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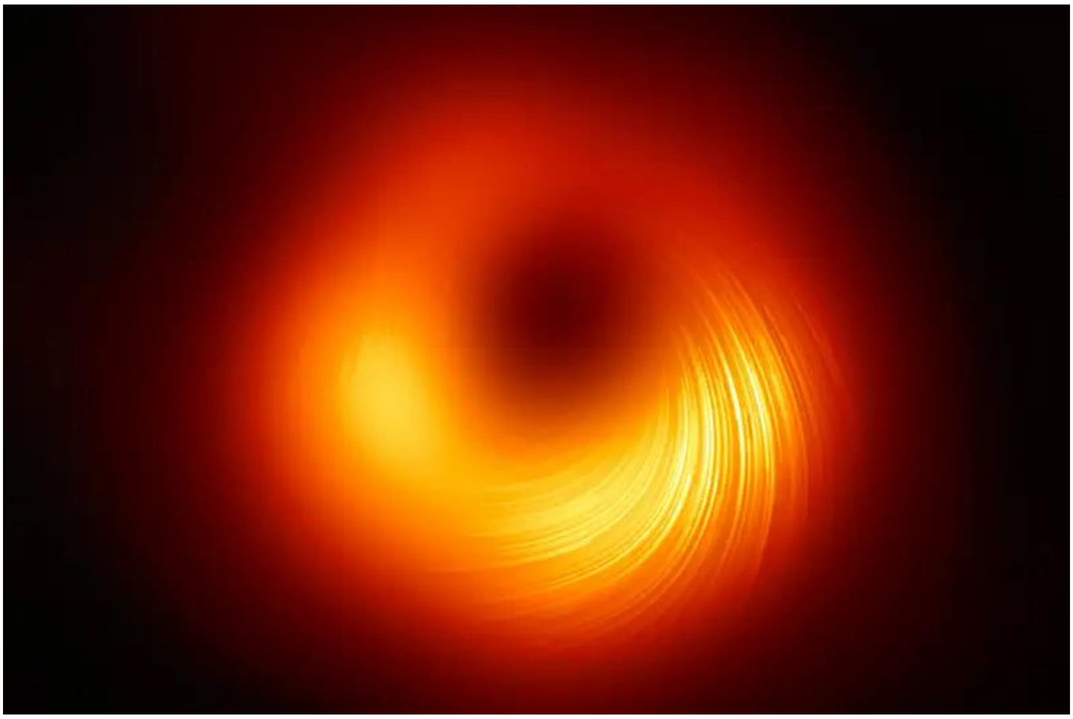
Shivanshi Bhatt

INSIDE THIS ISSUE



The famous Black Hole- now with its swirling magnetic field revealed.
Credits: The Astrophysical Journal Letters, DOI: 10.3847/2041-8213/abe71d and DOI: 10.3847/2041-8213/abe4de

CAFÉ SCIENTIFIQUE :

THE NEWSLETTER

EDITOR'S NOTE:

Welcome to a special issue of the Café Scientifique Newsletter in honour of British Science week, this time with a selections of articles and essays written by Amy and I about our personal scientific interests, ranging from a speculative article on the reality and illusion of time, to a very real-world look on a drug's affects and uses against COVID-19.

We hope you enjoyed science week and this follow up newsletter, and feel free to get in touch if you have any questions or thoughts.

I unfortunately don't have a particular topic or idea to talk about this time, however I would recommend reading a short essay by Paul Lockhart called 'A Mathematician's lament', which I think is an amazing read, and really encapsulates the purpose of Mathematics education, but in a way that is more intuitive and less reliant on formulae and memorisation.

Thanks for reading!

~ Shivanshi

THE FLOW OF TIME

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If I look at where we have paradoxes and what problems we have, in the end they always boil down to this notion of time.

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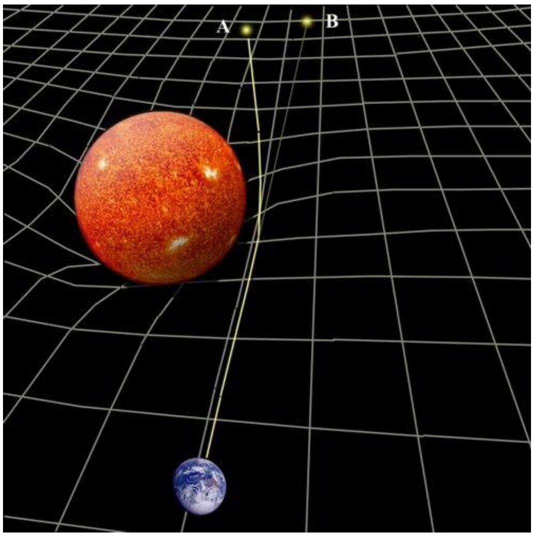
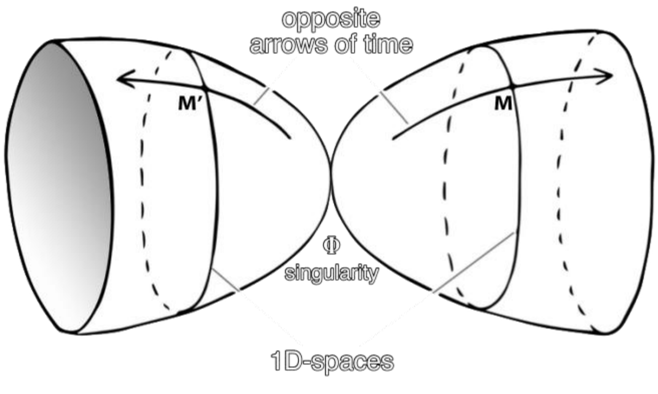
To think of time as a an entity as itself is something which fascinates me, however unintuitive the idea may be. To answer the question ‘*Does time flow two ways*’ we must first inspect and pick at what time really is, and how it is woven into the laws of physics. Einstein’s general relativity is based on how the fabric of the universe moves and reacts: space-time. Space and time are intrinsically linked together, and act as one body, which forms the basis of the landscape around us, forming a three-dimensional, malleable space-time continuum, encompassing all of the now, the past and what has yet to come in a ‘block universe’, where not surprises occur. The initial conditions of the cosmos determines what we perceive as ‘next’ in time. As Einstein famously wrote ‘The distinction between the past, the present and the future is only a stubbornly persistent illusion’. This notion, however unhinged, is popular among physicists as it follows from general relativity, which is an astonishingly accurate description of the universe, on a large enough scale that is. So what are the restraints that prevent us from having a two-directional pathway of time?



