ROLE OF NON-LINEAR INTERACTIONS BY THE ENERGY CONDENSATION IN FRÖHLICH SYSTEMS

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Abstract: Properties of the Fröhlich model of collective oscillations of polar molecules (such as proteins) residing inside, or in the plasma membrane, of biological cells, receiving energy from intracellular metabolic sources and giving it off to surroundings, are studied. The exchange mechanisms with the heat bath can be linear and non-linear. Particular attention is given to condensation of energy in the lowest-frequency (fundamental) mode. Occurrence of this phenomenon, which is of importance for generation of electromagnetic fields by the cells as well as for other functions, presupposes that the non-linear interaction coefficient exceeds certain limit; if it is too small, the incoming energy is distributed to all modes. This can happen e.g. in the context of cancerous conditions due to perturbation of high static electric fields around mitochondria which are necessary support for non-linear behaviour. On the contrary, if interaction with the heat bath is too high, the oscillator system leaks energy to surroundings and must be pumped heavily to attain condensation.

Key words: *Fröhlich systems, energy condensation in biology, bioelectromagnetic phenomena*

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1. Introduction

The contribution of physics to the panoply of experimental tools of biology and medicine is generally appreciated: the DNA double helix would not have been discovered without x-ray structural analysis; electron microscopy, nuclear magnetic resonance spectroscopy and imaging are household names in the biological and medical community these days. Less visible, but of comparable importance for the development, are theoretical concepts and thematic frameworks transferred from physics to the realm of biology. The work of the Anglo-German scientist Herbert

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Fröhlich is a prominent example of this process. Fröhlich had already made groundbreaking contributions to various branches of physics, most notably to the theory of dielectrics and superconductivity when, aged 63, he published his first paper in biophysics [1]. He was intrigued by the idea of a system whose bulk is near thermal equilibrium while some of its degrees of freedom are highly excited.

Fröhlich's attention was captured by the huge electric dipoles of large molecules (mostly proteins) populating membranes and interior of biological cells [2]. He suggested that interactions among these polar entities would lead to collective modes of behaviour, in particular to coherent longitudinal polarisation oscillations. A system of rate equations for quantum-mechanical occupation numbers of oscillation modes forms the core of the Fröhlich's model. As far as the frequency is concerned, Fröhlich's original estimate was in the vicinity of 10^{11} Hz, i.e. in the millimetre-wavelength region, but considering the diversity of oscillating species, both lower and higher frequencies may also be expected. Given the minute dimensions of the cells, the power of the oscillations is expected to be extremely small, on the order of femto-Watts or less [3]. In conjunction with the fact that measurements cannot be effected at low temperatures to suppress noise, this means that the search for experimental proofs lies at the frontier of possibilities offered by modern science [4–6]. Short spatial range of the endogenous electromagnetic fields (at the order of 100 nm) poses another serious difficulty. Progress in nanotechnology and cell-manipulation techniques [7, 8] holds significant promise in this direction. Recent employment of nanoparticles consisting of voltage-sensitive dyes [9] affords measurements of static or low-frequency (< 1 kHz) electric fields on a sub micrometer scale. These studies reveal an electrically complex landscape in the cell's interior.

Froehlich's ideas about the role of coherence in cellular physiology and the possible links to malignant processes have been pursued by a number of authors, e.g. [10–13], within the general frameworks of non-equilibrium thermodynamics and quantum mechanics.

In this paper, after a short prelude devoted to intracellular energy sources, the essentials of the Fröhlich's model are given with emphasis on the energy condensation phenomenon. (This appellation makes reference to the Bose and Einstein work on statistical mechanics of particles with integer spins – bosons - which can share quantum states without restriction. Quanta of oscillation modes can, in a certain sense, be likened to bosons.) Subsequently, influence of changing linear and non-linear interactions of the oscillating system with the ambient is examined. The dependences accompanying the exposition were computed using a diagrammatic method [14] which also provides useful insights into the causal texture of the model [15–18].

