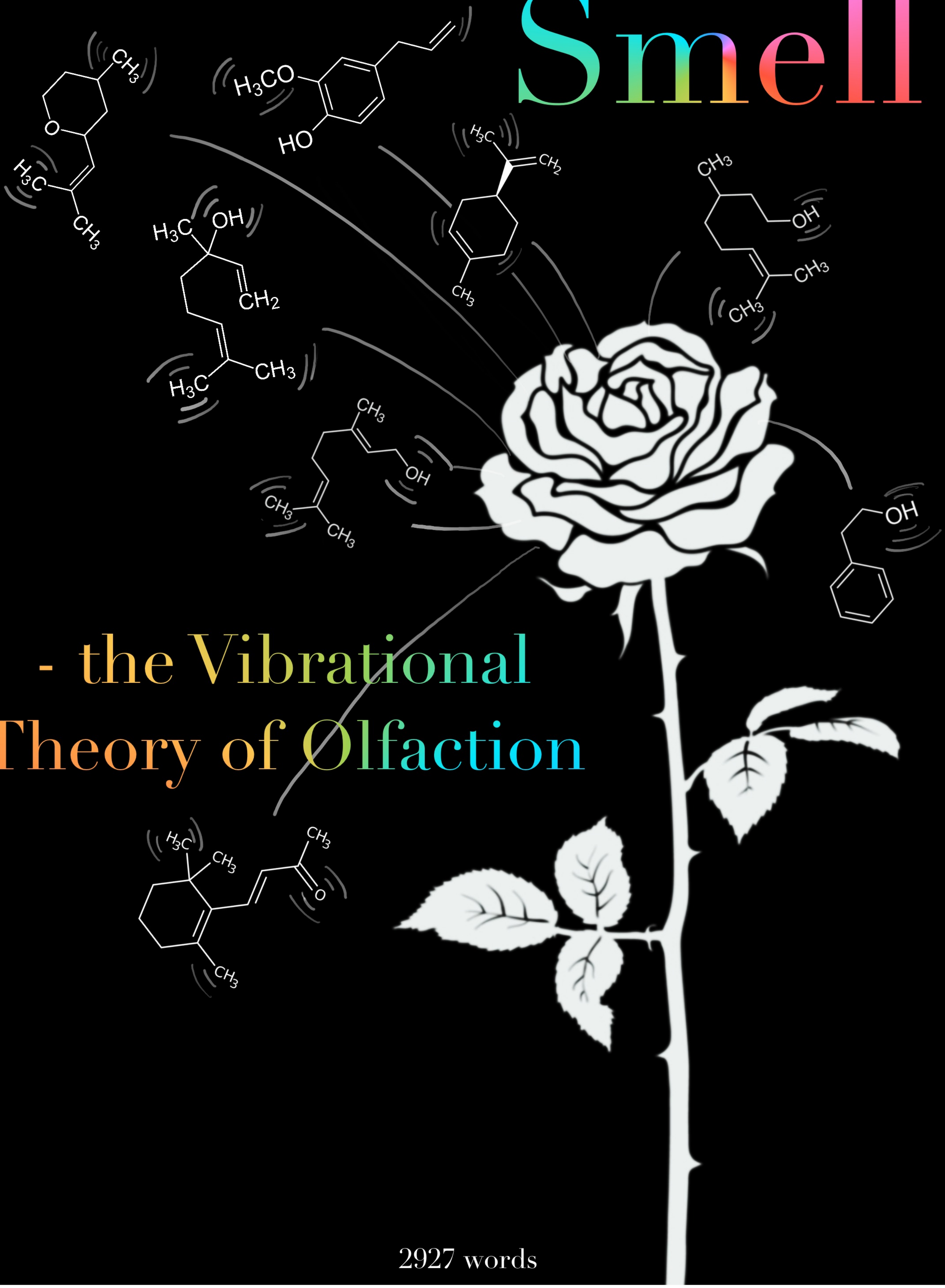
Quantum Smell

- the Vibrational Theory of Olfaction



2927 words

Quantum Smell - the Vibrational Theory of Olfaction

Nietzsche described our sense of smell as “the most delicate instrument at our disposal…capable of recording the most minimal changes that escape even spectroscopic detection”[1]. In the 130 years since these words were written, science has uncovered countless examples of the remarkable olfactory capabilities of animals. From polar bears who can detect a seal carcass from over 30km away, to salmon who can traverse an entire ocean to find the same tributary of a river each spawning season. Our sense of smell greatly affects our wellbeing and is intimately connected with our memories and emotions. Probing the mechanisms behind this highly refined sense has sparked passionate debate over the last century, with a more recent theory proposing that quantum mechanics plays a vital role in unravelling this osmic mystery. In this article, we’ll take a look at the physical basis for this theory a discuss whether or not we’re truly capable of ‘quantum smell’.

Biological Background

Our sense of smell starts of course in the nose, or more specifically a small patch of cells called the olfactory epithelium[2]. Measuring roughly 9cm^2 and positioned at the top of the nasal cavity, this patch is made up of over 10 million olfactory receptor neurones. Each neurone is shaped a bit like a string mop, with its cell membrane folding into hair-like cilia which protrude slightly into the air. As odour molecules waft past these cilia, they’re captured and identified, triggering a nervous signal which the brain translates into our sense of smell.

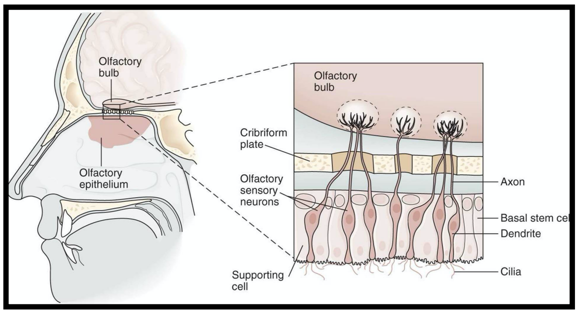


Fig. 1. The anatomy of the olfactory system[18]

