Dissipationless Waves for Information Transfer in Neurobiology – Some Implications

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We describe a biophysical framework for subneuronal processing of information via certain quantum mechanical processes and solitonic interactions as applicable to neuronal microtubules. In particular, we describe how certain energase actions and vibrationally assisted tunneling may influence the conformational dynamics of the neuronal cytoskeletal protein network. Some implications are also discussed in relationship to special neurophysiological processes as basic to the study of mind and memory.

Povzetek: Opisan je model neurobiološkega delovanja.

1 Introduction

Solitons are dissipationless waves whose theory and applications prevail in fields such as quantum physics, atmospherics, oceanography, cellular automata, and biophysical systems. Some well known examples appearing in the wealth of literature on the subject include the equations of Korteweg-de Vries, Boussinesq, Klein–Gordon, and the nonlinear Schrödinger (NLS) equation (Dodd et al. 1982, Calogero and Degasperis 1982, Davydov 1991). These robust, often bell–shaped waves can propagate in a pulsating manner while retaining their form and velocity in undergoing collisions; so in a sense they can be compared with interacting particles. On the other hand, their universality as a nonlinear scientific phenomenon suggests they are essential to understanding life and information within a unified framework, and therefore provide an essential contribution to the understanding of consciousness.

Soliton equations constitute part of a hierarchy of integrable, or 'solvable', systems admitting high degrees of symmetry (Ablowitz and Clarkson 1991, Calogero and Degasperis 1982, Miwa et al. 1982), but seen as solutions to nonlinear wave equations, solitons do not normally obey the superposition principle, so that when two solutions are combined, a complicated wave is formed. Eventually however, pairs of soliton waves are seen to actually pass through each other thus revealing an unusual phenomenon that has far–reaching applications. Of specific interest here are 'kink' and 'antikink' solutions which are common to a number of solvable systems where spatial derivatives are localized; typically, the resulting wave pulsates in a twisting fashion with certain asymptotic properties. Besides kink and antikink solutions, there may also be oscillatory solutions known as 'breathers' which will play an instrumental role in the discussion following.

For biomolecular/physical systems, the works of Davydov (1982, 1991) provide a foundation for applying the theory of solitons for dissipationless energy transfer in hydrogen bonded systems, DNA, membraneous flexing, muscular contraction and other phenomena (we refer also to the excellent article by Scott 1992 on this subject). Our interest here draws upon the role that soliton dynamics can play in neurobiology/neurophysiology in a particular situation; namely, we survey how such effects theoretically related to systems such as the sine–Gordon and the class of evolutionary equations considered in Davydov (1982, 1991), might influence the mechanisms of dendritic and axonal microtubules, subneuronal processing of information, and synaptogenesis in cerebral architecture.

2 Microtubules and C–terminal tubulin tails

Neuronal structures within the brain are known to be dynamically regulated by strings of self–assembling protein networks forming the cytoskeleton, a skeleton–like protein network that regulates cellular dynamics. The main constituents of the cytoskeleton consist of microtubules which are like hollow cylinders of 25 nm in diameter, of variable length (from micrometers to milimeters, depending on whether they are contained within dendrites or axons) and are composed of assemblies of α/β tubulin dimers. Microtubules interact with intermediary and actin filaments, MAPs (microtubule associated proteins), as well as different scaffold proteins, thus organizing the intracellular space and tuning the biochemical activity of microtubule anchored enzymes (mostly phosphatases and kinases). The assembly by α/β tubulin dimers is a process requiring nucleotide GTP (guanosine triphosphate) to bind to both α and β tubulins. The α–bound GTP never hydrolyzes, whereas the GTP–molecule which is tied to the β–tubulin, is hydrolyzed to nucleotide GDP (guanosine diphosphate) soon after the dimer is incorporated into the growing microtubule lattice. The released energy is then stored in the microtubule wall as an elastic strain, and the β–tubulin bound GDP cannot be further phosphorylated or exchanged for GTP because the successive α–tubulin in the protofilament occludes the preceding β–tubulin nucleotide binding pocket (Heald and Nogales, 2002).

Experimental data by Sackett (1995) revealed the form of microtubules not as smooth cylinders, since extending from each tubulin are tiny 'hairy' projections of 4–5 nm in length, referred to as *tubulin tails*. Since these projections are highly flexible, their PDB structure was revealed only recently by Jimenez et al. (1999) who determined the helicity of α (404–451) and β (394–445) tubulin C–terminal recombinant peptides with the use of NMR (nuclear magnetic resonance). They showed that the C–terminal domain of tubulins has a different length and structure in both α– and β–tubulin. In general, the C–terminal domain has a C–terminal helix H12 and a random coil C–terminal tubulin tail. In α–tubulin molecules aminoacid residues 418–432 form the C–terminal helix H12 and aminoacid residues 433–451 comprise the α–tubulin tail. The α–tubulin C–terminal tail aminoacid sequence is EEVGVDSVEGEGEEEGEEY. The α–tubulin tail is 19 aminoacids long and possesses 10 negatively charged residues. The situation in the β–tubulin C–terminal domain is more interesting. Jimenez et al. (1999) have computed a 9 aminoacid longer helix of the β–tubulin compared to previous PDB models (cf Nogales et al. 1998). This suggests an extension in the protein, supporting the possibility of a functional coil–to–helix transition at the C–terminal zone. The β–tubulin C–terminal helix H12 is formed by aminoacid residues 408-431, but it seems that the reversible transition between coil and helix of the last 9 aminoacid residues 423–431 from the C-terminal helix (with sequence QQYQDATAD) could either decrease or increase the length of the helix H12, at the same time increasing or decreasing the β–tubulin tail length. The β–tubulin tail aminoacid sequence (residues 432–445) is EQGEFEEEEGEDEA. It has 14 aminoacids and 9 negatively charged residues, but depending on the conformational status of the residues 423–431, the β–tubulin tail random coil can extend to 23 aminoacid residues bearing 11 negative charges. Following the C–terminal helices α–H12 and β–H12, the 19 and 14 C–terminal residues of the respective α– and β–tubulin tails are observed to be disordered by NMR. In particular, this is a dynamical disordering and is effectively the manifestation of the extreme sensitivity of the tubulin tails to environmental conditions, and local electric fields yielding a plethora of metastable conformations (Georgiev 2003a).

