

QUANTUM COHERENCE IN MICROTUBULES: A NEURAL BASIS FOR EMERGENT CONSCIOUSNESS? ¹

Stuart R. Hameroff²

Advanced Biotechnology Laboratory, Department of Anesthesiology, University
of Arizona Health Sciences Center, Tucson, AZ 85724, USA

Abstract: The paper begins with a general introduction to the nature of human consciousness and outlines several different philosophical approaches. A critique of traditional reductionist and dualist positions is offered and it is suggested that consciousness should be viewed as an emergent property of physical systems. However, although consciousness has its origin in distributed brain processes it has macroscopic properties — most notably the ‘unitary sense of self’, non-deterministic free will, and non-algorithmic ‘intuitive’ processing — which can best be described by quantum-mechanical principles.

There have been many attempts by physicists and philosophers to apply quantum-mechanical principles to the realm of consciousness, but they have been primarily speculative and analogical as there has been little supportive evidence from the neurosciences. This paper postulates that cytoskeletal microtubules within neurons could be a possible site for quantum effects.

Although the supportive evidence for such a thesis is, of necessity, highly technical, the article has been structured in such a way that the general arguments are accessible to the general reader. For those more technically minded, full supportive evidence is available in footnotes and appendices.

Introduction: Emergence of Consciousness

The nature of human consciousness is the greatest frontier facing science and mankind and is being approached by many disciplines — including neuroscience, cognitive science, computer science, physics, mathematics, medicine, pharmacology, philosophy and religion. Within this diverse approach exists a spectrum which, at one extreme, considers consciousness as simply the sum total of brain activities. This *reductionist* view is best exemplified by functionalist philosophers (e.g. Dennett, 1991) and proponents of ‘strong artificial intelligence’ or ‘strong AI’ (e.g. Minsky, 1986) who contend that all mental events may be reduced to an algorithm and that all brain functions, including consciousness, may eventually occur in computers. On the other end of the spectrum is a *dualist* view which considers the brain and mind as distinct, separate entities and consciousness as existing in a separate reality (e.g. Popper and Eccles, 1977). This reductionism/dualism dichotomy may potentially be resolved by views which contend that consciousness has a distinct quality, but one which *emerges* from brain processes which can be accounted for by natural science.

One aspect of natural science, quantum theory, may be especially relevant. In particular, the concept of *quantum coherence* leading to macroscopic quantum states may help

¹ Reprinted in part in the proceedings from the Abisko (Sweden) Conference on *Matter Matters — On the Material Basis of the Cognitive Activity of the Mind*, ed. Rolf Wasén, Peter Århem, and Uno Svedin.

² I am indebted to Alwyn Scott for guidance and suggestions, to Roger Penrose for validation and inspiration, to Richard Hofstad for patience and clerical talent, and to Gordon Globus, Jane Clark, Keith Sutherland and the journal’s referees for review, criticism and restructuring. Supported in part by NSF Grant No. DMS-9114503. Summer 1994 support from MIDIT, Danish Technical University is also appreciated.

explain several of the qualities of consciousness which are difficult to explain by conventional neuroscience. These properties, and their possible quantum correlates (in parentheses) are:

- The ‘binding problem’ or ‘unitary sense of self’ (quantum coherence, non-locality).
- Randomness, non-deterministic free will (quantum indeterminacy).
- Non-algorithmic ‘intuitive’ processing (computing via quantum superposition).
- Reversible ablation by general anaesthesia (prevention of quantum coherence by anaesthetic inhibition of quantum mobility in protein hydrophobic regions).
- Difference (and transition) between pre-, sub- and non-conscious processes and consciousness (collapse of the wave function).

This paper describes a potential ‘bottom-level’ mechanism in the brain’s recursive, hierarchical organization driven or selected by (and also driving and selecting) higher-level mechanisms (e.g. neural networks, attentional scanning circuits, coherent firing of distributed neurons). At this ‘bottom’ level, quantum events can couple directly to conformational states of cell proteins. Quantum coherence in cytoskeletal microtubules and associated water within each of the brain’s neurons may be a bottom level from which consciousness can emerge.

Emergence implies a qualitatively new property or phenomenon which appears at a hierarchical level above the level at which rules of interaction are implemented. Emergent properties (including chaos) occur in many complex systems including networks, vortices, lasers, chemical oscillations, genetic networks, weather and developmental patterns. Numerous authors have described consciousness as an emergent phenomenon arising from a hierarchy of lower-level brain processes.³ Emergent phenomena can exert downward modulation on lower-level interactions to provide reverberation, feedback, error correction and reward. In the brain’s hierarchy, consciousness (and sub-conscious factors) can regulate, by downward control, volitional actions and bodily functions.

Consciousness also appears to have emerged at some point in evolution. Perhaps occurring initially as a ‘helpless-spectator’ epiphenomenon, consciousness then assumed control of its biological environment (Jaynes, 1976). The emergence of consciousness in our brains (during each conscious moment, during evolution and during the development of each human being) may be likened to new properties of materials which develop from microscopic or quantum-level events. For example, the distinct properties of superconductivity and superfluidity emerge from materials as their individual atoms reach a high level of coherence. In these cases, ordered alignment or coherence is due to lowering temperature to near absolute zero to reduce thermal oscillations. Consequently, at a critical degree of coherence, totally new macroscopic properties (superconductivity, superfluidity) emerge (Leggett, 1989).

This paper suggests that consciousness may emerge as a macroscopic quantum state from a critical level of coherence of quantum-level events in and around a specific class of neurobiological microstructure: cytoskeletal microtubules within neurons throughout the brain.

³ Atkin (1992) has defined consciousness as emergent *information itself* at the moment of its generation — ongoing, self-organizing change in a self/world model. Baas (1994) has mathematically described ‘hyperstructures’ with intrinsic observer functions which emerge from hierarchies, and hierarchical schemes of brain organization leading to consciousness have been proposed (e.g. Scott, 1978, 1994; Somjen, 1983). Globus (1992) describes the brain as ‘fractal-like’, with recursive levels, each using ‘edge of chaos’ non-linear dynamic processing with ongoing tuning/detuning.

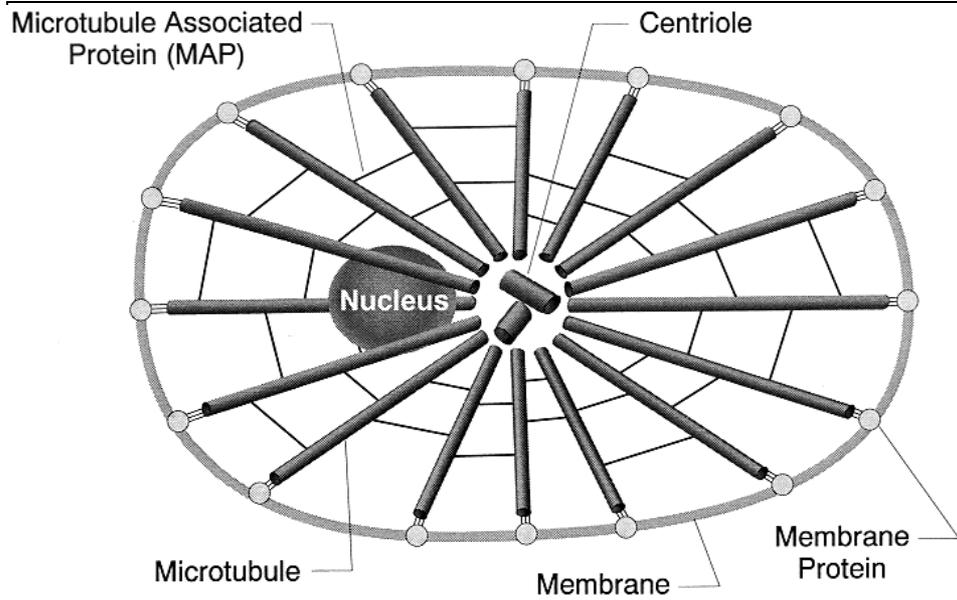


Figure 1. Schematic of simple cell with cytoskeletal microtubules organized radially around centriole near nucleus. Microtubule associated proteins (MAPs) interconnect microtubules to form

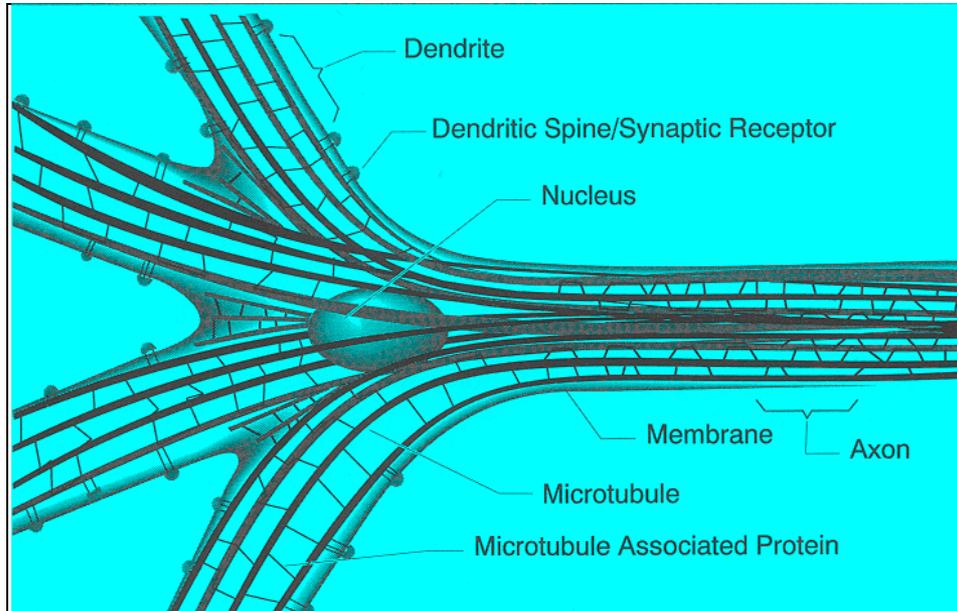


Figure 2. Schematic of central region of neuron (distal axon and dendrites not shown). Microtubules, interconnected by MAPs, are arranged in parallel. Linking proteins connect microtubules to membrane proteins including synaptic receptors on dendritic spines.

Microtubules (MTs) are cylindrical protein polymers interconnected by cross-bridging proteins (MAPs), which structurally and dynamically organize functional activities in living cells (see Figure 1), including synaptic regulation inside the brain's neurons (see Figure 2). In Sections II and III, we look at some of the current models of cognitive processes and make a case for the relevance of sub-neuronal structures. The basic thesis is that brain-wide microtubule-based quantum states, when coupled to synaptic events

and neuronal firing, can help account for the five properties of consciousness highlighted on page 92, and can provide a quantum/classical (mind/brain) interface.

