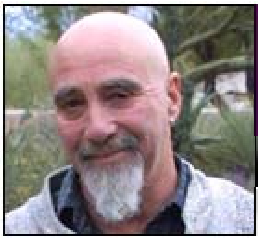

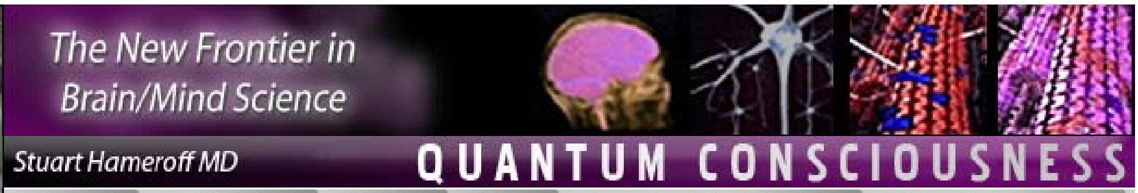

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Quantum computation in brain microtubules? The Penrose-Hameroff "Orch OR" model of consciousness

I. Quantum computation and consciousness

Proposals for quantum computation rely on superposed states implementing multiple computations simultaneously, in parallel, according to quantum linear superposition (e.g., Benioff, 1982; Feynman, 1986; Deutsch, 1985, Deutsch and Josza, 1992). In principle, quantum computation is capable of specific applications beyond the reach of classical computing (e.g., Shor, 1994). A number of technological systems aimed at realizing these proposals have been suggested and are being evaluated as possible substrates for quantum computers (e.g. trapped ions, electron spins, quantum dots, nuclear spins, etc., see Table 1; Bennett, 1995; and Barenco, 1995). The main obstacle to realization of quantum computation is the problem of interfacing to the system (input, output) while also protecting the quantum state from environmental decoherence. If this problem can be overcome, then present day classical computers may evolve to quantum computers.

The workings of the human mind have been historically described as metaphors of contemporary information technology. In ancient Greece memory was like a "seal ring in wax" and in the 19th century the mind was seen as a telegraph switching circuit. In this century the classical computer has been the dominant metaphor for the brain's activities. If quantum computation becomes a technological reality, consciousness may inevitably be seen as some form of quantum computation. Indeed enigmatic features of consciousness have already led to proposals for quantum computation in the brain.

Conventional explanations portray consciousness as an emergent property of classical computer-like activities in the brain's neural networks (e.g. functionalism, reductionism, physicalism, materialism, computationalism-Churchland, 1986; Dennett, 1991; Churchland and Sejnowski, 1992). The current leading candidate for a computer-like "neural correlate" of consciousness involves neuronal circuits oscillating synchronously in thalamus and cerebral cortex. Higher frequency oscillations (collectively known as "coherent 40 Hz") are suggested to mediate temporal binding of conscious experience (e.g. Singer et al 1990; Crick and Koch, 1990; Joliot et al, 1994; Gray, 1998). The proposals vary, for example as to whether coherence originates in thalamus or resonates in cortical networks, but "thalamo-cortical 40 Hz" stands as a prevalent view of the neural-level substrate for consciousness.

But how do neural firings lead to thoughts and feelings? Conventional ("functionalist") approaches fall short on the mind's enigmatic features. These include: 1) the nature of subjective experience, or qualia, our "inner life" (e.g. Nagel, 1974; Chalmers, 1996) 2) "binding" of spatially distributed brain activities into unitary objects in vision and a coherent sense of "self," 3) transition from pre-conscious processing to consciousness, 4) non-computability (Penrose, 1989; 1994; 1997), and 5) free will.

Functionalist approaches generally assume that conscious experience appears as a novel property at a critical level of computational complexity. On the surface this would seem to deal with issues 1 and 3, however a conscious threshold has neither been identified nor predicted, and there are no apparent differences in electrophysiological activities between non-conscious and conscious activity. Regarding the nature of experience (why we are not unfeeling "zombies") functionalism offers no testable predictions. Problem 2) of 'binding' in vision and self is often attributed by functionalists to temporal correlation (e.g. coherent 40 Hz), but it is unclear why temporal correlation *per se* should bind experience without an explanation of experience. As functionalism is based on deterministic computation, it is also unable to account for Penrose's proposed noncomputability (4), or free will (5). Something may be missing.

To address these issues, various proposals have been suggested in which macroscopic quantum phenomena are connected to the brain's known neural activity. For the problem of unitary binding, Marshall (1989) suggested that coherent quantum states known as Bose-Einstein condensation occurred among neural proteins (c.f. Penrose, 1987; Bohm and Hiley, 1993; Jibu and Yasue, 1995). Pre-conscious to conscious transitions were identified by Stapp (1992) with collapse of a quantum wave function in pre-synaptic axon terminals (c.f. Beck and Eccles, 1992). In another proposal, protein assemblies called microtubules within the brain's neurons are viewed as self-organizing quantum computers ("orchestrated objective reduction - Orch OR" e.g. Penrose and Hameroff, 1995; Hameroff and Penrose 1996a; 1996b; c.f. Hameroff 1997; 1998a; 1998b; 1998c; 1998d).

At first glance the possibility of macroscopic quantum states in biological systems seems unlikely, appearing to require either extreme cold (to avoid thermal noise) or laser-like energetic pumping to achieve coherent states. And as in technological proposals, perfect isolation of the quantum state from the environment (and/or quantum error correction codes) would be required while the system must also somehow communicate with the external world. Living cells including the brain's neurons seem unsuitably warm and wet for delicate quantum states which would seem susceptible to thermal noise and environmental decoherence. However specific conditions supporting quantum states in microtubules may have evolved (see Section III).

In addition to its biological setting, the Orch OR proposal differs significantly in another regard from technologically envisioned quantum computers. The latter would arrive at output states through reduction ("collapse") of quantum superposition to classical states by environmental decoherence the quantum state would be interrupted by the external world. The outcome states in technological quantum computers would therefore reflect deterministic processing influenced at reduction by some probabilistic randomness.

On the other hand Roger Penrose (1989; 1994; 1996) has proposed that isolated quantum systems which avoid environmental decoherence will eventually reduce nonetheless due to an objective threshold ("objective reduction" - OR) related to an intrinsic feature of fundamental spacetime geometry (see below). Unlike the situation following environmental decoherence, outcome states which reduce due to Penrose's objective reduction are selected by a non-computable influence on the deterministic, pre-reduction quantum computation. Noncomputability implies a non-algorithmic process which is neither deterministic nor random, a property which Penrose (e.g. 1997) also attributes to conscious thought and understanding. This clue suggests that quantum computation with objective reduction may be somehow involved in consciousness.

The objective factor in OR is an intrinsic feature of spacetime itself (quantum gravity). Penrose begins from general relativity with the notion that mass is equivalent to spacetime curvature. He concludes that quantum superpositionactual separation (displacement) of mass from itselfis equivalent to simultaneous spacetime curvatures in opposite directions, causing "bubbles", or separations in fundamental reality (Figure 1).

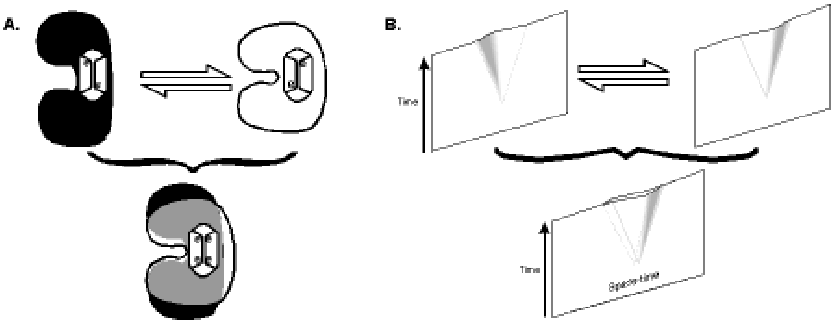

Figure 1a. *Schematized protein (tubulin) capable of switching between two conformational states governed by London force interactions in a hydrophobic pocket. (Tubulin may actually have multiple smaller collectively governing hydrophobic pockets and more than two possible states. For simplicity a one pocket, two state protein is illustrated). Top: Protein switching between 2 conformational states coupled to localization of paired electrons (induced dipoles) within a hydrophobic pocket (see Section II). Bottom: quantum superposition (simultaneous existence in two distinct states) of the electron pair and protein conformation.1bFour dimensional spacetime may be schematically represented by one dimension of space and one dimension of time: a two dimensional "spacetime sheet." Mass is curvature in spacetime, and the two spacetime curvatures in the top of Figure 1b represent mass (e.g. a tubulin protein) in two different locations or conformations respectively. Mass in quantum superposition (mass separated from itself) is simultaneous spacetime curvature in opposite directions, a separation, or bubble in spacetime. At a critical degree of separation, the system becomes unstable and must select either one state or the other (from Penrose, 1994 p. 338).*

Penrose views the bubbles as unstable, with a critical objective degree of separation resulting in instantaneous reduction to classical, unseparated states. Objective reductions are thus events which reconfigure the fine scale of spacetime geometry. As described in Section V, modern panpsychists attribute proto-conscious experience to a fundamental property of physical reality. If so, consciousness might involve self-organizing OR events rippling through an experiential medium.

Could OR events be occurring in the brain? If so, they would be expected to coincide with known neurophysiological processes with recognized time scales. The critical degree of spacetime separation causing Penrose's objective reduction is related to quantum gravity by the uncertainty principle:

E = hbar/T

where E is the gravitational selfenergy of the superposed mass (displaced *from itself* by e.g. the diameter of its atomic nuclei), is Planck's constant over 2, and T is the coherence time until OR selfcollapse. The size of an isolated superposed system is thus inversely related to the length of time until selfcollapse. Large superposed systems (e.g. Schrödinger's mythical 1 kg cat) would selfcollapse (OR) in only 10^{37} sec; an isolated superposed atom would OR only after 10^{6} years! If OR events occur in the brain coupled to known neurophysiology, then we can estimate that T for conscious OR events may be in a range from 10 to 500 milliseconds (msec). This range covers neurophysiological activities such as 25 msec "coherent 40 Hz," 100 msec EEG rhythms, and Libet's (1979) 500 msec sensory perceptions). OR events coupled to roughly 100 msec activities would require a few nanograms of superposed mass.

Biological materials best suited for quantum computation and objective reduciton are proteins, particularly assemblies of proteins called microtubules.

II. Proteins and qubits

Proteins are versatile macromolecules which perform a variety of functions by changing their conformational shape. Such functions include muscle movement, membrane firing via openings and closings of protein ion channels, molecular binding, enzyme catalysis, metabolism, movement and phase of cytoplasm. Life is organized by changes in protein shape.

Individual proteins are synthesized as linear chains of hundreds of amino acids which "fold" into 3 dimensional conformation. The precise manner of folding for each protein depends on attractive and repellent forces among its various amino acid side groups, and a current view is that many possible intermediate conformations precede the final one (Baldwin, 1994). Although complete linear sequences of amino acid chains are known for many proteins, predicting their final 3-dimensional folded shape using computer simulation has proven difficult if not impossible. This conundrum is known as the "protein folding problem" and so far appears to be "NP complete": the answer can be calculated in theory, but the space and time required of any classical computer is prohibitive. Perhaps protein folding is a quantum computation? (Crowell, 1996).

