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Some Problems in Modern Bioelectromagnetics

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One of the main problems of bioelectromagnetics—the unbelievable narrow resonance peaks at the cyclotron frequency of the alternating magnetic field—was considered. Modern electrodynamics of condensed matter clearly brings out that the reason of this phenomenon is extremely low viscosity within coherence domains of aqueous electrolytic solutions. The electrochemical model of action of combined static and alternating magnetic fields on aqueous solutions of amino acids is proposed. The possibility of arising a succession of changes in ionic forms in these processes was revealed. The dipole ions (zwitterions) together with water molecules electrostatically forming joint groups in the solution, create favorable conditions for arising mixed coherence domains there. Simultaneously with evolution of the coherent processes in these domains, the amino acid zwitterions are transforming into the usual ionic form, fit for cyclotron resonance. The development of cyclotron resonance under action of combined magnetic fields increases the ion kinetic energy, and the ions leave the domains for the incoherent component of the solution according to Del Giudice pattern (Comisso et al., 2006; Del Giudice et al., 2002), creating the peak current through the solution. Then the ions are transforming little by little into zwitterionic form again; after that, the solution becomes ready to react on exposure of magnetic fields again. The possibilities for formation of coherence domains composed of water molecules together with peptide molecules or protein ones are discussed.

Keywords Amino acid solution; Coherent domain; Combined magnetic fields; Cyclotron resonance; Ionic forms; Peptide; Protein; Zwitterion.

Introduction

In the mid 1980s, Blackman et al. (1985) and Liboff (1985) revealed that combined static (DC) and alternating (AC) magnetic fields (CDAMF) caused the increase in concentration of free calcium in nervous tissue. Such an increase manifested itself in the form of very narrow prominent resonance peaks with the maximum peak at the cyclotron frequency of AC magnetic field corresponding to Ca^{2+} ions:

$$f_C = \frac{q}{2\pi m} B_o,$$

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where B_o is the value of DC field, and q and m are the charge and mass of the ion, i.e., cyclotron frequency is determined by a charge-to-mass ratio for an ion exposed. These pioneering works opened a new line in development of bioelectromagnetics and initiated a large following and a lot of opponents. In these works, values of DC and amplitudes of AC fields were measured with tens of μT that were comparable with the natural geomagnetic fields. At that time such fields were considered as very weak for their biological action. In this connection, and also as a result of unexpectedness of the discovery of cyclotron resonance in biological systems where it is impossible to find the vacuum, these results were met with great surprise and distrust. They were not widely covered in the press, however in conferential discussions it was debated rather often. The extreme narrowness of resonance peak half-width of about very low cyclotron frequency also gave rise to doubts. According to theory of oscillation (Mandelshtam, 1972), it could take place only at viscosity of the surrounding medium of about several orders less than in water and aqueous solutions.

However, in the following experiments performed on nervous tissue again (Blackman et al., 1989) and on different objects and in different experimental situations, the diverse evidences of such sort of effect were obtained. The calcium cyclotron frequency turned out to affect the calmodulin regulation of calcium ion concentration in the solution (Shuvalova et al., 1991), the diatom mobility through the change in intracellular concentration of free calcium ions (Liboff et al., 1987a; Reese et al., 1991; Smith et al., 1987), the rate of cell proliferation in culture (Rochev et al., 1990), the pineal melatonin synthesis Lerchi et al. (1991), the calcium concentration in lymphocytes (Liboff et al., 1987b; Persson et al., 1992; Yost and Liburdy, 1992) and thymic cells (Persson et al., 1992), the germination and growth of seeds (Smith et al., 1993), the cephalic regeneration in planarian (Jenrow et al., 1995; Tiras et al., 1996), rat behavior (Zhadin et al., 1999), and others. The effects of cyclotron frequencies peculiar to other biologically active ions were also observed: the potassium cyclotron frequency exerted an effect on the rate of cell proliferation (Rochev et al., 1990) and on germination and growth of seeds (Smith et al., 1993); the lithium cyclotron frequency had an influence on operant behavior of animals (Thomas et al., 1986); the magnesium cyclotron frequency affected the rat's conditioned behavior in the radial arm maze (Lovely et al., 1993); the cyclotron frequencies changed conductivity of aqueous solutions of these amino acids (Zhadin et al., 1998); three cyclotron frequencies, the magnesium, vanadium, and manganese ones, were surmized as influencing the nerve growth factor-stimulated neurite outgrowth (Blackman et al., 1994).

Different theoretical models of such sort of resonance were advanced. Liboff (1985), McLeod and Liboff (1987) considered motion of free ions exposed by action of CDAMF in conditions close to vacuum and showed the possibility of arising of the phenomena similar to experimentally obtained ones. However, Liboff et al. (1987a) noted the difficulties of his model himself which consist of some classical features of charged particles:

(1) an acting cyclotron frequency in all experiments is determined by the mass of the pure ion whereas the ion in an aqueous solution really carries a heavy hydrated shell which makes the mass of a moving hydrated ion several times higher than without of the shell;

(2) at room temperature the average diameter of circular motion of an ion under the influence of DC magnetic field of several tens of μT is measured by meters. In order to avoid these difficulties, which at that time seemed to be intractable problems, the attention of investigators was paid to study the motion of trapped ions which was restricted with molecular sizes. A series of theoretical elaborations (Blanchard and Blackman, 1994; Edmonds, 1993; Lednev, 1991; Muehsam and Pilla, 1994; Zhadin, 1996, 1998) was devoted to analysis of thermal oscillation of such ions under the influence of CDAMF. But in these models the damping coefficient of ion oscillation was accepted to be very small in accordance with experimentally determined half-widths of resonance peaks that were much less than values allowed by Statistical Physics for such sort of conditions.

For ten years of the above investigations, the scientific society had got more or less accustomed to the works on biological action of weak (on the level of tens of μT) CDAMF developing in spite of some distrust showed to them by groups of physicists-theorists. In the mid 1990s, we experimentally revealed a prominent effect of brief increase of the current through the aqueous solution of glutamic acid under the CDAMF action when the scanned frequency of the AC field coincided with cyclotron frequency for this amino acid. The current was created by voltage difference applied to the electrodes placed into the solution. The DC field was equal to 40 μT, and the amplitude of AC field was about 20 nT; that is 500 times less than in previous experiments with weak CDAMF and than the geomagnetic field value. In 1994, we sent a manuscript to *Bioelectromagnetics*. It was not rejected, but its publication was delayed. Everything was stopped by their request to the authors to explain the mechanism of this effect. Only four years later was the article published (Zhadin et al., 1998), when the possible mechanism was proposed (Zhadin, 1998) on the basis of theoretical model of the influence of CDAMF on thermal motion of trapped ions in biomolecules or microcrystals.

