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Conduction pathways in microtubules, biological quantum computation, and consciousness

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Abstract

Technological computation is entering the quantum realm, focusing attention on biomolecular information processing systems such as proteins, as presaged by the work of Michael Conrad. Protein conformational dynamics and pharmacological evidence suggest that protein conformational states—fundamental information units ('bits') in biological systems—are governed by quantum events, and are thus perhaps akin to quantum bits ('qubits') as utilized in quantum computation. 'Real time' dynamic activities within cells are regulated by the cell cytoskeleton, particularly microtubules (MTs) which are cylindrical lattice polymers of the protein tubulin. Recent evidence shows signaling, communication and conductivity in MTs, and theoretical models have predicted both classical and quantum information processing in MTs. In this paper we show conduction pathways for electron mobility and possible quantum tunneling and superconductivity among aromatic amino acids in tubulins. The pathways within tubulin match helical patterns in the microtubule lattice structure, which lend themselves to topological quantum effects resistant to decoherence. The Penrose–Hameroff 'Orch OR' model of consciousness is reviewed as an example of the possible utility of quantum computation in MTs.

Keywords: Microtubules; Quantum computation; Consciousness; Protein conformation; Biolomolecular computation

1. Introduction: proteins, anesthesia and quantum computation

1.1. Moore's law and quantum biology

Technology is approaching the limit of classical computing through the operation of Moore's Law, which states that the number of transistors or fundamental switches that can be fabricated on a silicon integrated circuit doubles every 18–24 months. This amazing trend has been miniaturizing microelectronics for close to four decades, and today the smallest available silicon chips contain up to 100 million transistors on a few square centimeters of wafer. This translates into dimensions on the order of 200 nm or less per fundamental switch. As further miniaturization occurs, switching processes enter the quantum world, with extremely useful potential advantages inherent in quantum computation.

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Quantum computers are proposed to take advantage of the bizarre quantum property of superposition, in which particles may be in two or more states or locations simultaneously. Whereas conventional computers typically utilize binary 'bits' in which information is represented by particles in classical states of either 1 or 0, quantum computers utilize quantum superpositions of both 1 and 0 ('qubits'). While in superposition qubits interact with other qubits by another bizarre quantum feature, nonlocal entanglement, and ultimately each qubit 'collapses' or 'reduces' to classical states of either 1 or 0. The set of post-reduction classical bits is the solution, or output. Quantum computers will in principle solve at least certain types of difficult problems (e.g. searches, factoring large numbers into primes) with unprecedented speed, and other unique applications are likely to emerge. Quantum computation promises to be a dominant form of information technology.

Miniaturization also brings information technology into the biological realm. Moore's law predicts that in 10 years fundamental switches should reach a scale of about 2 nm roughly the size of proteins, which can act as conformational switches. Biology has had 4 billion years to evolve the most efficient form of information processing. It should not be surprising to find that protein conformational switching is regulated by quantum computation.

1.2. Protein conformational dynamics

Protein function—such as enzymatic catalysis, ion channel opening, cell movement and information processing—depends on regulated changes in protein shape, or conformation.

Individual proteins are synthesized as linear chains of amino acids which 'fold' into 3-D conformation. The precise folding depends on attractive and repulsive forces among various amino acid side groups, and a current view is that many possible intermediate conformations precede the final one (Baldwin, 1994). Predicting final 3-D 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?

The main driving force in protein folding occurs as uncharged non-polar amino acid groups join together, repelled by solvent water. These 'hydrophobic' groups attract each other by van der Waals forces and bury themselves within the protein interior. Intra-protein hydrophobic pockets result, composed of side groups of non-polar (but polarizable) amino acids such as leucine, isoleucine, phenylalanine, tryptophan, tyrosine and valine. Hydrophobic pockets range in size from single non-polar amino acids, up to groups of them occupying ~ 400 cubic Å, or 0.4 cubic nm (roughly 1/30–1/250 the total volume of a single protein). The physical solvent which most closely resembles hydrophobic pockets is olive oil, a medium in which anesthetic gases readily bind. Within hydrophobic pockets, quantum mechanical activities regulate protein conformational changes.

Proteins in a living state are dynamical, with transitions occurring at many scales. However, conformational transitions in which proteins move globally and upon which protein function generally depends occur in the ns (10^{-9} s) to 10 ps (10^{-11} s) time scale (Karplus and McCammon, 1983). Proteins are also only marginally stable. A protein of 100 amino acids is stable against denaturation by only ~ 40 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).

1.3. Quantum effects in proteins

Can electron movements influence protein conformation? The Born–Oppenheimer approximation assumes that electrons cannot significantly influence the position of atomic nuclei (and hence the position of the atom) because the electron mass is so small compared with protons and neutrons (like a soccer ball to the earth). However, as Michael Conrad pointed out (Conrad,

1994) the Born–Oppenheimer approximation does not apply because electron charge is equivalent to proton charge. Quantum processes such as electron tunneling, delocalization, and superposition could, therefore, couple to nuclear locations and influence conformational changes, particularly if the quantum processes are collective and self-organized. Proteins may be designed to amplify these quantum processes. Within proteins ideal sites for electron delocalization are hydrophobic pockets (sites of anesthetic effect), in particular those containing aromatic rings like that of tryptophan.

Electron movements and dipoles are among several forces operating among amino acid side groups within a protein. These include charged interactions such as ionic forces and hydrogen bonds, as well as interactions between dipoles—separated 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.

Type 3 induced dipole–induced dipole interactions are the weakest but most purely non-polar. They are known as London dispersion forces and they ensue from the fact that atoms and molecules which are electrically neutral and spherically symmetrical nevertheless have instantaneous electric dipoles due to asymmetry in their electron distribution ('electron cloud'). The electric field from each fluctuating dipole in an electron cloud couples to others in electron clouds of adjacent non-polar amino acid side groups. The couplings are quite delicate (40 times weaker than hydrogen bonds) but 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. Electron clouds in aromatic ring structures (i.e. tryptophan, tyrosine, phenylalanine, histidine) are larger and more complex, and may give rise to cooperatively organized London forces particularly suited to governing protein conformational states. Due to inherent uncertainty in electron localization, London forces are quantum effects which may couple to 'zero point fluctuations' of the quantum vacuum (London, 1937; Milloni, 1994).

1.4. Quantum neuropharmacology: anesthesia and psychedelia

Quantum dipole oscillations within hydrophobic pockets were first proposed by Fröhlich (1968) to regulate protein conformation and engage in macroscopic coherence. In a series of proposals Conrad (e.g. 1994) showed how electron superpositions could influence nuclear movement (conformation), and suggested that quantum superposition of various possible protein conformations occurs 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. And recently Matsuno (2001) has claimed to observe magnetic quantum coherence in actin, a main component of the contractile apparatus in muscle cells, and of the cytoskeleton in all cells.

Close examination of effects of general anesthetics (which erase consciousness) and hallucinogens (which are said to expand consciousness) reveal that both act in opposite ways on delicate quantum effects.

The mechanism of general anesthesia supports a role for quantum London forces in the phenomenon of consciousness. A century ago Meyer and Overton (working independently in Germany and England, respectively) showed a remarkable correlation between anesthetic potency and solubility in a particular lipid-like environment. Although these results were originally taken to imply that the anesthetics acted in lipids within the cell membrane, studies in the past decades (e.g. Wulf and Featherstone, 1957; Franks and Lieb, 1982, 1984, 1985, 1994; Halsey, 1989 and others) conclude that anesthetic gas molecules act in hydrophobic (lipid-like, water-excluding) regions within critical target proteins. The solubility/binding occurs by weak van der Waals London forces between the anesthetic and non-polar amino acid groups (the same type of endogenous interactions occurring between non-polar amino acid groups in the absence of anesthetics). Critical brain proteins affected by anesthetics include receptors for neurotransmit-

ters such as gamma amino butyric acid (GABA), acetylcholine, serotonin and glycine, as well as certain second messenger proteins, enzymes and tubulin which comprise microtubules (MTs) (Franks and Lieb, 1982, 1984, 1985). What do anesthetics do at their site of action?

