Hooke in Isolation

Edition 3

01/07/20

Contents

A brief note from the editors:

This is the third, and perhaps final, edition of Hooke in Isolation. Of course an obligatory thanks to anyone who contributed to this edition, and a reminder that we're always looking for new articles! We, as much as everyone, are very much looking forward to the easing of restrictions in the near future as well as the upcoming summer holidays. However, it is important to remember that the Covid-19 pandemic is far from gone, and we strongly recommend readers maintain social distancing and follow government guidelines. We hope not to be making another Hooke in Isolation!

Editors: Ben Weiss and Ethan Kang

Cover Art: Sinan Aramaz

Our genes' response to drugs

Zara Hussein

With the NHS doling out an average of 20 prescription drugs a year for every woman, man, and child in the UK, it might make you wonder - are we taking too many pills for our own good? There's no question that modern medicine has touched the lives of us all profoundly, but as a consequence, we now seem to think that even the most minor of health inconveniences is deserving of yet another quick-fix prescription. And when it comes to prescriptions it's a dual problem: patients are too quick to ask, and doctors are often too quick to give - ultimately leaving us with cupboards full of wasted medicines that our precious NHS is struggling to pay for.

Paradoxically, this is also costing us our health; prescription drug overdoses kill more people than heroin and cocaine combined. But even if we use them responsibly, 1 in 15 hospital admissions is linked to "adverse drug reactions" (ADRs) – the potentially fatal side-effects of taking 'safe' doses of medicines that simply weren't right for our bodies. There is a solution to this, however, and it lies in "precision medicine". Precision medicine is, at its core, about matching the right person with the right drug.

It is a fact that any particular medication is only effective in 30-60% of people who take it – but why doesn't this sit right with our intuition? With scientific knowledge and innovation accelerating at breakneck speed, everyday medical practice is lagging behind. It still operates under the age-old assumption that a drug should work the same for all patients. In fact, the assumption of one-dose-fits-all is so deep-rooted that it is hard for even the most brilliant of our doctors to shake it off. Despite being amongst the most knowledgeable in the world on the cutting-edge science behind drug response, in his Ted Talk, Dr Russ Altman, a Harvard graduate professor of biotechnology, genetics and medicine at Stanford admitted that if a patient called him up to say a medication wasn't working, even he would occasionally fall victim to the physician's default instinct: to suspect they either failed to take it

from every corner of the world to sequence the human genome. Today, you can get yours done for the equivalent of less than a thousand dollars with the results arriving at your fingertips faster than your next-day delivery service. Your genome is your complete set of DNA, specifically your genes, which contain all the information needed to build and maintain your unique body. All humans are 99.9% genetically identical, but this tiny margin for difference is responsible for the striking diversity across our species - in physical appearance, but also, as we are beginning to discover, in the internal biochemistry of our bodies.

This is principle is the bedrock of "pharmacogenomics"- an emerging science at the forefront of precision medicine. Pharmacogenomics studies how the genetic differences between us result in variation in the way we respond to the same drug. The hope is that this growing knowledge will soon enable doctors to browse the genome of an individual patient and, based on their particular genetic characteristics, select the drug and the dose that works optimally for their body and is least likely to cause side effects. It is true that there are other factors influencing a person's response to medicines, such as lifestyle, age, and environment, but understanding an individual's genetic makeup is the key to creating personalised drugs that are both effective and safe.

To get a better grasp of the science involved in pharmacogenomic research, the following case study will walk you through what happens in the bodies of three individuals who all respond very differently to the same drug.

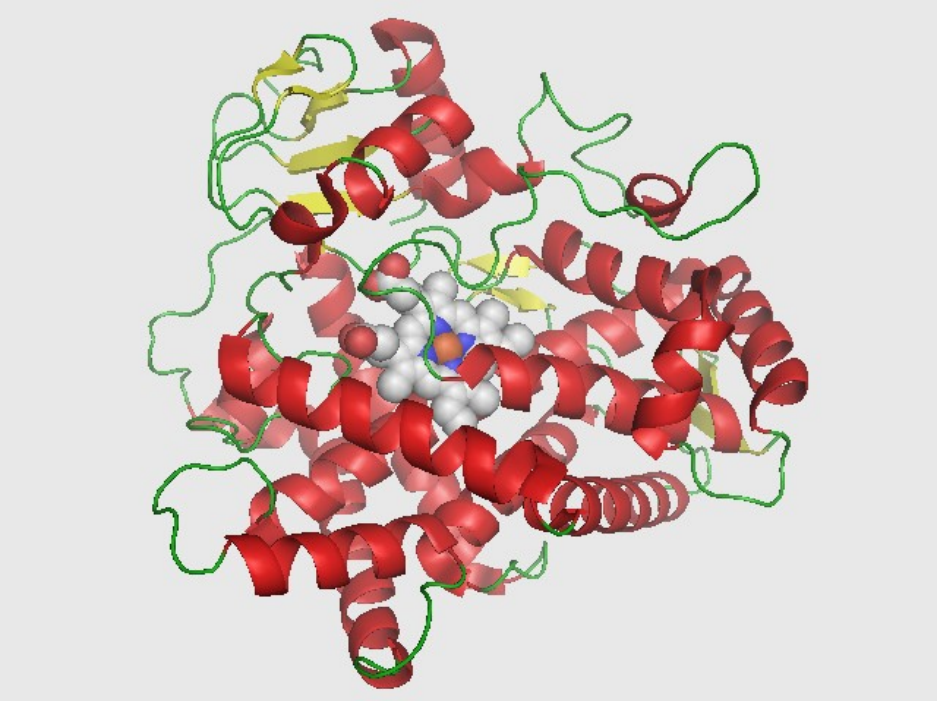
Three friends, Tom, Lucy, and Maya have all been suffering from persistent headaches following a heavy metal concert they attended last night. Lucy, who often gets headaches, digs out her usual fix of codeine - a common painkiller prescribed for her by her GP a while ago. The instructions list the recommend dose as one pill, and pain-relieving effects are expected within an hour of ingestion. She takes a pill and assures Tom and Maya, who had not taken codeine before, that it gets rid of headaches fantastically, so they too take a pill each.

