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Electromagnetic communication between cells through tunneling nanotubes

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Research Paper

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Abstract

Structures of tunneling nanotubes (TNTs) of the circular cross-section of 50 and 200 nm and length up to 1 mm form a communication system between cells. While transport of material such as endocytic vesicles, mitochondria, proteins, cytoplasmic molecules, etc., is experimentally proven, a possible transfer of electric and electromagnetic energy across TNTs corresponding to electrotechnical processes of excitation, propagation, and amplification in cavity systems is yet in a beginning stage of research. The ideas presented in this paper are based on technical mechanisms applied to submicroscopic systems. Main features of corrugated periodic structures, electromagnetic circular waveguides, the Manley–Rowe amplification, the Fröhlich non-linear interaction of coherent electric polar vibrations, and description of cut-off frequency propagating limits in the waveguide and cavities and along periodic structures are discussed. We suggest that cell-to-cell connection with TNTs may form a unified coherent cavity system which enables simultaneity and mutual cooperation in multicellular organisms.

Introduction

A striking property of biological systems regardless of their physical dimensions is their simultaneity in various dynamic processes, their subsequent continuation, their cooperation, and control at long distance. Information transfer and evaluation also belong to their unique activities. These special features are closely connected with the living state. A basic process which transfers a non-living material to a living state was searched in specific morphological transformations, biochemical reactions, cellular organization, etc. However, valence electron forces and dispersion forces are of a short-range nature (several nm) while the processes such as simultaneous cellular functions should be controlled over a long distance. This idea corresponds to a scientific requirement to formulate a general law of life governing all living systems. High velocity of propagation, fast interaction of components, and strong exerted forces are typical properties of electromagnetic field.

Coherent electromagnetic state generated in biological systems is considered to be a general condition of life. Excitation of the electromagnetic field can provide correlation of all biological processes and their correct function. These functional requirements can be fulfilled by the electromagnetic field which regardless of being generated by an enormous number of individual sources can form a unified system for organization, regulation, control, and signaling in biology. Generally, from the point of view of energy, the biological systems are far from thermodynamic equilibrium. Fröhlich [1–5] formulated a hypothesis of coherent electric polar vibrations in biological systems. Pohl *et al.* [6] measured the attraction of dielectric particles with high polarization to living cells. Direct measurement of biological electromagnetic field was performed by Hölzel [7] in the frequency range 1.5–52 MHz. Measurement at about 20 MHz is described by Pokorný [8]. Sahu *et al.* [9, 10] measured resonant frequencies of isolated microtubules from the classical to the UV frequency range. Kasas *et al.* [11] assumed that vibrations are a signature of life. Coherent electromagnetic state far from thermodynamic equilibrium excited and maintained by energy supply is assumed to be a principle condition of life by Pokorný *et al.* [12, 13]. Organization, transfer of information, and control depend on the generated electromagnetic field. The field has to be coherent, i.e. having the same phase not only in a cell but in a tissue and in the whole biological body. Interactions between cells and different tissues have to provide a coherent state. Tubulin nanotubes providing cell-to-cell connection may be an important part of electromagnetic communication and generation of a coherent state. This work suggests a waveguide-like functionality of tubulin nanotubes and brings a calculated estimate of their basic parameters. The work is an extended version of a proceedings paper [14].

Cell-to-cell communication

Nanotubes between cells

Apart from long-distance neuro-hormonal signaling, direct cell-to-cell communication is of crucial importance in multicellular systems. Direct communication is required to provide

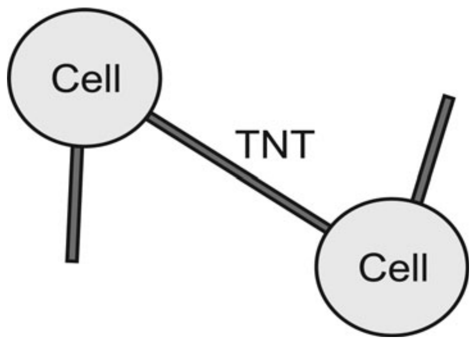

Fig. 1. A schematic picture of cells connected by TNTs [14].

simultaneity and continuity of fundamental biological processes while neuro-hormonal signaling provides a higher-level central control. Very likely the most significant intercellular connecting structures in mammals are tunneling nanotubes (TNTs) as described by Rustom *et al.* and Scholkmann [15, 16]. A schematic layout of a TNT is shown in Fig. 1. TNTs are also called membrane nanotubes by Zhang and Zhang [17] or intercellular nanotubes by Hurtig *et al.* [18]. The diameters of TNTs range from 50 to 200 nm and their lengths are in most cases up to several cell diameters. As an extreme case, the primary cell cultures prepared from human laryngeal squamous cell carcinoma samples exhibited cell-to-cell communication over a distance up to 1 mm through TNTs as described by Antanavičiūtė *et al.* [19]. The TNTs have been observed in many cell types *in vitro* and also in developing embryos of different species *in vivo* by Gerdes *et al.* [20]. Cells can actively exchange small membrane carriers through the channels which provides evidence for a new mechanism of cell-to-cell communication as was observed by Rustom *et al.* [15]. TNTs are ultrafine membranous channels containing F-actin and microtubules, formed between cells that were previously in contact or developed from extending protrusion of one of the cells [17]. TNTs transport different material objects such as endocytic vesicles, mitochondria, plasma membrane proteins, cytoplasmic molecules, etc. An overview of the cell-to-cell communication between cells is provided by Gerdes and Pepperkok [21] and Bloemendal and Kück [22].