Franks and Lieb (1994) suggested that anesthetics act simply by following the Meyer–Overton correlation: their mere presence in hydrophobic pockets prevents conformational switching. However, a variety of molecules, which follow the Meyer–Overton correlation and occupy the same pockets are nonanesthetic, or even convulsant (Fang et al., 1996). The mere presence of molecules in hydrophobic pockets may be insufficient to explain anesthesia.

Another view is that anesthetics somehow disrupt van der Waals London force interactions normally occurring in the critical hydrophobic pockets. Quantum superposition requires electron mobility—electron pairs must be relatively free to roam among allowed orbitals. Evidence shows that anesthetics retard electron mobility—the movement of free electrons in a corona discharge is inhibited by anesthetics (Hameroff and Watt, 1983). By forming their own London force attractions in hydrophobic pockets, anesthetics may inhibit electron mobility required for protein dynamics, quantum superposition and consciousness. Nonanesthetics may be understood as occupying hydrophobic pockets without altering electron mobility, and convulsants as forming cooperative van der Waals interactions, which promote excessive electron mobility and protein dynamics in excitatory proteins.

Another class of drugs, the hallucinogenic ('psychedelic') tryptamine, ergoline and phenylethylamine derivatives bind and act in hydrophobic pockets within serotonin receptors and elsewhere. For example the hallucinogens LSD (an ergoline) and DMT (a tryptamine) are based on indole rings, exactly like that in tryptophan. Nichols et al. (1977) showed that these psychedelic drugs bind in hydrophobic pockets of less than 0.6 nm (6 Å) length. Kang and Green (1970), Snyder and Merrill (1965) measured the capacity of a series of psychedelic drug molecules to donate electron orbital resonance energy. In both studies, the drug's electron resonance donation is correlated with psychedelic potency.

Taken together with dependence of protein conformational regulation on quantum van der Waals forces, the anesthetic and psychedelic studies suggest that (1) consciousness depends on quantum processes in hydrophobic pockets; (2) these quantum processes are inhibited by anesthetics which impair electron mobility in van der Waals London forces. The same processes are enhanced (hallucinations, but also enlightenment) in the presence of psychedelic drugs, e.g. those with indole rings donating electron resonance energy to indole rings in tryptophan within the hydrophobic pocket, forming a collective quantum state. Consciousness depends on quantum states of electrons within hydrophobic pockets in a class of brain proteins.

With conformational states controlled by a quantum process, proteins may thus be viewed as quantum bits, or 'qubits'. For quantum computation, qubits can be arranged in a geometrical lattice (Lloyd, 1993). In biological systems the protein tubulin is arranged in a particular geometrical lattice in MTs whose functions appear to include organization, communication and information processing. Are MTs quantum computers?

2. Information processing in microtubules

2.1. Microtubules and the cytoskeleton

Interiors of living cells are functionally organized by webs of protein polymers known as the cytoskeleton (Fig. 2). Major components of the cytoskeleton are MTs, self-assembling hollow crystalline cylinders whose walls are hexagonal lattices of subunit proteins known as tubulin (Fig. 3). Other major cytoskeletal components include actin, intermediate filaments, and centrioles, MT-based organelles, which orient the cell and guide cell movement and division.

MTs 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 (which lack centrioles), MTs self-assemble to extend axons

and dendrites and form synaptic connections. Microtubule-associated proteins (MAPs) interconnect MTs to form MT-MAP networks, which define cell architecture and function. Once established, MT-MAP networks maintain and regulate synaptic strengths responsible for learning and cognitive functions. MTs interact with membrane structures and activities (e.g. in actin-based dendritic spines) by linking proteins (e.g. fodrin, ankyrin) and 'second messenger' chemical signals. Woolf (1997) has shown that activation of neuronal acetylcholine receptors causes changes in MT-MAP connections. (For a more complete description of the role of MTs and other cytoskeletal structures in cognitive functions see Dayhoff et al., 1994; Hameroff and Penrose, 1996a; Hameroff, 1994). MTs have traditionally been considered as purely structural components, however, recent evidence has demonstrated MT mechanical signaling and communication functions (see Tables 1 and 2).

How might MTs signal and process information? Tubulin can undergo several types of conformational changes (e.g. Engelborghs, 1992; Cianci et al., 1986). In one example of tubulin conformational change observed in single protofilament chains, one monomer can shift 27° from the dimer's vertical axis (Melki et al., 1989). Whether that degree of mechanical deformation occurs in tubulin within intact MTs is unknown; neighbor tubulins in the MT lattice might be expected to constrain movement. However, cooperativity among MT subunit tubulins bound 'loosely' in the MT lattice by hydrophobic forces could coordinate conformational changes, and support propagation of wave-like vibrational sig-

Table 1
Experimental evidence for signaling in microtubules

Author(s), year	Signaling mechanism observed
Vassilev et al., 1985	MT bridge between two membranes conveys depolarization
Vernon and Woolley, 1995	Propagation of 'active zone' along flagellar MTs
Maniotis et al., 1997	Mechanical signals from membrane proteins through MTs to cell nucleus
Glanz, 1997	Force transduction through cytoskeleton

Table 2
Theoretical models of microtubule information processing

Author(s), year	Theoretical model
Sherrington, 1953	'Cyto-skeleton' as protozoan nervous system
Moran and Varela, 1971	MTs as mechano-ionic transducers
Atema, 1973	Propagating tubulin conformational changes in cilia and flagella
Hameroff, 1974	MT holography
DeBrabander, 1975	MTs as signal transducers between membrane and nucleus
Roth and Pihlaja, 1977	Information in tubulin conformational gradient within MTs MTs as signal transducers between membrane and nucleus
Bornens, 1979	Centrioles as gyroscopic gravity sensors
Albrecht-Buehler, 1981	MT-centriole signalling by infra-red photons
Conrad and Lieberman, 1982	MTs as vibrational computers
Hameroff and Watt, 1982	MT computation
Del Giudice et al., 1982	Energy self-focusing in hollow MT cores
Hameroff et al., 1984	MT molecular automata
Joshi et al., 1985	MT tensegrity signalling
Rasmussen et al., 1990	MT molecular automata; MT automata networks
Sataric et al., 1992	Solitons in MTs
Tuszynski et al., 1995	Ferroelectric, spin glass behavior
Penrose and Hameroff, 1995	MT quantum computation
Kirschner and Mitchison, 1986	MT probing/signalling
Puck and Krystosek, 1992	Phosphorylation/dephosphorylation along MT subunits
Wang and Ingber, 1994	Tensegrity signalling
Chou et al., 1994	Soliton propagation in MTs
Jibu and Yasue 1995	MT super-radiance, self-induced transparency
Mavromatos and Nanopoulos, 1997	Quantum computation in MTs with string theory collapse

nals. MTs are also ferroelectric with electron and proton conduction, which may couple by phonons to conformational vibrations. The crystal-like MT structure makes them attractive candidates for quantum coherent excitations, e.g. in the gigaHz range by a mechanism suggested by Fröhlich ('pumped phonons' Fröhlich, 1968, 1970, 1975, 1975 cf. Penrose and Onsager, 1956).