One must give its due to the long-suffering of the international scientific community, which, in spite of distrust to the new off-center line of work in the framework of Bioelectromagnetics, permitted publication of its results, naturally, along with critical reactions on them, and did not allow it to fade out forever. However, even now the problems of this line discussed above stay undecided. In the present article, we are giving more or less detailed analysis of these problems in the light of modern Theoretical Physics state.

Our Works on Biological Action of Combined DC and AC Magnetic Fields

In the mid 1990s, now too, though, the question on what ions, free or trapped, are the main target of CDAMF action, was rather actual. It was not unambiguously solved in experiments performed on complicated objects (cell, tissue culture, whole organism), where both of types of the above ions were exposed simultaneously. In this connection we carried out series of experiments on the simplest object—aqueous solution of glutamic acid—where, as we initially thought, the free ions of this amino acid were existed. Taking into account the above discussed difficulties of Liboff's model, we were ready for negative results from our experiments.

The method of most of our experiments was the following. The glutamic acid (Sigma, USA) solution (0.33 g/l) was prepared in distilled water; its pH was shifted

to 2.85 by adding dilute HCl solution. The cubic cell (8.0 ml in volume) was filled with the solution to be studied. The golden electrodes with an area of 20.0 mm^2 were located in the cell. The distance between electrodes was 10.0 mm and the potential difference between the two electrodes was 80.0 mV. The cell was placed within two coils with one coil being located inside another; the axis of the coils coincided with each other. The outer coil created DC magnetic field, B_0, and the inner coil made the AC field. The electric field between electrodes was perpendicular to the coils axis. The coils were located within a Permalloy chamber. The study was performed, using the DC magnetic field of 40 μT. The sinusoidal current through the inner coil caused the AC magnetic field around the cell. The AC field frequency was scanned in the range from 1 to 10 Hz with a speed of 0.05 Hz/s. The AC field amplitude was kept at 0.02 μT. The current passing through the solution was measured with a polarographic analyzer before and during magnetic field exposure. Control experiments were performed by measuring the currents through pure water and through pure HCl solution with pH of 2.85 before and during magnetic field exposure.

Initially, liking to find a minimal value of the AC field at which one could register a prominent change in the current through the solution, we intended in each series of experiments to increase the amplitude of AC field step by step starting with 10 nT. To our great surprise, already at the amplitude of 20 nT, we revealed quite prominent brief peaks of the current through the solution at the AC field cyclotron frequency corresponding to a glutamic acid ion. There was only one peak at the cyclotron frequency in the course of frequency scanning. In control experiments without AC or DC fields there was no such peaks. After revealing this effect we devoted all our time and forces to its investigation at the extremely weak AC magnetic field of 20–40 nT. In addition to glutamic acid, we investigated some other amino acids: asparagine, arginine, and tyrosine (Novikov and Zhadin, 1994). Working with these amino acids we obtained the analogous effects, but less prominent compared with glutamic acid.

In 1994, we published our results in the Russian journal, *Biophysics* (Novikov and Zhadin, 1994) and in the same year sent them to the *Bioelectromagnetics* journal, wishing to acquaint the international community with them too. This story was described in the end of the previous section of this article.

By the end of the 1990s, there were a lot of different publications about action of CDAMF not only on calcium ions, but on other biologically active ions too—potassium, lithium, magnesium, and some other ions in different experimental situations (see the previous section). Therefore, we (Zhadin et al., 1999) performed a series of experiments for investigation of effects of CDAMF with cyclotron frequencies peculiar to set of ions—calcium, potassium, sodium, chlorine, magnesium, or lithium—in order to reveal what of them could affect the animal's moving activity.

In these experiments, the magnitude of the DC and amplitude of parallel AC magnetic fields were equal to 500 μT and 250 μT, respectively, which were about order of magnitude more than the natural geomagnetic field. This was motivated by two reasons: (1) so that the magnitudes of experimental fields to be much more than any background field during the experiments and (2) to get more detectable effects, compared with the action of weaker fields. Here, the common control was the DC field alone, without any AC field.

The known (Walsh and Cummins, 1976) "open field" test was performed in a square (100 × 100 cm) box with a plastic bottom and opaque plastic walls 50 cm

high. The bottom was 100 small squares (10×10 cm) by lines. In the course of testing (3 min.) the number of border lines between small squares which were crossed by a moving animal was calculated. The work was concurrently performed on two groups of animals: the control and exposed ones, with ten animals in each group. Previously (the control day), the initial difference in the numbers of crossings between these two groups after sham exposure of both the groups of animals was determined. Within two days after the control day, the exposed group was subjected to real exposure and the control group was done to sham exposure (the exposed day), and the difference in the animals' behavior was determined again. The duration of exposure was 20 min. Two animals only were exposed at a time to either sham or real in the exposure installation. The influence of the magnetic fields was revealed at frequencies 380 and 630 Hz, as well as 38 and 63 Hz, corresponding to calcium and magnesium ions, respectively. The exposure with frequency 380 and 38 Hz manifested itself as a decrease in the moving activity, and the exposure to frequencies 630 and 63 Hz increased moving activity. Exposures to the cyclotron frequencies corresponding to the other investigated ions (potassium, sodium, chlorine, and lithium) did not give any noticeable results.

The influence of the magnesium cyclotron frequency, opposite in direction to the influence of the calcium cyclotron frequency, seems to be more or less understandable. The calcium and magnesium ions compete for the same binding centers of calcium-binding protein (Permyakov, 1993), and a portion of these centers are occupied by the magnesium ions. So if the magnesium cyclotron frequency favors the release of the magnesium ions from the binding centers, similar to action of the calcium cyclotron frequency on the binding calcium ions, the free binding centers become capable for the capture of calcium ions from the cytoplasm and thus to the decrease of the free calcium concentration in the cell in contrast to the action of the calcium cyclotron frequency.