Located within dendrites and axonal projections, microtubules serve as tracks for the transportation of post–Golgi vesicles by microtubule bound motor proteins (such as kinesin and dynein). Microtubules however are not passive elements in the vesicle transport and it has been shown that the tubulin C–terminal tails modulate kinesin function. Experiments performed by Skiniotis et al. (2004) have shown that the β–tubulin tail interacts with the kinesin switch II domain, while the α–tubulin tail possibly interacts with the kinesin α 7–helix in such a way that after the kinesin bound ATP (adenosine triphosphate) is hydrolyzed, the kinesin perambulates along the microtubule surface. Native microtubules that possess tubulin tails cannot be decorated by ADP (adenosine diphosphate)–kinesin molecules because of the weak ADP–kinesin/tubulin tail binding, while subtilisin treated microtubules that lack tubulin tails bind stably ADP–kinesin, thus blocking the kinesin walk. The conclusion is that the tubulin tails catalyze the detachment of the kinesin–ADP complex from the microtubule surface allowing the kinesin dimer to take a 'step' along the microtubule protofilament.

Microtubules do not only regulate motor protein function but also attach with their C–terminal tubulin tails different MAPs and protein kinases and phosphatases, thus organizing the intraneuronal space. The proper attachment/detachment of these proteins could regulate their enzymatic activity. In case studies of schizophrenia, Arnold et al. (1991) have found altered expressions of MAP2 and MAP5 that result in abnormalities in the neuronal cytoarchitecture. Whereas in Alzheimer's disease, the primary alteration is the phosphorylation status of axonal MAP–tau and the activity of protein phosphatase 2A (PP2A) regulated via attachment/detachment to microtubules (Sontag et al. 1999).

We propose that the mechanism of the tubulin tail enzymatic action is generated by vibrationally assisted tunneling – a key concept which emerged and was experimentally verified over the last several years (Sutcliffe and Scrutton, 2000). A locally formed tubulin tail standing breather could promote or suppress conformational tunnel-

ing of a molecule attached to the tubulin tail. The effect of vibrations on mixed-tunneling could be either to promote or to suppress the tunneling process and this depends on the boundary conditions (Takada and Nakamura 1994, 1995). Formally, the mechanism of the tubulin tail breathing action could be manifestly a form of enzymatic energase process. Energases do not have source of energy, but rather induce conformational transitions in a molecule that has accumulated energy in an intermediate highly energetic conformational state (Purich, 2001). The accumulated energy is derived from hydrolyzed ATP or GTP in previous biochemical steps, so for that reason this energy is usually called 'primed energy' and the process of energy accumulation in metastable protein states is referred to as 'priming'.

The idea that microtubules might be agents of subneuronal processing of information was originally suggested by Hameroff and Watt (1982). Hameroff and colleagues (Hagan et al. 2000) conjectured that the energy for computation could be delivered from the tubulin bound GTP molecules. Since it had been already observed that in stable microtubules there is no possibility for tubulin bound nucleotide cycling, we propose that tubulin tail energase action releases the energy accumulated in metastable conformational states of kinesin, dynein, or phosphorylated MAPs. The metastable states of these proteins are produced via ATP hydrolysis through previous 'priming' steps. We mention that ideas involving GTP–hydrolysis, ferroelectric phase and (C–terminal) tubulin tails as possible agents of information transfer, have been suggested in Georgiev (2003a, 2003c, 2004), Georgiev et al. (2004), Satarić and Tuszyński (2003) and the appropriate references therein.

3 The water laser as a pumping mechanism

As the organizing framework for special neurobiological processes, the cytoskeleton is the major intracellular structure providing a protein surface to which water molecules cling thus facilitating the water ordering. We point out that the term 'water' used here is not quite the same as its mundane sense, but instead should be regarded as a protein–like saturated mixture. Ordered (vicinal) water molecules are microscopic dipoles that interact with each other via hydrogen bonds whose effect influences a relatively high viscosity, surface tension and dielectric constant. They form the water electric dipole (WEDP)–field occurring on either side of a brain cell. Within the interior of the cell, the water molecules generate a WEDP–field in the vicinity of the cytoskeleton, whereas in the exterior of the cell, the molecules form an intercellular flow completing the regions between neighbouring cells. Del Giudice et al. (1983) have proposed that electromagnetic waves arising from the WEDP–field within the body of the cytoskeleton, create signals compatible in size with the internal diameter of a given microtubule.

To proceed, we adopt in part the development of Jibu et al. (1994, 1996, 1997). Let $\mathbb{V}$ denote a perimembranous region or a spatial region in the vicinity of a cytoskeletal microtubule. The WEDP–field in $\mathbb{V}$ taken within a cylindrical neighbourhood, is represented by a 2–spinor field

$$\psi(\mathbf{x},t) = \begin{bmatrix} \psi^+(\mathbf{x},t) \\ \psi^-(\mathbf{x},t) \end{bmatrix} , \tag{3.1}$$

where $\psi^+(\mathbf{x},t)$ and $\psi^-(\mathbf{x},t)$ are spinor components. The electric dipole moment is given by

$$\mu = \psi(\mathbf{x},t)^* \, \frac{\hbar}{2} \sigma \, \psi(\mathbf{x},t) , \tag{3.2}$$

where $\sigma = [\sigma_1, \sigma_2, \sigma_3]$ is a 3–vector whose components consist of the Pauli spin matrices. The dipole moment μ exhibits the water molecule as similar to a quantum–mechanical spinning top. In other words, it is due to μ that the water molecules interact dynamically with the quantized electromagnetic field in $\mathbb{V}$. If m_p and e_p denote the proton mass and charge respectively, then the average moment of inertia of a water molecule is estimated as $I = 2m_p d^2$ with $d \approx 0.82$Å, whereas μ is estimated as $\mu = 2e_p P$, with $P \approx 0.2$Å .

