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Electric field around microtubules

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Abstract

Living cells are organized by the cytoskeleton with a fundamental role of microtubules. The mechanisms of organization are largely unknown. We analyze the vibrations in the microtubules which are polar and are accompanied by polarization waves. Oscillating electric field generated around microtubules can be as high as 10^5 Vm^{-1} and may have an important role in information system and mass transport in living cells. Energy from hydrolysis of guanosine triphosphate (GTP) stored in microtubules can excite the vibrations above thermodynamic equilibrium level. © 1998 Elsevier Science S.A. All rights reserved.

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1. Introduction

Living cells are structurally and dynamically organized by protein polymer network which is called cytoskeleton. The cytoskeleton is a highly dynamic structure which reorganizes continually as the cell changes its shape, divides, and responds to its environment. The essential data and description of the cytoskeleton, its components, and function are given in the book by Alberts et al. [1]. The cytoskeleton is composed of intermediate filaments, of actin filaments (which are also called microfilaments), and of microtubules. The filaments and the microtubules are connected to a large variety of accessory proteins and form a three dimensional network in the cell. The cytoskeleton is connected to transmembrane proteins. The cytoskeleton enables transport of molecules, structures, and organelles (by means of motor proteins), receives signals from cellular environment through the membrane proteins, and has an important role in the mitotic spindle.

The microtubules are the main organizers of the cytoskeleton. They are formed by cylindrical structures (hollow tubes with the outer and the inner diameters of about 25 nm and 17 nm, respectively) composed of 13 (or 14) protofilaments which are one dimensional chains of heterodimer tubulin molecules. The structure of the microtubules was disclosed by Amos and Klug [2]—Fig. 1a. A tubulin molecule is formed by two globular proteins—α- and β-tubulins; each of them has the relative molecular mass of about 55,000 ('molecular weight' in daltons) but the masses are not equal. Conformation of the heterodimer molecule can be changed from the α state (non tilted) to the β state (tilted by 29° from the microtubule axis)—Fig. 1b. The heterodimer molecule is an electric dipole [3–5] (18 Ca^{2+} ions are bound in the β-monomer). Therefore, the microtubules are polar structures with the plus end (fast growing) and the minus end (slow growing) embedded in the centrosome—a centre of the cytoskeleton. Polarity of the microtubules are closely connected with their function [6,7]. The function of the microtubules can be regulated by phosphorylation and dephosphorylation of microtubule-associated tau protein [8].

The dynamics of the microtubules is one of the most prominent features. The microtubules are capable of rapid polymerization and depolymerization [9] which enables exchange of the subunits between soluble and polymer pools. The microtubules grow toward the cell periphery and then shrink back toward the centrosome. They may shrink partially and grow again or they may disappear to be replaced by new microtubules. This process is called the dynamic instability. The treadmilling (i.e. addition of the tubulin subunits at the plus end and removal of the tubulin subunits at the minus end at an identical rate)

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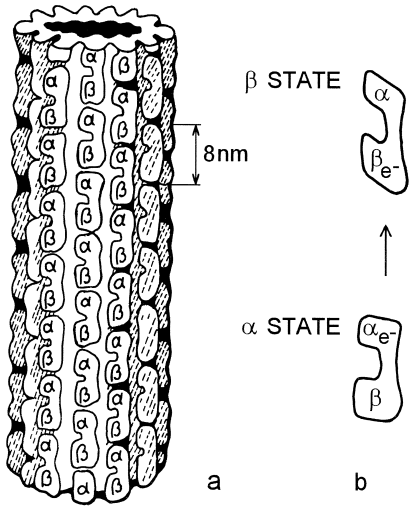


Fig. 1. A schematic picture of a microtubule (a), and of conformation change of a tubulin heterodimer from the α to the β state (b). After Refs. [2,4].

appears if both the ends of a microtubule are exposed [1]. Newly polymerized subunits (heterodimer molecules) contain energy rich nucleotide guanosine triphosphate (GTP). After polymerization the guanosine triphospate molecules bound to the β-tubulins are hydrolyzed to the guanosine diphosphate (GDP). The significance of the GTP in microtubule dynamics is analysed in Refs. [10–12]. The growth of a microtubule can continue if an energy rich cap at its plus end is maintained, i.e. if the GTP's in the cap subunits are not hydrolyzed to the GDP's. The microtubule dynamics may depend on kinetochores too [13].

