The Tangent

STEM topics seen from our own angle

Issue 3 - summer term 2023

Welcome to The Tangent!

Dear Reader,

Welcome to the Summer 2023 issue of The Tangent - OHS's very own student-run STEM magazine! This year, I have had the privilege of working with a number of year 12 and 13 students who have produced fascinating articles for the magazine, covering a wide variety of STEM related topics. Whatever your interest, I am sure that you will find an article which will fascinate you and maybe even encourage you to carry out some research of your own! I hope you enjoy reading this issue as much as I have enjoyed putting it together.

Please feel free to email me if you have any questions or comments!

Emma L(she/her), year 12

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The Three Principles of Flight - Introduction to Fluid Dynamics

By Tehya B

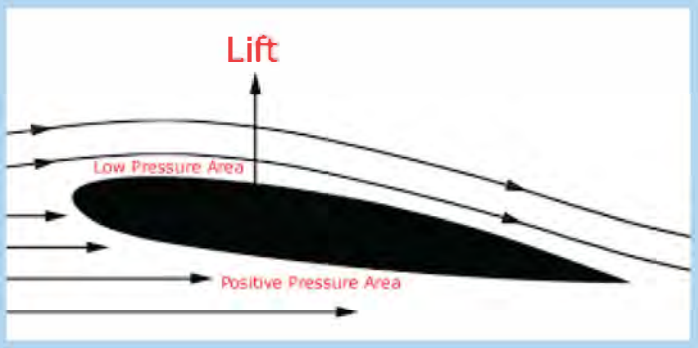
Anyone who has ever been on a plane must be fascinated by the magic phenomenon which is the ability to design a machine that can leave the ground carrying thousands and thousands of kilos not only off the ground, but across the world at over 30,000 feet. Of course the most prominent technology for doing so is a wing. However, instead of calling this a 'wing' I will be addressing it as an aerofoil. An aerofoil is defined as "a structure with curved surfaces designed to give the most favourable ratio of lift to drag in flight" (Oxford Languages, 2016). In this article I hope to increase your understanding of how an aerofoil achieves lift by introducing you to the Three Principles of Flight: Bernoulli's principle, Newton's Third Law of Motion, and The Coandă Effect.

The first, and most prominent principle that contributes to lift is Bernoulli's principle. A Swiss mathematician born in 1700, Daniel Bernoulli correctly predicted that fast flowing fluid (the word we use to name any liquid, gas or other compressible material) exerts less pressure on an object than a slower moving fluid. In order to use this principle to gain lift, an average aerofoil is curved on the top so air accelerates (we will discuss why this is later) and flat on the bottom so that air decelerates, creating a difference in pressure between the bottom and top of the aerofoil. This difference in pressure forces the aerofoil upwards, therefore creating lift.

The second principle is the application of Newton's Third Law to lift. Newton's Third Law of Motion states that: "every action has an equal and opposite reaction". Possibly the most well known of the Three Laws of Motion, it has two main applications in creating lift, and we will discuss one of them here. The first applies when the underside of an aerofoil is exposed to oncoming air flow. As air particles hit the underside of the aerofoil, they are deflected downwards, and if there is one action of the air particles moving downwards with momentum, therefore there must be an equal force in the opposite direction going upwards. This force going upwards pushes the aerofoil upwards with it, therefore creating some lift. Despite the fact that this happens on a relatively small scale, all little additions of lift count towards the final result.

The Coandă Effect, named after the man who first thought of the principle, Henri Coandă states that a fluid will follow the curvature of the shape it is flowing alongside, even if the shape bends away from the natural flow of fluid.

This principle changes not only the airflow close to the surface of the aerofoil, but the air above and below it as well. The changing curvature can change density underneath and above the wing enough to accelerate or decelerate the fluid (air flows faster in less dense medium as there is less resistance). This changes the speed on both sides of the wing, which allows Bernoulli's principle to be applied, and creates lift. There is also a second application for the Coandă effect. As air follows the curvature of the aerofoil even if it slopes downwards or away from the natural flow of fluid, a force is created by the change in momentum due to the changing direction of the air (this is due to Newton's Second Law of Motion which states that force is equal to the rate of change of momentum). This creates an equal and opposite force upwards, so more lift.



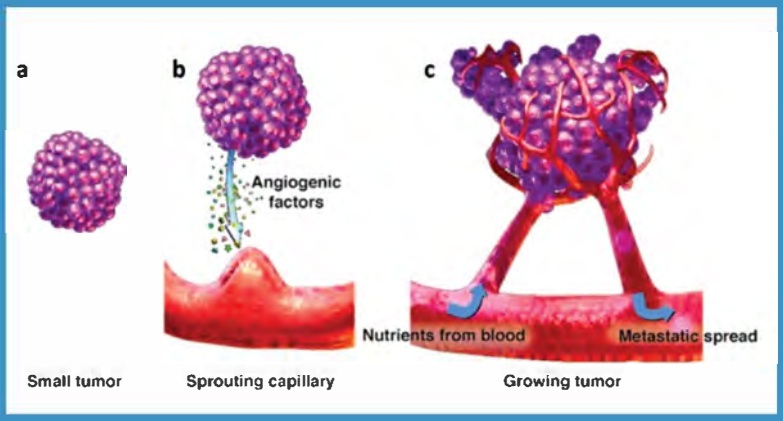
These three principles all combined are what allows that 80 tonne aeroplane to take off the ground and cruise at over 30,000 feet above the ground. Although I have presented them in a simple way in this article, they go into much more detail, to points where even the slightest change can make an enormous difference.

Angiogenic Signalling Pathways Involved in Tumour Angiogenesis and Therapy Targets

By Jess J

Successful cancerous cells are produced through a mutation in a cell's genome, giving the cell the ability to continuously proliferate past the Hayflick limit (~50 population doublings) and to escape cellular senescence due to the maintenance of their telomere lengths. These immortalised cells grow and divide to form daughter cells which eventually form a structure known as a tumour. Such structures are composed of a mass of unspecialised immortal cells undergoing uncontrolled cellular division and are known to have acidic microenvironments as a result of poor blood supply to certain areas and high rates of respiration associated with rapid cancer cell mitosis. In order to survive, the cancerous cells need access to a good blood supply to gain oxygen and nutrients and to dispose of toxins and carbon dioxide [1]. A positive correlation can be clearly observed between blood supply and the degree of activity within tumours with more active and rapidly proliferating tumours being heavily vascularised while dormant tumours have limited blood flow [1]. It is therefore beneficial for tumours to be situated in the vicinity of a blood vessel so as to ensure sufficient supply of nutrients and oxygen.