To date, nearly 390 types of functional olfactory neurones have been discovered in the human genome[3]. We are capable however of detecting nearly 10,000 distinct odours, implying that it’s combinations of firing neurones that allow for this larger discriminative ability. Indeed research has shown that each type of neurone is a specialist[4], only reacting to certain molecules and ignoring others. As these specialist cells fire in tandem, they can identify complex smells. Such as the scent of a rose, whose constituent molecules are shown on the cover illustration. The question of how each olfactory receptor identifies its own set of odour molecules, and not any of the other possible molecules floating past, is regarded as the central mystery of olfaction.

Shape Theories

So far, this mystery can only be partially solved by scientific inference. This is because directly observing olfactory receptors in a living nose has proven difficult. Like a beached jellyfish losing its true shape, the receptor protein becomes misshapen when extracted from its cell membrane and no one has yet been able to resolve this. As such, any theory hoping to explain the odour identification mechanism of these neurones must agree with experimental data and allow further (ideally correct) predictions to be made.

For most of the 20th century, research into our sense of smell was dominated by the shape theory of olfaction. Inspired by the ‘lock and key’ mechanism used by enzyme-substrate pairs, this theory proposed that odour molecules slot into uniquely shaped pockets within the cilia of the receptor neurones. As an odour molecule slots in, it triggers a minuscule opening in the neurone’s cell membrane. Positively charged calcium ions then flow into the cell, and once they’ve generated roughly one picoamp of current, an electrical signal gets passed to the brain[5].

