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Foreword

The connectedness of today's world enables us to unlock the boundless potential of human ingenuity. It is in this spirit that The Horizon Academic Research Program connects talented high school students from all over the world with professional researchers to work on meaningful academic research. The Horizon Academic Research Journal showcases the selected high quality work produced by high school students in the The Horizon Academic Research Program.

This journal issue represents diversity and excellence in research from our Summer 2020 term. Students from 27 countries, from our own zip code in New Jersey, to as far away as Vietnam, India, Armenia, and China, worked with researchers from 12 universities to produce scholarship on topics ranging from Bioinformatics to International Relations. By conducting the program online, we were able to cross physical boundaries that would have otherwise made such work impossible.

Out of more than 1,200 of applicants, 173 students were accepted and enrolled into the program. These students worked either individually or in small groups with researchers, with the goal of producing an impactful research project. Some students produced original research, while others filled gaps in the current literature using knowledge gained over the course of their time at Horizon Academic. Of these students, 12 were selected to publish their work in this issue.

Despite being written by high school students, these papers display a level of thoughtfulness, analytical rigor, and ambition more typical of undergraduate students. Some papers are approachable introductions to fields that are difficult for the average person to access, while others cause us to question our understanding of ideas that we may think we are familiar with.

We are pleased to make this Volume available to the public and hope that this provides a window, not only into the skill and ability of each author, but also into the abilities of high school students to do meaningful research without the use of physical lab spaces. It is our pleasure and honor to share this work with you.

Ani Nadiga
Horizon Academic Research Program, Project Advisor
Editor, Horizon Academic Research Journal, Vol. 1

The Effects of the Coronavirus Pandemic on Student Learning

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September 30, 2020

Abstract

The Coronavirus pandemic (COVID-19) has spread globally with catastrophic effects on the world, severely impacting lives, jobs, and the education of students. The health crisis impact has forced a shift towards online learning, transforming the delivery of education, and disrupting the schooling of every student. This paper looks at the comparison between traditional and online learning and the effects they have on social interactions, motivation, and stress on students. Although every learner has been negatively affected by this sudden adjustment to remote learning, learners from underprivileged societies have been more vulnerable, facing disproportionate losses in their education. Online learning has become the new "normal" as the virus's effect has shown to be longer than predicted. As discussed in this paper, it is crucial to take collaborative actions and policy changes to create online learning a more engaging and effective delivery method of education.

1 Introduction

The Coronavirus pandemic, or COVID-19, has revolutionized the educational system and its delivery to students across the world. The airborne disease transmits deadly droplets through close contact between people. Consequently, social distancing is enforced by governments across the world, leading to school shutdowns and an immediate switch to online education. Although online learning is not a novel concept, the virus acted as a catalyst, forcing learners and educators to adopt distance learning. Almost overnight, the education systems scrambled to transition completely to online distance learning with little time to plan and no clarity of what will happen next. Teachers and students who are used to interactive courses have begun to revise the curriculum and their learning methods to adapt to the new remote conditions. The spiraling crisis has overwhelmed every aspect of the teaching world. After a pneumonia epidemic without apparent cause, a novel strain of the Coronavirus – SARS-Cov-2 – was

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first identified as COVID-19 in December 2019 in Wuhan, China. On January 20th, 2020, the United States recognized its first case in Washington [CDC20] The virus was officially declared a pandemic on March 11th, 2020 [Org20] The exponential spread of this contagion has alerted many officials to take drastic measures for the safety and well-being of their nations' populations. To disrupt human-to-human contact, many counties, states, and countries have announced lockdowns, ordering civilians to isolate and shelter in place. [Org20] The global pandemic has led to a severe health and socioeconomic crisis. Immunocompro- mised and older populations in specific are compelled to take extreme precau- tions as they are at a greater risk of death by COVID-19 [fDCP20]. An estimated 195 million jobs will be lost, and 800 million people will not be able to meet basic needs [Pro20]. This unprecedented disaster has left millions in unstable living conditions and food insecure. Concerning the educational impact, China and Mongolia were the first countries to close schools on February 17th, 2020, affecting one million learners. By April 4th, 2020, 192 countries implemented school closures, affecting 1.6 billion learners, accounting for 91.2Certain popu- lations of students have been particularly affected by the transition to remote learning. Young children, for example, are faced with the disadvantage of being technologically illiterate, requiring additional assistance. Learners with learning disabilities are also an example of an affected population deprived of the proper help needed to continue a successful education. This paper focuses on the ad- ditional challenges of online learning that affect underprivileged students from lower socioeconomic societies including the deep digital divide and lack of many crucial elements to make learning more efficient. The infectious disease has im- pacted everyone in different ways. Individuals are having to use their cognitive resources on factors that could include one's health, employment, education, or lifestyle, taking away from their concentration, affecting their performance and well-being. The sudden impact of the Coronavirus pandemic has left everyone unprepared and isolated, leading to an inadequate education delivery system. The movement towards remote learning has been stressful to many students as important academic exams and events including the SATs/ACTs and AP ex- ams have been canceled, postponed, or relocated online. This paper explores the causes of increased anxiety and loss of motivation that learners are experiencing which is negatively reflected in their performance. To understand the radical changes in education, it is important to examine and evaluate the differences between traditional and online learning. Understanding the differences between the two education methods would clarify the effect of this sudden change from traditional to online learning and the impact it has left on learners.

2 Traditional Learning

Learning is recognized as an active progression that cannot be obtained but must be built by the learner. Traditional learning consists of four critical el- ements: an educator, or a knowledgeable person to share their proficiency; a conducive setting like a classroom or lab; materials such as textbooks, videos,

diagrams, and charts; and motivation to personalize learning. The purpose of an educator is to facilitate the learning process by encouraging and providing support to a student to actively create knowledge, building upon ideas that the learner already understands, for them to achieve their highest potential [D.08]. Domin states, "Knowledge cannot be transferred from one person to another; it must be actively constructed by the learner through interactions with the environment" [S.99]. A designated environment limits distraction and focuses the student on active and interactive learning. Reference models and hands-on experiences are tools used in traditional learning that motivate a student to take initiative to learn. Learning in a classroom setting with strong student-teacher and student-student relationships is an important component of traditional education. Face-to-face instruction allows educators to assess the knowledge and the progress of a learner to tailor teaching towards the development of the students. They teach their expertise based on modules and concepts that encourage student participation with the use of interactive tools such as group work, class discussions, debates, peer critiques, and more [C.06]. Group work allows students to discuss ideas amongst each other, developing deeper and more polished understandings of subject matters. The promotion of active learning and collaboration amongst educators and other peers to expand and build upon their prior knowledge. Learning is most effective when treated as a collaboration between peers rather than individual competition. Social interaction frequently improves student participation and allows for the sharing of ideas, sharpening students' understanding. The zone of proximal development refers to knowledge that is unobtainable for an individual independently but can be learned with guidance from another person. Active discussions and asking questions allow the instructor to evaluate and determine what the learners know and do not know and their average zone of proximal development [L05]. In traditional education, this assessment is especially helpful for a teacher to scrutinize students' performance and provide suitable commentary and criticism. Traditional learning improves critical thinking through the sociability of an in-person classroom environment. Discussions and debates, for example, allow a student to hear different perspectives and gain more understanding about a subject matter. Critical thinking is an advanced way of thinking to analyze and assess a judgment, centering on comprehension, analysis of various ideas and perspectives, and problem-solving [H.02]. It is an important skill that inspires a broader mindset and analytical thinking. An individual should be able to recognize and approach a problem, raise questions that challenge ideas that are simply informed to them, and develop creative solutions. Students who are taught in a classroom structured environment as a unit, learn concepts through a "lecture and questioning" method. This technique emphasizes critical thinking as it stimulates interactions between a learner, their peers, and an educator [C.06]. The mere "possession" of knowledge is not enough for critical thinking but requires further motivation and a desire to learn [E.03]. Active learning can also be utilized outside of classroom walls and structured exercises. There are multiple learning opportunities available for students such as simulations, internships, externships, autonomous studies, and hands-on programs. Learning

through experiences and the trial and error technique refers to experiential learning. According to American educationalist theorist, David Kolb, there are four stages of experiential learning which include concrete learning, reflective observation, abstract conceptualization, and active experimentation [K.09a]. Under Kolb's theory, an effective learner must go through all the following stages to thoroughly be knowledgeable about a topic. For instance, a person cannot learn by memorizing given information. Instead, they need to take the extra effort to become involved in the experience. A participant needs to reflect and recognize any common patterns or themes to help them with new experiences and to develop a more concrete understanding to apply in the future. Lastly, it is important to improvise, take risks, and experiment with new evolving theories and circumstances to discover new methods of improvement. This technique allows learners to 'learn by doing' and apply their knowledge to future situations.

3 Online Learning

The Coronavirus epidemic has become one of the largest challenges the educational system has ever had to face. Students from all over the globe are forced to adapt to new circumstances in all areas of their lives, as governments have authorized the ceasing of face-to-face education. As everyone obliged to shelter in place rules, education platforms have changed, transitioning to an online, or distance learning model [J.20]. Within a short period, students were required to switch from traditional education to online and virtual learning. Online learning is definitionally education that is executed through technology without the physical attendance of classes, lectures, or seminars. Remote education can be further categorized as synchronous and asynchronous e-learning. Synchronous e-learning refers to remote instruction where teachers and students communicate and collaborate electronically at the same time. Asynchronous e-learning is academic instruction without communication between the students and the teacher. This can occur via online forums, interactive school courses, emails, virtual telecommunications, and so forth. Online education has not been reported as an effective medium for learning as it lacks proper structure and necessary social interaction. Although there is limited research regarding the quality of online learning, there are multiple adverse experiences of remote learning which are based on poor online courses and pedagogy [J.05]. In comparison to traditional learning, distance learning does not provide the needed discipline for successful and efficient learning. Through traditional learning, an educator can easily identify a student's attentiveness and assess their teaching methods to ensure constant growth in a learner's progress. However, in remote learning, it is difficult to keep an eye on a large number of students in a class on a screen. There are a multitude of distractions, interrupting the class flow and creating challenges to teach the class. Distance learning does not allow instructors to maintain the same student-teacher relationships as it was in the classroom en- vironment. As many institutes have converted to online education, it is a harsh reality that many students do not have access to the technology and materials

needed. Students may not have a conducive environment or an appropriate device needed to support their learning remotely. Underprivileged children, in particular, discussed later in the paper, may not have access to the same level of technology at home – whether it is the latest model of the laptop or high-speed internet. In contrast, traditional, in-person schools are settings dedicated to the student's education and give them equal access to all materials, while online learning resources may not be uniformly available to every individual. Whether the signal is lost, content is missed, or electronics are not available, the lack of accessibility to such materials is one of the reasons virtual learning is not effective and cannot be a replacement for traditional learning. Learning is not just an intellectual process, but a social activity, requiring in-person contact amongst other materials. Through the means of traditional learning, students can interact with other individuals including their teachers, faculty, and their peers. However, while engaging in online education, the learner is not directly interacting with the educator and their classmates, making communication difficult and impersonal. Missing the day-to-day connections with a fellow student or teacher and the subsequent need to be self-motivated to push through schooling can prompt feelings of isolation. Discussions, for example, are a necessary component of social interaction between teachers, students, and classmates. This social activity demands active participation and allows for students to engage in active cognitive processing. They mandate students to articulate their knowledge, encouraging them to engage, contextualize, and apply what they know. According to the constructivist theory, learners require the ability to engage in opportunities to create meaning for themselves [S15]. Although discussions can be executed online, the inability to comprehend body language and chaos becomes an uninviting and hostile environment. Contrary to passive activities such as reading texts and listening to lectures, discussions necessitate learners to analyze and decipher what they have learned in their own words. Discussions excellently allocate students to hear different perspectives and compare and contrast ideas to enhance and better develop understanding and ideas of their own. Education and learning go beyond academics and lesson plans; it also includes discipline, manners, morals, and social interactions. These traits are difficult to teach remotely. The authors of "The Science of Learning and the Art of Teaching," Jerome Feldman and Doug McPhee, proclaim that kinesthetic learners are most successful when they are involved in an interactive activity that further promotes their learning [J.08]. Knowledge is easier to comprehend if it is being constructed by the learner who has undergone the intellectual process of reflection and analytical thinking. Students can retain more information at a quicker pace as they participate in a lab, presentation, skit, field trip, or other activities. They can take the information they receive and can evaluate, experiment, and modify their ideas while participating in such comprehensive processes that are available through traditional education [R.05]. Distance learning lacks the engaging and active experimentation process that is necessary for an effective learner to successfully acquire knowledge about a topic.

4 Effects of Traditional versus Online Learning

4.1 Stress

Stress can be defined as "when the perceived pressure exceeds your perceived ability to cope" [PSCCLT03]. In 2009, research done by Sulaiman, Hassan, Sapien, and Abdullah demonstrated that a majority of students experience some form of stress to some degree. In this study, the factors were subdivided by examining potential academic stressors including schoolwork, grades, and overall performance in school; and personal stressors that may exist in a learner's life such as extra-curricular involvement, self-esteem, and relationships [K.09b]. Stress, usually considered as a negative connotation, can bring an aspect of growth to certain conditions and individuals. Students deal with positive and negative stress on a daily basis. Positive stress, otherwise known as eustress, is invigorating as it is associated with conditions that provide challenges and opportunities for growth. Those who stress positively have an open mindset perspective, correlated with more success in learning and accomplishing their goals and ambitions. They often view obstacles as experiments to test themselves and find methods of improvement. In contrast, negative stress also referred to as distress, is correlated with threatening situations and the feeling of helplessness [A.84]. Students will often feel powerless or lost, adversely affecting their performance and prohibiting themselves to achieve their success. Stress has a significant impact on a student's academic performance. Of all the factors identified by student reports, stress was identified as the leading cause that was negatively affecting an individual's performance such as receiving a lower grade, not completing, or dropping out of a course [Ass10]. Reports illustrate trends that show more students are experiencing stress from this sudden change, which must be acted upon for the overall safety and wellbeing of all learners. Learners who are incapable of coping with stress develop tension, uneasiness, and anxiety. Stress this severe can lead to detrimental consequences on a learner's physical and mental health, affecting their performance [K.09b]. Multiple studies elucidate the importance of social support in maintaining an individual's physical and psychological health. There are three different forms of coping techniques identified which include: problem-focused coping, which correlates to the concept of identifying and confronting the source to relieve stress. Emotional-focused, or social coping refers to handling one's emotional response to a stressor, and third, avoidant coping, which refers to the avoid- ing of the stressor as much as possible [MCLAAB12]. Social support is a way of emotional coping where there are social connections available to an individ- ual for any form of support or reassurance. Four types of social support carry their individual benefits: Emotional social support, the encouragement of one's self-worth. Informational social support, relating to the sharing of advice and guidance to someone who may be undergoing a stressor. Tangible social sup- port includes the sharing of resources to relieve a stressor, and lastly, belonging social support, which refers to the act of offering inclusion [OFJDCDEMI07]. Furthermore, it appears that social support of all types can help to construct

and strengthen the resistance to stress. Coping mechanisms of stress that involve social support heavily depend on communal interactions. With the recent transition from traditional to online learning, social support coping processes can not be as effective to relieve the stress of learners as before. Through tradi- tional learning, students would frequently use their leisure time to reach out and interact with other classmates for emotional social support to relieve some of their stress. With the current absence of in-person communication in distance learning, students may find it more difficult to reach out and interact with their peers, limiting the availability and value of emotional social support. In tradi- tional learning, students can easily connect with teachers and counselors for the proper guidance and information social support needed to fully comprehend the knowledge they are learning. However, there are more difficulties and obstacles regarding communication between students and educators to ask questions, de- velop a thorough understanding of the curriculum, and build personal relation- ships with teachers in a remote-learning environment. Tangible social support includes all the information a classmate can receive from their peers about how to effectively deal with a course. In traditional learning, students can gain lots of tangible social support from the sharing of resources available such as class or lecture notes. On the contrary, the available materials through the distance learning model are limited to a student. Outside of academics, social support refers to the sense of support an individual can receive from social groups and teams that center on teamwork and involvement. Extracurricular activities that occur with traditional learning, such as team sports, clubs, volunteer work, and charities allow students to participate and create a feeling of belonging to a certain group with similar interests or situations. Distance learning, social distancing regulations, and shelter in place isolation rules prohibit and hurdle the group-related participation activities that provide belonging social support to an individual.

4.2 Motivation

Motivation is a powerful tool that disciplines and compels an individual to move forward with a goal or objective. It refers to the “why” of our actions and behaviors which are usually goal-oriented. Motivation can arise from external (extrinsic) or internal (intrinsic) factors. Extrinsic motivation is when individuals are inspired to behave or participate in activities because of exogenous components. This example of motivation can come from another person such as an educator and or friend or an incentive to seek a certain reward or escape punishment. A learner’s reasoning to be involved in an activity is an expectation to receive something in return such as a grade or praise or to avoid something negative including timeouts or a reduction in grades. Intrinsic motivation is the engagement of activity for reasons such as passion and self-growth. The activity is a reward in itself and is performed for the individual rather than an aspiration for an external incentive. A learner would have a perspective of a growth mindset, partaking in an activity for their interest and further development of their construct of knowledge. They would view things with eustress, taking on

a challenge for passion and improvement. Competition amongst peers can instigate stress and drive motivation – both intrinsic and extrinsic – to do better and have the satisfaction of completing the activity, or to achieve some sort of reward [F.11]. Eisenberg and Thompson experimented with two similar conditions to determine how competition affects the performance of improvisers. In the competition condition, participants were tasked to formulate an improvised musical piece that would be blindly judged to determine the "best improviser." In the condition with no stimulated competition, participants were told that the experimenters were interested in how people improvise. The study illus- trated that competition, a combination of motivation and eustress, results in higher creativity and an overall boost in performance [F.11]. A learner's educa- tional development and motivation are influenced by "how" rather than "what" they are taught. Every individual has different motivations from comfortable to risk-taking environments. There are different ways a student can be inspired such as hands-on and interactive activities that challenge and test a person's abilities. A traditional learning environment provides a conducive setting for students to dedicate time and space for their education. On the other hand, re- mote learning can take place in any setting, which can disrupt the line between personal and professional environments. The task to keep a student motivated and actively engaged is a challenge amongst all ages. Online learning courses, however, present themselves with more concerns as new difficulties arise. To be successful, students need to be disciplined, empowered, and self-regulated. Without the many elements of traditional learning such as face-to-face contact, educators are not able to detect any nonverbal clues from learners that signal their disengagement to the course.

4.3 Secondary Effects: Relations

An individual learns through social interactions, acquiring knowledge, and personality socially. According to the social constructivism theory, founded by Russian psychologist Lev Vygotsky, learners have more growth in their development when they incorporate the experiences, knowledge, and opinions of others to improve their learning [KCP09]. The evolution of individuality – personal to everyone – progresses with the agents of personality change: social relationships. Social collaborations act as building blocks to one's character in their personality development. Personality can identify as an individuals' psychological and behavioral pattern, such as the perceptions and emotional feelings that are different from each person. Evolving from social situations, these characteristics, and traits, are responsible for shaping an individual's personality. Through the simple means of communication, relations with others influence a person's character, allowing themselves to understand and develop their likes and dislikes, morals and ethics, and experiences and skills. Through the medium of online learning, social interactions which are a key component in the development of personality, individuality, and learning is limited to everyone. Traditional learning provides a conducive environment for social interactions. In a traditional learning environment, students connect in multiple different settings

including engaging activities in a teaching space (group projects, debates, and discussions) and outside the classroom (extracurricular activities and team sports). Commu- nication between learners allows them to progress and be exposed to new per- spectives, expanding their knowledge. These connections influence their views on many topics that concede a person to formulate their individuality [Nix13]. The ability to collaborate with peers is not an easy option through technology screens in comparison to a same-setting classroom or campuses. Beyond aca- demics, traditional schooling impresses core social and life skills that are crucial for success in the future. Social interactions improve and enhance the critical thinking and problem-solving abilities of learners as they are subjected to the different opinions and assessments of their peers they collaborate with [Nix13]. Communication and public speaking, for example, are common fears and vital aptitudes that can help a student in the workplace. Traditional learning allows students to speak in large groups, practicing the art of public speaking, as stu- dents present and articulate their thoughts and ideas in front of their educators and peers. In distance learning, speaking through virtual chats via computers does not teach public speaking.

5 Underprivileged Learners

As the Coronavirus pandemic continues to spread, millions of learners across the world are affected by school closures. The abrupt compulsion to convert to on- line learning has caused deep digital divides. Underprivileged students, whose family, social, or economic conditions impair their learning, are already at a disadvantage and are most susceptible to these technological gaps. Often these students do not have access to technology or an internet connection, which along with an overly stimulating home makes it difficult to concentrate. Re- search shows that learners from low socio-economic status families and societies progress slower in academic skills in comparison to those belonging in higher SES classes [MPLF09]. For example, growing up in a low SES community is associated with poor cognitive performance, linguistics, memory, and the over- all understanding of subjects. The educational systems in low socio-economic status areas frequently lack resources which adversely affects the academic de- velopment and performance of the students [N.15]. The addition of remote classes further challenges the underprivileged pupils. Many learners from low socio-economic backgrounds are not able to attend online classes for an array of reasons such as sharing or not having access to a laptop or device to be present at a class [L.20]. According to data collected over four weeks, ten per- cent of low SES children have little to no access to the equipment needed for online learning [Bur20] More than twenty-five percent of children who are ex- periencing food insecurity cannot access the internet to attend distant learning classes [Bur20]. The sudden change to distance learning has forced students to take the extra steps to participate in classes through the means of technol- ogy, which may not be available to many learners. Motivated to learn, many students are taking extreme measures to obtain access to the neededmaterials

to attend their online schooling. Multiple Chinese news reports have stated that children have walked and climbed for hours at a time to mountaintops for an adequate signal for remote classes [R.20]. An important element previously identified for effective learning was the need for a conducive learning environ- ment. The transformation to online learning removes the accessibility of many pupil's designated learning settings. Traditional learning offers classrooms and labs which are examples of encouraging environments that aid in the teaching and learning processes through hands-on activities between classmates. Remote learning requires pupils to attend their classes from their homes, which may not shelter the same designated settings for everyone. Some students, for instance, may have too many distractions or may have the added responsibilities of a sibling, pet, or elderly, taking away from their ability to concentrate on online learning. Online learning has further disadvantaged underprivileged students of lower socioeconomic status. Learners from low SES households and communi- ties are often challenged with the lack of the needed equipment and conducive space to attend distance learning classes. Traditional learning, on the other hand, offers students equal resources and a designated place for the education of all students.

6 Discussion

The Coronavirus pandemic has radically shifted traditional learning mechanisms to online learning. As the world tackles the sudden change to distance learning, students are missing important experiences that supplement their learning process. Attending remote classes in isolation at home confines a student, keeping them from important social interactions that encourage learning. A nod in the hallway, a wave in the cafeteria, or a smile in the locker room are a few examples of social gestures that help a student cope with stress. Social interactions appropriately address stress and motivate students, which is not remotely accessible. Hands-on involvements such as field trips, lab work, and group assignments, are also examples of crucial elements in educational development. The absence of these important components negatively impacts the education of students. The COVID-19 continues to reveal new layers of inequity within societies. An example of a vulnerable population with negative effects on their learning are children growing up in underprivileged societies. The absence of in-person schooling adds additional challenges to their education. Their inaccessibility of a designated quiet space and other fundamental equipment such as a device and internet connectivity place these children at a major disadvantage. As more than half a year has passed since school closures, the new school year has circled, leaving many in disagreement regarding the opening of schools. As the media covers one of the most controversial debates, it is important to remember the decision to re-open schools should not be driven by the pressure of politics but the evidence of science. As the current situation lingers and is becoming a new "normal" of learning, there are measures that can be taken to better improve upon the current conditions of education and fill the gaps

between traditional and online learning. For instance, it is important to make adjustments to ensure equal resources and access to all learners. Additional funding from the government can be provided for schools to be more resilient and be able to offer electronic materials such as laptops and hotspots to all students who do not have access to these materials. Public libraries can open with appropriate safety precautions to accommodate for a conducive setting for learners to be able to access a designated space to facilitate their learning. Educators can grant office hours to students with special needs or highly stimulus households for any additional help or support they may need. The potential solutions to this ongoing educational crisis will require more funding, new poli- cies, innovative lesson plans, new etiquettes, new attitudes, and much more, in which the communities and government have a crucial role to play.

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Melanoma Diagnosis using Convolutional Neural Networks

Ansh Chaurasia *

February 2021

Abstract

Melanoma is one of the most lethal forms of skin cancer in the USA, with an estimated 196,000 people being diagnosed by melanoma in 2020. Fortunately, melanoma can be much more straightforward to treat through skin excisions once it has been diagnosed, once again placing the brunt of the challenge on diagnosis. One of the primary techniques used by dermatologists to diagnose melanoma is known as dermoscopic imaging, which use high quality magnifying lenses to capture skin lesions in great detail. We believe that we can take advantage of this prominent imaging technique to create a Convolutional Neural Network that receives these dermoscopic images as input and outputs a binary classification - whether the melanoma is malignant or benign. To do this, we took a 100 GB Kaggle dataset from a Kaggle Competition and applied image transformations upon it to rigorously train a machine learning ensemble of models. Furthermore, we experimented with various machine learning architectures, techniques, and metrics to come up with a machine learning model that returns predictions with emphasis on accuracy and efficiency, boasting high AUROC and accuracy scores.

1 Introduction

A recent report by the World Health Organization (WHO) has included cancer in the top 10 causes of death [WHO]. More alarmingly, data from the same report also indicates the rate of patients diagnosed with cancer may double [Aus18]. Cancer can be lethal to patients, but its effects can be mitigated if detected and treated early [ski]. Therefore, it is worthwhile to invest time and research to improve our ability to diagnose cancers as early as possible.

Melanoma is one of the most lethal forms of skin cancer. It occurs in cells known as melanocytes, skin cells in the upper layer of skin. Melanocytes produce a pigment known as melanin to give the skin it's color. However, when skin is exposed to UV radiation, melanocytes produce more melanin than necessary,

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causing skin damage. Melanoma occurs when UV radiation causes mutations in these melanocytes, which leads to unrestrained cellular growth. Figure 1. gives a visual difference between benign and malignant melanoma images. By the end of 2020, about 196,060 people in the USA will be diagnosed with melanoma, and of these more than 100,000 people are expected to be diagnosed with invasive (penetrating the epidermis into the skin's second layer, the dermis) melanoma [noad],[ski]. About 6,850 patients suffering fatally from melanoma are likely to have died in 2020 [noaa]. Unfortunately over the past 40 years, melanoma cases have been steadily rising [noab]. Amidst this melonomic gloom, the good news is that melanoma can be cured through excisions when detected and diagnosed in its early stages [CKU+07],[CCB+11]. At present, the available detection and diagnosis options for melanoma are visual inspection, clinical screening, dermoscopic analysis, biopsy and histopathological examination of skin lesion. Among all options, dermoscopy is the most popular imaging technique. Dermoscopy refers to microscopic examination and evaluation of skin lesions. It is typically done with every high quality magnifying lens and powerful illumination system (aka Dermatoscope [noac]). However, dermoscopic images are not easy to interpret for diagnosis. Even with most experienced dermatologists, the evaluation of dermoscopic images can be laborious and error prone [CIS+08], [ACS+13]. The complex visual characteristics of skin lesions such as multi-sizes, multi-shapes, fuzzy boundaries, and low contrast when compared to the skin and noise presence such as skin hair, oils, air, and bubbles limit even an expert dermatologists's sensitivity to less than 80% [VMHM08]. Figure 1. gives a visual feel of some lesion images as classified by multiple expert dermatologists into benign and malignant melanoma.

Aforesaid challenges especially motivate the machine learning community to design algorithms to automatically diagnose melanoma in dermoscopic images. Computer-aided diagnosis (CAD) system automates interpretation of dermoscopic images to diagnose melanoma. This helps in early and successful diagnosis of melanoma, thereby making the treatment effective and reducing the mortality rate. Machine learning methods aim to 'train' models using labeled data (dermoscopic image of benign and malignant melanoma) and then provide prognosis on the new dermoscopic images of patients. Recently, a subfield of machine learning known as deep learning has shown success in automatic medical image interpretation comparable to the level of human specialists. Deep learning focuses on the construction of "neural networks", which comprises multiple layers of non-linear functions with coefficients/weights which are derived from the training data. These weights are the result of the 'training' process and hold the knowledge of differentiation between benign and malignant melanoma. Artificial Neural Networks (ANNs) were the first type of neural network to demonstrate success in medical imaging classification, including CadE/CadX to diagnose chest diseases given radiographs [QYSS18], diagnose general cancer given tumor and lymphatic node images [PMC16], and diagnose prostate cancer given MRI images [DVBF+16]. Researchers have developed specialized neural networks known as convolutional neural (CNN) networks which are designed to model the highly structured data present in images. Convolutional neural

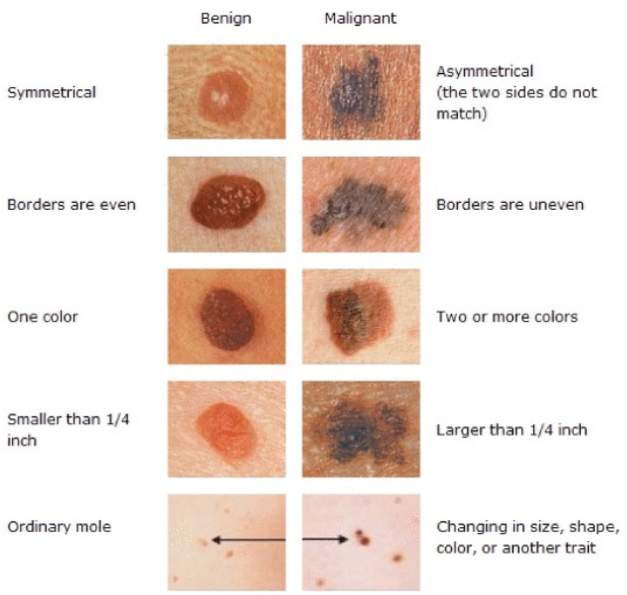

Figure 1: Two sets of dermoscopic images. Images on the left column show benign cases, while the images on the right show malignant cases

networks have been known for being effectively utilized to diagnose cancers and diseases in the past [CKK18]. Some recent examples of using CNNs for medical-imaging related tasks include diabetic retinopathy detection which performed on levels comparable to ophthalmologists [GPC$^+$16], chest X-Ray pathology detection in chest radiographs which matched the performance of radiologists [BNG$^+$19] , and knee abnormality detection in MRI scans [BRB$^+$18]. Given the recent success of convolutional neural networks on a variety of medical imaging tasks, there is a significant opportunity for research on developing models for other tasks [WFT$^+$19]. One of the early works using CNN to classify dermoscopic images into benign and malignant, with accuracy levels comparable to that of 21 board-certified dermatologists, came from Esteval et. al in 2017 [EKN$^+$17]. In this research paper, I developed deep learning models to classify dermoscopic images of skin lesions. The networks were trained and validated on a large dataset of dermoscopic images that were labeled by dermatologists as benign or malignant. I discovered that a ResNet model with 50 layers achieves an AUROC score of 0.78 on the validation set, while an EfficientNet model achieves a AUROC score of 0.90. The model leverages augmentations and ensembling of multiple smaller models to achieve that high performance on the validation set. Finally, I interpreted the model predictions through the use of Class Activation mappings to highlight where in the picture the model considered a possibly malignant tumor existed.

2 Methods

2.1 Data

The dataset consisted of 33,126 dermoscopic images in total and was split into a training set (25,932 images) to learn model parameters and a validation set (7,194 images) to compare models. As shown in Table 1., the training set consisted of 473 positive (malignant) cases or 1.8 % of the training set. The 25,459 images remaining were negative (benign) cases or 98.2 % of the training set. The validation set consists of 7,194 images. As shown in Table 1, the validation set consisted of 111 positive (malignant) cases or 1.6 % of the validation set. The 7,083 images remaining were negative (benign) cases or 98.4 % of the validation set. Both datasets had the exact same approximate age of 45, with the percent of female patients varying from 48.9% in the training set to 45.9% in the validation set. All images in the training and validation are in JPEG format and were resized to 224 x 224 pixels.

	Training	Validation
Positive No (%)	473 (1.8%)	111 (1.6%)
Negative, No (%)	25,459 (98.2%)	7,083 (98.4%)
Mean age	45.0	45.0
% Female	48.9 %	45.9 %
Total	25,932	7,194

Table 1: Data statistics across the data splits.

2.2 Convolutional Neural Networks

Convolutional neural networks are especially effective in machine learning due to their ability to leverage the structured format of imagery. Convolutional networks are composed of convolutional layers, which use a kernel and stride to extract certain features from the image. Conv layers are followed by non-linear Rectifier layers (aka ReLU in Figure 2.) which typically remaps the input to a manageable 'range' (e.g. -1 to +1). Typical CNNs are combinations of the three layers (convolution, rectifier, pooling). The final layer of a CNN is a fully-connected layer to produce the final output of the network (classification label). Certain CNN architectures are more effective for different types of tasks. To mitigate overfitting, two candidate models were investigated in this work for their relatively small neural network size - ResNet50 [HZRS15] and EfficientNet [TL19]. A diagram of the ResNet50 architecture is shown below with Figure 2. and the EfficientNet Architecture is shown in Figure 3.

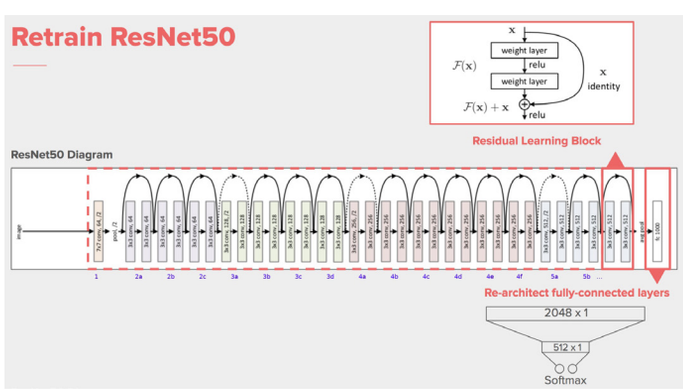

Figure 2: Diagram of the ResNet50 Architecture

In essence, the ResNet50 architecture functions by stacking up sets of the three layers 50 times [HZRS15]. The triplet consists of convolutional layers, normalization / pooling layers, and rectifier layers. The convolutional layer

extracts relationships from the image, the pooling layer aggregates the extracted features, the rectifier nonlinearities (ReLU) are applied to capture nonlinear structures within the image. One aspect that differentiates ResNet from other CNNs - is that it trains to learn the 'residual signal', which refers to the difference of a triplet's output with input of the previous triplet.

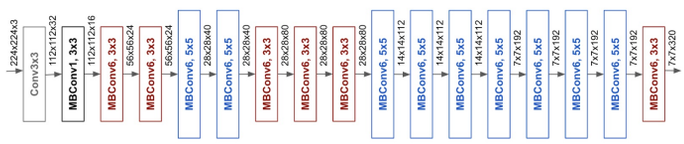

Figure 3: Diagram of EfficientNet Architecture Used

The EfficientNet architecture is composed of layers similar to the ResNet50 architecture but also efficiently balances the tradeoff between network depth (number of layers), width (number of channels), and image resolution. It is 8.4 times smaller and 6.1 times faster than the best convolutional neural network and achieves one of the highest accuracies on the ImageNet database, a large dataset of natural images which is the most commonly used benchmark for assessing convolutional neural network performance 24.

2.3 Training Procedure

A special training procedure was created to maximize the performance of the ResNet50 / EfficientNet models. In order to utilize the advantages of transfer learning, both models had weights initialized from a network pre-trained on data from ImageNet. Both models used a scheduler that reduced the learning rate each time performance on the validation set plateaued, an Adam optimizer, and the binary cross entropy loss function. The Adam optimizer was utilized with an initial learning rate of 0.001. The scheduler had a patience of 1, a threshold of $1 * 10^{-}5$ to measure when the validation performance plateaued, and a factor of 0.2 to reduce the learning rate by. Each model was trained for a maximum of 20 epochs (20 full passes over the training set) with a batch size of 32 and 4 workers (processors). The following augmentations were applied to each batch during training: random horizontal and vertical flips with a probability of 50%, random crops of the image, and random rotations of the image. After the model completed iteration over the training dataset, the model was directly tested on the validation set. The summary metric AUROC was computed for each epoch and the 5 models with the highest AUROC score were saved. These five models were used to generate an ensemble of models where the average of the probabilities predicted by each model was used as the prediction for the ensemble, as depicted in Figure 4. Finally, to limit training time and prevent overfitting on the training set, early stopping was used which terminates training once the marginal gains from training were lower than a specific threshold.

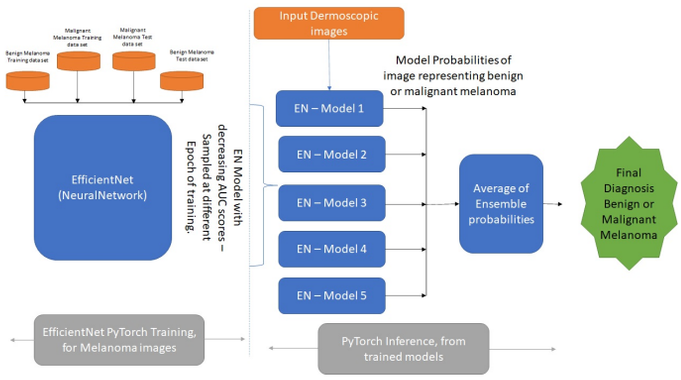

Figure 4: A Conceptual Diagram of how melanoma diagnosis is accomplished in the model.

2.4 Evaluation Metrics

I used a variety of performance metrics to evaluate the deep learning models. To evaluate the quality of the model probabilities, I computed the receiver operating characteristic (ROC) curve and precision recall curve (PR) . Then, to compress the curves into more comprehensive metrics, the area from the ROC and PR curves was computed to get AUROC and AUPRC. The model was primarily evaluated using the AUROC score, but AUPRC was also measured to provide a holistic evaluation of the models. To convert probabilities to binary predictions and compute point metrics, I used the threshold which led to the highest F1 score on the validation set. After the probabilities were converted to binary predictions at the optimal threshold, I computed the precision, which measures how many accurate malignant diagnoses were made over all malignant diagnoses the model predicted, recall, which measures how many accurate malignant diagnosis were made over all test images which were malignant, F1 score which is the harmonic mean of precision and recall, and accuracy of the model.

2.5 Model Interpretation

Once training and testing was complete, I sought to interpret the model predictions. In order to accomplish this, I used class activation maps (CAMs, Figures 5/6.) to highlight the regions of the image which contribute most to the model's prediction of melanoma. The class activation maps are computed using the feature maps right before the global average pooling layer (GAP) is reached, where feature map (1 per channel) is multiplied by the weight corresponding to the final fully connected layer, and then summed to create the CAM. The CAM is a heatmap that overlays the image where temperature/color highlights the regions of the image which contribute most to the model's classification. In Figures 5/6, the blue regions highlight areas which contribute more to the prediction of melanoma, while purple highlights areas which contribute less. Us-

ing these CAMs, especially for false negative / positive diagnosis cases, helped me understand possible causes that were derailing the model from an accurate prediction.

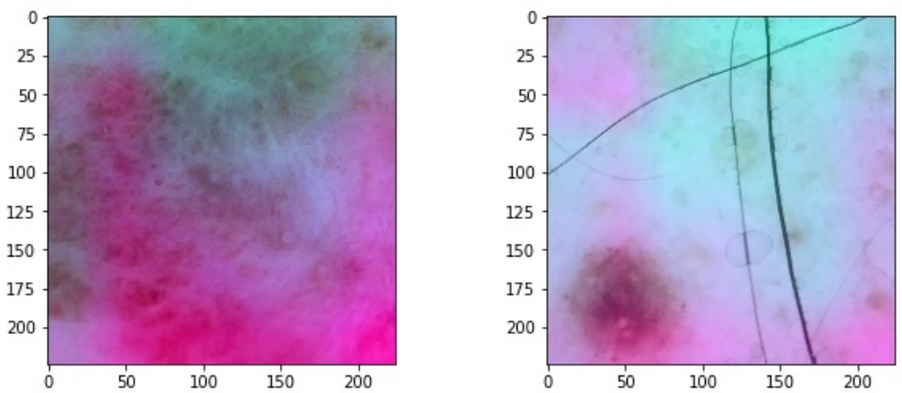

Figure 5: Class activation maps (CAM) of the best model on the validation set. The CAM on the left is an accurate diagnosis of benign melanoma, while the CAM on the right shows a false diagnosis (the model incorrectly predicted there was melanoma). Areas that have higher hues of blue indicate the model has a higher confidence that melanoma exists in that part of the image, while areas that are more purple indicate lower confidence.

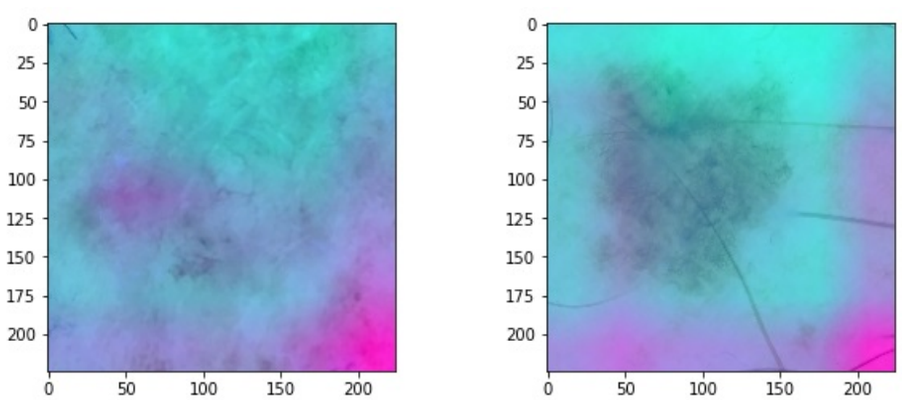

Figure 6: Class activation maps (CAMs) of the best model on the validation set. The CAM on the left is an accurate diagnosis of malignant melanoma, while the CAM on the right shows a false diagnosis (the model incorrectly predicted there wasn't melanoma). Areas that have higher hues of blue indicate the model has a higher confidence that melanoma exists in that part of the image, while areas that are more purple indicate lower confidence.

3 Results

		Point Metrics				Summary Metrics	
	Experiment	Precision	Recall	F1	Accuracy	AUROC	AUPRC
1	Pretrained ResNet50, with optimizer Adam, no early stopping, and CrossEntropyLoss loss function	0.03	0.91	0.06	0.56	0.79	0.05
2	Pretrained ResNet50, with optimizer Adam, no early stopping and BinaryCrossEntropyWithLogits (BCEL) loss function	0.13	0.32	0.19	0.96	0.86	0.15
3	Pretrained ResNet50 with optimizer Adam and scheduler, no early stopping, and BCEL loss	0.09	0.51	0.15	0.91	0.87	0.11
4	Pretrained ResNet50, with optimizer Adam and scheduler, early stopping, and BCEL loss	0.07	0.71	0.13	0.85	0.88	0.14
5	Pretrained EfficientNet with optimizer Adam and scheduler, early stopping, and BCEL loss	0.14	0.14	0.04	0.89	0.54	0.02

6	Pretrained EfficientNet with optimizer Adam and scheduler, early stopping, BCEL loss, and ensembling	0.21	0.20	0.20	0.98	0.87	0.13
7	Pretrained EfficientNet with optimizer Adam and scheduler, early stopping with increased threshold, BCEL loss and ensembling and data augmentation (Error in generating predictions)	0.42	0.16	0.23	0.98	0.57	0.08
8	Pretrained EfficientNet with optimizer Adam and scheduler, early stopping with highest threshold, BCEL loss and ensembling	0.1	0.66	0.28	0.91	0.90	0.17

Table 2: Performance metrics of the experiments on the validation set.

I experimented with a variety of models and training procedures in order to investigate their impact on performance, primarily in terms of AUROC.. Starting with a ResNet50 model and Experiment 1 metrics as a baseline, the loss function was changed to BinaryCrossEntropyWithLogits (BCEL) due to its specialty in binary classification, which led to an increase inAUROC score from 0.79 to 0.86 (Experiment 2). Next, a scheduler was added in order to anneal the learning rate (Experiment 3). Although the AUROC score does increase from Experiment 2 to 3, the gain is relatively small. In Experiment 4, early stopping was added to prevent overfitting on the training set which also led to minimal performance gains. In Experiment 5, the ResNet50 model being used

was replaced with an EfficientNet model. This caused the AUROC score to plummet. In Experiment 6, 5 EfficientNet models were put into an ensemble where the predictions would come as the arithmetic mean of the 5 predictions of the individual models. This increased AUROC from 0.54 to 0.87. The intention for Experiment 7 was to train the model more rigorously by augmenting the training set images. Once the bug was fixed, the model outputted the highest and final AUROC score at Experiment 8 - 0.9.

4 Discussion

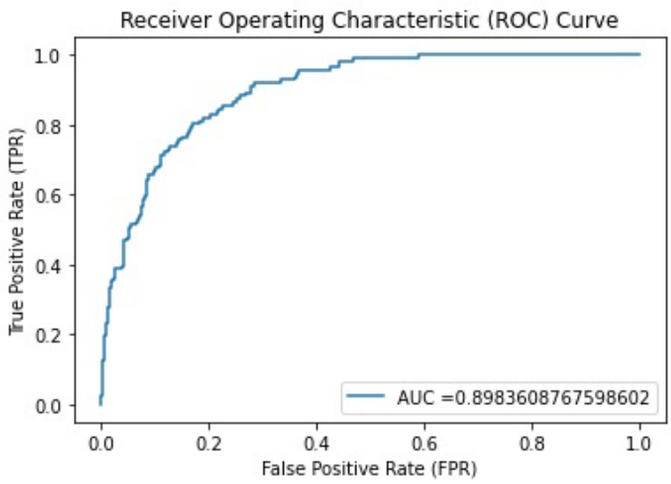

Figure 7: ROC curve of best model of the validation set.

In this work, I developed convolutional neural networks for the detection of melanoma in dermoscopic images. Two different models, ResNet50 and EfficientNet, were investigated together with a variety of training procedures. Through each experiment, one important variable was toggled, such as model type, loss function, use of scheduler, early stopping, data augmentation, and ensembling. Overall, the key methods used for the greatest gains in AUROC came from the use of early stopping and ensembling of the models. Apart from the model improvement methods, other techniques such as CAMs / graphs were utilized to figure out optimal values for certain variables and to analyze the models.

Major implications of our work lie mainly in the use of multiple techniques applied, and the gain of each technique. The set of techniques and their respective gains can be used by other researchers in the medical field to prioritize which techniques to use to maximize their own models' AUROC score. A second implication lies in the model's AUROC score. As the dermatologist accuracy of 75% [NFKA20] has been surpassed by our model's 91% accuracy and 90%

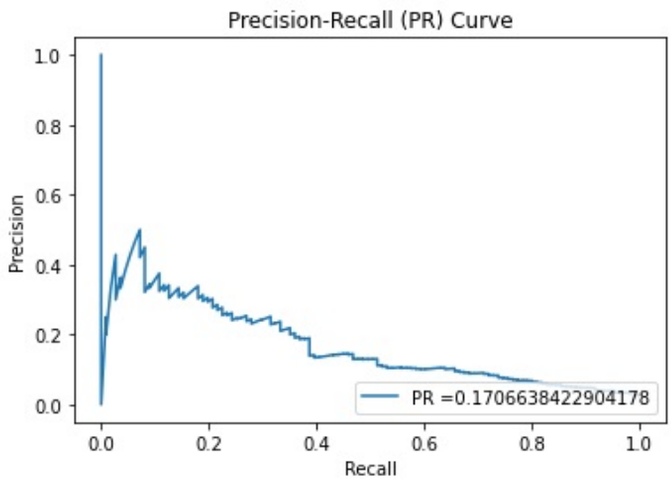

Figure 8: PR curve of best model of the validation set.

ROC AUROC, the model proposed has the potential to match or exceed human performance, implying it may be viable to assist humans in the detection of melanoma. This work also has important limitations which should be considered. First, data only came from 6 hospitals (Hospital Clínic de Barcelona, Medical University of Vienna, Memorial Sloan Kettering Cancer Center, Melanoma Institute Australia, The University of Queensland, and the University of Athens Medical School), so the model may not be representative of certain populations [noae]. As a result, the model will likely be less generalizable and over-represent the populations from where the dataset originated. Another limitation was the oversimplification of the task. In the case melanoma is classified, the severity must also be determined. One metric to determine this is called the Clark Scale, which ranks detected melanoma into 5 levels [Mel]. However in this work, melanoma was only classified based on existence, ignoring many nuanced details that are important to the diagnosis of cancer. Finally, skin lesions in different parts of the body may be treated differently. The models presented in this work do not utilize information about where the lesions originated in the body, which may be important information for classification. All such known limitations could be addressed with help of availability of a variety of data which covers different geographies, races, regions of the body, and severity levels of the melanoma. In future research, we plan to explore other model architectures, and versions of ResNet and EfficientNet which are available in PyTorch. Using K-Fold cross validation instead of saving the top 5 models would also be considered in order to improve the heterogeneity of models in the ensemble. Finally, generating custom augmentations such as inserting obstructions like hairs into the images for the training set could also improve the robustness of the model.

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Behavioural Economics and Education: Exploring possible methods by which heuristics could be used to improve the performance of students in the International Baccalaureate Diploma Program (IBDP)

Arzoo Usgaonkar *

April 2, 2021

Abstract

This research report examines the effect of three heuristics – the status quo effect, the conformity bias, and the present bias – on the performance of IB Diploma Program students, globally. It looks at several previously conducted studies and relates their findings to teaching and learning methods of IBDP teachers and students, respectively. The paper considers several, possibly unnoticeable, short-comings of the current education system, explains how heuristics may be employed to improve the formal education system, and proposes feasible and practical policy changes by which heuristics could be used to benefit student learning and performance.

1 Introduction

Behavioural economics is a branch of economics which considers psychology and recognises that choices made by consumers are based on various factors that may or may not agree with the classical or neoclassical approach to economics. The field studies and describes economic decision-making. According to theories of behavioural economics, actual human behaviour is less rational, stable, and selfish than traditional normative theory suggests, due to limited rationality and self-control, as well as social preferences.[1]

*Advised by: Dr Edoardo Gallo, Assistant Professor and Director of Studies (Economics) at University of Cambridge

[1] "Behavioral Economics." BehavioralEconomics.com — The BE Hub, 23 Oct. 2018, www.behavioraleconomics.com/resources/mini-encyclopedia-of-be/behavioral-economics.