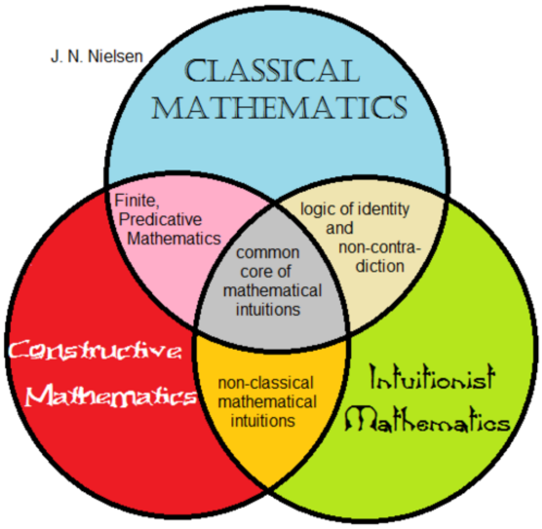
We can choose to move in all three spacial dimensions, so why is the temporal one so our of reach? The physical laws that describe the evolution of things within the universe are all time-reversible, and don’t care whether time ‘moves’ forwards or backwards. Some physicists like to think about time in terms of entropy; in a closed system ‘disorder’, for lack of a better definition, increases over time. If we view the moments after the big bang to be of low entropy, and what we have now as high, we now have a direction of events that we can characterize as time. However neat this may seem to be, there are several issues being that entropy is not a definitive and clear property, and there is no way to tell whether the universe is a closed system. Another theory by physicist Julian Barbour describes the big bang as a ‘Janus Point’: a point that looks simultaneously in two directions of time. Instead of time originating at the Big Bang, it is an inflection point where time runs off in two directions. In this universe it wouldn’t be disorder, or entropy, that determines the direction of time, it is complexity. Within the shapes of interesting objects, clumps of matter is the direction of time.



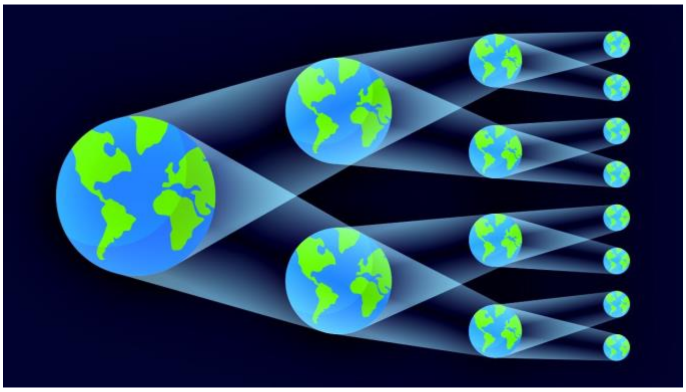
Theories aside, time is a rather ineffable thing, however is an experience that defines itself; to experience is in some ways a definition of the flow of time. But what do we mean by flow? Flowing implies a smooth progression of some property, entity or rate and is a more macroscopic view on what we experience as time. However we have seen that things on the smaller end have a knack for contradicting and siding against that of the everyday. At the quantum scale particles are a fuzzy blur of probability and uncertainty; a particle maintains simultaneous quantum states until it is measured, at which the wave function collapses and the particle comes to be at one certain position. Quantum effects when measured with a large sample size appears to follow patterns, however the nature of each particle is random and unpredictable. This property caused quantum mechanics and time has created uncertainty and confusion

Time could also have a deep link with the information; the deterministic nature of classical physics (assuming that the next moment in time is exactly determined by the initial conditions) implicitly assumes the existence of infinite information. If you could know measure every detail about everything in the universe, the future could not come as a surprise. For a deterministic universe, where time is the ‘unfolding’ of all these events, the initial state of every particle must have been encoded with infinite precision, otherwise there would come a time where the small errors would pile up, and the clockwork universe would break down. However information in itself is a physical quantity, it occupies space and requires energy. From this every unit of space would have a finite information capacity, and is therefore impossible to have infinite information squished into a finite space, which is an assumption of the block universe.