Physiological and pathological implications of TNT formation between cells are analyzed, and the function of these communication bridges is described by Sisakhtnezhad and Khosravi and Lu *et al.* [23, 24]. TNTs promote intercellular microbial transport to T24 bladder cancer cells followed by an increase of their invasiveness as described by Lu *et al.* [24]. Measurement of electrical activity across a cell is described by Bathany *et al.* [25]. Mitochondrial transfer from mesenchymal stromal cells (MSC) to innate immune cells leads to enhancement in phagocytic activity (which is an antimicrobial effect of MSC) [26]. TNT cell-to-cell transport of proteins and organelles such as mitochondria affects metabolism. Mesenchymal stem cells recruited to the tumor environment and their important role in tumor progression and resistance to therapy are described by Vignais *et al.* [27].

Evaluation of the function of TNTs disclosed the possibility of neuro-hormonal independent, non-diffusible cell-to-cell signaling as was observed by Chaban *et al.* [28]. Physical modes of communication could be widespread in nature, i.e. communication by sound waves, electromagnetic radiation, and electric current. These signals propagate rapidly and can be efficient even at a low intensity which was assessed by Reguera [29].

TNTs are expected to have important significance for intercellular communication, namely a transfer of electrical signals between remote cells which was described by Wang and Gerdes [30]. The electric coupling depends also on the connections interposed at the membrane interface between TNT and the connected cell. A hypothesis that two modes of energy and signal transmission may occur, i.e. electrical/electrochemical and electromagnetic, was published by Scholkmann [31]. TNTs mediate a bidirectional spread of electrical signals between TNT-connected normal rat kidney cells over distances of 10–70 μm [32]. Long-range cell-to-cell communication by electric signals can be facilitated by TNTs. The significance of electrical cell-to-cell coupling through TNT for neuronal communication has been observed by Scholkmann [31]. His short overview indicates that TNTs are important communication channels for the transfer of chemical, electrical, and electromagnetic signals.

It is reasonable to assume that connections between cells can be mediated by electric current if the electric conductivity of TNTs is increased, by dipole and multipole oscillations of the TNT membrane, and by electromagnetic excitation of the cavities of cells and TNTs by the field generated by microtubules and connected structures. Coherent excitation of the cavities seems to be important for biological functions. TNTs and cell cavities may form a united cavity system capable to provide a sufficient level of electromagnetic activity for all cells, even for the “weak” or “injured” ones. The cavity system thus should stabilize the function of the whole tissue. Our analysis of the system includes a theory of cavity waveguides and resonators and transfer of electromagnetic energy between different frequency modes. The microtubules are oscillators in a wide frequency spectrum from classical frequency bands up to UV spectrum which follows from the measurements of Sahu *et al.* [9, 10]. Scholkmann [16] emphasizes a large amount of mitochondria inside TNTs and suggests their role as the sources of energy for electric currents and electromagnetic fields. TNTs contain cytoskeleton components; most TNTs contain F-actin, some TNTs also contain microtubules. The most widely expressed gap-junction protein, connexin 43, is also present in some TNTs [17].

Electromagnetic field in living systems

Electric polarity depends on charge distribution in the macromolecular structures. It is well known that a peptide bond forms a large electric dipole moment whose inner electric field is oriented from nitrogen to oxygen explained by Pauling resonance between two hybrid electronic structures [33]. Other parts of the polypeptide structure are electrically polar too. One type of polarity of amino acids is formed by ionized side chains (positively and negatively charged), another type by partial atomic charges dependent on the electronegativity of the atom. Polypeptide chains and other chain compounds can contain short regions behaving like solid-state periodic systems with electrons moving in the “conduction” band or strictly bound in the “valence” band. The electrons in the “conduction” band can oscillate at high frequencies in the UV region and absorb or release photons.

An important protein structure in eukaryotic cells is formed by microtubules built from heterodimers consisting of two monomers called α and β tubulin. Each heterodimer represents an electric dipole originating from 18 calcium ions bound approximately between α and β monomers as described by Satarić *et al.* and Tuszyński *et al.* [34, 35]. An equal number of negative charges (electrons) is localized in the neighboring α monomer. After

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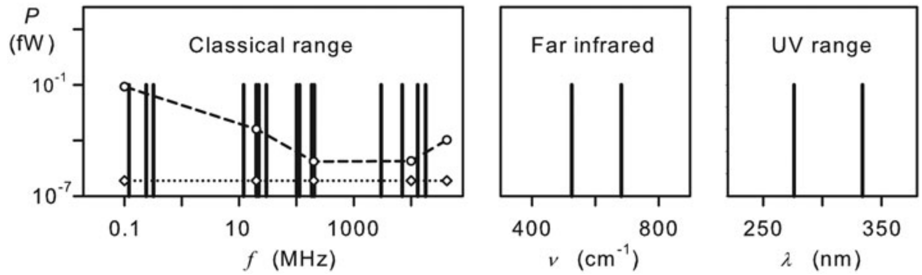

Fig. 2. Spectrum of microtubule resonant frequencies in the classical range below 20 THz, in the far infrared, and UV regions. The dashed line in the classical frequency range is evaluated from the Fröhlich rate equation. The dotted line denotes estimated excitation power. Significant Raman spectral lines are at about 526 and 686 cm^{-1}. Excitation and emission spectral lines in the UV range are 274 and 330 nm, respectively; the other spectral lines exhibit wavelengths: excitation 274, 561 nm and emission lines 671, 330 nm (not plotted) – measured by Sahu *et al.* [9, 10].

polymerization, the main component of the electric dipole vector is oriented along the axis of microtubule (dipole electric polarity corresponds to the direction fast–slow growing end). Hydrolysis of GTP to GDP in the β tubulin changes its conformation and position of the β tubulin is tilted (about 28°) with respect to α tubulin [34–37]. After hydrolysis of ATP in the β tubulin, the main component of the dipole moment has a reversed orientation.