The field of behavioural economics revolves around certain heuristics and how they affect behaviour. The term heuristic is commonly defined as a cognitive shortcut that simplifies decisions, especially under conditions of uncertainty.[2] As stated by Daniel Kahneman, heuristics represent a process of substituting a difficult question with an easier one.[3] They can also lead to cognitive biases. Several different heuristics exist and impact various sectors of human life.

Education is fundamental to raising an independent and successful future generation. This field is the foundation of the future, and optimising it for maximum benefit is essential. Thus, this research paper considers the impact of heuristics on education and proposes methods by which heuristics can be employed by schools, teachers, and students, to help improve the learning of students and consequently improve student performance in examinations. The paper looks at the impact of heuristics and their application specifically on students of the International Baccalaureate Diploma Programme (IBDP) but its proposals could be applied to other curricula as well, albeit with some modification. This paper considers the following heuristics:

1. The status quo bias
2. The conformity bias
3. The present bias

2 Context

The International Baccalaureate Diploma Programme (IBDP)[4]is an education curriculum that strives to be challenging and aims to lead to the holistic development of its students. It hopes that its students become inquirers, knowledgeable, thinkers, communicators, principled, open minded, caring, risk-takers, balanced, and reflective. It is a student-centric programme which consists of 3 core concepts and 6 groups of subjects which are taken by every IBDP Student. The three core concepts are CAS (Creativity, Activity, Service) which ensures that students are exposing themselves to activities other than academics, TOK (Theory of Knowledge) which allows students to question what knowledge is, where it comes from and how its applied, and the EE (extended essay) which is a 4000 word research report written by each student in a subject of their preference and on a topic of their choice. The IB has six groups of subjects as seen in figure 1 below[5].

[2] "Heuristic." BehavioralEconomics.com — The BE Hub, 28 Mar. 2019, www.behavioraleconomics.com/resources/mini-encyclopedia-of-be/heuristic.

[3] Kahneman, D. (2003). Maps of bounded rationality: Psychology for behavioural economics. The American Economic Review, 93, 1449-1475

[4] Iborganization. "Diploma Programme (DP)." International Baccalaureate®, www.ibo.org/programmes/diploma-programme/.

[5] "IB Subject Briefs: St. Andrews International School Bangkok." IB Subject Briefs — St. Andrews International School Bangkok, www.nordangliaeducation.com/our-schools/bangkok/learning/curriculum-overview/high-school/international-baccalaureate/ib-diploma-subject-briefs.

Figure 1: IB Subject Groups

Group 1 - Studies in Language and Literature (subjects include language and literature, literature)

Group 2 - language acquisition - learning a second or foreign language (subjects include hindi, spanish, french, italian, etc.)

Group 3 - individuals and societies - social sciences (subjects include history, geography, psychology, economics, etc.)

Group 4 - Sciences (subjects include physics, chemistry, biology, etc.)

Group 5 - Mathematics (analysis and approaches or analysis and interpretation)

Group 6 - Arts (subjects include art and design, music, theatre, etc.)

Most IBDP students study three subjects at the higher level and three at the standard level. Each student must take one subject from groups 1-5 (each) and as their 6th subject they may choose to take a form of the arts or a second subject from either group 3 or group 4. Each student is given a final score out of 45 at the end of this two-year programme. Each student is awarded a certain number of points from 1 to 7 (7 being the highest which is normally equivalent to an A or A* in IGCSE) for each of their 6 subjects. This compromises 42 of the 45 available IB points. The three remaining points are taken from the extended essay and theory of knowledge assessments. CAS is not evaluated but is necessary for the successful completion of the IBDP.

3 Status Quo Bias

"When faced with a choice among different options, people have a tendency to stick with the default". [6] This is known as the status quo bias. It is caused by loss aversion or the belief that "losses loom larger than gains" [7] and is affected by choice – the bias is stronger when more choices are available or when the choices available are more complex. To clarify, the status quo bias [8] is witnessed when people choose to make the same decision they had made previously without logically and fairly considering other choices or when individuals resist change. [9]

The status quo bias impacts several aspects of education. One significant impact of this bias is on the methods by which teachers teach their classes. Over the past decade, several research studies[10] have proven that students learn best in different ways and prefer certain teaching resources that are based on their preferred style of learning. However, it is often seen that teachers teach their classes in the style that is preferable to them rather than their students[11]. This is the status quo. Because of the status quo, a hypothetical teacher who prefers visual learning may use charts and diagrams to explain key terms and processes. This would be ideal for visual learners who grasp concepts easier and faster when displayed visually; however, it would not be optimal for auditory learners (learners who prefer learning through sound) or for kinaesthetic learners (learners who prefer to learn through movement and touch). So, if this hypothetical teacher's class were comprised of 90 percent of students being auditory or kinaesthetic learners, the visual teaching style would not be beneficial. To generalise, if the teaching style employed by a teacher closely matches a student's preferred style of learning, learning becomes easier, faster and relatively effortless for the student, and if it does not, learning becomes more time consuming, relatively difficult, and rather arduous.[12] If the teacher's style is beneficial for a large majority of students in their class it is the best possible, or ideal, teaching style and the status quo is working effectively; however, if it does not agree with the learning style of many students, it is ineffective and needs change.

Teaching in a style which is beneficial to a majority of students is encouraged

[6] Thaler, Richard H., and Cass R. Sunstein. Nudge: Improving Decisions about Health, Wealth, and Happiness. Yale University Press, 2008.

[7] Kahneman, D., and Tversky, A. (1982). The psychology of preference. Scientific American, 246, 160-173.

[8] "Status Quo Bias." BehavioralEconomics.com — The BE Hub, 28 Mar. 2019, www.behavioraleconomics.com/resources/mini-encyclopedia-of-be/status-quo-bias/.

[9] Samuelson, W., and Zeckhauser, R. J. (1988). Status quo bias in decision making. Journal of Risk and Uncertainty, 1, 7-59.

[10] Franzoni, Ana Lidia, et al. "Student Learning Styles Adaptation Method Based on Teaching Strategies and Electronic Media." 2008 Eighth IEEE International Conference on Advanced Learning Technologies, 2008, doi:10.1109/icalt.2008.149. See section on "related works".

[11] Franzoni, Ana Lidia, et al. "Student Learning Styles Adaptation Method Based on Teaching Strategies and Electronic Media." 2008 Eighth IEEE International Conference on Advanced Learning Technologies, 2008, doi:10.1109/icalt.2008.149.

[12] Rose, C. (1998). Accelerated Learning, New York: Bantam Dell Publishing Group.

hundreds of researchers who agree that teaching styles of teachers should be based on their students' preferred learning styles, as opposed to being a reflection of the teacher's ideal working style, but several problems – including learning ability, background knowledge, learning goals, and learning style of students – need to be overcome in order to reach a state where teaching styles can be easily optimised for their audience[13] In an effort to solve these problems and propose a method by which teaching can be modified for student benefit, Ana Lidia Franzoni and Saïd Assar, the co-authors of the study 'Student Learning Styles Adaptation Method Based on Teaching Strategies and Electronic Media[14] examined the learning styles model by Felder-Silverman.

The Felder-Silverman learning styles model[15] examines students' learning styles based on four parameters:

1. What kind of information does the student prefer to receive?

a. sensitive – prefers concrete, practical, and fact-based thinking and approaches

b. intuitive – prefers conceptual thinking and approaches such as theories

2. Through which sensorial channel does the student receive information more effectively?

a. visual representations (diagrams and charts)

b. verbal (spoken words, written explanations)

3. How does the student process information?

a. actively (groupwork, discussions, activities) or

b. reflexively (through introspection and reflection)

4. How does the student make progress?

a. sequentially (learns in small steps of increasing complexity), or

b. globally (learns through holistic thinking and prefers learning all, or most, of a concept at once)

These four parameters were analysed by Franzoni and Assar who used their results to create a metric using descriptions, ideal pedagogical methods, and characteristics of media to explain the ideal teaching styles and use of electronic methods based on students' learning styles (see figure 3).

For example, they found that visual learners relied heavily on visual components and tended to do better on assignments that asked them to visualise or explain concepts using visual representations. Specifically, they found that images, diagrams, and charts helped students understand and summarise their learnings. Based on these observations, Assar and Franzoni proposed that visual learners be taught using strategies and games, and that electronic media like electronic presentations, videos, and animations be used as learning aids. The two researchers repeated this process for several other learning types as

[13]Ford, N., and Chen, S. (2001). Matching/mismatching revisited: an empirical study of learning and teaching styles. British Journal of Educational Technology, 32 (1), 5-22.

[14]Franzoni, Ana Lidia, et al. "Student Learning Styles Adaptation Method Based on Teaching Strategies and Electronic Media." 2008 Eighth IEEE International Conference on Advanced Learning Technologies, 2008, doi:10.1109/icalt.2008.149.

[15] "Felder-Silverman." The Peak Performance Center, www.thepeakperformancecenter.com/educational-learning/learning/preferences/learning-styles/felder-silverman/.

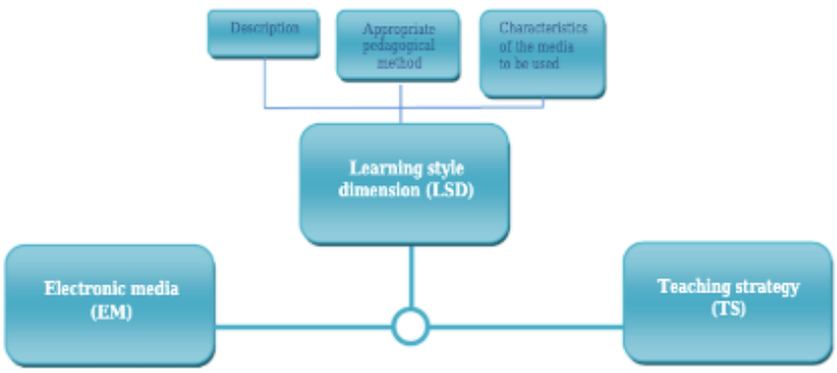

Figure 1. Adaptive Teaching Taxonomy relation entity diagram

Figure 2: Adaptive Teaching Taxonomy relation entity diagram

well. Their summarised learnings of recommended teaching styles and electronic methods can be seen in figures 3 and 4, respectively.[16]

Table 7. Adaptive taxonomy: LS dimensions and TS relationships

		Learning styles							
		Sensitive	Intuitive	Visual	Verbal	Active	Reflexive	Sequential	Global
Teaching strategy	Games and simulations		X	X		X			
	Learning based on problem solving	X				X			
	Role playing		X			X			X
	Presentation	X		X			X	X	
	Discussion panel		X		X	X			
	Brainstorming				X	X			X
	Case study		X				X		X
	Question and answer method	X			X		X	X	
	Project design method		X			X			X

Figure 3: Adaptive Taxonomy

While this study provides a logical sounding proposal to mitigate the status quo bias by matching teaching and learning styles, where they do not already, it is important to understand that this study only proposes a potential model and further research through experimental studies is needed to ensure that the model does, in fact, work and to prove a definite causal relationship between teaching styles and improvements in student performance. It is also important to mention that there are several counter-arguments to teaching based on learning styles as contradictory studies[17]have found no substantial benefit of modifying

[16]Franzoni, Ana Lidia, et al. "Student Learning Styles Adaptation Method Based on Teaching Strategies and Electronic Media." 2008 Eighth IEEE International Conference on Advanced Learning Technologies, 2008, doi:10.1109/icalt.2008.149.

[17]Kevin Donnelly Senior Research Fellow - School of Education. "'Chalk and

Table 8. Adaptive taxonomy: LS dimensions and EM relationships

			Learning styles							
			Sensitive	Intuitive	Visual	Verbal	Active	Reflexive	Sequential	Global
Electronic media	Audio	Audio Recording				X			X	
		Audioconference				X			X	
	Collaboration	Forums	X		X		X			X
		Online learning communities			X					X
		Weblog or blog	X				X			X
		Wikis	X		X		X			X
	Communication	Chat (Messenger)					X			X
		e-mail					X			X
	Diagrams	Animations	X		X					
		Graphics	X		X					
		Pictures	X		X					
		Simulations			X					
	Read	Digital magazines						X	X	
		Digital newspapers						X		
		eBooks			X			X	X	
		Hypertext (web pages)			X			X	X	
		Slideshows			X			X	X	
	Search	Internet research		X			X	X		X
	Tutoring	Course Legacy System		X						
		Student Response System						X		
		Tutorial systems		X				X		
		WebQuest		X				X		
	Video	Podcast				X				
		Recorded live events			X	X				
		Videoconference			X	X				
		Videos			X	X				
		Web seminars (broadcasts)								

Figure 4: Adaptive Taxonomy

teaching styles to match student's preferred learning styles[18] Overall, this study by Assar and Franzoni is a great example of how the status quo surrounding learning and teaching styles could be mitigated where needed. The study is also a good example for teaching styles IBDP teachers could use as it relates well to the holistic approach to education and the learning objectives that the IBDP aims for its students to achieve.

To understand their students' learning styles and adapt their teaching styles accordingly, teachers could use the Felder-Silverman learning styles model, posed in the form of a questionnaire. Adapting learning experience to learning styles in order to reduce the status quo bias can be done through several other methods as well. Classrooms could have various seating or non-seating options for students to stay comfortable while they learn. For this, classrooms could have regular desks, standing desks, floor-space, bean bags, etc. so that students can choose how they learn. This would be especially beneficial for kinaesthetic learners as

Talk' Teaching Might Be the Best Way after All." The Conversation, 12 May 2020, www.theconversation.com/chalk-and-talk-teaching-might-be-the-best-way-after-all-34478.

[18]Rogers, Vincent, and Joan Baron. Â Teaching Styles and Pupil Progress.â The Phi Delta Kappan, vol. 58, no. 8, 1977, pp. 622â 623. JSTOR, www.jstor.org/stable/20298722. Accessed 30 Aug. 2020

they would be able to stand or move around while learning. The mental status quo of sitting while learning could also be removed through having standing desks. Students could be allowed to take notes both digitally and by hand – as they prefer. This would allow visual learners to add images and diagrams to their notes with ease. Lastly, different teachers teach in different ways so if there are multiple batches of students in a grade who are studying the same subject, recordings of the classes could be shared with all students taking a given subject. This would be beneficial not only to auditory learners, who can play-back the recordings, but also to all learners to get access to teaching styles that may be closer to their preferred learning style. It is important to note that there are certain ethical considerations that must be thought of with regards to the recording of classes, before they are shared with students. A waiver for privacy and the ethical use of recordings could be sent to parents or legal guardians, of students, to ensure responsible data use. Allowing for these small changes in learning space and accessible resources would make it far easier for students to learn as they wish to and for teachers to teach in their preferred style while simultaneously reducing the status quo bias that exists between teaching and learning styles.

As stated by Liz Bergeron and Michael Dean in their study, "The IB Teacher Professional: identifying, measuring and characterising pedagogical attributes, perspectives and beliefs", one of the key features of any successful IBDP teacher is flexibility or adaptability [19]. This is because the IBDP reviews all of its program syllabi every seven years in an attempt to "ensure that each (subject) is fit for purpose in a changing world" and that each subject's syllabus "incorporates the latest educational research and lessons learned from a thorough evaluation of the existing curriculum. [20] This frequent change in syllabus is often the second main cause for the status quo bias impacting education.

The prevalence of the status quo bias due to syllabus changes can be compared to an example of a healthcare study done by Samuelson William and Richard Zeckhauser in their research paper "Status Quo Bias and Decision Making"[21]. In the study, which was based on field data from Harvard University's health plan enrolments of 9,185 employees in 1986, a large disparity was observed between the health plan choices of new and old enrolees. Each year, enrolees were allowed to transfer from one health plan to another at no transaction cost. It was found that enrolees who joined the program in 1986 preferred to stick with the plan they had originally chosen as compared to a new plan which had more favourable premiums and deductibles. This trend was not observed with new enrolees who joined the program in 1987, thus displaying the prevalence of the status quo bias in old enrolees – despite having no transaction cost (normally the main reason participants remain with the status quo is due

[19] "IBO Publication." Ibo.org - Global Assets,www.ibo.org/globalassets/publications/ib-research/continuum/theibteacherprofessional_final_march6.pdf

[20] Iborganization. "Latest Curriculum Updates." International Baccalaureate®, www.ibo.org/university-admission/recognition-of-the-ib-diploma-by-countries-and-universities/latest-curriculum-updates/.

[21] Samuelson, W., and Zeckhauser, R. J. (1988). Status quo bias in decision making. Journal of Risk and Uncertainty, 1, 7-59.

to transaction costs as human beings practise loss aversion). Evidence of these findings can be seen in figure 5 (below).

Table 11. Effects of 1986/1987 Transfers on Percentage Enrollments

Plan	1986 Enrollees	All Others	Add Transfers	Add Transfers × 10
BCBS	9.8	31.0	29.2	13.2
HUGHP	48.2	37.7	37.9	39.1
HCHP	19.3	13.2	13.4	15.4
MGHP	3.6	2.7	2.8	3.8
Bay St	3.8	6.6	7.1	11.3
Tufts	3.4	1.2	1.4	3.2
Lahey	1.9	1.5	1.5	1.0
BC Low	5.5	6.2	6.9	13.0
Total	100.0	100.0	100.0	100.0

Figure 5: Healthcare Plan Transfers

Similar to what is seen in the study above, is the effect of the status quo bias of teachers with regards to syllabus changes. Due to extremely frequent syllabus changes in the IBDP, teachers often have to simultaneously teach different syllabi of the same subject to two year groups. This may lead to teachers being confused and struggling to remain clear on the syllabi of each year group. In turn, may also lead to teachers preferring previous syllabi and books as they understand those better and have greater understanding of their subject matter. In this case they may continue teaching past syllabi, which may affect the performance of students (who have an adapted syllabus). Moreover, the status quo bias may be responsible for teachers choosing not to adapt their courses or teaching techniques to meet the requirements of the new syllabi. Essentially, teachers may not adapt their teaching style to fit the new syllabus thereby affecting students' performance, especially as the question types in exam papers often change with syllabus changes. It is important to note that further quantitative data analysis is required to validate these logical correlations and ensure the transferability between healthcare data and adaptations of teachers to changes in syllabi.

It is also important to consider cultural contexts with regards to the status quo bias. In several countries like India and China, local curricula are tend towards being more structured and less subjective than the IBDP[22]. Because of this, teachers teaching the IBDP in these nations may get intimidated by the curriculum's relative lack of structure. This may result in teachers creating a specific format based on previous answers that did well – a direct effect of the status quo bias. This is especially common for internal assessments and the extended essay which are in essay format. These preconceived notions of model answers, held by teachers, may lead to children with otherwise well-written

[22]The Swaddle. "How Learning Differs Across CBSE, ICSE, IB and CIE Education Boards." The Swaddle, 15 May 2018, theswaddle.com/learning-education-boards/.

work being scored less as the teacher's criteria – which is not a necessity by the IBDP – is not followed. To improve on this, the IBDP should have free, virtual teacher training workshops for teachers affiliated with IBDP schools explaining syllabus changes and how they can be adapted to with ease, as well as clarifying any doubts that teachers may have. The IBDP should also have a helpline for teachers to call so that they can clarify any doubts relating to syllabi, clearly and directly.

4 Conformity Bias

As defined by the McCombs School of Business, conformity bias is the "tendency of individuals to behave like those around them instead of using their own judgement"[23]. It relates to the behavioural aspect of herding, which has been a well-known concept in both psychology and philosophy for a centuries. Herding behaviour[24] is when people follow what those around them are doing instead of making their own individual and independent decisions, based on the information which is available to them. Herding behaviour is influenced by several factors: fear, uncertainty, the shared identity of decision makers, etc. This behaviour, of conformity bias and herding, could be both beneficial and dangerous depending on the context in which it is used. As such, it could be extremely beneficial for the education sector, but only if used effectively.

To test whether conformity bias is seen in the extracurricular activities offered by schools or undertaken by students, a simple google search is adequate. On the 27th of August, 2020 at 6:43pm I googled the following phrases, "popular extracurriculars in schools" and "the best extracurricular activities for college" and opened up the most popular 8 sites that appeared (the 8 sites that appeared closest to the top of the search with both key phrases). Below are the websites.

Note: the reliability of the websites was not checked, they were simply the ones that appeared closest to the search bar with both sets of key terms. The findings drawn from these websites (described below) are not hard evidence and their results need to be replicated through the use of experimentation and data gathering. They were the 8 most frequently visited websites that matched both selected key phrases.

The results yielded from these websites were almost identical to each other. All the websites focused on displaying 'leadership, passion and impact' or another variation of those same three words. To achieve these three goals, they recommended certain activities as well: academic clubs, the arts and sports were spoken about generally and Model United Nations (MUN), student government, debate club, yearbook, robotics, internships and volunteer work, specifically, were some common extracurriculars listed. Some websites did provide extensive lists of popular extracurriculars with a greater number of suggestions, however,

[23] "Conformity Bias." Ethics Unwrapped, 12 Dec. 2018, ethicsunwrapped.utexas.edu/glossary/conformity-bias.

[24] "Herd Behavior." BehavioralEconomics.com — The BE Hub, 29 Mar. 2019, www.behavioraleconomics.com/resources/mini-encyclopedia-of-be/herd-behavior/.

these were some of the most frequently observed results. The fact that some results were found more frequently than others suggests that these activities are extremely popular with students and may even be prioritised by schools. Thus this is clear evidence of the conformity bias at work.

The prioritising of certain extracurriculars can have a vast range of negative impacts. Prioritised extracurriculars become extremely popular in schools and may be given more importance and funding than other activities. While this is beneficial to some students who truly enjoy and are particularly skilled at these activities, it may hamper the holistic growth of other students who have different interests. As more and more students use the conformity bias and herd to popular activities, less priority is given to other extracurriculars and soon people stop opting for and exploring them, leading to their removal from the list of activities offered. This limits extracurricular choices for students in later years. Moreover, because these activities are prioritised, students feel peer pressure to participate in them for fear of missing out. Another important consequence of prioritising certain extracurriculars is that the conformity bias leads to them no longer being unique or special to students when applying to college. So, extracurriculars which would otherwise make students competitive and stand-out on college applications no longer do. This puts pressure on students to not only follow others and take part in the prioritised extracurriculars to be competitive, but also pushes them into taking part in additional extracurriculars to make them stand out. As Columbia University psychology professor, Dr. Suniya Luthar says, children get extremely caught up in extracurriculars and try to do everything often forgetting where to stop. This becomes an issue when the child starts to say "his or her performance determines his or her self-worth: I am as I perform". She believes that an increasing number of children are associating self-worth with their academic performance and involvement in extracurricular activities and that this is extremely dangerous[25]. Due to additional pressures to stand out, students' mental and physical health may be harmed as they may battle with anxiety, obesity from lack of physical exercise (caused by a lack of time), chronic stress at a young age, feeling lost, depression, feeling overwhelmed and getting panic attacks, etc. Essentially, though schools may prioritise certain extracurriculars to make their students competitive, this prioritisation may have several negative consequences on students.

In the case of extracurriculars, confirmation bias – when people try to find and analyse data such that it fits with their existing preconceptions[26] – along with the fear and uncertainty that is part of the college application process may be the cause for conformation bias. This is because students tend to assume that the only way to get to a certain institution is by doing exactly what someone, who got accepted into that institution previously, did.

To reduce conformation bias in extracurriculars, teachers should explain

[25] Ruthie, AAE. Association of American Educators, www.aaeteachers.org/index.php/blog/1154-how-far-is-too-far-students-and-extra-curricular-activities.

[26] "Confirmation Bias." BehavioralEconomics.com — The BE Hub, 29 Mar. 2019, www.behavioraleconomics.com/resources/mini-encyclopedia-of-be/confirmation-bias/.

the importance of doing what interests a student through voicing the negative impacts a lack of individuality could have on an individual. Additionally, schools should create lists of locally available extracurricular activities with details so that students can easily explore a range of interesting activities. This database could be based on the extracurriculars done by previous students in the school. Lastly, a new activity could be introduced in the school each year or each month to give students exposure to new creative outlets and skills that could help them through life. Examples include a cookery club or a financial literacy workshop.

The lack of conformation bias may also be problematic in educational institutions. When different teachers teach batches of a grade the same subject, some groups of students may learn more than others due to the different teaching styles of teachers[27]. This lack of conformation occurs as the IBDP syllabus is subjective (comparative to other curricula) and encourages various approaches to both teaching and learning[28]. As the syllabus has a broad scope, teachers may teach different things. This lack of conformity may negatively impact the results of some students while unfairly advantaging others due to their teacher's teaching style.

Consider a realistic hypothetical situation wherein there are three batches of an Economics Higher Level class for 11th grade students at School X in a given year (say 2020), and each of these three classes are taught by different teachers. Assume that teacher A who teaches Batch 1 teaches through real life examples but does not teach students key economic concepts with formal technology, Teacher B who teaches batch 2 explains economic concepts and defines key terms but does not cover real life examples in depth, and Teacher C who teaches batch 3 does both. This information is summarised in Figure 7. If all three batches are given the same exam, in which they are asked to explain a key concept using definitions, key terms and relevant, detailed real life examples, Batch 3 would be unfairly advantaged as Batch 1 would not be able to give a detailed real life example and Batch 2 would not be able to define or name key terms while Batch 3 would be able to do both. This would, thus, be a negative consequence of the lack of conformity between teachers and would negatively impact the performance of students.

In an attempt to reduce the negative impacts of the lack of conformity, recordings could be taken of each of the batches' sessions and be made available to all students taking that subject. In addition, teachers could collaborate and make a combined lesson plan for the year to ensure the same content, at least in terms of concepts, is covered.

Another area of education that may be affected by the conformation bias is somewhat contrasting to the previous point on the disadvantages of teachers having different teaching methods. It is when teachers imitate or copy other teachers' teaching styles. This imitation may be due to various factors such as

[27] Franzoni, Ana Lidia, et al. "Student Learning Styles Adaptation Method Based on Teaching Strategies and Electronic Media." 2008 Eighth IEEE International Conference on Advanced Learning Technologies, 2008, doi:10.1109/icalt.2008.149.

[28] "International Baccalaureate (IB) Program / Approaches to Learning (ATL)." / Approaches to Learning (ATL), www.bostonpublicschools.org/Page/5935.

seniority and experience of a certain teacher, or students of a certain teacher's batch performing consistently better than other batches. While copycat behaviour[29] by teachers may be beneficial in terms of ensuring that all students get the same learning in terms of content and teaching method, it has several disadvantages. Copycat behaviour or imitation may lead to teachers being out of their comfort zone and therefore not being able to impart education in the most successful manner – leading to students having difficulties learning and comprehending new concepts. Moreover, the lack of variety in teaching styles, caused by imitation, would logically increase the chance that a teacher's method of teaching does not relate to a students preferred learning style. Consider-ing the evidence supporting better comprehension and performance of students when teaching is catered to their preferred learning method[30] (discussed under the status quo effect) this may also be a major disadvantage of teaching style imitation.

A potential solution to imitation could be the encouragement of various teaching styles[31], as endorsed by the IBO (International Baccalaureate Organisation), paired with shared audio recordings of classes so that students can benefit from teaching styles of various teachers. (This policy change has been explored further in the previous section of the report – the status quo effect).

While the discussions, on both copycat behaviour and on variety in teaching styles, are based on logical assumptions which explore a valid area in which education in the IBDP may be negatively impacted by the conformation bias, both methods require further research in terms of quantitative evaluation lend them credibility and reliability.

5 Present Bias

In psychological literature, procrastination is normally defined as the practice of pushing impending tasks to a later time or date when such a task results in a "counterproductive and needless delay". It is generally considered to be a result of present-bias in psychology and economics, and results in an individual delaying unpleasant tasks that, in hindsight, they wish they would have com-pleted sooner[32]. ' The present bias refers to the tendency of people to give more consideration and weight to events and rewards that are closer to the present time when considering differences between two future moments'[33]. For exam-ple, a present-biased person might prefer to receive a hundred dollars today as

[29] "COPYCAT: Meaning in the Cambridge English Dictionary." Cambridge Dictionary, dictionary.cambridge.org/dictionary/english/copycat.

[30] Franzoni, Ana Lidia, et al. "Student Learning Styles Adaptation Method Based on Teaching Strategies and Electronic Media." 2008 Eighth IEEE International Conference on Advanced Learning Technologies, 2008, doi:10.1109/icalt.2008.149.

[31] "International Baccalaureate (IB) Program / Approaches to Learning (ATL)." / Approaches to Learning (ATL), www.bostonpublicschools.org/Page/5935.

[32] Bisin, Alberto, and Kyle Hyndman. "Present-Bias, Procrastination and Deadlines in a Field Experiment." 2014, doi:10.3386/w19874.

[33] O'Donoghue, T., and Rabin, M. (1999). Doing it now or later. American Economic Review, 89(1), 103-124.

compared to a hundred and ten dollars tomorrow, but would not mind waiting an extra day if the choice were for the same amounts one year from today versus one year and one day from today. In a general sense, the concept is often used to describe impatience or the preference for immediate gratification in an individual's decision-making[34]. In 'Present-Bias, Procrastination and Deadlines in a Field Experiment'[35], a study done by Alberto Bisin and Kyle Hyndman, it was found that subjects who face an absolute or set deadline start working on tasks earlier than subjects who do not have a definite or imposed deadline (Panel A of Figure 8). Yet, contrary to expectations, it was also noted that subjects with a definite deadline began working on tasks far closer to their deadline as compared to subjects who did not have a binding, approaching deadline (Panel B on Figure 8). Lastly, it was observed that subjects who began working on a task closer to its deadline were less likely to complete it than those who began earlier (Panel C on Figure 8). In fact, students who began their task on the same day as its deadline has a less than 50 percent chance of completing the task, and those who began a week, or more, before their deadline had a 70 percent or higher probability of completing it. Arguably, the most interesting finding of the study was that each additional day before the deadline that a task was started, the probability of it being completed increased by 2.6 percent. As such, it could be concluded that binding deadlines help ensure tasks are completed.

While this study in itself proves the existence of the present bias and its impact on education, it is worth noting that the results of this study prove the idea that humans underestimate the amount of time they need to complete disjunctive – independent – tasks as they are increasingly unable to map time accurately the further away the events are from present time. There are several negative consequences of mankind's inability to map future time accurately, on education.

As teachers are human, they tend to slow down their teaching speed in the beginning of an academic year while revising the basic topics or previously studied material and then later face a lack of time and rush through some of the most complex parts of the syllabus in order to meet their set syllabus completion date. This effect of the present bias may make it difficult for students to understand tougher, newer concepts, which are normally taught towards the end of an academic year. Moreover, when paired with the status quo effect, the present bias also leads to teachers spending more time on the syllabus content that is simplest for them to teach as they can explain it with clarity. However, this also means that teachers brush through complex concepts as a consequence – once again impacting students' understanding of complex concepts. In the case that teachers do not complete syllabus on time, students may get less time to study for their exams. This would impact their progress, ability to revise concepts in a timely manner, and lead to them not having enough time to prepare well for their tests or exams – possibly affecting their performance. On

[34] "Present Bias." BehavioralEconomics.com — The BE Hub, 28 Mar. 2019, www.behavioraleconomics.com/resources/mini-encyclopedia-of-be/present-bias/.

[35] Bisin, Alberto, and Kyle Hyndman. "Present-Bias, Procrastination and Deadlines in a Field Experiment." 2014, doi:10.3386/w19874.

May 3rd, 2000, the BBC News published an article titled "Unfinished courses bring exam panic" which contained quotes by students from across England on the lack of syllabus completion and its impact on their ability to study for their board examinations. One such quote read "Our English teacher hasn't finished our syllabus yet!!!!! That's why I'm here trying 2 do it myself!!!! How do they expect you to pass ya exams when they don't even teach you!!!" while another read, "with now 12 dayz to go till my IT exam, suicide is becomin a very attractive alternative and no teenz should feel like we do ..."[36]. As suggested by the anecdotal evidence, non-completion of syllabi, caused by the present bias, may lead to severe consequences including excessive stress, confusion, and mental health disorders in students.

While considering the substantial negative impacts, of teachers slowing their pace initially and increasing it towards the end of the academic year, it is worth noting the Blooms Taxonomy[37] (figure 9), the foundation of many educational courses and teachers' lesson plans, explains one reason why this is done. According to the taxonomy, teachers spend time on initial chapters to help students recall what they have previously learnt and to explain the methods in which the course would progress. Towards the end of the year, students are familiar with the methods in which to approach concepts and questions, thus teach-ers can speed through the syllabus and focus more on the aspects of analysis, evaluation, and creativity. Essentially, the taxonomy states that teachers move through their syllabi slowly, at first, not due to the present bias, but rather to help students learn and comprehend foundational information. While the existence of this taxonomy reduces the credibility of the link between present bias and teaching speed, it is a valid counterargument and thus must be consid-ered. Furthermore, the existence of the taxonomy does not mitigate the impact that present bias does have on teaching speed. Despite creating lesson plans with the help of the taxonomy, teachers do tend to run short of time and some-times struggle to complete syllabi at the end of an academic year – leading to a potential decrease in student performance.

Present bias also affects students. When students receive their exam time-tables thirty days prior to their first exam, they are not able to accurately visualise the time they have to revise their syllabus. This same trend may be noted when IBDP students have deadlines for internal assessments, lab reports, and their extended essay due months after they are notified (of the deadlines). As such, procrastination on these assignments, due to the present bias, would also impact the results of students.

An experiment conducted by Dan Ariely, mentioned in Chapter 6 of his book 'Predictably Irrational'[38], explains potential method by which the effect of the present bias could be lowered. In this experiment, Ariely used three batches of

[36] "EDUCATION — Unfinished Courses Bring Exam Panic." BBC News, BBC, 3 May 2000, news.bbc.co.uk/2/hi/uk_news/education/733362.stm.

[37] Mcdaniel, Rhett. "Bloom's Taxonomy." Vanderbilt University, Vanderbilt University, 25 Mar. 2020, cft.vanderbilt.edu/guides-sub-pages/blooms-taxonomy/.

[38] Ariely, Dan. Predictably Irrational: the Hidden Forces That Shape Our Decisions. Harper Perennial, 2010.

students of his economics class at Massachusetts Institute of Technology (MIT) as his subjects. Each student had to complete 3 assignments within 12 weeks, however, the deadlines for each batch of students differed. Batch 1 was told that they had no deadline; they just had to submit all three papers by the end of the semester. Batch 2 was told that they could choose any deadline for each paper (with the last possible deadline being the last day of the semester), but that they had to submit their chosen deadlines to Ariely by within 5 days of the start of the semester and would face penalties of increasing value each day that their paper was late (from their chosen deadline). Batch 3 was given fixed deadlines: Paper 1 was due at the end of Week 4, Paper 2 at the end of Week 8, and Paper 3 at the end of Week 12. There would be no benefit of submitting work early for any group. When Ariely assessed the students, oblivious to who was in which batch, then analysed the results, he found that Batch 3 had done the best, followed by Batch 2, and Batch 1 had done the worst. Thus, the study concluded that external influence was far more powerful at ensuring deadlines were met as compared to self-control and self-motivation. The practise of setting external deadlines could be an effective method for ensuring timely syllabus completion and lowering of the present bias. This may be achieved in several ways, for example, teachers could create a detailed checklist for everything that is to be done. This checklist could be shared with students as chapters are completed (to prevent choice overload by sharing the entire syllabus at once) to ensure that all essential aspects of the syllabus are completed. This would help both students and teachers understand the extent of syllabus that has been covered. Furthermore, adding estimated dates for when a certain part of the syllabus should be completed would help ensure that the syllabus is completed in a timely manner. This is because it would transform the syllabus from a single two-year long disjunctive event to a series of conjunctive events (a series of events that come one after another). This would be beneficial as humans tend to overestimate the amount of time they need to complete a series of small events.

6 Conclusion

Education leads to the creation of an intelligent and competent future generation. As such, imparting the best possible, or optimal, education, is key to delivering an intelligent and competent generation. The IBDP (International Baccalaureate Diploma Programme), which strives for holistic learning and aims to produce young adults who are aware of global affairs, sets out on this mission. However, heuristics, or systemic biases, as defined by the field of behavioural economics, may impact education negatively. Heuristics that tend to have a great impact on education include the status quo effect, the conformation bias, and the present bias. Findings related to each of these heuristics have been discussed in detail within the research paper.

This paper is based solely on observation and secondary data. Some of the studies mentioned in the paper need further research and evaluation to improve

the validity of their results. Additionally, the proposals in this study need to be tested to examine whether or not the suggestions have a positive impact on student learning and performance. That being said, this paper considers several sources of information and their application and is written with first-hand knowledge of the IBDP. It presents logical arguments and supports them with previously performed studies. It also considers counterarguments and examples where necessary. Lastly, it proposes a wide-range of methods by which the learning and performance of IBDP students may be improved. Thus, while further research is recommended in the subject area, it is reasonable to state that the paper provides feasible and logical methods by which the performance of IB students may be improved.

The paper concludes that status quo bias, conformity bias, and present bias do affect the formal education system and that, when employed correctly, their influence can be used to positively impact the learning and performance of IBDP students.

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Fastweb	https://www.fastweb.com/student-life/articles/impressive-extracurriculars
Unigo	https://www.unigo.com/admissions-advice/what-are-the-most-popular-extracurriculars
Education Corner	https://www.educationcorner.com/k12-extracurricular-activities.html
Testive	https://www.testive.com/extracurricular-activities/
Blog – PrepScholar (1)	https://blog.prepscholar.com/list-of-extracurricular-activities-examples
Blog – PrepScholar (2)	https://blog.prepscholar.com/best-extracurricular-activities-for-college
Blog – PrepScholar (3)	https://blog.prepscholar.com/extracurricular-activities-examples-for-college-applications
Nshss	https://www.nshss.org/blog/what-are-good-extracurricular-activities-for-college-applicants/

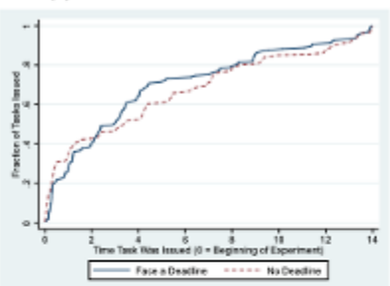
Figure 6: Extracurricular Advice Websites

Batch	Teacher	Teaching Method
1	A	Real life examples
2	B	Key terminology and definitions
3	C	Key terminology and definitions + real life examples

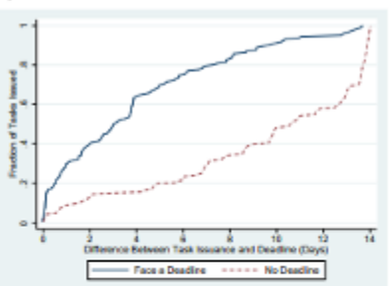
Figure 7: A Realistic Hypothetical Situation of Non-Conformity

Figure 8: The Time of Task Issuance (3T Treatments)

(a) Time At Which Task Was Issued



(b) Time From deadline At Which Task Was Issued



(c) Likelihood of Completing Task Given Time Issued From Deadline

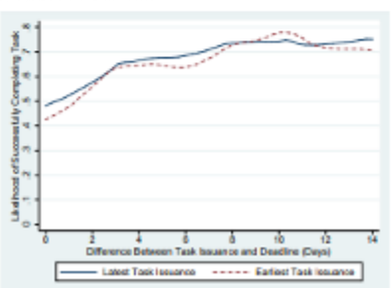


Figure 8: The time of task insurance

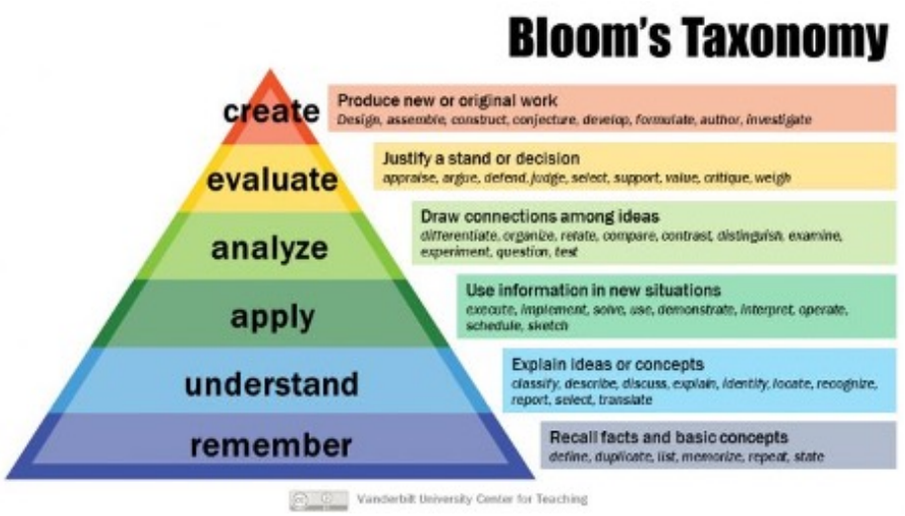


Figure 9: Bloom's Taxonomy

Oncogenic Viruses: A Potential CRISPR Treatment

Neha Matai *

April 2, 2021

Abstract

Oncogenic viruses promote carcinoma development by establishing long-term latent infections, obstructing tumor suppressor pathways, and transforming host cells into unchecked, proliferating malignancies. Epstein-Barr Virus, the first oncogenic virus to be discovered, can promote lymphomagenesis in T cells, NK cells, and most commonly, resting memory B cells through the expression of oncoprotein LMP-1 and other proteins which may aid in B cell transformation. Human Papillomavirus is a common infectious agent found in epithelial cells and has been shown to promote malignant transformation in host cells through the overexpression of oncoproteins E6 and E7. Hepatitis C Virus, whose life cycle is not fully known yet, can also lead to carcinoma development in hepatocytes, and HCV oncoproteins NS3, NS4A, and NS5B have been associated with oncogenic roles. A novel genetic approach involving a CRISPR/Cas treatment designed to dysregulate these viral oncogenes can be used to combat these infections and their resulting carcinomas. While the long-term effects of CRISPR treatments are still being researched, this gene therapy offers a robust selection of potential treatments regarding long term diseases such as oncogenic viral infections.

1 Introduction

The human population is prone to cancer through a wide variety of variables; in fact, 20% of which are caused by infectious agents such as bacteria, viruses, and other pathogens.[1] Oncogenic viruses alone are responsible for 12% of all cancers diagnosed worldwide. More specifically, 80% of viral cancer cases occur in the developing world today.[2] The first oncovirus was discovered in 1964 when researchers located the Epstein-Barr Virus in Burkitt's Lymphoma cells using electron microscopy.[3] Since this turning point in viral oncology, six more viruses have been confirmed to cause oncogenesis.

*Advised by: Everardo Hegewisch Solloa

[1] [Hau09]

[2] [Hau09]

[3] [MHT17]

While infections from oncoviruses are common, they rarely lead to malignancies and take a long period of time to transform host cells into an oncogenic state. For cancers to arise, these viral infections must be accompanied by chronic inflammation, environmental mutagens, or immunosuppression.[4] Additionally, oncogenic viruses do not follow a uniform path to oncogenesis since some of the viruses are considered to be direct carcinogens, while others are indirect carcinogens. Direct carcinogens cause cancer cell transformation by expressing oncogenes, while indirect carcinogens cause chronic infection or inflammation, which leads to carcinogenesis.[5] The seven known oncogenic viruses have been characterized by the class of genetic material they possess (e.g., DNA or RNA). The five known DNA oncoviruses include Epstein-Barr Virus (EBV), Hepatitis B Virus (HBV), Human Herpesvirus-8 (HHV-8), Human Papillomavirus (HPV), and Merkel Cell Polyomavirus (MCPyV). On the other hand, there are two oncogenic RNA viruses, which include Hepatitis C Virus (HCV) and Human T-Cell Lymphotropic Virus-1 (HTLV-1).[6]

Oncogenic viruses can be transmitted via the exchange of bodily fluids and direct skin to skin contact.[7] Viral cancers only arise 15 to 40 years after primary infection since chronic infection is a critical component of oncogenic transformation. Oncoviruses can achieve chronic infection by switching from a lytic to a latent stage after initially infecting host cells.[8] Viruses in a lytic phase actively induce the host cell to biosynthesize a wide variety of functional and structural proteins to produce more viral progeny. Contrarily, viral latency does not involve infectious virus production since, in a latent stage, viruses integrate a copy of their genome into the host cell's genome during viral replication and rely on host cell replication for survival.[9] The latent stage ensures that the virus exists in host cells without detection from the immune system. It is often latency that promotes oncogenesis since viruses in the lytic phase create a higher risk of DNA damage detection that results in programmed cell death, inhibiting the virus and host cell from replicating further. It is noted that cancer cells have little to no evidence of viruses in the lytic stage.[10]

The most common treatments for viral cancers are currently chemotherapy, such as lytic-inducing chemotherapies used for virus-related lymphomas, and resection, which is the surgical removal of tumorous tissue.[11] Additionally, preventative treatments include vaccinations, which exist for some oncoviruses. Other oncogenic viruses are treated using radiotherapy, immunotherapy, or antiviral drugs prescribed on a case to case basis.[12] However, these treatments cannot guarantee complete eradication of infection and many cases result in

[4] [MC10]
[5] [MC10]
[6] [MHT17]
[7] [MSFP14]
[8] [MC10]
[9] [CCY15]
[10] [MC10]
[11] [MHT17]and [BDA+13]
[12] [CKQ19]

reactivation of the virus.[13] Recent advancements in molecular biology research have allowed researchers to explore gene-editing tools as potential therapeutics for oncogenic viruses. Clustered regularly interspaced short palindromic repeats (CRISPR) technologies have now been considered for use in therapies to treat cancers, chronic viral infections, or genetic diseases.[14] In situ, the CRISPR/Cas system is a bacterial and archaeal "adaptive immune system" that recognizes bacteriophage genomes complementary to a guide RNA (gRNA), which is bound to a Cas protein. Once CRISPR/Cas has associated with its complementary target sequence in the phage genome, it induces a double-stranded break in the complementary DNA strand, inhibiting the phage's ability to replicate.[15] CRISPR/Cas was discovered as a potential gene-editing tool in 2013 for its ability to induce double-stranded breaks in a sequence-specific manner, resulting in either nonhomologous end-joining (NHEJ) or homology-directed recombination (HDR).[16] The ability to induce site-specific gene edits allows scientists to knock out a gene or introduce a gene with higher efficiency. Not only has CRISPR/Cas allowed scientists to further understand gene functions, but it also has the potential of serving as a therapy via either the deletion or correction of a mutated gene.

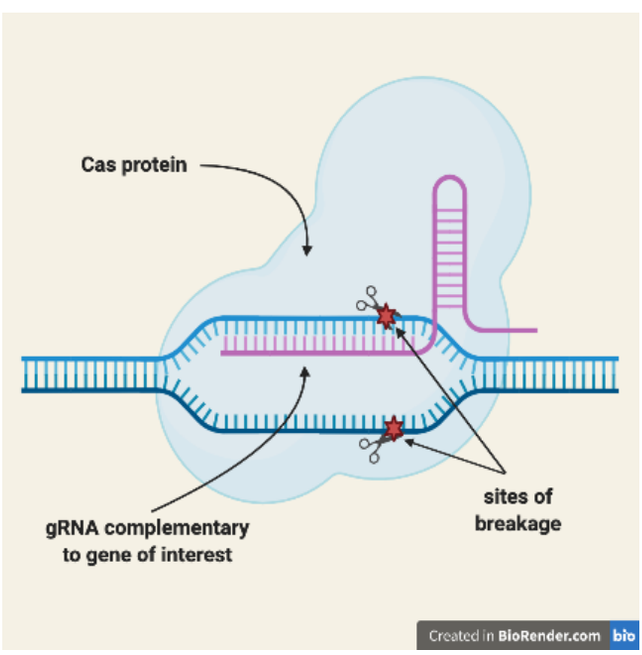


Figure 1: Double-stranded breaks are induced by the Cas-gRNA complex

[13] [GP16]
[14] [LdS19]
[15] [LdS19]
[16] [LdS19]and [WHK15]

Currently, novel virus-targeted therapies are being researched for oncogenic viruses, which include new immunotherapies, cellular therapies, and antibody therapies.[17] Gene therapies are treatments which consist of the application of zinc-finger nucleases (ZFN), transcription activator-like effector nuclease (TALEN), and CRISPR to treat a disease. The concept of gene editing for repairing mutated genes constitutes a new field of research that is being applied to various diseases and disorders. Here I will propose a novel CRISPR/Cas based therapy for treating Epstein-Barr Virus, Human Papillomavirus, and Hepatitis C Virus.