Some cancers, if exposed to conditions exhibiting stress on the cells such as hypoxia and hypoglycemia, exhibit the ability to control angiogenesis (blood vessel formation from preexisting blood vessels) through the production of pro-angiogenic factors or by triggering the production of pro-angiogenic factors in surrounding non-cancerous cells [2][3]. Vascular homeostasis within normal tissues throughout the body is maintained and regulated through the production of both pro-angiogenic factors and anti-angiogenic factors in equal amounts [1]. During vascular homeostasis endothelial cells of the blood vessels are not proliferating and new blood vessel growth is suppressed [1]. However, if an imbalance occurs and the pro-angiogenic factor concentration surpasses that of the anti-angiogenic factors then angiogenesis is triggered and vascular development and growth occurs in the area of imbalance [1]. Cancer cells possessing the ability to promote angiogenesis are able to influence the proportions of these factors through the production of additional pro-angiogenic factors [2]. This results in a greater proportion of pro-angiogenic factors present and the initiation of angiogenesis into the tumour, especially into

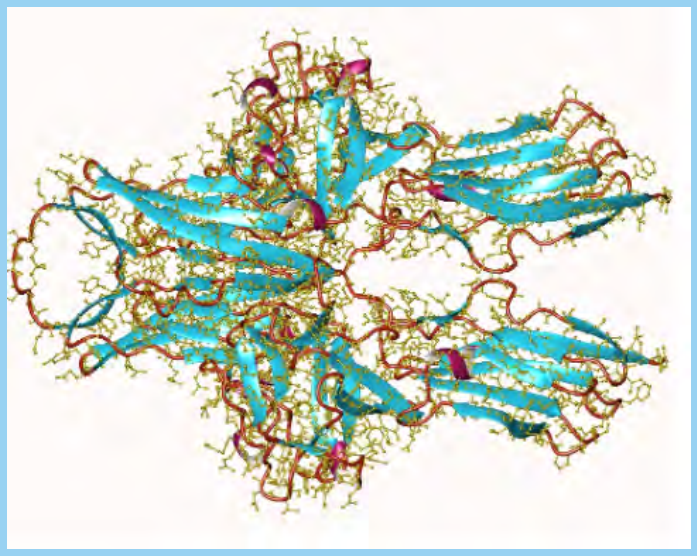


hypoxic and necrotic sections, facilitating rapid growth and proliferation and aiding the metastasis of malignant cells as they are transported via the blood to other parts of the body where they may establish separate growths from the primary site [1]. This is widely known as the "angiogenic switch" [1]. The formation and development of these new blood vessels in tumours is uncontrolled and upregulated meaning that the resulting vasculature can be identified by its abnormal and chaotic structure [2]. Many angiogenic factors directly control blood vessel formation from nearby vasculature through interactions with the blood vessels. When pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), bind to receptors found on the plasma membrane of the endothelial cells they result in vessel dilation, angiogenic sprouting, new vessel formation and vessel development [2][3]. Anti-angiogenic factors inhibit these processes and downregulate angiogenesis through interference with blood vessel formation [3].

As sufficient vasculature in a tumour is critical in enabling microscopic dormant tumours to become malignant, tumour angiogenesis holds great potential as a therapeutic target in cancer treatment. If tumour angiogenesis can be downregulated and inhibited, then the blood flow containing valuable nutrients and oxygen to the cancer cells can be controlled. A select few therapies targeting tumour angiogenesis have already been developed involving the use of angiogenesis inhibitor drugs which interfere directly with the angiogenesis signalling mechanisms [3]. Some of these drugs contain specifically shaped monoclonal antibodies which bind to the main pro-angiogenic factor vascular endothelial growth factor (VEGF), binding to the factor and preventing the VEGF from successfully binding to the VEGF-specific receptors found on the endothelial cells of blood vessels [3]. This means that the VEGF receptor does not become activated as the VEGF factor is unable to bind, therefore inhibiting the growth of new vessels [3]. Other angiogenesis inhibitors target the VEGF receptor itself or other specific receptors and proteins involved in the signalling mechanisms of tumour angiogenesis, through similar targeted binding and inhibition processes [3]. However, this treatment alone will not kill the tumour as it only aims to reduce the rate of proliferation and metastasis of the tumour cells through decreased blood flow and tumour starvation [3]. These angiogenesis inhibitor drugs are also only a temporary treatment and must be administered over a long period of time [3].

Such therapies are relatively new with many drugs still being developed and tested, but there are a select few which have been approved for medical use in cancer patients by the U.S. Food and Drug Administration (FDA) [3]. Medical research on possible therapies targeting tumour angiogenesis is still ongoing but the fast development and use of such drugs in the medical sector illustrates the huge potential for these treatments in cancer therapy and for the use of angiogenesis inhibitor drugs alongside other medication and procedures.

(VEGF receptor seen below)



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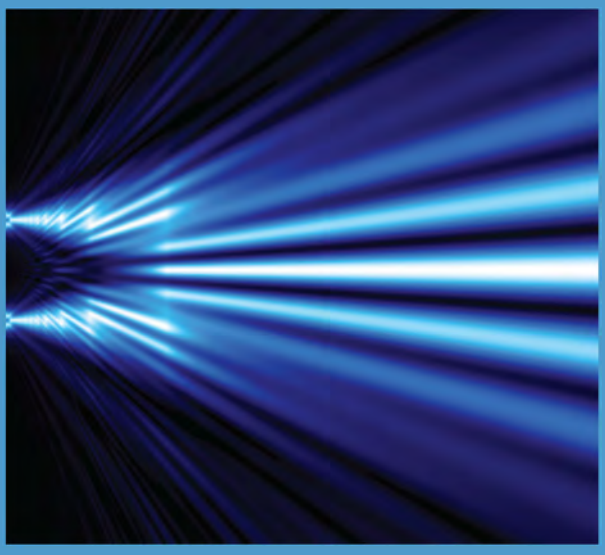
Wave-Particle Duality - A Paradox Of Quantum Physics

By Trisha T

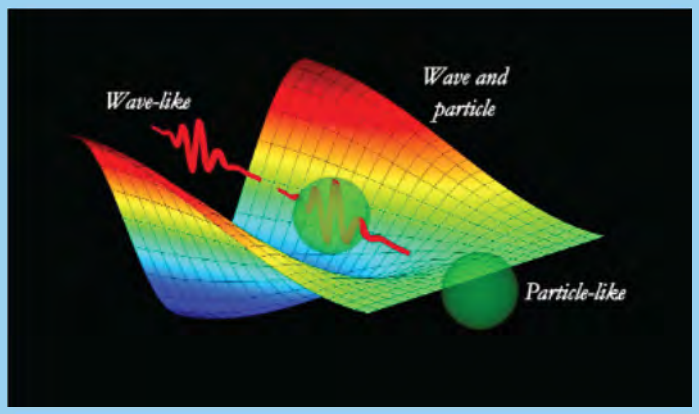
Wave-particle duality is one of the theories regarding the fundamental properties of matter where it has the potential to at one moment display the behaviour of a wave but at another moment acts like a particle [3]. This narrative, though contradictory in nature, guides us in comprehending how and why physical entities such as light and electrons behave the way they do which paves the way for further understanding our universe.