The described dipole orientation corresponds to microtubules in cells. Heterodimers have the largest component of the dipole moment in the normal direction to their axes (1669 Debye, i.e. 5.567×10^{-27} Cm). The C-termini extended outwardly from the microtubule carry a significant amount of negative electric charge (as much as 40%) of the total monomer amount. Oscillating high-frequency electric field aligns the microtubules parallel to the field direction [38]. The normal components of the heterodimer dipole moment may be compensated along the spiral turn of a microtubule and additon of heterodimer axial components forms a dipole moment along the microtubule axix (ferroelectric state) [39] or the electron charge forming the electric dipole may change their position in the microtubule (a redistribution of electrons may enhance or reduce the transverse component of the dipole moment in heterodimers). The kink excitation and propagation along the microtubule axis [39], and electromagnetic excitation of the inner microtubule cavity in the UV region may be important factors for the dipole orientation along the microtubule axis (after the release of water from the inner cavity, microtubule oscillations disappear [9]).

The energy state far from thermodynamic equilibrium is excited and maintained by energy supply. Important life processes and biological functions can be provided by a coherent electromagnetic field as suggested by Pokorný *et al.* [12, 13, 40]. A considerable part of the power supply to a cell (of the order of magnitude of 0.1 pW, as estimated from the metabolic turnover of a body and a number of cells) should excite coherent vibrations and coherent electromagnetic field. A microtubule is excited by about 0.1 fW and this power is distributed to the dipoles in all heterodimers which generate the electromagnetic field in the frequency spectrum up to and in the UV region. Some spectral lines can be selectively excited as follows from the excitation–emission measurements. Figure 2 displays resonant frequencies of microtubules measured in classical, far infrared, and UV regions by Sahu *et al.* [9, 10]. Power of the energy supply to a heterodimer dipole is of the order of magnitude of zW. Microtubule vibrational peaks condensed in a single mode and noise alleviation disappear when water is released from the inner microtubule cavity which was proved by Sahu *et al.* [9]. The UV spectrum has a specific property – excitation and emission lines exhibit different wavelengths: the excitation line 274 nm corresponds to emission lines 330 and 671 nm, and the excitation line 561 nm corresponds to the emission line 330 nm (the first excitation and emission lines are plotted in Fig. 2).

The electromagnetic spectrum in the UV region may have components in the short-wavelength UV part. Gurwitsch and Frank and Gurwitsch observed a weak radiation from onion roots in the UV region 193–237 nm and assumed their mitogenic function [41, 42]. Microtubule inner circular cavity with a diameter of 17 nm has properties of a resonator and/or of a waveguide which was analyzed by Jelínek and Pokorný [43]. Calculated cutoff frequencies of the transverse magnetic (TM) and transverse electric (TE) modes in a circular cavity with reflecting walls are presented under 'Microtubules and nanotube energy transfer'. The calculated cutoff frequencies of TNTs are lower but also in the short-wavelength part of the UV region.

Periodic structures

Frequency of resonance and propagation of the electromagnetic field in the cavities depend on geometrical dimensions of the cavity and permittivity and permeability of the medium inside it. Under the cutoff frequency, there is a region of evanescent modes. Transfer of electromagnetic signals in this frequency range is governed by structures inside the cavity. For example, if the cavity walls are not physically smooth, an effective increase of the shunt capacitance per unit length can be achieved without the decrease of a corresponding series inductance. The phase velocity of the propagating field is decreased compared to a plain waveguide. The lumped capacitance at periodic distances smaller than the wavelength of the electromagnetic field is used. An example of such a periodic structure shown in Fig. 3 is described by Collin in [44]. If the dimension a is large compared to b and this in turn is small compared to the wavelength of the electromagnetic field, the transfer is optimal.

The electromagnetic field can propagate in a limited space region to prevent damping at the cavity walls and be transferred along a guiding way. Propagation of the electromagnetic signals can also occur along a helix (or a sheath helix) which is another method of realization of a periodic structure. A conductive tape with helical structure is separated by a thin insulated slit. Conductivity along the tape is infinite (and, consequently, the current too) and zero in the perpendicular direction. However, all methods have passband–stopband characteristics. There are frequency bands throughout which a wave propagates unattenuated and bands through which the wave does not propagate [44].

Microtubules are helical structures while in TNTs the periodic structure may be formed by extensions of the membrane into the inner TNT cavity, by mitochondria which can be periodically arranged along the TNT and similarly by lumped macromolecules and structures such as microtubules. The helical periodicity of microtubules is convenient for the generation of the

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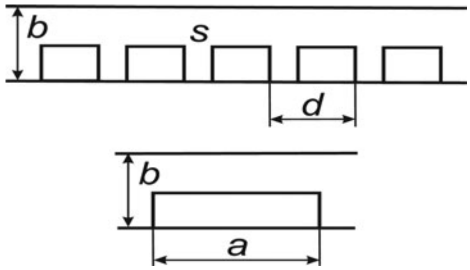

Fig. 3. Corrugated plane periodic structure with thick teeth [44]: *a* – tooth length, *b* – spacing between waveguide walls, *d* – teeth periodicity, *s* – teeth gap.

electromagnetic field at distinct frequencies. Mitochondria form a layer of hydrogen ions in the cytosol space with an attached layer of ordered water [45]. The induced changes of series capacitance C per unit length (as well as inductance L per unit length) result in changes of the energy storage and transfer, i.e. changes of phase velocity of the propagation of the electromagnetic field (the phase velocity is given by the relation $v_f = (LC)^{-1/2} = (\mu\mu_0\varepsilon\varepsilon_0)^{-1/2}$ where μ and ε are the relative permeability and permittivity, respectively). The wavelengths in the UV frequency range may be comparable or even shorter than dimensions of the reflecting lumps, and the propagation of the electromagnetic wave may be described by short time and space periods. The narrow ordered water layer at the upper surface of mitochondria proton layer forms a channel for the transfer of electromagnetic signals. Ordered water forms a dielectric or a conductive material (by releasing electrons) for different pH values [46]. The phase velocity depends on permittivity and permeability of the ordered water which seem to be different from those of the normal (bulk) water. The layers of ordered water in the TNT may form convenient conditions for the propagation of the electromagnetic field.

