

**Consciousness in the Universe:
Neuroscience, Quantum Space-Time Geometry and Orch OR Theory**

Roger Penrose, PhD, OM, FRS¹, and Stuart Hameroff, MD²

¹Emeritus Rouse Ball Professor, Mathematical Institute, Emeritus Fellow, Wadham College,
University of Oxford, Oxford, UK

²Professor, Anesthesiology and Psychology, Director, Center for Consciousness Studies, The
University of Arizona, Tucson, Arizona, USA

Abstract

The nature of consciousness, its occurrence in the brain, and its ultimate place in the universe are unknown. We proposed in the mid 1990's that consciousness depends on biologically 'orchestrated' quantum computations in collections of microtubules within brain neurons, that these quantum computations correlate with and regulate neuronal activity, and that the continuous Schrödinger evolution of each quantum computation terminates in accordance with the specific Diósi–Penrose (DP) scheme of 'objective reduction' of the quantum state (**OR**). This orchestrated **OR** activity (**Orch OR**) is taken to result in a moment of conscious awareness and/or choice. This particular (DP) form of **OR** is taken to be a quantum-gravity process related to the fundamentals of spacetime geometry, so **Orch OR** suggests a connection between brain biomolecular processes and fine-scale structure of the universe. Here we review and update **Orch OR** in light of criticisms and developments in quantum biology, neuroscience, physics and cosmology. We conclude that consciousness plays an intrinsic role in the universe.

KEY WORDS: Consciousness, microtubules, **OR**, **Orch OR**, quantum computation, quantum gravity

1. Introduction: Consciousness, Brain and Evolution

Consciousness implies awareness: subjective experience of internal and external phenomenal worlds. Consciousness is central also to understanding, meaning and volitional choice with the experience of free will. Our views of reality, of the universe, of ourselves depend on consciousness. Consciousness defines our existence.

Three general possibilities regarding the origin and place of consciousness in the universe have been commonly expressed.

(A) *Consciousness is not an independent quality but arose as a natural evolutionary consequence of the biological adaptation of brains and nervous systems.* The most popular scientific view is that consciousness emerged as a property of complex biological computation during the course of evolution. Opinions vary as to when, where and how consciousness appeared, e.g. only recently in humans, or earlier in lower organisms. Consciousness as evolutionary adaptation is commonly assumed to be epiphenomenal (i.e. a secondary effect without independent influence), though it is frequently argued to confer beneficial advantages to conscious species (Dennett, 1991; 1995; Wegner, 2002).

(B) *Consciousness is a quality that has always been in the universe.* Spiritual and religious approaches assume consciousness has been in the universe all along, e.g. as the

'ground of being', 'creator' or component of an omnipresent 'God'. Panpsychists attribute consciousness to all matter. Idealists contend consciousness is all that exists, the material world an illusion (Kant, 1781).

(C) *Precursors of consciousness have always been in the universe; biology evolved a mechanism to convert conscious precursors to actual consciousness.* This is the view implied by Whitehead (1929; 1933) and taken in the Penrose-Hameroff theory of 'orchestrated objective reduction' ('**Orch OR**'). Precursors of consciousness, presumably with proto-experiential qualities, are proposed to exist as the potential ingredients of actual consciousness, the physical basis of these proto-conscious elements not necessarily being part of our current theories of the laws of the universe (Penrose and Hameroff, 1995; Hameroff and Penrose, 1996a; 1996b).

2. Ideas for how consciousness arises from brain action

How does the brain produce consciousness? An enormous amount of detailed knowledge about brain function has accrued; however the mechanism by which the brain produces consciousness remains mysterious (Koch, 2004). The prevalent scientific view is that consciousness somehow emerges from complex computation among simple neurons which each receive and integrate synaptic inputs to a threshold for bit-like firing. The brain as a network of 10^{11} 'integrate-and-fire' neurons computing by bit-like firing and variable-strength chemical synapses is the standard model for computer simulations of brain function, e.g. in the field of artificial intelligence ('AI').

The brain-as-computer view can account for non-conscious cognitive functions including much of our mental processing and control of behavior. Such non-conscious cognitive processes are deemed 'zombie modes', 'auto-pilot', or 'easy problems'. The 'hard problem' (Chalmers, 1996) is the question of how cognitive processes are accompanied or driven by phenomenal conscious experience and subjective feelings, referred to by philosophers as 'qualia'. Other issues also suggest the brain-as-computer view may be incomplete, and that other approaches are required. The conventional brain-as-computer view fails to account for:

The 'hard problem' Distinctions between conscious and non-conscious processes are not addressed; consciousness is assumed to emerge at a critical level (neither specified nor testable) of computational complexity mediating otherwise non-conscious processes.

'Non-computable' thought and understanding, e.g. as shown by Gödel's theorem (Penrose, 1989; 1994).

'Binding and synchrony', the problem of how disparate neuronal activities are bound into unified conscious experience, and how neuronal synchrony, e.g. gamma synchrony EEG (30 to 90 Hz), the best measurable correlate of consciousness does not derive from neuronal firings.

Causal efficacy of consciousness and any semblance of free will. Because measurable brain activity corresponding to a stimulus often occurs *after* we've responded (seemingly consciously) to that stimulus, the brain-as-computer view depicts consciousness as epiphenomenal illusion (Dennett, 1991; 1995; Wegner, 2002).

Cognitive behaviors of single cell organisms. Protozoans like *Paramecium* can swim, find food and mates, learn, remember and have sex, all without synaptic computation (Sherrington, 1957).

In the 1980s Penrose and Hameroff (separately) began to address these issues, each against the grain of mainstream views.

3. Microtubules as Biomolecular Computers

Hameroff had been intrigued by seemingly intelligent, organized activities inside cells, accomplished by protein polymers called microtubules (Hameroff and Watt, 1982; Hameroff, 1987). Major components of the cell's structural cytoskeleton, microtubules also accounted for precise separation of chromosomes in cell division, complex behavior of *Paramecium*, and regulation of synapses within brain neurons (Figure 1). The intelligent function and periodic lattice structure of microtubules suggested they might function as some type of biomolecular computer.

Microtubules are self-assembling polymers of the peanut-shaped protein dimer tubulin, each tubulin dimer (110,000 atomic mass units) being composed of an alpha and beta monomer (Figure 2). Thirteen linear tubulin chains ('protofilaments') align side-to-side to form hollow microtubule cylinders (25 nanometers diameter) with two types of hexagonal lattices. The A-lattice has multiple winding patterns which intersect on protofilaments at specific intervals matching the Fibonacci series found widely in nature and possessing a helical symmetry (Section 9), suggestively sympathetic to large-scale quantum processes.

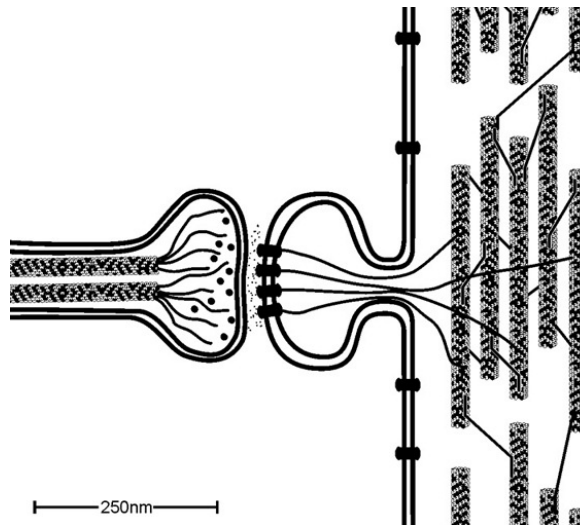


Figure 1. Schematic of portions of two neurons. A terminal axon (left) forms a synapse with a dendritic spine of a second neuron (right). Interiors of both neurons show cytoskeletal structures including microtubules, actin and microtubule-associated proteins (MAPs). Dendritic microtubules are arrayed in mixed polarity local networks, interconnected by MAPs. Synaptic inputs are conveyed to dendritic microtubules by ion flux, actin filaments, second messengers (e.g. CaMKII, see Hameroff et al, 2010) and MAPs.

Along with actin and other cytoskeletal structures, microtubules establish cell shape, direct growth and organize function of cells including brain neurons. Various types of microtubule-associated proteins ('MAPs') bind at specific lattice sites and bridge to other microtubules, defining cell architecture like girders and beams in a building. One such MAP is tau, whose displacement from microtubules results in neurofibrillary tangles and the cognitive dysfunction of

Alzheimer's disease (Brunden et al, 2011). Motor proteins (dynein, kinesin) move rapidly along microtubules, transporting cargo molecules to specific locations.

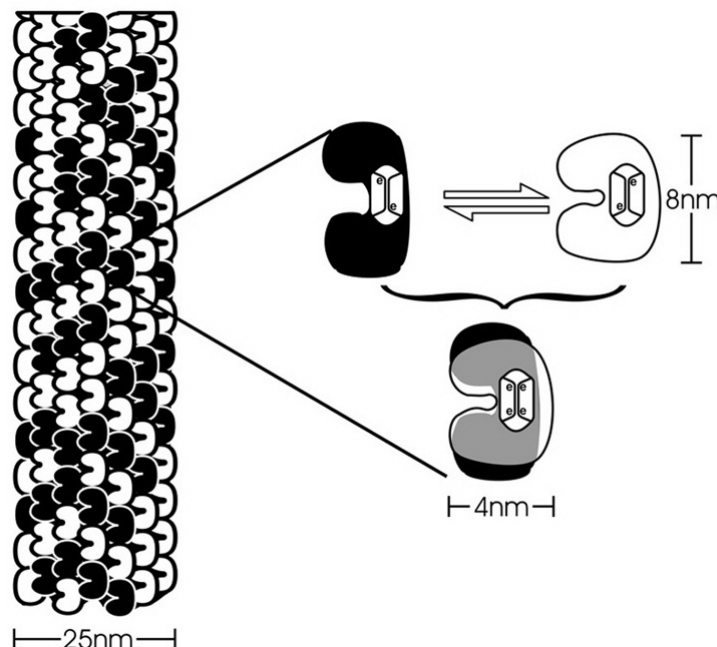


Figure 2. Left: Portion of single microtubule composed of tubulin dimer proteins (black and white) in A-lattice configuration. Right, top: According to pre-**Orch OR** microtubule automata theory (e.g. Hameroff and Watt, 1982; Rasmussen et al, 1990), each tubulin in a microtubule lattice switches between alternate (black and white) 'bit' states, coupled to electron cloud dipole London forces in internal hydrophobic pocket. Right, bottom: According to **Orch OR**, each tubulin can also exist as quantum superposition (quantum bit, or 'qubit') of both states, coupled to superposition of London force dipoles in hydrophobic pocket.

Microtubules also fuse side-by-side in doublets or triplets. Nine such doublets or triplets then align to form barrel-shaped mega-cylinders called cilia, flagella and centrioles, organelles responsible for locomotion, sensation and cell division. Either individually or in these larger arrays, microtubules are responsible for cellular and intra-cellular movements requiring intelligent spatiotemporal organization. Microtubules have a lattice structure comparable to computational systems. Could microtubules process information?

The notion that microtubules process information was suggested in general terms by Sherrington (1957) and Ateama (1973). With physicist colleagues through the 1980s, Hameroff developed models of microtubules as information processing devices, specifically molecular ('cellular') automata, self-organizing computational devices (Figure 3). Cellular automata are computational systems in which fundamental units, or 'cells' in a grid or lattice can each exist in specific states, e.g. 1 or 0, at a given time (Wolfram, 2002). Each cell interacts with its neighbor cells at discrete, synchronized time steps, the state of each cell at any particular time step determined by its state and its neighbor cell states at the previous time step, and rules governing the interactions. In such ways, using simple neighbor interactions in simple lattice grids, cellular automata can perform complex computation and generate complex patterns.

Cells in cellular automata are meant to imply fundamental units. But biological cells are not necessarily simple, as illustrated by the clever *Paramecium*. Molecular automata are cellular

automata in which the fundamental units, bits or cells are states of molecules, much smaller than biological cells. A dynamic, interactive molecular grid or lattice is required.

Microtubules are lattices of tubulin dimers which Hameroff and colleagues modeled as molecular automata. Discrete states of tubulin were suggested to act as bits, switching between states, and interacting (via dipole-dipole coupling) with neighbor tubulin bit states in 'molecular automata' computation (Hameroff and Watt, 1982; Rasmussen et al., 1990; Tuszynski et al., 1995). The mechanism for bit-like switching at the level of each tubulin was proposed to depend on the van der Waals–London force in non-polar, water-excluding regions ('hydrophobic pockets') within each tubulin.

Proteins are largely heterogeneous arrays of amino acid residues, including both water-soluble polar and water-insoluble non-polar groups, the latter including phenylalanine and tryptophan with electron resonance clouds (e.g. phenyl and indole rings). Such non-polar groups coalesce during protein folding to form homogeneous water-excluding 'hydrophobic' pockets within which instantaneous dipole couplings between nearby electron clouds operate. These are London forces which are extremely weak but numerous and able to act collectively in hydrophobic regions to influence and determine protein state (Voet and Voet, 1995).

London forces in hydrophobic pockets of various neuronal proteins are the mechanisms by which anesthetic gases selectively erase consciousness (Franks and Lieb, 1984). Anesthetics bind by their own London force attractions with electron clouds of the hydrophobic pocket, presumably impairing normally-occurring London forces governing protein switching required for consciousness (Hameroff, 2006).

In Figure 2, and as previously used in **Orch OR**, London forces are illustrated in cartoon fashion. A single hydrophobic pocket is depicted in tubulin, with portions of two electron resonance rings in the pocket. Single electrons in each ring repel each other, as their electron cloud net dipole flips (London force oscillation). London forces in hydrophobic pockets were used as the switching mechanism to distinguish discrete states for each tubulin in microtubule automata. In recent years tubulin hydrophobic regions and switching in the **Orch OR** proposal that we describe below have been clarified and updated (see Section 8).

