Eur Biophys J (2011) 40:747–759
DOI 10.1007/s00249-011-0688-1

ORIGINAL PAPER

Cancer physics: diagnostics based on damped cellular elastoelectrical vibrations in microtubules

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Received: 9 June 2010 / Revised: 7 February 2011 / Accepted: 17 February 2011 / Published online: 11 March 2011

Abstract This paper describes a proposed biophysical mechanism of a novel diagnostic method for cancer detection developed recently by Vedruccio. The diagnostic method is based on frequency selective absorption of electromagnetic waves by malignant tumors. Cancer is connected with mitochondrial malfunction (the Warburg effect) suggesting disrupted physical mechanisms. In addition to decreased energy conversion and nonutilized energy efflux, mitochondrial malfunction is accompanied by other negative effects in the cell. Diminished proton space charge layer and the static electric field around the outer membrane result in a lowered ordering level of cellular water and increased damping of microtubule-based cellular elastoelectrical vibration states. These changes manifest themselves in a dip in the amplitude of the signal with the fundamental frequency of the nonlinear microwave oscillator—the core of the diagnostic device—when coupled to the investigated cancerous tissue via the near-field. The dip is not present in the case of healthy tissue.

Keywords Cancer diagnostics · Bioscanner® TRIMprob™ · Physical processes in cancer · Biological electromagnetic field · Water ordering in cells · Nonlinear resonance interaction (NLRI)

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Introduction

Diagnosis of cancer in humans is mainly based on microscopic observation of morphological changes in cells and irregularities in tissues through the use of cytological and histological methods (Bibbo 1997). The diagnosis reveals the visible manifestation of processes that are of biochemical as well as physical nature. For a long time, disturbances in physical processes in cancer development were not adequately taken into consideration despite Warburg's experimental discovery of deteriorated oxygen metabolism (Warburg et al. 1924) caused by mitochondrial malfunction (Warburg 1956). Renewed interest in the Warburg effect has led to research on physical mechanisms in living cells. The Warburg effect is thoroughly described for instance by Pedersen (2007). Mitochondrial malfunction is a factor in cancer etiology and suggests new approaches for diagnosis and treatment (Brandon et al. 2006). The role of mitochondrial dysfunction and cytoskeleton disintegration in cancer diagnostics has been recently analyzed by Kobilková et al. (2010). There is no doubt that the pathological physical alterations express essential changes in cancer development.

Any diagnostic method has to detect important parameters disturbed by cancer process. A new diagnostic method developed by Vedruccio (Vedruccio and Meessen 2004; Gervino et al. 2007; Bellorofonte et al. 2005) utilizes frequency selective (resonant) absorption of electromagnetic waves in malignant tumors. In malignant tumors, therefore, we should expect to find structures oscillating at the frequencies of the emitted signals, whose dissipation is different from that of healthy tissue. As the measurement results do not depend on the tumor size, the electromagnetic resonant interactions might be assumed to take place in cancer cells. The damping of oscillations is significantly

increased during cancer development. A possible biophysical explanation for this new diagnostic method is suggested in this paper.

Firstly, this paper offers an overview of the electromagnetic system for measurement and the experimental results achieved. After this description, the altered physical links along the cancer transformation pathway and mechanisms of excitation, interaction, and damping of oscillations are analyzed.

Measurement system

In 1992, while conducting research on the back coupling effects of the damping of the near zone electromagnetic fields on transmitter-tuned circuits, Vedruccio discovered the possibility of noninvasive cancer detection. He also developed, and in 1999 patented, electronic equipment for this purpose. Since the mechanism of cancer detection wasn't clear, publication of the discovery was postponed and released later (Vedruccio and Meessen 2004) after elucidation of the technical background of the nonlinear radiofrequency resonance. Clinical tests of the system were done, but the biophysical background still wasn't known.

The principle of detection lies in the resonance between the coupled active nonlinear oscillator (the probe) and the passive oscillator (the tissue) in the radiofrequency range of the electromagnetic spectrum. The fundamental frequency of emitted waves is about 465 MHz. The first (930 MHz) and the second (1,395 MHz) harmonics are transmitted too. The probe consists of a linear oscillator fed from the nonlinear element T (Fig. 1), together forming a nonlinear active oscillator. In the equivalent circuit in Fig. 1, the oscillator is capacitively coupled to the passive one, the tissue, via the near field of the antenna (the equivalent capacitance is C_c). The tumor tissue represents a dissipative medium for the energy stored in the field near to source. The near field energy periodically flows out of the probe (the source) and returns to it. The frequency of the emitted signal is adjusted and locked at the point of the highest absorption. The receiver antenna is located beyond the immediate neighborhood of the source (Fig. 2). In comparison with electromagnetic wave propagation without interaction with a tumor, the received signal at the fundamental frequency decreases about fivefold due to damping effects of the cancerous tissue (Fig. 3). Results in healthy humans and prostate cancer patients are shown in the white and black columns, respectively, of Fig. 3.

The principle of detection was analyzed by Vedruccio and Meessen (2004) using an electrical circuit analogy (Fig. 1). The RF (radio frequency) current that feeds the probe oscillator of capacitance C_p and inductance L_p is a nonlinear function of the voltage containing a linear, a