2. Role of Mitochondria in Cell Energetics

Prior to delving into the patterns of energy flow in the Fröhlich systems, some basic information about intracellular energy sources might be useful. In eukaryotic cells, the universal energy currency, the ATP, is mainly synthesised in semi-autonomous double-membrane organelles called mitochondria. This is where respiratory chain subunits and enzymes assisting them reside and operate. The flux of electrons down

the chain results in an efflux of protons which is responsible for negative membrane potential. Using nanosize voltmeter technique [9], presence of high electrostatic fields, on the order of 10^6 VM^{-1}, was demonstrated around mitochondria. A prominent enzyme, the H^+-ATP synthase, uses the stored electrochemical energy of the barrier to synthesise ATP molecules.

Efficiency of mitochondrial ATP production is quite high, about 40% in healthy cells. Nonetheless, this leaves an important portion (about 60%) of energy carried in chemical form into mitochondria which is not utilised for ATP formation [19]. Given the general economy of processes in living matter, that was perfected over aeons of time, it can be reasonably supposed that this energy, instead of being wasted, is used in the cell's household for useful purposes. A prominent candidate would be the energy alimentation of Fröhlich-type systems such as microtubules.

In cancer cells this energy flow is disturbed: mitochondrial respiration is supplanted, in the role of major ATP producer, by fermentation delocalised in cytoplasm. The amount of ATP may not be much less than in healthy cells, but important structural features, among them energy influx to Fröhlich oscillators, are lost by this change. The ideas of suppression of mitochondrial energy production, elaborated 85 years ago by O. Warburg [20, 21], are now renascent and influence current cancer research [22–24].

3. Rate Equations for Occupation Numbers of the Collective Oscillation Modes

Fröhlich envisaged a set of N oscillating polar units (protein molecules or, according to modern notions, higher-order entities like microtubules and other cytoskeleton components) receiving energy from intracellular sources. If these units interact mutually, as they do, they form a system of N collective modes of oscillations with frequencies ν_i (i = 1, 2, ..., N). In thermodynamic equilibrium, the occupation numbers of the oscillators (number of energy quanta) are given by Bose-Einstein statistics: $n_{i0} = [\exp(h\nu_i/kT - 1]^{-1}$, with h and k the Planck and Boltzmann constants, respectively, and T the absolute temperature. The energy inflow excites the oscillator system and pours finally into the heat reservoir. Coupling with the reservoir can be linear (the Φ-process, oscillating mode exchanging energy with the heat bath) or non-linear (the X-process, involving simultaneous emission and absorption of quanta, energy transfer between two modes with participation of the heat bath). Temporal evolution of the occupation numbers under excitation s_i (number of energy quanta supplied per time unit) is given by the set of rate equations

$$\begin{aligned}\frac{dn_i}{dt} &= s_i - \Phi_i \left[n_i \exp\left(\frac{h\nu_i}{kT}\right) - (n_i + 1) \right] \\ &\quad - \sum_{j \neq i,\, j=1}^{N} X_{ij} \left[n_i \, (n_j + 1) \exp\left(\frac{h\nu_i}{kT}\right) - (n_i + 1) \, n_j \exp\left(\frac{h\nu_j}{kT}\right) \right]. \quad (1)\end{aligned}$$

The coupling coefficients Φ_i and X_{ij} represent transition probabilities. Perhaps the following shorthand version of these equations conveys more intuitive meaning for readers not versed in mathematics (dots above symbols mean time derivation, d/dt) :

$$\dot{n}_i = s_i - [\dot{n}_i]_\Phi - [\dot{n}_i(n_i, n_j)]_X. \tag{2}$$

It tells us that the total change of occupation numbers per second equals the rate of their increase by pumping minus the rate of losses to the heat bath by linear and non-linear processes. The latter two terms represent a damping of the oscillator system.

