

Kinklike excitations as an energy-transfer mechanism in microtubules

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A model is presented that is intended to provide a realistic physical picture of the energy-transfer mechanism in cell microtubules. A classical ϕ^4 model in the presence of a constant electric field is used as a conceptual basis. It is demonstrated that kinklike excitations arise as a result of the guanosine 5'-triphosphate (GTP) hydrolysis and that an intrinsic electrical force may cause them to propagate along a microtubule. A discussion is given on the possible effects of these excitations on the dynamics of microtubules.

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I. INTRODUCTION

The interiors of biological cells are structurally and dynamically organized through the presence of networks of interconnected protein polymers. These networks are referred to as the cytoskeleton due to their bonelike structure. Of the various filamentary structures which comprise the cytoskeleton, microtubules (MT's) appear to be the most prominent ones. It can safely be said that MT's are ubiquitous through the entire biology [1].

Parallel-arrayed MT's are interconnected by cross-bridging proteins which are called microtubule-associated proteins (MAP's), as shown in Fig. 1. These interconnections, together with MT's, are believed to be responsible for numerous cellular activities such as growth and division, which are essential for the living state. From the characterization of structure and function, MT's appear very well suited for dynamic information processing [1-3].

MT's represent hollow cylinders formed by protofilaments aligned along their axes (see Fig. 2) and whose lengths may span macroscopic dimensions. In vivo, the cylindrical walls of MT's are assemblies of 13 longitudinal protofilaments, each of which is a series of subunit proteins known as tubulin dimers. Each tubulin subunit is a polar, 8-nm dimer which consists of two slightly different 4-nm monomers with molecular weight of 55 kilodaltons. These two constituent parts are usually called α and β tubulin. Each dimer may be physically viewed as an electric dipole \mathbf{p} whose dipolar character originates from the 18 calcium ions bound within each β monomer. An equal number of negative charges required for the electrostatic balance are localized near the neighboring α monomer. Thus, MT's can be identified as an example of electret substances, i.e., oriented assemblies of dipoles. They are predicted to possess piezoelectric properties that may be quite important in their functions,

especially in the very interesting assembly and disassembly behavior [4,5].

A very important role is played by guanosine 5'-triphosphate (GTP), an energy-providing analog of adenosine 5'-triphosphate (ATP) which binds to polymerizing tubulin dimers. It is a very appealing mechanism from the biochemical point of view since the order of magnitude of the energy produced is just right. The chemical reaction involved is [6] the hydrolysis of GTP, which is



and under normal physiological conditions approximately 10 kcal/mol (0.42 eV/molecule) of free energy is released in this reaction, where GDP denotes guanosine 5'-diphosphate. It is known that the energy produced during GTP hydrolysis is delivered to assembled MT's,

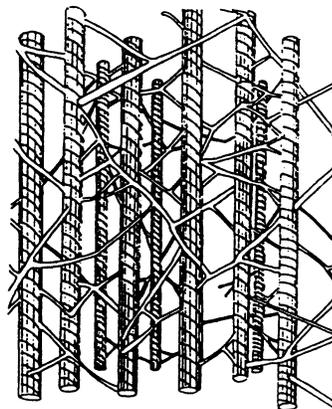


FIG. 1. A parallel microtubule network.

although a precise manner in which this energy is utilized is still not understood. One possible mechanism for the utilization of this form of energy is the production of coherent lattice vibrations as proposed by Fröhlich [7] and by the scores of other researchers that followed his idea of biological coherence over the past two decades. Although Fröhlich's theory has never been confirmed by experiment, we believe that the basic mechanism proposed by Fröhlich merits continued interest. Our approach in the present paper will not follow Fröhlich's theory but will be influenced to a certain degree by his ideas.

An interesting suggestion was made by Barnett [8] that filamentary cytoskeletal structures may operate much like information strings in analogy to semiconductor word processors. Barnett conjectured that MT's are indeed processing channels along which strings of information bits can move, transferring messages from place to place. In addition, within this context protofilaments could be envisaged as playing the role of parallel-arrayed memory channels. It was also suggested [2,3,9] that conformational states of tubulin dimers present within MT's may be coupled to charge or dipolar states, thereby allowing for cooperative interactions with neighboring tubulin states. Such interactions were modeled in the framework of molecular automata in which the conformational states of individual tubulin subunits represent bits of information that can change under the dynamic

influence of the neighbor subunits.

Another intriguing property of MT's is the process of their assembly. Since in solution containing their subunits MT's are not true equilibrium polymers, the process is rather complicated to model. Dark-field microscopy was the technique used to investigate the process experimentally [10]. It was found that when a single MT is monitored, its two ends grow at different rates. The active "+" end grows faster than the inactive "-" end. However, each end independently stops growing in a stochastic manner and then immediately begins to shorten at a high rate. After the shortening period, a microtubule suddenly stops and restarts the growth phase. A very important experimental observation was made that the presence of MAP's significantly suppresses uncorrelated phase conversions and stabilizes MT's in their growth phase.

