if a subject has a mental health problem, the value of 1 is assigned to the subject, otherwise, the value of 0 is assigned to the subject. Also, if a subject has remote-working conditions or family history, the value of 1 is assigned to the subject. Therefore, it only considers the presence of telecommuting and family history, without considering the extent.

First regression model:

$$Y(Mental\ consequnce)\ =\ \beta_1\ remot\_workplace\ +\ \beta_2 Family\_history\ +\ \varepsilon$$

What each coefficient implies is the probability of the explanatory variable contributing to the dependent variable when it changes. Therefore, the coefficients equal the marginal effects on dependent variables.

```
. reg mental_ remote_ fam_

      Source |       SS           df       MS      Number of obs   =       501
-------------+----------------------------------   F(2, 498)       =      4.05
       Model |  1.47566811         2  .737834057   Prob > F        =    0.0181
    Residual |  90.8157491       498  .182360942   R-squared       =    0.0160
-------------+----------------------------------   Adj R-squared   =    0.0120
       Total |  92.2914172       500  .184582834   Root MSE        =   .42704

------------------------------------------------------------------------------
     mental_ | Coefficient  Std. err.      t    P>|t|     [95% conf. interval]
-------------+----------------------------------------------------------------
     remote_ |   .0570865    .040075      1.42   0.155    -.0216504    .1358234
        fam_ |   .0938098   .0383926      2.44   0.015     .0183784    .1692412
       _cons |   .1819309   .0290434      6.26   0.000     .1248682    .2389936
------------------------------------------------------------------------------
```

The value of coefficient on remote work is a positive 0.37, which means the probability of having a mental problem increases by 30.7% when a worker is on remote-work. Also, the value of coefficient on family history is positive 0.50, which means the probability of having a mental problem increases by about 50% when a person has a family history of mental illness. As expected, remote-work and family history has a negative impact on mental health.

The binary variables in the linear regression model have only two variables 0 and 1, thus, the coefficient for the linear regression model can not easily be explained with the slope for the general linear equation. For dealing with this difficulty, there is an alternative, probit or logit model.

```
Multinomial logistic regression                 Number of obs =      501
                                                LR chi2(2)    =     7.98
                                                Prob > chi2   = 0.0185
Log likelihood = -274.11468                     Pseudo R2     = 0.0143

------------------------------------------------------------------------------
     mental_ | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
0            | (base outcome)
-------------+----------------------------------------------------------------
1            |
     remote_ |   .3071311   .2159142      1.42   0.155     -.116053    .7303152
        fam_ |   .5089054   .2099127      2.42   0.015      .097484    .9203267
       _cons |  -1.488623   .1711198     -8.70   0.000    -1.824012   -1.153234
------------------------------------------------------------------------------
```

```
Probit regression                               Number of obs =      501
                                                LR chi2(2)    =     7.97
                                                Prob > chi2   = 0.0186
Log likelihood = -274.12005                     Pseudo R2     = 0.0143

------------------------------------------------------------------------------
     mental_ | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
     remote_ |   .1806115   .1277129      1.41   0.157    -.0697011    .4309241
        fam_ |   .2989777   .1232661      2.43   0.015     .0573805    .5405749
       _cons |  -.9010857   .0976054     -9.23   0.000    -1.092389   -.7097827
------------------------------------------------------------------------------
```

Second regression model:
$$Y(Benefit) = \beta_3\, Treatment + \varepsilon$$

```
. probit benefit_ treatment_

Iteration 0:   log likelihood = -223.3683
Iteration 1:   log likelihood = -215.49509
Iteration 2:   log likelihood = -215.49386
Iteration 3:   log likelihood = -215.49386

Probit regression                               Number of obs =     324
                                                LR chi2(1)    =   15.75
                                                Prob > chi2   =  0.0001
Log likelihood = -215.49386                     Pseudo R2     =  0.0353


    benefit_ │ Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
─────────────┼────────────────────────────────────────────────────────────────
  treatment_ │   .5625933   .1424945     3.95   0.000     .2833092    .8418774
       _cons │  -.2058867    .106365    -1.94   0.053    -.4143583     .002585
```

The value of coefficient on treatment is positive 0.56 and statistically significant, which means the probability of having benefit increases by 56% when a worker is having treatment from the workplace.

With the previous literature and our estimation from the data, remote-workplace increases the probability of having mental problems. Also, providing mental health care-program could increase the level of satisfaction and well-being.

Limitation

Even though this type of study is very elaborate and well understood, there are still limitations to it. For this specific study, the data only counts technology industry workers that are from the U.S. and are aged between 30-60. If there are some unique characteristics about these workers from the data that others do not have, the results could be biased due to those confounding variables. There could also be multiple other confounding variables such as family history and other personal issues. On top of that, the results are too hard to generalize because there are too many conditions required for our variables. The questions asked for the survey could have caused different results since people have varying experiences of symptoms from mental illnesses.

Conclusion

The results of the current investigation provide concrete evidence for the benefits of health-care programs in tech companies and maybe even other companies as well. When people remotely work or have distressing family histories, their chances of getting mentally ill increases significantly. However, as proven from the research, when people receive health-care for their mental issues, they tend to increase worker satisfaction. Naturally, if people have high satisfaction and lower stress levels, productivity and other task completion rate and speed will increase. This is why I recommend that companies implement wellness programs to their welfare system.

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Natural Language Processing: the Pathway to ChatGPT By Zishun Zhou

Abstract

Natural Language Processing plays a pivotal role in computer science and artificial intelligence by enabling machines to comprehend and respond to human language. Its applications are diverse, encompassing language translation, social media monitoring, chatbots, and voice assistants. Particularly, with the increased popularity of ChatGPT, Natural Language Generation garners widespread interest. To better illustrate this technological advancement, this review paper presented a comprehensive overview of natural language generation, including its framework, algorithms, and applications. Two widely-used models are highlighted: Recurrent Neural Networks and Generative Pre-trained Transformer. With continued algorithm refinement and increased computational power, we anticipate more sophisticated, personalized, and domain-specific applications in the years to come.

Introduction

Natural Language Processing (NLP) is a critical pillar in the field of computer science and artificial intelligence, which enables machines to understand human language and respond accordingly. Language is an essential characteristic that distinguishes humans from other animals. The various intelligences of humans are closely related to language. Communicating with computers using natural language has long been a pursuit of people. People can command computers in their accustomed language without spending a lot of time and effort learning various computer languages that are not very natural.

To achieve that goal, we need NLP. NLP combines computer algorithms with machine learning and deep learning models to automatically extract, classify, and label elements of text and voice data and then assign a statistical likelihood to each possible meaning of those elements [1-3]. Today, deep learning models and learning techniques enable NLP systems that 'learn' as they work and extract ever more accurate meaning from huge volumes of raw, unstructured, and unlabeled text and voice data sets.

NLP has a wide range of applications, including:

- *Language translation.* In the early days, machine translation systems were based on dictionaries and specific rules, and their functions were very limited. With the development of neural networks and the availability of massive data, machine translation has become quite accurate. Tools such as Google Translate can easily convert text from one language to another.
- *Social media monitoring.* Nowadays, more and more people are using social media to post ideas about specific products, policies, or issues, which unintentionally contain personal preferences. Analyzing this unstructured data can help generate valuable information including understanding user experience to a certain product and identifying potential threats related to national security.
- *Chat robot (chatbot).* Customer service and feedback are the most common uses of

chatbots. It can help companies improve their products and maintain customer satisfaction. Recently, these chatbots have also developed into personal partners.

- *Voice Assistant.* Voice assistant is a software that uses speech recognition, natural language understanding, and natural language processing to understand users' verbal commands and perform corresponding operations. Examples include Google Assistant, Apple Siri, and Amazon Alexa. Over the years, voice assistants help us from setting morning alarms to handling interpersonal relationships. They have become very reliable and powerful friends.

Among these applications, with the increased popularity of ChatGPT, we will focus on the chatbot response in the following discussion. The main theme of chatbot is Natural Language Generation (NLG), representing the machine's capabilities to provide feedback based on the user input.

NLG Framework

To achieve NLG functionalities, a few tasks need to be completed sequentially. First, the context of the conversation needs to be extracted in the form of structured data, charts, or statistics. Then, the algorithm needs to learn the structure and content of the text, including topics, paragraph order, etc. Based on the content planning, structured data is transformed into natural language sentences through machine learning and natural language processing techniques. It then generates individual sentences or phrases based on the plan created in the previous step. This involves linguistic decisions, such as word choice, sentence structure, and grammar. The system may use predefined language patterns or templates to facilitate sentence generation. Finally, the generated sentences need to be integrated into complete text paragraphs or articles.

Technically, to first learn the context of the text, NLG algorithms will follow the steps below:

1. *Corpus preprocessing (text data cleaning).* First, non textual content (e.g., crawling HTML code, CSS tags, unnecessary punctuation) will be removed. The text will be segmented into a meaningful sequence of character strings (tokenization). using dictionary-, statistical-, or deep learning-based methods. Afterwards, the data will be tagged with speech labels (e.g., nouns, verbs, adjectives) with the aid of rule-based algorithms or statistical algorithms. Data with "stop word labels" will then be removed.
2. *Text vectorization.* To facilitate content generation, the cleaned text is further converted into feature vectors. The Bag of Words model and the Word2Vec model are widely deployed in this step.
3. *Model construction.* After text vectorization, appropriate machine learning or deep learning models need to be constructed to analyze the text. Commonly used machine learning models include KNN, SVM, Naive Bayes, decision trees, and K-means, while deep learning models examples are RNN, CNN, LSTM, Seq2Seq, FastText, TextCNN, etc. These models are capable of automating various tasks related to understanding,

generating, and extracting information from textual data.

Then, based on the learning results above, the algorithm will deploy the following steps to generate appropriate responses:

1. *Content Determination.* As the first step in generating text, the model needs to decide which information should be included in the text being constructed and which should not be included.
2. *Text Structuring.* After determining what information needs to be conveyed, the model needs to organize the text in a reasonable order. For example, when reporting on a basketball game, priority will be given to expressing 'when', 'where', and 'which two teams', followed by' overview of the game ', and finally' outcome of the game'.
3. *Sentence Aggregation.* Not every piece of information requires an independent sentence to express, merging multiple pieces of information into one sentence may make it smoother and easier to read.
4. *Grammaticalization.* Once the content of each sentence is determined, the information can be organized into natural language. This step will add some connecting words between various pieces of information, making it look more like a complete sentence.

NLG models

Following the frame above, various NLG models have been proposed and implemented. Here we will focus on two most widely-used ones: Recurrent Neural Networks (RNN) and Generative Pre-trained Transformer (GPT).

1. RNN

RNN is an artificial neural network with a tree-like hierarchical structure, where network nodes recurrently process the input information based on their connection order. Long Short-Term Memory (LSTM) and Gated Recurrent Unit (GRU) are variations of RNNs that better capture long-range dependencies. Particularly, as a nonlinear model, LSTM can be used as a complex nonlinear unit to construct larger deep neural networks.

Here we will use a simple example to illustrate RNN's mechanism. When you do online shopping, you usually check the reviews of users who have previously purchased the product. When browsing these comments, your brain subconsciously only remembers important keywords such as "amazing" and "awesome", and is less concerned about words such as "this", "give", "all" or "should". This automatic screening process is basically what RNN does. The algorithm only retains relevant information for prediction and forget irrelevant data.

Figure 1. Schematic of LSTM workflow [4]

Taking a closer look at LSTM, figure 1 shows the core concept of LSTM, featuring the cell state and "gate" structure. The cell state describes the information transmission pathway, allowing information to be transmitted through sequential connections, which can be seen as the "memory" of the network. The cell state continuously transmits information during the sequence processing. Therefore, information from earlier time steps can be carried to cells at later time steps, which overcomes the short-term memory challenge. The addition and removal of information are implemented through the gate structure, which determines which information to save or forget during the training process.

Elaborating on the functions of the gate structure, LSTM has three types of gate structures: forget gate, input gate, and output gate.

- *Forget Gate:* The function of forget gate is to determine which information should be discarded or retained. Information from the previous state and current input are simultaneously passed to a sigmoid function, with an output value between 0 and 1. The closer it is to 0, the more likely it will be discarded, and the closer it is to 1, the more likely it will be retained.
- *Input gate:* Input gate is used to update the cell state. Here a tanh function will be used additionally to create a new alternative value vector. Multiply the output value of sigmoid by the output value of tanh, and the output value of sigmoid will determine which information in tanh's output value is important and needs to be preserved.
- *Output gate:* The output gate is used to determine the value of the next state, which contains information previously input. Firstly, we pass the previous hidden state and current input to the sigmoid function, and then pass the newly obtained cell state to the tanh function.
  Finally, multiply the output of tanh with the output of sigmoid to determine the

information that the hidden state should carry. Then use the hidden state as the output of the current cell, and transfer the new cell state and new hidden state to the next time step.

After LSTM was proposed, it was quickly applied in various NLP fields such as speech processing, machine translation, and entity recognition. However, it also has certain limitations, including: 1) high complexity of LSTM's network structure increases the computational burden; 2) both RNN and its derivative LSTM are based on sequential processing, which inherently has low efficiency; 3) causal order of events: the input at time t cannot extract the content of sequence information after time t. This is particularly evident after the transformer comes out.

2. GPT

The GPT algorithm is a natural language processing model proposed by the OpenAI research and development team in 2018. It is based on the Transformer model and utilizes massive internet data for training, enabling it to grasp the hidden laws of language and to achieve strong language understanding and generation capabilities.

The core idea of the GPT algorithm is to transform natural language processing tasks into unsupervised learning problems. Through the pre-training and fine-tuning stage, the GPT algorithm can learn a large number of semantic and structural features of language. With this knowledge, GPT can generate human writing style statements based on given contextual information, and even complete articles, stories, and other long texts. GPT adopts self-supervised learning for pre-training, utilizing a large number of text corpora. With the deepening of training, the language generation quality of GPT technology will continue to improve.

Specifically, the OpenAI GPT model functions based on tags or token. As shown in Figure 2, words that are common or short in length typically correspond to a single token; long and infrequent words are usually broken down into several tokens (e.g., 'anthropomorphizing' in figure 2). Abbreviations such as 'ChatGPT' can be represented by a single token or broken down into multiple ones, depending on the degree to which the letters appear together.

Figure 2. Example sentence breakdown in GPT model. [5]

The model takes n tokens as input and generates one token as output. The generated token is then merged into the original input. A new token can be generated based on the modified input sequence. This process repeats until the stop condition is reached, indicating that it has completed generating the text you need.

One associated feature of this model is the lack of deterministicity - if you ask the exact

same question twice, you may get two different answers. This is because the model does not generate a single prediction deterministically; on the contrary, it generates the probability distribution of all possible answers. It returns a vector where each entry represents the probability of selecting a specific answer, and samples from this distribution to generate the output sequence. An example of generating the distribution of a single token is illustrated in Figure 3. This probability distribution is derived during the training phase. During training, the model is exposed to a large amount of text and adjusts its weight to predict a probability distribution given the input sequence. GPT model uses a large corpus from the internet for training, so their predictions reflect the combination of information they receive.

Figure 3. Schematic of token generation probability [5]

Despite its wide usage, the GPT model also still has its own limitations:

1. *Unidirectional text generation.* Unlike some bidirectional decoders (such as BERT), GPT uses a unidirectional decoder that can only generate text using the previous contextual information and cannot utilize the subsequent text information. Therefore, the coherence and logic of the generated text may not be as good as that of bidirectional decoders.
2. *Randomness in generating text.* Due to the use of optimization methods such as random gradient descent in GPT and the setting of some randomness in the fine-tuning process, each generated text may have certain randomness and differences.
3. *Long text processing capability.* Although GPT can generate relatively smooth and accurate short text, there may be some issues when processing long text. For example, when the length of the text to be generated is long, GPT needs to repeatedly calculate, resulting in low efficiency issues.
4. *High training costs:* The GPT model contains hundreds of millions of parameters, requiring a large amount of computing resources and time for training, and thus its training cost is relatively high. At the same time, the large number of parameters in the

model may also lead to higher model complexity, increasing the difficulty of model interpretation.

Outlook

In summary, NLG has made impressive progress during the past ten years. With the algorithm refinement and increasing computational power, we can expect the following trends in this field:

- Personalized text generation. Personalized text content can be generated based on user preferences and needs, providing a better user experience.
- Multimodal generation. Combining multiple media data such as images and videos with natural language generation to achieve richer content generation.
- Emotional and tone processing. Future NLG systems may be able to generate text with emotional colors and specific tones, making the generated text more vivid and rich.
- Domain expansion. NLG will be applied in more fields, such as education, law, scientific research, etc., providing the ability to automatically generate text for different fields.

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The Impact of Philosophical Theories on Landmark American Jurisprudence By Noah Barkan

Abstract

The 2022 United States Supreme Court decision for *Dobbs v. Jackson Women's Health Organization* overturned years of historical precedent established by *Roe v. Wade,* sparking protest, heated debate, and civic engagement. This review of *Dobbs* and *Roe* does not state opinions on the matter of abortion; instead, it explores the majority decision in each case to understand the relationship between law and morality further. By examining the two different conclusions in *Roe* and *Dobbs* through Aristotelian, Kantian, and libertarian philosophical lenses, this review demonstrates how nearly five centuries of philosophical thought have influenced the cases' rationales. Kantian theory limits the government's choice in moral decision-making and leaves it up to one's chosen community, aligning with the majority decision reached in *Roe*. In contrast, Aristotelian theory submits that it is the government's responsibility to create a virtuous society, aligning with the majority decision reached in *Dobbs*.

Introduction

Every year, as the Supreme Court of the United States rolls out its case decisions, debate surrounds the question of whether the court has arrived at the "right" decision. The unspoken assertion is that Americans share an understanding of what is "right" and the government's role in upholding those values. By looking through the lens of philosophy, however, this assertion fails to recognize the vast diaspora of views on the relationship between law and morality. This lens of philosophy provides a valuable tool to understand American jurisprudence by examining differing understandings of the relationship between law and morality. In a 2021 paper published in St. Andrews Law Review, author Michael Elliot employed this same lens to review historical legislative cases in the United Kingdom over time by considering the justices' philosophical beliefs about the regulation of morals through the government. Elliot approached *R v. Brown,* a landmark British case through the views of Nozick, Kant, and Aristotle and their subsequent theories, with Nozick and Aristotle providing the extreme polar opposite views and Kant providing the middle ground. Elliot's approach using all three views, thus spanning all the main perspectives on law and morality, can be applied to today's United States Supreme Court cases.

Dobbs v. Jackson overturned nearly half a century of the historical precedent set by *Roe v. Wade*. Both historic cases' majority decision's legal interpretation was applauded and critiqued en masse from many different perspectives, angles, and lenses. Elliot's philosophical lens provides another means of comparison based on the majority's differing beliefs on the intersection of law and morality.

Aristotelian

Credited as one of the first philosophical agents and famous in the 4th century BCE, Aristotle's theories are agent-centered, focusing on an individual's actions promoting society.

With regard to law and society, the Aristotelian theory views law and morality as inextricably intertwined. Aristotle suggests that individuals can create a virtuous society by acting with strong moral integrity.

Aristotelian philosophy defines moral integrity as appropriate emotional responses to situations and actions in accordance with those responses. Aristotle suggests, "We become just by doing just acts, moderate by doing moderate acts, brave by doing brave acts" (Aristotle, 1999, p. 73). The theory further states that acting in a certain way can generate "correct" emotions through which one can change and ultimately host moral integrity. Aristotelian theory follows that laws should enforce actions upon society that are capable of stimulating an emotional response that will lead to a virtuous population. Rather than examining multiple understandings of what is morally correct, Aristotelian theory establishes one core value set. The government's purpose is to establish what is ethically correct and debate how best to achieve those values. In his doctoral dissertation on Aristotelian ethical-political thought, Darren Weirnick states Aristotle believed "the political community aims at the most authoritative of all human goods" (Weirnick, 1998), revealing the assumption that the government works to achieve human well-being on a moral plane. Aristotelian theory conflates law and moral law. Individual choice is only defined as a decision about whether to follow the law rather than decide how to act with virtue. Aristotle states, "(one) must choose the acts, and choose them for their own sakes" (Aristotle, 1999), revealing that it is the Kantian belief that people must follow laws not due to aversion of consequences but rather because they lead to means of virtue and morality.

Libertarian

The libertarian model offers a countervailing understanding of the interplay of ethics and law. At its core, libertarian philosophy states the government's sole job is to protect fundamental rights of citizens and nothing more. While the Aristotelian view of the interdependence of law and morality stems mainly from Aristotle's writing, the libertarian model pulls from the work of numerous philosophers. Notable philosophers include Robert Nozick, Adam Smith, and John Locke, among others.

Locke's Natural Law claimed life, liberty, and the pursuit of happiness were unalienable rights to be afforded to all. Lock's Law served as the basis for many following libertarian philosophies.

Preceding Locke, Smith claimed the only rules worthy of judicial imposition are those for life, property, and civil rights protection in that order. He further espoused a libertarian approach to governing, recognizing that "[Laws that] call loudest for vengeance and punishment are the laws which guard the life and person of our neighbor; the next are those which guard his property and possessions; and last of all come those which guard what are called his personal rights, or what is due to him from the promises of others" (Smith, 2006[1790], p. 76)

Nearly two centuries after Smith, Nozick furthered his claims about libertarian governance, claiming that the government's implementation of morally based policies would intrude on citizens' liberties. Nozick finds that the government's role in society is not to enforce

virtuous behavior but to do the bare minimum to protect individuals' unalienable rights (Duignan, 2022).

Nozick went on to claim that the basis of society is self-ownership or the ability of citizens to make their own decisions over what is moral (van der Vossen, 2019). Later, libertarian philosopher Eric Mack builds on Nozick's self-ownership, claiming individual spheres of autonomy operate in isolation from societal freedom, each encompassing different things. Mack believes certain aspects of property are inherently individual while others are communal (van der Vossen, 2019). In libertarianism, the spheres of moral and legal rules are separate. One's idea of morality is strictly theirs to follow and should not affect widespread policies.

Kantian

Kantian theory offers a middle ground between the Aristotelian and Libertarian theories. While Kantian theory, like Aristotelian, recognizes that law is not amoral and, in many cases, overlaps with morality, it finds morality and law happen in different spheres of existence. One does not directly impact the other: following the law does not directly correlate to virtue or moral integrity, and not all moral or virtuous acts need to be legal obligations (Fletcher, 1987). Like Libertarianism, Kantian thought limits the government's enforcement of morals on society.

Kant's belief in social and economic autonomy and independence correlates directly with Libertarian theory (van der Vossen, 2019). What sets Kantian theory apart from Libertarian theory is the Kantian belief that the government has the right to regulate community and society. Kant defines the law as a "set of conditions under which the choices of each person can be united with the choices of others under a universal law of freedom." (as cited in Suhrkamp ed. 1956) Philosopher George P. Fletcher explains Kant's balance between Libertarian-aligned ideals and community-based ones by noting, "Kant's moral theory is communitarian; and the legal theory, individualistic or liberal" (Fletcher 1987, p. 543). For Kant, individuals should make moral decisions based on communal values. However, as moral values and laws are on different planes, the law's job is to protect individual choice to act on collective values rather than enforce those values themselves.

Roe vs. Wade

Writing for the majority in *Roe*, Justice Blackmun's decision reveals a Kantian understanding of the application of morality to law. Blackmun establishes that his decision does not align with an Aristotileon theory of morals. He clearly defines that all regulation of abortion from the government must be "tailored to the recognized state interests" (Blackmun, 1973, p. 165). Blackmun's decision affirms that during the first trimester, a compelling state interest is not yet present; during an approximate second trimester, the health of the mother presents a possible interest and may warrant regulation, and that, by the period of time subsequent to viability, a compelling state interest is present in the potentiality of life (Blackmun 1973). Blackmun rules out the mere question of morality as a basis for state interest, demonstrating his belief that virtue or morality is not enough of a qualification for government involvement or regulation.

He further embraces this view in his review of history on the subject. In discussing one of the theories behind the historic criminalization of abortion in Texas, Blackmun recounts, "It has been argued occasionally that these laws were the product of a Victorian social concern to discourage illicit sexual conduct," a moral-based line of reasoning for which he responds that "appellants and *amici* contend, moreover, that this is not a proper state purpose at all" further demonstrating Blackmun's concurrence with the view that social norms and understandings of virtue should not be weighted as interests of the government nor a part of the role of a legislature (Blackmun, 1973, p. 148).

The majority is at direct odds with Aristotelian legal theory, which, as previously mentioned, claims it is a governmental responsibility to set a standard moral theory and enforce it to create virtuous citizens.

Blackmun goes on to demonstrate that his thinking does not quite align with libertarian thought. Blackmun does not outright ignore the moral constraints placed upon the decision for an abortion as a Libertarian-based individualistic philosophy might. Justice Blackmun lays out in his decision that the choice around abortion is in the hands of communities, not just individuals:

> There has always been strong support for the view that life does not begin until birth. This was
> the belief of the Stoics. It appears to be the predominant, though not the unanimous,
> attitude of the Jewish faith (Blackmun, 1973, p. 160)

Blackmun states that the decision surrounding abortion should be decided based on these communal values, often stemming from shared religious or philosophical beliefs. Blackmun does acknowledge communities that allow moral decisions to be made by individuals. However, Blackmun only acknowledges individualism within the context of communal acceptance. Blackmun goes on to assert that the view that life does not begin until birth "may be taken to represent also the position of a large segment of the Protestant community" and that those communities have "taken a formal position on the abortion issue have generally regarded abortion as a matter for the conscience of the individual and her family" (Blackmun, 1973, 160). Unlike a libertarian approach, Blackmun doesn't reinforce his argument by stating anyone should make their own individual moral decisions but rather that some shared communal moral codes allow for individualism, placing the responsibility of moral regulation on the community in a Kantian fashion.

In essence, Blackmun prohibits governments from enforcing a moral code but acknowledges a communal moral basis. Blackmun's ideology aligns with Kant's legal theory, which is individualistic, giving power to an individual's moral theory while acknowledging its influence by a broader community. It is important to note that Blackmun never states explicitly that these communal values *need* to influence an individual's decision around abortion. He instead merely nods to the existence and influence of communitarian values. Blackmun can't mandate communal moral values without contradicting individualistic legal enforcement. Instead, he merely states they exist.

Dobbs vs. Jackson Women's Health Organization

Unlike *Roe*, the majority of *Dobbs vs. Jackson Women's Health Organization* relied on Aristotelian legal theory. Alito centers his argument around the power of state governments to host the power. In a similar manner to *Roe*, Alito first establishes the bounds of the Supreme Court. In discussing the debate over unborn lives, Alito does not weigh in on this debate but explains that the decision would come down to "ordered liberty" or the balance of competing interests(in this case, the right to abortion versus the right of the unborn to be born).

He claims *Roe* and *Planned Parenthood vs. Casey* determine a balance between the two interests that should be in the hands of the public. Alito explains that, "In some States, voters may believe that the abortion right should be even more extensive than the right that *Roe* and *Casey* recognized. Voters in other States may wish to impose tight restrictions based on their belief that abortion destroys an 'unborn human being.'" The power Alito is returning to the state is similar to Blackmun's description of communal source for moral decisions. Alito argues leaving moral decision making to the state legislation allows for "women on both sides of the abortion issue to seek to affect the legislative process by influencing public opinion, lobbying legislators, voting, and running for office." *Dobbs* allows for creating one standard policy where the voting majority determines what Alito has already described as a moral issue, such as the quantity of rights afforded to the unborn. The *Dobbs* decision, in effect, results in an Aristotelian form of law where one overarching moral law is imposed on a large group of people by the government.

That being said, there is one outstanding difference between the process described by Aristotle, which may result in different outcomes depending on the beliefs of the voting majority, namely, it being democratic. Alito specifically recognizes this difference with weight in his decision: "It is noteworthy that the percentage of women who register to vote and cast ballots is consistently higher than the percentage of men who do so." However, the difference between Alito's decision and Aristotle's structure is merely one in the process by which the overarching moral policy is determined, not the final result. The *Dobbs* decision allows the voting majority to examine for the minority one single interpretation of "ordered liberty" by prioritizing either the rights to an abortion or the rights of the unborn. The effect of the *Dobbs* decision follows Aristotle's bare-bones theoretical legal philosophy in creating a single moral standard.

While Alito's relegation of abortion-related laws to states may resemble communal decision-making in a Kantian fashion, it is essential to note the differences between Kant's and Alito's visions. Kant's moral theory exists on a different plane than his legal theory. Alito's decision betrays the separation established by Kant by making communal values legally enforced, as happens when states vote for uniform policy. Therefore, enforcement by the government of a uniform moral decision more accurately follows Aristotelian thought. While Blackmun nods to voluntary communities and their influence on decision-making, Alito obeys mandatory state community guidelines by the government.

Post *Dobbs*

In the wake of the *Dobbs* decision in June of 2022, echoes of Kantian and libertarian philosophical thought undergird challenges to recent changes in state abortion laws.

These cases fall under competing traditions of philosophy on the role of morals in law. In early January of 2023, Planned Parenthood South Atlantic, Greenville Women's Clinic, Katherine Farris, M.D., and Terry Buffkin, M.D. filed a case to the South Carolina Supreme Court against the State of South Carolina. In Planned Parenthood South Atlantic v. State of South Carolina, the South Carolina Supreme Court sided with Planned Parenthood, recognizing that the "The Fetal Heartbeat and Protection from Abortion Act" violated the South Carolina Constitution (Supreme Court of South Carolina, 2023). The justices specifically cited Article I, Section 10 which states, "The right of the people to be secure in their persons, houses, papers, and effects against unreasonable searches and seizures and unreasonable invasions of privacy shall not be violated, and no warrants shall issue but upon probable cause..." (South Carolina - Sectoral Privacy Overview, 2022, para. 1). The court found that the ban on all abortions with the exception of cases of incest, rape, or physical harm to the mother violates women's right to privacy and would be considered an unnecessary invasion. Planned Parenthood South Atlantic v.

In Kentucky, a different lawsuit was filed against a similar act following *Dobbs* in which the court followed a slightly different line of reasoning. In *Sobel v Cameron*, however, the plaintiff bases its argument on the protection of constitutional religious freedom in the state and that the abortion ban(Revised Statutes KRS 311.710 et seq.) by the Kentucky state legislature infringed upon the Jewish faith and halakha, Jewish law that they claim does not define birth at conception. Though at this time, the court has not come to a final decision, the line of reasoning used by the plaintiff can be seen to tie back to the idea of communal morals and individualistic laws as they are demanding an open legal structure that allows communities such as their Jewish synagogue to act in alignment with their collective morals.

Conclusion

As demonstrated by the language used in *Roe's* and *Dobbs'* majority opinions, differing philosophical understandings of law and morality can frequently lead to contrasting case outcomes. Michael Elliot's "Should Morality Influence Justice?" provides three separate philosophical lenses through which case decisions can be examined. Those lenses offer a more nuanced understanding of *Roe* and *Dobbs*.

The work of Aristotle and his strict moral enforcement by law mirrors Alito's case majority in *Dobbs*, allowing for a democratic decision of one single moral philosophy to be enforced by the government. Kant's understanding of separate spheres of law and morality is reflected in *Roe* through Blackmun's recognition that, while individual choices may be informed by communal morals, the law should not enforce moral code.

These philosophical lenses renew an ancient influence to the way we debate, study and converse, modern cases of today.

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Automation and Ethics: A Narrative on Past and Current Societal Trends and the Ethical Queries that Follow Them By Ziv Zusman

Abstract

This article analyzes past and current societal trends regarding automation and its effects on society, especially in the field of ethics. It begins by explaining the history of automation over the last 200 years and addresses the causes behind these developments. Through examining sources from various historical points, this article attempts to give credence to arguments that span the course of this issue's history, such as various accounts of Fordism, H.G. Wells, and Taylorism. It argues that to ensure humanity remains in control of a process that attempts to alienate humans from itself, the ethical management of automation is paramount. This article plainly lays out both ethical questions regarding automation and the effects of those questions being ignored.

Introduction

On a global scale, automation is regarded as the future of mankind. Since the Enlightenment, society has been defined by ages of advancement. As such, humanity has always strived to reach a new age. As H. G. Wells wrote in his famous 1914 book *The World Set Free*, "The history of mankind is the history of the attainment of external power. Man is the tool-using fire-making animal" (Wells 1). The trajectory Wells outlined in his book has continued through the century since it was published. In today's age, the Information Age, we utilize information widely available to make informed decisions and rapidly change and recreate society as we know it. In that recreation, a trend has started to form. A trend of advancement at the cost of others, namely at the cost of workers being replaced by machines. While this does not sound like an issue, as advancement is the due course for humanity, stretched across the world, and compounded by the rapid shifts seen due to the readily available information in our world, it starts to develop into more significant and more deep-seated issues. As we continue to advance, an ethical question must be raised regarding the loss of readily available jobs due to automation and how the bridge between workers and machines can be crossed to enhance both. Ultimately, is it ethically justifiable for society to remove humans from the production process, and how can it be ensured that those who are no longer needed still have a place?

Past and Present Trends

The Industrial Revolution served as the impetus for the framework of life as we know it today. It took a world that relied on manual labor and created a world where society could advance and better allocate its resources. The significant innovations that drove the revolution were utilizing steam power and production mechanization. A perfect example of these innovations can be seen in Henry Ford's assembly line, wherein both the number of employees and the time needed for production were vastly decreased thanks to the help of technology. However, the revolution went far beyond what Henry Ford achieved. The revolution took an

agrarian society and turned it into an industrial one in less than a century. It led to the growth of urban centers, which increased manufactured goods, further strengthening the economy. Beyond Ford's work, the creation of railways and the utilization of steam engines revolutionized both travel and business, leading to shorter transport times and a more comprehensive range of customers.

These technological changes, in turn, led to vast social changes that affected the bedrock of society, namely the push for urbanization to curb unemployment. Essentially, factories were based in cities due to defined supply lines, and with many people losing their jobs on farms due to technological advances, they came to the cities to find work in the factories. This, in turn, led to the establishment of the working class as we know it today. However, that is not to say that the working conditions were comparable to those of today, as the working conditions in the factories of the Industrial Revolution were dangerous and often fatal. On the flip side, the appearance and growth of the working class led to further and greater class inequity, highlighted by the resplendent manoirs built during the latter half of the revolution by the wealthy in comparison to the living conditions of the average factory worker in the recently overpopulated areas of the city.

In addition to the aforementioned social impacts, the environmental effects of the Industrial Revolution cannot be under-sold. Rampant deforestation and pollution were the immediate effects, with few caring for the environment as theft pushed the boundaries of traditional manufacturing. There was no pollution regulation, nor was there any ethical quarrel regarding the workers' safety at the factory owners' expense. Additionally, the shift in population density from the countryside to cities led to a lack of labor available for agriculture, which led to difficulties in feeding the growing cities. These difficulties were mitigated by increasing the pricing of common foodstuffs and further technological advancements.

Much like the past Industrial Revolution, the current technological boom, specifically in automation and artificial intelligence, is a turning point in our society. Society is in the process of phasing out humans from menial labor. We are only at this point due to specific societal drivers, such as automation and digitalization. The effects of automation are felt in all levels of society, including the economy, society itself, and the environment. Much like the revolution of the past, the current goal for automation in industry is to cut down on the number of employees required to achieve a goal. Similar to the Industrial Revolution, certain pieces of technology have enabled factories to downsize their workforces in favor of machines taking on repetitive tasks with much greater efficiency than humans would be capable of.

In addition to the economic shift, the social effects of automation are evident in our everyday society. Whole fields of work are in the process of being replaced by machines, and as such, job markets are shifting, leading more people to take up positions that are far removed from the push to automize society. The general goal in the practice of automation is the eventual cost cut seen by paying a one-time lump sum for machinery and infrastructure rather than a salary for a whole staff of workers. Ignoring the ethical qualms arising from this practice, the general social shifts seen by implementing the practice are twofold. On the one hand, the practice

removes the need for specific low-skill and low-wage jobs, allowing companies to save and grow in other areas, which leads to economic growth. On the other hand, the practice also leaves many unemployed, which leads to a rise in death and political strain in a social setting. In addition to the aforementioned shift in the job market, the globe has become far more connected due to the implementation of automation within manufacturing, allowing for more devices to be made and, in turn, for the world to be better connected and more socially aware.

Ethics of Automation

The most significant effect of automation can be found in the world around us. By utilizing automation in industry to its fullest, humanity has drained our planet of much of its former splendor. In our rush to automize and gather the most resources the fastest, we still need to remember the very concepts we set out to achieve when we began the push to automation in industry. Automation was developed to help both the employer and the employee. However, environmental factors were not a primary consideration at the time of its creation. Ultimately, the question is whether or not humanity can fully understand the issues at hand and accurately react to the world in such a way that we both continue to advance while not destroying the social foundation we model ourselves on.

The ethical stance on automation is constantly evolving, wherein societal needs and social drivers push against each other to no end. The ethical question is simple: when does the drive to advance become a danger to society, and to what degree can we push that danger? Societies go through waves of advancement, with each crest resulting in a rapid advancement yet leaving whole economic sectors out of work. One example is the cotton gin, which severely reduced the number of people required to work on a farm. While that is great for the farm owner, it leaves the worker out of a job they would have needed for survival. Thanks to mitigating circumstances, many people who once lived on farms moved to cities to find work at factories, but not all found work, and those who did not were left by the wayside in preference to advancement.

In this ethical question, the workers are at the crux. To what point can humanity eliminate jobs before there are too few, and what can be done to ensure that jobs remain available to those who need them most? As aforementioned, society develops positions to fill them, and as such, it is much simpler to assume that there will always be a new branch of jobs to serve when we automate an industry. However, what can be said of the alternative, that is, what would happen if no new sector of jobs requires filling? In this case, unemployment rates would spike, and without significant government intervention, thousands, if not millions, of people would lose their sole income source. That is the true social danger of automation, the assumption of future innovation.

Ethics were not the chief concern during the industrial revolution. They served as a backmarker to a broad and diverse community. However, in today's world, such a rapid shift from human labor to machine labor is seen regularly, from factory workers to waiters and waitresses. In a world where nearly every job can and is being automatized, how can worker's rights be protected and secured? The Industrial Revolution and subsequent social changes are the

perfect example of a society where ethics are not considered before implementing something that changes society at its core. The difference between advancement in today's world and that of that time is that society now looks at every decision under many factors, ensuring that the livelihoods of thousands are not wholly sacrificed but that there are different avenues for people who lose their jobs to pursue.

Is there any natural way to know whether or not we as a society can rely on the trends of ages past? I think not; however, those trends can be recreated. While there will never again be a push to urbanize as there was during the revolution, to discount the notion that new jobs can be artificially created to support different industries is to say that we, humanity, have nowhere left to go, which is simply untrue. There will always be advancement because it is the core factor that drives humanity. However, the ethical question remains: to what extent can we advance tolerably before exposing ourselves to the moral dilemma we work tirelessly to avoid? Moreso, who is to say that those who lose their jobs to automation should do so gracefully and simply uproot their lives to switch to a different industry? The autonomous society that we have created does not account for humanity's growth and prosperity. As such, concessions must be made to create a world where humanity can flourish and society does not become solely dependent on the state for survival.

Conclusion

Ultimately, society as we know it will change. That is an immutable fact of life. However, sheltering workers and others negatively impacted by automation must stand at the forefront of social endeavors. Society is as strong as its weakest, and to do nothing as the weak are made weaker in deference to advancement is a stark shadow across the history of advancement. To that end, there must be a moment wherein we as a society deem whether or not the livelihoods and lives of workers who are losing their jobs to advancement are a conscionable cost for advancing our society. To that end, the ethical question can be stated: Is it ethically justifiable for society to prioritize economic gain over people's lives, and how can we ensure that those who lose their lives can receive retraining and job transitioning?

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Quantifying the Implementation of Ocean Nuclear Power Plants as a Method of Improving South Korea's Carbon Footprint Using the Environmental Performance Index By Soren Cabinte

Abstract

Throughout its 200,000 year history, the human race has faced many threats towards its existence. However, one of the most glaring threats humanity faces right now is climate change. Spurred on almost exclusively by emissions of carbon dioxide, climate change threatens to raise the global temperature to an extent that is uninhabitable for humans in the status quo[8]. Many different countries have discussed various strategies to resolve this issue[9]. However, we believe one is being underutilized: Ocean Nuclear Power Plants (ONPPs). Often dismissed for being too dangerous or too costly, nuclear power plants possess both near-carbon neutrality and low expenses[10]. In this paper, we make the case for ONPP implementation as a strategy of mitigating common drawbacks of nuclear power plants by attempting to analyze scenarios of ONPP implementation in South Korea.

Introduction

1.1 The Climate Crisis

On average, the sun sends the earth 342 watts of energy per meter square every second via electromagnetic radiation. Around 30% of this energy is reflected back to space via clouds, aerosols, and light-colored areas of Earth's surface, such as snow, ice and deserts. In order to balance the other 70% of radiation, the earth must radiate the same amount of energy back in the form of longwave radiation. To maintain this equilibrium, the earth's surface must maintain an average temperature of 57.2°F colder than the mean surface temperature. The presence of greenhouse gasses (GHGs) constitutes this temperature disparity. In a phenomenon known as the the natural greenhouse effect, greenhouse gasses such as water vapor and carbon dioxide (CO_2) act as a blanket for the longwave radiation that the Earth's surface emits, trapping heat in the atmosphere[11].

But recently, human activities, primarily energy extraction, have led to the increase of a specific GHG: carbon dioxide. The atmospheric presence of CO_2 has increased by 50% since the

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[8] Levy, Barry S., and Jonathan A. Patz. "Climate change, human rights, and Social Justice." *Annals of Global Health*, vol. 81, no. 3, 2015, pp. 310–311, https://doi.org/10.1016/j.aogh.2015.08.008.

[9] Scott, Daniel, et al. "A report on the Paris Climate Change Agreement and its implications for tourism: Why we will always have Paris." *Journal of Sustainable Tourism*, vol. 24, no. 7, 2016, pp. 933–941, https://doi.org/10.1080/09669582.2016.1187623.

[10] "Nuclear energy–any solution for sustainability and climate protection?" *Energy Policy*, vol. 48, 2012, pp. 56–56, https://doi.org/10.1016/j.enpol.2012.04.047.

[11] Le Treut, Hervé, et al. "Contribution of Working Group I to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change." *Intergovernmental Panel on Climate Change Fourth Assessment Report,* 2007, https://www.ipcc.ch/site/assets/uploads/2018/03/ar4-wg1-chapter1.pdf.

beginning of the industrial revolution[12]. The cause of this unnatural increase of natural material in the atmosphere is attributed primarily to fossil fuels[13]. In order to indulge the energy needs of 8 billion people, society has developed a reliance on fossil fuels that has resulted in a massive proliferation of atmospheric CO_2 emissions.Although renewable energy sources are able to outskirt this unfortunate side effect, economic factors preclude the mass implementation of these[14].

1.2 The Nuclear Solution

Another proposed alternative to fossil fuels is nuclear energy. Far less expensive than most renewable sources of energy and completely carbon-free, nuclear power plants are a powerful resource for energy production. In South Korea, the levelized cost of energy (LCOE) for nuclear production ranged between 28.63 and 51.63 USD/MWh[15]. This is a significant improvement in energy cost when compared to other clean energy sources such as solar and wind, generating approximately triple the amount of energy for the same cost[16]. However, it is not that simple: nuclear energy does not come without its drawbacks.

Nuclear waste is very challenging and expensive to get rid of, and reactor meltdowns can be catastrophic[17]. The Chernobyl nuclear disaster had global implications and remained a radioactive site for decades[18]. Nuclear reactors also require massive amounts of water to use as coolants, with some nuclear reactors requiring up to 750,000 gallons per minute[19].

Additionally, the perception of the probability of reactor meltdown keeps public approval disapproving, increasing the difficulty of implementing nuclear power plants. Events like the 2011 Fukushima nuclear meltdown spread feelings of disapproval to nuclear energy in South Korea, such that negative emotions towards nuclear energy sharply increased from 5.5% to 22.5%[20].

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[12] Lindsey, Rebecca. "Climate Change: Atmospheric Carbon Dioxide." Edited by Ed Dlugokencky, *NOAA Climate.Gov*, 12 May 2023, www.climate.gov/news-features/understanding-climate/climate-change-atmospheric-carbon-dioxide.

[13] Covert, Thomas, et al. "Will we ever stop using fossil fuels?" *Journal of Economic Perspectives*, vol. 30, no. 1, 2016, pp. 118–118, https://doi.org/10.1257/jep.30.1.117.

[14] Seetharaman, et al. "Breaking barriers in deployment of renewable energy." *Heliyon*, vol. 5, no. 1, 2019, https://doi.org/10.1016/j.heliyon.2019.e01166.

[15] Ha, Vara. "Nuclear Power Plant Policy Comparison between the U.S. and Republic of Korea." *International Development, Community and Environment,* https://commons.clarku.edu/cgi/viewcontent.cgi?referer=&httpsredir=1&article=1095&context=idce_masters_papers.

[16] Maia, Sofia, et al. "South Korea." *Climatescope 2022*, 2022, www.global-climatescope.org/markets/kr/.

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Many options have been proposed to counter these negative side effects of nuclear energy. One possible method of mitigating these issues is the construction of Ocean Nuclear Power Plants (ONPPs).

1.3 The ONPP Concept

The primary benefits of ONPPs are as follows:

- By building power plants away from populated urban centers, ONPPs mitigate the potential damage of a reactor meltdown towards the general population. Additionally, they mitigate the "not in my backyard" mentality that prevents many voters from supporting nuclear energy.
- The core of the nuclear reactor would use the ocean as an infinite heat sink without relying on pumps driven by electricity, which are prone to error
- The ocean provides a virtually infinite supply of water for the plant moderator, eliminating the usage of irrigation or the action of pulling water from river ecosystems.
- An obsolete ONPP could be cleanly hauled away by a boat[21]

1.4 Russia and China

So far, many different countries have reached different levels of proposition and testing for ONPPs. Currently, China has begun construction for floating nuclear power plants, which are now being tested in the Bohai sea. It is possible that they will have up to three operational nuclear power plants in the South China Sea by 2025[22]. Also investing in floating-type ONPPs is Russia, whose large nature gives it massive coastlines with low human populations in need of energy. In 2010, the 144x30m Akademic Lomonosov was launched, equipped with a nuclear reactor with an electrical energy capacity of 35 MWe[23].

It is worth mentioning, however, that placing radioactive material in the ocean comes with some uncertainties. ONPPs are increasingly threatened by natural hazards such as tsunamis, marine collisions, and storms. Physical threat is also an issue, as their isolation from the mainland makes them a target for direct attack, armed intrusion, or sabotage. Additionally, reliability also becomes a minor issue, as floating ONPPs need to satisfy higher acceleration standards, and the working environment is likely more stressful with limited human resources.

To mitigate these issues, countries hold their ONPP prototypes to a higher standard of safety than their land-based counterparts. The Akademik Lomonosov has met demanding safety standards with international recognition. It maintains stability by partitioning the vessel into waterproof compartments that are sealed after the flooding of two adjacent compartments,

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[21] Lee, Kang-Heon, et al. "Recent advances in Ocean Nuclear Power Plants." *Energies*, vol. 8, no. 10, 2015, pp. 11470–11492, https://doi.org/10.3390/en81011470.
[22] Jha, Pankaj. "China Floating Nuclear Power Plants in South China Sea." *Modern Diplomacy*, 6 Apr. 2023, moderndiplomacy.eu/2023/04/04/china-floating-nuclear-power-plants-in-south-china-sea/.
[23] Lee, Kang-Heon, et al. "Recent advances in Ocean Nuclear Power Plants." *Energies*, vol. 8, no. 10, 2015, pp. 11470–11492, https://doi.org/10.3390/en81011470.

minimizing hydrostatic tilt to a maximum of three degrees. Its central placement of the nuclear reactor assures it protection in the instance of physical contact[24].

1.4 USA

In addition to Russia and China, another great power competitor, the United States has also proposed a prototype for an ONPP. A research group at MIT offered schematics for an offshore floating nuclear plant (OFNP). The OFNP would be placed on a spar-type floating platform with catenary mooring, placed 10-20 km from the shore in waters approximately 100 meters deep. The OFNP would have a low center of gravity, which would accomplish three things:
  - Elimination of the transmission of seismic loads from the ocean floor, as well as movement from tsunamis, waves, and wind
  - Allowing the nuclear reactor to be located below the waterline, enhancing physical protection from possible collisions
  - Providing access to the ultimate heat sink: the ocean

Also worth mentioning is the Submerged-Type ONPP proposed by DCNS in France named Flexblue. This reactor uses the small pressurized water reactor technology similar to submarines in order to maintain composure while being submerged on the sea floor for extended periods of time. Undersea cables would be used to bring electricity to customers, not unlike that of offshore wind turbines[25].

1.5 South Korea

Another smaller country has also introduced preliminary designs for ONPPs: South Korea, a country with a poor environmental reputation. Korean institutions have financed over 50 billion USD in coal power investment over the past decade, creating an unfortunate reliance on coal—it provides over 40% of South Korea's energy[26]. As a result, South Korea has received international criticism for their lack of ambitious GHG emission reduction programs. In the Paris Climate Agreement in 2015, South Korea released their official nationally determined contribution (NDC) for climate change, vowing to reduce GHG emissions by 37% by 2030. Amidst backlash from other nations, South Korea officially updated their initial NDC in 2021, announcing their new goal of a reduction to 149.9 million tons of CO_2 in the energy sector, a sharp increase in ambition since their last NDC update in 2020 which proposed a reduction of 237 million tons of energy production-related CO_2 emissions. However, this is not enough, as

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[24] Lee, Kang-Heon, et al. "Recent advances in Ocean Nuclear Power Plants." *Energies*, vol. 8, no. 10, 2015, pp. 11470–11492, https://doi.org/10.3390/en81011470.
[25] Lee, Kang-Heon, et al. "Recent advances in Ocean Nuclear Power Plants." *Energies*, vol. 8, no. 10, 2015, pp. 11470–11492, https://doi.org/10.3390/en81011470.
[26] Myllyvirta, Lauri, et al. "HIA South Korea April 2021 - Centre for Research on Energy and Clean Air." *The Health and Economic Cost of Coal Dependence in South Korea's Power Mix*, Center for Research on Energy and Clean Air, Apr. 2021, www.energyandcleanair.org/wp/wp-content/uploads/2021/04/HIA_South-Korea_April-2021.pdf.

additional policy measures and advanced policy measures will most likely be needed to further reduce CO2 emissions[27].

1.6 The GBS-ONPP

      This section is primarily a literature review of *Recent Advances in Ocean Nuclear Power Plants*. Published in 2015, this paper summarizes the South Korean Gravity-Based Structure Ocean Nuclear Power Plant.

      Scientists at the Korean Advanced Institute of Science and Technology propose one solution: the Gravity-Based Structure Ocean Nuclear Power Plant (GBS-type ONPP). The key distinctive feature of a GBS-type ONPP is the use of a gravity-based structure as both a container and a support structure for the nuclear reactor. Both the GBS as well as the nuclear reactor are assembled in a dry dock, and are then shipped out to sea. Then, the modules are placed down on the seabed via a ballasting system, and are then connected using steel and cement. There are four basic steps towards GBS-type ONPP implementation:

1) A GBS is constructed in a dry dock and the nuclear power plant is assembled
2) The nuclear power plants are mounted on the GBS
3) The GBS-type ONPP is floated and towed towards the installation site. Then the structure is weighted down until the structure reaches the seabed.
4) After system-testing procedures are implemented, the GBS-ONPP is ready to supply electricity to land

The most current GBS-type ONPP certified by the Korean nuclear regulatory body is the large-scale ONPP model using the Advanced Power Reactor 1400 MWe (APR1400), developed by the Korean Hydro and Nuclear Power company (KHNP).

      The unique concrete structure of the GBS-type ONPP gives it unique physical protection against physical attacks and armed intrusion. In addition to its durable and collision-resistant structure, it also comes with its fair share of safety procedures and modules. The Emergency Passive Containment Cooling System (EPCCS) and the Emergency Passive Reactor-Vessel Cooling System (EPRVCS) have both been put forward to maintain the safety of the nuclear module. The purpose of these systems are to cool the containment to prevent structural failure of the containment system, and cool the reactor vessel if the EPCCS can not prevent a meltdown, respectively[28].

1.7 Goal of the paper

      In this paper, I make the case for GBS-type ONPP implementation as a method of reducing South Korea's carbon footprint while maintaining a low threshold of environmental backlash. I will calculate to what extent a GBS-ONPP with an APR1400 reactor can remove

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[27] Jeong, Woo-Cheol, et al. "Scenario analysis of the GHG emissions in the electricity sector through 2030 in South Korea considering updated NDC." *Energies*, vol. 15, no. 9, 2022, p. 3310, https://doi.org/10.3390/en15093310.

[28] Lee, Kang-Heon, et al. "Recent advances in Ocean Nuclear Power Plants." *Energies*, vol. 8, no. 10, 2015, pp. 11470–11492, https://doi.org/10.3390/en81011470.

reliance on coal and other carbon emissions, and discuss how many ONPPs will be needed to mitigate energy-based carbon emissions. Next, I will quantify different scenarios of environmental harm that can arise from ONPP implementation. Finally, I will attempt to quantify my findings by using a simplified version of the Yale Environmental Performance Index, a globally used metric for quantifying the environmental friendliness of countries.

Methods and Data

In the writing of this paper, we pulled open-source data from various sources such as the International Agency and the Korean Advanced Institute of Science and Technology to analyze. Using dimensional analysis and mathematical equations, we calculated two scenarios of ONPP implementation: one in which we are able to remove South Korean reliance on coal, and one in which we remove South Korean reliance on fossil fuels altogether.

Next, we took data from the Yale Environmental Performance Index (EPI) and used it to create our own EPI. The 2022 EPI calculus is both confusing and not completely open-source, so we used the data we had to create a simplified version of it. Although not the same, we believe it to be a sufficient assessor of net environmental benefit.

$$EPI_{new} = C + CC_w\Big(CC_n + CC_m \cdot \big(1 - 0.01CC_n\big)\Big) + GHGP_w\Big(GHGP_n + GHGP_m \cdot \big(1 - 0.01GHGP_n\big)\Big)$$

Equation 1: Simplified EPI equation.

EPI_{new}	New simplified EPI calculus
C	The constant of South Korea's current EPI ranking, minus its score from the climate change and greenhouse gas reductions.
CC_w	The weight, out of 1 of climate change in the EPI pie chart.
CC_n	South Korea's current climate change score
CC_m	The percent reduction of climate change that ONPP implementation creates
$GHGP_w$	The weight, out of 1 of projected greenhouse gas emissions in the EPI pie chart.
GHG_n	South Korea's current greenhouse gas emissions score
GHG_m	The percent reduction of greenhouse gas

	emissions that ONPP implementation creates

Table 1: EPI variables.

We recognize that the projected greenhouse gas emissions of South Korea in 2050 is not the same of current greenhouse gas emissions. However, although South Korea has a plan to achieve GHG-neutrality in 2050, its EPI score is a 1.70 out of 100. This discrepancy is most likely equated to the lack of feasibility of South Korea's plan of action. However, we argue that there is a direct relationship between South Korea's current greenhouse gas emissions and its future emissions. The more we can do now to mitigate greenhouse gasses, the likelier GHG-neutrality will be in 2050. Therefore, we feel that current GHG-emissions are a sufficient metric of likelihood for GHG-neutrality in 2050.

We also understand that this equation does not take into account the possible pitfalls of ONPPs. This is because for the most part, we believe that the day-to-day pitfalls of ONPPs are relatively negligible. In the case of a nuclear meltdown, a different equation will most likely need to be used, a scenario whose probability we will discuss in the results section of this paper. In the instance of a nuclear meltdown, the EPI equation would need to be modified with an addendum.

Results

As stated before, the nuclear reactor most likely to be used in tandem with a GBS-ONPP is the APR1400 (Advanced Power Reactor 1400 MWe) reactor. The APR1400 has an average of 1455 MWe, with a minimum availability rate of 90% and an eighteen-month rejuvenation period every sixty years.

Thermal Energy Production	3983.00 MWt
Usable (Electric) Energy Production	1455.00 MWe
Percent Availability	90 percent
Rejuvenation Period	18 months every 60 years

Table 2: Relevant information on the APR1400 reactor[29].

Using this information, we used dimensional analysis to convert figure two into a working average energy output of the APR1400 reactor.

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[29] "Status Report 83 - Advanced Power Reactor 1400 MWe (APR1400)." *Advanced Power Reactor 1400 MWe (APR1400)*, International Atomic Energy Agency, aris.iaea.org/PDF/APR1400.pdf. Accessed Aug. 2023.

$$\frac{1400 \; MWe}{APR1400} \cdot \frac{1000000 \; \text{watts}}{1 \; \text{watt}} \cdot \frac{1 \; \text{joule}/\text{second}}{1 \; \text{watt}} = 1.455 \; x \; 10^9 \; joules/second$$

$$\frac{1.455 \; x \; 10^9 \; joules}{1 \; second} \cdot \frac{31536000 \; seconds}{1 \; year} = 4.588488 \; x \; 10^{16} \; joules/year$$

$$\frac{4.588488 \; x \; 10^{16} \; joules/year}{1} \cdot \frac{90\% \; availability}{100\%} \cdot \frac{720 \; months \; (60 \; years) \; not \; rejuevenating}{738 \; months} = 4.028916 \; x \; 10^{16} \; avg \; joules/year$$

Equation 2: Avg energy output of the APR1400 reactor.

Next, using open-source information, we calculated the annual energy output of the most impactful carbon-emitting energy sources. Then, we used our findings from the APR1400 reactor to quantify how many GBS-ONPPs were required to remove South Korean reliance on these energy sources.

Fig. 1 Annual energy production per source in South Korea in 2021[30].

$$\frac{208112 \; GWh \; in \; coal}{1 \; year} \cdot \frac{1000000 \; MWh}{1 \; GWh} \cdot \frac{3.6 \; x \; 10^9 \; joules}{1 \; MWh} = 7.492032 \; x \; 10^{17} \; joules/year \; in \; coal \; energy$$

$$\frac{7.492032 \; x \; 10^{17} \; joules/year \; in \; coal \; energy}{4.028916 \; x \; 10^{16} \; joules/year \; per \; ONPP} = 18.59 \; GBS - ONPPs \; to \; remove \; reliance \; on \; coal \; energy$$

$$\frac{403820 \; GWh \; in \; coal}{1 \; year} \cdot \frac{1000000 \; MWh}{1 \; GWh} \cdot \frac{3.6 \; x \; 10^9 \; joules}{1 \; MWh} = 1.453752 \; x \; 10^{18} \; joules/year \; in \; fossil \; fuel \; energy$$

$$\frac{1.453752 \; x \; 10^{18} \; joules/year \; in \; fossil \; fuel \; energy}{4.028916 \; x \; 10^{16} \; joules/year \; per \; ONPP} = 36.082953 \; ONPPs \; to \; remove \; reliance \; on \; fossil \; fuels$$

Fig. 2 Amount of ONPPs to meet energy production levels of other energy sources

[30] Iea. "Korea Electricity Security Policy – Analysis." *Korea Electricity Security Policy*, International Energy Agency, Mar. 2023, www.iea.org/articles/korea-electricity-security-policy.

Lastly, we calculated the total percent reduction in South Korean carbon emissions from each scenario and used the EPI_{new} formula to calculate the new EPI index rating for South Korea.

Fig. 3 Categories and weight of the Environmental Performance Index[31].

Energy Source	CO$_2$ productions (in Megatons)	Percentage of Predicted GHG emissions in 2050 (in percentage)	Percentage of South Korea Carbon Emissions
Coal	283.91	22.25	46.08
Gas	126.79	9.953	20.58
Oil	171.48	13.44	27.83
All	582.18	45.64	94.49

Table 3: South Korea energy and GHG statistics[32].

$EPI_{old} = 46.90$

Coal Scenario: 18.59 (19) GBS-ONPPs:

[31] Wolf, M.J. et al. "2022 Environmental Performance Index." *New Haven, CT: Yale Center for Environmental Law & Policy*, 2022, epi.yale.edu.

[32] Ritchie, Hannah, et al. "South Korea: CO2 Country Profile." *Our World in Data*, 11 May 2020, ourworldindata.org/co2/country/south-korea.

$$EPInew = 40.86 + 0.138(42.00 + 46.08 \cdot (1 - 0.42)) + 0.138(1.70 + 22.25 \cdot (1 - 0.017)) = 53.59$$

Fossil Fuel Scenario: 36.08 (37) GBS-ONPPs:

$$EPInew = 40.86 + 0.138(42.00 + 94.49 \cdot (1 - 0.42)) + 0.138(1.70 + 45.64 \cdot (1 - 0.017)) = 60.64$$

Fig. 3 EPI scenario results.

Discussion

Although South Korea is a very small country whose carbon emissions only equate to a fraction of global warming, its infrastructure is one of the hardest to modify to meet increasingly rigorous climate criteria. However, using South Korea as a model of ONPP implementation to prevent carbon emissions could prove the feasibility of ONPPs for the rest of the world.

Conclusion

By reviewing and creating statistics of relevant figures related to ONPPs and carbon emissions, we hope to contribute to the foundation of larger ONPP discussion and execution. We acknowledge that this paper does not engage with major economic and political conclusions, but we do argue that there is a direct function between the number of ONPPs and environmental benefit. Currently, climate change is the greatest threat to human existence, and cessation is of paramount importance.

If South Korea can find the economic allocation to make a concrete ONPP effort, they could serve as a stepping stone to a full-frontal assault by the human race on the presence of unnatural carbon dioxide in the atmosphere. We recognize that this paper does not include cutting-edge analysis. However, we hope that it will spark further discussion into methods of paving the economic and political path towards ONPP policy action.

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        www.energyandcleanair.org/wp/wp-content/uploads/2021/04/HIA_South-Korea_April-2
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Is India Tapping into its Potential to Become a Global Leader? By Kavya Gulati

Abstract

This paper focuses on the impact of India's strategic partnerships with various countries and regions across the globe on its global standing. To gain insights for this purpose, I have conducted a thorough literature review by referring to the works of other international relations scholars as well as state documents. Additionally, I have examined the summary of India's relationship with different regions in terms of trade and economic cooperation, including SAARC, ASEAN, the Middle East, Africa, Europe, America, and Latin America. Moreover, I have explored India's internal dynamics by analyzing population and demographic changes to gauge its development level. My argument is that India must broaden its focus beyond its economic capabilities and prioritize the education and anti-discrimination efforts aimed at the youth demographic, in order to attain the status of a global powerhouse. In terms of India becoming a world power, I have found that India needs to move beyond its economic capabilities and preference for bilateralism to engage on a multilateral level with regions and show initiative to take leadership to tackle global problems.

Introduction

There has been a transformation in India's status and material capabilities in the global order. In 2022, India became the world's fifth largest economy, having replaced the United Kingdom, and is expected to become the third largest economy by 2027, as projected by Morgan Stanley. India is aspiring for permanent membership in the UN Security Council. It has formed the Asian Infrastructure Investment Bank (AIIB) and the BRICS Contingent Reserve Arrangement (CRA) alongside other emerging economies. As part of its G20 presidency, India hosted a virtual 'Voice of the Global South' summit, hosting 120 countries to gather their priorities and understand how India can support these countries with its presidency. India is attempting to become a legitimate economic and political global power by expanding its influence in different regions through economic assistance, soft power, and political influence.

This paper discusses India's leadership capabilities and potential to become a world leader by exploring how it engages with the world's developing regions including Asia, Africa, and Latin America. It questions whether India is capable of increasing its power over and bettering its relationships with nations in order to fulfil its ambition. To this end, the paper examines India's internal capacity to become a global leader and the extent to which India's political and economic climate enable this global reach.

Figure 1: Top 10 countries by GDP, current prices in US$ billions

India's relationship within South Asian Association for Regional Cooperation (SAARC)

Strengths and Opportunities

Covering the countries of Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, and Sri Lanka, the South Asian Association for Regional Cooperation (SAARC) is an intergovernmental organisation for the region of South Asia. Founded in 1985, the core objective of SAARC is to increase regional cooperation amongst the South Asian nations in order to uplift them socially and economically. While SAARC has not been successful in the past decade, India maintains strong bilateral relations with most of the SAARC countries.

India has been committed to friendly relations with SAARC countries as part of its "Neighbourhood First" policy. India has entered into the Bangladesh-Bhutan-India-Nepal (BBIN) grouping and the Memorandum of Understanding (MoU) with its fellow SAARC countries. The BBIN group targets energy security and has allowed India to discuss connectivity issues with three SAARC countries and without Pakistan. These agreements ensure that there are multilateral relations between SAARC countries and a free flow of energy and goods.

India has strengthened its ties with SAARC countries bilaterally through economic and humanitarian assistance. Out if India's 2022-23 foreign aid, 37.5% was allocated to Bhutan, 12.5% to Nepal, 10% to Myanmar, and 5% to Bangladesh.[33] When a debt crisis hit Sri Lanka in 2022, India was the first country to provide aid. Totalling USD 3.8 billion[34], this aid took the form of lines of credit, loans, and grants. Similarly, India has also provided economic support to

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[33] "Development Partnership", Ministry of External Affairs, Government of India, August 2023, https://www.meadashboard.gov.in/indicators/92

[34] Ganeshan Wignaraja, "India as an emerging aid donor to debt crisis hit Sri Lanka", ODI, 27 July, 2022, https://odi.org/en/insights/india-as-an-emerging-aid-donor-to-debt-crisis-hit-sri-lanka/

Maldives, where India funded the Greater Male connectivity project, a project aiming to build infrastructure to link islands in the Maldives, through USD 400 million in lines of credit and USD 100 million in grants.[35]

India has the opportunity to better its relationship with SAARC through strengthening the South Asian Free Trade Agreement (SAFTA). Trading within South Asia proves difficult for SAARC countries due to numerous barriers, including para-tariffs, inadequate infrastructure, and abnormally high cost of trading. India can encourage reforms to SAFTA by supporting regional supply chains and lowering trade barriers, promoting more intra-regional trade in South Asia.

Weaknesses and Threats

Bhasin (2008) discusses India's hegemony in South Asia and examines India's leadership capabilities in the region.[36] The analysis concludes that India is threatened by the other SAARC countries' perception of India as the hegemon. Due to India being the largest member of SAARC and dominating the organisation economically and politically, India has been accused of meddling in domestic politics in SAARC countries to further its own interests, which has caused growing anti-India sentiments in countries such as Bangladesh and Nepal. Due to this, SAARC member states are increasingly turning to China as a partner to counter India's growing presence in the region. Aside from India and Bhutan, six of the eight SAARC countries have signed an MoU with China on China's Belt and Road Initiative. China is an observer state in SAARC, with its membership being continuously objected by India. China has presented itself as a stronger economic partner than India to SAARC and has increased military cooperation with SAARC countries. India's lack of leadership within SAARC is presenting an opportunity for China to replace India and reduce India's power in the region.

Bhasin (2008) also discusses India's preference for bilateralism while overlooking collective strategies which strengthens India's relations with SAARC members bilaterally, but not multilaterally. India rarely champions the group interest at international forums. South Asia is one of the most vulnerable regions to climate change, yet India has not been seen to be vocal about the need for climate finance for South Asian countries. Furthermore, India's own engagement in the region tends to be based on domestic interests. India has consistently dominated India's foreign aid budget as the development of Bhutan's extensive hydropower potential allows India to accessing cheap electricity to meet the mounting energy needs of its growing economy. Clearly, India's unwillingness to take leadership in the region is a key weakness for its cooperation within SAARC as a group. Finally, the economic disparities between India and the other countries in SAARC make it difficult for India to establish a

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[35] "US$ 500 million grant shared by India for the Greater Male Connectivity project in favour of infrastructure development", Ministry of External Affairs, Government of India, November 9, 2020, https://indbiz.gov.in/us-500-million-grant-shared-by-india-for-the-greater-male-connectivity-project-in-favour-of-infrastructure-development/#:~:text=Later%20in%20august%202020%2C%20India,400%20million%20from%20New%20Delhi

[36] Madhavi Bhasin, "India's Role in South Asia: Perceived Hegemony or Reluctant Leadership?", Indian Foreign Affairs Journal 3, no. 4 (2008): 72-88, http://www.jstor.org/stable/45340757

two-way trade and investment relationship. The current intra-regional trade between SAARC countries remains stagnant at 5%, which is relatively lower than both ASEAN, 35%, and the EU, 60%.[37]

Another threat to India's relationship with SAARC is India-Pakistan tensions as examined in Shishir and Sakib (2022)[38]. The paper notes that India's unwillingness to cooperate at a multilateral level when Pakistan is involved has damaged India's relations with other SAARC countries. 14 SAARC annual summits have been postponed, with the majority being due to hostilities between India and Pakistan. The dispute over Kashmir has fuelled disagreements between the two countries that have curbed the development of SAARC, such as India's accusations against Pakistan of backing out of SAFTA and Pakistan's obstruction of agreements proposed by India at SAARC summits. The rivalry between India and Pakistan has been intensifying and has expanded to more than bilateral tensions by preventing cooperation at a multilateral level between SAARC countries. For India to maintain its role as a regional power and build its capacity to become a global power, it needs to resolve its dispute with Pakistan and not allow it to interfere with India's cooperation with other countries.

Table 1: Summary of SWOT analysis of India's relationship with SAARC

Strengths	Weaknesses
Multilateral partnerships Economic and humanitarian assistance Historical bond and cultural affinity	Preference for bilateralism
Opportunities	Threats
Reducing trade barriers between SAARC countries Geographical cohesiveness	India-Pakistan hostilities China's influence

India's partnership with ASEAN–Strengths and Opportunities

India has had a relationship with the Association of Southeast Asian Nations (ASEAN) since Indian independence and as noted in Ganapathi (2019)[39], India became a Sectoral Dialogue partner of ASEAN in 1992 and a Full Dialogue partner in 1996. In order to channel its "Look-East Policy", India has been involved in ASEAN projects and agreements since its partnership with ASEAN, which include the ASEAN Regional Forum (ARF), the East Asia Summit, and the Expanded ASEAN Maritime Force. Notably, as pointed out by Jha (2008), India has consistently participated in ARF meetings dedicated to confidence building measures and has

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[37] "The potential of Intra-regional Trade for South Asia", The World Bank, May 24, 2016, https://www.worldbank.org/en/news/infographic/2016/05/24/the-potential-of-intra-regional-trade-for-south-asia

[38] Md. Foysal Jaman Shishir and Nurul Huda Sakib, "How Interests and Ideas of a Dominant Actor Make a Big Difference: Analyzing India's Role in SAARC and BIMSTEC", Chinese Political Science Review (2022): 1–23, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9528874/#Sec7

[39] M. Ganapathi, "Act East in India's Foreign Policy: India-ASEAN Relations", *Indian Foreign Affairs Journal* 14, no. 3 (2019): 195–206, https://www.jstor.org/stable/48636726

facilitated maritime cooperation by having joint naval exercises with Indonesia, Malaysia, and Singapore.[40] India's support to ASEAN through maritime security to protect trade routes and sea lanes and has allowed India to expand its power to Southeast Asia by presenting itself as a defence partner for ASEAN countries.

However, the biggest strength of India's partnership with ASEAN lies in trade. ASEAN is one of India's top trading and investment partners. Its trade with ASEAN has grown from a paltry 7.06 billion in 2000-01 to 131.57 billion in 2022-23[41], making ASEAN India's fourth largest trading partner. India's government has also created funds to support cooperative measures between India and ASEAN, including funds science and technology that have contributed to cooperation and development, such as training courses established to analyse contaminants in raw and processed products for ASEAN countries.

India has several opportunities to strengthen its relations with ASEAN. First, both India and ASEAN have thriving digital economies, with ASEAN being the fastest growing Internet market in the world, and the Indian is estimated to hit USD 1 trillion by 2030[42], and the ASEAN digital economies is expected to reach USD 2 trillion by 2030[43]. India's own digital capabilities offer an opportunity for growing ties with Asian as part of this objectivity of boosting connectivity. India can engage with ASEAN on financial technology (Fintech) and use existing Digital Economy Partnership Agreements to encourage Indian Fintech companies to increase their presence in ASEAN member states and promote financial transfers between India and ASEAN[44]. Second, part of the "Act East" policy includes Security And Growth for All in the Region (SAGAR), which stresses the importance of a rule-based order and refutes the notion of a single country's domination. This is a policy that resonates with ASEAN, and it provides an opportunity for India to strengthen cooperation with ASEAN as India has a history of non-alliance[45]. Third, India and ASEAN can partner on infrastructure as both have placed a focus in recent years on their infrastructure development. ASEAN intends to build a network of smart cities in its member countries and India intends to build 100 smart cities[46]. The development of a smart city in Maharashtra, India, is being assisted by Surbana Jurong, a Singaporean

[40] Ganganath Jha, "India's Dialogue Partnership with ASEAN", *India Quarterly* 64, no. 4 (2008): 1–34, http://www.jstor.org/stable/45073163

[41] "Foreign Trade (ASEAN)", Ministry of Commerce and Industry, Government of India, September 1, 2023, https://commerce.gov.in/about-us/divisions/foreign-trade-territorial-division/foreign-trade-asean/

[42] "India's internet economy to hit $1 trillion by 2030: Report", Economic Diplomacy Division, Ministry of External Affairs, Government of India, June 7, 2023, https://indbiz.gov.in/indias-internet-economy-to-hit-1-trillion-by-2030-report/

[43] "Digital Economy Framework Agreement (DEFA): ASEAN to leap forward its digital economy and unlock US$2 Tn by 2030", Association of Southeast Asian Nations, August 19, 2023, https://asean.org/asean-defa-study-projects-digital-economy-leap-to-us2tn-by-2030/

[44] J.P. Morgan, "Fintech and Financial Inclusion in Southeast Asia and India", Asian Economic Policy Review, 17 (2022): 183-208, https://doi.org/10.1111/aepr.12379

[45] Manjari Chatterjee Miller, "New Delhi Must Capitalize on ASEAN's Eagerness to Engage", Council on Foreign Relations, November 8, 2022, https://www.cfr.org/article/new-delhi-must-capitalize-aseans-eagerness-engage

[46] Hernaikh Singh, "ASEAN-India Relations: Potential for Further Growth", Institute of South Asian Studies, July 1, 2022, https://www.isas.nus.edu.sg/papers/asean-india-relations-potential-for-further-growth/

government-based company, and the Asian Development Bank (ADB) has provided loans to India for building of infrastructure and transportation. Similarly, the India-Myanmar-Thailand Trilateral Highway has been underway, with India and ASEAN nations aiming to increase regional connectivity[47]. This can be expanded to India and ASEAN using their sectoral advantages to assist each other with their projects and cultivate an ecosystem of shared learning of business and technology. Finally, India and ASEAN are faced with the challenges of climate change and sustainability, which can be tackled with a partnership between the two to develop solutions to mitigate the consequences of climate change[48].