Localization of mitochondria inside a TNT indicates that their function is connected with energy supply [16]. The additional energy supply may amplify electric or electromagnetic signals entering the TNT. Two possible amplification concepts are introduced: parametric amplification in a wave that has multiple frequencies, and Fröhlich's approach involving interaction with a heat bath.

Parametric amplification

Parametric amplifiers utilize non-linear properties of the medium or properties that can be varied as a function of time. In the technological region of electrical engineering, it concerns a non-linear reactance or a reactance oscillating as a function of time after the application of a suitable pump signal. Original description of Manley and Rowe [47] is further analyzed in [44] and [48]. Parametric amplification is mainly based on the time variation of a reactive parameter. The most notable variable reactance was produced by a semiconductor diode called a varactor. The analysis of these devices is based on the Manley–Rowe power relations

$$\sum_n \sum_m \frac{nP_{n,m}}{n\omega_1 + m\omega_2} = 0, \; \sum_m \sum_n \frac{mP_{n,m}}{n\omega_1 + m\omega_2} = 0, \qquad (1)$$

where n and m are the integers; in the first equation, n and m (in the second equation m and n) vary from 0 to $+\infty$ and from $-\infty$ to $+\infty$, respectively. There are two important applications called negative resistance parametric amplifier and parametric up-converter. The negative-resistance systems use the pump frequency ω_P, the idler frequency $\omega_I = \omega_P - \omega_S$ and the input and output signal frequencies ω_S are equal. For the signal frequency ω_S, the indices are $m = 1$ and $n = 0$, for the pump frequency ω_P, they are $m = 0$ and $n = 1$, for the idler frequency ω_I, they are $m = -1$, $n = 1$, and the corresponding powers are $P_S = P_{1,0}$, $P_P = P_{0,1}$, $P_I = P_{-1,1}$. (Power supplied to the non-linear element is positive, the delivered power is negative.) From the Manley–Rowe relations we get

$$\frac{P_{1,0}}{\omega_S} - \frac{P_{-1,1}}{-\omega_S + \omega_P} = 0, \; \frac{P_{0,1}}{\omega_P} + \frac{P_{-1,1}}{-\omega_S + \omega_P} = 0 \qquad (2)$$

and a maximum signal gain

$$\frac{-P_{0,1}}{P_{1,0}} = \frac{\omega_P}{\omega_S}. \qquad (3)$$

The up-converter uses the input signal at the frequency ω_S ($m = 1$, $n = 0$), pump signal at the frequency ω_P ($m = 0$, $n = 1$), and the amplified and up-converted output signal exhibits the frequency $\omega_S + \omega_P$ ($m = 1$, $n = 1$). For the up-converter $Ps = P_{1,0}$, $P_P = P_{0,1}$, and the up-converted power is $P_{1,1}$. From the Manley–Rowe relations we get

$$\frac{P_{1,0}}{\omega_S} + \frac{P_{1,1}}{\omega_S + \omega_P} = 0, \; \frac{P_{0,1}}{\omega_P} + \frac{P_{1,1}}{\omega_S + \omega_P} = 0 \qquad (4)$$

and a maximum signal gain

$$\frac{P_{0,1}}{P_{1,0}} = \frac{\omega_P}{\omega_S}. \qquad (5)$$

The maximum signal gain depends on frequency relations of the input and pump signals. Parametric amplifiers can be important for the amplification of electromagnetic signals propagating in the TNT as in a cavity waveguide. The negative-resistance parametric amplifier could mediate communication between cells with similar electromagnetic activities. Both connected cells would then generate signals with the same frequencies. The up-converter system could connect different frequency components of the generated electromagnetic field.

Fröhlich relation

Fröhlich analyzed basic properties of a biological energy system excited by its energy supply and proposed spectral energy transfer based on emission–absorption interaction with a heat bath [1–5]. He assumed energy supply to electric polar vibrations resulting in coherence and a strong excitation of one or a few modes of motion. The vibration system is stabilized due to low emission and friction losses, phases correlated over macroscopic regions, and superimposed on random thermal fluctuations. He assumed oscillating properties of the heat bath in biological systems formed by macromolecules and macromolecular structures which contain an extremely wide quasi-continuous spectrum of random electric polar vibrations. Fröhlich analyzed extraordinary dielectric properties, derived relation for the metastable ferroelectric state of

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biological systems [4], and suggested that cancer cells have shifted frequencies of their electromagnetic activity disturbing interactions with healthy cells [49]. Fröhlich formulated the main properties of the cellular electromagnetic activity and the rate equation in the form

$$\begin{aligned}\dot{n}_i = s_i - \phi_i[n_i \exp(\beta\nu_i) - (n_i + 1)] \\ - \sum_j \chi_{ij}[n_i(n_j + 1)\exp(\beta\nu_i) - (n_i + 1)n_j \exp(\beta\nu_j)],\end{aligned} \tag{6}$$

where n_i and n_j are the numbers of energy quanta in the modes with frequency ν_i and ν_j, respectively, $\dot{n}_i$ is the first derivative with respect to time, ϕ_i and χ_{ij} are the coefficients of energy transfer, and s_i is the energy supply (in the number of energy quanta).

