

Solitonic effects of the local electromagnetic field on neuronal microtubules

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Abstract

Current wisdom in classical neuroscience suggests that the only direct action of the electric field in neurons is upon voltage-gated ion channels which open and close their gates during the passage of ions. The intraneuronal biochemical activities are thought to be modulated indirectly either by entering into the cytoplasmic ions that act as second messengers, or via linkage to the ion channels enzymes. In this paper we present a novel possibility for the subneuronal processing of information by cytoskeletal microtubule tubulin tails and we show that the local electromagnetic field supports information that could be converted into specific protein tubulin tail conformational states. Long-range collective coherent behavior of the tubulin tails could be modelled in the form of solitary waves such as sine-Gordon kinks, antikinks or breathers that propagate along the microtubule outer surface, and the tubulin tail soliton collisions could serve as elementary computational gates that control cytoskeletal processes. The biological importance of the presented model is due to the unique biological enzymatic energase action of the tubulin tails, which is experimentally verified for controlling the sites of microtubule-associated protein attachment and the kinesin transport of post-Golgi vesicles.

1 Introduction

Microtubules are the main constituents of the cellular cytoskeleton together with microtubule associated proteins (MAPs), intermediary filaments and actin filaments. Microtubules are hollow cylinders with diameter of 25 nm and are composed from tubulin α/β dimers. Each tubulin has a nucleotide-binding site that binds a single GTP molecule. The α -tubulin bound GTP is nonhydrolyzable while the β -tubulin bound GTP is hydrolyzed soon after the dimer is incorporated in the growing microtubule. The β -tubulin bound nucleotide GTP embedded in the microtubule lattice, once hydrolyzed to GDP, cannot be further exchanged for new GTP molecule. However there remains a single layer of 13 GTP dimers at the microtubule plus end (composed of β -tubulins) that acts as a stabilizing “cap”. Hydrolysis of one of these plus end β -bound GTP molecules is sufficient to trigger rapid microtubule depolymerization. This rapid shrinking/depolymerization of the microtubule is known as a “catastrophe”. Usually biologists are attracted only by the dynamical instability of microtubules because it leads to a reorganization of the cytoskeleton and therefore a reorganization of the cellular morphology and functions. However in highly differentiated cells such as neurons there is a stable population of cytoskeletal microtubules that could act as waveguides for subneuronally flowing information and at the same time perform the function of tracks controlling kinesin and dynein motors which distribute post-Golgi vesicles containing newly synthesized proteins.

The idea for subneuronal processing of information performed by microtubules was originally suggested by Hameroff and Watt (1982) and further refined into a cytoskeletal automaton model (Rasmussen et al., 1990). The premise of the automaton model is that there is a mobile electron that could hop between α and β tubulin inside the dimer hydrophobic pocket. Further improving upon this scenario, Tuszynski et al. (1995) developed a ferroelectric lattice model in which the direction of the vector representing the tubulin dimer dipole moment was assumed to depend on electron hopping. The energy barrier for the electron hopping was estimated to be 0.4 eV for intra-dimer hopping and 1.0 eV for the inter-dimer hopping (Brown and Tuszynski, 2003). These high-energy barriers however make the suggested ferroelectric microtubule lattices apparently insensitive to the local cytoplasmic electric field, which is in the order 1-10 V/m for neurons (Georgiev, 2003). In contrast, for the reorientation of the tubulin dipoles in the Tuszynski model, the cytoplasmic electric field intensity must reach the extreme biologically unfeasible magnitude of 10^6 - 10^7 V/m.

Since in neurophysiology the main communication inside the neuron is achieved via passive and active electric signal transmission, one may tentatively assume that if microtubules perform any kind of subneuronal computation, then they must input the local electromagnetic information first (Georgiev, 2003). The paradox of the apparent electric insensitivity of tubulin to the local electric field indeed arises from the improper biophysical modeling because all of the aforementioned models did not take into consideration the last 14-19 C-terminal aminoacid residues, which are highly acidic and bear 9-10 negative charges con-

tributed by glutamate residues. These *C-terminal tubulin tails* project from the microtubular outer surface and could not be mapped by crystallographic X-ray studies, because of their extremely high sensitivity to the environmental conditions producing a disordered image (Lowe et al., 2001).

The inclusion of the tubulin tails in the biophysical model of microtubules allowed Georgiev (2003), Georgiev et al. (2004), Georgiev and Glazebrook (2006, 2007) to reveal a novel possibility for long-range microtubular communication in the form of tubulin tail sine-Gordon solitons. It was suggested that collision of kinks, antikinks and breathers could perform a form of subneuronal computation, which in turn is outputted by the tubulin tail energase action that controls MAP attachment and kinesin dynamics. In this paper we present the relevant mathematics stressing upon the importance of the ordered water molecule dynamics within the tubulin tail hydration shells and we interpret the results in the framework of the elastic ribbon model (reviewed by Dodd et al., 1982). Furthermore, we show that the presented biophysical model is particularly relevant to any further developments of the Q-mind hypothesis and we explain why the recently suggested experiment by Koch and Hepp (2006) cannot disprove the latter.

2 Tubulin domains

The overall folds of the α - and β -monomers are nearly identical, when composed of two β -sheets of six and four strands, flanked by 12 α -helices. Three functional domains have been assigned by Nogales et al. (1998) to each tubulin monomer: N-terminal, intermediate, and C-terminal domains.

The N-terminal domain (residues 1-205) forms a Rossmann fold, which is typical of nucleotide-binding proteins. Helices H1 and H2 are on one side of the sheet, whereas helices H3, H4, and H5 are on the other. The intermediate domain (residues 206-381) contains a mixed β -sheet and five surrounding α -helices, among which H8 lies at the longitudinal interface between monomers. The loop connecting B7 and H9 in α -tubulin (also known as the M-loop) makes strong lateral contacts between the protofilaments in the assembled microtubule (Keskin et al., 2002). The C-terminal domain of tubulins has different length and structure in α - and β -tubulin, but in general the C-terminal domain has a C-terminal helix H12 and a random coil C-terminal tubulin tail.

