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Effects of weak magnetic fields on biological systems: physical aspects

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Contents

Abstract. **The effect of weak magnetic fields on biosystems is the subject matter of the science of magnetobiology. There are objective factors, due to theory lagging far behind experiment, that are hindering the development of this science. Academic interest in the subject is restrained by the fact that experimental data lack a clear physical explanation. Besides, there is a strong imbalance in how physics and biology are involved in magnetobiology, the former being still in infancy in this respect. It is this imbalance which is currently the driving force for the development of the theory of magnetobiology. This brief analytical review focuses on the physical aspects of magnetobiological research. The task of magnetobiology is to explore the biological effects of weak magnetic fields and to understand mechanisms behind these effects. Magnetobiology is part of a more general issue of the biological impact of weak and hyperweak physico-chemical factors. It is believed that such factors operate even below the trigger threshold for protective biological mechanisms and are therefore capable of accumulating at the subcellular level. The so-called 'kT-problem' is discussed in detail, and the interference mechanisms of the molecular gyroscope and of molecular states in an idealized protein cavity are suggested as candidate solutions.**

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1. Introduction

Magnetobiology is a new synthetic discipline encompassing the principles and techniques of many sciences, from physics to medicine, and centered around biophysics. Magnetobiology has made notable advances only in the last 10 – 20 years. Moreover, both the theoretical foundation and general physical concepts of magnetobiology remain to be established. Suffice it to say that magnetobiology practically lacks predictive theoretical models. The problem relates to paradoxical biological effects of weak low-frequency magnetic fields of energy much smaller than the characteristic energy of biochemical processes. For many researchers, these effects, by their very nature, cast doubt on the reality of the problem despite the abundance of experimental evidence in its support.

Years of experience have shown that some electromagnetic fields may pose a threat to human health and should be considered on an equal footing with such important climatic factors as atmospheric pressure, temperature, and humidity. With the growing knowledge of this fact, investigations into the mechanisms of biological action of electromagnetic fields are becoming increasingly necessary.

There are no specific biological magnetoreceptors apart from biomagnetite particles in certain bacteria. Hence, the importance of understanding how a magnetic signal is

transformed into a biological response. A low-frequency magnetic field passes almost unobstructed through living tissue. It affects all tissue particles but not all particles are uninvolved in the transfer of information about the magnetic field to biological structures. Primary interactions of the magnetic field with tissue particles, electrons, atoms, and molecules are purely physical processes. Charged particles of living matter, i.e. ions and molecules, that participate in biophysical and biochemical processes act as mediators of magnetic signal transmission to consecutive biochemical levels. Biophysical mechanisms that involve ions and mediator molecules ensure fine regulation of enzymatic activities and account for the modulation of metabolic processes. Starting from this level, the effects of magnetic fields are observable as variations in the levels of metabolic end products.

Biological effects of magnetic fields are not infrequently estimated from the parameters of vital activity and behavior of individual organisms and their populations. As a rule, experiments designed to obtain such parameters have the objective to correlate characteristics of a given physical agent (e.g. external magnetic field) and its biological effects. However, they yield no information about events at intermediate organizational levels of living systems (biophysical, biochemical, physiological) that strongly influence the final result. This accounts for a sort of 'black box' with uncontrollable properties that precludes the achievement of a deeper insight into cause-and-effect relationships. The available physical and chemical methods prove to be of small value for the description of effects of weak magnetic fields on individual biochemical reactions and biophysical structures. In other words, objective difficulties encountered by magnetobiology are related to the involvement of problems that also face many other sciences, such as physics, biophysics, biochemistry, and biology.

Unlike biomagnetism studying magnetic fields (MF) of biological systems [1], magnetobiology focuses on biological reactions and mechanisms of action of weak (below 1 mT) magnetic fields. There is rapidly growing interest in the biological action of weak magnetic and electromagnetic fields. The American periodical Microwave News has published a list of hundreds of the Internet hyperlinks to organizations directly involved in electromagnetobiological research (http://www.microwavenews.com/www.html).

The aim of electromagnetobiology is to resolve part of a more general problem of biological impact of weak and hyperweak physico-chemical factors. It is believed that such factors operate below a threshold at which protective biological mechanisms are triggered; therefore, they are capable of cumulative action at the subcellular (e.g. genomic) level.

A powerful impetus to research in electromagnetobiology was given by the school of N D Devyatkov in the former USSR that developed EM generators of microwave radiation in the 1960s. These works were reproduced abroad. From the very beginning, it became clear that microwaves had marked biological effects [2]. Of special interest was the fact that the microwave power was frequently too low to cause an appreciable heating of tissues. At the same time, a quantum of radiation energy was two orders of magnitude smaller than the characteristic energy of chemical transformations kT. Moreover, microwave effects were observable only at selected frequencies which suggested their non-thermal nature. Also, they depended on low-frequency modulations. Reliable evidence of the biological effects of low-frequency magnetic fields proper (in the range of 10 – 100 Hz) was obtained in the 1980s. These facts are worth mentioning because this range covers the frequencies of industrial and household electrical appliances.

Interest in magnetobiology arises in the first place from environmental considerations. Human impact on natural processes has reached a dangerous level. The environment is heavily polluted by industrial and municipal wastes. Electromagnetic pollution is growing equally fast. The situation is aggravated by the absence of a clear understanding of the physico-chemical mechanisms that underlie the biological effects of natural and artificial hyperweak agents. Hence, it is opportune to speak about a paradox. Indeed, these phenomena are not only inexplicable but seemingly at variance with the currently adopted scientifically-based world picture. At the same time, a wealth of observations and experimental data suggest their reality. In a word, the biological action of hyperweak agents constitutes a fundamental scientific problem having important practical implications.

What factors should be regarded as hyperweak? They are intuitively distinguished by common sense. A signal may be called hyperweak if the effect or, more precisely, the correlation it produces goes counter to the accepted knowledge (i.e. an 'it can't be so' situation arises). In application to the problem of low-frequency electromagnetic fields (EMF), a hyperweak factor is a background level created by working industrial and even domestic electrical appliances [3]. Figure 1 illustrates the relative levels of magnetic fields, their sources, and areas of application.

In the past, weak low-frequency MF and non-thermal EMF were believed to pose no threat to human health because their biological effects seemed out of the question for physical considerations. Since then, however, experimental data have been obtained suggesting the potential risk of these fields and the radiation they emit [4, 5] even though their visible effects may not infrequently remain inapparent for months and even years. Environmental impacts of electromagnetic fields have become the subject matter of specialized studies. A simple calculation shows that, given enhanced background EM radiation increases the probability to get an oncological diseases by only 1%, a country with a population of 50 million may suffer the net annual loss of nearly 1000. This creates a social problem which the involved industries and governments in many countries try to resolve by providing financial support for relevant protective

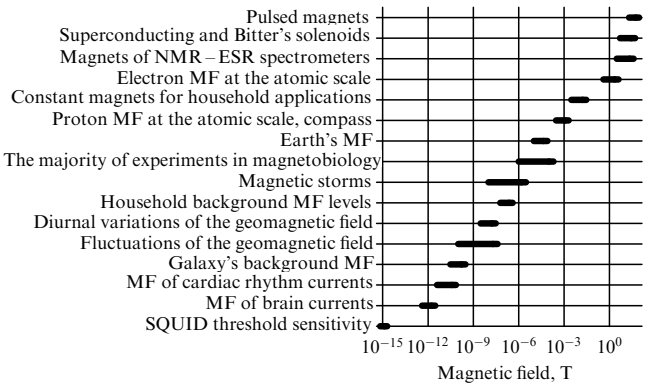

Figure 1. Magnetic field levels of various natural and artificial sources (approximate values).

measures. There are also reports relating background EM levels to the occurrence of cardiovascular diseases.

Introduction of sanitary-hygienic regulations, electromagnetic 'smog' monitoring and control are important aspects of electromagnetic ecology. Electromagnetic safety standards are worked out by many national and international institutions, such as the Comite Europeen de Normalisation Electrotechnique (CENELEC), the Deutsche Institut fur Normung (DIN), the American National Standards Institute (ANSI), the International Radiation Protection Association (IRPA), the Research Institute of Labour Medicine of the Russian Academy of Medical Sciences, etc.

The World Health Organization (WHO) coordinates these activities with a view to combining in a single system universally acceptable international standards. Today, safety standards for certain EMF ranges differ by tens and hundreds of times; this situation reflects the lack of research in this area.

Quite recently (in 1981) M V Vol'kenshteĭn, corresponding member of the Russian Academy of Sciences, wrote in the monograph *Biofizika* (Biophysics): ''Reliable data on the biological effects of a constant magnetic field are still virtually absent''. Within the next 10–15 years, a large magnetobiological data bank was created. It is worth noting that the first studies in the field of magnetobiology date to the early 20th century (see, for instance, a brief review by Warnke and Popp [6]).

The number of reviews of experimental magnetobiological studies, monographs, handbooks, and reports is very large and continues to increase. A short and incomplete list of such publications would include Refs [7–18]. In parallel, academic reviews have appeared [19, 20].

A good introduction to electromagnetobiology is provided by a 1000-page volume of materials presented at the Second World Congress on Electricity and Magnetism in Biology and Medicine [21] edited by F Bersani. This book published in 1999 includes more than 230 articles that treat a wide range of problems facing this discipline, from basic physical and biological to socio-political ones. There is an electronic database (http://infoventures.com) containing over 30,000 bibliographic references that cover all aspects of electromagnetobiology (scientific, medical, social). For comparison, the number of publications pertaining to the topical problem of higher-temperature superconductivity during the same 20-year period of its extensive development amounted to 200,000; they, however, failed to provide a reliable explanation of this phenomenon and its mechanisms. References to open bibliographic databases on various aspects of magnetobiology are available on the Internet site www.biomag.info. An interesting sketch of the history of magnetobiology can be found in a monograph of Yu A Kholodov [22]. It appears that over 6000 publications were subjected to analysis by 1982. A recent historical review of M Zhadin [23] is focused on the works (mostly experimental) of Russian authors.

At the same time, there are very few reviews of theoretical studies, in the first place for the lack of publications bearing on the matter at issue. Some papers contain a critical analysis in the light of the known physical mechanisms of MF action [24–27], but most of them are confined to the mere statement of ideas [11, 28–30]. There have been only a few (highly debatable) attempts to explain results of certain readily reproducible experiments with weak MF on physical grounds [31, 32].

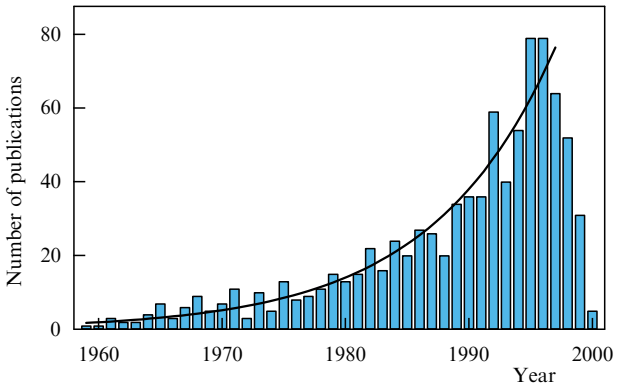

Figure 2. Distribution of the number of publications in magnetobiology by time periods (based on a sample of about 700 papers). Distribution prior to 1997 is approximated by the exponent.

An increasing public interest in magnetobiology is reflected in the results of analysis of the annual distribution of 700 publications over a forty-year period (Fig. 2). They were selected from nearly 2,000 available publications. The sole inclusion criterion was the presence of sufficiently detailed information about EMF parameters. Because there are a total of 30,000 publications on the subjects, it may be concluded that, in recent years, several thousand papers on various aspects of magnetobiology are published annually. The decrease in their number during the last few years is due to objective causes, besides the natural delay of publication. It is first and foremost attributable to the completion in the USA (1998) of the extensive RAPID program aimed to evaluate chronic effects of background industrial-frequency EMF on human health (in common belief, low-frequency EMF is a risk factor for various diseases). Secondly, the number of publications in Russia, many of which were devoted to magnetobiological problems, has decreased drastically. Finally, an important cause is the bitter disappointment with which a wide public received the failure to find an acceptable physical explanation of the observed magnetobiological effects.

In what follows, we shall frequently use the term 'magnetobiological effect' (MBE) to define any change in the characteristics of a biological system induced by variations of its magnetic environment (at weak MF). Such characteristics may be the biological properties of an organism *in vivo* as well as *in vitro* biochemical parameters of a living system.

Here are the results of two experiments. Blackman and coworkers [33, 34] undertook a series of studies to evaluate the dependence of biological responses on the amplitude ratio of alternating (45 Hz) to constant (36.6 μT) co-linear MF. The authors measured the inhibition of PC-12 neurite growth induced by a biostimulator. Experimental data were normalized bearing in mind the involvement of two modulating agents, the stimulator and MF. The results presented in Fig. 3 suggest a multipeak amplitude spectrum. The authors concluded that magnetoreception in PC-12 cells was mediated through Mg^{2+} ions. For these ions in the constant MF, the alternating field frequency corresponded to a cyclotron frequency subharmonic. Similar results were obtained in other studies (Fig. 4).

McLeod, Smith and Liboff [35] examined the motility of diatom algae placed in MF with a frequency corresponding to

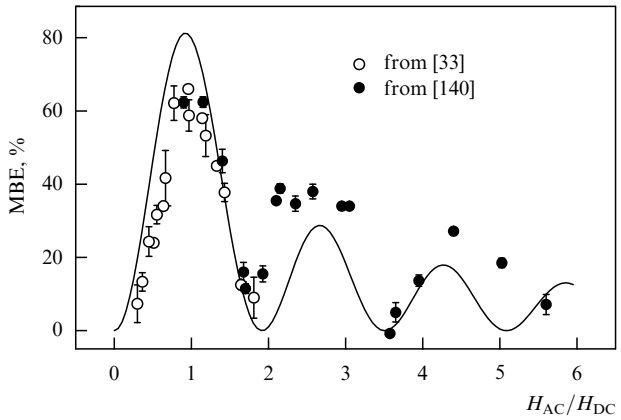

Figure 3. Dependence of MBE in PC-12 nerve cells on the amplitude of variable constituent in an uniaxial MF (from [33, 140]). The line shows function $J_1^2(2H_{AC}/H_{DC})$.

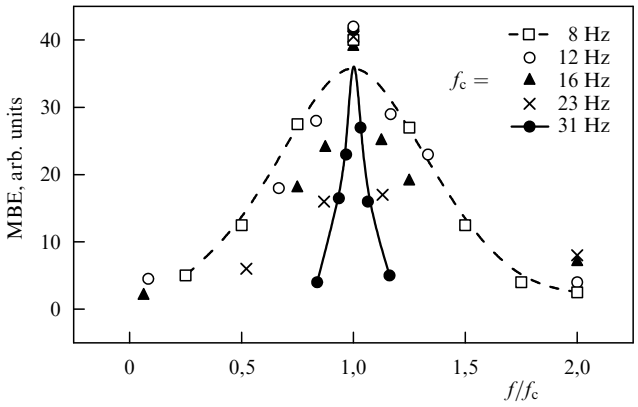

Figure 5. Motility of diatom algae in a low-frequency alternating MF (with a frequency in the vicinity of given cyclotron frequencies of calcium ion). Mean square deviation is around 3 – 5% (from [35] with slight modification).

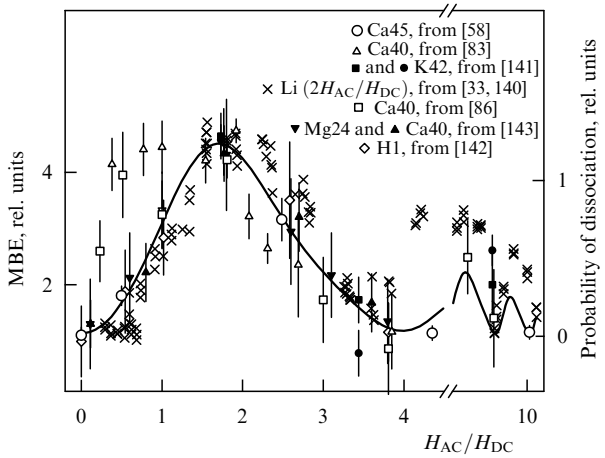

Figure 4. Experimental characteristics of MBE in an uniaxial MF [33, 58, 86, 140 – 143]. Theoretical amplitude spectrum is calculated for stationary ion – protein complexes.

the cyclotron resonance frequency of Ca^{2+} ions. The resulting MBE proved to be quantitatively similar regardless of the experimental regime and significantly different from control values obtained in a constant field. Measurement of bell-shaped frequency spectra in the vicinity of central frequencies shown in Fig. 5 revealed that the absolute width of the maxima was in all cases close to 10 Hz. The same value is characteristically reported in the majority of other works concerning frequency spectra in magnetobiology.

It should be noted that the results of magnetobiological experiments are on the whole poorly reproducible. Some 10 – 20% of the recent publications report failed attempts to observe MBE. Given a lengthy and uncontrollable process of transformation of a magnetic signal into a biological response, there is nothing extraordinary in the absence of the effect in a concrete experiment. Many researchers emphasize that MBE develops when an electromagnetic field affects a biological system in a proper physiological state. Also, the time factor is of prime importance because the system is capable of responding to MF within a relatively narrow time window. In the majority of experiments, their success depended on a rare happy coincidence of suitable electromagnetic and physiological conditions. Collectively, these limitations account for the difficulty to reproduce results of magnetobiological experiments. Many of them await confirmation by independent studies in other laboratories. Thus, there is seemingly no solid foundation on which to construct theoretical models. Nonetheless, the available data taken together (see, for instance, Refs [21, 20]) demonstrate a certain degree of similarity in MBE manifestations as reported by laboratories using different biological objects in a variety of experimental conditions. These common features provide a basis for theoretical generalizations.

2. Theoretical models of MBE

There is no simple answer to the question how a weak (of the order of 1 G or smaller) low-frequency magnetic field induces a biological response. The development of the magnetobiological effect involves processes that occur at different organizational levels of a living organism, from physical to complex adaptive biological processes [36]. Specialists representing different scientific disciplines give different answers. Medical researchers distinguish organs and general physiological processes sensitive to MF. Biologists look for cellular and subcellular structures capable of generating biological signals in response to magnetic fields. Biochemists are interested in targets, i.e. stages of biochemical reactions that become rate-limiting under effect of MF. (Bio)physicists study magnetosensitive processes involved in interactions between MF and relatively simple molecular structures. It is at this level that complex spectral and 'window' regimes occur under which biophysical processes are linked to MF biotropic parameters.

This section is designed to critically analyze hypotheses and models of biological reception of weak MF. Putative magnetoreception mechanisms in strong MF (fractions of a Tesla and stronger) have been reviewed by L A Piruzyan and A N Kuznetsov in Ref. [8].

2.1 Current state of theoretical magnetoreception research

It is appropriate to begin the analysis of the magnetoreception theory from a group of similar explanations of magnetobiological effects combined in Refs [11, 12, 28]. The review may be extended to the groups of physical processes and mechanisms [27] that supposedly underlie magnetoreception and can be divided according to the types of description (phenomen-

ological, macroscopic, and microscopic). A phenomenological description is unconcerned with the nature of the phenomenon of interest and employs only mathematical tools to characterize the outward features of the object. Conversely, macroscopic and microscopic descriptions seek an insight into the physical nature of the object and establish limits for the applicability of selected phenomenological models. They differ in terms of scale of the objects being described.

In addition, there is a group of theoretical studies the meaning of which can be illustrated by the following considerations. The thesis that *A exists* as a physical phenomenon is relatively easy to support. It is sufficient to confirm experimentally that it exists under *certain*, in fact any, acceptable conditions. An opposite thesis that *A does not exist* as a physical phenomenon is much more difficult to support. The validity of this thesis must be confirmed for *all* acceptable conditions. Not infrequently, it is simply impossible to turn over, even in one's mind, all the acceptable conditions. This is how things stand with the issue of biological reception of weak MF. Its corroboration is a matter of practical research activity. In the framework of positivist concepts, the thesis that MBE is non-existent is compromised by a totality of experimental data. Neither experimental findings nor formal logical reasoning can possibly refute the reality of this phenomenon. In the latter case, sorting out conditions, i.e. possible mechanisms of MF actions, can not be completed; there is always a probability that certain specific conditions are left unconsidered. Nevertheless, attempts to compromise MBE theoretically are continued despite their logical inconsistency. Relevant publications (see, for instance, papers by Adair [26], Pickard and Moros [37]) describe physical models of hypothetical processes underlying MBE proposed in the literature. However, these models tend to disprove the phenomena in question; they neither contain a constructive element nor have any predictive value. Their substance and meaning are impossible to verify.

For example, the authors of study [37] (supported by a MOTOROLA laboratory) maintain that, in the absence of an energy cumulation mechanism other than Debye or Joule heating, non-thermal biological effects at non-thermal powers in a frequency range of 0.3–3 GHz (cellular telephony) are unlikely. According to these authors, energy accumulation above a kT threshold in a single chemical bond is a necessary prerequisite for the manifestation of biological effects. They furthermore consider certain hypothetical processes of energy accumulation and conclude that these processes do not explain the appearance of biological effects of EMF in the UHF range. However, they take no account of a non-thermal mechanism of interference described in certain specialized journals. The interference mechanism does not require energy accumulation for a marked biological response to be manifest.

2.2 Classification of models of MBE mechanisms

Models of MBE mechanisms are arbitrarily categorized into three main groups.

Phenomenological models include complex behavior of the solutions of equations such as chemical kinetics equations [30, 38, 39]; stochastic resonance as an amplification mechanism in magnetobiology and other random processes [40–42]; magnetosensitive phase transitions in biophysical systems regarded as liquid crystals [43] or ordered membrane proteins [44]; 'radiotechnical' models in which biological microstructures and tissues are depicted as equivalent electrical circuits [45–48].

Macroscopic models: biomagnetite in a magnetic field and ferromagnetic contamination [49, 50]; Joule heat and eddy currents induced by alternating MF [51–53]; superconductivity at cellular and subcellular levels [54–56] and at the level of alpha-helical protein molecules [57]; magnetohydrodynamics (see review [24]).

Microscopic models: motion of charged particles and particles with a spin in MF including resonance [52, 58–60], oscillation [61–64], and interference [32, 65–70] effects, reactions of free radicals [71–73], collective excitations of multiple-particle systems [74–76].