One particular model of MT information processing potential utilizes Fröhlich excitations of tubulin subunits within MTs to support computation and information processing (e.g. 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 mediates logical interactions among neighboring tubulins, resulting in self-organizing patterns capable of information processing, memory and learning (Fig. 4).

In a series of simulations (e.g. Hameroff et al., 1984; Rasmussen et al., 1990) Fröhlich's excitations were used as a clocking mechanism and electrostatic dipole coupling forces as 'transition rules' for cellular automata behavior by dynamic conformational states of tubulins within MTs. In Fig. 3, each tubulin dimer conformation is ruled by a single London force electron pair coupling. For automata behavior, the dipole strength of each dimer is coupled to its six surrounding tubulin neighbors at each 'Fröhlich coherent' time step (e.g. 10^{-9}–10^{-11} s). The net electrostatic force F_{net} from the six surrounding neighbors acting on each tubulin can then be calculated as:

$$f_{net} = \frac{e^2}{4\pi\varepsilon} \sum_{i=1}^{6} \frac{Y_i}{r_i^3}$$

where y_i and r_i are inter-tubulin distances, e is the electron charge, and ε is the average protein permittivity. MT automata simulations (Fig. 5) show conformational pattern behaviors including standing waves, oscillators and gliders traveling one dimer length (8 nm) per time step (10^{-9}–10^{-11} s) for a velocity range of 8–800 m s^{-1}, consistent with the velocity of propagating nerve action potentials.

MT automata patterns can thus represent and process information through each cell; gliders may convey signals which regulate synaptic strengths, represent binding sites for MAPs (and thus neuronal and synaptic connectionist architecture) or material to be transported. Information could become 'hardened' in MTs by tubulin modifications or stored in neurofilaments via MAPs.

2.2. Tryptophan and histidine locations in tubulin

In conventional computers the 'currency' of information in semiconductors is electrons. Microtubule automata could utilize Fröhlich phonons for information currency, although other quasi-particles such as solitons, excitons, instantons, anyons, as well as photons, electrons and protons could serve. Electron propagation would be extremely useful, as conformational energy (e.g. in the form of phonons) could be coupled to electrons and both classical and quantum processes could be supported. However, proteins have never been considered especially conductive, nor in most cases semiconductive (of course neither has DNA which has recently been shown to be highly conductive, and perhaps superconductive (Barton, 1998; Kasumov et al., 2000)).

Electron (or proton) transfer within and among specific amino acid residues within proteins may mediate protein function. For example catalysis in the enzyme class 1 ribonuclease reductase utilizes electron or proton transfer over 3.5 nm from a tyrosine to a cysteine. Photoactivation in *E. coli* DNA photolyase enzyme involves electron 'hopping' or tunneling along a chain of three separate tryptophans (Aubert et al., 2000). Electron tunneling over significant distances within proteins has now been shown experimentally, and there is evidence of electron transfer from intra-protein tryptophan to DNA (Wagenknecht et al., 2000).

The amino acids tryptophan and tyrosine are convenient depots for electron hopping or tunneling because of the high polarizability of their ring structure. The 'aromatic' amino acids such as tyrosine, tryptophan, phenylalanine and histidine have residues with resonant ring structures in which electrons are mobile and delocalizable.

Tyrosine, phenylalanine and histidine have single rings; each tyrosine and phenylalanine have six-carbon benzene-like rings, and histidine has a

ring with three carbons and two nitrogens. Tryptophan has a particular double ring (an 'indole ring')—a six carbon ring conjoined with a five ring with one nitrogen and four carbons. The extra lines between the atoms in the rings in Fig. 1 signify shared, delocalized, or resonant electrons. Thus tryptophan has the greatest electron resonance (and thus is the most fluorescent), and histidine the lowest electron mobility, and least fluorescent. Becker et al. (1975) showed fluorescent resonance energy transfer (non-radiative photon exchange) between tryptophan and other aromatics in adjacent tubulins in MTs, and between MTs and membranes. Tryptophan is the most highly suited amino acid for transiting electrons and exchanging photons. In this study, we have begun to examine and map intra-tubulin locations of the aromatic amino acids tryptophan and histidine.

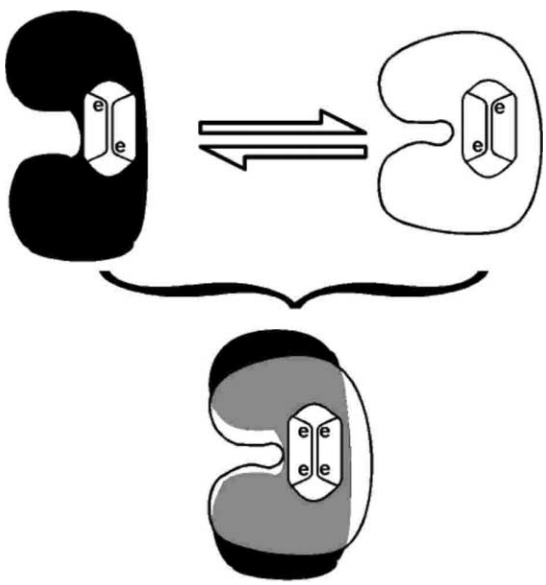

Fig. 1. Model of protein conformational switching. Tubulin is depicted as an example, and for simplicity one pair of electrons coupled by London forces is shown in a single hydrophobic pocket. Top: coupled electrons in one configuration in a single hydrophobic pocket correspond to 'open' (black) conformation. In the opposite London force electron coupling the protein is 'closed' (white). Bottom: since London forces are quantum mechanical, the electron pair may occupy both states, and the protein exist in a quantum superposition of both open and closed conformations. By going from bottom (quantum superposition) to top (one particular conformation) the protein functions as a qubit.

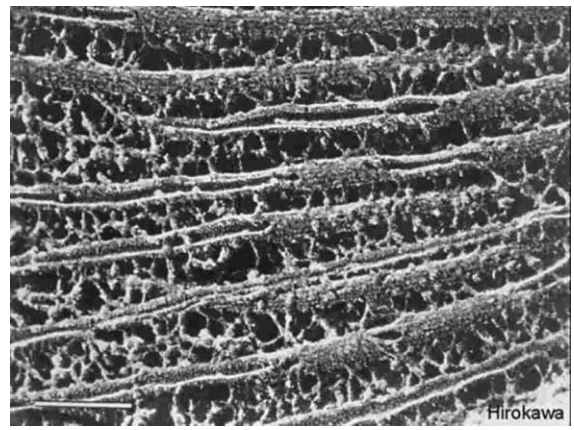

Fig. 2. The neuronal cytoskeleton. Immunoelectron micrograph of dendritic MTs interconnected by dendrite-specific MAPs. Some MTs have been sheared, revealing internal hollow core. The granular 'corn-cob' surface of MTs is barely evident to close inspection. Scale bar, lower left: 100 nms. With permission from Hirokawa, 1991.

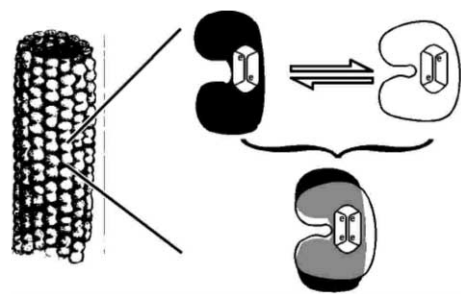

Fig. 3. Left: microtubule, a cylindrical lattice of tubulin proteins. Right (Fig. 1): coupled to position of a pair of quantum coupled electrons in an internal hydrophobic pocket, each tubulin may occupy two classical conformations (top) or exist in quantum superposition of both conformational states (bottom). A tubulin may thus act as a classical bit (top) or as a quantum bit, or 'qubit'.