Indeed, an hour later, Lucy's headache has cleared. Tom, however, feels no difference and insists the drug didn't work. Maya's response appears even stranger; almost as soon as she had taken the pill she describes feeling a sudden rush of exhilaration and positivity that made her forget all about her headache, but this only seemed to last a few minutes before wearing away and leaving her feeling exhausted and nauseous. How do we explain this?

When Lucy swallows the pill, it enters her stomach and is broken down by acidic gastric juices, releasing the codeine molecules inside it. Next, the free codeine molecules travel through her small intestine and pass into her bloodstream via its thin walls.

Interestingly, codeine itself is very inactive. It is classed as a "prodrug" meaning it has no effect on the body unless it is broken down into a new chemical – in this case, morphine, a very effective pain-relieving compound. Morphine can be highly-addictive and it is responsible for the euphoric relaxation effects associated with drugs in the opioid family, such as heroin and fentanyl - codeine's much stronger relatives.

The codeine molecules arrive at Lucy's liver which contains various drug-metabolising enzymes – these are proteins that break down drugs to produce molecules with just the right structure to bring about the desired effect in the body. In this case, an enzyme named CYP2D6 springs into action: as soon as it detects codeine it starts breaking it down into morphine.



Structure of CYP2D6

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We all have a gene containing the instructions that our body needs to make a CYP2D6 enzyme. However, just like the rest of our genes, it can come in a variety of slightly different forms commonly known as alleles. Every one of our genes is actually represented by two alleles (since we inherit one from each of our parents) and these have a combined effect. The shape of the enzyme, and therefore its metabolising ability (since having a very particular shape is key for an enzyme to work effectively), is determined by this combination of alleles. Now, because there are so many possible CYP2D6 alleles, for simplicity they can be put into three categories - functional, decreased function, and non-functional - according to the effect that each allele will have on the enzyme made. Then, taking into account the combined effect of both alleles, based on our enzyme's ability we can be "poor", intermediate", "rapid", or "ultra-rapid" metabolisers for any drug that is metabolised by CYP2D6 – which is, in fact, 25% of all prescribed drugs!

Lucy, who had a textbook response to the codeine, is a rapid metaboliser. This is the case for the vast majority of people, and it requires at least one functional allele. Prescription doses are usually determined according to the most common response within the population to any particular drug, so for most people a standard dose of codeine should work as expected.

However, this is not the case for Tom. Like 10% of the population he has two non-functional alleles, making him a poor metaboliser. This means that his CYP2D6 enzymes do not work at all, codeine is not converted to morphine in his body, and no pain-relief effects can be felt. Further, this means that for Tom, any drug needing to be broken down by CYP2D6 would also be ineffective.

Finally, Maya. She is among an even smaller percentage of the population who are ultra-rapid metabolisers. As result of a gene duplication, she has three functional alleles for her CYP2D6 gene instead of two. This extra set of instructions causes her body to produce far more enzymes than normal, making the break down of drugs to release their active compounds much faster and much more efficient. In Lucy's case, only about 10% of the codeine that enters her liver gets broken down into morphine. But despite ingesting the same amount of codeine as Lucy, Maya's many efficient enzymes work to quickly release dangerously high amounts of morphine. This surge explains why Maya momentarily experienced the heroin -like effects typical of a morphine overdose. However, as morphine progressively built up in her body it had a toxic effect, damaging healthy body tissue. The nausea and severe tiredness she experienced were just a by-product of the destructive ADRs occurring within her body. For people like Maya, a standard dose of codeine could represent a potentially fatal overdose, or a gateway into addiction.

To be able to kickstart the era of precision medicine the right way it is imperative that we all, as its future patients, do our bit to understand the unprecedented science, technology and ethics underpinning it. Our opinions have the power to shape its course.

Using AI to diagnose disease

Stefan Sarmo

Recent developments in machine learning and deep machine learning are being considered for the future of disease diagnosis. Two of the most promising programs include a program that diagnoses Parkinson's from various motor test results collected by iMotor and a programme that has been shown to outperform current radiology methods in diagnosing breast cancers from a mammography.