2.3 Concise description of MBE mechanisms

What follows is a short description of widely discussed magnetoreception mechanisms which supposedly underlie MBE.

Historically, one of the first ideas in magnetobiology was that of the so-called biogenic magnetite in a magnetic field. Tissues of certain animals as well as microorganisms are known to produce microscopic crystals (usually of magnetite) capable of being magnetized. In an external MF, such crystals possess a moment of rotation and exert pressure on the surrounding tissues that react accordingly. There is every reason to believe that this mechanism thoroughly investigated by Kirschvink [77] really operates. Magnetite crystals have been found in certain insects and bacteria (see review [78]) and in the brain of some avian species known to perfectly well orient themselves in the geomagnetic field.

An explanation of *in vitro* cellular effects of low-frequency MF taking into consideration ferromagnetic contamination [50] exploits the hypothesis of biogenic magnetite. Contaminants are small magnetic particles present not only in the dust in the air but also adsorbed on the surfaces of laboratory equipment, present within glass and plastics, and even in reagent-grade laboratory chemicals and water. Mean size of such particles is around 10^{-5} cm, they are composed of ferro- and ferrimagnetic substances, i.e. exhibit spontaneous magnetization. It has been shown that routine laboratory manipulations, such as liquid transfer and rinsing, concentrate magnetic particles in cell cultures where their amount can be tens of times the cell number. The energy present in a single magnetic particle may be almost three orders of magnitude higher than kT (here and hereinafter, k is Boltzmann constant and T is thermostat temperature). Such particle, if adsorbed on the cell surface can conceivably transfer its energy to contiguous cell structures, such as mechanically activated ion channels.

These magnetite-based mechanisms are not widespread and do not explain all magnetobiological effects. Suffice it to say that unicellular organisms containing no magnetite react just as well to magnetic fields. Moreover, many of them are capable of complex non-linear and multipeak response (depending on field characteristics). The main task of magnetobiology is to elucidate this phenomenon.

Biological effects of weak MF are sometimes explained on the assumption that living tissues and biophysical structures can be regarded as equivalent distributed electrical circuits. However, this phenomenological approach does not help to solve the problem either.

The hypothesis that eddy current induced by alternating MF may be active factors in biological tissues exposed to a low-frequency MF was many times subject to verification.

These currents can either heat tissues or compete with natural electric currents. It has been shown by Polk [53] that eddy currents can also induce electrochemical effects by means of charge redistribution. On the whole, the strength of the current matches that of the induced electrical field which is proportional to the product of MF amplitude and frequency. If the hypothesis is correct, experimental MBE must correlate with the variations of this quantity. Indeed, it has been shown in experiment that such correlation appears as the strength of alternating MF increases [79, 80]. It is however absent in the case of relatively weak MF (comparable to the Earth's magnetic field) [81–86]. For example, it was shown in Ref. [83] that MBE remained unaltered in a given frequency window when the strength of induced currents varied almost 40-fold. This suggests the existence of primary MBE mechanisms unrelated to eddy currents.

Effects of weak physico-chemical factors on biological systems are frequently described as being of information value, meaning that the systems are close to unstable dynamic equilibrium. A system needs only a slight push to pass to a different state at the expense of its inner resources. In other words, the so-called biological amplification of a weak MF signal will take place. Equations of chemical kinetics are used for the phenomenological description of this process. Under certain conditions, solutions of these equations exhibit bifurcation behavior (transition to a qualitatively different dynamic regime under the action of weak perturbation). G R Ivanitskiĭ et al. [87–89] reported a detailed study of mechanisms of formation of dissipative structures by which minor effects induce major changes due to multicascade amplification in systems with internal feedback. Kaiser [38] discussed the same approach in application to electromagnetobiology.

An important question is why thermal fluctuations, the energy of which is ten orders of magnitude higher than a quantum of magnetic field energy, do not destroy MBE. The answer lies in the cooperative effect between coherent action of an external force and the incoherent background thermal noise. In this case, repeated disturbances of a high Q oscillator (temporal coherence) can bring on a state in which its energy is sufficient to produce an initial impulse; likewise, synchronous swinging of a system of oscillators (spatial coherence) can make it emit an energy quantum of collective excitation [90, 91]. Alternatively, MF imparts properties important for the work of associated biophysical systems to oscillator parameters other than energy (e.g. polarization of oscillations). For example, M N Zhadin and E E Fesenko [92] and D T Edmonds [93] discussed the application of the Larmor theorem to an ion bound in a calmodulin microcavity. They suggested that the direction of ion oscillations is paramount for the shape of the protein, hence for its enzymatic activity. Changes of oscillation direction in alternating MF of different configuration were studied in the framework of classical dynamics. It was shown that the Larmor frequency was distinguished from the point of view of expected effects of orthogonal MF. However, it remained unclear why the parallel configuration of alternating and constant fields resulted in a change of enzymatic activity. Nonetheless, it was such a configuration that proved most efficient in the majority of experiments.

A variety of microscopic objects, molecular groups, plasma membranes, and intact organelles were used as oscillators. The concept behind these models implies a pendulum excited parametrically by a very weak signal in the presence of a considerably stronger random additive force. It is suggested that pendulum energy may significantly increase at a resonant frequency. A principal disadvantage of such models consists of that they 'do not work' even in the absence of noise-producing factors. In this ideal case, the system's energy is likely to change only a few months after coherent swinging of the pendulum. It is worthwhile to note that neither the oscillator-based nor the collective excitation concept has so far led to the proposal of predictable and verifiable mechanisms.

One more possibility to overcome effects of the thermal factor applies to the concept of stochastic resonance. This phenomenon consists of the enhancement of a small signal due to the added noise by means of energy redistribution in the spectrum of additive signal-noise mixture. It is important that noise is not a hindrance but a beneficial attribute of the system. Under stochastic resonance, small biological signals can markedly affect the behavior of a dynamic system in the presence of various relatively strong exciting factors. It was shown in Ref. [94] that the observed response of isolated mechanoreceptor cells of the crayfish to an acoustic stimulus in the form of a subthreshold signal mixed with Gaussian noise was due to stochastic resonance. This phenomenon was used to address the 'kT problem' in Refs [40, 41]. However, the obtained amplifications ($\sim 10^2$) with the concurrent loss of signal quality (coherence [95]), proved insufficient to account for biological effects of weak low-frequency MF.

The velocity of certain reactions involving free radicals depends on the constant MP strength [71]. The probability of the synthesis of a product composed of two radicals each having spin angular momentum depends on their total momentum, that is on mutual spin orientation. At the same time, this mechanism lacks frequency selectivity. The lifetime of a pair of radicals prior to reaction, or conversely to dissociation, i.e. in a state where the pair is sensitive to MF, is of the order of 10^{-9} s. The pair responds to MF as if it were a constant field and no resonance occurred. Therefore, to explain the extreme dependence of MBE on MP parameters, Grundler, Kaiser, and some other authors assume that a magneto-sensitive reaction of free radicals is a component of the system described by a set of non-linear equations of chemical kinetics [30, 38] with bifurcations. Difficulties encountered in this group of models arise from the primary action of alternating MP on the free radical reaction rate. Certain physico-chemical factors set a limit for rate sensitivity to MF at 1% per 1 mT which is insufficient to adequately explain biological effects of weak low-frequency MF with an amplitude of the order of 50 μT or less.

In some cases, the effects of weak MF have resonant characteristics, with effective frequencies close to cyclotron frequencies of Ca^{2+}, Na^{+}, and other ions. Liboff [96] suggested that the observed phenomena are underlain by cyclotron resonance. This concept in application to magnetobiology was developed by different authors but failed to be recognized because its correct justification encountered difficulties. At the same time, these experiments demonstrated the important role of ions (especially Ca^{2+}) in magnetobiological processes. It should be emphasized that the coincidence of effective and cyclotron frequencies can not be regarded as a convincing argument in favor of the concept of cyclotron resonance in biological systems. Suffice it to say that *any* theoretical model of MBE based on electric charge dynamics makes use of characteristic frequencies $\Omega_c = qH/(Mc)$, where q and M are the particle's charge and mass

respectively, H is the magnetic field strength, and c is the velocity of light. There is no other combination of parameters of the charge and MF with a frequency dimension.

In an attempt to overcome disadvantages of the cyclotron resonance concept, it was postulated that biological plasma contains macroscopic charged structures or vortices formed by ion clouds [97]. Such targets for weak MF are chosen taking into consideration their relatively high natural intrinsic energy comparable with kT. In this case, even weak MF can substantially change the energy of an object carrying a macroscopically large electrical charge provided the object's motion obeys certain strict conditions. Specifically, the motion of the center of mass must have an angular momentum [60]. The possibility of such macroscopic motion is doubted. Moreover, for the comparison of vortex energy with kT to have sense, a mechanism is needed for the conversion of macroscopic vortex energy into the energy of an individual degree of freedom, i.e. to the microscopic level. Such a mechanism is difficult to imagine. Equally unclear is the nature of molecular forces capable of supporting the existence and stability of such an ion cluster. Clustering in systems with thermal motion of particles polarized under effect of EMF, i.e. particles with a dipole moment, was described by G R Ivanitskiĭ and co-workers in the review [98]. But the authors considered ions of similar polarity undergoing the Coulomb repulsion.

Certain magnetobiological effects of modulated MF are frequency and amplitude-specific. Spectra of MF dependences of MBE are of high informative value for the elucidation of primary magnetoreception mechanisms. They were explained based on the mechanisms of transformation of MF signals at the level of microscopic dynamics, classical and quantum models of ion binding to proteins [59, 61, 64, 99]. Biological activity of a protein depends on its binding with a respective ion. It is assumed that the magnitude of certain magnetobiological effects is related to the intensity of transition between the ion's quantum levels modulated by MF. However, parallel static and low-frequency MF affect only wave function phases and do not induce transitions in Zeeman sublevels; nor do they change the intensity of transitions induced by other factors. The population of each state remains unaltered regardless of MF parameters. Nevertheless, it is shown [59] that amplitude spectra of certain MBE were similar to analogous amplitude dependences in parametric resonance effect in atomic spectroscopy [100] studying characteristics of quantum transitions. This finding gave impetus to a number of publications [63, 64, 101] that however failed to clarify this similarity.

The phenomenon of quantum state interference well-known in physics was used to explain the physical nature of magnetoreception in Refs [65, 102]. MF of varying strength alters the wave function phases of a charged particle. It is interference that links phase changes with the observed values. Interference of quantum states of bound or free (including such heavy ones as atoms) particles is recorded by physical measurements. In the case of bound particles, interference of their states is observable only as characteristics of a reemitted electromagnetic field. This likens particles that produce interference effects to electrons in an atom. The suggestion that interference of heavy bound particle (ion) states can be also observed by means of indirect measurements involving natural active biophysical structures is confirmed by their good agreement with experiment [65–67]. The phenomenon of quantum state interference well known in atomic spectroscopy is associated with coherent quantum transitions in the atom and unrelated to the internal structure of electron wave functions. At the same time, it is this internal structure of ion functions that makes possible ion interference in a protein cavity exposed to an alternating MF in the absence of quantum transitions. At present, the mechanism of ion interference predicts multipeak biological effects, viz. strength and direction-modulated MF, magnetic vacuum, constant MF taking into account intrinsic rotations of ion–protein complexes, pulsed MF coupled to a parallel constant MF, weak alternating electrical fields, and shifts of MBE spectral peaks rotating biological specimens.

Biological effects explainable in the framework of the interference mechanism were observed in a number of experiments. The formulas were obtained that describe the dependence of the probability of dissociation of ion–protein complexes on MP characteristics, variable component frequency, size and mutual orientation of constant and variable components. Important spectral properties and positions of extrema depend on masses, charges, and magnetic moments of the involved ions. In the majority of the examined cases, relevant ions included calcium, magnesium, zinc, hydrogen, and sometimes potassium.

3. Fundamental limit to EMF sensitivity

Increasingly more magnetobiological data indicate that 1–10 μT and smaller magnetic fields may influence biological processes. These very interesting data are schematically represented in Fig. 6. They do not agree with any proposed primary mechanism of biological action of MF. Hence, the problem of physical limitations accounting for possible fundamental nature of biological effects of hyperweak fields.

Rectangles marked by figures show the ranges of parameter variations of the following fields: *1* — low-frequency EMF used in most magnetobiological experiments, *2* — EMF of magnetic storms known to be time-correlated with exacerbation of cardiovascular diseases, *3* — background EMF generated by various household electrical appliances, television screens, and computer monitors, *4* — MF that induce changes in certain amino acid solutions [103, 104], *5* — magnetic fields used in Ref. [105] to compensate for adverse biological effects of EMF, *6* — EMF below the trigger quantum-electrodynamic (QED) threshold for biological responses in *E.coli* cultures [106], *7* — threshold sensitivity

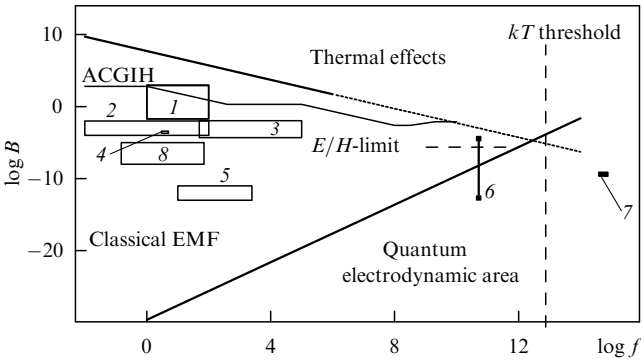

Figure 6. Different limits and areas of EMF biological effects as functions of two variables, EMF frequency f (Hz) and classical amplitude of its magnetic induction B (G).

of the human eye to optical range EMP, *8* — magnetic fields used for therapeutic purposes [107].

Also, the figure illustrates theoretical limits for various mechanisms and descriptions of EMF biological effects. The upper sloping line roughly divides areas of thermal and non-thermal effects. The lower sloping line stands for the QED threshold. The EMF below this line is natural to describe in a quantum way. The stepwise line is one of the known EMF safety thresholds proposed by the American Conference on Industrial Hygiene (ACGIH) [5]. Both thermal and kT thresholds are well known. Right of the dashed vertical line separating the 'paradoxical region', an electromagnetic energy quantum is many orders of magnitude smaller than the characteristic energy of chemical transformations $\sim kT$. Many physicists not directly involved in magnetobiological research believe that such fields can not induce biological reactions. Today, however, this standpoint appears superfluous and is refuted by numerous experimental findings.

Thermal threshold was obtained in many studies and works on the reglamentation of EMF radiation safety levels.

The dashed horizontal line in the area of relatively high frequencies was derived with respect to plane wave idealization. Below it, Zeeman splitting of the ion's quantum levels in a protein cavity prevails over quadratic Stark splitting.

3.1 Quantum-electrodynamic limit to EMF sensitivity

The QED threshold calls for comments. Interactions between EMF and a substance are classified in terms of classical or quantum description of both the field and the substance. The majority of the proposed primary mechanisms rely on the classical description of substance particles interacting with a classical electromagnetic wave field. Mechanisms explaining biological effects of EMF in terms of quantum description of ion particles in classical EMF are based on a semiclassical approximation. Applicability conditions for the classical description of EMF are established by quantum electrodynamics: populations of quantum states of EMF oscillators must be sufficiently greater than unity. Hence, the ratio relating the frequency and the classical amplitude of the EMF magnetic component:

$$H > \sqrt{\hbar c}\left(\frac{f}{c}\right)^2 .$$

This limit is depicted by the lower line in Fig. 6. It can be seen that classical EMF description using Maxwell's equations is permitted for low-frequency effects but not for hyperweak microwave radiation. In certain cases, however, it is possible to speak about quanta of low-frequency EMF. It appears that such field quanta are related to the natural fundamental threshold sensitivity to low-frequency fields.

A natural limitation upon electromagnetic sensitivity of biological systems, like that on any receiver of physical nature, must be dictated by general laws of quantum mechanics. All physical limitations proposed thus far are *a priori* based on the conjectured primary reception mechanisms rather than on the first physical principles. Hence, it is interesting to have estimates of threshold sensitivity, even if very approximate but proceeding from general physical laws.

To begin with, it needs to be emphasized that the question of minimal amplitude of an alternating MF recorded by the receiver is incorrect. The most general description of interacting field and idealized atom is quantized EMF and secondarily quantized oscillator. A quantum of low-frequency EMF initially delocalized in an indefinitely large volume is absorbed by an atom-like microscopic system in the course of reduction of the field's wave function. Simultaneously, the number of the atom's excitation quanta increases by unity. The QED threshold in Fig. 6 roughly determines the boundary of a MF value at which the notion of the classical field amplitude has no sense. This boundary corresponds to a few excitation quanta of field oscillators in the quantum description.

In the general case, an adequate quantity characterizing receptor sensitivity is energy flow p, i.e. number N of quanta $\hbar\Omega$ absorbed by the system for time t during which it coherently interacts with the field:

$$p = \frac{N\hbar\Omega}{t} .$$

However, this quantity has no unambiguous relation to field amplitude H in the area of applicability of the classical description; this suggests inapplicability of this notion in the sense of threshold sensitivity. Limitations upon p ensue from a fundamental quantum mechanics relationship between changes in quantum system energy e and time τ necessary to register this change: $e\tau > \hbar$. For the case of registration of N quanta, this relation can be written in the form of $\tau > 1/(N\Omega)$, since $e \sim N\hbar\Omega$. In no case, however, the time of registration of such changes can exceed the time of coherent interaction between the field and the atomic system.

In the case of low frequency EMF, the time of coherent interaction is essentially the lifetime of quantum state t which is determined by peculiarities of interactions with a thermostat. Hence, inequality $t > \tau > 1/(N\Omega)$, i.e. $t > 1/(N\Omega)$. Its substitution into the expression for p yields a simple estimate of threshold sensitivity

$$p > \frac{\hbar}{t^2} . \qquad (1)$$

Thus, threshold sensitivity to low-frequency EMF is determined by the lifetime of the quantized state of the receptor's target. For example, spin states of liquid water protons 'live' a few seconds. The corresponding threshold sensitivity $p \sim 10^{-19}$ W is close to that of physical measuring devices operated at room temperature. It should be recalled that threshold (1) follows only from fundamental principles. The sensitivity of devices including biophysical targets also depends on their ability to absorb electromagnetic quanta and in all likelihood may be less than (1). It is important, however, that probability of absorption of EMF quanta is determined by the peculiar structure of individual devices. First physical principles do not actually impose limitations upon threshold sensitivity. The microscopic structure of a biological receptor and the time of its coherent interaction with EMF determine the level of sensitivity in each concrete case. It is equally important that the time of coherent interaction may be sufficiently large because the state of living systems is far from being in thermal equilibrium.

3.2 Noise limits to EMF sensitivity of biological structures

In the framework of one of the phenomenological approaches to the evaluation of threshold sensitivity of biological systems to EMF, it is postulated that a biological EMF detector, regardless of its nature, can be represented as an, in a sense, equivalent electrical circuit or radiotechnical device consisting of resistors and capacitors. Such a representation is convenient in that intrinsic electrical noises can be easily

estimated using Nyquist's formula. Also, it is maintained that a putative biological detector having no *a priori* information about a signal to be detected can distinguish it only if the signal is stronger than the random noise inherent in all such detectors. In other words, evaluation of the sensitivity of a biological system may be reduced to the measurement of the detector's natural noise.

In a simple case, the biological detector is assumed to have an impedance $Z(\omega)$ with active resistance $R = \Re(Z)$. Then spectral density of a random electromotive force (EMF) is

$$(\epsilon^2)_\omega = 2kTR\,.$$

In this case, the validity conditions for Nyquist's formula are supposed to be fulfilled:

$$\omega \ll kT\,, \qquad \lambda \ll \frac{c}{\omega}\,,$$

where λ is the detector size, c is the velocity of light, and T is the thermostat temperature. Biological tissues and biophysical structures are supposed to show no inductive resistance whatsoever. The inductive component sometimes apparent in the measurements has been shown to arise from a delay in the electric current associated with initiating electrochemical processes [108]. For this reason, the reactive component of impedance is given by capacitance inversely proportional to the frequency, $\Im(Z) = 1/(\omega C)$, where C is the capacity of the detector. Then, the detector's effective frequency band is $\Delta\omega \sim 2\pi/(RC)$. In this band, Nyquist's formula gives the detector's mean square noise EMF $\epsilon^2 = 4\pi kT/C$.

Many authors advocate a hypothesis that ion channels of biological membranes serve as molecular targets of EMF. Membranes composed of phospholipids are about $d \approx 5 \times 10^{-7}$ cm wide and have dielectric permittivity around $\varepsilon \approx 10$. Because the capacity of a membrane segment with radius $r \approx 10^{-7}$ cm is $C \sim \varepsilon r^2/(4d)$, the noise EMF referred to the membrane width (i.e. noise electric field in an ion channel) is

$$E_{\text{noise}} \sim \frac{1}{r}\sqrt{\frac{\pi kT}{d}} \sim 3 \times 10^{-3} \text{ CGS units} \sim 100 \text{ V m}^{-1}\,.$$

It should be recalled that the field induced by alternating MF of 50 Hz and 100 μT in an 1 cm sample close to the solenoid axis is of the order of 0.1 mV m^{-1}. The reaction of biological systems to currents in tissues initiated by fields of $3-5$ mV m^{-1} has also been registered. Therefore, noise limits do not allow an isolated channel to function as a receptor of weak electrical fields in the framework of the 'radiotechnical' representation.

Formally, the inversely proportional dependence of E_{noise} on the membrane segment size r suggests that a detector occupying a relatively larger portion of the membrane would show a much higher sensitivity. The work of Astumian, Weaver, and Adair [47] offers some considerations of the possibility to apply such calculations to the estimation of sensitivity of a hypothetical detector of weak electrical fields in the form of a large ensemble of isolated channels or an individual cell.

Another line along which this theme is developed is represented by the study of Jungerman and Rosenblum [45] who hypothesized that the orientation of certain elasmobranch fish in the geomagnetic field is maintained by the EMF induced in a large (comparable with the fish body diameter) circuit by changing the magnetic flux through this circuit. The presence of very sensitive electroreceptors [109] along with conducting electrical circuits may account for magnetoreception in some fish species. It was reported [45] that electroreceptors of electric rays have a sensitivity of 0.1 μV cm^{-1} and a resistance of $10^5\ \Omega$. Suppose that the characteristic frequency associated with the ray's movements as well as the effective frequency band of electroreceptors is of the order of $\omega = 10$ Hz and the area of the conducting circuit $S = 10\ \text{cm}^2$. Then, assuming the equality of mean noise EMF and EMF $S\omega B/c$ induced by circuit slopes, it is easy to derive the relation for the threshold sensitivity to MF:

$$B = \frac{c}{S}\sqrt{\frac{2kTR}{\omega}} \sim 10\ \mu\text{T}\,.$$

This value does not contradict the hypothesis that relates magnetoreception in this fish to magnetic induction and electroreceptors. Nor does it contradict the experimental findings reported by Kalmijn [110].