Given the unique and greatly varied shapes of odourant molecules, this theory seems plausible. But as I have already stated, 390 receptor types can generate many thousands of smells and each receptor can respond to multiple different molecules. If the entire shape of a molecule were being detected, we would expect a one-to-one mapping of odourants to receptors, but this is not the case. As an alternative, the ‘weak shape’ or odotope theory was presented in 1994[6]. Olfactory receptors were hypothesised to only recognise small portions of a molecule, such as a specific bond type or side chain. Unfortunately, this theory suffers from similar problems to the original shape theory. For instance, the substances vanillin and isovanillin are isotopomers of one another (molecules with the same isotopes of the same atoms, but arranged differently), as shown in figure 2. Given that these substances have the same bonds and constituent chains, the odotope theory would predict an identical smell. But while vanillin smells like vanilla (of course), isovanillin has an unpleasant medicinal smell.

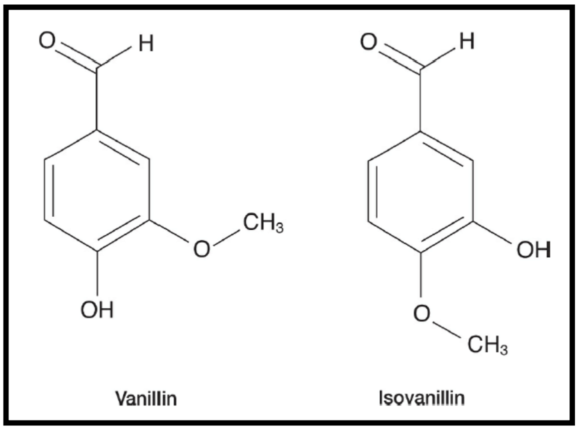


Fig. 2. Comparison of the bond arrangement of the isotopomers vanillin and isovanillin[17]

It seems that shape-based theories cannot fully explain odour identification, and a number of alternative theories have since emerged. In the 1920s, the chemist Malcolm Dyson made the speculative suggestion that the vibrational frequency of a molecule was connected to its scent[7]. Molecules vibrate about their chemical bonds and if excited, such as by an incoming photon, can vibrate at higher vibrational modes. Each molecule has a unique set of modes that result from its chemical structure. Dyson wondered whether the nose could act as a biological spectroscope and measure these vibrational modes, but the only contemporaneous method by which vibrational spectra could be probed was Raman spectroscopy. This technique would require a constant source of visible, near-ultraviolet or near-infrared light to scatter photons off odour molecules. But since we can easily smell in the dark, a biological Raman spectrometer was deemed implausible.

Turin's Tunnelling

Although the vibrational theory of olfaction was dismissed by many for its implausibility, the proposed link between molecular vibration and olfactory detection would eventually gain new momentum, thanks to a 1996 paper by the biophysicist Luca Turin[8]. Turin proposed that olfactory receptors make use of inelastic electron tunnelling (IET) to measure the vibrational frequency of odour molecules. Unlike Raman spectroscopy, IET has been deemed a biologically feasible mechanism for probing molecules in the frequency range required[9]. But what exactly is it? To answer that, we'll first look at the word 'tunnelling'.

Tunnelling is one of the many quantum mechanical phenomena which gives this branch of physics its oft-mentioned weirdness. The first postulate of quantum mechanics tells us that any isolated quantum system may be represented by something called a wavefunction Ψ, which is a mathematical description of the system from which the properties of the system may be obtained. For example, the wavefunction of an electron travelling through space encodes all information about its position, momentum, spin, etc. as it evolves through time. Being a complex-valued function, however, the wavefunction itself cannot be observed and is instead used to make predictions about the properties of the system. We may measure the position of an electron at a specific time t, but afterwards, we can only make predictions about the electron's whereabouts using the Schrödinger equation. This equation describes the temporal evolution of the wavefunction and crucially, the quantity $|\Psi|^2$ denotes the probability of finding the electron in a particular position at a particular time[10].