In this paper we will put forward a theoretical model based on the creation of kinklike excitations in MT's. Their presence will be linked to GTP hydrolysis and the energy released therein. This will offer a plausible explanation of this aspect of the very complex and intriguing MT dynamics. The model proposed in this paper will also provide a starting point for the physical description of a molecular computation system.

II. THE PHYSICAL MODEL

Biological systems in general, and MT's in particular, possess a high degree of order. This is predominantly in the form of functional organization but also, to a large degree, represents spatial arrangement. One basic physical idea concerning the nature of biological order was put forward by Fröhlich [11]. Fröhlich considered an ensemble of molecular dipoles that are capable of high-frequency oscillations that can be subjected to an external electric field and allowed to strongly interact among themselves. He conjectured that, provided the supply of energy to the dipolar system exceeds a critical value, a nonequilibrium metastable state may be formed that is characterized by long-range coherence manifested by a macroscopic occupation of a single mode. An example of such a system could be the dipoles of a cell membrane in the presence of a transmembrane potential [12]. The conditions described above may also apply to the assembly of dimers within a MT which was already described as an electret. The supply of biochemical energy in the form of ATP or GTP hydrolysis may be the source of nonequilibrium excitations.

We believe that the entire MT may be viewed within the context of the Fröhlich model as a regular array of coupled dipole oscillators interacting through resonant (i.e., frequency-specific) long-range forces. Furthermore, coherent vibrations within regions of a MT may take the form of kinklike excitations (KLE's) separating adjacent regions with opposite polarization vectors. The dipole orientation is in the direction of the protofilament axis. It should be mentioned that macroscopic mobile domain structures are of great practical interest due to their potential applications as active components in optical switching and memory devices [13]. It is the number of

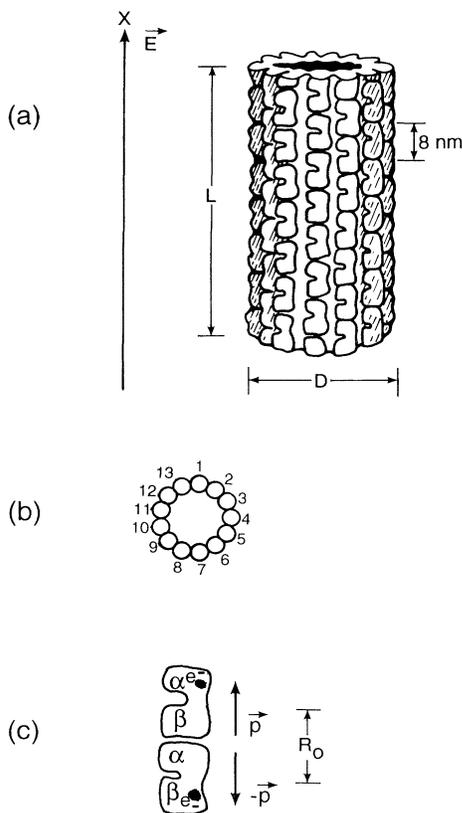


FIG. 2. (a) The structure of a microtubule, (b) its cross section, and (c) two neighboring dimers.

KLE's formed and their mobility that determine their most important characteristics, such as the switching time, effective polarization, power dissipation rate, and hysteretic behavior.

In the physical model that is put forward here, the basic argument is that the MT system has a strong uniaxial dielectric anisotropy so that the array of dipole oscillators can be effectively described in terms of only one degree of freedom. In fact, experiments showed [14] that tubulin undergoes a conformational change induced by the GTP-GDP hydrolysis in which one monomer shifts its orientation by 29° from the dimer's vertical axis. Thus, we deduce that the single degree of freedom retained in our description (analogous to Landau's order parameter; see Ref. [15]) is the projection on the MT cylinder's axis of the monomer's displacement from its equilibrium position. The inherent symmetry of a MT enables one to view them as nearly perfect one-dimensional crystals.

In this paper we intend to describe the nonlinear dynamics of dimer dipoles in one protofilament of a MT in terms of the well-known double-well potential model. This approach has been proven extremely useful in the physics of bistable molecular systems [16]. Its successes in other related areas, for example in the description of dipolar excitations in ferroelectrics [17], are widely acknowledged. The essential argument in favor of introducing the double-well model stems from the fact that the longitudinal projection of the dimer displacement interacts with the rest of the lattice through a mean-field force due to an anharmonic crystal-field potential. A similar inorganic ferroelectric, i.e., antimony sulphoiodide (SbSI), possessing a filamentary structure with parallel filaments [18], has been also analyzed in a similar manner.

