A Quantum Model of Olfactory Reception

Physics
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The exact mechanism by which we recognise different scent molecules is one of the great mysteries of our physiology. While a complete explanation of our sense of smell may fall under the purview of biology, the fundamental physical phenomena that we are in fact detecting might be only explainable by quantum mechanics. This theory, that olfactory receptors respond not to the shape of a molecule (as is the case in the majority of biological reactions), but its vibrations, was first put forward in 1938 by Malcolm Dyson. However, a plausible mechanism for detection of these vibrations by olfactory receptors wasn't fully developed until 1996 by Luca Turin. He postulated that the receptors in the nose acted as spectroscopes, detecting quantised atomic vibrations (phonons) by means of inelastic electron tunnelling. This vibrational theory reconciled many of the paradoxes of the traditionally accepted "lock-and-key" theory of odorant recognition, such as how different shaped molecules can smell the same, and similarly shaped molecules can have radically different scents. This has been a highly controversial theory in the olfaction community, due to the fact that many experiments designed to test it cannot conclusively prove whether or not it is correct. We would need to know the detailed atomic-scale structure of the olfactory receptor in order to confirm or dismiss the competing theories.

Introduction

The exact process by which odorant receptors detect individual molecules remains to this day, unclear. Structure based theories, which argue that recognition of molecules is determined by the shape of the molecules alone (informally referred to as "lock-and-key" models) are insufficient to explain odorant detection, due to a multitude of exceptions that cannot be reconciled with the theory. Molecules of radically different structures have been shown to exhibit remarkably similar odours, and minor structural differences can change the scent of compounds completely. The fact that the bitter almond scent is shared by benzaldehyde, hydrogen cyanide and up to 70 other chemicals, and that structurally similar chemicals like different metallocenes smell completely different cannot be explained by such a theory. They also fail to account for the fact that specific functional groups within molecules can give a characteristic odour, regardless of the structure of the rest of the molecule. The best known example of this would be the unique 'sulphurous' scent shared by any odorants containing a thiol (SH) group. The other problem with structure-based theories is that most of them suggest that each receptor would respond to a specific molecule shape. The fact that olfactory receptors can respond to chemicals that they have never encountered before suggests that there is no way they could have evolved to identify specific molecules (Brookes *et al.* 2012). They are far more versatile, and can detect new chemicals that they have never been exposed to before.

The quantum mechanical based theory (Turin 1996) suggests that olfactory organs can somehow detect molecular vibrations. Turin's theory of detecting molecular vibrations explains many of the anomalies of structure-based theories of scent.

The principle behind how these molecules are detected could be explained by inelastic electron tunnelling spectroscopy (IETS). IETS works by exploiting the quantised set of vibrational energy levels within a molecule, separated by an arbitrary energy equal to $E=\hbar\omega_0$, (ω_0 = resonant frequency of a particular vibrational mode) (Jacklevic *et al.* 1966, Adkins *et al.* 1985*).* In laboratory IET spectroscopes, two metal contacts are positioned, with a narrow insulating gap between them. A bias voltage is applied between

the contacts, and as a result, the energy levels on either side of the gap are different. When the gap is empty, electrons are capable of tunnelling across the gap at a constant energy.

When a molecule (simplified in the diagram as a simple harmonic oscillator) is present in the gap, it can absorb the energy of the incident tunnelling electrons, and excite a phonon in the molecule. The electrons then tunnel to the second metal with less energy than the incident electron. IET spectroscopes are capable of scanning a range of bias voltages, and thus, can build up a complete vibrational spectrum of the molecule present in the gap (Figure 1). If the second derivative of the current measured across the junction is plotted against the bias voltage, clearly defined peaks appear as Dirac delta distributions, and show the energies of the vibrational transitions of the molecule under inspection. (Adkins *et al.* 1985). This can be thought of as analogous to an ohmic junction, where the resistance value changes for each transitional state.