The microtubules depolymerize and repolymerize continually in animal cells. The majority of the microtubules can incorporate new subunits within 20–30 min although complete exchange of the subunits in a cell can be achieved within 1 h [14]. The half-life of an individual microtubule is of about 10 min [1]. Depolymerization removes the subunits with the GDP and repolymerization adds the energy rich subunits with the GTP to a microtubule. The hydrolysis energy is not used for polymerization. The majority of the hydrolysis energy is stored in the microtubule [15]. The mechanism of depolymerization and repolymerization provides continual supply of energy into the microtubule structures in a cell and signifies that the total energy storage is renewed within one hour.

The mechanisms of the cytoskeleton activity are still not well understood. The cytoskeleton exerts forces and generates movements without any major chemical changes [1]. A physical mechanism is probably responsible for the cytoskeleton function. Vibrations in the microtubules can be one of possible mechanisms as follows from the analysis given in Ref. [16]. As the tubulin heterodimers are polar the vibrations generate an oscillating electric field. The vibrations can be excited by the energy released from the hydrolysis of the GTP. The excited vibrations may be far from thermodynamic equilibrium and need not be of random nature. We will analyze the properties of the electric field generated by the microtubules and its possible effects on ordering and on the mass transport in living cells.

2. Vibrations in the microtubules

A part of the microtubule composed of protofilaments is shown in Fig. 1a. Fig. 1b shows the tubulin heterodimer molecule in the α and in the β states. The globular tubulins in a protofilament may be considered as mass units in a chain with translation symmetry. These units have internal vibrations (exerted by atoms and by parts of the tubulins) and external vibrations in the chain (i.e. the vibrations exerted by each tubulin as a whole). On account of translation symmetry the external vibrations may be analysed using a method which is similar to that employed in the solid state physics [17]. Nevertheless, we have to point out certain differences between crystalline solids with translation symmetry and the microtubules. The 'diameters' of atoms in solids are of about 0.1 nm and the distances between their centres are about twice or three times greater. The 'diameters' of the tubulins are of about 4 nm; they are only slightly smaller than the distances between their centres of mass. Atoms in a lattice are not rigid but in comparison with them the tubulin globules are highly elastic particles. The external vibrations will be analyzed without including dynamic deformations of tubulin globules.

Fig. 2 shows a scheme of the one-dimensional chain of particles. The circles denote the centres of mass of tubulins in equilibrium positions, the black spots show the theoretical equidistant control points (the distance between them is a), Δ_1, Δ_2 are distances of tubulins from the corresponding control points, m_1, m_2 are masses of tubulins, and f_1, f_2 are the elastic force constants which need not be equal.

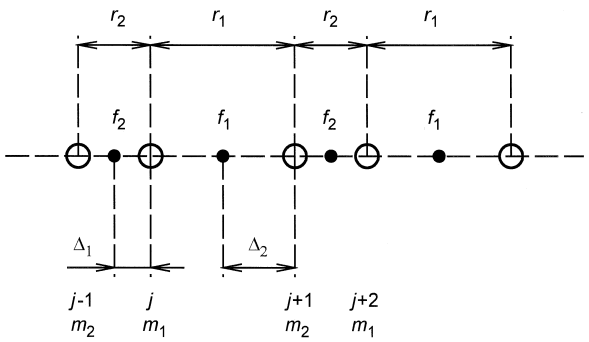


Fig. 2. Translation symmetry in a protofilament.

