*Electromagnetic Biology and Medicine*, 2012; Early Online: 1–8
© Informa UK Ltd
ISSN 1536-8378 print/ISSN 1536-8386 online
DOI: 10.3109/15368378.2012.735207

informa
healthcare

# Impact of mitochondrial electric field on modal occupancy in the Fröhlich model of cellular electromagnetism

Fedor Šrobár

*Institute of Photonics and Electronics, Academy of Sciences of the Czech Republic, Praha, Czech Republic*

Electromagn Biol Med Downloaded from informahealthcare.com by Dalhousie University on 08/19/13
For personal use only.

Fröhlich model describes emission of electromagnetic field in the interior of biological cells by oscillating polar units, now mostly identified with microtubule filaments. Central element of this theory is the system of rate equations for the quantum occupancy numbers $n_i$ of collective oscillation modes. These equations describe both linear and nonlinear properties of the system; presence of the latter can lead to condensation of the incoming energy into the lowest frequency mode – a phenomenon deemed to be of major importance for cell's biochemistry, because the excited mode can engage in chemical reactions while the major part of the system remains near the equilibrium, not exposed to energetic stress. This paper explores, using a simple model, the influence of strong static electric field created by mitochondria flanking the microtubules on nonlinear interactions and, in turn, on occupancy numbers. The computed results show that simultaneous presence of both sufficient metabolic pumping and adequately elevated static electric field is necessary for the full unfolding of the hallmark properties of the Fröhlich model. It is suggested that cancer-related mitochondrial dysfunction leading to metabolic transformation has additional adverse effect mediated by diminution of static fields which in turn reduces the nonlinear processes in the Fröhlich systems, essential for energy condensation in the fundamental mode.

**Keywords:** bioelectromagnetism, cancer transformation, energy condensation, Fröhlich systems, mitochondria

## Introduction

The main function of mitochondria is production of adenosine triphosphate (ATP), the universal energy currency of the cell. The final stages of the complex cascade of processes engaged in the oxidative phosphorylation involve creation and maintenance of a strong electrochemical gradient across the inner mitochondrial membrane due to action of pumps translocating protons from matrix into the intermembrane space. Strong electrostatic fields (up to between $10^6$ and $10^7\,\mathrm{Vm}^{-1}$) accompany these activities, covering large portions of the intracellular space (Tyner,

Correspondence: Fedor Šrobár, Institute of Photonics and Electronics, Academy of Sciences of the Czech Republic, Chaberská 57, 182 51 Praha, Czech Republic. Tel: 00420 266773473. Fax: 00420 284680222. E-mail: srobar@ufe.cz
*Received 21 March 2012; revised 13 July 2012; accepted 26 September 2012*

Kopelman, & Philbert, 2007). Electrically polar entities populating the cell's interior (small and large molecules as well as higher-order aggregates such as cytoskeletal filaments) are bound to react to such fields.

A particular instance of such interaction, the one involving microtubules, is the subject of this study. Microtubule filaments, a prominent component of the cytoskeleton, are hollow cylindrical structures composed of (typically) 13 protofilaments, polymers of α- and β-tubulin heterodimers, each possessing a dipole moment of approximately 1700 D $= 5.67 \times 10^{-27}$ Cm (Nogales et al., 1998). There is a spatial coordination between mitochondria and cytoskeletal filaments (Rappaport, Oliviero, & Samuel, 1998), so that the immersion of microtubules in the mitochondrial electrostatic field is strengthened.

In addition to fulfilling numerous roles of importance in the cell (in the areas of transduction of pressure and tension, motility, mitosis, ribosomal and vesicle transport), microtubules are now also a foremost candidate for the part of generators of intracellular alternating electromagnetic fields as envisioned by Fröhlich (1968). Pokorný, Hašek, Jelínek, Šaroch, and Palán (2001) observed close correlation between electromagnetic activity of the yeast cells and the phase of the cell division cycle with the attendant marked changes in microtubule configuration. Kirson et al. (2004, 2007) described the disruption of microtubule polymerization by applied alternating electric fields, thus demonstrating coupling of the orientation of heterodimer dipole moments to such fields. According to theoretical estimates of Wang, Ru, and Mioduchowski (2006), frequencies of microtubular longitudinal vibration modes fall into the Megahertz and Gigahertz domains; tubulin monomers, as most of the proteins, oscillate also in the Terahertz part of the spectrum (Orlando & Gallerano, 2009). Microtubule vibrations are facilitated by the ordered state of the surrounding cytosol as well as by the slip boundary conditions at their surface (Pokorný, 2004). Existence of electromagnetic fields accompanying the mechanical vibrations due to coupling between elastic and polarization properties has been experimentally corroborated in the Megahertz region by Pokorný et al. (2001).

