NONLINEAR MODEL OF MICROTUBULE DYNAMICS AND ITS IMPACT ON KINESIN MOTION

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Abstract

In this paper we elaborate the nonlinear model based on ferroelectric properties of microtubules (MTs) and triggered by hydrolysis of GTP (guanosine triphosphate) followed by conversion of chemical energy into large conformational rotation of corresponding tubulin dimer.

We attempted to elucidate some functional properties of microtubules pertaining kinesin motor protein on the basis of this elegant model.

Key words

microtubule, tubulin protein, ferroelectric, kink, kinesin motor protein, GTP

1 Introduction

Microtubules are actually nanotubes with diameter of 25 nm, (Fig. 1). They are found in nearly all eukariotic cells and are polymers of 13 filaments consisting of tubulin globular protein. MTs serve as tracks on which motor proteins may carry materials about the cell and serve as scaffolding to maintain the cell shape since they are among the most rigid structures within a typical cell.

The building block of a MT is a tubulin dimer consisting of two slightly different globular proteins named α and β tubulin, respectively. Tubulin protein contains approximately 900 amino acids comprising some 14.000 atoms with combined mass of 110 kDa [Amos, 1995].

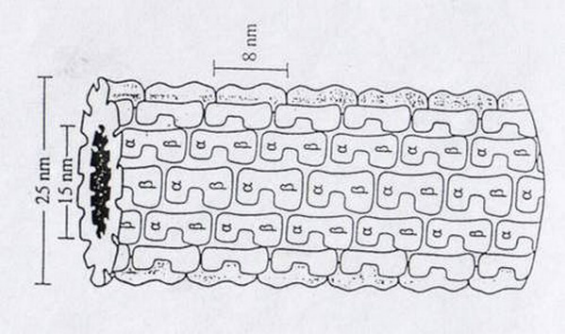

Fig. 1: A cartoon showing the construction of a MT from individual tubulin dimers, including characteristic dimensions.

Tubulin's secondary structure is of crucial significance to the model discussed in this paper. The core of tubulin globula consists of β-sheet surrounded by several α-helices terminated with loops protruding partially through the globular structure of the protein, (Fig. 2.a).

These loops are important either for the formation of weak bonds between neighboring proteins bringing about the polymerization of tubulin into microtubule; see one filament on (Fig. 2.b). Additionally, they provide a binding site for the energy giving molecule GTP.

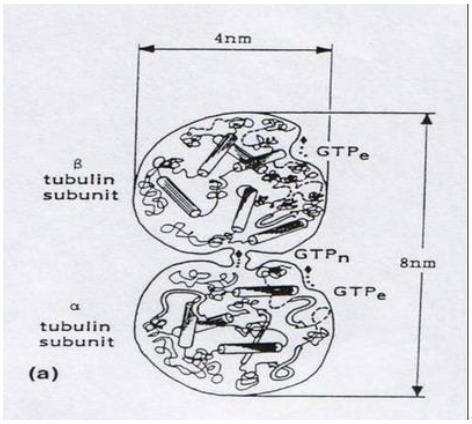

Fig. 2.a: The secondary structure of tubulin protein; cylinders represent α-helices.

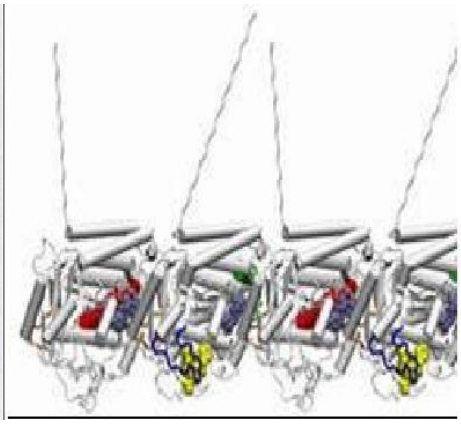

Fig. 2.b: The sketch of one MT filament consisting of tubulin dimers joined by protruding loops.Yellow sites are GTP molecules.