The interactions between the closest neighbours will be assumed. The dispersion relation is given by [16]

$$\omega_{\pm}^2 = \frac{(f_1+f_2)(m_1+m_2)}{2m_1m_2} \pm \sqrt{\left[\frac{(f_1+f_2)(m_1+m_2)}{2m_1m_2}\right]^2 - 4\frac{f_1f_2}{m_1m_2}\sin^2 ka} \quad (1)$$

where k is the absolute value of the wave vector and ω_+ and ω_- denote the frequencies of the optical and of the acoustical branches of vibrations, respectively. In the acoustical branch the neighbouring particles (tubulins) move in the same direction and in the optical branch the particles move in opposite directions under condition that the centre of gravity remains at rest [17]. The term vibration mode is used for the waves propagating in both directions along the chain with the same absolute value k of the wave vector.

The protofilaments in a microtubule are bound and build up a wall of a cylinder. The vibrations in particular protofilaments are not independent and form a common vibration system in a microtubule. As a microtubule is composed of 13 protofilaments we assume, that a microtubule 'particle' has 13 times greater mass than a protofilament 'particle' (this assumption may be considered as a zero order approximation). The elastic force constants in isolated parts of the protofilaments (oligomers) and in the microtubules may be different. Frequency vs. absolute value of the wave vector evaluated from Eq. (1) is shown in Fig. 3a for $f_1 = f_2$ and in Fig. 3b for $f_1 = 10f_2$ [16]. The elastic force constants are parameters of the curves. We used several values for the elastic force constants as they can vary in a wide range of values. We will not discuss here the dependence of the elastic force constants on the viscoelastic properties of the cytoskeleton including the entanglements, cross-linkings, and lengths of microtubule sections and filaments as it is beyond the scope of this paper. The reader may find it e.g. in Ref. [16]. We only note that they may be determined from the elastic shear moduli and Young's moduli. Fig. 3a,b shows strong dependence of the frequency of the vibrations on the elastic force constants [16].

The microtubule chain is composed of discrete mass units which we denote microtubule 'particles' and, therefore, the frequency spectrum of the vibrations is discrete. The boundary conditions enable us to determine the absolute values of the wave vector k. If we assume that the tubulins at the end of the microtubule are at rest we get [17]

$$k = \frac{\pi}{Na}g \quad (2)$$

where $N+1$ is the number of microtubule 'particles' in the chain, g is an integer $(1 \le g \le N-1)$, and the length

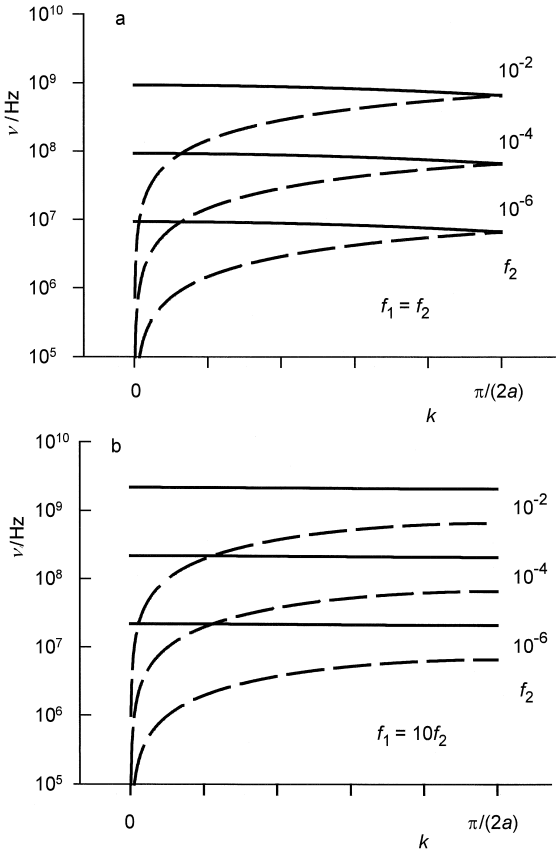


Fig. 3. Dispersion relation for a microtubule (frequency vs. wave vector). The full lines and the dashed lines denote the optical and the acoustical branches, respectively. Elastic force constants are assessed $f_1 = f_2$ (a), $f_1 = 10f_2$ (b). After Ref. [16].

