Quantum effects in the Nerves and Brain

by

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Abstract

Quantum biology is often referred to as an emerging field of research. In theory it shares its roots with the more general field of quantum physics. Many of the founding figures of quantum theory were intrigued as to whether its insights into the structure of matter might equally offer insights into living matter. Experimental evidence for quantum effects in biological systems took longer to emerge, with tunnelling in enzymes observed in the 1960s. More recently, advances in ultrafast experimental techniques have led to extensive investigation into the role of quantum coherence in energy and charge transfer in photosynthesis. Despite this long history, the role that quantum effects play in biological systems is still very much up for debate. Even more debatable is the role that quantum effects may play in that most complex biological system: the brain. Penrose and Hameroff, for example, have suggested that consciousness cannot be explained by classical processes, and their Orchestrated Objective Reduction theory has generated both interest and critique. Consciousness is the brain's most profound secret and it remains to be seen whether quantum mechanics will prove a likely explanation. But, less ambitiously, the brain can also be described as a collection of nerve cells, whose function involves physiological processes similar to those in other cells. The aim of this thesis is to investigate how progress made in quantum biology might be applied to the specific context of neurology. To this end, the thesis revisits two of the models currently employed in quantum biological research. The first of these is the Posner molecule model of cognition, developed by Matthew Fisher. This hypothesis involves the entangled spins of phosphorus nuclei in calcium phosphate molecules, which have an influence on the balance of free calcium ions and thus neural activation. This original model is further developed here to investigate how entanglement and coherence are altered by the inclusion of lithium isotopes, and whether this might offer an explana-

tion for the mode of action of lithium in treating bipolar disease. The second model investigated in this thesis is the vibration-assisted tunnelling model first developed in the context of olfaction. The hypothesis here is that olfactory receptors are potentially activated by an electron transfer that is facilitated by the vibrational modes of the olfactant. Ligand-receptor interactions are ubiquitous in biological systems and not least in the effective functioning of the nervous system. This thesis thus re-examines the vibration-assisted tunnelling model to determine how generalisable it might be, by taking the specific case of infection with the SARS-CoV-2 virus. While this virus-host interaction is not neurological, intriguing evidence that antidepressants can have antiviral effects as well as the profound effects that COVID-19 can have on the nervous system, suggests that this timely example might offer valuable neurological insights.

Preface

The work described in this dissertation was carried out in the School of Chemistry and Physics, University of KwaZulu-Natal, Durban, from March 2017 to January 2023, under the supervision of Professor Francesco Petruccione and Professor Ilya Sinayskiy.

These studies represent original work by the author and have not otherwise been submitted in any form for any degree or diploma to any tertiary institution. Where use has been made of the work of others it is duly acknowledged in the text.

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I, Betony Adams declare that

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Declaration 2- Publications

Publications most relevant to thesis

B. Adams, I. Sinayskiy, F. Petruccione. 'Coherence and entanglement in lithium-doped Posner molecules', arXiv:2310.13484 [quant-ph] (2023).

B. Adams, F. Petruccione. 'Nature's novel materials: A review of quantum biology', *Encyclopedia of Condensed Matter Physics 2nd Edition*, Academic Press: (2023).

B. Adams, I. Sinayskiy, R. van Grondelle, F. Petruccione. 'Quantum tunnelling in the context of SARS-CoV-2 infection', *Sci Rep.* **12** 16929 (2022).

B. Adams, F. Petruccione. 'Quantum effects in the brain: A review', *AVS Quantum Science* 022901 (2020).

Other publications during thesis

I. Galvan, A. Hassassfar, B. Adams, F. Petruccione. 'Isotope effects on radical pair performance in cryptochrome: A new hypothesis for the evolution of animal migration', *BioEssays: news and reviews in molecular, cellular and developmental biology*, e2300152 (2023).

A. Marais, B. Adams *et al.* 'The future of quantum biology', *J. R. Soc. Interface.* **15** 20180640 (2018).

B. Adams, I. Sinayskiy, F. Petruccione.'An Open Quantum System Approach to the Radical Pair Mechanism', *Sci Rep.* **8 (1)** 15719 (2018).

Popular science publications

B. Adams, F. Petruccione.'Birds, brains and magnetic fields', *Quest* **17 (3)** (2021).

B. Adams, F. Petruccione. 'The light of the mind', *Physics World* **34 (1)** (2021).

B. Adams, M. Schuld, F. Petruccione. 'Explainer: what is quantum machine learning and how can it help us?' (online) *The Conversation* (2019), republished in *Quest* **15 (3)** (2019).

Declaration 3- Presentations

'Spin quantum computing, spin quantum cognition' at the Gordon Research Conference on Quantum Biology, Galveston, Texas (2023).

'What is quantum biology' at Spring School on Theoretical and Computational Foundations of Quantum Technologies, Drakensberg South Africa (2022).

'Entanglement and nuclear spin dynamics in Posner molecules' at Quantum Effects in Biological Systems, Greece (2022).

'Entanglement and coherence in Posner molecules', Google AI meeting, online (2021).

'Quantum Biology' at Biophysical Society presentation, online (2021).

'Quantum biology and consciousness' at Space4Women show, online (2021).

'Quantum effects in the brain: how much do we know?' at the NITheP colloquium webinar series (2020).

'Quantum effects in the brain: a viable assumption' at the Neural Engineering Research Venture (NERV) webinar series (2020).

'Posner molecule spin dynamics' at the UCLA QuBiT webinar series (2020).

'Neural entanglement: An open quantum systems approach' at NITheP Bursary Workshop, Stellenbosch (2019).

'An open systems approach to Posner qubits' at Quantum Effects in Biological Systems, Mexico (2019).

'Quantum brain: A viable assumption' at SAIP, Polokwane (2019).

'An open quantum systems approach to the radical pair mechanism in a biological context' at Quantum Effects in Biological Systems, Lithuania (2018).

'An open quantum systems approach to the radical pair mechanism in a biological context' at SAIP, Bloemfontein (2018).

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Contents

Chapter 1

Introduction

1.1 Is the brain quantum?

[1] The idea that quantum physics might have something to do with explaining that most mysterious organ, the brain, has generated scepticism among scientists. Just because quantum theory and consciousness are both complex concepts does not mean they necessarily inform each other. Indeed the contexts in which both occur have long been assumed to be incompatible. The brain is a biological system, functioning at physiological temperatures and subject to the myriad interactions by which living organisms survive. Quantum effects, on the other hand, are conventionally limited to low temperature systems isolated from the detrimental effects of environmental interaction [1]. However, the mutual exclusion of biological and quantum systems is no longer so absolute. Research in the field of quantum biology has had some success in identifying how quantum processes might benefit living organisms [2–5]. On a fundamental level, it can be said that all biological systems are quantum mechanical, being composed of atoms and thus subject to the quantum theory of atomic structure first developed by Bohr and Rutherford at the beginning of the twentieth century [6, 7]. In the field of quantum biology these are considered to be trivial quantum effects, what is more interesting is whether quantum phenomena such as coherence, entanglement and tunnelling might play a non-trivial role in enhancing the efficacy of biological processes [1–5]. There is mounting evidence that quantum theory might

[1] This chapter is based on the following paper: B. Adams, F. Petruccione. 'Quantum effects in the brain: A review', *AVS Quantum Science* 022901 (2020).

contribute to a more accurate physical description of photosynthesis [8–13]. The avian compass has also been suggested to exploit quantum effects with behavioural evidence supporting the hypothesis [14–17]. Olfaction [18], enzyme catalysis [19] and the intricacies of DNA [20] have all fallen under the scrutiny of researchers working in the field of quantum biology. The basic biology of the brain, elevated though it is by the inexplicable phenomenon of consciousness, is perhaps not, on a mechanistic level, so very different from other processes that take place in the body. It is no wonder then that interest has grown in whether quantum biology might have some contribution to make towards understanding the detailed physiological mechanisms that constitute the central nervous system. There have been attempts to tackle the hard problem of consciousness [21–23], or apply quantum theory to human psychology and cognition [24–26]. This introduction, however, focuses on the various instances in which it has been suspected that quantum effects play a role in the structural mechanisms by which the brain performs its integral functions: the firing of nerves; the actions of anaesthesia, neurotransmitters and other drugs; the sensory interpretation and organised signalling that is central to the vast neural network that we identify as our *self*.

1.2 The classical brain

Neuroscience has made great strides in understanding how the brain works. However, if our model of the brain were already fully realised there would be no need to investigate whether quantum theory might offer any insights [27]. The question of how the brain works is, to state the very obvious, complicated. On one level it is a matter of *matter*, the network of cells and signalling processes that constitute the central nervous and related systems. But there is also the question of how this physiology gives rise to the phenomenon of consciousness. While advances in imaging techniques have resolved some of the structure of the brain, new discoveries are still being made [28]. Recently, previously unheard of lymphatic vessels were discovered in the meninges of the brain, suggesting a link between the central nervous system and the immune system and prompting research into their role in neurodegeneration [29, 30]. Even less well understood is the relationship between structure and function and to what extent functional connectivity, or an understanding of the mind, can be explained by the basic anatomy of the brain [31–34].

1.2.1 Brain organisation

The central nervous system is made up of the brain and the spinal cord [35]. The human brain is a complex organisation of neural tissue, with approximately 86 billion neurons [36]. While neurons are responsible for the electrical activity of the brain they are supported by glial cells, which have a number of functions [37]. Brain matter consists of both grey and white matter, where the former is mainly cell bodies and the latter is predominantly made up of myelinated axons that allow for the transport of signals and the connectivity of the different brain sections [38]. The brain is a network, dependent on the complex interaction of its different constituent parts, thus the assignment of specific function to specific region is a simplification. Nevertheless, for classification purposes it is often divided and subdivided into a number of regions [35].

1.2.2 Neural action

Nerve cells, the main constituents of the central nervous system, are elongated cells consisting of cell body, dendrites and axon [35]. A complex network of neurons throughout the body allows for the propagation of information that is facilitated by the firing or not firing of neurons, the measure of a neuron's action potential [35]. The biophysical mechanism of action potential in neurons is conventionally understood through the work of Hodgkin and Huxley [39]. In order for a neuron to fire the resting potential must be raised to the requisite threshold potential. This is mediated by the gradient of electrically charged ions distributed across the cell membrane [35, 39]. Communication between neurons is integral to their ability to convey information. There is still some contention as to exactly how nerves communicate, with evidence for both chemical and electrical signal transmission [40]. This thesis will focus on the former, where neural communication is mediated by the release of neurotransmitters. When an action potential propagating along a neuron reaches the axon terminal it triggers the opening of voltage gated ion channels which in turn stimulate exocytosis, or the release of neurotransmitters into the synaptic cleft [41]. These neurotransmitters diffuse across the synaptic cleft and bind to special receptors on the dendritic spines, opening other ion channels. Ions can now enter this nerve cell and change the membrane potential, potentially generating an action potential in the post-synaptic nerve cell [41]. While this is a simplistic model of the action of

neurons it serves as a means to locate the quantum effects discussed in the next section. Although neurons have a number of constituent parts, those important in the context of this introduction are as follows. Microtubules, as the location of effects described in theories of consciousness as well as coherent quantum transport. Mitochondria, as the site of electron transport processes. The axon, as mediator of electrical signals and possible site of biophoton transfer. A basic understanding of the synaptic mechanism will also be beneficial to the discussion of both quantum effects in neurotransmission as well as the neural action of Posner molecules. For a detailed illustration of the salient constituents of a nerve cell see Figure 1.1.

1.2.3 Consciousness

While this thesis is preoccupied with the simpler question of structure, that is, the quantum physics of certain physiological mechanisms in the brain, it does include some theories as to how this physiology manifests as consciousness. Biology based attempts to explain consciousness include identifying its neural correlates by means of neuroimaging methods which study the changes in neural activity between conscious and unconscious states as well as altered states of consciousness [42–47]. A formal description of consciousness, given the difficulty of quantifying its subjective experience, would likely borrow from complex network theory as well as disciplines ranging from physics to philosophy [31, 48–52]. The question is still open as to whether quantum physics has something to add to the debate.

1.3 Non-trivial quantum effects

In 1913, Bohr presented his model of the atom where, in contrast to classical orbits, electrons occupied discrete energy levels. This followed quickly on the heels of Planck's advances in understanding blackbody radiation and Einstein's explanation of the photoelectric effect which, along with Compton's work with X-rays, ushered in the new era of quantum mechanics [6, 7]. Fundamentally, all biology can be described as being quantum mechanical in the same way that all matter is quantum mechanical. However, the aim of this thesis is to investigate non-trivial quantum effects in biological systems, to widen the scope of quantum theory to include biological mechanisms and not merely the description of their constituent atoms. Quantum weirdness is

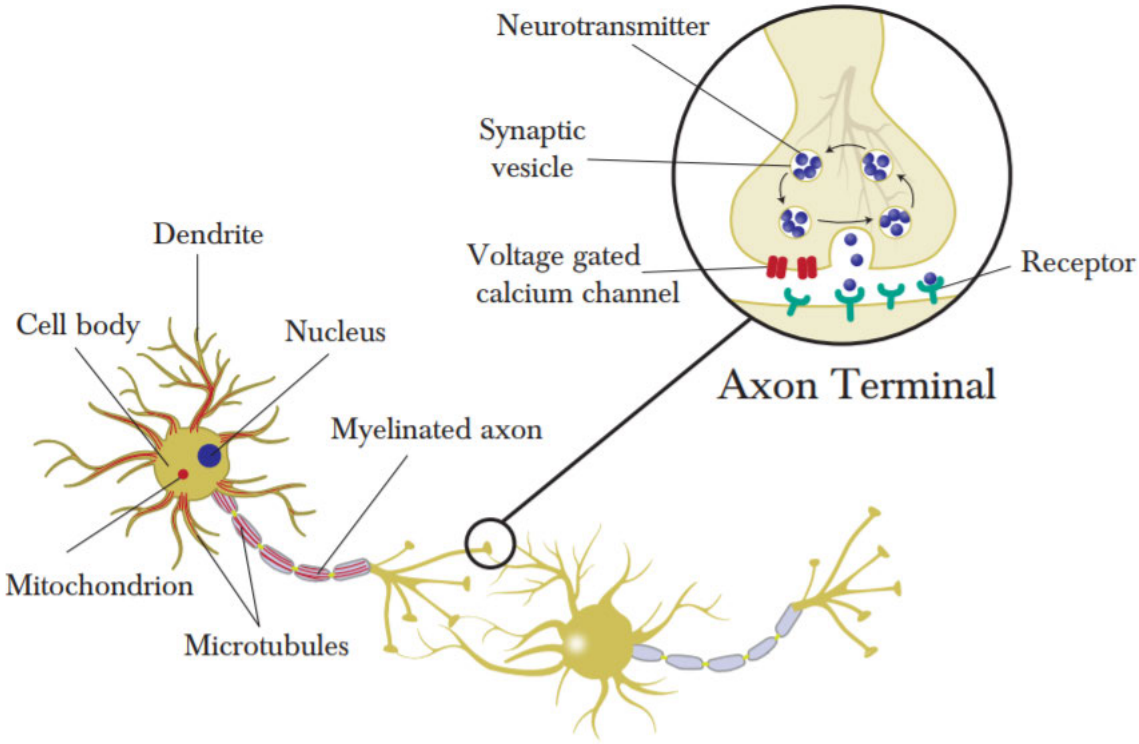

Figure 1.1: The basic structure of a nerve cell. Although a number of the organelles are missing this simplified schematic is sufficient to gain some understanding of the location of the various quantum effects discussed in this thesis. Of interest are the microtubules which occur in different arrangements throughout the nerve cell and the mitochondria, which will be discussed in the context of electron transfer. The myelin insulated axon has also been proposed as a wave guide for neural photonics. The meeting of dendritic spine and axon terminal at the synaptic cleft is enlarged for clearer understanding of the mechanism of neurotransmission and the transfer of neural signals. Synaptic vesicles, which are located at the synapses, are also the site of the proposed uptake of Posner molecules – and production of free calcium – during endocytosis.

the subject of much fascination [53]. First Planck and Einstein demonstrated that radiation, normally understood as behaving like a wave, can also behave like a particle [6,7]. De Broglie then suggested that matter, which seems discrete, can sometimes show wave-like effects such as interference [6,7]. Despite being famous for its uncertainty, the formalisation of the theory has proved extremely successful in describing the behaviour of microscopic systems. The mathematical framework of quantum mechanics associates a physical system with a quantum state that contains all possible information on the system. What is interesting is that within this framework, for two quantum states describing a system, a linear combination of these states also describes the system [6, 7]. It is this that gives rise to the uniquely quantum effect of superposition states, one of the non-trivial effects discussed in this thesis. The concept of quantum coherence, which quantifies the relationship between states in a superposition, is investigated in various biological contexts, as is entanglement, the non-classical correlation between different quantum states [1]. Entanglement is often discussed with reference to quantum spin, the property of elementary particles that determines their behaviour in a magnetic field [6, 7]. Electron tunnelling is also raised as a potential candidate for quantum effects in biological systems. An explanation of tunnelling follows from the probabilistic description of quantum mechanics which allows the possibility of a quantum particle passing through a classically forbidden potential barrier [6, 7]. This thesis is particularly focused on inelastic tunnelling, in which the tunnelling electrons are coupled to vibrational modes in their biological context [18]. For a summary of these non-trivial quantum effects and their implementation in a neural context see the table given in Figure 1.2.

1.4 Quantum effects in neural processes

It is perhaps misleading to talk about quantum processes in the brain. Nerve cells extend throughout the body. The quantum processes discussed in this thesis are not confined to the brain but take place within neurons and at synapses. They are therefore implicated in the biological functioning of the entire body. It might be more accurate to describe these effects as quantum enhanced neural processing.

Quantum processes and their neural manifestations

Quantum process	Coherent energy/charge transfer	Entanglement	Quantum spin	Inelastic tunnelling
Neural manifestation	Energy/charge transfer in microtubules and possibly mitochondria General anaesthetic Biophotons	Radical pair and reactive oxygen species Posner qubits	General anaesthetic Radical pair and reactive oxygen species Posner qubits	Neurotransmitters GPCRs

Figure 1.2: Non-trivial quantum effects and their neural context. Quantum spin and entanglement in the neural context are discussed in Chapter 3. Inelastic tunnelling in G-protein coupled receptors (GPCRs) and related receptors is discussed in Chapter 4.

1.4.1 Orchestrated Objective Reduction

Orchestrated objective reduction (Orch OR), the application of quantum mechanical formalism to the question of consciousness, was proposed by Stuart Hameroff and Roger Penrose in the 1990s [22, 54, 55]. In his 1989 book *The Emperor's New Mind: Concerning Computers, Minds and The Laws of Physics* Penrose addresses the possibility that the laws of classical physics are not sufficient to explain the phenomenon of consciousness, suggesting instead that quantum physics might be integral to this explanation [21]. His hypothesis initially lacked a biological context in which these quantum effects might occur. Hameroff, an anaesthesiologist by training, had been previously interested in microtubules and suggested that they could be a contender in which to situate a quantum model for consciousness. Hameroff and Penrose have subsequently collaborated on developing and refining the theory of Orch OR, by which quantum computations in microtubules influence neural firing and by extension constitute the neural manifestation of consciousness [22]. Microtubules in general have elicited interest from various researchers attempting to model quantum effects in the brain.

Microtubules

Microtubules are formed by the polymerisation of tubulin dimers, which consist of α and β tubulin proteins. Tubulin dimers first form longitudinal protofilaments; 13 of these protofilaments then form a microtubule with diameter of approximately 25 nm [22]. Microtubules form part of the cytoskeleton of eukaryotic and some prokaryotic cells and contribute to cellular shape and structure. They have a variety of functions. They are integral to cell division, forming the spindle apparatus that mediates the division of chromosomes into daughter cells [22,56,57]. Microtubules also act as tracks along which motor proteins move cellular constituents within the cell [22, 56, 57]. Whereas microtubules are present in all eukaryotic cells the theory of Orch OR is focused on microtubules in nerve cells and in particular those found in the dendrites and cell body (soma) of these cells. This is because microtubules in axons and non-neural cells have a radial, regular arrangement that is arguably less supportive of information processing. Microtubules in the dendrites and soma are less regularly arrayed, forming what Hameroff and Penrose refer to as recursive networks well suited to learning [22, 58]. Microtubules in non-neural cells are also dynamically unstable, able to disassemble in various ways. Microtubules in dendrites and nerve cell bodies are prevented from disassembly by microtubule associated proteins, rendering them more stable and able to encode the long-term information necessary to the theory of Orch OR [22, 59, 60]. The specific composition of tubulin has also lent strength to quantum models of neural processing due to the fact that it is partially composed of chromophores such as tryptophan, arranged in a manner similar to photosynthetic systems in plants and bacteria [61,62], which have been surmised to support coherent quantum effects.

The quantum model of Orch OR

Hameroff and Penrose hypothesise that quantum computations encode information in microtubules and objective reduction is how this quantum information results in a classical output. The details by which Penrose's conception of quantum gravity gives rise to the objective reduction of the quantum wavefunction are beyond the scope of this introduction. In this case Hameroff and Penrose's 2014 review of the theory is instructive [22]. The choice of microtubules, and more specifically tubulin dimers, as the biological context in which Orch OR takes place has been motivated by various reasons. It has

been suggested that the manifestation of consciousness is not axonal firing but rather the signal integration that occurs in the dendrites and cell bodies of nerve cells. This is given some support by the fact that gamma wave synchrony, which has been suggested to be the neural correlate of consciousness, is generated by dendritic-somatic integration potentials [22, 63]. As outlined above, microtubule arrangement in the dendrites and cell bodies of nerve cells is suitable for information processing, making them a good contender for the biological site of consciousness [22, 58, 60]. The localisation of Orch OR in microtubules also offers a way to model a biological qubit, which is integral to the quantum nature of the theory. A qubit, the basic unit of quantum information, is a two-state system that can exist in a superposition of both states at the same time. Initially Hameroff and Penrose proposed that tubulin dimers might exist in a superposition of mechanical conformations coupled to London force dipoles [22, 55, 64]. More recent iterations of the theory locate the quantum description firmly in the constituent aromatic rings (phenylalanine, tyrosine and tryptophan) that make up the tubulin proteins [22]. These have pi orbital electron clouds that demonstrate spatial delocalisation, giving rise to London force electric dipoles, that can exist in superposition. While Orch OR was originally formulated with electric dipoles in mind, the authors now propose magnetic dipoles related to electron spin [22].

Discussions around Orch OR

This section gives only a basic overview of the theory of Orch OR as a means to introduce the idea of quantum models of the brain and their biological sites of action. There have been a number of objections raised against Orch OR, the details of which are given in Hameroff and Penrose's 2014 review [22]. Those responses that deal with the structural viability of quantum effects in the brain are briefly addressed in this section. The problem of decoherence is an issue commonly cited against the application of quantum theory to biological systems. Quantum mechanics is conventionally applied to isolated systems at low temperatures whereas biological systems are typically described as being warm, wet and messy [1]. In 2000 Max Tegmark addressed the question of decoherence in the context of Orch OR, concluding that calculated decoherence time scales of 10^{-13}–10^{-20} seconds are much too short for quantum effects to play any role in cognitive processes [65]. Hagan *et al.* responded to this by asserting that Tegmark had based his calculations on a

model that did not closely resemble the one they had proposed. After recalculation for a more accurate model they conclude that decoherence times are closer to 10^{-5}–10^{-4} seconds [66]. With the development of quantum biology the question of whether quantum mechanics can contribute any meaningful insight into the functioning of biological organisms has shifted towards a positive answer. In particular the study of photosynthesis has revealed that the efficacy of energy transfer and charge separation might be enhanced by quantum effects [8–13]. Thus the decoherence argument against Orch OR perhaps holds less weight than other evidence contradicting the theory.

There has been some argument over the lattice arrangement of tubulin dimers in microtubules, which can be of two types: A and B. The predictions of Orch OR favour type A whereas actual mouse brain tissue points to the predominance of type B. Proponents of Orch OR argue that this does not necessarily discount the theory as quantum effects may only occur in that fraction of microtubules that are geometrically suitable [22, 67]. Objections by McKemmish *et al.* include the proposed conformational switching of the tubulin proteins that constitute the biological qubit [68]. They note that the theory demands significant changes in tubulin structure and that any processes that might drive these conformational changes would be metabolically expensive [68]. More recent reformulations of Orch OR do not require such extreme conformational switching and the different states necessary for the qubit can be achieved through superposed electric or magnetic dipoles in aromatic rings [22]. McKemmish *et al.* also note that the electrons in a single aromatic ring cannot exist in superposition states, being completely delocalised [68]. This can be incorporated by considering the electron clouds of two or more rings [22]. Reimers *et al.* take issue with the possibility of strong Fröhlich condensation in microtubules [69]. They explain megahertz coherence demonstrated in microtubules by Pokorný [70] as being due to weak classical Fröhlich condensation. They go on to suggest that as Orch OR involves coherent strong Fröhlich condensation the theory is flawed [69]. Hameroff and Penrose respond by citing experimental evidence of the discovery of gigahertz, megahertz and kilohertz resonance in single microtubules. They argue that the experimental evidence argues strongly in the favour of Orch OR [22, 71, 72]. Other criticisms have been aimed at the objective reduction part of the theory, and the way in which this translates into consciousness. These have been addressed in detail by Hameroff and Penrose [22].

Microtubules as a site for quantum effects

While Orch OR theory is not without controversy, the suitability of microtubules as a site for quantum effects has given rise to a number of related approaches. It seems probable that neuronal microtubules are indeed implicated in consciousness and cognition. This is supported by the fact that certain chemicals that influence both consciousness as well as cognitive function, such as general anaesthetics and antidepressants, involve microtubules [22, 73, 74]. The proposed quantum action and alternative biological sites of processes related to both anaesthetics and antidepressants will be discussed in the subsequent sections. Craddock *et al.* suggest an additional way in which microtubules might play a quantum role in neural processing. They take, as a comparative example, evidence of quantum beats in the light-harvesting complexes of plants and bacteria [8]. They then suggest that the tryptophan residues present in the tubulin proteins that constitute microtubules are structurally and functionally capable of supporting the possibility of quantum coherent energy transfer [61]. More recent experimental evidence by Kalra *et al.* demonstrates that not only are microtubules efficient light harvesters but that anaesthetics have an effect on these light-matter interactions [75]. The details of this research will be discussed further in the context of transfer processes.

1.4.2 Quantum models of general anaesthesia

One of the ways in which we might understand the mechanism of consciousness or, less ambitiously, the details of neural processes, is by looking at chemicals that disrupt these processes. As Luca Turin puts it, 'the only thing we are sure about consciousness, is that it is soluble in chloroform' [76]. To this end the study of general anaesthetics has offered some way of structuring research into quantum neural processing. There are a few theories as to how quantum effects are implicated in the action of general anaesthetics. One of these follows from the investigation of possible quantum effects in microtubules, initiated by Hameroff and Penrose's Orch OR theory [77]. Another looks at spin changes in anaesthetised fruit flies [78]. Both of these are preoccupied with the possibility that anaesthetic action disrupts electronic activity, a theory that first made its appearance in the 1980s [79–82]. There is also some suggestion that the nuclear spin of anaesthetic molecules might influence their efficacy [83].

The action of anaesthetics in tubulin proteins

Craddock *et al.* argue that understanding general anaesthetics as having a network [84] or synaptic based effect [85] does not explain how anaesthetics inhibit the cognitive abilities of simple single celled organisms such as slime moulds [86, 87]. The fact that this cognition is linked to cytoskeletal microtubules points to a possible site for the action of general anaesthetics [77,88]. There is some uncertainty concerning the exact biological location targeted by anaesthetics. The Meyer-Overton rule links the potency of anaesthetics to their increased lipid solubility. Further research suggests that anaesthetics act in lipid-like hydrophobic regions in proteins [77].

Anaesthetics bind to a number of membrane and cytoplasmic proteins [89–91], Craddock *et al.* propose that tubulin, the protein subunit of microtubules, seems the most likely due to the fact that gene expression after exposure to anaesthetic compounds is concentrated on microtubule dependent functions [77,92]. The quantum mechanism by which anaesthetics operate in microtubules is based on a number of theoretical observations. The application of quantum theory to biological systems has been particularly successful in the context of energy/charge transfer processes in photosynthesis.

Photosynthetic complexes harvest light and then transfer this excitation energy to reaction centres at which charge separation takes place [1]. This transfer was initially assumed to take the form of semiclassical hopping between discrete energy levels of chromophores bound to protein scaffolds. However, in the past few decades, with the advent of experimental techniques such as two-dimensional electronic spectroscopy, research suggests that this energy transfer has wavelike characteristics, with energy delocalised over more than one chromophore at a time [1, 8]. For a simple schematic illustrating the principle see Figure 1.3.

Although not without controversy, experimental observation of cross peaks that oscillate in time has been interpreted as evidence for coherent energy transfer [93,94]. Building on research that tryptophan rings arranged favourably in tubulin proteins can act as quantum channels supporting coherent electron dynamics in a manner similar to photosynthesis [61, 95, 96], Craddock *et al.* argue that anaesthetic gas molecules binding in these channels inhibit quantum effects and disrupt coherent energy transfer and that this is

responsible for the effects of general anaesthetics on consciousness [77, 88]. In a later paper Craddock *et al.* expand their theory to the prediction of anaesthetic potency. They argue that anaesthetic and related gases change collective terahertz dipole oscillations in a way that predicts the potency of their action [97]. While much of this work has been theoretical, exciting new experimental results by Kalra *et al* show that microtubules demonstrate quantum-like energy transfer which is disrupted by the administration of anaesthetics [75].

Quantum spin and general anaesthetics

In his early research relating to quantum biology, Turin hypothesised that the sense of smell, understood classically as a lock-and-key mechanism, might instead be better explained by quantum theory [98]. More recently he has addressed the common thread between the very different molecules that act as general anaesthetics. Turin's theory is that anaesthetic molecules perturb electron currents in their target proteins [78]. The molecules that comprise the group of general anaesthetics range from the structurally simple noble gas xenon to the much more complex molecule alfaxalone, a range that includes numerous other chemicals without any apparent similarities. It is this structure-function anomaly that is motivation to look at the underlying physics of anaesthetics [78, 99]. Being that it is structurally the simplest of the anaesthetics, more than one attempt has been made to understand the anaesthetic action of xenon.

In a recent paper Li *et al.* examine the differing anaesthetic effects of xenon isotopes. Xenon has nine stable isotopes. Seven of these have zero nuclear spin but xenon 129 has a nuclear spin of $\frac{1}{2}$ and xenon 131 of $\frac{3}{2}$ [83]. In their experiment Li *et al.* compare the loss of righting reflex in mice, which correlates with consciousness, under the influence of the different isotopes. In order to exclude electronic effects they also calculate the polarisabilities of the different isotopes, finding them to be undifferentiated. Their results demonstrate that xenon isotopes with non-zero nuclear spin have a lower anaesthetic effect. As the results do not show a correlation between anaesthetic effect and atomic mass they conclude that the differences must depend on the value of the nuclear spin. Although the details of the mechanism are not clear the authors hypothesise that as spin half particles have been shown to be better suited to quantum entanglement, perhaps entanglement pro-

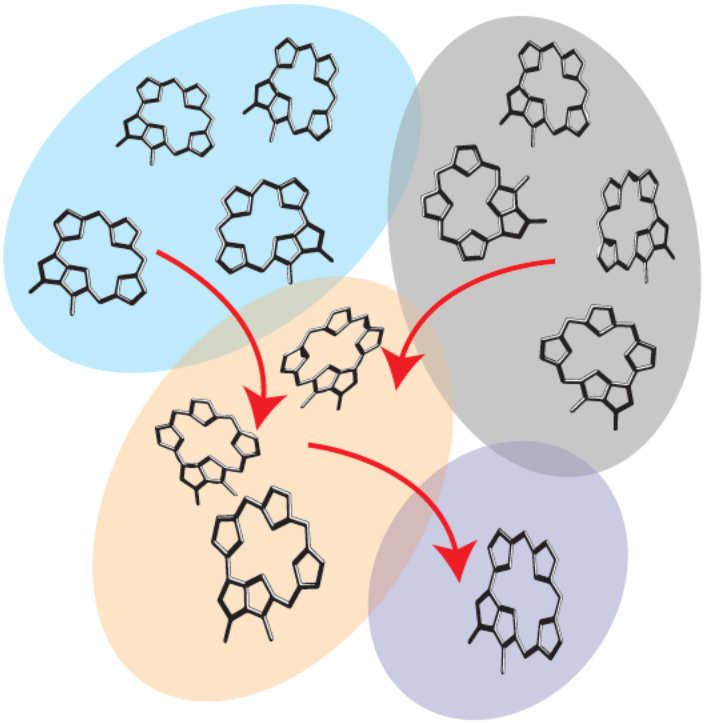

Figure 1.3: A simple illustration of resonant energy transfer in, for example, photosynthetic light-harvesting complexes or the tryptophan rings of microtubules. Chromophores over which the energy is delocalised are clustered by colour, and within these clusters coherent energy transfer occurs. Between clusters energy is transferred incoherently.

motes consciousness in opposition to the effects of anaesthetics [83]. Their results recall research done by Fisher *et al.* into a possible mechanism by which neural entanglement might proceed [100–102]. Of particular interest here perhaps are the isotope-dependent effects of lithium, another drug that alters conscious experience [100]. In order to investigate whether quantum physics plays any common role in their mechanism of action Turin *et al.*

also focus on the physics of the xenon atom. In 1989 IBM used a scanning tunnelling microscope to manipulate 35 xenon atoms on a nickel surface into spelling out the IBM logo; where the xenon atoms extend the conducting surface of the nickel [103]. In a similar manner, Turin *et al.* suggest that general anaesthetics might bind to sites in central nervous system proteins in a way that bridges the gap between electron donors and acceptors. Xenon atoms, for example, could extend the highest occupied molecular orbit (HOMO) of the protein they interact with, facilitating electron transfer [78].

In order to detect these currents in a whole living organism Turin *et al.* conduct an electron spin resonance (ESR) experiment using anaesthetised fruit flies, looking for increases in the total spin which could indicate an increase in unpaired electrons. ESR exploits the fact that unpaired electrons in an external magnetic field can occupy two possible spin-dependent energy states that are proportional to the field strength. Discounting free electron spin signals from melanin pigments the results of the experiment lead them to conclude that general anaesthetics cause a change in spin. Further support for the hypothesis is offered by the fact that spin changes differ for anaesthetic resistant flies [78]. In addition to this, using density functional theory they demonstrate that chemicals which display similar but less exaggerated central nervous system effects to anaesthetics, also extend the highest occupied orbital momentum but to a lesser degree. They conclude, however, with a degree of caution as to what exactly is the principle behind observed changes in spin: change in total spin or change in spin polarisation [78].