The idea that the changes in concentration of free calcium ions, Ca^{2+}, inside the cells, under the influence of CDAMF, which was revealed in the first experiments with CDAMF (Blackman et al., 1985, 1989; Liboff et al., 1987a; and others), could be caused by escape of ions Ca^{2+} from calcium-binding proteins (intracellular depot of calcium) under the influence of CDAMF was first outspoken by Lednev (1991). Really, the calcium-binding proteins contain essentially most part of intracellular calcium (Permyakov, 1993). This ion in the free state (Alberts et al., 1983) participates in transfer information from membrane receptors to intracellular effectors inducing cellular reactions: contraction of muscle cells, activation of excitatory and inhibitory neurons, secretion of secretory cells, cell proliferation, and so on. The release of a calcium ion from the calcium-binding protein in the most of different cells can cause a diversity of changes in the whole organism. In theoretical works (Blanchard and Blackman, 1994; Lednev, 1991) the escape of Ca^{2+} under the influence of CDAMF was connected by parametric resonance. But this is not right because the Larmor precession, which in this work (Lednev, 1991) was considered in the role of harmonic oscillator, really is not the harmonic oscillator at all (Mandelshtam, 1972; Tamm, 1989). However, the idea about participation of calcium-binding proteins in biological effects of CDAMF deserved further development.

In our theoretical works (Zhadin, 1998; Zhadin and Barnes, 2005), which were developed during seven years, we derived the differential equations describing action of CDAMF on thermal motion of trapped ions in a biological macromolecule, in

particular of calcium ion within the binding centers of a molecule of calcium-binding protein, and solved them. When deriving these equations, we did not use the idea about parametric resonance, but in solution we accepted the value of the damping coefficient of ion oscillation equal to the one corresponding to experimental data (Blackman et al., 1985, 1989; Liboff et al., 1987a). We showed that the excitation at the resonance cyclotron frequency can lead to a change in energy of ion thermal motion. After the establishment of a new equilibrium, the stored energy can be sufficient to change the conformation state of this macromolecule. On this basis, a diversity of medical and biological phenomena could be explained including the so-called "frequency" and "amplitude" windows without invoking the ideas of parametric resonance. Here the frequency windows are the sequence of resonance peaks with maximal peak at the cyclotron frequency, and the amplitude windows are the phenomenon such that an increase in the AC field amplitude periodically led to attenuation and strengthening effects of the magnetic fields—the phenomena usually observed under the action of CDAMF (Blackman et al., 1985, 1989). Thus, our model at the chosen damping coefficient was able to explain the main experimental effects.

We (Zhadin, 1998) applied this model to the bound ions in microcrystals within the aqueous solution of glutamic acid. We tried to understand the effects observed in experiments with CDAMF, taking into account that in these experiments (Zhadin et al., 1998) we worked with aqueous solutions at temperature and concentration close to saturated solution of glutamic acid. Therefore, we supposed that in the solution the microcrystals—nuclei of crystallization—could arise. These microcrystals could melt, releasing ions of glutamic acid at increasing of ion energy under the influence of CDAMF at cyclotron frequency of AC field and could increase the current through the solution. When the cyclotron resonance vanished the excess ions could be gathered by microcrystalls. All the process could be repeated at the arising the cyclotron resonance. Unfortunately, these processes can take place only at the very low damping coefficient corresponding to half-width of resonance peaks observed in experiments, but impossible from the point of view of Statistical Physics.

The situation became clear only after the development of new Quantum ElectroDynamics (QED) of condensed matter by a group of Italian physicists, headed up by Prof. Giuliano Preparata (1995). The following section of the present article is devoted to their achievements. These scientists became interested in our works with glutamic acid solution and gave a key to the solution of the main problem sof Bioelectromagnetics concerning very low viscosity on the microlevel of liquid water (Del Giudice et al., 2002). Our experiments were successfully replicated and our results were confirmed (Comisso et al., 2006; Pazur, 2004).

Coherence Domains in Water

Quantum ElectroDynamics (QED) is one of the most complicated divisions of Theoretical Physics which was quickly developing in the 20th century. Until recently, it mainly studied interaction of elementary particles between each other and with electromagnetic field. In spite of some uncommonness of its postulates and conclusions, QED gains full confidence by its contribution into solution of diverse practical problems in theoretical and applied Nuclear Physics. The capital contribution in development of this science were made by P. A. M. Dirac, W. Pauli, R. P. Feynman, L. D. Landau, E. Fermi, and other outstanding physicists.

During the last ten years, due to the works of outstanding Italian physicist Preparata (1995), the new line of QED was brought to the forefront: QED of condensed matter, the subject of investigation of which are processes of matter condensation—the transition from gas to liquid medium and from liquid to solid medium. Among different liquid media, specific attention was drawn to water because its viscosity, diffusion of foreign molecules, dependence of its density on temperature, as well as the nature of practically all its electrical constants presented a complex of puzzles inexplicable by Theoretical Physics before the development of QED of condensed matter.

In the solution of various tasks, QED demands the account of different forms of interaction between matter molecules and of interaction between these molecules and external, as well as internal electromagnetic (e.m.) fields. These interactions are described with a Hamiltonian—the operator of matter energy—in different approximations in dependence on a problem put by. The Hamiltonian, which considers all particles as noninteracting with each other, is usually chosen as an initial approximation. The further approximation is made with the account of electrostatic (usually, dipole) interaction between each pair of matter particles. Since the electrostatic fields quickly decrease when the distance between two particles increases, only particles distant from each other at a range of several Angstroems can be considered as interacting ones. In the presence of external e.m. fields, the following approximation is made with the account of their influence on the energy of particles in a matter volume considered. The influence of internal e.m. fields radiated by the multitude of matter particles on the matter particles of these multitude was considered as very weak comparatively with the above approximations and therefore was not taken into account.

Preparata (1995) investigated this approximation in detail and, deriving and solving the complicated system of equations corresponding to this task, showed that in this case the quite new effects appear with essential changes in energy of liquid matter particles. Especially prominently, they were manifested in changes in water features within the temperature range from 0–100°C. Preparata showed that in these conditions all over the water volume the self-forming of a multitude of stable molecular ensembles with surprising features appear. The shift of the quantum ground states of all molecules in these ensembles from the incoherent ground energetic state of the ensemble of water molecules to the lower coherent ground state (the so-called spontaneous superradiant phase transition), and the forming of coherent oscillations of e.m. field and water molecules generating it take place in such sort of self-organized ensembles. The former provides the minimum of potential energy of the coherent ensemble and the stability of this ensemble, and the latter leads to quite unique features of the coherent ensembles called by "coherent domains" (CD).

