6 Consciousness, Neurobiology and Quantum Mechanics: The Case for a Connection

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Summary. Consciousness is generally considered to emerge from synaptic computation among brain neurons, but this approach cannot account for its critical features. The Penrose–Hameroff "Orch OR" model suggests that consciousness is a sequence of quantum computations in microtubules within brain neurons, shielded from decoherence to reach threshold for objective reduction (OR), the Penrose quantum gravity solution to the measurement problem. The quantum computations are "orchestrated" by neuronal/synaptic inputs (hence "Orch OR"), and extend throughout cortex by tunneling through gap junctions. Each Orch OR is proposed as a conscious event, akin to Whitehead's philosophical "occasion of experience", occurring in concert with brain electrophysiology. This chapter discusses the need for such an approach and its neurobiological requirements.

6.1 Introduction: The Problems of Consciousness

Consciousness involves phenomenal experience, self-awareness, feelings, choices, control of actions, a model of the world, etc. But what is it? Is consciousness something specific, or merely a byproduct of information processing? Whatever it is, consciousness is a multifaceted puzzle. Despite enormous strides in behavioral and brain science, essential features of consciousness continue to elude explanation. Unresolved problems include:

1. Neural correlates of conscious perception apparently occur too late – 150 to 500 milliseconds (ms) after impingement on our sense organs – to have causal efficacy in seemingly conscious perceptions and willful actions, often initiated or completed within 100 ms after sensory impingement. For example, in the color phi and cutaneous rabbit anomalies, the brain apparently fills in conscious sensory information that is not yet available [130, 71, 40]. Preparation of speech can precede conscious identification of heard words to which one is responding [247, 248, 241]. And in tennis, specific movements to return a fast-moving ball precede conscious identification of ball location and trajectory [157, 81].[1] Nonetheless, sub-

[1] Visual information apparently flows from V1 in two streams [239, 160]. The dorsal stream from V1 to posterior parietal cortex is thought to provide visual

jectively (i. e. we feel as though) we consciously perceive and respond to these perceptions (e. g. [247, 81, 129]).
2. How does the brain provide binding: fusion of a) aspects in one modality (e. g. visual shape, color and motion), b) different modalities (e. g. sight and sound), c) temporal binding of synchronous events sensed asynchronously (e. g. sight and touch) and d) allocentric (simulated external world), egocentric (personal point of view) and enteroceptive (bodily sensation) spaces into unified conscious moments [81]?
3. Electrophysiological correlates of consciousness and attention (e. g. gamma EEG/coherent 40 Hz) may be incompatible with the presumed neural-level correlate of consciousness–trains of axonal action potentials (spikes) – and network-level correlate of consciousness – Hebbian assemblies of axonal-dendritic neurotransmitter-mediated synaptic networks.
4. The vast majority of brain activity is nonconscious. What distinguishes nonconscious activity from consciousness?
5. The hard problem: how does the brain produce qualia, the raw components of phenomenal experience – the smell of a rose, the felt qualities of emotions and the experience of a stream of conscious thought? Why is there conscious experience associated with the brain at all (e. g. [28])?

Prevalent approaches assume that consciousness arises from information processing in the brain, with the level of relevant detail varying among philosophical stances. Generally, all-or-none firings of axonal action potentials (spikes) are seen as the fundamental currency of brain function and equated to roles performed by unitary information states and switches in computers [31]. Consciousness is said to emerge from complex computation: nonlinear dynamics of axonal-dendritic neuronal networks sculpted by modulation of spike-mediated chemical synapses (Hebbian assemblies) form metastable patterns – attractors – identified with conscious experience (e. g. [198, 55, 56]).

I will refer to all contemporary approaches (perhaps unfairly) as classical functionalism. The implication is that if a robot were precisely constructed to mimic the brain activities that orthodox neuroscience assumes to be relevant to consciousness and perform functions that in a human being are associated with consciousness, then the robot would be conscious regardless of the material from which it was made.

Classical functionalist explanations of the problems stated above are (roughly):

1. Near-immediate conscious perception and volition are illusions; nonconscious processes initiate many actions (e. g. [247, 128, 256]).

information for online, nonconscious control of many kinds of actions. This pragmatic representation for immediate goal-directed behavior is created faster than the ventral stream semantic representation that corresponds with consciousness. The assumption is that the brain creates an illusion of conscious control of such dorsal stream-mediated actions.

2. Binding, e. g. temporal binding in Dennett's [39] multiple drafts model, results from edited memory, rather than real-time unified conscious perception.
3. Electrophysiological activities measured from scalp, brain surface or within brain extracellular spaces (e. g. gamma EEG/coherent 40 Hz, Sect. 6.3.4) that seem to correlate with cognition and consciousness are discredited, apparently because axonal spikes fail to account for synchrony [204, 34].
4. Nonconscious processes compete, with the content of the most active (or optimally synchronized) neuronal groups winning to gain consciousness (e. g. [39]).
5. Conscious experience is an emergent property of functional information processing (e. g. [198, 55]).

Consequently, classical functionalism deconstructs consciousness into an out-of-the-loop, after-the-fact illusory set of epiphenomena.[2] While this might prove true, the view is a default position due to lack of credible alternative and (I will argue) faulty assumptions. Neuronal activities presumed to be relevant are tailored to fit the computer analogy, omit essential neurobiological ingredients and miss the target[3]. Specifically, I will argue that axonal spikes and chemical synaptic transmissions are not the primary currency of consciousness, that electrophysiological correlates of consciousness derive from dendritic activities linked by window-like gap junctions, that glia are involved and that quantum processes in intradendritic cytoskeletal microtubules are the actual substrate for consciousness.

Twelve years ago Roger Penrose and I put forth a model called orchestrated objective reduction (Orch OR) based on quantum computation in cytoskeletal microtubules inside the brain's neurons[4] [174, 89–92, 264]. Orch OR has been viewed skeptically by mainstream scientists and philosophers. One apparently valid reason to discount Orch OR is that technological quan-

[2] Epiphenomenal in this case refers to the type of immediate actions that may be reflexive (e. g. dorsal stream-mediated) but seem conscious to the one performing them. Those who ascribe such actions to nonconscious activities (e. g. [129, 81, 142]) argue that consciousness plays important causal roles in other functions, e. g. veto, comparisons and longer-term planning and behaviors.

[3] Some scientists and philosophers do consider finer-grained details. For example, Koch [129] raises the issue of intracellular calcium ions in the context of the neural correlate of consciousness, but maintains that axonal spike are the primary medium. Chalmers [28] points out that even if the precise activity and state of every receptor, ion and molecule in the brain were known, the cause of conscious experience would not be explained. However, I will argue that certain types of organized quantum processes in the brain can account for conscious experience based on a Whiteheadian pan-protopsychist philosophy tied to modern physics.

[4] The original motivation put forth by Penrose [170, 171] was based on noncomputability (i. e. nonalgorithmic processes) of human thoughts and choices, as argued through Gödel's theorem.

tum computation is designed to occur in isolation at extremely low temperatures to avoid decoherence – disruption of seemingly fragile quantum states by thermal/environmental interactions. Thus quantum computing at brain temperature in an apparently liquid medium appears impossible. However, quantum processes in biological molecules not only occur, but are enhanced at higher temperature [167]. Furthermore, the neuronal interior can exist in an isolated, nonliquid gelatinous ordered state ([179], Sect. 6.5.2). Another objection – that quantum states inside one neuron could not extend to others across cellular boundaries – prompted the suggestion that quantum tunneling through window-like gap junctions (which essentially fuse neurons into hyperneurons, Sect. 6.3.5) could enable such extension. Gap-junction networks are now shown to be widely prevalent in the brain and to mediate gamma EEG/coherent 40-Hz neuronal activity, the best electrophysiological correlate of consciousness (Sect. 6.3.4). Finally, Orch OR has been discounted because it differs so markedly from conventional approaches, despite 1) the lack of progress by conventional explanations, and 2) Orch OR being perfectly consistent with neurobiology. Ten years after, known neurobiology has moved toward Orch OR.

In this chapter connections among consciousness, neurobiology and quantum mechanics are proposed. They are previewed here:

Consciousness and neurobiology (Sect. 6.3): Consciousness occurs in dendrites of cortical neurons interconnected by gap junctions, forming Hebbian "hyperneurons". Chemical synapses and axonal spikes convey inputs to, and outputs from, conscious processes in hyperneuron dendrites, consistent with gamma EEG/coherent 40 Hz and the postsynaptic mechanism of general anesthesia. The molecular correlate of consciousness is the intradendritic cytoskeleton, specifically microtubules and related proteins whose information processing triggers axonal spikes and regulates synapses.

Neurobiology and quantum mechanics: Quantum superposition, entanglement and other effects (Sects. 6.4.3 and 6.4.4) are considered to wash out at supramolecular levels due to environmental interactions (decoherence). However, certain proteins act as quantum levers whose functional conformational states are governed by weak quantum forces. Such proteins mediate effects of anesthetic gases that impair the quantum forces, erasing consciousness, while sparing other brain activities. Thus, only proteins directly involved in consciousness are quantum levers (which can function as quantum bits, or qubits in quantum computation). Evidence suggests that mechanisms have evolved to counter decoherence and enable large-scale quantum states in the brain at 37.6 ℃.

Quantum mechanics and consciousness (Sect. 6.5.1): The conscious observer has been implicated in quantum mechanics since its inception. Experiments show that quantum superpositions (particles/systems existing in multiple states or locations simultaneously, governed by a quantum wave function) persist until measured or observed, then reduce/collapse to definite states and

locations. Interpretations vary: in one form of the Copenhagen interpretation the conscious observer causes collapse/reduction of quantum superpositions, placing consciousness outside physics. David Bohm (e. g. [20]) proposed that the wave function contains active information that guides the movement of particles, and that consciousness was associated with active information. Like Bohm, the multiple-worlds hypothesis [50] avoids collapse/reduction but requires an infinity of minds for each individual[5]. Decoherence theory avoids isolated superpositions (and consciousness). Henry Stapp's view [221] identifies consciousness with collapse/reduction but doesn't specify a cause or distinction. The objective reduction (OR) of Roger Penrose identifies consciousness with collapse/reduction, specifies a cause and threshold, and connects consciousness to fundamental space-time geometry, introducing mechanisms for noncomputable Platonic influences and protoconscious qualia. And like Stapp's view, Penrose OR connects to Whitehead's philosophical approach to consciousness.

We begin with a consideration of the timing of conscious experience.

6.2 Time and Consciousness

6.2.1 Is Consciousness Continuous or a Sequence of Discrete Events?

William James [112] initially considered consciousness as a sequence of specious moments but then embraced a continuous stream of consciousness. Alfred North Whitehead [257, 258] portrayed consciousness as a sequence of discrete events: occasions of experience. As motion pictures – in which sequential frames are perceived as continuous – became increasingly popular, so did the notion of consciousness as discrete events, e. g. the perceptual moment theory of Stroud [205, 224]. Evidence in recent years suggests periodicities for perception and reaction times in the range of 20 to 50 ms (gamma EEG) and another in the range of hundreds of ms (alpha and theta EEG), the latter consistent with saccades and the visual gestalt [242, 243]. Based on a proposal for memory by Lisman and Idiart [145], VanRullen and Koch [242] suggested a multiplex for visual perception in which a series of fast gamma waves (each corresponding to specific components of vision) rides on a slower, e. g. theta wave (corresponding to an integrated visual perception). A similar, previous model of gamma/theta complex waves supporting quantum mechanisms underlying conscious vision [264] will be discussed in Sect. 6.8.1. Freeman [57] has shown cinematographic effects in neural excitations in the brain, supporting the notion of discrete conscious frames.

If consciousness is a sequence of events, what is its rate or frequency? Can it vary? In the midst of a car accident, victims often report that time

[5] Or a single universal mind. See Squires [219].

seems to slow down. Does this excited state involve an actual increase in the rate of subjective conscious moments per objective time? What *are* conscious moments, why are they subjective and how do they relate to neurobiology?

6.2.2 The Timing of Conscious Experience

Many behaviors apparently happen too quickly to be initiated by consciousness. Max Velmans [247] lists examples: analysis of sensory inputs and their emotional content, phonological and semantic analysis of heard speech and preparation of one's own spoken words and sentences, learning and formation of memories, and choice, planning and execution of voluntary acts. Consequently, subjective feeling of conscious control of these behaviors is deemed illusory [256].

In speech, evoked potentials indicating conscious word recognition occur at about 400 ms after auditory input, however, semantic meaning is appreciated (and response initiated) after only 200 ms. As Velmans points out, only two phonemes are heard by 200 ms, and an average of 87 words share their first two phonemes. Even when contextual effects are considered, semantic processing and initiation of response occurs before conscious recognition [241].

Jeffrey Gray [81] observes that in tennis "The speed of the ball after a serve is so great, and the distance over which it has to travel so short, that the player who receives the serve must strike it back before he has had time consciously to see the ball leave the server's racket. Conscious awareness comes too late to affect his stroke". John McCrone [157]: "[for] tennis players... facing a fast serve ... even if awareness were actually instant, it would still not be fast enough ..."

Visual recognition of an object's shape, color, motion and semantic meaning occur in different parts of visual cortex, and at different times [270, 269]. Yet we consciously perceive these features simultaneously (the temporal binding problem).

Touch also involves temporal binding. If you tap your foot with your finger, the foot and finger sensations occur simultaneously. Yet the sensory signal from your foot requires significantly longer to reach sensory cortex than does that from your finger. How does the brain provide synchrony?

In the cutaneous rabbit experiment [71, 72] a subject's arm is mechanically "tapped" at three locations along the arm, e. g. 5 taps at the wrist followed by 2 at the elbow then 3 more on the upper arm. However, subjects report a regular sequence of taps traveling in equidistant increments, as if a small animal were hopping along their arm. The "departure" from the wrist begins with the second tap, yet if the upper taps are not delivered, all 5 wrist taps are felt at the wrist. It is as if the brain knows in advance there will be (or not be) taps further along the arm.

In the "color phi" effect [130] a red spot appears briefly on the left side of a screen, followed after a pause by a green spot on the right side. Ob-

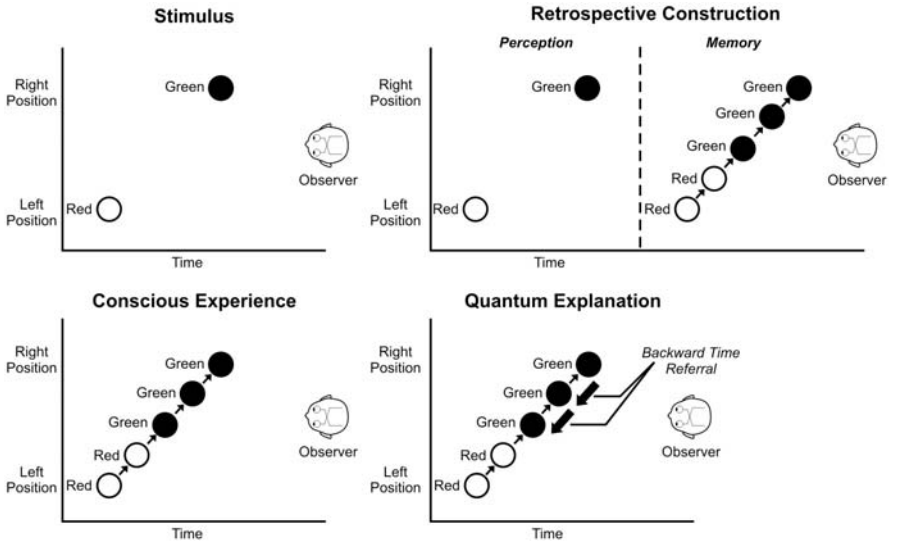

Fig. 6.1. The "color phi" phenomenon [130]. *Top left*: an observer views a screen on which a red circle appears on the left, disappears, and then a green circle appears on the right. *Bottom left*: the observer's conscious (reported) experience is of a red circle moving from left to right, changing to green half-way across. *Upper right*: the retrospective construction explanation is that the observer's real time perception is of two separate circles, subsequently revised and recorded in (delayed) memory as the red circle moving and changing to green half-way across. *Bottom right*: Quantum explanation in which the brain sends subconscious quantum information backward in time, filling in the red circle changing to green half-way across

servers report one spot moving back and forth, changing color half-way across (Fig. 6.1). Does the brain know in advance to which color the dot will change?

