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Review

Consciousness in the universe
A review of the 'Orch OR' theory

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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 a novel suggestion of 'beat frequencies' of faster microtubule vibrations as a possible source of the observed electro-encephalographic ('EEG') correlates of consciousness. We conclude that consciousness plays an intrinsic role in the universe.

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.

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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 [1–3]), and also illusory (largely constructing reality, rather than perceiving it [4]). Nonetheless, consciousness is frequently argued to confer beneficial advantages to species [5]. Overall, in this view, consciousness is *not* an intrinsic feature of the universe.

(B) *Consciousness is a separate quality, distinct from physical actions and not controlled by physical laws, that has always been in the universe*. Descartes' 'dualism', religious 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' [6]. In this view consciousness can causally influence physical matter and human behavior, but has no basis or description in science [7]. 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 [8]. 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 A.N. Whitehead [9,10] and also fleshed out in a scientific framework in the Penrose–Hameroff theory of 'orchestrated objective reduction' ('Orch OR' [11–16]). In the Orch OR theory, these conscious events are terminations of quantum computations in brain microtubules reducing by Diósi–Penrose '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 [1–5].
(B) Dualism/Spirituality, with consciousness (etc.) being outside science [6–8].
(C) Science, with consciousness as an essential ingredient of physical laws not yet fully understood [9–17].

2. Consciousness, computation and brain activities

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 [18,19]. 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, experience, or subjective feelings, composed of what philosophers call 'qualia' [19]. However perception and behavior may at other times be unaccompanied by consciousness. We could have evolved as full-time non-conscious 'zombies' performing complex 'auto-pilot' 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' [20]). How is conscious content bound together?

Synchrony Neuronal membrane polarization states may be precisely synchronized over large regions of brain [21], and also propagate through brain regions as synchronized zones [22]. 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 [23,24] 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 [25,26]. How do single cells manifest intelligent behavior?

2.2. Conscious moments and computation

Consciousness has often been argued to be a sequence of discrete moments. William James [27] 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 [28] 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 [29]. Buddhist texts portray consciousness as "momentary collections of mental phenomena", and as "distinct, unconnected and impermanent moments that perish as soon as they arise". Buddhist writings even quantify the frequency of conscious moments. For example the Sarvaastivaadins [30] described 6,480,000 "moments" in 24 hours (an average of one "moment" per 13.3 ms, 75 Hz), and some Chinese Buddhists as one "thought" per 20 ms (50 Hz). The best measurable correlate of consciousness through modern science is gamma synchrony electro-encephalography (EEG), 30 to 90 Hz coherent neuronal membrane activities 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 [31,32] (Fig. 11). Thus, we may argue that consciousness consists of discrete events at varying frequencies occurring across brain regions, for example 40 conscious moments per second, synchronized among neurons in frontal and parietal cortex. What are these conscious moments?

The over-arching presumption in modern science and philosophy is that consciousness emerges from complex synaptic computation in networks of brain neurons acting as fundamental information units. In digital computers, discrete voltage levels represent information units (e.g. 'bits') in silicon logic gates. McCulloch and Pitts [33] proposed such gates as integrate-and-fire artificial neurons, leading to 'perceptrons' [34] and other types of 'artificial neural networks' capable of learning and self-organized behavior. Similarly, according to the standard 'Hodgkin–Huxley' [35] model, 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 and 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 (Fig. 2), 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 [36] can self-organize and learn, their axonal firing outputs controlling downstream activity and behavior.

How does consciousness arise from neurocomputation? Some contend that consciousness emerges from computational complexity due to firings and other brain electrical activity [37,38]. 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 [18,39]. 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

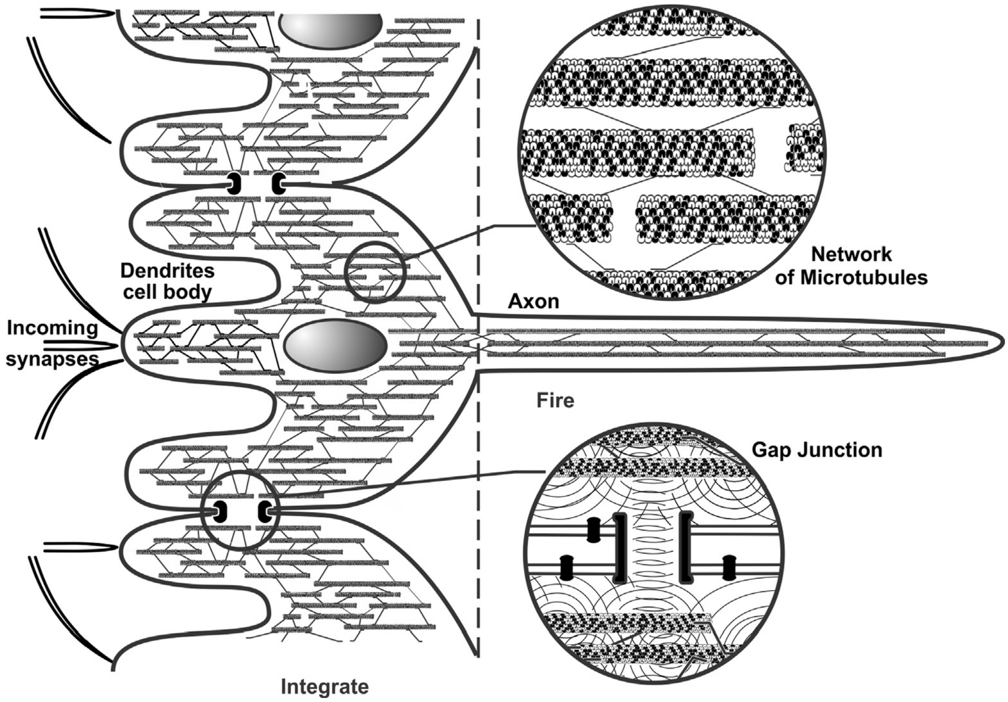

Fig. 1. An ‘integrate-and-fire’ brain neuron, and portions of other such neurons are shown schematically with internal microtubules. In dendrites and cell body/soma (left) involved in integration, microtubules are interrupted and of mixed polarity, interconnected by microtubule-associated proteins (MAPs) 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.