In order to demonstrate energy condensation properties of the rate equations, steady-state ($d/dt = 0$) condition is considered. In the terahertz frequency domain and for Φ and X values near 0.01 s^{-1}, the steady-state of the oscillator ensemble is reached within several minutes following application of the energy influx [25].

4. The Phenomenon of Energy Condensation

We have demonstrated [16] that prominent attributes of the Fröhlich systems are evinced already by oscillator ensembles encompassing small number of members ($N = 2$ and $N = 3$). This greatly facilitates examination of the Fröhlich systems given the non-linearity of the rate equations. In this study we work with an $N = 3$ ensemble; steady-state rate equations then have the form $s_i = f_i(n_1, n_2, n_3)$, $i = 1, 2, 3$; functions f_i are nonlinear. We assume, without loss of generality, that $\Phi_i = \Phi$ and $X_{ij} = X$. To make this text more palatable for readers with background in biology and medicine rather than in physics, we skip over the computation details involving diagrammatic analysis [14, 15] and present the results in the form of dependences relevant for demonstrating the energy condensation. Two triples of modal frequencies (ν_1, ν_2, ν_3) are chosen to flank what is called the microwave region of the electromagnetic spectrum – frequencies between 0.3 GHz and 0.3 THz, or wavelengths between 1 m and 1 mm. This might cover the frequencies of the breathing and rocking movements of biological macromolecules.

Fig. 1 shows, in log-log scales, the dependences of modal occupancy numbers n_i on the pumping rate s for frequencies ν_i in the terahertz region. Two sets of curves correspond to the cases of significant ($X = 0.001$ s^{-1}, solid lines) and negligible ($X = 10^{-8}$ s^{-1}, dotted lines) non-linear component of the energy transfer, respectively. The first instance (solid lines) exemplifies the phenomenon of energy condensation in the lowest-frequency, or fundamental, mode: while populations of the two higher-order modes ($i = 2$ and 3) are not responding to increasing energy influx, remaining virtually at their equilibrium values n_{20} and n_{30}, the fundamental mode has its population n_1 increased – beyond certain pumping level the incoming energy is channelled exclusively into this mode. The situation is diametrically different if the non-linear interaction with the heat bath is suppressed (dotted lines). Here populations of all three modes benefit equally from the increased pumping.

Fig. 2 shows the analogous situation in the gigahertz region. The energy quanta $h\nu_i$ ($\approx 4 \times 10^{-6}$ eV for 1 GHz) are now three orders of magnitude lower than in

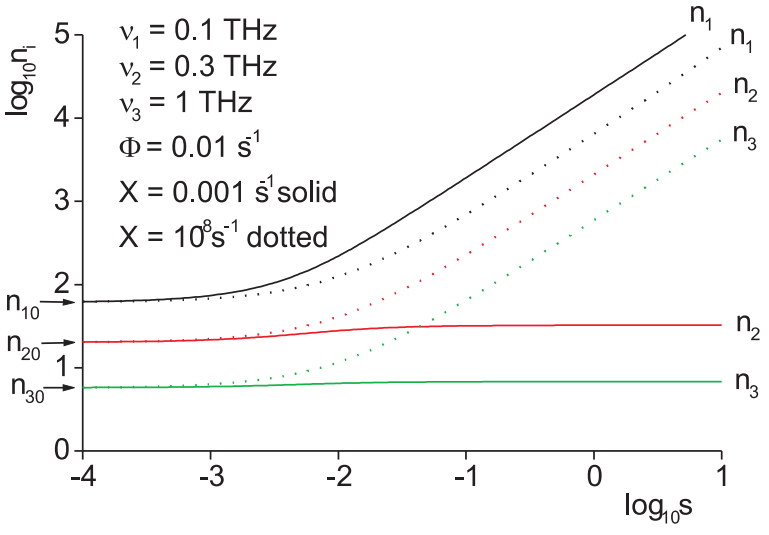


Fig. 1 *Dependences of the modal occupation numbers n_i on pumping p for frequencies in the terahertz (10^{12} s^{-1}) region. Log-log scales; numerical values of the parameters involved are indicated in the figure. Solid lines – feeble, dotted lines – strong non-linear coupling X with the heat bath.*