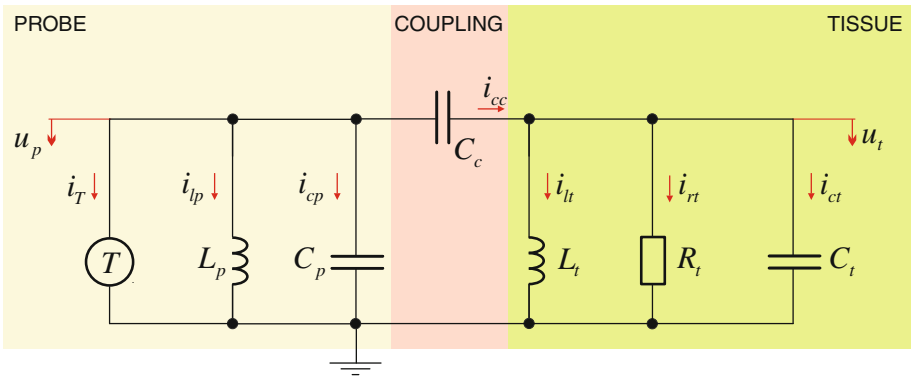

Fig. 1 Equivalent circuit of the probe-tissue system

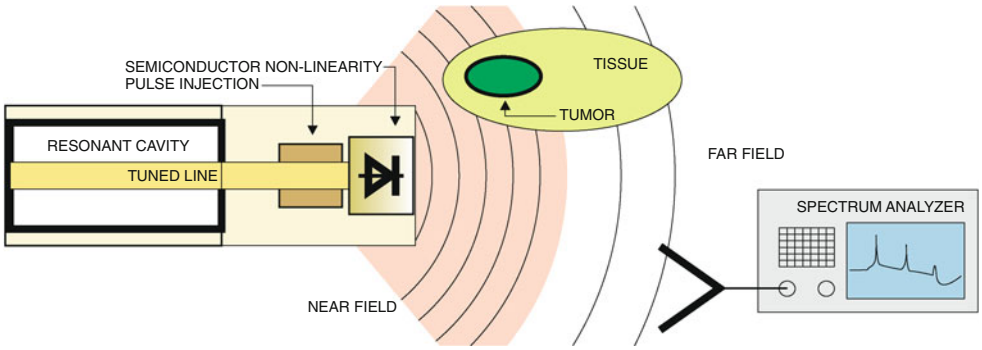

Fig. 2 Schematic picture of the Bioscanner® TRIMprob™

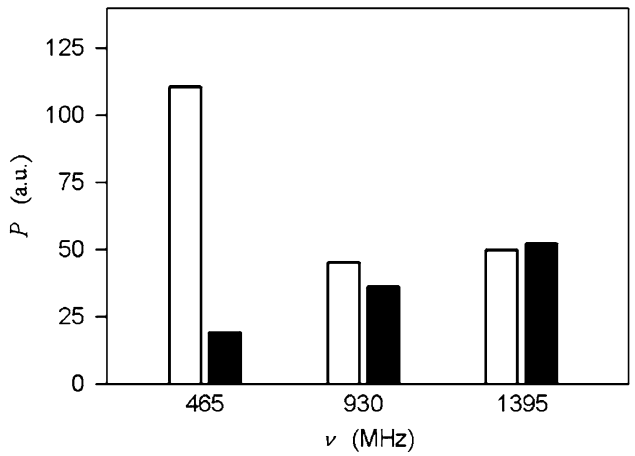

Fig. 3 Experimental results for a control group of healthy humans (*white columns*) and a group of prostate cancer patients (*black columns*). The differences between the control group and the cancer group are statistically significant at the fundamental (465 MHz) and at the first harmonic frequency (930 MHz). *Vertical axis* is logarithmic in arbitrary units

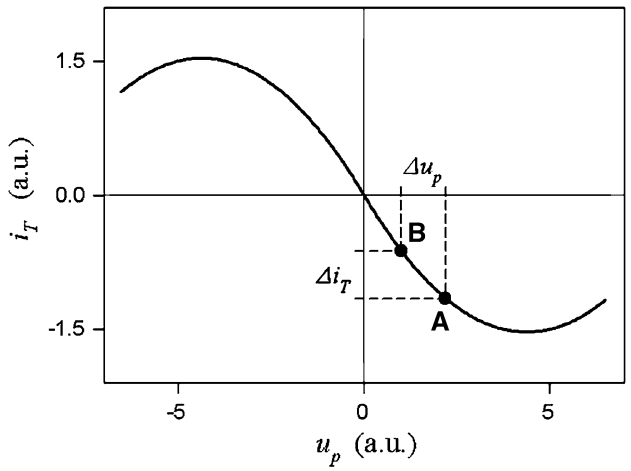

Fig. 4 Characteristic dependence of the current i_T on the voltage u_p of the nonlinear element T. Increment of voltage Δu_p is transformed into the current increment Δi_p and is amplified due to a change in negative conductance

quadratic, and a cubic term (with coefficients α, β, and γ, respectively). The assumed current (i_T) − voltage (u_p) characteristic is plotted in Fig. 4. In the working region of the T element, the negative differential conductivity increases (decreases) with increasing (decreasing) voltage.

By coupling the oscillations of the probe to those in biological tissue, a nonlinear resonant interaction is set. The probe and the tissue linked together form a joined nonlinear resonant circuit. The capacitive coupling to the tissue is represented by the equivalent capacity C_c. The passive oscillator is formed by a parallel combination of the capacity C_t, inductance L_t, and resistivity R_t. Other variables are according to Fig. 1. We will shortly analyze the nonlinear oscillation system in Fig. 1. If the coupling $C_c = 0$ (i.e., the probe is far from the tissue), the probe behaves like a van der Pol oscillator and may be described by

$$C_p \frac{d^2 u_p}{dt} - \left(\alpha + \beta u_p - \gamma u_p^2\right) \frac{du_p}{dt} + \frac{1}{L_p} u_p = 0 \qquad (1)$$