The main driving force in protein folding occurs as uncharged non-polar groups of particular amino acids join together and avoid water. Repelled by solvent water, "hydrophobic" non-polar groups attract each other (by van der Waals forcessee below) and bury themselves within the protein interior. As a result intra-protein hydrophobic pockets occur, composed of side groups of non-polar (but polarizable) amino acids such as leucine, isoleucine, phenylalanine, tryptophan, tyrosine and valine. Volumes of the pockets (~400 cubic angstroms, or 0.4 cubic nanometers) are roughly 1/30 to 1/250 the total volume of a single protein, and their physical solvent characteristics most closely resemble olive oil.

Though small, hydrophobic pockets may be critical to protein function. For example anesthetic gas molecules which reversibly ablate consciousness exert their effects in hydrophobic pockets of neural proteins (e.g., Franks and Lieb, 1982; 1985). Anesthetics bind in hydrophobic pockets by weak, physical interactions called London dispersion forces, a type of van der Waals force. Why are these weak, localized interactions so important to protein function and consciousness?

Proteins in a living state are dynamical, and only marginally stable. A protein of 100 amino acids is stable against denaturation by only ~40 kiloJoules per mole (kJ mol-^{1}) whereas thousands of kJ mol^{-1} are available in a protein from side group interactions including van der Waals forces. Consequently protein conformation is a "delicate balance among powerful countervailing forces" (Voet and Voet, 1995).

Transitions in proteins occur at many time and size scales. For example small amino acid side chains move in the picosecond to femtosecond time scale (10^{-12} to 10^{-15} sec), and conformational transitions in which proteins move globally and upon which protein function generally depends occur in the nanosecond (10^{-9} sec) to 10 picosecond (10^{-11} sec) time scale (Karplus and McCammon, 1983). These global changes (e.g. as schematically represented in Figure 1a) appear to involve collective actions of various intra-protein activities (e.g. hydrogen bond rearrangements, dipole oscillations, van der Waals forces).

The types of forces operating among amino acid side groups within a protein include charged interactions such as ionic forces and hydrogen bonds, as well as interactions between dipolesseparated charges in electrically neutral groups. Dipole-dipole interactions are known as van der Waals forces and include three types:

1) Permanent dipole - permanent dipole
2) Permanent dipole - induced dipole
3) Induced dipole - induced dipole

Induced dipole - induced dipole interactions are the weakest but most purely non-polar forces. They are known as London dispersion forces, and although quite delicate (40 times weaker than hydrogen bonds) are numerous and influential. The London force attraction between any two atoms is usually less than a few kiloJoules, however thousands occur in each protein. As other forces cancel out, London forces in hydrophobic pockets can govern protein conformational states.

London forces ensue from the fact that atoms and molecules which are electrically neutral and spherically symmetrical nevertheless have instantaneous electric dipoles due to instantaneous asymmetry in their electron distribution. The electric field from each fluctuating dipole couples to others in electron clouds of adjacent non-polar amino acid side groups. Due to inherent uncertainty in electron localization, London forces which govern protein conformation are quantum effects which apparently couple to "zero point fluctuations" of the quantum vacuum (London, 1937; Milloni, 1994).

Quantum level dipole oscillations within hydrophobic pockets were proposed by Frohlich (1968) to regulate protein conformation, and Conrad (1994) suggested proteins utilize quantum superposition of various possible conformations before one is selected. Roitberg et al (1995) showed functional protein vibrations which depend on quantum effects centered in two hydrophobic phenylalanine residues, and Tejada et al (1996) have evidence to suggest quantum coherent states exist in the protein ferritin. Could proteins be utilizing quantum superposition ("qubits") in determining their conformational states (bits)?

The possible situation may be characterized as in Figure 1a using the microtubule protein tubulin as an example. Tubulins are peanut-shaped dimers with two connected monomers and they undergo several types of conformational changes (e.g. Cianci et al, 1986). For example one monomer can shift 30 degrees from the tubulin dimer's vertical axis (Melki et al, 1989; c.f. Yagi et al, 1994). At the top of Figure 1a a tubulin protein switches between two such states, governed by hydrophobic pocket electron pairs coupled by London forces. (Tubulin may actually have several hydrophobic pockets and occupy more than two states, however for simplicity we consider one pocket and two states per protein.) The two possible states in the top of Figure 1a may be viewed as representing one bit of information. If however the hydrophobic pocket electron pair is superposed (Figure 1a, bottom), then protein conformation (if isolated from external environment) is also superposed and exists in both states simultaneously ("qubit"). A properly configured and isolated array of interactive protein qubits could constitute a quantum computer.

III. Microtubules

Interiors of living cells are functionally organized by webs of protein polymers-the cytoskeleton (Figure 2). Major components of the cytoskeleton are microtubules, self-assembling hollow crystalline cylinders whose walls are hexagonal lattices of subunit proteins known as tubulin (Figure 3). Microtubules are essential for a variety of biological functions including cell movement, cell division (mitosis) and establishment and maintenance of cell form and function. In neurons, microtubules self-assemble to extend axons and dendrites and form synaptic connections; microtubules then help maintain and regulate synaptic strengths responsible for learning and cognitive functions. (For a more complete description of the role of microtubules and other cytoskeletal structures in cognitive functions see Dayhoff et al., 1994; Hameroff and Penrose 1996a; Hameroff, 1994). While microtubules have traditionally been considered as purely structural components, recent evidence has demonstrated mechanical signaling and communication functions (Glanz, 1997; Maniotis et al., 1997a; 1997b; Vernon and Wooley, 1995). Microtubules interact with membrane structures and activities by linking proteins (e.g. fodrin, ankyrin) and "second messenger" chemical signals.

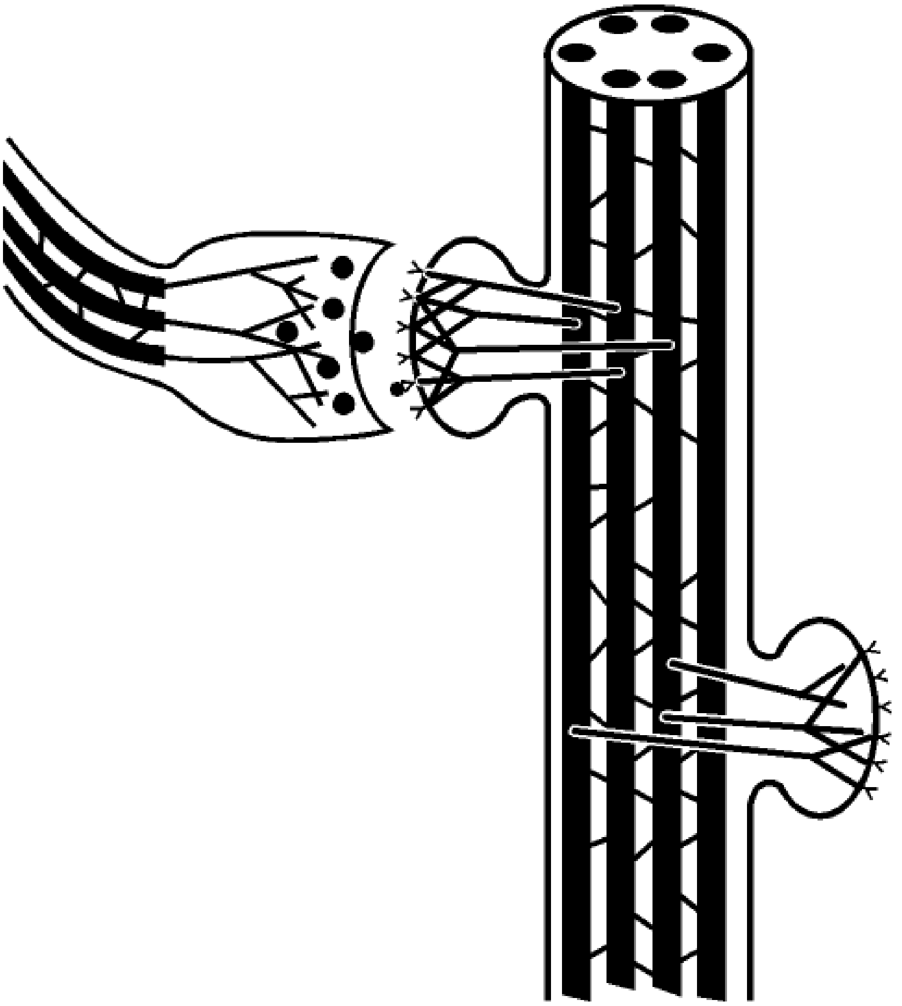

Figure 2. *Schematic of neural synapse showing cytoskeletal structures within two neurons. Left: Pre-synaptic axon terminal releases neurotransmitter vesicles (spheres) into synaptic cleft. Thick rod-like structures within axon are microtubules; thinner filaments (e.g. synapsin) facilitate vesicle release. Right: Dendrite on post-synaptic neuron with two dendritic spines. Microtubules in main dendrite are interconnected by microtubule-associated proteins. Other cytoskeletal structures (fodrin, actin filaments, etc.) connect membrane receptors to microtubules. Based on Hirokawa (1991).*

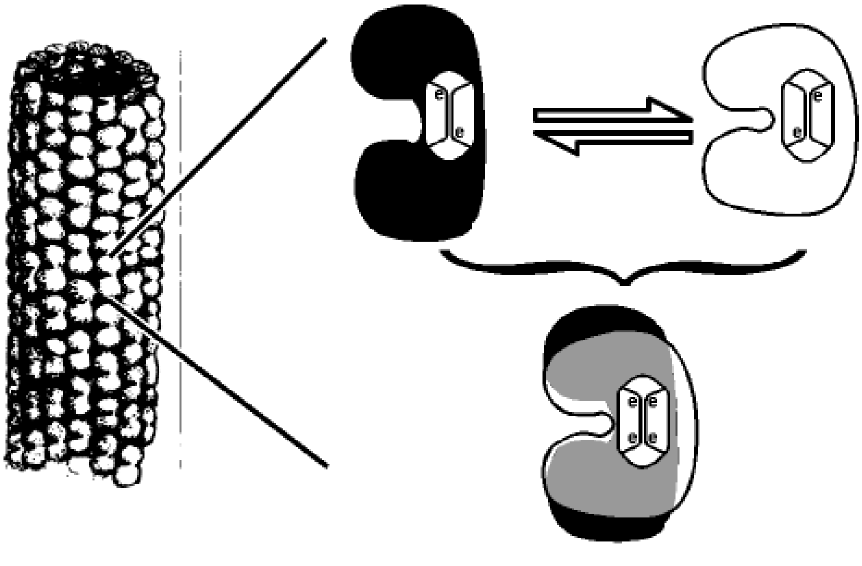

Figure 3. *Left: Microtubule (MT) structure: a hollow tube of 25 nanometers diameter, consisting of 13 columns of tubulin dimers arranged in a skewed hexagonal lattice (Penrose, 1994). Right (top): Each tubulin molecule may switch between two (or more) conformations, coupled to London forces in a hydrophobic pocket. Right (bottom): Each tubulin can also exist in quantum superposition of both conformational states (Figure 1a, c.f. Hameroff and Penrose, 1996).*

How could microtubules implement classical information processing? Theoretical models propose that microtubule subunit tubulins undergo coherent excitations, for example, in the gigaHz range by a mechanism suggested by Frhlich ("pumped phonons"-Frhlich 1968, 1970, 1975; c.f. O. Penrose and L. Onsager, 1956). Frhlich excitations of tubulin subunits within microtubules have been suggested to support computation and information processing (e.g. Hameroff and Watt, 1982; Rasmussen et al., 1990). The coherent excitations are proposed to "clock" computational transitions occurring among neighboring tubulins acting as "cells" as in molecular scale "cellular automata." Dipole coupling among neighboring tubulins in the microtubule lattice act as "transition rules" for simulated *microtubule automata* exhibiting information processing, transmission and learning (Figure 4 - Rasmussen et al, 1990).