These flexible loops are ideally suited for adjusting the positions of the many amino acid residues that participate in binding between two neighboring dimer in accordance with so called "hand and glove" strategy.

2 Ferroelectric properties of MTs and kink excitations due to GTP hydrolysis

The basic motivation for our model is the secondary structure of tubulin protein. Virtually every peptide group in an α-helix possesses a considerable dipole moment on the order of $p_0 = 1.2 \cdot 10^{-29} C \cdot m = 3{,}5D$.

All these dipoles are almost parallel to the helical axis, giving rise to an overall dipole moment of this particular helix. It is generally accepted that this large dipole moment of an α-helix has an important biological role. The idea that MTs are ferroelectrics was proposed some 30 years ago and farther quantitatively elaborated by [Satarić et al, 1993, 1998, 2003, 2005] on the basis of their piezoelectric properties. It is apparent that due to the strong curvature of an MT cylinder (see Fig. 3.a) the inner parts of the globular tubulin structure are compressed while the outer ones are stretched by a substantial amount of tension.

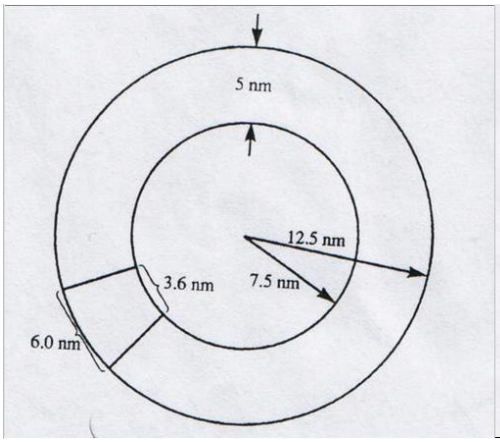

Fig. 3a: The cylindrical geometry of a microtubule with wedgelike compressed dimer .

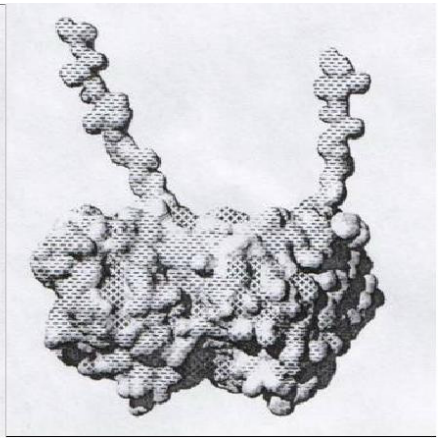

Fig. 3 b: The detailed map of the electric charge distribution in a dimer.

This leads to additional redistribution of excess negative charge enhancing the transversal component of the net dipole moment of every dimer comprising a MT. This was corroborated by a detailed map of the electric charge distribution for the tubulin dimer [Tuszynski et al, 2005], (Fig. 3b).

Taking into account the above arguments it is highly plausible to envisage the MT structure as a ferroelectric system with dipole moments of tubulins oriented as shown in (Fig. 4).

The tips of a MT therefore possess overall net charges $+Q$ and $-Q$ respectively. We therefore conclude that MT cylinder supports an endogenous electric field $\vec{E}$ parallel with axis of MT.

3 The role of GTP hydrolysis in nonlinear MT dynamics

In the case under consideration of tubulin within a MT, β-tubulin in dimeric structure has an exchangeable GTP site that is an active domain. The chemical potential energy of GTP hydrolysis is