In recent times the question on AI in disease diagnosis seems to have shifted from "will it be used?" to "should it be used?" as studies become more and more promising for the use of AI. Though recent developments may solve many issues such as the lack of radiologists/doctors in the UK and diagnosis in remote areas, they also raise potential issues such as over-diagnosis and patient mental welfare.

Detecting Parkison's

An article discussing recent studies published online on the 14th May 2019 aimed to provide preliminary evidence that artificial intelligence systems may be able to distinguish between a healthy volunteer (HV) or a patient with Parkinson's disease (PD) and if the motor afflictions were in an "on" or "off" state.

The end goal of this programme was to be able to diagnose PD patients using data collected from finger tapping tests collected by an app such as iMotor. This would enable remote and reliable diagnosis, reduce wait times for diagnosis appointments and ease the burden on under manned hospital workers.

How does it work?

The data collected from the iMotor is stored into three datasets: The first dataset is produced from the two-target finger tapping test: (tapping of the index finger on the screen). The second dataset is produced from the pronation-supination test (tapping your palm on the screen). The last dataset is Reaction time test.

Screenshots of the iMotor finger and hand tapping tests used to collect data

This is where the actual programme comes in, a classification model of a neural network is used to analyse all three datasets and weigh their importance accordingly, then based off all the data it is given the programme will try to tell if the person has PD or is a HV and if they are a PD patient, more specific things about their condition. A cluster of Intel machines running Linux were used to conduct the analysis.

Results

The results of the study were quite promising, the algorithm managed to discriminate HVs from patients with PD with 93.11% accuracy and identify the "on" vs "off" state with 76.5% accuracy. However, the size of the study was quite small with only 19 patients with PD and 17 HVs. This programme was only intended for a study, but it demonstrates the potential of the many others in development.

Detecting Breast Cancer

Every year, 11 500 women and 80 men die from breast cancer in the UK alone. To help improve the situation, Google Health and Imperial College are working on making an AI that can diagnose breast cancer from a mammogram. This would help the estimated shortage of 1000 radiologists in the UK as well speed up the diagnosis and hopefully reduce misdiagnosis.

How does it work?

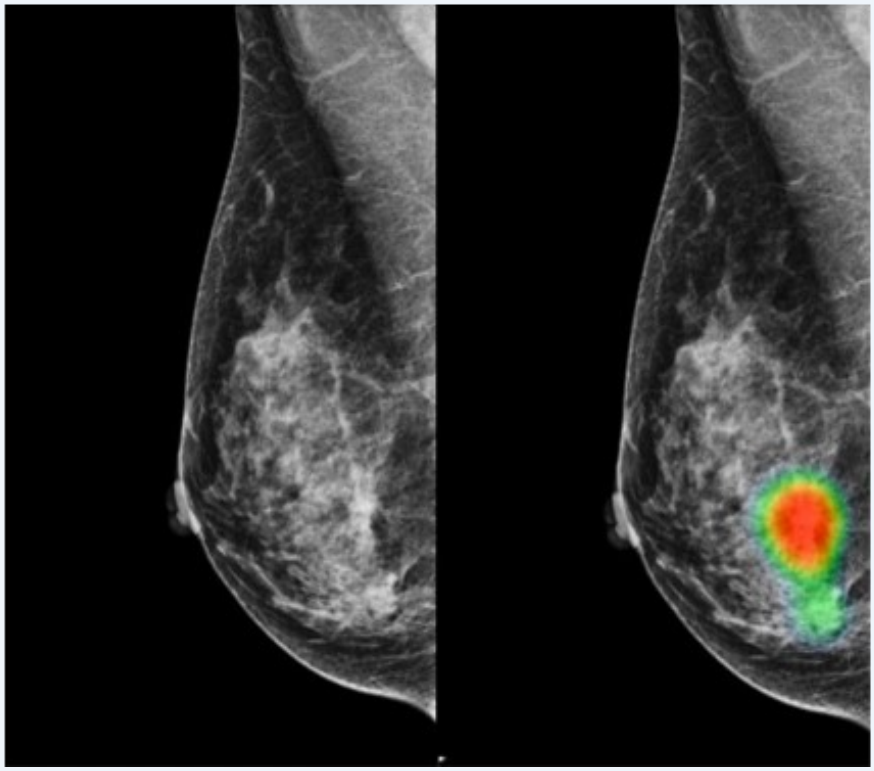
The algorithm was trained was designed and trained with x-ray images from nearly 29 000 women. The algorithm outperformed 6 individual radiologists and was on par with the current system of two radiologists working together. However, even more impressively the AI did not have access to patients past medical records.

So, Should AI Be Used?

While this is just a research study for now, when it is used in hospitals there would still be one radiologist working alongside the AI. This would still effectively double the number of available radiologists but would come with a few extra perks: the AI is tireless and once in place would provide substantial savings. Lastly, a radiologist normally takes over a decade to train and their lifetime experience is not really passed on when they retire.

There are still a few ethical and legal issues that need to be addressed. Firstly, while the AI identifies more cancers this is not necessarily better because it is already controversial as to what constitutes a cancer, especially in the early stages. As soon as you do call something cancer, it triggers a chain of medical intervention that can be painful, costly, and life changing even if the person could have lived a healthy life regardless. An AI programme will also in most cases not be able to explain its diagnosis in a way that we can understand which could cause patients much frustration in cases of misdiagnosis.