Classical microtubule automata switching in the nanosecond scale offer a potentially huge increase in the brain's computational capacity. Conventional approaches focus on synaptic switching (roughly 10^{11} brain neurons, 10^{3} synapses/neuron, switching in the millisecond range of 10^{3} operations per second) and predict about 10^{17} bit states per second for a human brain (e.g. Moravec, 1985). However as biological cells typically each contain approximately 10^{7} tubulins (Yu and Bass, 1994), nanosecond switching in microtubule automata predicts roughly 10^{16} operations per second, per neuron. This capacity could account for the adaptive behaviors of single cell organisms like paramecium, for example, who elegantly swim, avoid obstacles, and find food and mates without benefit of a nervous system or synapses. As the human brain contains about 10^{11} neurons, nanosecond microtubule automata offer about 10^{27} brain operations per second.

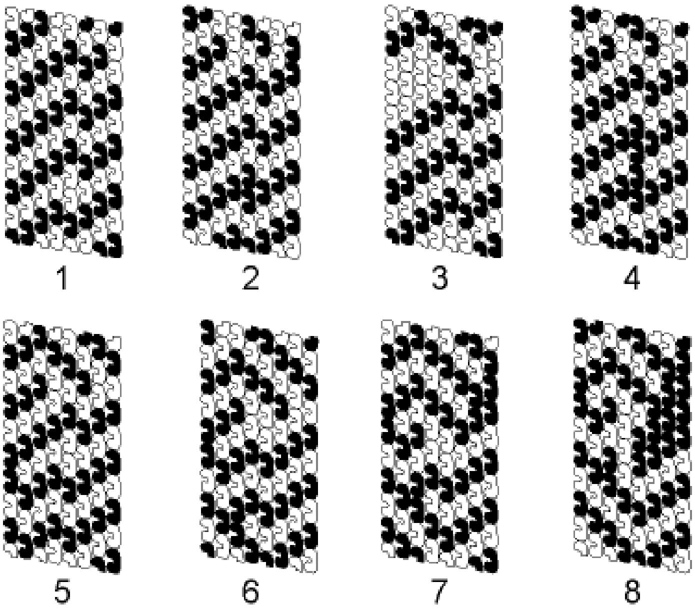

Figure 4. *Microtubule automaton simulation (from Rasmussen et al., 1990). Black and white tubulins correspond to black and white states shown in Figures 1a and 3. Eight nanosecond time steps of a segment of one microtubule are shown in "classical computing" mode in which conformational states of tubulins are determined by dipole-dipole coupling between each tubulin and its six (asymmetrical) lattice neighbors calculated by where y_i and r_i are intertubulin distances, e is the electron charge, and is the average protein permittivity. Conformational states form patterns which move, evolve, interact and lead to emergence of new patterns.*

However even a vast increase in computational complexity won't by itself address the difficult issues related to consciousness. Quantum coherent states and quantum computation with objective reduction (Orch OR) could possibly do so.

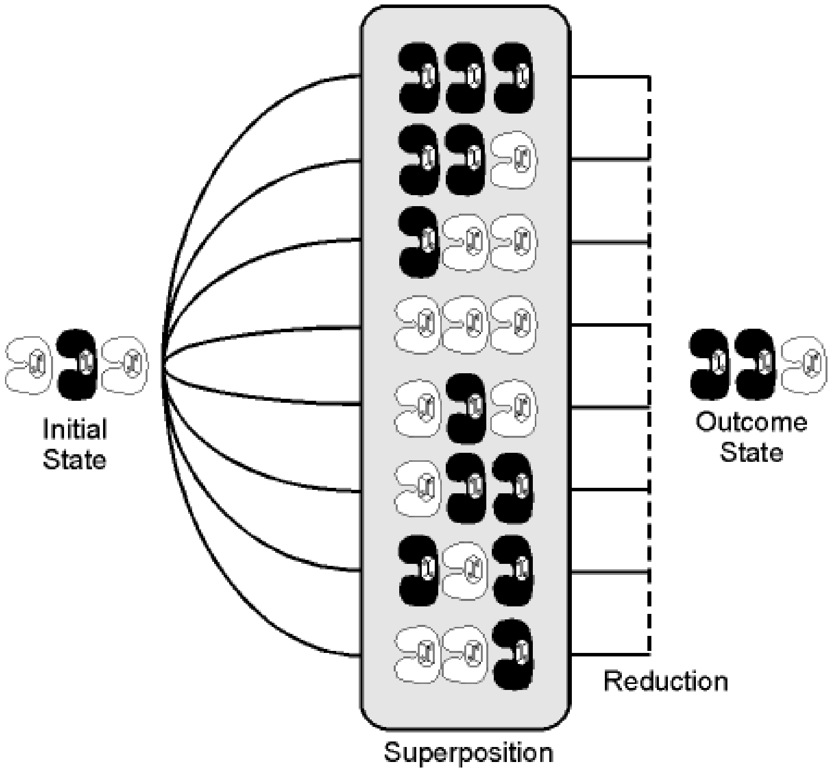

Figure 5. *Schematic of quantum computation of three tubulins which begin (left) in initial classical states, then enter isolated quantum superposition in which all possible states coexist. After reduction, one particular classical outcome state is chosen (right).*

Figure 5 illustrates the general idea for quantum computation with tubulins: 3 tubulins are shown in initial states, in isolated superposition of possible states during which quantum computation occurs, and in single post-reduction outcome states. Figures 6 shows microtubule automata entering quantum computation mode (gray) and meeting objective reduction threshold (between steps 6 and 7) for self-collapse to non-computably chosen outcome states. As described in Figure 7, pre-reduction quantum computation is suggested to correlate with pre-conscious processing, and the objective reduction process itself to a conscious moment. A series of such moments can give rise to a stream of consciousness (see Section V for a more complete description).

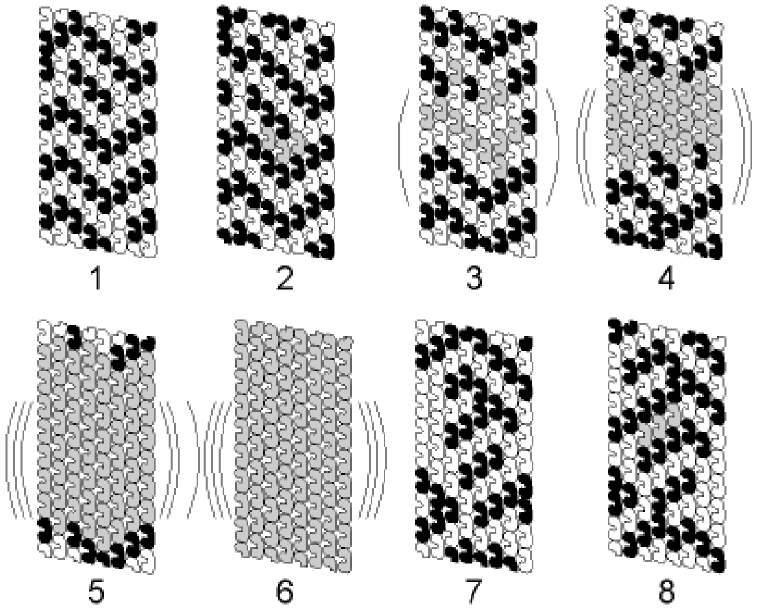

Figure 6. *Microtubule automaton sequence simulation in which classical computing (step 1) leads to emergence of quantum coherent superposition (steps 26) in certain (gray) tubulins due to pattern resonance. Step 6 (in coherence with other microtubule tubulins) meets critical threshold related to quantum gravity for selfcollapse (Orch OR). Consciousness (Orch OR) occurs in the step 6 to 7 transition. Step 7 represents the eigenstate of mass distribution of the collapse which evolves by classical computing automata to regulate neural function. Quantum coherence begins to reemerge in step 8.*

Macroscopic quantum states in brain microtubules would have to somehow avoid environmental decoherence and still communicate with the environment. Nature may have solved this problem with alternating phases of isolation and communication.

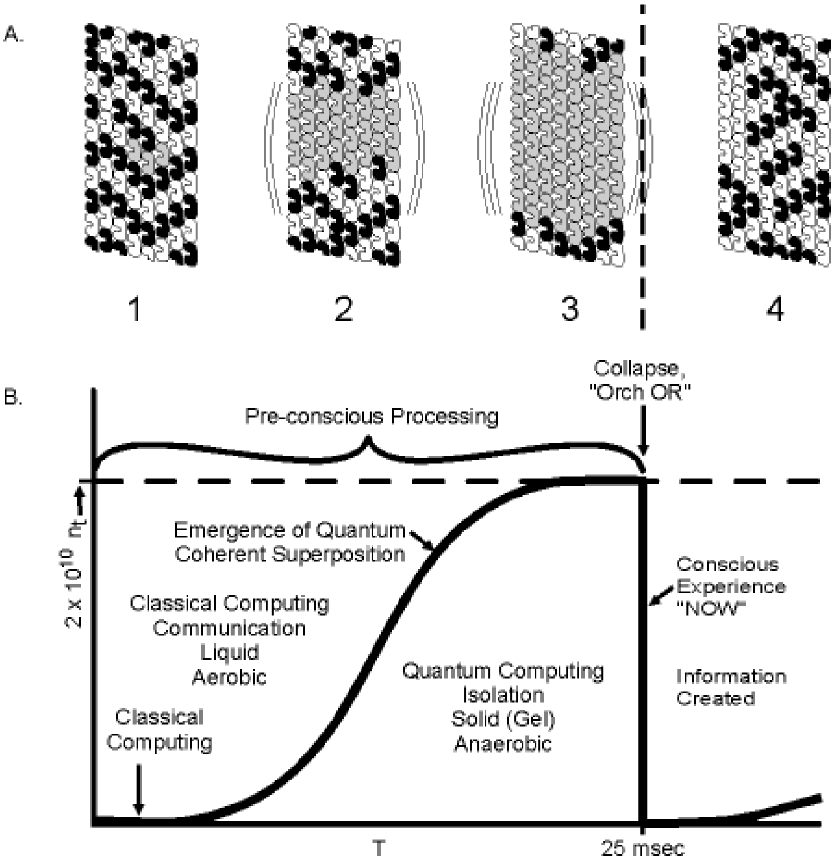

Figure 7. *An Orch OR event. a) Microtubule simulation in which classical computing (step 1) leads to emergence of quantum coherent superposition (and quantum computing (steps 23) in certain (gray) tubulins. Step 3 (in coherence with other microtubule tublins) meets critical threshold related to quantum gravity for selfcollapse (Orch OR). A conscious event (Orch OR) occurs in the step 3 to 4 transition. Tubulin states in step 4 are noncomputably chosen in the collapse, and evolve by classical computing to regulate neural function. b) Schematic graph of proposed quantum coherence (number of tubulins) emerging versus time in microtubules. Area under curve connects superposed mass energy E with collapse time T in accordance with E=/T. E may be expressed as* N_t, *the number of tubulins whose mass separation (and separation of underlying space time) for time T will selfcollapse. For T = 25 msec (e.g. 40 Hz oscillations),* $N_t = 2 \times 10^{10}$ *tubulins.*