The stability of these CD's is great, and the binding energy of water molecules holding them within spherical CD borders much exceeds the thermal fluctuations. By Preparata's estimate, the CD diameter is measured with tenths of a micron. It is comparatively large value because dimensions of small cells, for example neuron bodies containing multitude of diverse organellas, are measured by several microns. In such a CD, millions of water molecules are oscillating with the same frequency and in the same phase with e.m. field generated by these CDs which, in its turn, support the coherent oscillations of these molecules. The commons frequency of all molecules within CD coherent with the e.m. field oscillation has the value corresponding to the energy of quantum transition of 12.06 eV (Preparata, 1995).

The general tuning of the molecules in CD's to common unified frequency and to the same phase occurs, as Preparata (1995) writes, in the following way. At forming of CD "...the e.m. 'zero-point' fluctuations with frequency $\omega = 12.06\,\text{eV}$ start to build up and the water molecules will begin to oscillate between the ground state and the excited level at 12.06 eV: all the other levels will be from now on totally ignored by the dynamical evolution of the physical system: water molecules plus e.m. field." The e.m. field connected with oscillation of CD molecules becomes trapped by CD and gets to be its integral part. Its amplitude increases to high value: in the center of CD it has the value of about $10^9\,\text{V/cm}$ (Del Giudice and Preparata, 1994). This provides stability of CD to external hindrances, including thermal noise.

The space between CDs is thick with the multitude of water molecules in the usual incoherent state which oscillations are not connected with each other. When the temperature of water increases, the size of CD decreases and the total volume of incoherent surroundings increases. Within CD the water features drastically differ from the ones of usual water: viscosity of the medium and decrement of oscillation are great times depressed and fluidity is essentially increased, and all this is at the temperature close to room one. Considering two components of water, coherent and incoherent ones, QED of condensed matter first theoretically got all the electrical constants of water, close to experimentally obtained, and theoretically derived the dependence of water density on temperature close to real one (Preparata, 1995). And finally, discovered possibilities of understanding the mechanisms of biological action of weak CDAMF (Del Giudice et al., 2002). Preparata was worried by practical application of his theory in Medicine. In one of his last lectures devoted to these questions (Preparata, 2000), he wrote that there is "a bridge between QED and Medicine" which has "three arches:

(i) the new physics of water;
(ii) a possible origin of coherence in cell tissues;
(iii) the interaction of very weak, low frequency magnetic fields with the ions' systems of the cell.

The consolidation and the finishing of these arches will require... a deep exchange with biologists and physicians."

Possible Mechanisms of Action of Combined DC and AC Magnetic Fields on Aqueous Solutions of Amino Acids

The works of Del Giudice et al. (2002) and Comisso et al. (2006) were devoted to the replication of our experiments (Zhadin et al., 1998), described in the second section of the present article, and to theoretical understanding of these effects. In these works, the mechanisms of motion of an ion of glutamic acid, which found itself within CD, under the influence of CDAMF and the electrochemical processes near electrodes in the electrolytic solution were considered. Inside CD viscosity is very small, and resistance to the ion motion is very much depressed compared to the incoherent component around CD. The authors of the above works suppose that within CD the ion is drawn into coherent oscillation of water molecules and that, at the cyclotron frequency of AC field, this ion simultaneously performs an accelerated movement in shorts of a spiral trajectory under the action of CDAMF. The dimensions of these shorts are restricted with the small size of CD. At the collision with the spherical CD border, the ion, according to the authors of the

above works, endures the internal reflectance without loss of energy and keeps moving along the following short, and so on. As a result of consecutive accelerations of the ion along the every short, its energy increases until the critical value at which the ion penetrates through the CD border and goes out into incoherent component of the solution. The escaping ions cause an increase in the current through the solution. Let us quote the latter of the above articles (Comisso et al., 2006): "In summary, the transient increase of the current caused, in geomagnetic field, by a proper ELF stimulus on aqueous amino acids solutions, as originally discovered by Zhadin and later confirmed by Pazur and ourselves is fully accounted for qualitatively by the transient depolarization of the anode interface. A quantitative explanation, that is, the energetics of the phenomenon, has already been suggested within the frame of coherent Quantum ElectroDynamics whereby water is in part structured into CDs. The weakly bound electrons, contributed to these CDs by many millions H_2O molecules oscillating in phase between two definite states of their energy spectrum, electrostatically adsorb positively charged amino acids ions, at the domains' border, and the overall system can collectively interact with weak parallel static and oscillating low frequency magnetic field, magnifying their effects."

Performed by these authors (Comisso et al., 2006; Del Giudice et al., 2002), analysis of cyclotron resonance influence on ionic current through the amino acid solution is very interesting and gives some understanding of the processes taking place in the solution under the action of CDAMF. In particular, they explained, how the effect of cyclotron resonance in the solution can occur, even if the average radius of ion motion many times exceeds the size of the cell containing the solution. It is a very important achievement. However, several important aspects of the analyzed effect remain incomprehensible:

1. In what way does an ion find itself within CD?

2. Why in all successful experiments with CDAMF was used the cyclotron frequency corresponding to pure mass of an ion, in spite of the hydrated shell of an ion seemingly to essentially increase the moving mass of the ion and to decrease the cyclotron frequency?

3. The total number of glutamic acid molecules in the experimental cell is small because of poor solubility of this amino acid in water. Moreover, at pH $\sim$ 3, used in all experiments, the overwhelming majority of them was presented in form of zwitterions (from German word "zwitter" – hybrid) which is a dipole, electroneutral as a whole, and therefore unfit for cyclotron resonance. From where did appear the large number of glutamic acid ions within CDs sufficient for prominent peak of current on the background of ions of HCl added for the shift of pH of the solution to the acid range?

4. Can the zwitterion inside CD turn into an ion?

On the basis of available data about the amino acid structure and their mutual comparison, as well as (in the absence of necessary data) making the most probable assumptions, we were able to elaborate the following model of the processes arising in the aqueous amino acid solution under the influence of CDAMF.

Amino acids play very important role in organisms of all living beings as basic units of peptides and proteins, as well as some hormones and neurotransmitters (Metzler, 1977; White et al., 1978). From 300 known amino acids only 20 ones, called as α-amino acids, participate in construction and functioning of proteins.

Their basic functional elements are a carboxylic group – COOH and amides – NH_2 connected with the same α-carbonic atom. The amides is usually situated transversely to the main axis of the molecule, and the carboxylic group occupies a terminal position along this axis. Two amino acids—aspartic acid (*Asp*) and glutamic acid (*Glu*)—have two carboxylic groups situated on each side of molecule along the main axis. This feature of the above two amino acids is of particular interest for us, as we will see further. Other diverse elements of a molecule determine functions of different kinds of α-amino acids. The *Glu* molecule in linear notation is given by $HOOCCH_2CH_2CH(NH_2)COOH$: the two carboxylic groups are located on the ends—at the left and at the right, the amides is shown in parentheses, α-carbonic atom is shown as the atom C nearest at the left to the amides.