To synchronize discrete time steps in microtubule automata, tubulins in microtubules were assumed to oscillate synchronously in a manner proposed by Fröhlich for biological coherence. Biophysicist Herbert Fröhlich (1968; 1970; 1975) had suggested that biomolecular dipoles constrained in a common geometry and voltage field would oscillate coherently, coupling, or condensing to a common vibrational mode. He proposed that biomolecular dipole lattices could convert ambient energy to coherent, synchronized dipole excitations, e.g. in the gigahertz (10^9 s^{-1}) frequency range. Fröhlich coherence or condensation can be either quantum coherence (e.g. Bose-Einstein condensation) or classical synchrony (Reimers et al., 2009).

In recent years coherent excitations have been found in living cells emanating from microtubules at 8 megahertz (Pokorny et al., 2001; 2004). Bandyopadhyay (2011) has found a series of coherence resonance peaks in single microtubules ranging from 12 kilohertz to 8 megahertz.

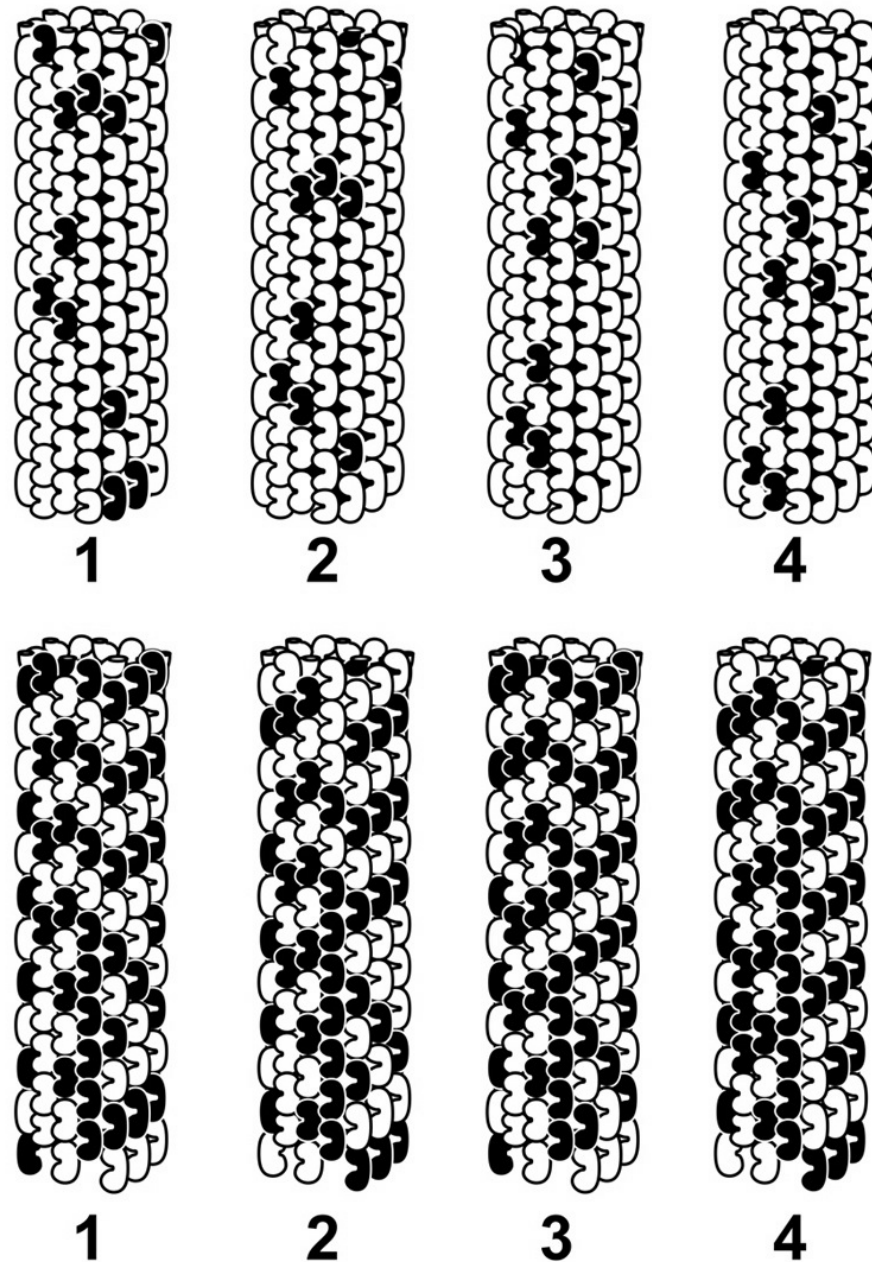


Figure 3. Microtubule automata (Rasmussen et al, 1990). Top: 4 time steps (e.g. at 8 megahertz, Pokorny et al, 2001) showing propagation of information states and patterns ('gliders' in cellular automata parlance). Bottom: At different dipole coupling parameter, bi-directional pattern movement and computation occur.

Rasmussen et al (1990) applied Fröhlich synchrony (in classical mode) as a clocking mechanism for computational time steps in simulated microtubule automata. Based on dipole couplings between neighboring tubulins in the microtubule lattice geometry, they found traveling gliders, complex patterns, computation and learning. Microtubule automata within brain neurons could potentially provide another level of information processing in the brain.

Approximately 10^8 tubulins in each neuron switching and oscillating in the range of 10^7 per second (e.g. Pokorny 8 MHz) gives an information capacity at the microtubule level of 10^{15} operations per second *per neuron*. This predicted capacity challenged and annoyed AI whose

estimates for information processing at the level of neurons and synapses were virtually the same as this single-cell value, but for the entire brain (10^{11} neurons, 10^3 synapses per neuron, 10^2 transmissions per synapse per second = 10^{16} operations per second). Total brain capacity when taken at the microtubule level (in 10^{11} neurons) would potentially be 10^{26} operations per second, pushing the goalpost for AI brain equivalence farther into the future, and down into the quantum regime.

High capacity microtubule-based computing inside brain neurons could account for organization of synaptic regulation, learning and memory, and perhaps act as the substrate for consciousness. But increased brain information capacity *per se* didn't address most unanswered questions about consciousness (Section 2). Something was missing.

4. Objective Reduction (OR)

In 1989 Penrose published *The Emperor's New Mind*, which was followed in 1994 by *Shadows of the Mind*. Critical of AI, both books argued, by appealing to Gödel's theorem and other considerations, that certain aspects of human consciousness, such as *understanding*, must be beyond the scope of any computational system, i.e. 'non-computable'. Non-computability is a perfectly well-defined mathematical concept, but it had not previously been considered as a serious possibility for the result of physical actions. The non-computable ingredient required for human consciousness and understanding, Penrose suggested, would have to lie in an area where our current physical theories are fundamentally incomplete, though of important relevance to the scales that are pertinent to the operation of our brains. The only serious possibility was the incompleteness of quantum theory—an incompleteness that both Einstein and Schrödinger had recognized, despite quantum theory having frequently been argued to represent the pinnacle of 20th century scientific achievement. This incompleteness is the unresolved issue referred to as the '*measurement problem*', which we consider in more detail below, in Section 5. One way to resolve it would be to provide an extension of the standard framework of quantum mechanics by introducing an objective form of quantum state reduction—termed 'OR' (objective reduction), an idea which we also describe more fully below, in Section 6.

In Penrose (1989), the tentatively suggested OR proposal would have its onset determined by a condition referred to there as 'the one-graviton' criterion. However, in Penrose (1995), a much better-founded criterion was used, now sometimes referred to as the *Diósi–Penrose proposal* (henceforth 'DP'; see Diósi 1987, 1989, Penrose 1993, 1996, 2000, 2009). This is an objective physical threshold, providing a plausible lifetime for quantum-superposed states. Other such **OR** proposals had also been put forward, from time to time (e.g. Kibble 1981, Pearle 1989, Pearle and Squires 1994, Ghirardi et al., 1986, 1990; see Ghirardi 2011, *this volume*) as solutions to the measurement problem, but had not originally been suggested as having anything to do with the consciousness issue. The Diósi–Penrose proposal is sometimes referred to as a 'quantum-gravity' scheme, but it is not part of the normal ideas used in quantum gravity, as will be explained below (Section 6). Moreover, the proposed connection between consciousness and quantum measurement is almost opposite, in the **Orch OR** scheme, to the kind of idea that had frequently been put forward in the early days of quantum mechanics (see, for example, Wigner 1961) which suggests that a 'quantum measurement' is something that occurs only as a result of the conscious intervention of an observer. This issue, also, will be discussed below (Section 5).

5. The Nature of Quantum Mechanics and its Fundamental Problem

The term 'quantum' refers to a discrete element of energy in a system, such as the energy E of a particle, or of some other subsystem, this energy being related to a fundamental frequency ν of its oscillation, according to Max Planck's famous formula (where h is Planck's constant):

$$E = h \nu.$$

This deep relation between discrete energy levels and frequencies of oscillation underlies the wave/particle duality inherent in quantum phenomena. Neither the word “particle” nor the word “wave” adequately conveys the true nature of a basic quantum entity, but both provide useful partial pictures.

The laws governing these submicroscopic quantum entities differ from those governing our everyday classical world. For example, quantum particles can exist in two or more states or locations simultaneously, where such a multiple coexisting superposition of alternatives (each alternative being weighted by a *complex* number) would be described mathematically by a quantum *wavefunction*. We don't see superpositions in the consciously perceived world; we see objects and particles as material, classical things in specific locations and states.

Another quantum property is 'non-local entanglement,' in which separated components of a system become unified, the entire collection of components being governed by one common quantum wavefunction. The parts remain somehow connected, even when spatially separated by significant distances (e.g. over 10 kilometres, Tittel et al., 1998). Quantum superpositions of bit states (quantum bits, or qubits) can be interconnected with one another through entanglement in quantum computers. However, quantum entanglements cannot, by themselves, be used to send a message from one part of an entangled system to another; yet entanglement can be used in conjunction with classical signaling to achieve strange effects—such as the strange phenomenon referred to as *quantum teleportation*—that classical signalling cannot achieve by itself (e.g. Bennett and Wiesner, 1992; Bennett et al., 1993; Bouwmeester et al., 1997; Macikic et al., 2002).

The issue of why we don't directly perceive quantum superpositions is a manifestation of the *measurement problem* referred to in Section 4. Put more precisely, the measurement problem is the conflict between the two fundamental procedures of quantum mechanics. One of these procedures, referred to as *unitary evolution*, denoted here by U , is the continuous deterministic evolution of the quantum state (i.e. of the wavefunction of the entire system) according to the fundamental *Schrödinger equation*. The other is the procedure that is adopted whenever a measurement of the system—or *observation*—is deemed to have taken place, where the quantum state is discontinuously and probabilistically replaced by another quantum state (referred to, technically, as an *eigenstate* of a mathematical operator that is taken to describe the measurement). This discontinuous jumping of the state is referred to as the *reduction* of the state (or the 'collapse of the wavefunction'), and will be denoted here by the letter R . The conflict that is termed *the measurement problem* (or perhaps more accurately as the *measurement paradox*) arises when we consider the measuring apparatus itself as a quantum entity, which is part of the entire quantum system consisting of the original system under observation together with this measuring apparatus. The apparatus is, after all, constructed out of the same type of quantum ingredients (electrons, photons, protons, neutrons etc.—or quarks and gluons etc.) as is the system under observation, so it ought to be subject also to the same quantum laws, these being described in terms of the continuous and deterministic U . How, then, can the discontinuous and probabilistic R come about as a result of the interaction (measurement) between two parts of the quantum system? This is the measurement problem (or paradox).

There are many ways that quantum physicists have attempted to come to terms with this conflict (see, for example, Bell 1966, Bohm 1951, Rae 1994, Polkinghorne 2002, Penrose, 2004). In the early 20th century, the Danish physicist Niels Bohr, together with Werner Heisenberg, proposed the pragmatic 'Copenhagen interpretation', according to which the wavefunction of a quantum system, evolving according to **U**, is not assigned any actual physical 'reality', but is taken as basically providing the needed 'book-keeping' so that eventually probability values can be assigned to the various possible outcomes of a quantum measurement. The measuring device itself is explicitly taken to behave *classically* and no account is taken of the fact that the device is ultimately built from quantum-level constituents. The probabilities are calculated, once the nature of the measuring device is known, from the state that the wavefunction has **U**-evolved to at the time of the measurement. The discontinuous "jump" that the wavefunction makes upon measurement, according to **R**, is attributed to the change in 'knowledge' that the result of the measurement has on the observer. Since the wavefunction is not assigned physical reality, but is considered to refer merely to the observer's knowledge of the quantum system, the jumping is considered simply to reflect the jump in the observer's knowledge state, rather than in the quantum system under consideration.

Many physicists remain unhappy with such a point of view, however, and regard it largely as a 'stop-gap', in order that progress can be made in applying the quantum formalism, without this progress being held up by a lack of a serious quantum ontology, which might provide a more complete picture of what is actually going on. One may ask, in particular, what it is about a measuring device that allows one to ignore the fact that it is itself made from quantum constituents and is permitted to be treated entirely classically. A good many proponents of the Copenhagen standpoint would take the view that while the physical measuring apparatus ought actually to be treated as a quantum system, and therefore part of an over-riding wavefunction evolving according to **U**, it would be the *conscious observer*, examining the readings on that device, who actually reduces the state, according to **R**, thereby assigning a physical reality to the particular observed alternative resulting from the measurement. Accordingly, before the intervention of the observer's consciousness, the various alternatives of the result of the measurement *including* the different states of the measuring apparatus would, in effect, still coexist in superposition, in accordance with what would be the usual evolution according to **U**. In this way, the Copenhagen viewpoint puts consciousness outside science, and does not seriously address the nature and physical role of superposition itself nor the question of how large quantum superpositions like Schrödinger's superposed live and dead cat (see below) might *actually* become one thing or another.

A more extreme variant of this approach is the 'multiple worlds hypothesis' of Everett (1957) in which each possibility in a superposition evolves to form its own universe, resulting in an infinite multitude of coexisting 'parallel' worlds. The stream of consciousness of the observer is supposed somehow to 'split', so that there is one in each of the worlds—at least in those worlds for which the observer remains alive and conscious. Each instance of the observer's consciousness experiences a separate independent world, and is not directly aware of any of the other worlds.