Microtubules and other cytoskeletal components are embedded in cytoplasm which exists in alternating phases of 1) "sol" (solution, liquid), and 2) "gel" (gelatinous, solid). Among the most primitive of biological activities, "solgel transformations" within neurons and other living cells are caused by assembly and disassembly of cytoskeletal actin (e.g. regulated by calcium ions through the protein calmodulin, in turn regulated by microtubules). Solgel transformations are essential in basic cellular activities such as ("amoeboid") movement, growth and synaptic formation, and neurotransmitter vesicle release (Miyamoto et al., 1995; Muallem et al., 1995). Transitions can occur rapidly (e.g. 40 solgel cycles per second), and some actin gels can be quite solid, and withstand deformation without transmitted response (Wacchstock et al., 1994). Cyclical encasement of microtubules by actin gels may thus be an ideal quantum isolation mechanism (Figure 8). A biphasic cycle of microtubule computing is thus suggested: 1) a "sol" liquid, communicative phase of classical computation, and 2) a "gel" solid state, isolated quantum computing phase.

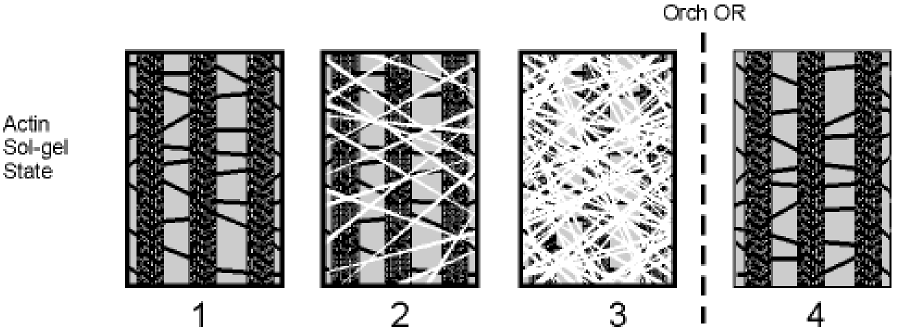

Figure 8. *Schematic sequence of phases of actin gelation/quantum isolation (13) alternating with phases of solution/environmental communication (4) surrounding microtubules. Cycles may occur rapidly, e.g., 25 msec intervals (40Hz).*

Key quantum events may also be shielded either in hollow microtubule cores or intra-protein hydrophobic pockets (where anesthetic gases are known to act). Feasibility of quantum coherence in the internal cell environment is supported by the observation that quantum spins from biochemical radical pairs which become separated retain their correlation in cytoplasm (Walleczek, 1995).

But if isolated cytoplasmic quantum states do occur within neuronal cells, could they traverse membranes and synapses to spread macroscopically throughout the brain? One possibility involves quantum tunneling through gap junctions, primitive electrotonic windows between neurons and glia (Figure 9). Cells interconnected by gap junctions form networks which fire synchronously, "behaving like one giant neuron" (Kandel et al, 1991), and possibly accounting for synchronized neural activity such as coherent 40 Hz (Jibu, 1990). Unlike chemical synapses which separate neural processes by 3050 nanometers, gap junction separations are 3.5 nanometers, within range for quantum tunneling. Widespread but unevenly distributed, high levels of gap junctions appear in thalamus and cortex (Micevych and Abelson, 1991). Thalamocortical networks of gap junctionconnected neurons with sol-gel phases coupled to synchronized 40 Hz activity could transiently isolate quantum states across large brain volumes.

1. **Quantum computing with objective reduction -**

   The Penrose-Hameroff Orch OR model

   Full rationale and details of the Orch OR model are given in Penrose and Hameroff (1995) and Hameroff and Penrose (1996a; 1996b). Key points are listed here:

   1. Conformational states of individual tubulin proteins in brain microtubules are sensitive to internal quantum events (e.g. London forces in hydrophobic pockets) and able to cooperatively interact with other tubulins in both classical and quantum computation (Figures 3-6). Classical phase computation (microtubule automata) regulates chemical synapses and other neural membrane activities (e.g. Figure 2).
   2. Quantum coherent superposition supporting quantum computation emerges among London forces in hydrophobic pockets of microtubule subunit tubulins (e.g. in a manner described by Frohlich, 1968; 1975). In this phase, quantum computation among tubulins evolves linearly according to the Schrdinger equation (quantum microtubule automata). Actin gelation and a condensed charge phase surrounds, isolates and insulates microtubules during the quantum phase.

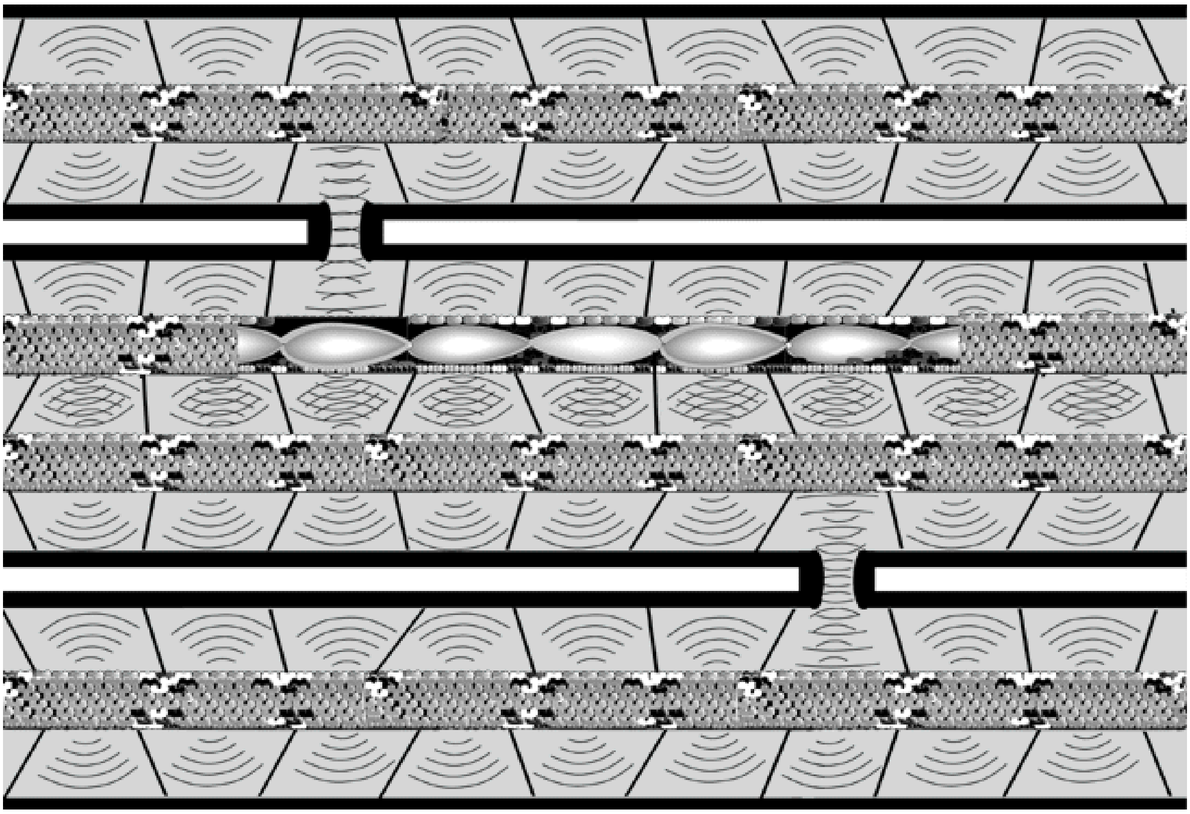

Figure 9. *Schematic of proposed quantum coherence in microtubules in three dendrites interconnected by tunneling through gap junctions. Within each neuronal dendrite, microtubuleassociatedprotein (MAP) attachments breach isolation and prevent quantum coherence; MAP attachment sites thus act as "nodes" which tune and orchestrate quantum oscillations and set possibilities and probabilities for collapse outcomes (orchestrated objective reduction: Orch OR). Gap junctions may enable quantum tunneling among dendrites in macroscopic quantum states.*

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3. The proposed quantum superposition/computation phase in neural microtubules corresponds to preconscious (implicit) processing, which continues until the threshold for Penrose's objective reduction is reached. Objective reduction (OR)-a discrete eventthen occurs (Figures 5-7), and post - OR tubulin states (chosen non-computably) proceed by classical microtubule automata to regulate synapses and other neural membrane activities. The events

are proposed to be conscious (to have qualia, experience) for reasons that relate to a merger of modern physics and philosophical pan-experientialism (see Section V). A sequence of such events gives rise to a stream of consciousness.

4. Microtubule quantum states link to those in other neurons and glia by tunneling through gap junctions (or quantum coherent photons traversing membranes - Jibu and Yasue, 1995; Jibu et al, 1994; 1996). This spread enables macroscopic quantum states in networks of gap junctionconnected cells (neurons and glia) throughout large brain volumes (Figure 9).
5. Probabilities and possibilities for pre-conscious quantum superpositions are influenced by biological feedback including attachments of microtubuleassociated proteins ("MAPs"), which tune and "orchestrate" quantum oscillations (Figure 9). We thus term the selftuning OR process in microtubules "orchestrated" objective reductionOrch OR.
6. Orch OR events may be of variable intensity and duration of preconscious processing. Calculating from E = /T, for a preconscious processing time of e.g. T = 25 msec (thalamo-cortical 40 Hz), E is roughly the superposition/separation of 2 x 10^{10} tubulins. For T = 100 msec (alpha EEG) E would involve 5 x 10^9 tubulins. For T = 500 msec (e.g. shown by Libet et al., 1979, as a typical preconscious processing time for low intensity stimuli), E is equivalent to 10^9 tubulins. Thus 2 x 10^{10} tubulins maintained in isolated quantum coherent superposition for 25 msec (or 5 x 10^9 tubulins for 100 msec, or 10^9 tubulins for 500 msec, etc.) will selfcollapse (Orch OR) and elicit a conscious event.
7. Each brain neuron is estimated to contain about 10^7 tubulins (Yu and Bass, 1994). If, say, 10 percent of each neuron's tubulins became coherent, then Orch OR of tubulins within roughly 20,000 (gapjunction connected) neurons would be required for a 25 msec conscious event, 5,000 neurons for a 100 msec event, or 1,000 neurons for a 500 msec event, etc.
8. Each instantaneous Orch OR event binds superposed information encoded in microtubules whose net displacement reaches threshold at a particular moment: a variety of different modes of information is thus bound into a "now" event. As quantum state reductions are irreversible in time, cascades of Orch OR events present a forward flow of time and "stream of consciousness."

