Electromagnetic Biology and Medicine, 26: 45–62, 2007

ISSN 1536-8378 print
DOI: 10.1080/15368370701205677

informa
healthcare

Magnetobiology: The kT Paradox and Possible Solutions

V. N. BINHI[1] AND A. B. RUBIN[2]

[1]General Physics Institute, Russian Academy of Sciences, Moscow, Russian Federation
[2]Moscow State University, Moscow, Russian Federation

The article discusses the so-called 'kT problem' with its formulation, content, and consequences. The usual formulation of the problem points out the paradox of biological effects of weak low-frequency magnetic fields. At the same time, the formulation is based on several implicit assumptions. Analysis of these assumptions shows that they are not always justified. In particular, molecular targets of magnetic fields in biological tissues may operate under physical conditions that do not correspond to the aforementioned assumptions. Consequently, as it is, the kT problem may not be an argument against the existence of non thermal magnetobiological effects. Specific examples are discussed: magnetic nanoparticles found in many organisms, long-lived rotational states of some molecules within protein structures, spin magnetic moments in radical pairs, and magnetic moments of protons in liquid water.

Keywords kT problem; Magnetobiological effect; Magnetosome; Molecular gyroscope; Proton exchange interaction.

Introduction

The nature of biological effects of weak electromagnetic fields remains unclear, despite numerous experimental data. The difficulty in explaining these effects is usually related to the fact that an energy quantum of the low-frequency electromagnetic field (EMF) is essentially less than the characteristic energy of chemical conversions, of the order of dozens of k_BT. It is generally recognized that this fact reveals a paradox and even seems to prove the impossibility of magnetobiological effects. This problem is known in the literature as the 'kT problem'.

We will specify that the magnetic fields (MFs) in question are the fields of the order of geomagnetic field intensity and frequencies at the extremely low-frequency

Address correspondence to V. N. Binhi, General Physics Institute, Russian Academy of Sciences, 38 Vavilova St., Moscow 119991, Russian Federation; E-mail: binhi@kapella.gpi.ru

(ELF) range, from units to hundreds of hertz. Such fields do not cause any essential inductive heating.

It is necessary to outline the difference between chemical and physical detecting of small magnetic signals. In physics, there is no kT problem in such an acute form. On the whole, it is understandable how weak MFs can affect one or another physical process. As a rule, detecting of a weak MF is performed by converting it into an electrical signal by means of a physical process or a device. There are quite a number of such devices: a frame antenna, flux-gate, magnetooptical sensor, SQUID, and others. Then, the electrical signal is accumulated by a well-known technique up to the level exceeding that of the thermal noise. Physical converters are so effective that measuring weak MFs of the order of the geomagnetic field is completed practically in a moment. Only detecting of superweak MFs below the pT level may require decreasing of the noise level by cooling the converter, as it takes place in magnetooptical and SQUID-magnetometers, and appreciably increasing the time of the signal accumulation.

The observed changes in biological characteristics under the MF exposure should be due to the substantial changes in concentrations of corresponding chemicals brought about by changes in the rates of chemical reactions. In contrast to the aforementioned physical measurements, a weak magnetic signal here should be detected by a chemical converter at the physiological temperature and at the limited time interval. However, at first sight, the reaction rates can not be changed under MF. In a constant field, magnetic energy of the reagents is many orders of magnitude less than their thermal energy, and in an ac field, a quantum energy of the field is extremely less than $k_B T$. The only reliable magnetochemical converter is a magnetosensitive process with free radical pairs, but such a process is ineffective in MFs of the order of the geomagnetic field. Consequently, magnetochemical converters in organisms should be based on some other principles. It is at this point the paradox arises since the nature of corresponding processes has not yet been revealed.

The kT problem seems to have been formulated for the first time in the 1960s, in the broad sense, with respect to the biological effects of electromagnetic (EM) microwaves. At that time, microwaves were discovered to cause different biological effects at rather small energy flux densities of the order of $0.1\,mW/cm^2$, well below the thermal limit (Devyatkov, 1973). Though the energy quantum of such EM fields was 1–3 orders lower than $k_B T$, some physical mechanisms have been developed that take into account collective excitations in biological structures (Fröhlich, 1968b; Pokorny and Wu, 1998).

Particularly effective were modulated microwaves, with a modulating signal in the ELF range (Bawin et al., 1973). Later, it was found that the modulating signal itself, as a weak magnetic field signal, can affect the state of an organism appreciably (Liboff et al., 1984). Since then, a number of evidences have been accumulated showing that weak static and ELF MFs cause variety of biological effects (Volpe, 2003). The kT paradox is especially dramatic in such cases, as the energy quantum of the ELF magnetic field was many orders of magnitude (11–12) less than $k_B T$.

However, the kT problem as formulated above clearly contains three implicit assumptions:

- Primary magnetoreception occurs at the atomic or molecular level;
- The interaction of an ac MF and a molecular target is a single-quantum process; and
- The interaction of the field and the target occurs under thermal equilibrium conditions.

At the same time, these assumptions or postulates are not quite substantiated and they should be clarified. In one form or another, the kT problem was discussed previously in Fröhlich (1968a), Chernavsky (1973), Betskii (1993), and Binhi and Savin (2003). However, there is no general opinion yet as to whether it is correctly formulated or not. In this article, we consider the postulates of the kT problem. Our analysis shows that the postulates are not completely correct: besides molecular targets, relatively large particles with almost macroscopic magnetic moment may be found in organisms. In regard to molecular targets, their interaction with low-frequency magnetic field is of multiple-quantum character and may develop in the absence of thermal equilibrium.

Submicron Level of Magnetoreception

In many organisms, magnetic nanoscale particles consisting of magnetite crystals were found. Magnetic moment μ of these particles exceeds the elementary one by 7–9 orders. The energy of their turn in the weak magnetic field H is significantly greater than the energy of thermal fluctuations $k_B T$.

Of particular interest are magnetite particles found in brain tissues of many animals and humans. They proved to have a biogenic origin, i.e., they form as a direct result of the crystallization in a brain matter. Particles of biogenic magnetite are often called 'magnetosomes'; they were first discovered in bacteria that displayed magnetotaxis (Blakemore, 1975). As was discussed recently, magnetic nanoparticles could be produced also in DNA complexes (Khomutov, 2004). The contents of magnetosomes in a human brain is greater than $5 \cdot 10^6$; in brain envelope, there are more than 10^8 crystals per gram (Kirschvink et al., 1992). The content of magnetite in human brain is equal to about 50 ng/g on average (Dobson, 2002).

