EFFECT OF TEMPERATURE ON THE DISCRETE SOLITONS IN MICROTUBULES

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Abstract: The cytoskeleton of eukaryotic cells is composed of several classes of protein polymers among which microtubules (MTs) are the most prominent. Inside the cell they usually exist in an unstable dynamic state characterized by a continuous addition and dissociation of the molecules of tubulin. The addition of each tubulin is accompanied by the hydrolysis of guanosine 5' triphosphate bound to the monomer of the molecule. In this paper, we formulate the Hamiltonian for the biophysical model of the MTs in the presence of Morse potential and derive the equation of motion that governs the dynamics of MTs and we carry out the molecular dynamics simulations. We perform a detailed analysis of the effect of the electric field of tubulin dimers in the process of energy localization in the form of long-lived discrete soliton excitations in the microtubulin protofilament.

Keywords: Discrete Solitons, Equation of Motion, Neuronal Microtubules, Simulation.

Introduction: Interiors of living cells are structurally and dynamically organized by networks of protein polymers called cytoskeleton [1]. The cytoskeleton network is made up of MTs, intermediate filaments and microfilaments (also known as actin filaments), which are filamentous biopolymers made up of various proteins and often regarded as polyatomic bio-composites contain a variety of chemical elements that are large in number. MTs are biologically one of the important cellular in eukaryotes. They are the largest filaments in the cell, having a high existing slenderness ratio, and frequently interweave as networks and spread throughout the cell. Cytoskeletal MTs are fundamental biopolymer filaments that play an important role in many cell functions and biomechanical performances, including cell division, intracellular material flow and transportation, vesicular transport and maintaining of cell shapes, etc. They are also important biomaterials that have a variety of usage in vitro as well as in vivo [2, 3]. It reorganizes continuously as the cells change their shape, divide and respond to their environment. MTs are more than twice the width of an intermediate filament and three times the width of a microfilament. The filaments and MTs are mutually connected and form a three-dimensional network in the cell [3–5]. The fundamental structure of the cytoskeleton formed by the MTs satisfies the basic requirements for excitation of vibrations and generation of endogenous oscillating electric field [5]. MTs are very important for cellular organization and information processing. MTs serve as structural components within cells and are involved in many cellular processes including mitosis, cytokinesis and vesicular transport. MTs are nucleated and organized by the microtubule organizing centers (MTOCs), such as centrosomes and basal bodies. The MTOCs are usually located near the nucleus during interphase. MTs grow out from the MTOC, forming a hub and spoke array, even during interphase [6].

An important feature of microtubule structure is polarity. Tubulin polymerizes end to end with α-subunit of one tubulin dimer contacting the β-subunit of the next. Therefore, in a protofilament, one end will have α-subunit exposed while the other end will have the β-subunit exposed. These ends are designated (-) and (+) respectively. The protofilaments bundle parallel to one another, so in a microtubule, there is one end, the (+) end, with only β-subunits exposed while the other end, the (-) end, only has a α-subunits exposed. The hetrodimer does not come apart, once formed. α-tubulin has a bound molecule of guanosine triphosphate (GTP), that does not hydrolyze. β- tubulin may have bound molecule of GTP or GDP (guanosine diphosphate). GTP must be bound to both α- and β-subunits for a tubulin hetrodimer to associate with other hetrodimers to

form a protofilament or microtubule. Subunit addition brings β-tubulin that was exposed at the plus end into contact with α-tubulin. This promotes hydrolysis of GTP bound to the new interior β-tubulin [7-10]. MTS continually assembly and disassembly, so the turnover of tubulin is ongoing. The characteristics of MTs lengthening (polymerization) and shortening (depolymerization) follow a pattern known as dynamic instability: that is, at any given instant some of the MTs are growing, while others are undergoing rapid breakdown. In general, the rate at which MTs undergo net
assembly or disassembly varies with mitotic stage; for example, during prophase the rate of MTs polymerization and depolymerization change quite dramatically.

In section 2, we formulate the Hamiltonian of the system and derive the equation of motion that governs the dynamics of the MTs. In section 3, we carry out the molecular dynamical simulations in MTs under the influence of the internal cell electric field. The results are concluded in section 4.