2 Epstein-Barr Virus (EBV)

The Epstein-Barr Virus is also known as human herpesvirus-4 and is one of the eight human viruses in the herpesviridae family 2. Today, EBV has infected 90% of the world's adults.[18] However, the majority of EBV carriers maintain lifelong, asymptomatic infections.[19] EBV is a double-stranded DNA virus that is transmitted primarily through saliva. After decades of research, it is confirmed that EBV is able to infect a wide variety of cells that encompasses B cells, T cells, NK cells, glandular and squamous epithelial cells, and smooth muscle cells. However, the virus is most commonly known to have oncogenic potential in B lymphocytes since it is able to create undetected DNA damage during a latent stage by inserting its genetic material into the host genome and then transforming B lymphocytes into proliferating lymphoblastoid cells through the large amounts of oncogenic protein made during a long span of latency.[20]

2.1 Lifecycle and Genome Properties of EBV

In its primary stage of infection, EBV is in a lytic phase and most commonly replicates in squamous epithelial cells and local lymphocytes.[21] Cases of infectious mononucleosis can sometimes occur as a result of an abnormal EBV-specific immune response.[22] After EBV has established a local infection in a lymph node, the secondary phase of infection begins when EBV spreads to B lymphocytes, transforming them into virus-producing 'factories.' Once in B cells, EBV downregulates the expression of its growth-transforming gene so that it can remain undetected in the host cell under a latent stage. Resting memory B cells infected with latent EBV then continue to circulate as part of the B cell pool. In a healthy host, EBV typically remains in a latent stage or is eradicated by the immune system, yet in cases when EBV re-enters the lytic stage of infection at a mucosal surface, new viral particles are released and can go on to infect more cells.[23]

[17] [MHT17]
[18] [MHT17]
[19] [PGS+15]
[20] [CCY15]
[21] [CCY15]
[22] [PGS+15]
[23] [CCY15]

The genome of Epstein-Barr Virus is a 172kb double-stranded DNA genome that encodes for lytic gene products and latent gene products. EBV infection is initiated when structural proteins gp350 and gp220 bind to CD21 receptors of B cells. EBV structural protein gp42 then completes viral fusion into B cells by binding to the human leukocyte antigen class II receptor.[24] Lytic gene products are then expressed during the early stages of EBV infection and consist of the early antigen (EA) complex, a complex of non-structural proteins, and the viral capsid antigen (VCA), which is composed of distinct structural antigen complexes. Both the expression of EA and VCA are significantly reduced or not present after EBV transitions into a latent stage.[25] EBV then expresses latent proteins which fall under two main categories: nuclear antigens (EBNA-1,2,3A,3B,3C,LP), and latent membrane proteins (LMP-1,2A,2B). All nine proteins are expressed in both post-transplant lymphoproliferative disorder (PTLD) cells and lymphoblastoid cell lines (LCL).[26] EBV latency is categorized into four stages (0-III) according to the proteins expressed during latency. B cell immortalization is associated with latency stage III, which includes the expression of all six nuclear antigen proteins and all three latent membrane proteins. Latency stage II encompasses the expression of proteins EBNA-1, LMP-1, LMP-2A, LMP-2B, and is most closely associated with Hodgkin Lymphoma. Latency stage I only involves the expression of the EBNA-1 protein and most commonly occurs in Burkitt Lymphoma. The EBV genome persists in host cells without the expression of any viral proteins in latency stage 0, the latency stage associated with non-dividing memory B cells.[27]

LMP-1 is the main oncogenic protein involved in EBV induced oncogenesis. LMP-1 mimics the function of the CD40 receptor, which is a member of the tumor necrosis factor receptor (TNFR) superfamily, and activates downstream signaling pathways that are critical to the expression of anti-apoptotic proteins and differentiation in B cells.[28] These signaling pathways include NF-B, MAPK/ERK, PI3K/AKT, Notch, and JAK/STAT. The most important pathways for EBV induced oncogenesis are the PI3K/AKT and JAK/STAT pathways, which, once activated, will contribute to genomic instability, apoptosis resistance, limitless replication, and tumor-promoting inflammation.[29] Other oncogenic proteins that have been shown to contribute to EBV related carcinomas include LMP-2A, EBNA-1, and EBNA-2 proteins. LMP-2A also contributes to oncogenesis by ensuring the survival of EBV infected cells through the inhibition of TGF-1-induced apoptosis and activation of the Lyn/Syk signaling pathway, which is a tyrosine kinase pathway essential for tumor survival. EBNA-1 is crucial for the maintenance and replication of the EBV genome and also exhibits oncogenic behavior by suppressing the promyelocytic leukemia protein, a tumor suppressor protein responsible for regulating p53 activation. To-

[24] [SKJL10]
[25] [YAM07]
[26] [ESZM18]
[27] [DCH19]
[28] [PGS+15]
[29] [MHT17]

gether, EBNA-2 and EBNA-LP proteins are essential for transcription initiation of viral proteins LMP-1 and LMP-2A and cellular proteins MYC, CD21, and CD23, all of which contribute to the transformation and immortalization of B cells.[30] The main oncogenic protein LMP-1 and oncogenic proteins LMP-2A, EBNA-1, and EBNA-2 are essential components of EBV, which can be used as potential targets in treatment.

2.2 Epstein-Barr Virus Treatments

Currently, the standard treatments for EBV associated carcinomas are systemic chemotherapy or radiotherapy. However, the majority of EBV associated malignancies remain unaffected by these treatments, and there is currently no effective therapeutic option for latent EBV tumors.[31] A more increasingly used form of therapy for patients is combination therapy, which includes lytic-inducing chemotherapy followed by the use of antiviral drugs. EBV viral replication is successfully suppressed by nucleoside analog antivirals, such as ganciclovir, acyclovir, and famciclovir, when the virus is in a lytic stage. These antiviral drugs rely on viral-encoded kinases, which are only expressed during a lytic phase, to convert them to their active form where they are able to inhibit DNA polymerase of host cells, prevent viral DNA synthesis and kill tumor cells. A lack of activation, which is facilitated by latent EBV malignancies, will prevent antiviral drugs from successfully inhibiting viral replication. In contrast to the success shown by antiviral drugs, this approach to treating EBV related carcinomas also leads to a higher risk of viral transmission to surrounding healthy cells since EBV can rapidly produce and spread new viruses during a lytic stage.[32]

New treatments that are currently being researched as effective EBV-induced carcinoma treatments include adoptive cell immunotherapy and the development of a vaccine to prevent primary EBV infection.[33] Extensive research on the use of adoptive T cell therapy, which involves the use of EBV-specific cytotoxic T cells (EBV-CTLs), on patients since 1995, is now confirming that this form of treatment can effectively prevent newly diagnosed and recurrent cases of EBV-PTLD.[34] In addition to adoptive T cell therapy, a recombinant glycoprotein gp350 vaccination was tested in healthy volunteers. While it has not been shown to prevent primary EBV infection yet, it has been shown to reduce cases of symptomatic infectious mononucleosis. Like adoptive cell immunotherapy for EBV, EBV vaccinations are aimed at preventing primary infection or EBV-related malignancies through the induction of EBV-specific T cell responses. These T cell responses can be achieved by stimulating T-cell mediated immunity against viral antigens expressed during a latent stage.[35] While these medical advancements have led to safer and more efficient EBV treatments, the preci-

[30] [MHT17]
[31] [MHT17]
[32] [MHT17]
[33] [KA14]
[34] [KA14]
[35] [KA14]

sion of EBV treatments can be improved by using a more specialized approach, such as gene therapy.

2.3 A Potential CRISPR Treatment for EBV

A CRISPR/Cas9 system designed to knock out EBV proteins LMP-1 And EBNA-1 can be used as a treatment for persons with latent EBV infections or EBV-induced B cell lymphomas since the Cas9 protein is able to induce double-stranded breaks in DNA. DNA repair such as homologous recombination (HR) or nonhomologous end-joining (NHEJ) will then follow.[36] The absence of LMP-1 protein will inhibit viral ability to activate downstream signaling pathways such as NF-B, MAPK/ERK, Notch, PI3K/AKT, and JAK/STAT, which, when activated, all facilitate genomic instability, apoptosis resistance, limitless replication, and tumor-promoting inflammation.[37] This will decrease resistance to apoptosis and prevent unchecked cell proliferation in the host. Additionally, with the absence of EBNA-1 protein, suppression of the promyelocytic leukemia protein, a tumor suppressor protein responsible for regulating p53 activation, will be prevented.[38] This will result in the renovation of p53 functions and will most likely lead to programmed cell death.

The main component of this treatment is a plasmid containing the CRISPR/Cas9 gene, and DNA sequences for each target gene (LMP-1, EBNA-1) would need to be produced. This plasmid will be delivered into EBV infected cells via an adenoviral vector, and will therefore also contain genes encoding for structural proteins of the viral vector and a packing signal to successfully package the plasmid into the adenoviral vector. Additionally, genes encoding for EBV structural proteins gp350, gp220, and gp42 will be included in the plasmid to ensure that the infection is directed towards B cells, the cells infected by EBV.[39]

Once in the host, these EBV-targeted viral vectors will execute fusion into B cells. In the event that a healthy B cell obtains the plasmid, no genetic editing will take place since the EBV DNA needed to initiate replication of the plasmid is not present. However, once the plasmid has been successfully inserted into EBV-infected B cells, transcription of the CRISPR engineered plasmid will be activated. After transcription, gRNAs complementary to oncogenes LMP-1 and EBNA-1 will associate with Cas9, and this Cas9-gRNA complex will bind to the complementary strands of DNA encoding for LMP-1 and EBNA-1. The Cas9 protein will then create a double-stranded break at these sites. Nonhomologous end joining (NHEJ) will follow, producing mutations that obstruct the function of these genes, and the targeted oncogenes will be nonfunctional.

Western blotting can be used to validate these intended knockouts. The initial preparation for this process includes cell lysis and protein extraction. Cells from an in vitro, CRISPR edited, EBV-positive B cell culture should be washed in a detergent, or buffer, such as phosphate-buffered saline, to induce cell dis-

[36] [LdS19]and [WHK15]
[37] [MHT17]
[38] [MHT17]
[39] [LBZ+17]

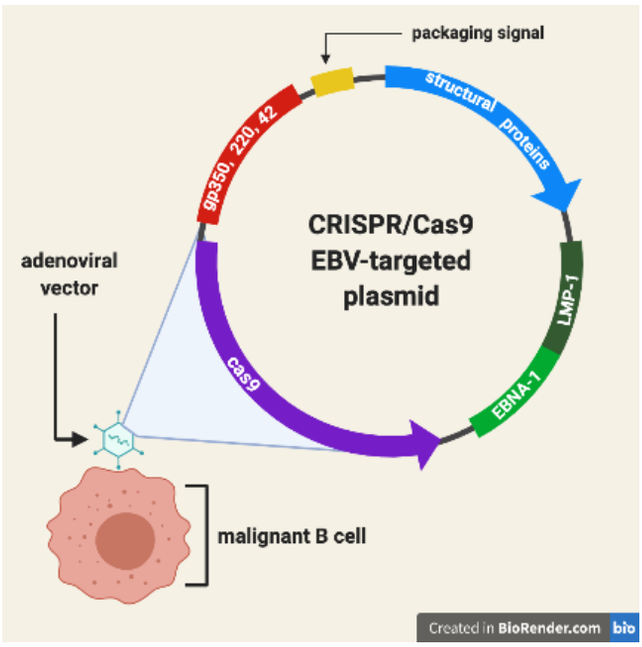


Figure 2: EBV plasmid containing Cas9 gene, oncogenes LMP-1 and EBNA-1, structural adenovirus proteins, a packaging signal, and genes encoding for EBV proteins gp350, gp220, and gp42

ruption. Protein extraction should then take place under a cold temperature with protease inhibitors so that the denaturing of proteins is prevented.[40] After protein extraction, the concentration of proteins should be measured using a spectrophotometer, and the protein sample should be diluted with a loading buffer containing glycerol so that the sample will easily sink into wells containing gel. The sample should then be heated since heating will denature the sample and give proteins a negative charge, a key component for movement in an electric field when a voltage is applied.[41] After this sample preparation, the protein sample will go through gel electrophoresis, which involves both a stacking and a separating agarose gel. The stacking agarose gel is above the separating gel and has an acidic pH of 6.8, which will separate the proteins into sharply defined bands. The separating agarose gel has a basic pH of 8.8, allowing for narrower gel pores, which will separate proteins by size since smaller proteins will sink faster.[42] After a voltage has been applied to the gel, the separated protein mixture will be transferred to either a nitrocellulose or polyvinylidene fluoride membrane via electrophoretic transfer. A blocking solution containing either 5% BSA or TBST diluted, nonfat dried milk should then be added to reduce the

[40] [MY12]
[41] [MY12]
[42] [MY12]

background on blots and prevent antibodies from non specifically binding to the membrane.[43] The membrane will detect antibodies corresponding to EBV proteins LMP-1 and EBNA-1 via an enzyme, such as horseradish peroxide, which will produce a signal based on the position of the target proteins. Finally, this signal will be captured on a film, quantifying the presence of target proteins.[44] The western blots from these CRISPR edited cells can then be compared to EBV-positive B cells, which did not receive treatment. After comparison, the intended knockouts can be considered successful if the demarcations of LMP-1 and EBNA-1 were faint or nonexistent on the CRISPR edited cell western blots compared to those of untreated EBV cells.

Trials for this treatment should first take place in vitro, using transgenic, EBV-positive mice cells, progress to in vivo mice trials after knockouts have proven successful, and then take place in EBV-positive human B cells in vitro before moving to human trials. Successful in vivo EBV trials centered around studying the role of EBV protein LMP-1 in lymphomagenesis in mice models have already been done by [ZKY$^+$12].[45] They generated a Rosa26 allele, which allowed for LMP-1 expression through the excision of a transcriptional/ translational STOP cassette via Cre/loxP-mediated recombination (LMP1flSTOP). LMP-1 expression was then induced in B cells from the pre-B cell stage by crossing the LMP1flSTOP mice to CD19-cre mice.[46] These B cells were then used to study various LMP-1 interactions and functions. A similar approach can be taken when modeling EBV-positive B cell lines and EBV-infected mice for in vitro and in vivo trials, respectively. Furthermore, trials testing the efficacy of a CRISPR-Cas9 treatment have already been carried out by [WQ14] in vitro using cells from Burkitt's lymphoma patients, and have shown to be successful.[47] EBV-positive cells from the Raji cell line, the first established long-term culture from Burkitt's lymphoma patients, were used for testing. This EBV-targeted CRISPR/Cas system included gRNA for EBNA1-7, and knockouts were validated using western blotting.[48] Results from these trials showed a significant decline in cell proliferation and viral load and showed restoration in apoptotic pathways. The research done by both Zhang et al. and Wang and Quake can be referred to when considering appropriate testing procedures and models for the potential CRISPR-Cas9 treatment.

3 Human Papillomavirus (HPV)

Human Papillomaviruses belong to the Papillomaviridae family, a large family of double-stranded DNA viruses.[49] HPV is the world's most commonly transmitted sexual disease and primarily infects epithelial cells through skin to skin

[43] [MY12]
[44] [MY12]
[45] [ZKY$^+$12]
[46] [ZKY$^+$12]
[47] [WHK15]and [WQ14]
[48] [WQ14]
[49] [GS16]and [HM17]

or mucosa to mucosa contact.[50] Over 200 types of HPV are known to exist and can be further classified into five genera which include alpha-papillomaviruses, beta-papillomaviruses, gamma-papillomaviruses, mu-papillomaviruses, and nu-papillomavirus.[51] Skin infections are caused by beta, gamma, mu, and nu-HPVs, while mucosa infections are caused by alpha-HPVs.[52] The most common visible outcome of chronic HPV infection is the appearance of benign epithelial warts around the site of primary infection. Healthy individuals that are infected with HPV rarely show symptoms, and few actually develop disfiguring warts. Still, the lifetime risk of a sexually transmitted HPV infection is 50%, and some cases of chronic and/or repetitive HPV infection can lead to the development of malignancies.[53] In terms of malignancies, HPV types can also be categorized into low risk and high risk types. HPV types 6 and 11 are the most common low risk types and cause external anogenital warts in 90% of infections.[54] All high risk types of HPV are classified as genera, with the most common types being HPV-16,18,31,33,52,58. Furthermore, HPV-16 and 18 are most commonly associated with malignancies. Although HPV-associated cancers are rare compared to other malignancies, they are still responsible for 99% of cervical cancer, 85% of anal cancer, and 50% of genital-associated cancers.[55]

3.1 Lifecycle and Genome Properties of HPV

While the majority of viruses can produce progeny viruses after infecting a target cell, HPVs are only able to synthesize new virions after target cells have undergone mitosis, and infected daughter cells have differentiated. In healthy epithelia, basal cells are the only proliferating cells and are exposed as a result of micro-wounds. These cells in the basal layer of stratified squamous epithelia serve as the site of primary infection for HPV.[56] After primary infection, an episome is established as the HPV genome and does not encode for the polymerases and enzymes responsible for viral replication. As a result, HPV relies entirely on host cells for replication. HPVs full life cycle matches the time it takes for epithelial cells to fully mature, a cycle which lasts 2-3 three weeks.[57] During this time, suprabasal cells continue to follow a normal life cycle while a subset of cells containing viral episomes re-enter the DNA synthesis phase (S phase) and engage in amplification, the process by which HPV genomes are replicated.[58] Over time, frequently recurring HPV infections lead to the accumulation of cellular mutations. After several decades of failure to clear persistent HPV infections, malignancies develop from the extensive accumulation of these mutations. In cancerous cells, the HPV genome is also commonly found to be integrated into

[50] [GS16]
[51] [MHT17]and [HM17]
[52] [MHT17]
[53] [MHT17]
[54] [BFM17]
[55] [GS16]
[56] [ML10]
[57] [MHT17]
[58] [ML10]

the host genome instead of existing as an episome.[59]

The HPV genetic material exists as an 8kb non-enveloped, circular DNA genome.[60] The HPV genome is composed of a long, non-coding control region, six early-transcribed genes (E1,2,4,5,6,7), which encode for the non-structural proteins, and two late-transcribed genes (L1,2) which encode for the structural viral capsid proteins.[61] Early proteins E1,2 and 4 are responsible for the gene regulation, replication, and pathogenesis of the virus, while late proteins L1 (major viral capsid protein) and L2 (minor viral capsid protein) are involved in assembling virus-like particles. In fully matured virions infecting new cells, L1 is also the protein responsible for facilitating entry into host cells by binding to the widely expressed, host cell surface receptor HSPG.[62] HPV proteins E1 and E2 facilitate viral DNA replication and regulate early transcription, and E4 is thought to aid in viral escape from the cornified layer of the epithelium.[63]

HPV genes E5,6 and 7 are shown to possess oncogenic properties with genes E6 and E7 playing the main role in transforming healthy host cells into malignant growths and gene E5 assisting in oncogenesis by promoting cell proliferation through the activation of tyrosine kinase receptors EGF and PDGF.[64] E6 and E7 proteins are the main difference between low risk and high risk HPV infections since they have been confirmed to function as oncoproteins in high risk infections and not low risk infections.[65] E7 is responsible for binding to cellular factors from the retinoblastoma (Rb) family, such as p105 (RB), p107, and p130, and degrading them. While this is done in all HPV infections, E7 binds extensively to Rb cellular factors in high risk infections.[66] Similarly, in high risk infections, E6 is able to efficiently bind to tumor suppressor p53 and degrade it via the ubiquitination-mediated pathway. On the other hand, E6 is unable to easily bind to p53 and inactivate it in low risk infections.[67]

Evidence from decades of cervical cancer research suggests that HPV has certain growth advantages when its genome is integrated into the genome of the host cell as opposed to remaining as an episome. Interestingly, HPV protein E2, which is a transcriptional repressor for oncoproteins E6 and E7, is often the site of integration. This disruption of E2 expression then results in an increased expression of E6 and E7. In high risk HPV infections, a combination of increased expression in both main oncoproteins and the inactivation of tumor suppressor pathways Rb and p53 lead to large amounts of genomic instability in the host and ultimately, an increased progression in malignancies.[68] These advancements in the understanding of the HPV genome can serve as a foundation for new HPV-targeted treatments.

[59] [ML10]
[60] [MHT17]
[61] [GS16]
[62] [HBR$^+$10]
[63] [HM17]and [ZB06]
[64] [HM17]and [ML10]
[65] [GS16]
[66] [ML10]
[67] [GS16]
[68] [GS16]

3.2 Human Papillomavirus Treatments

Several preventative HPV vaccinations have been created in the twenty-first century. Gardasil, a quadrivalent vaccine for prevention against HPV types 6, 11, 16 and 18 was licensed in 2006 for use in the United States. In 2009, Cervarix, a bivalent vaccination against HPV 16, and 18 was approved for use in the United States.[69] The most recent vaccination for HPV, a 9-valent vaccine (9vHPV) which prevents against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, was licensed in 2014 for use in the United States, and 2015, for use in Europe. Today, 9vHPV is the only HPV vaccination in the United States and is also licensed for use in Canada, Australia, Chile, Hong-Kong, Ecuador, South Korea, and New Zealand.[70] All preventative vaccines that have been created for HPV contain a synthetic recombinant L1 major capsid protein base. Still, while all HPV vaccines have proven effective in preventing HPV, the L1 base restricts these vaccinations to HPV type-specific responses and does not offer a broader spectrum of defenses against all human papillomaviruses.[71]

New treatments that are being researched for HPV prevention and HPV associated carcinomas include an L2 based vaccination and therapeutic vaccinations. The L2 minor capsid protein possesses homology across HPV types, which would provide broader coverage of HPVs if used as the base of a vaccine.[72] Therapeutic vaccinations are another treatment option for HPV induced malignancies or pre-malignancies. These vaccines are being aimed to generate antigen-specific, cellular-mediated immunities instead of the humoral immunities which can be gained from preventative HPV vaccinations. Therapeutic vaccines are designed to induce CD8+ cytotoxic T cells and CD4+ helper T cells to target epithelial cells that contain E6 and E7, the two main viral oncoproteins.[73] A similar precision-based approach, which can be applied directly to infected cells, can be achieved through the use of new tools involved in gene editing.

3.3 A Potential CRISPR Treatment for HPV

An engineered CRISPR-Cas9 system targeting main HPV oncogenes E6 and E7 can be used to treat HPV-related carcinomas. When knocked out, the absence of E6 will inhibit the degradation of tumor suppressor p53.[74] An E7 knock out will prevent degradation of cellular factors from the Rb family such as RB, p107, and p130.[75] By disabling the expression of both oncogenes, host cell tumor suppressors will be able to function and will detect tumorigenesis, leading to programmed cell death. Like EBV, the Cas9 protein will be used to cleave

[69] [MHT17]
[70] [SOC+17]
[71] [MHT17]
[72] [MHT17]
[73] [MHT17]
[74] [GS16]
[75] [ML10]

targeted sites since HPV is also a double-stranded DNA virus. This treatment will be inserted into HPV-infected cells via an adenoviral vector.

The plasmid containing the CRISPR-Cas system will include the CRISPR-Cas9 gene, DNA sequences for HPV oncogenes E6 and E7, genes encoding for structural proteins of the adenovirus, a packaging signal, and the gene for HPV structural viral capsid protein L1; the protein responsible for binding to basal layer epithelial cells. Once the plasmid is successfully inserted into HPV-positive cells and transcription has occurred, gRNAs complementary to HPV oncogenes E6 and E7 will associate with the Cas9 proteins. This Cas9-gRNA complex will then bind to the E6 and E7 sequences complementary to it, and Cas9 will induce double-stranded breaks in both oncogenes. Afterward, NHEJ will occur, and the mutations originating from this repair process will obstruct proper expression of HPV oncogenes E6 and E7, inhibiting their functions. These knockouts will also be validated using western blots. Westerns blots of in vitro, CRISPR edited, HPV-positive cells should be compared with western blots of untreated HPV-infected cells to confirm a significant decrease of E6 and E7 expression.

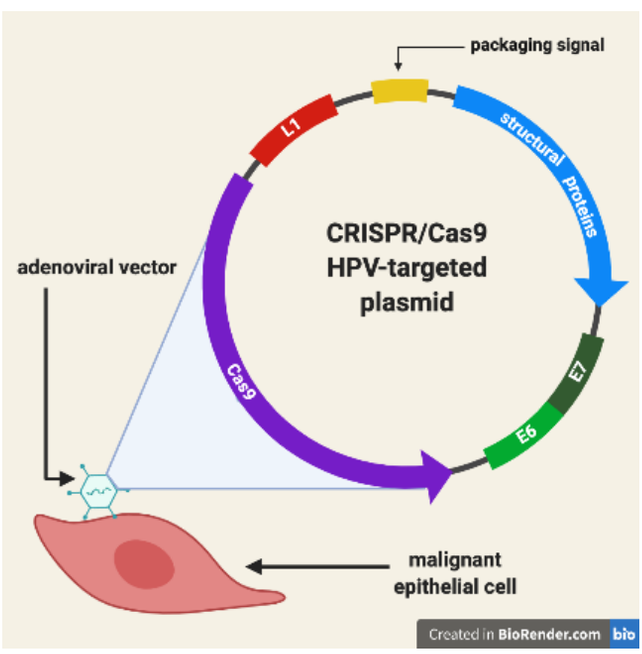


Figure 3: HPV plasmid containing Cas9 gene, oncogenes E6 and E7, structural adenovirus proteins, a packaging signal, and HPV gene L1

Like the proposed treatment for EBV, trials for this treatment should take place in humanized mice models both in vitro and in vivo before using in vitro human cell lines, and eventually progressing to in vivo human trials. [BPHD$^+$12] were able to achieve humanized mice models of HPV-associated pathology via

the expression of HPV protein E7.[76] Artificial human skin, which was prepared using primary keratinocytes engineered to express E7, was transplanted into nude mice. These E7 genes were obtained from HPV strains 5, 10, and 16 by using PCR and specific primers from plasmids pBP-5E7, pcDNA3-10E7, and pBP-16E7. Once transplanted into mice, these E7 transplants were stably maintained for six months and began to promote anogenital warts after this time period, a significant symptom of oncogenic strains of HPV.[77] A similar approach, based on the expression of both E6 and E7 oncogenes, can be taken when mimicking HPV in mouse models for this potential CRISPR treatment. Additionally, [KKG$^+$14] were able to achieve successful in vitro results from a CRISPR-Cas9 system designed to knock out HPV oncoproteins E6 and E7.[78] This treatment was applied to HeLa and SiHa cell cultures, which were grown in Dulbecco's modified Eagle medium and supplemented with 10% fetal bovine serum. The knockouts were verified using western blotting, and results showed reactivation of tumor suppressors such as p53 and cellular factors from the retinoblastoma family.[79] Both these studies can be used as procedure and analysis references for trials of the potential CRISPR treatment.

4 Hepatitis C Virus (HCV)

Hepatitis C Virus is a single-stranded RNA virus that belongs to the Hepacivirus genus and is a member of the Flaviviridae family.[80] HCV is primarily transmitted via percutaneous or mucosal contact with infected blood, while other routes of transmission include high risk sexual activities and contact with other infected body fluids.[81] HCV can cause both acute and chronic liver infections but has shown to progress to chronic infections in 75-85% of infected persons. An HCV infection is considered chronic if, six months after primary infection, HCV RNA persists in the blood. This type of infection is commonly induced by HCV because it is a frequently replicating virus with an RNA genome that is highly prone to replication errors, allowing for long-term evasion of the host immune system. As a result, innate immune responses in the host are significantly delayed, and a widespread HCV infection is often established before adaptive immune cell responses are activated.[82] Today, 170 million people are chronically infected with HCV worldwide, and the annual rate of newly diagnosed cases is 4 million per year.[83] Due to its high potential to cause chronic infections, HCV is the leading cause of cirrhosis and is considered an indirect carcinogen for hepatocellular carcinoma, which is mainly prevalent in developed countries.[84]

[76] [BPHD$^+$12]
[77] [BPHD$^+$12]
[78] [KKG$^+$14]
[79] [KKG$^+$14]
[80] [MHT17]and [CM06]and [SEKI$^+$16]
[81] [MHT17]and [CM06]
[82] [Dus17]
[83] [MHT17]
[84] [MHT17]and [SEKI$^+$16]

4.1 Lifecycle and Genome Properties of HCV

Like other oncogenic viruses such as EBV and HPV, HCV infections progress into malignancies after a long period of time, taking up to 20-40 years to fully progress into hepatocellular carcinoma.[85] On the other hand, while HPV and EBV are able to integrate their genetic material into the host genome, HCV is a single-stranded RNA virus that is incapable of genome integration. As a result, HCV spends the majority of its life cycle in the cytoplasm of host cells and is assumed to cause carcinogenesis through indirect mechanisms, even though some components of its life cycle remain unknown.[86] Upon primary infection, HCV attaches to host cells via target cell receptors such as CD81, SR-B1, LDL-R, EGFR, and EphA2. It then uses a clathrin-mediated endocytosis process to enter the host cell and release its RNA genome in the cytoplasm.[87] After successful translation of the HCV genome, new virions undergo assembly and maturation in an endoplasmic reticulum compartment where they are also surrounded by endogenous lipoproteins, which are believed to aid in immune escape. New virions are then believed to exit cells via exocytosis.[88] Chronic damage to hepatocytes as a direct result of chronic HCV infection induces the release of inflammatory and fibrotic mediators such as reactive oxygen species (ROS), cell death signals, hedgehog ligands, and nucleotides.[89] This creates genomic instability, making host cell genomes susceptible to modification and transformation by the expressions of HCV proteins believed to play roles in oncogenesis.

The HCV genome is an enveloped, single-stranded RNA genome, measuring approximately 9.6 kilo-bases, and encodes for ten proteins. These proteins include three structural proteins (Core, E1, E2) and seven non-structural proteins (p7 viroporin, NS2, NS3, NS4A, NS4B, NS5A, NS5B). HCV structural proteins Core, E1, and E2, as well as non-structural proteins p7 viroporin and NS2, are early expressed proteins involved in virus assembly and release.[90] It is also believed that E2 is the protein responsible for binding to HCV entry factors on host cell surfaces.[91] HCV non-structural proteins NS3 and NS4A make up the NS3-4A serine protease complex responsible for cleavage at four different sites of the HCV non-structural polyprotein precursor, which include NS3/NS4A (self-cleavage), NS4A/NS4B, NS4B/NS5A, and NS5A/NS5B.[92] Non-structural protein NS4B is a membrane-associated protein that provides mediation between virus-host interactions. Non-structural proteins NS5A and NS5B are both involved in HCV RNA replication; NS5A is a zinc-binding, proline-rich, hydrophilic, phosphoprotein, while NS5B is an RNA dependent RNA poly-

[85] [GH15]
[86] [BTBZ09]
[87] [Dus16]
[88] [Dus16]
[89] [GH15]
[90] [Dus16]
[91] [PE12]
[92] [Lin70]

merase.[93]

HCV is primarily known to promote carcinogenesis through indirect mechanisms, but direct oncogenic activity is also a possibility that is currently being researched. Indirect carcinomic mechanisms include the release of profibrogenic cytokines and chemokines such as TGF-, which has shown to tumor suppressor properties in healthy cells and fibrogenic activity under chronic inflammation.[94] While HCV has not explicitly shown direct carcinogenic properties, ongoing research suggests that structural protein Core and non-structural proteins NS3, NS4A, NS4B, NS5A, and NS5B could possess oncogenic qualities since they have shown to promote oncogenesis via direct interaction with cellular factors involved in host cell cycle progression, apoptosis, DNA replication, DNA repair, and angiogenesis.[95] Core, NS4B, and NS5A proteins have been shown to activate the Wnt/-catenin signaling pathway, a pathway associated with tumor cell growth, metastasis, and hepatocellular carcinoma recurrence, in Huh7 cells, which are from a well-differentiated hepatocyte derived carcinoma line.[96] NS3 and NS4A proteins have been shown to inhibit DNA repair processes and interact with ATM, a protein in host cells responsible for DNA damage detection.[97] Additionally, evidence suggests that NS5B protein binds to and inhibits host cell tumor suppressor protein Rb, allowing transformed cells to enter S phase undetected. While, NS5A blocks the activation of caspase-3, preventing TNF--mediated apoptosis, and NS3, NS4A, and NS5B proteins facilitate the relocalization of tumor suppressor p53 from the host cell nucleus to the cytoplasm; an occurrence which interferes with p53-induced apoptosis.[98] HCV proteins, which have shown potential oncogenic properties, serve as the basis of research for novel HCV-targeted treatments.

4.2 Hepatitis C Virus Treatments

HCV was historically treated with pegylated-interferon (PEG-IFN) alpha plus ribavirin (RBV) for 24 to 48 weeks and was designed to create a sustained virological response (SVR). However, this treatment only produced SVR in 40-50% of patients and frequently caused side effects such as hemolytic anemia, flu-like symptoms, and psychiatric disturbances after treatment.[99] In 2011, a combination of newly approved direct-activating antivirals (DAAs), boceprevir and telaprevir, and PEG-IFN plus RBV were able to increase SVR to almost 70% but required patients to take heavy dosages and confined them to strict dietary requirements.[100] DAAs simeprevir and sofosbuvir were released in 2013 and took a new approach to HCV treatment. They were the first oral daily treatments requiring one daily dose and were accompanied by no side effects, making

[93] [Dus16]
[94] [MHT17]
[95] [MHT17]
[96] [MHT17]
[97] [MHT17]
[98] [MHT17]
[99] [KAS17]
[100] [KAS17]

this form of therapy more tolerable for patients. When taken together or in combination with PEG-IFN plus RBV, simeprevir and sofosbuvir raised SVR rates to more than 90%.[101] Since this initial breakthrough, many other DAAs, many of which are oral, have become available for combating a wide variety of HCV genotypes and stages of liver infection. Today, different DAAs target different HCV proteins, which include the NS3/4A protease ("-previr" DAAs), NS5B polymerase ("-buvir" DAAs), and NS5A inhibitors ("-asvir" DAAs).[102] However, while DAAs have provided many advancements regarding the efficiency of HCV treatments through high rates of SVR, outcomes of these treatments have been limited to reducing the risk of HCV-induced hepatocellular carcinoma instead of eliminating it.[103]

4.3 A Potential CRISPR Treatment for HCV

Chronic HCV infections and HCV-induced malignancies can be treated using a CRISPR-Cas13 system targeting HCV genes NS3, NS4A, and NS5B, which have been shown to directly promote cell transformation and oncogenesis. The Cas13 protein is capable of inducing single-stranded breaks in RNA, making it compatible with HCV since it is a single-stranded RNA virus.[104] Without NS3 and NS4A expression, the HCV NS3/4A serine protease complex will be prevented from interacting with host cell protein ATM, a cellular factor involved in DNA damage detection.[105] This will allow for a better immune response to HCV since DNA damage is a significant outcome of chronic HCV infection, which can exist and progress unchecked when NS3/4A is expressed, leading to malignancies. An NSB knockout will prevent HCV NS5B protein from binding to and inhibiting host cell tumor suppressor protein Rb, allowing for proper tumorigenesis detection.[106] Together, the absence of NS3, NS4A, and NS5B will also prevent the relocalization of tumor suppressor p53 from the host cell nucleus to the cytoplasm.[107] This will allow p53 to induce apoptosis without interference or obstruction.

This treatment will consist of a CRISPR-Cas13 engineered plasmid, which will be inserted into host cells via an adenoviral vector. The plasmid will contain the CRISPR/Cas13 gene, HCV genes NS3, NS4A, and NS5B, genes encoding for structural proteins of the viral vector, a packing signal, and the gene encoding for HCV protein E2, which is needed for HCV entry into host cells. After the plasmid has successfully entered HCV-infected cells, transcription of the plasmid will occur. The gRNAs consisting of complementary sequences to HCV genes NS3, NS4a, and NS5B will then associate to Cas13 protein and form a Cas13-gRNA complex. Following this process, the Cas13-gRNA complex will bind to the respective HCV oncogene sequences, and Cas13 will induce a single-strand

[101] [KAS17]
[102] [KAS17]
[103] [GH15]
[104] [LdS19]and [SEKI+16]
[105] [MHT17]
[106] [MHT17]
[107] [MHT17]

break at these sites of the HCV RNA genome, disabling the expression and function of these genes. Like the potential CRISPR treatments for EBV and HPV, the intended knockouts in this treatment can be validated using western blots. A western blot of successful knockouts for NS3, NS4A, and NS5B should reveal a significant decrease in the quantity of these proteins in vitro, compared to HCV-positive cells that did not receive the CRISPR treatment.

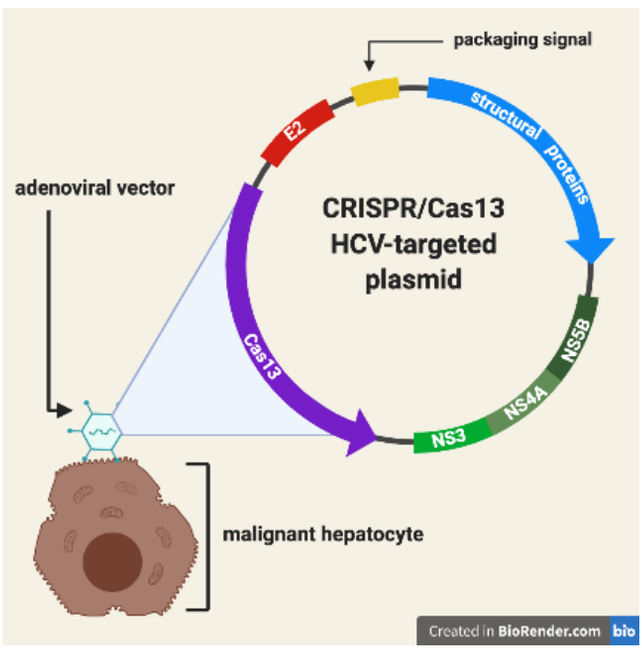


Figure 4: HCV plasmid containing Cas13 gene, oncogenes NS3, NS4A, and NS5B, structural adenovirus proteins, a packaging signal, and HCV gene E2

Unlike HPV and EBV, which can infect a variety of species, HCV has only been shown to infect humans and chimpanzees. As a result, no successful mouse models which mimic the rapid HCV replication found in human malignancies have been achieved yet, making it impractical to effectively execute preliminary trials of this potential CRISPR-Cas13 treatment in mice. However, [DHR+11] were able to induce a slight HCV infection in Rosa26-fluc mice.[108] Recombinant adenoviruses encoding for human cell surface receptors CD81, SCARB1, CLDN1, and occludin (OCLN) were inserted into murine livers, making the mice susceptible to HCV since it is able to bind to these receptors. While HCV did not express all proteins that would be expressed in a human HCV infection, and it did not replicate or spread with the same speed as it would in human hepatocytes, results from this experiment show that HCV infections can be induced in mice if they are able to express a minimum of human cell surface receptors CD81

[108] [DHR+11]

and ONCL.[109] These findings must be considered when developing a future HCV mouse model for testing potential treatments aimed at eliminating the risk of HCV-associated carcinomas. On the other hand, [PSR$^+$15] were able to carry out a successful in vitro trial of a CRISPR-Cas treatment, which prevented HCV replication.[110] [PSR$^+$15] constructed vectors encoding for a Francisella Novicida Cas9 endonuclease (FnCas9), which has been shown to cleave RNA strands in bacteria and archaea, and the HCV'5 untranslated region, which has been shown to be involved in translation of the viral polyproteins and replication of the viral RNA. The vectors were then inserted into HCV-infected human Huh7 cells in vitro, and knockouts were verified using PCR afterward.[111] The results showed a significant decrease in polyprotein translation and viral replication. While a mouse model might not be able to properly simulate a high risk HCV infection, CRISPR trials have been done using human Huh7 cell cultures, an approach that should be referenced when testing this potential CRISPR-Cas13 treatment.

5 Conclusion

Oncogenic viruses are an increasing cause of cancer worldwide, with 12% of all cancers resulting from these viral infections today.[112] Epstein-Barr Virus, Human Papillomavirus, and Hepatitis C Virus all play direct roles in carcinogenesis. EBV promotes B cell transformation by integrating its genome into the genome of the host cell, and expresses oncoproteins LMP-1, LMP-2A, EBNA-1, and EBNA-2. LMP-1 is the main mechanism of oncogenesis since it activates downstream signaling pathways, such as NF-B, MAPK/ERK, PI3K/AKT, Notch, and JAK/STAT, which all promote genomic instability, inflammation, resistance to apoptosis, and unchecked proliferation in host cells.[113] In the majority of HPV-associated malignancies, infected host cells are also found to have an HPV genome integrated into their own. This promotes the overexpression of HPV oncoproteins E6 and E7, which degrade cellular tumor suppressors such as p53 and members of the Rb family (RB, p107, and p130).[114] HCV has been known to indirectly cause malignancies via chronic infection and inflammation, which leads to tumor-promoting DNA damage. However, recent studies suggest that HCV proteins NS3, NS4A, NS4B, NS5A, and NS5B could potentially play direct roles in tumorigenesis by activating the Wnt/-catenin pathway, inhibiting DNA repair processes, preventing Rb functions, and relocalizing p53 from the host nucleus to the cytoplasm.[115] A thorough understanding of oncoproteins in EBV, HPV, and HCV is critical for the development of efficient, viru-targeted treatments.

The research field for oncogenic virus treatments is continuously evolving

[109] [DHR$^+$11]
[110] [PSR$^+$15]
[111] [PSR$^+$15]
[112] [Hau09]
[113] [MHT17]
[114] [GS16]and [ML10]
[115] [MHT17]

because of more precise therapies such as CRISPR. In the past, chemotherapy was the most common treatment for patients, but it often resulted in an inefficient or incomplete elimination of virus-related cancers. New treatment options involving antiviral drugs have been able to slow the process of tumor development, while preventative vaccinations have helped to lower the risk of infection that could result in malignancies. However, these options have not been able to eliminate the risk of oncogenesis because they do not target the specific mechanisms directly related to cell transformation and lack the precision to do so. Novel gene therapies are able to provide this level of precision, and a CRISPR based treatment designed to knock out oncogenic proteins can facilitate a safer and more efficient treatment compared to current treatments.

Results for trials of this precise, virus-targeted, CRISPR treatment have shown that this approach effectively induces the renovation of apoptotic pathways and cell death in infected cells. These natural methods of tumor suppression, induced by CRISPR treatments, might also allow for faster elimination of malignancies, therefore providing a more cost-efficient option for patients and treatment industries. However, more research regarding the likelihood of CRISPR-induced off-target edits and their effects must still be done. While CRISPR is able to precisely edit genes to correct their functions, it can also lead to off-target mutations that can dysregulate the expression of other, normal genes. This could result in secondary diseases, or it could potentially worsen the conditions of the existing disease. Both these desirable and counterproductive outcomes of CRISPR treatments must be fully considered before clinical use.

Additionally, while both in vitro and in vivo trials have produced desirable outcomes, the long term effects of CRISPR treatments are still unknown. The chances of viral infection recurrences and carcinoma regeneration must also be calculated. Current treatments are unable to fully eliminate the chances of these recurrences, but the efficacy of CRISPR in these aspects of treatment have not been fully observed yet because it has existed as a gene-editing tool for less than a decade. Virus-targeted CRISPR trials carried out on animal models, or human subjects will require years of observation after initial treatments to ensure that recurrences of viral infections and carcinomas do not occur. Furthermore, the ethical consequences of inaccurate gene edits and the manipulation of nature should be fully explored before using CRISPR in a clinical setting. Nevertheless, this approach to treating oncogenic viruses and a wide variety of other genetic diseases will be able to produce precise results in future treatment settings.

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Predicting NBA Playoffs Using Machine Learning

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Abstract

This project attempts to predict the NBA playoff bracket using machine learning methods. It will consider one self-constructed model and one machine learning model built from various machine learning algorithms. The project will also determine the most efficient model for predicting NBA results and which way to select data gives an accurate and consistent prediction. Finally, the project will investigate the effect of home and away variables on the teams' performance and the model's accuracy.

1 Introduction

The National Basketball Association (NBA) is considered as the premier basketball league for professional male basketball players in USA. It is made up of 30 teams, split into the Eastern and Western conferences [Aut01].

During the playoff, the top 8 teams from each conference (Eastern and Western) are chosen to compete for the championship. The rankings are decided based on the teams' performances during the regular season. Then, the teams play against each other with the 1st place playing against the 8th place, the 2nd place playing against the 7th place, etc. Each game will be a best-of-seven match, and teams will rotate between home and away.

Like AlphaGo in the Go Contest [Sil02], machine learning is a well-known prediction tool for complex process. The question of this research is, can machine learning be used to predict the NBA playoff bracket? And what is accuracy of such prediction compared with the real results? What machine learning method is the best solution for NBA playoff bracket prediction?

To better analyzing and comparing the performance of the machine learning in predicting the NBA playoff bracket, firstly we create a self-made prediction model based on several key game variables that will impact the game result mostly by our best knowledge about the NBA games. These variables include 1) effective field goal percentage, 2) free throw percentage, 3) turn over percentage, 4) Offensive rebound percentage, 5) Defensive rebound percentage. And We

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focused on working out the probability of Team A winning against Team B, then applying this to every game in the playoff. Base on the historic game data of 2014 to 2018, the playoff prediction of 2018,2017 and 2016 are carried out and comparison with the real playoff brackets are also presented.

As for the machine learning model for the NBA playoff bracket prediction, here, we are focusing on 5 different machine learning models that have already been implemented in the Python Machine Learning Library (Scikit-learn), i.e., Logistic Regression (LR), Linear Discriminate Analysis (LDA), Support Vector Machine (SVM), K-Nearest Neighbors (KNN) and Classification and Regression Tree (CART) [Dhi03] - [TA11]. For comparison with the self-made model, the same playoff prediction of 2018, 2017 and 2016 are carried out and comparison among different machine learning models are given accordingly.

2 Result

2.1 Exposition of self-made prediction model

Based on the testing results for our self-made prediction model, we have the following prediction results (Table 1). And the predicted playoff bracket with the original ones are shown in Figure 1 and 2, with the prediction difference highlighted in red color.

Figure 1: 2018 NBA Playoff (Prediction)

In summary, the self-built prediction model performed best when predicting the 2018 playoff, getting an accuracy of 80%. The second-best prediction was the 2017 prediction, obtaining an accuracy of 66.7%. The worst prediction was for the 2016 bracket, only getting an accuracy of 53.3%. For the 2018 playoff

Figure 2: 2018 NBA Playoff (Original)

Prediction Year	Total No. Of Match	No. Of Correct Predicted Match	Accuracy
2018	15	12	80%
2017	15	10	66.7%
2016	15	8	53.3%

Figure 3: Playoff Prediction Accuracy of Self-made Prediction Model

prediction, we used teams' statistics over 4 years from 2014-2018. For the 2017 playoff prediction, we used statistics of teams over a time of 3 years from 2014 - 2017. Finally, for the 2016 playoff prediction, we only used statistics of teams over two years from 2014-2016.

2.2 Exposition of the Machine Learning Models

In order to evaluate the performance of machine learning in NBA playoff bracket prediction, 5 different machine learning models are employed, which have been implemented by Python Machine Learning Library (Scikit-learn), i.e., 1) Logistic Regression (LR), 2) Linear Discriminate Analysis (LDA), 3) Support Vector Machine (SVM), 4) K-Nearest Neighbors (KNN) and 5) Classification and Regression Tree (CART) [Dhi03] - [TA11]. With two different training data selection methods and home/away investigation, the most accurate machine learning model for NBA playoff bracket prediction is finally presented.

There are two ways in which we chose to select the data to train the algorithm. 1. The first method was to consider each Team's performance when playing against all other teams 2. The second method was to evaluate a team's performance with one other specific Team to determine its win rate against that

specific Team

2.2.1 Method 1 – Selecting all data

In this model, we trained the different machine learning algorithms with all the statistics of every Team. Like the self-constructed model, the 2018 prediction used data over four years, the 2017 prediction used data over three years, and the 2016 prediction used data only over two years.

From the above data, algorithms generally performed relatively well and consistent in 2018 and 2017, except for the SVM model and the LR model (Figure 3). The SVM model generally had a low and consistent prediction accuracy in the three years, and the LR did significantly better in 2017 than in 2018.

Overall, LDA had the highest mean accuracy of 71.2%, followed by the CART model, with a mean accuracy of 69.2%. The worst performing model is the SVM algorithm with an accuracy of 0.436 only.

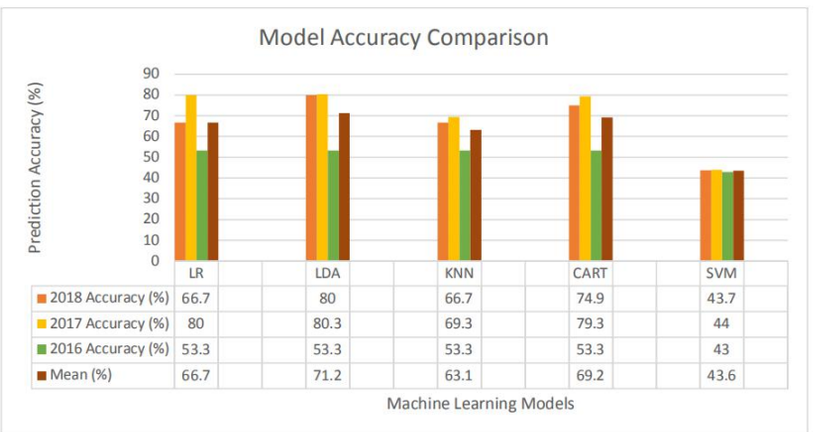


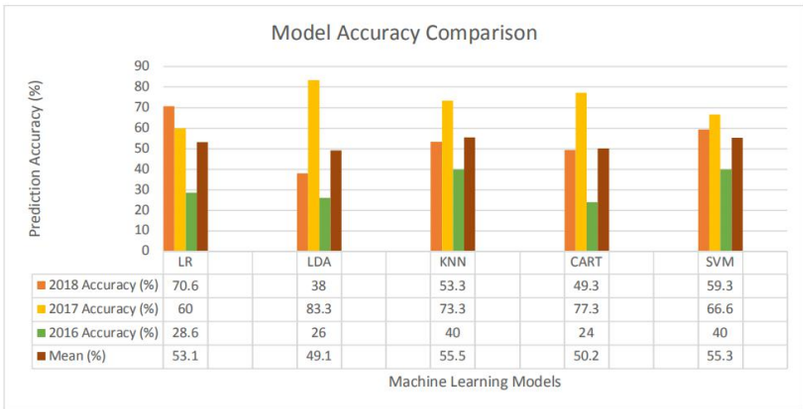
Figure 4: Playoff Prediction Accuracy of Different Machine Learning Models with all data selected and average 30 trial runs

2.2.2 Method 2 – Selecting Partial Data

In this model, we trained the machine learning models with a partial amount of data, which is only based on one Team's performance against a specific opponent. In other words, it is the data between two teams that we are trying to predict.

Based on the data collected (Figure 4), there are no clear trends or patterns available. All the model predictions have significantly large variations in each year. It also doesn't have a clear correlation to data size. Although 2016 was again the worst year of prediction, the 2017 prediction did significantly better than the 2018 prediction, proving that there are no trends.

In summary, selecting only the data where two teams played against each other resulted in inaccurate and inconsistent predictions. It also means that the models' accuracy in this data selection method will not be considered when calculating the best performing model due to the inconsistency and inaccuracy. Therefore, it can be concluded that selecting all data is a better data selection method.



	LR	LDA	KNN	CART	SVM
2018 Accuracy (%)	70.6	38	53.3	49.3	59.3
2017 Accuracy (%)	60	83.3	73.3	77.3	66.6
2016 Accuracy (%)	28.6	26	40	24	40
Mean (%)	53.1	49.1	55.5	50.2	55.3

Figure 5: Playoff Prediction Accuracy of Different Machine Learning Models with partial data selected and average 30 trial runs

2.2.3 Home and Away Investigation

The home and away variables are widely considered an essential variable on a team's performance and players. The home-court will have more fans, and the positive atmosphere will give the home team a spiritual boost, which may result in a better performance.