Weaknesses and Threats

India and ASEAN have differed on the Regional Comprehensive Economic Partnership (RCEP)[49], which is a free trade agreement between ASEAN's member states and the largest economies of the Indo-Pacific. After eight years of negotiations, India withdrew from RCEP due to concerns over India's trade deficit with China worsening due to RCEP and India's belief that the trade of services must be together with the trade of goods. Additionally, India has maritime partnerships secured with ASEAN, yet these are largely limited to bilateral partnerships, such as India having provided anti-submarine warfare training to Singapore's navy, technological support to Vietnam's navy, and training to personnel from the Malaysian air force. India's preference for bilateral partnerships with such countries is due to India's priorities to expand its strategic interests. For India to strengthen its partnership with ASEAN, India needs to have more multilateral partnerships with ASEAN to facilitate regional cooperation.

India's partnership with ASEAN may also face a challenge due to nuclear non-proliferation, as observed in Amador et al (2011)[50]. While India maintains nuclear power, it has a "no-first-use doctrine" which dictates that India's nuclear force may be used in retaliation against another state but may not be used to threaten any states that do not have nuclear power. ASEAN, on the other hand, has a different stance on nuclear non-proliferations. Its 10 full members have signed the Southeast Asia Nuclear-Weapon-Free-Zone Treaty, which prohibits them from developing, acquiring, and using nuclear weapons. While India's nuclear power creates friction with ASEAN, it does not pose the greatest threat to relations.

Rather, the threat to India's partnership with ASEAN arises from another nuclear power in the region: China. China has been ASEAN's largest trading partner since 2009, with a trade

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[47] Naina Bhardwaj, "Boosting India-ASEAN Economic Collaboration: Key Highlights from PM Modi's 12-Point Proposal", September 8, 2023,
https://www.aseanbriefing.com/news/boosting-india-asean-economic-collaboration-key-highlights-from-pm-modis-12-point-proposal/#:~:text=India%20is%20actively%20working%20on,and%20connectivity%20in%20the%20region

[48] Singh, "ASEAN-India Relations: Potential for Further Growth."

[49] Ibid.

[50] Julio S. Amador, Ariane Bobillo, and Amirah Peñalber, "Issues and Challenges in ASEAN-India Relations:" *India Quarterly* 67, no. 2 (2011): 111–27, http://www.jstor.org/stable/45072997

deficit of USD 102.9 billion in 2019[51], while India remains as ASEAN's sixth largest trading partner. India is not able to compete with China's trade links with ASEAN due to the China-ASEAN partnership being the largest free trade area globally and India's withdrawal from RCEP. However, while China is ASEAN's largest economic partner, the United States is considered ASEAN's largest security partner. As the rivalry between the two powers rise in the Indo-Pacific and China's territorial claims in the South China continue to pose threats to ASEAN members, the region is threatened with instability. This will provide India with the opportunity to strengthen its maritime and economic partnerships in the region so that India can counteract Chinese dominance in Southeast Asia.

Table 2: Summary of SWOT analysis of India's relationship with ASEAN

Strengths	Weaknesses
Maritime Trade	Regional Comprehensive Economic Partnership (RCEP) Preference for bilateralism
Opportunities	Threats
Digital cooperation Infrastructure Tackling climate change	Nuclear non-proliferation

India's affiliation with the Middle East–Strengths and Opportunities

India's has had strong relations with the Middle East for hundreds of years, with the relationship between India and the Middle East during the twentieth century being largely confined to economic ties, in particular oil and gas imports to India from the Middle East and the migration of workers for labour to the Middle East. As of April 2022, India's imports of oil from the Middle East were around 70% but have decreased to 50% as of April 2023[52], and approximately 8.9 million Indians reside in the Middle East[53], with a contribution of USD 40 billion in remittances annually in 2019. A common phrase said by those of Indian diaspora living in the Gulf is that Dubai is India's fifth largest city.

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[51] "ASEAN-China Economic Relation", Association of Southeast Asian Nations, https://asean.org/our-communities/economic-community/integration-with-global-economy/asean-china-economic-relation/

[52] Sambit Mohanty and Ratnajyoti Datta, "Russia, Middle East turn equal contributors to India's crude basket as flows shift", S&P Global, July 6, 2023, https://www.spglobal.com/commodityinsights/en/market-insights/latest-news/oil/070623-russia-middle-east-turn-equal-contributors-to-indias-crude-basket-as-flows-shift#:~:text=As%20per%20commerce%20ministry%20data,four%20months%20of%20this%20year

[53] "Population of Overseas Indians", Ministry of External Affairs, Government of India, https://mea.gov.in/images/attach/NRIs-and-PIOs_1.pdf

India's has had excellent bilateral relations with Israel since 1992, which are reviewed in Ningthoujam (2021)[54]. Ties between the two countries have exceedingly developed, particularly in the field of defence. Israel is India's second largest defence partner, accounting for 43% of India's defence imports from 2016 to 2020, while India is Israel's largest arms partner. While India preferred to counter Israel's policies twenty years ago, it no longer does so; rather, it endorses Israel's policies as those of counterterrorism and continues to remain neutral on any allegations by the United Nations that Israel has committed war crimes in the Gaza Strip. India and Israel have also been cooperating in the energy sector as both countries aim to diversify their energy sources and shift to renewable energy. India has also been negotiating with Israel to produce an India-Israel Free trade Agreement, which can help strengthen economic ties between the two as their relationship is largely limited to arms supply and defence cooperation. India's economic ties with Israel can also be increased through corporate ties, such as the acquisition of the Haifa Port by the India-based Adani Group and an Israeli partner for USD 1.2 billion in 2022.[55]

India's relations with the Arab world have also strengthened in the past decade. India has developed its relations with Israel, but it remains unchanged on its Palestine policy and continues to advocate for a two-state solution, with East Jerusalem as Palestine's capital. This has allowed India to continue engaging with the Gulf countries while maintaining relations with Israel as well.

The bilateral trade between India and the Gulf Cooperative Council, a union that consists of Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and the UAE, increased from USD 9.37 billion in 1999-2000 to USD 154.7 billion in 2021-2022. India has formulated strong relations with Saudi Arabia in particular due to a shared interest in security and defence measures. India set up a Joint Committee of Defence Cooperation with Saudi Arabia in 2012 as well as the Strategic Partnership Council in 2019.

Moreover, India's role in Afghanistan until the Taliban takeover has strengthened its ties with the Afghan people[56]. Afghanistan's principal source of development assistance after the United States was India, who did not intervene politically or militarily. Instead, India used soft power to forge people-to-people connections and attempted to prevent the humanitarian crisis by providing aid, including 60,000 metric tons of wheat in March 2023 and a USD 25 million development aid package as part of India's union budget for 2023-24. During 2022, India provided 45 tons of medical assistance, notably 500,000 doses of COVID-19 vaccines, medicines, and winter clothing. India's use of soft power through humanitarian assistance in Afghanistan has gained the goodwill of the Afghan people and while Afghanistan could have been a threat to India due to the Taliban takeover, India used its support of the country to

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[54] Alvite Singh Ningthoujam, "India-Israel Relations: Scaling Newer Heights", *Indian Foreign Affairs Journal* 16, no. 3 (2021): 227–41, https://www.jstor.org/stable/48714206

[55] Steven A. Cook, "India Has Become a Middle Eastern Power", Foreign Policy, June 30, 2023, https://foreignpolicy.com/2023/06/30/india-middle-east-power/

[56] Vinay Kaura, "India-Taliban relations: A careful balancing act, driven by pragmatism", Middle East Institute, May 30, 2023, https://www.mei.edu/publications/india-taliban-relations-careful-balancing-act-driven-pragmatism

cooperate with Afghanistan and prevent any challenges to India from the political instability in the country.

There are opportunities available for India to expand its growing economic ties besides oil which has traditionally dominated their economic relationship. India has been formulating an agreement with UAE to link UAE's electricity grid with India's electricity grid. This will be done under India's One Sun, One World, One Grid (OSOWOG) initiative and promote the use and transfer of renewable energy through connecting grids between countries. This is an opportunity for India to expand its network to more Middle Eastern countries and collaborate with them to produce interlinking electricity grids for renewable energy.

Furthermore, India's largest partners in the Middle East aside from Israel have become the countries which follow moderate Islam[57], with India welcoming the approaches taken by Middle Eastern countries to promote more moderate Islamic beliefs, such as the UAE's encouragement of political moderation and religious liberalism as well as the reforms in Saudi Arabia to allow women to drive and diversify the economy. Due to cross-border terrorism and radicalisation in India that has been attributed to Pakistani-led and jihadist groups, such as notorious terrorist groups Lashkar e-Taiba and Jaish e-Mohammed who fought alongside the Taliban and committed attacks in India[58], India is wary of radicalisation in the Middle East directly affecting the position of Muslims in India.

Weaknesses and Threats

Conversely, India's soft power has not extended to the rest of the Middle East as India has not yet achieved beneficial soft power in the Middle East and its cultural diplomacy is limited to the popularity of Bollywood, which is now being rivalled by the Turkish and Egyptian film industries. India lacks people-to-people diplomacy which will aid India in bettering its relations with the Middle East. India must consider expanding its cultural ties with the Middle East by promoting inter-faith dialogues, the teaching of Arabic, and Indian cultural centres in universities in Middle Eastern countries[59], as suggested in Dahiya (2015).

The biggest threat to India's relationship with the Middle East is rising islamophobia in India. India's governmental figures have many a time made controversial remarks on social media that have been anti-Arab[60], including social media posts that have portrayed Arab women negatively which UAE officials expressed anger over. India's poor treatment of its 400 million

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[57] Jon B. Alterman and C. Raja Mohan, "India's Middle East Strategy", Centre for Strategic and International Studies, December 13, 2022, https://www.csis.org/analysis/indias-middle-east-strategy

[58] Mohammed Sinan Siyech, "The Return of the Taliban: 'Foreign Fighters' and Other Threats to India's Security", Observer Research Foundation, Issue No. 515 (2022), https://www.orfonline.org/wp-content/uploads/2022/01/ORF_IssueBrief_515_ForeignFighters.pdf

[59] Rumel Dahiya, "India and West Asia: Challenges and Opportunities", *Indian Foreign Affairs Journal* 10, no. 4 (2015): 324–30, http://www.jstor.org/stable/45341057

[60] Omar Anis, "Growing Potential in India's Relations with the Middle East", Australian Institute of International Affairs, August 27, 2021, https://www.internationalaffairs.org.au/australianoutlook/growing-potential-in-indias-relations-with-the-middle-east/

Muslims have weakened relations between the Gulf countries and India. For India to strengthen relations with the Middle East, it needs to counter the islamophobia within its government and its country by ensuring that it is more open-minded towards Islam, which will also help India better its cultural diplomacy and soft power in the Middle East.

As with India's relationship with ASEAN, another growing threat to India's relations with the Middle east is China's growing regional footprint. China is the largest importer of hydrocarbons from the Middle East and has invested in infrastructure projects such as oil and gas infrastructure and transportation hubs[61], which have aided China in expanding its relations with the Middle East to more than trade, which it already dominates as the largest trading partner for the Middle East and North Africa (MENA) countries. India's relationship with the Middle East has largely been through trade and while it has extended militarily, it has not been able to compete with China's strategic investments in a number of fields that have aided in the economic growth of Middle Eastern countries.

Table 3: Summary of SWOT analysis of India's relationship with the Middle East

Strengths	Weaknesses
Defence cooperation Economic relationship	Soft power
Opportunities	Threats
Expanding energy collaboration Economic ties with Israel	Islamophobia in India China's regional footprint

India's role in Africa–Strengths and Opportunities

India has engaged with African countries with much success. India-Africa trade reached USD 76.9 billion in 2018 from USD 6.8 billion in 2003, with Africa being a source of fossil fuels and cash crops for India and India exporting agriculture and pharmaceuticals to the region[62]. India has also become the seventh-largest investor in Africa through its use of Lines of Credit (LoC), which are mainly supplied to East and West Africa. India's 182 LoC projects in Africa have been used to fund farm mechanisation and the building of railway and irrigation projects, which have helped the recipient nations in Africa develop and have created markets for Indian companies to explore. These LoCs were of particular success in Ethiopia, where USD 640 millions of LoCs helped Ethiopia become self-reliant in sugar production. Not only did this also lead to the installation of a water-purification plant, but it also provided jobs in the region. India's LoCs have also been extended to coordinate responses to climate change, with an LoC worth USD 2 billion to implement off-grid solar energy projects.

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[61] Md Muddassir Quamar, "China's Growing Strategic Inroads in the Middle East and Challenges for India", Raksha Anirveda, November 23, 2022, https://raksha-anirveda.com/chinas-growing-strategic-inroads-in-the-middle-east-and-challenges-for-india/

[62] Malancha Chakrabarty, "India-Africa relations: Partnership, COVID-19 setback and the way forward", Observer Research Foundation, April 26, 2021, https://www.orfonline.org/expert-speak/india-africa-relations-partnership-covid19-setback-way-forward

India has taken a different approach in Africa to other countries that have been involved in the region in that India's aim in Africa has been to help African countries develop through use of the Indian Development and Economic Assistance Scheme, which is highlighted in Chakrabarty (2016)[63]. India has provided aid to and cooperated with African countries based on what the country requires, rather than India's own intentions in the region, which has helped India differentiate itself from Western and Chinese influences in the region. Furthermore, India has extended its soft power to Africa, with Indian culture, cinema, and cuisine being popular in African countries, as examined by Alam et al (2014)[64]. India's identity which comprises of art, spirituality, and education among other things has aided India in presenting itself as contemporary and democratic in comparison to other countries in the region, while the celebration of Indian festivals and the shared colonial history of India and many African countries has strengthened public diplomacy. India's use of health diplomacy as a soft power tool has been effective in expanding Indian influence in the region as 20% of pharmaceutical exports from India go to Africa[65] and the COVID-19 pandemic helped India further its involvement with African countries. India provided medical equipment for 25 African countries, as well as 270 tonnes of food aid and online courses for training of professionals for management and protocols during the pandemic[66]. India's supply of 10 million vaccines to Africa displayed India's support for African countries at a time when developed countries had secured a majority of the vaccine supply and there was low availability for vaccines for low-income and developing countries.

India can further its partnerships with African countries through utilising the USD 10 million India-Africa Health Fund, which India can do by investing in the building of tertiary hospitals and laboratories[67]. This will promote local ownership while providing opportunities for Indian pharmaceutical companies to supply these facilities. India can also help African countries meet their increasing demand for energy and finance clean energy through the International Solar Alliance, which it can do by offering sustainable energy solutions. Moreover, India can advocate for African countries in global settings, such as the United Nations, the World Trade Organisation, and G20, where India can encourage the G20 to promote the African Union from a permanent invitee to the 21st member.

Weaknesses and Threats

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[63] Malancha Chakrabarty, "Understanding India's Engagement with Africa", *Indian Foreign Affairs Journal* 11, no. 3 (2016): 267–80 http://www.jstor.org/stable/45341961

[64] Mohammed Badrul Alam and Amit Kumar Gupta, "India's Policy Towards Africa", *World Affairs: The Journal of International Issues* 18, no. 2 (2014): 88–99, https://www.jstor.org/stable/48505440

[65] Patrick Burton, "Africa: The Launchpad for Indian Pharma", Pharma Boardroom, July 10, 2018, https://pharmaboardroom.com/articles/africa-the-global-launchpad-for-indian-pharma

[66] Chakrabarty, "India-Africa relations: Partnership, COVID-19 setback and the way forward"

[67] Abhishek Mishra, "Elevating the India-Africa partnership to new horizons", Observer research Foundation, July 22, 2022, https://www.orfonline.org/expert-speak/elevating-the-india-africa-partnership-to-new-horizons/

India has made much progress in its development cooperation in Africa; however, India still lacks a clear strategy in Africa[68]. Its use of LoCs have helped the development of African countries but are not directed at specific development goals. India has not expressed goals such as food security or education that it is aiming to target in Africa, thus the LoCs have funded smaller development projects without an overarching goal. LoCs are also instruments which support individual projects and are not linked to each other, which reduces the impact of India's assistance in Africa. The India-African relationship has also met challenges due to discrimination faced by African students who have studied in India as part of India's education programs with African countries. Many of these students have returned to Africa without completing their education due to violence against them in India.

The largest threat to India's cooperation with African countries is instability in the African continent. The Horn of Africa is a link between the Indian Ocean and the Suez Canal that is crucial to India and the increasing threats of terrorism and piracy pose security risks to India's investments in the region and further cooperation between India and African countries. However, India can use this as an opportunity to collaborate with African countries to promote democratic values and ensure peace and stability in the region. The other threat to India's partnership with African countries is the increased engagement of other countries in the region, notably China. China has provided economic and political support in Africa and is the Africa's largest trading partner. Not only were the African Union headquarters built by China in 2012, but China also has space programs in nine African countries[69]. China loaned USD 126 billion to African nations between 2001 and 2018, which resulted in 78% greater voting alignment in these countries[70]. India cannot match China's trade with African countries or investments in the continent. This poses a risk to India's partnership with Africa and India must continue its development cooperation strategy to ensure that it can maintain successful relations with African countries despite China's growing presence in the region.

Table 4: Summary of SWOT analysis of India's relationship with Africa

Strengths	Weaknesses
Economic relationship	Lack of a clear strategy
Indian investments in Africa	Discrimination against African in India
Soft power	
Humanitarian assistance	
Historical partnerships	
Opportunities	Threats
India-Africa Health Fund	Instability in the region

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68 Chakrabarty, "India-Africa relations: Partnership, COVID-19 setback and the way forward"
69 "China Regional Snapshot: Sub-Saharan Africa", Foreign Affairs Committee, November 14, 2022, https://foreignaffairs.house.gov/china-regional-snapshot-sub-saharan-africa/
70 Carla D. Jones, Hermann A. Ndofor and Megge Li, "Chinese Economic Engagement in Africa: Implications for US Policy", Foreign Policy Research Institute, January 24, 2022, https://www.fpri.org/article/2022/01/chinese-economic-engagement-in-africa/

Sustainable energy	China's influence

India and the West–Strengths and Opportunities

India has maintained a strong economic partnership with the United States and Europe. The United States is India's largest trading partner, with bilateral trade reaching USD 157 billion in 2021[71]. India's exports to the US have largely comprised of diamonds, packaged medicaments, and jewellery, while India has imported crude petroleum, diamonds, and petroleum gas from the US[72]. Additionally, approximately 200,000 Indian students are studying in the US, who have contributed USD 7.7 billion annually to the American economy and Indian investments in the US are estimated at USD 12.7 billion[73]. Both countries have engaged on the global stage at the Quad Leaders' Summit in May 2023 with Australia and Japan where they discussed various issues including infrastructure and maritime security, and the US has supported India in a reformed UN Security Council in which India becomes a permanent member.

India has also strengthened its partnership with Europe, with the European Union (EU) being the prime destination for Indian exported goods[74]. India and the EU have worked together to ensure the building of smart cities and clean water and sanitation. India and France co-founded the International Solar Alliance on the side-lines of COP21 to tackle climate change. The European Investment Bank has lent money for metro projects in three Indian cities, while the Erasmus+ Program has ensured that research cooperation between India and the EU has prospered through the partnership of 130 Indian universities with European institutes, which has made India the largest benefiter of the Erasmus+ program.

The US and Europe face challenges with China due to China's actions in the Taiwan Strait and China exerting influence across the globe, and India too must face China's growing power in order to become a global power itself. As directed in Coons and Talwar (2018)[75], an India and US partnership can facilitate development in low-income countries through means similar to India's development cooperation strategy in Africa, which will provide an alternative for countries to prevent them from falling into China's debt trap. Moreover, military cooperation between the West and India is an opportunity for both to secure their interests in the region. India has joined the Combined Maritime Forces based in Bahrain which the US is a part of, both countries conduct at least fifty military exercises every year, and the US and India have agreed to launch new defence space exchanges, but India can promote further defence cooperation and collaboration of cybersecurity with the US and European countries to strengthen military ties between the nations.

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[71] "US Relations With India", US Department of State, July 18, 2022, https://www.state.gov/u-s-relations-with-india/
[72] "India/ United States Bilateral Trade", Observatory of Economic Complexity, 2021, https://oec.world/en/profile/bilateral-country/ind/partner/usa
[73] "US Relations With India", US Department of State
[74] Ankita Dutta, "Unpacking the India-EU economic relationship", Observer Research Foundation, April 23, 2021, https://www.orfonline.org/expert-speak/unpacking-india-eu-economic-relationship/
[75] Chris Coons, Puneet Talwar, "The Case for a U.S.-India Partnership", *The National Interest*, no. 158 (2018): 10–19, https://www.jstor.org/stable/26557502

Weaknesses and Threats

India's partnership with Europe and the US has diverged at India's unwillingness to support the US and Europe in global matters due to its policy of non-alignment. India abstained from the UN resolution condemning Russia's invasion of Ukraine despite being pressured by the US and European countries to vote in favour. India also increased its imports of oil at a reduced price from Russia when the American and European markets placed sanctions on Russian exports. However, India can utilise its multiple alliances to act as a mediator between the West and other countries as India has been able to maintain strong relations with Western countries, as well as both Russia and China and developing countries in the Global South.

Table 5: Summary of SWOT analysis of India's relationship with the West

Strengths	Weaknesses
Economic relationship Indian diaspora Education and energy collaboration	India's non-alignment policy
Opportunities	Threats
Military cooperation Development cooperation	China's dominance

India's presence in Latin America–Strengths and Opportunities

Latin America is a region which India has not yet explored and engaged at a high level with. India's relationship with Latin American countries has recently strengthened due to India foreign minister S Jaishankar's visits to Columbia, the Dominican Republic, Guyana, and Panama. India has a strong relationship with Brazil, a BRICS counterpart and its ninth largest exporter with exports totalling USD 9.6 billion in 2022[76]. Brazil is a coveted market for pharmaceuticals and information technology which are sectors that India thrives in.

Moreover, it is observed in Bhojwani (2015) that India needs to boost its trade with Latin America in order to strengthen its relationship with the region. India's tariffs on Latin American agricultural goods are at 65%, which is more than five times greater than tariffs placed by China on the same goods[77]. India's lowering of these tariffs would encourage more imports from Latin American countries and boost trade. India and Latin American countries have potential to develop their relationship through a mutual interest in food security and climate change. Furthermore, India is the most populous country in the world and Latin America has agricultural

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[76] Hari Seshasayee, "Redrawing India-Latin America Relations in the 21st Century", Observer Research Foundation, April 29, 2023, https://www.orfonline.org/research/redrawing-india-latin-america-relations-in-the-21st-century/

[77] Deepak Bhojwani, "Latin America and India: Understanding Mutual Opportunities", *Indian Foreign Affairs Journal* 10, no. 1 (2015): 50–62, http://www.jstor.org/stable/45341011

land and natural resources which can provide opportunities for environmentally friendly practices and expanding production in the region.

Weaknesses and Threats

India's economic ties with Latin America are shadowed by China's trade with Latin American countries that India has not been able to rival. However, while the Indian private sector's total investments in Latin America, valued at USD 16 billion, are not as high as investments made by China, they have created jobs in value-added sectors. India has invested in manufacturing and services, with Indian IT companies employing locals in Latin America, and 27 Indian companies operating 72 subsidiaries in the region[78]. Due to the reliance of Latin American countries on India for pharmaceuticals, including drugs for HIV and cancer and vaccines, economic relations between India and Latin America have remained strong.

Unlike India's relationship with SAARC and ASEAN, India is yet to engage in multilateral relations with sub-groups in Latin America. India needs to further cooperation with the Central American Integration System (SICA), the Community of Latin American and Caribbean States (CELAC), and the Pacific Alliance in order to strengthen its presence in the region. Furthermore, India has yet to show interest in expanding its trade agreements with Latin American countries even though economic ties between the two are increasing. India has preferential trade agreements with Mercosur and Chile but free trade agreements with ASEAN and Japan, although India's trade with Mercosur has passed India's trade with Japan. India's trade with Latin America already faces geographical challenges due to the distance and poor connectivity between India and Latin America, which China has not faced due to its shipping links through the Panama Canal. For India to ensure that its economic influence in Latin America continues to prosper, India needs to sign comprehensive trade agreements with the region.

Table 6: summary of SWOT analysis of India's relationship with Latin America

Strengths	Weaknesses
Relations with Brazil	Preference for bilateralism
Economic ties	Connectivity
Opportunities	Threats
Expanding trade agreements	China's influence

India's untapped potential and internal capabilities–Social and political development

India has overtaken China to become the most populous country in the world, and it is predicted that Indian's median age will be approximately 33-34 years in 25 years' time[79]. This allows India to maximise its demographic dividend, which will help India's development and

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[78] Seshayasayee, "Redrawing India-Latin America Relations in the 21st Century"
[79] Jennifer Dabbs Sciubba, "What India Becoming the World's Most Populous Country Means", Center for Strategic and International Studies, April 28, 2023,
https://www.csis.org/analysis/what-india-becoming-worlds-most-populous-country-means

capacity to become a world power. However, India faces a major challenge in its development due to poverty, with 374 million people in India lacking nutrition, sanitation, housing, and cooking fuel[80]. While India has made significant efforts to reduce poverty, with 415 million people in India being lifted out of poverty in 15 years, India needs to overcome poverty and invest in its population if it wants to ensure the benefits of its demographic dividend. India also needs to ensure equal access to education for its youth population, as the Gross Enrolment Ratio for enrolment into higher education in India is 15%[81], which is largely attributed to poor education facilities, lack of qualified teachers, and barriers for students due to socio-economic class and gender. However, India has progressed in the field of technology, with India's USD 3 billion Start-up Initiative having made India the third largest start-up ecosystem in the world, after the US and China, and provides job opportunities and potential for India to develop itself digitally to rival global leaders.

India's Diplomatic Efforts

Debnath (2022) analyses India's diplomatic efforts and influences that have helped India tap into its potential to become a world leader[82], with India's leadership extending far beyond economic power. India created the New Education Program in 2020, intending to encourage foreign universities to build campuses in India and promote Indian universities to do the same abroad, which will encourage cooperation between India and other countries to collaborate of furthering education opportunities for students. India has also been a significant contributor to the UN Peacekeeping Force, with India providing an all-female contingent to the peacekeepers in 2007, being the first country to do so. Furthermore, India has extended cooperation and support to countries around the world through space cooperation, notably through building a ground station in Vietnam alongside ASEAN, and humanitarian support, highlighted during the 2004 tsunami in the Indian Ocean. While India has collaborated with other countries and supported them through policies and initiatives, India has the potential to cooperate further with other countries and further on its development cooperation strategy, which it has used in Africa, to aid the development of low-income countries around the world.

Conclusion

A world leader is a country that is capable of extending help to prevent global crises, aim to maintain peace, and lead the world on a global platform. India has the opportunity of becoming a global leader and leading the way for developing countries and becoming a stabilising force in the world. Not only is India strategically placed in the Indian Ocean, but India is also a nuclear power and has the most powerful military after the US, Russia, and China.

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[80] "Poverty rate in India was slashed, says report, but globally 1.2bn still poor", University of Oxford, October 17, 2022, https://www.ox.ac.uk/news/2022-10-17-poverty-rate-india-was-slashed-says-report-globally-12bn-still-poor

[81] Younis Ahmad Sheikh, "Higher Education in India: Challenges and Opportunities", Journal of Education and Practice, Vol.8, No.1 (2017), https://files.eric.ed.gov/fulltext/EJ1131773.pdf

[82] Roma Debnath, "India Emerging as a Global Leader", Indian Institute of Public Administration, 2022, https://www.iipa.org.in/cms/public/uploads/437251665376003.pdf

India's economy is growing at an explosive rate and the nation is the most populous country in the world, as well as the world's largest democracy.

India's strengths are not confined to its economic and military power. India's region-specific policies, including the Look East Policy and the Link West Policy, have aided India in engaging with countries in different regions and promoting Indian values and support. India's engagements in developing countries in Africa have followed its G20 priorities of ensuring food security, climate finance, global health resilience, and sustainable development. Similarly, India has aimed to improve its relationship with South-East Asian countries and dilute China's assertiveness in the region, while India has boosted its bilateral ties with both Arab countries and Israel while supporting a two-state solution to the issue of Palestine. India's leadership has certainly been shown in these regions and India's willingness to strengthen ties with and support developing countries demonstrates India's capability of becoming a global leader.

However, India has yet to show leadership and cooperation in its own region, illustrated through the failure of SAARC, and has preferred to engage bilaterally with countries rather than multilaterally. For India to become a global leader, it must be willing to exercise its power and engage with multiple countries on an international platform. India has sought after a permanent seat on the UN Security Council, but it has yet to show initiative to lead the world when tackling issues such as climate change, security, and trade. An example of this is seen in India's co-founding of the International Solar Alliance with France. This has proven India's willingness to utilise multilateral cooperation to mitigate environmental risks, but the Alliance does not effectively tackle climate change globally.

Furthermore, if India in unable to support inclusive development internally, its ability to do so on the global stage will be questioned. India needs to invest in youth and in their education to ensure that India's growing population is able to contribute to society, and India must recognise the potential of all Indians, despite their gender, religion, and caste. India is also plagued by poverty, with one of five Indians living in poverty. For India to become a global leader, it must be able to set an example to other countries and pave the way for them to better themselves. India has been able to reduce poverty in the country, but inequality of wealth and opportunities have risen. This does not set an example for other countries and if India cannot address its domestic challenges, it will be unable to address global challenges.

China's growing influence also limits India's potential to become a global power. China has developed its ties with India's neighbours and countries worldwide due to its Belt and Road initiative. India is unable to compete with China's economic and technological capacity and while it is ambitious to present itself as a competitor of China's, this remains an aspiration. India is a regional power in South Asia, which is vastly due to its size, population, and armed forces. But India needs more than a fast-growing economy to become a global power. It requires intent to collaborate with other countries and ensure that its voice is heard as a dominating force, which India has failed to do even in regions such as Africa and East Asia where India's engagement has been overshadowed by Chinese influence.

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Exoplanets, the Search for Life, and their Implications By Nairi Davidian

Abstract

Exoplanet research is rapidly establishing itself as one of the most popular topics in astronomy, and rightfully so. The concept of worlds beyond our solar system is not only fascinating, but it has a multitude of implications for our future, whether that's discovering the first extraterrestrial life or becoming an interstellar species. Indeed, from the vast accumulation of knowledge in the past couple decades, it is evident that the field will have both a scientific and philosophical impact on future generations. In this review, information is used from the most recent discoveries and insights from experts in exoplanet detection, atmospheres, and habitability. Because evidence suggests that Earth is not the only habitable world, it is all the more reason to continue exploring the cosmos.

Introduction

Throughout all of human history, we have been fascinated by the cosmos. In addition to fueling scientific curiosity, the subject of what's beyond Earth has been scrutinized for philosophical, theological, and scientific purposes. Sometimes, these fields would contradict each other, as people who made certain scientific claims that undermined religious teaching would be charged with heresy. Perhaps the most famous case of this was Galileo's support for Copernican heliocentrism[101]. Over the centuries, we have proven that Earth does not only orbit the sun, but that our Sol is one of 100 billion stars in our galaxy alone, and that the Milky Way has around two trillion companions in the observable universe alone. The sheer vastness of space begs the question: are we alone, and if not, are there other advanced civilizations we have yet to discover?

A common consideration when attempting to answer that question is the famous Drake Equation, which is a probability-based model for the amount of civilizations in the Milky Way with which communication might be possible, denoted as N. It states that

$$N = R_* \cdot f_p \cdot n_e \cdot f_l \cdot f_i \cdot f_c \cdot L,$$

where R_* is the average rate of star formation in the Milky Way, f_p is the fraction of those stars that have planets, n_e is the average number of planets that are potentially habitable per star that has planets, f_l is the fraction of planets that could support developable life, f_i is the fraction of planets with life that develop into civilizations, f_c is the fraction of those civilizations that utilize technology that releases signs which we can observe (technosignatures[102]), and L is the amount of time for which these detectable signs are released.

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[101] The model of the Earth orbiting around the sun rather than the sun orbiting around the Earth (geocentric model). The latter model was accepted for 1500 years.

[102] Indicators of an advanced extraterrestrial civilization

Unsurprisingly, the final three parameters are unknown, which makes this equation less of a calculable tool and more of a guide of the information we must obtain. Indeed, figuring out the nature of extraterrestrial existence – if it exists – is a cutting-edge field that requires experts in astronomy, physics, chemistry, and biology; comprising the growing field called *astrobiology*. This review will cover the basics of this subject, spanning from the detection of exoplanets and their atmospheres to what is currently known about habitability to further speculation about extraterrestrial existence. As the review progresses, please note that the matters discussed are reaching more and more educated speculation rather than clear-cut fact.

The Prime of Exoplanet Discovery

In 1992, periodic disturbances were observed from the pulsar[103] PSR B1257+12. This suggested that there were planets in stable orbits around the pulsar – a breakthrough discovery. Later on in the decade, the first exoplanets to orbit a main-sequence star were discovered. Then, with the advent of Kepler, a space-based telescope which sought terrestrial planets in a certain portion of the Milky Way galaxy, over 2,600 new exoplanets were found, kicking off the golden age of exoplanetary science.

Figure 1: This plot shows the diversity of exoplanet populations in regards to their orbital period and their radii in comparison with that of the Earth. The contributions of the Kepler mission are emphasized by the prevalence yellow dots in the figure.

As seen in Figure 1, most of the Kepler planets are concentrated around an orbital period of 10 days and a radius a couple times larger than that of Earth's. However, from what we can

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[103] Rapidly rotating neutron star which sends radiation out of its magnetic poles

tell from our cumulative discoveries to this day are that exoplanets are extremely diverse. For example, instead of orbiting one star, they can be in a binary star system, in which they can orbit the center of gravity of the two stars or take on a figure-8 shaped orbit. Additionally, many exoplanets have been found orbiting neutron stars[104] – a surprisingly common phenomenon.

Ironically, when it comes to exoplanet populations, the most common types of planets as we know them are those that are not present in our own solar system! For example, there are an ubiquitous amount of so-called "hot Jupiters" that we know of. These are gas giants with a particularly short orbital radius from their star. Understanding hot Jupiters can help us understand more about the evolution of our own solar system regarding gas giants and their migration. Exoplanets also differ largely when it comes to eccentricity[105] and obliquity[106]. This diversity makes for some very interesting possibilities not only for science fiction but also for possible life hosts.

One may be wondering how we know that all these planets even exist! It's certainly not like we can just see them in the night sky. We actually use many different methods for exoplanet detection, and some of them work better for certain types of planets. Described below are brief overviews of several methods along with their biases for certain types of planets.

*Transit***:** The predominant technique of exoplanet detection, the transit method involves tracking the brightness of a star and its patterns. When a planet passes in front of its star, some of the flux from that star is blocked. So, if the dimming occurs on a predictable basis, that is an indicator of an exoplanet. This method has a bias toward planets with shorter orbital periods, as this means there will be less time between transits.

Figure 2: This diagram conceptualizes the transit method of exoplanet detection. As shown in the graph, the dip in the overall flux from the star corresponds to the planet passing in front of the body.

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[104] Collapsed core of a massive star post-supernova
[105] How elliptical a planet's orbit is; the eccentricity of a circle is zero, and the eccentricities of ellipses (the shape of a planet's orbit) are between zero and one.
[106] The angle between a planet's rotational axis and its orbital axis. The latter axis is defined as being perpendicular to the plane of the planet's orbit.

Radial Velocity: This method uses spectroscopy to estimate the minimum mass of a planet. When a star is orbited by a planet, the gravitational pull of the planet causes the wavelength of the star's flux to shift. This method favors planets orbiting low-mass stars, as they are more obviously affected by the gravitational force of the orbiting planet.

Figure 3: In the Doppler shift of stars, red-shift indicates that the star is moving away from us and blue-shift indicates that the star is moving towards us. The radial velocity detection method measures the "wobble" in the doppler shift, which represents the star's orbit around a system's center of mass. This information can be used to infer the existence of planetary companions.

Microlensing: When a star passes in front of another star, its gravitational field bends the light from the posterior star like a lens. An exoplanet of the "lens" star can act like another lens, magnifying the brightness. This method is best for detecting very distant stars, but it is not helpful for detecting the same exoplanet more than once.

Figure 4: This model of microlensing shows how a passing body can act as a gravitational "lens" by amplifying a distant star's apparent luminosity.

Direct Imaging: The most straightforward method involves taking pictures of orbiting planets by blocking the light from its host star. This method works best for planets with larger separations from their star. Unfortunately, it is one of the most cumbersome methods, because compared to direct light from the star, the planet's atmosphere's reflected light is much dimmer.

Figure 5: In direct imaging, the light from the star is blocked so that the comparatively dim reflection of light off of companion planet(s) can be discerned.

With the advent of new technology, we will be able to discover a wider range of exoplanets which were too dim and too far away to be seen before. The James Webb Space Telescope, which launched in 2021, will capture images in the mid-infrared, a frequency invisible to the human eye. Its improved sensitivity will allow detection of planets with larger separations. Additionally, the JWST will use on-board coronagraphs to act as artificial eclipses that block the light of the planet's host star. This high-contrast imaging will open our eyes to the exoplanets that were previously too dim to be discovered, which will augment our perception of exoplanet populations.

Atmospheres of Exoplanets

The more information we want to know about an exoplanet, the more uncertainty there is in our findings. Because we can't observe an atmosphere directly, we use spectroscopy to detect certain materials, because each chemical has a unique signature. That is, when starlight passes through the planet's atmosphere, the intensity of certain wavelengths indicate the presence of different chemicals. Below are some examples of spectral profiles for different elements.

Figure 6: Here, the unique emission spectra of some sample elements are shown.

We can strategically detect atmospheric elements by tracking a planet through its orbit of its star. When the planet passes in front of its star – a primary eclipse – the star's radiation is filtered through the planet's atmosphere, allowing for effective observation of emission spectra. When a planet passes behind its star – a secondary eclipse – the difference in the light detected can be attributed to the thermal radiation emanating from the planet, allowing further clues in regards to the composition of the planet. Since secondary eclipses are more easily detected for larger and hotter planets, this strategy is ideal for hot Jupiters.

By using these methods, we can determine the planet's similarities to Earth. Since our atmosphere is mostly made out of nitrogen as well as oxygen, the presence of these species is a promising indicator for possible Earth-analogues. However, just because we can't detect certain elements doesn't mean they're not present. Clouds can obscure the features of a planet's atmosphere because of how it reflects the star's flux rather than allowing it to pass through the atmosphere. With the improvement of detection technology, we will be able to offset these obstacles more and more.

Habitability

One of the ultimate goals of exoplanet research is to determine whether or not our planet is unique in hosting life. When trying to solve this problem, we run into some major gaps in our certainty of what is required for life. See, with our own being the only planet we know of to host life, our sample size for analyzing habitability is ridiculously meager, and so the traits we look for in exoplanets are correspondingly limited. Even if we *think* certain conditions could host life, we don't *know* for sure if they can unless we have an example on Earth. Even with these constraints, planets that meet the accepted criteria are constantly being discovered.

The most general indicator we have regarding habitability is a planet's distance to its star. The "habitable zone" of a star is noted as the distance a planet can orbit such that said planet can have liquid water. Of course, "habitable" is a liberal term in this case, as water isn't the only requirement we accept for habitability – in fact, it's fairly possible that it isn't necessary. Yes, it is accepted that life requires some sort of solvent. In our case on Earth, of course, that would be water. However, it is hypothesized that – in liquid form – ammonia, methane, and ethanol can play this role. In addition to a solvent, life also requires substantially stable conditions such that organisms would be able to carry out metabolic and reproductive functions without hostile disturbances in their environment. In particular, stellar radiation can be detrimental to the development of life, which is why Earth's strong magnetic field is so important. It would follow that if a planet had a magnetic field strong enough to protect any of its possible inhabitants from solar wind, then it is all the more likely for that planet to be habitable.

Bioavailable energy must also be taken into consideration, as all organisms require some form of energy for maintenance, growth, and reproduction. Phototrophy, for example, is the process of capturing photons to form carbohydrates. Other types of energy-consumption

processes that we know of include chemolithotrophy[107] and chemoorganotrophy[108]. Of course, if there was extraterrestrial life, they could very well have methods of obtaining energy that we are not familiar with yet.

In addition to a solvent, appropriate conditions, and available energy being present, it is also known that six elements, known by the mnemonic CHNOPS, are required for life as we know it. That is, they make up most of the biomolecules we have observed. Namely, these elements are carbon, hydrogen, nitrogen, oxygen, phosphorus, and sulfur. If we find evidence of these elements being present in a planet's atmosphere via spectroscopy, then that planet becomes a strong candidate for being a host of life.

It is important to note that these are only the most fundamental requirements considered for habitability, and that there is much nuance in all of the different variables included in the equation of life. For instance, greenhouse gasses are necessary to allow a planet to retain and distribute heat throughout its atmosphere, but too much of them can be detrimental. Take Venus, which is theorized to have been very similar to Earth at one point. This is because in the earlier stages of our sun's life cycle, Venus was in the habitable zone. Once the sun matured and the sacred ring of habitability moved farther outward, its oceans began to evaporate, fostering the beginning of a runaway greenhouse gas effect. Now, its atmosphere is disconcertingly thick and its average temperature is 864 degrees Fahrenheit – even hotter than Mercury! Venus's history shows that habitability can change over time, and that it requires consistent and stable conditions of the system over time.

Figure 7: This is a depiction of some exoplanets which have qualities that could potentially make them habitable. Earth is included for size reference.

So far, we have found several planets that share similarities with Earth in size and shape, and distance from their star. The key factor that will separate the planets we truly consider habitable from the others will be their atmosphere, and with upcoming expeditions we will be able to weed out these candidates.The European Space Agency is planning to launch its Atmospheric Remote-sensing Infrared Exoplanet Large-survey (ARIEL) in 2029, and it will relay newfound discoveries regarding exoplanet atmospheres. It seems that every decade, we are

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[107] Oxidization of electron donors from inorganic molecules
[108] Oxidization of organic chemicals

inching our way closer to understanding how unique our world truly is.

Science vs. Science Fiction

In the search for life, scientists mostly search for what are called biosignatures. These are chemicals and characteristics, like those described above, that are signs of potential habitability. However, there is a field that is looked down upon by most other scholars, and that is the Search for Extraterrestrial Intelligence (SETI). These ambitious researchers spend their time searching for technosignatures, which are signs of an advanced alien civilization. These are hypothesized to be found in the form of radio waves, laser emissions, pollutants in atmospheres, megastructures – yes, I'm talking about dyson spheres[109] – and possibly even attempts at communication. While there have been claims of technosignatures, there is not any sufficient evidence that we are not alone in terms of technologically advanced species.

Perhaps the most famous detected "technosignature" was the "Wow! Signal." This short-lived narrowband radio signal was detected at Ohio State University's "Big Ear" radio telescope in 1977 – before the first exoplanet was confirmed. The frequency of the signal excited its analyst, so much so that he circled the computer reading of the signal and expressed his enthusiasm next to it.

Figure 8: Here lies the infamous "wow signal."

As promising as this discovery seemed at first for SETI, the fact that it never appeared again led most scientists to believe the signal was not in fact an attempt at communication from an advanced alien world. Some believe that there was a technical issue with the Big Ear, while others believe that a passing comet was responsible. In any case, this mix-up is an example of how fickle the knowledge in this area is, which leaves gaps of wisdom for the next generation of astrobiologists to fill.

The Philosophical Aspect

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[109] Dyson Spheres are hypothetical megastructures built around a star to utilize solar power. They would produce radiation in the infrared.

People have been speculating about extraterrestrials forever, but it is only recently that it has become a topic genuinely considered. With previously classified footage of UFOs being released and NASA holding its first public meeting on the subject, it seems that the possibility of aliens is being considered beyond science fiction and conspiracy theories. This shows that the advancement of science is breaking down the barriers of social norms, proving that every possibility should be considered.

An interesting thought experiment would be to imagine what would happen if we did discover unambiguous evidence of extraterrestrial intelligence. What would that mean in terms of our species' place in the universe, and what would it say about traditional religions and philosophy? Could we even handle the truth? Well, centuries ago people couldn't handle the fact that the earth orbited the sun. Perhaps our future is bound to be analogous to that age-old tale.

Figure 9: On May 31, 20203, panelists participate in a recent first for NASA – a public UFO conference.

Practical Significance

One might be wondering, what does all of this information mean for the future of the human race? Aliens or not, are we bound to traverse the cosmos as an interstellar species? Well, perhaps we are, but we have a long way to go. Even if we did determine that a planet was suitable for us to inhabit, we would have to deal with the trouble of getting there. Since we are nowhere near close to traveling at light-speed and have not figured out how to bend spacetime to form wormholes and the like, it is unlikely that we'll be visiting an exoplanet anytime soon. However, that doesn't mean that all of this research is futile.

As we all know, climate change is an ever-more prominent issue, and it seems almost impossible that humanity will change its ways before the damage is irreversible. With widespread factory farming and fossil fuel use, it is only inevitable that we will destroy this planet before it gets swallowed up by the sun as it turns into a red giant. So, a new world may be the only viable option for the future of humanity. It seems by refusing to make changes to our lifestyles, this species has declared that we would rather go through the trouble of finding a new home than being at a slight inconvenience for the sake of the common good. Is that truly our best

option? Will we find a new home before ours becomes inhabitable? Questions like this are what drives the cutting-edge field of exoplanet research.

Conclusion

In the coming decades, our knowledge of extrasolar planets will only begin to compound, making breakthrough discoveries in astrobiology more imminent than ever. The importance of this field in regards to the implications of humanity's future are bound to thrust it into the public eye. Its prevalence will be sure to guide funds and public interest in the near future, setting the stage for endeavors we never would have thought possible!

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The Enigma of Stigma: The Continued Stigmatization of Mental Illness Today By Paige Glowacki

Arising out of a lack of awareness and fear, stigmas surrounding mental health have become ingrained in most cultures. In colonial times in America, the mentally ill were treated like criminals and regarded as "sub-human beings."[1] For 300 years, treatment of mental illness was primitive and static, often brutal and inhumane, like being chained in kennels and cages like wild beasts. [2] In the 1800s, a period of institutionalization began, housing the mentally ill away from society. By the 1930s, electroconvulsive therapy and surgery were introduced as revolutionary ideas in treating mental illness with limited effectiveness. Pharmacotherapy, in particular, the discovery of antipsychotic medications, accelerated successful therapy into the 21st century. These medications offered the promise of curing mental illness and thus resulted in deinstitutionalization and outpatient therapy. Eventually, several antidiscrimination laws in the United States were enacted to protect the rights of the mentally ill and combat stigmas. However, these laws only target the discrimination component of stigma; cues, stereotypes, and prejudice are beyond the reach of legislation. [3] Besides social stigma, or the biased attitudes others have, many individuals suffering from mental illness experience self-perceived, or internalized, stigma. Both social and self-perceived stigma have negative consequences that impair self-esteem and character, obstruct access to treatment, and result in poorer outcomes. Despite advancements in treatment, awareness and education, and federal policies addressing mental illness in the United States, stigmas of mental illness remain exceedingly prevalent in society.

Stigma is comprised of stereotypes, prejudice, and discrimination. Stereotypes, though occasionally positive, become a problem when applied to all members of a broad group. Stereotypes not only fail to accurately represent the group as a whole but also are assumed to be true regardless of individual characteristics. As a result, stereotypes often elicit prejudice, which consists of prejudgment and automatic negative thoughts. Prejudiced attitudes can lead to discriminatory behaviors that restrict the rights of the target group and the opportunities available to them. Exploitation and domination, enforcement of social norms, and avoidance of disease and contagion are the main reasons that societies stigmatize.

The inhumane treatment of mental illness throughout history promoted the social acceptance of stigma. During the Middle Ages, the mentally ill were made outcasts in society. Many doctors viewed mental illness as either a result of demonic possession, physical illness, or a punishment from God. [4] In the American colonies, treatment of the mentally ill involved emotional torment, social isolation, and physical pain. These treatments were designed to minimize the trouble caused to the community by the mentally ill. [5] Doctors performed invasive surgeries on patients in an attempt to treat mental illness as early as the 16th century, such as trepanation, a procedure where doctors created holes in the patient's skull to alleviate pressure on the brain following a head injury or to release evil spirits from the mentally ill. [6] Both intrusive and life-threatening, these treatment methods did nothing to improve the patient's health, let alone their mental health. Instead, the treatments worked at a socioeconomic level to

exclude mentally ill people from society. Incarceration in response to atypical behaviors became another tactic to isolate this population. As a result, many people with mental illness found themselves in jail and could never receive proper treatment living as convicted criminals. [7] The first public mental health hospital in North America was the Public Hospital for Persons of Insane and Disordered Minds in Williamsburg, Virginia, established in 1773. Treatment in this hospital included solitary confinement, conditioned fear of the doctor, powerful but ineffective drugs, bleeding, shackles, and plunge baths. [8] In 1843, Dorothea Dix, an influential advocate of the mental health movement, saw the mentally ill placed in jails along with criminals. In her Memorial to the Legislature of Massachusetts, she writes, "I proceed, Gentlemen, briefly to call your attention to the present state of Insane Persons confined within this Commonwealth, *in cages, closets, cellars, stalls, pens! Chained, naked, beaten with rods,* and *lashed* into obedience!" [9] By drawing attention to these inhumane conditions, Dix paved the way for state hospitals nationwide.

Initially, such state institutionalization was considered the most effective way to care for the mentally ill. In reality, these "insane asylums" punished patients and were made into hostile environments of isolation, further reinforcing a negative view of mental illness in society. State hospitals were underfunded, understaffed, and so overcrowded that they resulted in extremely poor living conditions. The priority of the hospitals became custodial care instead of therapeutic care, with the role of medical professionals shifting from treatment to caretaking. In 1887, Nellie Bly, a journalist for the *New York World* newspaper, feigned insanity to be admitted covertly to the Women's Lunatic Asylum on Blackwell's Island, New York. She published a book detailing her experience called *Ten Days in a Mad-House,* in which she wrote, "The insane asylum on Blackwell's Island is a human rat-trap. It is easy to get in, but once there it is impossible to get out." [10] Her writing prompted an investigation of the asylum and resulted in New York City increasing funding for mental health care and making regulatory changes. Other reports detailing the human rights violations that occurred in institutions began to surface, and the institutional care system received harsh criticism. Thus, an effort for deinstitutionalization and outpatient treatment began.

As a result, in the late 1800s and early 1900s, psychiatrists began to work towards cures and preventative techniques. Doctors continued to question the possibility of curing mental illnesses, but they believed that preventing them would solve the problem in the future. Therefore, eugenics, or the attempt to improve the human species through "breeding out" undesirable characteristics, and forced sterilization were introduced. [11] Connecticut became the first state to prevent marriage for people with epilepsy and others whom they called "imbeciles and the feeble-minded." [12] Additional states began to mandate the sterilization of an individual when recommended by a board of experts. As a result of these human rights violations, over 65,000 mentally ill people were sterilized. The Supreme Court upheld the state's ability to do so in *Buck v. Bell*. The Virginia statute providing for the sexual sterilization of inmates of institutions afflicted with a hereditary form of insanity or imbecility was determined to be protected under the Fourteenth Amendment. [13] Evidence that the practice of sterilization

did not prevent mental illness was documented. Forced sterilization delayed the advancement of mental illness treatment and promoted stigmas. [14]

As the 20th century dawned, new treatment methods flourished, including electroshock therapy, the lobotomy, and antipsychotic drugs. Yet, many of these treatment methods only came about as a way to adjust the perception of mental illness in society rather than actually helping the mentally ill. [15] Electroconvulsive, or electroshock, therapy induces seizures in the patient via electrical currents directly applied to the skull. It effectively reduced symptoms for long periods of time; however, its earliest use was on non-consenting individuals and produced severe side effects. Though now only practiced with consent, electroconvulsive therapy remains controversial due to the history of its use.

Another extreme example of a physical treatment was the lobotomy. Doctors severed connections between the prefrontal cortex and the rest of the brain by either drilling through the skull or inserting an instrument through the patient's eye socket. One prominent example of a patient who underwent a lobotomy was Rosemary Kennedy, the sister of John F. Kennedy, who was born with a mild intellectual disability. The American Medical Association did not approve the lobotomy procedure. However, Joseph Kennedy, Rosemary Kennedy's father, decided to have her lobotomized. After the procedure, Rosemary experienced significant complications that left her unable to walk, talk, or care for herself. She was placed in institutional care for the remainder of her life. [16]

Introduced to the United States in 1954 as the first antipsychotic, chlorpromazine, brand-name Thorazine, proved effective at alleviating certain symptoms of mental illness to the point that patients could lead relatively normal lives and not be confined to institutions. [17] Partially motivated by personal experience, John F. Kennedy enacted the Community Mental Health Act in 1963. This bill was designed to encourage individuals with mental illness to live in their communities and was a turning point in society's outlook towards mental illness. [18]

In theory, deinstitutionalization was designed to improve the lives of many patients, but in reality, it was poorly implemented. With inadequate funding, the community mental health centers that were supposed to take over caring for released patients were overwhelmed and inadequate. The mentally ill failed to receive appropriate care after mass deinstitutionalization, with a lack of support from the community. Many became homeless or were taken into the correctional system. The results of this approach, though not as inhumane as containment in asylums, created a massive homeless population. People on the streets were not only severely impaired by their illness, but they also served as clear proof of the general public's reinforcement of stereotypes. Structural discrimination of the mentally ill, a form of institutional discrimination against individuals that restricts their opportunities, is still pervasive, both in rehabilitation efforts and in legislation. [19]

Federal policies expanded the legal protection of individuals with mental illness by directly addressing discriminatory behavior by others. However, these policies cannot legislate changes in beliefs and attitudes about mental illnesses. Stigma acts as a central contributing factor to the healthcare, education, and employment disparities that individuals with mental

illness face. Some commonly held stereotypes, often perpetuated in media depictions, create a biased image of the mentally ill as threatening persons who endanger society. As a result of these stereotypical views, discrimination and public stigma emerge. The laws that target this discrimination share three common features: expanded protections over time for people with mental illness, differential protections for subgroups with mental illness, and implementation challenges that stem from label avoidance that impair the capability and effectiveness of these laws. The Americans with Disabilities Act (ADA) of 1990 addresses workplace discrimination against those with disabilities, including the protection of those with psychiatric disabilities. Additionally, it requires the addition of "reasonable accommodations" for people with disabilities in the workplace unless the accommodations impose "undue hardship" on the employer. [20] While this legislation aimed to expand protections for all people with both physical and mental disabilities, many ambiguities in the guidelines remained as to how it pertains to those with mental illnesses. Furthermore, researchers documented continued challenges faced by those with psychiatric disabilities when seeking protection under the ADA. For example, the Supreme Court ruled that workers could not be classified as disabled if their condition was controlled by mitigating measures, like medication. The new legislation negatively impacted workers with mental illness whose symptoms were controlled by psychotropic medications.

The Education for All Handicapped Children Act of 1975 addresses discrimination against those with disabilities in school settings and also offers protections to students with mental health-related disabilities. It granted federal funding for states to provide an appropriate education for disabled students. Renamed the Individuals with Disabilities in Education Act in 1990, the law has been amended several times to increase protections for children with mental health-related disabilities.

Health insurance coverage for mental health and substance use disorder treatment has usually been less generous than regular medical care. The Mental Health Parity Act of 1996 was the first federal law that addressed equality between mental health and medical services, yet it was extremely limited. Later, the Mental Health Parity and Addiction Equity Act of 2008 expanded jurisdiction, requiring large private group health plans that offer mental health or substance use disorder insurance coverage to offer these benefits at parity with medical or surgical benefits in annual or lifetime dollar limits, financial requirements, and treatment limitations. Though it only applies to large group health plans, the law provided a foundation for further expansion of mental health and substance use disorder parity by the Patient Protection and Affordable Care Act of 2010. Although antidiscrimination protections for people with mental illness have become more expansive over time, the protections are not uniform for all subgroups with different types of mental illness due to explicit language about inclusion and exclusion criteria, vague language open to interpretation, and incentives created by the legislation that affect specific groups differently. [21]

Over the past few decades, increased education and awareness of mental illness have led to the recognition and acceptance of mental health, joining physical health, as an essential part of one's well-being. Many factors contribute to this amplified awareness of mental health and its

role in everyday life. Social media features countless individuals sharing their experiences with mental illness. Movies and television shows have started correctly portraying the realities of mental illness rather than just promoting stereotypes. Despite these normalized discussions about mental health, the stigma remains present and obstructs access to treatment. In particular, minority groups often experience difficulties accessing affordable and reliable mental health care. Additionally, federal laws attempted to put mental health on the same level as physical health. However, many sources, including insurers and healthcare market financial administrators, have found ways to undermine these federal protections. Implementing policies to make treatment more available is ineffective if not all individuals have equal access to mental health care. [22]

There is evidence that public stigma toward major depressive disorder has significantly decreased over the last twenty years. Researchers from Indiana University utilized data from interviews conducted in 1996, 2006, and 2018 where respondents were asked about their views on major depressive disorder, schizophrenia, and alcohol use disorder. The study measured people's beliefs about underlying causes, perceptions of likely violence, and rejection of these three disorders. In 2006, almost 50% of individuals reported an unwillingness to work closely with someone with depression, compared to 30% in 2018. However, stigmas of schizophrenia and alcohol dependence remain unchanged. The perception of threat associated with schizophrenia has actually increased over the course of the study, from around 55% in 1996 to almost 70% in 2018. [23]

A recent example of stigma surrounding depression has been on display in the media. Yale University has been faced with a federal lawsuit. Yale has been accused of pressuring suicidal students to withdraw from the school during their crisis. Furthermore, the students must go through a stressful readmittance process. Rachel Shaw-Rosenbaum, a freshman at Yale, committed suicide on campus in 2021 after contemplating the consequences of withdrawing from the school. Her death exposed the punitive way Yale treated suicidal students and the university's reinstatement policies. Yale renamed the process "reinstatement" instead of "readmission." Nevertheless, students had to write an essay, secure letters of recommendation, have an interview with Yale officials, and take two courses at another four-year university to return. One student who was struggling with panic attacks and feelings of worthlessness had heard about other students being forced to leave because of depression and the lengthy reapplication process. She feared Yale's response if she were to open up about her thoughts. Thus, she did not seek help. When it became unbearable to continue suppressing her depression, she attempted suicide. With the university perpetuating harmful stigmas, this student felt unable to open up about her struggles, leading her to attempt to solve the problem the only way she knew how. [24] The university is now being sued over "systemic discrimination" against students with mental health disabilities, claiming that the Ivy League institution unfairly treats students struggling with mental health and fails to modify policies to accommodate them. Another student, Hannah Neves, was encouraged by Yale psychiatrist Heather Paxton and mental health and counseling director Paul Hoffman to withdraw from the school. These officials added

that it would "look bad" for her if she was withdrawn involuntarily. They had not discussed alternative accommodations with her that would have allowed her to remain at Yale while receiving mental health treatment. [25] Instead, these oppressive and stringent policies would result in the loss of housing, community, health insurance, and removal from campus. The resulting trauma from involuntary withdrawal exacerbates the external and internal stigma experienced by the student. These policies only serve to amplify barriers to effective care and resolution. This evidence supports the fact that the stigma of mental illness flourishes in the intellectual elite of current society.

  "Everyone is depressed sometimes." "It is normal to have anxiety." "You seem fine" or "You do not look sick." These comments seem harmless and may actually be offered with a positive intention. However, they usually do more harm than help. Remarks like these are heard too often and are not easily forgotten. As a result, people with mental illness can believe they are overreacting. While everyone may experience depression and anxiety at some point in their lives, the severity of their burden is magnified. Thus, it becomes much more challenging to divulge to others. Often, the mental illness has already created permanent scars, both physically and mentally. While federal laws provide a foundation of protection against discrimination, legislation has fallen short. There must be a creative engagement of society to find alternative approaches that directly target other components of stigma. These challenges should involve ethical enlightenment and moral responsibility. Moving forward in this battle against stigmatization requires increasing interpersonal contact with individuals with mental illness and educating people on how stigma is a moral injustice. [26] How much longer will the mentally ill have to grapple with debilitating stigmas in addition to their illnesses?

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Artificial Intelligence for Healthcare Applications By Boyang Hu

Abstract

Artificial intelligence is revolutionizing healthcare by enabling the development of smart, self-learning systems that assist in disease diagnosis, treatment, and prevention. In this review paper, we discuss key models associated with this advancement and their enabling applications. Particularly, we focus on transformative applications of artificial intelligence in diabetes care. Capitalizing on the availability of rich patient data, artificial intelligence is playing a pivotal role in diabetes prevention, early detection, and effective management. With the proliferation of artificial intelligence models, we foresee a future of proactive disease control and improved quality of life for millions worldwide.

Introduction

Artificial intelligence (AI) focuses on creating smart, self-learning systems capable of performing tasks that typically require human intelligence, such as problem-solving, pattern recognition, and decision-making. Particularly, in the healthcare industry, AI is playing a vital role in disease diagnosis and treatment [1-2]. Below are some examples in this field:

- AI algorithms can be leveraged to detect and classify abnormalities in medical images (e.g., X-rays, magnetic resonance images [MRIs]) in order to assist radiologists in decision making.
- By analyzing patient data and medical literature, AI can predict the likelihood of disease occurrence and develop targeted treatment plans.
- When coupled with sensors and wearable devices, AI algorithms can perform comprehensive and real-time analysis based on a patient's vital signs, activity levels, and health trends. If there is a deviation from the normal pattern, the algorithm will alert the healthcare provider.
- Advanced AI models are capable of diagnosing rare diseases, which are often difficult to diagnose and treat due to the limited available datasets. Researchers have developed a deep learning algorithm acting as a search engine of pathology images [3]. Due to its self-supervised feature, it can find similar cases and make decisions without the need for manual annotations and large datasets.

Among these revolutionized applications, in this article, we will focus on discussing the use of AI in diabetes management. Diabetes is a chronic metabolic disease that has a heavy healthcare burden globally. Fortunately, a large amount of diabetes data generated by diabetic patients, including medical records and images, is readily available, serving as the opportunity for AI algorithm development [4]. In the sections below, we will first introduce widely-used AI models in healthcare applications, and then discuss their usage in diabetes care in detail.

AI models for healthcare applications

The field of Machine learning finds its origins within the AI community. Machine

learning, as a subfield of AI, is primarily concerned with the development of computer programs capable of empirically acquiring knowledge and performance metrics relevant to specific tasks.

Machine learning methodologies can be effectively categorized into two primary groups: supervised and unsupervised methods. In supervised learning, the model is provided with pre-labeled outputs, or there exists some priori knowledge of the dataset. In contrast, unsupervised learning operates without prior knowledge or labeled data. An intermediate approach, known as semi-supervised learning, strikes a balance between these two paradigms by working with a mix of labeled and unlabeled data points.

When confronted with a new machine learning task, the initial consideration typically revolves around the choice between supervised, unsupervised, or semi-supervised methods. If the goal is to elucidate the inherent patterns within the data rather than imposing predetermined labels, unsupervised learning is the preferred approach. Supervised learning is only applicable when a labeled training dataset is at hand. For instance, in the study titled "Ensemble Machine Learning on Gene Expression Data for Cancer Classification," where a substantial volume of gene expression data for diverse cancer samples is available, a classifier is constructed to achieve high-level cancer sample classification based on gene expression profiles [5]. The decision tree algorithm was chosen for its interpretability compared to other methods. Decision tree is a widely employed machine learning technique for classification and regression tasks. The fundamental concept involves constructing a tree structure through iterative partitioning of a dataset based on its features. Each node in the tree represents a test for a specific attribute value, while the leaves signify classes of instances that satisfy the test. The decision tree ultimately returns a binary determination when instances are assessed. The path from the root to the leaves, along with the nodes on the path, function as rule prerequisites, which, in turn, yield predictive rules for the leaf categories. Decision trees offer an intuitive decision-making process that is amenable to comparison with existing biological knowledge, thereby offering valuable insights to biologists and clinicians.

Neural networks, a highly popular machine learning model, draw inspiration from the biological nervous system, particularly in the way information is processed within the brain. The terminology within the machine learning domain is itself influenced by this model. A neural network comprises interconnected neurons, linked by weights, and utilizes activation functions to transmit and transform signals. Training a neural network typically involves the application of gradient descent methods to minimize the disparity between predictions and ground truth values.

Applications in diabetes care

Specifically, the proliferation of AI in the field of diabetes care presents a paradigm shift in how diabetes is prevented, detected, and managed.

Unlike type 1 diabetes, type 2 diabetes is often preventable or its onset can be delayed through lifestyle modifications, including maintaining a healthy diet, regular physical activity, and weight management. Thus, the prevention of type 2 diabetes is crucial for both individual wellbeing and public health. AI has been demonstrated to be powerful here. One of the widely

used algorithms is predictive population risk stratification model, which is a data-driven approach that uses various factors to identify individuals or groups at a higher risk of developing type 2 diabetes. By comprehensively analyzing patient information (e.g., age, family history, genetics, lifestyle, and medical history), this model can effectively predict the likelihood of diabetes occurrence and help healthcare providers and public health organizations target preventive interventions. These efforts collectively improve the efficiency and effectiveness of diabetes prevention.

Similarly, by leveraging the data from medical devices (e.g., glucose meter, continuous glucose monitoring device), AI can play a significant role in diabetes detection. For example, decision tree models have been developed to predict the development of type 2 diabetes in pregnant women with gestational diabetes, a prediction method that has better discriminatory power than routine monitoring of fasting blood glucose levels [6].

Once diabetes has been diagnosed, its management becomes critical for the patient. Effective diabetes management involves a multifaceted approach that includes blood sugar monitoring, medication adherence, and dietary control. In particular, complication prevention is paramount, as uncontrolled diabetes can lead to long-term health issues, such as heart disease, kidney problems, neuropathy, and vision impairment. Various AI models have been proposed here. For example, an AI-powered medical device named IDX-DR has been approved to analyze digital retinal images for early detection of diabetic retinopathy [7]. The American Diabetes Association (ADA) has recognized the use of autonomous AI for detecting diabetic retinopathy and macular edema. Early detection of diabetic retinopathy using AI can reduce diabetes-related ophthalmic complications and preventable blindness. On a different note, finding the right medication for the right patient is also critical for diabetes management. In that regard, decision tree models have been used to predict whether a patient will have an adverse reaction to certain medication [8].

Outlook

The application of machine learning in diabetes care is revolutionizing the management and treatment of this chronic condition. The use of machine learning in diabetes care is not limited to predictive analytics alone. These techniques also enhance decision support systems, aiding in medication adherence, dietary recommendations, and lifestyle modifications. Moreover, telemedicine solutions empowered by machine learning have made healthcare more accessible and efficient for individuals with diabetes, transcending geographical barriers. By harnessing the potential of AI, we are moving closer to a future where diabetes is not merely managed but proactively controlled, improving the quality of life for millions of individuals worldwide.

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How are Galaxies Formed, and in What Ways Have their Properties Evolved Over Time?
By Casey Bennett

The Big Bang and Emergence of Stars

The study of the universe's origins and the subsequent evolution of galaxies provides us with profound insights into the nature and structure of our cosmic realm. The journey begins with the monumental event known as the Big Bang, which occurred approximately 13.8 billion years ago [1]. In the immediate aftermath of this cataclysmic event, the universe was in an intensely hot and dense state, with temperatures reaching about 10^{32} Kelvin [2]. But as it expanded, it cooled down, eventually reaching a temperature of around 3000 Kelvin after about 380,000 years, setting the for the formation of galaxies and the emergence of the first stars [2].

Following the Big Bang, the universe underwent a remarkable cooling process. As the temperature dropped, subatomic particles, such as protons, neutrons, and electrons, began to take shape [3]. These particles are considered the fundamental building blocks of matter, and their formation marked a crucial milestone in the early universe's development. The cooling and condensation of these subatomic particles allowed for the formation of the first atoms [3].

Figure 1: Chronological events following the Big Bang.

Over time, the force of gravity exerted its influence on the atoms that filled the vast expanse of space [10]. Under the gravitational pull, these atoms started to congregate and form enormous clouds, known as stellar nurseries or molecular clouds [11]. These stellar nurseries played a pivotal role in the subsequent formation of galaxies and the birth of stars. Within these immense clouds, the ingredients necessary for stellar birth and evolution were assembled.

Within the stellar nurseries, gravity continued to act, causing the accumulation of matter and initiating the process of star formation. The first stars, known as Population III stars, emerged from the primordial gas clouds [4, 13]. These early stars were primarily composed of hydrogen and helium, the two lightest elements in the universe [4]. In contrast to the stars observed today, these initial stellar giants were significantly larger and more luminous [4, 5]. They blazed with surface temperatures approaching 100,000 Kelvin and could have masses ranging from tens to hundreds of times that of our Sun [5, 6].

The formation of the first stars was a transformative event in the history of the universe. Their immense size and luminosity had a profound impact on the surrounding cosmic environment. The radiation emitted by these early stars ionized the surrounding gas and created regions of ionized plasma [14], influencing the subsequent formation of galaxies. The high energy output of these massive stars, combined with their eventual explosive demise in supernova explosions, played a critical role in the enrichment of the interstellar medium.

The life cycle of Population III stars culminated in spectacular supernova explosions. These events released an enormous amount of energy and scattered the synthesized heavy elements, such as carbon, oxygen, and iron, into the interstellar medium. The injection of these heavier elements into the surrounding gas clouds paved the way for subsequent generations of stars and the formation of more complex stellar systems [3]. The enrichment of the interstellar medium with these heavier elements was essential for the evolution of galaxies and the eventual emergence of life-supporting planets.

The early universe, originating from the Big Bang, underwent a remarkable journey that led to the formation of galaxies and the birth of the first stars. The cooling process allowed for the formation of subatomic particles, which, under the force of gravity, gathered to create immense stellar nurseries. Within these nurseries, the first stars, composed primarily of hydrogen and helium, were born. These stars, with their immense size and energy output, played a crucial role in shaping the evolution of the universe. Their explosive supernova deaths enriched the interstellar medium with heavier elements, paving the way for subsequent generations of stars and the development of diverse galactic populations.

Formation of Galaxies

Galaxies find their origins in colossal clouds of gas and dust scattered throughout the cosmos. As gravity exerts its influence, these immense reservoirs of matter undergo a remarkable process of collapse. The gravitational contraction triggers a cascade of events, leading to the formation of a spinning disk-shaped structure. This process is driven by the conservation of angular momentum as the cloud collapses, causing the material to rotate around a central axis. As the collapse progresses, the cloud gradually assumes a flattened configuration, forming the basis for future galactic structures.

Within the flattened disk of gas and dust, stars begin to take shape, marking a pivotal stage in the formation of galaxies. As the material within the disk becomes increasingly concentrated, the intense gravitational forces induce clumping [12], giving rise to the birth of new stars. These nascent stars form from the collapse and condensation of dense pockets within the disk. Simultaneously, planetary systems begin to coalesce around these newly formed stars, fostering the potential for the emergence of diverse and dynamic worlds.

While galaxies often arise from the gradual accumulation of matter within a spinning disk, alternative paths to galactic formation exist, driven by dramatic collisions between galaxies. When two galaxies collide, their gas and dust clouds interact, creating a cosmic dance. The merging of galaxies leads to the fusion of their respective clouds, instigating intense star

formation and the birth of new planetary systems. These galactic collisions can also result in the expulsion of gas and dust, triggering a burst of star formation as the interstellar medium undergoes dynamic changes. The process of galactic mergers contributes to the creation of diverse galactic structures, including massive galaxies and elliptical galaxies.

The formation of galaxies is far from uniform across the expanse of the universe. Density fluctuations in the primordial matter distribution result in regions with varying concentrations of matter [15]. In regions of higher matter density, the gravitational pull is stronger, promoting a higher rate of galaxy formation [7]. These dense regions serve as cosmic nurseries, fostering the birth of numerous galaxies. In contrast, regions with lower matter density experience a reduced rate of galaxy formation. The interplay between gravitational forces and matter density variations shapes the intricate tapestry of galactic distribution across the universe.

The process of galaxy formation has undergone significant changes over the vast cosmic timeline. In the early universe, galaxy formation occurred at a more rapid pace compared to the present era [16]. As the universe aged, the rate of galaxy formation gradually diminished. The coaction between gravity, matter density, and cosmic expansion influenced this temporal evolution [16]. Understanding the factors that govern the pace of galaxy formation throughout cosmic history is crucial for unraveling the mysteries of the evolving universe.

The formation and evolution of galaxies encompass a captivating interplay of gravitational collapse, star formation, and galactic mergers. From the collapse of massive gas and dust clouds to the birth of stars within disk-like structures, the journey to galactic existence is one of awe-inspiring complexity. The non-uniform distribution of galaxies across the universe and the temporal variations in the rate of galaxy formation add further layers to this intricate narrative. By delving into the processes that shape galactic evolution, we deepen our understanding of the cosmos and our place within it.

Properties of Galaxies

The captivating realm of galaxies unveils a rich tapestry of diversity, with a myriad of unique appearances and properties. Classifying galaxies based on their distinct characteristics allows us to comprehend the vast array of cosmic structures that populate the universe. Galaxies can be categorized by their visual appearance, with the primary types being spiral, elliptical, and irregular [17]. Furthermore, their properties, such as mass, luminosity, and chemical composition, provide deeper insights into their nature and evolution [17]. Additionally, the environment in which galaxies reside plays a pivotal role in shaping their properties and dynamics.

Galaxies exhibit a remarkable assortment of visual forms, reflecting their internal structure and dynamics. Spiral galaxies, characterized by their rotating disks, prominent arms, and a central bulge, embody elegance and symmetry. Elliptical galaxies, on the other hand, lack the spiral structure and appear as smooth, ellipsoidal systems with no discernible disk component. Irregular galaxies defy conventional classification, displaying irregular shapes and a

more chaotic distribution of stars and gas. Understanding these distinct types of galaxies enables us to discern the underlying physical processes driving their formation and evolution.

Figure 2: Three major classifications of galaxies.

Beyond their visual appearance, galaxies possess a multitude of properties that shed light on their intrinsic characteristics. Mass serves as a fundamental parameter governing the structure and dynamics of a galaxy. The distribution of mass within a galaxy influences its rotation, stability, and interaction with other galaxies [22]. Luminosity, a measure of the total energy emitted by a galaxy, provides insights into its brightness and distance [7]. Determining the luminosity aids in unraveling the cosmic distances, aiding our understanding of the vast scale of the universe. Additionally, the chemical composition of galaxies offers a glimpse into their evolutionary history [7]. Abundance of elements such as hydrogen, helium, and heavier elements provides clues about the age and enrichment processes that have shaped the galaxy over time.

Over the eons, galaxies have undergone significant changes in their properties, reflecting a dynamic evolution. The earliest galaxies were smaller and less massive than their modern counterparts [7]. These primordial systems possessed lower chemical abundances, indicating a lower enrichment of heavy elements [7]. As stars formed and evolved within these galaxies, the synthesis of heavier elements through nucleosynthesis processes enriched the interstellar medium, leading to the rise in chemical abundances. This evolutionary trend has contributed to the diverse chemical compositions observed in galaxies today.