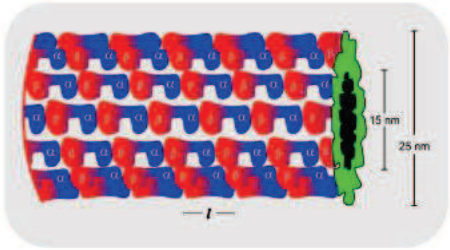


Fig. 1: Structural Subunits of Microtubule

The Model Hamiltonian and Dynamical Equation: The MT system has a strong uniaxial dielectric anisotropy so that the array of dimer oscillators can be effectively described in terms of only one degree of freedom, the net polarization. The microtubule structure is very likely nonlinear by itself. The nonlinear systems can generate higher harmonic components and components with combinational frequencies and enable spectral energy transfer too. Thus the n^{th} tubulin molecule of a protofilament can be approximately expressed by the following Morse potential

$$D(e^{-a\phi_n} - 1)^2,$$

with D and a representing the depth and the inverse width of the Morse potential well respectively. The total effective Hamiltonian describing the large oscillations of the dimer in a MTs is thus given by

$$H = \sum_{n=1}^{N} \left[\begin{array}{l} \frac{m}{2}\dot{\phi}_n^2 + \frac{k}{2}(\phi_{n+1} - \phi_n)^2 \\ -qlE\cos\phi_n + D(e^{-a\phi_n} - 1)^2 \end{array} \right]. \qquad (1)$$

The first term in the above equation represents the kinetic energy associated with the longitudinal displacement of constituent dimers, each of which has mass m and the integer n determines the position of the dimer considered in the protofilament. The overdot represents the first derivative with respect to time. The second term arises from the restoring strain forces between adjacent dimers in the protofilament and this term characterize the potential energy arises due to the chemical interaction between the neighbouring dimers, with k representing the intra-dimer stiffness parameter. As on electric dipole, a dimer in the presence of the intrinsic electric field $\vec{E}$ directed along the long axis of the MTs cylinder, acquires the potential energy given by

$$U = -\vec{p}.\vec{E} = qlE\cos\phi_n, \; . \qquad (2)$$

Where, 'l' is the length of the dimer and 'q' is the excess charge within the dipole, with q > 0, E > 0 as represented by the third term. The last term represents the overall effect of the surrounding dipoles on a chosen site 'n' which is supposed to be qualitatively described by the Morse potential.

Athenstaedt experimentally demonstrated that a tubulin dimer undergoes a conformational change induced by the GTP-GDP hydrolysis in which one monomer shifts its orientation by 29° from the vertical axis. This is what we termed the tilt of a dimer. Thus it can be deduced that the single degree of freedom is also related to the projection of the monomer's displacement from its equilibrium position on the MTs cylinder's axis. Now for large oscillations using Hamiltonian (1), the Hamilton's equation of motion can be immediately written as

$$\ddot{\phi}_n - \frac{k}{m}(\phi_{n+1} + \phi_{n-1} - 2\phi_n) + \frac{qlE}{m}(\phi_n - \frac{\phi_n^{\,2}}{6})$$
$$+2aD'[a\phi_n - \frac{a^2\phi_n^{\,2}}{2}][1 - a\phi_n + \frac{a^2\phi_n^{\,2}}{2}] = 0, \quad (3)$$

where, $D' = \frac{D}{m}$ and we look for nonlinear collective oscillations of tubulin dimers in the bottom of the potential wells. For this purpose, we assume

$$\phi_n \rightarrow \varepsilon u_n + u_0, \quad (4)$$

where ε << 1 and u_o is the ground state or potential minimum around which the oscillations will occur. For u_o = 0, the potential wells are symmetric and for $u_o \neq 0$, they are asymmetric. Expanding in terms of u_n in Eq. (3), one gets

$$\ddot{u}_n - \frac{k}{m}(u_{n+1} + u_{n-1} - 2u_n) + (\frac{qlE}{m})u_n$$
$$-(\frac{qlE}{6m})\varepsilon^2 u_n^{\,3} + 2a^2D'[u_n - \frac{3a\varepsilon u_n^{\,2}}{2}$$
$$+a^2\varepsilon^2 u_n^{\,3} + O(\varepsilon^3)] = 0. \quad (5)$$

Eq. (5) describes the dynamics of dimer at at the discrete level ignoring the effect of viscosity.

