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# Part I

## Introduction

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# 1

# Quantum biology: introduction

GRAHAM R. FLEMING AND GREGORY D. SCHOLES

## 1.1 Introduction

Key features of quantum mechanics are the uncertainty principle, wave–particle duality, quantization of energies and the modification of classical probability laws. Biology is concerned with how natural systems function – from understanding how genetically coded information is replicated, to attaining a mechanistic model for complex multistep reactions. Recently researchers have been asking whether quantum mechanics, normally the domain of physics, is also needed to understand some biological processes. This field includes fascinating developments in theory and experiment, as well as multidisciplinary discussion, and the state-of-the-art is documented in this book. Erwin Schrödinger, in his famous book *What is Life*? (Schrödinger, 1944), noted that quantum mechanics accounts for the stability of living things and their cellular processes because of our understanding, via quantum mechanics, of the stability and structure of molecules. The fact that quantum effects create, sometimes large, energy gaps between different states of a chemical system is also important. Such energy gaps, between electronic energy levels, enable living organisms to capture and store the energy carried from the sun by photons, and to visualize the world around them via optically induced chemical reactions. Davydov's view in *Biology and Quantum Mechanics* (Davydov, 1982) was that quantum mechanics is most relevant for isolated systems in pure states and therefore is of little importance for biological systems that are in statistical states at thermal equilibrium.

If we set aside the fact that quantum mechanics is required to explain the properties of molecules and their reactions – obviously important in biochemical processes ranging from the action of enzymes to genetic expression of phenotypes and the very construction of a living organism – then *quantum biology* identifies

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biological phenomena that make explicit use of quantum mechanics to attain functionality or to carry out a process. Of course the application of quantum mechanics to the study of biological problems is still important, but we do not include that in our definition of quantum biology. Early work pursuing such directions was the main focus of the, now discontinued, *International Journal of Quantum Chemistry: Quantum Biology Symposium* series. However, there remains the question of precisely where we draw the line separating unsurprising manifestations of quantum mechanics from those of interest for quantum biology. For example, intermolecular forces, including hydrogen bonding and van der Waals forces, are prevalent in defining protein structures, the helical motif of DNA; they account for enzyme–substrate association, aid protein synthesis, and cause membrane formation, to name just a few examples. In general, such non-bonding interactions, while described by quantum-mechanical models, do not appear to introduce special properties or function because of quantum mechanics, so we would exclude them from quantum-biological examples. Instead the field is mostly concerned with excited electronic states and their dynamics, long-range tunnelling through barriers, interference effects and other abilities conferred by quantum mechanics.

A molecular basis for biology, including atomic-scale descriptions of complex processes, has transformed biology over the past decades. One motivation for the emerging field of quantum biology is to elucidate new insights into biological function that may emerge from a quantum perspective. Hence the discovery and objective assessment of examples of quantum biology is important. Key criteria for identifying quantum-biological processes include their amenability to experimental verification and predictions or theoretical modelling using appropriate and rigorous frameworks. It is worthwhile distinguishing between phenomena where the detailed dynamics of the process are susceptible to experimental and theoretical investigation, and those in which only overall rates are observable and the challenge is to explain the magnitudes and trends found from experiments. The chapters that follow in this book will explore these examples in greater depth.

## 1.2 Excited states in biology

In 1962, Longuet-Higgins wrote in his paper entitled ‘Quantum mechanics and biology’ that quantum mechanics only helps us to understand a few biological processes that involve radiation (Longuet-Higgins, 1962). Research since then has revealed that this rather conservative view requires modification. Indeed, quantum phenomena in biological systems that require explicit reference to quantum theory abound. For example, the ‘energy wealth’ of a molecule defines the energy stored in quantum states; usually chemical bonds that can be transformed in reactions, thereby storing or releasing a quantum of energy. There are many examples that are of importance for biology, including nucleoside phosphates (ATP), thioesters, imidazoles and others (Pullman and Pullman, 1963). The special properties of molecules such as quinones that are important in electron transport chains can also be attributed to their quantum-mechanical energy gaps. Research at present, as documented in this book is, however, largely restricted to light-induced processes.