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 [40–42]. Integration implies reduction of uncertainty, merging and consolidating multiple possibilities to one, e.g. selecting conscious perceptions and actions.

2.3. Consciousness and dendritic integration

Neuronal integration is commonly approximated as linear summation of dendritic/somatic membrane potentials (Fig. 2a). However actual integration is not passive, actively involving complex processing [44–46]. Dendritic–somatic membranes generate local field potentials (‘LFPs’) that give rise to the electro-encephalogram (EEG), including coherent gamma synchrony, the best measurable neural correlate of consciousness (‘NCC’ [47,48]). 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–Huxley neurons would, apart from an entirely probabilistic (random) input, be completely algorithmic and deterministic, leaving no apparent place for a free will aspect of consciousness.

However neurons involved in conscious brain processes apparently deviate from Hodgkin–Huxley. Naundorf et al. [43] showed that firing threshold at the AIS in cortical neurons in brains of awake animals (compared to neurons *in vitro*) vary significantly spike-to-spike (Fig. 2b). 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

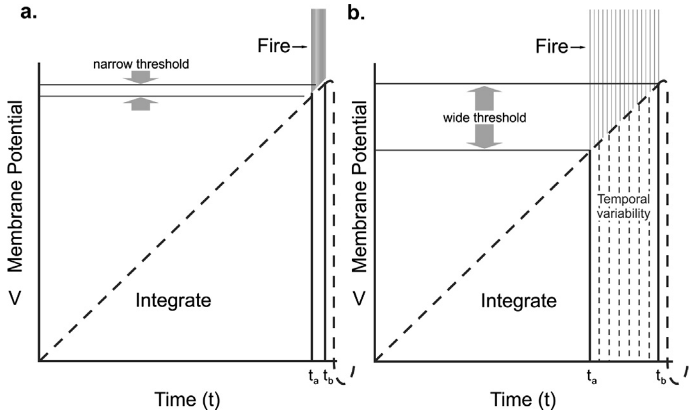

Fig. 2. Neuronal 'integrate-and-fire' behaviors. (a) The Hodgkin–Huxley model predicts integration by membrane potential in dendrites and soma reach a specific, narrow threshold potential at the proximal axon, and fire with very limited temporal variability (small $t_b - t_a$) for given inputs. (b) Recordings from cortical neurons in awake animals [43] show a large variability in effective firing threshold and timing. Some unknown 'x-factor' (related to consciousness?) modulated integration to exert causal influence on firing and behavior.

membrane polarization states, e.g. in gamma synchrony EEG [49–54]. 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 local field potentials in integration phases, but not necessarily synchronous axonal firing outputs. Gap junction-synchronized dendritic networks can thus *collectively* integrate inputs, enhancing computational capabilities [22]. 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. [43]. Finer scale processes from within neurons (and conveyed from interiors of adjacent neurons via open gap junctions) *would* alter firing threshold without changing membrane potentials, and could 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 [55] said in 1957: '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, well-positioned and uniquely arrayed (e.g. in dendrites and soma) to mediate consciousness and regulate firing.

3. A finer scale of neuronal information processing

3.1. Microtubules

Interiors of eukaryotic cells are organized and shaped by their cytoskeleton, a scaffolding-like protein network of microtubules, microtubule-associated proteins (MAPs), actin, and intermediate filaments [57]. Microtubules ('MTs', Fig. 3) are cylindrical polymers 25 nanometers ($\text{nm} = 10^{-9}$ 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 [58]), 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 5 and 8 tubulins, respectively, down any protofilament, and following along neighboring tubulin monomers repeat every 3 monomers, after winding twice around the MT (relating to the 13 protofilaments according to the Fibonacci sequence 3, 5, 8, 13).

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 dis-

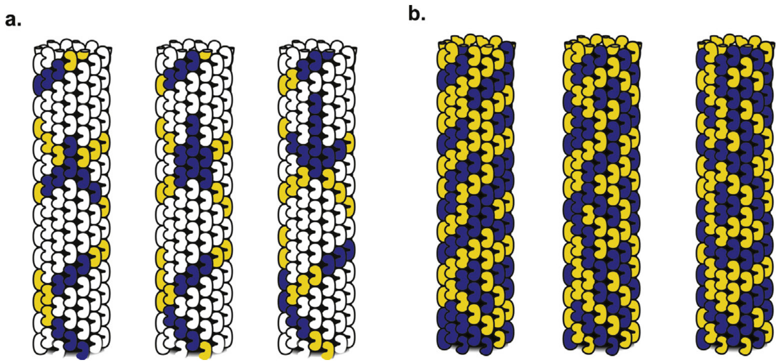

Fig. 3. Three time-steps (e.g. at 10 megahertz) of a microtubule automaton. Tubulin subunit dipole states (yellow, blue) represent information. (a) Spin currents interact and compute along spiral lattice pathways. For example (upper, middle in each microtubule) two upward traveling blue spin waves intersect, generating a new vertical spin wave (a 'glider gun' in cellular automata). (b) A general microtubule automata process [56].

placement from MTs results in neurofibrillary tangles and the cognitive dysfunction of Alzheimer's disease [59–61]. Other MAPs include motor proteins (dynein, kinesin) that 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. 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, don't 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 [56]. 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' [62]). Dendritic–somatic MTs are capped by special MAPs that prevent de-polymerization [63], and are thus stable and suitable for long term information encoding and memory (Fig. 4 [64]).

3.2. Microtubule information processing

After Sherrington's broad observation in 1957 about the cytoskeleton as a cellular nervous system, Atema [65] proposed that tubulin conformational changes propagate as signals along microtubules. Hameroff and Watt [66] 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') in which tubulin dipole and conformational states interact with neighbor tubulin states in hexagonal MT lattices by dipole couplings, synchronized by biomolecular coherence as proposed by Fröhlich [67–71].

Protein conformational changes occur at multiple scales [72], e.g. 10^{-6} s to 10^{-11} s 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 [13–17]. However all calculations were based on dipole couplings, and recent Orch OR papers do not make use of conformational changes, depending instead on tubulin dipole states alone to represent information (Section 3.3 below).