The Fröhlich rate equation describes energy transfer between oscillation modes in a frequency spectrum of a non-linear system. Energy condenses in the lowest frequency mode but condensation depends also on the coupling to the heat bath, energy transfer between modes (parameter χ_{ij}) and energy supply (s_i). The analysis of energy condensation for various conditions is evaluated in Pokorný and Wu [48].

Microtubules and nanotube energy transfer

In eukaryotic cells, microtubules form a well-organized filamentous structure which is a basis of the cytoskeleton. Microtubules are hollow tubes of a circular cross-section with the inner and outer diameter 17 and 25 nm, respectively, described by Amos and Klug [50]. In the interphase, they grow outward from the centrosome, a spherical structure in the center of the cell, and form radial fibers. Long-living microtubules (about 18 h) are bonded to structures at the membrane. In the M phase (cell division), the microtubules of the mitotic spindle emanate from two centrosomes.

Microtubule physical characteristics correspond to requirements for the generation of the electromagnetic field: they are electrically polar, non-linear, and excited by energy supply. Microtubules in cells are electric dipoles whose dipole moments differ from those in free microtubules (measured by Böhm *et al.* [38] and Schoutens [51]) by space orientation. Several mechanisms supply energy for the excitation of polar vibrations. Energy is supplied by the hydrolysis of GTP to GDP in tubulin after polymerization [52, 53], energy losses caused by the motion of motor proteins along microtubules [54], and very likely also by non-utilized energy liberated from mitochondria [55]. Photons released from chemical reactions may supply energy in the UV and visible wavelength region. In the M phase, energy is supplied by treadmilling.

Excitation of the electromagnetic field in TNTs may be a fundamental process of their function. We suggest a possible mechanism. A TNT may be considered as a circular waveguide connecting cells. If the axis of a microtubule coincides with the TNT axis, then microtubule field can excite signal in the TNT (z direction). In this case, the electromagnetic excitation corresponds to a TM mode. The theory of waveguides with conductive walls can be used for the description of excitation of the electromagnetic field as a zero-order approximation. The intensity of the electric field transferred from a microtubule into the TNT waveguide may be amplified if its cavity is excited by energy supply. In the TM mode, the electric field along the axis of the waveguide (in the z direction) may be described by

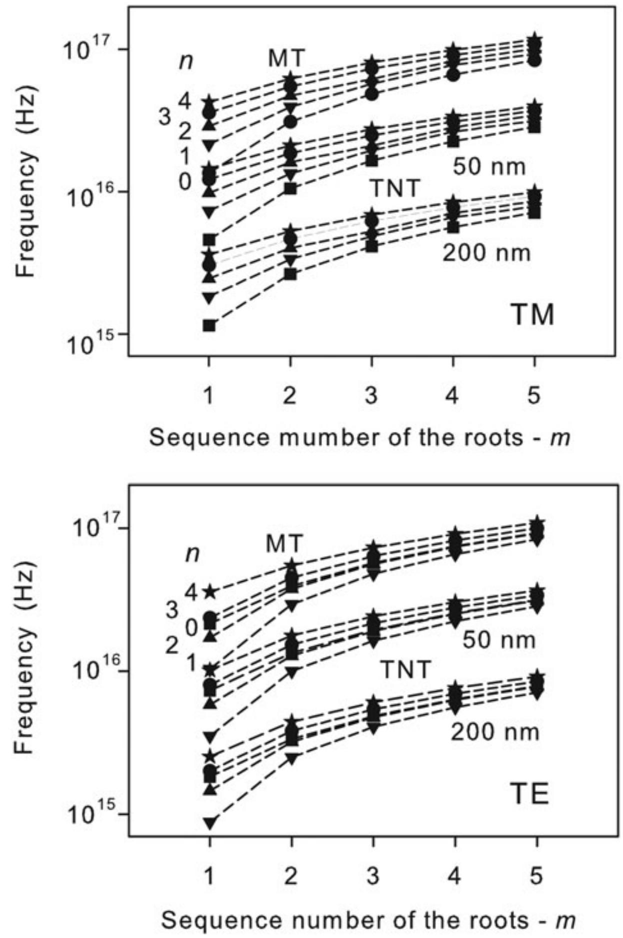

Fig. 4. The calculated cutoff frequencies of circular waveguides with conducting walls corresponding to a microtubule (MT) and a nanotube (TNT) as a function of the sequence number of roots *m* with parameter *n* (the order of the Bessel function). *m* determines the distribution of the electromagnetic field along the radius – radial variations, and *n* settles dependence on the rotation angle along the longitudinal axis – circumferential variations. TM and TE – transversal magnetic and transversal electric field, respectively [14].

$$E_z = \gamma^2 J_n(\gamma r)\cos(n\varphi)[C_1 \exp(j\Gamma z) + C_2 \exp(-j\Gamma z)], \tag{7}$$

where J_n is the Bessel function for $n = 0, 1, 2\ldots$, C_1, C_2 are constants, and j is the imaginary unit. The propagation constants (eigenvalues) Γ, γ, the wavenumber k, and the cutoff frequency ω_c are

$$\Gamma^2 = k^2 - \gamma^2, \quad \gamma = p_{nm}/a, \quad k^2 = \omega^2\mu\varepsilon, \quad \omega_c = \frac{\gamma}{\sqrt{\mu\varepsilon}}, \tag{8}$$

where p_{nm} is the m root of the Bessel function $J_n(\gamma a)$, a is the radius of the circular waveguide (of the nanotube), μ and ε are the permeability and permittivity of the inner medium, respectively. (Technical parameters of circular waveguides and resonators are described in [44].) For a diameter of the circular waveguide 50, 200, and 700 nm, the lowest cutoff frequencies of TM modes (and wavelengths) are 4.6×10^{15} Hz (65 nm), 1.1×10^{15} Hz (261 nm), and 3.3×10^{14} Hz (914 nm), respectively. The calculated cutoff frequencies of TM and TE modes of microtubule inner cavity

