

Quantum Physics Meets Biology: a Case Study

P. D. Jarvis

*School of Mathematics and Physics, University of Tasmania,
Private Bag 37, GPO, Hobart Tas 7001, Australia.*

Is there a role for fundamental quantum physics in biology or evolution? Quantum physics was invented about a century ago, but in recent years has been undergoing an epistemological exodus, with its ideas and methods expanding from physics into information and communication and associated technologies, but also, re-addressing fundamental questions of biology. This paper will give some background to explain these assertions, and will take up a particular case study showing how quantum mechanisms may be intimately involved in some key biological processes relating to molecular mechanisms of olfaction.

1. Introduction

Quantum physics was forged in the early decades of the last century, against a backdrop of intense debate about its radical implications, not only for the laws of physics and the workings of the subatomic world, but for the very meaning of scientific accounts of reality. It is remarkable that many of the founding figures, steeped in European traditions of learning, took this philosophical re-examination into realms well beyond physics, especially in their later scientific work. This interest was engendered by the prodigious progress during the golden years of physics in the 'twenties and 'thirties, when a huge range of physical phenomena at the atomic level – from chemical bonding to condensed matter, to say nothing of nuclear physics at subatomic scales – succumbed to the explanatory power of quantum mechanics. The optimism extended to an expectation that the fundamentals of biology and even the secret of life would also yield to the new quantum physics. No less a figure than Erwin Schroedinger himself was in the vanguard of this movement, with his monograph *Was ist Leben* [1]; but the same message can be inferred from the writings of other prominent figures of the time [2].

The post-war era saw the dispersal of many of the earlier leading theoretical institutes in Germany¹ and elsewhere in Europe; in the US, attention turned towards the cold war and technological progress. The more contemplative modes of physics education were supplanted by an engineering 'shut-up-and-calculate' attitude, which tended to stifle the philosophical debates. However, the deep questions from the early years had only been papered over, not resolved.

Arguably [3], it was only a rag-tag movement of physicists and fellow travellers on the fringe of academia, which kept the debates alive. They were aided by a few established figures, who could afford the luxury of serious contributions to what were otherwise perceived to be unimportant sidelines, without endangering their careers. The seminal 1964 paper of the CERN physicist John Bell [4] was initially met with only a trickle of citations, and it would be 20 more years before its astonishingly counter-intuitive predictions about quantum behaviour were verified experimentally.

¹ The first President of the Alexander von Humboldt Foundation was the physicist Werner Heisenberg.

What of the present, almost one century on? In a sense, physics is buried by its own success – it is taken for granted that atomic stability, chemical bonding, molecular structure and interactions, and *all that*, is the known, underlying domain of quantum physics, while the real action is played out in the biochemical machinery of the molecules of life, with their incredibly complex and subtle reaction cycles, and feedback and control mechanisms. On the biomedical side, one could be forgiven for thinking that the place of fundamental physics is as the handmaiden of biology, in supplying an increasingly sophisticated panoply of clinical precision tools – CT, PET, SPECT, MRI, and many more, not to mention the humble laser, for everything from microsurgery to optogenetics!

Meanwhile, technology has become nano, to the extent that many of the old ‘thought experiments’ about subatomic behaviour are now subject to experimental testing. Quantum physics itself has been undergoing an epistemological exodus, with key ideas and methods re-assimilated from the fringe into the mainstream, and expanding its purview from traditional domains into information and communication and associated technologies. Thus it is that there is currently a renewed, and more mature, examination of the role of quantum effects in biological processes. The molecular machinery of life has had billions of years of evolution to exploit nature's every loophole to do its bidding, and it is natural to ask if truly ‘quantum’ phenomena are already to be found at work in biological systems.

To answer this question with a qualified ‘yes’, we present a case study: the quantum mechanics of molecular mechanisms of olfaction, according to a model proposed about 15 years ago by Luca Turin [5]. We report below on a recent theoretical paper which provides confirmation of the dynamical feasibility of the model [6], and we note some recent experimental support for it [7]. The paper concludes with some remarks about the wider significance of this interdisciplinary common ground between physics and biology.

