

From quantum chemistry to quantum biology: a path toward consciousness

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This paper presents a historical overview of quantum physics methodology's development and application to various science fields beyond physics, especially biology and consciousness. Following a successful interpretation of several early 20th century experiments, quantum physics gradually provided a conceptual framework for molecular bonds via quantum chemistry. In recent years individual biological phenomena such as photosynthesis and bird navigation have been experimentally and theoretically analyzed using quantum methods, building conceptual foundations for quantum physics' entry into biology. Quantum concepts have also been recently employed to explain physiology's allometric scaling laws by introducing quantum metabolism theory. In the second part of this work, we discuss how quantum physics may also be pivotal to our understanding of consciousness, which has been touted by some researchers as the last frontier of modern science. Others believe that consciousness does not belong within the realm of science at all. Several hypotheses, especially the Orch OR theory, have been suggested over the past two decades to introduce a scientific basis to consciousness theory. We discuss the merits and potential extensions of these approaches.

Keywords

Quantum physics; quantum biology; quantum metabolism; consciousness

1. Introduction

Quantum mechanics emerged as the most fundamental theory of matter at the turn of the 19th and 20th centuries and, in subsequent decades, revolutionized the way we view not only Nature but also reality. Elementary background information about quantum physics can be found in the Appendix. Applications of quantum methodology to chemistry aimed at understanding the stability of chemical compounds and mechanisms of chemical reactions proved to be exceptionally successful, which led to the development of quantum. It was demonstrated that in the formation of chemical bonds, especially covalent bonds in which electrons are shared between neighboring atoms in a molecule, a quantum

mechanical wave function needs to represent the resultant molecular orbital. Since both chemistry and biochemistry require the creation and destruction of bonds between atoms through chemical reactions, quantum mechanical interactions occur in these processes (McQuarrie, 2008). Hence, by extension, all living systems, like non-living systems, depend for their structural stability on the existence of quantum mechanical wavefunctions representing states at the level of atomic and molecular orbitals. However, some researchers consider these quantum mechanical manifestations of living systems rather merely because they do not delve into animate matter's more fundamental characteristics. Such fundamental properties include the unitary sense of oneness and synchronization in living systems, whose explanation may call for higher-level quantum effects such as the Bose-Einstein condensation, quantum coherent superposition wave-function entanglement. It is still unclear if mechanisms involved in these exotic effects operate in biology, but they could explain some of the most enigmatic life features if they do. However, quantum effects are commonly claimed to be washed out due to thermal decoherence effects taking place at scales larger than those involving individual atoms or sub-atomic particles, at higher temperatures, and in aqueous media create a relatively noisy environment for molecular interactions. Thus, the possibility of quantum states playing important functional roles at mesoscopic or, especially, macroscopic scales in "warm, wet and noisy" biological systems seems problematic due to environmental decoherence effects (Davis et al., 2010).

On the other hand, it is reasonable to expect that evolution, through the process of natural selection over billions of years of experimentation and countless parallel attempts of trial and error, may have solved the decoherence problem so that mesoscopic/macroscale quantum states are indeed essential features of biological systems. If organized quantum states exist in cells, they are presumably integrated among their components and organelles. This introduces another critical issue into consideration, i.e., that the hierarchical multi-scale organization of living systems must have developed a way of processing information between scales. An efficient means of filtering noise must be present to maintain functional integrity.

Sixty years ago, it was commonplace to suppose that quantum mechanics held the key to the mystery of life. Following on their success in explaining the microscopic properties of non-living matter, the founders of quantum mechanics hoped their theory was powerful enough to explain the peculiarities of the living state of matter, too. Erwin Schrödinger, Niels Bohr, Werner Heisenberg, Eugene Wigner and their contemporaries all offered speculations. At the same time, Schrödinger's famous book *What is Life?*, published in 1944 (Schrödinger, 1944), paved the way for molecular biology's birth in the 1950s. Its major thrust was the author's attempt to understand biological organization and function achieved with apparent defiance of the second law of thermodynamics, i.e., by reducing the system's entropy. This paradox can be solved by the inclusion of metabolism, which provides the necessary physical work to overcome the otherwise inevitable increase of entropy. However, what is still very much a mystery is how perfectly synchronized biological processes are across spatial and temporal dimensions connecting the hierarchical organizational scales of a living system. Here, quantum mechanics may indeed come to the rescue, if only we could explain the required absence of decoherence.

Unfortunately, over 50 years, the great expectation that quantum mechanics could easily and powerfully explain living systems and life processes driving them as it had explained other types of matter so exquisitely and precisely has not yet come to fruition. However, parallels between the state of biology today and the state of physics a century ago are striking. Indeed, quantum mechanics is needed to explain the sizes and shapes of molecules and their chemical bonding details. Still, no enunciated "life principle" has emerged from the quantum realm that would single out the living state as in any way a unique form of a physical state. Furthermore, classical ball-and-stick models of protein and other biomolecules and their computational simulations using classical (Newtonian) molecular dynamics methods seem adequate for most molecular, structural, and cell biology explanations. Despite the rapid progress in using classical physics methodology applied to mesoscale systems of relevance to cell biology, there have been persistent claims that quantum mechanics can and should play a fundamental role in biology. For example, biological coherence could emerge through coherent superpositions, tunneling and entanglement. These claims range from plausible ideas like quantum-assisted protein conformational changes (Schempp, 2003) to more speculative suggestions, such as the genetic code having its origin in quantum computation algorithms (Patel, 2001) or quantum-mediated cognitive processing in the brain. Unfortunately, biological systems are so large and complex compared to standard physical systems that it is hard to separate "pure" quantum effects from many essentially classical processes that are also present. There is thus plenty of scope for disagreement about the extent to which life utilizes non-trivial quantum processes. The question also emerges whether biology would be better understood by direct application of quantum physics or by the introduction of quantum-like concepts with their validity limited to living systems.

Why should quantum mechanics be relevant to life, beyond explaining the basic structure and interaction of molecules? One general argument is that quantum effects can facilitate either too slow or impossible processes according to classical physics by

harnessing such phenomena as quantum tunneling, superposition, and entanglement, which can yield novel and unexpected phenomena. Given that biology's basic processes take place at a molecular level, employing quantum effects for greater efficiency does not seem impossible in principle. Quantum coherence, collective modes of excitation, and condensation phenomena represent additional attractive features that could explain the mechanisms behind biological organisms' manifest stability and integrity.

On the other hand, the Heisenberg uncertainty principle sets a fundamental limit on all molecular processes' fidelity. For the cell to perform appropriately, the right parts must be in the right place at the right time. This appears to be a much more relevant objective for living systems than the principle of energy minimization that drives physical processes. Quantum mechanics sets fundamental limits from the Heisenberg uncertainty principle and impacts the accuracy with which molecules can cooperate collectively. However, it is reasonable to expect that some of life's processes have evolved to the "quantum edge", where a compromise may be struck between speed, energy and accuracy. At any rate, the nineteenth-century view of life as "magic matter", exemplified by the use of the terms "organic chemistry" or "life force", is obsolete today and has been replaced by a model of the cell as a complex system of highly efficient and co-ordinated nano-machines operating under the control of genetic software encoded in DNA and implemented by the cellular transcription/translation machinery. These tiny components of the cell's molecular machinery are made mostly from proteins. They include pumps, motors, rotors, ratchets, scissors, cables, levers, sensors, and complexes, including protein polymers: actin filaments, intermediate filaments and microtubules. Their exquisite design, achieved by two billion years of evolution and natural selection, exhibits extraordinary efficiency and versatility and represents a challenge to 21st-century nanotechnologists. Having provided arguments both for and against quantum effects in biology, in the section below, we discuss the evidence currently in place for the importance of quantum mechanics in living systems.

It is abundantly evident that physics and chemistry critically benefitted from quantum mechanics' conceptual and quantitative power to obtain fundamental insights into the material world. Therefore, it is logical to investigate if biology offers other examples of the application of quantum mechanics. It is currently becoming clear that this may indeed be the case. However, examples of quantum effects in biology can be considered only exceptions rather than the rule (Abbott et al., 2008). Nonetheless, the situation with physical phenomena was not significantly different a hundred years ago. Below, we provide a brief overview of the efforts to apply quantum principles to biology.