An experiment is conducted by training and running the program three times with different data. One will have all data from home and away games, another will have only the data from home games, and the final one will have only the data from away games. Differences between the predicted results are analyzed and evaluated.

Based on the above data (Table 2), generally, teams had much better performance and a higher win percentage when playing as the home team.

To summarize, the home and away variable greatly influenced teams' performance level and win percentage in general. In theory, the variable should not affect model accuracy to a significant extent. But in this case, the model did impact the model accuracy, which can be caused by other factors in real life.

Considering Home and Away Variable		Considering only Home Variable		Considering only Away Variable	
HOU: 0.636	**HOU: 0.636**	**HOU: 0.879**	**HOU: 0.879**	**HOU: 0.576**	HOU: 0.576
MIN: 0.394	OKC: 0.568	MIN: 0.333	OKC: 0.788	MIN: 0.424	**OKC: 0.606**
OKC: 0.568	POR: 0.561	**OKC: 0.788**	POR: 0.697	**OKC: 0.606**	NOP: 0.515
UTA: 0.545	**GSW: 0.848**	UTA: 0.758	**GSW: 0.970**	UTA: 0.545	**GSW: 0.697**
POR: 0.561	**TOR: 0.667**	**POR: 0.697**	WAS: 0.667	POR: 0.454	TOR: 0.424
NOP: 0.462	CLE: 0.629	NOP: 0.667	**CLE: 0.818**	**NOP: 0.515**	**IND: 0.576**
GSW: 0.848	MIA: 0.561	**GSW: 0.970**	MIA: 0.545	**GSW: 0.697**	MIA: 0.394
SAS: 0.742	**BOS: 0.629**	SAS: 0.818	**BOS: 0.667**	SAS: 0.455	**BOS: 0.485**
TOR: 0.667	HOU: 0.636	TOR: 0.606	HOU: 0.879	**TOR: 0.424**	OKC: 0.606
WAS: 0.576	**GSW: 0.848**	**WAS: 0.667**	**GSW: 0.970**	WAS: 0.303	**GSW: 0.697**
CLE: 0.629	**TOR: 0.667**	**CLE: 0.818**	**CLE: 0.818**	CLE: 0.394	**IND: 0.576**
IND: 0.591	BOS: 0.629	IND: 0.636	BOS: 0.667	**IND: 0.576**	BOS: 0.485
PHI: 0.326	**GSW: 0.848**	PHI: 0.394	**GSW: 0.970**	PHI: 0.303	**GSW: 0.697**
MIA: 0.561	TOR: 0.667	**MIA: 0.545**	CLE: 0.818	**MIA: 0.394**	IND: 0.576
BOS: 0.629		**BOS: 0.667**		**BOS: 0.485**	
MIL: 0.477		MIL: 0.545		MIL: 0.394	
Accuracy: 66.7%		Accuracy: 73.3%		Accuracy: 60%	

Figure 6: 2018 LR Prediction Results

2.2.4 Most Accurate Machine Learning Model for NBA Playoff Prediction

To conclude, the most accurate machine learning model at predicting the NBA playoffs is LDA, which reached an accuracy of 71.2%. The performance of the models at predicting with a partial amount of data is neglected since it is considered that the data selection did not give useful information.

3 Discussion

3.1 Self-made prediction model

Based on the model's accuracy and the size of the data, we see a trend between the two variables, with 2018 having the largest dataset and the highest model accuracy and 2016 having the smallest dataset and the lowest model accuracy (Table 1). One possible explanation for the model's changing performance is that it works well with larger datasets while having lower performances when working with smaller datasets.

Another possible reason is that the model is simply not consistent in prediction. It might be a coincidence that there is a correlation between data size and model accuracy since we only have data for three years of prediction. Further investigation can be carried out to confirm the effect of the data size on the model's accuracy. This can be done by running the prediction model for more years with different data sizes to understand the correlation between the two variables better.

3.2 Machine learning prediction model

Similar as the results for the self-made prediction model, the prediction accuracy of 2018 is the highest while the one of 2016 is lowest when all data are selected to train the machine learning models (Figure 3). All algorithms except the SVM model performed significantly worse in 2016. One hypothesis is that the models reached a tipping point in 2016 when the data size is not big enough to support accurate predictions.

Team Performances (2016)				
LR	LDA	KNN	CART	SVM
GSW: 0.8625	**GSW: 0.8625**	**GSW: 0.9375**	**GSW: 0.8**	GSW: 1.0
HOU: 0.6	HOU: 0.5875	HOU: 0.625	HOU: 0.55	HOU: 1.0
LAC: 0.625	**LAC: 0.625**	**LAC: 0.6875**	**LAC: 0.675**	LAC: 1.0
POR: 0.5875	POR: 0.55	POR: 0.575	POR: 0.45	POR: 1.0
OKC: 0.6625	**OKC: 0.6375**	**OKC: 0.6625**	**OKC: 0.65**	OKC: 1.0
DAL: 0.525	DAL: 0.5125	DAL: 0.5125	DAL: 0.5375	DAL: 1.0
SAS: 0.75	**SAS: 0.8**	**SAS: 0.9125**	SAS: 0.7375	SAS: 1.0
MEM: 0.6	MEM: 0.6	MEM: 0.65	MEM: 0.6375	MEM: 1.0
CLE: 0.6875	**CLE: 0.7125**	**CLE: 0.75**	**CLE: 0.7**	**CLE: 1.0**
DET: 0.525	DET: 0.5125	DET: 0.4875	DET: 0.475	DET: 0.0
ATL: 0.6625	**ATL: 0.675**	**ATL: 0.725**	**ATL: 0.625**	ATL: 1.0
BOS: 0.525	BOS: 0.5	BOS: 0.575	BOS: 0.4875	BOS: 1.0
MIA: 0.45	MIA: 0.5	MIA: 0.5375	MIA: 0.4125	MIA: 0.0
CHO: 0.5750	**CHO: 0.5875**	**CHO: 0.6**	**CHO: 0.5625**	CHO: 0.0
TOR: 0.6125	**TOR: 0.6**	**TOR: 0.625**	**TOR: 0.6625**	**TOR: 1.0**
IND: 0.5625	IND: 0.5625	IND: 0.6125	IND: 0.6	IND: 0.0
GSW: 0.8625	**GSW: 0.8625**	**GSW: 0.9375**	**GSW: 0.825**	HOU: 1.0
LAC: 0.625	LAC: 0.625	LAC: 0.6875	LAC: 0.65	LAC: 1.0
OKC: 0.6625	OKC: 0.6375	OKC: 0.6625	OKC: 0.6625	DAL: 1.0
SAS: 0.75	**SAS: 0.8**	**SAS: 0.9125**	**SAS: 0.7**	MEM: 1.0
CLE: 0.6875	**CLE: 0.7125**	**CLE: 0.75**	**CLE: 0.7**	CLE: 1.0
ATL: 0.6625	ATL: 0.675	ATL: 0.725	ATL: 0.625	ATL: 1.0
CHO: 0.575	CHO: 0.5875	CHO: 0.6	CHO: 0.575	CHO: 0.0
TOR: 0.6125	**TOR: 0.6**	**TOR: 0.625**	**TOR: 0.675**	**TOR: 1.0**
GSW: 0.8625	**GSW: 0.8625**	**GSW: 0.9375**	**GSW: 0.8375**	LAC: 1.0
SAS: 0.75	SAS: 0.8	SAS: 0.9125	SAS: 0.725	DAL: 1.0
CLE: 0.6875	**CLE: 0.7125**	**CLE: 0.75**	**CLE: 0.7**	CLE: 1.0
TOR: 0.6125	TOR: 0.6	TOR: 0.625	TOR: 0.6375	TOR: 1.0
GSW: 0.8625	**GSW: 0.8625**	**GSW: 0.9375**	**GSW: 0.825**	LAC: 1.0
CLE: 0.6875	CLE: 0.7125	CLE: 0.75	CLE: 0.7125	TOR: 1.0
Accuracy				
LR: 0.53333	LDA: 0.53333	KNN: 0.53333	CART: 0.53333	SVM: 0.26666

Figure 7: 2016 Team Performance Prediction with All Data Selected

Another hypothesis is that there is an error in the program itself that is causing the 2016 prediction to deviate. This can be seen through the models' accuracy in 2016 (Table 3), except for SVM, all had an accuracy of 53.3%. Here, it demonstrated that each model except for SVM had the same playoff prediction for every round. Although teams have slightly shifting percentages in different models, which may symbolize that there isn't an error and that all models are independent of each other, it is still doubtful that each model had the same win percentage and same prediction. This will be a research question for future investigations to confirm if there is an error in the program causing the deviation in 2016, or the model reached a tipping point in data size that is causing the variation to occur.

For model training with partial data selection (Figure 4), it can be concluded that partial data selection method gives inaccurate and inconsistent predictions. This is likely because there is very little data for a given pair of teams. To be specific, two teams only play against each other ten times a year, with Team1 playing as the home team for five matches and Team2 playing as the home team for another five games. Additionally, only 80% of the data are used to train, meaning that only eight sets of data are provided for training each year. This resulted in inaccurate predictions with inadequate dataset. It also means that the prediction models will be more likely to give the two teams a 50 percent win rate each due to the small amount of data for testing and training. This will result in the program randomly selecting a winner between the two teams, making the prediction model inconsistent.

Additionally, the two sets of predictions namely home and away should have similar accuracy theoretically. This is because teams typically have a higher win percentage when playing as the home team and a lower win percentage when playing as the away team. If all teams perform better when playing as the home team, they should get roughly the same increase in performance level, so it should not affect the accuracy to a significant extent. This is the same when teams are playing as the away team. They should all perform relatively worse, so the models' accuracy should not shift by a significant amount.

However, in this case (Table 2), the model accuracy did shift significantly, at 13%. This is due to outliers like the team MIN, which had a better performance when playing as the away Team than as the home team. It is also because different teams had different performance levels when playing as the home team. For example, GSW had an increase in a win percentage of 30% when playing as the home team. On the other hand, team PHI only had a 9% increase in win percentage when playing as the home team. One hypothesis is that GSW has more fans than other teams, so they have a better atmosphere when playing as the home team. However, many other factors can decide a team's performance when playing as the home team and the away team. These factors can be further investigated in the future.

4 Methods

To test the effectiveness of our self-made NBA playoff prediction model and all the related machine learning algorithms, certain NBA historic statistics data from 2014 - 2018 are needed, which can be access from many open source NBA statistics. And these historic NBA statistics are usually saved as .csv file format, which we can use the Python pandas library read-csv module to load the dataset from the corresponding csv URL link, the format and header of the dataset is of the following form (in Figure 5.)

	WINorLOSS	Team	Game	Date	Home	Opponent	TeamPoints	OpponentPoints	FieldGoals	...	Opp.Blocks	Opp.Turnovers	Opp.TotalFouls
1	L	ATL	1	2014/10/29	Away	TOR	102	109	40	...	9	9	22
2	W	ATL	2	2014/11/1	Home	IND	102	92	35	...	5	18	26
3	L	ATL	3	2014/11/5	Away	SAS	92	94	38	...	9	19	15
4	L	ATL	4	2014/11/7	Away	CHO	119	122	43	...	7	19	30
5	W	ATL	5	2014/11/8	Home	NYK	103	96	33	...	6	15	29
6	W	ATL	6	2014/11/10	Away	NYK	91	85	27	...	2	15	26
7	W	ATL	7	2014/11/12	Home	UTA	100	97	39	...	8	11	17
8	W	ATL	8	2014/11/14	Home	MIA	114	103	42	...	3	14	20
9	L	ATL	9	2014/11/15	Away	CLE	94	127	40	...	2	13	14
10	L	ATL	10	2014/11/18	Home	LAL	109	114	41	...	0	11	24
11	W	ATL	11	2014/11/21	Home	DET	99	89	38	...	3	12	20
12	W	ATL	12	2014/11/25	Away	WAS	106	102	36	...	3	20	25
13	L	ATL	13	2014/11/26	Home	TOR	115	126	42	...	7	11	24
14	W	ATL	14	2014/11/28	Home	NOP	100	91	38	...	4	12	19
15	W	ATL	15	2014/11/29	Home	CHO	105	75	40	...	4	12	16
16	W	ATL	16	2014/12/2	Home	BOS	109	105	43	...	3	21	20
17	W	ATL	17	2014/12/3	Away	MIA	112	102	40	...	5	18	24
18	W	ATL	18	2014/12/5	Away	BRK	98	75	35	...	2	17	21
19	W	ATL	19	2014/12/7	Home	DEN	96	84	36	...	4	14	22
20	W	ATL	20	2014/12/8	Away	IND	108	92	40	...	2	17	22

Figure 8: NBA historic statistics dataset format and headers

4.1 Self-made prediction model

To start, we first created our own prediction model to predict the NBA bracket. We focused on working out the probability of Team A winning against Team B, then applying this to every game in the playoff.

We have to narrow our focus on specific game variables, which significantly impact the game result. After some research, we decided to use the following variables:

1)EFG% effective field goal percentage [Aut12], considers both 2pts field goals and 3pts field goals in one variable and considered their weight with three-pointers worth 1.5 times of a two-pointer.

2)FT% free throw percentage [Aut12], calculates the percentage of free-throw makes for a specific team.

3)TOV% turn over percentage [Aut12], is an estimate of turnovers by a team per 100 possessions.

4)ORB% Offensive rebound percentage [Aut12], is an estimate of the percentage of offensive rebound that a team gets.

5)DRB% Defensive rebound percentage [Aut12], is an estimate of the percentage of defensive rebounds taken by a team.

$$EFG\% = \frac{(2\_point\_field\_goals\_made + 1.5 * 3\_point\_field\_goals\_made) * 100}{Total\_field\_goals\_made}$$

$$FT\% = \frac{free\_throws\_made * 100}{free\_throws\_attempted}$$

$$TOV\% = \frac{number\_of\_turnovers * 100}{field\_goal\_attempted + 0.44 * free\_throws\_attempted + number\_of\_turnovers}$$

$$ORB\% = \frac{offensive\_rebounds * 100}{offensive\_rebounds + opponent\_defensive\_rebounds}$$

$$DRB\% = \frac{defensive\_rebounds * 100}{defensive\_rebounds + opponent\_offensive\_rebounds}$$

4.1.1 Algorithms

The five variables that were chosen are considered the most impactful factors in the game. The second step of our model is to decide on the algorithm we are going to use to calculate the probability of Team A beating Team B; the chosen algorithm was:

$$P_{win} = c_1P_1 + c_2P_2 + c_3P_3 + c_4P_4 + c_5P_5$$

Here, c_i is the proportional correlation of the variable v_i with winning. In other words, the larger the value of c_i, the more variable v_i will contribute to the winning of a game. Pi is the probability that Team A will have a higher score than Team B on variable v_i. By multiplying the probability of the two factors together and adding all the numbers up for all five different variables, we predict Team A beating Team B in a match.

4.1.2 c_i calculation

The formula for c_i is:

$$c_i = \frac{r_i}{r_1 + r_2 + r_3 + r_4 + r_5}$$

Here, r_i represents the Pearson correlation coefficient of the variable v_i with winning. However, winning is a categorical value that cannot be used in the Pearson correlation. Therefore we decided to represent winning with the point difference between the two teams.

4.1.3 P_i calculation

To calculate the value for P_i, we used the principle of confidence intervals, which is defined to be the probability that a parameter will fall between two sets of values with a specific confidence level. [Wil13]

1 - Calculate a 95% confidence interval of for both teams

2 - We defined the confidence intervals for Team A as [x_A,y_A] and Team B as [x_B,y_B]

3 – The first case is when the intervals don't overlap. In this situation, the Team with the higher interval has a 95% chance of scoring higher. (Note: The percentage might be slightly higher than 95%, but in this case, we consider it as 95%.)

4 - The second case is when the two intervals overlap, and Team A has a higher upper limit (y_A ¿ y_B). Here, the formula to calculate Pi is:

$$P_i = 0.95\frac{y_A - y_B}{y_A - x_B}$$

5 - The third case is when Team B has a higher upper limit (y_B¿y_A). Here, the formula to calculate P_i is:

$$P_i = 1 - 0.95\frac{y_B - y_A}{y_A - x_B}$$

6 – The last case is when the two sets of data have the same upper limit (yB=yA). Then Pi = 0.5 in this case.

4.2 Predicting the playoff bracket

In order to predict the playoff bracket, we created Python's function to calculate the probability of Team A defeating Team B, and we applied it to predict the playoff bracket for 2018.

```
#Calculates the winners for the quarter-final
q_t1 = select_team(tl[0],tl[1])
q_t2 = select_team(tl[2],tl[3])
q_t3 = select_team(tl[4],tl[5])
q_t4 = select_team(tl[6],tl[7])
q_t5 = select_team(tl[8],tl[9])
q_t6 = select_team(tl[10],tl[11])
q_t7 = select_team(tl[12],tl[13])
q_t8 = select_team(tl[14],tl[15])

#Calculates the winners for the semi-final
s_t1 = select_team(q_t1,q_t2)
s_t2 = select_team(q_t3,q_t4)
s_t3 = select_team(q_t5,q_t6)
s_t4 = select_team(q_t7,q_t8)

#Calculates the winners for the finals
f_t1 = select_team(s_t1,s_t2)
f_t2 = select_team(s_t3,s_t4)

#Calculates the winners
winner = select_team(f_t1,f_t2)

#Putting the results in a list
p_playoff = [q_t1,q_t2,q_t3,q_t4,q_t5,q_t6,q_t7,q_t8,s_t1,s_t2,s_t3,s_t4,f_t1,f_t2,winner]

#Comparing the predicted result to the original result and hence work out the accuracy of the model
for i in range(len(r)):
  if r[i] == p_playoff[i]:
    accuracy = accuracy + 1
accuracy = accuracy / len(r)
print(accuracy)
```

Figure 9: Python Code Snippet for Self-made Prediction Model

In the python code snippet (Figure 6), the function select team(), which predicts the winner between Team A and Team B, is called many times. This calculates the winners for the quarter-final, the semi-final, the finals, and in the end, it calculates the winner of the year. This predicted playoff is then appended to a list and compared to the actual result of the 2018 playoff to calculate a prediction accuracy. The original playoff is pre-loaded into the program beforehand.

4.3 Machine learning prediction models

In order to test if machine learning algorithm can be used to predict the NBA playoff bracket and evaluate which machine learning model has the best prediction accuracy, 5 different machine learning models that have been implemented in Python Scikit-learn machine learning library are employed with two linear (LR and LDA) and three nonlinear (KNN, CART and SVM) ones (Figure 6).

After loading the dataset from the historic NBA statistics CSV file, depending on the two different data selection methods, all data or partial data, together with home or away analysis, data related to year of 2016, 2017 and 2018 for NBA playoff prediction can be split into different data arrays, so that the prediction accuracy of different machine learning models can be analyzed accordingly.

To test the prediction accuracy for each different machine learning model, the dataset needs to be split into two sets, one for the model training and one for the model prediction on 8:2 randomly selection basis, which means 80% of the data will be used as training data and 20% will be used to evaluate the prediction accuracy and the data is randomly selected.

After the dataset is split for training and validation, the fit function for each machine learning model will be called to train each individual models. After model training, the predict function for each machine learning model will be called to make the final prediction based on the validation dataset generated before and the prediction accuracy for each models will also be calculated by the $accuracy_score$ function (Figure 7).

Note that in Python, loc function is a frequently used function to retrieve partial data in the dataset related to certain variable value, like certain year, certain team, etc.

```
# import python modules
import pandas
import scipy
import numpy
import sklearn
# import python functions
from pandas import read-csv
from sklearn.model_selection import train_test_split
from sklearn.model_selection import cross_val_score
from sklearn.model_selection import StratifiedKFold
from sklearn.metrics import classification_report
from sklearn.metrics import confusion_matrix
from sklearn.metrics import accuracy_score
from sklearn.linear_model import LogisticRegression
from sklearn.tree import DecisionTreeClassifier
from sklearn.neighbors import KNeighborsClassifier
from sklearn.discriminant_analysis import LinearDiscriminantAnalysis
from sklearn.svm import SVC
```