Perhaps the most perplexing experiments regarding time and mental events were done by Benjamin Libet and colleagues in the 1960s and 1970s. They studied awake, cooperative patients undergoing brain surgery with local anesthesia so that the patients' brains were exposed (e. g. [136, 138, 142]). In these patients Libet was able to access, identify, record from and stimulate specific areas of somatosensory cortex (postcentral gyrus) corresponding to the skin of each patient's hand (Fig. 6.2). He found that direct electrical stimulation of the somatosensory "hand" area of cortex resulted in brain electrical activity (DCR: direct cortical response due to neuronal dendritic activity). This in turn caused conscious sensation referred to the hand, but only after a train of threshold-level pulses (and DCR activity) lasting about 500 ms. This requirement of ongoing, prolonged electrical activity from direct cortical stimulation to produce conscious experience ("Libet's 500 ms") was confirmed by Amassian et al. [5], Ray et al. [187], Pollen [180] and others.

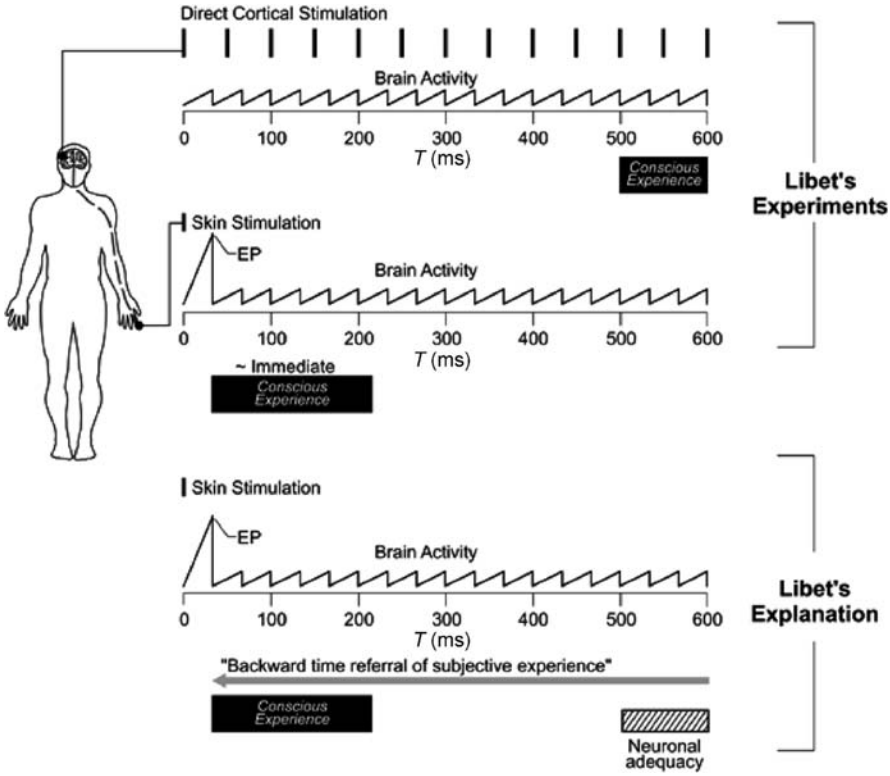

Fig. 6.2. Libet's experiments and explanation [138, 142]. Patient (*left*) was accessed 1) at hand area of somatosensory cortex, and 2) skin of corresponding hand. *Top*: Direct cortical stimulation of electrical pulses every 50 ms caused cortical brain activity that was required to proceed for 500 ms to cause conscious experience of a sensation in the hand. *Middle*: Single pulse to the skin of the hand caused primary evoked potential (EP) after 10 to 30 ms and ongoing brain activity for at least 500 ms. Conscious experience occurred concomitant with primary EP. *Bottom*: Libet's explanation – 500-ms ongoing activity required for neuronal adequacy, which refers subjective experience backward in time to the primary EP

But what about normal sensory perception? Single, threshold-level stimuli to the hand or elsewhere are seemingly perceived consciously almost immediately; no 500-ms delay occurs when we touch something. In the brain somatosensory cortex, threshold level stimuli at the skin of the hand cause a primary evoked potential (EP) 10 to 30 ms after skin stimulation, followed by ongoing activity of several hundreds of ms, very much like Libet's DCR.

But the primary EP is not sufficient for conscious experience:

- A single stimulus delivered to subcortical brain regions in the sensory pathway causes a primary EP without conscious experience or prolonged activity [139, 113][6].
- Subthreshold skin stimulation causes a primary EP, but no prolonged cortical activity nor conscious experience.
- Under general anesthesia, skin stimulation of any kind can cause a primary EP but no ongoing cortical activity nor conscious experience.
- On the contrary, prolonged cortical activity ("Libet's 500 ms") is both necessary and sufficient for conscious experience, but in the absence of a primary EP produces only delayed conscious experience.
- Libet's DCR patients (also Amassian et al. [5], Ray et al. [187]) had 500-ms delayed conscious experience of skin stimulation without a primary EP caused by a train of pulses delivered to the cortex. Pollen [180] showed a similar delay with visual phosphenes after occipital cortex stimulation.

Libet's conclusion was that the 500-ms prolonged cortical activity is the *sine qua non* for conscious experience – the NCC, or neural correlate of consciousness. The primary EP is necessary (but not sufficient) for near-immediate conscious experience[7]. Primary EP and prolonged activity together produce near-immediate conscious experience.

But if the neural correlate of conscious experience is delayed for 500 ms, how/why do we seem to perceive sensory events almost immediately? Are we living in the past, but remembering (falsely) being in the here and now, as Dennett suggests (next section)? To address the question, Libet and colleagues proposed and tested a rather outrageous hypothesis – that the perception of a stimulus was indeed delayed for 500 ms of brain activity but subjectively referred backward in time to the primary evoked potential 10 to 30 ms after stimulus.

Experiments were performed in which patients received both direct cortical stimulation of the hand area and stimulation of the actual skin of the hand. Although both were perceived in the hand, the two were qualitatively different so the subjects could distinguish them. Stimulation of the two sites were given in close, but varying temporal proximity (i. e. within one second), and the patients asked which stimulus was felt first. The patients reported that the sensations generated at the skin appeared before the cortically induced sensation, even when the skin pulse was delayed by some hundreds of ms after the start of the cortical stimulation. Only when the skin pulse

[6] Repetitive subcortical stimulation does cause a primary EP, prolonged activity and conscious experience.

[7] Libet contended that the duration per se of the pulse train and DCR was the critical factor in reaching threshold for consciousness, and that the delay was useful for psychic modification. Freud and many others have recognized that conscious experience may differ from raw sensory perception (or be repressed entirely). The delay would permit such modification (e. g. retrospective construction – Sect. 6.2.3).

was delayed for about 500 ms after the cortical stimulation did the subjects report feeling the two stimuli simultaneously. The skin-induced experience appeared to have no delay. The cortically induced experience was delayed 500 ms relative to the skin-induced sensation.

So both skin-induced and cortically-induced sensations required 500 ms of cortical processing, but the skin-induced sensation was experienced almost immediately. Unlike the cortically-induced experience the skin-induced sensation was marked by a primary EP. Was that the difference?

To investigate this question, Libet also studied patients with electrodes implanted (for therapeutic purposes) in the medial lemniscus below the thalamus, i. e. in the brain's sensory pathway en route from hand to cortex. He determined that stimulation of the medial lemniscus could produce a conscious experience only after 500 ms of stimulation and cortical activity. But unlike direct cortical stimulation (and like skin stimulation) medial lemniscus stimulation caused primary EPs. Libet and his colleagues then performed another set of experiments comparing stimulation of the hand with stimulation of medial lemniscus, coupling the two stimuli at varying time intervals. They found no delay of the medial lemniscus stimuli compared to skin stimuli. But the patients felt nothing if medial lemniscus stimulation was interrupted prior to the full 500-ms stimulation. So prolonged cortical activity was necessary for conscious experience, and the primary EP was necessary for near-immediate subjective experience.

Libet came to the following conclusions:

- Conscious perception requires brain activity for 500 ms to achieve neuronal adequacy.
- Information is referred up to 500 ms backward in time to the primary evoked potential – 10 to 30 ms after peripheral stimulation – for near-immediate conscious perception.

Libet's results and conclusions have been repeatedly challenged but never refuted [140, 141][8].

6.2.3 Taking Backward Time Referral Seriously

How do we resolve these temporal anomalies? The color phi effects apparently "... leave us a choice between a retrospective construction theory and a belief in clairvoyance" [76].

Daniel Dennett [39, 40] chose retrospective construction in the context of a multiple drafts model in which sensory inputs and cognitive processing

[8] For example Pockett [177], Breitmeyer [22], Pollen [180] and others argued that some type of facilitated buildup, or inhibition followed by excitation delayed the onset of effective cortical activity until late in the 500 ms, suggesting the delay in conscious experience was artifactual. However, Libet [140, 141] successfully rebutted these contentions and defended his results and conclusions.

produce tentative contents under continual revision. A definitive, final edition is inserted into memory, overriding previous drafts. A key feature is that consciousness (e. g. of a particular perception) occurs not at any one specific moment, but arbitrarily in time, like the onset of fame, or end of a war. The brain retrospectively creates content or judgment, e. g. of intervening movement in the color phi experiment[9].

According to retrospective construction (I presume): 1) tennis players see and hit balls unconsciously, but remember seeing and hitting consciously.[10] 2) Sensory components of objects or events are perceived asynchronously but remembered as being synchronous. 3) In the cutaneous rabbit experiment, the subjects feel wrist taps, then elbow taps, then upper arm taps, but remember a sequence of evenly spaced taps. 4) In the color phi phenomenon the observer sees the left-side red spot, then the right-side green spot, but remembers the red spot moving and changing colors midstream.

Thus according to Dennett and many others, smooth, real-time conscious experience is an edited construction – an illusion. Dennett and Kinsbourne [40] have a more difficult time dispensing with Libet's findings, describing them as "interesting but inconclusive".

Libet performed other experiments related to volition. Kornhuber and Deecke [131] had recorded over premotor cortex in subjects who were asked to move their finger randomly, at no prescribed time. They found that electrical activity preceded finger movement by 800 ms, calling this activity the readiness potential. Libet et al. [143] repeated the experiment except they also asked subjects to note precisely when they consciously decided to move their finger. This decision came approximately 200 ms before movement, hundreds of ms after onset of the readiness potential. Libet concluded that many seemingly conscious actions are initiated by nonconscious processes.

Libet didn't consider backwards referral in volition because antedating in his sensory experiments was pinned to the primary sensory EP, and no such marker existed in the spontaneous finger movement experiments. However,

[9] Dennett describes two possible methods of disinformation the brain might utilize in resolving temporal anomalies. The first is the Stalinesque show trial, in which the brain modifies sensory information before it reaches consciousness. For example, in the color phi experiment the red spot and the green spot are unconsciously perceived, and interstitial moving spots that change midway are inserted before the sequence reaches consciousness. In Orwellian revisionism, both the red spot and green spot are consciously perceived, but intervening movement and color change are inserted into the final draft for memory. Dennett claims that because of the arbitrary timing in multiple drafts, no distinction between the two methods need be made. However, if the time factor in consciousness is not arbitrary, Dennett's choice of retrospective construction becomes equivalent to Orwellian revisionism.

[10] The actual contact of ball against racket or bat is rarely, if ever, seen. I am referring to conscious recognition of the ball, its approach and initiation of the stroke or swing.

voluntary acts in response to stimuli (hitting a ball, choosing a word in a sentence) do have such markers, as would binding of temporally asynchronous perceptual components of synchronous events. Nor did Libet consider backward referral as implying an actual reversal in time, but a phenomenon akin to retrospective construction. Libet [137, p.7] says:

> "...the timing of a sensation is subjectively referred...not that the conscious sensation itself jumped backwards in time...the content of the subjective experience...is modified by the referral to the earlier timing signal."

But consciousness lagging a half second behind reality would render it largely epiphenomenal (and illusory)[11]. We would be (in the words of T.H. Huxley) "helpless spectators". Perception would be a jangle of disconnected events edited for memory, too late for conscious control of many seemingly conscious actions. Perhaps so, but is there a possible alternative?

Yes. To account for Libet's results, Roger Penrose ([170], cf. [259]) suggested that the brain sends unconscious quantum information backward through time. In the quantum world, time is symmetrical, or bidirectional (as it also appears to be in unconscious dreams – Sect. 6.6)[12]. Aharonov and Vaidman [1] proposed that quantum-state reductions send quantum information backward in time; backward time referral is the only apparent explanation for experimentally observed EPR effects in quantum entanglement (Fig. 6.3, Sect. 6.5.1, Penrose [173], cf. [15]).

Quantum information cannot actually convey information, and is thus a misnomer (Penrose now calls it "quanglement" because of its role in quantum entanglement). Quanglement can only modify classical information, but mere modification is highly significant in EPR experiments and quantum technology (Sect. 6.5). Quantum information/quanglement going backward in classical time is also constrained by possible causality violations, i. e. causing an observable change resulting in a paradox like going back in time to kill your ancestor, thereby preventing your birth. Any effect that could be even possibly measured or observed may be prohibited. However, nonconscious backward referral of quantum information/quanglement that modifies existing information in the brain at the moment of consciousness (e. g. adding qualia to primary evoked potentials, influencing choices) would not violate causality because the effects are unobservable before they occur.[13]

[11] Gray [81] suggests that consciousness serves a longer-term review and planning function, and Libet [142] suggests a veto role for consciousness. Thus consciousness would not be useless. But in terms of real-time executive actions, consciousness would indeed be epiphenomenal.

[12] The second law of thermodynamics may not operate in the quantum world.

[13] The problem of qualia has been framed in the well-known "knowledge argument" put forth by philosopher Frank Jackson [111]. He described a hypothetical color-blind visual neuroscientist named Mary who knew all facts related to color vision but had never experienced color. If Mary then received a retinal

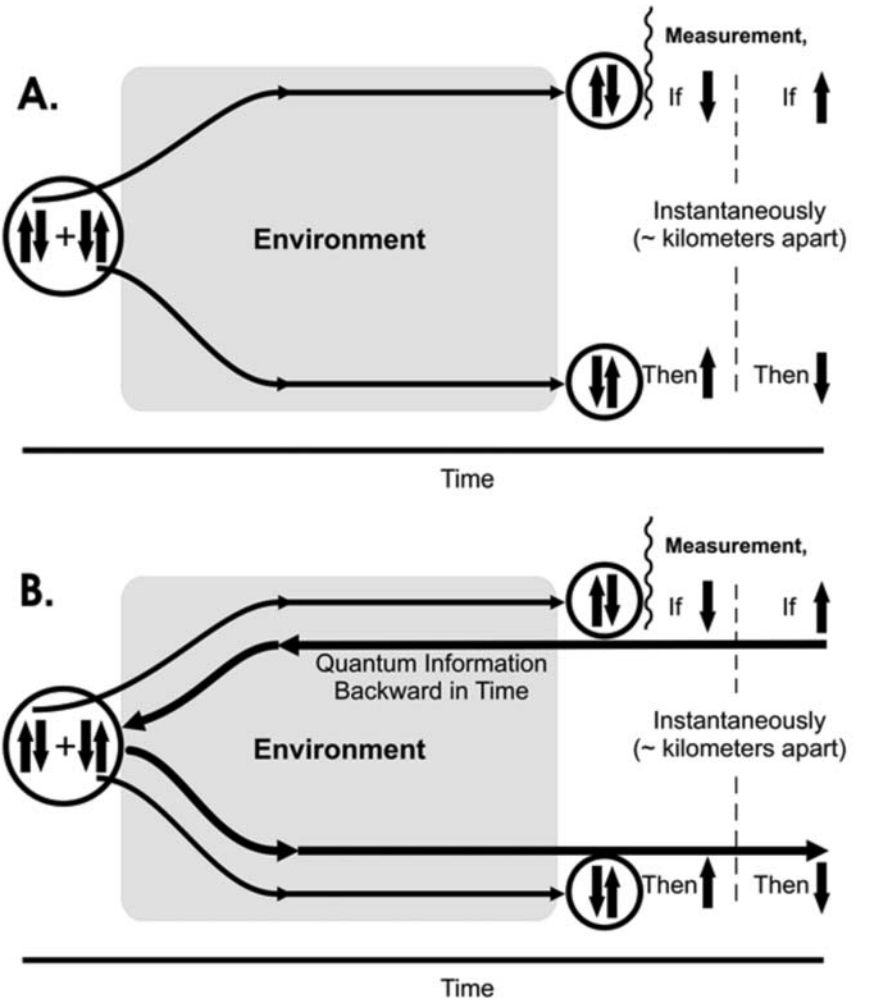

Fig. 6.3. Backward time in the EPR effect. A. The Einstein–Podolsky–Rosen (EPR) experiment verified by Aspect et al. [10], Tittel et al. [232] and many others. On the left is an isolated entangled pair of superpositioned complementary quantum particles, e. g. two electrons in spin-up and spin-down states. The pair is separated and sent (through environment but unmeasured) to different locations/measuring devices kilometers apart. The single electron at the top (in superposition of both spin-up and spin-down states) is measured, and reduces to a single classical state (e. g. spin-down). Instantaneously, its complementary twin kilometers away reduces to the complementary state of spin-up (or vice versa). The effect is instantaneous over significant distance, hence appears to be transmitted faster than the speed of light. B. The explanation according to Penrose ([173], cf. [15]) is that measurement/reduction of the electron at the top sends quantum information backward in time to the origin of the unified entanglement, then forward to the twin electron. No other reasonable explanation has been put forth

Backward time referral of unconscious quantum information/quanglement in the brain could provide temporal binding and near-immediate perception and volition, rescuing consciousness from illusory epiphenomenon (i. e. enabling near-immediate conscious decisions based on sensory information referred from the near future). How this could actually happen will be discussed in Sect. 6.7, but we next turn to where it could happen – the neural correlate of consciousness.