Within MTs, each tubulin may differ from among its neighbors due to genetic variability, post-translational modifications [73,74], phosphorylation states, binding of ligands and MAPs, and moment-to-moment conformational

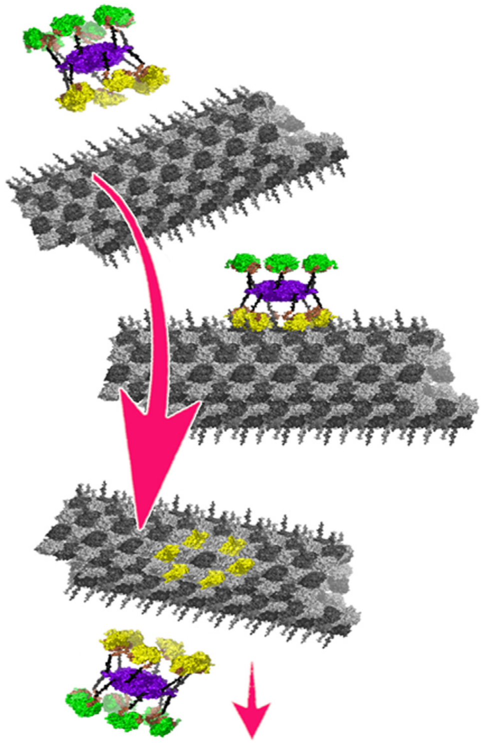

Fig. 4. Calcium-calmodulin kinase II ('CaMKII'), a hexagonal holoenzyme activated by synaptic calcium influx extends 6 leg-like kinase domains above and below an association domain. The 6 kinase domains precisely match hexagonal size and geometry in both A-lattice and B-lattice microtubules ([64], with permission from Travis Craddock).

and/or dipole 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 [64]). 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'.

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 [75]. Dipoles 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 [61]. 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 [74].

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 hyper-phosphorylated and dislodged from destabilized MTs, forming neurofibrillary tangles which correlate with memory loss [58–60]. Fourth, tubulin states can encode binding sites not only for tau, but also structural MAPs determining cytoskeletal scaffolding and thus directly regulate neuronal structure, differentiation and synaptic formation. Finally, MT information process-

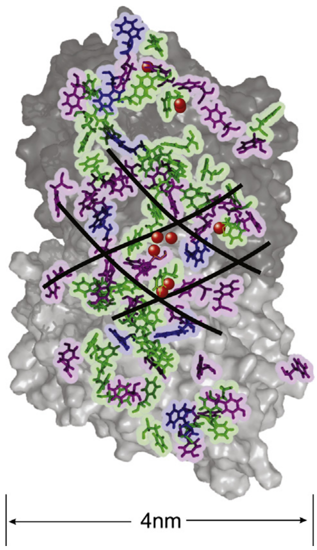

Fig. 5. Molecular modeling of tubulin dimer shows aromatic amino acids tryptophan (blue), phenylalanine (purple) and tyrosine (green) in non-polar, hydrophobic regions. Red spheres are anesthetic binding sites (with permission from Craddock et al. [79]). Curved lines enclose rings in particular aligned orientation along 5- and 8-start helical channels, containing anesthetic binding sites.

ing may be directly related to activities at larger scale 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 spatio-temporal scales in brain dynamics and structure [76,77]. These are generally considered at the scale levels of neurons and higher-level neuronal networks, but may extend downward in size (and higher frequency) to intra-neuronal MT dynamics, spanning 4 or 5 scale levels over many orders of magnitude.

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

3.3. Tubulin dipoles and anesthesia

Tubulin, like other proteins, is composed of a heterogeneous group of amino acid residues connected to peptide backbones. 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) [78].

Within intra-protein hydrophobic regions, anesthetic gas molecules bind by London force dipole couplings, and thereby (somehow) exert their effects on consciousness [79–83]. Historically, views of anesthetic action have focused on neuronal membrane proteins, but actual evidence (e.g. from genomics and proteomics) [84,85] points to anesthetic action in microtubules. In the most definitive anesthetic experiment yet performed, Emerson et al. [86] used fluorescent anthracene as an anesthetic in tadpoles, and showed cessation of tadpole behavior occurs specifically via anthracene anesthetic 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 nanometers [79]. 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 5- and 8-start helical winding pathways in the microtubule A-lattice.

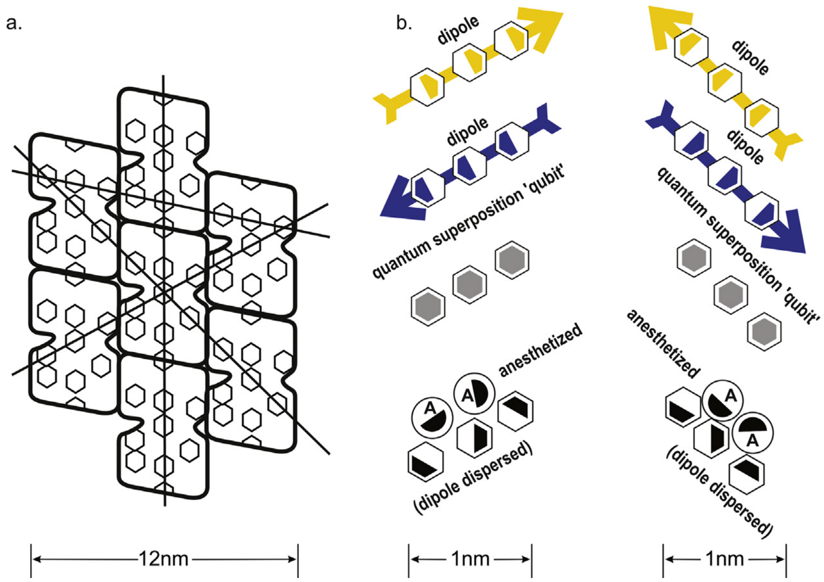

Fig. 6. Dipoles in tubulin and microtubule A-lattice 'quantum channels'. (a) Seven tubulin microtubule A-lattice neighborhood with schematized placement of aromatic rings along 3-, 5- and 8-start helical pathways. (b) 5-start (left) and 8-start (right) helical dipoles in aligned ring dipole 'bits' (blue, yellow) and superposition of both (gray—quantum bits, or 'qubits'). Bottom (both dipole pathways): anesthetic gas molecules (A) form their own (van der Waals London force) dipole couplings, dispersing collective dipoles and disrupting classical and quantum computations.