In an aqueous solution, the amino acids can be in four different ionic states, the concentrations of which are dependant on pH of the solution (Murray et al., 1988; Roberts and Caserio, 1964). For *Glu* these ionic forms look this way:

$$\underset{\text{at pH} < 1;\ \text{total charge} = +1}{HOOCCH_2CH_2CH(NH_3^+)COOH} \leftrightarrow \underset{\text{at pH} \sim 3;\ \text{total charge} = 0}{HOOCCH_2CH_2CH(NH_3^+)COO^-} \leftrightarrow$$

$$\underset{\text{at } 6 < \text{pH} < 8;\ \text{total charge} = -1}{^-OOCCH_2CH_2CH(NH_3^+)COO^-} \leftrightarrow \underset{\text{at pH} \sim 11;\ \text{total charge} = -.2.}{^-OOCCH_2CH_2CH(NH_2)COO^-} \quad (1)$$

The second dicarboxylic acid, *Asp*, has quite similar regularities. The value of pH at which the total charge of amino acid is equal to zero, that is the amino acid is a zwitterion or even is entirely electroneutral, is called "isoelectric point" and symbolized as pI. Other α-amino acids do not have the second carboxylic group. Many of them have the following ionic forms by the example of glycine NH_2CH_2COOH:

$$\underset{\text{at pH} < 1;\ \text{total charge} = +1}{NH_3^+CH_2COOH} \leftrightarrow \underset{\text{at } 3 < \text{pH} < 7;\ \text{total charge} = 0}{NH_2CH_2COOH} \leftrightarrow \underset{\text{at pH} > 7;\ \text{total charge} = -1.}{NH_3^+CH_2COO^-} \leftrightarrow NH_2CH_2\ COO^- \quad (2)$$

Some α-amino acid (for example lysine, alanine, arginine) have the isoelectric point located near the neutral pH = 7 (Murray et al., 1988). In this case, zwitterions predominate in the vicinity of pH = 7 and ionic forms like (2) for such amino acids are strongly shifted to the right.

When amino acid molecules combine into peptide or protein molecule, at the juncture of two neighbor amino acid molecules the oxygen atom is moved away from a carboxylic group and two hydrogen atoms is moved away from an amides. The removed atoms combine into a water molecule which goes to surrounding medium and the torn bonds of residua of the carboxylic group and amides join together into the so called "peptide bond" (Slabaugh and Parsons, 1979). At the ends of peptide or protein molecules, the untapped carboxylic group remains on one end and the amides, on the other end. The former mostly has the ionic form COO^-, and the latter has the form NH_3^+.

Since all experiments with aqueous solutions of *Glu* (Comisso et al., 2006; Pazur, 2004; Zhadin et al., 1998) were performed at pH ~ 3, the *Glu* molecules were present in the investigated solutions predominantly in the form of zwitterions incapable of cyclotron resonance because of electroneutrality of their total charges. However, by

virtue of their dipole charges and electrostatic interactions made by them, they have to group in the form of rather dense complexes of *Glu* molecules mixed with water ones. The mechanism of CD forming investigated by Preparata could be applied in the same degree to the mixture of dipole water molecules and *Glu* zwitterions, and these complexes could quite have capability for forming of common CD where molecules of *Glu* and H_2O participate on equal terms.

Being dicarboxylic acids, *Glu* and *Asp* have one by one carboxylic groups remaining after zwitterion forming. The spectra of water hydroxyls, –O–H, and those of carboxylic groups bear much resemblance to each other. In addition, a carboxylic group, more complicated than water molecule, has the spectrum containing more energetic levels of fine structure, than a water molecule spectrum. Therefore, at forming of joint coherent frequency of quantum transitions in all molecules in CD, the carboxylic groups can easily tune the frequency of their transitions up to the frequency of coherent H_2O transitions. Application of magnetic fields causing multiple splitting of spectral lines also will promote forming of common coherent oscillation in molecules of water and *Glu* or *Asp*. In fact, nothing also hinders in arising of general shift of the ground state of zwitterions in mixed CDs giving rise to stability of these CDs. Besides, the dense complexes containing many zwitterions will be drawn towards the already existing pure water CDs owing to the forces of attraction of foreign particles by pure water CDs derived by Del Giudice and Preparata (1994), that will also promote the forming of the mixed CDs.

The distance between charged centers in the zwitterion molecule is much more than that in the water molecule. Therefore, the dipole moments of zwitterions are much more than those of water molecules. So, more powerful electrostatic forces in mixed CD will create much denser complexes that will be lead to the increase of probability of forming such sort of CD and to acceleration of these processes. So the mixed CDs will be formed even quicker than usual water CDs.

After the forming of mixed CDs occur the interesting events important for our problems. The developing processes within CDs are operating with energy much more than energy of hydrogen bonds holding the hydrated shells around charged particles in the aqueous solution. The hydrogen bonds exceed energy of thermal noises by a negligible margin. Inside CD where power coherent processes and frequencies of quantum transitions are developing, all the water molecules are identical to each other and equally participate in coherent oscillation, and there is not any place for the hydrogen bonds. Therefore, the hydrate shells around zwitterions and usual ions of *Glu* are simply dissolved in water within CDs. It explains the old problem concerning a hydrated shell of an ion at cyclotron resonance discussed in the first section.

The high energy of quantum transitions of molecules within CDs on the excitation level (12.06 eV) is close to ionization potential of carboxylic groups and amides (Brief Chemical Encyclopedia, 1964). This energy is quite sufficient for the transition of zwitterion to the ionic form of the molecule *Glu* $HOOCCH_2CH_2CH(NH_3^+)COOH$, which with some probability occurs even spontaneously at pH $\sim$ 3 in the investigated solution (see Formulas (1)). Obviously, inside the mixed CDs there are transitions from the zwitterion form to the above ionic form with the total charge of (+1) and a shift of the ionic form equilibrium towards the increase in ion concentration more typical for pH $\leq$ 1 (see Formulas (1)) originating under the influence of CDAMF. At switching on CDAMF with very slow scanning of the AC field frequency and on reaching of the cyclotron frequency,

arises the ion cyclotron resonance in CDs according to the scheme considered by Del Giudice et al. (2002) and Comisso et al. (2006). Some portion of *Glu* ions escapes to the incoherent component around CDs, creating the increase of the current between the electrodes placed into the solution.