Given $\psi(\mathbf{x},t) \neq 0$ only holds at each position $\mathbf{x} = \mathbf{x}_k$ of the k–th manifestation of localization, the WEDP–field with N localizations are describable in terms of N spin variables as given by

$$s^k(t) = \psi(\mathbf{x}_k,t)^* \, \sigma \, \psi(\mathbf{x}_k,t) , \qquad 1 \leq k \leq N . \tag{3.3}$$

The Hamiltonian of the WEDP–field for N water molecules with energy difference ϵ, is given by

$$H_{WM} = \epsilon \sum_{k=1}^{N} s_3^k(t) , \tag{3.4}$$

where for a given wave vector k_0, it is convenient to assume that a normal mode has an angular frequency ω_{k_0} resonating to the energy difference between two principal eigenstates for which $\epsilon = \hbar\omega_{k_0}$ ($\epsilon \approx 24.8$ meV), in accordance with the predictions of dominance over other possible energy exchanges (Del Giudice et al. 1988). The radiation field of $\mathbb{V}$ is given by a scalar electric field operator $E = E(\mathbf{x},t)$ whose associated Hamiltonian is

$$H_{EM} = \frac{1}{2} \int_{\mathbb{V}} E^2 \, d^3\mathbf{x} . \tag{3.5}$$

A main premise of Jibu and Yasue (1997) is that the dynamics of the WEDP–field and the quantized electromagnetic (EM) field is an energy interchange through creation and annihilation operators of photons. In order to see this, consider a decomposition of the electric field operator $E = E^+ + E^-$ into its positive and negative frequency

components. Then the Hamiltonian for the interaction between the WEDP–field and the EM–field is given by

$$H_I = -\mu \sum_{k=1}^{N} \{E^-(r^k,t)s_-^k + s_+^k E^+(r^k,t)\}\ , \quad (3.6)$$

where $s_\pm^k = s_1^k \pm \iota s_2^k$. The total Hamiltonian H_{QM} which governs the quantum mechanical dynamics of the electromagnetic field, the dipolar vibrational field of water molecules along with their interaction, is then expressed by

$$H_{QM} = H_{EM} + H_{WM} + H_I\ . \quad (3.7)$$

Since parts of the region $\mathbb{V}$ in the vicinity of a cell can be considered as a cavity for the electromagnetic wave, we introduce the normal mode expansion of E given by

$$E^\pm(\mathbf{x},t) = \sum_\lambda E_\lambda^\pm(t)\ \exp[\ \pm\iota(\lambda\cdot\mathbf{x} - \omega_\lambda t)\ ]\ . \quad (3.8)$$

From a motivational viewpoint, let us mention that the process of signaling response in synapses is influenced by certain classes of cellular adhesive molecules (CAMs) in which the actin cytoskeleton provides a suitable structural mechanism for assimilating the signaling inputs. The formation of functional synapses at an axonal growth cone involves identifying and initiating contacts with suitable companion cells (Brose 1999). Of special importance for synapse formation are two types of CAMs known as β-*neurexin* and *neuroligin* forming a heterologous adhesive interaction. Remarkably, β-neurexin-neuroligin interaction alone has the unique ability to act as a bidirectional trigger of synapse formation (Dean and Dresbach, 2006). β–neurexin is located in axons and interacts presynaptically with CASK, a multidomain scaffolding protein that organizes the presynaptic space and emits signals to the actin cytoskeleton via protein 4.1. β–neurexin also directly interacts with the synaptic vesicle protein synaptotagmin-1, thus controlling exocytosis and neuromediator release (see later). Synaptotagmin-1 per se might act as MAP molecule binding to β–tubulin tails stabilizing microtubules in high Ca^{2+} concentration presynaptically. Neuroligins are located in dendrites and transmit information to postsynaptic density protein (PSD-95), which is a multidomain scaffold protein that anchors different ion channels to the active zones of the postsynaptic membrane. Neuroligin-1 is a specific CAM for excitatory (glutamatergic) synapses, while neuroligin-2 is a specific CAM for inhibitory (GABAergic) synapses. PSD-95 is anchored to postsynaptic microtubules via another protein known as CRIPT. Neuroligins on binding with presynaptic β–neurexins, comprise an adhesive system facilitating learning processes manifest as a morphological reorganization of the synapse. Relevant here is that the radiation field of (3.8) could be considered as falling within this junction as shielded by ordered water molecules, and so assists the signaling mechanism between neighbouring neurons (Georgiev 2003b, 2003c).

Next, we introduce collective dynamical variables $S_\lambda^\pm$ for water molecules given by

$$S_\lambda^\pm(t) = \sum_{k=1}^{N} s_\pm^k(t)\ \exp[\ \pm\iota(\lambda\cdot\mathbf{x} - \omega_\lambda t)\ ]\ . \quad (3.9)$$

On setting $S \equiv \sum_k s_3^k$, we can express (3.7) in the form

$$H_{QM} = H_{EM} + \epsilon S - \mu \sum_\lambda \{E_\lambda^- S_\lambda^- + S_\lambda^+ E_\lambda^+\}\ . \quad (3.10)$$

Equation (3.10) resembles that of the Hamiltonian for a laser radiation process, and in this way suggests that the water molecules of $\mathbb{V}$ exhibit a laser–like coherent optical property, *provided the energy is sustained above a certain threshold*; this threshold will be represented by equation (3.15) below. The dynamically ordered region of water molecules and quantized EM–field, are considered within a coherence length of $50\ \mu m$. The explanation given by Jibu et al. (1997) is that by increasing the ordering of water on the microtubule surface, spontaneous symmetry breaking occurs (see below), thus creating Nambu–Goldstone (NG) bosons, the quanta of long–range correlation waves of the aligned electric dipoles referred to as *dipole wave quanta*, denoted DWQ.