Figure 10: Python code snippet for importing modules, functions and models

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```
# Load dataset
url = "C:\Documents\nba.games.stats.csv"
dataset = read_csv(url)
# Split-out validation dataset
array = dataset.values
X = array[:,1:]
y = array[:,0]
X_train, X_validation, Y_train, Y_validation = train_test_split(X, y, test_size=0.20, random_state=1)
# Spot Check Algorithms
models = []
models.append(('LR', LogisticRegression(solver='liblinear', multi_class='ovr')))
models.append(('LDA', LinearDiscriminantAnalysis()))
models.append(('KNN', KNeighborsClassifier()))
models.append(('CART', DecisionTreeClassifier()))
models.append(('SVM', SVC(gamma='auto')))
# evaluate each model in turn
results = []
names = []
for name, model in models:
  model.fit(X_train, Y_train)
  predictions = model.predict(X_validation)
  # Evaluate predictions
  results.append(accuracy_score(Y_validation, predictions))
  names.append(name)
  print('%s: %f' % (name, results.mean()))
```

Figure 11: Python code snippet for dataset split and model cross-evaluation

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Extending the Drift Diffusion Model to the Cognitive Realm

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Abstract

The drift diffusion model has had great success as a computational model to study the underlying processes of sensory and value-based decision making and the diffusion process may actually mimic how the brain integrates evidence and makes decisions. Here I review recent applications and extensions of the drift diffusion model to self-control, loss aversion, driving behaviour, racial biases and reinforcement learning with the aim of finding out whether the model is applicable to more cognitive tasks

1 Introduction

Decisions are ubiquitous. Every day, we make thousands of decisions, ranging from automatic low-level tasks like whether or not to look at a section of the screen to high-level tasks which require more deliberation like which movie to watch. In the last thirty years, major progress has been made in understanding how decisions are made in the brain.To explain any aspect of decision making, experiments are designed and then computational models are built on this experimental data. To make the models more cohesive and increase their explanatory power, brain data is included to see how the deliberation corresponds to activity in the brain. Out of a plethora of methods, electrophysiology[1] and

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[1]Extracellular Electrophysiology - A recording technique which involves the insertion of electrodes into the brain. It measures the change in the electrical activity in the neurons near the electrode and thus measures firing rate of neurons in spikes per second. It gives a great temporal resolution making it a very powerful technique. However, it is an invasive method and can only be used to measure the activity of a few neurons at a time.

functional magnetic resonance imaging (fMRI)[2] are specifically used to measure firing rates and to gauge where the decision-related brain activity is taking place, respectively.

Many real-life decisions require accumulation of evidence and information, either from the environment or from our memories, until it passes a threshold. This accumulation-to-threshold is explained by a group of models called sequential sampling models. Through extensive research, one of these models stands out as the most effective: The Drift Diffusion Model (DDM).

The DDM (Ratcliff,1978) [Rat78] postulates that decisions are made by the accumulation of noisy evidence over time which terminates once it reaches a threshold or a bound. The decision threshold is the amount of evidence needed to choose an alternative and make a decision. In the DDM, there is only one accumulation process whereas in other accumulator models the evidence for each response is accumulated independently. These models are like a race. The accumulation process that reaches the threshold first is what the subject decides. In the DDM, evidence accumulation is competitive. Figure 1 shows the drift diffusion process for a perceptual discrimination task as well as an ideal accumulator model (also called a race model).

The beauty of the DDM is that the brain makes decisions as it has been portrayed in Figure 1. The DDM is not just a model made to explain decision making but could be how the brain integrates evidence and makes decisions. The simple DDM is defined by four parameters, the starting point, the drift rate(μ) i.e. the rate of evidence accumulation, the value of the bounds (a and b), and the non-decision time, also called latency time which is the sum of the time before initiation of the accumulation and the time taken for action once a decision is reached. (Ratcliff,1978) [Rat78]

This review will begin with an in-depth description of the DDM, its advantages and the research on the neuronal populations representing the subparts of the DDM. Following this, I will discuss the applications of the DDM to different domains, with the aim of looking at its performance in more cognitive tasks. The review will conclude with possible future avenues.

1.1 Why DDM?

Certain aspects of the Drift Diffusion Model have made it very successful in all its applications so far. This section looks at the advantages of using the DDM as an analytic tool. The DDM explains response times (RTs) very well for both correct and error responses. It helps us visualize the effects of attributes like task difficulty and time pressure on the RTs, which serve as an important tool in analyzing behaviour. This explanatory power helps to differentiate the

[2]Functional Magnetic Resonance Imaging (fMRI) - An imaging technique that measures brain activity by detecting changes in blood flow. It is used to measure BOLD signals (blood-oxygen-level-dependent signals). It gives us great spatial resolution and can provide a clear image of how brain activity is localised. Another advantage is that it is non-invasive and is a relatively safe technique. However, it gives poor temporal resolution and does not show us moment to moment changes in activity.

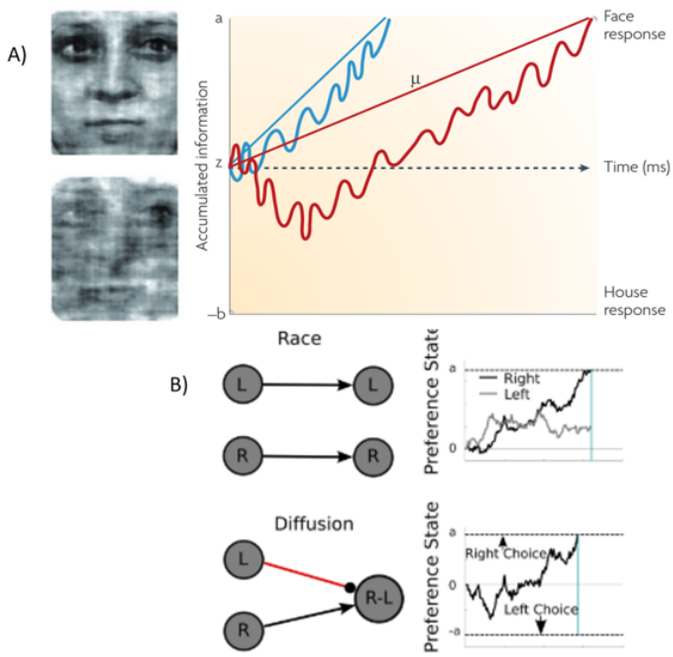

Figure 1: **A) z is the starting point for the process, a and -b are the thresholds. In the figure, there are two wobbly lines, which represent the decision process. The decision is encoded in a decision variable and this variable 'drifts' towards a threshold. A decision variable is a quantity which defines the possibility of one alternative over another and is driven by the integration of evidence over time. It can be thought of as a link between sensory evidence and the final choice. The straight lines connecting the starting point z and the thresholds are the drift rates. The image at the top is represented by the blue lines while the image at the bottom is represented by the red lines. In the figure, the blue lines have a much larger drift rate and as a result a short response time. Although intuitively we know that easier decisions will be made faster, this figure and the DDM, in general, gives us computational proof on the relation between decision difficulty and response time. Figure adapted from Heekeren et al., (2008) [HMU08]B) The graph adjacent to the race model shows two accumulation processes, one for each response for the race models, whereas, in the DDM, there is only one accumulation process which is a competition between the two alternatives. Figure adapted from Summerfield and Koechlin,(2008) [SK08]**

DDM from other sampling models like random walk models and accumulators which cannot model the RTs as accurately as the DDM (Ratcliff, 2004 [Rat04]). Although these conclusions are intuitive (harder tasks will have longer RTs), the DDM provides a computational framework for these conclusions. The response times are captured by RT distributions. These distributions can be represented by curves above their respective thresholds. The distribution encloses all the possible RT values for a particular experiment and its shape shows the variability in the response times and thus the variability in drift rates. The curves are shifted or skewed when task difficulty is changed or a time pressure is applied. Thus, the distributions help in giving an insight into the change in performances when task attributes are altered. Another advantage the DDM provides is that it explains the speed-accuracy trade-off well, (for an in-depth review see Bogacz et al., 2010 [BWFN10]). Higher decision thresholds will lead to more accurate answers since they require more evidence but will also lead to greater response times. On the other hand, lower thresholds will lead to fast responses, however, will result in a greater error rate. (see Figure 2A). Consider an investigation - more solid evidence will lead to catching the correct perpetrator but will take more time. However, quick justice could result in catching the wrong person. The DDM also provides a better understanding of choice biases. Biases can occur in two ways. First, there are starting point biases i.e. the starting point is closing to one bound, thus the decision-maker is inherently biased towards one decision. Second is the drift rate bias, in which the drift rate is higher for one response, biasing the decision to that alternative. Figures 2B and 2C show the effect of both these biases on the diffusion process.

2 Neural Correlates

While understanding the working of the brain is important, a major goal of neuroscience has been to map these processes to underlying circuits in particular regions of the brain. These regions are called neural correlates. This section will look at various studies pinpointing the correlates for the different sub-process of the diffusion process: evidence accumulation (drift rate), decision threshold, starting point bias, and comparison of alternatives. To find neural correlates in humans, the tool of choice would be fMRI, since it is non-invasive. However, causal studies[3] are also performed, giving more definitive proof that an area is responsible for a sub-process. Using fMRI, Rolls et al., (2010) [RGD10] found signatures in the dorsolateral prefrontal cortex (DLPFC) which could represent evidence accumulation. Philiastides et al., (2011) [PAHB11] showed the causal role of the DLPFC using trans-cranial magnetic stimulation.[4] They found that

[3]Causal Studies - Causal techniques are used to find direct causal relationships between brain regions and a specific function. Causal methods include inhibition of a particular area by stimulation, pharmacological inactivation and lesion studies. They have great explanatory power in finding neural correlates.

[4]Transcranial Magnetic Stimulation (TMS) - It is a non-invasive procedure in which neurons in the brain are stimulated by a magnetic field which induces electrical activity in those neurons.

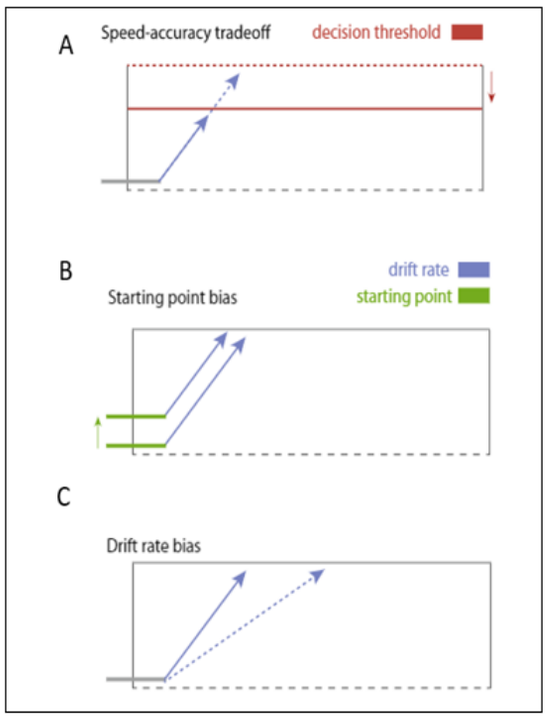

Figure 2: **a)The relationship between the speed-accuracy trade-off and the decision threshold. Lower thresholds can result in less accurate decisions. b) This figure shows the effects of the starting choice bias on the diffusion process. c)The effect of the drift rate bias on the diffusion process (Figures adapted from Mulder et al., 2014 [MvMF14])**

the drift rate was significantly reduced under the influence of the TMS while the non-decision time was almost unaffected, thus, showing the role of the DLPFC in evidence accumulation. Other studies have reported that areas like the frontal eye field (FEF) and intraparietal sulcus (IPS) could be responsible for evidence accumulation. (Basten et al., 2010 [BBHF10]; Ho et al., 2009 [HBS09]; Liu and Pleskac, 2011 [LP11])

The lateral intraparietal area (LIP), a subdivision of the IPS, has been also shown to represent sensory integration (Roitman and Shadlen, 2002 [RS02]). At this time, research points to a frontoparietal network (a network of areas in the frontal and parietal lobes of the brain) that is responsible for evidence accumulation. Studies regarding the decision threshold have pointed to a frontostriatal network which would include the anterior cingulate cortex (ACC), striatum, and the pre-supplementary motor area (pre-SMA) as candidate areas (Forstmann et al., 2008 [FDB$^+$08]; Ivanoff et al., 2008 [IBM08]; Van Veen et al., 2008 [VVKC08]; Winkel et al., 2012 [WvMR$^+$12]).

Kiani et al., (2014) [KCRN14] showed the response of neurons in the pre-arcuate gyrus during Changes of Mind. A change of mind would be a sudden change in the direction of the evidence accumulation. If the decision variable is drifting towards the upper threshold, a change of mind can be seen in a sudden reversal of direction towards the lower threshold. Mathematically, the sign of direction changes. The firing rates of these neurons peaked just before the saccade which could indicate the encoding of the decision threshold.

Various studies looking at value-based decision making have found encoding of subjective value and choice bias in the orbitofrontal cortex (OFC) (Forstmann et al., 2010 [FBD$^+$10]; Padoa-Schioppa and Assad,2006 [PSA06]; Summerfield and Koechlin, 2008 [SK08]). Other frontal areas such as the ACC, ventromedial prefrontal cortex (VMPFC), and DLPFC have been shown to encode starting point bias (Mulder et al., 2012 [MWR$^+$12]). The above-mentioned areas have also been shown to be responsible for the comparison of alternatives in choice tasks (Hare et al., 2011 [HSC$^+$11]; Hunt et al., 2012 [HKS$^+$12]).

Figure 3 summarizes the current research in finding neural correlates. Each dot in the figure represents a group of studies. The size of the dot represents the number of studies conducted. Thus, the figure shows every study conducted for the different parameters and sub-processes. The location of the dot shows the areas that are responsible for a sub-process. The colour of the dot shows the region of the brain the specific correlate is situated in and each region is represented by a unique colour as shown in the legend.

3 DDM In Perceptual and Lexical Tasks

This section will delve into the two most successful domains of applications of the DDM to behavioural data: perceptual tasks and lexical tasks. In the realm of perceptual decisions, researchers have applied the DDM to a simple dot motion-discrimination task (also called Newsome Dots or the Random Dot Kinematogram) and a categorization task. In the RDK task, the subject is shown a group of moving dots and needs to choose the average direction of the dots by a saccade. This task gives great control over task difficulty. It introduces motion perception and also requires the subject to compute the average motion of the dots which requires a large amount of integration. Figure 4 shows an RDK task.

Figure 1 shows an example categorization task, where the subject was required to place the given image in the house or the face category. This task also gives great control over changing the difficulty of the task but also requires evidence accumulation over time, and on the difficult trials, requires the comparison of the alternatives shown to the ideal response. For example, if the image has a low contrast the subject would need to compare the image to an ideal image of a face and that of a house and try to give the correct response. Both these tasks have been successfully modelled by the DDM. (see Gold and Shadlen, 2007 [GS07]; Heekeren et al., 2008 [HMU08] for an extensive review)

Ratcliff et al., (2004) [RMG04], showed the DDM applied to a lexical deci-

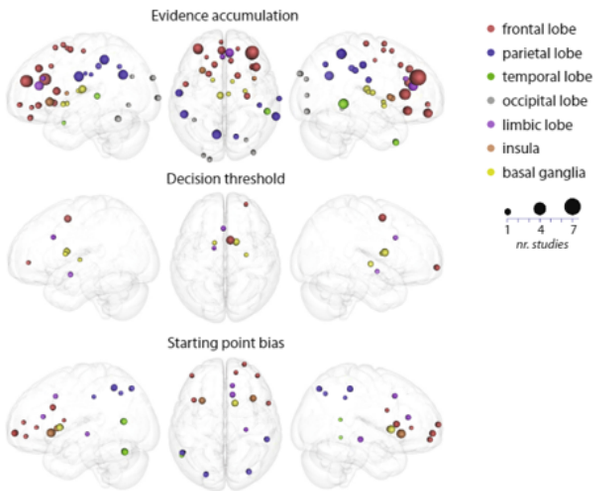

Figure 3: **Each dot is a separate group of studies. The size of the dot gives the number of studies conducted in a particular region. Regions have been highlighted as given in the legend. studies have been conducted to find correlates for evidence accumulation. This figure shows a frontoparietal network for the accumulation and a frontostriatal network for decision threshold. The starting point bias is almost only encoded by frontal networks. However, areas can have multiple functions and the distinctions are not always concrete. (Figure adapted from Mulder et al., 2014) [MvMF14]**

sion task. In this task, the human subject has to categorize the given stimuli into words and non-words. The stimuli were variable and were taken from a set of high-frequency words, low-frequency words, very low-frequency words, pseudowords, and non-words. The model explained the RTs for, both correct and error responses, and the probability of getting the decision correct very well for all types of stimuli. (see Table 3 in Ratcliff et al., 2004 [Rat04])

Recently, these applications have been extended to look at aging and IQ from a unique perspective. Studies have shown that older adults are slower than young adults due to longer non-decision times and a higher boundary, although age does not play a role in drift rate. This makes intuitive sense since older adults are usually more cautious and the decision thresholds prove this (Theisen et al., 2020 [TLvKV20]). Studies can also show how differences in IQ can affect decisions. Subjects with a higher IQ have higher drift rates but have almost equal non-decision times and boundary separations, as normal subjects. (Ratcliff et al., 2010 [RTM10]; Ratcliff and McKoon, 2011 [RM11]).

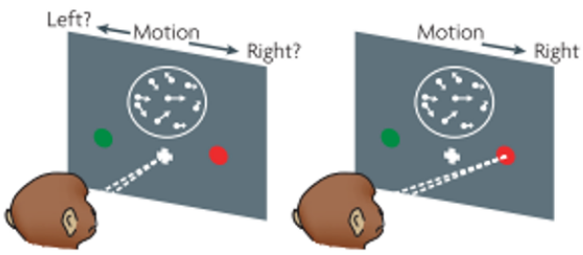

Figure 4: **An RDK task for a macaque monkey. The coherence of motion can be changed trial to trial. The monkey has to gauge the average motion and indicate its response by a saccade to one of the two targets on the screen. (Figure adapted from Heekeren et al., 2008) [HMU08]**

Studies looking at sleep deprivation, clinical populations, alcohol consumption, and reduced blood sugar have had success using a diffusion model analysis, thus proving that the DDM can be clinically useful. (See Forstmann et al., 2016 [FRW16] for an excellent review).

4 Extending the DDM to Economic Choices

This section will look at the modifications of the DDM for it to be applied to subjective tasks. All the tasks mentioned in the paper so far have had a defined correct response. This section will be an introduction into the domain of value-based choice. As I stated before, the model looked at so far is the simple DDM (sDDM) with 4 parameters. To extend the DDM to economic and subjective choices its computational framework behind the model needs to be modified. Milosavljevic et al., (2010) [MMH+10], compared the sDDM with 3 of its variants – the simple collapsing barrier DDM (scbDDM) [5], the full DDM (fDDM) [6], and the full collapsing barrier DDM (fcbDDM) [7], using the Bayes Information Criterion [8]. They found that the fDDM provided the best

[5]Simple Collapsing Barrier DDM (scbDDM) - It is a modification of the simple DDM in which the bound values (a and b) decrease as time progresses thus reducing the amount of evidence needed in the later stages of the trial. Just like sDDM it is defined by 4 parameters.

[6]Full DDM (fDDM) - Along with the 4 parameters of the sDDM it has an additional 4 parameters : a standard deviation parameter characterizing the noise in the accumulation process, a starting point bias parameter(zm), a range of latency times giving the distribution from which the latency time (non-decision time) is sampled every trial and a range of bias giving the distribution of the bias parameter.

[7]Full Collapsing Barrier DDM (fcbDDM) - It is defined by the same 8 parameters as the fDDM but now has collapsing barriers like the scbDDM.

[8]Bayes Information Criterion - BIC is a criterion used to compare different models for a given set of data samples. It strikes a balance between model complexity and model fit. Lower

quantitative description of their data and could be the model used by the brain. They conducted this analysis on a subjective value task in which the subjects had to choose between two food options.

However, the fDDM, as described in the paper, was suitable only for binary choice and did not take attention or fixations into account. When we choose between many alternatives, we often foveate (position our fovea centralis, the part of the eye with the sharpest vision) on the preferred option and this can bias our choice. This was not incorporated in the fDDM. To change this, Krajbich and Rangel, (2011) [KR11], proposed a novel drift-diffusion process for subjective multi-alternative decisions, the Attentional Drift Diffusion Model (aDDM). Their model included a fixation bias and explained the data for both binary and trinary value-based choices. The aDDM can also be extended to simple purchasing tasks, in which subjects need to decide whether or not to buy a product for the given price (Krajbich et al., 2012 [KLCR12]). The model explained RTs for different sets of stimuli but also showed the adverse impact of visual fixations. When subjects looked at the product more, they were more likely to buy it. On the other hand, if they looked at the price for a longer period, they were more likely to reject it. The effects of visual fixations and affection thus seem to bridge the perceptual and economic domains together. Thus, we can see that the DDM has been successfully modified to purchasing decisions and value-based choices, both for binary and trinary choices. Attempts have been made to extend the aDDM to quaternary choice (von Boguslawski and Mildén, 2015 [vBM15]), with mixed results. Although they have modeled choice well, the sample size may be small and the results may not be very significant. Still, it is another step towards modeling more complex tasks.

5 Cognitive Tasks

This section will look at novel applications of the DDM to more cognitive tasks. The purchasing and value-based experiments talked about in previous experiments were simplified accounts of real-life decisions. This section will address experiments looking at more complex behaviors and decisions.

5.1 Self-Control

Berkman et al. (2017) [BHL$^+$17], put forth an alternative model for self-control. Rather than a competition between the impulsive and deliberative processes, they defined self-control as a value-based choice between two alternatives. Rather than modeling self-control with dual-process models, they used the drift diffusion model. By using the example of a dieter choosing between a salad and a burger, they looked as self-control as a comparison between the subjective values of two alternatives, thereby eliminating the need for a 'control' system. The decision would be governed by the values of the decision thresholds

the Δ BIC score, better the model. It penalizes the model for having too many observations and parameters and rewards the model for fitting the data well.

and the two alternatives. Their model captures internal events like effort expenditure by incorporating it into the value-integration process. Effort can be an opportunity cost that is compared with the benefits that an alternative pose., thus the task that needs more effort can be avoided, favoring the impulsive option over the deliberative option. This view of self-control could lead to understanding why damage to prefrontal cortices, areas thought to participate in evidence accumulation and comparison of alternatives, results in more impulsive decisions. It can also lead to further research into the realms of goal-attainment and motivation.

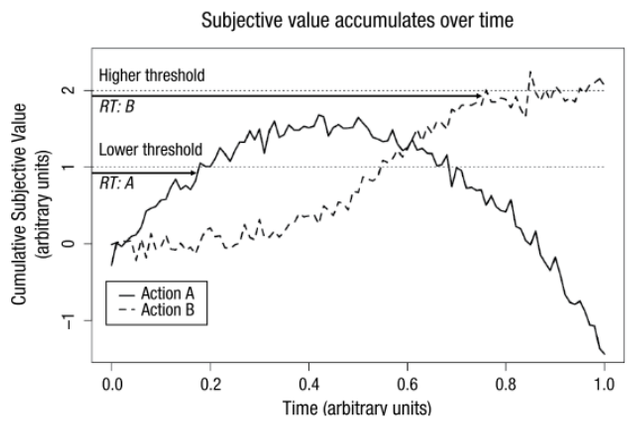

Figure 5: **Subjective value accumulates over time just as sensory information does. The value of Action A accumulates rapidly but falls over after some time whereas the value for Action B rises slowly but ultimately reaches a higher point. A person with a lower decision threshold would pick Action A and could have poor self-control. Under time pressure, A would be the action chosen. However, for a person with a higher decision threshold or with no time pressure, B would be chosen. This explanation can be heightened by taking the example of Action A being eating pizza and Action B as eating salad. (Figure adapted from Berkman et al., 2017 [BHL$^+$17])**

5.2 Loss Aversion

Loss Aversion is one of the central tenets of Prospect Theory (Kahneman and Tversky, 1979 [KT79]), which proposes that when faced with risk or uncertainty, decision-makers are loss averse i.e. they place a greater weight on losses than they do on gains. An experiment that highlights this is when decision-makers are offered a gamble with a 50% probability to gain 11$ and a 50 % probability to lose 10$, they often reject the gamble. Despite the gamble having a positive expected value, it seems unattractive and is rejected. Zhao et al.,

(2020) [ZWB20], applied the DDM to this psychological phenomenon. They modified the full DDM to incorporate the unequal weightage of losses against gains but also incorporated a pre-valuation bias. This bias behaved similarly to the starting point bias, and represented a predisposition towards rejection, by being closer to the rejection bound (Figure 6). Since the starting point for the diffusion process is closer to the rejection bound, the decision-maker is biased towards rejecting the gamble. It takes less evidence for the decision variable to cross the bound, thus the RTs for rejection will be shorter and the probability of rejection will be greater. This bias corresponds to prior experience and introduces the concept of learning into the experiment. As they show in their paper, during trial blocks with higher payoffs –i.e. trials in which the possible gains were much greater than the possible losses, this pre-valuation bias was closer to the rejection bound, meaning it took a larger gain to loss ratio to convince the subject to accept the gamble, in this case, 1.83, whereas in trial blocks with lower payoffs i.e. trials in which the possible gains were almost equal to the possible losses, the pre-valuation bias was farther from the rejection bound, meaning that it took a smaller gain to loss ratio to convince the subject to accept the gamble ,in this case, a 1.25 gain-to-loss ratio. Thus, they show the influence of prior gambles and the prior rewards on the current gamble. Using the Deviance Information Criterion, a model criterion similar to BIC which penalizes the model with greater variance, and thus uncertainty in the data, they showed how the DDM outperforms older models explaining loss aversion. Through the incorporation of a starting point bias, in the form of the pre-valuation bias, their model captures the choice probabilities and the RTs for both rejected and accepted gambles. Thus, the DDM has been successfully modelled for another task, more cognitive than those of the economic and perceptual domains.

5.3 Driving Tasks

Recently, the DDM has been modified for different types of driving tasks. Cooper and Strayer, (2008) [CS08] conducted an experiment to determine the effects of cell-phone usage on driving. They used a 3D driving simulation during which subjects were engaging in a conversation they found interesting using a hands-free phone. Ratcliff and Strayer, (2014) [RS14] conducted an analysis on this study using a one-boundary drift diffusion model (Figure 7A) and found that distracted drivers have longer non-decision times and lower drift rates resulting in longer response times and slower uptake of information. Thus, this study provided computational proof as to why distracted drivers have higher chances of being in a car crash.

Building on this, Daneshi et al., (2020) [DAT20] used a one-boundary DDM to model time-to-collision to an obstacle. In this task, the subjects had to stay on their trajectory for as long as possible but prevent collision with the lead vehicle. (Figure 7B). They conducted this task with and without time pressure and found that both the drift rate and the decision threshold were higher for the trials with time pressure. This could mean that under time pressure drivers have

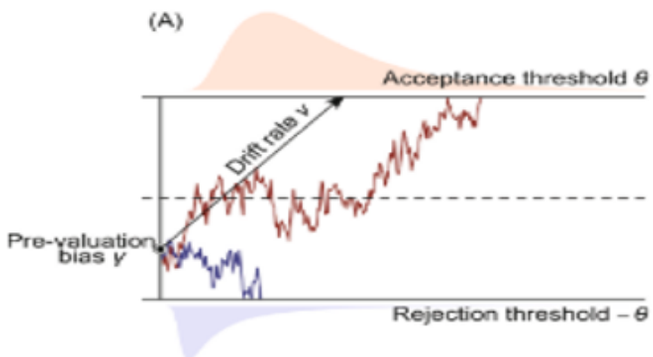

Figure 6: **A drift diffusion process for loss aversion. The pre-valuation bias γ appears as a starting point bias towards the rejection threshold. Since the distance from the thresholds is now unequal, rejection is more likely and will have a shorter response time since it takes less evidence to reach the threshold. (Figure adapted from Zhao et al., 2020 [ZWB20])**

greater evidence accumulation but also can be uncertain about their decisions thus increasing their decision thresholds and their margins of safety.

Both the previous studies have looked at simple braking and driving around tasks. The DDM has also been applied to more complex tasks such as accepting or rejecting a turn at an intersection. Zgonnikov and Abbink,(2020) [ZA20] used a modified full collapsing barrier DDM (fcbDDM) with variable drift rates to model a driving task which had subjects accept or reject a left turn with an oncoming car which could block them (Figure 7C). Evidence accumulation involved gauging the distance from the oncoming car and its speed and using this information to compute a time-to-arrival. Greater the time-to-arrival, greater the probability to turn. They found a positive relationship between response time and time-to-arrival (Figure 7D). Their model also accurately predicted their data well. This modification of a variable drift rate could be of huge importance to similar experiments that look at dynamic real-life scenarios. More research into driving behaviours could have applications in computer-driven cars and in making traffic interactions safer.

5.4 Racial Bias

In light of the increasing police brutality, researchers have tried to study racial biases in police officers and trainees and regular people. A first-person shooter task (FPST) has been developed for these studies. In the task, the participants are instructed to shoot armed targets and to not shoot unarmed targets. The

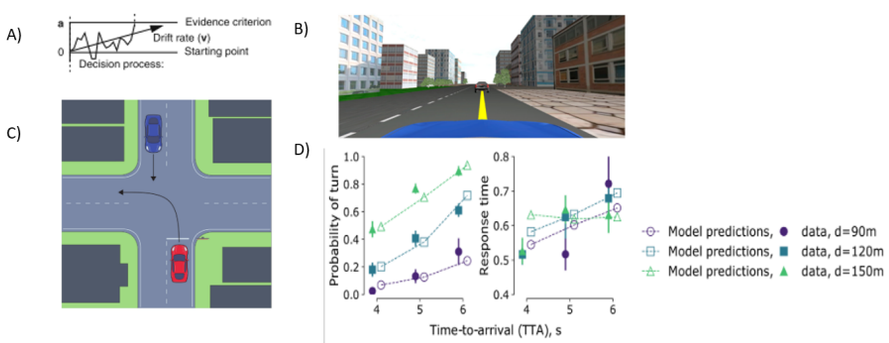

Figure 7: **A) A one-boundary diffusion model for driving tasks. The parameters remain the same as the sDDM. Figure adapted from Ratcliff and Strayer, (2014) [RS14] B) Participants have to stick to the yellow line for as long as possible and need to drive around once the obstacle gets too close. Figure adapted from Daneshi et al., (2020) [DAT20] C) The participants are in the red car. The speed of the blue oncoming car is variable. Participants have to decide whether or not to turn left. Figure adapted from Zgonnikov and Abbink, (2020) [ZA20] D) The model predictions are given by the dotted lines. They fit the data well. The probability to turn increases with an increase in time to arrival and an increase in distance from the oncoming car. The reaction time also shows a positive relationship with time-to-arrival. Figure adapted from Zgonnikov and Abbink, (2020) [ZA20]**

targets can be either Black or White men.

Using a hierarchical DDM [9], Johnson et al., (2017) [JHCP17] analysed an FPST in which participants were rewarded for correct shooting decisions. They found that participants had a starting point bias towards the to-shoot decision, however, this was independent of race and can be explained by the rewarding outcome for to-shoot decisions. Evidence accumulation was stronger to shoot armed Black men than to shoot armed White targets, thus participants have a higher drift rate when it comes to shooting armed Black men and this results in shorter response time and a greater likelihood to shoot armed Black men. Following this study, Johnson et al., (2020) [JSCF20] looked at the effects of sleep deprivation and caffeine on racial biases. They found that subjects were more likely to shoot unarmed Black men than unarmed White men and this bias was not affected by either sleep deprivation or caffeine. Caffeine did not mitigate the errors caused by sleep deprivation. It only reduced response times. They also found that subjects set a wider threshold for White men than for Black men, showing that they needed lesser evidence when it came to making a decision when they were shown a Black man as the target. Surprisingly, they found that overall, participants who were given a placebo had a higher starting point to shoot White targets.

This study reaffirmed a conclusion that Johnson et al., (2017) [JHCP17] had come to, proving that for unarmed targets, subjects had a lower drift rate for Black men than for White men and for armed targets, had a higher drift rate for Black men than for White men.

5.5 Reinforcement Learning

The DDMs looked at in the review so far have not incorporated an element of learning into the process, however, the drift diffusion process modeled for loss aversion hinted at the influence of past outcomes. Recently, the DDM has been applied to learning tasks as well. These groups of models are called reinforcement learning drift diffusion models (RLDDM). They unify the DDM and the theory of reinforcement learning (See Seo and Lee, (2012) for an excellent review [SL12]). These models have been applied to probabilistic selection tasks (PST), which present the participants with two options with the goal being to pick the option with a greater probability to be rewarded. However, the participants need to learn the probabilities and rewards of these options as the trials go on. The simplest RLDDM has 4 parameters: a learning rate [10], threshold

[9] Hierarchical DDM – The HDDM analyzes the data at the population level rather than at an individual level. This means that fewer trials can be conducted per participant, but the parameters can easily be recovered and can still capture all the aspects of the data as the simple DDM does.

[10] Learning Rate - The learning rate determines how sensitive the decision maker is to previous outcomes. A learning rate that is too low is not optimal since the learning will be very slow, however a learning rate that is too high will induce forgetting the outcomes that happened a few trials back.

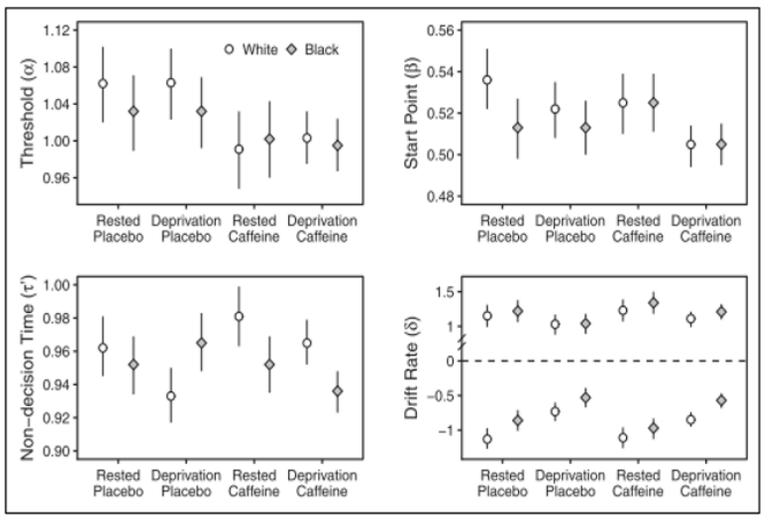

Figure 8: **The x-axis shows the 4 groups of patients: Patients with a whole night's sleep on a placebo, patients with a whole night's sleep on caffeine, patients who had not slept for 24 hours on placebo, and patients who had not slept for 24 hours on caffeine. The top left panel shows that subjects had wider thresholds for white men than for black men. The top right panel shows that subjects, surprisingly, had a starting point bias to shoot white men. The bottom left panel shows the effect of sleep deprivation and caffeine. The bottom right panel shows the drift rates for the different trials. All the negative drift rates i.e. below the dashed lines are for unarmed targets while those above the dashed lines are for armed targets. Thus, Black armed men produced a higher drift rate in the participants while subjects had a lower drift rate for unarmed black men than those for white men. Figure adapted from Johnson et al., (2020) [JSCF20]**

values, a scaling parameter vmod [11], which ensures that the difference in values and probabilities for the two choices are transformed into an appropriate scale in the DDM framework, and the non-decision time.

Fontanesi et al., (2019) [FGSR19] showed that the RLDDM can explain both reaction times and choice probabilities very well. However, it also shows the learning throughout the task and thus successfully combined the RL models and the DDM (Figure 9).

The accuracy of the responses increased steadily and the RTs decreased throughout the task, showing that the participants learnt the probability of

[11]Scaling Parameter - It is analogous to the drift rate in the DDM. It helps to convert the effect of previous outcomes into an appropriate scale that can be incorporated into the DDM framework.

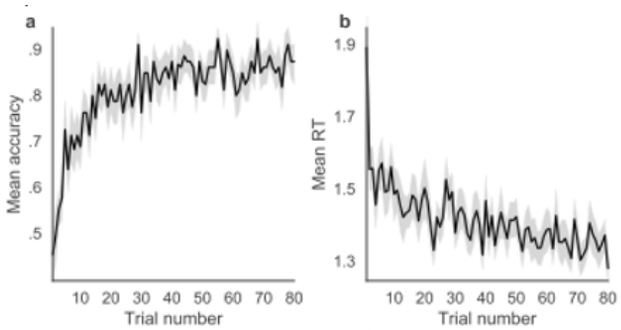

Figure 9: **The top panels show the power of the RL models whereas the bottom two represent the contribution of the DDM to the RLDDM. Thus, two prominent theories can be unified to give a better account of decision making, a) The accuracy increases as the trial number increases thus showing the effect of learning on the task. b) The RT decreases, once again showing the effect of learning. Figure adapted from Fontanesi et al., (2019) [FGSR19]**

the rewards and improved their performance. They also conducted an analysis to find out which RLDDM explained the data the best. The RLDDM can be modified by having different learning rates for negative and positive outcomes. The threshold can either be fixed or variable, and the scaling parameter can either be linear or sigmoid. Thus, there can be 8 types of the RLDDM. Using the Watanabe-Akaike Information Criterion [12], they found that the full RLDDM i.e. with dual learning rates, one for positive and one for negative outcomes, with sigmoid scaling parameters and with variable bounds explain the date the best (Figure 10).

Pedersen et al., (2017) [PFB17] used the RLDDM to gain a different perspective on ADHD patients and the effects of medication. They found that medication increased boundary separation, lowered learning rates, increased non-decision time, and increased the drift rate scaling, showing the shift towards focusing on accuracy rather than speed. Thus, the RLDDM has the potential to be used in many clinical experiments.

6 Discussion

Recently, researchers have tried applying the Drift Diffusion Model, a popular computational model for sensory decision-making, to more cognitive and complex tasks. These studies have shown that the DDM can explain a variety of psy-

[12]Watanabe Akaike Information Criterion - Another model criterion like BIC and DIC. It penalizes the model in a way, similar to that of DIC but it takes the summation of the variance of each posterior draw. It is more computationally taxing than both BIC and DIC but gives a better approximation of how good the model is.

Model	η	v	a	p_{WAIC}	$-$lppd	WAIC
RLDDM 1	One	Linear	Fixed	111	5129	10481
RLDDM 2	Two	Linear	Fixed	134	5051	10369
RLDDM 3	One	Linear	Modulated	145	4942	10174
RLDDM 4	Two	Linear	Modulated	159	4866	10048
RLDDM 5	One	Sigmoid	Fixed	137	4930	10135
RLDDM 6	Two	Sigmoid	Fixed	159	4861	10039
RLDDM 7	One	Sigmoid	Modulated	164	4672	9672
RLDDM 8	Two	Sigmoid	Modulated	190	4613	9607

Figure 10: **Lower the WAIC score, better the model. The dual learning rate means that positive and negative outcomes will have a different effect on the decision-maker. The threshold is variable, thus when the decision is the easiest the threshold is the lowest. The scaling parameter can be fixed or s-shaped.**

chological phenomena and real-life decisions. The model captures the response times and the behaviour of the participants in these tasks and helps in giving a greater insight into the underlying processes of deliberation and decision-making. Further research into the DDM could have powerful applications in consumer behaviour, traffic behaviour and laws, computer-driven vehicles and could have important clinical and social applications. Though the tasks looked at in this review are more complex than sensory and simple value-based choice, they are still a step away from explaining important and life-changing decisions. The model comparison criteria used in this review (BIC, DIC, WAIC) may represent a caveat in the literature. These criteria penalize the models in different manners and lack of uniformity in the literature could result in the selection of incorrect models (Churchland and Kiani, 2016 [CK16]) . Future research should aim to refine the DDM framework and attempt to resolve the debates about the dynamics of the drift-diffusion process. Future work should also aim to conduct more extensive research in finding definitive neural correlates and circuits for the parameters. New techniques such as calcium imaging and optogenetics, if adapted to work in primates, hold interesting possibilities. Another interesting innovation in the literature is the quantum drift-diffusion model (Rosendahl et al., 2020 [RBC20]), which looks at evidence as a quantum particle of information and the threshold as a square attractor. This may open new and fascinating avenues for improving computational models as a whole. In the last 10 years, the extensions of the Drift Diffusion Model have led to tremendous progress in understanding how cognitive decisions are made. The DDM has the potential to model more complex decisions and holds a lot of promise for the future.

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Anxiety and Procrastination: What is the Association?

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Abstract

Psychologically, procrastination is understood as a form of behavioral self-handicapping whereby an individual delays beginning or completing a task to strategically avoid situations that may show an adverse image. Given the high prevalence of procrastination in our daily lives, recent work has begun to investigate its connection with other psychological factors and psychopathology. Both theoretical models and people's first-hand experience have indicated a possible association between procrastination and anxiety. This review summarizes the existing literature and integrates findings within the conceptualization of procrastination. Anxiety and procrastination are concluded to be closely correlated and possible psychological mechanisms that help explain such correlation are proposed. It is speculated that anxiety can be both the result and the driver of procrastination, and procrastination can be a strong predictor of psychological conditions. These findings will contribute to a better understanding of procrastination and its psychological correlates, providing crucial implications for people who suffer from procrastination as well as for clinicians who are trying to help chronic procrastinators. Future research is still needed to further confirm the direction of the causal relationship, to determine the mediators and moderators of the relation, and to specify the clinical value of the conclusion.

1 Introduction

Simply defined, procrastination refers to the act of "put[putting] off intentionally the doing of something that should be done" [cdnd]. Psychologically, procrastination is understood as a form of behavioral self-handicapping whereby an individual delays beginning or completing a task to strategically avoid situations that may show an adverse negative image [FT00] [M.04]. Importantly, in addition to its behavioral components, procrastination also entails emotional and cognitive components [Fer1b] [RSM86] [M.04]

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Procrastination has long been a problem in society [FE95] [Mil08] and has recently gained significant attention in the field of clinical psychology. Globally, about 20-25% of adults are chronic procrastinators in a variety of life situations like academic pursuits, social relationships, professional settings, and finance management [BD07] [FDM14] [KC19]. Being one of the most prevalent problems among students, procrastination is found to be the major barrier in learning by one-third of the general population [SF13]; 95% of American college students reported engaging in academic procrastination, with almost half of them procrastinating on at least 50% of tasks [EK77] [BD07].

In fact, despite its high prevalence, procrastination is indeed a multifactorial psychological phenomenon that involves a complex interaction of behavioral, cognitive, and affective components [SR84]. It is identified as one of the least understood human behaviors, yet it leads to not only lower levels of wealth, health, and well-being, but also psychological distress [BD07] [SF13] [AA15]. More specifically, procrastination is closely connected to poor academic performance [PMM$^+$17] [GH19], reduction in work productivity [FBN$^+$15], negative emotional and behavioral reactions [SWS00] [FDM14], and more acute health problems [Sir07]. [SM13] even noted the fact that procrastinators make more errors, work slower, and miss more deadlines when compared to non-procrastinators. Although most procrastinators consider their behaviors as inappropriate, problematic, and in need of change [SM13] [KC19], it is quite possible that they do not have much insight into the psychological mechanisms of why they repeatedly engage in such undesirable behavior.

One psychological factor that may be linked to procrastination is anxiety, another phenomenon with profound effects on the global population. According to the World Health Organization (2017), 264 million adults around the world have anxiety and it is estimated that 31.3% of all U.S. adults will experience an anxiety disorder, the most common mental illness in the U.S., at some point in their lives [Sch07]. Large population-based surveys suggest that up to 33.7% of the population are affected by an anxiety disorder during their lifetime, and there is a substantial under-recognition and under-treatment of these disorders [BM15]. For example, for students who worry that they are inadequate to pass their classes, anxiety may force them to drop out of college; for adults, they carry such anxiety into life even after they graduate and it will continue to affect their work and social lives [CDMM05] [Mil08]. Though anxiety cannot kill people directly, more severe forms of anxiety can result in people committing suicide as an alternative to the suffering [Mil08]. As only 9.8% of those suffering received possibly adequate treatment globally [ALEL$^+$18], further research on anxiety, its related symptoms, and applicable treatments is crucial.

Based on the perspective of seeing procrastination as a manifestation of lack of self-control and time-management skills, current mainstream treatments for procrastination, such as Cognitive Behavioral Therapy (CBT), are rather more behavioral or developed from a motivational or volitional standpoint [B.13] [RBF$^+$18]. In particular, CBT for procrastination mainly targets improving self-regulation skills, goal-setting techniques, implementation intentions, and time management ability [B.13] [RBF$^+$18], and usually involves creating a prioritized

to-do list or even increasing the perceived pressure. In general, it is significantly different from the more well-known CBT for anxiety as relatively little attention is given to anxious thoughts, emotions, and physiological sensations. A recent meta-analysis showed that the benefit of current psychological treatments for procrastination is minimal and the effectiveness of CBT specifically is not as satisfactory as conventionally expected [RBF+18]. Although new forms and types of treatments like internet-based interventions [KAEB19], watching videos [BSPT20], and acceptance-based behavioral therapy (ACT) [GO15] are being developed, there is still a lack of effective and personalized treatments of procrastination. Thus, further research on the mechanisms and causal factors involved in procrastination is important.

Previous research on the topic of procrastination has mostly focused on its outcomes and interventions instead of the causes. For instance, [LLSN18] specify the negative influence of leader procrastination on group functioning at work, and [vE03] examines the effectiveness of time management on treating procrastination. In addition, previous studies mainly investigate forms of procrastination that are related to academic scores [ZH18], work performance [MPT18], internet use like video-game addiction [YWH+17], and bedtime delay [KSD18]. Furthermore, existing studies intensively focus on the cognitive processes of procrastination [Fer1b], leaving out the characterization of behavioral, arousal, affective and emotional factors like anxiety. Therefore, the relationship between anxiety and procrastination remains unclear.

The current review examines the association between anxiety and procrastination, whether anxiety and procrastination are related, whether anxiety is the result or the driver of procrastination, and whether procrastination can be a sign or predictor of psychopathology by reviewing evidence on the correlation between anxiety and procrastination, a potential causal relationship in both directions, as well as moderators of the relation. Elucidating the role of anxiety in procrastination will contribute to a better understanding of the psychological mechanism between anxiety and procrastination and provide crucial implications for people who procrastinate as well as for clinicians who are trying to help those chronic procrastinators. Furthermore, specifying whether anxiety is a key causal factor of procrastination will help inform the direction of future development of treatment and thus help reduce negative outcomes.

1.1 Possible Mechanisms Linking Anxiety and Procrastination

Several existing models of procrastination do indicate a potential relationship between anxiety and procrastination, where anxiety might be a key factor in explaining procrastination. Researchers have commonly viewed procrastination as a self-regulatory or cognitive failure [BHT94] [TS89] [FBN+16] and an illogical and non-goal directed behavior where irrational cognitions play a key role [EK77]. This could imply possible mechanisms of the relation between anxiety and procrastination. From the Rationale-Emotive Behavioral Therapy (REBT) perspective, there are two assumptions about procrastinators' irra-

tional beliefs; first, procrastinators hold poor competence beliefs, and second, they are fearful of the possible negative social consequences of failing to complete the task well enough [FBN+16]. Such fear of failure has also been discovered in empirical studies on procrastination; they have discovered not only a positive correlation but also a causal relationship between anxiety and procrastination, in which fear of failure would lead to a higher level of procrastination [ZDF+18]. Particular cognitive factors are further revealed in other studies. For example, task aversiveness, the extent to which a task or behavior is perceived to be unpleasant or difficult to perform by an individual [BP00], is proved to be closely related to procrastination [SR84]. Such aversiveness, or unpleasant feeling, can be seen as a result of excessive anxiety or fear of failure, as people clearly would not enjoy performing a task when overwhelmed with worries about negative future outcomes. A few studies further imply a close correlation between stress and task aversiveness as well as between task apprehension and fear of failure [BP00] [OC01]. Therefore, it is possible that as one is holding such a negative attitude towards future tasks and himself, one then experiences excessive stress, apprehension, and in other words, anxiety; then, such anxiety may lead to procrastination, being a mediator between irrational or negative cognitive beliefs and procrastination.

In addition, from a more behavioral perspective, some psychologists have viewed procrastination as an avoidance behavior that arises in response to anxiety. Procrastinators are found to avoid situations that may reveal information concerning their abilities [Fer1b] [RF20]. Procrastination is proposed to be closely related to short-term mood repair and emotion regulation [SP13]. Such findings have led theorists to suggest that procrastination is a type of avoidance whereby people procrastinate to prevent themselves from experiencing the anxiety of doing the task or confronting the idea that they might fail. The appraisal-anxiety avoidance (AAA) model states that avoidance, a behavioral response to stress, functions to reduce the perceived anxiety when people find themselves inadequately prepapred to cope with the threat. As avoidance is so effective at relieving immediate anxiety, it ultimately perpetuates the task avoidant pattern or the behavior of procrastinating, as well as reinforces anxiety [MT99]. In particular, some refer to procrastination as the manifestation of defensive avoidance, the attempt to avoid or postpone the stress of being exposed to relevant information of the decision or task [Eva90]. In a similar manner, Mowrer's two-factor model of anxiety [Mow47] highlights the important role of negative reinforcement and is consistent with avoidance behavior as a maintaining factor of procrastination [FE95]. Although this perspective may fail to consider individual differences among procrastinators [FE95], it does provide a powerful demonstration of the possible relation between anxiety and procrastination.

Irrational or negative thoughts resulting from a biased time perspective imply psychological mechanisms between anxiety and procrastination as well. Procrastinators are found to have the tendency of focusing more on past and present events as compared to the future, a cognitive orientation that is referred to as time perspective [Fer91] [RF20] [M.14]. It is possible that such a

past-oriented thinking style would lead to thought control problems like rumination, which is defined as a kind of intrusion that involves "repetitive, prolonged, and recurrent thought about one's self, one's concerns and one's experiences" [SLF00] [FSH+12]. It is suggested that procrastination is associated with a higher frequency of intrusive thoughts like rumination [RRBvdL18]. Therefore, we could speculate that it is those overwhelming negative thoughts that then lead to excessive anxiety, which in turn results in procrastination. Indeed, individuals with anxiety disorders are also shown to have a negative past time perspective, which is further related to rumination [ASWC18]; procrastinators might be experiencing the same cognitive bias and thus, anxiety as well.

On the other hand, although focusing more on the future orientation, worry could be another psychological pathway between anxiety and procrastination. Worry is understood as a cognitive phenomenon that occurred when the individual experiences a threat concerning possible future events and is often accompanied by feelings of anxiety [DGL01] [MWB91] [SJ01]. Both theoretically and empirically, worry shows a substantial relationship with procrastination and a significant positive causal effect on anxiety [SJ01] [GMC01].

Another model that helps explain the correlation between anxiety and procrastination is the utility expectancy-value theory [Ecc83] [dJEW02]. Central to the theory are two concepts: first, the utility value, which is defined as the perceived usefulness of a particular task or activity in achieving goals [SJ19], and second, the expectancy, a measure of the extent to which an individual believes that a given task will yield utility [FBN+17]. The perceived utility value is found to be closely related to avoidance intentions and procrastination [SJ19]; instead of procrastinating on tasks labeled as fun or pleasurable, procrastinators only procrastinate when the task was identified as evaluative – or in other words, valuable [FT00]. It might be explained by the fact that individuals may feel a greater emotional burden and higher anxiety when participating in more important and useful tasks [NLL11] [SBE11] [BGP17]. Those two factors that motivate people's achievement-related choices can be reasonably tapped into several cognitive constructs that have been implicated in procrastination and relevant to anxiety, namely fear of failure, task aversiveness and worry. Arguably people may choose to procrastinate because the subjective high importance of the task makes them feel excessively anxious.

Recent research has begun to investigate the neural substrates of procrastination [ZCX+20]. This type of research may be informative if similar neural circuits are implicated in procrastination compared to those implicated in the experience of anxiety. Research has shown that among chronic procrastinators, the volume of the amygdala is larger than normal and that the amygdala is less connected to the dorsal anterior cingulate cortex, which helps to regulate the amygdala's reactions [SFP+18]. The amygdala is also a key element of the anxiety circuitry and is responsible for fear and anxiety-related behaviors [BPCKB18]. Some work further suggests specific structures in the brain, specifally the right hippocampus, that could be account for the link between anxiety and procrastination [ZCX+20]. However, work in this area is currently limited, and specific hypotheses about which regions may be involved in pro-

crastination are still lacking.

2 Literature Review and Analysis

2.1 Evidence of a Correlation Between Anxiety and Procrastination

As researchers have begun to investigate the role of anxiety in the development of procrastination and to measure both procrastination and level of anxiety at the same time in recent years, there is more evidence showing a positive correlation between anxiety and procrastination. In general, a representative study conducted by Beutel and colleagues (2016) [BMA+16] showed that procrastination is consistently associated with higher stress and anxiety. The study examined over 2,500 participants who were between the ages of 14 and 95 years and demonstrated evidence of a strong correlation between anxiety and procrastination across the lifespan. Many other researchers have demonstrated the same result as well [CBM04] [KC19] [VFGI12] [HMS98]. Many studies have been done in academic settings and specifically examine academic anxiety and procrastination. For example, Custer (2018) [Cus18] administered the Test Anxiety Inventory and the Procrastination Assessment Scale for Students to over two hundred prelicensure nursing students, aged 19 to 53, in America, and found a statistically significant correlation between test anxiety and academic procrastination. Similarly, through self-report measures and a canonical correlation analysis, Vahedi and colleagues (2012) [VFGI12] found a positive association between a latent statistics anxiety factor and procrastination among Iranian undergraduate students. It is important to note that both of these studies were conducted in mostly female samples, which may limit the generalizability of their findings.

The relation between anxiety and academic procrastination has also been examined in younger populations. In a sample of younger participants (aged 13, 14, and 16) in Israel, it was also found that students who are under higher levels of anxiety are prone to procrastinate more on assignments like preparing for examinations and writing papers than those who are having less anxiety [MT99]. Similarly, Rosário and colleagues (2008) [RNS+08] conducted a study in two different samples, which consisted of over a thousand participants in total, of junior-high students in Portugal, and discovered a positive and significant correlation between test anxiety and procrastination. Overall, it is evident that the correlation between anxiety and academic procrastination exists among people of different ethnicities, living environments, and ages. Especially for academic procrastination, such a correlation between anxiety and procrastination could be better understood by viewing it from the REBT perspective and noting the role fear of failure has played. Students who spend a great amount of time and effort preparing for an exam or finish their papers on time and properly yet receive poor scores or evaluations are forced to shamefully acknowledge that they are deficient i n i ntellectual abilities compared t o t heir counterparts. Therefore,

in this case, procrastination, being a strategic cognitive choice, is adopted by those who are anxious due to the deep fear of their academic inadequacy and consequent failure when facing an assignment. Such a cognitive process is very common and shared by all groups of students.

Some studies have shown a more multifactorial and complex correlation between anxiety and academic procrastination. In a sample of American college students, a more complicated correlation is demonstrated: procrastinators experience less stress and anxiety early on when they procrastinate than do non-procrastinators, and there even appears to be a negative correlation between anxiety and procrastination earlier in the semester [TB97]. However, later on in the semester and in the overall process, procrastinators experience more stress and anxiety compared to those who do not procrastinate [TB97]. This can be explained by the two-factor model in which procrastinators procrastinate to reduce their level of stress and anxiety, and the result in fact may be seen as empirical evidence for the hypothesis that anxiety and procrastination are related through negative reinforcement. Although the behavior has been repetitively reinforced, when the deadline approaches, students are no longer allowed to put things off; therefore, the anxiety comes back and even becomes more intense since the reduction effect brought by procrastination no longer exists and most procrastinators do not master an alternative coping strategy. Therefore, timing and external factors like task requirements may also affect the relation between anxiety and procrastination.

A few researchers have come to a somewhat different conclusion on the correlation between anxiety and procrastination. In a study done by Milgram and Toubiana (1999) [MT99], when it comes to assignments like homework, the relation is reversed, in which students who were more anxious about their homework completed it more quickly than those who were less anxious. The authors speculate that homework involves less task-centered anxiety and consequence-centered anxiety, which may be different from the anxiety students experienced when facing exams and writing tasks. In fact, this can be understood as an application of the utility expectancy-value theory, in which the perceived value of completing daily homework may be lower than preparing for exams or finishing a paper and students may feel less anxiety and burdened to do it. However, the finding may also imply that types of anxiety, the severity of anxiety, or other moderators can play a key role in the relation. Mixed results on this correlation indicate a need for studies to further examine different possible factors.

Beyond the academic domain, a correlation is also found under other circumstances that involve other forms of anxiety or procrastination. In particular, Phillips and colleagues (2015) [PtDA15] examine how interpersonal skills anxiety, the anxiety one perceives due to the extent to which they believe in their capability to interact and communicate with others, relates to procrastination. They conclude that there is a positive association between interpersonal skills anxiety and procrastination. In the same study, "avoidance of help-seeking," another form of maladaptive avoidance behavior, is also found to be positively related to anxiety factor while being negatively related to interpersonal skills. Both of the findings are consistent with the AAA model, in which people try

to avoid certain tasks or behaviors to reduce the anxiety that comes from their perceived inadequacy to perform well. The results indicate that the correlation may apply to various types of anxiety and to different social settings, especially those that involve a self-appraisal process of individual skills or abilities.

In addition, other forms of procrastination like bedtime procrastination, which refers to the delay of bedtime with no external reasons, and workplace procrastination are both proposed to be closely and positively related to anxiety [CAS20] [PAZ18]. Further, procrastination may occur not only at the level of the individual but also with groups. Hooft and Mierlo (2018) [vHVM18] investigate team-level procrastination and arrive at a similar result, pointing out that team procrastination is closely connected to increased stress levels among the members. Evidence of the association between anxiety and procrastination in more diverse social settings is still necessary, but overall, there is strong evidence of a correlation between procrastination and anxiety across studies.

Additionally, researchers have begun to investigate the correlation from a neurobiological perspective. Zhang and colleagues (2019) [ZLF19] revealed that individual differences in procrastination can be attributed to "structural abnormalities and altered spontaneous metabolism in the parahippocampal cortex and the prefrontal cortex" (pp. 817–830), which are regions involved in thinking about the future and emotion regulation, respectively. This hints at how neural correlates of procrastination could help explain some psychological correlates of procrastination, particularly time perspective and anxiety. Furthermore, a pilot study done by Zhang and colleagues (2020) [ZCX+20] not only confirmed the existence of the correlation between anxiety and procrastination but also highlighted possible neurobiological evidence for an association between anxiety and procrastination. They found that anxiety and trait procrastination are each associated with the activity of the right hippocampus through conjunction analysis and pointed out a positive correlation between the right hippocampal grey matter volumes and trait anxiety, as well as procrastination. Although the study examined over 200 participants and provides compelling evidence, more biological studies on the correlation between anxiety and procrastination is needed to help answer the question of why exactly the correlation exists and to solidify or falsify existing theories.

2.2 Evidence of Anxiety Leading to Procrastination

There has been evidence showing a direct causal relationship between anxiety and procrastination, in which higher levels of anxiety lead to procrastination. By recording the daily affect and events each participant experienced for two weeks, [PH20] specified the direction of the relationship between procrastination and negative affect (NA), which mainly include stress and anxiety. Noting that people reported more frequent procrastination following the days that they experience higher levels of NA and implementing a multilevel regression model, they found that NA predicted next-day procrastination and concluded that negative emotion is the motivator of procrastination behavior. Similarly, by using a structural equation model, Paechter and colleagues (2017) [PMM+17]

revealed that statistics anxiety led to higher procrastination in a larger sample. Though such rigorous calculations should be done in more diverse samples, there is already some evidence that indicates a direct causal effect of anxiety on procrastination.

On the contrary, a few researchers have arrived at a different conclusion that does not support such a causal effect of anxiety on procrastination. For example, Rabin and colleagues (2011) [RFNU11] demonstrated that anxiety was not a predictor of procrastination when including demographic variables like age, sex and ethnicity, a number of medical and psychiatric diseases or conditions, as well as additional variables like estimated IQ, depressive symptoms, neuroticism, and conscientiousness in the linear regression models. Similarly, although they confirmed the positive correlation between anxiety and procrastination, Haycock and colleagues (1998) [HMS98] also found that anxiety was not a predictor of procrastination when entering variables including gender, age, efficacy expectations, and anxiety into the regression model. In particular, both depression and self-efficacy beliefs may be closely related to anxiety as well as procrastination [KBM07] [NL20] [BMA+16]. This suggests that there may not be a unique relationship between anxiety and procrastination and highlights the need for examining the potential role of other variables, like depression and efficacy expectations, simultaneously and interpreting anxiety in the context of its relationship with those variables.