In the following section, applications of the Orch OR model to enigmatic issues of consciousness will be examined.

1. Orch OR and enigmatic features of consciousness

Five enigmatic features of consciousness were described in Section I: 1) the nature of subjective experience, 2) "binding" in vision and sense of "self," 3) transition from pre-conscious processing to consciousness, 4) non-computability and 5) free will. Can Orch OR address these issues?

Problem (1) subjective experience is the most difficult. How does the brain produce 'qualia', raw feelings and sensations? There have always been two types of answers. Socrates argued that consciousness was created by the cerebrum, whereas Thales, Plotinus and other "panpsychists" saw conscious experience as a fundamental feature of reality.

Modern functionalists/computationalists generally follow Socrates: consciousness emerges from complexity in the brain's neural networks. However others find this view alone unable to accommodate subjective experience, and are driven to embrace some form of panpsychism, or pan-experientialism.

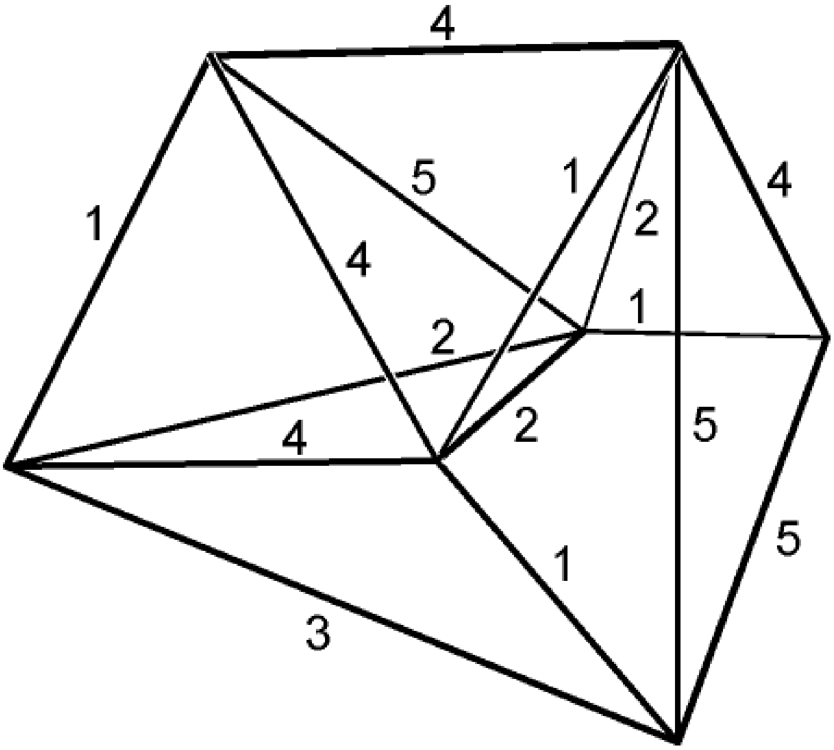

Figure 10. *A spin network. Introduced by Roger Penrose (1971) as a quantum mechanical description of the geometry of space, spin networks describe a spectrum of discrete Planck scale volumes and configurations (with permission from Smolin, 1997; Rovelli and Smolin, 1995a; 1995b). Average length of each edge is the*

Planck length (10^{33} cm). Numbers indicate quantum mechanical spin along each edge. Each quantum state of spacetime is a particular spin network (Smolin, 1997).

Following after ancient panpsychists, Spinoza (1677) assigned rudimentary consciousness to all particles and objects, and Leibniz (e.g. 1766) saw the universe as an infinite number of fundamental units ("monads"), each having a primitive psychological being. Whitehead (e.g. 1929) was a process philosopher who saw the universe as being comprised fundamentally of events. He described dynamic monads with spontaneity and creativity, interpreting them as mind-like entities of limited duration ("occasions of experience"). Each occasion, according to Whitehead, bears a quality akin to "feeling" by virtue of occurring in a "wider field of proto-conscious experience." Could this "wider field" be the universe itself? Could proto-conscious experience exist in empty space?

What is empty space? Democritus described empty space as a true void whereas Aristotle saw a background "plenum" filled with substance. Maxwell's 19th-century "luminiferous ether" sided with Aristotle but attempts to detect the ether failed and Einstein's special relativity agreed with Democritus: empty space was an absolute void. However Einstein's general relativity with its curved space and distorted geometry reverted to a richly-endowed plenumthe spacetime metric.

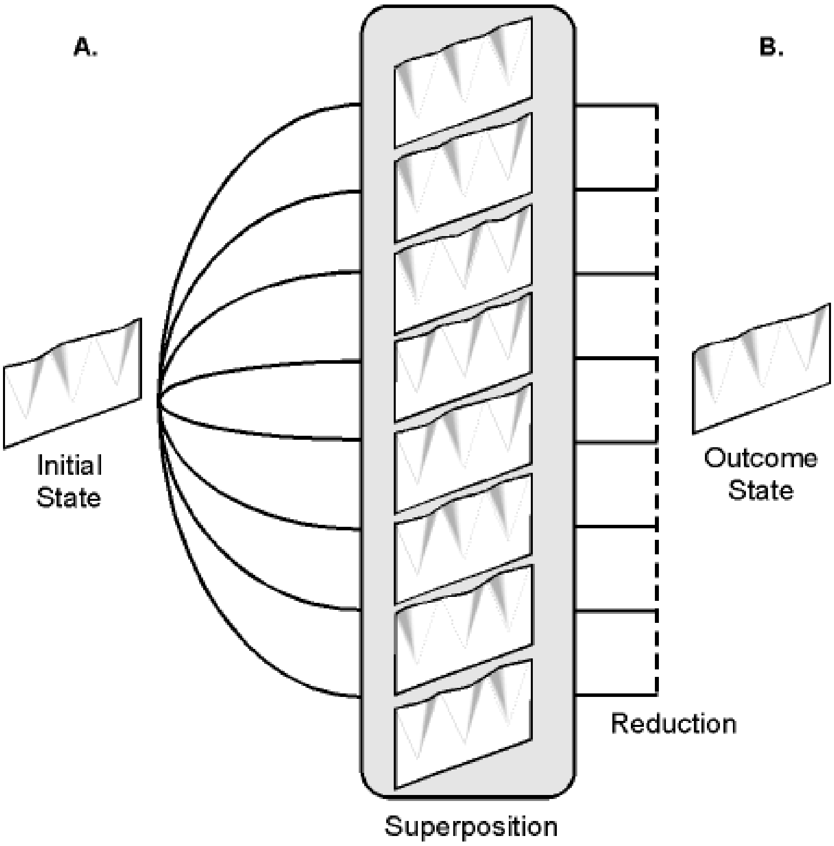

Figure 11. *Schematic quantum computation in spacetime curvature for three mass distributions (e.g. tubulin conformations in Figure 5) which begin (left) in initial classical states, then enter isolated quantum superposition in which all possible states coexist. After reduction, one particular classical outcome state is chosen (right).*

At very small scales spacetime is not smooth, but quantized. Granularity occurs at the incredibly small "Planck scale" (10^{-33} centimeters , 10^{-43} seconds) which Penrose (1971) portrays as a dynamical spider-web of quantum spin networks (Figure 10; Rovelli and Smolin, 1995a; 1995b; Smolin, 1997). Spin networks define spectra of discrete Planck scale volumes and configurations which dynamically evolve and define spacetime geometry. Planck-scale spin networks could provide Whitehead's basic field of proto-conscious experience. Shimony (1993) has suggested Whitehead occasions are quantum state reductions. As described in Section I, Penrose objective (quantum state) reductions are bubble-like separations and collapses in fundamental spacetime geometry extending downward to the level of spin networks. Figure 11 illustrates quantum superposition and objective reduction of spacetime geometry. Orch OR events could be Whitehead occasions of experience

In a panpsychist view consistent with modern physics, Planck scale spin networks encode proto-conscious ("fundamental"") experience (qualia) as well as Platonic values. Particular configurations of quantum spin geometry convey particular varieties of proto-conscious experience, meaning and aesthetics. The proposed Orch OR events occur in the brain, extending downward to processes in an experiential Planck scale medium. The basic idea is that consciousness involves brain activities coupled to self-organizing ripples in fundamental reality.

How can near-infinitesimal proto-conscious information link to macroscopic biology? As described in Section VI, the Orch OR process may be an emergent phenomenon in quantum geometry mediated through London forces in hydrophobic pockets of tubulin and other proteins.

The second difficult issue related to consciousness is (2) binding and it is potentially resolved by the unitary nature of quantum states (e.g. Penrose, 1987). Marshall (1989) suggested that binding was a feature of Bose-Einstein condensates among certain of the brain's neural proteins. In the Orch OR model, an instantaneous event binds superposed information whose net mass/spacetime displacement reaches threshold at a particular moment: different modes and time scales of information are bound into a unitary "now" event.

Problem (3) is the transition from pre-conscious processing to consciousness itself. In Orch OR pre-conscious processing is equivalent to the quantum superposition phase of quantum computation. Potential possibilities interact and then abruptly self-collapse, a slight quake in spacetime geometry. As quantum state reductions are irreversible, cascades of Orch OR events present a forward flow of subjective time and "stream of consciousness."

Quantum computation with objective reduction is potentially applicable to cognitive activities. Functions like face recognition and volitional choice may require a series of conscious events arriving at intermediate solutions. For the purpose of illustration consider single Orch OR events in these two types of cognitive activities.

Imagine you briefly see a familiar woman's face. Is she Amy, Betty, or Carol? Possibilities may superpose in a quantum computation. For example during 25 milliseconds of pre-conscious processing, quantum computation occurs with information (Amy, Betty, Carol) in the form of "qubits"superposed states of microtubule tubulin subunits within groups of neurons. As threshold for objective reduction is reached, an instantaneous conscious event occurs. The superposed tubulin qubits reduce to definite states, becoming bits. Now, you recognize that she is Carol! (an immense number of possibilities could be superposed in a human brain's 10^{19} tubulins).

