Exploration

Life Science Research with an Interface to Quantum Physics (Part I)

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Abstract

In this paper, we study the emission of human brain waves. The classical and quantum models are evaluated and compared to existing experimental data.

Part I of this two-part article includes: 1.The Brain waves. Overview of the research; and 2. Classical and quantum brain waves.

Keyword: Life science, interface, quantum physics, emission, human, brain wave.

1.The Brain waves. Overview of the research

Single-photon phenomena in the life sciences Single quanta of light have been relevant for illustrating fundamental quantum principles but they are also ubiquitous in the life sciences: The most efficient detection techniques for fluorescent biomolecules are sensitive on the single photon level. Individual particles of light are also of direct relevance in biological processes as they may affect the structure of individual molecules which in turn can transduce signals in living organisms. The retinal molecule can switch its conformation after absorption of very few photons and thus turns the human eye into one of the most sensitive light detecting devices that exist. Between two and seven photons are usually sufficient to be perceived by a dark-adapted human observer (Hecht et al., 1942).

Various studies indicated that test persons could even count the number of photons with a reliability that was only limited by quantum shot noise (Rieke and Baylor, 1998, and citations therein). Single photon detectors are of great interest for quantum communication and it has recently been suggested that octopus rhodopsin, chosen by evolution because it is well-adapted to the dark of the deep oceans, may be a useful component in such applications (Sivozhelezov and Nicolini, 2007). But also single photon sources are gaining increasing importance in quantum communication or computation protocols and single molecules are considered to be relevant emitters (Lounis and Orrit, 2005).

When we talk about the quantum properties of light we usually refer to its wave-particle duality, the grain- iness and quantum statistical properties, such as photon bunching, anti-bunching or

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squeezing (Glauber, 2006). Fluorescence correlation experiments with proteins (Sanchez-Mosteiro et al., 2004) have revealed both the discrete quantum nature of molecular energy states and the non-thermal quantum statistics of light: An excited single molecule may usually not absorb a second photon of identical wavelength - unless the excited state has decayed. The emitted photons are therefore released with a time structure which differs from that of thermal light sources. Photons emitted by a single molecule come in an anti-bunched rather than a bunched time series. It remains, however, still open whether single-photon emission is explicitly used by living systems.

In contrast to that, artificially grown quantum emitters have found many applications in the life sciences. The characteristic energy of a quantum system is connected with its spatial dimensions. This is in particular also true for semiconductor nanocrystals, which measure only a few nanometers in diameter and whose color can be changed from blue to red by growing them to larger sizes. Fluorescent quantum dots are used as highly efficient labels for biomolecular imaging and they allow to follow the dynamics of marked receptors in the neural membrane of living cells (Dahan et al., 2003). Similar results have recently also been achieved with nanodiamonds. Their nitrogen vacancy centers exhibit strong and stable fluorescence, they are biocompatible and they have also been proven to be highly sensitive quantum probes for magnetic fields on the nanoscale (e.g. Balasubramanian et al., 2008).

Q*uantum tunneling in biomolecules: from enzymatic reactions to the ol- factory sense?* Living organisms are enormous biochemical reactors, making and breaking zillions of chemical bonds every day. To a large extent the reaction rates are controlled both by thermal activation and enzymatic catalysis. It has been a long-standing question whether quantum tunneling is also involved and whether its presence provides an evolutionary advantage. This concerns the tunneling of electrons, protons and even entire small molecules. The theory of electron transfer has a long history (Marcus, 1956). First evidence for electron tunneling was derived from the oxidation rate of cytochrome (see Fig. 3b) in the bacterium chromatium vinosum. Since the reaction speeds were both large and temperature independent at low temperatures (<100 K) it was concluded that they are incompatible with a thermal activation model alone (De Vault and Chance, 1966).

Electron tunneling has actually been identified as a widespread process, found in photosynthesis (Blankenship, 1989), cellular respiration (Gray and Winkler, 2003) and electron transport along DNA (Winkler et al., 2005). While speculations about proton tunneling had also been around for long (Lo¨wdin, 1963), first experimental evidence was only given in 1989 (Cha et al., 1989) for the enzyme alcohol dehydrogenase, which transfers a proton from alcohol to nicotinamide adenine dinucleotide. Since tunneling depends on the mass of the object, the tunneling rates must change when hydrogen is replaced by the chemically equivalent deuterium which doubles the atomic mass. This kinetic isotope effect was confirmed and gives good evidence for the presence of proton tunneling. Since then, many other enzymatic reactions were ascribed to proton tunneling (Glickman et al., 1994).

It has to be noted, however, that the tunneling distances involved in all these reactions are typically shorter than 0.1 nm and the protons traverse the barrier at energies around 10 kcal/mol (0.4 eV) below the potential maximum (Masgrau et al., 2006). The simultaneous tunneling of several particles has also been discussed, including double, triple and even quadruple proton exchange in cyclic molecular networks (Brougham et al., 1999). The transition rates in these experiments were measured using NMR spectroscopy and the temperature dependence of the reaction rate as well as the kinetic isotope effect were taken as witnesses for the presence of hydrogen tunneling. Even the tunneling of entire small molecules, i.e. formaldehyde (CH2 O), was proposed based on the temperature dependence of its photo-induced polymerization rate (Goldanskii, 1979). Turin (Turin, 1996) also opened a public debate by suggesting that we are even able to smell quantum tunneling.

Most aspects of our sense of smell are very well understood without it. Linda Buck and Richard Axel received the Nobel prize for their description of the mammalian olfactory system. They identified transmembrane proteins that encode for odor receptors in the olfactory epithelium (Buck and Axel, 1991). Each of them can sense multiple odorants. And each odorant can be detected by different sensors. Most smells can be perfectly explained (Zarzo, 2007) by assuming a lock-and-key mechanism, where an odor molecule binds to a specific receptor combination depending on its size, shape and chemical groups.

