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Excitation of vibrations in microtubules in living cells

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Abstract

Microtubules, which are thought to be the primary organizers of the cytoskeleton, are electrical polar structures with extraordinary elastic deformability at low stress and with energy supply from hydrolysis of guanosine triphosphate (GTP) to guanosine diphosphate (GDP). At least a part of the energy supplied from hydrolysis can excite vibrations. Energy is mainly lost by viscous damping of the surrounding cytosol. Viscous damping is diminished by a slip layer which is formed by an attracted ionic charge layer and by a thin surface layer of the microtubule. Relaxation time caused by viscous damping may be several orders of magnitude greater than period of vibrations at 10 MHz. Energy supplied to the microtubule is of the order of magnitude of 10^{-14} W cm^{-1} (per unit length of the microtubule).

Keywords: Biological order; Cytoskeleton; Microtubules; Coherence; Fröhlich coherence

1. Introduction

Physical processes in living matter participating in its organization are still not adequately understood. Frauenfelder et al. [1] claim than physical mechanisms of organization are of electromagnetic nature. Fröhlich pointed out that biological systems exhibit relative stability in a way in which some modes of behaviour remain very far from thermal equilibrium, postulated the existence of long range quantum mechanical phase correlations, and very strong excitation of a few modes of motion. Strong polar character of biological objects suggests longitudinal oscillations as stabilising modes [2–4]. The postulated rate equation for the *i*-th vibration mode may be written in a symbolic form

$$\dot{n}_i = s_i - [\dot{n}_i]_\phi - [\dot{n}_i(n_i, n_j)]_\chi$$

where $\dot{n}_i$ is the total rate of change of occupation number n_i (in 1 s), and s_i, $[\dot{n}_i]_\phi$, $[\dot{n}_i(n_i, n_j)]_\chi$ is the rate of change of n_i by energy supply, and by the linear and by the nonlinear interaction with the heat bath, respectively. The linear and the nonlinear term of the interaction with the heat bath describes transfer of one energy quantum between a vibration mode and the heat bath and energy transfer between two vibration modes with participation of the heat bath, respectively. The steady state solution to the rate equation shows that due to nonlinear term the supplied energy is not thermalized but condensed in a vibration mode. Excitation depends on the amount of the energy supplied to the system but not on the manner of its supply [5].

Eucaryotic cells are structurally and dynamically organized by a protein polymer network called the cytoskeleton [6]. The cytoskeleton exerts forces and generates movements without any major chemical changes. The cytoskeleton is a highly dynamic structure which reorganizes continually as the cell changes its shape, divides, and responds to its environment. The fundamental structure of the cytoskeleton formed by the microtubules satisfies the basic requirements for excitation of vibrations and generation of endogenous oscillating electric field [7]. Viscous damping by surrounding cytosol may quench excitation of vibrations. Viscosity effects on vibrations were examined using a model with longitudinal vibrations parallel to the planar interface between the microtubular medium below and the cytosol medium above the interface [8]. Slip boundary conditions make possible excitation of vibrations. Foster and Baish [9] used a cylindrical model of a microtubule but without slip boundary conditions and claimed that damping is so strong that excitation of vibrations is not possible. A cylindrical model of microtubule with the slip boundary conditions used in Refs. [10,11] confirmed the possibility of excitation. We present assessment of excitation in microtubules including viscous damping.

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2. Subunits of the microtubule—electric dipoles

The microtubule is a hollow cylindrical polymer of tubulin heterodimers (Fig. 1a). The outer and the inner diameter is about 25 and 17 nm, respectively. Tubulin heterodimer—composed of α- and β-tubulins—may exist in two conformation states (Fig. 1b): the α state and the β state where the electron negative charge is placed toward the α-tubulin and the β-tubulin, respectively. In the β state, the heterodimer is tilted 29° with respect to the microtubule axis. In the interphase microtubules are organized in a radial structure extending from the centrosome to the periphery of the cell (Fig. 2a). In the M phase, microtubules assemble from the two separated centrosomes to form a mitotic spindle (Fig. 2b).