II

Organization of Consciousness within the Brain

The organization of consciousness has been approached along three general lines: 1) neural networks, 2) attentional scanning circuits, and 3) coherent activity of distributed neurons.

Neural networks

Neural networks originated from the work of McCulloch and Pitts (1943) describing threshold logic neurons and from Hebb's (1949; 1980) concept of the 'cell assembly': a three-dimensional array of interconnected neurons whose firing was predicted to correlate with a specific mental state.⁴

The neuronal cell assembly concept helped to lead the way to 'artificial neural networks' ('ANNs') — parallel, distributed computer systems designed to implement aspects of brain function (e.g. Hopfield, 1982). Weighted connections ('synapses') among processing elements ('neurons') provide ANNs with 'brain-like' learning, pattern recognition and self-organization. Churchland and Sejnowski (1992) have reviewed how 'ANN-like' parallel distributed processing can operate in the brain, and ANNs are clearly more similar to brain function than are conventional algorithmic-based AI schemes.

However, the brain/ANN analogy falters in at least two major areas. First, rather than being simple threshold logic switches as depicted in ANNs, neuronal synapses are complex, dynamic connections ('plasticity'). 'In living nets everything is continually fluctuating: connection weights, transfer functions, parameters, input, and even the very connectivity, without leaving any traces of the fluctuation' (Globus, 1992). Many of these fluctuating functions depend on the intra-neuronal cytoskeleton; for example Friedrich (1990) has shown that learning by increased synaptic efficacy requires cytoskeletal restructuring in the sub-synaptic region.

It has been claimed that the second major difference between ANNs and brain structure is that many types of ANNs (e.g. back-propagation, adaptive resonance, RCE, sigma pi, etc.) use internal processing within each 'neural element'. For example in ANNs such as the useful back-propagation type, resulting outputs are compared to expected outputs and the difference, or error, is conveyed back to an input layer. Werbos (1974) originated ANN back-propagation algorithms based loosely on Freud's notion of retrograde flow of 'psychic energy' serving feedback/reward functions. Because the back-propagation of error is counter to unidirectional membrane depolarization and synaptic transmission, these types of ANNs have been considered biologically irrelevant. However retrograde signalling is now known to occur across synapses (dendrite to axon via nitric oxide and other mediators (e.g. Barinaga, 1991)), and retrograde information flow *within* neurons could be conveyed within microtubules and other cytoskeletal structures (Dayhoff *et al.* 1994; Rasmussen *et al.*, 1990). Thus cognitive processes may extend below the level of synaptic connectionism and include molecular-level processing in the cytoskeleton.

⁴ Hebb estimated that simple assemblies fire for 1 to 5 milliseconds, more complex 'assemblies of assemblies' for a half-second, and a 'phase cycle' (a series of assemblies of assemblies) for ten seconds or more (Freeman 1975; Scott 1994). Repeated firing of any assembly would lower its threshold and result in learning or recognition as the assembly adapts to become more sensitive (by lowering of synaptic threshold — synaptic plasticity) to a given input.

Attentional scanning circuits and the problem of qualia

Where in the brain does consciousness occur? Early theories of consciousness invoked a single brain location of *self, observation and control*, now characterized as the search for the ‘grandmother neuron’. This focalized concept is often generalized to a ‘homunculus’ — the ‘little man’ inside the brain which observes, controls and represents the ‘self’. But where in the brain does the homunculus reside? Descartes proposed the pineal gland as a unitary focus of self (although acting as a channel for a dualistic mind entity) partly because it was the only single, midline brain structure. In his functionalist argument, Dennett (1991) criticizes such a ‘Cartesian theater’ within the brain whose ‘audience’ observes and controls.

Contrary to these focal models, the evidence gathered from many avenues of research — stemming from Lashley’s (1950) demonstration of the non-localized distribution of memory — suggests that aspects of consciousness are *distributed* throughout wide areas of the brain. Somehow, parallel-arrayed, distributed neuronal groups — perhaps analogous to Hebb’s assemblies of assemblies (e.g. ‘modules’, ‘cartels’ etc. (Freeman, 1975; Gazzaniga, 1985; Minsky, 1986)) — give rise to a serial, integrated stream of consciousness (Baars, 1993). Certain brain and brainstem areas appear to be involved in the regulation, control and focusing of attention and consciousness.⁵ Baars (1988; 1993) has formalized a ‘global workspace’ model in which multiple brain ‘processors’ compete for access to a broadcasting capability which disseminates the ‘winner’s’ information globally throughout the brain.⁶ Adding the brain stem/limbic ‘hedonic’ system and language centres to the external thalamo-cortical system, Edelman (1989) describes re-entrant circuitry from which global mappings of neuronal populations are ‘selected’ to reach consciousness by a Darwinian-like survival mechanism.

Mappings of neuronal activity which correlate with a specific mental event still fail to describe the content, meaning or subjective sense of self and observer/controller inherent in consciousness. These issues are addressed in Searle’s (1980) famous ‘Chinese Room’ thought experiment (a man sorting Chinese characters) which distinguishes syntactic (logical, algorithmic, computer-like) from semantic interpretation (meaning, understanding, human consciousness-like). Taylor (1992) observes that content may only be relevant when compared to previous memory: ‘the meaning of an input . . . is given by the degree of overlap such an input has to past inputs.’ But how do past inputs have meaning? What is the substance of *qualia*: ‘the phenomenal qualities of the things of which we are conscious, the raw feels and sensations that make up much of our conscious lives’ (Korb, 1993).

Functionalists like Dennett (1991) argue that qualia are illusory, while dualists believe they are ‘ineffable’ and cannot be understood. Can the redness of a red object be explained by a given pattern of neuronal firing, perhaps accented by a neurochemical bathing of a particular transmitter concoction? Do two people experiencing red have the

⁵ These include the reticular activating system which regulates wakefulness, the nucleus reticularis of the thalamus which directs attention to different regions of the brain (Scheibel, 1980; Crick, 1984), and the superior colliculus of the tectum which integrates sensory information (Strehler, 1991). Thalamo-cortical projections, along with reciprocal cortico-thalamic feedback have been implicated in directing attention to specific brain regions by ‘reentrant feedback loops’ (Edelman, 1989). Thalamo-cortico-thalamic feedback loops have been observed which sweep from frontal to occipital cortex approximately every 12.5 msec. and indicate brain-wide scanning at a frequency of about 80 Hz. (Ribary *et al.*, 1991).

⁶ For example, a cortical focus which by thalamo-cortical feedback is sufficiently self-sustaining may be broadcast ‘brain-wide’ by associative pathways.

same sense of redness in their minds? Are we little better than Searle's uncomprehending man (or Dennett's 'zombies') with only the illusion of sentient consciousness? Or do our senses of beauty, oneness, joy and despair come from another realm? Is there a middle ground between reductionism and dualism? Once again quantum coherence at the molecular level of the cytoskeleton offers a possibility. Consider the *qualia* of redness; red is 'merely' a specific frequency of the electromagnetic spectrum, a brand of photon. As will be described, the theory of quantum coherence in the cytoskeleton implies excitations of a ground state yielding a condensed field of coherent bosons (phonons, photons, etc.) with specific frequency characteristics. Red of the electromagnetic spectrum can then correlate with a specific frequency boson-condensed field excitation in the brain. If true, and when technologically possible, the frequency of boson-field excitations corresponding to red in two people could be compared. More complex qualia (e.g. love, a pepperoni pizza, etc.) can then be viewed as complex mixtures of coherent boson fields, which as macroscopic quantum states, may also have suitable properties for a unitary sense of self.

These quantum features, unlike neural firing correlates, convey more than a reductionist representation of sentience; quantum boson fields are unitary, though non-local states. Their components are indistinguishable from one another by any measuring technique and they can exist in superposition of many states, collapsing to a single one. To which state a superpositioned quantum wave function collapses can be seemingly random and 'non-deterministic'. Thus macroscopic quantum states, unlike neural firing-level correlates, can have non-deterministic properties suggestive of 'free will'.

Coherent activity of distributed neurons — the 'binding' problem

Current neurobiological approaches to explain how brain-wide activities result in a singular perceptual entity involve coherent firing of widely distributed neurons. Based on Hebb's cell assembly theory, Milner (1974) proposed that different neurons responding to a common 'figure' fire *synchronously*. Using multi-unit recording in awake monkeys, Abeles (1982) found that temporal correlation among groups of neurons were related to high-level perceptual tasks and formalized a 'synfire chain' model of cortex. Von der Marlsburg and Schneider (1986) showed how temporal synchronization of subsets of simultaneously active neurons could 'segment' different mental objects (e.g. two different speakers at a noisy cocktail party) by a postulated fast (ten to hundreds of milliseconds) Hebbian synaptic modulation mechanism. (Such rapid synaptic modulation requires cooperative activities of the intra-neuronal cytoskeleton.) Following Freeman's (1978) suggestive findings in olfactory cortex, Eckhorn *et al.* (1988) and Gray and Singer (1989) found rapid oscillations above EEG frequencies (40 Hz) in cat visual cortex and Gray *et al.* (1989) then showed that these oscillatory responses can become synchronized in a stimulus-dependent manner. Based on these findings, Crick and Koch (1990) formalized a theory of consciousness in which coherent firing of widely-distributed neurons in the range of 40 Hz 'bind' them together in mental representation and a unitary sense of self (see also, Koch, 1993). Studies of auditory-evoked responses in humans have shown inhibition of 40 Hz coherence with loss of consciousness due to induction of general anaesthesia (Madler and Poppel, 1987; Plourde and Picton, 1990).

