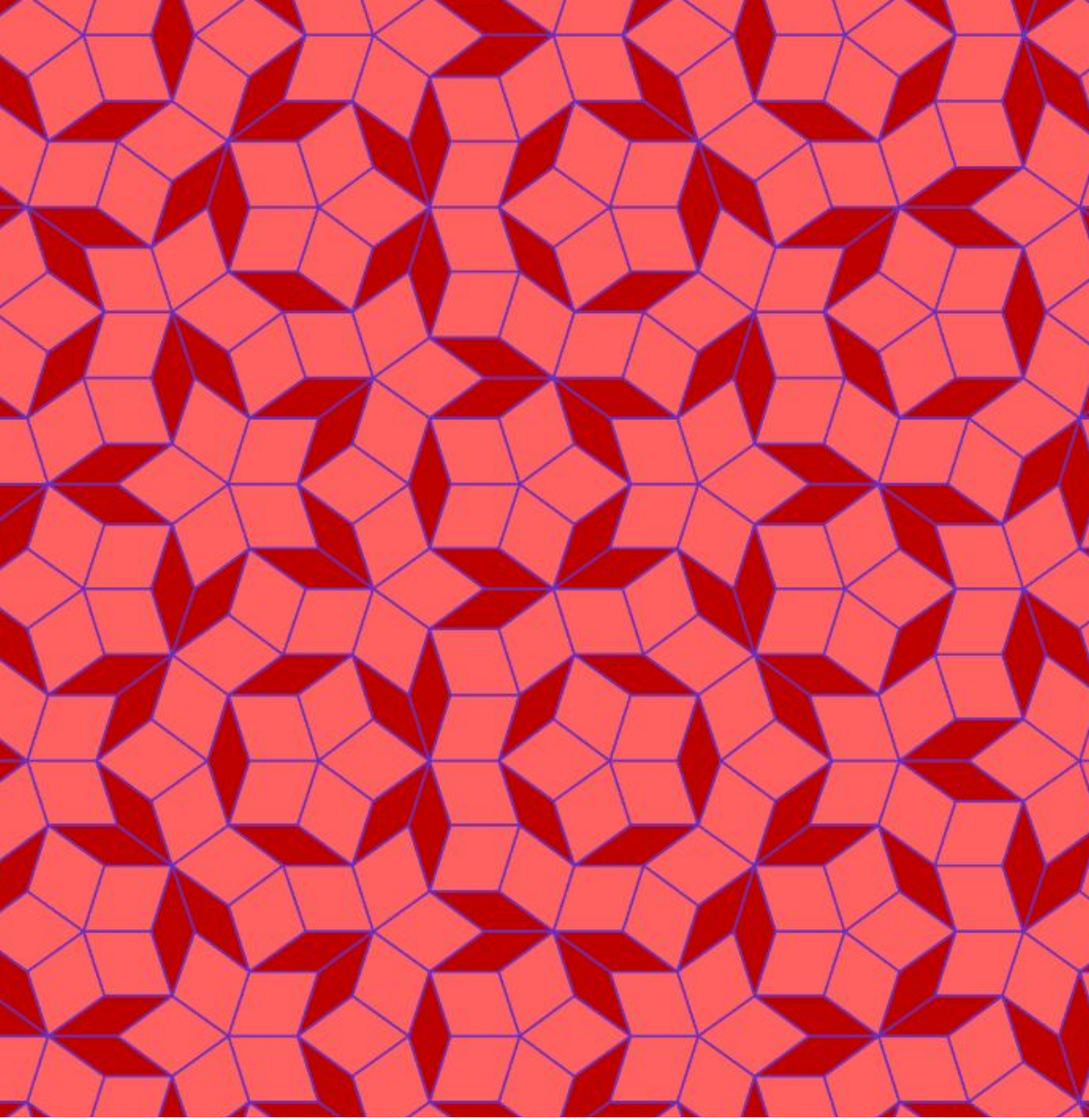

THE PENROSE MAGAZINE

STEM

Issue 10, 16 July 2026

Welcome to the Tenth Issue of Penrose Magazine!

Penrose is a STEM magazine where we hope to establish a community of young people who are passionate about STEM and want to share with their peers and further their knowledge beyond the curriculum. This installment of the magazine consists of the academic articles from the physics behind sound to mitochondria and the endosymbiotic theory. We hope to continue fostering an environment where people are encouraged to push themselves to create meaningful work and support each other to grow.

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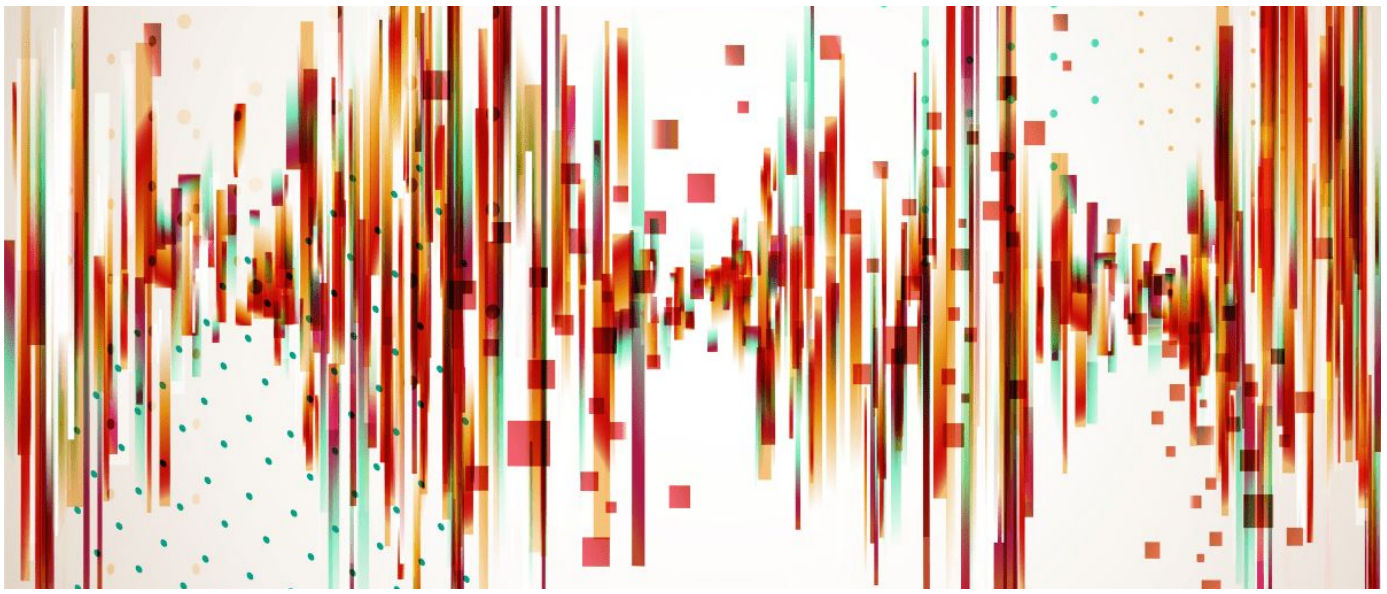

The Physics Behind Sound: Why Some Sounds Are More Enjoyable Than Others

Introduction

Sound composes a great part of the daily environment, ranging from intentional melodies to ambient noise. However, some sounds are more enjoyable than others. For example, with these two distinct scenarios: The screech of nails against a chalkboard versus a beautiful melody. While these preferences are often linked to subjective taste, the explanation for the harsh contrast between the perception of music and noise is rooted in the physics behind sound waves.

Sound

In physics terms, sound can be defined as a mechanical disturbance from a state of equilibrium that propagates through an elastic material medium, typically being air. It travels as a longitudinal wave, creating alternating compressions and rarefactions [1].

A sound wave is characterized as a mechanical wave. For sound to happen, there must exist an object capable of producing a vibration that causes a disturbance to a first particle, starting sound waves. The wave propagates from one location to another through particle-to-particle interaction: as this initial particle is disturbed within the medium, it exerts a push or pull on its nearest neighbors, causing them to be displaced from their equilibrium positions. When this happens, the particle interaction continues all throughout the medium with the disturbance pattern repeating, therefore producing sound [2].

Properties of Sound Waves

There are four main characteristics of sound waves: wavelength, amplitude, frequency, and period. Wavelength represents the distance a wave travels before repeating its pattern; which is measured from the center of one compression to the next.

Amplitude determines the perceived loudness or volume of a sound, mandated by the maximum displacement of particles disturbed from their equilibrium position as the wave passes through the medium. A higher amplitude is equivalent to a louder sound.

Frequency indicates the number of complete wave cycles produced per second, measured in hertz (Hz) [3]. It determines the pitch of a sound. The human ear can typically detect frequencies from 20 to 20,000 Hz, with the most sensitivity between 500 and 10,000 Hz [1].

Conversely, the period represents time required to complete an entire wave cycle, enclosing one full compression and rarefaction, as it passes through a specific point [3].

For any given material and temperature, the speed of sound is the same, around 340

meters per second in surface air at 20° Celsius, regardless of their wavelength or amplitude. This means that the only way to increase the frequency of the waves in a given space is to shorten their wavelength, an inverse relationship demonstrated in the following equation:

$f=v$

Where v is speed, f is frequency and λ is wavelength.

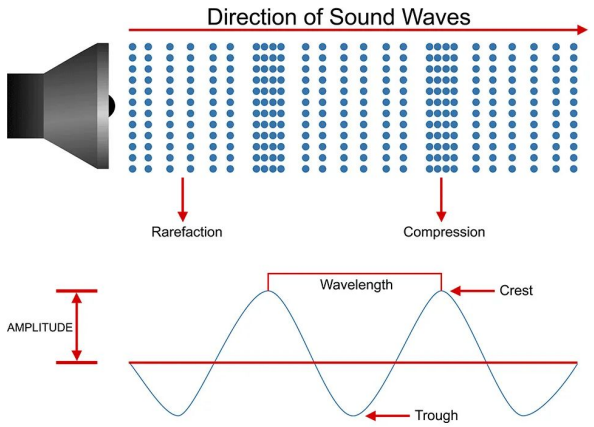

Figure 1: Sound Wave Diagram [3].

Physics of Harmony

More than one sound wave can exist at the same time in the same space. When more than one pitch is played at the same time, it is called an interval. Three or more notes are called a chord. As sound waves travel at a very high speed to occupy the volume of air around us, the waves overlap with one another and affect each other, resulting in a new wave, a process known as interference.

When two waves compress and refract the same regions of air it is known as constructive interference. When one wave tries to compress the air while the other tries to refract it, it is a destructive interference.

Even though the brain only processes one composite wave, it can understand that its components come from different sources, allowing it to comprehend more than one sound at the same time. That is the key to being able to hear harmony.

An “agreeable” harmony relates to a process known as consonance, when the sounds blend in a pleasurable way. In contrast, the quality of clashing harmony is known as dissonance. These are what makes harmony sound balanced and coherent, or jarring and unstable.

Consonance and dissonance are caused by the brain dividing the frequencies of the notes it hears at the same time. Therefore, on a physical level, all harmonies are mathematical ratios. The simpler the frequency ratio, the more consonant the harmony, while a more complex ratio results in greater dissonance. An example of a consonant harmony would be an octave, built with a 2:1 ratio. The song “Somewhere Over the Rainbow” from “The Wizard of Oz” uses octaves to create a magical feeling. In contrast to this enjoyable sensation, an example of a dissonant harmony would be a minor second, built with a 16:15 ratio, which is considered one of the most dissonant intervals. As it has a high-integer ratio, the frequencies do not align as often as they would with the octave, causing the brain to interpret it as clashing. The “Jaws” theme uses the minor second to create an immediate sense of impending danger and anxiety [4].

Harmonics and Timbre

It is observable that sounds produced by different instruments are distinctive from one another, even if they are playing the same note. This is because of the timbre, which is the textural nature of sound and is caused by the harmonic series, also known as overtone series.

For instance, if a set of vibrating strings are all vibrating at the same speed, then the second string will have half the period and thus double the frequency as the top, the third string will have thrice the frequency, and so on. When a physical body is set into vibration it will vibrate down its whole length, half its length at a smaller amplitude and a third of its length at an even smaller one; with each smaller vibration, called an overtone or harmonic, growing higher in pitch and quieter in volume. Each overtone

generates its own wave, with different volumes depending on what causes the sound.

Hence, as these multiple waves combine to create one resultant wave, the brain merges the overtones together to interpret them. The listener consciously hears the lowest, loudest overtone, and the brain compares the amplitudes of the remaining overtones to determine the timbre of a sound. Thus, the difference in sounds is caused by the differences in the volumes of overtones. The quieter these frequencies are, the clearer the sound becomes. When overtones do not line up in a neat way, the brain does not recognize any particular frequency in the sound, so it will sound like static [4].

The Role of The Brain: Psychoacoustics

When the human ear perceives sounds such as music, the brain performs significant amounts of computation. The brain's auditory system is organized tonotopically, which means that different areas of the brain respond to different frequencies. When it perceives a pleasant, consonant ratio, the neurons in these areas fire in a steady, synchronized rhythm. However, dissonance causes neural noise, where the firing patterns of neurons become chaotic.

Furthermore, the brain is constantly predicting the following note based on mathematical patterns, such as during the anticipation of a drop in a song. So, when a song follows physical rules by resolving a dissonant chord back to a consonant one, the brain experiences a sense of reward through the activation of the mesolimbic system, explaining why a sound can evoke happiness.

Studies also show that even infants prefer consonant intervals such as the 2:1 ratio of an octave over dissonant intervals, which supports the statement that when it comes to sound, enjoying it is not only a matter of personal taste, but is also influenced by harmonies. Conjointly, this demonstrates that the human brain is wired to mirror the physics of sounds, and to find consonance more agreeable than dissonance [5].

Conclusion

While it is true that emotions and subjectivity play an important role in the way in which sound is experienced, such as music and noise, the way in which our brains process it is aligned with the laws of physics. Human brains are intrinsically working along with mathematical ratios found behind sounds for every melody enjoyed or disliked.

By Andrea García

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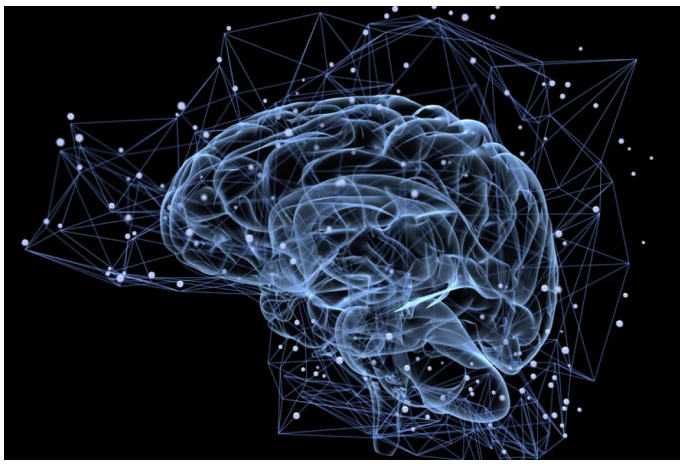

The Hidden Complexity Of Lifting A Finger

The saying, “you won’t even have to lift a finger,” implies simplicity. However, the neuroscience behind this is extremely meticulous and complex, requiring brain coordination alongside muscle contraction. Task execution within the brain relies on distributed, layered systems that deconstruct operations into manageable components.

A key system involved is the sensorimotor network (SMN), a group of functionally connected brain regions that are critical for the automatization, timing, and sequencing of behaviours [1]. This network is stimulated when performing motor activities such as finger tapping [2], [3]. This is supported by Fig.1, which shows activity within the SMN when carrying tasks. The significant negative correlation between longer symptom duration and negative SMN activity, suggesting that prolonged dysfunction reduces the efficiency of these motor pathways over time.

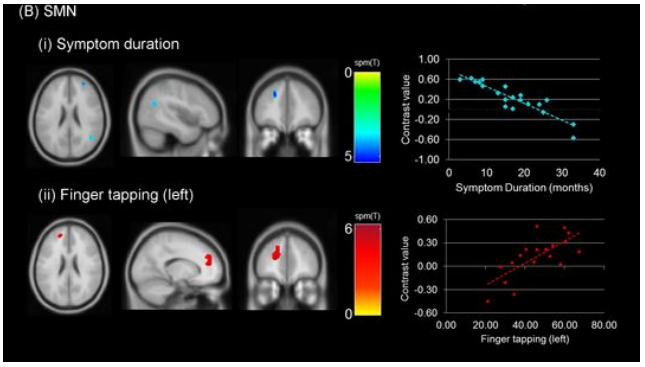

Figure 1: Correlation between symptom duration and finger tapping relative to SMN.

Seen in Fig 1, regional correlations in connectivity with clinical measures (i) shows a negative correlation between symptom duration and brain activity—proving that as symptoms last longer, activity decreases and (ii) shows increased activity during finger tapping, particularly in motor-related areas. The scatter graph on (i) proves relationships between brain activity and symptom duration or motor performance [4].

The SMN begins the process with motor planning in the premotor cortex and supplementary motor area, which together prepare and organise the movement. The supplementary motor area sits on the medial (inner) surface of the frontal lobe, above the premotor cortex. Its function is movement sequencing, response inhibition and action monitoring [5]. The primary motor cortex generates a command that is sent to the spinal cord, activating the muscles required to lift a finger [6]. The primary somatosensory cortex provides sensory feedback that informs and refines a movement. These areas interact with association cortices, which are large regions of the cerebral cortex and are responsible for complex processing and generation of behaviour, to help interpret and assess the initial sensory information delivered [7].

The brain predicts the sensory outcome of the expected movement using internal models that are generated in the cerebellum and the motor cortex. One such model is the forward model, which is a computational model of voluntary motor control that predicts the expected sensory consequences. As illustrated in Fig. 2, the forward model generates a prediction of sensory feedback. Then, it performs a rapid comparison between the intentional content of actions and their outcomes. This allows the brain to detect discrepancies and adjust movement rapidly [8]. It highlights how movement is not purely reactive but predictive, depending on continuous comparisons of expected and actual outcomes.

The forward model is how the brain predicts and corrects movement. A motor command is sent to the muscles, while a forward

model uses an efferent copy to predict expected sensory feedback. The predicted feedback is compared with the actual sensory feedback. Any sensory discrepancy is used to adjust and refine the movement in real time. The forward model and other predictive processes operate alongside the supplementary motor area, which handles coordination of sequential and voluntary movements [5].