The overall effect of the surrounding dipoles on a chosen site n can be qualitatively described by the double-well quartic potential

$$V(u_n) = -\frac{1}{2}Au_n^2 + \frac{1}{4}Bu_n^4, \quad (2.1)$$

where u_n is the longitudinal displacement of the n th dimer, A and B are model parameters such that $B > 0$ and is temperature independent, while A is typically a linear function of temperature that may change its sign at an instability temperature T_c , i.e., $A \cong \alpha(T - T_c)$. With $\alpha > 0$, below T_c $A > 0$ and $u_n = 0$ is a maximum of the potential such that $V(0) = 0$. Two symmetric local minima exist at $u_n = \pm\sqrt{A/B}$ for which $V_{\min} = -A^2/4B$. This is illustrated in Fig. 3. The anharmonic potential discussed here is meant to approximate the average effect due to the environment when all the neighboring dimers assume their equilibrium positions. As shown in Fig. 4, the mobile electron on each dimer can be localized either more toward the α monomer or more toward the β monomer. The latter possibility is associated with changes in dimer conformation. Experimental evidence indicates [14] that a conformational distortion of 29° from vertical occurs in the β state. We, therefore, identify the variable u_n with the amount of β -state distortion when the latter is projected on the vertical axis.

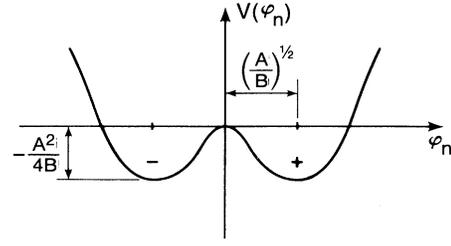


FIG. 3. The double-well on-site potential of Eq. (2.1).

In the next step of developing our model, account is taken of the experimental fact that the MT cylinder taken as a whole represents a giant dipole. When the cross section of a MT is viewed using electron microscopy, the outer surfaces of a MT are surrounded by a "clear zone" of several nm which apparently represents the oriented molecules of cytoplasmic water and enzymes [19]. This could be explained by the presence of an electric field produced by a MT. Therefore, we assume that, together with the polarized water surrounding it, a MT generates a nearly uniform intrinsic electric field parallel to its axis (see Fig. 2). Consequently, the additional potential energy due to this electric field and associated with each dipole is

$$V_{el} = -cu_n, \quad c = qE, \quad (2.2)$$

where q denotes the effective mobile charge of a single dimer and E is the magnitude of the intrinsic electric field.

We are now in a position to write the model Hamiltonian for a microtubule. It can be given as

$$H = \sum_{i=1}^N \left[\frac{1}{2}M \left(\frac{du_n}{dt} \right)^2 + \frac{1}{4}K(u_{n+1} - u_n)^2 - \frac{A}{2}u_n^2 + \frac{B}{4}u_n^4 - cu_n \right]. \quad (2.3)$$

The first term above represents the kinetic energy associ-

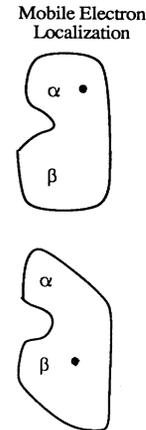


FIG. 4. An illustration of switching between conformational states (α and β) in microtubule dimers.

ated with the longitudinal displacements of constituent dimers, each of which has mass M . The second term arises from the restoring strain forces between adjacent dimers in the protofilament. If the stiffness parameter K is sufficiently large (so that the intersite strain energy exceeds the depth of the on-site potential well: $-A^2/4B$), then it is expected that large-amplitude long-wavelength excitations of the displacement field will be formed. They will be manifested by a slowly varying modulation of u_n along the MT axis.

In order to derive a realistic equation of motion for this system, it is indispensable to include the viscosity of the solvent and introduce the associated damping force. Assuming for simplicity that the solvent is made up of only water molecules, we may infer the following properties [20]:

(i) The dipolar water molecules will have a very significant effect on the long-range electrostatic energy between the dimer dipoles.

(ii) Water will provide a viscous medium that will damp out vibrations of dimer dipoles.

The first effect has already been mentioned, and it can be accounted for by an appropriate choice of the model parameters, especially by an inclusion of the dielectric constant. The second effect can be simply taken into account by adding the viscous force to the equation of motion with

$$F_v = -\gamma \frac{\partial u_n}{\partial t}, \quad (2.4)$$

where γ represents the damping coefficient that will be estimated in the next section. We are now in a position to obtain and analyze the relevant equation of motion for the displacement field.

III. THE EQUATION OF MOTION

Based on our assumption that the dipolar oscillations of dimers within a MT form a system that can be classified as displacive ferrodistoritive, we can use the continuum approximation whereby

$$u_n(t) \rightarrow u(x, t) \quad (3.1)$$

and

$$u_{n+1}(t) \rightarrow u(x, t) + R_0 \frac{\partial u(x, t)}{\partial x} + \frac{1}{2} R_0^2 \frac{\partial^2 u(x, t)}{\partial x^2} + \dots, \quad (3.2)$$

where R_0 represents the equilibrium spacing between adjacent dimers.