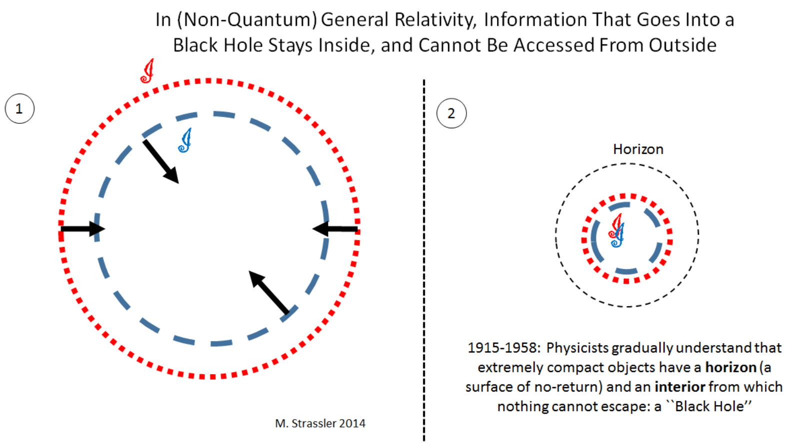
This brings up the notion of infinity, a deep and complex branch of mathematics and philosophy- we assume that time, whatever we define it to be, flows on forever, but if time is encoded in information, how 'real' is this intuition of infinity? It is widely accepted that there exists a continuum of real numbers, of which most have the property of an infinite amount of digits, such as 1/3, π, e and many more. We can manipulate these numbers on paper just like any other integer, however how 'real' are they really? Ask a computer to preform a calculation with a number with infinite digits, it cannot physically store the number- for that it would require infinite storage! You can see why the reality of these numbers breaks down in a physical universe, separate from the mind. What does it really mean to multiply something that hold an infinite amount of detail? People opposed to this notion of infinitely long numbers are called mathematical 'intuitionists', and are led by the Dutch topologies L.E.J Brouwer, who insisted that numbers are constructible creatures, finite and storable. This view may seem radial and naïve to many, however the truth is that a real number with infinite digits has no physical relevance or representation, which seems a key concept in the idea of a deterministic universe.



So deterministic predictions seem fundamentally impossible: we can't predict the exact weather because we cannot know the initial conditions of every atom on earth to an infinite precision, and so the same with time. Taking from this, the world now seems indeterministic; the future is not some ingrained part of space time that enfolds in front of us, but is instead a continuous creation of digits and information, and the notion of random movement. Dropping the classical view of the universe leads neatly on to the quantum mechanical interpretation of time, a universe ruled by randomness, probability and uncertainty. Quantum mechanics unlike classical physics is based on the idea that all things are quantised and discrete. Space itself is pixelated as there should exist a smallest distance, time period etc, and time seems to follow this strict passage alongside. Time in quantum systems is irreversible as determinism is not a concept, only probability, so 'reversing this clocks' wouldn't take you back the exact walked path. However there exist other popular interpretations of quantum mechanics, including the many-worlds interpretation, in which for each quantum state change, the outcome splits the universe into multiple branches, each which live their possible outcome, all of which were determined in advance. This means that all things, however quantumly complex, are all part of a bigger space time, in which we follow that path of whatever quantum decision happened to occurs in 'our' universe.



This interpretation allows for a deterministic quantum mechanical theory, however a better approach may be to provide an indeterministic theory for both classical and quantum mechanics. Quantum mechanics forbids the creation and destruction of information, however if the universe is not determined, then clearly, new information must be getting created in order to describe the growing state of the universe, and now we are in need of a new way of thinking about these ideas, as paradoxes are being continually created. General relativity says that information is destroyed in time, quantum mechanics says it's not. We need a formulation of quantum mechanics in terms of intuitionist Maths that allows information to be created by quantum measurements, and be destroyed.



This leads on to a famous paradox in physics: The black hole information paradox – is information destroyed in a black hole? If information can be destroyed in time, can it be destroyed in space?

Coming back to the physical reality of real numbers, quantum mechanics and its mathematics divides everything into discrete packets, rather than a continuum. A black hole, no matter he seemingly infinite number of internal states, would not be able to store or hide an infinitely long real number inside them, otherwise they'd be able to store an infinite amount of information. In this way, intuitionist's maths is very analogous to the physical world and may be necessary to solve the idea of the 'flow' of time. In a quantum mechanical world, reality is just a complex networks of events, onto which we project the seemingly linear sequence of past, present and future; time is an emergence of the laws of physics. At our level, all events look like the interaction of particles at a particular position and time, but space and time themselves really only manifest out of their interactions and the web of causality between them.

Temporal flow therefore seems to be an illusion, or a smooth effect that we characterise as the memory of experience. All we actually do is live in the present snapshot, which entails of a timescape of memories and imaginings. The past is simply what all the particles in the universe were doing before the present snapshot, just back a couple of particle interactions. If time 'flew backwards', none of us would even know that anything out of the ordinary had happened – you would have had no memory of actually travelling, otherwise you wouldn't have travelled. Time itself moving is a macroscopic effect characterised by the interaction of particles, seemingly irreversible. But if time actually is coded into the fabric of space, if Einstein's view of the nature of space is true, then could we find a way to access the temporal dimensions that is winded into our daily lives.

~ Shivanshi Bhatt

CONSCIOUS MACHINES

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Eventually, intelligent life will become mostly digital, except possibly for the low level biological infrastructure required to sustain human consciousness