Based on much earlier hypotheses (Dyson, 1938), Turin suggested that smell is, at least additionally, cor- related to the vibrational spectrum of molecules and that the receptors perform phonon-assisted inelastic electron tunneling spectroscopy to identify the odorant. This idea should explain why our nose is able to distinguish molecular groups of similar geometry but different vibrational spectra, such as for example OH and SH or ferrocene and nickelocene (Turin, 2002). However, recent experiments (Keller and Vosshall, 2004) rejected this theory, while newer theoretical work conceded a conceptual viability of the idea – even though without being quantitatively decisive (Brookes et al., 2007). Concluding, we see that quantum tunneling is certainly present in a large number of biological processes, but experimentally proven only on the level of small-scale chemical reactions.

Coherent excitation transfer in photosynthesis Photosynthesis is a key process for life and often considered as a role model for future light harvesting technologies (Blankenship, 2002). It is differently realized in plants, algae or bacteria. But they all convert light to chemical energy. A closer look reveals that photosynthesis involves a plethora of highly complex processes, such as long-ranged excitation transfer, redox-reactions, hydrolysis, proton transport or phospho-rylation. In many parts of the system – including the wet-chemical material transport – we don't expect to find significant quantum coherence or entanglement, but others may actually require the notion of quantum tunneling, coherent excitonic transfer or matter-wave interference.

The photosynthetic complex is a membrane-bound system with many embedded functional subunits. The energy conversion starts with the absorption of an incident photon by a pigment molecule, e.g. a chlorophyll, porphyrin or a carotenoid molecule embedded in a protein structure, the antenna complex. The large number of these dye units ensures a high photo-absorption probability, and their arrangement enables an efficient excitation transfer from the primary absorber to the reaction center. The reaction center is a pigment-protein complex which contains a dimer, called the special pair. When it is excited, it donates an electron to a neighboring acceptor molecule. Fast secondary processes prevent the recombination of the ion pair and trigger the release of protons that are first transferred across the membrane and later used to fuel, for instance, the synthesis of adenosine triphosphate (ATP) from adenosine diphosphate (ADP).

Several recent studies (van Grondelle and Novoderezhkin, 2006; Cheng and Fleming, 2009) emphasized how well the excitation transfer from the antenna pigments to the reaction center is optimized. A fast conversion is important since any delay would increase the chances of relaxation mechanisms to channel energy into heating instead of chemical potentials. Early explanations of the energy transport, based on incoherent and dipole-dipole-mediated excitation hopping between molecular sites (F¨orster, 1948), failed to explain the observed transfer rates. Delocalization and coherent exciton coupling between the closely packed antenna pigments were therefore suggested as the most likely explanation, with experimental support rapidly growing throughout recent years. Modern two-dimensional Fourier transform spectroscopy allowed to probe the various excitation transfer pathways between the molecules on a femtosecond time scale.

In particular, experiments performed on a 77 K cold bacteriochlorophyll Fenna–Matthews–Olsen antenna complex were able to reveal exciton delocalization (Brixner et al., 2005) and long-lasting coherence in the excitonic energy transfer observation of a spatially and temporally extended coherence, covering several nanometers and time- spans as long as a few hundred femtoseconds, is highly remarkable and it has triggered a growing number of scientific groups to focus their theoretical and experimental work on that question. As of today, a rich set of detailed data has already been collected to characterize the energy levels, transfer rates, intramolecular and intermolecular coherences. In particular the latter raised the question how to connect these findings to related fields in quantum physics.

When there is coherence, what is the role of constructive or destructive interference? And are we allowed to use the language of quantum information processing to describe the highly efficient natural transfer of information and energy in light-harvesting complexes? It has been suggested that a wavelike sampling of the energy landscape or even a quantum search algorithm might permit to find the fastest route from the antenna to the reaction center (Engel et al., 2007). The excitation transport has also been associated with quantum random walks (Mohseni et al., 2008). In contrast to classical random walks - which we also know from Brownian motion - the position of the quantum walker would not be a single random position but rather a superposition of positions.

The incorporation of interference effects in the theoretical reasoning led to further considerations concerning the possible role of the protein environment (Rebentrost et al., 2009; Olaya-Castro et al., 2008), since a close look at wave physics reveals that coherence can be both beneficial and a hindrance if the aim is to optimize the speed of transport. On the one hand, the simultaneous wavelike sampling of many parallel paths could possibly result in finding a faster way to the final goal. But on the other hand the presence of an irregular lattice of scattering centers (static disorder) may actually suppress wave transport because of destructive interference. This phenomenon, well known in solid state physics, is called Anderson localization (Anderson, 1958). In that case, thermal fluctuations of the protein environment might therefore be crucial and help to avoid localization and thus assist in the excitation transfer (Caruso et al., 2009).

The importance of protein dynamics in eliminating Anderson localization was actually already discussed in an earlier paper by (Balabin and Onuchic, 2000), where multiple quantum pathways and interference were proposed for the electron transfer after the reduction of the special The role of interference in transport phenomena can also be visualized by recalling the analogy to an optical Mach-Zehnder interferometer (as shown in Fig. 1d): Depending on the setting of phases, wave interference can guide all excitations to either one of the two exits. Quantum coherence may then be the best way to channel the interfering quanta to the desired output. But if the wave phases happened to be initially set to destructive interference, quantum coherence would be a severe handicap. In this case, even random dephasing processes would help to optimize the transport efficiency.