The energy of a 100-nm magnetosome in the geomagnetic field is approximately $24\ k_B T$. So, when exposed to an additional alternating magnetic field h, its regular changes are about $(h/H_{geo})24\,k_B T$. If these regular changes exceed thermal fluctuations $k_B T/2$, they can cause biological response.

The obvious inequality $(h/H_{geo})24\,k_B T > k_B T/2$ sets a natural limitation on the alternating MF magnitude capable to affect biochemical system: $h > 1 - 2\,\mu\mathrm{T}$. As was shown in Binhi and Chernavskii (2005), the biologically detectable level of the MF may be even tenfold less if magnetosomes rotate in a double-well energy potential. In this case, the thermal fluctuations contribute to the capability of a weak magnetic stimulus to cause a response. The MF produced by magnetosomes is rather intensive and is of the order of 0.1 T in the vicinity of the magnetosome surface. So, its rotations can distinctly affect the rate of free-radical reactions.

As proved today, such effects as precise orientation of many biological species during their seasonal migrations are based on the MF interaction with magnetosomes (Walker et al., 2002). Apparently, in this case there is no kT problem

in its traditional formulation as the primary magnetoreception does not occur at the molecular level but rather at the submicron level of relatively large particles interacting with MF. The real problem concerns particular biophysical mechanisms underlying this kind of magnetoreception and the limits of susceptibility to constant and alternating MFs (Binhi, 2006; Ritz et al., 2004).

Multiple-Quantum Magnetic Field Interaction with a Molecular Target

As suggested in the kT problem, atomic and molecular processes might be the target of MF in magnetobiological effects. However, then it is not clear whether other postulates of the kT problem are true, such as single-quantum MF interaction with the target. This question is closely related to the method of the EM field description, i.e., classical or quantum mechanical one.

The classical description is valid for the populations of the energy levels of elementary EMF oscillators, in a quantum treatment, large enough as compared with unity. A criterion for the validity of the classical description has been derived in Berestetskii et al. (1982) based on general estimates

$$H \gg \sqrt{\hbar c}\left(\frac{f}{c}\right)^2, \tag{1}$$

which relates the frequency f and the classical amplitude H of the magnetic EMF component. Numerically, $H \gg 10^{-29} f^2$. It follows that the classical description is valid, in the ELF range, up to vanishingly small amplitudes. The criterion (1) is derived assuming the isotropy and wide enough spectrum ($\Delta f \sim f$) of the EM radiation. Taking into account the directional characteristics of the MFs produced by laboratory solenoids and the frequency stability of low-frequency electric power generators just makes the application of the classical approach to ELF MFs even more justified.

In such a way, the so-called semiclassical approximation is sufficient to describe the state of a molecular target interacting with low-frequency MF. In that approximation, the dynamic equation of the system has the form of the Schrödinger equation, and the EMF enters into the equation in the form of *parameters*, as a vector **A** and a scalar A_0 potentials of the classical field, and not in the form of field variables or *quanta*.

In quantum electrodynamics, EMF states close to the classical states are known to be described by means of the so-called coherent states, which minimize the quantum uncertainty. The coherent states are multiple-quantum field excitations. Therefore, the interaction with the classical field is also a multiple-quantum one. Hence, the absorption of a single quantum of an ELF field is just a speculative process. Thus, such a process cannot be the real basis to assert the possibility or impossibility of the biological effects of ELF MFs.

The concept of EMF quanta, even those of the ELF MF, is useful when the transduction of a weak MF signal from the field to a target is considered. It is reasonable to define the process of energy transfer by a number of quanta absorbed by a target in the unit of time. The specific structure or the physical nature of the molecular target is an important question. However, this question should be analyzed separately from the general problem of ELF EMF interactions with a quantum system.

Generally, to evaluate the sensitivity of a detector, an energy flux p is usually introduced, that is the number n of quanta $\hbar\Omega$ absorbed by the receiver during the time interval t of its interaction with the field:

$$p = n\hbar\Omega/t.$$

It means that in order to determine the sensitivity, one needs to specify a time interval t and count the number of quanta absorbed at that interval. Since we try to find the sensitivity limit that follows from general laws of quantum physics, we shall consider an idealized quantum system isolated well enough from the thermostat.

How to choose the time interval t? It should characterize the process of the interaction with respect to the sensitivity and allow counting the number of quanta in principle. It is clear that t may not be arbitrarily large. It can be shown that the energy change of the system in ac MF has the form of oscillations superimposed on an exponential approaching to an asymptotic energy level. Evidently, with the increase in the observation period t, the mean energy change tends to zero. As well, the period t may not be arbitrary small: It takes a certain time θ for the quantum system to change its energy by ε.

It is convenient to choose an interval $t > \theta$ for which the energy of a quantum system does not reach the quasistationary value. Obviously, this time, i.e., time of the coherent interaction, is the least of the two times—the lifetime of the quantum state and the MF autocorrelation time. For the laboratory ELF MF, the autocorrelation time is usually no less than a few seconds, therefore the time of coherent interaction is mainly the lifetime of the quantum state τ determined by the interaction of the quantum system with the thermostat. Then we assume

$$p = n\hbar\Omega/\tau. \tag{2}$$

Constraints on the p value follow from the fundamental quantum mechanical relationship between the energy change of a quantum system ε and the time period θ, which is necessary to register that change (Landau and Lifshitz, 1977)

$$\varepsilon\theta > \hbar.$$

In the case of n quanta, and since $\varepsilon \sim n\hbar\Omega$, this relationship may be written in the form $\theta > 1/n\Omega$. However in any case, the time needed to measure these changes cannot exceed the time of coherent interaction between the field and the atomic system. Hence, the inequalities take place

$$\tau > \theta > \frac{1}{n\Omega},$$

that is $\tau > 1/n\Omega$. After substituting it into the expression (2), we obtain the straightforward estimation of the sensitivity limit

$$p \sim \hbar/\tau^2. \tag{3}$$

The less the measurable energy flux p, the higher is the sensitivity.