A more 'down-to-earth' viewpoint is that of *environmental decoherence*, in which interaction of a superposition with its environment 'erodes' quantum states, so that instead of a single wavefunction being used to describe the state, a more complicated entity is used, referred to as a *density matrix*. However decoherence does not provide a consistent ontology for the *reality* of the world, in relation to the density matrix (see, for example, Penrose 2004, Sections 29.3-6), and provides merely a pragmatic procedure. Moreover, it does not address the issue of how **R** might arise in isolated systems, nor the nature of isolation, in which an external 'environment' would not

be involved, nor does it tell us which part of a system is to be regarded as the 'environment' part, and it provides no limit to the size of that part which can remain subject to quantum superposition.

Still other approaches include various types of objective reduction (**OR**) in which a specific objective threshold is proposed to cause quantum state reduction (e.g. Kibble 1981; Pearle 1989; Ghirardi et al., 1986; Percival, 1994; Ghirardi, 2011). The specific **OR** scheme that is used in **Orch OR** will be described in Section 6.

The quantum pioneer Erwin Schrödinger took pains to point out the difficulties that confront the **U**-evolution of a quantum system with his still-famous thought experiment called 'Schrödinger's cat'. Here, the fate of a cat in a box is determined by magnifying a quantum event (say the decay of a radioactive atom, within a specific time period that would provide a 50% probability of decay) to a macroscopic action which would kill the cat, so that according to Schrödinger's own **U**-evolution the cat would be in a quantum superposition of being both dead and alive at the same time. If this **U**-evolution is maintained until the box is opened and the cat observed, then it would have to be the conscious human observing the cat that results in the cat becoming either dead or alive (unless, of course, the cat's own consciousness could be considered to have already served this purpose). Schrödinger intended to illustrate the absurdity of the direct applicability of the rules of quantum mechanics (including his own **U**-evolution) when applied at the level of a cat. Like Einstein, he regarded quantum mechanics as an incomplete theory, and his 'cat' provided an excellent example for emphasizing this incompleteness. There is a need for something to be done about quantum mechanics, irrespective of the issue of its relevance to consciousness.

6. The Orch OR Scheme

Orch OR depends, indeed, upon a particular **OR** extension of current quantum mechanics, taking the bridge between quantum- and classical-level physics as a 'quantum-gravitational' phenomenon. This is in contrast with the various conventional viewpoints (see Section 5), whereby this bridge is claimed to result, somehow, from 'environmental decoherence', or from 'observation by a conscious observer', or from a 'choice between alternative worlds', or some other interpretation of how the classical world of one actual alternative may be taken to arise out of fundamentally quantum-superposed ingredients.

It must also be made clear that the **Orch OR** scheme involves a different interpretation of the term 'quantum gravity' from what is usual. Current ideas of quantum gravity (see, for example Smolin, 2002) normally refer, instead, to some sort of physical scheme that is to be formulated within the bounds of standard quantum field theory—although no particular such theory, among the multitude that has so far been put forward, has gained anything approaching universal acceptance, nor has any of them found a fully consistent, satisfactory formulation. '**OR**' here refers to the alternative viewpoint that standard quantum (field) theory is not the final answer, and that the reduction **R** of the quantum state ('collapse of the wavefunction') that is adopted in standard quantum mechanics is an *actual* physical phenomenon which is not part of the conventional unitary formalism **U** of quantum theory (or quantum field theory) and does not arise as some kind of convenience or effective consequence of environmental decoherence, etc., as the conventional **U** formalism would seem to demand. Instead, **OR** is taken to be one of the consequences of melding together the principles of Einstein's general relativity with those of the conventional unitary quantum formalism **U**, and this demands a departure from the strict rules of **U**. According to this **OR** viewpoint, any quantum measurement—whereby the quantum-superposed alternatives produced in accordance with the **U** formalism becomes reduced to a

single actual occurrence—is *real* objective physical phenomenon, and it is taken to result from the mass displacement between the alternatives being sufficient, in gravitational terms, for the superposition to become unstable.

In the DP (Diósi–Penrose) scheme for **OR**, the superposition reduces to one of the alternatives in a time scale τ that can be estimated (for a superposition of two states each of which can be taken to be stationary on its own) according to the formula

$$\tau \approx \hbar/E_G.$$

Here $\hbar (=h/2\pi)$ is Dirac's form of Planck's constant h and E_G is the *gravitational self-energy* of the *difference* between the two mass distributions of the superposition. (For a superposition for which each mass distribution is a rigid translation of the other, E_G is the energy it would cost to displace one component of the superposition in the gravitational field of the other, in moving it from coincidence to the quantum-displaced location; see Disóí 1989, Penrose 1993, 2000, 2009).

According to **Orch OR**, the (objective) reduction is not the entirely random process of standard theory, but acts according to some non-computational new physics (see Penrose 1989, 1994). The idea is that consciousness is associated with this (gravitational) **OR** process, but occurs significantly only when the alternatives are part of some highly organized structure, so that such occurrences of **OR** occur in an extremely *orchestrated* form. Only then does a recognizably conscious event take place. On the other hand, we may consider that any individual occurrence of **OR** would be an element of *proto*-consciousness.

The **OR** process is considered to occur when quantum superpositions between slightly differing space-times take place, differing from one another by an integrated space-time measure which compares with the fundamental and extremely tiny Planck (4-volume) scale of space-time geometry. Since this is a 4-volume Planck measure, involving both time and space, we find that the time measure would be particularly tiny when the space-difference measure is relatively large (as with Schrödinger's cat), but for extremely tiny space-difference measures, the time measure might be fairly long, such as some significant fraction of a second. We shall be seeing this in more detail shortly, together with its particular relevance to microtubules. In any case, we recognize that the elements of proto-consciousness would be intimately tied in with the most primitive Planck-level ingredients of space-time geometry, these presumed 'ingredients' being taken to be at the absurdly tiny level of 10^{-35} m and 10^{-43} s, a distance and a time some 20 orders of magnitude smaller than those of normal particle-physics scales and their most rapid processes. These scales refer only to the normally extremely tiny differences in space-time geometry between different states in superposition, and **OR** is deemed to take place when such space-time differences reach the Planck level. Owing to the extreme weakness of gravitational forces as compared with those of the chemical and electric

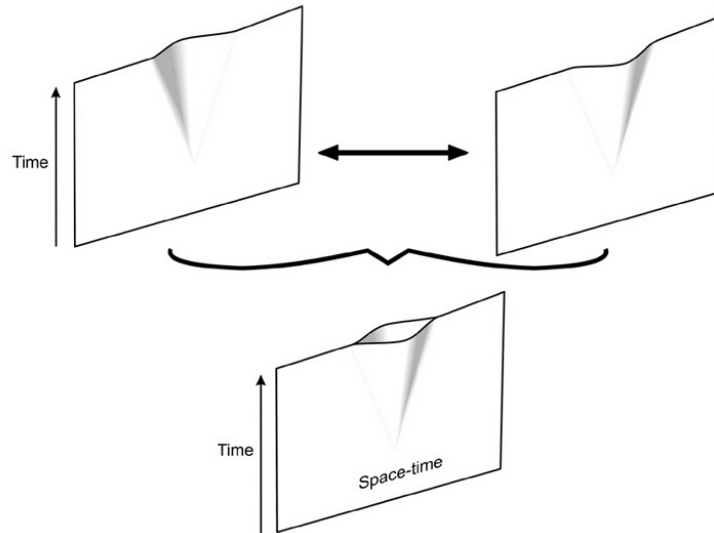


Figure 4. From Penrose, 1994 (P. 338). With four spatiotemporal dimensions condensed to a 2-dimensional spacetime sheet, mass location may be represented as a particular curvature of that sheet, according to general relativity. Top: Two different mass locations as alternative spacetime curvatures. Bottom: a bifurcating spacetime is depicted as the union ("glued together version") of the two alternative spacetime histories that are depicted at the top of the Figure. Hence a quantum superposition of simultaneous alternative locations may be seen as a separation in fundamental spacetime geometry.

forces of biology, the energy E_G is liable to be far smaller than any energy that arises directly from biological processes. However, E_G is not to be thought of as being in direct competition with any of the usual biological energies, as it plays a completely different role, supplying a needed energy uncertainty that then allows a choice to be made between the separated space-time geometries. It is the key ingredient of the computation of the reduction time τ . Nevertheless, the extreme weakness of gravity tells us there must be a considerable amount of material involved in the coherent mass displacement between superposed structures in order that τ can be small enough to be playing its necessary role in the relevant **OR** processes in the brain. These superposed structures should also process information and regulate neuronal physiology. According to **Orch OR**, *microtubules* are central to these structures, and some form of biological quantum computation in microtubules (most probably primarily in the more symmetrical A-lattice microtubules) would have to have evolved to provide a subtle yet direct connection to Planck-scale geometry, leading eventually to discrete moments of actual conscious experience.

The degree of separation between the space-time sheets is mathematically described in terms of a *symplectic measure* on the space of 4-dimensional metrics (cf. Penrose, 1993). The separation is, as already noted above, a space-time separation, not just a spatial one. Thus the *time* of separation contributes as well as the spatial displacement. Roughly speaking, it is the product of the temporal separation **T** with the spatial separation **S** that measures the overall degree of separation, and **OR** takes place when this overall separation reaches a critical amount. This critical amount would be of the order of unity, in *absolute units*, for which the Planck-Dirac constant \hbar , the gravitational constant G , and the velocity of light c , all take the value unity, cf. Penrose, 1994 - pp. 337-339. For small **S**, the lifetime $\tau \approx T$ of the superposed state will be large; on the other hand, if **S** is large, then τ will be small.

To estimate **S**, we compute (in the Newtonian limit of weak gravitational fields) the gravitational self-energy E_G of the difference between the mass distributions of the two superposed states.

(That is, one mass distribution counts positively and the other, negatively; see Penrose, 1993; 1995.) The quantity S is then given by:

$$S \approx E_G$$

and $T \approx \tau$, whence

$$\tau \approx \hbar/E_G, \text{ i.e. } E_G \approx \hbar/\tau.$$

Thus, the DP expectation is that **OR** occurs with the resolving out of one particular space-time geometry from the previous superposition when, on the average, $\tau \approx \hbar/E_G$. Moreover, according to **Orch OR**, this is accompanied by an element of *proto-consciousness*.

Environmental decoherence need play no role in state reduction, according to this scheme. The proposal is that state reduction simply takes place spontaneously, according to this criterion. On the other hand, in many actual physical situations, there would be much material from the environment that would be entangled with the quantum-superposed state, and it could well be that the major mass displacement—and therefore the major contribution to E_G —would occur in the environment rather than in the system under consideration. Since the environment will be quantum-entangled with the system, the state-reduction in the environment will effect a simultaneous reduction in the system. This could shorten the time for the state reduction **R** to take place very considerably. It would also introduce an uncontrollable random element into the result of the reduction, so that any non-random (albeit non-computable, according to **Orch OR**) element influencing the particular choice of state that is actually resolved out from the superposition would be completely masked by this randomness. In these circumstances the **OR**-process would be indistinguishable from the **R**-process of conventional quantum mechanics. If the suggested non-computable effects of this **OR** proposal are to be laid bare, if E_G is to be able to evolve and be orchestrated for conscious moments, we indeed need significant isolation from the environment.

As yet, no experiment has been refined enough to determine whether this (DP) **OR** proposal is actually respected by Nature, but the experimental testing of the scheme is fairly close to the borderline of what can be achieved with present-day technology (see, for example, Marshall et al. 2003). One ought to begin to see the effects of this **OR** scheme if a small object, such as a 10-micron cube of crystalline material could be held in a superposition of two locations, differing by about the diameter of an atomic nucleus, for some seconds, or perhaps minutes.

A point of importance, in such proposed experiments, is that in order to calculate E_G it may not be enough to base the calculation on an average density of the material in the superposition, since the mass will be concentrated in the atomic nuclei, and for a displacement of the order of the diameter of a nucleus, this inhomogeneity in the density of the material can be crucial, and can provide a much larger value for E_G than would be obtained if the material is assumed to be homogeneous. The Schrödinger equation (more correctly, in the zero-temperature approximation, the Schrödinger–Newton equation, see Penrose 2000; Moroz et al. 1998) for the static unsuperposed material would have to be solved, at least approximately, in order to derive the expectation value of the mass distribution, where there would be some quantum spread in the locations of the particles constituting the nuclei.

For **Orch OR** to be operative in the brain, we would need coherent superpositions of sufficient amounts of material, undisturbed by environmental entanglement, where this reduces in

accordance with the above **OR** scheme in a rough time scale of the general order of time for a conscious experience to take place. For an ordinary type of experience, this might be say about $\tau = 10^{-1}$ s which concurs with neural correlates of consciousness, such as particular frequencies of electroencephalography (EEG).

Penrose (1989; 1994) suggested that processes of the general nature of *quantum computations* were occurring in the brain, terminated by **OR**. In quantum computers (Benioff 1982, Deutsch 1985, Feynman 1986), information is represented not just as bits of either 1 or 0, but also as quantum superposition of *both 1 and 0* together (quantum bits or qubits) where, moreover, large-scale entanglements between qubits would also be involved. These qubits interact and compute following the Schrödinger equation, potentially enabling complex and highly efficient parallel processing. As envisioned in technological quantum computers, at some point a measurement is made causing quantum state reduction (with some randomness introduced). The qubits reduce, or collapse to classical bits and definite states as the output.

The proposal that some form of quantum computing could be acting in the brain, this proceeding by the Schrödinger equation without decoherence until some threshold for self-collapse due to a form of non-computable **OR** could be reached, was made in Penrose 1989. However, no plausible biological candidate for quantum computing in the brain had been available to him, as he was then unfamiliar with microtubules.