### *1.2.1 Photosynthetic light-harvesting*

Light-harvesting in photosynthesis has recently become the paradigmatic model for quantum effects in biology. Photosynthetic pigment–protein complexes collect sunlight and transfer energy in the form of electronic excitation to the reaction centre, where charge separation initiates a web of biochemical processes. Light-harvesting in photosynthetic organisms occurs with remarkable quantum efficiency; usually a quantum efficiency of >90% for initiation of charge separation per absorbed photon is found under conditions of low irradiance. Therefore it is of great interest to investigate the design principles of this extremely efficient process (Scholes *et al*., 2011).

The success of natural light-harvesting depends on ultra fast excited state dynamics including energy transfer and charge separation, where quantum superposition and coherence dynamics turn out to play roles (Ishizaki and Fleming, 2012). Thus, models based on quantum theory are crucial for the understanding of the primary process of photosynthesis. Moreover, the recent development of two-dimensional electronic spectroscopy and its utility for examining these systems has placed photosynthetic light-harvesting in a unique position for investigating quantum-dynamical phenomena in biological systems.

Many quantum phenomena are often regarded as exceedingly delicate and not likely to survive over relevant timescales in ‘warm, wet and noisy’ living things. Thus, the experimental observation by Engel *et al*. of long-lived quantum-electronic coherence in a photosynthetic protein (the FMO complex) (Engel *et al*., 2007) produced widespread interest. The initial experiments were carried out at 77 K, but subsequent work by Scholes and co-workers on a light-harvesting protein from marine algae (Collini *et al*., 2010) confirmed the persistence of quantum coherence at physiological (room) temperature. Engel and co-workers then demonstrated that quantum coherence in the FMO protein survives up to room temperature (Panitchayangkoon *et al*., 2010). These studies used femtosecond duration laser pulses. The relevance of the coherent phenomena observed in such experiments to the behaviour of systems illuminated by sunlight requires careful clarification (Jiang and Brumer, 1991). It might be worth saying that, while the experiments are carried out with coherent excitation, the underlying Hamiltonian probed by these experiments is the same Hamiltonian that governs the dynamics under sunlight

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irradiance. A key point is that the simulations inspired by these experiments do not need to assume coherent excitation, and it is really these simulations that ultimately give us an insight into how coherences modify the dynamics.

### *1.2.2 Other excited state processes: from vision to circadian clocks*

One way to answer the question of biological relevance would be to argue that the process would simply not work without quantum mechanics. Vision is perhaps one such example, because the quantum-mechanical arrangement of electronic states and their symmetries is responsible for light-activated isomerization. Light is absorbed by a chromophore in the rhodopsin protein, which initiates a photochemical isomerization. This is the quantum-mechanical process. After that, a series of enzymes are activated, culminating in hydrolysis of cyclic guanosine $3'$–$5'$ monophosphate which causes $Na^+$ ion channels to close. The resulting hyperpolarization induces an electrical impulse that is transferred to a nerve cell. This really is a remarkable sequence of events – initiated by a comparatively simple quantum-mechanical process.

Photochemical reactions like the photo-induced isomerization of retinal in rhodopsin protein are a subset of chemical reactions in general, and the mechanism of many ground state reactions can also only be understood from a quantum-mechanical viewpoint. For example, the Woodward–Hoffman rules for orbital symmetry explain how large barriers to chemical transformations in the electronic ground state can result from the way orbital symmetry must change in a discontinuous fashion during the transformation from reactant to product (Woodward and Hoffmann, 1969). In photochemical reactions (Michl, 1990), these kinds of barriers are greatly reduced by using photoexcitation to change the symmetry of the initial state and provide internal energy to surmount the thermal barrier. Similarly, the catalytic activity of enzymes can sometimes best be understood on a quantum-mechanical basis. It is therefore difficult to decide which chemical reactions, whether light-induced or not, constitute important examples of quantum-mechanical optimization in biology.

Lastly, it is worth documenting that vision is not the sole photochemical process important in biology. Other examples include deactivation of excited states in DNA, thus avoiding photodamage to the genetic code, vitamin D (calciferol) biosynthesis, photoinduced electron transfer in photosynthesis, cell photoprotection using melanin, bioluminescence and sophisticated sunscreens used by coral. An important class of proteins that operate by light activation are the phytochromes. They play a role in a multitude of processes including phototropism and phototaxis (growth/movement determined by response to a light source), photoperiodism, seed germination and circadian clocks.