So, the sensitivity limit to the ELF EMF is defined by the lifetime of the quantum states of the target–detector (Binhi, 2002). Thus, energy fluxes lower than

(3) cannot be measured. This should be understood as follows. If a detector registers n quanta of the field of a frequency Ω for a time t not larger than the lifetime of the target quantum states, and $n > 1/\Omega\tau > 1$, then the density of energy flux across the target of size a should be equal to

$$S \sim p/a^2 \sim \hbar\left(\frac{n\Omega}{a}\right)^2$$

In the plane wave approximation, the density S equals $cH^2/4\pi$, i.e., it is necessary that MF should be equal to

$$H \sim \frac{2n\Omega}{a}\sqrt{\frac{\pi\hbar}{c}}.$$

For example, let the values of the parameters a, Ω, and τ be equal to 10^{-7} cm, 100 rad/s, and 10 ms, correspondingly. This means that a molecular target of 1 nm in size is under MF of the ELF range and it interacts with the thermostat so that the lifetime of its quantum states is about 10 ms. Then we should take $n = 10^9$ so that the MF is equal to 0.1 mT or 1 G in order of magnitude.

Of course, it does not mean that in MF of that value a target of the given size will absorb 10^9 quanta for 10 ms. It should be stressed that the limit (3) follows only from the fundamental physical principles. The sensitivity of real systems, including biophysical targets, also depends on the probability to absorb EMF quanta. Evidently, it is significantly lower than the sensitivity limit determined by the energy flux (3).

However, it is very important that the probability for EMF quanta to be absorbed is now determined by a specific target structure only. It also determines what the target parameters are and how much they will change as a result of 'summing up' the MF quanta during the time of coherent interaction with the target.

Generally speaking, the above considerations are of a relative character. The use of such notions as number of quanta of EMF, as well as energy states of a quantum system, implies that the field and the quantum system are sufficiently isolated from each other. This means their interaction energy is significantly less than the energies of quantum jumps $\hbar\Omega$ and $\Delta\varepsilon$ between the states of the field and quantum system, correspondingly. For example, in the case of the interaction of optical radiation of a conventional HeNe-laser with an atom, we have

$$\hbar\Omega \sim \Delta\varepsilon, \quad \frac{eEa}{\hbar\Omega} \sim 10^{-7}.$$

Here, eEa is the interaction energy of an electron of charge e of an atom of the size a with an electrical field E. That is why the approach based on the field quanta and atom energy level notions appears to be effective. In other words, the states of the whole system 'atom + field' are reduced to the combination of the states of the atom and field separately. In another case, when an atom interacts with weak ELF MF, all three energies are of the same order of magnitude. The interaction energy (the energy μH of the magnetic moment of an orbital motion $\mu = e\hbar/2mc$ in a magnetic field H) practically coincides both with the Zeeman splitting $\hbar\Omega_c$ ($\Omega_c = eH_{\text{geo}}/mc$ is the cyclotron frequency) and with the quantum of the MF $\hbar\Omega$.

In this case, the interaction energy is not a small parameter. It means that the presentation of the state of the whole system 'atom + field' in the form of a combination of the states of atom and field taken separately is not fully true. Quantum electrodynamics may provide more reliable description. However, it is clear that the conclusion about the multiple quantum interaction made within the frames of quantum mechanics is also valid for an adequate description of the process in usual terms.

Thus, interaction of an ELF MF with a quantum target is a multiple quantum process; the conventional formulation of the kT problem and its consequences are not valid for such processes. The primary principles of physics impose virtually no limitations on the sensitivity limit. The microscopic structure of a MF bioreceptor and the lifetime of its states control the level of the sensitivity in any special case. It is important that the lifetime may be sufficiently great if the state of elements in the system is far from thermal equilibrium.

We will describe now in more detail an atom with an orbital magnetic moment in a ELF MF in terms of quantum electrodynamics.

In a precessing MF $H_x = h\cos(\omega t)$, $H_y = h\sin(\omega t)$, $H_z = H$, with a frequency ω, which changes only its orientation but not the magnitude, probabilities of the Zeeman states of a magnetic moment will oscillate with the Rabi frequency $\lambda = \sqrt{(\gamma H + \omega)^2 + (\gamma h)^2}$. In a resonance, i.e., when $\omega = -\gamma H$, the Rabi frequency is equal to γh. As was pointed out above, when $h \ll H$, one may consider quanta of EM field and levels of a quantum system or 'atom' separately. Then the Rabi frequency is less than the frequency of the field quantum in the proportion h/H. Then we may conclude that at the intervals of half-period $1/2\lambda$, the field quanta act coherently. At first they increase the energy of the atom by summing up their own energies and passing it over to the atom, then decrease it, and so on.

With regard to the possible mechanism of the primary magnetoreception, this scenario is not quite perspective since the changes in populations of the states, which are very close in their energy (by the order of a field quantum), could hardly affect a chemical reaction. Even if in some hypothetical ideal conditions field quanta energy was pumped to increase the energy of a quantum oscillator, this would take a very long time period about a year to accumulate the energy of the order of $k_B T$.

It is more realistic to suggest a scenario where populations of the states remain constant, but an interference pattern of their space distribution changes. In this scenario, a quantum system or an 'atom' with an orbital magnetic moment is placed, for simplicity, in a uniaxial MF. The latter varies just the magnitude but not the direction: $H = H_{dc} + h\cos(\omega t)$. In such MF, following quantum mechanical description, the atomic energy does not change at all. But what has changed here in a resonance-like manner is the space distribution of the density of the atomic quantum state. As a result, different orientations appear where the probabilities to find the atom are significantly distinct from each other. This redistribution of the probability density may influence the rate of a chemical process (Binhi, 2002; Binhi and Savin, 2002). One may speculate that such scenario is more perspective for magnetobiology.

However, in this scenario as was pointed above, the energy of an atom does not change. Therefore, it is not possible to estimate the sensitivity of the system, following the quantum mechanical and semiclassical approaches. In this case, a quantum description should be used also for ac MF, i.e., for the low-frequency EMF. Obviously, within this description it is not possible to consider EMF quanta

separately, since changes in their number do not correspond to any change in the energy of an atom, which remains constant. In this description just the whole atom–field system has stationary states, but not the atom and the field taken separately. At these stationary states, *dynamical* states of the atom and field may be distinguished, having no definite energies. The stationary states of the system differ by populations of the quantum states of the field oscillators, or, what is the same, by the amplitudes of the field oscillation, on the one hand, and by corresponding amplitudes of the oscillation of the interference pattern or the phases of atom states, on the other hand. Note that here the term 'field amplitude' appears, since in the ELF range multiple-quantum states are adequate, thus allowing to consider amplitudes.