of the microtubule is $L_m = Na$. The number of modes in one branch of vibrations is equal to the number of mobile particles (in the Brillouin zone). We will assess the lowest frequency of the acoustical branch. For a microtubule the lowest frequency for $\nu \neq 0$ of the acoustical branch is in the band of 5–50 MHz if the length of a microtubule is 10 μm $(= \lambda/2)$ and velocity of the acoustical waves is in the range from 10^2–10^3 ms^{-1}.

If the elastic force constants in a heterodimer and between two heterodimers are not equal (i.e. $f_1 \neq f_2$) the potential of 'the tubulin particle' as a function of distance is asymmetric with respect to the equilibrium position. Therefore, the system is non-linear and higher harmonic components (i.e. $\omega = n\omega_j$) and components with combination frequencies (i.e. $\omega = n\omega_j + m\omega_k + \ldots$) are generated ($n$, m, ... are integers). The dispersion relation (1) does not contain these harmonic and combination terms.

The biological reality can certainly yield more complicated patterns of vibrations in the microtubules than those derived in this paper as a number of simplifications was used. For example the internal vibrations were neglected and simple rigid structures of the tubulins were assumed. The internal vibrations are combined with the external

vibrations giving rise to complicated spectral patterns. On account of small mass and great values of the elastic force constants the frequencies of the internal vibrations are much higher than those of the external vibrations. The frequency spectrum can contain frequency lines in the millimeter and in the far infrared regions too.

3. Energy supply to the microtubules

When a microtubule grows tubulin heterodimers add to the free plus end and the GTP's attached to the β-tubulins are hydrolyzed to the GDP's [1,10–12,15]. The rate of polymerization may be greater than the rate of hydrolysis and an energy rich cap can be formed at the end of the microtubule. This energy rich cap is hydrolyzed later. The measurements of hydrolysis of the GTP analogue guanylyl-(a,b)-methylene-diphosphonate (GMPCPP) in solution, in tubulin heterodimers, and in tubulin subunits in the microtubules led to a conclusion that the free energy was -5.18, -3.79, and -0.9 kcal mole^{-1} (-21.7, -15.9, and -3.8 kJ mole^{-1}), i.e. 0.22, 0.16, and 0.04 eV per one entity, respectively [15]. Therefore, energy of about 4 kcal mole^{-1} (17 kJ mole^{-1}) was assumed to be potentially available from the hydrolysis of the GTP. A part of the energy is expended on dissociation of the inorganic phosphate P_i but the majority of it is stored in the microtubule lattice [15]. A remeasurement of the dissociation rate constant allowed better estimation of the free energy for hydrolysis and release of P_i which is $+0.7$ kcal mole^{-1} ($+2.9$ kJ mole^{-1}) [18] rather than -0.9 kcal mole^{-1} as was reported in Ref. [15]. The energy stored in the microtubule lattice is assessed to be 1.7 kcal mole^{-1} (7.1 kJ mole^{-1}). We have to emphasize that the measurements of the energy available from hydrolysis were carried out on the GTP analogue GMPCPP.