In conclusion, it is undeniable that AI has a place in the future of diagnosis but there are still side (non-technical) problems that need to be dealt with before it appears in day to day medicine. Soon, I believe that AI programmes will help save more lives, which is ultimately what matters most.



Mammograms of a 49-year-old woman with carcinoma used in a more recent AI study

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Issues with over-diagnosis:

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Is ageing a disease?

David Lee

Dying happens all the time. It's a fact of life. Hopefully, you were told as a kid that you are going to die, but not how, when or why. This is understandable, as there are so many ways that you can die; the list is stupendously big and I'm not going to bother listing any. But even if you are able to avoid all the 'miscellaneous' ways of dying, over time, your body weakens, and death eventually catches up to you. We all consider this to be a natural process, something that is inevitable, but a growing number of scientists are voicing their disagreement over this.

Moon jellyfish, aurelia aurita, are also called 'the immortal jellyfish' thanks to their ability to 'grow younger'. They begin as a polyp, but after going through metamorphosis, become a medusa – the form that most people associate jellyfish with when they think about them. This metamorphosis process is not a one-way street, hence their ability to 'grow younger'. Biologically speaking, this means that moon jellyfish have the ability to convert specialised older cells back into what they were in the past.

Of course, jellyfish still die; fish, turtles and even humans like to eat them. But this information sparks to life a new world of possibilities. What if there is a way to transport our malfunctioning frail bodies back to their youthful strength? Well, that's what Shinya Yamanaka won a Nobel Prize for in 2012.

Life for humans begins with a sperm and an egg cell. As you probably know, these cells fuse together to form zygote, which eventually divides to become an embryo. Both a zygote and the embryo are made from embryonic stem cells. These cells are undifferentiated, which means they have the potential to become any cell in the human body, and these cells divide and specialise (into skin/hair/brain cells etc.) to form the human body.

Shinya Yamanaka discovered four genes, which when inserted into skin cells from adult mice, resulted in these skin cells into turning into embryonic-like cells. The scientific community was astounded. Although this was carried out on skin cells from adult mice, this was still proof of concept of the potential to reverse ageing in humans. The fervour was so great that on 12 September 2014, a woman with macular degeneration underwent a trial using this technology.

Researchers took skin cells from the patient, applied the four factors and differentiated them into Retinal Pigment Epithelium Sheets. After inserting these RPE sheets back into the woman's right eye, researchers noted that the degeneration seemed to have come to a halt, and her vision was reported to have become brighter. However, this trial was stopped, due to the presence of mutations within the RPE sheets.

What I've just described concerning the human trial is somewhat disappointing and anticlimactic. However, fascinating and successful work on the reversal of ageing was done by Professor David Sinclair. He conducted a study, in which he was able to 'reverse age/injury -induced blindness' in a mouse. In order to do this, Professor Sinclair applied only three out of the four genes to retinal ganglion cells of an old blind mouse suffering from glaucoma, and this restored its vision. (If he had applied all four of the genes, then the mouse would have had a tumour in the back of its eyes).

We still have a long way to go. In fact, we are not even sure what causes ageing. In the middle of the 19th century, it was believed that the accumulative damage caused by mutations of our DNA resulted in ageing. Now, some people believe that ageing is a product of the accumulative damage of our metabolism, and there is another theory that ageing is caused by the loss of epigenetic information. But let's focus on what we have learnt. What we have learnt is proof of concept. We can fight ageing and it's not inevitable. But what we need now is attention. We need more people and more time to work on this, and maybe this is the way for humans to live longer, happier and healthier lives.