The concept of biophotons can be credited to Russian scientist Gurvich (1944), who tried to elucidate the enigmatic processes in embryology using so-called morphogenic fields to be proven correct. Later on, Popp (1988) showed that photons, or quanta of electromagnetic energy radiation, can be both absorbed and emitted by cellular biomolecules such DNA in processes that involve low-intensity ultraviolet ranges of the spectrum. More recently, Albrecht-Buehler (1992) found by innovative experimentation that living cells perceive infrared electromagnetic waves with a peak of their sensitivity close to the wavelength of 1000 nm, in the near-

infrared range of the spectrum. He hypothesized that mitochondria, by proton transfer involved in energy production, release photons. Conversely, centrioles, dubbed by him the cell's eye, are intricately structured to absorb these photons and trigger a signaling cascade. Albrecht-Buehler (1992) has been advocating a theory of cell functioning based on his conviction that the centriole plays a crucial role in orchestrating cellular activities by being both an eye and a cell's brain. Cell movement is not random but directed and intentional. This is a crucial characteristic that distinguishes living from non-living matter. Cells control the movement of every part of their body.

Furthermore, various parts of the cell can be likened to parts of the human body in their functional roles. The plasma membrane and cortex correspond to the skin and the musculature of a cell, consisting of small autonomously moving 'microplasts'. Their autonomy implies that cells contain a control system preventing the autonomous units from moving independently and randomly. The bulk cytoplasm, including the mitochondria, organelles and intermediate filaments, comprises the actual cell body excluding the nucleus and corresponding to the 'guts' and 'innards' of the cell body. Its main cytoskeletal components are the intermediate filaments, although microtubules traverse this compartment everywhere. Microtubules mediate between the control center (the centrosome composed of a pair of centrioles) and the autonomous domains. The control center detects objects and other cells by pulsating near-infrared signals. Cells have structures functioning essentially as their 'eyes' in the form of centrioles. They can detect infrared signals and steer the cell movements towards their source. Evidence has been put forward that the signal detection is strongly localized in a narrow band of the near-infrared spectrum. Suppose cells can detect light sources and measure space and time variables such as angles, distances, curvatures or durations. In that case, they must derive these abstract quantities from the physical objects or signals in their environment. In response to exogenous signals, the centrosome may send destabilizing signals along with its radial array of microtubules. The observed destabilization is the signal propagated along the microtubules like action potentials and nerve cells. The destabilization of the microtubules is strictly wavelength-dependent, and its peak area corresponds to the same near-infrared region in which Albrecht-Buehler found cell sensitivity to other objects.

The role of quantum coherence effects in biology was hypothesized by Fröhlich (1968, 1970), who suggested that the modes of vibration of cellular membranes coupled to dipole modes might exhibit the phenomenon of a Bose-Einstein condensate, in which many quanta settle into a single quantum state with long-range coherence. Bose-Einstein condensates are generally associated with very low temperatures. Still, Fröhlich (1968, 1970) hlich proposed that non-linear coupling between a collection of dipole oscillators and phonon modes of lattice vibrations driven by thermal fluctuations from the environment could quite generally channel energy into a single coherent oscillator even at biological temperatures. Fröhlich (1968, 1970) condensates have never been definitively demonstrated experimentally, but recently there has been renewed interest and experimental support, at least for weak condensates. The latter may be crucially important in various chemical kinetics processes taking place in far-from-equilibrium bi-

ological nano-systems. Importantly, Fröhlich (1968, 1970) hypothesized that quantum coherence is a property of living cells. Through long-range physical interactions involving dipole-dipole resonances, synchronizing such effects as cell division processes and cell-cell recognition. To date, only scant indirect experimental evidence has been found to support these predictions (Keilmann and Grundler, 1984; Webb et al., 1977). A recently published report implicated Fröhlich's condensation in the absorption and redistribution of THz electromagnetic energy in proteins (Lundholm et al., 2015).

Another example of quantum tunneling with biological relevance concerns the chemistry of proteins. Vaziri and Plenio (2010) described the action of ion channels using quantum tunneling. Some proteins contain active sites that bond to hydrogen, and to reach the sites, the hydrogen atom has to negotiate an elaborate and shifting potential energy landscape. Quantum tunneling can speed up this process. Studying just how important tunneling might be is highly challenging because many complicated interactions occur as the protein molecule jiggles around and changes shape due to thermal agitation. Vattay et al. (2015) suggested that life has evolved via protein behavior at the edge of quantum criticality. Recent results using deuterium by Klinman and Kohen (2013) seem to confirm that quantum tunneling is indeed significant, and they raise the fascinating question of whether some proteins have evolved to take advantage of this, making them in effect "tunneling enhancers" (Kohen and Klinman, 1998). If true, this could pave the way to understand how quantum effects can be amplified from molecular to cellular scales. Even a small advantage in speed or accuracy can bootstrap into overwhelming success in evolution because natural selection exponentiates the relative proportion of the winners over many generations. Mutations are the driver of evolution, so in this limited sense, quantum mechanics is a certainly contributory factor to evolutionary change, e.g., in environmentally-stressed bacteria (McFadden, 2000), which could boost their survivability.

An important study of photosynthesis by Engel et al. (2007) was a game-changer in quantum biology's emerging field. Photosynthesis is a highly complicated and sophisticated mechanism that harvests light energy to split water using individual photons to create a cascade of reactions. The process is extraordinarily efficient and represents a classic example of how evolution has fine-tuned a physical system's design to attain near-optimal performance. Recently, photosynthesis's quantum mechanical nature has been demonstrated theoretically and experimentally by several research groups (Arndt et al., 2009; Collini and Scholes, 2009; Collini et al., 2010). The light energy's primary receptor is a complex of pigment molecules known as chromophores that can become excited and pass on this dipolar excitation's energy in a multi-stage process to the final reaction center where charge separation occurs. Because the photon's wavelength is much larger than the molecular assemblage, a superposition state of many exciting pigment molecules is initially created and proceeds to evolve over a timescale of some hundreds of femtoseconds. Engel et al. (2007) used laser excitation and probe pulses to study these light-harvesting complexes' relaxation pathways and observed a "quantum beating" effect. The maximum amplitude of the excitation visits and revisits different molecules in the system coherently.

They claim that, with appropriate timing, the system can "grab" the coherent excitation (which persists for a few hundred femtoseconds) with greater probability than if it was merely distributed according to classical statistical mechanics, and this could lead to a many-fold increase in the speed of energy transfer. Their results have subsequently been augmented by [Collini and Scholes \(2009\)](#), who demonstrated room temperature coherence in electron excitation transfer processes along polymer chains. An important feature of photosynthesis is that the molecular architecture involved is structured in a highly unusual and compact manner, suggesting it has been "custom-tailored" to exploit long-range quantum effects. The particular configuration may be efficient at preserving coherence for surprisingly long durations, enabling the system to "explore" many pathways simultaneously and thus speed up a "solution" (i.e., delivering energy to the reaction center). In the light-sensitive complexes, reaction centers capture individual photons and transfer exciton energy by tunneling, avoiding decoherence even at room temperatures, which has been invoked on numerous occasions as a severe impediment to quantum biology in general ([Tegmark, 2000](#)) but also defended on various grounds ([Hagan et al., 2002](#)) as discussed below.

[Ritz et al. \(2000\)](#) have advocated using quantum mechanics by purple bacteria and light-harvesting in carotenoids. They demonstrated the feasibility of quantum effects using high-performance computing at the atomic level of simulation for the relevant enzymatic reactions. It should be mentioned that the use of quantum mechanics to explain photosynthesis can be viewed as a natural progression of theory development, which was preceded by extensive experimental ([Möbius and Kuhn, 1988](#)) and theoretical ([Tuszyński et al., 1999](#)) work on the so-called Scheibe aggregates. Scheibe aggregates are thin films composed of chromophore molecules that have been engineered to harvest light energy and funnel exciton quanta at specific sites through quantum hopping and funneling. Another example of quantum tunneling with biological relevance concerns the chemistry of proteins, which spontaneously fold into complex three-dimensional shapes, i.e., their tertiary structures. The protein folding problem has not been solved yet, and it can be indeed unsolvable within the methodology of classical physics. However, quantum search algorithms can provide a sufficiently quick way of finding a three-dimensional protein structure for an initially outstretched polypeptide chain.