Tubulin dimers are 8 nm in length, and 4 nm wide (and 4 nm 'deep'). The peanut-shaped dimer is composed of two roughly equal monomers, alpha tubulin and beta tubulin each approximately $4 \times 4 \times 4$ nm. The distances between the tryptophans is thus no more than 2 nm. The 3-D crystallographic structure of tubulin was solved in 1998 by Nogales, Wolf and Downing (Nogales et

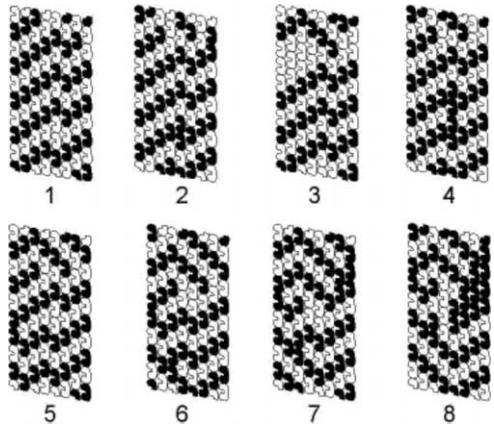

Fig. 4. Microtubule automaton simulation (from Rasmussen et al., 1990). Black and white tubulins correspond to states shown in Fig. 4. Eight ns time steps of a segment (eight of 13 protofilaments) of one microtubule are shown in 'classical computing' mode in which patterns ('gliders') move, evolve, interact and lead to emergence of new patterns.

al., 1998). Recently Alex Nip (now at University de Montreal) and Jack Tuszynski (University of Alberta, Starlab.org) simulated the locations of tryptophans and other aromatics in tubulin. Those results for tryptophan and histidine in 2-D projection are shown here. Tryptophan locations in the tubulin dimer are shown in Figs. 6–8, and histidine locations in Figs. 9–11.

Fig. 6 shows the 'front view'of tryptophan locations, looking at the tubulin dimer as looking at the microtubule from the outside, e.g. as in Fig. 3. However, the front view gives only a 2-D picture. We gain 3-D perspective by also looking at 'side' (within the MT wall) and 'top' (down the protofilament). There are eight tryptophans, four in the alpha (top) monomer, and four in the beta (bottom) monomer. Two tryptophans (one from each monomer) are in the neck, or hinge of the dimer.

The side view indicates that two of the tryptophans are alone in the extended portion of each monomer, separated from each other by exactly 4 nm. The other tryptophans are close to the inner surface and arrayed vertically. The top view shows that the tryptophans are arrayed vertically along three specific axes within the dimer.

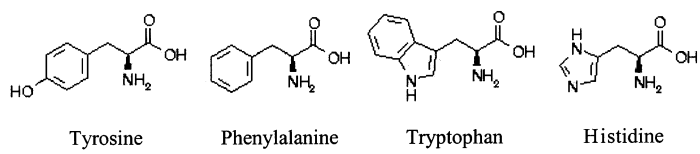

Fig. 5. The 'aromatic' amino acids contain ring structures with resonant (shared) electrons.

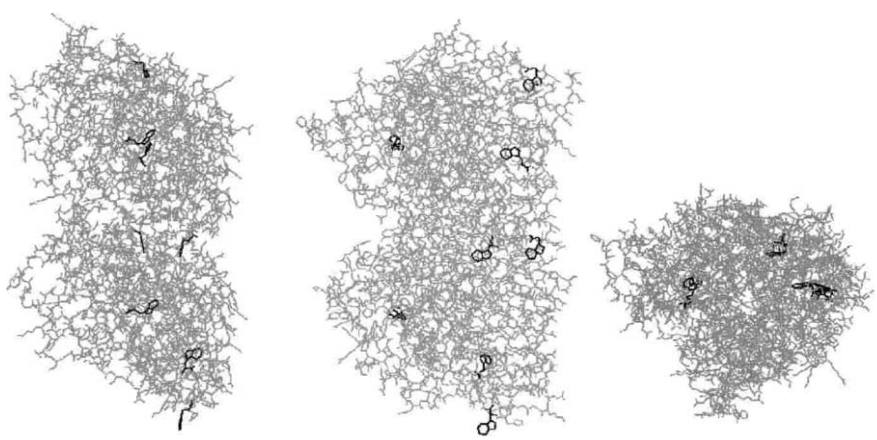

Fig. 6. Tryptophans (black) in the tubulin dimer. Left: front view (looking at the outer MT surface), Middle: side view (from within the MT wall), Right: top view (looking down on the MT protofilament).

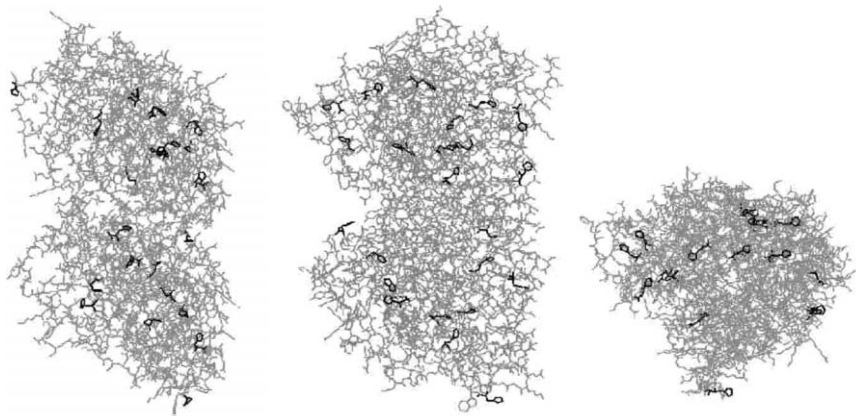

Fig. 7. Histidines (black) in the tubulin dimer. Left: front view, Middle: side view, Right: top view.

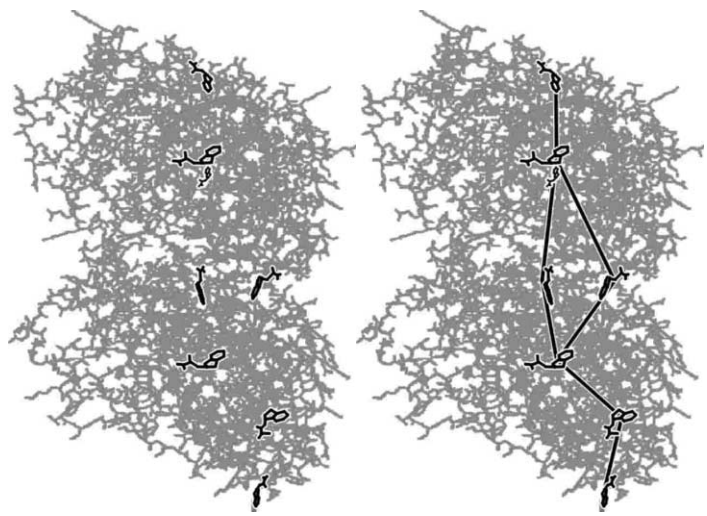

Fig. 8. Tryptophans in the tubulin dimer. Left: trypyophan locations in front view. Right: tryptophans interconnected by estimated shortest paths (2-D approximation). Typical separations are 2 nm, close enough for 'through-bond' hopping. The path separates near the cleft, or hinge of the dimer.