Generally, the voltage and current in the probe circuit contain time-dependent harmonic components of the type $\exp(im\omega_p t)$, where i is the imaginary unit, ω_p is the resonant frequency of the probe circuit, t is the time, and $m = 0, \pm 1, \pm 2 \ldots$ For $C_c \to \infty$, the tissue circuit with elements C_t, L_t, and R_t is coupled in parallel with the probe circuit. The combined probe and tissue circuit may be adjusted at the tissue resonant frequency. The tissue resistance R_t decreases the voltage u_p and as a consequence also the current i_T, which results in a decrease in the probe-transmitted power. The disturbances in the probe circuit are amplified. In this case the signal contains the combined harmonic components $\exp(im\omega_t t)$, where ω_t is the resonant frequency of the tissue. But the coupling capacitance is greater than 0 ($0 \leq C_c$) and finite. The admittance coupled in parallel to the probe circuit is given by

$$A_p = \left[\frac{1}{i\omega_{m,n} C_c} + \left(\frac{1}{i\omega_{m,n} C_t + \frac{1}{R_t} + \frac{1}{i\omega_{m,n} L_t}}\right)\right] \qquad (2)$$

where $\omega_{m,n} = m\omega_p + n\omega_t$ ($n = 0, \pm 1, \pm 2 \ldots$) are the frequencies of the harmonic components. The probe circuit is damped by the tissue conductance, but the damping depends on the coupling capacitance. Amplitudes of some frequency components of the probe oscillations are strongly reduced due to the nonlinear resonant interaction. A more detailed qualitative description of the behavior of the system should be based on analysis of fundamentally nonlinear systems (as was done by Vedruccio and Meessen 2004) and can be performed by numerical methods (Brenan et al. 1996), especially methods based on numerical differentiation formulas (NDFs). For low α/C_p ratio, the system may be considered nonstiff, and the classical Dormand and Prince (1980) method can be employed.

The above-described principle was implemented as the Bioscanner® in 1999 by Vedruccio and then licensed to be manufactured, marketed, and named TRIMprob™ (Galileo Avionica, Caselle, Italy) detection system. The transmitter probe with a resonant cavity incorporates a transmission line tuned to the frequency of oscillation, which is in the 65 cm wavelength band (465 MHz; Fig. 2). At the open end of this line, there is a semiconductor element with nonlinear characteristics that is activated by a nanosecond electromagnetic pulse. This transient provides an injection of electromagnetic energy into the tuned line, which performs a damped oscillation. This particular tunable

amplifier-oscillator represents the core of the Bioscanner® TRIMprob™ diagnostic device. It possesses lock-in or synchronization characteristics, and because of its particular construction, it produces a harmonically related group of coherent electromagnetic waves. These oscillations are radiated as a beam through the beam window of the oscillator dome at the end of the probe. After geometrical focusing, the beam is used to irradiate the investigated tissues.

The probe is brought close to the investigated region. Nonlinear resonance interaction between the nonlinear oscillator and the tissue reduces the energy of the emitted wave at distinct frequencies depending on the pathological state of the tested tissue. This energy is measured by the spectrum analyzer, which is fed by an antenna situated about 2 m away from the probe.

Diagnostic accuracy of the Bioscanner® TRIMprob™ was evaluated in several clinical studies. Bellorofonte et al. (2005), Da Pozzo et al. (2007), Tubaro et al. (2008), and Gokce et al. (2009) performed studies focused on the diagnosis of prostate cancer at 465 MHz. TRIMprob™ diagnostic findings were compared to those resulting from the standard prostate cancer diagnostic methods including digital rectal examination, biopsy, and prostate-specific antigen (PSA) level. Resulting values are shown in Table 1. Data presented are consistent across studies. Diagnostic methods are classified by the proportion of positives and negatives correctly identified, i.e., by sensitivity and specificity, respectively. Prostate cancer diagnosis using TRIMprob™ is characterized by high sensitivity; however, the specificity is rather low. Bellorofonte et al. (2005) moreover reported a significant difference between patients with benign prostatic hyperplasia and patients with prostate cancer.

System Bioscanner® TRIMprob™ was also tested for detection of breast cancer (De Cicco et al. 2006), bladder cancer (Gervino et al. 2007), rectal malignant lesions (Vannelli et al. 2009), carcinomas in patients with multinodular goiter (Sacco et al. 2007a), and gastric cancer (Sacco et al. 2007b). According to the clinical experience, the TRIMprob™ seems to be a simple and reliable investigation method with good diagnostic results.

Table 1 Results of Bioscanner® TRIMprob™ diagnosis of the prostate cancer

	TPR (%)	SPC (%)	PPV (%)	NPV (%)	Patients (*n*)
Bellorofonte (2005)	95.5	42.7	63.3	89.8	211
Da Pozzo (2007)	80	51	44	84	188
Tubaro (2008)	86	60	60	88	111
Gocke (2009)	76	61.3	39.6	88.5	100

TPR Sensitivity, *SPC* specificity, *PPV* positive predictive value, *NPV* negative predictive value, *No* no of paients

Oscillators in a cell

Before the biophysical explanation is given, we will review its theoretical and experimental basis. Vedruccio's method is sensitive to energy losses of the near zone field around the transmitting antenna at a discrete frequency, i.e., it detects damped oscillations at resonance. Damping determines the quality of oscillators, which is an essential parameter describing their basic behavior. Quality is expressed by the Q factor, which is given by the relation

$$Q = 2\pi \frac{W_s}{W_d} \tag{3}$$

where W_s and W_d are the energy condensed in the oscillator and the energy lost during a period of oscillations, respectively. An oscillator is in the oscillatory or in the aperiodic (overdamped) regime if the Q factor is greater or smaller than 0.5, respectively.

Before analyzing oscillators inside a cell, the effects of the cellular deformability must be described.

Beil et al. (2003), Suresh et al. (2005), and Suresh (2007) measured deformability and connected energy losses of pancreatic epithelial cancer cells (Panc-1) before and after treatment with a bioactive lipid SPC (sphingosylphosphorylcholine) that disturbs keratin filament structure and plays a critical role in the metastatic process. The microplate mechanical stretcher method was used to determine the effective spring constant and losses from a hysteresis loop (force versus displacement curve) at a stretching rate 0.5 μm s^{-1} (Suresh et al. 2005). The cancer process is connected to an increase in deformation energy losses. We can evaluate a quantity Q_D, similar to the Q factor, for deformability of the measured cancer cells, i.e., the ratio of the potential energy to the energy lost during deformation (hysteretic energy of the measured cell) multiplied by 2π. The Q_D factor for Panc-1 cells before SPC treatment is about 10. After SPC treatment, the Q_D factor is about 3. The SPC treatment causes collapse of the keratin network, which shrinks around the nucleus, and a part of the interfacial water is disorganized. The Q_D factor for deformability may be comparable with the Q factor of oscillators.