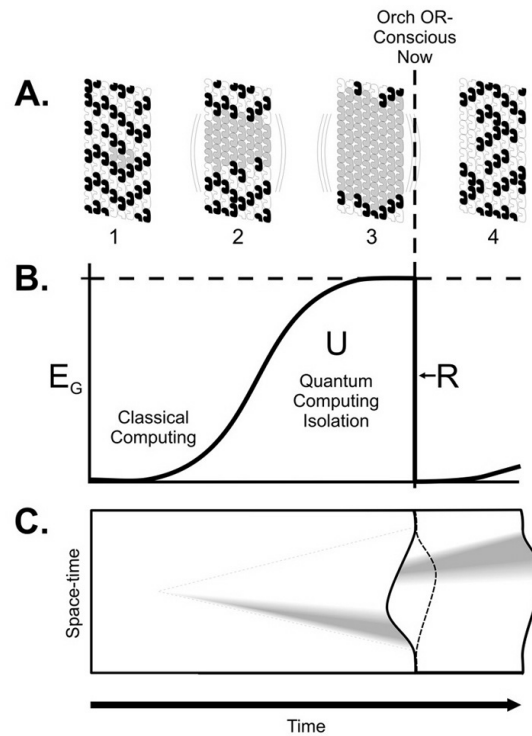


Figure 5. Three descriptions of an **Orch OR** conscious event by $E_G = \hbar/\tau$. A. Microtubule automata. Quantum (gray) tubulins evolve to meet threshold after Step 3, a moment of consciousness occurs and tubulin states are selected. For actual event (e.g. 25 msec), billions of tubulins are required; a small number is used here for illustration. B. Schematic showing U-like evolution until threshold. C. Space-time sheet with superposition separation reaches threshold and selects one reality/spacetime curvature.

7. Penrose-Hameroff Orchestrated Objective Reduction ('Orch OR')

Penrose and Hameroff teamed up in the early 1990s. Fortunately, by then, the DP form of OR mechanism was at hand to be applied to the microtubule-automata models for consciousness as developed by Hameroff. A number of questions were addressed.

How does $\tau \approx \hbar/E_G$ relate to consciousness? **Orch OR** considers consciousness as a sequence of discrete **OR** events in concert with neuronal-level activities. In $\tau \approx \hbar/E_G$, τ is taken to be the time for evolution of the pre-conscious quantum wavefunction between **OR** events, i.e. the time interval between conscious moments, during which quantum superpositions of microtubule states evolve according to the continuous Schrödinger equation before reaching (on the average) the $\tau \approx \hbar/E_G$ **OR** threshold in time τ , when quantum state reduction and a moment of conscious awareness occurs (Figure 5).

The best known temporal correlate for consciousness is gamma synchrony EEG, 30 to 90 Hz, often referred to as coherent 40 Hz. One possible viewpoint might be to take this oscillation to represent a succession of 40 or so conscious moments per second ($\tau=25$ milliseconds). This would be reasonably consistent with neuroscience (gamma synchrony), with certain ideas expressed in philosophy (e.g. Whitehead 'occasions of experience'), and perhaps even with ancient Buddhist texts which portray consciousness as 'momentary collections of mental phenomena' or as 'distinct, unconnected and impermanent moments which perish as soon as they arise.' (Some Buddhist writings quantify the frequency of conscious moments. For example the Sarvaastivaadins, according to von Rospatt 1995, described 6,480,000 'moments' in 24 hours—an average of one 'moment' per 13.3 msec, ~ 75 Hz—and some Chinese Buddhism as one "thought" per 20 msec, i.e. 50 Hz.) These accounts, even including variations in frequency, could be considered to be consistent with **Orch OR** events in the gamma synchrony range. Accordingly, on this view, gamma synchrony, Buddhist 'moments of experience', Whitehead 'occasions of experience', and our proposed **Orch OR** events might be viewed as corresponding tolerably well with one another.

Putting $\tau=25$ msec in $E_G \approx \hbar/\tau$, we may ask what is E_G in terms of superpositioned microtubule tubulins? E_G may be derived from details about the superposition separation of mass distribution. Three types of mass separation were considered in Hameroff–Penrose 1996a for peanut-shaped tubulin proteins of 110,000 atomic mass units: separation at the level of (1) protein spheres, e.g. by 10 percent volume, (2) atomic nuclei (e.g. carbon, ~ 2.5 Fermi length), (3) nucleons (protons and neutrons). The most plausible calculated effect might be separation at the level of atomic nuclei, giving E_G as superposition of 2×10^{10} tubulins reaching **OR** threshold at 25 milliseconds.

Brain neurons each contain roughly 10^8 tubulins, so only a few hundred neurons would be required for a 25msec, gamma synchrony **OR** event if 100 percent of tubulins in those neurons were in superposition and avoided decoherence. It seems more likely that a fraction of tubulins per neuron are in superposition. Global macroscopic states such as superconductivity ensue from quantum coherence among only very small fractions of components. If 1 percent of tubulins within a given set of neurons were coherent for 25msec, then 20,000 such neurons would be required to elicit **OR**. In human brain, cognition and consciousness are, at any one time, thought to involve tens of thousands of neurons. Hebb's (1949) 'cell assemblies', Eccles's (1992) 'modules', and Crick and Koch's (1990) 'coherent sets of neurons' are each estimated to contain some 10,000 to 100,000 neurons which may be widely distributed throughout the brain (Scott, 1995).

Adopting $\tau \approx \hbar/E_G$, we find that, with this point of view with regard to **Orch-OR**, a spectrum of possible types of conscious event might be able to occur, including those at higher frequency and intensity. It may be noted that Tibetan monk meditators have been found to have 80 Hz gamma synchrony, and perhaps more intense experience (Lutz et al. 2004). Thus, according to the viewpoint proposed above, where we interpret this frequency to be associated with a succession of **Orch-OR** moments, then $E_G \approx \hbar/\tau$ would appear to require that there is twice as much brain involvement required for 80 Hz than for consciousness occurring at 40 Hz (or $\sqrt{2}$ times as much if the displacement is entirely coherent, since then the mass enters quadratically in E_G). Even higher (frequency), expanded awareness states of consciousness might be expected, with more neuronal brain involvement.

On the other hand, we might take an alternative viewpoint with regard to the probable frequency of **Orch-OR** actions, and to the resulting frequency of elements of conscious experience. There is the possibility that the discernable moments of consciousness are events that normally occur at a much slower pace than is suggested by the considerations above, and that they happen only at rough intervals of the order of, say, one half a second or so, i.e. ~ 500 msec, rather than ~ 25 msec. One might indeed think of conscious influences as perhaps being rather slow, in contrast with the great deal of vastly faster unconscious computing that might be some form of quantum computing, but without **OR**. At the present stage of uncertainty about such matters it is perhaps best not to be dogmatic about how the ideas of **Orch OR** are to be applied. In any case, the numerical assignments provided above must be considered to be extremely rough, and at the moment we are far from being in a position to be definitive about the precise way in which the **Orch-OR** is to operate. Alternative possibilities will need to be considered with an open mind.

How do microtubule quantum computation avoid decoherence? Technological quantum computers using e.g. ion traps as qubits are plagued by decoherence, disruption of delicate quantum states by thermal vibration, and require extremely cold temperatures and vacuum to operate. Decoherence must be avoided during the evolution toward time $\tau (\approx \hbar/E_G)$, so that the non-random (non-computable) aspects of **OR** can be playing their roles. How does quantum computing avoid decoherence in the 'warm, wet and noisy' brain?

It was suggested (Hameroff and Penrose, 1996a) that microtubule quantum states avoid decoherence by being pumped, laser-like, by Fröhlich resonance, and shielded by ordered water, C-termini Debye layers, actin gel and strong mitochondrial electric fields. Moreover quantum states in **Orch OR** are proposed to originate in hydrophobic pockets in tubulin interiors, isolated from polar interactions, and involve superposition of only atomic nuclei separation. Moreover, geometrical resonances in microtubules, e.g. following helical pathways of Fibonacci geometry are suggested to enable topological quantum computing and error correction, avoiding decoherence perhaps effectively indefinitely (Hameroff et al 2002) as in a superconductor.

The analogy with *high-temperature* superconductors may indeed be appropriate, in fact. As yet, there is no fully accepted theory of how such superconductors operate, avoiding loss of quantum coherence from the usual processes of environmental decoherence. Yet there are materials which support superconductivity at temperatures roughly halfway between room temperature and absolute zero (He et al., 2010). This is still a long way from body temperature, of course, but there is now some experimental evidence (Bandyopadhyay 2011) that is indicative of something resembling superconductivity (referred to as 'ballistic conductance'), that occurs in living A-lattice microtubules at body temperature. This will be discussed below.

Physicist Max Tegmark (2000) published a critique of **Orch OR** based on his calculated decoherence times for microtubules of 10^{-13} seconds at biological temperature, far too brief for physiological effects. However Tegmark didn't include **Orch OR** stipulations and in essence created, and then refuted his own quantum microtubule model. He assumed superpositions of solitons separated from themselves by a distance of 24 nanometers along the length of the microtubule. As previously described, superposition separation in **Orch OR** is at the Fermi length level of atomic nuclei, i.e. 7 orders of magnitude smaller than Tegmark's separation value, thus underestimating decoherence time by 7 orders of magnitude, i.e. from 10^{-13} secs to microseconds at 10^{-6} seconds. Hagan et al (2001) used Tegmark's same formula and recalculated microtubule decoherence times using **Orch OR** stipulations, finding 10^{-4} to 10^{-3} seconds, or longer due to topological quantum effects. It seemed likely biology had evolved optimal information processing systems which can utilize quantum computing, but there was no real evidence either way.

Beginning in 2003, published research began to demonstrate quantum coherence in warm biological systems. Ouyang and Awschalom (2003) showed that quantum spin transfer through phenyl rings (the same as those in protein hydrophobic pockets) is enhanced at increasingly warm temperatures. Other studies showed that quantum coherence occurred at ambient temperatures in proteins involved in photosynthesis, that plants routinely use quantum coherence to produce chemical energy and food (Engel et al, 2007). Further research has demonstrated warm quantum effects in bird brain navigation (Gauger et al, 2011), ion channels (Bernroider and Roy, 2005), sense of smell (Turin, 1996), DNA (Rieper et al., 2011), protein folding (Luo and Lu, 2011), biological water (Reiter et al., 2011) and microtubules.

Recently Anirban Bandyopadhyay and colleagues at the National Institute of Material Sciences in Tsukuba, Japan have used nanotechnology to study electronic conductance properties of single microtubules assembled from porcine brain tubulin. Their preliminary findings (Bandyopadhyay, 2011) include: (1) Microtubules have 8 resonance peaks for AC stimulation (kilohertz to 10 megahertz) which appear to correlate with various helical conductance pathways around the geometric microtubule lattice. (2) Excitation at these resonant frequencies causes microtubules to assemble extremely rapidly, possibly due to Fröhlich condensation. (3) In assembled microtubules AC excitation at resonant frequencies causes electronic conductance to become lossless, or 'ballistic', essentially quantum conductance, presumably along these helical quantum channels. Resonance in the range of kilohertz demonstrates microtubule decoherence times of at least 0.1 millisecond. (4) Eight distinct quantum interference patterns from a single microtubule, each correlating with one of the 8 resonance frequencies and pathways. (5) Ferroelectric hysteresis demonstrates memory capacity in microtubules. (6) Temperature-independent conductance also suggests quantum effects. If confirmed, such findings would demonstrate **Orch OR** to be biologically feasible.

*How does microtubule quantum computation and **Orch OR** fit with recognized neurophysiology?* Neurons are composed of multiple dendrites and a cell body/soma which receive and integrate synaptic inputs to a threshold for firing outputs along a single axon. Microtubule quantum computation in **Orch OR** is assumed to occur in dendrites and cell bodies/soma of brain neurons, i.e. in regions of integration of inputs in integrate-and-fire neurons. As opposed to axonal firings, dendritic/somatic integration correlates best with local field potentials, gamma synchrony EEG, and action of anesthetics erasing consciousness. Tononi (2004) has identified integration of information as the neuronal function most closely associated with consciousness. Dendritic microtubules are uniquely arranged in local mixed polarity networks, well-suited for integration of synaptic inputs.

Membrane synaptic inputs interact with post-synaptic microtubules by activation of microtubule-associated protein 2 ('MAP2', associated with learning), and calcium-calmodulin kinase II (CaMKII, Hameroff et al, 2010). Such inputs were suggested by Penrose and Hameroff (1996a) to 'tune', or 'orchestrate' **OR**-mediated quantum computations in microtubules by MAPs, hence 'orchestrated objective reduction', '**Orch OR**'.

Proposed mechanisms for microtubule avoidance of decoherence were described above, but another question remains. How would microtubule quantum computations which are isolated from the environment, still interact with that environment for input and output? One possibility that **Orch OR** suggests is that perhaps phases of isolated quantum computing alternate with phases of classical environmental interaction, e.g. at gamma synchrony, roughly 40 times per second. (Computing pioneer Paul Benioff suggested such a scheme of alternating quantum and classical phases in a science fiction story about quantum computing robots.)

With regard to *outputs* resulting from processes taking place at the level of microtubules in **Orch-OR** quantum computations, dendritic/somatic microtubules receive and integrate synaptic inputs during classical phase. They then become isolated quantum computers and evolve to threshold for **Orch OR** at which they reduce their quantum states at an average time interval τ (given by $\tau \approx \hbar/E_G$). The particular tubulin states chosen in the reduction can then trigger axonal firing, adjust firing threshold, regulate synapses and encode memory. Thus **Orch OR** can have causal efficacy in conscious actions and behavior, as well as providing conscious experience and memory.

Orch OR in evolution In the absence of **Orch OR**, non-conscious neuronal activities might proceed by classical neuronal and microtubule-based computation. In addition there could be *quantum* computations in microtubules that do not reach the **Orch OR** level, and thereby also remain unconscious.

This last possibility is strongly suggested by considerations of natural selection, since some relatively primitive microtubule infrastructure, still able to support quantum computation, would have to have preceded the more sophisticated kind that we now find in conscious animals. Natural selection proceeds in steps, after all, and one would not expect that the capability of the substantial level of coherence across the brain that would be needed for the non-computable OR of human conscious understanding to be reached, without something more primitive having preceded it. Microtubule quantum computing by U evolution which avoids decoherence would well be advantageous to biological processes without ever reaching threshold for OR.