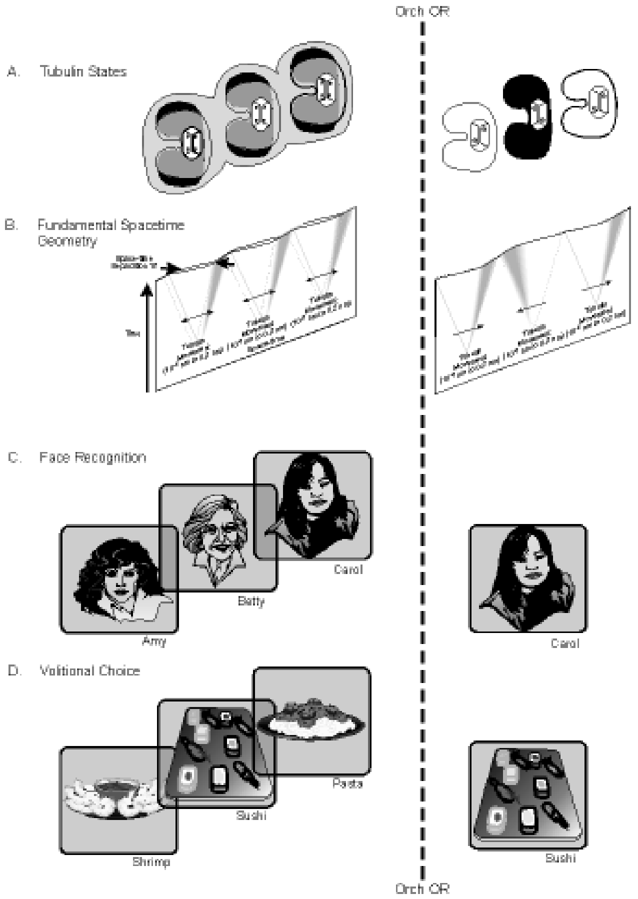

Figure 12. *An Orch OR event (continued from Figure 4). a) (left) Three tubulins in quantum superposition prior to 25 msec Orch OR After reduction (right), particular classical states are selected. b) Fundamental spacetime geometry view. Prior to Orch OR (left), spacetime corresponding with three superposed tubulins is separated as Planck scale bubbles: curvatures in opposite directions. The Planckscale spacetime separations S are very tiny in ordinary terms, but relatively large mass movements (e.g., hundreds of tubulin conformations, each moving from 10^6 to 0.2 nm) indeed have precisely such very tiny effects on the spacetime curvature. A critical degree of separation causes Orch OR and an abrupt selection of single curvatures (and a particular geometry of experience). c) Cognitive facial recognition. A familiar face induces superposition (left) of three possible solutions (Amy, Betty, Carol) which "collapse" to the correct answer Carol (right). d) Cognitive volition. Three possible dinner selections (shrimp, sushi, pasta) are considered in superposition (left), and collapse via Orch OR to choice of sushi (right).*

In a volitional act possible choices may be superposed. Suppose for example you are selecting dinner from a menu. During pre-conscious processing, shrimp, sushi and pasta are superposed in a quantum computation. As threshold for objective reduction is reached, the quantum state reduces to a single classical state. A choice is made. You'll have sushi!

How does the choice actually occur? Can the selection criteria be described by a deterministic algorithm? These questions relate to problems (4) non-computability and (5) free will.

The problem in understanding free will is that our actions seem neither totally deterministic nor random (probabilistic).

What else is there in nature? As previously described, in OR (and Orch OR) the reduction outcomes are neither deterministic nor probabilistic, but "non-computable." The microtubule quantum superposition evolves linearly (analogous to a quantum computer) but is influenced at the instant of collapse by hidden non-local variables (? quantum-mathematical logic inherent in fundamental spacetime geometry). The possible outcomes are limited, or probabilities set ("orchestrated"), by neurobiological feedback (in particular microtubule associated proteins-MAPs, Figure 9). The precise outcomeour free will actionsare chosen by effects of the hidden logic on the quantum system poised at the edge of objective reduction.

Consider a sailboat analogy for free will. A sailor sets the sail in a certain way; the direction the boat sails is determined by the action of the wind on the sail. Let's pretend the sailor is a non-conscious robot zombie run by a quantum computer which is trained and programmed to sail. Setting and adjusting of the sail, sensing the wind and position and so forth are algorithmic and deterministic, and may be analogous to the pre-conscious, quantum computing phase of Orch OR. The direction and intensity of the wind (seemingly capricious, or unpredictable) may be analogous to Planck scale hidden non-local variables (e.g. "Platonic" quantum-mathematical logic inherent in space-time geometry). The choice, or outcome (the direction the boat sails, the point on shore it lands) depends on the deterministic sail settings acted on repeatedly by the apparently unpredictable wind. Our "free will" actions could be the net result of deterministic processes acted on by hidden quantum logic at each Orch OR event. This can explain why we generally do things in an orderly, deterministic fashion, but occasionally our actions or thoughts are surprising, even to ourselves.

Biological quantum computation intrinsic to brain function such as the proposed Orch OR model can in principle address difficult issues related to consciousness.

VI. Are microtubules quantum computers?

The idea of biological quantum computation connected to fundamental geometry seems far-fetched. The Planck length is 24 orders of magnitude smaller than the diameter of an atom. Approximately 10^{78} discrete Planck scale volumes correspond to the space occupied by one protein, and 10^{105} such volumes to a brain. The energy of one proposed Orch OR (e.g. 25 msec) is only 10^{-28} joules, or 10^{-10} electron volts (eV) whereas the energy of thermal noise (kT) is much larger at 10^{-4} eV. How could near-infinitesimally small, weak and fast processes have macroscopic effects in biological systems? Orch OR may be viewed as a nonlinear phenomenon in which particular configurations of 10^{88} Planck scale volumes emerge 40 times per second to influence protein conformation through delicately balanced London forces. Conditions supporting quantum states and primitive consciousness would favor survival and have naturally evolved (Hameroff, 1998).

In an accompanying paper in this volume, Tuszynski and Brown (1998) review the physics of microtubules and critique the Orch OR proposal. They raise several issues which are discussed in Appendix I.

Here similarities are sought between microtubules and technological proposals for quantum computation. A "potentially realizable" quantum computer has been described by Lloyd (1993) as ". . . arrays of weakly coupled quantum systems. Computation is effected by . . . . a sequence of electromagnetic pulses that induce transitions between locally defined quantum states. . . in a crystal lattice."

In the Orch OR model, the microtubule assembly corresponds to Lloyd's crystal lattice. Rather than trapped ions or nuclear spins, quantum superposition is proposed to occur at the level of conformational states of tubulins, and the role of pulsed transitions played by coherent Frhlich excitations.

The Orch OR proposal may be compared to technological schemes in terms of a "Figure of Merit M" (Table 1; Barenco, 1996; DiVincenzo, 1995). M is the time $T_{decohere}$ until decoherence divided by the time t_{elem} of each elementary operation, and gives the number of operations allowable per computational unit before decoherence. With t_{elem} of 10^{9} secs (Frhlich frequency) and $T_{decohere}$ of e.g. 100 msec (EEG alpha), the Orch OR model yields a respectable M of 10^{8} operations per tubulin before a conscious event occurs.

TableFigure of Merit M for different proposed quantum computing technologies and microtubules. (Modified from Barenco, 1996 and from DiVincenzo, 1995).

Technology	**t_{elem} (seconds)**	**$T_{decohere}$ (in seconds)**	**M (pre-decoherence operations/qubit)**
Mossbauer nucleus	10^{-19}	10^{-10}	10^{9}
Electrons GaAs	10^{-13}	10^{-10}	10^{3}
Electrons Au	10^{-14}	10^{-8}	10^{6}
Trapped ions	10^{-14}	10^{-1}	10^{13}
Optical cavities	10^{-14}	10^{-5}	10^{9}
Electron spin	10^{-7}	10^{-3}	10^{4}
Electron quantum dot	10^{-6}	10^{-3}	10^{3}
Nuclear spin	10^{-3}	10^{4}	10^{7}

Superconductor islands	10^{-9}	10^{3}	10^{6}
Microtubule tubulins	10^{-9}	10^{-1}	10^{8}

According to the proposals put forth in the Orch OR model, microtubules seem to be well designed (perhaps ideally designed) quantum computers. If so, technological efforts can possibly mimic some of nature's design principles such as cylindrical lattice automata and alternating phases of isolation and communication. The massive parallelism and specific microtubule lattice geometry (e.g. helical patterns following the Fibonacci series) may also facilitate quantum error correction. However technology will be hard-pressed to emulate objective reduction which, it is argued, is required for consciousness. Presently envisioned technological quantum computers will implement superposition of ions, electrons, nuclei or other small entities. To achieve objective reduction in a reasonable and useful time scale, a fairly large superposed mass (i.e. nanograms) will be required. While such a task seems formidable, it is possible. Quantum computation with objective reduction may hold the only promise for conscious computers.

Regardless of whether or not the Orch OR proposal turns out to be correct (and unlike most theories of consciousness it is testable - Appendix 2), it is the type of multi-level, trans-disciplinary approach needed to address the problem of consciousness.

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References

Andreu, J.M. (1986) Hydrophobic interaction of tubulin. Ann. NY Acad. Sci. 466:626630.

Aspect, A., Grangier, P., and Roger, G. (1982) Experimental realization of Einstein-Podolsky-Rosen-Bohm *Gedankenexperiment*: a new violation of Bell's inequalities. Phys. Rev. Lett. 48:91-94.

Baldwin, R.L. (1994) Matching speed and stability. Nature 369: 183-84.

Barenco A (1996) Quantum physics and computers. Contemporary Physics 37(5):375-389

Beck, F. and Eccles, J.C. (1992) Quantum aspects of brain activity and the role of consciousness. Proc. Natl. Acad. Sci. USA 89(23):1135711361.

Benioff, P. (1982) Quantum mechanical Hamiltonian models of Turing Machines. J. Stat. Phys. 29:515546.

Bennett CH (1995) Quantum information and computation. Physics Today October:24-30

Bohm, D. and Hiley B.J. (1993) The Undivided Universe. Routledge, New York

Chalmers, D. J., (1996a) The conscious mind In search of a fundamental theory. Oxford University Press, New York.

Churchland, P.S. (1986) Neurophilosophy: Toward a Unified Science of the MindBrain, Cambridge, MA, MIT Press

Churchland, P.S., and Sejnowski, T.J. (1992) The Computational Brain, Cambridge, MA, MIT Press

Cianci, C., Graff, D., Gao, B., and Weisenberg, R.C. (1986) ATPdependent gelationcontraction of microtubules in vitro. Ann. NY Acad. Sci. 466:656659.

Conrad, M. (1994) Amplification of superpositional effects through electronicconformational interactions. Chaos, Solitons and Fractals 4:423438

Crick, F. and Koch, C. (1990) Towards a neurobiological theory of consciousness. Seminars in the Neurosciences 2: 263275

Crowell, L. (1996). Personal communication.

Cruzeiro-Hansson, L. (1996) Dynamics of a mixed quantum-classical system of finite temperature. Europhysics Letters 33(9):655-659.

Cruzerio-Hansson, L., Takeno, S. (1997) Davydov model: The quantum, mixed quantum-classical and full classical systems. Physical Review E 56 (1):894-906.

Dayhoff, J., Hameroff, S., Lahoz-Beltra, R., and Swenberg, C.E. (1994) Cytoskeletal involvement in neuronal learning: a review. European Biophysics Journal 23:79-83.

Dennett, D. (1991) Consciousness explained. Boston, Little, Brown.

Dermietzel, R., and Spray, D.C. (1993) Gap junctions in the brain:where what type, how many and why? Trends in Neurosciences 16(5): 186192

Deutsch, D. (1985) Quantum theory, the ChurchTuring principle and the universal quantum computer. Proc. Royal Soc. (London) A400:97117.

Deutsch, D., and Josza, R. (1992) Rapid solution of problems by quantum computation. Proc. Royal Soc. (London) A439:553556.

Devlin, T.M. (1992) Textbook of Biochemistry with Clinical Correlations, Third Edition. Wiley-Liss, New York, pp. 74-75.