Fig. 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 [80–83]. Electron cloud dipoles may be either charge separation (electric) or electron spin (magnetic). Tubulin dipoles in 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 in MTs. Spin is inherently quantum in nature, and quantum spin transfer through aromatic rings is enhanced at warm temperature [87]. 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 not be figurative only. 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' 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 alternating currents 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' alternating currents in MTs.

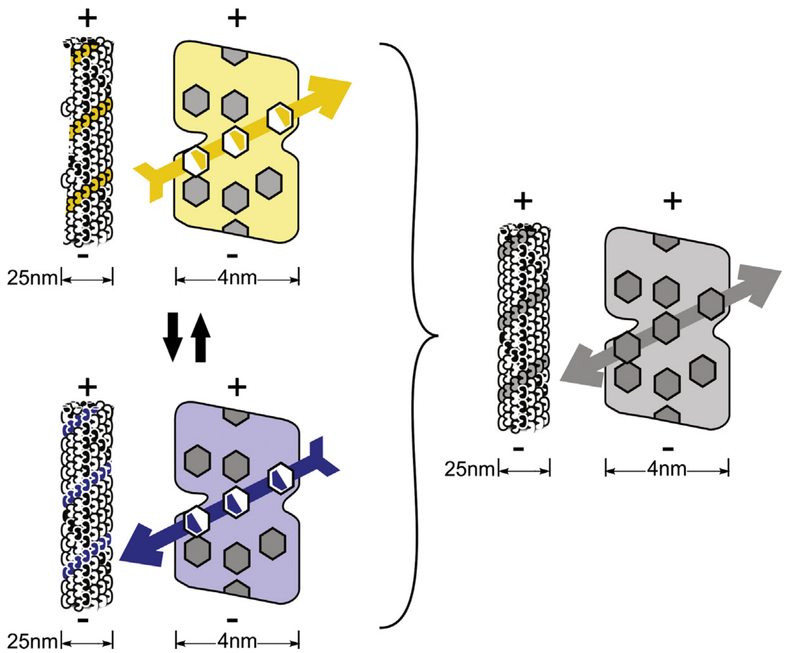

Fig. 7. Dipole qubit in microtubule, with classical and quantum dipole information states for the '5-start' helical pathway in tubulin and microtubules. Left: The '5-start' helix in microtubule A-lattice aligned with dipoles in intra-tubulin aromatic rings. Top: 'upward' dipole (yellow), bottom: 'downward' 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 8-start pathways, or other pathways.

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 alternating current at specific frequencies in gigahertz, megahertz and kilohertz ranges [88,89]. See Section 4.5.

Electron dipole shifts do have some tiny effect on nuclear positions via charge movements and Mossbauer recoil [90,91]. 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 [17,42]. As it turns out, femtometer displacement might be sufficient for Orch OR (Section 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 (Section 2.1). Something was missing. Was it some subtle feature of quantum mechanics?

4. Quantum physics and consciousness

4.1. Non-computability and objective reduction (OR)

In 1989 Penrose published *The Emperor's New Mind* [23], which was followed in 1994 by *Shadows of the Mind* [24]. 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 Section 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 more fully below, in Section 4.3 [92–95].

In Penrose [23], the tentatively suggested OR proposal would have its onset determined by a condition referred to there as 'the one-graviton' criterion. However, in Penrose [93,95], a much better-founded criterion was used, now frequently referred to as the *Diósi–Penrose proposal* (henceforth 'DP'; see Diósi's earlier work [96,97], 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 ([98–101], cf. [102–104]) 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 (Section 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 [105]) 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.

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 don't 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 kilometers [106]). 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 [107–109].

4.3. The measurement problem and objective reduction (OR)

The issue of why we don't 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 and gluons etc.) as is the system under observation, so it ought to be subject also to the same quantum laws, these being described in terms of the continuous and deterministic U. How, then, can the discontinuous and probabilistic R come about as a result of the interaction (measurement) between two parts of the quantum system? This is the paradox faced by the measurement problem.

There are many ways that quantum physicists have attempted to come to terms with this conflict [110–114]. In the early 20th century, the Danish physicist Niels Bohr, together with Werner Heisenberg, proposed the pragmatic 'Copenhagen interpretation', according to which the wavefunction of a quantum system, evolving according to U, is not assigned any actual physical 'reality', but is taken as basically providing the needed 'book-keeping' so that eventually probability values can be assigned to the various possible outcomes of a quantum measurement. The measuring device itself is explicitly taken to behave *classically* and no account is taken of the fact that the device is ultimately built from quantum-level constituents. The probabilities are calculated, once the nature of the measuring device is known, from the state that the wavefunction has U-evolved to at the time of the measurement. The discontinuous 'jump' that the wavefunction makes upon measurement, according to R, is attributed to the change in 'knowledge' that the result of the measurement has on the observer. Since the wavefunction is not assigned physical reality, but is considered to refer merely to the observer's knowledge of the quantum system, the jumping is considered simply to reflect the jump in the observer's knowledge state, rather than in the quantum system under consideration.

Many physicists remain unhappy with such a point of view, however, and regard it largely as a 'stop-gap', in order that progress can be made in applying the quantum formalism, without this progress being held up by a lack of a serious quantum ontology, which might provide a more complete picture of what is actually going on. One may ask, in particular, what it is about a measuring device that allows one to ignore the fact that it is itself made from quantum constituents and is permitted to be treated entirely classically. A good many proponents of the Copenhagen standpoint would take the view that while the physical measuring apparatus ought actually to be treated as a quantum system, and therefore part of an over-riding wavefunction evolving according to U, it would be the *conscious observer*, examining the readings on that device, who actually reduces the state, according to R, thereby assigning a physical reality to the particular observed alternative resulting from the measurement. Accordingly, before the intervention of the observer's consciousness, the various alternatives of the result of the measurement *including* the different states of the measuring apparatus would, in effect, still 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 [115] 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 [24], Sections 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 *objective* reduction (OR) in which a specific objective threshold is proposed to cause quantum state reduction [116–118]. 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' [119]. 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.