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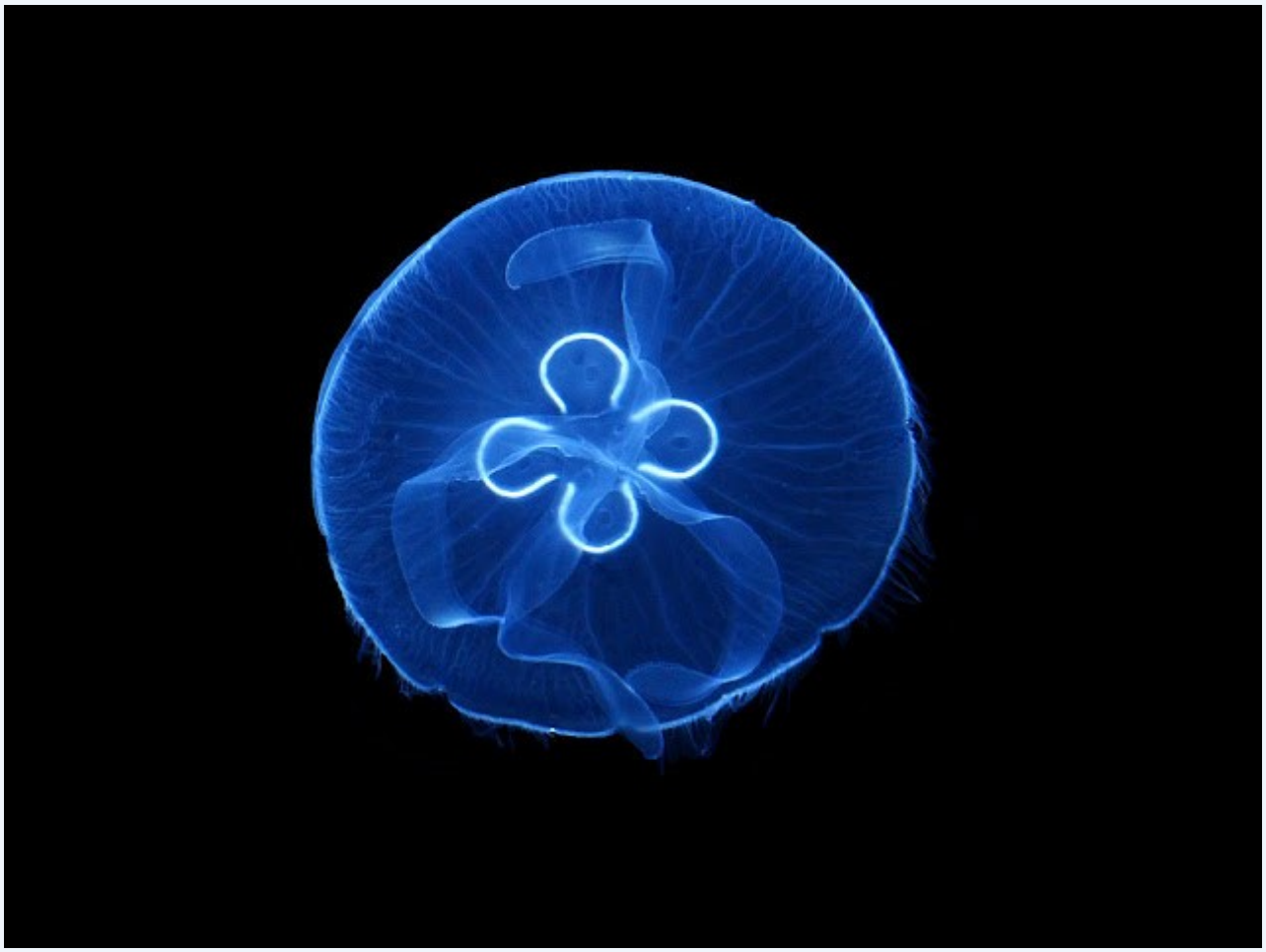
Moon jellyfish, aurelia aurita



Asymmetric Encryption

George Weston

Asymmetric encryption was first thought of by Whitfield Diffie and Martin Hellman in 1976. They envisioned it as a way to solve the key distribution problem which previously troubled symmetric encryption. In symmetric encryption, there is only one key used. This key is used both to encrypt the plaintext and to decrypt the ciphertext. Therefore, the key needed to be exchanged between the two communicating parties called Alice and Bob. The problem was that an eavesdropper called Eve could intercept the key and use it to decrypt any ciphertext that she also got a hold of.

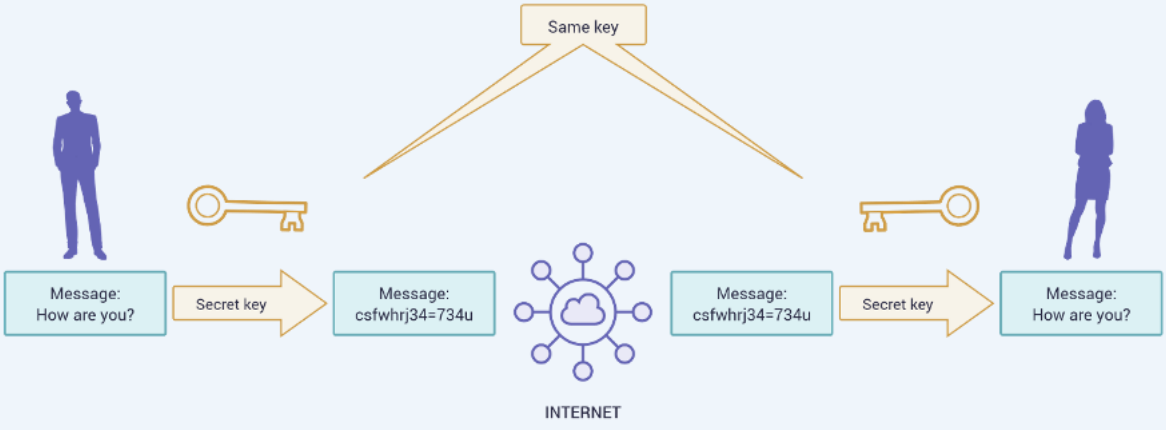
Asymmetric encryption/Public-key encryption is considered to be a much better mechanism and is where the keys come in pairs, thus solving the key distribution problem. Each user has a public and a private key.

Asymmetric encryption can be used the same way as symmetric encryption to encrypt and decrypt messages. The public key can be used to encrypt the plaintext. The private key is used to decrypt the ciphertext. As can be guessed from their names, the public key is distributed and available to everyone whilst the private key is only known by one party. This way, anyone can, for example, encrypt a message for Alice whilst Alice is the only one who can decrypt these messages. If Alice is careful, Eve will never get a hold of her private key and will only know her public key. Currently it would take too long (hundreds of years) to work out a user's private key from their public key so asymmetric encryption is a very secure mechanism.