Jimenez et al. (1999) determined the helicity of α (404-451) and β (394-445) tubulin C-terminal recombinant peptides with the use of NMR and have presented illustrations of fourteen different α - and β -tubulin tail conformations. In the α -tubulin molecule, 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 EEVGVDSVEGEGEEEEGEEY. 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 9 aminoacid longer helix of the β -tubulin compared to previous PDB models (Nogales et al., 1998). This suggests an extension in the

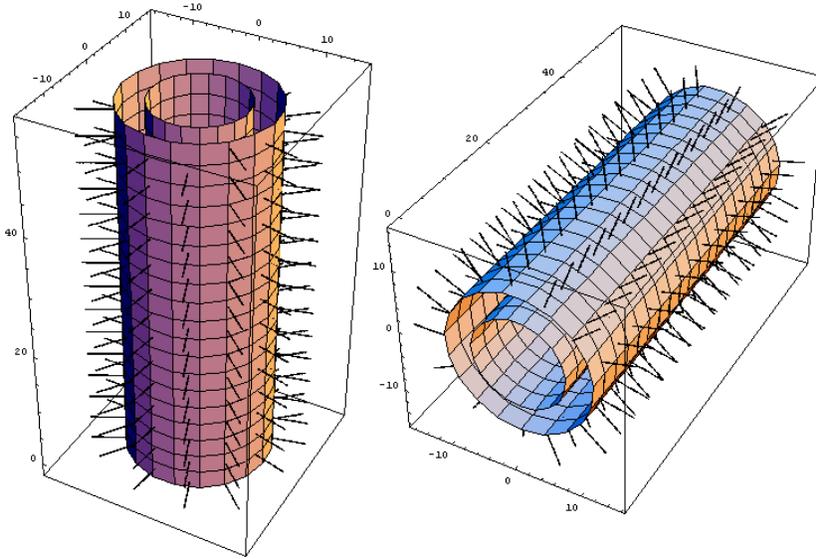


Figure 1: The assembled haired 13 protofilament left-handed 3-start helical microtubule (MT) with outer MT diameter of 22 nm, inner diameter of 14 nm, MT wall thickness of 4 nm, and tubulin tail length of 5 nm. The tubulin tails extending from each protofilament are visualized as rows of hairy projections. The image was computed and produced with Wolfram' Mathematica 5.0.

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 increase or decrease the length of the helix H12, in the same time decreasing or increasing 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 tubulin tails are observed to be disordered by NMR but we would like to note that this is dynamical disorder and indeed is a manifestation of the extreme sensitivity of the tubulin tails to the environmental conditions and the local electric fields.

3 Tubulin tails as energases

In the presence of physiological pH inside neurons the tubulin tails project out from the microtubular outer surface and strongly interact with their hydration shells as well as with attracted positively charged Ca^{2+} and Mg^{2+} ions from the cytoplasm. The strong coupling between the protein conformation and its hydration shell (Levitt and Sharun, 1988) is our motivation towards the mathematical model of the solitonic interaction between the local electromagnetic field in neurons, the water molecule dipoles from the tubulin tail hydration shells forming a 4-5 nm layer on the microtubule surface and the tubulin tails themselves. The tubulin tail conformational solitons could propagate along the outer microtubular surface providing a dissipationless mechanism for transmission of information. The soliton collisions might then conceivably perform the role of elementary logical gates thus implementing a subneuronal mode of computation.

The output of the computation can be ensured by the conformational status of the tubulin tails that determine the MAP attachment sites and control kinesin motor dynamics. Fujii and Koizumi (1999) have found that MAPs bind α -tubulin at amino acid sequence Lys430-Glu441 located in the end of the C-terminal helix α -H12 and in the initial segment of the α -tubulin tail. According to the same authors, MAPs bind β -tubulin at amino acid sequences Tyr 422-Gly 434 located in the C-terminal helix β -H12 and the initial segment of the β -tubulin tail. Since these binding sequences are located just at the base of the tubulin tails which bear 9-11 negative charges it is reasonable to suppose that the conformational state of the tubulin tails will be the main regulator of MAP binding. Microtubule C-termini bind different MAPs - MAP2, MAP1 and tau, and the specificity of this binding depends also on post-translational modifications of the tubulin tails. Tubulin tails undergo several post-translational modifications (Westermann and Weber, 2003): (i) *tyrosination/detyrosination*, (ii) *generation of $\Delta 2$ -tubulin*, (iii) *phosphorylation*, (iv) *polyglutamylolation* and (v) *polyglycylation*, so there is crosstalk not only between the tubulin tails and the local electromagnetic field, but also between tubulin tails and the membrane bound G-protein receptors that trigger different intraneuronal biochemical cascade pathways (Georgiev, 2003). Some of the mentioned modifications (polyglutamylolation and polyglycylation) produce bifurcations of the tails.

We suggest that the mechanism of the tubulin tail action is via *vibrationally assisted tunneling* - a key concept that emerged and was experimentally verified in the last several years (Basran et al., 1999; Scrutton et al., 1999; Sutcliffe and Scrutton, 2000a; 2000b). A locally formed standing breather could promote or suppress conformational tunneling 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 upon the boundary conditions (Takada and Nakamura, 1994; 1995). Formally, the mechanism of tubulin tail breathing action is a form of enzymatic energase action. *Energase* is an enzyme that makes or break noncovalent bonds in its interaction partner (Purich, 2001). Energases do not have a source of energy but rather induce conforma-

Table 1: Tubulin tail modifications

Modification	Function
Tyrosination/detyrosination	Involved in tubulin crosstalk to intermediate filaments and cell differentiation.
Generation of $\Delta 2$ -tubulin (only α -tubulin)	$\Delta 2$ -tubulin is a marker for stable microtubules. Removes tubulin from the tyrosination cycle and could be marker for polyglycylation.
Phosphorylation (better established for β -tubulin on Ser441/444)	Essential for neuronal differentiation.
Polyglutamylation of α - and β -tubulin (up to 20 glutamate residues)	Involved in the regulation of tubulin interaction with MAPs in neurons.
Polyglycylation of α - and β -tubulin (up to 30-40 glycine residues)	Essential for cytokinesis (severing residues of microtubules).

tional transitions in a molecule that has accumulated energy in an intermediate highly energetic conformational state. The accumulated energy is derived from hydrolyzed ATP or GTP in previous biochemical steps; for that reason it is usually called *primed energy* and the process is referred to as *priming*.

Skiniotis et al. (2004) have experimentally shown that a β -tubulin tail interacts with the kinesin switch II domain, while an α -tubulin tail possibly interacts with kinesin $\alpha 7$ helix in a way that after the kinesin bound ATP is hydrolyzed, the kinesin moves along the microtubule surface. Native microtubules that possess tubulin tails cannot be decorated by ADP-kinesin molecules because of the weak kinesin/tubulin tail binding, while subtilisin treated microtubules that lack tubulin tails bind to stably ADP-kinesin thus blocking the kinesin walk. This experimental data suggests that the tubulin tails catalyze the detachment of the kinesin-ADP complex from the microtubule surface thus allowing the kinesin dimer to take a “step” along the microtubule protofilament.

An analogous situation could arise if we consider the tubulin tail catalytic action upon phosphorylated MAP-2 molecules in dendrites. A local tubulin tail breather could catalyze the detachment of the MAP-2 molecule from the microtubule in dendritic projections starting cytoskeletal reorganization process.