Coherent neural activity raises the possibility of a holographic paradigm. Pribram (1971) proposed that interference of coherent electromagnetic fields at the level of dendritic-dendritic interactions results in a holographic mechanism of cognitive representation. The holographic paradigm is appealing because memory can be recalled by a 'reference' signal, and vast amounts of information can be stored in a distributed rather than localized manner. Quantum coherence, as proposed to occur in cytoskeletal micro-

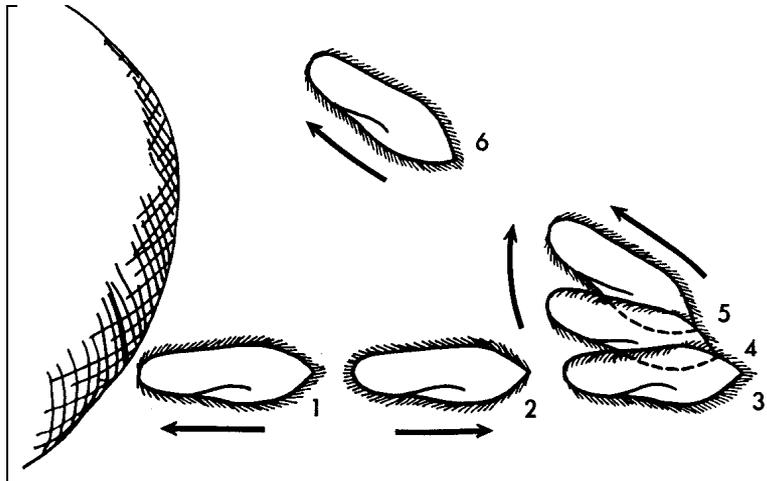


Figure 3. Rebounding reaction of Paramecia towards external stimulus. (1-3) short-lasting ciliary reversal; (3-5) pivoting and circling; (6) swimming in new direction. (With permission from Dryl, 1974)

tubules, can provide a mechanism for intracellular quantum holography (Hameroff, 1987; Schempp, 1993).

Neurobiological approaches (neural networks, attentional mechanisms and/or coherent activity) generally describe patterns of neural firing which may correlate with mental states, including consciousness. However, even if the exact patterns of neuronal firing correlating with specific mental activities become known, would consciousness be better understood? The reductionist view would be *yes* and strong AI advocates would be validated. To manifest consciousness, computers would merely need to reach the connectionist complexity of the brain's neurons and synapses — a feat strong AI advocates believe attainable within decades. The view of dualists would be emphatically *no*; the firing pattern *is* the brain's activity, but it is clearly not equivalent to consciousness. Emergence partially resolves this question; consciousness may indeed be a phenomenon derived from, but not equivalent to the brain's activity. But what exactly *is* consciousness? How are distributed neural activities, even coherently synchronized activities, bound into a unitary sense of self? Macroscopic quantum states offer one solution; but how could they be supported? Where and how could they exist?

III Cognition within Living Cells

One possible path to solving this question is by examining the complexity of neurons and their synaptic connections. Reductionists tend to overlook the fact that neurons are *alive* and most views of the hierarchical organization of the brain stop at the synapse as the fundamental switch, analogous to states or bits in computers. The complexity of neurons and their synapses, however, are closer to entire computers than individual switches. This implies the mechanism of consciousness may depend on an understanding of the organization of adaptive ('cognitive') functions *within* living cells.

Like the rest of our cells, neurons are eukaryotic cells which, unlike prokaryotic bacteria, have a true nucleus and cytoskeleton and exhibit mitotic cell division.⁷ Single eukaryotic cell organisms (protozoa) such as paramecia show remarkable, seemingly intelligent abilities without the benefit of a single synapse (Figure 3)! Observation of

⁷ According to Margulis (1975), eukaryotic life is the result of a symbiotic merger of prokaryotes (immobile chemical factories) and spirochetal invaders (highly motile flagellates with minimal

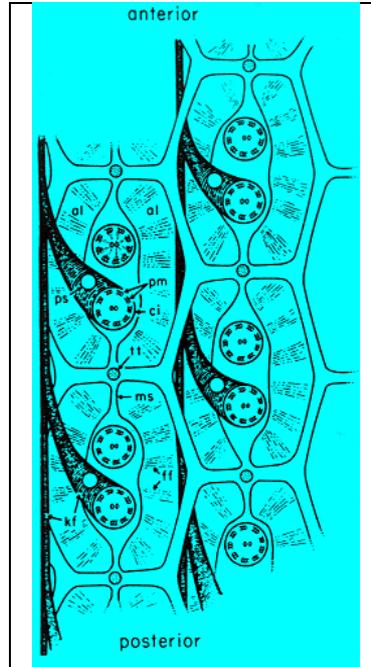
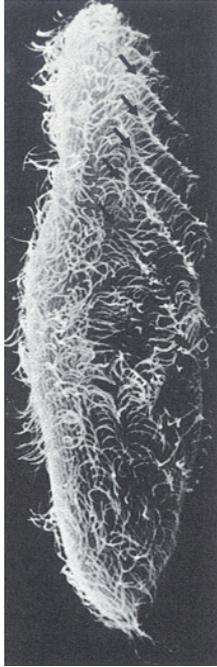


Figure 4a: Scanning electron micrograph (rapid fixation) of *Paramecium* showing protruding cilia. Arrows demonstrate ciliary movement in metachronal waves.
4b: Diagram showing *Paramecium* polygonal infraciliary lattice with cilia (ci), containing 9 + 2 sets of microtubules including peripheral microtubule (pm) doublets. (ms: median septum, al: alveoli, tt: trichocyst tips, ps: parasomal sacs, ff: fine fibrils, kf: kinetodesmal fibrils.) This illustrates how cilia (sensory and motor) are connected to intra-cellular cytoskeleton. (With permission from Wichterman, 1985).

amoebae hunting food and paramecia avoiding obstacles led Charles Darwin and other 19th century biologists to project human psychology and aspects of consciousness onto protozoa. Popular books of that era included *The Psychic Life of Microorganisms* by Alfred Binet and *The Animal Mind* by M.F. Washburn. Darwin viewed adaptive activities of single-cell organisms as rudimentary consciousness related to man through evolution. Others (e.g. Jaynes, 1976) objected to this linkage, stating that protozoan behaviour ‘depended entirely on physical chemistry rather than introspective psychology’. However it now seems introspective psychology itself may be an emergent function of physical chemistry (and quantum mechanics) at some level. The famous neuroscientist C.S. Sherrington (1951) wrote:

Many forms of motile single cells lead their own independent lives. They swim and crawl, they secure food, they conjugate, they multiply. The observer at once says ‘they are alive’; the amoeba, paramecium, vorticella, and so on. They have specialized parts for movement, hair-like, whip-like, spiral and spring-like. Sense organs, beyond a pigment spot, seem to inspection wanting. Of nerve there is no trace. But the cell framework, the cyto-skeleton, might serve. There is therefore, for such mind as might be there, no need for our imagination to call halt and say ‘the apparatus for it is wanting’.

As Sherrington observed, the cytoskeleton may act as the nervous system of single-cell organisms. *Paramecia*, for example, can apparently learn (Gelber, 1958), remember (Applewhite, 1979) and exhibit adaptive responses such as avoidance and habituation

chemistry). The motile spirochetes are thought to have invaded prokaryotes and found shelter and biochemical energy. The filamentous proteins which comprised the spirochetal flagellae and provided movement became the eukaryotic cytoskeleton and offered the new type of cell abilities to 1) divide chromosomes and thus mutate and evolve, 2) compartmentalize, leading to specialization, 3) move around, explore and avoid predators, 4) grow asymmetrically (e.g. neurons), and 5) generally adapt.

which involve movement performed by coordinated actions ('metachronal waves') of hundreds of hair-like appendages called cilia (Figure 4).⁸

External events which initiate adaptive responses via ciliary and/or membrane perturbation in paramecium are similar to receptor binding of neurotransmitter molecules in neuronal synapses.⁹ In paramecia, adaptive behavioural responses to external stimuli involve motor activities performed by complex activities of cilia; in neurons they include regulation of synaptic strengths, and cognitive functions related to learning, memory, and aspects of consciousness.

Is consciousness a property of protoplasm in general? Do single-cell organisms, such as paramecium, exhibit consciousness? If not, at what point in the evolutionary hierarchy does consciousness emerge? These distinctions may be somewhat arbitrary, but the *fabric* of consciousness may be present within all eukaryotic cells. If so, how low in the organizational hierarchy of single cells do the rudiments of consciousness extend? An extreme view ('panpsychism') is that consciousness is a quality of all matter: atoms and their subatomic components having elements of consciousness (Spinoza, 1677; Rensch, 1960). But then what distinguishes non-living material from living, and how are all the atomic and sub-atomic consciousness entities unified (the binding problem taken to extreme)?

Many contemporary thinkers feel that quantum mechanics may provide answers to at least some of these questions and that consciousness may emerge at a critical amount of non-local quantum processing linked to some neural structure. It is the particular proposal of this paper, developed in the next section, that cytoskeletal microtubules are the most likely location for such an effect. Preliminary technical arguments are developed in Appendices 1–3. Appendix 1 discusses the structure of microtubules in detail and reviews recent evidence for their role in cognition; Appendix 2 outlines Fröhlich's work on protein dynamics, whilst Appendix 3 outlines the mechanisms by which proteins may act as complex information processors and 'quantum computers'. The arguments are, of necessity, somewhat technical. Readers with a scientific background should read the appendices in full at this stage, while others may prefer to proceed to the next section.

⁸ Comprised of nine microtubule doublets arranged in a ring around a central microtubule pair, cilia are membrane-bound extensions of the cytoskeleton in cells ranging from protozoa to human epithelium. In addition to several types of motor movement, cilia have sensory function in that their perturbation is transmitted to the cell. Lund (1933) showed that microtubules within paramecia were 'conductile' and transmitted information, and Atema (1974) proposed that signal transduction in sensory cilia involved propagating conformational changes along ciliary microtubule subunits. Complex action of paramecium ciliary 'metachronal waves' are coordinated by a peripheral cytoskeletal network to which the cilia are anchored; this network is in turn connected to internal microtubules and other cytoskeletal structures. Several authors (e.g. Lund, 1933; 1941) identified a central confluence of cytoskeletal structures (the 'neuromotorium') characterized as the paramecium 'brain'. Metachronal waves of ciliary beating in paramecia are reversibly inhibited by the general anaesthetic chloroform (Parducz, 1962), suggesting some link to consciousness in higher organisms.

⁹ Each triggers 'second messenger' transduction cascades (G proteins, calcium ion flux, adenylyl cyclase, phosphatidylinositol, cyclic AMP, etc.) which in turn activate enzymes (e.g. dynein AT-Pases, cytoplasmic phosphatases and kinases such as calcium-calmodulin protein kinase, MAP kinase, calcineurin, protein kinases A and C (Eriksson *et al.*, 1992; Montoro *et al.*, 1993)). Among the responses of the enzymes (kinases in particular) are phosphorylation/dephosphorylation of cytoskeletal structures including microtubule-associated-proteins ('MAPs') and intermediate (neuro) filaments which can initiate cytoskeletal signalling and structural reconfiguration (Johnson and Pope, 1992). In addition, external events acting through membrane proteins can directly connect to the internal cytoskeleton by linking proteins such as fodrin, ankyrin and actin.

