Biophysics of Consciousness: A Foundational Approach
R. R. Poznanski, J. A. Tuszynski and T. E. Feinberg

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CONSCIOUSNESS IN THE UNIVERSE AN UPDATED REVIEW OF THE "ORCH OR" THEORY

Stuart R. Hameroff, and Roger Penrose†*

* *Anesthesiology and Psychology, Center for Consciousness Studies, Banner-University Medical Center The University of Arizona, Tucson, Arizona, USA*

† *Mathematical Institute and Wadham College, University of Oxford, Oxford, UK*

Abstract

The nature of consciousness, the mechanism by which it occurs in the brain, and its ultimate place in the universe are unknown. We proposed in the mid 1990's that consciousness depends on biologically "orchestrated" coherent quantum processes in collections of microtubules within brain neurons, that these quantum processes correlate with, and regulate, neuronal synaptic and membrane activity, and that the continuous Schrödinger evolution of each such process terminates in accordance with the specific Diósi–Penrose (DP) scheme of "objective reduction" ("OR") of the quantum state. This orchestrated OR activity ("Orch OR") is taken to result in moments of conscious awareness and/or choice. The DP form of OR is related to the fundamentals of quantum mechanics and space–time geometry, so Orch OR suggests that there is a connection between the brain's biomolecular processes and the basic structure of the universe. Here we review Orch OR in light of criticisms and developments in quantum biology, neuroscience, physics and cosmology. We also introduce novel suggestions of (1) beat frequencies of faster Orch OR microtubule dynamics (e.g. megahertz) as a possible source of the observed electroencephalographic ("EEG") correlates of consciousness and (2) that OR played a key role in life's evolution. We conclude that consciousness plays an intrinsic role in the universe.

Keywords: anthropic principle, consciousness, free will, Orch OR, microtubule, tubulin, objective reduction, OR, neuron, quantum, wavefunction, measurement problem, qualia, pi resonance, general relativity, space-time geometry, universe, electro-encephalography, EEG, anesthesia, memory, evolution, quantum computing.

14.1. Introduction: Consciousness in the Universe

Consciousness implies awareness: subjective, phenomenal experience of internal and external worlds. Consciousness also implies a sense of self, feelings, choice, control of voluntary behavior, memory, thought, language, and (e.g., when we close our eyes, or meditate) internally generated images and geometric patterns. But what consciousness actually *is* remains unknown. Our views of reality, of the universe, of ourselves depend on consciousness. Consciousness defines our existence.

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

(A) *Consciousness is not an independent quality but arose, in terms of conventional physical processes, as a natural evolutionary consequence of the biological adaptation of brains and nervous systems*. This prevalent scientific view is that consciousness emerged as a property of complex biological computation during the course of evolution. Opinions vary as to when, where and how consciousness appeared, e.g., only recently in humans, or earlier in lower organisms. Consciousness as an evolutionary adaptation is commonly assumed to be epiphenomenal [(i.e., a secondary effect without independent influence (Dennett, 1991; Dennett & Kinsbourne, 1991; Wegner, 2002)], and also illusory [(largely constructing reality, rather than perceiving it (Chalmers, 2012)]. Nonetheless, consciousness is frequently argued to confer beneficial advantages to species (Dennett, 1995). Overall, in this view, consciousness is *not* an intrinsic feature of the universe.

(B) *Consciousness is a separate ("spiritual") quality, distinct from physical actions and not controlled by physical laws, that has always been in the* *universe*. "Descartes' dualism," religous viewpoints and other spiritual approaches assume consciousness has been in the universe all along, e.g., as the "ground of being," "creator" or component of an omnipresent "God" (Chopra, 2001). In this view, consciousness can causally influence physical matter and human behavior, but has no basis or description in science (Nadaeu & Kafatos; 2001, Kant, 1998). In another approach, panpsychism attributes consciousness to all matter, but without scientific identity *or* causal influence. Idealism contends consciousness is all that exists, the material world (and science) being an illusion (Berkeley, 1975). In all these views, consciousness lies outside science.

(C) *Consciousness results from discrete physical events; such events have always existed in the universe as non-cognitive, proto-conscious events, these acting as part of precise physical laws not yet fully understood. Biology evolved a mechanism to orchestrate such events and to couple them to neuronal activity, resulting in meaningful, cognitive, conscious moments and thence also to causal control of behavior.* These events are proposed specifically to be moments of quantum state reduction (intrinsic quantum "self-measurement"). Such events need not necessarily be taken as part of current theories of the laws of the universe, but should ultimately be scientifically describable. This is basically the type of view put forward, in very general terms, by the philosopher Whitehead (1929, 1933) and also fleshed out in a scientific framework in the Penrose–Hameroff theory of "orchestrated objective reduction" ("Orch OR") (Penrose & Hameroff, 1995; Hameroff & Penrose, 1996a, 1996b, 2014; Hameroff, 1998a, 1998b; Penrose & Hameroff, 2011). In the Orch OR theory, these conscious events are terminations of quantum computations in brain microtubules reduced by Diósi–Penrose (DP) "objective reduction" ("OR"), and having experiential qualities. In this view, consciousness is an intrinsic feature of the action of the universe.

In summary, we have:

(A) Science/Materialism, with consciousness having no distinctive role.
(B) Dualism/Spirituality, with consciousness (etc.) being outside science.
(C) Science, with consciousness as an essential ingredient of physical laws not yet fully understood.

14.2. Consciousness, Computation and Brain Activities

14.2.1. *Unexplained features of consciousness*

How does the brain produce consciousness? Most scientists and philosophers view consciousness as an emergent property of complex computation among "integrate-and-fire" brain neurons which interconnect and switch at chemically mediated synapses. However, the mechanism by which such neuronal computation may produce conscious experience remains unknown (Koch, 2004; Chalmers, 1996). Specific unexplained features of consciousness include the following:

The "hard problem": What is the nature of phenomenal experience, and what distinguishes conscious from non-conscious cognition? Perception and behavior may be accompanied or driven by phenomenal conscious awareness, experinces or subjective feelings, composed of what philosophers call "qualia" (Chalmers, 1996). However, perception and behavior may at other times be unaccompanied by consciousness. We could have evolved as full-time non-conscious "zombies" performing complex "autopilot" behaviors without conscious awareness. How and why do we have phenomenal consciousness, an "inner life" of subjective experience?

'Binding': Disparate sensory inputs are processed in different brain regions, at slightly different times, and yet are bound together into unified conscious content "binding" (van der Malsburg, 1999). How is conscious content bound together?

Synchrony: Neuronal membrane polarization states may be precisely synchronized over large regions of brain (Fries *et al.*, 2002), and also propagate through brain regions as synchronized zones (Hameroff, 2010). Does precise synchrony require electrical synapses ("gap junctions") and/or quantum entanglement? Does synchrony reflect discrete, unified conscious moments?

'Non-computability' and causal agency: As shown by Gödel's theorem, Penrose (1989, 1994) described how the mental quality of "understanding" cannot be encapsulated by any computational system and must derive from some "non-computable" effect. Moreover, the neurocomputational approach to volition, where algorithmic computation completely determines all thought processes, appears to preclude any possibility for independent causal agency, or free will. Something else is needed. What non-computable factor may occur in the brain?

Cognitive behaviors of single cell organisms: Protozoans like *Physarum* can escape mazes and solve problems, and *Paramecium* can swim, find food and mates, learn, remember and have sex, all without synaptic connections (Nakagaki *et al*., 2000; Adamatzky 2012). They are not part of a network. How do single cells manifest intelligent behavior?

14.2.2. *Conscious moments and computation*

Consciousness has often been argued to be a sequence of discrete moments. James (1890) described the "specious present, the short duration of which we are immediately and incessantly sensible" (though James was vague about duration, and also described a continual "stream of consciousness"). The "perceptual moment" theory of Stroud (1956) described consciousness as a series of discrete events, like sequential frames of a movie (modern film and video present 24 to 72 frames per second, 24 to 72 Hertz, "Hz"). Consciousness is also seen as sequences of discrete events in Buddhism, trained meditators describing distinct "flickerings" in their experience of pure undifferentiated awareness (Tart, 1995). Buddhist texts portray consciousness as "momentary collections of mental phenomena," and as "distinct, unconnected and impermanent moments which perish as soon as they arise." Buddhist writings even quantify the frequency of conscious moments. For example the Sarvaastivaadins (Von Rospatt, 1995) described 6,480,000 'moments' in 24 hours (an average of one 'moment' per 13.3 ms, 75 Hz), and some Chinese Buddhism as one "thought" per 20 ms (50 Hz). The best measurable correlation of consciousness through modern science is gamma synchrony EEG, 30 to 90 Hz coherent neuronal membrane activity occurring across various synchronized brain regions. Slower periods, e.g., 4 to 7 Hz theta frequency, with nested gamma waves could correspond to saccades and visual gestalts (Woolf & Hameroff, 2001; Van Rullen & Koch, 2003). Thus, we may argue that consciousness consists of discrete events at varying frequencies occurring across brain regions, for example 40 conscious moments per second. What are these conscious moments?

The over-arching presumption in modern science and philosophy is that consciousness emerges from complex synaptic computation among brain neurons acting as fundamental information units. In digital computers, discrete voltage levels represent information units (e.g., "bits") in silicon logic gates. McCulloch & Pitts (1943) proposed such gates as integrate-and-fire artificial neurons, leading to "perceptrons" (Rosenblatt, 1962) and other types of "artificial neural networks" capable of learning and self-organized behavior. Similarly, according to the standard "Hodgkin–Huxley" model (Hodgkin & Huxley, 1952), biological neurons are "integrate-and-fire" threshold logic devices in which multiple branched dendrites and a cell body (soma) receive and integrate synaptic inputs as membrane potentials (Fig. 1). According to Hodgkin–Huxley, the integrated potential is then compared to a threshold potential at the axon hillock, or axon initiation segment (AIS). When AIS threshold is reached by the integrated potential, an all-or-none action potential "firing," or "spike" is triggered as output, conveyed along the axon to the next synapse. Cognitive networks of Hodgkin–Huxley neurons connected by variable strength synapses (Hebb, 1949) can self-organize and learn, their axonal firing outputs controlling downstream activity and behavior.

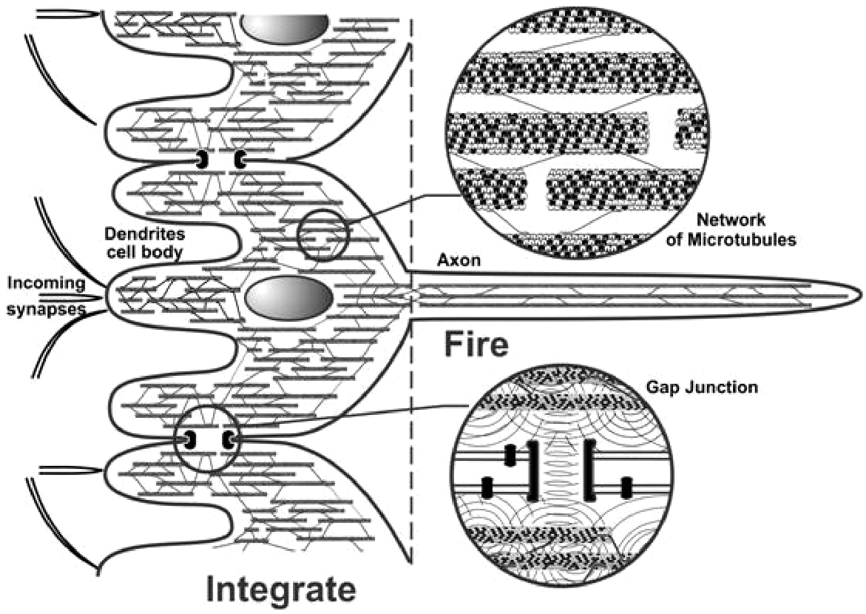

Fig. 1. An "integrate-and-fire" brain neuron, and portions of other such neurons are shown schematically with internal microtubules. In dendrites and cell body/soma (left) involved in integration, microtubules are interrupted and of mixed polarity, interconnected by microtubule-associated proteins (MAPs) in recursive networks (upper circle, right). Dendritic–somatic integration (with contribution from microtubule processes) can trigger axonal firings to the next synapse. Microtubules in axons are unipolar and continuous. Gap junctions synchronize dendritic membranes, and may enable entanglement and collective integration among microtubules in adjacent neurons (lower circle right). In Orch OR, microtubule quantum computations occur during dendritic/somatic integration, and the selected results regulate axonal firings which control behavior.

How does consciousness arise from neurocomputation? Some contend that consciousness emerges from computational complexity due to firings and other brain electrical activity (Scott, 1995; Tononi, 2004). However neither the specific neuronal activities contributing to complexity, nor any predicted complexity threshold for emergence of consciousness have been put forth. Nor is there a sense of how complexity *per se* could give rise to discrete conscious moments. Others contend large scale, cooperative axonal firing outputs, "volleys," or "explosions" produce consciousness (Koch, 2004; Malach, 2007). But coherent axonal firings are in all cases preceded and caused by synchronized dendritic/somatic integrations. Indeed, gamma synchrony EEG, the best correlate of consciousness, is generated not by axonal firings, but by dendritic and somatic integration potentials. Accordingly, some suggest consciousness primarily involves neuronal dendrites and cell bodies/soma, i.e., in integration phases of "integrate-and-fire" sequences (Pribram, 1991; Eccles, 1992; Hameroff, 2012). Integration implies reduction of uncertainty, merging and consolidating multiple possibilities to one, e.g., selecting conscious perceptions and actions.

14.2.3. *Consciousness and dendritic integration*

Neuronal integration is commonly approximated as linear summation of dendritic/somatic membrane potentials [(Fig. 2(a)]. However, actual integration is not passive, actively involving complex processing (Shepherd, 1996; Sourdet & Debanne, 1999; Poirazi & Mel, 2001). Dendritic–somatic membranes generate local field potentials ("LFPs") which give rise to EEG, including coherent gamma synchrony, the best measurable neural correlate of consciousness ("NCC") (Gray & Singer, 1989; Crick, 1990). Anesthetic molecules selectively erase consciousness, acting on post-synaptic dendrites and soma, with little or no effects on axonal firing capabilities. Arguably, dendritic/somatic integration is most closely related to consciousness, with axonal firings serving to convey outputs of conscious (or non-conscious) processes to control behavior. But even complex, active integration in Hodgkin–Huxey neurons would, apart from an entirely probabilistic (random) input, be completely algorithmic and deterministic, leaving no apparent place for consciousness.

However, neurons involved in conscious brain processes apparently deviate from Hodgkin–Huxley. Naundorf *et al.* (2006) showed that firing threshold at the AIS in cortical neurons in brains of awake animals

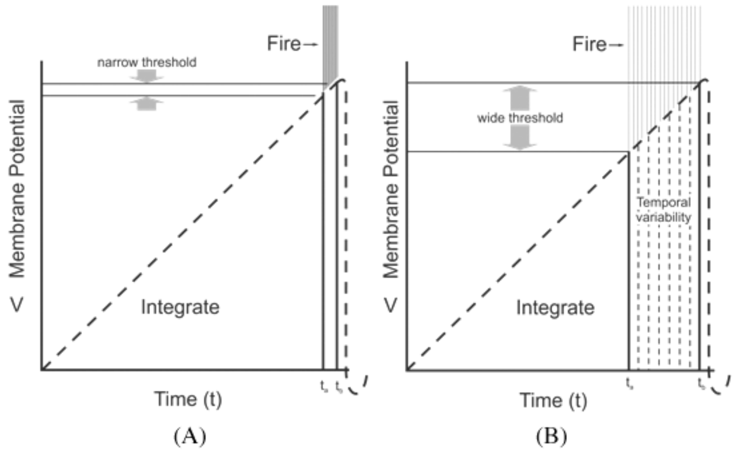

Fig. 2. Neuronal "integrate-and-fire" behaviors. (A) The Hodgkin–Huxley model predicts integration by membrane potential in dendrites and soma reach a specific, narrow threshold potential at the proximal axon, and fire with very limited temporal variability (small t_b — t_a) for given inputs. (B) Recordings from cortical neurons in awake animals (Naundorf (large t_b — t_a) *et al*., 2001) show a large variability in effective firing threshold and timing. Some unknown "x-factor" (related to consciousness?) modulates integration to exert causal influence on firing and behavior.

(compared to neurons *in vitro*) vary significantly spike-to-spike (Fig. 2(b)). Some factor in addition to inputs, synaptic strengths and the integrated AIS membrane potential apparently contributes to effective integration controlling firing, or not firing, ultimately influencing behavior. This unknown end-integration, pre-firing factor is perfectly positioned for conscious perception and action. What could it involve?

One possible firing-modulating factor comes from lateral connections among neurons via gap junctions, or electrical synapses (Fig. 1). Gap junctions are protein complexes which fuse adjacent neurons and synchronize their membrane polarization states, e.g. in gamma synchrony EEG (Dermietzel, 1998; Draguhn *et al*., 1998; Galaretta & Hestrin, 2001; Bennett & Zukin, 2004; Fukuda & Kosaka, 2000; Traub *et al*., 2002). Gap junction-connected cells have fused, synchronized membranes, and also continuous intracellular volumes, as open gap junctions between cells act like doors between adjacent rooms. Neurons connected by dendritic–dendritic gap junctions have synchronized LFPs (giving rise to the EEG) in integration phase, but not necessarily synchronous axonal firing outputs. Gap junction-synchronized dendritic networks can thus *collectively* integrate inputs, enhancing computational capabilities (Hameroff, 2010). However, membrane-based modulations via gap junction connections would be reflected in the integrated membrane potential, and unable to account for threshold variability seen by Naundorf *et al*. (2006). Finer scale processes from within neurons (and conveyed from interiors of adjacent neurons via open gap junctions) could alter firing threshold without changing membrane potentials, and serve as a potential site and mechanism for consciousness.

Finer scale intra-cellular processing, e.g., derived from cytoskeletal structures, are the means by which single-cell organisms perform cognitive functions without synaptic inputs. Observing intelligent actions of unicellular creatures, famed neuroscientist Charles Sherrington said "of nerve there is no trace, but perhaps the cytoskeleton might serve." Neurons have a rich and uniquely organized cytoskeleton, the major components being microtubules (Sherrington, 1957).

14.3. A Finer Scale of Neuronal Information Processing

14.3.1. *Microtubules*

Interiors of eukaryotic cells are organized and shaped by their cytoskeleton, a scaffolding-like protein network of microtubules, microtubule-associatied proteins (MAPs), actin and intermediate filaments (Tuszynski *et al*., 1995). Microtubules ("MTs," Fig. 3) are cylindrical polymers 25 nanometers (nm = 10^{-9} meter) in diameter, and of variable length, from a few hundred nanometers apparently up to meters in long nerve axons. MTs self-assemble from peanut-shaped "tubulin" proteins, each tubulin being a dimer composed of alpha and beta monomers, with a dipole giving MTs ferroelectric properties. In MTs, tubulins are usually arranged in 13 longitudinal protofilaments whose lateral connections result in two types of hexagonal lattices (A-lattice and B-lattice) (Amos & Klug, 1974), the protofilaments being shifted in relation to their neighbors, slightly differently in each direction, resulting in differing relationships between each tubulin and its six nearest neighbors. Helical pathways following along neighboring tubulin dimers in the A-lattice repeat every five and eight tubulins, respectively, down any protofilament, and following along neighboring tubulin monomers repeat every three monomers, after winding twice

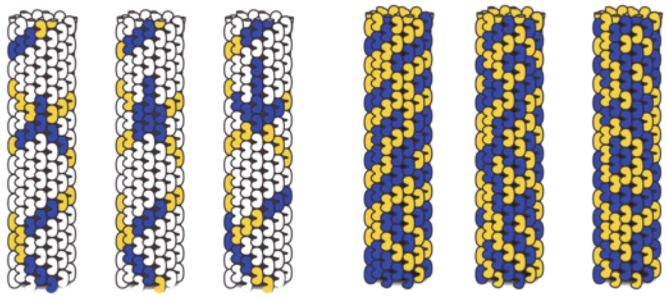

Fig. 3. Three timesteps (e.g., at 10 MHz) of a microtubule automaton. Tubulin subunit states due to aligned dipole orientations or spin currents (yellow, blue) represent information. (A) Dipole orientations or spin currents interact and compute along spiral lattice pathways. For example (upper, middle in each microtubule) two upward traveling (blue) dipole/spin waves intersect, generating a new vertical wave (a "glider gun" in cellular automata) (B) A general microtubule automata process (Rasmussen *et al.*, 1990).

around the MT. Thus helical winding pathways in the MT A-lattice follow the Fibonacci series (3, 5, 8...) found widely in nature.

Along with actin and other cytoskeletal structures, MTs self-assemble to establish cell shape, direct growth and organize functions including those of brain neurons. Various types of MAPs bind at specific lattice sites, and bridge to other MTs, defining cell architecture like girders and beams in a building. Another type of MAP is tau, whose displacement from MTs results in neurofibrillary tangles and the cognitive dysfunction of Alzheimer's disease (Brunden *et al.*, 2011; Craddock *et al.*, 2012; Rasmussen *et al.*, 1990). Other MAPs include motor proteins (dynein, kinesin) which move rapidly along MTs, transporting cargo molecules to specific synapses and locations. Tau proteins bound to MTs apparently serve as traffic signals, determining where motor proteins deliver their cargo (Dixit *et al.*, 2008). Thus, specific placement of tau on MT lattices appears to reflect encoded information governing synaptic plasticity.

MTs are particularly prevalent in neurons (10^9 tubulins/neuron), and are uniquely stable. Non-neuronal cells undergo repeated cycles of cell division, or mitosis, for which MTs disassemble and re-assemble as mitotic spindles which separate chromosomes, establish cell polarity and architecture, then depolymerize for tubulins and MTs to be re-utilized for cell function. However neurons, once formed, do not divide, and so neuronal MTs can remain assembled indefinitely. Dendritic–somatic MTs are unique in other ways. MTs in axons (and non-neuronal cells) are arrayed radially, extending continuously (with the same polarity) from the centrosome near the nucleus, outward toward the cell membrane. However MTs in dendrites and cell bodies are interrupted, of mixed polarity (Fig. 1), and arranged in local recursive networks suitable for learning and information processing (Dustin, 1985). Finally, MTs in other cells can assemble at one end and dis-assemble at the other ("treadmilling"), or grow and then abruptly dis-assemble ("dynamic instability" or "MT catastrophes" (Guillard *et al*., 1998). However dendritic–somatic MTs are capped by special MAPs which prevent de-polymerization (Mitchison & Kirschner, 1984), and are thus especially stable and suitable for long-term information encoding and memory (Craddock *et al*., 2012a)

14.3.2. *Microtubule information processing*

After Sherrington's broad observation in 1957 about the cytoskeleton as a cellular nervous system, Atema (1973) proposed that tubulin conformational changes propagate as signals along microtubules. Hameroff and Watt (1982) suggested that distinct tubulin dipoles and conformational states — mechanical changes in protein shape — could represent information, with MT lattices acting as two-dimensional Boolean switching matrices with input/output computation occurring via MAPs. MT information processing has also been viewed in the context of cellular ("molecular") automata ("microtubule automata," Fig. 3) in which tubulin dipole and conformational states interact with neighboring tubulin states in hexagonal MT lattices by dipole couplings, synchronized by biomolecular coherence as proposed by Fröhlich (Fröhlich, 1968, 1970, 1975; Smith *et al*., 1984; Hameroff, 2006a).

Protein conformational changes occur at multiple scales (Karplus & McCammon, 1983), e.g., 10^{-6} sec to 10^{-11} sec transitions. Coordinated movements of the protein's atomic nuclei, far more massive than electrons, require energy and generate heat. Early versions of Orch OR portrayed tubulin states as alternate mechanical conformations, coupled to, or driven by London force dipoles in non-polar hydrophobic pockets (Hameroff & Penrose, 1996a, 1996b; Hameroff, 1998a, 1998b; Penrose & Hameroff, 2011). However, recent Orch OR papers do not make use of such large conformational changes, depending instead on tubulin dipole or spin states alone to represent information (Sec. 3.3 below).