Notwithstanding the seemingly general character of these estimates, the sphere of their applicability is restricted by the mechanisms underlying current fluxes through the detector in the presence of an additional determined EMF of the signal. Indeed, were the signal modulated, say, by only the intrinsic resistance of the detector, any detection would be impossible. Mechanisms in which a signal changes the velocity of chemical reactions are also beyond the scope of this scheme; this process has no electrical analog. Mechanisms that support amplitude windows of MF efficiency can not be analyzed in the framework of this approach either since even the most complicated linear electric circuits (just because they are linear systems) possess only frequency but not amplitude selectivity. On the other hand, *ad hoc* introduction of additional non-linear elements into equivalent electrical structures would make it impossible to use the Nyquist formula. The fluctuation-dissipation theorem behind Nyquist's formula is restricted to systems capable of a linear response.

It is worthwhile to note that the very possibility of representing a biological system as an electrical circuit needs to be justified. Pilla, Naser, and Kaufman [46] believed that a biological tissue can be depicted as a one-dimensional linear sequence of electrically bound individual cells, each having an equivalent electrical circuit with resistors. Under certain conditions, such a structure allows a noise threshold to be surmounted starting from field values of the order of 1 mV m^{-1}. However, the biological tissue can not be actually reduced to a one-dimensional chain. On the other hand, the effects of weak EF are observable at the level of cell systems regardless of direct intercellular communication. Thus far, there is no evidence that estimates of threshold sensitivity in the framework of this representation agree with the entire experimental *curve* rather than with a number. Barnes [48] proposed to regard neurons (pyramidal cells of the brain cortex) as peculiar radiotechnical devices, phased-array antennas equipped with amplifiers and filters. Such devices could distinguish the coherent signals induced by external low-frequency fields in dendrites of sensory neurons from background thermal noise. However, the author did not propose a method to verify their hypothesis. Hence, there is every reason to search for alternative (unrelated to electrical currents) non-linear mechanisms of biological reception of weak MF.

Provided the discussion is restricted to biological effects of MF comparable with those of the geomagnetic field, two equally paradoxical problems appear to be most important from the standpoint of fundamental physics:

(1) the mechanism or process of conversion of a MF signal to a biological response with a kT energy scale ten orders of magnitude MF energy quantum;

(2) why do thermal fluctuations of the same kT scale not interfere with the conversion?

At first sight, the latter problem looks truly paradoxical whereas the 'obvious' solution of the former lies in the fact of MF signal energy accumulation or amplification. No wonder, much more attention has been given to the second problem whereas the mechanism of conversion used to be chosen almost arbitrarily. In the meantime, it is actually the conversion mechanism that is important for the description of 'window' multipeak spectra observed in experiment; moreover, it determines predictive power of a model. Today, there are no models of predictive value suitable to consider the two problems at a time, probably with the sole exception of Ref. [32]. At the same time, predictive models have been proposed for the solution of the first problem [65, 69]. This circumstance marks an important stage in the development of basic magnetobiological research. The availability of these models means that biological effects of weak magnetic fields as an important environmental factor are becoming predictable.

In what follows, we consider at greater length some of the proposed mechanisms underlying MBE.

4. Models based on equations of chemical kinetics

Equations of chemical kinetics are written down for concentrations $C_i(\mathbf{x}, t)$ of substances involved in reactions:

$$\frac{\partial}{\partial t} C_i = d_i \nabla^2 C_i + \sum_i a_i C_i + \sum_{i,k} b_{ik} C_i C_k + \dots , \qquad (2)$$

where ∇^2 is the Laplacian, d_i are the diffusion coefficients of molecules or other objects of interest, $a_i, b_{ik}, \dots$ are the coefficients depending on the reaction rates and, through their agency, on extraneous factors. In a more general case, these coefficients may also depend on coordinates, representing sources and discharge of chemical reagents.

The above equations, especially those for biochemical systems, are very complicated non-linear systems of differential equations even if no account is taken of the spatial distribution of the reagents. Such systems usually suggest a large number of possible solutions, including vibrational ones, depending on both parameter values and initial conditions. A phase portrait of such systems may have several areas of 'attraction' for the dynamic point. Once in such an area, the system undergoes oscillatory motion, i.e. is in a dynamic equilibrium. Such systems referred to as polystable ones can not pass to other stability areas unless their parameters or other variables are modulated by external governing factors. If a system is close to instability, i.e. placed between areas of stability, then even minor governing or noise-induced perturbations may 'switch it over' from one dynamic regime to another. Then, the so-called bifurcations occur.

Under the condition $\partial C_i/\partial t = 0$, i.e. in a stationary regime, certain solutions of (2) have the form of so-called dissipative structures (patterns). These are non-uniform reagent density distributions developing in the presence of mass or energy fluxes through the systems under consideration (in the present case, open ones). The existence of dissipative spatial structures also depends on the combination of parameters and may undergo bifurcation if the parameters vary.

At present, the above equation and its derivatives find numerous applications for the description and investigation not only of chemical but also of biological and social processes. Relevant data can be found in monographs of G R Ivanitskiĭ, V I Krinskiĭ and E E Sel'kov [87], I Prigogine [111], D S Chernavskiĭ [112] and in the review of A B Medvinskiĭ and co-workers [89].

In application to the problems of magnetobiology, the majority of the authors proceed from the proposition that EMF can change velocities of one or several biological reactions in the system of interest. Furthermore, it has been shown that the system *can* exist in a quasi-unstable area, and different dynamic patterns of chemical processes are studied at small variations of selected parameters. If the dynamics turn out to resemble those of the experiment, it is concluded that the experimental system is actually in an unstable equilibrium, and EMF acts on that link in the chain of biochemical transformations that underwent variation.

Evidently, this scheme does not cover physical or biophysical processes of primary MF reception. The relation between the reaction rate and MF value is usually postulated in the form of a linear dependence. Both frequency and amplitude spectra of the response of a dynamic system to perturbations of a potentially EMF-sensitive constant could be compared with experimental findings. However, such a comparison has no absolute value. The process of primary reception may also show a certain degree of frequency and amplitude selectivity. Hence, there is little hope to obtain good correlation between responses to EMF in experiment and in models using equations of chemical kinetics. Whenever a correlation occurs it is difficult to interpret. Some publications describe 'through' models in which the primary reception process with all its characteristics is built in a kinetic system. Grundler [30] and Kaiser [38] considered several such mechanisms and postulated some properties of the primary process. Other authors considered interactions between MF and traveling spatial structures like self-sustained waves in excitable media (e.g. spiral waves [113]) which are also solutions of special cases of Eqn (2).

Equations of chemical kinetics having specific solutions were used by T Yu Plyusnina et al. [114] to describe perimembrane processes in EMF. The model of Eichwald and Kaiser [115] is based on experiments designed to study effects of low-frequency fields on immune cells, such as T-lymphocytes. The latter authors discussed the possibility that an external field influences signal transfer between activated membrane receptors and G-proteins. They demonstrated that the reaction may differ considerably depending on specific combinations of intracellular biochemical and external physical factors.

The number and variety of models of this class are great. The search for MF targets was consistently pursued by Kaiser [38] and Galvanovskis and Sandblom [39]. The authors of [39] studied fluctuation spectra of intracellular Ca^{2+} levels induced by an external stimulus at periodic modulation of the rate of an intracellular reaction involving calcium ions. A system of ordinary non-linear differential equations proposed

in Ref. [116] was used to construct a mathematical model of Ca^{2+} oscillations. It was shown that the response of the system expressed as the total spectral oscillations power is rather complicated and depends on the frequency and amplitude of the modulating signal. Frequency windows of this effect occurred at a characteristic oscillation eigenfrequency of 0.01 Hz and its harmonics. An amplitude window was observed too. The authors varied all the system's parameters in order to identify the most sensitive constituent in the system of reactions. It turned out to be the release of calcium into the cell from its intracellular complexes with proteins.

The value of this model is apparent in the context of chemical kinetics. The most sensitive elements of biochemical systems are identified in the course of development and comparison of different models. This facilitates the search for primary mechanisms because the circle of EMF-sensitive reactions becomes more clearly delimited.

5. Stochastic resonance in magnetobiology

There is little doubt of the importance of taking into account thermal perturbations of the medium in theoretical models of MBE. Nevertheless, models in which a consistent consideration of thermostat effects does not compromise the expected effect of MF are still lacking. Thermal perturbations of the medium manifest themselves as random forces acting on a putative target of MF (most frequently charged particles). Studies are underway to elucidate subtleties of the behavior of dynamic systems in the presence of random forces facilitating the preservation and transformation of a weak MF signal into a biochemical response. In fact, these works pertain to the essence of the so-called 'kT problem'.

Today, there are a few lines of research in this field where thermal noise is explicitly taken into account as a random stationary process of one or another spectrum. It becomes clear that methods of equilibrium thermodynamics or statistical physics can hardly yield the desired result. Studies are largely focused on dynamic systems with a quasi-chaotic behavior (see, for example, the monograph of W Horsthemke and R Lefever [117]).

5.1 Stochastic resonance

Benzi, Sutera, and Vulpiani [118] proposed the term stochastic resonance for the phenomenon of relatively strong redistribution of the power spectrum of a dynamic variable in a non-linear multistable system under effect of a weak determined component due to the added noise under certain resonance-type conditions. This mechanism is not strictly a resonance in the sense of an increased response when a driving frequency is tuned to a natural frequency to the system. There is however a useful analogy to resonance in that the output signal-to-noise ratio is maximized when some parameter (in this case, the input noise) is tuned near a certain value.

Stochastic resonance occurs not only in bistable systems but also in systems with a single stable state where cooperative effect between the signal and the added noise tends to disequilibrate the system and, having overcome a certain threshold, triggers another process. An example is firing of a neuron by the joint action of the signal and fluctuations of the mediator level. In this way or another, all biological sensor systems are threshold devices. Hence, it is safe to affirm that magnetoreception in living organisms is due to the stochastic resonance mechanism or somehow utilizes it. The efficiency of detection of weak MF signals can be increased by added noise.

Theoretical consideration of different stochastic resonance models gives an approximate formula for the dependence of the signal-to-noise ratio R on the noise level D near a maximum

$$R \propto \left(\frac{U_1}{D}\right)^2 \exp\left(-2\,\frac{U_0}{D}\right), \tag{3}$$

where U_0 is the height of the energy barrier between different states of the system, U_1 is the signal amplitude, and D is the noise amplitude.

It is interesting how the signal-to-noise ratio grows with increasing noise D. In accordance with (3), the maximum R value at constant U_0, U_1 is

$$R_{\max} = \left(\frac{U_1}{U_0}\right)^2 e^{-2}.$$

It is achieved on condition of *optimal* noise level

$$D = U_0. \tag{4}$$

As D decreases, the signal-to-noise ratio drops, theoretically to zero:

$$R_{\min} = \lim_{D \to 0} R = 0.$$

Seemingly, it is possible to obtain an arbitrarily large signal 'amplification coefficient' $K = R_{\max}/R_{\min}$ due to the added noise. It is not so, however, for the following reasons.

At low levels of noise D, the probability W of the transition between the wells becomes exponentially low. This leads to arbitrarily small R values. At the same time, such rare transitions take exponentially more time to be observed. Therefore, small D values are of no practical significance. A reasonable estimate of the real amplification K can be obtained from Kramers' formula for the average time of the first transition through the barrier

$$\tau = W^{-1} = \exp\left(\frac{2U_0}{D}\right), \tag{5}$$

where τ is dimensionless and expressed in units of the time scale for system relaxation.

Suppose that a biological receptor recognizes a subthreshold signal at a certain optimal noise level $D' = U_0$ for time $\tau_s(D')$. By way of example, let it be such that roughly N transitions are needed for the receptor to respond to the signal for time

$$\tau_s(D') = N\tau(D').$$

At a lower noise level D'' and certain ideal conditions, it would take the receptor more time to detect the signal: $\tau_s(D'') = N\tau(D'')$. It should be borne in mind that the receptor remains physiologically and biochemically ready to recognize the signal only during a certain characteristic time τ_0. In experiment, it is unable to detect the signal at a given noise level if $\tau_0 < \tau_s(D'')$. Accordingly, the signal-to-noise ratio can not be found. This means that the 'lifetime' of the receptor τ_0 determines the lower noise threshold in experiment when the signal-to-noise ratio still has practical sense.

For the purpose of evaluation, the lifetime of the receptor τ_0 is n orders of magnitude greater than its optimal (i.e. at $D' = U_0$) reaction time $\tau_s(D')$. Hence,

$$\frac{\tau(D'')}{\tau(D')} = 10^n . \tag{6}$$

Using (3), (5), the relation for a given maximum amplification can be written as

$$K = \frac{R(D')}{R(D'')} = \left(\frac{\ln \tau(D')}{\ln \tau(D'')}\right)^2 \frac{\tau(D'')}{\tau(D')} .$$

Taking into account Eqns (6) and $\tau(D') = \tau(U_0) = e^2$, this expression can be written in the form

$$K = \left(\frac{\ln \tau(D')}{\ln \tau(D') + n \ln 10}\right)^2 10^n = \frac{10^n}{(1 + 1.15n)^2} . \tag{7}$$

Thus, if the lifetime of the receptor is greater than its reaction time by $n = 1, 2, 3, 4$ orders of magnitude, the maximum amplification is $K \approx 2, 9, 50, 320$ respectively or 3, 9.5, 17, and 25 if expressed in decibels [1].

It is worthwhile to note that the lifetime of the receptor is such that biochemical conditions at which the reception is possible continue throughout this period. Homeostasis or the process by which living things maintain relative stability of their functions, composition, and other properties exists only as *dynamic* equilibrium. It is therefore possible to assert that some receptors undergo metabolic degradation or inactivation whereas others become activated. Because the reaction time of the majority of the receptors does not exceed fractions of a second, n should be 3 and 4 at the most. Hence, the lifetime of receptors is of the order of minutes.

Under experimental conditions, amplifications are somewhat smaller. The dependence of the signal-to-noise ratio on the noise level obtained from the results of various experiments and numerical models of stochastic resonance allows for the following inferences (the data are reported in Refs [95] and [94] that summarize results of several studies). Amplification in a ring laser would be 11 dB, in crayfish mechanoreceptors 6 dB, and in computer models: 4 dB for double-well potential, 7 dB for a neuron, 12 dB for SQUID, and 10 dB for a trigger. This means that the signal-to-noise ratio in the majority of systems studied thus far increased under the action of added noise by one order of magnitude on the average. If a higher noise-induced amplification is to be detected, the noise should be reduced and the observation period prolonged. A real experiment does not always provide an opportunity for such modulations.

5.2 Limitations upon identifiable signal level

Evidently, the signal-to-noise ratio following amplification must approximate unity. Otherwise, an additional system of the next organizational level should be implied to be able to distinguish the signal.

There are certain limitations upon the determined signal U_1 that needs to be 'amplified'. On the other hand, the signal must not be too strong, i.e. sufficient for a particle to surmount barrier U_0 regardless of the noise level. Therefore, the maximum signal value may be assumed to equal U_0.

[1] One decibel (dB) equals 10 times the common logarithm of the power ratio.

On the other hand, detection of a weak signal against the background noise is possible if it is 'accumulated' over a sufficiently long time. As mentioned before, this time t_0 is limited in experiment or in a biological system for a variety of reasons. Hence, there are limitations upon the weak signal level if it is to be detected.

The following line of reasoning leads to a rough estimate (sufficient for our purpose) of a minimally detectable signal. Given that the signal changes slowly and does not affect the statistics of transitions (adiabatic approximation), Kramers' time is

$$\tau \propto \exp\left[\frac{2\big(U_0 + U_1 \cos(\Omega t)\big)}{D}\right] .$$

Changes of Kramers' time, i.e. difference $\Delta\tau$ between

$$\tau(U_0) \sim \exp\left(\frac{2U_0}{D}\right)$$

and

$$\tau(U_0 + U_1) \sim \exp\left[\frac{2(U_0 + U_1)}{D}\right] ,$$

permit signal detection. This difference is noticeable only as the system passes from one well to another. To become apparent, it (i.e. the signal) must be reproduced several times, say during n transitions, and $n\Delta\tau$ must correspond to a characteristic scale of the process, that is

$$n\big[\tau(U_0 + U_1) - \tau(U_0)\big] = \tau(U_0) .$$

Hence,

$$n \frac{\mathrm{d}\tau(U_0)}{\mathrm{d}U_0} U_1 = \tau(U_0) , \qquad \text{i.e.} \qquad U_1 = \frac{D}{2n} .$$

If a weak signal is to be detected, the number of transitions n should be sufficiently large. However, it is limited by the receptor lifetime: $n\tau(U_0) < \tau_0$. Therefore, detectable signals occur in the optimal noise range $D = U_0$, $U_1 \sim U_0\tau(U_0)/(2\tau_0)$ and fall into

$$\frac{D\tau(D)}{2\tau_0} < U_1 < D . \tag{8}$$

Bearing in mind the above speculations about the lifetime of biological receptors, it can be concluded that minimally detectable signals equal $(10^{-1} - 10^{-4})D$.

This estimate suggests that the concept of stochastic resonance is hardly applicable to a microparticle as a potential target of MF because

(a) the 'amplification coefficient' of the signal under conditions of stochastic resonance is not always of the order of 10^{10} necessary to account for MBE in a low-frequency range;

(b) the amplitude of magnetic signals does not necessarily match the expected level of noise-induced perturbations of the particle.

Moreover, as far as biological receptors are concerned, a discrimination system is needed, i.e. a system which 'makes the decision' that the noise contains a signal. From the standpoint of a discriminator, the signal-to-noise ratio is not

the sole important parameter. Coherence is one more equally important characteristic that determines signal quality. However, amplification of the signal-to-noise ratio under stochastic resonance is achieved either by broadening the signal's spectral line or by the loss of coherence. The discriminator having to make a decision with less information at its disposal, the probability of correct detection falls and that of false detection (in the absence of a signal) increases. This gives reason to suggest that the probability of correct detection monotonically decreases as the noise level grows under stochastic resonance despite the improved signal-to-noise ratio. This inference is in step with common sense since the addition of noise does not increase the reliability of signal detection.

The concept of stochastic resonance contributes to the explanation of MBE but does not solve the 'kT problem'. It may be that the notion of 'amplification' of an alternating MF signal is inapplicable in principle to the elucidation of the primary MBE mechanism because its energy quantum is small compared with kT. Moreover, if stochastic resonance does occur in a certain system, the question is whether it is used by nature to realize its aims or is simply an epiphenomenon?

6. Biomagnetite

All substances in some way or other display magnetic properties. Diamagnetics and paramagnetics are magnetized, i.e. acquire magnetic moment in an external MF. Ferromagnetics exhibit spontaneous magnetization. In all cases, the magnetic moment $\boldsymbol{\mu}$ of a magnetized particle interacts with an external MF $\mathbf{H}$ and induces mechanical momentum

$$m = \frac{\mathrm{d}}{\mathrm{d}\varphi}(-\boldsymbol{\mu}\mathbf{H}), \quad \text{or} \quad \mathbf{m} = \boldsymbol{\mu} \times \mathbf{H},$$

that tends to turn a particle to a least-energy state. This tendency is opposed by random forces of thermal perturbations of the medium. Under certain conditions, e.g. when magnetic forces acting on the rotational degree of freedom impart to it an energy comparable with the thermal fluctuation energy per one degree of freedom $kT/2$, the particle orientation is no longer totally chaotic. Instead, the particles orient their direction of movement which may lead to a biological response if they are involved in metabolic processes.

Many authors advocate the biomagnetite concept which postulates the presence of crystals of a ferromagnetic substance, magnetite, in living multicellular organisms. Placed in a constant MF, such crystals possesses a moment of rotation several orders of magnitude greater than that in diamagnetics. Due to this, they can compress a nearby receptor [77, 119]. In all likelihood, such a mechanism takes place in nature. Crystals of magnetite have been found in the brain of certain bird species known to be capable of directional orientation in the Earth's magnetic field [49, 120–122]. Similar crystals have been discovered in insects [123, 124] and bacteria [125, 126].

At the same time, the assumption of this magnetoreception mechanism does not solve the main problem of magnetobiology because unicellular organisms having no magnetite crystals are also known to perceive magnetic fields.

Kobayashi, Kirschvink, and Nesson [50] proposed an explanation of the biological action of low-frequency MF on living cells *in vitro* based on the assumption of ferromagnetic contamination. According to these authors, contaminants are small magnetic particles present not only in the airborne dust but also adsorbed on the surfaces of laboratory equipment, present within glass and plastics, and even in reagent-grade laboratory chemicals and water. The mean size of such particles is around 10^{-5} cm; they are composed of ferro- and ferrimagnetic substances, i.e. exhibit spontaneous magnetization. The magnetic induction of saturation varies over the range of $4\pi J_s = 500-7000$ G.

The energy present in a magnetic particle of volume V exposed to a $H = 0.5$ G MF is of the order of $\varepsilon_p = 4\pi J_s V H \sim 10^{-11}$ erg, i.e. nearly three orders of magnitude higher than kT. The authors hypothesize that such a particle, if adsorbed on the cell surface, can transfer its energy to contiguous cell structures, i.e. to mechanically activated ion channels.

The difficulty consists in that the energy of a magnetic particle much in excess of kT does not in itself explain the final effect. This energy needs to be transferred to the molecular level. Meantime, such a transmission of kinetic energy is hardly possible because the mass of the particle is incommensurate with the molecular mass. Therefore, if there is a mechanism for the utilization of the particle's magnetic moment energy, it should be realized through a pressure exerted by the particle on the surrounding tissue, i.e through the transfer of potential energy. In this case, however, the energy is transferred to a large number of molecules, each receiving a fraction of it much smaller than kT. Detailed calculations are needed to clarify this issue.