External perturbations may also be important for energetic reasons: the electronic excitations have to be transferred between complexes of different energy. If the molecular states were too well defined, the lacking energy overlap would reduce the transfer rate. External perturbations may broaden the transition bands and thus increase the coupling between neighboring molecules. Recent experiments by (Collini and Scholes, 2009) however hint also at another possible role of the protein environment. In their experiments they could show that coherent electronic excitation transfer along con- jugated polymer chains occurs even at room temperature. These long lasting coherences (200 fs) could only be observed in intrachain but not in interchain electronic excitation transfers. All of the models described above bear in common that they rely on quantum coherence and decoherence and that they may be robust even under ambient environmental conditions – over short time scales. It is thus the fine interplay of coherent exciton transfer, decoherence and dephasing that yields the best results and which seems to reign one of the most important reactions in nature.

Conformational quantum superpositions in biomolecules. Since atoms can exist in a superposition of position states this may also lead to a superposition of confor- mational states in molecules. A tunneling-induced superposition of conformation states is conceivable. It becomes, however, highly improbable when many atoms have to be shifted over large distances and across high potential wells during the state change. Photoisomerization is another way of inducing

structural state changes in molecules - now using photon exchange, instead of tunneling. This opens the possibility to connect even energetically separated states. The photo-induced all-trans–13-cis transition of retinal is a famous example where a single photon can cause a sizeable conformation change. But much of the subsequent atom rearrangement occurs in interactions with the thermal environment (Gai et al., 1998).

In spite of that, it was possible to gain coherent quantum control in this process. Applying pulse-shaped femtosecond laser excitation to retinal in a native protein environment (Prokhorenko et al., 2006) achieved a modulation of the isomerization yield by ±20 %. The detected dependence on the laser phase is a good indication for the relevance of quantum interference among vibrational states. But a coherent superposition of functionally different configuration states, instead of electronic or vibrational states, has not been achieved for any large biomolecule, so far.

Decoherence has often been named to explain the prevalence of chirality in biomolecules. If a molecule may exist in two enantiomers, quantum mechanics allows, in principle, also for a coherent superposition of the left-handed and the right-handed state. In practice, however, this is not observed for larger particles. An intuitive argument is based on the fact that various scattering processes between a molecule and its environment depend on its chirality. This may include the scattering of polar light and elementary particles or the interaction through higher-order London dispersive forces between polarizable bodies.

Such events may act as quantum measurements and pro jections onto a chirality state. And in many cases, the energy barrier between the symmetric ground states will then be too high to allow for their spontaneous mixing on a time scale comparable to the scattering events (Trost and Hornberger, 2009). The generation and controlled decoherence of chirality superposition states in biological molecules thus still remains an open challenge. The lack of any experimental evidence for coherent conformation superpositions in large molecules also seriously questions a recent model by Hameroff and Penrose who suggested that the collapse of such superpositions in microtubuli may be the cause for the emergence of human conscious- ness (Hameroff and Penrose, 1996).

Spin and the magnetic orientation of migratory birds. It is well established that various animals are able to derive direction information from the geomagnetic field (Wiltschko and Wiltschko, 1995; Ritz et al., 2000; Johnsen and Lohmann, 2008). Some mammals per- ceive the Earth's field as a polarity compass, distinguishing north and south, while birds and reptiles rely on an inclination compass that discriminates between polewards and equatorwards and which exploits both the intensity and the gradient of the field. Interestingly, it could be shown (Wiltschko and Wiltschko, 2006 and refs. therein), that the the orientation in the magnetic field requires the presence of visible light beyond a certain photon energy and that an oscillating magnetic field (0.1-10 MHz) can disturb the bird's senses.

It has therefore been argued that vision-based magnetosensing might be rooted in the light-induced formation of a radical pair (Schulten et al., 1978), a mechanism originally invoked to explain the photochemically induced dynamic polarization in nuclei (Closs, 1969; Kaptein and Oosterhoff, 1969): When light falls onto a donor molecule in the bird's eye, it may excite it to a singlet state (Fig. 3c). The molecule may then transfer an electron to a neighboring acceptor molecule. The freshly formed pair of radical molecules usually starts in a singlet state (total spin quantum number: s=0), but in the presence of hyperfine couplings with the molecular nuclei it will undergo an interconversion between the singlet and the triplet state (s=1). Since spin is otherwise rather well protected from environmental influences on a short time scale, it is assumed that the spin pair remains quantum correlated, i.e. entangled in this process. This is also supported by a recent calculation (Rieper et al., 2009) where even a weak external oscillatory magnetic field noise was admitted and not able to fully destroy entanglement.

The evolution of the electron spins both in the presence of the nuclei and the earth's magnetic field will vary the ratio between singlet and triplet states. Since many chemical reactions are spin-dependent – in particular also the back-transfer of the electron from the acceptor to the donor – the spin evolution should also influence the ratio of molecular products that are finally formed in the bird's eye. A model for the transduction from the radical pair to the neuronal correlates was proposed by (Weaver et al., 2000) who also estimated the requirements on the size and the temperature dependence of the system in order to yield a certain sensitivity. The radical pair mechanism was ascribed to the signalling protein cryptochrome that can be found in the bird's retina (Wiltschko and Wiltschko, 2006). Both the electron transfer from a photo-excited flavin adenine dinucleotide along a chain of tryptophan molecules and the reverse recombination reaction are supposed to be sensitive to the geomagnetic field (Solov'yov and Schulten, 2009).

The idea is further supported by recent experiments of (Maeda et al., 2008) who showed that the radical pair mechanism in the earth's field is actually sufficiently strong to alter the chemical end products in a custom-designed complex that was built from a carotenoid, a porphyrin and a fullerene C60. In order to further corroborate that magneto-sensing is related to quantum-correlated (entangled) electrons, (Cai et al., 2009) suggested to use a sequence of short radio-frequency pulses to obtain active quantum control over the radical pair spins, immediately after their creation. Such and related experiments are still required to further elucidate this intriguing phenomenon.