Within MTs, each tubulin may differ from among its neighbors due to genetic variability, post-translational modifications (Janke & Kneussel, 2010; Hameroff, 2007), phosphorylation states, binding of ligands and MAPs, and moment-to-moment conformational and/or dipole or spin state transitions. Synaptic inputs can register information in dendritic–somatic MTs in brain neurons by metabotropic receptors, MAP2, and CaMKII, a hexagonal holoenzyme able to convey calcium ion influx to MT lattices by phosphorylation (Fig. 4, (Craddock *et al*., 2012a). Thus, tubulins in MTs can each exist in multiple possible states, perhaps dozens or more. However for simplicity, models of MT automata consider only two alternative tubulin states, i.e., binary "bits."

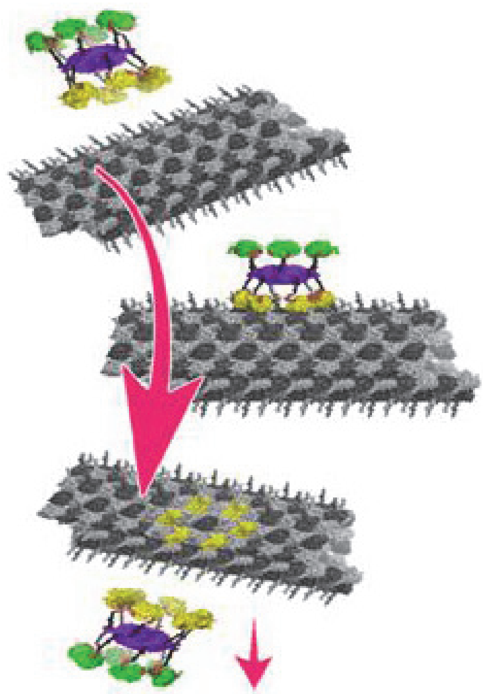

Fig. 4. Calcium-calmodulin kinase II ('CaMKII'), a hexagonal holoenzyme activated by synaptic calcium influx extends six leg-like kinase domains above and below an association domain. The six kinase domains precisely match hexagonal size and geometry in both A-lattice and B-lattice microtubules (Craddock, 2012a) with permission from Travis Craddock).

Another potential factor arises from the specific geometry of MT lattices in which helical winding pathways (in the A-lattice) repeat according to the Fibonacci sequence (3, 5, 8…) and may correlate with conduction pathways (Hameroff, *et al.*, 2002). Dipoles or spin states aligned along such pathways may be favored (and coupled to MT mechanical vibrations) thus influencing MT automata computation.

MT automata based on tubulin dipoles in hexagonal lattices show high capacity integration and learning (Rasmussen *et al.*, 1990). Assuming 10^9 binary tubulins per neuron switching at 10 megahertz (10^7) gives a potential MT-based capacity of 10^{16} operations per second *per neuron.* Conventional neuronal-level approaches based on axonal firings and synaptic transmissions (10^{11} neurons/brain, 10^3 synapses/neuron, 10^2 transmissions/s/synapse) give the same 10^{16} operations per second for the entire brain! MT-based information processing offers a huge potential increase in brain capacity (Hameroff, 2007).

How would MT processes be "read out" to influence neuronal and network activities in the brain? First, as previously mentioned, MT processing during dendritic–somatic integration can influence axonal firings to implement behavior. Second, MT processes may directly result in conscious awareness. Third, MT processes can regulate synaptic plasticity, e.g., as tracks and guides for motor proteins (dynein and kinesin) transporting synaptic precursors from cell body to distal synapses. The guidance mechanism in choosing the proper path is unknown, but seems to involve placement of the MAP tau at specific sites on MT lattices. In Alzheimer's disease, tau is hyperphosphorylated and dislodged from destabilized MTs, forming neurofibrillary tangles which correlate with memory loss (Matsuyama & Jarvik, 1989; Brinden *et al.*, 2011; Craddock *et al.*, 2012). Fourth, tubulin states can encode binding sites not only for tau, but also structural MAPs determining cytoskeletal scaffolding and thus directly regulate neuronal structure and synaptic formation. Finally, MT information processing may be directly related to activities at the levels of neurons and neuronal networks through something of the nature of scale-invariant dynamics. Several lines of evidence point to fractal-like (1/f) self-similarity over different spatiotemporal scales in brain dynamics and structure (He *et al.*, 2010; Kitzbichfer *et al.* 2009). Scale-invariance is generally considered at scale levels of neurons and higher-level neuronal networks, but may extend downward in size (and higher in frequency) to intra-neuronal MT dynamics, spanning 4 or 5 scale levels or more, each level separated by several orders of magnitude.

MT information processing depends on interactive states of individual tubulin proteins. What are those states, and how are they governed?

14.3.3. *Tubulin dipoles and anesthesia*

Tubulin, like other proteins, is composed of a heterogeneous group of amino acid residues connected to a peptide backbone. The residues include both water-soluble polar, and water-insoluble non-polar groups, the latter including "aromatic" amino acids (phenylalanine, tyrosine and tryptophan) with "π" orbital electron resonance clouds in phenyl and indole rings. π orbital clouds are composed of electrons able to delocalize across a spatial region. Like oil separating from water, non-polar electron clouds coalesce during protein folding to form isolated water-excluding "hydrophobic regions" within proteins with particular ("oily," "lipid-like") solubility. Driving the folding are non-polar, but highly polarizable π orbital electron cloud dipoles which couple by van der Waals London forces (instantaneous dipole-induced dipole attractions between electron clouds) (Voet & Voet, 1995).

Within intra-protein hydrophobic regions, anesthetic gas molecules bind by London force dipole couplings, and thereby (somehow) exert their effects on consciousness (Craddock *et al*., 2012b, 2015; Hameroff, 2006a; Hameroff, 1998c; Hameroff *et al*., 1982; Hameroff & Watt, 1983). Historically, views of anesthetic action have focused on neuronal membrane proteins, but actual evidence (e.g., from genomics and proteomics (Xi *et al*., 2004; Pan *et al*., 2007) points to anesthetic action in microtubules. In the most definitive anesthetic experiment yet performed, Emerson *et al*. (2013) used fluorescent anthracene as an anesthetic in tadpoles, and showed cessation of tadpole behavior that occurs specifically via anthracene binding in tadpole brain microtubules. Despite prevailing assumptions, actual evidence supports anesthetic action on microtubules.

Tubulin (Fig. 5) contains 32 aromatic (phenyl and indole) amino acid rings with π electron resonance clouds, most within a Forster resonance transfer distance of 1 to 2 nm (Craddock *et al*., 2012b). Resonance rings align along grooves which traverse tubulin, and appear to meet those in neighbor tubulins along helical lattice pathways (Fig. 6A). Simulation of anesthetic molecules (Fig. 5, red spheres) shows binding in a hydrophobic channel aligned with the five- and eight-start helical winding pathways in the microtubule A-lattice.

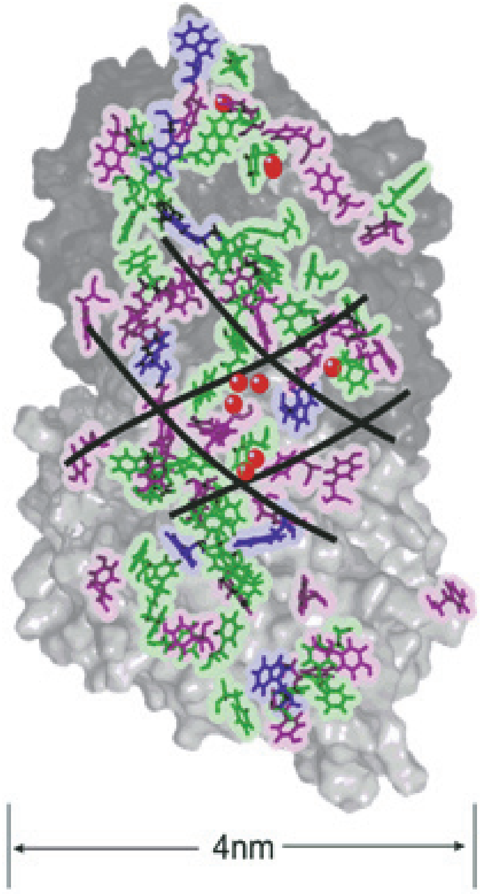

Fig. 5. Molecular modeling of tubulin dimer shows aromatic amino acids tryptophan (blue), phenylalanine (purple) and tyrosine (green) in non-polar, hydrophobic regions. Red spheres are anesthetic binding sites (with permission from Craddock *et al*., (2012b). Curved lines enclose rings in particular aligned orientation along five and eight-start helical channels, containing anesthetic binding sites.

Figure 6B shows collective dipole couplings in contiguous rings. Quantum superposition of both states is shown in gray. Anesthetics (lower right) appear to disperse dipoles necessary for consciousness, resulting in anesthesia (Hameroff, 2006a; Hameroff, 1998c; Hameroff *et al*., 1982; Hameroff & Watt, 1983). Electron cloud dipoles may be either charge separation (electric) or electron spin (magnetic). Tubulin dipoles in

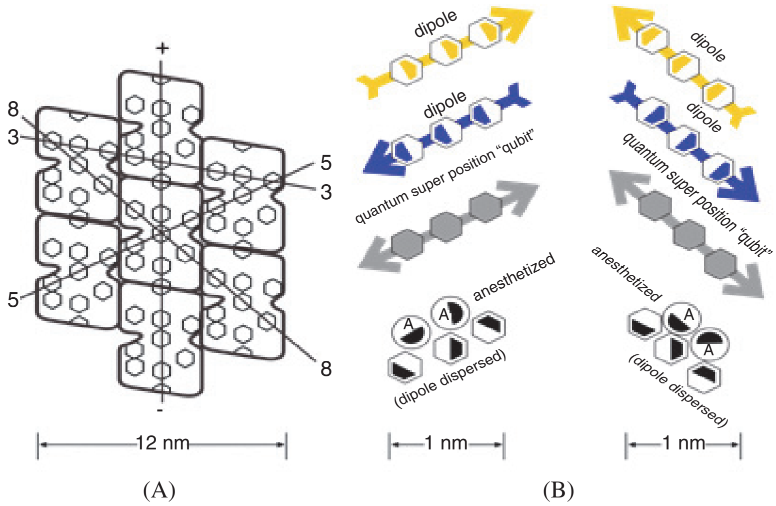

Fig. 6. Dipoles in tubulin. (A) Seven tubulin neighborhood in microtubule A-lattice with schematized placement of aromatic rings along three, five and eight-start helical pathways. (B) Five-start (left) and eight-start (right) helical pathways represented by aligned aromatic ring dipole "bits" and superposition of both (quantum bit, or "qubit"). Bottom: anesthetic gas molecules (A) form their own dipole couplings with amino acid rings, dispersing collective dipoles and disrupting quantum and classical computation.

Orch OR were originally described in terms of London-force electric dipoles, involving charge separation. However we now suggest, as an alternative, *magnetic* dipoles, which could be related to electron spin — and possibly related also to nuclear spins (which can remain isolated from their environments for long periods of time). 'Spin-flips' might perhaps relate to alternating currents (ACs) in MTs. Spin is inherently quantum in nature, and quantum spin transfer through aromatic rings is enhanced at warm temperature (Ouyang & Awschalom, 2003). In Figs. 6 and 7, yellow may be considered "spin up," and blue considered "spin down."

It should be made clear, however, that the notions of 'up' and 'down' referred to here need be figurative only. Yet, there are, in fact, directional aspects to the notion of spin; in essence, the spin direction is the direction of the axis of rotation, where conventionally we regard the rotational direction to be *right-handed* about the direction being referred to, and "up"

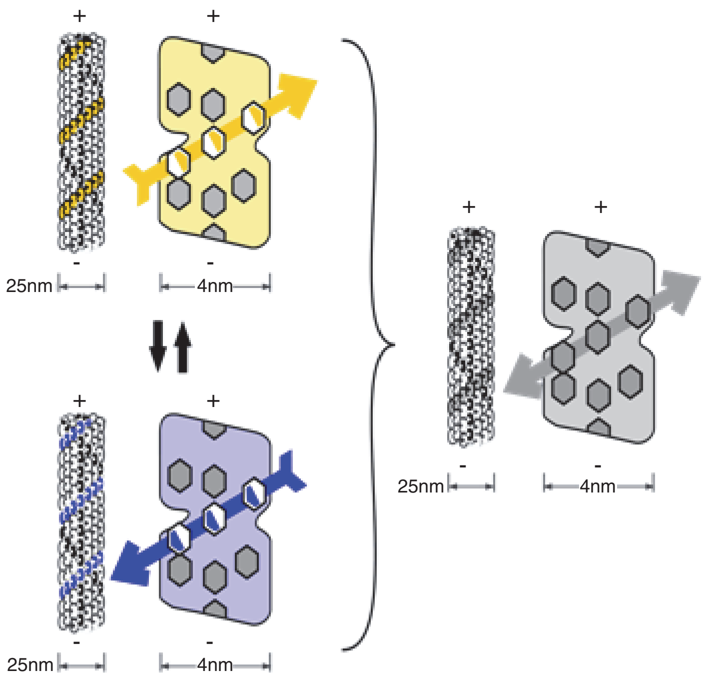

Fig. 7. Classical and quantum dipole information states for the "five-start" helical pathway in tubulin and microtubules. Left: The "five-start" helix in microtubule A-lattice aligned with dipoles in intra-tubulin aromatic rings. Top: "upward" dipole (yellow), Bottom, "downward" dipole (blue). Right: Quantum superposition of both upward and downward helical paths coupled to dipole orientations, i.e., "qubits." Dipoles may be electric dipoles due to charge separation, or magnetic dipoles, e.g., related to electronic (and/or nuclear) spin. Similar qubit pathways may occur along eight-start pathways, or other pathways.

would refer to some arbitrarily chosen spatial direction and "down" to the opposite direction. If the particle has a magnetic moment (e.g., electron, proton or neutron), its magnetic moment is aligned (or anti-aligned, according to the type of particle) with its spin. Within a microtubule, we might imagine "up" and "down" are chosen to refer to the two opposite directions along the tube's axis itself, or else some other choice of alignment might be appropriate. However, as indicated earlier, spin is a quintessentially quantum-mechanical quantity, and for a spin-one-half object, like an electron or a nucleon (neutron or proton), all possible directions for the spin rotation axis arise as quantum superpositions of some arbitrarily chosen pair of directions. Indeed the directional features of quantum spin inter-relate with the quantum superposition principle in fundamental ways.

Here, we may speculate that chains of correlated ("up–up–up," "down–down–down") or possibly anti-correlated ("down–up–down," "up–down–up") spin along lattice pathways in microtubules or perhaps something more subtle might provide biologically plausible ways of propagating quantum bit pairs (qubits) along the pathways. If such correlated spin chains make physical sense, one might speculate that periodic spin-flip or spin-precession processes (either electric or magnetic) might occur, and could be correlated with ACs in microtubules at specific frequencies. Electron cloud dipoles can result from either charge separation (electric) or electron spin (magnetic). Tubulin dipoles in Orch OR were originally described in terms of London force electric dipoles, charge separation. However we now favor magnetic dipoles, e.g., related to electron spin, possibly enabling "spin-flip" ACs in MTs.

The group of Anirban Bandyopadhyay at National Institute for Material Sciences in Tsukuba, Japan, has indeed discovered conductive resonances in single microtubules that are observed when there is an applied AC at specific frequencies in gigahertz, megahertz and kilohertz ranges (Sahu *et al.*, 2013a, 2013b; 2014). See Sec. 4.5.

Electron dipole shifts do have some tiny effect on nuclear positions via charge movements and Mossbauer recoil (Sataric *et al.*, 1998; Brizhik *et al.*, 2001). A shift of one nanometer in electron position might move a nearby carbon nucleus a few femtometers ("Fermi lengths," i.e. 10^{-15} m), roughly its diameter. The effect of electron spin/magnetic dipoles on nuclear location is less clear. Recent Orch OR publications have cast tubulin bits (and quantum bits, or qubits) as coherent entangled dipole states acting collectively among electron clouds of aromatic amino acid rings, with only femtometer conformational change due to nuclear displacement (Penrose & Hameroff 2011; Hameroff, 2012). As it turns out, femotometer displacement might be sufficient for Orch OR (Sec. 5.2).

An intra-neuronal finer–scale of MT-based information processing could account for deviation from Hodgkin-Huxley behavior and, one might hope, enhanced computational capabilities. However, like neuronal models, approaches based on MT information processing with classical physics, e.g., those developed by Hameroff and colleagues up through the 1980's, faced a reductionist dead-end in dealing with consciousness. Enhanced computation *per se* fails to address certain aspects of consciousness (Sec. 14.4.1.). Something was missing. Was it some subtle feature of quantum mechanics?

14.4. Quantum Physics and Consciousness

14.4.1. *Non-computability and OR*

In 1989 Penrose published *The Emperor's New Mind* (Penrose, 1989), which was followed in 1994 by *Shadows of the Mind* (Penrose, 1994). Critical of the viewpoint of "strong artificial intelligence" ("strong AI"), according to which all mental processes are entirely computational, both books argued, by appealing to Gödel's theorem and other considerations, that certain aspects of human consciousness, such as *understanding*, must be beyond the scope of any computational system, i.e., "non-computable." Non-computability is a perfectly well-defined mathematical concept, but it had not previously been considered as a serious possibility for the result of physical actions. The non-computable ingredient required for human consciousness and understanding, Penrose suggested, would have to lie in an area where our current physical theories are fundamentally incomplete, though of important relevance to the scales that are pertinent to the operation of our brains. The only serious possibility was the incompleteness of quantum theory — an incompleteness that both Einstein and Schrödinger (and also Dirac) had recognized, despite quantum theory having frequently been argued to represent the pinnacle of 20th century scientific achievement. This incompleteness is the unresolved issue referred to as the "*measurement problem*," which we consider in more detail below, in Sec. 4.3. One way to resolve it would be to provide an extension of the standard framework of quantum mechanics by introducing an objective form of quantum state reduction — termed "OR" (objective reduction), an idea which we also describe in detail further in Penrose (1992, 1996, 2000, 2009).

In Penrose (1989), the tentatively suggested OR proposal would have its onset determined by a condition referred to as "the one-graviton" criterion. However, in Penrose (1999, 2009), a much better-founded criterion was used, now frequently referred to as the *Diósi–Penrose proposal* (henceforth "DP;" see Diósi's earlier work, which was a similar gravitational scheme, though not motivated via specific general relativistic principles). The DP proposal gives an objective physical threshold, providing a plausible lifetime for quantum-superposed states. Other gravitational OR proposals have been put forward, from time to time (Karolyhazy 1966; Karolyhazy *et al*., 1986; Percival, 1995; Ghirardi *et al*., 1990; Kibble 1981; Pearle, 1989; Pearle & Squires, 1994) as solutions to the measurement problem, suggesting modifications of standard quantum mechanics, but all these differ from DP in important respects. Among these, only the DP proposal (in its role within Orch OR) has been suggested as having anything to do with the consciousness issue. The DP proposal is sometimes referred to as a "quantum gravity" scheme, but it is not part of the normal ideas used in quantum gravity, as will be explained below (Sec. 4.4). Moreover, the proposed connection between consciousness and quantum measurement is almost opposite, in the Orch OR scheme, to the kind of idea that had frequently been put forward in the early days of quantum mechanics (see, for example Wigner, (1976) which suggests that a "quantum measurement" is something that occurs only as a result of the conscious intervention of an observer. Rather, the DP proposal suggests each OR event, which is a purely physical process, is itself a primitive kind of "observation," a moment of "proto-conscious experience." This issue, also, will be discussed below.

14.4.2. *The nature of quantum mechanics*

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

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

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

Another quantum property is "non-local entanglement," in which separated components of a system become unified, the entire collection of components being governed by one common quantum wavefunction. The parts remain somehow connected, even when spatially separated by very significant distances [(the present experimental record being 143 km (Xiao *et al*., 2012)]. Quantum superpositions of bit states (quantum bits, or qubits) can be interconnected with one another through entanglement in quantum computers. However, quantum entanglements cannot, by themselves, be used to send a message from one part of an entangled system to another; yet entanglement can be used in conjunction with classical signaling to achieve strange effects — such as the phenomenon referred to as *quantum teleportation* — that classical signaling cannot achieve by itself (Bennett & Wiesner, 1992; Boouwmeester *et al*., 1997; Macikic *et al*., 2002).

14.4.3. *The measurement problem and OR*

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

There are many ways that quantum physicists have attempted to come to terms with this conflict (Bell, 1966; Bohm, 1983; Rae, 2002; Polkinghorne, 2002; Penrose, 2004). In the early 20th century, the Danish physicist Niels Bohr, together with Werner Heisenberg, proposed the pragmatic "Copenhagen interpretation," according to which the wavefunction of a quantum system, evolving according to U, is not assigned any actual physical "reality," but is taken as basically providing the needed "bookkeeping" so that eventually probability values can be assigned to the various possible outcomes of a quantum measurement. The measuring device itself is explicitly taken to behave *classically* and no account is taken of the fact that the device is ultimately built from quantum-level constituents. The probabilities are calculated, once the nature of the measuring device is known, from the state that the wavefunction has U-evolved to at the time of the measurement. The discontinuous "jump" that the wavefunction makes upon measurement, according to R, is attributed to the change in "knowledge" that the result of the measurement has on the observer. Since the wavefunction is not assigned physical reality, but is considered to refer merely to the observer's knowledge of the quantum system, the jumping is considered simply to reflect the jump in the observer's knowledge state, rather than in the quantum system under consideration.

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

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

A more "down-to-earth" viewpoint is that of *environmental decoherence*, in which interaction of a superposition with its environment "erodes" quantum states, so that instead of a single wavefunction being used to describe the state, a more complicated entity is used, referred to as a *density matrix*. However, decoherence does not provide a consistent ontology for the *reality* of the world, in relation to the density matrix (see, for example, Penrose (1994), Secs. 29.3–29.6), and provides merely a pragmatic procedure. Moreover, it does not address the issue of how R might arise in isolated systems, nor the nature of isolation, in which an external "environment" would not be involved, nor does it tell us which part of a system is to be regarded as the 'environment' part, and it provides no limit to the size of that part which can remain subject to quantum superposition.

Still other approaches include various types of OR in which a specific objective threshold is proposed to cause quantum state reduction (Percival, 1994; Moroz *et al.*, 1998; Ghirardi *et al.*, 1986). The specific OR scheme that is used in Orch OR will be described below.

The quantum pioneer Erwin Schrödinger took pains to point out the difficulties that confront the U-evolution of a quantum system with his still-famous thought experiment called "Schrödinger's cat" (Schrödinger, 1935). Here, the fate of a cat in a box is determined by magnifying a quantum event (say the decay of a radioactive atom, within a specific time period that would provide a 50% probability of decay) to a macroscopic action which would kill the cat, so that according to Schrödinger's own U-evolution the cat would be in a quantum superposition of being both dead and alive at the same time. According to this perspective on the Copenhagen interpretation, if this U-evolution is maintained until the box is opened and the cat observed, then it would have to be the conscious human observing the cat that results in the cat becoming either dead or alive (unless, of course, the cat's own consciousness could be considered to have already served this purpose). Schrödinger intended to illustrate the absurdity of the direct applicability of the rules of quantum mechanics (including his own U-evolution) when applied at the level of a cat. Like Einstein, he regarded quantum mechanics as an incomplete theory, and his 'cat' provided an excellent example for emphasizing this incompleteness. There is a need for something to be done about quantum mechanics, irrespective of the issue of its relevance to consciousness.

14.4.4. *OR and quantum gravity*

DP objective reduction is a particular proposal for an extension of current quantum mechanics, taking the bridge between quantum- and classical-level physics as a "quantum-gravitational" phenomenon. This is in contrast with the various conventional viewpoints, whereby this bridge is claimed to result, somehow, from "environmental decoherence," or from "observation by a conscious observer," or from a "choice between alternative worlds," or some other interpretation of how the classical world of one actual alternative may be taken to arise out of fundamentally quantum-superposed ingredients.