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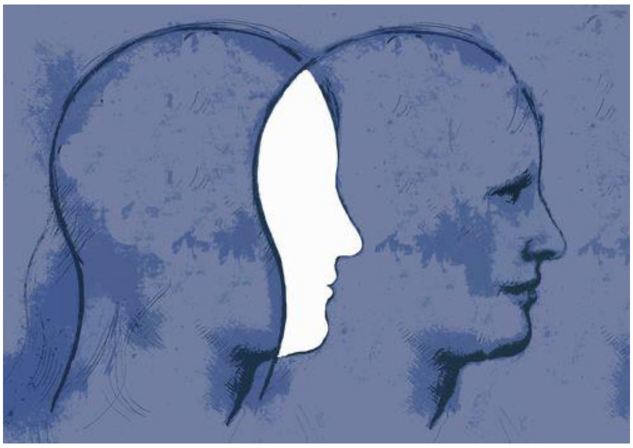
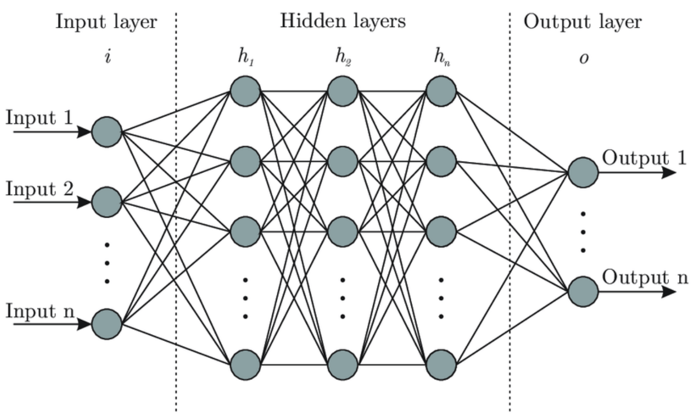
Conscious artificial intelligence systems are the centre of many things science-fiction, with countless mentions of humanity's inventions turning malicious and taking over the world, but how much of these hypotheses are possible or achievable? The basis of all these possible outcomes is based on the attribute of consciousness, something that we all possess, but is still uncertain whether our technology and machines will ever be able to achieve it. Consciousness has many definitions and interpretations, ranging from a science-based neurobiology perspective, to more philosophical approaches; the most vague yet common introduction to describing the state of consciousness is the ability to be aware of, and be responsive to one's surroundings or 'sentience'. Opinions may differ, however there are certain attributes to a conscious entity that don't necessarily define it, however make a dent into defining its existence: intuition, experience, cognition and many more. Maybe consciousness will forever remain ineffable, however in order for artificial intelligence to ever 'turn evil', there must be some motive or thinking involved in order to stimulate a seemingly random attack.



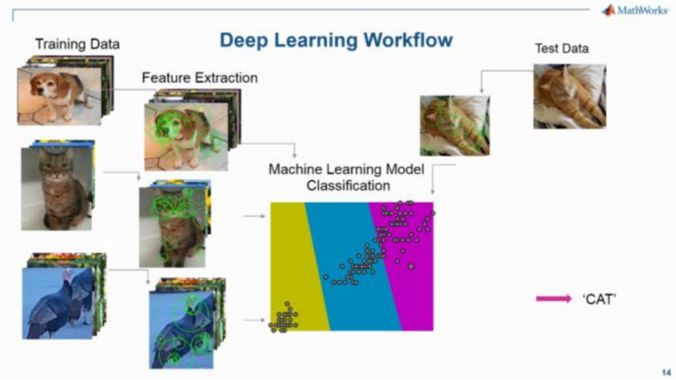
To make it clear, at the moment AI is no where near the level of complexity needed to live out any nightmares, but why is that? Common terms thrown around are Machine Learning, Deep Learning, Neural Networks etc; these allude to the idea that machines are capable of understanding ideas and concepts- but this is not the case! Networks are not taught to *understand* in any human sense, instead adjusting internal connections and nodes to anticipate events. Although artificial neural networks are loosely modelled after the neural network of the brain, they don't result in the complexities of a human mind; it is not conscious thinking that emerges, more application of a lengthy data analysis process. In addition, little is known about biological neural networks, and so ANNs as they currently are have little chance of developing into a biological mirror. However this doesn't mean that machines will be fundamentally weaker than humans; there are countless ways in which a computer can best us in something that seems to rely on 'thinking', such as chess, poker etc. As yes, they are all combination of algorithms and ANNs in the end, however we can all agree that computation offers an incredible tool and process that is just not achievable by a biological mind.



But will there ever come a time when technology itself will be able to form a conscious thought, and learn on it own, without the assistance of constant data flow and external input and instructions? Overall researchers tend to agree that current machines and technology are not conscious beings, but is consciousness really a requirement for AI in order to progress and evolve further? In the context of biological systems, intelligent life is conscious life, one does not exist without the other however an AI system may grow to become an intelligent life form without the need for consciousness. In fact consciousness may only be an emergence of a biological system; Biological naturalists believe that consciousness depends on the particular chemistry of biological systems, and that even the most sophisticated forms of AI will be devoid of it. So you can have a machine that performs a task to an extraordinarily high level of skill, however still lacks this innate ability that we all possess.

On the other side of the spectrum you have the 'techno-optimists-, those who believe that consciousness is the byproduct of intelligence itself, and that the complex AI system will inevitably be conscious. This view of the theory of consciousness draws conclusions about the brain, saying that it is simply a logical breakdown of different components, which will we eventually recreated by hardware and software, allowing computers and machinery to think and live the way we do. However will the integration of a human-like consciousness be of any use to a machine? In our lives, our consciousness allows us to think, problem solve and live our daily lives by managing different functions such as walking, eating, socialising and all the other talks that keep us going. These are all at the most basic level a set of instructions that we have learnt through experience and failure, and are now 'hard-coded- into our minds. Some tasks, such as walking, are repeated so often that they don't require an active conscious presence to perform; you can walk without thinking through the steps of moving your feet etc.

However this is that way that computers are told how to do things; a neural network can be trained to recognise letters and different objects in images -albeit not very easily, which is why you have those annoying security checks where they give you blurred out images and asks you to click all the ones with traffic lights, or recognise a string of letters that have been distorted. However with a lot of time, examples and computing power you can imagine that a computer may one day 'have the eyes' that we do. The thing about computers is that if the algorithm is perfect, and the situation is regular, then it will most likely be correct. This is why computers are great of calculations, simulations and other mathematical processes. However this may also be their downfall. The biological mind has a power of that of a computer which is the idea of randomness and chaos. Computers can't generate random numbers, or make a choice between objects without being told criteria, conditions etc. For us as humans this seems a menial task; I can simply just generate a random number; it may be influenced by my surroundings, events earlier in the day or thoughts I've had, however we don't follow a mathematical procedure to come up with them, they just are.