The Hamiltonian H_{EM} can also be expressed in terms of canonical operators (observables) $P_\lambda(t)$ and $Q_\lambda(t)$ as defined by

$$\begin{aligned} P_\lambda(t) &= \sqrt{\frac{\hbar\omega_\lambda}{2}}\ \iota(E_\lambda^- - E_\lambda^+)\ , \\ Q_\lambda(t) &= \sqrt{\frac{\hbar}{2\omega_\lambda}}\ (E_\lambda^- + E_\lambda^+)\ , \end{aligned} \quad (3.11)$$

and which satisfy the well–known canonical commutation relations of the Heisenberg algebra. On making the necessary transformations and substituting into (3.10), we obtain

$$\begin{aligned} H_{QM} = \frac{1}{2}\sum_\lambda \{P_\lambda^*(t)P_\lambda(t) + \omega_\lambda^2 Q_\lambda^*(t)Q_\lambda(t)\} \\ + \epsilon\sum_{k=1}^{N} s_3^k(t) \\ - \sqrt{\frac{2}{\hbar}}\mu\ \sum_{k=1}^{N}\sum_\lambda \{\sqrt{\omega_\lambda}Q_\lambda(t)s_1^k \\ - \frac{1}{\sqrt{\omega_\lambda}}P_\lambda(t)s_2^k\}\ . \end{aligned} \quad (3.12)$$

Consider when a system possesses a certain symmetry but through which the vacuum state is altered (through this symmetry) and may be transformed into some other degenerate state, whereas the Lagrangian symmetry remains independent of the vacuum solution. In other words, the Hamiltonian may be invariant under the symmetry transformation but the vacuum (or lowest energy) state is not. In this way, spontaneous symmetry breaking (SSB) occurs

and results in massless quanta governed by Bose–Einstein (BE) statistics that are assigned to repair the broken symmetry. The NG bosons are understood to be the quanta of long range coherence induced by the vacuum state, which violated the original dynamical symmetry. Typically, what might otherwise be two massive fields emerge from SSB as one massive and one massless field, the latter in this case is a NG boson. In Jibue–Yasue (1997) this is explained when the corresponding Heisenberg equations of (3.12) are considered in order to study the dynamically ordered state of the WEDP–field in terms of a long–range alignment of associated spin variables. Under an $\mathrm{SO}(2)$–transformation of the canonical variables, the Hamiltonian H_{QM} is invariant, whereas a time independent solution is not invariant.

In order for the coherent emission of photons to have the proper biological impact, it is necessary to consider timescales of the order of 10–15 picoseconds which are compatible with that of protein action. In the presence of a disordered thermodynamic system, thermal fluctuations, noise and dissipation have to be take into consideration. However, the laser–like emission of coherent photons may still be realized under such circumstances once the protein molecules achieve dynamics sufficient to engage a pumping effect of the WEDP–field. This 'slow phenomenon' involving the water laser is preferred in this situation to the 'fast phenomena' of superradiance. Jibu and Yasue (1997) consider the relevant system of Heisenberg–Langevin equations governing the collective dynamics of the quantized EM–filed in $\mathbb{V}$. On assuming a certain coherent state representation, these are seen to reduce to the stochastic Langevin equation

$$\frac{dZ}{dt} = \alpha_1 Z - \alpha_2 \overline{Z} Z^2 + B \,, \tag{3.13}$$

where $Z = Z(t)$ is a Markov process in $\mathbb{C}$ of the corresponding EM–field operator, $B = B(t)$ is a (complex) Gaussian white noise of thermal fluctuations of quantized EM–field, and α_1, α_2 are particular constants depending on the volume V of the region, thermal fluctuations for the EM and WEDP–field, damping coefficients (denoted γ, γ_0) for the WEDP–field, and a parameter of pumping rate (denoted S_∞) resulting from the interaction of the WEDP–field with the dynamics of the microtubule protein molecules. In turn, these parameters are used to define a diffusion constant D, which along the probability density function $f = f(z, \bar{x}, t)$ of $Z(t)$, transform equation (3.13) to its corresponding Fokker–Planck equation

$$\frac{\partial f}{\partial t} = -\frac{\partial}{\partial z}[(\alpha_1 z - \alpha_2 \overline{z} z^2) f] + D \, \frac{\partial^2 f}{\partial z \, \partial \overline{z}} \,. \tag{3.14}$$

Finally, and again referring to Jibu and Yasue (1997) for details, the required level of excitations of the quantized EM–field, namely the photon emission as induced by the electric dipoles of tubulin, is attained when the pumping rate S_∞ satisfies the estimate

$$S_\infty > \frac{\hbar^2 V \gamma_0 \gamma}{4\pi\epsilon f^2} \,. \tag{3.15}$$

Thus it is suggested that the energy for the coherent pulse emission by vicinal water in a proximity of 4-5 nm of the microtubule's outer surface could be gained from the tubulin electric dipole oscillations and/or from vibrations along the microtubule walls. The transmission of pulse mode coherent photons is determined by Maxwell's equation as derived from the total Hamiltonian H_{QM} . For $E = E(z,t)$ it is given by the quantum dynamical equation of motion (Jibu et al. 1994, 1997, Abdalla et al. 2001) :

$$\frac{\partial E^\pm}{\partial z} + \frac{1}{c}\frac{\partial E^\pm}{\partial t} = \mp\iota \frac{2\pi\epsilon\mu}{\hbar V} S^\pm \,. \tag{3.16}$$

In terms of a quantum average, denoted $\langle \, \rangle_q$, the expression for the electric field is

$$\theta^\pm(z,t) = \frac{2\mu}{\hbar} \int_{-\infty}^{t} \langle E^\pm(z,u) \rangle_q \, du \,. \tag{3.17}$$

This leads to a soliton equation of sine–Gordon type

$$\frac{\partial^2}{\partial t \partial \sigma} \theta^\pm = -2A \sin \theta^\pm \,, \tag{3.18}$$

expressed in Lorenztian coordinates, where $A = \frac{2\pi\epsilon\mu^2 N}{\hbar^2 V}$, in which $\frac{N}{V}$ is the number of water dipoles per unit of volume, and $\sigma = t + \frac{z}{c}$. The indices $\pm$ indicate the transverse directions of the electric field where it is assumed there is no propagation in the longitudinal direction. The soliton equation (3.18) is an equation characteristic of self–induced transparency as realized in nonlinear optics and here suggests how the cumulative effects of the WEDP–field might induce a transfer of energy via dissipationless waves. Time–differentiating (3.17), leads to

$$E = \frac{\hbar}{\mu}\sqrt{A\rho} \, \mathrm{sech} \, [\, \sqrt{A\rho} \, (t - \frac{z}{c}) \,] \,, \tag{3.19}$$

where $\rho = \frac{v_0}{c - v_0}$. The above equations were taken up by Abdalla et al. (2001) who studied the correspondence between information configurations induced by solitonic interactions and the DWQ at certain levels of excitation. As is part represented by the sine–Gordon equation (3.18), the cumulative effect of the WEDP–field then induces a source of resonant–propulsive energy.