IV Quantum Physics and Consciousness

Quantum theory describes fundamental properties of matter and energy which comprise our universe. Seemingly bizarre and counter-intuitive, quantum properties — including wave/particle duality, the (Heisenberg) ‘uncertainty principle’, randomness or acausality, and quantum inseparability or non-locality (quantum coherence) — have been repeatedly verified by experimentation over much of this century. These strange properties may help explain the mysterious nature of consciousness. ‘Perhaps our minds are qualities rooted in some strange and wonderful feature of those physical laws which actually govern the world we inhabit’ (Penrose, 1989).

At the base of quantum theory is the wave/particle duality of atoms and their components. When *unobserved*, an atom or sub-atomic particle behaves as a ‘wave of possibilities’; *observation* in effect ‘collapses the wave function’ and a particle appears. The Heisenberg uncertainty principle dictates that either the position or momentum of a particle (but not both) can be known with arbitrary precision. Beginning over four decades ago, these properties prompted very general comparisons to mental processes. As observation of a quantum particle alters its state, Bohm (1952) observed that thoughts and mental processes, when focused upon, become altered and might therefore have some basis in quantum mechanics. Szent-Gyorgyi (1960) and Pullman and Pullman (1963) made broad analogies between wave/particle and mind/brain dualities.

Quantum randomness stems from the superposition of an unobserved atom or particle in many possible states; which particular state will be observed is apparently random. Einstein objected to this quantum randomness or acausality: ‘I cannot believe that God would play dice with the Universe’. However as Pagels pointed out ‘if things at base are utterly random, nothing can make them more disordered. Complete randomness at the heart of things is the most stable situation imaginable’ (Herbert, 1993). Noting that the ‘material’ world consists of nothing but ‘relentlessly unrealized vibratory possibilities’, von Neumann proposed and Wigner and others elaborated (Wheeler and Zurek, 1983) that by observing (measuring) the real world, the conscious mind collapses wave functions and confers solidity, single-valueness and dependable constancy. Globus (1987) argues that

possible worlds are superposed *within the brain* — the ‘holoworld’, and perception, both waking and dreaming, selects a world for unfolding from the holoworld. The collapse of the wave function is a selection process from *a priori* implicate worlds.

These ideas are comparable to Bohm’s (1980) ‘implicate order’, and Everett’s (1957) many universe view. But then what is it about the conscious mind which causes this collapse?

Another view is that matter consists of fleeting vibratory patterns in a vast field of consciousness: a universal mentality interpenetrates the physical world. This concept (‘quantum animism’) suggests that every quantum wave contains consciousness and vice versa: ‘where there’s a will, there’s a wave’ (Herbert, 1993). This view is a quantum version of dualist and idealist concepts such as Cartesian mental substance or Hegelian world spirit (Searle, 1980); the quantum/mental realm interacts with the physical realm in the structures of our brain. Several approaches to elucidate the site and mechanism of this quantum interaction have focused on the synapse.

Beck and Eccles (1992) proposed that quantum randomness results in what appears to be probabilistic, acausal synaptic function. Noting that in an apparently random fashion

only one of approximately six axonal action potentials results in synaptic release of neurotransmitter vesicles, they pinpoint the quantum effect as the ‘movement of a hydrogen bridge by electronic rearrangement’ acting on vesicle release through the pre-synaptic vesicular grid. A hexagonal lattice on the inner surface of the presynaptic region, the vesicular grid was chosen by Beck and Eccles as the site for quantum influence because of its ‘paracrystalline structure’ which ‘makes it possible to have long-range interactions between the constituents’. (A similar argument can be made for more ubiquitous paracrystalline microtubule arrays.) Other candidates for mediation of quantum randomness effects include ion channels (Bass, 1975; Donald, 1990) and ions (e.g. calcium ions) themselves (Stapp, 1993).

Quantum coherence

The greatest surprise to emerge from quantum theory is quantum inseparability or non-locality which implies that all objects that have once interacted are in some sense still connected! Schrödinger observed in 1935 that when two quantum systems interact, their wave functions become ‘phase entangled’. Consequently, when one system’s wave function is collapsed, the other system’s wave function, no matter how far away, instantly collapses too (Herbert, 1993). The non-local connection (quantum coherence) is not only instantaneous and independent of distance but impervious to shielding. Einstein, Podolsky and Rosen (1935) proposed an experimental method for testing inseparability involving observation of polarization states of two photons emitted in different directions from a common source. J.S. Bell in 1964 (e.g. Bell, 1987) formulated the notion that, if quantum inseparability were false, then changing the measurement context of one photon would not affect the other photon’s behaviour (‘Bell’s theorem’). Amazingly, experiments by Clauser *et al.* (1969) and Aspect and Grangier (1986) disproved Bell’s theorem by showing that choice of context of measurement of one photon instantly affects outcome of measurement of a distant photon. The quantum world is truly interconnected; *quantum entities are ‘aware’ of the states of their spatially separated relatives!*

Such ‘knowing’ has prompted linkage of non-local quantum coherence to mental processes. Bohm (1951) described the quantum world as an ‘undivided wholeness’ or ‘implicate order’ and related it to a holographic model of consciousness which accents the wave nature of experience. Pribram (1971) has proposed that mental representation occurs holographically by interference of coherent waves (e.g. dendritic field potentials). Non-local quantum effects among different individuals have been related to ‘Jungian synchronicity’ (‘meaningful coincidence’) originating from what the famous psychoanalyst C.G. Jung termed the ‘collective unconscious’ (Peat, 1992; Insinna, 1992).

Quantum coherence has also been linked to more specific biological function and computation. Conrad (1992) has argued that superposition of spatially-separated electron states facilitates common biomolecular interactions such as antigen–antibody, neurotransmitter–receptor, enzyme–substrate, protein self-assembly and other functions. Conrad further suggests that quantum coherence and parallelism inherent in the quantum-mechanical wave function can enhance the speed, reliability, and energy dissipation of elementary switches such as those involved in molecular computation (including, perhaps, tubulins within microtubules). Theoretical descriptions of quantum computers propose utilizing quantum coherence, superposition and parallelism for technological purposes.¹⁰ Penrose (1989; 1994) sees such quantum computing in the brain as a mechan-

¹⁰ For example Deutsch (1985; 1992) and Lloyd (1993) foresee quantum-level bit states (e.g. 1,0) which can be in quantum superposition of both 1 and 0. If the bit state sites (in an array or polymer)

ism for ‘non-algorithmic’ processing intrinsic to human consciousness. He speculates that conscious thinking involves resolution of alternatives that were previously in linear superposition.

Coherent quantum phenomena cannot perform computation if the system undergoes significant ‘measurement-like interactions’ with the outside world; only well-isolated quantum computers are possible. Inherent isolation implies a ‘subjectivity’, or internal information inaccessible to external observation within quantum computers, a property suggestive of consciousness (Deutsch, 1992). An appropriate ‘classical’ interface for quantum computers could be ‘selective driving of resonances’ (Haddon and Stillinger, 1982). Lloyd (1993) proposes an array of weakly-coupled quantum systems which would be subjected to sequences of electromagnetic pulses of well-defined frequency and length, permitting loading, processing and unloading of information. Cytoskeletal polymers subjected to neuronal firing might constitute such a system.

Penrose (1989) has also invoked the possibility of quantum superposition in synaptic plasticity. Non-periodic tiling patterns of quasi-crystals (‘Penrose tiles’) require ‘non-local’ effects; it appears necessary to ‘know’ the state of the pattern many tiles away from the point of assembly. Rather than classical crystal growth in which individual units attach themselves at a continually moving growth line, Penrose considers this to occur as an ‘evolving quantum linear superposition of many different alternative arrangements’ and likens this situation to learning and memory by synaptic plasticity in which neuronal connections are rapidly formed, activated or deactivated. ‘Thus not just one of the possible alternative arrangements is tried out, but vast numbers, all superposed in complex linear superposition’ (Penrose, 1989). Synaptic connections are formed and regulated by cytoskeletal polymers, including microtubules. Complex linear superposition of many cytoskeletal configurations corresponding to synaptic connection patterns collapsing to a single one could account for the extremely rapid synaptic plasticity required for cognition. Penrose (1989; 1994) also considers that collapse of superpositioned states and conversion from quantum to classical behaviour depends on a threshold related to quantum gravity. He predicts that gravity, although an extremely weak force, influences the quantum realm because it acts on the spacetime structure itself. Objects that become larger than a crucial size spontaneously actualize one of their possibilities; spacetime curvature causes the system’s wave function to collapse ‘under its own weight’. Herbert (1993) has used a ‘quantum realm’ approach to estimate a mass value for ‘quantumness’ and obtains a rough estimate of 10^6 daltons. This is the size of Eccles’ pre-synaptic ‘microsite’ and also of about ten tubulin subunits within a microtubule. Penrose calculates a higher number of tubulins whose coherence for a critical time will self-collapse, and result in a single conscious event. According to Penrose, the manner in which quantum gravity can act as a bridge between the quantum world and the classical world will await new discoveries in quantum physics.¹¹

Bose-Einstein condensates

Concluding that quantum effects are necessary to explain the ‘unity of conscious experience’, Marshall (1989) has searched for a quantum mechanism that is extended in space

are locally interactive as in a cellular automaton (e.g. from overlap among unit–unit electron wave functions, van der Waals forces, conformational changes of subunits, dipole coupling, etc.), then parallel logic and quantum coherence can result in quantum computation; multiple computations collapse into a macroscopic quantum state.

¹¹ See also (in this volume) Nunn *et al.* (1994)

(non-local, long-range order), capable of many states, and has a 'shared identity' un-analyzable into parts ('diversity in unity'). Marshall concludes these properties are unique to systems known as 'Bose-Einstein condensates' (see Appendix 2). Usually, each particle/wave in a quantum system possesses its own wave function. However, under certain circumstances, many quantum particle/waves move coherently, described by the same wave function. Arising in quantum field theory, Bose-Einstein condensates are collective, macroscopic quantum states named after Indian physicist Satyandra Nath Bose and Albert Einstein who independently predicted the types of particle/waves ('bosons') and conditions necessary for realization of such states (Zohar and Marshall, 1994).