To understand wave-particle duality together we must first look at how they function separately. We can see examples of what we classify as particles in everyday life from ordinary things like balls and sand to concepts we learn about in the classroom such as atoms and electrons. The properties of particles in general can best be demonstrated using the example of a small rubber ball. For a moment, consider the ball to be a spherical object that is located at some point on an empty plane. Flicking the rubber ball with our finger causes kinetic energy to be imparted to it. This energy is what compels the ball to move. If we then picked up the ball and threw it into the air, it would inevitably come crashing down due to gravity no matter how much force we apply to it. It would then impart energy to the floor when it comes back down [1]. This demonstration displays the basic movement of particles and is imitated by entities that display wave-particle duality. Waves are greatly different to particles. While particles can bounce off each other and remain unchanged, colliding waves can interfere with each other. When waves are pushed through two narrow slits, such as in Thomas Young's double slit experiment, the waves spread out in all directions and interfere leading to regions where the wave disappears and regions where it becomes stronger. This is an example of diffraction as well as superposition and is a property of light behaving as a wave [4].



For many years it was believed that light only functioned as a wave but during the early 20th century this notion was dispelled due to the theories of light waves emitted from hot objects. The light emitted from these objects is called black-body radiation. The theories surrounding it would always predict infinite energy for the light emitted which could not be the case as the heat eventually dissipated. The answer that was come up with was to consider that the energy of the light waves was not continuous but came instead in set quanta as if it were comprised of many particles. Hence the notion came about that light waves act

like particles [1]. This dualism to the nature of light was then better demonstrated by Einstein's photoelectric effect where it was shown that a weak UV light produced a current flow but a strong red light does not release electrons no matter how intense the red light is due to light being made up of "packets" of energy carrying different amounts of energy at different wavelengths. These packets later became known as photos through Einstein's quantum theory of light [2].



It was then argued if light, which was once thought to function mainly as a wave, could display particle properties then perhaps entities that were thought of as particles could potentially display wave-like properties. It was then concluded that if this statement was indeed true, a particle should display diffraction when passed through a pair of closely spaced holes, just like a wave. To test this a variation of Young's experiment was utilised. Electrons were fired through two closely spaced holes similar to its predecessor wave experiment. When measurements were taken of the distribution of electrons on the other side of the slits the expected two peaks for each opening were absent. Instead, a complete diffraction pattern was found to be almost identical to how the waves behaved in the prior experiment. The strange feature of the experiment was that the energy of the electron wave was not deposited over the whole surface of the detector but at a point, much like you would expect from a particle. It was concluded that electrons will interact at a point as if they were a particle, but travel through space as if they were a wave.

Though seemingly nonsensical, wave-particle duality shows us that perhaps to understand the universe's dilemmas merely one answer might not be sufficient. It provides a creative approach to what appears to be a contradictory phenomenon but perhaps this idea of a paradox is merely an idealistic notion of humans for, as insightfully stated by Richard Feynman: "the 'paradox' is only a conflict between reality and your feeling of what reality ought to be".

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Advancing Treatment for Neurodegenerative Diseases

By Jessica K

With the rise of scientific and technological development in the world, especially after the COVID-19 pandemic, advancing and experimental treatments for various diseases are emerging. Neurodegenerative diseases, such as Parkinson's and Alzheimer's, are one of the many groups of diseases that do not currently have a cure. The process of neurodegeneration comes in many forms but is generally classified as the nerve cells degrading over time, leading to loss of function and structure. Neurodegeneration is most common in the elderly, approximately over the age of 65, when the first signs of disease are present (Przedborski et al., 2003)

Parkinson's disease is a neurodegenerative disease which causes the muscles of the body to go stiff and cause involuntary tremors in parts of the body. Not only does it affect the physical movements of a person, but can also affect a person psychologically, causing depression, affecting sleep and losing sense of smell. Parkinson's is caused by the damaged nerve cells in the basal ganglia, a part of the brain controlling movement, and the loss of nerve endings. The basal ganglia release dopamine which is directly related to the stiff movements in Parkinson's. The absence of norepinephrine, released by the nerve endings, explains the irregularity and abnormal internal activity of the body, like spikes and drops of blood pressure (National Institute on Aging, 2022).

Alzheimer's disease is a type of dementia that slowly makes you lose your cognitive functions, the main symptom being losing your memories. This happens because of damage caused to the entorhinal cortex, hippocampus and cerebral cortex, which all control the areas of the brain controlling memory and social behaviour. The exact cause of the damage is unconfirmed so family history, untreated depression and increasing age are thought to increase the risk of developing Alzheimer's (National Institute on Aging, 2021).

Epilepsy is a different type of neurodegenerative disease which causes abnormal and sudden seizures and sometimes unusual behaviour. Seizures in people with epilepsy are frequent and have varying signs, some include stiff muscles, jerking movements of arms and legs, loss of consciousness and confusion. In some cases of epilepsy, there is no clear cause, however, in some

cases, the disease can be traced back to several factors. Epilepsy can arise from: head trauma such as car accidents, infections like Meningitis, abnormalities in the brain for example, vascular malformations, injury in the brain during birth and developmental disorders like autism (Mayo Clinic, 2021). Certain cases of epilepsy, especially ones that occur at birth, can decrease or worsen development and growth in children. The post-epileptic state is when the cognitive functions are reduced and repetition of seizures can cause permanent degradation of spatial abilities. This cognitive impairment, which includes impairment in memory, attention span and functions, can reduce the quality of life of children with epilepsy (Novak et al., 2022).

Various types of medication have been developed as a supportive treatment for Parkinson's. Carbidopa-levodopa, the most effective Parkinson's disease medication, is a chemical that can be processed into dopamine in the brain. This medication can be orally administered or inhaled or infused through feeding tubes. There are numerous other medications like dopamine agonists, Anticholinergics and MAO-B inhibitors which help contribute to managing Parkinson's disease. As well as medication, surgical treatments include deep brain stimulation and MRI-guided focused ultrasound. Deep brain stimulation (DBS) is when surgeons place electrodes in the brain and send electrical impulses which reduce symptoms. DBS is proven to help stabilise medication, decrease tremors and sudden movements, and increase flexibility in muscles (Mayo Clinic, 2022). MRI-guided focused ultrasound is where focused beams of ultrasonic energy are directed at areas in the brain to induce relief by interrupting tremors. The ultrasound has the potential to treat the underlying disease and prevent further deterioration of Parkinson's, which DBS is unable to do. It is a minimally invasive form of treatment and targets specific areas so does not do damage to neighbouring tissues (Focused Ultrasound Foundation, 2022). Other than surgical procedures and medication, stem cell therapy is an upcoming treatment for Parkinson's which can utilise embryonic stem cells and induced pluripotent stem cells, to make dopamine neurons that can be used for cell transplantation to reverse the damage of the nerve cells in the brain. Currently, research on the dopamine neurons from stem cells is in animal models of Parkinson's disease and clinical trials are carried out to experiment on the effectiveness and safety of the therapy (Eurostemcell, 2016).