An equation of motion for dipolar oscillations can be now derived using the Hamiltonian of Eq. (2.3), applying the continuum limit of Eqs. (3.1) and (3.2) and adding the viscous force of Eq. (2.4) to the thus-obtained Euler-Lagrange equation. We therefore find that

$$M \frac{\partial^2 u}{\partial t^2} - KR_0^2 \frac{\partial^2 u}{\partial x^2} - Au + Bu^3 + \gamma \frac{\partial u}{\partial t} - qE = 0. \quad (3.3)$$

Note that the x coordinate is along the protofilament

axis. Moreover, for longitudinal sound waves the dispersion relation $\omega = \sqrt{K/M}$ can be used to identify the sound velocity with $v_0 = \omega R_0 = \sqrt{K/M} R_0$.

We now seek solutions of Eq. (3.3) in the traveling-wave form where the moving coordinate ξ is given by

$$\xi = \left[\frac{|A|}{M(v_0^2 - v^2)} \right]^{1/2} (x - vt) = \alpha(x - vt), \quad (3.4)$$

where v denotes the propagation velocity and the coefficient α is, of course,

$$\alpha = \left[\frac{|A|}{M(v_0^2 - v^2)} \right]^{1/2}. \quad (3.5)$$

Consequently, Eq. (3.3) is reduced to the ordinary differential equation below:

$$M\alpha(v^2 - v_0^2)u'' - \gamma\alpha u' - Au + Bu^3 - qE = 0, \quad (3.6)$$

where $u' \equiv du/d\xi$. This is an equation for an anharmonic oscillator with linear friction, and a recent paper [21] was devoted to describing analytical solutions, one of which will be discussed shortly. In addition, Lal [22] discussed a similar problem concerning the existence of kink solutions when friction is present and emphasized its importance in biological applications.

For the sake of convenience we now introduce a normalized displacement field as

$$\psi(\xi) = u(\xi)/\omega, \quad (3.7)$$

where the normalizing coefficient $\omega = \sqrt{|A/B|}$ corresponds to the minimum of the double-well potential in Eq. (2.1). The dimensionless equation of motion now takes the form of the ordinary differential equation below:

$$\psi'' + \rho\psi' - \psi^3 + \psi + \sigma = 0, \quad (3.8)$$

where we have used the symbols

$$\rho = \gamma v [M(v_0^2 - v^2)|A|]^{-1/2} \quad (3.9)$$

and

$$\sigma = q\sqrt{B}|A|^{-3/2}E. \quad (3.10)$$

It has been shown [17] that Eq. (3.8) has a unique bounded solution which is given by the formula (and illustrated graphically in Fig. 5)

$$\psi(\xi) = a + \frac{b-a}{1 + \exp(\beta\xi)}, \quad (3.11)$$

where

$$\beta = (b-a)/\sqrt{2} \quad (3.12)$$

and the parameters a , b , and d satisfy the cubic equation

$$(\psi - a)(\psi - b)(\psi - d) = \psi^3 - \psi - \sigma. \quad (3.13)$$

It is important to note that the above kinklike solution propagates along the protofilament with a fixed velocity

$$v = v_0 \left[1 + \frac{2\gamma^2}{9d^2 M v_0^2} \right]^{-1/2}. \quad (3.14)$$

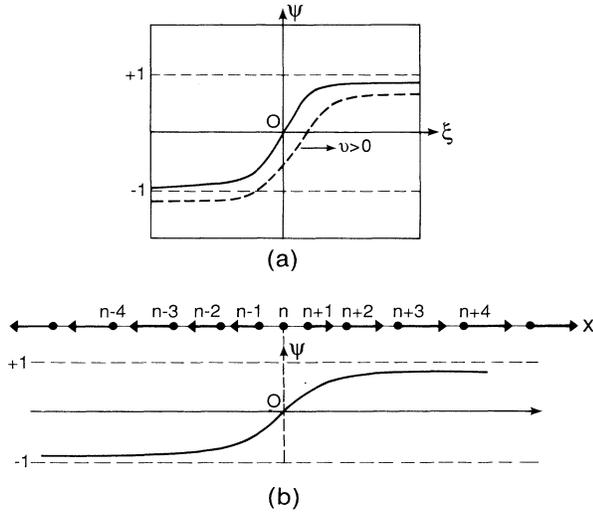


FIG. 5. The form of a kinklike excitation of Eq. (3.11).