Each heterodimer binds 18 calcium ions [12–14]. The electric dipole moment is about 1000 Debye (10^{-26} Cm). The induced dipole moment per dimer arising only from the motion of mobile electrons or protons was estimated to be 200–400 Debye [15]. Ionic concentration inside a cell is of about 150 mM of cations and the same concentration of anions [6]. The ions from the cytosol form a charge layer—a cylindrical envelope around the microtubule [15]. Similar situation may be inside the microtubule (Fig. 3) as the liquid medium in the inner circular cavity is very likely to be cytosol. The ionic charge layer, which is schematically shown in Figs. 1 and 3, screens electrical potential generated by the charges in the microtubule [15]. Within a distance of about 2 Debye lengths the static potential is considerably screened. The Debye length is of about 0.8 nm [16]. Due to hydration, the ions are surrounded by bound water molecules up to a distance of 0.4–0.5 nm. Charged proteins of considerably greater size than ionized atoms may be in the ionic layer too. The majority of water molecules in the charge layer are not free and its viscous properties are dependent on hydrated ions. Some ions can penetrate inside the tubulin structure and behave like a part

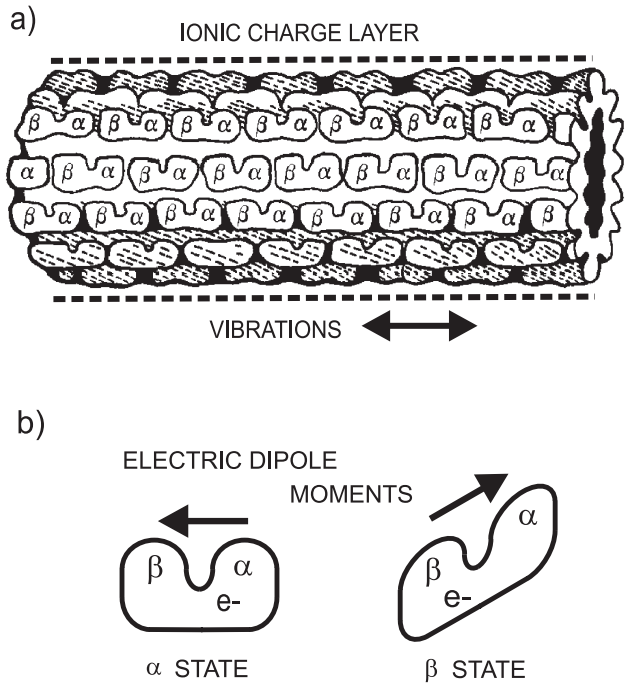

Fig. 1. (a) A schematic picture of a microtubule with tubulin heterodimers in parallel protofilaments and (b) conformation change of a heterodimer from the α to the β state after hydrolysis of GTP (guanosine triphosphate) to GDP (guanosine diphosphate) in the β-tubulin (b). The lines with arrows indicate the dipole moment vectors.