Quantum field theory describes the underlying reality of everything in the universe (including consciousness) as consisting of three components: the *vacuum*, space and time. A 'field of fields' which contains no particles, the vacuum gives rise to quantum wave/particles as excitations or energy fluctuations within it (like 'sound from a drum skin' (Zohar, 1990)). A *ground state* is a component field of the vacuum whose excitation can yield the two types of wave/particles: fermions and bosons. Fermions are the ingredients of matter (electrons, protons, and neutrons) which tend to be individual; their wave functions cannot overlap entirely (although fermion *pair* wave functions have bosonic properties and *can* overlap as in superconductors, supermagnets and superfluids). Bosons are wave/particles of relationship which convey forces and which can *merge* as their wave functions overlap; they can coherently share identities. Bosons include photons, virtual photons, phonons and other entities including possibly gravitons; the forces they convey include electromagnetic, weak and strong nuclear and possibly gravity. In concert with the uncertainty principle, a set of boson ground-state excitations can act coherently by entry into the lowest momentum state so that position becomes undefined (Tilley and Tilley, 1986). Consequently, a large set of bosons is described by a single wave function and coherent, collective macroscopic quantum states result (Herbert, 1993).

Quantum field theory was initially linked to consciousness by Ricciardi and Umezawa (1967) who proposed that each brain cell contains a spatially distributed system with a full complement of quantum-mechanical degrees of freedom. Without specifying the intraneuronal structural correlate, they suggested that memory of an external stimulus is imprinted as a perturbation of the vacuum ground state of the unspecified intraneuronal system. By violating the system's original dynamical symmetry, long-range correlation waves (bosons) condense and correlate with mental processes.

Examples of known Bose-Einstein condensates include the laser, in which many photons occupy exactly the same optical state, superconductors, in which numerous linked electrons ('Cooper pairs') take on identical quantum possibilities, supermagnets in which micro-dipoles align, and superfluids like helium, in which quantum synchronized atoms create a friction-free fluid. In each case the overlapping of position gives a shared identity and the ground state has a long-range order (coherence).

Superconductors, supermagnets and superfluids require temperatures near absolute zero to reduce thermal oscillations and bring the particles into coherence. Lasers require high energy to drive crystals into coherent excited states. Of known systems akin to Bose-Einstein condensates, only Fröhlich's proposed pumped phonon system (see Appendix 2) can operate at body temperature (Marshall, 1989). Fröhlich predicted that a set of proteins in a common electromagnetic field (e.g. proteins within a polarized membrane, subunits within an electret polymer like microtubules) undergo coherent conformational excitations if biochemical energy were supplied ('pumped phonons').

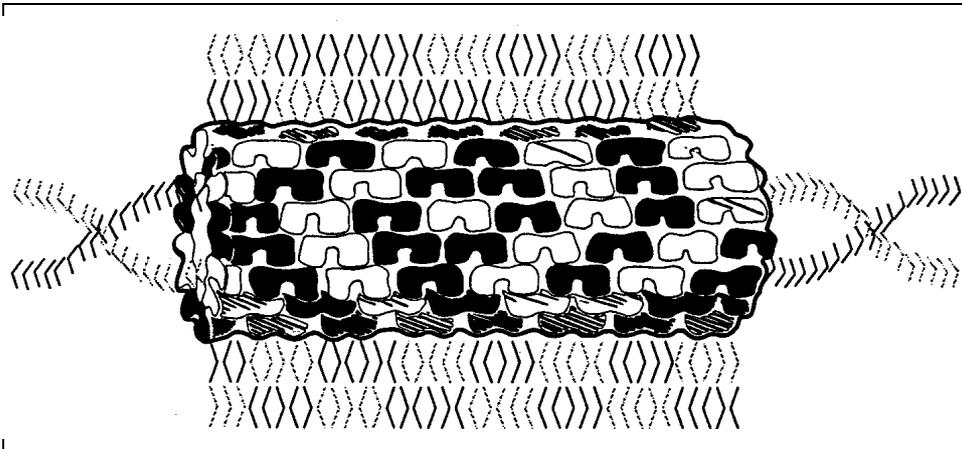


Figure 5 Microtubule automata (MTA) with ordered water.

Using a set of assumptions for a layered sheet of dipoles, Clarke (1994) has questioned the feasibility of Fröhlich's biological Bose-Einstein condensates. However cooperative effects of coupled, ordered water and non-planar geometries (in particular cylindrical protein lattices like microtubules) make Fröhlich's biological Bose-Einstein condensates more likely (e.g. Sataric *et al.*, 1993; Jibu *et al.*, 1994).

Citing Fröhlich's pumped phonons in unspecified 'neural proteins' as a Bose-Einstein condensate, Marshall predicted that conscious phenomena (thoughts, images, etc.) would occur as excitations of the ground state, like waves in superfluid helium or holograms in laser light. He reasoned that such a condensate could suffice even as only a minor facet of brain dynamics (in a superconductor only one material part in ten thousand participates in the phase change, but the macroscopic properties are dramatically altered). Cytoskeletal microtubules have suitable qualifications to act as a brain substrate for Bose-Einstein condensates related to consciousness.¹² Consciousness may then be seen as a *dynamic* macroscopic quantum state originating from a mixture of coherent states originating in microtubules.

Super-radiance

Quantum coherence has been theoretically applied not only to membranes and cytoskeletal structures, but to water molecules ordered at their surfaces (Figure 5).¹³ Using

¹² Fröhlich pumped phonons have already been considered in microtubules as a basis for information processing via spin-glass behaviour and as a clocking mechanism for cellular automata functions. The cooperative coupling resulting in coherence has been assumed to be phonons (bosons) coupled to dipoles or electrons 'trapped' in hydrophobic regions (e.g. aromatic amino acid residues with resonant orbitals). Microtubules' paracrystalline periodic lattice and cylindrical configuration provide an ideal coherent structure, and the functions of microtubules are crucial to intracellular cognition. Thus spin-glass and automata models, similar if not equivalent to Bose-Einstein condensates, may manifest quantum computing by interactive patterns of coherent sets of pumped phonons (bosons).

¹³ Fröhlich theorized that energy could be stored without thermal loss in coherent, dipolar propagating proteins or in a thin layer of water and ions just beneath the cell membrane. Watterson (1987) has shown how organized, dynamic water clusters ('pixels') can represent information at membrane and cytoskeletal surfaces. Considering the layer of ordered water outside and inside microtubules, Del Giudice *et al.* (1983) proposed that microtubules' cylindrical structure may be understood by quantum-vacuum symmetry breaking and boson self-focusing by ordered water. Like the Meissner

quantum field theory, Jibu *et al.* (1994) have proposed that ordering of water molecules and the quantized electromagnetic field confined inside the hollow microtubule core manifest a specific collective dynamics called *super-radiance*. Accordingly, each microtubule can transform incoherent, disordered energy (molecular, thermal, or electromagnetic) into coherent photons within its hollow core. Furthermore, coherent photons created by super-radiance may penetrate without loss along the microtubule as if the optical medium were made 'transparent' by the propagating photons themselves. This is a quantum phenomenon called *self-induced transparency* (McCull and Hahn, 1987) (Figure 6). Some evidence suggests weak photoemission from living cells, and Popp (1986) has proposed a regulatory role for 'coherent biophotons'. Thus Jibu *et al.* suggest that microtubules can behave as optical waveguides which result in coherent photons; they estimate that this quantum coherence is capable of superposition of states among microtubules spatially distributed over hundreds of microns. These in turn are in superposition with other microtubules hundreds of microns away in other directions and so on. Consequently microtubule quantum dynamics may be coupled over brain-wide areas, a superposition which could solve the 'binding problem' and account for unity of thought and consciousness.

To summarize, cytoskeletal microtubules are likely candidates for quantum coherence relevant to consciousness because:

- Microtubule individual subunit (tubulin) conformation may be coupled to quantum-level events (electron movement, dipole, phonon) in hydrophobic protein regions.
- Microtubule paracrystalline lattice structure, symmetry, cylindrical configuration and parallel alignment promote long-range cooperativity and order.
- Hollow microtubule interiors appear capable of water-ordering, waveguide super-radiance and self-induced transparency.

It is proposed, therefore, that microtubules' ubiquitous presence and crucial involvement in regulatory and cognitive functions in neurons and other eukaryotic cells can mediate quantum effects in a wide range of significant biological functions. In particular, quantum coherence (Fröhlich pumped phonons, Bose-Einstein condensation, ordering of water) in cytoskeletal microtubules and related structures can lead to quantum computing and emergence of macroscopic quantum states suitable for a unitary sense of consciousness.

V

Anaesthesia, Quantum Coherence and Consciousness

As a putative mechanism for consciousness, microtubule-based quantum coherence should be sensitive to general anaesthesia. Brains of patients under general anaesthesia are commonly quite active: EEG, evoked potentials, respiratory and autonomic drives and other brain functions persist despite a lack of consciousness. Thus, at just the right level, general anaesthesia is the *absence* of consciousness.¹⁴

effect for superconducting media, electromagnetic energy would be confined inside filamentous regions around which the microtubule subunits gather. Del Giudice's group (1983) showed that this self-focusing should result in filamentous beams of radius 15 nanometers, precisely the inner diameter of microtubules!

¹⁴ A variety of different types of gas molecules constitute general anaesthetics; they range from halogenated hydrocarbons to ethers to inert gases such as xenon. What they share in common are 1)

If quantum coherence in microtubules is essential for consciousness, anaesthetics must somehow inhibit or prevent it, either indirectly or directly.¹⁵ At concentrations of anaesthesia just sufficient for ablation of consciousness, anaesthetic action at hydrophobic regions of membrane receptors and channels, tubulins and other proteins could have profound effects by retarding mobility of dipoles/electrons in those hydrophobic regions, thereby inhibiting conformational dynamics, coherent phonons and Bose-Einstein condensation. Wulf and Featherstone (1957) showed that anaesthetic-protein binding within hydrophobic regions alters protein-water binding at the protein surface. Thus anaesthetic-tubulin interaction would alter cooperative water-binding and ordering, with consequent effects on quantum vacuum symmetry breaking and attendant 'super-radiance' and 'self-induced transparency'. By having such effects in hydrophobic regions of tubulin and other proteins, anaesthetics can reduce and prevent quantum superposition and coherence. This is consistent with the quantum realm interacting with the brain via a collection of quantum-level events in hydrophobic regions of brain proteins — in particular tubulin subunits within microtubules.