While electron spin changes under the influence of general anaesthetics points towards a possible quantum mechanism, there is still some scepticism as to whether the experimental evidence is sufficient proof of principle. Turin *et al.* themselves note that the spin changes could be due to melanin. Although they checked their results against flies deficient in one of three possible melanins, they concede that particularly neuromelanin, the grey in grey matter, might play a role [78]. This is potentially interesting in the context of recent research investigating the quantum role of neuromelanin facilitated electron transport in sections of the brain [104]. Turin *et al.* also document the fact that the experiment was performed under distinctly unphysiologic conditions. In order for the flies to remain immobile and not disturb the readings they were kept at 6 °C. Although some temperature variation was tested this was only between 2 °C and 10 °C. In addition to this the flies

were kept in anoxic conditions to isolate the effects of anaesthetic gases from those of oxygen. The potential role of oxygen in the experimental results points to the involvement of respiration, more specifically the movement of electrons in the electron transport chain of mitochondria [105]. Turin *et al.* cite a number of instances in which it has been shown that mitochondria are involved in the action of anaesthetics [78, 106–108]. In a more recent collaboration with Turin, Gaitanidis *et al.* invite speculation on an unpublished preliminary report of spontaneous radiofrequency emission from fruits flies subjected to a magnetic field. They suggest that these emissions originate from the nervous system due to the fact that they stop under the influence of chloroform anaesthetic and that they are related to spin-polarised electron currents in cells. The authors note that these cellular currents could reflect mitochondrial metabolism but that the variable signal and reaction to anaesthetic suggests some more complex biological activity connected to neuronal activity [109].

The outlook on quantum models of general anaesthesia

While the comparison of electron dynamics in photosynthetic and microtubule proteins is largely theoretical the authors suggest its experimental verification is possible via two-dimensional electronic spectroscopy, a technique well established in the analysis of photosynthetic systems [1]. They propose that quantum beating in tubulin will be altered under the influence of anaesthetics and that this is a measurable phenomenon [77]. While this has yet to be attempted there has been some recent experimental work investigating the possibility that quantum effects play a role in the action of anaesthetics. Using entangled as well as classical two-photon spectroscopy, Burdick *et al.* report that, in contrast to nonhalogenated ethers, halogenated ethers interact with entangled photons of specific wavelength [110]. They motivate the research by citing the fact that nerves have been shown to interact with light and biophotons have been identified in neural cells and thus the optical properties of molecules that act on nerves might be of interest. Ethers, both nonhalogenated and halogenated, act as general anaesthetics. Burdick *et al.* use Raman spectroscopy of sevoflurane and isoflurane, to demonstrate that these halogenated ethers have many vibrational modes in the low frequency shift region which would allow for their interaction with entangled light. They emphasise, however, that this does not necessarily have anything to do with their anaesthetic properties as nonhalogenated di-

ethyl ether, which does not interact with entangled light, also acts as an anaesthetic [110].

1.4.3 Neurochemical binding and activation mechanisms

For the purposes of this thesis the term neurotransmitter is used with respect to a variety of neurochemicals that fall into this category, binding to neuroreceptors and modulating neural signalling. Neurotransmitters emitted by one nerve cell bind to receptors on an adjacent nerve cell and facilitate the opening of ion channels [35]. This is fundamental to the generation of action potentials and disruption of this process is believed to contribute to mental illnesses [111, 112]. Although the focus here is on the action of neurotransmitters it has been suggested by Vaziri *et al.* that the mechanism by which ion channels allow the selective transmission of ions might also not be strictly classical, showing evidence of quantum coherence [113]. The binding action of neurotransmitters is conventionally understood as a lock and key mechanism whereby the shape of the neurotransmitter matches its specific receptor [328, 333]. The lock and key or docking mechanism is implicated in a number of biological processes: neurotransmission [328]; the action of enzymes [116]; olfaction [117]; DNA binding [118], all depend to some extent on lock and key theory. Despite the success of the theory however, an alternative view suggests that something more than molecular shape might be necessary to explain olfaction and, more recently, neurotransmission.

Lock and key or quantum vibration

Neurotransmitters are a class of molecules that bind to G protein coupled receptors (GPCRs). GPCRs are a group of receptors that, upon detection of appropriate molecules known as ligands, activate signalling pathways in cells [119]. GPCRs play an important role in medical innovation, as targets for drug action [120]. In addition to neurotransmitters, there are a number of biological molecules that bind to GPCRs; these include odourants [121]. Olfaction is classically understood as depending on the respective shapes of the chemical/receptor pair. However, an alternative vibrational theory of olfaction was first developed by Dyson as long ago as the 1930s [18, 122]. In his 1996 paper Turin suggested that the vibrational frequency of a given odourant contributes to quantum tunnelling at the receptor [98]. In 2011

Franco *et al.* presented experimental evidence in support of the theory. In particular they claimed that fruit flies could differentiate between deuterated odourants [123]. There is also some evidence that more complex species such as lake whitefish and the American cockroach can differentiate between isotopes of amino acids and pheromones [124–126]. Horsfield *et al.* document a number of experiments that test the theory on both the behavioural and physiological level [18]. Deuterated odourants are a useful means to test the vibrational theory of receptor activation due to the fact that replacing hydrogen by deuterium shifts vibrational modes, for instance to the 2150 cm^{-1} vibration of the carbon-deuterium bond [18, 127, 128]. However, there has also been some recent discussion as to the fact that a differential olfactory receptor response between undeuterated and deuterated odourants could in fact be due to a minute contaminant in one of the samples [128]. Paoli *et al.* conclude that although their results do not prove the vibrational theory of olfaction they also do not disprove it, merely calling for caution in experimental approach [128]. While there is little verification for a vibrational olfactory mechanism in mammals, a number of the experiments support the theory for the case of insects. It should be noted, in a discussion of GPCR mechanisms, that insect olfactory receptors differ from mammalian G protein related olfactory receptors and thus experimental results may not be generalisable [18].

While the theory remains controversial it has recently been re-examined in the context of neurotransmission. A number of different neuroreceptors have been investigated. Adenosine receptors are rhodopsin-related G protein coupled receptors that bind the neuromodulator adenosine, but can also bind a variety of other agonist and antagonist molecules [129]. The stimulating action of caffeine, for instance, is due to its antagonistic binding to adenosine receptors [130]. Because GPCRs are such an important target for pharmaceutical intervention the classification of molecules that act as agonists or antagonists is a well-developed research field. Molecules can be classified using various molecular descriptors which include information from molecule structure, topology and geometry, to dipole moment, electric polarisability and electrostatic potential [129]. Following on from the fact that adenosine receptors and olfactory receptors are both class A GPCRs, Chee and Oh present research that tests whether vibrational frequency might also be an effective molecular descriptor. They suggest that classifying ligands by vibrational frequencies is an effective way of discriminating agonist from antagonist [129]. Chee *et al.* then refine this research using a machine learning

approach and conclude that selected features of molecular vibration allow for ligand classification of adenosine receptor agonism [131].

Whereas Chee *et al*'s research investigates adenosine receptors Hoehn *et al.* focus in particular on the neurotransmitter serotonin and its receptors [124, 132]. Although it has a number of other functions in biological systems serotonin is perhaps most well known for the role it plays in mood. A widely prescribed class of antidepressants, the SSRIs (selective serotonin reuptake inhibitors) target this neurotransmitter [133]. In their research Hoehn *et al.* address the possibility that serotonin neurotransmission might utilise vibration assisted inelastic tunnelling effects [124]. Using inelastic electron tunneling spectroscopy (IETS) theory that was first developed to understand olfaction they investigate the tunnelling spectra of endogenous and non-endogenous agonists that bind to the serotonin receptor. Non-endogenous agonists of this receptor include LSD (lysergic acid dimethylamide), DOI (2,5-dimethoxy-4-Iodo-amphetamine) and other psychedelic phenethylamines [124]. Their results suggest that the serotonin molecule shares an inelastic electron tunnelling spectral peak with other agonists that activate the serotonin receptor. Although the lock and key mechanism has been very successful in modelling certain aspects of the action of signalling proteins one of the ways in which it falls short is the prediction of agonist potency. In addition to the shared spectral peak of related agonists Hoehn *et al.* also report that the intensity of this peak might be used as a predictor of agonist potency [124].

Experimental probing of the vibration assisted tunnelling hypothesis

Experimental investigation of the vibrational theory of neuroreception follows the lead of Franco *et al.* in the context of olfaction, where the effects of deuterated odourants are investigated [123]. Hoehn *et al.* report the results of an experiment to test the feasibility of their theoretical approach by measure of receptor affinity and activation. Once again, agonists of the serotonin receptor were chosen, specifically 2,5-dimethoxy-4-iodoamphetamine (DOI) and N,N-dimethyllysergamide (DAM-57). However, the experiment failed to confirm the vibrational theory of neuroreception as they report that selective deuteration had no influence on binding affinity or activation [132].

In another study regarding the binding mechanism of the neurotransmitter histamine, authors Kržan *et al.* report a significant distinction in the binding patterns of histamine and its deuterated counterpart, as well as for other agonists of the histamine receptor [134]. In particular they found that deuterating histamine increased its binding affinity. They discuss this in the context of the vibrational theory of olfaction and GPCRs more broadly. Instead of confirming the theory they propose an alternative reason for the fact that experiments suggest that animals can differentiate between deuterated odourants, concluding that it is a nuclear quantum effect governed by differences in the strength of hydrogen bonds before and after deuteration [134]. In contrast to this, theoretical work comparing the structure-activity/vibration-activity relationship of the histamine receptor and its various ligands suggests that molecular vibration does play some role in ligand function. In the study 47 ligands that bind to histamine receptors were investigated using a computational approach to molecular vibration. This led to the conclusion that the many varying agonists and antagonists can be to some extent classified by their molecular vibrations [135].

The functional mechanisms of GPCRs in general

The lack of experimental verification for vibrational quantum effects in the context of central nervous system GPCRs prompts Hoehn *et al.* to suggest that either olfactory receptors function differently from other GPCRs or the vibrational theory of receptor activation is wrong. Gehrckens *et al.* address the latter criticism in a recent preprint, in which they use density functional theory to investigate the electronic structure of rhodopsin [121]. They choose to look at rhodopsin rather than olfactory GPCRs due to the fact that a high resolution structure of rhodopsin is available for research purposes. Rhodopsin also shares important features with olfactory receptors and is considered the evolutionary ancestor of GPCRs [136, 137]. The main aim of their research is to demonstrate a mechanism for electron transfer in olfactory receptors. They go on to identify a tryptophan donor and zinc mediated acceptor site that would allow electron transfer in rhodopsin. The zinc ion, surrounded by a tryptophan, a histidine and a conserved glutamate, lowers the lowest unoccupied molecular orbital (LUMO) of a tryptophan side chain to below the energy of the highest occupied molecular orbital (HOMO) of the donor tryptophan, allowing for electron transfer [121]. They also emphasise the fact that this capacity for electron transfer does not necessarily

play a role in the functionality of rhodopsin. In the context of whether this effect might be generalisable to GPCRs they conclude that an electron transfer mechanism might have been exploited by the offshoots of rhodopsin, in particular olfactory receptors. They do however suggest that in this sense olfactory receptors may be unique in that they are relatively non-specific, a requirement made necessary by the novelty and variety of odourants that will bind to them. Neurotransmission, they argue, depends on a binding that is much more specific. On the subject of neurotransmitters, they hypothesise that the anomalous binding structure of the antagonist metitepine to serotonin related receptors can be explained if the metitepine is in the form of a radical, having gained an electron in binding to the receptor. This mechanism is in line with the idea that GPCRs are electronic devices rather than simply lock-and-key [121].

Both theoretical and experimental results do not offer any clear conclusions with respect to the vibrational theory of neurotransmission for adenosine, serotonin and histamine receptors and their related ligands. Further research is necessary to clarify the viability of the approach and its specific relation to the different actions of neurotransmitter binding affinity and activation capability [131]. Understanding the mechanism or mechanisms of ligand-GPCR interaction is particularly important due to the fact that GPCRs are a major drug target associated with one third of all pharmaceuticals [120, 131].

1.4.4 Alternative signalling processes and biophotons

It is perhaps interesting that GPCRs, in addition to binding with molecules such as neurotransmitters and odourants, also interact with photons [138]. There has recently been some suggestion that cellular communication and even possibly neural signalling might make use of biophotons in addition to more well established mechanisms such as neurotransmitters [139–141]. Biophotons are spontaneous ultra-weak photons in the near-UV to near-IR spectral range produced by biological systems, in particular through oxidative processes in mitochondria [141, 142]. As noted in a recent paper on the subject, it is known that biophotons are produced in brains [141]. Correlations have been found between biophoton intensity and neural activity as well as oxidative dysfunction of neural cells in rat and mouse brains [143–145]. There has even been some attempt to explain human intelligence in the context of biophoton emission. Following on from a study that demonstrated that glu-

tamate, a key neurotransmitter, can mediate biophoton production [344], Wang *et al.* examine the spectral characteristics of biophoton emission in a range of species. They conclude that there is a correlation between higher order intelligence and the spectral redshift of biophotons emitted by sample brain slices. This redshift increases in the order of frog, mouse, chicken, pig, monkey, and human, which reflects with some accuracy the phylogenetic tree, although they concede that there is no completely objective means to measure intelligence across species [147]. Their argument has met with some scepticism, with Salari *et al.* responding that the experimental results insufficiently support the hypothesis and that without a mechanistic connection between spectral shift and intelligence, their correlation is more likely to be coincidence [148].

Biophotons have been implicated in cellular signalling in plants, bacteria and even kidney cells. Following from this Sun *et al.* present experimental evidence that nerve cells can also conduct biophotons, and that this effect can be inhibited by the application of a neural conduction block anaesthetic [140, 149]. In their attempt to model the mechanistic details as to how biophotons are utilised in information transfer, Kumar *et al.* argue that neurons are well suited to photonics [141, 150]. They cite evidence that nerve cells contain possible photon sources from mitochondrial respiration or lipid peroxidation, as well as photon detectors such as centrosomes and chromophores [141, 152–155]. They then hypothesise that myelin-coated axons of nerve cells act as waveguides for biophotons and that this might facilitate quantum effects such as entanglement [141]. In order to demonstrate proof of principle the authors develop a theoretical model of light guidance in axons, solving the three dimensional electromagnetic field equations in the relevant context. They investigate a number of limiting factors and potential pitfalls and conclude that axons are mechanistically viable as waveguides. They go on to suggest various experiments in which the different aspects of their hypothesis might be put to the test [141, 150]. Experimental evidence supports the case for optical properties in axons, demonstrating directional-dependent photon propagation in myelinated axons [151].

Quantum effects in energy and charge transfer

In a review that addresses the possibility of quantum neurobiology, Jedlicka suggests that cognition, typified by complex signal processing and integra-

tion, can potentially be thought of as occurring outside of strictly neural systems and that the quantum information processing abilities demonstrated by plants and bacteria could be useful to the study of cognition in higher animals [24]. Thus far, the theoretical and experimental advances made in understanding the role of quantum effects in biological systems have been primarily to do with photosynthesis, in particular light harvesting energy and charge transfer processes [1]. As noted by Toole *et al.*, however, coherent energy transfer in photosynthesis is less a unique feature of photosynthetic systems than it is the result of the specific arrangement of chromophores within a protein [62].

Kurian *et al.* propose that biophoton production in mitochondria is absorbed and channelled via resonant energy transfer by co-localised microtubules. They argue that neurodegenerative diseases related to compromised microtubule networks could result from ineffective channelling of biophotons into signalling or dissipation. Experimental evidence shows that microtubules undergo organisational changes after exposure to photons, particularly in the absorption range of tryptophan and tyrosine [156]. As previously noted, a related paper presents a computational approach to quantum coherent energy transfer in microtubules [61]. The authors argue that similarly to the arrangements of chromophores in light harvesting photosynthetic complexes, the tubulin proteins that constitute microtubules have appropriate arrangements of chromophores such as tryptophan. They conclude that it is feasible that tubulin proteins could support coherent energy transfer in microtubules [61, 95]. This is supported by experimental results from Kalra *et al*, which demonstrate that microtubules show efficient light harvesting and energy transfer that cannot be wholly explained by classical theory [75]. In a recent related paper Celardo *et al.* extend the similarities between photosynthetic antenna complexes and microtubules by demonstrating that tryptophans in microtubules can theoretically exhibit superradiant excitonic states [96].

The possible role of tryptophans in transfer processes has also been previously addressed with respect to the action of neurotransmitters in binding to and activating GPCRs. In their investigation of rhodopsin, Gehrckens *et al.* outline a mechanism by which a tryptophan donor and zinc acceptor facilitate electron transfer [121]. Tryptophan seems particularly interesting with respect to neural processes as it is the precursor to serotonin, an

important neurotransmitter. This connection prompts Tonello *et al.* to hypothesise that the structure of consciousness emerges in a manner analogous to the serotonin dependent movement of plants towards their source of energy [157]. In neural processing this is extrapolated as biophoton harvesting by tryptophans and concomitant serotonin-mediated neural communication and plasticity [157] In a later paper Tonello *et al.* expand on this idea with the hypothesis that the gastrointestinal-brain axis in higher animals might have evolved from the root-branch axis of plants, and that light plays an important role in both systems [158].

While these ideas remain for the moment largely theoretical, much of the theory of electron transport and resonant energy transfer has focused on the involvement of microtubules. Alternatively, the role of biophoton use and energy transfer in neural processes could be furthered by a closer look at the electron transport chain of mitochondrial respiration. As previously noted, mitochondria are already implicated in the action of general anaesthetics [78, 106–108]. They are also the primary production site of biophotons [141, 142]. They might serve as an alternative biological location in which quantum effects could be investigated. Research suggests that the arrangement of chromophores in bacteria allows for quantum coherence in their photosynthetic processes [159]. Similarities between the DNA of bacteria and eukaryotic mitochondria has led to the theory that mitochondria are descended from bacteria, though recent research suggests they are less directly related [160–163].

While the ancestry of mitochondria remains uncertain their similarity to bacteria could arguably manifest in biological structures that support quantum effects. Both photosynthesis and mitochondrial respiration make use of an electron transport chain, which powers the charge gradient necessary for ATP synthesis [164]. For a simple comparison of these electron transport chains see Figure 1.4. A group of researchers from the Quantum Biology and Computational Physics research group at the University of Southern Denmark are already investigating proton-coupled electron transfer in the cytochrome bc1 complex in photosynthetic bacteria and higher organism cellular respiratory systems. The group has published a number of papers motivated by the fact that malfunctions in the bc1 complex lead to many different diseases. They also hope to better understand photosynthesis in order to optimise energy conversion research [165–167]. The reduction and oxidation of ubiquinone is

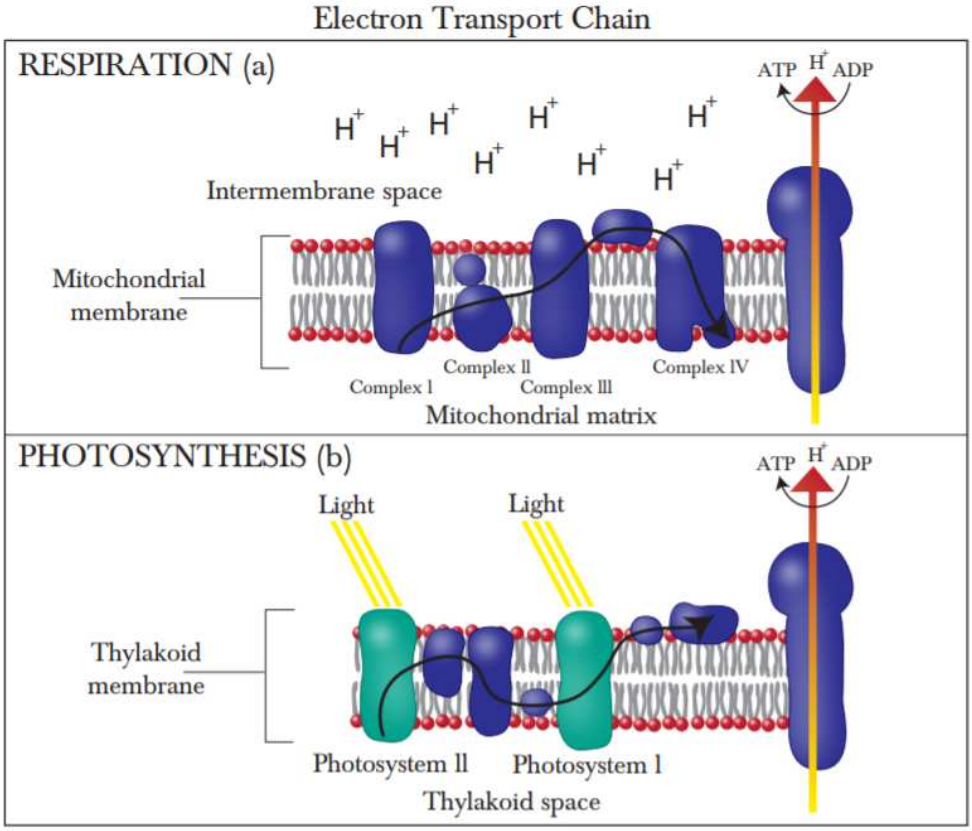

Figure 1.4: Simplistic comparison of the electron transport chains of respiration and photosynthesis. Electrons are transported through a series of complexes or photosystems, which results in the creation of a proton gradient. This is used to drive the production of ATP. While the specific complexes differ between chains they share some features relevant to the possibility of quantum effects: the presence of chromophores, for instance, which arguably support coherent energy transfer. Oxidative processes in the electron transport chain of mitochondria are thought to be the main source of biophotons. The function or target of these photons, however, is less clear. It has been proposed that microtubules close to mitochondria absorb and channel biophotons in a quantum coherent manner [156]. Mitochondria themselves also demonstrate the capacity for photon absorption, in particular complex IV in the electron transport chain, which is the target of therapeutic application of infrared light to treat disorders of the brain [169, 171, 176].

essential to the electron transfer reactions in cytochrome bc1 and the concentration of ubiquinone is particularly high in the high energy consumption environment of the brain [168,169]. There is some evidence that transcranial photobiomodulation, the application of red or near-infrared laser light to the cranial area, is an effective treatment for various brain disorders [170,171]. It has also shown promise in treating depression [172] and when coupled with ubiquinone supplementation [169]. Research suggests that, among other effects, photobiomodulation can improve attention, memory, executive function and even rule-based learning [173–175]. The mechanism of this effect is still not completely clear but the site of the effect is most likely the mitochondrial electron transfer chain, in particular the chromophores in the different complexes that constitute the chain [169, 171, 176]. Given that the role of quantum effects in light harvesting, electron and charge transfer has contributed to a better understanding of elements of the electron transfer chain in photosynthesis, this knowledge might be fruitfully applied to the mitochondrial electron transport chain.

Magnetic field effects and the brain

The role of tryptophan chromophores has been discussed with respect to energy transfer processes in microtubules. Tryptophans also play a potential role in another well established field of quantum biology: the avian compass. A leading theory of bird migration suggests that birds utilise the earth's magnetic field as a guiding tool by means of the radical pair mechanism [14, 15, 177]. The radical pair model of avian magnetoreception has been a subject of study for over four decades. However, in the past few years there has been growing interest in applying the radical pair mechanism to novel biological contexts [178–181]. For an excellent review of radical pairs in new contexts in biology, including potential radical candidates, see the paper by Zadeh-Haghighi and Simon [182]. The radical pair mechanism is conventionally summarised in three main steps. First, a photon incident on a molecule causes electron transfer and pair formation. Second, the radical pair, originally in singlet spin state, interconverts between singlet and triplet state under the influence of the nuclear hyperfine and geomagnetic Zeeman effects. And finally spin-dependent recombination leads to some signalling state that the bird interprets as a spatial directive [177]. It is generally accepted that the molecule in which this occurs is the blue light activated flavoprotein cryptochrome [183–187]. Theoretical research, backed

by spectroscopic evidence, suggests that light-activated electron transport occurs between a flavin adenine dinucleotide (FAD) cofactor and tryptophan residues in cryptochrome [177], although recent studies suggest a light-independent radical pair, which will be discussed in the context of reactive oxygen species [188, 189]. There has also been some controversy over which of the various types of cryptochromes are expressed with bound FAD and what this might mean for magnetoreception. Whereas type I animal cryptochromes, found in invertebrates, demonstrate FAD binding, type II animal cryptochromes, found also in vertebrates, do not bind securely to the photoactive flavin cofactor. Recent research suggests that in the context of avian migration, type IV cryptochromes that are present in birds are the only viable candidate for bound FAD in a physiological environment [190, 191, 305]. More recent experimental evidence suggests that radical-dependent magnetoreception can occur independent of cryptochrome, relying solely on high levels of intracellular FAD [193].

Although it is well known that a number of species have a functioning magnetic sense, humans have not yet been added to that list. In a recent paper, Wang *et al.* present the results of an experiment that demonstrates the effects of earth strength magnetic fields on the human brain [194]. The authors report that magnetic field changes result in a decrease in amplitude of alpha frequency (8-13 Hz) brain waves, an effect normally associated with the brain's processing of external stimuli. They conclude that the effect is likely to be due to ferromagnetism rather than the radical pair mechanism. This is because the effect is dependent on the polarity of the field, for subjects in the Northern Hemisphere the alpha wave response only occurs for horizontal rotations if the static component is directed upwards [194]. While this would appear to exclude the radical pair compass which is dependent on inclination, the corresponding effects would perhaps need to be confirmed for subjects in the Southern Hemisphere. It has been suggested, in the context of avian migration, that birds employ both ferromagnetism and the radical pair mechanism for navigation [15, 195–197] and this could also be true of humans' magnetic sense, the question being whether there is any evidence that might link magnetic effects in humans with the radical pair mechanism.

Cryptochrome, the proposed site of the avian compass, is also present in humans [198]. Foley *et al.* use a transgenic approach to show that human cryptochrome can act as magnetosensor in the magnetoreception of fruit

flies [199]. It is also potentially interesting that it is alpha waves that are effected by the magnetic field changes. Van Wijk *et al.* present evidence that biophoton fluctuation is correlated with the strength of alpha wave production, where they measure biophoton production in terms of the fluctuations of reactive oxygen species (ROS) [140,200]. Whereas the majority of research conducted in the context of avian magnetoreception builds on the hypothesis that the radical pair is the light-activated FAD-tryptophan pair, new research suggests that another light-independent radical pair may be responsible for magnetic effects mediated by cryptochromes [188,189]. Upon light-activation cryptochromes undergo a redox cycle: after photo-reduction and the formation of the radical pair that is conventionally assumed to be responsible for the magnetic effects observed in birds, light-independent re-oxidation results in a second radical pair. Experimental results from both birds and plants now suggest that it could be this dark state radical pair that allows for magnetic effects [188, 189], although it should be acknowledged that light is still required to set the redox cycle in motion [195]. The exact form of this pair is yet to be determined, although it has been hypothesised to involve a superoxide [188]. The involvement of a superoxide is not a new theory, having been suggested as a way to improve the sensitivity of the compass, although there is still some scepticism as to the viability of this hypothesis [201]. Experimental evidence shows, however, that illumination of cryptochrome and the subsequent redox cycle results in the formation and accumulation of reactive oxygen species [202–205]. The production of ROS and how this relates to the radical pair mechanism has been the motivation for various papers published in the field of quantum biology. Marais *et al.* outline a quantum protective mechanism in photosynthesis [206]. They hypothesise that the high spin iron in the reaction centres of photosystem II of the electron transport chain exerts a magnetic field effect that reduces the triplet yield of radical pairs that are formed during electron transfer. Triplet states are instrumental in forming ROS which are toxic to living cells [206, 207]. In another paper, Usselman *et al.* show how yields of ROS in live cells are altered by radical pair dynamics, in particular coherent singlet-triplet mixing under the influence of oscillating magnetic fields at Zeeman resonance [208]. If ROS are correlated with alpha wave production [140, 200] and ROS yields are altered by the Zeeman effect [208, 209], then this might point to a mechanism that explains the influence of geomagnetic fields on alpha waves in the human brain.

Reactive oxygen species participate in cellular signaling [210] and have been

implicated in aging and numerous diseases including mental conditions such as depression and schizophrenia [211–216]. If humans do have physiological systems that depend on the dynamics of radical pairs then it is expedient to understand exactly how these function. The avian compass is disrupted by broadband radiofrequency electromagnetic radiation that is well below the WHO-recommended level [217, 218]. This radiation might equally be upsetting the balance of ROS in other species and in turn leading to biological malfunction. Indeed, a recent study has demonstrated the cryptochrome-mediated accumulation of ROS under the influence of weak pulsed electromagnetic fields [219]. There has also been some suggestion that the radical pair mechanism is implicated in the development of cancer through circadian rhythm disruption and related ROS levels [220]. Though the threat of radical pair mediated carcinogenesis is debatable, being equivalent, as one study finds, to the risk of travelling some kilometres towards or away from the earth's magnetic poles [221]. Nevertheless, the disruption of circadian rhythms has also been linked to mood disorders and cognitive function [222–224]. Although the evidence remains contentious, there is also some documentation of the psychological effects of geomagnetic storms, which alter the earth's magnetic field for a limited period of time [225–227]. The radical pair mechanism could offer a testable hypothesis as to how these effects occur [225].

1.4.5 Neural entanglement

One of the first and strongest objections to quantum models of consciousness was the phenomenon of decoherence: that the non-ideal environment of biological systems would destroy any quantum effects before they could prove useful. As initially calculated by Max Tegmark in response to Orch OR theory, the timescales on which decoherence occurs in the environment of the brain are considerably shorter than neural firing rates of the order of 10^{-3}–10^{-4} seconds [65]. This conclusion has subsequently been challenged not simply by researchers interested in Orch OR, but also by the development of the field of quantum biology. If quantum effects play a role in photosynthesis and possibly other biological contexts, then it is not such a stretch to consider that they may play a role in neural processes, at the very least in processes similar to photosynthesis, such as coherent transfer in microtubules. Decoherence, it has been argued, might even enhance energy transfer [228]. Research suggests that long-lived coherence in photosynthetic systems lasts

Timescale	Biological context
Picoseconds	Coherent transfer in photosynthesis/microtubules
Microseconds	Coherent electron spin dynamics (RPM)
Milliseconds	Approximate neural firing rates
Seconds to hours	Coherent Posner spin dynamics

Table 1.1: Timescales for different biological phenomena.

for picoseconds [229]. The coherence lifetime of the radical pair mechanism is discussed in terms of milliseconds though attempts to measure or compute this lifetime put it closer to microseconds [177, 230, 231]. It seems unlikely that coherence in biological systems extends beyond these timescales. This suggests that coherence would probably not play a role in the explicit firing of nerves and corresponding cognitive states. However, a new hypothesis concerning neural entanglement proposes coherence that could last for hours or even days [100]. For a simple comparison of timescales see Table 1.1.

Entangled Posner molecules

The hypothesis is this: that phosphorus nuclear spin might function as a neural qubit to allow for quantum processing to play a role in cognition [100–102]. Following on from the proposal by Hu and Wu, that consciousness is linked to quantum spin [232], Fisher argues that the spin-half phosphorus nucleus seems the only likely candidate for this role due to the fact that for any nucleus with spin greater than half, the electric quadropole moment means quicker decoherence due to electric field interactions in addition to the slower decoherence caused by the magnetic fields of nearby nuclei. Spin-half nuclei are thus more favourable in terms of decoherence times. Out of the various elements and ions that play an essential role in biological systems, only hydrogen and phosphorus have spin-half nuclei. Fisher goes on to describe the details of how the quantum information carried by phosphorus nuclei is created and preserved [100–102].

Phosphorus is bound into phosphate or polyphosphate ions such as pyrophosphate. Phosphate ions constitute part of the adenosine triphosphate (ATP) molecule, an organic chemical that acts as a source of energy for the many essential actions that sustain living organisms [100, 233]. The electron trans-

port chain in both photosynthesis and respiration creates a proton gradient in order to drive ATP production. Fisher postulates that when adenosine triphosphate is hydrolysed to adenosine monophosphate and pyrophosphate the two phosphorus nuclei in the pyrophosphate ion will have a specific spin alignment, either a singlet or one of three triplet states. A quantum mechanical treatment of the enzyme catalysed reaction that creates two phosphate ions out of pyrophosphate demonstrates that this reaction depends on the nuclear spin state. More specifically, the enzyme conditional outcome of the reaction, where the spin dynamics of the triplet states are unfavourable, mean that the phosphorus nuclear spins in the two distinct phosphate ions will emerge in a singlet entangled state [100].

Coherence timescales for Posner molecules

Phosphorus in the phosphate ion is surrounded by an oxygen cage, where the oxygen nuclei all have zero spin. Despite this the coherence time is still very short for solvated phosphates, approximately one second, due to the fact that hydrogen quickly binds to phosphate and the non-zero proton spin contributes to decoherence. A coherence lifetime of a second is long enough for the quantum effects to be sustained over the process of cellular diffusion [100]. However in order for effects such as memory storage and retrieval to utilise quantum effects, coherence lifetimes need to be significantly longer. Fisher argues that if binding with the hydrogen can be pre-empted by a spin zero cation such as calcium, then longer coherence times might be possible. He identifies a possible molecule as the Posner molecule [234], thought to be involved in the formation of hydroxyapatite, an important constituent of bone tissue [236, 237, 268]. A Posner molecule is, simplistically, a distorted cube with a calcium ion at each vertex, a ninth at the centre and a phosphate ion on each of the six faces of the cube [268]. The entangled phosphate spins then result in entangled Posner molecules [100]. For a schematic illustrating entangled Posner molecules see Figure 1.5.

Fisher estimates that for phosphorus spins in Posner molecules, coherence times could be as long as hours [100] or, in a later paper, 21 days [101]. Posner clusters were first identified by Betts and Posner in hydroxyapatite [234]. However, subsequent research on simulated body fluids suggests that free-floating calcium phosphate clusters, seen to be stable in solution for long periods of time, are solvated Posner clusters [102, 236, 238–241]. For sol-

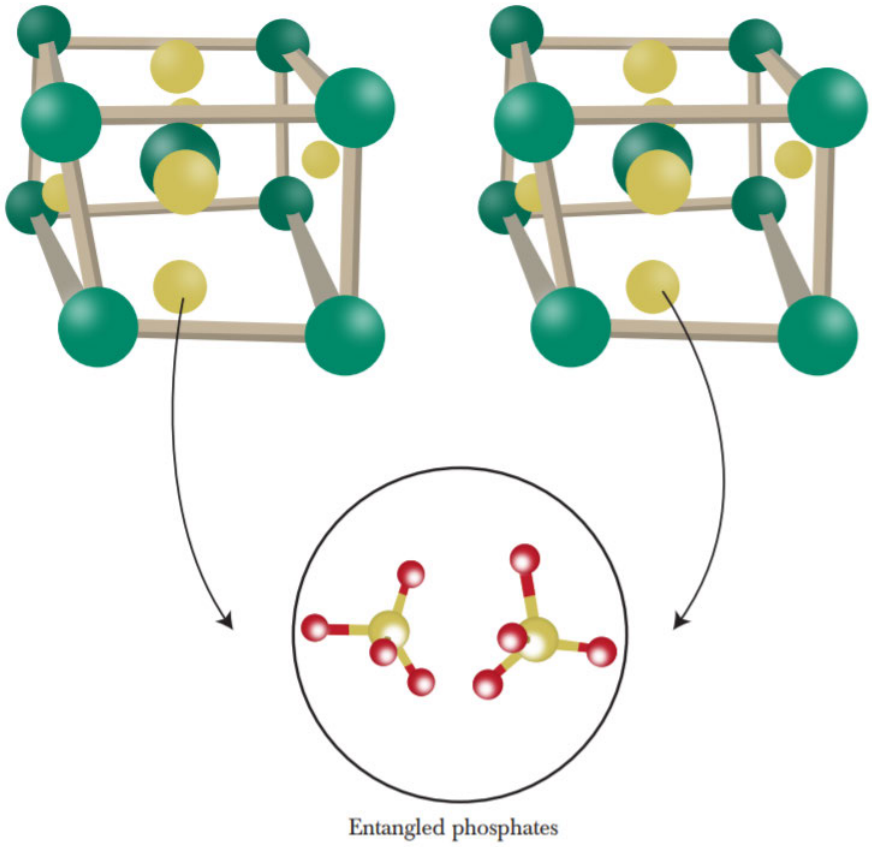

Figure 1.5: A scheme for neural entanglement. The Posner molecule structure is interpreted loosely here as a distorted cube with calcium ions (green) at each vertex and at the centre, and a phosphate ion (yellow) on each of the six faces [268]. This diagram is not meant to accurately convey the exact geometry of the Posner molecule but rather give some sense of Fisher's proposed qubit. The two Posner molecules share an entangled pair of phosphate ions. When two entangled Posner molecules are spatially separated and subsequently taken up into different presynaptic neurons in the process of vesicle endocytosis, their entanglement results in the correlated release of neurotransmitters and the coordination of firing across neurons [100].

vated Posner molecules the magnetic fields from protons in surrounding water molecules cause decoherence but, as Fisher argues, the rapid tumbling of Posner molecules means that the average magnetic field felt by a phosphorus nucleus will be zero. Decoherence will then only happen from residual magnetic field fluctuations and coherence times will thus be much longer [100, 101]. Player *et al.* respond to this with their own calculation of coherence times for Posner molecules. They acknowledge that long lived spin states in nuclei are well accepted, with relaxation times of up to an hour being recorded [242, 268]. However, they argue that these extended times are partly due to experimental control of the coherent spin dynamics, a condition that Fisher does not take into account [268]. In their analysis of Posner spin dynamics they take a number of other factors into account such as dipolar and scalar couplings within Posner molecules as well as the Zeeman interaction of the phosphorus spins with the geomagnetic field [268]. With intramolecular dipolar interactions as the dominant relaxation pathway they arrive at a relaxation time of 37 minutes, as opposed to Fisher's shortest estimation of approximately a day. They also discuss other ways in which this relaxation could take place even more quickly [268].