Microtubules may have appeared in eukaryotic cells 1.3 billion years ago due to symbiosis among prokaryotes, mitochondria and spirochetes, the latter the apparent origin of microtubules which provided movement to previously immobile cells (e.g. Margulis and Sagan, 1995). Because **Orch OR** depends on $\tau \approx \hbar/E_G$, more primitive consciousness in simple, small organisms would involve smaller E_G , and longer times τ to avoid decoherence. As simple nervous systems and arrangements of microtubules grew larger and developed anti-decoherence mechanisms, inevitably a system would avoid decoherence long enough to reach threshold for **Orch OR** conscious moments. Central nervous systems around 300 neurons, such as those present at the early Cambrian evolutionary explosion 540 million years ago, could have τ near one minute, and thus be feasible in terms of avoiding decoherence (Hameroff, 1998d). Perhaps the onset of **Orch OR** and consciousness with relatively slow and simple conscious moments, precipitated the accelerated evolution.

Only at a much later evolutionary stage would the selective advantages of a capability for genuine understanding come about. This would require the non-computable capabilities of **Orch OR** that go beyond those of mere quantum computation, and depend upon larger scale infrastructure of efficiently functioning microtubules, capable of operating quantum-computational processes. Further evolution providing larger sets of microtubules (larger EG) able to be isolated from decoherence would enable, by $\tau \approx \hbar/E_G$, more frequent and more intense moments of conscious experience. It appears human brains could have evolved to having **Orch OR** conscious moments perhaps as frequently as every few milliseconds.

How could microtubule quantum states in one neuron extend to those in other neurons throughout the brain? Assuming microtubule quantum state phases are isolated in a specific neuron, how could that quantum state involve microtubules in other neurons throughout the brain without traversing membranes and synapses? **Orch OR** proposes that quantum states can extend by tunneling, leading to entanglement between adjacent neurons through gap junctions.

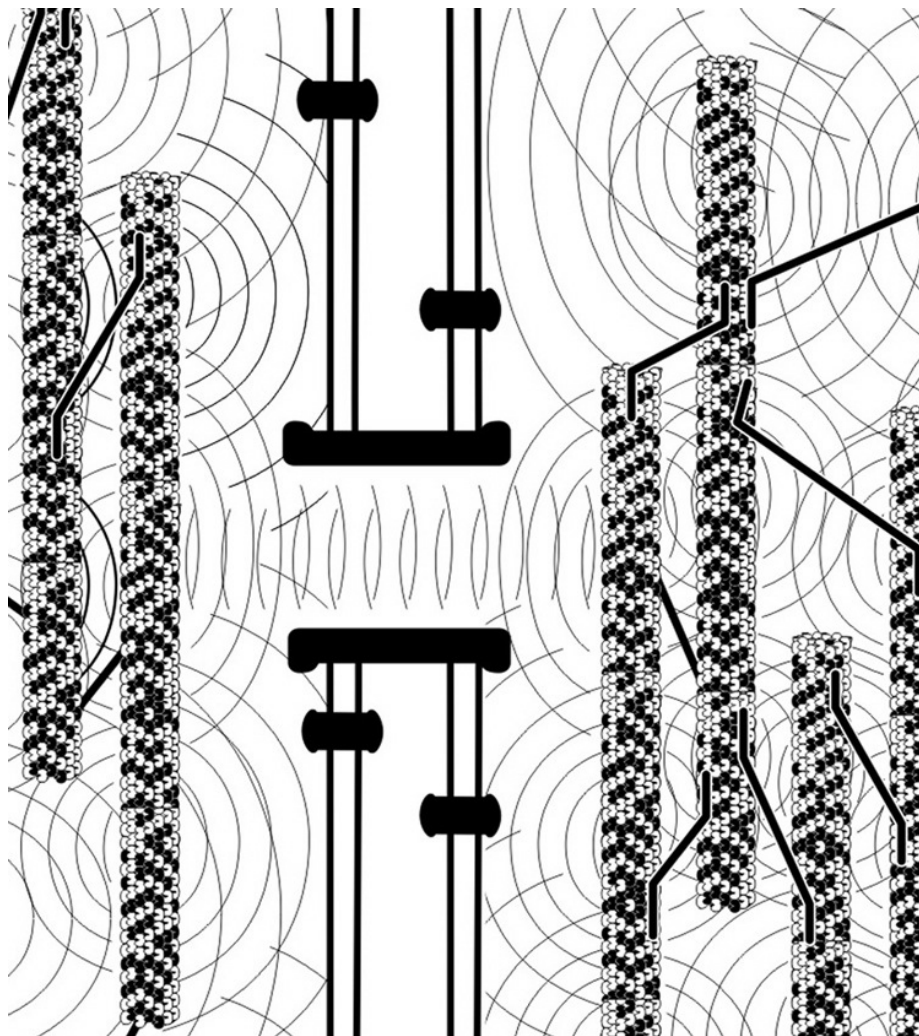


Figure 6. Portions of two neurons connected by a gap junction with microtubules (linked by microtubule-associated proteins, 'MAPs') computing via states (here represented as black or white) of tubulin protein subunits. Wavy lines suggest entanglement among quantum states (not shown) in microtubules.

Gap junctions are primitive electrical connections between cells, synchronizing electrical activities. Structurally, gap junctions are windows between cells which may be open or closed. When open, gap junctions synchronize adjacent cell membrane polarization states, but also allow passage of molecules between cytoplasmic compartments of the two cells. So both membranes and cytoplasmic interiors of gap-junction-connected neurons are continuous, essentially one complex 'hyper-neuron' or syncytium. (Ironically, before Ramon-y-Cajal showed that neurons were discrete cells, the prevalent model for brain structure was a continuous threaded-together syncytium as proposed by Camille Golgi.) **Orch OR** suggests that quantum states in microtubules in one neuron could extend by entanglement and tunneling through gap junctions to microtubules in adjacent neurons and glia (Figure 6), and from those cells to others, potentially in brain-wide syncytia.

Open gap junctions were thus predicted to play an essential role in the neural correlate of consciousness (Hameroff, 1998a). Beginning in 1998, evidence began to show that gamma synchrony, the best measureable correlate of consciousness, depended on gap junctions, particularly dendritic-dendritic gap junctions (Dermietzel, 1998; Draguhn et al, 1998; Galaretta and Hestrin, 1999). To account for the distinction between conscious activities and non-conscious 'auto-pilot' activities, and the fact that consciousness can occur in various brain regions, Hameroff (2009) developed the "Conscious pilot' model in which syncytial zones of dendritic gamma synchrony move around the brain, regulated by gap junction openings and closings, in turn regulated by microtubules. The model suggests consciousness literally moves around the brain in a mobile synchronized zone, within which isolated, entangled microtubules carry out quantum computations and **Orch OR**. Taken together, **Orch OR** and the conscious pilot distinguish conscious from non-conscious functional processes in the brain.

Libet's backward time referral In the 1970s neurophysiologist Benjamin Libet performed experiments on patients having brain surgery while awake, i.e. under local anesthesia (Libet et al., 1979). Able to stimulate and record from conscious human brain, and gather patients' subjective reports with precise timing, Libet determined that conscious perception of a stimulus required up to 500 msec of brain activity post-stimulus, but that conscious awareness occurred at 30 msec post-stimulus, i.e. that subjective experience was referred 'backward in time'.

Bearing such apparent anomalies in mind, Penrose put forward a tentative suggestion, in *The Emperor's New Mind*, that effects like Libet's backward time referral might be related to the fact that quantum entanglements are not mediated in a normal causal way, so that it might be possible for conscious experience not to follow the normal rules of sequential time progression, so long as this does not lead to contradictions with external causality. In Section 5, it was pointed out that the (experimentally confirmed) phenomenon of 'quantum teleportation' (Bennett et al., 1993; Bouwmeester et al., 1997; Macikic et al., 2002) cannot be explained in terms of ordinary classical information processing, but as a combination of such classical causal influences and the acausal effects of quantum entanglement. It indeed turns out that quantum entanglement effects—referred to as 'quantum information' or 'quanglement' (Penrose 2002, 2004)—appear to have to be thought of as being able to propagate in *either* direction in time (into the past or into the future). Such effects, however, cannot by themselves be used to communicate ordinary information into the past. Nevertheless, in conjunction with normal classical future-propagating (i.e. 'causal') signalling, these quantum-teleportation influences can achieve certain kinds of 'signalling' that cannot be achieved simply by classical future-directed means.

The issue is a subtle one, but if conscious experience is indeed rooted in the **OR** process, where we take **OR** to relate the *classical* to the *quantum* world, then apparent anomalies in the

sequential aspects of consciousness are perhaps to be expected. The **Orch OR** scheme allows conscious experience to be *temporally non-local* to a degree, where this temporal non-locality would spread to the kind of time scale τ that would be involved in the relevant **Orch OR** process, which might indeed allow this temporal non-locality to spread to a time $\tau=500\text{ms}$. When the 'moment' of an internal conscious experience is timed externally, it may well be found that this external timing does not precisely accord with a time progression that would seem to apply to internal conscious experience, owing to this temporal non-locality intrinsic to **Orch OR**.

Measurable brain activity correlated with a stimulus often occurs several hundred msec after that stimulus, as Libet showed. Yet in activities ranging from rapid conversation to competitive athletics, we respond to a stimulus (seemingly consciously) *before* the above activity that would be correlated with that stimulus occurring in the brain. This is interpreted in conventional neuroscience and philosophy (e.g. Dennett, 1991; Wegner, 2002) to imply that in such cases we respond non-consciously, on auto-pilot, and subsequently have only an *illusion* of conscious response. The mainstream view is that consciousness is epiphenomenal illusion, occurring after-the-fact as a false impression of conscious control of behavior. We are merely 'helpless spectators' (Huxley, 1986).

However, the effective quantum backward time referral inherent in the temporal non-locality resulting from the quanglement aspects of **Orch OR**, as suggested above, enables conscious experience actually to be *temporally non-local*, thus providing a means to rescue consciousness from its unfortunate characterization as epiphenomenal illusion. Accordingly, **Orch OR** could well enable consciousness to have a causal efficacy, despite its apparently anomalous relation to a timing assigned to it in relation to an external clock, thereby allowing conscious action to provide a semblance of free will.

8. Orch OR Criticisms and Responses

Orch OR has been criticized repeatedly since its inception. Here we review and summarize major criticisms and responses.

Grush and Churchland, 1995. Philosophers Grush and Churchland (1995) took issue with the Gödel's theorem argument, as well as several biological factors. One objection involved the microtubule-disabling drug colchicine which treats diseases such as gout by immobilizing neutrophil cells which cause painful inflammation in joints. Neutrophil mobility requires cycles of microtubule assembly/disassembly, and colchicine prevents re-assembly, impairing neutrophil mobility and reducing inflammation. Grush and Churchland pointed out that patients given colchicine do not lose consciousness, concluding that microtubules cannot be essential for consciousness. Penrose and Hameroff (1995) responded point-by-point to every objection, e.g. explaining that colchicine does not cross the blood brain barrier, and so doesn't reach the brain. Colchicine infused directly into the brains of animals does cause severe cognitive impairment and apparent loss of consciousness (Bensimon and Chemat, 1991).

Tuszynski et al, 1998. Tuszynski et al (1998) questioned how extremely weak gravitational energy in Diósi-Penrose OR could influence tubulin protein states. In Hameroff and Penrose (1996a), the gravitational self-energy E_G for tubulin superposition was calculated for separation of tubulin from itself at the level of its atomic nuclei. Because the atomic (e.g. carbon) nucleus displacement is greater than its radius (the nuclei separate completely), the gravitational self-energy E_G is given by: $E_G = Gm^2/a_c$, where a_c is the carbon nucleus sphere radius equal to 2.5 Fermi distances, m is the mass of tubulin, and G is the gravitational constant. Brown and

Tuszynski calculated E_G (using separation at the nanometer level of the entire tubulin protein), finding an appropriately small energy E of 10^{-27} electron volts (eV) per tubulin, infinitesimal compared with ambient energy kT of 10^{-4} eV. Correcting for the smaller superposition separation distance of 2.5 Fermi lengths in **Orch OR** gives a significantly larger, but still tiny 10^{-21} eV per tubulin. With 2×10^{10} tubulins per 25 msec, the conscious **Orch OR** moment would be roughly 10^{-10} eV (10^{-29} joules), still insignificant compared to kT at 10^{-4} eV.

All this serves to illustrate the fact that the energy E_G does not actually play a role in physical processes as an energy, in competition with other energies that are driving the physical (chemical, electronic) processes of relevance. In a clear sense E_G is, instead, an energy uncertainty—and it is this uncertainty that allows quantum state reduction to take place without violation of energy conservation. The fact that E_G is far smaller than the other energies involved in the relevant physical processes is a necessary feature of the consistency of the OR scheme. It does not supply the energy to drive the physical processes involved, but it provides the energy uncertainty that allows the freedom for processes having virtually the same energy as each other to be alternative actions. In practice, all that E_G is needed for is to tell us how to calculate the lifetime τ of the superposition. E_G would enter into issues of energy balance only if gravitational interactions between the parts of the system were important in the processes involved. (The Earth's gravitational field plays no role in this either, because it cancels out in the calculation of E_G .) No other forces of nature directly contribute to E_G , which is just as well, because if they did, there would be a gross discrepancy with observational physics.

Tegmark, 2000. Physicist Max Tegmark (2000) confronted **Orch OR** on the basis of decoherence. This was discussed at length in Section 7.

Koch and Hepp, 2006. In a challenge to **Orch OR**, neuroscientists/physicists Koch and Hepp published a thought experiment in *Nature*, describing a person observing a superposition of a cat both dead and alive with one eye, the other eye distracted by a series of images (binocular rivalry). They asked 'Where in the observer's brain would reduction occur?', apparently assuming **Orch OR** followed the Copenhagen interpretation in which conscious observation *causes* quantum state reduction. This is precisely the opposite of **Orch OR** in which consciousness *is* the orchestrated quantum state reduction given by OR.

Orch OR can account for the related issue of bistable perceptions (e.g. the famous face/vase illusion, or Necker cube). Non-conscious superpositions of both possibilities (face and vase) during pre-conscious quantum superposition then reduce by **OR** at time τ to conscious perception of one or the other, face *or* vase. The reduction would occur among microtubules within neurons interconnected by gap junctions in various areas of visual and pre-frontal cortex and other brain regions.