This velocity is less than the sound velocity v_0 and it obviously decreases with an increase of the friction coefficient γ . It is clear that v depends on the magnitude of the electric field E through the parameter d . The dependence of d on E is not very simple, since it involves the cubic equation (3.13). However, for $T < T_c$ and large fields E , we know that $d \sim E^{1/3}$, while for small fields $d \sim \psi_0 + \lambda E$, where $\psi_0 = \pm 1$ is the mean-field solution for $E = 0$ and λ is a constant coefficient. In order to gain a more quantitative understanding of this result, we now wish to estimate the magnitude of the intrinsic electric field E in the protofilament. To this end, we assume that the length of a MT, L , is much greater than the diameter D , $L \gg D$. Hence, for points along the protofilament that are sufficiently removed from its ends, the magnitude of the electric field can be approximated simply as

$$E \cong \frac{Q}{4\pi\epsilon_0 r^2}, \quad (3.15)$$

where Q represents the effective charge on the ends of the hollow cylinder and r is the distance between the selected point and the end of the protofilament.

Taking, as an example, a moderately long MT consisting of approximately 10^2 dimers gives $L \sim 10^{-6}$ m. Then the effective charge Q consists of 2×13 protofilament end dimers, each of which has a charge of $18 \times 2e$ due to the presence of 18 Ca^{2+} ions. Consequently, $Q \cong 26 \times 36e \cong 9.4 \times 10^2 e$ with $e = 1.6 \times 10^{-19}$ C. Therefore, the field in the vicinity of the middle point on the protofilament is found to be on the order of $E \sim 4 \times 10^6$ V/m. Taking into account the dielectric effects of the surrounding water molecules, this value must be reduced by almost two orders of magnitude to approximately $E \sim 10^5$ V/m. As shown in Fig. 6, the magnitude of the electric field $E(x)$ sharply increases as we approach the end points.

Unfortunately, no reliable experimental data exist at present regarding the values of the potential coefficients

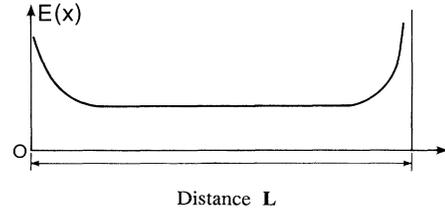


FIG. 6. Plot of the intrinsic electric-field distribution along the MT axis.

A and B or indeed whether the form of our potential is suitable. In principle, at least, neutron-scattering experiments should provide a dynamic structure factor for microtubules which could be used for modeling purposes in a manner similar to that used for ferroelectrics [23]. In the absence of any hard data for MT's we can use some typical values for crystalline ferroelectrics, knowing that they do not vary substantially between different compounds. For example, the well-studied [23] ferroelectric $\text{Pb}_5\text{Ge}_3\text{O}_{11}$ has been demonstrated to support the formation of kinklike domain walls. There, $A(T) = \alpha(T - T_c)$ with $\alpha = 10^2 \text{ J m}^2$ and $B \cong 1.6 \times 10^{24} \text{ J m}^{-4}$, while $T_c \cong 500$ K. Assuming that the critical temperature T_c for MT's is in the room-temperature range or somewhat above it, we take $T_c \sim 320$ K and estimate that in the room-temperature region

$$A(T = 300 \text{ K}) \cong 200 \text{ J m}^{-2}, \quad B \cong 10^{24} \text{ J m}^{-4}. \quad (3.16)$$

Thus, with the parameter values obtained in this section we find

$$\sigma \cong 2 \times 10^{-9} E. \quad (3.17)$$

It is, therefore, clear that even for very strong electric fields ($E \sim 10^8$ V/m) the inequality $\sigma \ll 1$ holds right up to the protofilament ends. Under these circumstances we can safely approximate the KLE of Eq. (3.11) as

$$u(\xi) = u_0 \left[1 - \frac{\sigma}{2} - \frac{2}{1 + \exp(\sqrt{2}\xi)} \right] \cong u_0 \left[1 - \frac{2}{1 + \exp(\sqrt{2}\xi)} \right], \quad (3.18)$$

where the amplitude of the dimer displacement field has the value $u_0 = \sqrt{|A|/B} \cong 1.4 \times 10^{-11}$ m. Let us now assess other consequences of smallness of the electric field. First, the propagation velocity of a KLE is approximated (for T well below T_c and large values of γ) as

$$v \cong \frac{3v_0}{\gamma|A|} \left[\frac{MB}{2} \right]^{1/2} qE \quad (3.19)$$

and it is generally much smaller than the sound velocity ($v \ll v_0$). Equation (3.19) can be interpreted as a linear response between the propagation velocity v and the magnitude of the electric field E . The coefficient of proportionality in this relationship represents the KLE mobility

$$\mu \cong \frac{3v_0}{\gamma|A|} \left[\frac{MB}{2} \right]^{1/2} q. \quad (3.20)$$