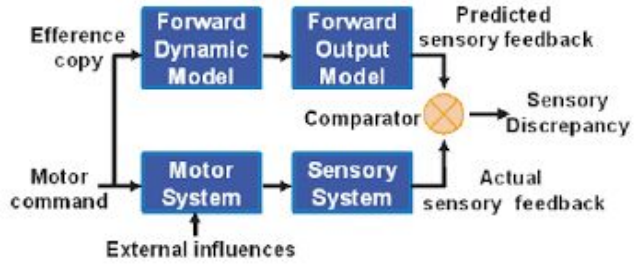

Fig. 2: The forward model.

As the motor command is executed, the finger begins to lift while continuous feedback refines the movement in real time. The Golgi tendon organ detects force, and muscle spindles detect changes in muscle length, both of which are specialised sensory receptors [9]. Skin receptors also detect and provide information for contact and pressure. At this moment, a loop happens, where the information travels back to the primary somatosensory cortex, the cerebellum, and the spinal cord interneurons. This process is essential as without it finger movement would lack precision, possibly leading to conditions such as ataxia, which is a group of disorders that affect co-ordination, balance and speech [10], [11]. Ataxia emphasises the importance of the cerebellum in coordinating smooth and accurate movement because it shows what happens when the brain region fails.

Basal Ganglia are another critical motor component, as they initiate desired movements and regulate movement amplitude [12]. When these circuits are disrupted, movements can become too small, which is prevalent in Parkinson's disease (PD), or too excessive, as seen in Huntington's disease. There are two distinct pathways that compete to either release or inhibit movement, these are the direct pathway and the indirect pathway. Huntington's disease is over-activity of the direct pathway and PD is over-activity of the indirect pathway [13]. They require a delicate balance of signals, primarily dopamine. Without dopamine the circuits are disrupted [14].

A common misconception is that the cause of movement is a direct flow chart. For example, the brain to the spinal cord to muscle. This is far from reality, as there is a dynamic loop—such as the cortex to the cerebellum and back, cortex to the Basal Ganglia and back, and cortex to spinal cord and back. Overall, there are constant changes in movement until it ends.

In conclusion, what feels like a trivial task, like lifting a finger, is subject to intention formation, predictive modelling, command generation, specific coordination, motor selection, feedback, correction and so much more. These processes occur simultaneously rather than in a strict sequence, with continuous interaction between cortical and subcortical regions. Additionally, individual variation like genetic factors and age-related changes can significantly change the efficiency of the system's functions. It is important to remember that this is just a brief overview of some of the systems involved; brain power should never be overlooked— the smallest actions require complex underlying processes.

By Anfal Ismail

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Food Safety In Food Delivery: From Convenience To Concern

Food delivery services have become an integral part of modern daily life which allow meals to be enjoyed at home. This may appear as a modern practice, but in reality the idea of food delivery itself has a long global history. Despite its benefits, food delivery raises an important concern on whether food safety remains intact when food is consumed after being delivered through such services.

Food safety is a scientific method describing handling, preparation, and storage of food in a way that prevents foodborne illness [1]. Thus, it can be said that the handling of food is one of the key factors to maintain food safety. It is important for accessing sufficient amounts of safe and nutritious food, which is key to sustaining life and promoting good health. More than two hundred diseases can be caused by harmful bacteria, viruses, parasites, or chemical substances, which contaminate food items and make them unsafe for consumption. It can cause diseases ranging from diarrhoea to cancer [2].

Beginning in ancient Rome, around 753 B.C. to 476 A.D., the Romans first introduced the concept of food delivery. During that period, people mainly relied on thermopolium, a commercial establishment where ready-to-eat food was sold [3], [4]. This gradually evolved through the decades and took the shape of organized food delivery.

Several food delivery service providers promote their services by emphasizing the maintenance of proper hygiene during the delivery. However, concerns still remain regarding whether these promises are consistently fulfilled. Therefore, it is important to understand the food delivery process that is widely practiced today.

After collecting an order, a delivery agent travels through busy and polluted roads to complete the delivery process. Although food handling practices within restaurants are often monitored closely, the hygiene and handling protocols followed by delivery personnel may not always be regulated strictly. Many delivery agents may not wash their hands regularly, use proper protective gear, or store food safely and properly during transit, including leaving food uncovered in delivery bags. As a result, the food may be exposed to external sources of contamination [5]. Contamination of food refers to the condition in which food comes in contact with substances, chemicals, or microorganisms that are harmful to your health [6].

In contrast, it can be observed that food safety can become compromised when hot food is placed into plastic containers for delivery. According to the British Plastics

Federation (BPF), these kinds of food takeaway containers are made up of polypropylene, polyethylene, or a combination of both. Other chemicals like colourants or substances are also added during the process of manufacturing these to make the containers flexible. Many studies have shown that some of the thousands of substances used to make these can 'leach' into the food we consume [7]. For better understanding, leaching is a process when chemicals such as BPA are transferred from the plastic to food. It is commonly transferred through changes in temperature [8]. This leaching process falls under the phenomenon known as chemical migration [9]. This is a major concern when we are using plastic containers, as it is directly affecting the safety of food.

If the temperature of food is not regulated properly, it will also affect the safety of the food, which may contribute to the growth of bacteria including Salmonella, E. coli, and Listeria. Apart from these factors, improper cleaning of food delivery bags or containers may also lead to cross-contamination. If a food delivery personnel is carrying raw food items and cooked or ready-to-eat food together in the same bag without any adequate separation, then it raises a higher risk of foodborne illnesses [5].

Foodborne pathogens and their biofilms are major causes of foodborne diseases, posing a significant threat to both the food industry and public health. Approximately 40% to 80% of microorganisms are capable of forming biofilms. In food processing environments, several biofilm-forming microorganisms are human pathogens that can adhere to and develop biofilm structures on a variety of abiotic surfaces, including stainless steel, polyethylene, wood, glass, polypropylene, and rubber. The formation of these biofilms enhances microbial persistence, increases resistance to cleaning and disinfection procedures, and contributes to the risk of cross-contamination during food production [10].

Human handling is a major source of viral contamination. Viruses do not multiply or produce toxins in food like bacteria. Instead, food items act as vehicles for their transfer or transmission. Involved frequently in foodborne infections are human Norovirus (NoV) and hepatitis A virus (HAV), but other viruses such as Enterovirus (EV), human Rotavirus (HRV), hepatitis E virus (HEV), and astrovirus (AstV), can also be transmitted by food [11].

Another area of concern is the risk that ordered food may be tampered with by delivery personnel before it reaches the customer [5]. There was a case reported in India in which a woman recorded and shared a video on social media showing a delivery agent from a well-known food delivery service provider opening a food package, eating from it, and then repacking it before completing the delivery [12], [13].

To conclude, food ordered from outside does not automatically become unsafe. However, certain risks associated with food delivery services, such as improper handling, and poor packaging, may contribute to foodborne illnesses among consumers who may be unaware of such contamination.

By Aratrik Chakraborty

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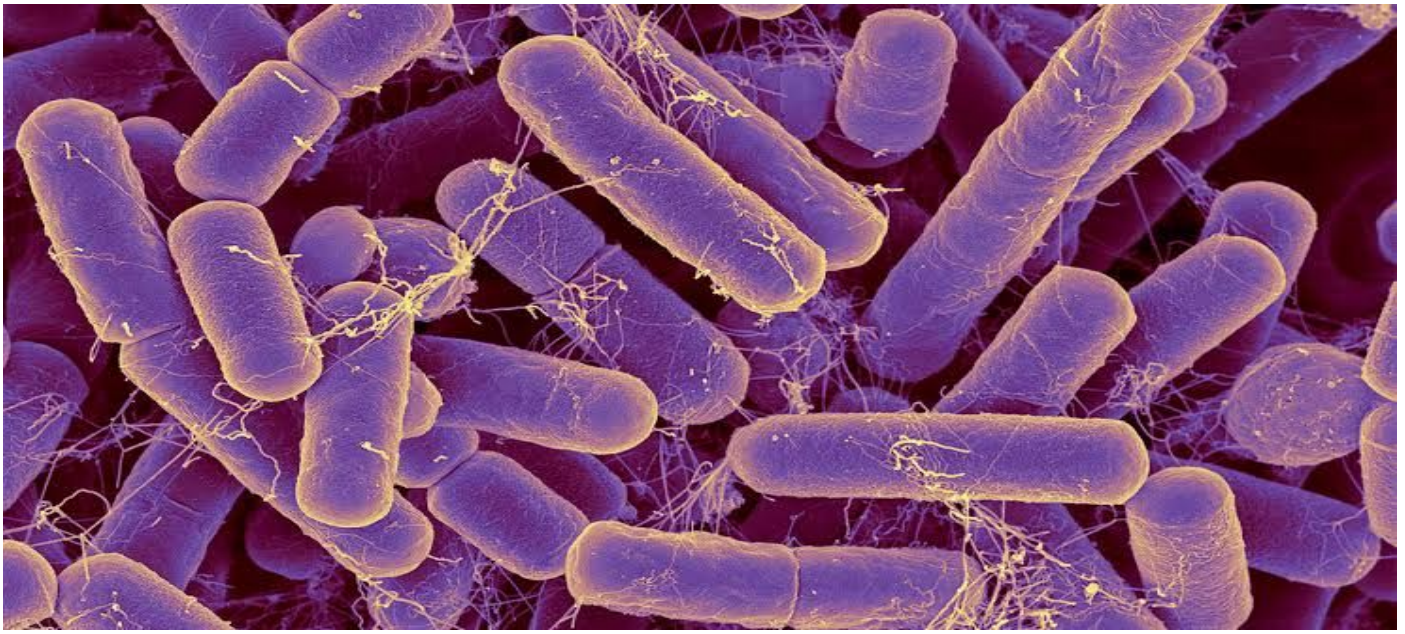

How The Gut Microbiome Impacts Overall Health

The gut microbiome is a supporting organ that contains all of the microorganisms that are within the gut. It is located within the gastrointestinal tract (Gi), and the majority of the microbiomes are located within the colon. The gut microbiome is responsible for fighting pathogens, providing immunity support, and manufacturing important vitamins [1]. It communicates with and impacts the rest of the body, which is visible when we refer to the brain-gut-microbiome axis. The brain-gut-microbiome axis is a multi-directional communication network that allows communication between the brain and the microbiome through the vagus nerve, immune signals, and the endocrine system.

It may be argued that host health and the health of the gut microbiome are directly related to each other. By emphasizing the importance of maintaining a healthy gut microbiome, it is possible to reduce the likelihood of numerous diseases. The importance of a healthy gut microbiome can be examined by analyzing the supporting role the gut microbiome plays on diseases, the brain-gut-microbiome axis and its impacts on mental health, and how to effectively maintain a healthy gut microbiome.

The Causal Relationship Between the Gut Dysbiosis and Diseases

Gut ‘dysbiosis’ is a term used to refer to an unbalanced gut microbiome. In this event, the body’s immunity is compromised, and the host is more susceptible to an overgrowth of pathogens (usually parasites, viruses, or fungi), a weaker intestinal lining, and metabolic disruption [2]. Patently, gut dysbiosis is believed to be the cause for an increase in disease. According to a research paper published by the National Library of Medicine, approximately 20% of all cancer cases in the globe are thought to be linked to the gut microbiota [3]. This statistic highlights that an unbalanced gut microbiome poses severe detriments to overall health and increases susceptibility to disease.

Further stated in the article, when dysbiosis occurs due to a high fat diet, the microorganisms ‘Firmicutes’ and ‘Proteobacteria’ increase while ‘Bacteroidetes’ decrease [3]. The ratio of Firmicutes to Bacteroidetes is linked to body weight, and a larger ratio is correlated with obesity. Additionally, the compromised intestinal barrier caused by dysbiosis results in chronic inflammatory status, another leading cause of obesity.

Moreover, Crohn’s disease can also be directly linked to the gut microbiome. Crohn's disease patients have a higher number of ‘Enterobacteriaceae’, which is a bacterial family, compared to a healthy individual. Additional discoveries have found

a reduced number of ‘Erysipelotrichales’ bacteria in their gut microbiome. Reduced amounts of ‘Erysipelotrichales’, ‘Bacteroidales’, and ‘Clostridiales’ microorganisms, but higher amounts of ‘Enterobacteriaceae’, ‘Pasteurellaceae’, ‘Veillonellaceae’, and ‘Fusobacteriaceae’ microorganisms have been found in Crohn's disease patients. This pattern of ratios may be used to link the illness to an issue in the gut microbiome.

Nonetheless, it should be noted that dysbioses will not directly cause a specific disease, including Crohn’s disease, though the imbalance of specific microbes is the root of disease. The resulting effect of gut dysbiosis is dependent on the ratio of imbalanced microbes and overall gut health. Through the prioritization of overall gut health, most of the mentioned illnesses may have been avoided. With a healthy gut microbiome, the body will not only be healthier physically, but mentally as well. Through the maintenance of a healthy gut microbiome, it may be believed that chances of developing these diseases is reduced.

The Brain-Gut-Microbiome Axis And Its Impacts On Mental Health

In connection with the impacts of the gut microbiome on the physical state of the host, there is a distinctive relationship between the gut microbiome and the brain. This is called the brain-gut-microbiome axis, and is connected via the vagus nerve and enteric nervous system as well as several hormones and neurotransmitters. Communication occurs through neuroimmune and neuroendocrine signals [4].

On the intestinal microbes, there appear neurotransmitter-receptor sites that allow for efficient communication. Because of this axis, the state of the gut microbiome impacts the brain and mental state [5]. In a study, a sample of the gut microbiome from depressed rats was extracted and placed into healthy rats, and vice versa [6]. As a result, the healthy rats began showing signs of depression. The depressed rats that were injected with the gut microbiome of the healthy rats began showing progress. Based on this study, it may be concluded that the gut microbiome is directly related to our mental health [7].

Moreover, a balanced gut microbiome includes microbes that aid in the regulation of serotonin, dopamine, and tryptophan metabolism. When there is an imbalance, the signaling of the chemicals that regulate psychological state are not functioning regularly. Likewise, dysbiosis influences how the hypothalamic-pituitary-adrenal axis (HPA) reacts to stress. This makes the brain more susceptible to reactivity and increases depression or anxiety-like states. In relation to the impacts of gut dysbiosis on mental health, it may reduce short-chain fatty acids (SCFAs).

SCFAs are small fat molecules with two to six carbon atoms that are mainly produced in the colon by gut bacteria fermenting dietary fiber. Normally, these help reduce inflammation and support gut and brain health. Additional research states that anxiety, depression, bipolar disorder, schizophrenia, and certain neurodevelopmental disorders like autism spectrum disorder have all been linked to gut-brain axis dysfunction [8]. By aiming to prevent dysbioses, it is possible to prevent the above mentioned issues.

The Importance of Fiber and Gut Microbes

Fiber is considered the most important nutrient for the gut microbiome because it provides most of the essential nutrients. The absorption and fermentation of fiber are vital for gut microbiome health. However, not all types of fiber ferment at the same rate. Dietary fiber with a smaller degree of polymerization, relating to the size of the molecule, is fermented faster, yielding a faster effect on the body [9].

Relative to fiber, the types of fiber categorize into soluble and insoluble fiber. Soluble fiber supports the gut microbiome by feeding the healthy bacteria and

supplying the microbiome with essential nutrients. It dissolves within the bodily fluids, and moves to the colon. In comparison, insoluble fiber absorbs the bodily fluids, resulting in stool. Both are essential for a healthy gut microbiome, though soluble fiber should be prioritized as it feeds the microbe living in the biome [10], [11].

Regarding the absorption of fiber, the bacteria within the gut microbiome use the enzymes glycoside hydrolases (GHs) and polysaccharide lyases (PLs) to break down and absorb the fiber. However, these enzymes do not occur in the human body naturally. It is necessary to have a sufficient intake of fermented foods and plant-based foods in order to have a sufficient intake of bacteria which allow the breaking down of fiber.

Foods High In Soluble Fiber	Foods High In Insoluble Fiber
Psyllium husk	Wholewheat grains & bread
Flaxseeds and Chia seeds	Fruits with skins
Oats	Nuts & Seeds
Beans	Most vegetables
Peas	Brown Rice

Probiotics and Prebiotics

Moreover, fermented foods play an essential role in the health of the gut microbiome [12]. Fermented foods, once in the gut microbiome, formulate bioactive compounds and acids that support useful bacteria and cause further difficulty for harmful microbes to grow [13]. A supporting reason for this is their richness in probiotics. The introduction of these beneficial microbes boost microbial diversity, gut strength, and barrier function.

In addition to that, fermented foods support butyrate-producing microbes. In fact, butyrate is linked to anti-inflammatory benefits and a stronger gut barrier. Paired with probiotics, prebiotic-rich foods are essential for feeding the bacteria within the gut microbiome. While probiotics introduce new live bacteria, prebiotics keep them alive. The regular intake of prebiotics allows the gut microbiome to remain balanced [14], [15].

Foods High In Probiotics	Foods High In Prebiotics
Kefir	Onions
Kimchi	Garlic
Sauerkraut	Banana
Miso	Lentils
Kombucha	Oat

Regular Activity

Regular physical exercise is essential for the health and diversity of the gut microbiome. According to studies cited in a 2022 Pubmed article, physical activity increases the availability of a physiologically functional microbiota. Adding on to the bowel disturbances associated with a lack of physical activity, differences in the qualitative and quantitative microbial composition of the GI tract may have negative effects on the entire body as an integrated system. Via exercise in homeostasis and the regulation of energy, physical activity causes changes in the intestinal microbial composition [16].

Conclusion

The gut microbiome is an entire ecosystem that lives within the human body. Due to its impacts on the body, on mental health, and overall susceptibility to disease, it is important to aim towards achieving a healthy gut microbiome. This may be accomplished by having a wide range of gut microbes, participating in regular exercise, and intaking the required amounts of nutrients.

By Ayia Ali

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Role Of Metamathematics In Consistency Proof

Normal mathematics is thought of as a discipline that describes the quantitative world. This view seems natural when the measurable properties of the world are discussed. However, “natural language,” our everyday language, is ambiguous and can produce confusion. Metamathematics is essential in reducing this confusion. Similar to any metalanguage, metamathematics allows mathematics to be discussed without using mathematical language itself. Metamathematics can make a statement about mathematics without using mathematical signs [1]. Two systems, X and Y, would both have certain properties and relations. They would be described by simple mathematics [1]. However, to describe the relationship between these properties, metamathematical language must be used [1].