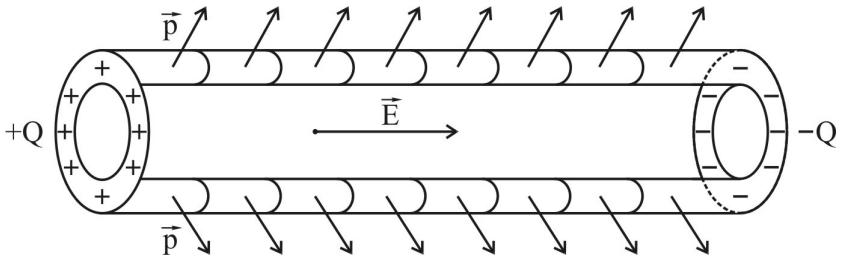

Fig. 4: The MT ferroelectric scheme with overal electrically charged tips and intrinsic electric field E.Arrows indicate dipole moments of dimmers.

converted into mechanical motion as follows. The dissociation of the inorganic phosphate group (P_γ) in the reaction $GTP \rightarrow GDP + P_\gamma$ causes a shift of a few angstroms in the GTP binding site that contains a polypeptide loop called a sensor or switch loop. This displacement causes a further conformational change which propagates along a tightly associated α-helix that is called realy-helix. The relay-helixserves as a "piston" that transmits sensor stimulus to adhere to a specific site on the opposite side of the same β-tubulin latching it in a "closed" conformation.

This state of the relay-helix pertains to a prestressed spring, to use a mechanical analogy. The next stage of the conformational scenery is triggered by the release of GDP and causes the relay-helix to unlatch allowing tubulin to tilt rotating by angle θ in (x,r) plane in the filament direction as shown in Fig. 5.

This transformation is evolutionary consistent with the conformational strategies exhibited by motor proteins due to ATP hydrolysis [Tuszynski et al, 2005].

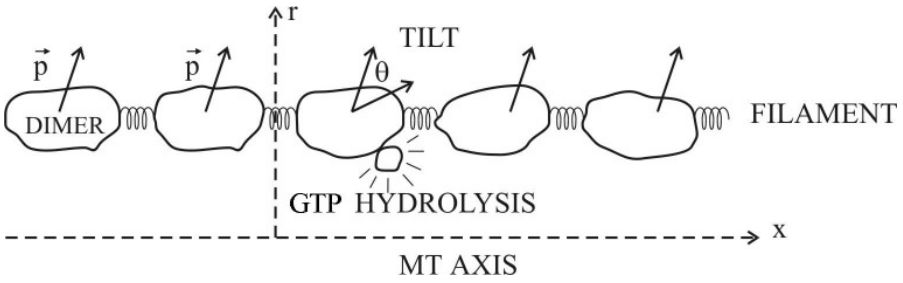

Fig. 5: The tilt deformation of MT dimers caused by GTP hydrolysis.

The force estimated elsewhere [Vale and Milligan, 2000] results in the tilt of the tubulin dimer by an angle

$$\theta_0 \approx 0{,}5 rad. \qquad (1)$$

Consequently we calculated [Vale and Milligan, 2000] the work done by the pistonlike movement of relay-helix to be $2 \cdot 10^{-20} J = 0{,}13 eV$. Since the energy released in one GTP hydrolysis event is approximately $0{,}25 eV$ it follows that the most part of it is utilized in above tilt of tubulin dimer.

Therefore we treat a tubulin dimer with just hydrolyzed GTP and released GDP as rotational pendulum with respect to tilt angle θ and with corresponding rotational inertia per unit volume *J*, possessing kinetic energy

$$w_{kin} = \frac{1}{2} J \left(\frac{\partial \theta}{\partial t} \right)^2 . \qquad (2)$$

The splay energy density has the form

$$w_{sp} = \frac{1}{2} k \left(\frac{\partial \theta}{\partial x} \right)^2 \qquad (3)$$

where *k* denotes splay elastic modulus. The crucial part of total energy is the energy of dimer-dimer coupling within a protofilament which we expand in terms of tilt angle θ as even function up to fourth order as follows

$$w_{el} = \frac{1}{r^2} \left(- A\theta^2 + B\theta^4 \right) \qquad (4)$$

where *A* and *B* are coefficients that are expressed in terms of cylindrical components of the elasticity tensor.The details are widely ellaborated in [Sataric et al, 2005].