In axons, the solitonic control of MAP-tau attachment could be both direct via catalysis of its attachment/detachment and indirect via decision on its phosphorylation status by means of the attachment/detachment of microtubule bound *protein phosphatase 2A* (PP2A). Sontag et al. (1999) reported that AB α C, the dominant brain isoform of PP2A is localized on microtubules, binds directly to tau, and is a major tau phosphatase in brain chemistry. The experimental findings indicate that structural interactions among AB α C, tau, and microtubules might control the phosphorylation state of tau. Disruption

of these normal interactions could contribute significantly to development of tauopathies such as Alzheimer's disease (it is well known that in Alzheimer's disease brain tau is more heavily phosphorylated).

4 Hydration shell interaction with the local EM field

We have already discussed the coupling between the tubulin tails and the microtubule vicinal water that forms a layer 4-5 nm thick on the outer microtubule surface. The volume of this water layer will be hereafter denoted with V . Having fixed this volume V we can label the number of water molecules, say N . The position of the j^{th} water molecule will have coordinates $r^j = (x^j, y^j, z^j)$. Since the water molecule has a constant electric dipole moment it can be considered as a quantum mechanical spinning top with an electric dipole moment $\mu = 2e_P P$ and average moment of inertia $I = 2m_P d^2$. Here, m_P denotes the proton mass, e_P the proton charge, $d = 0.082$ nm and $P = 0.02$ nm. Although the water molecule has as many energy eigenstates as a quantum mechanical spinning top and so is capable of exchanging energy between the quantized electromagnetic field over many different values, it was revealed that the processes in which only the two principal energy eigenstates take part in the energy exchange are dominant (Del Giudice et al., 1988). The energy difference ϵ between the two principal energy eigenstates is 24.8 millielectronvolts. The quantum dynamics of the j^{th} water molecule can be suitably described by a spin variable $s^j = \frac{1}{2}\sigma$, where $\sigma = (\sigma_x, \sigma_y, \sigma_z)$ and σ 's are Pauli spin matrices denoting the three components of the angular momentum for spin $\frac{1}{2}$. Following Jibu and Yasue (1997), the Hamiltonian governing the quantum dynamics of the j^{th} water molecule is given by ϵs_z^j , and so the total Hamiltonian for N water molecules becomes:

$$H_{\text{WM}} = \sum_{j=1}^N \epsilon s_z^j \quad (1)$$

Two energy eigenvalues of the former Hamiltonian are $-\frac{1}{2}\epsilon$ and $\frac{1}{2}\epsilon$ reflecting the fact that only the two principal energy eigenstates with energy difference ϵ are taken into account.

The linearly polarized quantized electromagnetic field along the axis of the neuronal projection could be described in terms of an electric field operator $E = E(r, t)$. The Hamiltonian is:

$$H_{\text{EM}} = \frac{1}{2} \int_V E^2 d^3r \quad (2)$$

The interaction between the quantized electromagnetic field and the totality of water molecules can be understood as an exchange of energy in terms of the creation and annihilation of photons. Let us divide the electric field operator into positive and negative frequency parts

$$E = E^+ + E^- \quad (3)$$

Then, the interaction Hamiltonian of the quantized electromagnetic field and the totality of water molecules becomes

$$H_I = -\mu \sum \left[E^-(r^j, t) s_-^j + s_+^j E^+(r^j, t) \right] \quad (4)$$

where

$$s_{\pm}^j = s_x^j \pm i s_y^j \quad (5)$$

The total Hamiltonian governing the quantum brain dynamics of the local neuronal electromagnetic field, the dipolar vibrational field of water molecules, and their interaction is given by

$$H = H_{WM} + H_{EM} + H_I \quad (6)$$

Since the spatial region \mathbb{V} in the vicinity of the microtubule may be considered as a cavity for the electromagnetic wave, it is convenient to introduce the normal mode expansion of the electric field operator obtaining:

$$E^{\pm}(r, t) = \sum E_k^{\pm}(t) \exp[\pm i(k \cdot r - \omega_k t)] \quad (7)$$

Here, ω_k , denotes the proper angular frequency of the normal mode with wave vector k . We are mainly interested in the ordered collective behavior among the water molecules and the quantized electromagnetic field in the cavity region \mathbb{V} . Hence, let us introduce collective dynamical variables for the water molecules as given by

$$S_k^{\pm} \equiv \sum_{j=1}^N s_{\pm}^j(t) \exp[\pm i(k \cdot r^j - \omega_k t)] \quad (8)$$

$$S \equiv \sum_{j=1}^N s_z^j \quad (9)$$

Then, the total Hamiltonian H becomes:

$$H = \frac{1}{2} \int_{\mathbb{V}} E^2 d^3r + \epsilon S - \mu \sum [E_k^- S_k^- + S_k^+ E_k^+] \quad (10)$$

This total Hamiltonian for the system of N water molecules and the quantized electromagnetic field in the region \mathbb{V} vicinal to the microtubule is essentially of the same form as a Hamiltonian for a laser system. Therefore, it can be expected that water molecules in \mathbb{V} manifest a laser-like coherent optical activity, that is, a water laser if the energy surpasses a certain threshold.

If we investigate the collective dynamics of water molecules in \mathbb{V} starting from the total Hamiltonian H , then we will see that a continuous rotation of the water dipoles around the third axis leads to *spontaneous symmetry breaking*

(SSB) of the vacuum state and emergence of *Goldstone bosons* known as *soft polaritons*, which mediate long-range quantum coherence. For this it is convenient to introduce the canonical variables of the electromagnetic field through the relation:

$$P_k(t) = \sqrt{\frac{\hbar\omega_k}{2}} i(E_k^- - E_k^+) \quad (11)$$

$$Q_k(t) = \sqrt{\frac{\hbar}{2\omega_k}} i(E_k^- + E_k^+) \quad (12)$$

These canonical variables satisfy the canonical commutation relations:

$$[P_k(t), Q_h(t)] = -i\hbar\delta_{kh} \quad (13)$$

$$[P_k(t), P_h(t)] = [Q_k(t), Q_h(t)] = 0 \quad (14)$$

$$P_k^*(t) = P_{-k}(t) \quad (15)$$

$$Q_k^*(t) = Q_{-k}(t) \quad (16)$$

Here, A^* denotes the adjoint operator of A . In terms of the canonical variables, the total Hamiltonian H becomes:

$$H = \frac{1}{2} \sum_k [P_k^*(t)P_k(t) + \omega_k^2 Q_k^*(t)Q_k(t)] + \sum_{j=1}^N \epsilon s_z^j - \sqrt{\frac{2}{\hbar}} \mu \sum_{j=1}^N \sum_k \left[\sqrt{\omega_k} Q_k(t) s_x^j - \frac{1}{\sqrt{\omega_k}} P_k(t) s_y^j \right] \quad (17)$$

Thus, it is seen that the total Hamiltonian H remains invariant under the transformation of the canonical variables as given by

$$Q'_k(t) = Q_k(t) \cos \theta - \frac{1}{\omega_k} P_k(t) \sin \theta \quad (18)$$

$$P'_{-k}(t) = \omega_k Q_k(t) \sin \theta + P_{-k}(t) \cos \theta \quad (19)$$

$$s_x'^j(t) = s_x^j(t) \cos \theta + s_y^j(t) \sin \theta \quad (20)$$

$$s_y'^j(t) = -s_x^j(t) \sin \theta + s_y^j(t) \cos \theta \quad (21)$$

$$s_z'^j(t) = s_z^j(t) \quad (22)$$

for a continuous parameter θ . This transformation corresponds to a continuous rotation around the third axis and is an element of the Lie group $\text{SO}(2)$ of rotations in two-dimensional space.