Cytoskeleton seems to be the intracellular structure capable of electric oscillations. The cytoskeleton consists of microfilaments, intermediate filaments, microtubules, and associated proteins. Microtubules form the main organizing structure of the cytoskeleton. They are composed of tubulin heterodimers, which are strong electric dipoles. Each heterodimer has a net mobile negative charge

and binds 18 calcium ions (Satarić et al. 1993; Tuszyński et al. 1995). The electric dipole moment is about 1,000 Debye (10^{-26} cm). Elastic and electric (polarization) oscillations in the microtubule structures are, therefore, mutually connected. Anisotropic elastic properties are described by Tuszyński et al. (2005). Theoretical treatment of the microtubule structure discloses their capability for mechanical (elastic) oscillations over a wide frequency range from acoustic to GHz frequencies (Sirenko et al. 1996; Wang et al. 2006; Qian et al. 2007; Tuszyński et al. 2005). Nonlinear interaction between elastic and electric polarization fields (predicted by Fröhlich) may be a source mechanism leading to the generation of electrodynamic activity in living cells.

Conditions for excitation of electrically polar oscillation in microtubules and their damping were analyzed (Pokorný et al. 1997; Pokorný 2003). Electric oscillations measured in the cellular membrane of living yeast cells in the M phase display enhanced electric activity in some periods coinciding with mitotic spindle formation and its specific development features (Pokorný et al. 2001). To say the least—the experimental results support the idea that generation of electrodynamic activity is related to microtubules.

Interaction of mitochondria with microtubules

Biological systems are far from thermodynamic equilibrium. Energy production by anaerobic fermentative and oxidative reactions is one of the essential conditions of life. The main part of energy consumption in a cell is covered by mitochondrial oxidative activity. But production of ATP and GTP (adenosine and guanosine triphosphate) is only one of the mitochondrial functions (Pokorný et al. 2008; Pokorný 2009a, 2009b). During normal production of ATP and GTP, the mitochondrion pumps protons across the inner membrane, forms a zone of strong static electric field around it, liberates nonutilized energy, and conditions apoptosis.

A zone of strong static electric field is formed up to a distance on the order of 1 μm from the mitochondrion (Tyner et al. 2007). Protons transported across the inner membrane diffuse through the outer membrane into the surrounding medium and create a proton space charge layer. At the outer mitochondrial membrane, the intensity of the static electric field is about 3.5 MV/m. Efflux of energy nonutilized for ATP and GTP production in mitochondria (generally called the wasted energy) may be an important factor too. A mitochondrion converts about 40% of the input chemical energy into ATP and GTP (Alberts et al. 2008). The remaining part (about 60%) is liberated from mitochondria in the form of photons (in the ultraviolet, visible, and infrared regions) and heat. The photon emission is derived from the mitochondria transport chain in the inner membrane (Van Wijk and Schamhart 1988; Kobayashi et al. 1999)—reactions linked to singlet oxygen production (Hideg et al. 1991; Hideg 1993). The reactions are preserved in submitochondrion particles (Cadenas et al. 1980). The emitted spectrum spreads over the visible wavelength range (Hideg et al. 1991). Yeast cells emit photons not only in the visible region but also in the UV band from 200 to 400 nm (Tilbury and Quickenden 1992). The maximum number of photons is emitted at about 600–700 nm. Carcinoma cell culture spectrum has a maximum around 530 nm (Takeda et al. 1998). The main part of the liberated energy is absorbed in the ambient medium around mitochondria. In a nonlinear medium, this energy may be transformed into coherent vibrations, especially into oscillations of the cytoskeleton.

It is well known that mitochondria are aligned along microtubules. A strong static electric field around mitochondria may create nonlinear conditions for energy transformation from random to coherent forms (a schema of cooperation of mitochondria with microtubules is in Fig. 5). Moreover, nonutilized energy flowing out of mitochondria may excite oscillations in the cytoskeleton. The cytoskeleton structure is thus assumed to be capable of cellular oscillations generating electromagnetic fields (Pokorný et al. 1997; Pokorný and Wu 1998; Pokorný 2004; Cifra et al. 2010) because of extraordinary electric polarity of cytoskeleton subunits (Tuszyński et al. 1995).

In the following, we will show the cytoskeleton-based cellular elastoelectrical oscillations—whether endogenous or driven—to be significantly influenced by cancer process.

Water ordering in a strong electrostatic field

We consider the organization of the cellular water to be a crucial phenomenon influencing elastoelectrical properties, namely damping, of the cytoskeleton vibration system. A few of the most fundamental concepts regarding cellular water will be pointed out.

In general, water can exist in three phases (gas, liquid, solid). The phase of the water depends on the physical parameters of the environment: temperature, pressure, and other physical conditions. In the cell environment, properties of water differ significantly compared to those of bulk liquid water, so the cell can be hardly considered a mere sack filled with organelles and salt water. The reason for this lies in the fact that water molecules at the interfaces, such as membranes, hydrophilic surfaces, and polar molecular backbones, become ordered due to the electric field of the surface charge at the interface (Ling 2006). Ordering of the water molecules takes place in the form of layers parallel to the surface in the ideal case of a flat