Why besides quadratic term hould we keep the potential to fourth order? Since the triggering tilt angle ranges to $\theta_0 \sim 0{,}5$ *rad,* we have $\theta^4 \sim \frac{1}{16}$ which is not negligible in comparison with $\theta^2 \sim \frac{1}{4}$.

The last, but not the least important, part of total energy of pendulum is the density of polarization energy

$$w_{pol} = \frac{1}{2} \left(\frac{p_l^2}{\chi_l} + \frac{p_t^2}{\chi_t} \right) - p_l E - \mu_p p_t \theta , \qquad (5)$$

where p_l, p_t are longitudinal and transversal projections of tubulin (pendulum) polarization, χ_l, χ_t the anizotropic dielectric susceptibilities of MT, while μ_p is phenomenological constant of model and *E* is the constant intrinsic electric field within a MT.

We also accounted the presence of viscosity of the medium surrounding the MT (cytosol). This effect was modeled by including a friction term in the equation of motion by corresponding torque

$$\tau_{vis} = -\Gamma \frac{\partial \theta}{\partial t} \qquad (6)$$

which is subsequently involved in the equation of motion using Euler-Lagrange procedure. Γ depends both on the viscosity coefficient and the structural details of the MT through the Stokes-Einstein formula.

Combining all terms in Eqs. (2-6) in the context of Euler-Lagrange equation, then using scaled variables and traveling wave form, one obtains the following nonlinear ordinary differential equation

$$\frac{d^2 \eta}{d^2 \xi} + \beta \frac{d\eta}{d\xi} - \eta^3 + \eta + \varepsilon = 0 , \qquad (7)$$

with abbreviations

$$\eta = \frac{\theta}{\theta_0}; \quad \xi = \alpha (x - vt)$$

θ_0 is the amplitude of tilt; *v* is the velocity of kink excitation and α is the

kink's wave number. Coefficients β and ε involve elastical and ferroelectrical parameters and intrinsic electric field *E*.

Eqution (7) is formally equivalent with softening biased Duffing equation which can exibit heterociclic solutions.Such equations appear in the case of damped biased nonlinear mechanical pendulum and in Josepson junctions wih intermediate phase differences.

The most important consequences of Eq. (7), in the absence of disipation and applied torque, are kink and antikink excitations resembling to domino-effect in the well-known tangent hyperbolic shape, (Fig. 6)

$$\theta(\xi) = \pm\theta_0 \tanh\sqrt{2}\xi\,, \tag{8}$$

which propagate in opposite directions with constant terminal velocity v_T obeying Ohm's law

$$v_t = \mu E. \tag{9}$$

Actual solution of Eq. (7) is slightly distorted kink expressed by Eq. (8)

The kink's mobility μ depends on the model parameters including the ferroelectric character of MT and of its elastic properties as well as of viscous dissipations on the very natural way.

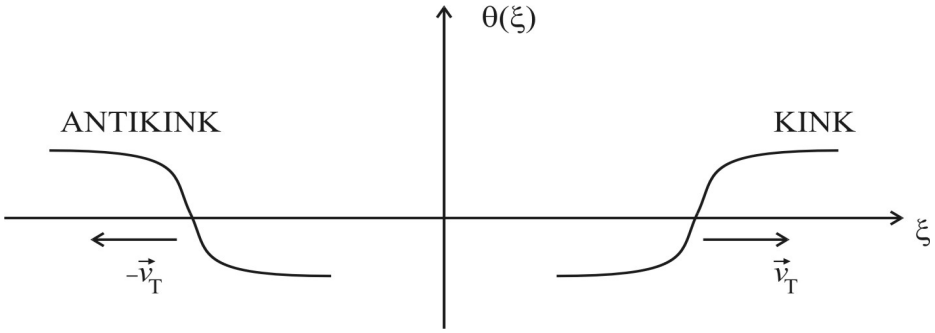

Fig. 6: The kink and antikink excitations propagating in opposite directions along MT filaments

This linear response holds even for very strong fields of the order of $10^5 V/m$.