Since the discovery of potassium K^+ channels, a surge of interest has been aroused to explain their fascinating molecular mechanisms. These complexes, which are assembled by several proteins creating circular pores through the membrane, operate quickly and precisely. KcsA is a potassium channel conducting K^+ ions with a high efflux rate ($\sim 10^7 - 10^8$ ions per second ([MacKinnon, 2003](#)) while selecting K^+ over Na^+ with a remarkable rate of 10^4 to 1 ([Doyle et al., 1998](#)). It is worth noting that the difference in atomic radii of K^+ and Na^+ is about 0.38 nm. In many ion-channel proteins, the flow of ions through the pore is controlled by a gate comprised of a selectivity filter activated by electrical, chemical, light, thermal and/or mechanical interactions. Following the determination of an atomic resolution structure of the bacterial KcsA channel by [Jiang et al. \(2003\)](#), doubt has been cast on the appropriateness of classical descriptions such as the "snug-fit" model ([Noskov et](#)

[al., 2004](#)), which are unlikely to adequately explain such a subtle selectivity process. Recently, [Vaziri and Plenio \(2010\)](#) and [Ganim et al. \(2011\)](#) put forth a quantum coherence mechanism for the operation of a selectivity filter and investigated quantum vibrational excitations in K^+ ion-channels. They calculated resonant effects at the picoseconds (ps) scale taking place in the backbone amide groups and concluded that they play an important role in mediating ion-conduction and ion-selectivity processes selectivity filter. [Summhammer et al. \(2012\)](#) also carefully studies the interaction of a single potassium ion within the surrounding carbonyl dipoles by solving the Schrödinger equation for the bacterial KcsA ion-channel and analyzing its solutions. They discovered that alkali ions could become highly delocalized in the selectivity filter region even at temperatures as high as the physiological temperature.

[Beck and Eccles \(1992, 2003\)](#) investigated the neurotransmitter release process occurring in the neuronal synapses and proposed that it is subject to the Heisenberg uncertainty principle. They further suggested that this process involves quantum mechanical tunneling. They also stated that quantum indeterminacy into neurotransmitter release mechanisms would provide a means for the emergence of the human free will of action. In particular, a quantum process involved in this mechanism, such as an electron tunneling through a potential energy barrier, could trigger exocytosis. While this is a desirable possibility, the vesicle's physical size and many neurotransmitter molecules encapsulated in it appear to make it very improbable that this could lend itself to quantum tunneling. In conclusion, while the Beck-Eccles model contains very attractive ideas, the theory's main assumptions are not easily reconcilable with modern views of the molecular biology of vesicular neurotransmitter release ([Smith, 2009](#)).

[Lowenstein \(2013\)](#), in a most exciting book, made argued convincingly in favor of the usefulness of quantum mechanical processes in receptor functions, which could facilitate molecular recognition. Since sensory inputs depend on molecular recognition between ligands and receptors (in molecular processes underlying such physiological functions as olfaction, vision, sound, touch), they all involve single molecules behaving as triggers for amplifying these signals at the neuron level and leading to an eventual brain-level activation. This amplification mechanism involving quantum signaling connects the microscopic and macroscopic levels, critical to our understanding of the so-called binding problem in human cognition and consciousness.

[Gauger et al. \(2011\)](#) have recently demonstrated that bird navigation is based on quantum entanglement that persists for at least 20 μs , which is longer than the currently maintained laboratory experiments at comparable temperatures. It is well-known that some birds perform amazing navigation feats using various cues that include the local direction of the Earth's magnetic field. The nature of the magnetic sensor has, however, remained something of a mystery. How is the angle of the field relative to the bird translated into neural information? The problem is particularly acute because the magnetic field penetrates the entire organism. Still, in the case of the European robin, at least a plausible case has been made that the key lies with a class of proteins found in the bird's retinas. In effect, the robin actually "sees" the magnetic field. The mechanism being studied by [Ritz \(2011\)](#) and [Ritz et al.](#)

(2009) appeals to photo-activation above the thermal noise of a two-dimensional array of aligned proteins, producing radical ion pairs involving singlet two-electron states. So long as electrons in an entangled state experience identical magnetic environments and quantum coherence is preserved, the spins precess in synchrony. However, in addition to the Earth's ambient field, nuclear magnetic fields present hyperfine splitting. If one of the electrons in a singlet pair moves away, the combined nuclear and terrestrial magnetic field it experiences will change, causing the singlet state to oscillate with a triplet state with a periodicity depending in part on the strength and relative orientation of the Earth's field. The system may then de-excite in stages and initiate a reaction that acts as a chemical compass because the relative proportion of the reaction products can depend on the singlet-triplet oscillation frequency.

McFadden (2002) maintains that biological evolution, such as present in bacterial mutations under toxic stress, must involve quantum computing to explain its efficiency, including anticipatory steps. Another early and recurring speculation is that some biological mutations come about as a result of quantum tunneling. The genetic basis of life is written in the four-letter alphabet of nucleotides A, G, C, and T that pair together to make up the rungs of the helical ladder structure of DNA. The normal assignment is that T pairs with A and G pairs with C are held together by two or three hydrogen bonds, respectively. According to a proton's position, the nucleotide bases can exist in alternative chemically related forms, known as tautomers. Quantum mechanics predicts a finite probability for the proton to tunnel through the potential barrier separating these two states, leading to mispairing, for example, of T with G instead of A. Mutations are the driver of evolution, so in this limited sense, quantum mechanics could become a certainly contributory factor to evolutionary change. McFadden (2000, 2002) has built on this process to suggest a quantum model of adaptive change, in which environmentally stressed bacteria seem able to select favorable mutations that boost their survivability. Even for a medium-sized protein, the number of possible amino acid mutations is astronomical. Over the biological scale of evolution on Earth, there could be no possibility of attempting all of these mutations to select favorable ones. Therefore, a quantum search algorithm could once again come to the rescue and solve an otherwise unsolvable problem.

Experimental data show that signaling and ionic conductivity in cells via microtubules (MTs) may offer real potential for both classical and quantum information processing at a subcellular level. However, there are numerous arguments in the literature both for and against the role of quantum effects in MTs. Theoretical and computational models investigated the conditions for quantum processing of information in microtubules and microtubule assemblies. For example, Craddock et al. (2009) used an approach based on cellular automata and investigated classical and quantum neighbor interaction rules. With a characteristic MT geometry and a tubulin dimer neighborhood in a hexagonal configuration, the interior of tubulin was represented electrostatically, showing two nanoscale regions with a positive electric charge separated by a negative potential region forming a double-well potential. The position of a mobile electron oscillating within this double potential well was the critical factor for the state of indi-

vidual tubulin. It resulted in transitions between two local energy minima found from conditions for minimizing the system's energy associated with electrostatic interactions between the neighboring electrons and exposed to thermal fluctuations of the environment. This model's classical version allows only transitions for electrons with sufficiently high energy to overcome the potential barrier (approx. 100-150 meV). The new configuration lowers the system's energy.

Conversely, if the new configuration raises the system's energy, the transition occurs with a probability proportional to the Boltzmann factor, namely $\exp(-\Delta E/kT)$ where ΔE is the energy quantum, k is the Boltzmann constant and T is the temperature. On the other hand, the quantum cellular automata model allows electron tunneling to occur through the potential barrier even for transitions when the electron does not possess sufficient energy to overcome the potential barrier. These simulations have indicated the feasibility of information processing at physiological temperatures through microtubules in neurons and suggested that a global clocking mechanism is at play. We should stress that some of the simulation parameters are still not available experimentally.

Speaking of clocking mechanisms, metabolism at a cellular level appears to provide the most fundamental life rhythm. Demetrius (2003) proposed a more general theory called quantum metabolism, discussed in more detail below, which states that metabolic energy is universally generated by all living systems using quantum mechanics principles. It involves collective quantum oscillations of metabolic enzymes, which we discuss separately below.