Molecular dynamics simulations in MTs: In this section, in order to analyze the effect of temperature on the evolution of solitons, we recast the discrete version of Eq. (5) as including dissipation terms

$$iu_{1t} = \frac{P}{2\omega_1\gamma^2}[u_{1n+1} + u_{1n-1} - 2u_1]$$
$$+\frac{\beta}{2\omega_1}|u_1|^2 u_1 + \frac{iQ}{2\omega_1\gamma}[u_{1n+1} + u_{1n-1}]$$
$$-M\Gamma u_{1t} + F_{1n} \quad (6)$$

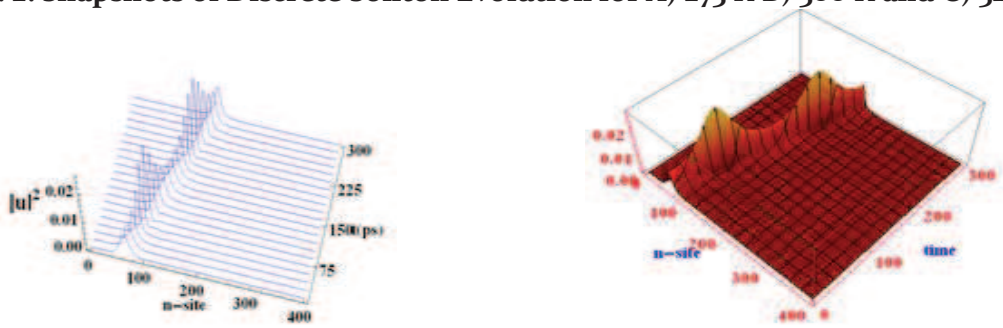
In order to analyze the effect of thermalization on the evolution of solitons subject to the Boltzman distribution in the few-ps range, we carry out molecular dynamics simulation studies for the discrete equation

$$iu_t + \frac{p}{2q\gamma^2}(u_{1n+1} + u_{1n-1} - u_{1n})$$
$$+\frac{1}{\gamma}[iQ + M\Gamma](u_{1n+1} - u_{1n-1})$$
$$+\beta|u_{1n}|^2 u_{1n} + T = 0. \quad (7)$$

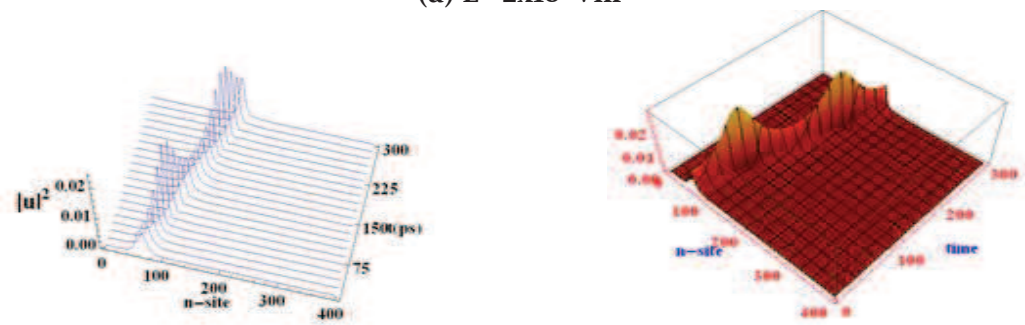
where Γ is the damping coefficient of the medium, which is about 0.3 × 108 s^{-1} for dimers of MTs. In Eq.(7), a decay term $M\Gamma\dot{q}_n$ and random noise term $F_n(t)$, resulting from the interactions between the environment at finite temperature T and the dimers of MTs, have been added to the discrete equation along the lines of the Lomdahl and Kerr method [11, 12]. The explicit representation for the correlation function of the random noise force is $< F(x,t)F(0,0) >= 2M\Gamma kBTd(x)d(t)1/\tau'$, τ' is a damping constant. In our algorithm, we use an ensemble of Gaussian forces Fn with variance equal to $\sigma = 2MkB\Gamma T/\tau'$ and we also assume that the deviation of the random noise satisfies the normal distribution and has zero expectation value expressed by $N(F_n) = \left(\frac{1}{\sqrt{2\pi\sigma}}\right)\exp\left(\frac{-F_n^2}{2\sigma}\right)$. The above choice of Gaussian width is highly compatible with the fluctuation–dissipation theorem and time discretization. In order to analyze the effects of temperature and random thermal noise forces of the medium, we numerically solve (7), with the above decay term and random noise force by the fourth-order Runge–Kutta method. The evolution of soliton for different temperatures (273, 300 and 320 K) are depicted in Fig. 2 in the case of the long time of 300 ps for the parametric values, η=0.5,