It should be stressed again that it is not correct to consider the number of quanta absorbed by an atom in the MF that changes only the magnitude. The states with different numbers of quanta are stationary states of the EMF; however, there are no atomic stationary states that could match them. The states of an atom with different phases of its eigenfunctions are not stationary states, i.e., they have no definite energies at all.

A chemical reaction as shown in Binhi (2002) is more probable at certain amplitudes of atomic phase oscillations, and consequently, at certain amplitudes of the field. By changing the field amplitude, we reach such a stationary state of the atom–field system, when the reaction occurs. One can put a formal question about the number of field quanta or photons that correspond to the certain amplitude. However, to make the actual calculation of this number it is necessary to determine a space region, in which EM field is considered, or to normalize photon wave functions. But it is not possible, since the notion of photon coordinates makes no sense and a photon wave function is not a probability amplitude of its space localization.

This well-known principle has difficulty relating to the intrinsic problems of quantum electrodynamics. The above presented analysis of the sensitivity limit overcomes this difficulty since it is based only on general quantum mechanical regularities and shows that limiting sensitivity is related only to the time of the coherent field–atom interaction.

Non Equilibrium States as the Basis of Molecular Mechanisms of Magnetoreception

The conventional formulation of the kT problem brings about the skepticism in regard to the plausibility of the observed magnetobiological effects and, as it is, does not provoke any efforts to overcome the paradox. Therefore, we believe it is useful to concentrate on two aspects of the paradox: (i) what is the mechanism of the weak MF signal conversion into a (bio)chemical signal; and (ii) why such mechanism could be efficient on the background of thermal disturbances of the medium?

It is worthwhile to bear in mind two points. First, the notion of kT itself comes from statistical physics. This notion is justified for the systems, which are near thermal equilibrium. Indeed, in such systems, neither a single quantum nor many quanta corresponding to a weak ELF MF can practically change the mean energy of dynamical degrees of freedom. However, in the systems just weekly bound to the thermostat, the process of thermalization is relatively slow so that such systems may remain for a long time far from the equilibrium. Then a MF can bring about a great

relative change in energy of some dynamical variables, the energy of which may be low due to some reason. In other words, the notion of the temperature itself, in its traditional thermodynamic meaning, is not applicable to some degrees of freedom, if the thermalization time of these degrees of freedom is greater than the characteristic lifetime of the system. It follows that there is no sense comparing changes in their energy with $k_B T$ at the absorption of EMF quanta.

An example of the non equilibrium processes are changes in protein structures proceeding at slower rate as compared to their functioning. That is, some of their relevant degrees of freedom have no time to thermalize. This may happen also in other biophysical nanostructures. We suggest that weak MFs may change the state of such non thermalized degrees of freedom and thereby affect the functioning of proteins.

Second, the interaction energy of an ELF MF with a molecular target is rather low. It takes at least one year for the energy of an ideal molecular or ion oscillator to change by the amount of $k_B T$ even under magnetic resonance conditions (Binhi, 2002). It follows that MF may play a role of a controlling signal rather than a power factor. Therefore, specific mechanisms are possible, where MF controls the probabilities of the processes to proceed in one or another direction rather than triggers the processes themselves.

In this regard, non equilibrium or metastable state of a target and probabilistic character of the weak MF signal conversion into a biochemical response are necessary properties for the molecular mechanism of magnetoreception. How do these properties interplay in the process of magnetoreception where a magnetosensitive target is embedded in a protein complex? Let conformational rearrangements in some proteins result in the appearance of particular molecular groups, some of whose degrees of freedom are magnetosensitive, i.e., the group is a target of MF. Such target influences the probabilities of the protein to evolve from the intermediate state to one of the final states, active or inactive. Since the target has a lifetime less than its thermalization time and so the target is in a non equilibrium state, the MF then controls the state of the target: the portion of the protein molecules in the active state depends on MF. Thus the MF determines the probabilities of the protein to follow one or the other pathway in metabolism.

An example of the metastable target is presented in Binhi and Savin (2002). It is a molecular gyroscopic rotator: its probability to react with the surrounding medium depends on MF. In this model, an ac MF produces the eddy electric field. On the whole, the charge density in a molecular rotator is distributed non uniformly over the molecule volume. Hence, the electric field exerts a torque, which accelerates or slows down the random thermal rotations of the molecule. The molecule is assumed to be inside of a protein cavity so that its two edges form covalent bonds, i.e., supports with the cavity walls. In this case, thermal oscillations of the supports produce only zero torque about the rotation axis. Therefore, the gyroscopic degree of freedom thermalizes slowly, due to the relatively weak van der Waals interaction with the cavity walls. Then the MF efficiently controls the rotation of the molecule by the eddy electric field.

Under particular combinations of the frequency and amplitude values, the MF induces very specific non uniform rotation of the molecule. The molecule remains practically still almost over the entire period of the MF oscillation. Then it quickly rotates over the complete angle, and so on. In such dynamic mode of the rotation, the reaction probability of the side groups of the molecule with its surrounding

increases. In Binhi and Savin (2002), the molecular rotations are described in a quantum way, as the interference of quantum states, since the de Broglie wavelength of the molecule over the angle variable is of the order of π even at the room temperature. Such rotations partly isolated of the thermostat are described in substances of non protein nature (Orville-Thomas, 1974).

Reactions involving free radical pairs give a clear example of another case where MF target is in a metastable state. An idealized magnetosensitive chemical reaction may be depicted as $AB \rightleftarrows \dot{A}\dot{B} \rightleftarrows \dot{A} + \dot{B}$, where the intermediate $\dot{A}\dot{B}$ is a spin-correlated radical pair in a virtual cage formed by the molecules of the surrounding viscous medium. The rate of recombination $\dot{A}\dot{B} \rightarrow AB$ and so the rate of free radical formation may change depending on the MF value. Magnetic processes based on spin dynamics of the radicals develop so quickly that the thermodynamic equilibrium has no time to be established. This means spins move coherently and no temperature of spins exists within these small time intervals, usually 1–10 ns, for which the term "spin lifetime" is used. The MF dephases coherent spin motion and changes the probability of the pair recombination.