For example, ‘1 + x = 2’ is a mathematical statement. The meaning is clear and can be easily interpreted because each sign has a common meaning. In comparison, ‘x is a variable’ is a metamathematical statement as it describes the nature and definition of mathematical signs that are used. In a way, metamathematics is a discourse about mathematics itself, properties and their relations [1].

The foundation of metamathematical theory is linked to the foundation of logic, which is attributed to Gottlob Frege’s *Begriffsschrift* [2]. This work lays out the logical foundation of mathematics, proceeding to translate the mathematical relation into a formal reasoning. Formal reasoning being one that uses formal language, to reveal the underlying structure of an argument.

The first real distinction between mathematics and metamathematics was conceptualized by David Hilbert. He used metamathematics, especially in its form of mathematical logic, in order to explore whether the consistency of a mathematical system can be proven. Before Hilbert, the consistency of a mathematical system was established in terms of a different system; their consistency proofs were linked, which was problematic. If both systems are inconsistent by themselves but their union is consistent, the problem is being placed in a different system. When a system is consistent, a logical contradiction cannot be derived from it, meaning an axiom that is both true and false at the same time would not be possible.

Hilbert proposed a new way to do it; he was looking for an absolute proof, one that shows the consistency of one system without interaction with another [3], [4]. When a system is said to be complete, consistent, and non-contradictory it is a metamathematical statement, so the role of metamathematics in this proof is evident. For this method to work, he needed to completely formalise the system and then prove its consistency by transformations [3]. This task demands the use of metamathematics in order to formalise the mathematical expression.

Hilbert’s ambitions were proved to be unachievable, due to Gödel's theory of incompleteness. Gödel showed that for any formal system containing “basic” mathematical operations, for example, multiplication or addition, it is impossible to derive a metamathematical statement that proves its consistency [4], [5]. Metamathematics allowed for the development of Gödel’s theorem.

As metamathematics became more influential, more mathematical contradictions were discovered. This was due to the previous habit of mathematicians

and logicians to displace the problems of consistency.

To prove that system X is consistent, the main axioms of this system should be consistent in a different system. While this seems like a reliable method, it is in fact not. This is what is meant by displacing the problem. Proving the consistency of a system cannot depend on a different system whose consistency is yet to be proved. The truthfulness of an axiom in a given system, whether X, Y or both, does not verify the consistency of the system. In other words, if an axiom is consistently true in every mathematical system it does not mean that the system is consistent in itself [1], [3].

The inability to prove that a mathematical system is consistent is something that was discovered as a result of metamathematics. Additionally, metamathematics revealed that mathematicians make assumptions based on consensus rather than proof and about the consequences that these assumptions can make on mathematics. It also acts as a reminder that accepted truths can later be proven to be misleading [5].

By Diana Iliuchok

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The Role of AI in the Modernisation of Forensic Chemistry: Redefining Expertise in Forensic Chemistry

Introduction

The emergence of artificial intelligence has enabled laboratories globally to obtain molecular fingerprints of substances in seconds instead of tens of minutes [1]. AI is a transformative tool that is expanding and supporting chemists rapidly, especially when traditional identification methods are impractical, cause a delay in criminal investigations, or go beyond human capabilities.

Overview of Forensic Chemistry

Forensic chemistry is the application of chemical principles and techniques to analyse and identify physical evidence from crime scenes such as biological fluids, explosives, or arson debris. Forensic chemists use specialized tools like mass spectrometers, infrared spectrometers and gas chromatographs to aid them in identifying unknown substances and linking them to potential suspects [2]. Mass spectrometers identify chemical substances by sorting gaseous ions in electric and magnetic fields based on their mass-to-charge ratios [3]. Infrared spectroscopy measures a matter's interactions with infrared light, and due to its accuracy and speed, it is effective in forensics [4]. Gas chromatography is a technique for separating chemical substances by vaporising them and carrying them through a tube using an inert gas [5].

Why AI is Needed in Forensic Chemistry

New synthetic drugs, toxic chemical compounds, and poisons are constantly developing. As a result, given the immense pressure forensic scientists are under to deliver fast results, sometimes their analyses are too time-consuming to produce. This is one of the main reasons artificial intelligence is needed as it can interpret extensive sets of chemical data efficiently, enhancing speed while still maintaining high accuracy levels, [6]. Accuracy is critical in forensic chemistry because errors can lead to the wrong analysis and subsequently, incorrect conclusions. As a result, wrongful convictions and unjust legal outcomes may be implemented.

In addition to its advanced interpretations, AI reduces the risk of human biases through recognising anomalies. Nevertheless, algorithmic biases may still arise. There may be embedded assumptions due to previous forensic evaluations and this could cause a systematic misclassification of evidence in areas such as drug profiling. Depending on the model, human oversight is still required to ensure the reliability of the forensic analysis, [7].

How AI is Used in Forensic Chemical Analysis

The integration of AI and machine learning transforms forensic investigations to extraordinary levels of accuracy, efficiency, and reliability across various areas: biometric identification, digital forensics, forensic pathology, and crime scene analysis [8].

In biometric identification, AI and machine learning technologies have significantly enhanced fingerprint analysis and voice and facial recognition to make it faster, [8]. Additionally, AI systems proficiently process vast datasets to detect cyberthreats and refine malware detection in data forensics [8]. This is done by AI systems that have been trained to identify several malware samples and system behaviour logs, allowing them to detect misconduct.

In the field of forensic pathology, the introduction of AI has advanced autopsy reporting and time-of-death estimation by enabling more detailed post-mortem examinations. Furthermore, chemometrics, the application of mathematical methods when analysing chemistry data, is empowered by generative AI and deep learning. Many laboratories also utilise direct analysis in real time mass spectrometry (DART-MS) [1]. This technology generates a rapid stream of molecular data that are then processed by AI algorithms and models to predict the molecule's chemical quality and bioactivity. Typically, this task requires extensive manual work from forensic scientists in the lab.

In addition to this, according to [8], crime scene analyses driven by AI are providing law enforcement agencies with new, innovative methods to visualise and interpret crime scenes, improving the overall effectiveness of forensic investigations.

Critical Ethical Considerations

As forensic laboratories expand their employment of and reliance on new technologies, they must adhere to ethical guidelines that protect human rights when collecting and storing evidence, according to [9]. They are required to implement robust data protection measures like encryption protocols and access controls to enable integrity when handling forensic data [9]. Moreover, forensic personnel need to be provided with training and awareness programs on data governance principles [9].

The Role of Chemist Expertise in AI-Driven Forensics

According to [4], people in forensic science often review their colleagues' work in a process called "technical review." With the growing adoption of AI in the field, it is still crucial that there is human oversight of the analysis to ensure that the AI models being used are applied consistently in the same way each time and devoid of any irregularities. Furthermore, human involvement is also hugely important because an expert will have to present their evidence to a court, so findings heavily involving AI will need to be explained [10].

This would only be feasible if humans were already regulating the AI algorithms at work. The report, [7], also highlights the risks of human review. There could be biases such as confirmation or automation bias, the human tendency to over-rely on decisions made by automated systems like AI. This places uncertainty on the reliability of the forensic analysis undertaken by AI.

The Future of AI in Forensic Chemistry

Notably, there is a range of additional values for and applications of AI in chemical forensic analysis. According to the report [7], recent research has shown AI assisting experts in analyzing impressions of footwear outsoles, flammable liquids, and traces of automotive paint.

In addition to this, AI can aid with classifying drug samples by combining pre-existing compound identification methods, like mass spectrometry, with machine learning models for advanced categorisation.

Lastly, AI may also be able to replicate expert scientist analysis of human remains

as recent publications have showcased that it can estimate attributes, such as sex, from 2D and 3D computed imagery scans of skeletal remains [7]. Often, AI is renowned on social media for completing images with a filler background; in forensics, AI can help chemists attribute incomplete body remains in images with their missing parts.

Overall Development of AI in Forensic Chemistry

Artificial intelligence has remarkably elevated the forensic chemistry industry through the enhancement of speed, reliability, precision, and consistency. AI provides forensic chemists with the opportunity to handle complex cases productively as algorithms process and detect patterns beyond human capabilities. The responsible integration of AI has the potential to substantially revolutionise aspects of the justice system.

By Drishti Singh

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Pharmacogenomics of Adolescent Depression

Adolescent depression is a complex clinical challenge. For many teens, the path to recovery is complicated by a "trial-and-error" approach to medication, which involves multiple cycles of treatment before finding an antidepressant that is both effective and tolerable. A substantial portion of this variability can be traced back to biological foundations: specifically, genetic differences that dictate how a body metabolizes a drug. Variants in the CYP2D6 and CYP2C19 genes can significantly alter blood levels of common Selective Serotonin Reuptake Inhibitors (SSRIs), a class of antidepressants. This may impact both the efficacy of the treatment, and the risk of debilitating side effects [1], [2].

The Role of Pharmacogenomics

Pharmacogenomics (PGx) represents the intersection of pharmacology and genomics. It aims to move clinical practice away from universal dosing and toward a model tailored to a patient's unique genetic profile [3]. In the treatment of depression, PGx focuses on two primary areas, the first of which is pharmacokinetics, the study of how the body processes a drug [4]. Genetic variations dictate the speed at which liver enzymes, specifically the CYP450 system, break down a medication. These variations determine if drug concentrations remain in a therapeutic range or shift into levels that are either toxic or ineffective. The second is pharmacodynamics which describes the drug's effect on the body, involving genetic variations in brain receptors or transporters that might make someone more or less sensitive to a specific antidepressant [5].

If the metabolic process moves too slowly, the active drug accumulates, leading to toxicity and side effects. If it moves too quickly, the drug is deactivated and flushed out before it can reach a therapeutic level in the brain [6]. By identifying where a patient falls on this spectrum, clinicians can categorize them into one of four phenotypes, allowing for predictable adjustments to drug choice and dosage. Those identified as poor metabolizers have little to no enzyme activity. This means that there is a high risk that side effects will occur. Intermediate metabolizers have reduced enzyme activity and may require lower doses. Normal metabolizers break down and remove the medication at an average, expected rate. This rate is considered the standard baseline. Rapid or ultrarapid metabolizers have accelerated enzyme activity. They carry high risk of treatment failure due to subtherapeutic levels.

The Evidence & Nuance

In adults, randomized implementation studies have already demonstrated that genotype-guided prescribing can reduce side effects and accelerate the time to stable therapy. Organizations like the Clinical Pharmacogenetics Implementation Consortium (CPIC) provide guidance for several SSRIs based on these findings [1]. However, the evidence for routine use in adolescents is still undergoing research. While current

pharmacokinetic studies in adolescents generally align with adult biology demonstrating a relationship between genotype and drug exposure, large-scale randomized controlled trials (RCTs) with adolescent-specific clinical endpoints are still sparse [2], [7]. Consequently, clinical recommendations for adolescents can extend adult data while prioritizing close clinical monitoring in pediatric settings [8].

Human development further complicates implementation. Drug metabolism is not static; it changes as a child grows. While many CYP enzymes reach adult activity levels by late childhood, there is significant inter-individual variability and pubertal influence that can alter drug clearance [9]. Furthermore, variables like body weight, co-medications, and treatment adherence are important modulators. Therefore, a genetic test result should not be viewed as a standalone answer, but should be interpreted alongside the patient's age, weight, and clinical status [10].

An Age-Stratified Framework

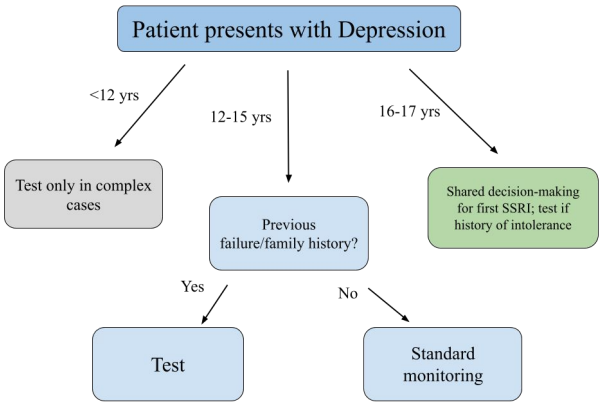

Figure 1: Clinical approach guidelines for testing according to age.

A structured clinical framework may help guide implementation of these findings. Because evidence levels vary by age group, an age-stratified approach can be considered. For ages under 12, testing should be reserved for exceptional or complex cases. The pharmacokinetic evidence is currently weakest for this younger group [9]. For ages 12–15, testing is appropriate if there is a history of treatment failure or a strong family history of metabolic issues. It may be considered for first-line treatment in high-risk contexts if the lab turnaround time is short. Finally, for teens ages 16–17, it is reasonable to offer testing as part of shared decision-making for the first SSRI, and it is strongly indicated following any treatment intolerance.

Additional Indications for Testing

The decision to test should be based on the patient's history and risk profile. Testing is highly recommended for adolescents who have already experienced SSRI treatment failure, which is defined as two or more adequate trials, or those who have had significant adverse reactions. It is also indicated for patients on interacting medications or those managing complex polypharmacy [1]. Cases of complex polypharmacy involve managing multiple concurrent prescriptions that significantly increases the risk of drug-drug interactions and side effects. Clinicians should also consider testing for first-time SSRI prescriptions in adolescents when families specifically request testing after being counseled on its limitations or for adolescents with moderate-to-severe depression where rapid stabilization is vital, like with those with a high risk of suicidality [3]. Universal preemptive testing for all adolescents at their first SSRI is discouraged unless the local clinic has dedicated decision support and monitoring resources in place [11].

From Phenotype to Action

Once a patient's genotype has been established, treatment can be adjusted accordingly. For drugs primarily cleared by CYP2C19 (such as escitalopram and citalopram), a "poor metabolizer" should be started on a lower dose or a different medication entirely. On the other hand, an "ultrarapid metabolizer" may require a higher dose or an alternative drug to avoid subtherapeutic levels [1], [2]. Similar logic applies to CYP2D6. For a medication like paroxetine, a poor metabolizer will often require a dose reduction. While these rules provide a practical starting point, healthcare professionals should consult CPIC tables for drug-specific dosing when they are available [1].

Implementation and Evaluation in the Clinic

Successful implementation starts with a clear ordering process where a healthcare professional receives consent from a guardian. Samples, usually saliva or blood, should be processed quickly to remain relevant for outpatient treatment. Once results are integrated into the electronic health record (EHR), clinicians should be supported by a guide to help interpret the findings [12]. Follow-up is essential, with a reassessment of symptoms and side effects scheduled for 4 to 8 weeks after any genotype-guided change [2].

Limitations and Equity

Finally, practitioners should remain mindful of the limitations of PGx. Genetic testing does not account for all variables in drug response, such as environmental factors and adherence. There are also significant concerns regarding access, cost, and insurance coverage that need to be addressed to ensure equitable care [13]. Because pharmacogenomic testing can carry high out-of-pocket costs and is not universally covered by insurance, it is largely restricted to well-funded healthcare systems, creating a barrier for low-income and rural patients. Overcoming this requires the development of lower-cost testing technologies. Data privacy and the implications of genetic storage must be discussed carefully with families and adhere to regulations for minors [14]. Additionally, rates of poor metabolizers vary based on ethnicity, meaning that using a 'one-size-fits-all' approach should be avoided. This approach leads to less accurate clinical outcomes for minority populations since standard dosing guidelines are often based on majority populations, and fail to account for distinct regional genetic variations. For example, the rate of CYP2C19 poor metabolizers in Europe is only 2-5%, while in East Asian populations it is closer to 15-25% [6], [13].

Conclusion

Pharmacogenetic testing for CYP2D6 and CYP2C19 is a powerful tool that can refine SSRI care for adolescents. Healthcare professionals can offer a more precise and personalized path toward mental health recovery by bridging the gap between adult data and pediatric needs through an age-stratified approach. Importantly, patient perspectives highlight that mental health treatment may not always feel individualized. A national GeneSight Mental Health Monitor survey reported that 74% of respondents who were still searching for an effective mental health medication felt that mental health treatment was 'one-size-fits-all' [15]. The necessity of this approach is illustrated by modeling: based on known allele frequencies, approximately 5–10% of adolescents are CYP2C19 poor metabolizers, and 3–7% are ultrarapid metabolizers (although this varies greatly between ethnicities) [2], [6]. In a clinic serving 1,000 adolescents annually, many patients will have actionable phenotypes. This volume justifies targeted testing for high-risk groups.

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Eutrophication and Ecological Effects in Lake Erie: *Microcystis* Algal Blooms

Introduction

Michigan is known for its five grandiose lakes large enough to see from an atmospheric satellite. An additional feature that can be seen from this angle is the green hue most often exhibited by Lake Erie. This is a result of a mass collection of cyanobacteria, or blue-green algae. Cyanobacteria is a photosynthetic bacterium that thrives in the euphotic zone—the depth to which sunlight best supports aquatic plant life—of Lake Erie. In this space, *Microcystis* cyanobacteria feed on runoff phosphorus and excess nitrogen, thriving during the warmer months of the year. The exponential growth of *Microcystis* poses a threat of limited sunlight availability, hypoxia (lack of oxygen), water quality degradation, and toxin production. The lives of all aquatic trophic levels are affected by these changes, and suitable drinking water for local terrestrial organisms becomes limited.

Microcystis Takeover: The Process of Eutrophication

Eutrophication is the process of nutrient overloading causing a degradation in water quality over time. In Lake Erie, phosphorus is the largest most influential nutrient deposit that allows cyanobacteria to thrive. Phosphorus is a chemical that promotes higher crop yields considering its ability to develop improved cell storage, including that for ATP, DNA, and fats [1]. This nutrient is part of local biogeochemical cycles, as it lacks an atmospheric, or gaseous, component. The runoff of phosphate fertilizers from nearby farms, thus, remains in deposited water systems and creates a surplus of nutrients that plants need to grow.

Microcystis dominates the uptake of these nutrients, blocking other photosynthetic organisms, due to their unique cell structures, with vesicles filled with gas that allows them to sit atop the surface of Lake Erie [2]. As cyanobacteria metabolize this abundance of nutrients, their population grows exponentially. Consequently, the sunlight availability below the surface worsens, and the chemical composition of water fluctuates as the bloom then consumes increasing amounts of dissolved oxygen and accumulates excess carbon [3]. Water composition is further fluctuated by the release of cyanotoxins throughout the

life cycle of *Microcystis*. These attack the liver of fish inhabitants, inhibiting protein photophases that allow the liver to undergo typical functions and maintain its structure. These chemicals can also cause liver damage in humans and death in smaller mammals and livestock upon drinking water with visible scum [4].