These ions quickly gather near the electrodes, strengthening polarization in the immediate vicinity of the electrodes. As a result, the prominent brief pulse of the current arises. When the frequency of AC field leaves the cyclotron frequency, the *Glu* ions near the electrodes begin to transform gradually into zwitterions again under the action of pH $\sim$ 3 and, having the total charge equal to zero, they begin to spread throughout the solution. They begin to group around purely water CDs and create new mixed CDs, restoring the previous equilibrium determined by temperature of the solution. After that the solution becomes ready to the new switching of the scanning of the AC field frequency. And, in such a way, the experiment can be repeated several times.

One cannot exclude the possibility of ionization of the second carboxylic group of *Glu* molecules, that could also transform the zwitterion into the ion with total charge equal to +1, and the same series of events according to the above scheme becomes to be possible. The similar effects could arise with molecules *Asp* too. For some of amino acids different from dicarboxylic ones, the strong deviation from usual scheme of ionic forms (Formulae (1–2)) can take place. As was pointed out earlier, for lysine, alanine, arginine, which have the isoelectric point near pI $\sim$ 7, the zwitterions predominate in the vicinity of pH = 7 and ionic forms like (2) for such amino acids are strongly shifted to the right (Murray et al., 1988). Therefore, it could be expected that their aqueous solutions will manifest rather weak effects in the experiments analyzed here, and maybe it would be better to perform the above experiments with solutions with pH $\sim$ 7. In principle, of course, it is impossible to exclude the possibility of ionization (the escape of an electron) or protonation (the escape of a proton (H^+)) of some other groups of amino acid molecules under the action of coherent processes in CDs, but it is already the area of a quite vague guess-work.

The above-described electrochemical model of CDAMF action on the current through the aqueous solution of amino acids to some extent resembles our previous model of action of CDAMF on the process of crystallization in the aqueous solution of amino acid which was briefly described in the end of the second section.

(1) the cyclotron resonance in CDs;
(2) the change in ionic state of *Glu* molecules under the influence of cyclotron resonance;
(3) the escape of ions from CDs under the influence of CDAMF;
(4) the increase of current through the solution owing to these ions;
(5) the prolonged reestablishment of the initial state of the solution after pulse of the current;
(6) the reverse coming of *Glu* molecules in CDs in initial form; and
(7) the return of all processes to their initial state and total readiness to the following cycle. CD itself resembles microcrystal by high degree of its order depending on the temperature, and its ionic exchange with the surrounding medium. And really it is CD from that begins the phase transition from liquid water to the ice. However, what is the most important is that the CD, as distinct from microcrystal, provides extremely small viscosity, i.e., extremely small damping coefficient of oscillatory processes and very narrow resonance

peaks. It is the feature that was so much required to all old models of resonance effects under the action of CDAMF.

But let us return to our amino acids. The analysis performed by us in this article allows us to advance in general outline some ideas about possible participation of coherent processes in organization and functioning of peptide and protein molecules.

It is known (Pauling, 1982; Roberts and Caserio, 1964; Slabaugh and Parsons, 1979), as we pointed earlier, that in the combination of amino acids into peptide or protein molecule, almost all amino acids loose their carboxylic groups and amides, except for 1) terminal amino acids, where they exist in the charged form with the carboxylic group or amides located along the main axis of the molecule–the former usually has the form of $-COO^-$, and the latter has the form of $-NH_3^+$, and 2) internal amino acids where they have two carboxylic groups (*Glu* and *Asp*) or two amides (cystine, arginine, and lysine), situated across the main axis of peptide or protein molecule.

The peptide molecules are the very long zwitterions. Because of their length they must have very big dipole moments, and, therefore, must have ability to form large and dense complexes in water and in aqueous solutions, and we have every reason to believe that they can quickly form the mixed CD together with molecules H_2O. So all our argumentation concerning these CDs hold in full measure. We may expect that CDAMF could exert strong influence on aqueous solution of peptides. Some medicines and many important hormones are peptides. Some of them are used in Medicine for correction of proper deficiencies. Different antibiotics (for example, valinomicin, gramicidin) and some antitumoral medications (for example, bleomycine) are peptides too. This opens new perspectives for use of CDAMF in Medicine. One might suppose that in the future by means of CDAMF one would be able to locally regulate the spreading of medicines of peptide nature or of hormones-peptides in the patient's organism in their different ionic forms for the increase or decrease of their activation.

The protein molecules, as a rule, have huge molecular weights and complicated forms conditioned by their tertiary and quarternary structures. The biggest of them cannot be placed into CD. They have carboxylic groups from residua of *Glu* and *Asp* and amides from residua of cystine, arginine, and lysine, which are situated across the main axis of a molecule, and, of course, the terminal charged carboxylic group and amides. Certainly, these groups are almost immovable, but molecules H_2O almost always surround all parts of protein molecules and have great mobility. In essence, the immobile carboxylic groups and amides are practically no different from the groups belonging to mobile independent amino acids and are the same way able to participate in CD forming. But in this case, the protein molecules will not be located into mixed CDs, but the CD will be located on the huge protein molecule and even, because of complicated large three-dimensional tertiary and quarternary structures, sometimes could be situated inside the protein molecule, enveloping a lot of carboxylic groups and amides belonging to this protein molecule. And first of all, these CDs could be glue elements. The bonding energy between coherent molecules inside CD is much more than energy of thermal noise and of hydrogen bonds. Until now, lacking something better, hydrogen bonds were considered as glue elements of tertiary and quarternary structures of protein molecules. But having the bonding energy not much exceeding the energy of thermal noises, the hydrogen bonds are unstable and easily split under the action of thermal noise. Unlike more or

less constant value of bonding energy between atoms within molecules, the thermal noise energy is inherently stochastic impulse value and, being comparatively small on average, it can in some of its pulses from time to time turn out to be much more than its average value, that would affect the tertiary and quarternary structures by destructive way. These structures are quite stable at least till 40–50°C and living organisms safely exist at 36°C in spite of stochastic rage of thermal noises. Only at further increase of temperature protein do structures become less stable. The bonding energy of CDs behaves in the same way, being rather high until 40°C and essentially falls at further increase and at 100°C it becomes equal to zero.

CDs are rather big structures—their size is about one-tenth of a micron (Del Giudice and Preparata, 1994; Preparata, 1995). Most of protein molecules, except of the biggest ones, could go in CD. CDs can envelop wide parts of the biggest molecules, including many thousands of carboxylic groups and amides. At room temperature the total volume of CDs is about 30% of aqueous solution, and at temperature of 37°C it is about 20–25%. Such a neighborhood of protein molecules and CDs continues during the one and a half billion year-old history of the development of life on Earth. And, of course, proteins adapted themselves to use CDs in their functioning a long time ago.