Medication-related treatment in Alzheimer's disease is targeted at the protein beta-amyloid plaques, which are a common sign of the disease. Drugs are developed to prevent the protein, beta-amyloid, from clumping together to form plaque or clear the plaque. Medications like Aducanumab (Aduhelm) and Lecanemab have shown signs of improvement in cognitive function for Alzheimer's disease. Other medications like blockers and Saracatinib were used: blockers are experimental drugs used to block the activity of enzymes that cause the production of

beta-amyloid; Lecanemab is originally a drug developed for cancer but is tested in Alzheimer's as it was shown to perform a reversal of memory loss in mice. Aside from medication, further studies into other factors that play into Alzheimer's are underway. The effect of inflammation, insulin, the heart and hormones are all factors that therapies are derived from to help treat Alzheimer's (Mayo Clinic, 2022). Similar to Parkinson's, stem cell therapy is also being tested to help treat Alzheimer's. Embryonic stem cells were developed into basal forebrain cholinergic neurons, the neurons in the brain that control memory and thinking skills, and transplanted into rat models. Results show that there was an improvement in memory loss and learning ability. In addition, the stem cells were able to produce hippocampal tissues which connected to the existing neural tissue (Liu et al., 2020).

There are many potential therapies for treating epilepsy. Vagus nerve stimulation is when a pacemaker-like device is implanted underneath the skin and wires are connected to the vagus nerve in the neck and send electrical impulses to the brain. This is similar to responsive neurostimulation which analyses brain activity to detect seizures and deliver electrical signals or drugs to stop the seizure before cognitive behaviour is affected. Some people, generally children, can reduce seizures by going on a ketogenic diet as it reduces your carbohydrate intake so fats are broken down instead. Also used in Parkinson's, deep brain stimulation can be used in epilepsy to reduce seizures for people who do not improve with medication. With epilepsy, there are advanced treatments like minimally invasive surgery with either ultrasound or magnetic fields to target areas of the brain without opening for surgery. There is also continuous stimulation of the seizure onset zone, otherwise called subthreshold stimulation, which repeatedly stimulates an area of the brain to improve seizures as it stops the seizure from happening (Mayo Clinic, 2021). Preclinical and clinical studies are taking place with the experiment of using stem cells in epilepsy. The transplantation of neural stem cells, a type of multipotent stem cell, was able to reduce involuntary motor seizures. GABAergic cells, which control the synaptic activity of an area, were replaced in areas that had a loss of these cells, which showed an effect on the control of movements (Rao et al., 2017).

Despite there not being a known cure for neurodegenerative diseases such as Parkinson's, Alzheimer's and epilepsy, the development of new procedures and ongoing trials for new therapies pave a new research pathway into the degeneration of human nerve cells. People suffering from neurodegenerative diseases have access to a wide range of alternative therapies and medication which can help relieve symptoms, in turn improving their own wellbeing and the wellbeing of the people around them.

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Do Polymeric Nanoparticles Hold the Answer to Side-Effect Free Chemotherapy?

By Emma L

Cancer is becoming increasingly common in today's society, with it being suggested by the NHS that 50% of the population will develop some form of the illness within their lifetime [1]. Twenty eight percent of these people will undergo chemotherapy in an attempt to cure or at least slow down the progression of their disease [2]. Despite the huge number of people who will undergo this treatment, chemotherapy remains riddled with issues. Through the use of polymeric nanoparticles for chemotherapeutic drug delivery, many of the characteristic side effects of chemotherapy can be mitigated.

What are polymeric nanoparticles?

Polymeric nanoparticles are particles which range in size from 10 to 1000 nm and have great potential for revolutionising drug delivery. The active ingredients are placed inside the nanoparticle which is then used for drug delivery [3]. Under the title 'nanoparticle', there are both nanospheres and nanocapsules. Nanocapsules have a spherical shape, within which the drug is placed in the oily centre, surrounded by a polymeric membrane. Nanospheres, on the other hand, have an uninterrupted polymeric structure, hence there is no oily core. Within the continuous polymeric structure, the drug can be contained inside or alternatively simply incorporated onto the outside of it [3,4].

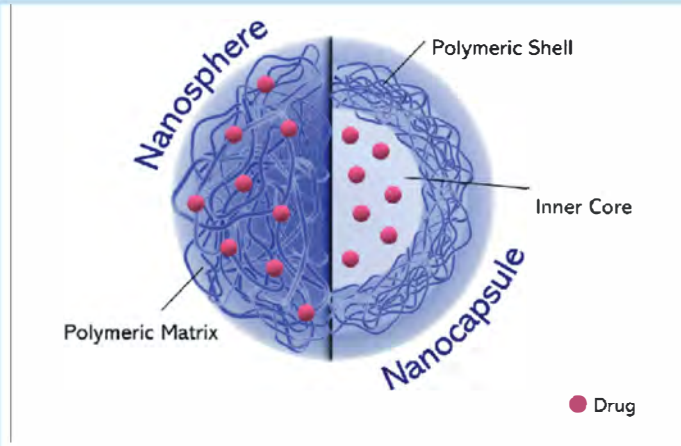


Diagram of the structure of both nanospheres and nanocapsules[5]

How can they be used for drug delivery?

Polymeric nanoparticles hold great potential in cancer treatments. Commonly used for cancer treatment is chemotherapy, a type of treatment whereby any cells which grow and divide quickly are targeted by chemotherapy drugs, which then damages the DNA of the cell. This instigates the DNA damage response which then, in many cases, causes cell death. This happens to a large number of cells within the tumour, causing it to shrink [6]. While this is often effective at