6.3 The Neural Correlate of Consciousness

6.3.1 Functional Organization of the Brain

Most brain activities are nonconscious; consciousness is a mere "tip of the iceberg" of neural functions. Many brain activities – e. g. brainstem-mediated autonomic functions – never enter consciousness. While consciousness is erased during general anesthesia, nonconscious brain EEG and evoked potentials continue, although reduced.[14]

Functional units corresponding to particular mental states are generally considered as networks or assemblies of neurons, originally described by Donald Hebb ([100], see also [199]). Hebb described assemblies as closed causal loops of neurons that could be ignited by particular inputs and remain active for hundreds of ms, following which another related assembly would ignite, then another and so on in a phase sequence. Hebb described assemblies as "three-dimensional fishnets" of many thousands of neurons. At any one time a single particular assembly would be the neural correlate of consciousness (NCC).

Why would a particular assembly be conscious? Dennett's multiple-drafts model proposes, as does Susan Greenfield's [82] epicenter model, that brain

transplant, or gene therapy or brain implant to gain color vision, would she be acquiring new facts about color? If so, qualia are facts and no different from information in a computer (as materialists so argue). But quantum information/quanglement could modify the nonconscious (nonqualia) facts/information about color in Mary's brain to provide the phenomenal experience of color while not conveying classical information. Thus, qualia as quanglement avoids causality violation and can defeat the materialist interpretation of the knowledge argument.

[14] There are unfortunate cases of intraoperative awareness. There can also be implicit learning/memory during light anesthesia. Some authors have conflated these two situations to suggest that anesthesia involves awareness with amnesia, not loss of consciousness. Because consciousness is unobservable there is no absolute resolution of this question. However, there is no reason to believe that intraoperative awareness occurs except during rare instances due to inadequate anesthesia. Clinical signs of pain/awareness (pupillary size, heart rate and blood pressure, lacrimation, diaphoresis, mucus secretion, EEG power spectrum/40 Hz, etc.) are used to indicate adequate anesthesia and lack of consciousness.

activity accompanying consciousness is the same in kind as unconscious brain activity, except more so. Regardless of location, if activity of a neural assembly representing a specific set of content exceeds all other in some type of competition, it takes the prize of entering into consciousness.

The precise neural activity accompanying consciousness remains to be elucidated. Global workspace theory describes *where* it is likely to occur: multiple specialized brain areas interconnected in a coordinated, though variable manner. Bernie Baars [12] introduced the concept that was elaborated anatomically by Changeux and Dehaene [29] (see also [38]). Crick and Koch [33], and Edelman and Tononi [48] have similar approaches.

Global workspace describes a horizontal layer of interconnected cortical neurons sandwiched between ascending, bottom-up inputs from thalamus and basal forebrain, and top-down executive functions from prefrontal cortex.[15] Bottom-up inputs convey sensory information, as well as general arousal and highlighted saliency such as emotional context from basal forebrain inputs [261, 263]. Top-down influences categorize and manipulate unexpected features [129], e. g. those associated with danger, reward, etc. Acting together, bottom-up and top-down activations select a neural assembly – a specific subset of cortical-cortical projections – for attention and consciousness, prompting sufficient activity for the assembly to become the NCC. Over time, the NCC and its contents change with dynamically shifting, temporary alliances of neurons and assembly makeup. Global workspace models demonstrate a functional architecture that could accommodate consciousness.

Placing consciousness between bottom-up and top-down neuronal pathways agrees with Ray Jackendoff's [110] intermediate level theory, which notes we are not normally aware of pure sensation, nor of pure conceptual structures, but an optimized admixture of the two. The intermediate level is also consistent with Jeffrey Gray's [79, 80] comparator hypothesis in which consciousness is the output of a process that compares available (e. g. incoming, bottom up) information against anticipatory (executive, top down) schemata.

Evidence from vision supports both Jackendoff's contention and the global workspace theory. Visual inputs synapse in thalamus and project raw data mostly to primary visual area V1 in the posterior occipital cortex. V1 then sends information forward to other regions of visual cortex[16], e. g. V2, where shape and contour are recognized, V4, where color is perceived and V5, where motion is detected. These and other secondary visual areas project to prefrontal cortex for categorization and planning. Prefrontal cortex then projects back toward V1 and other visual areas. Crick and Koch [34] have argued the NCC of vision lies not in V1 or prefrontal cortex but in intermediate areas. In Jackendoff's terms, V1 houses "pure sensation unaffected by conceptual in-

[15] Some accounts include thalamocortical projections as part of the workspace, and parietal cortex in the top-down influences. Also, top-down influences from prefrontal or parietal cortex may loop through the thalamus.

[16] Apparently in two streams: See Footnote 1.

terpretation". Visual consciousness occurs in the middle–shifting assemblies of cortical-cortical projections sandwiched between (but possibly including) V1 and prefrontal cortex.

However, Zeki [268] has shown that excessive activity in any feature-selective region may be sufficient on its own for that feature to enter consciousness. Thus, activity in V4 alone can result in the experience of color.

Other NCC candidates include the hippocampus in Jeffrey Gray's comparator hypothesis, and the brainstem in Antonio Damasio's [35] and Jaak Panksepp's [168] separate views of emotional core consciousness. Thus, while consciousness occurs generally in what is termed a global workspace, it may also arise in more localized and perhaps separate regions. The question remains how/why consciousness arises in any region. What aspect of neural activity gives rise to consciousness?

6.3.2 Cerebral Cortex and Neuronal Assemblies

Cerebral cortex is hierarchical in two different ways [129]. Microscopically, layer 4 receives primary sensory inputs from the thalamus and is thus on the bottom. Geography aside, layers 1–3 and 6 are more or less in the middle. In layer 5 giant pyramidal cells (which convey the verdicts of cortical processing to subcortical regions) are at the top of the hierarchy. This arrangement is nested in a larger-scale anatomical hierarchy with primary sensory areas (such as V1 for vision) at the bottom, and prefrontal executive cortex at the top. Consistent with Jackendoff's intermediate theory, shifting assemblies of many types of neurons sandwiched throughout numerous cortical regions appear to act as the NCC.

Particular Hebbian assemblies may be formed and strengthened primarily by alterations in dendritic morphology leading to enhanced synaptic activity and lowered threshold for specific circuits. Assemblies sculpted by postsynaptic changes – synaptic plasticity – are the cornerstone of theoretical mechanisms for learning, memory and the NCC. The mechanisms of plasticity include altered number, sensitivity and clustering of postsynaptic receptors, optimal geometry of dendritic spines and branchings, dendro-dendritic connections, and changes in decremental conductance of postsynaptic potentials (e. g. Hausser et al. [98]). All these changes are mediated by structures within neuronal dendritic interiors, namely the cytoskeleton (e. g. Dayhoff [37]).

6.3.3 Axons and Dendrites

Since Cajal, the neuron doctrine has been that information flows from an incoming axon across a chemical synapse to a dendrite or cell body of another neuron. When a postsynaptic threshold is met from accumulation of excitations (offset by inhibitions), the second neuron's axon fires and an action potential or spike is triggered at the proximal axon hillock. Mediated

by sodium ion fluxes across membrane channels, spikes propagate along the axon to reach another synapse where they influence release of neurotransmitters. Each neuron has only one axon, though they may branch downstream. Thus multiple postsynaptic inputs are integrated to lead to one output, the all-or-none firing of a spike.[17]

Spikes can be quantified by electrodes that traverse or pass near axonal membranes. Thus we know that spike frequency (and possibly patterns) correlates with intensity of stimulus and/or behavior (e. g. Britten et al. [23]). Spikes travel rapidly and are robust, not degrading over long distances. They are widely assumed to be the primary means of signaling and information transfer in the brain, and thus the currency – the neural code – of consciousness. The notion of multiple inputs integrated to a threshold leading to a single output lends itself well to computer analogies. Spike = bit!

However, there are other cellular-level candidates for the NCC. Electrodes on scalp or brain surface detect mostly dendritic dipole potentials from pyramidal cells with axial symmetry, i. e. oriented perpendicular to the brain surface [55]. Electrodes implanted into the brain detect mainly local field potentials (LFPs) generated from cortical interneurons with radial symmetry, linked mostly by dendrodendritic gap junctions and inhibitory chemical synapses. Thus synchrony in the EEG and LFPs derives not from axonal spikes but from dendritic activities. Moreover, the BOLD signal used in fMRI, widely assumed to represent neural metabolic activity related to consciousness, corresponds more closely with LFPs than axonal spikes [147].

Some have argued (e. g. Libet [142], McFadden [156], Pockett [176]) that the brain's complex electromagnetic field (global LFPs and surface potentials) constitutes the NCC. However, as Koch [129] points out, the brain's electromagnetic field per se is a crude and inefficient means of communication. On the other hand, dendritic activities that generate LFPs and/or surface potentials may indeed best represent the NCC. Eccles [47] as well as Pribram [182] suggested that dendrites host consciousness, with axonal spikes conveying the results of consciousness.

Neurotransmitter binding at synaptic receptors changes voltage potentials across dendritic or cell-body membranes, causing either excitatory or inhibitory postsynaptic potentials (IPSPs, EPSPs) and in some cases dendritic action potentials [27, 201]. These are then presumed to summate as membrane potentials to reach threshold for spike initiation at the proximal axon hillock.

However, integration of membrane potentials to trigger spikes is not the full extent of dendritic function. Some cortical neurons have no axons, den-

[17] Axonal sodium channels are activated by membrane voltage potentials and modulated by intracellular cytoskeletal proteins [109, 223]. Sodium channels clustered at the axon hillock are connected to, and regulated by proteins ankyrin and spectrin that link them to underlying microtubules and other cytoskeletal proteins [220, 21].

drites interact with other dendrites (e. g. Isaacson and Strowbridge [108], Sassoè-Pognetto and Ottersen [196]) and extensive dendritic activity may occur without causing spikes. Evidence shows complex logic functions in local dendritic compartments, signal boosting (e. g. at branch points), filtering and changing axon hillock sensitivity [217, 178, 207, 208, 209]. Dendritic membrane fluctuations below spike threshold (generally considered noise) may oscillate coherently across wide regions of brain [9, 51]!

Nor is dendritic processing limited to membrane potentials. Many postsynaptic receptors are metabotropic, sending signals internally into the dendritic cytoskeleton, activating enzymes,[18] causing conformational signaling and ionic fluxes along actin filaments and dephosphorylating microtubule-associated protein 2 (MAP2) that links microtubules into cytoskeletal networks. MAP2 activity is necessary for learning and memory, and is the largest

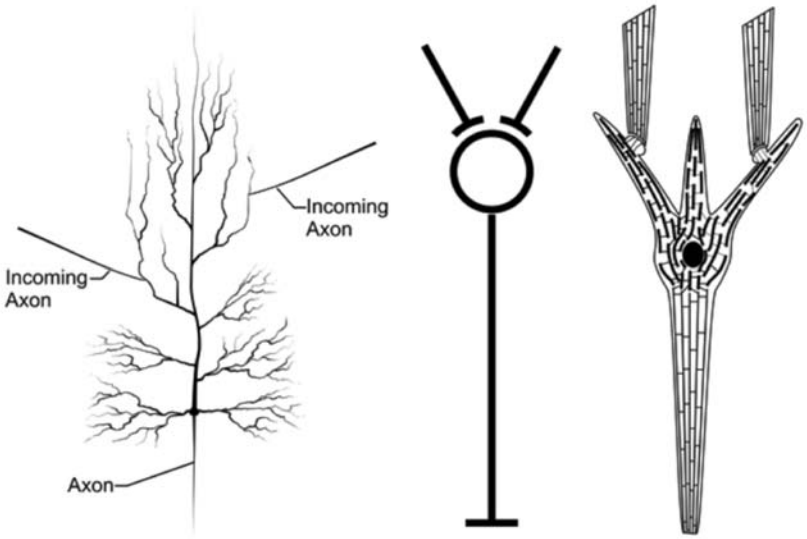

Fig. 6.4. Characterizing neurons. *Left*: Illustration of an actual pyramidal neuron with multiple apical and basilar dendrites (*top and middle*) and a single axon heading downward. Two incoming axons are shown synapsing on apical dendrites. *Middle*: A cartoon neuron as depicted in neural network and functionalist models. Two incoming axons are shown synapsing on the cell body/dendrite. *Right*: A cartoon neuron as utilized in this chapter, showing three dendrites, cell body and a single axon heading downward. The internal cytoskeleton – microtubules interconnected by microtubule-associated proteins – is shown schematically; in dendrites and cell body the microtubules are short, interrupted (and of mixed polarity, not visibly apparent). In the axon the microtubules are continuous (and of uniform polarity, not visibly apparent). Two incoming axons synapse on dendritic spines

[18] For example, calcium-calmodulin protein kinase and protein kinase C.

consumer of dendritic metabolic energy [230, 8, 118]. Changes in the cytoskeleton regulate synaptic plasticity [86, 240, 262, 165, 255, 265, 53, 195, 155, 125].

Dendritic processing is assumed to be constrained by global all-or-none output through the axon, and to exist merely to trigger axonal spikes. But neither assumption is substantiated. The full extent of dendritic internal processing is unknown but its capabilities are enormous. For example, synaptic activity causes glycolytic production of ATP in dendritic spines, energy that may be used for ion channels as well as protein synthesis and signal transduction into the dendritic cytoskeleton [266, 211]. Accordingly, Kasischke and Webb [124] suggested that brain function might be "... more refined on a higher temporal and smaller spatial scale".