Apart from encrypting and decrypting messages, another use of asymmetric encryption is digital signatures in which a user signs off a message with their private key. The recipient who has access to the user's public key can verify that the message came from the user. The proves that the message has not been altered. A variation on this mechanism is also applied when using Bitcoin as outlined by the mysterious Satoshi Nakamoto in his infamous Bitcoin white paper. When transferring bitcoins, the current owner signs with their private key to prove ownership of the bitcoins, and the public key of the new owner is attached as well to show whom the bitcoins are being sent to.

Asymmetric encryption is a concept but one of the first techniques to actually make use of it was RSA getting its name from the surnames of Ron Rivest, Adi Shamir, and Leonard Adleman. The problem that RSA was tackling was the generation of the public key and private key pair. These keys needed to be related; however, in order to make the system secure, it also needed to be very hard, i.e. take a very long time (hundreds of years) for an eavesdropper to work out the private key from solely the public key. To accomplish this, RSA makes use of large prime numbers to generate the public and private keys.

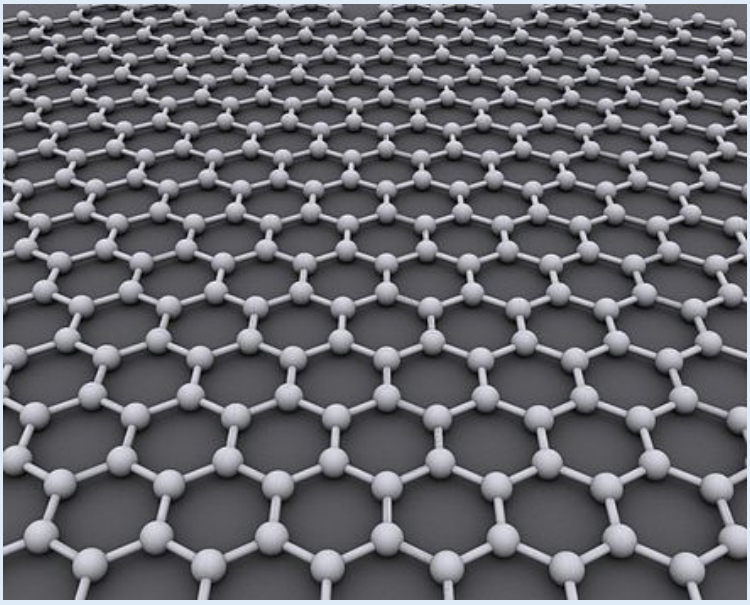
Despite the security benefits of asymmetric encryption, there are still some modern-day applications for the older system, symmetric encryption. Symmetric encryption is a much faster process, so it is preferred when encrypting and transmitting data in bulk. For these uses, asymmetric encryption is simply too slow. Other applications including the SSL protocol and WhatsApp, use a mixture of both forms of encryption.



Frequently Asked Science Questions

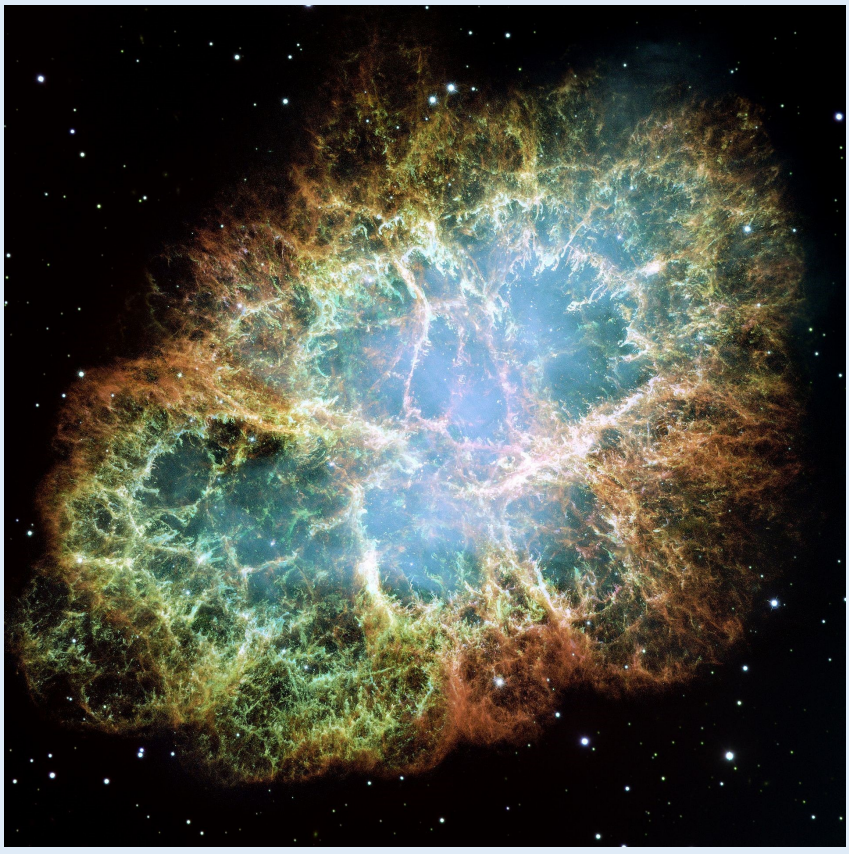
George Weston

"What is graphene?"