The luminosity of galaxies has also witnessed transformations throughout cosmic history. Factors such as the presence of massive stars or the activity of supermassive black holes at their centers can significantly impact a galaxy's luminosity [8]. Galaxies hosting intense star formation or harboring active galactic nuclei display heightened luminosities, outshining their counterparts.

The environment in which galaxies reside plays a vital role in shaping their properties and characteristics. Galaxies that belong to dense galaxy clusters experience different evolutionary pathways compared to those residing in less dense regions [18]. In galaxy clusters, gravitational interactions, and mergers between galaxies are more prevalent, leading to increased mass and higher metallicities [18]. The influence of the cluster environment induces transformations in the structure and dynamics of galaxies, contributing to the observed variations in their properties.

The vast diversity of galaxies manifests through their varied appearances and properties. The classification of galaxies based on their visual characteristics and intrinsic properties allows us to comprehend their nature and unravel their evolutionary stories. As galaxies have evolved over time, their properties have transformed, reflecting the interplay of stellar processes, environmental factors, and cosmic interactions. Exploring the types, properties, and environmental influences on galaxies deepens our understanding of the dynamic and ever-evolving universe we inhabit.

Dark Matter and its Impact on Galaxies

In the vast expanse of the universe, an elusive and mysterious substance known as dark matter is sought to exist. Constituting a significant fraction of the universe's total mass, dark matter operates beyond the grasp of our conventional senses. It remains invisible to telescopes, evading direct detection due to its non-interaction with light and other forms of electromagnetic radiation [19]. Yet, its presence can be inferred through the gravitational effects it exerts on visible matter, providing a tantalizing glimpse into its enigmatic nature [19]. Dark matter's gravitational influence plays a pivotal role in shaping the cosmos, dictating the structure, dynamics, and evolution of galaxies.

Dark matter, despite its invisibility, leaves behind an indelible imprint through its gravitational pull. This ethereal substance acts as the gravitational glue that holds galaxies together and governs the vast-scale structure of the universe. While its direct detection remains elusive, the influence of dark matter is revealed through its gravitational effects on visible matter, including stars and galaxies.

One intriguing manifestation of dark matter's gravitational dominance lies in the peculiar rotational behavior of galaxies [9]. According to the laws of physics, objects situated farther from the center of rotation should exhibit slower speeds compared to those nearer to the center [9]. In the context of galaxies, stars and gas in the outer regions should display diminished velocities relative to the inner regions [9]. However, meticulous observations have uncovered a perplexing anomaly — an unexpected constancy in the rotational speeds throughout the galaxy [9]. This conundrum, aptly known as the "galactic rotation problem

Figure 3: Measured rotational speed curve versus the calculated rotational speed curve.

To reconcile the observed uniform rotational speeds of galaxies, an extraordinary hypothesis emerges: the existence of dark matter. This invisible cosmic entity provides the missing gravitational force required to harmonize the motion of stars and gas throughout the galaxy. Dark matter's pervasive influence counters the gravitational dilution that would typically decelerate outer regions, ensuring that the rotational speeds remain consistent across galactic scales. It is the enigmatic presence of dark matter that resolves the puzzle of galactic rotation, weaving an intricate tapestry of invisible yet influential cosmic dynamics.

Beyond its impact on galactic rotation, dark matter transcends the boundaries of individual galaxies, shaping the broader structure and evolution of the universe. Its gravitational clout governs the formation of large-scale cosmic filaments, clusters, and superclusters, weaving an intricate cosmic web. The distribution of dark matter dictates the locations of galaxies within this web, sculpting the vast cosmic structure we observe. By unraveling the mysteries of dark matter, we gain invaluable insights into the underlying forces driving the cosmic ballet of galaxies, illuminating the fundamental workings of the universe itself.

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Performance of Housing Designs in Developing Nations During Floods By Alexander Chen

Abstract

      This paper covers a simulation testing different housing structures to determine flood resistance. Two locations, Vietnam and Egypt, were selected due to their high flood rate and classification as 'developing countries'. The materials and architectural styles from each of the locations were researched and compared. Analyzing material properties such as tensile strength and thermal density, custom housing structures were chosen for a stilt house, which is used in Vietnam and compared to an Egyptian style mud brick house. These structures were made into three dimensional models in SolidWorks, a computer aided design (CAD) software, before undergoing a stress test with similar properties to a flood. The results were compared, and the highest performer was determined by the structure which held up the best against the controlled stress test.

Introduction

      Floods cause the most death and destruction of all natural disasters due to their prevalence throughout the world. Here, we analyze two contrasting methods of housing designed to cope with floods, one being stilt housing found in Vietnam and the other being mud brick housing from Egypt. flood-exposed regions.

      The goal is to examine current designs of housing in these countries, and what possible weaknesses they have. By modeling these homes with CAD, stress tests can be performed to find possible weak points and areas of the housing designs that seem weaker, and see what possible improvements could be made. Furthermore, technologically advanced areas can often build houses that are far more resilient, so it's interesting to compare how well traditional, rural housing compares to those modern buildings in the event of a flood.

a.   Location 1 - Vietnam

      Vietnam is a country in southeastern Asia characterized by its mountainous terrain, humid climate, and heavy exposure to weather. Vietnam is ranked first in terms of flood exposure, due to the prevalence of many types of flooding in the area as well as typhoons (Vietnam Embassy, n.d)

      The primary factors of flooding in Vietnam is a topic that's been thoroughly researched, given how common flooding is. One study analyzed 68 research papers, and the primary cause of flooding (cited as such 29 times) was found to be rainfall. Other drivers included high tides (17), increase in water discharge and river flow (17), climate change (12) and storm surges, typhoons, and cyclones (11) while the rest argued that human driven causes such as urbanization and dams were the primary issue (Nguyen et. al, 2021).

      A large portion of Vietnam's population is concentrated near the Mekong River because of accessibility to water and fertile land, but also heightens the risk for flooding. Since almost 85% of the nation lives in possible flood zones (areas where floods are possible), and the Red

River Delta of Vietnam is both where the population is most densely concentrated as well as where flooding is most common, floods pose a significant risk to the people of Vietnam (Alpuerto, 2023).

In rural areas, many Vietnamese live in stilt houses, much similar to designs from 4,000 years ago. These houses are propped up on stilts, with room for raising livestock underneath the house itself. Materials for these rural houses include wood, bamboo, cane, or rattan (Robinson, 2016).

b.   Location 2 - Egypt

Annual nile floods overflow the riverbank, causing structural damage to many of the buildings in the area. The buildings in this region, especially those of the poor, are similar to how they were thousands of years ago, made of mud bricks. These houses could easily be damaged or destroyed by floods, but were quite simple to build or fix due to the large amount of mud washed up by the Nile during the floods. Therefore, the houses are often rebuilt or repaired after floods (Aladdin Travel, n.d).

Egyptian mud houses along the Nile river, for the most part, are not designed to last. In these houses, the central room was most used with a kitchen nearby. The houses had stairs leading to the roof, which doubled as living space since interiors tended to be dark due to the lack of natural lighting (Britannica, 2023).

Methods - Stilt House

a.   Material Properties - Bamboo

Since Solidworks doesn't have bamboo as a usable material, a custom material had to be designed and implemented for the stilt house. Custom materials must include properties such as elasticity modulus and density. The following are the material properties of bamboo, one of the main materials used in the stilt house (Javadian et. al, 2019).

1. Modulus of elasticity of bamboo ranges from 20,000 MPa to 40,000 MPa. The statistic used was 28,230 MPa, which is equivalent to **4094415.3 psi**
2. The Poisson Ratio ranges from 0.180 to 0.334, it "decreased with the increasing bamboo age, growth height, and the radial position" between the outer and inner layers. For the purpose of this simulation, the average ratio of **0.257** was used.
3. The Shear modulus was converted from gigapascals to psi, as was the requirements for solidworks: 1.44099999949 Gigapascals is about **208999.38 psi**
4. Mass density was converted from kilograms per cubic meter to pounds per square inch, using imperial units in the simulation instead of metric:
   350 kg/m^3 is about **0.0126446 lbs/in^3**
5. Tensile strength of bamboo is about **1400 psi**
6. The specific heat is about **0.33134 Btu/(lbs℉)**

b.   Custom Material Construction

With the custom bamboo material Fig 1, a set of panels was modeled to represent sections of the structure. The panels were used to construct the flooring, along with wooden stilts that were made of teak wood. The full flooring and stilt structure was modeled, as shown in Fig 2.

Fig 1 shows the results of the bamboo after adding the material properties and the appearance models.

c.   Stilt House Design

Fig 2: Flooring Design

Fig 2 displays the floor of the stilt house. A bamboo flooring is layered on top of 5 foot high stilts made of teak wood.

Fig 3: Walls

The walls of the house are made of hollow bamboo, held together by metallic rods to keep the bamboo in place, shown in Fig 3.

Methods - Egyptian Mud Brick House

a.   Material Properties - Mud Brick
1. Modulus of elasticity of mud brick is about **600 psi**
2. The Poisson Ratio is found to be about **0.25**
3. Mass density was converted from kilograms per cubic meter to pounds per square inch, using imperial units in the simulation instead of metric:
2000 kg/m³ is about **0.07225458 lbs/in³**
4. Yield strength of mud brick is about **4000 psi**
5. The specific heat is about **0.33134 Btu/(lbs℉)**

b. Egyptian Mud Brick House CAD design

Fig 4: Mud brick house design

The Egyptian house was made of mud brick, with a rounded rectangular entrance and windows, as well as stairs leading up to a flat roof area above the structure.

Results

A typical flood tends to range from 1 to 3 feet in depth. Since the stress test is designed as a simulation for structural damage, the force of three feet of water will be used as the standard. In addition, each foot of water holds about 500 pounds of force. Thus, for the purposes of this simulation, three feet of water or 1500 pounds of force will be applied as the external force on the models in a static study.

a. Vietnamese Stilt House

Fig 5: bamboo shaft under stress test of 1500 pounds

Fig 5 shows a simulation of how the bamboo would hold up against 1500 pounds of force pushing on one end. According to this simulation, there will be slight bending towards that edge, but the bamboo retains its overall shape and structure.

Fig 6: the same stress test is applied to the stilts, causing moderate bending yet maintaining overall structure without deformation.

Fig 7: another angle of the stress test in Fig 6

Fig 6 and Fig 7 display the results of the stress test. Since the upper portion of the stilt house lies far above the flooding height, it was not included in the simulation to reduce meshing errors and calculation time. The results show little structural damage to areas above the stilt, and slight bending in the stilt themselves.

b.   Egyptian Mud Brick House

Fig 8: The stress test of 1500 pounds was applied to one of the walls on the mud brick house, causing severe deformation.

Fig 9: A different angle of the stress test in Fig 8.

Fig 8 and Fig 9 show the results of the simulation, where 1500 pounds of force are used to push against one of the walls in the structure. Moderate to severe deformation could be seen throughout the model, where the wall on which the force was applied has caved in, causing structural damage to the faces next to it as well as the roof and flooring.

Discussion

The controlled stress test, where an equal force of 1500 pounds were applied onto each structure shows that the Vietnamese style stilt house is more resilient to floods than the mud brick house. Aside from the physical deformation that can be seen, the deformation scale of the two models shows almost twice the value in the mud house in comparison to the stilt house. Though the stilts were able to withstand the flood with less physical deformation, the bend in the teak-wood logs are far from ideal. Possible methods to improve resistance could be burying the stilts deep in the earth and reinforcing each stilt with weights, which would prevent the wood from bending as much.

Based on the simulated results, the stilt house yielded a deformation scale (a function relating the size of the model to the maximum displacement of deformation) of about 36.6647, while the mud brick house had a scale of about 72.8888. These results are plausible, since the stilt house is designed to withstand the floods with their high wooden stilts taking the blunt force and damage while the house remains intact, while the mud brick house is designed to be easily rebuilt.

Conclusion

In this paper, simulations were used to test flood resistance of housing in developing nations. With the advancement of technology, such simulations could be used more frequently in developing areas to improve overall safety and mitigate risks. The goal of the paper is to demonstrate as such, looking at a possible way of exposing risks in housing. With floods being among the most dangerous natural disasters, it's important to take any measures possible to improve flood resistance, especially in developing nations without strong infrastructure.

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Effects of SAQ, Continuous, and Fartlek Training on Overuse Injuries and Performance in Young Athletes By Vikram Pal

How can high intensity training methods such as SAQ (speed, agility, and quickness), Continuous, and Fartlek training, increase performance by reducing overuse injuries of high school swimmers and track runner athletes?

Overuse Injuries are not just injuries, but injuries due to an athlete's own actions. They can range from muscular inflammation, tendonitis, and other injuries caused by the overuse of actions or frequent training within athletic programs, causing detrimental effects to an athlete's health and possibly their career in the long-term. Different people use different training methods, ranging from high volume training (distance) to short distance training and more. The overuse injury problem is extremely common due to repetitive movements in racing athletes. In order to glean which method is most effective for performance and reduced overuse injuries, this paper will review multiple articles and studies that show correlation between various training methods and overuse injuries. Training methods relate to overuse injuries, which also are heavily related to performance goals, whether they are short distance sprints or long distance marathons. This paper seeks to find results and correlations from studies that indicate which method of high-intensity training works best for reducing overuse injuries, and in the long term, increasing performance. Specifically focusing on racing sports, like swimming and track, this article includes data that represents the physical effects after different types of training. The collected data represents differences in certain methods of high-intensity training and how each separate variation affects the likelihood of getting an overuse injury. It eventually concludes by determining the most beneficial training to reduce overuse injuries. These results should determine what method is the most favorable for long-term performance and injury reduction in racing sport athletes. The collected data shows results inferring how athletes respond physically from different types of training methods. These athletes showcase the results of their specific variation of training. After exploring these results, my conclusions show which training method is most beneficial for athletes in terms of reduced overuse injuries and how it can affect long-term performance.

Out of 3 selected training methods, SAQ, Continuous, and Fartlek, one of these training methods is slightly more beneficial to an athlete. Overuse injuries and different types of training are correlated because of an athlete's muscular and cardiovascular stress during training. Sometimes an overwhelming volume of repetition in practice can harm an athlete's performance due to incomplete recovery time, which then could lead to overuse injuries. Overuse injuries are one of the most common injuries in high level athletes, and they are a common cause for certain athletes being prevented from achieving their goals. This research paper aims to find the answer to which training method is most effective for athletic performance by looking at which is less likely to cause overuse injuries. [5] SAQ, Continuous, and Fartlek training are 3 very commonly used methods for young athletes, especially in high school sports. In competitive swimming and running, overuse injuries appear very frequently due to the constant repetitive motions of the

body, ranging from the lower extremities all the way to the upper body. SAQ training is known to be incredibly useful for sprinters and the overall speed of an athlete, rather than endurance. It includes high intensity and low volume sets, being more beneficial to sprint athletes than endurance athletes. However, it still is beneficial to both because of the overall power an athlete generates. Even though overuse injuries are generally known to be from high repetition, it can also happen under high intensity.[6] SAQ training and overuse injuries are related in this way, considering the amount of effort in a short amount of time the athlete needs to use. In SAQ training, there are many rest intervals due to the intensity the athlete needs to exert during the set. This training method's goal is to increase neuromuscular efficiency (NME), which allows muscle fibers to move quicker. It requires short, high intensity bursts. The aim of SAQ training is to increase muscular power, endurance, running economy (amount of energy necessary to go at a certain pace), and overall motor skills. Sprinters or athletes using very high intensity bursts use SAQ training a lot because of how it is targeted to power and speed, aiming to use the body's max capability.

Fartlek and Continuous training are forms of training which intend to increase endurance. Fartlek training is a mix of speed and endurance training, having separate intervals with different intensities. In Swedish, Fartlek means "speed play." Endurance athletes also use this type of training, even though it is not as consistent as a sprinter athlete. [10] Racing athletes use all 3 training methods at a high level. Continuous training is one of the most commonly used, especially for beginner athletes. Continuous training is the idea of no intervals, or non-stop movement, aiming to increase muscular and cardiovascular endurance. This training method hugely benefits athletes' ability to sustain a pace for a long time. However, it doesn't massively allow an athlete to utilize the full capability of the body in a short burst sprint. In comparison to SAQ training, continuous training requires continuous training that allows you to constantly expend energy, without using all of it at the same time. Continuous training methods can be used in running, swimming, or even other stamina-based movements. This method is very commonly used because it allows athletes to sustain their split times during competition. Split times are measured segments, slicing the race into pieces, so coaches can analyze where you started to go at a slower pace. As an example, in a 200 meter freestyle competitive swimming race, there are 4 segments of 50 yards. Every 50 yards, there are split times which can vary, allowing athletes to analyze consistency and endurance. Coaches use these splits to help further train the athlete, focusing on what they need to fix and improve. That is where continuous training comes in handy, because the athlete will be able to sustain speed for longer, allowing their performance to be further enhanced and improved upon. [9]

The final training method that will be used as a comparison is fartlek training. Fartlek training is different from SAQ training and endurance/continuous training. Fartlek is Swedish for "speed play," and is used especially by runners and swimmers. In practice, there are sets involving high intensity intervals, unlike continuous training, which either has no interval, or very little rest, with high distance and volume. The point of Fartlek training is almost combining SAQ training and continuous training into one. Fartlek training aims to help both endurance and

sprinting. During practice, Fartlek training methods can involve many different changes in intensity. For example, a swimmer swims 75 meters then another 25 meters at a higher intensity. The idea of this "speed play," is to train the body to adapt to going at fast speeds while also under fatigue from distance. This method is incorporated by having slow and fast training segments, which triggers athletes' bodies and forces them to go at a fast speed even after a long distance. This way, athletes can develop endurance and speed at the same time, aiming to go faster for longer.[4] SAQ training, continuous training, and fartlek training all have a related effect on the performance of athletes. However, they can also easily cause overuse injuries within athletes. Certain training methods are better or worse for an athlete's health. For performance, the best training option is a method that is difficult, but also safe, so athletes can get results without suffering from an overuse injury. [3] This creates a question whether high intensity or high volume training methods are more effective for performance. Continuous training is known to be extremely high volume, targeting endurance based results, with little rest. Continuous training is also referred to as endurance training. An NIH study recorded information about shoulder injuries that sprout from distance competitive swimmers. Another survey conducted over 5 years explained how there are more than 2500 shoulder revolutions every practice. This can be interpreted as continuous endurance training, considering the high volume of strokes taken by the swimmer. The study explains how more hours and revolutions of the shoulder over time can cause overuse injuries. "Elite swimmer injury rates were 4.00 injuries per 1000 hours training for men and 3.78 injuries per 1000 hours training for women. Shoulder injuries are the most common injuries, with prevalence between 40% and 91% ." [2] Based on this data, it is clear that more repetition can easily backfire and cause overuse injuries, and less volume usually can possibly help reduce the average number of injuries per athlete. [8]

Continuous training is one of the largest causes of overuse injuries, mainly due to the overwhelming amount of training volume and distance. Even though this data by the NIH proves that continuous training is high risk for an overuse injury, it all depends on how the athlete ramps up before jumping into too much distance. Continuous training is still very effective for endurance athletes, and athletes that want to sustain pacing in a sport. Fartlek training can also be put into this category. While it requires significantly less volume than continuous training, fartlek distance can still be relatively high. Additionally, the "speed play" in fartlek training can also cause an athlete to suddenly change pace, which can also be dangerous due to extremely sudden changes in speed. If training intensity and distance aren't gradually increased, there is a high chance for an overuse injury to occur if an athlete does something too far outside their usual training regimen. Studies have shown many different causes of overuse injuries, ranging from an overload of intensity, poor technique, or too much volume and distance. "The musculoskeletal system, if subjected to excessive stress, can suffer from various types of overuse injuries which may affect the bone, muscles, tendons, and ligaments." Despite the fact that overuse injuries are more commonly prevalent in endurance athletes, they still occur with sprinters. [5]

Fartlek training is generally more safe than continuous training, considering that there are segments and intervals during which the athlete can rest or go at a slower pace. This allows the athlete to recover better, which in turn can reduce overuse injuries while also increasing endurance and speed. In comparison to continuous training, fartlek training isn't extremely high in volume, where athletes are completely overusing their muscles for a period of time that is too long. Fartlek training aims to generate endurance and speed at the same time, allowing athletes to avoid overuse and extremely long and continuous training sessions. A study from the National Library of Medicine shows the correlation between distance athletes and sprinters, and the rate of overuse injuries for every athlete. The injury incidence rate was 1.81 injuries per 1000 athletics hours of training. Middle and long-distance runners had the highest injury incidence rate (2.38), followed by jumpers (1.62), and sprinters (1.34). The rate for sprinters was almost half of the rate for middle to long distance runners. Even though this is a single study, it has still been shown countless times that the distance and volume that an athlete performs is more likely to lead to overuse injuries, in comparison to high intensity. High volume training is more likely to cause overuse injuries than high intensity training with lower amounts of volume. Fartlek training is neither long distance nor sprinting but a mix of both. While fartlek is known to be speed play, it is still nowhere close in terms of distance in comparison to continuous training. With this logic, we can hypothesize the incidence rate would be in the middle of long distance runners, and sprinters.[3]

SAQ training is logically the safest form of training in terms of results while also avoiding injury. This method aims to increase strength and power in your body, which also can help injury prevention by strengthening and upgrading the toughness of your body. While doing this, you are able to get twitchy and fast movement, allowing the body to have an increase in performance during sports. SAQ training is by no means for endurance but for speed, agility, and quickness. Even though it is generally used by sprinters, it can also benefit endurance athletes. Every stroke or step in a racing sport requires a certain amount of power. If that level of power can be increased, the distance per stroke or stroke rate in swimming for example, then the overall performance and time of the race can be improved upon. It doesn't necessarily help maintain and pace yourself, but it can still hugely benefit overall speed and rate of movement rather than pacing. Despite this, an overload on the body can still happen to cause an overuse injury, such as stress fractures from constant load on a bone.

SAQ, continuous, and fartlek training all have their strengths and weaknesses. However, data shows us that distance runners have a higher injury rate than sprinters. If you do something even at a lower intensity over and over, the body will never have time to recover from the activity, causing constant and repetitive damage to bones and muscles, which can very likely lead to an overuse injury. This data from the Library of Medicine: "Middle and long-distance runners had the highest injury incidence rate (2.38), followed by jumpers (1.62), and sprinters (1.34)." This information from the Library of Medicine later states how middle and long distance runners have almost double the amount of injuries. This data pushes us to ask how you can improve endurance or speed without injury. The answer to that is a gradual increase in intensity or

distance. Even if an athlete attempts to gradually increase distance or intensity, it can easily go wrong with continuous training. Continuous training is not the safest option if the aim is to get results and avoid overuse injuries at the same time. This does not mean that you will always get injured, or it won't give results. Continuous training is one of the most useful ways to increase endurance and pacing ability in athletes. However, the rate of injury is too high to ignore. Many of these injuries are due to overly repetitive movements like shoulder impingement in swimmers, tendonitis, and stress fractures. The reason why it is so easy to get injured with continuous training is because of the massive volume and distance. It is extremely difficult to gradually increase distance when its volume is so large. An athlete will be told to try a new amount of distance for more time, and they push through. Up to a point, pushing your limits is good, until it is too much for tendons, bones, and muscles to handle. For this reason, continuous training is the most likely to cause overuse injuries.

The next 2 methods are fartlek training and SAQ training. SAQ training is commonly used for sprinters, which can help us figure out why the data from the Library of Medicine shows almost a 2x injury rate for distance runners than sprinters. SAQ training isn't anywhere as dangerous as continuous training. For distance runners, it is very hard to increase endurance without actually running high volumes of distance. This problem can be solved by fartlek training, combining a safe amount of distance, while also adding speed to make it help increase endurance at a faster pace. Due to statistics, and the experience of athletic coaches, SAQ training is the most beneficial in terms of speed and power, including rehabilitation from overuse injuries. The summary of SAQ training is speed, agility, and quickness. All of which require an increase in strength within tendons, bones, and muscles. This durability increase is shown to actually help rehabilitate athletes that have overuse injuries, and can help prepare them for higher distances. A professional trainer explains the science behind how sprinting can actually build up and create a base for endurance. "When you sprint, you are using maximum power and muscle endurance," says Aaptiv trainer Jaime McFaden. She adds that because sprints push the body to its max efforts, it can actually build up a higher VO2 max and increase overall endurance. Another Aaptiv trainer mentions: "According to Aaptiv trainer Rochelle Moncourtois, sprints require quick energy and can lead to more efficient running by increasing the amount of glycogen that can be stored in the muscles." Glycogen is a form of energy storage in the muscles. When athletes start going into sprint training, the force output is actually higher, and the stored energy is also higher. This can lead to the overall speed being faster, disregarding pacing. An athlete who can pace themselves, and goes at a slower speed will look better, but it won't be as fast as an athlete who has greater overall speed. Sprint training plus endurance training at the same time can prove to be extremely useful, which is why Fartlek and SAQ training are very good ways to avoid overuse, but also increase performance. [12]

Despite evidence, there are also multiple sources opposing SAQ training and Fartlek training. In contrast, continuous training is distance training, however it is not as intense as fartlek and SAQ training. SAQ and fartlek training have extremely high intensities requiring the majority of the body's capacity. Just because distance is generally minimal in fartlek and SAQ

training, it doesn't mean that overuse injuries can't happen. If an athlete's body is too intensely worked even in a short period of time, it can lead to overuse. Examples include stress fractures, increased soreness, and overtraining, which can then later lead to injury if not given adequate rest, or a decrease in intensity. A study from Rutgers University shows the injuries in young men from starting high-intensity training. This study mentions that: "Knee and ankle sprains and strains were the most common injuries from high-intensity interval workouts, people should do neuromuscular training -- especially those that focus on strength, jumping and balance." The study aimed to see how to build up to high-intensity training. In the second half of this sentence, the study mentions "neuromuscular training." This can actually be interpreted as SAQ training, standing for speed, agility, and quickness. SAQ training includes strength training, jumping, and balance while aiming for speed, agility, and quickness. SAQ training actually incorporates the base of strength necessary to work up to harder high intensity interval training sessions. This evidence partially disproves previous statements. This way, we can actually notice a similarity with the wording, by calling this high-intensity training. SAQ training can be praised as the better training method in terms of injury prevention. However, this study was about unathletic men, who were not heavily engaged in athletics. For the average athlete, basic SAQ neuromuscular training is not needed as much. Still, it is extremely useful for athletes if they are suffering from overtraining. SAQ training can help both athletes and non athletes to create a good base of strength, durability, balance etc. Despite the fact that fartlek training is less distance than continuous training, it is also very difficult to keep track of. When you get faster, it might be difficult to increase the intensity without getting injured. We can say it is common for multiple sources to agree that fartlek training can easily cause overuse injuries in beginner athletes.

Fartlek training is only recommended for intermediate and high level athletes, rather than beginner athletes. For this reason, continuous training can actually have something positive to bring for beginner athletes. Despite the injury rate for continuous training, it actually can have some benefit in terms of slowly ramping up training to prepare for fartlek training and other high intensity methods. An article from Nuffield Health explains the advantages of practicing endurance training before high intensity training. "If you are new to exercise then continuous exercise is a great way of building a good level of cardiovascular fitness before moving onto more advanced methods of training such as intervals or high intensity interval training (HIIT)."

Swimmers and track runners, and even all racing athletes, have extremely intense training sessions. Taking into account SAQ, Fartlek, and Continuous training, there are many other training methods used by athletic coaches. SAQ, Fartlek, and Continuous are just 3 very popular methods for the average racing athlete. Every athlete is different, from speed, size, strength, and experience. Racing athletes range from sprinters to long distance to mid distance athletes. Almost half of the injuries in athletes result from overuse, rather than actual performance. We can solve this by finding the most efficient way to enhance performance, and reduce the likelihood of an overuse injury. SAQ, Fartlek, and Continuous training are all beneficial for an athlete's performance. However, certain methods have more downsides than others. Multiple sources of evidence constantly prove the difference in sprinters and distance athletes. This

difference is overuse injury. Distance athletes get almost twice the amount of overuse injuries in comparison to sprinter athletes. This is because of the high volume and repetition they have. It is clear that continuous training can cause more injury than the other training methods mentioned. Fartlek and SAQ training are the remaining two training methods that are close in debate. Considering that Fartlek training needs prerequisites, or experience, it is safe to say that SAQ training is the best for all types of athletes, ranging from beginners, to professionals. Beginners usually need endurance or strength before going into fartlek workouts. Athletes that are more experienced usually can handle fartlek workouts, and injuries are few and far between. SAQ training is designed for an athlete that needs speed, agility, and quickness, rather than high volume distance training. This type of training allows athletes to reduce overuse injury, and increase speed, without overworking. This can be easily sustainable, and can allow athletes to have beneficial increases in performance, while also avoiding overtraining. While there is an obvious pattern that the higher distance an athlete goes, the more likely it is for them to get an overuse injury, it doesn't mean that fartlek and continuous training are automatically worse. It all depends on the level of each athlete and which training method is most beneficial for them. For this reason, SAQ training is the best training method for overall athletes, not just intermediate, or professional, but even beginners.

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The Effects of Curcumin and Pycnogenol on Novel Targets in Parkinson's Disease By Anne Zhu

Abstract

Parkinson's disease (PD) is a prominent neurodegenerative disorder that presently has no curative agent. Rotenone (ROT), an insecticide with acaricidal properties linked to PD, induces oxidative damage and dopaminergic neuronal loss. Curcumin (CUR) and pycnogenol (PYC), natural compounds known for their anti-inflammatory properties, were explored as potential treatments for ROT-induced PD. Cell adhesion, MTT, caspase assays, and ELISA tests were conducted to assess the effects of LPS, ROT, CUR, and PYC on inflammation, proliferation, apoptosis, and protein expression in U937, a human leukemia cell line, and CCD-18 cells, derived from healthy colon tissue. LPS, an endotoxin correlated with PD, elevated cancer cell adhesion significantly, but both CUR and ROT successfully reversed the effects. During a series of MTT assessments, all molar concentrations of CUR and PYC were able to significantly mitigate the effects of rotenone in human colon cells and notably decrease cancer cell proliferation over the span of 24 and 48 hours. Furthermore, CUR and PYC countered the increased caspase activity induced by ROT, retaining apoptosis levels in CCD-18 cells. This study also revealed ROT's reduction of MMP-9 expression in colon cells with CUR and PYC significantly attenuating this effect. Similarly, CUR and PYC exerted an ameliorative effect on decreased BDNF levels induced by ROT. Molecular docking revealed that CUR had strong binding affinities with Casp3, GSK-3β, MAOA, IL-1β, and BDNF, providing insight into potential interaction with these PD-associated protein signaling mechanisms to counter ROT's effects. This research aligns with prior studies on neuroprotective and anti-cancer attributes of CUR and PYC and identifies ROT as a novel target for further PD investigation. Moreover, it underscores CUR and PYC as viable treatment candidates for PD.

Introduction

1.1 Background on Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder that involves the loss of dopaminergic neurons in the substantia nigra and affects over 10 million people worldwide (Holden and G. Goldman). This progressive disease is caused by the accumulation of Lewy bodies from α-synuclein aggregation, oxidative stress, and neuroinflammation– all of which contribute to the degeneration of neurons in the brain (American Parkinson Disease Association). The absence of dopaminergic neurons in the brain leads to debilitated overall motility, cognitive executive functions, tremors, and gastrointestinal symptoms (Calabresi et al.).

1.2 Impact on Public Health

Parkinson's disease tremendously impacts public health– its disability and death rate is increasing faster than any other neurological disorder in the world. Statistically, PD has more than doubled over the past two decades, an increase of over 100% since 2000. It has caused 5.8

million disability-adjusted life years along with 329,000 fatalities (World Health Organisation). Fox Foundation in partnership with Parkinson's Foundation and other community organizations revealed that the economic burden of PD is nearly $52 billion annually (J). Moreover, Parkinson's disease exacts a heavy social toll on our society. Diagnosed patients severely struggle with social symptoms ranging from stigma to dehumanization. Many can no longer maintain activities, relinquish poor roles and relationships, and suffer from depression and poor mental health due to effects such as dementia and hallucinations (Butters).

1.3 Pathology of PD

This chronic neurodegenerative disease is characterized by the accumulation of misfolded alpha-synuclein protein (Lewy bodies) in dopaminergic neurons of the substantia nigra (Mahul-Mellier et al.). The substantia nigra, a constituent of the basal ganglia, plays a pivotal role in synthesizing dopamine, a neurotransmitter that contributes to numerous central nervous system functions (Cleveland Clinic). Elevated levels of α-synuclein in the PD brain result in diminished mitochondrial complex I activity and heightened production of reactive oxygen species (ROS). Consequently, this provokes oxidative stress and triggers neuroinflammation. In addition, the metabolism of dopamine gives rise to the generation of ROS, potentially reducing the threshold for apoptotic cell death (Devi et al.). The pathological presence of these exacerbated Lewy bodies disrupts the normal functioning of the brain; they interfere with the transmission of signals between nerve cells and compromise motor control, hence precipitating the degeneration of vital neuronal populations (Gilbert).

1.4 PD-associated cell signaling mechanism

While the pathology of PD is still not fully understood, apoptosis serves as the principal mechanism for neuronal loss in this neurodegenerative disease, as substantiated by postmortem examinations (Erekat, "Apoptosis and Its Role in Parkinson's Disease"). These investigations have discerned DNA fragmentation and modifications in apoptotic chromatin specifically within the dopaminergic neurons of individuals afflicted with Parkinson's disease. The involvement of apoptosis in the pathogenesis of this disease is further supported by in vitro studies, which have demonstrated the augmented activity of caspase-3 and enhanced expression of its active form in the substantia nigra pars compacta. The application of caspase inhibitors has exhibited their ability to rescue neurons from death in cell-based Parkinson's disease models, proposing that apoptosis represents the primary mechanism driving neuronal demise in Parkinson's disease (Erekat).

Neuroinflammation, which involves the activation of immune cells in the microglia and the release of inflammatory molecules, also plays a role in PD (Wang, Liu, et al.). For example, microglia may interact with α-synuclein and promote its propagation and aggregation, contributing to neuronal death (George et al.). On the contrary, extracellular α-synuclein can directly activate microglia and trigger a phagocytic reaction, releasing harmful substances such as proinflammatory cytokines, reactive oxygen intermediates, proteinases, and complement proteins (Isik et al.). Activated microglia express various cell-surface receptors, leading to increased levels of cytokines such as TNF-α and interleukin-1β (IL-1β) in the substantia nigra of

PD patients (Song et al.). Persistent and excessive activation of microglia, accompanied by the release of pro-inflammatory mediators, can instigate a state of chronic neuroinflammation (Gomes-Leal). This sustained inflammatory condition within the central nervous system poses a significant threat to neuronal well-being and actively participates in the process of neurodegeneration (Thameem Dheen et al.).

1.5 Current research of Curcumin and Pycnogenol in neuroprotection and immune regulation

Current research has shown that suppressing neuroinflammation with anti-inflammatory drugs can protect dopaminergic neurons in individuals with Parkinson's disease (Jin et al.). Pycnogenol (PYC), a compound of natural chemicals extracted from French maritime pine bark, has been examined for its ability to reduce inflammation and protect neurons (Griffin). It contains various beneficial compounds like phenolic monomers, flavonoids, and phenolic acids which are known for their antioxidant properties.

In a study utilizing a Rot-induced cell model of PD, PYC treatment was found to significantly increase cell viability and reduce cell apoptosis in Rot-treated PC12 cells in a dose-dependent manner. Furthermore, PYC exhibited the ability to diminish Rot-induced NF-κB activation. Inhibition of NF-κB signaling with its inhibitor replicated the biological impact of PYC on Rot-induced iNOS and NO expression levels, along with neurotoxicity in PC12 cells. These findings implied that the protective effects of PYC against Rot-induced neurotoxicity in PC12 cells may be linked to the modulation of the NF-κB-iNOS signaling pathway (Gao et al.). PYC treatment also significantly inhibited the activation of nuclear factor-kappa B (NF-κB), a key regulator of inflammation, and demonstrated the ability to hinder the buildup of reactive oxygen species. PYC showcased the capability to rejuvenate the body's antioxidant defense mechanisms and further accentuated the increase in striatal dopamine levels (Khan et al.).

Another naturally occurring compound that has been studied for potential neuroprotective abilities is curcumin (CUR), the primary bioactive polyphenolic substance in turmeric (Patel). Curcumin has the ability to regulate the functions of multiple signal transduction pathways linked to reducing disease progression (Wang, Jiang, et al.). It is considered neuroprotective in PD using its anti-inflammatory effects, specifically by interacting with transition factors, growth factors and their receptors, enzymes, and genes that regulate cell rapid production and programmed death (Cole et al.). The inhibition of ROS formation, glial cell activation, a-syn aggregation, and neuronal cell apoptosis are additional ways that curcumin supports the neuroprotection of Parkinson's disease (Nebrisi). The capacity of CUR to exert inhibitory effects on the monoamine oxidase-B (MOA-B) enzyme, thereby augmenting the levels and accessibility of dopamine (DA) within the brain, has garnered significant interest in the scientific field recently (Juvekar and Khatri). In the SNc of rotenone-induced PD model rats, CUR treatment was found to significantly improve the electrical activity of neurons (Darbinyan et al.). The anti-inflammatory properties exhibited by pycnogenol and curcumin interventions provide valuable insights into their prospective neuroprotective capacities in the context of Parkinson's disease.

1.6 Hypothesis

Curcumin and pycnogenol will be able to mitigate the effects of rotenone on cell adhesion and proliferation, MMP-9, and BDNF expression, and prevent rotenone-induced neuroinflammation to maintain levels of apoptosis in U937 and CCD-18 cells.

1.7 Purpose and Rationale

This research aimed to explore potential treatments for the adverse outcomes of ROT associated with PD. Hence, a comprehensive evaluation of curcumin and pycnogenol was conducted against ROT exposure on CCD-18 immune cells. These chemicals were also subjected to examination against cancer cells to determine if their anti-inflammatory effects had any significant impact on cancer life proliferation. The ensuing investigations encompassed a spectrum of assessments including cell adhesion, MTT, caspase assays, and ELISA tests, along with an in silico screening test to calculate the binding affinities of PD-associated targets.

Materials and Methods

2.1 Solution Preparation

A single dose of curcumin and pycnogenol was obtained for this study, sourced from Nature Made Turmeric 500 mg Capsules and NOW Supplements Pycnogenol 100g. 7 mg of curcumin was transferred along with 3 mg of pycnogenol into separate empty microcentrifuge tubes. Following, 5 mg of dimethyl sulfoxide (DMSO) was dispensed into the curcumin microcentrifuge tube, while 1 ml of water was added to the pycnogenol microcentrifuge tube. Dilutions of 1x, 10x, 100x, and 1000x were made sequentially and 5 μL of curcumin and pycnogenol was added to either 96-well plates or six-well plates to make concentrations of 0.1 μM, 1 μM, 10 μM, 0.3 μM, 3 μM, and 30 μM.

2.2 Cell Culture

U937, a human leukemia cell line, was derived from the histiocytic lymphoma of a 37-year-old male by Sundstrom and Nilsson (Chanput et al.). CCD-18 cells are a human fibroblast cell line derived from the healthy colon tissue of a black, two-and-a-half-month-old, female patient (REPROCELL). These cells were cultured separately in flasks containing Eagle's Minimum Essential Medium (MEM), supplemented with 10% fetal bovine serum (Invitrogen, USA). The flasks were then placed in an incubator (Thermo Scientific, USA) set to a temperature of 37°C, 5% carbon dioxide, and 95% air. For the cell culturing procedure, the existing medium was aspirated from the flask, and 4 ml of trypsin was added. Subsequently, the flask was incubated for 4 minutes. After incubation, the flask was gently tapped to dislodge cells from the flask's surface, and 5 ml of fresh MEM was introduced to halt the trypsin activity. The entire cell suspension was then transferred to another tube and subjected to centrifugation at 3000 rpm for 4 minutes, resulting in the formation of a cell pellet at the tube's bottom, which was utilized for later experiments.

2.3 U937 Cell Image Analysis

Cell imaging analysis was employed to assess the impact of curcumin and pycnogenol on U937 cell number and adhesion to augment comprehension of their relation to inflammation. The U937 cells derived from the cell culture were transferred into 10 wells of a 24-well plate, with

two wells each for the following treatments: control, CUR 0.1 μM, 1 μM, 10 μM, PYC 0.3 μM, 3 μM, 30 μM. Following a 24-hour incubation period, the cell media in the well plate containing U937 cells treated with curcumin and pycnogenol was aspirated, and each well was supplemented with 400 μL of Hema-3 fixative. After 2 minutes, the Hema-3 fixative was taken from each well and replaced with 300 μL of Hema-3 stain. After another 2 minutes, the stain was discarded, and each well was rinsed twice with 1000 μL of distilled water. The cells were observed under 40x magnification and analyzed using ImageJ software to quantify the cellular density.

2.4 U937 and CCD-18 Cell Proliferation Assay

The Cell Proliferation Assay was conducted to evaluate the effects of curcumin and pycnogenol on the viability of U937 and CCD-18 cells utilizing MTT (3-(4, 5-dimethylthiazol-2)-2, 5-diphenyltetrazolium bromide).

The MTT cell viability assay protocol was executed in 96-well plates, adhering to ATCC guidelines, for both U937 and CCD-18 cells, with the exception of incorporating 70 μL of dimethyl sulfoxide as opposed to the recommended 100 μL [46]. Rows 1 and 6 were designated as controls, where U937 cells received no curcumin or pycnogenol treatment. Rows 7 and 8 encompassed curcumin dilutions of 0.1 μM and 1 μM, while Rows 9, 10, 11, and 12 comprised pycnogenol dilutions of 0.3 μM, 3 μM, and 30 μM, respectively. Post-treatment, the well plate underwent a 24-hour incubation period.

The procedure was repeated for both U937 and CCD-18 cells, except for a lengthened incubation period. The same steps were followed until the initial 24-hour incubation period, following which each plate received 5 μL of DEP concentrations again (no MTT yet). The cells were then subjected to another 24-hour incubation. Subsequently, 10 μL of MTT was introduced into each plate, and the identical ATCC protocol was employed after.

The following formula was applied to calculate the percentage decrease in cell survival while comparing control cells to treated cells: 100 * ((control cell survival - sample cell survival) / control cell survival).

MMP-9 and BDNF ELISA Test

An Elisa test was conducted on CCD-18 cells using the assay protocol provided by the Boster Bio kit. Two rounds of testing were carried out, each focusing on a specific protein-encoded gene: Matrix Metalloproteinase 9 (MMP9) in the first round, and Brain-Derived Neurotrophic Factor (BDNF) in the second round. MMP9 serves as a marker for processes such as inflammation, tissue remodeling, wound healing, and the mobilization of growth factors and tissue-bound cytokines (Tesař and Zakiyanov). BDNF serves as a modulator of neurotransmitters, and its expression is observed in the central nervous system, gastrointestinal tract, and various other tissues (Bathina and Das).

2.6 Caspase-3 Colorimetric Assay

Caspase-3 is a cysteine–aspartic acid protease that plays a vital role in cleaving specific cellular targets and executing cellular demise (Ponder and Boise). The Caspase-3 Colorimetric

Assay was used to investigate the potential apoptotic effects of curcumin and pycnogenol on cell demolition.

CCD-18 cells were cultured in a six-well plate and subjected to different treatments including control, 10 μL of rotenone, 10 μL of rotenone with the addition of 10 μL of curcumin and pycnogenol in molar concentrations of 0.1μM and 0.3μM in the following two wells. After the cells were incubated for 24 hours, the culture medium was removed, and 500 μL of trypsin was added to facilitate the detachment of the cells from the plate surface. The trypsin was incubated for 3-minute and 500 μL of MEM was added. Following, the medium along with the detached cells were transferred into 1.5 mL tubes and centrifuged for 3 minutes. The medium was removed, leaving behind the cell pellet at the bottom of each tube, and 50 μL of lysis buffer was added to each tube containing the cell pellet and vortexed. On a 96-well plate, 50 μL of assay buffer was dispensed into each well, followed by the addition of 45 μL of lysis buffer. 5 μL of the cell lysate from the tubes, along with 5 μL of a caspase substrate solution, were transferred into the respective wells on the 96-well plate. The plate was placed into a microplate reader (iMark, USA) and absorbance readings were taken at 0 minutes, 15 minutes, 30 minutes, 45 minutes, and 1 hour at a wavelength of 415 nanometers, allowing for the assessment of caspase activity over time.

2.7 Molecular Docking

An *in silico* test was performed to assess the binding affinity between curcumin and 10 different receptors through the PyRx v.08 software using the AutoDock Vina option. The macromolecules were sourced from the Protein Data Bank and downloaded as .pdb files. Diethyl phthalate was acquired as a .sdf file from the PubChem Compounds Database and subsequently converted into a .pdb file through the SMILES translator. VinaWizard was employed for the evaluation of binding affinity.

Both the macromolecule and ligand files were imported in the form of .pdb files into Discovery Studio (DS) Visualizer. Within DS Visualizer, an assessment of 2D interactions was performed between the macromolecule and the ligand. This analysis facilitated the identification of specific amino acid residue interactions occurring between the macromolecule and the ligand.

2.8 Statistical Analysis

Two-tailed T-tests were conducted with significance values of $p < 0.05$, $p < 0.01$, and $p < 0.001$. Error bars were used to denote standard error.

Results

3.1 The Effects of 24-Hour Exposure of CUR and PYC on U937 Cell Number and Density

A) Control

B) LPS

C) CUR 10 μM

D) CUR 1 μM

E) PYC 30 μM

F) PYC 3 μM

Effect of Curcumin and Pycnogenol on Cell Adhesion VS LPS

Fig. 1 Percent Change of U937 Cell Number after 24-Hour Exposure to Curcumin and Pycnogenol. A) Control viewed at 40x magnification. B) LPS viewed at 40x magnification. C) Curcumin 10 µM viewed at 40x magnification. D) Curcumin 1 µM viewed at 40x magnification. E) PYC 30 µM viewed at 40x magnification. F) PYC 3 µM viewed at 40x magnification. G) CUR & PYC effect on U937 cell adhesion compared to LPS. Results were analyzed using a Bio-rad microscope. All concentrations in µM. * = p<0.01   ** = p<0.001.

Cell Imaging Analysis was performed to determine the effect of curcumin and pycnogenol on U937 cell adhesion after 24 hours. Control U937 cells, which did not undergo any treatment, experienced intermediate levels of cell aggregations and density (**Fig. 1A**). The U937 cells induced with Lipopolysaccharide (LPS), bacterial toxins, demonstrated a 62.41% growth in cell adhesion compared to the control, promoting cell inflammation and a high increase in cell density (**Fig. 1B**). However, upon curcumin and pycnogenol addition to the U937 cells, cell adhesion was reduced significantly. CUR concentrations of 0.1, 1, and 10 µM reduced U937 cell adhesion by 65.27%, 67.42%, and 78.22%, respectively. Pycnogenol decreased the amount of cell adhesion by 65.88%, 79.69%, and 87.31% in concentrations of 0.3, 3, and 30 µM, respectively (**Fig. 1G**).

3.2 The Effects of 24-Hour Exposure of CUR and PYC on U937 Cell Viability

Fig. 2 A) Effect of curcumin on U937 cells during MTT Assay after 24 hours. B) Effect of pycnogenol on U937 cells during MTT Assay after 24 hours.*p<0.05, **p<0.01, ***p<0.001 compared to respective controls. Error bars denote standard error.

MTT Assay was performed to determine the effect of curcumin and pycnogenol on U937 cell proliferation rates after 24 hours. The control was established by untreated U937 cells. Curcumin and pycnogenol at all molar concentrations had significantly decreased U937 survival rates **(Fig 2)**. PYC 0.3 µM reduced U937 cell survival by 62.41% while CUR 10 µM showed the most significant change, with a 61.91% decrease in U937 cell proliferation (p<0.001; **Fig. 2A**).

3.3 The Effects of 48-Hour Exposure of CUR and PYC on U937 Cell Viability

Fig. 3 A) Effect of curcumin & pycnogenol on U937 cells during MTT Assay after 48 hours. B) Effect of curcumin combined with pycnogenol on U937 cells during MTT Assay after 48 hours. *p<0.05, **p<0.01, ***p<0.001 compared to respective controls. Error bars denote standard error.

The MTT assay was performed again over the span of 48 hours to help provide more data for long-term effects. After 48 hours, all molar concentrations of curcumin and pycnogenol still

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significantly decreased the survival of U937 cells by 46.42%, 34.31%, 29.84%, 42.43%, and 31.12%, respectively (**Fig. 3A**). These effects remained significant even when combined, resulting in percentages of 33.74%, 18.51%, and 43.81%, respectively (**Fig. 3B**).

3.4 The Effects of 24 & 48 Hour Exposure of CUR and PYC on CCD-18 Cell Viability

Fig. 4 A) Effect of curcumin & pycnogenol in comparison to rotenone on CCD-18 cells during MTT Assay after 24 hours. B) Effect of curcumin & pycnogenol in comparison to rotenone on CCD-18 cells during MTT Assay after 48 hours. *p<0.05, **p<0.01, ***p<0.001 compared to respective controls. Error bars denote standard error.

MTT Assay was performed to determine the effect of curcumin and pycnogenol on CCD-18 cell proliferation rates. This study entailed two separate experimental replicates, one conducted over a 24-hour period and the other spanning 48 hours, to comprehensively assess the effects of these chemicals. The control was established by untreated CCD-18 cells.

Rotenone significantly killed the healthy colon cells, decreasing the survival rate by -45.64% and -48.19% after 24 and 48 hours, respectively (p<0.001; **Fig. 4A**). All molar concentrations of curcumin and pycnogenol did not have any significant impact on healthy colon cells at both times. However, they demonstrated significant change when compared to rotenone. After 24 hours, CUR 0.1 & 1 µM and PYC 0.3 & 3 µM reversed rotenone effects by 76.64%, 53.28%, 66.65%, and 58.88%, respectively (p<0.001; **Fig. 4A**). After 48 hours, CUR 0.1 & 1 µM and PYC 0.3 & 3 µM reduced rotenone effects by 75.31%,65.38%, 66.19%, and 96.80%, respectively (p<0.001; **Fig. 4B**).

After 24 hours, the combined presence of rotenone with curcumin at concentrations of 0.1 µM and 1 µM, as well as pycnogenol at concentrations of 0.3 µM and 3 µM, resulted in the suppression of rotenone's effects by 54.84%, 43.04%, 52.59%, and 48.19%, respectively. After 48 hours, the inhibitory effects were further observed, yielding percentages of 20.93%, -15.66%, 28.41%, and 43.32%, respectively. Additionally, a synergistic evaluation of pycnogenol and curcumin was conducted to counteract rotenone's effects to achieve optimal results. Upon the simultaneous addition of CUR at 0.1 µM and PYC at 0.3 µM to cells treated with ROT at 0.01 µM, cell viability exhibited an augmentation of 47.23% after 24 hours, and a respective increase

of 40.77% in CUR 1 μM and PYC 3 μM. After 48 hours, results were still significant with percentages of 27.20% and 34.85%, respectively **(Fig 4)**.

3.5 The Effects of 24-Hour Exposure of CUR & PYC VS ROT on MMP9 Expression

Fig. 5 *p<0.05, **p<0.01, ***p<0.001 compared to respective controls. Error bars denote standard error.

Elisa Assay was performed to determine the effect of curcumin and pycnogenol on MMP9 expression in CCD-18 cells. Rotenone significantly decreased MMP9 expression by -12.54%. However, when CUR 0.1 μM and PYC 0.3 μM were added to rotenone, they had the opposite effect of rotenone and increased MMP9 expression by 15.18 % and 22.77%, respectively **(Fig 5)**.

3.6 The Effects of 24-Hour Exposure of CUR & PYC VS ROT on BDNF Expression

Fig. 6 *p<0.05, **p<0.01, ***p<0.001 compared to respective controls. Error bars denote standard error.

The BDNF Elisa Test was performed to assess how curcumin and pycnogenol influence BDNF expression in CCD-18 cells. Rotenone caused a substantial reduction of BDNF levels in CCD-18 cells, decreasing it by 72.58%. However, the addition of CUR at a concentration of 0.1 μM and PYC at a concentration of 0.3 μM to the rotenone-treated cells resulted in a significant reversal of rotenone's effects, showing increases of 8.62% and 9.51%, respectively **(Fig 6)**.

Fig. 7 *p<0.05, **p<0.01, ***p<0.001 compared to respective controls. Error bars denote standard error.

Caspase-3 Colorimetric Assay was performed on rotenone-induced CCD-18 cells to investigate the impact of curcumin and pycnogenol on caspase-3 expression. Rotenone led to a notable 665% upregulation of caspase-3 expression. However, the incorporation of CUR at a concentration of 0.1 µM and PYC at a concentration of 0.3 µM into rotenone-treated cells resulted in a remarkable mitigation of rotenone's effects, exhibiting reductions of 335% and 230.63%, respectively **(Fig 7)**.

3.8 Molecular Docking
Table 1: Binding affinity of 10 different receptors and Curcumin

Receptors	Average Binding Affinity to Curcumin
Caspase-3	-8.5
GSK-3 beta	-8.2
MAOA	-7.2
IL-1β	-6.9
BDNF	–6.8
MMP9	–6.4
NF-κB	-6.4
TNF-α	-6.3
Beta Catenin	-6.1
Alpha-synuclein	-5.0

Curcumin had the highest binding affinity with Caspase-3 at -8.5 kcal/mol and GSK-3 Beta at -8.2 kcal/mol. Curcumin had the lowest binding affinity with alpha-synuclein at -5.0 kcal/mol **(Table 1).**

Discussion

Curcumin and pycnogenol exhibited significant impacts on human cancer and healthy colon cells, effectively mitigating the influence of rotenone on the viability of CCD-18 cells and inducing apoptosis in U937 leukemia cancer cells.

The initial phase of this comprehensive study involved Cell Imaging Analysis to quantify the percentage variation in cell adhesion between untreated U937 cells and ones subjected to different treatments, including curcumin, pycnogenol, and LPS, a main outer membrane component of gram-negative bacteria (Farhana and Khan). LPS activation triggers the synthesis of various proinflammatory substances, including IL-1β, TNF, MMPs, and free radicals (ROS), which are known to be associated with Parkinson's disease (Huang and Kraus). Both CUR and PYC demonstrated significant attenuation of U937 cell agglutination across all molar concentrations, effectively reducing cell adhesion compared to the control group and, most importantly, compared to LPS treatment. The opposing effects of curcumin and pycnogenol on LPS-induced U937 cells suggest that these compounds may inhibit the inflammatory effects of the bacterial toxin that potentially contributes to the development of PD. Furthermore, a previous study demonstrated that curcumin effectively attenuated the upregulation of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) expression induced by LPS, thereby acting as a preventive measure against the onset of leukemia carcinogenesis. In vitro, pycnogenol

induced apoptosis in human breast cancer cells and reduced neuronal apoptosis by decreasing free radical generation, providing more insight into these chemicals bearing potential anti-cancer effects [36,21].

The outcomes of the MTT cell proliferation assay revealed that following both 24 and 48 hours, curcumin and pycnogenol effectively diminished the survival of U937 cells across all molar concentrations. In addition, these effects remained statistically significant even when combined and exhibited enduring effects. Preceding studies have demonstrated curcumin's capacity to impede tumor progression and confer chemopreventive effects on carcinogenesis, further corroborating the outcomes of the current investigation (Shanmugam et al.). During a study involving cancer patients who were supplemented with pycnogenol, it was observed that PYC treatment had the potential to alleviate adverse effects during oncologic treatment. Their apoptotic effects on leukemia cancer cells provide valuable indications of the potential anti-cancer properties associated with these compounds (Belcaro et al.).

In contrast, these agents did not exert significant effects on the viability of healthy colon cells during the course of another MTT assay and ameliorated the damage inflicted by rotenone. Rotenone (ROT), a crystalline isoflavone used as a universal pesticide, demonstrates the ability to trigger cell death in primary dopaminergic culture by stimulating the generation of reactive oxygen species while concurrently inhibiting mitochondrial respiration. The resultant elevation in ROS levels from ROT exposure inflicts damage upon various components of the mitochondria, including its DNA, ultimately culminating in the initiation of apoptosis (Heinz et al.).

Rotenone triggers apoptosis through the augmentation of mitochondrial reactive oxygen species generation and the activation of caspase-3, subsequently leading to DNA fragmentation. Prolonged exposure to ROT enhances the susceptibility to Parkinson's disease-like symptoms in diverse animal models. In an in vivo experimental setup, rotenone induced the degeneration of dopaminergic neurons in the substantia nigra, mirroring a distinctive hallmark of Parkinson's disease neuropathology. Furthermore, rotenone recapitulates the clinical manifestations of Parkinson's disease, encompassing the aggregation of α-synuclein and the formation of Lewy bodies. The hallmarks of dopaminergic cell loss from rotenone induction result in the development of Parkinson's symptoms such as bradykinesia, rigidity, selective nigrostriatal dopaminergic degeneration, and formation of α-synuclein-positive nigral inclusions (Sivagurunathan et al.).

Rotenone elicited a notable reduction in the survival of healthy colon cells, whereas curcumin and pycnogenol mitigated the inflicted damage and substantially fostered CCD-18 cell proliferation during the initial 24-hour phase. These effects sustained their significance after the 48-hour mark, thereby providing valuable insights into their long-term implications. Additionally, a collaborative assessment of pycnogenol and curcumin was carried out to counteract the effects of rotenone for potential synergistic effects. When added simultaneously, they still demonstrated an ability to mitigate rotenone's effects, although the outcomes were not

as pronounced. Curcumin and pycnogenol's suppression of ROT-induced CCD-18 cell death indicates their potential to mitigate ROT-induced dopaminergic neuron demise in vitro.

In regards to MMP9 expression, the results obtained from the Elisa Assay presented that rotenone downregulates MMP-9 levels in CCD-18 cells significantly. Both curcumin and pycnogenol were able to mitigate the amount by which ROT decreased MMP-9 levels.

One possible mechanism by which ROT reduces MMP-9 levels involves the Wnt signaling pathway. GSK-3β, a recognized tau kinase, regulates this particular pathway. Additionally, a key protein within the Wnt pathway is β-catenin. MMP-9 has been identified as a target influenced by the Wnt signaling, and earlier investigations have indicated that increased activity of both GSK-3β and β-catenin leads to a decrease in MMP-9 expression. It is conceivable that ROT diminishes MMP-9 expression by activating GSK-3β and β-catenin, thereby stimulating the Wnt pathway (ZHANG et al.). Furthermore, prior research has demonstrated ROT-induced activation of GSK-3β in cultured rat retinal cells (Han et al.). CUR retains relatively high binding affinities with GSK-3β and β-catenin that exhibit the potential to have a significant impact on their protein expression. In fact, out of all the proteins tested, CUR had the strongest binding affinity with GSK-3β. Thus, GSK-3β and β-catenin exist as targets for further testing for ROT in PD as well as potential treatment with CUR.

Regarding BDNF expression, which was also evaluated using an Elisa Test, the obtained results provide further corroborative evidence in support of curcumin and pycnogenol's potential in neurodegeneration prevention. In terms of neurodegeneration, previous studies have explored its potential to slow down the progression. Rotenone induced a substantial decrease in BDNF levels within CCD-18 cells. Nevertheless, the introduction of curcumin and pycnogenol led to a noteworthy reversal of rotenone's effects, resulting in an elevated BDNF expression (Johnson et al.). Because BDNF is involved in the process of generating new neurons, it appears that ROT stunts brain growth and repair by decreasing the amount of BDNF, resulting in the cognitive decline seen in PD.

Results obtained from the Caspase-3 Colorimetric Assay exhibited the mitigation of rotenone's effects on caspase-3 expression in CCD-18 cells. While caspase-3 canonically functions as a hallmark of programmed cell death, recent findings implicate this protease as a pivotal molecule in the development of various cancers and neurodegenerative disorders. The activation of caspase-3 bears significance in the context of Parkinson's disease, as it can trigger neuronal apoptosis and microglia activation, thereby exerting a dual effect on brain pathogenesis. Consequently, inhibiting caspase-3 activation holds the potential to offer a synergistic approach to halting the progression of Parkinson's disease. Rotenone, notably, amplified caspase 3 expression, leading to pronounced apoptosis and subsequent reductions in colon cell proliferation rates. Nevertheless, with the introduction of curcumin and pycnogenol, these effects were remarkably diminished, reinstating apoptotic levels to a state of equilibrium (Van Opdenbosch and Lamkanfi). These observations imply the plausible neuroprotective attributes of CUR and PYC in mitigating the upregulation of caspase-3 induced by rotenone, underscoring their importance in the realm of neurotoxicity investigations.

An in silico test was conducted through molecular docking to evaluate curcumin's binding affinity with ten PD-associated targets (Casp3, GSK-3β, MAOA, IL-1β, BDNF, MMP9, NF-κB, TNFα, β-catenin, and αS). CUR retained the highest binding affinities with Casp3, GSK-3β, and MAOA. PYC treatment is yet to be tested using molecular docking to determine its ability to bind with PD-associated proteins.

Conclusion

These findings in this study highlight the potential neuroprotective properties of curcumin and pycnogenol and warrant further investigation to elucidate their mechanisms of therapeutic action to serve as a potential treatment for PD. *In vitro*, both chemicals were able to reverse the increased cell adhesion caused by ROT on colon cells. Curcumin and pycnogenols amelioration of U937 cell density in LPS-treated cells suggest that these chemicals may mitigate LPS-induced neurodegeneration. They were both also able to significantly decrease leukemia cell proliferation rates, without causing any adverse effects on healthy colon cells. During the MTT assays, CUR and PYC were able to effectively mitigate rotenone-induced damage on CCD-18 cells. Both assays were conducted over the span of 24 and 48 hours, to evaluate the effects of each chemical and provide more insight into long-term effects. This study also revealed that ROT decreased MMP-9 and BDNF expression and aggravated apoptosis levels in colon cells, with CUR and PYC effectively attenuating these effects. In addition, they effectively reduced heightened caspase activity induced by ROT in colon cells, restoring apoptosis levels to normal. Finally, molecular docking revealed several potential targets and further indicated the CUR has the potential to interact with these molecules and mitigate adverse effects *in silico*.

While this study investigated the effects of these chemicals on *in vitro* cell models, it would also be beneficial to examine the impact on *in vivo* models, such as PD mice. Additionally, extending the treatment duration beyond 24 hours in cell adhesion, Elisa, and Caspase assays could yield different outcomes. Moreover, for the cell adhesion, Elisa, and Caspase assays, the cells were incubated for 24 hours after treatment, and a longer treatment period could provide different results. Pycnogenol did not undergo molecular docking analysis, which could also provide promising results. Although CUR and PYC exhibited similar effects, evaluating their combined impact and potential synergistic effects in treating PD across all assays could be valuable. Furthermore, considering the testing of other neurotoxins associated with PD, in addition to LPS and Rotenone, might provide comprehensive insights.

Overall, this study demonstrated curcumin and pycnogenol were able to mitigate the damage of rotenone in both cancer and colon cells through multiple assessments and exhibit potential properties for reversing the effects of novel PD targets, indicating a compelling rationale for their inclusion in prospective investigations to explore their suitability for Parkinson's disease treatment.

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Dealing with the Invisible Scars of War: PTSD in Veterans By Alexandra Dimitrova

Abstract

       The long-term effects of war are extremely present in modern society. However, mental injuries such as posttraumatic stress disorder are commonly overlooked, as they are more obscure than physical wounds and casualties. Today, PTSD continues to affect veterans, and many treatments that have been developed so far are still lacking in effectiveness or have not been thoroughly tested. Prevention treatments can target groups that match characteristics such as deployment details and demographics of those who are most likely to develop PTSD. These can include both demographics and details about deployment. HRVB and CBM-I have been able to decrease PTSD scores in certain populations. Social support, specifically from civilians, is also crucial in protecting veterans from developing PTSD or worsening the severity of PTSD symptoms. Various first-line treatments such as evidence-based psychotherapies and pharmacotherapies show significant lowering in symptoms as well as PTSD remission rates, but these treatments are still ineffective for many patients, whether this is because of personal preference or a general lack of efficacy of therapies. The use of psychedelics and psychedelic–assisted psychotherapy, alcohol interventions, breathing-based meditative sessions, and potentially 3-MDR have shown a decrease in PTSD symptoms for those who preferred not to use first-line treatments or found them to be ineffective. More research should be done to find and assess the current alternative treatments. They have generally proven to be less effective than other, common evidence-based treatments, but are still possible replacements for traditional treatments for some veterans with PTSD.

Introduction

       Humanity has always been evolving and will continue to do so, developing new technologies and life-saving medications to improve society, and discovering new regions of the world and universe; however, there seems to be a perpetual, unavoidable pitfall that has followed society during all of its successes: war. Its effects can easily be observed by simply viewing and comparing maps, as the world's countries' borders are constantly being established and fluctuate throughout history. Earth is divided by extremely precise borders of nations, and relentless wars and conquests have been the primary factors in determining these barriers. There are various types of wars, some of which hold much more devastating effects on life than others. The world is perhaps most familiar with traditional, physical, army-against-army warfare. However, there are types of silent wars that precede actual combat. Physical war is often the last resort, and it, along with its devastating effects, could perhaps be prevented if we invest in these preceding events before engaging in physical war–which has devastating effects on all sides.

       Combat has terrible consequences in the surrounding environment, which is demonstrated in the enormous amounts of both civilian and military deaths. Casualties of United States military personnel reached a total of 364,511 in the Civil War, 116,516 in World War I, 405,399 in World War II, and 58,220 in the Vietnam conflict (DeBruyne). These statistics do not

account for injuries or the multitude of additional civilian deaths, which are harder to accurately survey and record. In addition to these reductions in physical health, many veterans are subjected to posttraumatic stress disorder as a result of enduring horrendous events. During recent wars, high percentages of returning US soldiers were recorded to have PTSD: a population-based survey of 30,000 participants concluded that PTSD's prevalence in Gulf War veterans was 10.1% or about 70,000 deployed troops (Kang et al.), and a RAND study conducted with 1,965 participants showed that the probable rate of PTSD in Operation Iraqi Freedom and Operation Enduring Freedom was 13.8% (Tanielian et al.).

PTSD can present long-term limitations in veterans' ability to re-assimilate to their society and return to civil life. PTSD can also predict lower quality of family relationships and work function in addition to dissatisfaction with life (Vogt et al.). Studies are necessary to determine which current and new treatments can reliably reduce PTSD symptoms and cause remission in patients. This field is still somewhat lacking in data since most studies conducted to test the severity of symptoms and improvements are undertaken by self-response surveys administered to groups with limited diversity.

Certain preventive measures and various treatments, including pharmacological and physiological therapies, psychedelics, and various new alternatives to first-line treatments can reliably diminish the severity and development of PTSD and improve the quality of life in returning veterans. Although current treatments have limited success rates, more experiments and research will further our knowledge of new improvements and alternatives and will allow us to deal with the invisible wounds of war.

Risk factors

Although we are unable to make completely accurate predictions about which individuals may be subjected to the development of PTSD, certain demographic factors and characteristics have been found to result in an increased risk. Such factors are observable in pre-trauma characteristics as well as in during and post-trauma situations. These factors primarily include age, gender, the area of deployment, whether or not the military agent had previous exposure to deployment, and, importantly, the overall amount (or lack) of social support upon returning from deployment.

A meta-analysis of 32 studies (comprised mainly of studies using self-surveying methods) shows pre-traumatic demographics and peri-traumatic characteristics which a majority of veterans who suffer from PTSD are more likely to have; these include having prior traumatic experiences or psychological health problems, lower education, being of the female gender, being non-white, undergoing more or longer deployments as opposed to little or no combat exposure, weapon discharge and extreme conditions (Xue et al.). Perhaps military leaders can watch out for peri-traumatic risks and retain contact with individuals. They can also administer specific prevention treatments to those who have been exposed to prior trauma, mental problems, or the aforementioned demographics to limit the possibility of developing PTSD before it has already affected veterans' lives and requires treatment. Higher levels of social care after

deployment contribute to a positive environment which can also lower the advancement of PTSD in veterans (Xue et al.).

Prevention

Preventative measures and training have been developed to prepare military personnel for coping with the events of the war. While they may not result in a major, observable effect, they have been shown to help certain sub-groups profoundly. Two of these interventions are heart rate variability biofeedback (HRVB), a mechanism that may be able to regulate cognitive control, and cognitive bias modification for interpretations (CBM-I), a "cognitive vaccine" that can build resilience to the development of PTSD symptoms (Pyne et al.). A randomized control trial tested the effectiveness of these two preventative interventions; it should be noted that the use of interventions during deployment was largely untrackable and determined by self-report methods and that soldiers encountered multiple circumstantial challenges in using these apps. Results showed that the use of the intervention app BreathPacer (HRVB) demonstrated a 3-month benefit after deployment in reducing PCL scores in groups of older age and had no prior combat exposure than in the control group which did not receive this intervention, as well as producing a noticeable 12-month benefit in soldiers who were of ages 45 and older (Pyne et al.). IMAT (CBM-I) was able to also lower symptom scores in soldiers with previous combat exposure and with ages ranging from 23 to 42 (Pyne et al.), while no benefit was observed during the 12-month follow-up.

In addition to prevention apps, long-term memory inhibitors can be used to block the formation of posttraumatic memories. However, some of the primary drugs used in prevention, which are administered before a possibly traumatic event, may affect the health or critical performance during a mission–unlike HRVB and CBM-I. Sympatholytic medications such as alpha and beta blockers, drugs that prevent the binding of norepinephrine and epinephrine to certain receptors and therefore suppress their stress effects, were shown to have some undesirable physical effects and relatively no undesirable mental effects, but had the highest potential to be effective out of other tested drugs when used in PTSD therapy (Burbiel 2015). Further research is needed to continue to test alpha and beta blockers and other methods' true efficacy, especially since current primary prevention methods can contribute to decreased tactical performance.

Social support after traumatic combat-related experiences functions as another crucial protector against the development of PTSD in returning veterans. A meta-analysis of 37 studies noted that lower levels of social support were associated with higher levels of posttraumatic stress disorder symptoms, along with indicating that support that veterans received from non-military sources was more effective in protecting against PTSD as opposed to that of military sources–although support from both populations led to a significant decrease in PTSD symptom severity (Blais et al.). This means that support from the veterans' civilian community and families is critical in preventing PTSD, and more protective community measures should be established to help veterans who have experienced scarring events.

Psychotherapies

Among current first-line treatments for PTSD are cognitive processing therapy (CPT) and prolonged exposure therapy (PE), which are both non-pharmacological therapies. Cognitive processing therapy is one of the most commonly used evidence-based treatments in war veterans. The United States Departments of Veterans Affairs and Defense recommend first-line psychotherapy treatments which include cognitive processing therapy and prolonged exposure therapy (Card). A small controlled trial that used both a control and test group evaluated veterans with chronic posttraumatic stress disorder, demonstrating that the test group, to which individual, 12-session cognitive processing therapy was administered by thoroughly-trained therapists, showed a reliable decrease in PTSD symptoms in about 50% of patients; a regression analysis of change also revealed that average Clinician administered PTSD scale (CAPS) scores decreased by about 20 points (a score of 35 or less is considered remission on this scale) from baseline scores to the 1-month follow-up, and re-experiencing and emotional numbing symptoms significantly improved when compared to the control group (Monsoon et al.). During CPT, a type of cognitive behavioral therapy, instructors teach participants how to identify and manage memories and unwanted re-experiences of such traumatic events. Although it is one of the more effective and reliable treatments for PTSD, many patients are still unresponsive to CPT and drop-out rates are high. These individuals require other methods to improve their quality of life and mitigate the effects of PTSD. Prolonged exposure therapy is another commonly used evidence-based treatment. Guided by instructors, patients can process traumatic memories and manage PTSD symptoms. In a randomized clinical trial in which 67 participants attended 13 sessions of prolonged exposure therapy over 24 weeks (and no other treatments), CAPS scores declined by about 29.4 points (Rauch et al.). Both cognitive processing therapy and prolonged exposure therapy in these studies met the criteria of a significant change of 20 points and can be considered effective treatments.

Compressed and intensive outpatient programs have been gaining popularity in treating PTSD. A recent study with 234 randomized participants conducted a randomized clinical trial comparing massed prolonged exposure therapy (M-PE) and intensive outpatient prolonged exposure therapy (IOP-PE), both of which are compressed forms of prolonged exposure therapy. This study showed that CAP-5 scores declined from a mean of 37.5 to 22.5 for both treatments and 53% remission rates for patients who went through IOP-PE and 52% remission rates of participants in M-PE after a 6-month follow-up, and it demonstrated that compressed treatments likely will result in more patients completing the treatment program and smaller drop-out rates (Peterson 2023). Intensive treatments can quickly deliver therapies and still significantly improve symptoms and remission rates. Another IOP study (self-report reliant) recorded data from 191 patients undergoing a 3-week long intensive outpatient program comprised of group and individual CPT, mindfulness, yoga, and psychoeducation in 15 daily sessions; its results showed that 92.1% of participants completed the program and PCL (self-report PTSD checklist containing 20 items) scores declined from a mean of 57 to 40 (Zalta et al.). These two studies imply that compressed formats of widely used psychotherapies can effectively decrease symptom

scores and retain remission rates/scores over time, despite patients learning the material in a short period.

Pharmacotherapies

A common form of pharmacological therapy is selective serotonin reuptake inhibitors (SSRIs). These pharmacotherapies prevent the reabsorption of serotonin and are used to relieve depression. The Departments of Veterans Affairs and Defense recommend pharmacotherapy–including SSRIs such as sertraline and paroxetine as first-line treatments–when individual psychotherapy is unavailable or is not preferred (Card). SSRIs are a viable alternative to psychotherapies if patients do not achieve either desired effects or wish not to use cognitive processing or prolonged exposure therapies. The least emotional regulatory brains likely stand to benefit the most from SSRIs since they appear to adjust abnormal BOLD signals in the prefrontal cortex (MacNamara).

A randomized clinical control trial testing the effectiveness of SSRI sertraline and its combination with prolonged exposure therapy demonstrated a decline of the mean CAPS score from 75.5 to 41.7 when 71 patients were only administered sertraline and similar scores of 76 to 43.3 in 69 participants when administered both the psychotherapy and pharmacotherapy (Rauch et al.). This result was also similar to the control PE group, whose scores declined 29.4 points, showing that sertraline, its combination with PE, and PE did not show any significant differences in treatment effectiveness.