Ecological Effects of Eutrophication

The key aspect of a disturbance such as an algal bloom is the process of diminishing resources and habitats. All trophic levels rely on one another to regulate and support their populations in order for a community to be in equilibrium based on biomass and limited resources. The ability of primary producers to survive affects all consumers, and as primary producers are blocked off from the sun and unable to photosynthesize, primary consumers begin to starve. As this population slims, and the toxins produced by dying *Microcystis* increases, bioaccumulation in smaller organisms further worsens the population decline of secondary and tertiary consumers' food sources [5]. This causes further loss, with the habitats they form through ecological interactions diminishing.

Effects of Eutrophication in Lake Erie Communities

In the eutrophic Lake Erie, bioaccumulation and hypoxia threaten the habitats of secondary consumers and the phenologic interactions and bioaccumulation risk of primary consumers.

A dominant primary consumer, zooplankton, experiences a phenologic—biological timing based on climate indicators—abundance in the fall and spring seasons. With increasing temperatures due to climate change, the growth of algal blooms becomes greater. This alters their ability to sustain themselves in their typical habitats, have enough food due to dying producers, and breed despite the threat of cyanotoxins. However, due to temperature's influence on biological timing, zooplankton continues to breed up to three weeks earlier than in 1995 [6]. This further alters and complicates the food web in Lake Erie.

Hypoxia-based water quality degradation has decreased the suitable habitats of many secondary consumers. These smaller fish, of which, also rely on zooplankton and benthic invertebrates to feed. Considerable habitat loss has been recorded as early as 2011 by a metric of recorded oxygen levels in habitats of Lake Erie fish. This includes the rainbow smelt (35% loss of oxygen), round goby (35% loss), emerald shriner (12% loss), and the yellow perch (8.5% loss) [7].

Drinking water for land-dwellers local to the Lake Erie area have also been affected by the algal blooms of *Microcystis*. Water quality must be closely monitored during an algal bloom for the safety of over 12 million residents who use Lake Erie for drinking water. At its worst in recent years, such as the 2014 Toledo Water Crisis, the amount of cyanotoxins present in the lake called for a "No Touch, No Drink" mandate, leaving residents without drinking water for nearly two weeks [8]. Less severely, the blooms of Lake Erie usually cause moderate skin irritation in humans, however, companions such as dogs and other food resources such as livestock have had many reports of death upon contact with the water [9].

Lake Erie Now and What Can Be Done

This year's algal bloom of Lake Erie is predicted to be 'moderate', showing ratings of severity of about 4.5. Compared to previous years, the harmfulness of algal blooms seems to be at a decline from a peak rating of 10 in 2011 [10]. Ratings are produced by NOAA's National Center for Coastal Ocean Science, who monitor the location, size, and toxicity of harmful algal blooms through modern filtering tools. These tools collect water and measure the density of dissolved nutrients, which can be indicative of algae that will form in concurrence with these deposits. The likelihood of being able to predict harmful algal blooms as far as five days in advance can be shown with this data, allowing scientists to better prepare water treatment solutions to keep toxicity at bay [11]. This

breakthrough can contribute to the declining rates of severity, which better protects the ecosystem in and surrounding Lake Erie. However, despite advances and declining severities, there have been reports that, similar to zooplankton's phenology, that algal blooms have been appearing earlier and lasting longer due to the effects of climate change.

Conclusion

Water quality testing is essential for protecting aquatic organisms, but prevention is the greatest and most effective solution. Lake Erie has one of the most diverse mineral deposits of all Michigan lakes, with a high amount of watersheds and rivers from highly populated areas such as Detroit. The amount of nutrient runoff into Lake Erie that triggers algal blooms thus comes from many different areas, making an effective solution more difficult. Switching to organic fertilizers is the most highly suggested step in the right direction, as harmful chemical runoff and food for Microcystis would be limited [12]. Beyond that, many changes in Lake Erie and its ecosystem are due to temperature and weather changes due to global warming. This highlights a greater issue seen worldwide that threatens the biodiversity and livelihood of all organisms.

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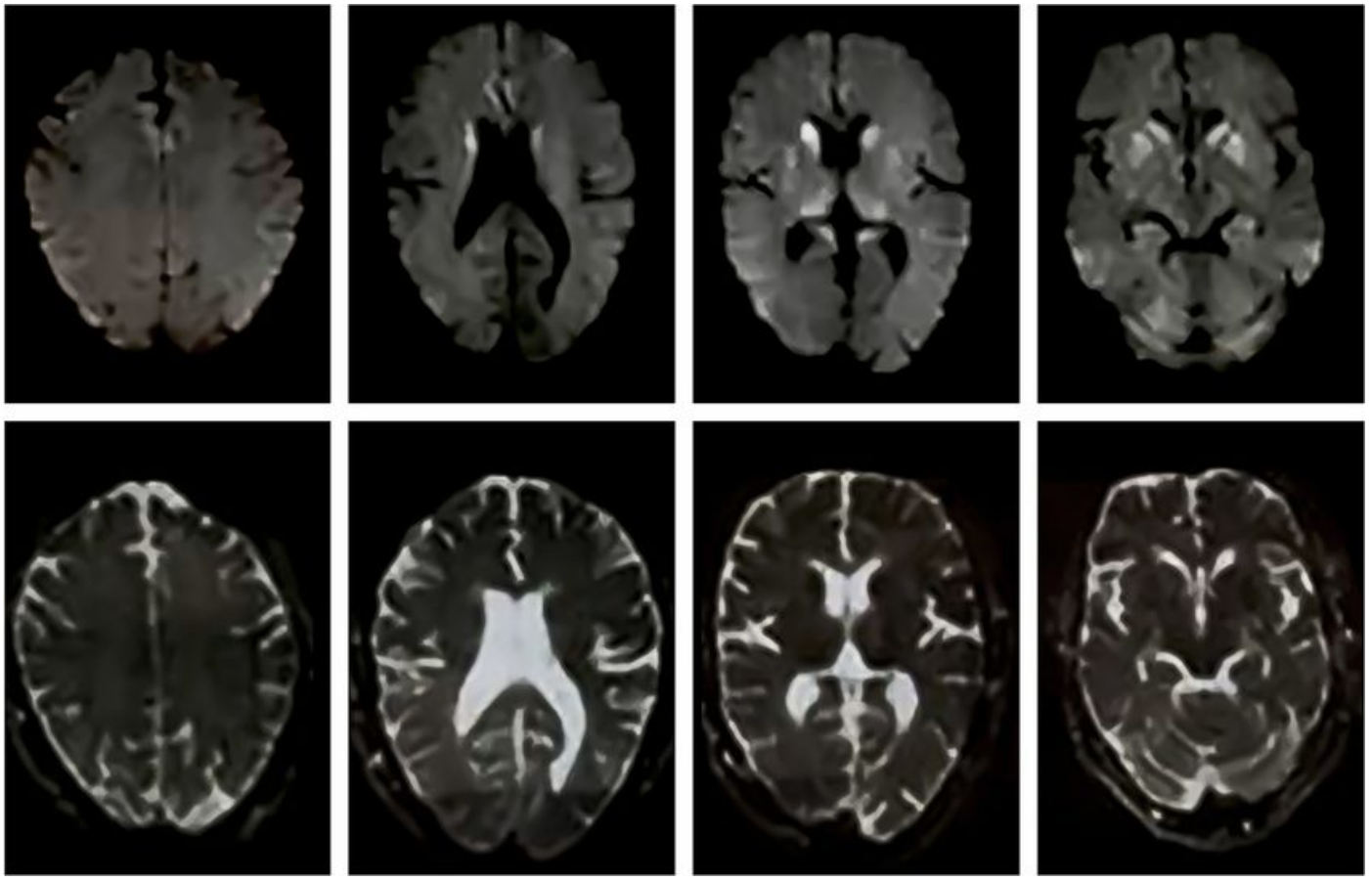


How Prion Diseases Differ From Other Neurodegenerative Disorders

Introduction

The uniquely rapid and fatal nature of prion diseases comes from the combination of prion self-propagation, resistance to normal cellular clearance, and their ability to invade the brain through interconnected neural circuits. As a result, faster and more catastrophic neurodegeneration will occur than in other major brain disorders [1].

Prions are misfolded protease-resistant proteins that cause infectious neurodegenerative diseases affecting animals and humans [1]. They have long incubation periods, cause spongiform brain changes with neuronal loss, do not trigger an effective inflammatory response, and are rapidly progressive and invariably fatal [2]. They are able to transmit biological information through propagation of alternative protein folding which can expand phenotypic diversity without changes in the genome [3]. The pathological isoforms form a conformational change whereby the alpha helical content of the normal protein diminishes and the beta sheet content amplifies, resulting in changes in biochemical properties, such as protease resistance [4].

The prion hypothesis states that a single protein is the sole component of the infectious agent responsible for prion diseases [1]. Proteins can behave like a living microorganism. This affects an individual as it survives metabolic clearance and self-replicates in the body, finally reaching the target organ to induce a cascade of neurodegenerative damage [2]. PrPSc, which is the infectious form of the prion, is able to convert normal PrPC proteins into the infectious isoform by changing their conformation, in return, altering the way the proteins assemble [1]. A disease caused by prions includes the Creutzfeldt-Jakob disease (CJD). CJD is a fatal neurodegenerative illness which is rare and rapidly progressing. Similar to other prion diseases, CJD causes problems with muscle coordination, thinking and memory. In CJD, PrPSc builds up in brain cells and destroys them, resulting in memory loss and confusion, also possibly resulting in behavioral and movement changes too [2].

How People Get Prion Disease

One is able to obtain prion disease by inheriting a genetic mutation, being infected by the disease or by consumption of meat from an animal with a prion disease. However, it is not limited to them. Sporadic prion disease happens when normal proteins turn into prions for no known reason. This includes CJD and sporadic fatal insomnia, which is very rare and even less common than fatal familial insomnia, and also variable protease-sensitive prionopathy [5].

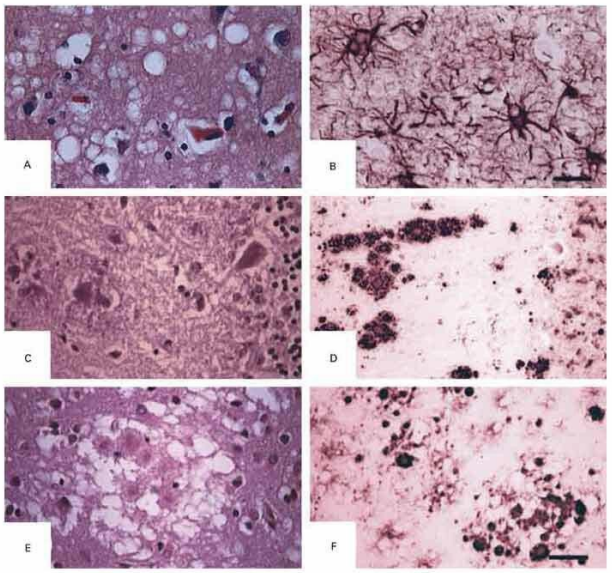


Fig 1: Brains of different patients with CJD shows that there are often no recognisable abnormalities in their brains. The microscopical features of CJD are the spongiform degeneration and astrogliosis as shown in the figure above [6].

Concerns Of Misdiagnosis Among Prion Diseases

Due to its low frequency and clinical heterogeneity, diseases such as sCJD, a form of CJD, are likely under-recognized especially in low and middle–income nations. Several difficulties relating to the diagnosis of CJD have been reported, including financial limits, lack of testing facilities, underdeveloped healthcare infrastructure, scarcity of specialists and regional disparities between rural and urban centers [6]. This deprives the nations of the ability to verify the identity of the disease accurately, leading to possible misdiagnosis and delayed palliative care, sometimes not even receiving the proper care at all. Furthermore, it puts patients at risk due to iatrogenic transmission due to improper sterilization [6].

Parkinsonism As An Initial Presentation Of CJD

A 69-year old lady was presented with the initial symptoms of gait difficulty, tremor, and bradykinesia. Later on, she developed cognitive impairment, ataxia, chin tremor, and myoclonic jerks. Her condition progressed to akinetic mutism and she was ultimately diagnosed with sporadic CJD following detection of 14-3-3 protein in cerebrospinal fluid and characteristic MRI findings, including basal ganglia hyperintensities and cortical ribboning [6].

The Difference Between Prion Diseases And Other Neurodegenerative Diseases

Nonetheless, prion diseases and other neurodegenerative diseases do have their differences. Previous studies report that apart from cognitive decline, the most common symptom for prion disease is gait ataxia, but several neurodegenerative diseases such as Alzheimer's disease and dementia with Lewy bodies (DLB) can both present with rapidly progressive dementia. Alzheimer's disease typically progresses more slowly and lacks the prominent extrapyramidal signs, myloclonus and visual disturbances seen in CJD [7]. Similarly, DLB manifests with dementia, parkinsonism and visual hallucinations like CJD. Conversely, it usually has a more gradual onset [8]. Frontotemporal dementia may resemble CJD in terms of behavioral changes and cognitive impairment but it progresses more slowly and lacks prominent extrapyramidal features, similar to Alzheimer's disease. Cases of CJD with an initial presentation of extrapyramidal symptoms have also been reported before [6].

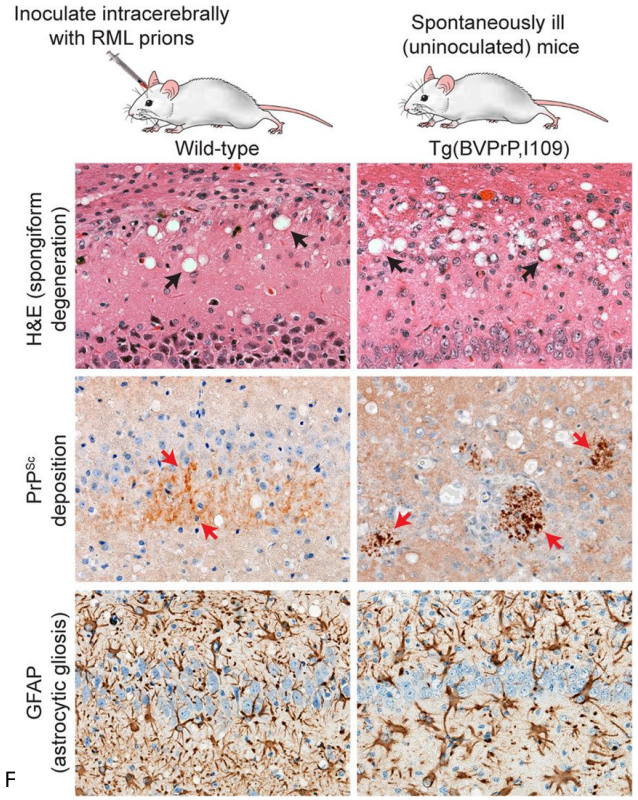
Other Protein Misfolding Diseases

The ability to misfold and self-propagate is not exclusive to prion proteins. To date, over 20 different misfolding proteins have been reported in humans and animals, including α-syn in Parkinson's Disease and Multiple System Atrophy, amyloid precursor

protein (APP), and tau in AD, TDP-43 in ALS and FTD, huntingtin in Huntington disease, and amyloid polypeptide in systemic amyloid disorders [9]. Moreover, evidence supporting prion-like infectious properties of α-syn has been reported. However, unlike prions, infectious transmission between individuals have not been documented with any other prionoid so far [10].

The Similarities Between Prion Diseases And Neurodegenerative Diseases

At a molecular level, they share key features with other neurodegenerative disorders, including the accumulation of misfolded protein aggregates that lead to progressive neuronal loss [9]. Some examples include amyloid-β plaques in Alzheimer's disease, image A shows the structure of HET-s (218-289) fibrils showing the stacked, parallel β-sheets. B shows the top view of a singular β-sheet Mouse model used to study the formation and propagation of prions [9].



In humans, sporadic and genetic forms of prion disease are more common. Nonetheless, the amount of mice that express physiological amounts of the mutant protein do not develop spontaneous disease, which suggests that overexpression is necessary for the disease to manifest within the normal lifespan of a mouse. Diseases can be transmitted from mice expressing high amounts of the mutant protein to mice expressing lower amounts of protein expressing lower amounts of the protein [5].

Mouse Models Used To Study Alzheimer's Disease

Mouse models of Alzheimer's disease are designed to replicate key pathological features, such as amyloid-β plaque accumulation, tau pathology, and progressive memory impairment. The majority of models target early-affected regions such as the hippocampus and medial temporal lobe. Transgenic models (e.g., APP/PS1, 5xFAD) accelerate amyloid-β deposition, while tau-based and knock-in models more closely mimic human disease progression without excessive protein overexpression [11].

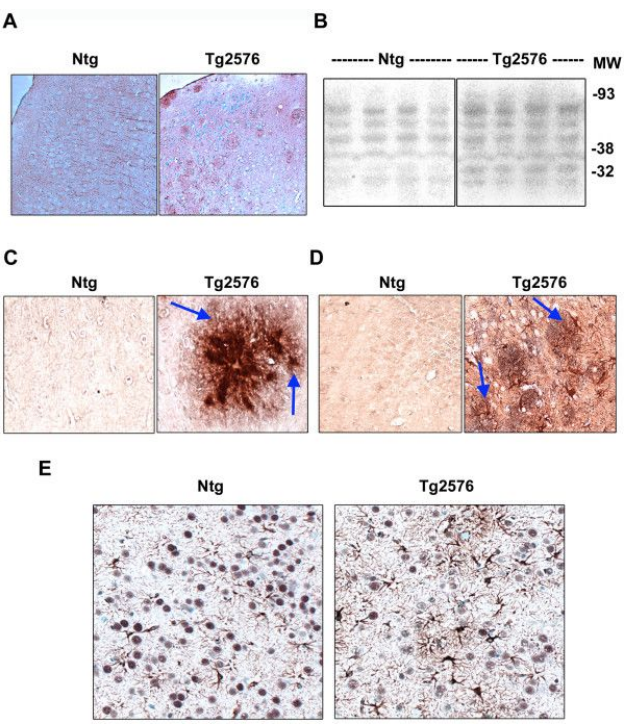


Figure 3: The effect of Alzheimer's on the brain of mice, showing oxidative stress which leads to neuronal dysfunction and neuron loss [12].