Graphene is an allotrope of carbon that is a single layer of graphite. Despite being so thin, graphene is very strong in contrast to graphite, and graphene is even stronger than diamond. This is due to the strong bonds between the carbon atoms (Graphite is not strong because of weak forces between the layers). Graphene is also a very good conductor of electricity better than even copper and almost as good as superconductors (these need to be cooled down to low temperatures, but graphene conducts almost as well even at room temperature). This is because normally each carbon atom has 4 bonds but in graphene, each carbon atom is bonded to three other atoms leaving 1 electron available in the third dimension for electronic conduction.

"What causes a supernova?"



According to NASA, supernovae are the largest explosions that take place in space. One way in which a supernova happens is after a massive star becomes a red supergiant. Eventually it is not possible to fuse iron into other elements and release energy, so the star runs out of fuel. The gravitational force is therefore much greater than the force due to the radiation pressure so the star collapses inwards on itself. This results in a supernova, a huge explosion expelling matter into space. After a supernova, the star either becomes a neutron star or a black hole depending on the mass of the core.

The Crab Nebula, a supernova remnant in the constellation of Taurus

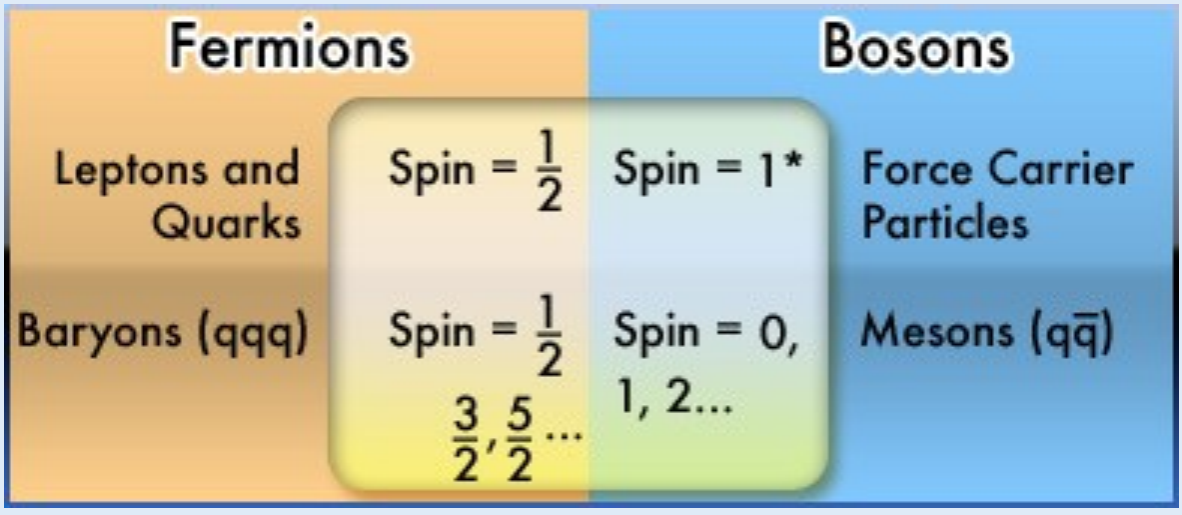
"What is plasma, the fourth state of matter?"

Plasma is the fourth state of matter, next after gas. Plasma occurs when the electrons in a gas are stripped from their nuclei. This ionized gas contains free electrons so plasma can conduct electricity. Plasma is found naturally in lightning.