Let us mention several alternative models which consider different dynamics, based on equations of 'solvable' type, which are relative to the lattice structure of microtubules. For instance, in Chou et al. (1994) energy releasing effects of GTP–hydrolysis could generate certain kinks and pulsations which propagate along the microtubule via elastic flexing of the dimers. In Satarić and Tuszyński (2003) a liquid crystal property of microtubules is considered relative to kink 'shifting' through GTP hydrolysis whose rate may increase given additional Ca^{2+} and where possible impediments to the kink motion, polymerization, and microtubular caps are taken into account. These models, however, investigate effects in dynamic microtubules that undergo assembly/disassembly while not addressing

the contrasting situation for stable microtubules (such as the neuronal types). Another model involving solitonic interactions, as considered by Mavromatos et al. (2002), entails possible quantum coherent states of the DWQ on the tubulin dimer walls where the DWQ are paired to electrons in the dimer hydrophobic pockets via Rabi field coupling.

A model suggested in Georgiev (2004) relates to how the water dipoles from the tubulin tail hydration shells that form a 4–5 nm layer on the outer microtubular surface, strongly interact with the local electromagnetic field thus affecting the conformational state of the tiny C–tubulin tails. The model is based on a long–range interaction of the water molecule dipoles and local EM field resulting in a coherent emission of photon pulses propagating via tunneling. The resulting solitons could be viewed as traveling conformational waves in the tubulin tails that do not dissipate under thermal fluctuations, but could be pumped by the water laser provided the threshold inequality (3.15) is satisfied. This model also considers solutions to the sine–Gordon equation as providing the necessary dynamics. To facilitate matters, consider a change of parameters from Lorentzian coordinates to laboratory coordinates, so that equation (3.18) is now expressed by :

$$u_{tt} - u_{xx} = \pm \sin u \ , \ \ u \equiv u(x,t) \ . \tag{3.20}$$

We have chosen for now a description based on the elastic ribbon model, and recall that a kink soliton involves a twist in a solution, $u = u(x,t)$ say, which moves from one solution $u = 0$ to an adjacent solution $u = 2\pi$. Vacuum states as constant solutions of zero energy, correspond to $u = 0(mod\ 2\pi)$. In this respect, the traveling solitons of Jibu–Yasue can be regarded as tunneling photons coupled with tubulin tail hydration shells. The assumption is that there is a prevailing coherence time of 10–15 picoseconds.

Such a kink (K) solution u_K of (3.20) as given by :

$$u_K = 4 \tan^{-1} \exp[\ \gamma_K (x - v_K t - x_K)\ ] \ , \tag{3.21}$$

where $0 \leq v_K < 1$ is the kink velocity, x_K the kink position at $t = 0$, and

$$\gamma_K^{-1} = (1 - v_K^2)^{\frac{1}{2}} \ , \tag{3.22}$$

the kink width. The kink energy is given by $E_K = 8\gamma_K$.

On setting $G = \gamma_K(x - v_K t - x_K)$, one also finds the derived equations :

$$\begin{aligned} u_x &= 2\gamma_K \ \mathrm{sech}\ G \ , \qquad \text{(magnetic field)} \\ u_t &= -2\gamma_K v_K \ \mathrm{sech}\ G \ , \qquad \text{(electric field)} \\ \sin \frac{1}{2} u &= \mathrm{sech}\ G \ , \end{aligned} \tag{3.23}$$

(see Dodd et al. 1982).

The antikink (AK) solutions correspond to reversing the velocity, $v \mapsto -v$, and taking the negative square root in (3.22). At this stage we mention the role of certain solutions, called *breathers* which are manifestly local oscillating waves resulting from how a kink and antikink can merge into a combined state. Breathers admit more structure compared to a usual traveling wave because of the former's internal oscillations, and in contrast to (topological) ribbon solitons, can evolve without energy activation. In practice they have been realized as linear phonon modes which are excitable within thermal fluctuations (Russell et al. 1997). It was suggested earlier that some class of propagating solitons may influence the conformational states of the tubulin tails. To this extent, in Georgiev (2004, 2003a) several possibilities involving sine–Gordon kink–antikink–breather soliton collisions were proposed, where for instance, a standing breather soliton could be coupled to the energase action of the tubulin tails through vibrationally assisted tunneling. Further, we are reminded how the β–tubulin tails may interact with kinesin switches and the role of the α–tubulin tail in activating the kinesin walk (Skiniotis 2004).