Histidines are more numerous than tryptophans, 22 per dimer, and their arrangement is more complex (Fig. 7).

We next consider possible electron pathways between tryptophans and histidines within tubulin.

2.3. Conduction pathways within tubulin

Conventional wisdom indicates that electron tunneling or hopping in proteins is only possible over distances under 1 nm. This is the 'Foerster distance' (maximum length of an excitation to travel). However the Foerster distance pertains to free hopping via an inert medium like an ionic solution. Within proteins electron movements may be facilitated by 'through bond hopping' over distances of 3 nm or more. Furthermore, if there are sufficient available electrons to fill half or more of the available sites, then conditions can exist within proteins at physiological temperature for (semi)conductivity comparable with silicon or

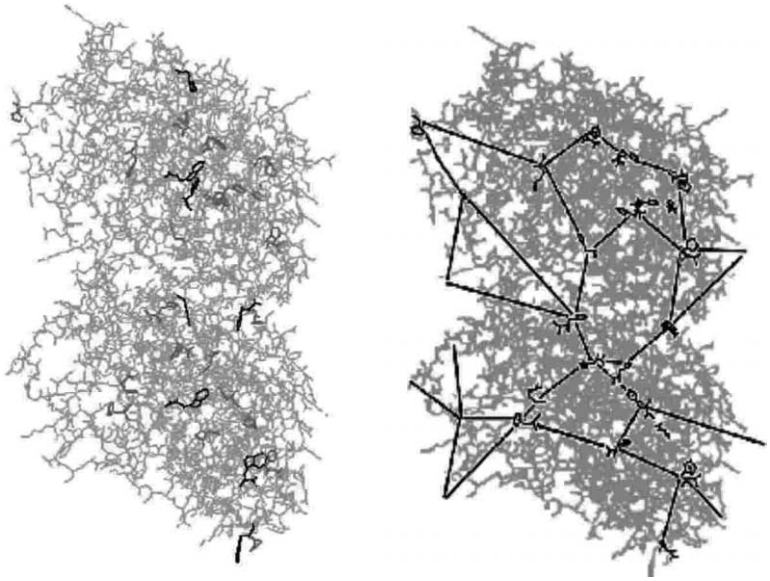

Fig. 9. Histidines in the tubulin dimer. Left: histidine locations in front view. Right: Histidines interconnected by estimated shortest paths. Typical separations are 1 nm.

even semi-metals (e.g. Brown, 1999). With dynamic water ordered at the protein surface, conductivity may be even further enhanced, and proton conduction can also occur.

As described earlier, in some enzymes electron hopping between amino acid residues may span 3.5 nm or more, and electron hopping along 3 tryptophans is known to occur in some enzymes. Based on a qualitative 2-D approximation, Fig. 8 estimates shortest direct paths between tryptophans in the tubulin dimer.

The tryptophan paths are mostly vertical, along the protofilament axis. The path separates near the cleft, or hinge of the tubulin. Occupation of one path versus the other path may control the dimer conformation, for example bending at the hinge.

In Fig. 9, we examine possible paths between histidines.

Estimation of shortest paths between histidines shows multiple loops and alternate possible routes. The average distance between histidines is about 1 nm.

Electron conduction between aromatic tryptophan and histidine amino acid residues is within range of known conduction mechanisms in proteins (tunneling, 'hopping', semiconduction).

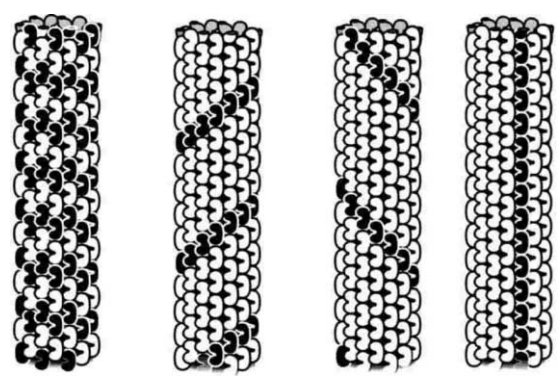

Fig. 10. Helical winding patterns of tubulin subunits within MTs. The windings repeat on any given protofilament according to the Fibonacci series: from left to right, 3, 5, 8 and 13 step repeats. The 3-step repeat is based on monomers, whereas the 5 and 8 step repeats are based on dimmrs. The 13-step repeat is simply the direct path along the vertical protofilaments. These patterns form the basis for attachment patterns of MAPs.

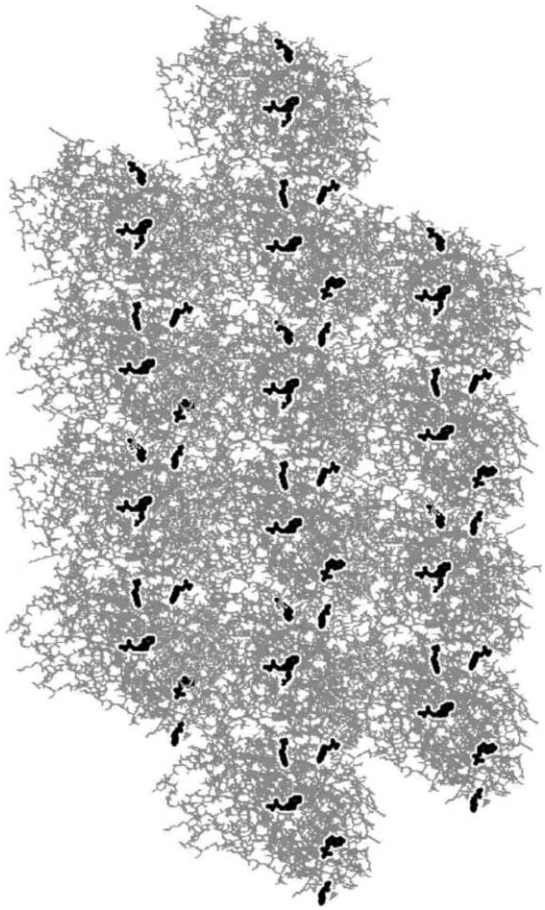

Fig. 11. A lattice neighborhood of seven tubulin dimers as found in a microtubule with tryptophans highlighted in black.

2.4. Inter-tubulin conduction pathways in microtubules

Tubulin dimers are arranged not only in vertical protofilament chains, but form a particular skewed hexagonal lattice whose crystal structure gives rise to helical winding patterns with regular repeat intervals. Increasingly steep winding patterns complete one cycle around the cylinder at a certain number of tubulins above where the cycle started (Fig. 10). These numbers, 3, 5, 8, 13, 21 etc. follow the well known 'Fibonacci series' found throughout nature. The repeating patterns also determine binding sites of MAPs'.

A neighborhood of seven tubulin dimers with tryptophans represented in black is shown in Fig. 11.

If we then show the intra-tubulin tryptophan paths in the lattice format by connecting nearest tryptophans (as in Fig. 12), we see that the tryptophan paths extend vertically along each protofilament.

Tryptophans seem oriented vertically whereas histidine locations suggest helical paths. When added to tryptophan, all possible structural winding pathways appear available (Figs. 13 and 14). In Section 4, we will discuss the possible implications for topological quantum error correction in microtubular computation.