Posner molecules in their biological context

Fisher also outlines the way in which entangled Posner molecules give rise to quantum effects in neural processes. The entanglement of the spin and rotational states of Posner molecules leads to correlations in the chemical reactions of spatially separated Posner molecules. These entangled molecules are taken into presynaptic glutamatergic neurons in the process of vesicle endocytosis. The acidic environment causes Posner molecules to bind and release calcium which stimulates exocytosis and further release of glutamate, which enhances neural firing. Thus, because the chemical reactions of Posner molecules are entangled the subsequent release of glutamate and resultant neural firing might also be considered entangled [100, 102]. Fisher outlines a number of possible experiments that might verify the various stages of the theory, most pressingly whether Posner molecules are present in bodily fluids. Whereas free-floating calcium phosphate clusters resembling Posner molecules have been found to be stable in simulated body fluids [238], there is still some uncertainty as to whether they are present in vivo [100, 101]. Less fundamental but more interesting in the context of this thesis is the suggested investigation of the effects of a chemically viable replacement of the central

calcium in a Posner molecule with lithium ions [100, 101]. There is some evidence that lithium, used to alleviate the symptoms of bipolar disorder, has isotope dependent effects on the behaviour of rats [100, 243]. There is also experimental evidence to support the differential lithium isotope dependence of calcium phosphate cluster size distribution and calcium capacity in mitochondria [244]. Fisher postulates that the efficacy of lithium as a treatment for mental disorders could be due to the increased decoherence induced by the lithium nuclear spins included in the Posner molecule [100, 102].

Neural qubits and quantum computing

While the results of experiments to verify this model of entangled neural processes are yet to be completed the theory has caught the interest of researchers working in the field of quantum information theory. Halpern and Crosson apply Fisher's Posner molecule theory in the context of quantum communication, quantum computation and quantum error correction. They address how a quantum information based model of Posner molecules might contribute to the understanding of Posner chemistry and vice versa, what insights Posner molecules have for quantum information processing. They also demonstrate how entanglement can change molecular binding rates, which goes some way to supporting Fisher's neural entanglement hypothesis [245]. The authors conclude that the quantum information based formulation of Posner molecules might be a way of framing biological Bell tests [245], a claim that is potentially interesting in light of recent observations of entanglement between living bacteria and quantised light [246].

This is not the first time that phosphorus spin and quantum computing have crossed paths. In 1998 Kane proposed a scalable quantum computer where information is encoded onto spin half phosphorus nuclei in a substrate of spin zero silicon, ensuring the long decoherence time necessary for quantum computing. Computations are then performed through the interaction of nuclear spin with donor electrons [247]. Kane's idea has recently been reworked by Tosi *et al.* into what they call the flip-flop qubit, where the combined electron-nuclear spin states of a phosphorus donor are controlled by microwave electric fields. This research, along with work done by He *et al.* into engineering a viable exchange interaction between two phosphorus

bound electrons has done much to advance the course of spin based quantum computing [248, 249]. The fields of quantum computing and quantum neurobiology might inform each other in other ways too. Quantum dots have been proposed as an alternative means to implement a quantum computer [250]. They have also been used to model the mechanism by which anti-acetylcholine receptor antibodies contribute to the neuromuscular disorder myasthenia gravis [251]. Even more recently, graphene quantum dots have been shown to prevent and even undo the protein clumping of neurons in the brain that leads to Parkinson's disease [252]. A separate study study demonstrated similar results for Alzheimer's disease [255].

1.5 An outline of the thesis

The field of neurophysics already attests to the fact that the study of the brain borrows from ideas across the spectrum of physics: electricity and magnetism, mechanics, thermodynamics, optics [31]. It is perhaps not completely surprising that quantum physics might contribute too. A number of the hypotheses included in this introductory dicussion rework, to some extent, ideas already established with respect to other biological systems. Coherent energy transfer in photosynthesis is reimagined in the tryptophan rings of neural microtubules. The vibrational theory of olfaction is reapplied to the binding action of neurotransmitters. And while Fisher's Posner qubits depend on nuclear spin, unlike the radical pair model developed with respect to avian migration, their spin dynamics mediate the outcome of signalling processes in a potentially illuminating fashion. As it stands, the future of quantum neurobiology is the future of quantum biology more generally; progress made in either will further the other. With this in mind, Chapter 2 gives an overview of how quantum physics is relevant to biology, and the tools, such as open quantum systems theory, that are required to undertake this investigation.

This mechanistic focus would seem to ignore the question of consciousness and how it emerges from these underlying neural mechanisms. Lynn *et al.* describe the future of brain network research, albeit in a classical capacity, as a cross-scale approach that links the microscopic to the macroscopic: protein reactions in neurons to synaptic connectivity to brain region connectivity to social networks [31]. Jedlicka, in his review of the future of quantum neuro-

biology, touches on the evidence that quantum physics has also been used to describe human behaviour [24–26]. A recent study using behavioural as well as brain imaging data showed that value-based decision-making was more accurately described by quantum rather than classical reinforcement learning [256].

The use of a quantum framework to accurately describe human behaviour does not necessarily mean that this behaviour results from quantum effects in neural processes. A clearer understanding of these processes, however, could also elucidate to what extent quantum physics is involved in the emergence of cognition from neural activity [24]. It is towards this clearer understanding that this thesis aims, by looking more closely at two specific instances of the way in which quantum biology more generally might be leveraged towards understanding quantum effects in the brain and nerves.

The first of these examples entails a focus on quantum effects related to spin coherence and entanglement, in particular nuclear spin in Posner molecules. Chapter 3 thus looks more closely at Fisher's Posner molecule hypothesis, investigating to what extent specific biological parameters, such as coupling strength and symmetry, impact quantum measures of coherence and entanglement. Fisher's model is then extended to look at the impact that doping with lithium ions has on measures of coherence and entanglement.

The second subject of interest in this thesis is that of vibration assisted electron tunnelling and its role in receptor activation mechanisms. The overt subject of interest in Chapter 4 – SARS-CoV-2 invasion of host cells – is not specifically nerve and brain related. However, the aim is to investigate how generalisable are theories of vibration assisted tunnelling in the context of biological receptors. The aim is also to look at how physiology and neurology intersect. For instance, COVID-19 has been reported to have serious neurological effects, the origins of which are not yet fully understood. In addition to this, therapeutic drugs that target the nerves and brain, such as antidepressants, have been suggested to play a therapeutic role in treating COVID-19, though how they do this also remains to be explained. By better understanding how ligands such as the SARS-CoV-2 spike protein interact with host cell receptors this research was aimed at better understanding receptor mechanisms to hopefully gain some insights into specific neurological contexts.

Chapter 2

Quantum Tools

2.1 Quantum physics in biology

While the founding figures of quantum mechanics speculated on the role that quantum effects might play in living systems, the field would remain mostly theoretical until experimental techniques were developed for the investigation of systems on such small time and length scales. Many of the relevant processes – such as energy transfer – happen on ultrafast timescales such as pico and femtoseconds. Developments in experimental techniques such as ultrafast spectroscopy, single-molecule spectroscopy, time-resolved microscopy and single-particle imaging have contributed much to the recent accumulation of research in quantum biology [1, 258]. Most of this experimental investigation, however, has been in the context of photosynthetic systems. There has also been some suggestion that more tractable, hybrid or artificial models of these systems would be useful in advancing the field [258]. It remains to be seen how techniques used fruitfully in investigating coherent energy and charge transfer processes might be applied to other contexts in quantum biology. For investigations into tunnelling, the widely adopted experimental approach is selective deuteration or the exploration of isotope effects, given that tunnelling is strongly dependent on the mass of the tunnelling quantum object. This approach is also used to investigate vibration-assisted tunnelling in olfaction and related phenomena, though caution is noted with respect to the possibility of contaminants skewing the results [128]. Direct evidence for radical pairs in avian magnetoreception is lacking, with most of the evidence being behavioural [177]. However, a recent experiment has demonstrated

autoluminescence in the context of radical pair dynamics, opening a new era in experimental techniques relating to radical pairs [259].

Theoretically the field is more widely developed. A number of models have been used to describe the dynamics of quantum systems in biological environments, many of which begin with a simple Hamiltonian describing the charge transport or spin dynamics. Classically, energy transport has been modelled using Förster resonance energy transfer (FRET) theory. Quantum theoretical frameworks of this transport use a variety of approaches including Redfield theory and the numerically exact hierarchical equations of motion (HEOM) [258]. In the case of the spin dynamics, the initial density matrix treatment of radical pair reactions initiated by Haberkorn has garnered discussion [263–265]. A number of other open quantum systems approaches have been applied to the problem [263–265]. Open systems approaches have also been applied to proton tunnelling in DNA [266]. In modelling the effects of quantum tunnelling in enzymes, reaction rates following from transition state theory are modified by multiplication with a tunnelling correction factor [258]. Another theoretical approach widely employed in quantum biology is density functional theory, which is often used to calculate relevant parameters. Finally, a number of theoretical approaches use different measures of coherence – such as relative entropy – or entanglement – such as concurrence or negativity – in order to investigate how quantum a given biological system is [268, 269, 278].

2.2 Quantum mechanics in brief

Quantum mechanics is conventionally described as arising out of the failure of classical physics to explain key experimental interactions between light and matter. This prompted Planck, in 1900, to postulate that interactions between matter and electromagnetic radiation of frequency ν are quantised, occurring only in integer multiples of $h\nu$, where h is the fundamental Planck's constant. Further contributions from Einstein, in the context of the photoelectric effect, led to the development of quantum mechanics, a theory that has proved extremely successful in predicting and describing microphysical systems [6, 7]. The initial mathematical formulation of quantum mechanics included Schrödinger's use of wave mechanics as well as the earlier matrix mechanics employed by Heisenberg [6, 7].

2.2.1 The postulates of quantum mechanics

Quantum mechanics is a mathematical framework that describes a physical system such as an electron or photon with a quantum state that completely characterises the system and is denoted by $|\psi\rangle$. All states available to this system are contained in the appropriate Hilbert space $\mathcal{H}$. The fundamental postulates of quantum mechanics are given below [6].

- At a given time t the state of a system is fully described by a state vector $|\psi(t)\rangle$ in an abstract complex linear complete inner-product vector space known as a Hilbert space $\mathcal{H}$. In quantum mechanics the wave function $|\psi(\vec{r},t)\rangle$ is square-integrable or normalised which is to say that it satisfies
$$\int |\psi(\vec{r},t)|^2 d^3r = 1,$$
where $|\psi(\vec{r},t)|^2 d^3r$ represents the probability of finding the particle, at time t, in the volume d^3r around the point defined by $\vec{r}$.

- A measurable physical quantity or observable such as position, angular momentum or energy can be represented in quantum mechanical formalism by a linear Hermitian operator A which acts on the state vector of the Hilbert space to produce another state vector. In the case of finite dimensional Hilbert spaces an operator can be represented as a matrix in the basis of the space. The eigenvectors of A form a complete basis.

- The measurement of a specific observable can be formalised as the action of the corresponding operator A on the state vector $|\psi\rangle$. The outcome of this measurement is always one of the eigenvalues a_n of the operator. As A is Hermitian the eigenvalues are real. When a measurement on a system in one of the eigenstates $|\psi_n\rangle$ gives the outcome a_n, the state of the system immediately after measurement is given by the projection of $|\psi\rangle$ onto the subspace corresponding to the outcome, that is
$$A\,|\psi_n\rangle = a_n\,|\psi_n\rangle\,.$$
If, for example, m eigenvectors correspond to the same eigenvalue a_n then a_n is m-degenerate.

- For a system in a state $|\psi\rangle$ the probability of measuring an observable with non-degenerate eigenvalue a_n is given by

$$P_n(a_n) = \frac{|\langle\psi_n|\,\psi\rangle|^2}{\langle\psi|\,\psi\rangle}.$$

For an m-degenerate eigenvalue this probability is

$$P_n(a_n) = \frac{\sum_{j=1}^{m}|\langle\psi_n^j|\,\psi\rangle|^2}{\langle\psi|\,\psi\rangle}.$$

When the system is already in an eigenstate $|\psi_n\rangle$ of the observable then measurement is certain to yield the corresponding eigenvalue a_n.

- The quantum analog of the classical Hamilton function is the Hermitian linear operator H, the Hamiltonian, which represents the energy of a quantum system. The time evolution of a system described by a state vector $|\psi(t)\rangle$ obeys the Schrödinger equation,

$$i\hbar\frac{d}{dt}|\psi(t)\rangle = H(t)\,|\psi(t)\rangle\,. \tag{2.1}$$

2.2.2 The density operator

The density operator ρ is a mathematical tool that is used to describe quantum systems that cannot be represented using a pure state vector. Instead this system is considered to be in an incoherent mixture of states $|\psi_i\rangle$ with weights ω_i where the density operator can be written as

$$\rho = \sum_i \omega_i\,|\psi_i\rangle\,\langle\psi_i|\,.$$

In the non-relativistic case the density operator must satisfy the following mathematical conditions, where Tr is the trace over the Hilbert space of the system [271, 272]:

1. $\mathrm{Tr}\rho = 1$;
2. ρ is non-negative, $\rho \geq 0$;
3. ρ is Hermitian, $\rho^\dagger = \rho$;

4. $\mathrm{Tr}\rho^2 \leq 1$, with $\mathrm{Tr}\rho^2 = 1$ only for pure states, that is $\rho = |\psi\rangle\langle\psi|$

The density operator can also be used to express expectation values for a system in a mixed state represented by an incoherent mixture of pure states. For an observable A the expectation value is given by

$$\langle A \rangle = \mathrm{Tr}\{A\rho\}.$$

The unitary dynamics of a density operator ρ are given by the *Liouville-von Neumann equation*

$$\frac{\mathrm{d}}{\mathrm{dt}}\rho(t) = -\frac{i}{\hbar}[H(t), \rho(t)], \tag{2.2}$$

where the square brackets represent the commutator:

$$[A, B] = AB - BA.$$

Equation (2.2) can be derived from the Schrödinger equation given in Eq. (2.1), given that the density operator evolves as

$$\rho(t) = U\rho(t_0)U^\dagger. \tag{2.3}$$

where $U(t)$ is the unitary operator and converts the initial state $|\psi(0)\rangle$ at time $t = 0$ into the state $|\psi(t)\rangle$ at some later time t:

$$|\psi(t)\rangle = U(t)|\psi(0)\rangle$$

2.3 Open quantum systems

Quantum mechanics, as formulated in Equation (2.1), conventionally describes the behaviour of isolated systems. Biological systems, however, cannot be described in such simplistic terms, due to the fact that they interact with what is often described as a warm, wet and messy environment. As such, quantum mechanical descriptions of biological systems use principles from the theory of open quantum systems. This involves modelling the composite system of subsystem and environment as a closed system, before tracing out the environment or bath using the partial trace. For a simple schematic of an open system see Figure 2.1.

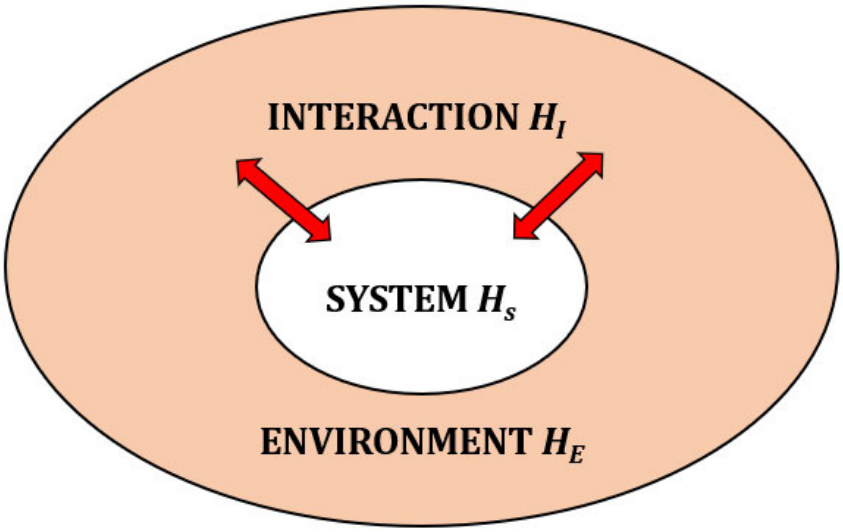

Figure 2.1: A schematic illustrating the concept of an open quantum system, including the Hamiltonians (H) that mathematically describe the system and environment as well as the interaction between the two. Biological systems interact with their environments and thus are often modelled using an open systems approach. This involves modelling the system and environment as a closed system, the environment is then traced out to arrive at the reduced system dynamics. Image from [262].

2.3.1 The partial trace and open system dynamics

For a composite quantum system the Hilbert space is given by the tensor product of the individual Hilbert spaces of subsystem and bath

$$\mathcal{H} = \mathcal{H}_S \otimes \mathcal{H}_B.$$

For this composite system the partial trace allows for the elimination of the degrees of freedom corresponding to the bath [272], The reduced density operator ρ_S is obtained by taking the partial trace over subsystem B of the total density operator $\rho \in H$:

$$\rho_S(t) = \mathrm{Tr_B}\rho(t).$$

Chapters 3 and 4 of this thesis both use an open quantum systems master equation approach. In particular the approach is Markovian, where quantum Markov processes are the simplest representation of open system dynamics, neglecting memory effects under the assumption that future behaviour is independent of the past. To derive the Markovian master equation as set out by Breuer and Petruccione [272], we employ the concept of a dynamical map. This assumes that the state of the composite system can be prepared in an uncorrelated product state

$$\rho(0) = \rho_S(0) \otimes \rho_B,$$

at $t = 0$, where $\rho_S(0)$ is the initial state of the reduced system and ρ_B is a reference state for the environment, such as a thermal equilibrium state [272]. The evolution of the density operator for the composite system is given by

$$\rho(t) = U(t,0)\rho(0)U^\dagger(t,0) = U(t,0)[\rho_S(0) \otimes \rho_B]U^\dagger(t,0).$$

The dynamics of the reduced system at some time $t > 0$ can then be given by

$$\rho_S(t) = \mathrm{Tr}_B\{U(t,0)[\rho_S(0) \otimes \rho_B]U^\dagger(t,0)\} = V(t)\rho_S(0).$$

For a fixed final time t and reference state ρ_B, $V(t)$ is a dyamical map which maps the reduced system onto itself. It can also be shown that

$$\mathrm{Tr}_S\{V(t)\rho_S\} = \mathrm{Tr}_S\rho_S = 1$$

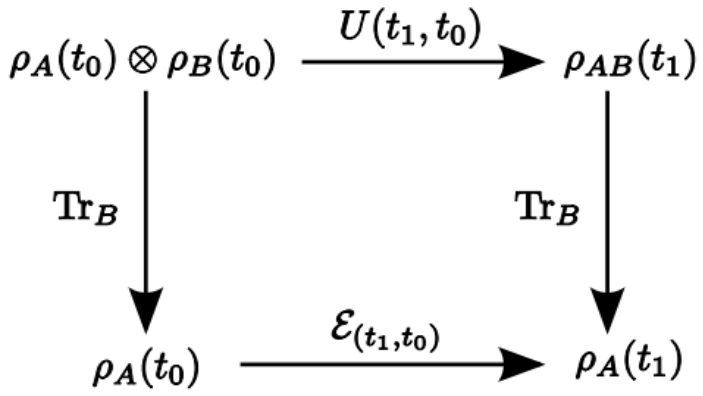

Figure 2.2: A schematic illustrating the dynamics of open quantum systems, where ρ_A is the subsystem of the composite system $\rho_A \otimes \rho_B$ and the partial trace is used to recover the reduced dynamics of the subsystem of interest. Image from [272, 273].

from which it can be concluded that the quantum operation represented by $V(t)$ is convex-linear, completely positive and trace-preserving.

If t is allowed to vary the result is a one-parameter family of dynamical maps $\{V(t)|t \geq 0\}$, with $V(0)$ the identity map, which describe the full time evolution of the open system. The Markovian approximation can be made if the reservoir correlation functions decay much faster than the system evolution. This can be formalised using the semigroup property

$$V(t_1)V(t_2) = V(t_1 + t_2), \qquad t_1, t_2 \geq 0.$$

Under specific mathematical conditions, the semigroup $V(t)$ can be represented in exponential form

$$V(t) = e^{\mathcal{L}t},$$

where the linear map $\mathcal{L}$ is the generator of the semigroup. From this it is possible to derive the Markovian quantum master equation for the reduced system

$$\frac{d}{dt}\rho_S(t) = \mathcal{L}\rho_S(t).$$

2.3.2 The master equation

Given that the composite system is unitary the dynamics can be represented by Equation (2.2) where H is the Hamiltonian of the composite system

$$H = H_S \otimes \mathbb{I}_B + \mathbb{I}_S \otimes H_B + H_I,$$

and H_S, H_B and H_I are the Hamiltonians of the subsystem, the bath and the interaction respectively, $\mathbb{I}_S$ and $\mathbb{I}_B$ are corresponding identity matrices. Tracing out the bath gives the dynamics of the reduced system:

$$\frac{d\rho_S(t)}{dt} = -i\mathrm{Tr}_B[H_I, \rho(t)]. \tag{2.4}$$

To make the solution of this more tractable some approximations are applied. In the interaction picture the Liouville-von Neumann equation is given by:

$$\frac{d}{dt}\rho_I(t) = -i[H_I(t), \rho_I(t)], \tag{2.5}$$

which has the integral form:

$$\rho_I(t) = \rho_I(0) - i\int_0^t [H_I(t'), \rho_I(t')]dt'. \tag{2.6}$$

Substituting this into the reduced system dynamics gives:

$$\frac{d}{dt}\rho_S(t) = \mathrm{Tr}_B\left[H_I(t), \rho(0)\right] - \int_0^t \mathrm{Tr}_B\left[H_I(t), [H_I(t'), \rho(t')]\right] dt' \tag{2.7}$$

We now institute the first of the approximations, which is the Born or weak-coupling approximation. This assumes that if the system S is weakly coupled to a bath B that is very large then the influence of the system on the bath is small and we can express the total density matrix as $\rho(t) = \rho_S(t) \otimes \rho_B(0)$. Applying the Born approximation to Equation (2.7) gives

$$\begin{aligned}\frac{d}{dt}\rho_S(t) = -i\mathrm{Tr}_\mathrm{B}\big[H_I(t), \rho_S(0) \otimes \rho_B(0)\big] \\ - \int_0^t dt'\ \mathrm{Tr}_\mathrm{B}\big[H_I(t), \big[H_I(t'), \rho_S(t') \otimes \rho_B(0)\big]\big].\end{aligned} \tag{2.8}$$

A second approximation is made by replacing $\rho_S(t')$ with $\rho_S(t)$, making the master equation local in time and the time evolution of the system at some

time t only dependent on the present state $\rho_S(t)$. The Markov approximation is then allowed if the time scale over which the bath correlation functions decay is small compared to the time scale over which the system changes. We can then substitute $t' = t - s$ and let the top limit of the integral go to infinity [272]. This gives

$$\frac{d}{dt}\rho_S(t) = -i\mathrm{Tr}_\mathrm{B}\big[H_I(t), \rho_S(0)\otimes\rho_B(0)\big] - \int_0^\infty ds\ \mathrm{Tr}_B\big[H_I(t), \big[H_I(t-s), \rho_S(t)\otimes\rho_B(0)\big]\big]. \quad (2.9)$$

Timescales for the evolution of the system are typically defined by $|\omega - \omega_0|^{-1}$ where $\omega \neq \omega_0$ are frequencies of bath harmonic oscillator modes. If the timescale on which the relaxation of the reduced system occurs is much less than the evolution of the system, then the non-secular terms for which $\omega \neq \omega_0$ may be neglected. This is known as the secular or rotating wave approximation. To perform the rotating wave approximation the Hamiltonian is decomposed into operators A that act on the reduced system and operators B acting on the environment, with the standard assumption that

$$\langle B(t)\rangle = \mathrm{Tr}[B(t)\rho_B] = 0.$$

For more details about the explicit assumptions made and how the final form of the master equation follows from the bath correlation functions, see [272].

Following these various approximations we arrive at the final Born-Markov master equation. In the finite-dimensional case, the most general form of the Markovian quantum master equation is given by:

$$\frac{d}{dt}\rho_S(t) = i[H_S, \rho_S] + \sum_{k=1}^{N}\gamma_k\left(A_k\rho_S A_k^\dagger - \frac{1}{2}\{A_k^\dagger A_k, \rho_S\}\right), \quad (2.10)$$

where the first term represents the unitary dynamics while the second term describes the effects of dissipation and decoherence, and $\{\}$ indicates the anticommutator. The operators A_k are often referred to as Lindblad operators, while the γ_k are interpreted as rates.

2.3.3 Solving the master equation

While it would be useful to have exact solutions for the master equations employed in the biological context, the systems are often complex and in-

tractable and lend themselves to numerical rather than analytical solutions. This has been the approach of this thesis. It should be stated, however, that these solutions are contingent on the given parameters of the biological system of interest, for example coupling strengths in organic materials. This remains a point of contention in quantum biology, where some of these parameters come from experiment and some from techniques auch as density functional theory, with variable results. For further discussion of this point in specific biological contexts see Chapter 3 and 4. An example of some of the Mathematica code used in the numerical calculations of this thesis can be found on GitHub here: $https://github.com/BetonyAdams/PHD-code$.

Chapter 3

Nuclear spin entanglement in the brain

3.1 Overview

[1] The role of quantum spin in biological systems is one of the primary topics of quantum biology [1, 2, 252]. A pivotal question in the field is whether quantum coherence – and possibly entanglement – may contribute to the functional importance of biological processes, such as the charge transfer that underpins photosynthesis or the spin-dependent chemical reactions that may constitute the mechanism of the avian compass. Spin chemistry has a long history, with its origins in the 1960s [253, 254]. Spin biology, in which spin-dependent chemical reactions are modulated by the geomagnetic field, has almost as long a history. In the 1970s it was first proposed that the radical pair mechanism might explain how birds navigate so accurately across great distances [14]. The radical pair mechanism focuses on the spin states of paired electrons. More recently, however, it has been suggested that nuclear spin is better suited to playing a role in biological processes, due to the fact that nuclear spin has much longer coherence times than electron spin [100–102]. In particular, it has been suggested that phosphorus nuclear spin, bound into calcium phosphate molecules known as Posner molecules, is ideally suited to play a role in cognition and memory. Spin half phosphorus nuclei have very long decoherence times, a factor that is increased by their

[1] This chapter is based on the following paper: 'Coherence and entanglement in lithium-doped Posner molecules', arXiv:2310.13484 [quant-ph] (2023).

'shielding' in Posner molecules by spin-zero calcium nuclei [100–102].

Quantum to biological transduction is an integral step in the modelling of quantum effects in biological processes. In the radical pair mechanism this step is achieved by the electronic spin selectivity of the chemical reactions involved in biological functioning [260,274,275]. In the Posner molecule model, it has been suggested that the binding and hydrolysis of Posner molecules is dependent on the phosphorus nuclear entanglement [100]. Hydrolysis of Posner molecules releases free calcium ions, which in turn play a powerful role in cellular and neural signalling. In this way quantum entanglement is implicated in coordinated calcium signalling [100].

In this chapter we take a closer look at the quantum properties of Posner molecules, such as coherence and entanglement. Given that there are six phosphorus nuclei in each Posner molecule, we investigate the spin interactions and how these influence coherence and entanglement. To begin with we use established measures of coherence and concurrence to quantify these quantum resources in pure Posner molecules, by which we mean those molecules that only contain calcium and phosphate ions. We then extend this model to look at the common phenomenon of doped Posner molecules, in which spin zero calcium ions are replaced by other ions with nuclear spin, such as lithium and hydrogen.

In particular we look at the effects of lithium ion substitution on coherence and entanglement. Our motivation for investigating lithium is the evidence that different lithium isotopes have different behavioural effects in animal studies [243, 288]. Lithium is an important drug in the treatment of bipolar disease. It has been suggested that the different outcomes of lithium treatment could be explained by the different nuclear spins of lithium isotopes, which, when incorporated into Posner molecules, would differently modulate the spin dynamics [100,101]. We model the spin dynamics in order to confirm whether different lithium isotopes have different effects on entanglement and thus Posner hydrolysis and free calcium ions.

In order to determine whether it is only the spin entanglement that is instrumental in the different effects of lithium ions we investigate other ways in which lithium isotopes may differ in their mode of action. In particular we look at the role of spin in relaxation mechanisms and whether the different

isotopes induce spin relaxation to different degrees. We also apply results from radical pair literature, such as the effects of electromagnetic noise of different frequencies, to gain insight into nuclear spin dynamics. And finally, we investigate a novel way in which entanglement between phosphorus nuclei, before they are bound into Posner molecules, is enhanced rather than destroyed by interaction with hydrogen ions.

3.2 The radical pair mechanism: electron spin

The radical pair model of avian magnetoreception has given rise to a number of papers outlining how birds might sense the Earth's magnetic field through the spin states of paired electrons. This radical pair compass can be outlined in the following three steps. First an incident photon transfers its energy to a donor molecule causing electron transfer, which results in a spatially separated electron pair that is conventionally taken to be in a singlet state. Second, under the influence of the geomagnetic Zeeman effect and the hyperfine interaction with surrounding nuclei, the spin state begins to interconvert between singlet and triplet states. Finally, recombination occurs, which is dependent on the spin state [260, 274, 275]. In this way spin states translate into biologically relevant signalling states.

The role that spin coherence might play in the sensitivity of this magnetic compass has been investigated in a number of papers [276–278]. There has also been discussion of the importance of quantum entanglement in this mechanism [269, 279–281]. This follows from the fact that the radical pair is conventionally taken to originate in the entangled singlet state. For two spin-half electrons, if the first electron of the pair is in a state given by the vector

$$|\uparrow\rangle = \begin{pmatrix} 1 \\ 0 \end{pmatrix},$$

and the second electron is in the state given by the vector

$$|\downarrow\rangle = \begin{pmatrix} 0 \\ 1 \end{pmatrix},$$

then the singlet state can be written as:

$$S = \frac{1}{\sqrt{2}}(|\uparrow\downarrow\rangle - |\downarrow\uparrow\rangle). \tag{3.1}$$

However, once this singlet is exposed to the nuclear environment it can undergo conversion to the triplet states, only one of which is entangled,

$$T_0 = \frac{1}{\sqrt{2}}(|\uparrow\downarrow\rangle + |\downarrow\uparrow\rangle). \tag{3.2}$$

While the subject is still up for debate, there is some indication that, while coherence is important, entanglement is not strictly necessary for the radical pair mechanism to function [269, 277, 282]. What is potentially interesting, however, is that should entanglement play a role in this mechanism, one way in which to enhance the entanglement lifetime is the application of appropriate magnetic fields. This would create a subspace in which almost all mixed (singlet and triplet) states are entangled due to increasing the energy separation of the two non-entangled triplet states $T_+ = |\uparrow\uparrow\rangle$ and $T_- = |\downarrow\downarrow\rangle$ [283]. In this chapter we investigate coherence and entanglement in a model that is analogous to the radical pair mechanism but utilises correlated nuclear spins rather than correlated electron spins.

3.3 The Posner molecule mechanism: nuclear spin

Calcium ions are integral to physiological processes in the body. They play an important role in, among other things, the release of neurotransmitters and the activation of nerve cells [284, 285]. Amorphous calcium phosphate has been proposed as an essential reservoir for calcium ions in biological systems [287]. One of the forms that calcium phosphate can take is the Posner cluster, first identified by Betts and Posner and referred to in this paper as the Posner molecule [234]. A recent hypothesis suggests that quantum effects could play a role in Posner molecule formation and dissolution and thus also the storage and release of calcium ions. In this way, entanglement of spin-half phosphorus nuclei that are subsequently assembled into Posner molecules may play a role in quantum cognition [100]. Phosphorus nuclei make for good qubits due to the fact that spin-half nuclei have no quadrupole moment and longer relaxation times [100]. In Fisher's initial hypothesis, entangled phosphorus nuclei are achieved through the enzyme-catalysed hydrolysis of pyrophosphate, which consists of two phosphates [100]. Pyrophosphate is a byproduct of adenosine triphosphate (ATP), a molecule integral to energy processes in cells. It has been suggested that due to spin constraints on the

molecular dynamics of a pyrophosphate molecule bound to the enzyme pyrophosphatase, the two phosphates are produced with their phosphorus nuclei in a singlet (entangled) state. If these entangled phosphates are bound with calcium into separate Posner molecules, then this might be thought of as creating entangled Posner molecules, where the phosphorus spin is shielded from decoherence by a spin-zero cage of oxygen and calcium [100]. Furthermore, this entanglement may influence Posner molecule dynamics and future binding, which causes the molecules to melt and release calcium, which then has an effect on neural activation. In this way phosphorus nuclear spin entanglement might play a role in neural excitability. It has also been suggested that Posner molecules can be doped with ions other than calcium, such as magnesium or lithium, and that the non-zero nuclear spin of these ions would change the spin dynamics of the phosphorus nuclei [100–102]. See Figure 3.1 for a schematic of undoped and doped Posner molecules. The relative composition of Posner molecules has been shown to depend on other ions available during their formation [237]. Two monovalent lithium ions, for example, might take the place of the central divalent calcium ion [100]. The non-zero spin of the lithium nuclei would then have a resultant effect on phosphorus spin dynamics and potential neural activation. This could also explain the interesting experimental result that lithium isotopes, ^{6}Li and ^{7}Li, have differing effects on parenting behaviour as well as hyperactivity in rats [243, 288]. With this in mind we model the spin dynamics of a pair of spin-correlated phosphorus nuclei in two Posner molecules doped with different lithium isotopes. We use this model to investigate some of the questions raised by the Posner molecule model of neural entanglement: how might we measure nuclear coherence and entanglement, do different lithium isotopes have an effect on this entanglement, and what effects do these isotopes have on the spin dynamics?