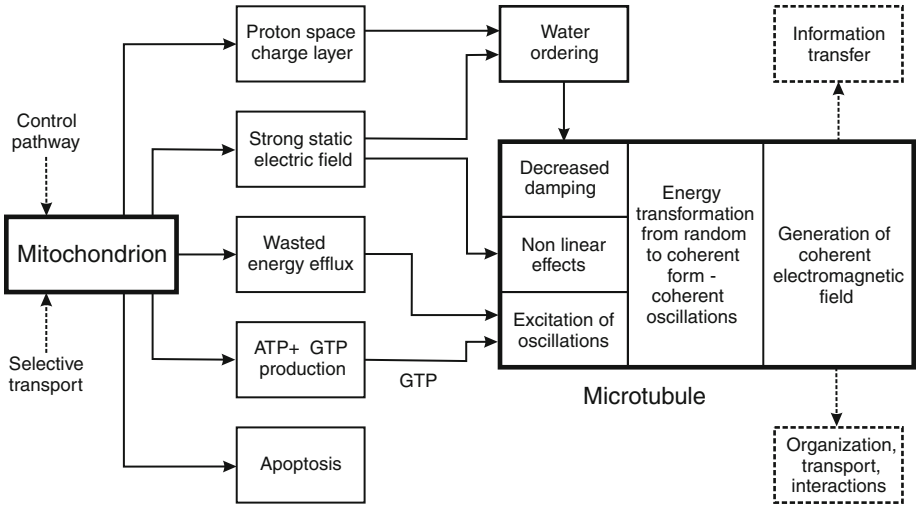

Fig. 5 Physical links in the biological activity of living cells. A unique cooperation of mitochondria and microtubules is shown together with the areas of input controlling signals and output effects

interface. This organization of water at the interface, which contains several layers, can also be measured by atomic force microscope (Kimura et al. 2010; Fukuma 2010).

Here it needs to be noted that the cell is filled with interfaces (average distance between non-water molecules in a cell is about 2 nm), thus all of the cellular water will be organized to some degree. It has been experimentally proven that the organized water has different physical properties compared to bulk water including higher viscosity (Pollack et al. 2006), lowered thermal motion of molecules (Zheng et al. 2006), different pH (Chai et al. 2009), and different spectroscopic properties (Chai et al. 2008). Ordered layers of water exhibit separation of charge (Chai et al. 2009) and solvent exclusion (Zheng and Pollack 2003; Zheng et al. 2006). It has been found that infrared radiation promotes the formation of exclusion zones (Chai et al. 2009). Further properties of ordered water may be found, for instance, in Pollack et al. (2006, 2009).

Organization of water can be achieved not only by an electric field of charges in the hydrophilic interfaces, but also by an electric field of external sources. Fuchs et al. (2007, 2008, 2009) and Giuliani et al. (2009) have shown that a strong electric field (about 600–700 kV/m) organizes water and forms a floating water bridge (about 1–3 cm long) between two glass beakers.

Ordering of the water is not only a matter of a few molecular layers but can also extend to macroscopic distances from strongly hydrophilic interfaces, e.g., a few hundreds of micrometers as in the case of the exclusion zone found by Zheng and Pollack (2003) and Zheng et al. (2006). This zone takes its name from the process it was visualized with: micrometer-sized particles (e.g., latex particles) are excluded in such a manner that two distinct water phases are visible at the hydrophilic interface observed under the microscope. The adjacent phase contains no particles (they are excluded), while beyond a rather sharp boundary, particles are present in the second water phase.

A basic self-organization of water also takes place at the phase transition from the gas state to the liquid state. Based on the quantum electrodynamic theory of matter (Preparata 1995; Del Giudice et al. 2009), it was shown that in what we consider "liquid" water there are actually two mixed phases—coherent domains that form the ordered water phase and a gas-like water phase. The exclusion zones that are observed at the interfaces are actually a macroscopic manifestation of the partial separation of ordered water domains and bulk water regions. Because of the physical properties of coherent domains (e.g., as reservoirs of quasi free electrons), they are expected to have tremendous impact on biological activity (Del Giudice et al. 2009; Del Giudice and Tedeschi 2009). Theoretical treatment that does not take into consideration the formation of coherent domains (Booth 1951) contradicts the experimental findings (Fuchs et al. 2007, 2008, 2009; Giuliani et al. 2009; Zheng and Pollack 2003).

Microtubules are known to form clear zones 5–20 nm thick around them depending on the concentration of cations (Amos 1979; Stebbings and Hunt 1982). These clear zones correspond to the exclusion zones described by Pollack. Such zones of layered water may cause a significant reduction in the microtubule vibration damping due to (1) reduced thermal motion of water molecules, (2) reduced energy transfer across the layers because of physical realization of the slip-boundary between the water layers (Duncan-Hewitt and Thompson 1992; Ferrante et al. 1994; Hayward and Thompson 1998), and (3) viscoelastic transition of hydrated water, which reduces damping of the biomolecule vibrations (Van Zandt 1986, 1987).

Mitochondria contain ordered water within their inner polar interfaces (López-Beltrán et al. 1996), and water is

also ordered by mitochondria in their surroundings (Trombitás et al. 1993). If the function of the mitochondria is unperturbed, they are the source of the strong static electric field (Tyner et al. 2007), which is related to the ordering of the surrounding water.

Water ordering in living cells may be monitored by nuclear magnetic resonance (NMR) spectroscopy too. The shorter the T_1 spin lattice relaxation time, the higher the level of water order. For instance, the water order is increased at metaphase in the development of the fertilized eggs of the sea urchin (*Strongylocentrotus purpuratus*). Zimmerman et al. (1985) experimentally proved that an increased state of ordered water molecules at metaphase is maintained by nonmicrotubular factor(s) of the metaphase egg.