This paper starts, for easy reference, with rudimentary information about the Fröhlich systems and the procedure used for quantitative evaluation of their behavior. This is followed by modeling the impact of an external static electric field on nonlinear terms of the rate equations for modal populations that form the core of Fröhlich's approach. The rest of this paper presents computed results and their interpretation. The prime objective is to show that the presence of intracellular static electric fields enhances nonlinear processes that are a prerequisite for the full unfolding of the hallmark properties of the Fröhlich model, such as condensation of energy in the lowest frequency mode.

## The Fröhlich model

Fröhlich (1968) proposed a semi-phenomenological model, considering a set of $N$ coupled oscillating polar units which is equivalent to an ensemble of $N$ collective vibration modes with discrete frequencies $\nu_1 < \nu_2 < \cdots < \nu_N$. The ensemble forms an open thermodynamic system receiving energy from metabolic pumping source and exchanging it with the intracellular surroundings forming a heat bath with temperature $T$. Excitation of individual modes is expressed by numbers $n_i$ of the energy quanta $h\nu_i$ (h is the Planck constant) resident in the mode $i$, called the occupancy numbers. Accordingly, the pumping



Electromagn Biol Med Downloaded from informahealthcare.com by Dalhousie University on 08/19/13
For personal use only.

is given by number $s_i$ of quanta supplied to the $i$th mode per time unit. Fröhlich postulated a system of equations expressing the balance of changes of the occupancy numbers (k is Boltzmann's constant):

$$\frac{\mathrm{d}n_i}{\mathrm{d}t} = s_i - \Phi_i\left[n_i \exp\left(\frac{\mathrm{h}\nu_i}{\mathrm{k}T}\right) - (n_i+1)\right] - \sum_{j\neq i, j=1}^{N} X_{ij}\left[n_i(n_j+1)\exp\left(\frac{\mathrm{h}\nu_i}{\mathrm{k}T}\right) - (n_i+1)n_j \exp\left(\frac{\mathrm{h}\nu_j}{\mathrm{k}T}\right)\right]. \quad (1)$$

The term on the left is the total rate of change of the occupancy numbers; the second and third terms on the right-hand side represent rates of change of occupancy number $n_i$ due to linear and nonlinear interactions with the heat bath, respectively. The linear interaction, proportional to coupling coefficient $\Phi_i$, represents direct exchange between mode and the heat bath; the nonlinear processes involving simultaneous emission and absorption of quanta – energy transfer between two modes with participation of the heat bath – are proportional to coupling coefficient $X_{ij}$. (*Stricto sensu*, the coupling coefficients themselves may depend on occupancy numbers or temperature. Here we are concerned with effects of the basic nonlinearity given by the last term on the right-hand side of Equations (1) and neglect this possibility.)

Equations in system (1) are mutually coupled and nonlinear which poses a serious obstacle to the study of Fröhlich systems. We developed a diagrammatic representation that affords both numerical evaluations and qualitative insights (Šrobár, 2005, 2009; Šrobár & Pokorný, 1996, 1999) for ensembles with small $N$ values which were shown to evince the essential property of the Fröhlich systems, the condensation of energy in the lowest order mode ($i = 1$). In this study we will work with three oscillators.

To get the $n_i$ versus $s$ dependence, we start with the steady state ($\mathrm{d}/\mathrm{d}t = 0$) form of the equation set (1), which for $N = 3$ and using shorthand notation $p_i = \exp(\mathrm{h}\nu_i/\mathrm{k}T)$ reads

$$\begin{aligned} s &= \Phi[n_1p_1 - (n_1+1)] + X[n_1(n_2+1)p_1 - (n_1+1)n_2p_2 + n_1(n_3+1)p_1 \\ &\quad - (n_1+1)n_3p_3], \\ s &= \Phi[n_2p_2 - (n_2+1)] + X[n_2(n_1+1)p_2 - (n_2+1)n_1p_1 + n_2(n_3+1)p_2 \\ &\quad - (n_2+1)n_3p_3], \\ s &= \Phi[n_3p_3 - (n_3+1)] + X[n_3(n_1+1)p_3 - (n_3+1)n_1p_1 \\ &\quad + n_3(n_2+1)p_3 - (n_3+1)n_2p_2]. \end{aligned} \quad (2)$$