Figure 6.4 shows 1) an actual pyramidal neuron with multiple dendrites; two incoming axons synapse on two different dendrites (a pyramidal neuron is likely to have many thousands of such incoming synapses), 2) a cartoon neuron with two axonal inputs synapsing on a cell body (as presumed in

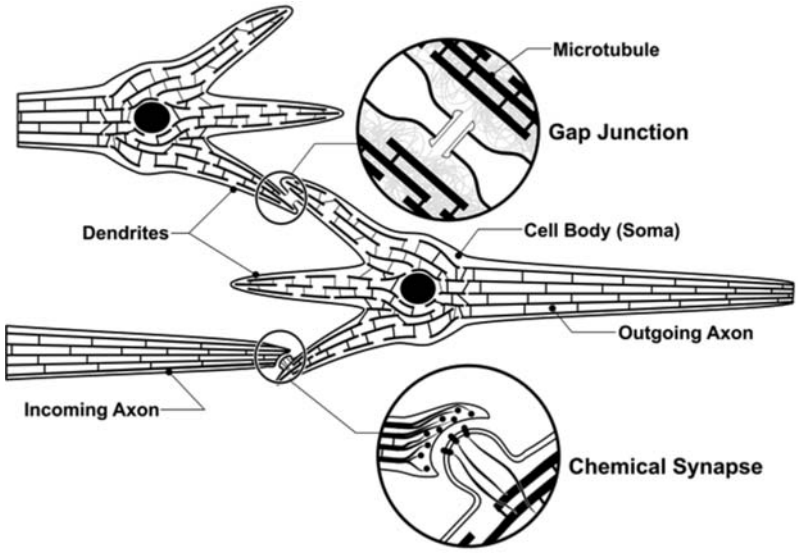

Fig. 6.5. Cartoon neuron with two types of connections. Internal structure represents nucleus (*dark circle*) and cytoskeletal microtubules (MTs) connected by strut-like microtubule-associated proteins (MAPs). MTs in axons are continuous (and unipolar) whereas dendritic MTs are interrupted (and of mixed polarity). *Lower left*: An incoming axon forms a chemical synapse on a dendritic spine. Close-up shows neurotransmitter vesicles in presynaptic axon terminal, and postsynaptic receptors on spine connected to intraspine actin filaments that link to MTs. *Upper left*: Dendritic–dendritic gap junction is a window between the two neurons. Both the membranes and cytoplasmic interiors of the two cells are continuous

functionalist models), and 3) a more elaborate cartoon neuron with three dendrites (and two incoming synapses) showing the internal cytoskeleton. Figure 6.5 shows this type of cartoon neuron with a chemical synapse and dendritic-dendritic gap junction.

6.3.4 Neural Synchrony

Evidence supports a correlation between consciousness and synchronous brain activity. Electrical recording from scalp, brain surface or implanted electrodes reveal synchrony at various frequencies of the electroencephalogram (EEG) due to LFPs or surface potentials. Among these, the so-called gamma frequency range between 30 and 70 Hz correlates best with attention and consciousness. Gray and Singer ([77], cf. [78]) found coherent gamma oscillations in LFPs of cat visual cortex that strongly depended on specific visual stimulation. Though the synchrony occurred in the gamma EEG range between 30 and 70 Hz, the phenomenon became known as coherent 40 Hz.

Following a suggestion by von der Malsburg [251] that synchronous neural excitations could solve the binding problem, von der Malsburg and Singer [252], Crick and Koch [33][19], Varela [244] and others proposed that the neural correlate of any particular conscious content was an assembly of neurons excited coherently at 40 Hz or thereabouts. Varela [244] succinctly observed that neural synchrony operated whenever component processes subserved by spatially separate brain regions were integrated into consciousness.

Neural synchrony in the gamma frequency range has been observed in many animal studies using multiunit scalp, surface and implanted electrodes. They demonstrate synchrony within and across cortical areas, hemispheres and sensory/motor modalities that reflects perceptual gestalt criteria and performance (for a review: Singer and Gray [212], Singer [213]). Among human studies using scalp EEG and MEG, most support a role for synchrony in integration and binding [119, 213, 245, 236]. Gamma synchrony correlates with perception of sound and linguistic stimuli [161, 169, 190], REM dream states [146], attention [60, 231], working memory [225, 226], face recognition [162], somatic perception [42] and binding of visual elements into unitary percepts, with the magnitude of synchrony diminishing with stimulus repetition [83]. Loss of consciousness associated with onset of general anesthesia is characterized by a decrease in gamma EEG activity that returns when patients awaken [117][20].

[19] Crick and Koch subsequently retreated from this contention, maintaining that 40-Hz synchrony alone is insufficient for consciousness but may boost assemblies of neurons (in competition with other assemblies) into consciousness [129].

[20] Anesthesia is also marked by an increase in slower bands and a marked "anteriorization" of power. Additionally, prefrontal and frontal regions of each hemisphere become more closely coupled. Uncoupling occurs between anterior and posterior regions on each hemisphere, as well as homologous regions between the two hemispheres [117].

Some human studies have failed to support neural synchrony in perception and cognition. Menon et al. [159] found gamma synchrony restricted to less than 2 cm regions of cortical surface, arguing against long-range coherence. However, the study only examined a 7 cm × 7 cm region and other studies show that synchrony drops off at intermediate ranges but then reappears at long-range distances [164]. Some discrepancies have ensued from differences in methodology [236]. Overall, synchronous gamma EEG/coherent 40 Hz is the best electrophysiological correlate of consciousness.

How is gamma synchrony mediated? Coherence over large distances, in some cases multiple cortical areas and both cerebral hemispheres, shows zero, or near-zero phase lag. Significant phase lags would be expected from the speed of axonal conduction and delays in synaptic transmission [233].

There is no evidence to support coordinated axonal spiking as the source of gamma synchrony. As Koch [129] states:

> "Gamma oscillations can be routinely observed in the local field potential and, less frequently, when recording multi neuron activity

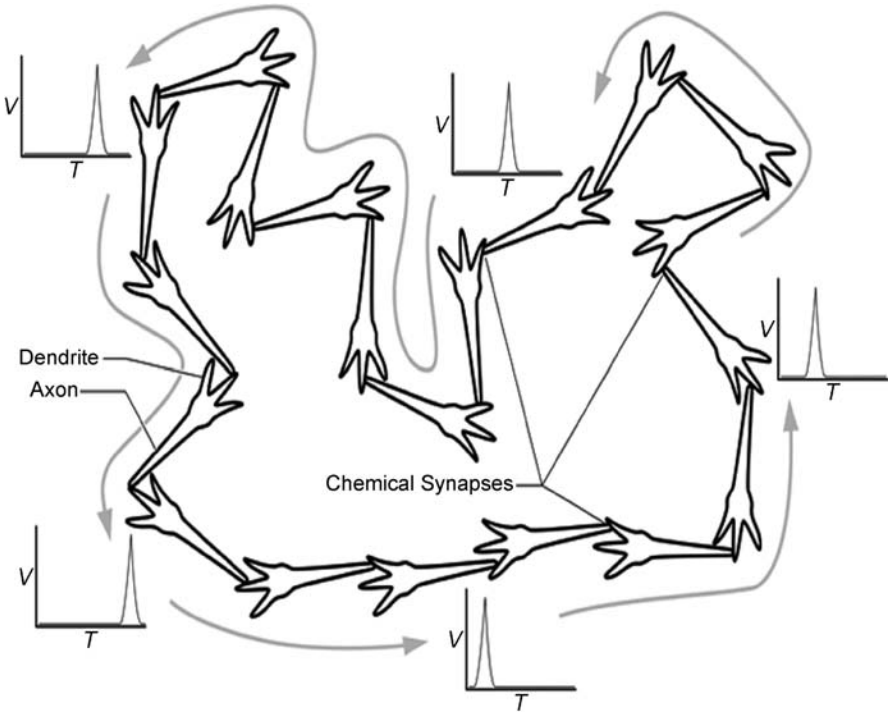

Fig. 6.6. Neural network/Hebbian assembly of cartoon neurons linked by axonal–dendritic chemical synapses. Information/excitation flows unidirectionally from axon to dendrite through the network. Electrical recordings at various points show single voltage spike potential propagating through the network

(that is, the summed spikes of neighboring cells). Detecting these rhythms in the spiking patterns of individual neurons has proven to be more problematic . . . ".

A critical review [204] rejects the relevance of synchrony to temporal binding (and consciousness) based on the lack of coherence of spike activity, perhaps throwing away the baby with the bathwater. However, many studies have shown gamma frequency synchronized by dendritic gap junction electrical synapses. Measuring both spikes and dendritic LFPs in multiple regions of cat visual cortex, Fries et al. [60] showed that visual recognition corresponded with gamma-frequency EEG emanating from LFPs, not with spikes.

Figure 6.6 shows a cartoon neuronal network based on axonal spikes and chemical synapses. Excitation/information flows through the network; there is no coherence. Figure 6.7 shows a gap-junction-linked neuronal network (a hyperneuron, including glial cells) with continuous membrane and cytoplasm. Dendritic membrane throughout the hyperneuron is excited coherently.

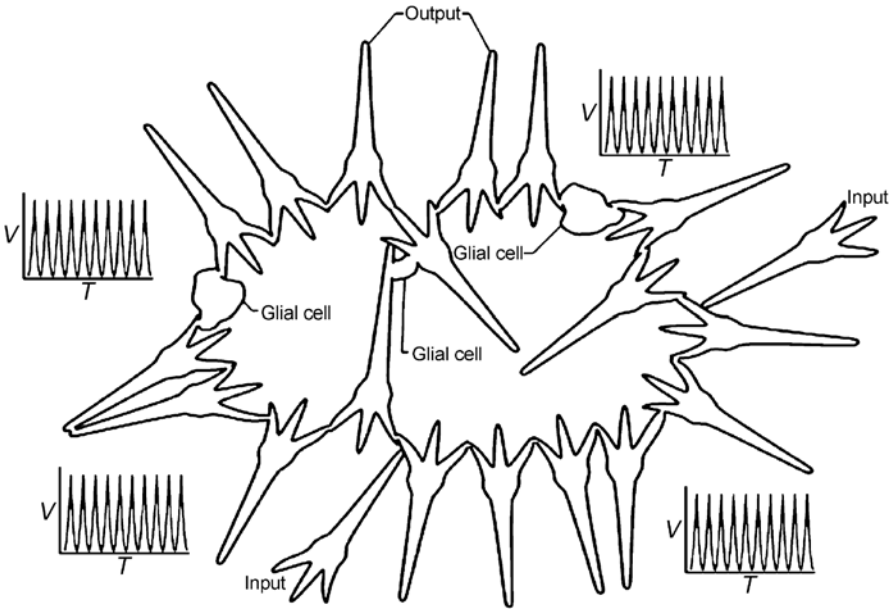

Fig. 6.7. Neural network/Hebbian assembly ("hyperneuron") linked by window-like gap junctions, mostly dendritic–dendritic but also by glial cell gap junctions. Inputs to the hyperneuron are from axonal–dendritic chemical synapses. Outputs from the hyperneuron are from axons of hyperneuron components. Because gap-junction-connected neurons depolarize synchronously like "one giant neuron", electrical recordings at various points show synchronous voltage depolarizations, e. g. at coherent 40 Hz. Both membranes and cytoplasmic interiors are continuous throughout the hyperneuron

6.3.5 Gap-Junction Assemblies – "Hyperneurons"

Gap junctions, or electrical synapses, are direct open windows between adjacent cells formed by paired collars consisting of a class of proteins called connexins [101, 193]. Gap junctions occur between neuronal dendrites, between axons and axons, between neurons and glia, between glia, and between axons and dendrites – bypassing chemical synapses [234, 61, 235, 17]. Ions, nutrients and other material pass through the open gaps, so gap-junction-connected neurons have both continuous membrane surfaces and continuous cytoplasmic interiors. Neurons connected by gap junctions are electrically coupled, depolarize synchronously and "behave like one giant neuron" [121].

In early development gap junctions link pyramidal cells with each other, with nonpyramidal neurons, and with glia during formation of cortical circuits [18]. The number of cortical gap junctions then declines so gap junctions were considered irrelevant to cognition or consciousness. However, many studies show that gap junctions persist significantly in the adult mammalian brain. Moreover, gap-junction circuits of cortical interneurons in adult brains mediate gamma EEG/coherent 40 Hz and other synchronous activity [41, 45, 105, 16, 135, 59, 26, 194, 175, 68, 75].

At least ten different connexins are found in mammalian brain, and their placement and function are dynamic [25, 16]. A single neuron may have numerous gap-junction connections, only some of which are open at any one time, with rapid openings and closings regulated by cytoskeletal microtubules, and/or phosphorylation via G-protein metabotropic receptor activity [97]. Thus gap-junction networks are at least as dynamic and mutable as those crafted by chemical synapses, and may include glial cells [62]. They fulfill the criteria for Hebbian assemblies with the added advantage of synchronous excitations. Networks of gap-junction-linked neurons (and glia) have been termed hyperneurons [116][21].

Cortical inhibitory interneurons are particularly studded with gap junctions, potentially connecting each cell to 20 to 50 others [6]. Many have dual synapses – their axons form inhibitory GABA chemical synapses on another interneuron's dendrite, while the same two cells share dendrodendritic gap junctions [227, 66, 67, 69]. Within each cortical hemisphere there is no apparent limit to the extent of interneuron gap junction networks – hyperneurons – in which they may form a "large, continuous syncytium" [6].

The case for gap-junction hyperneurons involving primary neurons such as pyramidal cells in mature brains, and extending to both hemispheres is less clear. However, Venance et al. [249] showed gap junctions between interneurons and excitatory neurons in juvenile rat brain. Pyramidal cells in hippocampal slices show axo-axonal gap-junction coupling [235], and glial

[21] Ironically, prior to Santiago Ramon-y-Cajal's [184] determination that the brain was composed of individual neural cells, Camille Golgi had proposed that the brain was a syncytium – a threaded reticulum of fibers.

cells envelope both axons and dendrites in many chemical synapses. Neuron–glia–neuron gap junctions could thus provide chemical synapses with alter egos as links in hyperneurons. Thalamocortical cells generating synchronous alpha and theta cortical activity are linked by gap junctions in thalamus [106], so thalamocortical projections (or trans-corpus callosum pathways) could couple both hemispheres in hyperneurons to account for bilateral synchrony.

In principle, all the brain's neurons and glia could be linked together by gap junctions. However, too many active gap junctions and near total synchrony (e. g. as in seizures) would reduce the brain's information-processing capacity. More than three active gap junctions per neuron (i. e. with three different neurons or glia) would connect the entire brain into a single hyperneuron topology.[22] Thus pruning and sparseness are necessary. For the purpose of this chapter, hyperneurons will imply gap-junction-linked cortical interneurons, glia, primary cortical neurons such as pyramidal cells and perhaps others such as thalamocortical neurons that can extend throughout both cerebral hemispheres and subcortical areas.

Brain-wide gamma synchrony mediated by gap-junctions is the best electrophysiological NCC. A logical conclusion is that gap-junction networks – hyperneurons – are the cellular-level NCC. Can that help explain consciousness?

A key feature of gap-junction hyperneurons is continuous dendritic membranes that depolarize coherently. Another key feature is continuous cytoplasmic interiors.

6.3.6 The Next NCC Frontier – Neuronal Interiors and the Cytoskeleton

Membrane-based neuronal input–output activities involve changes in synaptic plasticity, ion conductance, neurotransmitter vesicle transport/secretion and gap-junction regulation – all controlled by intra-neuronal networks of filamentous protein polymers known as the cytoskeleton. If simple input–output activities fully described neural function, then fine-grained details might not matter. But simple input–output activities – in which neurons function as switches – are only a guess, and most likely a poor imitation of neurons' actual activities and capabilities.

To gauge how single neuron functions may exceed simple input–output activities, consider the single-cell organism paramecium. Such cells swim about gracefully, avoid obstacles and predators, find food and engage in sex with partner paramecia. They may also learn; if placed in capillary tubes they escape, and in subsequent attempts escape more quickly. As single cells with no synaptic connections, how do they do it? Pondering the seemingly intelligent

[22] Personal communication from Roger Penrose.

activities of such single-cell organisms, famed neuroscientist C.S. Sherrington [206] conjectured:

"of nerve there is no trace, but the cytoskeleton might serve".

If the cytoskeleton is the nervous system of protozoa, what might it do for neurons?