4.4. OR and quantum gravity

Diósi–Penrose objective reduction (DP) 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 (see Section 4.3), 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 [120]) 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

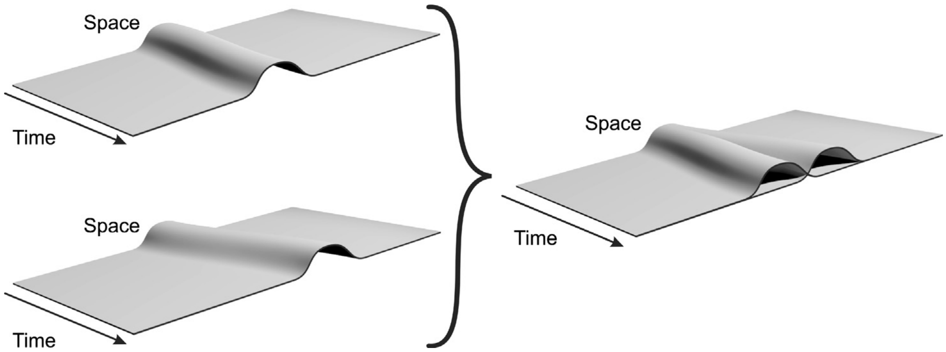

Fig. 8. Space–time geometry schematized as one spatial and one temporal dimension in which particle location is represented as curvature. Left: Top and bottom show space–time histories of two alternative particle locations. Right: Quantum superposition of both particle locations as bifurcating space–time depicted as the union ('glued together version') of the two alternative histories (adapted from Penrose [24], p. 338).

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 [121].)

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 3-dimensional space and a 1-dimensional time, combined together into a 4-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 a 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 [92–95].

In the current context, superposed quantum states for which the respective mass distributions differ significantly from one another will have space–time geometries that also correspondingly differ. For illustration, in Fig. 8, we consider a 2-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 2-dimensional, whereas the actual space–time constituents are 4-dimensional. Moreover, there is no significance to be attached to the imagined '3-dimensional space' within 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

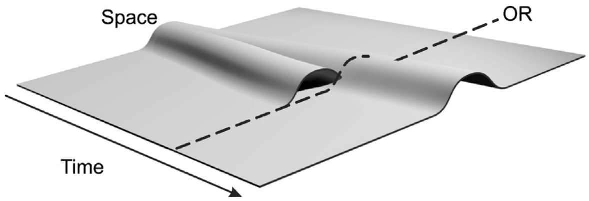

Fig. 9. As superposition curvature E reaches threshold (by $E_G = \hbar/\tau$), OR occurs and one particle location/curvature is selected, and becomes classical. The other ceases to exist.

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 4-dimensional metrics (cf. [92,121]) 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.

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 [93,95]. 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 ($\sim$10 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. [24], 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 [92,114,121].) 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.

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 effected 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 [122]). For example, one ought to begin to see the effects of this OR scheme if a small object, such as a 10-μm 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 [102,117]) for the static *un*superposed 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 [87] 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) are enhanced at increasingly warm temperatures. (Spin flip currents through microtubule pathways, as suggested in Section 3.3 above, may be directly analogous.)

In the past 6 years, evidence has accumulated that plants routinely use quantum coherent electron transport at ambient temperatures in photosynthesis [123,124]. 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) [125].

Quantum conductance through photosynthesis protein is enhanced by mechanical vibration [126], and microtubules appear to have their own set of mechanical vibrations (e.g. in megahertz as suggested by Sahu et al. [88,89]). 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 [127].

Further research has shown warm quantum effects in bird-brain navigation [128], ion channels [129], sense of smell [130], DNA [131], protein folding [132], and biological water [133]. What about quantum effects in microtubules? In the 1980s and 1990s theoretical models predicted 'Fröhlich' gigahertz coherence and ferroelectric effects in microtubules [61,66,70]. 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 Pokorný in Prague [134,135].

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 [88,89]. 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 alternating current (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 AC conductance through 25-nm-wide microtubules is greater than through single 4-nm-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, indicative of quantum mechanisms.

The resonance conductance ('Bandyopadhyay coherence' – 'BC') through tubulins and microtubules is consistent with the intra-tubulin aromatic ring pathways (Section 3.3, 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.

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 [114], Sections 29.4, 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 for conscious moments (see Fig. 11) has been assumed to correlate with physiological EEG parameters, 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 a (complex) oscillatory nature with a time-dependence that is proportional to $e^{-iEt/\hbar}$ (see, for example, [114], Chapter 21) so that it oscillates with frequency E/h (where we recall that $h = 2\pi\hbar$). If we have a state $\boldsymbol{\Psi}$ which is a superposition of two slightly different states $\boldsymbol{\Psi}_1$ and $\boldsymbol{\Psi}_2$, 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 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 $a = -E_1 t/\hbar$ and $b = -E_2 t/\hbar$ 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 $\boldsymbol{\Psi}_1$ 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 $\boldsymbol{\Psi}_1$ and $\boldsymbol{\Psi}_2$. 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 $\cos^2\{\frac{1}{2}(a-b)\} = \{1 + \cos(a-b)\}/2$ 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 [136].)

To be more explicit about how this comes about, it is necessary to appreciate, first, that the eigenstates of energy, $\boldsymbol{\Psi}_1$ and $\boldsymbol{\Psi}_2$, 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* $\boldsymbol{\Lambda}$ and $\boldsymbol{\Pi}$ (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 $\boldsymbol{\Psi}_1$ and $\boldsymbol{\Psi}_2$ 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 $\boldsymbol{\Lambda}$, $\boldsymbol{\Pi}$, so that $\boldsymbol{\Psi}_1$ and $\boldsymbol{\Psi}_2$, when expressed in terms of these location states, take the form

$$\boldsymbol{\Psi}_1 = (\boldsymbol{\Lambda}\cos\theta + \boldsymbol{\Pi}\sin\theta)e^{ia} \quad \text{and} \quad \boldsymbol{\Psi}_2 = (\boldsymbol{\Lambda}\sin\theta - \boldsymbol{\Pi}\cos\theta)e^{ib}$$

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 $a = -E_1 t/\boldsymbol{\hbar}$ and $b = -E_2 t/\boldsymbol{\hbar}$, as above. The initial quantum state is taken to be a superposition

$$\boldsymbol{\Psi} = \alpha\boldsymbol{\Psi}_1 + \beta\boldsymbol{\Psi}_2,$$

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

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

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 moduli of the coefficients of $\boldsymbol{\Lambda}$ and $\boldsymbol{\Pi}$, namely

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

and

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

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 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 $h/|E_1 - E_2|$ of the beat frequencies $|E_1 - E_2|/h$. Following Bandyopadhyay's findings, these primary frequencies may be around 10 megahertz, with time periods of $\sim 10^{-8}$ s. Decoherence might need be avoided for a mere ten-millionth of a second with consciousness occurring at far slower beat frequencies. For example if E_1 and E_2 were 10.000000 megahertz and 10.000040 megahertz 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 milliseconds for 40 Hz gamma synchrony (Fig. 11). 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 there quired overall ranges such as gamma synchrony (30 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 40 Hz 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.