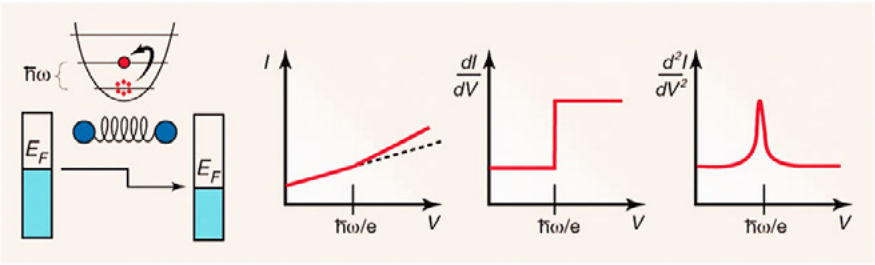

Figure 1: *(Fu et al., 2010) Schematic of basic principal of inelastic electron tunnelling spectroscopy, showing excitation of a phonon within the molecule, a V-I curve, and the resulting Dirac delta distribution pinpointing the energy of the transition.*

The quantum model for olfaction posits that a form of biological IETS is responsible for the sense of smell. The theory put forward by Turin describes such a theoretical bio-spectroscope. A source and removal mechanism for electrons at well-defined energies would need to be present in the receptor; electron transfer within biology is universally accepted, acting by a series of oxidation and reduction reactions across biological molecules (Rawson *et al.* 2002), so this is a reasonable assumption to make in an organism. One side of the gap could have an electron donor (such as NAD(P)H), and the other, an acceptor. For the type of tunnelling described above

to occur, an odorant with a vibrational energy matching the energy difference between the energy levels of the donor and acceptor would need to be present in the gap. Electrons could then tunnel across the gap, and reduce a part of the G-protein coupled receptor known to be part of the structure of olfactory receptors (Axel *et al.* 1991), in a form of biological signal transduction that is well understood (Rawson *et al.* 2002) (Figure 2). The receptor protein could then act as a spectrometer designed to detect a specific quantised vibration, related to this energy difference.

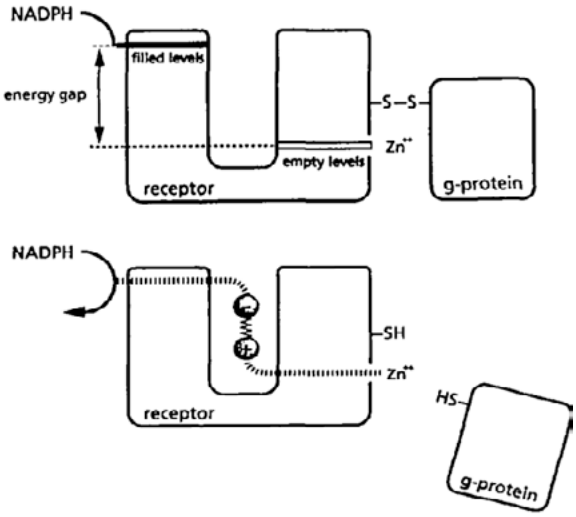

Figure 2: *(Turin 1996) Turin's proposed schematic for a biological IET spectroscope for olfactory reception, showing the G-protein coupled receptor, and inelastic electron tunnelling.*

Is Such A Quantum Model Viable?

The question is, are Turin's ideas viable from a physics standpoint? There is evidence that correlates with Turin's assertions, and that this could indeed be the process by which odorants are detected, but definitive evidence for the theory has yet to be established.

Obviously, metallic junctions and a range of bias voltages are absent in biology, so a biological analogue to this arrangement is

argued. The theory simply constructs a hypothetical arrangement of a biological IETS, constructed from molecular components known to be present elsewhere in other biological systems (Rawson *et al.* 2002). Performing IETS with proteins would require a number of prerequisites.

A biological IETS could not scan over a range of frequencies, but would instead build up a spectrum piecewise (Turin 1996), using receptors tuned to a range of different frequencies. The scanning range is limited only by the bias voltage. As the vibrational energies of most molecular bonds found in odorants range from 0 to 0.5eV (0-4000cm^{-1}), typical biological voltages of 0.5V could easily sample the necessary range. A number of types of receptor would be required, each one tuned to a different range of the vibrational spectrum. This is analogous to the fact that the sense of vision uses a number of types of receptor to cover segments of the complete spectrum.