The above mechanism may be used to explain the reception of constant MF. However, it is of doubtful value as it comes to the explanation of effects of alternating MF. Eigenfrequencies of oscillations of a magnetic particle introduced into an elastic tissue are far beyond the low-frequency range. Hence, the mechanism under consideration is unfit for the explanation of low-frequency and especially amplitude windows of efficiency.

7. Reactions of free radicals

The course of reactions involving radical pairs (RP) has been an object of extensive studies reported in many publications on the behavior of free radicals in MF. The well-known reviews of Salikhov, Molina et al. [127], Buchachenko, Sagdeev, and Salikhov [71], and Steiner and Ulrich [72] provide a good introduction to these themes. Processes of magnetosensitive recombination of radical pairs may be supposed to underlie biological effects of weak MF. This is a widespread and attractive idea. To begin with, all such processes are practically independent of temperature. Hence, there is no 'kT problem'. Assuming this primary mechanism of magnetoreception, frequency and amplitude windows in the efficiency of MF parameters can be related to non-linear equations of chemical kinetics. A reaction of free radicals is a sensitive element of a complex biological system described by non-linear equations [30]. At the same time, there are theoretical limitations upon MBE induction by this mechanism. It may probably underlie biological effects of both constant and alternating magnetic fields of relatively high intensity (over 1 mT).

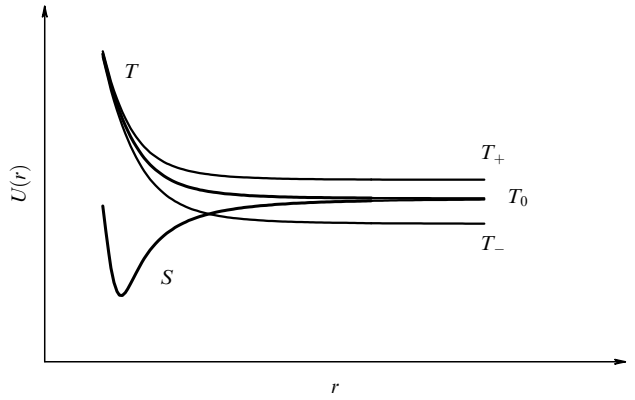

Figure 7. Coulomb interaction energy of RP $U(r)$ including exchange interaction energy in singlet S and triplet T states T_+, T_0, T_- of electrons in the pair.

Certain organic molecules are composed of two relatively large and firm portions, A and B, held together by a covalent bond. The bond may be broken by thermal perturbations: AB $\rightleftharpoons$ A + B. Separation of the two particles is hampered by their large size and high viscosity of the medium. As a result, they remain 'enclosed' in the cell. The reagents enter a specific state that can be identified neither with A and B nor with the AB. Products of AB catabolism are radicals $\dot{\mathrm{A}}$ and $\dot{\mathrm{B}}$, molecules having unpaired valence electrons. Therefore, the reaction is represented as

$$\mathrm{AB} \rightleftharpoons \dot{\mathrm{A}}\dot{\mathrm{B}} \rightleftharpoons \dot{\mathrm{A}} + \dot{\mathrm{B}}\,,$$

where the intermediate state $\dot{\mathrm{A}}\dot{\mathrm{B}}$ is a radical pair (RP) with unpaired electrons inside a cell.

The spin state of RP with spins 1/2 is described by singlet-triplet states using the following notation universally accepted in RP chemistry: S — singlet state with total spin 0, and T — triplet state with total spin 1. In the latter case, spin 1 may have projections on a distinguished axis 1, 0, and -1. These states are denoted as T_+, T_0, and T_-, respectively. Of importance is the exchange interaction between electrons of the pair that depends not only on the spin state of RP but also on the distance between the radicals (Fig. 7). This figure illustrates RP terms in a relatively strong MF where spin and orbital momenta interact separately with MF.

It can be seen that a stable state (product of recombination) of RP is possible only in the singlet state. At present, there is no detailed description of the process of AB formation from $\dot{\mathrm{A}}\dot{\mathrm{B}}$. A phenomenological description is used instead in which the AB production rate is assumed to be on the whole proportional to the probability (or population, or intensity) of the RP singlet state. Production of AB is accompanied by a decrease of the relative proportion of RP in the singlet state (chemical polarization of electrons, CPE). Because MF can in principle affect the evolution of the RP spin state, it may change the equilibrium ratio of free radicals $\dot{\mathrm{A}}$, $\dot{\mathrm{B}}$, and AB molecules. Such may be one of the MBE mechanisms.

The dynamics are described using the magnetic Hamiltonian of RP which contains inter alia Hamiltonians of magnetic moments of each radical. Magnetic moment operator $\mathcal{M} = (\mu/S)\mathcal{S}$ for an electron and the respective Hamiltonian have the form

$$\mathcal{M} = 2\mu_{\mathrm{B}}\mathcal{S}\,, \qquad \mathcal{H} = -\mathbf{H}\mathcal{M} = -2\mu_{\mathrm{B}}\mathbf{H}\mathcal{S}\,.$$

However, the operator of magnetic moment in a weak MF should be written as $\mathcal{M} = \mathcal{G}\mathcal{J}$, where $\mathcal{G}$ is the scalar operator and $\mathcal{J}$ is the operator of the sum total magnetic moment. In a uniform MF H_z, magnetic Hamiltonian has the form $\mathcal{H} = \mathcal{G}\mathcal{J}_z H_z$ and determines level splitting proportional to

$$\Delta\varepsilon = -\mu_{\mathrm{B}} g H_z\,, \tag{9}$$

where the g-factor is

$$g = \left[1 + \frac{j(j+1) + i(i-1) - l(l+1)}{2j(j+1)}\right]. \tag{10}$$

The active electron of the radical is influenced by an effective molecular field (in the solid body theory the term 'crystal field' is used). This leads to chaotic precession of the electron's orbital momentum the mean value of which is equal to zero. This is referred to as 'frozen' orbital momentum: $\langle\mathcal{L}\rangle = 0$. This means that the magnetic Hamiltonian contains only spin operator $\mathcal{H} = \alpha\,\mathcal{S}_z H_z$. This Hamiltonian appears to split electron levels according to

$$\Delta\varepsilon = \alpha H_z\,.$$

Comparison of this expression with (9) yields $\alpha = -\mu_{\mathrm{B}}\, g$. Therefore, the magnetic Hamiltonian of an electron in the radical is formally written as

$$\mathcal{H} = -\mu_{\mathrm{B}}\, g H_z \mathcal{S}_z\,. \tag{11}$$

Ideally, in the case of complete freezing of the orbital momentum, the substitution of (10) into quantum numbers for electron $i = 1/2$, $l = 0$ (formally, because $\langle\mathcal{L}\rangle = 0$), $j = 1/2$ gives $g = 2$. In reality, the motion of an electron in the molecular field is not totally chaotic. A certain degree of order is preserved depending on specific characteristics of the molecular field of a given molecule species. In this case, the orbital motion of the electron generates an additional small MF that should be taken into account in the calculation of spin dynamics [128]. In experiment, this effect in a fixed external MF is manifest as a small deviation of g-factor from an ideal value of 2. This provides a basis for the identification of molecular radicals from their electron paramagnetic resonance (EPR) spectra.

Let us consider a simple model in which a molecule in the singlet spin state resulting from thermal excitation dissociates into two neutral radicals. The so-called exponential model is easiest to idealize. It postulates Poisson's flux for radical release from the cell. Accordingly, the lifetime of radicals in the cell is a random quantity having an exponential distribution:

$$f(t) = \frac{1}{t_{\mathrm{c}}} \exp\left(-\frac{t}{t_{\mathrm{c}}}\right), \tag{12}$$

where t_{c} is the mean lifetime of RP in the cell is an important parameter of the model. Lifetime t_{c} is of the order of R^2/D, where $R \sim 10$ Å is the cell size for neutral radicals and $D \sim 10^{-5}$ cm^2 s^{-1} is diffusion coefficient for non-viscous solvents (e.g. water). Hence, $t_{\mathrm{c}} \sim 10^{-9}$ s.

Initially, RP is in a singlet state. In this state, the radicals recombine at a certain rate K. External and internal MF induce singlet-triplet transitions. Because the rules of spin selection permit recombination only from the S-state, its rate

in a general case decreases. Clearly, at a low $S-T$ transition rate, the lifetime of RP is too short for its spin state to change. In this case, the recombination rate equals K and is obviously independent of MF. In the opposite case of intense $S-T$ transitions, correlation between RP spins rapidly disappears. The recombination rate is also independent of MF, being determined only by the average weight of the S-state in case of a random choice of the radicals' spin states, i.e. $K/4$. Thus, there is a distinguished MF interval (usually from one to hundreds of mT) where the statistical weight of the S-state changes significantly for time t_c. This leads to MF dependence of the recombination rate. Evidently, the position of this MF interval is proportional to $1/t_c$. Moreover, it depends on intracellular magnetic interactions which also determine the type of $S-T$-transition mechanism. There are several such types.

Relaxation mechanism. RP being formed, its spin state changes due to the relaxation of each spin toward respective equilibrium states. In general, the relative weights of S- and T-states in superposition also change which suggests $S-T$ transitions. The spin relaxation time of neutral radicals in liquids with viscosity similar to that of water (~ 1 sP) is $10^{-7}-10^{-6}$ s, i.e. it is much greater than t_c. For this reason, this mechanism is of importance in intracellular recombination of oppositely charged ion-radicals for which t_c may be much greater than 10^{-9} s due to mutual attraction.

Δg*-mechanism*. Spins of RP undergo precession in MF which is the superposition of an external MF and a field of magnetic moments of radical nuclei. Suppose the latter field is zero, i.e. all radical nuclei are even and have no magnetic moment. Then, precession occurs in the external MF with the Larmor frequency. It is proportional to Zeeman splitting and, in the general case, different for each radical because g-factors differ too:

$$\omega_1 = \frac{1}{\hbar}\,\mu_B g_1 H_z\,, \qquad \omega_2 = \frac{1}{\hbar}\,\mu_B g_2 H_z\,.$$

The relative rate of disphasing, i.e. the difference between these frequencies is

$$\frac{1}{\hbar}\,\mu_B \Delta g H_z\,.$$

The Δg-mechanism of MF action functions when the MF is sufficiently strong for disphasing to reach a high value (e.g. 1 rad) during the lifetime of RP. Then, the effective MF at $\Delta g \sim 10^{-3}$ are of the order of

$$H \sim \frac{\hbar}{\mu_B \Delta g \tau_c} \sim 10^5 \text{ Oe}\,.$$

These fields are too strong to account for MBE in magnetic fields of the order of 1 Oe or less.

Resonance excitation. If precession frequencies of RP spins differ, it is possible to tune to the magnetic resonance of one of the spins by choosing the frequency of the external alternating field. Then, the state of this spin will oscillate with Rabi's frequency $\gamma H_{AC} = 2\mu_B H_{AC}/\hbar$ making possible $S-T$ transitions of the spin state of RP. Disphasing of the order of unity occurs in fields $H_{AC} \sim \hbar/(2\mu_B \tau_c) \sim 100$ Oe. Evidently, this mechanism of mixing singlet-triplet states has nothing to do with effects of weak magnetic fields.

HFI-mechanism. Hyperfine interaction (HFI) or interaction of electrons with nuclear spins provides a more optimistic option. For example, when one of the radicals has nuclei with a magnetic moment, radical spin precession takes place in a markedly different MF. RP terms are mixed and $S-T$ transitions occur even if the difference between g-factors is insignificant. Let the external MF be zero. Disphasing is roughly determined by precession of the magnetic moment of only one electron of the pair in the magnetic field of the nucleus (~ 100 Oe). Then, the resulting phase difference for the lifetime of RP is $\mu_B g H \tau_c/\hbar \sim 1$, i.e. sufficiently large to observe. The question is whether an additional external MF comparable with the geomagnetic field can appreciably change the $S-T$ transition rate.

A relatively simple model of the effect of an externally-induced MF on the recombination of RP with one magnetic nucleus having spin $1/2$ has been the object of many studies [71]. The Hamiltonian of the model includes, besides Zeeman spin energy, the exchange interaction

$$\mathcal{H}_{exch} = -\hbar J(r)\left(\frac{1}{2} + 2\mathcal{S}^1\mathcal{S}^2\right)$$

with constant $J(r)$ and the hyperfine interaction in which only the isotropic part

$$\mathcal{H}_{hf} = \hbar A \mathcal{S}\mathcal{I}$$

remains in the cell due to rapid chaotic rotations of the radicals. The spin Hamiltonian of RP in external MF $H \| z$ has the form

$$\begin{aligned} &\mathcal{H} = \mathcal{H}_0 + \hbar A \mathcal{S}^1\mathcal{I}\,, \\ &\mathcal{H}_0 = -\mu_B g H(\mathcal{S}_z^1 + \mathcal{S}_z^2) - \hbar J(r)\left(\frac{1}{2} + 2\mathcal{S}^1\mathcal{S}^2\right), \end{aligned} \tag{13}$$

where the g-factors are for simplicity assumed to be identical and the Zeeman energy of the nuclear magnetic moment is neglected. It is known that the eigenfunctions of Hamiltonian $\mathcal{H}_0$ are singlet-triplet states that in terms of one-particle spin states ψ_α (eigenstates of operator $\mathcal{S}_z$) are expressed as

$$v_m = \begin{cases} \psi_2^1\psi_2^2\,, & m = -1\,, \\ \dfrac{1}{\sqrt{2}}(\psi_1^1\psi_2^2 + \psi_2^1\psi_1^2)\,, & m = 0\,, \\ \psi_1^1\psi_1^2\,, & m = 1\,, \\ \dfrac{1}{\sqrt{2}}(\psi_1^1\psi_2^2 - \psi_2^1\psi_1^2)\,, & m = 2\,. \end{cases} \tag{14}$$

Here, the first three base vectors make up the triplet T_-, T_0, T_+ symmetric with respect to permutation of particles while the last vector is an antisymmetric state or singlet S. A range of index $m = -1, 0, 1, 2$ changes is chosen such that it coincides for triplet states with the magnetic quantum number — z-projection of summarized spin $\mathcal{S}^1 + \mathcal{S}^2$. If the nuclear spin state is denoted as χ_α, then the basis for the study of the dynamic equation with Hamiltonian (13) is

$$\xi_{m\alpha} = v_m \chi_\alpha\,.$$

In this case, an arbitrary state of RP may be presented as a superposition

$$\Psi = \sum_{m,\,\alpha} c_{m\alpha}\xi_{m\alpha}\,.$$

Indices labeled by Latin letters take values $-1, 0, 1, 2$ (for the singlet state) and those denoted by Greek letters values 1 and 2 (up and down spin states). Density matrix the diagonal elements of which are actually populations of electron singlet-triplet terms is defined as

$$\sigma_{nm} = \sum_{\alpha,\beta} c^*_{n\alpha} c_{m\beta} \,. \tag{15}$$

It is found by solving equations of motion for the density matrix

$$\mathrm{i}\hbar\dot{\sigma}_{nm} = \sum_k \left[\mathcal{H}_{nk}\sigma_{km} - \sigma_{nk}\mathcal{H}_{km}\right] .$$

In certain cases, it is supposed that radicals of a pair are at a fixed distance from each other. Thereafter, the population of the singlet state $\sigma_{22}(t)$ is found. The recombination rate p is assumed to be proportional to time-averaged population of the singlet state. Because RP lifetimes in the cell are distributed in accordance with (12), averaging is performed with the given exponential distribution:

$$p \sim \frac{1}{\tau_c}\int_0^\infty \sigma_{22}(t)\exp\left(-\frac{t}{\tau_c}\right)\mathrm{d}t \,.$$

In a more realistic case, spin dynamics is considered together with the spatial motion of radicals in the cell (their repeat contacts due to diffusion). Then, the density matrix depends not only on spin variables but also on inter-radical distance r. The dynamic equation changes accordingly. Spin effects of RP recombination taking into account molecular motion of radicals are discussed in detail in the monograph of Buchachenko, Sagdeev, and Salikhov [71].

Analytical studies of RP dynamics, even those disregarding molecular motion, are complicated by the appearance of three-particle spin functions in the calculations. We do not describe here solutions for concrete model situations and use instead rough estimates and known results of numerical analysis of equations.

It follows form Eqn (13) that important changes of spin dynamics should be expected when the scales of Zeeman energy and energy of HFI are roughly identical, i.e. when $\mu_B g H \sim \hbar A$. HFI constant is of the order of $A \sim 10^8 - 10^9$ Hz. Hence, the corresponding MF scale is

$$H \sim \frac{\hbar A}{\mu_B g} \sim 0.5 - 5 \text{ mT} \,.$$

Results of numerical calculations (see, for instance, reviews [71, 72]) indicate that in the majority of cases maximal changes of the recombination rate in such fields at a characteristic lifetime of RP $\sim 10^{-9}$ s do not exceed one percent. If the field/effect dependence in this range is assumed to be approximately linear, the effect in the geomagnetic field of ~ 0.05 mT is 0.1% or smaller. This estimate is confirmed by experimental dependences of radical reaction rates in MF [129]. Using numerical methods, Brocklehurst and McLauchlan [73] obtained a $\sim 10\%$ change in the reaction rate for the case of geomagnetic field in a model with one magnetic nucleus, but they used the time value of $\tau_c \sim 2 \times 10^{-7}$ s. Here, for usual values of $\sim 10^{-9}$ s, we also have 0.1%. This value appears to be quite suitable for the evaluation of possible biological effects in MF as strong as the Earth's magnetic field. Such insignificant changes in the reaction rate imply the necessity of further 'biochemical' amplification. Grundler, Kaiser, and other authors [30, 38] considered reactions of free radicals as components of a system described by a set of nonlinear equations of chemical kinetics with bifurcations. In this interpretation, minor variations in the reaction rate can result in significant, even qualitative, changes in the behavior of biological systems.

8. 'kT problem' in magnetobiology

Today, there is no physically sound understanding of how low-frequency MF induce a response in biological systems. Paradoxically, such fields can change biochemical reaction rates by a resonance mechanism. The physical nature of this phenomenon remains unclear and constitutes an important, if not the most important, problem of magnetobiology.

Many physicists not directly involved in magnetobiological research ask an almost rhetorical question incorrect in terms of form but justified in essence. An individual act of chemical transformation needs an impulse with an energy of the kT order (i.e. of thermal scale) to be initiated. How then can a ten orders of magnitude smaller energy quantum of low-frequency MF influence this process? The same question in a different form arises from the fact that an act of chemical transformation with characteristic energy kT is localized in a microscopic volume. A similar (of the kT order) energy of weak MF H (e.g. geomagnetic one) is contained in a 12 orders of magnitude larger volume V (corresponding to the biological cell volume). It is easy to derive from the formula for MF energy density

$$kT \sim \frac{1}{8\pi}\int H^2 \,\mathrm{d}V \,.$$

How can the energy of a macroscopic volume be collected and transferred to the microscopic level? It is a widespread opinion that such a question reflects the unreality of MBE which makes the problem intractable. At the same time, a variety of counterarguments to such a view have been provided.

Firstly, there are non-thermally activated reactions, e.g. enzymatic reactions of the 'key – lock' type.

Secondly, the very notion of the electromagnetic quantum has a limiting sense. At a given intensity of MF, an adequate physical description of EMF is provided by Maxwell's equations of classical electrodynamics.

Thirdly, notions of equilibrium thermodynamics, e.g. thermal scale of kT, are inapplicable to living systems. In a thermodynamically equilibrated system, kT is the mean energy of thermal motion per dynamic variable or, otherwise, per degree of freedom. In the general case, a non-equilibrium system contains no objects that could be characterized by kT. On the one hand, the thermodynamic factor of kT needs to be taken into consideration. On the other hand, it is clear that one has to deal with an intermediate region where mechanical laws and principles of thermodynamics "... lose their constructive nature, i.e. the ability to describe phenomena and predict them" [130].

Fourthly, the two forms of the above question that compare kT energies with the field quantum in one case and with field energy density in the other refer to different aspects of EMF essential nature. This points to the logical inconsistency of the question.

There are probably more counterarguments. It is however important that they have not yet resulted in the construction of an acceptable physical mechanism of magnetoreception.

In fact, the problem under consideration gives rise to two paradoxical questions while the problem of biological action of low-frequency MF has two clear-cut aspects:

(1) what is the *mechanism of conversion* of a weak low-frequency MF signal responsible for kT-scale changes at the level of the (bio)chemical process?

(2) what is the *mechanism of stability* or, otherwise, how can such small effects remain distinguishable from kT-scale thermal perturbations of the medium?

The 'kT problem' formulated in this form admits of physical analysis.

The second question might be constructive if a conversion mechanism were either known or postulated. An answer to the first question alone (concerning the conversion mechanism) does not solve the problem although it is an integral part of the solution. At the same time, the problem can not be solved without analysis, i.e. without breaking it into constituent elements. There are as yet no models or systems of equations taking into consideration both magnetic and thermal factors and at the same time having solutions adequate to experience.

It is strange that the problem has remained unresolved for a few decades while the formulation of dynamic and statistical theories have been practically completed. This and the absence of an universally accepted theoretical concept, give many scientists reason to question the very existence of the problem and consider results of electromagnetobiological research as artefacts. The proposed conversion mechanisms are frequently put in doubt on the ground that they give nothing to the solution of the second question cited above, i.e. fail to solve the entire problem.

As mentioned earlier, the paradoxical action of weak EMF due to cooperative effect of thermal noise is frequently explained with reference to EMF coherence and the possibility of energy accumulation by an oscillator.

The postulate of energy accumulation appears to be fairly well justified when field quantum energy is only two or three orders of magnitude lower than kT. However, it is totally inapplicable to low-frequency MF because it would take a few years to pump MF energy into an ion oscillator and raise it to the kT level even under ideal conditions, e.g. in the case of an infinitely high Q oscillator.

Thus, the distinction between MF coherent action and non-coherent noise is of itself insufficient and fails to add to the understanding of mechanisms of action of weak MF. It would be probably helpful to somehow take into account the qualitative difference between the magnetic field and thermal effects, i.e. the field's peculiar property as a physical entity.

A peculiarity of MF is apparent in the first place from its behavior in dynamic equations. Characteristics of MF and thermal noise actions have qualitatively differential effects on dynamic variables. Naturally, this accounts for the quantitative energetic incommensurability of triggering factors of different nature (magnetic and thermal) that cause similar responses. In other words, the answer to the question should be sought at the level of primary magnetoreception processes described by dynamic equations for MF-exposed microparticles. It is understandable that at this stage considerations of disequilibrium, instability, and the like are of minor importance; rather, they may be indispensable for the explanation of the further long chain of events, from primary physical or biophysical acts of MF reception to experimentally observed biological responses.