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

In the DP scheme for OR, the superposition reduces to one of the alternatives in a timescale τ that can be estimated (for a superposition of two states each of which is assumed to be taken to be stationary on its own) according to the formula $\tau \approx \hbar/E_G$. An important point to make about τ, however, is that it represents merely a kind of *average* time for the state reduction to take place. It is very much like a *half-life* in a radioactive decay. The actual time of decay in each individual state-reduction event, according to DP (in its current form), is taken to be a random process. Such an event would involve the entire (normally entangled) state, and would stretch across all the superposed material that is involved in the calculation of E_G. According to DP (in its current form), the actual time of decay in a particular state-reduction event occurs simultaneously (in effect) over the entire state involved in the superposition, and it is taken to follow the $\tau \approx \hbar/E_G$ formula on the *average* (in a way similar to radioactive decay). Here $\hbar$ $(=h/2\pi)$ is Dirac's form of Planck's constant h and E_G is the *gravitational self-energy* of the *difference* between the two (stationary) mass distributions of the superposition. (For a superposition for which each mass distribution is a rigid translation of the other, E_G is the energy it would cost to displace one component of the superposition in the gravitational field of the other, in moving it from coincidence to the quantum-displaced location (Penrose, 2002).)

It is helpful to have a conceptual picture of quantum superposition in a gravitational context. According to modern accepted physical theories, reality is rooted in three-dimensional space and a one-dimensional time, combined together into a four-dimensional *space–time*. This space–time is slightly curved, in accordance with Einstein's general theory of relativity, in a way which encodes the gravitational fields of all distributions of mass density. Each different choice of mass density effects a space–time curvature in a different, albeit very tiny, way. This is the standard picture according to *classical* physics. On the other hand, when *quantum* systems have been considered by physicists, this mass-induced tiny curvature in the structure of space–time has been almost invariably ignored, gravitational effects having been assumed to be totally insignificant for normal problems in which quantum theory is important. Surprising as it may seem, however, such tiny differences in space–time structure *can* have large effects, for they entail subtle but fundamental influences on the very rules of quantum mechanics (Penrose, 1992, 1996, 2000, 2009).

In the current context, superposed quantum states for which the respective mass distributions differ significantly from one another will have space–time geometries which also correspondingly differ. For illustration, in Fig. 8, we consider a two-dimensional space–time sheet (one space and one time dimension). In Fig. 8, at left, the top and bottom alternative curvatures indicate a mass in two distinct locations. If that mass were in superposition of both locations, we might expect to see both curvatures, i.e. the bifurcating space-time depicted in the right of Fig. 8, this being the union ("glued together version") of the two alternative space–time histories that are depicted on the left. The initial part of each space–time is at the upper left of each individual space–time diagram, and so the bifurcating space–time diagram on right moving downward and rightward illustrates two alternative mass distributions evolving in time, their space–time curvature separation increasing.

Quantum-mechanically (so long as OR has not taken place), the "physical reality" of this situation, as provided by the evolving wavefunction, is being illustrated as an actual superposition of these two slightly differing space–time manifolds, as indicated on the right of Fig. 8. Of course there is additional artistic license involved in drawing the space-time sheets as two-dimensional, whereas the actual space–time constituents are four-dimensional. Moreover, there is no significance to be attached to the imagined "three-dimensional space" within

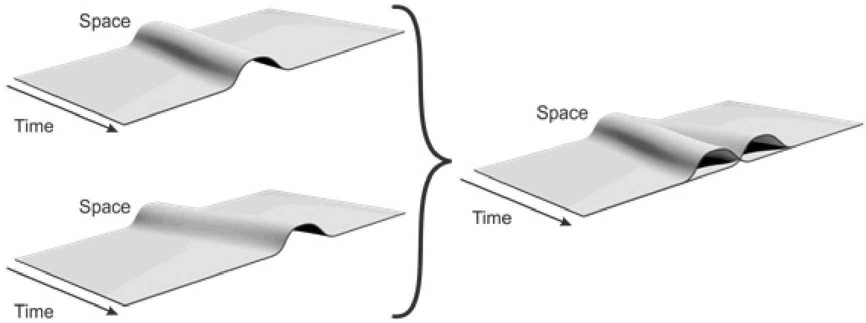

Fig. 8. Space–time geometry schematized as one spatial and one temporal dimension in which particle location is represented as curvature. Left: Top and bottom show space–time histories of two alternative particle locations. Right: Quantum superposition of both particle locations as bifurcating space–time depicted as the union ("glued together version") of the two alternative histories. [Adapted from Penrose (1994) p. 338].

which the space–time sheets seem to be residing. There is no "actual" higher dimensional space there, the "intrinsic geometry" of the bifurcating space–time being all that has physical significance. When the "separation" of the two space–time sheets reaches a critical amount, one of the two sheets "dies" — in accordance with the OR criterion — the other being the one that persists in physical reality. The quantum state thus reduces (OR), by choosing between either the curved or flat space–time in each of the two separations in Fig. 8.

It should be made clear that this measure of superposition separation is only very schematically illustrated as the "distance" between the two sheets in Fig. 8. As remarked above, there is no physically existing "ambient higher dimensional space" inside which the two sheets reside. The degree of separation between the space–time sheets is a more abstract mathematical thing; it would be more appropriately described in terms of a *symplectic measure* on the space of four-dimensional metrics [(cf. Penrose (1992); Penrose & Bell (2002)]; but the details (and difficulties) of this will not be important for us here. It may be noted, however, that this separation is a space–time separation, not just a spatial one. Thus, the *time* of separation contributes as well as the spatial displacement. It is the product of the temporal separation T with the spatial separation S that measures the overall degree of separation, and OR takes place when this overall separation reaches the critical amount.

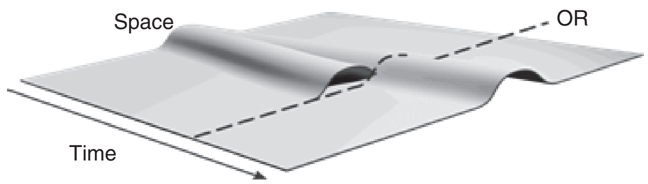

Fig. 9. As superposition curvature E reaches threshold (by $E_G=\hbar/\tau$), OR occurs and one particle location/curvature is selected, and becomes classical. The other ceases to exist.

In the absence of a coherent theory of quantum-gravity there is no accepted way of handling such a superposition as a separation (or bifurcation) of space–time geometry, or in any other way. Indeed the basic principles of Einstein's general relativity begin to come into profound conflict with those of quantum mechanics (Penrose, 1996, 2009). Some form of OR is needed.

The OR process is considered to occur when quantum superpositions between such slightly differing space–times take place (Fig. 9), differing from one another by an integrated space–time measure which compares with the fundamental and extremely tiny Planck (4-volume) scale of space–time geometry. As remarked above, this is a 4-volume Planck measure, involving both time and space, so we find that the time measure would be particularly tiny when the space-difference measure is relatively large (as with Schrödinger's hypothetical cat), but for extremely tiny space-difference measures, the time measure might be fairly long. For example, an isolated single electron in a superposed state (very low E_G) might reach OR threshold only after thousands of years or more, whereas if Schrödinger's (~1 kg) cat were to be put into a superposition, of life and death, this threshold could be reached in far less than even the Planck time of 10^{-43} s.

As already noted, the degree of separation between the space–time sheets is technically a symplectic measure on the space of 4-metrics which is a space–time separation, not just a spatial one, the time of separation contributing as well as spatial displacement. Roughly speaking, it is the product of the temporal separation T with the spatial separation S that measures the overall degree of separation, and (DP) OR takes place when this overall separation reaches a critical amount. This critical amount would be of the order of unity, in *absolute units*, for which the

Planck–Dirac constant $\hbar$, the gravitational constant G and the velocity of light c, all take the value unity, [cf. Penrose (1994, pp. 337–339)]. For small S, the lifetime $\tau \approx T$ of the superposed state will be large; on the other hand, if S is large, then τ will be small.

To estimate S, we compute (in the Newtonian limit of weak gravitational fields) the gravitational self-energy E_G of the difference between the mass distributions of the two superposed states. (That is, one mass distribution counts positively and the other, negatively; [see Penrose (1992, 2002, 2004)]. The quantity S is then given by: $S \approx E_G$ and $T \approx \tau$, whence $\tau \approx \hbar / E_G$, i.e., $E_G \approx \hbar / \tau$. Thus, the DP expectation is that OR occurs with the resolving out of one particular space–time geometry from the previous superposition when, on the average, $\tau \approx \hbar/E_G$.

The Orch-OR scheme adopts DP as a physical proposal, but it goes further than this by attempting to relate this particular version of OR to the phenomenon of *consciousness*. Accordingly, the "choice" involved in any quantum state-reduction process would be accompanied by a (miniscule) proto-element of experience, which we refer to as a moment of *proto-consciousness,* but we do not necessarily refer to this as *actual* consciousness for reasons to be described.

14.4.5. *OR and Orch OR*

For Orch OR and consciousness to occur, quantum superpositions of gravitational self-energy E_G would need to avoid environmental decoherence long enough to reach time τ by $\tau \approx \hbar/E_G$. Indeed, it is essential for Orch OR that some degrees of freedom in the system are kept isolated from environmental decoherence, so that OR can be made use of by the system in a controlled way. It should be made clear that in the DP scheme environmental decoherence need not necessarily be playing an important role in any particular instance of state reduction, although in uncontrolled situations the environment may well supply the major contribution to E_G. What DP does require is that when state reduction R takes place, this *always* occurs spontaneously, by this gravitational criterion. In nearly all physical situations, there would be much material from the environment that would be entangled with a quantum-superposed state, and it could well be that the major mass displacement — and therefore the major contribution to E_G — would occur in the environment rather than in the system under consideration. Since the environment will be quantum-entangled with the system, the state-reduction in the environment will effect a simultaneous reduction in the system. This could shorten the time for the state reduction R to take place in a superposed system very considerably from what it would have been without the environmental influence. The environment would also introduce an uncontrollable random element into the result of the reduction, so that any non-random (albeit non-computable) element influencing the particular choice of state that is actually resolved out from the superposition would be completely masked by this randomness. In these circumstances, the OR-process would be indistinguishable from the standard R-process of conventional quantum mechanics, which could be considered to be affected by standard environmental decoherence.

If, however, a quantum superposition is (1) "orchestrated," i.e., adequately organized, imbued with cognitive information, and capable of integration and computation, and (2) isolated from non-orchestrated, random environment long enough for the superposition E_G to evolve by the U formalism to reach time τ by $\tau \approx \hbar/E_G$, then Orch OR will occur and this, according to the scheme, will result in a moment of consciousness. Thus, if the suggested non-computable effects of this OR proposal are to be laid bare, where DP is being adopted and made use of in biological evolution, and ultimately orchestrated for moments of actual consciousness, we indeed need significant isolation from the environment.

As yet, no experiment has been refined enough to determine whether the (DP) OR proposal is actually respected by Nature, but the experimental testing of the scheme is fairly close to the borderline of what can be achieved with present-day technology (see Marshall *et al*., 2013). For example, one ought to begin to see the effects of this OR scheme if a small object, such as a 10-micron cube of crystalline material could be held in a coherent superposition of two locations, differing by about the diameter of an atomic nucleus, for some seconds, or perhaps minutes to reach threshold by $\tau \approx \hbar/E_G$.

A point of importance, in such proposed experiments, and in estimating requirements for Orch OR, is that in order to calculate E_G it is not enough to base the calculation on an average density of the material in the superposition, since the mass will be concentrated in the atomic nuclei, and for a displacement of the order of the diameter of a nucleus, this inhomogeneity in the density of the material can be crucial, and may well provide a much larger value for E_G than would be obtained if the material is assumed to be homogeneous. The Schrödinger equation (more correctly, in the zero-temperature approximation, the Schrödinger–Newton equation, [(see Kibble (1981) and Moz *et al*. (1998)] for the static unsuperposed material would have to be solved, at least approximately, in order to derive the expectation value of the mass distribution in each of the two separate components of the superposition. In the stationary wavefunction of each component, there would be some quantum spread in the locations of the particles constituting the nuclei (i.e., each component's wavefunction would not normally be very sharply peaked at these particle locations, as the locations would be considerably spread out in most materials).

In the situations under consideration here, where we expect a conscious brain to be at far from zero temperature, and because technological quantum computers require zero temperature, it is very reasonable to question quantum brain activities. Nevertheless, it is now well known that superconductivity and other large-scale quantum effects can actually occur at temperatures very far from absolute zero. Indeed, biology appears to have evolved thermal mechanisms to *promote* quantum coherence. In 2003, Ouyang and Awschalom (2003) showed that quantum spin transfer through phenyl ring π orbital resonance clouds (the same as those in protein hydrophobic regions, as illustrated in Figs. 5–7) is enhanced at increasingly warm temperatures. (Spin flip currents through microtubule pathways, as suggested in Sec. 14.3.3. above, may be directly analogous.)

In the past nine years, evidence has accumulated that plants routinely use quantum coherent electron transport at ambient temperatures in photosynthesis (Engel *et al*., 2007; Hildner *et al*., 2013). Photons are absorbed in one region of a photosynthetic protein complex, and their energy is conveyed by electronic excitations through the protein to another region to be converted to chemical energy to make food. In this transfer, electrons utilize multiple pathways simultaneously, through π electron clouds in a series of chromophores (analogous to hydrophobic regions) spaced nanometers apart, maximizing efficiency (e.g. via so-called "exciton hopping"). Chromophores in photosynthesis proteins appear to enable electron quantum conductance precisely like aromatic rings are proposed in Orch OR to function in tubulin and microtubules (Figs. 5–7).

Quantum conductance through photosynthesis protein is enhanced by mechanical vibration (Chin *et al*., 2013), and microtubules appear to have their own set of mechanical vibrations [(e.g., in megahertz as suggested by Sahu *et al.*, (2013a, 2013b; 2014)]. Megahertz mechanical vibrations is ultrasound, and brief, low intensity (sub-thermal) ultrasound administered through the skull to the brain modulates electrophysiology, behavior and affect, e.g., improved mood in patients suffering from chronic pain, perhaps by direct excitation of brain microtubules (Hameroff *et al.*, 2013).

Further research has shown warm quantum effects in bird-brain navigation (Gauger *et al.*, 2011), ion channels (Bernroider & Roy, 2005), sense of smell (Turin, 1996), DNA (Rieper *et al.*, 2011), protein folding (Luo & Lu, 2011) and biological water (Reiter *et al.*, 2011). What about quantum effects in microtubules? In the 1980s and 1990s theoretical models predicted "Fröhlich" gigahertz coherence and ferroelectric effects in microtubules (Rasmussen *et al.*, 1990; Hameroff & Watt, 1982; Smith *et al.*, 1984). In 2001 and 2004, coherent megahertz emissions were detected from living cells and ascribed to microtubule dynamics (powered by mitochondrial electromagnetic fields) by the group of Jiri Pokorny in Prague (Pokorny, 2004; Pokorny *et al.*, 2001).

Beginning in 2009, Anirban Bandyopadhyay and colleagues at the National Institute of Material Sciences in Tsukuba, Japan, were able to use nanotechnology to address electronic and optical properties of individual microtubules (Sahu *et al.*, 2013a, 2013b; 2014). The group has made a series of remarkable discoveries suggesting that quantum effects do occur in microtubules at biological temperatures. First, they found that electronic conductance along microtubules, normally extremely good insulators, becomes exceedingly high, approaching quantum conductance, at certain specific resonance frequencies of applied AC stimulation. These resonances occur in gigahertz, megahertz and kilohertz ranges, and are particularly prominent in low megahertz (e.g. 8.9 MHz). Conductances induced by specific (e.g., megahertz) AC frequencies appear to follow several types of pathways through the microtubule — helical, linear along the microtubule axis, and "blanket-like" along/around the entire microtubule surface. Second, using various techniques, the Bandyopadhyay group also determined that AC conductance through 25nm-wide microtubules is greater than through single 4nm-wide tubulins, indicating cooperative, possibly quantum coherent effects throughout the microtubule, and that the electronic properties of microtubules are programmed within each tubulin. Their results also showed that conductance increased with microtubule length, also indicative of quantum mechanisms.

The resonance conductance ("Bandyopadhyay coherence" — 'BC') through tubulins and microtubules is consistent with the intra-tubulin aromatic ring pathways (see Figs. 5–7) which can support Orch OR quantum dipoles, and in which anesthetics bind, apparently to selectively erase consciousness. Bandyopadhyay's experiments do seem to provide clear evidence for coherent microtubule quantum states at brain temperature.

14.4.6. *Beat frequencies*

Quantum-coherent behavior does indeed appear to be relevant, in a way that applies even to biological systems, at surprisingly warm temperatures. Accordingly, we appear to need an extension of the DP proposal that can be used in such "warm" situations. Although such a theory is not yet at hand, it will be of some importance here to indicate certain of the key issues, so that we can get a feeling for the role that we are requiring for DP-related ideas in the suggested proposals put forward in the sections below.

In the first place, it should be pointed out that in standard quantum treatments of systems at non-zero temperature, the description would be in terms of a *density matrix* rather than a simple wavefunction. Such a density-matrix description can be viewed as a *probability mixture* of different wavefunctions — although such an ontology does not reveal the full subtleties involved, since a single density matrix can be interpreted in many different ways as such a probability mixture [(see for example Penrose (2004, Secs. 29.4 and 29.5)]. As yet, a fully appropriate generalization of the DP scheme to a density-matrix description has not been provided. But in any case it is unlikely that this would be an appropriate thing to do in the present context, and here we shall explore an alternative route to the understanding of quantum effects in warm-temperature systems.

It is important to bear in mind that biological systems are very far from being in thermal equilibrium, so that a crude assignment of an overall 'temperature' to such a system is unlikely to be very revealing. Whenever we are asking for the manifestation of large-scale quantum effects in a warm system, we are not expecting that all the degrees of freedom should be simultaneously involved with these effects and therefore uniformly thermalized. What we really require is that certain of these degrees of freedom can be excited in ways that remain isolated from most of the others, and that these excited degrees can be maintained in some form of quantum oscillation that can preserve its quantum nature for an appreciable time, without dissipation, this time being long enough for the system to reach Orch OR threshold, given by $\tau \approx \hbar/E_G$.

In previous Orch OR publications, the relevant time τ has been assumed to correlate with physiological parameters of the electro-encephalogram (EEG), i.e., 10 to several hundred milliseconds, which is relatively long for isolated quantum systems. But here we suggest an alternative way in which such oscillation frequencies might come about, namely as *beat* frequencies, arising when OR is applied to superpositions of quantum states of slightly different energies. This makes the task of finding an origin for these observed frequencies far simpler and more plausible.

In order to get some feeling of how the ideas of DP might relate to such situations, let us first address the assumption of *stationarity* that is involved in the DP scheme where, in order to apply DP strictly, we must consider that each of the states in superposition is to be regarded as being stationary, if taken on its own. In standard quantum mechanics, a stationary state is an eigenstate of energy — i.e., a state of definite energy E — which tells us that this quantum state has an (complex) oscillatory nature with a time-dependence that is proportional to $e^{-iEt/\hbar}$ [see, for example, Penrose (2004, Chapter 21)] so that it oscillates with frequency E/h (where we recall that $h=2\pi\hbar$). If we have a state Ψ which is a superposition of two slightly different states Ψ_1 and Ψ_2, each of which would be stationary on its own, but with very slightly different respective energies E_1 and E_2, then the superposition would not be quite stationary. Its basic *r* frequency would be the average $(E_1+E_2)/2h$ of the two, corresponding to the average energy $\frac{1}{2}(E_1+E_2)$, but this would be modulated by a much lower *classical* frequency ("beats") that is the difference between the two, namely $|E_1-E_2|/h$, as follows, very roughly, from the following mathematical identity (where we may take $a=-E_1t/\hbar$ and $b=-E_2t/\hbar$ to represent the quantum wavefunctions for the two energies):

$$e^{ia} + e^{ib} = 2e^{i(a+b)/2} \cos\frac{a-b}{2}.$$

If we imagine the complex oscillatory term e^{ia} to represent one quantum state Ψ_1 and e^{ib} to represent the other, then we see that their superposition has a complex quantum oscillation $e^{i(a+b)/2}$, which has a frequency which is the average of the two, but this is modulated by a classical oscillation as given by the cosine term, with a much lower frequency determined by the *difference* between the quantum mechanical frequencies E_1 and E_2 of the two individual states Ψ_1 and Ψ_2. This classical "beat" frequency is in fact $|E_1-E_2|/h$ rather than $|E_1-E_2|/2h$ because when passing from a quantum amplitude to a classical probability we need to take the squared modulus of the amplitude, and in this case it amounts to taking the squared modulus of half the right-hand side of the above expression, namely $\cos^2\{½(a-b)\}=\{1+\cos(a-b)\}/2$ for finding one component of the superposition and $\{1-\cos(a-b)\}/2$ for the other. (This phenomenon is closely related to that found in neutrino oscillations, [see Pontecorvo (1968)].

To be more explicit about how this comes about, it is necessary to appreciate, first, that the eigenstates of energy, Ψ_1 and Ψ_2, in the superposition — i.e., the two stationary states of which the quantum state is composed, in superposition — will, in the situation under consideration, be different from the two distinguishable *location states* Λ and Π (taken to be normalized and mutually orthogonal, and without any time-dependence) that would be the states of location arising as a result of the OR process in the original DP proposal (which is concerned with the degenerate case of equal energy eigenvalues) or as the two states between which (as we shall argue) *classical oscillation* takes place (in the case of unequal energy eigenvalues). We consider here the case of unequal energy eigenvalues, so the eigenstates Ψ_1 and Ψ_2 must be distinct and orthogonal to each other, and we may assume that each is normalized. Accordingly, we can choose phases for the location-state basis $\mathit{\Lambda}$, $\mathit{\Pi}$, so that Ψ_1 and Ψ_2 when expressed in terms of these location states, take the form

$$\Psi_1=(\mathit{\Lambda}\cos\theta+\mathit{\Pi}\sin\theta)e^{ia} \text{ and } \Psi_2=(\mathit{\Lambda}\sin\theta-\mathit{\Pi}\cos\theta)e^{ib}$$

for some angle θ (measuring the "angle" between the energy basis and the location basis), where the time-dependence of these states is now provided by $a=-E_1t/\hbar$ and $b=-E_2t/\hbar$, as above. The initial quantum state is taken to be a superposition

$$\Psi=\alpha\Psi_1+\beta\Psi_2,$$

where α and β are complex constants satisfying $|\alpha|^2+|\beta|^2=1$. In terms of the location states Λ and Π, we find

$$\Psi=\Lambda(\alpha e^{ia}\cos\theta+\beta e^{ib}\sin\theta)+\Pi(\alpha e^{ia}\sin\theta-\beta e^{ib}\cos\theta).$$

To find the classical oscillation that this ought to reduce to, according to our extended DP proposal, we calculate (in accordance with standard quantum mechanics) the time-dependent probabilities that a measurement to distinguish between the two location states would give us, this being obtained by taking the squared modulus of the coefficients of Λ and Π, namely

$$|\alpha|^2 \cos^2\theta + |\beta|^2 \sin^2\theta + (\alpha\bar{\beta}\, e^{i(a-b)} + \beta\bar{\alpha}\, e^{i(b-a)}) \cos\theta \sin\theta$$

and

$$|\alpha|^2 \sin^2\theta + |\beta|^2 \cos^2\theta - (\alpha\bar{\beta}\, e^{i(a-b)} + \beta\bar{\alpha}\, e^{i(b-a)}) \sin\theta \cos\theta,$$

respectively. These two probabilities are seen to sum to 1, as they should, and provide us with a probability value that oscillates between the two locations (though perhaps preferentially with respect to one or the other, depending on the parameters) with a frequency determined by $|a-b|$, namely "beat" difference frequency $|E_1-E_2|/h$, as asserted above. There is also a much higher quantum oscillation frequency which in particular cases (e.g., $|\alpha| = |\beta|$ and $\theta=\pi/4$) we can identify as the average $(E_1+E_2)/2h$ of the two constituent quantum frequencies, but where in general this frequency is not so precisely defined, though can be thought of as being a quantity of this order of size.