In order to evaluate the magnitude of μ we require an estimate of the damping coefficient γ . To do so we will use simple fluid mechanic arguments. First of all, note that each dimer can be roughly viewed as a sphere of mass M . Then, using the well-known result for a sphere of radius R moving through fluid with velocity du/dt , the drag force exerted by the fluid on the sphere is

$$F_d = -6\pi R \eta \frac{du}{dt} = -\gamma \frac{du}{dt}, \quad (3.21)$$

where η is the absolute viscosity of the fluid. In our case, the fluid is assumed to be water and its viscosity is temperature dependent. However, at physiological temperatures (~ 300 K) we take

$$\eta \cong 7 \times 10^{-4} \text{ kg m}^{-1} \text{ s}^{-1}. \quad (3.22)$$

Substituting $R \cong 4 \times 10^{-9}$ m into Eq. (3.21) we obtain

$$\gamma \cong 5.6 \times 10^{-11} \text{ kg s}^{-1}. \quad (3.23)$$

The last quantity required in our estimate is the sound velocity v_0 . The experimental results [24] of v_0 for DNA produced the value

$$v_0 = 1.7 \times 10^3 \text{ m/s}. \quad (3.24)$$

Finally, then, putting $M = (55 \times 10^3) \times (2 \times 10^{-27})$ kg $\cong 1 \times 10^{-22}$ kg and $q = 18 \times 2 \times (1.6 \times 10^{-19})$ C $\cong 6 \times 10^{-18}$ C, Eq. (3.21) yields

$$\mu \cong 2 \times 10^{-5} \text{ m}^2 \text{ V}^{-1} \text{ s}^{-1}. \quad (3.25)$$

Thus, taking $E = 10^5$ V m $^{-1}$ as a representative average value of the electric field, the propagation velocity of a KLE is on the order of

$$\bar{v} \cong 2 \text{ m/s}. \quad (3.26)$$

However, in close proximity of MT ends E may reach 10^7 V m $^{-1}$ and, consequently, the KLE may accelerate up to $v \sim 10^2$ m/s.

Assuming a smooth journey from one end of the protofilament to the other, we estimate the average time of propagation for a single KLE to be

$$\bar{\tau} = L/\bar{v} \cong 5 \times 10^{-7} \text{ s}. \quad (3.27)$$

However, increasing the length of the protofilament will increase $\bar{\tau}$ on two accounts: (a) increasing the numerator in Eq. (3.27), and (b) affecting the mean velocity through the dependence of the electric field on L . Indeed, $E \sim L^{-2}$ and hence $\bar{v} \sim L^{-2}$. Consequently,

$$\bar{\tau} \sim L^{+3}, \quad (3.28)$$

leading to a rapid increase of $\bar{\tau}$ with L .

While the model presented here is very closely related to the one developed by Collins *et al.* [17] for ferroelectrics, we should mention that the effects of discreteness of the lattice may play an important role. For example, Kimball's analysis [25] of kink dynamics for a discrete lattice indicates that there may exist a threshold value of

the external field required to sustain kink motion. Moreover, it appears that fast-propagating kinks are more stable than slow ones. Similar conclusions were obtained by Sánchez and Vázquez [26], who studied the propagation of topological kinks in a stochastically perturbed ϕ^4 model. Their numerical simulations confirmed the conclusion that for all noise strengths studied slow kinks were more affected by the perturbation than fast ones. Finally, in this context, Combs and Yip [27] demonstrated that discreteness of the lattice may be accommodated by continuous equations of the form in Eq. (3.3) by adding higher powers of the time derivative of the field, i.e., terms like $(\partial u/\partial t)^2$. A general discussion on the propagation and stability of kinks and their generalizations in dissipative nonlinear models can be found in Ref. [28].

IV. STATISTICAL PROPERTIES OF THE KLE ENSEMBLE

It is well known that extra energy is required in order to create a kink, since kinks are not solutions of the equation of motion with the lowest energy. Thus, outside the immediate proximity of the critical temperature T_c , kinks are not easily formed. Due to their topological stability, however, they are not readily destroyed once they are formed. An injection of energy into the system in the form of incoherent pulses of electromagnetic radiation is expected to stimulate kink creation. This extra energy can be produced, for example, during the hydrolysis of ATP or GTP, as was already mentioned in this paper. Due to their mutual repulsion over short distances, the number of KLE's formed is limited from above.

In order to formulate a statistical description of an ensemble of KLE's we must first calculate the energy of a single kink. This is found by substituting the displacement field solution of Eq. (3.18) into the model Hamiltonian of Eq. (2.3) so that

$$E = \frac{1}{R_0} \int_{-\infty}^{+\infty} dx H(x, t), \quad (4.1)$$

and we find

$$E = \frac{2\sqrt{2}}{3} \frac{A^2}{B} + \frac{\sqrt{2}}{3} K \frac{A}{B} + \frac{1}{2} \left[\frac{4}{3\sqrt{2}} \frac{MA\alpha}{R_0 B} \right] v^2. \quad (4.2)$$