3. Quantum computation in microtubules

3.1. Penrose–Hameroff 'Orch OR' model

Quantum theory and consciousness have been intertwined since the days of Schrödinger's cat when conscious observation was believed to cause collapse of the wave function. More recently, consciousness has itself been viewed as a collapse process, analogous to quantum computation. Penrose (1989, 1994) correlated the multiple possibilities of quantum superposition with multiple sub-conscious, or pre-conscious possibilities 'collapsing' to distinct choices or perceptions (cf. Stapp, 1993). In his early work in this area, Penrose suggested quantum superpositions of neurons both firing and not firing, collapsing or reducing (by his quantum gravity 'objective reduction' process, OR) to either firing or not firing. Thus the neuron was acting as qubit. However, for a variety of reasons MTs within each neuron were deemed better candidates for biological quantum computation, with individual tubulins within MTs acting as qubits.

The Penrose–Hameroff 'Orch OR' model portrays consciousness as quantum computation in MTs which collapse or reduce by an objective factor related to quantum gravity. For detailed explanations see Penrose and Hameroff, 1995; Hameroff and Penrose, 1996a,b; Hameroff, 1998, etc. The basic ideas are these:

- Conformational states of individual tubulins within neuronal MTs are determined by quantum mechanical London forces within the tubulin interiors which can induce conformational quantum superposition (Fig. 3).
- While in superposition, tubulins communicate/compute with entangled tubulins in the same microtubule, and in other MTs in the same neuron.
- Quantum states in MTs in any given neuron may extend to MTs in neighboring neurons, and through macroscopic regions of brain via tunneling through gap junctions (see Section 3.3, Fig. 16).
- Quantum states of tubulin/MTs are isolated/protected from environmental decoherence by biological mechanisms which include phases of actin gelation, ordered water, coherent pumping and topological quantum error correction (see Section 3.2).
- Microtubule quantum computations/superpositions are tuned or 'orchestrated' by MAPs during a classical, liquid phase which alternates (e.g. at 40 Hz) with a quantum, solid state phase.
- Following periods of pre-conscious quantum computation (e.g. on the order of tens to hundreds of milliseconds) tubulin superpositions reduce or collapse by Penrose quantum gravity 'objective reduction' (OR Fig. 15). The classical output states which result from the OR process are chosen non-algorithmically ('non-com-

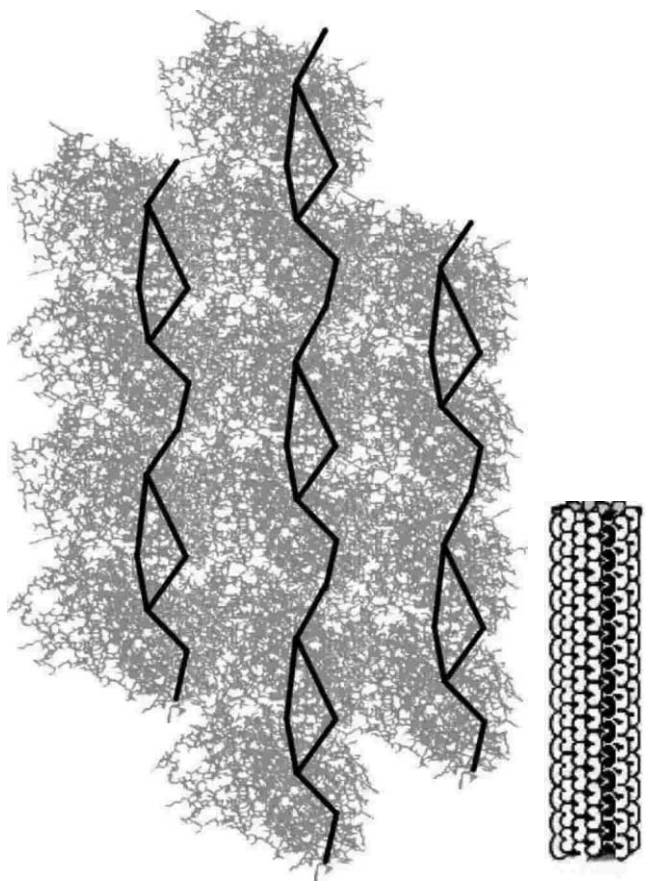

Fig. 12. Left: a lattice of seven tubulin dimers as found in the microtubule lattice. Black lines connect tryptophans. Right: vertical path along protofilament ('13 start' winding pattern) which corresponds with tryptophan conduction path.

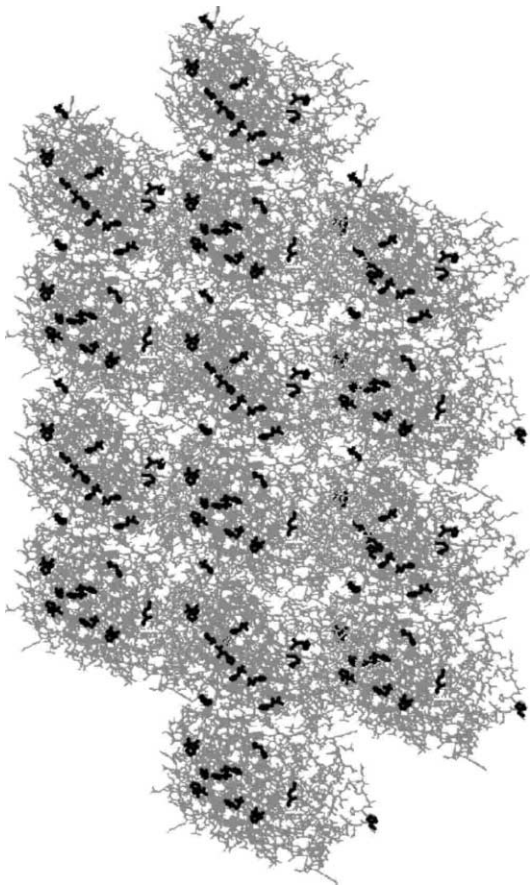

Fig. 13. A lattice neighborhood of seven tubulin dimers as found in a microtubule with histidines highlighted in black.

putably') and then govern neurophysiological events by binding of MAPs, regulating synapses and membrane functions etc.

- The reduction or 'self-collapse' in the orchestrated objective reduction 'Orch OR' model is suggested to be a 'conscious moment', linked to Penrose's quantum gravity mechanism which ties the process to fundamental spacetime geometry. This connection enables a panprotopsychist approach to the 'hard problem' of subjective experience (Chalmers, 1996a).

Other quantum models related to consciousness include those of Marshall (1989), Beck and Eccles (1992), Stapp (1993), Jibu and Yasue (1995).

Quantum models have potential explanatory value for the enigmatic features of consciousness (Table 3), but face at least two conceptual obstacles: (1) the apparent likelihood of rapid 'decoherence' (loss of quantum state) due to environmental thermal interactions in the seemingly-too-warm brain (Tegmark, 2000; Seife, 2000); and (2) the question of how a quantum state or field located within neurons might extend across membranes and anatomical regions to approach 'brain-wide' proportions. The next section deals with these issues.

3.2. Quantum states in the brain? Decoherence and biological feasibility

Quantum computing surpasses classical computing in certain critical functions (e.g. Grover's quantum search algorithm) and would be of extreme benefit to biological organisms for survival and adaptation. Billions of years of evolution may have solved the problems of decoherence and spatiotemporal spread. A number of mechanisms to prevent environmental decoherence have been suggested, specifically for quantum computation in MTs. These include (1) coherent pumping of the environment; (2) screening due to counterion Debye double layers surrounding MTs; (3) screening by actin gelation and ordered water; (4) quantum error correction; (5) topological effects of the microtubule cylindrical lattice. Recent calculations of protein decoherence times indicate quantum superpositions may indeed survive for neurophysiological time durations (Hagan et al., 2000), and brain imaging by 'quantum coherence MRI' utilizes quantum couplings of proton spins in proteins and water to give a neuroanatomical correlate of consciousness (Richter et al., 2000; Rizi et al., 2000). This quantum coherence is a MRI-induced artifact, but shows that quantum coherence of some sort can indeed occur in the brain.