Another question that is usually disregarded in the discussion of the informational value of weak electromagnetic fields can be formulated as follows: where and in what form is the information brought in with MF stored at the very first stage of its action? Only a constructive answer to this question may give sense to the concept of MF informativeness. It appears that the sole way to preserve information about MF is to transduce it into a microparticle(s) state in a proper biophysical system provided such a storage does not contradict other principles. There is so far no alternative to this option.

Thus, this line of reasoning leads to understanding of the necessity to study microparticle dynamics in MF. Such studies have a long history. It turns out, however, that the quantum dynamics of sufficiently heavy particles, such as ions, taken together with non-linear properties of biophysical systems exposes some peculiarities in their dynamics that appear to fairly well account for biological effects of weak low-frequency MF.

In accordance with one of the general propositions of quantum physics, the energy of a quantum system can not be measured to an accuracy of $\Delta\varepsilon$ for a shorter time than $\hbar/\Delta\varepsilon$. This means that any observation of the consequences of absorption of a photon with energy $\varepsilon = \hbar\Omega$ by a quantum system will take at least $1/\Omega$ time. More or less well reproducible magnetobiological experiments normally make use of low frequency fields starting from 1 Hz. Hence, the conditions necessary for energy measurements should persist for at least 0.1 s. Specifically, lifetimes of the states of a quantum system that absorbs a photon must be of the same order of magnitude or greater.

The existence of such long-living states at $T \sim 300$ K may be doubted. However, the assumption of long-living modes looks justified if MF of these frequency range produces biological effects under experimental conditions. By way of example, spin states of liquid water protons 'live' around 3 s at room temperature. Moreover, their lifetime increases with increasing temperature, contrary to expectation. This is a result of peculiar interactions between water proton spins and thermal perturbations.

Spin relaxation is governed by relativistic spin-orbital interaction proportional to the gradient of a microscopic electrical field. Because a proton possesses marked diffusion-mediated mobility which further increases with temperature, the microrelief of an electrical field for this particle is markedly averaged or smoothed. For this reason, the proton 'sees' the electrical field as essentially uniform and does not actually interact with it. The above assertions hold for spin-lattice relaxation. Spin-lattice relaxation is due to dipole-dipole interaction between protons. The averaged magnetic field on a proton on the side of magnetic moments of other protons is relatively small and spin-spin relaxation is also hampered. It does not mean, however, that spin states of protons are not manifest at all.

A relatively large duration of spin states is due to peculiar features of spin interactions with thermal lattice vibrations. Similarly, metastability of certain spatial (alternatively called orbital or non-spin) degrees of freedom may be due to *peculiarities* of their interactions with thermal fluctuations.

When discussing the 'kT problem', it should be borne in mind that the very notion of kT originates in statistical physics. It has sense only for systems in a state not far from

statistical equilibrium. Indeed, in such systems quantum $\hbar\Omega$ does not significantly change mean statistical energy of one degree of freedom in a dynamic system. However, in systems far from equilibrium (e.g. in those weakly connected to thermostat where the process of thermalization is relatively slow), a field quantum causes a marked change in the energy of certain degrees of freedom. It is generally known that metabolism in living systems is a combination of primarily non-equilibrium processes. The origin and breakdown of biophysical structures at time intervals smaller than the time of thermalization of all degrees of freedom in these structures provide a good example of systems that are far from equilibrium where even weak field quanta can be manifested in system's breakdown parameters. In other words, if the life (thermalization) time of certain degrees of freedom interacting with field quanta is larger than the system's characteristic time of life, then such degrees of freedom exist in the absence of temperature proper. Therefore, a comparison of their energy changes due to field quanta absorption with kT has no sense.

A model of ion quantum state interference in a protein cavity has been proposed as a probable 'candidate' for the solution of the 'kT problem' [102]. According to this model, an ion enters the protein cavity through a relatively narrow 'gate' and remains there in superposition of quantum states (eigenfunctions of Hamiltonian). The ion probability density contains an interference contribution that accounts for its non-uniform distribution in the cavity. In a constant MF, the interference pattern (fringes) rotates around the MF direction as an whole with the cyclotron frequency. It turns out that superposition of an additional alternating MF having specific characteristics causes the pattern rotation to stop. A long period of arrest or very slow rotation is followed by a rapid turn. The pattern gets frozen. In such a state, the ion tunneling rate from the protein cavity as a non-linear function of ion probability density near the gate changes strikingly. Formulas were derived to relate the 'magnetic' part of the probability of ion – protein complex dissociation to MF parameters. The formulas predict multipeak spectra of MF frequency and amplitude.

First of all, let us illuminate this model by a mental experiment on microparticle wave interference. Charged particles from a source can pass through two slits and create an interference fringe pattern on the screen (Fig. 8). The screen has a hole in the center and a target (particle counter) behind it. An alternating MF $H(t) = H\sin(\Omega t)$ induces a circular electric field shifting wave field phases in the opposite direction. As a result the interference pattern vibrates with the MF frequency relative to a position corresponding to $H = 0$.

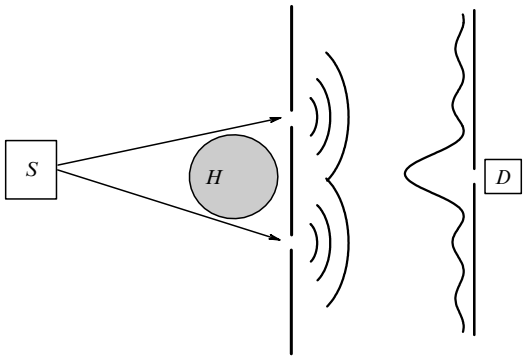

Figure 8. Interference of charged particles in an alternating magnetic field: S — source of particles, H — MF, orthogonal planes, D — particle detector.

Evidently, the characteristic frequency here is a combination of MF and particle parameters that has a necessary physical dimension, i.e. $\Omega_c = qH/(Mc)$. Therefore, variations of MF will cause particles to reach the target with phase difference $\varphi \sim q/(Mc)\int H(t)\,dt$ or

$$\varphi \sim \frac{\Omega_c}{\Omega}\sin(\Omega t)\,.$$

It is easy to see that the interference fringe pattern will be either static (when external MF frequencies are high) or totally obscure (when MF frequencies are low). Evidently, the most important changes occur in a frequency range corresponding to the particles' cyclotron frequency, although cyclotron resonance is out of the question.

It follows from the latter expression that the amplitude of interference pattern vibrations should change with variations of both MF frequency and amplitude. If they are chosen such that interference maxima reach the target from terminal positions of the pattern, the counter will record a maximum particle flux. However, in the general case, the dependence of measurements on any MF parameter will have a multipeak character.

It is appropriate to ask in the context of this scheme why a weak MF whose energy quantum is many orders of magnitude smaller than the characteristic energy of the processes in the particle counter induces significant changes in the particle flow intensity. The non-paradoxical answer ensues from Fig. 8. Interference events arising from phase shifts are essentially underlain by classical properties of electromagnetic fields. The form of the above question suggests that interference events correspond to a multiquantum processes. This means that the question implying an single-quantum process is incorrect.

The interference observability condition requires commensurability of task characteristic length R and the particles' de Broglie wave length $\lambda_B = 2\pi\hbar/p$. This means that MF-dependent interference of ions should be observable on microscales, the de Broglie wave length for biologically significant ions at physiological temperatures being a few tenths of an angstrom. Interestingly, the cavities of certain ion-binding proteins are such as to allow one to realize the described scheme at the microlevel.

9. Interference of bound ions

Interference or mutual amplification and annulment of wave trains is a common property of wave systems of different nature (elastic, electromagnetic, etc.) for which the superposition principle holds. According to de Broglie's hypothesis (1924) of wave-particle duality, wavelike properties are exhibited by all matter particles, not only photons or electromagnetic field quanta. The characteristic wave length λ_B corresponding to a particle with momentum p is $\lambda_B = 2\pi\hbar/p$. An obvious criterion for the observability of interference suggests commensurability of the de Broglie wave length and the scale r of the system under study. This important limitation makes it impossible to observe for example interference of macroscopic particles. At the same time, interference of electrons, atoms, and even molecules is a well-known phenomenon.

Also feasible is the interference of bound states, such as atomic ones. Suppose there is an instrument that permits one to measure the distribution of probability density of a particle bound in an arbitrary central potential in the area of its location. Let the measured characteristic be angular density distribution $p(\varphi)$. Given the particle is in a p-state, the orbital and quantum numbers are $l = 1$, $m = 0, \pm 1$. The angular mode of the wave function in state $m = 1$ equals $\exp(i\varphi)$ (unessential normalization coefficients are omitted); hence, uniform angular density distribution: $p(\varphi) = |\exp(i\varphi)|^2 = 1$. The same line of reasoning holds for a particle in state $m = -1$. However, in the case of superposition of $m = 1$ and $m = -1$, the probability density non-trivially depends on the angle, e.g.

$$p(\varphi) = \left| \frac{1}{\sqrt{2}} \exp(i\varphi) + \frac{1}{\sqrt{2}} \exp(-i\varphi) \right|^2 = 2\cos^2 \varphi .$$

In other words, the particle is in certain angular sectors of the location area close to $\varphi = 0$ and $\varphi = \pi$.

Also, the particle's wave functions have phase factors dependent on the state energy and time, $\exp(-i\varepsilon t/\hbar)$. For states $m = \pm 1$, the energies are similar, and the presence of additional phase factors does not change the situation. Changes occur in the magnetic field **H**. In this case, Zeeman splitting of the initially degenerated states $m = \pm 1$ needs to be taken into account whose energies are now equal to $\varepsilon_\pm = \varepsilon \pm \Delta\varepsilon$. Then, for the probability density

$$p(\varphi) = \left| \frac{1}{\sqrt{2}} \exp(i\varphi) \exp\left(-\frac{i\varepsilon_+ t}{\hbar}\right) + \frac{1}{\sqrt{2}} \exp(-i\varphi) \exp\left(-\frac{i\varepsilon_- t}{\hbar}\right) \right|^2 = 2\cos^2\left(\varphi - \frac{\Delta\varepsilon}{\hbar} t\right) .$$

In a laboratory reference frame, sectors of preferential location of a particle rotate at angular speed $\Omega = \Delta\varepsilon/\hbar$. If the measuring device has an inertia that makes it impossible to record changes for a time less than Ω^{-1}, then the angular distribution can not be determined. The device will report it as being uniform. Nevertheless, sector rotation can be effectively stopped by superposition of an additional alternating MF of given frequency and amplitude. As a result, it becomes possible to elucidate the sectoral structure of the wave function.

Thus, there a few regimes of MF that permit one to observe interference of bound quantum states. These are zero MF (magnetic vacuum) and a variety of combinations of constant and alternating MF having definite characteristics that depend on both constant MF strength and bound particle properties (see below).

What instrument or method might be employed to record the sector structure of the wave function of a bound particle exposed to MF? In atomic spectroscopy, atom state polarization in the case of electronic states is estimated from the polarization of the reemitted electromagnetic field. Is it possible to record polarization or density non-uniformities beyond the scope of probing radiation measurements?

Let a particle be enclosed in a sealed sphere with a hole at which the particle's potential is reduced to a finite value. The particle penetrates the potential barrier by the process of tunneling. Because the probability of tunneling transition depends on the probability density of the particle's location near the 'hole', dissociation of the bound state (i.e. emergence of the particle from its metastable location area) might serve as an indicator of specific MF conditions responsible for the appearance of the sectoral structure.

Microscopic cavities of ion-binding protein macromolecules are of special interest for magnetobiology. Because protein activity with respect to other molecules including enzymes depends on the presence of bound ions, MF action resulting in bound state breakdown (dissociation of ion–protein complexes) can probably induce a biological response. Interestingly, this hypothesis agrees with the data obtained in magnetobiological experiments [65–70].

The majority of ions of biological significance, even at $T = 300$ K, have de Broglie waves only 3–6 times smaller than their radii and close to the size of effective potential of binding cavities. For example, the ion–ligand distance at a calcium-binding site of the protein troponin C is 2.4 Å [131]. This site also binds magnesium ions. Ion binding radii for Ca^{2+} and Mg^{2+} are 1.74 and 1.36 Å, respectively. Hence, the effective potential radius is 0.7–1.0 Å. At the same time, their de Broglie waves $\lambda = 2\pi\hbar/p$ are 0.28 and 0.36 Å at average thermal momentum $p = \sqrt{2MkT}$. This means that at the atomic scale ions exhibit properties that can not be reduced to the behavior of classical particles. Ion states inside protein cavities should be described in terms of quantum mechanics.

9.1 Dissociation of ion–protein complexes in magnetic fields

Reaction between ion and binding protein

$$\text{protein}(..) + \text{ion} \rightleftharpoons \text{protein}(\text{ion})$$

proceeds as follows. An ion enters a protein cavity containing ligands. This causes a change in protein activity. Because MF disturbs equilibrium of this reaction, a further change of activity is finally manifest as a biological response.

The ion enters the binding cavity through a 'gate' and finds itself in a 'trap' (Fig. 9). After a short time (of the order of 0.1 s), it leaves the cavity. The assumption behind the model below is that the probability of ion emergence from the cavity depends on the ion state inside it. This assumption seems reasonable because the ion is a charged particle interacting with cavity walls. We also assume that the possibility for the ion to leave the cavity or the ion–protein complex to dissociate shows non-linear dependence on the ion probability density near the 'gate'. Because of interference of ion quantum states, MF causes redistribution of the ion cloud and thereby exerts influence on the reaction equilibrium constant.

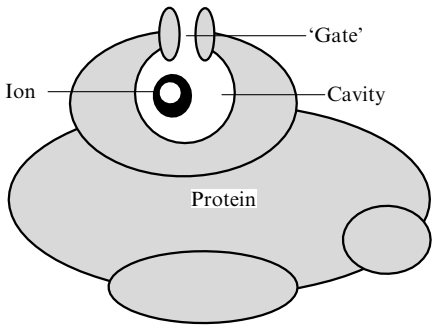

Figure 9. Ion enters protein binding cavity through the 'gate' formed by oxygen ligands.

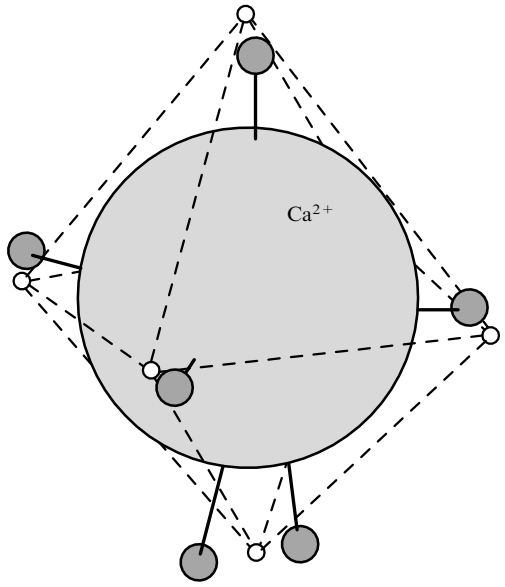

Figure 10. Octahedral coordination of calcium ion in a binding protein cavity; relative proportions of ion, ligand, and cavity dimensions are retained. From Refs [131, 132].

The structure of certain Ca-binding proteins is known well enough to give an idea of the internal geometry of binding cavities. Reference [131] reports the results of diffractometric analysis of the troponin C structure. The use of a synchrotron radiation source provided a high resolution of approximately 2 Å. Troponin C binds four Ca^{2+} ions in two cavities having high affinity for calcium and in two low-affinity ones. The former two also bind Mg^{2+}. Binding results in marked conformational changes of the troponin C molecule that are translated into an observable biochemical or physiological response. When in a cavity, the coordination number of a calcium ion is nearly seven. The structure of a high-affinity cavity is depicted in Fig. 10. Coordinate positions of the ligands give rise to a roughly octahedral figure with the distance between them $R \approx 2.4$ Å. Ionic radii of calcium atoms and oxygen ligands are 1.74 and 0.136 Å, respectively. Very similar results have been obtained in Ref. [132] for binding cavities of the protein calmodulin.

It appears from Fig. 10 that the area of motion for calcium ions is restricted. As a result, the potential of the ion inside the cavity is very much like a spherically symmetric or central potential. For the purpose of approximate numerical estimation, ions can be represented as hard spheres of a given radius, ligands as fixed in their idealized coordinate positions, and movements of the central ion as limited by the neighboring ionic spheres alone. Let an ion move in the horizontal plane. The smallest shift it undergoes is toward a ligand, the largest one toward an interligand space. The dependence of a maximally possible shift x on the polar angle arises from geometrical considerations,

$$x(\varphi) = R\cos\varphi - \sqrt{(r_{\rm ca} + r_{\rm ox})^2 - R^2\sin^2\varphi}\,,$$

where $r_{\rm ca}$ and $r_{\rm ox}$ are the ionic radii of calcium and oxygen atoms respectively. This function contains a constant constituent related to the central potential and an angle-dependent part, an additional potential function with low-order symmetry. Without concern for calculation details, suffice it point out that, at given ion and cavity dimensions, some 80% of the potential function is constituted by the central symmetric potential with radius 0.7 Å which is slightly larger than Bohr's electron radius. Therefore, mathematically, the model describes a point charge in the effective potential of radius 0.7 Å rather than an ion in a cavity measuring a few angstroms.

9.2 Models

Let us adopt an idealization in terms of which the ion is a particle with charge q and mass M having, in the general case, intrinsic angular momentum I (in $\hbar$ units) and nuclear magnetic moment μ. The ion is in a spherically symmetric potential $U(r)$ created by the protein cavity walls. It enters the cavity through a relatively narrow 'gate' the width of which depends on the ion probability density near the gate.

The Hamiltonian of a free particle in MF up to terms $\propto c^{-1}$ has the form [128, 133]

$$\mathcal{H} = \frac{(\mathcal{P} - q\mathbf{A}/c)^2}{2M} + qA_0 - \gamma\hbar\mathcal{I}\mathbf{H}\,.$$

Here, $\mathcal{P} = -\mathrm{i}\hbar\nabla$ is momentum operator, $\mathbf{A}$, A_0 are vector and scalar potentials of the electromagnetic field, respectively, $\mathbf{H} = \nabla\times\mathbf{A}$ is MF strength, $\hbar$ — Planck's constant, $\gamma = \mu/(I\hbar)$ — gyromagnetic ratio, M — particle mass. Let us choose potentials of the external uniform field as $\mathbf{A} = \mathbf{H}\times\mathbf{r}/2$, $A_0 = 0$. Then, for the spherically symmetric potential U,

$$\mathcal{H} = \frac{\mathcal{P}^2}{2M} + U - (\hbar b\mathcal{L} + \hbar\gamma\mathcal{I})\,\mathbf{H} + \frac{q^2}{8Mc^2}(\mathbf{H}\times\mathbf{r})^2\,. \qquad (16)$$

Here, $\mathcal{L} = -\mathrm{i}\mathbf{r}\times\nabla$, $\mathcal{I}$ are operators of angular and spin momenta and $b = q/(2Mc)$ is the ion parameter. It is held that

$$\mathbf{A}\nabla = \nabla\mathbf{A} = \frac{1}{2}\nabla(\mathbf{H}\times\mathbf{r}) = -\frac{1}{2}\mathbf{H}(\nabla\times\mathbf{r})\,,$$

$$\mathrm{i}\,\frac{q\hbar}{Mc}\,\mathbf{A}\nabla = -\frac{q\hbar}{2Mc}\,\mathbf{H}\mathcal{L}\,.$$

Let us neglect the contribution $\propto \mathbf{A}^2$, i.e. the last term of the Hamiltonian that determines the low diamagnetic sensitivity of the system. Then, Hamiltonian (16) includes kinetic, potential, and Zeeman (orbital and spin) energies. Let us consider now interference of ions with spin 0. If only the strength but not the direction of MF varies, i.e.

$$H_x = H_y = 0\,, \qquad H_z = H_{\rm DC} + H_{\rm AC}\cos(\Omega t)\,, \qquad (17)$$

the potential $U(r)$ retains a projection of the momentum on axis z. The corresponding operator is substituted by its eigenvalues $l_z = m$, and the Hamiltonian assumes the form

$$\mathcal{H} = \mathcal{H}_0 - \eta_m H_z\,, \qquad \mathcal{H}_0 = \frac{\mathcal{P}^2}{2M} + U\,, \qquad \eta_m = m\hbar b\,. \qquad (18)$$

In the absence of MF, ion wave functions (eigenfunctions $\mathcal{H}_0$) have, up to normalization, the form [133]

$$\psi_{klm} = R_{kl}(r)P_l^m(\theta)\exp(\mathrm{i}m\varphi)\,, \qquad (19)$$

where R_{kl} are radial functions depending on the form of $U(r)$, P_l^m are the associated Legendre polynomials, k, l, m are the radial, orbital (or azimuthal), and magnetic quantum numbers, and r, θ, φ are spherical coordinates. Evidently, operator $-\eta_m H_z$ reduced to the operation of multiplication

has no effect on functions (19) and therefore changes only instantaneous values of the energies of these states (Zeeman splitting). No quantum transitions in ion states occur under field (17) action; accordingly, there are no resonance conditions for transitions. What then depends on MF parameters?

Let us write the solution of the Schrödinger equation with Hamiltonian (18):

$$\Psi = \sum_{k,l,m} a_{klm} R_{kl}(r) P_l^m(\theta) \exp\left[\mathrm{i}m\varphi - \frac{\mathrm{i}}{\hbar}\,\varepsilon_{kl} t + \frac{\mathrm{i}}{\hbar}\,\eta_m \int H_z\,\mathrm{d}t\right], \tag{20}$$

where ε_{kl} are the unperturbed energies of states ψ_{klm}, and the coefficients a_{klm} give the initial conditions.

Values for comparison with experimental data will be obtained by averaging over an ensemble of independent particles. For this purpose, Eqn (20) should contain random phases of angular modes $\exp(\mathrm{i}m\varphi)$ obtained on the ensemble. Taking into account that statistical distributions of these phases are uniform over the interval $[0, 2\pi)$, the mathematical expectation of the corresponding harmonic processes can be sought in the ergodic approximation as a limit of the average over an infinite time interval. In what follows, this form of averaging is used as easier to expound. Random phases are omitted, and all formulas derived by averaging over the infinite time interval should be regarded as formulas for averaged-over-the-ensemble particles.