2.2.1 Evidence of Anxiety as a Mediator Between Procrastination and Other Factors

Currently, there is relatively more research that characterizes anxiety as a mediator between procrastination and other psychological factors, but the results are mixed. One of the most promising findings is the mediating role of stress and anxiety in the relationship between time perspective and procrastination. A meta-analysis that contained over four thousand participants showed that procrastination is negatively correlated with future time perspective yet positively correlated with present time perspective [M.14]. Further, it is demonstrated that stress and positive affect (PA) partially mediated the relationship between future time perspective and procrastination [M.14]. It is particularly noteworthy that stress was negatively correlated with future time perspective and positively associated with procrastination [M.14]. These results suggest that procrastinators are cognitively biased to focus less on the future, and that this is partially due to stress. It is clear that stress is closely connected to the level of anxiety since anxiety can actually be seen as a reaction or an integral of stress [AoAAnd]. Further, it is found that anxiety symptoms are closely associated with negative past and fatalistic present time perspective, rather than a future perspective [KLMSD+19]. Therefore, it can be concluded that people with a future time perspective probably experience less anxiety and thus less procrastination. These results are highly consistent with the idea of viewing procrastination in the context of individual time perspectives, implying a possible mechanism or a more fundamental cause of the relation between anxiety

and procrastination.

Other findings have also underlined the key role of time perspective in connecting anxiety and procrastination together and explaining the effect of other psychological factors. For instance, it is found that lower resilience leads to procrastination both directly and indirectly; in particular, social anxiety serves as a partial mediator in the negative relationship between resilience and procrastination, as shown in a structural equation model analysis [KC19]. In other words, both resilience, the individual capacity to overcome or to adapt to adversity through social interactions [Che14], and social anxiety, which is closely related to negative beliefs about one's self, are highlighted to be important contributors to the development of procrastination. For possible explanations of those findings, according to [Fer1a], procrastinators tend to experience greater public self-consciousness and social anxiety; further, it is also known that people with anxiety disorders are much more inclined to have negative past time perspectives and therefore experience more repetitive negative thinking like rumination [ASWC18]. Such a biased time perspective makes people dwell on the past and continuously ruminate on themselves and the events that have already happened, particularly focusing on the negative aspect; those people result in possessing negative self-efficacy beliefs about themselves and thus experiencing excessive anxiety when making social interactions. Further, according to Vassilopoulos and Watkins (2009) [VW09], rumination indeed maintains those negative beliefs among those with social anxiety. Therefore, the mediation role of social anxiety here may be understood as a consequence of procrastinators' past-focused mode of thinking. In general, viewing anxiety as a mediator in the relationship between time perspective and procrastination provides critical insights for understanding the relationship between anxiety and procrastination.

In addition, anxiety is also found to be a mediator of the relationship between certain cognitive beliefs and procrastination. In particular, [DPMM$^+$17] investigated how positive and negative metacognitive beliefs about procrastination influence decisional procrastination. They concluded that anxiety partially mediated the relationship between positive beliefs and procrastination and fully mediated the relationship between negative beliefs and procrastination; moreover, both negative and positive beliefs predicted higher levels of anxiety. Put more simply, the cognitive perception of procrastination as a useful coping strategy or as an uncontrollable tendency to delay may indeed contribute to a higher level of worry about one's own performance. In this case, it can be speculated that such engagement in the maladaptive metacognitions may occupy many mental assets that should have been responsible for initiating or completing tasks and reinforce negative self-efficacy beliefs by causing more worries. Anxiety, consisting of negative beliefs, thoughts and emotions about one's abilities, intelligence or the likelihood of success [WM96] [DPMM$^+$17], is thus experienced and then results in the tendency of escaping from or postponing task execution.

Similarly, [CBM04] examined how anxiety might mediate the relation between locus of control and procrastination. Locus of control refers to the extent to which an individual believes that they have control over life events; under

this scenario, it reflects how students perceive the causes of their academic success or failure [CBM04]. It is found that students who are internally oriented experience less procrastination and debilitating test anxiety compared to students who are externally oriented [CBM04]. The result appears to be logical since students who believe in the strong connection between behavior and consequences and the effectiveness of exam preparation would feel less anxious and then procrastinate less compared to those who believe in luck, fate and chance. These results support the conceptualization of procrastination as a cognitive self-regulatory failure, resulted from certain maladaptive cognitions. After all, anxiety may serve as a key link that connects some of the people's fundamental cognitions to the induction of certain behaviors like procrastination.

One promising area for future research on anxiety as a mediator is specifying its role in the relationship between life satisfaction or other individual socio-economic conditions and procrastination. Beutel and colleagues (2016) [BMA+16] pointed out that procrastination is negatively correlated with overall life satisfaction and that specific individual conditions like lack of a partnership and unemployment are all predictors of procrastination. It can be speculated that lower life satisfaction that may be due to any of those predictive measures may lead to procrastination by causing excessive anxiety or perceived stress. Such a conclusion is not well-supported and few studies have examined this mediation role of anxiety in the relationship between individual living status and procrastination, but overall, there is now evidence suggesting an important role of life-condition-related anxiety and stress, having particularly large social and clinical implications.

2.2.2 Evidence of Mediators Between Anxiety and Procrastination

In addition to causing procrastination directly or serving as a mediator in other associations with procrastination, anxiety is also hypothesized to cause procrastination through mediators like counterfactual thinking. Counterfactuals are thoughts about what things might have been, particularly focusing on alternatives to past events; better alternatives are termed upward counterfactuals, while worse alternatives are termed downward counterfactuals [ER08] [MGSM93]. [M.04] suggested that procrastination is overall associated with avoiding upward counterfactuals (i.e., thinking about how things could have been better) and making more downward counterfactuals (i.e., thinking about how things could have been worse). When facing an anxiety-provoking task, procrastinators tend to avoid upward counterfactuals and think about how things may have been worse, in response to the anxiety and to restore mood. More importantly, Sirois highlighted the crucial role of "the involvement of a self-enhancement motive," particularly mood repair, in explaining procrastination and procrastinators' downward counterfactuals. [SP13] made a similar point asserting that procrastination is very closely related to short-term mood repair and emotion regulation. The findings are again consistent with how the two-factor model has conceptualized procrastination, in which procrastination functions to reduce anxiety and repair mood. Though there is currently a lack of evidence on

mediators in the relationship between anxiety and procrastination, it is probable that when people are under excessive anxiety or other unpleasant emotions, they think much more irrationally and pessimistically to avoid upward counterfactuals and prefer downward counterfactuals, which can be seen as an attempt to restore positive mood through escaping the unpleasant state and avoiding stressors. Such maladaptive cognition then leads to procrastination.

2.2.3 Evidence of Moderators of the Relation Between Anxiety and Procrastination

Several moderators of the relation between anxiety and procrastination have been implied. One of the most supported moderators is future time perspective. Empirically, it is suggested that future time perspective is negatively correlated with effort cost, avoidance intentions, and procrastination; it may buffer the causal effect of anxiety on procrastination by reducing effort cost and avoidance intentions [SJ19]. Theoretically, such speculation is consistent with the time perspective theory: people with a future time perspective may experience less rumination and put more emphasis on the big picture or long-term goals. Overall, time perspective could be an important moderator in the relation between anxiety and procrastination.

There is also evidence suggesting a moderating effect of age on the relation between anxiety and procrastination. In general, the research on the relation between age and procrastination are inconclusive [RFNU11], with some studies reporting negative correlations [BRM88] [PMAP00] [vE03] and others reporting no meaningful correlations [HMS98] [HWPB06]. In a recent study, [BMA$^+$16] assessed people's level of procrastination across life domains and demonstrated that lower age is a predictor of procrastination through multivariate analysis.

Additionally, [RFNU11] found that increased age was a significant predictor of academic procrastination, which is consistent with the prior result. Other studies have also underlined the negative association between age and procrastination [FBN$^+$17]. Further evidence is needed but it may be that the relation between anxiety and procrastination similarly depends on age and is stronger among younger people who procrastinate more. Being constantly immersed in intense academic settings, those young procrastinators oftentimes do not have better ways of regulating anxiety and coping with stress; also, both their inaccurate metacognitive beliefs about procrastination or themselves and their relatively immature executive function system may also contribute to such intentional or unintentional avoidance behavior. The conclusion is still speculative and research is needed to understand whether the relation between anxiety and procrastination is moderated by age.

In addition, findings of the role of gender in the relation between anxiety and procrastination are mixed. According to Beutel and colleagues (2016) [BMA$^+$16], male sex is found to be a predictor of procrastination. However, a considerable amount of studies has found that women are prone to experience more anxiety in general compared to males [PMM$^+$17]. Such inconsistencies suggest that there may be multiple pathways to procrastination other than

anxiety. It can be speculated that for women, excessive anxiety may be one of the few drivers of procrastination behavior; however, for men, they could end up procrastinating due to a variety of reasons, like poor executive function and bad time management skills, other than anxiety. Future studies may try to explain why such gender difference occurs with more theoretical and empirical support.

2.3 Evidence of Procrastination Leading to Anxiety

As for the opposite direction of the causal relationship, there is also evidence suggesting that procrastination can lead to anxiety. [LFF19] noted that teachers reported experiencing significant negative emotions when procrastinating and perceiving their dilatory behavior as stressful, pointing out that procrastination may be one of the common stressors that cause anxiety in teachers' lives. Such findings may have larger generalizability beyond the domain of the teaching profession and imply the possibility of procrastination being a general causal factor of anxiety. Furthermore, it is highlighted that Unintentional Procrastination Scale (UPS) scores were independent predictors of anxiety and depression (CITATION). Being a particularly strong marker of anxiety, unintentional procrastination may indeed cause anxiety and its related symptoms. In addition, [lRP19] specifically investigated media procrastination, a form of procrastination that involves delaying tasks due to maladaptive engagement in digital media use. They argued that such procrastination is a key contributor to negative affect, including stress and anxiety. To better understand the results, they explained that the involvement of off-task media use (OTMU) when facing certain academic tasks can be seen as media procrastination and is often in conflict with the achievement of long-term academic goals; such ongoing goal-conflict experience therefore leads to feelings like anxiety, which then perpetuates this cycle of self-regulation failure. This finding is consistent with the conceptualization of procrastination as a failure of self-regulation whereby students fail to effectively regulate their use of digital media deviates from academic work, resulting in negative affect. Overall, it is reasonable to speculate that procrastination may lead to anxiety, although more studies that are done under different settings and among different samples are needed.

Further, some pilot studies have proposed possible cognitive mechanisms between anxiety and procrastination. [J.09] showed that scores on the Criticism of Self and Behavior and Difficulty in Achievement questionnaire mediated the influence of trait procrastination on anxiety, confirming a causal effect of procrastination on anxiety. These results provide preliminary evidence of a causal relationship where procrastination leads to anxiety.

However, findings on whether procrastination leads to anxiety are currently somewhat mixed. In particular, Pollack and Herres (2020) [PH20] conducted a longitudinal study that measures the level of procrastination and daily negative affect (NA) for two weeks and examined whether procrastination leads to a higher level of NA in the following day, controlling for prior levels of affect (both PA and NA). They found that procrastination did not predict changes in NA and highlighted that the relationship between anxiety and procrastination is

not bidirectional. It is possible that changes in affect following procrastination may take more than one day to occur and that the reverse causal impact of procrastination to anxiety may be a relatively long-term effect. Future research may look at the relationship in more varied time frames to determine whether the result of the study is only limited to a day-to-day relationship between the variables and whether procrastination increases anxiety.

2.3.1 Evidence of Procrastination Predicting Anxiety Symptoms in Psychopathology

To specify the clinical value of an association between anxiety and procrastination, it is proposed that procrastination may play a key role in predicting psychopathology. [FBN+17] examined whether unintentional procrastination can be a marker of common mental disorders using the results of PHQ-9, which is used to assess depressive symptoms, and GAD-7, which is used to measure anxiety symptoms. They pointed out that UPS scores, which measure the level of unintentional procrastination, are a strong predictor of psychological conditions like depression and excessive anxiety. This implies possible relations between mental disorders and procrastination, especially unintentional procrastination, as well as the clinical value of characterizing the role of procrastination in psychological treatments. Further, it is demonstrated that procrastination is closely correlated with a variety of anxiety-related symptoms, including panic disorder, social anxiety disorder, and health anxiety [HPC18]. They also found that panic disorder symptoms in particular predicted procrastination. Those results are consistent with the assertion that anxiety and procrastination are closely associated and underline the potential clinical value of understanding procrastination and its relation with anxiety.

3 Conclusions

Based on the pattern of results reviewed above, it can be concluded that there is a strong correlation between anxiety and procrastination. Such a conclusion is consistent with several widely accepted conceptualizations of procrastination. The correlation is evident among samples of people of different ages, sexes, ethnicities, nationalities, social identities, and living environments. Although most of the findings focused on investigating anxiety and procrastination in the academic domain, the correlation is found in various settings, including academic and workplace performance, social interacting, bedtime decisions and teams with multiple members. In addition, there is recent neurobiological evidence that confirms such correlation and tries to explain it from an anatomical perspective [ZCX+20]. Further, some researchers have found a more complex relation between anxiety and procrastination and have highlighted the importance of some psychological factors like types of anxiety and some external factors like timing and task requirements in understanding the association. Although more research that examines different types of procrastination and anxiety un-

der more diverse social settings is needed to explain the nuanced inconsistencies, overall, the assertion that the correlation between anxiety and procrastination is well-supported.

To specify the direction of this possible causal relationship, it is suggested that anxiety can be a driver of procrastination. There are limited but well-designed studies that show a direct causal effect of anxiety on the development of procrastination. Moreover, most of the studies have demonstrated anxiety as a mediator of the relationship between procrastination and other psychological factors, such as resilience, time perspective and some metacognitive beliefs. Overall, it is found that anxiety plays a critical role in leading to the ultimate decision of delaying the initiation or completion of a task. Further, the relation between anxiety and procrastination may be mediated by factors like counterfactual thinking and moderated by factors like gender and age. However, evidence for potential mediators and moderators in the relationship between anxiety and procrastination is limited and more research is needed.

Overall evidence of a causal impact of procrastination on anxiety is inadequate and mixed, although some researchers have come to the conclusion that procrastination leads to anxiety. Some studies that implied a possible causal effect of procrastination on anxiety, and others have investigated and confirmed the effect in a limited setting or sample. Theoretically, as a self-regulatory failure, procrastination may lead to anxiety through causing goal-conflict experiences; empirically, it is noted that certain groups of procrastinators have reported that their behaviors are debilitating stressful and mediators like Criticism of Self and Behavior and Difficulty in Achievement are proposed. Although the evidence is preliminary, it is possible that procrastination leads to anxiety, forming a vicious cycle.

Although the field has great clinical potential, findings on the role of procrastination in predicting anxiety disorders are highly limited. Studies have suggested that procrastination is closely associated with a variety of mental health problems like depression, social anxiety disorder, and panic disorder. Specifically, some find procrastination to be a strong predictor of depression and anxiety symptoms. This is consistent with the conclusion that anxiety and procrastination are closely and strongly associated. Current research has agreed on the close relation between procrastination and psychopathology, but few have thoroughly examined whether and why procrastination is a marker of other clinical symptoms. Further research is needed to verify this prediction role of procrastination and to better understand the clinical value of procrastination and its relation with anxiety and psychopathology.

The results of this paper are largely consistent with most of the models about anxiety and procrastination yet have some nuanced inconsistencies with the others. As explained above, the AAA model and the two-factor model are both helpful for understanding the correlation between anxiety and procrastination; they highlight the mechanism of negative reinforcement in the process of procrastination being in line with the empirical results and the author's speculations. However, when it comes to the expectancy-value theory, a few confusions arise. As traditionally viewed, the two general sources of motivation are one's

expectation of success and the value one places on the goal; however, in the case of procrastinators, they are found to be less motivated to initiate tasks that are more valuable. It suggests the possibility that there may be other cognitive and emotional factors that also influence people's, especially procrastinators', motivation. Further, the time perspective theory fails to explain why engaging in future time perspective moderates the relation between anxiety and procrastination; a negative future perspective may as well lead to excessive worries about possible consequences of the present behavior and about uncertain future events, resulting in anxiety. Overall, the conceptualization of procrastination as an avoidance behavior is highly consistent with the conclusion that anxiety and procrastination are closely associated; future research is needed to examine how procrastination could fit in the framework of expectancy-value theory and time perspective theory.

4 Future Directions

Much of the research on procrastination and anxiety relies on simple correlation analyses. However, theory and empirical results suggest that procrastination is a complex phenomenon to which there are multiple psychological pathways. For example, there is shown to be a strong association between anxiety and procrastination, but there is also an association between depression and procrastination [BMA+16] [J.09]. We currently do not know whether these emotional factors have an overlapping connection to procrastination or whether there might be unique relationships between each type of symptoms and procrastination behavior. As a first step, researchers should assess multiple relevant factors and include them in more sophisticated models. Examination of the association between anxiety and procrastination is a promising and burgeoning field. In general, researchers should pay more attention to the influence of anxiety when looking at procrastination. Instead of only investigating the pure correlation between anxiety and procrastination, future research should also pay attention to potential causal relationships, whether procrastination leads to anxiety or whether anxiety leads to procrastination. Clarifying the nature of the relation would be very helpful in understanding procrastination, having large clinical and social implications. Particularly, it is important to specify the direction of the causal relationship and to determine whether the causal effect is bidirectional or unidirectional; identifying the fundamental cause would provide valuable insights into future treatments of both procrastination and anxiety. Specifically, longitudinal studies that are done under varied time frames and regression analysis that takes more relevant variables like depression and stress into account are needed to better identify a causal influence and to define the correlation. Building on the current basis that anxiety and procrastination are strongly associated, future research should try to better establish and characterize the causal relation.

Research is also needed to characterize the underlying mechanisms of the relationship between anxiety and procrastination. Knowing why anxiety and

procrastination are so closely correlated and through what processes do they influence one another would help conceptualize procrastination and identify other relevant psychological factors. Moreover, treatments can be developed to target those mediating variables. Future studies may try to conduct mediation analysis on potential variables like perfectionism, self-evaluation, self-compassion and level of rumination and worries. Further, more pieces of neurobiological evidence are necessary to help explain the biological mechanism of the correlation and to solidify or falsify the existing theories. This research area is still young and fresh as more evidence is required to make stronger and more compelling conclusions. Specifying the intermediate processes between anxiety and procrastination is the next step of understanding their relation.

Investigating moderators of the relation is another critical future direction. Possible moderators include age, gender, culture, socio-economic status and other cognitive factors like self-esteem and self-efficacy beliefs. Examining whether those factors are moderators helps decide whether the relationship exists across all populations or whether certain populations may experience it differently. Since most of the studies are done under the academic domain, it is also important to determine whether an academic or non-academic setting is a moderator of the relation; if so, this would limit the generalizability of the conclusions to students only. Moderators are important determinants of the applicability of all of the above findings. Further research is burdened to prove the generalizability of such a correlation between anxiety and procrastination.

5 Possible Implications

Elucidating the relation between anxiety and procrastination has significant implications. Noting that anxiety may be the cause as well as the result of procrastination, it helps people understand some of the psychological mechanisms of both anxiety and procrastination. For procrastinators, this could help them develop insights into the emotional factors that have driven their maladaptive behaviors and how they may get rid of procrastination by solving certain emotional problems. For clinicians, such new finding may shift their clinical focus from being entirely behaviorally-based to paying more attention to the emotional and cognitive components of the dilatory behaviors. Treatments that target anxiety or stressors or therapies that aim to change maladaptive cognitions may be helpful to solve procrastination. Thus, the conclusions of this paper may be beneficial for researchers, clinicians, and patients.

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Prioritizing missense mutations in BDNF to predict variant pathogenicity in Alzheimer's Disease (AD)

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Abstract

The number of elder people will double from 2000 to 2050. When older, people become more susceptible to neurodegenerative disorders. One gene that affects the phenotypes of neurodegenerative diseases is Brain-Derived Neurotrophic Factor, BDNF. BDNF is a protein with 5 different isoforms in the human Chromosome number 11. For this study, only missense mutations were analyzed. By limiting the analysis, we can develop strategies to predict potential pathogenic effects. These missense mutations could be one of the risk factors for developing neurodegenerative diseases. The bioinformatics tools MARRVEL, NCBI, Clustal Omega, STRING, and TMHMM 2.0 were used to analyze the mutations. We extracted missense mutations data, related parameters through Geno2MP, and added amino acid change, conserved up to, and an amino acid change position in the domain columns. In addition to this analysis, the structural analysis of the well known pathogenic mutations of BDNF were analyzed. With this data, the most potential damaging mutation was found by prioritizing characteristics of the mutations, and we determined it is V66M.

Keywords: Alzheimer's Disease, BDNF, missense, pathogenicity, Geno2MP, MARRVEL

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1 Purpose:

In finding the most pathogenic mutation of the known missense mutations, the goal is to raise awareness for those with specific mutations to be more careful so they can decrease their chances of developing AD or AD-like symptoms. The BDNF Val66Met polymorphism should be considered as a target for the novel Alzheimer's disease therapeutics.

2 Hypothesis:

If the val66met polymorphism occurs in the BDNF protein, then the protein will be most likely to cause Alzheimer's related symptoms among the mutations that we studied. We predict this because there have been previous studies that show that the V66M mutation causes reduced BDNF protein in the brain, thus causing Alzheimer's and Alzheimer's related symptoms.

3 Introduction

What is BDNF?

Brain-derived neurotrophic factor (BDNF), a molecule known to regulate neuronal survival and plasticity, is widely expressed in the developing and adult mammalian brain [ZYC08]. Alzheimer's is an illness that is a dynamic, unalterable mind issue that gradually demolishes memory and thinking aptitudes and, inevitably, the capacity to complete the most straightforward errands. In the vast majority with the sickness, side effects initially show up in their mid-60s [Fac19]. The disease is multifactorial, meaning that the disease mechanism has both genetics and epigenetics contribution [BDN20]. People's lifestyle, diet, and environment are also involved [Fac19]. Thus, while there are multiple genes that can increase the risk to develop this disorder, it does not guarantee that one will get the disorder. Due to the complexity, the disease mechanism is not fully understood, but one of the potential candidates to understand it is BDNF, or Brain Derived Neurotrophic Factor. It is a potential factor because there have been many studies [JB15] showing that the BDNF gene has caused an increased risk of older people developing some of the symptoms like those of Alzheimer's.

Effect of BDNF on Humans

The reduction of BDNF has shown to cause problems in elderly people [ZYC08]. These problems include short term memory loss, difficulty completing familiar tasks, and confusion with time or place, all common symptoms of Alzheimer's Disease. Some interventions like exercise or antidepressant administration, enhance the expression of BDNF in normal and pathological conditions. Thus, if one stays active, he or she can have a reduced risk of developing Alzheimer's [ZYC08].

The BDNF gene encodes a protein called a brain-derived neurotrophic factor, found in the brain and spinal cord, and localized in the hippocampus [BDN20]. This protein advances the endurance of nerve cells by assuming a job in the

development. In the brain, the BDNF protein capacities at the associations of neural connections, where cell-to-cell correspondence happens. The neural connections can change and adjust after some time considering understanding, a trademark called synaptic plasticity [JB15].

Effects of reduced BDNF:

Changes in BDNF articulation are related to both typical and neurotic maturing and mental sickness, in structures significant for memory procedures, for example, the hippocampus and parahippocampal regions. BDNF is urgent to learning and memory since it directs long term depression (LTD) and long-term potentiation (LTP), synaptic versatility, axonal growing, multiplication of dendritic arbour, and neuronal separation [JB15]. In addition, reduced BDNF messenger RNA and protein levels have been found in the hippocampus and other cortical areas in patients with AD. Thus, mutated BDNF proteins can lose functionality so there will be lowered protein levels and many long term ailments can arise.

Isoforms in BDNF:

In Brain Derived Neurotrophic Factor, there are five isoforms, with the longest being 247 amino acids long. Isoforms occur when a gene is trascripted from the same locus but are different in their transcription start sites. The sequences that are common among the five isoforms are the more important sequences because they are used every time. When modeling, we will look at the five isoforms and how they structurally change with the most influential mutations found from the bioinformatic analysis. This will help us understand which of the mutations found from the bioinformatic analysis are showing significant structural problems resulting in AD symptoms.

Mutations in BDNF:

To predict the effect of BDNF on AD, one approach could be analyzing missense alterations in the gene. In each human genome, there are polymorphisms, slight changes in genes that result in genetic variation, making each human genome distinct from others. An example of mutations in BDNF impacting Alzheimer's is the Val66Met polymorphism is implicated in synaptic excitation and neuronal integrity, and has previously been shown to moderate amyloid-β-related memory decline and hippocampal atrophy in preclinical sporadic Alzheimer's disease. From previous studies, the val66met polymorphism has influenced memory in people from ages 20-93 [ZYC08]. In studies of brain morphometry using structural magnetic resonance imaging (MRI) scans, Val/Met individuals have repeatedly been shown to have a smaller hippocampal volume relative to controls which are homozygous for Val allele [ZYC08]. In other studies, it is shown that Met66 carriers showed greater dysfunction in cognition, glucose metabolism and tau, with implications for clinical trial design [YYL16]. Finally, Val66Met also has shown an increased risk of developing AD in women, and Caucasian women, specifically [FMN].

Predicting effect of BDNF on Alzheimer's with Bioinformatics:

To see how this polymorphism and others affect the phenotype of Alzheimer's Disease, we used the bioinformatic tools MARRVEL (Geno2MP) and NCBI (protein database) to compare different alterations of BDNF gene to prioritize

more deleterious missense mutations. With this information, we can sort and filter the different characteristics of each mutation to better understand which mutations are more harmful than the others. When filtering, the more important characteristics can be prioritized.

To see how this polymorphism and others affect the phenotype of Alzheimer's Disease, we used the bioinformatic tools MARRVEL (Geno2MP) and NCBI (protein database) to compare different alterations of BDNF gene to prioritize more deleterious missense mutations. With this information, we can analyze the various scores that tell information about the mutations, like Grantham Score, PolyPhen2 Score, and Conserv Score. Grantham score predicts the effect of the polymorphisms based on the chemical properties, like polarity and molecular size, and PolyPhen2 Score is the probability that a mutation is harmful. A score below 50 for the Grantham score is considered more harmful and a score above .80 for PolyPhen2 is considered pathogenic. Also, Conserv Score tells how conserved a mutation is.

Predicting effect of BDNF on Alzheimer's with modeling:

Additionally, the structural effects of the mutation can be seen by modeling the proteins with and without the mutations using UniProt to get the FASTA sequence and PyMol modeller Server to model them. By looking at these alterations we tried to understand the causative reasons for the protein dysfunction.

In this study, we analyzed the structural features of the BDNF and predicted the potential pathogenic or non-pathogenic alleles reported in databases. We used bioinformatic tools, such as: TMHMM which a server to predict transmembrane domain in BDNF protein, Clustal Omega which can compare the FASTA sequences of BDNF from different species, STRING to see proteins interacting with BDNF, and Geno2MP in MARRVEL to extract and compare the missense mutations in BDNF. Once we found what was the most harmful mutation from the bioinformatic analysis, we used the Swiss model server in order to model the proteins to see the structural changes that occurred because of the mutations. In finding the most pathogenic mutation of the known missense mutations, the goal is to raise awareness for those with specific mutations to be more careful so they can decrease their chances of developing AD or AD-like symptoms.

4 Materials and Methods:

A Computer with high speed internet access and online Kinematics tools were required.

4.1 MARRVEL/Geno2MP

Individuals with a missense mutation in the BDNF/BDNF-AS gene can be found using Geno2MP (2020). With this data, an excel sheet was made and the columns, amino acid change, hydrophilic/hydrophobic change, significance, and conservation were added. Then, with the amino acid change, a hydrophilic/hydrophobic

change can be found by seeing if it changed from a hydrophobic protein to a hydrophilic protein, vise versa, or stayed the same structure/chemistry/property. If the property stayed the same, the change is not significant. If the structure did change radically, then it is significant. - Find Individuals with a missense mutation in the BDNF/BDNF-AS gene using Geno2MP (2020)

- Create an excel sheet with the columns amino acid change, hydrophilic/hydrophobic change, significance, and conservation

- With the amino acid change, a hydrophilic/hydrophobic change can be found by seeing if it changed from a hydrophobic protein to a hydrophilic protein, vise versa, or stayed the same.

- Check the structure; If there is a change then it is significant otherwise it is not significant. Check for Grantham score, gerpscore, and PolyPhen2 score.

4.2 Missense mutation positioning in NGF Domain

Proteins have domains which are amino acids generating functional regions in the protein. If there is a mutation in a functional domain, it is expected that this mutation might affect the protein function. To interpret whether the amino acid changes negatively affect the protein function we need to know the positions of these changes. We used MARRVEL/DIOPT 7.1 interphase to know the NGF domain (amino acids 212-329) of the isoform 'NP001137282.1 [MMB19]. The data was used from Geno2MP is for the isoform sp|$P23560.1$|. NGF domain was found manually in the isoform sp|$P23560.1$| as it is the analyzed isoform in Geno2MP. NCBI was used to have FASTA amino acid sequences of these two isoforms and the NGF region was detected after having alignment from Clustal Omega. Amino acids were counted, and changes were checked whether they are in the NGF domain or close to the domain.

- Download FASTA amino acid sequences of the isoform sp|$P23560.1$| from NCBI

- Find NGF domain manually in the isoform sp|$P23560.1$| using data collected from Geno2MP in step 4.1

4.3 Analysing missense alleles for conservation/position

To determine the severity of a mutation, criteria such as gerpscore, grantham score, conservation of amino acids and pathogenicity prediction from Geno2MP were used. Using Table 1, the several strategies were applied. For example, for strategy 1 we applied sorting/filtering in the order gerp score biggest to smallest, pathogenicity, important change II. To apply this strategy, we first sorted the gerpcores from highest to lowest. Then, Grantham scores are filtered as higher 100. By filtering the important traits by following different strategies, the most likely damaging mutation can be found. We tried different strategies to get the most possible damaging alterations and to test our approaches.

4.4 Analyzing secondary structure changes in Polymorphisms

1. Using www.Uniprot.org, collect the data for BDNF Natural variant P23560
2. DOPE scores were found for all of the known missense mutations
3. The mutations with the least DOPE scores were T2I, V66M, Q75H, M122T, R125M, and R127L.
4. Preparing file Multiple Sequence Alignment
   - Copy the FASTA format sequence of all 5 isoforms in text document
   - The fasta format of BDNF gene isoforms paste into the large text box in SOPMA and submit to get the results.
5. Homology modeling/ tertiary structure prediction
   - Use modeller software to modelle Structures
   - BLAST was performed and 3QB5 was selected as target
   - Structures were modelled by running Python script
   - Structures with least DOPE score were selected for superimposing
   - The reference structure and modelled structure were imported to PyMol and commands were performed to superimpose the two structure

5 Results

5.1 MARRVEL/Geno2MP

5.1.1 BDNF Missense mutations reported in Geno2MP

There are 25 missense mutations reported. The data comes with many characteristics like gene information (Chr:Pos, Alleles) and protein information (Protein change, amino acid change, and significance) as well as pathogenicity prediction. Here we tried to improve that pathogenicity prediction and apply an approach that we can filter missense variants more specific.

5.1.2 Prioritizing the most pathogenic variants with 2 different strategies

Strategy 1: In this strategy, we sorted and filtered the table based on gerp-score biggest to smallest, pathogenicity, important change II.
Strategy 2: In this strategy, we sorted and filtered the table based on polyPhen2 score → pathogenicity → Grantham score.

5.2 5 missense alleles were found in NGF domain of BDNF

As shown in Figure 1, the 2 isoforms have the same domains, but the coordinates are different. From amino acids 83-329 in the long isoform, the sequence is

repeated in the short isoform. In addition, the NGF domain can be found from the amino acids 212-329. This means that 5 of the mutations are in the NGF domain.

5.3 Conservation of mutated amino acids in Isoforms

Conservation is an important feature for an amino acid. Throughout evolution it is observed that essential amino acids are conserved among organisms for the proteins which have similar functions. We checked BDNF protein and tested conservation of amino acids which carry missense mutations. The Clustal Omega comparing the eight FASTA sequences of the isoforms shows which amino acids are conserved among different isoforms. The number of isoforms that are conserved of a specific amino acid location can be used to determine if a mutation is conserved or not. The mutation that occurs at the 66th and 120th position, V66M and A120T, is conserved in isoforms 1, 7, 4, 5, and 6. The mutations that occur at the 144th position, and I144T. The amino acids that are conserved in all species are favored over others when analyzing the data.

5.4 Secondary and tertiary structural analysis

The Root Mean Square Deviation (RMSD) of two aligned structures indicates their divergence from one another. In Pymol RMSD will be printed as RMS and the units are Angstroms. Pymol shows the structure changes in the mutated protein as cyan and the wild type protein in green. T2I shows no significant structural changes, and as a RMS score of 0.233.

V66M shows a significant structural change because of how the sticks differ where Figure 4 has the protein structure highlighted. Additionally, this mutation also had a RMS score 0.364, the highest among the mutations. Therefore, based on our structural analysis, the most pathogenic missense mutation in BDNF is the Val66Met mutation.

Homology modeling/ tertiary structure prediction

6 Data Analysis:

Alzheimer's Disease is one of the common neurodegenerative diseases and is currently the sixth leading cause of death [Fac19]. It affects mostly elderly people and makes them dependent on caregivers. There is no cure and the disease mechanism is not completely understood. BDNF is one of the potential players in the disease mechanism [Fac19]. BDNF promotes the survival and differentiation of selected neuronal populations of the peripheral and central nervous systems. Therefore, a decrease in BDNF protein in the brain can result in AD-like symptoms. There are several missense mutations reported in the Geno2MP database generated by the human genome project. Missense mutations may or may not affect protein function. If there is a missense mutation generating dysfunctional protein this could increase the risk of developing AD or cause some other detrimental symptoms. Here we showed that bioinformatic analysis could help us to understand and prioritize some of these mutations for future research. In doing this research, we have found that based on our analysis, V66M was the most pathogenic mutation. This was determined by focusing on the chemical structure and nature of the protein and finding which amino acid changes were significant, conserved and in the NGF domain, and thus the effect on the secondary and tertiary structure. We tried different strategies to have the best potential prediction. With these findings, we predict that those with a genetic history of these pathogenic mutations could be in the risk of developing AD or AD-like symptoms. There are no reported cases diagnosed with AD and carrying those mutations. Our prediction is based on having a dysfunctional protein which eventually could lead to neurodegeneration and AD mechanism or similar outcomes. However, we cannot be sure without experiments which test the effect of the mutation in vivo.

Once we can define the most pathogenic mutations, we will have a better understanding of the disease mechanism. Since the amino acid changes cause alterations in the protein's property, the cause of Alzheimer's disease can be found on a molecular level and this could help us understand the heterogeneity

of the disease.

7 Conclusion

AD is one of the mysterious diseases that we need to solve. Finding a cure for the disease is based on the knowledge we have about disease mechanisms. Here we tried to develop a strategy based on chemical changes in BDNF protein due to missense mutations in the gene. We extracted data from MARRVEL. The chromosome position (Chr:Pos), alleles, gene, annotations, protein change, hydrophilic/hydrophobic change, significance, conservation in other species, NGF domain, and pathogenicity was found by using the tools Geno2MP/MARRVEL, Clustal Omega, String, ClinVar, and NCBI. After gathering all the data (Table 1), the most pathogenic mutations were found by sorting and filtering for the strategies we defined in the Results (3.6). Results showed that like what is stated in the hypothesis, the most pathogenic mutations was V66M based on possibly having a dysfunctional protein which eventually could lead neurodegeneration and AD mechanism or similar symptoms. However, there are other pathogenic mutations and thus we can analyze missense variants for their pathogenicity to help us understand disease mechanisms. This can help us show what mutations have an effect on Alzheimer's Disease or AD related symptoms (6, 7). Although having this mutation cannot be changed, individuals can still not develop Alzheimer's Disease or AD-like symptoms. This could be either due to their environment, diet, life standards, and mental activities or the complexity of the AD mechanism. We are not claiming that carrying one pathogenic variant could lead AD alone. However, it would be beneficial to consider studying potential pathogenic variants to understand the disease mechanism.

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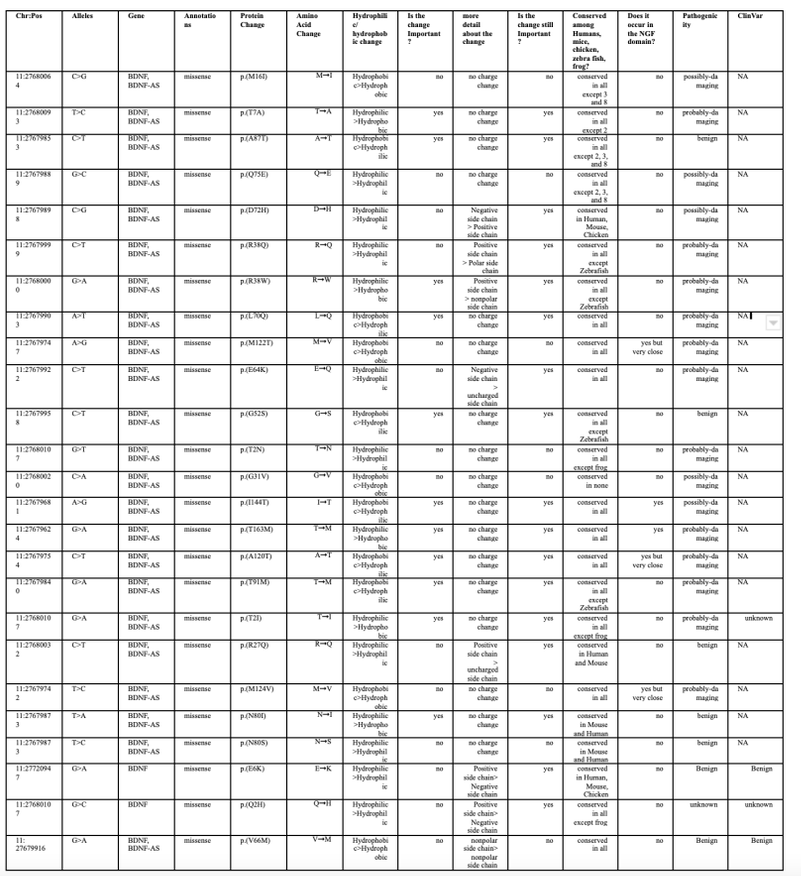

Chr:Pos	Alleles	Gene	Annotations	Protein Change	Amino Acid Change	Hydrophilic/ hydrophobic change	Is the change Important ?	more detail about the change	Is the change still Important ?	Conserved among Humans, mice, chicken, zebra fish, frog?	Does it occur in the NGF domain?	Pathogenicity	ClinVar
11:27680064	C>G	BDNF, BDNF-AS	missense	p.(M16I)	M→I	Hydrophobic>Hydrophobic	no	no charge change	no	conserved in all except 3 and 8	no	possibly-damaging	NA
11:27680093	T>C	BDNF, BDNF-AS	missense	p.(T7A)	T→A	Hydrophilic>Hydrophobic	yes	no charge change	yes	conserved in all except 2	no	probably-damaging	NA
11:27679853	C>T	BDNF, BDNF-AS	missense	p.(A87T)	A→T	Hydrophobic>Hydrophilic	yes	no charge change	yes	conserved in all except 2, 3, and 8	no	benign	NA
11:27679889	G>C	BDNF, BDNF-AS	missense	p.(Q75E)	Q→E	Hydrophilic>Hydrophilic	no	no charge change	no	conserved in all except 2, 3, and 8	no	possibly-damaging	NA
11:27679898	C>G	BDNF, BDNF-AS	missense	p.(D72H)	D→H	Hydrophilic>Hydrophilic	no	Negative side chain > Positive side chain	yes	conserved in Human, Mouse, Chicken	no	possibly-damaging	NA
11:27679999	C>T	BDNF, BDNF-AS	missense	p.(R38Q)	R→Q	Hydrophilic>Hydrophilic	no	Positive side chain > Polar side chain	yes	conserved in all except Zebrafish	no	probably-damaging	NA
11:27680000	G>A	BDNF, BDNF-AS	missense	p.(R38W)	R→W	Hydrophilic>Hydrophobic	yes	Positive side chain > nonpolar side chain	yes	conserved in all except Zebrafish	no	probably-damaging	NA
11:27679903	A>T	BDNF, BDNF-AS	missense	p.(L70Q)	L→Q	Hydrophobic>Hydrophilic	yes	no charge change	yes	conserved in all	no	probably-damaging	NA
11:27679747	A>G	BDNF, BDNF-AS	missense	p.(M122T)	M→V	Hydrophobic>Hydrophobic	no	no charge change	no	conserved in all	yes but very close	probably-damaging	NA
11:27679922	C>T	BDNF, BDNF-AS	missense	p.(E64K)	E→Q	Hydrophilic>Hydrophilic	no	Negative side chain > uncharged side chain	yes	conserved in all	no	probably-damaging	NA
11:27679958	C>T	BDNF, BDNF-AS	missense	p.(G52S)	G→S	Hydrophobic>Hydrophilic	yes	no charge change	yes	conserved in all except Zebrafish	no	benign	NA
11:27680107	G>T	BDNF, BDNF-AS	missense	p.(T2N)	T→N	Hydrophilic>Hydrophilic	no	no charge change	no	conserved in all except frog	no	probably-damaging	NA
11:27680020	C>A	BDNF, BDNF-AS	missense	p.(G31V)	G→V	Hydrophobic>Hydrophobic	no	no charge change	no	conserved in none	no	possibly-damaging	NA
11:27679681	A>G	BDNF, BDNF-AS	missense	p.(I144T)	I→T	Hydrophobic>Hydrophilic	yes	no charge change	yes	conserved in all	yes	possibly-damaging	NA
11:27679624	G>A	BDNF, BDNF-AS	missense	p.(T163M)	T→M	Hydrophilic>Hydrophobic	yes	no charge change	yes	conserved in all	yes	probably-damaging	NA
11:27679754	C>T	BDNF, BDNF-AS	missense	p.(A120T)	A→T	Hydrophobic>Hydrophilic	yes	no charge change	yes	conserved in all	yes but very close	probably-damaging	NA
11:27679840	G>A	BDNF, BDNF-AS	missense	p.(T91M)	T→M	Hydrophobic>Hydrophilic	yes	no charge change	yes	conserved in all except Zebrafish	no	probably-damaging	NA
11:27680107	G>A	BDNF, BDNF-AS	missense	p.(T2I)	T→I	Hydrophilic>Hydrophobic	yes	no charge change	yes	conserved in all except frog	no	probably-damaging	unknown
11:27680032	C>T	BDNF, BDNF-AS	missense	p.(R27Q)	R→Q	Hydrophilic>Hydrophilic	no	Positive side chain > uncharged side chain	yes	conserved in Human and Mouse	no	benign	NA
11:27679742	T>C	BDNF, BDNF-AS	missense	p.(M124V)	M→V	Hydrophobic>Hydrophobic	no	no charge change	no	conserved in all	yes but very close	probably-damaging	NA
11:27679873	T>A	BDNF, BDNF-AS	missense	p.(N80I)	N→I	Hydrophilic>Hydrophobic	yes	no charge change	yes	conserved in Mouse and Human	no	benign	NA
11:27679873	T>C	BDNF, BDNF-AS	missense	p.(N80S)	N→S	Hydrophilic>Hydrophilic	no	no charge change	no	conserved in Mouse and Human	no	benign	NA
11:27720947	G>A	BDNF	missense	p.(E6K)	E→K	Hydrophilic>Hydrophilic	no	Positive side chain>Negative side chain	yes	conserved in Human, Mouse, Chicken	no	Benign	Benign
11:27680107	G>C	BDNF	missense	p.(Q2H)	Q→H	Hydrophilic>Hydrophilic	no	Positive side chain>Negative side chain	yes	conserved in all except frog	no	unknown	unknown
11:27679916	G>A	BDNF, BDNF-AS	missense	p.(V66M)	V→M	Hydrophobic>Hydrophobic	no	nonpolar side chain>nonpolar side chain	no	conserved in all	no	Benign	Benign

Figure 1: Missense mutations of BDNF and BDNF-AS reported in the Geno2MP database. 25 missense mutations were found in the Geno2MP database and analyzed for their effect on protein nature. In this table we have information about chromosome position (Chr:Pos), Alleles, gene, annotations, protein change, hydrophilic/hydrophobic change, significance, conservation in other species, NGF domain, and Pathogenicity.

Alleles	rsID	Gene	cDNA Change	Protein Change	Hydrophilic/ hydrophobic change	more detail about the change	still Important?	In the NGF domain?	conserv Score	Gerpscore	polyphe n2var	Grantham score	Pathogenicity
C>G	NA	BDNF,BDNF-AS	c.48G>C	p.(M16I)	Hydrophobic>Hydrophobic	sulfur > no sulfur	yes	no	1	6.17	0.805	43	possibly-damaging
T>C	NA	BDNF,BDNF-AS	c.19A>G	p.(T7A)	Hydrophilic>Hydrophobic	no charge change	yes	no	1	6.17	0.994	10	probably-damaging
C>G	NA	BDNF,BDNF-AS	c.214G>C	p.(D72H)	Hydrophilic>Hydrophilic	Negative > Positive	yes	no	1	6.16	0.789	29	possibly-damaging
G>A	NA	BDNF,BDNF-AS	c.112C>T	p.(R38W)	Hydrophilic>Hydrophobic	Positive > nonpolar	yes	no	1	6.16	0.999	43	probably-damaging
A>G	NA	BDNF,BDNF-AS	c.365T>C	p.(M122T)	Hydrophobic>Hydrophobic	sulfur > no sulfur	yes	yes	1	6.07	0.98	21	probably-damaging
G>A	NA	BDNF,BDNF-AS	c.488C>T	p.(T163M)	Hydrophilic>Hydrophobic	no charge change	yes	yes	0.996	6.08	0.997	45	probably-damaging
G>C		BDNF		p.(Q2H)	Hydrophilic>Hydrophilic	Positive > Negative	yes	no				24	unknown
G>A	rs6265	BDNF, BDNF-AS	C>T	p.(V66M)	Hydrophobic>Hydrophobic	no sulfur > sulfur	yes	no			0.822	21	Risk-Factor

Figure 2: Table 2: Grantham Score → Is the change important II. For this strategy, we started with filtering all Grantham score values higher than 50 out. Then, we chose only yes in the "is the change still Important?" column. From this filtering, we obtained these 8 mutations.

Alleles	rsID	Gene	cDNA Change	Protein Change	Hydrophilic/ hydrophobic change	more detail about the change	still Important?	In the NGF domain?	conserv Score	Gerpscore	polyphe n2var	Grantham score	Pathogenicity
T>C	NA	BDNF,BDNF-AS	c.19A>G	p.(T7A)	Hydrophilic>Hydrophobic	no charge change	yes	no	1	6.17	0.994	10	probably-damaging
C>T	NA	BDNF,BDNF-AS	c.259G>A	p.(A87T)	Hydrophobic>Hydrophilic	no charge change	yes	no	1	6.16	0.32	81	benign
C>G	NA	BDNF,BDNF-AS	c.214G>C	p.(D72H)	Hydrophilic>Hydrophilic	Negative > Positive	yes	no	1	6.16	0.789	29	possibly-damaging
G>A	NA	BDNF,BDNF-AS	c.112C>T	p.(R38W)	Hydrophilic>Hydrophobic	Positive > nonpolar	yes	no	1	6.16	0.999	43	probably-damaging
A>G	NA	BDNF,BDNF-AS	c.365T>C	p.(M122T)	Hydrophobic>Hydrophobic	no charge change	no	yes	1	6.07	0.98	21	probably-damaging
C>A	NA	BDNF,BDNF-AS	c.92G>T	p.(G31V)	Hydrophobic>Hydrophobic	no charge change	no	no	1	5.25	0.735	101	possibly-damaging
A>G	NA	BDNF,BDNF-AS	c.431T>C	p.(I144T)	Hydrophobic>Hydrophilic	no charge change	yes	yes	1	6.08	0.555	81	possibly-damaging
G>A	NA	BDNF,BDNF-AS	c.488C>T	p.(T163M)	Hydrophilic>Hydrophobic	no charge change	yes	yes	0.996	6.08	0.997	45	probably-damaging
T>A	rs37038	BDNF,BDNF-AS	c.239A>T	p.(N80I)	Hydrophilic>Hydrophobic	no charge change	yes	no	0	-1.24	0.242	58	benign
T>C	rs37038	BDNF,BDNF-AS	c.239A>G	p.(N80S)	Hydrophilic>Hydrophilic	no charge change	no	no	0	-1.24	0.004	149	benign
G>A	rs6265	BDNF, BDNF-AS	C>T	p.(V66M)	Hydrophobic>Hydrophobic	nonpolar > nonpolar	no	no			0.822	21	Risk-Factor

Figure 3: PolyPhen2 score → pathogenicity → Grantham score. For this strategy, we started with filtering all PolyPhen2 score values less than 0.8 out. Then, we filtered the pathogenicity column to only have probably damaging, risk factor, and unknown. Finally, filtering out all Grantham score values higher than 50 out. From this filtering, we obtained these 11 mutations.

Long isoform
>NP_001137282.1 brain-derived neurotrophic factor isoform e [Homo sapiens]
MCGATSFLHECTRLILVTTQNAEFLQKGLQVHTCFGVYPHASVWHDCASQKKGCAVYL
HVSVEFNKLIPENGFIKFHQVRRVMTILFLTMVISYFGCMKAAPMKEANIRGQGGLAYPG
VRTHGTLESVNGPKAGSRGLTSLADTFEHVIEELLDEDQKVRPNEENNKDADLYTSRVM
LSSQVPLEPPLLFLLEEYKNYLDAANMSMRVRRHSDPARRGELSVCDSISEWVTAADKK
TAVDMSGGTVTVLEKVPVSKGQLKQYFYETKCNPMGYTKEGCRGIDKRHWNSQCRTT
QSYVRALTMDSKKRIGWRFIRIDTSCVCTLTIKRGR

>sp|P23560.1|BDNF_HUMAN RecName: Full=Brain-derived neurotrophic factor; Short=BDNF; AltName: Full=Abrineurin; Contains: RecName: Full=BDNF precursor form; Short=ProBDNF; Flags: Precursor
MTILFLTMVISYFGCMKAAPMKEANIRGQGGLAYPGVRTHGTLESVNGPKAGSRGLTSL
ADTFEHVIEELLDEDQKVRPNEENNKDADLYTSRVMLSSQVPLEPPLLFLLEEYKNYLDA
ANMSMRVRRHSDPARRGELSVCDSISEWVTAADKKTAVDMSGGTVTVLEKVPVSKGQL
KQYFYETKCNPMGYTKEGCRGIDKRHWNSQCRTTQSYVRALTMDSKKRIGWRFIRIDTS
CVCTLTIKRGR

Figure 4: NGF domain of two BDNF isoforms. NP_001137282.1 is isoform e of human and sp|P23560.1| form is used by Geno2MP.

Figure 5: Clustal Omega comparison of BDNF in Isoform 1-8. The figure shows the alignment of 8 different isoforms of the BDNF protein. The figure shows a symbol, either a star, color, a period, or nothing below. A star signifies an amino acid that is the same among all of the species, a colon means it is similar in all but one, and a period means it is random. In addition, when there is a dash in the sequence, that means that part of the sequence is not there.

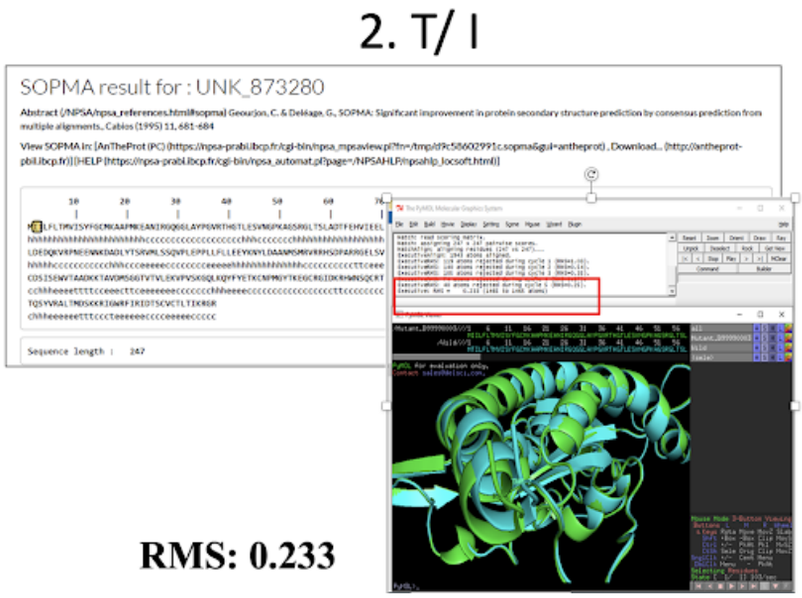

Figure 6: Sopma results of missense mutation T2I with sequence length 247. The figure shows the RMS of 0.233 with Superimpose of the two structures in Pymol and mutated protein as cyan and the wild type protein in green.

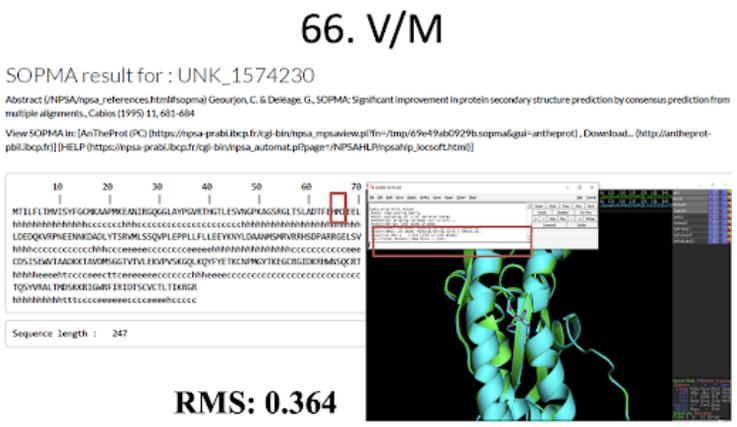

Figure 7: Sopma results of missense mutation V66M with sequence length 247. The figure shows RMS of 0.364 with Superimpose of the two structures in Pymol and mutated protein as cyan and the wild type protein in green.

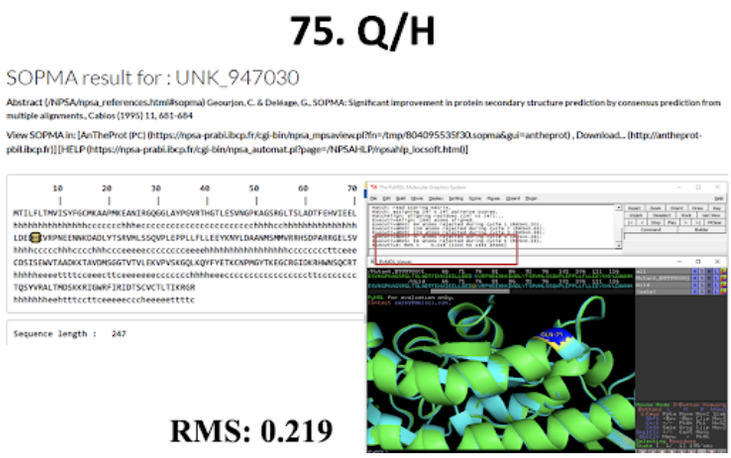

Figure 8: Sopma results of missense mutation Q75H with sequence length 247. The figure shows RMS of 0.219 with Superimpose of the two structures in Pymol and mutated protein as cyan and the wild type protein in green.

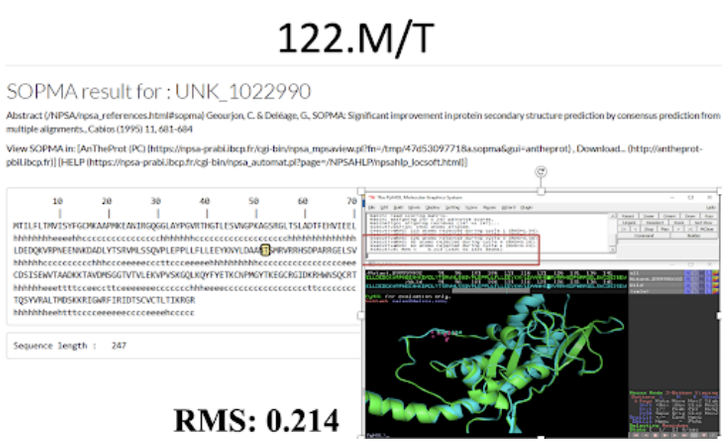

Figure 9: Sopma results of missense mutation M122T with sequence length 247. The figure shows RMS of 0.214 with Superimpose of the two structures in Pymol and mutated protein as cyan and the wild type protein in green.

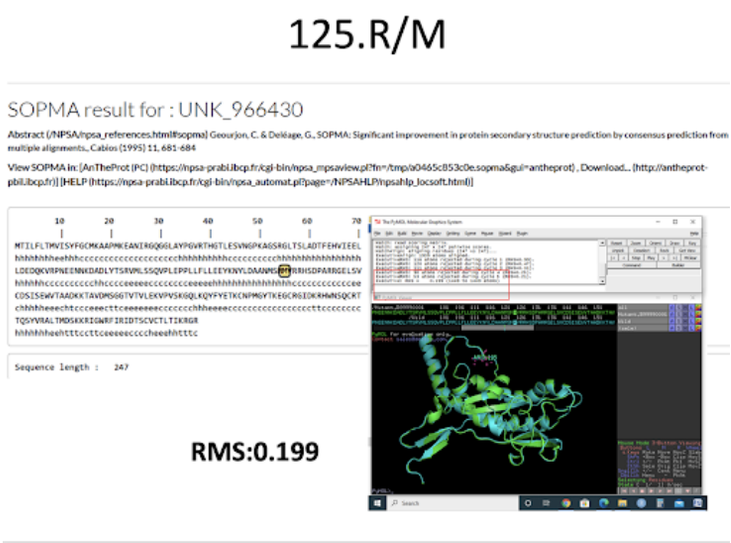

Figure 10: Sopma results of missense mutation R125M with sequence length 247. The figure shows RMS of 0.199 with Superimpose of the two structures in Pymol and mutated protein as cyan and the wild type protein in green.

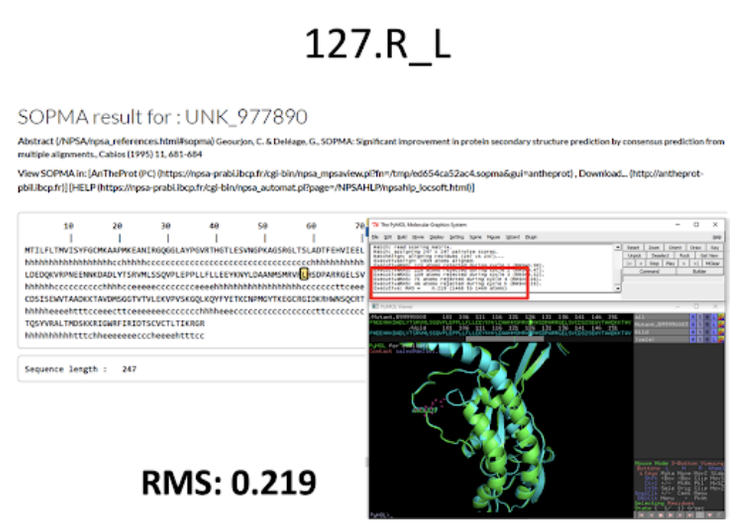

Figure 11: Sopma results of missense mutation R127L with sequence length 247. The figure shows RMS of 0.219 with Superimpose of the two structures in Pymol and mutated protein as cyan and the wild type protein in green.

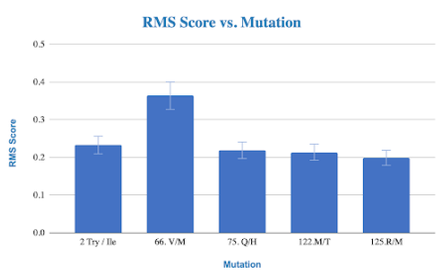

Figure 12: Represents RMS score and Mutations with error bars.

A Perspective on Novel Proteins

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Abstract

Proteins facilitate many necessary processes for life in our bodies and in nature. Since the late 1900s, scientists have been able to design novel proteins, which are proteins not found in nature. These novel proteins have shown to possess more desirable properties than proteins found in nature, and thus can be used to benefit society. They are usually made by modelling their structure computationally first, then synthesized using techniques such as recombinant methods. Two major methods of modelling are template modelling, in which there is a known template such as the protein sequence, or de novo, in which the protein structure is built from the bottom up. With modelling, the goal is to find a thermodynamically stable conformation that the protein folds into. However, designing proteins is not easy, and among many of the challenges is Levinthal's paradox, which states there are too many protein conformations to sample. Despite these challenges, there are countless areas where novel proteins can be used, and this paper details some uses of these proteins in the medical field and industrial field.

1 Introduction

Proteins are natural biological molecules that perform many essential functions, such as cellular division, in our bodies and in nature. Considering that proteins are made in nature, it is remarkable that scientists are capable of designing proteins. Their main goal is to create proteins that have customized functions and in fact, research into protein design has been done since the 1900s. Among the first synthetic proteins created was ribonuclease, and this particular protein, which plays important roles in RNA metabolism, was designed by Ralph F. Hirschmann and his team [Hev09]. As protein design advanced over the years, scientists have been able to create novel proteins, which are completely new proteins that are not found in nature. This paper will discuss the reasons for making novel proteins, what to consider before making novel proteins, the methods used to make novel proteins and its challenges, and the applications of novel proteins.

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2 Novel Proteins

Novel proteins can either be made from scratch, or based on a similar protein [n.andb], and to make these novel proteins, scientists first identify the target protein structure (their desired protein structure). The protein can then be synthesized, for instance, by expanding the genetic code and assigning non-canonical amino acids to a stop codon or having a tRNA carry it with another amino acid [PDRK12]. In addition, recombinant methods may also used and organisms such as *Escherichia coli* (*E. coli*) can be used to mass produce the proteins. Other approaches to synthesizing proteins include directed evolution [RECZ12], in which the protein is modified to acquire the desired properties.

As it turns out, novel proteins have many advantages, such as performing functions as well as or even better than existing proteins. For example, an artificial enzyme was able to catalyze CO_2 hydration with an efficiency comparable to some naturally occurring carbonic anhydrases and within 350-fold of the fastest isozyme, CAII [DeN]. In addition, scientists have more control when designing the functions of proteins because the conformations of natural proteins are only a subset of the possible conformations that proteins can have. Consequently, novel proteins can take on different conformations that may allow them to perform functions not found in nature [Bak19]. Ultimately, creating novel proteins allows scientists to have a better understanding of how proteins fold and their functions because they can alter a part of the protein such as its amino acid sequence and study the effects of the modification [MM05].

Even so, there are many things to consider in order to design novel proteins, particularly depending on whether the primary structure or the tertiary structure is used as the starting point when modelling protein structure. If beginning with primary structure, one must consider the protein folding problem - can a protein's structure be predicted from its amino acid sequence? Scientists also need to identify the target structure that they are aiming to create, or begin to design from a tertiary structure. To do this, they must contend with the inverse protein folding problem, or given a protein structure, are scientists able to identify the amino acid sequence that will fold into that structure?

2.1 Modelling Novel Proteins

A key idea when designing novel proteins is Anfisen's dogma, which states that the amino acid sequence determines the structure of the protein and that the protein's shape is the thermodynamically favorable structure [n.andd]. As a matter of fact, there are numerous protein modelling softwares such as Rosetta [n.andc] that are designed to generate a thermodynamically favorable structure for a protein. In general, proteins can be modelled based on the similarity of their tertiary structure, sequence (primary structure), or function with another protein. As such, the two ways to model proteins are template based modelling, in which an existing protein structure is used as a scaffold for modeling proteins,

and non-template based modelling (de novo), in which the model of the protein structure is generated from scratch [BBB20].

While the approach to modelling proteins can vary, there are some common basic steps. For template based modelling, a similar sequence is identified from a protein database such as The Protein Data Bank (PDB) [n.ande], and a criteria is designed for comparing the similarities between the target sequence and the template sequences. Afterwards, the sequences are aligned to start modelling. In a type of template based modelling called comparative modelling, or homology modelling, a 3D structure and an atom model of a target protein is built based on similar sequences [Fis10]. Another method, protein threading, models structures in which only similar protein folds are known [PX09].

For cases where a template does not exist, de novo modelling can be used. In this type of modelling, a target protein backbone (the primary sequence of amino acids) that will fold into the desired structure is identified. Then simulations are run and it follows different mathematical parameters and finds a thermodynamically favorable structure. After the protein samples many possible structural ensembles, the combinations of proteins are usually narrowed down, and the generated protein model is refined to resemble the native structure (the structure that the protein naturally folds into). In modelling protein structures, computational methods such as Monte Carlo Simulation, which uses random sampling to obtain a numerical value, are used very often. Another widely used method is molecular dynamics, in which Newton's laws are applied to track the movement of atoms. In general, these algorithms may be deterministic, in which the output is determined by the input or parameters, or stochastic, in which an answer may be determined randomly [KB19]. Then for selecting from these thermodynamically favorable structures and evaluating how close they are to the native structure, force fields such as physics based energy fields, which are governed by the laws of physics, and knowledge based energy functions, which are based on information from experimentally solved structures, are used [JLZ17].

2.2 Challenges in Modelling Novel Proteins