Psychedelics

Individual veterans may be either reluctant to use first-line therapies or might find that they, along with popular pharmacotherapies such as SSRIs, have limited efficacy in treating PTSD. Lesser-known psychedelics such as ibogaine and 5-MeO-DMT have been used in assisted therapy as an alternative method to treat such individuals assisted with psychedelics was shown to significantly reduce cognitive impairment and PTSD symptoms (change in symptom score was -34.2) after a small amount of time and limited doses of ibogaine and 5-MeO-DMT, and 84-88% of participants reported this experience as being extremely spiritually significant, psychologically insightful, and personally meaningful (Davis et al.). Unlike some SSRIs, continued consumption of psychedelics seemed to not be required for significant, lasting effects. However, for potential adverse effects and other qualities to be determined, further research is needed.

In addition to the effectiveness of psychedelics in mitigating PTSD, they can potentially also be paired with evidence-based psychotherapies for improved effects. After a preparatory phase in which participants are briefed about the treatment and expectations, the psychedelic drug can be individually distributed to patients in a relaxed environment, potentially allowing participants to open up about their conditions and thoughts during a final integration session; this process is thought to allow a comfortable exchange between participants and their therapist(s)

and allow them to work through painful memories together (Reiff et al.). The use of psychedelics may also encourage veterans suffering from PTSD to meaningfully interact with therapists.

Alternative Treatments

Although conventional methods are extremely effective in some cases, they have limited success rates among certain individuals, and alternative methods have similarly been proposed and tested. These include non-trauma-focused, breathing-based meditations such as Sudarshan Kriya yoga (SKY) as well as brief alcohol interventions. A clinical trial with 21 Iraq and Afghanistan war veterans, which tested the efficacy of the Sudarshan Kriya yoga experiment, expressed a mean 36.6 to a 25.6 PTSD checklist score as opposed to the control groups in which PCL scores increased over the same time, as well as showing high completion rate (over 90% of participants remained in the program), implying that the program yielded high acceptability among veterans (Seppala et al.). A study with a moderate sample size of 88 participants presented a claim that SKY met non-inferiority criteria to traditional CPT since PCL-C score symptoms presented a mean decline of 6.8 with CPT and 5.2 with SKY (Bayley et al.). The SKY form of breathing-based meditation yielded a score decline that was comparable to first-line treatments, suggesting that it is a feasible alternative to psychotherapy. Sudarshan Kriya yoga also correlates with more improvement in emotional regulation (poor emotional regulation is a symptom of PTSD) than cognitive processing therapy (Mathersul et al.).

Alcohol misuse tends to be common in veterans with PTSD as demonstrated by misuse in Operation Enduring Freedom and Operation Iraqi Freedom veterans; furthermore, emotional numbing and hyperarousal post-traumatic stress disorder symptoms are correlated with alcohol misuse (Jakupcak et al.). Successful alcohol interventions have therefore been associated with higher PTSD scores. A larger clinical analysis trial with 523 participants showed a positive correlation between PTSD symptom severity and alcohol misuse, and participants with higher PCL scores had a greater reduction in alcohol misuse than scores of patients with lower levels of PTSD symptoms (Brief et al.). This meant that veterans who had high levels of PTSD stood to benefit the most from alcohol interventions, and, in addition to improving misuse issues, PTSD symptoms could also be addressed during alcohol interventions. Another study of 68 combat veterans undergoing a brief, one-session alcohol intervention to decrease alcohol misuse and distribute individualized feedback on coping with PTSD revealed decreased CAPS scores

Moral injury also highly correlates to treatment-resistant posttraumatic stress disorder, and, in an attempt to provide alternative treatments for resistant PTSD and moral injury, Multi-modal Motion-Assisted Memory Desensitization and Reconsolidation (3MDR) can potentially be used to reduce PTSD symptom severity. A mixed methods study explains that 3MDR is an exposure-based therapy assisted by technology that has been used in treating PTSD; it determines that it may be a potential treatment for treatment-resistant PTSD since participants reported that 3-MDR was accepted by veterans as an acceptable treatment and repaired damaged global beliefs and re-interpreted meaning and purpose, based on a small preliminary study

(Smith-MacDonald 2023). 3-MDR seems to be a possible solution for treatment-resistant PTSD, but more research must be done to determine its full quantitative efficacy.

Conclusion

Since the war, and therefore combat and deployment-related posttraumatic stress disorder, continues to plague our society, traditional psychotherapies, and pharmacotherapies, which are known to cause relatively high remission rates and significantly lower symptom severity, and potential new treatments continue to be tested and improved. As a result, the effects of both these traditional and newer treatments (both positive and adverse) are becoming more well-known. In addition to treatments after the fact, prevention methods are also being developed to address the risks of certain populations–such as age, gender, deployment length, and frequency–and protect against PTSD development. Although first-line treatments recommended by the VA/DoD are effective for a majority of individuals, many others may seek different, yet still effective, non-trauma-focused alternatives. The use of psychedelics and psychedelic-assisted psychotherapy, breathing-based exercises, and alcohol intervention have all shown a decrease in PTSD symptoms for those who preferred not to use traditional first-line treatments or attempted to use them and found them to be ineffective.

Future Directions

It should also be noted that studies of these treatments are subjected to multiple limitations. Many lack generalizability to other non-veteran populations suffering from posttraumatic stress disorder, while others have relatively underpowered test groups. Some studies were also unable to retain contact with participants for a longer period for follow-up appointments to track participant retention of positive effects. Additionally, many studies were conducted with self-surveying methods, which can be subject to user bias. For these reasons, additional research is crucial in understanding and managing combat-related PTSD in veterans.

More resources and effort should be put into creating more extensive research on both PTSD and its treatments which could take the form of clinical trials assessing more diverse populations' reactions to treatment methods and prevention methods that are effective for a larger variety of veterans. They can also examine new potential solutions to treatment-resistant PTSD. Becoming knowledgeable about treatments may also expand the scope of their effectiveness, and allow use for various other groups, including civilians exposed to war, and suffering from posttraumatic stress disorder.

Involvement and awareness in communities with veterans is also a vital factor in protecting against PTSD. This can take both the forms of military leaders keeping watch for potential, well-known risk factors and civilian community and family support.

Acknowledgments

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When Bodies Become Battlefields: A Hidden Narrative Depicting Women During the India-Pakistan Partition By Rhea Nachnani

"Impunity for crimes of conflict-related sexual violence remains the norm and the pace of justice remains painfully slow" (United Nations Report).[110] Historically, men have used, suppressed, and forced women into silence, especially during times of conflict. Although this tactic never dominated reports of the India-Pakistan partition, it was enormously present. [111]The India-Pakistan partition was one of the largest human migrations in history.[112] After World War Two, the idea of partition surfaced as the British prepared to grant India independence.[113] In August of 1947, after 300 years of occupation, the British left India, rendering the state liberated and broken.[114] The Partition separated India by religion, into Hindu-majority India and Muslim-majority Pakistan, and initiated a violent migration that ended the lives of more than two million and displaced over 15 million.[115] Religious conflict and violence between Hindus and Muslims was a dated occurrence that stemmed from the British ideology of divide and rule, and it continued long after the partition. Amidst the violent inclinations between these two religions, women were targeted and subjected to a tremendous amount of violence; nearly 75,000 women were raped, abducted, and killed.[116] Men inflicted intentional and repeated trauma upon women during and after the India-Pakistan partition to further religious conflict. Hindus and Muslims abused female bodies, murdered wives and daughters, and used women as political tools, which resulted in long-term intergenerational trauma.

During the India-Pakistan partition, attackers purposefully violated and targeted female bodies as an act of religious violence to shame their communities. The religious values, customs, and cultures present in pre-partition India influenced these attacks. Before the partition, Indian culture was patriarchal, and the primary role of women served to bear children and maintain the household.[117] In this culture, women were expected to submit to the men in their lives, and they were treated as property.[118] Specifically, in the Hindu religion, "purity" was sacred, and a victim

[110] United Nations. "Conflict-Related Sexual Violence." UN.org. Last modified March 29, 2002. Accessed February 20, 2023.

[111] Meera Patel, "Rape Accounts Still Surface from India's Partition 65 Years on," Women's Media Center, last modified June 26, 2013, accessed November 8, 2022, https://womensmediacenter.com/women-under-siege/rape-accounts-still-surface-from-indias-partition-65-years-on.

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[114] Dalrymple, "The Great Divide"

[115] Dalrymple, "The Great Divide"

[116] Dalrymple, "The Great Divide"

[117] Aindrila Haldar, "Hinduism as a Political Weapon: Gender Socialization and Disempowerment of Women in India," The University of San Francisco, last modified May 15, 2020, accessed November 8, 2022, https://repository.usfca.edu/cgi/viewcontent.cgi?article=2389&context=thes.

[118] Rajwant Mangat, "Legislating Women's Lives: Women and the Partition of India," *Canadian Woman Studies* 19, no. 4 (Winter 2000): [Page #], https://link.gale.com/apps/doc/A63858134/AONE?u=tel_oweb&sid=googleScholar&xid=46df07b0.

of sexual assault was considered "shameful" and dishonored by her community.[119] As the conflict between India and Pakistan surfaced, members of both parties aimed to degrade and humiliate every aspect of the opposite religion and culture.[120] During this violence, attackers violated female bodies to torment and mock entire religious communities. [121]

　　　　As men targeted the purity of women from the opposite religion, a vicious cycle emerged, which instrumentalized women as a commodity for revenge.[122] The torture inflicted upon women was purposefully used to achieve an ulterior motive, and these painful methods were efficient at crippling the victim and dishonoring their community. Many attackers dismembered women's breasts to remove their femininity and take away their purpose, which was motherhood. These women were rendered barren and useless in Indian society. [123]By annihilating a woman's ability to bear or nurture a child, attackers sent a message to the opposite religion regarding their desire to eliminate the enemy.[124] Additionally, men commonly tattooed women with praises to their country, writing "Pakistan Zindabad (praise Pakistan)" and "Hindustan Zindabad (praise India)," and paraded them in sacred spaces, such as mosques and temples. These tattoos permanently engraved a family's dishonor onto a woman's body and served as a physical representation of the separation of India and Pakistan. [125] Around 37,000 women were abducted and forced into marriage during the partition.[126]This furthered religious conflict because women were taken from one religion and given to the other, which warranted revenge. The majority of crimes against women symbolized a deeper resentment for the women's religion as a whole, and in expressing this hatred, women remained the scapegoat. During the partition, men forced women to act as pawns in an increasingly violent game by using and putting them through humiliation, anguish, and trauma.[127] The recurrent pattern of religious gender-based violence was set into action as men dehumanized women, and as a result, a different type of violence emerged.

　　　　Inter-familial violence against women rampaged during the partition to counteract acts of religious violence. Families killed and encouraged their wives and daughters to commit suicide to prevent them from imposing shame upon the family by being sexually violated. [128] Hindu and

[119] Haldar, "Hinduism as a Political Weapon"

[120] Erin Blakemore, "The Partition of India Still Casts a Long Shadow over the Nation," National Geographic, last modified August 2, 2022, accessed October 24, 2022, https://www.nationalgeographic.com/history/article/partition-of-india-and-pakistan-history-legacy.

[121] Luke Campbell, "Violence Against Women During the Partition," Rampages.us, last modified April 4, 2017, accessed November 16, 2022, https://rampages.us/lucaswcamp/2017/04/04/violence-against-women-during-the-partition/.

[122] Menon, Ritu, and Kamla Bhasin, *Borders and Boundaries* (University Press, 1998), 43.

[123] Menon andBhasin, *Borders and Boundaries* (University Press, 1998), 44.

[124] Nikita Sachdev, "Deconstructing the 1947 Partition: The Effect of the Central Recovery Operation through a Gendered Lens in India and Pakistan," Colgate University libraries, last modified 2017, accessed November 8, 2022, https://core.ac.uk/download/pdf/229475513.pdf.

[125] Menon, and Bhasin, page 43.

[126] Himanshi Nagpal, "The Partition Of Punjab: A Tale Of Violation Of Women's Rights," Feminism India, last modified June 27, 2017, accessed November 17, 2022.

[127] Arunima Dev, "Violence Against Women During the Partition of India: Interpreting Women and Their Bodies in the Context of thnic Genocide," Dialnet, accessed November 8, 2022,file:///Users/rheanachnani/Downloads/Dialnet-ViolenceAgainstWomenDuringThePartitionOfIndia-5858222.pd

[128] Urvashi Butallia. *The Other Side of Silence*. Durham: Duke University Press,

Muslim men exacerbated and repeated violence against their own women in an attempt to save their religious pride. Many women and girls "chose" to make the greatest sacrifice of all because it was seen as a heroic act to save the honor of an entire religion. [129] Women who sacrificed themselves were considered "martyrs" for saving the community's dignity.[130] This created a paradox because women gave everything to a community that treated them as nothing. In Azad Kashmir, all the women in a family of Hindus, except three, killed themselves when Muslims began to surround their village. Iqbal, a male member of this family, recounted the events. "My three sisters swallowed poison- the hospital compounder distributed poison to anyone who wanted it….No one tried to stop them, not even my father. We tried to persuade Veeran, a young cousin, to take Opium, but she refused." [131] During the India-Pakistan partition, in a society governed by religious conflict and a deathly honor code, losing family members was not a debilitating loss, but a goal that warranted persuasion. The families of "sacrificed" women gained a higher place in society as well. The death of a woman benefited everyone except the women.[132] Many men also killed their families to prevent them from being taken, converted, or raped. Charanjit Singh Bahitta decapitated all thirteen of his wives and daughters to prevent them from marrying Muslim men. [133] This example exacerbated the religious hatred that fueled all of the violent acts against women during the partition. The inter-familial killing showed another case of repeated trauma against women during partition at a time when religion held greater importance than female life. Whether women were used to uphold honor or destroy it, gender-based violence capitalized on male-oriented religious conflict, not the victims, and this trend continued after the partition.

After the partition, governmental leaders attempted to facilitate recovery by passing laws that ignored the female experience, which victimized women once again. In the aftermath of the migration, the Indian and Pakistani governments arrived at the Inter-Dominion Treaty of December 6, 1947, which was later known as the Central Recovery Operation to find as many abducted women as possible. [134] Two years later, this agreement became the Abducted Persons Recovery and Restoration Ordinance, a bill that became an act. [135] When the logistics of the bill were being debated in the Constituent Assembly, Indian leaders fabricated an opportunity to make themselves appear more "civilized." [136] Within this debate, one thing was lost: the women. Political leaders used the Recovery and Restoration Act to insert dominance over the opposite country, which withdrew focus from abducted women and victimized them for a second time.[137]

    2000, 154.

[129] Arunima Dev. "Violence Against Women During the Partition of India"

[130] Menon and Bhasin, page 46.

[131] Meno and Bhasin, page 51.

[132] Menon and Bhasin, page 45.

[133] Menon and Bhasin, page 48.

[134] Manan Mehra, "An Overactive State: The Case of Abducted Women at Partition," cjp, last modified February 10, 2020, accessed November 8, 2022, https://cjp.org.in/an-overactive-state-the-case-of-abducted-women-at-partition/.

[135] Butallia. *The Other Side of Silence*, 114.

[136] Mangat. "Legislating Women's Lives: Women and the Partition of India."

[137] Himanshi Nagpal. "The Partition Of Punjab: A Tale Of Violation Of Women's Rights." Feminism India. Last modified June 27, 2017. Accessed November 17, 2022.

Within the act, the state disregarded women's rights by forcing them to return to the "correct" country.[138] According to the Recovery and Restoration Act, an abducted woman was, "a female of whatever age who…has become separated from his or her family and is found to be living with or under the control of any other individual or family" [139]Women were denied the ability to classify their own relationships, which was detrimental because many women formed relationships with their abductors and adjusted to their new life. [140] One such instance was Zainab, an abducted Muslim girl, who fell in love with her abductor, Buta Singh. They had a family and a life together before Zainab was forced to return to Pakistan and marry another man that she didn't love.[141] The Recovery and Restoration Act silenced female voices, which made women vulnerable to physical and emotional devastation. The act also gave police officers the power to search a home without a warrant, determine the status of the woman inside, and forcibly remove her from her home. [142] Mirdula Sarabhai, who worked at camps for abducted women said," In all of this sometimes a girl would be killed or she would be wounded…or they would be handed over to police officers in some places to please them." [143] Although it appeared implausible, in many situations, the rescue of abducted women worsened their situation by traumatizing them for the second time. One abducted woman asked a police official, "Why should I return,"…"Why are you particular to take me to India? What is left in me now of religion or chastity?" [144] Many women were ostracized upon returning to their country because their purity had been taken by a man of the opposite religion, which was shameful and dishonorable. [145] Many women, who had mixed children, were obligated to choose between returning to their family and keeping their children.[146] Women whose families had moved on without them resided in an Ashram, a facility created to temporarily house abducted women, and many never left. [147] Rather than rescuing them, the Recovery and Restoration Act left women alone and homeless. Although this act was created with women in mind, it perpetrated unimaginable violence against vulnerable victims to fulfill the needs of the Indian and Pakistani governments and their rivalry. Furthermore, the repeated trauma caused by the Recovery and Restoration Act diminished women to objects that could be taken and traded from hand to hand. The political conflict surrounding the Recovery and Restoration Act ran parallel to the religious

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[138] Nikita Sanchev. "Deconstructing the 1947 Partition: The Effect of the Central Recovery Operation through a Gendered Lens in India and Pakistan."

[139] "Abducted Persons (Recovery and Restoration) Act, 1949." casemine. Last modified 1949. Accessed November 16, 2022. https://www.casemine.com/act/in/ 5a979d8e4a93263ca60b7040.

[140] Himanshi. "The Partition Of Punjab: A Tale Of Violation Of Women's Rights."

[141] Butallia. *The Other Side of Silence*, 101.

[142] "Abducted Persons (Recovery and Restoration) Act, 1949."

[143] Butallia. *The Other Side of Silence*, 118.

[144] Debarsi Basu. "Restored, or doubly displaced?: Women and the Recovery Commission in India's Partition Narratives." Café Dissensus. Last modified May 4, 2018. Accessed November 17, 2022. https://cafedissensus.com/2018/05/04/restored-or-doubly-displaced-women-and-the-recovery-commission-in-indias-partition-narratives/.

[145] Mangat, "Legislating Women's Lives: Women and the Partition of India."

[146] Butallia. *The Other Side of Silence*. 128.

[147] Abducted Persons (Recovery and Restoration) Act, 1949."

conflict during the partition, and in both cases, women were compromised and used, which solidified the irreversible effects of partition and ensured generational trauma.

   The experiences that many women faced during and after the partition challenged and impacted future generations. During the partition, 75,000 women were abducted, raped, forced into marriage, forced to convert, and killed on both sides of the border. [148] The partition took their family, their bodies, and their honor, which subsequently changed the lives of generations to come. The children of women involved in inter-religious marriages faced direct consequences. Although few families accepted women after they lost their purity, even fewer took in taboo mixed-race babies. The state viewed the children of mixed unions as illegitimate, and they could not identify in either county.[149]These women chose between giving up their child or living in an Ashram for the rest of their lives, and their decisions determined their child's future. [150] One such child spent her entire life in an Ashram in Jalandhar, and her identity was encompassed by her mother's experiences.[151] A similar situation affected the children who were given away or kept by their fathers. They grew up ostracized from half of their culture and lacked a piece of themselves.[152]Another level of generational trauma impacted the descendants of women who migrated during the partition and rebuilt their lives from scratch. Their experiences significantly impacted their quality of life and the values that they raised their children with. The emotional effects of the partition were transmitted to these children by their ancestors. [153]According to the Ommani Center for Integrative Medicine, for many offspring of parents with PTSD, the gene expressed itself in the child on a cellular and molecular level.[154] Rachel Yehuda, the child of a woman who was left an orphan after migrating to India said, " As her firstborn, I have carried all of her emotions with an other-worldly amplification."[155] Grandchildren and great-grandchildren of those involved in the partition continued to be affected by the cultures and customs ingrained in post-partition life. Traumatic experiences shaped the way the narrative was told, and because of this, many younger generations only heard one side of the story, which caused them to harbor feelings of hatred.[156] Kalpana Gidwani, a Hindu, whose grandmother was involved in the partition said, "We don't visit Pakistan even though our ancestors were born and brought up there and lived there all of their lives, and we don't prefer for the girls in our families to get married

[148] Dalrymple, "The Great Divide"

[149] Himanshi. "The Partition Of Punjab: A Tale Of Violation Of Women's Rights."

[150] Butallia. *The Other Side of Silence*, 129.

[151] Butallia. *The Other Side of Silence*, 129.

[152] Butallia. *The Other Side of Silence,* 130.

[153] "Generational Trauma: An Emerging Science to Facilitate Deeper Healing." Ommani
 Center for Integrative Medicine. Last modified August 12, 2019. Accessed November 17, 2022.
https://www.ommanicenter.com/blog/generational-trauma-an-emerging-science-to-facilitate-deeper-healing/.

[154] "Generational Trauma: An Emerging Science to Facilitate Deeper Healing." Ommani Center for Integrative
Medicine.

[155] "Generational Trauma: An Emerging Science to Facilitate Deeper Healing." Ommani Center for Integrative
Medicine.

[156] Katvia Puri. "Enduring trauma: the legacy of partition." History Extra. Last
 modified August 13, 2022. Accessed November 17, 2022.
 https://www.historyextra.com/period/20th-century/
 legacy-of-partition-british-india-trauma/.

into Muslim or Pakistani families."[157] The experiences of women during the partition shaped the lives of future generations. More than a violent conflict, the partition was a historical landmark that altered millions of lives through humanity's most sacred jewel: their children.

During the partition, women were targeted, objectified, violated, and dismissed time and time again, which allowed the effects of partition to survive and possess future generations. The acts of religious violence inflicted upon female bodies served as an attack on their communities and dehumanized women. This was further shown when women were burdened with upholding community honor and encouraged to sacrifice themselves to defend it. After the partition, political leaders created the Restoration and Recovery Act to promote nationwide religious conflict, and in doing this they forced abducted women to undergo another unspeakable trauma at the hands of their own government. As more time elapsed, generations of survivors continued to experience and grapple with the traumatic effects of partition. The violent narrative of partition was a complex story of betrayal, hatred, and deception, and at its core, lay women, forced into submission and trampled by men who used them and threw them away. The story of women, turned into puppets during a time of conflict, remained hidden from the public by politics, religion, and the patriarchy. Although petitions were created, political leaders failed to formally apologize to the women hurt during the partition. [158] Articles published about the partition were plentiful, but in most of them, the experience of women was a single sentence. For everything they went through, these women deserved more than a single sentence. They deserved recognition, validation, and reparations, not just for themselves, but for women everywhere. When conflict shattered the routine of everyday life, women were the first sacrifice, and that needs to change. Women are not objects, they are human beings who deserve control over their lives, bodies, and futures.

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Effects of Digitalization on the Shadow Economy in India By Abhinav Praneeth R. Nallamilli

Abstract

In July 2015, the government of India launched the "Digital India" campaign to leverage technology to bridge the digital divide and to ensure the growth of the country. The rapid progress of technology coupled with the widespread adoption of digital platforms has resulted in a transformative shift across all areas including economic activities. A noteworthy example is India's exceptional experience with digitization over recent years. Individuals and businesses have witnessed exponential growth in their usage of various digital technologies. Online platforms such as UPI (United Payments Interface) and Net Banking have also played a significant role in this trend. As a consequence, we see an increased reliance on digital platforms alongside a surge in demand for related products and services that serve as key drivers powering the robustness of the country's digital economy. The underground economy in India, which refers to unreported or illegal economic operations that operate outside of the ambit of formal legislation and taxation, has been significantly impacted by this wave.

Introduction:

In this paper, we examine the effects of digitalization on the shadow economy in India. The shadow economy includes all economic activities that are hidden from official authorities for monetary, regulatory, and institutional reasons. Monetary reasons include avoiding paying taxes and all social security contributions, regulatory reasons include the avoidance of government bureaucracy or the burden of the regulatory framework, while institutional reasons include corruption law, the quality of political institutions, and weak rule of law. For our study, the shadow economy reflects mostly legal economic and productive activities that, if recorded, would contribute to national GDP, therefore the definition of the shadow economy in our study tries to avoid illegal or criminal activities, do-it-yourself, or other household activities. The Indian government has implemented several measures to combat the circulation of these kinds of assets, and digitalization has emerged as a key tool in this process. This paper explores the impact of digitalization on black money (money in physical cash on which taxes haven't been paid), including the measures taken, the outcomes achieved, and the challenges encountered in the process. However, challenges such as technology accessibility and illiteracy amongst the elderly still prevail. We also highlight potential policy implications and areas for further investigation.

For policymakers, economists, and other stakeholders involved in India's economic growth, it is essential to comprehend how digital payments affect the shadow economy. The government wants to reduce corruption, improve financial inclusion, and promote a more transparent economy through promoting digital financial transactions. However, it is unknown how much the shadow economy has been impacted by digital payments, demanding thorough research to determine how these two phenomena are related.

Methodology

      Our comprehensive study makes use of solid primary as well as secondary data sources—most notably information gathered from RBI (Reserve Bank of India), and the Federal Reserve Bank—to conduct an in-depth analysis of our chosen subject matter. By incorporating an extensive range of qualitative as well as quantitative data, we ensure an all-inclusive understanding while exploring this area further. The inclusion of diverse data enriches our analysis by adding depth; furthermore, it enhances reliability and validity when it comes to drawing conclusions based on these findings. Additionally, this approach allows us to interpret our research topic from a more nuanced perspective.

Objectives of the paper:

- What is the shadow economy in India?
- Review the current state and extent of the shadow economy in India
- Analyze the rise of digital transactions in India
- Investigate the relationship between digital financial inclusion and the reduction of the shadow economy
- Analyze the impact of these digital transactions in India - challenges and benefits

1.What is the Shadow Economy?

      The shadow economy in India refers to economic activities not regulated by formal frameworks like government regulations and laws—the term used for it ranges from "informal" to "parallel" economies. These activities have far-reaching implications for India's overall economic landscape. Multiple factors contribute to their existence in India—high poverty rates; an extensive population participating in informal economies; arcane regulations with bureaucratic hurdles; and insufficient social security measures are some prominent examples.

      One key characteristic is individuals' and businesses' tendency to report only fractional incomes—or sometimes none at all—and avoid paying taxes that they are obligated by law to pay such as income tax and goods and services tax (GST). To accomplish this transactions are often conducted in cash, off-the-books employment is common and some even choose to operate unregistered businesses. Another significant component of India's shadow economy is informal labor. A significant proportion of the population is engaged in informal employment characterized by a lack of job security, social benefits, and legal protections. Street vendors, domestic workers, daily wage laborers, and small-scale farmers exemplify this sector.

      Moreover, the shadow economy encompasses unregistered businesses or enterprises that completely operate outside the formal sectors. These businesses typically refrain from registering themselves due to the complexities of regulations, high costs associated with compliance, and limited access to formal financial services. They may encounter difficulties in obtaining licenses and permits, and maintaining proper records. Or adhering to labor laws and regulations. The impact of the shadow economy in India has both positive and negative aspects. On a positive note. It offers employment opportunities for a significant portion of the population and contributes to economic growth. It also provides flexibility and survival options for individuals

Currency in Circulation (in ₹ Billion)

Values by year:
- 2016-17: 13102
- 2017-18: 18044
- 2018-19: 21138
- 2019-20: 24130
- 2020-21: 28317
- 2021-22: 31076
- 2022-23: 33504

Source: RBI Data

Currency in Ciruculation to GDP (%)

Values by year:
- 2016-17: 8.7
- 2017-18: 10.7
- 2018-19: 11.2
- 2019-20: 12
- 2020-21: 14.4
- 2021-22: 13.7
- 2022-23: 14

Source: RBI Data

who face limited formal job prospects. However, The shadow economy also presents challenges for the government and the overall economy. It diminishes the tax base resulting in a loss of revenue for the government and hindering its ability to furnish essential public services and infrastructure. Additionally. It can perpetuate income inequality as informal workers often earn lower wages and lack social protections.

2. Extent of Shadow Economy in India:
Current measure of cash:
While there is no accurate estimate of the cash payments, the value of Currency in Circulation (CIC) versus Gross Domestic Product (GDP) can be used to answer the question.

a) **Currency In Circulation:**
It can be inferred from the graphs that the CIC in India increased at a Compounded Annual Growth Rate (CAGR) of 14.35% over the past 7 years, i.e., between the financial years (FY) 2016-17 and 2022-23. It is generally assumed that having a high CIC relative to GDP indicates that cash is highly preferred as a payment method. Although demonetization of the large currency notes in 2016 has significantly reduced the CIC as a percentage of GDP to 8.7% in FY 2016-17, it is now back to pre-demonetization levels. However, The rate of increase is lower indicating a perceptible shift away from cash.

3. Estimates of Cash Payments:
It is challenging to find the amount of informal transactions in India because such transactions by definition, are not recorded and documented officially. Some surveys/reports have taken an attempt to measure the volume of cash transactions in India. Even though many of the reports are only estimates, they do provide some indication of cash usage and digitization in the country as well as across the world. According to the estimates of the reports, cash still reigns king not only in India but in many other countries as well.

Estimates of the Older Reports:
a) According to a 2019 report by Credit Suisse Group AG, nearly 72% of India's consumer transactions took place in cash. In particular, many merchants, especially in rural areas,

E-Commerce Payment Methods in India as %

Fig. 3.1

Source: JP Morgan 2019 Global Payments Trends Report

Payment methods in India as a % of total payments

Fig. 3.2

Source: Worldpay Global Payments Report 2018

■ Card Present Transactions   ■ Card Absent Transactions

remain unable or unwilling to accept digital transactions due to network connectivity issues and a reluctance to pay charges for what are often low-value transactions.

b) The JP Morgan 2019 Global Payments Trends Report - India Country Insights observed that the Indian payments market is evolving to meet the demands of smartphone led online shopping culture, with cards and digital wallets rising in prominence. (Fig. 3.1)

c) The Worldpay Global Payments Report 2018 observed that in India, while cash continued to be the primary payment method for point of sale purchases (card present), eMoney dominated the online payments (card not present). The report observed that as internet penetration and the the digital economy continues to grow, there will be room for ongoing shift of payment forms. (Fig. 3.2)

4. Digitalisation of the Indian Economy:

Although India's demonetization policy had a big impact on the economy, it also sped up the development of digital payments in that country. Digital payments made up only 10% of all

transactions in India before demonetization, but over the following years, that percentage increased to over 20%. India's Prime Minister, Sh. Narendra Modi, declared on November 8th, 2016, that all 500 and 1,000 rupee notes, which made up 86% of the money in circulation, would be demonetized. This strategic move sparked aggressive adoption and promotion of the digital ecosystem in India.

The government's push for digitalization, rising internet and smartphone penetration, and the development of e-commerce are just a few of the factors that have contributed to the expansion of India's digital ecosystem. Through several programs like Digital India, Make in India, and Startup India, the Indian government has been actively promoting the use of digital technologies. These initiatives seek to increase the use of digital technologies across several industries, including healthcare, education, and agriculture, as well as to foster an environment that will support start-ups. The expansion of the digital ecosystem has been significantly aided by the rise in internet and smartphone use in India. According to a report by the Internet and Mobile Association of India, the number of Internet users in India is expected to reach 800 million by 2023. This increase in internet users has also led to an increase in the number of mobile wallet users in India, which is expected to reach 900 million by 2025.

This has been a significant step towards the government's goal of increasing the use of digital payments and reducing the dependence on cash transactions. The government's mission is to target 2,500 crore digital transactions in the 2017–18 Union Budget through UPI, USSD, Aadhar Pay, IMPS, and debit cards. Since smartphones and internet access have been rapidly increasing in popularity in India, digital payments have taken on greater significance. The government is attempting to change this by promoting the use of digital payments because a sizable portion of the population still relies on cash transactions. Various initiatives to promote digital payments will use this. Giving merchants incentives to accept digital payment methods will be one of the main initiatives. This could involve tax breaks for companies that accept electronic payments as well as subsidies for retailers to buy point-of-sale terminals.

As a result of several government initiatives, an increase in internet and smartphone use, and the growth of e-commerce, the digital payments ecosystem in India has also experienced significant growth in recent years. The Unified Payments Interface (UPI), which enables real-time interbank transactions, and the Bharat Interface for Money (BHIM) app, which streamlines the process of conducting digital transactions, are two of the key initiatives.

UPI has seen a humongous growth since its launch in 2016 by the National Payments Corporation of India (NPCI).

Volume of Trasactions via UPI (in ₹ INR Million)

Source: National Informatics Centre, India

The expansion of the digital payments ecosystem has been greatly aided by the rise in internet and smartphone use in India. E-commerce has also played a significant role in the expansion of India's digital payments ecosystem. By 2026, the Indian e-commerce market is projected to develop at a CAGR of 31% and reach $200 billion. By 2025, there will be 220 million more online shoppers in India as a result of the expansion of the e-commerce industry. Numerous additional private firms also help India's digital payments ecosystem. These companies provide numerous digital payment options, including mobile wallets, UPI transactions, and QR code-based transactions.

5. How is digitalization going to affect the shadow economy?

The digitalization of the economy and the shadow economy in India are interconnected in several ways. Digitalization aims to bring economic activities into the formal sector and enhance transparency, while the shadow economy represents informal and unregulated economic activities that often evade taxation and government oversight.

One way digitization relates to the shadow economy is through the adoption of digital payment systems. As the economy becomes more digitized, there is a shift towards cashless transactions and digital payment platforms. This reduces the reliance on cash, making it more challenging for the shadow economy to operate. Digital payment platforms leave electronic trails, making it easier for authorities to track financial transactions and detect potential tax evasion.

Net Volume of Transactions through Digital Payment Methods (in ₹ INR Million)

Source: National Payments Corporation of India (NPCI)

Digitalization can also improve tax compliance. With increased digital transactions and people preferring digital transactions over traditional cash, making it harder for businesses to conceal income or under report sales, thereby reducing the scope for operating in the shadow economy. The implementation of the Goods and Services Tax (GST) in India is a significant step towards formalizing the economy. The GST framework relies heavily on digitalization, requiring businesses to maintain digital records and file returns online. This shift helps curb tax evasion and brings more economic activities into the formal sector, reducing the influence of the shadow economy. According to an article in The Economics Times Newspaper, In the last three years, India has added almost 58,000 taxpayers with an income of more than INR 10 million —a jump of 51% in that tax bracket.

In summary, digitalization plays a crucial role in reducing the size and impact of the shadow economy in India. It enables cashless transactions, promotes financial inclusion, improves tax compliance, and supports the implementation of reforms such as the GST. However, comprehensive approaches involving policy reforms, awareness campaigns, infrastructure development, and financial inclusion initiatives are necessary to achieve significant progress in formalizing the economy and minimizing the influence of the shadow economy.

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Examining Gender Bias in Media Coverage of the Battle of the Sexes By Meiyin Ren

Abstract

While acknowledging the progress made in striving for gender equality in sports, a clear disparity in the presence of gender bias in various forms of media coverage is still evident. Diving into the evolution of the societal narrative surrounding a historical milestone like the Battle of the Sexes will help us to better understand the transformation we have undergone and provide insights for future progress. This study is designed to closely examine and analyze the variation in media descriptions and the underlying gender bias of media articles from both the year 1973 and the past ten years discussing Battle of the Sexes. In general, the results indicate a growing awareness of gender bias in media. However, the fight to abolish gender bias continues, requiring further efforts to foster an inclusive and unbiased media landscape.

1. Introduction

A pivotal moment in the fight for female empowerment took place in the Houston Astrodome on September 20, 1973, between tennis greats Billie Jean King and Bobby Riggs. By demonstrating that women can compete at the highest level and emerge victorious against male opponents, King's victory surpassed the tennis court and shattered the prevailing notions that women were inferior to men in physical and mental abilities. This Battle of the Sexes symbolized the larger struggle for women's rights and equality in society and played a vital role in propelling the feminist movement. King's dedication to this noble cause laid the groundwork for the success of talented female athletes such as the Williams sisters, and her legacy continues to inspire the ongoing pursuit of female empowerment over the decades. While acknowledging the considerable progress achieved since King's victory, empirical research indicates that there remain significant disparities in media portrayal of women compared to their male counterparts. As noted in Fabrizio Santoniccolo and colleagues' review on gender and media representation, despite a rise in media coverage over recent years, female representation as experts remains inadequate, comprising only 24% of the total (Santoniccolo et al. 61). In the present day, representations of women in a variety of media platforms remain consistent with gender stereotypes: girls are often portrayed as emotional and superficial, while boys are dominant and assertive. In advertising, female characters are often depicted as leisurely, devoid of professional pursuits; in video games, female characters are the subject of the hero's salvation; in music videos and lyrics, female characters tend to be reduced to one-dimensional characters that are submissive to the male artist (Santoniccolo et al. 62). Unsurprisingly, gender representation in sports-related media consistently mirrors prevailing patterns observed in other fields. The media narrative often falls into a dichotomy, with men being celebrated for their achievements based on merit and substance, while women are frequently commented on for their physical appearances and affiliations. An incident exemplifying such media bias took place at the 2016 Wimbledon Championships, where news reports opted to focus extensively on Serena Williams' attire rather than lauding her superlative on-court performance (Ellemers 284).

2. Existing Research
2.1. Televised Media

As a prevailing form of mass media, televised media has perpetuated conventional gender expectations about both men and women. A study led by researcher Nathalie Koivula (592) conducted a comprehensive analysis of the portrayal of sports on three prominent Swedish national television networks over the course of one year. The findings revealed a pervasive gender bias, with male athletes receiving significantly more coverage (86.7%) than their female counterparts (11.7%). While occasional instances of equitable media coverage of women in sports did emerge, they remained sporadic. This pattern was further accentuated in the case of athletes' names, with women more often identified by their first names while men were predominantly referred to by their last names. Additionally, the media often reduced women's sports coverage to family-oriented narratives, emphasizing their roles as wives and mothers. Female athletes are constantly undervalued and marginalized, perpetuating and normalizing traditional gender expectations through televised media portrayal.

2.2. Online Media

The recurring theme of gender bias is not limited to televised media but is also online media. In 2018, researcher Adrian Yip conducted a study on the biased gender representations of the 2015 Australian Open in online media (522). Using content analysis as the analytical framework, Yip evaluated 357 articles from ESPN and the Australian Open within the research timeframe, spanning from January 18 to February 2, covering the entire two-week tournament. The findings indicated that both media outlets tended to employ higher proportions of irrelevant and negative portrayals regarding female athletes, including their skill levels, failures, and age. On the contrary, they tended to use a significantly higher proportion of descriptors highlighting athletic prowess and strength when depicting male tennis players. Furthermore, both the Australian Open and ESPN employed several strategies perpetuating traditional gender biases. Specifically, the Australian Open praised the mental strength of male athletes more than their female counterparts, while female players were frequently associated with family members. Their achievements and motivations were consistently linked to significant males in their lives. Such portrayals may imply a dependence on others and attribute their athletic ability, at least in part, to familial or relational ties, thereby undermining their professional image as athletes.

3. Purpose

Female athletes continue to grapple with insufficient media coverage despite some improvements in representation for those participating in gender-appropriate sports. Nevertheless, discernible disparities persist as mass media portrays them distinctly compared to their male counterparts. Despite abundant research examining general gender biases prevalent in media coverage, there exists a lack of targeted investigations on the transformation of media portrayals of specific events, such as the Battle of the Sexes. Conducting such a study, encompassing various timeframes, is imperative, considering the emergence of novel media

platforms such as online media and the evolution of societal perceptions concerning gender equality over the past half-century. Media outlets serve a dual role as both a mirror reflecting existing beliefs, values, and norms and as a creator shaping social focuses (Yip 527). Studying the evolution of the narrative of a historical milestone can educate us about the societal transformation that has occurred over the years and enable us to evaluate if we are progressing in the right direction as a society. Therefore, this paper employs content analysis as a methodological approach to investigate the presence of gender stereotyping in narratives of the Battle of the Sexes both at the time of its occurrence and in more recent times.

4. Methodology

The study focuses on the Battle of the Sexes, a renowned mixed-gendered tennis match in 1973 between accomplished athletes Billie Jean King and Bobby Riggs, which concluded with King's celebrated victory. The data collection timeframe was divided into two sections: one from 1973, including articles from both before and after the match, and the other from the past 10 years. This division allows for a more just evaluation and discussion of the evolution of gender representations in sports media since 1973. Articles from 1973 mainly focused on predicting and reporting the match's outcomes, while reports from the present day focus more on the symbolism of King's victory in the debate of athletic prowess between genders. During data collection in 1973, due to the limited number of published articles discussing the match, ten articles were selected from sources such as *Los Angeles Times* (2 articles), *New York Times* (6 articles), and *The Times of India* (2 articles). For the ten articles from recent years, a more diverse selection of publication sites was chosen to enhance the diversity of information sources, including *New York Times* (1 article), *The Guardian* (2 articles), *ESPN* (2 articles), *Yahoo Sports* (1 article), *US Open* (1 article), *Metro* (1 article), *History* (1 article), and *WBUR* (1 article).

Content analysis formed the analytical framework for this study. A thematic coding scheme of 9 categories was developed based on previous research (Yip, 2018; Kian et al., 2011) concerning gender representations in sports media. These categories were used to address the media coverage of the two participating athletes separately. The categories, as illustrated in Table 1, include: (1) Physical Appearance/Attire; (2) Training/Attitude Prior to the Game; (3) Personal Life/Relations; (4) Athletic Prowess/Strength; (5) Athletic Weakness/Limitations; (6) Comment on Gender Differences/Limitations; (7) Age; (8) Excuse/Justification; and (9) Sarcasm. The pilot stage involved the participation of two independent coders, one of whom was the author. A total of 20 articles were randomly selected for this pilot study, including 10 from the year 1973 (both before and after the competition) and 10 from the last 10 years. After discussing any disparities, the author coded the remaining articles using the same 9 categories.

Table 1. Coding examples for categories from the dataset.

Category	Examples from text
1. Physical Appearance/Attire	"Riggs played the first three games wearing a yellow jacket with the "Sugar Daddy" logo on the back" (Antonucci).

2. Training/Attitude prior to the game	"She had studied films of Riggs, especially of the Court debacle" (Eskenazi 52).
3. Personal Life/Relations	"Ms. Barnett was having an affair with Ms. King and, years later, would out her as a lesbian" (Fortin).
4. Athletic Prowess/Strength	"She beat Bobby to the ball, dominated the net and ran him around the baseline to the point of near exhaustion in the third set" (Amdur 1).
5. Athletic Weakness/Limitations	"Billie jean is at her worst against baseliners" (Lichtenstein 5).
6. Comment on Gender Differences/Limitations	"She's a woman and they don't have the emotional stability" (Greenspan).
7. Age	"55-year-old Bobby Riggs … 29-year-old Wimbledon champion, Mrs. Billie Jean King" (Eskenazi 41).
8. Excuse/Justification	"He is not in the peak physical shape that he was for the May Match with Mrs. Court" (Amdur 60).
9. Sarcasm	"He hustled himself out of $10,000 and perhaps out of business as a salesman for male chauvinism" (Amdur 21).

5. Findings

5.1. Physical Appearance/Attire

The results and analysis of the categories covered by sports media regarding the two participating athletes, Billie Jean King and Bobby Riggs, are presented in Tables 2-4. After reviewing the 20 articles, it can be concluded that media coverage has placed significant emphasis on both King's and Riggs's physical appearances and attires. Specifically, King's appearance was mentioned in 75% of the articles, while Riggs's was mentioned in 70% of them. King's entrance was commonly portrayed, highlighting the "Cleopatra-style gold litter that was held aloft by four muscular track-and-field athletes" (Amdur 31). On the other hand, portrayals of Riggs's entrance often emphasized the presence of six professional models, dubbed "Bobby's Bosom Buddies" (Amdur 31), who accompanied his entrance. This emphasis on muscular athletes and professional models creates a distinct contrast and intensifies the prevailing theme of gender in media coverage.

5.2. Training/Attitude prior to the game

As for the description of the two athletes' attitudes before the game, while that of King's remained relatively constant, the focus on Riggs's lack of practice has seen a significant increase in recent articles. It can be noted that in articles from the year of the iconic match, the theme of preparation for both athletes often tied into justifying Riggs' loss. Media outlets argued that his defeat was not indicative of his inferior athletic skill but rather a consequence of inadequate preparation. However, in recent years, the mention of Riggs's disinterest in training before the

game has evolved from a form of justification into mere reasoning that explains his loss, thereby acknowledging the role of preparation in Riggs' loss without diminishing King's achievements.

5.3. Personal Life/Relationship

When examining the category related to the personal lives and relationships of the athletes, a comparison reveals a notable shift. In the past, Riggs's personal life was referenced in approximately 60% of the articles, while King's was mentioned in about 70% of the articles. However, in recent times, King's personal life references have decreased to approximately 30%. The discussion of Riggs's personal life used to focus on his tendency to bet on his own games. However, a new revelation suggests that Riggs had fixed the game to compensate for sports bets amounting to over $100,000 that he owed to local mafias. As a result, the focus on Riggs's personal relationships shifted towards his association with the mafias. As for King, the primary focus on her personal life used to revolve around her relationship with Margaret Court, another gifted female tennis player who had lost to Riggs in the match known as "Mother's Day Massacre." However, recent media attention has shifted from King's relationship with Court to her affair with Marilyn Barnett, her former secretary, who later publicly disclosed King's lesbian identity.

5.4. Athletic Prowess and Weakness

In terms of athletic prowess and weakness, as years have passed, there has been a general increase in concentration on the athletic strength of the two sportspeople. However, when it comes to discussions regarding their weakness on the court, present media have been demonstrated to favor King over Riggs. This phenomenon is evident in the increase in articles discussing King's athletic strength, rising from 70% to 80%, while those examining her weaknesses have decreased from 60% to 20%. In Riggs's case, while the number of articles reviewing his athletic prowess has increased from 40% to 70%, those mentioning his limitations have also increased, reaching 60%. This observed trend may be attributed to the contemporary media's awareness of the match's outcome, leading them to glorify King's abilities while downplaying Riggs's. Moreover, the awareness of King's victory may have influenced media outlets to portray her as a symbol of female empowerment and a triumph over gender stereotypes, resulting in an increased emphasis on her athletic strengths.

5.5. Comment on Gender Differences/Limitations

Of all the categories examined, the comments on gender differences and limitations have undergone significant changes. When discussing the two athletes, the coverage of this topic has essentially reversed, with King's coverage decreasing from 60% to 30% and Riggs's increasing from 30% to 80%. However, the content is drastically different when the media discusses the two under the same category. In 1973, when the media discussed King, they often argued that, due to perceived differences in the physical structure of genders, King would never win against Riggs. Yet, when comments on gender differences were mentioned regarding Riggs, articles used it to

argue why Riggs would win. The stark contrast in portraying the athletes based on gender underscores the prevailing gender biases and stereotypes that were present in media coverage during that time. Fortunately, along with King's victory, discussions surrounding her concerning the differences and limitations of the sexes have reduced immensely. Conversely, there has been a significant rise in media coverage of the sexist comments made by Riggs, which has been used to highlight King's contribution and significance in the fight for gender equality in sports.

5.6. Age

Due to the significant age difference between the two players, with King at 29 and Riggs at 55, the most widely discussed category across the 20 articles is the age of the participating athletes. This phenomenon can be concluded from the analysis section in Table 4, which shows that King's age has been referred to in 85% of the articles, and Riggs's has been mentioned in 90% of them. Moreover, the age gap between the players also plays a vital role in the excuse and justification category, as writers commonly use Riggs's age to justify his loss.

5.7. Justification and Sarcasm

As the years have passed and through an examination of the occurrences in the two categories of justification and sarcasm, it becomes evident that the media industry has evolved to become more professional and objective when examining such competitions. Both the justification and sarcasm related to King have dropped to 0% in recent years, and those regarding Riggs have dropped to low ranges of 10% and 20%. However, in 2013, one of the most notable justifications for Riggs's loss in recent years was introduced in the *ESPN* article titled "The Match Maker" by Natta. The article attributed his loss to mafia involvement, leading to skepticism and speculation about the legitimacy of King's triumph.

Table 2. Media coverage of the two athletes in the year of 1973 by category

Category	Present (1)/Absent (0)																		
	Los Angeles Times				New York Times												The Times of India			
	Destroying a Myth		It's a Ms. Match		She Played Too		Discussed and Dissected		Mrs. King Defeats Riggs		Riggs Will Win		King Will Win		$100,000 Tennis Match		Billie Jean Silences		I'll shut his	
	BJK	BR	BJK	BR	BJK	BR	BJK	BR	BJK	BR	BJK	BR	BJK	BR	BJK	BR	BJK	BR	BJK	BR

Physical Appearance/Attire	1	0	1	1	0	0	0	0	1	1	1	1	1	1	1	1	0	0	1	0
Training/Attitude prior to the game	0	0	0	0	1	1	1	1	0	0	1	0	1	0	1	1	0	0	1	0
Personal Life/Relations	0	0	1	1	1	1	1	1	1	1	0	0	1	0	1	1	0	0	1	1
Athletic Prowess/Strength	1	0	1	1	1	0	0	0	1	0	0	1	1	0	1	1	1	1	0	0
Athletic Weakness/Limitations	1	0	1	1	0	0	0	0	1	1	1	0	1	1	0	0	1	1	0	0
Comment on Gender Differences/Limitations	1	0	0	0	1	0	1	0	1	1	0	0	1	0	1	1	0	0	0	1
Age	1	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	0	1	1	1
Excuse/Justification	1	1	0	1	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Sarcasm	1	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	1

Table 3. Media coverage of the two athletes in recent 10 years by category

Category	Present (1)/Absent (0)																			
	New York Times	The Guardian		ESPN		Yahoo Sports		US Open		Metro		History		WBUR						
	The 'Hustler' vs.	Four Decades After	BJK: It's Not	The Match Maker	An Iconic Moment	Remembering History: Billie	Milestones in Equality	BJK on the	BofS: When Billie Beat	BofS: It Isn't What										
	BJK	BR	BJK	BR	BJK	BR	BJK	BR	BJK	BR	BJK	BR	BJK	BR	BJK	BR	BJK	BR	BJK	BR

Physical Appearance/Attire	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	0	1
Training/Attitude prior to the game	0	1	1	1	1	0	1	1	0	0	0	1	1	1	0	0	1	1	0	1
Personal Life/Relations	1	0	0	0	1	1	0	1	0	1	0	0	0	0	1	1	0	1	0	1
Athletic Prowess/Strength	1	1	0	0	1	1	1	1	1	0	1	1	1	1	1	0	1	1	0	1
Athletic Weakness/Limitations	0	1	0	0	0	0	0	0	0	1	1	1	0	1	0	1	1	1	0	0
Comment on Gender Differences/Limitations	0	1	1	1	1	1	0	1	0	0	0	1	1	1	0	1	0	1	0	0
Age	1	1	1	1	1	1	1	1	1	0	1	1	1	1	0	1	1	1	1	1
Excuse/Justification	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0
Sarcasm	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1

Table 4. Analysis of the media coverage of the two athletes by category

Category	% Present					
	1973		Present		Total	
	BJK	BR	BJK	BR	BJK	BR
Physical Appearance/Attire	70%	50%	80%	90%	75%	70%
Training/Attitude prior to the game	60%	30%	50%	70%	55%	50%
Personal Life/Relations	70%	60%	30%	60%	50%	60%
Athletic Prowess/Strength	70%	40%	80%	70%	75%	55%
Athletic Weakness/Limitations	60%	40%	20%	60%	40%	50%

Comment on Gender Differences/Limitations	60%	30%	30%	80%	45%	55%
Age	80%	90%	90%	90%	85%	90%
Excuse/Justification	10%	40%	0%	20%	5%	30%
Sarcasm	10%	40%	0%	10%	5%	25%

6. Discussion

Upon comprehensive examination across all coding categories, the findings indicate a promising trajectory toward more inclusive media representations. Media outlets have shown increased awareness of the prevalence of gender stereotyping and have striven to mitigate its manifestation to the best of their abilities. Notably, the mention of categories often associated with gender stereotypes has declined over the past years. However, over several decades, a persistent trend of media outlets has been attempting to justify Riggs's loss with a litany of extenuating circumstances. One particularly noteworthy instance is the *ESPN* article "The Match Maker" by Don Van Natta Jr., which sparked a wave of similar narratives seeking to justify Riggs' loss by attributing it to alleged mafia influence over the game. Hence, while progress is evident, the journey toward eradicating gender stereotyping remains ongoing, necessitating further conscious efforts to foster an inclusive and unbiased media landscape.

6.1. Comparison

In line with earlier studies (Santoniccolo et al. 57-70; Yip 517-32; Ellemers 275-98) on the media presentation of women in sports, a pronounced emphasis on the physical appearance and attire of female athletes is evident in media coverage from both 1973 and recent years. The prevalence of King's appearance in media coverage was noticeable in 70% of the articles from 1973, and this trend has persisted, with a further increase to 80% in present-day articles. This continued emphasis on her physical appearance underscores a concerning pattern in media representation. Such perpetuation of the superficial objectification of female athletes inevitably hinders societal advancements toward gender equality. In line with previous research, these findings highlight the need for continued efforts to challenge and reshape media narratives, fostering a more equitable and respectful portrayal of female athletes that duly recognizes their skills and accomplishments on the field rather than focusing on their external attributes.

In contrast to the findings in Adrian Yip's study, where descriptions of negative skill levels or failures were observed in the portrayal of female tennis players, the articles examined in the present study have predominantly centered on King's athletic prowess. This discrepancy in media representations within studies in the same realm highlights the complex nature of gender portrayals in sports media. While it is encouraging to witness a focus on King's athletic abilities, it is essential to recognize that these findings may not necessarily indicate an absence of gender biases or stereotyping altogether. In this case, the knowledge of King's victory in the Battle of the Sexes significantly influences the content of most articles. Aware of her triumph, authors appear

inclined to explain the reasons behind her victory, emphasizing her athletic strength rather than her weaknesses.

6.2. Limitations

While the present study contributes valuable insights into the transformation of gender bias in media coverage of the Battle of the Sexes, it is essential to recognize and address certain limitations inherent in its methodology. One potential limitation lies in the analytical framework: content analysis can offer valuable insights into media representations, but it carries the inherent risk of introducing biases into the analysis. The subjective interpretation and coding of the data may influence the results, potentially affecting the objectivity and validity of the findings. Another significant limitation in the present analysis is the relatively small sample size, as only twenty articles written in English were consulted for data collection. The study may inadvertently overlook valuable perspectives offered by media coverage in other languages. This limitation may not fully capture the breadth and diversity of media representations during the time under examination, potentially leading to an incomplete or skewed understanding of gender bias in media coverage.

6.3. Recommendation

Despite the limitations, the present study serves as a valuable stepping stone toward a more comprehensive understanding of gender bias in media coverage and its implications for gender equality. By addressing these methodological challenges, future investigations continue to shed light on the evolving landscape of media representation and contribute to fostering a more inclusive and equitable media environment.

Additionally, incorporating non-English media representations can offer a more holistic understanding of gender bias in global media coverage, illuminating the influence of cultural norms and values on gender portrayals. Employing multiple coders can provide a more comprehensive understanding of media representations and help mitigate potential biases.

Examining gender bias within new forms of mass media is essential for better understanding how gender stereotypes persist and evolve in the digital age. Coupled with rapid technological advancements, the ways in which gender bias is normalized and reinforced has also undergone noteworthy transformations. Analyzing the underlying gender bias within these new forms of media can provide valuable insights into how stereotypes are perpetuated and amplified in the digital age.

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Simulation of Vibrations of Objects Using Vibration Motors By Mert Kaan Atan, Ada Balıkcı, Duru İbişağaoğlu, Gülsün Yaz Soydan, Mehmet Mert Türkmenoğlu

Abstract

Handling of physical objects is crucial in VR (virtual reality) and AR (augmented reality) applications and remote physical jobs such as construction work or surgeries. Especially in tasks requiring sensitive physical perception of the items and the environment, simulating vibrations accurately is challenging. We developed a sensor-based haptic device with two vibrational motors embedded in it to simulate the experience of holding and shaking a water bottle, in collaboration with the RML Laboratory of Koç University and with the guidance of Prof. Dr. Çağatay Başdoğan. Our design is practical and innovative and models the vibration of the water bottle to the haptic device accurately.

1. Introduction

1.1 Handling Physical Objects in VR and AR

Touch is an important and essential aspect of our reality and has been long avoided in virtual and augmented realms. For technologies such as computer simulations and control of virtual objects, haptics takes a crucial part as visuals and sounds. As VR (virtual reality) and AR (augmented reality) got more and more popular, the sense of touch plays an important role to create a more realistic experience. Mesmerizing steps in technology are now breaking this barrier and introducing us to a new era of tactile experiences in VR and AR. From haptic feedback to sensory interface, these kinds of innovations are redefining our interactions within the digital world. In addition, the word "haptic" derives from the Greek word "haptesthai" meaning "to touch" which later on evolved to the word "hapticē" meaning "science of touch" in New Latin. Today, the word "haptic" means "relating to the sense of touch" according to Cambridge Dictionary.

Cutting-edge advancements in technology are now bringing the sense of touch to virtual and augmented experiences and also transforming how we perceive and engage with these technologies. For instance, TurkDeck, an immersive VR system that reproduces what users see, hear and feel, creates "physical representations on the fly by making a group of human workers present and operate the props only when and where the user can actually reach them" (Cheng et al. 1).

In the ever-evolving concept of VR and AR, technologies related to haptic devices have become a crucial stimulus in elevating immersion and interactivity within these realms. Haptic devices that are designed to simulate our sense of touch create novel opportunities for exploration within these digital realms. Haptic devices play the role of a bridge between virtual and physical world and create a sense of touch through vibration patterns, force feedback, and tactile sensations. In other words, the haptic technology allows us to interact with the digital world by presenting force feedback to users. This allows users to feel textures, interact with objects and experience sensations like never before.

Technologies related to haptic devices are a major field. Haptic devices come in various forms each designed to provide a distinct haptic experience. We can see them in gloves, vests, touchscreens, exoskeletons, and many more. The range and capabilities of haptic devices continue to expand to enrich our sensory experiences. Agharese et al. developed a haptic device that grows out of a compact housing unit, providing a combination of directional and haptic force feedback to a user (Rećko et al. 1). Escobar-Castillejos, D., Noguez, J., Neri, L. et al. published an article that reviews haptic devices used in medical simulators, focusing on palpation, endoscopy, orthopedics, and other medical procedures (Escobar-Castillejos et al. 1). Basdogan, Cagatay & Srinivasan, Ayam worked on Haptic rendering in virtual environments: Techniques, applications, and user experience analysis (Basdogan et Srinivasan 1). H. Culbertson, J. Unwin, B. E. Goodman, and K. J. Kuchenbecker presented a new method for creating haptic texture models from data recorded during natural and unconstrained motions using a new haptic recording device (Di Bartolomeo et al. 1).

In summary the demand for haptic devices in VR and AR applications has piqued both industry's and academia's interest. Thanks to the availability of 3D printing technology, creating low-cost and lightweight devices has become achievable. These developments in haptic devices play an important role in many sectors but still have persistent challenges in optimizing their form to embody a wide range of actuators and sensors for richer haptic experiences.

1.2 Simulating Vibrations of Objects

In haptics, different types of haptic devices can be effectively utilized and in our project, the sense of vibration is considered a powerful tool to enhance the user's tactile experience. These precise yet influential tools play an important role in simulating experiences with virtual reality (VR), allowing us to have a realistic encounter.

The aim of our project is to simulate the experience of holding and shaking a water bottle. We developed a hand-held device for this simulation (see fig. 1). The device was designed with Fusion360 and utilizes 3D printing technology to house two haptic vibration motors. Through several iterations of experimenting with the device's form factor, we optimized the ergonomic grip on a standard 500ml water bottle while providing a secure realistic feel. Later on with programming and circuitry involved, we used an L298N motor driver to control motor speeds based on accelerometer output. A 7.9 Volt powers our system while extended wires, breadboard, and other modifications improve our device's functionality and ease of use. The working principle is that top and bottom motors run inversely proportional to each other. Such as when holding the water bottle, the bottom motor vibrates more stronger than the top one. When the water bottle is held sideways, the bottom motor loses, and the top motor gains power. Likewise, holding the bottle upside down will give more power to the top motor and less power to the bottom motor. Briefly, in our findings, we managed to work out the significance of meticulous design considerations and achieved to mimic a water bottle holding experience using haptic motors.

Fig. 1. 3D design of the hand-held device.

2. Methods

2.1 Design of the Haptic Device

      The housing for the two vibration motors was a 3D-printed object that was attached to a water bottle. The hand-held device was modeled using Fusion360 and had custom indentations that were fit to hold two haptic motors and an MPU6050 sensor unit. The part was designed to have an ergonomic hold and fit a standard water bottle of 500 ml in its inner diameter to provide a secure grip on the system.

      After several trials of the experiment, a decision was made to leave the housing of the MPU6050 empty. It was concluded that the vibrations produced by the two motors attached to the device caused the MPU6050 sensor to vibrate excessively, which in turn resulted in a distortion of accelerometer reading values. As the motor speeds were determined by the changes in accelerometer values, the relative stability of the values was crucial to simulating the desired physical sensation of the water bottle. Taking this into account, the MPU6050 was affixed directly onto a water bottle using double sided tape. It was observed that the effect of the vibrations on the sensor values decreased significantly.

2.2 Circuiting, Sensors and Drivers

      A MPU6050 acceleration and gyro sensor received data for the acceleration of an object. The acceleration sensor was stuck on a water bottle using double sided tapes (see fig. 2). The MPU6050 library by Electronic Cats was used to program the sensor.

Fig. 2. MPU6050 acceleration sensor attached on a water bottle.

A L298N pair motor driver was attached to two ERM (Eccentric Rotating Mass) mini vibration motors (see fig. 3). The motor driver was programmed to control the speeds of the motors according to the output coming from the acceleration sensor.

Fig. 3. A L298N pair motor driver and attached to two ERM (Eccentric Rotating Mass) mini vibration motors.

The power input to the motor driver was provided by a 7.4 Volt battery, consisting of two 3.7V Lithium Ion batteries. The motor driver automatically feeds the vibration motors 3.5V, even though it requires about a 7.5V input itself.

Fig. 4. Diagram for the final circuit.

For the final product, the jumpers were extended using additional male–female jumper wires. Additionally, A breadboard was added to simplify the circuit, and electrical tape was applied to prevent short-circuiting from soldered endpoints and to organize long jumper groups (see fig. 5).

Fig. 5. The final product.

2.3 Programming

A total of three libraries were imported. First one is, MPU6050 by Electronic Cats to communicate with the acceleration sensor. Secondly, the Default Wire module enables I2C communication. The third library is L298N by Andrea Lombardo to communicate with the haptic motor driver. Excluding the default void() and loop() functions, four functions were written. Firstly, *convertToG* was written to convert the MPU acceleration readings to an

acceleration value in m/s^2 (see fig. 6). In the setup, MPU6050 read the value 16384 for the vertical axis when it was set to a stable, straight surface. Since the gravitational acceleration is 9.81 m/s^2, it was assumed that 16384 corresponded to 9.81. *convertToG* function takes the MPU6050 input, divides it by 19384, and multiplies the value with 9.81 to obtain the value read in terms of m/s^2. The function is only used for printing the acceleration values. The operations of mapping the input into speed were conducted using default MPU6050 readings.

```cpp
float convertToG(int input) {
  float updatedValue = 9.81*(static_cast<float>(input)/16384);
  return updatedValue;
}
```

Fig. 6. converToG function.

Another function *calculateForce* was written to calculate the force exerted by the object with the sensor attached on it to the surface (see fig. 7). The function returns F using $F = ma$, where m is mass of the object and a is the acceleration. The values are divided by 1000, since the input will be taken in units of grams and kilograms are required to calculate the force. To print the data to the Serial Monitor, *printToSerial* function was written (see fig. 8).

```cpp
float calculateForce(float accel, int massInput) {
  float Force = (massInput * accel) / 1000;
  return Force;
}
```

Fig. 7. calculateForce function.

```cpp
void printToSerial(int accelValx, int accelValy, int accelValz,
int outputValA, int outputValB, float SerialInput) {
  float inGx= convertToG(accelValx);
  float inGy = convertToG(accelValy);
  float inGz= convertToG(accelValz);
  float ForceX = calculateForce(inGx, SerialInput);
  float ForceY= calculateForce(inGy, SerialInput);
  float ForceZ = calculateForce(inGz, SerialInput);


  Serial.print("X axis accel= ");
  Serial.print(inGx);
  Serial.print(" | Y axis accel= ");
  Serial.print(inGy);
    Serial.print(" | Z axis accel= ");
  Serial.print(inGz);
  Serial.print(" | motorA = ");
  Serial.print(outputValA);
  Serial.print(" | motorB = ");
  Serial.print(outputValB);
  Serial.print(" | X axis force= ");
  Serial.print(ForceX);
  Serial.print(" | Y axis force= ");
  Serial.print(ForceY);
  Serial.print(" | Z axis force= ");
  Serial.println(ForceZ);

}
```

Fig. 8. printToSerial function.

In order to map the acceleration input into the speeds of motors, two functions *SpecialMapA* and *SpecialMapB* were written. The range of the acceleration readings was theoretically limitless. However, effective speed change should have only been applied within the regular range, which was between 0 and 30000. To solve this problem, SpecialMapB and SpecialMapA map the readings over a wider speed range when the readings are within the common range of 0 and 30000. Below is the table for these mappings (see table 1).

Table 1: Corresponding Ranges Of Inputs And Speeds

Motor A		Motor B	
Input Range	Speed Range	Input Range	Speed Range
-7000, 0	0, 20	17000, 50000	20, 0
0, 17000	20, 120	0, 17000	200, 20
17000, 30000	120, 250	-3000, 0	250, 200
30000, 50000	250, 255	-7000, -3000	255, 250

The reason for these choices of ranges were to make the experience as close to what was felt on a water bottle. The data read at standing point was about 17000. Since at a standing point, water is at the bottom and there is close to no vibration at the top, Motor A vibrates at 120 speed and Motor B vibrates at 20 speed. In the case of shaking, the values were observed to vary between -17000 and 50000 at maximum. A wider range of 20 and 200 was chosen for Motor B compared to Motor A, since most of the time the values stayed between 0 and 17000, in which it was harder to feel changes in Motor B due to values being closer to 17000 most of the time. Therefore, to feel the instant vibration change more significantly, a higher value of 200 was chosen compared to 120.

The main *loop()* function receives the object's mass as an input to the Serial monitor (see fig. 11). When the value is entered, the program starts by getting the acceleration values, mapping them to speeds, printing the information (speeds, forces, accelerations), and lastly running the motors with the given speed.

```
void loop() {
  // Read sensor value
  SerialInput= Serial.readString().toInt();
  SerialInput = SerialInput;

  while (SerialInput >0) {

    sensor.getAcceleration(&accelX, &accelY, &accelZ);

    speedA= SpecialMapA(accelX);
    speedB = SpecialMapB(accelX);
    // Print sensor value to Serial Monitor
    printToSerial(accelX, accelY, accelZ, speedA, speedB, SerialInput);

    motors.setSpeedA(speedA);
    motors.setSpeedB(speedB);
    motors.forward();

  }

  delay(10);
}
```

Fig. 11. loof function.

3. Results

The results obtained show a successful calculation of forces and motor output was successfully calculated. For an object with an inputted mass of 345 grams, and acceleration read as 4.91 m/s^2, the force output is predicted to be

$$0.345 \ * \ 4.91 \ = 1.693 \ N$$

The application correctly calculates the force output to two decimal places: 1.69 (see fig. 12).

Accordingly, the acceleration value 4.91 is below the gravitational acceleration 9.81, so it is predicted that motor A will run with a speed less than its default at standing position 120, and motor B will run with a speed more than its default 20. It successfully outputs that motor A ran with a speed of 63, and motor B ran with a speed of 114. These results also show that the object was in a downward motion (see fig. 12).

Fig. 12. Results

The device successfully simulated the vibrations of the water bottle it was attached to. In cases of shaking and spinning the water bottle, vibration differences between the two motors were clear and accurate to the vibrations felt while holding the water bottle.

One source of error was the delay caused by Arduino. It was experienced that there was about 25 milliseconds of delay before the vibration read by the sensor outputted to the motors. Another source was the format of printing data to the serial. Arduino automatically reduced the values to two decimal points. However, instead of rounding, it removed the digits after the second decimal point, which went unnoticed while experimenting since the system was successfully working. Even though this did not affect the system, it caused incorrect data to be printed.

4. Discussion

As our goal of simulating a water bottle became successful, this project also contributed to the usage of haptic robots for the sense of touch in a virtual environment. The results of our project suggest that we reached our intention by feeling the reactions of the water inside the bottle to our hand movements such as shaking and changing the position of the water bottle. The 3D-printed hand-held device's shape helped us to achieve the feeling of a bottle. The pair of ERM (Eccentric Rotating Mass) mini-vibration motors start to vibrate according to the output from the MPU6050 sensor unit and work in inverse proportions. The results suggest that the motor output was calculated successfully as explained in the results section. The vibrations were clear and the feeling we aimed for was achieved. On the other hand, a considerable limitation for this project can be that the MPU6050 sensor unit was not attached to the 3D-printed hand-held device, but rather to a water bottle. In this case, we need to change the position of the water bottle in order to mimic the behavior of the device, and changing the position of the device is not enough. That's because when the MPU6050 sensor was attached to the device, the vibration of the haptic motors disrupted the true input to the sensor. Since the sensor did not read the values correctly, it was not an option to attach the MPU6050 sensor and the haptic motors to the same device. Nevertheless, our project works perfectly in simulating the intended outcome. Moreover, we believe that our research makes a contribution to the usage of haptic motors and touch simulations.

5. Conclusion

5.1 Objectives, Findings, and Limitations of Our Project

We developed a hand-held haptic device that simulates the tactile experience of holding and shaking a water bottle. Utilizing advanced haptic feedback, motion capture, and visual rendering we created an immersive encounter with realistic sensations. By simulating vibrations through vibration motors, we achieved a life-like sensation of holding and shaking a water bottle. Through iterative advancements in our design and attaching the MPU6050 directly to the water bottle, we mitigated the accuracy issue caused by motor vibrations. The use of the motor driver, battery, and other extensions improved our device's functionality.

Our findings highlight the importance of diligent design considerations in optimizing users' haptic experiences, making the way for more sophisticated interactions in virtual and augmented realities. Also, our project represents an important step towards bridging the gap between virtual reality and our world through the innovative use of haptic devices. The integration of haptic vibration motors in this project has demonstrated the significance of haptic device technology. Haptic feedback enhances users' experiences, improves accessibility, and contributes to safety and efficiency. Potential future applications of this technology are set to play a pivotal role in shaping a more immersive interaction between humans and machines. Addressing existing challenges and focusing on effective design will further optimize the use of haptic vibration motors, making this technology a key element in shaping various industries.

While developing our project we ran into some limitations that led to the project's course. Although this project gave us promising results and valuable insights, it is essential to acknowledge some limitations encountered. These included equipment shortages, some MPU6050 errors, and cable contact issues. We had limited equipment to work with and that caused the scope of our project to get a little narrower than expected. Secondly, MPU errors were occasionally observed during the first week of the project which led us to have some disruptions in the experimental process. Finally, the cable issues led us to have intermittent haptic feedback and in some scenarios complete signal loss that we had to constantly solder the cables. We managed to mitigate these issues but future research should still be mindful of these constraints and ensure a more comprehensive approach to overcome them.

5.2 Further Research and Applications

Our project that simulated the vibrations of an object using vibration motors has opened up possibilities for future research and development in the field. Moving forward, further research could explore advanced haptic algorithms to create more realistic tactile experiences. For instance, MPU6050 sensor can be replaced with computer vision techniques to understand the water bottle's behavior through cameras. By leveraging image processing and machine learning algorithms, we can understand the water bottle's movements and orientation. This will offer us a more accurate and dynamic haptic feedback system resulting in enhancing the users' interactions with virtual reality and minimizing the inaccuracy that might be caused by MPU6050 data. Additionally while considering the potentials, future directions could involve collaborative projects that involve experts in their relevant fields to have more accurate results. Moreover, by expanding the scope of the project, multimodal haptic feedback that connects vibration motors with other sensory cues like temperature, stiffness, texture, and pressure could enhance the overall experience. Also, rapid advancements in wearable technology are an important cofactor and could lead to novel applications of this technology. Embracing these future directions will surely push haptic simulation technology to new heights.

This technology has significant potential across various industries. In the field of virtual reality, our findings open up new avenues, especially in gaming and training simulations. In the context of product design and testing, our project of haptic simulations can enable engineers and

designers to assess the ergonomics and usability of products like water bottles without the need for physical prototypes, saving time and resources. In the field of medical training, this technology can be adapted to simulate precise movements and sensations experienced during certain medical procedures. Additionally, in education, haptic simulations can engage students in more interactive learning experiences. Embracing this kind of practical implications will give a lead in various fields.

In conclusion, our project on the simulation of vibrations using vibration motors, simulating the sensation of holding and shaking a water bottle, opens the door to the thrilling future of haptic innovations. Through this tactile journey, we anticipate a world where technology can truly touch and transform the way we experience the digital realm.

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<center>**John Locke By Rachel Lee**</center>

On a dreary March evening in 1979, an engineer working in the Three Mile Island nuclear facility's control room discovered a malfunctioning switch. Thankfully, it was a simple matter and could be left for the day shift to fix—and so the operator simply left a repair tag hanging from it and moved on.

As the engineer's footsteps left the room, the tag slowly slid downwards until it settled into a position covering one of the many indicators on the dashboard.

At 4AM the following morning, a relatively minor obstruction in the plant's water filtration system stopped the flow of cold water into the steam generator. In the event of such a blockage, which was common, the backup system would simply take over. Unfortunately, by sheer coincidence, the valves for the backup were closed, and the indicator showing their status now lay hidden beneath the night shift engineer's ill-placed label (Perrow). By the time they were finally opened, four hours later, the lack of coolant had brought the reactor core dangerously close to a meltdown.

The near disaster at Three Mile Island is just one example of a chain of seemingly innocuous lapses slowly compounding into a critical failure. Indeed, it seems as though for every plan, there have been several unforeseen mistakes capable of derailing it through mere luck and happenstance. Even history's most successful plans have not been immune to such human error, as this paper will seek to establish. Indeed, it is this inevitability of imperfection and its disproportionate impact which ensures that the course of history is shaped by the mistakes of the powerful rather than their plans.

Externalities

Unlike a deliberate plan with defined boundaries, a mistake by definition has no boundaries. Even the grandest of plans is surgical by nature; plans are called plans because they aim for the achievement of a specific goal within a distinct theater of operations, whether it be a certain subsection of society or a particular nationwide issue. In contrast, a mistake, however small, generally tends to ripple simultaneously across several socioeconomic axes like a pebble thrown into a still pond.