Let us find the ion probability density near the 'gate', i.e. at a certain value $\varphi = \varphi_0$:

$$\begin{aligned} p(\varphi_0, t) &= \left\langle \Psi(\varphi_0, t) | \Psi(\varphi_0, t) \right\rangle_{r,\theta} \\ &= \sum_{m,m'} a_{mm'} \exp\left[\mathrm{i}\Delta m\,\varphi_0 + \mathrm{i}\Delta m\, b \int H_z\,\mathrm{d}t\right], \end{aligned} \tag{21}$$

where Δm is the difference $m' - m$ of quantum numbers. Coefficients

$$\begin{aligned} a_{mm'} = \sum_{k,k',l} a^*_{klm} a_{k'lm'} \exp\left[\frac{\mathrm{i}}{\hbar}(\varepsilon_{kl} - \varepsilon_{k'l})t\right] \\ \times \langle R_{kl} | R_{k'l} \rangle \langle P_l^m | P_l^{m'} \rangle \end{aligned} \tag{22}$$

are elements of the density matrix in the representation of eigenfunctions of operator l_z. They consist of constant ($k = k'$) and rapidly oscillating ($k \neq k'$) terms. Indeed, for Ca^{2+} ions in the ground and first excited states in a trap of size $R \sim 0.7$ Å, the frequency of these oscillations is of the order of $f_{10} = \varepsilon_{10}/(2\pi\hbar) \propto \hbar/(MR^2) = 10^{11}$ Hz. This size matches that of a Ca-binding cavity of troponin C [131]. Calmodulin (low molecular weight regulatory protein widespread in living tissues) has binding cavities of a similar size [132]. The dimensions of various cavities in other proteins are presented in Ref. [134]. Because of the averaging over the time interval $\bar{t} \gg 10^{-10}$ s below, elements $a_{mm'}$ may be regarded as constants. The transformation of (21) taking into account (17) leads to[2]

$$\begin{aligned} p(\varphi_0, t) &= \sum_{m,m'} a_{mm'} \exp\left[\mathrm{i}\Delta m\left(\varphi_0 + \omega_0 t + \frac{\omega_1}{\Omega}\sin(\Omega t)\right)\right], \\ \omega_0 &= bH_{\mathrm{DC}}\,, \qquad \omega_1 = bH_{\mathrm{AC}}\,, \qquad b = \frac{q}{2Mc}\,. \end{aligned} \tag{23}$$

[2] For transition to MKS, it should be assumed that $b = q/(2M)$.

The frequency $\omega_0 = qH_{\mathrm{DC}}/(2Mc)$ is called the Larmor frequency. It should be noted that the quantity in brackets in (23) is proportional to the phase difference between interfering angular modes.

It can be shown that, averaged over time, $\overline{p} = \mathrm{const}$. Let us first write the average of p over a finite time interval $[-\bar{t}, \bar{t}]$ which we shall need in further calculations:

$$\begin{aligned} p_{\bar{t}} \equiv \frac{1}{2\bar{t}} \int_{t-\bar{t}}^{t+\bar{t}} p(\varphi_0, t')\,\mathrm{d}t' = \frac{1}{2\Omega\bar{t}} \sum_{m,m'} a_{mm'} \exp(\mathrm{i}\Delta m\varphi_0) \\ \times \int_{\Omega(t-\bar{t})}^{\Omega(t+\bar{t})} \exp(\mathrm{i}\alpha z\tau) \exp(\mathrm{i}z\sin\tau)\,\mathrm{d}\tau\,, \end{aligned} \tag{24}$$

where the following notation is used:

$$z = \Delta m\,\frac{\omega_1}{\Omega}\,, \qquad \alpha z = \Delta m\,\frac{\omega_0}{\Omega}\,, \qquad \alpha = \frac{\omega_0}{\omega_1} = \frac{H_{\mathrm{DC}}}{H_{\mathrm{AC}}}\,. \tag{25}$$

Because

$$\exp(\mathrm{i}z\sin\tau) = \sum_{n=-\infty}^{\infty} \mathrm{J}_n(z) \exp(\mathrm{i}n\tau)\,, \tag{26}$$

integral (24) is easy to calculate as

$$2\sum_n \mathrm{J}_n(z)\,\frac{\sin\left[(\alpha z + n)\Omega\bar{t}\right]}{\alpha z + n} \exp\left[\mathrm{i}(\alpha z + n)\Omega t\right].$$

Its substitution into (24) yields

$$\begin{aligned} p_{\bar{t}} = \sum_{m,m',n} a_{mm'} \exp\left[\mathrm{i}\Delta m\varphi_0 + \mathrm{i}(\alpha z + n)\Omega t\right] \\ \times \frac{\sin\left[(\alpha z + n)\Omega\bar{t}\right]}{(\alpha z + n)\Omega\bar{t}}\,\mathrm{J}_n(z)\,. \end{aligned} \tag{27}$$

In the general case, when $\alpha z + n \neq 0$,

$$\overline{p} = \lim_{\bar{t}\to\infty} p_{\bar{t}} = \sum_m a_{mm}\,, \tag{28}$$

because all terms of sum (27) c $m' \neq m$ tend to zero. This expression does not depend on MF, and we arrive at a trivial result that can not be related to experimental findings.

In a particular case, the frequency of an external MF can be chosen such that the condition $\alpha z + n = 0$ is fulfilled:

$$\Omega = -\frac{\Delta m}{n}\,\omega_0\,.$$

This condition is met for a few terms of the sum for which m, m', n are such that $\Delta m/n$ is identical. These terms make a time-independent contribution to $p_{\bar{t}}$:

$$\sum_{m,m',n} a_{mm'} \exp\left[\mathrm{i}\Delta m\varphi_0\right] \mathrm{J}_n(z)\,.$$

In other words, the substitution of $z = -n/\alpha$ under these special conditions leads to

$$\overline{p} \sim \mathrm{const}_1 + \mathrm{const}_2 \sum_n \mathrm{J}_n\left(-n\,\frac{H_{\mathrm{AC}}}{H_{\mathrm{DC}}}\right). \tag{29}$$

This expression may seem to describe the behavior of the model system. Certain external field frequencies defined by

the equality

$$\Omega_p = \frac{\Delta m}{n}\,\omega_0\,, \tag{30}$$

create a specific situation in which the probability of ion location at some angular position φ_0 shows a non-trivial dependence on the strength of the constant MF and amplitude of alternating MF, in conformity with (29). This situation seemingly admits of experimental verification by evaluating MBEs that occur under the above magnetic conditions. It is, however, impracticable because the equality $\alpha z + n = 0$ is physically unrealizable in experiment. Any infinitely small deviation would lead to $\overline{p} = \text{const}$ which is at variance with (29). The probability density $\overline{p}$ regarded as a function of MF frequency Ω is not continuous at points (30):

$$\lim_{\Omega \to \Omega_p} \overline{p}(\Omega) \neq \overline{p}(\Omega_p)\,.$$

The available experience suggests a different (smooth) frequency dependence of MBE. This discrepancy might be interpreted as broadening of the resonance curve as a result of damping. But there is no resonance in the given case; hence, the notion of resonance width has no meaning. Moreover, the expression for quantity (29) being compared with MBE depends on the angle φ_0 that is not a model parameter. Averaging over it also leads to the trivial result $\overline{p} = \text{const}$ in conflict with experiment.

The way out is to take into consideration the non-linear character of the relationship between probability density $p(t, \varphi_0)$ and an intermediate quantity (probability of ion emergence from the binding cavity) changes of which finally result in MBE.

Let the probability P of a biochemical reaction proper (dissociation of ion–protein complex) *non-linearly* depends on the probability p of the particle's location near the 'gate'. We confine ourselves to taking into account only linear and quadratic terms of the expansion [3]

$$P(p) = P(\overline{p}) + P'_p\,\tilde{p} + \frac{1}{2}\,P''_{pp}\,\tilde{p}^2 + \ldots\,, \tag{31}$$

where $\tilde{p} = p - \overline{p}$. Averaging over time yields $\overline{P} = c_1 + c_2\,\overline{\tilde{p}^2}$, where $c_{1,2}$ are constants. Of interest is the quantity $\overline{\tilde{p}^2}$ that determines the dependence of $\overline{P}$ on MF parameters. In what follows, this quantity is denoted as P. Let us take advantage of the fact that relatively rapid fluctuations of density $\tilde{p}$ fail to cause a non-linear response of the protein but enable it to change conformation in such a way as to have 'the gate open'. In this case, it is natural to first average $\tilde{p}$ over a certain time interval $\bar{t}$ commensurate with the response time and then find the resulting mean square value

$$\mathsf{P} \sim \overline{(\tilde{p}_{\bar{t}})^2}\,. \tag{32}$$

From the physical point of view, the time $\bar{t}$ is a measuring time or a time during which probability density changes are cumulated, i.e. the time during which the protein 'permits' a particle to remain in a state phase-correlated with MF. When such a time is large, the protein slows down only those changes that have accumulated during this period. For the changes accumulated during time $\sim \bar{t}$ to manifest themselves, the process of probability density alteration must contain a slow constituent. In other words, the frequency of the external field must be close enough to the interference maximum frequency. Thus it is clear that the time $\bar{t}$ is the parameter of the model connected with the broad biological frequency response.

This situation is illuminated by a simple example. Let us consider the behavior of the function $p(\varphi_0, t)$ c $a_{mm'} = 1$. The introduction of dimensionless variables $t' = \omega_0 t$, $h' = H_{\mathrm{AC}}/H_{\mathrm{DC}}$, $\Omega' = \Omega/(2\omega_0)$ gives

$$p(\varphi_0, t') = \sum_{m,m'} \cos\left[\Delta m\left(\varphi_0 + t' + \frac{h'}{2\Omega'}\,\sin(2\Omega' t')\right)\right].$$

In order to demonstrate the general character of the probability density behavior, it is necessary to consider the interference between angular states and magnetic quantum numbers differing by 1 at the frequency $\Omega' = 1/2$. It will be shown below that this frequency corresponds to one of the interference maxima of angular modes. The probability density up to an unessential factor is

$$p_{\Delta m = 1}(\varphi_0, t') = \cos\left(\varphi_0 + t' + h'\sin t'\right).$$

It is only that part of the probability density which depends on the MF; it may have a negative value. Then, the angular position of the probability density maximum is defined by the equation

$$\varphi_0(t', h') = -t' - h'\sin t'\,.$$

This function at different field amplitudes h' is shown in Fig. 11. Clearly, at a certain h' value, the probability density maximum remains almost stationary for rather a long time because the phase difference of interfering modes remains virtually unaltered within the same period. Thereafter, the maximum is rapidly shifted to an equivalent position, i.e. turns at the total angle. Thus, the phase difference becomes 'frozen', and the density maximum remains in a certain angular position. In the general case, when the field frequency is not accurately correlated with the frequencies of interference maxima, the rapid turn is somewhat different from 2π. This accounts for the slow rotation of the sector corresponding to the maximum. As a result, $\overline{p} = \text{const}$, if

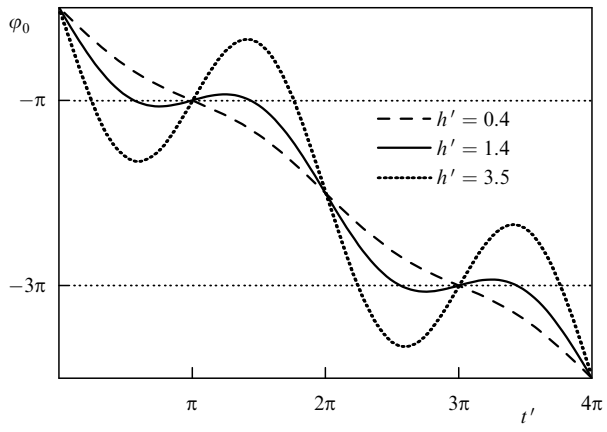

Figure 11. Shift of the ion probability density maximum depending on the time t' at frequency $\Omega' = 1/2$ and different values of the relative amplitude h'.

[3] It is assumed that the real dependence $P(p)$ is close enough to a function with continuous derivatives of the needed order; hence, it has a power series expansion.

averaged over a large time interval. However, if the time of the protein's response to the thickening of probability cloud is smaller than the period of this slow rotation, the protein is able to react. Then, averaging over the ensemble or an infinite time period should be done after the protein's response to density thickening is taken into account. Conversely, sliding averaging to smooth relatively fast fluctuations should not be delayed.

Taking into consideration that $\overline{p} = \sum_m a_{mm}$ (with the exception of physically unrealistic cases), formulas (23) and (27) may be used for $\tilde{p}$ and $\tilde{p}_{\bar{t}}$, respectively, where, in summing over m, m', it is assumed that $m \neq m'$:

$$\tilde{p}_{\bar{t}} = \sum_{m \neq m';\, n} a_{mm'} \exp\left[\mathrm{i}\Delta m \varphi_0 + \mathrm{i}(\alpha z + n)\Omega t\right] \times \frac{\sin\left[(\alpha z + n)\Omega \bar{t}\right]}{(\alpha z + n)\Omega \bar{t}}\, \mathrm{J}_n(z)\,. \tag{33}$$

In order to obtain P, take an average of the square of (33) over a time interval $\gg \bar{t}$. It is understandable that only those terms of $\tilde{p}_{\bar{t}} \cdot \tilde{p}_{\bar{t}}$ will contribute to the expression for P which are products of complex conjugate terms of (33). They do not contain an oscillating time dependence, and their contribution does not disappear after the final averaging. In other words, in this case, the squared sum (33) is the sum of squares of individual terms. Hence,

$$\mathsf{P} = \sum_{m \neq m';\, n} |a_{mm'}|^2 \left(\frac{\sin\left[(\alpha z + n)\Omega \bar{t}\right]}{(\alpha z + n)\Omega \bar{t}}\right)^2 \mathrm{J}_n^2(z)\,. \tag{34}$$

The dependence of φ_0 disappeared as expected. Indeed, the angular position of the 'gate' relative to the spherically symmetric potential must not interfere. In order to have a formula of ion interference in a convenient form, with dimensionless arguments, we denote

$$h' = \frac{H_{\mathrm{AC}}}{H_{\mathrm{DC}}}\,, \qquad \Omega' = \frac{\Omega}{\Omega_{\mathrm{c}}} = \frac{f}{f_{\mathrm{c}}} = f'\,, \tag{35}$$

i.e. introduce dimensionless parameters, the amplitude of a variable MF component h' and its frequency Ω' or f' measured in H_{DC} and Ω_{c} (or f_{c}), respectively. In new notation, (25) is replaced by

$$\alpha = h'^{-1}\,, \qquad z = \frac{\Delta m}{2}\frac{h'}{f'}\,, \qquad \alpha z = \frac{\Delta m}{2}\frac{1}{f'}\,.$$

Then, formula (34) has the form

$$\mathsf{P} = \sum_{m, m', n} |a_{mm'}|^2 \frac{\sin^2 A}{A^2}\, \mathrm{J}_n^2\left(\frac{\Delta m}{2}\frac{h'}{f'}\right), \qquad A = \left(\frac{1}{2}\Delta m + n f'\right)\Xi\,. \tag{36}$$

Here, $\Xi = \Omega_{\mathrm{c}}\bar{t}$ is the sole quantity dependent on the properties of an ion and protein binding cavity. Interestingly, the parameters of ion $\Omega_{\mathrm{c}}(H_{\mathrm{DC}})$ and protein $\bar{t}$ enter the formula in the form of a dimensionless product characterizing the entire ion–protein complex.

The effect described by formula (36) is not resonance, that is it is not coupled to resonance pumping of oscillator energy from one sort of mode to another. In fact, it is the effect of interference of quantum states of an ion inside the protein's cavity. At certain MF parameters, the interference leads to the thickening of the ion probability cloud in some angular position. The thickening moves slowly and triggers complex dissociation as it passes through the 'gate'.

9.3 Limits for applicability of the ion interference mechanism

The most usual argument made against the choice of Hamiltonian (16) is that it neither takes into consideration deviations from spherical symmetry of the binding cavity potential nor contains terms describing interactions between the ion and thermal fluctuations of the binding ligands.

It has been mentioned above that its potential is mainly constituted by the centrally symmetric part. In the next approximation, the ion's potential may be presented as the sum

$$U(\mathbf{r}) = U(r) + \zeta\, u(\theta, \varphi)\,, \qquad \zeta \ll 1\,.$$

In this approximation, the small octahedral contribution $u(\theta, \varphi)$ might be regarded as a constant perturbation of the Hamiltonian. Then, each Zeeman sublevel of the ion would be split once again in compliance with the irreducible representation of the octahedron symmetry group. In the context of the model under consideration, it would lead to the appearance of a new quantum number labeling sublevels with one and the same magnetic quantum number and to the necessity of averaging over this number too. This new splitting is much greater than the magnetic one. Thus, the new quantum number does not influence interference of similar states with different magnetic quantum numbers. Certainly, the computed spectra would look modified but only in minor details.

It is worthy of note that $U(r)$ enters only coefficients $a_{mm'}$ in formula (36). Therefore, neither positions of frequency spectrum peaks nor amplitude spectrum depends on the exact form of the central potential. For example, it can have a maximum in the cavity center and thus determine a shift of the ion's equilibrium position toward ligands. There is every reason to consider potentials of this type to be a more realistic model than potentials with a minimum in the center.

Another objection is pertinent to the presence of the ion gate which is believed to considerably distort the ion's central potential. The ion gate in a binding cavity is the conventionality designed to facilitate visualization of ion binding and complex dissociation. The ion can tunnel between any three neighboring ligands of the octahedron. The ion gate is a local reduction of the potential function at these sites. Because ion leakage from the cavity is very rare (with a characteristic time of 0.1 s), this reduction is small. Therefore, it can be argued with a high degree of confidence that the gate does not perturb the ion's potential. The probability of leakage depends only on exponentially small 'tails' of the ion wave function between the ligands.

Thermal fluctuations of ligands appear to be a central issue. It is known that excitation of one of the normal coordinates of a dynamic system does not influence dynamics of the remaining normal coordinates. This accounts for the different thermal relaxation rates of normal variables depending on the type of the relationship between the mode of the particle's motion and a random force. There is a wide range of energy relaxation times in gases, liquids and solids. Usually, at room temperature, relaxation times of the order of picoseconds are characteristic of Cartesian coordinates of free particles, atoms, and ions embedded in liquids.

Relaxation times are of the order of microseconds for electron spins and of seconds for nuclear spins; moreover, there is a variety of specific times for the so-called collective variables in ordered multiparticle systems, e.g. crystals. Biological membranes and other macromolecules are also systems subject to collective excitations. Not infrequently, they exhibit general quantum properties and are described by equations of quantum dynamics.

In quantum mechanics, normal modes of quantum fluctuations (eigenfunctions of the Hamiltonian) play the part of normal variables. For bound particles, normal modes are usually a discrete set of functions, labeled by quantum numbers. The particle's wave function in the central potential has radial, azimuthal, and polar modes. This means that the wave function factorizes into three eigenfunctions. An external force excites different modes in compliance with quantum selection rules. Specifically, pulses produced by a uniform and even relatively strong electrical field displace an ion in approximately the same way as collisions do. However, the pulses do not induce transitions between Zeeman levels of polar modes as prohibited by the parity selection rules. At the same time, transitions between the states of radial and azimuthal quantum numbers do occur.

Turning back to general objections that weak MF ($\hbar\Omega_c \ll kT$) can not control thermally perturbed ion dynamics, it is opportune to make the following observations. This argument would hold if the ion underwent complete thermalization prior to leakage, i.e. if it remained in the cavity sufficiently long. This is not the case however. The ion occurs in the cavity at a certain moment after which thermalization starts. The model postulates an abnormally slow thermalization of the polar mode. The ion enters a state thermalized with respect to radial and azimuthal modes and a metastable state with respect to the polar mode $\exp(im\varphi)$ the level of which is split in MP into Zeeman sublevels. It is exactly that state which is described by Hamiltonian (16) over an interval smaller than the relaxation time. In this state, there is no need to introduce a 'thermal term' into the Hamiltonian because it does not influence angular polar modes. Its action on other modes results in a statistical distribution by their quantum numbers and is taken into account by final averaging. By virtue of the system's unusual geometry, the relaxation time τ_L of the *phase difference* of polar modes may be very large, supposedly a few hundredths of a second. It is quite enough for interference mechanisms to manifest themselves. Certainly, the idealization $\tau_L > \Omega^{-1}$ adopted in the model is none other than an idealization. Its application is justified by the excellent agreement between theoretical and experimental curves. At the same time, the cause of good performance of this idealization needs theoretical substantiation.

The initial distribution by magnetic numbers depends on many characteristics of the binding protein and is hardly predictable. There is little doubt, however, that thermal perturbations of the potential can not excite states with large quantum numbers. The characteristic energy of ion vibrations is of the order of

$$n^2\frac{\hbar^2}{MR^2}\,,$$

where n is the sum of radial and azimuthal quantum numbers. By way of example, energy $\hbar^2/(MR^2)$ for a calcium ion in the effective potential of radius 0.7 Å is only two orders of magnitude smaller than kT. Therefore, only states with quantum numbers of a few units are populated under thermodynamic equilibrium, and the modulus of the magnetic quantum number does not exceed the modulus of the azimuthal number.

In such a cavity, an electron would be in the ground state, and thermal fluctuations comparable with kT would not excite other states. Accordingly, interference would be impossible. Ions in an imaginary cavity of a larger size would be characterized by excitation of states with large quantum numbers, so interference would be of fine-grained structure and therefore unobservable. Surprisingly, ion masses and binding cavity dimensions are such that they ensure commensurability of inhomogeneities of the interference pattern and the ion gate. It is this commensurability that makes interference possible to observe.

The current mechanism of ion interference describes multipeak effects: strength and direction-modulated MP, magnetic vacuum, constant MF taking into account intrinsic quantized and classical regular rotations of ion – protein complexes, pulsed MF coupled to parallel constant MF, strength-modulated MF in the NMR frequency range taking into account the ions' spin degrees of freedom; in low-frequency electrical fields and in an amplitude-modulated microwave field; interference between the states of rotating molecular groups, shifts of dissociation probability spectral peaks in rotating biological specimens.