So, if a biological IET spectroscope is the method by which scent molecules are detected in organisms, the vibrational modes of the molecules, along with their partial charges will affect the perceived scent of the chemical. (Partial charges would be involved in electron scattering within the molecule, and thus alter the energies of the electrons as they tunnel across the gap.) (Turin 1996)

Recent computational work by Brookes *et al.* (2006) has tested the physical viability of Turin's model. They estimated the timescales involved for IETS at that scale, to see if it could indeed occur in the same time frame that olfaction occurs. Olfaction generally occurs in the course of a few milliseconds, so the estimate breaks down olfaction into its constituent steps:

1. Time taken for electron carrier to diffuse through the cytoplasm to the donor site

2. Time taken for electron to pass to donor site

3. Time taken for electron to elastically or inelastically tunnel across the gap

4. Time taken for electron to pass from acceptor site

The assumption was made that the electron had to diffuse through an aqueous medium, and that the odorant is already present in the receptor site. Using a standard method for computing diffusion of material through a solution and the Stokes-Einstein relation for the diffusion coefficient, diffusion time was estimated to be:

$$\tau_X = \frac{3\eta}{2n_X k_B T}$$

where η is the viscosity of the fluid, n_X is the concentration of X, T is the temperature (Kelvin), & k_B is the Boltzmann constant. Substituting values typical of biological systems into this equation yielded a value for diffusion time to be in the range from 0.01-1ms. The values for electron transport were assumed to be typical values of electron transport rates in other biological systems, ranging from 0.001-1ms for each one.

For approximating the rate at which electrons tunnel across the gap, Fermi's Golden Rule was used:

$$\frac{1}{\tau_{i\to f}} = \frac{2\pi}{\hbar}\left|\langle\Psi_f|\hat{H}|\Psi_i\rangle\right|^2 P$$

where Ψ_i is the eigenfunction of the initial eigenstate, Ψ_f is the eigenfunction of the final eigenstate, & P is the density of final states. Equations for the complete system, described by the Hamiltonian $\hat{H}$ based on a quantum oscillator, were derived by Brooks *et al*. (2006)

Again, values typical of biological systems were chosen for the parameters of their derived equation, and the results gave values that indicate elastic tunnelling times (τ_{T0})≈100ns, and inelastic tunnelling times (τ_{T1})≈0.1ns. The fact that $\tau_{T1} << \tau_{T0}$ indicates that inelastic electron tunnelling could indeed be a viable mechanism for the detection of odour molecules. This validation of the physics behind the theory only proves that it is plausible, as the total time for all of these processes to occur could theoretically be within the order of milliseconds required (Brookes *et al.* 2006).

If Turin's theory is correct, then certain predictions can be made based on the model. Firstly, it is possible to alter the vibrational modes of molecules without altering the chemistry by

altering the mass using stable isotopes of the constituent atoms in the molecules. Theoretically, the physics behind the model can be explored directly through this method. Also, we should be able to use predicted vibrational spectra of molecules to predict their smell. If these criteria cannot be observed experimentally, Turin's model cannot be the case.

Experiments were conducted in 2004 to determine the effect of isotopes in the scent of a molecule (Keller *et al.* 2004). They conducted a double-blind smell test, comparing acetophenone, and its deuterated counterpart acetophenone-d8. The vibrational spectra of acetophenone and acetophenone-d8 are noticeably different, and vibrational olfaction theory predicts that they should smell very different. They concluded from the experiment that the theory had no basis in scientific fact, as none of the test subjects were able to distinguish between the original molecule and the deuterated molecule.

However, the experiment was repeated in 2013 to confirm the results (Gane *et al.* 2013). Turin was involved in the conduction of this experiment, and they also found that subjects could not discriminate between acetophenone and acetophenone-d8. However, they conducted a second set of experiments using deuterated versions of much larger molecules, noteably musks such as cyclopentadecanone. These molecules contained up to three times as many hydrogen atoms to deuterate, and subjects were able to detect a noticeable difference between the deuterated and undeuterated musks. Other experiments on human subjects have been carried out to examine if there is a noticeable smell difference between different isotopes of benzaldehyde (Fortin *et al.* 2001), which there were. Clearly there is a discrepancy in the theory if humans only perceive this change in vibrational energies in certain cases.