Turning to possible quantum biology effects occurring in organs and tissues of the human body, it has been shown that the human eye can detect light at an extremely low threshold, with as few as 2-3 photons being detected at a time (Hecht et al., 1942). Similarly, the seminal work of Turin (1996) and Brookes et al. (2007) has provided strong arguments to the claim that the sense of smell (olfaction) is based on a quantum resonant energy transfer mechanism involving vibrational degrees of freedom of aromatic molecules and receptors in the membranes of olfactory nerves.

Although the preceding examples have been in the literature for some years, they have not led to a widespread acceptance that quantum physics is essential for biology. The main reason for this skepticism is the problem with decoherence mentioned above but requires a closer analysis.

2. The decoherence problem

While the examples listed above provide a case for quantum mechanics playing a biological role, they all confront a profound and fundamental problem. Effects such as coherence, entanglement and superposition can be maintained only if the quantum system avoids decoherence caused by interactions with its environment. In the presence of environmental noise, the delicate phase relationships that characterize quantum effects get scrambled, turning pure quantum states into irregular mixtures and marking a transition from quantum to classical behavior. Only if decoherence can be kept at a sufficiently low level will explicitly quantum effects be allowed to persist. Therefore, quantum biology claims stand or fall on the precise determination of the decoherence time scale. If decoherence happens too fast, the sys-

tem will equally rapidly find itself in the classical regime before any biochemical or biological effects of interest happen.

In recent years, much attention has been given to decoherence, and its avoidance, by physicists working in quantum computation and quantum information science. A quantum computer can process information more efficiently using quantum states to perform logical operations through quantum superpositions' coherent evolution. Decoherence represents a source of computational error, so the idea is to design architectures that minimize the impact of decoherence. A key parameter is a temperature: the higher the temperature is, the stronger the decoherence. For this reason, most attempts at quantum computation employ ultra-low temperature environments such as superconductors or cold atom traps.

At first glance, a living cell's warm and wet interior seems a very unpromising environment for low decoherence and long-range coherence. Approximate calculations suggest decoherence times on the order of 10^{-13} s for most biochemical processes at body temperature. However, there are reasons why real biological systems might be less susceptible to decoherence than this might suggest. First, biological organisms are highly non-linear, open, driven systems that operate far away from thermodynamic equilibrium. Such systems' physics is not well understood and could conceal novel quantum properties, which are yet to be discovered. More accurate calculations indicate that decoherence rates may be longer than expected. For example, [Cai et al. \(2010\)](#) have found that a two-spin quantum system dynamically driven away from equilibrium can exhibit on-going coherence even when coupled to a hot and noisy environment that would rapidly decohere a static system. A calculation based on the spin-boson model by [Leggett \(2002\)](#) also suggests dramatically extended decoherence times for low-frequency phonons. Leggett also points out that an acoustic mismatch between the quantum system's immediate and more distant environment could prolong coherence at low frequencies. Furthermore, all degrees of freedom do not need to experience the same level of decoherence. Some quantum biological effects might require only a small subset of degrees of freedom to be protected from thermal decoherence.

There are two other ways decoherence could be diminished for long enough to enable biologically important processes to occur. The first is screening: if the system of interest can be quasi-isolated from the decohering environment, decoherence rates can be sharply reduced. According to [Matsuno \(1999\)](#) and [Matsuno and Paton \(2000\)](#), organisms may exploit thermodynamic gradients by acting as heat engines, thereby drastically reducing certain molecular complexes' effective temperature. An example of this situation is the slow release of energy from ATP molecules at actomyosin complexes, which implies an effective temperature for the actomyosin of a mere 1.6×10^{-3} K. Moreover, the knowledge gained in the study of the physics of high-temperature superconductivity indicates that in complex states of matter, simplistic arguments which only focus on energies above kT and dismiss energy levels below kT as thermal noise can sometimes be missing the point since non-linear interactions do not satisfy the equipartition theorem on which this argument is based.

The second possibility involves decoherence-free subspaces. As part of the effort to build a quantum computer, much attention has been given to identifying Hilbert space subspaces unaffected

by the system's coupling to its environment. Paradoxically, when a system couples very strongly to its environment through certain degrees of freedom, it can effectively "freeze" other degrees of freedom by the quantum Zeno effect, enabling coherent superpositions and even entanglement to persist. A relevant example is that of a double-well one-dimensional potential Hamiltonian. A particle placed in the lowest energy state of one well will tunnel back and forth through the intervening barrier, oscillating with a specific frequency. If the particle is placed instead in an excited state of the well, this flip-flop frequency will differ. Thus, an initial state consisting of a superposition of lowest energy and excited states will soon evolve into a complicated combination as the flip-flops get out of phase. However, suppose the particle is allowed to interact strongly with an external heat bath. In that case, the environment will have the effect of forcing the disparate oscillations into synchrony (entrainment), maintaining some amount of quantum coherence paradoxically because not despite environmental interactions.

The critical assumption that quantum coherence is eliminated by increased temperature is no longer assured when non-equilibrium states and non-linear interactions are included. For example, this is the case with laser action, and possibly laser-like coherent pumping hypothesized to take place in biological cells and, in particular, with periodic lattice structures such as microtubules or actin filaments. Recent experimental evidence demonstrates that quantum spin-transfer processes between quantum dots can be more efficient at room temperature than at or near absolute zero ([Ouyang and Awschalom, 2003](#)). The critical factor in these processes is that the temperature-enhanced quantum interaction involves benzene rings, which are organic molecules having delocalized electron charge density. Another set of experiments has shown that quantum waves are generated by biological porphyrin molecules ([Hackermüller et al., 2003](#)). These molecules are found in heme groups of the red blood cells, for example.

By analogy, in living cells, delocalized electrons in aromatic amino acids, for example, may allow proteins to harness thermal environmental energy to promote, rather than destroy, quantum states. Quantum interactions among tryptophans in hydrophobic pockets (nonpolar, water excluding intra-protein regions) govern protein folding ([Klein-Seetharaman, 2002](#)), and similar effects appear to mediate potassium channel function ([Jiang et al., 2003](#)).

Finally, in this connection, special attention must be paid to the hierarchical structural organization of biological systems, which in turn translates into an interlocking hierarchy of time scales. Faster time scales may inform processes at slower time scales about much faster processes associated with a small spatial level. For example, the neurotransmitter systems undergo changes synchronized with endogenous circadian rhythms and fluctuate in accordance with the seasons of the year. This results in a vast range of time scales over 8 to 10 orders of magnitude along the time axis. Because neuronal processes at the millisecond time scale readily affect neural states at the circadian level, it can be argued that picosecond-scale quantum states can affect millisecond-scale neural activity. Therefore, a postulated requirement that MT information processing must involve long-lived coherent states with lifetimes at or above a millisecond time may not condition *sine qua non* for it to affect neural events. However, multiple oscilla-

tors must stay interdependent and sensitive to redundant patterns. Such interdependence allows processes operating at the shortest time scales where quantum mechanisms dominate to affect more extended time-scale events and broader size-scale processes. Here again, the coupling between spatiotemporal scales and amplification of quantum effects may offer a solution to some of these problematic issues.

While quantum mechanics was developed with elementary particles in mind, its subsequent applications extended its validity to systems of many particles such as those encountered in condensed matter physics, e.g., describing the conduction electron "sea", excitons, magnons, polarons, polaritons, etc. These types of quantum properties of macroscopic physical systems are called collective excitations. Many particles under specific conditions cannot be separated into individual wave functions for each particle; instead, the system is described by a single wave function describing its collective behavior. This physical property is called quantum coherence, and it is characterized by individual particles losing their separate identities such that the entire system acts as a whole. Particles that were once unified in a shared quantum state remain physically connected even at a distance. Measurements made on one particle cause the collapse of the entire wave function for the system, resulting in an instantaneous effect for all particles, no matter where they are spatially located. This intrinsically quantum-mechanical interaction over distance is referred to as non-local quantum entanglement. Decoherence occurs when such a system interacts with its environment in an irreversible thermodynamic manner, causing different particles engaged in a quantum superposition state to no longer interfere with one another. Decoherence plays an important role in the criticisms leveled at quantum mechanics to describe macroscopic systems, especially biological ones, as we discuss later.