Predictions of the ion interference theory are formulated so that they admit of experimental verification. At the same time, this theory is thus far a semiphenomenological one. On the one hand, it deals with microscopic particle dynamics. On the other hand, it proceeds from the postulate of long lifetimes of angular modes and is not concerned with physical processes that maintain projection of angular momentum on the MF direction.

The metastability of angular modes can be probably explained by peculiarities of interaction between the ion and cavity walls. The ion's position in the center of the cavity is unstable. The ion tends to move and bind to a selected ligand. Its motions and ligand adjustment in response to them are of the same time scale as ion vibrational dynamics. For this reason, an ideal equation for ion dynamics must include the ion's self-action. As the ion probability density increases, its potential decreases due to ligand adjustment. In a dynamic equation, this situation corresponds to the presence of an additional term of the Hamiltonian proportional to the squared wave function module that describes the self-action. The wave function appears to deepen the well for itself especially where its density is large. The resulting equation is, up to the energy of interaction with MF, a non-linear Schrödinger equation (NSE) that has a soliton-like solution in the one-dimensional case.

If binding ligands are located in nodes $\mathbf{r}_a$, the ion states in MF can be described by the following NSE-type equation taking into account both magnetic and thermal factors:

$$i\hbar\frac{\partial}{\partial t}\Psi(\mathbf{r},t) = \left(\frac{\mathcal{P}^2}{2M} - \frac{q\hbar}{2Mc}\,\mathcal{L}\mathbf{H} + \sum_a U_a\right)\Psi - \alpha\hbar\sum_a f\bigl(\mathbf{r}-\mathbf{r}_a(t)\bigr)|\Psi|^2\Psi\,.$$

Here, $\mathcal{L} = -i\mathbf{r}\times\nabla$ is the angular momentum operator, as before; U_a is the ion potential in the field of the ath ligand; α,

$f(\mathbf{r})$ are the parameters of the model. The fluctuating coordinate of the ath ligand $\mathbf{r}_a(t)$ corresponds to the thermal oscillations of the medium. A numerical solution of such equations is sometimes realized in the form of soliton-like perturbations persisting over a certain parameter range of thermalizing factors [135, 136].

9.4 Comparison with experiment

A path from the physical cause of a magnetic field to a biological response as its after-effect is of necessity mediated through a variety of factors at biochemical and physiological levels. Because these factors are many and uncertain, they can not be comprehensively taken into consideration. The transformation of electromagnetic energy into a biological response may occur by several metabolic pathways at a time [11]. Moreover, biological systems may exhibit sensitivity even to such 'exotic' factors as a temperature derivative of the order of $1\,^{\circ}\mathrm{C\,h^{-1}}$ that induce MBEs with the opposite sign [137].

This imposes limitations upon the method by which experimental and theoretical findings are compared. Because a principal objective of the magnetobiological theory is to elucidate primary biochemical mechanisms of magnetoreception, its predictions are of necessity restricted to physicochemical processes. At the same time, such predictions are usually extrapolated to the biological level. As mentioned before, the cause-effect relationship in this case may be very complicated due to a great variety of unaccountable factors.

However, if MF-induced perturbations at the level of biophysical structures are in a sense small, a linear approximation may be considered for a multilevel non-linear system relating these perturbations to a measurable biological reaction. In this case, extreme dependence in a biophysical response to MF will bring about a similar extreme dependence of the biological reaction to MF. This gives an opportunity to compare experimental findings and theoretical predictions of magnetic conditions giving rise to the extrema, i.e. MF parameters responsible for extreme MBE. Because the correct criterion for the agreement between the theory and experiment in magnetobiology is the coincidence of observed and computed conditions for the development of peak responses, all forms of theoretical dependences obtained by means of displacing and scaling on axis y should be regarded as equivalent. Furthermore, it is assumed for the purpose of comparison that the transformation of theoretical curves and experimental data is performed so as to obtain the best visual correlation.

Both theoretical analysis and experimental findings indicate that MBE amplitude spectra in the mechanism of ion interference are virtually independent of the type of ions involved in magnetoreception. This makes it possible to compare data obtained in different biological systems with one and the same theoretical dependence. To an accuracy of 10%, this dependence is determined by the function $J_1^2(h')$.

Figure 4 shows a theoretical amplitude spectrum and experimental characteristics of MBE obtained by different authors, in different laboratories, with different biological systems, and under different magnetic conditions. Common to all these studies was the parallelism of alternating and constant MF.

E D Alipov and I Ya Belyaev [138] investigated the biological responses of *E.coli* cells K12 AB1157 to a combined MF in a frequency range of 6–69 Hz. The alternating MF contained a 30 μT component parallel to the 43 μT constant field. The maxima were recorded at 8.9, 15.5, 29.4, and 62 Hz.

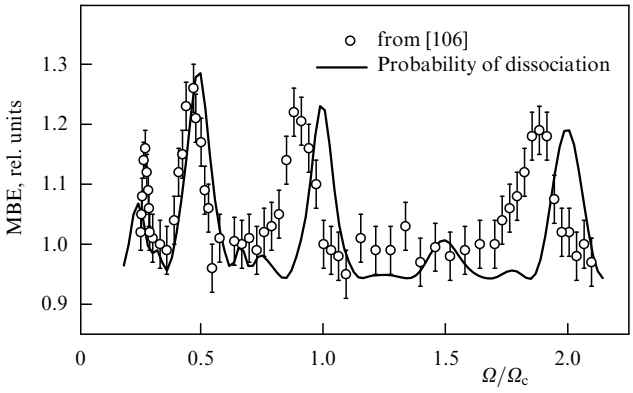

Figure 12. Interference spectrum derived from formula (36) for calcium ions and experimental data on viscosity changes in E.coli cell suspension placed in combined MF [138].

Calculations were made for $^{40}Ca^{2+}$ ions using formula (36) and the above field values H_{AC}, H_{DC}. The perpendicular component was disregarded bearing in mind the results of a special study [62]. The averaging period roughly corresponded to a dissociation constant of the Ca–calmodulin complex of $\bar{t} = 0.1$ s. The cyclotron frequency was $f_c = 32.9$ Hz. The best correlation of theoretical and observed peak heights was obtained at the following values of density matrix elements: $a_{mm'} = 1$, $\Delta m = 1, 2$; $a_{mm'} = 0.5$, $\Delta m = 3$; $a_{mm'} = 4$, $\Delta m = 4$. The calculated curve and experimental data [138] fitted to the dimensionless frequency are shown in Fig. 12. Good agreement between calculated and observed maxima can be seen both right and left of the cyclotron frequency f_c. Experimental peaks are somewhat displaced relative to the theoretical values towards lower frequencies. This 'red shift' of MBE maxima may be due the loss of a part of the ionic charge as a result of ion binding. Indeed, any chemical bond, even a relatively weak ionic bond, implies either displacement or attraction of the external electron cloud of the ligand toward the ion (cation). Hence, a decrease of the effective ionic charge q manifest as the 'red shift' because MBE peak frequencies are proportional to $\Omega_c = qH/(Mc)$.

Calculated probabilities of dissociation for ion–protein complexes in pulsed MF [67], magnetic vacuum [69], constant MF [70], weak electrical fields [68], and for rotating ion–protein complexes [69] also agree in general with the available experimental data.

10. Molecular gyroscope

The long lifetimes of angular modes is the sole serious idealization underlying the mechanism of ion interference. This idealization is difficult to justify in the framework of the model of an ion in a protein cavity. It has to be assumed that ion binding to the cavity walls gives rise to polaron-like states. The explanation of long lifetimes of polaron angular modes requires, in its turn, new idealizations. Hence, a 'vicious circle' which it is difficult to break without modification of the essential part of the model. Thus, despite obvious advantages of the ion-in-the-cavity model, such as simplicity and high predictive value, there are serious limitations for its applicability necessitating the search for other approaches [32].

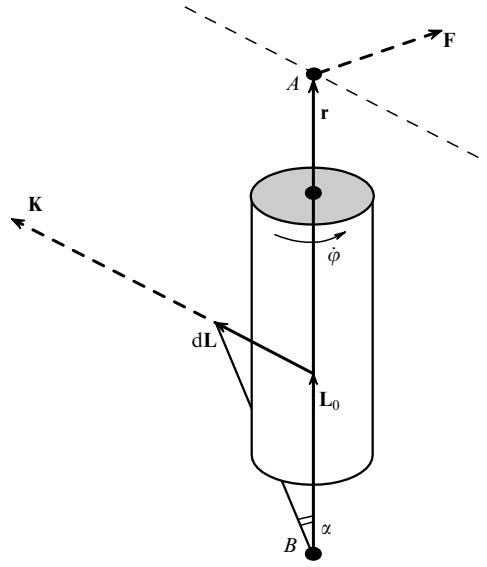

Figure 13. Forces, moments of forces, and angular momenta in a revolving top.

One of them is to apply conservation laws of rotating body dynamics. The rotation of a solid body obeys the equation

$$\frac{\mathrm{d}\mathbf{L}}{\mathrm{d}t} = \mathbf{K}\,, \tag{37}$$

where **L** is the angular momentum and **K** is the sum of moments of forces acting upon the body. Imagine, for simplicity, a symmetrical top that is made to spin about one of its main axes of inertia while the point of support A undergoes force **F** (Fig. 13). Evidently, the moment of force with respect to this axis is equal to zero. It follows from Eqn (37) that

$$\mathbf{L} = \mathbf{L}_0 + \mathrm{d}\mathbf{L}\,, \qquad \mathrm{d}\mathbf{L} = \mathbf{K}\,\mathrm{d}t = \mathbf{r}\times\mathbf{F}\,\mathrm{d}t\,.$$

Since $\mathbf{K}\perp\mathbf{F}$, then $\mathrm{d}\mathbf{L}\perp\mathbf{F}$, i.e. the action of the force causes perpendicular displacement of the rotation axis. Moreover, vector **r** being directed along the rotation axis, vector d**L** is also perpendicular to $\mathbf{L}_0$.

Therefore, the constant action of force **F** leads to forced precession of the top around direction **F** with an angular velocity determined by the angle of deviation from its own rotation axis per unit time, i.e.

$$\Omega_{\mathrm{pr}} = \frac{\mathrm{d}\mathbf{L}/\mathbf{L}_0}{\mathrm{d}t} = \frac{K}{L_0} = \frac{rF}{L_0}\,.$$

The vector **r** length depends on how the top is operated. If point B is in a fixed position, **r** originates in B. If B is free, **r** originates from a point on line AB, depending on the parameters of the top. For the purpose of evaluation, it is essential that r is of the order of the top's length.

The top being considered may be used as a model of a rigid molecule the motions of which are restricted only by thermal fluctuations of one of its points of support, e.g. A. Let us determine the mean deviation angle of the top's axis if **F** is a random force that induces chaotic vibrations of the point of support. It should be noted from the very beginning that the top's gravitational energy $\sim MgR$ is many orders of magnitude smaller than its kinetic energy $\sim L^2/(2I)$ and gravitational effects may be neglected. In the last formulas, M, R, I are the top's mass, dimension, and moment of inertia respectively, and g is acceleration of gravity.

The energy of the top's own rotation is $\varepsilon_0 = L_0^2/(2I)$. The energy of the top's own rotation taking into account forced chaotic revolutions is $\varepsilon_0 + kT$. On the other hand, the mean energy value taking into consideration the perpendicularity of $\mathbf{L}_0$ to d**L** equals (here, angle brackets indicate averaging over the ensemble)

$$\left\langle \frac{1}{2I}(\mathbf{L}_0 + \mathrm{d}\mathbf{L})^2 \right\rangle = \frac{1}{2I}\left\{L_0^2 + 2\langle \mathbf{L}_0\,\mathrm{d}\mathbf{L}\rangle + \langle \mathrm{d}^2\mathbf{L}\rangle\right\}$$
$$= \varepsilon_0 + \frac{\langle \mathrm{d}^2 L\rangle}{2I}\,.$$

Then, $\langle \mathrm{d}^2 L\rangle/(2I) \sim kT$. If the average deviation angle is

$$\alpha = \frac{\sqrt{\langle \mathrm{d}^2 L\rangle}}{L_0}\,,$$

$\alpha^2 \sim 2IkT/L_0^2$. The smaller L_0 the larger the random deviations of the molecule due to thermal perturbations of its point of support, i.e. the covalent bond between the molecule and the protein matrix. Estimates of minimal L_0 values ensue from the Heisenberg uncertainty relation which is written in the following form for a complementary pair of noncommutative operators of angular variable φ and angular momentum $\mathcal{L} \sim \mathrm{d}/\mathrm{d}\varphi$:

$$\Delta L\,\Delta\varphi \sim \frac{\hbar}{2}\,.$$

Because $\Delta\varphi \sim \pi$, then $\Delta L \sim \hbar/(2\pi)$; accordingly, the angular momentum can not be smaller than its uncertainty, i.e. $L_0 \sim \hbar/(2\pi)$. Finally:

$$\alpha^2 \sim 8\pi^2\,\frac{IkT}{\hbar^2}\,.$$

It can be seen that deviations become greater as the molecule's size increases. However, the estimate of the deviation looks unrealistic even for small molecules. This means that molecules in lower rotational states will slant and therefore lose their angular momentum if the point of support is perturbed. It should be emphasized that we are interested in angular states with small quantum numbers. Otherwise, the interference fringe patterns considered below become fine-grained and supposedly fail to manifest themselves in any measurable characteristics.

It follows from the above that if a protein matrix is to acquire 'immunity' to thermal perturbations of its supports, the second point of support needs to be fixed, the same as the first one. A construction consisting of a spinning unit mounted in a framework that permits it to rotate about any axis is a sort of *gyroscope*, i.e. a device for measuring angular deviations and velocities. In essence, the system described above is a gyroscope at the molecular level where a relatively large molecular group is set in a protein cavity so that its either side forms a covalent bond (support) with the cavity's walls. Importantly, thermal fluctuations of the supports create but zero torques with respect to the group's own axis of rotation. For this reason, the gyroscopic degree of freedom φ undergoes no thermalization. This does not however exclude its energy dissipation. Radiation damping is negligi-

bly small. The interference of the molecular gyroscope and its halting as a result of van der Waals interactions are considered below.

Rotations of large molecules are much slower than electronic and vibrational processes. Therefore, a rotating molecular group may be represented as a rigid system of point charged masses (atoms of the molecule with partially polarized chemical bonds). A good example are amino acids that can penetrate into sufficiently large protein cavities, form two chemical bonds on the opposite ends of their molecules, and thus give rise to a molecular gyroscope. Amino acids are known to be the chief components of polymer protein macromolecules; also, they are present in biological plasma in the form of free monomers. The formula of a general amino acid is well known. It has the form:

$$\begin{array}{c} \mathrm{R} \\ | \\ \mathrm{H_2N^+ - CH - COHO^-}, \end{array}$$

where R is the radical which is unique to each amino acid. Group polarities are indicated for aqueous solutions. The radical of, say, glutamic acid has the structure $-\mathrm{CH_2} - \mathrm{CH_2} - \mathrm{COOH}$. If either end of such a molecule is attached to the inside of a binding cavity as a whole dynamic unit, it has one degree of freedom, a polar angle φ, which makes it easier to observe its behavior in MF.

Lagrange's function of a single charged particle for the case of small velocities has the form

$$\mathsf{L} = \frac{Mv^2}{2} + \frac{q}{c}\,\mathbf{Av} - qA_0\,, \tag{38}$$

where $\mathbf{v}$ is the particle's velocity and q is the arbitrary charge. Let MF $\mathbf{H} = (0, 0, H)$ be directed along axis z and the particle bound by a holonomic bond so that it moves on circular path in plane xy. The equation for bonding in a spherical system of coordinates is written in the form

$$r = R = \text{const}\,, \qquad \theta = \frac{\pi}{2}\,. \tag{39}$$

The vector potential is chosen as

$$\mathbf{A} = \left(-\frac{1}{2}\,Hy, \frac{1}{2}\,Hx, 0\right). \tag{40}$$

The particle's velocity in the spherical system of coordinates taking bonds (39) into account is $v = R\dot{\varphi}$, and the velocity vector in Cartesian coordinates

$$\mathbf{v} = \left(-R\dot{\varphi}\sin\varphi, R\dot{\varphi}\cos\varphi, 0\right). \tag{41}$$

Substitution of this equality into (38) gives Lagrange's function in the spherical system of coordinates

$$\mathsf{L} = \frac{MR^2\dot{\varphi}^2}{2} + \frac{qH}{2c}\,R^2\dot{\varphi} - qA_0\,. \tag{42}$$

If the generalized momentum $l = \partial\mathsf{L}/\partial\dot{\varphi}$ and Hamiltonian function $\mathsf{H} = l\dot{\varphi} - \mathsf{L}$, then

$$\mathsf{H} = \frac{1}{2MR^2}\left(l - \frac{qH}{2c}\,R^2\right)^2 + qA_0\,. \tag{43}$$

In the absence of an electromagnetic field, $\mathsf{H} = l^2/(2MR^2)$ from which it is clear that l is the particle's angular momentum. The Hamiltonian operator or Hamiltonian is also defined by (43), the sole difference being that l denotes the operator of angular momentum $\mathcal{L} = -\mathrm{i}\hbar\,\partial/\partial\varphi$.

Suppose now that several particles rotate at a time, and bonding equations for the ith particle in a spherical system of coordinates have the form

$$r_i = \text{const}\,, \qquad \theta_i = \text{const}\,.$$

Then, by analogy with the derivation of formula (42), Lagrange's function of the system of particles in an uniaxial MF can be written as

$$\mathsf{L} = \frac{I}{2}\,\dot{\varphi}^2 + \frac{HQ}{2c}\,\dot{\varphi} - \sum_i q_i A_0(r_i, \theta_i, \varphi_i)\,, \tag{44}$$

where

$$I = \sum_i M_i\, r_i^2 \sin^2\,\theta_i\,, \qquad Q = \sum_i q_i\, r_i^2 \sin^2\,\theta_i \tag{45}$$

is the moment of inertia and the 'moment of inertia of the charge' of the system with respect to the axis of rotation. It can be seen that Lagrange's function of the system is derived from Lagrange's function (42) using the formal substitution of coefficient MR^2 by I, qR^2 by Q, and qA_0 by the respective sum. Therefore, the Hamiltonian of the system immediately ensues from (43) where the analogous substitution needs to be made:

$$\mathcal{H} = \frac{1}{2I}\left(\mathcal{L} - \frac{QH}{2c}\right)^2 + \sum_i q_i A_0(r_i, \theta_i, \varphi_i)\,.$$

Here, there are two more operators, besides $\mathcal{L}^2/(2I)$. There is reason to neglect the term quadratic in H: it follows from the ratio of coefficients of terms quadratic and linear in H that $QH/(4c\hbar) \sim 10^{-7}$, where $Q \sim eR^2$, $R \sim 10^{-7}$ cm, $H \sim 1$ G. Omitting this term and assuming that an electrical field is absent, i.e. $A_0 = 0$, the Hamiltonian can be written in the convenient form

$$\mathcal{H} = \frac{\mathcal{L}^2}{2I} - \omega(t)\mathcal{L}\,, \qquad \omega = \frac{QH}{2Ic}\,. \tag{46}$$

The eigenfunctions and energies of the time-independent part of the Hamiltonian (46) are

$$|m\rangle = \frac{1}{\sqrt{2\pi}}\exp(\mathrm{i}m\varphi)\,, \qquad m = 0, \pm 1, \ldots, \qquad \varepsilon_m = \frac{\hbar^2}{2I}\,m^2\,.$$

Let us now consider an ensemble of gyroscopes with density operator σ that obeys Liouville's equation

$$\mathrm{i}\hbar\dot{\sigma} = \mathcal{H}\sigma - \sigma\mathcal{H}\,, \qquad \sigma = \sum_\alpha w_{(\alpha)}\sigma^{(\alpha)}\,. \tag{47}$$

Such physical quantities as the intensity of spontaneous or ensemble-scattered radiation exhibit a linear dependence on the density matrix of the ensemble:

$$\sigma_{mm'} = \sum_\alpha w_{(\alpha)}\sigma^{(\alpha)}_{mm'}\,.$$

The probability of the biochemical reaction under consideration is not a physical quantity of this type. The probability is

not directly related to the density matrix of the ensemble. Indeed, it is the probability of reaction of an individual gyroscope averaged over the ensemble. Therefore, the density matrix $\sigma^{(\alpha)}_{mm'}$ of the gyroscope with number α is the first to be found followed by the probability of a gyroscope reaction showing a non-linear dependence on $\sigma^{(\alpha)}_{mm'}$; in the end, the result is averaged over the ensemble.

Let the ensemble consist of gyroscopes that appear at a constant rate at random moments of time. Also, let new gyroscopes appear in the superposition of states close to the ground state:

$$\sigma^{(\alpha)}_{mm'}(0) = \begin{cases} \text{const}\,, & m, m' \sim 1\,, \\ 0\,, & m, m' \not\sim 1\,. \end{cases}$$

The process of thermalization results in the population of levels with energies of up to $\varepsilon_m \sim kT$, i.e. with numbers of up to $m \sim (1/\hbar)\sqrt{IkT} \sim 10^3$ for gyroscopes with moments of inertia of the order of $I \sim 10^{35}$ g cm^2. However, we are interested in the dynamics of the lowest states because only their dynamics is related to the observed effects.

In the representation of eigenfunctions of the Hamiltonian $\mathcal{H}_0$, the equation for the density matrix can be written, using formulas (46) and (47), in the form

$$\dot\sigma_{mm'} = -(\Gamma_{mm'} + \mathrm{i}\omega_{mm'})\sigma_{mm'} - \frac{\mathrm{i}}{\hbar}\sum_l (\mathcal{V}_{ml}\,\sigma_{lm'} - \sigma_{ml}\mathcal{V}_{lm'})\,, \tag{48}$$

where

$$\omega_{mm'} = \frac{\hbar}{2I}(m^2 - m'^2)\,, \qquad \mathcal{V}_{ml} = -\hbar\omega(t) m\,\delta_{ml}\,.$$

Phenomenological relaxation of matrix elements is taken into account here via damping coefficients $\Gamma_{mm'}$. As a result of relaxation, elements $\sigma_{mm'}$ decrease in lower modes and increase in upper ones. Because we are not interested in stationary dynamics of individual gyroscopes, the equation takes no account of pumping upper modes, i.e. population redistribution into states with larger m.