These experiments tell us that prion diseases may require higher protein levels to see pathology in mice, suggesting spontaneous disease is rare, whereas Alzheimer's models can artificially speed up

disease to study early pathology [5], [11]. Furthermore, prion diseases are unique in their infectious and propagating nature, while Alzheimer's disease is more about intrinsic accumulation and degeneration in specific brain areas [11], [13]. Alzheimer's mouse models are also region and pathology-specific, while prion models are more about protein misfolding, propagation, and levels. Prion disease seldom arises spontaneously in mice unless the prion protein is overexpressed, whereas Alzheimer's disease can be replicated more readily through targeted genetic alterations. Finally, Prion diseases are transmissible, unlike Alzheimer's.

Conclusion

In conclusion, the nature of prion diseases are similar to other neurodegenerative disorders to the extent that people get misdiagnosed. Nonetheless, there are some factors that make prion diseases stand out from other neurological diseases, including brain scans, making them unique, apart from their propagating nature. Despite that, one thing we have to keep in consideration is that not all nations have the resources to accurately diagnose prion diseases as it requires extensive research and adequate finance. Other protein misfolding diseases apart from prion diseases are also prevalent, and 20 of them have been identified [9].

By Janice Phoebe

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Whether AI is Based or Biased

Artificial Intelligence has undergone extensive development in the past few years. Answers do not have to be searched for website by website, when they can be presented immediately by chatbots. Additionally, AI has been causing the enhancement of efficiency, such as through assisting researchers to allow additional time to focus on their studies. This process has been displayed in many areas, including cybersecurity [1]. Furthermore, AI has contributed to creating countless new work opportunities, especially in fields like tech or finance.

The concept of AI is moderately simple. The original idea was to mimic the human brain, to get a computer that can master, recognize, and associate new concepts on its own. This works by collecting dozens of data sets, which are then provided for the AI [2]. The most popular AI Systems are currently Large Language models (LLMs), such as ChatGPT, which was released by OpenAI in 2022. These are chatbots that are specialised in a field, including as tax law or everyday life. Millions of people use LLMs daily for undemanding questions about decision making, or asking for help with tasks.

LLMs are based on machine learning, which is a subset of artificial intelligence. Specifically, machine learning recognises Specifically, machine learning recognises patterns, spots outliers, and makes inferences about new data. This enables machines to make informed decisions and predictions independently [3]

The algorithm is also a necessary part of this process, as it analyses the data and “tokenises” it. Tokenisation refers to the input, such as a prompt from a user, being converted into numbers. With enough data in the form of texts, the AI can sort and categorise the tokens to be capable of forming sensible sentences.

To be able to form unique sentences, AI also applies specific parameters to each input. After the tokenisation, the AI attempts to examine the tokens' relationships to comprehend the context. Then an attention mechanism is applied to focus on the essential information. The AI then generates an answer and converts one token at a time from its numerical system into an understandable text [3].

There are multiple technologies used for creating images, the most famous one being generative adversarial network (GAN). GAN was founded on the concept of two systems working together to “fool” each other. There is a “generator” that generates the requested image from pure noise, based on the training data. The generated image is then passed to the “discriminator”, which judges whether the picture is realistic or not. The generator collects the data to be capable of generating more realistic images,

whereas the discriminator keeps record of how to spot real or fake pictures, with the examples of the mistakes made.

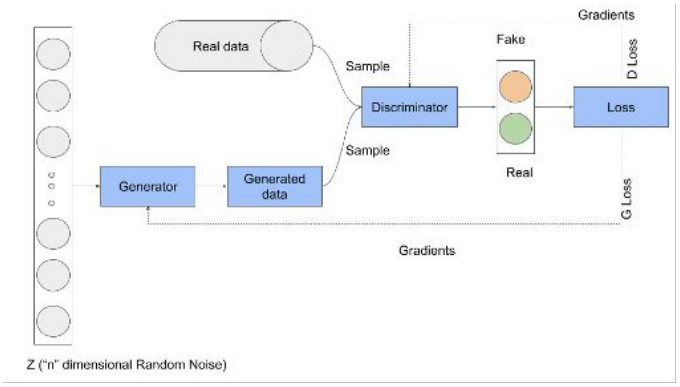

Figure 2: [4].

The process of picture building is called “diffusion”. Machines see images as pixels, each pixel has three numbers, dedicated to the three primary colours, red, green and blue, referring to their intensity. The mix of these colours then determines the final colour of the pixel. The AI then slowly builds every pixel from the pure noise to an actual picture [4].

AI has many advantages; however, it is important to pay attention to its drawbacks as well. Firstly, AI may spread false information in a process known as hallucinating. Hallucinations can occur if the data the model was trained with shows large gaps or is insufficient. As a result, the AI may produce inaccurate or biased outputs [5]. For example, bias may lead to a retelling of an event from a narrow perspective, which then can increase stereotypes and biases about different person groups [6].

AI is overtaking different jobs and careers, especially in the art and entertainment field. Companies have found it cheaper to let an LLM generate a picture, rather than hiring a real artist. This mindset has led to repeated layoffs in the field of arts, since 2022.

Furthermore, AI has a significant impact on the environment. AI, and especially LLMs, use 30 times as much electricity as search algorithms. The servers the AI uses need to be cooled regularly, to prevent overheating. By 2028, AI data centres are estimated to use 1,06 billion litres per year. Contrastingly, the average person uses about 243,17 litres. Overall, the environmental damages AI produces, and the technological field generally, contribute to 4% of the CO_2 emissions [7].

In conclusion, AI carries opportunities for economic and technical development; however, the disadvantages are not to be ignored, since they not only affect society, but also the planet.

By Luise Link

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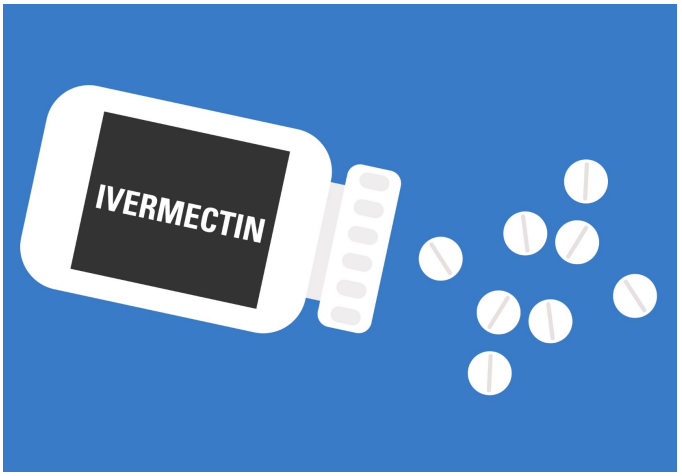

Ivermectin and Cancer

1.0 Introduction

A recurring claim holds that the well-established antiparasitic agent ivermectin possesses anticancer properties. This claim originates from laboratory studies that have demonstrated cytotoxic effects of ivermectin on malignant cell lines under controlled experimental conditions [1], [2]. The translation of such observations into clinically actionable treatment demands a more thorough evidentiary framework than laboratory data alone can provide [3], [4].

Ivermectin's proposed anticancer activity can be evaluated through lenses of mechanistic plausibility and pharmacological feasibility, and clinical evidence. A biological signal refers to a measurable effect observed under experimental conditions. Therapeutic validity requires that such an effect be reproducible in living organisms at safe and achievable concentrations and that it be confirmed through designed clinical trials in human patients. These are fundamentally different standards [4].

2.0 Ivermectin Development

2.1 Origins and Discovery

The origins of ivermectin trace back to 1970 when Japanese microbiologist Satoshi Ōmura of the Kitasato Institute began systematically screening soil microorganisms for novel antibiotic compounds [5]. Ōmura isolated a strain identified as Streptomyces avermitilis which had not been identified in any other soil sample worldwide [6]. This strain was sent to parasitologist William C. Campbell at the Merck Institute for Therapeutic Research where his team identified one of its fermentation products named avermectin as extraordinarily effective against parasites in farm animals [7]. Selective chemical modification of avermectin produced ivermectin [5], [8].

2.2 Human Approval and Global Health Impact

Ivermectin received approval for veterinary use in 1981 and was shown to be highly effective against parasites responsible for onchocerciasis [6]. Merck committed to donating ivermectin freely to endemic countries for as long as it was needed in 1987 following field studies conducted in collaboration with the World Health Organization. This established what became the Mectizan Donation Program [9]. Over its first two decades this initiative delivered more than 570 million treatments across 33 endemic countries [10], [11]. In 2015 Satoshi Ōmura and William C. Campbell were awarded the Nobel Prize in Physiology or Medicine for their work on avermectin and its derivatives [5].

2.3 Chemical Composition

Ivermectin is a semi-synthetic macrocyclic lactone derived from avermectin B1, structurally characterized as a 16-membered macrocyclic lactone featuring spiroketal benzofuran and disaccharide moieties with molar mass of approximately 875 g per mol [12]. The commercial formulation consists of an 80 to 20 mixture of 22, 23-dihydroavermectin B1a and B1b which differ by a single methylene group. This structural difference influences pharmacokinetic behavior and arises during the selective hydrogenation process used in production [8]. In its antiparasitic role ivermectin acts by binding to glutamate-gated chloride ion channels in invertebrate nerve and muscle cells which induces hyperpolarisation that causes paralysis and death of the parasite. Its selectivity in mammals is attributable to the absence of these channels in most

mammalian tissues and to the drug's limited ability to cross the human blood-brain barrier at approved doses [13], [14].

3.0 Mechanistic Evidence from Preclinical Research

Preclinical studies have identified several metabolic pathways through which ivermectin may exert anticancer effects. The drug has been shown to activate caspase-dependent apoptotic pathways and reduce cell viability through mitochondrial dysfunction and oxidative stress in leukemia and breast cancer models [1]. Ivermectin in colorectal cancer models is reported to suppress beta-catenin transcriptional activity within the WNT signalling pathway which is a frequently dysregulated axis in gastrointestinal malignancies [15]. Interference with the Pi3K and AKT signalling axis which is a central regulator of cell survival has been documented alongside evidence of reduced proliferation in breast and ovarian cancer contexts [16]. Ivermectin has also been identified as a specific inhibitor of importin alpha and beta-mediated nuclear transport. This is a mechanism relevant to the regulation of oncogenic transcription factors [17], [18]. These findings represent a credible biological signal but do not constitute evidence of clinical efficacy.

4.0 Pharmacological Constraints

The principal barrier to translating these findings into clinical use is pharmacokinetic. In vitro anticancer effects are typically observed at micromolar concentrations while standard human dosing of ivermectin produces plasma concentrations in the low nanomolar range. This is several orders of magnitude below what cell culture experiments require [13]. Pharmacokinetic analysis confirms that the maximum plasma concentration achievable under standard dosing conditions falls well below the threshold needed to reproduce in vitro anticancer activity [13], [19]. Dose escalation sufficient to close this gap would likely produce neurotoxicity along with central nervous system depression and other adverse effects that have been documented at high doses [13]. Even in a hypothetical scenario where higher concentrations were tolerated systemically the distribution into tumour tissue would remain uncertain given the additional physiological barriers governing drug penetration [19].

5.0 Understanding In Vitro and In Vivo Evidence

A methodological distinction that is frequently overlooked in public discussions is the difference between in vitro and in vivo experimental systems. In vitro experiments test a compound on isolated cells in a controlled laboratory environment. While they allow precise observation of cellular responses the two-dimensional cell culture lacks the intercellular complexity along with extracellular matrix interactions and pharmacokinetic constraints of living organisms [20]. Drug concentrations required to produce an effect in cell culture frequently exceed those achievable in vivo. Sensitivity observed in a dish also is often not reproducible in animal or human studies [20].

In vivo studies that are conducted in living animal models introduce absorption, distribution, metabolism, and excretion dynamics alongside immune system interactions and the tumour microenvironment. Some murine studies have reported reduced tumour growth following ivermectin administration, particularly in xenograft models [2]. However, the dosing regimens in these studies often exceed human-equivalent exposures with results that have not been consistently replicated across tumour types and methodological quality also varies considerably [2], [3]. These findings offer preliminary support for continued investigation rather than evidence of clinical viability.

6.0 Clinical Evidence

At the clinical level evidence supporting ivermectin as a cancer treatment is minimal.

No large-scale randomised controlled trials have demonstrated efficacy in cancer patients. Existing studies are predominantly small and exploratory or observational in design. No oncology guidelines from any major regulatory or professional body recommend ivermectin for any oncological indication. Neither the U.S. Food and Drug Administration nor Health Canada has approved it for such use. Systematic reviews of repurposed drugs in oncology consistently classify ivermectin as preclinical or investigational with insufficient evidence to support clinical application [3].

7.0 Drug Repurposing Context

The scientific interest in ivermectin reflects the broader strategy of drug repurposing that seeks to identify new therapeutic indications for existing compounds. This approach carries advantages including established safety data along with reduced development timelines and lower research costs compared with de novo drug discovery [4]. Precedents for successful oncological repurposing include thalidomide and imatinib.

Thalidomide was originally withdrawn as a sedative due to teratogenic effects but later approved for multiple myeloma following rigorous clinical evaluation [21]. Imatinib was developed to target the BCR-ABL kinase in chronic myeloid leukaemia and gastrointestinal stromal tumours through its cross-reactivity with KIT tyrosine kinase [21]. Each of these cases progressed through structured mechanistic validation and preclinical studies as well as phased clinical trials before regulatory approval [4]. Ivermectin has not yet advanced beyond early-stage investigation in this pipeline.

7.0 Why the Claim Persists

The persistence of claims about ivermectin's anticancer potential reflects a pattern of misinterpretation that is common at the interface of scientific research and public communication. In vitro cytotoxicity is frequently presented as though it were equivalent to clinical efficacy and amplified through non-peer-reviewed channels before independent replication has occurred.

In reality a large number of substances are capable of killing cancer cells in laboratory conditions. High-dose ascorbate at pharmacological concentrations of 0.3 to 20 millimoles per litre has been shown to selectively kill cancer cells through hydrogen peroxide generation and oxidative stress induction [22]. It has not demonstrated clear antitumour activity in clinical trials at doses achievable in patients [22]. This example illustrates why in vitro cytotoxicity is an insufficient basis for therapeutic claims. The defining questions for any candidate anticancer agent are whether it acts selectively and safely in living organisms at concentrations achievable through tolerable dosing [20]. Ivermectin has not yet satisfied these criteria.

8.0 Conclusion

Ivermectin demonstrates measurable effects on cancer cells in laboratory settings. The pharmacokinetic gap between effective experimental concentrations and those achievable through safe human dosing combined with the absence of robust in vivo validation and high-quality clinical trial data means that the available evidence does not support its use as a cancer treatment.

Based on current evidence ivermectin is more accurately characterized as an investigational compound in oncology than as a therapeutic agent. The methodological principle this case illustrates extends beyond ivermectin itself. Biological plausibility is necessary but insufficient basis for clinical application. Sound oncological practice requires evidence that progresses through reproducible preclinical studies and pharmacologically feasible dose relationships as well as prospective clinical trials demonstrating patient benefit. These are the standards by which any proposed cancer treatment should be assessed.

By Mudassra Zahoor

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The Inheritance of Colonialism and Androcentrism in Computational Biology

Artificial intelligence is frequently presented as a tool capable of liberating scientific inquiry from centuries of narrow sampling and the persistent treatment of a single "standard" human body as the universal reference. With the capacity to analyse data points across populations, environments, and genomes at scale, computational biology promises a future in which diversity is structurally inevitable. Yet, this remains entangled with older colonial and androcentric frameworks. The male body continues to function as the implicit default reference in many computational models, shaping which data are prioritised and how biological norms are defined [1].

These inherited frameworks are not incidental to computational biology; they are encoded directly into the architecture of its models. Despite their considerable analytical power, AI systems have reproduced legacy sampling distortions with a precision and scale that manual research could not match [1], [2]. Tools designed to integrate vast biological complexity continue to structure outcomes such that certain populations are treated as normative while others are rendered peripheral [3].

Bias in biology predates the emergence of artificial intelligence and is rooted in long-standing methodological practices [1].

Clinical drug trials disproportionately excluded women well into the late 20th century, citing hormonal variability as a confounding factor rather than a biological reality worth studying [1].

Consequently, biomedical standards were derived predominantly from male cohorts, producing measurable disparities in clinical outcomes. Women have experienced higher rates of adverse drug reactions and less predictable therapeutic responses [4]. When such baselines are subsequently converted into training datasets, bias becomes a question of architecture: systems do not reproduce inequality through error but through statistically validated design. Nevertheless, the field has replicated historical patterns of exclusion in two particularly consequential forms: population-level underrepresentation and gender-based modelling asymmetries.

Cardiovascular risk models, for instance, have been shown to perform less reliably for women because foundational datasets disproportionately represent male presentations of cardiac disease, and diagnostic imaging systems have demonstrated reduced accuracy in identifying conditions that present differently across sexes, reflecting the model's insufficient exposure to anatomical and physiological variation [6].

Consider Polygenic Risk Scoring (PRS), a widely used AI-driven method for predicting

disease susceptibility from genomic data. These models perform significantly better for populations of European descent than for African, Asian, or Indigenous populations, not because the biology is simpler, but because the training data is narrower [5].

Because models prioritise patterns that appear most frequently in their training sets, uneven datasets translate directly into uneven performance: some populations are modelled with high fidelity while others are not. Large-scale genome-wide association studies (GWAS) compound this problem by continuing to overrepresent specific ancestral groups, limiting the transferability of findings across populations and narrowing the clinical applicability of genomic medicine [5].

What once required individual researchers to make a series of exclusionary methodological choices now unfolds automatically, through datasets optimised for computational efficiency [2], [3]. The presence of a population in a dataset does not guarantee its patterns will influence model outputs; representational inclusion and analytical equity are not equivalent. In this respect, AI has not dismantled colonial structures of knowledge production; it has rendered them computationally efficient.

The downstream consequences of these representational asymmetries are both measurable and clinically significant. Polygenic risk scores derived from skewed datasets can misestimate disease risk in non-represented populations, leading to reduced predictive accuracy in clinical genomics [5]. Similarly, pathogenic variants that are well-characterised in European reference datasets may be misclassified or remain unrecognised in other populations due to incomplete genomic representation [5].