As outlined in Dodd et al. (1982), the scheme of Bäcklund transformations can be employed to derive 3–soliton from 2–soliton solutions. In relationship to the kink solution u_K in (3.21), we follow Dmitriev et al. (1998) to describe a 3–soliton solution u_{KB} representing the elastic collision (without exchange of energy or momentum) between a kink and a breather, as it is given by the sum

$$u_{KB} = u_K + w_B \ , \tag{3.24}$$

where the term w_B is explained as follows. Firstly, if ω denotes the frequency of the breather, $0 \leq \omega < 1$, we set $\eta = (1 - \omega^2)^{\frac{1}{2}}$. Then

$$\begin{aligned} w_B = 4 \tan^{-1} \Big\{ \Big(& 2\omega\eta(\sinh D - \cos C \sinh G) \\ & + 2\eta\gamma_K\gamma_B(v_K - v_B) \sin C \cosh G \Big) \cdot \\ & \Big(2\omega\eta(\cos C + \sinh D \sinh G) \\ & - 2\omega\gamma_K\gamma_B(1 - v_K v_B) \cosh D \cosh G \Big)^{-1} \Big\} \ , \end{aligned} \tag{3.25}$$

where we have set

$$C = -\omega\gamma_B(t - v_B(x - x_B)) + 2\pi m \ ,$$

m an integer,

$$D = \eta\gamma_B(x - x_B - v_B t) \ ,$$

$\gamma_B^{-1} = (1 - v_B^2)^{\frac{1}{2}}$ is the kink width in which v_B denotes the velocity of the breather $0 \leq |v_B| < 1$, and lastly, x_B denotes the position of the breather at time $t = 0$. In the continuum limit, the breather's wavelength λ and period T are related via

$$|v_B| = \frac{\lambda}{T} \ , \ \lambda = 2\pi\gamma_B |v_B| \frac{1}{\omega} \ , \tag{3.26}$$

whereas the amplitude A and energy E_B are given by $A = 4\tan^{-1}(\frac{\eta}{\omega})$, $E_B = 16\eta\gamma_B$.

Particularly interesting is the collision between a standing breather ($v_B = 0$) and a traveling kink. After the collision the kink and breather recover their velocity and shape. However, the interaction results in a phase shift of the standing breather that oscillates at a new position. Therefore we can consider the sine–Gordon soliton collisions as a kind of application of computational gates.

In the process of collision between a moving kink and a standing breather, the shift Δ_B of the breather is given by the formula

$$\Delta_B = \frac{2\tanh^{-1}\sqrt{(1-\omega^2)(1-v_K^2)}}{\sqrt{1-\omega^2}}\,, \qquad (3.27)$$

where v_K is the velocity of the kink. If the original position is denoted x_0, then post–collision, the new position will be $x = x_0 + \Delta_B$.

Thus as a result of a pushing/pulling kink or antikink collision with a standing breather, the latter through its phase shift is conjectured to cause a deflection of the tubulin tails so as to influence the kinesin walk across the microtubule surface. Making the necessary change in parameters, a kink–breather or an antikink–breather collision might actually implement the required 'pushing' effect (this question remains open) if indeed a breather does function as a catalytic agent registering transitions, influencing MAPs and as noted, the workings of the prevailing motor proteins (kinesin and dynein) through tunneling and the energase action. It is possible there are other combinations and permutations of kink–antikink–breather collisions in, say, the pendulum or discrete models (cf Miroshnichenko et al. 2000, even perhaps a configuration of moving breathers as in Russell et al. 1997), which could provide the relevant dynamics. At the same time we keep in mind the kink etc. counterparts in other integrable/solvable systems which might also serve as models of regulatory or computational gates that could influence cytoskeletal processes.

These last issues are discussed in Georgiev (2004) in relationship to some finer neurobiological processes. Concerning these, we comment on two important mechanisms corresponding to protein constituents such as synapsin-1 and synaptotagmin-1. Hirokawa et al. (1989) have proposed that phosphorylation of synapsin-1 by Ca^{2+} dependent kinases, on releasing synaptic vesicles from actin filaments, may accelerate vesicles to the presynaptic membrane. In Honda et al. (2002) it is shown that cytoskeletal protein tubulin binds directly to synaptotagmin-1 which promotes tubulin assembly. At the same time, synaptotagmin-1 functions by attaching synaptic vesicles to microtubules in high concentrations of Ca^{2+}. Presynaptic microtubules may attach directly to the synaptotagmin/SNARE complexes (SNARE abbreviates *soluble NSF attachment protein receptor*, where NSF abbreviates *N-ethyl-maleimide-sensitive fusion protein*) where β–tubulin tails may trigger synaptotagmin dimerization which is essential for accomplishing exocytosis. A further open possibility is that presynaptic microtubules remain crosslinked to docked synaptic vesicles by means of a complex presynaptic scaffold protein network referred to as *the cytomatrix of the active zone* (CAZ).

The SNARE complex, while functioning as a fusion mechanism, may be capable of receiving Ca^{2+} signals transmitted by synaptotagmin-1 Ca^{2+} binding, which may result in the fusion of synaptic vesicle with the presynaptic membranes. This opens up the possibility that a traveling antikink (for instance) on collision with a stationary breather, typically located at a penultimate tubulin tail, may push the breather to the microtubule end β–tail which is attached to the synaptotagmin Ca^{2+} sensor molecule located above the SNARE complex. If indeed the case, then such a model should be relevant to questions posed by Chapman (2002) concerning how synaptotagmin-1 may be realized as a catalyst of exocytosis. Answering these and other questions may well reflect upon the earlier ideas of Beck and Eccles (1992) who hypothesized long–range quantum correlation resulting from the exocytosis of synaptic vesicles when propagating into a bouton.

4 Solitons in α–helix protein molecules

The relevance of soliton dynamics to biophysics can be traced back in part to the studies of Fröhlich (1968, 1975) who considered one–dimensional electron systems occurring in biology. When these systems admit holes of some kind, it was conjectured that electron–hole pairing leads to the existence of intracellular solitonic dynamics inducing dissipationless energy transfer. Fröhlich postulated unusual protein dipole moments and wave frequencies as exhibited by cell membranes and certain enzymes. Such dielectric systems were considered as producing longitudinal electric oscillations across the matter. At suitable levels, energy can be channeled into a single mode and sufficiently ordered so as to sustain coherent electric waves, an ordering suggestive of long range quantum–coherence comparable to BE–condensation. In short, particles forsake their individual characteristics and unite into a condensate regulated by a single wave function, whereas particles outside of the condensate disperse erratically.