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and TNTs are in Fig. 4. A total reflection from the walls is assumed. In real biological systems, a part of the energy should penetrate into the surrounding medium. Except for this, the values of permittivity and of permeability used in evaluation correspond to vacuum. Therefore, the evaluated cutoff frequencies are only a rough approximation of the actual values. It should be noted that the photon energy of signals with frequencies in this region may correspond to the energy of electrons in atoms.

The wave excited in the waveguide (TNT) may amplify electric signals transferred between cells. Generally, TNTs may be parts of a unified cavity system which sustains coherence in the whole space, supplies energy to weaker parts, and provides functional unity.

Discussion

The paper brings a brief overview of tubulin nanotubes, their properties and significance for intercellular communication, and suggests a waveguide-like propagation of electromagnetic field. Description of the possible mechanism is based on the overview of the properties of macroscopic technical systems applied to the submicroscopic biological structures. Cooperation, coordination, simultaneity, synchronicity, and time sequence of processes in multicellular biological systems are irreplaceable. Coherent electromagnetic field is supposed to play a fundamental role in these processes and TNTs form structures for the realization of these requirements. The way of transfer of the electromagnetic field should correspond to standard technological mechanisms known from technical engineering and propagation of electromagnetic waves. TNTs are structures corresponding to waveguides and resonators at very high frequencies, Manley–Rowe amplification and Fröhlich frequency transformation explain spectral development and frequency shifts. Periodicity along the helix and along the axis of the microtubule-generating structure enables space and time coherence of the electromagnetic field.

Observation of TNTs, their structure, and function has led to a discovery of the yet unknown mechanism of communication between cells. These structures can transport material, energy, and information in a reliable way. Cells with TNTs are composed into a unified system forming a cooperating, mutually dependent living community. Non-chemical and non-contact cell-to-cell communication offering a new fundamental insight into biological processes is analyzed by Scholkmann *et al.* [56]. This paper presents an overview of published data and analysis of a possible mechanism of information and energy transfer based on the technology of electromagnetic waves. Some authors assume that electric and electromagnetic energy is transported at least for communication and transfer of coherence [16, 21, 28, 29]. Different mechanisms can transfer electric and electromagnetic signals through TNTs and provide instantaneous communication between cells in biological systems. Possible mechanisms may be also based on electric current in a layer inside TNT with increased conductivity or on the propagation of electromagnetic wave which spectrum is wide – from acoustic frequencies up to UV band. Coherence seems to be provided by signals in the short wavelength part of the UV region which is in agreement with experiments demonstrating the relevance of UV radiation in long-distance communication of living systems [40, 41].

Propagation of electromagnetic field along a TNT cavity is only one possible method. Currents in layers of increased conductivity and oscillations of the TNT membrane may also form a convenient way for the transfer of energy, coherence, and information. The medium inside a TNT may have layers of increased conductivity, for instance by increased concentration of electrons released from ordered water layers formed at charged surfaces [13, 45, 46]. If the pH value is higher than a specific value, the electric field in the layer transports released electrons outside the layer. If the electric conductivity in the TNT is increased, the electric signal may be transferred by electric current. A possible measurement of electrical conductance through a gap junction channel by a microfluidic chip is described by Bathany *et al.* [25]. Another mechanism may depend on the oscillations of the TNT membrane. Electric polar structures in the TNT membrane may be excited and generate coherent electric oscillations mediating communication. There is a large amount of mitochondria inside the nanotubes which may supply energy.

Our short overview manifests a reasonable possibility that electric and/or electromagnetic field are excited inside the nanotube cavity and may amplify the transmitted signals. It points to a strong coupling between cells.

Conclusion

Electromagnetic activity is capable of governing simultaneity not only in a cell or tissue but in the whole biological body which cannot be achieved by diffusion or short-range chemical bonds. This work suggests a unified cavity system formed by living cells connected by TNTs. Our calculations indicate its operation in the short-wavelength UV range. Due to energy condensation, the coherence of signals in the UV spectrum can provide simultaneity of all lower frequency spectral lines. Excitation of the electromagnetic field in the cavity system, transfer of energy across the system, and condensation of energy in some spectral lines provide conditions for the function and organization of the multicellular biological activity. The system providing material and energy transfer would govern tissue orchestration as well as a support function of weak and injured cells. Excitation of the coherent electromagnetic field and its function in the living bodies is supposed to be a fundamental property of multicellular biological systems and should be experimentally investigated. Suggested transfer of the electromagnetic field and its amplification is based on classical technological mechanisms. Formation of nanotubes, their excitation by electromagnetic energy, the parametric amplification, and the Fröhlich spectral energy transfer are assumed to be important mechanisms for interaction, cooperation, and generation of simultaneity in biological systems.