DiVincenzo, D. (1995) Physical Review A 50:1015.

Engelborghs, Y. (1992) Dynamic aspects of the conformational states of tubulin and microtubules. Nanobiology 1:97105.

Feynman, R.P. (1986) Quantum mechanical computers. Foundations of Physics 16(6):507531.

Frohlich, H. (1968) Longrange coherence and energy storage in biological systems. Int. J. Quantum Chem. 2:6419.

Frohlich, H. (1970) Long range coherence and the actions of enzymes. Nature 228:1093.

Frohlich, H. (1975) The extraordinary dielectric properties of biological materials and the action of enzymes. Proc. Natl. Acad. Sci. 72:42114215.

Franks and Lieb (1985) Mapping of general anesthetic target sites provides a molecular basis for cut-off effects. Nature 316:349-351.

Franks, N.P., and Lieb, W.R. (1982) Molecular mechanisms of general anesthesia. Nature 316:349351

Genberg, L., Richard, L., McLendon, G., and DwayneMiller, R.J. (1991) Direct observation of global protein motion in hemoglobin and myoglobin on picosecond time scales. Science, 251:10511054.

Genzel, L., Kremer, F., Poglitsch, A., and Bechtold, G. (1983) Relaxation processes on a picosecond time scale in hemoglobin and poly observed by millimeterwave spectroscopy. Biopolymers 22:1715 1729.

Glanz, J. (1997) Forcecarrying web pervades living cell. Science 276:678679

Gray, J.A. (1998) Creeping up on the hard question of consciousness. In: Toward a Science of Consciousness II The Second Tucson Discussions and Debates. Eds S Hameroff, A Kaszniak, A Scott. MIT Press, Cambridge MA pp 279-291

Grundler, W., and Keilmann, F. (1983) Sharp resonances in yeast growth prove nonthermal sensitivity to microwaves. Phys Rev Lett 51:12141216.

Halsey, M.J. (1989) Molecular mechanisms of anesthesia. In: General Anaesthesia, Fifth Edition. J.F. Nunn, J.E Utting and B.R. Brown, Jr. (Eds.) Butterworths, London, pp. 19-29.

Hameroff S.R., and Watt R.C. (1982) Information processing in microtubules. Journal of Theoretical Biology 98:549561

Hameroff S.R. and Watt R.C. (1983) Do anesthetics act by altering electron mobility? Anesth. Analg. 62, 936-940.

Hameroff SR (1997a) Quantum computing in microtubules-An Intra-neural correlate of consciousness? Japanese Bulletin of Cognitive Science 4 (3): 67-92.

Hameroff, S (1998b) Did consciousness cause the Cambrian evolutionary explosion? In: Toward a Science of Consciousness II The Second Tucson Discussions and Debates. Eds S Hameroff, A Kaszniak, A Scott. MIT Press, Cambridge MA pp 421-437

Hameroff, S (1998c) "More neural than thou": Reply to Churchland's "Brainshy" in: Toward a Science of Consciousness II The Second Tucson Discussions and Debates. Eds S Hameroff, A Kaszniak, A Scott. MIT Press, Cambridge MA pp 197-213

Hameroff, S. (1998a) Fundamental geometry: The PenroseHameroff Orch OR model of consciousness. In: Geometry and the foundations of science. Contributions from an Oxford conference honoring Roger Penrose. Oxford Press (in press)

Hameroff, S.R. (1994) Quantum coherence in microtubules: A Neural basis for emergent consciousness. Journal of Consciousness Studies 1 (1):91-118.

Hameroff, S.R. (1998) "Funda-Mentality" - Is the conscious mind subtly connected to a basic level of the universe? Trends in Cognitive Science (in press).

Hameroff, S.R., and Penrose, R. (1996b) Conscious events as orchestrated spacetime selections. Journal of Consciousness Studies 3(1):3653.

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, S.R. Hameroff, A. Kaszniak and A.C. Scott (eds.), MIT Press, Cambridge, MA. Also published in Mathematics and Computers in Simulation 40:453480.

Haroche S, Raimond JM (1996) Quantum computing: Dream or nightmare? Physics Today (August) 5152

Hirokawa, N. (1991) Molecular architecture and dynamics of the neuronal cytoskeleton. In The neuronal cytoskeleton, Ed. R. Burgoyne. New York, Wiley-Liss, pp. 5-74

Hunt C, Stebbings H (1994) Role of MAPs and motors in the bundling and shimmering of native microtubules from insect ovarioles Cell Motility and the Cytoskeleton 27:6978

Jibu M, Pribram K.H., Yasue K (1996) From conscious experience to memory storage and retrieval: The role of quantum brain dynamics and Boson condensation of evanescent photons. Int J Modern Physics B 10 (13 and 14):17351754

Jibu, M., (1990) On a heuristic model of the coherent mechanism of the global reaction process of a group of cells. Bussei Kenkyuu (Material Physics Research) 53 (4):431436 (in Japanese)

Jibu, M., Hagan, S., Hameroff, S.R., Pribram, K.H., and Yasue, K. (1994) Quantum optical coherence in cytoskeletal microtubules: implications for brain function. BioSystems 32:195209.

Jibu, M., Yasue, K. (1995) Quantum brain dynamics: an introduction. John Benjamins, Amsterdam

Joliot M, Ribary U, Llinas R (1994) Human oscillatory brain activity near 40 Hz coexists with cognitive temporal binding. Proc. Natl. Acad. Sci. USA 91(24):1174811751

Kandel ER, Siegelbaum SA, Schwartz JH (1991) Synaptic transmission. In Principles of Neural Science (Third Edition) Eds: ER Kandel, JH Schwartz, TM Jessell. Elsevier NY pp 121134

Karplus, M., and McCammon, J.A. (1983) Protein ion channels, gates, receptors. In pp 263300. Dynamics of Proteins: Elements and Function, Ann. Rev. Biochem., J. King (ed.), Benjamin/Cummings, Menlo Park.

Leggett, A.J. (1984) Schrdinger's cat and her laboratory cousins. Contemp. Phys. 25(6):582.

Leibniz, G.W. (1768) Opera Omnia. 6 volumes, Louis Dutens, ed. Geneva

Libet, B., Wright, E.W. Jr., Feinstein, B., and Pearl, D.K. (1979) Subjective referral of the timing for a conscious sensory experience. Brain 102:193224.

Lloyd, S. (1993) A potentially realizable quantum computer. Science 261:15691571

London, F. (1937) Transactions of the Faraday Society 33:8.

Maniotis A.J., Bojanowski K, Ingber D.E. (1997a) Mechanical continuity and reversible chromosome disassembly within intact genomes removed from living cells. Journal of Cellular Biochemistry 65:114130

Maniotis A.J., Chen C.S., Ingber D.I. (1997b) Demonstration of mechanical connections between integrins, cytoskeletal filaments, and ucleoplasm that stabilize nuclear structure. Proc. Natl. Acad. Sci. USA 94:849854 Cell Biology

Marshall, I.N. (1989) Consciousness and BoseEinstein condensates. New Ideas in Psychology 7:73 83.

Melki, R., Carlier, M.F., Pantaloni, D., and Timasheff, S.N. (1989) Cold depolymerization of microtubules to double rings: geometric stabilization of assemblies. Biochemistry 28:91439152.

Micevych, P.E., Abelson, L (1991) Distribution of mRNAs coding for liver and heart gap junction protein in the rat central nervous system Journal of Comparative Neurology 305:96118

Milloni (1994) The Quantum Vacuum.

Miyamoto S. (1995) Changes in mobility of synaptic vesicles with assembly and disassembly of actin network. Biochimica et Biophysica Acta 1244:8591

Moravec H.P. (1987) Mind Children. University Press, San Francisco

Muallem S, Kwiatkowska K, Xu X, Yin HL (1995) Actin filament disassembly is a sufficient final trigger for exocytosis in nonexcitable cells. Journal of Cell Biology 128:589598

Nagel, T. (1974) What is it like to be a bat? Philosophical Review 83:435-450.

Neubauer, C., Phelan, A.M., Keus, H., and Lange, D.G. (1990) Microwave irradiation of rats at 2.45 GHz activates pinocytoticlike uptake of tracer by capillary endothelial cells of cerebral cortex. Bioelectromagnetics 11:261268.

Nogales, E., Wolf, S.G., Downing, K.H. (1998) Structure of the tubulin dimer by electron crystallography. Nature 391:199-203.

Penrose, O., Onsager, L. (1956) BoseEinstein condensation and liquid helium. Phys. Rev. 104:576584.

Penrose, R. (1971) in Quantum Theory and Beyond. ed E.A. Bastin, Cambridge University Press, Cambridge, U.K.

Penrose, R. (1987) Newton, quantum theory and reality. In 300 Years of Gravity, Eds. S.W. Hawking and W. Israel, Cambridge, U.K., Cambridge Press

Penrose, R. (1989) The Emperor's New Mind, Oxford Press, Oxford, U.K.

Penrose, R. (1994) Shadows of the Mind, Oxford Press, Oxford, U.K.

Penrose, R. (1996) On gravity's role in quantum state reduction. General relativity and gravitation. 28(5): 581600

Penrose, R. (1997) On understanding understanding. International Studies in the Philosophy of Science 11(1):7-20.

Penrose, R., Hameroff, S.R. (1995) What gaps? Reply to Grush and Churchland. Journal of Consciousness Studies 2(2):99-112.

Pribram, K.H. (1991) Brain and Perception (Lawrence Erlbaum, New Jersey)

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 42:428449.

Roitberg A, Gerber RB, Elber R, Ratner MA (1995) Anharmonic wave functions of proteins: quantum selfconsistent field calculations of BPTI. Science 268:(5315):13191322

Rovelli C, Smolin L (1995a) Discreteness of area and volume in quantum gravity. Nuclear Physics B 442:593619

Rovelli C, Smolin L (1995b) Spin networks in quantum gravity. Physical Review D 52(10)57435759

Shimony, A., (1993) Search for a Naturalistic World View Volume II. Natural Science and Metaphysics. Cambridge University Press, Cambridge, U.K.

Shor, P.W. (1994) Polynomial time algorithms for discrete logarithms and factoring on a quantum computer. In: Algorithmic Number Theory. First International Symposium, ANTS1 Proceedings, Eds. L.M. Adleman and M.D. Huang, SpringerVerlag, Berlin.

Singer, W., Gray, C., Engel, A., Konig,P., Artola, A., Brocher, S. (1990) Formation of cortical cell assemblies. Cold Spring Harbor Symposia on Quantitative Biology 55:939952.

Smolin, L. (1997) Life of the Cosmos, Oxford Press, N.Y.

Spinoza, B. (1677) Ethica in Opera quotque reperta sunt. 3rd edition, eds. J. van Vloten and J.P.N. Land (Netherlands: Den Haag)

Stapp, H.P. (1993) Mind, matter and quantum mechanics. Berlin, SpringerVerlag

Stebbings, H., Hunt, C. (1982) The nature of the clear zone around microtubules. Cell Tissue Res. 227:609-617.