This may seem like a trivial fact, but it reveals key ideas about the human brain and how it can be replicated. If I told a computer to choose between two objects with no data, criteria and context, then it would simply crash as I haven't told it to follow a particular algorithm for making choices, and it is unable to simply pick one. As a human, we are able to consciously make decisions and can deal with unfamiliar situations by drawing from out experiences, and using our moral compass along with many other factors, can choose a course of action. This is the basis of conscious thinking, having the ability to actively *think* and use whatever comes to mind to get the job done. One could argue that a super-intelligent AI that already knows everything (if that is really possible) would have no need for conscious thinking, and would only need unconscious processing in order to traverse through life.

Another point that this brings up is the many ethical issues of having a conscious systems- would their be policy in place for the use of conscious AI? Would they be recognised as legal citizens, and possess all the same rights as us? This may become a serious issue of commercial entities continue to dominate AI research, and companies may decide that the issues associated with conscious AI outweigh their potential help in research, and stick with unconscious AI. But how beneficial would a conscious AI system be? The first major change would be the ability to feel empathy, perhaps leading to a safer AI world, in which the machines are aware of the damage that they can cause, and can exercise restraint. Empathetic AI may also have a large commercial use in customer service, and entertainment, in the same way that humans do.

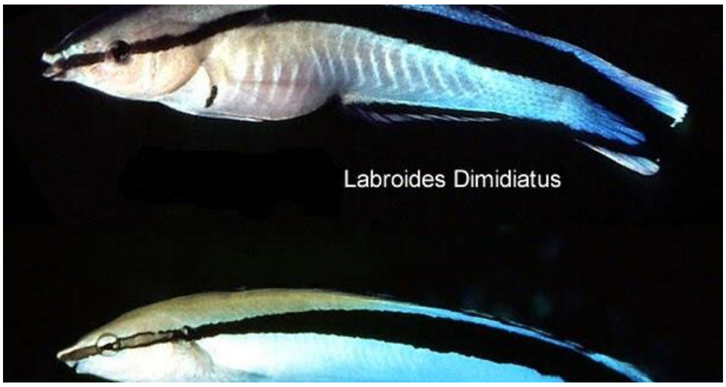
Perhaps further research in theoretical computer science and quantum mechanics will solve this mystery in the future, but for now we will have to be content with no evil AIs talking over all our systems and influencing the world.

~Shivanshi Bhatt

MUTUALISTIC RELATIONSHIPS

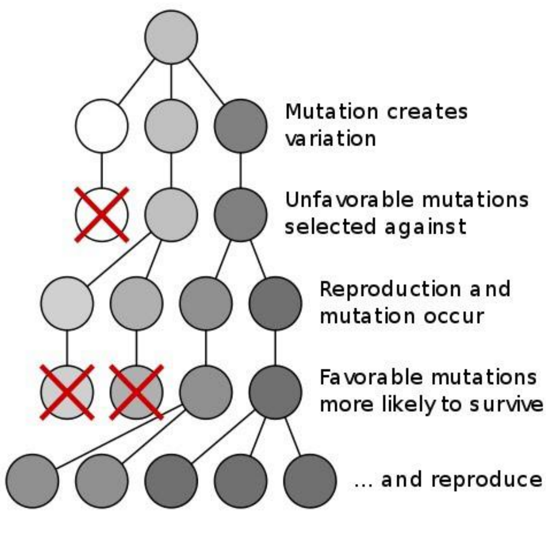
Mutualistic relationships, which are ubiquitous in the natural world and affect almost all living things, are most simply defined as 'interactions between organisms of two different species, in which each organism benefits from the interaction in some way'.1 Mutualistic relationships can be either obligative (where for one or both organisms their survival is dependent on the relationship) or facultative (where the relationship is not vital for either organism's survival). Overall, they come under the umbrella of symbiotic relationships, a category including parasitism and commensalism.2 The purpose of this essay is to consider not only how these relationships have come to be, influenced evolution and been maintained in a selfish world such as our own, but to consider whether they are actually, as described, a 'win-win situation'.

Mutualistic relationships occur when the selfish needs of two organisms, each manipulating the other to achieve them, intersect and provide both with a benefit. For example, trillions of bacteria in the human intestines digest the extra food that we cannot digest ourselves, benefiting both the human and bacteria, as the bacteria also get nutrients. Over time, evidently 'organisms in a mutualistic relationship evolved together, each was part of the other's environment, so as they adapted, they "made use" of each other in a way that benefitted both.'3 Pollinators, such as bees, have a facultative mutualism with plants, because self-fertilisation less efficient co-evolution has resulted in the 'bee orchid' mimicking the appearance of a female bee. The attracted bees drink nectar from flowers, picking up and spreading the plant's pollen aiding plant reproduction. Nevertheless, selfish goals are still prevalent, ideally, for the plant, the pollinator would only feed on a limited volume of nectar before meeting their nutrition requirement from other flowers, therefore fulfilling the reproductive aims of the plant. However, the pollinator's aim is to gain sufficient nutrition with minimum effort, so, they sometimes stay on a particular flower eating their full requirement of nectar. This simultaneous conflict and fulfilment of interests is the result of evolutionary changes within relationships.