5. Orch OR and quantum brain biology

5.1. Quantum computing in the brain

Penrose [23,24] 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 [137–139], 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 [23] 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 Section 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^{-8} 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, 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 [23,24]).

Fig. 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 selecting one space–time. Fig. 10 (bottom) shows a schematic of the same process, e.g. one conscious moment in a sequence of such moments (Fig. 11).

The idea is that consciousness is associated with this (gravitational) OR process, but (see Section 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 microtubule 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 take 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 some 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.

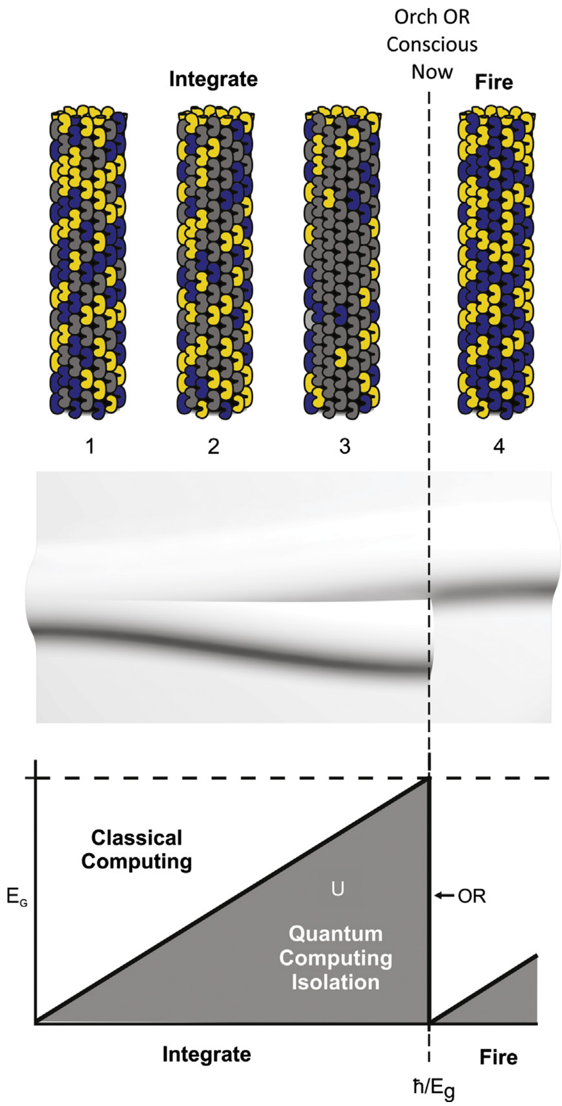

Fig. 10. Top: Tentatively proposed picture of a conscious event by quantum computing in one of a vast number of microtubules all acting coherently so that there is sufficient mass displacement for Orch OR to take place. Tubulins are in classical dipole states (yellow or blue), or quantum superposition 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 $\tau \approx \hbar/E_G$.

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 in 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 have evolved 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.

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 $\boldsymbol{E}_G$, 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 electro-encephalography (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 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 femtometers; 2.5×10^{-15} meters). 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 0.1 percent 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 [140] 'cell assemblies', Eccles's [141] 'modules', and Crick and Koch's [48] 'coherent sets of neurons' are each estimated to contain some 10,000 to 100,000 neurons which may be widely distributed throughout the brain [37]. In the 'beat frequency' approach, a much smaller time $\tau = 10^{-8}$ s might perhaps suffice, but require much larger microtubule superposition $\boldsymbol{E}_G$, roughly 10^9 neurons, or one percent 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) [85], 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 it 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 measurable correlate of consciousness, depended on gap junctions, particularly dendritic–dendritic gap junctions [49–54]. 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 [22] 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. Alternatively, spatially separated microtubules may entangle, possibly between different neurons [142], so that gap junctions aren't required for Orch OR or conscious pilot modes.

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 [143]. Thus, according to the viewpoint proposed above, where we interpret this frequency to be associated with a succession of Orch OR moments, then $E_G \approx \hbar/\tau$ would appear to require that there is twice as much brain involvement required for 80 Hz 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^{-8} s, while E_G is large, at roughly 10^9 neurons, one percent of the brain.

There is also the possibility that discernible 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 ∼25 ms. 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 [31,32] (Fig. 11). 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.

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 [13] that microtubule quantum states avoid decoherence by being pumped, laser-like, by Fröhlich resonance, and shielded by ordered water, C-termini Debye layers, actin gel and strong mitochondrial electric fields.

Moreover quantum states in Orch OR are proposed to originate in hydrophobic channels in tubulin interiors, isolated from polar interactions, and involve superposition of only atomic nuclei separation.

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 [144]. This is still a long way from body temperature, of course, but increasing evidence suggests functional quantum effects operate in biology.

As described in Section 4.5, research in the past 10 years has clearly shown quantum coherence in warm biological systems. Electronic quantum effects occur at ambient temperatures in proteins involved in photosynthesis [123,124], these being thought to be mediated by coherent protein mechanical vibrations [125], 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 support quantum coherence are chemically close to aromatic ring pathways in tubulin (Section 3.2, Figs. 5–7) [126]. Warm quantum effects have also been discovered in bird brain navigation [128], ion channels [129], sense of smell [130], DNA [131], protein folding [132], and biological water [133]. 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 [145].) 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.