3. Quantum metabolism: the key to life

In this section, we have drawn on the lessons learned from the quantum theory of solids. An adequate mathematical representation of solids (e.g., crystals or semiconductors) leads to energy ϵ being quantized at a finite temperature T . In a seminar theory of specific heats of solids, Debye introduced a dimensionless variable $x = hf/kT = \epsilon/kT$ where k is the Boltzmann constant, h the Planck constant and f the frequency of atomic vibrations in a solid. Debye was able to accurately quantify the specific heat of a solid through a formula where the Planck constant, h , is hidden in the definition of x , such that in 3-dimensional space (Ashcroft and Mermin, 1995):

$$C_v(T) = 9Nk \left[\left(\frac{T}{T_D} \right)^3 \int_0^{\infty} \frac{x^4 e^x}{(e^x - 1)^2} dx \right] \quad (1)$$

where the integral above is from $x = 0$ to $x = x_D$ and $x_D = \epsilon/kT_D$, N is the number of atoms, k the Boltzmann constant, T the absolute temperature and T_D is called the Debye temperature. This property, specific heat, $C_v(T)$, is shown in Eqn. 1 is plotted as a function of normalized temperature in Fig. 1.

It can be shown that the quantum nature of solids manifests itself at temperatures up to the characteristic value (T_D) depends on the size of the solid and its rigidity, which determines the propagation velocity of the sound waves (phonons). As a consequence

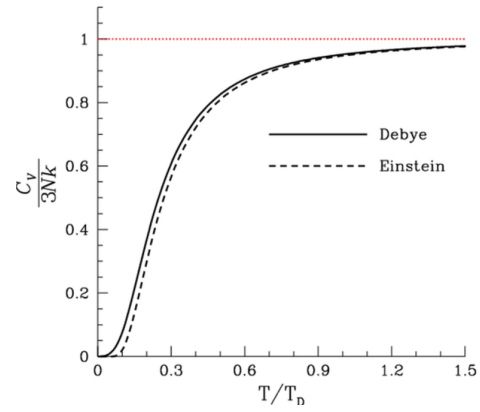


Fig. 1. A characteristic plot of the specific heat of solids as a function of temperature based on https://en.wikipedia.org/wiki/Debye_model where discussion can be found about the comparison between the Debye model of a solid and the Einstein model. In contrast to the Debye model's correct assumptions, the Einstein model considered lattice nodes as oscillating independently around their equilibrium positions.

of many-body systems' collective behavior, quantum mechanics' hallmarks can be seen in the properties of macroscopic objects such as crystals or ferromagnets, even above room temperature. The functional dependence of properties such as specific heat and magnetic susceptibility is different in the quantum (low temperature) and classical (high temperature) regimes. There are also more exotic direct manifestations of quantum behavior in macroscopic systems, such as superconductors (with no measurable resistance to electrical current and ideal diamagnetism) or superfluids (with no viscosity and infinite vorticity) (Anderson, 1984). However, these latter two examples have so far been limited to very low temperatures. Yet, the boundary's precise location (in terms of both the object's dimensions and ambient temperature) between quantum and classical approaches is still debatable. It appears to be moving more and more toward higher temperatures and larger dimensions.

The specific heat of solids satisfies an empirical relationship, expressed by the Dulong and Petit law, which states that above a characteristic temperature (Debye temperature), the specific heat of solid increases in proportion in the high-temperature regime to $3NkT$. At low temperatures, the relationship between specific heat and temperature is a cubic dependence on absolute temperature. As developed by Debye, the quantum theory of solids was proposed to explain these empirical relations. The crucial observation in these models was the heat capacity's consideration as associated with the propagation of vibrations of atoms (phonons) in a crystalline solid, not individual atomic oscillations as proposed by Einstein.

However, temperature as an independent variable is not relevant to live organisms, which are essentially isothermal. Energy flow in living organisms is mediated by differences in the turnover time of various metabolic processes in the cell, which occur cyclically. Empirical studies that go as far back as Lavoisier's work but mainly to the studies done by Kleiber (1961) demonstrate that metabolic processes are characterized by cycle times,

which are related to the metabolic rate. Basal metabolic rate is defined as the rate at which the organism transforms the free energy of nutrient molecules into the body's metabolic work, including maintaining its physiological temperature. The recently proposed theory of Quantum Metabolism (Demetrius, 2003; Demetrius and Tuszyński, 2010) has employed the methodology of the quantum theory of solids developed by Einstein and Debye to provide a molecular-level explanation of these empirical relations called allometric scaling laws.

Debye (see Ashcroft and Mermin, 1995) made a significant advance in condensed matter physics by considering the heat capacity as associated with harmonic vibrations of atoms in a crystalline solid. The vibrations were assumed to propagate within the solid due to the interactions between the neighboring atoms. They were then treated according to quantum theory and satisfied with the following quantization condition. The energy stored by an oscillator with frequency ω can only be an integer factor of a fundamental energy quantum $h\omega$: $E_n = nh\omega$, $n = 1, 2, 3, \dots$. The model proposed by Debye, which proved to be consistent with empirical observations, assumed that the atoms in the solid execute coupled vibrations about the fixed lattice site leading to the propagation of waves in the solid and the frequencies of these vibrations span a range of values from zero to a maximum (Debye) frequency.

ATP's production, the energy currency of living organisms, is mediated by the coupling of two molecular chains: (a) The redox chain, which describes the transfer of electrons between redox centers within the electron-transport chain. (b) The ATPase motor, which is involved in the phosphorylation of ADP to ATP. There are two distinct mechanisms by which these two events are coupled: oxidative phosphorylation, which involves an electrical process, and substrate phosphorylation, which implicates a purely chemical process. This cyclic process's transit time determines the total metabolic flux, i.e., the number of proton charges released by the redox reactions. This transit time, or the metabolic cycle time, denoted τ , plays a fundamental role here. In oxidative phosphorylation, which occurs in the mitochondria, the electron transport between redox centers is coupled to protons' outward pumping across the mitochondrial membrane, thus generating an electrochemical gradient, called the proton motive force, Δp . Substrate phosphorylation, which is localized within the cytosol, is driven by enzymes that couple ADP phosphorylation to the electron transport chain.

The molecular dynamics model proposed to investigate this coupling by electrical and chemical means assumes that the energy generated by the redox reactions can be stored in terms of coherent vibrational modes of enzymatic oscillators embedded in the cellular organelles. Quantum Metabolism rests on the notion that the enzymatic oscillations in cellular organelles and the material oscillators in crystalline solids can be analyzed using essentially the same mathematical formalism used by Debye in the quantum theory of solids. This realization is deduced from a formal correspondence between the thermodynamic variables in physical systems and biological processes' metabolic quantities. The principal variables in the quantum theory of solids are the specific heat, the Gibbs-Boltzmann entropy and the absolute temperature T . The fundamental unit of energy is given by $E = k_B T$, the typical thermal energy per degree of freedom of a molecule.

On the other hand, the critical variables in the theory of quantum metabolism are the metabolic rate, the entropy production rate and the mean cycle time, τ . This latter quantity describes the mean turnover time of the redox reactions within the cellular organelles. The fundamental unit of metabolic energy is now given by $E(\tau) = g\tau$. Here, the value assumed by g depends on the mechanism, electrical or chemical, by which the electron transport chain is coupled to ADP phosphorylation. Note that since physical systems are described here at thermodynamic equilibrium, their parameters involve thermodynamic variables. Biological systems operate far from thermodynamic equilibrium (albeit close to steady states). Hence their bioenergetic quantities involve fluxes, i.e., rates of change of energetic values.

Demetrius (2003) introduced the term enzymatic oscillator since enzymes undergo electrochemical oscillations about their fixed positions. These oscillations are generated by the metabolic energy associated with electrons' transfer between donor and acceptor pairs in the mitochondria's electron transfer chain. Since their power spectrum exhibits an exponent vastly different from that for random behavior, a description of the metabolic activity involving mitochondrial proteins involves coupled quantum oscillators of the Debye type.