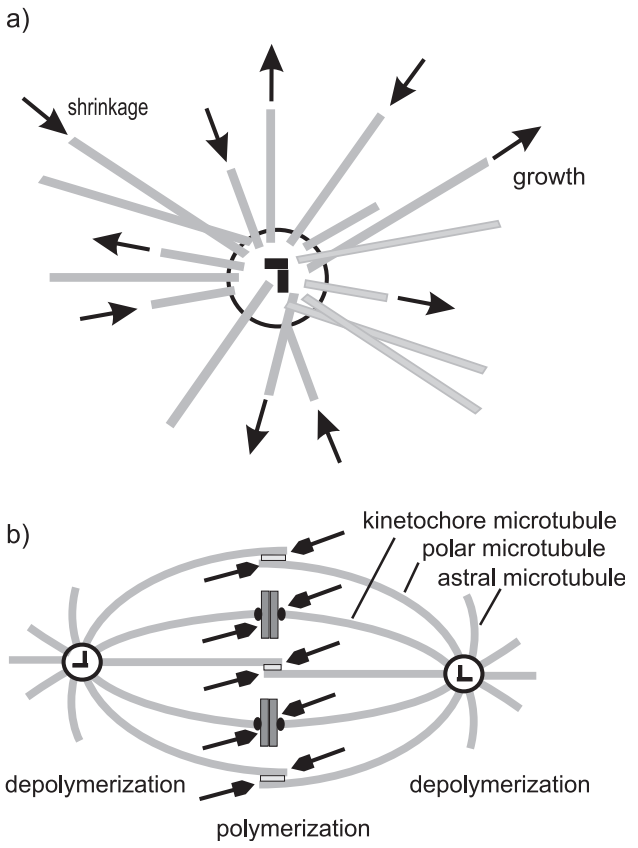

Fig. 2. (a) A centrosome with attached microtubules in the interphase. (b) The mitotic spindle in the M phase. The heterodimers with exhausted energy are exchanged for energy rich ones by the dynamic instability—the growth and shrinkage are indicated by arrows (a) and by the treadmilling—polymerization (indicated by arrows) and depolymerization take place at the center and at the poles of the mitotic spindle, respectively (b).

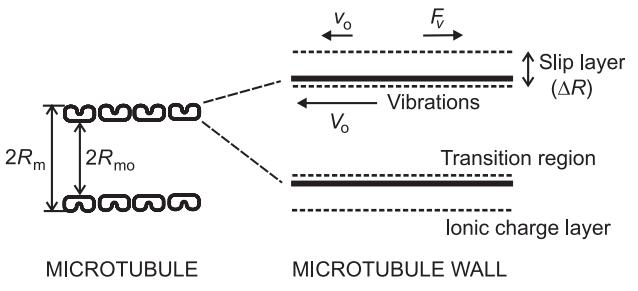

Fig. 3. A schematic picture of the microtubule wall with the slip layers. Each slip layer includes the ionic charge layer and the transition layer in the microtubule.

of the tubulin (as well as water molecules). Ions in the cytosol have small mobility and, therefore, there is slip between the charge layer and the microtubule surface.

We have to mention here that the cytoskeleton is a complicated structure with associated proteins cross-linking its parts, changing elastic properties of the structures and the viscosity effects. There are e.g. microtubule-associated proteins (MAP-1, MAP-2 forming sidearms), tau proteins and motor proteins. Phosphorylation of tau proteins plays very likely a role in microtubule binding and function [17]. Skeletor reticular matrix, spring like lattice around kinetochore microtubules, and protein cross-linked lattice around the spindle poles [18], are formed in the M phase. These structures might diminish viscosity damping but their description and analysis of their effects on excitation of microtubules is outside the scope of this paper.

3. The microtubule—a highly deformable structure

In contrast with actin and intermediate filaments the microtubules can be easily deformed and begin to flow without limit when the strain exceeds 50% (Fig. 4, [6,19]). Dynamic shear modulus G is of 5 N m^{-2} [19,20]. The dynamic shear modulus was measured in medium with ionic concentration similar to that in cytosol [19]. As the thickness of the ionic charge layer at the inner and at the outer surface of a microtubule are comparable with the thickness of the microtubule wall the measured dynamic shear modulus is an average value representing shear properties of the microtubule together with the charge layer. Therefore, as a rough approximation we will use the measured G value of the shear modulus for slip conditions inside the slip layer which consists of the microtubule surface layer (transition layer) and of the charge layer (Fig. 3). Fig. 3 shows similar slip layers on the outer and on the inner side of the microtubule wall. Large deformability is an important property for slip boundary conditions at the microtubule surface.

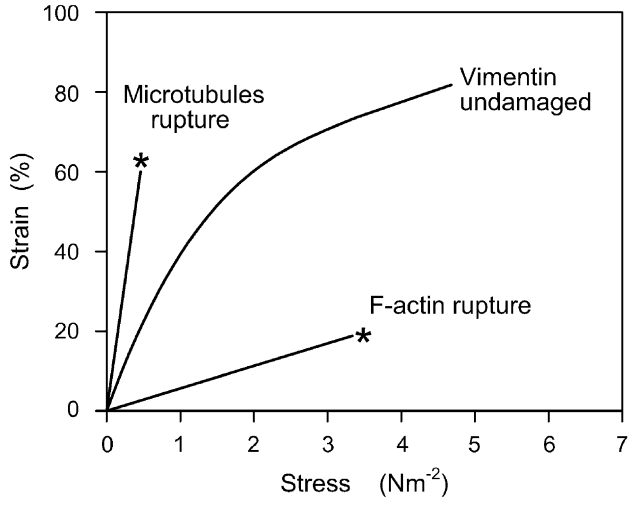

Fig. 4. Strain versus stress of actin, vimentin, and tubulin filaments. The microtubules are capable of large elastic deformation at low stress. After Refs. [6,19].