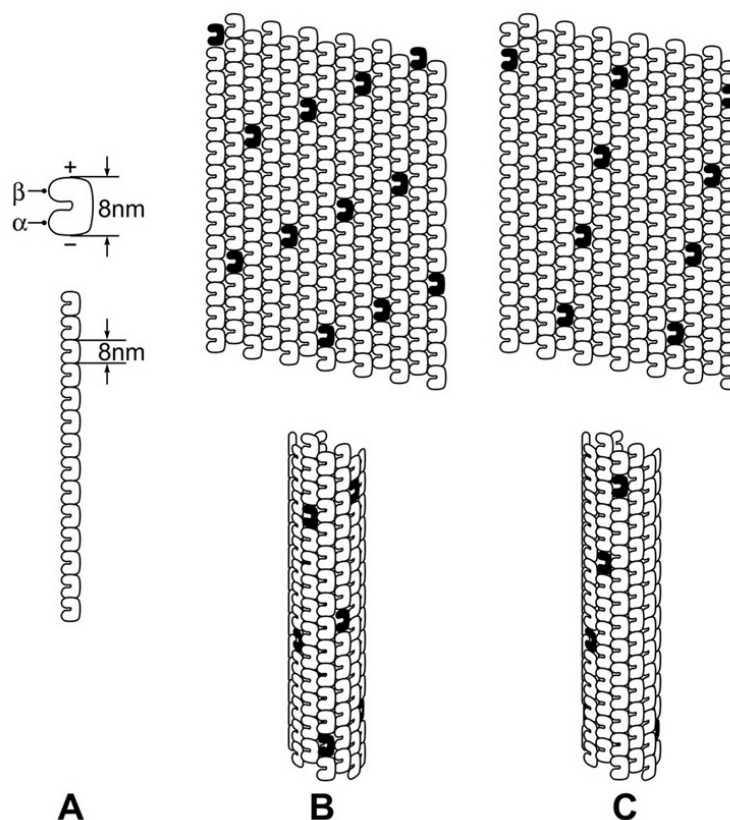


Figure 7. Simulating Fröhlich coherence in microtubules. A) Linear column of tubulins (protofilament) as simulated by Reimers et al (2010) which showed only weak Fröhlich condensation. B) and C) 2-dimensional tubulin sheets with toroidal boundary conditions (approximating 3-dimensional microtubule) simulated by Samsonovich et al (1992) shows long range Fröhlich resonance, with long-range symmetry, and nodes matching experimentally-observed MAP attachment patterns.

Reimers et al (2009) described three types of Fröhlich condensation (weak, strong and coherent, the first classical and the latter two quantum). They validated 8 MHz coherence measured in microtubules by Pokorný (2001; 2004) as weak condensation. Based on simulation of a 1-dimensional linear chain of tubulin dimers representing a microtubule, they concluded only weak Fröhlich condensation occurs in microtubules. Claiming **Orch OR** requires strong or coherent Fröhlich condensation, they concluded **Orch OR** is invalid. However Samsonovich et al (1992) simulated a microtubule as a 2-dimensional lattice plane with toroidal boundary conditions and found Fröhlich resonance maxima at discrete locations in super-lattice patterns on the simulated microtubule surface which precisely matched experimentally observed functional attachment sites for microtubule-associated proteins (MAPs). Further, Bandyopadhyay (2011) has experimental evidence for strong Fröhlich coherence in microtubules at multiple resonant frequencies.

McKemmish et al (2010) challenged the **Orch OR** contention that tubulin switching is mediated by London forces, pointing out that mobile π electrons in a benzene ring (e.g. a phenyl ring without attachments) are completely delocalized, and hence cannot switch between states, nor exist in superposition of both states. Agreed. A single benzene cannot engage in switching. London forces occur between two or more electron cloud ring structures, or other non-polar groups. A single benzene ring cannot support London forces. It takes two (or more) to tango. **Orch OR** has always maintained two or more non-polar groups are necessary (Figure 8). McKemmish et al are clearly mistaken on this point.

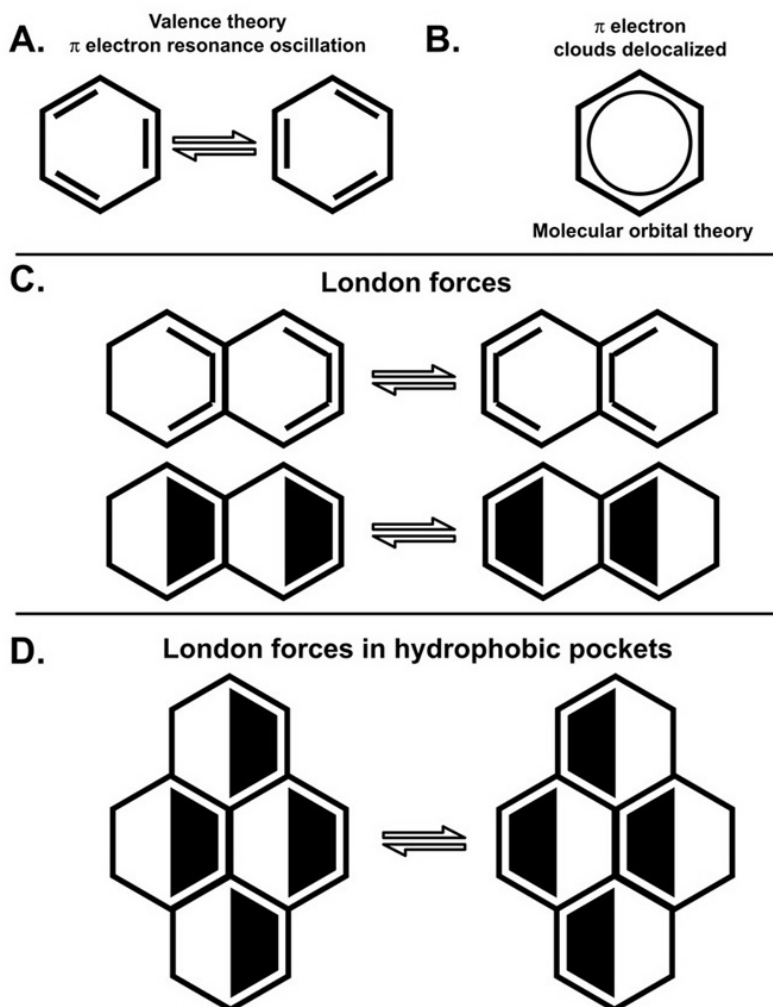


Figure 8. A) Phenyl ring/benzene of 6 carbons with three extra π electrons/double bonds which oscillate between two configurations according to valence theory. B) Phenyl ring/benzene according to molecular orbital theory in which π electrons/double bonds are delocalized, thus preventing oscillation between alternate states. No oscillation/switching can occur. C) Two adjacent phenyl rings/benzenes in which π electrons/double bonds are coupled, i.e. van der Waals London (dipole dispersion) forces. Two versions are shown: In top version, lines represent double bond locations; in bottom version, dipoles are filled in to show negative charge locations. D) Complex of 4 rings with London forces.

McKemmish et al further assert that tubulin switching in **Orch OR** requires significant conformational structural change (as indicated in Figure 2), and that the only mechanism for such conformational switching is due to GTP hydrolysis, i.e. conversion of guanosine triphosphate (GTP) to guanosine diphosphate (GDP) with release of phosphate group energy, and tubulin conformational flexing. McKemmish et al correctly point out that driving synchronized microtubule oscillations by hydrolysis of GTP to GDP and conformational changes would be prohibitive in terms of energy requirements and heat produced. This is agreed. However, we clarify that tubulin switching in **Orch OR** need not actually involve significant conformational change (e. g. as is illustrated in Figure 2), that electron cloud dipole states (London forces) are sufficient for bit-like switching, superposition and qubit function. We acknowledge tubulin conformational switching as discussed in early **Orch OR** publications and illustrations do

indicate significant conformational changes. They are admittedly, though unintentionally, misleading.

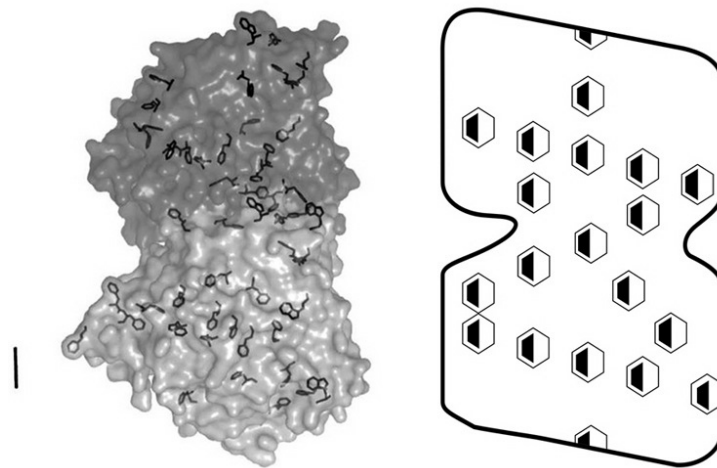


Figure 9. Left: Molecular simulation of tubulin with beta tubulin (dark gray) on top and alpha tubulin (light gray) on bottom. Non-polar amino acids phenylalanine and tryptophan with aromatic phenyl and indole rings are shown. (By Travis Craddock and Jack Tuszynski.) Right: Schematic tubulin with non-polar hydrophobic phenyl rings approximating actually phenyl and indole rings. Scale bar: 1 nanometer.

The only tubulin conformational factor in **Orch OR** is superposition separation involved in E_G , the gravitational self-energy of the tubulin qubit. As previously described, we calculated E_G for tubulin separated from itself at three possible levels: 1) the entire protein (e.g. partial separation, as suggested in Figure 2), 2) its atomic nuclei, and 3) its nucleons (protons and neutrons). The dominant effect is 2) separation at the level of atomic nuclei, e.g. 2.5 Fermi length for carbon nuclei (2.5 femtometers; 2.5×10^{-15} meters). This shift may be accounted for by London force dipoles with Mossbauer nuclear recoil and charge effects (Hameroff, 1998). Tubulin switching in **Orch OR** requires neither GTP hydrolysis nor significant conformational changes.

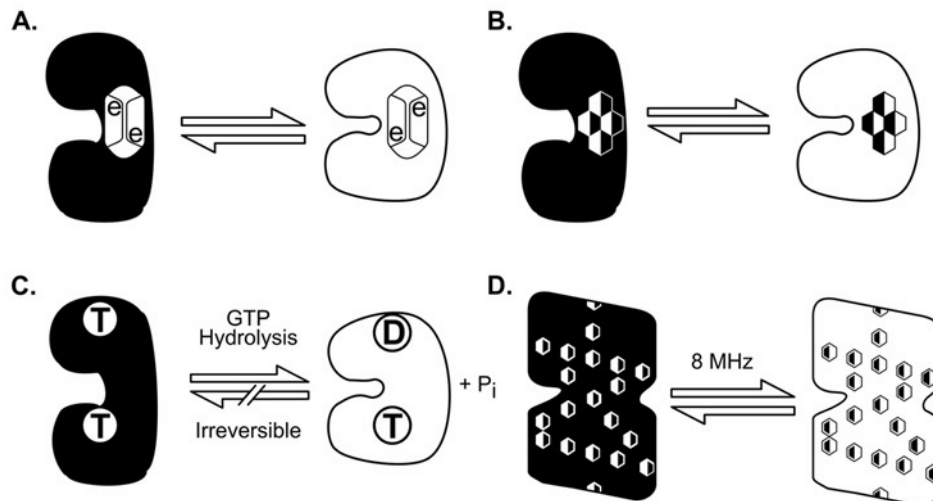


Figure 10. Four versions of the schematic **Orch OR** tubulin bit (superpositioned qubit states not shown). A) Early version showing conformational change coupled to/driven by single hydrophobic pocket with two aromatic rings. B) Updated version with single hydrophobic pocket composed of 4 aromatic rings. C) McKemmish et al (2009) mis-characterization of **Orch OR** tubulin bit as irreversible conformational change driven by GTP hydrolysis. D) Current

version of **Orch OR** bit with no significant conformational change (change occurs at the level of atomic nuclei) and multiple hydrophobic pockets arranged in channels.

Schematic depiction of the tubulin bit, qubit and hydrophobic pockets in **Orch OR** has evolved over the years. An updated version is described in the next Section.

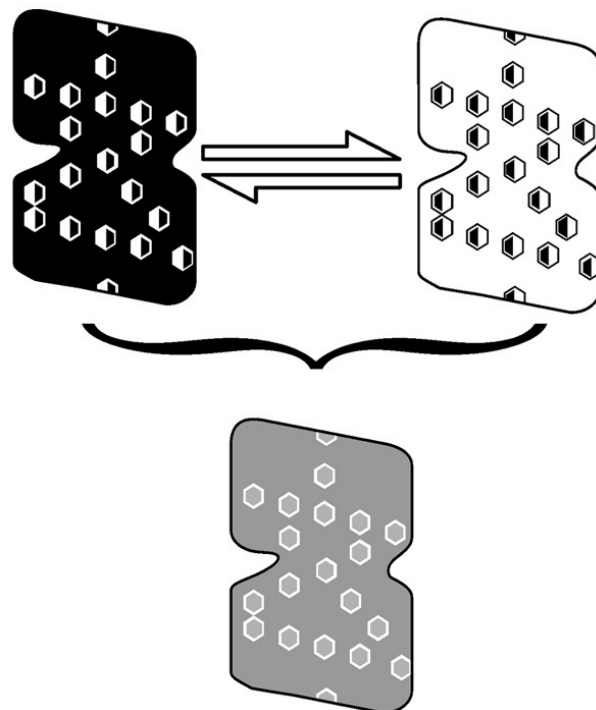


Figure 11. 2011 **Orch OR** tubulin qubit. Top: Alternate states of tubulin dimer (black and white) due to collective orientation of London force electron cloud dipoles in non-polar hydrophobic regions. There is no evident conformational change as suggested in previous versions; conformational change occurs at the level of atomic nuclei. Bottom: Depiction of tubulin (gray) superpositioned in both states.