Computational biology already possesses the methodological tools to do better. Sex-aware modelling, population-stratified analyses, and context-sensitive training have all demonstrated improved performance across diverse biological groups [3]. The limitation is not computational capacity but institutional will.

If computational biology is to move beyond the “default body,” it will require more than larger datasets or faster models; it demands a rethinking of what counts as a biological signal, whose data is considered foundational, and which questions are deemed worth asking. Without this shift, computational systems will remain what they currently are: not the end of structural imbalances in biology, but their most elegant automation.

These systems should not be condemned for producing such outcomes, but instead used as an example of how tools often presented as “fix-it-all” solutions can amplify the assumptions embedded within their training frameworks [3]. As a result, it may be concluded that the real intersection may not be with computational biology alone, but with historical blind spots, amplified, automated, and encoded into computation itself.

By Saanvi

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Why Music is Physics

Introduction

In the modern day, music is everywhere and more accessible than ever before. With the rise of streaming platforms like Spotify and Apple Music, listening to music has become a common part of daily life, yet the mechanisms of music are rarely explored. This can be examined through the different sounds produced by each instrument, the optimal note combinates for enjoyment, and the number of notes in an octave.

Sound and Instruments

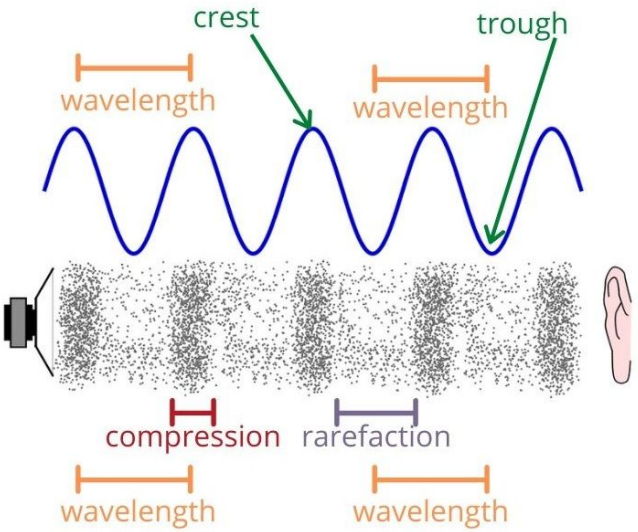

Figure 1: Visual representations of transverse and longitudinal waves.

There are two types of waves, transverse and longitudinal. Sound waves are longitudinal, meaning their direction of energy transfer is parallel to the direction of oscillations, which is the repetitive back-and-forth motion of the wave. Waves on a string are transverse, so their energy transfer is perpendicular to their oscillations.

Plucking an instrument's string sends a transverse wave along it and causes it to vibrate. The string's motion pushes air molecules away, producing slight changes in air pressure that form a longitudinal sound wave [1]. This sound wave propagates outwards and is detected by the eardrum upon reaching the listener. Figure 1 shows a transverse wave on top, and the corresponding longitudinal sound wave it would produce underneath. The wave travels along the string and is reflected at the ends and travels back through the string. It overlaps with the initial wave, superposing to form a stationary wave.

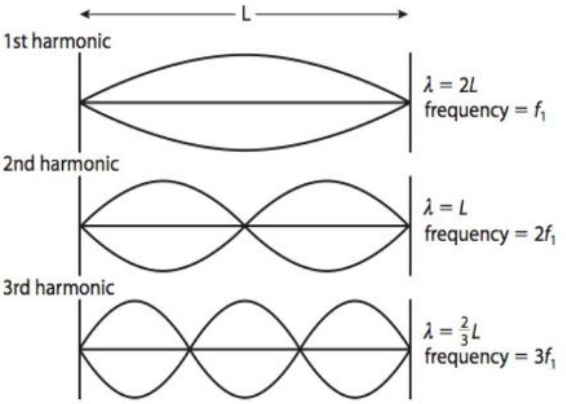

Figure 2: Visual representation of different harmonics.

The first harmonic is the lowest frequency that a stationary wave forms at. It has two points where amplitude is zero, known as nodes, and one point of maximum displacement, known as an antinode. The second harmonic is double the frequency of the first and the string appears to vibrate in two halves. The third is three times the frequency of the first, the fourth is four times, and so on.

The Mathematical Intervals of Notes

Upon understanding the formation of sound waves, it is also important to examine their relationships. The intervals, or distances, between notes are the mathematical relationship between their frequencies. Each interval has a different effect: some may sound pleasant, others dissonant. Understanding these intervals can help

musicians create music with the right tone and emotion.

Firstly, octaves are the fundamental building block of the music system. Octave intervals double the frequency of the note. An example of this is that from an A at 440 Hz, with the next A being double the frequency at 880 Hz. Then to form the rest of the notes, the octave is divided up. Although theoretically any number of notes could be used, a good example is the twelve-note system of Western music. To get the next semitone (A#) from the note A (440 Hz), the frequency is multiplied by $2^{1/12}$, because the frequency needs to double every twelve notes while keeping in mind the fraction of the octave being advanced.

As a formula this would be 440 $2^{n/12}$, where n is the distance of the note from A. As a graph this forms an exponential curve, which is necessary to preserve the frequency ratios between notes [2]. Perception of music notes depends on these ratios, rather than a linear difference in frequencies. The ratio 2:1 represents an octave.

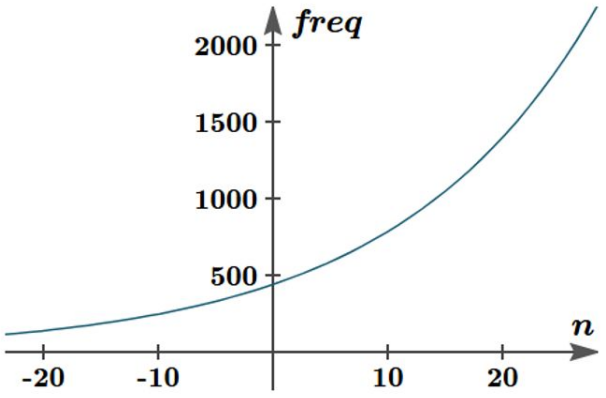

Figure 3: How frequency changes with ratio.

Doubling the frequency is effectively the same as the doubling of frequency from the first harmonic to the second. However, harmonics must not be confused with octaves. The third harmonic is not an octave above the second; the fourth is. It is only an octave when the frequency doubles. For harmonics of A, the 1st = 110 Hz, 2nd = 220 Hz, 3rd = 330 Hz, 4th = 440Hz. The frequency only doubles from 1st to 2nd, and 2nd to 4th.

The brain processes sound through frequency pattern recognition; aligned harmonics have a stable and predictable wave pattern that it interprets as pleasant sounding. Misaligned harmonics disrupt this as the brain struggles to recognise a pattern, causing it to make incorrect predictions and work harder to process the sound. So, the sound is interpreted as unpleasant. Octaves are the strongest interval as their waves share many peaks and troughs, allowing them to align well.

The third harmonic makes the next strongest intervals, the perfect fifth and perfect fourth. The third harmonic is triple the frequency of the first; 110 3 = 330 Hz. Or, it can also be 1.5 times the frequency of the second, 220 1.5 = 330 Hz. This creates a 3:2 frequency ratio. Using the equation from earlier, with the second harmonic as our starting point: 220 x $2^{7/12} \approx$ 330 Hz.

As n=7, the third harmonic is seven semitones above the starting note. From an A, this would correspond to an E. It is called a perfect fifth in music because of how musical scales are defined, but note that a fifth here means it is 7 semitones above the starting note. The perfect fifth (3:2) interval is between the 2nd and 3rd harmonics, like an A to an E. Whereas a perfect fourth (4:3) is between the 3rd and 4th, like an E to an A. They are very subtly different. These intervals are slightly less ‘predictable’ and pleasing than an octave as the waves are more misaligned.

Chords combine the strongest intervals and generally consist of the first, third and fifth note. An A chord would be A (first), C# (major third 5:4), and E (fifth). Chords are the basis of nearly every song, so they are highly important to music theory.

As the frequency ratio of the intervals increases, their harmonics align less often, their wave pattern is less stable, and the clashing harmonics disturb the brain’s auditory processing. Playing the same note twice produces a 1:1 ratio, an octave represents 2:1, a perfect fifth is 3:2, and a perfect fourth would be 4:3. Then there are

major thirds as 5:4, minor thirds as 6:5, major seconds as 9:8 and minor seconds or semitones as 16:15 [3]. Each note gradually becomes more dissonant sounding as the frequency ratio between notes increases and their waves align less.

However, dissonance is not necessarily bad; it is a tool for musicians to add contrast and character to a song. For example, the use of alternating semitones at the beginning of Beethoven's 'Für Elise'.

Why Instruments Sound Different

Instruments can play the same note at the same frequency but still be distinguishable from one another because of their unique timbre. A note is not just one harmonic vibrating on a string. In reality, the string is vibrating at all of its harmonics simultaneously, each with varying amplitudes where higher amplitudes result in louder sounds. Instruments have a unique combination of amplitudes for each harmonic, some may be louder than others, which gives it its timbre and helps distinguish between different instruments' sounds [4], [5].

Additionally, though instruments produce sound in different ways, the underlying physics is the same. For string instruments, the stationary waves form on the string. For wind instruments, they form in the air in the tubes and for percussion instruments, they form either throughout the instrument itself or in the air inside.

Alternate Music Systems

In Western music, the octave is divided into 12 notes, but it could theoretically be divided into any number of notes. The 13th century Arabic system used 17 notes, and the modern Arabic system uses double the Western's at 24 notes [6]. There really is no limit because there are an infinite number of frequencies in an octave. American composer Harry Partch even designed his own instruments that played 43 unequally spaced tones [7]. Additionally, fretless string instruments such as the violin are not restricted to just 12 notes; they can play many microtones between these [8]. However, musicians typically stick to one system.

Western music systems are the most widely used partly due to how highly divisible twelve is. Twelve can be divided by two, three, four, six and twelve which makes it easier to create the third, fourth and fifth intervals discussed earlier [9]. But this is only improved by Arabic's twenty four notes, making it even more divisible. There is no mathematical reason for choosing twelve over twenty four, anecdotally musicians simply find fewer notes are easier to work with, read and play. Though there is certainly some beautiful microtonal music that makes a good case for using more than just twelve notes.

Conclusion

Music is perceived as a very creative field, whereas physics and mathematics are often stereotyped as more rigid. However, they are more intertwined than they may seem. The physics of waves and the mathematical ratios of frequencies puts logic behind why some music sounds better to some people more than others. Understanding how sound waves actually work together can enhance a musician's skill and art. It also helps question the system and explore beyond the basic twelve notes, leading to more innovation and better self-expression.

By Savannah Pearl Bamford

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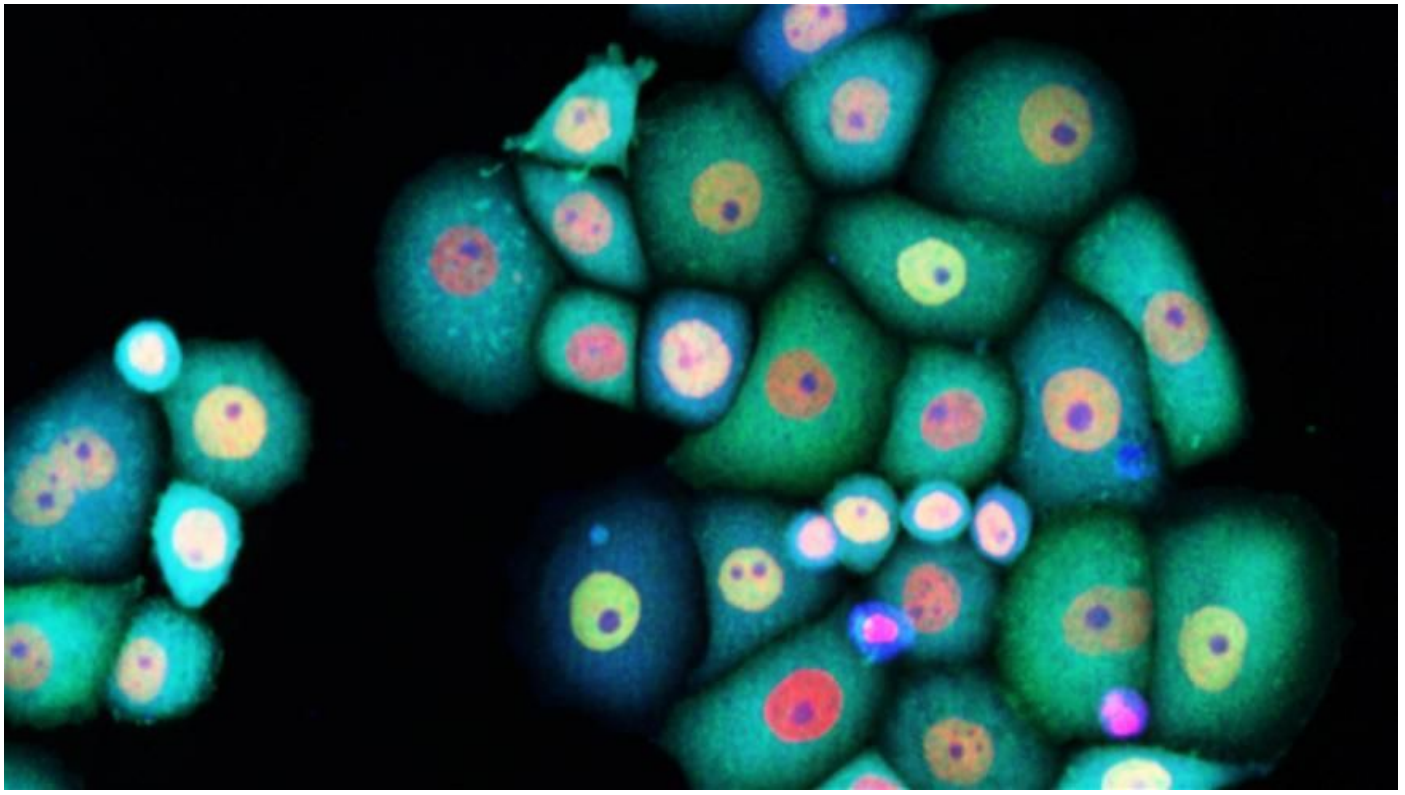

The Secret Life of Cancer Cells

Almost all cells carry a built-in expiration date. In fact, they can only divide around 40-60 times before they permanently stop growing. This limit is the body's natural defense system against uncontrolled growth. However, cancer cells can find ways to escape this limit and continue to divide long after typical cells would die. In biology, this ability is often described as "immortality."

Elizabeth Blackburn's research suggests that cancer cell "immortality" is not a sign of strength but the result of escaping the mechanisms that typically limit cell division. Despite their ability of dividing indefinitely, cancer cells still rely on telomeres, the protective caps at the ends of chromosomes that gradually shorten with each cell division and ultimately limit a cell's lifespan. Telomeres function much like the plastic tips on shoelaces, protecting chromosomes from fraying and damage during DNA replication.

In most body (somatic) cells, telomeres shorten over time until the cell cannot divide any longer, forcing it to enter senescence, a natural process where the cell stops dividing. Cancer cells overcome this barrier using certain telomere maintenance mechanisms; the most common one works by activating telomerase, an enzyme that rebuilds telomeres. Others rely on Alternative Lengthening of Telomeres (ALT), a mutation-prone process that lengthens telomeres without relying on telomerase [1], [2]. ALT is commonly associated with aggressive and therapy-resistant malignancies; but, the early cellular conditions that contribute to its emergence remain incompletely understood.

A key feature of tumor evolution is the development of cellular heterogeneity, in which subpopulations within the same tissue exhibit distinct survival and growth behaviors under stress. Oxidative stress, the damage of cells due to excess oxygen molecules, is a major component of the tumor microenvironment and contributes to DNA damage, replication stress, and genomic instability, especially in telomerase-deficient systems where telomere maintenance is already compromised [3]. In this high stress environment, stress does not necessarily produce uniform cell death but may instead select for rare subpopulations capable of tolerating genomic damage. This selective survival is thought to contribute to early adaptive trajectories that precede full oncogenic transformation, because

accumulated DNA damage can gradually alter genomic stability and influence long-term cellular evolution over time.

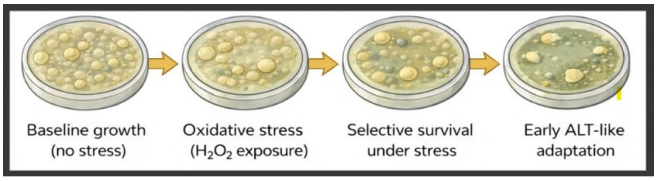

Figure 1: Oxidative stress following telomerase loss creates selective pressure that eliminates most cells while enriching rare survivor subpopulations with heterogeneous growth, modeling early recombination-based telomere maintenance consistent with ALT in cancer [1], [2].

To investigate the relationship between oxidative stress and early adaptive survival patterns, telomerase-deficient *Saccharomyces cerevisiae* (yeast) was used as a model system. This organism is widely used for studying telomeres and genome stability because it shares key telomere mechanisms with human cells and is easy to grow and replicate in controlled experiments [4]. Oxidative stress was induced using hydrogen peroxide (H_2O_2), a reactive oxygen species that causes DNA damage and is commonly used to mimic the type of cellular stress in cancer cells and tumor environments. Cultures were exposed to increasing concentrations of H_2O_2, and survival was assessed through serial dilution plating and time-dependent colony growth analysis.

Figure 2: Increasing oxidative stress reduces survival in a dose-dependent manner and increases colony heterogeneity in the yeast, visually revealing rare survivor subpopulations that are similar to early ALT-associated survival behavior observed in cancer cells [5].

Increasing oxidative stress produced a clear, stepwise reduction in overall colony formation relative to control conditions, indicating strong selection pressure against the majority of the population. However, survival was not uniform across all cells. A small subset of colonies consistently persisted even under high-stress conditions and continued to proliferate over time. This persistence suggests that survival was not purely stochastic but reflected the presence of distinct subpopulations with enhanced tolerance to oxidative damage.