Physical links along the cancer transformation pathway

The interplay of mitochondria with microtubules seems to be fundamental in fully functional cellular vibration systems (see Fig. 5). Mitochondria are aligned along microtubules (Alberts et al. 2008) and contribute to water organization. The proton charge layer and the zone of strong static electric field are organizing factors for a high level of water ordering in a cell. A strong static electric field in the immediate surroundings of the mitochondria (Tyner et al. 2007) organizes water; even an electric field several times smaller organizes the floating water bridge (Fuchs et al. 2007, 2008, 2009; Giuliani et al. 2009). UV photons (Tilbury and Quickenden 1992; Batyanov 1984, 1995) and infrared radiation (IR) as a form of "wasted" energy are released in the course of the citric acid cycle. IR extends the exclusion zones that contain the phase of organized water (Chai et al. 2009). Protons diffused through the pores in the outer membrane (Tyner et al. 2007) form organized water envelopes by hydration. Therefore, mitochondrial activity may provide a high level ordering of water.

Surface charges on the interfaces are also present in cancer cells and provide only the basic organization of water. For the full organization of cellular water, which provides low damping of cellular vibration states, fully functional mitochondria are necessary. Warburg et al. (1924) and Warburg (1956) disclosed the suppression of oxidative metabolism in cancer cells, which may condition disturbances of physical processes utilizing energy. He assumed that "ATP synthesis by respiration … involves more structure than ATP synthesized by fermentation." In a general way he predicted the function of mitochondria in organization of the cell. Warburg's experimental findings were recently revisited, for instance by Carew and Huang (2002) and Cuezva et al. (2002). Physical links seem to be to prevailing in the clinical phase of cancer (Pokorný et al. 2008; Pokorný 2009a, b; Jandová et al. 2009a).

Disturbance of mitochondria function results in reduced organization of water. Efflux of nonutilized energy is diminished, the proton space charge layer is sparsely populated, and the strong static electric field is pressed down. Mitochondrial inner membrane potential is decreased (in absolute value) in cancer cells (Bonnet et al. 2007), which inevitably causes weakening of the electric field around mitochondria. Decreased mitochondrial production of ATP in cancer cells is compensated by the fermentative production. However, the outflow of nonutilized energy, and the reduced zone of the proton space charge layer and of the strong static electric field are not replaced. Due to the diminished zone of the static electric field, the nonlinear conditions in microtubules are shifted towards linear region. Decreased energy supply of nonutilized energy efflux and weakening of the nonlinear parameters for energy transformation from random to coherent form result in low power and coherence of oscillations in microtubules.

The diminished proton space charge layer and the decreased static electric field around mitochondria have a negative impact on water ordering. As long as the cytoskeleton is not disturbed, the interfacial organization of water remains unchanged. But the higher level of water ordering by the proton layer and by the static electric field around mitochondria is disturbed. (The mitochondria occupy about 22% of the volume of the cell and the strong static electric field around them the rest.) This decreased level of water ordering leads to increased damping of oscillations in microtubules. In fact, the ability to detect tumorous tissue by NMR imaging by measuring different states of water in healthy and tumorous tissue has been known for almost 40 years (Damadian 1971). Disrupted organization of water (due to a lowered electric field around functionally perturbed mitochondria) will increase the damping of cellular oscillations, including that of microtubule vibrations.

One of the key roles of organized water in cellular vibrations is its ability to substantially lower the damping of vibrations in cytoskeleton structures.

Damping of microtubular oscillations

If a microtubule were in direct contact with normal bulk water (not ordered) with dynamic viscosity $\eta = 0.000697$ Pa s, the quality factor would be about 0.5. This value is determined using circular cylindrical geometry and shear stress according to $\tau = \eta \mathrm{d}v/\mathrm{d}r$ (where v is velocity in the axial direction and r is radius). But even a slip layer at the microtubule surface with thickness of about 1 nm and

shear modulus 5 Nm^{-2} protects vibration from water viscosity effects (Pokorný 2003).

Howard stated that global and stretching motions of proteins as well as of cytoskeletal filaments inside cells are overdamped (Howard 2001). He assumed a model of intermolecular bonds between protein and the surrounding water that form rigid surfaces and that the viscosity depends on breaking the crosslink bonds. But in normal bulk water, due to intermolecular forces, the molecules form molecular clusters and coherent domains that bind to the protein and may move together. Therefore, the viscosity may depend on bonds between water molecules (i.e., on the mass of the water clusters and coherent domains) and between water molecules and proteins. But the main difference between bulk water and water in living cells is in the level of ordering due to the strong electric field. Interfacial water ordering depends on the surface charge of protein molecules and structures. Water molecules should move together with the protein (at least its nearest layers). In contrast, mitochondrial water ordering is independent of the protein surface. Elastic and damping properties of ordered water are not yet well established. But experimental results show decreased damping by ordered water. Higher hydration levels of hydration shells result in a viscoelastic transition that reduces the viscous damping of acoustic vibrations of hydrated particles (for instance, spherical viruses 30 nm in diameter) from water molecules (Liu et al. 2009).

Water ordering may be assumed to change a viscous water system with random heat motion into a quasi elastic medium. The ordering level should depend on organizing forces acting upon individual water molecules and coherent domains and on the coupling forces between them. The coupling force may depend on the electric dipole moment of water molecules (6.2×10^{-30} Cm) and on the intensity of the organizing electric field. The ordered structure may form its own electric field, which decreases random behavior and contributes to ordering. The level of the order may be assessed from the size and the stiffness of the ordered structures and from the ratio of the number of molecules in the ordered structure to that of free or partially free molecules and clusters of molecules.

Damping by the surrounding medium with mobile molecules or clusters of molecules may be roughly rated using a model of particles moving to and from the microtubule, transferring energy outside it, and converting energy into heat. We may suggest a simple model with two phases—random and ordered. The Q factor of a microtubule in water may be evaluated as a ratio of kinetic energy stored in the microtubule to the kinetic energy transported outside by clusters of molecules (three molecules are assumed) within a period of oscillations. Figure 6 shows an increase in the Q factor as a function of the level of water ordering. For a 99% level of ordering, the Q factor is about 50. The initial point with all free clusters corresponds to the bulk water surroundings. This model coincides with the experimental findings of Damadian (1971), who stated that malignant tissues are characterized by an increase in the motional freedom of tissue water. Decreasing the strong static electric field around mitochondria leads to disturbances of water ordering.