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References

1. **Fröhlich H** (1968*a*) Long-range coherence and energy storage in biological systems. *International Journal of Quantum Chemistry* **II**, 641–649.
2. **Fröhlich H** (1968*b*) Bose condensation of strongly excited longitudinal electric modes. *Physics Letters A* **26**, 402–403.
3. **Fröhlich H** (1969) Quantum mechanical concepts in biology. In Marois M (ed.), *Theoretical Physics and Biology*. Amsterdam, Netherland: North Holland, pp. 13–22. *Proc. 1st Int. Conf. Theor. Phys. Biol.*, Versailles, France, 1967.
4. **Fröhlich H** (1973) Collective behaviour of non-linearly coupled oscillating fields (with applications to biological systems). *Journal of Collective Phenomena* **1**, 101–109.
5. **Fröhlich H** (1980) The biological effects of microwaves and related questions. In Marton L and Marton C (eds), *Advances in Electronics and*

Electron Physics, vol. **53**. Elsevier, Academic Press, New York, London, Toronto, Sydney, San Francisco, pp. 85–152.
6. **Pohl HA, Braden T, Robinson S, Piclardi J and Pohl DG** (1981) Life cycle alterations of the micro-dielectrophoretic effects of cells. *Journal of Biological Physics* **9**, 133–154.
7. **Hölzel R** (2001) Electric activity of non-excitable biological cells at radio frequencies. *Electro- and Magnetobiology* **20**, 1–13.
8. **Pokorný J, Hašek J, Jelínek F, Šaroch J and Palán B** (2001) Electromagnetic activity of yeast cells in the M phase. *Electro- and Magnetobiology* **20**, 371–396.
9. **Sahu S, Ghosh S, Ghosh B, Aswani K, Hirata K, Fujita D and Bandyopadhyay A** (2013) Atomic water channel controlling remarkable properties of a single brain microtubule: correlating single protein to its supramolecular assembly. *Biosensors & Bioelectronics* **47**, 141–148.
10. **Sahu S, Ghosh S, Fujita D and Bandyopadhyay A** (2014) Live visualizations of single isolated tubulin protein self-assembly via tunneling current: effect of electromagnetic pumping during spontaneous growth of microtubule. *Scientific Reports* **4**, 7303.
11. **Kasas S, Ruggeri FS, Benadiba C, Maillard C, Stupar P, Tournu H, Dietler G and Longo G** (2015) Detecting nanoscale vibrations as signature of life. *PNAS* **112**, 378–381.
12. **Pokorný J, Pokorný J and Kobilková J** (2013) Postulates on electromagnetic activity in biological systems and cancer. *Integrative Biology* **5**, 1439–1446.
13. **Pokorný J, Pokorný J, Foletti A, Kobilková J, Vrba J and Vrba J Jr.** (2015) Mitochondrial dysfunction and disturbed coherence: gate to cancer. *Pharmaceuticals* **8**, 675–695.
14. **Pokorný J, Pokorný J and Vrba J** (2019) Electromagnetic communication between cells through tunnelling nanotubes. *2019 European Microwave Conference in Central Europe (EuMCE)*, Prague, Czech Republic.
15. **Rustom A, Saffrich R, Markovic I, Walther P and Gerdes H-H** (2004) Nanotubular highways for intercellular organelle transport. *Science (New York, NY)* **303**, 1007–1010.
16. **Scholkmann F** (2016) Long range physical cell-to-cell signalling via mitochondria inside membrane nanotubes: a hypothesis. *Theoretical Biology and Medical Modelling* **13**, 16.
17. **Zhang JH and Zhang YY** (2013) Membrane nanotubes: novel communication between distant cells. *Science China Life Sciences* **56**, 994–999.
18. **Hurtig J, Chiu DT and Onfelt B** (2010) Intercellular nanotubes insights from imaging studies and beyond. *Wiley Interdisciplinary Reviews. Nanomedicine and Nanobiotechnology* **2**, 260–276.
19. **Antanavičiūtė I, Rysevaite K, Liutkevicius V, Marandykina A, Rimkutė L, Sveikatienė R, Uloza V and Skeberdis VA** (2014) Long-distance communication between laryngeal carcinoma cells. *PLoS ONE* **9**, e99196.
20. **Gerdes HH, Rustom A and Wang X** (2013) Tunneling nanotubes, an emerging intercellular communication route in development. *Mechanisms of Development* **130**, 381–387.
21. **Gerdes HH and Pepperkok R** (2013) Cell-to-cell communication: current views and future perspectives. *Cell and Tissue Research* **352**, 1–3.
22. **Bloemendal S and Kück U** (2013) Cell-to-cell communication in plants, animals, and fungi: a comparative review. *Naturwissenschaften* **100**, 3–19.
23. **Sisakhtnezhad S and Khosravi L** (2015) Emerging physiological and pathological implications of tunneling nanotubes formation between cells. *European Journal of Cell Biology* **94**, 429–443.
24. **Lu J, Zheng X, Li F, Yu Y, Chen Z, Liu Z, Wang Z, Xu H and Yang W** (2017) Tunneling nanotubes promote intercellular mitochondria transfer followed by increased invasiveness in bladder cancer cells. *Oncotarget* **8**, 15539–15552.
25. **Bathany C, Beahm DL, Besch S, Sachs F and Hua SZ** (2012) A microfluidic platform for measuring electrical activity across cells. *Biomicrofluidics* **6**, 034121.
26. **Jackson MV, Morrison TJ, Doherty DF, McAuley DF, Matthay MA, Kissenpfennig A, O'Kane CM and Krasnodembskaya AD** (2016) Mitochondrial transfer via tunneling nanotubes is an important mechanism by which mesenchymal stem cells enhance macrophage phagocytosis in the in vitro and in vivo models of ARDS. *Stem Cells (Dayton, Ohio)* **34**, 2210–2223.