q_1=0.02, k=5 Nm^{-1}, ε=0.1, R_o=3 nm, a=1x10^7m^{-1}, D=1 eV, q=10^{-18} C, l=8nm and m= 10^{-22} kg. From Fig. 2, the top panels represent the evolution of soliton for T = 273 K, the middle panels represent T = 300 K and the bottom panels represent the evolution for T = 320 K. It should also be noted that the first row of Fig. 2 represents the evolution of the soliton for an applied electric field which could be seen as a significant control mechanism in tubulin dynamics, i.e., E = 2x10^2Vm^{-1}. Generally, applying an external electric field of a microtubule may halt the soliton motion and 'freeze' the information carried by it.

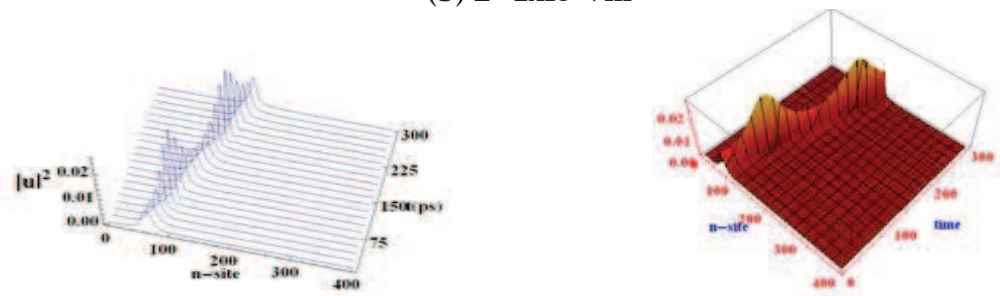
Fig. 2: Snapshots of Discrete Soliton Evolution for A) 273 K B) 300 K and C) 320 K



(a) E= 2x10^2 Vm^{-1}



(b) E= 2x10^3 Vm^{-1}



(c) E= 2x10^4 Vm^{-1}

Conclusions: The cytoskeleton of eucaryotic cells is composed of several classes of protein polymers among which MTs are the most prominent. The mathematical modeling presented in this paper is mainly focused to describe quanta of energy travelling in the form of discrete solitons along MTs. As has been suggested before these solitons may be excited by the free portion of the energy of the GTP hydrolysis whose role in the MTs behaviour is largely unknown. We demonstrated the numerical simulations and the evolution of the soliton for an applied electric field which could be seen as a significant control mechanism in tubulin dynamics. The biological importance of the presented model is due to the unique biological enzymatic action of the tubulin dimers, which is energy localization in the form of long-lived discrete soliton excitations in the microtubulin protofilaments.

Acknowledgment: L.K gratefully acknowledges the financial support byNBHM(2/48(9)/2011/-R andDII/1223), India, in the form of a major research project;DAE-BRNS (2009/20/37/7/BRNS/1819), India, in the form of Young Scientist Research Award, and ICTP, Italy, in the form of Regular Associateship. R. P gratefully acknowledges UGC for the Rajiv Gandhi National Fellowship.

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