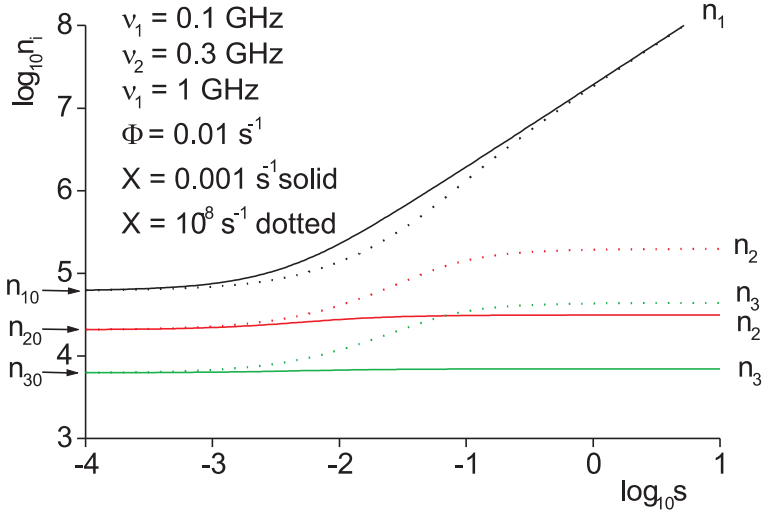


Fig. 2 *Dependences of the modal occupation numbers n_i on pumping p for frequencies in the gigahertz (10^{9} s^{-1}) region. Log-log scales; numerical values of the parameters involved are indicated in the figure. Solid lines – feeble, dotted lines – strong non-linear coupling X with the heat bath.*

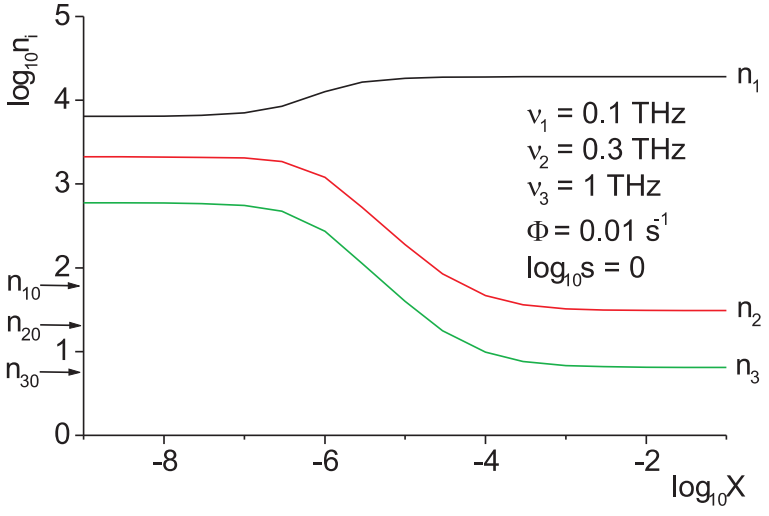


Fig. 3 *Dependences of modal populations n_i at fixed pumping level $s = 1$ on the magnitude of non-linear transition probability X (log-log scale, terahertz frequency region).*