Let us stay a little on calcium-binding proteins (calmodulin, parvalbumin, troponin C, and so on), controlling free calcium concentration inside the cells. In fact, these proteins are intracellular calcium depot capturing free ions Ca^{2+} from cytoplasm at its comparatively high concentration and return them at low concentration. The background concentration of Ca^{2+} in the intracellular cytoplasm are extremely small: near 10^{-7} M (Alberts et al., 1983). Therefore, the escape of even a very small amount of calcium from calcium-binding proteins can increase their concentration in the cytoplasm till 10^{-6} M that is enough for activation of the cell. The question arises: In what way can CDAMF cause the escape of Ca^{2+} from the binding centers of these molecules into the surrounding medium?

The calcium-binding molecules are rather small. For example, the calmodulin contains of only about 150 amino acid residua and a great number of its molecules can be located in CD. It is built of two types of subunits: 4 binding subunits and one regulatory subunit. The regulatory subunit determines concentration of Ca^{2+} in the surrounding medium and establishes one of two conformational states of the binding subunit: binding of the ion or its release. When the calmodulin molecule is within CD, the coherent oscillation envelop not only all water molecules, but all the groups of atoms and separate atoms itself in the calmodulin molecule which able to participate in coherent processes. The calcium atom having many electrons has so huge number of quantum levels that the bound calcium atom is quite able to take more or less part in this overall coherent process where it can get sufficient energy to escape from the binding center; moreover, when CDAMF are tuned to its resonance frequency as it is in all experiments with cyclotron resonance of calcium ion. The escape of calcium ion from the calcium binding center was studied in detail in our theoretical work (Zhadin and Barnes, 2005). The energy for escaping of the ion from the binding center should not be very high compared to the energy of coherent oscillation within CD. And after the escape from the binding center, this ion will get the further increase of energy in CD, being already free ion under the influence of CDAMF tuned on the cyclotron frequency of calcium ion analogously to cyclotron resonance of *Glu* ion in detail considered by us earlier.

We should point that as a result of comprehension of the role of CDs in mediation of the CDAMF influence, the old problem—what ions, free or bound

ones, do CDAMF affect?—was exhausted because the free ion, falling into CD, temporarily becomes to be the ion bound of CD borders until its escape from CD under the influence of cyclotron resonance.

On the basis of all considered questions we may say that CDAMF could be of great importance in medicine. It seems to be quite probable that, at properly chosen parameters, CDAMF would be able not only to locally destruct the tertiary and quarternary structures of harmful protein molecules, for example in oncology, but even to cut the protein molecule in proper places. The practical example could be the works of Fesenko et al. (2003) and Bobkova et al. (2006), performed in the Institute of Cell Biophysics, Pushchino, Russia, where the application of CDAMF strongly accelerated hydrolysis of molecules of beta-amyloid, the protein inducing development of Alzheimer disease, *in vitro* and decreased the level of this protein in the brain of mice–animal model of sporadic Alzheimer disease.

The development of bioelectromagnetics along the lines analyzed in this article seems to be very promising in the solution of many problems from pure fundamental ones in Physics and Biology to the creation of new lines in practical Medicine.

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References

Alberts, B., Bray, D., Lewis, J., Raff, M., Roberts, K., Watson, J. D. (1983). *Molecular Biology of the Cell*. New York: Garland Publishing.

Blackman, C. F., Benane, S. G., Rabinowitz, J. R., House. D. E., Joines, W. T. (1985). A role for the magnetic field in the radiation induced efflux of calcium ions from brain tissue in vitro. *Bioelectomagnetics* 6:327–337.

Blackman, S. F., Kinney, L. S., House, D. E., Joines, W. T. (1989). Multiple power-density windows and their possible origin. *Bioelectromagnetics* 10:115–128.

Blackman, C. F., Blanchard, J. P., Benane, S. G., House, D. E. (1994). Empirical test of an ion parametric resonance model for magnetic field interactions with PC-12 cells. *Bioelectromagnetics* 15:239–260.

Blanchard, J. P., Blackman, C. F. (1994). Clarification and application of an ion parametric resonance model for magnetic field interactions with biological systems. *Bioelectromagnetics* 15:217–238.

Brief Chemical Encyclopedia. (1964). Moscow: Soviet Encyclopedia Press.

Bobkova, N. V., Novikov, V. V., Medvinskaya, N. I., Aleksandrova, I. Yu., Fesenko, E. E. (2006). Decrease of the level of brain amyloid in the brain under the influence of weak combined magnetic fields on the model of sporadic form of Alzheimer disease. *Biophysics*, accepted for print.

Comisso, N., Del Giudice, E., De Ninno, A., Fleischmann, M., Giuliani, L., Mengoli, G., Merlo, F., Talpo, G. (2006). Dynamics of the ion cyclotron resonance effect on amino acids adsorbed at the interfaces. *Bioelectromagnetics* 27:16–25.

Del Giudice, E., Preparata, G. (1994). Coherent dynamics in water as possible explanation of membrane formation. *J. Biol. Phys.* 20:105–116.

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

Edmonds, D. T. (1993). Larmor precession as a mechanism for the detection of static and alternating magnetic fields. *Bioelectrochem. Bioenergetics* 30:3–12.

Fesenko, E. E., Novikov, V. V., Bobkova, N. V. (2003). Decomposition of beta-amyloid protein under action of weak magnetic fields. *Biophysics* 48:317–220.

Jenrow, K. A., Smith, C. H., Liboff, A. R. (1995). Weak extremely-low-frequency magnetic fields and regeneration in the planarian Dugesia tigrina. *Bioelectromagnetics* 16:106–112.

Lednev, V. V. (1991). Possible mechanism for the influence of weak magnetic fields on biological systems. *Bioelectromagnetics* 12:71–75.

Lerchi, A., Reiter, R. J., Howes, K. A., Nonaka, K. O., Stokkan, K. A. (1991). Evidence that extremely low frequency Ca-cyclotron resonance depresses pineal melatonin synthesis in vitro. *Neurosci. Lett.* 124:213–215.

Liboff, A. R. (1985). Cyclotron resonance in membrane transport. In: Chiabrera, A., Nicolini, C., Schwan, H. P., eds. *Interactions Between Electromagnetic Fields and Cells*. New York: Plenum Press, pp. 281–296.