Perhaps the best instance of this effect can be seen in the downfall of the Roman Empire. Although the complex factors behind the decay of this once great civilization remain disputed, many of the issues that plagued Rome in its later years can be traced back to a single mistake. Enacted by the emperor Caracalla in 212, the so-called Antonine Constitution granted all Roman subjects automatic citizenship in a supposedly emancipatory gesture. Despite the highly favorable optics, the Constitution was problematic because it effectively eliminated the *peregrini*, the non-citizen class which made up the vast majority of the Roman population and whose contributions to the Empire's finances were invaluable (Gibbon, 152). In fact, because citizenship was so widely available to *peregrini* who were enlisted or in public service, this system was serving as a vital safeguard against social stagnation. With its removal and upward

mobility at a standstill, the once legendary Roman ethic now lay dormant, and Caracalla's "careless profusion…[had become] the inevitable ruin of the empire" (Gibbon, 155). Throughout the next two centuries, the Roman empire would come under assault from a torrent of unexpected repercussions, many from which it would never recover.

Almost a century after the death of Caracalla, a little-known captain of the Praetorian Guard named Diocles—later to be known as Diocletian—was named emperor. He inherited an empire which was almost unrecognizable, being wracked almost daily by violent civil conflicts, precarious questions of imperial succession, and increasingly lackadaisical governance of its expansive territories. In order to respond to the crisis, Diocletian implemented an entirely new form of governance known as the Tetrarchy—the rule of four (Waldron). The plan was to establish a council of four emperors who each held authority in different provinces and could serve as stabilizing forces in times of need. This push towards greater bureaucracy in governance was amplified throughout the lower ranks, with the state seeking to effectively replace private institutions once powered by the now-obsolete Roman ethic.

Unfortunately for Diocletian, his carefully planned vision of the revitalized Roman state was to be short-lived. Despite successfully ending a century-long interregnum where no less than sixty men tried to claim the throne (Birley, 4), the Tetrarchy was unable to overcome the deeply entrenched social fractures that had persisted since the Edict of Caracalla. Within the next two decades, Diocletian's empire would once again descend into civil war as ambitious regional authorities exploited its decentralized power structure. Meanwhile, the burgeoning administrative state he constructed would quickly grow to embody almost every modern criticism of big government—corruption, ineptitude, and the crippling taxation which was emblematic of later Roman emperors (Waldron). In the end, the successes of Diocletian were fleeting at best, not because his planning was deficient, but because his campaign of renewal could not revive the civil institutions which had been instrumental in holding the Empire together.

Inaccuracies

Of course, not all plans are as cohesive or successful. For a plan to fully succeed, for events to proceed exactly as projected, is an exceedingly rare event. In fact, many monumental plans throughout history have been "mistakes in plan's clothing", where the result is far more attributable to the unintended moments rather than the predetermined path of progression.

This phenomenon is most easily observable in large-scale planning catastrophes, most notably the series of five-year plans launched throughout Eastern Europe beginning with Josef Stalin in the 1920s. Having inherited a largely agrarian, traditional Russia, Stalin immediately launched an overhaul of the economy, directing the Soviet State Plan Committee (*Gosplan)* to pour funding into heavy industry while cramming peasants into collective farms subject to state control. In some aspects, the first five-year plan was successful—the Soviet authorities reported a remarkable 350 percent surge in output, though the veracity of their claims remains debated (Hunter, 241). However, the sudden upheaval of Russian society and massive repression of the peasantry quickly turned Stalin's triumph sour. Harvests plummeted almost immediately, and by

the time grain supplies began to flow again in 1933, almost 4 million Ukrainians had starved to death in a colossal famine known as the *Holodomor* (Kulchytskyy et al.). Combined with the many other command-economy calamities across the Eastern Bloc, Stalin's failure eventually served to near single-handedly disprove the notion that top-down planning has a place in economic management.

An examination of more successful macrosocial plans is even more telling—take, for example, what is perhaps the greatest reorganization of society in recent memory. Initially created as an emergency response to the Great Depression, the New Deal quickly transformed the American landscape, building bridges, reorganizing farms, and introducing regulatory agencies with sweeping powers in an effort to provide "Relief, Reform, and Recovery". From 1933 to 1935, the Public Works Administration alone spent $3.3 billion in subsidies to fund 34,599 construction projects (Winkler). By all accounts, the Roosevelt administration's push to increase government spending and provide essential services to the elderly and impoverished had been straightforward and successful.

Unfortunately for Roosevelt, the short-term effect of his herculean efforts on the economy remains fiercely contested. Although increased government spending arguably helped cushion the impact of the economic downturn, it failed to foster a rapid return to normal employment rates as he promised (Cole et al, 4). Some have even gone as far as to say that "government intervention helped to make the Depression Great" (Shales, 9) through the limiting of market competition. In the end, it was not Roosevelt's elaborate rebuilding of America that would end the Depression, but rather the infamous flight of Zeroes over Pearl Harbor—another mistake—and the massive demand for military production fueled by World War II.

In contrast, while mistakes are typically defined as errors that deviate from the intended plan, there have also been instances of complete serendipity which have proved pivotal. Famously, during the 1914 assassination of Archduke Franz Ferdinand in Sarajevo, the Archduke curiously chose to continue his visit of the city even after the initial botched attempt at bombing his car (Clark). Unfortunately for the Archduke and his wife Sophie, their driver took a wrong turn on the Appel Quay near an unassuming delicatessen by the name of *Schiller's*. As the driver realized his mistake, he stopped outside the store just as 19-year-old Gavrilo Princip emerged from beneath the awning and fired two shots at point-blank range into the stationary vehicle. That single moment, immortalized in so many textbooks, was in fact a comedy of fatal errors on the part of both the Archduke and his assassins—and yet today it is credited with plunging the globe into World War I. Once again, a simple twist of fate had torn through the pages of history.

The Fog of War

As with the demise of Franz Ferdinand, wars, covert operations, and other life-and-death situations have historically provided the most fertile ground for mistakes to wreak havoc. As the renowned military strategist Carl von Clausewitz explains, war is particularly devious because it is "more than a mere chameleon, because it changes its nature to some extent in each concrete [series of events]" (Simpson). This creates the oft-cited "fog of war", which deprives generals

and spymasters alike of total knowledge and forces them to engage in the classic back-and-forth of inherently deficient snap decisions which heighten the frequency and impact of mistakes.

With the odds stacked so far against them, it is perhaps unsurprising that the vast majority of would-be master tacticians have their names trampled into the dust. At the Milvian Bridge, Maxentius's decision to confront Constantine across what was effectively a rudimentary pontoon bridge led to a complete rout, with the young Emperor drowned by his own army as it fled across the Tiber without room to breathe or maneuver (Speidel, 258). Meanwhile, at Dien Bien Phu, the French committed arguably one of the most egregious unforced tactical errors in modern history, isolating their forces in an indefensible salient on the low ground in a move reminiscent of Hitler's misguided attack on Stalingrad (Shull). In both cases, credit for the outcome ought go not to the victor, but to the vanquished—despite superiority in numbers and equipment, they blundered away their advantage and granted their enemy the chance to reshape history.

Lest the military historians object, the past has also had its share of soldierly masterpieces—carefully crafted campaigns which were able to penetrate the "fog of war". In 216 BC, the famed heavy infantry of Rome was virtually annihilated by Hannibal Barca at Cannae, considered today by many to be the "perfect battle" (Coco, 39). Fifteen centuries later, at Austerlitz, the armies of the Third Coalition would meet their maker in Napoleon Bonaparte, ironically another famed conqueror of the Alps. Both battles incorporated revolutionary tactics and left their victors masters of Europe; yet, neither engagement was sufficient to guarantee perpetual military supremacy. Barely more than a decade after their respective triumphs, both Hannibal and Napoleon would suffer their final defeats at the hands of Scipio and the Duke of Wellington—two commanders who, despite relative lack of inventiveness or ingenuity, adopted the strategies of their opponents to great effect (Shean). In the end, Cannae and Austerlitz proved that genius wins battles, not wars—not even the best commanders are immune to the unyielding grasp of Fortune.

Conclusion

Our analysis reveals that history cannot be read as a single, cohesive tale of neatly ordered actions taken by some "great man" sitting alone in a smoke-filled room. Instead, the narrative quickly disintegrates into a haphazard collection of outlandish mishaps and remarkable coincidences. Unlike plans, which take place along predetermined axes, we have seen that a single mistake can give rise to an array of ramifications ranging from psychological to military to socioeconomic. This epistemic gap is further widened by the fact that no plan is ever perfect, especially in do-or-die situations where thousands of lives often hang in the balance. Ultimately, it suggests that it is chaos, rather than order, which governs the affairs of mankind.

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COVID-19 and its Effects on Black Americans: A Syndemic Perspective by Shiza Saad

Abstract

The COVID-19 virus claimed millions of lives around the world; there were upwards of one million deaths in the US alone. Though COVID impacted everyone, the virus was particularly devastating for Black Americans, especially when compared to white Americans. Since slavery, when individuals from various African countries were forcibly removed from their homes and brought to America, Black people have experienced discrimination in numerous forms. Racial discrimination in healthcare, employment, and housing have plagued the Black American community, making it nearly impossible to gain equal footing with other racial groups. When the COVID-19 virus spread rapidly throughout the country, Black Americans felt the combined weight of pre-existing structural racism and the unfolding medical catastrophe. The joint effects of structural racism and a medical crisis created a uniquely dangerous situation for Black people, making the term 'pandemic' inadequate to describe what they experienced. Rather, Black Americans experienced COVID-19 as a synergistic epidemic, or 'syndemic', because COVID-19 had far-reaching effects that went beyond biology or medicine. Calling COVID-19 a syndemic with respect to its impact on Black Americans captures the pre-existing structural inequalities that made the virus especially deadly. This paper explores the nuances of labeling COVID-19 as a syndemic for Black Americans, and investigates the intertwining of historical, socio-political, and economic forces with the coronavirus that resulted in devastation for them.

Introduction

In 1793, Yellow Fever struck Philadelphia, Pennsylvania. It is estimated that the epidemic claimed over 5,000 of the city's 50,000 inhabitants (Bordewich). Black people were believed to be immune, and were consequently the ones who volunteered to help the sick. Later, a racist dialogue emerged, accusing Black people of taking advantage of the epidemic to steal and extort. Similarly, in 2020, Black people were believed to be unclean or careless when it came to the spread of COVID-19—a virus that has led to the death of over six million people worldwide—even though there is no evidence suggesting that to be true. There is a striking resemblance between what happened in 1793 and 2020, despite the two pandemics being over two hundred years apart.

When the Yellow Fever hit Philadelphia, Pennsylvania, the nation's prominent capitol, in 1793, Black people were thought to be immune to the virus. Later, mortality rates showed that communities of color were in fact disproportionately affected during the epidemic. Nonetheless, when the city's leading physician, Benjamin Rush, asked two prominent leaders of the free Black community–Absalom Jones and Richard Allen–to help the sick as a result of this erroneous belief, they agreed. Volunteers tended to the sick, fed the abandoned, prepared medicines, collected bodies, and supplied coffins. Black Philadelphians performed the tasks that no one else was willing to do, not unlike the disproportionate number of Black people doing essential jobs during the COVID-19 pandemic. On the other hand, most of the wealthy and white population

fled the city. President George Washington and other officials were part of the twenty-thousand who did so (Gamble).

When winter arrived and allowed for the fever to subside a little, Matthew Carey, a prominent publisher who had initially fled town, penned a pamphlet titled *A Short Account of the Malignant Fever Lately Prevalent in Philadelphia: With a Statement of the Proceedings That Took Place on the Subject in Different Parts of the United States*. In it, he disparaged the efforts of the Black volunteers, claiming that they looted the homes of the sick and overcharged for their services. He wrote, "The great demand for nurses, afforded an opportunity for imposition, which was eagerly seized by some of the vilest of the blacks. They extorted two, three, four, and even five dollars a night for such attendance, as would have been well paid for, by a single dollar. Some of them were even detected in plundering the houses of the sick" (Carey 77). The basis for these accusations stemmed from the widespread racism in the nation. Slavery would soon end in Pennsylvania, but the beliefs that allowed for its existence would continue to pervade American thought. Black people were still restricted to the lowest bounds of society, and had little access to the resources that white people had. Their societal inferiority disallowed them from jobs, homes of good quality, and wealth. Such inequalities still persist today and were particularly detrimental for Black people during COVID. In *A Short Account*, Carey presented the medical effects of the fever through a thoroughly white lens. Although he admitted that Black people "did not escape the disorder," he erroneously claimed that "the number of them that were seized with it, was not great" and as he was "informed by an eminent doctor," they responded to medicine "'more readily than…whites'" (qtd. in Carey 77).

In response, Jones and Allen published their own pamphlet, *A Narrative of the Proceedings of the Black People, During the Late Awful Calamity in Philadelphia, in the Year 1793; and a Refutation of Some Censures, Thrown Upon Them in Some Late Publications*, that meticulously refuted Carey's claims, provided details of the acts of mercy that the Black community had performed, and highlighted the suffering of the Black population as a result of the yellow fever. *A Narrative* impassionately defended the Black volunteers; Jones and Allen claimed "two thirds of the persons, who rendered … essential services, were people of colour" (Jones and Allen 5). Moreover, they also claimed that most volunteers provided their services without expecting any pay, and those who were paid were given a higher fees as a result of simple supply-and-demand, not extortion (Gilder Lehrman Institute of American History). Jones and Allen pointed out that whilst Carey had left the city, Black people had stayed behind and considered it a moral obligation to help those who suffered. They also refuted the white perspective that Black people were immune to the virus when they wrote, "We have suffered equally with the whites, our distress hath been very great, but much unknown to the white people" (Jones and Allen 15). History repeated itself approximately two centuries later.

In 2020, a similar racial phenomena would appear with the COVID-19 pandemic. When the COVID-19 virus began spreading throughout the country in March, many thought that it would be a "great equalizer." Perhaps, in the face of a common enemy that no one quite understood, Americans would set aside their differences and work together, for the betterment of

the nation. Unfortunately, the opposite was true. COVID deepened the already-existing cracks in America's armor. Not only was it not an equalizer, it highlighted inequalities across many different aspects of society.

Just as a racist dialogue manifested in 1793, a similar one emerged during the COVID-19 pandemic. Texas Lt. Gov. Dan Patrick blamed Black people for the increasing number of COVID cases in his state in August 2021, claiming that they were "the biggest group in most states… who have not been vaccinated" (Lybrand and Subramaniam). Patrick did not note that his lax COVID prevention policies were much more likely to blame for the recent uptick of cases in Texas, with a 24% rise over the past two weeks.[6] Data from the Kaiser Family Foundation showed that white adults were, in fact, the largest share of unvaccinated adults and that vaccination rates among Black people continued to increase while the rate among White people was on the decline.[6] Patrick is just one of many who spread false, racist notions and represented the unequal treatment of Black people, even during a time as harrowing as the COVID era.

The pandemic affected everyone's lives in differing capacities. Black people experienced disproportionately high rates of COVID-related deaths and hospitalizations because of structural racism in many areas of their lives. They were employed in high exposure professions, lived in underfunded neighborhoods, experienced more homelessness, were of lower economic status, were imprisoned at higher rates, and feared interactions with the police. The COVID-19 era was eerily similar to the Yellow Fever Epidemic that struck Philadelphia, Pennsylvania two centuries ago. Black people endured structural racism in employment, housing, and socioeconomic patterns in 1793 and 2020. Myths surrounding Black people's health existed in 1793 and 2020; they were intrinsically immune to the Yellow Fever yet intrinsically susceptible to COVID-19. Disproportionate numbers of Black people were doing the essential jobs in 1793 and 2020. What Absalom Jones and Richard Allen published two hundred years ago still rings true today: Black people's "distress hath been very great, but much unknown to the white people."[2]

In this paper, I will argue that syndemic theory is better suited for COVID-19, as opposed to labeling it as a "pandemic." I explain that the term "pandemic," while correct in describing a medical phenomenon, is not completely accurate when discussing how Black Americans experienced COVID-19. Pandemic implies indiscriminate effect—it does not account for any disproportionate impacts like those that COVID-19 had on Black Americans. The more appropriate term for COVID is "syndemic" because of the structural racial inequalities that caused Black Americans to suffer in unique ways. In Section I, I will define three key terms: structural racism, medical racism, and syndemic. These terms will lay the foundation to the following sections in which I explore the history of medical racism and how said history explains the distinct way Black Americans experienced COVID-19. In Section II, I will provide a summary of the history of medical racism, to illustrate how it continues to persist today and what roles it played in the dramatically disproportionate impacts on the Black community in America during the era of COVID. In Section III, I will analyze how structural racism impacted Black people during COVID, and specifically focus on the fields of employment, housing, and healthcare, in order to provide evidence as to why COVID is a syndemic.

Definition of Terms: structural racism, medical racism, and syndemic

In this section, the following terms will be defined: structural racism, medical racism, and syndemic. It is vital to understand these terms, because they lay the foundation for demonstrating the disparate effects of COVID-19 on Black people. Historic structural and medical racism are key components in the recognition of Black people's unique struggles during the pandemic—the combined existence of both these categories of racism suggests that the nature of COVID-19 is more so of a syndemic, rather than a pandemic.

Structural racism can be defined as "the totality of ways in which societies foster racial discrimination through mutually reinforcing systems of housing, education, employment, earnings, benefits, credit, media, health care, and criminal justice. These patterns and practices in turn reinforce discriminatory beliefs, values and distribution of resources" (De Maio). Thus, structural racism pervades every area of Black people's lives and affects them mentally and physically. For example, neighborhoods that are predominately Black usually have less space, less economic investment, and fewer resources, such as places to exercise or play, which is also associated with higher rates of cardiovascular disease risk for Black women (Mobley et al. 327). Such inequalities played major roles in the disparate effects of COVID on Black populations, especially when combined with medical racism.

Medical racism, or the systematic, widespread racism against Black people and other people of color by professionals in the medical field, has been part of American history since the era of slavery. The history of medicine and healthcare in this nation has been marked by racism and violence: inequitable access to healthcare, segregated medical facilities, and Black people being barred from medical education are just some examples. One of the most infamous examples of medical racism is the US Public Health Service "Tuskegee Study of Untreated Syphilis in the Negro Male." A 40-year long study that began in 1932, the Tuskegee study involved hundreds of Black men without their informed consent. Most of these men were poor sharecroppers from Macon County, Alabama, who relied on white farmers for their livelihoods. The men were told they were being treated for "bad blood" whilst the experimenters kept treatment for syphilis, namely penicillin, from them when it became available in 1947. The inhumane research methods used in the Tuskegee made a direct impact on medical ethics and development of regulations to protect participants in studies and research.[28] Medical racism, along with structural racism in housing, employment, and healthcare, produces health disparities in Black people; analyzing COVID completely requires taking such factors into account, which is why "syndemic" is a more accurate term. The recurring presence of medical racism throughout American history will be a concept repeatedly visited throughout the paper, and explored more deeply in the following section.

Synergistic epidemic or "syndemic" is a term that was coined by Merrill Singer in the early 1990s to describe the HIV epidemic that was disproportionately impacting communities of color and lower economic status in North America (Singer 931). A syndemic is a synergistic interaction between biological and socioecological factors (Yadav et al. 323). The core tenets of syndemic theory are disease concentration, disease interaction, and the large-scale socio-political

forces that ultimately drive a syndemic's disproportionate effects. Disease concentration refers to multiple epidemics occurring at the same time as a result of adverse social conditions and political-economic forces, whilst disease interaction refers to how overlapping epidemics exacerbate the health effects of adverse social conditions, through either biological interactions between diseases or through interactions between biological and social processes (Gravlee 341). Put simply, the term "syndemic" casts a wider net than the term "pandemic," because it takes into account not only the biological aspects of a disease, but also the social, political, and economic disparities at play that result in a disease's disproportionate effects on a population. Examining COVID-19 through the lens of it being a syndemic allows for *all* of its impacts to be taken into account, in addition to the medical and biological impacts it had on people, like its exacerbation of certain non-communicable diseases (NCDs) and certain mental health disorders.

All three of these terms (structural racism, medical racism, and syndemic) will be thoroughly examined in this paper in the context of COVID-19.

Medical Racism throughout History

Medical racism has long pervaded the lives of Black Americans. There are numerous examples, both historic and modern, of Black people receiving inadequate healthcare or no healthcare at all, such as the previously mentioned 1930s Tuskegee syphilis study. Another example of medical racism is how enslaved people were used as anatomical material to develop some of the core aspects of American medicine. Medical schools in the 19th and early 20th centuries used Black bodies for dissection and display. They also used Black people to serve as their "resurrectionists," or the ones to steal bodies from cemeteries, because the entry of Black people in segregated cemeteries was less suspicious than the entry of white people (Nuriddin et al. 949). The Cincinnati Radiation Experiment conducted from 1960 to 1971 by Dr. Eugene Sanger is also a case of medical racism. Dr. Sanger overused radiation on 88 terminal cancer patients, 60 percent of whom were Black and aged 9 to 84. The patients did not give their consent, nor were they informed of the experiment's true purpose; the project was being funded by the Pentagon, because the government was interested in the effects of radiation from nuclear weapons, as the Cold War was on-going at the time. Out of the patients that were experimented on during the 11-year-study, about a quarter are believed to have died from radiation exposure. Sanger admitted to what he did, deeming it necessary, and was never implicated in any crime (Color of Change). Mistreatment of Black people in healthcare did not only occur in such extreme examples; American laws also worked against them.

Medical racism did not only exist in the form of experimentation and anatomical use of Black bodies; it was also perpetuated through federal legislation. An example would be the Hospital Survey and Construction Act, otherwise known as the Hill-Burton Act, which was enacted by the government in 1946 to provide for the construction of public hospitals and long-term care facilities; the act mandated that health care facilities be made available to all without consideration of race. However, it allowed states to construct racially separate and unequal facilities (Yearby et al. 542). Furthermore, federal programs such as the Medical

Assistance for the Aged program (also known as Kerr-Mills) were underfunded and few states participated, especially states with large populations of Black Americans, even though the purpose of the program was to provide health care to the poor. Such legislation demonstrates that medical racism does not have to be overt, such as through experimentation on Black people, to harm Black people's health. When it comes to medical racism, Black women are notable victims.

In addition to a long history of medical experimentation and racist legislation, some groups within the Black community faced compounded discrimination due to the intersectional identities they held. For example, Black women have, arguably, been the most unprotected demographic in American history, especially when it comes to the medical field and their health. There have been numerous instances in history where Black women have been subjected to experimentation and medical abuse, and in many ways, that abuse continues today. The presumed founder of American gynecology, James Marion Sims, experimented on enslaved women in the 19th century, using their bodies to come to his medical conclusions. The women were also forced to perform domestic duties and serve as nurses in his clinic. As historian Deirdre Cooper Owens stated, to early gynecologists enslaved women were "flesh-and-blood contradictions, vital to their research yet dispensable once their bodies and labor were no longer required" (qtd. in Nuriddin et al. 949). This trend of Black women being stripped of their reproductive rights continued decades later, with involuntary, coercive, and compulsory sterilization under early 20th century eugenics laws. The growing movement led to the sterilization of an estimated 60,000 people. Such compulsory sterilization laws targeted poor, disabled, and institutionalized people, and were disproportionately weaponised against people of color. For instance, of the nearly 8000 people sterilized through the North Carolina Eugenics Board, nearly 5000 of them were Black. Some Black women were sterilized without their knowledge or consent into the 1970s and 1980s (Nuriddin et al. 949). In 1972, approximately 20 women, mostly young, Black, and poor, suffered unintentional abortions as a result of the super coil, which was a device that caused uncontrollable bleeding and, in some cases, led to hysterectomies, abdominal pain, and anemia (Prather et al. 249). Additionally, the infamous "Tuskegee Study of Untreated Syphilis in the Negro Male" also affected the families of the subjects. Lesser known consequences of this heinous medical experiment were that some of the subject's wives acquired syphilis, and some of their children suffered complications from congenital syphilis as well. Medical racism's impact on Black people's health has been immeasurable, and it is important to discuss its origin (Prather et al. 249).

There are two schools of thought regarding the reasons behind why Black people in America have experienced and continue to suffer from disproportionate health disparities: Black people are biologically inferior to the white race or structural racism has worked against Black people throughout history. In the 1900s, Dr. L. C. Allen addressed the American Public Health Association with "The Negro Health Problem," a reasoning for the poor health of Black Americans. In it, he diagnosed the "negro" population of the South with a biological inferiority to white people and susceptibility to illness and death. Allen stated, "The negro health problem is one of the 'white man's burdens,' and it is by no means the least of those burdens. […] It is

undoubtedly true that the negro race has deteriorated physically and morally since slavery times" (Allen, L. C. 194). His rhetoric was echoed in the late 18th and early 19th century, as the medical community believed blackness to be a fundamental marker of inferiority (Dickinson et al. 14). Allen's argument was used by slavery apologists to justify the stealing of Black people from Africa, keep the chattel system in place, mentally and physically dominate the enslaved people, and perpetuate notions of white supremacy (Dickinson et al. 14). On the other hand, a differing school of thought also existed. W. E. B Du Bois, a prominent civil rights activist and sociologist, published *The Philadelphia Negro: A Social Study* in 1899. He wrote, "The most difficult social problem in the matter of negro health is the peculiar attitude of the nation toward the well-being of the race. There have, for instance, been few other cases in the history of civilized peoples where human suffering has been viewed with such peculiar indifference" (Du Bois 163). With his argument that the "peculiar indifference" of the nation toward the struggles of Black people and their "condition of living," Du Bois became the first to call structural issues the root cause of the poor health of Black people, instead of biological inferiority (Dickinson et al. 14).

Over a century later, these two schools of thought are still in battle for the explanation of the disparate health problems experienced by Black people in America. Many healthcare professionals still opt to believe that Black people's biology is significantly different than that of white people, thus resulting in the existence of numerous misleading medical myths. Modern medical myths are a major aspect of medical racism that prevent Black Americans from receiving equal treatment by healthcare professionals. Black people are believed to have thicker, denser bones that are less bound to fracture (Schultz 325). The belief that Black people's bones are less likely to break perpetuates ideas about black "hardiness," a suggestion that dehumanizes individuals. Similarly, some doctors are still likely to believe that Black people are more tolerant of pain; one study found physicians are twice as likely to underestimate Black patients' pain relative to other racial groups (Raphael). A 2016 study of almost one million children with appendicitis in the United States showed that Black children are less likely to receive any pain medication for moderate pain. According to the study, they are also less likely to receive opioids for severe pain (Goyal et al. 996). Another study at the University of Virginia that examined the beliefs of 222 white medical students and residents found that 50% had false physiological beliefs about Black people, 60% thought their skins were thicker, and 12% thought their nerve endings were less sensitive than those of white people (Raphael). Other studies have shown that physicians, especially white physicians, implicitly prefer white patients, believing them to be more intelligent and more likely to follow professional advice (Raphael).

Such modern medical racism continued to affect Black people through the COVID era, along with structural racism in various areas of life, creating a deadly combination.

How Structural Racism in Healthcare, Employment, and Housing Exacerbated the Impact of COVID-19 on Black Americans

Analyzing COVID-19 as a syndemic requires considering the social and political turmoil of the era as part of the effects of the virus. For instance, East Asians were blamed for the spread

of COVID and experienced numerous hate crimes and racial violence. Videos of police brutality went viral. Anti-mask and -vaxx movements flew in the face of government restrictions. The impacts of COVID varied, and unsurprisingly, Black people were disproportionately impacted by the virus. The Centers for Disease Control and Prevention (CDC) estimates that the death rate for Black people was 1.6 times higher than white people and that they were hospitalized twice as much as their white counterparts. In many areas, Black people were a minority in the community but suffered much higher rates of COVID cases. In Chicago, Illinois, Black people accounted for 29% of population, but made up 70% of COVID-19 related deaths of those whose ethnicity is known (Ramos and Zamudio). They represented just 12% of the population in Washtenaw County, Michigan but suffered 46% of COVID-19 infections (Stafford et al.). According to the CDC, Black death rates at the peak of winter 2021 were greater than those of white people by 34 percent in rural areas, 40 percent in small or medium cities and 57 percent in big cities and their suburbs (Mueller). Many would be quick to blame Black people for these disproportions; their lifestyles, their ignorance, or intrinsic biological susceptibilities are the common suspects. Evidence, however, suggests that the long-rooted structural racism in America—in areas of life such as employment, housing, and healthcare—is the culprit.

A. **The healthcare system failed Black people during the pandemic, when they needed it most.**

COVID-19 had far-reaching influences in every aspect of people's lives. Quarantine meant that people could no longer go outside as often. This led to a decrease in physical activity for many, alongside the closure of gyms and pools. For those who suffered from NCDs such as obesity, hypertension, and diabetes, this lack of access to exercise could have had crucial impacts on their health (Sharifi et al. 448). Quarantine also resulted in reduced social contact, stress, and fear. As a consequence, mental health disorders such as loneliness, anxiety, paranoia, depression, panic, and hoarding were augmented. Such long-term psychosocial impacts disproportionately affected older people, migrants, refugees, and those of lower socio-economic status (Sharifi et al. 448). The exacerbation of other diseases by COVID-19 and the negative health impacts created by the policies of the time suggests that it was indeed a syndemic. These extensive impacts of COVID on health were, unsurprisingly, disproportionate in Black populations because of medical racism.

The COVID-19 pandemic demonstrated that racism that many think of as ancient or long-gone still exists today. Medical racism that dates back centuries revealed itself to be a current and very relevant issue is Black people's lives, as numerous medical myths surrounding the disproportionate numbers of Black people diagnosed with COVID-19 arose. Racist myths surrounded Black people during the era of COVID-19, as it was a popular belief that they did not take proper precautions to prevent the spread of the virus and did not take enough care about their health or that of others to do so. The Pew Research Center, however, found that "in particular, older adults, black and Hispanic people, and those with no college experience are especially likely to view the coronavirus as a major threat to their own health." Additionally, it

was also found that "46% of black people and 39% of Hispanics view the coronavirus as a major threat to their own health, compared with 21% of white adults." A 6-state online survey conducted in May and June 2020 showed that "Black, Asian, and other racial/ethnic group respondents were 8%, 11%, and 10%, respectively, more likely to wear masks compared with White respondents" (Dickinson et al. 14). The survey also observed "higher levels of concern about the financial impacts of COVID-19 among Black, Hispanic, and other/multiracial groups compared with White respondents. Black respondents perceived a 9.3% higher likelihood of running out of money in the next 3 months compared with White respondents" (Dickinson et al. 14). The strain on healthcare systems due to COVID-19 compounded pre-existing inequities in access to healthcare, continuing the long history of medical racism in America.

Black individuals were severely mistreated by hospitals during COVID. More than half of all in-hospital deaths due to COVID-19 during the first six months of 2020 were among Black and Hispanic patients (White). A study by the University of Michigan surveyed the health outcomes of 2,217 Covid patients in Michigan, and according to the results, more than 50 percent of patients of color were readmitted to the hospital within 60 days after being released. Patients of color were also more than 65 percent more likely to experience moderate to severe financial impact because of COVID-19 (Robinson-Lane et al. 2245). Hospitals have a history of neglecting Black patients and not believing them. Deshaun Taylor, a 23-year-old Black father and assisted living safety coordinator, was sent home twice from a Chicago hospital, even though he had tested positive for the virus and was both diabetic and asthmatic (Cauguiran). Gary Fowler, a 56-year-old Black stepfather and husband, was denied COVID-19 testing and hospital admission by three Detroit emergency rooms whilst having shortness of breath. He was told by healthcare professionals that he had "bronchitis" (Shamus). Reginald Relf, a 50-year-old Black engineer, was turned away from an urgent care clinic in suburban Chicago without being tested in spite of his labored breathing, fever, and cough (Burch and Eligon). Kimora Lynum, a 9-year-old Black girl, was sent home from a Florida academic medical center without being tested, despite having a fever of 103 degrees. She was instead diagnosed with a urinary tract infection (Lyons). All of these individuals died soon after being denied proper medical treatment. Black women, in particular, were disbelieved and turned away from health professionals; their interactions with the American healthcare system has a disturbing past.

As previously established, the relationship between Black women and American healthcare has long been a turbulent one; the COVID-19 pandemic was no exception to that pattern. In March 2020, a 63-year-old Michigan healthcare worker named Deborah Gatewood went to the hospital where she worked four times, with worsening symptoms each visit. She was given cough syrup, told to rest, and sent away. By the end of the month, she developed bilateral pneumonia alongside COVID-19, and collapsed. She died shortly thereafter (S. Kim). Deborah Gatewood is just one of many Black women who were dismissed by hospitals when they had COVID-19. Rana Zoe Mungin, a 30-year-old Brooklyn social studies teacher, called 911 when she could barely breathe. They believed she had a panic attack and quickly moved on to their next call. She had gone to the hospital earlier, believing that she had COVID-19, but the doctors

told her that her lungs sounded clear. Less than 24 hours later, she was on a ventilator. She died days later (Brown et al.). Dr. Susan Moore, an Indiana 52-year-old doctor, posted a video on Facebook lying in a hospital bed, detailing how the white medical staff made her feel "like a drug addict" when she complained of pain and asked for relief. After being released and admitted once again, she was transferred to a different hospital due to her and her family's advocacy. She died two days later (Eligon). Even being an educated doctor is not enough to prove that a Black woman is competent enough to know what is wrong with her body. Bias in medicine has led to deaths from COVID-19, but this lack of care is one that dates to the slavery era. Black women have long been rejected and abused, and medical racism is to blame.

COVID's drastic effects on patients' health was compounded by biases in the healthcare system, resulting in more lives lost. Thus, COVID is a syndemic because its impacts were exacerbated by pre-existing racist beliefs and practices.

B. **The disproportionate representation of Black Americans as essential workers, and the subsequent unemployment of those who filled those jobs, led to increased hardship for Black Americans.**

Employment concerned almost everyone when COVID hit. Thousands of people lost their jobs, had to take pay cuts, or had to risk being exposed to the virus on a daily basis. A syndemic perspective not only emphasizes that social inequalities lead to a greater risk of COVID-19, but also that COVID-19 exacerbates social inequalities, furthering the damage to people's health. For instance, drastic job losses during the pandemic disproportionately affected Black Americans, and the economic damage from COVID-19 has increased racial inequities in housing and income. Those who didn't lose their jobs were very likely to have jobs considered to be "essential."

Black people held more essential jobs and therefore couldn't social distance as much and were more exposed, leading to higher counts of COVID cases in their communities (Jin and McGill). Essential jobs result in higher risk of exposure because they require frequent or close contact with other workers or the public, involve activities that cannot be done remotely or from home, and may lack benefits such as paid sick days (University of Illinois-Chicago). Black essential workers shoulder more of the burden and risks of work that is critical to keeping the country functioning during the pandemic. Of all the jobs across the economy, Black workers occupy about only 13%, but they make up around 19% of essential jobs that pay less than $16.54 an hour, the wage necessary to meet the basic needs of a family of four (University of Illinois-Chicago). A report based on data from 2018 by the Urban Institute that represented 152.7 million workers stated that 33 percent of Black workers were in essential jobs that required them to work in person and close to others. Conversely, 26 percent of White workers had similar jobs. In 2021, 33 percent of New York City's frontline trucking, warehouse, and postal service workers were Black (University of Illinois-Chicago). The CDC found that Black people account for 30% of all licensed practical and vocational nurses. Millions of Black essential workers fulfill roles such as nursing assistants and home health aides, caring for society's most vulnerable

during the pandemic. These essential but undervalued jobs—held by a disproportionate number of Black workers, especially Black women—often pay poverty wages and offer few, if any, benefits such as paid leave or health insurance (University of Illinois-Chicago).

Several 2020 surveys found that Black workers were much more concerned than their white counterparts about the risks they faced from exposure to the virus at work, and significantly more fearful of infecting their families. In interviews, several Black essential workers used words such as "petrified" and "scared" to describe how they felt in their roles cleaning hospital rooms and caring for vulnerable patients (Kinder and Ford).

If an employee is infected with COVID, Black patients, specifically, experienced challenges returning to the workplace after recovering from COVID. It took Black patients 35.5 days on average to return to work, the longest delay of any racial group. Black adults were also less likely to be offered workplace accommodations when they returned to work in comparison to other racial groups (Robinson-Lane et al. 2245). Data from the U.S. Bureau of Labor Statistics showed that Black and Hispanic workers were less likely to have paid sick days as a benefit than White workers (University of Illinois-Chicago). For these essential workers who were also parents, their children had less support at home. As schooling shifted online, racial inequalities in education increased, as federal policies subsidized internet access in white, rural contexts but not in cities where more of the residents are Black and other people of color (Dickinson et al. 14). For many of these workers, the struggle did not end when they went home at the end of the day; structural racism impacts housing as well.

C. Modern residential segregation worsened COVID-19's negative effects on Black people's health.

Housing played a major role in the spread of COVID in Black communities. The 2020 US Census showed that the median household income for Black households ($45,870) was less than that of other race and Hispanic groups (Waddington). The Census Bureau's Supplemental Poverty Measure found the poverty rate in 2020 was higher for Black (14.6%) populations than for white (8.1%) and Asian (8.8%) populations (Waddington). It was also found that 10.4% of the Black population did not have health insurance (Waddington). The Survey of Income and Program Participation shows the net worth of households with a Black householder (the person who owns or rents the home) was $9,567 in 2017, while the net worth of households with a non-Hispanic white householder was $171,700 (Waddington). The fact that racism extends to housing goes to show that structural racism does, in fact, affect every single aspect of Black people's lives.

Racial residential segregation systemically shapes the distribution of resources, which in turn, reinforces unequal social, economic and environmental conditions that give rise to poor health. A neighborhood's built environment impacts access to quality food, transportation, educational and employment opportunities, recreation and preventative health services (Nat'l Community Reinvestment Coalition). Racially segregated neighborhoods that are predominately Black usually have less space, less economic investment, and fewer resources, such as places to

exercise or play, which is also associated with higher rates of cardiovascular disease risk for Black women (Mobley et al. 327). These neighborhoods also have more overcrowded housing stock, pollution, and noise. These environmental factors are associated with asthma, obesity, and cardiovascular disease (Ellen et al. 391), which in turn increases the susceptibility of contracting COVID-19 (Blumenshine et al. 709).

Formerly redlined neighborhoods are also more susceptible to COVID-19. Redlining was a practice of the Home Owners' Loan Corporation, which evaluated the mortgage lending risk of neighborhoods. In the 1930s, a major standard of the HOLC was the residency of Black Americans and immigrants. HOLC assumed that the share of foreign and black families compromised the values of homes and security of mortgages. In modern day, neighborhoods that were formerly redlined are still lacking in investments. For example, according to a 2020 report by the National Community Reinvestment Coalition, one in three people living in historically redlined areas is obese, compared to lower obesity rates in neighborhoods that were not redlined; this is due to the lack of healthy options available in such neighborhoods (C. Kim).

Poor neighborhoods tend to have more residents that use Medicaid, which has payment rates that are often too low to cover the costs of care. Consequently, hospitals that are located in poorer neighborhoods have less funds to utilize, and often lack the resources needed to provide adequate health care. As a result, doctors and hospitals in the United States are paid less to take care of Black patients than they are paid to take care of White patients (Asch). A study based on data from 44,000 patients hospitalized with COVID-19 in a diverse set of nearly 1,200 hospitals across 41 states and Washington D.C. was conducted from January through Sept. 21, 2020. Its conclusion was that if COVID-19 patients that were Black were cared for in the same hospitals where White patients went, their mortality rate would have been 10 percent lower (Asch).

When discussing housing, it is important to note that there are, unfortunately, people who have no homes at all. According to the Annual Homeless Assessment Report to Congress, Black Americans account for about 40% of the nation's homeless population, though they only make up 13% of the US population (Allen). People experiencing homelessness live in close quarters, have weak immune systems, and are aging–therefore, they are incredibly susceptible to COVID-19.

Furthermore, it is important to note that in their homes, the shelter-in-place period of COVID was a dangerous time for those who were being abused. This was especially true for women and women of color. Intimate partner violence and domestic violence increased dramatically during quarantine, with vulnerable women being kept isolated (Pirtle and Wright 168). Since COVID-19's effects went as far as to increase domestic abuse, it is obvious that it is a syndemic–its impacts went far past plain health or biology.

Conclusion

All these effects, in addition to the millions of deaths, are what make COVID-19 a syndemic. The term "pandemic," though widely used to refer to COVID, is not comprehensive enough to capture what COVID truly was. It did not just have medical effects; it brought

widespread social and psychological change. It did not just affect people's bodies, but also their minds, their emotions, their livelihoods, their relationships, and their education. "Pandemic" is biological, whilst syndemic is much more than that. It can even be said that calling COVID-19 a pandemic may erase the experiences and hardships of those who suffered more than others, because it implies the spread of an indiscriminate, medical disease. But COVID-19 was not, in fact, indiscriminate. Its far-reaching effects, especially those that went further than physical health, impacted some people more than others—it is clear that Black people were a major part of those who were disproportionately affected. The COVID-19 syndemic was a tumultuous time for the world. A study that examined the correlation between experiencing vicarious racism and mental health in Black and Asian Americans concluded that greater self-reported vicarious racism was associated with more symptoms of depression and anxiety (Chae et al. 508).

156,074 Black Americans are known to have lost their lives to COVID-19 through June 21, 2023. Nationwide, Black Americans have experienced 13.7% of all deaths, while they represent 12.6% of the population. For every 100,000 Black Americans, about 377 have died from the coronavirus (Gawthrop). The 1793 Yellow Fever epidemic of Philadelphia, Pennsylvania claimed nearly 5,000 lives, with close to 400 of them being Black lives (Historical Society of PA). It is a jarring realization that these two tragic events, though hundreds of years apart, are very similar, in that racism played a major role in each disease's impact.

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Differences in Nicotine Action and Dopamine During Nicotine Withdrawal By Mehul Anand

Abstract

Nicotine addiction is a significant public health issue, as it greatly raises the risk of chronic health issues such as lung cancer and cardiovascular disease, with adolescents being especially susceptible to addiction. Nicotine is the main active component found in tobacco products and works by binding to nicotinic acetylcholine receptors (nAChRs). This leads to the release of dopamine, a neurotransmitter that plays a key role in reinforcing and maintaining the addictive properties of nicotine by triggering the brain's reward pathway. In this review I will be looking at differences in nicotine action and dopamine function via dopamine transporters and dopamine-metabolizing enzymes in humans and animals, which play a pivotal role in the reuptake and degradation of dopamine. These are key factors in the regulation of dopamine levels within the brain, influencing the manifestation of nicotine withdrawal symptoms upon cessation of nicotine use that draw people back towards use of the drug.

Introduction

Nicotine addiction is a major public health issue, especially among adolescents, with over 8 million (11.3%) of middle and high school students in the United States reporting that they were currently using tobacco products in 2022 (Park-Lee, et al.). This is especially concerning since tobacco smoking increases the risk of contracting tuberculosis, chronic obstructive pulmonary disease (COPD), and developing three major types of lung cancer (Schuller; St Claire, et al.). These diseases are not limited to just tobacco smoking and personal nicotine use; secondhand smoke also contributes to developing diseases and the large-scale effects. In 2019, there were over 8 million tobacco related deaths, including secondhand smoke and chewing tobacco in relation to tobacco smoking . In addition to the large-scale health effects, there are large-scale economic effects as well, with the total global cost related to smoking tobacco is estimated to be over 1 trillion US dollars annually (Goodchild, et al.).

Nicotinic acetylcholine receptors (nAChRs) are a crucial part of nicotine's effects. These receptors are found on neurons throughout the central and peripheral nervous systems and are responsible for rapid synaptic signaling. nAChRs are pentameric structures made up of a combination of five individual subunits, including α2–α10, and β2–β4 subunits in varying organizations (Hogg, et al.). Being ligand gated, nAChRs require a ligand such as nicotine or acetylcholine to bind to the receptor to initiate a response. Once nicotine binds to a receptor, it allows the flow of positive ions (Na^+) into the neuron, causing it to fire (Albuquerque, et al.). Nicotine also binds to the nicotinic acetylcholine receptors present on dopaminergic neurons leading to the release of dopamine in the synapse (Markou; Wise, and Robble) .

Dopamine (DA) is an important neurotransmitter responsible for reinforcement learning and the pleasurable sensation associated with nicotine intake (Wise, and Robble). Along with this mild sense of euphoria, acute nicotine consumption also leads to temporary heightened cognitive

function. Both are favorable symptoms which serve as positive reinforcement for the individual to continue nicotine use to maintain these symptoms (Markou). However, these initial positive symptoms are not the sole cause of nicotine dependence. For instance, a 2005 study by Chaudhri et al. found that nicotine's reinforcement properties due to positive acute symptoms were relatively weak, yet there was still prolonged use. This suggested multiple roles for nicotine and its reinforcing properties, including visual stimuli and the avoidance of withdrawal (Chaudhri, et al.).

Oftentimes with nicotine addiction, people experience intense feelings of withdrawal and/or cravings for the source of the nicotine. Withdrawal refers to a collection of physical and psychological symptoms that arise after an individual stops drug use after forming an addiction to the substance. Withdrawal symptoms have been shown in both human and animal models. In a 2021 study by Chellian et al., after cessation of nicotine exposure in various forms, both mice and rats showed signs of anxiety, depression, increased appetite, attention deficits, and cognitive deficits. These symptoms were similar to many withdrawal symptoms shown in humans as well (Chellian, et al.). These withdrawal symptoms occurred due to the formation of an addiction to nicotine, where dopamine and acetylcholine neurotransmission has gone haywire.

After nicotine exposure over an extended period of time, nAChRs become desensitized and have less of a response to nicotine binding, making it less likely for dopaminergic neurons to fire as a result (Changeux, and Taly). Chronic nicotine use was also associated with a decrease in D2/D3 dopamine receptor availability. In a study conducted by Fehr et al. in 2008, nicotine dependent smokers were shown to have significantly lower amounts of D2/D3 dopamine receptors when compared to non-smokers, but the severity of dependence seemed to have no impact on receptor amount (Fehr, et al.). As nAChRs lose sensitivity and dopamine receptor availability decreases from chronic nicotine stimulation, this builds nicotine dependence, where cessation can cause withdrawal symptoms. These symptoms serve as additional motivation for a return to nicotine use. This was backed up in another human study by Robinson et al. in 2019, which showed that more negative withdrawal symptoms are associated with a higher likelihood of relapse (Robinson, et al.). There are many forms of therapy for smoking addiction, including nicotine replacement therapy, prescription drugs such as bupropion and varenicline, as well as behavioral therapy (Khan, et al.; Potts, and Garwood; Rasmussen, et al.; Thrul, et al.). These forms of treatment target different areas of nicotine dependence and withdrawal to improve chances of smoking cessation. In order to improve smoking cessation treatments, it is important to understand the mechanisms behind nicotine dependence and withdrawal.

Nicotine transmission and degradation

Nicotinic interneurons are abundant and crucial regulators of neural signaling in the nucleus accumbens (NAc). The NAc is an area of the brain that regulates stimuli related to emotions and reward, using information from other parts of the emotional circuits of the brain, also known as the limbic system. The NAc is connected to many disorders related to emotion and reward such as depression and addiction, as well as being involved in motivational behaviors

like eating and drinking (Xu, et al.). Nicotine increases the amount of extracellular dopamine in the nucleus accumbens due to mesolimbic dopaminergic projections to the cell of the nucleus accumbens being activated (Pontieri, et al.). This increase in dopamine could lead to increased motivation and contribute to positive reinforcing factors. In a 2022 human neuroimaging study by Kroemer et al. looking at links between depression and appetite, differences in nucleus accumbens activity were linked to differences in appetite in patients with depression (Kroemer, et al.). This link between the NAc and appetite motivation may suggest the NAc's role in relapse, as nicotine cravings seek positive reinforcement and avoid negative withdrawal similar to cravings for food during hunger.

All dopaminergic projections driving motivational behaviors in the NAc are based in the ventral tegmental area (VTA) (Gunaydin, et al.; Yang, et al.; Zhou, et al.) . The VTA supplies dopamine throughout the limbic circuit, driving reinforcement, and is stimulated by nAChRs on dopaminergic neurons. A 2021 study by Nguyen et al. looking at responses to nicotine injections in anesthetized mice saw different responses for DA neurons projecting to different areas of the brain. They saw inhibition of VTA DA neurons projecting to the amygdala, shown to increase anxiety. On the other hand, they saw activation of VTA DA neurons projecting to the nucleus accumbens, part of the reward pathway. These are part of two separate circuits in the brain, with each facilitating different effects on behavior (Nguyen, et al.). This further supports the role of the NAc in nicotine addiction, as well as potentially displaying a role for the amygdala in anxiogenic symptoms apparent during withdrawal.

In addition to the NAc, the VTA also sends major dopaminergic projections to the prefrontal cortex (PFC) (Chaudhury, et al.; Senba, and Kami). The prefrontal cortex (PFC) is involved with attention and decision making and matures rapidly during adolescence. Because of this, looking at the effects of nicotine on the prefrontal cortex during adolescence can reveal different reasons for the susceptibility to addiction and withdrawal of nicotine in adolescents (Goriounova, and Mansvelder). There are many nAChR expressing neurons within multiple layers of the PFC that have direct effects on transmission. Presynaptic nAChRs can augment glutamatergic signals, including input from the thalamus in layer V pyramidal neurons in the PFC, which have projections to the hypothalamus and striatum (Goriounova, and Mansvelder). In a 2004 study by Young et al. looking at nicotine's effects on attention in normal mice, mice were given microgram doses of nicotine prior to completing the 5-choice serial reaction-time (5-CSR) task. Nicotine was shown to increase prolonged attention, and the number of correct responses. These same researchers also looked at the impact of the α7 nAChR subunit, by seeing how α7 nAChR knockout mice did in the 5-CSR task after nicotine dose. These knockout mice both had more omissions in responses and took more time to learn the task, showing the possibility that α7 nAChR subunits contribute to regulation of attention (Poorthuis, et al.; Young, et al.). This improvement in attention for the standard mice supports other human studies that show improved attention post nicotine use (Potter, and Newhouse). This may play a role in the positive reinforcement associated with nicotine use and thus contribute to nicotine dependence.

However, a possibly larger impact of the PFC may be during withdrawal, as it is involved with reward processing, and may play a large role in nicotine seeking behavior.

The striatum is an interconnected neuron structure that makes up a significant part of the basal ganglia. The striatum plays a part in many complicated behaviors, including motor control, habit formation, reward, and emotion (Bamford, and Bamford; Prager, and Plotkin). It consists of the dorsal and ventral striatum, and the location from which dopaminergic signals arrive varies depending on the region of the striatum. For ventral striatum which includes the nucleus accumbens, dopaminergic input originates from the VTA. For dorsal striatum, there are dopaminergic projections which come from the substantia nigra pars compacta, which controls general motor movements (Chen, et al.). Medium spiny projection neurons (MSNs) are found on the striatum and play a key role in striatal neurotransmission. NAChRs are not expressed on MSNs, however chronic nicotine use has been shown to modulate neurotransmission in the striatum (Licheri, et al. "Nicotine-Induced Neuroplasticity in Striatum Is Subregion-Specific and Reversed by Motor Training on the Rotarod"). A 2018 study by Licheri et al. looked at the effects of nicotine on electrical signals in brain slices containing striatum prepared from juvenile male rats. In their study, they found that nicotine reduced the frequency of excitatory inputs to MSNs and decreased dorsal striatum neurotransmission. NAChR desensitization was also found to repress DA release in the striatum including the NAc shell (Licheri, et al. "Complex Control of Striatal Neurotransmission by Nicotinic Acetylcholine Receptors Via Excitatory Inputs onto Medium Spiny Neurons").

The hippocampus is part of the limbic system and deals with the processing of memories, regulating emotions, and learning (Tatu, and Vuillier). NAChRs are found throughout the hippocampus and with nicotine, are involved with synaptic plasticity in the hippocampus (Kutlu, and Gould). A 2005 study by Ge and Dani looked at slices of the hippocampus in wild-type mice to see possible associations between nAChRs and pyramidal neurons in the CA1 region of the hippocampus. They found that presynaptic nAChRs increased the release of glutamate, and that enough nAChR expression on CA1 pyramidal neurons influenced synaptic plasticity in the hippocampus (Ge, and Dani). Another study in 2014 by Damborsky et al. looked at the effects of neonatal nicotine exposure in rats. They observed persisting functional changes in the hippocampus and an increase in overall excitatory neuronal signaling, with no change in inhibitory signaling. Additionally, they found an overall decrease in presynaptic nAChR function on GABAergic neurons, which along with their other findings, could play a role in the behavioral changes observed after nicotine exposure in both animals and humans (Damborsky, et al.).

Degradation of nicotine transmission
In addition to nicotine transmission in various areas of the brain, the degradation of nicotine through various enzymes may also play a role in addiction and withdrawal. The majority of nicotine is metabolized in the liver, with the CYP2A6 enzyme being responsible for 90% of nicotine deactivation (Tanner, et al.). During the degradation process, 70-80% of nicotine metabolization leads to cotinine, a primary metabolite of nicotine. The ratio of cotinine to

3′-hydroxycotinine (another nicotine metabolite) is used as a biomarker for the activity of the CYP2A6 enzyme to observe the rate of nicotine metabolism (Benowitz, et al.). Genetic differences in the CYP2A6 enzyme impact nicotine metabolism and smoking related behaviors, including withdrawal symptoms (Tanner, et al.). A 2008 study by Rubinstein et al looked at adolescent smokers categorized into fast and slow nicotine metabolizers. Even after factoring in an increased number of cigarettes per day, faster nicotine metabolizers were shown to have more severe withdrawal symptoms compared to slower metabolizers, presenting an increased risk of addiction (Rubinstein, et al.).

Acetylcholinesterase (AChE) is an important enzyme in the nervous system and is responsible for stimulating the breakdown of acetylcholine to end transmission and prevent constant nerve firing. AChE is found primarily in the central nervous system, specifically in neuromuscular junctions and cholinergic synapses (Lionetto, et al.). To observe the effects of AChE on nicotine addiction, many studies looked at acetylcholinesterase inhibitors such as Donepezil. A 2012 study by Kimmey et al. showed that donepezil administration in rats led to reduced nicotine seeking behavior (Kimmey, et al.). This is supported by other studies showing various other AChE inhibitors being linked to reduced nicotine seeking behavior in rats (Ashare, et al.; Hopkins, et al.). Together, these results may also indicate that increased acetylcholine activity is related to reduced nicotine reinforcement.

Dopamine transmission/ degradation

A large part of nicotine reinforcement is regulated by dopamine transmission in the mesolimbic dopamine system (Corrigall, et al.). A key part of the mesolimbic dopamine system is the ventral tegmental area (VTA), a brain structure that plays a pivotal role in motivation and the reward pathway (Lammel, et al.). A 2003 study by Laviolette and van der Kooy explored dopamine transmission in the VTA and its role in nicotine reward. They applied nicotine directly to the VTA in rats and looked at the effects that dopamine receptor blockades had. Their results confirmed the VTA as a vital part of regulating aversive and rewarding effects of nicotine. Blocking the DA receptors showed to reverse nicotine's effects and switch previously negative nicotine symptoms into rewarding ones (Laviolette, and van der Kooy). Different DA receptors play varying roles, as a 2005 study by Bruijnzeel and Markou observed the role of D1 and D2 receptors in the posterior hypothalamus/anterior VTA by using D1-like and D2-like antagonists in rats. They found that blocking D1 receptors in saline treated rats increased reward thresholds to a significantly greater degree compared to nicotine treated rats. When looking at D2 receptors, reward thresholds were similar regardless of nicotine administration, indicating a larger role for D1 receptors in the effects of nicotine on reward (Bruijnzeel, and Markou).

The nucleus accumbens also plays a large role in dopamine transmission, and DA transmission in nucleus accumbens directly regulates aversive and rewarding effects of nicotine (Sun, and Laviolette). The nucleus accumbens is composed of its shell and core, with the shell of the nucleus accumbens being the most sensitive to dopamine transmission after acute nicotine use (Di Chiara). A 2000 study by Cadoni and Di Chiara studied the effects of behavioral

sensitization to nicotine in dopamine transmission in the shell and core of the nucleus accumbens in rats. They observed a lower dopamine response in the shell of the nucleus accumbens, while seeing the opposite, an increased response, in the core. This suggests differing roles and responses for the core and shell of the nucleus accumbens (Cadoni, and Di Chiara). Not only do different regions of the nucleus accumbens play different roles, the nucleus accumbens may also play a role in sex differences for nicotine withdrawal. A 2017 study by Carcoba et al. used rats to investigate whether sex differences in nicotine's aversive withdrawal symptoms was regulated by the nucleus accumbens. They found that male rats experienced lower amounts of dopamine during nicotine withdrawal compared to females, possibly explaining part of the variation in withdrawal symptoms based on sex (Carcoba, et al.).

The prefrontal cortex makes up a major part of the brain and is responsible for decision making and executive control. However, during drug addiction, its capacity to provide responses and execute decisions is greatly reduced. Simultaneously, the prefrontal cortex becomes hyperactive in response to drug seeking stimuli based on the predictability of a reward being obtained (Kalivas, and Volkow). The prefrontal cortex's response to nicotine varies in some ways compared to other parts of the brain such as the nucleus accumbens. Depending on the type of stimuli, levels of dopamine transmission can be higher or lower in the prefrontal cortex when compared to the nucleus accumbens (Bassareo, et al.). A 2013 study conducted by Gozen et al analyzed whether nicotine exposure influenced D1 receptor expression in various areas of the brain including the prefrontal cortex. After administering nicotine in rats, they found significantly higher D1 receptor expression in nicotine treated rats in comparison to the control group. This increase was seen in all three of the brain areas observed, the prefrontal cortex, VTA, and STR (Gozen, et al.). This higher expression of D1 receptors likely corresponds to increased activity in these brain areas to reward and cues related to nicotine. Thus, dopamine transmission in these brain areas may increase when presented with nicotine associated cues, leading to further nicotine seeking and craving during withdrawal.

As previously mentioned, the striatum also plays an important role in dopamine release and the reward pathway. In the striatum, reward signaling is primarily conveyed through the release of dopamine in rapid bursts, rather than through individual spikes and sustained activity (Goutier, et al.). Different dopamine receptors in the striatum also have been shown to have varying effects on nicotine response. A 2006 study by Tammimäki et al. explored the effects of chronic nicotine administration on dopamine transmission in dorsal striatum in mice. They found that during nicotine administration, both overall dopamine transmission and extracellular dopamine levels were elevated in the dorsal striatum. Quinpirole, a D2/D3 agonist that generally reduces locomotor activity was given to mice, and mice treated with nicotine were slightly less affected by quinpirole. This may mean that D2/D3 receptors play a minor role in dopamine transmission differences in nicotine addiction (Tammimäki, et al.). As many of these studies were observed in rats and mice, striatal dopamine release after smoking has been analyzed in humans as well. A 2013 study by Le Foll et al used neuroimaging technology to look at dopamine levels in humans after smoking, especially in striatal regions with abundant D2 and D3

receptors. After smoking, subjects had significantly decreased withdrawal symptoms and cravings, and motivation to smoke corresponded with the amount of dopamine released in the striatum. D3 areas had increased dopamine release after smoking compared to other areas, indicating a possible role for D3 receptors in cravings and withdrawal symptoms (Le Foll, et al.).

The dorsal hippocampus is involved with feelings of anxiety, and therefore D1 and D2 receptors in the hippocampus may play a role in anxiety produced by nicotine (Nasehi, et al.). A 2010 study by Zarrindast et al. looked at the role of ventral hippocampal dopamine receptors on nicotine's anxiogenic effects in rats. They found that D1 receptor antagonist SCH23390 and D2 receptor antagonist sulpiride both decreased anxiety-like symptoms due to nicotine use. This may suggest that blocking D1 and D2 receptors reduces the anxiogenic response caused by nicotine induced dopamine release (Zarrindast, et al.).

Dopamine Transporter (DAT) and Dopamine Reuptake

Dopamine transporters (DAT) are crucial to dopamine function, since they are responsible for facilitating dopamine reuptake, moving extracellular dopamine back into the neuron. DAT is especially present in clearing dopamine in the striatum, where 80% of the dopamine is transmitted (Savchenko, et al.). Differences in DNA methylation for the DAT gene has been linked to varying levels of nicotine dependence, supporting other evidence for the link between DAT and the effects of nicotine (Chmielowiec, et al.). In addition to differences in DNA methylation, genetic differences also play a role in the link between DAT and nicotine. The SLC6A3 gene is responsible for the DAT protein, and the 10r/10r genotype of this gene could decrease SLC6A3 expression in humans. Those who are homozygous for the 10r allele have less DAT proteins and therefore an increased amount of extracellular dopamine and are less likely to be nicotine dependent compared to people with the minor allele (Ohmoto, et al.). Both looking at DNA methylation and genetic differences can open doors to treatments targeting the DAT protein in reducing withdrawal symptoms.

On top of genetic differences, nicotine use has been shown to impact DAT protein activity in many areas of the brain. A study by Hadjiconstantinou et al in 2010 looked at the DAT protein structure and function in rat striatum during nicotine withdrawal. They observed increased DAT activity, meaning faster DA clearance which contributes to lower DA levels observed during withdrawal. After later using DAT inhibitors, DA level increased and reached similar levels to rats not treated with nicotine, which further confirms DAT's role in reduced extracellular DA during nicotine withdrawal (Hadjiconstantinou, et al.). Other studies have had similar results, showing unregulated DAT levels after chronic nicotine exposure contributing to reduced extracellular dopamine levels (Li, et al.). The relationship between nicotine and DAT does not appear to be strictly linear, however. A 2016 study by Kambeitz et al looked at the interaction of DAT and nicotine in humans in decision making based on reward. Interestingly, they found that performance on decision making tests were dependent on an individual's DAT binding potential. For those with low DAT binding potential, nicotine negatively affected their learning rate and consistency on test performance. However, for those with higher DAT binding

potential, these effects were not observed (Kambeitz, et al.). This presents another avenue to explore nicotine-DAT protein interactions, based on DAT binding potential.

Monoamine Oxidase (MAO) and Dopamine Degradation

Monoamine Oxidase (MAO) is an enzyme responsible for the breakdown of dopamine. There are two types of Monoamine Oxidase, MAO-A and MAO-B. In the brain, 80% of MAO is MAO-B, with presynaptic MAO metabolizing dopamine, and MAO-B metabolizing dopamine in glial cells and the synaptic cleft (Tan, et al.). Tobacco smokers are shown to have reduced MAO-B activity, and smoking reduces overall MAO activity in the brain and other tissues. During withdrawal, these reduced MAO levels and activity in the brain slowly return to normal. This means decreased extracellular dopamine, which contributes to the depressive symptoms experienced during withdrawal (van Amsterdam, et al.). However, MAO seems to have differing effects on somatic withdrawal symptoms compared to depression. A 2013 study by Malin et al looked at the effect of inhibiting MAO on somatic nicotine withdrawal symptoms in rats. They observed that when inhibiting both MAO A and B, somatic withdrawal symptoms were significantly increased in nicotine treated rats. When inhibiting only MAO A, similar increases were observed. However, when solely inhibiting MAO B, somatic withdrawal symptoms were reduced. This suggests differences in MAO A and B in terms of nicotine interaction and the intensity of withdrawal symptoms (Malin, et al.).

COMT and Dopamine Degradation

Catechol-O-methyltransferase (COMT) is an enzyme involved with the breakdown of neurotransmitters including dopamine. While DAT is primarily responsible for dopamine breakdown in brain areas such as the nucleus accumbens and striatum, COMT breaks down dopamine in areas with low levels of DAT, such as the prefrontal cortex. COMT is only found on postsynaptic neurons and glial cells, and accounts for about 50% of dopamine elimination in the prefrontal cortex (Tammimäki, and Männistö). Polymorphisms in the COMT gene have been shown to impact nicotine withdrawal. A 2013 study by Herman et al. analyzed the impact of the COMT Val158Met polymorphism on nicotine effects in humans. They found that the Val/Val genotype was associated with more severe withdrawal symptoms and worse subjective feeling in people (Herman, et al.). Another study added to the link between the Val158Met polymorphism and nicotine dependence, and added that on the other hand, the Met/Met genotype has been linked to higher quitting success rates with nicotine replacement therapy (De Ruyck, et al.).

Role of Nicotine in Withdrawal and Relapse

During nicotine withdrawal, people experience a variety of symptoms known as withdrawal symptoms after cessation of drug use. These symptoms include both somatic and cognitive symptoms and play a large role in drug relapse. These symptoms include depression, appetite changes, anxiety, irritability, and other negative symptoms (Chellian, et al.; McLaughlin, et al.). Acute nicotine use has been found to increase nAChR activity, however over longer

periods of nicotine use, nAChRs experience desensitization, where they become less receptive to neurotransmitters over time (Picciotto, et al.). Since nicotine desensitizes nAChRs over time, chronic nicotine use plays a role in altering mesolimbic dopamine neuron function. Desensitization over chronic use may play a large role in nicotine withdrawal symptoms as it influences nicotine dependence (Pidoplichko, et al.). A 2009 study examined saturation of α4β2 nAChRs in tobacco-dependent smokers. They found for these tobacco-dependent smokers, 96% to 98% of α4β2 nAChRs were occupied during the day, and that around 50% of these nAChRs were desensitized. They also found that almost all of the α4β2 nAChRs needed to be occupied to satiate nicotine cravings, as smoking a quarter of a cigarette occupied around 75% but had little effect on reducing cravings (Brody, et al.). These results may indicate that keeping nAChRs occupied is a motivation for nicotine cravings and that activation of non-desensitized α4β2 nAChRs provides positive reinforcement contributing to addiction. Furthermore, this may indicate a link to the prefrontal cortex, where keeping nAChRs occupied serves as motivation for nicotine seeking during withdrawal.

There is evidence showing that nAChR desensitization is directly related to its upregulation, as more nAChRs may be required to achieve similar responses after desensitization (Brody, et al.; Fenster, et al.). NAChRs upregulation plays a significant role in the manifestation of withdrawal symptoms, especially after chronic nicotine use. After chronic nicotine administration, smokers experience an increase in the number of nicotine binding sites, or nAChRs (Benwell, et al.; Wills, and Kenny). The upregulation of nAChRs has been shown in vitro for both human and animal cells, and may depend on multiple underlying processes, of which many are currently unknown (Buisson, and Bertrand; Govind, et al.). A study conducted by Trauth et al. in 1999 looked at nAChR upregulation in adolescent and adult rat brains in response to nicotine use. They found upregulation of nAChRs in both adolescent and adult rats, however they varied depending on brain areas. Adolescent rats showed mostly uniform upregulation throughout brain areas with nAChRs, while adult rats displayed significantly less upregulation in the midbrain in relation to the cerebral cortex and hippocampus. Thus, midbrain nAChR upregulation was significantly higher in adolescent rats compared to adults (Trauth, et al.). Upregulation of nAChRs has also been shown to be dependent on nAChR subtypes. A 2007 study by Mao et al. looked at nAChRs in adult rat brains to see the effects of nicotine use on nAChR upregulation. They observed that α4β2 receptors containing the α5 subunit were resistant to upregulation, while those without the α5 were consistently prone to upregulation after chronic nicotine use. This may suggest a regulatory role for the α5 subunit in nAChR upregulation (Mao, et al.). Considering these variables, both nAChR desensitization and upregulation play significant roles in nicotine withdrawal, especially nicotine cravings leading to relapse.

Dopamine in Withdrawal and Relapse

Dopamine also plays a significant role in withdrawal as there are unusually high DA levels following nicotine use, and chronic nicotine administration leads to adaptations in dopaminergic neurons and DA reuptake (Grieder, et al.). Alongside high DA levels, increased

DA reuptake is present following nicotine administration. During withdrawal, there is a significant drop in extracellular DA levels, due to both decrease in DA release and increased DA reuptake (Paolini, and De Biasi). A 2013 study by Zhang et al. tested DA levels in mice during nicotine withdrawal and observed decreased basal DA concentration in the nucleus accumbens. Re-exposing the mice to nicotine temporarily increased the DA concentration and reversed the previously low dopamine levels (Zhang, et al.). This return to normal DA levels may serve as positive reinforcement for nicotine cravings during withdrawal.

As previously mentioned, the dopamine transporter (DAT) is responsible for a large part of DA reuptake, and therefore plays a role in the hypo-dopaminergic state during withdrawal. A study conducted in 2010 by Hadjiconstantinou et al examined DAT function in male mice during withdrawal and found increased DAT function and upregulation of DAT soon after cessation of nicotine (Hadjiconstantinou, et al.). This supports the theory that increased dopamine reuptake plays a role in the reduced DA levels during withdrawal.

Treatment of Nicotine Addiction

Nicotine patches are one of the most popular options for treating smoking addiction and are a form of nicotine replacement therapy through a patch attached to the skin using an adhesive (Rasmussen, et al.). Responses to nicotine patches can vary, but the nicotine metabolite ratio used to determine nicotine metabolism can also be used to anticipate response to nicotine patches. Those with a lower nicotine metabolite ratio are fast nicotine metabolizers and have greater success with these nicotine patches (Lerman, et al.). A 2019 study by Walker et al looked at nicotine patches in combination with e-cigarettes and saw improvements in smoking cessation results (Walker, et al.).

Nicotine gum is another popular form of nicotine replacement therapy for smoking cessation. It is administered through chewing, and produces similar nicotine levels to smoking tobacco, however it has slower absorption compared to smoking (Russell, et al.). Results for nicotine gum as an aid for smoking cessation are varied, as one study in 2019 by Shiffman et al showed little to no improvement in smokers trying gum as a method for treatment (Shiffman, et al.). Other forms of nicotine replacement therapy exist, including lozenges and nasal sprays. A 2019 study by Lindson et al found that combining multiple forms of NRT had more success compared to only using one form.

Bupropion is an antidepressant and smoking cessation treatment that has been shown to have success in smoking cessation (Khan, et al.). Bupropion was shown to have a 52% to 77% higher likelihood that an individual will effectively quit smoking. However, the use of bupropion has also been associated with adverse side effects which are unwanted, but is not associated with severe or lethal effects (Howes, et al.). A 2021 study by Kranzler et al looked at the effectiveness of bupropion in pregnant women. They found that in pregnant women, bupropion was ineffective for improving chances of smoking cessation. However, they did find that there were no pregnancy complications associated with bupropion (Kranzler, et al.).

Varenicline is another prescription smoking cessation therapy and works as a partial agonist for α4β2 nAChRs. Since it is a partial agonist, it mediates DA release and reduces the reinforcement of smoking, while also mitigating withdrawal symptoms by activating these nAChRs (Jordan, and Xi). Varenicline is administered orally, and has fewer adverse effects compared to bupropion while also having significant effect on improving chances for smoking cessation (Potts, and Garwood). A 2016 study by Ebbert et al. looked at Varenicline in light smokers and saw that it was both safe and effective in increasing cessation in light smokers (Ebbert, et al. "Varenicline for Smoking Cessation in Light Smokers"). In comparison to other smoking cessation treatments, Varenicline has been shown to be the most effective. A 2022 study by Cinciripini et al compared Varenicline to Bupropion, nicotine patch and placebo, and found Varenicline to be the best option (Cinciripini, et al.). For those looking for the most effective prescription nicotine treatment option with minimal side effects, Varenicline seems to be the best option currently.

In addition to NRT and prescription solutions for nicotine dependence, behavioral intervention is another popular treatment for smoking cessation. When studying its effectiveness, a 2015 study by Thrul et al looked at the extent of participation in behavioral intervention in relation to other smoking factors. They found that a previous attempt at quitting, strong nicotine dependence, and a high motivation to quit were all factors associated with increased participation in behavioral intervention programs (Thrul, et al.). Behavioral intervention has been observed in combination with various other nicotine treatments. In a 2010 study by Ebbert et al they looked at behavioral intervention in addition to nicotine lozenges. Their results showed that both increased chances of smoking cessation, and that behavioral intervention on its own may also improve results (Ebbert, et al. "Smokeless Tobacco Reduction with the Nicotine Lozenge and Behavioral Intervention"). Thus, behavioral intervention, especially in combination with other treatment methods is an effective method for improving chances of smoking cessation.

Conclusion

Both nicotine and dopamine play significant roles in the development of nicotine addiction and the manifestation of withdrawal symptoms. Looking at factors such as differences in nAChRs, nicotine degradation, and dopamine reuptake can reveal possible solutions for the development of addiction treatments. Although a lot is known about nAChRs and dopamine, we can look further at their role in nicotine seeking behavior in relation to different areas of the brain for the advancement of treatment methods targeted at these areas.

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HIV Telemedicine on a Continuum of Care During Covid-19 By Vivian Lin

Abstract

The current advancements in HIV management and prevention, strategies such as immediate antiretroviral therapy (ART) after being tested positive for HIV [1][2], oral ART for pre-exposure prophylaxis (PrEP) for individuals who are at risk of HIV [3], and post-exposure prophylaxis (PEP) following HIV exposure [4] have been available for more than a decade.

This rapid review contributes to the literature by examining the current landscape of telemedicine-based HIV prevention and treatment services that have been provided around the globe since the onset of the COVID-19 pandemic. We describe HIV prevention, testing, and treatment through telemedicine, detailing service locations, settings, providers, recipients, and associated barriers for each service type. These insights offer clarity on the current role of telemedicine in the HIV care continuum and highlight service gaps and areas for future research and service enhancement.

Introduction

A silver lining of the COVID pandemic has been the rapid rise of telemedicine, which has been a landscape transformation of healthcare delivery [5][6]. Telemedicine is defined as the use of electronic information and communications technologies to provide and support health care when distance separates the participants [7]. In the HIV/AIDS field, telemedicine services may include teleconsultations, e-prescriptions of ART and/or PrEP medicine, and video-based adherence monitoring and support [8] [9]. For individuals with HIV, telemedicine offers a unique advantage in bridging the gap between specialty providers and underserved populations, thereby mitigating geographic distance as a barrier to care [10]. In addition, telemedicine holds the potential to alleviate the anticipated stigma associated with seeking in-person HIV care and bolster the protection of patient confidentiality [11]. Therefore, telemedicine may be a valuable approach to expand access to HIV prevention and treatment and reduce health disparities in HIV care continuum globally even beyond the COVID pandemic [12][13].

I: General Coordination and Patient Care

Rogers and colleagues describe telemedicine service in Open Door Health, a clinic dedicated to providing primary and sexual health care to the Rhode Island LGBTQ + community. After COVID, patients could book appointments by phone, receive a Zoom link via text, check in with front desk staff on Zoom, and then join providers in a private session. Pre-visit paperwork, including consent forms, demographic information, and social and medical histories, could be completed on the electronic patient portal. During virtual visits, providers conducted visual assessments to substitute some physical examination, and patients were instructed to self-collect vital signs and submit pictures for assessment via an encrypted email. In-person visits and laboratory testing were scheduled when needed [15].

II: HIV Testing

Telemedicine strategies were employed to encourage HIV testing amid the COVID-19 pandemic. In a demonstration project targeting MSM and transgender women in adolescence and early adulthood, social media channels such as Instagram, Facebook, and WhatsApp were utilized to engage with those at risk for HIV during the pandemic. Through online informed consent, participants were provided with HIV self-testing kits and instructions by fast delivery services or mail based on their preference [16]. In a separate study also pertaining to MSM and adolescents, to mitigate the needs of patients during self-testing, video and picture instructions were provided so patients could collect biospecimen themselves. These results were confirmed during remote sessions as staff required patients to hold completed kits to the screen to verify results. Certain tests need to be sent back to the care providers for further analysis, causing the implementation of pre-paid envelopes for patients to mail back to care providers [17][18].