Speculations on quantum information and biology on the large scale. Most puzzles of quantum physics are related to the way information is encoded and processed. Some re- searchers would therefore demand that quantum biology should be defined by its use of quantum information. The present section recapitulates two recent speculations which aim at much larger scales than that of a few molecules. We clearly state that, as of today, these hypotheses are without any experimental justification and even disputed on theoretical grounds. But as some of them have gained rather high popularity in discussions they merit mentioning and brief comments.

Quantum physics and the human mind About two decades ago, Roger Penrose raised the question whether classical physics alone could suffice to explain the enormous problem solving capabilities of the human brain (Penrose, 1989). And he speculated that a combination of currently irreconcilable pieces of physics, namely quantum theory and general relativity, might open a new window to our understanding of human consciousness, i.e. another phenomenon which is hardly understood. Together with the consciousness scientist Stuart Hameroff he proposed a model, that assumes that the human mind may exploit at least two conformations of microtubuli as values of a quantum bit. The quantumness of the proteins was suggested to solve complex computational problems in the brain while the act of consciousness would be linked to a gravity-induced objective collapse of the quantum wave function (Hameroff and Penrose, 1996).

Intriguing as the idea of macroscopic quantum coherence may be, the proposed model hits several hard bounds and controversies: As of today, no one has ever been able to prepare and characterize a useful coherent macroscopic quantum superposition of two conformations in a macromolecule, not even in the lab. And even if it existed in nature, decoherence is believed to be orders of magnitude too fast to make it relevant on physiological time scales (Tegmark, 2000; Eisert and Wiseman, 2007). An objective collapse of the wave function is currently also only one of many models to explain the emer- gence of classicality from quantum physics. The dynamics of the proposed gravitational collapse is neither theoretically understood nor experimentally observed. It may also surprise that microtubuli were chosen as the decisive agents in quantum consciousness.

They are by no means special to the human brain but rather ubiquitous cell support structures. In spite of its potential deficiencies, the model serves a purpose in that it stretches the scientific fantasy to its very limits. And even though it is unlikely that all details of the proposal will survive future scientific explorations, experimental efforts in proving or disproving these details will lead to new insights into the relevance of quantum phenomena within the life sciences. *Quantum aspects of the brain waves* If highly transient neuron assemblies are indeed a key feature of the brain operations that cause consciousness, a critical issue—for scientists especially—is how they might actually be formed.

The idea developed in this book is that because we have only one consciousness at any one moment (Arieli, 1995), then the dominant assembly for that moment would have to be so massive that it precluded the formation of any other sufficiently large rivals—the recruitment of, say, 10^7 neurons in less than 250 milliseconds. However, even this large number is simply the response of a group of neurons to a flash of light and does not necessarily entail consciousness. The requisite size of an appropriate neuron assembly might be far greater still.

Classical synaptic transmission is perfectly adequate for coordinating the firing of a million or so neurons in a fraction of a second. It is important to remember that neuron firing of an action potential is not linear, with one domino causing the fall of its neighbor one at a time. Yet if the firing of one neuron causes N neighbors to fire, then after S steps, -N^5 neurons will fire in a huge

three-dimensional domino effect. Even if *N* were as small as 10, only 6 steps would be needed to assemble a million neurons.
But suppose that synaptic transmission is not, after all, doing the job. According to the calculations, the spread of activity from the epicenter activated by the flash of light is some 100 to 250 cm/s. This is much faster than a wave of seizure in epilepsy (1 cm/s), yet it is actually much slower than classic synaptic signaling, where an action potential can be propagated down the neuron axon at speeds of up to 10, 000 cm/s. Whereas classic synaptic signaling is useful in local circuits of neurons, perhaps a different process is operational in the more gradual recruitment of very large, global assemblies that will in turn be necessary for consciousness.

A synapse is a highly specialized point of contact, as different from a mere gap as riverboat stations are from featureless banks facing each other across the water. (Levitan and Kaczmarek, 1996). A simpler but less specialized system involves the mere fusion of one dendrite of one cell with that of another, so that electrical current spreads passively, without the need for a participating chemical. These points of fusion are called "gap junctions." Perhaps spread of activation through the agency of gap junctions is what distinguishes the formation of a very large neuronal assembly. In support of this idea, John Jefferys and his colleagues have confirmed that the much-studied oscillations of some 40 Hz are generated as a result of normal synaptic transmission. What is particularly intriguing, however, is that Jefferys has also shown that it is possible for neurons to work collectively at a much faster rate, that there are in addition much faster oscillations of some 200 Hz. This higher-frequency orchestration is mediated not by synapses but by gap junctions. (Draguhn, 1998)

Perhaps the very extensive type of neuron assembly that mediates consciousness will be composed of synchronous neuron firing at a frequency far higher than the much-studied 40 Hz. However, because this type of activity depends on coherent gap junction signaling—which is less efficient than classic synaptic transmission—the time taken for large numbers of neurons to be recruited into a synchronous, large-scale assembly will be slower—the good half a second observed. These features—relatively slow-to-form but yet high-frequency coherence once established—might be advantageous in first stabilizing a moment of consciousness, and second in optimizing conditions, a very high-frequency firing, for the signature peptide profile to then be released.

Another alternative to the traditional picture involves a very different mechanism that might operate at a much more minuscule level, beyond the cell itself, and beyond the classic physics of Newton which is successful for describing events in the everyday world, and with it, in principle at least, traditional neuroscience. Just such a vision has captured the imagination of the mathematician Roger Penrose and the anesthetist Stuart Hameroff. (Hameroff, Penrose, 2003) Their version of events does not rely on the classic generation of action potentials, but rather on a faster and far more speculative process that is based on quantum theory.