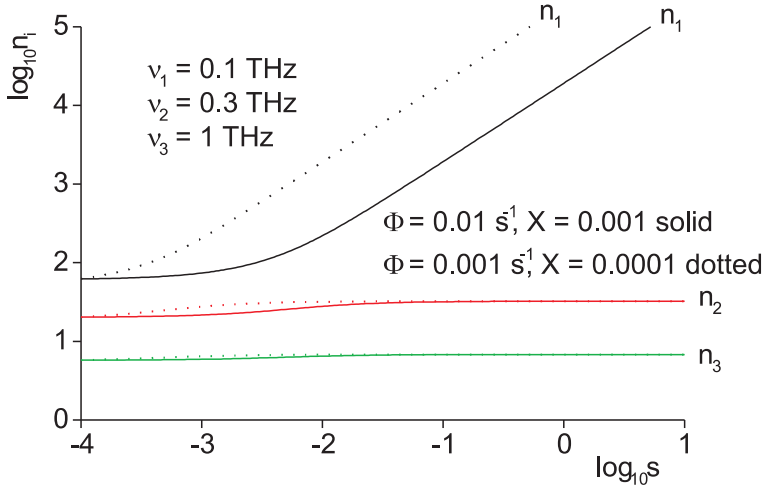


Fig. 4 *Dependences of the modal occupation numbers n_i on pumping p for two sets of transition probabilities Φ and X, representing strong (solid lines) and feeble (dotted lines) interaction with the heat bath. (Log-log scale, terahertz frequency region).*

the THz domain ($\approx$ 4 meV for 1 THz). (The energy deposited in oscillators is not that much different, as the occupancy numbers are now by about three orders of magnitude higher, see difference in the vertical scales of both figures.) With a sizeable contribution of the non-linear term in the rate equations ($X = 0.001$ s^{-1}, solid lines), there is again energy condensation in the fundamental mode. With negligible non-linear interaction ($X = 10^{-8}$ s^{-1}, dotted lines), however, one can see the condensation pattern eroded: even though pumping energy is preferentially channelled into the fundamental mode, the two higher-order modes also receive a not inconsiderable portion of the energy flow.

The impact of the magnitude of non-linear interactions with the heat bath on behaviour of Fröhlich systems is further pursued in Fig. 3 in which populations of the three modes at a fixed high level of pumping ($s = 1$, corresponding to well-developed energy condensation in cases where it can occur) are plotted against transition probability X. One can see that energy condensation, i.e. condition $(n_1 \gg n_2)$ & $(n_1 \gg n_3)$, requires elevated values of $X (X > \approx 3x10^{-6}$ s^{-1} in the THz region). For lower values of X the incoming energy flow is distributed in a more equalitarian manner. Note that even for negligible non-linear coupling ($X = 10^{-9}$ s^{-1}) all three modes are – at this high level of pumping – populated substantially in excess of the thermal equilibrium values n_{i0} that are marked on the vertical axis with arrows.

High values of the transition probabilities Φ and X mean that the oscillator system is more leaky, hence more intense pumping is necessary to attain condensation in the fundamental mode than in the case where Φ and X are smaller (Fig. 4). Increased phosphorylation of the protein side chains, which may be caused by cancer protein kinases [19], is an example of a mechanism intensifying energy exchange with the surrounding medium (increasing values of Φ and X) and thereby rendering energy condensation less attainable.

We have envisaged three modes in the Fröhlich ensemble; in real situations their number would be much higher. Therefore condensation of metabolic energy into just one mode affords to achieve marked departure from thermal equilibrium, which is required e.g. for generation of electromagnetic fields or for some other intracellular operations, with high efficiency.

5. Conclusions

The Fröhlich model envisages energy flow from intracellular sources through the oscillator ensemble to the heat reservoir. Part of the energy is deposited, or condensed, in the highly excited state of the fundamental mode. This happens only if the non-linear component of the energy exchange with the heat reservoir surpasses certain limit. However, if the coupling with the heat bath is too strong, as may be the case of protein phosphorylation caused by cancer protein kinases, the oscillator system must be more heavily pumped to reach threshold of condensation. The phenomenon of energy condensation is crucial for creation of conditions favourable for formation of electromagnetic fields by biological cells. If these effects play an important part in the vital intracellular processes, as we feel they do, here one has a link between the Fröhlich theory and an important facet of the cancer research.

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