4 Biological implications of model

In this paper we analyzed an interesting mechanism of utilization of GTP hydrolysis energy in MTs for creation of highly localized kink excitation which propagates along a MT filament combining mechano-elastic and dipolar energy and being controlled by an intrinsic electric field provided by ferroelectric character of MTs. The intensity of this field depends on the length of the MT as well as on the physiological conditions of the solution (pH, ion concentration and temperature), due to screening effects of counter-ions. The shorter the MT's, the stronger the field and greater the kink's terminal velocity, (Eq. 9).

The interesting case are MTs in long neuron cells. The axon potential propagating along neuron carries electric field of the order of $10^5 V/m$. This field even partially screened along MTs causes high terminal velocities of kinks involved reaching several meters per second. If such fast (hot) kink encounters a motor protein (kinesin) bound to the same filament it may cause a tug-of-war [Vale and Milligan, 2000] effect on the motor disrupting its two directional random walk. Since much faster than loaded kinesin, hot kink goes farther pushing many motors in the same direction.

Let us now estimate the kink motion in MTs in non neuronal cells. For a stable MT with a typical length $L = 4\mu m$ the intrinsic electric field in the central region of MT can be calculated to be

$$E = \frac{Q}{\pi\varepsilon_0\varepsilon_r L^2}. \qquad (10)$$

Taking $Q = 13e$ ($e = 1{,}6\cdot10^{-19}$ C), i.e., one excess charge per filament tip, (Fig. 4) , and letting the relative dielectric constant to lie in the range $10 < \varepsilon_r < 80$, as being the function of solution's composition, one finds the values of intrinsic electric field in the range ($0{,}6 < E < 5$) *V/m,* resulting in the window of kink terminal velocities given by

$$(0{,}2 < v_T < 2)\mu m / s\,. \qquad (11)$$

Experimental evidences show that, depending on the ATP and salt concentrations, and the load placed on the kinesin molecule, it propagates along the MT with velocities ranging in the window ($0 < v_{MP} < 1$) *μm/s*, i.e. there is a good overlap in the velocities of these two types of biological motions that may interact with each other.

Using an easy-to-grasp analogy, the kinesin motor can be viewed as a surfer and the moving kink as a water wave. Thus, when properly matched, the motor may be able to "catch the wave" and travel on its crest for a while, (Fig. 7).

Our new findings [Sataric et al, 2007] about kink's dynamics show that even in the case where a MT is subjected under the harmonic force (sinusoidal electric field) kinks and antikinks are pulled to travel in the opposite directions. The kink's velocity depends on amplitude and frequency of applied field.

At some critical values of the frequency of the driving force the directions of kink (and antikink) motions change to the opposite ones.

This is very promising fact which means that intrinsic electric fields, possibly generated by cell membrane or other parts of cell, could play the decisive role as controlling mechanism for motor protein activities.

It is also likely that applied external electromagnetic fields interferes cell's processes through stimulating or impeading activities of motor proteins.

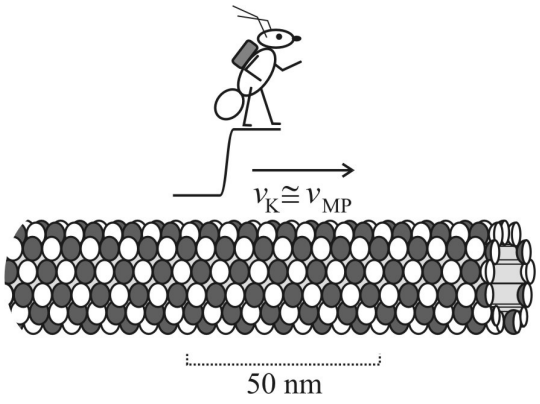

Fig.7: Motor protein as a surfer on the moving kink

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