4. Energy excitation of the microtubular structure

The microtubule is a highly dynamic polymer that continuously exchange subunits (heterodimers) by the mechanism of dynamic instability (growth and shrinkage of the microtubules) and by treadmilling (heterodimers are continually added to one end and lost from the other one) [6,21,22]. After polymerization, guanosine triphosphate (GTP) bound to the β-tubulin in the heterodimer is hydrolyzed to guanosine diphosphate (GDP) and considerable amount of energy is stored in the microtubule [23,24]. Dynamic instability and treadmilling are important processes for energy supply to the microtubule structure.

The average rate of growth of a microtubule may be determined from histograms of lengths published e.g. in Refs. [25,26]. The mean microtubule length in histogram reported by Melki et al. [25] is about 0.5 μm and, therefore, the rate of growth is about 0.5 μm per 20 s. Five percent of heterodimers is incorporated into a microtubule in 1 s. For simplicity, we will assume microtubular structure where microtubules have the total length of 1 cm, and that 5% of it is exchanged in 1 s, i.e. $n = 8 \times 10^5$ of heterodimers may be replaced. From the energy released by hydrolysis of GTP to GDP, the amount $\epsilon = 7.1$ kJ mol^{-1} [23,24] is stored in the microtubule. Energy supplied within 1 s (i.e. power) $P_m = \epsilon n/L \approx \times 10^{-14}$ W cm^{-1} (where L is Avogadro's number). In the M phase of the cell cycle, the rate of exchange of heterodimers is more than one order of magnitude greater than that in the interphase and energy supply corresponds to this rate.

It is known that energy produced during GTP hydrolysis is delivered to microtubules and may be used for increase of tension in the microtubule, may excite solitons, may be transformed into vibrations and excite coherent states of the Fröhlich's type. In the last case, longitudinal polar vibrations (polarization waves) in the direction of the microtubule axis are of particular interest. These vibrations can generate electromagnetic field with dominant electric component around microtubules. Intensity of the electric field in the near vicinity of the outer surface and inside the circular cavity may be high.

Hydrolysis of GTP to GDP takes place at the fast growing end (plus end) below the cap with nonhydrolyzed GTP. The released energy may relax inside a microtubule which is from 1 to 10 μm long within about 1–10 ns for the velocity of vibration modes about 10^3 ms^{-1}. We cannot exclude energy transfer to the whole microtubule structure by this mechanism in a very short time of the order of magnitude of 10^{-8} s.

5. Viscous force at the upper surface of the slip layer

The microtubule may be approximated by a cylindrical layer with circular cross section and with rotation symmetry with respect to the microtubule axis. We will assume longitudinal harmonic vibrations along the axis of the cylinder (but independent of the distance along the axis). Due to viscosity oscillations in the microtubule excite oscillations in the liquid medium (in the cytosol) around the microtubule. The viscous force exerted by Newtonian liquid per unit area of the slip layer is given by

$$F'_v = \eta\left(\frac{\partial v}{\partial r}\right)_{r=R}, \tag{1}$$

where $\eta = \rho\kappa$ is the dynamic viscosity of the cytosol (ρ is the density of mass and κ is the kinematic viscosity), and $v = v_0\exp(i\omega t)$ is the velocity of vibrations in the direction of the microtubule axis (v_0 is the amplitude). In this case, the momentum equation is given by the diffusion equation $\partial v/\partial t = \kappa\nabla v$ [27]. Solution to the momentum equation in cylindrical coordinates can be found using Kelvin's functions [28,29] which can be expressed by Macdonald's functions (K_0, K_1). We get for the viscous force per unit length (shown in Fig. 3) [11]

$$F_v = -\beta v_0\exp(i\omega t) \quad \text{where}$$

$$\beta = \exp\left(i\frac{\pi}{4}\right)\sqrt{\omega\rho\eta}\,\frac{K_1\left(R\sqrt{i\frac{\omega}{\kappa}}\right)}{K_0\left(R\sqrt{i\frac{\omega}{\kappa}}\right)}S_i, \tag{2}$$

where R is the radius of the outer cylindrical surface and $S_i = 2\pi R$ is the area of the cylindrical surface of unit length.