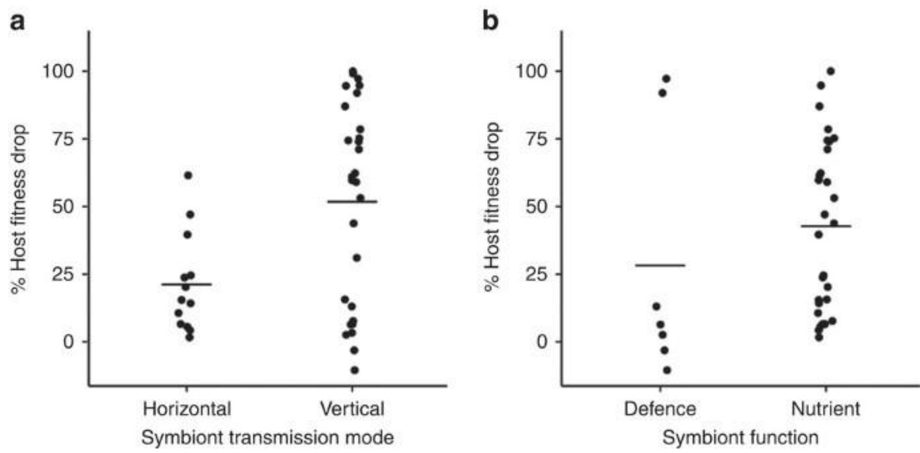
Evolution can drive an originally mutualistic relationship into one of a parasitic or similar nature. Take, for example, the relationship of a 'cleaner wrasse', a small fish that eats any dead skin, infected tissue or external parasites on larger fish. Consider the situation where the cleaner wrasse, clumsily bites the larger fish, therefore gaining a disproportionate benefit from the interaction in the form of additional nutrients, consequently giving the fish an advantage over the other members of its own species. This increases its chances of survival and reproduction, passing on the 'clumsy cleaning genes', if they were hereditable. Over time all individuals in this species would eat the flesh of the larger fish, due to natural selection, this could explain the 'blue striped fangblenny', which looks identical to a juvenile bluestreak cleaner wrasse and has also evolved an 'opioid-based venom' that numbs the pain of the larger fish, while they eat a chunk of its flesh, allowed due to its assumed identity as a cleaner wrasse. Similarly, the vampire finch, as the name suggests, drinks the blood of the Nazca booby, without much objection. This may be due to a similar evolutionary history whereby this similarly parasitic relationship originated from the smaller organism cleaning the larger organism.

Natural selection has been understood since Charles Darwin published 'The Origin of Species', in 1859.9 However, in later years the understanding of this process has been developed from the idea that individuals who survive and reproduce are genetically favoured, to the 'selfish gene' hypothesis.10 As mutualisms are built on the 'same genetically selfish principles as antagonistic relationships', many having evolved from antagonistic interactions, they are vulnerable to invasion by 'cheaters', organisms that that 'exploit an existing relationship without reciprocating an advantage'. The cleaner wrasse example above shows how that can occur, though there are many other pathways that a cheater can manipulate to break down a symbiotic relationship.



Richard Dawkins revolutionary book The selfish gene explains how 'the fundamental unit of selection and therefore of self-interest ... is the gene, the unit of heredity'. Therefore, organisms sometimes act altruistically towards others of the same species as the probability that they possess the same gene may be high, kin selection. Their survival increases their chance of reproduction which fuels the only ambition of the gene, to 'survive' and by replication to become dominant in the gene pool. Dawkins highlights that organisms are just a 'survival machine', a temporary vehicle for a short-lived combination of genes, whereas the genes themselves, which control the survival machine's behaviour indirectly, could survive through many individual bodies. The idea of evolutionary stable strategies (ESS), which can be practical enactments of game theory, is discussed in multiple chapters and relates to mutualistic relationships. The key conclusions being that due to the fitness costs the proportions of different roles in the population will fluctuate, the root of co- evolution, before reaching an ESS which presents an answer for the maintenance of mutualistic relationships, in a world of selfish genes, that they are frequently changing prompted by selection pressures until they settle in an ESS, though it is noted that over time the ESS may swing from one extreme to another.

However, a journal article on the establishment of mutualistic microbial symbioses, which also serves as a review article for research on the theories of how mutualisms are sustained, states that 'the evolution of interspecific symbiosis cannot be explained by either of these models' (those being kin selection or game theory – also called the strategic alliance model). The exclusion of kin theory is obvious as in mutualisms the organisms are different species, yet the reason that the second fails is that 'it requires memory of past interactions, the recognition of individuals and is dissipated by forms of mixing', therefore, these traditional explanations are insufficient in explaining the evolutionary stability of symbiosis.



According to the article the current consensus is that the two main theories constructed from theoretical work, both offer solutions explaining the evolutionary stability of symbiosis. The first is that conflict avoidance factors, can alter the extent of the association between host and symbiont. These include 'A study exploring correlations between tightness of association and these factors, discussed that the strength of association ultimately levels of dependence. Symbiont function influences the costs and benefits of the relationship. Evidence shows that hosts have a higher dependence on symbionts that provide nutrients, as these are utilised every generation, whereas the opposite was true when defence was provided, as it is only beneficial in certain environments. Vertical transmission, from parent to offspring, leads to shared reproductive interests which favours cooperation. Whereas horizontal transmission, such as from the environment, does not result in a shared fate, therefore, can lead to 'multiple symbiont lineages per host' this incites intraspecific competition resulting in greater host exploitation. Conversely, vertical transmission ensures a consistent inheritance of the 'same lineage of symbionts' allowing co-adaption and dependence.