Substitution of the above relations into (48) gives the equation

$$\dot\sigma = -\Gamma\sigma + \mathrm{i}\sigma\big[(m - m')\omega(t) - \omega\big]\,,$$

where the indices m, m' are tentatively disregarded for convenience. With notation

$$g(t) \equiv -\Gamma + \mathrm{i}f\,, \qquad f \equiv (m - m')\omega(t) - \omega$$

the equation takes a simple form $\dot\sigma = g(t)\sigma$. The constants C in the solution of this equation $\sigma = C\exp\left(\int g(t)\,\mathrm{d}t\right)$ are found from the initial conditions.

Let MF contain both constant and alternating constituents; then,

$$\omega(t) = \omega_\mathrm{g}\big(1 + h'\cos(\Omega t)\big)\,, \qquad \omega_\mathrm{g} \equiv \frac{QH_\mathrm{DC}}{2Ic}\,, \qquad h' \equiv \frac{H_\mathrm{AC}}{H_\mathrm{DC}}\,.$$

Let us further distinguish the constant and alternating components in $g(t)$:

$$g(t) = -x + \mathrm{i}z\Omega\cos(\Omega t)\,, \qquad x \equiv \Gamma + \mathrm{i}\omega - \mathrm{i}(m - m')\omega_\mathrm{g}\,,$$
$$z \equiv (m - m')\omega_\mathrm{g}\frac{h'}{\Omega} = (m - m')\frac{h'}{\Omega'}\,, \qquad \Omega' \equiv \frac{\Omega}{\omega_\mathrm{g}}\,.$$

Hence,

$$\int g(t)\,\mathrm{d}t = \int\big(-x + \mathrm{i}z\Omega\cos(\Omega t)\big)\,\mathrm{d}t = -xt + \mathrm{i}z\sin(\Omega t)\,,$$

therefore,

$$\sigma = \sigma(0)\exp\left[\int g(t)\,\mathrm{d}t\right] = \sigma(0)\exp(-xt)\exp\big[\mathrm{i}z\sin(\Omega t)\big]$$
$$= \sigma(0)\exp(-xt)\sum_n \mathrm{J}_n(z)\exp(\mathrm{i}n\Omega t)\,.$$

Reintroduction of indices m, m' gives the equation the form

$$\sigma_{mm'} = \sigma_{mm'}(0)\exp\big\{-\big[\Gamma_{mm'} + \mathrm{i}\omega_{mm'} - \mathrm{i}(m - m')\omega_\mathrm{g}\big]t\big\} \times \sum_n \mathrm{J}_n(z_{mm'})\exp(\mathrm{i}n\Omega t)\,.$$

All damping coefficients are assumed to be equal to Γ. Designating

$$\beta \equiv \Gamma + \mathrm{i}\omega_{mm'} - \mathrm{i}(m - m')\omega_\mathrm{g} - \mathrm{i}n\Omega\,,$$

allows the last equation to be rewritten in the form

$$\sigma_{mm'} = \sigma_{mm'}(0)\sum_n \mathrm{J}_n(z_{mm'})\exp(-\beta t)\,,$$

to be used below.

Let us now find the probability density for a gyroscope to have a certain angular position φ, indeed the sole one favoring its reaction with an active binding site at the cavity's wall:

$$p(t) = \Psi^*(t,\varphi)\Psi(t,\varphi)$$
$$= \frac{1}{2\pi}\sum_m c^*_m(t)\exp(-\mathrm{i}m\varphi)\sum_{m'} c_{m'}(t)\exp(\mathrm{i}m'\varphi)$$
$$= \frac{1}{2\pi}\sum_{m,m'}\sigma_{mm'}\exp\big[-\mathrm{i}(m - m')\varphi\big]\,,$$

i.e.

$$p(t) = \frac{1}{2\pi}\sum_{m,m',n}\sigma_{mm'}(0)\exp\big[-\mathrm{i}(m - m')\varphi\big] \times \exp(-\beta t)\,\mathrm{J}_n(z_{mm'})\,.$$

Averaging may be beneficial in that it eliminates relatively fast density oscillations that do not affect the slow reaction with the active binding site having a characteristic time constant τ, i.e.

$$p_\tau(t) = \frac{1}{2\tau}\int_{t-\tau}^{t+\tau} p(t')\,\mathrm{d}t'\,.$$

In fact, the factor $\exp(-\beta t)$ needs to be averaged:

$$\big(\exp(-\beta t)\big)_\tau = \frac{\sinh(\beta\tau)}{\beta\tau}\exp(-\beta t)\,,$$

therefore,

$$p_\tau(t) = \frac{1}{2\pi}\sum_{m,m',n}\sigma_{mm'}(0)\,\frac{\sinh(\beta\tau)}{\beta\tau}\exp\big[-\mathrm{i}(m - m')\varphi\big] \times \exp(-\beta t)\,\mathrm{J}_n(z_{mm'})\,. \tag{49}$$

Let us assume now, on the analogy with the ion interference model, that the probability of the reaction of the side chain of a rotating molecule with an activated binding site is a non-linear function of probability density (49). In the absence of any information about this function, there is every reason to take into consideration the first non-vanishing, quadratic, term (see Ref. [65]). The probability of the reaction can be found by taking the square of (49) and averaging over the ensemble of gyroscopes.

Product $p_\tau(t)\cdot p_\tau(t)$ contains: (1) complex conjugate terms, pairs with indices n, m, m' and $-n$, m', m that do not oscillate; (2) rapidly oscillating terms that we omit in view of subsequent averaging. If the non-existent coefficient is also disregarded, it is possible to write

$$p_\tau^2(t) \simeq \exp(-2\Gamma t) \sum_{m,m',n} \left|\sigma_{mm'}(0)\right|^2 \left|\frac{\sinh(\beta\tau)}{\beta\tau}\right|^2 \mathrm{J}_n^2(z_{mm'}) .$$

In this expression, the factor

$$S \equiv \sum_{m,m',n} \left|\sigma_{mm'}(0)\right|^2 \left|\frac{\sinh(\beta\tau)}{\beta\tau}\right|^2 \mathrm{J}_n^2(z_{mm'})$$

contains an MF dependence.

Let a gyroscope appear at moment t'; then, the probability of reaction (within a unit time) at moment t is

$$u(t,t') = \begin{cases} S\exp\left[-2\Gamma(t-t')\right], & t \geqslant t', \\ 0, & t < t'. \end{cases}$$

Assuming that the moments of time t' are distributed over the ensemble of gyroscopes in the interval $(-\theta,\theta)$ with uniform density w [instead of discrete distribution $w_{(\alpha)}$ in (47)], the averaged probability P can be found by integrating over parameter t':

$$\mathsf{P} = \lim_{\theta\to\infty} w\int_{-\theta}^{\theta} u(t,t')\,\mathrm{d}t' = \frac{wS}{2\Gamma} .$$

In order to relate this quantity to an observable one, e.g. the concentration of relaxation products, the kinetic equation for the number of gyroscopes per unit tissue volume should be written in the form:

$$\dot N = w - \mathsf{P}N ,$$

which gives $N = w/\mathsf{P} = 2\Gamma/S$ in the stationary regime for the ensemble. Let S_0 and N_0 denote the corresponding quantities in the absence of alternating MF, i.e. at $h' = 0$. We need to know a relative change ρ in the concentration of relaxation products in an alternating MF. This change is the number of gyroscopes involved in the reaction, i.e.

$$\rho \equiv \frac{N_0 - N}{N_0} = 1 - \frac{S_0}{S} . \tag{50}$$

Let us now find quantities S and ρ using the following notation

$$\beta\tau \equiv \eta + \mathrm{i}\xi , \quad \eta \equiv \Gamma\tau , \quad \xi \equiv \left[\omega_{mm'} - (m-m')\omega_\mathrm{g} - n\Omega\right]\tau .$$

Then, the expression for S assumes the form

$$S = \sum_{m,m',n} \left|\sigma_{mm'}(0)\right|^2 \frac{\sinh^2\eta + \sin^2\xi}{\eta^2+\xi^2}\,\mathrm{J}_n^2\left[(m-m')\frac{h'}{\Omega'}\right] . \tag{51}$$

Because η is constant, the frequency spectrum is largely defined by the equation $\xi = 0$, i.e.

$$\omega_{mm'} - \omega_\mathrm{g}(m-m') - n\Omega = 0 .$$

For arbitrarily small values of m, m', the frequencies $\omega_{mm'}$ fall into the microwave range. The effects of low-frequency MF depend on interference of levels $m' = -m$, when $\omega_{mm'} = 0$. Then,

$$\omega_\mathrm{g}(m-m') + n\Omega = 0 ,$$

Hence,

$$\Omega' = \frac{2m}{n} . \tag{52}$$

The series in powers of n in (51) rapidly converges; therefore, terms with $n = 1$ are the main contributors to the probability of the reaction. For this reason, at frequencies corresponding to the maximum probability ($\Omega' = 2m$), the contributions of these terms equal

$$S_m \equiv \left|\sigma_{m,-m}(0)\right|^2 \frac{\sinh^2(\Gamma\tau)}{\Gamma^2\tau^2}\,\mathrm{J}_1^2(h') .$$

Evidently, contributions of terms with $n = 2$

$$\left|\sigma_{m,-m}(0)\right|^2 \frac{\sinh^2(\Gamma\tau) + \sin^2(6m\omega_\mathrm{g}\tau)}{\tau^2(\Gamma^2 + 36m^2\omega_\mathrm{g}^2)}\,\mathrm{J}_2^2(2h') ,$$

are at least an order of magnitude smaller in the case of $\omega_\mathrm{g} \gtrsim \Gamma$, i.e. when the examination of interference has any sense at all. Therefore, terms with $n > 1$ are disregarded for the purpose of rough estimation. For the above reasons, only contributions of terms with $n = 0$ are essential for the ground state $m = 0$. These terms make a contribution independent of alternating MF:

$$S_0 = \left|\sigma_{00}(0)\right|^2 \frac{\sinh^2(\Gamma\tau)}{\Gamma^2\tau^2} .$$

Similarly, only terms with $m = -m' = m^*$ are of importance at the given frequency $\Omega' = 2m^*$. Now, it is easy to estimate a relative change in the concentration of relaxation products at a MF frequency, say, $\Omega' = 2m$. Bearing in mind that $\mathrm{J}_{-1}^2(h') = \mathrm{J}_1^2(h')$ and taking into consideration that, in the present case, $S = S_0 + S_m$, it can be found from (50) that[4]

$$\rho = 1 - \left[1 + 2\,\frac{\sigma_{-mm}^2(0)}{\sigma_{00}^2(0)}\,\mathrm{J}_1^2(h')\right]^{-1} .$$

[4] After the original version of this article is published in Russian, J C Gill of H Wills Physics Laboratory, U.K. noted [144] the equation (53 here) included inaccuracy in the coefficient at Bessel function that is always less than or equal to 1/2. To seize an opportunity, we thank J C Gill and provide below the corrected equations that are true in the more general case of n equally populated states. It is the equation that precedes (53):

$$\rho = 1 - \left[1 + \frac{\sigma_{-m,m}^2(0)}{\sum_m \sigma_{mm}^2(0)}\,\mathrm{J}_1^2(h')\right]^{-1} ,$$

and equation (53):

$$\rho = 1 - \frac{1}{1 + \mathrm{J}_1^2(h')/2n} .$$

Of course, by no means, these corrections do not change our conclusions. (*Author's note for English translation.*)

It appears that the magnitude of magnetic effect depends on the ratio of density matrix elements at the initial moment, i.e. immediately after the appearance of the gyroscope. For example, if the ground state and state m (beyond consideration of Zeeman splitting) are equally populated at $t = +0$, then

$$\rho = 1 - \frac{1}{1 + \mathrm{J}_1^2(h')} \,. \tag{53}$$

This function is similar to that in Fig. 4. It can be concluded that relative values of amplitude spectrum maxima depend on the initial distribution of populations over gyroscope levels whereas their positions are independent of the distribution.

The frequency spectrum (52) defines only the feasible locations of extrema. The real shape of the spectrum depends on the initial conditions for the density matrix, i.e. on the population of levels with different rotational quantum numbers m.

It is worthwhile to note that the molecule need not necessarily have a dipole moment $\sum_i q_i \mathbf{r}_i$ for the magnetic effect of interference to appear. What is important is that 'moment of inertia of the charge' Q (45) be other than zero. Such a situation can take place even in the absence of a dipole moment, e.g. for an ionic, as opposed to zwitterion-like, molecule.

The main properties of interference of gyroscopes and ions are essentially similar: (1) multipeak amplitude and frequency spectra, (2) dependence of the positions of frequency spectrum maxima on constant MF value, and (3) independence of the positions of amplitude spectrum maxima of alternating MF frequency.

The interference of a molecular gyroscope differs from that of bound ions. Firstly, the frequencies of the frequency spectrum maxima are related to the rotational velocity ω_g — a rotational equivalent of the cyclotron frequency. These frequencies depend on the electric charge density distribution over the molecule and may be different from cyclotron harmonics and subharmonics. Secondly, the axis of rotation of a molecular gyroscope is fixed relative to the protein cavity which, in the general case, provides an additional averaging parameter. However, these differences are not fundamental. Concrete interference spectra can be calculated for any configuration of magnetic and electrical fields taking into account rotations of protein molecules, organelles, and biological systems *per se*.

The most important property of interference of molecular gyroscopes consists of its relative refractoriness to molecular thermal perturbations. Molecular gyroscopes may serve as efficacious biophysical targets for externally-induced MF.

It follows from (51) that the absolute value of magnetic effect maximized by selecting MF parameters depends in the first place on the value of $\eta = \Gamma\tau$ that must be minimal to ensure an appreciable effect. For interference to be observable, the protein's reaction time τ and MF frequency Ω must satisfy the relation $\Omega\tau \gtrsim 1$. This relation along with properties of function $\sinh^2\eta/\eta^2$ accounts for the magnetic effect observability condition

$$\Gamma^{-1} \gtrsim \Omega^{-1} \sim 0.01 \text{ s} \tag{54}$$

in a low-frequency range.

Being a putative mechanism of MBE, an interfering molecular gyroscope may serve as a tool for the solution of the 'kT problem'. Indeed, the walls of a protein cavity do not interact directly with gyroscopic degree of freedom via short-acting chemical bonds. The contribution of van der Waals electromagnetic forces caused by wall vibrations to relaxation is small and depends on the cavity size. Numerical modeling of gyroscope dynamics [32] has demonstrated that the relaxation time t_r of gyroscope rotation grows exponentially with cavity diameter b (Fig. 14). For example, for a gyroscope composed of phenylalanine residue ($C_\alpha C_6H_5$) in a cavity 33 Å in diameter, the relaxation time exceeds 1 s while radiation damping is negligibly small. Finally, vibrations of gyroscope supports create zero moment of forces with respect to the rotation axis and have no effect on angular momentum. Thermalization of gyroscopic degree of freedom is very slow and characterized by coherent dynamics. This allows slow interference effects to be manifest. Certainly, the very existence of more or less water-free cavities 30 Å or more in diameter needs to be confirmed, but it is important that their reality is no longer regarded as paradoxical.

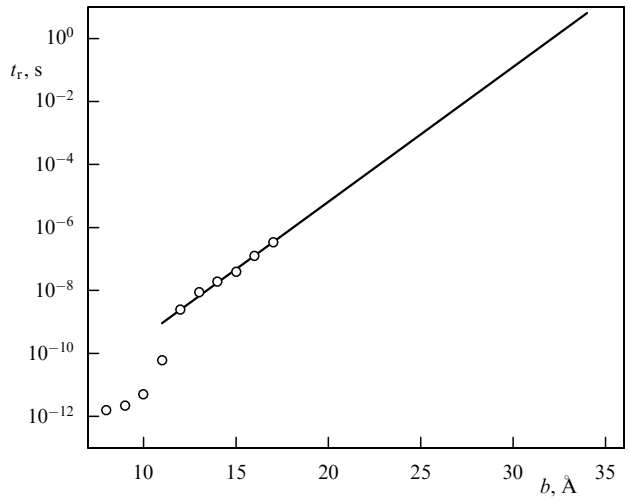

Figure 14. Plot of relaxation time t_r of molecular gyroscope $C_\alpha C_6H_5$ versus cavity diameter b. Markers give values obtained by numerical modeling gyroscope dynamics; straight line extrapolates this dependence to the area of larger b values.

Short sequences of polypeptide and nucleic acid chains built in globular proteins or between associated globules may probably function as molecular gyroscopes. Watson and Crick's nitrogen-containing base pairs of adenine – thymine and guanine – cytosine that join together strands of the DNA double helix and some other complexes of nitrogen bases bound by hydrogen bonds are of great interest as possible candidates. The rotation of such complexes is hampered by their steric configuration. However, DNA-specific enzymes can eliminate steric hindrance and make molecular complexes free to rotate. Whether molecular constructions with gyroscopic properties exist in nature is largely a matter of conjecture. They are hardly possible to discover by X-ray diffraction techniques which imply the crystallization of proteins for X-ray structural analysis. However, this procedure most likely leads to freezing rotation or, if there is any rotation, mobile groups produce no discernible replicas. Other methods are needed to work with native proteins the structure of which is not distorted by crystallization.

Generally speaking, the very possibility of using molecular gyroscopes for the physically consistent explanation of the

scientific fact of MBE suggests its reality. Future studies will either prove or disprove this assertion. Today, however, interfering molecular gyroscopes constitute the sole physically realistic mechanism that agrees on the whole with the available experimental findings.

11. Conclusions

The concrete behavior of frequency and amplitude spectra depends on a variety of factors even in the framework of a relatively simple interference mechanism. In the general case, the following factors are most likely to be involved:

— non-linearity of transformations of the signal of a primary MF target in a sequence of biophysical and biochemical processes;

— unique response of each molecular target in the concrete magnetic environment;

— operation of several magnetoreception mechanisms in one biological system;

— dependence on the initial conditions in a macromolecule cavity that are in turn determined by protein conformation; hence, temperature and pressure dependence of the particle's behavior.

Other factors influencing conformation and metabolism include intraspecific genetic variations, concentrations of different substances and MF targets.

The great diversity of factors and their intricate interactions make observation of MBEs that are in good agreement with theoretical predictions a matter of experimental luck and enlightening disclosure. Hence, the importance of the search for experimental models refractory to factors other than MF. Such biological systems, if any, would provide a deeper insight into the physical nature of MBE.

Another conclusion from the above discussion is that the majority of the available experimental models of MBE are unsuitable for the elucidation of the physical nature of this phenomenon. It goes without saying that theoretical models are of equally little help in this respect. The task of a theoretical model is to provide an adequate explanation of the nature of a concrete MBE mechanism. In the light of the principles outlined earlier in this review, the correct explanation is such that agrees with the results of a limited number of specially designed experiments provided the model itself is physically non-contradictory.

Today, it may be argued that major MBE characteristics have been reliably established in numerous experiments and convincingly reproduced in different models under a variety of magnetic conditions. These characteristics include

— multipeak spectra of MBE frequency and amplitude;

— biological efficiency of magnetic vacuum;

— commensurability of effective frequencies with harmonics and subharmonics of cyclotron and sometimes NMR frequencies of different ions;

— paradoxically small energy of magnetic fields that induce biochemical and physiological responses.

The theory of ion-molecular interference makes it possible to explain these general features of magnetobiological reception. The explanation proceeds from the observation that MBE involves angular quantum states of atom-ions and rotational states of molecules exposed to MF. Such states are de Broglie waves in the angular coordinate space at microscopic scales that interfere with each other giving rise to slowly rotating nodes and clusters of density probability. The refractoriness of the interference fringe pattern to thermal fluctuations of the medium can be accounted for by peculiarities of their interaction with angular and rotational states. The theory of ion-molecular interference provides a few general formulas of the 'field – effect' type and the possibility of their experimental verification. Magnetic conditions calculated by these formulas for a number of known experiments turned out to be in excellent agreement with the observed values.

It is more or less clear why relatively strong MF, unlike weak ones, rarely produce manifest biological effects. The fact is MF have practically no effect on particles. Large amplitudes of MF are responsible for high phase shift frequencies that may be orders of magnitude different from natural frequencies of ions and molecules in the geomagnetic field. Hence, they fail to impart a new quality to biological systems. Glaser, Michalsky, and Schramek [139] carried out a detailed study of EMF action on the calcium pump located in membranes of human erythrocytes. No distinct biological effects were documented in low-frequency MP in excess of 1 mT. Evidently, such MF are not involved in interference events considered in the present review.

Naturally, a great variety of the available data can hardly be explained taking into consideration a single mechanism or a group of similar mechanisms. It may be hypothesized that principles of magnetoreception in biological objects differ in different MF ranges. For example, the most likely mechanisms in relatively strong MF (from 1 mT up) are those that utilize magnetosensitive reactions of free radicals. It should be noted that this inference remains to be confirmed in experiments specially designed for the purpose.

To conclude, the following physical problems of magnetobiology await clarification:

— identification of ion-molecular targets of MF in readily reproducible MBE;

— mechanisms of biological action of moderate constant MF;

— mechanisms of refractoriness of ion interference to thermal perturbations of the medium;

— mechanisms of biological action of hyperweak (less than 1 μT) MF:

— directed EMF action on distinguished physiological/biochemical subsystems;

— mechanisms of delivery of complex MF to local sites in biological systems;

— general methods for the correction of immune processes by low-frequency magnetic fields;

— development of methods for the protection from harmful action of EM radiation by destroying possible interference effects;

— mechanisms of MF action on intercellular, population, interspecfic, and other interactions and their utilization for population management.

The developing science of magnetobiology encounters a number of objective difficulties rooted in the poor state of its theoretical basis. Parallel development of theory and experiment is badly needed.

Academic interest in magnetobiological problems is hampered by the absence of a clear physical explanation of the observed phenomena. For this reason, magnetobiological studies are currently supported by interested commercial companies manufacturing equipment and devices that make use of electromagnetic radiation. Such companies strive to demonstrate the safety of their production, such as cellular telephones and common electrical appliances or, conversely

the high clinical efficiency of biomedical electromagnetic technologies. In either case, orders from these customers limit the extent of studies to rather a narrow range of electromagnetic regimes. A leading scientific journal *Bioelectromagnetics* publishes numerous papers on biological effects of EMF restricted to industrial frequencies (50 and 60 Hz) and some gigahertz frequency ranges employed in mobile communication systems. It is clear that neither the objectives of these studies nor frequency-amplitude limitations imposed upon them can effectively promote investigations into the physical nature of MBE.

The authors hope that this publication will prove helpful and give a new impetus to magnetobiological research.

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