Here we suppose uniform pumping $s_i = s$ and equal coupling coefficients $\Phi_i = \Phi$, $X_{ij} = X$ ($i = 1,\ 2,\ 3$). These simplifications do not present a significant loss of generality and help to highlight the essential features of the model. The diagrammatic method of extracting explicit $n_i$ versus $s$ dependences from Equation (2) is described in the study of Šrobár and Pokorný (1996, 1999).

Figure 1 presents an example demonstrating the general character of the $n_i - s$ dependences in the millimeter-wavelength spectral region. Two cases are considered, both having equal value of the linear coupling ($\Phi = 0.01\,\mathrm{s}^{-1}$) and differing in the value of nonlinearity coefficient. For strong nonlinear coupling ($X = 0.001\,\mathrm{s}^{-1}$, solid lines), the phenomenon of energy condensation is observed: for sufficiently high pumping $s$ the incoming energy is deposited in the lowest order (or fundamental) mode ($i = 1$), whereas the quanta occupancy of the higher-order

Electromagn Biol Med Downloaded from informahealthcare.com by Dalhousie University on 08/19/13
For personal use only.

© Informa UK Ltd

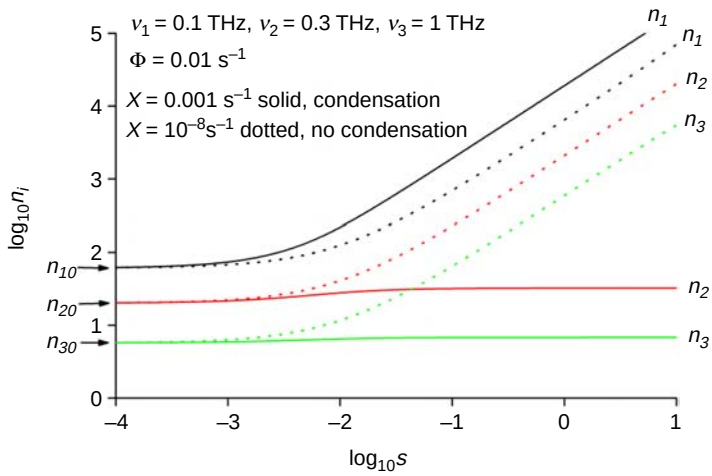



Figure 1. Dependences of modal occupancy numbers $n_i$ on pumping rate $s$ for modal frequencies in the millimeter-wavelength spectral region. Solid lines: large nonlinear coupling coefficient $X = 10^{-3}\,\mathrm{s}^{-1}$; dotted lines: $X = 10^{-8}\,\mathrm{s}^{-1}$, small nonlinear coupling. Value of the linear coupling coefficient is $\Phi = 0.01\,\mathrm{s}^{-1}$ in both cases.

modes 2 and 3 remains unchanged. For negligible nonlinear coupling ($X = 10^{-8}\,\mathrm{s}^{-1}$, dotted lines), populations of all three modes benefit equally from the energy inflow.

## Dependence of the nonlinear coupling coefficient *X* on the static electric field intensity *E*

The quantum mechanical platform for the Fröhlich model, created *ex post facto*, is the Wu–Austin Hamiltonian (Wu & Austin, 1977, 1981); it contains coupling quantities that can be put in relation to Fröhlich's coupling coefficients Φ and *X*. The Wu–Austin Hamiltonian has certain properties that evoke reservations (Bolterauer & Ludwig, 1994) which have not been satisfactorily corrected (Turcu, 1997); anyway, trustworthy numerical values of parameters figuring in the first-principles approach