2. A case study: can you smell the shape of a molecule?

About 20 years ago, Buck and Axel [8] identified the transmembrane proteins and genes involved in human olfaction, thereby revolutionising our knowledge of the associated molecular mechanisms. Hitherto it had been assumed that a traditional steric, or lock-and-key, process was at play, allowing recognition of a limited number of odorant molecules, which in combination would provide sensing of a spectrum of odours. However, with several hundred actively expressed genes, each coding for a particular transmembrane protein, and as many (non-coding) pseudogenes, in the case of humans accounting for 3% or so of the genome, it became clear that a very significant investment in hardware was involved in olfaction, and that the molecular mechanisms would be highly sophisticated [9].

Turin's ‘swipe card’ model [5] proposes a radically quantum mechanism for olfaction. The central claim is that inelastic electron or hole tunnelling occurs, between donor and acceptor sites on different helices of a trans-membrane G-coupled receptor protein, across a docked olfactant molecule, together with emission of a single vibrational phonon. The release of the G protein, which initiates ion-channel opening and ultimately a nerve impulse in the olfactory neuron, is thus tuned resonantly to the vibrational spectrum of the odorant.

The phenomenon of tunnelling is of course a quintessentially quantum effect, described in popular accounts by images of material objects being mysteriously able to pass through solid barriers. In text book understanding of electronic energy levels, the resonant phenomena underlying MRI, and some types of electron microscopy, tunnelling is a consequence of the

wave-particle duality of electrons (and protons, in the case of H-bonds). However, the assertion that tunnelling is implicated in a read-out mechanism as subtle as that described above, reads like the technical specifications of some new nano-device, and goes well beyond the ‘business as usual’ place of quantum physics as merely part of the underpinnings of the biochemistry of life.

Turin’s model has been studied in detail in a recent paper by Brookes *et al* [6]. According to their analysis, the mechanism entails a molecular reaction cycle whereby specific intracellular reducing reagents provide a supply of electrons to one of the transmembrane helices on the olfactory neuron, which are then transported by hopping to an active local site. Having tunneled to an acceptor site on an adjacent helix, the electron undergoes further hopping and is able to reduce a disulphide bond, releasing the G-protein and initiating the electrochemical trigger for an action potential (see figure [10]):

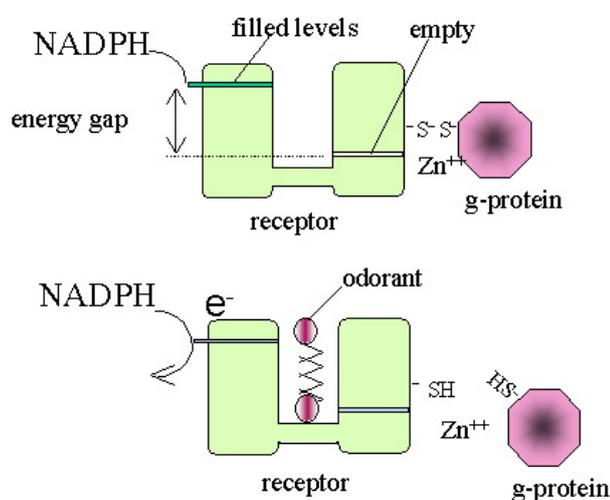


Figure. Molecular level schematic of Turin’s ‘swipe-card’ model of olfaction [5].
(Figure courtesy of Tim Jacobs [10]).

Assuming that the initial and final electron transfer stages occur at rates typical of other cellular reaction mechanisms, the efficacy of the model hinges on the tunnelling rate, for which a detailed calculation is required. In the paper of Brookes *et al* [6], the situation is idealised as a ‘quantum dissipative system’ [11] in which a quantum system, with explicitly given energy levels and interactions, interacts with a complex perturbing environment, consisting of a spectrum of oscillation frequencies. In this case the quantum system consists of just two states, the localised electronic states on the ‘donor’ helix (the upper energy level), and the ‘acceptor’ helix (the lower level), respectively. The environmental frequencies and couplings are described in a statistical way [11], except that one oscillation frequency is very special, in that it is assumed to stem from the docked odorant molecule (corresponding to one of its infrared vibrational levels), and it is tuned to the energy difference between the upper and lower levels.