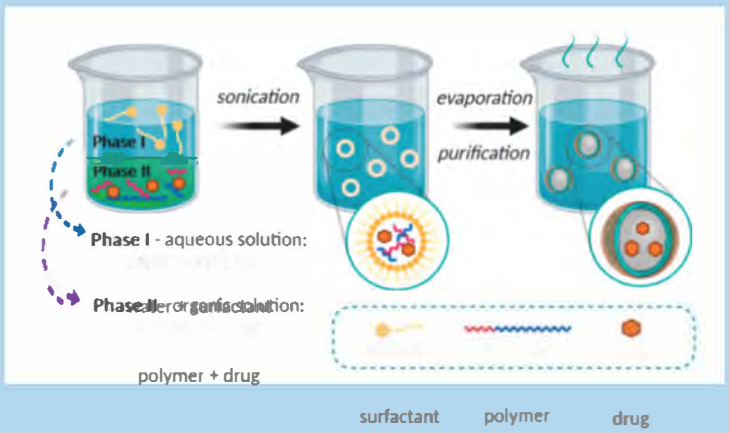
shrinking the tumour, there are also some serious side effects involved. This is due to the fact that chemotherapy drugs are non-specific, targeting any cell which divides frequently. While this does target the tumour, it also targets other cells in the body such as those found in bone marrow, hair follicles and skin, causing a wide variety of side effects such as hair loss and extreme fatigue [7]. Through the use of polymeric nanoparticles, these side effects can be mitigated. This is due to the fact that polymeric nanoparticles have been shown to better be able to differentiate between malignant and benign tissue, hence reducing the impacts to healthy tissue, minimising side effects [8]. This is because, as a malignant tumour grows, it grows very rapidly. As a result, the vascular network supplying the tumour must grow rapidly to meet the increasing needs of the tumour for the delivery of nutrients such as oxygen and glucose for aerobic respiration and in order to remove waste products such as carbon dioxide. However, as a result of this rapid vascularisation, the blood vessels grow with large pores, ranging in size from 40 nm to 1μm, between the endothelial cells lining the vessels. This is known as the enhanced permeability and retention [EPR] effect and it allows the nanoparticles to enter into the tumour through these pores, due to their small size. As a result, the particles accumulate there, releasing the drugs contained within them, damaging the cancerous cells whilst leaving other cells virtually untouched [9]. As well as this, most polymeric nanoparticles used for drug delivery are highly biocompatible, hence they are not toxic and do not induce an immune response by the body, making them a suitable candidate for drug delivery [3]. Furthermore, the smallest microcapillaries in the human body have a diameter of around 5-6 μm in diameter, hence nanoparticles are far smaller than this, allowing them to reach everywhere in the body without risking embolism (blockage of blood vessels) which could cause a multitude of problems including death (particularly when the embolism is found in the brain or lungs [10]).

What are polymeric nanoparticles made of?

Many different types of polymer are used in the formation of polymeric nanoparticles including dextran, heparin and hyaluronan[11]. Chitosan is another polymer used in polymeric nanoparticles. It is derived from chitin which is a major component of fungi cell walls as well as the exoskeleton of insects and fish scales. Chitin is a polysaccharide, hence it is made up of many monosaccharides - in this case, modified glucose molecules - covalently bonded together, forming bonds known as glycosidic bonds, to form a long chain repeating polymer [12]. As a result of the naturally occurring nature of chitin, it is a more biocompatible option [13] for use in drug delivery, helping to reduce side effects from potentially toxic polymers. Heparin based polymeric nanoparticles are also a good option for drug delivery. Heparin, which is produced in the body by mast cells [14] (a type of immune cell), is formed from long repeating chains of glucosamine (a monosaccharide with the formula $C_6H_{13}NO_5$) and uronic acid [16] (a type of sugar where the CH_2OH group has been oxidised to form a carboxylic acid [15]). Due to the fact that heparin is already naturally formed in the body, it means that the body recognises heparin based polymers as 'self', hence minimising the risk of an unwanted immune response.

How are polymeric nanoparticles made?

There are multiple methods used to produce polymeric nanoparticles. One of these methods is the solvent evaporation method whereby the polymer compounds are first dissolved in a volatile organic solvent, such as ethyl acetate ($CH_3COOCH_2CH_3$) or acetone ($(CH_3)_2CO$) [17], along with the drug being encapsulated, and then an emulsion is formed either through single emulsion or double emulsion [18]. In single emulsion, oil is added to the dissolved polymer compound along with an emulsifying agent. This is a type of surfactant which contains both a hydrophobic and hydrophilic end, hence drawing the hydrophobic oil molecules and the hydrophilic water molecules together [19]. In a double emulsion, the molecule being emulsified (i.e., the inner phase), is surrounded by emulsifiers, hence allowing it to make an emulsion with the other molecule (i.e the outer phase).
However, unlike in a single emulsion, this liquid is then also surrounded by emulsifiers, allowing this to be emulsified in the other liquid, forming a 'double layer' of emulsion [20]. This can either be classed as an (oil-in-water)-in-oil emulsion, where the oil droplets are dispersed within water which, in itself, is then covered in surfactants and then dispersed in oil. Alternatively it can be classed as a (water-in-oil)-in-water emulsification where a water molecule is dispersed in oil molecules which are covered by surfactants and then dispersed in water molecules. In both processes, a high speed homogenizer is then used to rapidly stir the mixture, forming an emulsion. The solvent is then allowed to evaporate whilst the mixture continues to be stirred constantly by a magnetic stirrer at room temperature. This forms the polymeric nanoparticles which are then ultra-centrifuged and rinsed to remove unreacted and unwanted residues [21]. By varying the concentration of the emulsifier, this allows the size of the nanoparticles produced to be controlled, hence producing the optimum nanoparticles for their specific function. As well as this, size can be controlled by changing the evaporating temperature and the stirring rate, amongst other parameters [21].



Once the nanoparticle has successfully been circulated into the body, there comes the question of how the drug contained within the nanoparticle is released. Over time, the structure of the polymeric nanoparticle is degraded, allowing the drug contained inside the particle to be released into the target tissue. Alternatively, especially in nanospheres, the drugs can simply diffuse out of the particle [22] into the target tissue where it acts, as there is a lower concentration of the drug inside the tissue than inside the nanoparticle. The rate at which the drug is released from the nanoparticle is controlled by a number of factors, namely pH and temperature as these affect how quickly and to what extent the nanoparticle is eroded, hence varying how much of the drug is released and at what rate. Drug solubility also impacts the rate at which the drugs can be released [23].

Whilst polymeric nanoparticles do hold great potential for the future of drug delivery, particularly for that of chemotherapeutic drugs and other targeted medications, there are still several issues surrounding them. The main issue is that of toxicity concerns [24]. Whilst most polymeric materials used are either already produced in the human body or are known to be non-toxic, thorough trials are necessary to ensure that the polymers are indeed safe for use in the body. As a result of this, very few nanoparticles are currently available for use in medicine, however, in the future there is expected to be a great rise in their use, particularly in drug delivery where their size gives them desirable properties which are currently lacking from conventional methods. Should scientists be able to develop and refine polymeric nanoparticles in such a way that they could deliver chemotherapy agents as discussed previously, this could hold the answer to virtually side-effect free chemotherapy. This would help to drastically improve the lives of the millions who undergo cancer treatment every year.

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Using AI in the Drug Discovery Process

By Gabi P

Biological pathways

The human body is an immensely complex machine. In order to stay alive it must continually respond to chemical changes brought on by prompts from both the outside world and from within itself, such as an increase in temperature, an injury, or a change in blood sugar levels. These responses consist of a finely-tuned balance of biochemical reactions and signals, known as biological pathways, which allow cells to interact with each other to carry out the required functions. Biological pathways are responsible for many different events, like the production of an essential protein by a gene-regulation pathway, or the production of ATP from food molecules by a metabolic pathway (National Human Genome Research Institute, 2020). Even mechanical actions, like walking and breathing are, at a molecular level, controlled by a large number of events within biological pathways.