Now let us consider a time-independent solution to the Heisenberg equations for canonical variables in order to investigate the dynamically ordered state of the system of the electromagnetic field and water molecules in \mathbb{V} . The Heisenberg equations are given by

$$\frac{dQ_k(t)}{dt} = \frac{1}{\hbar} [Q_k(t), H] \quad (23)$$

$$\frac{dP_k(t)}{dt} = \frac{1}{\hbar} [P_k(t), H] \quad (24)$$

$$\frac{ds_x^j(t)}{dt} = \frac{1}{\hbar} [s_x^j(t), H] \quad (25)$$

$$\frac{ds_y^j(t)}{dt} = \frac{1}{\hbar} [s_y^j(t), H] \quad (26)$$

$$\frac{ds_z^j(t)}{dt} = \frac{1}{\hbar} [s_z^j(t), H] \quad (27)$$

and the time-independent solution is obtained as follows:

$$Q_k(t) \equiv Q_k^0 \quad (28)$$

$$P_k(t) \equiv 0 \quad (29)$$

$$s_x^j(t) \equiv u \quad (30)$$

$$s_y^j(t) \equiv 0 \quad (31)$$

$$s_z^j(t) \equiv w \quad (32)$$

Here Q_k^0 is a constant taking a different value for each different value of a wave number k , and u and w are also constants. Each spin variable $s^j = s_x^j, s_y^j, s_z^j$ describing the j^{th} water molecule is found to be aligned in one and the same direction as represented by a constant vector $(u, 0, w)$. Such a long-range alignment of spin variables is nothing but the manifestation of a dynamical order of the system of the quantized electromagnetic field and water molecules. Namely, there exists a long-range order so that the spin variable of water molecules in \mathbb{V} is systematized globally to realize the uniform configuration.

It is interesting to note that this time-independent solution, representing a dynamically ordered state of the system of the quantized electromagnetic

field and the water molecules in \mathbb{V} , is no longer invariant under the continuous transformation of the canonical variables in equations (18)-(22). The aligned direction is transformed into another direction under such a continuous rotation about the third axis. Thus, a peculiar situation is realized in which the total Hamiltonian, governing the quantum dynamics of canonical variables is invariant under a certain compact continuous transformation, whereas it admits to a stable time-independent solution which is not invariant under the same transformation. As we have mentioned this leads to SSB and the creation of Nambu-Goldstone bosons.

5 Coherent photon emission pulse modes

Among the long-range order creating phenomena induced by the interaction between the water dipoles and the local electromagnetic field we may find a specific one in which the collective dynamics of the water electric dipole (WEDP) field in the spatial region of linear dimension up to $50 \mu\text{m}$ can give rise to a cooperative emission of coherent photons with induced energy by certain systems external to the quantum system of the electromagnetic field and the WEDP field. If we wish this coherent emission of photons to have any biological relevance, then it is necessary to consider timescales comparable with the dynamical timescale of protein action, which is in the order of 10-15 picoseconds. In such cases the collective dynamics has a characteristic time comparable to that of thermally disordered dynamics and is affected by thermal fluctuation and dissipation. It will be shown that the laser-like emission of coherent photons can be realized even in such a situation prone to thermal noise and loss, provided that the metabolic supply of energy is sufficient to “pump up” the WEDP field. Jibu and Yasue (1997) noted that in such a case the Heisenberg-Langevin equation for water laser system requiring pumping could be of crucial importance.

First we will assume for simplicity that only a single eigenmode with specific eigenvalue, say ω_{λ_0} , resonates with the energy difference ϵ between the two principal energy eigenstates. Effectively, we have $\epsilon = \hbar\omega_{\lambda_0}$, and all the other eigenmodes are neglected. In conventional laser theory, this is known as a *single mode laser*. Since we have only one eigenmode with eigenvalue ω_{λ_0} , we may omit all the eigenvector indices of the dynamical variables. The three collective dynamical variables, S and S^\pm , for the WEDP field and the two variables, a^* and a , for the electromagnetic field are given by the Heisenberg-Langevin equations:

$$\frac{dS}{dt} = -\gamma(S - S_\infty) - i\frac{f}{\hbar}(a^*S^- - S^+a) + \eta \quad (33)$$

$$\frac{dS^+}{dt} = i\frac{2f}{\hbar}Sa^* - \gamma_0S^+ + i\frac{\epsilon}{\hbar}S^+ + \eta^+ \quad (34)$$

$$\frac{dS^-}{dt} = -i\frac{2f}{\hbar}Sa - \gamma_0S^- - i\frac{\epsilon}{\hbar}S^- + \eta^- \quad (35)$$

$$\frac{da^*}{dt} = -\gamma_{\text{EM}}a^* - i\frac{2\pi\epsilon f}{\hbar V}S^+ + \eta_{\text{EM}}^* \quad (36)$$

$$\frac{da}{dt} = -\gamma_{\text{EM}}a + i\frac{2\pi\epsilon f}{\hbar V}S^- + \eta_{\text{EM}} \quad (37)$$

Here, γ and γ_0 are damping coefficients for the WEDP field, γ_{EM} is a damping coefficient for the electromagnetic field, η and η^\pm are thermal fluctuations for the WEDP field, η_{EM} and η_{EM}^* are thermal fluctuations for the electromagnetic field, and S_∞ is a parameter denoting the rate of pumping due to supply of metabolic energy.

The collective dynamical variables of the WEDP field can be deleted in the adiabatic approximation, and the Heisenberg-Langevin equations Eqs.(33)-(37) can be reduced approximately to a system of Heisenberg-Langevin equations for the quantized electromagnetic field, as given by

$$\frac{da^*}{dt} = \alpha a^* - \beta a a^* a^* + \xi^* \quad (38)$$

$$\frac{da}{dt} = \alpha a - \beta a^* a a + \xi \quad (39)$$

Here, α and β are constants as given by

$$\alpha = -\gamma_{\text{EM}} + \frac{4\pi\epsilon f^2 S_\infty}{\hbar^2 V \gamma_0} \quad (40)$$

$$\beta = \frac{16\pi\epsilon f^4 S_\infty}{\hbar^4 V \gamma_0^2 \gamma} \quad (41)$$

and ξ^* and ξ are *effective thermal fluctuations* for the quantized electromagnetic field.