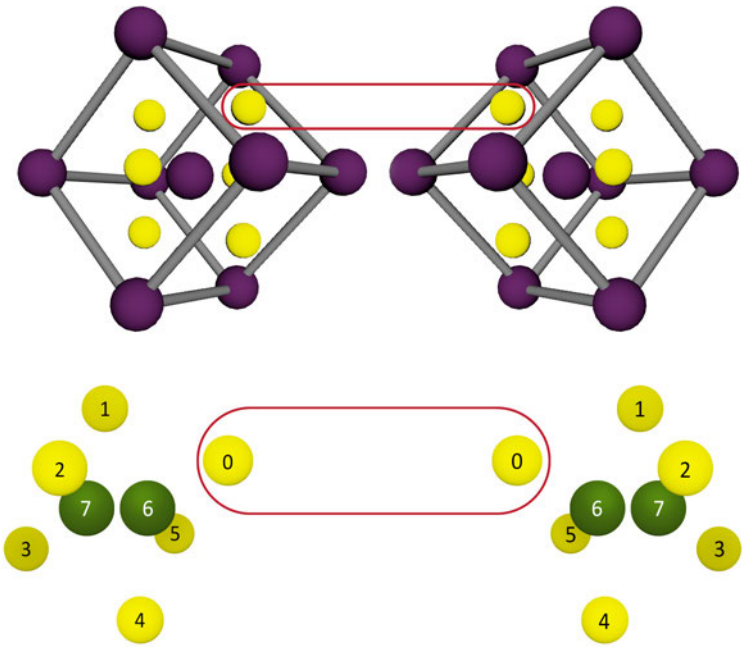

Figure 3.1: A schematic representation of undoped and doped Posner molecules. At the top are two Posner molecules, with eight calcium ions (purple) at the corners of the cube and one calcium ion at the centre. On each of the faces of the cube is a phosphate (yellow). The red loop represents one set of entangled phosphates, with correlated phosphorus nuclear spin. At the bottom, we have removed the calcium ions (no nuclear spin) to simplify our representation of the spin dynamics. We have also introduced two lithium ions (doped Posners) instead of the calcium ion at the centre. For clarity in our results section we have numbered the relevant spins 0–5 for the phosphorus spins and 6–7 for the lithium spins. This means that an interaction between spin 0 and 1 will have J-coupling strength J_{01} and so forth. The initial entanglement in our model is between spins 0 and 0 in each Posner molecule, which are in a singlet state. In our model we consider intermolecular entanglement and coherence, between phosphorus nuclei in distinct Posner molecules, and not intramolecular entanglement.

3.4 Theory

3.4.1 A simplified model

In a recent paper Player and Hore investigate the claim made by Fisher [100] that the lifetime of the entangled phosphorus nuclear spins might extend to as long as 21 days [289]. By considering intramolecular spin interactions rather than intermolecular spin interactions, as Fisher does [100], they reach a much reduced, though still appreciably long, lifetime of 37 minutes. In their paper they use concurrence to illustrate the dependence of entanglement on the singlet character of the phosphorus nuclear spins [289]. Following their example we construct a spin Hamiltonian for three different variations of a pair of entangled Posner molecules: no lithium, ^{6}Li (nuclear spin 1) and ^{7}Li (nuclear spin $\frac{3}{2}$). The coherent spin Hamiltonian is given by:

$$\hat{H_S} = B_0 \sum_k \gamma_k S_z^k + \sum_{i<k} 2\pi J_{ik} \vec{S^i} \vec{S^k}. \tag{3.3}$$

For pure Posner molecules: $k = 1, ..., N_P$. For Posner molecules doped with lithium $k = 1, ..., N_P, N_{P+1}, ..., N_P + N_L$. This gives $\gamma_k = \{k \leq N_P : \gamma_P \mid k > N_P : \gamma_L\}$, where γ_P and γ_L are the gyromagnetic ratios of ^{31}P and the different lithium isotopes and B_0 is the geomagnetic field. The first term represents the Zeeman interaction for the phosphorus and lithium nuclei. The second term represents the indirect spin coupling or scalar coupling between the various nuclei in the pure Posner molecule or lithium doped Posner molecule, where J_{ik} is the strength of the coupling between nucleus i and k. We follow the lead of Swift*et al.* [101] who arrive at an effective Heisenberg-like Hamiltonian by discounting the anisotropic contribution to J-coupling, which tends to be averaged out by the rotational motion of the Posner molecules. Here,

$$S_\alpha^k = \left\{ \begin{array}{l} k \leq N_P : S_\alpha^P \\ k > N_P : S_\alpha^L \end{array} \right\},$$

where S_α^P and S_α^L are the spin operators for phosphorus and lithium, with $\alpha = x, y, z$.

It has been proposed that introduction of lithium into Posner molecules might exert its influence through the interaction of lithium nuclear spin with phosphorus nuclear spin [100]. To investigate how lithium isotopes change

the quantum behaviour of Posner molecules we include measures for both coherence as well as entanglement. As a coherence measure we use the basis-independent coherence given by [278]:

$$C_{BI}(\rho) = \log_2 d - S(\rho), \tag{3.4}$$

where

$$S(\rho) = -\mathrm{tr}[\rho \log_2 \rho], \tag{3.5}$$

is the von Neumann entropy. $C_{BI}(\rho)$ is the relative entropy distance to the maximally mixed state with dimension d and $|i\rangle$ representing each of the singlet and triplet states,

$$\mathbb{I}_d/d = \sum_{i=0}^{d-1} \frac{1}{d} |i\rangle \langle i| . \tag{3.6}$$

To measure entanglement we follow the example of Player and Hore [289], using concurrence as originally formulated by Wootters [290], given by

$$C(\rho) = \max(0, \sqrt{\lambda_1} - \sqrt{\lambda_2} - \sqrt{\lambda_3} - \sqrt{\lambda_4}), \tag{3.7}$$

where the λ_i are the eigenvalues in decreasing order of the matrix

$$\rho(\sigma_y \otimes \sigma_y)\rho^*(\sigma_y \otimes \sigma_y), \tag{3.8}$$

where ρ^* is the complex conjugate of ρ and σ_y is the relevant Pauli matrix.

Exactly how quantum effects such as coherence and entanglement potentially mitigate bipolar disorder is unclear. For undoped Posner molecules, Fisher hypothesises that the rotational entanglement inherited from their spin entanglement modulates their chemical binding. Binding in turn allows Posner molecules to melt and release calcium which is implicated in neural activation [100]. A recent paper by Halpern and Crosson translates Fisher's ideas into quantum information formalism. Among other things the paper details how entanglement might increase molecular binding rates [245]. Increased binding rates would mean increased calcium production, enhanced neurotransmitter release (Fisher specifies glutamate) and altered neural activity. Glutamate is an excitatory neurotransmitter [291]. Bipolar disease may be related to calcium signalling [292–294] as well as neural excitability. Neurons from patients with bipolar disorder are hyperexcitable and, furthermore, this

hyperexcitability was reversed by lithium treatment [295, 296]. With this in mind it is instructive to investigate what effect lithium might have on Posner molecule entanglement and thus neural excitability. And to what different degree ^{6}Li and ^{7}Li might attenuate this excitability.

3.4.2 The (problem of) parameters

Parameters for the Zeeman part of the coherent Hamiltonian are well defined. The gyromagnetic ratios of ^{31}P, ^{7}Li and ^{6}Li in MHz.T^{-1} are 17.24, 16.55 and 6.27, respectively [297, 298]. We take the Earth's magnetic field to be 50μT. The primary problem we encountered in modelling the spin system is the lack of definitive J-coupling strengths. For pure Posner molecules we use, as a starting point, the phosphorus-phosphorus J-coupling strengths as calculated by Swift *et al.* [101]. It should be noted, however, that these coupling constants depend on the fact that Swift *et al.* assume the Posner molecules have symmetric configurations. Other Posner molecule configurations would alter and multiply the possible J-coupling constants and there is some evidence that Posner molecules prefer low symmetry states at room temperature [299]. Agarwal *et al.* recently published a detailed analysis of J-coupling constants in the context of Posner molecules of varying symmetries [300]. Both Swift *et al.* and Agarwal *et al.* estimate the coupling constants from theoretical first principles calculations [101,300]. Phosphorus-phosphorus J-coupling strengths in adenine triphosphate, a source of the pyrophosphate used to assemble Posner molecules, have been reported as being approximately two orders of magnitude bigger [306] than the values calculated by Swift *et al.* [101]. For this reason, and given the lack of experimentally verified parameters, we examine how phosphorus nuclear coherence and entanglement in Posner molecules depends on the size of the J-coupling coupling constants.

Lithium coupling constants are also difficult to estimate accurately from the literature. For this reason the J-coupling constants between relevant atoms were calculated using ORCA [301]. Specifically, we performed DFT calculations using the pcseg-2 basis set [302] for all atoms, and the pcJ-2 basis set [303] - built specifically for the calculation of these coupling constants - for phosphorus and lithium atoms. The hybrid B3LYP exchange-correlation functional was used. Agarwal *et al.* conclude in their paper that although J-coupling constants play an important role in Posner spin dynamics, it is

ultimately the size of the spin system that has the greatest effect. We were interested to see whether our results confirmed their conclusion as we add the extra spins of the lithium isotopes [300]. What is also interesting in the context of a discussion of the different effects of lithium isotopes on the spin dynamics of Posner molecules is that ^{6}Li and ^{7}Li have J-coupling strengths that vary to a measurable degree. Scalar or J-coupling is the indirect interaction of nuclear spins through their intermediate interaction with surrounding electrons. For lithium isotopes the different gyromagnetic ratios of the nuclei in question have an effect on the coupling strength, with larger gyromagnetic ratio of ^{7}Li resulting in larger J-coupling constants. Comparison of ^{6}Li and ^{7}Li gyromagnetic ratios gives $\gamma_7/\gamma_6 = 2.6$ [298, 304, 305]. We have used this ratio to compare the effects of different lithium isotopes on nuclear coherence and entanglement in lithium substituted Posner molecules.

3.5 Results

3.5.1 Pure Posner molecules

Before considering phosphate nuclear entanglement in the context of lithium doped Posner molecules we consider the simplest case of an undoped Posner molecule to be clear as to what we mean by coherence or concurrence. Coherence, in this context, refers to the distance of a given state from a maximally mixed state. Concurrence corresponds to the probability of the entangled singlet state being above one half. In Figure 3.2 we show how increasing the strength of the J-couplings increases the coherence and concurrence. We have illustrated this by plotting the coherence and concurrence for J-coupling strengths beginning with those calculated by Swift *et al.* and increasing in increments up to at least two orders of magnitude. There are now two papers in which Posner molecule J-coupling constants have been estimated using theoretical calculations [102, 300]. However, in the brain, ATP, the molecule from which phosphates are hypothetically assembled into Posner molecules, has been measured to have J-coupling strengths up to two orders of magnitude greater [306] than those calculated by Swift *et al.* for Posner molecules. The J-coupling constants calculated by Swift *et al.* [101] are also for a very specific Posner molecule configuration and it is unclear whether this is the energetically preferred configuration [299]. In order to investigate what effect the symmetry of the molecule might play we plotted

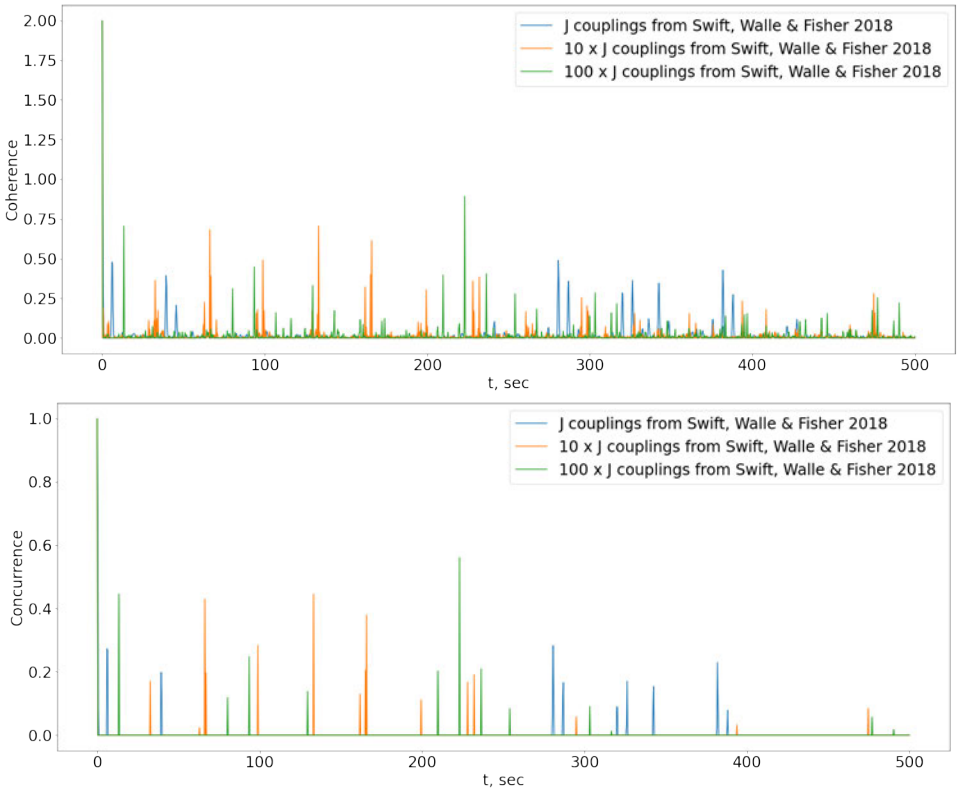

Figure 3.2: Dependence of coherence (top) and concurrence (bottom) on the J-coupling strengths from smaller to larger values: For coupling strengths of the order of those calculated by Swift *et al.* [101] very little coherence and concurrence remain when the interactions of all phosphorus nuclei are considered. Both can be increased by increasing the J-coupling strength. Phosphorus-phosphorus J-coupling strengths in adenine triphosphate, a source of the pyrophosphate used to assemble Posner molecules, have been reported as being approximately two orders of magnitude bigger [306] than the values calculated by Swift *et al.* [101] for Posner molecules with specific symmetries.

the coherence (Figure 3.3) and concurrence (Figure 3.4) for two asymmetric Posner configurations. We approximated the asymmetry by using different J-couplings. For the first configuration the two halves of the Posner molecules, with respect to the entangled nuclei, were comparably strongly coupled. For the second configuration there was one very strongly coupled half. In the

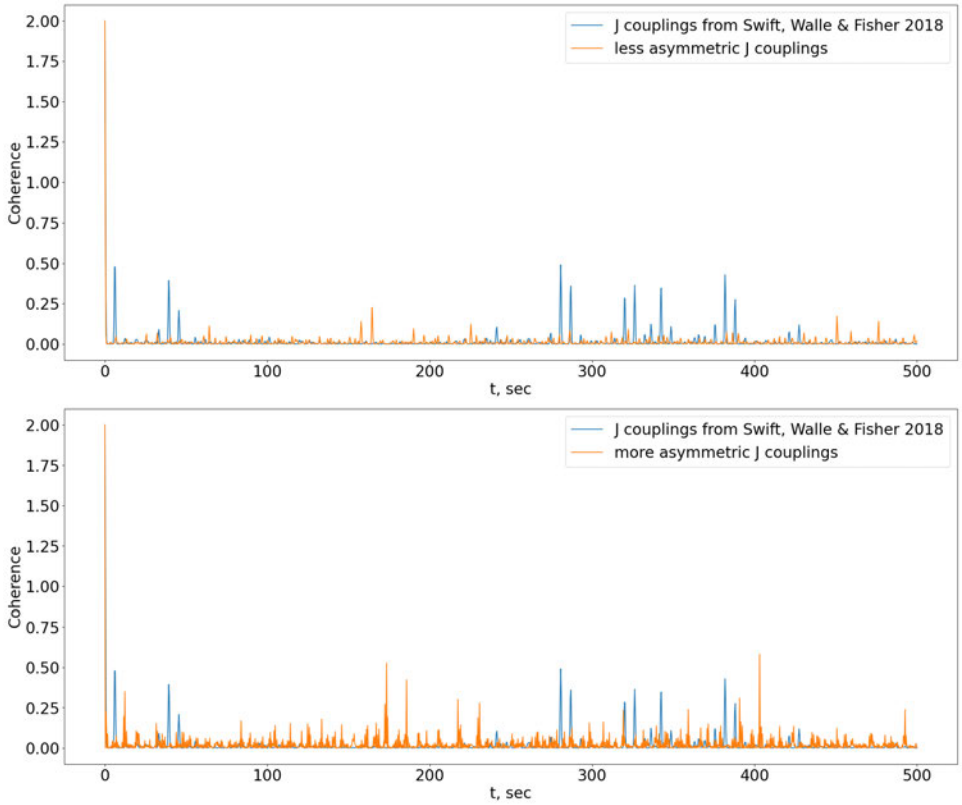

Figure 3.3: Dependence of coherence on the specific symmetries of the Posner molecules: We tried two different asymmetric configurations by varying the J-couplings. In the top graph, where the J-couplings are all different but both halves of the molecule are comparatively strongly coupled the coherence is attenuated compared to the symmetric case. In the bottom graph the asymmetry is more pronounced, with one side of the Posner molecule being very strongly coupled in comparison to the other half. Surprisingly, this caused an increase in coherence, possibly due to the strongly one-sided coupling effectively reducing the dimension of the Posner molecules.

weakly asymmetric case coherence and concurrence were both attenuated compared to the symmetric case. This would appear to be in agreement with the conclusion by Agarwal *et al.* that on average entanglement is better supported by symmetric molecules [300]. However, in the case of the very strongly asymmetric Posner molecule, the coherence and concurrence

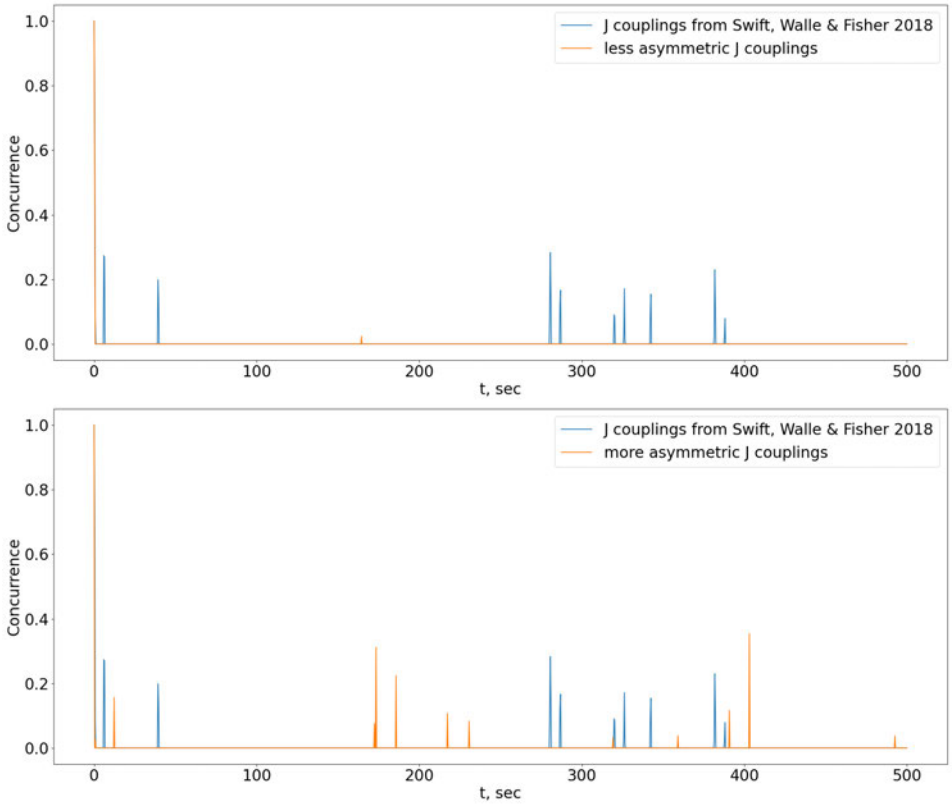

Figure 3.4: Dependence of concurrence on the specific symmetries of the Posner molecules: Similarly to the case for coherence, we tried two different asymmetric configurations by varying the J-couplings. In the top graph, concurrence is almost nonexistent. In this case the J-couplings are all different but both halves of the molecule are comparatively strongly coupled, with very weak concurrence between 100 and 200 seconds. These results appear to be partially in agreement with the conclusion in the recent paper by Agarwal *et al* that on average symmetric molecules are expected to have a better entanglement yield [300]. However, when we arranged the J-couplings so that there is a very strongly coupled half of the Posner molecule (with respect to the entangled nuclei) then the concurrence is markedly increased. Very strong asymmetry in effect reduces the dimension of the Posner molecules, which appears to have the effect of increasing the entanglement.

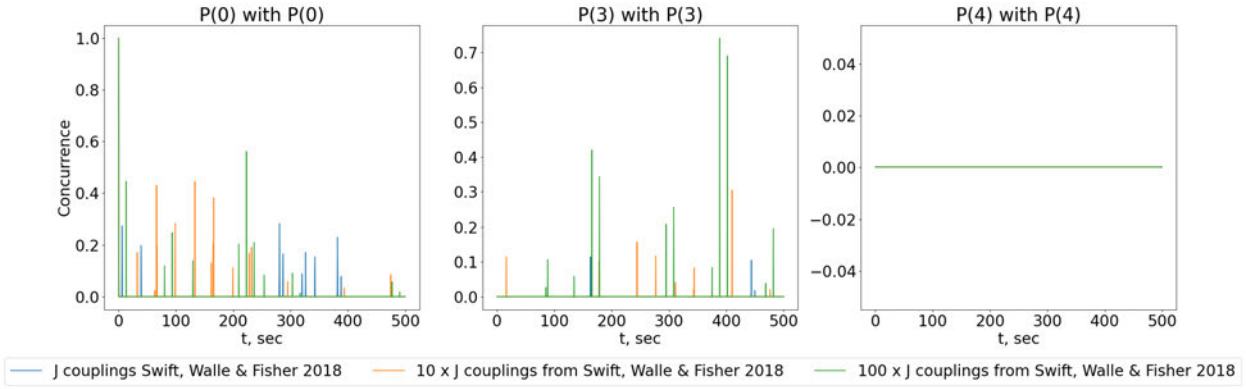

Figure 3.5: Entanglement transfer between the different phosphorus nuclei in a Posner molecule, where only one of the nuclei of each Posner molecule is initially entangled, P(0) with P(0): Entanglement is only transferred between the initial phosphorus P(0) and the furthest phosphorus P(3) in each of the entangled Posner molecules, regardless of J-coupling strength. There is zero entanglement seen between any of the other pairs, where P(4) and P(4) is given as an example.

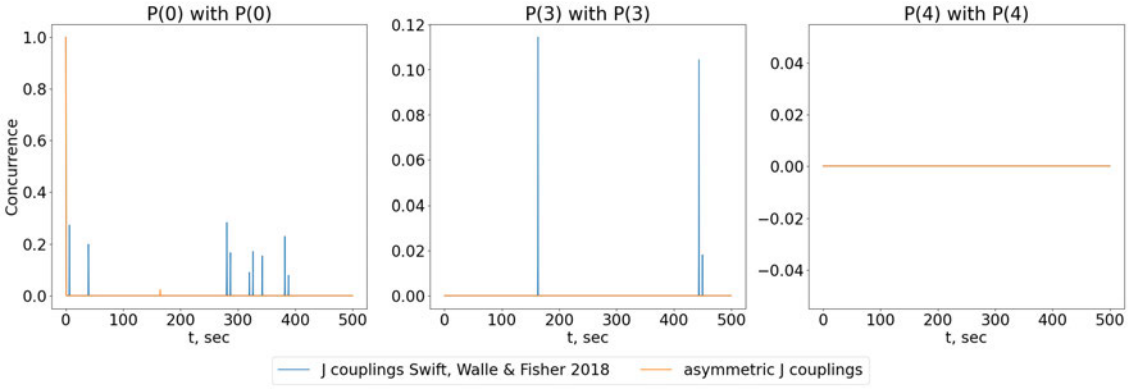

Figure 3.6: Dependence of entanglement transfer on symmetry constraints: Entanglement transfer depends on the symmetry of the molecule with the weakly asymmetric case (orange) having no entanglement transfer. There is zero entanglement seen between any of the other pairs, in both symmetric and asymmetric cases where P(4) and P(4) is given as an example, (the blue graph is beneath the orange).

are surprisingly increased. This may be due to a combination of increased J-coupling strengths as well as an effectual reduction in dimension of the Posner molecule due to the unequal coupling strengths. The latter is potentially interesting given the suggestion that entanglement is increased in calcium phosphate dimers as compared to trimers [300]. Following the example of Player and Hore [289] we also investigated how entanglement is transferred between the different phosphorus nuclei in a Posner molecule, where only one of the nuclei is initially entangled. Entanglement is only transferred between the initial phosphorus and the furthest phosphorus in each of the entangled Posner molecules, regardless of J-coupling strength, see Figure 3.5. We also investigated how entanglement transfer depends on the symmetry of the molecule with the weakly asymmetric case having no entanglement transfer whatsoever, see Figure 3.6.

3.5.2 Doped Posner molecules

It was noted that it is possible to replace calcium ions in calcium phosphate aggregates with other appropriate ions, such as sodium, magnesium or lithium [100, 101, 237]. Lithium is monovalent, therefore to replace a calcium ion in a pure Posner molecule requires two lithium ions [101]. As with pure Posner molecules the spin state oscillation depends on the J-coupling constants. In Figure 3.7 we consider how the different lithium isotopes change the coherence and concurrence of a pair of phosphorus nuclei. In the case of coherence, the two isotopes do have different effects, with more coherence in the ^{6}Li case. However the coherence in both cases is so small as to be almost negligible. In the case of concurrence, both ^{6}Li and ^{7}Li destroy any entanglement, as measured by singlet state population. There is also no entanglement transfer. These results are not promising with regards to Fisher's suggestion that lithium's mode of action is through being incorporated into Posner molecules. They also reiterate the conclusion in Agarwal *et al.* that the size of the spin system is the main constraint on the entanglement [300].

What, if anything, does the incorporation of lithium do to the spin dynamics of entangled phosphorus nuclei? The answer might lie in a closer inspection of the Zeeman interaction. We investigated what effect the lithium isotopes have on the spin dynamics of the singlet and three triplet states, see Figure 3.8. For pure Posner molecules (top graph) the three triplet states are degenerate and out of phase with the singlet state. Introducing ^{6}Li and ^{7}Li causes

the entangled triplet state to instead oscillate in phase with the entangled singlet state. This might be seen as analogous to the high field effect for a radical pair, when the hyperfine interaction is sufficiently smaller than the external magnetic field and the two non-entangled triplet states are separated in energy from the entangled states. Coherent mixing of the singlet and entangled triplet states in radical pairs can be driven by different Larmor precession frequencies, with the frequency of mixing related to the difference in gyromagnetic ratio [259]. In the Posner analogy the Earth's magnetic field is at least three orders of magnitude larger than the J-coupling interaction. In addition to this, the small gyromagnetic ratio of ^{6}Li gives a precession frequency of ≈ 1970 Hz whereas ^{7}Li gives ≈ 5200 Hz, very close to phosphorus at ≈ 5420 Hz.

3.6 Discussion

3.6.1 Relaxation pathways

In the previous sections we have considered only the coherent dynamics. For example we plotted the dynamics of lithium doped Posner molecules for up to 500 seconds (see Figure 3.8). If spin relaxation is taken into account then it must be acknowledged that both lithium isotopes have a quadrupolar moment that means they relax faster than the spin $\frac{1}{2}$ phosphorus nuclei. Lithium lifetimes vary in the literature; Fisher's original papers discussing entanglement in Posner molecules notes the difference in coherence lifetimes between solvated ^{6}Li (≈ 5 minutes) and ^{7}Li (≈ 10 seconds) while hypothesising that phosphorus lifetimes might be as long as 21 days [100, 102]. In their paper on the spin dynamics of Posner qubits, Player and Hore dispute this, invoking intramolecular dipole interactions to arrive at an estimate of 37 minutes [289]. They also discuss a number of ways in which this lifetime might be significantly reduced, one of which is the replacement of calcium by other ions such as sodium [289]. We add to this a possible relaxation pathway that is specific to the case of lithium isotopes, that is scalar relaxation. For a spin half nucleus A (phosphorus) coupled to a second nucleus B (lithium) that is undergoing fast quadrupolar relaxation, the fluctuating magnetic field associated with fast relaxing nucleus B offers an additional relaxation mechanism for nucleus A. This is known as scalar relaxation and

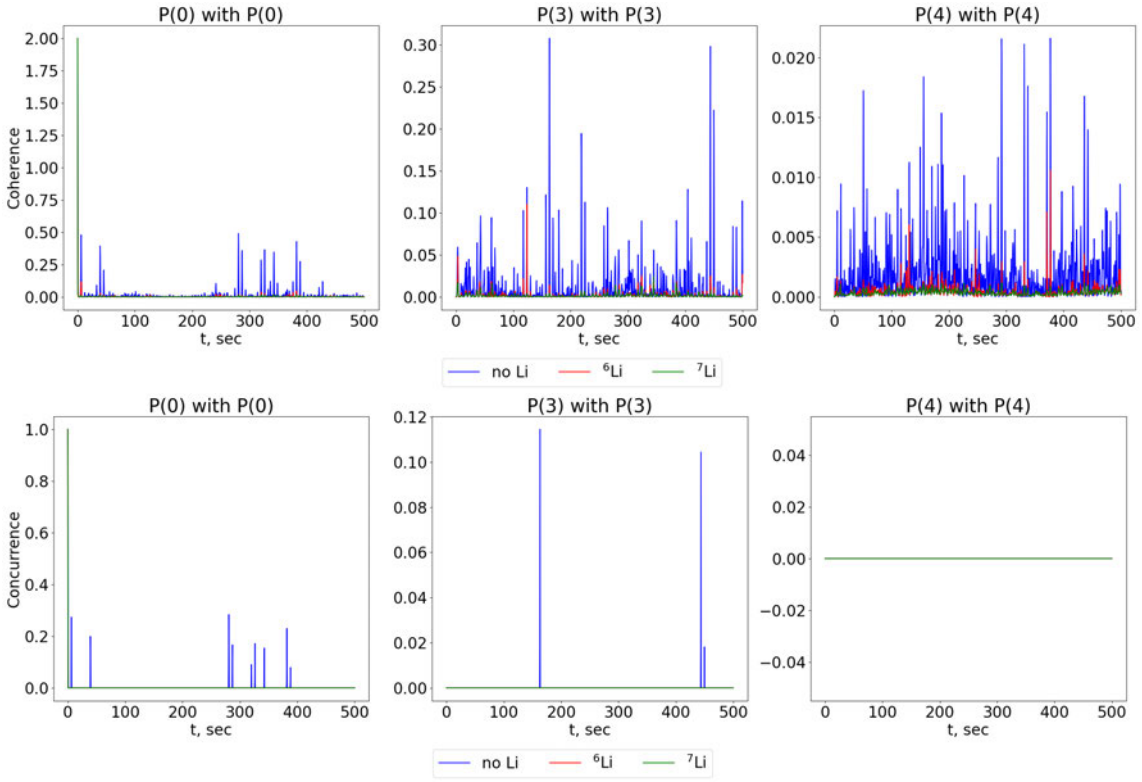

Figure 3.7: Effect of lithium isotopes on coherence (top) and entanglement (bottom) transfer: For the case of coherence we have increased the scale of the y-axis to illustrate how coherence is transferred differently between different nuclei. For two entangled spins initially P(0) and P(0) the maximum coherence is transferred to the furthest spins in each molecule, although there is a very small degree of coherence between other pairs, see for example P(4) with P(4) (with attention to the y-axis scale). Greatest coherence transfer is seen in pure Posner molecules (blue), followed by lithium 6 (red) and lithium 7 (green). However, the overall coherence is still minimal. In the case of entanglement, only pure Posner molecules (blue) show any entanglement and entanglement transfer.

is seldom taken into account due to the fact that it is most effective for nuclei that have similar Larmor frequencies [307]. This dependence is given in the

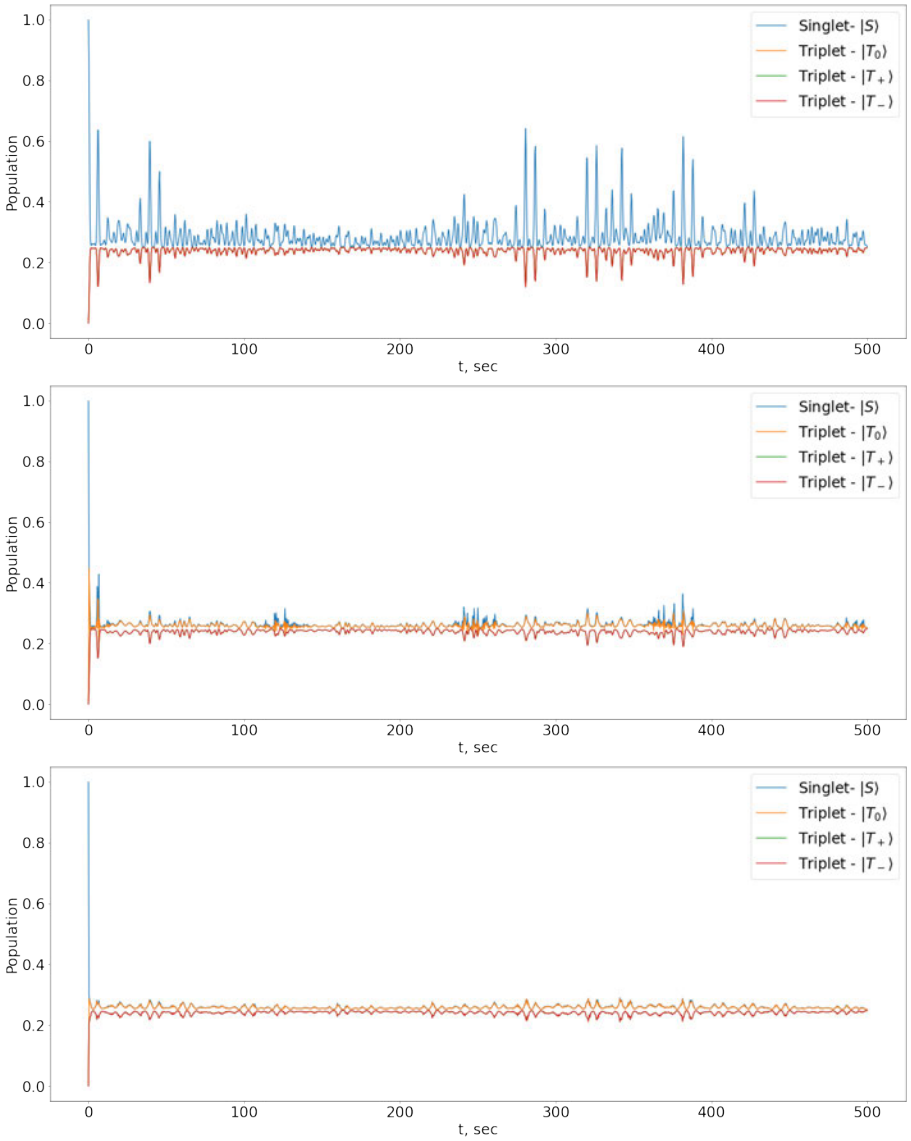

Figure 3.8: Effect of lithium isotopes on the spin dynamics: For pure Posner molecules (top graph) the three triplet states are degenerate and out of phase with the singlet state. Introducing lithium 6 (middle) and lithium 7 (bottom) causes the entangled triplet state to instead oscillate in phase with the entangled singlet state.

formula for the scalar relaxation lifetime

$$R_{\mathrm{sc}} = \frac{8\Pi^2 J^2}{3} I(I+1) \frac{\tau_{\mathrm{sc}}}{1 + (\omega_B - \omega_A)^2 \tau_{\mathrm{sc}}^2}, \tag{3.9}$$

where R_{sc} is the relaxation rate of nucleus A, J is the scalar coupling constant between A and B, I is the spin of the quadrupolar nucleus B, τ_{sc} is the correlation time associated with the scalar relaxation and ω_A and ω_B are the respective Larmor frequencies, given by

$$\omega_L = \frac{\gamma B_0}{2\pi}, \tag{3.10}$$

where γ is the gyromagnetic ratio and B_0 is the magnetic field in question [307]. Scalar relaxation is described by two types. We are interested in type 2, which occurs at low fields such as the geomagnetic field, which we here take to be 50μT. For type 2 scalar relaxation τ_{sc} is the T_1 of the fast relaxing quadrupolar nucleus [307]. What is of interest is that the Larmor frequencies of ^{6}Li and ^{7}Li differ to a large degree, whereas the Larmor frequencies of ^{31}P and ^{7}Li are close enough that scalar relaxation might offer a viable relaxation mechanism. To test this theory we calculated the relaxation rates and lifetimes for phosphorus nuclei in Posner molecules doped with either ^{6}Li or ^{7}Li. We use relaxation time scales for lithium isotopes as given in Fisher's original paper on Posner molecules, although spin-relaxation times for lithium isotopes vary widely across the literature. Due to the similarities between the Larmor frequencies of ^{7}Li and ^{31}P, scalar relaxation contributes an additional relaxation mechanism for the phosphorus nuclei in a Posner molecule, resulting in a phosphorus relaxation time of only seconds. Due to the large difference between the Larmor frequencies of ^{6}Li and ^{31}P the corresponding scalar relaxation lifetimes are at least five orders of magnitude greater.