According to a (crude) direct application of DP, we might imagine that this "measurement" (i.e., OR action) would be a spontaneous reduction to one or other of these two locations in a timescale of the general order of $\tau \approx \hbar/E_G$ (where E_G is the gravitational self-energy of the difference between the expectation values mass distributions of the two states), but with much apparent randomness as to which of the two locations is taken up upon reduction. However, for an oscillating system like this, where the original quantum state is a superposition of two stationary states of slightly different energies E_1 and E_2, and which therefore behaves as a state effectively undergoing a *quantum* oscillation with frequency of around $(E_1+E_2)/2h$ and a *classical* "beat" oscillation of frequency $|E_1-E_2|/h$, it seems appropriate that we adopt this suggested *extension* of the original DP proposal, whereby the interfering quantum oscillations reduce spontaneously to a *classical oscillation* whose frequency is the beat frequency, rather than it simply reduces to one location or the other in a seemingly random way that would then not clearly manifest this beat frequency. We take the *time* for the combined quantum oscillation of the state to reduce to be $\tau \approx \hbar/E_G$ (on average), just as in the original DP proposal, but we now take the reduction to be to a classical oscillation (with this beat frequency), rather than to one or the other of the original pair of states. It is the *phase* of this oscillation that becomes definite upon reduction (OR), rather than one or the other of the two locations being singled out. We note that in the limiting situation, where we take E_1 and E_2 to be identical, the beat period would become infinite, so that in such a situation the reduction simply takes the state to one location or the other, in an average time of the order of $\tau \approx \hbar/E_1 = \hbar/E_2$, just as in the original DP proposal.

We are taking it that τ is very much larger than the quantum oscillation period $\sim 2h/(E_1+E_2)$, but it could presumably be a lot smaller than the "beats" period $h/|E_1-E_2|$. We must bear in mind that there will be a considerable spread in the actual times at which the reduction will take place (since, as we recall, the role of τ is really only as a kind of half-life for reduction), but here this only affects the *phase* of the oscillation, the frequency itself being simply the well-defined beat frequency $|E_1-E_2|/h$. Accordingly, if we consider that our system consists of a large number of identical quantum superpositions of the same kind, then this beat frequency would become evident across the system as a whole (as with an orchestra, with many violinists playing the same note, but not phase coherently). Thus, according to this extended DP proposal, we ought to see evidence of this difference frequency $|E_1-E_2|/h$, as a result of the OR process, which would be far lower than the exceedingly high individual frequencies E_1 and E_2, and the oscillation period $h/|E_1-E_2|$ could be significantly longer than τ.

Thus, we may consider conscious moments to be Orch OR events occurring with beat frequencies $|E_1-E_2|/h$, rather than primary frequencies E_1/h and E_2/h. This makes the task far simpler and more plausible than it had been within our earlier scheme. Quantum superpositions need to avoid environmental decoherence only for a time that, while considerably longer than the periods of the primary frequencies, E_1 and E_2, might nevertheless be short compared with the time period $h/|\mathrm{E}_1-E_2|$ of the beat frequencies $|E_1-E_2|/h$. Following Bandyopadhyay's findings, these primary frequencies may be around 10 MHz, with time periods of $\sim 10^{-7}$ s. Decoherence might need be avoided for a mere 10-millionth of a second with consciousness occurring at far slower beat frequencies. For example if E_1 and E_2 were, 10.000000 MHz and 10.000040 MHz, respectively, a beat frequency of 40 Hz (by $|E_1 - E_2|/h$) could correlate with discrete conscious moments.

These considerations had not been taken into account in our simpler earlier viewpoint that the frequencies of oscillation that appear to be associated with conscious processes are the result of repeated occurrences of OR, and that the periods of oscillation are therefore to be identified with the value of tau itself, e.g., 25 ms for 40 Hz gamma synchrony. It must be borne in mind, in relation to this earlier proposal, that τ is only a kind of *average* reduction time (like the half-life of a radioactive decay). On that basis, Orch OR events would occur at distinctly irregular intervals, and could be only very roughly related to the required overall ranges such as gamma synchrony (30Hz to 90 Hz) or other EEG frequency bands. It is a little difficult to see how this previous, provisional viewpoint could give rise to a fairly definite characteristic frequency of oscillation, like the 40Hz gamma synchrony EEG.

Nevertheless, for the sake of continuity with our earlier discussions, we shall also refer to this earlier scheme concurrently with our present "beat frequency" point of view, but even this newer perspective must be considered as tentative in various respects. It is to be expected that the actual mechanisms underlying the production of consciousness in a human brain will be very much more sophisticated than any that we can put forward at the present time, and would be likely to differ in many important respects from any that we would be in a position to anticipate in our current proposals. Nevertheless, we do feel that the suggestions that we are putting forward here represent a serious attempt to grapple with the fundamental issues raised by the consciousness phenomenon, and it is in this spirit that we present them here.

14.5. Penrose–Hameroff "Orchestrated Objective Reduction"

14.5.1. *Orch OR quantum computing in the brain*

Penrose (1989, 1994) suggested that consciousness depends in some way on processes of the general nature of *quantum computations* occurring in the brain, these being terminated by some form of OR. Here the term "quantum computation" is being used in a loose sense, in which information is encoded in some discrete (not necessarily binary) physical form, and where the evolution is determined according to the U process (Schrödinger's equation). In the standard picture of quantum computers

(Benioff, 1982; Deutsch, 1985; Feynman, 1986), information is represented not just as bits of either 1 or 0, but during the U process, also as quantum superposition of both 1 and 0 together (quantum bits or "qubits") where, moreover, large-scale entanglements among many qubits would also be involved. These entangled qubits would compute, in accordance with the Schrödinger equation, in order to enable complex and highly efficient potential parallel processing. As originally conceived, quantum computers would indeed act strictly in accordance with U, but at some point a measurement is made causing a quantum state reduction R (with some randomness normally introduced). Accordingly, the *output* is in the form of a definite state in terms of classical bits.

A proposal was made in Penrose (1989) that something analogous to quantum computing, proceeding by the Schrödinger equation without decoherence, could well be acting in the brain, but where, for *conscious* processes, this would have to terminate in accordance with some threshold for *self*-collapse by a form of non-computable OR. A quantum computation terminating by OR could thus be associated with consciousness. However, no plausible biological candidate for quantum computing in the brain had been available to him, as he was then unfamiliar with microtubules. Penrose and Hameroff teamed up in the early 1990s when, fortunately, the DP form of OR mechanism was then at hand to be applied in extending the microtubule-automata models for consciousness as had been developed by Hameroff and colleagues.

As described in Sec. 2.3, the most logical strategic site for coherent microtubule Orch OR and consciousness is in post-synaptic dendrites and soma (in which microtubules are uniquely arrayed and stabilized) during integration phases in integrate-and-fire brain neurons. Synaptic inputs could "orchestrate" tubulin states governed by quantum dipoles, leading to tubulin superposition in vast numbers of microtubules all involved quantum-coherently together in a large-scale quantum state, where entanglement and quantum computation takes place during integration. The termination, by OR, of this orchestrated quantum computation at the end of integration phases would select microtubule states which could then influence and regulate axonal firings, thus controlling conscious behavior. Quantum states in dendrites and soma of a particular neuron could entangle with microtubules in the dendritic tree of that neuron, and also in neighboring neurons via dendritic–dendritic (or dendritic–interneuron–dendritic) gap junctions, enabling quantum entanglement of superposed microtubule tubulins among many neurons (Fig. 1). This allows unity and binding of conscious content, and a large E_G which reaches threshold (by $\tau \approx \hbar/E_G$) quickly, such as at end-integration in EEG-relevant periods of time, e.g., $\tau=0.5$ s to $\tau=10^{-2}$ s. In the Orch OR "beat frequency" proposal, we envisage that τ could be far briefer, e.g., 10^{-7} s, a time interval already shown by Bandyopadhyay's group to sustain apparent quantum coherence in microtubules. In either case, or mixture of both, Orch OR provides a possible way to account for frequent moments of conscious awareness and choices governing conscious behavior.

Section 3 described microtubule automata, in which tubulins represent distinct information states interacting with neighbor states according to rules based on dipole couplings which can apply to either London force electric dipoles, or electron spin magnetic dipoles. These dipoles move atomic nuclei slightly (femtometers), and become quantum superpositioned (along with superpositioned atomic nuclei), entangled and perform quantum computation in a U process. In dendrites and soma of brain neurons, synaptic inputs could encode memory in alternating classical phases, thereby avoiding random environmental decoherence to "orchestrate" U quantum processes, enabling them to reach threshold at time τ for orchestrated objective reduction "Orch OR" by $\tau \approx \hbar/E_G$. At that time, according to this proposal, a moment of conscious experience occurs, and tubulin states are selected which influence axonal firing, encode memory and regulate synaptic plasticity.

An Orch OR moment is shown schematically in Fig. 10. The top panel shows microtubule automata with (gray) superposition E_G increasing over a period up to time τ, evolving deterministically and algorithmically by the Schrödinger equation (U) until threshold for OR by $\tau \approx \hbar/E_G$ is reached, at which time Orch OR occurs, accompanied by a moment of conscious experience. In the "beat frequency" modification of this proposal, these Orch OR events could occur on a faster timescale, for example in megahertz. Their far slower beat frequencies might then constitute conscious moments. The particular selection of conscious perceptions and choices would, according to standard quantum theory, involve an entirely random process, but according to Orch OR, the (objective) reduction could act to select specific states in accordance with some non-computational new physics (in line with suggestions made in Penrose (1989, 1994).

Figure 10 (middle) depicts alternative superposed space–time curvatures (Figs. 8 and 9) corresponding to the superpositions portrayed in MTs in the top of the figure, reaching threshold at the moment of OR and

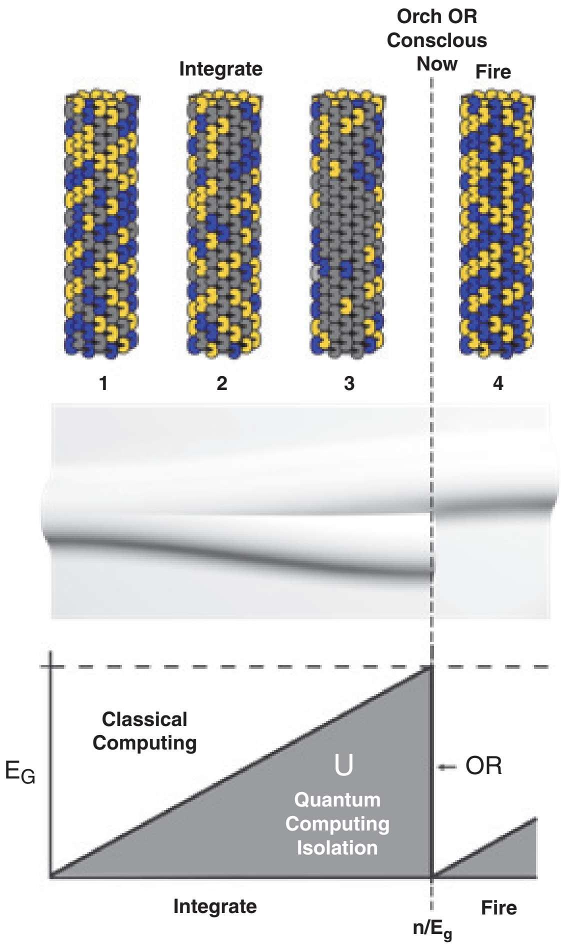

Fig. 10. Top: Tentatively proposed picture of a conscious event by quantum computing in one of a vast number of microtubules all acting coherently so that there is sufficient mass displacement for Orch OR to take place. Tubulins are in classical dipole states (yellow or blue), or quantum superposition of both dipole states (gray). Quantum superposition/computation evolves during integration phases (1–3) in integrate-and-fire brain neurons, increasing quantum superposition E_G (gray tubulins) until threshold is met at time $\tau \approx \hbar/E_G$, at which time a conscious moment occurs, and tubulin states are selected which regulate firing and control conscious behavior. Middle: Corresponding alternative superposed space–time curvatures reaching threshold at the moment of OR and selecting one space–time curvature. Bottom: Schematic of a conscious Orch OR event showing U-like evolution of quantum superposition and increasing E_G until OR threshold is met, and a conscious moment occurs by $\tau \approx \hbar/E_G$.

selecting one space–time. Figure 10 (bottom) shows a schematic of the same process.

The idea is that consciousness is associated with this (gravitational) OR process, but (see Sec. 4.5) occurs significantly only when (1) the alternatives are part of some highly organized cognitive structure capable of information processing, so that OR occurs in an extremely *orchestrated* form, with vast numbers of microtubules acting coherently, in order that there is sufficient mass displacement overall for the $\tau \approx \hbar/E_G$ criterion to be satisfied. (2) Interaction with environment must be avoided long enough during the U process evolution so strictly orchestrated components of the superposition reach OR threshold without too much randomness, and reflect a significant non-computable influence. Only then does a recognizably conscious Orch OR event takes place. On the other hand, we may consider that any individual occurrence of OR without orchestration would be a moment of random *proto*-consciousness lacking cognition and meaningful content.

We shall be seeing orchestrated OR in more detail shortly, together with its particular relevance to microtubules. In any case, we recognize that the experiential elements of proto-consciousness would be intimately tied in with the most primitive Planck-level ingredients of space–time geometry, these presumed "ingredients" being taken to be at the absurdly tiny level of 10^{-35}m and 10^{-43}s, a distance and a time of 20 orders of magnitude smaller than those of normal particle-physics scales and their most rapid processes, and they are smaller by far than biological scales and processes. These scales refer only to the normally extremely tiny differences in *space–time geometry* between different states in superposition, the separated states themselves being enormously larger. OR is deemed to take place when such tiny space–time differences reach the Planck level (roughly speaking). Owing to the extreme weakness of gravitational forces as compared with those of the chemical and electric forces of biology, the energy E_G is liable to be *far* smaller than any energy that arises directly from biological processes.

OR acts effectively instantaneously as a choice between dynamical alternatives (a choice that is an integral part of the relevant quantum dynamics) and E_G is not to be thought of as being in direct competition with any of the usual biological energies, as it plays a completely different role, supplying a needed energy *uncertainty* that then allows a choice to be made between the separated space–time geometries, rather than providing an actual energy that enters into any considerations of energy balance that would be of direct relevance to chemical or normal physical processes. This energy uncertainty is the key ingredient of the computation of the reduction time τ, and it is appropriate that this energy uncertainty is indeed far smaller than the energies that are normally under consideration with regard to chemical energy balance, etc. If it were not so, then there would be a danger of *conflict* with normal considerations of energy balance.

Nevertheless, the extreme weakness of gravity tells us there must be a considerable amount of material involved in the coherent mass displacement between superposed structures in order that τ can be small enough to be playing its necessary role in the relevant OR processes in the brain. These superposed structures should also process information and regulate neuronal physiology. According to Orch OR, *microtubules* are central to these structures, and some form of biological quantum computation in microtubules (perhaps in the more symmetrical A-lattice microtubules) would have to be involved to provide a subtle yet direct connection to Planck-scale geometry, leading eventually to discrete moments of actual conscious experience and choice. As described above, these are presumed to occur primarily in dendritic–somatic microtubules during integration phases in integrate-and-fire brain neurons, resulting in sequences of Orch OR conscious moments occurring within brain physiology, and able to regulate neuronal firings and behavior.

14.5.2. *Tubulin qubits and Orch OR conscious moments*

For Orch OR to be operative in the brain, we would need coherent superpositions of sufficient amounts of (e.g., microtubule) material accounting for E_G, undisturbed by environmental entanglement, where this reduction occurs in accordance with the above OR scheme in a timescale of the general order for a conscious experience. For an ordinary type of experience, this might be about $\tau=0.5$s to $\tau=10^{-2}$s which concurs with neural correlates of consciousness, such as particular frequencies of EEG, visual gestalts and reported conscious moments.

In order to see whether Orch OR can be implemented for some particular chosen reduction time τ, determined according to $\tau \approx \hbar/E_G$, the gravitational self-energy E_G must be calculated for this τ, which is taken to correspond to the duration of, or perhaps the interval between, conscious moments. We could calculate E_G from the difference between the mass distributions between two states of tubulin in superposition, but as previously mentioned, the use merely of an average density may not be adequate, as the mass is concentrated in the nuclei. There is, however, a large uncertainty about how "smeared out" these nuclei must be considered to be, as referred to above, which is related to how "crystalline" the microtubules may be considered to be. Accordingly, we calculated E_G for tubulin (Hameroff & Penrose, 1996a) separated from itself at three possible levels of separation: (1) the entire smoothed-out protein (partial separation), (2) its atomic nuclei and (3) its nucleons (protons and neutrons). In our picture, the dominant effect is likely to be (2) separation at the level of atomic nuclei, e.g., 2.5 Fermi length for carbon nuclei (2.5 fm; 2.5×10^{-15} m). This shift is the same as that predicted to be caused by electron charge separations of one nanometer, e.g., London force dipoles within aromatic amino acid rings.

Using $\tau \approx \hbar / E_G$, where we may choose τ as 25 ms for "40 Hz" gamma synchrony conscious moments, we calculated the number of required tubulins in superposition, separated by the diameter of their (carbon) atomic nuclei. Because the carbon nucleus displacement is greater than its radius, the gravitational self-energy E_c for superposition separation of one carbon atom is roughly given by: $E_c = Gm^2/a_c$, where G is the gravitational constant, m is the carbon nuclear mass and a_c is the carbon nucleus sphere radius equal to 2.5 fermi distances. We calculated that roughly 2×10^{10} tubulins displaced in coherent superposition for 25 ms will, on this basis, self-collapse in that time period, and elicit Orch OR. For a τ of 500 ms, $\sim 10^9$ tubulins would be required.

Neurons each contain roughly 10^9 tubulins, but only a fraction per neuron are likely to be involved in consciousness (e.g., a fraction of those in dendrites and soma). Global macroscopic states such as superconductivity ensue from quantum coherence among only very small fractions of components. If 1% of tubulins within a given set of neurons were coherent for 25 ms, then 20,000 such neurons would be required to elicit OR. In human brain, cognition and consciousness are, at any one time, thought to involve tens of thousands of neurons. Hebb's (1949) "cell assemblies," Eccles's (1992) "modules," and Crick & Koch's (1990) "coherent sets of neurons" are each estimated to contain some 10,000 to 100,000 neurons which may be widely distributed throughout the brain (Scott, 1995). In the "beat frequency" approach, a much smaller time $\tau = 10^{-7}$s might perhaps suffice, but require much larger microtubule superposition E_G, involving roughly 10^9 neurons, or 1% of the brain.

As electron movements may shift atomic nuclei by a distance of the order of a nuclear diameter, we assume that electron-superposition separations of around a nanometer could result in atomic (e.g., carbon) nuclear superposition separations of a few femtometers (Fermi lengths) (Pan *et al.*, 2007), which is about a nuclear diameter, thereby appearing to meet DP requirement for OR.

Assuming that microtubule quantum states occur in a specific brain neuron, how could they involve microtubules in other neurons throughout the brain? Orch OR proposes that quantum states can extend by entanglement between adjacent neurons through gap junctions, primitive electrical connections between adjacent cells (Fig. 1). Structurally, gap junctions are windows which may be open or closed. When open, gap junctions synchronize adjacent cell membrane polarization states, but also allow passage of molecules between cytoplasmic compartments of the two cells. So both membranes and cytoplasmic interiors of gap junction-connected neurons are continuous, essentially one complex "hyper-neuron" or syncytium. (Ironically, before Ramon-y-Cajal showed that neurons were discrete cells, the prevalent model for brain structure was a continuous threaded-together syncytium as proposed by Camille Golgi.) Quantum states in microtubules in one neuron can, we propose, extend by entanglement and tunneling through gap junctions to microtubules in adjacent neurons (including inter-neurons), potentially extending to brain-wide syncytia. Beginning in 1998, evidence began to show that gamma synchrony, the best measureable correlate of consciousness, depended on gap junctions, particularly dendritic–dendritic gap junctions (Dermietzel, 1998; Draguhn *et al.*, 1998; Galaretta & Hestrin, 2001; Bennett & Zukin, 2004; Fukuda & Kosaka, 2000; Traub *et al.*, 2002). To account for the distinction between conscious activities and non-conscious "auto-pilot" activities, and the fact that consciousness can occur in various brain regions, Hameroff (2010) developed the "Conscious pilot" model in which syncytial zones of dendritic gamma synchrony move around the brain, regulated by gap junction openings and closings, in turn regulated by microtubules. The model suggests consciousness literally moves around the brain in a mobile synchronized zone, within which isolated, entangled microtubules carry out quantum computations and Orch OR. Taken together, Orch OR and the conscious pilot distinguish conscious from non-conscious functional processes in the brain.

Applying $\tau \approx \hbar / E_G$ to large numbers of brain neurons, we find that, with this point of view with regard to Orch OR, a spectrum of possible types of conscious events might be able to occur, including those at higher frequency and intensity. It may be noted that Tibetan monk meditators have been found to have 80 Hz gamma synchrony, and perhaps more intense experience (Lutz *et al.*, 2004). Thus, according to the viewpoint proposed above, where we interpret this frequency to be associated with a succession of Orch OR moments, then $E_G \approx \hbar / \tau$ would appear to require that there is twice as much brain involvement for 80 Hz as for consciousness occurring at 40 Hz. More appropriately, it might be $\sqrt{2}$ times as much, since for the calculation of E_G, the displacement ought to be entirely coherent, and then the mass enters quadratically in E_G. Even higher (frequency), expanded awareness states of consciousness might be expected, according to this scheme, with more neuronal brain involvement. In the beat frequency approach, we might consider that megahertz or higher frequencies might be directly relevant to Orch OR, for which τ is very low, at 10^{-7}s, while E_G is large, at roughly 10^9 neurons, 1% of the brain, or perhaps even faster, larger components with more intense experiences.

There is also the possibility that discernable moments of consciousness are events that normally occur at a much slower pace than is suggested by the considerations above, and that they happen only at rough intervals of the order of, say, several hundreds of milliseconds, rather than ~25ms. One might indeed think of conscious influences as perhaps being rather slow, in contrast with the great deal of vastly faster unconscious computing that might be some form of quantum computing, but without OR. Another possibility is that conscious moments such as visual gestalts may be slower events, e.g., correlating with 4 to 7 Hz theta frequency, with nested gamma waves (Woolf & Hameroff, 2001; VanRullen & Koch, 2003). Yet another possibility, consistent with recent findings of scale-invariant processes in brain function, is that consciousness, according to this version of Orch OR's $\tau \approx \hbar / E_G$ can occur at varying frequencies, moving up and down in scales, with higher frequency events involving more of the brain having greater experiential intensity. At the present stage of uncertainty about such matters it is perhaps best not to be dogmatic about how the ideas of Orch OR are to be applied. In any case, the numerical assignments provided above must be considered to be extremely rough, and at the moment we are far from being in a position to be definitive about the precise way in which the Orch OR is to operate, even according to the particular version of Orch OR that is being described here. Alternative possibilities will need to be considered with an open mind.

14.5.3. *Microtubules and environmental "decoherence"*

Technological quantum computers, e.g., those using ion traps as qubits, are plagued by disruption of seemingly delicate quantum states by environmental interactions including thermal vibration. Such technology requires extremely cold temperatures and vacuum to operate. The role of environmental decoherence, according to OR schemes, is that R is effected in a system through its entanglement with its much larger effectively random environment, so that when OR takes place in that environment, the system itself is carried with it and therefore reduces, seemingly randomly, in accordance with a conventional R process. Thus, if we require non-random aspects of OR to play a role in (conscious) brain function, as is required for Orch OR, we need to avoid premature entanglement with the random environment, as this would result in state reduction without non-computable aspects or cognition. For Orch OR, environmental interactions must be avoided during the evolution toward time τ ($\approx \hbar/E_G$), so that the non-random (non-computable) aspects of OR can be playing their roles. How does quantum computing avoid environmental interaction ("decoherence") in the "warm, wet and noisy" brain?