6. Transfer of vibrations across the slip layer

As a first order approximation, we assume that the oscillations in a microtubule act on the damped upper surface of the slip layer by the force [11]

$$F_i = f\,Y_0\exp[i(\omega t + \phi)] \quad \text{where} \quad f = \frac{GS_i}{\Delta R}, \tag{3}$$

Y_0 is the amplitude of oscillations below the transition region in the microtubule, f is the elastic force constant, and ΔR is the thickness of the slip layer. The force F_i acts in the direction of the microtubule axis. Equation of motion for forced vibrations at the upper surface of the slip layer has the form

$$\frac{d^2y}{dt^2} + \frac{\beta}{m}\frac{dy}{dt} + \omega_0^2 y = \frac{F_i}{m} \tag{4}$$

(where ω_0 is the characteristic angular frequency, y is the displacement along the microtubule axis, and m is the mass of the slip layer). Under steady state conditions we get from Eqs. (2)–(4) for $\omega = \omega_0$ [11]

$$\frac{y_0}{Y_0} = \frac{f}{|\beta|\omega} \tag{5}$$

where y_0 is the amplitude of the displacement and $|\beta| = \sqrt{\Re(\beta^2) + \Im(\beta^2)}$. The same relation is valid for v_0/V_0 where V_0 is amplitude of velocity in the microtubule (shown in Fig. 3).

7. Relaxation time and energy losses

The average kinetic energy stored in the microtubule per unit length and the average rate of energy loss per unit length caused by viscous damping (as follows from Eq. (2)) are given by [11]

$$E = \frac{1}{4}\pi(R_m^2 - R_{m0}^2)\,\rho V_0^2 \quad \text{and} \quad E' = -\frac{1}{2}|\beta|v_0^2, \tag{6}$$

respectively. R_m and R_{m0} in Eq. (6) are the outer and the inner radius of the microtubule (Fig. 3). Using Eq. (6) the relaxation time τ and its relative value τ_{rel} (in the number of periods of oscillations) may be evaluated from

$$\tau = \frac{E}{|E'|} = \frac{1}{2}\pi(R_m^2 - R_{m0}^2)\rho\,|\beta|\,\frac{\omega^2}{f^2} \quad \text{and} \quad \tau_{rel} = \frac{\omega\tau}{2\pi}. \tag{7}$$

Fig. 5 shows the relative relaxation time as a function of frequency for $\eta = 5\times10^{-4}$ (the dashed lines) and 10^{-3} Pa s (the full lines). The range of magnitude from 5×10^{-4} to

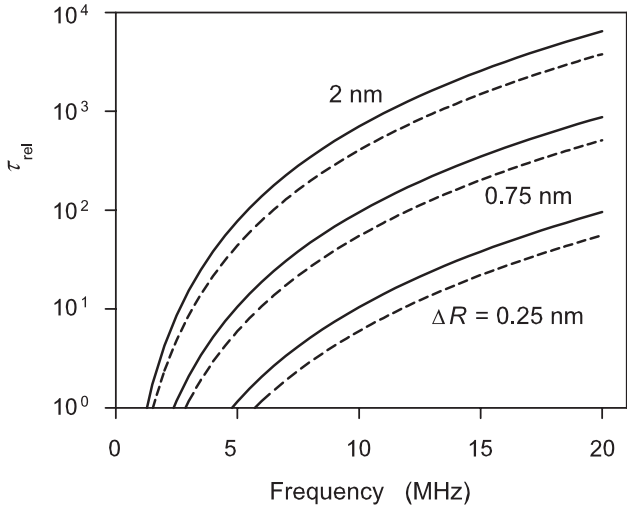

Fig. 5. Relative relaxation time τ_{rel} caused by viscous damping in a microtubule versus frequency. Parameter is the thickness of the slip layer ΔR (0.25, 0.75, and 2 nm). Dynamic viscosity η of the liquid medium is 5×10^{-4} (the dashed lines) and 1×10^{-3} Pa s (the full lines). The shear modulus G is 5 N m^{-2}.