Penrose and Hameroff's speculations about the nature of consciousness begin by noting that in one interpretation of quantum theory, the very act of observation causes a system to be in one type of unpredictable state, a phenomenon they call "subjective reduction It is subjective because it requires an observer. In the brain, however, there is no outside observer, and hence the appropriate conditions might prevail under which quantum events are not downgraded subjectively, but rather occur spontaneously, without anyone watching. This hypothetical phenomenon has been called objective reduction (OR) by Penrose and Hameroff, who believe that the concept of OR could underpin a new type of physics. Because OR would not obey the computable and established rules of either quantum physics or Newtonian physics, they consider that this new physics would be most appropriate for generating consciousness—another incomputable phenomenon.

Quantum theory offers the appropriate time and space scales for assembling millions of neurons in a fraction of a second into a working assembly. This procedure is known as quantum coherence. However, we have seen that classical processes can proceed just as well. Yet here, too, in quantum coherence, there might be a good candidate for a neural correlate of consciousness.

Penrose and Hameroff have speculated that the medium of such orchestration could be the tiny, fluid-filled microtubules, which are present in virtually every cell in the body. Coherence would occur, they suggest, by exciting water molecules buried in a protein, *tubulin* the building block of microtubules. Tubulin can undergo conformational changes in molecular structure. The idea runs that these changes could support wavelike signals propagated in accord with quantum theory comes Penrose and Hameroff speculation: Once the number of neurons is sufficiently large, then in accord with the as yet nonexistent *New Physics*, there would be a spontaneous downgrading of the wave, an OR across large numbers of cells. This OR, a sudden commitment to one type of physical state, would somehow correspond to a moment of consciousness in the macro brain.

As it stands, the existence of microtubules and the idea of quantum coherence as a basis for consciousness has not so much been shown to be wrong, but on its own, it has simply been unhelpful for biologists—it is too abstract to be usefully applied to the tangible brain, and it is without experimental motivation.

For Penrose and Hameroff idea to qualify as a successful correlate of consciousness, three basic issues still need to be resolved before biologists can make use of it. First, we need a further feature to the scheme whereby the number of requisite coherent neurons can be increased from the tens and hundreds of thousands, to tens and hundreds of millions. Second, a means of catering for the role of chemically diverse transmitter systems is needed. Third, we need a reason for discriminating between certain microtubules, such that only those in certain neurons, and not in just any old cell, are appropriate to mediate consciousness at certain times.

One possible way of overcoming these problems lies in a scheme advanced by the neuroscientist Woolf. (Woolf, 1975). Woolf's model starts off conventionally enough. Neurons in a certain brain region, the *basal forebrain,* are active and release the transmitter acetylcholine, in the accepted fashion, on to neurons in the cortex. Acetylcholine will, again in the traditional way, act via its normal molecular targets, its receptors, on discrete modules of neurons, stretching some 1 to 2 mm^2 in the cortex. But now some of the consequences might be unexpected: in addition to its action within local circuitry, Woolf has suggested a chemical-selective and site-selective means whereby the quantum coherence based on microtubule operations could be set in train.

Models such as the one we have just explored, based on Woolf's imaginative exploitation of the known actions of MAP2 and acetylcholine, are at the very least useful in that they cross the traditional disciplines of physics and neuroscience to show how a combination of phenomena, rules, and constraints from each can make a more robust and plausible model.

Note that this hybrid theory is once again dependent on good old-fashioned transmitter signaling. We cannot rule out the possibility that acetylcholine—as a prototype neurochemical—plays an important role in triggering other, nonclassical events as well as at the more macro level of brain function; for example, as a neuromodulator, putting cells on red alert. All the electrical signals are generated in the same rhythm of oscillations. However, no single cell joins in all the activity all the time, but overall there are sufficient cells to maintain a synchronous activity for very long periods of time. Acetylcholine in this instance has enabled a whole population of cells to become more important than the individual units.

Whatever the eventual mechanisms of attaining a transient coherence in a very large assembly of neurons turn out to be, there is no shortage of candidates even at the moment. The future will no doubt reveal more, along with means for testing which ones really do play a part in formation of assemblies, and hence in the reality of a neural correlate of consciousness that is not just necessary but sufficient.

2. Classical and quantum brain waves

Classical theory of brain waves How the brain differ from hearts, livers, and other organs? All organ systems are enormously complicated structures, able to repair themselves and make detailed responses to external control by chemical or electrical input. Yet, only brains yield the amazing phenomenon of consciousness (Nunez, 2010). Complex adaptive systems, for which human brains provide the most prominent examples, are composed of smaller parts interacting both within and across spatial scales. They typically exhibit emergent behavior not obviously predictable from knowledge of the individual parts and have the added capacity to learn from experience and change their global behaviors by means of feedback processes. Other examples include stock markets, ecosystems, and all living systems.

Several general features distinguish human brains from other organs, including the hallmark of richer hierarchical (or multi-scale) interactions. In contrast to simple cognitive "theories Nunez's papers explicitly acknowledges brains as highly complex adaptive systems, emphasizing the critical contribution of cross scale interactions to their dynamic behaviors. In order to minimize communication barriers due to the complicated mathematics, several analog systems from disparate fields are employed. Neuroscientists are typically skeptical of brain analogs, typically for good reason; however, we are *not* claiming that brains are actually just like stretched strings, social systems, quantum structures, resonant cavities, hot plasmas, disordered solids, chaotic fluids, or any other non-neural system.