VI Summary

Consciousness is described as an emergent macroscopic quantum state driven or selected by neurobiological mechanisms (neural networks, attentional scanning circuits, coherent firing of distributed neurons) with origins in quantum coherence in cytoskeletal microtubules within the brain's neurons. Microtubule quantum coherence is thought to derive from two possibly inter-related mechanisms:

- Bose-Einstein condensates stemming from a 'Fröhlich pumped phonon' mechanism of dipoles in hydrophobic pockets of microtubule subunits.
- A quantum-dynamical system of water molecules and the quantized electromagnetic field confined inside the hollow microtubule core. The latter induces a specific collective dynamics called super-radiance by which coherent photons are created and penetrate without dissipation in the microtubule core in a quantum effect called self-induced transparency (Jibu *et al.*, 1994).

A macroscopic quantum state approaching brain-wide dimension can provide properties which define consciousness. These include: 1) a unitary sense of self, 2) randomness or non-deterministic 'free will', 3) non-algorithmic 'quantum' computing. Coupling of solubility in a specific 'hydrophobic' environment, and 2) binding by weak van der Waals forces (e.g. Halsey, 1983). After many years of investigating effects in hydrophobic *lipid* regions of membranes, anaesthetic gas molecules are now recognized to reversibly inhibit consciousness by weak, van der Waals binding in hydrophobic regions of some set of neural (presumably synaptic membrane) *proteins* (Franks and Lieb, 1982). As previously described, quantum-level events (dipole/electron oscillations, phonons) in protein hydrophobic regions are thought to couple to functional dynamic protein conformational states. Anaesthetics are known to retard mobility of electrons (Hameroff and Watt, 1983), and by doing so in hydrophobic regions anaesthetics may prevent protein conformational responsiveness.

¹⁵ Possible indirect ways include inhibition of activities of membrane, second messenger or membrane-cytoskeletal linking proteins which could disconnect and isolate cytoskeletal dynamics from the external milieu. Anaesthetics may also disrupt hydrophobic links among microtubule-associated-proteins (MAPs) which interconnect microtubules into functional networks (Lewis *et al.*, 1989). Alternatively, anaesthetics may directly alter cytoskeletal quantum coherence. General anaesthetics are known to bind to microtubules and at high enough concentrations cause their depolymerization (Allison and Nunn, 1968).

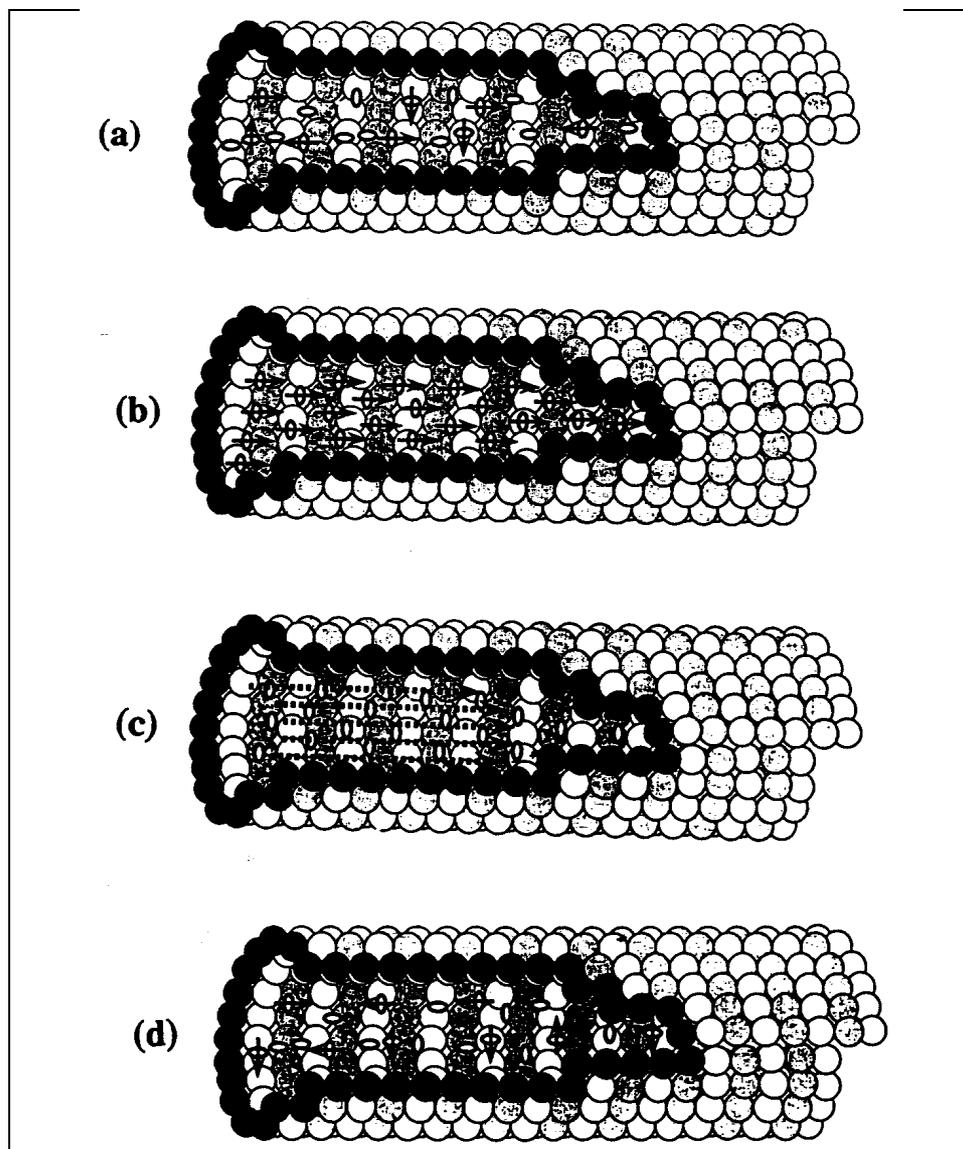


Figure 6. A schematic representation of the process of super-radiance in a microtubule

Each oval without an arrow stands for a water molecule in the lowest rotational energy state. Each oval with an arrow stands for a water molecule in the first excited rotational energy state. The process is cyclic (a), (b), (c), (d), (a), (b), and so on.

(a) Initial state of the system of water molecules in a microtubule: energy gain due to the thermal fluctuation of tubulins increases the number of water molecules in the first excited rotational energy state.

(b) A collective mode of the system of water molecules in rotationally excited states: a long-range coherence is achieved inside a microtubule by means of spontaneous symmetry breaking.

(c) A collective mode of the system of water molecules in rotationally excited states loses its energy collectively, and creates coherent photons in the quantized electromagnetic field inside a microtubule.

(d) Water molecules, having lost their first excited rotational energies by super-radiance, start again to gain energy from the thermal fluctuation of tubulins, and the system of water molecules recovers the initial state (a). (With permission from Jibu *et al.*, 1994).

this quantum state to microtubule subunit conformational states can account for cellular control, adaptive behaviour, synaptic regulation and cognition by propagating signals through cytoskeletal networks and information processing via mechanisms including molecular ('cellular') automata, spin-glass and holography. Microtubules are appropriate candidates for quantum coherence leading to consciousness because their subunit conformation (and consequent function) can couple to quantum events in hydrophobic regions, their paracrystalline lattice structure and symmetry promote long-range order and their hollow cylindrical core can lead to water ordering with waveguide super-radiance and self-induced transparency. The essential and ubiquitous roles microtubules play in cellular control and regulation and their communication and proximity with membrane proteins, cell nucleus and other biomolecular structures can link microtubule-based quantum events to basic biological functions.

General anaesthetic gas molecules, which selectively inhibit consciousness at appropriate concentrations, act at hydrophobic protein regions and are known to inhibit electron mobility. Thus anaesthetics, whether acting directly on microtubules or indirectly via membrane proteins or membrane-cytoskeletal connections, can reversibly erase consciousness by inhibiting quantum-level events in protein hydrophobic regions and thus disrupting quantum coherence.

As a model of consciousness, quantum coherence in microtubules is reductionist in that a specific molecular structure is featured as a site for consciousness. It is seemingly dualist in that the quantum realm (which is actually intrinsic to all of nature) is seen to act through microtubules. General anaesthesia is viewed as reducing and preventing quantum superposition and coherence in protein hydrophobic regions, a view which also speaks to an intrinsic quantum nature of consciousness.

APPENDIX

I

Microtubules and the Cytoskeleton

Interiors of living eukaryotic cells are structurally and dynamically organized by networks of interconnected protein polymers. Originally termed the cytoskeleton because of their 'bone-like' structural support, these networks also orchestrate and control dynamic cellular activities and may be considered as the cell's nervous system. The cytoskeleton consists of microtubules ('MTs'), actin microfilaments, intermediate filaments and an organizing complex called the centrosome whose main components are MT supercylinders called centrioles (Dustin, 1984). Parallel-arrayed MTs are interconnected by cross-bridging proteins (MT-associated proteins: 'MAPs') to other MTs, organelles, filaments and membranes to form dynamic networks. Contractile MAPs such as dynein and kinesin participate in cell movement as well as intra-neuronal ('axoplasmic') transport which moves material and plays a major role in maintaining and regulating synapses. MAPs which form structural bridges stabilize MTs, prevent their disassembly and may be phosphorylated and impart energy into the cytoskeleton. Thus MAP-MT cytoskeletal networks determine cell architecture and dynamic functions (e.g. mitosis, growth, differentiation, movement, synapse formation and function, etc.) essential to the living state.

Of the filamentous structures which comprise the cytoskeleton, MTs are the best characterized. MTs are hollow cylinders 25 nanometers (25×10^{-9} meters) in diameter whose walls are 13 chains of subunit proteins known as tubulin. Each tubulin subunit is a polar, 8 nm dimer which consists of two slightly different classes of 4 nm monomers

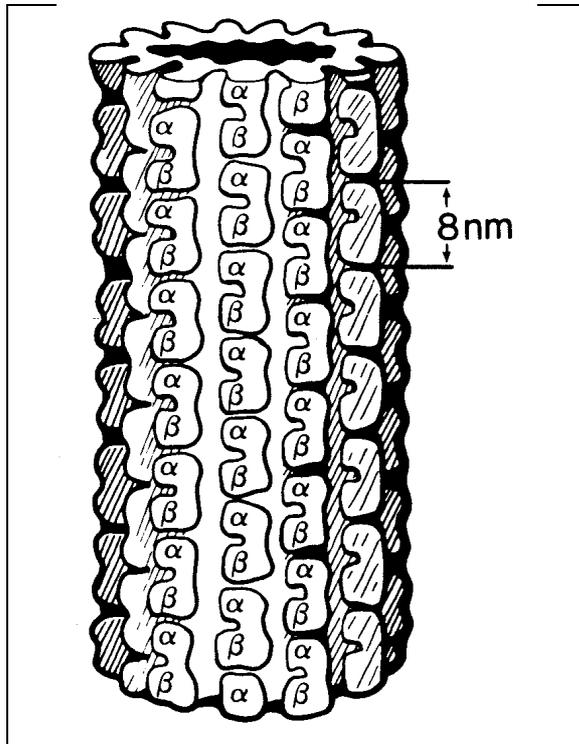


Figure 7.