Further experimental evidence that isotopes can be detected by scent alone has been carried out using common fruit flies *(Drosophila melanogaster)* as the subjects (Franco *et al.* 2011). The drosophila were trained to have an aversion to either acetophenone, or acetophenone-d8, and were placed in a t-shaped maze with a sample of one of the molecules at each end. The drosophila were able to discriminate between acetophenone and acetophenone-d8,

where humans could not. Furthermore, the drosophila trained in this experiment to avoid the deuterated compound were able to detect deuterium in other, structurally unrelated molecules. This provides strong evidence for the vibrational theory of olfaction.

The theory also postulates that the smell of chemicals can be predicted from their vibrational spectra, despite their structural characteristics. An example of this is the distinct ambergris note shared by the following collection of molecules:

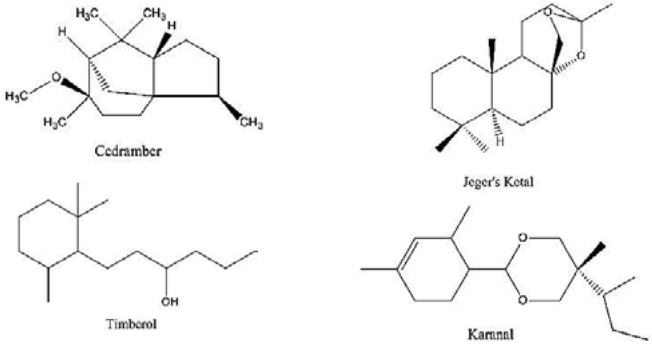

Figure 3: *A selection of molecules of different structural form, yet all share the same "ambergris note" in their smell.*

When the spectral data were examined by Turin's CHYPRE algorithm (Turin 1996), their vibrational spectra agree with the similarity of their smell (Figure 4).

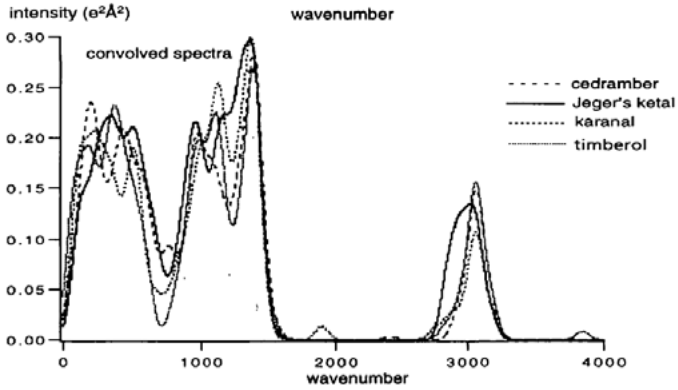

Figure 4*: Convolved vibrational spectra of the molecules shown in Figure 3. The similarity of the spectra may be the explanation as to why they all smell of ambergris. (Turin, 1996)*

Further evidence supporting the theory comes from work done by Flexitral Inc. (of which Turin was CTO.)(Turin 2004). In an attempt to find a molecule that had the same scent as coumarin (1-benzopyran-2-one), a new molecule with an identical scent was discovered. Using the vibrational spectrum of coumarin, a molecule with an almost identical spectrum was theorised, and subsequently produced. This was benzo[4,5]thieno[3,2-b]pyran-2-one, or 'Tonkene'®; this molecule smells identical to coumarin (Figure 5). While accurately determining a molecule's scent from its theorised vibrational spectra is not conclusive evidence for the theory, it strongly suggests that vibrational energies are involved in some way in how smell is detected.