Damping may shift the resonance to lower frequencies with respect to the undamped oscillator. Damping of oscillations given by the Q factor depends on the level of water ordering. Frequency shift may be determined by the relation

$$f_r = \frac{f}{f_0} = \sqrt{\left(1 - (2Q)^{-2}\right)}$$

where f_0 is the frequency of an undamped oscillator. The relation between the Q factor and the relative frequency f_r is shown in Fig. 6. For $Q = 2$ (the dotted line in Fig. 6), the frequency shift is about 3%. For $Q < 2$ the frequency decrease is significant and the aperiodic regime is reached at $Q = 0.5$, i.e., $f_r = 0$. Therefore, for $Q < 2$ there may be an essential decrease in the resonant frequencies.

Direct evidence of damping can be obtained from spectroscopy. While some spectroscopic and theoretical studies suggest that the collective vibrations of proteins are overdamped by water (Hayward et al. 1993), which is a major constituent of the cytosol, there are indications (Romanovsky et al. 2003) that the broadening of the spectral lines (a physical signature of a damping) may not be solely due to the damping but also due to inhomogeneous broadening of the spectral line—a slight difference

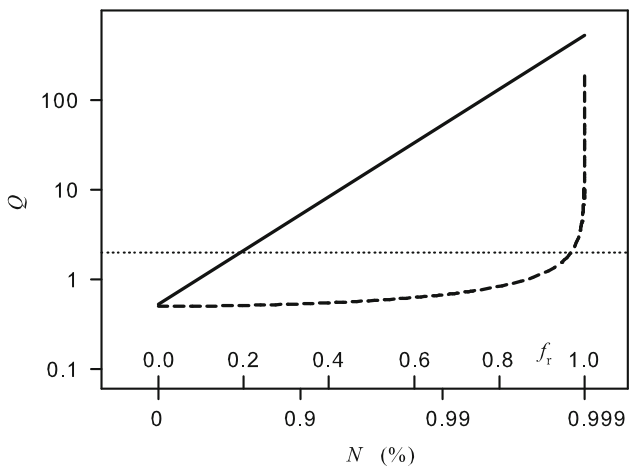

Fig. 6 Dependence of the microtubule Q factor on the level of order of the special phase of the ambient water (*solid line*). N denotes the percentage of ordered water clusters of molecules containing three molecules. The *dashed line* denotes the relation between the Q factor and the relative frequency $f_r = f/f_0$. The *dotted line* represents $Q = 2$

in the mode frequency due to conformational differences in the protein molecules in the ensemble under study. Actually, nonlinear spectroscopy has already provided experimental evidence that the lifetime (similar to the quality factor Q of the oscillating system—inversely proportional to damping) of certain protein modes can be rather large, over 1,000 (Xie et al. 2001). Currently, direct spectroscopic studies on microtubules in the MHz–GHz region are sparse. Hameroff et al. (1986) reported 8 GHz acoustic mode of microtubules with Brillouin spectroscopy; from the sole figure they provided, the half width of the peak (Δf) is about 2 GHz, giving a Q factor ($f/\Delta f$) of about 4. Pizzi et al. (2011) measured very weak microwave absorption (0.5 dB) of in vitro microtubules with a mean length of 2 μm at 1,510 MHz. Regarding these experimental findings, it needs to be noted that inhomogeneous broadening contributes to broadening of the peak, thus leading to underestimation of the real Q factor. If the resolution of the spectroscopy technique used is low, multiple spectral peaks will be merged into one broad one, additionally clouding the real Q factor of oscillations. Further, longitudinal modes (which are most electromagnetically active) that conserve microtubule length will be damped much more weakly than, e.g., bending modes, since they do not cause any displacement of the surrounding water. It is also important to realize that microtubules are in a cellular environment where the surrounding water is strongly organized due to numerous interfaces (Pollack et al. 2006) and by the strong static electric field of mitochondria as measured by Tyner et al. (2007). We can expect that the in vivo damping of microtubule elastic vibrations will be lower than that measured on extracted microtubules. This can be reasonable if the amplitude of oscillations is small and comparable to the size of the damping units (water molecules or water clusters). In such a case, classic hydrodynamic treatment (such as in Howard 2001) of the damping (Stokes' formula) fails, and the Q factor of protein oscillations is underestimated (Mitrofanov et al. 2006).

Implications for diagnostics

Electromagnetic signals emitted by the Vedruccio's transceiver system interact with cells in the irradiated tissue. The vacuum and the bulk water medium wavelengths of the 465 MHz signal are 65 and 6.5 cm, respectively. The electromagnetic field interacts with electric dipoles of heterodimers in microtubules and excites their oscillations. Due to interactions between elastic and electric polarization fields, microtubule oscillations are excited. Elastic wave propagation in microtubules was analyzed by Sirenko et al. (1996), Wang et al. (2006), and Qian et al. (2007). Dependence of frequency or velocity of propagation on the wave vector was evaluated for isotropic and orthotropic shell models with different parameters. In particular, the resonant condition for a 10 μm long microtubule corresponding to half of the wavelength ($\lambda/2$) at a frequency of about 460 MHz may occur for longitudinal oscillations with Young's modulus 1.7–2 GPa. These results hold for the orthotropic microtubule axisymmetric ($n = 0$) and nonaxisymmetric ($n = 1$) shell models published in Wang et al. (2006). A resonant wave form of oscillations of microtubules is shown in Fig. 7.