Further studies revealed molecules beneath the cell membrane as exhibiting dipolar vibrational activity where thin layers appear to act like biological superconductors in which the resulting wave propagation leads to Fröhlich waves possessing a frequency of order 10^{11} to $10^{12}\,\mathrm{sec}^{-1}$ (see e.g. Grundler and Keilmann 1983). The evidence suggests that protein dipoles in a common electromagnetic field exhibit resonating effects when energy is supplied. Such waves are seen to be induced by dipolar oscillations maintained by hydrogen bonds and non–localized electrons

within hydrophobic regions of protein molecules. The interaction between dipolar excitations and harmonic vibrations of certain biological lattice structures can be modeled on a Hamiltonian from which, as shown in e.g. Satarić et al. (1991), Davydov solitons can be derived relative to rates of chemical reactions. In a broader perspective, the ideas of Fröhlich are linked to electron superconductivity and are closer to utilizing this class of solitons.

Next, we recall the basic principle of how proteins act in converting chemical into mechanical energy, and when aided by lipids they generate the traffic of ions and molecules in and around cellular membranes. As we have mentioned, the protein chain can coil into a helix-like form which is manifestly the structure of hydrogen bonded peptide groups of the protein molecule. Protein molecules incorporated into the cytoskeleton create transduction energy and intracellular couplings all of which assist and determine energy release of hydrolysis of ATP molecules while at the same time portions of the helix constitute part of the cytoskeleton's protein composition. On the other hand, the excited states of a protein molecule are related to the resonant interaction between peptide groups within distinct chains.

According to Davydov (1982, 1991), a class of solitons evolve at the origin of each chain and so can be created within short intervals of α–helix proteins. The propagation of a soliton within an α–helix protein molecule could be either symmetric or asymmetric. Of these, the asymmetric soliton is the more stable and its radiation life–span does not depend on velocity and can increase sharply as the angle between the spiral axis and vibrational dipole moment decreases. This explains why the asymmetric solitons are favourable for transferring the energy of ATP hydrolysis without loss of energy along the α–helix protein chain over suitably large distances. Recall that Jiminez et al. (1999) have predicted a helicial structure to the C–terminal domains, and for certain C–terminal recombinant peptides, this helicity has been determined with evidence supporting a functional coil to the helix transition at the C–terminal zone. As also seen in Amos (2000), each tubulin monomer possesses twelve α–helices (labeled from H1 to H12), so in terms of short–range localization, it is plausible that the above asymmetric soliton propagation is applicable.

In order to see how the corresponding solutions arise, consider the Hamiltonian H_{PM} for collective excited states of the protein molecules as given by

$$\begin{aligned} H_{PM} = \sum_{n,\alpha} \Big\{ & (\mathcal{E} + D_{n\alpha}) B^*_{n\alpha} B_{n\alpha} \\ & + J_{n,\alpha;n+1,\alpha}(B^*_{n\alpha} B_{n+1\alpha} + B^*_{n+1\alpha} B_{n\alpha}) \\ & + J_{n\alpha;n,n+1}(B^*_{n\alpha} B_{n\alpha+1} + B^*_{n\alpha+1} B_{n\alpha}) \Big\} \\ & + H_{ph} \ , \end{aligned} \tag{4.1}$$

(Davydov 1982). In this expression the $B^*_{n\alpha}$ and $B_{n\alpha}$ are creation/annihilation operators for the excitation $\mathcal{E}$ of the peptide group $n\alpha$; the term $J_{n\alpha;m\beta}$ denotes the energy of the resonance inter–dipolar coupling between the peptide groups $n\alpha$ and $m\beta$; $D_{n\alpha}$ denotes the deformation energy of interaction with neighbouring groups arising from excitations of the group $n\alpha$, and H_{ph} is the displacement operator of the groups from their equilibrium position along hydrogen bonds. This is given by

$$H_{ph} = \frac{1}{2} \sum_{n\alpha} [\ \frac{1}{M} P^2_{n\alpha} + w(U_{n\alpha} - U_{n+1\alpha})^2\ ] \ , \tag{4.2}$$

where M denotes the effective mass displaced along with the peptide group, w is the elasticity coefficient of the chain along the hydrogen bonds, and $P_{n\alpha}$ is the momentum operator conjugated to the displacement operator $U_{n\alpha}$ of the peptide group.

Associated to the Hamiltonian H_{PM} is the wave function describing the collective vibrations of the system as given by :

$$|\Psi(t)\ \rangle = \sum_{n\alpha} a_{na}(t) e^{\sigma(t)} B^*_{n\alpha} |0\ \rangle \ , \tag{4.3}$$

where $|0\rangle$ denotes a function for which all of the groups are in the ground-state with vibrationless excitations away from their equilibria, and where

$$\sigma(t) = -\frac{\iota}{\hbar} \sum_{n\alpha} [\ \beta_{n\alpha}(t) P_{n\alpha} - \pi_{n\alpha}(t) U_{n\alpha}\ ] \ . \tag{4.4}$$

In this last expression, the functions $\beta_{n\alpha}(t)$ and $\pi_{n\alpha}(t)$ depend on the average values for the displacement of the groups $n\alpha$ and their momenta in the above state. The coefficient function $a_{n\alpha}(t)$ satisfy $\sum |a_{n\alpha}(t)|^2 = 1$, where the latter corresponds to the distributive probability over the groups $n\alpha$ in their collective excitation states. The complex–valued functions $a_{n\alpha}(t)$ and the real–valued functions $\beta_{n\alpha}(t), \pi_{n\alpha}(t)$ are obtained from minimizing the functional

$$\langle \Psi(t) | H | \Psi(t) \rangle \ , \tag{4.5}$$

and on applying a certain approximation, the following system of equations is deduced (Davydov 1982 §22.4). Firstly, since the functions $a_{n\alpha}(t), \beta_{n\alpha}(t)$ are continuous in n, they are replaced by $a_\alpha(\xi, t), \beta_\alpha(\xi, t)$ respectively. The system in question is then :

$$\begin{aligned} & \Big\{ \iota\hbar \frac{\partial}{\partial t} - [\ \mathcal{E}_0 + W - 2J\ ] - 2\chi\ \frac{\partial \beta_\alpha}{\partial \xi} \Big\} a_\alpha \\ & + J\ \frac{\partial^2 a_\alpha}{\partial \xi^2} - L(a_{\alpha+1} + a_{\alpha-1}) = 0 \ , \\ & [\ \frac{\partial^2}{\partial t^2} - v_\alpha \frac{\partial^2}{\partial \xi^2}\ ] \beta_\alpha = \frac{2\chi}{M}\ \frac{\partial}{\partial \xi}\ |a_\alpha|^2 \ . \end{aligned} \tag{4.6}$$