Cell membranes were also considered as a potential MF target. In order to estimate the thermal electrical noise that could limit the sensitivity of the membranes to externally applied ELF MFs, a cell membrane was considered as an impedance that generates the electrical noise. The Nyquist relation was used to estimate its value. However, the question on the sensitivity limit has not yet been solved completely. An analysis made in Bier (2005) has exposed some weaknesses in known estimates of the sensitivity. In particular, an electrical noise, generated across the membrane by thermal fluctuations, should be essentially non equilibrium, or "color", noise, which changes the sensitivity limit previously estimated for the case of "white" noise. Also, it is unlikely that MF targets occur directly in the cell membrane or coincide with it (Liboff, 2005b). None of the known specific models involve highly insulating, and consequently generating a high noise, biological membranes as MF targets. It is more reasonable to consider proteins attached to or lodged within the membrane. But their effective resistances are orders of magnitude lower than that of the membrane, which makes the estimates of the sensitivity limit much more optimistic. We note also, that these estimates are based on the proposition that magnetic effects develop through eddy electric fields induced by variable MFs, while the targets that directly interact with MFs by their magnetic moments are also exist.

Yet another example of a molecular target is water medium. The suggestion that water medium may be a mediator in the MF signal transduction at the biological level was made by many scientists. There are theoretical and experimental works to support this idea (Belov et al., 1996; Del Giudice et al., 2002; Fesenko et al., 2002).

In this case, the target is located not inside the protein molecule, but surrounds it and interacts with its surface. The state of water influences the protein conformation changes and, consequently, its activity. Elementary targets in water matrix are most likely the magnetic moments of protons forming the hydrogen bonds in water. Concerted simultaneous MF effect on the magnetic moments, and thus on the proton spin states, may affect hydrogen bond rearrangements owing to the Pauli exclusion principle for spins (Binhi, 1998). Another interesting conceptual framework for water-mediated magnetic effects is domains of low viscosity in water (Preparata, 1995). They ensure a coherent motion for a part of ions and effective interaction with an ELF MF. In this model, the MF controls the probability of charge transfer reactions. In both

cases, the MF target is a distributed system of elementary targets, magnetic moments of water protons, or ions in some water regions, which are in long-living metastable states. In this way, MF may influence conformational mobility of proteins.

Proton Subsystem in Liquid Water as a MF Target

A magnetic proton subsystem is a constituent factor of water medium, where biochemical reactions proceed. It may be of particular and independent interest in magnetobiology due to the following facts. First, the mechanical moment, i.e., spin of a proton is the same as that of an electron. Electron spins take part in the exchange interaction of electrons and thereby they play a key role in chemical reactions. In a similar manner, the exchange interactions of protons may partly control proton transfer reactions and the mobility of water structure defects mediated by proton jumps (Binhi, 1998). Second, proton spins have long relaxation times, of the order of seconds; therefore they have sufficient time to become susceptible to the external magnetic field. And third, unlike free radical pairs, which are also possible candidate as MF target, protons are abundant in water and actually take part in many biochemical processes.

According to modern concepts, in many aspects and particularly with regard to its electrical properties, liquid water is a net of hydrogen bonds with different disorders. For example, generation of ionic defects, hydroxyl and hydroxonium ions, is considered as a violation of the rule that each oxygen atom binds two hydrogen atoms or protons. The so-called 'relay' von Grotthuss mechanism controls the motion of ionic defects: an elementary displacement of the defect occurs due to the proton jump over the H-bond; the following displacement occurs due to the jump of another proton on the neighboring H-bond. Real time studies with ultrafast infrared spectroscopy have shown that proton transfer between molecules in aqueous solution actually proceeds by a sequential von Grotthuss proton-hopping mechanism through H-bonds (Mohammed et al., 2005).

Of interest are also orientational defects (Bjerrum, 1952), that have been studied for a long time in ices (Petrenko and Whitworth, 1999), but not in water (Kryachko, 1998). They violate another rule that only one proton is in between the neighboring oxygen atoms. Such defects can be of interest with regard to the kT problem.

Most of hydrogen bonds in water contain only one proton. Usually, a proton potential energy varies manifesting a characteristic double-well dependence on the proton position along a hydrogen bond (Pimentel and McClellan, 1960). To describe orientational disorders in the net, a part of bonds are assumed to contain two protons (D-defect) or no protons (L-defect). With regard to the orientational defects, some authors prefer to use the term 'water bridges' rather than 'H-bonds', as in both cases of D- and L-defects the term 'H-bond' is conditional. However, it is convenient, developing simple models of water defects, to consider 'water bridges' in a united manner, as a double-well potential that can carry one, two, or no protons (Zolotaryuk et al., 1994). Many unusual properties of water originate from the fact that some of the protons occupy 'wrong' positions in the hydrogen bond net, so that the corresponding bonds carry extra or no protons. Advanced models investigate soliton-like dynamics of the defects, where they are delocalized over a space occupied by several oxygen atoms rather than by two atoms (Davydov, 1984). Figure 1 illustrates the motion of a 'wrong' proton or D-defect of water structure, related to stable violation of the proper orientation of water molecules. A jump of

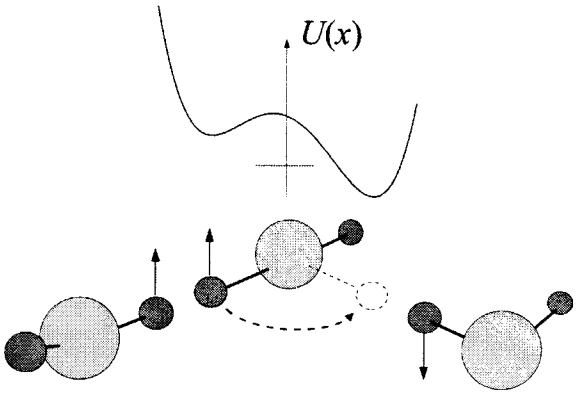

Figure 1. Motion of a D-defect: Potential energy of the proton, tunneling between hydrogen bonds, depends on the spin states of the protons.

the proton from one bond to another means a displacement of the wrongly oriented molecules.

Besides proton-electron interactions, which form hydrogen bonds, protons interact with each other. The interaction of protons, coulomb repulsion, includes an exchange energy that depends on the mutual orientation of their spins. As is derived below, the exchange energy of protons may be many orders of magnitude greater than their magnetic dipole–dipole interaction and compared with $k_B T$.

Figure 1 shows the potential function of a proton moving between bonds with different orientations of resting proton spins. The potential is asymmetric for spins having opposite orientations. If the asymmetry is sufficiently great, a jump to the state with larger energy may not occur at all, until a proton with 'right' spin occupies the corresponding place. Evidently, this impedes relaxation of the local spin equilibrium and affects the mobility of water structure defects.