9. Topological Quantum Computing in Orch OR

Quantum processes in **Orch OR** have consistently been ascribed to London forces in tubulin hydrophobic pockets, non-polar intra-protein regions, e.g. of π electron resonance rings of aromatic amino acids including tryptophan and phenylalanine. This assertion is based on (1) Fröhlich's suggestion that protein states are synchronized by electron cloud dipole oscillations in intra-protein non-polar regions, and (2) anesthetic gases selectively erasing consciousness by London forces in non-polar, hydrophobic regions in various neuronal proteins (e.g. tubulin, membrane proteins, etc.). London forces are weak, but numerous and able to act cooperatively to regulate protein states (Voet and Voet, 1995).

The structure of tubulin became known in 1998 (Nogales et al, 1998), allowing identification of non-polar amino acids and hydrophobic regions. Figure 9 shows locations of phenyl and indole π electron resonance rings of non-polar aromatic amino acids phenylalanine and tryptophan in tubulin. The ring locations are clustered along somewhat continuous pathways (within 2 nanometers) through tubulin. Thus, rather than hydrophobic pockets, tubulin may have within it quantum hydrophobic channels, or streams, linear arrays of electron resonance clouds suitable for cooperative, long-range quantum London forces. These quantum channels within each tubulin

appear to align with those in adjacent tubulins in microtubule lattices, matching helical winding patterns (Figure 12). This in turn may support topological quantum computing in **Orch OR**.

Quantum bits, or qubits in quantum computers are generally envisioned as information bits in superposition of simultaneous alternative representations, e.g. both 1 and 0. Topological qubits are superpositions of alternative pathways, or channels which intersect repeatedly on a surface, forming 'braids'. Quasiparticles called anyons travel along such pathways, the intersections forming logic gates, with particular braids or pathways corresponding with particular information states, or bits. In superposition, anyons follow multiple braided pathways simultaneously, then reduce, or collapse to one particular pathway and functional output. Topological qubits are intrinsically resistant to decoherence.

An **Orch OR** qubit based on topological quantum computing specific to microtubule polymer geometry was suggested in Hameroff et al. (2002). Conductances along particular microtubule lattice geometry, e.g. Fibonacci helical pathways, were proposed to function as topological bits and qubits. Bandyopadhyay (2011) has preliminary evidence for ballistic conductance along different, discrete helical pathways in single microtubules

As an extension of **Orch OR**, we suggest topological qubits in microtubules based on quantum hydrophobic channels, e.g. continuous arrays of electron resonance rings within and among tubulins in microtubule lattices, e.g. following Fibonacci pathways. Cooperative London forces (electron cloud dipoles) in quantum hydrophobic channels may enable long-range coherence and topological quantum computing in microtubules necessary for optimal brain function and consciousness.

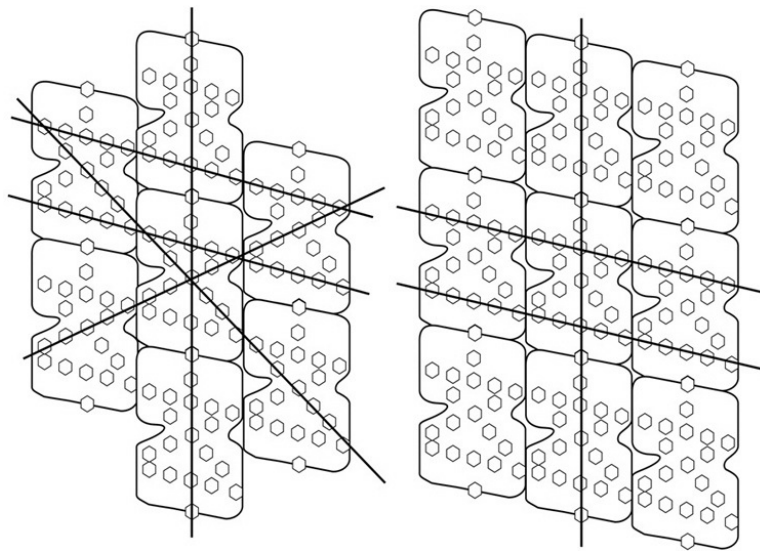


Figure 12. Left: Microtubule A-lattice configuration with lines connecting proposed hydrophobic channels of near-contiguous (<2 nanometer separation) electron resonance rings of phenylalanine and tryptophan. Right: Microtubule B-lattice with fewer such channels and lacking Fibonacci pathways. B-lattice microtubules have a vertical seam dislocation (not shown).

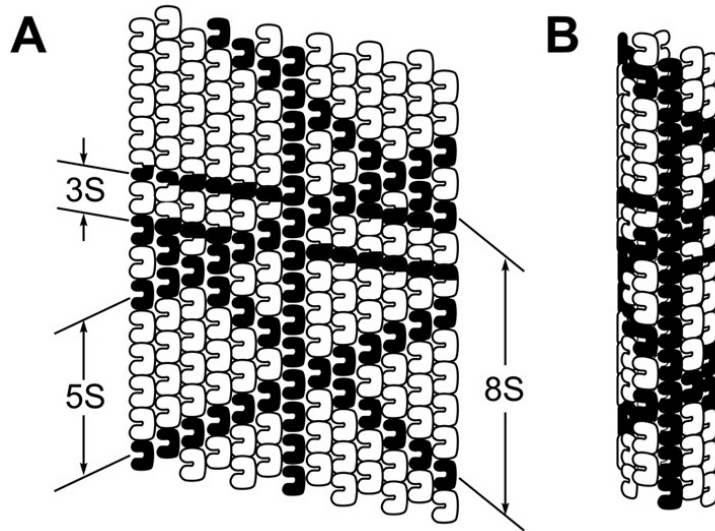


Figure 13. Extending microtubule A-lattice hydrophobic channels (Figure 12) results in helical winding patterns matching Fibonacci geometry. Bandyopadhyay (2011) has evidence for ballistic conductance and quantum interference along such helical pathways which may be involved in topological quantum computing. Quantum electronic states of London forces in hydrophobic channels result in slight superposition separation of atomic nuclei, sufficient E_G for **Orch OR**. This image may be taken to represent superposition of four possible topological qubits which, after time $T=\tau$, will undergo **OR**, and reduce to specific pathway(s) which then implement function.

10. Conclusion: Consciousness in the Universe

Our criterion for *proto*-consciousness is **OR**. It would be unreasonable to refer to **OR** as the criterion for actual consciousness, because, according to the DP scheme, **OR** processes would be taking place all the time, and would be providing the effective randomness that is characteristic of quantum measurement. Quantum superpositions will continually be reaching the DP threshold for **OR** in non-biological settings as well as in biological ones, and usually take place in the purely random environment of a quantum system under measurement. Instead, our criterion for consciousness is **Orch OR**, conditions for which are fairly stringent: superposition must be isolated from the decoherence effects of the random environment for long enough to reach the DS threshold. Small superpositions are easier to isolate, but require longer reduction times τ . Large superpositions will reach threshold quickly, but are intrinsically more difficult to isolate. Nonetheless, we believe that there is evidence that such superpositions could occur within sufficiently large collections of microtubules in the brain for τ to be some fraction of a second.

Very large mass displacements can also occur in the universe in quantum-mechanical situations, for example in the cores of neutron stars. By **OR**, such superpositions would reduce extremely quickly, and classically unreasonable superpositions would be rapidly eliminated. Nevertheless, sentient creatures might have evolved in parts of the universe that would be highly alien to us. One possibility might be on neutron star surfaces, an idea that was developed ingeniously and in great detail by Robert Forward in two science-fiction stories (*Dragon's Egg* in 1980, *Starquake* in 1989). Such creatures (referred to as 'cheelas' in the books, with metabolic processes and **OR**-like events occurring at rates of around a million times that of a human being) could arguably have intense experiences, but whether or not this would be possible in detail is, at the moment, a very speculative matter. Nevertheless, the **Orch OR** proposal offers a possible route to rational argument, as to whether life of a totally alien kind such as this might be possible, or even probable, somewhere in the universe.

Such speculations also raise the issue of the 'anthropic principle', according to which it is sometimes argued that the particular dimensionless constants of Nature that we happen to find in our universe are 'fortuitously' favorable to human existence. (A *dimensionless* physical constant is a pure number, like the ratio of the electric to the gravitational force between the electron and the proton in a hydrogen atom, which in this case is a number of the general order of 10^{40} .) The key point is not so much to do with human existence, but the existence of sentient beings of any kind. Is there anything coincidental about the dimensionless physical constants being of such a nature that conscious life is possible at all? For example, if the mass of the neutron had been slightly less than that of the proton, rather than slightly larger, then neutrons rather than protons would have been stable, and this would be to the detriment of the whole subject of chemistry. These issues are frequently argued about (see Barrow and Tipler 1986), but the **Orch OR** proposal provides a little more substance to these arguments, since a proposal for the possibility of sentient life is, in principle, provided.

The recently proposed cosmological scheme of *conformal cyclic cosmology* (CCC) (Penrose 2010) also has some relevance to these issues. CCC posits that what we presently regard as the entire history of our universe, from its Big-Bang origin (but without inflation) to its indefinitely expanding future, is but one *aeon* in an unending succession of similar such aeons, where the infinite future of each matches to the big bang of the next via an infinite change of scale. A question arises whether the dimensionless constants of the aeon prior to ours, in the CCC scheme, are the same as those in our own aeon, and this relates to the question of whether sentient life could exist in that aeon as well as in our own. These questions are in principle answerable by observation, and again they would have a bearing on the extent or validity of the **Orch OR** proposal. If **Orch OR** turns out to be correct, in its essentials, as a physical basis for consciousness, then it opens up the possibility that many questions may become answerable, such as whether life could have come about in an aeon prior to our own, that would have previously seemed to be far beyond the reaches of science.

Moreover, **Orch OR** places the phenomenon of consciousness at a very central place in the physical nature of our universe, whether or not this 'universe' includes aeons other than just our own. It is our belief that, quite apart from detailed aspects of the physical mechanisms that are involved in the production of consciousness in human brains, quantum mechanics is an incomplete theory. Some completion is needed, and the DP proposal for an **OR** scheme underlying quantum theory's **R**-process would be a definite possibility. If such a scheme as this is indeed respected by Nature, then there is a fundamental additional ingredient to our presently understood laws of Nature which plays an important role at the Planck-scale level of space-time structure. The **Orch OR** proposal takes advantage of this, suggesting that conscious experience itself plays such a role in the operation of the laws of the universe.

Acknowledgment We thank Dave Cantrell, University of Arizona Biomedical Communications for artwork.

References

- Atema, J. (1973). Microtubule theory of sensory transduction. *Journal of Theoretical Biology*, 38, 181-90.
- Bandyopadhyay A (2011) Direct experimental evidence for quantum states in microtubules and topological invariance. Abstracts: Toward a Science of Consciousness 2011, Stockholm, Sweden, HYPERLINK "<http://www.consciousness.arizona.edu>"www.consciousness.arizona.edu
- Barrow, J.D. and Tipler, F.J. (1986) *The Anthropic Cosmological Principle* (OUP, Oxford).
- Bell, J.S. (1966) *Speakable and Unspeakable in Quantum Mechanics* (Cambridge Univ. Press, Cambridge; reprint 1987).
- Benioff, P. (1982). Quantum mechanical Hamiltonian models of Turing Machines. *Journal of Statistical Physics*, 29, 515-46.
- Bennett C.H., and Wiesner, S.J. (1992). Communication via 1- and 2-particle operators on Einstein-Podolsky-Rosen states. *Physical Reviews Letters*, 69, 2881-84.
- Bensimon G, Chemat R (1991) Microtubule disruption and cognitive defects: effect of colchicine on teaming behavior in rats. *Pharmacol. Biochem. Behavior* 38:141-145.
- Bohm, D. (1951) *Quantum Theory* (Prentice-Hall, Englewood-Cliffs.) Ch. 22, sect. 15-19. Reprinted as: The Paradox of Einstein, Rosen and Podolsky, in *Quantum Theory and Measurement*, eds., J.A. Wheeler and W.H. Zurek (Princeton University Press, Princeton, 1983).
- Bernroider, G. and Roy, S. (2005) Quantum entanglement of K ions, multiple channel states and the role of noise in the brain. *SPIE* 5841-29:205-14.
- Bouwmeester, D., Pan, J.W., Mattle, K., Eibl, M., Weinfurter, H. and Zeilinger, A. (1997) Experimental quantum teleportation. *Nature* 390 (6660): 575-579.
- Brunden K.R., Yao Y., Potuzak J.S., Ferrer N.I., Ballatore C., James M.J., Hogan A.M., Trojanowski J.Q., Smith A.B. 3rd and Lee V.M. (2011) The characterization of microtubule-stabilizing drugs as possible therapeutic agents for Alzheimer's disease and related tauopathies. *Pharmacological Research*, 63(4), 341-51.
- Chalmers, D. J., (1996). *The conscious mind - In search of a fundamental theory*. Oxford University Press, New York.
- Crick, F., and Koch, C., (1990). Towards a neurobiological theory of consciousness. *Seminars in the Neurosciences*, 2, 263-75.
- Dennett, D.C. (1991). *Consciousness explained*. Little Brown, Boston. MA.