Quantization of metabolic energy is due to integer ATP numbers being produced in the cell's mitochondria and their relatively low energy content comparable to physical quantum processes. The almost universal energy currency in biological systems is the ATP molecule. ATP synthesis in a mitochondrion or a chloroplast requires approximately 60 kJ/mol of energy delivered through electron transport reactions or absorption of photons, respectively. ATP hydrolysis releases 30.5 kJ/mol of free energy ($\Delta E = 5 \times 10^{-20}$ J), which can be viewed as a biological energy quantum. It is interesting to note that the particle-wave duality principle indicates that the wavelength of electromagnetic energy that corresponds to the biological energy quantum ΔE can, therefore, be estimated as:

$$\lambda = hc/\Delta E = 9 \times 10^{-6} \text{ m} \quad (2)$$

which is very closely related to the average size of a living cell (micrometer range). Assuming that metabolic processes propagate in a wave-like fashion, and using the relationship between the wavelength, λ , propagation velocity, v , and frequency, f , we have $\lambda = v/f$, with v on the order of $1 \mu\text{m/s}$ and $f = 1000 \text{ Hz}$. Thus, we find that λ is on the order of 1 nm . This is consistent with the value of proton displacement in electric fields of mitochondrial membranes. It is also intriguing to find an approximate value of the Debye temperature for the so-called biological energy quantum. We assume that enzymatic reactions in the metabolic cycle involving ATP generation occur periodically but are correlated spatially since they occur on a lattice with mitochondria as its nodes, which is reminiscent of the Debye solid. We then find that $T_D = \Delta E/k_B = 3 \times 10^3 \text{ K}$ and since the physiological temperature is $T_0 = 300 \text{ K}$, it follows that $T_0/T_D < 1$. This then indicates that cellular metabolism operates in the quantum regime consistent with the tenets of Quantum Metabolism in the statistical sense.

4. Emerging quantum science framework

Integrating this development of quantum effects in biology into a broader quantum science framework, we can delineate two

distinct thought lines. First, quantum phenomena and theories dealing with individual particle interactions. This approach goes back to the photoelectric effect and the Compton scattering effect, where a photon interacts with an electron demonstrating the particle aspect of electromagnetic radiation in the first case and wave nature of an electron in the latter. Most of the so-called "quantum weirdness" can be ascribed to binary interactions between individual microscopic entities with properties such as entanglement, long-range correlations, delocalization, tunneling, etc., providing striking examples of how quantum physics differs from the classical paradigm. The current focus within the emerging field of quantum biology on photosynthesis parallels early quantum physics development through individual particle experiments, especially the role of the photoelectric effect.

On the other hand, the first experiment correctly interpreted using the quantization principle, namely the black body radiation and Planck's energy quantization formula (Planck, 1959), to speak to a different group of quantum phenomena theoretical building blocks of quantum theory, i.e., quantum statistical mechanics. Applications of quantum statistics dominated quantum theory in several fields, particularly condensed matter physics (Ashcroft and Mermin, 1995). This approach gave rise to the explanations of specific heats of solids first by Einstein, then by Debye, and the development of quantum theories of magnetism, semiconductivity, and other collective quantum effects. It is worth mentioning that within condensed matter physics, one finds examples of macroscopic quantum phenomena countering the objections voiced by some that quantum theory is limited to the microscopic world. Both superconductivity and superfluidity exhibit "quantum weirdness" at a macroscopic scale, although they still require extremely low temperatures to be sustained. However, magnetism is an inherently quantum state of matter that could not arise without spin, a quantum variable, and it exists at both macroscopic scales and high temperatures. Laser action is an example of a macroscopic quantum coherent state at high temperatures. Due to a non-equilibrium condition created by external energy pumping, Fröhlich claimed to provide a blueprint for a fundamental explanation of the living state of biological matter. Quantum metabolism is a theory that closely parallels the Debye theory of the specific heat of solids in the realm of quantum statistical properties of living systems.

Table 1 provides a general overview of the areas of science where quantum physics found applications, both in equilibrium and non-equilibrium situations (A) refers to quantum science's totality as is known today, (B) includes equilibrium quantum phenomena that include individual particles and their statistical ensembles, (C) encompasses nonequilibrium quantum phenomena in physics and biology. Since living systems are out of thermodynamic equilibrium, in principle, all quantum mechanics' biological applications should be considered nonequilibrium quantum phenomena. An extension of these phenomena to the realm of neuroscience is a vast and hugely challenging endeavor that may require many decades to complete. In the sections that follow, we discuss these challenges and our current understanding of quantum models of consciousness.

5. Quantum consciousness

Does the study of consciousness belong in natural sciences, or is it a philosophical or even metaphysical inquiry area? These questions have been pondered by many scientists, philosophers and spiritual leaders whose opinions diverge mainly due to the subjective nature of consciousness. The existence of this phenomenon cannot be denied, as we all experience it as sentient humans. The author of this paper firmly subscribes to the assertion that not only is the study of consciousness a valid area of scientific research but, indeed, one of the most fundamental unsolved scientific problems of the modern age. The enigma of consciousness has challenged all conventional theories. The brain is considered an information processing device similar to a classical computer, with neurons and synapses playing the roles of bit states storage devices and logical gates, respectively. Specifically, the following unresolved issues await elucidation: 1) the so-called "hard problem" related to the nature of conscious experience, i.e., "qualia", 2) the binding problem, i.e., how disparate brain processes can be unified into a sense of "self", 3) the mechanism of the transition from pre-conscious processes to consciousness itself, 4) the existence, limitations and manifestations of free will, or non-algorithmic (e.g., intuitive) processes, 5) subjective perception of the flow of time, 6) nonlocality, i.e., paranormal connections between humans and also between humans and other-than-human species cross large spatial and temporal domains (e.g., precognition, telepathy, etc.).

Most conventional neuronal-level computational approaches suggest conscious experience "emerges" at a critical level of computational complexity. Binding is proposed to involve temporal synchronization (e.g., via coherent 40 Hz oscillations). However, it is clear that with no sense of conscious experience, temporal synchronization amounts simply to a correlative epiphenomenon and not an explanatory mechanism. On a positive note, potentially the easiest to tackle is the problem involving the transition from pre-conscious processes to full consciousness. It is currently almost universally agreed upon that most of the brain processes are non-conscious. Hence, consciousness constitutes the "tip of an iceberg" of the totality of brain activities. However, no specific region of the brain can be identified as housing consciousness; neural activity in a given area may be non-conscious at one moment and be involved with consciousness at another.

Inspired by applying quantum theoretical methods to studying the brain and other biological structures, scientists began to investigate brain functioning from the microscopic quantum physics level. One of the first attempts to describe the brain, especially the concept of memory as a broken symmetry state, using quantum physics terminology was made by Ricciardi and Umezawa (1967). Based on experimental observations of brain activity, they proposed that the brain could be understood as a spatially-distributed system placed into specific quantum states by external environmental stimuli. Thus, information can be thought of as being coded into the brain in the form of metastable excited quantum states, representing short-term memory. This type of memory code could then be transferred more permanently to the system as a condensation transition to the ground state, similarly to the Bose-Einstein condensation effect in superfluids and other exotic physical systems. The process was envisaged as explaining learning

Table 1. Schematic outline in the development of quantum ideas both within physics, chemistry and biology. (A) refers to quantum science's totality as is known today. (B) includes equilibrium quantum phenomena that include individual particles and their statistical ensembles. (C) encompasses nonequilibrium quantum phenomena in physics and biology. Since living systems are out of thermodynamic equilibrium, in principle, all quantum mechanics' biological applications should be considered nonequilibrium quantum phenomena.