It was suggested (Hameroff & Penrose, 1996a) that microtubule quantum states avoid decoherence by being pumped, laser-like, by Fröhlich resonance, and shielded by ordered water, C-termini Debye layers, actin gel and strong mitochondrial electric fields. Moreover, quantum states in Orch OR are proposed to originate in non-polar, hydrophobic channels in tubulin interiors, isolated from polar entanglements. These regions are where anesthetic gas molecules bind and act to erase consciousness, are conducive to quantum coherent states, and described collectively as the "quantum underground" in an accompanying chapter in this book (Craddock *et al*, 2016). Further, superpositions in Orch OR are proposed to originate with superposition of only atomic nuclei separation, or spin.

The analogy with high-temperature superconductors may indeed be pertinent. As yet, there is no fully accepted theory of how such superconductors operate, avoiding loss of quantum coherence from the usual processes of environmental decoherence. Yet there are materials which seem to support superconductivity at temperatures roughly halfway between room temperature and absolute zero (He *et al*., 2011). This is still a long way from body temperature, of course, but increasing evidence suggests functional quantum effects operate in biology.

As described in Sec. 4.5, research in the past nine years has clearly shown quantum coherence in warm biological systems. Electronic quantum effects occur at ambient temperatures in proteins involved in photosynthesis (Engel *et al*., 2007; Hildner *et al*., 2013), these being thought to be facilitated by coherent protein mechanical vibrations (Chin *et al*., 2013), very similar to a mechanism proposed by Fröhlich over 40 years ago, and to the mechanism we propose here in tubulin. Evidence for resonance-enhanced quantum conductance along helical pathways in tubulin and microtubules by Bandyopadhyay's group appears to be very supportive of Orch OR. Synthetic systems which function as systems for quantum coherence are chemically close to aromatic ring pathways in tubulin (Sec. 3.2, Figs. 5–7) (Hayea *et al*., 2013). Warm quantum effects have also been discovered or proposed in bird brain navigation (Gauger *et al*., 2011), ion channels (Bernroider & Roy, 2005), sense of smell (Turin, 1996), DNA (Rieper, 2011), protein folding (Luo & Lu, 2011) and biological water (Reiter *et al*., 2011). Since Nature has already been found to be able to utilize quantum coherence at biological temperatures in many of the biological systems that have been closely studied, quantum coherence could well be a near-ubiquitous factor in living systems.

If microtubule quantum computations are isolated from the environment, how do they interact with that environment for input and output? Orch OR suggests phases of isolated quantum computing alternate with phases of classical environmental interaction, e.g. at gamma synchrony, roughly 40 times per second. [Computing pioneer Paul Benioff suggested such a scheme of alternating quantum and classical phases in quantum computing robots (Benioff, 1998)]. Strictly, according to OR (the DP version or otherwise), it is, in any case precisely the OR procedure that gives rise to the "classical world" that we find in macroscopic systems. All the basic ingredients are, after all, quantum particles of one kind or another, and it is the reduction process (here DP OR) that provides our picture of classicality. According to the DP viewpoint, the classical world actually arises because of continuing OR actions.

14.5.4. *Temporal non-locality and free will*

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

Indeed that *might* be the case. However, quantum processes in the brain offer what appear to be loopholes to such implications, where the apparent temporal progression of conscious experience and willed action need not correlate in a clear-cut way with the precise timings of an external clock. In the 1970s, neurophysiologist Benjamin Libet performed experiments on patients having brain surgery while awake, i.e., under local anesthesia (Libet *et al*., 1997). Able to stimulate and record from conscious human brains, and gather patients' subjective reports with precise timing, Libet determined that conscious perception of a stimulus required up to 500 ms of brain activity post-stimulus, but that conscious awareness occurred at 30 ms post-stimulus. The brain at 30 ms "knew" that activity would continue, or not continue, for several hundred more milliseconds, i.e., that subjective experience was referred "backward in time." Numerous other experiments have also provided strong indications of temporal anomalies in perception and willed choice (Bem, 2012; Bierman & Radin, 1997; Ma *et al*., 2012).

Bearing such apparent anomalies in mind, Penrose put forward a tentative suggestion (Penrose, 1994) that effects like Libet's backward time referral might be related to the fact that quantum entanglements are not mediated in a normal causal way, so that it might be possible for conscious experience not to follow the normal rules of sequential time progression, so long as this does not lead to contradictions with external causality. In Sec. 4.2, it was pointed out that the (experimentally confirmed) phenomenon of "quantum teleportation" (Bennett & Wiesner, 1992; Bouwmeester *et al*., 1997; Macikic *et al*., 2002) cannot be explained in terms of ordinary classical information processing, but as a combination of such classical causal influences and the causal effects of quantum entanglement. It indeed turns out that quantum entanglement effects — encompassed by such terms as "quantum information" or "*quanglement*"

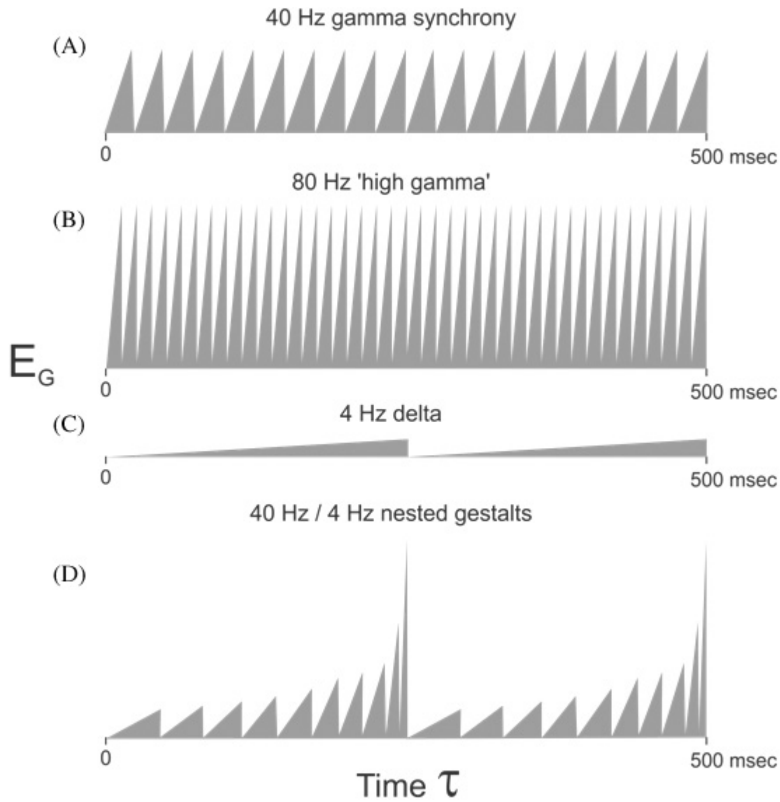

Fig. 11. According to a scheme proposed earlier (Fig. 10, bottom), sequences of Orch OR conscious moments occurring by $\tau \approx \hbar / E_G$ with intensity of experience correlated with orchestrated E_G. (A) "Normal" Orch OR conscious moments every 25 ms in "40 Hz" gamma synchrony. (B) Heightened, enhanced conscious moments occurring every 12.5 ms in 80 Hz "high gamma" synchrony. (C) Low intensity conscious moments occurring every 250 ms (4 Hz delta wave EEG). (D) Gamma wave conscious moments nested in delta waves in visual gestalts. (Woolf & Hameroff, 2001).

(Penrose, 2004; Percival, 1994) — appear to have to be thought of as being able to propagate in *either* direction in time (into the past or into the future). Such effects, however, cannot by themselves be used to communicate ordinary information into the past. Nevertheless, in conjunction with normal classical future-propagating (i.e., "causal") signaling, these quantum-teleportation influences can achieve certain kinds of "signaling" that cannot be achieved simply by classical future-directed means.

The issue is a subtle one, but if conscious experience is indeed rooted in the OR process, where we take OR to relate the *classical* to the *quantum* world, then apparent anomalies in the sequential aspects of consciousness are perhaps to be expected. The Orch OR scheme allows conscious experience to be *temporally non-local* to a degree, where this temporal non-locality would spread to the kind of timescale that would be involved in the relevant Orch OR process, which might indeed allow this temporal non-locality to spread to a time of Libet's 500 ms or longer. When the "moment" of an internal conscious experience is timed externally, it may well be found that this external timing does not precisely accord with a time progression that would seem to apply to internal conscious experience, owing to this temporal non-locality intrinsic to Orch OR. The effective quantum backward-time referral inherent in the temporal non-locality resulting from the quanglement aspects of Orch OR, as suggested above, enables conscious experience actually to be *temporally non-local*, thus providing a possible means to rescue consciousness from its unfortunate characterization as epiphenomenal illusion. Accordingly, Orch OR could well enable consciousness to have a causal efficacy, despite its apparently anomalous relation to a timing assigned to it in relation to an external clock, thereby allowing conscious action to provide a semblance of free will (Hameroff, 2006b, 2012).

14.5.5. *Orch OR and evolution*

In conventional views, the experiential qualities of conscious awareness are assumed to have emerged from complex neuronal computation at some point in evolution, whether recently in human brains, or at some earlier, but unspecified level of development. In these views, consciousness is an emergent property of complex computational activity. On the other hand, Orch OR follows the notion that OR events with primitive "experiential" qualities have been occurring in the universe all along, in the reduction R of quantum superpositions to classical reality. Small superpositions lacking isolation would entangle directly with the random environment, rapidly reaching OR threshold by $\tau \approx \hbar/E_G$, resulting in non-orchestrated OR events. Each such event would lack cognition or any non-computational influence, but *would* be associated with an undifferentiated "proto-conscious" experience, one without information or meaning, but entailing primitive feelings or "qualia," including perhaps rudimentary pleasure. Such undifferentiated experiences are taken, in the Orch OR scheme, to be irreducible, fundamental features of "Planck scale geometry," perhaps ultimately having a role as important to basic physics as those of mass, spin or charge. And undifferentiated, proto-conscious OR events may be significant in biological evolution.

Life on earth is considered to have begun three to four billion years ago in a simmering liquid called the "primordial soup," proposed independently in the 1920's by JBS Haldane and Alexander Oparin. In a famous experiment, Miller & Urey (1959) chemically and energetically simulated a primordial soup and found that it produced "amphipathic" biomolecules having both polar and non-polar components, e.g. non-polar pi electron resonance rings on one end, and charged, polar groups on the other. As "oil and water don't mix," non-polar pi resonance rings of amphipathic biomolecules apparently coalesced, according to Oparin, leading to primitive "micelle" structures with polar ends pointing outward into an aqueous environment (Figure 12), micelles being precursors to more complex biomolecules and cells. For example amphipathic phospholipids coalesce into lipid membranes, amphipathic purines and pyrimidines form DNA and RNA, and amphipathic amino acids form proteins. Non-polar pi resonance groups of amphipathic molecules thus resulted in regions within biomolecules conducive to quantum coherence, entanglement and superposition — the "quantum underground" (Craddock *et al.*, 2016), regions where, in human and animal brains, anesthetics act to selectively erase consciousness. It is perhaps noteworthy that dopamine, an amphipathic biomolecule similar to those apparently

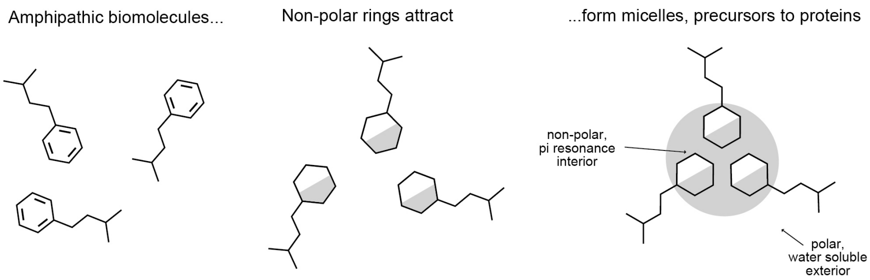

Fig. 12. A simplified schematic view of the origin of life. Dopamine-like amphipathic molecules attract and couple by pi electron resonance dipoles forming an Oparin "micelle" with non-polar interior and polar, water-soluble exterior.

present in the primordial soup and early micelle-like biosystems is a brain neurotransmitter which mediates pleasure and reward. We may take the view that OR and primitive pleasure in non-polar, "quantum underground" regions composed of dopamine-like molecules could have played a key role in evolution.

Darwin's theory of natural selection suggests that life evolved by incremental steps and random mutations. Therefore one would not expect the substantial level of coherence across the brain that would be needed for the non-computable Orch OR of human conscious understanding to be reached without something similar, but more primitive, having preceded it. Proto-conscious OR-mediated feelings might themselves have evolved incrementally during evolution, and perhaps even have driven it.

At some stage in biomolecular development, quantum-superposed states of pi resonance groups and their associated atomic nuclei in "quantum underground" regions may have been able to partially avoid polar interactions and premature (i.e. random environment-driven) OR, and therefore might sustain superpositions sufficiently to experience slightly more coherent OR-mediated qualia including, in some cases, primitive feelings of ("proto")-pleasure. As adjacent pi resonance groups arrange in specific geometric relations ("pi stacks"), such primitive feelings might have provided a feedback fitness function to optimize proto-pleasure, or avoid negative feelings ("proto-pain") by pi stack geometry. Primitive proto-pleasure and proto-pain could then have provided positive and negative reinforcement for structure and behavior promoting survival, e.g. in simple biosystems before the advent of genes.

An early, essential role for microtubules and similar structures in living systems is suggested by their deep-rooted genetic origins (Duggin *et al*, 2014). Life on earth is divided into three types of cells, (1) animal (eukaryotic) and plant cells, (2) prokaryotic bacteria, and (3) archaebacteria, the latter existing at extreme temperatures. In (1) animals and plants, microtubules composed of tubulin organize cell activities, movement and behavior. In (2) bacteria, lattice polymers of tubulin analog FtsZ proteins regulate structure and activities, and in (3) archaebacteria, polymers of another tubulin analog, CetZ, control cell shape and function, e.g. converting discoid cells to tube-like shapes able to swim.

Initially, we might presume, rudimentary quantum computing in microtubules or their more primitive counterparts would likely fail to isolate adequately, and consequently the OR threshold would only be reached with considerable randomness of environmental entanglement and therefore no effective qualia. Nevertheless microtubule quantum computing by U evolution could well be advantageous to biological processes, and one may speculate on the presence of positive, if mixed, pleasurable feelings and feedback even without fully reaching threshold for Orch OR and non-computational influence. Indeed, this type of proto-conscious but effective processing is likely to be occurring in microtubules, FtsZ and CetZ protein polymers throughout all of biology.

With further evolution, better isolation, resonance with electromechanical vibrations (e.g. at "quantum criticality," Vattay *et al*, 2015), wider entanglement and advent of mixed polarity networks amenable to beat frequencies in dendrites and soma of brain neurons, microtubule quantum superpositions, we argue, led to OR events that became increasingly "orchestrated." Accordingly, our picture is that Orch OR underlies full conscious experience with perceptions and choices influenced by non-computable Platonic values intrinsic to the structure of the universe.

The origin of eukaryotic animal cells 1.3 billion years ago is suggested to have been a symbiotic event in which motile spirochetes invaded bacterial prokaryotes, spirochetal flagellae being the apparent origin of microtubules which provided movement and internal organization to previously immobile cells (Margulis & Sagan, 1995). As OR events in microtubules became more orchestrated over the course of evolution, the content of conscious experience became more cognitively useful, e.g., representative of the external world, and pleasurable, e.g., food, sex. Pursuit of positive conscious experience would foster survival. Optimization of Orch OR in conscious experience and associated non-computational effects *per se* may be driving evolution.

As simple nervous systems and arrangements of MTs grew larger and developed isolation mechanisms, quantum cognitive systems would gain selective advantage by avoiding premature OR through environmental decoherence for long enough to be fully orchestrated and reach the OR threshold without involving the random environment. These Orch OR moments can occur across a spectrum defined by $\tau \approx \hbar/E_G$. For small superpositions E_G, τ will be large, requiring prolonged isolation. Larger systems with more frequent conscious moments would be increasingly useful, but more difficult to isolate. In the course of evolution, Orch OR conscious moments (in accordance with $\tau \approx \hbar/E_G$) began in simple organisms involving smaller E_G, but requiring longer times τ during which environmental decoherence is avoided. The scale of E_G would appear also to be related to intensity of experience, so we may anticipate that low E_G, with large τ moments, might be rather dull compared to more intense moments of large E_G and small τ. If this is the case, then such low frequency conscious moments would also be slow and out of step with real-world activities. As systems developed to allow E_G to became larger, the frequency of conscious moments, according to $\tau \approx \hbar/E_G$, could approach present-day biological timescales.

Central nervous systems consisting of approximately 300 neurons, such as those present in tiny worms and urchins at the early Cambrian evolutionary explosion 540 million years ago, theoretically had sufficient microtubules to reach τ under one minute, and it might thus be just feasible for them to make use of Orch OR (Hameroff, 1998d). Accordingly, one might speculate that the onset of Orch OR and primitive consciousness, albeit exceedingly slow and simple but still with useful conscious moments, precipitated the accelerated evolution of the Cambrian explosion.

Only at a much later evolutionary stage would the selective advantages of a capability for genuine understanding come about, requiring the non-computability of Orch OR that goes beyond mere quantum computation, and depends upon larger scale infrastructure of efficiently functioning MTs, capable of operating quantum-computational processes. Further evolution providing larger sets of MTs (hence larger E_G) able to be isolated from decoherence would enable, by $\tau \approx \hbar/E_G$, more frequent and more intense moments of conscious experience, e.g., eventually in human brains every 25 ms in 40 Hz gamma synchrony EEG, or faster. Future evolution might enable brains to accommodate even larger values of E_G and shorter values of τ. At least this is one possibility. Another evolutionary improvement would be to increase the intensity of parallel Orch OR processing, without a requirement that τ should necessarily become shorter.

14.5.6. *Orch OR criticisms and responses*

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

Grush and Churchland (1995) took issue with the Gödel's theorem argument, as well as several biological factors. One objection involved the MT-disabling drug colchicine which treats diseases such as gout by immobilizing neutrophil cells which cause painful inflammation in joints.

Neutrophil mobility requires cycles of MT assembly/disassembly, and colchicine prevents re-assembly, impairing neutrophil mobility and reducing inflammation. Grush and Churchland pointed out that patients given colchicine do not lose consciousness, concluding that microtubules cannot be essential for consciousness. Penrose & Hameroff (1995) responded point-by-point to every objection, e.g., explaining that colchicine does not cross the blood–brain barrier, and so does not reach the brain, and that brain neurons do not disassemble/re-assemble anyway. Colchicine infused directly into the brains of animals does cause severe cognitive impairment and apparent loss of consciousness (Bensimon & Chernat, 1991).

A-lattice vs. B-lattice microtubules MTs have two types of hexagonal lattices, A- and B-. Tubulin is a peanut-shaped dimer with alpha and beta monomers. In a 13-protofilament MT A-lattice, tubulin–tubulin sideways interaction occur between alpha monomer on one tubulin, and beta tubulin on the other, i.e. alpha–beta, and beta–alpha interactions (Amos & Klug, 1974). This gives a seamless lattice and Fibonacci geometry which are optimal for quantum computing, and preferred in Orch OR. In the B-lattice, sideways interactions are alpha–alpha and beta–beta, except for a vertical seam of (A-lattice-like) alpha–beta and beta–alpha alignment. Orch OR has predicted A-lattice MTs, but critics point to analysis of MTs from neurons, e.g., from whole mouse brains which are said to show predominantly B-lattice MTs. However, these "B-lattice" (Mandelkow *et al*., 1992; Kikkawa *et al*., 1994) brain MTs have multiple seams involving four or more or protofilaments, so A-lattice configuration occurs in a third of so-called B-lattice MTs. Other work shows mixed A and B lattice microtubules (McEwen & Edelstein, 1980).

Orch OR is expected to occur in only a fraction of suitable dendritic and somatic MTs, and perhaps only transiently, and partially. Bandyopadhyay has preliminary evidence MTs may switch between A- and B-lattice configurations. The MT A-lattice configuration may be rare, exist transiently as patches in otherwise B-lattice MTs, and be specifically involved in quantum coherence, Orch OR and consciousness.

Georgiev (2009) questioned Orch OR on the basis of "not enough tubulins." By $\tau \approx \hbar/E_G$, the superposition (E_G) required for 25 ms Orch OR events is about 2×10^{10} tubulins. Depending on the number of tubulins per neuron, and the percent of tubulin involvement, predictions can be made for the number of neurons, and percent of brain involvement, for Orch OR conscious events. This percentage may be small, as for example superconductors have only a tiny percentage of components in quantum states. Moreover, A-lattice MTs (or A-lattice portions of B-lattice MTs) may be relatively rare, and distributed throughout many neurons. In any case, it might be that many more tubulins are involved (such as in some versions of the beat frequency approach), e.g., 10^{17} tubulins, 10^{9} neurons, 1% of the brain, or more. It should be noted that Orch OR is the only theory able to meaningfully entertain such quantitative speculation.

Tuszynski *et al.* (1998) questioned how extremely weak gravitational energy in the DP version of OR could influence tubulin protein states. With 2×10^{10} tubulins for 25 ms Orch OR, E_G would be roughly 10^{-10} eV (10^{-29} joules), seemingly insignificant compared to ambient energy kT at 10^{-4} eV. All this serves to illustrate the fact that the energy E_G does not actually play a role in physical processes *as* an energy, in competition with other energies that are driving the physical (chemical, electronic) processes of relevance. As stated in Sec. 5.1, E_G is, instead, an *energy uncertainty* — and it is this uncertainty that allows quantum state reduction to take place without violation of energy conservation. The fact that E_G is far smaller than the other energies involved in the relevant physical processes is a necessary feature of the consistency of the OR scheme, particularly with regard to energy conservation. It does not supply the energy to drive the physical processes involved, but it provides the energy uncertainty that allows the freedom for processes having virtually the same energy as each other to be alternative actions. In practice, all that E_G is needed for is to tell us how to calculate the lifetime τ of the superposition. E_G would enter into issues of energy balance only if gravitational interactions between the parts of the system were important in the processes involved. (The Earth's gravitational field plays no role in this either, because it cancels out in the calculation of E_G.) No other forces of nature directly contribute to E_G, which is just as well, because if they did, there would be a gross discrepancy with observational physics.

Tegmark (2000) published a critique of Orch OR based on his calculated decoherence times for microtubules of 10^{-13} s at biological temperature, far too brief for physiological effects. However Tegmark did not include Orch OR stipulations and in essence created, and then refuted his *own* quantum microtubule model. He assumed superpositions of solitons separated from themselves by a distance of 24 nm along the length of the microtubule. As previously described, superposition separation in Orch OR is at the Fermi length level of atomic nuclei, i.e., seven orders of magnitude smaller than Tegmark's separation value, thus underestimating decoherence time by seven orders of magnitude, i.e., from 10^{-13} s to 10^{-6} s.

Hagan *et al*. (2001) used Tegmark's same formula and recalculated microtubule decoherence times using Orch OR stipulations, finding 10^{-4} to 10^{-3} s, or longer. In any case, experimentally, Bandyopadhyay's group has found 10 kHz resonance, i.e., 10^{-4} seconds coherence times. Also, as stated earlier, there are versions of the beat-frequency scheme that would require much shorter decoherence times, though at the expense of correspondingly larger bodies of material, more of the brain, being involved in the quantum-coherent states.

Koch and Hepp (2006) challenged Orch OR with a thought experiment, describing a person observing a superposition of a cat both dead and alive with one eye, the other eye distracted by a series of images ("binocular rivalry"). Without explaining how an observable superposition of this kind could be prepared (where according to OR, by $\tau \approx \hbar/E_G$, the cat would already be either dead or alive long before being observed), they asked "Where in the observer's brain would reduction occur?," apparently assuming Orch OR followed the version of the Copenhagen interpretation in which conscious observation, in effect, *causes* quantum state reduction (placing consciousness outside science). This is precisely the opposite of Orch OR in which consciousness *is* the orchestrated quantum state reduction given by OR. But in the straightforward case of conscious observation of an already dead or alive cat, reduction (Orch OR) and consciousness would most likely occur in dendritic-somatic microtubules in gap junction–connected neurons in visual and associative cortex and other brain areas.