3.6.2 Electromagnetic noise

It is often stated that a diagnostic test for the radical pair mechanism is the use of electromagnetic fields at frequencies equal to the singlet-triplet transition frequencies. In a previous paper we applied an open quantum systems approach to the radical pair mechanism to investigate transition operators and their related frequencies [308]. We reapply this model to the case of entangled phosphorus nuclei. In our model we only need consider

the open systems description of a single Posner molecule as the entangled Posner molecules are coupled only through their initial conditions and are sufficiently separated to not interact further. The Hamiltonian of the open quantum system is the sum of a free term H_0 and an interaction term H_{SB}

$$H = H_0 + H_{SB}, \tag{3.11}$$

where

$$H_0 = H_S + H_B.$$

We will describe the dynamics in the interaction picture, in which both state vectors and operators evolve in time. The system, in this case for a pure Posner molecule, includes the six phosphorus nuclear spins of the Posner molecule and how these interact with the Earth's magnetic field (Zeeman effect) and each other (J-coupling). This is given by Equation (3.3). This system then interacts with a bath given by

$$H_B = \sum_n \omega_n a_n^\dagger a_n, \tag{3.12}$$

where the ω_n are the frequencies of the $n-$th bosonic operator, $a_n^\dagger$ is the creation operator and a_n is the annihilation operator. Each Posner molecule of the entangled pair interacts with a separate but identical bath. The interaction Hamiltonian for one Posner molecule can thus be written as

$$H_{SB} = \sum_k \sum_n (g_{n,k} a_n + g_{n,k}^* a_n^\dagger) \otimes (\alpha_k S_x^k + S_z^k), \tag{3.13}$$

where the index k keeps track of the different phosphorus nuclei and S_x^k or S_z^k represent dissipation and decoherence respectively, with $\alpha_k \geq 0$ a model parameter weighting the extent to which S_x^k and S_z^k contribute. What is of interest in a discussion of the entanglement are the transitions between possible states. The transition operators result from the decomposition of the operator $V^k = \alpha_k S_x^k + S_z^k$ in the basis of the eigenoperators of the diagonalised system Hamiltonian H_S. They are found using

$$[H_S, V_q^k] = -\omega_{k,q} V_q^k \quad \text{and} \quad [H_S, V_q^{k,\dagger}] = \omega_{k,q} V_q^{k,\dagger},$$

where q here labels the number of transition operators and the transition frequencies corresponding to each operator V^k, $\omega_{k,q} \geq 0$, are expressed in

terms of the parameters of the system Hamiltonian, that is the magnetic field and the coupling constants [308]. A transition frequency equal to zero corresponds to decoherence in the system, which is found using

$$[H_S, V_0^k] = 0.$$

Given that the transition frequencies depend on the specific parameters of the system Hamiltonian, they will vary according to the relative strengths of the Zeeman and scalar coupling terms. For the radical pair mechanism, which is concerned with electron spin, hyperfine coupling strengths range from kHz to MHz [260]. This gives transition frequencies that range from kHz to MHz, which seems consistent with the fact that the avian compass is disrupted by broadband electromagnetic noise [308, 309]. For the Posner molecule nuclear spin states the transition frequencies vary according to the strength of the Zeeman and J-coupling terms. In particular the two entangled states, which are unaffected by the external magnetic field, have transition frequencies which reflect the J-coupling constants, which are of the order of Hz. This is potentially interesting in light of the fact that the brain emits electromagnetic radiation of the order of Hz, colloquially known as 'brain waves' or neural oscillations. The origin of brain wave radiation is yet to be fully understood, and may have no association with (entangled or other) calcium ion production. However, given that the interconversion of entangled states is of similar frequencies, the background electromagnetic radiation generated by the brain (and other organs) should be taken into account as a possible source of noise or driven interconversion when discussing the spin dynamics of Posner molecules.

3.6.3 Entangled subspaces

In Fisher's original Posner molecule hypothesis, the entanglement is important in the context of quantum to biological transduction: how do the quantum effects result in measurable biological outcomes? Fisher contends that the Posner molecule entanglement results in modified molecule binding, melting and free calcium ion release [100]. If entanglement is indeed important with regards to Posner molecules and neural activation, how might biological systems have maximised this quantum resource? Agarwal *et al.* [300], for instance, suggest that different forms of calcium phosphate, for example dimers rather than trimers, are better suited to neural processing, having

very long lived entanglement. We suggest here that the parameters supplied by the particular environmental context – the specific values of the Zeeman effect in the Earth's field relative to the strength of the J-coupling constants – act to naturally enhance the entanglement. In a paper investigating entanglement in radical pairs, Tiersch *et al.* suggest that one way in which to enhance the entanglement lifetime is the application of appropriate magnetic fields. This would create a subspace in which almost all mixed (singlet and triplet) states are entangled due to Zeeman shift of the two non-entangled triplet states [283]. We were interested in how this could apply in the case of nuclear spin entanglement. Entangled phosphates are hypothesised to be created by the hydrolysis of pyrophosphate [100]. Before these entangled phosphates bind to spin zero calcium and form Posner molecules, they might also end up binding to hydrogen [100]. Hydrogen has a large gyromagnetic ratio. We were interested to see whether hydrogen binding to phosphates could instead be beneficial to enhancing the entanglement, by creating an entangled subspace. In Figure 3.9 we demonstrate what happens to the different spin states of the entangled phosphates bound with hydrogen. When the external magnetic field is of comparable strength to the J-coupling then there is mixing between all four of the spin states. However, for an external magnetic field that is much stronger than the J-coupling, as is the case for Posner molecules in an Earth strength field, then the two non-entangled triplet states are sufficiently separated in energy to prevent mixing. The result is an entangled subspace, where only the entangled states mix. In Figure 3.10 we illustrate this using concurrence as a measure of entanglement. The usefulness of this increased entanglement is debatable. Indeed, a paper by Eisert *et al.* argues that in a diffusion model the loss of position information can degrade entanglement considerably [310]. However, in the radical pair mechanism, for example, it is less the entanglement than it is the spin state that is important. Singlet and triplet states have differential reactivity. In our example of nuclear spin entanglement, increased entanglement also means increased singlet state. If this increased singlet yield plays a role in any biologically relevant chemical reaction, then the high field effect we describe here may be functionally important. Phosphorus is also found within cell membranes, which are composed of phospholipids. In this case the binding of hydrogen to fixed phosphates may possibly exploit this entanglement 'distillation'. Entangled subspaces in the context of nuclear spin dynamics could also give insight into ways of enhancing entanglement in spin models of quantum computers, where the spins are fixed rather than diffusive.

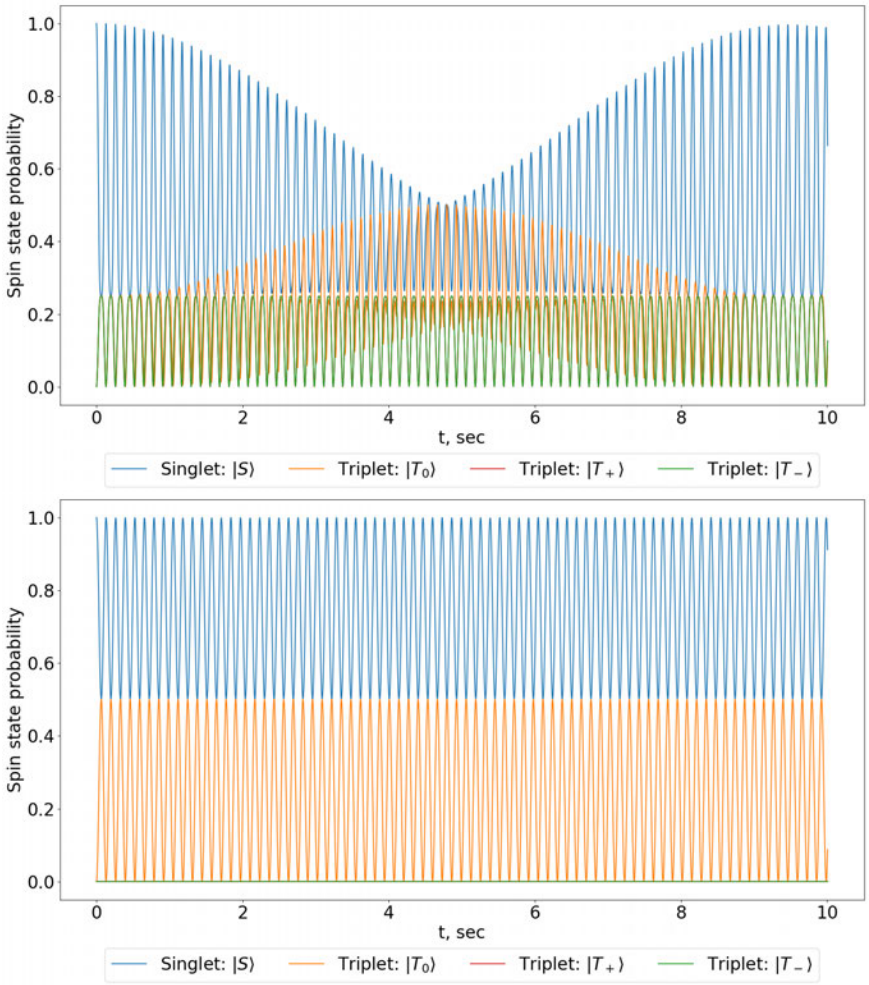

Figure 3.9: Different spin states of the entangled phosphates bound with hydrogen: When the external magnetic field is of comparable strength to the J-coupling there is mixing between all four of the spin states, (top). Note the red and green states are degenerate. However, for an external magnetic field that is much stronger than the J-coupling, as is the case for Posner molecules in an Earth strength field, then the two non-entangled triplet states are sufficiently separated in energy from the entangled states to prevent mixing. The result is an entangled subspace, where only the entangled states (blue and orange) oscillate and the non-entangled triplets (green and red are degenerate) show a straight line (bottom).

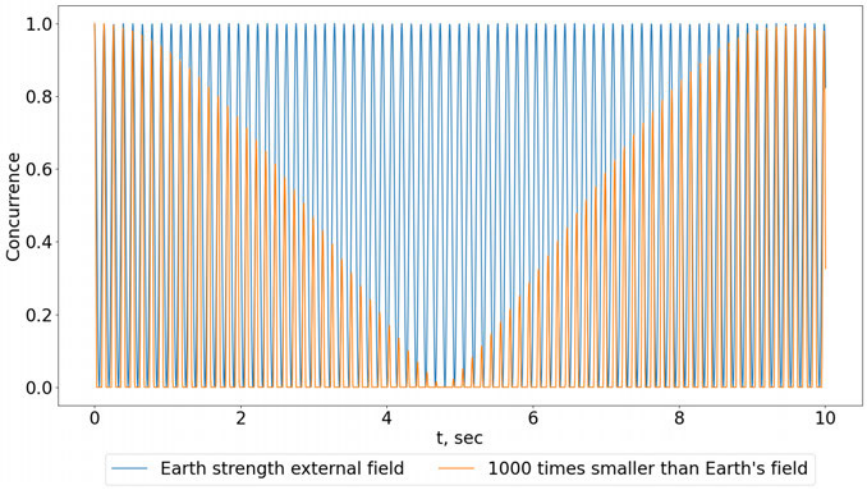

Figure 3.10: Comparison of entanglement for different strengths of the external field with respect to the J-couplings. The blue graph shows how entanglement is increased for an external field, such as the Earth's field, that is three orders of magnitude greater than the J-coupling strengths. The orange graph shows the decreased entanglement for an external field that is of the order of the J-couplings. Our measure of entanglement is concurrence which looks at singlet character. However there is also an entangled triplet state. Including this in the measure of entanglement should give us a fully entangled subspace.

3.7 Conclusion

Our conclusions are tentative given the lack of definitive parameters in the context of Posner molecules, both with or without lithium. Indeed, what this highlights is the importance of parameters in quantum biology. For instance we demonstrated that across a viable range of J-coupling constants, increased coupling strength increased phosphorus nuclear coherence and concurrence in Posner molecules. Given that these coupling strengths depend on the symmetry of Posner molecules and that this symmetry is disputed, more research remains to be done to determine the relevant parameters. For lithium-doped Posner molecules our results do not support the hypothesis that different lithium ions differently influence phosphorus nuclear coherence or concurrence. Although there is a marginal difference between the isotopes, both isotopes result in almost negligible coherence and concurrence.

This conclusion appears to be in agreement with the conclusion by Agarwal *et al.* that is is primarily the number of spins in the system that attenuate the entanglement [300]. What is potentially interesting is that lithium does change the spin dynamics of the correlated phosphorus nuclei. If this were to translate to spin-dependent binding and thus free calcium ion production, then an argument could be made for lithium modulating the production of free calcium and thus neural excitability. A way to test this might be to confirm that treatment with lithium changes levels of free calcium and phosphate ions, and that this holds to different degrees for different isotopes. There is some evidence to suggest that administration of lithium does indeed have an effect on serum concentrations of these ions, though the mechanism remains debatable [311, 312].

While our results for coherence and concurrence in lithium substituted Posner molecules remain inconclusive, the spin dynamics highlight a potentially interesting phenomenon. When entangled phosphates bind to hydrogen instead of calcium, it is proposed that quantum effects are destroyed. However, the fact that the external magnetic field is much larger than the scalar spin coupling allows for an effect analogous to the high-field effect in the radical pair, where mixing occurs only between the entangled states. In effect the Earth's magnetic field supplies an entangled subspace. This means that any travel outside of this magnetic field, such as space exploration and settlement will have to factor in these changes to the Zeeman splitting and the physiological implications thereof. This has further implications outside of biology, for example in the use of quantum computers that might use spin entanglement as a resource. Phosphates and phosphorylation are also ubiquitous in biological systems, and entangled phosphates may play a role outside of their incorporation into Posner molecules. Smolin [313], for instance, hypothesises how Fisher's theory of entangled phosphates might be combined with ideas from spin quantum computing and applied to the biological context of cell membranes, which are composed of phospholipids. While the viability of this remains to be seen, the parallel between phosphorus nuclear spin in the quantum computing and biological case – especially given the potential for entanglement preservation – leads us to the conclusion that the topic deserves further attention.

Chapter 4

Vibration assisted electron transport in receptors

4.1 Overview

[1]In biology there are many instances in which the binding of two molecules leads to an important functional outcome; this is the case with biological receptors, for instance. The correct recognition of appropriate binding molecules or 'ligands' underscores this functionality. At the same time one of the underlying principles of biological systems is their adaptability. This means that recognition and activation of receptors is not relegated to a single specific ligand. Instead receptors are to some extent promiscuous; responding – to a greater or lesser degree – to a number of different ligands. This has implications for drug discovery, but also for the understanding of endogenous ligands and how they compete for specific receptors. Many of the receptors necessary for the efficient functioning of the brain and nervous system are activated by ligands that also play a fundamental role in biological functions which would not fall under a strict definition of cognitive function. Serotonin, perhaps most widely recognised as the neurotransmitter associated with happiness, binds and activates a number of serotoninergic receptors. These receptors are found in the brain, the central and peripheral nervous systems, but also in epithelial cells, such as those in the intestine and else-

[1]This chapter is based on the following paper: B. Adams, I. Sinayskiy, R. van Grondelle, F. Petruccione. 'Quantum tunnelling in the context of SARS-CoV-2 infection', *Sci Rep.* **12** 16929 (2022).

where [314, 315]. In the context of this thesis, which focuses on quantum effects in the brain and nerves, any insights into receptor binding are useful. The application of quantum theory to more general receptor mechanisms in biological systems will hopefully shine light on the more specific case of neural activation and motivates the focus of this chapter on SARS-CoV-2 binding to host receptors. Viruses offer a novel case study, straddling, as they do, the properties of both living and non-living systems [316]. As such, they might also offer a novel application for quantum biology. There has been some research into investigating how quantum mechanics and viruses intersect. For example, Park *et al.* engineered a virus to obtain enhanced energy transport in excitonic networks [317]. Quantum dots have been used to label viral proteins in an attempt to enhance live imaging of virus-host interactions [318,319]. They have also been suggested to have antiviral properties [320–322]. There has even been an attempt to simulate the life cycle of a virus using quantum gates [323].

Meanwhile, the new coronavirus SARS-CoV-2 has fundamentally changed the world we find ourselves in. While SARS-CoV-2 vaccine development has been integral, there is some suggestion that we have entered a new era of pandemics [324]. It seems imperative that research into understanding viral mechanisms is accelerated. One way in which this might be achieved is to look at how research outside of established disciplines might allow new insights into physiological mechanisms. Quantum biology, which looks at how non-trivial quantum effects, such as coherence, tunnelling and entanglement, might play a role in biological systems, is one such field of research [1, 2, 4].

The phenomenon of energy and charge transfer is central to much of the research emerging in this field. There is some evidence that coherent energy and charge transfer play a role in photosynthetic networks [1, 8–10]. This is perhaps the best known application of quantum effects in the biological context. Charge transfer, however, is also important in the context of tunnelling in enzymes, which was first observed a number of decades ago [325]. Electron tunnelling has also been proposed to be the mechanism, or one of the mechanisms, by which olfactants activate olfactory receptors [18, 117]. Olfactory receptors are a class of rhodopsin-like receptors known as G-protein coupled receptors, or GPCRs [121, 326]. These receptors are implicated in numerous important physiological phenomena from the regulation of inflammation to the binding of neurotransmitters, the latter of which is currently emerging

as a new application of vibration-assisted electron tunnelling [124, 129, 135]. Electron tunnelling in these contexts has been investigated as an alternative to the lock-and-key mechanism, a shape-based explanation of receptor binding.

Our primary motivation in this chapter is the following: given the importance of receptor recognition, binding and activation in the biological context and given the expansion of the lock-and-key model to include the possibility of vibration-assisted tunnelling, it is salient to review the evidence for tunnelling in the context of viral mechanisms of host invasion. This chapter follows two main threads. First we outline the case for quantum tunnelling as an alternative or augmentation to the lock-and-key mechanism in the context of enzyme function, olfaction and neurotransmitter reception. We then review those aspects of SARS-CoV-2 infection that suggest a role for quantum tunnelling, specifically the involvement of enzymes as well as certain types of receptors. We also address the possible consequences of this connection using three aspects of SARS-CoV-2 infection: host cell invasion, medical intervention and post-viral syndrome.

4.2 A quantum approach to biological receptor mechanisms

4.2.1 Broader biological context

While quantum coherence in photosynthesis might garner more attention, quantum tunnelling in a biological context is arguably the oldest exemplar of the field of quantum biology. In the 1960s, Löwdin suggested that proton tunnelling might be the physical basis of DNA mutations [3, 327] an idea that is still very much of interest today [270]. Also in the 1960s, enzymes, first described over a century ago by Fischer as operating through a lock-and-key mechanism [328], were subsequently suggested to exploit quantum tunnelling [3, 325, 327]. Both electron and proton tunnelling in enzymes is now a well established field of research [329–332]. Other biological phenomena have also been characterised as utilising the lock-and-key mechanism of receptor binding. Cellular receptors bind with specific ligands and are integral to signalling processes throughout the body [333]. Receptor recognition and binding accounts for a range of physiological phenomena [334].

An important class of these receptors are G-protein coupled receptors (GPCRs), examples of which are receptors that mediate the sense of smell or the binding of neurotransmitters in order to open ion channels. What is interesting about GPCRs, in the context of quantum biology, is that they are related to rhodopsin [121, 326]. Rhodopsin is a retinal photoreceptor protein which consists of the light-sensitive chromophore retinal in an opsin protein [335]. Chromophores are a central theme with respect to quantum effects in photosynthesis, where it has been suggested that quantum coherence might play a role in energy and charge transfer [8–10]. This is perhaps less a unique feature of photosynthesis than it is due to the more general arrangement of chromophores in a protein [62]. Chromophores, then, would appear to be important to redox activity in biological materials. There is also a growing focus on the role that the protein scaffold might play in enhancing energy or charge transfer. Far from the warm, wet, decoherent environment that is often cited as an argument against quantum effects in biology, the vibrational or spin states of proteins might be coupled to electronic states in a favourable way [336,337]. Interaction with proteins can fundamentally change the properties of a chromophore. Rhodopsin and related opsins, for instance, absorb across a range of frequencies even though they share the same chromophore: retinal. What differs is the opsin protein, which tunes the chromophore's absorption frequency [338].

The coupling of vibrational to electronic states is most often imagined with respect to the proteins in which the chromophore is embedded, but it might be re-imagined in terms of protein-receptor bonding. While it is still debatable that GPCRs, being related to rhodopsins, operate through a mechanism related to electron transfer, both olfaction and neurotransmitter binding have been of interest in the context of quantum biology. Olfaction has conventionally been described as operating through the recognisable shapes of olfactants [117]. However, this model has to some extent failed at fully describing the intricacies of our olfactory apparatus. This has given rise to an alternative vibrational theory of olfaction. In this theory, the vibrational spectrum of a ligand rather than its shape is responsible for receptor activation by facilitating electron tunnelling [18,339]. While there is some evidence to support the differentiation of deuterated odorants in various species [123–126], there remains some scepticism with regards to the theory [340]. The suggestion has been made that the mechanism of olfaction might be closer to a swipe

card model, with various different factors contributing [341].

More recently, attempts have been made to apply the vibrational theory of olfaction in a different physiological context: the binding of neurotransmitters. Neurotransmitters are integral to the process of neural signal transmission. Signals travelling along the axon of a nerve cell are communicated to adjacent nerve cells by the release of neurotransmitters across the synaptic cleft between cells [41]. These neurotransmitters bind to membrane receptors which facilitate the opening of ion channels and thus initiate the activation of nerve cells [41]. Theoretical research suggests that the action of specific neurotransmitters such as serotonin and related ligands is correlated to their vibrational spectra [124, 132]. Similar theoretical effects have been suggested for the binding of histamine [135] and adenosine [129, 131] although experimental verification is still lacking. What we would like to highlight, however, is the fact that charge transfer is a well established topic in quantum biology. More specifically, the biological context of this transfer is very often that of membrane-embedded proteins. Within this research much attention is paid to how the biological environment might assist transfer processes, through, for example the vibrations of the protein scaffold or the vibrations of a binding ligand. It is thus potentially informative to consider this in the context of infection by the SARS-CoV-2 virus, which utilises membrane-embedded proteins to invade host cells, see Figure 4.1.

4.2.2 The specific context of SARS-CoV-2

Our current knowledge of the SARS-CoV-2 virus touches on a number of the specific biological instances outlined in our discussion of tunnelling effects: enzymes, receptor binding and olfaction. Before it can proliferate, the virus first needs to invade its host cell. Research suggests that the SARS-CoV-2 virus most likely invades host cells by interaction with host enzymes, in particular angiotensin converting enzyme (ACE2) [342, 343]. The spike protein of the virus, which is also the target of the vaccine, binds with membrane-embedded ACE2 and facilitates the fusion of virus and host membrane [344, 345]. In its ordinary cellular context, ACE2 is an enzyme that modulates the form of the GPCR-binding ligand angiotensin, a hormone that is part of the renin-angiotensin-aldosterone system (RAAS). Among other things, angiotensin is important to the balance of vasodilation and vasoconstriction and is integral to cardiovascular function [346–348]. The exact

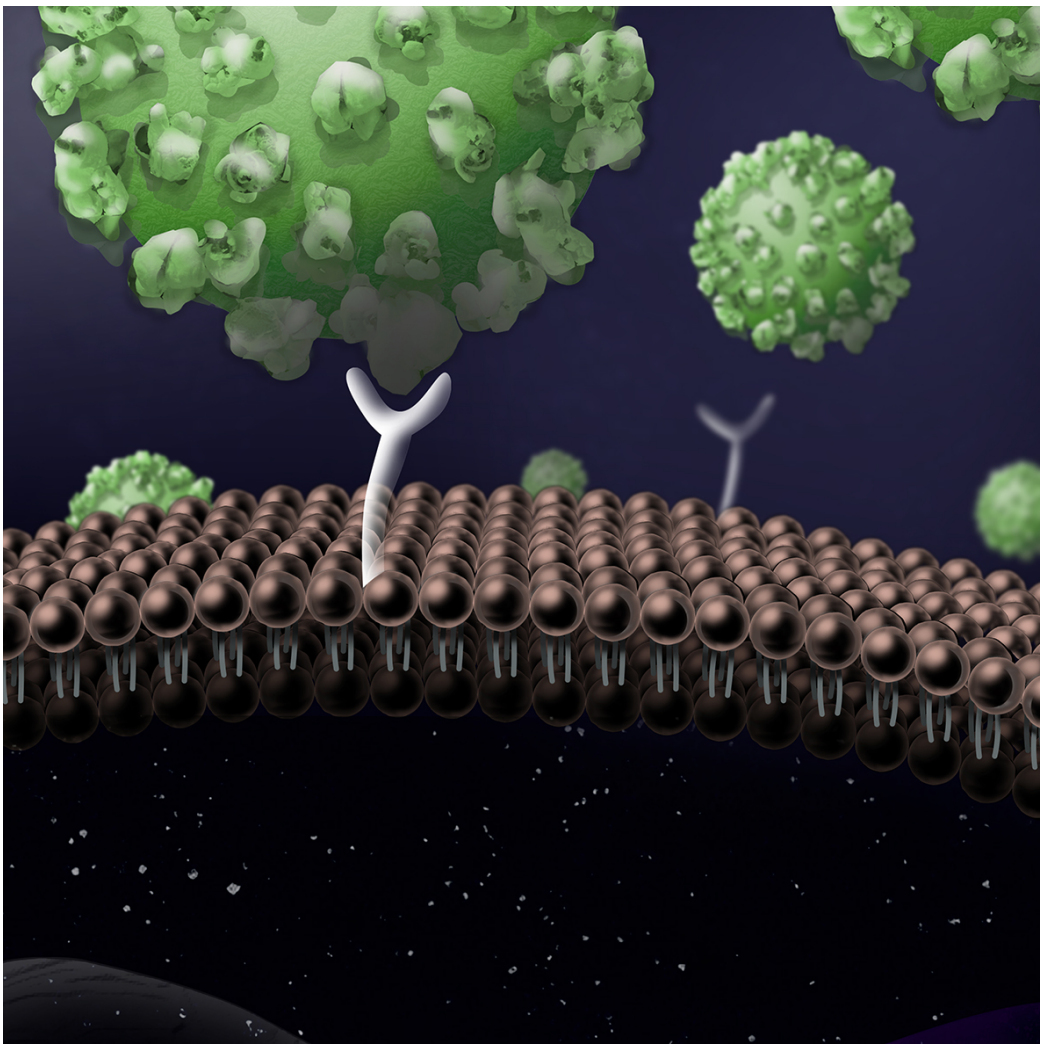

Figure 4.1: The SARS-CoV-2 spike protein facilitates host cell invasion by binding with cell membrane embedded ACE2 receptors. Illustration by Angela Illing.

interaction of the coronavirus spike protein with its host cell is also of potential importance in light of the new mutated versions of the virus [349, 350]. Mutations in the viral genome that code for the spike protein have led to fears of increased transmissability [351,352]. While the ACE2 enzyme is currently the focus of much of the research, other enzymes have also been implicated in SARS-CoV-2 viral infection. Research suggests that the host cell enzyme serine protease TMPRSS2 is necessary for protein priming of the spike protein and facilitates the virus entering the host cell [353, 354]. Another enzyme, cathepsin L, has been linked to spike protein cleavage and enhanced viral entry into host cells [353, 355]. Given the importance of enzymes in viral activity and given the fact that quantum tunnelling plays a role in enzyme activity it seems a closer look at quantum effects in the context of viruses might prove fruitful.

More generally, a closer look at receptor mechanisms might offer some insights. Criticism of the vibration assisted tunnelling theory of olfaction often points to the fact that there isn't evidence for electron transfer in olfactory receptors, which are GPCRs [356]. However, a recent, as yet to be reviewed, paper suggests that there is the potential for electron transfer in certain types of GPCRs. Various possibilities for the specific site of this electron transfer are explored in detail in the paper [356]. In the context of SARS-CoV-2, one of these is of particular interest: the disulfide bridge. ACE2 is not a G-protein coupled receptor. Evidence does suggest, however, that its interaction with the spike protein might involve redox activity [357–359]. This redox status is also suggested to involve a disulfide bridge. Both spike protein and ACE2 are rich in cysteine residues, which are implicated in intramolecular disulfide bonds [357]. Indeed, the infectivity of SARS-CoV-2 appears to depend on the disulfide redox potential with resistant animals lacking a redox-active disulfide [357,358]. Binding affinity has also been demonstrated to be significantly impaired when the disulfide bonds of ACE2 and SARS-CoV-2 spike proteins are reduced [359]. ACE2 receptors have a disulfide bridge in common with certain types of GPCRs. While we acknowledge that this is far from definitive, we think there is enough evidence to at least inspire some interest in the possibility of electron transfer in receptors in general and in COVID infection in particular. We think this for the following reasons. Firstly, the identification of the disulfide bridge in GPCRs, which is also found in the ACE-2 receptor that we model. Secondly, electron transfer through proteins is well established in quantum biology, as is the fact that this transfer is aided

by protein vibrations. It is thus not completely unfounded to consider that electron transfer might play a role in the proteins that constitute receptors, especially given the presence of cysteine and tyrosine sites, which have been implicated in electron transfer reactions in other contexts.

GPCRs themselves also appear to play a role in the disease associated with SARS-CoV-2 infection. The effects of COVID-19 on olfaction have been widely documented as one of the defining symptoms of the disease [360, 361]. ACE2 has elevated expression in the olfactory epithelium, where olfactory GPCRs are also located, which might account for the anosmia or altered sense of smell associated with COVID-19 [362]. GPCRs are also important in the context of COVID-19 inflammatory responses. Increased morbidity has been linked to the cytokine storm induced by the virus. Cytokines are small proteins produced by immune cells. The overproduction and dysregulation of cytokines, however, may lead to tissue damage and death [363–365]. As such, cytokines have been suggested as a possible therapeutic target to ameliorate COVID-19 mortality [363, 364]. A specific class of cytokines known as chemokines, and the chemokine receptor system, have been implicated in the severe clinical sequelae of COVID-19 [366]. Chemokine receptors belong to a group of rhodopsin-like transmembrane GPCRs similar to those activated by neurotransmitters and odorants [121, 367]. Whether or not quantum effects might be at play in any of these facets of SARS-CoV-2 infection and COVID-19 is debatable. However, molecular recognition and binding in the physiological context is integral to viral infection. As a common factor to enzyme function, receptor binding, olfactory symptoms and immune response, it deserves closer scrutiny through as many lenses as possible.