Here χ is formed from coupling parameters for internal excitations of the peptide groups and their displacements from the equilibrium positions; J denotes the resonant energy of inter–dipolar interactions between neighbouring groups in the same chain, and L the energy of the

same interaction between neighbouring groups from different chains ($J \approx 967$ μeV, $L \approx 1537$ μeV). Also, $v_\alpha^2 = w/M$, the term W is the average density for displacement of molecules from the equilibria position, and $\mathcal{E}_0$ is the excitation energy of the peptide group relative to the deformation potential. It is from this system that the symmetric and asymmetric solitons are derived (see Davydov 1982 §22.4 for explicit details).

It is worth pointing out that Davydov solitons can subserve the function of local effectors (e.g. responsible for local tubulin–kinesin interaction) but are not suitable for long–range dissipationless transfer of information. The BE condensation of tunneling photons in a macroscopic coherence region of $\approx 50\mu m$, however, is sufficiently long–ranged to mediate a global coupling between distant parts within the neuron. The tunneling photons have boson mass of 13.6 eV and their condensation is sustainable even at body temperature of 310 K (Jibu and Yasue, 1997). This is the main reason to didactically separate the possible quantum effects into local (Davydov solitons) and global (BE–condensation of tunneling photons) interactions.

5 DWQ and arrows of time

5.1 Dipole wave quanta and arrows of time

Following the model of Ricciardi and Umezawa (1967) (cf Stuart et al. 1979) that memory entails a phase transition from a chaotic vacuum state to one that is relatively ordered, Vitiello (1995, 2003) proposes the DWQ when in their lowest ground state as inducing a stability of memory with the distinctions of long–term as 'stable' and inherent to the vacuum state, whereas short–term (memory) corresponds to the excitations of the DWQ condensates which were described earlier. Order parameters correspond to the WDQ, 'symmetron' (Riccardi and Umezawa 1967, Vitiello 1995) and the WEDP field electric polarization, the 'corticon' (Stuart et al 1979, Vitiello 1995). These order parameters are considered as corresponding to the code strength specifying the vacuum, the value of which is determined by the density of condensed NG bosons. In turn, information storage is proposed to be represented by coding of the ground state via symmetron condensation.

We have described the vacuum state in a conventional QM–sense, but now we mention an alternative characterization following Vitiello (1995, 2003). Firstly, on denoting the DWQ by $A(k)$ for some k, the number $N(A)$ for all k of the $A(k)$–modes in the vacuum state $|0(N)\rangle$, is taken to define a coding of information relative to the order parameters. Taking a time reversal $\widetilde{A}(k)$ of the copies of the $A(k)$, the vacuum state is then characterized by setting $N(A) - N(\widetilde{A}) = 0$, for all k . The same applies to differing values of the code $N(A)$, that is, all ground states for which $N'(A) \neq N(A)$. It is proposed that the brain ground state is the entirety of memory states $|0(N)\rangle$, for all N, and further, memory is manifestly how the brain may accomodate a multitude of co-existent macroscopic quantum states.

Such a proposition commences with the premise that the brain forms an 'open system' and its environment, in the appropriate sense, forms the 'closure'. Given that the DWQ frequency depends on time t, modes $A(k,t), \widetilde{A}(k,t)$, are considered so that the coupled system of differences $A - \widetilde{A}$ is describable in terms of an oscillator frequency. In the continuum limit, the system of differences $A - \widetilde{A}$ also becomes closed. A finiteness of size for the corresponding domains implies then a transition through distinct vacuum states for a given t . In the presence of external stimuli, the reversal of time symmetry is broken and the purported dissipation results in multifold degenerate vacuua, in turn, resulting in a vast memory storage. Possibly the memory state $|0(N)\rangle$ as a finite temperature state corresponds to thermodynamic effects in brain activity, further suggesting that in view of increasing entropy, the thermodynamic arrows of time may have the same orientation as the psychological arrows as emergent in the dissipative process.

It is possible that there may be any number of experimental studies that could prove or disprove such a hypothesis. The question bears some similarity to the relationship between (brain) cortical versus thermodynamical phase transitions (Steyn–Ross et al. 2001): how cortical entropy varies under the effects of anesthetics from a state of consciousness (ordered phase transitions) to unconsciousness (disordered phase transitions). On the surface, such findings might suggest an 'emergent' process through objective time intervals, at least as far as clinical consciousness is concerned. The soliton–like mechanisms we have described are in essence derived from time evolution equations, and thus mathematically involve a time flow. However, the mechanisms by themselves do not explain away the questions of objective versus subjective time. The various models in which they feature, suggest how they may be tied to memory storage and retrieval, and to the irreversibility of consciousness. We can see the relevance of the mechanisms to objective time as manifest in the brain within certain cortical regions, but we cannot tie these (mechanisms) to the subjective feeling of time, as exemplified in the case of individuals suffering from time agnosia : the comprehension of time is altogether lost, although most normal mental processes may still function nevertheless.

6 Conclusion

We have discussed some mechanisms for solitonic interactions ambient to microtubular surfaces, suggesting possibilities for interaction between local EM–fields of electro–neural impulses and the cytoskeletal structure. The broader model suggests how these processes might actually recover an EM–field through the chain of events *EM–field* $\Longrightarrow$ *tubulin–tail solitons* $\Longrightarrow$ *exocytosis* $\Longrightarrow$ *EM–field*. This progression may be crucial towards understanding the neurobiological basis for mind and memory, as well

as for the possible implementation of quantum or semi–classical computational schemes which are to be assessed in a future work.

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