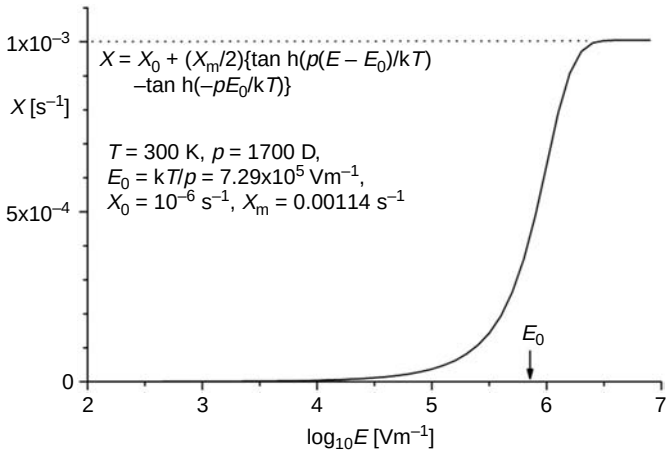



Figure 2. Plot of analytic expression constructed to represent the dependence of nonlinear coupling coefficient $X$ on electric field intensity $E$.



Electromagn Biol Med Downloaded from informahealthcare.com by Dalhousie University on 08/19/13
For personal use only.

are difficult to obtain. Here, in line with the spirit of the original Fröhlich work, we use a phenomenological ansatz for the dependence of coefficient $X$ on static electric field intensity $E$ constructed so as to comply with certain plausibility conditions.

In the first place, the basic mechanism involved is molecular dipole orientation in the external field. This may be accompanied by a decrease in symmetry of the potential profile in which the dipoles are embedded. In such a case, field dependence of polarization would contain higher-order terms as is the case in nonlinear optics (Boyd, 2008), meaning spectral redistribution as envisaged by Fröhlich. One can further expect that the $X$ versus $E$ dependence would start for $E = 0$ with some small residual value $X_0$, achieve the greatest steepness $dX/dE$ at or near the point $E_0$ for which dipole energy in the field equals thermal energy, $pE_0 = kT$ (with $p$ the dipole moment), and would saturate at high electric fields, after all dipoles have been oriented by the field.

Figure 2 shows an example of such dependence prepared so that $X$ starts with $X_0 = 10^{-6}\,s^{-1}$ for $E = 0$, reaches the limit of $1 \times 10^{-3}\,s^{-1}$ for $E \to \infty$ and exhibits maximal steepness at $E = E_0$. It is given by the expression:

$$X = X_0 + \frac{X_m}{2}\tanh\frac{p(E - E_0)}{kT} - \tanh\left(-\frac{pE_0}{kT}\right), \tag{3}$$

where $X_m = 1.14 \times 10^{-3}\,s^{-1}$, $E_0 = kT/p = 7.29 \times 10^5\,Vm^{-1}$, $T = 300\,K$ and $p = 1700\,D$. (The latter value pertains to tubulin dimers.) This is the $X(E)$ dependence used in the numerical examples that follow. It should be stressed once more that it was not derived but constructed so as to fulfill the above requirements.

## Numerical study: The mode occupation numbers versus electric field for various excitation levels

The series of Figures 3–5 presents the dependences of modal occupancy numbers $n_i$ ($i = 1, 2, 3$) on intensity of the applied static electric field for three pumping regimes: low ($s = 10^{-4}\,s^{-1}$), medium ($s = 0.01\,s^{-1}$) and high ($s = 1\,s^{-1}$). The (rather laborious) procedure used to obtain these data involved computing a set

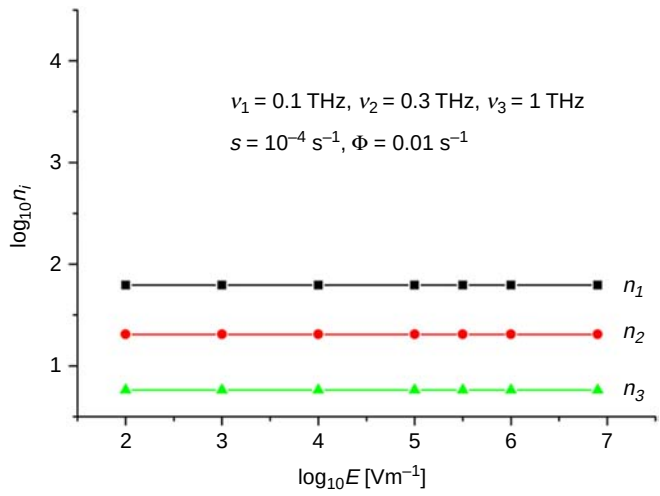



Figure 3. Dependence of the modal occupancy numbers $n_i$ on electric field intensity $E$ for small level of the pumping rate $s = 10^{-4}\,s^{-1}$.