6.4 The Neuronal Cytoskeleton

6.4.1 Microtubules and Networks inside Neurons

Shape, structure, growth and function of neurons are determined by their cytoskeleton, internal scaffoldings of filamentous protein polymers that include microtubules, actin and intermediate filaments. Rigid microtubules (MTs) interconnected by MT-associated proteins (MAPs) and immersed in actin form a self-supporting, dynamic tensegrity network. The cytoskeleton also includes MT-based organelles called centrioles that organize mitosis, membrane-bound MT-based cilia, and proteins that link MTs with membranes. Disruption of intraneuronal cytoskeletal structures impairs cognition, such as tangling of the MAP tau linking MTs in Alzheimer's disease [153, 107].

Actin is the main component of dendritic spines and also exists throughout the rest of the neuronal interior in various forms depending on actin-binding proteins, calcium, etc. When actin polymerizes into a dense meshwork, the cell interior converts from an aqueous solution (sol state) to a quasisolid, gelatinous (gel) state. In the gel state, actin, MTs and other cytoskeletal structures form a negatively charged matrix on which polar cell water molecules are bound and ordered [179]. Glutamate binding to NMDA and AMPA receptors triggers gel states in actin spines [53].

Neuronal MTs self-assemble, and with actin enable growth of axons and dendrites. Motor proteins transport materials along MTs to maintain and regulate synapses. Direction and guidance of motor proteins and synaptic components (e. g. from cell body through branching dendrites) depends on conformational states of MT subunits [132]. Thus MTs are not merely passive tracks but appear to actively guide transport. Among neuronal cytoskeletal components, MTs are the most stable and appear best suited for information processing. Wherever cellular organization and intelligence are required, MTs are present and involved.

MTs are cylindrical polymers 25 nanometers (nm = 10^{-9} m) in diameter, comprised of 13 longitudinal protofilaments that are each chains of the protein tubulin (Fig. 6.8). Each tubulin is a peanut-shaped dimer (8 nm by 4 nm by 5 nm) that consists of two slightly different monomers known as alpha and beta tubulin, (each 4 nm by 4 nm by 5 nm, weighing 55 000 daltons). Tubulin subunits within MTs are arranged in a hexagonal lattice that is slightly twisted, resulting in differing neighbor relationships among each

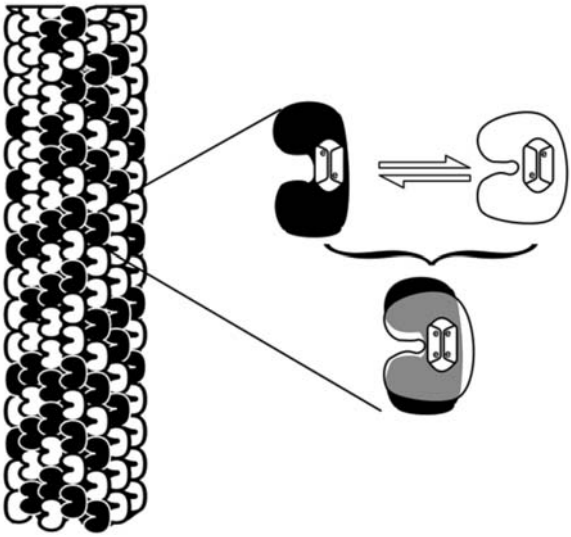

Fig. 6.8. Microtubule (*left*) is a cylindrical polymer of subunit proteins known as tubulin arranged in a skewed hexagonal lattice. Each tubulin can exist in two or more conformational states, e. g. open (*black*) or closed (*white*). *Right*: Each tubulin state is governed by quantum-mechanical London forces – collective positions of hundreds of electrons (represented here as two electrons) in nonpolar hydrophobic regions within the protein. Because of governance by quantum forces, it is proposed that tubulins can exist in quantum superposition of both conformations (*black* and *white* = *gray*). The actual displacement in the superposition separation need only be the diameter of a carbon atom nucleus, but is illustrated here as roughly 10% of the protein volume

subunit and its six nearest neighbors (Fig. 6.9). Thus pathways along contiguous tubulins form helical patterns that repeat every 3, 5, 8, etc. rows (the Fibonacci series). Alpha tubulin monomers are more negatively charged than beta monomers, so each tubulin (and each MT as a whole) is a ferroelectric dipole with positive (beta monomer) and negative (alpha monomer) ends[23].

In non-neuronal cells and in neuronal axons, MTs are continuous and aligned radially like spokes of a wheel emanating from the cell center. MT negative (alpha) ends originate in the central cell hub (near the centrioles, or MT-organizing-center adjacent to the cell nucleus) and their positive (beta) ends extend outward in the case of axons, where the negative ends of continu-

[23] The skewed lattice symmetry matches the polarity. Thus in the "alpha (positive) up" orientation, the 3-start and 5-start helical windings go to the left, and the 8-start helical windings go to the right. The intervals on any protofilament between the tubulins on which the various windings repeat match the mathematical Fibonacci series (Figs. 6.8 and 6.9).

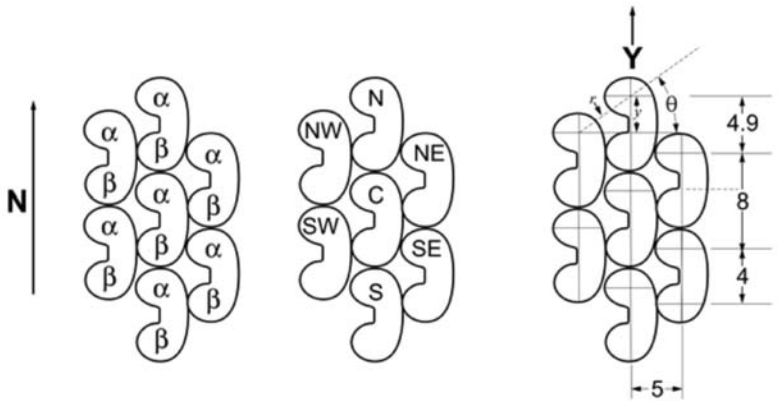

Fig. 6.9. The lattice of tubulins in microtubules. *Left*: The lattice showing the tubulin dimers as (negatively charged) alpha monomers and (positively charged) beta monomers. *Middle*: A tubulin neighborhood is defined by identifying the central tubulin C and its 6 surrounding neighbors by compass points: N (north), NE (northeast), SE (southeast), S (south), SW (southwest), NW (northwest). *Right*: The spacings (in nanometers) and definition of angle theta. y is the vertical distance between (the same points on) any two neighboring dimers and r the absolute distance. While y varies, the horizontal distance is always 5 nanometers. Curvature around the cylinder is ignored and the dipole force between dimers is related to $y/r3$. From [185]

ous MTs originate in the axon hillock, and positive ends reach the presynaptic region.

However, the dendritic cytoskeleton is unique. Unlike axons and any other cells, MTs in dendrites are short, interrupted and mixed polarity. They form networks interconnected by MAPs (especially dendrite-specific MAP2) of roughly equal mixtures of polarity. There is no obvious reason – from a structural standpoint uninterrupted MTs would be preferable, as in axons. Networks of mixed polarity MTs connected by MAPs may be optimal for information processing.

Intradendritic MT-MAP networks are coupled to dendritic synaptic membrane and receptors (including dendritic spines) by calcium and sodium flux, actin and metabotropic inputs including second messenger signaling, e. g. dephosphorylation of MAP2 [86]. Alterations in dendritic MT-MAP networks are correlated with locations, densities and sensitivities of receptors (e. g. Woolf et al. [265]). Synaptic plasticity, learning and memory depend on dendritic MT-MAP networks.

Since Sherrington's observation in 1957, the idea that the cytoskeleton – MTs in particular – may act as a cellular nervous system has occurred to many scientists. Vassilev et al. [246] reported that tubulin chains transmit signals between membranes, and Maniotis et al. [148, 149] demonstrated that

MTs convey information from membrane to nucleus. But MTs could be more than wires. The MT lattice is well designed to represent and process information, with the states of individual tubulins playing the role of bits in computers. Conformational states of proteins in general (e. g. ion channels opening/closing, receptor binding of neurotransmitter, etc.) are the currency of real-time activities in living cells. Numerous factors influence a protein's conformation at any one time, so individual protein conformation may be considered the essential input–output function in biology.

6.4.2 Microtubule Automata

The peanut-shaped tubulin dimer switches between two conformations in which the alpha monomer flexes 30 degrees from vertical alignment with the beta monomer. These are referred to as open and closed states (Fig. 6.8, [158, 104, 186])[24].

Atema [11] proposed that tubulin conformational changes propagated as signals along MTs in cilia. Hameroff and Watt [87] suggested the MT lattice acted as a two-dimensional computer-like switching matrix with tubulin states influenced by neighbor tubulins, and input/output occurring via MAPs[25]. MT information processing potential came to be viewed in the context of cellular automata [214, 185].

Cellular automata are self-organizing information systems based on lattices of fundamental units (cells) whose states interact with neighbor cells at discrete time steps. In a two-dimensional checkerboard lattice, each cell has eight neighbors (corner neighbors included) and exists in two (or more) possible states. Neighbor-interaction rules determine each cell's state at the next time step.

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[24] Pharmacological studies suggest five possible ligand-induced conformations. In addition to these dynamical states, more permanent variability in tubulin within microtubules depends on genetics (22 different tubulin isozymes in brain) and post-translational modification, addition or removal of amino acids to specific tubulins. Thus, intact MTs may be mosaics of slightly different tubulins, allowing for a baseline memory or programming upon which dynamical changes can occur.

[25] Other proposals include the following: Roth et al. [192] proposed that conformational gradients among tubulins created patterns that dictated function, Puck and Krystosek [183] suggested that waves of phosphorylation/dephosphorylation along tubulins conveyed information, and Wang and Ingber [254] described a tensegrity communication structure among MTs and actin filaments. Nonlinear soliton waves along MTs have been proposed [197, 30], and Lader et al. [133] suggested that ion transfer along actin conveyed functional signals [237]. Tuszynski et al. [238] predicted MT ferroelectric effects and "spin glass" behavior, Albrecht-Buehler [2, 3] suggested MTs convey infrared photons as the "nerves of the cell", and Jibu et al. [114, 115] proposed MTs as quantum optical waveguides. For a review of classical models of cytoskeletal information processing see Hameroff [88] and Rasmussen et al. [185]

A well-known example is the game of life in which two possible states of each cell whimsically represent either alive or dead on a checkerboard lattice [70]. There are three neighbor rules:

- If the number of live neighbors is exactly two, the cell maintains the status quo into the next generation. Thus a live cell stays alive, a dead cell stays dead.
- If the number of live neighbors is exactly three, the cell will be alive in the next generation. A dead cell is "born", a live cell lives on.
- If the number of live neighbors is 0, 1, or 4–8, the cell will be dead in the next generation due to not enough support (0 or 1) or overcrowding (4–8).

The generations are synchronized by a universal clock mechanism. Starting from random initial patterns, complex behaviors emerge, for example chaotic dynamics [260, 134]. However, common types of patterns generally appear: stable objects, oscillators/blinkers and gliders that move through the grid. Streams of gliders can perform all logic and memory functions on which computers are based. The game of life and cellular automata in general are universal computers.

MTs were modeled as automata in which tubulin conformational states (open, closed) interacted with neighbor tubulin states by dipole interactions. Dipole strengths in open and closed conformations were used to generate interaction rules. Thus the dipole-coupled conformation for each tubulin was determined at each generation by the sum of the dipoles of its six surrounding neighbors[26]. Because of the skewed hexagonal geometry, contributions from each of the six neighbors differed (Fig. 6.9). The generations, or time steps were assumed to be nanoseconds, following Fröhlich's suggestion of coherent excitations.

Herbert Fröhlich [63–65] proposed that a set of dipoles constrained in a common geometry and electric field would oscillate in phase, coherently like a laser[27] if biochemical energy were supplied. Membrane proteins and tubulins in MTs are predicted to oscillate in the range of 10^{-9} to 10^{-11} s[28].

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[26] In which $f_{\text{net}} = \frac{e^2}{4\Pi\epsilon} \sum_{i=1}^{6} \frac{y_i}{r_i^3}$ is the sum of the six neighbor dipole forces on each tubulin dimer, e is the electron charge, epsilon is the average permittivity for proteins, typically ten times the vacuum permittivity, y is the vertical offset between (identical points in each of the) dimer pairs, and r is the absolute distance between (identical points in each of the) dimer pairs. We assumed that only the y-component of the interaction forces is effective and neglected any net force around the MT circumference. Absolute values of the forces may be found in Rasmussen et al. [185].

[27] Essentially forming a Bose–Einstein condensate.

[28] Fröhlich pointed out that living systems should be sensitive to effects of specific microwave frequencies, and indeed many such effects have been reported. Vos et al. [253] showed coherent nuclear motions of membrane proteins.

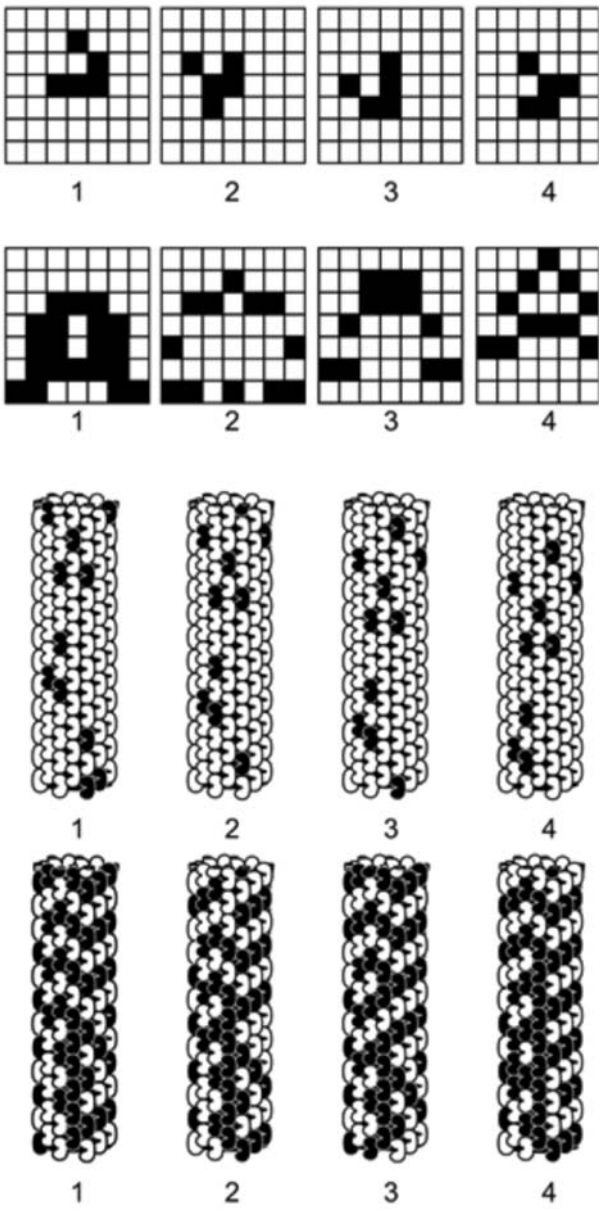

Fig. 6.10. Cellular automata. *Top two rows*: Two different sequences of gliders moving in the game of life. In the *first row* the glider moves downward; in the *second row* the glider moves upward. *Bottom two rows*: Two different sequences of gliders moving and patterns evolving in microtubule automata. In the *third row*, gliders move downward through the microtubule; in the *fourth row*, patterns move both upward (*black column*, *4th protofilament*) and downward (*white column, 2nd protofilament*)

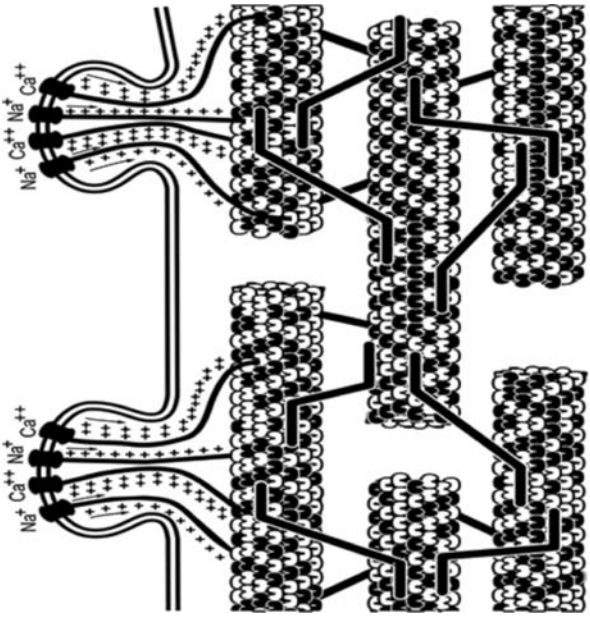

Fig. 6.11. Interior schematic of dendrite showing unique mixed polarity networks of microtubule automata interconnected by microtubule-associated proteins (MAPs). Inputs to microtubule automata (orchestration) from, e. g. glutamate activation of dendritic spine receptors are conveyed by sodium and calcium ion flux along actin filaments. MAPs convey information between MTs to form an automaton network. Output/results of MT automaton network processing can trigger axonal spikes, regulate synapses and hardwire memory

Simulations of MT automata showed stable patterns, blinkers and propagating gliders (velocity 8 to 800 m/s[29], Fig. 6.10). Two MT automata interconnected by MAPs exhibited recognition and learning (Fig. 6.11; [185]).