The Heisenberg-Langevin equations Eqs.(38)-(39) governing the collective dynamics of the quantized electromagnetic field in \mathbb{V} can be reduced to the Langevin equation if Glauber's coherent state representation is adopted (Jibu and Yasue, 1997):

$$\frac{dZ}{dt} = \alpha Z - \beta \bar{Z} Z^2 + B \quad (42)$$

Here, $Z = Z(t)$ is a *Markov process* in the complex plane denoting the complex eigenvalue of the electromagnetic field operator a , $B = B(t)$ is a complex Gaussian white noise representing the thermal fluctuation of the quantized electromagnetic field, and \bar{z} denotes the complex conjugate of a complex number z .

The mean and variance of the complex Gaussian white noise are given by

$$\langle B(t) \rangle = 0 \quad (43)$$

$$\langle \overline{B(t)}B(s) \rangle = 2D\delta(t-s) \quad (44)$$

respectively, where $\langle \rangle$ indicates the expectation value, $\delta(t)$ is the Dirac delta function and D is a diffusion constant given by

$$D = \frac{M\pi^2\epsilon^2 f^2 \gamma_0}{2\gamma_{\text{EM}}^2 \hbar^2 V^2} + \frac{2\pi\epsilon\gamma_{\text{EM}}}{V} \left[\frac{1}{2} + \frac{1}{\exp(\frac{\epsilon}{k_B T}) - 1} \right] \quad (45)$$

with k_B Boltzmann's constant. The Langevin equation Eq.(42) is equivalent to the *Fokker-Planck equation*:

$$\frac{\partial}{\partial t} f = -\frac{\partial}{\partial z} [(\alpha z - \beta \bar{z} z^2) f] + D \frac{\partial^2}{\partial z \partial \bar{z}} f \quad (46)$$

for the probability distribution function $f = f(z, \bar{z}, t)$ of the complex Markov process $Z(t)$. The stationary solution of the Fokker-Planck equation Eq.(46) can be obtained immediately:

$$f = C \exp \left[\frac{2\alpha \bar{z} z - \beta (\bar{z} z)^2}{2D} \right] \quad (47)$$

where C is a normalization constant such that the following equation holds:

$$\int \int f(z, \bar{z}, t) dz d\bar{z} = 1 \quad (48)$$

This stationary solution Eq.(47) of the Fokker-Planck equation Eq.(46) is nothing but the unique equilibrium probability distribution function of the Markov process $Z(t)$. By the explicit form given by Eq.(47), it is immediately clear that the characteristics of the equilibrium probability distribution of the Markov process $Z(t)$, denoting the dynamics of the quantized electromagnetic field in \mathbb{V} , depend sensitively on the rate of pumping S_∞ provided by metabolic energy. Namely, for smaller values of S_∞ such that $\alpha < 0$, the most probable value for the intensity of the electromagnetic field $I = \sqrt{Z\bar{Z}}$ vanishes, while it becomes nonvanishing for larger values of S_∞ such that $\alpha > 0$, obtaining

$$I = \sqrt{\frac{\alpha}{\beta}} \quad (49)$$

Jibu and Yasue (1997) have shown that the collective dynamics of the quantum system of electromagnetic field and the WEDP field in \mathbb{V} manifests a long-range cooperative phenomenon of photon emission even if the thermal fluctuation and dissipation are taken into account. An excitation of the quantized electromagnetic field, that is, an emission of photons in \mathbb{V} , is induced if the pumping rate exceeds a threshold value as given by:

$$S_\infty = \frac{\hbar^2 V \gamma_0 \gamma_{\text{EM}}}{4\pi\epsilon f^2} \quad (50)$$

On briefly summarizing the mathematics we could say that the energy for the coherent photon pulse emission by the vicinal water in the proximal 4-5 nm of the microtubule outer surface could be gained from the metabolic energy released by cytoskeletal bound enzymes.

In order to model the coherent photon emission pulse we could suppose that the electromagnetic field that interacts with the water dipole spin, has a fast dependence on $z - ct$ and a slow dependence on z and t ; here z refers to the longitudinal direction of the microtubule, which coincides with the direction of propagation of the electric field in the neuron (there are few but important exceptions that will be discussed later). We have the expansion:

$$\vec{E}(\vec{x}, t) = \sum \vec{E}_{tr}^n(z, t) \exp [ik_n(z - ct)] \quad (51)$$

where \vec{E}_{tr} is the electric field transversal to the wave propagation direction. Using the equations of motion derived from the total Hamiltonian H we arrive at:

$$\frac{\partial E^\pm}{\partial z} + \frac{1}{c} \frac{\partial E^\pm}{\partial t} = \pm i \frac{2\pi\epsilon\mu}{\hbar V} s^\mp \quad (52)$$

This is a quantum equation of motion. Since we do not have any practical means to either measure the spin variable s , or account for its dynamical details, we assume its quantum average as suggested by Abdalla et al. (2001). Such an average is easily obtained due to the simple description of s in terms of the Pauli matrices, leading to a result expressed in terms of the exponential of the field θ , defined by:

$$\theta^\pm(z, t) = \frac{\mu}{\hbar} \int_0^t \langle E^\pm(z, t) \rangle_{qu} du \quad (53)$$

where we take the quantum average $\langle \rangle_{qu}$. Following such a procedure in Eq.(52) leads to the semiclassical equation of motion (Abdalla et al., 2001):

$$\frac{\partial^2 \theta^\pm}{\partial t \partial \varsigma} = - \frac{4\pi\epsilon N \mu^2}{\hbar^2 V} \sin \theta^\pm \quad (54)$$

where $\frac{N}{V}$ is the number of water dipoles per unit of volume, and $\varsigma = t + \frac{z}{c}$.

Above, the indices \pm correspond to the usual combinations of the transversal direction of the electric field, and we also assumed that the longitudinal direction does not propagate. This is a version of the well-known *sine-Gordon equation*. The 1-soliton solution is given by the expression:

$$E = \frac{\hbar}{\mu} A \operatorname{sech} A \left(t - \frac{z}{v_0} \right) \quad (55)$$

$$A = \sqrt{\frac{2\pi\epsilon\mu^2 N v_0}{\hbar^2 V (c - v_0)}} \quad (56)$$

where A is the angular frequency characteristic of the model and v_0 is the velocity of the soliton.