To keep the body healthy and functional, it is vital that the steps of these pathways are not disrupted. Interactions between different biological pathways must also happen in the right way, similar to how individual components in an electronic circuit have to work with one another. Errors in pathways might lead to disease, with even small alterations having the potential to have devastating effects. For example, if a gene undergoes a mutation and is then expressed, the resulting protein could cause uncontrolled cell growth, leading to cancer (Novartis, 2013). Equally, if tumour-suppressing genes are inhibited, cancer could just as easily be caused. The first step in finding the cure to a disease is figuring out where within the biological pathway the problem lies.

Targets

A target is defined as a biological entity, such as a protein or gene within a biological pathway, which is significant in causing a disease. In drug discovery, researchers aim to find molecules that can modify the behaviour of said targets, therefore stopping or reducing the detrimental symptoms of the illness (Hughes J.P. *et. al.*, 2011). For example, the target of a drug like morphine would be the opioid receptors so that pain signals are blocked and the person no longer feels them.

It is important that these targets are ‘druggable’. This means it must be possible to alter their activity through a therapeutic (Lansdowne L.E., 2018). Therapeutics include both chemically synthesised ‘small molecules’ (typically between 10s and 100s of atoms) and ‘biologics’, which originate from natural sources and are more complex and larger in size, like antibodies (U.S. Food & Drug Administration, 2018).

A target's druggability can be assessed through its structure, as the therapeutic works by binding to it, similar to the 'lock-and-key' model used in enzymology. The therapeutic must have the correct shape and chemical complementarity in order to modulate the misbehaving protein or gene's activity.

Compound screening

Once a target has been identified and validated, drug developers move on to finding a compound that will have the desired effect on it. A commonly used screening paradigm is high throughput screening, in which as many as 100,000 molecules from compound libraries are tested in 'assays' to discover what effects each one may have on the selected target (Brazil R., 2018). Assays can be both biochemical and cell-based, with biochemical assays being the simpler of the two and typically applied to enzyme and receptor targets. The more complex cell-based assays are used for targets of membrane receptors, nuclear receptors, and ion channels, and can give information on properties of the molecule including toxicity and efficacy (Gleichmann N., 2020).

Compounds that are able to modulate the target's behaviour are considered 'hit' molecules, and undergo further testing to determine their suitability. Something that must be considered during compound screening is 'off-target effects', which happen when a hit compound produces unwanted effects on pathways aside from the target. These are more commonly known as 'side effects' and range from mild to life-threatening.

Hits are then grouped into series, and those with the most desirable properties are taken through to the hit-to-lead phase, in which they are refined with the goal of producing more effective compounds that can be tested in living organisms. An example of a property taken into consideration in this phase is solubility, as drugs commonly need to be able to enter a patient's circulation to have an effect (Hughes J.P. *et. al.*, 2011).

Finally, the chosen lead compounds are further improved in the lead optimization phase where, ideally, desirable qualities are maintained, potency is increased, and unwanted properties and side effects are reduced. The leads are narrowed down to a single compound, which moves forward to preclinical development, and later clinical trials.

AI in compound screening

The traditional process of selecting a preclinical candidate outlined above is very time-consuming due to the sheer number of molecules that have to be tested in high throughput screening, often

taking as long as 5 years. This makes drug development extraordinarily expensive, with the typical cost of producing a new drug from start to finish sitting as high as $1 billion.

A way to get this timeframe and cost down is through the implementation of artificial intelligence in the drug discovery field. Instead of testing hundreds of thousands of molecules, existing datasets can be extensively analysed to generate a much smaller list of potential hits with profiles that are likely to be suited to the target (Exscientia, 2022).

This has already started to be used in drug development, with 2021 seeing biotechnology company Evotech announce a new anticancer drug going to clinical trials after being selected with the use of AI techniques. This candidate had been discovered in just 8 months with the help of Exscientia, an Oxford-based company, which created the 'Centaur Chemist' AI design platform, which allowed just a handful (10-20) of potential hits to be synthesised and improved from a list of millions (Savage N., 2021).

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Circadian Rhythms

By Olivia C

Circadian rhythms (from the Latin *circa* 'about', *diem* 'day) are a biological version of a clock and are one of the ways life on earth is adapted to the rotation of our planet. We have known for centuries that living organisms, including humans, have an endogenous (from within) biological clocks that help them anticipate and adapt to the regular rhythm of the day, but only recently has research discovered the exact location of the master clock within the hypothalamus, how it synchronises to the billions of additional peripheral clocks regulating activity, and most recently research has focused on the health risks associated with living out of synch with these natural rhythms.

In 1729 the French scientist Jean-Jacques d'Ortous de Mairanin experimented with the rhythmic opening and closing of leaves in Mimosa plants under constant conditions of darkness, giving us one of the first descriptions of circadian rhythms in Biology [1]. Studies using brain lesions in rodents published in 1972 demonstrated unequivocally that the suprachiasmatic nuclei (SCN), a region of the hypothalamus consisting of 50,000 cells, several peptides (short chains of amino acids, the 'building blocks' of proteins) including antidiuretic hormone (ADH) and vasoactive intestinal peptide (VIP), and neurotransmitters, generates neuronal and hormonal activities which regulate many different body functions in a 24-hour cycle. Phase one showed the presence of metabolic and electrical activity rhythms in the SCN *in vivo* (i.e., in a living organism). It was assumed that circadian rhythms are the product of cell cell interactions, a circuit property that would generate a 24-hour oscillation in electrical activity. However, phase two showed that the SCN maintains rhythmicity *in vitro* (i.e., in a lab in a test tube rather than a living organism), demonstrating that single SCN 'clock cells' exhibit independent 24-hour oscillations [2]. A cohesive circadian network is created within the SCN, by intercellular coupling, and we now know that this 'central circadian pacemaker' [3], or masterclock within the brain, orchestrates the rhythmic behaviour of billions of individual 'cellular peripheral' clocks'. Current research is focused on advancing our understanding of how this synchronicity is achieved through multiple interconnected oscillators within the SCN [4].

Circadian rhythms researchers Jeffrey C. Hall, Michael Rosbash, and Michael W. Young won the Nobel Prize in 2017 for studies using *Drosophila* (fruit flies), chosen because these tiny insects have a similar fundamental biological make-up as humans (they are a vital model organism for medical research as they share 75% of the genes that cause disease in the human population) [5]. They isolated a gene which produces a protein (period circadian protein or PER) that builds up in cells

overnight, then breaks down during the day. This process can affect when you sleep, and how sharply your brain functions. Almost all life on earth (including some types of bacteria) adapts its physiology to the different phases of the day in response to light. These 'clocks' regulate critical functions such as behaviour, hormone levels, sleep, body temperature and metabolism. For example, when we wake up in the morning our blood glucose metabolism is increasing, our stress hormones are rising and our blood pressure is rising in anticipation of activity.