As one can imagine, modelling proteins is a complicated task and scientists may encounter many difficulties. One of the main problems is that protein modelling is time consuming. As stated in Levinthal's Paradox, there are too many possible conformations, which would take more time than the universe offers to sample [VM18].There are 20 amino acids, resulting in 2^n combinations for a protein with n number of amino acids, and with the current time steps (increments of time in the simulation), it is not feasible to run through all the combinations. Continuing on with challenges in modelling proteins, for template based modelling, sometimes there may not be an available template to use as a scaffold for modelling proteins and the accuracy of the modelling depends heavily on the similarities between the sequences. In addition, the force fields

used in de novo modelling may not be accurate and the shape outputted by the simulation may not resemble the actual protein shape in nature. Another issue is that the number of conformations the protein can sample may be limited by the energy levels in the simulation. Of course, there are other difficulties such as rotamer optimization [JMS00] and allosteric regulation that are not covered in this text [AH15].

One way to obtain more accurate models of proteins is to create more efficient algorithms or increase computational power. In particular, volunteers can be used to speed up the calculations by spreading the computational burden over many users. For example, volunteers can download the software Folding@Home [n.anda] and run simulations for protein folding on their own computer in the background. To address the inadequacies of the force fields, simulated annealing, which is raising the temperature of the simulation, can also be used to allow the protein to fold into more possible conformations [AH15].Furthermore, to address the challenge that the templates used in template modelling may only be distantly related, multiple templates may be used so that there are more overlapping sequences, which will provide more accurate results [Zha08].

3 Applications of Novel Proteins

There are countless areas that these novel proteins can be used after the protein structure is modelled and the protein is made, as proteins perform a variety of functions, such as digestion, transport, catalysis, contraction for muscles, storage, protection, and structural support [KAT19]. Proteins are especially relevant in biotechnology, which seeks to use biology to solve problems in the world. Some of the major fields in biotechnology that novel proteins are used in include the medical sector and the industrial sector.

3.1 Novel Proteins in the Medical Sector

Due to novel proteins, many new possibilities have been opened in fields such as immunology. Neoleukin-2/15 (Neo-2/15), developed by scientists at the University of Washington, is one example of a de novo therapeutic protein, aimed at targeting cancer without producing side effects such as toxicity. The protein was created using Rosetta and it resembles the cytokine interleukin-2 (IL-2), which controls the differentiation and homeostasis of both pro- and anti-inflammatory T cells by binding to receptors such as CD25 [RC18]. IL-2 is used in cancer treatment in the drug Proleukin, but IL-2 has a short window of effectiveness and it may cause severe damage such as capillary leak syndrome when high doses are needed because it may also affect healthy cells.

Neo-2/15, on the other hand, will not produce these side effects because it enables activation of on-target tumor-fighting cells without preferentially activating the off-target cells responsible for toxicity and immunosuppression. IL-2

functions by inducing the binding of two IL-2 cell-membrane receptors, IL-2β (IL-2Rβ) and the common-gamma (γ or IL-2Rγ) receptor, which form the IL-2R$\beta\gamma$ complex [TJR18]. Afterwards, a cascade of cell signaling is triggered in immune cells. However, some off-target cells have IL-2 alpha-subunits (IL-2Rα or CD25) that can bind with the other two membrane receptors to form IL-2R$\alpha\beta\gamma$ trimers, which have a greater affinity for binding to IL-2. Therefore, the off-target cells are affected more than the target cells. Fortunately, Neo-2/15 will not have this problem because the binding site and dependency of CD25 is eliminated, while the binding of IL-2R$\beta\gamma$ complex is still maintained.

Even still, creating novel therapeutic proteins has its difficulties, because as with any other drugs, it must be ensured that the protein does not provoke a severe immune response in a patient. In addition, the therapeutic proteins may not be stable if a natural protein is used as a starting conformation. This is because natural proteins themselves are not stable, and changes such as amino acid substitutions when designing the protein may cause the protein to coagulate. So far, Neo-2/15 has been found to elicit a low immune response, and with de novo modelling, scientists can alter the hydrophobic interactions and other areas to make the protein more stable. More proteins may be made based on the same methods used to create Neo-2/15 to treat many diseases such as autoimmune diseases. In autoimmune diseases, the body attacks its own cells as it views those cells forgein. But since Neo-2/15 resembles IL-2, which triggers regulatory T-cells that can suppress the immune system, proteins similar to Neo-2/15 may play a role in the development of a cure for autoimmune diseases [AQRS20].

In addition to their use in therapy, novel proteins can also be used to improve or create new vaccines. Vaccines such as the yearly influenza (flu) vaccines are crucial, and with novel proteins, David Baker's group and researchers at the National Institute of Allergy and Infectious Diseases' Vaccine Research Center (NIAID) are among those at the brink of creating a universal flu vaccine [Boy18] that may be effective for several years. A universal flu vaccine is important because flu strains rapidly mutate and it is difficult to predict which one will be more potent one year. The influenza strains are able to escape detection in the body because they change the shape of proteins on their surfaces called antigens. Usually, the body neutralizes antigens from foreign substances by producing proteins called antibodies binding to them. Vaccines exploit this idea and display the antigens from a specific virus to stimulate a patient's body to produce antibodies for the antigens. However, since influenza mutates rapidly, even if antibodies are created, it will not protect the body from the new strain.

The universal flu vaccine resolves this by displaying the antigens from various flu strains. The major antigen of influenza is hemagglutinin, which possesses a globular head domain that mediates receptor binding and a stalk domain at the membrane-proximal region [Boy18]. When creating the universal flu vaccine, scientists aim to target the stalk domain of hemagglutinin, a more conserved region. The globular head can be removed by chemical methods and then neu-

tralizing antibodies for the stalk domain can be created [Kra15]. A challenge to this is that the antibodies for the stalk domain may not be as effective as antibodies for the head. There are few antibodies for the stalk part because the stalk domain evolves slower than the head region. Mutations in the stalk do not spread rapidly and are therefore not usually detected [EKK18]. More research is needed but so far antibodies that target the stalk domain are promising.

Of course, having preventive measures to reduce the possibility of illness is optimal. Novel proteins such as fluorescent proteins can be applied in diagnostics as well. There are intrinsically fluorescent proteins, which become fluorescent after folding without addition of a fluorophore, and extrinsically fluorescent proteins that must bind an endogenous molecule or ligand to fluoresce. These fluorescent proteins can be used to visualize cells, tissues, and organs; to monitor division and migration of cells in development, transplantology, inflammation, and cancerogenesis; and to decipher neural circuits. However, it is uncertain if fluorescent proteins result in cellular toxicity because of the aggregation of the fluorescent proteins or the generation of free radicals due to the excitation of the fluorophores. There are other disadvantages, such as fluorescent proteins may not be bright enough [Jen12]. Also, when fluorescent proteins are tagged to other proteins to trace those proteins, fluorescent proteins may hinder other protein functions as fluorescent proteins are of a relatively big size.

Novel fluorescent proteins may overcome many of these challenges and in particular, David Baker's team and Barry Stoddard's team have developed a de novo fluorescent protein, similar to Green Fluorescent Protein (GFP), that can bind other molecules. Fluorescent proteins have a chromophore, which is the part that allows for fluorescence. Chromophores consist of about 220 to 240 amino acid residues which fold into a β-barrel formed by 11β-sheets that accommodate an internal distorted helix [DMCL10], and the researchers were able to model the β-barrels and allow them to bind to target ligands using Rosetta [JDB18]. This is a significant breakthrough because until recently, no β-barrel proteins were successfully modelled because β-strands tend to coagulate if they are not perfectly aligned [Str18]. Furthermore, it is difficult to customize the proteins to bind to a specific target of interest due to the many possible orientations of positions of a molecule in a protein cavity where ligands bind [LIM18].

The researchers sought to create properly folding β-barrels and identified that large local deviations in ideal β-strand twist were necessary to maintain continuous hydrogen bond interactions between strands in the β-barrels. With this new understanding, they were able to refine their methods to model the backbone, side chains, and other parts. And as some fluorescent proteins required binding to other molecules such as ligands to function, they used a new algorithm which rapidly modelled the different areas that ligands could bind to (for their experiment they designed it to bind to a compound called DFHBI). The novel protein that they were able to design was found to bind to DFHBI with great affinity. It also emitted greater fluorescence and was smaller than GFP [JDB18].

Fluorescent novel proteins such as the ones designed by Baker and Stoddard's teams may be able to address the challenges associated with natural fluorescent proteins to improve their usage.

3.2 Novel Proteins in the Industrial Sector

Besides the medical field, industry is another major sector that novel proteins can be used in. They can be used to make a variety of new materials, such as synthetic spider silk can be made, for example. Indeed, that is the goal of many companies such as the Kraig Biocraft Laboratories because spider silk is strong, elastic, thin, and biodegradable [RS08]. As a comparison, spider silk has a material toughness of 120,000 - 160,000 joules per kilogram (J/kg) while Kevlar has a material toughness of 30 - 50,000 J/kg and steel has a material toughness of 2,000 - 6,000 J/kg [n.andf]. Spider silk's properties are due to the highly repetitive structure of the proteins that make up spider silk. For example, spider silk proteins contain many glycine residues, especially in their cores. Spider silk however, cannot be mass produced by farming spiders because spiders are cannibalistic and territorial and they would have to be housed individually, which is inefficient. In addition, an individual spider does not produce a large amount of silk, so harvesting silk from spiders would be impractical.

Therefore, in order to acquire a large amount of spider silk for industrial purposes, it has to be produced artificially. To do that, the first step is to get the proteins for spider silk by mass producing the silk proteins with recombinant methods in organisms such as *E. coli* or silk worms. After the silk proteins are produced, scientists can create spider silk by emulating the process that spiders use to make silk. Spider silk is made up of proteins called spidroins, which are stored in a liquid state and at high concentration in the ampulla of the spinning gland in the spider's abdomen [CRN18] As the proteins pass through the spinning gland, they go through an acid environment and removal of water that will solidify it into silk, which can then be excreted. In a similar way, spider silk can be made in labs by using a spinning apparatus. *E. coli* are first used to generate artificial proteins and the proteins are made in a liquid state. Afterwards, it goes through processes such as electrospinning, which is beyond the scope of this text, but in short, liquids go through a phase transition from liquid to solid and fibers are formed. The fiber can then be spun into thread by a spinning wheel.

Although it is promising so far, the fibers produced do not have the same quality of natural spider silk yet. One of the reasons is that recombinant methods to produce the proteins provide challenges. The length and size of the spider proteins make them difficult for bacterial hosts to synthesize and secrete, and for researchers to isolate and purify in solution. In addition, there is an incomplete understanding of the underlying gene and/or amino acid sequences of most of the spider genes, so the proteins produced may tend to coagulate and function differently [SJBF20]. But even still, the fibers produced are great progress.

Spider silk is a remarkable material and as methods to produce it continue to improve, spider silk can be used to reinforce military gear or weapons and other environmental friendly materials.

A different use of novel proteins in industry is water purification. Many membrane proteins such as aquaporins have qualities namely high osmotic water permeability and rejection of ions that are desirable for purifying water [IKB18]. In fact, some water filtration companies such as Aquaporin are using artificial aquaporins. Aquaporins are a type of transport protein that can be found in the cell membranes and they help facilitate the diffusion of water molecules into the cell. In particular, aquaporins are channel proteins and they have pores where water molecules can enter the cell.

Specifically, aquaporins have NPA motifs and aromatic/arginine (ar/R) regions in their pores that give them the selectivity for water. NPA motifs are areas with the amino acids asparagine, proline, and alanine. These amino acids are known to play a role in blocking protons from entering by creating a positive electrostatic field and breaking hydrogen bonds from water molecules, although there is still controversy as to the specifics. There is also an ar/R region in the pores with the amino acid arginine, which is positively charged. The ar/R region is known to form hydrogen bonds with water molecules, forcing the water molecules to pass through aquaporin's pore in a single file. It excluses ions and is also narrow enough to exclude other molecules based on size.

Artificial aquaporins can be incorporated into biosynthetic membranes that are used in water filtration. These membranes can then be used to purify water using forward or reverse osmosis. Even so, aquaporins are not stable enough for industrial purposes when they are incorporated into the biosynthetic membranes, as chemicals such as detergent may denature the proteins. One way to increase the stability is to place vesicles that naturally have aquaporins into the synthetic membranes. More research is also being done to improve the aquaporins as they cannot filter small ions such as sodium ions that well yet and therefore cannot be used for desalination (filtering salt water), which is important in places that have a lack of access to fresh water. Lack of safe water in places such as rural Africa is still an issue and it would be a huge advantage if the production of de novo aquaporins could be refined.

Another significant way novel proteins can be useful in industry is the use of novel enzymes. Many biological functions would be impossible without enzymes, which are proteins that speed up chemical reactions necessary for life. Many chemical reactions such as those in cellular respiration would take far too long to happen on their own for us to survive. As a brief description of enzymes function, they bind to substrates (the substance the enzyme is acting on and can be thought of as reactants in a chemical reaction) at active sites and convert them into products. Since enzymes are very important and it is not surprising that scientists have worked hard to create synthetic enzymes. One of the first de

novo enzymes made that can perform catalytic functions for biological processes is Syn-F4, designed by Hecht and others in 2011 [DeN]. At first, they designed de novo proteins that performed catalytic functions, in particular, a four-helix protein called Syn-IF. They then experimented with *E. coli* and looked for genes that would be lethal to the bacteria if the genes were removed, in order to test the de novo proteins.

The *E. coli* were modified so that they did not contain an enzyme called FeS. *E. coli* acquires iron, an essential mineral for life, from their environment using a molecule called enterobactin, and FeS is needed to extract the iron from enterobactin in order for the bacteria to use it. The *E. coli* without FeS were rendered almost dead without an iron supply and *E. coli* colonies began to turn red as the iron that the bacteria could not use built up. That provided a perfect environment for the researchers to test the abilities of the de novo proteins they had and they used directed evolution to make newer de novo proteins that could extract iron better than Syn-F1. Syn-F1 did not show much enzymatic activity, but they eventually hit upon one particular protein derived from Syn-IF, called Syn-F4, when it was added to the modified *E. coli* colonies, it turned the bacteria into a healthy color again. This meant that Syn-F4 was able to extract iron from enterobactin just as FeS did and functioned as an enzyme.

Syn-F4 is significant because it is a non-biological catalyst that can perform catalytic functions. It was not thought possible that something non-natural could perform natural processes. In addition, it is challenging to create de novo enzymes for many reasons, for example, it is difficult to identify the optimal locations on a protein for the active site and model the active site with sufficient accuracy to enable the protein to function appropriately [NK09]. Some ways scientists have tackled these difficulties are to use both computational modelling and experimental methods. Many attempts have been made to improve the computational methods, which are too detailed to be covered in this paper, and one such example is a new Rosetta platform that the Baker Lab has used to design de novo enzymes [FRB11]. Once a model for the protein is created, proteins can be refined with methods such as directed evolution, similar to how Syn-F4 was made. Certainly, many chemical functions can be performed as more artificial enzymes are created.

4 Conclusion

These novel proteins that scientists have created can be widely used for medical purposes such as therapy, vaccine development, and diagnosis, or even for industrial purposes such as the creation of new biomaterials, water filtration, and chemical processes with enzymes. There are endless possibilities that these new proteins can offer, and an essential part of designing these proteins is modelling them, as mentioned earlier in the paper. But whether template modelling or de novo modelling is used, generating the structure of the protein requires signifi-

cant computational power and data. Furthermore, the protein models generated are not always accurate. There are also added difficulties when synthesizing the proteins, such as ensuring the proteins are stable and properly functioning.

In general, it is a long process for proteins to go from the laboratory to the market, one major example being that vaccine development often takes years to complete. After sequencing the virus's genetic material, a protein for the vaccine has to be created and optimized, which involves much research. Once the vaccine is created, it has to go through numerous clinical trials before it can be used. Improving the accuracy and speed of the protein models predicted is one possible way to speed up the process of vaccine development. Going back to the example of the vaccine, using computational methods to understand the virus's structure and how a new drug interacts with it can help scientists to refine the protein and get it to clinical trials sooner. It would be to our advantage to find ways to develop these novel proteins faster so that they can be used.

Indeed, this is perfectly summed up by Ryan Bethencourt's words, "Our world is built on biology and once we begin to understand it, it then becomes a technology." Proteins can be used to create things that benefit us such as medicines. For example, the synthetic protein Kuma030 [CWP15] can be used in developing a cure for celiac disease, a serious autoimmune disease in which people cannot eat gluten because the ingestion of gluten can trigger an inflammatory response in their intestines [n.a20]. And even besides the medical and industrial sector discussed in this paper, novel proteins have many uses such as in protein switches [Bak17] and biosensors [CWP15] and even for waste management in space. Many things seem to naturally work so well, so why not emulate or refine them? With the current progress scientists are making, imagine what will be possible in the future.

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A Deconstructive Approach to Hippocampal Neurogenesis as a Function of Aerobic Exercise

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Abstract

Aerobic exercise, specifically running, leads to neural benefits in rodents and humans. In this review, a deconstructive approach is taken to understand the neural benefits of aerobic exercise in terms of cognition, hippocampal size, brain-derived neurotrophic factor (BDNF), and hippocampal neurogenesis. These four benefits were positively impacted as a result of running in rodents and the same was seen in humans except for with hippocampal neurogenesis. Human hippocampal neurogenesis has been demonstrated to continue throughout the lifespan but there was not evidence for it as a result of running. Therefore, future directions address potential ways to study hippocampal neurogenesis in humans in relation to aerobic exercise. The future directions also discuss potential dosage curves in regards to intensity, duration, and frequency of aerobic exercise on cognition, hippocampal size, and BDNF.

1 Introduction

For a long time, it has been known that exercise and cognition are positively connected [Rob94]; [Art99]. Recently, there has been a rise in people taking up running as an independent form of aerobic exercise [Yan19]; [Jac19]. Scientists have recently started to elucidate the neural underpinnings that may mediate this positive relationship between aerobic exercise and cognition. While the neural mechanisms are more clear in rodents than they are in humans, studies have shown that hippocampal neurogenesis, the birth and development of new neural cells [Pet98], is a likely mediator of the relationship between aerobic exercise and enhanced cognition [Hen99a]; [Hen05].

In humans, the hippocampus is one brain region in which there has been evidence that neurogenesis occurs [Ola15]. The hippocampus is one of the major parts of the brain which is involved with the cognitive functions of learning and memory [Kul12]. One part of the hippocampus that has been the focus of hippocampal neurogenesis research, is the dentate gyrus, which connects sensory

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stimuli with memories, thereby demonstrating its important function in learning and memory [Gil15].

In order to understand cognition, neurogenesis, and the molecular mechanisms that mediate the neural underpinnings of aerobic exercise's benefits, this review will take a deconstructive approach, starting with cognition and hippocampal volume. It will then explore a mediating neurotrophic factor, BDNF, that may be involved in this process and influence hippocampal neurogenesis. At the end, future directions to better understand the effects of aerobic exercise on these processes are discussed.

2 Hippocampal Neurogenesis in Humans

There has been controversy over whether hippocampal neurogenesis occurs in adult humans [Mau18]; [Sha18]. One paper suggests that neurogenesis continues through aging by looking at cells that are positive for the markers DCX/PSA-NCAM, which label immature granule neurons. DCX/PSA-NCAM+ neurons were found to be consistent in number throughout age and were seen in at least the thousands in the anterior, mid, and posterior dentate gyrus [Mau18]. Another paper, which looked at the same cell marker in immature neurons in the various layers of the dentate gyrus, the molecular zone, subgranular zone, granular cell layer, and hilus, determined that hippocampal neurogenesis decreases in children to minuscule levels in adults [Sha18]. Both papers also looked at other markers such as the protein Ki67 for proliferating cells, the transcription factor SOX2 and protein Nestin for early neural progenitors, and the protein NeuN for mature neurons [Mau18]; [Sha18]. In [Mau18], Sox2+ cells declined throughout aging but Ki67+ cells, Nestin+ cells, and NeuN+ cells remained stable. In [Sha18], Ki-67+Sox2+ cells decreased in the first years in almost all cases.

There could be multiple reasons that could explain the discrepancies between the two studies, but one outstanding factor is related to the brains that were used. [Mau18] used intact brains whereas [Sha18] used brains of varying neurological conditions including twelve subjects with epilepsy. The reasons for death were various and not explicitly given for the subjects who died at 14 gestational weeks up to death at 77 years old in [Sha18]. Another factor could be the postmortem interval which was between 4 to 26 hours in [Mau18] but in [Sha18], it was 48 hours or less.

Two more recent papers both show that adult hippocampal neurogenesis continues in older human brains [Mat19]; [Ele19]. Unlike the other two papers, these studies did not look at hippocampal neurogenesis in people of all ages but focused on a specific age group of 79 to 99 in [Mat19], 43 to 87 for the healthy brains, and 52 to 97 for subjects with Alzheimer's disease [Ele19]. While both studies found persistent hippocampal neurogenesis in healthy older adults, they did not find the same results for people with Alzheimer's disease. [Ele19] looked for DCX/PSA-NCAM+ cells and found that immature neurons declined as Alzheimer's disease progressed in the brain and were in lower counts com-

pared to healthy brains. [Mat19] looked at DCX+PCNA+ immature neurons and found that hippocampal neurogenesis was present in people with mild cognitive impairment and Alzheimer's disease. While there has been controversy about neurogenesis continuing past the first years of life in humans, overall, more recent studies suggest that neurogenesis does continue in healthy people [Mau18]; [Ele19]; [Sha18]; [Mat19]. Neurogenesis has been further studied in rodents, and evidence suggests that neurogenesis continues throughout life and aerobic exercise enhances neurogenesis [Yi-18]; [Tae18]; [Hen99a]; [Hen99b]; [Hen05].

3 Aerobic Exercise's Neural Impact in Rodents

3.1 Aerobic Exercise Improves Cognition

Aerobic exercise does enhance cognition in young adult, middle aged, and aged mice [Yi-18]; [Tae18]; [Hen99a]; [Hen05]. A study with young rats found that aerobic exercise improved spatial learning as seen by decreased path length and latency when finding the platform in the Morris water maze task, a widely used spatial learning task for rodents [Nas03]. It has also been observed that young adult mice who run voluntarily, compared to those that did not run, have improved spatial learning [Hen99a]. This increase in spatial learning has also been seen using the Radial arm water maze, a hybrid Morris water maze type task which can also determine errors [Nic10]. This study also found that the young mice who ran voluntarily and were trained on the Radial arm water maze 1 week after aerobic exercise did better on the maze than right after aerobic exercise or 2 weeks after aerobic exercise. In middle aged mice, it was found that spatial learning is better improved in mice that did intermittent exercise, which means voluntary running for 2 weeks and no running for 1 week being repeated for a total of 12 weeks, compared to continuous voluntary exercise and no exercise [Yi-18]. Similarly, this finding was consistent in a study with 1 hour of daily forced treadmill aerobic exercise with mild exercise (15 m/min) being better at improving spatial learning than intense exercise (40 m/min) or no exercise [Kos15]. In aged mice, voluntary wheel running increased their spatial learning as well [Hen05]. In older mice, the magnitude of change in latency and path length is greater between older runners and older control mice than between young runners and young controls. The older runner mice's latency and path length decreased to similar amounts as in young mice suggesting that older age may not restrict aerobic exercise's improvements on spatial learning. Forced treadmill running also had positive cognitive improvements on short term memory, which was assessed using the step-down avoidance task, as well as spatial learning [Tae18]. Another study looking at rats found that specifically lower intensity forced aerobic exercise (15 m/min for 40 minutes a day) had more beneficial effects on short term delayed working memory, which was assessed using the delayed spatial alternation task, compared to mid (20 m/min) and high intensity aerobic exercise (30 m/min) [Xia16].

3.2 Hippocampal Volume and Density Likely Increases as a Result of Aerobic Exercise

In a study on mice with Alzheimer's disease, it was found that mice who ran had increased hippocampal volumes, as measured by Nissl staining, compared to mice that did not run. This was the case in both mice that voluntarily exercised on a wheel as well as mice that were forced to run on a treadmill [Car09]. Multiple studies in rats have also found increased hippocampal density of neurons resulting from aerobic exercise [Edu19]; [Xia16].

3.3 Aerobic Exercise Increases BDNF

BDNF aids with neuronal development, particularly with differentiation, maturation, and survival [Sir15], and it has been found to be required for neurogenesis [Chi06]. Aerobic exercise increased BDNF, measured using Western blotting, in the hippocampus [Tae18]. A few days of voluntary wheel running has been found to result in increased BDNF mRNA levels in the hippocampus [S. 95]; [Car02]. The increase of BDNF mRNA after aerobic exercise has been seen to last throughout just one week of voluntary exercise [S. 96]; [Sho03]) as well as over the course of several weeks [Ame99]. Hippocampal BDNF protein levels were also increased in young mice directly after voluntary wheel running for three weeks and, following the three weeks of running, BDNF protein levels began decreasing after one and two weeks and returned to baseline levels by weeks three and four [Nic10]. While BDNF increase as a result of aerobic exercise has mainly been seen in males, it is also true that females who voluntarily run have increased levels of BDNF mRNA and BDNF protein [Nic01]. BDNF has been shown to mediate the positive effects of aerobic exercise on cognition directly [Sho04]. When BDNF action was blocked in exercising rats, their spatial learning, as measured by the Morris Water Maze Task, dropped to the levels of the control group.

While BDNF expression has been linked to improvements in cognitive functioning, there is a mechanism that demonstrates how exercise can increase BDNF expression. Exercise, specifically aerobic exercise, stimulates the increased expression of the hippocampal gene Fndc5 (a glycosylated type I membrane protein) in the brain. The gene is stimulated by the transcriptional regulators Pgc1a and Erra which are induced by skeletal muscles as a response to aerobic exercise. As a result of the increased Fndc5 gene expression, BDNF expression also increases which consequently will lead to better cognitive functioning due to the positive effects of BDNF in the hippocampus.

3.4 Aerobic Exercise Enhances Hippocampal Neurogenesis

Running enhances hippocampal neurogenesis in young adult, middle aged, and aged mice. [Yi-18]; [Tae18]; [Hen99a]; [Hen99b]; [Hen05]. Hippocampal neurogenesis in mice has been measured using cells that were at least double marked

for BrdU, which is a marker for proliferating cells, and NeuN [Tae18]; [Hen99a]; [Hen99b]; [Hen05]. It has also been measured using anti-BrdU, which are the antibodies marking BrdU positive cells [Yi-18]. This study also found that intermittent aerobic exercise in middle-aged mice was better at increasing hippocampal neurogenesis compared to continuous aerobic exercise and no aerobic exercise. Further, one study found that mild long term forced aerobic exercise was better at enhancing hippocampal neurogenesis than intense long term aerobic exercise over a period of six weeks [Kos15].

4 Aerobic Exercise's Neural Impact in Humans

4.1 Aerobic Exercise Enhances Cognition

Aerobic exercise has been shown to improve cognitive function in humans [Art99]; [Cha08]. In children, aerobic fitness positively impacts cognitive control, assessed by the flanker task (a selective attention paradigm), likely through increases of brain volume in areas like the hippocampus [Lau10b]. A clinical trial in young adults found that executive functioning, which was measured using set switching between tasks and The Groton Maze Learning Test, improved with aerobic exercise as well [Yaa19]. Another clinical trial in older adults, which consisted of a cross-sectional study and longitudinal study of 6 months, found that higher cardiovascular fitness training is connected to improved executive functioning performance as assessed by the flanker task [Sta04]. A more recent meta-analysis of 39 studies also found that moderate or higher intensity aerobic exercise of 45 to 60 minutes improved cognition of adults over 50 years old no matter their initial cognitive status [Jos18].

4.2 Aerobic Exercise Increases Hippocampal Volume

Aerobic fitness and spatial learning are both positively associated with hippocampal volume [Kir09]. Aerobic exercise specifically has been shown to increase hippocampal volume in both the left and right hippocampus as seen by MRI scans in elderly human adults [Kir11]. On the opposite age spectrum, comparing preadolescent children, those who have higher aerobic exercise levels have increased hippocampal volumes as well [Lau10a]. For early and middle aged adults, the findings were similar in a study where physical activity was self-reported and results showed that higher hippocampal volume positively correlated to aerobic exercise amount [Wil13]. The mechanism underlying increased hippocampal volume is the positive change in tissue density, which in turn increases hippocampal volume [Mai16].

4.3 Aerobic Exercise Results in BDNF Increase

A study on healthy college men found increased plasma, platelet, and serum BDNF after exercising on a treadmill in comparison to their levels at rest before the aerobic exercise [Hyu12]. In another study that also looked at BDNF

levels immediately after aerobic exercise in young males who did acute exercise and chronic exercise for both 3 and 5 weeks, 60 minutes to 90 minutes of acute exercise resulted in an increase in serum BDNF for the groups [Ead11]. Similarly, a study in young, healthy men also found increased serum BDNF after moderate intensity aerobic exercise compared to before training [Jer08]. A study looking at healthy, older people between the ages of 65 and 80 found that serum BDNF was elevated after a 35 minute session of aerobic exercise [Kri17].

BDNF amounts have been seen to increase by over 3 fold after aerobic exercise [Cam14]. One study found that from 20 minutes of vigorous aerobic exercise to 40 minutes there was a 2.7 times increase and a 1.4 times increase for the moderate aerobic exercise group [Mat13]. This suggests that aerobic exercise intensity affects the magnitude of BDNF increase.

5 Conclusions and Future Directions

Evidence for aerobic exercise related neurogenesis in humans is currently lacking, but it has been clearly demonstrated in rodents. It has been observed in both rodents and humans that aerobic exercise enhances cognition, hippocampal size, and BDNF. In general, neurogenesis in humans has still been disputed over the past few years with more recent evidence suggesting it continues into adulthood. This section will first discuss aerobic exercise's benefits on cognition, hippocampal size, and BDNF levels in regards to a dosage curve and at the end of this section, future directions in this field to help better understand the relationship between aerobic exercise and neurogenesis are discussed.

One main area in humans that is lacking knowledge is regarding a potential dosage curve between aerobic exercise and cognition, hippocampal size, and BDNF increase, as well as potential age-dependent effects. Determining the dosage curve shape (inverted U-shaped, J-shaped, etc.) would help show what duration, intensity, and frequency of aerobic exercise is needed to get the best benefits for cognition, hippocampal volume, and BDNF increase while looking at age could help people personalize their exercise regimes for optimal neurological benefit. Conducting a study regarding dosage curves in rodents as well could help show connections between cognition, hippocampal volume, BDNF, and neurogenesis so that the nature of their relationship could be extended to better understand neurogenesis in humans.

A study in rodents that could show the connection between aerobic exercise benefits and dosage curve in humans would consist of healthy rodents of four various age groups: adolescents, young adults, middle-aged, and elderly. For healthy humans, there would be five various age groups: preadolescents, adolescents, young adults, middle-aged adults, and elderly adults. Preadolescents are excluded from being an age group tested in rodents since mice and rats do not open their eyes until adolescence which begins at 2 weeks old [Abi17]; [Ste02]. The age groups in rodents and humans would be split into seven groups that would have to do aerobic exercise for either 0, 30, 60, 90, 120, 150, or 180 minutes. These groups would also be split to account for three different intensities

of aerobic exercise (low, moderate, and high) as determined by percent of heart rate reserve. They would be further split, to account for frequency, into groups that exercise for 1, 2, 3, 4, 5, 6, or 7 days a week.

Before and after each group does their treadmill exercise, rodents would complete the Morris water maze task to assess spatial learning and the step-down avoidance task to assess short term memory. To look at hippocampal size, specifically volume and density, they would also get MRI scans and Nissl staining, which stains neurons [And09]. Humans would complete the flanker task to look at cognition and get MRI scans to look at hippocampal size before and after exercise. Both rodents and humans would also have their plasma, platelet, and serum BDNF measured to determine a potential dosage curve between aerobic exercise and BDNF. In rodents, one further aerobic exercise benefit that would be tested is neurogenesis. Before aerobic exercise, BrdU would be injected to measure proliferating brain cells, after aerobic exercise DCX/PSA-NCAM would be used to mark immature neurons and NeuN would be used to mark mature neurons. Measuring the amount of these types of neurons after aerobic exercise every day until the fluctuation of neuron amounts levels out and then comparing the amounts to the individuals' baselines could help determine a dosage curve relationship between aerobic exercise and neurogenesis.

The results of this study could likely show an inverted U-shaped curve or exponential curve for cognition, hippocampal size, and BDNF increase in all ages of rodents and humans since injecting BDNF has been observed to show inverted U-shape for neuronal regeneration in rodents [Lau00] and since around an hour or more of aerobic exercise has been shown to increase BDNF in humans [Ead11]. For age dependence, this study could likely show that older adults and rodents can still gain the benefits of improved cognition, increased hippocampal size, and heightened BDNF levels that younger adults and rodents do since this was seen with cognition before in mice [Hen05]. Moderate intensity will likely be best for these three benefits as observed in young men for BDNF levels [Jer08]. Around 3 to 6 days a week of aerobic exercise would likely be best for cognition, hippocampal size, and heightened BDNF levels since 3 days a week has been observed to improve cognition in humans [Sta04]; [Yaa19] and 6 days a week did the same in mice [Tae18]. Overall, these results would likely demonstrate a duration of 1 to 2 hours of moderate intensity aerobic exercise done 3 to 6 days a week to be most beneficial to humans regardless of age. Having this information could help humans know how to best support their brain health through their exercise regime.

The results regarding hippocampal size, specifically volume, in rodents and humans will likely be similar as in the mice with Alzheimer's [Car09] and the mechanism behind it in rodents will likely correspond with humans [Mai16] while potentially showing redundancy in the mechanism. The MRI scans and Nissl staining of the hippocampus could help find out whether aerobic exercise increases hippocampal density, hippocampal volume or both, as well as if the specific mechanism through which this occurs in rodents is the same as in humans. This study could provide important results regarding whether density increases as a result of connections forming within existing circuits in the hip-

pocampus or if volume increases as a result of periphery neurons and expansions occurring. It could also potentially rule out the effects of angiogenesis.

Since BDNF directly supports neurogenesis [Chi06] and BDNF injections' neuronal benefits have an inverted U-shape [Lau00], it may be likely that neurogenesis in rodents would follow this inverted U-shape as well. In rodents, moderate intensity and 3 to 5 days would likely be best for neurogenesis since mild aerobic exercise [Kos15] and intermittent aerobic exercise [Yi-18] were found to be most beneficial. The results could be extended to better understand the relationship between aerobic exercise and neurogenesis in humans. To fully test the possibility of exercise induced hippocampal neurogenesis in humans, the best way to do so would be to find out a noninvasive way of assessing the levels of immature neurons and other neurons in the developmental stage. The reason why a noninvasive way is needed is because one of the only other ways to test this would be by testing the effects of aerobic exercise in terminal patients or via unethical routes; therefore, the main way to do this would be to develop new techniques to measure neurogenesis in vivo and noninvasively.

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The Neural Relationship Between Smooth Movement and Musical-Motor Entrainment and Applications in Musical Rehabilitation

Curie Cha *

April 2, 2021

Abstract

This paper reviews the major individual areas of the nervous system responsible for smooth movement and neural entrainment to auditory stimuli, and how the overlapping areas are related to these two phenomena. The relationship between the two is then applied to suggestive methods of rehabilitation.

1 Movement

Smoothness is an element of motion that is characterized by the fluidity and continuity of a movement. It can be easy to overlook this significant quality of movement and take it for granted despite its valuable purpose. Smoothness allows for precision and predictability [T. 98]. A lack of smoothness can cause a motion to appear jerky, which is also known as intermittency, or the fluctuation of acceleration and deceleration in a movement [S. 15]. Hence the more intermittency, the less smooth a movement is. Many factors can influence intermittency, two of the most significant being movement control and the specific task being performed [S. 15]. Considering these two highly variable circumstances, movement smoothness can be productively studied and analyzed. It is important to distinguish smoothness from similar terms in order to effectively characterize and examine it. Similar to smoothness, the term ataxia is used to describe the execution of a motion. Ataxia is a condition that can be seen as a series of symptoms that cause uncoordinated movement. Ataxia can be observed in those with damage to critical motor areas of the nervous system and may also be inherited. There is an overlap between smoothness and ataxia, however they are not perfectly synonymous. Ataxia is a broader term that represents multiple aspects of motion that may be impaired. This can include features such as balance, oscillation, gait, posture, sensory information, and speech [T. 16]. In essence, ataxia is an umbrella term that includes smoothness.

*Advised by: Andrew Savoy from the University of Chicago

Another crucial point that relates everything discussed above is voluntary movement. As suggested by the term "voluntary," these types of movements require input from the brain. Muscles that are involved in voluntary motions are composed of muscle cells known as muscle fibers which are controlled by alpha motor neurons. Alpha motor neurons are located in the brainstem and spinal cord, also known as the central nervous system. These neurons and the muscle fibers associated with the neurons are called motor units and are the basis of voluntary movement. On the other hand, movements such as reflexes occur unconsciously thus requiring no input from the brain. Rather, they work through neural circuits to rapidly and automatically carry out a motion. These movements are called automatic movements. Regardless of brain input, movements involve the skeletal muscles and occur as a response to either internal or external stimuli [S. 18].

Regarding smooth movement, voluntary movement is inhibited when there is intermittency. This unregulated and unwanted movement is seen in disorders of movement and is called involuntary movement. Some examples of involuntary movement are tremors and sudden jerking.

Voluntary movement is primarily controlled by the motor cortex of the brain, which is located in the back of the frontal lobe. The motor cortex comprises the primary motor cortex, somatosensory cortex, premotor cortex, and supplementary motor areas. The primary motor cortex contains designated regions that are responsible for controlling certain body parts, creating a body map on the surface of the cortex.

There are two important descending pathways of the motor system known as the pyramidal pathway and the extrapyramidal pathway. These pathways allow for motor signals to travel from the motor cortex to motor neurons, causing muscles to move. The pyramidal pathway is related to voluntary motion of the body and the extrapyramidal pathway is responsible for automatic movement. Suggested by the pyramidal pathway's control of voluntary movement, the origin of this pathway is the brain. There are two tracts that constitute the pyramidal pathway: the corticospinal tract and the corticobulbar tract. The corticospinal tract starts at the motor cortex, specifically receiving signals from the primary motor cortex, premotor cortex, and supplementary motor area. These signals travel between the thalamus and basal ganglia to the midbrain and then split into two different tracts: the lateral corticospinal tract and the anterior corticospinal tract. The corticobulbar tract transports motor signals to move the muscles of the face and neck. It starts at the motor cortex and continues through a space between the thalamus and basal ganglia and joins with lower motor neurons to control face and neck muscles. The extrapyramidal pathway, as mentioned before, is responsible for automatic movement. As automatic movement does not involve the cortex of the brain, the extrapyramidal pathway begins in the brain stem and travels through the spinal cord.

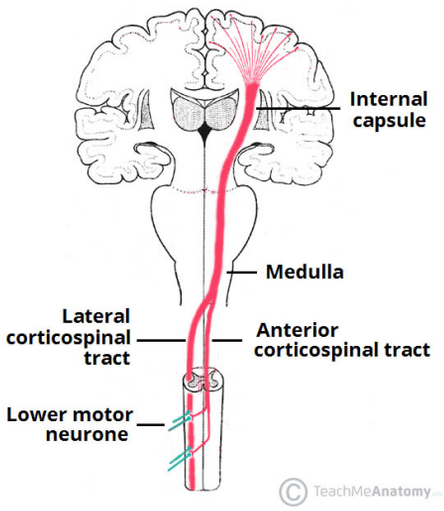

Figure 1: The corticospinal tract is shown in the diagram, beginning at the cortex and descending down the spinal cord.

1.1 Structures

The thalamus is a relay center that receives inputs from various areas of the brain and sends out signals to corresponding regions of the cortex. Concerning motor functions, the thalamus is composed of specific nuclei that are responsible for movement. These nuclei, collectively known as the motor thalamus, lie near the motor cortex, basal ganglia, and cerebellum, all areas important to movement [5]. It is important to smooth movement because it allows signals to reach the important areas of the cortex.

The basal ganglia are structures of the brain made of a network of loops and circuits that are important in voluntary movement. The basal ganglia include the striatum, the globus pallidus, the subthalamic nucleus, and the substantia nigra. These structures are related in the two pathways of the basal ganglia: the direct pathway and the indirect pathway. These pathways allow wanted movements to occur and inhibit unwanted movements. The direct pathway excites the thalamus and allows it to send signals to other areas to produce movement. It starts at the cortex and synapses with neurons in the striatum, releasing the neurotransmitter glutamate that excites the inhibitory neurons of the striatum. GABA is released and inhibits the internal globus pallidus and substantia nigra. Under no change, the thalamus is usually inhibited by the globus pallidus but by inhibiting the inhibitor, the thalamus is not subdued, as it normally is, but excited and more activity occurs. This sends more signals from the thalamus to the cortex then eventually to the muscles to produce movement. On the other hand, the indirect pathway inhibits movement. It starts at the cortex and synapses with the neurons of the striatum, releasing glutamate,

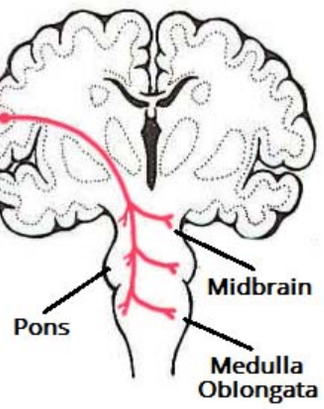

Figure 2: The corticobulbar tract is shown in the diagram, beginning at the cortex and descending towards regions of the face and neck.

which stimulates the striatum. Then GABA is released from the striatum to the external globus pallidus. The external globus pallidus, which usually hinders the activity of the subthalamic nucleus, is suppressed, so the subthalamic nucleus has more activity. This sends excitatory signals to the internal globus pallidus, creating more action potential and releasing more inhibitory neurons to the thalamus, and in turn, inhibiting movement. These two pathways work together and balance each other to allow for coordinated movement. If this balance is disrupted and there is overactivity in one of the pathways, it can lead to uncontrolled, unrestrained movement or block certain movements, depending on the pathway [H. 03]. Essentially, the coordination of the two pathways plays a major role in producing smooth movements. In movement disorders that cause unsmooth movements such as Parkinson's disease, there is overactivity in one of the pathways. In the case of Parkinson's disease it is the indirect pathway.

The cerebellum is a structure near the brainstem that is important in movement and learning. It can be divided into three functional regions: the cerebrocerebellum, the spinocerebellum, and the vestibulocerebellum. The cerebrocerebellum is related to movement planning and learning. The spinocerebellum receives sensory data from the spinal cord and information about limb location. The vestibulocerebellum controls balance and posture. In relation to smooth movement, the cerebellum allows for the prediction and correction of motor functions. This is evident in the effects of cerebellar damage. Those with cerebellar damage can experience motor deficits such as ataxia, tremors, and difficulties with aim; these can result in unsmooth movements. This suggests the cerebellum plays a necessary role in motor execution and planning [A. 06].

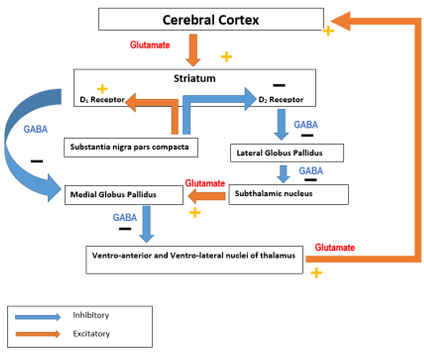

Figure 3: This is a feedback pathway diagram of the basal ganglia and the right shows how the pathways are connecting the areas of the brain.

2 Entrainment

Entrainment can be described as the locking of frequencies between two separate systems. This means the occurrence of one event lines up with the occurrence of another. A common example is the synchronization of metronomes initially clicking at different times. Eventually the clicking becomes synchronized through a common medium such as a table the metronomes are placed on. In the instance of music, the brain entrains to the beat of the music. When this occurs, the firing rates of auditory neurons and motor neurons are entrained [M. 15], therefore creating a period of rhythmic synchrony. This involves the auditory system and calls attention to the high connectivity between the auditory and motor systems. Important structures involved in rhythmic entertainment are the auditory pathway, cerebellum, and inferior colliculus.

It is important to discuss the auditory pathway regarding entrainment to music. The auditory pathway allows sound to be taken in and processed by the brain. This pathway starts with the cochlear nucleus; this structure receives input from the inner ear and sends information to the superior olive and the lateral lemniscus. Then, information is sent to the inferior colliculus, which is a key structure in entrainment. Afterwards, signals arrive at the medial geniculate body, which is in the thalamus. The thalamus relays information to multiple areas of the brain and in this case, mainly the auditory cortex. At the auditory cortex the signals are projected across many areas of the brain that allow the sound to be processed.

2.1 Structures

The cerebellum is involved with entrainment, specifically with sensorimotor synchronization and the auditory system. The cerebellum is associated with sensory information and this includes auditory stimuli. A meta-analysis showed that areas of the cerebellum were active during auditory stimuli [A. 05]. This means in

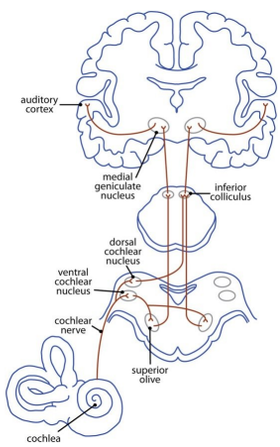

Figure 4: The ascending auditory pathway involving the cochlear nuclei, superior olive, inferior colliculus, and medial geniculate nucleus.

many of the studies proved the cerebellum's involvement in auditory processing. So along with the auditory pathway, the cerebellum can play a role in music processing, therefore entrainment as well.

The inferior colliculus is a part of the auditory pathway and is crucial in entrainment. The IC sends information to the thalamus which is sent to the cortex but it also sends signals to the cerebellum; it receives input from auditory structures and cerebral cortex and sends information to dorsolateral pontine nuclei [A. 13]. This structure is crucial because it is a component that is early in the auditory pathway and has projections to motor-related areas.

3 Synthesis

After discussing the areas of the nervous system related to movement and neural entrainment to auditory input, it is evident there is an overlap of common structures within the two domains. These areas could be the answer to effective treatment for movement disorders.

The cerebellum seems to be directly involved with both activities of movement and entrainment. However, it is important to further examine the high connectivities of the cerebellum with other structures. These neural connections will surely be affected in various motor deficits and therefore the treatment of those motor deficits; for instance, the cerebellum and basal ganglia. As the cerebellum and basal ganglia have connections through the dorsolateral pontine nuclei, motor deficits resulting in damage to one of those two areas can be detrimental, especially in overlapping functions. Further, major areas influencing movement can be affected due to the circuitry and connectivity of movement execution.

The link between the two main ideas of movement smoothness and entrain-

ment becomes relevant when discussing methods of neurorehabilitation. Due to the predictive nature of rhythmic entrainment, it can provide a pattern that outlines the time for which a movement must be executed [8]; this is the main concept. The structure music can lay out partly compensates for the lacking predictive model.

There have been many different uses of music in therapies. A method that uses rhythmic stimulation is known as Rhythmic Auditory Stimulation or RAS. It uses metronomic beats in music to provide timing for walking. RAS is commonly used for Parkinson's patients in gait rehabilitation. This method of music therapy and similar methods applies the neurobiology explained. RAS has been proven to be successful for these patients evident in stride length and speed [J. 07]. This relates to the pattern or time frame that is established by rhythm and music. This can be practiced further in future therapeutic techniques. Perhaps the application of musical melody compared to just rhythm can affect the outcome. Maybe even the syncopation of rhythm can yield different results. Syncopation is an aspect of music that is characteristic of off-beat rhythms and differing beats. This can evoke desire to move and this approach may be more influenced by affective means as well [M. 14]. In culmination, crucial regions of the brain, body, and auditory system work together to allow functions of movement and entrainment. When movement is inhibited or uncontrolled in some way, these motor areas are lacking proper function. With the absence of proper function, there comes a need for external stimuli to promote rehabilitation of the impacted structures. This is where entrainment and music therapy can play a crucial role in motor rehabilitation. The strengthening connections and unique aspects between entrainment and movement can target the problem in a different way that may not be possible with other means.

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A NATO intervention: The Right Choice for Libya

Anya Nedungadi

1、THE NATO INTERVENTION HAD THE INTENTION OF REGIME CHANGE

NATO arguably intervened with the 'wrong intent'; they pushed for a regime change instead of focusing on saving civilian lives. During the war, when NATO exhibited questionable actions, scholars believed that NATO was not operating within the boundaries of the mandate 'Responsibility to Protect' that the international community (led by the UNSC) agreed that NATO would intervene under. The UN mandate 'Responsibility to Protect' is defined by the United Nations Office of Genocide Prevention and Responsibility to Protect as an international norm that seeks to ensure that the international community does not fail to halt the crimes of genocide, war crimes, ethnic cleansing and crimes against humanity.[1] It does not mandate a regime change. However, the war that followed in Libya was one in which the Western powers worked in close collaboration with the rebel forces; serving them with their air forces, but also providing them with arms, training and propaganda support.[2] The NATO powers also supposedly had hundreds of operatives on the ground in Libya, training the rebels and giving them intelligence and other support, therefore violating UN resolution 1973's prohibition of an occupation force "in any form" and overstepping their initial aim of a no-fly zone.[3] On the day that the aerial attacks on Libya started, concerns were already raised about military overreach. The Chinese government expressed regret at the American and European assault on Libya, and Russia condemned the attack.[4] The African Union began stressing that only dialogue and consultation could bring solutions in Libya.[5] Scholars (Gregory, 2016)[6] declare that the Libyan intervention was no different to previous invasions in the Middle East because NATO's actions suggested that they were more focused on killing Gaddafi rather than saving civilian lives. Therefore, a NATO intervention was the wrong choice for Libya.

In response to scholars who believe that NATO intervention had an ulterior motive (Forte, 2012), I would like to pose a question: Was it possible to meet the

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[1] United Nations Office of Genocide Prevention and Responsibility to Protect <https://www.un.org/en/genocideprevention/>

[2] ibid

[3] Forte, Maximilian Christian 2012.

[4] The Guardian, (2011) 'Libya Attacks under Way'.

[5] African Union, press release (2011) 'The African Union Deeply Concerned about the Situation in Libya'

[6] Gregory, Robert H (2015)

mandate of civilian protection without affecting regime change? NATO did not have an ulterior motive of removing Gaddafi, instead, they actually could not complete their aim of civilian protection with Gaddafi in power. This does not mean that they took any direct aims at Gaddafi's government, rather they fought for civilian protection and in turn, Gaddafi's forces died as collateral damage. In addition, if we examine the boundaries of 'R2P' and UN R-1973 we see that a regime change is not out of the question and it is even considered in UN R-1973. Therefore, the exclamations of the African Union and Russia that declared that NATO was overstepping its instructions were misinformed because the international community had accepted the possibility of regime change before the intervention even began.

The UN Resolution 1973 did not specifically mandate a regime change but allowed 'all necessary measures' as well as finding a 'solution…which responds to the legitimate demands of the Libyan people…to lead the political reforms necessary to find a peaceful and sustainable solution.'[7] Interpreting this text delivers its own set of challenges; it might either allow permissive or restrictive actions depending upon one's political and moral perspective.[8] If NATO could help the Libyan people without overthrowing Gaddafi, this could not be condemned in the eyes of UN Resolution 1973. In reviewing statements made by coalition members following the UN Resolution 1973, the Libya Contact group, members of the London conference and North America concluded that it would be impossible to fulfil the 'Responsibility to Protect' mandate with Gaddafi in power, particularly considering his government's deliberate denial of electricity, water, fuel and food to ordinary Libyans.[9] This means that Gaddafi's death and the subsequent power vacuum could not be blamed on NATO both because the UN mandate under which they intervened and included the possibility of regime change, and because there was an international consensus that a regime change was an expected occurrence. NATO cannot and should not be penalised for operating appropriately under a legitimate authority.

It was impossible to meet the mandate of civilian protection without a regime change. The intervention's chance of success of lowering civilian casualties by protecting civilian areas should not be inhibited by trying to maintain the current regime. In response to Alan J Kuperman, this paper argues that NATO did actually have a very limited scope of intervention which supports its sole aim of civilian protection. They intervened with a no-fly zone which means that they didn't have troops on the ground and they only bombed areas where Gaddafi was harming civilians.[10] For example, at the time NATO and its allies initiated airborne attacks on pro-Gaddafi forces in the city of Misrata, the city had already been under attack by government tanks and artillery for several days.[11] This was also the case when NATO began its airstrikes of Gaddafi's troops within Ajdabiua, where government soldiers, tanks and warplanes had been bombarding the town.[12] In considering that NATO dropped about 8,000 bombs in almost 18,000 sorties, the results were impressive: there were few civilian deaths. This success was due to the precision-

[7] Wedgwood, Andrew, and A. Walter Dorn (2015)
[8] ibid
[9] ibid
[10] Pattison, James (2011)
[11] Ulfstein, Geir, and Hege Fosund Christiansen (2013)
[12] ibid.

guided munitions and meticulous planning based on solid intelligence for each NATO action.[13] It was impossible to escape this war without casualties on Gaddafi's side because they were the ones committing atrocities and murder, however, the precision by which NATO handled their intervention proved that they were not intent on killing any more of Gaddafi's forces than what was needed. All of these precautions reinforce the fact that NATO intervened with the intent of civilian protection, and any other political or social ramifications were only collateral damage.

2、Gaddafi's actions were not serious enough to warrant a military intervention

Critics (Pattison, 2011) of the NATO intervention assert that the Western media exaggerated the actions of Gaddafi in order to portray him as the main perpetrator of mass atrocities, consequently, the situation in Libya did not need an intervention. In Eastern Libya, where the uprising began as a mix of peaceful and violent protests, Human Rights Watch documented only 233 deaths in the first days of the fighting, not 10,000, as had been reported by the Saudi news channel Al Arabiya.[14] The rebels had put up very little defence against government forces; with their rudimentary equipment and inadequate training, they were in no shape to win a war. Therefore, Gaddafi's forces would have perhaps captured Benghazi by March 20th, thereby supposedly ending the one-month conflict at a total cost of just over 1,000 lives. On March 17th, Gaddafi pledged to protect the civilians of Benghazi, as he had those with other recaptured cities, adding that his forces had 'left the way open' for the rebels to retreat to Egypt.[15] The violence was supposedly on the 'verge of ending' when NATO decided to supply rebel forces with ammunition, giving them the strength that they needed to carry on the war.

Critics also claim that there were many occurrences of misinformation where the Western media exaggerated attacks by Gaddafi's government. Supposedly the number of deaths was minimal-- only 24 protestors in three days were killed.[16] According to Human Rights Watch, the death count of protestors in Libya was less than the number of black mercenaries executed by the Libyan rebels in mid-February and fewer than the number of protester deaths in Tunis or Egypt which elicited no intervention or UNSC aid.[17]