Quantum tunnelling appears when we apply these probability calculations to a particle meeting a potential barrier, where the barrier's height (or energy) is greater than the energy of the particle. Classical mechanics would deem it impossible for a particle on one side of the barrier to reach the other without an input of energy. But by solving the time-independent Schrödinger equation in this case, it can be shown that the quantum particle's wavefunction follows an exponential decay through the barrier. As a result, the wavefunction to the right of the barrier is non-zero. This means that there's a finite, albeit small, probability of the particle tunnelling through to the 'classically forbidden' side of the potential barrier. This is akin to a tennis ball flying towards a wall and teleporting through it without losing any kinetic energy or damaging the wall. …

Since its discovery, quantum tunnelling has proven essential to a variety of new technologies, from quantum computers to scanning tunnelling microscopes. But it was a new analytical technique called inelastic electron tunnelling spectroscopy (IETS) which piqued Turin's interest and inspired his theory. IETS involves placing two metal plates very close to one another, with a minuscule insulating gap separating them[11]. When a potential difference is applied to the plates, the electrons gather at the surface of one plate as they are attracted to the other. The negative electron-dense plate is called the donor and the positive plate is the acceptor. Classical physics would tell us that for a given voltage, the electrons lack the energy required to bridge the gap (unless of course that voltage is very high). However, we've just seen how electrons, being quantum objects, can tunnel across such a potential gap provided that it's narrow enough. So the electrons begin to traverse the insulating layer from the donor to the acceptor, generating a small current in the process.

The ability of a given electron to tunnel depends on whether or not an energetically suitable ‘hole’ is present in the acceptor. The electron can only tunnel if it can conserve its energy during the transition, this is known as elastic tunnelling. If however a substance (like an odour molecule) is placed between the plates, an electron can deposit a quantum of energy onto the molecule as it tunnels to a lower-energy hole. Crucially this requires that the energy difference between the electron in the donor and the lower-energy hole in the acceptor is equal to one of the excitable vibrational modes of the molecule in question. When the electron loses energy in this way, we have inelastic electron tunnelling. IETS then involves placing a molecule in the gap, changing the energy difference between the electron and hole (by changing the PD), and measuring where the tunnelling effect is greatest (highest current). This technique allows us to calculate the vibrational modes of a molecule and thus identify it.

So in his paper, Turin suggested that our nose uses a biological version of IETS. He claimed that since electron transfer is ubiquitous in biology, it would be entirely possible for an organic donor site (such as a charged amino acid side chain or redox ready metal) to exist on one side of the olfactory receptor. When the correct odour molecule docks inside, electrons then tunnel from this donor to the other side, triggering the release of a ‘G-protein’ which causes the influx of calcium ions mentioned earlier on. Each type of olfactory receptor is then thought to have a unique energy gap, allowing it to react only to molecules of an appropriate frequency. If Turin’s theory is correct, then we really are using quantum mechanics to smell! But even if it’s biologically possible, is there any evidence?

War of the Noses

Turin’s quantum vibrational theory makes a simple prediction: changing the vibrational frequency of a molecule should change its smell. To test this, Turin compared the odourant acetophenone with a deuterated version of the same molecule. Deuteration involves replacing hydrogen atoms within a molecule with their heavier counterpart, deuterium. Acetophenone and its deuterated counterpart are examples of isotopologues: molecules with the same chemical formula and bonding arrangement, but differing numbers of neutrons in at least one atom. These differing neutrons provide more mass which then reduces the vibrational mode frequencies of the molecule. So in the case of acetophenone, replacing each of the eight hydrogen atoms in its C-H bonds with deuterium reduces the high note frequency from around 90 THz to 66 THz. After carefully purifying a very expensive batch of deuterated acetophenone and comparing it with the standard sample, Turin was confident that he could smell a difference. However, in a subsequent study by Vosshall and Keller, a panel of twenty-four independent human subjects weren’t so sure[12]. Further studies have since confirmed this result[13], almost all participants cannot smell the difference between the two types of acetophenone!