Technological quantum computation became feasible with the advent of quantum error correction codes. This means that algorithms run on the quantum computer which detect and correct errors (random localized decoherence) before they destroy the global quantum state. In some cases topological structure of the quantum computer enhances the error correction. For example

toroidal surfaces (e.g. Kitaev, 1997) may have global, topological degrees of freedom which are protected from local errors and decoherence. Topological quantum computation and error correction have been suggested to occur in MTs by Porter (2001) and the helical windings discussed in Section 2 may correspond to quantum-computational 'basis states' distinguished by 'winding number' (Figs. 12 and 14).

3.3. Spatio-temporal spread of quantum states in the brain

Regarding spatial extension of a quantum (or 'quantum-like' (John, 2001)) field throughout the brain, a possible solution may be gap junctions-window-like 'electrical' connections between cells including neurons (e.g. Dermietzel and Spray, 1993). Gap junctions are more primitive and less

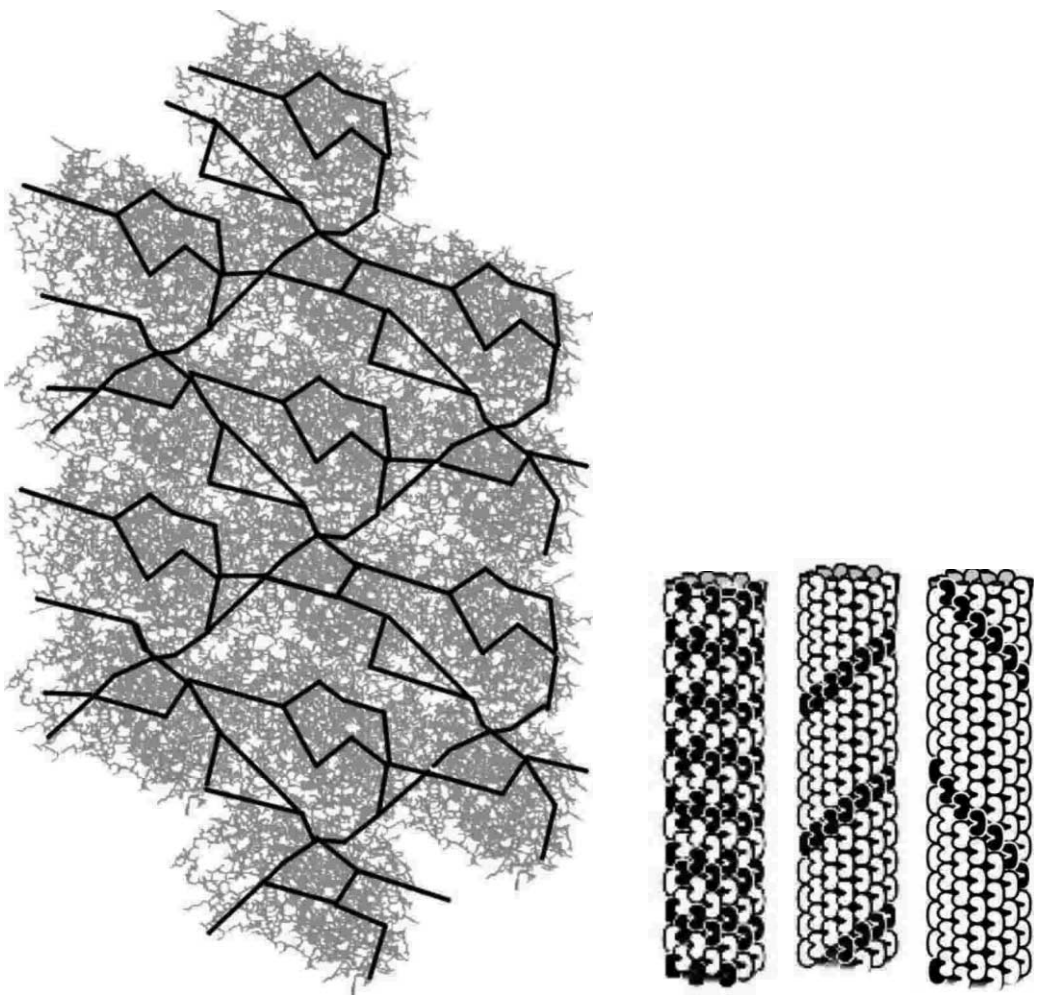

Fig. 14. Left: a lattice of seven tubulin dimers as found in the microtubule lattice. Black lines connect histidines. Right: 3, 5 and 8 start helical winding patterns in MTs. Histidine pathways in the lattice may be seen to follow these winding patterns.

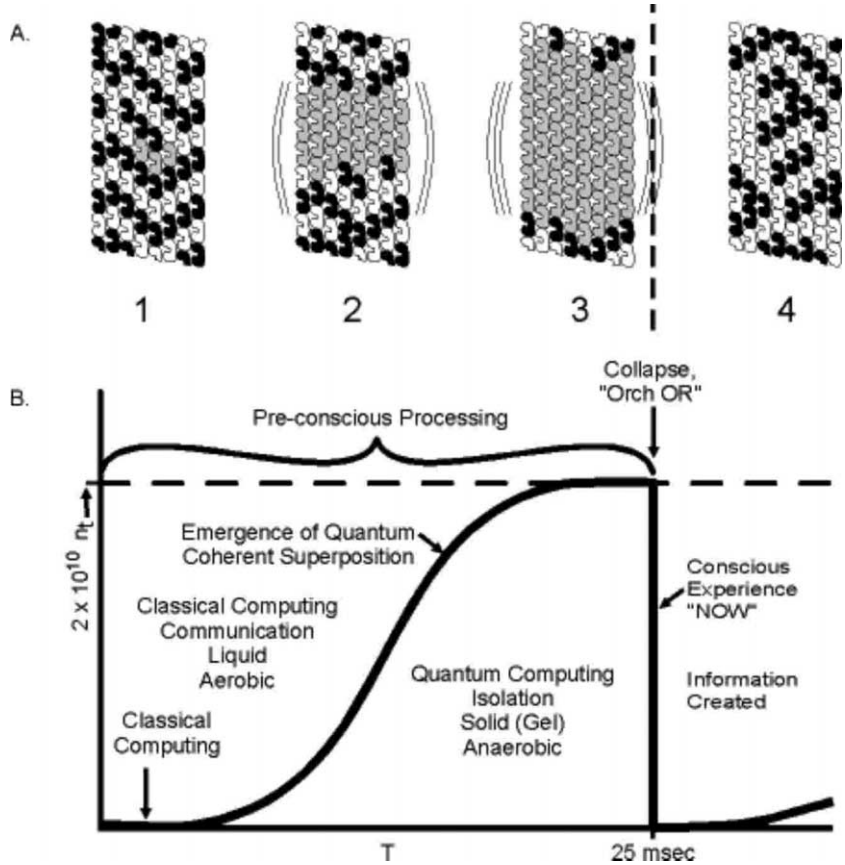

Fig. 15. An Orch OR event. (a) Microtubule simulation in which classical computing (step 1) leads to emergence of quantum coherent superposition and quantum computing (steps 2, 3) in certain (gray) tubulins. Step 3 (in coherence with other microtubule tublins) meets critical threshold related to quantum 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 MTs. Area under curve connects superposed mass energy E with collapse time T in accordance with $E = h - \mathrm{bar}/T$. 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 $T = 25$ ms (e.g. 40 Hz oscillations), $N_t = 2 \times 10^{10}$ tubulins.