The biological importance of the suggested model is easily seen if we investigate the ontology hidden behind the mathematical equations. In brief, we have shown that the water dipoles from the tubulin tail hydration shells strongly interact with the local electromagnetic field. This interaction results in long-range ordering of the water molecule dipoles and Goldstone bosons (viz soft polaritons) that emerge to induce information of this macroscopic order. The interaction of the ordered water dipoles with the electromagnetic field further leads to a coherent emission of photon pulses, which propagate via tunneling (Jibu and Yasue, 1997). The formed solitons are not dissipated by the thermal fluctuations, but could be pumped with metabolic energy if the energy supply surpasses the threshold S_∞ as above. Since the tubulin tails in the presence of physiological pH project out from the microtubule outer surface and are strongly coupled with their hydration shells, the propagating water dipole electromagnetic solitons will affect the tubulin tail conformational states. Thus the propagating electromagnetic soliton will be coupled to a protein conformational soliton physically propagating upon the tubulin tails. In turn, the quantum dynamics of the tubulin tails manifested as a soliton-induced conformational change could control the attached MAPs and motor molecules (kinesin, dynein) via vibrationally assisted tunneling and energase action.

6 The elastic ribbon model of tubulin tail soliton collisions

The 1-soliton solutions of the sine-Gordon equation:

$$\frac{\partial^2}{\partial t^2}\phi(x,t) - \frac{\partial^2}{\partial x^2}\phi(x,t) + \sin[\phi(x,t)] = 0 \quad (57)$$

can be obtained after integration using the boundary conditions $\phi \rightarrow 0(\text{mod}2\pi)$:

$$\phi(x,t) = 4 \tan^{-1} \exp[m\gamma(x - vt) + \delta] \quad (58)$$

where

$$\gamma^2 = \frac{1}{1 - v^2} \quad (59)$$

The 1-soliton solution in which we have chosen the positive root for γ , is called a *kink*, and represents a twist in the variable ϕ which takes the system from one solution $\phi = 0$ to an adjacent with $\phi = 2\pi$. The states $\phi = 0(\text{mod}2\pi)$ are known as *vacuum states* as they are constant solutions of zero energy. The solution in which we take the negative root for γ is called an *antikink*.

2- and 3-soliton solutions, as well as their elastic collisions can be obtained by applying Bäcklund transformations. In terms of characteristic coordinates (ξ, τ) we have:

$$\xi = \frac{1}{2}(x - t) \quad (60)$$

$$\tau = \frac{1}{2}(x + t) \quad (61)$$

and knowing two soliton solutions ψ and φ , then via a Bäcklund transformation we obtain a further system of equations:

$$\frac{1}{2}(\psi + \varphi)_\xi = \alpha \sin \frac{1}{2}(\psi - \varphi) \quad (62)$$

$$\frac{1}{2}(\psi - \varphi)_\tau = \frac{1}{\alpha} \sin \frac{1}{2}(\psi + \varphi) \quad (63)$$

We visualize the traveling water dipole sine-Gordon soliton solutions with the use of the elastic ribbon sine-Gordon model as discussed by Dodd et al. (1982). Here we take a clockwise twist of the elastic ribbon to be a *kink* with topological charge $\vartheta_K = +1$. The alternative counterclockwise twist with topological charge $\vartheta_{AK} = -1$ will be an *antikink*.

Computer simulations were performed on Maple 5.1 with the use of the algorithms developed by Miroschnichenko et al. (2004). In our case the ontological interpretation of the line of blue arrows could be a protofilament with tubulin tails projected out from the outer microtubule surface. The surrounding water dipoles are visualized only at the site of the local twist in yellow-green, which could be interpreted as the advancing electromagnetic pulse mode.

On taking into account the results by Abdalla et al. (2001), we could say that the applied longitudinal voltage (i.e. voltage along the neuronal projection and respectively along the microtubule z -axis) results in the generation and propagation of kinks or antikinks along the microtubule protofilaments. The tubulin tails are coupled to the vicinal water of the microtubule outer surface and they alter their conformational status at the site of the soliton twist. The following animations represent the motion of the tubulin tails, where in fact they could not make a full turn at 2π because of geometrical reasons. Instead, the tubulin tails could oscillate forth and back. The water dipole rotation at 2π however is possible and it is the water dipole rotation that is “*projected*” upon the C-terminal tubulin tail conformation.

ANIMATION 1. [Available as a supplementary GIF file online] The traveling kink soliton describes a propagating clockwise twist. The ontological interpretation of the line of blue arrows should be a protofilament with tubulin tails projected out from the outer microtubule surface. The surrounding water dipole ordering is visualized only at the site of the local twist in yellow-green, which could be interpreted as the advancing electromagnetic pulse mode.

ANIMATION 2. [Available as a supplementary GIF file online] The traveling antikink soliton describes a propagating counterclockwise twist. The ontological interpretation of the line of blue arrows should be a protofilament with tubulin tails projected out from the outer microtubule surface. The surrounding water

dipole ordering is visualized only at the site of the local twist in yellow-green, which could be interpreted as the advancing electromagnetic pulse mode.

The 2-soliton solutions of the sine-Gordon equation however suggest novel possibilities. The traveling kinks and/or antikinks pass through each other as if perfectly permeable, and the only observed effect is a phase shift. Since the colliding solitons recover their velocity and shapes such kind of interaction is called an *elastic collision*.

ANIMATION 3. [Available as a supplementary GIF file online] An antikink-kink collision. The ontological interpretation of the line of blue arrows should be a protofilament with tubulin tails projected out from the outer microtubule surface. The surrounding water dipole ordering is visualized only at the site of the local twist in yellow-green, which could be interpreted as the advancing electromagnetic pulse mode.

ANIMATION 4. [Available as a supplementary GIF file online] A kink-kink collision. The ontological interpretation of the line of blue arrows should be a protofilament with tubulin tails projected out from the outer microtubule surface. The surrounding water dipole ordering is visualized only at the site of the local twist in yellow-green, which could be interpreted as the advancing electromagnetic pulse mode.

Another interesting 2-soliton solution concerns the possibility for coupled swinging kink-antikink solution called a *breather*. There are known three types of breathers: (i) a *standing breather*, (ii) a *traveling large amplitude breather* and (iii) a *traveling small amplitude breather*. Of great interest to us could be the standing breather, which might be coupled to the energase action of the tubulin tails via vibrationally assisted tunneling.

ANIMATION 5. [Available as a supplementary GIF file online] A standing breather is swinging in synchrony with a coupled kink-antikink soliton. The ontological interpretation of the line of blue arrows should be a protofilament with tubulin tails projected out from the outer microtubule surface. The surrounding water dipole ordering is visualized only at the site of the local twist in yellow-green, which could be interpreted as the advancing electromagnetic pulse mode.