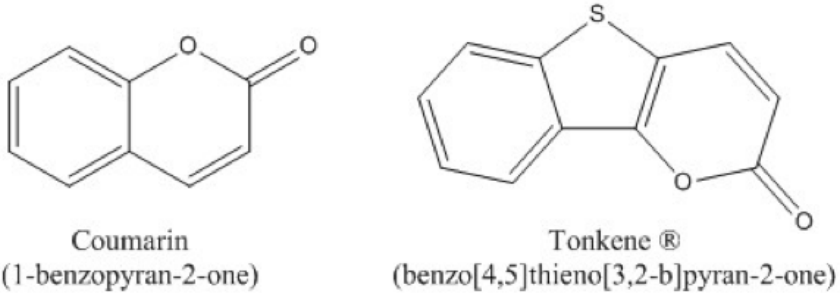

Figure 5: *Coumarin, a sweet-smelling, warm, tobacco-like odorant; Tonkene®, a molecule theorised by its vibrational spectrum to have the same scent as Coumarin. Despite structural differences, both molecules smell identical.*

Many antagonists of the vibrational theory state that it cannot reconcile the fact that many enantiomers smell different. The classic example of the carvone molecule is often debated. S-carvone smells of caraway, while R-carvone is the flavourant in spearmint confectionary (Figure 6). Both molecules obviously have identical vibrational spectra, but smell nothing like each other. A simple model of vibrational olfaction cannot explain this (Dyson 1938).

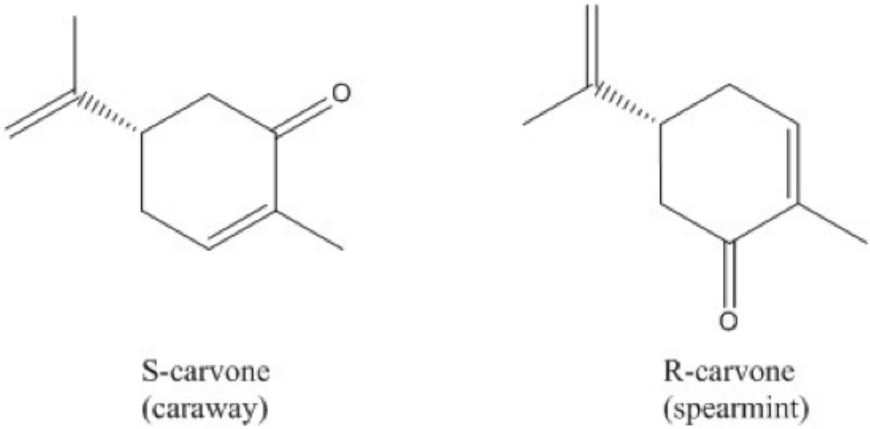

***Figure 6**: The two enantiomers of carvone (2-methyl-5-(1-methylethenyl)-2-cyclohexenone), smell nothing like each other, despite having obviously identical vibrational spectra.*

Turin has attempted to explain this experimentally, by stating that due to the different geometry of the enantiomers, some of the vibrational modes are not being detected by the olfactory receptors. In the specific example of carvone, he has postulated that it is the carbonyl stretch (C=O stretch) that is going unnoticed by the receptor, due to the molecule sitting in the wrong orientation. To prove his theory, he suggested that if one were to "add" an additional carbonyl stretch frequency (at $\hbar\omega_0$=0.223eV) to R-carvone by smelling another molecule with the C=O stretch frequency simultaneously, one could recover the caraway scent of S-carvone. In fact, a mixture of R-carvone and simple ketones (like pentanone) is indistinguishable from S-carvone (Turin 1996).

Conclusions

Turin's model of a quantum mechanical based method for odour recognition is interesting, and is gaining more traction in the scientific community as experimental evidence mounts in support of it. Combining this theory with our understanding of biological signal transduction from nasal receptors could lead to a far more complete understanding of human olfaction than has ever been compiled previously. The exact interaction of the odorants with the

receptors is yet to be fully explored by biologists, and more study is still needed in the fields of physiology and neurobiology to solve this problem; however the underlying physics of the detection method seems to be sound (Brookes *et al.* 2012).

There is also a noticeable flaw in the model, which is also present in structure-based theories of olfactory recognition; neither theory can fully explain why the scent of some molecules are concentration dependant. This is a problem well known to perfumers, and yet unexplained (Gross-Isseroff *et al.* 1988).

Though still not fully proven, biological mechanisms based on quantum mechanics are gaining more and more attention, and could encourage further research into the trans-discipline field of quantum biology. (Al-Khalili & McFadden 2014).

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