In many complex systems, as spatial-temporal scales of observation are increased, new phenomena become evident by virtue of synergistic interactions among smaller-scale entities, which serve to explain data, typically in a mathematically aesthetic fashion For example, in the classical thermodynamics of equilibrium systems, it is possible to transition from microscopic molecular scales to macroscopic scales and employ the macroscopic variable temperature to describe the average kinetic energy of microscopic molecular activity. Many complex systems, however, operate in non-equilibrium states, being driven by nonlinear and stochastic interactions. For such systems, classical thermodynamics typically does not apply For example, the description of weather and ocean patterns, which includes important features such as turbulence, rely on semi-phenomenological mesoscopic models, in agreement with molecular theories but not capable of being rigorously derived from them.

Phase transitions in magnetic systems and many systems similarly modeled require careful treatment of a continuum of scales near critical points. In general, rather than having a general theory of non-equilibrium nonlinear process, several overlapping approaches are employed, typically geared to classes of systems and often expanding on nonlinear treatments of stochastic systems (Gardiner, 1983).Given this general outline of complex systems, it should not be surprising that human brains support many phenomena arising at different spatial-temporal scales.

One can study macroscopic neocortical phenomena such as electroencephalography (EEG) by appealing to a chain of arguments dealing with overlapping microscopic and mesoscopic scales. Such work is detailed in a series of papers presenting a theory of statistical mechanics of neocortical interactions (Ingber & Nunez, 1990). This approach permits us to develop EEG and other models of dynamic processes whose variables and parameters are closely identified with ensembles of synaptic and neuronal interactions. The mathematical formalism supporting this approach has only recently been made possible by developments in mathematical physics since the late 1970s, in the field of nonlinear non-equilibrium statistical mechanics. The origins of this theory are in quantum and gravitational field theory.

EEG allows for accurate identification of distinct sleep stages, depth of anesthesia, seizures and other neurological disorders. It also reveals robust correlations with cognitive processes

occurring during mental calculations, working memory and selective attention. Scientists are now so accustomed to these EEG correlations with brain state that they may forget just how remarkable they are. The scalp EEG provides very large-scale and robust measures of neocortical dynamic function. A single electrode yields estimates of synaptic action averaged over tissue masses containing between roughly 100 million and 1 billion neurons. The space averaging of brain potentials resulting from extra-cranial recording is a fortuitous data reduction process forced by current spreading in the head volume conductor.

Much more detailed local information may be obtained from intracranial recordings in animals and epileptic patients. However, intracranial electrodes implanted in living brains provide only very sparse spatial coverage, thereby failing to record the "big picture" of brain function. Furthermore, the dynamic behavior of intracranial recordings depends fundamentally on measurement scale, determined mostly by electrode size. Different electrode sizes and locations can result in substantial differences in recorded dynamic behavior, including frequency content and coherence. Thus, in practice, intracranial data provide different information, not more information, than is obtained from the scalp (Nunez, Srinivasan, 2006a).

In practice, intracranial EEG may be uncorrelated or only weakly correlated with cognition and behavior. The information content in such recordings is limited by sparse spatial sampling and scale-dependent dynamics. Furthermore, most intracranial EEG data are recorded in lower mammals; extrapolation to humans involves additional issues. Thus, higher brain function in humans is more easily observed at large scales. Scientists interested in higher brain function are fortunate in this respect. The technical and ethical limitations of human intracranial recording force us to emphasize scalp recordings. These extra-cranial recordings provide estimates of synaptic action at the large scales closely related to cognition and behavior. Thus, EEG provides a window on the mind, albeit one that is often clouded by technical and other limitations.

Since the first human recording in the early 1920s the physiological bases for the wide variety of rhythmic EEG activity, a proverbial "spectral zoo, " has been somewhat of a mystery. In particular, human alpha rhythms, which are quite robust in wide awake (but relaxed) subjects with closed eyes, may be recorded over nearly all of the upper scalp or cortex and have preferred frequencies near 10 Hz. Given any unknown physical or biological system that produces oscillations at some preferred (or resonant) frequency $f = \omega / 2\pi$, one of the first questions a scientist might ask concerns the origin of the implied underlying time delay $\boldsymbol{x}$ roughly estimated as

$$\tau = \omega^{-1} \tag{1}$$

The implied physiological time scales for the most robust human EEG rhythms (1 to 15 Hz) are t = 10 -160 ms. How does this delay range compare with mammalian physiology? Whereas early studies of membrane time constants in mammalian cortex were very short, typically less than 10

ms, more modern studies with improved recording methods report the wide range 20 -100 ms). But apparently in voltage-gated channels, the effective time constant becomes a "dynamical parameter" that depends on both membrane voltage and on time, thus genuine time constants are not really "constant." (Koch, 2004) argues that the voltage response to very brief synaptic inputs is essentially independent of the classically defined time constant, which typically provides overestimates of the response time of neurons. In summary, these studies suggest that while synaptic delays (PSP rise and decay times) lie in a general range (within a factor of perhaps five or ten) that might account for dominant EEG frequencies, claims of close agreement between the details of observed EEG spectra and dynamic theories based on membrane time constants are not credible. Model parameters can be chosen to "match" favored EEG data sets, which, in any case, can vary widely between individuals and brain states.

By contrast to these "local" delays at the single neuron level, axonal ("global" delays along the (corticocortical) fibers between anterior and posterior regions are estimated to be roughly in the 30 ms range in humans (Nunez, 1995). Such global delays depend on axon length distribution and axon propagation speed; thus they are expected to be much shorter in smaller mammalian brains if axon diameters (or propagation speed) are unchanged across species. To complicate matters, creation of serial connections between cell assemblies can apparently modify both local (PSP) and global (axon) characteristic delay times. While both local and global delays appear to be in a general range favorable for EEG production, this semi quantitative observation tells us little about the physiological mechanisms responsible for "special frequencies" like the narrow band human alpha rhythms or gamma oscillations (about 40 Hz), the latter recorded mostly from inside the craniums of humans and lower mammals. Neither local theories (based on PSP rise and decay times) nor global theories (based on axon delays) can honestly claim close agreement with EEG data based *only* on predicted EEG spectral properties; the underlying physiological parameters (e.g., time constants and axonal delays) are not known with sufficient accuracy to make such claims credible. While PN Nunez has suggested that the parameters of the global standing wave theory appear to be known more accurately than local parameters, others may disagree. Nevertheless, we *can* agree to search for qualitative and semi quantitative connections between theory and EEG experiments that do not require precise physiological parameter knowledge.