Microtubule (MT) structure from X-ray crystallography (Amos and Klug, 1974). Tubulin subunits are 8 nm dimers comprised of α and β monomers.

(molecular weight 55,000 daltons) known as α and β tubulin (Figure 7). Each dimer (as well as whole MTs) has a dipole with negative charges localized towards α monomers (DeBrabander, 1982). Thus MTs are 'electrets': oriented assemblies of dipoles with piezoelectric properties (Athenstaedt, 1974; Mascarenhas, 1974). Dimers self-assemble into MTs, apparently in an entropy-driven process which can quickly change by MT disassembly and reassembly in another orientation ('dynamic instability' (Kirschner and Mitchison, 1986)). The tubulin dimer subunits within MTs are arranged in a slightly twisted hexagonal lattice, resulting in differing neighbour relationships among each subunit and its six nearest neighbours. Tubulin undergoes conformational changes induced by hydrolysis of bound GTP to GDP (high energy phosphate molecules analogous to ATP and ADP (Engelborghs 1992; Melki *et al.*, 1989)) and biochemical energy can also be pumped into MTs by phosphorylation/dephosphorylation of MAPs (Theurkauf and Vallee, 1983). Genes for α and β tubulin are complex and give rise to varying tubulin primary structure. For example, at least 17 different β tubulins can exist in mammalian brain MTs (Lee *et al.*, 1986). Tubulin in MTs can also be modified by binding various ligands, MAPs, enzymatic addition or removal of amino acids ('post-translational modification') and conformational state changes. Thus, the number of different possible combinations of tubulin states (and information capacity) within MTs is extremely large.

In addition to providing structural support and transport, a role as the cell's nervous system is suggested by evidence that links the cytoskeleton with cognitive function. For example, production of tubulin and MT activities correlate with peak learning, memory and experience in baby chick brains (Mileusnic *et al.*, 1980). When baby rats first open their eyes, neurons in their visual cortex begin producing vast quantities of tubulin (Cronley-Dillon *et al.*, 1974). Selective destruction of animal brain MTs by the drug colchicine causes defects in learning and memory which mimic the symptoms of

Alzheimer's disease (in which neuronal cytoskeleton becomes tangled and dysfunctional (Bensimon and Chernet, 1991)).¹⁶

The cytoskeleton could serve cognitive functions by propagation, storage and processing of information within neurons and other cells. Tubulin subunits in closely arrayed MTs have a density of about 10^{17} per cm^3 , close to the theoretical limit for charge separation and thus have maximal density for information representation by charge. In general, proteins function by coupling their conformational state to a variety of factors; in essence each protein is a computer element with multiple inputs determining a specific conformational state as output.

II

Protein Conformational Dynamics

Proteins undergo conformational motions over a wide range of time and energy scales. However significant conformational changes related to protein function generally occur in the nanosecond (10^{-9} sec) to 10 picosecond (10^{-11} sec) time scale (Karplus and McCammon, 1983). Related to cooperative movements of protein sub-regions and charge redistributions, these changes are linked to protein function (signal transduction, ion channel opening, enzyme action etc.) and may be triggered by factors including phosphorylation, ATP or GTP hydrolysis, ion fluxes, electric fields, ligand binding, and neighbouring protein conformational changes. In the case of tubulin within MTs, such programmable and adaptable states can represent and propagate information.

Fröhlich (1968, 1970, 1975) proposed that protein conformational changes are coupled to charge redistributions such as dipole oscillations or electron movements within specific *hydrophobic* protein regions (Figure 8). Hydrophobic regions within proteins are comprised of non-polar side chains of amino acids which exclude water; general anaesthetic gas molecules apparently act there to prevent protein conformational responsiveness. Fröhlich predicted that quantum-level events such as the movement of an electron within these hydrophobic regions (for example among resonant bond orbitals of amino acid side chains like the aromatic rings of tyrosine, tryptophan or phenylalanine) act as a trigger or switch for the conformational state of the entire protein. Fröhlich further proposed that a set of proteins connected in a common electromagnetic field such as within a polarized membrane (or polar polymer electret like a microtubule) would be excited *coherently* if biochemical energy such as protein phosphorylation or ATP or GTP hydrolysis were supplied. Coherent excitation times on the order of 10^{-9} to 10^{-11} sec (the time domain for functional protein conformational changes, and in the microwave or

¹⁶ Other evidence for cytoskeletal involvement in cognition comes from studies of long term potentiation ('LTP'), a form of synaptic plasticity that serves as a model for learning and memory in mammalian hippocampal cortex. MAP2 (found only in dendrites) is linked to membrane receptors and their activities by 'second messengers' (G proteins, cyclic AMP, phosphatidylinositol, calcium ions, and protein kinases and phosphatases). MAP2 crosslinks MTs, is essential for LTP and consumes a large proportion of brain biochemical energy by phosphorylation/dephosphorylation (e.g. Theurkauf and Vallee, 1983; Wang and Resnick, 1991; Surridge and Burns, 1992). Excitatory neurotransmitter activation of LTP post-synaptic receptors induces rapid dephosphorylation of dendritic MAP2 (Halpain and Greengard, 1990), causes rearrangement of MAP2 connections on MTs (Bigot and Hunt, 1990) and potentiates excitatory synaptic pathways in rat hippocampus (Montoro *et al.*, 1993). In cat visual cortex MAP2 is dephosphorylated when visual stimulation occurs (Aoki and Siekevitz, 1985). In animals whose brains are temporarily deprived of oxygen, the degree of cognitive damage correlates with reduction in dendritic MAP2 (Kudo *et al.*, 1990). Studies of protein kinase C suggest learning and memory are structurally represented in a more complex and interconnected sub-synaptic cytoskeleton (Friedrich, 1990).

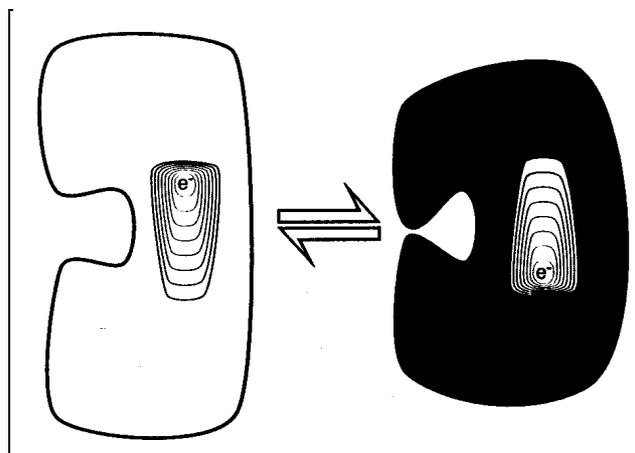


Figure 8. Two states of protein (e.g. tubulin) in which quantum event within hydrophobic region couples to conformational change with 10^{-9} to 10^{-11} sec transitions. Quantum event shown within hydrophobic region as electron (e^-) density probability topography. General anaesthetics bind within these hydrophobic regions and prevent conformational transitions by van der Waals forces acting on quantum event.

gigaHz (GHz) spectral region) were deduced by Fröhlich, who termed them acousto-conformational transitions, or coherent ‘pumped’ phonons. Such a system of coherent excitations in quantum-mechanical terms is called a ‘Bose-Einstein condensate’ (Wu and Austin, 1978). Fröhlich also predicted metastable states (longer-lived conformational state patterns stabilized by local factors) and polarization waves (travelling regions of dipole-coupled conformations).

Experimental evidence for Fröhlich excitations in biological systems includes observation of GHz-range phonons in proteins (Genberg *et al.*, 1991), sharp-resonant non-thermal effects of microwave (GHz) irradiation on living cells (Grundler and Keilmann, 1983), GHz-induced activation of microtubule pinocytosis in rat brain (Neubauer *et al.*, 1990) and Raman detection of Fröhlich frequency energy (Genzel *et al.*, 1983). Vassilev *et al.* (1985) demonstrated propagating signals in microtubules.

III

Models of Microtubule Information Processing

Consideration of MTs as lattice arrays of coupled (tubulin) dipoles which cooperatively interact with their immediate neighbours leads to two types of systems suitable for information processing: spin glasses and cellular automata.

In general, three types of arrangements of dipoles in lattices may occur: a) random, b) ferroelectric (parallel-aligned) and c) spin-glass (regions of locally frozen orientations). Tuszynski *et al.* (1994) have examined behaviour of MTs in this context; depending on the values of assumed parameters, MT dipole lattices may exhibit ‘frustration’, conflict in satisfying all dipole couplings. This phase structure is defined as a spin-glass which exists close to the edge of chaos and has properties suitable for efficient information processing and computation. By slightly altering temperature and external field (both within physiological conditions), MT dipole coupling lattices may assume a ferroelectric phase with long-range order and alignment with capabilities to propagate kink-like excitations or solitons. The ferroelectric phase appears to be optimal for propagation of signals and regulation of assembly/disassembly.