The crucial calculation is then to compare the tunnelling rate both without, and with, the emission of a single phonon from the odorant. With all these simplifications, the tunnelling rates can be worked out in terms of the corresponding spectral distribution functions in a fairly standard way. The details are technical, but the final result is simple enough to give in full arithmetical form.

Let τ_1 , τ_0 be the mean lifetime (the inverses of the rate) for inelastic tunnelling – with a single phonon in the final state, and elastic (no phonon) tunnelling – determining the background firing rate, respectively. We have

$$\frac{\tau_1}{\tau_0} = \frac{s_1}{s_0} e^{-\frac{E_{DA}(E_{DA} - E_R)}{4k_B T E_R}}.$$

Up to a suppression factor ratio, estimated from changes to the average force on the odorant associated with the electronic transition, the inelastic tunnelling rate is thus determined by the energy factors in the exponential. Here $E_{DA} = E_D - E_A$ is the energy difference between the donor state energy level E_D , and the acceptor state energy level E_A . $k_B T$ is a measure of average thermal energy at temperature T ($=RT$ per mole in chemical terms), and E_R is the crucial ‘rearrangement energy’, a weighted spectral sum over all oscillator frequencies, of the difference between the environmental couplings and energies of the upper and lower states.

Given the available energy difference $\Delta E = E_{DA}$, one would expect a rate enhancement of the Arrhenius type, $\exp(\Delta E/k_B T)$; however E_R brings another energy scale into the problem, and the Arrhenius form is *exponentially* modulated by a further factor $(E_{DA} - E_R)/4E_R$. The inelastic rate is greater, the larger this factor, and conversely. Ball-park estimates for these various quantities give an indication of whether the Turin mechanism can possibly provide an acceptable ‘signal-to-noise’ ratio. If we take $E_{DA} \sim 200$ meV, a typical infrared mode, $k_B T \sim 25$ meV at room temperature, and $E_R = 30$ meV, the exponent is

$$\frac{E_{DA}(E_{DA} - E_R)}{4k_B T E_R} \cong \frac{200}{4 \times 25} \times \frac{140}{30} \cong 9$$

which, with $\log_{10} e \sim 0.4$, and against a suppression factor ratio s_1/s_0 of around 10^2 , leads finally to a rate ratio of something less than 100. Specifically, it is found [6] that

$$\tau_1 \cong 1.3 \text{ ns}, \quad \tau_0 \cong 87 \text{ ns}$$

The outcome is thus that the mechanism is indeed plausible, but it is extremely sensitive to the rearrangement energy – note that if this were increased from 30 meV to 50 meV, the inelastic rate enhancement would be minimal, and the mechanism would be ineffectual. However, a positive indication of the reasonableness of the model seems to be that, as E_R depends crucially on the precise nature of the molecular environment of the active sites, there is opportunity for an active role for selection: not only to achieve tuning to the appropriate infrared band (by adjustment of the electronic energies), but also, to provide adequate shielding to minimise E_R (via optimisation of the neighbouring residues).

Finally we turn briefly to experimental evidence. The role of ‘vibrations’ in smell seems to have been inspired early on by such folklore as the lure of the candle flame to the moth, with the inference that some recognition in the infrared (as in heat radiation) was involved in smell. But the early proposals were mechanical, rather than quantum-mechanical, in their details. Turin's model met with some skepticism after its publication, but a recent study of fruit-fly behaviour [7] provides some confirmation. The argument is well summarised by the paper's abstract:

*A common explanation of molecular recognition by the olfactory system posits that receptors recognize the structure or shape of the odorant molecule. We performed a rigorous test of shape recognition by replacing hydrogen with deuterium in odorants and asking whether *Drosophila melanogaster* can distinguish these identically shaped isotopes. We report that flies not only differentiate between isotopic odorants, but can be conditioned to selectively avoid the common or the deuterated isotope. Furthermore, flies trained to discriminate against the normal or deuterated isotopes of a compound, selectively avoid the corresponding isotope of a different odorant. Finally, flies trained to avoid a deuterated compound exhibit selective aversion to an unrelated molecule with a vibrational mode in the energy range of the carbon-deuterium stretch. These findings are inconsistent with a shape-only model for smell, and instead support the existence of a molecular vibration-sensing component to olfactory reception.*