In addition to differences in survival rate, pronounced morphological heterogeneity was observed among colonies exposed to stress. Control populations exhibited relatively uniform colony size and density, whereas treated populations showed substantial variability in growth patterns, including differences in colony diameter, shape, and expansion rate. This variability increased with higher treatment levels, suggesting that oxidative conditions actively shape the phenotypic distribution of surviving cells rather than simply reducing population size.

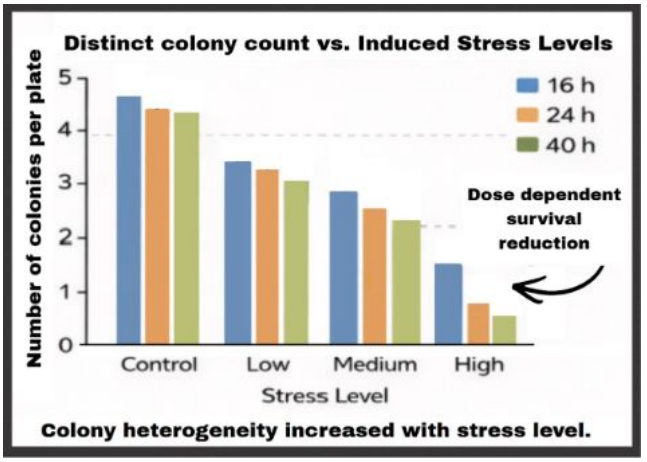

Figure 3: Colony survival decreases with increasing oxidative stress, while small survivor populations persist, consistent with selective pressures preceding ALT activation [5].

The combination of reduced survival and increased heterogeneity is consistent with early cellular adaptation, where only the most resilient cells persist. In telomerase-deficient systems, oxidative damage may accelerate telomere dysfunction and increase reliance on alternative DNA repair and recombination pathways. The observed survival patterns do not represent ALT itself, but rather resemble early behaviors that lead to and are associated with the development of ALT-positive cells, including non-uniform growth and persistence under genomic

stress conditions [5].

These findings of increased heterogeneity and the existence of rare surviving subpopulations under oxidative stress support the hypothesis that such stress can act as a selective force promoting early-stage adaptive heterogeneity in telomerase-deficient populations, a process that may also contribute to the development of treatment resistance in cancer. Instead of causing uniform cell death, stress appears to favor the survival of distinct subpopulations that are likely to serve as early precursors to mechanisms like ALT. This stress-driven selection of survivors provides a potential framework for understanding how therapy-resistant cancer phenotypes may emerge prior to full activation of standard telomere maintenance pathways.

In conclusion, oxidative stress in telomerase-deficient yeast leads to reduced overall survival while promoting the emergence of heterogeneous, stress-resistant subpopulations. These results suggest that stress-driven selection may play a role in early adaptive processes that resemble ALT-like survival behavior. Understanding these early dynamics may provide insight into how therapy-resistant cancer cells develop and highlight the role of cellular stress in shaping long-term patterns of genomic instability.

By Sragvi Madishetty

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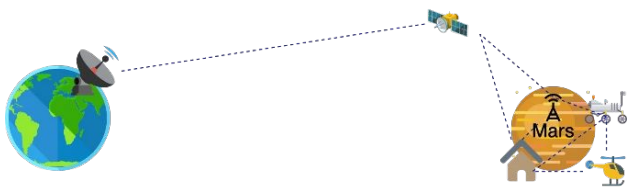
The Transition to AI-Driven Autonomous Space Navigation

Deep space exploration presents many challenges due to the vast distances between Earth and spacecraft operating outside of our planet. Reliable communication is essential for maintaining accurate navigation and assuring mission success. However, these vast distances establish underlying limitations that restrict real-time control and decision-making. For example, signals exchanged from Earth to Mars experience round-trip delays that can range anywhere from a few minutes up to 40 minutes [1]. These delays also come with interruptions that can result in extended periods with lost communication.



In November 2023, a Martian solar conjunction took place, during which no messages could be exchanged between the planets for 2 weeks. All communication windows are specified and planned in advance, so if one cannot be used, the opportunity is lost. These relays do not create a true network, so there is no option to use alternate paths or make any routing decisions. This highlights a key limitation in deep-space communication systems, where latency can prevent timely data exchange [1]. To mitigate these challenges, artificial intelligence is being integrated into space systems, enabling autonomous decision-making and reducing reliance on communication with Earth.

To understand why autonomous navigation is used, it is important to first analyze how traditional spacecraft operate under the control of Earth-based systems. Guidance, navigation, and control systems rely on integrated hardware including sensors, actuators, and onboard processors to maintain spacecraft orientation and trajectory [2]. These systems work together under strict resource and power constraints and are designed for reliability rather than flexibility. Data from multiple sensors is used for navigation. Each of these sensors has limitations, leading to the use of algorithms like Kalman filters to estimate a spacecraft's state. These navigation systems are preprogrammed and follow fixed control logic. These architectures rely on deterministic algorithms where the same inputs always produce identical outputs. NASA's Deep Space network supports spacecraft positioning and communication,

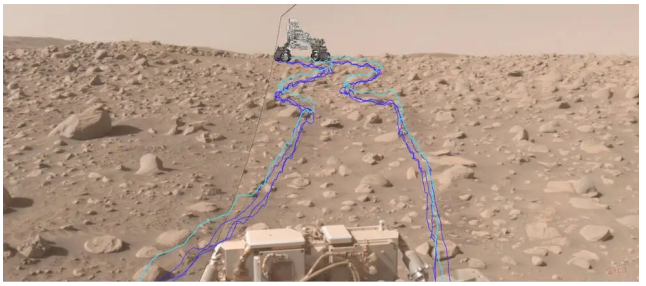
forming a unified framework that integrates both Earth and spacecraft systems. Spacecraft navigation systems are also designed with redundancy to make sure that if one component fails, the others can maintain system stability [3].

Artificial intelligence plays a significant role in many operations today, including autonomous space navigation. The transition to AI-based systems allows spacecraft operation to move from pre-programmed behavior to adaptive, data-driven computation using machine learning models. These machine learning models help improve accuracy and predict behaviors by learning from past data. Instead of relying on predefined strategies, machine learning enables pattern recognition and generalization, allowing spacecraft to operate effectively in uncertain environments. This can improve space navigation, especially when sensor data is unreliable [4], [5].

Reinforcement learning is a machine learning paradigm in which an agent learns to make decisions by interacting with its environment and receiving feedback in the form of rewards and penalties, with the goal of maximizing long-term cumulative rewards. In this context, the spacecraft acts as the agent, operating within an environment and making decisions that promote efficiency, reliability, and mission success. Over time, the system learns optimal trial strategies through repeated experiences, optimizing long-term performance rather than immediate outcomes [6].

Spacecraft navigation also involves optimization, ensuring that the most efficient path is taken under constraints like fuel and time. AI algorithms extend traditional computer science approaches like algorithmic optimization, shortest-path computation, and dynamic programming by incorporating real-time data and uncertainty. AI planning enables the spacecraft to recompute trajectories in response to different conditions rather than following a pre-programmed path, effectively turning navigation into a continuous optimization problem under constraints.

Ultimately, the shift from traditional navigation systems to AI in autonomous space navigation represents a transition from fixed, static control to adaptive, data-based decision-making. Earlier models relied heavily on Earth-based tracking systems and precomputed trajectories, which later systems could reuse to improve decision-making and respond to uncertainty in changing environments. This transformation directly addresses the communication delays and limitations introduced earlier, enabling more resilient deep space exploration. In scenarios like Martian communication blackouts, AI allows spacecraft to continue navigation and operate efficiently without relying on Earth systems.



A prominent example of AI in space exploration is NASA's Perseverance rover, which uses its AutoNav feature to 'autonomously re-plan its route around rocks or other obstacles on its way to a pre-established destination,' enabling navigation without human control. Using videos and images captured by its navigation cameras, the rover analyzes terrain and adjusts its path in real time as part of a mission to collect and cache Martian rock and regolith. The rover also uses decision-making algorithms such as computer vision and real-time path planning to effectively operate as a system that perceives its environment and acts upon changes [7], [8].

A key challenge in utilizing artificial intelligence for space navigation is reliability and accuracy in critical systems. Since these spacecraft systems do not depend on human control, a single incorrect prediction could result in a mission failure or worse.

This is a major constraint for using AI systems, as they may produce incorrect results under uncertain conditions. This relates back to model robustness and error tolerance, where systems must preserve stable performance, especially when inputs differ, to maintain accuracy.

Another major limitation is the scarcity of available data. Space environments are difficult to replicate, which can lead to models performing well on training data but failing in real-world conditions. Spacecraft also impose strict computational constraints due to limited storage capacity, memory, and processing power. Transmission of data back to Earth is a slow process, so efficient systems and optimized algorithms are needed to deal with substantial amounts of information. Additionally, AI systems trained on data based on Earth environments can struggle to generalize due to different factors like unfamiliar terrain and gravity. This makes it difficult to guarantee consistent performance in a diverse pool of missions [9].

Regardless of AI limitations, deep space navigation challenges the traditional computing models due to latency and the inability to rely on control systems. The communication delays between Earth and spacecraft make real-time remote decision-making impractical. As a result, autonomous navigation has shifted from Earth-based systems to AI algorithms designed to operate independently of remote decisions and function under uncertainty. In this way, AI directly resolves the communication constraints introduced at the beginning, enabling spacecraft to operate continuously even when experiencing communication blackouts, and reinforcing the essential role of computer science in future deep space exploration.

By Sreenya Audireddy

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Hilde Mangold: The Woman Who Discovered Cellular Induction

In the past, women were denied access to education and their own work. They were restricted to the traditional roles that were forced upon them. Hilde Mangold demonstrated to the world how a woman can break these stereotypes through her exceptional work in the field of science. Her work laid the foundation for the field of embryology.

Hilde Mangold was born on October 20, 1898, in Gotha, Thüringen [1], [2], [3]. Throughout her formative years, Hilde's parents raised her and her sisters in a household where they were encouraged to fulfil their potential, as they received one of the finest educations of that time [1]. Following high school, Hilde enrolled in Gymnasium Ernestinum at the age of 16, which was unusual for girls during that era. Still, Hilde obtained her degree with exceptional grades. Subsequently, she was sent to a boarding school where she was taught to do household chores and follow social etiquette. She left the boarding school after 6 months, and she enrolled at the University of Jena as a chemistry student [1]. She realised that chemistry did not suit her interests because she was more dedicated to biology and zoology [1]. Therefore, she moved to Frankfurt, where she did zoology [1], [4], [3].

In Frankfurt, Hilde Mangold heard a guest lecture by Hans Spemann, renowned for his research in experimental embryology. His work elucidated the process of cells and tissues becoming specified in the developing embryo [1], [2], [3], [4]. This lecture made Hilde keen to explore prospects for embryology research in graduate school. In 1920, she started her doctoral work at the University of Freiburg in Germany [1], [2], [3], [4]. Shortly afterwards, she joined Spemann's laboratory for her doctoral work [1], [2]. Hilde felt rejected, as her given thesis project was to replicate Abraham Trembley's findings from the 1700s about the freshwater genus *Hydra*, which were said to be capable of regeneration [2]. Historic records indicate that Spemann showed a great amount of discrimination against women in his lab, as this was not the only time he gave his female graduate student routine laboratory tasks [2].

Hilde worked on this assignment for a year. However, it was impractical to do, as her *Hydras* were intractable. Even Spemann was unable to flip it. Consequently, Hilde started pressuring Spemann into providing her with a new research project [2]. Her new project was about how cell identity was specified during gastrulation; it was built upon Spemann's earlier research [2].

Both Hilde and Spemann hypothesised that the dorsal lip of the blastopore, located in the back of an organism, plays a pivotal role in the process of gastrulation. The best way to prove this theory was through the process of cell transplantation [5]. Hilde performed this experiment using the embryos of the new species of newts. The dark-coloured newts are identified as *Triturus cristatus*, and the light-coloured newts are also known as *Triturus taeniatus* [4]. Mangold began her experiment by

transplanting the cells of the dark-coloured embryo onto the light-coloured one. Because the embryos were different colours, Hilde would be able to create a fate map and track the cell migration of the tissue [2], [4], [5].

If their theory were true, then the transplanted cell would permeate gastrulation to the other cells in the host embryo and, in particular, would lead to the development of the second body axis [2], [3].

Hilde took a long time observing the embryo after it was fertilised [2]. She then had to carefully remove the outer membrane and dissect some parts of the cells using a glass needle. [2], [4]. Spemann made these glass needles for his embryological research purposes [1], [2]. He even engineered his child's hair into a loop; since a child's hair is small and soft, it makes the loops the optimal tool to pinch a cluster of dividing salamander cells [1], [2], [4], [5].

Following the long procedures, the embryos were developed in their natural environment, that is, the ponds [4]. However, the ponds were not sterile, as they contained various bacteria causing infections in the embryos. This resulted in a high mortality rate among the embryos [4]. Out of the hundreds of manipulations, only six survived [4]. After two days, Hilde discovered that the hypothesis was right, as the surviving embryos had a second neural tube and, subsequently, second heads, brains and spinal cord [2], [4]. It took her two years to finish this project.

These findings formed the basis of her dissertation, "On the Induction of Embryonic Anlagen by Implantation of Organizers from Different Species." She obtained her PhD in February 1923, and Spemann added his name as an author on the dissertation, ignoring Hilde's objection [1], [3].

In 1921, during the experiment, Hilde fell in love with Otto, Spemann's chief advisor. In 1924, she had a son with him and moved from Freiburg to Berlin because Otto accepted a directorship at the Kaiser Wilhelm Institute for Biology [1], [2]. In the same year, Hilde's dissertation was published in Wilhelm Roux's Archiv für Entwicklungsmechanik der Organismen, one of the most famous journals for embryology [2]. On the 4th of September 1924, Hilde passed away due to severe burns caused by a kitchen explosion in her apartment at the age of 26 [2].

Subsequently, Hilde's dissertation received the Nobel Prize in Physiology or Medicine for discovering the Organiser. Although Hilde wrote the dissertation, Spemann received the Nobel Prize due to his forced authorisation [2]. Spemann gave credit to Hilde in his acceptance speech. Nevertheless, he did not reveal the fact that it was Hilde's dissertation [2].

Later, it was revealed that the experiment had been carried out primarily by Hilde, which caused it to be renamed from the 'Spemann Organiser' to the 'Spemann-Mangold Organiser'. This change demonstrates Hilde's legacy, which is her passion for science. Her doctoral thesis provides conclusive proof of the discovery of cellular induction, which continues to play a pivotal role in the fields of embryology and biology to this day.

By Srithu-Hilde Mangold

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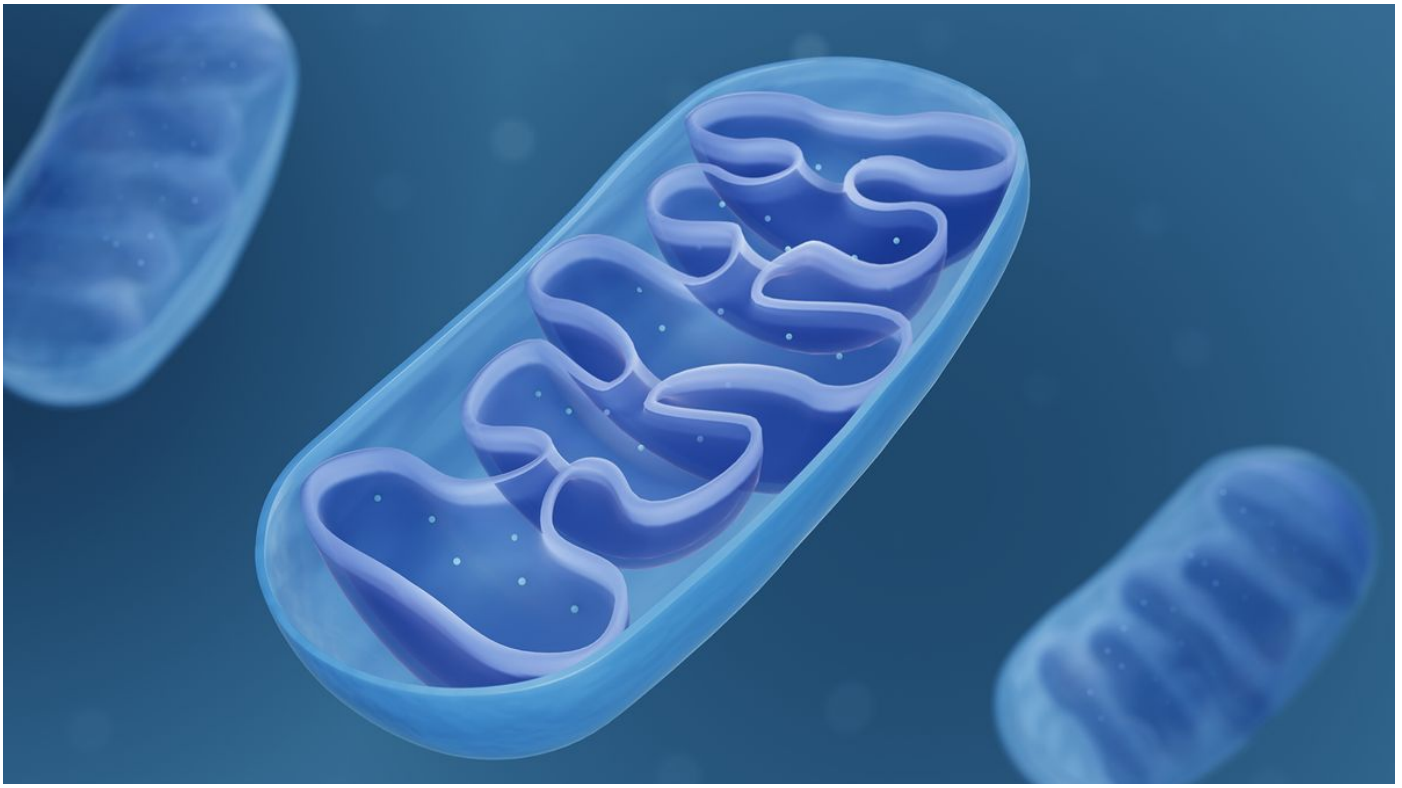
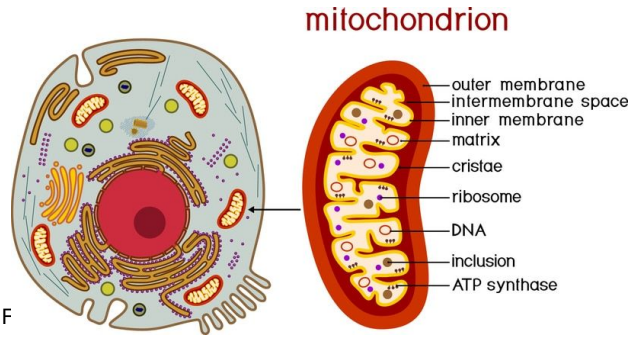


Mitochondria And The Endosymbiotic Theory

Introduction

The cell is widely recognized as the fundamental structural and functional unit of all living organisms, and its survival depends on the coordinated activity of specialized organelles that perform distinct yet interconnected roles [1]. Among these organelles, mitochondria occupy a central position because they are responsible for both the production of cellular energy and also for the regulation of numerous essential biological processes. These include metabolic integration, intracellular signaling pathways, and the initiation of programmed cell death, which is crucial for maintaining tissue balance and organismal health [2]. Mitochondria act as dynamic regulators of cellular physiology and play a role in sustaining life at the molecular level.