The experimental findings given e.g. in Refs. [15,18] show that energy from hydrolysis is stored in the microtubules. The form in which the energy is stored in the microtubule lattice is a special issue. Mandelkow et al. [11] assume that the tubulin–GDP subunit prefers a conformation which leads to coiling of the protofilaments and as a consequence energy may be stored in the form of a tense state of the microtubule lattice. Caplow et al. [15] come to the conclusion that energy is stored in protein conformation and presumably as a repulsive force between subunits. A similar mechanism of energy storage in the microtubules is given in Ref. [4], i.e. that energy from the hydrolysis of the GTP to the GDP is imparted into the microtubule lattice via tubulin conformation changes. Real physical mechanisms of energy transformation are irreversible and a part of the energy is always transferred to the random heat vibrations. Even if the energy levels of two conformation states of a tubulin subunit are different (e.g. if the level of the β state is higher than that of the α state) after the transition to the higher energy level a part of the energy which is used to surmount the potential barrier between the conformation states can be transformed into vibration energy. The opposite relaxation process and restoration of the α conformation state should convert energy to the microtubule vibrations too. Creation of the tense state with altered forces between the subunits in the microtubule has to supply energy into the lattice. Therefore, we may assume that energy is stored in the microtubule lattice not only in the conformation changes and in the tense state of the lattice but also in the vibration states. Besides energy stored in the cytoskeleton during polymerization a part of the energy from the ATP hydrolysis supplied to motor proteins moving along a microtubule [1] can be transferred to the microtubule as random excitations of the vibrations.

The energy stored in the microtubule can do work in the cell [15] but a precise manner in which the energy is utilized is still not understood [19]. As the cytoskeleton is not subjected to any major chemical changes [1] the energy has to be used in some biophysical processes. The hydrolysis energy can change bond strength [19] and excite solitons or soliton like waves [3,19]. As it causes the conformation changes of the tubulin heterodimers kink wave reorientation of the heterodimer dipoles can be excited in the microtubule [3]. It can excite the lattice vibrations and polarization waves, which may be coherent on account of the Fröhlich mechanism [19] or the intrinsic non-linear mechanism. (The Fröhlich mechanism is described e.g. in Refs. [20–22]). Regardless of the primary mechanisms of the energy storage at a later stage at least a part of it is always supplied to the vibrations in the microtubules. Nevertheless, the majority of the energy stored in the microtubules may be converted into the vibrations. Therefore, the vibrations are excited and can be far from thermodynamic equilibrium. We suggest that the mechanism of the coherent polar vibrations in microtubules utilizing the stored energy is a tool for the microtubule organization function. The electric fields generated by the polar vibrations can do work in the surroundings of the microtubules. A mechanism of this type (large scale quantum coherent phenomena in microtubules) is suggested and supported by theoretical analysis e.g. in Refs. [23,24]. The mechanism discussed e.g. in Ref. [23] assumes interaction between coherent modes in the microtubule with water in its surroundings, especially in the microtubule cavity. Experimental data necessary for assessment of the energy transfer between the microtubule and its ambient medium and of damping of the vibrations are still missing.

We assess the amount of energy which might be supplied to the cytoskeleton vibrations from the hydrolysis of the GTP. If the energy supplied by the hydrolysis of the GTP is 4 kcal mole^{-1} (17 kJ mole^{-1}) then energy per one entity is about 7 times greater than energy in thermodynamic equilibrium in the frequency range from 10^7 to 10^{11} Hz. On account of non-linear mechanism the energy may be accumulated in certain vibration modes.

4. Oscillating electric field

The thermal vibrations are omnipresent and biological systems are no exception. The typical feature of the vibrations in thermodynamic equilibrium is their randomness. Using classical concepts we may state that the 'amplitude' and the 'phase' have no coherent components. The tubulin heterodimers are polar and the vibrations create oscillating dipoles or oscillating multipoles. The polar vibrations generate an electric field. We will adopt a linear model of a microtubule with a length of $L_m = 3$ μm where each heterodimer carries an oscillating electric dipole $p = bel_h$ (e is the elementary charge, $l_h = 8$ nm, and $b = b(x)$ where x is the distance along the microtubule axis). Except for b the dipole moments are identical. The frequency of vibrations $\nu = 100$ MHz and the relative permittivity of the ambient medium $\varepsilon' = 81$. We evaluate the intensity of the electric field along the lines parallel with the microtubule axis.