III: Recruitment for PrEP

Strategies to identify potential PrEP candidates during COVID-19 involved information dissemination through social media, such as Instagram, Facebook, and WhatsApp [19]. An article from Brazil reported that, prior to COVID, an AI chatbot named Amanda, portrayed as a transgender woman, was integrated into social media platforms like Facebook Messenger to simulate discussions about sex and HIV. This chatbot was designed to identify individuals at a higher risk of HIV and arrange appointments for them to discuss PrEP at the study clinic. This digital recruitment strategy was further streamlined during COVID-19, supplemented with smartphone text message-based peer navigation and teleconsultations with PrEP providers [20]. In in-depth interviews involving PrEP-eligible women in New York, participant feedback regarding their chatbot experience varied significantly, ranging from high acceptance to skepticism about the chatbot's limited ability to provide individualized answers and the potential to give misleading information [21].

IV: Initiation of PrEP

During COVID, the initial appointment for PrEP initiation was conducted either via a brief face-to-face visit or through teleconsultation [22][23]. Teleconsultations were conducted through either a voice or video call with a doctor, nurse specialist, or clinical nurse [24]. In a Tele-PrEP program in Scotland, patients initiating PrEP during COVID had a twenty-minute phone consultation followed by short clinic attendance to complete necessary laboratory testing and medication collection. In-person appointments remained available for medically or socially complex patients, which represented only 4% of the PrEP appointments [25]. A PrEP program in Brazil implemented home delivery PrEP services rather than in-person dispensation; the feasibility of doing so, although preferred by patients, largely depends on the socioeconomic status of the clinic and patients [26]. Providers in a Rhode Island clinic relaxed the requirement of monitor kidney function prior to PrEP initiation, they concurrently ordered laboratory testing and wrote prescriptions for PrEP and encouraged healthy patients who are at low risk for renal

function problems to initiate PrEP as soon as prescriptions were filled, without waiting for kidney function results [27].

V: PrEP Follow-up teleconsultations, Adherence, and Support

The modality and frequency of PrEP follow-up visits were often decided in consideration of patients' personal characteristics, preferences, and clinical profiles [28]. In the Brazilian cohort of adolescents and young adults on PrEP, telehealth appointments were scheduled according to both the patients' availability and the providers' assessment of their adherence level and health conditions [29]. The frequency of virtual PrEP follow-up visits varied from once every two weeks to once every two months, depending on the patient's level of stability and the presence of comorbidities. Given the increased risk of domestic violence and deteriorating mental health among these patients, social and mental health support services were offered via telehealth [30]. To support patients in PrEP adherence, an HIV prevention service targeted towards adolescents implemented support groups and peer navigators as a means of telemonitoring. Navigators conducted follow ups, biweekly and monthly, using social media text messages, that simultaneously emphasized and monitored patients on PrEP adherence [31].

Other means of ensuring PrEP adherence included PrEP adherence kits. These kits included urine tenofovir immunoassay and tenofovir hair concentrations. Providers would instruct patients during remote sessions to collect biospecimens for instantaneous PrEP adherence results [32].

VI: ARTTelemedicine Initiation

Procedures to initiate ART were modified during COVID-19, with certain procedures leveraging telemedicine. Amatavete and colleagues described the adaptation of same‑day antiretroviral therapy (SDART) initiation at the Thai Red Cross Anonymous Clinic after the COVID pandemic. The initial ART supply duration was extended from 2 weeks pre-COVID to 4 weeks post-COVID [33]. ART medications were prescribed digitally. A hospital center in Brooklyn used EPIC, an electronic medical record that was developed at the beginning of the pandemic. Nursing staff forwarded requests to the clinical pharmacists through EPIC. The clinical pharmacists then would review the patient chart, perform medication reconciliation, and e-prescribe medication [34]. Retrieval time of ART varied among HIV clinics; a Kaiser Permanente Hospital Nothern California (KNPC) prescription was filled at a KPNC pharmacy within 7 days, while a service in Thailand issued same-day ART retrieval [35]. Articles that mentioned ART prescription rage ranged from 4 weeks to 3 months [36][37].

VII: ART Follow-up Teleconsultations and Adherence Support.

After commencing ART, telemedicine-based follow-up was usually provided for patients who were compliant, clinically stable, and virally suppressed, whereas in-person care remained available for patients who were either clinically challenged or had difficulties using technology [38]. In Thailand, patients who are on ART were given the option to have follow-up

consultations via video calls on the LINE application, a widely-used messaging platform in Thailand. Unless patients reported adverse symptoms during these consultations, they could refill their ART medication refills through the mail without physically returning to the clinic [39]. In a Ryan-White funded HIV program in New York, patients with HIV and co-occurring chronic conditions, such as hypertension and diabetes mellitus, were managed through either virtual interdisciplinary visits or virtual pharmacotherapy visits [40]. One HIV prevention study for adolescents and MSM tested ART adherence using home-delivered blood tests, where used kits would be mailed back to providers for research and analysis [41].

VIII: Results of ART on viral load

Clinical operation of clinical management of patients on ART varied by clinic settings. Rogers' article noted that, in their *Open Door Health* Clinic (an LGBTQ+ centered community clinic in Rhode Island), the HIV viral load and CD4 testing frequencies for HIV patients on ART regimens were extended from every 3–4 months to once every 6-12 months for those who reported good adherence and have no other comorbidities [42]. In an HIV treatment center in New York, CD4 testing was only required for patients who demonstrated recent ART non-adherence or detectable viral loads [43]. In contrast, in a large urban HIV clinic in California, viral load testing was facilitated via rapid laboratory visits, with at least quarterly monitoring recommended during shelter-in-place [44].

IX: Acceptability, Challenges, and Solutions

The articles generally reported that telemedicine HIV services were feasible and well-received. Both patients and providers valued the continuity of care provided by telemedicine during COVID and recognized the benefits of flexibility, convenience, time-saving, and reduced concerns of stigma [45-48]. Patients expressed feeling more comfortable receiving care from their homes than in a clinical setting [49], and providers appreciate the opportunity to observe patients' home environments and engage family support via telemedicine [50]. In a survey among HIV patients, participants gave high ratings for the quality (median score 6.5/7), usefulness (median score 6.0/7), and satisfaction (median score 6.3/7) of telemedicine services they had received [51]. No-show rates for telemedicine appointments were found to be lower than for in-person visits, as evidenced by formal statistical testing (aOR 0.56, 95% CI=0.36–0.86 reported by Spinelli et al.[52], 2020; 21% no-show for telemedicine vs. 38% for in-person visits, p<0.0001 by Boshara et al., 2022)[53] and corroborated by anecdotal reports [54]. For patients receiving ART in Thailand, the retention in care at 3 months (97.5% vs. 98.0%, p = 0.963) and 6 months (94.1% vs. 98.4%, p = 0.148) were similar for those receiving in‑person and telehealth follow‑up [55]. Ender et al., reported a reduction in gaps in care (defined as no provider encounter within 6 months) and an improving trend in service satisfaction among patients with HIV as telemedicine implementation overtime in a Ryan White–Funded HIV Clinic during the first year of the pandemic [56]. Sorbera et al. reported that, with the implementation of

telemedicine, the proportion of patients who were virally suppressed in their HIV clinic in New York remained at a comparable level post-COVID [57].

While the data on acceptability and feasibility is encouraging, telemedicine undeniably presents challenges, especially for certain vulnerable populations. The technical challenge was one of the most prominent issues, especially for elder individuals who often had trouble downloading or navigating the applications for telemedicine [58-60]. Patients residing in low-income areas also had difficulty navigating telemedicine due to internet issues [61].In one study, providers had to call patients several times for a response and also spent the appointment time teaching the patient how to navigate telemedicine applications instead of focusing on the clinical aspect of the appointment[62]. For patients with limited private spaces at home (e.g., adolescents) or those living in shelters, receiving telemedicine calls could potentially result in inadvertent disclosure of their sexual identity and/or HIV status [64]. Spinelli and colleagues reported that in their HIV clinic, people experiencing unstable housing offered telehealth for only 32% of visits, much lower than 54% among their general patients (p<0.001). This discrepancy is likely attributable to the technological barriers and confidentiality concerns discussed above.

Suggestions to improve telehealth were discussed in the included articles as well. Technological support and compensation on digital devices should be in place to address the digital divide experienced by underserved patients and ensure equity in telemedicine service delivery [65]. In addition, accessing patients' situations to individualized service provision was recommended. Staff should make an effort by communicating with participants before each visit to create a supportive environment, and to make a comforting environment [66]. Clinic providers called for staffing support to help patients navigate technology more efficiently, as well as appropriate reimbursement schemes [67]. Payment parity for audio-only visits was suggested as a safety net option to reduce disparity in telemedicine service provision [68]. There was also a perceived need for provider training, guidance, care coordination, and informational technical support in telemedicine [69-70].

Discussion

The scope of telemedication runs beyond the individual and provider level, and needs changes for more efficient future use.

Since providers have a primary influence on patients' telemedicine experience, specific guidelines and training should be enforced on them to enhance patients' telemedicine care. Staff should first receive training on telemedicine itself to successfully be able to conduct virtual appointments. To make sure providers are familiarized with current and future prospects of telemedicine procedures, training should occur quarter or semi-annually. These trainings should include cultural humility training as well, where staff and providers can familiarize themselves and combat stigmas related to HIV [Centers for Disease Control and Prevention]. Cultural humility training addresses power imbalances in a patient-provider relationship, especially between vulnerable patients, while committing providers to self-evaluation and critique [71-72].

Similar demographics of individuals often face similar disparities within the field of telemedicine [73]. Disparities occur on the structural and policy level and need solutions whether it is for the utilization of different races, ages, or living situations. The intersectionality of these problems affects most vulnerable patients, often due to systemic racism. Because of this, further research done on sub-group-specific challenges is needed [74]. Delivering and providing care for homeless patients was especially challenging; individuals lacked addresses's needed for home delivery of medication, access to internet and devices to run telehealth appointments, and privacy to share sensitive information with their care provider [75-77].

Government-issued phones could be a solution, but oftentimes have limited data plans and are incompatible with telemedicine applications [78]. A possible solution to this is having pharmacies lend phones to patients for specific telemedicine use [79]. This service can help tackle rural individuals' lack of technological devices and internet. Studies have shown that insurance plans significantly influence patients' accessibility to certain telehealth services; reimbursement prices play a large role in the feasibility of service [80-82]. To combat this, some providers assisted patients in enrolling in certain insurance programs to reduce the price of medication. More clinicians and service providers should aid patients socially with support beyond just medical services; updated guidelines should be enforced for more ethical usage of telemedicine for all patients [83].

There are limitations to this review. The entirety of studies and reports done on telemedicine post-Covid-19 were not submitted to academic journals or published, resulting in a publication bias in this review which leads to missing information or misleading conclusions. In conclusion, due to COVID-19, telemedical has advanced greatly in usage and provided many patients with care that would otherwise be inaccessible. The usage of telemedicine is anticipated to continue due to the acceptability for the number of patients. However future research is to be done to increase its accessibility and minimize the disparities it causes for certain patients. The growth of access to the internet, stable housing, insurance, and the training of providers will expand the population's use of telemedicine and propel its use further.

Methods

Search Strategy:

The rapid review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [14]. Literature search was conducted on three electronic databases, including PubMed, Embase, and Web of Science. The search was performed using four concepts: 1) telemedicine (including telehealth, remote care, mHealth, digital health, teleconsultation, virtual care, synchronous/asynchronous telehealth, teletherapy); 2) HIV (including Human immunodeficiency virus [HIV], acquired immune deficiency syndrome [AIDS]), 3) HIV- related healthcare (including HIV testing, pre-exposure prophylaxis [PrEP], post-exposure prophylaxis [PEP], HIV diagnosis, HIV counseling, adherence, CD4, viral load testing), and 4) COVID (including COVID-19, SARS-CoV-2).

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How can Artificial Intelligence Detect if a Patient has Cervical Cancer Based on the Symptoms they Provided? By Naman Deswal

My research project was about AI (Artificial Intelligence) taking data from other patients about what types of symptoms they had during cervical cancer like what is their age, how many sexual partners they had etc. Then based on that data, can AI detect if a random patient is also diagnosed with cervical cancer based on the data they have provided?

Cervical cancer is cancer that starts in the cells of the cervix (a lower narrow end of the uterus). Before cancer appears in the cervix, the cells of the cervix go through changes known as dysplasia, in which abnormal cells begin to appear in the cervical tissue[1]. Over time, if these cells are not removed or destroyed these abnormal cells can lead to cancer cells and will start to grow and spread deeply into the cervix and to the surrounding areas[2]. I am doing this because cervical cancer was a sickness on which data could easily be found and many factors/diagnoses could lead to cervical cancer. There are many things that cause cervical cancer, but one of the main causes of cervical cancer is Human Papillomavirus(HPV)[3]. HPV affects your genitals, and the most common sign of the virus is warts in your genital area. Genital warts are rough, cauliflower-like lumps that grow on your skin. Genital warts are contagious but not harmful like all forms of HPV. High risk forms of HPV often don't cause symptoms until they have progressed to cancer. Cervical cancer is the most common type of HPV related cancer[4] . This is a virus that can be passed from one person to another during sex. The dataset I have chosen also includes this virus as a risk factor of Cervical Cancer. Women have to take a PAP test in order to figure out if they are diagnosed with cervical cancer.

At the start, I found my data on cervical cancer from a website called UCI Machine Learning Repository. On this website, there was a data set about cervical cancer and it included the different causes that could potentially lead to cervical cancer. After that, I uploaded that file to google collaboratory and cleaned the data. By cleaning the data I mean more than half of the data was impractical because it was missing. To clean the data I set up a threshold in my code that dropped any rows and columns where more than half of the data was missing. Then I imported a bunch of different libraries which were Numpy, Pandas, and learn. These libraries have their unique purposes. After importing the libraries I took the first 27 columns as my input data and the last column called biopsy as my output data. Here is a overview of what my inputs my data had:

Age	STDs	STDs:Hepatitis B
Number of sexual partners	STDs (number)	STDs:HPV
First sexual intercourse	STDs:condylomatosis	STDs: Number of diagnosis
First sexual intercourse	STDs:cervical	STDs: Time since first

	condylomatosis	diagnosis
Smokes	STDs:vaginal condylomatosis	STDs: Time since last diagnosis
Smokes (years)	STDs:vulvo-perineal condylomatosis	
Smokes (packs/year)	STDs:syphilis	
Hormonal Contraceptives	STDs:pelvic inflammatory disease	
Hormonal Contraceptives (years)	STDs:molluscum contagiosum	
IUD (years)	STDs:HIV	
Schiller	Cytology	

From there I split my data into tests and training. The test size of my data was 30% and the train size of my data was 70%. After that, I used a StratifiedShuffleSplit, which was used to split my data randomly. Then I implemented a feature scale for helping my ROC AUC value get better. Then I choose Logistic Regression as the model. The metric that I chose for my data was called ROC AUC and then I implemented that in my code. Some things that I added to make my ROC AUC value get better was that I used max iter($1 * 10^5$), classweight, standard fit transform and standard transform. After that, I did 10 trials to find out the average of my ROC AUC value. The average value of the ROC/AUC I got was 0.68. The standard deviation of this plot was 0.0932.

Trials that were done to figure out the average value:

Trials	Test/Train Split	Random State	ROC/AUC value
1	Test:20% Train:80%	1	0.688
2	Test:20% Train:80%	2	0.489
3	Test:20% Train:80%	3	0.781
4	Test:20% Train:80%	4	0.652
5	Test:20% Train:80%	5	0.630

6	Test:20% Train:80%	6	0.532
7	Test:20% Train:80%	7	0.658
8	Test:20% Train:80%	8	0.449
9	Test:20% Train:80%	9	0.586
10	Test:20% Train:80%	10	0.603

The code to figure out the Standard Deviation and ROC/AUC value:

```
[87]  1   # Figuring out the mean
      2   average_scores = [0.688, 0.489, 0.781, 0.652, 0.630, 0.532, 0.658, 0.449, 0.586, 0.603]
      3   np.mean(average_scores)

0.6068
```

```
  1   # This is going to be the standered diviation value
  2   np.std(average_scores)

0.09325320369831805
```

The top 4 Coefficients that were the most important and which showed as important factors with almost every random state that was changed were STDs:condylomatosis, STDs HIV, STDs:molluscum contagiosum, Smokes(years), and Number of sexual partners. These coefficients impacted the data in a lot of good ways by helping the ROC/AUC value get better. These features were really predictive because these are the main reasons about why cervical cancer happens.

In conclusion, the average ROC/AUC(a.k.a regression value) came to a 0.68 which is not that good in the field of medical studies however this value could be somewhat more promising if there was feature engineering feature selection, algorithm tuning and cross validation. All these types of methods can help enhance the accuracy of the model and the AI can detect better than it was before.

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Using Neural Networks to Plot Emulations of the Sky-averaged 21-cm Signal to Deepen Understanding of the Cosmic Dawn and Epoch of Reionization By Rain Jha

Abstract

This research project focuses on the emulation of the 21-cm signal of neutral hydrogen during the epoch of reionization, using a trained neural network to generate different signatures of this signal. The project employs the "globalemu" network (Bevins et al, 2021) which utilizes training of 10,000 signals generated from semi-numerical simulations to emulate the 21-cm signal. The primary objective of this research is to investigate variations in the astrophysical parameters within the neural network and their subsequent impacts on the emulated signal. A specific area of interest is establishing correlations between changes in these parameters and the occurrence of signal minima corresponding to the maximum signal amplitude. This research was conducted under the guidance of Dr. Saurabh Singh, Associate Professor at the Department of Astronomy and Astrophysics, Raman Research Institute, Bengaluru, India, starting from June 2023.

Introduction & Theory of the 21-CM Signal

There has been much progress in our understanding of the universe from 400,000 years after the Big Bang to the present day, 13.7 billion years on. Yet, the first billion years, during which the first stars and galaxies formed, remains a mystery. The speed of light gives astronomers a tool to look into the past. Telescopes have enabled astronomers to observe galaxies to distances corresponding to a time when the universe was a billion years old.

Moreover, observations at microwave frequencies illustrate the "cooling afterglow" of the Big Bang. This cosmic microwave background (CMB) decoupled from the cosmic gas 400,000 years after the Big Bang (Pritchard and Loeb, 2012), when the universe cooled sufficiently for protons and electrons to combine to form neutral hydrogen. Radiation from this time reaches us directly, providing a snapshot of the primordial universe.

Still, connecting these two periods poses a challenge as the middle phase is largely untested by observations. To improve on this, astronomers are pursuing two key routes. One, deploy larger, more sensitive, telescopes: work is progressing on the Giant Magellan Telescope (GMT) in Atacama Desert, Chile; and the Thirty Meter Telescope (TMT) in Hawaii, US, that can detect an individual galaxy out to redshifts $z > 10$. Launched in 2021, the James Webb Space Telescope (JWST) can potentially image some of the first galaxies at $z \sim 10$–15. (James Webb, NASA)

This project focuses on the second route: the redshifted 21-cm line of neutral hydrogen. This line is produced by splitting caused by the interaction between electron and proton magnetic moments. Hydrogen amounts to almost three-quarters of the gas mass in the intergalactic medium. As such, it provides a convenient tracer of the properties

The cosmic dawn and epoch of reionization are critical chapters in early cosmic history, and are surrounded by mysteries concerning the formation of the first stars and galaxies. Within

this context, the 21-cm signal is a very important tool to further understand the characteristics and causes of events in these epochs. This signal, originating from the red-shifted 21-cm line of neutral hydrogen, undergoes a distinctive change that describes the transformation of the universe.

This research project seeks to explore the changes in this signal's characteristics depending on its various parameters using an emulator to visualize the sky-averaged 21-cm signal during these transformative cosmic epochs, shedding light on the universe's formative years.

Problem Statement & Parameterization

The challenge lies in accurately modeling the complex 21-cm signal, which can depend on multiple parameters. The paper delves into the problem of enhancing the emulation process and refining signal modeling, by modifying the underlying astrophysical parameters to observe changes in the final function of signal brightness against redshift/frequency.

Initially, during the "Dark Ages," before the first stars ignite, the 21-cm signal exhibits absorption features, revealing the cool, inhomogeneous gas that has been decoupled from background radiation.

As the first galaxies take shape, their radiation alters the gas properties, resulting in spatially varying absorption. Subsequently, X-ray emissions heat the gas, transitioning the signal to emission mode. Finally, ultraviolet photons ionize the gas, introducing dark holes in the 21-cm signal brightness within ionized bubbles around galaxy clusters, leaving only isolated pockets of neutral hydrogen.

From this broad sequence of events, the seven parameters that globalemu takes as inputs can be summarized as follows:

1. f_* **(Star Formation Efficiency):** This parameter characterizes the amount of gas converted into stars in dark matter halos. Varying f_* helps improve understanding of the impact of star formation on the 21-cm signal, particularly its initial local minima.

2. V_c **(Minimal Virial Circular Velocity):** This is related to the minimum threshold mass for star formation. Changing the value of V_c provides an insight into how the minimum mass affects the timing of Lyman-α coupling that determines how well the signal brightness correlates with the gas temperature and the absorption feature in the 21-cm signal.

3. fX **(X-ray Efficiency of Sources):** This parameter controls the total X-ray luminosity of sources. Adjusting fX reveals insights into the timing of X-ray heating, the depth of absorption, and emission features during reionization.

4. τ **(CMB Optical Depth):** This measures the ionizing efficiency of sources. Varying τ investigates the impact of early or late reionization of hydrogen gas on the 21-cm signal.

5. α **(X-ray Spectral Slope):** This parameter defines the slope of the X-ray spectral energy distribution. Changing α helps evaluate the weak dependence of the 21-cm signal on α, especially at low redshifts.

6. ν**min (Low Energy Cut-off of X-ray SED):** It determines the energy distribution of X-rays. Adjusting νmin assesses the influence of a soft or hard X-ray spectrum on the 21-cm signal.

7. R**mfp (Mean Free Path of Ionizing Photons):** It measures the distance over which ionizing photons travel. Varying Rmfp studies the weak effects of ionization on neutral hydrogen gas, primarily at low redshifts, although its effects are not very prevalent.

By varying these parameters and observing their effects on the 21-cm signal, we can gain valuable insights into the astrophysical processes that shape the Universe's evolution, and relate the measurements to actual observational capabilities.

Training and Test Data

The project utilizes data from the 21CMGEM dataset, available at
https://doi.org/10.5281/zenodo.4541500.

This dataset plays a pivotal role in training and testing the neural network-based emulator, globalemu. globalemu, which we use to an extent in this research, relies heavily on the dataset to train the neural network model.

Parameter Variation

Plot Preparation:

To understand the impact of parameter variations on the emulated 21-cm signal, we delve into an analysis of the variations of the seven parameters outlined in our model. To achieve this, Python code was used to apply the neural network. By systematically modifying these parameters at a time and examining the resulting changes in the signal's characteristics, we can unravel the relationships between the signal brightness and each of the parameters.

The created graphs involve changing input values and then plotting brightness against both frequency and redshift to provide a visual view of the effects. Given the poor understanding of the early universe, these parameters are vastly unconstrained as reflected in their variations.

The seven plots prepared are:

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1.   X-ray efficiency

2.   Star formation efficiency

3.   Minimal virial circular velocity

4.   CMB optical depth

5.   Power of X-ray SED slope

6. Low Energy cutoff of X-ray SED

7. Rmfp, the Mean Free Path of Ionizing Photons

This parameter measures the distance over which ionizing photons travel. While its effects are relatively subtle, we explore the impact of varying Rmfp on neutral hydrogen gas, primarily at low redshifts.

Local Minima Analysis:

One of the parameters, star formation efficiency, is subjected to varying levels. Through analysis, it is revealed that the variation in this parameter showcases a scalar relationship with the minimum points or maximum amplitude of the signal.

We can see that due to the high star formation efficiency, Lyman-α coupling takes place earlier, and therefore the gas temperature is lower and the overall brightness temperature minima is lower as well.

Conclusion

This research project sheds light on the utility of neural networks in emulating the intricate 21-cm signal. By using the globalemu framework and conducting thorough parameter analysis, the project enhances our understanding of the cosmic dawn and epoch of reionization. The scalar relationships discovered between parameter variations and signal minima offer valuable insights into the underlying physics of these phases.

Acknowledgement

The successful execution of this project is attributed to several key sources, including the Globalemu framework and the 21CMGEM dataset. The guidance of Dr Saurabh Singh from the Raman Research Institute, Bengaluru, played a vital role in shaping the project's direction and outcomes.

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Allograft By Sia Saheba

Abstract

Placental tissue allografts provide numerous benefits for potential in regenerative medicine due to their vast wound healing properties and as such there has been an increase in its usage. Current applications include applications in dermatology, ophthalmology, and other chronic wound healing. However, despite its great success, there has been limited investigation of the material's mechanical properties which has restricted its usage in internal surgical wound care. Through a two-part experiment, the material's potential for usage in surgical wound care of the peritoneal cavity was investigated. It was found to have potential in this application. The material stability testing indicated that the material could withstand peritoneal conditions for a time period suitable for wound healing as it was seen to behave similarly to the control group. Additionally, tensile testing found the material could withstand the force needed for surgical application found desirable by medical professionals. One limitation however, was the material's variability and integrity does not allow it to be easily sutured, indicating further studies investigating how to improve its mechanical properties should be performed. Overall,the material has shown to possess potential for surgical application in traumatic wound care to the peritoneal cavity due to its tensile strength and stability in peritoneal conditions.

Definitions:
1. Allograft: a tissue graft from someone of the same species, but it is not genetically to the recipient, in this case made out of the placental membrane
2. Minimal Manipulation: processing that does not alter the original relevant characteristic of the tissue
3. Simulated Peritoneal Fluid: a manufactured solution that is biomemic of the buffer of salts that are found in the peritoneal cavity, a space between the wall of the abdomen and the organs inside.
4. Traumatic Injuries: sudden and severe physical injuries that require immediate medical attention
5. Wound Healing: the replacement of destroyed or damaged tissue with newly produced tissue
6. Tensile Strength: a material's resistance to break under tension
7. Peritoneal Cavity: the space in between the abdominal and pelvic layer

Literature Review

Placental tissue allografts are made from donor placenta and have been used to treat a variety of wounds. They contain numerous biological components that promote wound healing and have therefore proven a viable treatment option in the fields of dermatology and ophthalmology (Silini et al., 2015). However, their full potential has yet to be explored particularly in surgical applications.

Previous studies demonstrate the potential of the placental allografts for surgical wound healing (Silini et al., 2015). However, further investigation into the material's mechanical integrity and stability in its use environment is necessary. These studies can lead to a more robust understanding of placental allograft properties and consequently, an increased use during surgical procedures. A major gap in wound care where placental allografts may present a useful solution is traumatic wound care requiring internal wound healing, such as injuries in the peritoneal cavity.

Ninety percent of mortalities associated with penetrating abdominal injuries come from abdominal gunshot wounds. More effective methods of treating this type of traumatic injury are therefore needed. Current post operative care for gunshot wounds to the abdomen restricts the immediate closure of abdominal incisions in order to prevent infection, necrosis, and other complications, in turn requiring a temporary mesh, patch, or split-thickness graft covering (Cohen et al., 2001). This treatment regimen has been seen to have a high success rate with limited complications and thus should be investigated with the addition of placental tissue allografts due to their known beneficial components for wound healing.

i. Background

Placental tissue has exhibited a wide array of uses throughout history. Its origins date back to traditional Chinese medicine, where the Chinese Medical text The Compendium of Materia Medica states that the human placenta has numerous medical uses or "zi he chi" (Silini et al., 2015). At this time, it was common for mothers to consume the placenta for its beneficial nutrients. Further studies showed that it could have regenerative properties. Placental allografts showcased a rich supply of bioactive molecules, growth factors, cytokines, and microRNAs capable of promoting tissue repair and enhancing wound healing (Wassmer & Berishvilli, 2020). The first surgical application of the fetal membrane came more than three decades after its initial discovery. It was used as a skin transplantation more than three decades after discovering its medicinal properties (Silini et al., 2015). As another 20 years passed, another study was published reporting its usage in wound repair. Today, placental allografts are being used for their therapeutic potential and will continue to develop new uses in a clinical setting.

ii. Viewpoint on Placental Tissue Allografts

The use of placental tissue to make allografts has been a long-standing practice that the public has supported. A study done in 1990 by Fennin and Kent recruited and interviewed women in South West England who donated their placentas after giving birth. After donating their placentas, the women stated that they supported using them as biological materials for medical purposes. The majority of the women stated that they did not believe that the placenta belonged to them or their baby after it had served its purpose and that as there was research that stated the placenta and allografts made from it could help others, it was regarded as a donation to the future of research (Fannin & Kent, 2015). Thus, using placental tissue in medical settings for its benefits is ethical and widely supported by donors and researchers.

iii. Composition of Placental Tissue

The placental membrane consists of the amnion, the intermediate layer, and the chorion. Each layer contains unique regulatory proteins and structures. The intermediate layer alone contains over 900 regulatory and signaling components, including chemokines, growth factors, interleukins, and protease inhibitors (Roy & Griffiths, 2020). The amniotic membrane is the innermost layer of the fetal placenta. It can be credited with numerous beneficial physical and biological properties, making this a helpful material in regenerative medicine. For example, the amnion contains components that can aid in promoting epithelialization (moving cells upward for wound repair), transporting nutrients, increasing scaffolding, and providing hemostatic properties to prevent hematoma or excessive blood clotting. The intermediate layer contains hyaluronic acid and different collagens, which provide scaffolding and cushioning hydration and elasticity to the membrane. The chorion contains collagen and other components that aid membrane integrity, scaffolding, and stabilization. Chromium has been seen as a critical component of placental allografts as it prevents infection and rejection of the allograft in wounds (Roy et al., 2022). As a result of the regulatory proteins present, the placental membrane is an effective tool in wound healing and aiding in anti-inflammation, scar reduction, and enhancing cellular proliferation and migration (Roy & Griffiths, 2020).

iv. Current Applications

The twenty-first century has brought numerous opportunities for placental tissue and its therapeutic potential. Currently, it is used in clinical settings to provide rapid and complete healing of wounds (Silini et al., 2015). From its initial application as a skin transplant for the treatment of skin burns and superficial wounds to its current applications in the urinary tract, oral cavity, skin, stomach, larynx, head and neck, pelvic and abdominal surgery, and more, numerous studies have identified the unmodified amniotic membrane benefits in medical care. However, more studies are needed to prove its biological properties and efficiency (Tehrani, 2021). Thus, a more stable mechanical and biological product for wound healing is necessary. This is a membrane created through a "minimally manipulated" amniotic membrane and still possesses the relevant characteristics of the tissue in order to aid in modulating inflammation, reduce scar tissue formation, and enhance healing; however, it possesses relevant mechanical and structural characteristics to simply its usage in wound healing (Lim & Koob, 2016). Placental tissue has undoubtedly made its mark in wound healing in clinical settings. Through further research, the application of this biomaterial will surely spread through a vast field of application.

The placental tissue's wound healing and antimicrobial properties make it an ideal candidate for surgical wound care. Studies have shown that Placental allografts reduce scarring, inflammation, pain, bacterial contamination, and healing time in skin wound care and increase the wound closure rate (Klama-Baryla et al., 2020). Thus, it raises the question of whether this would be possible inside the body as well. Faster wound healing periods and decreased complications could result in better surgical outcomes; thus, it is essential to investigate. Additionally, the amniotic and chorionic membranes of the placenta have shown to have "growth inhibitory effects on eight bacterial strains including seven pathogens: E. Coli, bacillus cereus, Klebsiella pneumonia, Streptococcus pyogenes, Pseudomonas aeruginosa, Staphylococcus

aureus, Shigella flexneri, and one probiotic plantarum" (Bidaki et al., 2017). Through minimal manipulation, placental allografts maintain their beneficial components and structures even when made into allografts and thus have promising potential in surgical wound healing and preventing post-surgical infections.

vi. Gap

Placental Allografts fall under the FDA's minimal manipulation and homologous use category, which entails that the processing of this tissue cannot "alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement" (FDA, 2020). This has limited its usage in surgical settings as there is a controversy on whether the material possesses the material integrity and mechanical properties for this application. Thus an experiment assessing the allograft's behavior under these conditions will be used to determine its possible usage inside the body. The experiment will test the hypothesis that placental tissue allografts are suitable for wound healing in surgical applications if placental allografts maintain mechanical integrity under simulated peritoneal conditions for a time that is suitable for wound healing and placental tissue allografts possess a tensile strength suitable for materials for surgical applications. This study assumes that if the material could behave ideally for 28 days, it could remain intact for a period of time suitable for a surgical wound. For peritoneal or abdominal surgeries, this period is 1-2 months (Campsen, 2018).

Also, if the material shows a degradation pattern similar to that of a control, it is assumed that the wound healing properties are maintained, and it is possible to use it in this application. The pH of the peritoneal cavity is 7.46-8.10, and the pH of pure water is 7 (Noh, 2003). Thus, the hypothesis assumes that the material will act similarly under treatment and control conditions. If the hypothesis is accepted, the placental tissue allografts are considered viable under these conditions, implying its potential for surgical wound care of the peritoneal cavity.

In order to test this hypothesis, new data must be collected on the material integrity and stability of the allograft as the material has never been investigated under these conditions. Thus a study was done to measure the stability of the material in a physiologically relevant environment for its potential use in traumatic wound care to abdominal surgery. Studies with similar goals have conducted similar methods done to the ones done in this study. For example, a study investigating the susceptibility of human tendons used for reconstruction to collagenase degradation utilized a similar procedure in that it placed samples in collagenase solution for different lengths of times and measured the loss of dry weight and tensile strength of the samples (Ventura et al., 2022). The same was done for this study except placental tissue and peritoneal solution was utilized and a suture pull out test was added. The tensile strength procedure and suture pull-out was adapted from a StimLabs unreleased protocol (Stimlabs, unreleased internal protocol, 2020).

Investigation of Placental Allografts for Use in Traumatic Wound Healing

i. Methods

a.   Material Stability Testing

To test the allograft's material stability, the allograft's mass change over time was observed when it is placed in simulated peritoneal fluid. This test utilized 18 1x1cm samples of placental allografts and two 12-well plates with 1ml of simulated peritoneal fluid in 12 of them and then 1ml of H_2O in the remaining 6 to serve as the control group. This will be incubated at 37℃, and fluid levels will be maintained as needed.

First, eighteen 1x1 cm squares (3 for each of the 6 targeted analysis timepoints) were cut and placed in an oven at 37℃ overnight in order to take out any moisture the tissue may have gained in processing. Next, each sample's preliminary measurements (length, width, thickness, and initial mass) were taken and recorded. The samples were then placed in a 12-well plate and labeled based on target analysis time point and treatment as depicted by Figure 1. Each time point had one control and two treatment samples, which were then filled with 1ml of the corresponding solution while ensuring that the sample was fully submerged beneath it. The treatment solution was a buffer which replicated the physiological components present in the peritoneal cavity and the control was water. The well-plates were then covered and put into an incubator at 37℃ and 5% CO_2 to mimic normal body conditions. Simulated peritoneal fluid was replaced about 2 times a week or as needed. The solution was replaced by aspirating old solution with serological pipet and adding 1 ml of simulated peritoneal fluid or control depending on the sample At the end of the allotted study time, the sample was taken out of the well plate and placed into a pre-weighted centrifuge tube to dry in oven at 37℃ overnight. The next day, the tubes were weighted and the final weight of the samples were calculated using this formula below:

$Final\ weight(mg) = tube\ with\ dried\ sample(mg) - initial\ empty\ tube\ weight(mg)$

Figure 1. Example of well plate setup. Day 1, 3, 7, 14, 21, and 28 control and treatment samples.

Using the initial and final sample masses, a percent sample remaining was also calculated using the following formulas below:

$$Percent\ degraded(\%) = \frac{start\ weight(mg) - final\ weight(mg)}{starting\ weight\ (mg)} \times 100$$
$$Percent\ Sample\ remaining(\%) = 100 - percent\ degraded\ (\%)$$

b.   Tensile Strength Testing

To test the material's tensile strength, a tensile test was utilized. A tensile test is an experiment that provides lots of information about the strength or the mechanical behavior of a material. The experiment placed a hydrated sample of a material between two fixtures called "grips" then began to apply weight in increasing increments while measuring the length of the sample.

First nine 5x1cm untreated samples of the placental tissue (3 from each donor) were cut and initial measurements (length, weight, upper thickness, middle thickness, and lower thickness) were taken. One sample at a time was taken and then hydrated for 1 minute and tested. To test the sample, it was positioned vertically in the lower and upper clamps making sure to accommodate the length of the test sample. It was double checked to ensure the material laid flat against each clamp. After securing the sample, the test on the extensometer was started. While the extensometer elongates with the standardized speed, the data gathering software presented the material's test parameters as well as changes in the gauge length. This also monitored the force placed upon the specimen and displayed the stress-strain curve to help analyze the materials behavior. When the sample broke, the test stopped and the material was unlatched from the tensile clamps.

c.   Suture Pull-Out Testing

To test how much force it takes for a suture to rip through a material, a suture pull-out test was utilized. The experiment consists of three 2x3cm samples and a suture placed about 1-2 mm from its edge that is fixated between two fixtures called "grips" which clamps the material at one end and the suture at the other end. then begin to apply weight in increasing increments while measuring the length of the sample. Utilizing this method and the force at which the material breaks help determine the strengths and mechanical behaviors of the material.

First, a three 3x2cm untreated sample of the placental tissue was cut and initial measurements (length, weight, upper thickness, middle thickness, and lower thickness)were taken. A suture was then placed approximately 1-2mm from the edge of the longest side. After the lower and upper clamps were in the proper position to accommodate the length of the test sample, the material was placed in the clamps vertically to alight the sample from upper to lower clamp. The top clamp was placed on the suture approximately 30mm from the suture point and the bottom clamp was placed on the material itself. After securing the sample, the test on the extensometer was started. During the test, the machine monitored and measured the changes in the material and used a standardized speed and the data gathering software to record the material's test parameters as well as changes in the gauge length. This also monitored the force placed upon the specimen and displayed it on a stress-strain curve to help analyze the materials behavior. Eventually, the suture broke and then the specimen was unlatched from the clamps.

Results

The research conducted derived quantitative data for both parts of the experiment. The tissue was placed in a simulated peritoneal environment to assess its stability and then in a ZwickRoell machine to assess its mechanical properties. The material's stability was then assessed through an analysis of its mass changes over the time period and comparisons between

the control and treatment. The materials mechanical integrity was assessed through a series of tests and their corresponding stress-strain curves. The tissue's inherent variability was taken into account but due to limited sample size and limited testing time, a small sample size of three control and three treatment per time point was utilized for the material stability test, a sample size of three replicates per test for three tests was utilized for the tensile strength test, and a sample size of three was utilized for the suture pull-out test.

a.   Material Stability Testing Results

For the material stability testing, 18 1x1 cm placental tissue allografts were utilized (1 control and 2 treatment per 7 timepoints). The samples initial measurements and weights were taken. Each sample was placed in either a control of water or simulated peritoneal fluid which was made out of a buffer of salts replicating the ones present in the peritoneal cavity. The samples were then incubated at standard body conditions ($37^\circ C$ and 5% CO_2) for the allotted time period and their final weight was recorded. After this the mean average percent remaining mass per time point was calculated by first calculating the percent remaining sample for each sample and then taking the average. The percent remaining sample was calculated by taking the final weight minus the initial weight, dividing it by the initial weight, and multiplying by 100. The mean percent remaining sample for the control and treatment were then plotted.

As we can see in Figure 1 below, the average percent remaining mass for the control and treatment are very similar in the way they degraded. With the percent sample remaining after the first 24hrs for the treatment group being 62.91% and for the control group 58.19%, we can observe that there was an initial drop in sample mass. After The first 24 hours both groups are relatively stable. By the end of the 28-day experimental period, the %sample remaining for the treatment was 47.01% and the control was 34.53%. After calculating error bars and placing them on the graph, it was observed that at each timepoint there was an overlap of the bars suggesting that there was no statistical difference in the groups. So a t-test was performed at each timepoint and p-values were found and compared to the critical value of 0.05. As seen in Figure 3, all the p-values calculated were greater than the critical value of 0.05.

Figure 2. Material Stability- Mass Changes of Placental Tissue over 28 Days in Simulated Peritoneal Fluid (blue) compared to F (green)
Mass Change explanation (y-axis)

	p-value	critical value	significance
Day 1	0.2830	0.2830> **α**=0.05	Fails to reject null
Day 3	0.07534	0.07534> **α**=0.05	Fails to reject null
Day 7	0.5259	0.5259> **α**=0.05	Fails to reject null
Day 14	0.7810	0.7810> **α**=0.05	Fails to reject null
Day 21	0.8551	0.8551> **α**=0.05	Fails to reject null
Day 28	0.2679	0.2679> **α**=0.05	Fails to reject null

Figure 3. Two sample t-test assuming unequal variances
Two-tail p-value compared to **α**=0.05

b.   Tensile Strength Testing Results

For the tensile testing, we utilized a ZwickRoell tensile testing machine to run 9 total tests on three 2x3cm replicates from three placental allograft samples. The data was automatically transferred to an excel sheet and then tensile strength curves and stress-strain curves were made. The maximum tensile strength from the stress-strain curves of each of the 9 graphs were taken and averaged to find the average maximum tensile strength.

The force-strain curves can be seen in Figure 4. The highest point on the graph represents the maximum force which was divided by the surface area of each sample to calculate the tensile strength. This was then averaged and compared to the maximum tensile strength of 0.164 N/mm^2 which was found to be a suitable benchmark for mechanical strength for other surgical wound care products based on key opinion leaders and usability testing (StimLabs, Data on file, 2021). The average maximum tensile strength sustained by the placental allografts was 0.914 N/mm^2 with the standard deviation of 0.690 N/mm^2. A t-test was then performed to see if the observed values meet and exceed the desirable criteria. The test found the data to have a p-value of 0.00576. The large standard deviation is due to the variability in tissue and the small sample size due to limited resources so if this experiment is replicated, using a larger sample size would be favorable.

(a)

429

(b)

(c)

Figure 4.
4(a)- Force-Strain Curves for 3 replicates from Donor 1
4(b)-Force-Strain Curves for 3 replicates from Donor 2
4(c)-Force-Strain Curves for 3 replicates from Donor 3

(a)

(b)

(c)

Figure 5.
5(a)- Stress-Strain Curves for 3 replicates from Donor 1
5(b)-Stress-Strain Curves for 3 replicates from Donor 2
5(c)-Stress-Strain Curves for 3 replicates from Donor 3

c.   Suture Pull-Out Testing Results

For the suture pull-out testing, a ZwickRoell testing machine was utilized to analyze a sample of three 5x1cm of placental allograft. The data was automatically transferred to an excel sheet and then stress-strain curves were made. The ultimate stress point from each of the 3 graphs was taken and averaged to find the average maximum stress point.

The average maximum force that it took for a suture to rip through the tissue was found to be 115.785 N/mm^2 with a standard deviation of 66.673 N/mm^2. A t-test was then performed to see if the observed values meet and exceed the desirable criteria. The test found the p-value for this data set to be 0.065. Again, the standard deviation is fairly high due to limited sample size and if this experiment is being replicated, increasing the sample size to reduce the standard deviation would be ideal.

Figure 6. Suture Pull-Out Stress-Strain Curve for n=3

iii: Discussion and Conclusions

After analysis of the data from the two-part experiment, it is found that the hypothesis is accepted and thus placental tissue allografts may be suitable for wound healing in surgical applications. It was found that the placental allografts maintain mechanical integrity under simulated peritoneal conditions and placental tissue allografts possess a tensile strength suitable for materials for surgical applications.

a.   Material Stability Testing Results

In the material stability test, it is seen that the allograft degrades at a similar rate for the control and treatment that is statistically similar. Thus, in terms of its potential usage in these conditions, it is likely that the tissue will uphold its material integrity and behavior in peritoneal conditions and is suitable for this particular surgical application. Even generally, the material degrades at a relatively stable rate after the initial 24 hours and thus will most provide a stable release of beneficial components for a suitable period of time. The initial loss of mass for both groups is likely due to all the soluble tissue components that are released upon initial hydration

and thus is not a cause for concern. Additionally, after conducting the t-test it was found that all the p-values were greater than the critical value, indicating that the experiment failed to reject the null that the treatment and control group do not differ in their degradation. Thus, we have statistically significant evidence to support that the treatment and control groups were similar in the way they degregaded. Thus, since the material may be able to maintain its integrity for its potential usage in traumatic injury to the peritoneal cavity is possible.

b.   Tensile Strength Testing Results

A one-tail t-test comparing the observed average maximum force of 0.914 N/mm^2 with the standard deviation of 0.690 N/mm^2 to the desirable value of 0.164 N/mm^2 was conducted (StimLabs, unreleased internal study, 2022). Through the test, the material was found to meet the desirable tensile strength of 0.164 N/mm^2, and thus the material can withstand the force needed to suture. This is because the p-value of 0.00576 is less than the critical value of 0.05, suggesting that we can reject the null hypothesis. This implies that the material may be able to withstand the force needed for surgical application and thus the second criteria of the hypothesis is accepted.

c.   Suture Pull-Out Testing Results

Through a one-sided t-test using the observed average maximum force that it took for a suture to rip through the tissue of 115.785 N/mm^2 with a standard deviation of 66.673 N/mm^2 compared to the desirable value of 20.2 N a p-value of 0.065 was found (StimLabs, unreleased internal study, 2021). Since the p-value of 0.065 is greater than the critical value of 0.05, we fail to reject the null. This indicates that the material does not meet the criteria to be surgically applied. However, due to the limited sample size of three, it is important future studies focused on this test are conducted with an increased sample size to make reasonable claims. For the purposes of this study, the probability of this outcome can be seen as quite low. For example, the p-value indicates that if the material cannot withstand the force needed to be sutured, there is a 0.065 probability of observing this result by chance alone. In this case since the tensile strength test already implied that this material can withstand the desirable force for surgical materials, the suture pull-out data serves as an additional point of reference for the material which could be further investigated through additional studies to rule out a Type II error (an error indicating that the null was failed to be rejected when in fact the alternative is really true). This can be done by increasing the sample size or increasing the significance level.

d.   Further Implications

Knowing that the material may be suitable for surgical application due to its tensile strength and suture pull-out results, studies focusing on its integrity in different environments can be done. With previous studies which outline that the usage of placental allografts eliminates the need for a second surgical site and can decrease the surgical time and recovery time for a patient, a potential increase in its usage in other fields will aid in the likelihood of numerous other successful surgical outcomes Hartford Healthcare).

Additionally, it could further increase the potential of placental tissue through additional studies on possible modification of the allograft. Knowing that this material is suitable for

application under these conditions by the material stability resting, in the future we can go even further and investigate other modifications.

In fact studies are already being done on how to improve its mechanical and degradation rates through modifications. It has been found that by adding a polymeric layer or gels the degradation rate and the mechanical properties not only significantly improved, but the inflammatory response and compatibility did too (Tehrani et. al, 2021). With additional research, placental allografts could aid in improving many more surgical outcomes. Although this would no longer classify as a minimally manipulated material, it is still possible that with additional testing, the beneficial properties can be maintained while making it more efficient.

Another proposal would be to investigate whether the addition of Hpx to the placental tissue is possible and whether it would help with wound healing for traumatic wounds. When traumatic injury occurs, the patient becomes susceptible to infection due to the release of heme, a protein released in excess after traumatic injury that suppresses the immune system (Lee et. al, 2021). Theoretically, when Hpx is put into the allograft and then into a surgical wound it can bind to the heme. This could potentially aid in prevention of the main causes of surgical infection as the Hpx binding to heme would reduce the impairment of the immune response and the placental tissue would provide its wound healing properties (Poillerat, 2020).

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David in a World of Economic Goliaths: How Israel Became a Major Economic Power in Less Than a Century By Gabriel Messerman

"In Israel, in order to be a realist you must believe in miracles." — David Ben-Gurion

Abstract

   Israel — a little country created less than a century ago on land that is incredibly poor in natural resources and comprising a population of immigrants from all over the world — is today one of the world's centers of technological development, a symbol for entrepreneurship and innovation. It is extremely rare that a country so young and volatile can achieve what Israel has achieved in such a short life span. The focus of this paper is to find a fulfilling answer to the question: How does a country with infertile land, a population consisting largely of immigrants, and surrounded by enemies turn into the high-tech capital of the world, second only to Silicon Valley, and a prosperous state in only 75 years? This paper examines Israel's economic journey from its creation in 1948 up until today. For the sake of understanding, the nation's life span is divided into three eras — early existence: 1948-1967, the creation and establishment of the country, economic challenges, and context needed for further understanding; plummet: 1967 - 1984, Israel's economic "lost era"; and "rebirth": 1985 - present, Israel's emergence as a technological superpower — that best portray Israel's economic history, challenges, and path that have lead it from what Mark Twain described as a land that "sits in sackcloth and ashes" to the "Silicon Wadi" it is known as today.

Early Existence: 1948 - 1967

   Israel's creation was disrupted by an attack by five of its Arab neighbors, which marked the start of what Israelis call the Independence War. Apart from its rough beginnings, however, Israel was also faced with several economic and social issues upon creation. To understand Israel's economic situation at the time, it is important to examine three areas of the country: population, land, and economic circumstances.

   Israel's population following the 1948 Arab-Israeli War consisted of roughly 1.2 million people. "514,653" (Clarmont 308) new immigrants arrived in the country between 1948 and 1950, most of whom were refugees from either post-Holocaust Europe, or those fleeing persecution in Northern Africa and the Middle East, and all of whom needed to be housed, employed, and educated. The vast diversity of the new immigrants coming to Israel caused additional hardship for the country. A 1954 survey showed that of the Jewish population aged 15 and over, 2 percent of male immigrants from Asian and African countries either did not attend school or did not complete primary education; for the women, the percentage was 84 percent. In contrast, the comparable percentages for the Israeli-born population were 26 and 30, respectively (Creamer 173). As a result of the discrepancies in education, unemployment rates for immigrants from Asian and African countries were considerably higher than those of the native population — 11.2 percent of the immigrant population were unemployed; in comparison, the same statistic

for the native population was 2.9 percent (Creamer 173). Furthermore, of the new population, less than "5 percent" (Patterson 311) had a background in agriculture. For Israel, this meant that after roughly one million Arabs, most of whom engaged in agriculture, left the land following the 1948 War, no Jewish farmers were available to fill the vacancy. This might not have presented a major issue if not for the fact that Israel's main exports were agricultural.

The land of the Jewish state was incredibly poor in natural resources; therefore, unlike some of its neighboring countries, it could not rely on gas, oil, or other natural goods for its main exports. There was, however, a large domestic production of citrus fruits, cultivated by mostly Arab farmers who had previously occupied the land. Yet, in its first years of existence, Israel exported only "4,221,810 cases of citruses" (Clarmont 316). In contrast, in 1939, British Palestine exported "15,310,437 cases" (Clarmont 316). This plummet can be largely explained by the fall of markets during WWII, and the fact that nearly all of the citrus industry was composed of Arab growers, who abandoned their fields when leaving (either due to war or after their land was purchased). Despite the roughly 72.5 percent plummet in Israeli citrus exports, citrus still accounted for "47.4 percent of Israel's total exports" (Clarmont 317). Unfortunately for Israeli farmers, the Arab League, consisting mainly of Israel's neighboring countries — Egypt, Iraq, Syria, Jordan, Lebanon, Saudi Arabia, and Yemen — had imposed a boycott on Israel. The Arab states wanted no economic relations with Israel, making it even harder for it to export goods to the countries that would, otherwise, likely be its main consumers. Furthermore, the British government had also stopped the mass import of Israeli (formerly Palestinian) citrus fruits when the country was created. As a result, Israeli farmers were unable to compete in the European market, and the government resorted to paying export premiums. In the 1949-1950 season it paid a "15 percent" (Clarmont 317) premium on all net earnings of Israeli farmers' exports. Israel had lost most of the market for its largest export, and it seemed as though the country wouldn't have been able to maintain an economy. Surprisingly, the nation continued to house and subsidize the arriving immigrants and otherwise build its infrastructure. It is estimated that the upper limit for the total cost of housing, subsidizing, and rehabilitating the immigrants from 1950 to 1958 was "roughly 380 million 1952 [Israeli] pounds" (Winch 179). Israel's budget for 1952 was "168,450,000 Israeli pounds" ("Israel Attaining Balanced Budget", 6), assuming a relatively similar budget for the years 1950-1958, the total amount allocated for immigrant needs totals approximately 28% of the budget over the years mentioned.

It is very curious that a country so unstable with so few resources and such a small working population was able to sustain its incredibly weak economy. Many have attributed it to the so-called "Jewish genius," creativity, or cleverness; in reality, however, the truth lies in quite the opposite. The answer is Israel's closest friend and ally — the United States. The United States played a major role in Israel's development, especially in its early years, and a lot of the success that the Jewish state has seen could arguably be attributed to the support it has received from the U.S. Since Israel's very creation, the U.S. has been providing it with abundant aid. In its first two decades of existence, Israel received an average of "$63 million" (Mark 1) per year in foreign aid from the United States; to put this into perspective, the Marshall Plan provided $13.3

billion for the restoration of war-torn Europe during the same years. Per capita, the U.S. awarded roughly $24 to restore war-torn Europe, while in Israel, the per capita amount equals roughly $52.50 every year for two decades. Combined with private contributions by foreign Jewish organizations, as well as German reparations for the atrocities of the Holocaust, U.S. aid allowed Israel to exist in a strange economy where it was able to defy the fundamentals of economics by living with a negative balance of payments, meaning it imported more than it exported, for nearly all of its existence. In fact, due to such circumstances, up until the late 1960s, Israel was able to focus mostly on "getting up from its knees" — building infrastructure, housing and employing its growing population, and maintaining its large military force. Nonetheless, the toll of dependency upon others still weighed heavily on the country, but during these years of early development Israel had no choice but to continue depending on foreign aid to build itself up. Because of this peculiar situation, this era in the nation's existence holds relatively minor importance when examining its history through the lens of economic progress. However, by examining this period, it is possible to grasp some central challenges that the country faced — a land poor in resources, plagued by conflict, suffering hardship in export, and with a population of immigrants from all over the world. This period shows Israel's deep ties to the United States, an era of economic dependence on its ally, meaning that Israel owes a large part of its success and relative stability at that time to the United States. In the late 1960s, however, a shift occurred, a chain of unfortunate events that showed the Jewish state that only Israel was able to always stand for Israel, but to do so it had to be able to sustain itself.

Plummet: 1967 - 1985

1967 marks a watershed year in Israel's history. On June 5, 1967, following an increase in tension between Egypt and Israel, the latter launched a series of strikes upon Egyptian military bases, destroying nearly all of the Egyptian air force's cargo planes and military jets. This marked the beginning of the Six-Day War, which until today is one of Israel's most impressive military accomplishments and a national pride for many. This "accomplishment" might be surprising to grasp in the context of the title given above; however, what is more important in the context of this paper is not the war itself, but the events that took place prior to it.

One of Israel's closest allies during the time leading up to the Six-Day War was France. The nations established a relationship following the Soviet Union's grand arms sale to Egypt in 1955. The actions of the Soviet Union threatened the Tripartite Declaration, a promise made by France, the United Kingdom, and the United States to ensure stability and peace in the Middle East. In 1956, following the Soviet sale, France started transferring arms to Israel. This relationship benefitted both parties, as Israel guaranteed French access to the Suez Canal to transport foreign goods into Europe. On the brink of the Six-Day War, however, France imposed an embargo on Israel. French president Charles De-Gaulle claimed that he did not want to support a nation that was willing to draw its weapons first, as Israel was only three days away from a planned attack on Egypt and tensions were at a peak. In reality, however, it seems that De-Gaulle chose to switch sides before the war, as following France's withdrawal from North

Africa after the Algerian War (1954-1962), it no longer had the same common enemy as Israel (the Arab world). Seeing as this was the situation, France seemed to benefit greatly from strong relationships with Arab nations, thus it chose them over the Jewish state. This was a major blow to Israel, losing its largest weapons supplier mere days before executing a major attack against Egyptian forces. In hindsight, the Six-Day War signifies Israel's greatest military achievement; what resulted from De-Gaulle's "betrayal" of the Jewish state has led to much greater achievements than the Six-Day military victory.

Although the French betrayal might seem as such, in reality, it was possibly one of Israel's greatest blessings. As mentioned earlier, up until this point in time Israel has largely managed to sustain its economy thanks to foreign aid and dependence upon its allies. Following the French embargo, however, Israelis realized a harsh fact: it is perilous for a country to depend on another for its survival. Following the Six-Day War, Israel began to develop its own military infrastructure, building tanks, jets, and guns that were made for Israel by Israel. The Merkava tank, the Lavi and Kfir fighter jets, and the Nesher aircraft, to name a few, were all created as a result of the French embargo. This signified not only the creation of a domestic defense industry in Israel but also served as a minor remedy for one of Israel's greatest economic problems — exports.

In 1967, Israeli arms exports were valued at $13 million, an increase of $8 million from the $5 million in 1964. After 1967, however, Israel's arms exports have grown exponentially, growing $10 million in the first year, and reaching $195 million after a decade ("Arms Exports"). Since then, exports of arms from Israel have only continued to rise, peaking at more than "$12.5 billion in 2022" ("Ministry of Defense"), mostly due to the Russo-Ukrainian War. Israel has had tremendous success in the defense and arms industries since 1967, and this might have not happened if not for the French embargo of 1967. But not all was well for Israel during this era, as the title suggests. Following Israel's greatest military accomplishment and the creation of a domestic defense industry, the country experienced one of the worst upsets in its history, both military and economic.

In 1973, the country was still filled with overwhelming national pride for its accomplishments seven years prior, but these feelings quickly faded away on October 6, 1973, the holiest day in the year for Jews — Yom Kippur. The Yom Kippur War broke out when Syria and Egypt attacked Israel as it was least prepared for war. This is because Yom Kippur is a day when the whole nation of Israel shutters — grocery stores, malls, public transport, and even schools shut down. It is even an unspoken rule that Israelis don't drive their cars on this day. The Yom Kippur War symbolized perhaps Israel's greatest military failure ever. Though Israel emerged victorious, it came at the cost of more than 10,000 Israeli casualties and an estimated 1,000 vehicles and aircraft destroyed or captured (Jennings and Trottier). The casualties were harsh. In addition to the loss of life, following the Yom Kippur War Israel experienced an economic tragedy and entered its "lost decade".

What is commonly misunderstood about the period between the Six-Day War and the Yom Kippur War is that the fighting never stopped. The War of Attrition was an armed conflict

between Israel and Egypt, the Palestinian Liberation Organization, and Jordan, as well as some Cuban and Soviet forces. The war lasted from 1967 to 1970, and while it is not as widely known as Israel's prior military accomplishment or the tragedy that followed, it is important to acknowledge it to understand Israel's "lost decade." Economically, the War of Attrition shows one of the reasons Israel found itself in the unfortunate situation it did following the Yom Kippur War. The seven years of armed conflict took a toll and destabilized the Israeli economy in a way never seen by the country before. Apart from the losses from war, the country has experienced an obvious increase in military expenditure every time it has engaged in military conflict. While Israel is historically known for having to endure constant military readiness and conflict, its military expenditure during this time was the highest in its history. In 1966, Israel's military expenditure as a percent of GDP was 9.4 percent; the following year it increased to 15.4 percent and continued growing until its eventual all-time peak in 1975 when it reached 30.5 percent ("Military expenditure…Israel"). To put these numbers into context, the USA's all-time military expenditure was in 1967 during the peak of the Vietnam War, reaching "9.4 percent"(Military expenditure…United States"). Even after the Yom Kippur War ended, at the end of 1973, Israel's military expenditure continued to grow, and while it has been decreasing ever since, the effects of such a high military cost had shaken up the country's economy. In addition, during the Yom Kippur War, "30 percent" (Greenwald 34) of Israel's labor force was withdrawn from the economy in order to fight. But at times of war, it is not only the supply that tends to fall but also the demand. During uncertain times, the population is not eager to make major financial decisions, such as buying a home or making other investments in the economy. There was, however, a silver lining to the situation, as the Israeli government had stockpiled goods and commonly needed supplies, avoiding the scarcity of necessities during the war. But in the months following the war, Israeli soldiers were still mobilized, and those reservists who were among them continued to receive parts of their salary while not participating in the economy. As a result, the Israeli economy stagnated and GDP "was running a third below normal" (Greenwald 34). Other factors like global inflation and the 1970s oil crisis only worsened the situation for the Jewish state.

At the end of 1967, the inflation rate in Israel was 1.71 percent, while in 1974 it had risen to a whopping 39.68 percent ("Israel Inflation Rate"). Additionally, Israel's surging trade deficit went from $20 million to $1.6 billion over the same period, with foreign debt rising 27 percent in 1974 alone ("Current Account Balance"). To combat rising inflation and its trade deficit, the Israeli government implemented a six-month ban on imports of luxury goods, limiting imports to solely military goods. Furthermore, in 1975, the government devalued the Israeli Pound by 43 percent and increased the prices of state-controlled basic foods such as sugar, eggs, and milk, which rose by 200 percent (Greenwald 37). This was done to increase the cost of living, thus limiting imports into the country even more. But by increasing the price of imported goods, Israel slowed its consumption of imports but also created a different problem for itself. Israel's industries relied on imported goods, and with import prices rising, these industries were unable to continue operating. Despite the government's efforts to reduce inflation and the trade deficit,

the turn of a new decade had no good news for Israel. By 1984, the inflation rate reached an astronomical "373.22" ("Israel Inflation Rate") percent, and the trade deficit grew even more, hitting "$987.7 billion" ("Current Account Balance") in the same year . In 1985, however, one man managed to save the Israeli economy.

Rebirth (1985-Present)

Nations often have a historical leader figure who is idolized and romanticized for their great accomplishments — Napoleon for the French, Churchill for the British, and Washington for the Americans — and while Israel does not have such a commonly glorified figure, I would argue that one of the men who comes closest to earning such status for the Israelis would be Shimon Peres. Known to many as the Nobel Peace Prize winner who initiated the Oslo Accords, but Peres has a less famous but arguably equally important accomplishment. While Peres accumulated just under four total years as acting prime minister in Israel, it is not by the time he spent in office we should judge him, but by the effect he's had on the country. He was elected as the eighth prime minister of Israel in 1984 and served his first term until 1986. During this time, Peres managed to do what politicians had failed to do for the past decade — slow down inflation — which earned him the title of savior of the Israeli economy.

In 1984, Peres' government brokered a deal that froze wages and prices in order to combat inflation. Following the deal, the inflation rate in Israel plummeted to "4.5 percent per month over the next two months" (Fischer 276); but wages couldn't be frozen for longer, and neither could prices. In 1985, inflation was standing at an annual rate of "308.79" ("Israel Inflation Rate") percent. Following this failure, the government had to take more drastic action to ensure a permanent decrease in inflation rates. As a result, on July 1, 1985, the Israeli Stabilization Plan was passed by the Israeli Knesset. The plan was devised by Peres and a coalition of Israel's leading economists and focused on four main goals: a sharp reduction in government expenditure; a devaluation of the Israeli Shekel; a freeze on wages and prices; and setting a fixed exchange rate to the U.S. dollar. By freezing wages and prices, as well as reducing government expenditure, mainly in subsidies, the government hoped to decrease the amount of money held by the population, therefore reducing its purchasing power. The Stabilization Plan reduced government spending by 7.5 percent and devalued the Shekel by 20 percent (Sachs); this allowed the country to boost exports, as the devaluation of the Shekel made Israeli exports more attractive to the rest of the world, and a fixed exchange rate helped assure importers and acted as an inflation-regulatory force of its own. A general rise of 14 percent on all wages was also implemented, and, as the first month of the program saw a price rise of 27.5 percent, mostly as a result of subsidy cuts and devaluation of the Shekel, wages were raised once again in July, with another 12 percent raise from December 1985 to February 1986 (Fischer 277). Overall, the plan was incredibly successful, lowering inflation from a staggering 309.93 percent in 1985 to 47.89 percent the following year and an even lower 19.07 percent in 1987 ("Israel Inflation Rate"). The economy was back in its stable form, but stability did not imply growth, and the government was worried that it would not be able to achieve economic growth following stabilization. Luckily,

part of the Stabilization Plan included liberal and free-market reforms. The Bank of Israel, which was formerly government-owned, became an independent entity, and the government was no longer allowed to print money. Additional reforms were made, which included a hike in interest rates and a reduction in the government's involvement in the market. Israel's new, more capitalist economy allowed for more growth opportunities than ever, which was proven in the following years.

Following the collapse of the USSR, the 1990s saw a great influx of Soviet immigration to Israel. A million Soviet immigrants arrived in Israel between 1990 and 2000. For the country, on one hand, this meant large spending on accommodations and acclimation of the new immigrants, who did not speak the language and were unfamiliar with Israelis' now increasingly capitalistic way of life. On the other hand, the influx of Soviet immigrants also meant that the country would receive a major boost to its human capital. On average, the "head of household" in a Soviet immigrant family had a higher education level, 14 years, when compared to the Israeli national average, 13.3 years, and a higher percentage held bachelor's degrees than the Israeli population — 41.1 percent and 29.5 percent respectively (Razin 9). Highly educated immigrant doctors, engineers, scientists, and many other professionals could greatly benefit Israel's economy, especially its growing high-tech industries. The highly educated immigrants arrived in an already educated Israel, with a growing technological industry; this was exceptional timing. High tech was developing at a high pace by the time the Soviet immigrants stepped foot into the Promised Land: Israeli software exports hit $110 million in 1991, an incredible number when compared to the $5 million in 1984 (Rosenbaum). Following the mass Soviet immigration, Israel had the highest percentage of engineers in the world, an incredible achievement for the country, and one of many that powered its technological leap during these years. New as well as home-grown engineers were soon to be in very high demand, as the global high-tech boom of the 1990s hit Israel. Demand for engineers during these years increased tremendously, and the Soviet immigrants were able to provide their knowledge and skills. Many of these highly educated immigrants chose to settle in the center of Israel, mainly in Tel Aviv and its surrounding towns, which became the main area for technological development in Israel, later nicknamed "the Silicon Wadi." The international high-tech boom hit, and paired with an already existing industry and an influx of new high-tech workers from the former Soviet Union, Israel became a breeding ground for startups. Thousands of startups were established in Israel during the 1990s and early 2000s, most famously Mirabilis, creators of ICQ, which was purchased by America Online for $407 million in 1998. Many of these startups were created by former IDF soldiers, who used their acquired skills in civilian life, another unique aspect of Israel. Many IDF soldiers who dealt with military technology during their service found ways to utilize their skills after completing their service. One of the primary examples of this phenomenon is Avishai Avrahami, one of the founders of the Israeli tech company Wix, who served in Unit 8200, one of the IDF's most elite cybersecurity units. This unique Israeli system allowed for a large population of young, innovative, and skillful people to pursue high tech. High-tech development, however, needed investment, and startups were unable to rely solely on government investment. So in 1993, the

Israeli government created the Yozma program to attract private investment in Israeli technology. The program promised to double any private investments with government funds, insurance for the investments, and further tax incentives. Yozma was a success, raising $150 million in private foreign capital, which was invested in over 200 startups, and led to the creation of ten Israeli venture capital firms between 1993 and 1997 (Cole). High tech continued to grow, with 1997 high-tech exports reaching $5.6 billion, an increase of 14.2 percent over the previous year (Cohen). In 2003, the final major step in Israel's economic success was taken.

  In 2003, the Israeli government started a privatization campaign, during which it cut tax rates, public employee wages, and four thousand government jobs. Major, previously government-owned companies, were privatized, most notably: El Al, Israel's national airline, Leumi, Discount, and Bezeq banks. These reforms further decreased the government's influence and strengthened the private sector in Israel, which allowed for larger opportunities for private Israeli industries. Since then, Israeli high tech has become world-renowned and a core aspect of the country's economy, with high-tech output nearly doubling in the past decade, and high tech accounting for "18.1 percent of Israel's GDP in 2022" ("High-Tech's Contribution"). Recent major Israeli high-tech successes include Mobileye, which sold for $15.3 billion in 2017, and NDS, which sold for $5 billion in 2012, as well as some true IDF-fashion cybersecurity startups such as Imperva, which sold for $2.1 billion in 2018, and Ensilo, which sold for $20 million in 2019.

  Looking at the tremendous success of the Israeli high-tech scene, it is difficult not to ask, why Israel? There are numerous countries with developed high-tech infrastructures, but none seem to be as innovative as Israel. It is hard to propose a direct answer to such a question, but my hypothesis lies in Israel's history, society, and circumstances. Comparing Israel to South Korea, which would be relatively similar when considering geopolitical status and high tech, shows a similar impressive economic growth rate and a very developed high-tech industry (South Korea is not a direct counterpart to Israel, and is simply used as a relatively close comparison in the aspects mentioned above). But why is South Korea not seen as the startup capital of the world? My answer would lie in the fact that South Korea has a much more established, comfortable society than Israel, with a massive service industry accounting for the majority of its GDP, as well as other pre-established industries such as electronics and automobile production. A similar situation can be witnessed in many other countries; when there are successful pre-established industries, people do not tend to take risks on new, unknown industries. Countries like South Korea have a lot to lose from taking the gamble on underdeveloped industries, such as high tech in its early years, and are further disincentivized by already existing economic sectors that sustain the country. Israel, on the other hand, did not have the luxury of having such sectors that the economy can rely on, there are not many other ways apart from tech and innovation, whether it is in military or civil use, for the tiny Middle Eastern country to survive — Israelis were always forced to innovate.

Conclusion

As Israel continues to thrive as the startup capital of the world, it is important to ask, and understand, how is a country the size of New Jersey able to achieve such economic success in under a century? Israel's economic success is not rooted in the discovery of precious resources; rather it was built up over years of hardship and unfortunate events, as well as by new opportunities and support from outside. From its very creation, Israel has been heavily supported by the United States, which allowed for it to have a swifter and more secure rise in its early years. Israel was able to spend beyond its means, as it knew that support from the U.S. was guaranteed. Throughout Israel's history, its unfortunate geopolitical situation, which is one of its greatest burdens, has managed to push Israel onto new paths of success and innovation. Constant armed conflict, as brutal as it might be, is bound to result in innovation. Especially due to Israel's size and the disproportionate amount of its enemies, it had to innovate in order to constantly survive and thrive as the underdog. The French embargo of 1967 also played a large role in Israel's military success, as it helped create new developments in the Israeli defense industry, as well as jumpstart its military-technological industry. Following the economic plummet of the 1970s, Peres' Economic Stabilization Plan helped not only rescue the Israeli economy but also raise a capitalistic Israel. Later, the fortunate timing of mass Soviet immigration, which brought thousands upon thousands of professionals to Israel, combined with the high-tech boom of the 1990s and the Yozma program, which made Israeli startups very attractive to investors, allowed Israel to become a leader in technology.

Another key aspect of Israel's success, which does not have a timestamp, is, yet again, one of its greatest burdens — a land poor in natural resources. Israelis were not blessed with a large plot of land: furthermore, the land Israel does possess is one-third desert, so the agricultural industry was never able to fully sustain the country. There is little to no oil or gas beneath Israel's land, and no precious stone or heavy metal mines either. Israel was, in a way, doomed to be innovative, as it had no other way of sustaining itself. Finally, there are the people of Israel. Israel is a true immigrant nation, with a highly diverse population, the vast majority of whom moved to the land during the last century escaping from persecution elsewhere in the world with little to nothing to their name. Because of its unique society, the people of Israel were not afraid to take risks; in fact, they *had* to take risks in order to build something for themselves. The risk-taking nature of Israel is additionally rooted in the fact that it had no real sustainable industries that people could take part in — everything had to be built from nothing. A population that arrives at nothing, with nothing, is forced to invent and take risks, and Israelis have shown the world exactly what you can achieve with some ambitious risk-taking.

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Private Funding in Hong Kong's Arts and Cultural Sectors By Ziyan Miller

Abstract

Hong Kong is a city with a plethora of sectors containing many cultural and artistic institutions. However, in a city of nearly 7.5 million people, these museums, art galleries, academies and heritage sites receive almost all of their funding from the government of the HKSAR or the Hong Kong Jockey Club Charities Trust. According to a report by Hong Kong Arts Centre, "subsidy from the taxpayer to the arts averages between 70-80% and, in the case of some companies and events, it can be as high as 93%" (Hong Kong Arts Centre 2). However, according to Ms. Chin Chin Teoh, the director of Jockey Club CPS Limited and who also oversees and leads the management of Tai Kwun's operations, for museums and exhibitions that do not have any government support, the trust will provide the funding necessary to run the museums as dictated in the trust's mission statement. During my interview with Ms. Chin Chin Teoh, she said that Tai Kwun receives 90% or even more of its funding from the Hong Kong Jockey Club Charities Trust and that there are similar cases all around Hong Kong.

How Other States Fund the Arts

In the U.S., only about 15% of the arts budget is paid for by the government and museums and exhibitions have to rely on private funding. Other countries such as the UK, Australia, and Canada, have the government only subsidizing roughly 50%. Yet, museums in these countries are some of the most revered and famous in the world and function extremely well with many even making profits. You may wonder where the other parts of the funding come from–the answer is private funding. Private funding refers to money that is directly donated by an individual, a business/corporation, or an endowment or foundation, or more generally, from a non-public source (i.e. not from the government). These countries in the West are able to employ numerous strategies to raise significant amounts of private funding that can fund the operations of cultural and artistic institutions and enlighten millions of people around the world as they visit these establishments. Hong Kong's arts and cultural sectors need private funding, not just to gain more funding in order to better exhibitions and performances, but to split up the sources of funding. No institution should be reliant on one source of funding because you never know what may happen and that source may falter and the primary source of funding will have disappeared.

Funding the Arts in Hong Kong

In order to figure out the best way to bring in private funding, I interviewed the deans, directors, and chairmans of some of the most recognized academies and museums in Hong Kong. For about an hour each time, I talked with Ms. Anna Chan, Ms. Chin Chin Teoh, and Mr. Bernard Chan. Ms. Anna Chan is the Dean of the School of Dance, a part of the Hong Kong Academy for Performing Arts. Ms. Chin Chin Teoh is one of the directors of Tai Kwun (Hong Kong's Centre for Heritage and Arts). Mr. Bernard Chan is the founding chairman of the Hong Kong Palace Museum and the current chairman of M+.

Interview with Anna Chan

During my interview with Ms. Anna Chan, she told me about how the Academy is not as reliant on private funding as other countries' academies may be, due to the fact that HKAPA is a tertiary educational institution, meaning that the government provides enough funding to bear the minimum operation cost. In a 2016 P.A.C. Report by The Audit Commission, the government subsidy of $309 million accounted for 66% of HKAPA's total income of $467 million. While the report may have come out roughly seven years ago, the number was confirmed to remain largely the same. Ms. Chan and I discussed where the other sources of funding came from: public philanthropy, the Hong Kong Jockey Club Charities Trust, sponsorships, money from renting out venues, and donations.