A. QUANTUM SCIENCE			
PHYSICS, CHEMISTRY, BIOLOGY			
B. EQUILIBRIUM QUANTUM PHENOMENA			
QUANTUM MECHANICS		QUANTUM STATISTICS	
INDIVIDUAL PARTICLE REPRESENTATION		STATISTICAL ENSEMBLE	
FEW PARTICLES		MANY PARTICLES	
PHYSICAL	BIOLOGICAL	PHYSICAL	BIOLOGICAL
Photoelectric effect	Photosynthesis	Einstein/Debye solids	Quantum metabolism
C. NONEQUILIBRIUM QUANTUM PHENOMENA			
PHYSICAL		BIOLOGICAL	
Laser action		Fröhlich coherence	

and long-term memory. This Ricciardi-Umezawa model views the brain as representing a biological equivalent of spontaneous symmetry breaking in the brain's dynamics (Stuart et al., 1978). It relates macroscopic quantum states with long-range correlations to memory specifically, and it was later extended to mixed physical states whereby the brain is considered to consist of two separate interacting parts. The first part involves classical electrochemical interactions of the brain's neurons, while the second generates and sustains a macroscopic quantum state responsible for creating and maintaining memory. Extensions of these early quantum field theory models to higher dimensions, networks and non-equilibrium situations have been recently proposed (Nishiyama et al., 2020).

Subsequently, a major effort has been placed on the mechanistic explanations of the role of the material substrate for conscious processes, namely protein polymers and their networks located within individual cells and referred to collectively as the cytoskeleton, especially the microtubules and their axonal and dendritic bundles (Hameroff, 1987, 1998). Penrose (1989, 1994) investigated the relationship between consciousness and modern physics in a fascinating exposition of Turing machines, Gödel's theorem, chaos, classical and quantum mechanics, thermodynamics, relativity, cosmology, quantum gravity, quasi-crystals, and brain neurophysiology. Penrose strongly argued that quantum effects play a fundamental role in understanding human consciousness by enabling the brain to perform non-computable operations related to cognitive functions. In his work, Penrose argued that a new type of physics is required to explain the mind's workings and the fundamental nature of consciousness. Consequently, he examined the distinctions between classical and quantum physics, focusing closely on the measurement problem, and relating the collapse of the quantum wave function to conscious events. In this latter aspect, he drew on the so-called Objective Reduction phe-

nomenon, which causes a gravitationally-induced wave function collapse. This has subsequently led to the hypothesis about a concrete realization of this process, jointly formulated by Hameroff and Penrose (2014). They predicted that microtubules within neurons provide the brain with the requisite structures, which can orchestrate the wave function's collapse via quantum computations if sufficiently abundant and strongly correlated. This combination has become known as the Penrose-Hameroff Orchestrated Objective Reduction (Orch OR) theory.

The Orch OR theory's main idea rests on is that microtubules within the brain's neurons function as quantum information processors at physiological temperature. They are composed of microtubule protein subunits ("tubulin dimers"), which transiently occupy quantum superposition states involving two or more conformational (or electronic) states (i.e., quintessential quantum bits, or "qubits"). Orch OR further asserts that tubulin-based qubits, when in a quantum superposition, interact/compute with other superpositions of qubits localized in tubulins arrayed over microtubule lattices. These interactions involve nonlocal quantum entanglements, eventually reducing ("collapsing") to particular classical tubulin states after approximately 25 ms (which corresponds to the frequency of 40 Hz mentioned above). This type of quantum state reduction could be interpreted as yielding conscious perceptions and volitional choices, which then when transmitted to the next level of organization, would control neuronal actions. This idea is very similar to that on which technological quantum computing is based, with the exception that Orch OR proposes the representation of qubits to involve tubulin protein conformations (Hameroff et al., 2014) and that the reduction/collapse events occur as a result of a specific objective threshold (objective reduction) rather than environmental interaction controlling the process.

Therefore, the Orch OR theory regards a conscious event to

represent a quantum computation process, which concludes with objective state reduction representing a realized thought. The brain's biological conditions, including synaptic activity, influence the quantum computations, thus orchestrating the qubits' collapse and giving rise to a conscious event at a specific moment in time. The Orch OR theory's central postulate can be stated as placing consciousness within the brain's microtubules, which operate at the interface between classical neurophysiology and quantum mechanical forces. These are very bold claims that have found both ardent supporters and vocal critics in the scientific community. However, the enduring power of attraction of Orch OR for a solid base of support across science, philosophy and beyond is a testament to the creative influence of this work on the field of scholarly inquiry. It should also be stated that there appears to be no competing theory at this level of microscopic abstraction. Moreover, Orch OR is experimentally testable, although no tests have been performed yet.

The main issues the critics of Orch OR have identified can be broadly grouped into the following three questions:

1) Experimental evidence, which would link the activity of a single synapse with the dynamics of neural assemblies, is still lacking. Hence, the relevance of quantum processes to cognitive processes remains a claim requiring clear experimental validation.

2) To date, there seem to be no specific and compelling quantum mechanical properties needed to explain psychological and neurological phenomena. The relevance of quantum effects on the brain's structure and function does not necessitate their involvement in explaining consciousness, although this point can be argued because of the "hard problem" (Smith, 2009).

3) Biological structures of relevance to Orch OR, such as microtubules and neurons, are relatively large and function at high temperatures in non-equilibrium systems, hence they do not neatly fit into the class of quantum mechanical systems from the quantum physics point of view. As such, it appears that it is next to impossible for them to remain in states of linear superposition capable of coherently interfering with one another. Thus, at first sight, thermal and environmental decoherence would eliminate any possibility of quantum effects playing a role in brain processes. This point is still an open issue.

Additionally, specific representations of Orch OR to date have side-stepped quantum chemistry, which appears to be an important link between quantum physics and quantum biology. This needs to be revisited. Shielding of quantum effects in neuronal microtubules has been used to explain the lack of decoherence but without validation of this claim by controlled experiments. Finally, the involvement of quantum gravity's role in spacetime geometry as opposed to causing decoherence is a major claim that so far has been outside of the scope of experimental techniques available today. However, recent reports (Donadi et al., 2020) have shown that quantum gravity can only play a role in quantum collapse for large enough systems.

Concerning empirical validation of quantum hypotheses about consciousness, there have been no serious attempts to validate any of these claims until now. However, recent advances in nanotechnology allow the initiation of precise studies into the biophysical workings of sub-cellular structures such as microtubules, actin filaments and mitochondria. With this in mind, the present lack

of evidence supporting quantum brain theories such as Orch OR should not be regarded as proof of their incorrectness. Instead, we should consider this research area as requiring intense scientific investigations using the most up-to-date experimental and computational tools. Note also that most of the enigmatic features of consciousness are still unexplainable using classical neuroscience.

On the other hand, quantum theories seem to provide a means to address these questions and a methodology for new and more fruitful investigations into consciousness. It is particularly significant to mention here that macroscopic quantum phenomena such as superconductivity, superfluidity, magnetism, and laser action exist at relatively high temperatures (although they sometimes require very finely tuned parameters) and that these phenomena cannot be explained using classical physics but necessitate the use of macroscopic quantum coherence within a condensate. By extension, not all phenomena observed in macroscopic systems can be expected to behave classically. Hence, while the first two arguments against quantum consciousness could be viewed as representing a general resistance to the idea of quantum consciousness, the third is an argument that warrants serious concern. Further, macroscopic quantum phenomena such as superconductivity and superfluidity require a high degree of environmental isolation to avoid decoherence.

Consequently, for such phenomena to emerge and exist in the brain, Nature would have to have discovered mechanisms that isolate the active system against environmental decoherence. On the other hand, ferromagnetism requires no such isolation, only a sufficiently low temperature below the Curie temperature value. The subject of decoherence in quantum computation in microtubules has been particularly vigorously discussed in the literature, with strong arguments for and against the discussions.

Specifically, Tegmark (2000) made a strong objection to the Orch OR theory and the notion of quantum brain dynamics in general. He based his arguments on calculations of neural decoherence rates for regular neuron firings and kink-like polarization excitations in microtubules within neurons. Tegmark stated that the degrees of freedom in the human brain must be considered classical and not quantum due to the major gap in the time scales involved. The thermal decoherence time-scales he computed for superpositions of solitons moving along a single microtubule are approximately 10^{-13} - 10^{-11} s; they are much shorter than the relevant time-scale for cognitive processes, which are on the order of 10^{-3} - 10^{-1} s. He then concluded that quantum coherence within the brain is not feasible as far as microtubules' role is concerned. However, Hagan et al. (2002) re-examined Tegmark's calculations and asserted that the assumptions used were based on a false representation of Orch OR.