Despite these thorough experiments, it is probably still not possible to draw any definitive conclusions from them about the role of the specific quantal effects proposed by Turin in the process of olfaction. Whatever the complete explanation, it is clear that this case is illustrative of the rich insights and explanatory possibilities opened up by exploring mechanisms for molecular behaviour going well beyond the classical 'ball and stick' regime.

3. Conclusions

In this paper we have argued for a re-examination of a fundamental role for quantum effects in biological processes, and we have illustrated one such case, Turin's model of olfaction by inelastic electron tunnelling, in detail. Discussions of the type alluded to in the introduction are to be found in the professional physics (and biology) literature, and more floridly, in popular science books and magazines. The review article whose title inspired that of the present paper [12] explains the distinction between the new literature, and 'run-of-the-mill' textbook physics dealing with the underpinnings of chemistry and biochemistry. It identifies several 'quantum' scenarios which might be at large in various biological systems, illustrative of characteristic signatures like path interference, entanglement, and tunnelling (as we have already seen).

However, as with the modelling of olfaction described in this paper, the details are complicated – for example, there are simply no 'double slit' experiments going on in our heads, whose outcomes might magically confer on us free will and indeterminism! Rather, the quantum mechanisms typically involve subtle aspects of the interaction of the system with its complex environment. This is the case for recent investigations of the physics of energy transport in the photosynthetic light gathering complexes of the chromophores [13], where the environmental coupling is thought to conspire to negate the tendency of excitons to get locally trapped rather than arrive at the active site. The same caveats apply for proposals for the physics of avian and other animal magnetonavigation [14]. There, it is hypothesised that a supply of UV photons in the retina creates radical pairs, which exist as correlated entangled electronic states, subject to anisotropic hyperfine interactions with aligned magnetic materials. This results in differential rates for subsequent chemical changes, ultimately providing a kind of 'heads up' retinal display of the earth's magnetic field. Beyond these specific scenarios, there is also current enthusiasm for a renewed look at 'quantum life' [15] – can basic physics cast light on some of the deepest questions of biology and evolution?

There is a further moral to our account of the tunnelling rate calculation. In typical theoretical physics fashion, the calculation brashly sweeps under the carpet, all of the details of the molecules, binding sites, and reaction processes involved. Instead a kind of general purpose, simplistic proxy model is used, the so – called 'quantum dissipative system' [11]. At the same time, one has the hope that results derived using such a coarse approach are robust to

the very details which have been omitted, and so have a universal validity. If understanding of a phenomenon under study has reached this stage, then intensive computational work to model all the details is warranted. This methodological paradigm is common in theoretical and mathematical physics, and is grounded in practical experience derived especially from statistical physics. There, it is found that critical behaviour and phase transitions can be mathematically identical, or universal – irrespective of whether they are in a magnetic system, a pile of granular material near its critical angle of rest, or in a solid-liquid melting phase, for example. In the same way, there is some point to exploring variations on the theme of elucidating the properties and solutions of so-called ‘exactly solvable’ quantum dissipative systems, and there are rich veins of investigation of the solutions and properties of different classes of such models [17].

The ‘classical’ physics of Alexander von Humboldt’s time had not yet developed into the ‘crisis’ which engulfed it in the late nineteenth century, which eventually ushered in relativity and quantum mechanics. Instead, Humboldt would have been steeped in the heroic traditions of the mechanical paradigm of Newton, and the mathematical heritage of Leibniz, as manifested in the achievements of his near-contemporary, Karl Friedrich Gauss [16]. Of course, had he lived a hundred years later, Humboldt the philosopher-scientist would have warmed to the early twentieth century debates on the ‘interpretation’ of quantum mechanics. And as a precursor of Darwin, he would also have been impressed by our conclusion – that the story of evolution is not complete, until an accommodation of biology with the fundamental workings of the quantum world has been effected.

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