The most important way to increase private funding revolves around the marketing and fundraising strategies one employs. When asked what methods HKAPA uses, Ms. Chan said that HKAPA has a unit called the Development Office that is tasked with extending the Academy's network of friends and partners, while also acquiring and securing donors and sponsors. Ms. Chan also says that the Academy takes to social media, specifically Instagram and YouTube, to market performances and projects and bring in more students and people. Magazines, public news channels, and posters in the MTR are also strategies to increase publicity. HKAPA also established SAPA, The Society of the Academy for Performing Arts, they contribute to the development of the Academy and allow HKAPA retain its performers and technical artists. As a tertiary educational institution, Ms. Chan says that the Academy is devoted to the best interests and needs of the students, and this includes fundraising for overseas students to study here in Hong Kong.

When asked about challenges that HKAPA has with fundraising, Ms. Chan expressed that there weren't many extreme challenges due to the fact that the Academy was a public institution and received much of its funding from the government. However, the thing we discussed the most was the desire to focus on the needs of the students and make their performances the best they can be. In addition, one challenge that stuck out to me was the discussion about the difficulty of getting parents to see the purpose and good that art, specifically dance, can imprint on the student's wellbeing.

Interview with Chin Chin Teoh

As noted above, in my interview with Ms. Chin Chin Teoh, she talked about how the funding for Tai Kwun came primarily from the Hong Kong Jockey Club Charities Trust, with the Jockey Club being the primary private funder of culture in the HKSAR. Ms. Teoh informed me that even though the Jockey Club is a private business with minimal government influence, the money received by Tai Kwun from the Jockey Club is still treated as public money due to the fact that the money acquired is from the general public and redistributed. First, $6 billion dollars were donated by the Trust to conserve and revitalize the former Central Police Station and establish the site as Tai Kwun, then $200 to $250 million dollars are donated annually. No government funds are provided to Tai Kwun and the small remainder of the money needed to

operate Tai Kwun that does not come from the Jockey Club comes from rental income, family foundations, corporate sponsors, venue hire, or philanthropy. Tai Kwun is a public museum and the Jockey Club Charities Trust is dedicated to keeping the arts and culture as accessible to Hong Kong as possible, so for a vast majority of exhibitions and viewings are free of charge. Rental income refers to the money that different companies or groups pay to establish a small business on the premises, for example, Between Coffee which is a small, quaint coffee shop on the second floor of the JC Contemporary building.

When asked about marketing and fundraising strategies, Ms. Teoh brought up similar strategies to those mentioned by Ms. Chan from HKAPA, namely social media, a business development team that will approach corporations and businesses, advertisements on trams or other public transportation, and press reviews. However, she brought up some new ones including something called Tai Kwun fans which is a mailing list that will send emails encouraging people to come visit. When I asked if Tai Kwun has any plan of action on enticing members of the general public to donate, Ms. Teoh said that they never go to the public for funding as it is their policy and the Trust does not want that. Surplus profits are added onto the next year's budget, or are returned back to the Trust to put into a different program. Ms. Teoh says that she is trying to incentivize them into reallocating that surplus into a new Tai Kwun program.

Ms. Teoh provided some unique insights on the challenges that she and her team face when trying to convince corporate sponsors and that is trying to get people to understand the positive value of art and how it improves lives. Her analogy was that it is harder to convince someone to donate to art, instead of pouring funds into constructing a hospital since that displays a tangible benefit. She discussed how it was difficult to educate people on the intangible value of art and the difficulty of being able to articulate how art contributes to the economy and improves the wellbeing of others. The Bilbao Effect was used by Ms. Teoh to describe how Hong Kong can indeed flourish due to the creation of museums and cultural institutions. By investing and sponsoring more museums, a spillover effect is created and more job opportunities are created and the whole area blossoms. She described another challenge was retaining sponsors since Tai Kwun only has eight permanent exhibitions and the other areas rotate and change exhibitions so many sponsors see the opportunity of putting their logo on an exhibition is ephemeral. To them, there is no point in sponsoring an exhibition that is only going to last for three months.

Interview with Bernard Chan

When I interviewed Mr. Bernard Chan, he started off the interview by giving some statistics; M+ was running at a 46% recovery cost and Hong Kong Palace Museum was running at a 44% recovery cost. This means that even with all the government support, ticket sales, and financial sponsors, the museums are still losing roughly 55% of money. When asked about where the main sources of funding come from, Mr. Chan discussed commercial sponsorships as being the biggest source, followed by regular sponsorships and individual donations. Commercial sponsorship is when a company or group pays a sum of money for access to the exploitable

commercial potential associated with that property. The Hong Kong Jockey Club Charities Trust is also the biggest funding source and that is mostly due to the fact that the government tells the Jockey Club to donate to whatever the Hong Kong government deems as good for the community. Because the Hong Kong Jockey Club is authorized by the government to participate in gambling and betting; the Jockey Club is only able to make money due to the government's permission, and so the HKSAR government can influence what the Jockey Club does with their earnings.

The West Kowloon Cultural District (WKCD) receives much of its funding for these two museums (M+ and Hong Kong Palace Museum) by developing the surrounding area into office and residential areas and using that money to subsidize the losses. The actual WKCD is supported by the government so the original funding for the projects such as the M+ and Palace Museum and the future institutions were funded by an endowment provided by the government, but according to Mr. Chan that endowment has almost run dry. Individual donations are fairly high, with one couple donating roughly $10 million USD (the couple had an entire wing named after them). Mr. Chan talked about how individual donations were easier to accommodate compared to corporate sponsorships due to the fact that it is easier to manage how much recognition someone can receive with the amount of money they donate.

The biggest challenge with running these two museums that Mr. Chan discussed was making sure that the big corporations that were sponsoring the exhibitions and events did not make the space their own and overshadow the main purpose of letting the world-class museum get more recognition.

Arts Funding in the US

Now that we've reviewed the sources of funding, fundraising strategies that these groups employ, and the challenges they face, we can turn to other countries and see how they bring in private funding and overcome the challenges that establishments in Hong Kong are met with.

A 2012 report by the National Endowment for the Arts found that roughly 6.7% of United States museum's revenue came from public funds including local, federal, and state agencies and a 2008 report by the Institute of Museum and Library Services concurred and stated that between 7% and 24% of the museum's budget is government provided. However, the disclaimer was that it heavily depended on what kind of museum it was. The other sources of funding come from private funding and income the museums generate, as well as interest and endowment income. While these reports are dated, they still provide the information needed to understand what I am getting at. Instead of having one singular ministry of culture, the U.S. system of support is decentralized and dynamic. Even specific federal government groups dedicated to the arts and culture comprise less than 2% of funding; even the National Endowment for the Arts makes up less than 1% of support.

Under the U.S. system, any donation to a tax-exempt nonprofit organization (i.e. museums and cultural institutions) qualifies as a potential deduction for the tax-paying donor. As said in a 2004 NEA report, "for these individuals, the donation of a dollar to a nonprofit

institution reduces taxes between 28 and 40 cents per dollar, depending on the individual's tax position" (Cowen 23). This maximizes the amount of donations private individuals can give and it's been adopted in many European countries and even in Hong Kong, but it's less known. The U.S. also has diplomacy programs set in place to display American art abroad. By displaying the arts abroad, the audience is widened and more people want to visit. The U.S. is an immensely diverse country with people from all around the globe; the latest U.S. Census estimates that there are at least forty five million immigrants and around 25% of the population being non-white. Therefore, the U.S. is a melting pot of different cultures and identities and people want to preserve that. There are museums that focus on specific groups of people such as the Asian Art Museum or the Birmingham Civil Rights Institute. Museums are homes to different cultures and arts so people are invested in preserving that so we can learn about the past. In the U.S., the private sector donates an overwhelming majority of the money in hopes of being able to preserve the diversity of its population. Crowdfunding is also a popular method of fundraising, because it allows for even small donations to contribute to something larger, and as mentioned by Mr. Chan, endowments are also very large in the U.S. system of financial support.

Arts Funding in Europe

The European Parliament's Committee on Culture and Education recently investigated how to bring in private funding into the EU Member State's cultural sectors and wrote up their findings in a report. The main focus of this report "is on the importance of the economic, political and cultural aspects of the funding modes and mechanisms developed by governments" (Čopič 6). The committee identified that there were four subcategories of private investment: direct/capital investment, sponsorship, donations and patronage, and earned income.

Just like in the U.S., many European nations have tax incentives, and institutions in those countries fundraise through matching grants and favorable banking schemes, and have private-public partnerships. Public-private partnerships are when a government agency partners with a private group; it allows for the government to provide public services and infrastructure to the private sector and have the private sector take care of the expenditures. Matching grants is used to describe the condition that stipulates that a private donation has to be matched by a certain amount proportional to the value of the donation from a third party. Europe also uses crowdfunding, venture philanthropy, and banking schemes.

How to Encourage Private Funding

So far, I've discussed three different institutions (M+ and Palace Museum are combined since they fall under the same authority, the West Kowloon Cultural District Authority) and their sources of funding, their marketing schemes if discussed, and the challenges they face. Next I looked at the U.S.' and various European country's strategies on encouraging private funding into the cultural and arts sector. Lastly, I will discuss the variety of strategies that can be used to increase private funding in response to the challenges that were discussed.

Halfway through writing this report, I began to realize that a majority of the ways to bring in private funding had been exhausted. Article after article discussing private funding and the various ways to bring it into the museums led me to the same strategies that had already been employed countless times and worked as best they could. Everytime I could come up with possible new solutions, another problem stood in the way. Many of the viable options relied on the use of government funds such as private-public partnerships, venture philanthropy, and the build-operate-transfer model, and so they did not promote an increase in private funding. While researching this issue, one difference between the American and European methods of private funding that stood out was that the American method discussed how much of the private funding came because people were invested in the preservation of culture (and also tax incentives). Through these interviews my goal was to narrow down the challenges to their core essence and try a new fundraising strategy that would specifically target what made these challenges happen. In my interviews, I was hit with only one big challenge, trying to get people/corporations invested in the preservation and exhibition of culture and the arts. That reason plus others including tax incentives (which are semi-present in Hong Kong, but aren't taken advantage of due to the already extremely low tax rate) is why the U.S. has been able to receive a majority of funding from the private sector. I believe the way to increase private funding in the HKSAR for cultural and artistic institutions is not through increasing awareness of potential tax or social benefits, but rather is through demonstrating to potential donors the value of the arts to both the artists and performers and to the patrons of museums and shows.

The U.S. has a vast number of programs dedicated to enlightening people and getting people invested in the arts and culture. Schools have classes about art history and classes dedicated to the history of other cultures, and many American institutions hold regular seminars and webcasts that intrigue people. If M+ or Palace Museum or another Hong Kong museum were to set up something similar and market it properly, it could reach a vast number of people and help to convince them that the art and cultural sector are worth funding. In order to cultivate an appreciation of the arts and culture in Hong Kong, museums should expand the scope of exhibitions and present topics that are closer to home, so they feel more inclined to donate.

Social media is rampant all around the world and that is the same in Hong Kong with about 90% of Hong Kong residents being active on social media. Partnering with brands or other influencers on social media can grow your following and can allow for more people to recognize museums when mentioned. Regularly posting and creating a memorable brand identity are the key ways to grow the institution's following. It also helps to interact with followers and see what they want, because then their input can possibly be used and if they were to know that, then they may be more inclined to donate since they contributed. Posting specific content, but with the relevant hashtags can also be an amazing tool. For example in the case of HKAPA, showcasing a teacher or student or in the case of museums showcasing specific exhibitions or even pieces in an exhibition and the history behind it.

Even though creating an interest in the arts and culture is the biggest way to increase private funding there are other strategies. While interviewing with Mr. Chan, he discussed how

the West Kowloon Cultural District had an endowment, but it has almost dried out, so now lots of funding is being put back into the endowment. In my interview with Ms. Chan and Ms. Teoh, an endowment was not mentioned, so I believe starting an endowment is the first step in increasing private funding. Similar to the U.S., Hong Kong allows for "donations to tax-exempt charities or to [the] Government for charitable purposes can be deducted from your net assessable income under salaries tax, assessable profits under profits tax and total income under personal assessment" (The Fred Hollows Foundation). Even though Hong Kong has a low tax rate, letting this be more known can help push potential donors into donating. Partnerships with brands is another viable option. By partnering with brands or other corporations, these groups can allow for more coverage and for more people to know about whatever is happening with the museums. It also can help immensely if the brand is an international group so when international visitors visit Hong Kong they can visit these museums and possibly support them. The U.S. is also keen on matching donations with multiple companies and groups being created for the purpose of matching donations for a good cause. In Hong Kong, if there are means, then private funding can be increased if the Jockey Club Charities Trust would be willing to match any donation that Hong Kong locals or international visitors make to any Hong Kong museum. A recent survey found that 84% of people said they were more likely to donate if a match of their donation is offered. Ms. Teoh discussed how one thing that Tai Kwun struggles with is keeping sponsors so one strategy could be to have contracts stipulating that corporations have to stay for a certain amount of time and fund exhibitions during that time. Lastly, similar to the Cartier and Women exhibition showcased in Palace Museum, by having brands come and create their own exhibitions while using museum premises, that is another way to bring in private funding without having to entirely provide the funding for the objects showcased.

Conclusion

Even though many private fundraising strategies are already being used, there are always new ones that can be created. While the search for private funding has been delayed due to the reliance on government aid, here are some strategies on how to increase private funding. Hong Kong is a diverse city in of itself and the biggest way to receive funding is to embed an appreciation of culture and the arts into the Hong Kong people. In order to embed this appreciation, educating people of tax benefits and possibly setting up corporate matches can also be a way to maximize private funding.

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Using Stem Cell Transplants to Restore Damage Caused by Hematologic Cancer Treatment
By Krish Sekhar Mishra

Abstract

This review article analyzes and discusses the potential of utilizing stem cell transplantation to reverse and/or restore bone marrow damage caused by cancer treatment administered to those with hematologic malignancies. An overview of stem cells, bone marrow transplants, and the effects of cancer treatment provides background information for the study covered. The clinical trial analyzed consists of a 15-year study, from 2006 to 2020, of 17 patients with hematologic malignancies undergoing allogeneic stem cell transplantation due to bone marrow damage caused by high levels of chemotherapy administered. The clinical trial recorded successful bone marrow engraftment rates and survival post-transplant. The clinical study showed that the allogeneic stem cell transplant procedure has a 100% successful engraftment rate, as well as a moderate proportion of the patients that survived long past the procedure. The conclusion was made that stem cell transplantation could be a groundbreaking procedure helping patients in remission live a long, healthy life post-cancer treatment. However, further clinical trials would need to be done before the procedure can be labeled as a viable, safe, and affordable solution, as the mortality rate and cost of the allogeneic stem cell transplant procedure are currently too unrealistic and dangerous to be used commonly.

Keywords: Biomedical and Health Sciences; Cell, Organ, and Systems Physiology; Stem Cell, Bone Marrow Transplant, Disease Treatment, and Therapies, Immunology

Introduction
Damages from Cancer Treatment

Cancer Treatment, including Chemotherapy and Radiation Treatment, have been crucial developments in treating Hematologic or blood-related cancers. However, high doses of treatment are commonly required to combat and destroy the rapid mutation of the cancerous cells, most often in the form of radiation therapy or chemotherapy [1]. Clinical studies of cancer survivors treated from childhood reveal that certain chemotherapies can cause a wide range of long-term side effects associated with cognitive impairment and aging. Furthermore, cytotoxic and genotoxic drugs are used to treat cancers, often targeting proliferating cells, leading to cellular senescence, a response to treatment where cells irreversibly lose their ability to proliferate and acquire challenges in gene expression [2]. High doses of cancer treatment are subject to commonly cause complications, including fatal organ damage such as bone marrow [1]. Bone marrow is a spongy tissue found in bones, found in the thighs, ribs, and sternum, which functions to produce various types of blood cells such as platelets, white blood cells, and platelets [3]. These cells are vital for transporting oxygen, promoting blood clotting, and fighting infection [4]. When high doses of chemotherapy are administered, the drugs affect not just cancerous cells but rapidly dividing cells in the bone marrow [1]. There are several ways that

chemotherapy can inflict damage on the bone marrow. Bone marrow suppression involves the suppression of the functions of bone marrow, resulting in a reduction of blood cells produced [5]. Chemotherapy targets rapidly dividing cells, including stem cells found in bone marrow [1]. This fragmentation reduces the production of all types of red blood cells, which can lead to anemia (fewer red blood cells), leukopenia (fewer white blood cells), and thrombocytopenia (fewer platelets) [6]. White blood cells are essential for the functioning of the body's immune system, as they help the body fight infection. Low white blood cell counts caused by high levels of chemotherapy can lead to mild infections. Other blood cell count symptoms include fever, chills, mouth sores, rashes, redness, and swelling. Common symptoms of a low red blood cell count include pale skin, nails, and lips, increased heart rates, dizziness, and shortness of breath. Furthermore, low platelet counts can result in bleeding through the nose, gums, or mouth, blood in the urine, tiny red spots on the skin, bruising, and black or dark bowel movements. Stem cell replacement procedures, also known as bone marrow transplantation or hematopoietic stem cell transplantation, can be used to combat bone marrow degeneration caused by chemotherapy [1].

Stem cell Transplantation

Stem cells are specific cells in human life's embryonic, fetal, and adult stages. They are crucial to the development of tissues and organs. The significant traits of stem cells include clonality, self-renewal, and potency, which is the ability to differentiate into a specialized cell type. However, these characteristics may differ between various types of stem cells [7]. Stem cell transplants are surgical procedures to replace and/or restore damaged cells [1]. The damaged cells are replaced with specialized cells and divided into a human body to function appropriately and generally in the respective body area. Stem cell transplants in cancer treatment can restore blood-forming cells in the body that have been damaged or destroyed by high levels of chemotherapy or radiation therapy [1]. Stem cell transplants do not commonly treat cancer directly. Instead, they aid in the body's recovery of its ability to continuously generate new stem cells, combatting any potential blockage or damage caused by high treatment doses used to destroy cancerous cells [1]. Stem cell transplants are primarily seen in cases of lymphoma or leukemia, both blood-related cancers, due to the high levels of chemotherapy, radiation therapy, or both often required when treating these cancers [8]. However, the potential of using stem cell transplants for more cancer types is currently being studied through clinical trials [1]. There are two main types of stem cell transplants: autologous and allogeneic [3]. In autologous transplants, the patient's own stem cells are harvested and preserved. In addition to chemotherapy, the harvested stem cells are returned to the patient's bloodstream [3]. These stem cells then migrate into the bone marrow and begin producing new red blood cells, helping to restore damaged bone marrow. Allogeneic transplants usually obtain stem cells from a family member or an unrelated donor. Chemotherapy or radiation is given to the patient to eliminate the cancer cells and suppress their immune response [8]. Then, the donor stem cells are injected into the patient's bloodstream. The new stem cells migrate to the bone marrow and begin producing healthy blood cells, replacing the initially damaged bone marrow [3].

Risk of Stem Cell Transplantation

A risk involving allogeneic stem cell transplantation is the potential development of graft - versus - host – disease [9]. This occurs due to white blood cells from the donor or the graft recognizing normal, noncancerous cells in the body or the host as foreign. This triggers the white blood cells from the donor to attack normal cells. This issue can result in damage to the liver, skin, intestines, and many additional organs. This can occur at any stage post-transplant, including a few weeks after or much later in the future after the transplant. This disease is treated with steroids or other drugs that work to suppress your immune system. The likeness of the development of graft versus host disease depends on the quality of a patient's match with a donor. The closer the donor's blood-forming stem cells match the patient, the less likely the patient is to develop the disease. Doctors also sometimes administer drugs to a patient before the disease's development in hopes of prevention. Stem cell transplantation can be effective in restoring bone marrow damage. However, close monitoring and medical care are essential during the transplant process and the following recovery period. The attempt to balance effective immune recovery, lasting control of disease, and minimalizing the likeliness of graft - versus host disease has been a challenging obstacle to overcome in the last few decades. An approach still used that has proven to be successful in avoiding significant effects of graft - versus host disease is the infusion of T cell-depleted grafts in hematopoietic stem cell transplantation [10].

Discussion

Possible Therapeutic Usages of Bone Marrow Stem Cells After Cancer Treatment. A clinical trial study conducted at Dartmouth-Hitchcock Medical Center analyzed the success rate of bone marrow engraftment following allogeneic stem cell transplantation [11]. Clinical investigations have enabled addressing a wide range of stem cell types [12]. The transplant procedure was performed as a direct response to bone marrow damage caused by high levels of chemotherapy administered to participants with hematologic malignancies. Allogeneic stem cell transplantation is a surgical procedure that extracts healthy stem cells from a donor and inserts those stem cells into a matching patient [3]. In this clinical trial, healthy stem cells were extracted from donors and performed as a replacement of the damaged, abnormal stem cells in the bone marrow of each participant damaged by chemotherapy [11]. The clinical trial analyzed the bone marrow engraftment rates and survival of each participant following allogeneic stem cell transplantation. Successful bone marrow engraftment ensures and relays that the cells in the bone marrow are healthy, restored, and function correctly [13]. The clinical trial consisted of 18 participants recruited based on the study's eligibility criteria. Each participant was required to be between 18-75 years of age with a type of hematologic malignancy. The trial consisted of 12 female and six male participants. The race and ethnicity of each participant were not evaluated. The study was conducted from 2006 to 2020, with a 30-day post-transplant engraftment analysis, as well as a 15-year survival rate analysis. The stem cell donors were matched with each participant. However, 1 participant did not complete the clinical trial in its entirety [11].

Results of the Clinical Trial

      When analyzing the clinical trial outcome, it is displayed that the allogeneic stem cell transplantation procedure performed successfully on all 17 participants analyzed. 16 of 17, or 94.1% of the participants analyzed, were successfully engrafted by 30 days post-transplant, with most of the participants (n=15) successfully engrafting between 16 to 30 days post-transplant (Figure 1). The survival of each participant following the stem cell transplantation was also measured for up to 15 years post-transplant. It is important to note that the causes of death of each participant analyzed following the trial are not specified. However, there have only been a few reports of safety issues linked to allogeneic transplants [12]. Therefore, each participant's death can only be assumed to be related to the clinical trial. The study record showed that 10 of 17, or 58.82% of participants, were affected and/or at risk of mortality post-transplant. The records presented that 10 of the 17 participants analyzed were, in fact, pronounced dead under five years post-transplant. 2 participants did not survive past a year following the transplant [11]. Additionally, the following 8 participants pronounced dead survived between 1 and less than five years post-trial. Furthermore, the remaining seven participants survived over ten years post-transplant, exceeding the 15-year survival analysis.

Figure 1. The proportions of participant bone marrow engraftment throughout the post-transplant analysis. Most participants analyzed had successful bone marrow engraftment between 16-30 days post-transplant.

Figure 2. Represents the range of survival and mortality of the 17 participants analyzed post-transplant. 58.82% of participants did not survive to 5 years post-transplant. However, those who did survive past five years following the procedure were able to survive over a decade following the clinical trial.

Conclusion

The potential of using stem cell transplants to restore damage caused by cancer treatment could be a groundbreaking possibility. Further clinical trials being administered would ensure that the procedure can be labeled as a safe, common procedure. Further assessment of additional treatments for hematologic malignancies is also needed [14]. The allogeneic bone marrow stem cell transplant procedure enabled multiple years of life for many of the participants, including a moderate proportion that was able to survive long past the treatment. However, the proportion of long-term survival post-transplant would need to increase significantly for this procedure to be viable, safe, and applicable for common use. Additionally, it is worth noting that the cost of stem cell transplantation is exceptionally high, which limits this procedure from becoming a practical solution for many individuals/patients suffering from hematologic malignancies or any other form of cancer [11]. Other methods and/or practices of treating bone marrow suppression/damage could include modern developments in chemotherapy, which is proven to be less damaging to non-cancerous cells or body parts. Nonetheless, using stem cell transplants could potentially lead to longevity in cancer patients' lives in remission, with less damage caused by cancer treatment.

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Authors

Krish Mishra is a junior at John T. Hoggard High School at Wilmington, North Carolina in USA. He is passionate about biology and medical sciences. He is looking for a future career in medicine to improve health of human society.

Advancements in Immunotherapies: A Comprehensive Review of Their Applications to Cancer Therapies By Pranav Janjanam

Abstract

Cancer is a leading cause of global health problems, and requires more effective and less onerous treatments than traditional approaches such as chemotherapy and radiation therapy. Immunotherapies are a relatively new form of treatment that hone in on the body's standard immune responses to fight against the cancer. This review discusses four prominent immunotherapeutic methods: Tumor Infiltrating Lymphocyte (TIL) therapy, Chimeric Antigen Receptor T-Cell (CAR-T) therapy, Cancer Vaccines, and Immune System Modulators. TIL therapy relies on extracting the T cells directly from the tumor, expanding them, and then reinfusing them to fight the tumor. Recent studies show the improved effectiveness when the cultured T cells are tethered with interleukin-12 to enhance its effectiveness and reduce side effects. CAR-T therapy consists of engineering T cells to recognize specific antigens on tumor cells. Studies are being done to expand the usage of CAR-T therapy to numerous types of cancers. Cancer vaccines provide a piece of tumor or a specific target found on the cancer to help educate the immune system and consequently elicit an immune response against that tumor . Innovations are being implemented to implant different cells to augment T cell response. Immune System Modulators aid in the immune response to different therapies and can be added to improve efficacy of each immunotherapy. This review explores the prominent immunotherapies in the field of immuno-oncology, current advancements to improve each immunotherapy, and specific studies related to each immunotherapy.

Introduction

Cancer is one of the leading health problems worldwide and results in approximately 10 million deaths each year (National Cancer Institute, 2019). It is defined as the uncontrolled growth and replication of cells in a specific part of the body. These replicated cells are dangerous because they can divide uncontrollably or prematurely, and they can also avoid detection by the immune system (Mayo Clinic, 2023). Because there are a greater number of cells, the body does not have sufficient resources to provide for all of these cells, and the specific organ fails due to lack of proficient cells. Cells become cancerous from gene mutations, which can be inherited, developed over time, or develop in response to dangerous external stimuli, such as X-rays, radiation, cigarette smoke, or alcohol (Mayo Clinic, 2023). The most common types of cancer are breast cancer (~300,000 new cases per year), prostate cancer (~288,000 new cases per year), and lung cancer (~238,000 new cases per year). In terms of mortality rates, lung and bronchus cancers have a 21% mortality rate, colon and rectal cancer has a 9% mortality rate, and pancreatic cancer has an 8% mortality rate (National Cancer Institute, 2019).

The current most effective cancer treatments include chemotherapy, radiation therapy, and surgery. Chemotherapy is the use of drugs and medication to destroy cancerous cells and keep more cancer cells from growing and dividing(National Cancer Institute, 2023). In most

cases, chemotherapy is effective; however, in specific cases, chemotherapy drugs can damage cells in other vital organs, weaken immune response, and have many dangerous side effects such as fatigue, nausea, and hair loss (National Cancer Institute, 2023). Radiation therapy uses radiation to kill cancer cells and tumors by damaging the DNA of the cells and preventing replication by causing early cell death (National Cancer Institute, 2023). This form of therapy is harmful because it has the potential to harm nearby healthy cells, and can cause immense fatigue or skin changes and irritation (National Cancer Institute, 2023). Finally, surgery can be used to remove the cancerous tumor from the body. This process has risks related to any surgical procedures, as well as the potential shedding of cancer cells into the circulatory system, which can result in the spread of the cancer into other parts of the body (National Cancer Institute, 2023).

Existing cancer treatments have many unintended side effects, which may alter patients' lives drastically. To combat this, new cancer treatments, called immunotherapies, are being developed. Immunotherapies harness the body's own immune response to target and destroy the cancerous tumors and cells in the body (Cleveland Clinic, 2023). This differs from traditional treatments in that it uses the body's own immune response to fight off the cancers, and in turn, it is seen as more natural and less harmful to the healthy parts of the body. This field is still in development, and many of the immunotherapies still have to be improved to be more effective and more widely used clinically. This review highlights several types of developing immunotherapies, including Chimeric Antigen Receptor (CAR) T- cells, Tumor Infiltrating Lymphocytes (TILs), cancer vaccines, and monoclonal antibodies. This review further discusses the unique characteristics, current applications, and future research directions for each therapy.

Tumor Infiltrating Lymphocytes

Tumor Infiltrating Lymphocyte (TIL) therapy is an immunotherapy that uses the patient's own T-cells to fight cancer.The TILs also enhance immune response by increasing the number of tumor-specific T-cells and have proved effective to many different cancers such as melanoma and cervical cancer (Jianjin et al., 2013).TILs are taken from the tumor microenvironment, however, there are limited numbers of T-cells, and not enough to fight the tumor effectively. To generate more T-cells, a tumor sample is removed from the patient through processes of surgery and needle biopsy (Jianjin et al., 2013). Next, the TILs are cultured in a solution containing human AB blood serum and growth factors, which result in the growth of the TILs (Fig. 1). The expanded TILs are infused back into the body where they recognize and target cancerous cells (Jianjin et al., 2013). They then recognize antigens expressed on the tumor surface and kill the tumor cells(Jianjin et al., 2013).

Figure 1: Schematic of how TIL works to fight against cancerous cells. MedMaven (2020).

TIL cell therapy has been an exciting area of research in cancer immunotherapy. Studies have focused on refining and enhancing TIL therapy to improve its efficacy and applicability. Researchers have explored various methods to expand TILs in the laboratory, optimize their tumor-targeting capabilities, and overcome tumor microenvironment challenges (National Institute of Health, 2023). Additionally, investigations into combining TIL therapy with other immunotherapies or treatment modalities have shown promising results. These include decreased mortality rates and decreased tumor progression in experiments, enhancing overall patient outcomes (National Institute of Health, 2023). These studies offer hope for more effective TIL therapies, providing cancer patients with new avenues for personalized, and potentially curative, treatment options (National Institute of Health, 2023).

Currently, researchers are studying ways to improve the efficacy of TIL therapy. A study by Liselotte Tas et al. (2023) aimed to improve the efficacy of TIL therapy to work in the presence of high systemic toxicities. The authors took tumor-specific T-cells and tethered them with an immune-activating cytokine, called interleukin-12 (IL-12), and observed the behavior of these T-cells when inserted back into mice (Tas et al, 2023). The study also addresses challenges in adoptive T cell therapies (ACTs) for solid tumors due to the suppressive tumor environment (Tas et al, 2023). IL-12, an immune-activating agent, has potential, but systemic use leads to toxicity (Tas et al, 2023). To achieve this goal, the authors created tethered T-cells and were successful in loading cytokines to the surfaces of these cells in a controlled and uniform manner (Tas et al, 2023).

To validate the cells, did experiments *in vitro*. The authors concluded that the data demonstrates that tethered cells improve function, cytotoxicity, and survival of tumor-specific human T-cells (Jones II et al., 2022). Next, they proceeded *in vivo* and validated that the efficacy of the IL-12-tethered T-cells were improved, and safely enhanced the efficacy of the T-cells (Jones II et al., 2022). Attempts to genetically engineer T-cells for controlled IL-12 production upon encountering tumors showed promise in animal models and clinical trials, but unregulated expression caused severe side effects and manufacturing complexities (Jones II et al., 2022).

The new method of attaching IL-12 to T-cells improves immune activation control and treatment efficacy. Jones *et al.* extracted clusters of differentiated T-cells from the spleens of mice and then tethered the cells to IL-12. The authors allowed the T-cells to combat the tumor and then analyzed the ability of the cells to fight against the tumor. They found that the tethered IL-12 reshaped the suppressive tumor microenvironment and triggered a repolarization of cells from myeloid-deprived cells to activate inflammatory cells (Jones II et al., 2022). As a result, the tethering support has promise for not just improving the efficacy of TIL therapy, but the IL-12 cells can also be thethered in other types of immunotherapies to improve their efficacies as well (Jones II et al., 2022).

Chimeric Antigen Receptor T-Cell

Chimeric Antigen Receptor T-Cell (CAR-T) therapy is the process by which the patient's T-cells are taken and modified with chimeric antigen receptors (CAR), which recognize cancerous cells (National Cancer Society, 2023). Next, the modified T-cells are reintroduced into the body and begin to attack cancerous cells (National Cancer Society, 2023). The modified cells now recognize the antigen on cancerous cells and initiate an immune response (Fig. 2) (National Cancer Society, 2023). This therapy has shown success in treating cases of lymphoblastic leukemia and certain types of lymphomas (National Cancer Society, 2023). CAR-T has provided long-term remission and improved survival rates for patients who had limited or no treatment options (National Cancer Society, 2023). However, CAR-T therapy has side effects, such as cytokine release syndrome (CRS) and neurologic toxicities (National Cancer Society, 2023). CRS is an immune response that can cause flu-like symptoms, fever, low blood pressure, and organ dysfunction (National Cancer Society, 2023). Neurologic toxicities affect the neural pathways and can lead to confusion, seizures, and other neurological problems (National Cancer Society, 2023). Ongoing research is being conducted to expand the use of CAR-T cell therapy, as well as to improve its safety and efficacy (National Cancer Society, 2023).

Figure 2: The process of CAR-T therapy in the body (Cancer Research UK, 2021)

The future of CAR-T therapy holds immense promise in revolutionizing cancer treatment. As researchers continue to delve into this groundbreaking immunotherapy approach, they are focused on addressing several key aspects. One area of future research involves enhancing the durability and persistence of CAR-T cells within the patient's body to ensure prolonged anti-tumor effects, as in some cases, the CAR-T cells degrade and quickly become ineffective (Mayo Clinic, 2022). Research is being done to implement more resistant membranes and protection so the cell does not degrade as quickly. Additionally, scientists are exploring novel strategies to overcome the challenges posed by the tumor microenvironment, enabling CAR-T cells to effectively target solid tumors (Mayo Clinic, 2022). Furthermore, efforts are being made to minimize potential side effects, such as nausea and headaches, and improve the safety profile of CAR-T therapy, ensuring its broader applicability across various cancer types (Mayo Clinic, 2022). As more clinical trials are conducted and data is gathered, the future research on CAR-T therapy is likely to expand its scope, optimize treatment protocols, and uncover new possibilities in the quest for more effective and personalized cancer therapies (Mayo Clinic, 2022).

A current study of CAR-T cell therapy shows how to make CAR-T therapy effective against castrate-resistant prostate cancer (Freiling et al., 2023). Advanced prostate cancer often becomes resistant to standard treatments, frequently leading to bone metastasis in up to 90% of cases. This bone metastatic castrate-resistant prostate cancer (mCRPC) not only results in

bone-related complications but also contributes to patient mortality (Freiling et al., 2023). Although nitrogen-containing bisphosphonates (nBPs), like ZOL, are administered to address bone mCRPC by targeting bone-resorbing cells, they do not significantly improve overall survival (Freiling et al., 2023). Immunotherapy, such as checkpoint inhibitors, have demonstrated limited success due to the low immunogenicity of cancer cells (Freiling et al., 2023). In this context, researchers are investigating the potential of γδ T-cells, a subset of T-cells, as a platform for CAR-T therapy. These γδ T-cells possess enhanced cytotoxic abilities and can identify phosphoantigens such as isopentenyl pyrophosphate (IPP), which accumulate in the bone-cancer environment after ZOL treatment. Prostate stem cell antigen (PSCA) is identified as a suitable target antigen due to its high expression in prostate cancer cells, especially those in bone metastasis (Freiling et al., 2023). Engineered γδ T-cells with anti-PSCA CAR exhibit remarkable efficacy against bone mCRPC cells, especially when combined with ZOL (Freiling et al., 2023). This combined approach displays minimal adverse effects in mice and effectively reduces cancer-related bone complications. The study indicates that γδ T-cell based CAR therapy, complemented by ZOL, holds promise for combating bone metastatic prostate tumors, offering potential advancement in treating advanced prostate cancer (Freiling et al., 2023).

Cancer Vaccines

Cancer vaccines are a group of immunotherapies that aim to stimulate the immune system to recognize and destroy cancer cells (National Cancer Institute, 2023; Fig. 3). Cancer vaccines work in a similar way to regular vaccines, where the vaccine introduces a small amount of the cancer into the body to prime the body to fight against the cancer (National Cancer Institute, 2023; Fig. 3). There are two primary types of cancer vaccines: preventive vaccines and therapeutic vaccines. Preventive vaccines target types of viruses that cause cancer (American Cancer Society, 2023). An example of a preventive vaccine is the human papillomavirus (HPV) vaccine, which helps prevent cervical, anal, and other HPV-related cancers (American Cancer Society, 2023). In contrast, therapeutic vaccines treat existing cancer by training the immune system to recognize and attack cancer cells (American Cancer Society, 2023). The vaccines stimulate the immune system to recognize the antigens as foreign and mount an immune response against them (Fig. 3) (American Cancer Society, 2023). Cancer vaccines work by introducing specific antigens or genetic material from cancer cells into the body (American Cancer Society, 2023). This material can be derived from cancer cells themselves or from cancer-related viruses or proteins. To improve the effectiveness of the vaccines, additional materials, called adjuvants, are added to help recruit and stimulate immune cells (American Cancer Society, 2023). Cancer vaccines involve extensive preclinical and clinical testing to ensure safety and efficacy, and research is ongoing for their development and improvement

(American Cancer Society, 2023).

Figure 3: The implementation of a cancer vaccine in fighting against cancerous cells.
(UCIR, 2020)

Researchers are actively investigating the potential of cancer vaccines as an innovative approach to combating various types of cancer. These vaccines can be tailored to target specific tumor antigens, such as neoepitopes resulting from tumor mutations, or even whole-tumor extracts. The goal is to provoke a robust immune response, enabling the body to identify and destroy cancer cells more effectively. Despite challenges and previous limitations in clinical settings, recent advancements show promise. For instance, studies involving vaccines prepared from oxidized tumor lysates and dendritic cells have demonstrated improved T cell responses and potential efficacy in preclinical models and patient trials. Through the use of oxidized tumor lysates, there have been improvements in the prioritization of tumor-rejecting neoepitopes, which are peptides which track tumors and elicit immune response on the tumors, and result in more efficacious vaccines (Fritah et al., 2023). Combining cancer vaccines with other immunomodulatory treatments, such as immune checkpoint inhibitors, holds potential for enhancing the immune response against cancer and improving patient outcomes. By making use of multiple different types of immunotherapies, the cancerous tumor can be negated quicker and more effectively, with less risk of spreading of the tumor and damage being done to the body. (Mayo Clinic, 2022).

The current standard treatment for advanced epithelial ovarian cancer involves surgery and chemotherapy, but resistance to chemotherapy is common and often results in cancer recurrence. Ovarian cancers express various tumor-associated antigens and some show infiltration of tumor-infiltrating lymphocytes, which are linked to better survival. Immunotherapy has potential, but initial results with immune checkpoint inhibitors have been

modest. Challenges to immunotherapy in ovarian cancer include tumor-specific T cells struggling to reach tumors due to factors like vascular endothelial growth factor A (VEGF-A), which blocks T cell entry. Cancer vaccines that trigger T cell responses have potential but have not fully succeeded due to using single antigens. Using multiple tumor-specific antigens like neoepitopes resulting from tumor mutations or whole-tumor extracts shows promise. A vaccine with oxidized lysate-pulsed dendritic cells (DCs) demonstrated success in priming T cell responses in preclinical ovarian cancer models and patient trials. Other barriers include immune tolerance by regulatory T cells and immunosuppressive molecules. Combination immunomodulatory treatments are needed to overcome these barriers. The article advances clinical development by combining the DC-based vaccine with VEGF-A blocking antibody bevacizumab and low-dose cyclophosphamide, commonly used in ovarian cancer patients. The combination proved safe, feasible, and well-tolerated, generating antitumor immunity and improved survival. The vaccination approach also prompted new T cell responses against private tumor neoepitopes (Tanvi et al., 2018).

Immune System Modulators

Immune system modulators are a class of drugs used in immunotherapy to enhance the immune system response against cancer. These modulators work by targeting specific components of the immune system to regulate or stimulate its activity, and they work on many different areas relating to the body, such as immune cells, cytokines, or signaling pathways involved in immune response regulation. These immune modulators can be used either as monotherapy or in combination with other treatments, such as chemotherapy or other targeted immunotherapies. Through their minimal use in the medical field, they have shown success in treating various cancers, but contain many different types of side effects which vary depending on the type of drug administered. For instance, when administered with the thalidomide drug, patients have been seen to commonly face different types of side effects similar to flu symptoms, which include fever, chills, weakness in the muscles, and headache (National Cancer Institute). Ongoing research on immune system modulators are targeted to focus on the optimization of the use of these modulators, exploring new targets in tumors, and finding combinations with other treatments, such as CAR-T or TIL therapies. Research is also being done in specific cases with personalized approaches. These cases identify specific biomarkers or genetic factors in the body's cells to predict response to immune system modulators. This eventually results in risk reduction of using these modulators(National Cancer Institute).

In the field of cancer treatment, researchers are intensifying efforts to enhance immunomodulators, substances pivotal for either stimulating or curbing immune responses. Innovations aim to revolutionize therapeutic approaches for more effective and precise outcomes. One avenue involves advanced genetic editing, like CRISPR-Cas9, to engineer immune cells for heightened tumor-targeting capabilities and potent antitumor responses, minimizing damage to healthy tissues. Through the use of genetic editing, immunomodulators' signal receiving organelles and processes can be heightened, resulting in higher efficacy to fight

cancerous tumors. Personalized medicine is also key, tailoring immunomodulatory treatments based on individual patient genetics, immune profiles, and cancer attributes to optimize efficacy and minimize side effects. Another interesting use is the application of nanotechnology in improving tumors. Nanotechnology plays a role by encapsulating immunomodulators within nanoparticles, ensuring controlled release and targeted distribution for improved impact on tumors (Zhang et al., 2021).

Currently, many solid cancers contain many different types of dysfunctional immune microenvironments. In order to overcome these immunosuppressive microenvironments and fight the cancer, researchers make use of immune system modulators to initiate responses to the cancer. To do this, researchers made use of functional mRNA and injected these into mice. The mRNA enters the cells and translates into cytokines, which produce anticancer responses in a wide range of tumor microenvironments. The synthesis of the cytokines resulted in regression of established tumors in the mice. Along with that, general inflammatory response and increased activation of the immune response throughout the body was shown through the mRNA treatments. Further,intratumoral delivery through injection proved more effective than other local routes of inhibition. As a result of the improved efficacy, the tumor was shown to decrease at distal sites. Treatment with the mRNA induced cytokine and chemokine expression and resulted in more production of dendritic and T cells (Hewitt et al., 2019).

Conclusion

This research underscores the transformative potential of immunotherapies in reshaping cancer treatment. Tumor Infiltrating Lymphocyte therapy (TIL) emerges as a promising approach, utilizing techniques like interleukin-12-tethered T cells to enhance efficacy while reducing potential toxicities. The success of Chimeric Antigen Receptor T-cell (CAR-T) in specific cancers is evident, with ongoing studies focusing on fortifying its durability, effectiveness, and safety. Cancer vaccines, encompassing both preventive and therapeutic strategies, offer a dual mechanism for engaging the immune system against cancer. Combining these vaccines with other treatments, like immune checkpoint inhibitors, showcases potential synergies for bolstering immune responses and improving tumor control. Immune System Modulators, targeting crucial immune components, present a dynamic approach to cancer therapy. Advances such as CRISPR-Cas9-mediated genetic editing hold promise for enhancing the tumor-targeting abilities of immune cells, while personalized medicine tailors treatments to individual patient profiles. The integration of nanotechnology for precise immunomodulator delivery underscores their potential for refined therapeutic outcomes. This research highlights evolving strategies to address challenges within the tumor microenvironment, as seen with functional mRNA inducing robust immune responses. These insights underscore ongoing progress in harnessing the immune system's potential to combat cancer, offering more effective, targeted, and tailored treatment options.

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Prediction of Heart Failure Using Random Forest and XG Boost By Aidan Gao

Author Biography

Aidan Gao is a sophomore attending The Westminster Schools in Atlanta, Georgia. He is interested in the uses of computer science and machine learning in the medical realm. He hopes to study computational medicine in the future.

Abstract

Heart Failure (HF), a type of Cardiovascular Disease (CVD), is a prevalent illness that can lead to hazardous situations. Each year, approximately 17.9 million patients globally die of this disease. It is challenging for heart specialists and surgeons to predict heart failure accurately and on time. Fortunately, there are classification and prediction models available that can assist the medical field in efficiently using medical data. The objective of this study is to enhance the accuracy of heart failure prediction by prediction modeling a Kaggle dataset composed of five sets of data over 11 patient attributes. Multiple machine learning approaches were utilized to understand the data and forecast the likelihood of heart failure in a medical database. The results and comparisons show a definite increase in the accuracy score of predicting heart failure. Integrating this model into medical systems would prove beneficial for aiding doctors predictions of heart disease in patients

Keywords*: machine learning, heart failure, diagnosis, prediction modeling, binary classification, random forest, XGBoost, cardiovascular disease*

Introduction

The primary cause of heart stroke is the obstruction of arteries, also known as cardiovascular disease or arterial hypertension **World Health Organization (n.d.)**. Heart disease affects approximately 26 million people worldwide, and this number is expected to rise rapidly if effective measures are not taken **(Savarese & Lund, 2017)**. Unhealthy food, tobacco, excessive sugar, and obesity are common contributors to heart disease **(Benjamin et al., 2019)**. Pain in the arms and chest are common symptoms, but the disease often presents with different symptoms based on sex and age. In addition to maintaining a healthy lifestyle and diet, timely diagnosis and comprehensive analysis are critical factors in identifying heart disease. However, many patients undergo multiple tests that can be physically and financially burdensome. Proper analysis of this type of data can improve the diagnosis process and assist heart surgeons. Previous research has used various techniques such as Random Forest, Support Vector Machine, and other AI classification models **(Alotaibi, 2019)**. This study aims to surpass previous studies' random forest model accuracy in order to better predict heart failure before it manifests.

Literature Review

Previous work has utilized a subset of the dataset used in this paper to predict heart failure. The University of California Irvine (UCI) used Decision Tree, Logistic Regression, Random Forest, Naïve Bayes, and SVM reaching results around the ~85% accuracy mark. Through the use of tenfold cross validation and an enlarged dataset, previous studies have enhanced the accuracy of the UCI models (see Table. 1) **(Alotaibi, 2019)**.

Table 1. Performance Comparison

Model	Alotaibi (Alotaibi, 2019)	UCI, 2019 (Bashir et al., 2019)	UCI, 2017 (Ekiz and Erdogmus, 2017)	UCI, 2017 (Ekiz and Erdogmus, 2017)
Decision Tree	93.19%	82.22%	60.9%	67.7%
Logistic Regression	87.36%	82.56%	65.3%	67.3%
Random Forest	89.14%	84.17%	X	X
Naïve Bayes	87.27%	84.24%	X	X
SVM	92.30%	84.85%	67%	63.9%

Data overview

The dataset utilized in this paper is collected from Kaggle under the name "Heart Failure Prediction Dataset" **(Ortega, 2021)**. The dataset combines five datasets with over 11 common attributes. These five datasets combine data from Cleveland, Hungarian, Switzerland, Long Beach VA, and Stalog datasets. In total, the dataset contains 918 rows. Row definitions are provided below:

1. Age: age of the patient [years]
2. Sex: sex of the patient [M: Male, F: Female]
3. ChestPainType: chest pain type [TA: Typical Angina, ATA: Atypical Angina, NAP: Non-Anginal Pain, ASY: Asymptomatic]
4. RestingBP: resting blood pressure [mm Hg]
5. Cholesterol: serum cholesterol [mm/dl]
6. FastingBS: fasting blood sugar [1: if FastingBS > 120 mg/dl, 0: otherwise]
7. RestingECG: resting electrocardiogram results [Normal: Normal, ST: having ST-T wave abnormality (T wave inversions and/or ST elevation or depression of > 0.05 mV), LVH: showing probable or definite left ventricular hypertrophy by Estes' criteria]
8. MaxHR: maximum heart rate achieved [Numeric value between 60 and 202]

9. ExerciseAngina: exercise-induced angina [Y: Yes, N: No]
10. Oldpeak: oldpeak = ST [Numeric value measured in depression]
11. ST_Slope: the slope of the peak exercise ST segment [Up: upsloping, Flat: flat, Down: downsloping]
12. HeartDisease: output class [1: heart disease, 0: Normal]

Methods

Data Preprocessing

Before putting the data into the model, data preprocessing methods are applied in order to make it useful for modeling **(Al-Mudimigh et al., 2009)**. Binary values, such as *sex*, were converted to binary numbers (*1* and *0*). *ExerciseAngina* was converted to binary as well. One hot encoding was employed in *ChestPainType*. The ordinal encoder from SKLearn was employed in the ordinal variables, *ST_Slope* and *RestingECG*.

This research focuses on two models to predict heart disease: Random Forest and XG Boost. Random Forest was implemented with the goal to surpass previous research accuracy with its cross-validation score. XGBoost was also implemented as a popular model among many Kaggle dataset winners. Both models were cross-validated ten times across an 80-20 split of training and test data, respectively. In order to further increase accuracy, HyperOPT **(Komer et al., 2019)** and RandomizedSearch **(Agrawal, 2021)** were used to finetune the hyperparameters for XGBoost and Random Forest, respectively.

Random Forest

The Random Forest algorithm is utilized to address classification issues. Its approach is based on ensemble learning, which combines multiple classifiers to enhance the algorithm's performance. The algorithm is composed of several Decision Trees classifiers to create a forest **(Donges, 2018)**, each working on a subset of data, and the average is calculated to improve prediction accuracy. Rather than relying on the prediction of a single tree, the Random Forest algorithm combines the trees using an estimated outcome and voting procedure **(Bashar et al., 2019)**. The model then considers predictions from each tree and determines the outcome based on majority voting.

XGBoost

XGBoost, which stands for "Extreme Gradient Boosting," is a popular machine learning model that has been used for a variety of tasks such as regression, classification, and ranking. XGBoost creates a model in the form of boosting an ensemble of weak classification trees by gradient descent which provides optimization to the loss factor **(Cui et al., 2017)**. It is an ensemble learning algorithm that combines multiple decision tree models to improve the accuracy and robustness of predictions. XGBoost has gained popularity due to its speed, scalability, and performance. It uses a gradient-boosting framework and can handle missing values, regularization, and parallel processing. Additionally, it has various hyperparameters that

can be tuned to achieve better performance. Overall, XGBoost is a powerful machine learning model that is widely used in industry and academia.

Results

When looking at binary classification problems, there are four relevant metrics: true positives, true negatives, false positives, and false negatives. Out of these four metrics, the most harmful to prediction would be false negatives, or results that report no risk of heart failure despite the patient being at risk. The goal of this research was to reduce the number of false negatives and false positives in order to improve accuracy in predicting heart disease. Using these models and methods, the result was 91.56% accuracy after cross validation for XGBoost, with 9 false negative cases out of 181 cases (see Fig. 1). In Random Forest, there was 92.90% accuracy after cross validation with 6 false negatives out of 181 cases (see Fig. 2). In comparison to Alotaibi (2019), Random Forest performed considerably better, increasing from 89.14 to 92.90% accuracy. The accuracy increase may be due to the hyperparameter tuning for Random Forest or the cross-validation method. Also taken into consideration is the artificial addition of rows. In Alotaibi (2019), the size of the Cleveland data was too low to implement machine learning approaches. Alotaibi increased the size of the data artificially by randomizing values between minimums and maximums. The issue with randomizing these values is that there is no way to tell whether the target value is right for the artificial patient, thus creating noisy data that is useless for the model. This causes much of the data to carry either a random target value or no target value, which would cause the accuracy of the model to go down[159].

Another metric used in binary classification problems is the ROC curve, or the area under the receiver operating characteristic, a common metric for evaluating binary classification models. A model with a higher AUC is thought of as a better model **(Javeed et al., 2019)**. This value was 0.92 for XGBoost and Random Forest. Both models performed well in terms of accuracy and the area under the ROC curve, indicating their effectiveness in predicting heart disease.

Fig. 1. Confusion Matrix of XGBoost Model

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[159] This may not be the case, but there is no evidence in the paper or the references to explain the choice made by Alotaibi (2019).

Fig. 2. ROC_AUC Plot of XGBoost

Fig. 3. Confusion Matrix of Random Forest Model

Fig. 4. ROC_AUC Plot of Random Forest Model

Table 2. Performance Comparison

Model	This Study	Alotaibi (Alotaibi, 2019)	UCI, 2019 (Bashir et al., 2019)	UCI, 2017 (Ekiz and Erdogmus, 2017)	UCI, 2017 (Ekiz and Erdogmus, 2017)
Decision Tree	X	93.19%	82.22%	60.9%	67.7%
Logistic Regression	X	87.36%	82.56%	65.3%	67.3%
Random Forest	92.90%	89.14%	84.17%	X	X
Naïve Bayes	X	87.27%	84.24%	X	X
SVM	X	92.30%	84.85%	67%	63.9%
XGBoost	91.56%	X	X	X	X

Discussion

The results of this research reveal the potential use of machine learning in the landscape of cardiovascular healthcare. The degree of accuracy achieved by the current models opens up a pathway for research that may dramatically impact the diagnosis of heart disease. If integrated into medical information systems, these models could facilitate the collection and analysis of live data from patients, allowing doctors to make predictions in real-time. Hypothetically, machine learning models could form a network. Accessible to healthcare providers across the world, such a system could flag patients the models decide show significant risk of heart disease, prompting immediate intervention and follow-up. This would have a profound effect on the field of heart disease management, further shifting it from a reactive to a proactive field. Moreover, the system could be used in more rural, underserviced, areas where traditional diagnostic resources are unavailable.

This study helps to revolutionize early detection methods for heart disease, which in turn, significantly impacts patient outcomes. When applied on a larger scale, this approach could reduce mortality rates and enhance quality of life in patients diagnosed with this condition.

Limitations and Further Work

These models are trained on historical data and their predictions are based on patient data patterns exhibited in past cases. However, upon application on a larger scale, much more patient data could be collected, training the model to keep up with modern times. One limitation of this

study is that the dataset utilized to model was relatively small. Therefore, the dataset may not be able to accurately mirror large populations, a significant limitation for a model meant to be used at the population level. To increase the accuracy and reliability of these models, future research should aim to expand the dataset in not just rows but also columns. With the addition of more lifestyle variable columns, the model's accuracy is likely to rise. Future studies should explore handling outlier cases that do not align with patterns in historical data. This could involve using hybrid models that incorporate machine learning with other predictive tools. With further development, these models could potentially bring the rise of a new era of predictive healthcare in cardiology.

Conclusion

Heart failure is a significant health issue that affects millions of people worldwide. Machine learning models, specifically Random Forest and XGBoost, can be used to accurately predict heart failure based on medical data. These models can be integrated with medical information systems to improve the accuracy of predictions and assist healthcare providers in detecting heart disease early.

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Machine Learning and Artificial Intelligence Approaches for Diagnosis of Cardiac diseases in Fetal and Pediatric Patients By Aisha Nurakhmet

Abstract

Diagnosing heart problems in infants is challenging as their symptoms may be complex and varied. Detecting cardiac issues early and accurately is crucial for effective treatment and outcomes. This research explores how machine learning and artificial intelligence can help healthcare providers diagnose heart diseases in fetal and pediatric patients. In this study, a literature review was performed to classify the literature on how AI/ML analyzes various types of data, including fetal echocardiograms (ultrasound of the heart in infants still in the womb), MRI of the heart in children, and electronic medical records of children with confirmed heart problems. Utilizing a range of ML/AI algorithms, including recurrent neural networks (RNNs), random forests, and gradient boosting machines, critical indicators were identified to categorize patients into distinct heart disease groups. The study evaluated the performance of the model using indicators such as sensitivity, specificity, and AUC-ROC (a measure of model accuracy). Using ML/AI to diagnose heart disease in fetal and pediatric patients has the opportunity to improve outcomes. The models can detect intricate patterns in medical images and clinical information, leading to more precise and timely diagnosis. This integration of ML/AI in healthcare has the potential to transform how young patients with heart issues are cared for, allowing for early treatments and personalized plans to improve their health and quality of life. However, before fully these technologies can be fully utilized, more research on larger datasets from a diversity of health centers is needed. Medical experts, data scientists, and healthcare regulators must work together to ensure safe and responsible implementation in this special area of medicine.

Introduction

Cardiac diseases are an 8th leading cause of morbidity and mortality worldwide, affecting both fetal and pediatric populations (Current Causes of Death in Children and Adolescents in the United States | NEJM). Early and accurate diagnosis of these conditions is crucial for timely intervention and improved patient outcomes. In recent years, machine learning (ML) and artificial intelligence (AI) techniques have emerged as promising tools for the diagnosis of cardiac diseases in fetal and pediatric patients (Frontiers | Cardiovascular Diseases Prediction by Machine Learning Incorporation with Deep Learning; The Primary Use of Artificial Intelligence in Cardiovascular Diseases: What Kind of Potential Role Does Artificial Intelligence Play in Future Medicine? - PMC; Uzun Ozsahin et al.). This research paper aims to explore the various ML and AI approaches employed in the diagnosis of cardiac diseases in these populations, focusing on their effectiveness, challenges, and prospects.

Congenital heart defects (CHD) are the most common congenital anomaly, occurring in approximately 1% of live births. The majority of CHD can be diagnosed during prenatal life by fetal echocardiography, which has been utilized to detect CHD *in utero* since 1980. Advances in

ultrasound technology have led to improved prenatal and perinatal management and prognostication of both simple and complex CHD (Sun). In pediatric patients, AI technologies have been applied in cardiovascular medicine, including precision medicine, clinical prediction, cardiac imaging analysis, and intelligent robots (The Primary Use of Artificial Intelligence in Cardiovascular Diseases: What Kind of Potential Role Does Artificial Intelligence Play in Future Medicine? - PMC).

Various ML techniques have been employed in the diagnosis of cardiac diseases, such as logistic regression, random forest, and naive Bayes algorithms. These techniques have demonstrated a high accuracy in predicting heart disease using data from the UCI machine learning repository (Diagnosis of Chronic Ischemic Heart Disease Using Machine Learning Techniques - PMC). Additionally, AI and ML have been used to examine genes within DNA, which can help clinicians predict cardiovascular diseases, such as atrial fibrillation and heart failure (HealthITAnalytics).The integration of AI and ML in cardiac disease diagnosis has shown promising results, with each new study bringing great knowledge towards diagnosing patients with more accurate and efficient tools (Uzun Ozsahin et al.). However, challenges remain in processing numerous datasets which may not be standardized and ensuring the generalizability of approaches across different populations and healthcare settings (Ahsan and Siddique). Despite these challenges, the future of diagnostic AI and ML in the field of cardiac disease appears promising, with the potential to revolutionize the way healthcare providers diagnose and treat fetal and pediatric cardiac disease (Uzun Ozsahin et al.; Frontiers | Cardiovascular Diseases Prediction by Machine Learning Incorporation with Deep Learning; The Primary Use of Artificial Intelligence in Cardiovascular Diseases: What Kind of Potential Role Does Artificial Intelligence Play in Future Medicine? - PMC).

1.1 Background on Machine Learning

Machine learning (ML) and artificial intelligence (AI) are two interrelated fields that have transformed numerous industries. As a subset of AI that focuses on developing algorithms and models, machine learning enables computers to improve and make predictions or decisions based on collected data without being explicitly programmed ("Machine Learning"). These algorithms are often derived from probability theory and linear algebra, enabling computers to automatically solve predictive tasks. Deep learning, a subset of machine learning, relies on multilayered neural networks to solve complex tasks (Harness).

Artificial neural networks (ANNs) are composed of node layers, containing an input layer, one or more hidden layers, and an output layer. Each node, or artificial neuron, connects to another and has an associated weight and threshold. If the output of any individual node is above the specified threshold value, that node is activated, sending data to the next layer of the network. Otherwise, no data is passed along to the next layer of the network.(What Are Neural Networks?)

Artificial intelligence is a broader field that encompasses machine learning and other techniques, such as natural language processing, computer vision, and robotic process

automation (A Complete Introduction to AI and Machine Learning). AI systems are designed to perform complex tasks in a way that simulates human behavior or thinking, and they can be trained to solve specific problems (Top 18 Artificial Intelligence (AI) Applications in 2023 | Simplilearn 18). (SITNFlash; What Is the History of Artificial Intelligence (AI)? | Tableau) AI and ML have relevant applications in numerous industries, including healthcare, finance, marketing, and transportation (9 Applications of Machine Learning from Day-to-Day Life | by Daffodil Software | App Affairs | Medium; 24 Top Machine Learning Applications & Examples for 2023 | Built In).

1.2 **ML/AI algorithms such as Recurrent neural networks (RNNS), Random Forests, and Gradient-Boosting Machines**

Fig 1: Describing relationship between concepts: Deep Learning, Machine Learning, Artificial Intelligence. (Day et al.)

The concept of artificial intelligence includes the concept of machine learning, and when taken a level deeper – Deep Learning, which comprises conventional neural networks, recurrent neural networks, and other algorithms. Artificial intelligence is the most generalized, with divisions by categories already inside of it. Machine learning is a type of artificial intelligence, but not vice versa. Examples of Machine Learning techniques includeRandom forests, Support vector machines, Logistic regression, and other algorithms. Deep Learning techniques include Convolutional neural networks, Recurrent neural networks, and other algorithms.

2.1 Importance of Early and Accurate Diagnosis

Early detection offers the best chance for early treatment and intervention, which can prevent adverse events. Often, once symptoms have already occurred, treatment may be too late. Early detection can help prevent the disease from progressing to an untreatable stage (MD).Early detection is crucial in situations where there is a family history of certain diseases, significant suspicion of serious disease, clear symptoms pointing to a cause of concern, or routine blood tests suggesting there may be an underlying problem. Early detection allows doctors to design an effective treatment plan that can prevent the progression of the disease or at least manage it effectively (ARE EARLY DETECTION AND TREATMENT ALWAYS BEST?).

Aspect	Benefits	Risks
Emotional and Social Benefits	- Reduces maternal anxiety("Why Get Checked?") - Provides an explanation for symptoms(*Alzheimer's Disease – Why We Need Early Diagnosis - PMC*) - Allows patients and families to maximize time together and access resources and support programs("Why Get Checked?")	- May affect privacy and confidentiality in relation to employment, driving license, insurance premiums, and financial management(*Alzheimer's Disease – Why We Need Early Diagnosis - PMC*)
Health Outcomes	- Increases chances of positive health outcomes(Balogh et al.) - Allows for tailored clinical decision-making(Balogh et al.) - Some conditions can be cured if caught early (e.g., congenital heart defects)(MD)	- Delayed diagnosis can cause irreversible harm(*Preventing and Treating Birth Defects*) - Preventable complications can arise from a delay in treatment(*Preventing and Treating Birth Defects*) - Infections that go undiagnosed could spread to vital organs, causing irreparable damage(*Preventing and Treating Birth Defects*)

Diagnostic Process	- Early diagnosis begins with a medical history and involves using neuroimaging, standardized neurological, and standardized motor assessments(Gembruch et al.)	- Delayed diagnosis is more common, costly, and harmful than any other patient safety threat(Kashyap et al.)
Cost Savings	- Early diagnosis saves costs of medical and long-term care for both families and the U.S. government("Why Get Checked?")	- Reducing delayed diagnosis in contemporary medicine comes with a risk of overdiagnosis, which can lead to severe harm due to unnecessary treatment or unnecessary diagnostic tests(Kashyap et al.)

Table 1: Benefits and Risks for different aspects of Early diagnosis.

2.2 How Heart Diseases are Diagnosed in Patients

Modern technologies allow people to diagnose heart diseases by different methods. These methods differ in their effectiveness. The table below shows the most used diagnostic tools for cardiovascular diseases:

Test Name	Description	Development Stage

Echocardiogram	A specialized ultrasound test performed during pregnancy to evaluate the position, size, structure, function, and rhythm of the unborn baby's heart. It is used to look for any major problems with the developing baby's heart walls and valves, the blood vessels leading to and from the heart, and the heart's pumping strength(*Cost-Effectiveness of Prenatal Screening Strategies for Congenital Heart Disease - PMC*; *Diagnostic Accuracy of Fetal Echocardiography in Congenital Heart Disease - ScienceDirect*; *Diagnostic Value of Fetal Echocardiography for Congenital Heart Disease - PMC*)	After the birth (the baby should be over 3 kg) and before the birth (intrauterine)
MRI of the Heart	A non-invasive imaging procedure that uses magnetic technology to create detailed images of the heart. It provides high-resolution images of the moving heart and blood vessels, so doctors can see how the heart looks and functions. It is used to diagnose and even treat congenital heart disease(*Cardiovascular Magnetic Resonance: Diagnostic Utility and Specific Considerations in the Pediatric Population - PMC*; *Compact Pediatric Cardiac Magnetic Resonance Imaging Protocols | SpringerLink*; Puricelli et al.)	Intrauterine (before the birth)
Electronic Medical Records	Electronic medical records (EMRs) contain clinical information, such as doctor visit notes, lists of medications, and test results. EMRs can be used to screen for critical congenital heart disease in newborns(*Do Electronic Medical Records Improve Quality of Care? - PMC*; *Improved Diagnostics & Patient Outcomes | HealthIT.Gov*; Kao et al.)	Any stage

Electrocardiogram (ECG or EKG)	An ECG records the electrical signals in the heart. It's a common and painless test used to quickly detect heart problems and monitor the heart's health. An ECG can detect irregular heartbeats, heart attacks, and heart damage or failure[34,35]	After the birth
Cardiac Catheterization	A procedure in which a thin, flexible tube (catheter) is guided through a blood vessel to the heart to diagnose or treat certain heart conditions, such as clogged arteries or irregular heartbeats. It gives doctors important information about the heart muscle, heart valves, and blood vessels in the heart. It is commonly used to assess the presence and severity of coronary artery disease, heart valve problems, heart muscle dysfunction, and congenital heart disease[36–38]	After the birth (strictly according to indications)
Chest X-rays	A chest X-ray is a quick and painless imaging test that produces pictures of the structures inside your chest, such as your heart, lungs, and blood vessels. It can be used to diagnose heart problems, such as heart failure	After the birth
Genetic Testing	Genetic testing can be used to identify inherited heart conditions, such as hypertrophic cardiomyopathy, long QT syndrome, and familial hypercholesterolemia. It involves analyzing a sample of blood or saliva for changes or mutations in genes that may be associated with heart disease	Any stage

Table 2: Technologies used to diagnose heart diseases with the description for each.

Fetal Diagnostic

A fetal echocardiogram is a very common procedure. It includes the use of specialized ultrasound tests performed during pregnancy to evaluate the unborn baby's heart. Such as the position, size, structure, function, and rhythm. This technology is designed to look at and identify problems with the walls and valves of the heart, as well as the blood vessels leading to and from the heart, and the pumping power of the unborn babies' heart.

MRI of the heart is a common hospital procedure. It is a non-invasive imaging procedure that uses magnetic technology to create detailed images of the heart. It provides a high-resolution image of the moving heart and blood vessels so that doctors can see how the heart looks and functions. It is used to diagnose and even treat congenital heart defects. This practice uses magnetic technology to fully visualize and create accurate images of a child's heart. This technology provides doctors with high-resolution visualization of the working heart and blood vessels. This procedure enables doctors to see how the heart of the observed person looks and functions.

Electronic Medical Records are electronic medical information about patients, organized into categories. These categories include records of doctors' visits, medications, and test results. This information can help identify critical congenital heart defects in newborns.

Electrocardiogram (ECG or EKG) uses the registration of electrical signals in the heart. This procedure is used to quickly identify heart problems and monitor their health. This technology detects cardiac arrhythmia, heart attacks, as well as heart damage or heart failure.

Catheterization is often performed to diagnose and treat heart diseases, such as blocked arteries or irregular heartbeat. During this procedure, the catheter is pushed through a blood vessel. This procedure provides significant information about the heart, including details about the heart muscle, heart valves, and blood vessels in the patient's heart. Moreover, catheterization is mainly used to assess the presence and severity of coronary heart disease, heart valve problems, cardiac muscle dysfunction, and congenital heart defects.

A chest X-ray is a quick and painless imaging procedure that captures images of structures inside your chest, such as the heart, lungs, and blood vessels. It can be used to diagnose heart problems, such as heart failure by providing visual images of structures (heart, lungs, blood vessels) in the patient's chest.

Genetic Testing includes analysis of a blood or saliva sample for changes or mutations in genes that may be associated with various heart diseases. Genetic testing can be used to detect hereditary heart diseases, such as hypertrophic cardiomyopathy, long QT syndrome, and familial hypercholesterolemia. Genetic testing is often done if something wrong on ultrasound or if the mother has a family history of genetic disorders.

3 How ML Can be Used to Diagnose Heart Diseases

Reference	Diagnosed diseases	Technique used	Machine learning method

Nurmaini et al. (Nurmaini et al.)	Congenital Heart Diseases	Fetal Echocardiography	Deep Learning
Pardasani et al. (Pardasani et al.)	Respiratory Distress Severity	Not specified	Machine Learning and Deep Learning
Ambale-Venkatesh et al. (Ambale-Venkatesh et al.)	Cardiovascular Events	Population Studies	Random Survival Forests
Kheradvar et al. (Kheradvar et al.)	Cardiac Function and Treatment	Cardiac Imaging	AI
Arafati et al. (Arafati et al.)	Congenital Heart Disease	Cardiac MRI	Artificial Intelligence and Deep Learning
Zhang et al. (Zhang et al.)	Heart Failure	Electronic Health Records	BERT-style Transformer-based Language Model
Rescinito et al. (Rescinito et al.)	Intrauterine Growth Restriction	Pregnancy Screening	Artificial Intelligence and Machine Learning
Perens et al. (Perens et al.)	Congenital Heart Disease	MRI and CT Scans	3D Printing
England et al. (England and Cheng)	Medical Image Analysis	Not specified	AI

Table 3: Examples of other research papers. Study of AI and ML methods, techniques in diagnostics of different congenital diseases.

Fig 2: How fetal echocardiogram data (1) might be incorporated into a neural network can be seen in Figure 2. (2), and how the network is composed of multiple perceptrons (3) bias, weight, input data, prediction (Day et al.).

3.1 **Performance of the model using indicators such as sensitivity, specificity and AUC-ROC (a measure of model accuracy).**

Performance indicators such as sensitivity, specificity, and AUC-ROC (Area Under the Receiver Operating Characteristic Curve) are essential for evaluating the performance of machine learning models in medical research. Sensitivity, also known as the true positive rate, measures the proportion of actual positive cases that are correctly identified by the model. Specificity, or the true negative rate, measures the proportion of actual negative cases that are correctly identified (Receiver Operating Characteristic (ROC) Curve Analysis for Medical Diagnostic Test Evaluation - PMC). The ROC curve is a graphical representation that plots sensitivity against (1-specificity) for all possible threshold values(Time-Dependent ROC Curve Analysis in Medical Research: Current Methods and Applications | BMC Medical Research Methodology | Full Text). The area under the ROC curve (AUC) is a combined measure of sensitivity and specificity, which describes the inherent validity of diagnostic tests (Receiver Operating Characteristic (ROC) Curve Analysis for Medical Diagnostic Test Evaluation - PMC). A higher AUC value indicates better model performance in distinguishing between classes, such

as predicting the presence or absence of a disease(Understanding AUC - ROC Curve | by Sarang Narkhede | Towards Data Science).

In medical research, the AUC-ROC curve is widely used to evaluate the diagnostic accuracy of continuous markers and risk scores computed from regression or other models. Time-dependent ROC curve analysis can be employed for markers that change over time, allowing for the evaluation of time-dependent sensitivity and specificity (Time-Dependent ROC Curve Analysis in Medical Research: Current Methods and Applications | BMC Medical Research Methodology | Full Text). Comparing AUCs of individual diagnostic predictors within the same ROC analysis can help identify the most accurate predictors. Some fields have established guidelines for accuracy as determined by AUC, which can guide the interpretation of model performance (Bowers and Zhou). Overall, sensitivity, specificity, and AUC-ROC are crucial performance indicators for assessing the accuracy of machine learning models in medical research (Receiver-Operating Characteristic Analysis for Evaluating Diagnostic Tests and Predictive Models | Circulation).

3.2 ML/AI approaches for cardiac disease diagnosis in fetal and pediatric patients

Machine learning (ML) and artificial intelligence (AI) have shown significant potential in improving the diagnosis of cardiac diseases in fetal and pediatric patients. AI can enhance the evaluation of fetal cardiac function and help with the diagnosis, surveillance, prevention, and intervention of congenital heart diseases. By improving the diagnostic value of cardiac magnetic resonance imaging (MRI), echocardiograms (ECHO), computer tomography (CT) scans, and electrocardiographs (ECG), AI can augment the diagnostic accuracy of pediatric heart diseases(Artificial Intelligence in Pediatric Cardiology: A Scoping Review - PMC).

Fetal Intelligent Navigation Echocardiography (FINE) is a novel method for rapid, simple, and automatic examination of the fetal heart using ultrasound. AI has also been applied in the field of fetal cardiology to improve the rates of prenatal diagnosis of congenital heart disease. In addition, AI can provide more accurate prognosis for individuals and automatically quantify various metrics related to cardiac function (Day et al.).

Machine learning has been applied in maternal and fetal health for the detection or prediction of particular pathological conditions, as well as for other purposes such as identification of important variables, correlation analysis, data management and extraction, noise removal, and dimensionality reduction (Machine Learning Applied in Maternal and Fetal Health: A Narrative Review Focused on Pregnancy Diseases and Complications - PMC). AI has also been used in the prediction, risk stratification, and personalized treatment planning for congenital heart diseases(Cureus | The Role of Artificial Intelligence in Prediction, Risk Stratification, and Personalized Treatment Planning for Congenital Heart Diseases | Article).

 Deep learning models have been developed for prenatal detection of complex congenital heart disease lesions(JCM | Free Full-Text | Artificial Intelligence in Pediatric Cardiology: A Scoping Review). In another study, a cardiac deep learning model (CDLM) was proposed for the detection of fetal congenital heart disease using residual learning diagnosis systems (Diagnostics

| Free Full-Text | A Cardiac Deep Learning Model (CDLM) to Predict and Identify the Risk Factor of Congenital Heart Disease). Machine learning-based heart disease diagnosis using non-invasive methods has also been explored, with the goal of automating the diagnosis process and providing guidelines for new researchers in the domain of machine learning (Kumar and Kumar).

3.3 Utilizing large datasets of medical images and clinical records

Big data in healthcare includes various sources such as hospital records, medical records of patients, and results of medical examinations. The field of image analytics is making an impact on healthcare by actively extracting disease biomarkers from biomedical images using ML and pattern recognition techniques. This approach can draw insights from massive volumes of clinical image data to transform the diagnosis, treatment, and monitoring of patients (Dash et al.).