The general idea of standing EEG waves (Nunez, 1974) was based on a very simple idea. Any kind of weakly damped, non-dispersive wave phenomenon propagating in a medium with characteristic speed v can be expected to form standing waves due to wave interference that depends on the system's size and shape (the boundary conditions). Such phenomena occur, for example, in violin and piano strings and many other vibrating systems. Whereas waves in strings and flutes are reflected from boundaries, waves in closed systems like spherical shells or tori interfere because of periodic boundary conditions causing waves traveling in opposing directions to meet and combine. As a result of this interference, preferred (resonant) frequencies persist in such systems.

Examples of standing waves in spherical geometry include the quantum wave function of the hydrogen atom (both radial and tangential waves) and the Schumann resonances of electromagnetic waves in the spherical shell formed by the earth's surface and the bottom of the ionosphere (tangential waves only). The lowest frequency, often dominant in such systems, is the fundamental mode. This fundamental frequency is given for the geometries of a spherical shell of radius R or a one dimensional loop of length $L = 2nR$, perhaps a closed loop of transmission line (Nunez, 1995) by

$$f = \frac{g\nu}{L} \tag{2}$$

Here the geometric constant g is either β (spherical shell) or 1 (one dimensional loop). Each cortical hemisphere is topographically essentially a spherical shell. On the other hand, the postulated medium characteristic speed v is the axon propagation speed in the longer systems of corticocortical axons forming in the white matter layer. Since these fibers may be substantially anisotropic with a preferred anterior-posterior orientation, it is unclear whether the shell or loop model is the most appropriate.

The wrinkled surface of each cortical hemisphere can be reshaped or mentally inflated (as with a balloon) to create an equivalent spherical shell with effective radius R related to its surface area by the relation

$$R = \sqrt{\frac{A}{4\pi}} \tag{3}$$

Thus, cerebral cortex and its white matter system of (mostly) corticocortical fibers is a system somewhat analogous the earth-ionosphere shell. With a brain hemispheric surface area A~ 800—1500 cm^2 or alternately an anterior-posterior closed cortical loop of L~ 50—70 cm (ellipsoid-like circumference), and a characteristic corticocortical axon propagation speed of v~ 600—900 cm/sec (data reviewed from four independent studies in (Nunez, 1995), the predicted fundamental cortical frequency predicted by the naive application of Eq (2) is then

$$\nu = 2 \text{ to } 26 \text{ Hz} \tag{4}$$

This estimate is "naive" because the fundamental mode frequency depends on both the physical shape and material properties of the wave medium (cortex-white matter). These latter properties determine the dispersive nature of the waves; that is, the precise manner in which waves distort when propagating. Such dispersive properties in cortex are expected to depend on the nature and interactions of the synaptic and action potential fields. Furthermore, cortical frequency must depend on at least one additional parameter determined by brain state. Thus, estimates in Eqs. (2) and (4) cannot be expected to represent genuine brain waves, even if the cortex were actually a spherical shell or closed loop; the postulated brain waves are much more likely to be dispersive (if for no other reason than most of Nature's waves are dispersive).

Furthermore, the expected neural networks of cognitive processing (believed to be embedded in global synaptic wave fields) would be expected to cloud experimental observations of standing wave phenomenon. One may guess that such networks involve thalamocortical interactions that can generate preferred frequencies in several bands, including alpha and gamma. Thus, our scalp potentials may be viewed as some mixture of interacting global and local activity, both of which underlie and are correlated with various cognitive events.

These general ideas do not, by any stretch of the imagination, constitute a brain theory; rather they simply suggest a hypothesis and related experiments to test for *traveling* and *standing brain waves.* If estimate Eq. (4) had been obtained before the discovery of the human alpha rhythm in the 1920s, it would have provided a plausible, testable prediction. The appropriate experimental question would have been, "Can brain states be found in which neural network activity is sufficiently suppressed to allow observation of simple standing waves?" Such imagined experiments would have found the predicted EEG oscillations in the 8-13 Hz band in relaxed subjects (minimal mental load implying minimal network activity) with closed eyes (minimal visual processing).

If anything, the estimate Eq. (4) is almost *too good,* perhaps raising suspicion by critics that parameter estimates have been fudged to make a good story. But, only two parameters v and L are involved in the crude frequency estimate. Even if the cortical area estimate were off by a factor of two, the frequency estimate Eq. (4) would only change by V2. The axon speed estimate is based on the four independent studies reviewed in (Nunez, 1995). When PN Nunez first proposed the idea in 1972, corticocortical propagation speeds were poorly known. Axon speeds in (myelinated) peripheral axons and intracortical (non myelinated) axons are roughly ten times faster and ten times slower, respectively, than corticocortical axon speeds. That is, human axon speeds vary over at least three orders of magnitude depending mainly on axon diameter and myelination. Thus, the observed alpha frequency provided a blind prediction of corticocortical axon speed.

The simple standing brain wave model employs *Galilean idealizations* in which many essential properties of genuine brains are deliberately neglected in order to create a simple, useful model. Galileo modeled falling bodies with no air resistance even though he lacked the technology to make the air go away. Similarly, we may lack the technology to fully suppress the brain networks that might eliminate or obscure standing and traveling brain waves, although some anesthesia states may come close to this goal.