The intensity of the electric field for random orientations of the dipole moments is given in Fig. 4. (We note that this case may correspond to the thermal vibrations.) E_r and E_x shown in Fig. 4a,b are the absolute values of the intensity in the r and x directions (where r denotes the radial direction perpendicular to the microtubule axis),

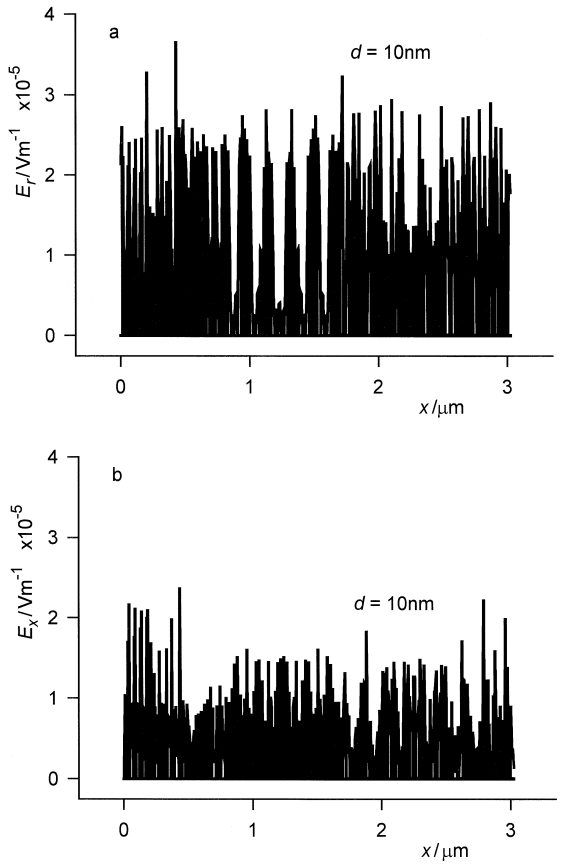


Fig. 4. The thermal vibrations: The absolute value of the intensity of the electric field E_r (a) and E_x (b) as a function of x.

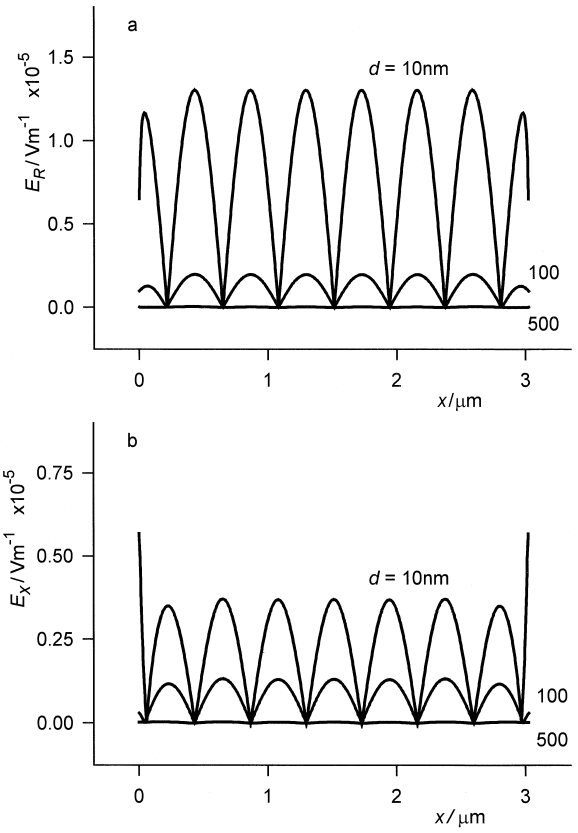


Fig. 5. The coherent vibrations of a vibration mode: E_r (a) and E_x (b) as a function of x.

respectively. The distance d from the 'surface' of the model microtubule is 10 nm. The greatest absolute value of the intensity is of the order of 10^5 Vm^{-1}. At a distance 0.1 and 0.5 μm the peak values are about 10^2 and 1 V m^{-1}, respectively. We used the generator of random numbers to determine the orientations of dipole moments in particular heterodimers ($b = \pm 1$). The intensity of the electric field has random fluctuations in space and time and can decrease to very small values. In the random case the space–time distribution of the dipole moments should correspond to the maximum value of entropy (on account of the Second Law of Thermodynamics).