MT automata potentially increase cellular and brain-wide information processing enormously. Neurons each contain at least 10^7 tubulins [267]; switching in nanoseconds (10^9/s) predicts roughly 10^{16} operations per second per neuron.[30] But enhanced information processing per se fails to answer fundamental questions about consciousness. A clue lies in the mechanism of state switching present in proteins.

[29] Using the Fröhlich oscillation time of 10^{-9} to 10^{-11} s, gliders move one tubulin dimer length (8 nm) per oscillation, hence 8 to 800 nm/ns, or 8 to 800 m/ s. This is essentially the range of velocities for action potentials.

[30] Conventional approaches focus on synaptic switching (roughly 10^{11} brain neurons, 10^3 synapses/neuron, switching in the millisecond range of 10^3 operations per second) and thus predict about 10^{17} bit states per second for a human brain. Nanosecond MT automata offer about 10^{27} brain operations per second for a human brain.

6.4.3 Protein Conformational Dynamics – Nature's Bits and Qubits

Proteins are the engines of life, dynamically changing conformational shape at multiple scales [123]. Functional changes occur in 10^{-6} s to 10^{-11} s transitions. Proteins have large energies with thousands of kiloJoules per mole (kJ mol^{-1}) but are only marginally stable against denaturation by 40 kJ mol^{-1}. Consequently, protein conformation is a "delicate balance among powerful countervailing forces" [250].

Individual proteins are linear chains of amino acids that fold into three-dimensional conformations.[31] The driving force in folding is attraction of uncharged nonpolar amino acid groups, repelled by solvent water. These hydrophobic groups attract each other by van der Waals forces, avoiding water and burying themselves within protein interiors forming (in some proteins) hydrophobic pockets.[32] Volumes of pockets (0.4 cubic nanometers) are 1/30 to 1/250 the volume of single proteins. Though tiny, hydrophobic pockets are critically important in the determination of protein conformation both in folding and regulation of conformational dynamics. Hydrophobic pockets may act as the brain of a protein.

Nonpolar (but polarizable) amino acid side groups within hydrophobic pockets interact by van der Waals London forces. Electrically neutral atoms and nonpolar molecules can have instantaneous dipoles in their electron-cloud distribution. Electrons in clouds from neighboring nonpolar amino acid side groups repel each other, inducing mutual fluctuating dipoles that then couple to each other like oscillating magnets. As high energy forces cancel out, weak but numerous (thousands per protein) London forces govern protein conformation (Fig. 6.8).[33]

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[31] The precise folding depends on attractive and repellent forces among various amino acid side groups, and a current view is that many possible intermediate conformations precede the final one. Predicting the final three-dimensional folded shape using computer simulation has proven difficult if not impossible. This conundrum is known as the "protein-folding problem" and so far appears to be "NP complete": the answer can be calculated in theory, but the space and time required of any classical computer is prohibitive. Klein-Seetharaman et al. [127] showed nonlocal interactions among nonpolar groups in protein folding, suggesting a form of quantum computation.

[32] Such as leucine, isoleucine, phenylalanine, tryptophan, tyrosine and valine.

[33] Due to the Mossbauer effect [24] electronic motions in tubulin should be coupled to nuclear motions via a recoil phenomenon, connecting protein conformation to London forces. The movement would be slight due to the disparity in mass between single electrons and the mass of protons – a one-nanometer shift in location of a single electron would shift the nuclear mass, and hence protein conformation, by only 10^{-8} nm. However, such a shift per electron (thousands of electron London forces per protein) would be significant if all nuclei were affected collectively. The conformational superposition/separation distance in Orch OR is precisely 2.5 fermi lengths (carbon atom nuclear diameter) of 10^{-6} nm. So ∼250

Due to inherent uncertainty in electron localization, London forces are quantum-mechanical effects. Thus proteins governed by London forces in hydrophobic pockets are quantum levers, amplifying quantum forces to govern conformational changes and physical effects. Prevention of quantum leverage accounts for the action of anesthetic gases.

6.4.4 Anesthesia

Millions of people every year undergo general anesthesia for surgery with complete and reversible loss of consciousness. At a critical concentration of anesthetic drug, consciousness is erased while many nonconscious functions of brain and other organs continue (e. g. EEG, evoked potentials, control of breathing). How does this happen?

The situation seems confusing, with many different types of anesthetic drugs acting on many different types of brain molecules. Purely inhalational anesthetic gases that travel through the lungs and blood to the brain constitute a variety of types of molecules: halogenated hydrocarbons, ethers, the inert element xenon, nitrous oxide, etc. However, there is one important unifying feature.

All anesthetic gas molecules are nonpolar, and thus poorly soluble in water/blood, but highly soluble in a particular lipid-like, hydrophobic environment akin to olive oil. The potency of anesthetic gases in erasing consciousness correlates perfectly with solubility in such an environment. The brain has a large lipid-like (olive oil-like) domain, both in lipid regions of neural membranes and hydrophobic pockets within certain proteins. Anesthetics were originally thought to act in lipid regions of membranes, but protein hydrophobic pockets were determined to be their primary sites of action [54]. Anesthetic gases bind to nonpolar amino acid groups in the pockets (e. g. the benzene-like ring in phenylalanine, and the indole ring in tryptophan) by van der Waals London forces, the same quantum forces that form the pockets and govern conformational dynamics.

Why do weak quantum forces have such profound and selective effects? Anesthetic gas molecules form their own London force interactions with nonpolar amino acid groups, preventing or altering normally occurring London forces necessary for protein conformational dynamics and consciousness. Anesthetic gases prevent quantum leverage.

Most protein conformational changes are unaffected by general anesthetics – muscle contractility, enzyme function and most brain activities (as evidenced by EEG and evoked potentials) continue during anesthesia. Axonal action potentials are also relatively unaffected by general anesthetics. Pro-

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London forces (among thousands per protein) would be required. The charge shift of a single electron, equal to a proton charge, is even more likely to exert an effect on conformation [32]. Roitberg et al. [191] and Tejada et al. [229] also suggest quantum states in proteins.

teins that are affected include postsynaptic receptors for acetylcholine, serotonin, GABA and glycine [54], connexins in gap junctions [151, 99], tubulin in microtubules [4] and actin, which disassembles in dendritic spines when exposed to anesthetics [120].

Anesthetics act (and consciousness occurs) not in any one brain region, or in any one type of neuron or particular protein. Rather, anesthesia and consciousness occur in hydrophobic pockets of a class of proteins in dendrites throughout the brain [93]. In these pockets, quantum London forces govern protein function responsible for consciousness. Does that imply that consciousness is a quantum process?

6.5 Quantum Information Processing

6.5.1 Quantum Mechanics

Reality is described by quantum physical laws that reduce to classical rules (e. g. Newton's laws of motion) at certain large-scale limits. According to quantum physical laws:

- Objects/particles may exist in two or more places or states simultaneously – more like waves than particles and governed by a quantum wave function. This pheneomenon of multiple coexisting possibilities is known as quantum superposition.
- Multiple objects/particles can be unified, acting as a single coherent object governed by one wave function. If a component is perturbed, others feel it and react. This is called nonlocality and is the main difference between classical and quantum physics. If the objects remain together, nonlocality is known as Bose–Einstein condensation.
- If unified objects are spatially separated they remain unified. This nonlocality is also known as quantum entanglement.

Why don't we see quantum superpositions in our world? How are quantum particles connected over distance?

Experiments show that quantum superpositions persist until they are measured, observed or interact with the classical environment (decohere). If such interactions occur, quantum superpositions reduce, collapse or decohere to particular classical states, with the particular choice of states apparently random. What actually constitutes the act of measurement/observation is unclear, as is the fate of isolated, unmeasured quantum superpositions. Interpretations of quantum mechanics address this issue:

- The Copenhagen interpretation (measurement or conscious observation collapses the wave function)[34] puts both consciousness and fundamental reality outside physics.

[34] This is one form of the Copenhagen interpretation, parodied in Schrödinger's famous thought experiment of the dead-and-alive cat [200].

- The multiple-worlds view suggests each superposition is amplified, leading to a new universe. There is no collapse, but an infinity of realities (and conscious minds) is required.
- David Bohm's interpretation avoids reduction/collapse but requires another layer of reality. Objects are guided by complex waves of possibility (active information, associated with consciousness).
- Henry Stapp views the universe as a single quantum wave function. Reduction of part of it within the brain is a conscious moment (akin to Whitehead's "occasion of experience" – [257, 258]. Reduction/collapse is consciousness.
- In decoherence theory any interaction (loss of isolation) of a quantum superposition with a classical system (e. g. through heat, direct interaction or information exchange) erodes the quantum system. But 1) the fate of isolated superpositions is not addressed, 2) no quantum system is ever truly isolated, 3) decoherence doesn't actually disrupt superposition, just buries it in noise, 4) some quantum processes are enhanced by heat and/or noise.
- An objective threshold for reduction (objective reduction, or) exists due to, e. g., the number of superpositioned particles (GRW theory [73, 74]) OR quantum gravity as in the OR proposals of Károlyházy et al. [122], Diosi [44] and Roger Penrose [170].

How can objects actually be in multiple locations or states simultaneously? Penrose [170, 171] takes superposition as an actual separation in underlying reality at its most basic level (fundamental space-time geometry at the Planck scale of 10^{-33} cm).[35] This is akin to the multiple-worlds view (superpositions/separations are amplified to form a separate universe), however, according to Penrose the separations are unstable and (instead of branching off completely) spontaneously reduce (self-collapse) due to an objective threshold in space-time geometry.[36] Accordingly, the larger the superposition, the more rapidly it reduces. For example an isolated one kilogram object in superposition would meet OR quickly, in only 10^{-37} s. An isolated superpositioned electron would undergo OR only after 10 million years. Penrose OR is currently being tested experimentally [150].

[35] Penrose brings in general relativity in which matter equates to space-time curvature. An object in any particular location is a specific curvature in underlying space-time geometry; the same object in a slightly different location is curvature in a different (e. g. opposite) direction. Hence superposition (object in two places) implies a separation, bubble or blister in fundamental space-time geometry.

[36] By $E = \hbar/t$ where E is the gravitational self-energy, $\hbar$ is Planck's constant over 2π, and t is the time until or occurs. E is the amount, or degree of superposition given for superposition/separation at the level of atomic nuclei by $E = Gm^2/a_c$ where G is the gravitational constant, m is the superpositioned mass, and a_c is the distance of separation, i. e. the diameter of a carbon nucleus equal to 2.5 fermi distances (2.5×10^{-6} nm). See [89] and [172] for details.

In *The Emperor's New Mind* Penrose [170] suggested that choices resulting from OR were not random, but influenced by Platonic information embedded at the Planck scale, the fundamental level of the universe. Moreover, this particular type of nonrandom, nonalgorithmic (noncomputable) selection is characteristic of conscious choices, differing in a basic way from the output of classical computers. Penrose proposed that OR-mediated quantum computation must be occurring in the brain. Quantum computation (see next section) relies on both superposition and entanglement.

Entanglement is stranger than superposition. Quantum theory predicted that complementary quantum particles (e. g. electrons in coupled spin-up and spin-down pairs) would remain entangled even when separated. Einstein, Podolsky and Rosen [49] described a thought experiment intended to disprove this notion (Fig. 6.3). An entangled complementary pair of superpositioned electrons (EPR pairs) would be separated and sent in different directions along two different wires, each electron remaining in superposition. When one electron was measured at its destination and, say, spin-up was observed, its entangled twin miles away would correspondingly reduce instantaneously to spin-down, which would be confirmed by measurement. This would require a faster-than-light signal that Einstein's special relativity had precluded. Nonetheless since the early 1980s [10, 232] this type of experiment has been performed through wires, fiber optic cables and via microwave beams through the atmosphere. Entanglement has been repeatedly confirmed. The mechanism of instantaneous communication remains unknown, seeming to violate special relativity.

To explain entanglement, Penrose ([173], cf. [15]) suggested backward time referral of quantum information, i. e. from the measurement back in time to the unified complementary pair, then forward in time to the opposite twin (Fig. 6.3). In the quantum world, time is symmetric (bidirectional), or the flow of time doesn't exist.

Although poorly understood, entanglement and superposition are used in quantum computing and related technologies.

6.5.2 Quantum Computation

Initially proposed by Benioff [14], Deutsch [43] and Feynman [52], quantum computers (and quantum cryptography and teleportation) are being developed in a variety of technological implementations.

The basic idea is this. Conventional computers represent digital information as binary bits of either 1 or 0. Quantum computers can represent quantum information as superpositions of both 1 and 0 (quantum bits, or qubits). While in superposition (isolated from environment) qubits interact with other qubits by nonlocal entanglement, allowing interactions to evolve[37] resulting in computation of enormous speed and near-infinite parallelism.

[37] Linearly and deterministically according to the Schrödinger equation.

After the interaction/computation is performed, qubits reduce/collapse to specific classical bit states by measurement, giving the output or solution.[38]

The major hurdle to quantum computing is the sensitivity of fabricated superpositioned qubits to disruption by thermal vibration or any interaction with the environment – decoherence. Consequently, quantum-computing prototypes have been built to operate at extremely low temperatures to avoid thermal noise, and in isolation from the environment.

In the mid-1990s quantum error-correcting codes were developed that could detect and correct decoherence, preserving the quantum information [222]. Topological quantum error correction was developed in which the geometry of the quantum computer lattice was inherently resistant to decoherence. For example, a quantum computer could utilize the Aharonov–Bohm effect in which alternate possible paths of a quantum particle are considered as a superposition of paths [126]. So lattice pathways (rather than individual components of those pathways) can be global qubits resistant to decoherence.

6.5.3 Quantum Computing with Penrose OR

Technological qubits reduce/collapse by measurement, introducing randomness averaged out by redundancy. According to Penrose [170] quantum computation that self-collapses by OR avoids randomness, instead providing a noncomputable influence stemming from Platonic values embedded at the Planck scale. Such quantum computation would be algorithmic up to the instant of OR, with an added modification then occurring.

The Penrose argument for noncomputability using Gödel's theorem was harshly criticized but not refuted. For consciousness, OR also provides explanations for:

[38] Qubits may be manifest as switches that utilize superpositions of various quantum states including electron spins, photon polarization, ionic states, nuclear spin, magnetic flux in a Josephson junction superconducting loop, or "quantum dots" – confined spaces in that single electrons or atoms are mobile but can occupy only discrete sites. Many other possibilities for qubits have also been suggested including some that could be mass produced in silicon. Quantum computers remained largely theoretical curiosities until 1994. Bell Labs mathematician Peter Shor developed a quantum algorithm that would be capable of factoring large numbers into their primes exponentially faster than conventional computers, assuming a quantum computer could be built to run it. Factoring large numbers into primes is the basis for banking and military cryptography, and so governments and industry became extremely supportive of efforts to build quantum computers. A functional quantum computer would make all classically supported cryptography obsolete. The race was on. Subsequently, other algorithms for quantum computers were developed that would provide exceedingly faster search capabilities. There is no doubt quantum computers will be revolutionary if technical obstacles to their construction and operation can be overcome.