This research is aligned with the factors identified as those which 'facilitate the evolution ofmutualistic relationships': '1) Vertical transmission, 2) Genotypic uniformity of symbionts within a host, 3) Spatial structure of population leading to repeated interactions between individuals, and 4) restricted options outside the relationship'. Crucially, however, this does not explain the fact that there are many mutualisms that rely on horizontal transmission, for example 'rhizobia, and luminescent bacteria in fish and cephalopods.' The journal article that explores this problem, explains several reasons as to why the researchers believe this type of mutualism can be stable. Including, that the three factors above also apply to local horizontal transmission, if each partner responds directly to the others action within their own lifetimes the probability of exploitation is low, vertical transmission may 'facilitate an important evolutionary market effect', partner choice is allowed, and the list goes on. Nevertheless, it is noted that 'several of our suggestions are necessarily speculative.'16 Furthermore, though the overall theory can promote stability in some relationships, conflict avoidance factors may not be necessary or sufficient to deliver required evolutionary stability. The second proposed solution to the 'paradox of mutualism', which is less established and frequently questioned, is a model that centres around 'policing'. A journal article states that 'the policing analogy implies that sanctions are adaptations to cheating.' One example, that is commonly referenced, is that nitrogen fixing rhizobia are favoured for growth, by soybeans, over others whose function is restricted experimentally, presenting how more cooperative symbionts are favoured or rewarded. However, the coevolution of cheating combined with either partner choice or sanctions presents another paradox, shown using theoretical models; cheaters are necessary to maintain these responses but having these responses removes cheaters therefore, removing the selective incentive to maintain the responses. According to this source the evidence was more consistent with the theory that the host feedback mechanisms, that stabilize many relationships, are 'preadaptations with respect to their effect on symbionts', having existed before the mutualism did. Their proposed explanation is that these mechanisms may have 'generated the selective environment that favoured symbiont cooperation.' Therefore, that stability 'does not fundamentally depends on host evolving novel sanctions to retaliate against cheating symbionts.' Another journal article addresses the question in relation to by-product effects. The example used is that of the 'active pollination in yucca moths and fig wasps', where 'yuccas abort flowers that are heavily exploited by yucca moth oviposition, thereby avoiding investment in tissue with little or no fitness return'. The argument was that many natural mutualisms support the overall idea that defences, which includes sanctions, that limit the cost of exploitation are important for the evolutionary maintenance of cooperation.

Subsequently, the original article moves onto address its key purpose, that these complex adaptions do not adequately explain the origin of mutualisms, as there would not be sufficient time for their evolution. Due to the complexity of the stabilising methods and their variety it is most likely that they 'must have evolved subsequent to establishment, even if the fundamental aspects were pre- adaptations', assuming that significant limitations existed creating the conditions where establishment mechanisms could initiate a mutualistic symbiosis. Consequently, the article's proposed alternative theory of the origin and development of mutualistic microbial relationships from parasitic relationships, a widely accepted overarching idea, is that a larger host partner would capture and exploit a smaller symbiont, enclosing it in the hosts membrane. This path to establishment would not 'require complex stabilising mechanism to supress conflict', as the 'core nutrient exchange between partners does not in itself provide mutual benefits.' Subsequently, the fitness benefits of symbiotic existence would enforce the exploitative relationship, potentially resulting in dependence and mutual benefit. The alternative proposed route is that mutualisms developed when a parasitic organism living in or on the host evolved reduced virulence becoming beneficial to the host, which is supported by alternative experiments.

In conclusion, as both organisms in the mutualism are manipulating the other to meet their own selfish needs, their maintenance and stability is an interesting consideration. Due to the co-evolution that drives the development of these relationships, the emergence of cheaters should be common, therefore, destabilising the relationship, however, the evolution of stabilising strategies is key to combat this. Nevertheless, as has been detailed above, the original intersection of self-serving needs which happened to have mutual benefits is clearly not stable in certain relationships despite these complex mechanisms. In this case the relationship turns into a parasitic one, whilst one organism benefits the other, appears to be naive of the transition, therefore, decidedly not a win-win situation. Furthermore, the development of these complex stabilising adaptations must have a fitness cost associated with them, but the key point is that cost must be less than the cost of being exploited, and the gain from the exploitation, for the other organism, must be greater than the cost of evolving mechanisms to obtain it. This back and forth is just another way of explaining the principle of co- evolution, as it is driven by selfish genes with the single motivation of survival and reproduction. Therefore, due to co-evolution these relationships continue to be stable, after achieving an ESS. This results in the foundation of an established mutualistic relationship, thereby, delivering each organism with a benefit, though that will change with time, the average fitness cost vs benefit of the relationship, in the majority of situations, must continue to be positive, therefore, on average in most circumstances, a win-win situation.

~ Amy Power

THE CHEMISTRY OF DEXAMETHASONE

Dexamethasone is a synthetic corticosteroid, a corticosteroid being 'any group of steroid hormones produced in the adrenal cortex or made synthetically', (synthetic corticosteroids are structurally similar to the hormone cortisol). Corticosteroids are split into two subgroups: glucocorticoids (e.g. dexamethasone) and mineralocorticoids. Glucocorticoids are secreted by the Zona fasciculata, 'under control of ACTH of adenohypophysis' whereas mineralocorticoids are secreted from the Zona glomerulosa in the Adrenal cortex, controlled by the angiotensis system'. Dexamethasone, an anti-inflammatory used numerous treatments, was granted FDAapproval in 1958, after its discovery in 1957. Its formula is C22H29FO5; 392.5g/mol is its molecular weight (to four significant figures); there are no recorded isomers and dexamethasone has a melting point of between 260-264˚C(with some discrepancies between sources). A further definition of this drug, with more structural reference, is 'A fluorinated steroid that is 9-fluoropregna-1,4-diene substituted by hydroxy groups at positions 11, 17 and 21, a methyl group at position 16 and oxo groups at positions 3 and 20.' After exploring the chemistry of dexamethasone, I will analyse how effective the drug is in its use against Covid-19.

Physically dexamethasone is an odourless, 'white to off-white crystalline powder' with a 'slightly bitter taste'. When heated to decomposition three toxic fumes are emitted: carbon monoxide, carbon dioxide and hydrogen fluoride, whilst exposure to light for long periods of time may affect it. Furthermore, though oxidation may occur when reacted with bases, it is thought to be 'incompatible with strong oxidised, strong acids, acid chlorides and acid anhydrides'. Additionally, the compound is a member groups such as 'alcohols and polyols, ketones, hydrocarbons which are aliphatic unsaturated, and fluorinated organic compounds.'Dexamethasone is soluble in water (at 25 °, 10mg per 100mL), acetone, ethanol and chloroform. The mean terminal half-life of 'a 20mg oral tablet is 4 hours', whilst 'A 1.5mg oral dose is 6.6±4.3h, while a 3mg intramuscular dose has a half-life of 4.2±1.2h'.