The proposed global model is based mostly on the following idea. Scalp potentials (EEG) are generated by synaptic current sources at small scales; each cubic millimeter of cortical tissue contains more than 100 million synapses. In contrast to this small scale activity, EEG data are recorded at macroscopic (centimeter) scales, thereby presenting major problems for network models attempting connections to genuine large scale data. The brain wave model follows the

macroscopic dependent variables *action potential and synaptic potential densities,* for example, the number of excitatory synaptic events per square millimeter of cortical surface. All dependent variables are expressed as functions of time and cortical location. The basic approach ignores embedded network activity, although networks have been included (approximately) in more advanced models (Nunez, 1989). The predicted resonance frequencies for standing waves in cortex are:

$$f_n = \frac{v}{L}\sqrt{n^2 - (\frac{\beta\lambda L}{2\pi})^2} \tag{5}$$

The symbols and estimated values are:

v: corticocortical propagation speed (600 - 900 cm/sec).

L: effective front-to-back circumference of one cortical hemisphere after inflation to a smooth surface, roughly the shape of a prolate spheroidal shell or rugby ball (50 - 70 cm).

λ *:* parameter indicating the fall-off in fiber density with cortical distance for the longest corticocortical fiber system (0.1 - 0.3 cm^{-1}).

β *:* nondimensional parameter controlled by neuromodulators; β increases correspond to increased background excitability of cortex (perhaps from thalamocortical interactions, either chemical or electrical). Wave frequency and damping decrease as *(5* increases. 4 temporal frequencies (Hz) of fundamental mode *(n* = 1) and overtones *(n* > 1) of standing waves. Does the theoretical *dispersion relation* Eq. (5) have any connection to genuine EEG? Surely nothing so simple can do justice to any complex brain! At best it may enjoy some approximate connections to brains in their more globally dominated states, possibly coma, anesthesia, deep sleep, some generalized epileptic states, and the more globally dominant parts of alpha rhythms. A few experimental predictions rely on this equation, but others follow only from the more general idea of standing and traveling brain waves (Nunez, 2010).Note that this model can provide only relationships not comprehensive explanations of complex physiological processes

In order to distinguish theories of large-scale neocortical dynamics, we have proposed the label *local theory* to indicate mathematical models of cortical or thalamo-cortical interactions for which cortico-cortical axon propagation delays are assumed to be zero. The underlying time scales in these theories typically originate from membrane time constants giving rise to PSP rise and decay times. Thalamocortical networks are also “local” from the viewpoint of a surface electrode, which cannot distinguish purely cortical from thalamocortical networks. Finally, these theories are “local” in the sense of being independent of global boundary conditions dictated by the size and shape of the cortical-white matter system. By contrast, we adopt the label *global theory* to indicate mathematical models in which delays in the cortico-cortical fibers forming most of the white matter in humans provide the important underlying time scale for the large

scale EEG dynamics recorded by scalp electrodes. Periodic boundary conditions are generally essential to global theories because the cortical-white matter system is topologically close to a spherical shell.

While this picture of distinct local and global models grossly oversimplifies expected genuine dynamic behaviors with substantial cross- scale interactions, it provides a convenient entry point to brain complexity. To facilitate our discussion, string displacement is governed by the basic string equation, (Nunez, 2010)

$$\frac{\partial^2\Phi}{\partial t^2} - v^2\frac{\partial^2\Phi}{\partial x^2} + [\omega_0^2 + f(\Phi)]\Phi = 0 \tag{6}$$

For the simple case of homogeneous linear springs attached to a homogeneous linear string of length *a* and wave speed *v,* the normal modes of oscillation ω_0 are given by

$$\omega_n^2 = \omega_0^2 + (\frac{n\pi v}{a})^2 \tag{7}$$

In this simple limiting case, the natural oscillation frequencies are seen as having distinct local and global contributions given by the first and second terms on the right side of the last equation, respectively. This same dispersion relation occurs for waves in hot plasmas and transmission lines, which might form closed loops more similar to the periodic boundary condition appropriate for neocortical standing waves. If the springs are disconnected, only the global dynamics remains. Or, if the string tension is relaxed, only the local dynamics remains. Next we approach the behavior of the nonlinear system described by the basic string equation, in which local and global effects are integrated.

The quantum model of the brain waves. The structure of the spectrum of the brain waves strongly depends on the state of the brain (Ecless, 1989) The illness of the brain is reflected in the spectrum of the waves. In physics physicist we can invent of the mathematical models which help in the understanding of the processes. Take as an example cosmic relic radiation (CRR). The spectrum of the CRR is well analyzed with the help of the "black body" formula. However nobody imagine that somewhere, 10^{17} s ago the Universe was "black body". In this paper we develop the " black body" formula for the wave emission of the brain source (Marciak-Kozlowska and Kozlowski, 2006) We take as granted the empirical fact. The electrodes measure detects the electromagnetic, very weak waves: *delta, theta, alpha, beta, gamma*, Table 1. The waves have the prescribed frequencies in the range of Hz and amplitudes in the range of μV. In order to put forward the classical theory of the brain waves, Eq. (6) we will quantize the field Φ (x, t). In the model we assume (i) the brain is the thermal source in local equilibrium with temperature T. (ii) The spectrum of the brain waves is quantized according to formula

$$E = \hbar\omega \tag{8}$$

where E is the photon energy in eV, $\hbar$=Planck constant, $\omega = 2\pi\nu, \nu$ -is the frequency in Hz. In Table 1 the frequencies and amplitudes are presented (Tuszyński, Dixon, 2002). (iii). The number of photons emitted by brain is proportional to the (amplitude)^2 as for classical waves. The energies of the photons are the maximum values of energies of waves mentioned in Table 1

(*Continued on Part II*)