© Informa UK Ltd

Electromagn Biol Med Downloaded from informahealthcare.com by Dalhousie University on 08/19/13
For personal use only.

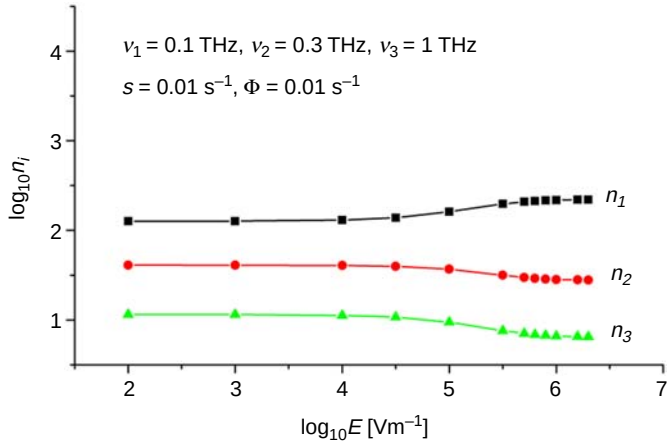



Figure 4. Dependence of the modal occupancy numbers $n_i$ on electric field intensity $E$ for medium level of the pumping rate $s = 0.01\,\mathrm{s}^{-1}$.

of the $n_i$ versus $s$ dependences for constant Φ values ($0.01\,\mathrm{s}^{-1}$ in all cases) and various $X$ values, grouping together $n_i$ values pertaining to given $s$ and $X$, and converting $X$ values into $E$ using Equation (3).

At low excitation ($s = 10^{-4}$ s, Figure 3), the field has no apparent influence on occupation numbers. Increasing excitation to medium levels ($s = 0.01\,\mathrm{s}^{-1}$, Figure 4) leads to signs of energy condensation at sufficiently high fields ($E > 10^5\,\mathrm{Vm}^{-1}$): occupation of the fundamental mode ($i = 1$) is increased at the expense of the higher-order modes ($i = 2$ and 3). At the high excitation level $s = 1\,\mathrm{s}^{-1}$ (Figure 5), there is full-blown energy condensation phenomenon apparent already at relatively modest fields ($E > 10^4\,\mathrm{Vm}^{-1}$), whereby populations of the higher-order modes are drastically depleted with increasing field intensities whereas the fundamental mode occupancy increases.

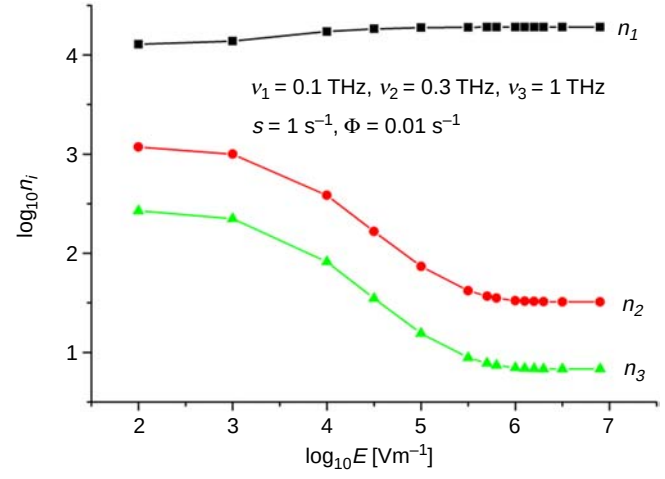



Figure 5. Dependence of the modal occupancy numbers $n_i$ on electric field intensity $E$ for high level of the pumping rate $s = 1\,\mathrm{s}^{-1}$.



Electromagn Biol Med Downloaded from informahealthcare.com by Dalhousie University on 08/19/13
For personal use only.

## Discussion and conclusions

The computed results suggest that simultaneous presence of both sufficient metabolic pumping and sufficiently high static electric fields is necessary for the full unfolding of nonlinear properties of the Fröhlich model, in particular the energy condensation in the fundamental mode. To a certain degree, a mild insufficiency in one of these two factors can be compensated by increased level of the other.