Our temporal structure (the five temporal lobes in our brain responsible for processing auditory information, emotions, the encoding of memory, language, visual perception) is set to the external world by receptors in the eye which detect the light in the dawn/dusk cycle. While visual cells (rods and cones) give us a sense of space, a third receptor in the eye, the photosensitive retinal ganglion cells (pRGCs) which form the optic nerve, detect the light and regulate our internal molecular clockwork [6]. Individual variation in our endogenous circadian period is known as our chronotype, and often simplified as to whether we are a morning (lark) or an evening (owl) person, and is dependent on our genes, environment and changes as we age [6]. Adolescents, for example, have a biological predisposition for a delayed sleep/wake cycle, or 'delayed chronotype' [7] tending to fall asleep later in the evening, wake later than adults (approximately two hours later than individuals in their mid 50s) with maximum lateness occurring around 19.5 years for women and 21 years for men. A lack of awareness of these differences can lead to misperceptions of laziness and can also influence learning outcomes. For this reason, the Royal Society for Public Health (RSPH) is recommending school start times to be 'carefully researched to be more comparable with the adolescent circadian rhythm' [8].

Risks to health arise when there is a mismatch between our external environment and our endogenous biological clock. A classic example of sleep and circadian rhythm disruption (SCRD) is when we travel across several time zones and experience "jet lag". It takes, on average, a day for every time zone crossed for us to synchronise our clock to the new light/dark cycle [9]. Night shift workers have difficulty adapting their clock to their work schedule due to exposure to bright natural daylight on the way to and from work compared to the low-intensity light in the workplace.This means that the circadian rhythms of night shift workers is almost the same as that of day shift workers. Risks in the short term include impaired cognitive function – so much so that our ability to process information at 4am-5am is as impaired as if we consumed sufficient alcohol to make us legally drunk [10]. Another consequence of a short-term disruption is emotional de-regulation, for example, sleep loss has been shown to cause the brain to forget positive experiences and remember negative ones. Fluctuations in mood, impulsivity and loss of empathy are additional symptoms associated with circadian rhythm disruption and sleep loss [11].

Longer term circadian rhythm disruption has even more serious health consequences for groups who cannot avoid SCRD including doctors, nurses, pilots, air crew, police, ambulance crews and shift workers in factories including reduced immunity, cardiovascular problems, mental illness

such as depression and psychosis, type 2 diabetes and increased risks of cancer [12]. One way to mitigate these might include increased health checks for these groups for early detection of conditions associated with disruption in circadian rhythms. Given that 57% of junior doctors have either crashed their cars or had a near miss on the way back from a night shift [13], vigilance devices could be fitted on cars to detect head nod or eye roll. Night shift workers could be provided protein-rich, low fat, low sugar food instead of the ultra-processed food commonly served to them in order to help maintain metabolic health.

For many of us making small changes to move towards closer alignment to our circadian rhythms will improve our cognition, metabolism, fitness and overall wellbeing. Simple steps towards this could include taking a walk outside close to dawn to encourage a better night's sleep, eating our evening meal earlier and taking medications (or having vaccinations) when circadian rhythms have not been disrupted as there are 100 different drugs with a known time of day effect [14].

The origin of circadian rhythms can be traced back to the beginning of life itself 3.4bn years ago. Fossils of cyanobacteria (blue green algae) show circadian rhythms on a 22-hour cycle with three proteins gathering around and protecting DNA from ultra violet light during the day and moving away at night. They are a response to the most predictable condition of life on earth; the dark/light cycle. Concerns about risks to health due to circadian rhythm disruption are driven by the rapidly decreasing amount of time we spend in daylight; in the UK time spent outside has decreased by 1hr in less than 20 years. Long work hours, commutes, and the internet has desynchronised our lives from these rhythms and it is worth remembering the importance of our circadian rhythms for out long term health and wellbeing.

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What is "Creepiness" and Why Do We Experience It?

By Alex N

Fear is an essential part of life: it enabled our ancient ancestors to avoid the jaws of a hungry lion, or the danger of a tall cliff. Over time, those with a predisposition towards caution were more likely to evade death and pass on their genes, giving us all the unpleasant but useful capacity to feel fear. However, the line between danger and safety often blurs, and it is not always clear whether or not something is a threat. Study the picture below:

This image generally inspires a mixture of horror, revulsion and apprehension. What is depicted in the photo is neither completely human nor completely inhuman: it has unnatural proportions, and seems to be malnourished and decomposing.

You may be familiar with something known as the 'uncanny valley', which is a hypothesised relationship between how much something resembles a person, and the emotional response it elicits. For example, a screwdriver does not resemble a human at all; thus, it does not produce any emotional response. As an object becomes increasingly human, from a moving industrial robot to a teddy bear to a humanoid robot, the empathy we feel for it increases. However, as something becomes *almost* human, it suddenly becomes perverse and repulsive. This is used to explain why some humanoid robots and video game characters look unnatural, as they nearly look like a normal, healthy person, but fall short, and instead end up in the uncanny valley.

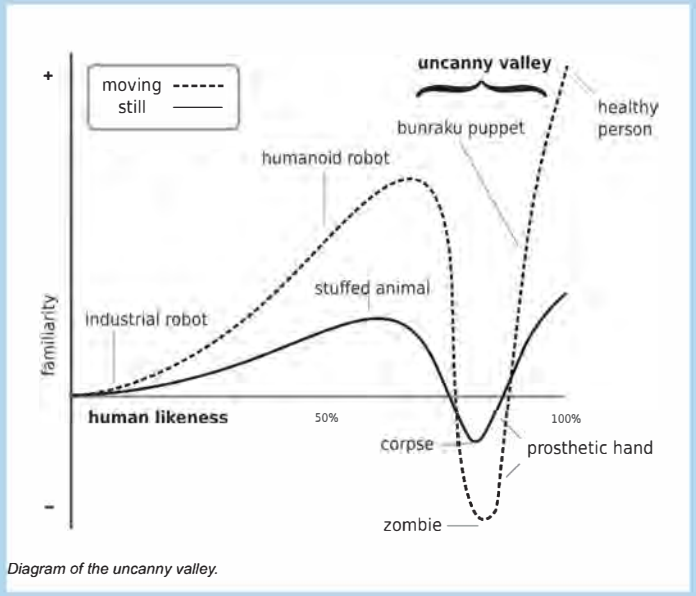

Diagram of the uncanny valley.

There are many possible explanations as to the existence of the uncanny valley, but they primarily revolve around the cognitive conflict of something being simultaneously considered 'human' and 'inhuman', producing the feeling of discomfort and creepiness. The more human something looks, the more important it is to be able to distinguish its defects, as defects are what signal disease or illness. The possibility of contracting a disease from another organism increases with your genetic similarity, so avoiding diseased humans is necessary to increase the possibility of survival. Furthermore, the uncanny valley effect may also play a role in avoiding possible mates with undesirable traits, such as low fertility or poor immune systems.