Coupling among tubulin dipoles within MTs in the context of coherent Fröhlich excitations has been proposed as a basis for information processing, signalling and cognition in a paradigm of *cellular automata*, a universal system of computation in a lattice structure. Von Neumann described cellular automata (which include computers as special cases) as systems that consist of a large number of identical ‘cells’ connected in

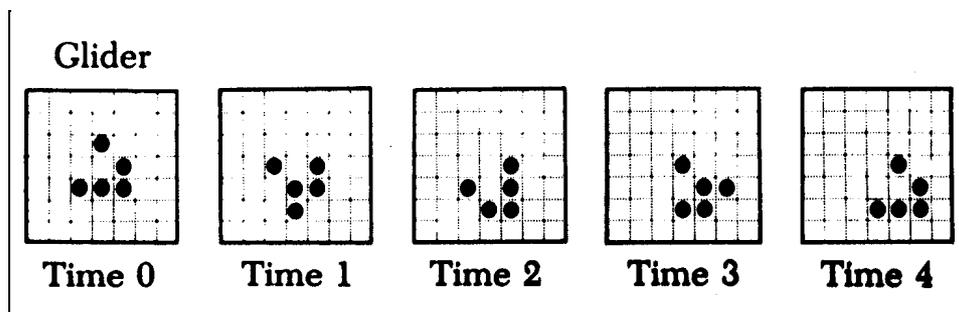


Figure 9. Five time steps from Conway's 'Game of Life' cellular automaton. Black dot: 'alive', white space: 'dead'. Squares ('cells') with two or three live neighbours are 'born' in the next generation; cells with zero or one (insufficient nourishment) or four to eight (overcrowding) die. After four time steps, the unchanged glider has moved rightward and downward.

a uniform pattern. The essential features of cellular automata are: 1) at a given time, each cell is in one of a number of finite states (usually two for simplicity). 2) The cells are organized according to a fixed geometry. 3) Each cell communicates only with other cells in its neighbourhood; the size and shape of the neighbourhood are the same for all cells. 4) There is a universal clock. Each cell may change to a new state at each tick of the clock (or 'generation') depending on its present state and those of its neighbours. The neighbour 'transition' rules for changing states, though simple, can lead to complex, dynamic patterns manifesting chaos, fractal dimensions, partial differential equations and computation. Patterns which move through the lattice unchanged are called 'gliders'; Von Neumann proved mathematically that with sufficient time and cellular automaton space, gliders can solve virtually any problem. One popular example of cellular automata is Conway's the 'Game of Life' in which each 'cell' in a rectangular grid is alive ('on') or dead ('off'). Each cell's state at a given time depends on the state of its eight neighbours in the previous time step. Cells with 0–1 (too few) or 4–8 (too many) live neighbours will be 'dead'; cells with 2 or 3 live neighbours ('parents') will be 'alive'. Despite these simple rules, complex 'life-like' behaviours can ensue (Figure 9).

Cellular automata are theoretically advantageous for molecular computing because the internal connections are intrinsic to the material, external connections need only occur in one limited region, and computation can occur by local interactions with speed dependent on the clocking frequency. Quantum automata, in which each state can exist in 1,0 or alive/dead superposition (like Schrödinger's cat) have been proposed (e.g. Albert, 1983). An extreme view has been taken by Fredkin (e.g. Wright, 1985) who contends that the universe is a cellular automaton — a lattice of interacting sub-atomic logic units, each one deciding billions of times per second whether it will be 'off' or 'on' at the next instant. Conrad (1974) used the concept of 'molecular' automata within neurons as an information processing system subserving the brain's synaptic connectionism. In a series of papers (e.g. Hameroff *et al.*, 1982; 1984; 1986; 1987; 1989; 1992; Rasmussen *et al.*, 1990) cellular ('molecular') automata principles were applied to the dynamic conformational states of tubulin within cytoskeletal microtubules ('microtubule automata'; MTA). A rough estimate for the time steps, assuming one coherent phonon or 'sound' wave across the MT diameter $\approx 25\text{nm}$ and $V_{\text{sound}} \approx 10^3$ meters/second, yields a clocking frequency of approximately 4×10^{11} Hz and a time step of 2.5×10^{-11} second. Thus Fröhlich's coherent excitations can provide a 'clocking frequency' for MT automata. Transition rules were derived for each tubulin using electrostatic coupling forces from each of its six neighbours (Figure 10).

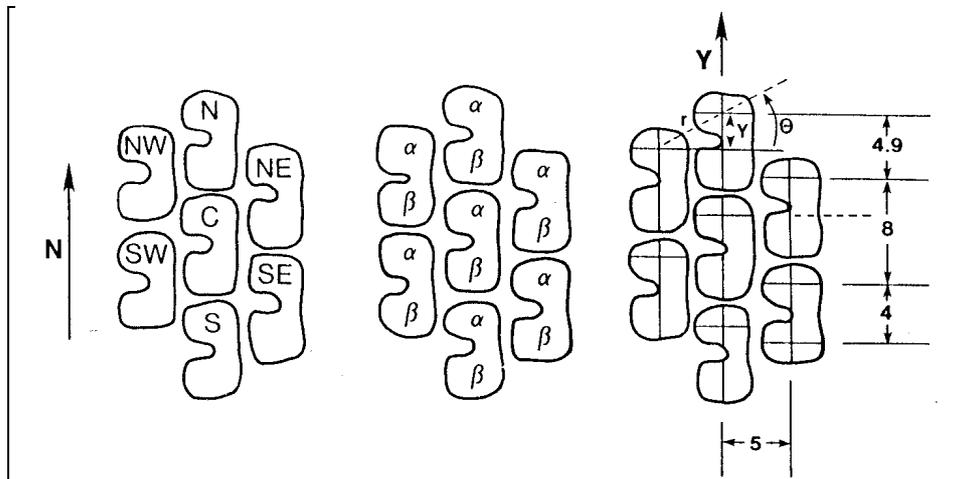


Figure 10 Microtubule automata (MTA) neighbourhood: left, definition of neighbourhood dimers; centre, and monomers within each dimer; right, distances in nm and orientation among lattice neighbours. Transition rules for MTA are based on net electrostatic coupling forces on each tubulin from its surrounding six tubulin neighbours. Coupling force values (described in text) are given in Hameroff *et al.*, 1989 and Rasmussen *et al.*, 1990.

The net force

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

where y and r are defined as illustrated in Figure 10, e is the electron charge and ϵ is the average protein permittivity, yields forces of ± 1.5 picoNewtons. Energy per tubulin state change is estimated as 10^{-21} Joules, an order of magnitude greater than random thermal fluctuations without considering cooperative, shielding effects from MT-ordering or surrounding water.

Using these transition rules, simulations of MT automata reveal gliders (including bidirectional gliders), travelling and standing wave patterns, oscillators, linearly growing patterns, and frozen patterns (Figure 11). What functions could such gliders and patterns have? They could represent information being transmitted through the cell; glider numerical quantities and patterns may manifest signals, binding sites for ligands, MAPs or material to be transported. By determining MAP binding sites, MT-assembly/disassembly, cytoskeletal network architecture and thus cell structure and function could be regulated. Frozen patterns may store information in a memory context, information may become 'hardened' in MT by post-translational modifications, and/or MT automata patterns could transfer and retrieve stored information to and from neurofilaments via MAPs.

MT automata gliders travel one dimer length (8 nm) per time step (10^{-9} to 10^{-11} sec) for a velocity range of 8 to 800 meters per second, consistent with the speed of travelling nerve-membrane potentials. Thus travelling MT automata patterns or gliders (equivalent to phonons, Fröhlich depolarization waves, kink-like excitations or solitons) may propagate in the cytoskeleton in concert with membrane depolarizations and ion fluxes. Membrane-related voltages, ion fluxes or direct structural links could induce transient waves of conformational switching along parallel-arrayed MT. Consequently, external inputs and activity of a particular cell could directly elaborate patterns within that cell's

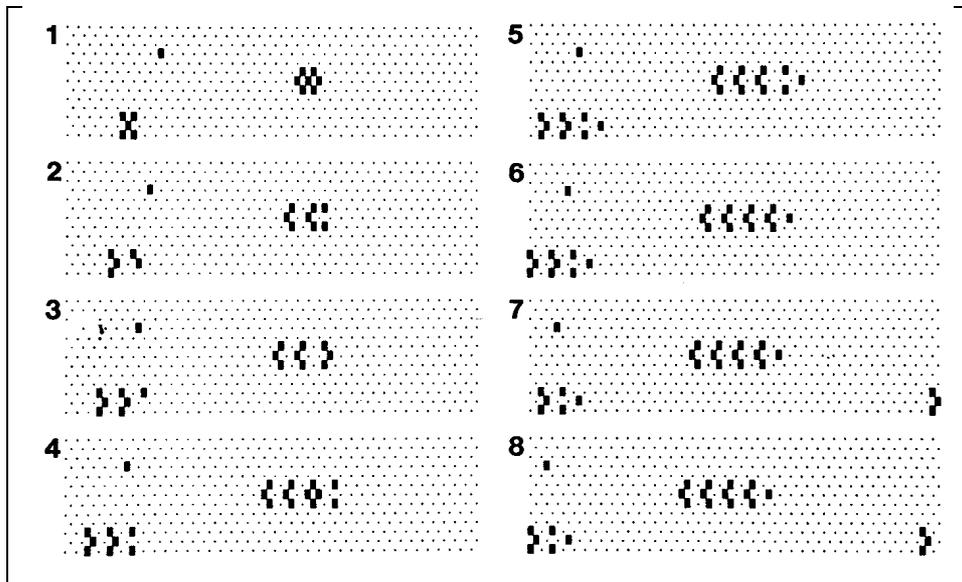


Figure 11. Eight time steps of a microtubule automata (MTA) computer simulation. MT is shown as horizontal open rectangle. Initial pattern is black 'seeds' (beta state conformations of tubulin) on white background (alpha state conformations). Seeds 'wiggle', expand bidirectionally and organize into 'bus' gliders which move leftward at a velocity of 8 to 800 meters per second (from Hameroff *et al.*, 1989).

MT automata — phenomena important in cognitive and behavioural functions ranging from simple organisms to human brains. Long-range cooperativity, resonances and phase transitions emerging from locally-determined microtubule automata patterns may occur among spatially-distributed microtubules as quantum coherence phenomena and correlate with some aspect of consciousness.

Viewing the cytoskeleton as the cell's nervous system, with microtubules serving as processors or signal carriers and MAPs as molecular cross-bridge connections ('synapses') suggests that the cytoskeleton within each of the brain's neurons could be viewed as a 'fractal-like' sub-dimension in a hierarchy of adaptive networks. This is consistent with Globus's (1992) observation that 'nervous tissue has fractal geometric, statistical, and dynamic properties and that there are fractal correlates of cognitive activity'. Exploring only a few facets of the possible parameter space for cytoskeletal automata, an enormous information-processing capacity is implied. For example, the 'strong AI' information-processing capacity of a human brain based on consideration of conventional neural synaptic transmissions as fundamental switches has been estimated as 100 billion neurons, each with over 1000 synapses 'switching' 100 times per second to yield approximately 10^{16} 'bits' per second (Moravec, 1987). Considering the *simplest* case of microtubule automata (two conformational states per microtubule subunit switching at 10^{-9} sec. intervals, 10^4 microtubule subunits per neuron) yields about 10^{23} brain 'bits' per second.

Whether computer-like information processing and molecular automata in the cytoskeleton can help explain consciousness remains questionable. Considering only local interactions, the concept takes the reductionist argument to a molecular level, increasing the complexity of the brain (and goal for strong AI) about 7 orders of magnitude, but does not address emergent properties of consciousness. For this, quantum coherence provides a possible resolution.

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