10^{-3} Pa s corresponds to the viscosity of water for temperatures from 55 to 25 °C, respectively (more detailed information about viscosity of cytosol is in the discussion). $R_m = 12.5$ nm, $R_{m0} = 8.5$ nm [6], $R = R_m + \Delta R$, and the shear modulus $G = 5$ N m^{-2} [19]. The relative relaxation time τ_{rel} for $\Delta R = 2$ nm is about 10^3 at 10 MHz. The curves for $\Delta R = 0.25$ nm in Fig. 5 may correspond to the relaxation time for a slip in the transition surface layer of the microtubule. τ_{rel} is greater than 10 at 10 MHz. Assessment of damping for the magnitude of viscosity from 10^{-4} to 10^{-2} Pa s is in Ref. [11].

The average rate of energy loss is given by Eq. (6). We determine v_0 from Eq. (5) for amplitude of oscillations in the microtubule 0.5 nm. At 10 MHz power lost per 1 cm length is about 3.3×10^{-14} W cm^{-1} ($\eta = 5 \times 10^{-4}$ Pa s). This power is of the same order of magnitude as the power P_m supplied by hydrolysis of GTP to GDP.

8. Discussion

Fröhlich postulated that excitation of vibrations, condensation of energy in a vibration mode, and creation of the state far from thermodynamic equilibrium are fundamental physical properties of the living system [2–4]. This paper is a contribution to Ref. [7] in which we concluded that microtubules may satisfy the requirements for the Fröhlich's structure. Theoretical treatment describes a real biological mechanism of energy supply and possibility of energy excitation of a polar structure. Polar structures generate an electromagnetic field with dominant near zone electrical component which can participate for instance in the directional transport of reaction component [30], in orientation of macromolecules and polymer structures, and in polymerization processes.

We will make remarks on energy supply and energy losses conditioning excitation of the Fröhlich's system. The energy supply by hydrolysis of GTP to GDP seems to be sufficient for excitation even if we take into account losses at the outer and at the inner surface of the microtubule. Vibrations in bodies immersed in liquids are strongly damped by viscosity. Description of the properties of cytoplasm, especially of its viscosity, is contained in Ref. [31]. Cytoplasmic viscosity was measured as high as 0.011 Pa s—the value more than 10 times greater than that of water. (About 30% of mass in a mammalian cell is in the solid state form but due to compartmentalization its concentration is not uniform [6].) Other measurements revealed that apparent viscosity did not significantly differ from the viscosity of bulk water. Water is the major part of cytosol (a typical cell contains about 70% of water). Nevertheless, surface associated layers of ordered water up to the thickness of 200 nm may exist. Therefore, properties of water in living cells do not appear to be greatly altered in comparison with pure water but layers of ordered water may exist. Consequently, properties of cytosol around microtubules may differ from those of pure water and low damping of vibrations by viscosity may exist. Viscous losses from the inner surface might be very small as all the liquid medium in the cavity may be in an ordered state. We may conclude that even for viscosity of water excitation of vibrations is possible on account of the slip boundary conditions.

Experimental proof of the postulated theory is rather difficult as we have to measure living cells or subcellular structures of micrometer or submicrometer dimensions. Measurement method of electromagnetic emission from individual cells using special microelectronic sensors is described e.g. in Ref. [32]. Each detection structure in a microelectronic sensor has two electrodes 10 μm wide with a small gap between them. The electromagnetic emission of a sedimented cell at the gap is measured. The measurement results are promising. Nonetheless, the microtubular structures organized inside a cell need not be a source of electromagnetic emission from the cell. Two needle electrodes pricked inside a cell may be more convenient for measurement of the oscillating electric field generated by microtubules.

9. Conclusions

Microtubules satisfy conditions for excitation of vibrations and energy condensation. The damping effects of cytosol viscosity are minimized by slip layer at the boundary between the microtubule and cytosol. Formation of the slip layer depends on large deformability of microtubules at low stress and on the ionic layer at their surface. Energy supplied to the microtubule from the hydrolysis of GTP to GDP may be sufficient for excitation.

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