Estimations show that classic and quantum transitions of protons over the network of hydrogen bonds may be comparable in their intensity (Bockris and Conway, 1964). That is why the mobility of water structure defects are due, at least partly, to the fact that wave functions of protons located in potential wells cover the neighboring potential wells. The exchange interaction of protons, resulted from indistinguishability of identical particles in quantum mechanics, is the other consequence of that fact: wave functions of two protons located in neighboring wells overlap with each other. As MF controls the evolution of spin magnetic moments, it also controls the exchange interaction.

Usually, proton wave functions are assumed to have an exponentially small overlap, and so the proton exchange interaction is inessential. We will show that the overlap of the wave functions strongly depends on the potential of an extra proton in a D-defect area. The exchange interaction becomes significant, if the proton binding energy is low. In such a case, the exchange interaction of protons may play an important role in magnetoreception. Later on, appropriate estimates are given.

It is worth noting that the energy of MF interaction with proton magnetic moment is rather low, of the order of $10^{-10} k_B T$; on the other hand, it controls relatively strong exchange interaction (which may be even more than $k_B T$), since proton spin and magnetic moment are inherently strictly bound. Therefore, MF

controls *probabilities* of proton transitions that cause variations in the overall mobility of water structure defects and thus, as was discussed above, biochemical reactions by affecting proteins activity.

Let us estimate the exchange energy value for two protons in a D-defect. Here we cannot use the hydrogen bond potential, since it is determined only for a single proton in the bond. As a very rough approximation, we use the known idealization, singular attractive potential $-\lambda\delta(x)$, where x is a particle coordinate in the bond, $\delta(x)$ is the Dirac delta-function, and λ is the parameter of the potential. The wave function for this potential is well known (Baz' et al., 1966): $\psi(x) = e^{-|x|}$, where x is measured in units of $x' = (\hbar^2/2\,m|\varepsilon|)^{1/2}$, m is the particle's mass, and ε is the energy of an eigenstate that further should be considered as the binding energy of an extra proton. So, the wave functions of the two protons read, correct to a normalizing coefficient

$$\psi(x) = e^{-|x+a|}, \quad \xi(y) = e^{-|y-a|}, \tag{4}$$

where x, y are coordinates of the protons, and $\pm a$ are positions of the potentials in the bond.

It is known that acceptable wave functions for the system of two identical particles, which should be symmetric or antisymmetric with regard to $x \leftrightarrow y$ permutation, may be written as

$$\Psi = \frac{1}{\sqrt{2}}[\psi(x)\xi(y) \pm \psi(y)\xi(x)].$$

Proton interaction energy $U_c \propto 1/|x-y|$ has the following mean value that depends on the symmetry of Ψ: $\langle\Psi||x-y|^{-1}|\Psi\rangle = U \pm J$, where

$$U = \iint U_c\psi^*(x)\psi(x)\xi^*(y)\xi(y)dx\,dy, \quad J = \iint U_c\psi^*(y)\psi(x)(\xi^*(x)\xi(y)dx\,dy.$$

Integrating over the interval $[-a, a]$ makes up main contributions to the values of these integrals, called coulomb and exchange integral, respectively, due to exponential decrease of the wave functions. Substituting (4), we write, omitting a common insignificant coefficient,

$$U \propto \iint_{-a}^{a} \frac{e^{-2(x+y)}}{|x-y|}dx\,dy, \quad J \propto \iint_{-a}^{a} \frac{1}{|x-y|}dx\,dy. \tag{5}$$

Changing variables to $u = x - y$ and $v = x + y$ we reduce (5) to the single integrals

$$U \propto \int_0^{2a} \frac{\mathrm{sh}(4a-2u)}{u}du, \quad J \propto \int_0^{2a} \frac{4a-2u}{u}du.$$

Both the improper integrals diverge in zero, the fact being the known consequence of the point charge idealization. However, we are interested just in the relative value of the exchange integral with regard to the coulomb one:

$$J_r = J/U.$$

One can find this value taking into account that the upper limit of integration is a finite quantity and, consequently, the integrals exist if the lower limit is a small number ϵ, i.e., $U(\epsilon) \neq \infty$, $J(\epsilon) = \infty$. Then, using L'Hôpital rule, we arrive at the estimate

$$J_r = \lim_{\epsilon \to 0} \frac{dJ(\epsilon)/d\epsilon}{dU(\epsilon)/d\epsilon} = \frac{4a}{\mathrm{sh}(4a)}.$$

It is a rapidly decreasing function, so that for the binding energy ε equaled to that of hydrogen bond ($\varepsilon = 5$ kcal/M or $\sim 8\, k_B T$) we would get the half-distance between δ-potentials $a \approx 4$ and the exchange integral $J_r \sim 10^{-5}$, where the actual value of the half-distance $a' = x'a$ is taken to be 0.4×10^{-8} cm, i.e., the half of the distance between the wells of H-bond potential. However, the value of J_r exponentially increases with decreasing ε. Reasonable values for the exchange energy, on the order of the coulomb energy, could be reached only for the binding energy below 0.3 kcal/M (or 0.08 kcal/M for doubled $x'a$). This means that D-defects (Fig. 1), so weakly bound to the nodes of the net, would almost freely migrate over the net, however being constrained by 'spin rules'.

There are no available experimental or theoretical data on the binding energies of the orientational defects in water. We shall hypothesize it is of the order of or below 0.3 kcal/M and hence, $J_r > 0.1$. Since the coulomb interaction of protons in D-defect is of the order of q^2/r, where $q \approx e/3$ is the shielded proton charge and $r \sim 10^{-8}$ cm, i.e., $U \sim 60\, k_B T$, the proton exchange interaction can be a factor strictly prohibiting all migration trajectories of D-defects except those allowed by the Pauli exclusion principle in each of their steps.

In this case, the statistics of orientational defects must differ from Boltzmann statistics. Indeed, recombination of orientational defects is impeded due to topological reasons, since for the recombination to occur many water molecules must be oriented simultaneously in proper angular positions, which is not always possible. It resembles the '15' puzzle, where pieces may be arranged in a desired combination through many steps only, due to the restriction: pieces can slide only in directions allowed by their neighbors.

In liquid water, the number of such pieces (molecules) is great. As has been already said, the restriction is provided here by the Pauli exclusion principle, which controls the allowed directions of proton jumps. Accordingly, it takes an enormous number of proton steps (jumps) reorienting water molecules, before the necessary configuration is achieved, where D and L-defects become beside each other and therefore can recombine. It means that water states are metastable with respect to their local spin ordering, in spite of seemingly chaotic molecular rotations. This means also that molecular associates with stable spin configurations are possible. D-defects, migrating within such associates or domains, play the role of a stabilizing factor. As we discussed above, MF can control such spin states.