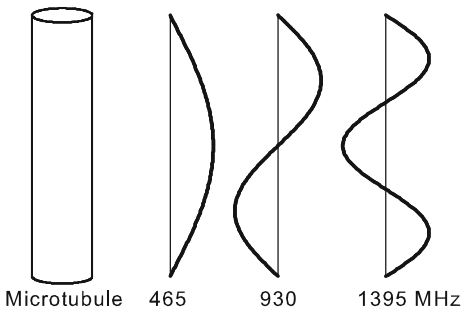

Fig. 7 A schematic picture of longitudinal elastic resonant oscillations in a microtubule at frequencies of 465, 930, and 1,395 MHz

Vedruccio's diagnostic electromagnetic method of cancer detection is based on detection of damped microtubule oscillations in cells. Damping is caused by ambient water in which its high level of order is disturbed due to the diminished proton space charge layers and the static electric fields around mitochondria.

Discussion

The diagnostic method developed by Vedruccio is based on measurement of frequency selective effects of the interaction of the external electromagnetic field with cancer cells. There are special features of the absorption and damping of the electromagnetic oscillations. Gervino et al. (2007) found that application of monochromatic 465 MHz emissions only does not lead to measurable interaction, compared to emissions with nonharmonic components. Simultaneous radiation of fundamental and harmonic waves might be essential for excitation of resonant interaction. A simple assumption that the difference in interactions may only be based on differences in complex permitivity between the healthy and cancerous tissues (which depend on content of water) is hardly tenable. Differences in tissue impedance are strongly related to the fluid volume and its distribution as was analyzed by Foster and Lukaski (1997).

Microtubules are assumed to form the oscillation structures. The damping does not originate in the cytoskeleton itself but is caused by the ambient medium, i.e., by

the cytosol water. The cytosol water in a healthy cell undergoes two levels of ordering—the basic interfacial and the high level, which is dependent on the mitochondrial strong static electric field (i.e., on the mitochondrial function). Ordered water forms a special phase with spectacular properties. We assume that ordering changes the viscous phase into a quasi elastic one. Physical parameters of this phase have still not yet been completely revealed. Theoretical analysis and measurement of the parameters will be a great challenge for the future.

The aspects of water ordering have been totally neglected by some workers (Foster and Baisch 2000; Reimers et al. 2009; McKemmish et al. 2009), probably being unknown to them, and they assumed that there are highly damped oscillators in cells. Reimers et al. (2009) and McKemmish et al. (2009) in their assessment of the Fröhlich's energy condensation hypothesis (Fröhlich 1968a, b, 1969, 1980)[1] used a parameter that roughly corresponds to SQ (where S is energy supply), which makes the Q factor—an essential parameter of oscillation systems—indistinguishable (in different cases with the same SQ values). Therefore, their results are not applicable to living cells as the ordered water parameters are quite different from those of the bulk water.

The mitochondrial dysfunction seems to develop during the transition from precancerous to cancer cell (Jandová et al. 2009a). It disturbs the high level of order of the cytosol water, increases damping, diminishes electromagnetic activity, and, as a result, prepares conditions for local invasion of the cell. Disintegration of the microfilament structure overturns the basic interfacial order and prepares the metastatic process (Beil et al. 2003; Suresh et al. 2005). Therefore, cancer development is connected with increasing damping of the microtubule oscillation system, which has an electrodynamic character. Measurement of the quality factor of the tumor cells might disclose the developmental phase of the tumor. The specificity of the process in connection with cancer and other diseases should be investigated too. The mitochondrial dysfunction seems to be connected not only with cancer (Jandová et al. 2009b). Specific features caused by particular pathological states are yet not known.

The increased damping might cause a shift in the resonance frequency of oscillations in cells. Frequency changes in cancer cells were predicted by Fröhlich (1978). If the quality factor is greater than 2, the frequency shifts are negligible. But for smaller quality factors, the frequency may not only be extremely low, but the oscillator regime may be altered to an aperiodic one. It is not clear whether the cancer process could cause such changes. But shifts in the oscillation frequencies of cancer cells might depend on tensegrity disturbances too. Nevertheless, the oscillation frequencies in healthy cells have not been measured as yet. The physical mechanism of the cancer transformation pathway presented in this paper is in agreement with experimental findings on mitochondria, water ordering, and properties of microtubules.

The measurements provided by Vedruccio have a macroscopic character. The whole tumor is responding. Individual cells may differ in their properties. Measurement of individual cells may disclose a wide spectrum of parameters. Such measurements are, however, at the boundary of present technological possibilities (Kučera et al. 2010).

Conclusion

Microtubules in biological cells are electrically polar oscillation units that are capable of interaction with the external electromagnetic field. Moreover, they can generate an electromagnetic field. Damping of elastoelectrical oscillations in microtubules depends on the ordering of the surrounding water. Basic ordering of water is caused by surface charges of biological molecules and structures. This interfacial water is ordered at a certain distance from the charged surface of microtubules. A further increase in the level of order seems to be caused by the proton space charge layers and the strong static electric fields around mitochondria. Cooperation between mitochondria and microtubules is a unique physical process in living cells. As a consequence of mitochondrial dysfunction, which occurs in cancer cells, the high level water order is disturbed, and damping of oscillations in microtubules in tumors is enlarged. The external field can excite oscillations in microtubules, but the supplied energy is continually lost by damping. The resonant coupling and the damping mechanism could explain electromagnetic cancer detection as proposed by Vedruccio. The Bioscanner® TRIMprob™ system seems to be very promising, but there are still many open questions concerning technical implementation of this apparatus.

Acknowledgments The research results presented in this paper were partly supported by grant nos. P102/10/P454, 102/08/H008, P102/11/0649, and 102/11/0649 of the Czech Science Foundation GA CR, and by the grant no. SGS10/179/OHK3/2T/13 of the Grant Agency of the Czech Technical University in Prague.

[1] Due to special spectral transformation, energy is channeled to the lowest frequency modes, which may be strongly excited, oscillate coherently, and generate coherent electromagnetic fields (Fröhlich 1973, 1980). Generated coherent electromagnetic fields may participate in directed transport of molecules and particles (Pokorný 2001; Pokorný et al. 2005a), cytoskeleton dynamic organization (Pokorný et al. 2005b), interaction between cells (Pokorný 2006), and information transfer.

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