Orch OR can (at least in principle) account for the related issue of bistable perceptions (e.g., the famous face/vase illusion, or Necker cube). Non-conscious superpositions of both possibilities (face and vase) during pre-conscious quantum superposition then reduce by OR at time $\tau \approx \hbar/E_G$ to a conscious perception of one or the other, face *or* vase. The reduction could be taken to occur among microtubules within gap junction-connected neurons in various areas of visual and pre-frontal cortex and other brain regions.

Reimers *et al.* (2009) described three types of Fröhlich condensation (weak, strong and coherent, the first classical and the latter two quantum). They validated 8 MHz coherence measured in microtubules by Pokorny (2004) and Pokorny *et al.*, (2001) as weak condensation. Based on simulation of a one-dimensional linear chain of tubulin dimers representing a microtubule, they concluded that only weak Fröhlich condensation occurs in microtubules. Claiming that Orch OR requires strong or coherent Fröhlich condensation, they concluded Orch OR is invalid. However Samsonovich *et al*. (1992) simulated a microtubule as a two-dimensional lattice plane with toroidal boundary conditions and found Fröhlich resonance maxima at discrete locations in super-lattice patterns on the simulated microtubule surface which precisely matched experimentally observed functional attachment sites for MAPs. In any case, these simulations are superseded by experimental evidence for gigahertz, megahertz and kilohertz resonance discovered in single MTs by the Bandyopadhyay group ("Bandyopadhyay coherence," "BC")

McKemmish *et al.* (2009) challenged the Orch OR contention that tubulin switching is mediated by London forces, pointing out that mobile π electrons in a benzene ring (e.g., a phenyl ring without attachments) are completely delocalized, and hence cannot switch between states, nor exist in superposition of both states. Agreed, a single benzene cannot engage in switching. London forces occur between two or more pi electron cloud ring structures, or other non-polar groups. A single benzene ring cannot support London forces. It takes two (or more) to tango. Orch OR has always maintained two or more non-polar groups necessarily, and now invokes contiguous arrays of such groups in quantum channels through tubulin and through microtubules. Moreover, we now add the possibility that magnetic spin dipoles mediate Orch OR.

McKemmish *et al.* (2009) further assert that tubulin switching in Orch OR requires significant conformational structural change, and that the only mechanism for such conformational switching is due to GTP hydrolysis, i.e., conversion of guanosine triphosphate (GTP) to guanosine diphosphate (GDP) with release of phosphate group energy, and tubulin conformational flexing. McKemmish *et al.* correctly point out that driving synchronized MT oscillations by hydrolysis of GTP to GDP and conformational changes would be prohibitive in terms of energy requirements and heat produced. This is agreed. However, we clarify that tubulin switching in Orch OR need not actually involve significant conformational change, that electron cloud dipoles (London forces), or magnetic spin dipoles are sufficient for bit-like switching, superposition and qubit function (Figs. 5–7). We acknowledge tubulin conformational switching as discussed in early Orch OR publications and illustrations do indicate significant conformational changes. They are admittedly, though unintentionally, misleading. Discovery of gigahertz, megahertz and kilohertz BC in single microtubules supports dipole states providing a favorable signal with regard to the underlying ideas of Orch OR.

The only tubulin conformational factor required in Orch OR is superposition separation at the level of atomic nuclei, e.g., 2.5 Fermi length for carbon nuclei (2.5 femtometers; 2.5 x 10^{-15} meters). This shift may be accounted for by electronic cloud dipoles with Mossbauer nuclear recoil and charge effects (Sataric *et al*., 1998; Brizhik *et al*., 2001). Tubulin switching in Orch OR requires neither GTP hydrolysis nor significant conformational changes, depending on collective London force dipoles, or magnetic spin dipoles in quantum channels of aromatic rings (Fig. 5–7).

14.5.7 *Testable predictions of Orch OR — current status*

Orch OR involves numerous fairly specific and essentially falsifiable hypotheses. In 1998, 20 testable predictions of Orch OR in nine general categories were published (Hameroff, 1998a). They are reviewed here with our comments on their current status in *italics*.

Neuronal microtubules are directly necessary for cognition and consciousness

1. Synaptic plasticity correlates with cytoskeletal architecture/activities. *The current status of this is unclear, although microtubule networks do appear to define and regulate synapses*.
2. Actions of psychoactive drugs, including anti-depressants, involve neuronal microtubules. *This indeed appears to be the case. Fluoxitene (Prozac) acts through microtubules* (Bianchi *et al*., 2009)*; anesthetics also act through MTs* (Emerson *et al*., 2013).
3. Neuronal microtubule stabilizing/protecting drugs may prove useful in Alzheimer's disease. *There is now some evidence that this may be so; for example, MT-stabilizer epithilone is being tested in this way* (Brunden *et al*., 2010).

Microtubules communicate by cooperative dynamics

4. Coherent gigahertz excitations will be found in microtubules. *Indeed in some remarkable new research, Anirban Bandyopadhyay's group found coherent gigahertz, megahertz and kilohertz excitations in single MTs.* (Sahu *et al*., 2013a, 2013b; 2014).
5. Dynamic microtubule vibrations correlate with cellular activity. *Evidence on this issue is not yet clear, although mechanical megahertz*

vibrations (ultrasound) do appear to stimulate neurons and enhance mood (Hameroff *et al*.,2013).

6. Stable microtubule patterns correlate with memory. *The evidence concerning memory encoding in MTs remains unclear, though synaptic messengers CaMKII and PkMz do act through MTs. Each CaMKII may encode (by phosphorylation) six information bits to six tubulins in a microtubule lattice* (Craddock *et al*., 2012a, Figure 4).
7. "EPR-like" non-local correlation between separated microtubules. *This is not at all clear, but such things are very hard to establish (or refute) experimentally. Bandyopadhyay's group is testing for "wireless" resonance transfer between separated MTs* (Bandyopadhyay, personal communication).

Quantum coherence occurs in microtubules

8. Phases of quantum coherence will be detected in microtubules. *There appears to be some striking evidence for effects of this general nature in Bandyopadhyay's recent results* (Sahu *et al*., 2013a, 2013b; 2014)*, differing hugely from classical expectations, where electrical resistance drops dramatically, at certain very specific frequencies, in a largely temperature-independent and length-independent way.*
9. Cortical dendrites contain largely "A-lattice," compared to "B-lattice," microtubules. *Although there is some contrary evidence to this assertion, the actual situation remains unclear. Orch OR has been criticized because mouse brain microtubules are predominantly B lattice MTs. However, these same mouse brain MTs are partially A-lattice configuration, and other research shows mixed A and B lattice MTs* (Amos & Klug, 1974; Mandelkow *et al*., 1992; Kikkawa *et al*., 1994; McEwen & Edelstein 1980)*. Bandyopadhyay has preliminary evidence that MTs can shift between A- and B- lattice configurations* (Bandyopadhyay, personal communication)*, and A-lattices may be specific for quantum processes. Orch OR could also utilize B lattices, although apparently not as efficiently as A-lattice. In any case, A- lattice MTs could well be fairly rare, specific for quantum effects, and sufficient for Orch OR since the A-lattice may be needed only in a fraction of MTs in dendrites and soma, and perhaps only transiently.*
10. Coherent photons will be detected from microtubules. *A positive piece of evidence in this direction is the detection of gigahertz excitations in MTs by Bandyopadhyay's group, which may be interpreted as coherent photons.* (Sahu *et al*., 2013a, 2013b, 2014)

Microtubule quantum coherence is protected by actin gelation

11. Dendritic–somatic microtubules are intermittently surrounded by tight actin gel. *This is perhaps a moot point, now, in view of recent results by Bandyopadhyay's group, as it now appears that coherence occurs at warm temperature without actin gel.*
12. Cycles of actin gelation and solution correlate with electrophysiology, e.g. gamma synchrony EEG *Again, this now appears to be a moot point, for the same reason as above.*
13. Sol–gel cycles are mediated by calcium ion flux from synaptic inputs. *No clear evidence, but again a moot point.*

Macroscopic quantum coherence occurs among hundreds of thousands of neurons and glia inter-connected by gap junctions

Gap junctions between glia and neurons have not been found, but gap junction interneurons would now appear to fill the need, interweaving the entire cortex.

14. Electrotonic gap junctions synchronize neurons *Gap junction interneurons do appear to mediate gamma synchrony EEG* (Dermietzel,1998; Draguhn *et al.*, 1998; Galaretta & Hestrin, 2001; Bennett & Zukin, 2004; Fukuda & Kosaka 2000; Traub *et al.*, 2002).
15. Quantum tunneling occurs across gap junctions. *As yet untested.*
16. Quantum correlations between microtubules in different neurons occurs via gap junctions. *As yet untested. However Bandyopadhyay has preliminary evidence that spatially separated MTs, perhaps even in different neurons, become entangled in terms of their BC resonances (Bandyopadhyay, personal communication).*

The amount of neural tissue involved in a conscious event is inversely related to the event time by $\tau \approx \hbar/E_G$

17. Functional imaging and electrophysiology will show perception and response time shorter with more neural mass involved. *As a "prediction" of Orch OR, the status of this is not very clear; moreover it is very hard to provide any clear exstimate of the neural mass that is involved in a "perception." As a related issue, there does appear to be evidence for some kind of scale-invariance in neurophysiological processes* [He *et al.*, (2010); Kitzbichler *et al.* (2009)].

An unperturbed isolated quantum state self-collapses (OR) according to $\tau \approx \hbar/E_G$

18. Technological quantum superpositions will be shown to undergo OR by $\tau \approx \hbar/E_G$ *Various experiments are being developed which should supply an answer to this fundamental question (*Bouwmeester *et al.*, 1997*), but they appear to remain several years away from being able to achieve firm conclusions.*

Microtubule-based cilia/centrioles are quantum optical devices

19. Microtubule-based cilia in retinal rod and cone cells detect photon quantum information. *This appears to be untested, so far.*

A critical degree of microtubule activity enabled consciousness during evolution

20. Fossils will show organisms from the early Cambrian period (540 million years ago), had sufficient microtubule capacity for OR by $\tau \approx \hbar/E_G$ of less than a minute, perhaps resulting in rudimentary Orch OR, consciousness and the "Cambrian evolutionary explosion." *It is clearly hard to know an answer to this one, particularly because the level of consciousness in extinct creatures would be almost impossible to determine. However, present day organisms looking remarkably like early Cambrian creatures (actinosphaerum, nematodes) are known to have over 10^9 tubulins (Dustin, 1985).*

It would appear that the expectations of Orch OR have fared rather well so far, and it gives us a viable scientific proposal aimed at providing an understanding of the phenomenon of consciousness. We believe that the underlying scheme of Orch OR has a good chance of being basically correct in its fundamental conceptions.

14.6. Discussion — Consciousness in the Universe

Section 1 described three possibilities regarding the origin and place of consciousness in the universe: (A) as an emergent property of complex brain neuronal computation, (B) as a spiritual quality of the universe, distinct from purely physical actions and (C) as composed of discrete "proto-conscious" quantum events acting in accordance with physical laws not yet fully understood. The Orch OR theory follows (C), and includes aspects of (A) and (B). Orch OR suggests consciousness consists of discrete moments, each an "orchestrated" quantum-computational process terminated by the DP version of OR, an action rooted in quantum aspects of the fine structure of space–time geometry, this being coupled to brain neuronal processes via microtubules.

In standard quantum mechanics, the R procedure is adopted for the action of a *measurement* upon a quantum system, whereby a quantum superposition of two states, these two being distinguishable by that measurement, is probabilistically replaced by one or the other of those states ("reduction of the quantum state" or "collapse of the wavefunction"). But this action is normally taken to be *illusory* in some sense, not being a *real* physical action, but somehow the result of some kind of approximation, or perhaps just as a convenience, or as a shift in the observer's viewpoint, or even as a "split" in the observer's awareness. The hypothesis of OR (objective reduction), on the other hand, asserts that R is a *real objective* physical phenomenon, independent of any observer. Moreover it would be OR that provides the "bridge" between the quantum and classical worlds. This, however, necessitates some kind of modification of the standard U-evolution (i.e. of the Schrödinger equation) for massive-enough systems. The DP version of OR is such a particular scheme, according to which a massive physical body, placed in a quantum superposition of two different stationary locations, would spontaneously find itself located in one or other of these locations in a timescale of order of $\tau \approx \hbar/E_G$, where E_G is the gravitational self-energy of the difference between the expectation values of the two mass distributions in the constituent stationary states. Accordingly, we might say that a quantum-theoretic separation of a material object "from itself" (like Schrödinger's hypothetical dead/alive cat), would be *unstable* and would decay to one or the other of the component states in a timescale that approximates the value τ. The quantity τ can also be understood as the tiny difference, in fundamental Planck-scale units, between the space–time geometries of the two alternative states. Such superposition/separations tend not to be isolated from their environment, however, and would then entangle with other material in the environment, so that it would be the *entire* entangled system that would evolve until reaching this objective threshold for reduction (OR) at time around $\tau \approx \hbar/E_G$, where E_G is now the gravitational self-energy of the difference between the two superposed mass distributions *including* the relevant entangled environments. At the moment of OR, at an average time of around τ after the formation of the superposition, the alternative space–time possibilities reduce to just one or the other of the space–time configurations.

So far, this is just the original DP proposal. However, Orch OR goes further than this, and puts forward the suggestion that each action of OR (taken to be in accordance with DP) is accompanied by a moment of *proto-consciousness*. These events would be thought of as the elemental constituents of "subjective experience," but the vast majority of such OR events act without being part of some coherent organized structure, so that the relevant material is normally totally dominated by random behavior in the entangled environment. Accordingly, there would normally be no significant, meaningful experience associated with these ubiquitous proto-conscious events. Yet, these moments of proto-consciousness are taken to be the primitive ingredients of actual full-blown consciousness, when they are appropriately orchestrated together into a coherent whole, somewhat like how sounds, tones and noise (e.g. of an orchestra warming up) become music.

In the version of the DP proposal put forward in (Penrose, 1992; Penrose, 1996; Penrose, 2000; Penrose, 2009) it was, technically speaking, an (not always explicit) assumption that the energies of the two stationary quantum states involved in the superposition were taken to be equal to one another. Here (Sec. 4.6), we generalize DP in a novel way, which allows us to consider superposed stationary states of *unequal* energy. We argue that for energies that differ only slightly from one another, the action of OR takes us not just to one or the other of these two constituent states in an average time of about $\tau = \hbar / E_G$, but the result of the OR process is to reduce the superposition to an *oscillation* between the two, whose frequency is given by the *beat* value, given by the *difference* between the two far larger quantum-mechanical frequencies associated with the energies of the two previously superposed states. We suggest that it is these beat frequencies, resulting from the Orch OR processes that involve the reduction of coherently superposed tubulin states with slightly different energies, that result in the characteristic frequencies, such as 40 Hz gamma synchrony which appears to be correlated with conscious states.

In an uncontrolled situation occurring in the physical world, with systems in quantum superposition, OR would normally occur spontaneously when significant environment is entangled with the system, and

E_G can rapidly become relatively large, so τ is reached quickly, and the choice of particular space–time configuration includes a dominant component of randomness owing to the random nature of the environment. The moment of "subjective experience" that would be associated with this type of OR is an undifferentiated, non-cognitive, insignificantly experiential ("proto-conscious") quality. Due to the random component, such environment-induced OR "experience" would lack information, cognition or meaning, be very brief (low τ due to high environmental E_G) and ubiquitous, playing merely the role of "decoherence" that is familiar in standard interpretations of quantum mechanics.

However, according to Orch OR, biological evolution provided isolated non-polar, quantum-friendly regions, e.g. in structures such as microtubules, within which OR events could be "orchestrated," enabling functional quantum computing in isolated non-polar "aromatic," pi resonance channels (the "quantum underground") within microtubule proteins. With further evolution, orchestrated quantum superpositions in microtubules would have been able to persist for progressively longer times with larger values of E_G, with entanglements with other parts of the structure playing meaningful roles, thereby allowing significant "quantum computing" to occur. Yet, with only partial isolation, the OR threshold $\tau \approx \hbar/E_G$ would still only be reached by including unorchestrated environmental entanglement, which introduces randomness in the selection of states. Accordingly, such OR quantum computing would lack fully "orchestrated" cognition, so the claimed non-computable aspects of DP OR would not come into play at this stage. Yet, the advantages of some form of "quantum computation" in these processes could still be of significant relevance, even though the OR action would be only at this "proto-conscious" level.

With even more advanced evolutionary development, biological factors could orchestrate and further isolate microtubule quantum computing so that the OR threshold $\tau \approx \hbar/E_G$ could now be reached by orchestrated microtubule quantum superpositions by themselves, and a relatively large E_G could be achieved without environmental randomness. Such Orch OR moments could provide rich cognitive subjective experience, and control conscious behavior, with a non-computable "willed" influence. Moreover, since the DP version of OR is a *gravitational* proposal, this relates experiential phenomena to the fundamentals of space–time geometry. Evolution may well have favored orchestrated superpositions with larger E_G values, allowing briefer times τ which are increasingly useful to the organism's cognition. In accordance with our earlier ideas, we might speculate that these eventually reached sufficient E_G for τ near 25 ms for gamma synchrony with 40Hz or more Orch OR conscious events per second. Alternatively, according to the Orch OR "beat frequency" approach introduced here, natural MT megahertz resonances (perhaps with much larger E_G values) enable much slower beat frequencies in the gamma synchrony range.

Philosophically, Orch OR perhaps aligns most closely with Whitehead (1929, 1933) who viewed mental activity as a process of "occasions," spatio-temporal quanta, each endowed — usually on a very low level, with mentalistic characteristics which were "dull, monotonous, and repetitious." These seem analogous, in the Orch OR context, to "proto-conscious" non-orchestrated OR events. Whitehead viewed high level mentality, consciousness, as being extrapolated from temporal chains of such occasions. In his view, highly organized societies of occasions permit primitive mentality to become intense, coherent and fully conscious. These seem analogous to Orch OR conscious events. Shimony (1993), Stapp (2007) and others recognized that Whitehead's approach was potentially compatible with modern physics, specifically quantum theory, with quantum state reductions — actual events — appearing to represent "occasions," namely Whitehead's high level mentality, composed of "temporal chains…of intense, coherent and fully conscious occasions," these being tantamount to sequences of Orch OR events. These might possibly coincide with gamma synchrony, but with our current "beat frequency" ideas gamma synchrony is more likely to be a beat effect than directly related to the OR reduction time τ. As Orch OR events are indeed quantum state reductions, Orch OR and Whitehead's process philosophy appear to be quite closely compatible.

Whitehead's low-level "dull" occasions of experience would seem to correspond to our non-orchestrated "proto-conscious" OR events. According to the DP scheme, OR processes would be taking place all the time everywhere and, normally involving the random environment, would be providing the effective randomness that is a characteristic of quantum measurement. Quantum superpositions will continually be reaching the DP threshold for OR in non-biological settings as well as in biological ones, and OR would usually take place in the purely random environment such as in a quantum system under measurement. Nonetheless, in the Orch OR scheme, these events are taken to have a rudimentary subjective experience, which is undifferentiated and lacking in cognition, perhaps providing the constitutive ingredients of what philosophers call *qualia*. We term such un-orchestrated, ubiquitous OR events, lacking information and cognition, "proto-conscious." In this regard, Orch OR has some points in common with the viewpoint (B) of Sec. 1.1, which incorporates spiritualist, idealist and panpsychist elements, these being argued to be essential precursors of consciousness that are intrinsic to the universe. It should be stressed, however, that Orch OR is strongly supportive of the *scientific* attitude that is expressed by (A), and it incorporates that viewpoint's picture of neural electrochemical activity, accepting that non-quantum neural network membrane-level functions might provide an adequate explanation of much of the brain's *unconscious* activity. Orch OR in microtubules inside neuronal dendrites and soma adds a deeper level for conscious processes.

Conditions for Orch OR and consciousness are fairly stringent in our scheme: orchestrated superposition must be isolated from the decoherence/OR effects of the random environment for long enough to reach the DP threshold while continuing to perform quantum computation. Small superpositions are easier to isolate for a limited time, but require longer reduction times τ, so that the isolation would need to be correspondingly more perfect.

Large superpositions will reach threshold quickly, but are intrinsically more difficult to isolate. If we consider that the *beat frequency* picture is the appropriate one with regard to the evocation of consciousness, then we may speculate that beat frequencies of faster, e.g. megahertz processes might possibly require only very brief reduction times. These might be even as brief as 10^{-7} secs if we take the view that it is actually the case that our extended DP OR proposal allows reduction times to be much briefer than the beat period, while still giving rise to classical beats, as speculated in Sec. 4.6. Accordingly, one suggestion that we can make is that "*Bandyopadhyay coherence*" ("BC") — the megahertz resonance, found by Bandyopadhyay's group, suggesting coherence times of 10^{-7} secs, or the tens of kilohertz resonance they found suggesting 10^{-4} sec — provide good evidence that such superpositions within sufficiently large collections of microtubules could persist in the brain for reduction times τ and Orch OR processes that could be relevant to brain function and consciousness.

What about Orch OR in non-biological systems? After all, $\tau \approx \hbar / E_G$ happens everywhere. What kind of role might there be for it in consciousness elsewhere in the universe?

Very large masses can be involved in quantum superpositions, occurring in the universe in quantum-mechanical situations, for example in the cores of neutron stars. One might imagine that τ would then be rediculously tiny. But E_G could still be relatively small if the mass-displacement remains small owing to the uniformity of the material. But generally, by OR, such large-scale superpositions would reduce extremely quickly, and classically unreasonable superpositions would be rapidly eliminated. Whether such quantum systems could be orchestrated to have meaningful, cognitive Orch OR conscious moments is unknown, but it is certainly conceivable that sentient creatures might have evolved in parts of the universe that would be highly alien to us, for example on neutron-star surfaces, with very large scale superpositions, and presumably very high frequency OR events, an idea that was developed ingeniously and in great detail by Robert Forward in two science-fiction stories (*Dragon's Egg* in 1980, *Starquake* in 1989 (Forward 1980, 1989)). Such creatures (referred to as "cheelas" in the books), with metabolic processes and presumably Orch OR-like events occurring at rates of around a million times that of a human being, could arguably have intense experiences, but whether or not this would be possible in detail is, as of now, a very speculative matter. Nevertheless, the Orch OR proposal offers a possible route to rational argument, as to whether conscious life of a totally alien kind such as this, or some other form of quantum superposition, might be possible, or even probable, somewhere in the universe.

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

The recently proposed cosmological scheme of *conformal cyclic cosmology* (CCC) (Penrose, 2010; Gurzadyan & Penrose, 2010) also has some relevance to these issues. CCC posits that what we presently regard as the entire history of our universe, from its Big-Bang origin (but without inflation) to its indefinitely expanding future, is but one *aeon* in an unending succession of similar such aeons, where the "infinite" future of each matches to the big bang of the next via an infinite change of scale. A question arises whether the dimensionless constants of the aeon prior to ours, in the CCC scheme, are the same as those in our own aeon, and this relates to the question of whether sentient life could exist in that aeon as well as in our own. Could the dimensionless constants change with each successive aeon, might they perhaps "mutate" and evolve to optimize consciousness? Could evolution over aeons thereby account for the anthropic principle? Smolin (1997) has suggested an idea that is somewhat similar to this, but in his scheme, the drive of selective advantage would be for more black holes and baby universes, rather than for consciousness or even for life. Nevertheless, the question of the constancy of these numbers is in principle answerable by observation in CCC, and this issue could have a bearing on the extent or validity of the Orch OR proposal. If Orch OR turns out to be correct, in its essentials, as a physical basis for consciousness, then it opens up the possibility that many questions may become answerable, such as whether life and consciousness could have come about in an aeon prior to our own, that would have previously seemed to be far beyond the reaches of science.