Since the proton spin subsystem is rather well isolated from the thermostat of water matrix, we hypothesize that it may produce virtual spin ordered macroscopic domains. The spin ordering here means conservation of a local spin configuration within the domains at time intervals greater than the spin-lattice relaxation time in water. It does not mean a predominant orientation of the total spin or magnetic moment, as it happens in known magnetically ordered substances. As a matter of fact, we may say that the spin-spin relaxation is impeded for some groups of spins or within the domains. It is important that the domain spin configuration allows a lot

of different states. Therefore, such domains may be regarded as the repository of information about factors responsible for the generation of those states, and hence 'memory of water'.

The consumption of the excessive proton of a D-defect in biochemical reactions is energetically favorable as its binding energy is lower than that of a hydrogen bond. This process may be accompanied by the creation of another water structure defect, hydroxyl–radical (Binhi, 2002), which indicates to the biological role of the orientational defects in water and possible simple mechanism of biological transduction of weak magnetic signals. In this respect, a few experimental works are known (Belov et al., 1996; Konyukhov and Tikhonov, 1995; Konyukhov et al., 1995) to demonstrate that proton nuclear spins can contribute to the magnetoreception. The authors managed to produce samples of liquid water where stable deviations from the equilibrium numbers of molecules in ortho and para states, in ratio 3:1, are expected.

Following this hypothetical scenario, which might be conveniently named as a proton-exchange mechanism of magnetoreception, one can also find the solution of the kT problem, since both the 'magnetic' control over *probabilities* (of quantum jumps) and the *metastability* of the target (individual or collective spin states) are also present here.

The role of water medium in biological systems is important and diverse (Aksyonov, 2004; Drost-Hansen and Clegg, 1979; Vuks and Bezrukov, 1991). It should be expected that changes in physical characteristics of water will necessarily be reflected in the functioning of proteins, since their conformational and biochemical properties are affected by the state of surrounding water structures. As is shown in this section, MF can change dynamic metastable states of the proton water subsystem; in particular, MF can affect the mobility of orientational defects. Specific mechanisms that bind the dynamic proton states and the mobility of defects may be different. For example, it is clear that orientational rearrangements of water molecules are impeded in some water regions, if it becomes inaccessible for the motion of the orientational defects due to MF-induced spin effects. Obviously, in this region, the value of the electrical field and the character of its fluctuations will change, and that should affect the state of proteins in this region. In this way, the general proton-exchange mechanism of magnetoreception may display itself.

Due to the variety of proteins surrounded by water structures and external physico-chemical factors, MF can affect protein functions in rather different ways. Such an uncertainty means that the specific response of a biological system to the MF action through the proton-exchange mechanism is hardly predictable. This may be another reason why experimental results in magnetobiology are poorly reproducible.

Conclusion

Many ingenious mechanisms have been suggested to explain magnetobiological effects of weak ELF MFs: ion cyclotron mechanism as a basic concept focusing on the similarity of biologically effective frequencies of magnetic exposures and the cyclotron frequencies of biologically relevant ions (Liboff, 1985, 2005a), a parametric resonance of ions focusing on a nonlinear amplitude dependence in some magnetobiological effects (Lednev, 1993), a model focusing on phase relations in nucleotide oscillations (Matronchik et al., 1996), and others briefly reviewed

in Binhi and Savin (2003) and circumstantially considered in Binhi (2002). Only a few of them discussed the kT problem in part. The present article studies the problem in detail for the first time. It is proved that the kT problem is misleading in its traditional wording; it cannot be an argument in favor of the idea that magnetobiological effects are not possible physically. Possible mechanisms of magnetobiological effects, which directly address the kT paradox, include: (i) stochastic nonlinear dynamics of magnetosomes in biological tissues; (ii) interference of the angular modes of long-living molecular states; (iii) radical pair mechanism; and (iv) proton-exchange mechanism related to the metastable states of the proton subsystem in liquid water. The main principles that underlie these mechanisms are probabilistic character of magnetic effects and non equilibrium state of weak MF molecular targets. This unequivocally shows that biological effects of weak ELF magnetic fields are not at variance with physical laws and may be explained in terms of classical and quantum physics.

Acknowledgment

This work is supported by CHILDREN with LEUKAEMIA.

References

Aksyonov, S. I. (2004). *Water and Its Role in Regulation of Biological Processes.* Moscow—Izhevsk: Comp. Res. Inst. In Russian.

Bawin, S. M., Gavalas-Medici, R. J., Adey, W. R. (1973). Effects of modulated very high frequency fields on specific brain rhythms in cats. *Brain Res.* 58(2):365–384.

Baz', A. I., Zeldovich, Ya. B., Perelomov, A. M. (1966). *Scattering, Reactions, and Decays in Non-Relativistic Quantum Mechanics.* Moscow: Nauka, In Russian.

Belov, A. A., Konyukhov, V. K., Logvinenko, V. P., Tikhonov, V. I. (1996). Determination of permittivity of spin-modified water. *Bull. Lebedev Phys. Inst.* (3):38–42.

Berestetskii, V. B., Lifshitz, E. M., Pitaevskii, L. P. (1982). *Quantum Electrodynamics.* 2nd ed. Oxford: Pergamon Press.

Betskii, O. V. 1993. Millimeter waves in biology and medicine. *Radiotekhnika i Elektronika* 10:1760–1782. In Russian.

Bier, M. (2005). Gauging the strength of power frequency fields against membrane electrical noise. *Bioelectromagnetics* 26(7):595–609.

Binhi, V. N. (1998). On structural defects of liquid water in magnetic and electric fields. *Biomed. Radioelektron.* 2:7–16. In Russian.

Binhi, V. N. (2002). *Magnetobiology: Underlying Physical Problems.* San Diego: Academic Press.

Binhi, V. N. (2006). Stochastic dynamics of magnetosomes and a mechanism of biological orientation in the geomagnetic field. *Bioelectromagnetics* 27(1):58–63.

Binhi, V. N., Savin, A. V. (2002). Molecular gyroscopes and biological effects of weak extremely low-frequency magnetic fields. *Phys. Rev. E* 65(051912):1–10.

Binhi, V. N., Savin, A. V. (2003). Effects of weak magnetic fields on biological systems: Physical aspects. *Physics—Uspekhi* 46(3):259–291.