- Dennett, D.C. (1995) *Darwin's dangerous idea: Evolution and the Meanings of Life*, Simon and Schuster.
- Dermietzel, R. (1998) Gap junction wiring: a 'new' principle in cell-to-cell communication in the nervous system? *Brain Research Reviews*. 26(2-3):176-83.
- Deutsch, D. (1985) Quantum theory, the Church–Turing principle and the universal quantum computer, *Proceedings of the Royal Society (London)* A400, 97-117.
- Diósi, L. (1987) A universal master equation for the gravitational violation of quantum mechanics, *Physics Letters A* 120 (8):377-381.
- Diósi, L. (1989). Models for universal reduction of macroscopic quantum fluctuations *Physical Review A*, 40, 1165-74.
- Draguhn A, Traub RD, Schmitz D, Jefferys (1998). Electrical coupling underlies high-frequency oscillations in the hippocampus in vitro. *Nature*, 394(6689), 189-92.
- Eccles, J.C. (1992). Evolution of consciousness. *Proceedings of the National Academy of Sciences*, 89, 7320-24.
- Engel GS, Calhoun TR, Read EL, Ahn T-K, Mancal T, Cheng Y-C, Blankenship RE, Fleming GR (2007) Evidence for wavelike energy transfer through quantum coherence in photosynthetic systems. *Nature* 446:782-786.
- Everett, H. (1957). Relative state formulation of quantum mechanics. In *Quantum Theory and Measurement*, J.A. Wheeler and W.H. Zurek (eds.) Princeton University Press, 1983; originally in *Reviews of Modern Physics*, 29, 454-62.
- Feynman, R.P. (1986). Quantum mechanical computers. *Foundations of Physics*, 16(6), 507-31.
- Forward, R. (1980) *Dragon's Egg*. Ballentine Books.
- Forward, R. (1989) *Starquake*. Ballentine Books.
- Fröhlich, H. (1968). Long-range coherence and energy storage in biological systems. *International Journal of Quantum Chemistry*, 2, 641-9.
- Fröhlich, H. (1970). Long range coherence and the actions of enzymes. *Nature*, 228, 1093.
- Fröhlich, H. (1975). The extraordinary dielectric properties of biological materials and the action of enzymes. *Proceedings of the National Academy of Sciences*, 72, 4211-15.
- Galarreta, M. and Hestrin, S. (1999). A network of fast-spiking cells in the neocortex connected by electrical synapses. *Nature*, 402, 72-75.
- Gauger E., Rieper E., Morton J.J.L., Benjamin S.C., Vedral V. (2011) Sustained quantum coherence and entanglement in the avian compass <http://arxiv.org/abs/0906.3725>.

- Ghirardi, G.C., Rimini, A., and Weber, T. (1986). Unified dynamics for microscopic and macroscopic systems. *Physical Review D*, 34, 470.
- Ghirardi, G.C., Grassi, R., and Rimini, A. (1990). Continuous-spontaneous reduction model involving gravity. *Physical Review A*, 42, 1057-64.
- Grush R., Churchland P.S. (1995), 'Gaps in Penrose's toilings', *J. Consciousness Studies*, 2 (1):10-29.
- Hagan S, Hameroff S, and Tuszynski J, (2001). Quantum Computation in Brain Microtubules? Decoherence and Biological Feasibility, *Physical Review E*, 65, 061901.
- Hameroff, S.R., and Watt R.C. (1982). Information processing in microtubules. *Journal of Theoretical Biology*, 98, 549-61.
- Hameroff, S.R.(1987) *Ultimate computing: Biomolecular consciousness and nanotechnology*. Elsevier North-Holland, Amsterdam.
- Hameroff, S.R., and Penrose, R., (1996a). Orchestrated reduction of quantum coherence in brain microtubules: A model for consciousness. In: *Toward a Science of Consciousness ; The First Tucson Discussions and Debates*. Hameroff, S.R., Kaszniak, and Scott, A.C., eds., 507-540, MIT Press, Cambridge MA, 507-540. Also published in *Mathematics and Computers in Simulation* (1996) 40:453-480.
- Hameroff, S.R., and Penrose, R. (1996b). Conscious events as orchestrated spacetime selections. *Journal of Consciousness Studies*, 3(1), 36-53.
- Hameroff, S. (1998a). Quantum computation in brain microtubules? The Penrose-Hameroff "**Orch OR**" model of consciousness. *Philosophical Transactions of the Royal Society (London) Series A*, 356, 1869-1896.
- Hameroff, S. (1998b). 'Fundamentality': is the conscious mind subtly linked to a basic level of the universe? *Trends in Cognitive Science*, 2, 119-127.
- Hameroff, S. (1998c). Anesthesia, consciousness and hydrophobic pockets – A unitary quantum hypothesis of anesthetic action. *Toxicology Letters*, 100, 101, 31-39.
- Hameroff, S. (1998d). HYPERLINK "<http://www.hameroff.com/penrose-hameroff/cambrian.html>"Did consciousness cause the Cambrian evolutionary explosion? In: *Toward a Science of Consciousness II: The Second Tucson Discussions and Debates*. Eds. Hameroff, S.R., Kaszniak, A.W., and Scott, A.C., MIT Press, Cambridge, MA.
- Hameroff, S., Nip, A., Porter, M., and Tuszynski, J. (2002). Conduction pathways in microtubules, biological quantum computation and microtubules. *Biosystems*, 64(13), 149-68.
- Hameroff S.R., & Watt R.C. (1982) Information processing in microtubules. *Journal of Theoretical Biology* 98:549-61.

Hameroff, S.R. (2006) The entwined mysteries of anesthesia and consciousness. *Anesthesiology* 105:400-412.

Hameroff, S.R, Craddock TJ, Tuszynski JA (2010) Memory 'bytes' – Molecular match for CaMKII phosphorylation encoding of microtubule lattices. *Journal of Integrative Neuroscience* 9(3):253-267.

He, R-H., Hashimoto, M., Karapetyan. H., Koralek, J.D., Hinton, J.P., Testaud, J.P., Nathan, V., Yoshida, Y., Yao, H., Tanaka, K., Meevasana, W., Moore, R.G., Lu, D.H., Mo, S-K., Ishikado, M., Eisaki, H., Hussain, Z., Devereaux, T.P., Kivelson, S.A., Orenstein, Kapitulnik, J.A., Shen, Z-X. (2011) From a Single-Band Metal to a High Temperature Superconductor via Two Thermal Phase Transitions. *Science*, 2011;331 (6024): 1579-1583.

Hebb, D.O. (1949). *Organization of Behavior: A Neuropsychological Theory*, John Wiley and Sons, New York.

Huxley TH (1893; 1986) *Method and Results: Essays*.

Kant I (1781) *Critique of Pure Reason* (Translated and edited by Paul Guyer and Allen W. Wood, Cambridge University Press, 1998).

Kibble, T.W.B. (1981). Is a semi-classical theory of gravity viable? In *Quantum Gravity 2: a Second Oxford Symposium*; eds. C.J. Isham, R. Penrose, and D.W. Sciama (Oxford University Press, Oxford), 63-80.

Koch, C., (2004) *The Quest for Consciousness: A Neurobiological Approach*, Englewood, CO., Roberts and Co.

Koch C, Hepp K (2006) Quantum mechanics in the brain. *Nature* 440(7084):611.

Libet, B., Wright, E.W. Jr., Feinstein, B., & Pearl, D.K. (1979) Subjective referral of the timing for a conscious sensory experience. *Brain* 102:193-224.

Luo L, Lu J (2011) Temperature dependence of protein folding deduced from quantum transition. <http://arxiv.org/abs/1102.3748>

Lutz A, Greischar AL, Rawlings NB, Ricard M, Davidson RJ (2004) Long-term meditators self-induce high-amplitude gamma synchrony during mental practice *The Proceedings of the National Academy of Sciences USA* 101(46):16369-16373.

Macikic I., de Riedmatten H., Tittel W., Zbinden H. and Gisin N. (2002) Long-distance teleportation of qubits at telecommunication wavelengths *Nature* 421, 509-513.

Margulis, L. and Sagan, D. 1995. *What is life?* Simon and Schuster, N.Y.

Marshall, W, Simon, C., Penrose, R., and Bouwmeester, D (2003). Towards quantum superpositions of a mirror. *Physical Review Letters* 91, 13-16; 130401.

McKemmish LK, Reimers JR, McKenzie RH, Mark AE, Hush NS (2009) Penrose-Hameroff orchestrated objective-reduction proposal for human consciousness is not biologically feasible. *Physical Review E*. 80(2 Pt 1):021912.

Moroz, I.M., Penrose, R., and Tod, K.P. (1998) Spherically-symmetric solutions of the Schrödinger–Newton equations: . *Classical and Quantum Gravity*, 15, 2733-42.

Nogales E, Wolf SG, Downing KH. (1998) HYPERLINK
"http://dx.doi.org/10.1038/34465"Structure of the $\alpha\beta$ -tubulin dimer by electron crystallography. *Nature*. 391, 199-203.

Ouyang, M., & Awschalom, D.D. (2003) Coherent spin transfer between molecularly bridged quantum dots. *Science* 301:1074-78.

Pearle, P. (1989). Combining stochastic dynamical state-vector reduction with spontaneous localization. *Physical Review A*, 39, 2277-89.

Pearle, P. and Squires, E.J. (1994). Bound-state excitation, nucleon decay experiments and models of wave-function collapse. *Physical Review Letters*, 73(1), 1-5.

Penrose, R. (1989). *The Emperor's New Mind: Concerning Computers, Minds, and the Laws of Physics*, Oxford University Press, Oxford.

Penrose, R. (1993). Gravity and quantum mechanics. In *General Relativity and Gravitation 13. Part 1: Plenary Lectures 1992. Proceedings of the Thirteenth International Conference on General Relativity and Gravitation held at Cordoba, Argentina, 28 June - 4 July 1992*. Eds. R.J.Gleiser, C.N.Kozameh, and O.M.Moreschi (Inst. of Phys. Publ. Bristol and Philadelphia), 179-89.

Penrose, R. (1994). *Shadows of the Mind; An Approach to the Missing Science of Consciousness*. Oxford University Press, Oxford.

Penrose, R. (1996). On gravity's role in quantum state reduction. *General Relativity and Gravitation*, 28, 581-600.

Penrose, R. (2000). Wavefunction collapse as a real gravitational effect. In *Mathematical Physics 2000*, Eds. A.Fokas, T.W.B.Kibble, A.Grigouriou, and B.Zegarlinski. Imperial College Press, London, 266-282.

Penrose, R. (2002). John Bell, State Reduction, and Quanglement. In *Quantum Unspeakables: From Bell to Quantum Information*, Eds. Reinhold A. Bertlmann and Anton Zeilinger, Springer-Verlag, Berlin, 319-331.

Penrose, R. (2004). *The Road to Reality: A Complete Guide to the Laws of the Universe*. Jonathan Cape, London.

Penrose, R. (2009). Black holes, quantum theory and cosmology (Fourth International Workshop DICE 2008), *Journal of Physics, Conference Series* 174, 012001.

Penrose, R. (2010). *Cycles of Time: An Extraordinary New View of the Universe*. Bodley Head, London.

Penrose R. and Hameroff S.R. (1995) What gaps? Reply to Grush and Churchland. *Journal of Consciousness Studies* 2:98-112.

Percival, I.C. (1994) Primary state diffusion. *Proceedings of the Royal Society (London) A*, 447, 189-209.

Pokorný, J., Hasek, J., Jelínek, F., Saroch, J. & Palan, B. (2001) Electromagnetic activity of yeast cells in the M phase. *Electro Magnetobiol* 20, 371–396.

Pokorný, J. (2004) Excitation of vibration in microtubules in living cells. *Bioelectrochem.* 63: 321-326.

Polkinghorne, J. (2002) *Quantum Theory, A Very Short Introduction*. Oxford University Press, Oxford.

Rae, A.I.M. (1994) *Quantum Mechanics*. Institute of Physics Publishing; 4th edition 2002.

Rasmussen, S., Karampurwala, H., Vaidyanath, R., Jensen, K.S., and Hameroff, S. (1990) Computational connectionism within neurons: A model of cytoskeletal automata subserving neural networks. *Physica D* 42:428-49.

Reimers JR, McKemmish LK, McKenzie RH, Mark AE, Hush NS (2009) Weak, strong, and coherent regimes of Frohlich condensation and their applications to terahertz medicine and quantum consciousness *Proceedings of the National Academy of Sciences USA* 106(11):4219-24

Reiter GF, Kolesnikov AI, Paddison SJ, Platzman PM, Moravsky AP, Adams MA, Mayers J (2011) Evidence of a new quantum state of nano-confined water <http://arxiv.org/abs/1101.4994>

Rieper E, Anders J, Vedral V (2011) Quantum entanglement between the electron clouds of nucleic acids in DNA. <http://arxiv.org/abs/1006.4053>.

Samsonovich A, Scott A, Hameroff S (1992) Acousto-conformational transitions in cytoskeletal microtubules: Implications for intracellular information processing. *Nanobiology* 1:457-468.

Sherrington, C.S. (1957) *Man on His Nature*, Second Edition, Cambridge University Press.

Smolin, L. (2002). *Three Roads to Quantum Gravity*. Basic Books. New York.

Tegmark, M. (2000) The importance of quantum decoherence in brain processes. *Physica Rev E* 61:4194-4206.

Tittel, W, Brendel, J., Gisin, B., Herzog, T., Zbinden, H., and Gisin, N. (1998) Experimental demonstration of quantum correlations over more than 10 km, *Physical Review A*, 57:3229-32.

Tononi G (2004) An information integration theory of consciousness *BMC Neuroscience* 5:42.

Turin L (1996) A spectroscopic mechanism for primary olfactory reception *Chem Senses* 21(6) 773-91.

Tuszynski JA, Brown JA, Hawrylak P, Marcer P (1998) Dielectric polarization, electrical conduction, information processing and quantum computation in microtubules. Are they plausible? *Phil Trans Royal Society A* 356:1897-1926.

Tuszynski, J.A., Hameroff, S., Sataric, M.V., Trpisova, B., & Nip, M.L.A. (1995) Ferroelectric behavior in microtubule dipole lattices; implications for information processing, signaling and assembly/disassembly. *Journal of Theoretical Biology* 174:371–80.

Voet, D., Voet, J.G. 1995. *Biochemistry*, 2nd edition. Wiley, New York.

von Rospatt, A., (1995) *The Buddhist Doctrine of Momentariness: A survey of the origins and early phase of this doctrine up to Vasubandhu* (Stuttgart: Franz Steiner Verlag).

Wegner, D.M. (2002) *The illusion of conscious will* Cambridge MA, MIT Press.

Whitehead, A.N., (1929) *Process and Reality*. New York, Macmillan.

Whitehead, A.N. (1933) *Adventure of Ideas*, London, Macmillan.

Wigner E.P. (1961). Remarks on the mind-body question, in *The Scientist Speculates*, ed. I.J. Good (Heinemann, London). In *Quantum Theory and Measurement*, eds., J.A. Wheeler and W.H. Zurek, Princeton University Press, Princeton, MA. (Reprinted in E. Wigner (1967), *Symmetries and Reflections*, Indiana University Press, Bloomington).

Wolfram, S. (2002) *A New Kind of Science*. Wolfram Media incorporated.