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

14.7. Conclusion

"Orchestrated objective reduction" ("Orch OR") is a theory which proposes that consciousness consists of a sequence of discrete events, each being a moment of OR of a quantum state (according to the DP scheme), where it is taken that these quantum states exist as parts of quantum computations carried on primarily in neuronal microtubules. Such OR events would have to be "orchestrated" in an appropriate way (Orch OR), for genuine consciousness to arise. OR itself is taken to be ubiquitous in physical actions, representing the "bridge" between the quantum and classical worlds, where quantum superpositions between pairs of states get spontaneously resolved into classical alternatives in a timescale $\sim\tau$, calculated from the amount of mass displacement that is between the two states. In our own brains, the OR process that evokes consciousness would be actions that connect brain biology (quantum computations in microtubules) with the fine scale structure of space–time geometry, the most basic level of the universe, where tiny quantum space–time displacements are taken to be responsible for OR. The Orch-OR proposal therefore stretches across a considerable range of areas of science, touching upon the foundations of general relativity and quantum mechanics, in unconventional ways, in addition to the more obviously relevant areas such as neuroscience, cognitive science, molecular biology and philosophy. It is not surprising, therefore, that Orch OR has been persistently criticized from many angles since its introduction in 1994. Nonetheless, the Orch OR scheme has so far stood the test of time better than most other schemes, and it is particularly distinguished from other proposals by the many scientifically tested, and potentially testable, ingredients that it depends upon.

It should be mentioned that various aspects of the Orch OR theory have themselves evolved in response to scientific advances and, in some cases, constructive criticism. We here list some recent adaptations and developments that we have now incorporated into the theory.

Biological Adaptations and Developments in Orch OR

- For both classical and quantum computing, information states of tubulins within microtubule lattices correlate with dipole orientations, without significant protein conformational changes.
- Tubulin dipoles originate in pi electron resonance clouds in non-polar regions, and may be either electric (London force charge separation), or magnetic (electron spin states and currents). Dipoles oscillate, couple to mechanical movement and nuclear spin at the level of atomic nuclei, and become quantum superpositions of multiple possible dipole orientations. Hence individual tubulins may act as quantum bits, or qubits, as suggested initially in Orch OR (Hameroff & Penrose, 1996a, 1996b) though we now favor pathway qubits.
- Intra-tubulin non-polar pi resonance regions conducive to quantum states appear to align with those in neighboring tubulins, perhaps enabling collective quantum dipoles among many tubulins along helical pathways through microtubule lattices, e.g. along Fibonacci 3, 5 and 8-start helical winding patterns. Collective ("giant dipole," Fröhlich, 1970) pathway dipoles may then form superpositions of possible orientations, now proposed to function as pathway qubits in Orch OR.
- Orch OR qubit pathways may correlate with enhanced electron conductances discovered by Anirban Bandyopadhyay's group (Sahu *et al*, 2013a, 2013b, 2014) in microtubules in warm temperature at specific gigahertz, megahertz and kilohertz frequencies ("Bandyopadhyay coherence," "BC"), strongly supporting Orch OR.
- Non-polar pi resonance channels mediating BC occur not only within microtubules, but lie generally within proteins, lipid membranes, DNA and RNA, apparently pervading all living systems (the "quantum underground," Craddock *et al*, 2016).
- Anesthetic gases bind and act in such non-polar pi resonance regions in tubulin, presumably dispersing microtubule quantum dipoles necessary for consciousness, e.g. in mixed polarity microtubules in dendrites and soma of cortical layer 5 pyramidal neurons.
- Scale-invariant (1/f, fractal-like) processes observed at neuronal and network levels might perhaps extend downward to intra-neuronal BC in microtubules, e.g. megahertz excitations. If so, microtubules in mixed-polarity networks vibrating at slightly different megahertz frequencies would interfere, e.g. in layer 5 pyramidal neurons whose apical dendrites rise vertically toward the brain surface, and are primarily responsible for EEG. Interference of microtubule megahertz

vibrations could give rise to much slower "beat frequencies," e.g. between 0 and 100 Hz seen as the electro-encephalogram (EEG).
- As Alzheimer's disease, brain trauma and other disorders are related to microtubule disturbances within brain neurons, therapies including transcranial ultrasound ("TUS," megahertz mechanical vibrations) are in clinical trials to treat such disorders.
- Orch OR with conscious understanding and non-computable Platonic influences, as suggested to occur in human and animal brains, would have been preceded during the course of evolution by simple "proto-conscious" OR events in non-polar pi resonance regions of primitive systems. Behaviors and mutations promoting OR-mediated "proto-pleasure," and avoidance of "proto-pain," may have played significant roles in the evolution of life, and the brain.

The Orch OR proposal suggests conscious experience is intrinsically connected to the fine-scale structure of space–time geometry, and that consciousness could be deeply related to the operation of the laws of the universe.

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APPENDIX A

Reply to Seven Commentaries on "Consciousness in the Universe: Updated Review of the 'Orch OR' Theory"

Here we respond to seven commentaries (Tuszynski, 2014; Chopra, 2014; Ghosh *et al*., 2014; Jumper & Scholes, 2014; Lucas, 2014; Tandy, 2014; Pino & Mauro, 2014) which accompanied "Consciousness in the universe: Review of the Orch OR theory" in *Physics of Life Reviews*: The eighth commentary by Reimers *et al*. (2014) is discussed separately in Appendix B. We thank authors of these seven commentaries, and reply to some of their key points.

A.1. *Jack Tuszynski ("JT") (Tuszynski, 2014)*

First, Orch OR appears to be decoupled from the animate/inanimate divide.... Divorcing consciousness from life forms puts it back into the spiritual/dualistic type of reasoning that Orch OR rejects. How can one account for metabolism taking place in neurons, which would be a minimal requirement for making Orch OR account for life?

Hameroff and Penrose ("H&P")

Orch OR does not divorce life from consciousness, but marries them within non-polar "quantum channels" inside microtubule cylindrical walls. Although life is commonly equated with some of its properties, e.g., metabolism, reproduction, adaptation, and evolution, these phenomena also occur in inanimate complex systems. They do not define life.

In living cells, metabolism occurs in polar, aqueous environments isolated from nonpolar, water-excluding "quantum channels" (Hameroff & Penrose, 2014; Craddock *et al*., 2014; 2015). Biological metabolism is no different than inanimate chemical activity ubiquitous in nature. While metabolism, reproduction, adaptation and evolution may be necessary for life and consciousness, they are not sufficient. As suggested by Schrödinger (1944) life, as we know it, depends essentially on quantum processes. In Orch OR, consciousness is a particular manifestation of life's quantum activity, involving "orchestrated" quantum coherent superpositions that persist sufficiently to reach the physical threshold for "objective reduction."

JT

"Second, the emphasis based on the gravitational interactions is difficult to accept within conventional physics. Gravitational interactions are many orders of magnitude weaker than even thermal noise (Tuszynski *et al*. 1998)."

H&P

This is a frequent misunderstanding. The role of gravitation in Orch OR is quite different from that of other forces, and it is not in competition with them. The DP proposal, upon which Orch OR relies, is not even a form of "quantum-gravity" in the normal sense of that term, where the rules of quantum (field) theory would be imposed upon classical gravitational theory. In DP objective reduction, we consider the opposite effect, where principles underlying Einstein's gravitational theory (general relativity) have their effect on quantum mechanics itself. With regard to issues of energy balance, the extremely tiny contribution from gravitation would be merely at the level of basic *uncertainties* in energy conservation. It is good that, in the circumstances under consideration, the gravitational contributions *are* extremely tiny, since they represent only a minute *uncertainty* in the normal energy balance (called upon only when the quantum state reduces according to OR), this balance thereby holding to an enormous precision, *by virtue* of gravitational energy contributions *necessarily* being ignored, as is normal practice.

Indeed, we say in Sec. 14.5.1. of our review: "Owing to the extreme weakness of gravitational forces…the energy E_G is liable to be *far* smaller than any energy that arises directly from biological processes.… E_G is not to be thought of as being in direct competition with any of the usual biological energies, as it plays a completely different role, supplying a needed energy *uncertainty* that then allows a choice to be made between the separated space–time geometries… This energy uncertainty is the key ingredient of the computation of the reduction time τ, and …it is appropriate that this energy uncertainty is indeed far smaller than the energies that are normally under consideration with regard to chemical energy balance, etc. If it were not so, then there would be a danger of *conflict* with normal considerations of energy balance. Nevertheless, the extreme weakness of gravity tells us there must be a considerable amount of material involved in the coherent mass displacement between superposed structures in order that τ can be small enough to be playing its necessary role in the relevant OR processes in the brain."

Microtubules may be thought of as "quantum switches," acting within the quantum energy uncertainty that comes about through the influence of Einstein's gravitational principles in a quantum context, thereby — according to Orch OR — enabling weak gravity-related influences to affect conscious thought and behavior.

JT

"I foresee major progress in bridging the gap between nanoscience and consciousness in the area of nanoneuroscience (Woolf *et al*., 2010) where MT's, actin filaments and motor proteins connect between neurophysiology and molecular biology. Studying the neural phenomena at a nanoscale will lead to monumental breakthroughs in science and medicine and aid in consciousness studies."

H&P

Agreed. Anirban Bandyopadhyay's group has used nanoscience to find quantum resonances at multiple gigahertz, megahertz and kilohertz frequencies in single brain microtubules at warm temperatures (Sahu *et al*., 2013a, 2013b).

A.2. *Deepak Chopra ("DC") (Chopra, 2014)*

"The choice is between two non-dual explanations for how mind came into being. [The Eastern spiritual tradition of] Vedanta says that mind is innate in creation. To be viable, this brand of monism must show how mind created matter and energy. The challenge from the Penrose–Hameroff side is to show how matter and energy created mind. Of the two, Vedanta, in my view, has the upper hand. Mind creates matter every time we have thoughts that generate unique electrochemical activity in the brain. But no one has credibly shown how molecules learned to think."

H&P

Dr. Chopra is espousing "View B" in Sec. 1 of our review, that "*Consciousness is a separate quality, distinct from physical actions and not controlled by physical laws, that has always been in the universe*." This is in marked contradistinction to the conventional "View A" that "*Consciousness is not an independent quality but arose, in terms of conventional physical processes, as a natural evolutionary consequence of the biological adaptation of brains and nervous systems*."

We agree with Dr. Chopra that "View A" fails to show how matter and energy create mind, how molecules can "think" (i.e., perform cognition accompanied by conscious experience). But we also recognize the shortcomings of his "View B," e.g., how can mind create energy and matter? Orch OR and "View C" bridge these two views, and, in principle, point to a solution for both their problems: (C) *Consciousness results from discrete physical events (objective reductions, OR); such events have always existed in the universe as non-cognitive, proto-conscious events, these acting as part of precise physical laws not yet fully understood*. Thus, in our view, a "proto-conscious" source of mind is omnipresent in the universe as OR events which shape reality (as in "View B"). However, experientially rich, human-like consciousness required biological evolution of a mechanism to "orchestrate" OR events, and couple them to brain neuronal activity (as in "View A").

DC

"Orch OR provides a credible, testable model for how mental activity enters the physical world. I would take its optimism and turn it around: the mind–brain problem is indeed closer to being solved, not because quantum events give rise to mind but because these events indicate that an invisible agency (consciousness) is producing orderly, intelligent, information-infused activity at the very interface where space–time emerges.

H&P

In Orch OR, fundamental Planck scale geometry ("where space–time emerges") is indeed considered to contain Platonic values producing such activity. Orch OR embraces both View A and View B.

A.3. *Subrata Ghosh, Satyajit Sahu and Anirban Bandyopadhyay ("SSA") (Ghosh et al., 2014)*

The blind faith that Hodgkin–Huxley type neuron bursts explain neural information processing completely will collapse soon, and then brain building projects (Markram, 2006) all over the world will face the danger of banking on an incomplete picture of a neuron.

H&P

SSA are alluding to the assumptions that (1) Hodgkin–Huxley "integrate-and-fire" neuron models adequately represent neuronal functions, and (2) mapping and simulating such functions will capture essential brain features including consciousness. We completely agree with SSA that these assumptions are wrong, as they ignore intra-neuronal classical and quantum computation in microtubules, and non-computability necessary for consciousness, memory and synaptic regulation.

SSA

The recent finding of microtubule resonant oscillations (Sahu *et al*., 2013a, 2013b; 2014) that could vibrate (the neuronal) axon (and dendrites/soma) brings Orch-OR into the picture as an extremely essential concept to fill the vacuum.

H&P

SSA refers to their own landmark discovery of gigahertz, megahertz and kilohertz quantum vibrations in single microtubules, experimental findings which strongly support theoretical assertions of Orch OR. They imply that such finer scale, deeper order processes are needed for a proper picture of neuronal function. We agree.

SSA

Stuart and Roger have rightly argued here (Hameroff & Penrose, 2014) that the wireless communication of axons via resonant vibrations around 100 μm diameter domain alleviates the biggest criticism of the Orch-OR proposal. The orchestration of resonant vibrations can occur globally among all neurons across the entire brain….This paper therefore closes the series of historical argument/counterargument on the "gap junction" forever.

H&P

SSA refer to the issue in Orch OR of how microtubule-based quantum coherence can extend globally in neurons throughout the brain, enabling sufficiently large E_G to reach OR threshold (by $E_G \approx h/\tau$) in times τ brief enough to be useful. Orch OR has previously suggested entanglement via window-like gap junctions (avoiding noisy membranes, synapses and neuropil). However SSA have shown "wireless" communication among microtubules in different neurons, possibly obviating the need for gap junctions. This still does not properly explain the necessary *quantum* entanglements that would be needed, between separated microtubules, however. In order for the respective "E_Gs" of separated parts of a system to add up appropriately, in order to reach the required level for OR to occur, the entire mass displacement needs to be quantum-coherent, i.e., entangled. Quantum entanglements cannot be set up simply by classical communication. One might envisage gap junctions achieving the needed entanglements, but there does not appear to be any evidence, as yet, that SAA's "wireless communication" has thus required quantum-coherent character. This would seem to be an important issue for future research.

As a further point, "wireless" communication detected by the Bandyopadhyay group occurs between microtubule bundles in axons and dendrites/soma of different neurons. Orch OR has emphasized microtubule quantum computation in neuronal dendrites and cell bodies/soma (rather than those in axons) because dendritic–somatic processes correspond with integration in integrate-and-fire neurons, and such processes can trigger (or not trigger) axonal firings, thereby controlling the behavior (Sec. 2.3 in our review). Microtubules in neuronal dendrites and soma are uniquely arrayed in mixed polarity networks of short, stabilized microtubules, whereas axonal microtubules extend continuously in unipolar bundles. The functional distinction for the two types of arrays is as yet unknown.

SSA

"…objective reduction also gets a new dimension because resonance frequency bands of brain materials cover a wide range." Therefore, the discovery of resonance and wireless processing lead to a layered architecture of multiple space–time metric stacked one above another (Penrose, 2005). This is exactly what Roger and Stuart have been arguing for as the foundation of brain information processing for decades…. This paper (Hameroff & Penrose, 2014) therefore marks the beginning of developing a comprehensive mathematical modeling of the brain. Hopefully, in the near future, with more experimental understanding of the space–time metric, Orch-OR would evolve to a complete deductive mathematical expression of consciousness, — a dream that entire mankind is eagerly waiting to see.

H&P

SSA refers first to their own discovery of gigahertz, megahertz and kilohertz resonances in microtubules, vibrations which appear to have a fractal-like relationship. Based on their results, we proposed that collective brain oscillations in the range of 10 to 100 Hz seen as the EEG are actually "beat frequencies," interference patterns, of much faster microtubule megahertz vibrations inside neurons. Observed and recorded for over a century, EEG origins have never been understood.

In Orch OR, microtubule quantum events correlate with fluctuations in the structure of space–time geometry ("space–time metric"). SSA are referring to a scale-invariant conscious connection between brain processes and the structure of the universe. One must be careful about drawing too strong of a conclusion of this kind here. The Planck scale of quantum gravity is, indeed, a particular *scale* of size, and scale-invariance for such fluctuations is not to be expected.

A.4. Chanelle Jumper and Gregory Scholes (J&S)

"…A primary issue is decoherence, a process where the phases of quantum wavefunctions are randomized to reduce quantum phenomena to classical processes." Decoherence arises from dynamic disorder, or 'energy noise', and is expected to be extremely rapid in biological environments.

For example, the Orch OR theory requires quantum superposition on a time scale that is not currently accepted for biological, or even chemical, systems (McKemmish *et al.*, 2009).

H&P

As J&S assert, avoidance of decoherence is critical to Orch OR and functional quantum biology. Previous versions of Orch OR called for microtubule coherence times (avoidance of decoherence) for times τ on the order of EEG frequency intervals, e.g., 10^{-1} to 10^{-2} s, lengthy in terms of quantum systems, and too long for Bandyopadhyay's measured coherence times (Sahu *et al.*, 2013a, 2013b; 2014) of 10^{-4} s (10 kilohertz resonance). However, in the present updated version of Orch OR, EEG markers of consciousness are seen as beat frequencies of much faster microtubule resonances and Orch OR events, e.g., 10 MHz with coherence times of a mere 10^{-7} s. Given the Bandyopadhyay coherence times of 10^{-4} s, Orch OR seems to now be on firm ground from the standpoint of decoherence.

The DP version of OR essentially replaces decoherence (or, rather, incorporates it within a broader objective scheme), as described in Sec. 4.5, but environmental interaction must still be avoided for significant times τ to have cognitive and meaningful conscious moments.

J&S

"....biological systems are purported to be 'warm, wet and noisy,'… a messy business, incapable of supporting 'delicate' quantum processes...." On the contrary, it appears that living systems are governed by cycles and correlations, requiring massive cooperation across a large range of time and length scales.... Whether it is an acceptance of quantum behavior, or generating a foundation for the study of difficult questions in biology, should we reconsider the premise that living entities are founded on uncorrelated and chaotic machinery?

H&P

Absolutely. Correlations over multiple spatiotemporal scales in living systems may be explained by a largely scale-invariant dynamics derived from quantum processes in non-polar, hydrophobic regions, e.g., quantum channels in microtubules (similar to quantum coherence in π-conjugated systems as described by Hwang & Scholes (2011)).

Regarding the "warm, wet and noisy" description of the biological environment: warm, yes, biological systems are indeed warm compared to quantum systems developed in laboratory conditions. However as proposed by Fröhlich, biology can utilize thermal energy to drive coherence, in a manner roughly analogous to a laser. "Wet"? No, at least not in non-polar, hydrophobic "quantum channels" within microtubules and other biomolecular interiors isolated from polar, aqueous portions of cell interiors and the extracellular milieu. These "dry," non-polar regions are precisely where anesthetic gases bind to selectively erase consciousness. "Noisy?" Noise-like fluctuations in brain electrical activity appear to be globally correlated, and therefore not noise at all. Of course, J&S are merely pointing out flaws in the common criticisms of schemes like Orch OR that depend upon quantum processes, and with that, we heartily agree.

J&S

…one of the next scientific revolutions will involve the evolution of a new framework for unraveling the extraordinary nature of life.

H&P

Agreed. And microtubule-based quantum resonance may well be a major part of that framework.

A.5. *Reply to John Lucas (2014)*

Lucas (1961, 1970, 2013) had suggested in 1961 that Gödel's incompleteness theorem indicates that the human mind is non-computable, that some non-algorithmic factor is necessary. This anti-mechanistic argument was joined and elaborated by Penrose (1989, 1993, 2005) who suggested "objective reduction" as the non-computable factor, bringing quantum mechanics into the brain/mind picture. In his commentary, Lucas eloquently summarizes Orch OR positions, with particular reference to the thorny issue of freedom ("free will").

A.6. *Reply to Charles Tandy (2014)*

Tandy (2014) continues with Gödel non-computability ("hyper-algorithmicity," as Tandy calls it) a property which Lucas and Penrose have attributed to the conscious mind. Although non-computability has usually been taken as bad news for artificial intelligence ("strong AI") and "Singularity" attempts to emulate conscious brain functions in computers, Tandy concludes that Orch OR and hyper-algorithmicity could in principle lead to such a goal — an Orch OR-based "artificial consciousness."

A.7. *Reply to Samantha Pino and Ernesto Di Mauro (2014)*

Pino & Di Mauro (2014) put Orch OR in a larger context, relating it, and the problem of consciousness, to issues raised by Popper, Descartes, Darwin, Jung, Pauli, Heisenberg and others. They suggest the failure of the Higgs boson to account for super-symmetry leaves the makeup of the universe as mysterious as ever, perhaps requiring consciousness to complete the picture. Irrespective of the Higgs boson, this is also the essential conclusion of our review.

P&D

Hameroff & Penrose theory proposes an explanation by quantum physics of an intricately unapproachable phenomenon, of an *unknown*. To do this they feel comforted by the lack of different alternative explanations, possibly overinterpreting the possibilities and the role of quantum physics. However, this might after all not be that negative, potentially opening an experimental field to falsifiable verification.

H&P

It is worth pointing out that the DP proposal may be fairly close to either experimental confirmation or refutation. Following on from an early proposal (Marshall *et al.*, 2003), Bouwmeester has recently intimated (Penrose, 2013) that within 7 or 8 years we may well have an experimental answer to the viability of DP.

In closing, we refer back to the question of CCC as discussed in Sec. 6 of our review. The reference (Gurzadyan & Penrose, 2010) in the review may now be updated (Gurzadyan & Penrose, 2013). An independent analysis of the WMAP satellite data (Meissner *et al*., 2013) supports CCC, and groups are now analyzing the more recent (and precise) Planck satellite data (An *et al*., 2013). Orch OR and consciousness may well have preceded the Big Bang!

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APPENDIX B

Reply to criticism of the "Orch OR Qubit" — "Orchestrated Objective Reduction" *is* Scientifically Justified

The critical commentary by Reimers *et al*. (2014) regarding the Penrose–Hameroff theory of "Orch OR" is largely uninformed and basically incorrect, as they solely criticize non-existent features of Orch OR, and ignore (1) actual Orch OR features, (2) supportive evidence, and (3) previous answers to their objections (See Sec. 14.5.6 above.) Here we respond point-by-point to the issues they raise.

Jeffery Reimers, Laura McKemmish, Ross McKenzie, Alan Mark, Noel Hush (Reimers et al., 2014)

…For quantum information processing one must have quantum information storage units such as *qubits*…. the involvement of quantum-gravity in the manifestation of consciousness would need to be described in terms of how quantum-gravity affected the operation of these qubits…

H&P

Basically true. And this is just what we have done. Qubits involve (1) superposition of alternative possible states, and (2) a mechanism by which the possible states reduce, or collapse to definite states.

With regard to (1), any type of superposed state can, in principle, serve as a qubit, e.g., simultaneous alternative electric charge location, spin, dipole orientation, photon polarization, Fock state, topological pathway ("braid"), or current flow direction (e.g., superconducting Josephson junctions).

In Orch OR, the qubit involves electric or magnetic (spin) dipole orientations in "quantum channels" within each tubulin (microtubule subunit proteins), and between such tubulins along helical pathways through microtubule lattices. The dipoles occur due to coupled London force or spin dipole attractions among phenyl and indole rings of aromatic amino acids (tryptophan, phenylalanine, and tyrosine) which comprise "quantum channels," these electron states coupling to position or spin of their atomic nuclei. The coupled dipoles oscillate between alternative orientations, and become superpositions of both states to function as qubits (Figs. B.1(B), and 5–7 in our review).

This helical pathway version of the Orch OR qubit (akin to a "topological qubit" (Collins, 2006)) was developed in 2002 (Hameroff *et al.*, 2002), after the structure of tubulin was elucidated by electron crystallography (Nogales, et al., 1998) to reveal clustered arrays of electron resonance rings ("quantum channels," Fig. 5 in our review) (Craddock, *et al.*, 2012). The helical pathway qubit replaced the earlier notion (1996–1998, Fig. B-1 (A), (Hameroff & Penrose, 1996a, 1996b; Hameroff, 1998a) that oscillating dipoles in individual tubulins were the fundamental qubits. Helical pathway qubits are inherently resistant to decoherence, can couple to natural resonances in microtubule lattices, and associate with alternating current ("AC"). Indeed, Bandyopadhyay's group (Sahu *et al.*, 2013a, 2013b, 2014) has shown remarkable AC conductance at warm temperature through single microtubules at certain resonant frequencies (e.g., gigahertz, megahertz, and kilohertz). This evidence is consistent with oscillating dipoles extending along helical pathways through microtubules, and thus appears to provide considerable support for Orch OR.