Binhi, V. N., Chernavskii, D. S. (2005). Stochastic dynamics of magnetosomes in cytoskeleton. *Europhys. Lett.* 70(6):850–856.

Bjerrum, N. (1952). Structure and properties of ice. *Science* 115(2989):385–390.

Blakemore, R. P. (1975). Magnetotactic bacteria. *Science* 190(4212):377–379.

Bockris, J. O'M., Conway, B. E. eds. (1964). *Modern Aspects of Electrochemistry.* London: Butterworths.

Chernavsky, D. S. (1973). Scientific session of the department of general physics and astronomy of the Soviet Academy of Siences. *Usp. Fiz. Nauk* 110(3):469. In Russian.

Davydov, A. S. (1984). *Solitons in Molecular Systems*. Kiev: Naukova Dumka. In Russian.

Del Giudice, E., Fleischmann, M., Preparata, G., Talpo, G. (2002). On the "unreasonable" effects of ELF magnetic fields upon a system of ions. *Bioelectromagnetics* 23(7):522–530.

Devyatkov, N. D. (1973). Effect of a SHF (mm-band) radiation on biological objects. *Usp. Fiz. Nauk* 110(3):453–454 (July).

Dobson, J. (2002). Investigation of age-related variations in biogenic magnetite levels in the human hippocampus. *Exper. Brain Res.* 144(1):122–126.

Drost-Hansen, W., Clegg, J. S. eds. (1979). *Cell-Associated Water*. New York: Elsevier Science & Technology Books.

Fesenko, E. E., Popov, V. I., Novikov, V. V., Khutsyan, S. S. (2002). Structure formation in water by the action of weak magnetic fields and xenon. Electron microscopy analysis. *Biofizika* 47(3):389–394. In Russian.

Fröhlich, H. (1968a). Bose condensation of strongly excited longitudinal electric modes. *Phys. Lett. A* 26:402–403.

Fröhlich, H. (1968b). Long-range coherence and energy storage in biological systems. *Int. J. Quantum Chem.* 2(5):641–649.

Khomutov, G. B. (2004). On the possible role of iron ions in changes in the composition of DNA complexes and their magnetic properties during the cell cycle. *Biophysics* 49(1):128–132.

Kirschvink, J. L., Kobayashi-Kirschvink, A., Woodford, B. J. (1992). Magnetite biomineralization in the human brain. *Proc. Natl. Acad. Sci. USA* 89(16):7683–7687.

Konyukhov, V. K., Tikhonov, V. I. (1995). Adsorption of water molecules on cluster surface under the conditions of proton NMR in weak magnetic fields. *Kratk. Soobshch. Fiz. FIAN* 1–2:12–18. Translated into English as *Bull. Lebedev Phys. Inst.*

Konyukhov, V. K., Logvinenko, V. P., Tikhonov, V. I. (1995). Separation of water to its spin modifications and determination of the spin conversion time of water molecules. *Kratk. Soobsh. Fiz. FIAN* (5–6):83–86. Translated into English as *Bull. Lebedev Phys. Inst.*

Kryachko, E. S. (1998). Water cluster approach to study hydrogen-bonded pattern in liquid water: ab initio orientational defects in water hexamers and octamers. *Int. J. Quant. Chem.* 70(4–5):831–853.

Landau, L. D., Lifshitz, E. M. (1977). *Quantum Mechanics*. Vol. 3 of *Theoretical Physics*. Oxford: Pergamon.

Lednev, V. V. (1993). Possible mechanism for the effect of weak magnetic fields on biological systems: correction of the basic expression and its consequences. In: Blank, M., ed. *Electricity and Magnetism in Biology and Medicine*. San Francisco: San Francisco Press, pp. 550–551.

Liboff, A. R. (1985). Geomagnetic cyclotron resonance in living cells. *J. Biol. Phys.* 13(4):99–102.

Liboff, A. R. (2005a). A rational biology. *Electromagn. Biol. Med.* 24(3):211–220.

Liboff, A. R. (2005b). The charge-to-mass ICR signature in weak ELF bioelectromagnetic effects. In: Lin, E. C., ed. *Advances of Electromagnetic Fields in Living Systems*. Berlin: Springer Verlag, pp. 189–218.

Liboff, A. R., Williams, T. Jr., Strong, D. M., Wistar, R. Jr. (1984). Time varying magnetic fields: effect on DNA synthesis. *Science* 223(4638):818–820.

Matronchik, A. Yu., Alipov, Ye. D., Belyaev, I. Ya. (1996). A phase modulation model of high-frequency oscillations of a nucleotide in the response of *E. coli* cells to weak static and low-frequency magnetic fields. *Biofizika* 41(3):642–649.

Mohammed, O. F., Pines, D., Dreyer, J., Pines, E., Nibbering, E. T. (2005). Sequential proton transfer through water bridges in acid-base reactions. *Science* 310(5745):83–86.

Orville-Thomas, W. J. ed. (1974). *Internal Rotation in Molecules*. New York: Wiley.

Petrenko, V. F., Whitworth, R. W. (1999). *The Physics of Ice*. Oxford: Oxford University Press.

Pimentel, G. C., McClellan, A. L. (1960). *The Hydrogen Bond*. San Francisco: Freeman.

Pokorny, J., Wu, T.-M. (1998). *Biophysical Aspects of Coherence and Biological Order*. Prague, Heidelberg: Academia, Springer-Verlag.

Preparata, G. (1995). *QED Coherence in Matter*. New York: World Scientific.

Ritz, T., Thalau, P., Phillips, J. B., Wiltschko, R., Wiltschko, W. (2004). Resonance effects indicate a radical-pair mechanism for avian magnetic compass. *Nature* 429(6988):177–180.

Volpe, P. (2003). Interactions of zero-frequency and oscillating magnetic fields with biostructures and biosystems. *Photochem. Photobiol. Sci.* 2(6):637–648.

Vuks, M. F., Bezrukov, O. F. eds. (1991). *Physico-Chemical Properties of Water Systems*. Molecular Physics and Biophysics of Water Systems No. 8. St. Petersburg: St. Petersburg University.

Walker, M. M., Dennis, T. E., Kirschvink, J. L. (2002). The magnetic sense and its use in long-distance navigation by animals. *Curr. Opin. Neurobiol.* 12:735–744.

Zolotaryuk, A. V., Savin, A. V., Economou, E. N. (1994). Nonlinear collective proton dynamics in ice crystal: square lattice model for ionic defects. *Phys. Rev. Lett.* 73(21):2871–2874.