A science direct book source, Synthesis of essential Drugs by Ruben S Vardanyan and Victor J Hruby, details in full the multistage process in which dexamethasone is synthesized, from an initial reaction of 3α-acetoxy-16-pregnen-11,20-dione with methylmagnesium bromide, in the presence of a lithium bromide catalyst.

Amongst dexamethasone's most important features are its 'potent anti-inflammatory properties.' According to Drug Bank, Corticosteroids bind to the glucocorticoid receptor, inhibiting pro-inflammatory signals, 'NF-Kappa B and other inflammatory transcription factors', and promoting anti-inflammatory signals, such as 'interleukin-10'. Which causes the inhibition of neutrophil apoptosis and demargination, along with phospholipase A2, 'which decreases the formation of arachidonic acid derivatives'; this is the case for low doses whereas higher doses can be immunosuppressive.Furthermore, continuing the high dose over a long period of time results in the glucocorticoid 'binding to the mineralocorticoid receptor, raising sodium levels and decreasing potassium levels.' Additionally, Dexamethasone's administration route (predominantly intramuscular or intravenous injections, oral tablets, intravitreal implants or ophthalmic formulations) varies its duration and focus ofaction.

In further detail, the mechanism of action of corticosteroids is:after diffusion across cell membranes they form complexes with 'specific cytoplasmic receptors', which bind to DNA, stimulating transcription, which progresses through translation and protein synthesis producing specific proteins, enzymes, which are then instrumental in achieving the anti-inflammatory effects. Furthermore, glucocorticoids can have multiple reaction pathways, for example they can 'interact with specific intracellular receptor proteins in target tissues' this, again, alters the expression of corticosteroid-responsive genes. Additionally, hormone-receptor complexes are formed when steroid ligands bind to Glucocorticoid-specific receptors in the cytoplasm; these are the complexes mentioned earlier in relation to general corticosteroids. Some of the newly synthesised proteins have other effects in the body, such as 'lipocortin, a protein known to inhibit PLA2a and thereby block the synthesis of prostaglandins, leukotrienes, and PAF.' Glucocorticoids can also 'inhibit the production of other mediators including AA metabolites such as COX, cytokines, the interleukins, adhesion molecules, and enzymes such as collagenase.'

With the remainder of this essay, I will analyse the efficiency of dexamethasone in the COVID-19 pandemic, in relation to its chemistry. In patients with severe respiratory diseases caused by SARS-CoV-2, the infection appears to 'promote the expression and release of proteins called pro-inflammatory cytokines' (an inappropriately violent immune response) which can lead to tissue damage. This is the most pressing issue and where dexamethasone can be used as an immunosuppressant, therefore, the drug isn't actually used directly against the virus.

A press release on the 16th of June 2020 from the COVID-19 RECOVERY trial led to changes in NHS treatment promoting dexamethasone's use in certain situations. In the trial, for the 2104 participants given 6mg of dexamethasone daily, the 28-day mortality rate was reduced by 17% in comparison to the 4321 patients 'receiving standard care'. A chief investigator on the trial stated that low or moderate doses were given 'minimising the side effects while maximising the benefits.' A significant benefit that the drug is 'inexpensive and readily available.' This strongly implies cost efficiency, a consensus to which I cannot find an opposition, which is crucial in the development of and widespread use of any drug.

Nevertheless, an article from the BMJ questions several areas of the trial. Firstly, that the results remain 'neither peer reviewed nor published' with only a pre-print available and a lack of exploration into the optimal type of corticosteroid, timing, dose or duration of treatment. Furthermore, the dose tested was around half what would be given 'to prevent treatment induced acute respiratory distress syndrome in moderate or severe pneumocystis pneumonia'. Though this has a defence, as detailed earlier, additionally, the harms associated with steroids are generally related to high doses which will have influenced this choice. Moreover, it is unclear if this class of drug is the best option for all patients (e.g.those with diabetes), that the mean age of adults requiring ventilation was 59, which is relatively young, and as dexamethasone did not benefit the two older age groups, the benefits or risks are unclear there. Crucially, corticosteroids have on broad effects on innate and adaptive immunity due to their mechanism of action, as an immune suppressant; adaptive immunity is integral to the immunopathology of the disease, via the production of a specific antibody.

Though glucocorticoid treatments have been widely used against respiratory syndromes closely related to COVID-19 (like SARS and MERS), a lack of large, randomised, controlled trials and other factors means evidence both for and against their use is weak. Therefore, their beneficial effect in these treatments is dependent on 'the selection of the right dose, at the right time, in the right patient.' This implies reliance on luck, which has only partially been absolved, therefore an unsettling thought, though their use in severe cases is crucial as drastic measures should be taken to prevent fatality even with marginal chances of success.

In conclusion, the long-term follow-up of the patients treated with dexamethasone will provide significant evidence on the potential harms of its use, though, despite the concerns on areas of the RECOVERY trial and its implementation, the quick, admirable response of the researchers, during a global pandemic, should be celebrated. No scientific research is without scrutiny which is key in driving researchers further, especially when regarding human life, therefore, due to current circumstances, based on the chemical and biological knowledge of dexamethasone I have uncovered in this essay, despite drawbacks, the reduction in mortality rates and its implied cost efficiency, make the drug's continued use crucial whilst further research is carried out.

~Amy Power