How does the "DP" gravitational OR scheme influence the operation of Orch OR qubits? We first point out that DP is not really "quantum-gravity" in the normal sense of that term, as explained in Appendix A in response to Jack Tuszynski ("JT"), and in Sec. 14.4.4. — though Reimers *et al.* continually use this terminology. This relates to (2), a mechanism by which the possible qubit states reduce, or collapse to definite states, the so-called "wavefunction collapse" of the *measurement problem* of quantum mechanics (see Sec. 5.4.3). In Orch OR, "quantum-gravity" (DP objective reduction) causes reduction, or collapse, of superpositions to classical states in accordance with $E_G \approx \hbar/\tau$ (Fig. 10). It may be mentioned that there are current experimental programs aimed at testing the validity of DP, and these ideas have recently become quite popular (Wolchover, 2013).

So in answer to this question raised by Reimers *et al.* ("how does quantum-gravity affect operation of the qubit?"), Orch OR is very clear: it is the gravitational proposal DP that causes microtubule qubits to reduce, or collapse (in a time $\tau \approx \hbar/E_G$), to definite classical microtubule states (which then regulate brain neurons).

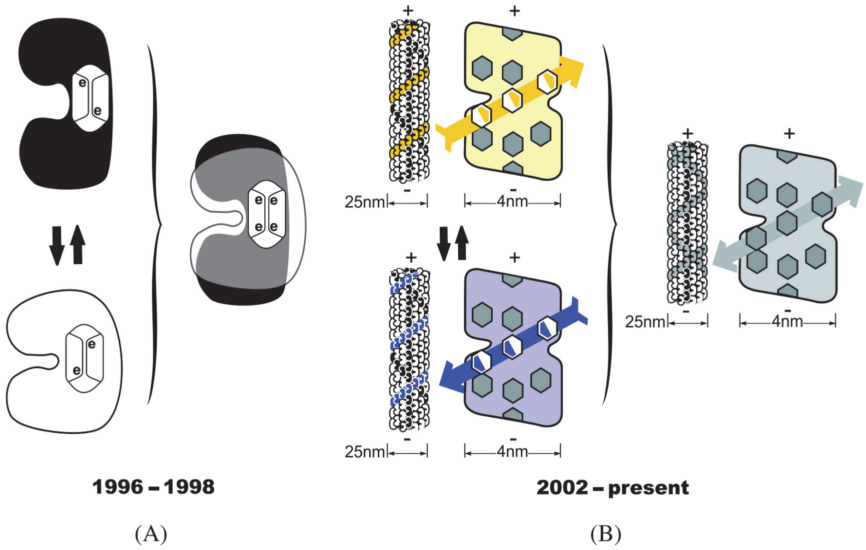

Fig B.1. Early, and current, versions of the Orch OR qubit. (A) Schematic cartoon version of Orch OR tubulin protein qubit used in Orch OR publications mainly from 1996 to 1998. On left, tubulin oscillates between 2 states with ~1 nm conformational flexing (~10% tubulin diameter). On right, both states exist in quantum superposition. (Irrespective of the schematic cartoon, the 1 nm displacement has never been implemented in Orch OR calculations.) The states are shown to correlate with electron locations (dipole orientations) in two adjacent phenyl (or indole) resonance rings in a non-polar "hydrophobic pocket." (B) Schematic cartoon version of Orch OR qubit used since 2002 (following identification of tubulin structure by electron crystallography (Hameroff *et al.*, 2002; Nogales *et al.*, 1998). Each tubulin is shown to have 9 rings representing 32 actual phenyl or indole rings per tubulin, with coupled, oscillating London force (or spin) dipole orientations among rings traversing "quantum channels," aligning with rings in adjacent tubulins in helical pathways through microtubule lattices. On the right, superposition of alternative tubulin and helical pathway dipole states. There is no conformational flexing. Mechanical (femtometer) displacement occurs at the level of tubulin atomic nuclei (not shown). Reimers *et al.* continually, and exclusively, criticize the obsolete, non-implemented cartoon version on left (A), and ignore the actual Orch OR qubit version on right (B).

Reimers *et al.*

In the current review Hameroff and Penrose suggest that the qubit could be either: (a) "interactive dipole states of individual tubulin proteins"…

H&P

"Interactive dipole states" YES, "individual tubulin proteins" NO. The Orch OR qubit is a dipole state extending through mesoscopic helical pathways of many tubulins in microtubule lattices (Figs. B.1(B), 6 and 7 in our review). This is a change from early Orch OR theory in which each tubulin was a qubit (Fig. B.1(A), though without the significant conformational flexing shown there — see below).

Reimers *et al.*

…interactive dipole states….such as "London-force dipoles" or (b) magnetic dipoles or (c) nuclear spins. "London force electric dipoles" have been discussed in previous publications but the other two options have been introduced for the first time.

H&P

True. London force "electric dipoles," magnetic dipoles (electron spin), nuclear spins and AC current flows are possibly synergistic modes. For example microtubule electron dipoles may induce longer-lived nuclear spin states for short-term memory. As we say in Sec. 14.4.6 above: "It is to be expected that the actual mechanisms underlying the production of consciousness in a human brain will be very much more sophisticated than what we can put forward at the present time."

Reimers *et al.*

Previously, Hameroff and Penrose had also proposed that conformational switching could produce coupled electron-vibration qubits but this claim is withdrawn in the current review.

H&P

Not true. There are least two types of "conformational switching" to consider. The type (1) to which Reimers *et al*. refer (see below) was considered and rejected by us in 1996, but implied in cartoon form through 1998, and occasionally thereafter [Fig. B.1(A)]. Reimers *et al*. continually, and exclusively, criticize the obsolete, non-implemented version in Fig. B.1(A), and ignore the actual Orch OR qubit version in Fig. B.1(B) as if they never read our review.

Type (1) conformational switching is shown in Fig. B.1(A). Early Orch OR illustrations showed such conformational "flexing" of entire tubulin proteins (e.g., ~1 nm displacement, ~10% of tubulin diameter) correlating with discrete information states (and superposition of states). It is no longer relevant to Orch OR except historically for the following reason.

In 1996, in attempting to connect brain biology to gravity-induced OR (Hameroff & Penrose, 1996a), we calculated E_G for superposition separation of three different conformational changes in tubulin: (1) a ~10% conformational flexing (~1 nm, 10^{-9} m), as shown in Fig. B.1(A), (2) movement and separation at the level of atomic nuclei, e.g., carbon atoms (~5 fm, 5×10^{-15} m), and (3) movement and separation at the level of nucleons, i.e., protons and neutrons (~femtometers, 10^{-15} m). The dominant effect was found to be separation of intra-tubulin atomic nuclei (5×10^{-15} m), and all Orch OR calculations have used separation at that level. Nanometer flexing was rejected in 1996, not "withdrawn in the current review." However, schematic cartoon illustrations (e.g., Fig. B.1(A) used through 1998 and occasionally thereafter were admittedly, though unintentionally, misleading.

Type (2) conformational switching can occur at the aforementioned much smaller level of atomic nuclei, 5×10^{-15} m, femtometers, shown to be optimal for E_G. This is also the calculated displacement of one (e.g., carbon) atomic nucleus caused by a one nanometer shift in nearby electrons by charge and Mossbauer recoil (Sataric *et al*., 1998, Brizhik *et al*., 2001). Thus, nanometer electron dipoles (London forces) or spin can couple to femtometer nuclear displacements, as needed for E_G in Orch OR.

Slight mechanical, conformational vibrations at the level of atomic nuclear displacement are likely to be associated with (e.g., megahertz) AC electronic resonances discovered by Bandyopadhyay's group in piezoelectric microtubules, e.g., mediated by electric or magnetic dipoles oscillations. London repulsive forces (Pauli exclusion when electron clouds get too close and overlap) are 100 times stronger than attractive forces, likely to promote nonlinear mechanical vibrations in microtubules with displacement at the level of atomic nuclei.

Reimers *et al.*

The London force is of quantum-mechanical origin. An instantaneous fluctuation of the electronic distribution creates a dipole in one molecule that in turn induces a dipolar response in a neighboring molecule. This leads to a net attractive force.

H&P

True. Quantum-mechanical London ("dipole dispersion") force attractions are precisely how anesthetic gas molecules bind (e.g., in brain microtubules; Fig. 6 above) to disperse quantum dipoles and selectively erase consciousness (sparing non-conscious neuronal brain activities (Hameroff *et al.*, 1982; Hameroff & Watt, 1983; Hameroff, 1998; Hameroff, 2006). London forces are weak, but numerous and influential, and able to govern protein function (Voet & Voet, 1995).

Reimers *et al.*

The key feature is that these electric dipoles are *fluctuations*, not *states.* Individual *states* are needed to construct a qubit, and the review makes no attempt at specifying how qubit states could be associated with these London fluctuations.

H&P

Not true, as Fig. 7 in our review demonstrates. London force dipoles are coupled, and "fluctuate" collectively ("oscillate") between two alternative orientation states, with quantum superposition of both states. The London force-mediated shifts themselves are indeed instantaneous, but lifetimes of particular states following each shift are finite, e.g. up to 10^{-4} s as shown in microtubule resonances by Bandyopadhyay's group (Sahu *et al.*, 2013a, 2013b, 2014). The evidence appears to be in support of our contention.

It is somewhat gratifying to note that Reimers *et al*. have dropped their previous misguided criticism that electrons within a phenyl or benzene ring are delocalized, and therefore cannot constitute a switch (McKemmish *et al.*, 2009). As we show in Sec. 14.5.6, this would apply only to single phenyl rings, not coupled rings or contiguous arrays of such rings, as exist in tubulin.

Reimers *et al.*

No model of Orch OR can be treated seriously without the following: (i) a precise description of the quantum states of the qubit.

H&P

In an explorative work of this nature, where there remain many unknown factors, it is unreasonable to demand great precision at this stage. Nevertheless, we have provided a plausibly precise description (see above), as dipole states mediated by London forces and/or spin currents in resonance rings aligned in helical pathways through microtubules. Reimers *et al*. ignore this, appearing not to have read or understood our review, criticizing, instead, an irrelavant cartoon. If Reimers *et al*. are asking for, say, a Hamiltonian operator as a precise description for a microtubule quantum state, see our suggestions below.

Reimers *et al.*

"…(ii) a description of the mechanism through which the wavefunctions representing these states become entangled,"

H&P

Orch OR has always linked qubit entanglement to Fröhlich-type coherence, or condensation among pi electron resonance dipoles akin to laser-induced entanglement in technological quantum systems.

Reimers *et al.*

"…including specification of the basis in which measurements of the qubit's properties are performed *in situ*,…"

H&P

"Measurement" of microtubule qubits is taken to occur by the DP proposal for gravitational OR by $E_G = \hbar/\tau$, a "self measurement." Reimers *et al*. appear to have missed the key point.

Reimers *et al.*

(iii) A means of achieving quantum coherence over the required time scale.

H&P

The non-polar, hydrophobic environment within "quantum channels" shields quantum coherence from polar environmental interactions. This is the solubility phase in which anesthetics act (the "Quantum underground," Craddock *et al.*, this volume) and the likely origin of consciousness. Ambient energy, electric fields and mechanical vibrations pump coherence (as occurs in photosynthesis, and as suggested by Fröhlich). Most importantly, apparent quantum coherence up to 10^{-4} s has been shown by Bandyopadhyay's group (Sahu *et al.*, 2013a, 2013b, 2014) to occur in single microtubules at warm temperature, which may be sufficient for Orch OR.

Reimers *et al.*

Hameroff and Penrose provide only a vague set of qubit possibilities. By not specifying the qubits in the current review they fail to provide a means by which the postulated links between quantum-gravity and conscious behavior could be assessed.

H&P

As remarked upon above, to ask for too much precision in our suggested mechanisms is, at this stage, an unreasonable request. Nevertheless, we have clearly specified our proposal for an Orch OR qubit, as the Orch OR helical pathway that Reimers *et al*. appear to ignore.

Unlike previous proposals for a physical basis for consciousness, Orch OR provides a detailed, testable, falsifiable and moderately rigorous theory, not only for consciousness, but also for microtubule dynamics. It is a broadly based scheme, addressing areas of molecular biology, neuroscience, quantum physics, pharmacology, philosophy, quantum information theory, and even aspects of quantum-gravity. Orch OR has been repeatedly challenged but, in our view, remains to be seriously threatened.

Reimers *et al.*

In previous versions of Orch OR, they *did* define a qubit that at the time might have been considered a reasonable proposition to advance and test. They proposed that conformational switching produced a coupled electron-vibration qubit that interacted with the cellular environment through associated large changes in microtubule structure and with quantum-gravity via the significant mass displacement associated with vibration.

H&P

The electron-vibrational coupling in Orch OR is between (1) pi electron resonance dipoles in aligned tubulin proteins in microtubules, and (2) conformational vibrations at the level of their atomic nuclei, i.e. 5 femtometers.Vattay *et al* (2015) have shown pi resonance rings in proteins are arrayed at "quantum criticality," the precise distance separating quantum and classical behaviors. Conformational vibrations, even slight ones, can thus cause proteins to oscillate between quantum and classical states, e.g. Bandyopadhyay coherence in microtubules.

Reimers *et al.*

Coupled electron-vibration qubits are indeed considered as possibilities for use in modern quantum information technologies (Ferguson *et al.*, 2002; Hines *et al.*, 2004; McKemmish *et al.*, 2011). Quantum coherence was postulated to be provided by Fröhlich condensation (Fröhlich, 1968a, 1968b, 1970), a predicted but unobserved macroscopic quantum effect. The original proposal thus contained a critical testable hypothesis.

H&P

Fröhlich condensation remains in Orch OR, and we consider Bandyopadhyay's gigahertz, megahertz, and kilohertz resonance in microtubules to be clear evidence for Fröhlich condensation, e.g., mediated by oscillating London force dipoles or spin currents (Sec. 14.4.5).

Reimers *et al.*

We tested this hypothesis and found two fatal shortcomings, resulting in it being withdrawn from Orch OR in this current review.

H&P

It is not withdrawn (Sec. 14.4.5). Large scale (nanometer) conformational flexing never was part of Orch OR except in cartoon illustrations (Fig. B-1). The supposed "fatal shortcomings" were in Reimers *et al*. misconceptions. In Orch OR and microtubules, Fröhlich condensation is alive and well as Bandyopadhyay coherence.

Reimers *et al.*

First, we showed the conformational-switch was not a vibration, as is required for the qubit, but instead involves an irreversible chemical reaction (McKemmish *et al*., 2009).

H&P

There is no requirement for a qubit that it should be a vibration. But Reimers *et al*. again refer to the long-rejected (and non-existent, in terms of underlying calculations) nanometer flexing of tubulin (Fig. B.1(A), instead of femtometer (six orders of magnitude smaller) displacement at the level of atomic nuclei. We agree that coherent tubulin nanometer flexing would require significant GTP hydrolysis, an irreversible chemical reaction, and is not feasible (nor did we ever propose such an idea). Fröhlich condensation and Bandyopadhyay coherence are pumped by ambient energy and mitochondrial electric fields (Hameroff & Penrose, 2014).

Reimers *et al.*

Second, we examined the postulate that Fröhlich condensation could deliver unprecedented quantum coherence in a qubit involving electronic motion (Reimers *et al*., 2009). Whilst Fröhlich proposed that the coupled non-linear equations that he solved would show *Bose-Einstein*-like behavior, we found that instead a Fröhlich condensate would be *extremely incoherent*.

Further, we showed that significant *classical* effects of Fröhlich condensation did not manifest unless the system was very far from thermal equilibrium, with component parts needing to be at temperatures in excess of 500 K for room-temperature operation. Fröhlich condensation could not sustain quantum coherence in biological systems and could not support Orch OR.

H&P

The calculations behind these criticisms have nothing to do with Orch OR, microtubules or biology, and are faulty.

In the paper to which they refer (Reimers *et al*., 2009), Reimers *et al*. applied the Wu-Austin Hamiltonian to "a linear chain of coupled oscillators *as envisaged in the Orch OR proposal*." This is false. Orch OR does ***not*** envisage microtubules as a one-dimensional chain of oscillators. We envisage microtubules as three-dimensional crystalline lattices with Fibonacci geometry and gigahertz, megahertz, and kilohertz resonances.

Moreover, the Wu-Austin Hamiltonian is suspect, as it lacks a lower bound, does not converge, and is therefore considered "unphysical" (Bolterauer, 1999). Moreover it addresses quantum states in rigid polar alpha helical regions in proteins rather than non-polar "quantum channels" as addressed in Orch OR. Using a different Hamiltonian, Samsonovich *et al*. (1992) simulated microtubules as two-dimensional lattice planes with toroidal boundary conditions (approximating three-dimensions). They found strong Fröhlich coherence in super-lattice patterns which precisely match experimentally-observed attachment sites for microtubule-associated-proteins ('MAPs').

Reimers *et al.*

We also note that the observed decoherence times for quantum processes involving electronic motion are usually in the range of 10 fs to 30 ps. A qubit with dynamics even slightly coupled to electronic motion would not retain quantum coherence on the 25 ms timescale required for Orch OR which Hameroff and Penrose suggest in this current review. This has consequences for all proposed qubits.

H&P

This, at last, is a reasonable objection, but an anticipated one. Bandyopadhyay's findings of gigahertz, megahertz and (as low as) 10 kilohertz resonances indicate microtubule "decoherence times" (duration for which decoherence is avoided, i.e., "coherence times") for microtubules can persist as long as 10^{-4} s. This same "coherence time" of 10^{-4} s was also calculated based on Orch OR stipulations (Hagan *et al.*, 2001), but is indeed 250 times briefer than the 25 ms we invoked for Orch OR events, e.g., correlating with (40 Hz) gamma synchrony EEG.

In a supplemental modification, we suggest in our review that Orch OR events occur at much higher frequencies (e.g., megahertz) than previously proposed (e.g., at 40 Hz), and that interference between sets of coherent microtubule vibrations (e.g., ~10 MHz) results in much slower "beat frequencies," e.g., at 40 Hz gamma synchrony. Indeed, EEG rhythms (whose origins have never been understood) may actually be "beats" of much faster megahertz Orch OR events in intra-neuronal microtubules.

Moreover, recently-observed very high frequency (kilohertz) EEG (Usui *et al.*, 2010), too fast for membrane depolarizations, may reflect intra-neuronal microtubule dipole oscillations.

Orch OR occurring at ~10 MHz compared to Orch OR occurring at 40 Hz would have greater E_G involving more of the brain (~1% of brain tubulins) and, we suggest, greater experiential intensity. Decoherence, or premature OR, would then need to be avoided for a mere 10^{-7} s compared to 10^{-1} to 10^{-2} s. Bandyopadhyay's group has already shown decoherence time 1000 times longer, at 10^{-4} s, so Orch OR is on more solid ground with respect to decoherence.

Orch OR has some support from experimental evidence and it is a scientifically justified proposal. The riddle of how EEG is generated (including kilohertz EEG (Usui *et al.*, 2010) may also perhaps be solved in terms of Orch OR.

Reimers *et al.*

In an effort to perpetuate their model they now include "electron-cloud dipoles (London forces)," magnetic spin dipoles and nuclear spins in a list of possible qubits, without suggesting how any of these phenomena could in fact be used to make a relevant qubit.

H&P

Decoherence (or premature OR) need be avoided for only 10^{-7} s for 10 MHz Orch OR events. Superposition of pi electron resonance dipole states couples to nuclear position (and spin) in specific helical pathways of tubulins in microtubules. The superposition corresponds to separated space–time geometry and gravitational self-energy E_G which undergoes OR at time $\tau \approx \hbar/E_G$. and "self-collapses" to classical states, accompanied by a moment of conscious experience.

The Orch OR proposal is aimed at perpetuating truth and scientific knowledge. If it were to be shown invalid, we would drop the model and acknowledge accordingly. But we believe that, so far, it has survived many extensive criticisms, such as those by Reimers *et al*. (see Sec. 5.6 in our review). Nevertheless, as said earlier, in accordance with scientific principles we have tried to improve the theory when the need arises and to introduce new ideas. Reimers *et al.* do not even address most of these developments.

Indeed we have modified and adapted the original Orch OR proposal as new information has come forth (though "electron cloud London force dipoles" have always been key components). For example quantum channels, helical pathway qubits, and faster (megahertz) Orch OR events with EEG beat frequencies are adaptations based on new knowledge of tubulin structure and Bandyopadhyay coherence.

Magnetic spin dipoles and nuclear spin are indeed also suggested in this review, and for good reasons. Quantum (magnetic) spin transfer through phenyl rings is increased with temperature (Ouyang & Awschalom, 2003), and likely to be important biologically. Oscillating spin currents, or spin-flips, may propagate through quantum channels as easily as electric (London force) dipoles), or together, synergistically, along with nuclear spin and displacement.

Reimers *et al.*

The review is thus neither self-consistent or scientifically coherent and violates the basic tenants of good scientific practice (van Gunsteren, 2013).

H&P

Orch OR *is* self-consistent, scientifically coherent, and increasingly supported by evidence. Reimers *et al*. then accuse us of a lack of good scientific practice. Their reference (van Gunsteren, 2013) describes "Seven deadly sins" of good scientific practice, e.g., "using pretty pictures instead of solid science". We have repeatedly stated that conformational flexing as shown in Fig. B.1(A) (developed and used before tubulin structure was known) is unrelated to the underlying scientific calculations based on atomic nuclear displacement. Figure B1(B) more closely describes the present Orch OR helical pathway qubit, but still is a simplification, e.g., showing 9 rings per tubulin rather than the actual 32 rings per tubulin. These rings within tubulin also are where anesthetic gas molecules bind and act to erase and prevent consciousness.

With regard to the use of "pretty pictures" instead of solid science, in the original criticism of Orch OR (Reimers *et al*., 2009) by Reimers *et al*., they depict individual coupled oscillators (presumably tubulins) floating in a bath, the cell as "minestrone soup" in their Fig. B.1. Tubulins and microtubules do not float but exist as solid state crystalline lattices. By their own criteria, Reiner's *et al*.'s Fig. B.1 violates basic tenants of good scientific practice.

However, the "minestrone soup" picture of cell interiors as presented by Reimers *et al*. relates to a critical point raised by Jumper and Scholes (2014) in their constructive commentary:

Jumper and Scholes (2014)

"…what do we really know about the fundamental nature and properties of the biological environment? The concept of 'warm, wet and noisy' is put forth when one imagines the complex components and workings of a biological system to be… a messy business, incapable of supporting 'delicate' quantum processes…. Should we reconsider the premise that living entities are founded on uncorrelated and chaotic machinery? [Why] do we expect incoherence in biology?... On the contrary, it appears that living systems are governed by cycles and correlations, requiring massive cooperation across a large range of time and length scales."

Reimers *et al.*

The specification of the quantum qubit should be the centerpiece of the proposal. All other aspects of the Orch OR proposal are only relevant in terms of how they affect the qubits. Without a viable qubit specification there is no connection between the proposal and the observations of Bandyopadhyay and others. Without a qubit there is no connection to postulated effects of quantum-gravity. Without a qubit there is no testable hypothesis linking together the phenomena of quantum-gravity, elementary biochemical function, and consciousness, and no basis on which "Orch OR theory" can be considered as a proposal worthy of further consideration.

H&P

We agree. That's why we have defined an Orch OR qubit based on oscillating London force dipoles and/or spin dipoles in resonance rings in helical pathways through microtubule lattices. The oscillations occur in kilohertz, megahertz, and gigahertz, and appear to be in line with Bandyopadhyay's findings. Reimers *et al.* ignore our specified qubit and continue to criticize an irrelevant cartoon.

We believe that Orch OR is a detailed, testable, falsifiable, and reasonably rigorous approach to a theory of consciousness, and microtubule function. Supportive evidence for Orch OR (Bandyopadhyay megahertz coherence (Sahu *et al*., 2013a, 2013b), Eckenhoff anesthetic effects on microtubules (Xi *et al*., 2004; Pan *et al*., 2007; Emerson *et al*., 2013), quantum channels (Craddock *et al*., 2012)) is of a kind not yet found in other relevant theories. Orch OR has been repeatedly challenged but we do not feel that it has yet been seriously threatened.

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