- Transition from nonconscious (superpositioned quantum information) to classical information, with consciousness the transition itself.
- Binding via quantum coherence, condensation and/or entanglement.
- Libet's backward time referral and other temporal anomalies.
- The hard problem of conscious experience via Whitehead pan-protopsychism connected to fundamental space-time geometry (Sect. 6.8.4, [90]).

Penrose initially suggested the possibility of superpositions of neurons both firing and not firing as qubits. Microtubules seemed ideal for the type of quantum computation Penrose was suggesting.

Penrose implied that nonconscious processes capable of becoming conscious utilize quantum information. What do we know about nonconscious processes?[39]

6.6 The Quantum Unconscious

German psychologist Frederic Meyer in 1886 described subliminal consciousness, followed by William James' transmarginal consciousness or fringe, a region of the mind just outside consciousness but accessible to it (e. g. access consciousness, [19]).

Sigmund Freud saw dreams as the "royal road to the unconscious" whose bizarre character was due to censorship and disguise of thwarted drives. Freud's ideas became downplayed, and dreams characterized as mental static (e. g. [102, 103]). However, recent brain imaging shows dream-associated REM sleep activity in regions associated with emotion and gratification [215, 216].

Chilean psychologist Ignacio Matte Blanco ([154], cf. [188]) compared logic structure in dreams to the Aristotelian logic of waking consciousness in which, for example, the logic statement:

If x, then y

does not imply the statement:

If y then x.

This is obvious to our conscious minds. For example:

If the light turns green, then I go

[39] I equate nonconscious, unconscious, subconscious and preconscious processes as potentially capable of consciousness. That is, they utilize both classical processes and quantum superposition. However, there are clearly brain processes that are almost exclusively nonconscious and utilize classical processing. But in principle such processes could become conscious. For example, practitioners of certain types of yoga gain conscious control over normally nonconscious processes such as intestinal peristalsis.

Does not imply:

If I go, then the light will turn green.

However, from decades of dream analysis Matte Blanco determined two non-Aristotelian axioms of the logic of the unconscious: symmetry and generalization. In dreams:

If x then y

(according to symmetry) implies that also:

If y then x.

In dreams, according to Matte Blanco:

If the light turns green, then I go

implies that also:

If I go, then the light turns green.

Generalization means that any entity is a part of a whole, and when symmetry and generalization are combined, paradox occurs. For example:

If a hand is part of the body

then also:

The body is part of the hand.

The seeming contradiction of any set being a subset of itself defines an infinite set, and is also holographic (and fractal). Any part of a whole also contains the whole within the part.[40]

Symmetry also means that:

If event a happened after event b,

then also:

Event b happened after event a.

From this Matte Blanco concluded: "...the processes of the unconscious ...are not ordered in time".

Another implication of unconscious logic is that apparently negating propositions (e. g. p and not p) may be true, resulting in coincidence of con-

[40] According to neuroscientists Karl Lashley and Karl Pribram, memory is holographic. Multiple overlapping homunculi in both the central and peripheral nervous systems also suggest holography. Finally, there are serious suggestions that the universe is holographic.

traries. For example (to use Matte Blanco's example):

x is alive

and

x is dead

are both true (e. g. when time is removed). More generally, according to Matte Blanco, "the unconscious is unable to distinguish any two things from each other".

The unconscious utilizes multiple coexisting possibilities, inseparability and timelessness, very much like quantum information. Matte Blanco summarized the unconscious as "where paradox reigns and opposites merge to sameness", also an apt description of the quantum world.

6.7 Quantum Computation in Microtubules – The Orch OR Model

6.7.1 Specifics of Orch OR

In a proposal for the mechanism of consciousness, Roger Penrose and I suggested that microtubule (MT) quantum computations in neurons are orchestrated by synaptic inputs and MT-associated proteins (MAPs), and terminate (e. g. after 25 ms, 40 Hz) by Roger's objective reduction (OR) mechanism. Hence, the model is known as orchestrated objective reduction, Orch OR. Complete details may be found in Penrose and Hameroff [174], Hameroff and Penrose [89, 90] and Hameroff [91]. The key points are:

1. Conformational states of tubulin protein subunits within dendritic MTs interact with neighbor tubulin states by dipole coupling such that MTs process information in a manner analogous to cellular automata that regulate neuronal activities (trigger axonal spikes, modify synaptic plasticity and hardwire memory by MT-MAP architecture, etc.).
2. Tubulin conformational states and dipoles are governed by quantum-mechanical London forces within tubulin interiors (nonpolar hydrophobic pockets) so that tubulins may exist as quantum superpositions of differing conformational states, thus acting as quantum levers and qubits.[41]

[41] Proteins may be optimally leveraged as qubits in terms of being 1) large enough to exert causal efficacy in the macroscopic world, and 2) small enough/delicately balanced to be regulated by quantum forces. In Hameroff and Penrose [89] the gravitational self-energy E was calculated for tubulin superpositions at the level of 1) entire tubulin protein separation, 2) separation at the level of atomic nuclei, and 3) separation at the level of nucleons, i. e. protons and neutrons. The dominant effect is for separation at the level of atomic nuclei, the Fermi length of 10^{-6} nm. The eigenstates (differing possible classical positions) of such slight

3. While in superposition, tubulin qubits communicate/compute by entanglement with other tubulin qubits in the same MT, other MTs in the same dendrite, and MTs in other gap-junction-connected dendrites (i. e. within a hyperneuron). Thus quantum computation occurs among MTs throughout macroscopic regions of brain via tunneling through gap junctions or other mechanisms.[42]
4. Dendritic interiors alternate between two phases determined by polymerization of actin protein: a) In the liquid (solution: sol) phase, actin is depolymerized and MTs communicate/process information classically (tubulin bits) with the external world. During this phase synaptic activities provide inputs via MAPs that orchestrate MT processing. After reduction, sol-phase MT output states regulate axonal firing and synaptic plasticity. b) As actin polymerizes (e. g. triggered by glutamate binding to receptors on dendritic spines), dendritic cytoplasm enters a quasisolid gelatinous (gel) phase, MTs become isolated from environment and enter quantum superposition mode in which tubulins function as quantum bits or qubits (Fig. 6.12). The two phases alternate, e. g., at 40 Hz (Fig. 6.13).
5. Quantum states of tubulin/MTs in gel phase are isolated/protected from environmental-decoherence by biological mechanisms that include encasement by actin gelation, ordered water, Debye screening, coherent pumping and topological quantum error correction (Sect. 6.7.2).
6. During quantum gel phase, MT tubulin qubits represent preconscious (unconscious, subconscious) information as quantum information – superpositions of multiple possibilities, of which dream content is exemplary.
7. Preconscious tubulin superpositions reach threshold for Penrose OR (e. g. after 25 ms) according to $E = \hbar/t$ in which E is the gravitational self-energy of the superpositioned mass (e. g. the number of tubulins in superposition), $\hbar$ is Planck's constant over 2π, and t is the time until OR. Larger superpositions (more intense experience) reach threshold faster. For $t = 25$ ms (i. e. 40 Hz) E is roughly 10^{11} tubulins, requiring a hyperneuron of minimally 10^4 neurons per conscious event (Hameroff and Penrose [89]). The makeup of the hyperneuron (and content of consciousness) evolves with subsequent events.
8. Each 25 ms OR event chooses 10^{11} tubulin bit states that proceed by MT automata to govern neurophysiological events, e. g. trigger axonal spikes, specify MAP binding sites/restructure dendritic architecture, regulate synapses and membrane functions. The quantum computation is algo-

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shifts will be significant if they are collective for all nuclei in a protein, tipping into basins of attraction upon reduction. Thus superposition of conformations need involve only separation at the level of atomic nuclei. The delicate balance of powerful countervailing forces determining protein conformation lends itself to functioning as a qubit.

[42] Centriole entanglement [96], quantum optical photons, Bose–Einstein condensation.

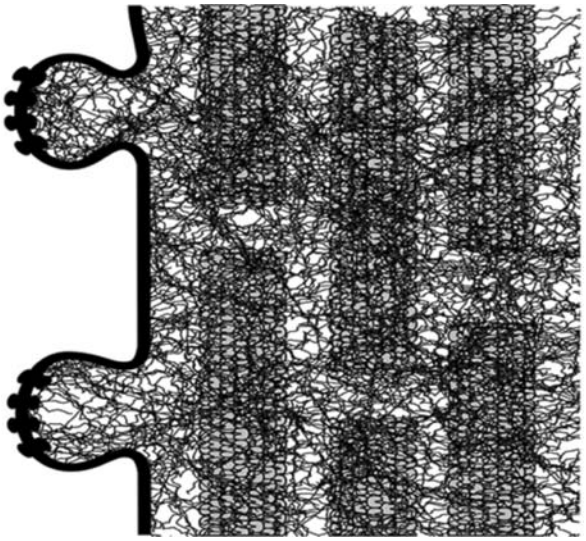

Fig. 6.12. Interior schematic of dendrites in quantum isolation phase. Actin has polymerized into the gel meshwork and MAPs detached, shielding and isolating MTs whose tubulins have evolved into quantum superposition

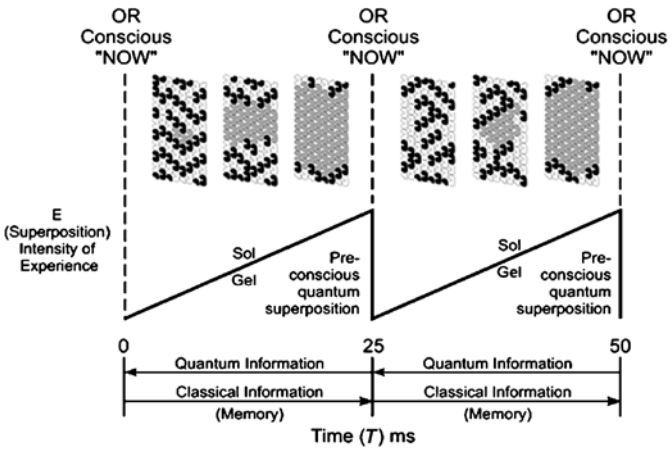

Fig. 6.13. Conscious events. *Top*: Microtubule automata enter preconscious quantum superposition phase (gray tubulins) until threshold for OR is met after 25 ms (this would involve superposition of 10^{11} tubulins in tens of thousands of neurons interconnected by gap junctions). A conscious moment (NOW) occurs, new classical states of tubulins are chosen and a new sequence begins. *Middle*: Phase diagram of increasing superposition in gel phase that meets threshold after, e. g., 25 ms. A conscious event (NOW) occurs, and the cycle repeats. *Bottom*: After each OR event, quantum information is sent backward in time to influence previous event. Classical information (memory) goes forward in time

rithmic, but at the instant of OR a noncomputable influence (i. e. from Platonic values in fundamental space-time geometry) occurs.
9. Each OR event ties the process to fundamental space-time geometry, enabling a Whiteheadian pan-protopsychist approach to the "hard problem" of subjective experience. A sequence of such events gives rise to our familiar stream of consciousness.

Applications of Orch OR to aspects of consciousness and cognition will be considered in Sect. 6.8.

6.7.2 Decoherence

Decoherence is the disruption of quantum superposition due to energy or information interaction with the classical environment. Consequently, quantum technology is generally developed in ultracold isolation, and physicists are skeptical of quantum computing in the "warm, wet and noisy" brain.

However, biological systems may delay decoherence in several ways [36]. One is to isolate the quantum system from environmental interactions by screening/shielding. Intraprotein hydrophobic pockets are screened from external van der Waals thermal interactions; MTs may also be shielded by counterion Debye plasma layers (due to charged C-termini tails on tubulin) and by water-ordering actin gels [95]. Biological systems may also exploit thermodynamic gradients to give extremely low effective temperatures [152].

Another possibility concerns decoherence-free subspaces. Paradoxically, when a system couples strongly to its environment through certain degrees of freedom, it can effectively "freeze" other degrees of freedom (by a sort of quantum Zeno effect), enabling coherent superpositions and entanglement to persist [163]. Metabolic energy supplied to MT collective dynamics (e. g. Fröhlich coherence) can counter decoherence (in the same way that lasers avoid decoherence at room temperature). Finally, MT structure seems ideally suited for topological quantum error correction by the Aharonov–Bohm effect [95].

Attempting to disprove the relevance of quantum states in consciousness, Max Tegmark ([228], cf. [203]) calculated MT decoherence times of 10^{-13} s, far too brief for neural activities. However, Tegmark did not address Orch OR nor any previous proposal, but his own quantum MT model, which he did indeed successfully disprove. Hagan et al. [85] recalculated MT decoherence times with Tegmark's formula[43] but based on stipulations of the Orch OR model. For example, Tegmark used superposition of solitons "separated from

[43] The time tau to decoherence due to the long-range electromagnetic influence of an environmental ion is $\tau \simeq \frac{4\pi\epsilon_0 a^3\sqrt{mkT}}{Nq_e^2 s}$ where T is the temperature, m is the mass of the ionic species, a is the distance from the ion to the position of the superposed state, N is the number of elementary charges comprising that superposed state, and s is the maximal separation between the positions of the tubulin mass in the alternative geometries of the quantum superposition.

themselves" along MTs by a distance of 24 nm. In Orch OR, superposition separation distance is the diameter of a carbon atom nucleus, 6 orders of magnitude smaller. Since separation distance is in the denominator of the decoherence formula, this discrepancy alone extends the decoherence time 6 orders of magnitude to 10^{-7} s. Additional discrepancies (charge versus dipole, correct dielectric constant) extend the calculated decoherence time to 10^{-5} to 10^{-4} s. Shielding (counterions, actin gel) extends the time into physiological range of tens to hundreds of ms[44]. Topological (Aharonov–Bohm) quantum error correction may extend MT decoherence time indefinitely [181].

Is the brain truly "wet and noisy"? In gel phase MTs are in a quasisolid environment with ordered water. As for "noisy", electrophysiological background fluctuations show ongoing "noise" to actually correlate over distances in the brain [9, 51].

Quantum spin transfer between quantum dots connected by organic benzene molecules is more efficient at room temperature than at absolute zero [167]. The same structures are found in amino acids (phenylalanine, tyrosine, tryptophan) in hydrophobic pockets of proteins. Other experiments have shown quantum wave behavior of biological porphyrin molecules [84], and still others that noise can enhance some quantum processes [13]. Evolution has had billions of years to solve the decoherence problem (Sect. 6.8.6).