Gaddafi's actions did not need a military intervention; the number of causalities were low despite the Western media's exaggerations and the rebel forces were on the verge of being subdued.

While this argument has some validity, it fails to recognise that there was no way to prevent future mass atrocities from being committed without an intervention by NATO. Gaddafi was a ruthless, unpredictable dictator, desperate to keep his power without consideration for the deaths of innocent people. As shown in a 2011

[13] Pattison, James (2011)
[14] Wedgwood, Andrew, and A. Walter Dorn (2015)
[15] Kuperman, Alan J (2013)
[16] Forte, Maximilian Christian 2012.
[17] ibid

Forbes article,[18] when compared to dangerously infamous dictators such as Stalin, we see that the two leaders follow the same principles;

1) No alternative source of power or authority, no matter how seemingly weak or trivial.

2) No freedom of the press or expression. Even private derogatory comments are criminal acts.

3) Imprison, execute or banish all enemies, actual or potential.

4) Do not worry about punishing innocent people.

5) At all costs, prevent any combination of internal and external enemies. Failing to do so can be fatal.[19]

Gaddafi was a classic, unconstrained dictator; he followed similar ideology to Stalin and he was not against murdering innocent people for power. Therefore, when critics state that the conflict was on the 'verge of ending' before NATO intervened, I am surprised that they did not view him as a future threat. The 1988 bombing of Pan Am Flight 103 over Lockerbie, Scotland, the 1989 Union de Transports Aériens [UTA] Flight 772 bombing, and the 1996 massacre of 1,000 inmates at the Abu Salim prison were crimes directly connected to the Gaddafi regime.[20] Internally, Gaddafi oppressed Libyans through the banning of foreign language education, restricting travel, eliminating political parties, criminalising minority cultures, and developing a variety of oppressive internal security organisations.[21] These actions show Gaddafi's disregard for his peoples' lives and his unwillingness to protect his own citizens.

In addition, a report released by the UNHRC concluded that Gaddafi's forces had committed a wide range of abuses against his people such as rape, torture, murder, indiscriminate attacks and a range of other human rights abuses. If there remained any doubt about Gaddafi's potential for future human rights abuses, Gaddafi erased this doubt himself by claiming on the 17th March 2011, 'We will come house by house, room by room… We will find you in your closets. We will have no mercy and no pity.' Gaddafi wasn't content with just recapturing a city, he wanted justice and he wanted to 'cleanse Libya,'[22] actions that would have resulted in more mass atrocities against civilians.

Finally, the NATO intervention was needed to combat Gaddafi's forces because it was clear that he was becoming a potential threat not only to domestic security, but to international security. By ignoring the 1970 UNSCR resolution, which demanded an arms embargo, a travel ban and an assets freeze, he demonstrated his inability to comply with non-military intervention and his apparent disregard of the international community's decisions. The Security

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[18] Gregory, Paul (2011)
[19] ibid
[20] Wedgwood, Andrew, and A. Walter Dorn (2015)
[21] ibid
[22] Morris, Justin (2013)

Council only then took measures to enforce a military intervention. Again and again, Gaddafi showed that he was capable of massacres and he was unafraid of the consequences. The Libyan situation was unlike previous Western interventions in the Middle East. The intervention was not based on dodge dossiers of faked evidence and lies, but on the live unfolding of crimes against humanity. Gaddafi was a potential danger to the lives of the Libyans as well as to international security, therefore the NATO intervention was a necessity.

3、Introduction to the argument in support of the NATO intervention

As the 8-year-long Libyan civil war continues to wreck the lives of ordinary Libyan civilians, NATO has been blamed on multiple accounts of starting the political instability in Libya. The country has been riddled with insecurity since the removal of Gaddafi: multiple factions are vying for control particularly within the capital.[23] With competing governments in the country's east and west, and armed militias, who are not held accountable for any of their actions, controlling large parts of the country and exerting coercive political influence, Libya is effectively unable to provide for its people.[24] In exploring how Libya got to this point, analysts, journalists and politicians often point their fingers at the 2011 intervention. Many have said that the mess they are in is what inevitably ensues when NATO intervenes in a country. But who should actually be blamed for the outbreak of civil war?

It was failures of the international community after the intervention that resulted in a civil war. The NATO intervention was extremely successful in preventing the immediate massacre of civilians, and if it wasn't for their actions, the beloved city of Benghazi would most likely not exist today. As the British Prime Minster David Cameron put it: doing nothing in Libya would have been to 'facilitate murder.'[25] NATO succeeded in its job to prevent this murder and followed through in all areas of the resolution that they intervened under. It was the failure of the international community, specifically the UK, to build a strong and stable state after the intervention that caused a civil war to break out in Libya. A 2016 UK foreign affairs committee report criticised David Cameron, the British Prime Minster, for failing to develop a plan for post-intervention Libya, pointing out that the amount of funds spent on development - £25m ($31m) - was less than a tenth of the cost of the actual intervention.[26] "Your friends in Britain and France will stand with you as you build your country and build your democracy for the future," Cameron promised - but in practice, that support was in short supply, particularly as time wore on and attention drifted elsewhere. Ironically, those who blame the 2011 intervention for the crisis in Libya are guilty of precisely the same mistake as the intervention itself: not paying any further attention to the country after September 2011, until it had fallen apart. They accuse advocates of intervention of seeing it as the solution to every problem, but they themselves disregard all nuance, advocating avoidance as the solution, irrespective of the problem.

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[23] Green Matthew (2019)
[24] Dahan, Nadine (2019)
[25] ibid
[26] ibid

NATO cannot be blamed for the Libyan civil war which reinforces my argument that the intervention was the right choice.

4、The comparison of Libya and Syria

The Syrian civil war is a very beneficial case study as it proves a parallel for scholars to draw on between the road of war with a military intervention, and the road of war without. Syria did not receive the help of a NATO intervention because NATO's chosen means of implementing the mandate 'R2P' in Libya paved the path for those who were sceptical of the mandate to delegitimize the norm. This resulted in the prevention of international aid to Syria, where it was needed the most.

Both countries were at war due to the "Arab Spring" uprisings of 2011 which triggered a wide set of social movements and regime change across the Middle East and North Africa.[27] The two countries had similar sizes of protester deaths in 2011--400 for Syria, and at least 233 for Libya, according to Human Rights Watch,[28] and were both being ruled by ruthless dictators who were abusing their citizens. However, the death count in Syria is vastly greater than the death count in Libya. Since 2011, the Syrian civil war has lowered life expectancy by 20 years. Syrian civilians have constituted 70.6% of deaths (101,435) compared with the 29.4% of deaths of oppositionist combats (42,177). Proportions of children among civilian deaths increased from 8.9% (388 of 4254 civilian deaths) in 2011 to 19.0% (4,927 of 25,972) in 2013 and to 23.3% (2,662 of 11,444) in 2016.[29] In Libya, there was an estimated minimum of only 727 total civilian deaths.[30] Yes, proportionally Syria is a larger country with 22.5 million people versus Libya's 6.6 million people[31] which may account for a slight variation of death count, but considering that these wars started out so similarly, the difference in death count is shocking.

A NATO intervention was ultimately the right choice for Libyan citizens because it prevented the spread of wide scale terrorism and death as it is in Syria- where Libya has as many as 6,000 Islamic State soldiers on the ground, Syria has 20,000 to 30,000 according to the CIA- and because politically, Libya is faring much better than Syria. After a long negotiation led by the U.N., a Government of National Accord is working to consolidate power in Libya;[32] success is not assured, but there is a clear path forward, a growing consensus around that path, and a reasonable chance of real political reconciliation. This is very unlike the chaos that is occurring in Syria where amidst the chaos of fighting between the government and anti-government fighters, the Islamic State is taking over large parts of Iraq and then moving into eastern Syria, where they are gaining land and power.[33] A

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[27] Shapiro, Ari (2013) 'Why Syria is more complicated than Libya"

[28] Human Rights Watch <https://www.hrw.org>

[29] Guha-Sapir, Debarati (2018)

[30] Washington Post (2020) "Civilian casualties surge in Libya during Tripoli battle, study finds"

[31] The Guardian (2011) "How Libya and Syria compare"

[32] Rogin, Josh (2016) 'Obama's Biggest mistake isn't Libya. Its Syria'

[33] https://www.bbc.co.uk/newsround/16979186

NATO intervention was the right choice for Libya because it prevented the disasters that have occurred in Syria.

5、Conclusion

A NATO intervention was the right choice for Libya in 2011. In response to this conclusion, we must rethink the delegitimization of the norm R2P and accept the mandate as a suitable and successful means of military intervention. As proven in this paper, an intervention under this mandate can prevent significant life loss and can protect civilians, if carried out in the appropriate manner. If the international community hadn't been so eager to rule out the norm after the NATO intervention in Libya, many lives in other Middle Eastern countries, such as Syria, could have been saved. The information gathered about the use of the mandate during the intervention in Libya should be used to strengthen the boundaries and analyse the methods of military intervention so that it continues to save lives.

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What, if Anything,

is Wrong with Surveillance Capitalism?

Aaron Chen

Abstract

This paper tackled existing literatures and evidences on the emergence of a supposedly new socioeconomic phenomenon —"surveillance capitalism"— focusing specifically on the question "what, if anything, is wrong with surveillance capitalism?" I explored this by referencing three established conceptions of freedom: freedom as autonomy, non-interference, and non-domination. On autonomy, I explored how the consumerist landscape fueled by surveillance capitalism may encroach upon the authenticity and rational capacity of consumers, thus preventing individuals from leading a "good" life; On non-interference, I analyzed the implications of data's implementation, considering the nuances behind its support; On freedom as non-domination, I shifted away from applications of data, and instead, evaluated how the act of appropriating data itself may be problematic. In considering the unprecedented arbitrary power that firms are able to accumulate during the appropriation-stage, I have shown how surveillance capitalism manifests in ways ethically unacceptable, intrinsic, unique, and dangerous in social implications.

1、INTRODUCTION

Just as the abundance of human labor once was to the foundation of industrial capitalism, it seems that a new information civilization characterized by its ubiquitous digital traces has similarly birthed the emergence of what various contemporary scholars deem to be "surveillance capitalism", an economic order founded upon the extraction of this new data. This paper, though, is not so much concerned with a historical account that traces how surveillance capitalism came to develop. Rather, it will focus on a critique of this new economic order: what, if anything, is wrong with surveillance capitalism?

Before moving on, it is important to establish what is meant by 'wrong'. An economic order such as surveillance capitalism can be wrong in various ways— it can be dysfunctional (a functional critique), where it fails to function as intended. For example, a knife used for cutting is said to be dysfunctional if it has a blunt blade[1]. The cutting knife can also be inherently dysfunctional if it does not have a blade or is equipped to function in a way that is actively contradictory to what is intended[2]; an economic order can also be morally abhorrent (a moral critique), where the system is unfair and exacerbates injustice; a system can also be ethically unacceptable (an ethical

[1] Rahel Jaeggi, "What (If Anything) Is Wrong with Capitalism? Dysfunctionality, Exploitation and Alienation: Three Approaches to the Critique of Capitalism." pp. 44-65.

[2] In the case of capitalism, if one assumes that such a system is supposed to function by allocating resources to fulfill consumer needs, then it can be inherently dysfunctional if it indeed prevents resource allocation or prevents the fulfillment of those needs. In this scenario, capitalism functions against its purpose.

critique[3]), where it inhibits us somehow from leading and living a fulfilling life. This paper is only interested in the ethical critique of surveillance capitalism, as it pertains to a reasonably broad exploration of implications that such a system has on our mode of living and interacting, and thus leaves ample room for normative judgment and debate.

In order to further focus this paper, surveillance capitalism will only be assessed from the lens of freedom and the various conceptions of it, namely freedom as autonomy, non-interference, and non-domination. Surveillance capitalism's implications on the preservation of freedom is quite a relevant and potent topic, to be sure, as freedom is often regarded as a prerequisite to leading a fulfilling life—a popular standard by which to gauge whether a system is ethically acceptable.

At this point, then, one can begin to develop a normative criterion for assessing surveillance capitalism: To be considered 'wrong', some implication that the system has on our freedom must be

> 1. ethically unacceptable, insofar as it inhibits us somehow from leading and living a fulfilling and happy life

It will also be added that what can be identified as ethically unacceptable must be

> 2. intrinsic to the surveillance system, where surveillance capitalism as it is cannot be conceived without the feature that perpetrates the identified 'wrong'.

This second prong is imperative, as to identify a feature that is only wrongful in some instances is only telling to the extent that surveillance capitalism *could* be implemented in a way that has perverse implications, not that it is inherently concerning-- which is not enough for the purposes of this paper.

If the two aforesaid requirements are met, then there must be something that is wrong with surveillance capitalism. That being said, if this paper fails to meet these requirements, conclusions only stem so far as the ethical critique of surveillance capitalism; perhaps, one might resolve to different conclusions when assessing surveillance capitalism from other perspectives.

However, as it currently is, this metric is quite trite. Surely, it wouldn't be quite so meaningful if what we find evidently wrong in surveillance capitalism also be happens to manifest in other forms of capitalism, economic systems, or human institutions. If that is the case, we can at best claim disillusionment against the generic modern society and human civilization, which isn't quite sufficient for the purpose of this paper. Or worse, if whatever wrong we identify is comparatively worse under other, for example, previous manifestations of capitalism in terms of social and economic impacts, that would imply surveillance capitalism to be in fact an improvement for the better.

Hence, I will add two potential points of discussion on top of the aforesaid metric that primarily focuses on the comparatives to surveillance capitalism:

> 3. whether the 'wrong' identified is unique to surveillance capitalism in comparison to alternative forms of capitalism

[3] Here, the differentiation between ethical and moral critique refers to a common philosophical distinction for the sake of discussion. See Richard Kraut, "Aristotles Ethics".; for a more specific account pertaining to capitalism, see also Ibid.

4. whether this 'wrong' is worse than previous forms of capitalism in its effects, which will constitute a general discussion of the economic and social impact that results from some feature of surveillance capitalism. Both economic and social consequences are relevant, given that surveillance capitalism — a new form of capitalism — is at the end of the day an economic system that has close ties to the public sphere.

If these latter two prongs are met, then providing that there is an identifiable wrong in surveillance capitalism, I can claim that 'wrong' manifests in a unique and worse manner in surveillance capitalism in comparison to alternative forms of capitalism.

2、WHAT IS SURVEILLANCE CAPITALISM?

Before moving on to the normative concerns of surveillance capitalism, it is important to understand its underlying economic logic. Essentially, what is surveillance capitalism?

Surveillance capitalism is interpreted as an economic logic that emerges with the practice of data extraction, in which it "claims human experiences as free raw material" for private appropriation and commercial practices.[4] These "human experiences as free raw material" become what is understood in this paper as 'data'. Interpreted in such a manner, then, we must first understand the nature of data itself before moving on to an exploration of surveillance capitalism as a whole.

First, data under surveillance capitalism is extracted at an unprecedented "scale".[5] Being 'free', data under surveillance capitalism differs from other forms of assets in that the notion of 'finite resource' that applies to all other factors of production does not apply. While what it is used for can have value, it itself has no inherent cost. In combination with better technological advancements that allow much of the extraction process to be undergone in an opaque manner in which consumers and regulators are largely ignorant of, this transforms the economic logic of production by allowing firms to extract data on an unprecedented scale in an ever-going manner.

Second, being "human experiences", data now profiles consumers and identifies them with "scope" and "depth".[6] It can range from a consumer's digital footprint, to behavioral patterns, and to even offline information pertaining to one's socioeconomic demographic.[7] What is crucial to note is that consumers don't need to actively provide any of this data—as opposed to limited information actively given up by the consumer in traditional forms of data collection. For example, as opposed to optional surveys and rating features that are traditionally used to gauge consumer interest and preferences online, we are seeing a surge in the use of browser cookies, where companies place cookies on their websites and pay for permission to place cookies across the internet so as to effectively relay data pertaining to user identification and user activity back to websites—all of which is done via technology and without necessarily requiring a user's active input.[8]

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[4] Shoshana Zuboff, The Age of Surveillance Capitalism: The Fight for the Future at the New Frontier of Power.
[5] Ibid.

[6] Ibid.
[7] Karen Yeung, "Five Fears about Mass Predictive Personalization in an Age of Surveillance Capitalism." pp. 258-269.

[8] Sarah Myers West, "Data Capitalism: Redefining the Logics of Surveillance and Privacy." pp. 20-41.

These characteristics are intimately related to data's new functions, where because of data's "scale", "scope", and "depth" in profiling consumers, data no longer just tells what consumers explicitly want, but can tell firms who consumers are as decision-making individuals beyond what consumers are willing to reveal. Essentially, while traditional forms of data may tell firms 'what' consumers want, they don't tell firms 'why' — yet now data does. Consequently, unlike data's traditional applications, in which information is compiled for the improvement of services and better fulfillment of consumer needs, data in its new form is collected so that firms can also interpret how consumer choice is formed on an individual basis with optimum accuracy and precision—"total certainty".[9] Data's value is thus underpinned by not just telling what the consumer wants and how to meet those wants, but also *how* to make a particular consumer want a product irrespective of its actual utility.

Given that these changes to data's characteristics and functions are driven by technological development, data and its extraction in this new form is a

> 3.) unique phenomenon to information civilization and the surveillance capitalism that emerged with it.

These unique attributes of data under surveillance capitalism generate a similarly unique form of market competition, where the economic value of potentially gaining "total certainty" over consumer behavior, and in turn, increasing profits drastically makes the accumulation of data a new form of power. It is powerful because access to this vacuum of wealth is controlled strictly by firms that are first adopt this business model and secure high barriers of entry against other potential competitors. The most prominent example of this is perhaps Google. By being essentially the pioneer in mining data for "targeted advertising", it accessed abnormal margins of profit when the company went public in 2004, where revenues increased by 3,590 percent.[10] Yet this concentration of data and wealth was limited to those who had access to "historical search query logs and their corresponding search result clicks",[11] which improved the accuracy of search results up to 31%[12] ——a lopsided competitive advantage that Google had possessed (and still considerably capitalizes upon) as the pioneer of such technology. Without access to past pools of behavioral data, even corporate giants such as Microsoft (which owns the search engine Bing) still find it hard to compete with Google simply due to their late entry into the search engine market—even with acknowledgement of the Microsoft-Yahoo Search Deal, which had already allowed Microsoft access to Yahoo's considerable amount of past user search behavior data. As shown, the market for data extraction is governed by high barriers to entry that prevent new firms from competing against immensely powerful and established surveillance capitalists, even if they have better algorithms.[13]

This is notable for consideration, as previous forms of capitalism do not necessarily entail corporate hegemony in the same way that surveillance capitalism ensures its beneficiaries. For industrial[14] and managerial[15] capitalism, for example, which places power in those who control

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[9] Shoshana Zuboff, *The Age of Surveillance Capitalism: The Fight for the Future at the New Frontier of Power*.
[10] Shoshana Zuboff, "You Are Now Remotely Controlled".

[11] Kira Radinsky, "Data Monopolists Like Google Are Threatening the Economy".

[12] Eugene Agichtein, Eric Brill, and Susan Dumais, "Improving Web Search Ranking by Incorporating User Behavior Information".

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[14] Shoshana Zuboff, "You Are Now Remotely Controlled".
[15] Alfred D. Chandler. "The Emergence of Managerial Capitalism."

the means of production, wealth and power is at the very least disseminated amongst a class of individuals involved in different corporate bodies; this ensures a relative degree of competition and interdependence between stakeholders within free market economies. Under surveillance capitalism, however, since the extreme "concentrations of data, wealth, and power" is monopolized by a controlled handful of firms,

> 3.) this "concentration" leads to the establishment of total market control on an unprecedented level.

First, this degree of market control is unprecedented because it is expansive in nature and not limited to a specific industry: For example, unlike a monopolist that develops certain agricultural technologies specific to its industry, surveillance capitalists' authority (such as Google's) is recognized in across sectors. This is powerful because the economic value of data extraction and consumer profiles in aiding profit maximization is something that can be recognized as important by most profit-driven firms; the vastly favorable reception towards the surveillance capitalist logic makes it possible for data extraction techniques to be applied and reproduced in many sectors. This allows established surveillance capitalists to replicate their wealth, barriers to entry, and by extension, power.

Furthermore, corporate hegemony under surveillance capitalism is unique because the very ones who pioneer the surveillance capitalist logic are also the predominant innovators in many facets of technological research. In an age where information technology is at development's core, these firms can hence employ their expertise, invest in R&D using their vast capital, and utilize their influential market power to integrate the logic of data extraction as an integral component of future industries— for example, Google currently in most markets for "smart products". [16] Even for large corporations like Apple, who don't necessarily extract data from customers in such a manner directly [17], it is fair to say that many of its products still require the integration of data extraction technologies and services pioneered by surveillance capitalists in order to compete in its own market. Examples include the integration of popular browser search engines like Google Chrome (runs on third-party search algorithms) in Apple products, Apple's development of Apple Maps (which runs on first-party data algorithms) and so forth, which all show the expansive influence of the data extraction logic in traditionally non-surveillance capitalist sectors. This means that surveillance capitalists, by virtue of their implications on competition and broader market conditions, are able to guarantee their relevance to information civilization to an unprecedented extent. This allows the corporate hegemony under surveillance capitalism to also be sustained on much longer terms.

Therefore, because *a.* the market for data extraction as observed currently is so unprecedently exclusive in nature and *b.* so potent in its implications on free market economies at large, data and its particular method of extraction has become an economic imperative that is both

3.) unique in how it entails long-term corporate power for beneficiaries, which is hardly possible to undermine (as of currently)

and

2.) intrinsic to surveillance capitalism, where as a result of the previous statement, one cannot compete on a viable surveillance capitalist business model if one is unable to strictly rely upon,

[16] Josef Drexl, "Designing Competitive Markets for Industrial Data - Between Propertisation and Access."

[17] Evgeny Morozov, "Capitalism's New Clothes."

duplicate, and perfect the logic of data extraction and hegemonic corporate narrative that predecessors have pushed for.

3、FREEDOM AS AUTONOMY

Given such a portrayal of surveillance capitalism, it is clear to see that surveillance capitalism's most quintessential characteristics are underpinned by data extraction. Then, it is important to ask if there is anything wrong with the act of extraction of data itself. This is quite crucial, since if there is something wrong with data extraction, then there is naturally something wrong with surveillance capitalism as well, as its business model cannot be conceived without data.

In response, I argue that the extraction of data is wrong because it simultaneously strips away the autonomy of consumers. Here, autonomy[18] is interpreted as the capacity to a.) obey oneself [19] and b.) control one's own appetite.

To clarify, 'obey oneself' is a conception of subjective autonomy, where a person is acting upon their own reasons and motives in order to live a life that does not feel restrained. In this view, if there must be any form of obedience to another authority, that obedience must be self-imposed. If obedience is self-imposed, that person will not feel bounded or inhibited. For example, if a citizen obeys civil laws and norms of a community so that they can enjoy the benefits of citizenship and legal protection in exchange, the citizen can still be *subjectively* autonomous in this case, since their obedience is self-imposed and subjectively empowering[20]. On the other hand, to 'control one's own appetite' is interpreted as a form of *objective* autonomy. In this view, for someone to be autonomous, it is not enough for that person to subjectively *feel* unrestrained. In order for someone to truly obey themselves, the reasons and motives that one obeys must also be authentic and independent, where they shouldn't be the result of "distortion" by an external source.[21] For example, addicts subject to mindless consumption might not necessarily 'feel' like they are obeying someone else, but their actions may still be objectively a product of an appetite or addiction that they don't have genuine control over. For these addicts, their lives can't be said to be truly self-driven. Hence, from this two-part view of autonomy, the capacity to a.) subjectively obey oneself and b.) objectively control one's own appetites are both essential to maintaining a consumer's freedom as autonomy.

Understood in this sense, the extraction of data under surveillance capitalism may strip away the autonomy of consumers due to the implications data has on consumers' ability to maintain control over their needs for consumption.

Since it was previously established that the extraction of data —in its highly precise and accurate form that tells firms how to make a particular consumer want and choose— is intrinsic to surveillance capitalism, it follows that

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[18] From '*autonomos*', from *autos* 'self' and *nomos* 'law'. Contrasts with heteronomy, 'hetero-' meaning 'other/another/different' and '-nomy' from *nomos*.
[19] Joel Feinberg, "The Moral Limits of the Criminal Law Volume 3: Harm to Self".

[20] People may bound themselves to society and its norms "to find a form of association that will defend and protect the person and goods of each associate with the full common force, and by means of which each, uniting with all, nevertheless obey only himself and remain as free as before." *See* Jean-Jacques Rousseau and Richard W. Crosby, *Of the Social Contract*. Pp. 49-50.

[21] John Christman, "Autonomy in Moral and Political Philosophy".

2.) the violation of a consumer's autonomy is an intrinsic outcome when data is used for commercial practices because a consumer can't be said to have genuine control over their own appetite when data extraction provides firms with the knowledge of how to trigger that appetite and alter it. Taking Google's targeted advertising techniques as an example[22], a consumer might feel that the product displayed is what they actually want, but that doesn't change the fact that it is in fact a product of external imposition made possible by data analytics and undergone by a profit-driven actor. For such consumers, they cannot be said to be truly autonomous.

In response, some may argue that such a violation is contingent on the latter act of data being used in some way[23]. If data was not used to actually distort a consumer's appetite, the extraction of data is not necessarily problematic[24]. However, firms *will* act upon the data they gain by virtue of surveillance capitalism's very economic logic. As elaborated upon in the previous section, if a firm wishes to be competitively viable and profitable as a surveillance capitalist, it must replicate all factors of the business model entailed by its pioneers and predecessors in order to compete with established competitors. That is to say, if a firm is a surveillance capitalist, it must use the data it extracts to shape and manipulate consumer appetite; otherwise, the firm is either rendered uncompetitive in such a market or not a surveillance capitalist at its core.

This is paramount to refuting proponents of surveillance capitalism, who often claim that the benefits of personalization that data extracting strategies allow could in fact improve the standard of living for customers that are considered favorable for consumption[25]. As long as firms are inherently inclined to distort these consumers' awareness of what is genuine, there is no guarantee that the higher 'standard of living' that is conceived by consumers doesn't eventually become a mere construct or illusion. To consumers who are looked upon favorably because of their capacity or tendency to consume, the promotion and display of data's goodness is implied to run simultaneous to the underlying corporate agenda that aims to nudge further consumption, whereby consumers, ideally, will routinely and indefinitely consume in bulk and rely on data-driven services irrespective of whether there is an authentic desire to actually consume in the future. This trend leads to an inevitable shift in the dynamics of capitalism from one centered around fulfilling genuine consumer needs to one in which firms can afford to pursue profit-maximization via harnessing consumer appetite in a way that is irrespective of their genuine desires.

However, why this violation of autonomy should be *ethically* unacceptable has so far only been implied rather than addressed explicitly. Why is the quality of being self-driven and autonomous such an ethical imperative?

To respond, maintaining autonomy in itself is necessary to leading and living a good and fulfilling life. It is necessary because only by having self-driven appetites and genuine needs can one also begin to accordingly define fulfillment for oneself and progress towards that goal; when mindlessly consuming, an individual is not being fulfilled. As afore-explained, if firms are able to alter consumer appetite, consumers are dependent on firms in determining what is satisfying and when one is actually satisfied. And given that firms inherently profit off of never-ending consumer desire and are invested into sustaining it, it is unconceivable why consumption driven by corporate influence via the use of data to alter consumer behavior will result in consumers' genuine fulfillment as opposed to the generation of more desires, and subsequently, more needs.

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[22] Shoshana Zuboff, "You Are Now Remotely Controlled".
[23] Titus Stahl, "Indiscriminate Mass Surveillance and the Public Sphere."
[24] This view is elaborated upon and discussed later on from the lens of Freedom as Non-Domination.

[25] Frank Pasquale, *The Black Box Society.*

As such, consumers who are driven by external and superimposed needs to consume will only be further away from fulfillment. Hence, it can be concluded that in this market context, autonomy of consumers is a prerequisite to ever achieving self-fulfillment; subsequently,

> 1.) by breaching autonomy, the act of data extraction is ethically unacceptable, since it prevents us from living a fulfilling life.

While the first two prongs of the criteria (1. ethically unacceptable and 2. intrinsic to surveillance capitalism) are met, it isn't immediately apparent why the violation of consumer autonomy is unique to surveillance capitalism.

One may raise the objection that the manipulation of consumer needs irrespective of genuine need has been a strategy that firms have employed way before the emergence of surveillance capitalism in its current form. For one, firms have long tried to increase likelihood of consumption through devious means. Studies have shown that firms have developed cognitive strategies such as "option-framing" in selling customizable products with add-ons, where they can influence "consumers' decision making regarding the total number of finally chosen product options" [26] by presenting information in a way that is linked to a specific mode of informational-processing so as to take advantage of consumers' bounded rationality in a limited information environment.[27] For example, experimental results show that "consumers choose a higher number of options in the delete (versus add) frame," where a consumer is more likely to purchase a product with the full set of add-ons if all of them were presented in the "default" option.[28] This shows how the tendency and ability to exploit consumer irrationality rather than to increase sales by persuasion could have been and likely has been in practice without involving data extraction at all.

Even ignoring these specific instances of behavior influencing and instead observing the broader concept of 'genuine needs', are we really only pursuing genuine needs anyway? Take smart devices or the internet—many would very well conceive of these goods and services as indispensable, yet the reality is that they are all super-imposed by an information civilization and new modes of social interaction that is to a large extent fueled by corporations that develop these technologies.

This sheds insights upon how firms' intent to impose 'fake' needs stems beyond the economic logic of surveillance capitalism. Firms act in such a manner not just because they must in cases of surveillance capitalism, but also because profit maximization is their private economic objective[29]. As stakeholders wholly invested into maintaining the existence and relevance of the market economy as a central allocative mechanism, the desire to sustain consumer needs and societal demand infinitely is a natural byproduct. And if the usurpation of consumers' autonomy is a means to do so, it would seem reasonable that firms will gravitate towards such strategies.

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[26] Dipayan Biswas, "The Effects of Option Framing on Consumer Choices: Making Decisions in Rational versus Experiential Processing Modes." pp. 284-299.

[27] Daniel Kahneman, "Maps of Bounded Rationality: Psychology for Behavioral Economics." Pp. 1449-1475.

[28] Dipayan Biswas, "The Effects of Option Framing on Consumer Choices: Making Decisions in Rational versus Experiential Processing Modes." pp. 284-299.

[29] Craig Dunn and Brian K. Burton, "Friedman's 'The Social Responsibility of Business Is to Increase Its Profits': A Critique for the Classroom."

Thus, it might not be the case that violation of consumer autonomy is a unique phenomenon to surveillance capitalism.

To rebut, one can argue that in previous cases of capitalism, the violation of consumer autonomy was a byproduct of a *dysfunctional*[30] system rather than its *intentions*: previous forms of capitalism did not conceive the violation of consumers' autonomy as a necessary component of a firm's business model, nor was it essential to the broader economic order; the system may still have had that objective of serving consumer needs. Instances of abuse are thus not intrinsic, but rather, at best habitual as a result of perverse applications of marketing strategies. Contrarily, data extraction and the violation of consumer autonomy that inevitably follows is engrained into the very logic of surveillance capitalism. Granting that to be true,

> 3.) perhaps one can claim that the logic of creating and 'controlling' consumer appetite is only fully actualized in surveillance capitalism and is thus unique to this extent.

However, even then, it isn't quite clear why this is deserving of greater concern other than that it is intrinsically wrong: to acknowledge that the violation of consumer autonomy was observed before surveillance capitalism is to concede that this new 'wrong', in effect, may just be at best a culmination of development from the past.

Therefore, from a discussion of freedom as autonomy and how data extraction violates it, we can conclude that there is indeed something intrinsically wrong with surveillance capitalism that also happens to be unique to a certain extent. Thus, we have satisfied the first two prongs of our criteria and began to tackle the third. However, the fourth prong remains unaddressed—how is this wrong any worse than what we had before? Greater yet, is the violation of autonomy that could occur as a result of data extraction really our greatest concern? In broader terms, having established that companies *will* act upon the data they extract, are we ultimately worried because of all the ways in which data can be used (which results in violation of consumers' autonomy), or because of how companies are in a position to do so?

The lenses of freedom as non-interference and non-domination may provide us with answers.

4、FREEDOM AS NON-INTERFERENCE

In the previous section, we have identified violation of autonomy as a 'wrong' that occurs under surveillance capitalism. However, it is perhaps only one of many wrongs that can be identified in relation to the usage of data. This poses the question of how all those wrongs might cumulatively reflect something even worse about the state of corporate surveillance.

To do so, one might try extending the argument of the previous section: consumer will is not just affected by distorting one's appetite, but outright and continuously violated in all the ways that a consumer can be wronged. Essentially, violation of autonomy and all the other wrongs that can arise are significant in whole because they all ultimately interfere with what a consumer wants.

If this is true, surveillance capitalism can be said to be ethically problematic by the conception of freedom as non-interference[31]. In this view, when there is an external force that is acting directly against a consumer's will, the consumer is prevented from actualizing what would have been an

[30] *See* Introduction on interpretation of 'dysfunctionality'.
[31] Philip Pettit, *Republicanism: a Theory of Freedom and Government*.

actionable desire. As such, they are both objectively and subjectively constrained. Thus, one might argue that the consumer is prevented from freely living a good life according to their own will.

First, how might surveillance capitalists be able to consistently violate consumer will in its numerous ways? One might say that surveillance capitalists are able to do so via "hidden" commercial processes, which originates with the opaque nature of data extraction. [32] If a consumer was to be unwilling to give data and data was forcibly extracted from them, there is no meaningful way to counter that.[33] The lack of recourse stems beyond the extraction of data itself, since the opacity implies that even traditional activities that involve the interference with consumption (such as price discrimination, [34] "market segmentation", [35] and "behavioral modification"[36]) all can be done in a way that is undetectable and unobjectionable, unlike previously—After all, how can one detect data being used if one is oblivious to data being collected in the first place?

To validate such an argument, we must first prove that corporate surveillance techniques are intrinsically opaque. The opacity of data extraction may be intrinsic for two reasons: For one, data can only be useful if consumers are largely ignorant of its procedures. If consumers are aware of the goings-on, they are able to develop mechanisms of defense (for example, by seeking legal recourse). At the very least, those consumers will likely consciously or subconsciously alter their behavior in some way that is less natural and useful towards a firm's purposes of individualistic consumer profiling. If optimum individualistic consumer profiling is intrinsic to surveillance capitalism, then so must the opacity of data's extraction. Second, data extraction is intrinsically opaque because there is no meaningful way for even policymakers to combat such behavior, unlike before.[37] If there are no means of oversight and ways to combat such behavior, profit-driven firms will not naturally subject themselves to regulation, since firms will likely be incentivized by the extra profit margins that opaque data extraction can entail.

One might counter that while that may have been the case at one point, in the near future, one can reasonably expect policymakers to develop the capacity to counter surveillance capitalists. This can be seen in the increasing scrutiny of major surveillance capitalists such as Facebook by regulators such as the EU aimed to pressure Facebook into adopting changes.[38] It is also not unconceivable that some firms will ally themselves to the state. Baidu, the prominent search engine in China and major proponent of data-analytics and face recognition technologies, is known for partnering with the Chinese government in providing the data and the extraction-

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[32] Shoshana Zuboff, *The Age of Surveillance Capitalism: The Fight for the Future at the New Frontier of Power.*

[33] Sarah Myers West, "Data Capitalism: Redefining the Logics of Surveillance and Privacy." pp. 20-41.

[34] Akiva A Miller, 'What Do We Worry About When We Worry About Price Discrimination?: The Law and Ethics of Using Personal Information for Pricing.' pp. 41-95.

[35] Karen Yeung, "Five Fears about Mass Predictive Personalization in an Age of Surveillance Capitalism." pp. 258-269.

[36] Zuboff, *The Age of Surveillance Capitalism: The Fight for the Future at the New Frontier of Power.*

[37] Rinie van Est and Joost Gerritsen, *Human Rights in the Robot Age.* 43.

[38] Paul M. Schwartz. "The EU-U.S. Privacy Collision: A Turn to Institutions and Procedures."

technologies to improve national security and streamline queues for public services, for example.[39] As such, many governments are gaining an awareness of these firms' operations.

However, in these cases, regulation is ultimately contingent on these practices first being exposed to the public or the regulators. In other words, if Facebook was able to conceal that it was extracting data in the manner it did or does, regulation would have still been rendered rather useless; if Baidu was unwilling to ally itself to the state, the government would not have known what it now knows. This is a crucial premise, as surveillance capitalists are also the very ones that pioneer technologies—not necessarily just data extraction technologies, but often tech on many fronts (as explained in previous sections). In combination with market provisions and legal protections for own-brand data technologies, even if current operations are exposed, it is likely that surveillance capitalists will still be able to develop new methods of opaque data extraction to ensure that their commercial practices remain undetected in the near future. Even if we suppose that these firms are dependent on state funding [40] and that states can try transferring this funding towards competing research efforts against surveillance capitalists, government actors may still lack the corporate expertise, organization, and capital to compete on the same platform.

> 2.) As such, it makes the hidden quality of a surveillance capitalist's operations a likely permanent and *intrinsic* component of its business model so long as surveillance capitalism is the economic order.

Because the hidden nature of these operations allows surveillance capitalists to go undetected,

> 3.) extraction of data under surveillance capitalism is also for this very reason *unique* compared to other methods that firms can use to violate consumers' autonomy, as governmental scrutiny has traditionally been the predominant mechanism for constraining corporate behavior.

In order to prove the hidden nature of data extraction to be ethically problematic from the lens of freedom as non-interference, though, it must also be proven that the act of interfering with consumer will is necessary for surveillance capitalism to function; We must prove why for all instances, it is intrinsically the case that consumers must stand opposed to hidden commercial practices. This might not yield as clear a conclusion.

The most intuitive argument in support would be to utilize the logic of the previous section, where hidden practices such as data extraction intrinsically violates one's autonomy and is ethically unacceptable. Since data extraction violates a consumer's autonomy, one might say that it is irrational to tolerate such procedures.

However, what is missed is the fact that consumers don't always choose based upon what is reasonable and apparently rational. Consumers are often subject to a "double-bind", where they are "caught between desires for privacy and the ability to form meaningful communities with other users online without opting out of these services".[41] Facebook famously makes "the use of its social network conditional on its being allowed to limitlessly amass every kind of data generated by using third-party websites and merge it with the user's Facebook account. These third-party sites include firstly services owned by Facebook such as WhatsApp or Instagram, and

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[39] Jiangping Zhou, Qihao Wang, and Haitao Liu, "Evaluating Transit-Served Areas with Non-Traditional Data: An Exploratory Study of Shenzhen, China."

[40] Mariano-Florentino Cuéllar, and Aziz Z. Huq. "Economies of Surveillance."

[41] Sarah Myers West, "Data Capitalism: Redefining the Logics of Surveillance and Privacy." pp. 20-41.

secondly websites and apps of other operators with embedded Facebook API."[42] This enormous sphere of influence over what are often the "essentials" to how we as people interact, communicate, and live in the contemporary day and age means that consumers are often inclined to tolerate a firm's data extraction even if it is against their will or coerced. While one might find this ethically problematic for other reasons, freedom conceived as non-interference doesn't take into account the conditions under which the consumer choice is made, strictly construed. A choice is a choice made.

In fact, even if one grants that a consumer is acting rationally, it isn't necessarily the case that they will object to data extraction because it violates their autonomy. For example, most websites would ask the user to consent to their privacy settings and use of browser cookies. For these users, it isn't unconceivable that at least some of them will agree, as there are reasonable and perceivable benefits [43] such as personalized webpages that comes with accepting those settings, which some users might desire. Similarly, as long as there are any possible rationales for a consumer to agree to the hidden data extraction process and the commercial practices that follow, it can't be said that firms necessarily interfere with consumer will. Thus, surveillance capitalism may not be ethically unacceptable by the standard of freedom as non-interference.

Of course, one may object that this is similar to subjective autonomy, where the consumer *feels* that they are acting upon their own will even though it could be in reality a guided and externally influenced response. However, if consumers feel "empowerment" as a result[44], why must this be ethically wrong? If a consumer's fulfillment in life can be subjectively determined, why can't one's subjectively perceived satisfaction be legitimate as well? A consumer may still be able to live a subjectively satisfying life without having all needs fulfilled. In fact, without the conveniences that can be offered data-driven services[45], a consumer may perceive themselves to be worse off. Then, from a consideration of the various ways in which data can be used, surveillance capitalism might even offer various considerable consumer-benefits---even if its commercial practices may be worryingly hidden from the public eye.

5、FREEDOM AS NON-DOMINATION

What, then, is so concerning about firms being able to use data extracted from consumers?

Perhaps, one might be concerned because of the very fact that firms are in a *position* to use data, where data extraction is problematic not because of what can follow, but because it is characteristic of an arbitrary power that surveillance capitalists gain through the process of data extraction; firms accumulate not just market power, but the capacity to facilitate social control as well—which is wrong in and of itself from the view of freedom as non-domination.

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[42] "Press Release: Preliminary Assessment in Facebook Proceeding: Facebook's Collection and Use of Data from Third-Party Sources is Abusive."

[43] Mariano-Florentino Cuéllar, and Aziz Z. Huq. "Economies of Surveillance."

[44] Shoshana Zuboff, "You Are Now Remotely Controlled."

[45] Karen Yeung, "Five Fears about Mass Predictive Personalization in an Age of Surveillance Capitalism." pp. 258-269.

To clarify, to possess freedom as non-domination is to not be subject to any arbitrary power that can prevent one from acting upon their will. A power is arbitrary if there are no mechanisms in place to limit the extent to and the conditions under which the power can be exercised. One is unfree if subject to arbitrary power because there is no sense of security.[46] A slave under the dominion of a master is insecure because the master is able to tyrannize over the slave at any moment; even if the master is benevolent, the duration is indefinite and up to the discretion of the master.

In the context of surveillance capitalism, firms gain arbitrary power since data extraction places firms in a position to disregard the consumer. As afore-explained in previous sections, by extracting data, firms are able to manipulate consumer appetite. In the context of total domination, this is problematic because firms gain the power of taking a consumer's self-control away irrespective of whether the consumer actually welcomes this intervention. This ethical concern is contingent not on the later act of triggering and altering a consumer's appetite itself--which can manifest in the form of manipulation, "behavioral modification", and so forth[47] -- but on the very ability to do so, which is entailed by data extraction. This is because once a firm possesses data and is in a position to alter consumer appetite, the notion that only consumers can alter and choose what they need is lost. Consequently, firms also lose respect for a consumer's will. Under such conditions, firms with the economic-objective of profit-maximization[48] have no reason not to capitalize upon their newly gained advantage.

This distinction between the "position to" and the "act of" altering consumer appetite is important because while many scholars like Zuboff talk about what is wrong with the following acts or ways in which data can be or is used, they don't elaborate upon why the appropriation of data in this form is in itself something intrinsically bad[49]. Hence, critics such as Morosov assert that Zuboff might as well rename "surveillance capitalism" to be, for example, "behavior modification capitalism" since it appears that the "latter is [her] real object of concern".[50] This can be addressed by considering data extraction as a feature of surveillance capitalism is ethically wrong due in the very *position* to use data (which is inherent in the stage of data appropriation) and not just wrong by the potential ways that data can be used.

> 2.) Since these corporations' arbitrary power is driven by the hidden nature of these commercial practices, which has been proven in the previous section to be intrinsic, this position to dominate must also be an intrinsic outcome of surveillance capitalism.

Certainly, traditional forms of corporate power over consumers did exist, such as how "Apple regularly pushes customers around, even preventing from using third-party repair services."[51] However, because corporate actions were traditionally detectable, that form of power could be restrained—it didn't need to be arbitrary to the fullest extent. Essentially, while capitalism in its traditional forms may tend to favor non-regulation, regulation was still possible if needed.

Now, however, not only is the consumer insecure against the surveillance capitalist, the consumer is unaware of their insecurity and government regulators are unable to regulate these opaque commercial procedures or develop methods of regulation because a.) only surveillance capitalists control access to the technologies and means of further developing them, b.) it is largely up to

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[46] Philip Pettit, *Republicanism: a Theory of Freedom and Government*.
[47] Shoshana Zuboff, *The Age of Surveillance Capitalism: The Fight for the Future at the New Frontier of Power*.
[48] Craig Dunn and Brian K. Burton, "Friedman's 'The Social Responsibility of Business Is to Increase Its Profits': A Critique for the Classroom."
[49] Evgeny Morozov, "Capitalism's New Clothes".
[50] Ibid.
[51] Ibid.

firms to expose themselves and c.) there is no meaningfully instituted obligation or leverage by which to compel firms to do so (as elaborated upon in the previous section). This not only reinforces the ability to extract data indefinitely in the marketplace, but implies that the same corporate power can be applied to social spheres and political domains without effective resistance—all of which done with the right of total discretion vested in the firm.

3.) This accumulation of arbitrary power is therefore unique to surveillance capitalism in comparison to previous forms of capitalism.

Moreover, the lack of recourse against surveillance capitalists' arbitrary power in executing its commercial procedures makes our societal norms and values vulnerable to being undermined. For example, a study using an automated tool that runs browser-based experiments regarding the relation between user behavior, Google ad settings, and the ads displayed to users found that for the high-paying job ads subject to experimentation, Google's targeted advertising techniques had led to the ads being shown "1852 times to the male group but just 318 times to the female group".[52] As a regular female user, one would not even be aware of this disparity, even though it is quite problematic for obvious reasons. Data extraction for targeted-advertising in ways such as this demonstrates just how social inequalities and injustices can be exacerbated by corporations, yet will go inevitably unaddressed because of the opacity of surveillance capitalists' operations.

Perhaps it may appear that "nary a day goes by when we do not gain in some material way from the extraction and deployment of" data,[53] yet it can't be neglected that a sense of security in the values and moral decency of our societal environment is also essential for us as moral beings to lead a good life.[54] This implies that the violation of consumer autonomy which data extraction entails (as aforesaid) is not just wrong because the power to do so is arbitrary,

4.) but also much worse in its effects under surveillance capitalism compared to what we had faced before. This is because the logic and methods behind surveillance capitalism does not merely actualize a perverse corporate desire for profit-maximization that has been culminating for all this time, but its business model also increasingly equips corporations with the ability to disregard the moral grounds that constitute much of modern liberal society, and ultimately, human nature.

Therefore, even if one is not to buy the violation of consumer autonomy as an intrinsic wrong in the economic order, there must still be something wrong and much worse in surveillance capitalism because of its implications on the creation of arbitrary social and economic power, where the emergence of surveillance capitalism actualizes a tyrannical corporatocracy that has no meaningful obligation to the advancement and preservation of our humanity.

6、CONCLUSION

In this paper, I assessed whether there is something wrong with surveillance capitalism in terms of a four-pronged metric, where the identified wrong must be:

1. ethically unacceptable

[52] Amit Datta, Michael Carl Tschantz, and Anupam Datta, "Automated Experiments on Ad Privacy Settings." pp. 92-112.

[53] Mariano-Florentino Cuéllar, and Aziz Z. Huq. "Economies of Surveillance."

[54] Francisco J. Ayala, "The Difference of Being Human: Morality." pp. 9015-9022.

2. intrinsic to surveillance capitalism

and to be worse than previous or existing forms of capitalisms,

3. a unique feature to surveillance capitalism
4. worse in terms of societal impact in general

To focus my analysis, I discussed surveillance capitalism's ethical status in terms of the philosophical concept of freedom, as understood in three different ways: freedom as autonomy, non-interference, and non-domination:

In an exploration of freedom as autonomy, I have proven that the extraction of data under surveillance capitalism prevents a consumer from being autonomous, where they are unable to truly obey themselves and maintain genuine control over their own appetite. I have shown how this usurpation of autonomy necessarily prevents consumers as individuals from pursuing and living a good and fulfilling life, where this violation is 1.) ethically unacceptable, 2.) intrinsic to surveillance capitalism, and 3.) unique to surveillance capitalism compared to existing forms of capitalism to a limited extent.

In a discussion of freedom as non-interference, I tried to extend the previous section's discussion of autonomy to a broader exploration of how the vast number of ways in which data can be used are cumulatively and unprecedently harmful and unacceptable. Although this section did not yield definitive conclusions, it provided insights into to the nuances behind support for surveillance capitalism, where it could provide considerable consumer benefits in some instances.

In an investigation of freedom as non-domination, I shifted away from analyzing surveillance capitalism based on the ways in which data can be applied, and instead, evaluated how surveillance capitalism might be problematic in the act of appropriating data itself. In considering the unprecedented arbitrary power that surveillance capitalists are able to accumulate during the appropriation-stage, I have shown how the corporate dominion that underlies corporate surveillance manifests in such a way that is 1.) Ethically unacceptable, 2.) intrinsic to surveillance capitalism, 3.) unique, and 4.) with dangerous societal implications.

This allowed me to finally conclude that the same features of surveillance capitalism that had led to the usurpation of consumers' freedom as autonomy manifests in a 4.) far worse manner as opposed to what occurs under other forms of capitalism due to the emergence of corporate domination it makes possible. Even if the usurpation of autonomy is not to be held against surveillance capitalism, there will still be another identified feature in this paper that makes this new economic order wrong and far worse.

That being said, there are various limitations to this paper. Namely, that all the normative judgments made are premised upon "surveillance capitalism" indeed being exactly the same as described in this paper. However, although the depiction of surveillance capitalism in this paper may be true, it is conceded that it may only represent a narrow conception of what surveillance capitalism can be; given that "surveillance capitalism" is still a new and novel notion at the time of writing, we may yet to have understood what we are truly confronted with. "Surveillance capitalism" can potentially refer to much more to what is underpinned by this paper, such as in the gradual integration of portions of the surveillance capitalist business model into the healthcare sector and so forth, where data may be used in much more distinct ways due to the differing natures and structures of these markets[55]. This may entail more subtle motives and precise regulatory frameworks in these specific cases that are not fully considered in this paper. The same concerns that are brought up in this paper, then, may not apply as the concept of "surveillance capitalism" develops to include much more territory in the future.

Nonetheless, this paper does have several useful implications, which can be developed in future studies and research. First, such an ethical critique in this paper alludes to a potential exploration of the social responsibilities of corporations as well as how those responsibilities might differ for

[55] Mariano-Florentino Cuéllar, and Aziz Z. Huq. "Economies of Surveillance."

firms in this day and age given the changing circumstances of an information civilization. Second, this paper's concerns pertaining to the role of state scrutiny in restraining corporate action invites further inquiries regarding the dynamics of corporate-state relationships, which would constitute a much more detailed normative investigation of how our political and economic domains should interact.

Despite the critical approach adopted in this paper, it should also be noted that this paper is by no means pessimistic; although surveillance capitalism has been identified in this paper to be problematic for various reasons, it should not be taken that society is beyond repair. Rather, it is merely implied that now that we have more insights into grasping what surveillance capitalism might be, although we may still be oblivious to much of what is going on, we ought not to be willfully ignorant to the trends that we do see. It is by gaining this awareness as consumers, individuals, and governments that we can start making the first small steps towards bringing change in the economic domain for the better.

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