A feeling of dread or unease is also elicited by the sight of a corpse or zombie (for those interested in horror films), most likely because it triggers an innate fear of death and reminds us of our own mortality. Robots and androids are often particularly creepy, as they simultaneously challenge the idea of humanity as a unique, irreplaceable species and blur the lines between living and dead.

In their 2016 study titled "On the nature of creepiness", researchers McAndrew and Koehnke hypothesised that the feeling of creepiness is 'an evolved adaptive emotional response to ambiguity about the presence of threat', which enables us to remain attentive when safety is not guaranteed. In their study, they surveyed 1,341 people about what they considered creepy, and found that the results were consistent with their hypothesis: people tend to find it creepy when they can't predict how someone will behave, and find it less creepy if they think they understand what someone's intentions are.

Generally, those who didn't follow social conventions (either through their appearance or mannerisms) were considered to be creepy: people who dressed oddly, had very pale skin, a peculiar smile, or laughed at unpredictable times. While people who display these characteristics are not overtly threatening, they are unpredictable, and we experience the feeling of "creepiness" as we try to discern whether or not they are a true threat.

Similarly, certain hobbies and professions were also considered more creepy than others. The respondents to the survey judged those who worked as clowns, taxidermists and funeral directors to be among the creepiest. Fear of death is a fundamental part of human nature (which itself is a fear of the unknown), so it stands to reason that those who work closely with the dead (taxidermists and funeral directors) are considered strange, and therefore elicit apprehension. It is somewhat unsurprising that clowns were considered to have the creepiest profession, as the fear of clowns has become such a large cultural phenomenon that you are more likely to encounter a clown at Halloween than at a birthday party.

This can be explained, in part, by the "masks" that clowns wear. Anthropologist Claude Levi-Strauss wrote in 1961 that the masks 'temporarily eliminated from social intercourse that part of the body through which [...] the individual's personal feelings and attitudes are revealed'. That is to say that masks hide the true emotions and intentions of the person underneath, preventing us from gauging whether or not they are a threat. Therefore, the face paint clowns wear, alongside their artificial smiles, prevent us from identifying their identity and emotional state, triggering apprehension and the feeling of creepiness. This effect is also amplified by the fact that they are interacting with some of society's most vulnerable members: children.

Although this study focused on the things that make an *individual* creepy, the experience of creepiness is not limited to social interactions. Situations that do not directly involve others are also often considered frightening and creepy. Imagine coming home to find that your front door was unlocked, yet you live alone. Or, that during the night, you suddenly heard something fall in another room. These experiences are creepy, not due to any immediate threat, but the ambiguity and uncertainty as to whether you should feel afraid. Is there someone hiding behind the door, or did you just forget to lock it?

The recurrent threat posed by dangerous predators and rival hominids meant that our ancient ancestors may have evolved a way to quickly detect agents (a person, thing or animal that has agency and can act independently). In his book *Why Would Anyone Believe In God?* (2004), experimental psychologist Justin L. Barrrett put forward the idea that discriminating agents from non-agents (and distinguishing different types of agents) can be difficult because "sensory information is often ambiguous and fleeting in the natural world," yet "detecting a potential threat amidst ambiguous stimuli could mean the difference between life and death." It was evolutionarily advantageous for humans to over-detect agents (false positive) rather than to under-detect them (false negative), because the cost of not detecting a dangerous predator was far greater than seeing danger where there was none. Therefore, Barrett proposed that humans have a hypothetical HADD (hyperactive agency detection device) that predisposes us to give things agency when they have none.

This is exemplified by the 2018 study by Tratner *et al.*, which sought to use virtual reality to investigate the link between agency detection and supernatural belief. Seated at a desk with a computer, keyboard and mouse, the participants wore an Oculus Rift VR headset and played a small portion of the open-world horror game *Slender: The Arrival*. They were told to click the right button of the mouse every time they 1) saw someone or something else in the environment, or 2) saw someone or something in their environment following them. Despite the fact that they were playing a part of the game where the eponymous supernatural entity Slenderman was, in fact, absent, over 90% of the participants right-clicked at least once, suggesting a high degree of false agency detection.

A screenshot from the game Slender: The Arrival*, demonstrating the ominous atmosphere and lack of visual input, which contributes to a heightened state of tension and hyperawareness.*

It is theorised that this hypersensitivity to agency detection is a necessary component to belief in the supernatural, whereby unexplainable occurrences (ambiguous stimuli) are assigned agents (such as ghosts or demons) to counteract the ambiguity of the situation.
The tendency to assign agency to non-agents is amplified, in part, by the way humans also over-detect faces in inanimate objects. A study done in 2021 by Alais *et al.* found that both illusory and human faces shared a common expression mechanism, indicating that the processing of human expressions is broadly tuned, rather than being closely linked to only human faces. This suggests that our brain favours rapid detection of expressions over precision, leading to an effect known as face pareidolia, where we see faces (and expressions) in inanimate objects. Much like the over-detection of agents, the cost of detecting faces in inanimate objects is much less than missing a relevant emotional cue in a social situation. This does, however, have the unintended consequence of making us see faces outside of normal social situations, and experiencing face pareidolia as you are walking alone at night is undoubtedly a creepy experience.

An image of a Danish plug socket. It is frequently described as looking 'happy', despite being no more than three holes in a wall. This is an example of face pareidolia.

To conclude, the feeling of creepiness stems from *ambiguity*: when the line between safety and danger begins to blur. In social situations, someone is considered creepy when their appearance or behaviour lies outside the norm, as we may find them unpredictable and threatening to our way of life. Those with taboo hobbies and occupations, which straddle the boundaries of life and death, or childhood and adulthood, are considered creepy because we are not comfortable with these grey areas. This aversion to ambiguity may be an ancient survival strategy, but it is often unproductive in our modern, multicultural society, because the idea of what is 'outside the norm' varies greatly from culture to culture. As our society grows, our idea of 'normal' expands to encompass the natural variation from person to person, granting us all a richer experience of what human life is like. However, the feeling of 'creepiness' is still very useful to us, as it can mean the difference between heeding an early warning, or falling prey to someone standing behind your door.

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First image: Posted by Tradr on Nightmare Fuel Wiki: Pure Nightmare Fuel (Photo Gallery)

https://nightmarefuel.fandom.com/wiki/Pure_Nightmare_Fuel_(Photo_Gallery)

Slenderman: The Arrival gameplay image:
http://cassieshouseofhorror.blogspot.com/2012/08/slender-man-video-game-slender-is.html

Uncanny valley image: By Smurrayinchester - self-made, based on image by Masahiro Mori and Karl MacDorman at http://www.androidscience.com/theuncannyvalley/proceedings2005/uncannyvalley.html, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=2041097

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