Tejada J, Garg A, Gider S, Awschalom DD, DiVincenzo DP, Loss D (1996) Does macroscopic quantum coherence occur in ferritin? Science 272:424426

Tuszynski J.A., Brown, J.A. (1998) Dielectric polarization, electrical conduction, information processing and quantum computation in microtubules, are they plausible? This Volume

Tuszynski, J., Hameroff, S., Sataric, M.V., Trpisova, B., and Nip, M.L.A. (1995) Ferroelectric behavior in microtubule dipole lattices; implications for information processing, signaling and assembly/disassembly. J. Theor. Biol. 174:371380

Vernon GG, Woolley DM (1995) The propagation of a zone of activation along groups of flagellar doublet microtubules. Experimental Cell Research 220 (2):482494

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

Vos, M.H., Rappaport, J., Lambry, J. Ch.,Breton, J., Martin, J.L. (1992) Visualization of coherent nuclear motion in a membrane protein by femtosecond laser spectroscopy. Nature 363:320325.

Wachsstock DH, Schwarz WH, Pollard TD (1994) Crosslinker dynamics determine the mechanical properties of actin gels. Biophysical Journal 66 (3 Pt 1):801809

Walleczek, J. (1995) Magnetokinetic effects on radical pairs: a possible paradigm for understanding subkT magnetic field interactions with biological systems. in Electromagnetic Fields: Biological Interactions and Mechanisms. M Blank (ed) Advances in Chemistry No 250 American Chemical Society Books Washington DC

Watterson, J.G. (1991) The interaction of water and proteins in cellular function. Prog. Molec. Subcell. Biol. 12:113-134

Wheeler, J.A. (1990) Information, physics, quantum: The search for links. In (W. Zurek, ed.) Complexity, Entropy, and the Physics of Information. AddisonWesley.

Whitehead, A.N., (1929) Process and Reality. Macmillan, N.Y.

Yagi T, Kamimura S, Kamiya R (1994) Nanometer scale vibration in mutant axonemes of Chlamydonas Cell Motility and the Cytoskeleton 29:177185

Yu, W., and Baas, P.W. (1994) Changes in microtubule number and length during axon differentiation. J. Neuroscience 14(5):28182829.

Appendix 1. Reply to Tuszynski and Brown

In an accompanying article in this volume, Tuszynski and Brown (1998) review physics of microtubules and critique the Orch OR proposal. They raise several issues discussed here.

Gravitational effects should be entirely overshadowed by the remaining processes. The energy from an Orch OR event is indeed very small compared to thermal noise (kT) and would seemingly drown in an aqueous medium. Isolation/insulation mechanisms are thus required to shield microtubules from thermal noise or any type of environmental decoherence. The Orch OR model suggests that quantum coherent superposition occurs in microtubules which are immediately surrounded by an insulating charge condensation and encased (cyclically) in actin gelation (Section III). Cyclical isolation allows for alternating phases of communication (input/output) and isolated quantum computation.

In addition to isolation, microtubule subunits (tubulins) must also be sensitive to quantum influences from other superposed tubulins and non-computable influences in Planck scale geometry. In questioning the robustness of proposed quantum effects, Tuszynski and Brown ascribe the gravitational energy for a tubulin protein in Orch OR to be the attraction between two masses given by the standard Gm^2/r, where G is the gravitational constant, m is the mass of tubulin, and r

is the distance between the two masses which Tuszynski and Brown take to be the radius of tubulin. This would accurately describe the gravitational attraction between two adjacent tubulins (or tubulin monomers), and yields an appropriately small energy of 10^{-27} eV. However the relevant energy in Orch OR is the gravitational self-energy E of a superposed mass m separated from itself by distance a, given (for complete separation) by $E=Gm^2/a$. In Hameroff and Penrose (1996) we calculated this energy for three cases: 1) partial separation of the entire protein by one tenth its radius, and 2) complete separation at the level of each proteins atomic nuclei (a=2.5 fermi lengths), and 3) complete separation at the level of each protein's nucleons (a=0.5 fermi). Of these, highest energies were for separation at the level of atomic nuclei, roughly 10^{-21} eV per tubulin (although separation at the level of, say, atoms or amino acids may yield higher energy). As roughly 2×10^{10} tubulins are involved in each proposed Orch OR event (e.g. for superpositions lasting 25 msec) the energy is on the order of roughly 10^{-10} eV, or 10^{-28} joules, still extremely tiny (kT is about 10^{-4} eV). However the 10^{-28} joule energy emerges abruptly, e.g. within one Planck time of 10^{-43} seconds. This may be equivalent to an instantaneous jab of 10^{13} watts (joules/sec), roughly 1 kilowatt per tubulin.

The size of the tubulin protein is probably too large to make quantum effects easily sustainable. Nanometer size proteins such as tubulin (8 nm x 4 nm x 4 nm) may be optimal scale for a quantum/macroscopic interface (Watterson 1991, Conrad 1994). Smaller biomolecules lack causal efficacy of structural protein conformational changes responsible for a host of biological functions. Larger molecules would be insufficiently sensitive to quantum effects.

Conformational effects are expected to involve distances of 10 angstroms (1 nanometer), larger than those called for in the Orch OR model. The superposition separation distance (e.g. 1 atomic nucleus, 10^{-6} nanometer in the case cited) is indeed much smaller than conformational changes which may approach 1 nanometer. As described in Section II proteins are relatively unstable and their conformation regulated through nonlinear "quakes" mediated through quantum-level London forces.

Physiological temperature requirements make it extremely difficult to defend the use of the quantum regime due to the persistence of thermal noise. A biological quantum state must be isolated/insulated from thermal noise, a feature nature may have evolved in cytoplasmic actin gelation and condensed charged layers (Section III). Some evidence supports biological quantum states (e.g. Tejada et al, 1996; Walleczek, 1995). According to the Frhlich mechanism, thermal energy in biological systems may condense to a coherent mode.

EI>microtubules are extremely sensitive to their environmentEe doubt that microtubules can be shielded. As described in Section III, nature may have solved the problem of both isolation and communication by alternating cytoplasmic phases of solution ("sol", liquid, sensitive to environment, classical) and gelation ("gel", solid, shielded/insulated, quantum). Thus microtubules can be both sensitive to their environment ("sol" phase) and isolated/shielded ("gel" phase).

Ewo (or possibly more) conformational states of tubulin are separated by a sizable potential barrier which again requires an external stimulus (such as GTP hydrolysis) to overcome it. Tubulin has numerous possible conformations which can interchange without GTP hydrolysis (Section II). The two state tubulin model is a simplification. The structure of tubulin has recently been clarified (Nogales et al, 1998) so molecular simulations will soon be available.

Ehe 500 msec preconscious processing time may be directly related to the action potential travel time along the axon plus the refractory lag time in synaptic transmission rather than to the quantum collapse time. In the Orch OR model the "quantum collapse time" T is chosen to match known neurophysiological time intervals related to pre-conscious processes; the gravitational self-energy E and related mass may then be calculated. For example we have used 25 msec (e.g. in coherent 40 Hz oscillations), 100 msec (e.g. EEG alpha rhythm), and 500 msec (e.g. Libet's pre-conscious threshold for low intensity sensory stimuli).

If quantum superposition correlates with pre-conscious processing, then dendritic activities (more than axonal firings) are likely to be relevant to consciousness (e.g. Pribram, 1991). Microtubules in dendrites are of mixed polarity (unlike those in axons), an arrangement conducive to cooperative computation.

Tuszynski and Brown raise valid objections; quantum states in a biological milieu appear at first glance to be unlikely. However nature may have evolved specific conditions for isolation, thermal screening and amplification. Life itself may be a macroscopic quantum state.

Appendix 2. Testable predictions of the Orch OR model

Here major assumptions **(bold)** and corresponding testable predictions (numbered) of the Orch OR model are listed:

Neuronal microtubules are directly necessary for consciousness

1. Synaptic sensitivity and plasticity correlate with cytoskeletal architecture/activities in both presynaptic and postsynaptic neuronal cytoplasm.

2. Actions of psychoactive drugs including antidepressants involve neuronal microtubules.

3. Neuronal microtubulestabilizing/protecting drugs may prove useful in Alzheimer's disease, ischemia, and other conditions.

Microtubules communicate by cooperative dynamics of tubulin subunits

4. Laser spectroscopy (e.g. Vos et al, 1993) will demonstrate coherent gigaHz Frhlich excitations in microtubules.

5. Dynamic vibrational states in microtubule networks correlate with cellular activity.

6. Stable patterns of microtubulecytoskeletal networks (including neurofilaments) and intramicrotubule diversity of tubulin

states correlate with memory and neural behavior.

7. Cortical dendrites contain largely "Alattice" microtubules (compared to "Blattice" microtubule, Alattice microtubules are preferable for information processingTuszynski et al., 1995)

Quantum coherence occurs in microtubules

8. Studies similar to the famous "Aspect experiment" in physics (which verified nonlocal quantum correlationsAspect et al., 1982) will demonstrate quantum correlations between spatially separated microtubule subunit states a) on the same microtubule, b) on different microtubules in the same neuron, c) on microtubules in different neurons connected by gap junctions.

9. Experiments with SQUIDs (Superconducting Quantum Interference Device) such as those suggested by Leggett (1984) will detect phases of quantum coherence in microtubules.

10. Coherent photons will be detected from microtubules.

Microtubule quantum coherence requires isolation by cycles of surrounding actingelation

11. Neuronal microtubules in cortical dendrites and other brain areas are intermittently surrounded by tightly cross-linked actin gels.

12. Cycles of gelation and dissolution in neuronal cytoplasm occur concomitantly with membrane electrical activity (e.g. synchronized 40 Hz activities in dendrites).

13. The solgel cycles surrounding microtubules are regulated by calcium ions released and reabsorbed by calmodulin associated with microtubules.

Macroscopic quantum coherence occurs among MT in hundreds/thousands of distributed neurons and glia linked by gap junctions

14. Electrotonic gap junctions link synchronously firing networks of cortical neurons, and thalamocortical networks

15. Quantum tunneling occurs across gap junctions.

16. Quantum correlation occurs between microtubule subunit states in different neurons connected by gap junctions (the microtubule "Aspect experiment" in different neurons)

The amount of neural tissue involved in a conscious event is inversely proportional to the event time by E=hbar/T

17. The amount of neural mass involved in a particular cognitive task or conscious event (as measurable by nearfuture advances in brain imaging techniques) is inversely proportional to the preconscious time (e.g. visual perception, reaction times).

An isolated, unperturbed quantum system selfcollapses according to E=hbar/T

18. Isolated technological quantum superpositions will selfcollapse according to E=/T. (Preliminary discussions of such experiments involving superposition of crystals have begun between Roger Penrose and Anton Zeilinger.)

Microtubulebased cilia/centriole structures are quantum optical devices

19. Microtubulebased cilia in rods and cones directly detect visual photons and connect with retinal glial cell microtubule via gap junctions.

A critical degree of cytoskeletal assembly (coinciding with the onset of rudimentary consciousness) had significant impact on the rate of evolution.

Fossil records and comparison with presentday biology will show that organisms which emerged during the early Cambrian period with onset roughly 540 million years ago had critical degrees of microtubule-cytoskeletal size, complexity and capability for quantum isolation (e.g. tight actin gels, gap junctions; see Hameroff, 1998b).

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