Since the pioneering work of Warburg (1924, 1956), mitochondria dysfunction has been associated with cancerous states, the most striking feature being the supplantation of respiratory processes of oxidative phosphorylation of ATP production in healthy cells by the less efficient glycolytic reaction sequences in malignant cells (Carew & Huang, 2002). The aim of this paper was to demonstrate, with the help of a simple model, the possibility of the existence of effect collateral to this metabolic transformation that bears on the character of collective vibrations in microtubules. If these, or rather the accompanying high-frequency electromagnetic fields, fulfill an important part in the cell, the metabolic problem (inefficient ATP production) is compounded by disarray in the physical processes underpinning cell's normal functioning. Diminished Fröhlich-like electromagnetic activity can also disturb intercellular forces, a condition that can facilitate the penetration of malignant cells into healthy tissue by local invasion and metastasis (Pokorný, Hašek, Vaniš, & Jelínek, 2008).

### Declaration of interest

This work was supported by the Czech Science Foundation (project #102/11/0649). The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

Electromagn Biol Med Downloaded from informahealthcare.com by Dalhousie University on 08/19/13
For personal use only.

## References

Bolterauer H, Ludwig LA (1994). Difficulties in the theoretical foundation of Fröhlich's model. Neural Netw World 4:255–268.

Boyd RW (2008). *Nonlinear optics* (Chapter 1). London: Academic Press.

Carew JS, Huang P (2002). Mitochondrial defects in cancer. Mol Cancer 1:9–20.

Fröhlich H (1968). Bose condensation of strongly excited longitudinal electric modes. Phys Lett 26A: 402–404.

Kirson ED, Gurvich Z, Schneiderman R, Dekel E, Itzhaki A, Wasserman Y, Schatzberger R, Palti Y (2004). Disruption of cancer cell replication by alternating electric fields. Cancer Res 64:3288–3295.

Kirson ED, Dbalý V, Tovaryš F, Vymazal J, Soustie R, Wasserman Y, Salzberg M, et al. (2007). Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. Proc Natl Acad Sci USA 104:10152–10157.

Nogales E, Wolf S, Downing KH (1998). Structure of the tubulin dimer by electron crystallography. Nature 291:199–203.

Orlando AR, Gallerano GP (2009). Terahertz radiation effects and biological applications. J Infrared Milli Terahz Waves 30:1308–1318.

Pokorný J (2004). Excitation of vibration in microtubules in living cells. Bioelectrochemistry 63: 321–326.

Pokorný J, Hašek J, Jelínek F, Šaroch J, Palán B (2001). Electromagnetic activity of yeast cells in the M phase. Electro Magnetobiol 20:371–396.

Pokorný J, Hašek J, Vaniš J, Jelínek F (2008). Biophysical aspects of cancer electromagnetic mechanism. Indian J Exp Biol 46:310–321.

Rappaport L, Oliviero P, Samuel JL (1998). Cytoskeleton and mitochondrial morphology and function. Mol Cell Biochem 184:101–105.

Šrobár F (2005). Fröhlich system with modulated access to pumping source. Electromagn Biol Med 24: 265–272.

© Informa UK Ltd

Šrobár F (2009). Occupation-dependent access to metabolic energy in Fröhlich systems. Electromagn Biol Med 28:194–200.
Šrobár F, Pokorný J (1996). Topology of mutual relationships implicit in the Fröhlich model. Bioelectrochem Bioenerg 41:31–33.
Šrobár F, Pokorný J (1999). Causal structure of the Fröhlich model of cellular electromagnetic activity. Electro Magnetobiol 18:257–268.
Turcu I (1997). A generic model for the Fröhlich rate equations. Phys Lett A 234:181–186.
Tyner KM, Kopelman R, Philbert MA (2007). Nanosized voltmeter enables cellular-wide electric field mapping. Biophys J 93:1163–1174.
Wang CY, Ru CQ, Mioduchowski A (2006). Vibration of microtubules as orthotropic elastic shells. Physica E 35:48–56.
Warburg O (1924). Über den Stoffwechsel der Carcinomzelle. Biochem Z 152:309–318.
Warburg O (1956). On the origin of cancer cells. Science 123:309–314.
Wu TM, Austin SJ (1977). Bose condensation in biosystems. Phys Lett A 64:151–152.
Wu TM, Austin SJ (1981). Fröhlich's model of Bose condensation in biological systems. J Biol Phys 9: 97–107.

Electromagn Biol Med Downloaded from informahealthcare.com by Dalhousie University on 08/19/13
For personal use only.