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 [1–3] to imply that in such cases we respond non-consciously, on auto-pilot, and subsequently have only an *illusion* of conscious response. The mainstream view is that consciousness is epiphenomenal illusion, occurring after-the-fact as a false impression of conscious control of behavior. Accordingly, we are merely 'helpless spectators' [146].

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 [147]. 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 [148–150].

Bearing such apparent anomalies in mind, Penrose put forward a tentative suggestion [23] that effects like Libet's backward time referral might be related to the fact that quantum entanglements are not mediated in a normal causal way, so that it might be possible for conscious experience not to follow the normal rules of sequential time progression, so long as this does not lead to contradictions with external causality. In Section 4.2, it was pointed out that the (experimentally confirmed) phenomenon of 'quantum teleportation' [107–109] cannot be explained in terms of ordinary classical information processing, but as a combination of such classical causal influences and the acausal

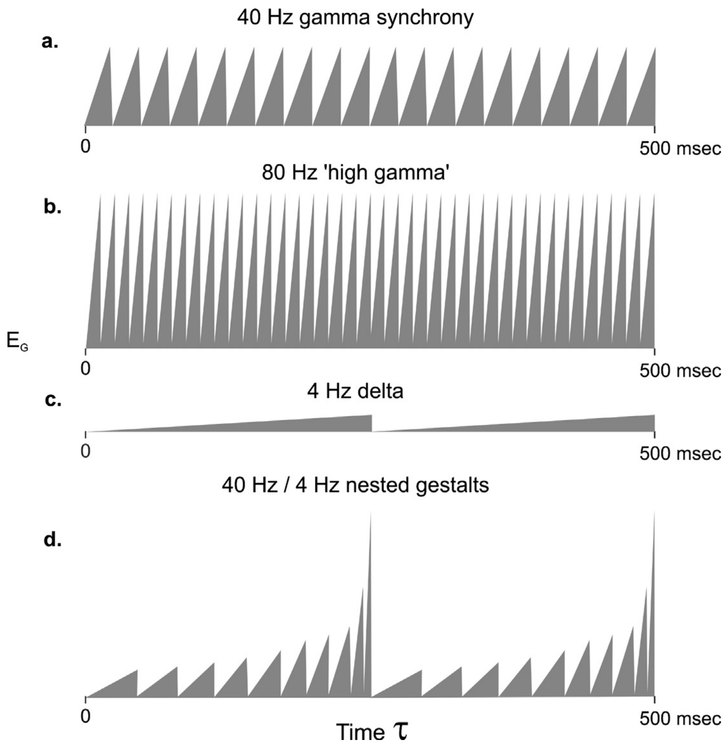

Fig. 11. According to a scheme proposed earlier (Fig. 10, bottom), sequences of Orch OR conscious moments occurring by $\tau \approx \hbar/E_G$ with intensity of experience correlated with orchestrated E_G. (a) 'Normal' Orch OR conscious moments every 25 ms in '40 Hz' gamma synchrony. (b) Heightened, 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. These waves may be 'beat frequencies' of faster microtubule vibrations.

effects of quantum entanglement. It indeed turns out that quantum entanglement effects—encompassed by such terms as 'quantum information' or '*quanglement*' (Penrose [114,116])—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 milliseconds ('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-nonlocal*, with backward time effects seen as temporal variability in axonal firing threshold (Fig. 2b), consciously regulating behavior and 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 [42]. (See Fig. 2—quantum backward time referral can account for temporal variability.)

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. Such undifferentiated experiences are taken, in the Orch OR scheme, to be irreducible, fundamental features of 'Planck scale geometry', perhaps ultimately having a physical role as important to basic physics as those of mass, spin or charge.

The following scenario seems plausible. As organic biomolecules appeared in primitive biology, non-polar collections of electron resonance rings, e.g. in lipids, nucleotides, and hydrophobic protein pockets, offered protective isolation for quantum superpositions (as described in Section 5.3). As biomolecules became larger and more functional, quantum states in non-polar regions persisted, delaying the environmental interactions which serve to increase E_G and thereby cause OR. As biomolecules self-organized into assemblies such as microtubules, more extensive and organized quantum-superposed states became available which could better maintain isolation from the random environment, and could then interact cooperatively by entanglement so as to process information in some form of primitive *quantum computing*. Initially such quantum computing would fail to isolate sufficiently, and the various 'E_G's would be insufficient to achieve OR threshold without the randomness of environmental entanglement, Nevertheless, these processes might still achieve effects not easily accessible by classical computing, and provide non-conscious, but still useful information processing. Only with further evolutionary development, better isolation, and 'orchestration', was OR reached without environmental decoherence, allowing for Orch OR to play its vital role.

This last possibility is strongly suggested by considerations of natural selection, since some relatively primitive MT infrastructure, still able to support quantum computation, would have to have preceded the more sophisticated kind that we now find in conscious animals. Natural selection proceeds in steps, after all, and one would not expect that the capability of the substantial level of coherence across the brain that would be needed for the non-computable Orch OR of human conscious understanding to be reached, without something more primitive having preceded it. Microtubule quantum computing by U evolution, which delays the effects of environmental interaction, could well be advantageous to biological processes without ever reaching threshold for Orch OR and non-computational influence. Indeed, this type of non-conscious but effective processing is likely to be occurring in MTs throughout biology.

Microtubules appeared in eukaryotic cells 1.3 billion years ago, perhaps due to symbiosis among prokaryotes, mitochondria and spirochetes, the latter the apparent origin of microtubules that provided movement and internal organization to previously immobile cells [151]. 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 [152]. 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.

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 [153] 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 and Hameroff [12] responded point-by-point to every objection, e.g. explaining that colchicine does not cross the blood brain barrier, and so doesn't reach the brain, and that brain neurons don't disassemble/re-assemble anyway. Colchicine infused directly into the brains of animals does cause severe cognitive impairment and apparent loss of consciousness [154].

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 (alpha–beta, and beta–alpha) [155]. 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. 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' [156,157] brain MTs have multiple seams involving 4 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 [158].

Orch OR is expected to occur in only a fraction of suitable dendritic and somatic MTs, and perhaps only transiently, and partially. Bandyopadhyay [142] 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 [159] 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^{18} tubulins, 10^9 neurons, one percent of the brain. It should be noted that Orch OR is the only theory able to meaningfully entertain such quantitative speculation.