4.2.3 Relationship between transfer likelihood and vibrational modes

Theory

We model the interaction of the spike protein and the ACE2 receptor as a vibration assisted electron transfer [337, 368]. Biological systems interact with their environments and thus are often modelled using an open systems approach. In this approach the ligand protein, the receptor and environment are considered a closed system before tracing out the environment to get the reduced dynamics of the system of interest. The Hamiltonian describing

the system, environment and their interaction is used to derive the master equation [272]. Using this open systems approach and borrowing from a model developed for olfaction [369], we outline here the relationship between the maximum transfer probability in an ACE2 receptor and its coupling to a single vibronic mode associated with a SARS-CoV-2 spike protein. To simplify things we model the receptor as a dimer (see Figure 4.2) where the Hamiltonian is given by:

$$H_R = \epsilon_D \left|D\right\rangle \left\langle D\right| + \epsilon_A \left|A\right\rangle \left\langle A\right| + J(\left|D\right\rangle \left\langle A\right| + \left|A\right\rangle \left\langle D\right|), \tag{4.1}$$

where ϵ_D and ϵ_A are the energy levels of the donor (D) and acceptor (A) levels and J describes the coupling between levels and the likelihood of transition. For a dimer isolated from external interaction, the maximum probability of a transition from donor to acceptor is given by

$$\mathrm{Max}[P_{D\to A}(t)] = \frac{J^2}{J^2 + \Delta^2}, \tag{4.2}$$

where $\Delta = (\epsilon_A - \epsilon_D)/2$. When the energy of the donor and the acceptor are equal then the probability of transfer $[P_{D\to A}(t_0)] = 1$ at time $t_0 = \pi/2J$ [368]. For a dimer that is not isolated the total Hamiltonian is given by:

$$H = H_R + H_P + H_{R-P} + H_E + H_{R-E}. \tag{4.3}$$

The receptor is represented by the dimer with Hamiltonian, H_R. The Hamiltonian of the ligand, in this case the spike protein, is represented as a harmonic oscillator with frequencies ω associated with the protein:

$$H_P = \omega(a^\dagger a + \frac{1}{2}). \tag{4.4}$$

The interaction between the receptor and the protein is given by:

$$H_{R-P} = \sum_{i=D,A} \omega \left|i\right\rangle \left\langle i\right| \gamma_i (a + a^\dagger). \tag{4.5}$$

The sum runs over the interaction of the protein with both the donor and the acceptor; the latter is presumed to be zero in the numerical solution. The coupling strength between ligand protein and receptor is given by γ and a and $a^\dagger$ are the creation and annihilation operators associated with the spike protein vibrations, with associated frequency ω. The Hamiltonians H_R,

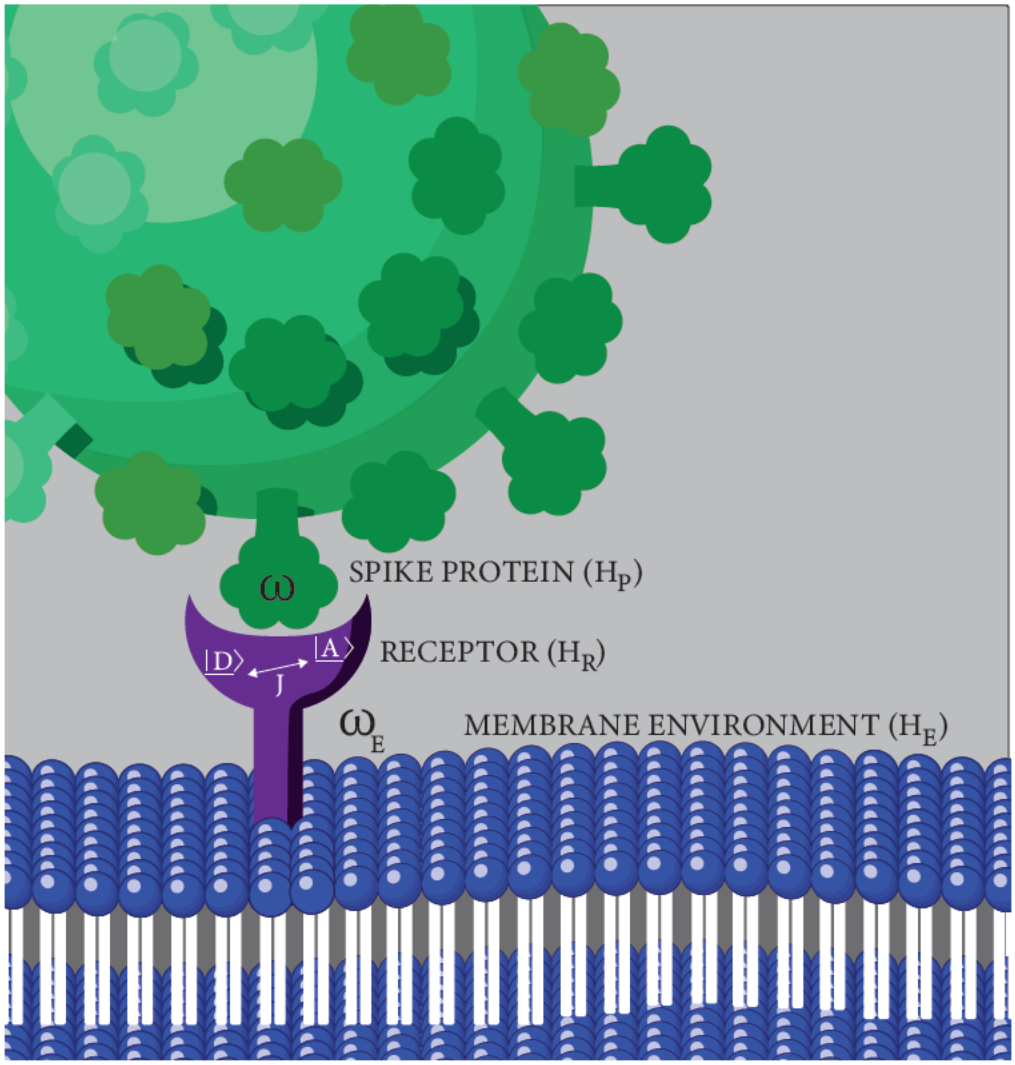

Figure 4.2: A simplified illustration of vibration assisted tunnelling in the context of SARS-CoV-2 infection. The spike protein vibrational spectrum matches the energy of transition for an electron in the ACE2 receptor, facilitating electron transfer and the activation of the receptor.

H_P and H_{R-P} represent the system in our model of SARS-CoV-2 receptor tunnelling. The membrane environment H_E and its interaction with the receptor H_{R-E} are similarly approximated as:

$$H_E = \sum_E \omega_E (a_E^\dagger a_E + \frac{1}{2}), \tag{4.6}$$

and:

$$H_{R-E} = \sum_{i=D,A} \sum_E \omega_E \left|i\right\rangle \left\langle i\right| \gamma_{iE} (a_E + a_E^\dagger), \tag{4.7}$$

where γ_{iE} represents the coupling between the receptor and its membrane environment. This coupling is taken to be weaker than the spike protein coupling to the receptor. The Hamiltonians H_{R-P} and H_{R-E} represent competing interactions, H_{R-P} is essential for receptor recognition of the spike protein, H_{R-E} on the other hand describes undifferentiated coupling to a multitude of environmental vibronic modes in the vicinity of the receptor. The spike protein vibrations are discriminated from the environment vibrations through their specific frequencies as well as the stronger coupling constants [369]. Here the sum runs over both the donor and the acceptor as well as all the possible environmental vibrations.

We now employ an open systems approach. The total density matrix of the receptor, protein and membrane environment satisfy Liouville's equation:

$$\frac{d\rho_{R+P+E}}{dt} = -i[H, \rho_{R+P+E}], \tag{4.8}$$

where H denotes the total Hamiltonian describing the spike protein, receptor and membrane environment (Eq. 4.3). Here we are interested in the reduced dynamics of the protein and receptor only. This can be achieved by tracing out the membrane environment degrees of freedom, namely

$$\rho_{R+P} = \mathrm{Tr}_E[\rho_{R+P+E}]. \tag{4.9}$$

If we assume a weak coupling between the receptor and the membrane environment, we can apply the Born-Markov approximation and replace Liouville's equation for the total system (Eq 4.8) by the corresponding master equation for the reduced system (for receptor and protein only) as follows [272]:

$$\frac{d}{dt}\rho_{R+P} = -i[H_R + H_P + H_{R-P}, \rho_{R+P}] \tag{4.10}$$

$$-\int_0^\infty d\tau \mathrm{Tr}_E\{[H_{R-E},[H_{R-E}(-\tau),\rho_{R+P}\otimes\rho_E]]\},$$

where $H_{R-E}(t)$ denotes the interaction Hamiltonian between receptor and membrane environment in the interacting picture and is given by,

$$H_{R-E}(t) = e^{it(H_R+H_P+H_{R-P}+H_E)}H_{R-E}e^{-it(H_R+H_P+H_{R-P}+H_E)} \tag{4.11}$$

$$\approx \sum_{i=D,A}\sum_E \omega_E \left|i\right\rangle\left\langle i\right| \gamma_{iE}(a_E e^{-i\omega_E t}+a_E^\dagger e^{i\omega_E t}).$$

To calculate the sum over the environmental degrees of freedom we introduce the spectral density as,

$$\sum_E \omega_E^2\gamma_{iE}\gamma_{jE}\delta(\omega-\omega_E) = \delta_{ij}J_i(\omega). \tag{4.12}$$

After integrating over the environmental degrees of freedom and time τ we obtain the following master equation,

$$\frac{d}{dt}\rho_{R+P} = -i[H_R+H_P+H_{R-P},\rho_{R+P}] \tag{4.13}$$

$$+\sum_{j=A,D}\kappa_j(\left|j\right\rangle\left\langle j\right|\rho_{R+P}\left|j\right\rangle\left\langle j\right| - \frac{1}{2}\{\left|j\right\rangle\left\langle j\right|,\rho_{R+P}\}_+),$$

where $\kappa_j = \pi(J_j(0-)+J_j(0+))$ denotes respective decoherent coupling of donor and acceptor to the membrane environment. We assume that the initial state of the dimer (receptor) is at the donor site, and the vibronic mode is initially in the thermal state (T = 300K). Using numerical simulation, we would like to understand if coupling to a vibronic mode could enhance the transition probability in the dimer system: from donor to acceptor. To this end, we will measure the usefulness of the vibronic mode coupling by considering the following difference:

$$\Delta P_{\mathrm{Max}} = \mathrm{Max}[P_{D\to A}(t)]_{\text{vibronic mode}} - \mathrm{Max}[P_{D\to A}(t)], \tag{4.14}$$

where $\mathrm{Max}[P_{D\to A}(t)]_{\text{vibronic mode}}$ denotes the maximum probability of the transition in the dimer system calculated from the numerical integration of Equation (4.13), while $\mathrm{Max}[P_{D\to A}(t)]$ represents the maximum probability of transition without vibronic mode coupling, given by Equation (4.2).

Table 4.1: Parameters for numerical solution [369, 370]

$\epsilon_A - \epsilon_D$ (cm^{-1})	J (eV)	γ_D (eV)	ω_1 (cm^{-1})	ω_2 (cm^{-1})	ω_3 (cm^{-1})
$500 - 1700$	$0.0001 - 0.1$	$0 - 0.419$	1669	1240	1000

Results

The difference $\mathrm{Max}[P_{D\to A}(t)]_{\text{vibronic mode}} - \mathrm{Max}[P_{D\to A}(t)]$ is plotted for a range of parameters. These parameters have been estimated with respect to comparable biological contexts, in particular Solov'yov *et al.*'s model for vibration-assisted tunnelling in olfactory receptors [369]. For clarity we have collected these parameters in Table 4.1. The coupling between spike protein and receptor (γ) is plotted from weak to strong coupling and we have assumed that the coupling only occurs between the spike protein and the donor level, that is $\gamma_A = 0$. This coupling strength is plotted as a fraction of the vibronic frequency and hence is unitless. Average energy levels and level coupling are estimated with respect to redox processes in other biological systems [369,371]. This coupling between levels in the dimer (J) is then plotted for a range of different values for each vibronic frequency: 0.0001, 0.001, 0.01 and 0.1 eV. The frequencies of the vibronic mode of the spike protein are taken from studies that investigate SARS-CoV-2 using Raman spectroscopy [370]. This includes the vibrational spectrum for both the S1 and S2 subunits as well as the full spike protein and the receptor binding domain [370].

We have plotted results for three different frequencies $\omega_1 = 0.2069$ eV ($1669\mathrm{cm}^{-1}$), $\omega_2 = 0.1537$ eV ($1240\mathrm{cm}^{-1}$) and $\omega_3 = 0.1240$ eV ($1000\mathrm{cm}^{-1}$), see Figures 4.3–5. For closer reference, we have taken the specific peaks corresponding to the spike protein Amide I, Amide III and phenylalanine, see Table S1 in reference (79) [370] for details. All three cases show a parameter regime in which the vibronic mode enhances electron transfer probability. White regions represent parameter regions where vibronic modes do not enhance electron transfer probability. Redder regions are where vibronic modes have a negative effect on electron transfer probability. Bluer regions represent where vibronic modes enhance electron transfer probability.

Vibronic modes have a marked effect on transfer probability in a selective

parameter regime, with this effect growing as coupling strength between levels increases. However when coupling between dimer levels is too weak (J = 0.0001 eV) the vibronic mode has no effect. And when the coupling is too strong (J = 0.1 eV) the vibronic mode begins to have a negative effect. This suggests a distinct biologically relevant parameter window in which vibration-assisted tunnelling takes place. Although the different frequencies of the vibronic mode display similar effects, the higher frequency (see Figure 4) appears to only have a single parameter regime in which the vibronic mode shows marked enhancement. However, lower frequencies (see Figures 4.4 and 4.5) appear to have two regimes in which the vibronic mode enhances transfer probability.

Whereas Figures 4.3, 4.4 and 4.5 demonstrate the effects of the proposed model over a range of biologically viable parameters, we were also interested in testing the model at the extremes of these parameters. To this end we have chosen the dimer coupling strength with the least favourable outcome (J = 0.1 eV) and plotted the effects of the vibronic coupling (γ_D) for very strong coupling to the vibronic mode. While this has an unfavourable effect at small dimer detuning, at larger dimer detuning the effect becomes favourable, showing enhanced transfer probability in distinct regions, especially for higher frequencies of the vibronic mode (see Figure 4.6).

In our simple model we have used only some of the peaks of the spike protein spectrum. However, we suspect that all vibrational modes of the spike protein will have some effect on electron transfer over the biologically relevant parameter range that we have chosen, either enhancing (blue regions) or decreasing (red regions) transfer, as we have shown on the graphs. We wanted to illustrate this as simply as possible, even though the real transfer may rely on the cumulative effects of all vibrational modes. This is why we have plotted the graphs over parameter ranges rather than for exact parameters, which are lacking. Our approach demonstrates which parameters are favoured for which vibrational frequencies. It would be interesting, given more accurate parameters for dimer coupling strength and protein-receptor coupling strength, to check whether these exact parameters correspond to enhancement at the strong vibrational modes. For now our model is an idealised one which we nonetheless hope serves as a useful overview of the concept.

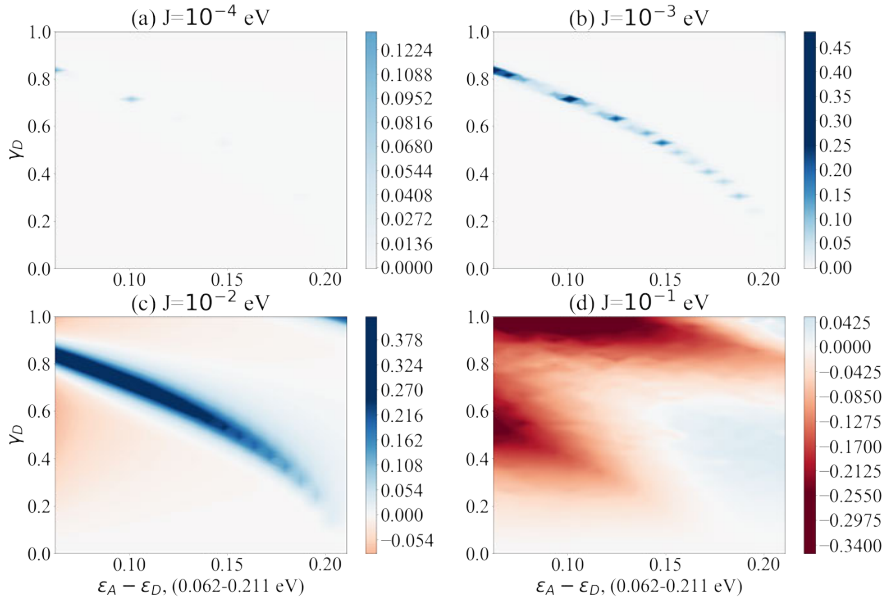

Figure 4.3: The difference between the maximum probability of transition with and without vibronic mode ΔP_{Max} as a function of the dimer detuning ($\varepsilon_A - \varepsilon_D$) and the coupling strength between donor and vibronic mode (γ_D). Results show coupling to vibronic mode frequency $\omega = 0.2069$ eV (1669cm^{-1}). Bluer regions show enhanced transfer with vibronic modes, white regions show no enhancement while redder regions demonstrate decreased transfer. Graphs (a)–(d) show the effects of increasing dimer coupling strength by an order of magnitude from J = 0.0001 eV to J = 0.1 eV. The results effectively illustrate the window of (biologically relevant) parameters within which vibration-assisted tunnelling has an effect.

4.2.4 Possible implications

Novel therapies for COVID-19

A better understanding of the various ways in which viruses and host cells interact through molecular recognition and binding might also lead to novel treatments for COVID-19. It has already been suggested that treatment with ACE2 inhibitors might have an effect on the severity of the disease. However,

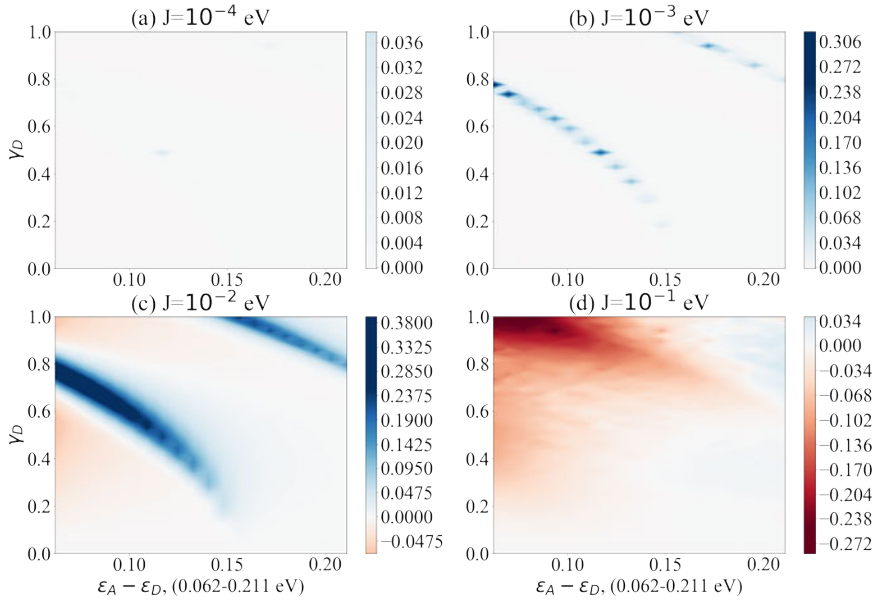

Figure 4.4: The difference between the maximum probability of transition with and without vibronic mode ΔP_{Max} as a function of the dimer detuning $(\varepsilon_A - \varepsilon_D)$ and the coupling strength between donor and vibronic mode (γ_D). Results show coupling to vibronic mode frequency $\omega = 0.1537$ eV (1240cm^{-1}). Bluer regions show enhanced transfer with vibronic modes, white regions show no enhancement while redder regions demonstrate decreased transfer. Graphs (a)–(d) show the effects of increasing dimer coupling strength by an order of magnitude from J = 0.0001 eV to J = 0.1 eV. The results effectively illustrate the window of (biologically relevant) parameters within which vibration-assisted tunnelling has an effect.

reviews are mixed as to whether this treatment may help or harm [372,373]. It has also been suggested that introducing soluble ACE2 might work against the virus by binding to the viral spike protein before it can bind to membrane ACE2 receptors [374]. ACE2 receptors also catalyse the different forms of angiotensin that bind with GPC receptors, in particular angiotensin receptors [346,347]. Whereas ACE2 inhibitors prevent the production of different angiotensin proteins, angiotensin receptor blockers prevent the action of angiotensin proteins. What is interesting is that there is some evidence that

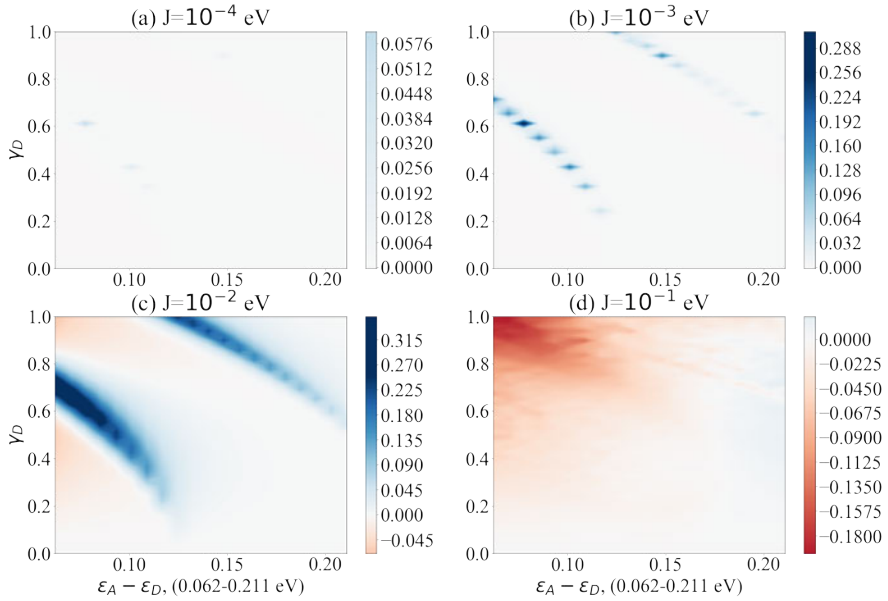

Figure 4.5: The difference between the maximum probability of transition with and without vibronic mode ΔP_{Max} as a function of the dimer detuning ($\varepsilon_A - \varepsilon_D$) and the coupling strength between donor and vibronic mode (γ_D). Results show coupling to vibronic mode frequency $\omega = 0.1240$ eV (1000cm^{-1}). Bluer regions show enhanced transfer with vibronic modes, white regions show no enhancement while redder regions demonstrate decreased transfer. Graphs (a)–(d) show the effects of increasing dimer coupling strength by an order of magnitude from J = 0.0001 eV to J = 0.1 eV. The results effectively illustrate the window of (biologically relevant) parameters within which vibration-assisted tunnelling has an effect.

targeting angiotensin receptors with receptor blockers also confers some protection against the SARS-CoV-2 virus [375–377].

Mechanisms of receptor binding are an important factor in pharmaceutical development. GPCRs, for instance, are one of the major targets of many pharmaceutical drugs and bind to a broad spectrum of ligands [378]. The specificity of this binding is complicated by receptor promiscuity and related antagonism or partial agonism [379]. Does the spike protein's affinity

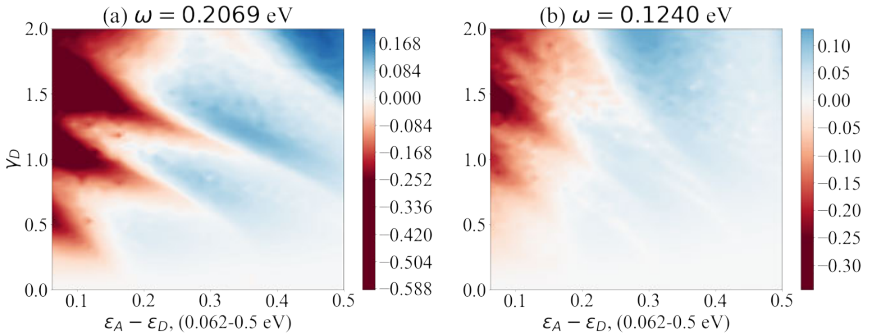

Figure 4.6: The difference between the maximum probability of transition with and without vibronic mode ΔP_{Max} as a function of the dimer detuning $(\varepsilon_A - \varepsilon_D)$ and the coupling strength between donor and vibronic mode (γ_D). Comparison of highest and lowest vibronic frequencies $\omega = 0.2069$ eV (1669cm^{-1}) and $\omega = 0.1240$ eV (1000cm^{-1}) for very strong coupling to vibronic mode. Coupling strength with respect to frequency is plotted up to a maximum of 2 rather than 1, as in previous figures. The detuning between the dimer levels is plotted up to 0.5 eV rather than 0.2 eV as in previous figures.

for ACE2 receptors also mean an affinity or partial agony for related angiotensin receptors, and GPCRs more generally? The involvement of GPCRs in viral infection has already been investigated in the context of the Ebola and Marburg viruses which employ a glycoprotein to facilitate host invasion. Chemical screening allowed for the indentification of a number of inhibitory agonists of various GPCRs, including receptors for serotonin, histamine, and acetylcholine, which showed antiviral action [380]. The SARS-CoV-2 spike protein is also a glycoprotein and screening for appropriate GPCR agonists might also yield novel therapeutic options. Tryptophans, for instance, have been demonstrated to play a potentially therapeutic role in SARS-CoV-2 infection [381, 382]. Tryptophan is the precursor to serotonin, perhaps most widely known as a neurotransmitter implicated in mental illnesses such as depression [383]. In the field of quantum biology there has been recent interest in whether quantum effects play a role in the binding of serotonin to its relevant GPCRs [124, 132].

What makes this more interesting in the context of COVID-19 is that antide-

pressants known as selective serotonin reuptake inhibitors (SSRIs) have been shown to be somewhat effective against the SARS-CoV-2 virus [384–386]. While the studies are far from being conclusive this isn't the first time that these antidepressants have been investigated as antivirals, although the mechanism of action appears to be less to do with serotonin modulation than viral replication [387,388]. Recent studies also suggest that SSRIs are not alone in their potential as a COVID-19 therapeutic. Other antidepressants, including venlafaxine, appear to improve the prognosis of patients hospitalised with COVID-19 [385]. Venlafaxine targets both serotonin and norepinephrine, both of which bind to GPCRs to activate ion channels [389, 390].

Other GPCR agonists have also been reported to have some effect in mitigating COVID-19 infection. Histamine, which plays a role in neuromodulation and transmission in addition to mediating immune and allergy responses, is an agonist that binds to a number of GPCRs [391]. Antihistamines, on the other hand, bind to histamine GPCRs and act as blockers or reverse agonists. There is some evidence that certain antihistamines protect against SARS-CoV-2 infection by disrupting the way in which the virus binds to its host cell [392]. There is still some doubt as to whether nicotinic receptors act, as least in part, as GPCRs [393]. These receptors, which bind the neurotransmitter acetylcholine as well as the agonist nicotine, do however open ion channels [394, 395]. Whereas there is little debate that smoking itself offers any protection against COVID-19, surprising statistics around the hospitalisation of smokers and non-smokers with COVID-19 has led to some speculation that nicotine might be a potentially therapeutic intervention against severe disease. It remains unclear, however, whether the effects of nicotine are helpful or harmful [396, 397].

The generalisation of the vibrational theory of olfaction to the binding of neurotransmitters has led to some suggestion that the agonist and antagonist action of certain ligands might be classified according to their vibrational spectra [129, 131, 135]. In the context of SARS-CoV-2, new therapeutics might be discovered by screening and selecting related ligands through, for example, their Raman spectra. The different vibrational spectra of mutated spike proteins might also allow some prediction of the infectivity of new variants of SARS-CoV-2. This chapter has focused on the SARS-CoV-2 spike protein binding to ACE2 receptors and its possible interaction with G-protein coupled receptors. In particular it has looked at at how the spike protein vi-

bronic mode might alter electron transfer in certain receptors. What many of these receptors potentially have in common is a disulfide bridge and the potential for redox activity [356,357]. Targeting the disulfide bonds has been shown to modulate host cell invasion [358]. This interest in the redox activity of the SARS-CoV-2 virus might also be extended beyond host cell invasion to offer insights on other aspects of COVID-19. ACE2 is a regulator of oxidative stress and it has been suggested that increased vulnerability to COVID-19 is related to increased oxidative stress, through factors such as increased age or underlying health issues [357,398–400]. Redox reactions proliferate in the body, not least in the electron transport chains within mitochondria. The spike protein has also been shown to directly modulate mitochondrial activity, most probably through ACE2 signalling [401]. Whether or not the spike protein is involved, a growing body of research suggests that mitochondria are implicated in COVID-19 and as such might inform novel therapeutic options [398, 402, 403].

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Post-viral syndrome: Long COVID

While redox considerations, receptor binding mechanisms and the involvement of GPCRs in SARS-CoV-2 infection might lead to possible novel treatments for the disease, it might also offer insights into the post-viral condition referred to as 'long COVID' [404]. Research into this condition is still in the very early stages, and much of it is focused on the urgent need for more research to be undertaken, due to the large number of people who appear to experience long term symptoms relating to COVID-19 [404–406]. Long COVID is not necessarily correlated with the severity of the active infection, with some patients reporting mild symptoms during the initial, acute stage of the disease before going on to experience lingering sequelae [404, 407]. Some of the long-term effects may be due to damage wrought by COVID-19 to organs such as the lungs and heart [407–409]. However, an appreciable portion of those reporting long term effects show no obvious biomarkers to account for their disorienting collection of symptoms, ranging from fatigue and joint pain to brain fog, memory problems, mood swings and mental illness [407, 408].

In its lack of defining mechanism and broad range of symptoms, long COVID resembles the condition that is sometimes called myalgic encephalomyelitis

(ME) or chronic fatigue syndrome (CFS) [404, 408]. It is well known that viral infections can cause a range of long term effects [410, 411]. Despite this, the condition remains under-researched, and, due to its various psychological manifestations often prompts suggestions that the syndrome is psychosomatic [412,413]. There is some research, however, that points to the involvement of GPCRs in both ME and CFS, in particular the disruption of GPCR function by autoantibodies [414–416]. GPC receptors control a wide range of essential functions and bind to a broad spectrum of different ligands, which makes them an excellent target for drug development. However this also means that specific ligands might interact with receptors other than their primary receptor, contributing, for example, to the side-effects of a GPCR-targeting drug [378]. Whether long COVID involves GPCR disruption remains to be seen. But if ACE2 can bind both the SARS-CoV-2 virus as well as molecules such as angiotensin, then perhaps the virus can mimic, at least partially, the way in which angiotensin binds to GPCRs, either through specific viral proteins or through autoantibodies.

GPCR disruption would also potentially explain the wide-ranging array of symptoms reported by long COVID sufferers, as GPCRs are implicated in many different physiological processes [326]. GPCR involvement in ion channel action might also prove an avenue of research for potential therapeutics. Viruses or the virome play an important, as yet not fully understood, role in the body [417]. It is thus conceivable that long COVID is a manifestation of some aspect of the SARS-CoV-2 virus being incorporated into host cells even beyond the infected stage. Viroporins, for instance are viral proteins that can oligomerise in host cell membranes to form ion channels of their own [418,419]. The physiological mechanisms behind both ME and CFS have been suggested to involve ion channels [420]. It might thus be interesting to investigate this in the context of long COVID, particularly as the envelope protein found in the SARS-CoV-2 virus has been shown to have viroporin capabilities [421, 422]. Ion channels are instrumental in maintaining membrane potential. While it is more common knowledge that membrane potential is integral to the activation and efficient function of nerve cells, all cells have an associated membrane potential. It is also becoming clearer that this membrane potential plays an important role in disease, not least cancer [423, 424].

Membrane potential is also integral to mitochondrial function, where it is coupled to energy and charge transfer in metabolic processes. Both ME and

CFS have been suggested to involve metabolic processes [425, 426]. It has recently been suggested that long COVID resembles ME and CFS in redox imbalance, inflammation, an impaired ability to generate adenosine triphosphate (ATP), and general hypometabolic state, all of which implicate mitochondria in the process [398, 403]. There is some evidence that supporting redox processes, through co-enzymes for instance, may help with metabolic illnesses [427, 428]. There is even some evidence that the ingestion of chlorophyll, the chromophore central to photosynthesis, might alter mitochondrial ATP production [429]. It is thus perhaps not too much of a stretch to suggest that elements of the SARS-CoV-2 virus might be incorporated into the redox function of mitochondria. These issues are peripheral to our main purpose in this chapter, which is to model the binding of the SARS-CoV-2 spike protein as an electron transfer process. However, we hope that the discussion might lead to the consideration of other contexts in which protein binding might disrupt the electronic properties of cells and how this might inform both novel treatments as well as post-viral long-term symptoms.

4.3 Future Perspectives

This chapter has been structured around two related assertions. The first of these builds on the possibility that the lock-and-key or shape-based mechanism used to describe a number of biological phenomena might be replaced or augmented by a quantum tunnelling mechanism. As such, quantum tunnelling is worth investigating in a variety of contexts where molecular recognition and reception play a role; in particular, in this chapter, in the context of membrane-receptor binding of SARS-CoV-2. The second assertion addresses this specific context and the way in which quantum tunnelling might be implicated in the receptor binding of the SARS-CoV-2 spike protein, either through the role of enzymes or the involvement of GPCRs. In the event of the latter, the degeneracy that no doubt allows biological systems their flexibility, also allows for the wide range of symptoms attributed to COVID-19 and long COVID. If GPCR-targeting pharmaceuticals can target more than the specific receptor they are aimed at, causing a variety of side-effects, then perhaps the spike protein behaves in a similar manner. And perhaps a better understanding of receptor recognition might contribute to better medical intervention. Regardless of whether these assertions prove to be true, the point remains that questions of interest in quantum biology, such as tunnelling in

the context of enzymes and GPC receptors, intersect with some of the open questions in SARS-CoV-2 research. As such, quantum biology can add to the store of knowledge that will offer protection against the SARS-CoV-2 virus as well as novel future viruses.

Techniques used in quantum biology, such as the comparison of vibrational spectra to predict GPCR agonist potency [124], might also inform approaches to virus research. The vibrational characteristics of the SARS-CoV-2 spike protein have already been used to gain insight into its structure by translating the protein into music [430]. More prosaically, SARS-CoV-2 infection has also been investigated using Raman spectroscopy [431, 432]. This might be extended to comparing the spectra of mutated spike proteins and whether this correlates with how infectious the mutated versions are, in a manner similar to how the potency of serotonin receptor ligands might be classified by vibrational spectra [124,433]. Vibrational spectra might also be used to identify new drugs to protect against infection. Vibration-assisted tunnelling in the context of neurotransmitters has already inspired research into the use of vibrational spectra to classify different ligands that bind to specific receptors [129, 135]. This could be generalised to the case of SARS-CoV-2 infection using the appropriate vibrational spectra. One example of this is the use of soluble ACE-2, or angiotensin blockers, to protect against SARS-CoV-2 [372,373]. If vibrational frequency is implicated in this binding, then pharmaceuticals with similar vibrational frequencies to these treatments could be investigated for their potential protective effects.

Quantum biology might also offer some insights into the long term debilitating effects of COVID-19 and shape possible treatments. While the focus in this chapter has been on quantum tunnelling in enzymes and GPC receptors, other related mechanisms of interest in quantum biology offer further avenues of research. ACE2, for example, is a regulator of oxidative stress [357]. Reactive oxygen species (ROS) have also been implicated in GPCR activity [434]. ROS are important signalling molecules but are also implicated in cellular inflammation and damage [435]. The production of ROS has been demonstrated to be sensitive to magnetic fields, a fact that has been attributed to the involvement of radical pairs, one of the primary topics of interest in quantum biology [208]. Inflammation is a contributing factor in both acute infection with the SARS-CoV-2 virus as well as in long COVID [436, 437]. Recently it has been shown that the application of electromagnetic fields can

significantly ameliorate the inflammation associated with COVID-19 [438]. Progress made in quantum biology may thus have even more to offer the study of viruses than the preliminary ideas laid out in this chapter.

Chapter 5

Conclusion

Quantum mechanics is often cited when it comes to trying to understand the phenomenon of consciousness. This may be less from any properly identified characteristic of the former which lends itself to explaining the latter and more to do with the fact that both are conceptually 'difficult' subjects. Is there a more specifically practical sense, then, in which quantum mechanics might be useful in better understanding the brain? The brain, strange though its emergent effects might seem, is, in a hardware sense, not that much more than a collection of nerve cells. In this sense, the aim of this thesis was not to attempt an explanation of consciousness, but to investigate to what extent quantum effects may play a role in the hardware of the brain. Despite their special function, the underlying processes associated with nerve cells are not all that much different from processes that occur in other cells more generally. Indeed, there is growing interest in the fact that the membrane potential by which nerve cells generate their action is a more general feature of all cells, playing a fundamental role in morphogenesis and regeneration. Key to this membrane potential are transmembrane proteins which control how porous cells, including nerve cells, are to the passage of different molecules. Receptor binding and activation are central to the action of these transmembrane proteins. Receptor binding and activation are also a growing field of research in quantum biology. This interest grew out of the vibrational theory of olfaction, in which it was suggested that the vibrational spectra of olfactory molecules caused vibration-assisted electron transfer to take place in the corresponding receptors [18]. While the theory is still up for debate, olfactory receptors resemble those receptors that neurotransmitters bind to, to facilitate nerve activation, which is fundamental to how nerves – and the

brain – work. Due to this similarity the olfactory research has been reapplied in the context of neurotransmitter and receptor binding in nerves, particularly with respect to serotonin, histamine and adenosine [124,129,135]. While the experimental evidence is lacking and the theory still elicits debate, one of the aims of this thesis was to investigate just how much of a general principle vibration-assisted receptor activation might be. While this question hints at the ways in which physical and mental processes might begin to overlap in simple but no less profound ways, it is also of practical relevance. Given the enormous impact of the SARS-CoV-2 pandemic, and the emerging research that COVID-19 has neurological as well as physiological symptoms, focusing on how viruses hijack transmembrane receptors to infect cells seemed an apt choice. The aim of this was multifold. On the theoretical side of things the aim was to generalise the theory from a specific context such as olfaction to a mechanism that may take place not only in receptors but in the context of any protein/ligand facilitated electron transfer. While there is growing acceptance of vibronic coherence in photosynthetic charge transfer, it has not been fully articulated how exactly this differs from vibration assisted transfer in receptors. The aim of this thesis was to suggest that vibration assisted tunnelling in receptors is as likely to occur as in other contexts where the protein scaffold plays a role. On the more practical side, the aim was to further understand how illnesses such as COVID-19 can have severe neurological as well as physiological effects, and, the flip side of this, to understand why medicines targeting a specific receptor can partially activate other receptors. A better understanding of receptor mechanisms might hopefully lead to the repurposing of old drugs to new contexts and develop a new understanding of – and novel treatments for – mental illnesses.