27. **Vignais ML, Caicedo A, Brondello J-M and Jorgensen C** (2017) Cell connections by tunneling nanotubes: effects of mitochondrial trafficking on target cell metabolism, homeostasis, and response to therapy. *Stem Cells International* **2017**, 6917941.
28. **Chaban VV, Cho T, Reid CB and Norris KC** (2013) Physically disconnected non-diffusible cell-to-cell communication between neuroblastoma. *American Journal of Translational Research* **6**, 69–79.
29. **Reguera G** (2011) When microbial conversation gets physical. *Trends in Microbiology* **19**, 105–113.
30. **Wang X and Gerdes H-H** (2012) Long-distance electrical coupling via tunneling nanotubes. *Biochimica et Biophysica Acta* **1818**, 2082–2086.
31. **Scholkmann F** (2015) Two emerging topics regarding long-range physical signaling in neurosystems: membrane nanotubes and electromagnetic fields. *Journal of Integrative Neuroscience* **14**, 135–153.
32. **Wang X, Veruki M, Bukoreshtliev NV, Hartveit E and Gerdes H-H** (2010) Animal cells connected by nanotubes can be electrically coupled through interposed gap-junction channels. *PNAS* **107**, 17194–17199.
33. **Schulz GE and Schirmer RH** (1979) *Principles of Protein Structures*. New York, Berlin, Heidelberg: Springer.
34. **Satarić M, Tuszyński JA and Žakula RB** (1993) Kinklike excitations as an energy transfer mechanism in microtubules. *Physical Review E* **48**, 589–597.
35. **Tuszyński JA, Hameroff S, Satarić MV, Trpisova B and Nip MLA** (1995) Ferroelectric behavior in microtubule dipole lattices: implications for information processing, signaling and assembly/disassembly. *Journal of Theoretical Biology* **174**, 371–380.
36. **Hyman AA, Chrétien D, Arnal I and Wade RH** (1995) Structural changes accompanying GTP hydrolysis in microtubules: information from a slowly hydrolyzable analogue guanylyl-(α, β)-methylene-diphosphonate. *Journal of Cell Biology* **128**, 117–125.
37. **Melki R, Carlier M-F, Pantaloni D and Timasheff SN** (1989) Cold depolymerization of microtubules to double ring: geometric stabilization of assemblies. *Biochemistry* **28**, 9143–9152.
38. **Böhm KJ, Mavromatos NE, Michette A, Stracke R and Unger E** (2005) Movement and alignment of microtubules in electric fields and electric-dipole-moment estimates. *Electromagnetic Biology and Medicine* **24**, 319–330.
39. **Sataric MV and Tuszynski JA** (2005) Nonlinear dynamics of microtubules: biophysical implications. *Journal of Biological Physics* **31**, 487–500.
40. **Pokorný J, Pokorný J, Kobilková J, Jandová A, Vrba J and Vrba J Jr.** (2014) Cancer–pathological breakdown of coherent energy states. *Biophysical Reviews and Letters* **9**, 115–133.
41. **Gurwitsch A** (1924) Physikalisches über mitogenetische Strahlen. *Archiv für Mikroskopische Anatomie und Entwicklungsmechanik* **103**, 490–498.
42. **Frank GM and Gurwitsch A** (1927) Zur Frage der Identität mitogenetischer und ultravioletter Strahlen. *Wilhelm Roux' Archiv für Entwicklungsmechanik der Organismen* **109**, 451–454.
43. **Jelínek F and Pokorný J** (2001) Microtubules in biological cells as circular waveguides and resonators. *Electro- and Magnetobiology* **20**, 75–80.
44. **Collin RE** (1966) *Foundations for Microwave Engineering*. New York, St. Louis, San Francisco, Toronto, London, Sydney: McGraw–Hill Inc.
45. **Pokorný J, Pokorný J and Borodavka F** (2017) Warburg effect – damping of electromagnetic oscillations. *Electromagnetic Biology and Medicine* **36**, 270–276.
46. **Zheng J and Pollack GH** (2003) Long-range forces extending from polymer–gel surfaces. *Physical Review E* **68**, 031408-1–7.
47. **Manley JM and Rowe HE** (1956) Some general properties of nonlinear elements – part I. General energy relations. *Proc. IRE* **44**, 904–913.
48. **Pokorný J and Wu T-M** (1998) *Biophysical Aspects of Coherence and Biological Order*. Praha: Academia; Berlin–Heidelberg–New York: Springer.
49. **Fröhlich H** (1978) Coherent electric vibrations in biological systems and the cancer problem. *IEEE Transactions on Microwave Theory and Techniques* **26**, 613–617.
50. **Amos LA and Klug AJ** (1974) Arrangement of subunits in flagellar microtubules. *Journal of Cell Science* **14**, 523–549.
51. **Schoutens JE** (2005) Dipole–dipole interactions in microtubules. *Journal of Biological Physics* **31**, 35–55.
52. **Pokorný J, Jelínek F, Trkal V, Lamprecht I and Hölzel R** (1997) Vibrations in microtubules. *Journal of Biological Physics* **3**, 171–179.

53. **Pokorný J** (2004) Excitation of vibration in microtubules in living cell. *Bioelectrochemistry* **63**, 321–326.
54. **Pelling AE, Sehati S, Gralla EB, Valentine JS and Gimzewski JK** (2004) Local nanomechanical motion of the cell wall of *Saccharomyces cerevisiae*. *Science (New York, N.Y.)* **305**, 1147–1150.
55. **Pokorný J** (2009) Biophysical cancer transformation pathway. *Electromagnetic Biology and Medicine* **28**, 105–123.
56. **Scholkmann F, Fels D and Cifra M** (2013) Non-chemical and non-contact cell-to-cell communication: a short review. *American Journal of Translational Research* **5**, 586–593.

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