numerous connections than chemical synapses, and occur between dendrites, axons, cell bodies and/or glial cells. Dendritic–dendritic gap junctions in particular have been implicated in the mediation of conscious processes (Pribram, 1991; Eccles, 1992). Cell interiors (cytoplasm) are continuous through gap junctions so that cells connected by gap junctions have actually one complex interior. Quantum states isolated in one cell interior may thus extend to neighboring cells by quantum tunneling of electrons across the 4 nm gap junction. Specific intracellular organelles have been discovered in dendrites, immediately adjacent to dendritic–dendritic gap junctions. These are layers of membrane covering a mitochondrion, and are called 'dendritic lamellar bodies' (De Zeeuw et al., 1995). The dendritic lamellar bodies are tethered to small cytoskeletal proteins anchored to MTs, and it is suggested that the mitochondria within the bodies provide free electrons for tunneling, forming a tunneling diode pair or Josephson junction between cells (Fig. 16). As few as three gap junction connections per cortical neuron (with perhaps thousands of chem-

ical synapses) to neighboring neurons and glia which in turn have gap junction connections elsewhere may permit spread of cytoplasmic quantum states throughout significant regions of the brain, weaving a widespread syncytium whose unified interior hosts a unified quantum state or field (Hameroff and Penrose, 1996a,b; Woolf and Hameroff, 2000).

Kandel et al. (1991) remarked that neurons connected by gap junctions fire synchronously,

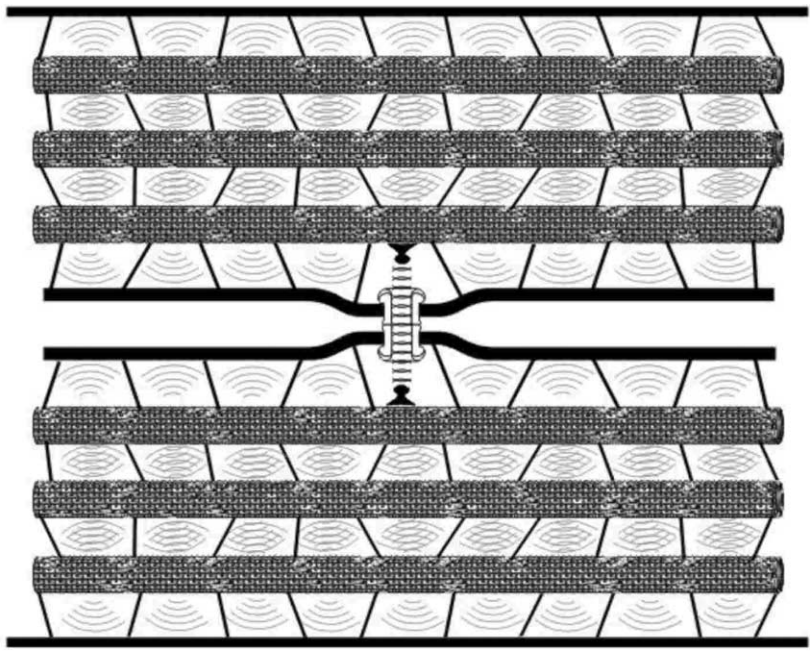

Fig. 16. Schematic representation of a gap junction connecting two dendrites in which MTs are in quantum superposition/quantum computation 'tuned' by interconnecting MAP proteins as suggested in the Penrose–Hameroff Orch OR model. On either side of the gap junction, dendritic lamellar bodies (DLBs) containing mitochondria may act as tunneling diodes to convey the quantum state between the dendrites.

Table 3
Enigmatic features of consciousness and possible solutions via the Orch OR model

Enigmatic feature of consciousness	Classical explanations	Possible Orch OR solutions
Essential nature of human experience ('qualia', the 'hard problem')	'Emergence': conscious experience emerges from computational complexity	Pan-protopsychist philosophy; qualia are fundamental features of spacetime geometry, accessed by quantum gravity OR
Unitary sense: 'binding problem'	Temporal synchrony e.g. coherent 40 Hz	(1) Non-local quantum coherence; indivisible macroscopic quantum state (e.g. Bose-Einstein condensate); (2) Instantaneous self-collapse of superpositioned states (Orch OR)
Transition from pre-conscious processes to consciousness	No apparent threshold	Collapse, or reduction of the quantum wave function, a la quantum computation
(Apparent) 'free will'	None	Non-computability in quantum gravity OR

Table 4
Potential single-body approaches to microtubule electronics

Single body theory
Diffusion equations for single mobile electrons
Microtubule as solenoid
Crystal field theory (microtubule as paracrystal, tubulin dimer as unit cell)

Table 5
Potential many body theory approaches to microtubule electronics

Many body theory
2-D models from condensed matter physics (e.g. chiral spin liquid, Bonesteel, 2000)
Quantum-classical phase transition in quantum computers (Aharonov, 1999)
Topological quantum computation and error correction (Kitaev, 1997)
Josephson-junction arrays (Ivanov et al., 2001)
Band theory (Brown and Tuszynski, 2001)

behaving like 'one giant neuron', and E.R. John (2001) has suggested that gap junction-connected neurons ('hyper-neurons') mediate zero phase lag coherence. Dendritic lamellar bodies are associated with synchronously firing neurons (De Zeeuw et al., 1997) and several studies (Galarreta and Hestrin, 1999; Gibson et al., 1999; Velasquez and Carlen, 2000) implicate gap junction-connected interneurons in the mediation of coherent ('40 Hz') oscillations. These gap junction-connected interneurons form 'dual' connections (gap junctions and GABAergic chemical synapses) with pyramidal cells and other cortical neurons. GABA inhibition could quiet membrane activities, avoiding decoherence to enable quantum states in neuronal cytoplasmic interiors to develop and spread among many gap junction-linked cells across wide areas of the brain. Thus gap junction-connected coherent 40 Hz neurons may support spatially extended quantum states.

4. Conclusion

Scientists speak of 'levels of theory', a hierarchy of models ranked by physical detail. The ultimate level would be a 'Theory of Everything'. One possible over-arching approach (suggested by Roger Penrose) attributes quantum state reduction to gravity. The Orch OR model asserts that this ultimate level is relevant to the physics of consciousness.

The discovery of the aromatic lattice within the microtubule has no immediately discernible implications at this ultimate level, but it suggests a host of new possibilities at simpler levels of theory (one-body quantum models, many-body quantum models, and quantum-field models). For example, in the Orch OR model it is assumed that neighboring dimers become entangled by the dipole–dipole interaction, which appears in the classical cellular automaton models of the microtubule. But it may be that mobile electrons following these newly recognized pathways contribute more to the entanglement process; tubulin dimers may become entangled indirectly, by way of interaction with strongly correlated mobile electrons.

Tables 4 and 5 list a few theoretical approaches to motion of electrons within the lattice of aromatic amino acids. These and others need to be explored and their predictions calculated (Brown and Tuszynski (2001) is a promising starting point). The structures of other biomolecules must also be examined, in order to show whether these pathways are unique to tubulin or found in many proteins. Logical candidates for examination include actin and other cytoskeletal proteins, the bacterial protein FtsZ, which is related to tubulin, and microtubule associated proteins such as MAP-2, MAP-4 and tau (Eva Nogales, personal communication).

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