ANIMATION 6. [Available as a supplementary GIF file online] A large amplitude moving breather. The ontological interpretation of the line of blue arrows should be a protofilament with tubulin tails projected out from the outer microtubule surface. The surrounding water dipole ordering is visualized only at the site of the local twist in yellow-green, which could be interpreted as the advancing electromagnetic pulse mode.

ANIMATION 7. [Available as a supplementary GIF file online] A small amplitude moving breather - appears exotic but has essentially a breather envelope. The ontological interpretation of the line of blue arrows should be a protofilament with tubulin tails projected out from the outer microtubule surface. The

surrounding water dipole ordering is visualized only at the site of the local twist in yellow-green, which could be interpreted as the advancing electromagnetic pulse mode.

The standing breather soliton could be *in vivo* obtained in situations where the vector of the electric field acts perpendicular to the microtubule z -axis. If a local vortex of the electromagnetic field is created somewhere in the neuron, then the exerted action of the electric field vector along the z -axis will be zero and no traveling soliton would be born. The standing breather swinging at certain tubulin tail (or breather formed by several coupled swinging tubulin tails) could catalyze MAP attachment/detachment and promote or inhibit the kinesin walk.

Since we are interested in the mechanism for microtubular decoding of the information induced by the electromagnetic field, let us discuss the geometry of the dendritic tree. It is well known that each neuron receives inputs from hundreds to thousands of other neurons mainly via synaptic neurochemical transmission. Since each neuron inputting information into another given neuron K can excite only certain post-synaptic spines s_1, s_2, \dots, s_n , which possess unique geometric coordinates $G(x_1, y_1, z_1), G(x_2, y_2, z_2), \dots, G(x_n, y_n, z_n)$, we can be sure that given any specific synaptic activity pattern, only a unique set of traveling and standing tubulin tail conformational sine-Gordon solitons will be realized.

Since the 3-soliton collisions between a traveling kink and a standing breather (or, a traveling antikink and a standing breather) results in a phase shift of the standing breather, it is possible that the sine-Gordon soliton collisions function in a way similar to ‘computational gating’. In the process of a collision between a moving kink and a standing breather, the shift of the breather Δ_B is given by the formula:

$$\Delta_B = \frac{2\text{arctanh}\sqrt{(1-\omega^2)(1-v_K^2)}}{\sqrt{1-\omega^2}} \quad (64)$$

where v_K is the velocity of the kink. If the original position of the standing breather is x_0 , then post-collision its new position will be $x_0 + \Delta_B$.

By further analyzing matters, we arrive at the possibility that the initial states of the generated set of standing breathers is analogous to a *data input* (metaphorically “the formulation of a given problem”). The dynamics of the electric field of the neuron will lead to sequential changes of the longitudinal electric voltages along the microtubular z -axis. The sequential generation of traveling kinks and antikinks along the microtubule protofilament could then induce a mechanism analogous to that of elementary logical gates on the initial input state of the standing breathers in such a way that their distribution will vary with time along the length of the microtubule protofilaments. The net effect would then resemble a form of processing of the initial data input. At a certain time depending on the soliton collisions and the summation of phase shifts in time, any of the standing breathers could be established at a potential attachment site for a MAP molecule or a kinesin motor. Depending on the

time spent on this new position, the swinging breather could catalyze a conformational transition in the attached to the tubulin tail MAP or motor molecule (via CTT energase action). This will ensure the *data output* of the proposed computational cycle. It should be emphasized that the input, processing and output steps were didactically separated for an improved presentation of the model. One should be aware that these three steps dynamically occur simultaneously, that is, there is a continuous generation of new standing breathers that undergo collisions and catalyze a biochemical reaction when placed at the proper position.

ANIMATION 8. [Available as a supplementary GIF file online] A moving kink-standing breather collision results in a shift of the standing breather. The ontological interpretation of the line of blue arrows should be a protofilament with tubulin tails projected out from the outer microtubule surface. The surrounding water dipole ordering is visualized only at the site of the local twist in yellow-green, which could be interpreted as the advancing electromagnetic pulse mode.

ANIMATION 9. [Available as a supplementary GIF file online] A moving antikink-standing breather collision results in a shift of the standing breather. The ontological interpretation of the line of blue arrows should be a protofilament with tubulin tails projected out from the outer microtubule surface. The surrounding water dipole ordering is visualized only at the site of the local twist in yellow-green, which could be interpreted as the advancing electromagnetic pulse mode.

7 The local electric field vortices in neurons

Finally, we outline a characterization of the potential sites in neurons in which the electric field could act perpendicularly to the microtubule z -axis and generate standing breathers. Usually in neurophysiology one considers only the longitudinal voltages of neurons, but there are several sites at which local electric field vortices might arise.

One of the most important sites is the space under the dendritic spines (Georgiev, 2003). It was shown that under the latter the electric intensity vector acts in perpendicular direction to the microtubule z -axis.

A second site in which the electric field vector acts in an oblique or perpendicular direction to the microtubule z -axis, is at the point of dendritic branching that usually is enriched in voltage-gated ion channels - the so-called “hot spot”. A “hot spot” is a place in the dendritic membrane that has a specific lipid composition forming a “lipid raft” with specific protein clustering (e.g. voltage-gated ion channels). The current lipidology succeeded in the identification of several types (or classes) of lipid rafts, some of which are highly specific for neuronal membranes.

In the myelinated axons the sites of interest are the *nodes of Ranvier*, which are enriched in voltage-gated ion channels and are responsible for the saltatory conduction of the action potentials (Georgiev, 2004). The axonal spikes have

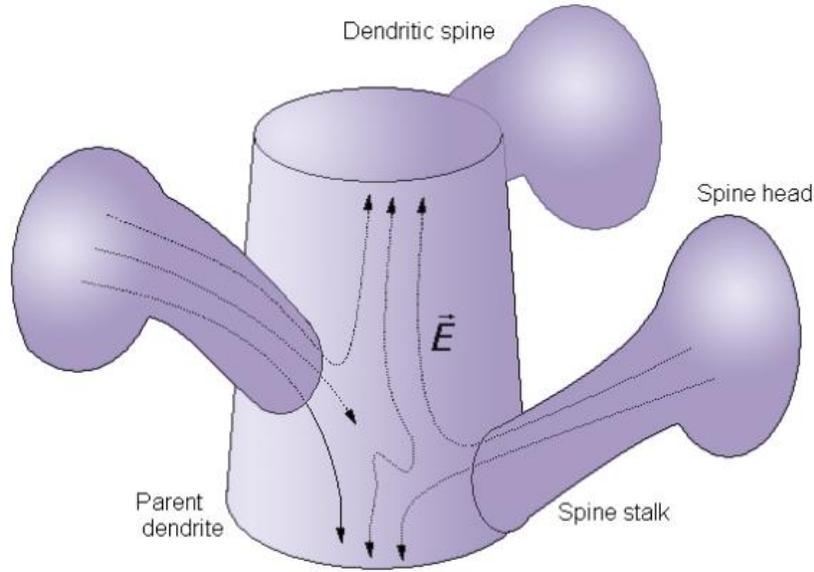


Figure 2: Under the dendritic spines the electric field intensity vector acts perpendicularly to the microtubular z -axis and might generate standing breathers.

all-or-nothing biological behavior and theoretically, the pattern of electric spots perpendicular to the microtubule z -axis will appear the same at every axonal spike. This could be significant, since in applying quantum computational algorithms, one needs “blank registers” in which to copy the obtained information. In contrast to the classical case where one can safely erase intermediate steps from the computation, if we perform quantum computation we are not allowed to erase the intermediary “bulk of unnecessary qubits” that occurs in the course of the computation (Vedral and Plenio, 1998).