Liboff, A. R., Smith, S. D., McLeod, B. R. (1987a). Experimental evidence for ion cyclotron resonance mediation of membrane transport. In: Blank, M., Findl, E., eds. *Mechanistic Approaches to Interaction of Electric and Electromagnetic Fields with Living Systems*. New York: Plenum Press, pp. 109–132.

Liboff, A. R., Rozek, R. J., Sherman, M. L., McLeod, B. R., Smith, S. D. (1987b). Ca-45 cyclotron resonance in human lymphocytes. *J. Bioelectricity* 6:13–22.

Lovely, R. H., Creim, J. A., Miller, D. L., Anderson, L. E. (1993). Behavior of rats in a radial arm maze during exposure to magnetic fields: Evidence for effects of magnesium ion resonance. In: 15th Annual Meeting BEMS, Abstract E1-6, Los Angeles, June, pp. 13–17.

Mandelshtam, L. I. (1972). *Lectures on Oscillation*. Moscow: Russian Scientific Publishing House.

McLeod, B. R., Liboff, A. R. (1987). Cyclotron resonance in cell membranes: the theory of the mechanism. In: Blank, M., Findl, E., eds. *Mechanistic Approaches to Interactions of Electric and Electromagnetic Fields with Living Systems*. New York: Plenum Press, pp. 97–108.

Metzler, D. (1977). *Biochemistry*. New York, SanFrancisco, London: Academic Press.

Muehsam, D. J., Pilla, A. A. (1994). Weak field modulation of ion dynamics in a potential well: Mechanistic and thermal noise considerations. *Bioelectrochem. Bioenergetics* 28:355–365.

Murray, R. K., Granner, D. K., Mayes, P. A., Rodwell, V. W. (1988). *Harper's Biochemistry*. Norwalk-San Mateo: Appleton & Lange.

Novikov, V. V., Zhadin, M. N. (1994). Combined action of weak static and low frequency alternating magnetic fields on ionic current in aqueous amino acid solutions. *Biofizika* 39:45–49 (In Russian).

Pauling, L. (1982). *General Chemistry*. Dover, New Tork: Freeman.

Pazur, A. (2004). Characterisation of weak magnetic field effects in an aqueous glutamic acid solution by nonlinear dielectric spectroscopy and voltammetry. *Biomagnetic Research and Technology* 2:8

Permyakov, E. A. (1993). *Calcium-Binding Proteins*. Moscow: Science (In Russian).

Persson, B. R. R., Lindval, l. M., Malmgren, L., Salford, L. G. (1992). Interaction of low-level combined static and extremely low-frequency magnetic fields with calcium transport in normal and transformed human lymphocytes and rat thymic cells. In: Norden, B., Ramel, C., eds. *Interaction Mechanisms of Low-Level Electromagnetic Fields and Living Systems*. Oxford: Oxford University Press, pp. 199–209.

Preparata, G. (1995). *QED Coherence in Matter*. New York: World Scientific.
Preparata, G. (2000). QED and medicine. *Rivista di Biologia/Biology Forum* 93:467–512.
Reese, J. A., Frazier, M. E., Morris, D. L. (1991). Evaluation of changes in diatom mobility after exposure to 16-Hz electromagnetic fields. *Bioelectromagnetics* 12:21–25.
Roberts, J. D., Caserio, M. C. (1964). *Basic Principles of Organic Chemistry*. New York, Amsterdam: Calif. Inst. Technology.
Rochev, Y. A., Narimanov, A. A., Sosunov, E. A., Kozlov, A. N., Lednev, V. V. (1990). Effect of weak magnetic field on the rate of cell proliferation in culture. *Studia Biophysica* 2:93–98.
Shuvalova, L. A., Ostrovskaya, M. V., Sosunov, E. A., Lednev, V. V. (1991). Influence of week magnetic field at parametric resonance on rate of calmodulin-dependent phosphorylation of myosin in the solution. *Proc. AS USSR* 317(1):227–230.
Slabaugh, W. H., Parsons, T. D. (1979). *General Chemistry*. New York, Sydney, Toronto: J. Wiley.
Smith, S. D., McLeod, B. R., Liboff, A. R. (1987). Calcium cyclotron resonance and diatome mobility. *Bioelectromagnetics* 8:215–227.
Smith, S. D., Mcleod, B. R., Liboff, A. R. (1993). Effects of CR-tuned 60 Hz magnetic fields on sprouting and early growth of Raphanus-sativus. *Bioelectrochem Bioenergetics* 32:67–76.
Tamm, I. E. (1989). *Foundations of Electricity Theory*. Moscow: Science (in Russian).
Thomas, J. R., Schrot, J., Liboff, A. R. (1986). Low intensity magnetic fields alter operant behavior in rats. *Bioelectromagnetics* 7:349–357.
Tiras, Kh. P, Srebnitskaya, L. K., Ilyasova, E. N., Klimov, A. A., Lednev, V. V. (1996). The influence of weak combined magnetic field on the rate of regeneration in planarians. *Dugesia tigrins. Biophysics* 41:826–831.
Walsh, R. N., Cummins, R. A. (1976). The open-field test: A critical review. *Psychol. Bull.* 83:482–504.
White, A., Handler, P., Smith, E., Hill, R., Lehman, I. R. (1978). *Principles of Biochemistry*. New York, London: McGraw Hill.
Yost, M. G., Liburdy, R. P. (1992). Time-varying and static magnetic fields act in combination to alter calcium signal transduction in the lymphocyte. *FEBS Lett.* 296:117–122.
Zhadin, M. N. (1996). Effect of magnetic fields on the motion of an ion in a macromolecule: theoretical analysis. *Biophysics* 41:843–860.
Zhadin, M. N. (1998). Combined action of static and alternating magnetic fields on ion motion in a macromolecule: theoretical aspects. *Bioelectromagnetics* 19:279–292.
Zhadin, M., Barnes, F. (2005). Frequency and amplitude windows at combined action of DC and low frequency AC magnetic fields on ion thermal motion in a macromolecule: Theoretical analysis. *Bioelectromagnetics* 26:323–330.
Zhadin, M. N., Novikov, V. V., Barnes, F. S., Pergola, N. F. (1998). Combined action of static and alternating magnetic fields on ionic current in aqueous glutamic acid solution. *Bioelectromagnetics* 19:41–45.
Zhadin, M. N., Deryugina, O. N., Pisachenko, T. M. (1999). Influence of combined DC and AC magnetic fields on rat behavior. *Bioelectromagnetics* 20:377–386.