Big data has contributed to changes in research methodology, enabling the analysis of large clinical datasets to create awareness of the ramifications for big data and encourage readers that this trend is positive and will likely lead to better clinical solutions (A Review of Big Data and Medical Research - PMC). The integration of machine learning models with medical information systems can be useful to predict heart failure or any other disease using live data collected from patients (Abdeldjouad et al.).

3.4 Feature extraction and selection methods for identifying relevant patterns

Feature selection and extraction methods are essential in pattern analysis, especially in the context of high-dimensional data, such as microarray data. These methods aim to remove redundant and irrelevant features so that classification of new instances will be more accurate (Hira and Gillies). In medical image analysis, feature selection and extraction methods have been widely used to analyze large datasets and address issues related to data storage and analysis (Wang and Krishnan).

Various aspects of feature selection and extraction methods have been reviewed in the literature, including their theory, motivation, and applications ([PDF] Feature Selection and Feature Extraction in Pattern Analysis: A Literature Review | Semantic Scholar). These methods have been applied in different domains, including medical image analysis, to provide better definitions of objective functions, feature construction, feature ranking, multivariate feature selection, and more (Nguyen et al.).

3.5 Model training and optimization

Model training and optimization are crucial steps in machine learning-based heart disease diagnosis. Several studies have focused on building optimized models for predicting heart disease using different machine learning algorithms. For example, one study achieved an accuracy of 89.4 percent using a RandomForest classifier to predict heart diseases(Ahmed). Another study proposed a hybrid approach for heart disease prediction that combines all

techniques into one single algorithm, demonstrating that accurate diagnosis can be made using a combined model from all techniques (Abdeldjouad et al.).

Emerging areas for future research include the opportunity for training and testing using larger datasets and modifying different hyperparameters for further improvement(Ahmed).

4 Ethical considerations
4.1 Ethical considerations in using ML/AI for medical diagnosis
The application of AI in healthcare has the potential to significantly improve various aspects of the medical field, including imaging, electronic medical records, laboratory diagnosis, treatment, and new drug discovery. However, this advancement also brings about various ethical and legal challenges. The four principles of medical ethics, namely autonomy, beneficence, nonmaleficence, and justice, should be considered in all aspects of healthcare. Patients have the right to be informed of their diagnoses, health status, treatment process, therapeutic success, test results, costs, health insurance share, or other medical information. Any consent should be specific per purpose, be freely given, and unambiguous. The rise of AI in healthcare applications has increased concerns about these ethical principles(Ethical Issues of Artificial Intelligence in Medicine and Healthcare - PMC)

In addition, the lack of accountability in AI systems raises concerns about the possible safety consequences of using unverified or unvalidated AI systems in clinical settings. This lack of transparency and accountability can affect each stakeholder differently, leading to ethical dilemmas(Frontiers | Legal and Ethical Consideration in Artificial Intelligence in Healthcare: Who Takes Responsibility?)

Moreover, the application of AI in healthcare is not accessible to all societies. Many low-income and developing countries still do not have access to the latest technologies, leading to social gaps and ethical dilemmas (Ethical Issues of Artificial Intelligence in Medicine and Healthcare - PMC)

4.2 Privacy concerns and data protection
The rapid advancement of AI in healthcare has raised privacy issues relating to the implementation and data security. Private entities that own and control many AI technologies have a greater than typical role in obtaining, utilizing, and protecting patient health information. This raises privacy issues relating to implementation and data security (Murdoch)

The use of health data for AI development raises important data privacy concerns, both at an individual and group level. There is a tension between incentives and actions that promote AI and incentives and actions that limit access to the required data. This leads to complex dilemmas (Bak et al.)

4.3 Ensuring transparency and interpretability of ML models in healthcare
Interpretability is an important concept within clinical ML as model performance is unlikely to be perfect, and the provision of an interpretable explanation can aid in decision-making using ML models. The importance of interpretability for all ML-based

decision-making algorithms is demonstrated in the United States Government's Blueprint for an AI Bill of Rights which introduces "Notice and Explanation" as a key principle for ML-based prediction models (Lu et al.)

However, the demands for explainability, model fidelity, and performance in general in healthcare are much higher than in most other domains. In order to build patient trust in ML solutions and incorporate them in routine clinical and healthcare practice, medical professionals need to understand clearly how and why an ML solution-driven decision has been made(Interpretability of Machine Learning Solutions in Public Healthcare: The CRISP-ML Approach - PMC)

4.4 **Potential biases in data and their impact on diagnostic accuracy**

Shortcomings in study design can affect estimates of diagnostic accuracy, but the magnitude of the effect may vary from one situation to another. Design features and clinical characteristics of patient groups should be carefully considered by researchers when designing new studies and by readers when appraising the results of such studies. Unfortunately, incomplete reporting hampers the evaluation of potential sources of bias in diagnostic accuracy studies (Evidence of Bias and Variation in Diagnostic Accuracy Studies - PMC)

Intrinsic to AI are issues such as biases, which can lead to poor or negative outcomes due to the use of inadequate or poor testing and training datasets. These biases can affect the accuracy of AI-driven healthcare solutions and lead to ethical and legal challenges (The Ethical Issues of the Application of Artificial Intelligence in Healthcare: A Systematic Scoping Review | AI and Ethics)

Conclusion

In conclusion, the application of machine learning and artificial intelligence in diagnosing cardiac diseases in fetal and pediatric patients holds significant promise. The ability of these technologies to analyze complex data, including fetal echocardiograms, MRI of the heart in children, and electronic medical records, has the potential to revolutionize the diagnosis and treatment of heart diseases in young patients.

The use of various ML/AI algorithms, such as recurrent neural networks (RNNs), random forests, and gradient boosting machines, has shown to be effective in identifying critical indicators and categorizing patients into distinct heart disease groups. This ability to detect intricate patterns in medical images and clinical information can lead to more precise and timely diagnosis, which is crucial for effective treatment and improved outcomes.

However, while the potential of these technologies is immense, it is important to note that their full implementation in healthcare requires further research and collaboration among medical experts, data scientists, and healthcare regulators. The need for larger datasets from multiple centers is evident, as is the need for safe and responsible implementation of these technologies in medicine.

Moreover, the ethical considerations and potential biases that come with the use of AI/ML in healthcare cannot be overlooked. These include issues related to data privacy, transparency, and interpretability of ML models, as well as potential biases in data that could impact diagnostic accuracy. Addressing these challenges is crucial for the successful integration of AI/ML in healthcare.

In summary, the integration of machine learning and artificial intelligence in the diagnosis of cardiac diseases in fetal and pediatric patients has the potential to significantly improve patient outcomes. However, the successful implementation of these technologies requires careful consideration of ethical issues, further research, and collaboration among various stakeholders in healthcare.

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Impact of Artificial Intelligence on the Mental Health, Therapy, and Well-being of Empty-Nest Youth By Mandy Tao

Abstract

The "empty-nest youth" phenomenon comprises individuals aged 20-35 who live independently, are away from familial ties, have relatively secure employment, or pursue higher education. Exceeding 58 million in China, their demographic is confronted with distinctive stressors: solitude, financial concerns, absence of social affiliations, and heightened expectations, among several others, as they traverse the realm of independent adulthood without the aid of familial structure (Yu, 2018). Additionally, empty-nest youth represents a demographic facing complex psychological predicaments that surpass initial expectations, thus garnering societal and scholarly attention. In this milieu, the ascendancy of artificial intelligence (AI) has engendered a paradigm shift in mental health, therapy, and well-being. AI-powered tools and applications offer the possibility of democratizing tailored mental health care, granting individuals universal access to aid and resources. Furthermore, AI's capacity to expedite diagnostics and treatment by examining extensive data and uncovering latent patterns enhances the efficacy of mental health professionals.

This paper uses the method of literature review to analyze the psychological status of empty-nest youth as well as the different possibilities of AI. By reviewing literature pieces, the potential of AI used in supporting mental health and well-being of empty-nest youths are extremely high. This exposition endeavors to identify a solution through AI to ameliorate the psychological well-being of emotionally distressed empty-nest youths, underscoring the need for a symbiotic rapport with AI technologies while upholding the fundamental role of human connectivity and self-care.

Keywords: Empty-nest youth, Artificial intelligence (AI), Mental health, Therapy, Well-being

Due to the unbalanced social and economic development, facing the attraction of employment opportunities and wages in more developed cities, young adults are forced to leave parental abodes in order to pursue better development opportunities. Meanwhile, real problems such as high housing prices, high consumption, work intensity, commuting pressure, and weak social relationships cause them have to face "empty-nest", resulting in a series of problems, such as problems in mental health and well-being. Understanding these individuals' specific needs and experiences is crucial in developing effective mental health interventions and support networks. While compared with youths who are living with families or roommates, young people living alone have better control over their finances and make independent decisions regarding their careers, expenses, and investment, yet, the shadow of isolation looms prominently. Living in isolation can precipitate sentiments of estrangement and truncated social networks, culminating in a deleterious psychological toll, especially if they are not actively seeking social activities (Wei, 2022). According to Maslow's theory, individuals have a hierarchy of needs that they seek to fulfill sequentially. These needs include physiological needs (such as breathing, food, water, and shelter), safety and security needs (such as employment and property), love and belonging

needs (such as friendship, intimacy, and sense of connection), self-esteem needs (such as confidence, achievement), and self-actualization needs (such as morality, creativity) (Mcleod, 2023). Empty-nest youths fulfill their physiological requisites and security concerns after exiting parental abodes. The reason for empty-nest youths to leave their parents is to seek employment or pursue higher education. Thus, in this case, empty-nest youths should be able to earn income and provide themselves with physiological and security needs—consequently, their focus pivots toward the yearning for love and a sense of belonging. An insubstantial social support framework exacerbates stress and compromises overall well-being. Herein, interventions necessitate a strategic orientation towards augmenting social integration and nurturing substantive connections tailored to this cohort's exigencies.

The emergence of AI has engendered a transformative vista within mental health support. AI-driven chatbots, meticulously designed to extend emotional succor and coping strategies for anxiety, stress, and depression, are rapidly gaining traction. These AI chatbots function like virtual therapists by providing immediate responses to commonplace queries, furnishing guidance, and dispensing technical assistance, providing a haven for self-expression, attentive listening, and informed guidance. The potential interactions between AI chatbots and AI watches provide an even more efficacious support mechanism for empty-nest youths. MediBOT for instance, developed a sustainable healthcare system that accomplished this (Sivaraj et al, 2021). AI-infused watches continuously monitor heart rate, emotional fluctuations, and psychological well-being. AI chatbots, leveraging user data and behavioral patterns, proffer personalized recommendations, be it product suggestions aligned with individual preferences or informed by prior interactions. In a study exploring the potential of using ChatGPT as a therapist assistant illustrates that ChatGPT is capable of holding positive conversations, actively listening, and providing validation and potential coping strategies without veering off to explicit medical advice (Eshghie et al., 2023). These chatbots serve as virtual therapists, providing individuals a safe space to vent, feel heard, and receive guidance. Furthermore, the advent of AI companions provides company and emotional support to those feeling isolated or lonely. To achive this, natural language processing (NLP) is central to this efficacy, the crux enabling chatbots to discern and generate responses reminiscent of human exchanges. Various NLP techniques have been studied and integrated into chatbot algorithms to improve language understanding capabilities, such as named entity recognition, sentiment analysis, and part-of-speech tagging (Schoene et al., 2022). Innovations such as chatbots provide a private space for users to express their feelings and concerns without fear of judgment or embarrassment, increasing the accessibility of care for individuals who may be hesitant to seek help (Pham et al., 2022). As a problem many empty-nest youths face, AI-powered chatbots can efficiently address the fear of judgment and hesitation to seek help. Furthermore, they expedite access to immediate support, steering individuals through relaxation techniques and mindfulness exercises that mitigate mental turbulence. We can bridge the gap between individuals in need and the aid they seek by harnessing AI in mental health care, promoting a more inclusive and supportive environment for mental well-being. Furthermore, AI companions can help individuals monitor and analyze their

mental health over time, providing valuable insights and individualized recommendations for self-improvement. Since most empty-nest youths are preoccupied with seeking employment, education, and involvement, this ongoing support can empower individuals to take an active role in their mental well-being and make educated decisions about their care. Furthermore, the application of AI in mental health treatment can assist in relieving the strain on healthcare workers by allowing them to concentrate their time and expertise on more challenging cases. The infusion of AI companions into mental health care embodies the potential to revolutionize the paradigms of addressing mental health challenges, ushering accessible, personalized, and timely succor to those most in need.

Figure 1: MeditBOT

AI's potential extends beyond therapeutic applications, serving to foster communities and strengthen social bonds among those feeling isolated or emotionally barren. The social tapestry of humanity is intricately threaded with interpersonal connections, essential for our collective progression (Karim et al., 2020). Central to the Self-Determination Theory is the innate drive for social connectivity, a cornerstone of human progress (Deci & Ryan, 1985). As such, social support, defined as "support available to an individual through social ties to other individuals, groups, and the broader community," stands as a crucial buffer against stress, anxiety, and depression (Lin et al., 1979). Research indicates that robust and functional social networks deter risky behaviors, minimize negative perceptions, and enhance adherence to treatments. AI-powered algorithms can design social interaction structures, pairing like-minded individuals based on shared interests, and thereby fostering virtual support environments that promote deep connections. Moreover, AI's influence permeates social media, shaping timely responses and informative content. For instance, BiAffect is an app that employs machine learning algorithms, using keyboard metadata like typing dynamics variability, errors, and pauses in user messaging

to forecast manic and depressive episodes in those with bipolar disorder (Pham et al., 2022). Through such platforms, users can fortuitously connect with peers, weaving a network of support that diminishes feelings of isolation. These digital refuges provide an environment where individuals can bond with others facing similar challenges or harboring aligned goals. Bolstered by AI, these digital spaces also promote personal growth by offering myriad educational tools and resources. Users can access educational content, participate in online courses, and join interactive workshops, thereby fostering a sense of achievement and empowerment. These platforms also promote behaviors beneficial for well-being, including goal setting, habit formation, and reminders for self-care activities. Additionally, they present immersive experiences and dialogues that enhance mental wellness. AI's role in this realm facilitates the formation of virtual communities bound by mutual interests, providing individuals with a sense of belonging and an outlet for self-expression. Within these platforms, individuals can pursue personal growth by developing new skills and nurturing emerging talents.

However, amidst the euphoria of AI's potential, circumspection is imperative regarding its undue dependency as a fount of emotional succor. While AI-driven chatbots and companions provide a simulacrum of connection and solace, they ought not to supplant genuine human communion. The echelons of human empathy and understanding elude algorithmic replication. Moreover, excessive reliance on AI for emotional bolstering jeopardizes cultivating vital coping mechanisms and resilience. The incipient stage of AI application within clinical settings lacks standardization and cohesive benchmarks, engendering challenges in risk evaluation and management during technological maturation (Pham et al., 2022). The inertia exhibited by certain psychiatrists, valuing person-to-person interactions, underscores a protracted diffusion of innovation within the mental health community. Concomitantly, the rapid proliferation of mental health applications exacerbates the complexity of risk assessment, predisposing potential harms to manifest prior to preemptive mitigation.

In summation, while AI-powered technologies orchestrate a profound metamorphosis in emotional support and connectivity, equilibrium must be preserved between virtual interactions and authentic human bonds. These platforms undeniably, engender a sense of kinship and wellsprings of self-improvement. Alongside these salutary advancements, it is crucial to recognize the plausible adverse repercussions on the psychological health of emerging adults, poised at a pivotal juncture of their personal growth. Minimizing potential harm necessitates the prudent cultivation of judicious digital engagement and the awareness of AI's constraints. Most importantly, they must never eclipse the genuine human resonance of empathy and compassion. Succumbing to an unwarranted dependence on AI for emotional support jeopardizes the acquisition of crucial coping strategies and grit. Amid the navigational contours of the digital age, an indelible imprint of human connection on emotional well-being ought to be steadfastly upheld.

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Exploring Key Design Elements of a Novel Soft Robotic Glove for Enhanced User Safety and Performance By Prisha Bhagavathi

Abstract

Soft robotic systems have been demonstrated to have numerous benefits as wearable devices. These devices have many benefits as prosthetic devices and can especially aid older individuals and those with disabilities to perform daily tasks. This review paper proposes a new type of robotic wearable glove designed to assist individuals. It uses the use case of those working in hazardous environments where sharp objects pose a risk of cuts and punctures. This novel glove could be well-suited for individuals working in recycling centers, gardens, and other industrial settings with an inherent risk of contact with sharp objects. The paper focuses on a unique approach that would allow users to work with improved grip and tactile feedback while safeguarding them against harmful cuts and punctures. The paper discusses in depth possible actuation systems and sensors for this glove. Other aspects could potentially be the self-healing materials or a silica-based gel material that can expand to protect the wearer. Furthermore, it could utilize sensors that detect and alert the user of any tears or punctures or provide visual cues to the location of the tear, resulting in longer glove life and increased user safety. The methodology employed for this review paper involved using Google Scholar as the database and conducting searches using keywords such as prosthetics and soft actuators and sensors. Inclusion criteria focused on the latest developments in soft robotic and wearable technologies, specifically for prosthetic applications. The selected articles encompassed English papers published from 1993 to 2021, including review papers and conference proceedings.

Introduction

Soft robotic gloves are a cutting-edge technology that can potentially improve the quality of life for the elderly and individuals with mobility impairments. These gloves are designed to mimic the natural movements and dexterity of the human hand, using soft and flexible materials in their construction (Ismail et al. 2019). Unlike traditional robotic gloves, which are often bulky and rigid, soft robotic gloves are lightweight and conform to the shape of the hand, providing a more natural and comfortable fit (Lee et al. 2017).

One use of soft robotic gloves for the elderly is to assist with activities of daily living (ADLs). These gloves can help seniors with limited hand mobility due to stroke, or other conditions, to perform tasks such as grasping and manipulating objects so that they can feed, or groom themselves (Polygerinos et al 2015). Soft robotic gloves can also provide support during physical therapy exercises, allowing people to improve their range of motion and strength (Jiralerspong et al. 2018).

Another potential use of soft robotic gloves is that they can also be beneficial for the elderly who work in manual labor jobs or have hobbies that require the use of their hands, such as gardening or woodworking. These individuals may be more prone to injuries from sharp objects, such as knives or saws, due to decreased hand strength and dexterity. Soft robotic gloves

can provide an additional layer of protection, allowing the elderly to work with greater safety and confidence. Furthermore, soft robotic gloves can help prevent strain injuries associated with repetitive hand motions, such as opening and closing medication bottles or handling medical equipment (Jiralerspong et al. 2018).

Overall, soft robotic gloves offer a wide range of benefits for the elderly who work with sharp objects or perform manual labor jobs. They can improve safety, reduce the risk of injuries, and enhance overall hand function, allowing the elderly to maintain their independence and quality of life

Methodology

The database Google Scholar was used and was searched using the following keywords: prosthetics, robotic gloves, soft robotic wearables, soft actuators, and soft sensors. To be included, papers were required to focus on the latest developments in soft robotic and wearable technologies, specifically for prosthetic use cases. Additionally, the papers were expected to discuss the incorporated actuation systems and sensors used in the devices mentioned, especially addressing challenges such as better grip, and user protection which are important elements of the proposed glove. The selected articles were English papers published during the timeframe from 1993 to 2021. Published literature, including review papers, were eligible as well as conference proceeding papers.

Types of Actuation Systems

Soft robotic gloves require different types of actuators than traditional robotic devices. Traditional robotic devices typically use rigid or stiff actuators, such as electric motors or hydraulic/pneumatic systems, and require actuators designed to work with such components (Lee et al. 2017). However, Soft robotic gloves are made of flexible materials which allow for a greater range of motion and better interaction with the users (Lee et al. 2017). To achieve this, different types of actuators are needed that can produce compliant and flexible movements.

Pneumatic Actuators:

Pneumatic actuators are powered by compressed air or gas and work by inflating or deflating soft, flexible chambers. In soft robotic gloves, these actuators are often used to provide a bending or twisting motion to the fingers, allowing the wearer to grip and manipulate objects. Soft robots require actuation systems that match the compliant materials they are built with. In one study that used pneumatic actuators, they made a system split into a portable pneumatic box and positive-negative pneumatic actuators made of bellows (Hu et al. 2020). This design has many benefits. The gloves are made light so that they are portable, even for the elderly or people with disabilities. They are easy to wear, not requiring any complicated knowledge as to how to put them on (i.e., not many buttons, hooks, or zippers) (Hu et al. 2020). They are made comfortable, allowing people to wear them for long durations considering they will be an important tool in their day-to-day lives. They can be made customizable for hands of all shapes

and sizes. The gloves are, as a result, safe to wear and easy to make while also being made of cost-effective materials.

Hydraulic Actuators:

Similar to pneumatic actuators, hydraulic actuators use fluid to create movement. However, they typically use a denser fluid, such as oil, and can generate higher forces than pneumatic actuators (Lee et al. 2017). These actuators can be used to provide a greater range of motion and force than pneumatic actuators. In a paper by Polygerinos, et al. (2015) hydraulic soft actuators are cited as inexpensive. This glove uses soft actuators made from flexible materials known as elastomeric materials strengthened with fiber to control the fingers. They are mounted in an open-palm design, and all electromechanical components are secured into a portable waist belt (Polygerinos et al. 2015). This allows the user more freedom of movement since the glove can work untethered.

Shape Memory Alloys (SMAs):

Shape memory alloys can change shape in response to heat (Hadi et al. 2018). In soft robotic gloves, SMAs can be used to actuate fingers or other parts of the hand by heating and cooling specific areas of the glove. The ASR glove from the paper by Hadi et al., made using a 0.25-mm shape memory alloy wire for tendon actuation, allows for movement of three different finger joints in 70, 80, and 90-degree angles.

Electroactive Polymers (EAPs):

EAPs are materials that can change shape in response to an electrical signal. EAPs can provide a gentle, yet precise movement to the fingers and other parts of the hand (Lee et al. 2017). There are two main types of EAPs: Electronic and Ionic. Electronic EAPs are most commonly used since they are easier to operate in the open air (Lee et al. 2017). However, ionic EAPs have the potential to be safer for human use because of their lower activation voltage which is a useful tool in making wearable robots (Lee et al. 2017). EAP sensors show promise in being used to mimic touch and grip in prosthetics.

String Tendons:

Motor-tendon or string-tendon actuators can be used to mimic human muscles. This mechanism simply requires types of string and some material that can withstand the pulling and stretching of the material (Ismail et al. 2019). For instance, in a Fabric-based Soft Robotic Glove for Hand Function Assistance by Ismail et al., such actuation was used to make the glove more compact. In this study, rope and nylon tendons were employed to enable the flexion and extension of separate finger segments. The nylon tendon served as a linking mechanism between the hooks present on the finger segments and a linear actuator responsible for exerting tension and extending the finger's movement (Ismail et el. 2019).

Summary

Among the types of actuators discussed, pneumatic actuators are particularly well-suited for wearable gloves. Pneumatic actuators offer lightweight and flexible actuation, which is a requirement of soft robotic gloves (Lee et al. 2017). These actuators can help with bending or

twisting motions to the fingers, which helps improve grip and manipulation of objects. Additionally, since they can be portable as Hu et al. suggests, they allow for easy use in terms of wearable applications.

Types of Sensors

One of the key considerations in creating soft robotics-based gloves that can potentially help people around sharp objects is their ability to detect the pressure being faced by the person's hand as they use it to touch things. Another is to measure the hand movement angles to be aware of the orientation of the fingers when a sharp object is encountered. Several types of pressure sensors have been used in soft robotic gloves, each with their advantages and limitations.

Resistive sensors

One of the most commonly used pressure sensors in soft robotic gloves is the resistive sensor. These sensors are typically made of a conductive material that changes its resistance when subjected to pressure. The amount of pressure applied can be inferred by measuring the change in resistance. Resistive sensors are relatively inexpensive and easy to manufacture, making them a popular choice for researchers (Mechael et al. 2021). For instance, in the Ready-to-wear strain-sensing gloves for human motion sensing, a straightforward approach was adopted, where a disposable glove readily available in the market was enhanced with the integration of a thin film of resistive sensors on its surface which effectively merged functionality and wearability as mentioned in the paper by Mechael et al. However, these types of sensors are sensitive to changes in temperature and humidity, which can affect their accuracy and reliability.

Capacitive sensors

Another type of pressure sensor that has been used in soft robotic gloves is the capacitive sensor. These sensors work by measuring changes in capacitance, which is the ability of a material to store an electric charge. In the study titled Soft Robotic Glove with Integrated Sensing for Intuitive Grasping Assistance Post Spinal Cord Injury by Zhou et al., textile elastomers were employed on the fingers to detect finger flexion through strain and object contact through force. When pressure is applied to a capacitive sensor, the distance between the conductive plates changes, resulting in a change in capacitance. Capacitive sensors are more immune to changes in temperature and humidity than resistive sensors, making them a more reliable option for some applications (Puers 1993). However, they are often more expensive and difficult to manufacture than resistive sensors.

Piezoelectric sensors:

Piezoelectric sensors are also used in some soft robotic gloves. These sensors generate an electric charge when subjected to pressure, allowing the small amounts of pressure to be inferred from the amount of charge generated (Song et al. 2020). However, they can be expensive and difficult to manufacture, and their sensitivity can make them susceptible to noise and interference (Tressler et al. 1998). When used in a glove they can be used to detect finger motions and touch. They are mainly being targeted for VR applications as demonstrated in the paper by Song et al.

titled: Pneumatic Actuator and flexible piezoelectric sensor for soft virtual reality glove system. There is also research by Ulisse et al. that suggests that they could be useful in harvesting some energy from movements, thereby creating self-charging gloves.

Summary

When it comes to sensors, resistive sensors, and capacitive sensors work well for wearable gloves. Resistive sensors are cost-effective and easy to make (Mechael et al. 2021). As per Mechael et al., they can be integrated into the glove surface, enabling the detection of pressure changes, and providing feedback to the wearer. Capacitive sensors would provide very accurate pressure detection by measuring changes in capacitance as pressure is applied.

Discussion & Conclusion

In this review paper, our goal was to describe a glove that can assist the user in terms of movement, while also helping with grip, aiding movement, and protecting the user from cuts. We started by considering the actuation and sensing aspects of the glove and decided, as previously discussed, that the best actuation system would be a pneumatic one and the best sensors would be resistive or capacitive. Furthermore, to analyze what such a glove should look like, we took the use case of gardening as an example, as it involves various challenges that require specialized equipment.

One of the key factors that we identified was grip. To hold objects comfortably, the user needs to have a strong grip, regardless of the object's material. This includes soft objects, such as petals, hard, such as bark, or sharp, such as thorns. To address this issue, the glove needs to provide a tactile and secure grip that allows the user to hold and manipulate objects with ease.

Another factor that we considered was protection from sharp objects. In gardening, there is a risk of getting cut by thorns, fences, or other sharp objects, which can cause serious injuries. Therefore, the glove needs to be designed in such a way that it can protect the entire hand, not just the palm side.

In addition to grip and protection, we also identified the need for aid. Gardening is enjoyed by people of all ages and abilities, including those with disabilities. Therefore, it is important to design a glove that can cater to their needs and provide aid to help with movement. This could involve incorporating additional features, such as adjustable straps, to ensure that the glove fits snugly and comfortably, regardless of the user's hand size. Some other features that could be included are padding on the palm and fingers, and a flexible and breathable design.

In conclusion, the design of a glove that can aid the user in terms of movement, as well as sense, stop, and protect the user from a cut is a complex task. To create such a glove, it is essential to consider various factors, such as grip, protection, and aid, as well as the needs of different users. While our analysis has identified some key features that such a glove should have, further research and development are needed to execute the design effectively. With continued progress in this field, we believe that a glove with these capabilities will become a reality in the near future.

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Guidance For Fencers Fencing During Hot Weather: An Overview By Asmi Sawant

Abstract

Earth's temperature has been rising since the Industrial Revolution. As per NASA's GISS study[1], the average global temperature on Earth has increased by at least 1.1ºC (1.9ºF)/century since 1880. Increased temperature, combined with the fencer's overall uniform, which is made of rugged cotton or nylon, and layers of various protective gear, could raise concerns about the potential health risk for the athlete's exacerbation of heat stress. Fédération Internationale d'Escrime (FIE) – International Fencing Federation – has not proposed indoor environmental parameters. Therefore, there may be a need to develop guidelines for the fencers to protect fencers from future heat stress if the fencing hall has no air conditioning. Through this review, we aim to study the impact of environmental conditions on the fencer's body temperature, which can help formulate guidelines for the fencer and clubs during regular practice and tournaments.

Introduction

Global Warming, as it is referred is a long-term heating of the Earth's surface observed since the pre-industrial period. National Aeronautics and Space Administration (NASA), in its study released in January 2023[1], clearly mentions that not only is the temperature increasing by 1.1ºC/100 years but also the rate of increase in temperature is accelerating, as the past nine years have been the warmest years since 1880. The fencing uniform is made of rigid cotton or nylon. Kevlar – a heat-resistant solid synthetic fiber – and Dyneema – a lightweight and high-strength polyethylene - are added to the top for increased protection.[2] The complete fencing kit contains various layers such as a Jacket, Plastron, Lame, Chest Protector, Sleeve, Glove, Breeches, Socks, Shoes, and Mask and covers the whole body. The uniform has evolved over centuries to ensure that the athlete's safety is a prime consideration. Increasing environmental temperature combined with the layers of uniform may increase the fencer's body temperature during the long tournament hours, which could be catastrophic for the fencers, so there is a need to conduct formal research in the area. Many indoor sports venues do not have air conditioning, so an increase in environmental temperature will result in an increased temperature indoors. This paper will discuss the environmental parameters of various indoor sports facilities and the fencing athletes' thermal comfort in Indoor sports. We will review the different guidelines and suggest approaches based on the multiple literature surveys and the future work needed in the area.

Review of Indoor Environment Parameters for Fencing

Fencing is mainly practiced in indoor facilities. With the global increase in temperature, it is essential to ensure that we have proper Indoor Environmental Quality (IEQ) so that air quality and thermal comfort can be maintained[3]. As discussed further in the review paper, international federations often provide environmental standards, such as air temperature, relative humidity, and air velocity. Table 1 below shows the environmental parameters followed by the International Olympic Committee (IOC) recognized by various sports federations.

Table 1: Environmental Parameters to be maintained by various sports as reported by IOC[3]

Sport	Air Temperature (ºC)	Relative Humidity (%)	Maximum Air Velocity (m/sec)
Badminton	18-30	-	< 0.2
Basketball	16-20	< 50	-
Boxing	-	-	-
Fencing	-	-	-
Gymnastics	Humidex (22-38)		-
Tennis	13-17 (winter) 6-8 below the external temp (summer)	55-60	-
Volleyball	16-15	-	-

As we can notice, most sports have at least a specific air temperature mentioned, except Boxing and Fencing, which don't have any environmental values mentioned. The lack of Air Temperature, relative humidity recommendations, and a fencing uniform prevents athletes from adapting to the thermal environment. So, specific studies need to be performed further to define these environmental parameters or the guidelines that need to be established for the athletes. As discussed in the paper, the thermal and moisture management of the clothing are essential for the thermal performance management of the athlete. Figure 1 shows the heat from the body to the environment through conduction, convection, radiation, and evaporation. In the case of Fencing, when the uniform offers high thermal resistance/insulation, the heat transfer through conduction, convection, radiation, and evaporation will be minimal.

In contrast, in the case of boxing, the thermal resistance will be low as minimal clothing is worn. Additionally, as discussed by Fantozzi and Lamberti[3], the metabolic heat – a waste product of the metabolism – must be dispersed in the environment to maintain the body temperature. Table 2 shows that fencing has a relatively high metabolic rate, and due to this, heat is generated, which could compound the high environmental temperature. As you can notice, to determine thermal comfort, the complex physiological model would need to be developed considering the various factors between Environmental parameters, metabolism, and the work factor during the matches, and it is further explored in Oates et al.[4] as probably the 1st formal study for the fencing sport.

So, the fencing athlete produces great heat due to high metabolic rates. As further discussed in Fantozzi et al.[3], due to fencing uniform, only a modest part of the heat produced by the body is transferred to the environment, and most of it increases the body's internal temperature. This heat storage in the body will cause more significant fatigue, thus having a negative impact on performance and could lead to heat exhaustion. It is advised that an athlete's body temperature should not go above 40ºC; however, with high environmental temperatures and

thick uniform, there is a high potential for it to occur. So, the report highlights that thermal comfort may affect athletes' performance and health if thermal comfort is not maintained. So, developing a methodology to measure and track IEQ during fencing matches and practice is vital.

Figure 1: Heat Transfer Through Clothing (Frantozzi et al.[3])

Table 2: Metabolic Rate for various sports in Table 1[3]

Sports	Metabolic Rate (Met)
Badminton	5.5
Basketball	8.0
Boxing	12.8
Fencing	6.0
Gymnastics	3.8
Tennis	7.3
Volleyball	4.0

Review of Cooling Intervention Techniques

During a fencing competition, the athletes need to compete for almost 9-11 hours/day by covering multiple layers of protective clothing, which could pose challenges in heat dissipation[4], the gastrointestinal temperature (T_{gast}) has been reported up to 37.8°C - 38.4°C, with peak values of >39°C during the Direct Elimination (DE) rounds. Additionally, the typical time between fights is only 10-15 minutes. As well as practical limitations about the time required to remove and re-wear the uniform, the fencers only remove their masks and gloves between the fights. This could impact the body's ability to dissipate heat and cause an increase in thermal load

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through core body temperature (T_{core}), skin temperature (T_{skin}), heat storage, and perceptual responses. This imbalance in heat gain and loss could cause a decrease in fencing performance and early development of fatigue as the competition progresses. Therefore, finding a way to reduce body temperature could positively impact performance.

Bongers et al.[5] have extensively discussed using cooling techniques. There are three types of cooling methods in the sports literature:

1. Cooling Before Exercise (Pre-Cooling)
2. Cooling During Exercise (Per-Cooling)
3. Cooling directly after the Exercise (Post-Cooling)

Cooling Intervention techniques, if adequately used, not only help to maintain the T_{core} but also increase the heat storage capacity, reducing the exercise-induced increase in T_{core} and accelerating the recovery of muscles after intense activity.

Pre-Cooling

Bongers et al.[5] discuss various Pre-cooling techniques; however, based on the applicability on the field during the fencing competition, we suggest using the following methods as per Table 3. As indicated in the paper, we could use either the individual or the combination of these techniques to get better cooling (lower Tcore) for individual athletes. The report also confirms that the Pre-Cooling techniques increase the athletes' performance during the exercise.

Table 3: overview of cooling techniques for fencing[5]

Cooling Technique	Timing of Cooling	Advantages	Disadvantages
Cold Water Ingestion	- Pre-Cooling - Per-Cooling	- Direct Effect on T_{core}.	- Less Aggressive
Cooling Packs	- Pre-Cooling - Post-Cooling	- Aggressive Cooling	- Can restrict Movement

Per-Cooling

Since the benefit of Pre-Cooling reduces after 20-25 minutes, as discussed by Oates et al.[4], the thermal strain due to the increase in T_{core} is highest during the fencing; the Per-Cooling techniques could have a significant potential benefit on thermoregulation and the performance improvement. Also, as discussed by Bongers et al.[5], the ambient temperature has a direct impact on the effectiveness of the Per-Cooling techniques – better performance benefit in the moderate (< 30ºC) vs. hot (>= 30ºC) ambient temperature.

Cooling

Post-cooling helps to reduce T_{core}, T_{skin}, and muscle temperature, which helps to improve recovery by reducing muscle soreness.

Discussion of the Cooling Techniques

As discussed in prior sections, Pre-Cooling helps reduce the T_{core} before the exercise, so the margin for metabolic heat production and heat gain increases. As mentioned by Bongers *et al.*[5], when the T_{core} reaches 40^0C, it invokes hyperthermia-induced fatigue. Therefore, reducing T_{core} with Pre-Cooling and Per-Cooling can help delay hyperthermia-induced fatigue. Additionally, during heat stress, the skin's blood flow increases, minimizing the muscles' blood flow to dissipate the heat. So, the oxygen flow is limited, so the heart rate increases. By effective Cooling technique, the T_{skin} is reduced, which helps to increase the oxygen flow in muscles, reducing the heart rate and cardiovascular strain during recovery less[5], and a quick recovery in the central blood volume. The central blood flow and volume increase the athlete's ability to remove lactate and improve healing. The reduction in muscle temperature reduces metabolism in muscles and muscles' energy demand.

In Fencing, athletes must maintain their best performance levels for longer during the Direct Elimination (DE) bouts. Therefore, simulating a fast recovery between the intense bouts is essential. As suggested by Bongers *et al.*[5], the application of cold is often recommended to decrease muscle strain and damage. British Fencing offers to loosen or remove the fencing uniform between bouts to reduce overheating and changing T-shirts[6]. Other techniques are used, such as using electrolytes in water, eating fruits like watermelon, or using a cold towel at the back of the neck.

Development of Heat Policies

Even if fencing is an indoor primary sport, the nature of the sport, combined with the layers of clothing, requires extra precaution during the hot weather. Since there are no formal guidelines, there is a need for increasing awareness at a grassroots level – players and local clubs – as well as at the governing body level – Fédération Internationale d'Escrime (FIE) – International Fencing Federation. Because of the lack of formal research and the complexities involved, developing a heat policy is challenging; however, general guidance disseminated to fencers in an easy, understandable way could help increase awareness within the available infrastructure at the clubs and tournaments. As suggested by a draft guidelines proposal by the British Fencing[6], it is essential that fencers stay hydrated and parents/guardians support appropriately by ensuring the high water content food is also consumed –

1. Stay Hydrated. Consume extra water during practice and matches.
2. Add Electrolytes to water and eat high water-content fruits like watermelon.
3. A cold towel at the back of the neck.
4. Loosen or remove your clothing to reduce overheating when not actively fencing. Change T-shirts when it's saturated.

5. Adapt training sessions: reduce time to remain in full fencing uniform and take regular breaks.
6. Do cool-down stretches.
7. Weigh in before and after sessions and matches. Replace the lost weight with equivalent fluids.

Based on the guidelines discussed above, we developed the Infographics, as shown in Figure 2, to be displayed in various local clubs to increase awareness for the fencers and their parents.

Conclusion

In conclusion, on long and hot competition days, fencing uniforms could impact the fencer's thermoregulatory response due to the lack of ability to dissipate heat. This could impact overall fencers' performance negatively and develop fatigue during the DE stages of the competition. So, it's essential to follow the guidelines to maintain the appropriate temperature and fluid in the body.

Based on the work, I plan to develop awareness in the local clubs and with k – The National Governing Body (NGB). Further research on fencers' responses in various temperatures and humidity levels is possible, which will help FIE and IOC develop specific monitoring levels during the competition.

Figure 2: Infographic to increase awareness of Fencers for fencing during regular practice and tournaments in Hot Weather

Acknowledgments

Author

Asmi Sawant is a High School Junior at Basis Independent Silicon Valley, San Jose, CA. She is a competitive Saber Fencer and is very keen on working at the intersection of technology, engineering, and humanity to improve the Quality of Life. She plans to pursue Computer Science as a major in college.

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Anomaly Detection in Biology - A Survey

Vincent Wu[*][†]

Abstract

The rapid accumulation of biological data necessitates efficient techniques for identifying anomalies that can offer critical insights. This paper provides a brief survey on the applications of anomaly detection in various biological domains, including genomics, proteomics, metabolomics, and medical imaging. We overview the statistical and machine learning techniques employed for anomaly detection, emphasizing their algorithmic foundations and operational nuances. Through this paper, we aim to explore the current state-of-the-art, discuss associated challenges, and outline potential directions for future research of biological anomaly detection.

Keywords: Anomaly Detection, Biology, Genomics, Proteomics, Metabolomics, Medical Imaging, Machine Learning.

1 Introduction

In recent years, the field of biology has witnessed a surge of data generated from various sources. This wealth of information has led to significant advancements in our understanding of complex biological systems and provided insights into various diseases and their underlying mechanisms (Marx 2013; Shendure et al. 2017; Emmert-Streib and Moutari 2016). However, as the amount and size of data grow larger, extracting meaningful patterns and identifying anomalous observations that can have profound implications on research outcomes and clinical decision-making have become more challenging than ever (Karczewski et al. 2020).

As a fundamental problem in data science, Anomaly detection is crucial in various biology researches. Anomaly detection involves the identification and characterization of observations that deviate significantly from the expected normal behavior (Aggarwal 2017). Anomalies in biological data can manifest in diverse forms, ranging from outliers in gene expression profiles to aberrant cellular structures in medical images. Detecting and interpreting these anomalies have become the key to discovery of novel biomarkers, understanding disease etiology, and developing effective diagnostic and therapeutic interventions (Ribeiro, Singh, and Guestrin 2016; Naylor et al. 2019).

Traditionally, anomaly detection in biology has heavily relied on manual inspection and expert domain knowledge. However, with the exponential growth of data, these conventional approaches are no longer scalable, efficient, or accurate (Stephens et al. 2015). Therefore, the integration of mathematical, statistical, and machine learning techniques has emerged as promising avenues to tackle the complexity and scale of biological datasets (Angermueller et al. 2016). In particular, machine learning algorithms enable automation in anomaly detection on large scale datasets and offers the potential to uncover subtle patterns and outliers that might otherwise go unnoticed (Zou, Beam, and Mcdermott 2019; Jiang et al. 2017). These techniques have contributed significantly to our understanding of complex biological phenomena, such as the identification of long noncoding RNAs and the analysis of cancer genomes (Creixell et al. 2015).

This paper aims to provide a overview of the applications of anomaly detection in biology, specifically, in a range of biological domains, including genomics, proteomics, metabolomics, and medical imaging, where anomaly detection techniques have been successfully employed. Furthermore, we will discuss the challenges and limitations associated with applying anomaly detection techniques based on machine learning algorithms to biological data and propose potential strategies to address these issues (Erhan et al. 2010; L. Zhang et al. 2018; Ching et al. 2018).

This paper is organized as follows: In Section 2, we will provide a brief background on anomaly detection and its significance in biology. Section 3 will delve into the various machine learning techniques utilized for anomaly detection, highlighting their strengths and weaknesses. Section 4 will present case studies and real-world examples of anomaly detection in different biological applications. In Section 5, we will discuss the challenges, open research questions, and future directions in this field. Finally, in Section 6, we will conclude the paper by summarizing the key findings and emphasizing the

potential impact of machine learning-based anomaly detection in advancing biological research and healthcare.

2 Background

Anomaly detection, also referred to as outlier detection, is one of the fundamental challenges in data science and machine learning. The main goal of anomaly detection is to identify observations in a dataset that deviate significantly from the expected normal behavior or patterns. These deviant observations are referred to as anomalies or outliers (Chandola, Banerjee, and Kumar 2009). Anomalies can represent unusual events, rare occurrences, errors, or potential data points that hold critical information.

The challenge of anomaly detection arises from the fact that anomalies are usually scarce and randomly distributed within a dataset, making it difficult to distinguish them efficiently or effectively with measurable metrics from the regular data (Zimek, Schubert, and Kriegel 2012). Additionally, the definition of normal behavior can vary depending on the specific application and context. In recent years, many machine-learning algorithm based anomaly detection techniques have been developed to automate the process of identifying these unusual patterns, which can be crucial for various domains, including finance, cybersecurity, healthcare, and, as in our case, biology.

For many decades, the concept of anomaly detection has been studied and applied across various fields. The origins of anomaly detection can be traced back to statistical quality control methods developed in the early 20th century (Montgomery 2009). These methods were primarily used in industrial settings to detect defects in manufacturing processes. In the early approaches, anomalies were identified based on statistical measures such as mean, standard deviation, and control charts, which is still suitable for simple data with reasonably low dimension and complexity.

In the later half of 20th century, with the advent of computer science and machine learning, anomaly detection techniques evolved to encompass a broader range of methods. In the 1970s and 1980s, researchers began exploring the use of clustering algorithms and distance-based methods to identify outliers in multidimensional data (Agrawal and Srikant 1998). However, these methods often suffered from computational inefficiency and struggled to handle complex and high-dimensional datasets.

In the 1990s, as the field of machine learning advanced, researchers started

investigating probabilistic approaches to anomaly detection. One of the notable methods was the use of Gaussian mixture models and probabilistic modeling to identify anomalies based on the likelihood of data points being generated from the normal distribution (Feller 2008).

Another significant development in anomaly detection came with the introduction of support vector machines (SVM) in the late 1990s (B. Schölkopf et al. 2000). SVM is a popular machine learning algorithm that can learn multi-dimensional boundary around normal data points and identify anomalies as instances lying outside the boundary.

In more recent years, thanks to the surge of big data and deep learning, anomaly detection techniques have further advanced. Deep learning approaches, such as autoencoders and variational autoencoders, have shown promise in learning complex representations of data and detecting anomalies in high-dimensional datasets (LeCun, Bengio, and Hinton 2015; Erhan et al. 2010; L. Zhang et al. 2018).

The application of anomaly detection techniques in biology is a relatively more recent development. With the increasing availability of large-scale biological data, researchers have begun exploring the use of machine learning, including deep learning, to detect anomalies in genomics, proteomics, metabolomics, and medical imaging data. These applications hold significant potential for discovering novel biological insights and improving disease diagnosis and treatment.

As the field of anomaly detection continues to evolve, researchers are constantly exploring new algorithms, techniques, and applications, with the aim of pushing the boundaries of knowledge discovery and problem-solving in various domains, including biology.

3 Anomaly Detection Techniques

There are many ways to categorize anomaly detection techniques. In this section we discuss 5 widely-used groups of anomaly detection techniques: statistical methods, proximity-based methods, clustering-based methods, high-dimensional outlier detection, and machine learning-based methods.

3.1 Statistical Methods

Statistical methods, which were among the first techniques used for anomaly detection, operate under the assumption that the data adheres to specific statistical distributions (Barnett and Lewis 1994). These methods usually involve establishing a statistical model for what constitutes "normal" behavior, and subsequently comparing each data point against this model. Data points that have a low probability of being generated by this model are considered anomalies.

Classical statistical methods for anomaly detection include parametric methods and non-parametric methods. Parametric methods assume that the normal data points are characterized by a specific probability distribution, such as the Gaussian distribution. These methods often employ measures such as the Z-score, which represents the number of standard deviations a data point is from the mean. A data point is considered anomalous if its Z-score exceeds a certain threshold (Iyer 1994). Parametric methods are simple and computationally efficient, but they often fail when the data doesn't follow the assumed distribution.

Non-parametric methods, on the other hand, do not make any prior assumption about the distribution of the normal data points. Techniques like the Histogram-based Outlier Score (HBOS) fall under this category (Goldstein and Dengel 2012). HBOS calculates the degree of abnormality based on the histogram of the data, where data points falling into less populated bins are considered anomalous. Non-parametric methods are more flexible than parametric methods and can handle a wider variety of data distributions. However, they often require more computational resources and may not perform well with high-dimensional data.

Another notable statistical method for anomaly detection is the Grubbs' test, which is specifically designed to detect outliers in univariate data (Grubbs 1950). The Grubbs' test calculates the Z-score for each data point and tests the null hypothesis that there are no outliers in the data. While the Grubbs' test is robust and widely used, it is limited to univariate data and assumes that the data follows a normal distribution.

Overall, despite the simplicity and efficiency of statistical methods, these techniques may struggle to capture complex patterns in the data and often rely heavily on the assumptions made about the data distribution. Hence, they may not always be suitable for datasets with complex structures or non-standard distributions (Chandola, Banerjee, and Kumar 2009).

3.2 Proximity-Based Methods

Proximity-based methods, also known as distance-based methods, are among the most common and intuitive techniques for anomaly detection. The fundamental premise of these methods is that normal data points occur in dense neighborhoods, whereas anomalies are far from their nearest neighbors or have only a few neighbors.

One of the earliest and simplest proximity-based methods is the k-nearest neighbor (k-NN) algorithm (Ramaswamy, Rastogi, and Shim 2000). Given a data point, the k-NN algorithm calculates the distance to its k nearest neighbors and determines whether it is an anomaly based on these distances. Points with a large average distance to their neighbors are considered anomalies. Variations of the k-NN algorithm use the distance to the kth nearest neighbor or the relative density of each point to identify anomalies.

Local Outlier Factor (LOF) (Breunig et al. 2000) is another widely used proximity-based method. Unlike k-NN, which considers the global structure of the dataset, LOF calculates the local density deviation of a given data point with respect to its neighbors. This approach allows for improved detection of local anomalies that may not be noticeable when considering the overall data distribution.

Density-Based Anomaly Detection (DBAD) (Pokrajac, Lazarevic, and Latecki 2007) is also a proximity-based method that considers the density of data points in the feature space. It treats regions of low density as potential anomalies. DBAD is particularly useful for datasets with complex distributions and non-linear boundaries.

While proximity-based methods are effective and intuitive for anomaly detection, they often struggle with high-dimensional data due to the "curse of dimensionality". This issue, along with their computational complexity, can be mitigated through dimensionality reduction techniques and approximate nearest neighbor search algorithms.

3.3 Clustering-Based Methods

Clustering-based methods for anomaly detection assume that the normal data points belong to a single or a set of clusters, while the anomalies do not belong to any of these clusters or form very small, sparse clusters. Anomalies are detected as points that are far away from any clusters.

One of the earliest and most widely used clustering algorithms is k-means

(MacQueen [1967]). In the context of anomaly detection, after applying the k-means algorithm, points that are far away from the centroid of their assigned cluster can be considered as anomalies.

DBSCAN (Density-Based Spatial Clustering of Applications with Noise) is another clustering algorithm, which does not require the user to specify the number of clusters a priori and can discover clusters of arbitrary shape (Ester et al. [1996]). In DBSCAN, anomalies are usually detected as points that do not belong to any cluster.

An extension to the DBSCAN method for anomaly detection in data streams, known as incremental DBSCAN, was proposed by Pokrajac et al. (Pokrajac, Lazarevic, and Latecki [2007]). This approach addresses the limitations of DBSCAN, such as its inability to handle evolving data streams and update clusters incrementally.

However, these methods have a common limitation: they are sensitive to the initial parameters. For instance, the initial centroids in k-means or the density threshold in DBSCAN significantly affect the clustering results, and thus, the anomaly detection results, which could be a challenge to tune for biological data.

3.4   High-Dimensional Outlier Detection

High-dimensional outlier detection is a category of techniques to detect outliers while attempting to conquer the so-called "curse of dimensionality": As the number of dimensions increases, the data becomes sparse, and the distance between data points, which is the key measure in many anomaly detection methods, becomes less meaningful (Beyer et al. [1999]).

A common approach to high-dimensional outlier detection is subspace methods. These methods search for outliers in various subspaces of the high-dimensional data. An example of a subspace method is the Outlier Detection in Axis-Parallel Subspaces (ODIN) (Kriegel et al. [2009]). This method defines an outlier score for each data point based on the number of subspaces in which the point is considered an outlier.

Another approach is the projection method. The basic idea is to project the high-dimensional data onto a lower-dimensional space and then apply an outlier detection method. One of the popular projection methods is Principal Component Analysis (PCA). However, it has been found that PCA may not be very effective for outlier detection because it tries to retain the variation of the normal data and might discard the directions along which the outliers lie.

There are also stochastic approaches designed for high-dimensional outlier detection, such as the High Contrast Subspaces (HiCS) method. HiCS selects attributes randomly and assesses the contrast of the density between a point and its surrounding points in the subspaces spanned by the selected attributes (Kriegel et al. 2012). This method has shown to be effective for outlier ranking in high-dimensional breast cancer diagnostic data. Despite the advances, high-dimensional outlier detection is still an active area of research with many open problems, such as how to choose the right subspace or how to define the contrast in the case of HiCS.

3.5 Machine Learning-Based Methods

Machine Learning-based methods are increasingly popular in the field of anomaly detection due to their capability to learn complex patterns and relationships in data. These techniques often leverage supervised, semi-supervised, or unsupervised learning to identify anomalous instances.

Supervised anomaly detection methods require labelled training data, both normal and anomalous. They train a model on the given dataset and then classify unseen data points as normal or anomalous (Zhou and Paffenroth 2017). One example is the use of Deep Autoencoders, which are effective at capturing nonlinear relationships in the data. They compress the data to a lower-dimensional representation and then reconstruct it, where high reconstruction errors indicate anomalies.

Semi-supervised anomaly detection assumes that the training dataset only contains normal data. Anomalies are detected based on their dissimilarity to the normal instances. One notable method in this category is the One-Class Support Vector Machine (SVM) (Bernhard Schölkopf et al. 2001), which learns the boundary of normal data instances and labels a test instance as an anomaly if it falls outside this boundary.

Unsupervised anomaly detection methods do not require any labels. They usually rely on certain assumptions about the normal and anomalous instances. Technically it includes clustering-based methods. In recent years, the application of deep learning methods for unsupervised anomaly detection has garnered significant attention. For instance, Long Short Term Memory (LSTM) networks have been used for anomaly detection in time-series data (Malhotra et al. 2016).

It should be noted, however, that machine learning-based methods also present challenges, such as the need for large amounts of training data and

the risk of overfitting, especially in high-dimensional datasets.

4 Biological Applications

Anomaly detection techniques find numerous applications in biology, spanning areas such as genomics, proteomics, metabolomics, and medical imaging. These techniques help in identifying unusual patterns that may correspond to diseases, genetic disorders, and many other biological phenomena.

4.1 Genomics

Genomics, the study of an organism's complete genetic material or genome, is a rapidly evolving field. Advances in high-throughput sequencing technologies have resulted in an explosion of genomic data, which often contain anomalies representing significant genomic events such as mutations or variations. Detecting these anomalies is paramount in genomic analysis and has critical implications for understanding diseases, evolution, and biological functions (Goodwin, McPherson, and McCombie 2016).

4.1.1 Single Nucleotide Polymorphisms

Single nucleotide polymorphisms (SNPs) are one of the most common types of genetic variation among individuals, each representing a difference at a specific location in the DNA. These variations occur approximately once every 300 nucleotides on average, which means there are roughly 10 million SNPs in the human genome (Brookes 1999). Given their ubiquity, SNPs serve as critical biomarkers for predicting an individual's susceptibility to diseases, response to drugs, and other health-related traits (Botstein and Risch 2003).

One major application of SNP detection is in the field of personalized medicine, where understanding genetic variations can significantly impact treatment strategies. For example, certain SNPs are known to affect the metabolism and effectiveness of various drugs, thus allowing healthcare professionals to customize medication plans based on a patient's unique genetic makeup (Marsh et al. 2007). Notably, rs1061170 is a SNP associated with age-related macular degeneration, a leading cause of blindness in the elderly. A specific variant in this SNP, particularly the presence of a 'T' allele, can substantially increase the risk of developing this disease (Kanda et al. 2007).

In the context of anomaly detection, methods like clustering algorithms and outlier detection have been employed to identify unusual patterns or rare SNPs that deviate significantly from what is typically observed in the population. For instance, the Apriori algorithm, a machine learning method traditionally used for market basket analysis, has been adapted to detect SNP-SNP interactions indicative of disease susceptibility (Liu et al. 2010). Such techniques allow researchers to not only identify individual SNPs but also to understand the combined effects of multiple SNPs, thus enhancing our ability to predict and prevent diseases on a more personalized level.

4.1.2 Structural Variations

Structural variations (SVs) are genomic rearrangements that involve segments of DNA larger than one kilobase. They include insertions, deletions, duplications, inversions, and translocations. Given their scale, these SVs often have a significant impact on an organism's phenotype as they can alter gene structure, dosage, and regulation (Feuk, Carson, and Scherer 2006). Detecting these SVs is a fundamental aspect of genomics, especially in cancer research, where such anomalies can disrupt tumor suppressor genes or activate oncogenes.

One notable example is the deletion of the PTEN gene, a tumor suppressor that is frequently observed in several types of cancer, including prostate and brain cancers (Li et al. 2005). The PTEN gene helps regulate cell division and prevents cells from growing and dividing too rapidly or in an uncontrolled way. Deletion of this gene disrupts its normal function, thereby allowing cells to divide uncontrollably and form tumors.

Another significant SV is the amplification of the HER2 gene, often found in breast and ovarian cancers. This gene produces the HER2 protein that promotes cell growth. When the HER2 gene is amplified, it leads to overproduction of the HER2 protein, which can cause cells to proliferate excessively, leading to aggressive forms of cancer (Slamon et al. 1987).

Machine learning-based anomaly detection methods, including clustering and classification algorithms, can aid in identifying such significant alterations in genomic datasets. For instance, the Copy Number Analysis Tool (CNAT) uses statistical segmentation and a Hidden Markov Model to detect copy number changes in high-resolution array Comparative Genomic Hybridization (aCGH) data (Venkatraman and Olshen 2007). Other machine learning techniques, such as support vector machines and random forests, have been

applied to detect complex structural variations, providing valuable insights into cancer genomics (Rampasek and Goldenberg 2014).

These examples underline the importance of anomaly detection in understanding the genetic basis of various diseases and potentially informing treatment strategies.

4.1.3 Gene Expression

Gene expression is the process by which the genetic information encoded in a gene is used to produce a functional product, usually a protein. By studying gene expression, researchers can understand when and where each gene is turned on or off in the cells of an organism, revealing the functional roles of genes in normal cellular processes and disease states.

Anomaly detection in gene expression analysis involves identifying genes that show atypical expression patterns, which could be indicative of dysregulation associated with diseases. Gene expression data is typically high-dimensional, with measurements for thousands or tens of thousands of genes across numerous biological samples. This high-dimensionality makes the task of identifying anomalous expression patterns challenging.

Microarray technology and more recently, RNA sequencing (RNA-seq), are commonly used tools to measure gene expression levels. For instance, a study by Golub et al. employed microarrays to generate gene expression data for leukemia patients (Golub et al. 1999). The authors used anomaly detection methods based on decision trees to identify genes showing unusual expression patterns between two types of leukemia, acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL). This application highlights the power of anomaly detection in distinguishing disease subtypes and improving the accuracy of diagnosis.

Moreover, machine learning-based techniques like clustering and classification have been employed for anomaly detection in gene expression analysis. For example, the Robust Multi-array Average (RMA) and the Hierarchical Ordered Partitioning and Collapsing Hybrid (HOPACH) clustering methods have been utilized to detect anomalous gene expression patterns in breast cancer samples, identifying potential molecular subtypes of the disease (De Wiel et al. 2003).

Deep learning techniques have also been applied in this context, with autoencoder neural networks used for anomaly detection in gene expression data. For example, a study by Zhou and Troyanskaya used an autoencoder model to

capture the normal variability in gene expression data across different tissues. The model could then detect anomalies representing tissue-specific dysregulation, providing insights into disease mechanisms (Zhou and Troyanskaya 2018).

These examples underscore the utility of anomaly detection in gene expression analysis, offering opportunities for more precise disease characterization, early detection, and the development of personalized treatments.

4.2 Proteomics

Proteomics is the comprehensive study of proteomes, i.e., the entire set of proteins expressed by a genome, cell, tissue, or organism at a certain time. It's a critical field in functional biology and disease research, where anomaly detection can significantly contribute (Wilkins et al. 1996).

4.2.1 Biomarker Discovery

Biomarkers are biological molecules found in blood, other body fluids, or tissues that signal normal or abnormal processes, conditions, or diseases. They can be proteins, DNA, mRNA, or metabolites and have a broad spectrum of applications in clinical research, drug development, and disease diagnosis, prognosis, and treatment.

Anomaly detection plays a significant role in biomarker discovery in clinical proteomics. It helps identify proteins showing abnormal expression or modification patterns that can be associated with disease states. These protein anomalies can serve as potential biomarkers, offering insights into disease mechanisms and providing targets for therapeutic interventions.

For example, in the field of oncology, the overexpression of the HER2/neu protein is a common anomaly in certain breast cancers. This overexpression, detectable using immunohistochemistry or fluorescence in situ hybridization, is indicative of a more aggressive disease course. However, it also helps clinicians select patients who might respond to targeted therapies like trastuzumab, a drug specifically designed to target HER2 positive cells (Ross and Slodkowska 2009).

Machine learning-based anomaly detection methods, such as support vector machines (SVM), have proven effective in biomarker discovery. These methods can handle the high dimensionality of proteomic data and help identify proteins with abnormal expression profiles. For instance, SVM-based

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methods were used in a study by Furey et al., which aimed to identify serum proteomic patterns for ovarian cancer (Furey et al. 2000). Their results showed that SVM could accurately distinguish cancer from non-cancer based on these patterns, demonstrating its potential in cancer diagnosis.

Proteomic biomarker discovery is not limited to cancer. It has applications across a range of diseases, including neurological disorders, cardiovascular diseases, and diabetes. In all these cases, anomaly detection is crucial in identifying the protein signatures that can serve as potential disease biomarkers. For instance, an elevated level of the protein alpha-synuclein in cerebrospinal fluid is an anomaly associated with Parkinson's disease, potentially serving as a diagnostic marker (Tokuda et al. 2010).

These examples underscore the value of anomaly detection in clinical proteomics and its potential to advance personalized medicine, early disease detection, and targeted therapeutics.

4.2.2 Protein Modification

Proteins are the workhorses of the cell, fulfilling a broad range of functions from structural support to signal transduction and enzymatic activity. However, the functionality of proteins often extends beyond what is encoded in the DNA sequence, with various chemical modifications occurring after protein synthesis, known as post-translational modifications (PTMs). These modifications, which include phosphorylation, methylation, acetylation, and ubiquitination, among others, significantly expand protein functionality by altering activity, localization, and interactions.

PTMs play essential roles in various biological processes, including cellular signaling, DNA repair, and gene regulation. Consequently, abnormal PTMs often result in diseases. This notion is particularly evident in the context of neurodegenerative disorders. An example is the hyperphosphorylation of the Tau protein, which is associated with diseases like Alzheimer's. In a healthy brain, Tau proteins stabilize microtubules, but in Alzheimer's disease, they detach from the microtubules and form tangles in the neuron, contributing to neurodegeneration (Ballatore, Lee, and Trojanowski 2007).

Anomaly detection techniques can be employed to identify unusual PTMs from mass spectrometry-based proteomics data. These techniques can include unsupervised learning algorithms like clustering or more complex machine learning algorithms, and they are capable of detecting unexpected PTM patterns that might signify disease. For example, in a study by Hornbeck

et al., anomaly detection methods were used to identify aberrant protein phosphorylation in cancer cells (Hornbeck et al. 2012).

Furthermore, the application of machine learning in anomaly detection can help in the identification of novel PTMs that could serve as potential therapeutic targets. In the case of Tau protein hyperphosphorylation in Alzheimer's disease, understanding the pattern of this abnormal PTM could lead to targeted drug development and a potential treatment for this currently incurable condition.

The applications of anomaly detection in protein modifications represent a crucial area in proteomics, expanding our understanding of diseases at the molecular level and contributing to the development of more precise and targeted therapeutics.

4.2.3 Structural Anomalies

Proteins are remarkably complex molecules, and their functionality is intricately tied to their three-dimensional structure. Proteins are dynamic molecules that can adopt various structures, folding into unique shapes that allow them to perform their specific tasks in the cell. However, when this folding process goes wrong, it can result in what are known as misfolded proteins. These misfolded proteins, which are a type of structural anomaly, are implicated in several diseases, especially neurodegenerative disorders such as Parkinson's and Alzheimer's.

An example of such structural anomalies is the misfolding of the protein alpha-synuclein in Parkinson's disease. Alpha-synuclein is a protein found abundantly in the human brain. Under normal circumstances, alpha-synuclein folds into a helical structure and assists in the regulation of synaptic vesicles in neurons. However, in Parkinson's disease, alpha-synuclein misfolds into beta-sheet-rich structures that aggregate into what are known as Lewy bodies. These protein aggregates are toxic to neurons and are characteristic anomalies in Parkinson's disease (Spillantini et al. 1997).

Machine learning-based anomaly detection methods, including deep learning techniques, have been increasingly used to detect such structural anomalies from protein structure data. One such technique is the use of convolutional neural networks (CNN), which can identify patterns in high-dimensional data and have shown promise in the field of protein structure prediction and analysis (Senior et al. 2020).

In a study by Senior et al., a deep learning-based algorithm called Al-

phaFold was employed to predict protein structures. AlphaFold could also be adapted to identify structural anomalies in proteins, including misfolded regions or unusual structural motifs (Senior et al. 2020).

The ability to detect structural anomalies in proteins holds great potential for understanding disease mechanisms and could pave the way for the development of new therapeutic strategies that target misfolded proteins.

4.3 Metabolomics

Metabolomics is the systematic study of the metabolome, the complete set of small molecules or metabolites in a biological organism, at a given time. Metabolites are the end products of cellular processes, and their levels can be regarded as the ultimate response of biological systems to genetic or environmental changes. Machine learning approaches, including anomaly detection, have been increasingly applied to metabolomic studies, contributing to disease diagnostics, drug discovery, and personalized medicine (G. Zhang et al. 2019).

4.3.1 Biomarker Discovery

In metabolomics, anomaly detection often plays a crucial role in biomarker discovery. It can identify metabolites that are present at abnormal concentrations in certain disease states. These anomalous metabolites can serve as potential biomarkers, providing insights into disease mechanisms and indicating possible targets for therapeutic interventions (Johnson, Ivanisevic, and Siuzdak 2016).

Machine learning techniques such as random forests, support vector machines, and deep learning have been used to classify disease states based on metabolic profiles and to identify potential biomarkers. For instance, Wishart et al. employed machine learning techniques to identify serum metabolic biomarkers for cardiovascular disease (Wishart 2018). In another study, an unsupervised machine learning approach was used to detect anomalous metabolite levels in urine samples, leading to the discovery of biomarkers for bladder cancer (Pasikanti et al. 2010).

The power of metabolomics in biomarker discovery lies in its capacity to capture the complex interactions between genes, environment, and disease in a holistic manner. This approach opens up new avenues for precision medicine, allowing for more accurate disease prediction, prevention, and treatment.

4.3.2 Metabolic Pathway Analysis

Metabolites are the end products of cellular processes and as such, can provide a snapshot of the cellular state at a given time. Abnormalities in metabolic pathways can lead to disease states. Thus, detecting anomalies in these pathways is crucial for understanding the pathogenesis of various diseases.

Machine learning techniques have been used to model and analyze metabolic networks, identify key enzymes and metabolites, and detect anomalies in metabolic pathways. For instance, in a study by Kim et al., machine learning was used to analyze metabolic networks in cancer cells, revealing the vital role of the lipid metabolism pathway in cancer development (Kim et al. 2019).

These examples underscore the potential of machine learning and anomaly detection in elucidating the intricate relationships within metabolic networks, providing insights into disease mechanisms and potential therapeutic targets.

4.3.3 Drug Metabolism

Drug metabolism is a key consideration in pharmacology and toxicology, determining the efficacy and potential toxicity of therapeutic agents. Each individual's unique metabolic profile, or metabotype, can significantly influence the body's response to drugs. As such, understanding the interindividual variability in drug metabolism is essential for personalized medicine.

Anomaly detection in metabolomics can help identify individuals with unusual metabolic responses to drugs, leading to adverse effects or therapeutic failure. Machine learning methods can be used to predict these abnormal responses based on individual metabotypes, thereby guiding personalized drug treatment strategies (El et al. 2019).

For example, Ellero-Simatos et al. used a machine learning approach to predict the variability in response to the antidiabetic drug metformin based on metabolomic data. Their model could identify patients who were less likely to respond to metformin, indicating a need for alternative treatment strategies (Ellero-Simatos et al. 2015).

These applications of anomaly detection in drug metabolism highlight the potential of metabolomics in advancing personalized medicine, contributing to more effective and safer drug treatments.

4.4 Medical Imaging

Medical imaging techniques like MRI, CT, and X-ray scans are vital in diagnosing and monitoring diseases. Anomaly detection plays a key role in analyzing these complex imaging data, assisting clinicians in accurate diagnosis and treatment planning (Hosny et al. 2018).

4.4.1 Lung Cancer Detection

Lung cancer is one of the most common and deadly types of cancer, often due to its late-stage diagnosis. Early detection can significantly improve patient outcomes, and computed tomography (CT) scans of the chest have become a vital tool in identifying lung cancers at an earlier, more treatable stage. In these scans, doctors look for nodules, small lumps of cells, that may be early-stage lung cancer. However, finding these nodules can be like finding a needle in a haystack, and their interpretation can be subjective and error-prone, even by experienced radiologists.

In this context, anomaly detection methods have shown great promise in identifying nodules, a potential sign of early-stage cancer, in chest CT scans. Deep learning algorithms, specifically Convolutional Neural Networks (CNN), have been effectively used for this task. CNNs are a type of deep learning model that are especially good at processing images. They can learn to identify complex patterns in large datasets, and their performance often improves with the amount of data they are trained on (LeCun, Bengio, and Hinton 2015).

One of the significant breakthroughs was the work by Ardila et al., who developed a deep-learning algorithm that analyzed volumetric CT scans and outperformed six radiologists in detecting malignant lung nodules. The algorithm showed superior performance compared to radiologists in both sensitivity and specificity, and was particularly effective in reducing false positives and false negatives (Ardila et al. 2019).

This application of anomaly detection in lung cancer screening holds significant potential to reduce the mortality of the disease by aiding in early detection and diagnosis. However, further validation in prospective studies is needed before these tools can be broadly implemented in clinical practice.

4.4.2 Breast Cancer Diagnosis

Breast cancer is the most common cancer among women worldwide. Early detection through mammography screening has been effective in reducing mortality from this disease. Mammography is an X-ray technique used to visualize the internal structure of the breast. Radiologists interpret mammograms by looking for anomalies such as suspicious masses or calcifications that might indicate the presence of a tumor. However, interpreting mammograms can be challenging due to the subtle nature of these anomalies and the variability in breast tissue density.

Deep learning-based methods have recently been employed to augment the capabilities of radiologists in mammography interpretation. These algorithms, trained on large datasets of mammograms, have proven effective in detecting these anomalies, thereby aiding in the early diagnosis of breast cancer. For instance, Lehman et al. demonstrated a deep learning model that could identify breast cancer in screening mammography with better accuracy than an average radiologist (Lehman et al. 2020).

The model was trained using a large dataset of more than 200,000 screening mammograms, and the study showed that it achieved higher sensitivity, specificity, and area under the ROC curve compared to the human readers. Importantly, the deep learning model significantly reduced false positives and false negatives, both of which can lead to patient harm through unnecessary interventions or missed cancers respectively.

This application of anomaly detection in breast cancer screening presents a promising step towards improving breast cancer prognosis by enabling more accurate and earlier detection. Nonetheless, like other AI applications in healthcare, these methods need to be validated on diverse and representative populations before widespread clinical adoption.

4.4.3 Diabetic Retinopathy

Diabetic retinopathy is a complication of diabetes that affects the eyes, caused by damage to the blood vessels of the retina. It is a leading cause of blindness in working-age adults and presents a significant public health challenge. The early stages of diabetic retinopathy are often asymptomatic, emphasizing the importance of regular screening for early detection and treatment. However, the process of manual grading of retinal images by clinicians is time-consuming and can suffer from inter-observer variability.

Machine learning and anomaly detection have been leveraged to automate the process of diabetic retinopathy detection. Specifically, machine learning algorithms are trained to identify anomalies like microaneurysms, hemorrhages, or exudates in retinal fundus photographs. For instance, Gulshan et al. developed a deep learning algorithm that performed at or above the level of trained ophthalmologists for the detection of referable diabetic retinopathy (Gulshan et al. 2016).

The algorithm was trained on a large dataset of over 128,000 retinal images and demonstrated high sensitivity and specificity in detecting referable diabetic retinopathy. Importantly, the model also proved effective at grading the severity of diabetic retinopathy, highlighting the potential of such machine learning approaches for aiding clinicians in treatment decisions.

This example showcases the potential of anomaly detection in automating and augmenting the diagnosis process, leading to early intervention and treatment, reducing the burden on healthcare systems, and ultimately improving patient outcomes.

Nonetheless, while promising, these models need rigorous testing and validation across diverse populations, and their integration into healthcare systems must be thoughtfully managed to address potential challenges, such as explainability, data privacy, and ethical issues.

5   Challenges and Open Questions

Anomaly detection presents promising avenues for biological and medical applications, but several challenges and open questions remain that require attention from researchers and practitioners.

Data Availability and Quality: Data availability and quality are crucial for the performance of anomaly detection algorithms. Obtaining high-quality, labeled genomic or proteomic data can be difficult due to the cost and time required for data collection and annotation (Costello et al. 2013). Moreover, data quality can be affected by batch effects, noise, and other experimental variations. Addressing these issues through robust data preprocessing techniques and data augmentation strategies can help enhance the performance of anomaly detection methods.

Algorithmic Robustness and Validation: Validation of anomaly detection algorithms is another significant challenge. Given the critical nature of many biological and medical applications, it is crucial that these

algorithms are rigorously validated on independent test sets and across diverse populations. Further, understanding the robustness of these algorithms under various conditions, such as differing levels of noise or varying sample sizes, is of paramount importance (Libbrecht and Noble 2015).

Interpretability: Interpretability is a key requirement for the clinical adoption of anomaly detection methods. Given the complexity of biological systems, understanding the rationale behind an algorithm's decision is necessary for trust and adoption by clinicians. While some machine learning methods, like decision trees, offer interpretability, others, particularly deep learning methods, are often considered "black boxes" (Rudin 2019).

Integration into Healthcare Systems: Lastly, the successful integration of anomaly detection methods into healthcare systems poses a significant challenge. Issues such as data privacy, ethical considerations, and the need for explainability must be addressed. It's crucial that healthcare professionals are adequately trained to use and understand these tools, and that these tools are designed with user-friendly interfaces to ensure broad adoption (Topol 2019).

6 Conclusion

This paper has explored the crucial role of anomaly detection in various biological applications, from genomic, metabolomics, and proteomic analysis to medical imaging and disease diagnosis. We highlighted how various machine learning techniques, such as clustering, decision trees, support vector machines, and deep learning, have been employed to detect anomalies in vast and diverse biological datasets. We've seen the value these techniques bring to different scenarios, such as detecting genetic variations that underpin disease susceptibility, finding abnormal gene expression patterns indicative of disease onset, and identifying anomalies in medical imaging that support early disease diagnosis.

However, it is clear that many challenges and open questions still lie ahead. These include concerns about data quality and availability, the need for robust validation of machine learning algorithms, the demand for interpretability in clinical settings, and the integration of these techniques into healthcare systems. Addressing these challenges is critical to unlocking the full potential of anomaly detection in biology and medicine.

In conclusion, anomaly detection represents a promising field of research

in biology with immense potential to enhance our understanding of biological systems and improve disease diagnosis and treatment. By integrating advanced machine learning techniques, we can extract valuable insights from large-scale and complex biological datasets. We hope this review inspires further research in this area, fostering the development of innovative machine learning approaches that can contribute to transformative discoveries in biology and medicine.

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