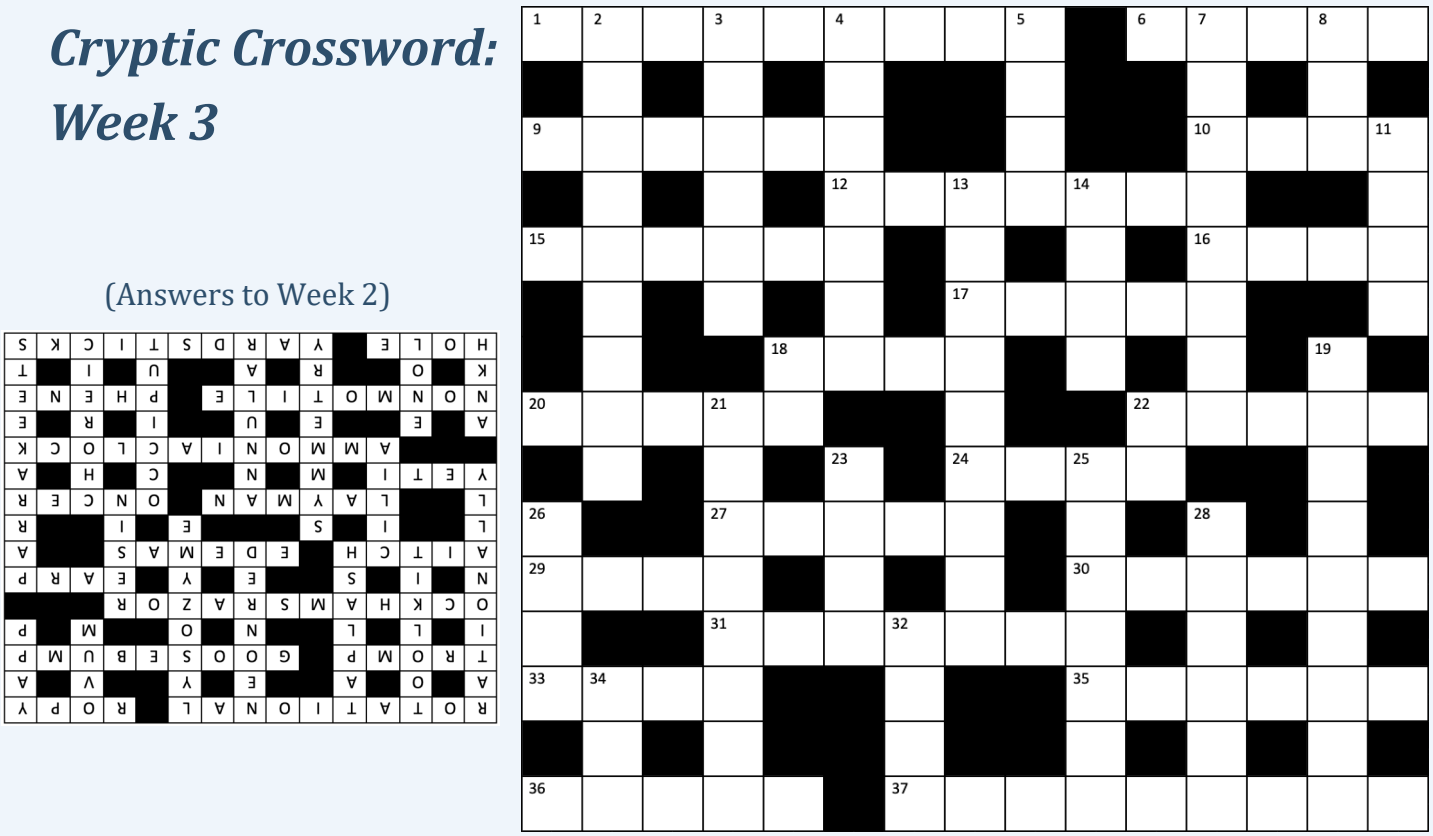
What is the difference between bosons and fermions?

There are two fundamental classes of particles: bosons and fermions. To understand what differentiates these two classes, we have to understand what spin is.

Spin is an intrinsic property of all elemental particles and it is a quantum form of angular momentum. Bosons have integer spins. Fermions have half odd integer spins. Interestingly, bosons can be thought of as force carrying particles that mediate the interactions between fermions, which can be thought of as matter particles. A notable fermion is the electron whilst a notable boson is the gluon (the carrier for the strong nuclear force).



Cryptic Crossword: Week 3



(Answers to Week 2)

ACROSS:

1 C_2HO_2 manufactured before adding Lanthanum and Tellurium to make addictive snack (9)
6 Drunkard reverses in ship towards glacier (5)
9 Blood types right for one's arteries (6)
10 Organ sounds self-aware (4)
12 Ritual at home, naturally (7)
15 Friend of bear with odd eyes long ago (6)
16 First person, now in the morning (4)
17 Stage 1: day before, put in case of luminol (5)
18 Seventh day following inclusion in Urdu task (4)
20 How the French young take on water? (3,2)
22 Final letter, love? Great! (5)
24 Sounds like seven days wasted (4)
27 Embarrassed after Ullathornes's head gets old skin condition (5)
29 Lost fish: in retrospect a bad sign (4)
30 OWs take double salt to Northen Ireland (6)
31 Chase after male bovine or canine (7)
33 King Einstein's first irrational hat (4)
35 Got on horse again after error, disheartened and mixed with dull emotions, principally (6)
36 Check verticality of lead around chimney (5)
37 Water down oddly abnormal amnesia (5,4)

DOWN:

2 What governs RHSC's operations under Mr Ullathorne? (6,3)
3 Beware non-universal charged particle (6)
4 He's into avarice, but only the most attractive will do! (7)
5 Priest doubly heartened goddess of old (4)
7 Volunteer thanks about new endless mass of element (8)
8 Signal over in six dots (3)
11 Mixes lemon endlessly - what a muppet! (4)
13 Looking back, Scooby used to be another breed or material (5,4)
14 Griddle set with overlapping articles (4)
18 One of six flavours in School? (2)
19 Dinosaur's undoing was mixing it with top-grade oxygen (9)
21 What came before Copernicium, element 112? (8)
22 Alright at absolute zero! (2)
23 Prison made of polysaccharides? (4)
25 What makes Richard Kowenicki kick down chair with ire? (7)
26 Philosopher's detailed mechanism (4)
28 Argument about rough edge down the rabbit hole? (6)
32 Pack animal beheaded for its biological rank (4)
34 General returns fish (3)

Created by Mr Coward