Mental illness and its interventions was also the launching point for the other point of focus of this thesis: specifically the role that lithium plays in ameliorating bipolar disorder, and what might explain the different actions of lithium isotopes. Once again the aim was to begin with a mechanism or model developed in the context of quantum biology and extend this into the neurological context. In this case the model in question was the radical pair mechanism of coupled electron spins. For the purposes of this thesis, however, the spin pairs were taken to be phosphorus nuclei in calcium phosphate molecules, as envisaged by Matthew Fisher [100, 101]. The original model was then extended to include lithium ions in order to investigate their effects on quantum parameters such as coherence and entanglement. While

the results suggest that coherence and entanglement do not survive the decohering effects of either isotope, one intriguing outcome of the research was the observation that the earth's magnetic field creates a subspace in which the entangled spin states of two phosphorus nuclei are preferred. While this thesis was very much focused on investigating the hardware of the brain, that is neural processing, entangled calcium phosphate molecules might begin to bridge the gap between this hardware and the consciousness it gives rise to. If, as it is sometimes suggested, consciousness arises out of global rather than local interactions of the brain, then the particularly quantum flavour of non-locality that is entanglement might advance our understanding of consciousness. Should it turn out that experimental evidence supports hypotheses of quantum enhanced neural processing we might turn this knowledge towards thinking about how we think.

Bibliography

[1] A. Marais *et al.*, *J. R. Soc. Interface* **15**, 20180640 (2018).

[2] J. Al-Khalili, J. McFadden, *Life on the edge: the coming of age of quantum biology*, London, UK Bantam Press (2014).

[3] J. McFadden and J. Al-Khalili, *Proc. R. Soc. A* **474**, (2018).

[4] M. Mohseni,Y. Omar, G.S. Engel, M.B. Plenio (eds). *Quantum effects in biology*, Cambridge, UK Cambridge University Press (2013).

[5] N. Lambert, Y.N. Chen, Y. Cheng, C. Li, G. Chen and F. Nori, *Nature Physics* **9**, 10 (2013).

[6] Zettili N., *Quantum Mechanics Concepts and Applications: Second Edition* John Wiley & Sons Ltd, UK (2009).

[7] Haken H & Wolf HC., *Atomic and Quantum Physics* Springer-Verlag, Berlin Heidelberg (1987).

[8] G.S. Engel *et al.*, *Nature* **446**, 782 (2007).

[9] T. Brixner, J. Stenger, H.M. Vaswani, M. Cho, R.E. Blankenship and G.R. Fleming, *Nature* **434**, 625 (2005).

[10] R. van Grondelle and V.I. Novoderezhkin, *Proc. Chem.* **3**, 198 (2011).

[11] G.S. Schlau-Cohen *et al.*, *J. Phys. Chem. B* **113**, 15352 (2009).

[12] G. Panitchayangkoon *et al. Proc. Natl. Acad. Sci. USA* **107**, 12766 (2010).

[13] E. Collini *et al. Nature* **463**, 644 (2010).

[14] K. Schulten, C.E. Swenberg and A. Weller *Z. Phys. Chem.* **111**, 1 (1978).

[15] W. Wiltschko and R. Wiltschko, *J Comp Physiol A* **191**, 675 (2005).

[16] W. Wiltschko, U. Munro, H Ford and R. Wiltschko, *Nature* **364** (6437), 525–527 (1993).

[17] H.G. Hiscock, S. Worster, D.R. Kattnig, C. Steers, Y. Jin, D.E. Manolopoulos, H. Mouritsen and P.J. Hore, *PNAS* **113** (17), 4634–4639 (2016).

[18] A.P. Horsfield, A. Haase and L. Turin, *Advances in Physics: X* **2** (3), 937 (2017).

[19] M.J. Sutcliffe and N.S. Scrutton, *Philos Transact A Math Phys Eng Sci.* **358** (1766), 367–386 (2000).

[20] P. Kurian, G. Dunston and J. Lindesay, *J Theor Biol.* **391**, 102–112 (2016).

[21] R. Penrose, *The emperor's new mind: Concerning computers, minds, and the laws of physics*, New York, US: Oxford University Press, (1989).

[22] S.R. Hameroff and R. Penrose, *Physics of Life Reviews* **11** (1), 39 (2014).

[23] C. Simon. Can Quantum Physics Help Solve the Hard Problem of Consciousness? *Journal of Consciousness Studies 26:5-6*, 204-218 (2019).

[24] P. Jedlicka, *Front Mol Neurosci.* **10**, 366 (2017).

[25] P.D. Bruza, Z. Wang, J.R. Busemeyer, *Trends Cogn. Sci.* **19**, 383 (2015).

[26] J.R. Busemeyer, P. Fakhari, P. Kvam, *Prog. Biophys. Mol. Biol.* **130**, 53 (2017).

[27] N. Savage, *Nature* **574**, S49-S51 (2019).

[28] N. Williams and R.N. Henson, *Brain and Neuroscience Advances* **2**, 1–4 (2018).

[29] A. Louveau *et al.*, *Nature Neuroscience* **21**, 1380 (2018).

[30] A. Louveau *et al.*, *Nature* **523**, 337 (2015).

[31] C.W. Lynn, D.S. Bassett, *Nature Reviews Physics* **1**, 318 (2019).

[32] K. Batista-García-Ramó and C.I. Fernández-Verdecia, *Behav Sci* **8** (4), 39 (2018).

[33] B. Vázquez-Rodríguez *et al.*, *Proceedings of the National Academy of Sciences*, 201903403 (2019).

[34] A. Messé, D. Rudrauf, H. Benali and G. Marrelec, *PLoS Comput Biol* **10** (3), e1003530 (2014).

[35] P. Brodal, *The Central Nervous System: Structure and Function. 3rd ed.* New York, NY: Oxford University Press, (2004).

[36] F.A. Azevedo, L.R. Carvalho, L.T. Grinberg, J.M. Farfel, R.E. Ferretti, R.E. Leite, F.W. Jacob, R. Lent, S. Herculano-Houzel, *J Comp Neurol.* **513** (5), 532 (2009).

[37] A. Araque and M. Navarrete, *Philos Trans R Soc Lond B Biol Sci.* **365** (1551), 2375 (2010).

[38] A. Tameem, H. Krovvidi, *Continuing Education in Anaesthesia Critical Care & Pain* **13** (4), 113 (2013).

[39] A.L. Hodgkin and A.F. Huxley, *J Physiol* **117** (4), (1952).

[40] A.E. Pereda, *Nat Rev Neurosci.* **15** (4), 250 (2014).

[41] H. Lodish, A. Berk, S.L. Zipursky, P. Matsudaira, D. Baltimore and J. Darnell, *Molecular Cell Biology, 4th edition*, W.H. Freeman New York (2000).

[42] F. Cavanna, M.G. Vilas, M. Palmucci, E. Tagliazucchi, *NeuroImage* **180**, 383 (2018).

[43] A.E. Cavanna, A. Nani, H. Blumenfeld, S. Laureys, *Neuroimaging of Consciousness*, Springer Berlin (2013).

[44] A.M. Owen, *Annual Review of Psychology* **64**, 109 (2013).

[45] B. Rohaut, A. Eliseyev and J. Claassen, *Critical Care* **23**, (2019).

[46] M. Boly, M. Massimini, N. Tsuchiya, B.R. Postle, C. Koch and G. Tononi, *Journal of Neuroscience* **37** (40), 9603 (2017).

[47] J. Aru, M. Suzuki, R. Rutiku, M.E. Larkum and T. Bachmann, *Front. Syst. Neurosci.* **13**, 43 (2019).

[48] D. Godwin, R.L. Barry and R. Marois, *PNAS* **112** (12), 3799 (2015).

[49] G. Tononi, *Biol Bull.* **215** (3), 216 (2008).

[50] G. Tononi, M. Boly, M. Massimini, C. Koch, *Nat. Rev. Neurosci.* **17**, 450 (2016).

[51] X.D. Arsiwalla and P. Verschure, *Front Neurosci.* **12**, 424 (2018).

[52] A. de Sousa, *Mens Sana Monogr.* **11** (1), 100 (2013).

[53] P. Ball, *Beyond Weird: Why Everything You Thought You Knew about Quantum Physics Is Different*, University of Chicago Press, (2018).

[54] S.R. Hameroff and R. Penrose, *Math Comput Simul* **40**, 453 (1996).

[55] S.R. Hameroff and R. Penrose, *J Conscious Stud* **3** (1), 36 (1996).

[56] S. Meunier, I. Vernos, *Journal of Cell Science* **125**, 2805 (2012).

[57] M.J. Shelley, *Annual Review of Fluid Mechanics* **48**, 487 (2016).

[58] P. Dustin, *Microtubules* (2nd edition), Springer-Verlag, New York (1985).

[59] G. Guillaud, C. Bosc, A. Fourest-Lieuvin, E. Denarier, F. Priollet, L. Lafanachère, D. Job, *Cell Biol* **142**, 167 (1998).

[60] T. Craddock, J. Tuszyński, S. Hameroff, *PLoS Comput Biol* **8** (3), e1002421 (2012).

[61] T.J. Craddock, D. Friesen, J. Mane, S. Hameroff, J. Tuszyński, *J R Soc Interface* **6** 11(100), 20140677 (2014).

[62] J.T. Toole, P. Kurian, T.J.A. Craddock, *Journal of Cognitive Science* **19**, 115 (2018).

[63] S. Hameroff, *J Biol Phys.* **36** (1), 71 (2010).

[64] S. Hameroff, *Cogn Sci* **31**, 1035 (2007).

[65] M. Tegmark, *Physical review. E* **61** (4), 4194 (2000).

[66] S. Hagan, S. Hameroff, J. Tuszyński, *Phys Rev E* **65**, 061901 (2001).

[67] E. Mandelkow, Y.H. Song, E.M. Mandelkow, *Trends Cell Biol* **5** (7), 262 (1992).

[68] L.K. McKemmish, J.R. Reimers, R.H. McKenzie, A.E. Mark, N.S. Hush, *Phys Rev E* **80**, 021912 (2009).

[69] J.R. Reimers, L.K. McKemmish, R.H. McKenzie, A.E. Mark, N.S. Hush, *Proc Natl Acad Sci USA* **106** (11), 4219 (2009).

[70] J. Pokorný, *Bioelectrochemistry* **63**, 321 (2004).

[71] S. Sahu, S. Ghosh, B. Ghosh, K. Aswani, K. Hirata, D. Fujita, A. Bandyopadhyay, *Biosens Bioelectron* **47**, 141 (2013).

[72] S. Sahu, S. Ghosh, K. Hirata, D. Fujita, A. Bandyopadhyay, *Phys Lett* **102**, 123701 (2013).

[73] D. Emerson, B. Weiser, J. Psonis, Z. Liao, O. Taratula, A. Fiamengo, X. Wang, K. Sugasawa, A.B. Smith, R.G. Eckenhoff and I.J. Dmochowski, *J Am Chem Soc* **135** (14), 5398 (2013).

[74] M. Bianchi, A.J. Shah, K.C. Fone, A.R. Atkins, L.A. Dawson, C.A. Heidbreder, M.E. Hows, J.J. Hagan, C.A. Marsden, *Synapse* **63**, 359 (2009).

[75] A. Kalra, et al. Electronic Energy Migration in Microtubules. *ACS Cent. Sci.* **9:3**, 352–361 (2023).

[76] A. Rinaldi, *EMBO Rep.* **15** (11), 1113 (2014).

[77] T.J.A. Craddock, S.R. Hameroff, A.T. Ayoub, M. Klobukowski and J.A. Tuszyński, *Current Topics in Medicinal Chemistry* **15**, 523 (2015).

[78] L. Turin, E.M.C. Skoulakis and A.P. Horsfield, *PNAS* **111** (34), E3524 (2014).

[79] S.R. Hameroff, R.C. Watt, J.D. Borel and G. Carlson, *Physiol. Chem. Phys.* **14**, 183 (1982).

[80] S.R. Hameroff and R.C. Watt, *Anesth. Analg.* **62**, 936 (1983).

[81] S.R. Hameroff, *Toxicol. Lett.* **31**, 100-101 (1998).

[82] S.R. Hameroff, *Anesthesiology* **105** (2), 400 (2006).

[83] N. Li *et al. Anesthesiology* **129** (2), 271 (2018).

[84] L.J. Voss, P.S. Garcia, H. Hentschke and M.I. Banks, *Anesthesiology* **130** (6), 1049 (2019).

[85] C.D. Richards, *BJA: British Journal of Anaesthesia* **89** (1), 79 (2002).

[86] M. Perouansky, *Anesthesiology* **117**, 465 (2012).

[87] E.F. Keller, L.A. Segel, *J. Theor. Biol.* **26**, 399 (1970).

[88] T. Craddock *et al.*, *PloS one* **7**, e37251 (2012).

[89] R.G. Eckenhoff, J.S. Johansson, *Pharmacol Rev.* **49** (4), 343 (1997).

[90] R.G. Eckenhoff, *Anesth Analg.* **107** (3), 859 (2008).

[91] J.M. Sonner, R.S. Cantor, *Annu Rev Biophys.* **42**, 143 (2013).

[92] J.Z. Pan, J. Xi, M.F. Eckenhoff, R.G. Eckenhoff, *Proteomics* **8**, 2983 (2008).

[93] G. Panitchayangkoon, D. Hayes, K.A. Fransted, J.R. Caram, E. Harel, J. Wen, R.E. Blankenship, and G.S. Engel, *Proc. Natl Acad. Sci. USA* **107**, 12766-12770 (2010).

[94] E. Collini, C.Y. Wong, K.E. Wilk, P.M.G. Curmi, P. Brumer, G.D. Scholes, *Nature* **463**, 644-647 (2010).

[95] T. Craddock, A. Priel and J. Tuszyński, *Journal of integrative neuroscience* **13**, 293 (2014).

[96] G. Celardo, M. Angeli, P. Kurian and T. Craddock, *New Journal of Physics* **21**, (2018).

[97] T.J.A. Craddock, P. Kurian, J. Preto, K. Sahu, S.R. Hameroff, M. Klobukowski and J.A. Tuszyński, *Scientific Reports* **7**, 9877 (2017).

[98] L. Turin, *Chemical Senses* **21** (6), 773 (1996).

[99] A. Albert, *Selective Toxicity: The Physico-Chemical Basis of Therapy*, Chapman & Hall, London (1985).

[100] M.P.A. Fisher, *Annals of Physics* **362**, (2015).

[101] M.W. Swift, C.G. Van de Walle and M.P.A. Fisher, *Physical Chemistry Chemical Physics* **20** (18), (2017).

[102] C.P. Weingarten, P.M. Doraiswamy and M.P.A. Fisher, *Frontiers in Human Neuroscience* **10**, (2016).

[103] D.M. Eigler, E.K. Schweizer, *Nature* **344**, 524 (1990).

[104] C.J. Rourk, *Biosystems* **171**, 48 (2018).

[105] L. Turin and E.M.C. Skoulakis, *Methods Enzymol.* **603**, 115 (2018).

[106] J.M. Kater, *Science* **82** (2124), 256 (1935).

[107] P.J. Cohen, *Anesthesiology* **39** (2), 153 (1973).

[108] S.A. Pshenichnyuk and A. Modelli, *Phys Chem Phys* **15** (23), 9125 (2013).

[109] A. Gaitanidis, A. Sotgiu, L. Turin, arXiv:1907.04764 [physics.bio-ph] (2019).

[110] R.K. Burdick, J.P. Villabona-Monsalve, G.A. Mashour and T. Goodson III, *Scientific Reports* **9** (11351), (2019).

[111] J. Pan *et al.*, *Translational Psychiatry* **8(130)**, (2018).

[112] D.J. Nutt, *J Clin Psychiatry* **69**, 4 (2008).

[113] A. Vaziri and M.B. Plenio, *New Journal of Physics* **12**, (2010).

[114] E. Fischer, *Ber. Dtsch. Chem. Ges.* **27**, 2985 (1894).

[115] A. Tripathi and V.A. Bankaitis, *J Mol Med Clin Appl.* **2** (1), (2017).

[116] H. Mitsuda *et al.*, *Journal of Physical Chemistry Letters* **1** (7), 1130 (2010).

[117] A. Reese, N. Holmgaard List, J. Kongsted, I.A. Solov'yov, *PLOS ONE* **11** (3), e0152345 (2016).

[118] M.D.H. Samee, B.G. Bruneau, K.S. Pollard, *Cell Systems* **8** (1), 27 (2019).

[119] D.M. Rosenbaum, S.G.F. Rasmussen and B.K. Kobilka, *Nature* **459** (7245), 356–363 (2009).

[120] M. Rask-Andersen, M.S. Almén, H.B. Schiöth, *Nat. Rev. Drug Discov.* **10**, 579 (2011).

[121] A. Gehrckens, A. Horsfield, E. Skoulakis and L. Turin, preprint on biorxiv 10.1101/650531, (2019).

[122] G.M. Dyson, *J. Soc. Chem. Industry* **57**, 647 (1938).

[123] M.I. Franco, L. Turin, A. Mershin, E.M. Skoulakis, *Proc Natl Acad Sci USA* **108** (9), 3797 (2011).

[124] R.D. Hoehn, D. Nichols, H. Neven and S Kais, *Sci Rep.* **5**, 9990 (2015).

[125] J. Hara, *Experientia* **33** (5), 618 (1977).

[126] B.R. Havens and C.D. Melone, *Dev. Food. Sci.* **37**, 497 (1995)

[127] K.D. Klika, *ISRN Org Chem*, 515810 (2013).

[128] M. Paoli, D. Münch, A. Haase, E. Skoulakis, L. Turin and C.G. Galizia, *eNeuro* **4** (3), 0070 (2017).

[129] H.K Chee and S.J. Oh, *Genomics Inform* **11** (4), 282 (2013).

[130] J.A. Ribeiro, A.M. Sebastiao, *J Alzheimers Dis.* **20** (l), S3–15 (2010).

[131] H.K. Chee, J. Yang, J. Joung, B. Zhang, S.J. Oh, *FEBS Letters* **589** (4), 548 (2015).

[132] Ross D. Hoehn, David E. Nichols, John D. McCorvy, Hartmut Neven, and Sabre Kais, *PNAS* **114** (22), 5595 (2017).

[133] S. Lin, L. Lee and Y.K. Yang, *Clin Psychopharmacol Neurosci.* **12** (3), 196 (2014).

[134] M. Kržan, R. Vianello, A. Maršavelski, M. Repič, M. Zakšek, K. Kotnik, E. Fijan and J. Mavri, *PLoS One* **11** (5), e0154002 (2016)

[135] S.J. Oh, *Genomics Inf.* **10** (2), 128 (2012).

[136] K. Palczewski, *Annu Rev Biochem.* 75, 743 (2007).

[137] A. Krishnan, M.S. Almén, R. Fredriksson, H.B. Schiöth, *PLoS One*, **7** (1), e29817 (2012).

[138] D. Wacker, R.C. Stevens and B.L. Roth, *Cell* **170(3)** (3), 414 (2017).

[139] D. Fels, *PLoS One* **4**, e5086 (2009).

[140] M. Rahnama, J.A. Tuszyński, I. Bókkon, M. Cifra, P. Sardar, J. Salari, *Integr Neurosci.* **10** (1), 65 (2011).

[141] S. Kumar, K. Boone, J. Tuszyński, P. Barclay and C. Simon, *Scientific Reports* **6**, 36508 (2016).

[142] M. Cifra, P.J. Pospíšil, *Photochem Photobiol B* **139**, 2 (2014).

[143] M. Kobayashi, M. Takeda, T. Sato, Y. Yamazaki, K. Kaneko, K. Ito, H. Kato, Humio Inaba, *Neurosci. Res.* **34**, 103 (1999).

[144] Y. Isojima, T. Isoshima, K. Nagai, K. Kikuchi and H. Nakagawa, *NeuroReport* **6**, 658 (1995).

[145] Y. Kataoka *et al.*, *Biochem. Biophys. Res. Commun.* **285**, 1007 (2001).

[146] R. Tang and J. Dai, *PLoS One* **9**, e85643 (2014).

[147] Z. Wang, N. Wang, Z. Li, F. Xiao and J. Dai, *PNAS* **113**, 8753 (2016).

[148] V. Salari, I. Bókkon, R. Ghobadi, F. Scholkmann and J.A. Tuszyński, *PNAS* **113**, E5540 (2016).

[149] Y. Sun, C. Wang, J. Dai, *Photochem Photobiol Sci.* **9** (3), 315 (2010).

[150] P. Zarkeshian, S. Kumar, J. Tuszyński, P. Barclay, C. Simon, *Front Biosci (Landmark Ed).* **23**, 1407 (2018).

[151] D. DePaoli *et al.* Anisotropic light scattering from myelinated axons in the spinal cord. *Neurophotonics* **7:1**, 015011 (2020).

[152] A.I. Zhuravlev, O.P. Tsvylev and S.M. Zubkova, *Biofizika* **18**, 1037 (1973).

[153] J.A. Tuszyński and J.M. Dixon, *Phys. Rev. E* **64**, 051915 (2001).

[154] G. Albrecht-Buehler, *Cell Motil. Cytoskeleton* **27**, 262 (1994).

[155] M. Kato, K. Shinzawa and S. Yoshikawa, *Photobiochem. Photobiophys.* **2**, 263 (1981).

[156] P. Kurian, T.O. Obisesan, and T. Craddock, *Journal of Photochemistry and Photobiology B: Biology* **175**, (2017).

[157] L. Tonello, M. Cocchi, F. Gabrielli, J.A. Tuszyński, *J Integr Neurosci.* **14** (3), 295 (2015).

[158] L. Tonello, B. Gashi, A. Scuotto, G. Cappello, M. Cocchi, F. Gabrielli and J.A. Tuszyński, *Journal of Integrative Neuroscience* **17**, 177 (2019).

[159] S. Baghbanzadeh and I. Kassal, *J. Phys. Chem. Lett.* **7**, 3804 (2016).

[160] M.W. Gray, G. Burger and B.F. Lang, *Science* **283**, 1476 (1999).

[161] Z. Wang and M. Wu, *Sci. Rep.* **5**, 7949 (2015).

[162] A. Harish and C.G. Kurland, *Journal of Theoretical Biology* **434**, 88 (2017).

[163] J. Martijn, J. Vosseberg, L. Guy, P. Offre and T.J.G. Ettema, *Nature* **557**, 101 (2018).

[164] D.R. Martin & D.V. Matyushov, *Scientific Reports* **7** (5495), (2017).

[165] P. Husen, I.A. Solov'yov, *Journal of Physical Chemistry B* **121**, 3308 (2017).

[166] A.B. Salo, P. Husen, I.A. Solov'yov, *Journal of Physical Chemistry B* **121**, 1771 (2017).

[167] A.M. Barragan, K. Schulten, I.A. Solov'yov, *Journal of Physical Chemistry B* **120**, 11369 (2016).

[168] D. Xia, L. Esser, W. Tang, F. Zhou, Y. Zhou, L.Yu, C. Yu, *Biochimica et Biophysica Acta (BBA) - Bioenergetics* **1827**, 1278 (2013).

[169] F. Salehpour *et al.*, *Brain Research Bulletin* **144**, 213 (2019).

[170] M.R. Hamblin, *BBA Clinical* **6**, 113 (2016).

[171] M.R. Hamblin, *J Neurosci Res.* **96** (4), 731 (2018).

[172] J. Chang, Y. Ren, R. Wang, C. Li, Y. Wang, X. Chu, Xiang-Ping. *Neuropsychiatry* **08**, (2018).

[173] D.W. Barrett, F. Gonzalez-Lima, *Neuroscience* **230**, 13 (2013).

[174] N.J. Blanco, W.T. Maddox and F. Gonzalez-Lima, *J Neuropsychol.* **11** (1), 14 (2017).

[175] N.J. Blanco, C.L. Saucedo, F. Gonzalez-Lima, *Neurobiology of Learning and Memory* **139**, 69 (2017).

[176] T.I. Karu and S.F. Kolyakov, *Photomed Laser Surg.* **23** (4), 355 (2005).

[177] C.T. Rodgers and P.J. Hore, *PNAS* **106** (2), 353 (2009).

[178] H. Zadeh-Haghighi and C. Simon. Entangled radicals may explain lithium effects on hyperactivity. *Sci Rep* **11**, 12121 (2021).

[179] H. Zadeh-Haghighi and C. Simon. Radical pairs can explain magnetic field and lithium effects on the circadian clock. *Sci Rep* **12**, 269 (2022).

[180] J. Smith, H. Zadeh Haghighi, D. Salahub and C. Simon. Radical pairs may play a role in xenon-induced general anesthesia. *Sci Rep* **11**, 6287 (2021).

[181] H. Zadeh-Haghighi and C. Simon. Radical pairs may play a role in microtubule reorganization. *Sci Rep* **12**, 6109 (2022).

[182] Zadeh-Haghighi H, Simon C. Magnetic field effects in biology from the perspective of the radical pair mechanism. *J. R. Soc. Interface* **19**, 20220325 (2022).

[183] T. Ritz, T. Yoshii, C. Helfrich-Forster and M. Ahmad, *Communicative and Integrative Biology* **3**, 24 (2010).

[184] A. Pinzon-Rodriguez, S. Bensch, R. Muheim, *J. R. Soc. Interface* **15**, 20180058 (2018).

[185] M. Liedvogel and H. Mouritsen, *J. R. Soc. Interface* **7**, S147 (2014).

[186] A. Günther, A. Einwich, E. Sjulstok, R. Feederle, P. Bolte, K.W. Koch, I.A. Solov'yov, H. Mouritsen, *Curr Biol.* **28**, 211 (2018).

[187] Xu, J., Jarocha, L.E., Zollitsch, T. et al. Magnetic sensitivity of cryptochrome 4 from a migratory songbird. *Nature* **594**, 535–540 (2021).

[188] R. Wiltschko, M. Ahmad, C. Nieβner, D. Gehring and W. Wiltschko, *J. R. Soc. Interface* **13**, 20151010 (2016).

[189] M. Pooam, L. Arthaut, D. Burdick *et al.*, *Planta* **249**, 319–332 (2019).

[190] R.J. Kutta, N. Archipowa, L.O. Johannissen, A.R. Jones and N.S. Scrutton, *Scientific Reports* **7**, 44906 (2017).

[191] B.D. Zoltowski, Y. Chelliah, A. Wickramaratne, L. Jarocha, N. Karki, W. Xu, H. Mouritsen, P.J. Hore, R.E. Hibbs, C.B. Green and J.S. Takahashi, *PNAS* **116**, 19449–19457 (2019).

[192] A. Gunther *et al.*, *Curr. Biol.* **28**, 211–223 (2018).

[193] A.A. Bradlaugh, G. Fedele, A.L. Munro, et al. Essential elements of radical pair magnetosensitivity in Drosophila. *Nature* **615**, 111–116 (2023).

[194] C.X. Wang, I.A. Hilburn, D. Wu, Y. Mizuhara, C.P. Cousté, J.N.H. Abrahams, S.E. Bernstein, A. Matani, S. Shimojo and J.L. Kirschvink, *eNeuro* **6** (2), 0483 (2019).

[195] R. Wiltschko and W. Wiltschko, *J. R. Soc. Interface* **16**, 20190295 (2019).

[196] R. Wiltschko and W. Wiltschko, *Commun Integr Biol.* **2** (2), 100 (2009).

[197] D.A. Kishkinev, N.S. Chernetsov, *Zh Obshch Biol.* **75** (2), 104 (2014).

[198] D.S. Hsu *et al.*, *Biochemistry* **35**, 13871 (1996).

[199] L.E. Foley, R.J. Gegear and S.M. Reppert, *Nat Commun.* **2**, 356 (2011).

[200] R. Van Wijk, S. Bosman, J. Ackerman, E.P.A. Van Wijk, *NeuroQuantology* **6**, 452 (2008).

[201] T.C. Player and P.J. Hore, *The Journal of Chemical Physics* **151** (22), 225101 (2019).

[202] L.D. Arthaut, N. Jourdan, A. Mteyrek, M. Procopio, M. El-Esawi, A. d'Harlingue, P.E. Bouchet, J. Witczak, T. Ritz, A. Klarsfeld, S. Birman, R.J. Usselman, U. Hoecker, C.F. Martino and M. Ahmad, *PLoS One*, **12** (3), e0171836 (2017).

[203] P. Muller, M. Ahmad, *Journal of Biological Chemistry* **286**, 21033–21040 (2011).

[204] L. Consentino, S. Lambert, C. Martino, N. Jourdan, P.E. Bouchet, J. Witczak *et al.*, *New Phytologist* **206** (4), 1450–1462 (2015).

[205] N. Jourdan, C. Martino, M. El-Esawi, J. Witczak, P.E. Bouchet, A. d'Harlingue *et al.*, *Plant Signaling & Behavior* **10** (8), e1042647 (2015).

[206] A. Marais, I. Sinayskiy, F. Petruccione and R. van Grondelle, *Scientific Reports* **5**, 8720 (2015).

[207] C. Schweitzer and R. Schmidt, *Chem. Rev.* **103**, 1685 (2003).

[208] R.J. Usselman, C. Chavarriaga, P.R. Castello, M. Procopio, T. Ritz, E.A. Dratz, D.J. Singel and C.F. Martino, *Scientific Reports* **6**, 38543 (2016).

[209] R.J. Usselman , I. Hill, D.J. Singel, C.F. Martino, *PLoS ONE* **9** (3), e93065 (2014).

[210] H. Wang and X. Zhang, *Int J Mol Sci.* **18** (10), 2175 (2017).

[211] M.K. Shigenaga, T.M. Hagen,and B.N. Ames, *Proc. Natl. Acad. Sci.* **91**, 10771 (1994).

[212] E.R. Stadtman and B.S. Berlett, *Chem. Res. Toxicol.* **10**, 485 (1997).

[213] T.M. Michel, D. Pülschen, J. Thome, *Curr Pharm Des.* **18** (36), 5890 (2012).

[214] S. Salim, *J Pharmacol Exp Ther.* **360** (1), 201 (2017).

[215] S. Salim, *Curr Neuropharmacol.* **12** (2), 140 (2014).

[216] P. Kovacic and W. Weston, *Chronicles of Pharmaceutical Science* **1** (6), (2017).

[217] P. Thalau, T. Ritz, K. Stapput, R. Wiltschko and W. Wiltschko, *Naturwissenschaften* **92**, 86 (2004).

[218] S. Engels, N.L. Schneider, N. Lefeldt, C.M. Hein, M. Zapka, A. Michalik, D. Elbers, A. Kittel, P.J. Hore and H. Mouritsen, *Nature* **509**, 353 (2014).

[219] R.M. Sherrard, N. Morellini, N. Jourdan, M. ElEsawi, L.D. Arthaut, C. Niessner *et al.*, *PLoS Biol* **16** (10), e2006229 (2018).

[220] J. Juutilainen, M. Herrala, J. Luukkonen, J. Naarala, P.J. Hore, *Proc Biol Sci.* **285** (1879), 20180590 (2018).

[221] P.J. Hore, *eLife* **8**, (2019).

[222] L.M. Lyell *et al.*, *Proc Biol Sci.* **285** (1879), 20180590 (2018).

[223] P. Boyce, E.A. Barriball, *Fam Physician* **39** (5), 307 (2010).

[224] A. Ferguson *et al.*, *EBioMedicine* **35**, 279 (2018).

[225] J. Close, *Proc Biol Sci.* **279** (1736), 2081 (2012).

[226] R.W. Kay, *Br. J. Psychiatry* **164**, 403 (1994).

[227] V.N. Oraevskiĭ, V.P. Kuleshova, I.F. Gurfinkel, A.V. Guseva, S.I. Rapoport, *Biofizika* **43**, 844 (1998).

[228] M.B. Plenio and S.F. Huelga, *New J. Phys.* **10**, 113019 (2008).

[229] G.S. Engel, *Procedia Chemistry* **3**, 222 (2011).

[230] D.R. Kattnig, I.A. Solov'yov and P.J. Hore, *Phys. Chem. Chem. Phys.* **18**, 12443 –12456 (2016).

[231] S. Worster, D.R. Kattnig and P.J. Hore, *J. Chem. Phys.* **145**, 035104 (2016).

[232] H. Hu and M. Wu, *Medical Hypotheses* **63**, 633 (2004).

[233] L.A. Cole, *Biology of Life: Biochemistry, Physiology and Philosophy*, Academic Press (2016).

[234] A.S. Posner and F. Betts, *Acc Chem Res.* **8** (8), 273 (1975).

[235] T.C Player and P.J. Hore, *J. R. Soc. Interface* **15** (147), (2018).

[236] L. Wang, S. Li, E. Ruiz-Agudo, C.V. Putnis, A. Putnis, *Cryst. Eng Comm.* **14** (19), 6252 (2012).

[237] G. Mancardi, C.E.H. Tamargo, T.D. Di, N.H. de Leeuw, *J Mater Chem B.* **5** (35), 7274 (2017).

[238] K. Onuma and A. Ito, *Chem. Mater.* **10**, 3346 (1998).

[239] X. Yin and M.J. Stott, *J. Chem. Phys.* **118**, 3717 (2003).

[240] L.W. Du, S. Bian, B.D. Gou, Y. Jiang, J. Huang, Y.X. Gao, Y.D. Zhao, W. Wen, T.L. Zhang and K. Wang, *Cryst. Growth Des.* **13**, 3103 (2013).

[241] A. Dey, P.H.H. Bomans, F.A. Müller, J. Will, P.M. Frederik, G. de With and N.A.J.M. Sommerdijk, *Nat. Mater.* **9**, 1010 (2010).

[242] G. Stevanato *et al.*, *Angew Chem Int Ed.* **54** (12), 3740 (2015).

[243] J.A. Sechzer *et al.*, *Biol. Psychiatry* **21**, 1258 (1986).

[244] M.L. Deline *et al.* Lithium isotopes differentially modify mitochondrial amorphous calcium phosphate cluster size distribution and calcium capacity. *Front. Physiol.* **14** (2023).

[245] N.Y Halpern and E. Crosson, *Annals of Physics* **407**, 92 (2019).

[246] C. Marletto *et al.*, *J. Phys. Commun.* **2**, 101001 (2018).

[247] B.E. Kane, *Nature* **393**, 133 (1998).

[248] G. Tosi, F.A. Mohiyaddin, V. Schmitt, S. Tenberg, R. Rahman, G. Klimeck and A. Morello, *Nature Communications* **8**, (2017).

[249] Y. He, S.K. Gorman, D. Keith, L. Kranz, J. G. Keizer and M.Y. Simmons, *Nature* **571**, 371 (2019).

[250] C. Kloeffel and D. Loss, *Annual Review of Condensed Matter Physics* **4**, 51 (2013).

[251] C.W. Lee, H. Zhang, L. Geng and H.B. Peng, *PLoS One* **9** (2), e90187 (2014).