And the last but not least option is the recently discovered interaction between axonal collaterals via axo-axonal gap junctions. These fast (over 200 Hz) electric activities assist the coupling of axonal firings between cortical neurons. Hence, in such cases not all axonal spikes of a given neuron K will look in the same way, because some of the smallest axonal collaterals of the neuron K could be excited via a gap junction coupling to an adjacent firing axon. The rest of the axonal collaterals might not be affected because in the reverse direction, the diameter of the axon increases and the current density flowing in such a direction could decrease very fast and sink below the threshold for triggering of an action potential.

The suggested mechanisms for the generation of tubulin tail conformational standing breathers as well as a generation of traveling kinks, antikinks, and possibly large-amplitude or small-amplitude traveling breathers, present us with novel possibilities for the direct interaction between the local electromagnetic

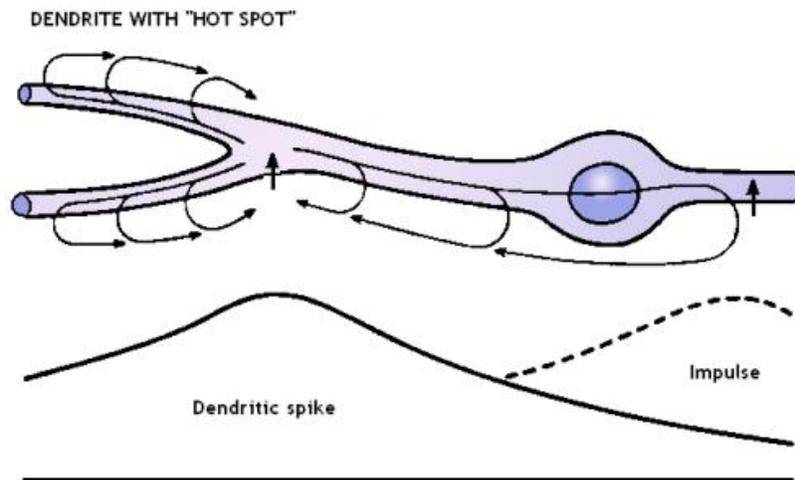


Figure 3: A dendrite with a “hot spot” (at the place of dendritic branching) acting in non-linear way allowing for a sudden surge of sodium and calcium ions when the membrane voltage reaches a threshold potential. When active the “hot spot” creates a local vortex of the electric field acting perpendicularly to the microtubule z -axis.

field and the cytoskeletal structures in neurons. We would like to point out that the sine-Gordon equation is not the only possible system for describing solitary waves propagating along microtubules. As discussed in Georgiev and Glazebrook (2007), the sine-Gordon system, as a special case of the larger class of Klein-Gordon systems, has been studied extensively both in theory and application. For instance, in relationship to the quantum sine-Gordon equation, the kink and antikink phonon phase shifts were considered in view of a Bose-Fermi correspondence by Timonen et al. (1986). We also point out that systems within the Klein-Gordon family admit perturbations and transformations to other types including those of certain double-well companions. Such perturbations may be realized by environmental effects. In the case in question, effects occurring within the cytoplasm may be caused by factors such as thermal fluctuations and levels of resonance. Such relationships between various solitonic mechanisms have been surveyed in Georgiev and Glazebrook (2007) where it was suggested that a subneuronal processing of information induced by such mechanisms may indeed occur *in vivo*.

Finally, we would like to add a brief note on a recently proposed experiment by Koch and Hepp (2006). The quoted authors mistakenly claim that because photons carrying superposed information would collapse in the retina of the observer, the Q-mind hypothesis is necessarily untrue. It has been clearly explained by Georgiev (2002, 2006) that superposed information cannot be inputted to human consciousness by any of the (sensory) analysators. The *brain*

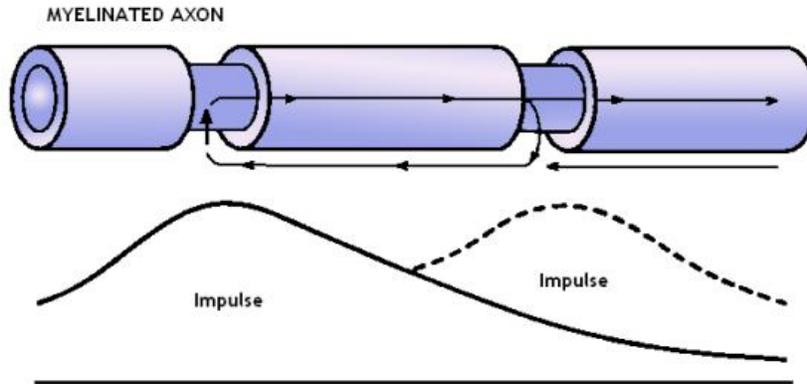


Figure 4: A myelinated axon with nodes of Ranvier. The inward rush of sodium ions at the nodes of Ranvier creates a local distortion of the electric field that acts perpendicularly to the microtubular z -axis.

cortex is the host of human consciousness and all sensory information from the analysators enters the brain cortex in the form of electric impulses. Thus if the visual information enters the brain cortex in the form of a classical electric signal, it cannot preserve the superposed quantum states of visual photons. However, there is no problem for the incoming electro-pulsative information to be converted into protein quantum mechanical states within neurons. The essence of this present paper is exactly that - to explain how the neuronal electric field can input sensory and other information down to the subneuronal level of microtubules, and how in turn the microtubules, via their C-terminal tubulin tails, produce a biologically significant output. If one postulates that brain cortical microtubules are involved in cognitive processes, then there need be no obstacle to the *proper* development of a Q-mind theory. Photons *do really collapse in the retina*, but this is not experimental evidence by itself that the human mind is detached from quantum mechanical processes occurring at the neurobiological level within the human brain cortex.

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