The first term in the formula above represents the well-known binding energy of a KLE. Its magnitude is much greater than that of the remaining two, being on the order of 1 eV. The second term in Eq. (4.2) corresponds to the resonant transfer of energy responsible for the propagation of KLE's along the MT. The third term is the classical kinetic energy of a KLE, which can be expressed as

$$E_k = \frac{1}{2} M^* v^2, \quad (4.3)$$

where the effective mass M^* is

$$M^* = \frac{4}{3\sqrt{2}} \frac{MA\alpha}{R_0 B}. \quad (4.4)$$

Thus, the total energy can be rewritten more compactly

as

$$E = \Delta + \frac{1}{2}M^*v^2, \quad (4.5)$$

where

$$\Delta = \frac{2\sqrt{2}}{3} \frac{A^2}{B} \left[1 + \frac{K}{3A} \right]. \quad (4.6)$$

Using the same set of parameters as before, including the DNA value for K ($=32 \text{ N m}^{-1}$), we obtain the following estimates for a MT:

$$\begin{aligned} \frac{2\sqrt{2}}{3} \frac{A^2}{B} &\cong 0.4 \times 10^{-19} \text{ J}, \\ \frac{\sqrt{2}}{3} K \frac{A}{B} &\cong 0.3 \times 10^{-20} \text{ J}, \\ M^* &\cong 5 \times 10^{-27} \text{ kg}. \end{aligned} \quad (4.7)$$

This estimate appears to indicate that thermal energy is insufficient to create a significant number of KLE's. Thus, we must seriously consider the hydrolysis of GTP from the surrounding medium (or injection of energy pulses of another type) as a main potential source of KLE formation. At normal concentrations of attached GTP molecules one expects a few KLE's to be generated so that their mean separation by far exceeds their width. In this regime, KLE's can be viewed as a gas of weakly interacting quasiparticles whose velocities are thermalized.

In the following we provide a more quantitative statistical calculation [29] intended to demonstrate that thermal generation of KLE's is negligibly small. The partition function for a single KLE with a number of available momenta p is

$$Z = \frac{1}{D} \int_0^L dx \int_0^{M^*v_0} dp \exp(-\beta E), \quad (4.8)$$

where D is a normalization constant, $d\Gamma = dx dp$ is an element of the phase space, $p = M^*v$ is the momentum of one KLE, and $\beta = (k_B T)^{-1}$, where k_B is the Boltzmann constant and T is the absolute temperature. In order to calculate the mean number of KLE's, we first define the grand partition function Ξ as

$$\Xi \equiv \sum_{i=1}^{\infty} \frac{1}{i!} Z^i \exp(i\beta\mu) = \exp[Z \exp(\beta\mu)], \quad (4.9)$$

where Z^i is an i -particle partition function and μ is the chemical potential. Then, standard thermodynamic relations give

$$F = -k_B T \ln \Xi, \quad \langle n \rangle = -\frac{\partial F}{\partial \mu}, \quad (4.10)$$

and the mean number of KLE's is found as

$$\langle n \rangle = Z \exp(\beta\mu). \quad (4.11)$$

The mean density of KLE's in the MT is their number per unit length, i.e.,

$$\begin{aligned} \rho_0 &\equiv \frac{\langle n \rangle}{L} \\ &= \frac{1}{D} \left[\frac{M^*}{2\beta} \right]^{1/2} \text{erf} \left[v_0 \left[\frac{M^*\beta}{2} \right]^{1/2} \right] \exp \left[\frac{\mu - \Delta}{k_B T} \right], \end{aligned} \quad (4.12)$$

where $\text{erf}(\cdot)$ denotes the error function which stems from the p integration in Eq. (4.8). However, the most important factor in Eq. (4.12) is $\exp(-\Delta/k_B T)$, since at room temperature $\Delta \cong 0.2 \text{ eV}$, $k_B T \cong 0.02 \text{ eV}$, and the expression for ρ_0 is *reduced* by a factor of e^{10} . This fully supports our earlier predictions and also agrees with the results of Koehler *et al.* [30].

Finally, the thermodynamic equation of state for an ensemble of KLE's on a MT can be found as

$$\lambda L = \left[\frac{Z}{\beta} \right] \exp(\beta\mu) = \langle n \rangle k_B T, \quad (4.13)$$

where λ is the uniaxial stress on the MT. This result takes the form of an ideal-gas equation relating the space occupied by KLE's with the magnitude of the electric field that influences the value of the chemical potential. This is consistent with the emergence of piezoelectric properties of MT's.

V. SUMMARY AND CONCLUSIONS

This paper provided a general biophysical picture regarding the structure and function of microtubules. A physical model has been developed based on nonlinear dipolar excitations. Although this is but a first step in the direction of quantitative modeling of microtubular behavior, we believe that it will be very useful in future investigations. The basis of our model has been the approach due to Collins *et al.* [17] that has proved very useful in ferroelectric and ferroelastic applications. In our model, we have assumed the existence of an intrinsic electric field in MT's and included its interactions with dipolar oscillations in the constituent dimers. Lastly, the presence of the surrounding water molecules has been accounted for by the addition of an effective viscous force that opposes the motion of dimers in an aqueous environment. We have estimated the required model parameters using available experimental data.