The scientific understanding of these organelles has evolved significantly, a key milestone being the development of the endosymbiotic theory, which provides a coherent explanation for their evolutionary origin. This theory links cellular biology with evolutionary science and proposes that complex eukaryotic cells emerged through ancient symbiotic relationships between distinct prokaryotic organisms, fundamentally reshaping the understanding of the origin of life's complexity [3], [4].



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Structure of Mitochondria

Mitochondria are highly specialized organelles characterized by a unique double-membrane structure that reflects their evolutionary origin and functional complexity. The outer membrane serves as a protective boundary that regulates the exchange of molecules between the mitochondrion and the surrounding cytoplasm, while the inner membrane is highly folded into structures known as cristae. These folds significantly increase the surface area available for biochemical reactions, particularly those involved in energy production, making mitochondria highly efficient metabolic centers within the cell [5].

Inside the inner membrane lies the mitochondrial matrix, an internal space densely packed with soluble enzymes, substrates, cofactors, and ribosomes responsible for key metabolic pathways. Most notably, this includes the citric acid cycle, also known as the Krebs cycle [5]. This cycle plays a central role in cellular respiration by producing high-energy electron carriers such as NADH and $FADH_2$, which are later used in oxidative phosphorylation to generate ATP. The structural organization of mitochondria is therefore directly linked to their function, allowing them to efficiently convert biochemical energy into a usable form for the cell [5].

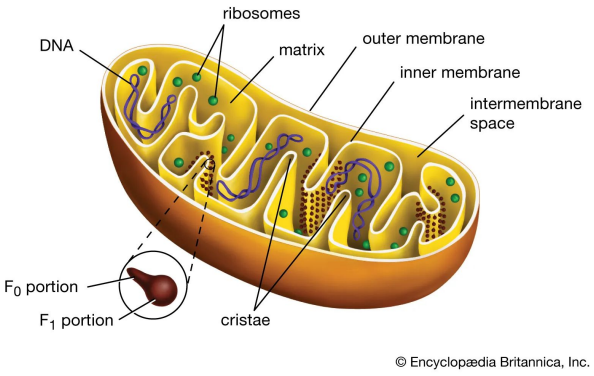


Figure 2: Structural anatomy of a mitochondrion [6].

Mitochondrial DNA

Mitochondria feature the presence of their own genetic material, known as mitochondrial DNA (mtDNA). Unlike nuclear DNA which represents the primary linear genome contained within the cell nucleus and is inherited from both parents, mtDNA is a small, circular double-stranded molecule. It encodes a limited number of genes, 37 in humans, that are primarily involved in encoding core subunits of the oxidative phosphorylation machinery, as well as the transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs) necessary for localized mitochondrial protein synthesis. Crucially, mitochondria display a high level of genetic autonomy; they actively replicate their own DNA independently of the cell cycle, utilizing their own specialized replication machinery. This independent replication and gene expression capacity signifies a profound autonomy from the host cell. Having a separate genome is highly abnormal for intracellular structures; in fact, mitochondria, along with plant plastids like chloroplasts, are the only organelles to possess this trait.

Another important characteristic of mtDNA is its strict maternal inheritance pattern. In most species, including humans, mitochondria are transmitted almost exclusively through the oocyte, while sperm mitochondria are actively ubiquitinated and degraded after fertilization. This inheritance pattern has important implications for genetics, evolution, and the study of human ancestry. Because mtDNA does not undergo meiotic recombination and accumulates neutral mutations at a relatively steady and rapid rate over time, it acts as a highly precise molecular clock, allowing evolutionary biologists to trace maternal lineages back to common ancestors, such as "Mitochondrial Eve."

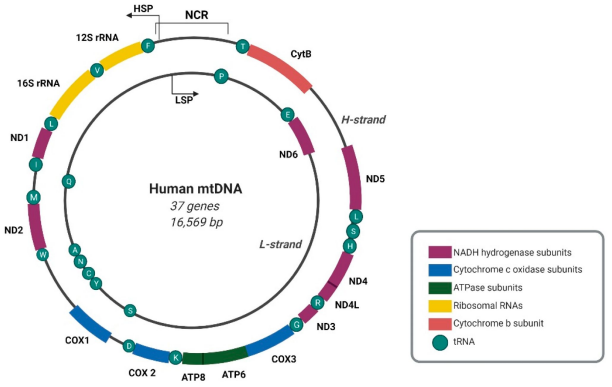


Figure 3: Map of the circular human mitochondrial genome [8].

Endosymbiotic Theory

The endosymbiotic theory, strongly associated with the work of biologist Lynn Margulis, proposes that mitochondria originated from ancient aerobic bacteria that were engulfed by primitive eukaryotic cells. Instead of being digested, these bacteria established a stable and mutually beneficial relationship with their host cells. The host cell provided protection and nutrients, while the internalized bacteria supplied energy through aerobic respiration, creating a highly efficient biological partnership [3]. Over

evolutionary time, this relationship became permanent, leading to the gradual integration of the bacterial symbiont into the host cell architecture. An important aspect of this integration is that modern eukaryotic cells cannot synthesize mitochondria de novo; instead, existing mitochondria must grow and replicate inside the cell through a process akin to bacterial division.

During this evolutionary co-habitation, a massive horizontal gene transfer occurred: many of the original bacterial genes were either transferred directly to the host nucleus or lost entirely, leaving the remaining mitochondrial genome specialized strictly for vital bioenergetic functions. Despite millions of years of integration, mitochondria still retain several undeniable bacterial characteristics. These include their circular DNA architecture, ribosome structures that are sensitive to bacterial antibiotics, and the ability to reproduce independently within the cytoplasm through binary fission [9].

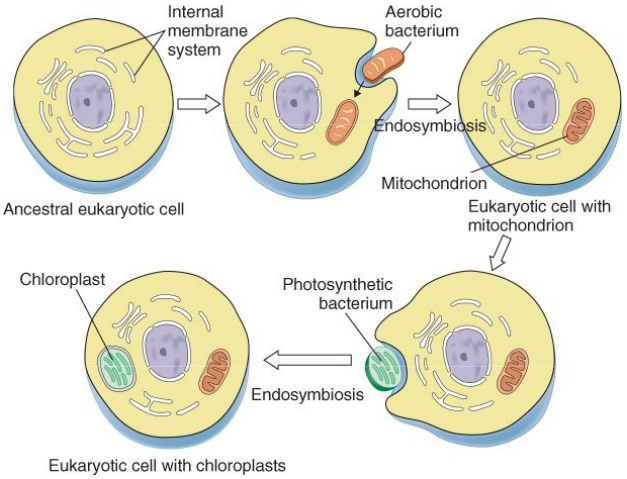


Figure 4: Evolutionary stages of endosymbiosis leading to modern mitochondria [10].

Additional Functions of Mitochondria

Beyond their essential role in ATP production, mitochondria are involved in a wide range of cellular functions that are critical for maintaining homeostasis. They regulate intracellular calcium levels, which are essential for processes such as muscle contraction and neurotransmission. Additionally, mitochondria participate in lipid metabolism and act as key signaling hubs within the cell [11].

They also produce reactive oxygen species (ROS), which, although potentially damaging in excess, serve important roles as signaling molecules involved in cellular communication and stress responses. However, excessive ROS production can lead to oxidative stress, which damages proteins, lipids, and DNA, contributing to aging and various degenerative diseases [12].

Mitochondria are also central to apoptosis, a tightly regulated process of programmed cell death. This mechanism is essential for development, immune function, and the removal of damaged or potentially harmful cells. During apoptosis, mitochondria release specific proteins that activate enzymatic cascades, ultimately leading to controlled cellular dismantling without causing inflammation [13].

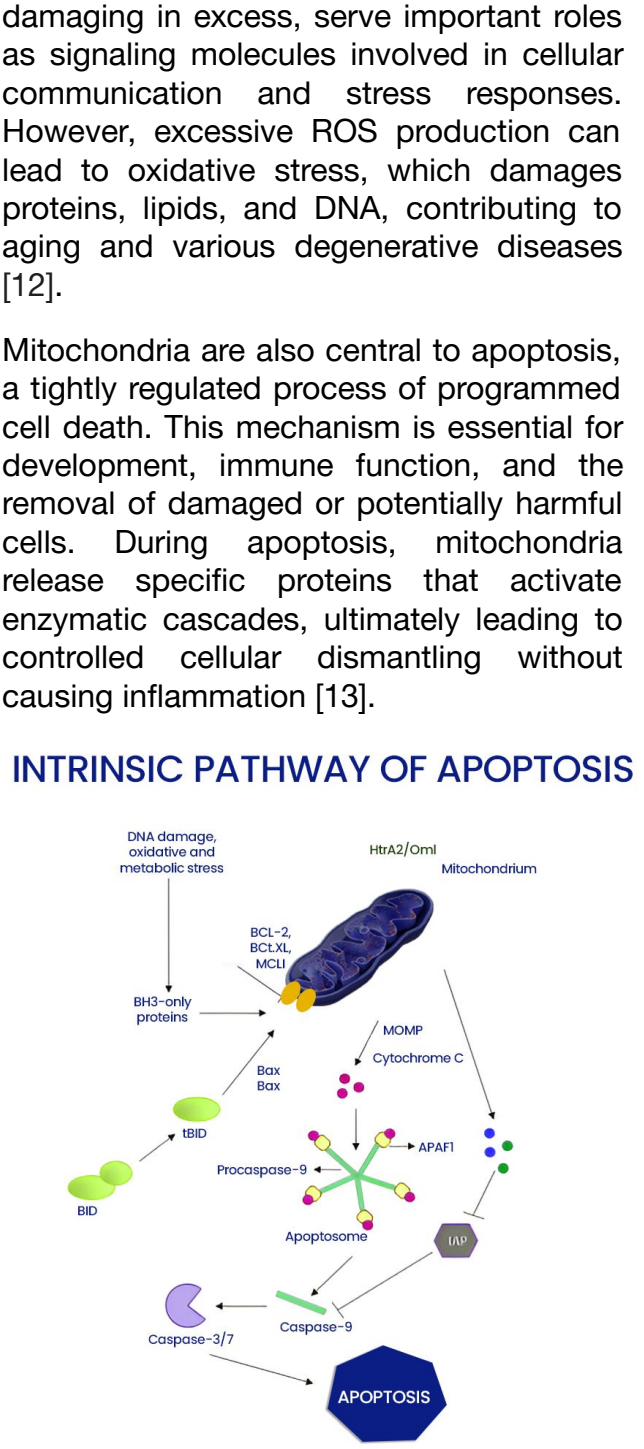


Figure 5: Mitochondrial mediated intrinsic apoptotic pathway [14].

Mitochondrial Diseases and Aging

Because mitochondria contain their own unique genome, they are particularly vulnerable to mutations that can significantly impair cellular energy production. This stems from mtDNA having a significantly higher mutation rate than nuclear DNA, caused by several factors: a lack of protective histone proteins, relatively limited DNA repair mechanisms, and close,

continuous exposure to the highly mutagenic reactive oxygen species generated by the electron transport chain. When mutations accumulate beyond a specific threshold, ATP synthesis is disrupted, leading to catastrophic bioenergetic failure.

Mitochondrial diseases primarily affect tissues with high energy demands, such as the brain, muscles, and heart. Examples include MELAS syndrome and Leber Hereditary Optic Neuropathy, both of which are associated with neurological and muscular impairments [15], [16]. In addition to rare genetic disorders, mitochondrial dysfunction has also been linked to common diseases such as diabetes, cardiovascular disorders, and neurodegenerative conditions [17].

In aging research, the mitochondrial theory of aging suggests that the gradual accumulation of oxidative damage and mtDNA mutations contributes to the progressive decline in cellular function over time. Although aging is a complex process influenced by multiple factors, mitochondrial dysfunction is considered a key contributor [18].

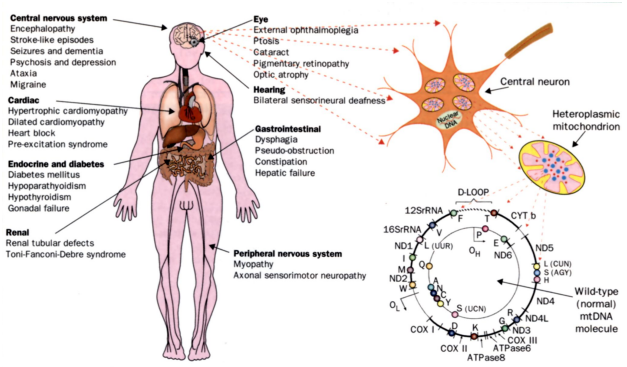
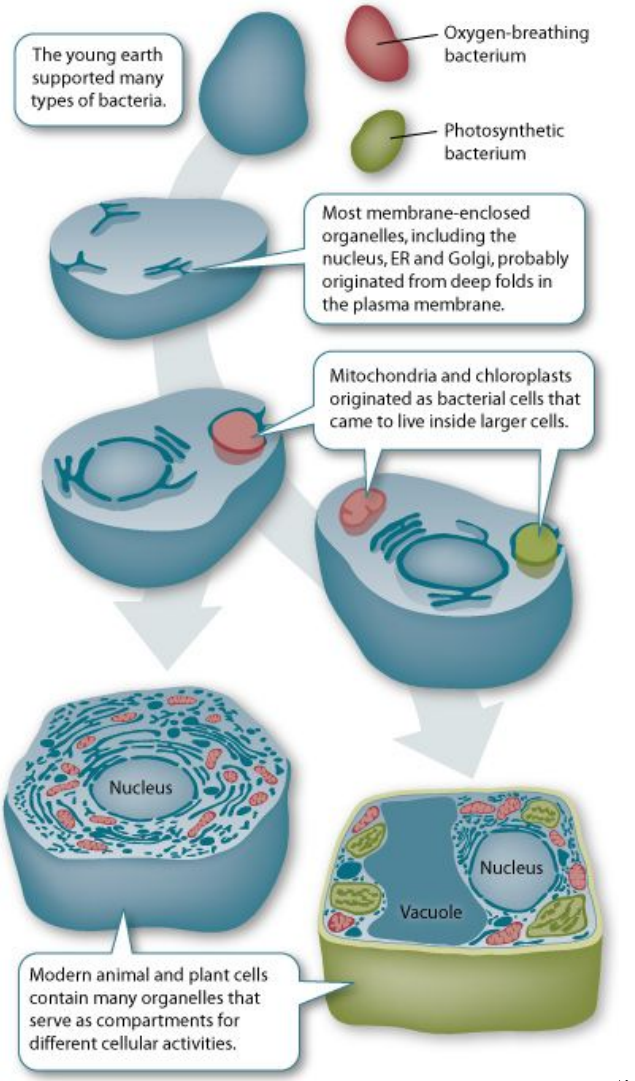


Figure 6: Systemic impact of mitochondrial diseases on high-energy tissues [19].

Evolutionary Importance

The acquisition of mitochondria was fundamental to driving the radiation of eukaryotic organisms. Additionally, permanent integration of aerobic bacteria into the protoeukaryotic host cell overcame bioenergetic barriers. By housing hundreds of internal, highly folded energy generators, the ancestral eukaryotic cell experienced a massive surge in available energy per gene.

This increase in energetic efficiency is believed to have been a crucial factor in the emergence of complex eukaryotic organisms, including plants and animals. Without mitochondria, the evolution of complex life forms as we know them would likely have been impossible [10].



F... endosymbiosis [20].

Modern Research and Applications

Modern scientific research continues to explore mitochondrial function using advanced technologies such as high-resolution microscopy, next-generation DNA sequencing, and multi-omics approaches. These methods allow scientists to study mitochondria at unprecedented levels of detail, revealing their dynamic behavior and complex

interactions within the cell [21].

In addition, mitochondria are now recognized as important regulators of immune responses, as they can influence inflammatory signaling pathways [22]. This has expanded their role beyond energy production to include broader physiological regulation.

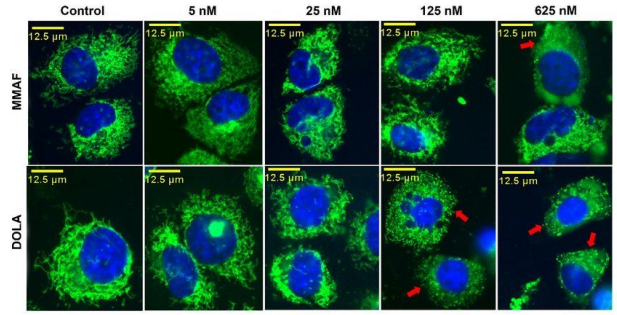


Figure 8: Microscopic visualization of mitochondrial networks in living cells [24].

Emerging therapeutic approaches include mitochondrial gene therapy, mitochondrial replacement techniques, and pharmacological strategies aimed at reducing oxidative stress or enhancing mitochondrial efficiency [23]. These innovations represent promising directions for the treatment of mitochondrial disorders and age-related diseases.

Conclusion

Mitochondria are vital, complex organelles responsible for cellular energy production, metabolic integration, cell signaling, and apoptosis, all originating from an ancient bacterial endosymbiosis. Far from static powerhouses, modern science views them as dynamic, interconnected networks that dictate cell fate, immunity, and aging. Looking forward, mitochondrial research stands at the forefront of personalized and regenerative medicine.

By Vanessa Apuzzo

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Thank You!

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Finally, we would like to thank our team for all the work they put into editing, promoting, and formatting this issue.

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