Tuszynski et al. [160] 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 Section 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 [161] published a critique of Orch OR based on his calculated decoherence times for microtubules of 10^{-13} seconds at biological temperature, far too brief for physiological effects. However Tegmark didn't include Orch OR stipulations and in essence created, and then refuted his *own* quantum microtubule model. He assumed superpositions of solitons separated from themselves by a distance of 24 nanometers along the length of the microtubule. As previously described, superposition separation in Orch OR is at the Fermi length level of atomic nuclei, i.e. 7 orders of magnitude smaller than Tegmark's separation value, thus underestimating decoherence time by 7 orders of magnitude, i.e. from 10^{-13} s to microseconds at 10^{-6} seconds. Hagan et al. [162] used Tegmark's same formula and recalculated microtubule decoherence times using Orch OR stipulations, finding 10^{-4} to 10^{-3} seconds, 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 being involved in the quantum-coherent states.

Koch and Hepp [163] 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 neurons in visual and associative cortex and other brain areas, anatomically the same as in neuronal-based theories, except at an additional, 'deeper order'.

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 neurons in various areas of visual and pre-frontal cortex and other brain regions, again the same as neuronal-based theories but at a deeper, quantum level inside neurons.

Reimers et al. [164] described three types of Fröhlich condensation (weak, strong and coherent, the first classical and the latter two quantum). They validated 8 MHz coherence measured in microtubules by Pokorný [134,135] as weak condensation. Based on simulation of a 1-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. [165] simulated a microtubule as a 2-dimensional lattice plane with toroidal boundary conditions and found Fröhlich resonance maxima at discrete locations in super-lattice patterns on the simulated microtubule surface which precisely matched experimentally observed functional attachment sites for microtubule-associated proteins (MAPs). 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. [166] 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 π electron cloud ring structures, or other non-polar groups. A single benzene ring cannot support London forces. It takes two (or more) to tango. Orch OR has always maintained two or more non-polar groups are necessary, 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. 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; 2.5×10^{-15} meters). This shift may be accounted for by electronic cloud dipoles with Mossbauer nuclear recoil and charge effects [90,91]. 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 (Figs. 5–7).

5.7. Testable predictions of Orch OR – current status

Orch OR involves numerous fairly specific and essentially falsifiable hypotheses. In 1998 twenty testable predictions of Orch OR in 9 general categories were published [15]. 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 antidepressants, involve neuronal microtubules. *This indeed appears to be the case. Fluoxitene* (*Prozac*) *acts through microtubules* [167]; *anesthetics also act through MTs* [86].
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* [168].

Microtubules communicate by cooperative dynamics

4. Coherent gigahertz excitations will be found in microtubules. *Indeed; in some remarkable new research, Anirban Bandyopadhyay's group has found coherent gigahertz, megahertz and kilohertz excitations in single MTs* [88,89].
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* [127].
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*) 6 *information bits to* 6 *tubulins in a microtubule lattice*.
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* [142].

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* [88,89]*, 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* [156–158]*. Bandyopadhyay has preliminary evidence that MTs can shift between A- and B-lattice configurations* [142]*, 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* [88,89].

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 interweave the entire cortex.

14. Electrotonic gap junctions synchronize neurons. *Gap junction interneurons do appear to mediate gamma synchrony EEG* [49–54].
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* [142]*, so gap junctions may be unnecessary for Orch OR*.

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 estimate 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* (*Section* 3.2 [76,77]).

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* [108]*, 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 early Cambrian (540 million years ago), had sufficient microtubule capacity for OR by $\tau \approx \hbar/\boldsymbol{E}_G$ 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* [56].

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.

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 spiritual quality of the universe, distinct from purely physical actions, and (C) as composed of discrete 'proto-conscious' 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 a particular such 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 time scale 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 be a moment of *proto-consciousness*. These events would be thought of as the elemental constituents of 'subjective experience', or qualia, 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 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.

In the version of the DP proposal put forward in [92–95] it was, technically speaking, a (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 (Section 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 that appear 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 $\boldsymbol{E_G}$) 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 structures such as microtubules, within which OR events could be 'orchestrated', enabling functional quantum computing in isolated non-polar 'aromatic' channels 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 40 Hz 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 Alfred North Whitehead [10,11] 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. Abner Shimony [169], Henry Stapp [170] 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 might 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 to 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 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 Section 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^{-8} s 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 Section 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} s, or the tens of kilohertz resonance they found suggesting 10^{-4} s—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 ridiculously 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 [171, 172]). 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, 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 and Tipler [173]), 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 [174], Gurzadyan and Penrose [175]) 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 [176] 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.

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 'objective reduction' (OR) of a quantum state (according to the DP scheme), where it is taken that these quantum states exist as parts of a 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 there is between the two states. In our own brains, the OR process that evoke 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.

Cell and molecular biology

- Tubulin information states in Orch OR quantum and classical computation are now correlated with dipoles, rather than mechanical conformation, avoiding heat and energy issues.
- Tubulin dipoles mediating computation and entanglement may be electric (London force charge separation), or magnetic (electron 'spin' states and currents), as presented in this paper.
- Enhanced electronic conductance discovered by Anirban Bandyopadhyay's group [88,89] in single microtubules at warm temperature at specific alternating current gigahertz, megahertz and kilohertz frequencies ('Bandyopadhyay coherence', 'BC') strongly supports Orch OR.
- BC and Orch OR may well be mediated through intra-tubulin quantum channels of aromatic rings, like in photosynthesis proteins, plausibly for quantum computing in microtubules.
- Anesthetics bind in these tubulin quantum channels, presumably to disperse quantum dipoles necessary for consciousness.

Brain science

- Alzheimer's disease, brain trauma and other disorders are related to microtubule disturbances; promising therapies are being aimed at BC in the brain.
- Scale invariant (1/f, 'fractal-like') processes at neuronal and network levels might perhaps extend downward to intra-neuronal BC in microtubules, e.g. megahertz excitations.
- Orch OR conscious moments, e.g. at 40 Hz, are now viewed as 'beat frequencies' of BC megahertz in MTs, the slower beat frequencies coupled to neuronal membrane physiology and accounting for EEG correlates of consciousness.

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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