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## 1.3 Light particles and tunnelling

### *1.3.1 Electron tunnelling*

Electron flow between distant (greater than 15 Å) redox-active cofactors is central to the operation of aerobic respiration and photosynthesis. Proteins are not electrical conductors, yet charge needs to move in such biological processes. The quantum-mechanical process of tunnelling allows classical energy barriers to be circumvented to some extent, basically by virtue of the time–energy uncertainty principle. Electrons can thereby be directed through space by protein backbones. Such long-range electron transfer in the biologically relevant timescales of milli- to microseconds plays a key role in the energy transduction pathways of life.

Tunneling in biological systems was first reported for electron-transfer reactions in proteins (Marcus and Sutin, 1985). Investigations on ruthenium-modified proteins carried out by Gray and co-workers in the past two decades have yielded a remarkably detailed description of the distance- and driving-force dependences of long-range electron tunnelling rates in proteins (Gray and Winkler, 2003). Experimental observations of weak temperature dependence in rates and exponential decay of the transfer rate as distance increases indicate that long-range electron transfer in proteins occurs by single-step electron tunnelling across a long distance. This mechanism is in contrast to a multistep hopping mechanism. The protein medium provides electronic states associated with pathways along its backbone that help donor and acceptor wavefunctions delocalize towards each other. The result is a ‘superexchange’ mechanism that speeds up electron tunnelling rates, usually by $>10$ orders of magnitude compared with similar distances through a vacuum. Theoretical analysis has even predicted the dominant pathways the electron transfer will take through proteins, and these involve not only covalent bonds, but also hydrogen bonds or even van der Waals contacts. In spite of the prediction of tunnelling pathways, Dutton and co-workers have shown that an empirical model based on average protein density, effectively treating the protein as a structureless random medium, also explains the experimental data (Page *et al*., 2003). Whether or not proteins have evolved efficient and specialized pathways for electron transduction is still an open question.

### *1.3.2 Proton tunnelling*

In many enzymatic catalytic reactions, the rate-determining step involves the transfer of a proton, hydride or hydrogen atom (Allemann and Scrutton, 2009). The simultaneous transfer of a proton and an electron from different sites (so-called proton-coupled electron transfer) also plays an important role in a wide range of biological functions. Moreover, in some enzymes, quantum effects may contribute

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to catalytic rates because of the energy shift due to the zero-point energy that gives a quantum correction to the classical activation free energy and the H-tunnelling effects (Nagel and Klinman, 2006). Such nuclear quantum effects represent another class of quantum phenomena in biological systems. It is the short de Broglie wavelength of the proton wavefunction that makes H-tunnelling extremely sensitive to distance fluctuations, leading to the possibility of strong coupling between protein motions and the H-tunnelling kinetics. A hotly debated issue in enzymatic catalysis is whether or not the couplings to slow protein dynamics serve to control the quantum tunnelling and contribute to an increase in the catalytic reaction rate. Such 'gating dynamics' have been proposed to explain anomalous temperature dependences found in several enzymes.

### *1.3.3 Olfaction*

A related area of interest is olfactory reception (Turin, 1996; Brookes *et al*., 2007; Brookes, 2010). Olfaction is the sense of smell, or the activation of related sensory cells in invertebrates (for instance to detect pheromones). How these systems work and particularly how such a range of odorants can be discriminated by a restricted number of distinct olfactory receptors has not been fully elucidated. It has been suggested that odorants are not discriminated solely by their shape and therefore how they bind to olfactory receptors. Among the various theories, it has been suggested that a second ingredient acts together with the lock and key model; that is, the vibrational spectrum of the odorant is important. It has been suggested that the mechanism in play here is a phonon assisted tunnelling of an electron between two receptor sites via the odorant. Here is an example where a more detailed understanding of the protein, as well as its interactions with a bound analyte, are critical for testing this hypothesis for the operation of olfactory receptors and the possible role of quantum-mechanical tunnelling. A recent detailed study of the Drosophila odorant receptor mechanism could not find good evidence for the vibrational theory (Guo and Kim, 2010), yet other (Franco *et al*., 2011) clinical studies show fascinating evidence in its favour.

## 1.4 Radical pairs

### *1.4.1 Magnetoreception*

There is compelling evidence that numerous organisms, including magnetotactic bacteria, insects, amphibians, birds, fish, sharks and rays, and some animals orient themselves using the Earth's magnetic field (Wiltschko and Wiltschko, 1995a; Kirschvink *et al*., 2001; Rodgers and Hore, 2009; Wajnberg *et al*., 2010). It has been shown, for example, that homing pigeons can be trained to recognize a weak magnetic anomaly. Their response after training can be upset by attaching a magnet

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to a part of their beak known to contain a biogenic magnetite body, suggesting that this structure – also found in the organisms mentioned above – is involved in sensing the magnetic field. Other studies have established how the magnetic field lines are sensed in order to derive direction. There is now no doubt that many creatures can navigate using a magnetic sense.