In thermodynamic equilibrium the Planck's Law determines the distribution of energy in the normal modes. A vibration mode is equivalent to the harmonic oscillator which is subjected to random disturbances. The resulting vibrations are given by superposition of vibrations of all the modes. Nevertheless, under certain conditions the excited vibrations can be far from thermodynamic equilibrium with an important coherent component. In a coherent state certain mode (or modes) is (are) excited; its (their) energy is far from thermodynamic equilibrium value. An example is shown in Fig. 5. Fig. 5a,b shows E_r and E_x, respectively, of the vibration mode $k = 7\pi/L_m$ as a function of x. The distance d is 10 nm, 0.1, and 0.5 μm. The vibrations generate a dynamic periodic potential around

the microtubule. The k value may be considerably greater than that used in Fig. 5 and the period of the standing waves may be comparable in size to the heterodimers. The intensity of the electric field depends on the excitation of vibrations in the microtubule.

5. Discussion

The potential energy U of a dipole in the external electric field E is given by

$$U = -p \cdot E \tag{3}$$

where p is the dipole moment. If $E = 10^6$ V m^{-1}, $p = 10^{-28}$ Cm then the absolute value of U is of the order of 10^{-22} J, i.e. about one order smaller than the energy kT.

The electric field exerts forces on charges, dipoles and multipoles, and even on neutral molecules and particles on account of dielectrophoretic effect. For instance the force exerted on a dipole by the generated field is equal to the gradient of the scalar product

$$F = \nabla(p \cdot E). \tag{4}$$

If the intensity of the electric field decreases from 10^6 to 10^5 V m^{-1} within a distance of 10 nm then for a dipole moment $p = 10^{-28}$ Cm parallel to the intensity of the electric field the force is of the order of 10^{-14} N. The force acts in the direction of the gradient if the dipole is free, i.e. if it is capable of the flip–flop reorientation of the dipole moment.

The inhomogeneous electric field can exert forces on and cause translation motion of neutral dielectric particles. The particle is polarized and the field acts on the induced dipole. The relation for the dielectrophoretic force can be written in the form [25,26]

$$F \propto V(\varepsilon_2' - \varepsilon_1')\varepsilon_0 \nabla(E^2) \tag{5}$$

where ε_2' (ε_1') is the relative permittivity of the particle (of the ambient medium), ε_0 is the permittivity of free space, and V is the volume of the particle. If $\varepsilon_2' > \varepsilon_1'$ the particle is attracted in the direction of the gradient of the intensity of the electric field. If $\varepsilon_2' < \varepsilon_1'$ the force acts in the opposite direction (i.e. the particle is expelled from the field). If the difference of $\varepsilon_2' - \varepsilon_1' \approx 70$, $V = 10^{-27}$ m^3 we can derive for the same electric field as in the case of the dipole that F is of the order 10^{-16} N.

If the vibrations in particular parts of the source structure are random then the generated electric field has the same random properties. If the vibrations are coherent the generated electric field is coherent too. The oscillating electric field in biological systems may have an important role in cell signaling system. Motion of matter and its transport may be caused or organized by the electric oscillating field generated by the cytoskeleton (especially the long distance transport). The endogenous electric field generated by the microtubules can be an organizing factor in living cells.

6. Conclusions

The thermal vibrations are an omnipresent phenomenon existing in inorganic as well as in organic and biological matter. A method similar to that employed in the solid state physics can be used to analyse vibrations in the microtubules. The optical and the acoustical branches of vibrations can exist in microtubules. As the tubulin heterodimer molecules are polar the vibrations generate an oscillating electric field. Generation of the electric field by the microtubules was not analysed yet.

The energy supplied from the hydrolysis of the GTP's to the GDP's can cause excitations of the vibrations to a state far from thermodynamic equilibrium. The generated electric field can have a strong effect on the long distance mass transport and on the organization of chemical reactions in living cells.

Acknowledgements

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