Our main result is that a unique kinklike excitation exists which may propagate with a unique velocity that, in the given range of parameters, is proportional to the magnitude of the electric field E . We predict that these excitations may be observed experimentally, for example, through neutron-scattering and polarization experiments. In the past, somewhat similar ferroelectric materials possessing filamentary structure [23] (e.g., Sb-Si) have been precisely analyzed using light-, neutron-, and x-ray-scattering data [31,32].

Although quantitative experimental evidence to support our model appears rather tenuous at present, there are a number of facts that are consistent with the qualitative features of our approach. For example, the observed growth rates of MT's are different at both ends in spite of

an identical concentration of the surrounding monomers. This can be explained on the basis of the following argument. We assume that KLE formation is mainly due to the hydrolysis of GTP into GDP so that one act of hydrolysis corresponds to the conformational change resulting in the formation of a single KLE. However, a KLE is preferentially oriented towards the direction of the intrinsic electric field. The propagation of a KLE will then distribute the energy of hydrolysis at the preferred end of a MT. This energy will then be used to detach dimers from the MT. This picture is in accordance with a hypothesis put forward in a recent paper by Krischner and Mitchison [33], who stated that on-rate (growth) is limited in principle only by the rate of diffusion of the monomer subunits into the MT polymer (i.e., by the concentration of the constituent monomers in solution). On the other hand, the off-rate (depolymerization) can be extremely rapid and the net amount of MT polymer formed can be regulated independently by the hydrolysis of GTP. Our model can be especially useful in the explanation of a peculiar dynamical effect known as “treadmilling.” In it, the “+” end grows at the same rate as the “-” end shortens so that the overall length of the MT remains constant under the condition of constant temperature and concentrations. See Fig. 7 for an illustration of this process.

It is reasonable to expect that at the onset of the MT assembly process, when MT's are very short, the formation of KLE's is very unlikely (or even impossible), since for a short chain the displacement field gradient required would be very high and the associated energy to form it prohibitively large. However, when the length of a MT reaches a threshold value, kink formation could become a real possibility. Excitation of kinks, being related to GTP hydrolysis, would become dependent on the GTP concentration. As MT's become longer, KLE propagation becomes an important new factor, and it introduces disassembly at the “-” end, whose rate is proportional to the rate of KLE's arriving per unit time at the “-” end.

It has been emphasized [33] that the existence of a so-called “cap” of dimers containing GTP near the “+” end is a factor stabilizing the growth of GTP. If dimers within this cap do not hydrolyze, the growth of a MT is maintained. However, an intensive hydrolysis of this cap is a trigger mechanism for the disassembly of MT's occurring at *both* ends. We also attribute this instability to the energy transfer through KLE's, since the probability of a growing MT to start shrinking is thought to be governed by the stochastic loss of the fluctuating GTP cap.

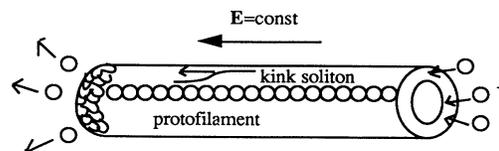


FIG. 7. Schematic representation of the “treadmilling” process involving tubulin dimers of a microtubule which takes place at the (-) end with disassembly and at the (+) end with assembly.

We have seen in our model that the intrinsic electric field governs the rate of propagation of KLE's. By adding an external electric field to the Hamiltonian we can introduce a new control mechanism in the MT dynamics. An applied electric field will result in a faster-moving population of KLE's and thus a greater stability against thermal fluctuations; if, on the other hand, the intrinsic and applied electric fields are oriented in opposite directions, then KLE's motion may be slowed down or stopped altogether. This then can be seen as a basis for treating MT's as artificial information strings. Each KLE within a MT can be viewed as a bit of information whose propagation can be controlled by an external electric field.

Another important experimental fact is that stability of MT's is greatly enhanced by the presence of lateral cross-bridging proteins (MAP's). From the physical point of view, these bridges represent lattice impurities in the MT structure. Interactions between solitonlike pulses and impurities have been studied very extensively in the past few years. It was demonstrated that impurity modes play an important role in soliton propagation. In particular, kinks may be totally reflected by an attractive impurity if their velocities lie in specific resonance velocity “windows” [34]. Hence, if the velocity of KLE's lies within such a “window,” the rate of arrival of KLE's at the “-” end will decrease or even stop as the number of MAP's increases. This mechanism can lead to a significantly reduced rate of MT disassembly. This mechanism together with a control mechanism offered by an external electric field may provide a number of interesting possibilities for information transmission and storage in MT's.

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