Vosshall and Keller's result seemed like a major blow to the vibrational theory of olfaction. But refusing to take it lying down, Turin teamed up with a group at the Alexander Fleming Institute in Greece to determine whether fruit flies had a keener sense of smell than our own[14]. They set up a T-maze test, in which the flies would be released and have the choice to turn left or right at the T junction. Their choice would be influenced by differently scented air being pumped from the left and right-hand sides. As an initial test, standard acetophenone was wafted down the right-hand arm, and almost all the flies were drawn to its pungent sweet aroma. The researchers then introduced deuterated acetophenone into the other arm of the T-maze, but with varying levels of deuteration (i.e. replacing 3, 5, or 8 of the hydrogen atoms with deuterium). With the 3-deuterium sample in one arm and the standard acetophenone in the other, the flies seemed to go left or right randomly. But when the 5 or 8-deuterium samples were used, the flies showed a strong aversion to the deuterated variant. Remarkably, it seems the fruit flies could tell the difference between the standard and deuterated forms of an identically shaped molecule. Two additional odourants were then tested; octanol and benzaldehyde. The flies could differentiate standard octanol from its deuterated isotopologue, but the same result was not found for benzaldehyde.

The team went on to perform an even more fascinating test on the flies. By training them to associate a molecule of a certain vibrational frequency with punishment (by administering a negative electronic stimulus to the feet), the researchers were able to generalise this aversion to other molecules with the same frequency! More precisely, the flies were taught to avoid the scent of compounds with a carbon-deuterium bond (of vibrational frequency 66 THz). And when these same flies were presented with the scent of compounds called nitriles (whose carbon-nitrogen bond also vibrates at roughly 66 THz), they showed an equally strong aversion. It seems that these flies weren't associating the shape or chemical composition of the nitriles with punishment, but rather the frequency with which their strongest bond vibrates. These tests provide strong evidence for a vibrational component to olfaction.

So far we've seen evidence that fruit flies smell molecular vibrations, but what about humans? Although the acetophenone deuteration test proved unsuccessful in human trials, other studies have demonstrated our possible vibration-based olfactory abilities. Gane et al. carried out tests involving both trained (perfumers) and untrained human subjects[13]. They focussed specifically on our ability to discriminate deuterated musk-smelling odourants. These molecules are much larger than acetophenone, containing up to twenty-eight hydrogen atoms that could be replaced by deuterium. It was therefore hoped that the different isotopologues of each musk scent would be differentiable, and they were! Upon analysis of the data from 11 subjects, the deuterated musk odourants were deemed distinguishable from their standard counterparts.

If the conclusions of these studies are accepted, then fruit flies and humans really are capable of differentiating odour molecules not by their shape, but by the frequency with which they vibrate! The same result has been found in other species too, such as bees or whitefish[15].

Controversy Remains

We've so far looked at the plausible physical basis for quantum smell and seen some convincing experimental evidence. Why then does this theory remain so controversial within scientific circles?

Since its conception, glaring problems in the vibrational theory of olfaction have been identified. For one thing, a purely vibration-based sense of smell would not explain the scent differences between isotopomers like vanillin and isovanillin. They have the same chemical bonds and constituent atoms, therefore the same vibrational spectra. VTO would predict an identical smell but this of course is not the case. Another problem is that of chiral molecules. If two molecules are chiral, they come if left and right-handed varieties which are non-superposable mirror images of one another. Figure 3 shows the common odourant limonene (an important component of citrusy scents) and its mirror-image dipentene. As expected these molecules vibrate in the same way due to their identical molecular bonds, but smell very different.

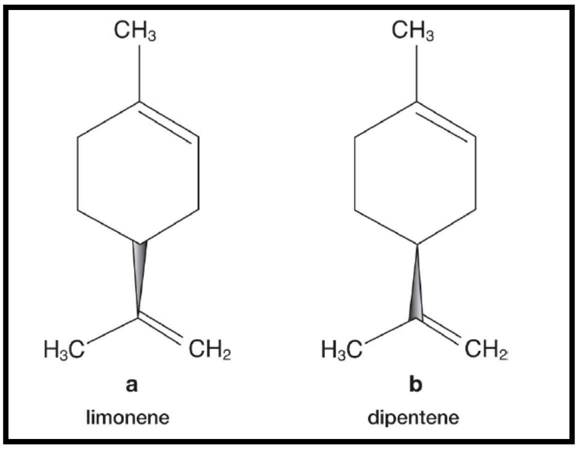


Fig. 3. Comparison of limonene with its chiral molecule dipentene. They have the same vibrational spectra but different smells.[17]