Moreover, Hagan et al. (2002) discussed various mitigating factors such as the effects of screen thermal fluctuations, for example, the layers of ordered water, ions, and gel states surrounding microtubules in neurons. Recalculating the effects using corrections for the parameter values, Hagan et al. (2002) found new decoherence rates in the range 10^{-5} - 10^{-4} s, which could be viewed as sufficiently close to the relevant dynamical times of biological phenomena and hence seriously reconsidered. However, these arguments were refuted by Rosa and Faber (2004), who found, based on revised decoherence calculations, that the Orch OR the-

ory based on gravitational collapse is incompatible with decoherence. They also stated that the notion of quantum phenomena in the brain is still feasible if decoherence is understood only as a quantum collapse mechanism rather than a quantum wave function collapse due to gravitational self-interactions. Coherence times can be extended by the aforementioned effects such as counterion shielding, ordered water, ionic effects and actin shielding, and intrinsic error correction; nevertheless, decoherence remains a severe issue (Hagan et al., 2002).

As mentioned above, various meticulously conducted experiments clearly showed room-temperature quantum effects in photosynthetic systems (Engel et al., 2007) and conjugated polymer chains (Collini et al., 2010). Moreover, nonthermal radiation at a frequency of 8.085 MHz was observed being emitted from MTs. While this is not necessarily an indication of quantum condensation or coherence, it remains a distinct possibility (Pokorný, 1999). Reimers et al. (2009) and McKemmish et al. (2009) stated in their critical assessment of quantum states in microtubules that this radiation could simply result from a weak condensate being formed but not from any form of coherence required by the Penrose-Hameroff model. These results, however, are based on a linear chain of coupled oscillators in contrast to the cylindrical geometry of MTs, leaving the question still open. Another issue worthy of serious consideration is the wide range of dynamical behavior expected to occur in tubulin dimers when they are polymerized into MTs. This casts doubt on the claim that intact MTs allow two potential conformations of tubulin dimers.

Nonetheless, McKemmish et al. (2009) demonstrated that repeated exchanges between the GTP and GTP-bound forms of tubulin within MTs are not supported by current experimental evidence. While the conformational states are generally identified as tubulin-GTP and tubulin-GDP, the Penrose-Hameroff model does not specify the precise nature of the conformational states envisaged, so alternatives remain a possibility. These alternatives could involve charge transfer mechanisms, electronic transitions to excited states, and exciton-phonon coupling mechanisms. Notably, there is evidence for conformational changes (i.e., tilting to one or the other side) for β -tubulins in intact MTs depending on whether they are bound to motors such as kinesin to MAPs such as tau (Santarella et al., 2004). However, the timescales' consistency involving such interactions and the Orch OR requirements indicates that this remains an open question. These issues are still far from being entirely resolved. Thus, investigations into the quantum nature of microtubules are still badly needed, especially high-quality, precise experimental measurements using physical probes such as lasers and spectroscopic techniques.

In terms of molecular biophysics, based on their ability to propagate signals through the neuron, MTs and actin filaments can be viewed as computationally relevant nanowire networks that operate within neurons (Woolf et al., 2010). Rather than inputs to neurons being limited to causing discrete responses, this viewpoint offers the possibility of local and global neuroplasticity, based on the cytoskeleton computing and storing templates that translate patterns of inputs across widespread synapses into the "behavioral" output of the neuron. This behavioral output of the neuron is not limited to axonal firing and dendritic integration of electrochemically-mediated inputs. Instead, it includes connect-

ing the cell nucleus with the postsynaptic density, initiating transport of receptor molecules, membrane proteins, organelles, and mRNA, regulating neurite motility, restructuring of spines and complex dendrite architecture, the lateral movement of receptor and membrane proteins of neurons, governing the availability of ion channels in the membrane, and more dynamical processes. Potential computational modes for MTs and actin filaments are only now beginning to be understood. Quantum computation in the brain would certainly be beneficial from an evolutionary perspective. It can be argued that biology has had more than 2 billion years to solve the decoherence problem by many parallel experiments. Insights into the biological and biochemical mechanisms of quantum coherent superposition and entanglement would enormously help understand consciousness's enigmatic features. This would also undoubtedly inspire future quantum information technologies.

Finally, ultimate validation or falsification of Orch OR must be achieved by careful experimentation. This is still very demanding since the current "gold standard" in neuroscience is fMRI, whose spatial resolution is on the 1 mm scale while the temporal resolution is on the 1 s scale. These parameter values are several orders of magnitude larger than the 1 nm and 1 ns scale relevant for tubulin's size/time operational dimensions as studied by molecular biophysics, let alone the quantum gravity effects hypothesized by Orch OR to be occurring on the Planck scale of space-time geometry (10^{-35} m; 10^{-44} s). This huge gap between the current experimental capabilities and the predictions made by Orch OR poses the greatest challenge to the acceptance of these tenets.

6. Future outlook

We foresee major progress in bridging the gap between nanoscience and consciousness in nano-neuroscience areas where MT's, actin filaments, ion channels and motor proteins connect between neurophysiology and molecular biology. Studying the nanoscale's neural phenomena will lead to monumental breakthroughs in science and medicine and aid in consciousness studies. Further possibilities involving physically-based quantum mechanisms of consciousness should also be considered. The basic idea is to investigate if other quantum network architectures could also be operating in the brain. First of all, quantum entanglement in such a network could provide at least a partial answer to consciousness's binding problem, allowing for a delocalized quantum state involving many neurons. This requires a thorough understanding of quantum networks. It is worth emphasizing that quantum networks may lead to quantum memories whereby entangled states store information such as visual, auditory or tactile inputs. Moreover, quantum networks could generate communication channels that would transport information and process it, performing complex operations. Recent experiments involving solid-state physics devices based on nuclear spins demonstrated that quantum information storage on the time scales of seconds and beyond is possible, as demonstrated by Tyryshkin et al. (2012) in their research on super-long quantum information storage using phosphorus ions in silicon-based materials.

However, several challenging issues still need to be elucidated. First, given the presence of thermal fluctuations, a magnetic field of sufficient strength would be needed to prepare the spin sys-

tem in a sufficiently pure state. To our knowledge, there are no naturally existing large magnetic fields. Moreover, we know that strong magnetic fields, such as those produced by MRI machines, do not have a detectable effect on the state of consciousness of the person undergoing MRI scans. In terms of quantum communication channels, photon emission and absorption appear to be the best candidate mechanisms for such effects. This can be studied by researchers in the field of biophotons, which is an emerging field despite its long history of false starts and intermittent periods of dormancy. A recent review (Cifra and Pospisil, 2014) summarizes the landscape in this field, pointing to a relatively narrow range of wavelengths playing a role in biophotonics, namely between 350 and 1300 nm. The generation of photons inside living cells is mainly related to the recombination of reactive oxygen species. It is also a major puzzle to elucidate the mechanisms involved in electrical signal amplification and transmission over macroscopic distances along axons and neurons' dendrites. The tenuous connection between quantum biology, consciousness and electromagnetic fields, if adequately supported by precise experimental investigations, could become a nexus for rigorous explorations of how our brain operates beyond the confines of conventional neuroscience.

Abbreviations

ADP, adenosine diphosphate; ATP, adenosine triphosphate; DNA, deoxyribonucleic acid; GDP, guanosine diphosphate; GTP, guanosine triphosphate; MAP, microtubule associated protein; MHz, megahertz; MRI, magnetic resonance imaging; mRNA, messenger ribonucleic acid; MT, microtubule; Orch OR, orchestrated objective reduction.

Author contributions

J.A.T conceived the idea for the topic of this manuscript and wrote the paper.

Ethics approval and consent to participate

This study did not require ethics approval or consent to participate.

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Conflict of Interest

The author declares no conflict of interest.

Appendix

Appendix associated with this article can be found, in the online version, at <https://jin.imrpress.com/EN/10.31083/j.jin.2020.04.393>.

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