One hypothesis for the mechanism underlying magnetoreception is that magnetite bodies (arranged as an oriented string) are coupled to special receptors so that mechanical torque in response to magnetic field variations activates an ion channel to initiate signalling. This hypothesis explains the presence and use of the chains of magnetic bodies that have been clearly identified. Nevertheless, precisely how the signalling happens is unknown. In some studies it has been found that magnetoreception, at least in the case of newts and birds, is light dependent. This work has strengthened the case for a second hypothesis for the mechanism of magnetoreception, whereby a light-initiated chemical reaction, possibly occurring in a cryptochrome photoreceptor, is tuned by changes in magnetic field. Changes in rate of a reaction involving radical pairs, caused by changes in magnetic field orientation, are suggested to provide magnetic field transduction. A substantial amount of experimental evidence shows that the light dependence includes wavelength specificities and is evidently complex.

The magnetic sense has obvious biological relevance because it aids navigation, orientation and long-range migration, but is the underlying mechanism quantum mechanical? The answer depends on which mechanism is ultimately found to underpin magnetoreception. The first mechanism described above is based on classical electromagnetism and can therefore be anticipated without resort to quantum mechanics. The second mechanism builds on the idea that ladders of electronic states are prevalent in biological examples of quantum mechanics, but in this case those ladders, specifically the relative energies of singlet and triplet states, are used to sense an external stimulus. The explicit dependence of this proposed mechanism on electron spin means that quantum mechanics lies at the heart of the explanation. The possibility that biological systems are performing a kind of magnetic resonance experiment to guide their seasonal migration patterns or other navigation is fascinating. Crucial advances, however, are needed to obtain compelling experimental connections between the behaviour of organisms and the molecular level mechanisms underlying the traits.

## 1.5 Questions for the present

### *1.5.1 Do quantum effects introduce new functions in biology?*

This is a critical question and one that is being actively pursued by researchers at present. Finding new ways that quantum mechanics helps biological function will drive the field forward. Examples might include sensors, catalysis, photoprotection

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Table 1.1 *Examples of biological phenomena and putative underlying quantum-mechanical processes*

| Biological phenomenon | Quantum process |
|---|---|
| Vision, bioluminescence, light-sensing/ response (e.g. phytochromes), vitamin D biosynthesis | Large energy gaps because of electronic excited states |
| Respiration, photosynthesis | Electron tunnelling |
| Magnetoreception | Radical pairs and electron spin |
| Light-harvesting in photosynthesis | Electronic energy transfer involving quantum coherence |

and the use or production of light. Thinking in terms of realistic high-level biological function, this may be one of the hardest questions to answer.

Viewed as a ‘control knob’ or design tool in the construction of biological devices, one important question is: do quantum effects enable the introduction of qualitatively new functions in biological systems? In other words, are some biological phenomena operating in a regime where classical approximations break down (see Table 1.1)? Answering this question in general terms is a goal of the present volume. More specifically, taking photosynthetic light-harvesting as an example, the answer is clearly yes. A natural pigment–protein system at finite temperature will of necessity have variations in local energies, producing a rough energy landscape. Quantum coherence allows temperature insensitivity and robustness to trap states. It also enables construction of energy flow rectifiers (Ishizaki and Fleming, 2009a), thereby influencing the relative rates of forward and backward energy flow.

Coherent energy transfer, in principle, allows constructive or destructive interference between multiple pathways. We are not aware of specific examples of this phenomenon in natural systems, but it clearly provides a new type of control feature. For maximum efficiency of transport processes, the key point is to correctly balance coherent behaviour and dephasing timescales (Rebentrost *et al.*, 2009a). Exact models of quantum transport as a function of coupling strength to the environment (proportional to dephasing rate) show a maximum in the rate for a given reorganization energy (Ishizaki and Fleming, 2009b). Our present understanding is that natural photosynthetic light-harvesting systems operate in a parameter range at or around this maximum value.

### *1.5.2 Are our experimental methods adequate?*

Single-molecule studies of enzyme action have produced remarkable new insights into enzyme function (Min *et al.*, 2005). These phenomena were previously hidden in the ensemble average common to, and necessary for, all earlier