[252] D. Kim *et al.*, *Nature Nanotechnology* **13**, 812 (2018).

[253] Steiner, U.E. & Ulrich, T. Magnetic field effects in chemical kinetics and related phenomena. *Chem. Rev.* **89**, 51–147 (1989).

[254] P.J. Hore1, K.L. Ivanov and M.R. Wasielewski. Spin chemistry. *Chem. Phys.* **152**, 120401 (2020).

[255] Y. Liu, L. Xu, W. Dai, H. Dong, Y. Wen and X. Zhang, *Nanoscale*,**7**, 19060 (2017).

[256] J.A. Li, D. Dong, Z. Wei, Y. Liu, Y. Pan, F. Nori, X. Zhang, *Nature Human Behaviour*, (2020).

[257] V.M. Mazhul, and D.G. Shcherbin, *Biofizika* **44**, 676 (1999).

[258] Y. Kim et al. Quantum Biology: An Update and Perspective, Quantum Reports, 2021, 3, 80.

[259] J.R. Woodward. Radical pairs in solution. *Progress in Reaction Kinetics and Mechanism* **27**, 165–207 (2002).

[260] C.T. Rodgers and P.J. Hore. Chemical Magnetoreception in Birds: The Radical Pair Mechanism. *PNAS* **106(2)**, 353 (2009).

[261] N. Ikeya and J.R. Woodward. Cellular autofluorescence is magnetic field sensitive. **PNAS 118 (3)** e2018043118, (2021).

[262] B. Adams, I. Sinayskiy, R. van Grondelle, F. Petruccione. 'Quantum tunnelling in the context of SARS-CoV-2 infection', *Sci Rep.* **12** 16929 (2022).

[263] R. Haberkorn. Density matrix description of spin-selective radical pair reactions. *Mol. Phys.* **32**, 1491 (1976).

[264] M. Tiersch, U.E. Steiner, S. Popescu, & H.J. Briegel. Open Quantum System Approach to the Modeling of Spin Recombination Reactions. *J Phys Chem A.* **116:16**, 4020–8 (2012).

[265] I.K. Kominis. The radical-pair mechanism as a paradigm for the emerging science of quantum biology. *Mod. Phys. Lett. B* **29**, 1530013 (2015).

[266] L. Slocombe, M. Sacchi & J. Al-Khalili. An open quantum systems approach to proton tunnelling in DNA. Commun Phys 5, 109 (2022).

[267] T. Le, A. Olaya-Castro. Basis-independent system-environment coherence is necessary to detect magnetic field direction in an avian-inspired quantum magnetic sensor, *arXiv: Quantum Physics* (2020).

[268] T.C. Player and P.J. Hore, *J. R. Soc. Interface* **15(147)**, (2018).

[269] E.M Gauger, E. Rieper, J.J.L. Morton, S.C. Benjamin, V. Vedral. Sustained quantum coherence and entanglement in the avian compass. Phys Rev Lett 106(4):040503 (2011).

[270] L. Slocombe, J.S. Al-Khalili & M. Sacchi. Quantum and classical effects in DNA point mutations: Watson–Crick tautomerism in AT and GC base pairs. *Phys. Chem. Chem. Phys.* **23**, 4141-4150 (2021).

[271] M.A. Nielson and I.L. Chuang. *Quantum computation and Quantum information*, (Cambridge University Press, UK: 2001).

[272] H.P. Breuer & F. Petruccione. *The Theory of Open Quantum Systems* (Oxford University Press: 2007)

[273] A. Rivas and S. Huelga. *Open Quantum Systems: An Introduction* (Springer Berlin, Heidelberg: 2011)

[274] T.P. Fay, L.P. Lindoy, D.E. Manolopoulosa and P.J. Hore. How quantum is radical pair magnetoreception? *Faraday Discussions 221*, (2020).

[275] P.J. Hore, H. Mouritsen. The Radical-Pair Mechanism of Magnetoreception. *Annu Rev Biophys.* **45**, 299–344 (2016).

[276] J. Rakshit, *et al.* The avian compass can be sensitive even without sustained electron spin coherence. *Proc. R. Soc. A.* **477** 20200778 (2021).

[277] D.R. Kattnig, P.J. Hore, The sensitivity of a radical pair compass magnetoreceptor can be significantly amplified by radical scavengers. *Sci Rep* **7**, 11640 (2017).

[278] T. Le, A. Olaya-Castro. Basis-independent system-environment coherence is necessary to detect magnetic field direction in an avian-inspired quantum magnetic sensor, *arXiv: Quantum Physics* (2020).

[279] J. Cai, G.G. Guerreschi, H.J. Briegel. Quantum control and entanglement in a chemical compass. *Phys Rev Lett* **104(22)**, 220502 (2010).

[280] J.A. Pauls, Y. Zhang, G.P Berman, S. Kais. Quantum coherence and entanglement in the avian compass. *Phys Rev E Stat Nonlin Soft Matter Phys* **87(6)**, 062704 (2013).

[281] Y. Zhang, G.P. Berman, S. Kais. Sensitivity and entanglement in the avian chemical compass. *Phys Rev E Stat Nonlin Soft Matter Phys* **90(4)**, 042707 (2014).

[282] H.J. Hogben, T. Biskup, and P.J. Hore. Entanglement and Sources of Magnetic Anisotropy in Radical Pair-Based Avian Magnetoreceptors. *Phys. Rev. Lett.* **109**, 220501 (2012).

[283] M. Tiersch, G.G. Guerreschi, J. Clausen, and H.J. Briegel J.Approaches to Measuring Entanglement in Chemical Magnetometers. *Phys. Chem. A* **118**, 13–20 (2014).

[284] T.C. Südhof. Calcium control of neurotransmitter release. *Cold Spring Harb Perspect Biol.* **4(1)**, (2012).

[285] E. Neher, T. Sakaba. Multiple roles of calcium ions in the regulation of neurotransmitter release. *Neuron. 59(6)*, 861–72 (2008).

[286] T.J.B. Simons. Calcium and neuronal function. *Neurosurg. Rev.* **11**, 119–129 (1988).

[287] S.G. Wolf *et al.* 3D visualization of mitochondrial solid-phase calcium stores in whole cells. *eLife* **6**, e29929 (2017).

[288] A. Ettenberg, *et al.* Differential effects of lithium isotopes in a ketamine-induced hyperactivity model of mania. *Pharmacol. Biochem. Behav.* **190**, 172875 (2020).

[289] T.C. Player and P.J. Hore. Posner qubits: spin dynamics of entangled Ca9(PO4)6 molecules and their role in neural processing. **J. R. Soc. Interface 15** 20180494 (2018).

[290] W. K. Wootters. Entanglement of formation and concurrence. *Quantum Information and Computation* **1(1)**, 27–44 (2001).

[291] Y. Zhou, N.C. Danbolt. Glutamate as a neurotransmitter in the healthy brain. *J Neural Transm (Vienna).* **121(8)**, 799–817 (2014).

[292] J.J. Warsh, S. Andreopoulos, P.P. Li. Role of intracellular calcium signaling in the pathophysiology and pharmacotherapy of bipolar disorder: current status. *Clinical Neuroscience Research.* **4(3–4)**, 201–213 (2004).

[293] M.J. Berridge. Calcium signalling and psychiatric disease: bipolar disorder and schizophrenia. *Cell Tissue Res.* **357(2)**, 477–92 (2014).

[294] P.J. Harrison, N. Hall, A. Mould, *et al.* Cellular calcium in bipolar disorder: systematic review and meta-analysis. *Mol Psychiatry*, (2019).

[295] S. Stern, R. Santos, M.C. Marchetto *et al.* Neurons derived from patients with bipolar disorder divide into intrinsically different sub-populations of neurons, predicting the patients' responsiveness to lithium. *Mol Psychiatry.* **23(6)**, 1453–1465 (2018).

[296] J. Mertens, Q.W. Wang, Y. Kim *et al.* Differential responses to lithium in hyperexcitable neurons from patients with bipolar disorder. *Nature* **527**, 95–99 (2015).

[297] M.A. Bernstein, K.F. King, X.J. Zhou. Handbook of MRI Pulse Sequences. San Diego, CA: Elsevier Academic Press. 960

[298] T.L. Spencer, N.W. Plagos, D.H. Brouwer and G.R. Goward. The use of 6Li7Li-REDOR NMR spectroscopy to compare the ionic conductivities of solid-state lithium ion electrolytes.*Phys. Chem. Chem. Phys.* **16**, 2515-2526 (2014).

[299] S. Agarwal, C.D. Aiello, D.R. Kattnig, and A.S. Banerjee. The Dynamical Ensemble of the Posner Molecule Is Not Symmetric. *J. Phys. Chem. Lett.* **12: 42**, 10372-10379 (2021).

[300] S. Agarwal, D.R. Kattnig, C.D. Aiello, and A.S. Banerjee. The Biological Qubit: Calcium Phosphate Dimers, Not Trimers. *J. Phys. Chem. Lett.* **14:10**, 2518–2525 (2023).

[301] F. Neese. Software update: The ORCA program system—Version 5.0. *Wiley Interdisciplinary Reviews: Computational Molecular Science* **12(5)**, e1606 (2022).

[302] F. Jensen. Segmented contracted basis sets optimized for nuclear magnetic shielding. *Journal of Chemical Theory and Computation* **11(1)**, 132–138 (2015).

[303] F. Jensen. The basis set convergence of spin- spin coupling constants calculated by density functional methods. *Journal of Chemical Theory and Computation*, **2(5)**, 1360–1369 (2006).

[304] Advanced Applications of NMR to Organometallic Chemistry Marcel Gielen (Editor), Rudolph Willem (Editor), Bernd Wrackmeyer (Editor), Wiley: 1996.

[305] H. Gunther. Selected topics from recent NMR studies of organolithium compounds. *J. Braz. Chem. Soc.* **10(4)**, (1999).

[306] W.I. Jung, A. Staubert, S. Widmaier, T. Hoess, M. Bunse, F. van Erckelens, G. Dietze, O. Lutz. Phosphorus J-coupling constants of ATP in human brain. *Magn Reson Med.* **37(5)**, 802-4 (1997).

[307] E. Chiavazza *et al.* Earth's magnetic field enabled scalar coupling relaxation of 13C nuclei bound to fast-relaxing quadrupolar 14N in amide groups. *J Magn Reson.* **227**, 35-8 (2013).

[308] B. Adams, I. Sinayskiy & F. Petruccione. An open quantum system approach to the radical pair mechanism. *Sci Rep* **8**, 15719 (2018).

[309] S. Engels, et al. Anthropogenic electromagnetic noise disrupts magnetic compass orientation in a migratory bird. Nature 509, 353–356 (2014).

[310] J. Eisert, T. Felbinger, P. Papadopoulos, M. B. Plenio, and M. Wilkens. Classical Information and Distillable Entanglement. Phys. Rev. Lett. 84, 1611 (2000).

[311] C. Dorflinger, M. Fuller. Lithium-induced hypercalcemia with normal parathyroid hormone: A case report. *Ment Health Clin.* **9(5)**, 318-321 (2019).

[312] H.W. Woo. The Effects of Lithium Treatment on the Serum Calcium, Ionized Calcium & Phosphate in Bipolar Disorder. *Ewha Med J.* **15(4)**, 337-346 (1992).

[313] L. Smolin. Natural and bionic neuronal membranes: possible sites for quantum biology. arXiv:2001.08522 [quant-ph] (2020).

[314] G.M. Mawe, J.M. Hoffman. Serotonin signalling in the gut–functions, dysfunctions and therapeutic targets. *Nat Rev Gastroenterol Hepatol.* **10(8)**: 473–86 (2013).

[315] H. Bayer. *et al.* Serotoninergic Receptors on Human Airway Epithelial Cells. *American Journal of Respiratory Cell and Molecular Biology* **36(1)**, (2006).

[316] N.R. Hegde, M.S. Maddur, S.V. Kaveri & J. Bayry. Reasons to include viruses in the tree of life. *Nature Reviews Microbiology* **7**, 615 (2009).

[317] H. Park *et al.* Enhanced energy transport in genetically engineered excitonic networks. *Nat Mater.* **15(2)**, 211-6 (2016).

[318] Y. Yamauchi. Quantum dots crack the influenza uncoating puzzle. *PNAS* **116(7)**, 2404-2406 (2019).

[319] C. Qin *et al.* Real-time dissection of dynamic uncoating of individual influenza viruses. *Proc Natl Acad Sci* **116**, 2577–2582 (2019).

[320] A. Loczecin *et al.* Functional Carbon Quantum Dots as Medical Countermeasures to Human Coronavirus. *ACS Appl. Mater. Interfaces* **11(46)**, 42964–42974 (2019).

[321] S. Manivannan *et al.* Quantum dots as a promising agent to combat COVID-19. *Appl Organomet Chem.*, e5887 (2020).

[322] S. Kotta *et al.* Exploring the Potential of Carbon Dots to Combat COVID-19. *Front. Mol. Biosci.* **7**, (2020).

[323] F. Shojaie & M. Dehestani. The simulation of virus life cycle with quantum gates. *Computers in Biology and Medicine* **40(3)**, 359-362 (2010).

[324] M.A. Peters. The coming pandemic era. *Educational Philosophy and Theory* Routledge (2020).

[325] D. DeVault & B. Chance. Studies of photosynthesis using a pulsed laser: I. Temperature dependence of cytochrome oxidation rate in chromatium. Evidence for tunneling. *Biophys. J* **6**, 825–847 (1966).

[326] Rosenbaum, D.M, Rasmussen, S.G.F & Kobilka, B.K. The structure and function of G-protein-coupled receptors. *Nature* **459** (7245), 356–363 (2009).

[327] P. Löwdin. Proton Tunneling in DNA and its Biological Implications. *Rev. Mod. Phys.* **35**, 724 (1963).

[328] E. Fischer, *Ber. Dtsch. Chem. Ges.* **27**, 2985 (1894).

[329] M.J. Sutcliffe & N.S. Scrutton. Enzymology takes a quantum leap forward. *Philos Transact A Math Phys Eng Sci.* **358(1766)**, 367–386 (2000).

[330] O. Pusuluk *et al.* Proton tunnelling in hydrogen bonds and its implications in an induced-fit model of enzyme catalysis. *Proc. R. Soc. A.* **474**, 20180037 (2018).

[331] J.P. Bothma *et al.* The role of quantum effects in proton transfer reactions in enzymes: quantum tunneling in a noisy environment? *New J. Phys.* **12**, 055002 (2010).

[332] C. Moser *et al.* Guidelines for tunneling in enzymes. *Biochimica et Biophysica Acta (BBA) - Bioenergetics* **1797(9)**, 1573-1586 (2010).

[333] A. Tripathi & V.A. Bankaitis. Molecular Docking: From Lock and Key to Combination Lock. *Journal of molecular medicine and clinical applications* **2 (1)**, 10.16966/2575-0305.106 (2017).

[334] Uings, I.J., & Farrow, S.N. Cell receptors and cell signalling. *Molecular pathology: MP* **53 (6)**, 295–299 (2000). https://doi.org/10.1136/mp.53.6.295

[335] Filipek, S., Stenkamp, R. E., Teller, D. C., & Palczewski, K. G protein-coupled receptor rhodopsin: a prospectus. *Annual review of physiology* **65**, 851–879 (2003).

[336] Abramavicius, D., Valkunas, L. Role of coherent vibrations in energy transfer and conversion in photosynthetic pigment-protein complexes. *Photosynth Res.* **127 (1)**, 33–47 (2016).

[337] Marais, A., Sinayskiy, I., Kay, A. Petruccione, F. and Ekert, A.Decoherence-assisted transport in quantum networks. *New Journal of Physics* **15** 013038 (2013)

[338] Wang, W., Geiger, J.H., Borhan, B. The photochemical determinants of color vision: revealing how opsins tune their chromophore's absorption wavelength. *Bioessays* **36 (1)**, 65–74 (2014).

[339] K. Maniati *et al.*, 'Vibrational Detection of Odorant Functional Groups by Drosophila melanogaster', *eNeuro* **4(5)**, (2017).

[340] E. Block *et al.* Implausibility of the vibrational theory of olfaction. *PNAS* textbf112 (21), E2766-E2774 (2015).

[341] J.C. Brookes, A.P. Horsfield, A.M. Stoneham. The swipe card model of odorant recognition. *Sensors (Basel)* **12 (11)**, 15709-49 (2012).

[342] W. Ni *et al.* Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. *Critical Care* **24 (422)**, (2020).

[343] V. Bhalla, C.A. Blish & A.M. South. A historical perspective on ACE2 in the COVID-19 era. *J Hum Hypertens*, (2020).

[344] T. Tang, M. Bidon, J.A. Jaimes, G.R. Whittaker, S. Daniel. Coronavirus membrane fusion mechanism offers a potential target for antiviral development. *Antiviral Research* **178**, 104792 (2020).

[345] J.A. Malik *et al.* Targets and strategies for vaccine development against SARS-CoV-2. *Biomedicine & Pharmacotherapy* **137**, 111254 (2021).

[346] C. Tikellis & M.C. Thomas. Angiotensin-Converting Enzyme 2 (ACE2) Is a Key Modulator of the Renin Angiotensin System in Health and Disease. *International Journal of Peptides*, (2012).

[347] L.M. Burrell, C.I. Johnston, C. Tikellis, M.E. Cooper. ACE2, a new regulator of the renin-angiotensin system. *Trends Endocrinol Metab* **15 (4)**, 166-9 (2004).

[348] M. Gheblawi. Angiotensin-Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System. *Circulation Research* **126**, 1456–1474 (2020).

[349] H. Tegally, E. Wilkinson, M. Giovanetti *et al.* Detection of a SARS-CoV-2 variant of concern in South Africa. *Nature* **592**, 438–443 (2021).

[350] K. Tao *et al.* The biological and clinical significance of emerging SARS-CoV-2 variants. *Nat Rev Genet* (2021).

[351] E. Volz *et al.* Evaluating the Effects of SARS-CoV-2 Spike Mutation D614G on Transmissibility and Pathogenicity. *Cell* **184 (1)** 64-75 (2021).

[352] L. Zhang *et al.* SARS-CoV-2 spike-protein D614G mutation increases virion spike density and infectivity. *Nat Commun* **11**, 6013 (2020).

[353] Seth, S., Batra, J. & Srinivasan, S. COVID-19: Targeting Proteases in Viral Invasion and Host Immune Response. *Frontiers in Molecular Biosciences* **7**, 215 (2020).

[354] Hoffmann, M. *et al.* SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* **181 (2)**, 271-280 (2020).

[355] Gomes, C.P., Fernandes, D.E., Casimiro, F., da Mata, G.F., Passos, M.T., Varela, P., Mastroianni-Kirsztajn, G., & Pesquero, J.B. Cathepsin L in COVID-19: From Pharmacological Evidences to Genetics. *Frontiers in cellular and infection microbiology* **10**, 589505 (2020).

[356] Gehrckens, A.S., Horsfield, A.P., Skoulakis, E.M.C and Turin, L. Evidence for Free Radical Drug Ligands in class A G-protein Coupled Receptors. bioRxiv 2021.08.30.458164.

[357] J. Singh, R.S. Dhindsa, V. Misra and B. Singh. SARS-CoV2 infectivity is potentially modulated by host redox status. *Computational and Structural Biotechnology Journal* **18**, 3705–3711 (2020).

[358] M. Manček-Keber *et al.* Disruption of disulfides within RBD of SARS-CoV-2 spike protein prevents fusion and represents a target for viral entry inhibition by registered drugs. *The FASEB Journal* **35: 6**, e21651 (2021).

[359] S. Hati and S. Bhattacharyya. Impact of Thiol–Disulfide Balance on the Binding of Covid-19 Spike Protein with Angiotensin-Converting Enzyme 2 Receptor. *ACS Omega* **5: 26**, 16292–16298 (2020).

[360] J.R. Lechien *et al.* Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol 277*, 2251–2261 (2020).

[361] A.R. Sedaghat, I. Gengler, M.M. Speth. Olfactory Dysfunction: A Highly Prevalent Symptom of COVID-19 With Public Health Significance. *Otolaryngol Head Neck Surg.* **163 (1)**, 12-15 (2020).

[362] M. Chen *et al.* Elevated ACE2 expression in the olfactory neuroepithelium: implications for anosmia and upper respiratory SARS-CoV-2 entry and replication. *European Respiratory Journal*, 2001948 (2020).

[363] R. Ragab, H.S. Eldin, M. Taeimah, R. Khattab & R. Salem. The COVID-19 Cytokine Storm; What We Know So Far. *Front Immunol.* (2020).

[364] S. Hojyo *et al.* How COVID-19 induces cytokine storm with high mortality. *Inflammation and Regeneration* **40 (37)**, (2020).

[365] J.R. Tisoncik *et al.* Into the eye of the cytokine storm. *Microbiology and molecular biology reviews: MMBR* **76 (1)**, 16–32 (2012).

[366] F. Coperchini, L. Chiovato, L. Croce, F. Magri, M. Rotondi. The cytokine storm in COVID-19: An overview of the involvement of the chemokine/chemokine-receptor system. *Cytokine Growth Factor Rev.* **53**, 25-32. (2020).

[367] D.T. Lodowski & K. Palczewski. Chemokine receptors and other G protein-coupled receptors. *Current opinion in HIV and AIDS* **4 (2)**, 88–95 (2009).

[368] I. Sinayskiy, A. Marais, F. Petruccione and A. Ekert. Decoherence-Assisted Transport in a Dimer System. *PRL* **108**, 020602 (2012).

[369] A.I. Solov'yov, P. Chang. and K. Schulten, Vibrationally Assisted Electron Transfer Mechanism of Olfaction: Myth or Reality? Phys Chem Chem Phys. **14 (40)**, 13861–13871 (2012).

[370] J. Huang *et al.* On-Site Detection of SARS-CoV-2 Antigen by Deep Learning-Based Surface-Enhanced Raman Spectroscopy and Its Biochemical Foundations. *Anal. Chem.* **93 (26)**, 9174–9182 (2021).

[371] F. Fassioli, R. Dinshaw, P.C. Arpin and G.D. Scholes. Photosynthetic light harvesting: excitons and coherence. *J. R. Soc. Interface.* **11**, 20130901 (2014).

[372] J. Hippisley-Cox. Risk of severe COVID-19 disease with ACE inhibitors and angiotensin receptor blockers: cohort study including 8.3 million people. *Heart* **106**, 1503-1511 (2020).

[373] J. Nunes. Mortality and use of angiotensin-converting enzyme inhibitors in COVID 19 disease: a systematic review. *Porto biomedical journal* **5 (6)**, e085 (2020).

[374] T.M. Abd El-Aziz, T.M., Al-Sabi, A. & Stockand, J.D. Human recombinant soluble ACE2 (hrsACE2) shows promise for treating severe COVID19. *Sig Transduct Target Ther* **5**, 258 (2020).

[375] G. Yang *et al.* Effects of Angiotensin II Receptor Blockers and ACE (Angiotensin-Converting Enzyme) Inhibitors on Virus Infection, Inflammatory Status, and Clinical Outcomes in Patients With COVID-19 and Hypertension: A Single-Center Retrospective Study. *Hypertension* **76 (1)**, 51–58 (2020).

[376] C.G. Derington. Angiotensin II receptor blocker or angiotensin-converting enzyme inhibitor use and COVID-19-related outcomes among US Veterans. *PLoS ONE* **16 (4)**, e0248080 (2021).

[377] C.J. Pirola and S. Sookoian. Estimation of Renin-Angiotensin-Aldosterone-System (RAAS)-Inhibitor effect on COVID-19 outcome: A Meta-analysis. *Journal of Infection* **8 (2)**, 276–281 (2020).

[378] K. Sriram & P.A. Insel. G Protein-Coupled Receptors as Targets for Approved Drugs: How Many Targets and How Many Drugs?. *Mol Pharmacol.* **93 (4)**, 251–258 (2018).

[379] K.A. Berg and W.P. Clarke. Making Sense of Pharmacology: Inverse Agonism and Functional Selectivity. *International Journal of Neuropsychopharmacology* **21 (10)**, Pages 962–977 (2018).

[380] H. Cheng. Inhibition of Ebola and Marburg Virus Entry by G Protein-Coupled Receptor Antagonists. *J Virol.* **89 (19)**, 9932-8 (2015).

[381] M.M. Essa. Possible role of tryptophan and melatonin in COVID-19. *Int J Tryptophan Res.* **13** (2020).

[382] G. Anderson, A. Carbone, G. Mazzoccoli. Tryptophan Metabolites and Aryl Hydrocarbon Receptor in Severe Acute Respiratory Syndrome, Coronavirus-2 (SARS-CoV-2) Pathophysiology. *Int J Mol Sci.* **22 (4)**, 1597 (2021).

[383] P.L. Delgado. Serotonin and the neurobiology of depression. Effects of tryptophan depletion in drug-free depressed patients. *Arch Gen Psychiatry.* **51 (11)**, 865-74 (1994).

[384] E.J. Lenze, C. Mattar, C.F. Zorumski *et al.* Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19: A Randomized Clinical Trial. *JAMA* **324 (22)**, 2292–2300 (2020).

[385] N. Hoertel, M. Sánchez-Rico, R. Vernet. *et al.* Association between antidepressant use and reduced risk of intubation or death in hospitalized patients with COVID-19: results from an observational study. *Mol Psychiatry* (2021).

[386] M.G.M Hamed & Hagag. The possible immunoregulatory and anti-inflammatory effects of selective serotonin reuptake inhibitors in coronavirus disease patients. *R.S. Med Hypotheses* **144**, 110140 (2020).

[387] J. Zuo, K.K Quinn, S. Kye, P. Cooper, R. Damoiseaux, & P. Krogstad. Fluoxetine is a potent inhibitor of coxsackievirus replication. Antimicrobial agents and chemotherapy, 56(9), 4838–4844 (2012).

[388] M.A. Benkahla, E.K. Alidjinou, F. Sane, R. Desailloud, D. Hober. Fluoxetine can inhibit coxsackievirus-B4 E2 in vitro and in vivo. *Antiviral Research* **159**, 130-133 (2018).

[389] J.D. McCorvy, B.L Roth. Structure and function of serotonin G protein-coupled receptors. *Pharmacol Ther.* **150**, 129-42 (2015).

[390] N.T. Vasudevan, M.L. Mohan, S.K. Goswami & S.V. Naga Prasad. Regulation of β-adrenergic receptor function: an emphasis on receptor resensitization. *Cell cycle (Georgetown, Tex.)* **10 (21)**, 3684–3691 (2011).

[391] S. Nuutinen, P Panula. Histamine in neurotransmission and brain diseases. *Adv Exp Med Biol. 709*, 95-107 (2010).

[392] Reznikov, L.R. *et al.* Identification of antiviral antihistamines for COVID-19 repurposing. *Biochem Biophys Res Commun.* **538**, 173–179 (2021).

[393] Kabbani, N. Are nicotinic acetylcholine receptors coupled to G proteins? *Bioessays* **35 (12)**, 1025-34 (2013).

[394] Govind, A.P., Vezina, P. & Green, W.N. Nicotine-induced Upregulation of Nicotinic Receptors: Underlying Mechanisms and Relevance to Nicotine Addiction. *Biochem Pharmacol.* **78 (7)**, 756–765 (2009).

[395] Changeux, J. Structural Identification of the Nicotinic Receptor Ion Channel. *Trends Neurosci.* **41 (2)**, 67-70 (2018).

[396] Leung, J.M., Yang, C.X., Sin, D.D. COVID-19 and nicotine as a mediator of ACE-2. *European Respiratory Journal* **55**, 2001261 (2020).

[397] Farsalinos, K. *et al.* Smoking prevalence among hospitalized COVID-19 patients and its association with disease severity and mortality: an expanded re-analysis of a recent publication. *Harm Reduction Journal* **18 (9)**, (2021).

[398] Nunn, A.V.W., Guy, G.W., Brysch, W. *et al.* SARS-CoV-2 and mitochondrial health: implications of lifestyle and ageing. *Immun Ageing* **17**, 33 (2020).

[399] Chernyak, B.V., Popova, E.N., Prikhodko, A.S., Grebenchikov, O.A., Zinovkina, L.A., & Zinovkin, R.A. COVID-19 and Oxidative Stress. *Biochemistry. Biokhimiia.* **85 (12)**, 1543–1553 (2020).

[400] Forcados, G.E. *et al.* Metabolic Implications of Oxidative Stress and Inflammatory Process in SARS-CoV-2 Pathogenesis: Therapeutic Potential of Natural Antioxidants. *Front. Cell. Infect. Microbiol.*, (2021).

[401] Lei, Y., *et al.* SARS-CoV-2 Spike Protein Impairs Endothelial Function via Downregulation of ACE 2. *Circulation Research* **128**, 1323–1326 (2021).

[402] Riya, G. Hemachandra, R.P. Impact of COVID-19 on Mitochondrial-Based Immunity in Aging and Age-Related Diseases, *Frontiers in Aging Neuroscience* **12**, 502 (2021).

[403] Paul, B.D., Lemle, M.D., Komaroff, A.L. and Snyder, S.H. *PNAS* **118 (34)**, e2024358118 (2021).

[404] Callard, F. & Perego, E. How and why patients made Long Covid. *Soc Sci Med.* **268**, 113426 (2021).

[405] Nalbandian, A., Sehgal, K., Gupta, A. *et al.* Post-acute COVID-19 syndrome. *Nat Med* **27**, 601–615 (2021).

[406] Nabavi, N. Long covid: How to define it and how to manage it. *BMJ* **370**, m3489 (2020).

[407] Ladds, E. *et al.* Persistent symptoms after Covid-19: qualitative study of 114 "long Covid" patients and draft quality principles for services. *BMC Health Services Research* **20 (1144)**, (2020).

[408] Marshall, M. *Nature* **585**, 339-341 (2020).

[409] del Rio, C., Collins, L.F., Malani, P. Long-term Health Consequences of COVID-19. *JAMA* **324 (17)**, 1723–1724 (2020).

[410] Bannister, B.A. Post-infectious disease syndrome. *Postgrad Med J.* **64 (753)**, 559–567 (1988).

[411] Archer, M.I. The post-viral syndrome: a review. *J R Coll Gen Pract.* **37 (298)**, 212–214 (1987).

[412] Underhill, R., Baillod, R. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Organic Disease or Psychosomatic Illness? A Re-Examination of the Royal Free Epidemic of 1955. *Medicina (Kaunas)* **57 (1)**, 12 (2020).

[413] Friedman, K.J. Advances in ME/CFS: Past, Present, and Future. *Front. Pediatr.* **7**, 131 (2019).

[414] Johnston, S.S.D., Klein, A. Marshall-Gradisnik, S. A targeted genome association study examining transient receptor potential ion channels, acetylcholine receptors, and adrenergic receptors in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. *BMC Med. Genet.* **17 (1)**, 1-7 (2016).

[415] Loebel, M.G. *et al.* Antibodies to b adrenergic and muscarinic cholinergic receptors in patients with Chronic Fatigue Syndrome. *Brain Behav. Immun.* **52**, 32-39 (2016).

[416] Wirth, K., Scheibenbogen, C. A Unifying Hypothesis of the Pathophysiology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): Recognitions from the finding of autoantibodies against ß2-adrenergic receptors. *Autoimmunity Reviews* **19 (6)**, 102527 (2020).

[417] Adiliaghdam, F., Jeffrey, K.L. Illuminating the human virome in health and disease. *Genome Med* **12**, 66 (2020).

[418] Nieva, J., Madan, V. & Carrasco, L. Viroporins: structure and biological functions. *Nat Rev Microbiol* **10**, 563–574 (2012).

[419] Scott, C. & Griffin, S. Viroporins: structure, function and potential as antiviral targets. *J Gen Virol.* **96 (8)**, 2000-2027 (2015).

[420] Chaudhuri, A., Watson, W.S., Pearn, J. Behan, P.O. The symptoms of chronic fatigue syndrome are related to abnormal ion channel function. *Med Hypotheses* **54 (1)**, 59-63 (2000).

[421] Mandala, V.S., McKay, M.J., Shcherbakov, A.A. *et al.* Structure and drug binding of the SARS-CoV-2 envelope protein transmembrane domain in lipid bilayers. *Nat Struct Mol Biol* **27**, 1202–1208 (2020).

[422] Schoeman D. & Fielding, B.C. Coronavirus envelope protein: current knowledge. *Virology Journal* **16 (69)**, (2019).

[423] Abdul, K.L, Stacey, M. and Barrett-Jolley, R. Emerging Roles of the Membrane Potential: Action Beyond the Action Potential. *Frontiers in Physiology* **9**, 1661 (2018).

[424] Chernet, B.T., Levin, M. Transmembrane voltage potential is an essential cellular parameter for the detection and control of tumor development in a Xenopus model. *Dis Model Mech.* **6 (3)**, 595–607 (2013).

[425] Nilsson, I. *et al.* Metabolic Dysfunction in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Not Due to Anti-mitochondrial Antibodies. *Front Med (Lausanne)* **31 (7)**, 108 (2020).

[426] Tomas, C., Newton, J. Metabolic abnormalities in chronic fatigue syndrome/myalgic encephalomyelitis: a mini-review. *Biochem Soc Trans* **46(3)**, 547-553 (2018).

[427] Quinzii, C.M and Hirano, M. Coenzyme Q and Mitochondrial Disease *Dev Disabil Res Rev.* **16 (2)**, 183–188 (2010).

[428] Hargreaves, I.P. Coenzyme Q10 as a therapy for mitochondrial disease. *Int J Biochem Cell Biol.* **49**, 105–11 (2014).

[429] Chen, X., Zhang, J., Mihai, D.M and Washington, I. Light-harvesting chlorophyll pigments enable mammalian mitochondria to capture photonic energy and produce ATP. *J Cell Sci.* **127**, 388-99 (2015).

[430] Buehler, M.J. Nanomechanical sonification of the 2019-nCoV coronavirus spike protein through a materiomusical approach. arXiv: Popular Physics (2020).

[431] Zhang, D. Ultra-fast and onsite interrogation of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in environmental specimens via surface enhanced Raman scattering (SERS). medRxiv 2020.05.02.20086876.

[432] Jinglin, H., Minjie, Z., Wei, L. *et al.* Detection of spike protein of SARS-CoV-2 by surface enhanced Raman spectroscopy. *High Power Laser and Particle Beams* **32**, 069001 (2020).

[433] Li, Q. *et al.* The Impact of Mutations in SARS-CoV-2 Spike on Viral Infectivity and Antigenicity. *Cell* **182**, 1284–1294 (2020).

[434] Ushio-Fukai M. Vascular signaling through G protein-coupled receptors: new concepts. *Current opinion in nephrology and hypertension* **18 (2)**, 153–159 (2009).

[435] Auten, R., Davis, J. Oxygen Toxicity and Reactive Oxygen Species: The Devil Is in the Details. *Pediatr Res* **66**, 121–127 (2009).

[436] Tay, M.Z., Poh, C.M., Rénia, L. *et al.* The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* **20**, 363–374 (2020).

[437] Doykov, I., Hällqvist, J., Gilmour, K.C. *et al.* The long tail of Covid-19 - The detection of a prolonged inflammatory response after a SARS-CoV-2 infection in asymptomatic and mildly affected patients [version 2; peer review: 2 approved]. *F1000Research* **9**, 1349 (2021).

[438] Pooam M., Aguida B., Drahy S., Jourdan N., Ahmad M. Therapeutic application of light and electromagnetic fields to reduce hyper-inflammation triggered by COVID-19. *Commun Integr Biol.* **14 (1)**, 66-77 (2021).