6.7.3 Testability and Falsifiability

In 1998 twenty testable predictions of Orch OR were published [91]. Among them, the following have been validated: signaling along MTs [148, 149], correlation of synaptic function/plasticity with cytoskeletal structure [125, 262, 165], actions of psychoactive drugs involve MTs [7], and gap junctions mediate gamma synchrony/40 Hz (numerous references cited in Sect. 6.3.5). Others are currently being tested, and all are listed in Appendix 1. None have as yet been proven wrong. With the possible exception of the link to Planck-scale geometry, all are imminently testable. Orch OR is falsifiable – it need only be shown that consciousness can occur without dendrites, gap junctions (or some other mechanism for brain-wide quantum coherence), microtubules or quantum computation and Orch OR is falsified

6.8 Applications of Orch OR to Consciousness and Cognition

6.8.1 Visual Consciousness

Visual components (e. g. shape, color, motion) are processed in separate brain areas and at different times but integrated into unified visual gestalts. How does this occur? And how do 40-Hz excitations relate to longer periods as-

[44] The decohering effects of radiative scattering on microtubules is negligible.

sociated with the visual gestalt (e. g. 250 to 700 ms)? Thalamic inputs to V1 are fed-forward to areas V2, V3, V4 and LO for shape recognition, then to V8 and V4v for color, to V5, V3A and V7 for motion, then back to V1 and prefrontal cortex. In Woolf and Hameroff [264] we suggested that each component step corresponded with a 40-Hz excitation, and microconsciousness as proposed by Zeki [269]. To unify components in a visual gestalt after hun-

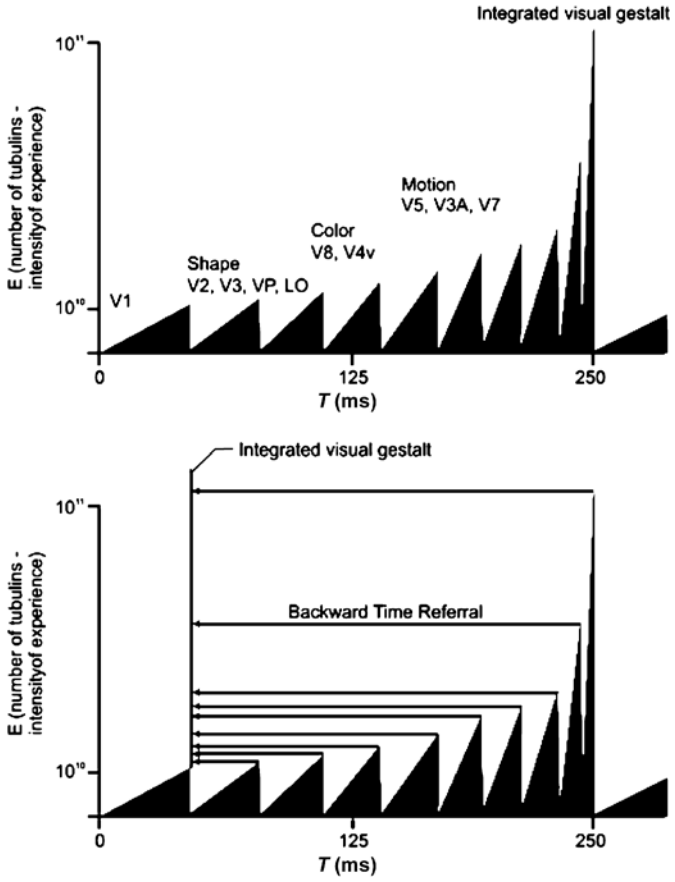

Fig. 6.14. A visual gestalt. *Top*: A crescendo sequence of 25-ms/40-Hz quantum computations/conscious events of components of conscious vision culminating in an integrated visual gestalt after, e. g. 250 to 700 ms (modified from Woolf and Hameroff [264]). The intensity (y-axis) is related to the amount of superposition represented by $E = \hbar/t$. Thus the slope/intensity for each event is inversely proportional to time to OR. *Bottom*: Modified version in which components are referred backward in time as nonconscious quantum information. The duration backward in classical time is related to slope/intensity of each component event. Thus an integrated visual gestalt occurs early in visual processing

dreds of ms, a cumulative snowball effect – a crescendo of crescendos – occurs (corresponding with the growth of a hyperneuron, Fig. 6.14). Commenting on this proposal Gray [81] points out that we are conscious only of the visual gestalt, not incremental components. This suggests that each Orch OR event refers quantum information/qualia of visual components backward in time (the duration proportional to E) to the initial V1 potential, resulting in an integrated visual gestalt early in the integration process. Consequently tennis and baseball players consciously see and recognize the ball's shape, color and motion early enough to respond successfully. In the color phi phenomenon the brain fills in the gap by backward referral from the subsequent location. Thus unlike retrospective construction, conscious sensation actually occurs in transit between the two locations.[45]

6.8.2 Volition and Free-Will

Volition and free-will raise two major issues. One is time, in which we apparently act prior to processing the relevant inputs to which we respond. Backward time referral of unconscious quantum information can solve this problem. The other issue is determinism. If brain processes (including nonconscious processes) and events in our environment are algorithmic – even if highly nonlinear/chaotic – then our actions are deterministic products of genetic influences and experience. Wegner [256] concludes that free-will is the (illusory) conscious experience of acting deterministically. The noncomputable aspect of Penrose OR can help.

Suppose I am playing tennis about to return my opponent's ground stroke. As I begin to get my racket in position, I consider hitting a) to his forehand, b) to his backhand, c) a drop shot. A quantum superposition of these three possibilities (manifest as tubulin qubits) in a premotor cortical hyperneuron evolves and reaches threshold for OR, at which instant one set of tubulin states corresponding with one action (e. g. hit to his forehand) is chosen resulting in the appropriate set of axonal spikes to execute the choice.

Could such actions be completely algorithmic and classical? Yes, but in addition to the beneficial time effect, the noncomputable influence in Penrose OR can provide intuition, tipping the balance to the appropriate choice.[46] Sometimes (it seems to me at least) we do things and we're not quite sure why we do them.

[45] The same effect can account for tactile binding (we feel our foot strike the ground, and refer the sensation backwards in time to match the visual input) and the cutaneous rabbit (we feel the upper-arm, elbow and wrist sensations after the first tap and refer them to the appropriate spatial location). If no elbow or upper-arm sensations occur, no referral of the second and subsequent wrist sensations occur.

[46] From either Platonic influences embedded at the Planck scale, entangled quantum information from my opponent or an image from the near future, e. g. my opponent leaning the wrong way.

This is not free-will in the sense of complete agency because the noncomputable influence is ultimately deterministic.[47] What we experience as free-will is algorithmic processes influenced by noncomputable factors. This differs from Wegner's [256] view in that 1) our actions are not completely algorithmic, and 2) because of backward time referral, decisions are made consciously, concomitantly with the experience of the choice and action, and 3) consciousness is not epiphenomenal.

6.8.3 Quantum Associative Memory

Evidence suggests memory is hard-wired in dendritic cytoskeletal structure [125, 262, 165]. Woolf and Hameroff [264] suggested that perception of a stimulus precipitates conscious awareness of associated memory via EPR-like OR of entangled (associated) information. This implies that disparate contents of unified consciousness remain entangled in memory [96].

6.8.4 The Hard Problem of Conscious Experience

How the brain produces phenomenal experience composed of qualia – the smell of a rose, the felt qualities of emotions, and the experience of a stream of conscious thought – is the "hard problem" [28].

Broadly speaking, there are two scientific approaches: 1) emergence (experience arises as a novel property from complex interactions among simple components in hierarchical, recursive systems), and 2) some form of panpsychism, pan-protopsychism, or pan-experientialism (essential features or precursors of conscious experience are fundamental components of reality, accessed and organized by brain processes).

Emergence derives from the mathematics of nonlinear dynamics, e. g. describing weather patterns, candle flames and self-organizing computer programs. Is consciousness an emergent property of interactions among neurons (or among tubulin proteins in microtubules)? Perhaps, but emergent phenomena generally have predictable and testable transition thresholds, and none are evident for consciousness.

Panpsychism, pan-protopsychism, and pan-experientialism view consciousness as stemming from fundamental, irreducible components of physical reality, like electrical charge, or spin. These components just are. Panpsychism holds that primitive consciousness is a quality of all matter: atoms and their subatomic components having subjective, mental attributes (e. g. [218], [189]). Whitehead [257, 258] eschewed panpsychism (as do I), arguing for processes rather than objects and properties. In Whitehead's pan-experientialism, consciousness is a sequence of events – occasions of experience – occurring in what he described as a wider, basic field of protoconscious experience. Philosopher

[47] One could say that free-will involves the choice of whether or not to allow oneself to be influenced by noncomputable factors.

Abner Shimony [210] observed that Whitehead occasions could be construed as quantum state reductions, consistent with Penrose OR. If so, what is Whitehead's basic field of protoconscious experience?

Penrose OR describes events in fundamental space-time geometry, the foundational level of the universe. Going down in scale below the size of atoms (10^{-8} cm) space-time is smooth until the Planck scale at 10^{-33} cm where coarse granularity (i. e. information) accurs.[48] The Planck scale is approached in modern physics through string theory, quantum gravity, twistor theory, spin networks, etc. Although the correct description is unknown, it is known that the Planck scale is quantized and nonlocal, and the level at which Penrose suggests quantum superpositions occur as separations, and where Platonic values exist. It is also at this ubiquitous level that protoconscious qualia are proposed to be embedded [90], hence pan-protopsychism.

If so, Whitehead's occasions of experience may be Orch OR events occurring in a pan-protopsychist field manifest at the Planck scale. Quantum computations with OR in microtubules connect our brains to the fundamental level of reality. Each Orch OR event accesses and selects a particular set/pattern of proto-conscious qualia that manifests as consciousness at the instantaneous moment of reduction – an occasion of experience.[49] A sequence of such events gives rise to our stream of consciousness.

6.8.5 What is Consciousness?

Orch OR is a threshold-based event, fulfilling Freeman's [58] criterion for consciousness: self-organized criticality occurring in the brain. Consciousness is OR. OR is consciousness. To be consistent: 1) all quantum superpositions are protoconscious, and 2) any Penrose OR must be conscious, regardless of where or how it occurs. Are brains the only site?[50]

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[48] The quantum world is generally considered to be random, however, EPR entanglement demonstrates that order exists. Measurement and decoherence may introduce randomness and indeterminacy avoidable through Penrose OR.

[49] Protoconscious qualia are presumed to exist in Planck scale geometry everywhere, including the space-time geometry within the brain. Because space-time at the Planck-scale is nonlocal (e. g. as evidenced by entanglement according to Penrose) the Planck scale configurations manifesting a particular set of qualia would exist both in the external world and in the brain. This is perhaps akin to the sensorimotor account of consciousness put forth by O'Regan and Noe [166].

[50] What about quantum superpositions in nonbiological systems? Technological quantum computers presently use superpositions of qubits with low mass separation/low E (e. g. ions, electrons, or photons) and reduction occurs by measurement well before OR threshold could be met. Hence these systems will not be conscious by the criteria of Orch OR. However, in principle, quantum computers using superpositions of larger mass qubits such as perhaps fullerene technology could reach the threshold for OR and have conscious moments.

Superpositions are common (ubiquitous at the Planck scale, hence panprotopsychism) but Penrose OR requires stringent conditions. The time to reach threshold for OR is inversely related to the amount of superpositioned mass ($E = \hbar/t$, the larger the superposition, the more quickly it reaches threshold). Decoherence (i. e. by interaction with the environment) must be avoided by isolating the superposition until threshold is met. Small superpositions are easier to isolate/avoid decoherence but require longer times to reach threshold. Large superpositions reach threshold quickly but are more difficult to isolate. Conscious brain activities occur in the range of tens to hundreds of ms (e. g. 25 ms for 40 Hz), requiring nanograms of superpositioned proteins. Only in the brain can relatively large superpositions be isolated (e. g. in dendrites of hyperneurons) and linked to cognition.

Proteins are optimal quantum levers, large enough to exert causal efficacy in the macroscopic physical world but small (and delicately balanced) enough to be in superposition and mechanically governed by quantum London forces. Protein-based OR/consciousness is a self-organizing process on the edge between the quantum and classical worlds.

6.8.6 Consciousness and Evolution

Has evolution favored consciousness? The functionalist view of consciousness as illusory epiphenomenon seems to offer few advantages for adaptation and survival. However, Orch OR offers the following: 1) Quantum computing (e. g. search algorithms) offers faster (near-infinitely parallel) processing than conventional computing, 2) Penrose noncomputability would confer intuitive unpredictability, e. g. in predator–prey relationships, and 3) Backward time referral and near-instantaneous semantic perception and response would also be beneficial, e. g. in predator–prey relationships. Thus evolution would favor quantum isolation mechanisms for progressively larger superpositions, e. g. proteins, assemblies of proteins, assemblies of assemblies of proteins (neurons), assemblies of neurons/hyperneurons ... brains, resulting in faster and more useful times to OR[51]. There is also the possibility that biology evolved and adapted to a pre-existing protoconsciousness.

Large-scale quantum superpositions may exist naturally in the universe, for example in the cores of neutron stars, or the very early universe [271], able to reach OR threshold quickly. Such OR events would presumably lack organized information and cognition (OR without Orch). But to be consistent with the Orch OR criteria, yes, they would be conscious/have conscious experience, perhaps as flashes of meaningless awareness. This issue is faced by any theory: are all emergent phenomena conscious? Are all information processing systems such as computers and thermostats conscious? Functionalists often obfuscate this issue by saying, e. g., a thermostat is conscious in a thermostat-like way whereas humans are conscious in a human-like way, cats in a cat-like way, etc.

[51] The onset of consciousness in the course of evolution is speculated upon in Hameroff [94].

6.9 Conclusion

The Penrose–Hameroff Orch OR theory "goes out on a limb" to address the puzzling facets of consciousness. It has engendered criticism because 1) it differs markedly from conventional wisdom, and 2) significant quantum processes seem unlikely in the warm brain milieu. But conventional wisdom fails to address puzzling facets of consciousness, and evidence suggests that biology has evolved mechanisms for brain-temperature quantum processes. Orch OR is consistent with all known neuroscience, cognitive science, biology and physics although it extends these disciplines theoretically. Moreover, unlike conventional theories Orch OR is testable and falsifiable. Spanning neurobiology, physics and philosophy, it is the most complete theory of consciousness.

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Appendix

Testable predictions of the Orch OR model [91]. Major assumptions are in bold, specific predictions are numbered in lower case and pertinent supportive references are in brackets.

Neuronal microtubules are directly necessary for consciousness

1. Synaptic sensitivity and plasticity correlate with cytoskeletal architecture/activities in both presynaptic and postsynaptic neuronal cytoplasm [125, 120, 155, 165].
2. Actions of psychoactive drugs including antidepressants involve neuronal microtubules [7].
3. Neuronal microtubule stabilizing/protecting drugs may prove useful in Alzheimer's disease, ischemia, and other conditions [107].

Microtubules communicate by cooperative dynamics of tubulin subunits [148, 149, 246].

4. Laser spectroscopy (e. g. Vos et al. [253]) will demonstrate coherent GHz Fröhlich excitations in microtubules. (Preliminary work using surface plasmon resonance, see Lioubimov et al. [144].)
5. Dynamic vibrational states in microtubule networks correlate with cellular activity.
6. Stable patterns of microtubule cytoskeletal networks (including neurofilaments) and intramicrotubule diversity of tubulin states correlate with memory and neural behavior [125, 262, 165].

7. Cortical dendrites contain largely "A lattice" microtubules (compared to "B lattice" microtubule, A lattice microtubules are preferable for information processing).

Quantum coherence occurs in microtubules

8. Studies similar to the famous "Aspect experiment" in physics (which verified nonlocal quantum correlations [10] will demonstrate quantum correlations between spatially separated microtubule subunit states a) on the same microtubule, b) on different microtubules in the same neuron, c) on microtubules in different neurons connected by gap junctions.
9. Experiments with SQUIDs (Superconducting Quantum Interference Device) will detect phases of quantum coherence in microtubules.
10. Coherent photons will be detected from microtubules.

Microtubule quantum coherence requires isolation by cycles of surrounding actin gelation.

11. Neuronal microtubules in cortical dendrites and other brain areas are intermittently surrounded by tightly crosslinked actin gels. (Glutamate binding to NMDA and AMPA receptors causes actin polymerization in dendritic spines: [53].)
12. Cycles of gelation and dissolution in neuronal cytoplasm occur concomitantly with membrane electrical activity (e. g. synchronized 40-Hz activities in dendrites).
13. The sol gel cycles surrounding microtubules are regulated by calcium ions released and reabsorbed by calmodulin associated with microtubules.

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

14. Electrotonic gap junctions link synchronously firing networks of cortical neurons, and thalamocortical networks [68, 75, 227].
15. Quantum tunneling occurs across gap junctions.
16. Quantum correlation occurs between microtubule subunit states in different neurons connected by gap junctions – the microtubule EPR experiment in different neurons (proposal by Andrew Duggins).

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

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

An isolated, unperturbed quantum system self-collapses according to $E = \hbar/t$.

18. Isolated technological quantum superpositions will self-collapse according to $E = \hbar/t$ (being tested – Marshall et al. [150]).

Microtubule-based cilia/centriole structures are quantum optical devices.

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

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

20. Fossil records and comparison with present-day biology will show that organisms which emerged during the early Cambrian period with onset roughly 540 million years ago had critical degrees of microtubule-cytoskeletal size, complexity and capability for quantum isolation (e. g. tight actin gels, gap junctions; see Hameroff [94]).

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