Another problem raised concerning earlier VTO studies (such as the fruit fly test) is that of sample impurity[16]. It was claimed that minute impurities such as trace solvents would be present as a result of the deuteration process. These impurities may have influenced the flies' behaviour rather than the deuteration itself. Thankfully though, subsequent experiments (such as the human musk trial by Gane et al.) sought to address this issue with strict purity tests.

The problems posed by chiral molecules and isotopomers remain however, leading many proponents of the VTO to accept some combination of both shape-based and vibration-based identification. Perhaps certain receptors come in left and right-handed varieties. They first check the rough shape of the molecule, and if it fits the molecular vibrations are then probed via IET. Until the structure of these receptor neurones can be observed directly, we won't know for certain. But if animals can truly differentiate molecules whose only distinguishing factor is their vibrational modes, then quantum mechanical tunnelling of electrons is the only plausible mechanism behind it. Our most ancient and evocative sense may well depend upon electrons which vanish and reappear, bringing us back a message from the quantum world.

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Quantum Article Plan

CID: 01707617

- In my quantum article I shall explore the ongoing debate surrounding the science of olfaction in animals, focussing specifically on the ‘vibration theory of olfaction’. This theory proposes that odour receptors in the nose (whose structure cannot as yet be directly measured) make use of inelastic electron quantum tunnelling to identify the vibrational frequencies of odour molecules, and in doing so, create the sensation of smell. To put the vibration theory in context, I shall also briefly describe the older ‘shape theory of olfaction’ and move on to discuss the problems with both theories and how their validity may be determined through experiment. This topic directly relates to the quantum module since, if the vibration theory is at least partially true, our sense of smell may be dependent upon electron tunnelling (which is of course a purely quantum effect).
- I hope that upon reading my article, the reader will gain an understanding of quantum tunnelling and appreciate its (potential) application in quantum biology. In this way, it should be clear that quantum mechanics isn’t as disconnected from our daily lives as some may think. Perhaps more importantly, I hope also that the reader will see a clear example of how the scientific tools of inference and prediction can be used to form competing hypotheses, which can then be refined through experiment.
- I plan to structure my article as follows:
    - Introduction to the debate
    - A brief description of both the anatomy of the olfactory system and the ‘shape theory of olfaction’.
    - An introduction to the quantum mechanical effects (namely tunnelling) and the concept of vibrating molecules
    - A detailed explanation of the ‘vibration theory of olfaction’, including how inelastic electron tunnelling may be used by odour receptors.
    - A discussion of experimental evidence and how it supports (or doesn't support) the theories.
- Examples of preliminary resources I’ll use:
    - Turin L. A Spectroscopic Mechanism for Primary Olfactory Reception. *Chemical Senses.* Volume 21. 1996
    - Young HD & Freedman RA. *University Physics with Modern Physics*. 14th ed. 2015. pp. 1365
    - Hoehn RD, Nichols DE, Neven H, Kais S. Status of the Vibrational Theory of Olfaction. *Frontiers in Physics.* 2018
    - Al-Khalili J & McFadden J. Life on the Edge: The Coming of Age of Quantum Biology. 2015

TUTOR FEEDBACK: “Very interesting subject so please make sure to concentrate on the quantum topic. Relevant references. You are explaining what your article will include but the structure of it should be made more obvious giving a better sense of how much content is allocated to each section.”

STUDENT RESPONSE: I tried to focus on the quantum tunnelling aspect as much as possible while also exploring its use within the context of the vibrational theory. I would’ve added more figures but ran out of time :(