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Stochastic dynamics of magnetosomes in cytoskeleton

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Abstract. – Considered are the rotations of nanoscopic magnetic particles, magnetosomes, embedded in the cytoskeleton and subjected to the influence of an ac magnetic field and thermal noise. The rotations are studied within a double-well potential formed by mechanical and magnetic forces. It is shown that the motion of the magnetosomes meets the conditions of the so-called "stochastic resonance" under not-too-tight constraints on the elasticity of the cytoskeleton medium. The excursion of regular rotations reaches the value of 2 rad that facilitates explaining the biological effects of low-frequency weak magnetic fields and geomagnetic fluctuations. Slow magnetic-field variations on the order of 200 nT control the rotations effectively.

There are many hypothetical mechanisms suggested to explain the biological effects of weak low-frequency magnetic fields. The detailed discussion of the mechanisms may be found in [1] and a brief review in [2,3]. At the same time, the physical nature of these effects remains unclear. The basic problem is that the interaction energy of biologically active molecules and earth-strength magnetic fields (MFs) is very small [4]. It is much smaller than the energy of thermal fluctuations $\kappa T \approx 4 \times 10^{-14}$ erg at physiological temperatures.

However, it is well known that many organisms contain submicron magnetic particles [5]. In a weak magnetic field H, the energy of their turn is substantially greater than κT. For single-domain magnetite particles of radius $r = 10^{-5}$ cm or 100 nm in the geomagnetic field the energy μH equals approximately $24\kappa T$, where $\mu \approx vJ$ is the magnetic moment of the particle, v and $J = 480$ G are the volume and the saturation magnetization.

The cytoplasm near cell membranes has such visco-elastic properties that the turning of a nanoparticle may serve as a stimulus to cell division or ignite a nerve impulse [6]. Magnetite particles found in the brain tissues of animals and humans [5, 7] are of particular interest: based on this fact, a possible mechanism of the effect of weak MFs on the human organism has been proposed [8,9]. The nerve tissue of the brain is separated from the circulatory system

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by the blood-brain barrier impermeable to most chemicals. In turn, the circulatory system is separated from the digestive system. Therefore, relatively large ferro- or ferrimagnetic particles cannot penetrate into brain tissue as a pollutant. They are found to have a biogenic origin, *i.e.* they appear over time as a direct result of the crystallization in brain matter. The particles of biogenic magnetite are often called "magnetosomes"; they were first discovered in bacteria that displayed magnetotaxis [10].

The density of magnetosomes in the human brain is more than 5×10^6, and in meninges more than 10^8 crystals per gram [7]. In fact, about 90% of the particles measured in this work were 10–70 nm in size, and 10% were 90–200 nm. Subsequent studies have shown that the concentration of magnetite/maghemite in the human brain varies from tens to hundreds ng/g and equals about 50 ng/g on average [11]. Magnetite levels may be even higher when considering superparamagnetic particles, diseased tissue and age [12, 13].

Given the fact that the magnetic moment is in direct proportion to the particle's volume, it is easily seen that the inequality $\mu H_{\rm geo} < \kappa T$ is approximately true for particles less than 30 nm in size, at physiological temperatures. Due to thermal disturbances, such particles can spontaneously switch their magnetic flux without rotation, *i.e.* they are in a superparamagnetic state. Then, considering 100 nm particles in the model below, we may safely neglect superparamagnetic switching. The particles that are several hundred nm and more in size go to multiple-domain states (the energy of magnetic domain walls is less than that of the MF produced by a single-domain state). In earth-strength magnetic fields, these particles experience almost no torque per unit mass and barely contribute to the magnetic effect described below. In this article we consider the dynamics of an idealized particle, the magnetosome with the radius $r \sim 100$ nm in a single-domain state.

The energy of the magnetosome in the geomagnetic field $H_{\rm geo}$ is $\approx 24\kappa T$; when exposed to an additional variable magnetic field h, its regular changes are about $(h/H_{\rm geo})24\kappa T$. If these changes exceed thermal fluctuations $\sim \kappa T/2$, they can cause a biological response. The equation $(h/H_{\rm geo})24\kappa T \sim \kappa T/2$ sets a natural constraint on the MF magnitude capable of affecting a biophysical or biochemical system appreciably: $h \gtrsim H_{\rm geo}/48 \sim 1$–$2\,\mu$T. However, in the special case of magnetosomes bound to a visco-elastic medium so that they rotate in a double-well angular potential, the biologically detectable level of the MF may be less. In this case, the thermal fluctuations contribute to the capability of a weak magnetic stimulus to cause a response.

Oscillations of a protein macromolecule (dipole resonator) in a microwave EMF have been studied in [14]. Theoretical evaluations of the magnetoreception mechanism based on magnetosome rotations in MF have been worked out by many authors since the 1970s [15].

A model, named "ferromagnetic transduction model", has been proposed in [6, 8]. The model describes the interaction of a single-domain magnetosome with mechanically activated transmembrane ion channels. It was suggested that magnetic ELF biological effects arise from membrane deformations produced by magnetosome-induced cytoskeletal tension. Using the known mechanical properties of mechanically sensitive ion channels, the authors calculated that to open the gate with a spherical magnetosome of radius 100 nm, it has to rotate through an angle of about 16°. Based on this, it was shown that 60 Hz fields on the order of 0.1 mT are capable of changing the probability of open/closed state on the background of κT-level thermal disturbances. As was shown in [9], the ferromagnetic transduction model might be used to explain not only effects of power frequency magnetic fields but also some biological effects of dc and pulsed fields.

In known works, the dynamics of magnetosomes was modelled by using the linear differential equation of *free rotations* in a viscous liquid, since the elastic properties of structures to which magnetosomes may be attached were not assessed. Quasi-elastic torque had been considered only in relation to the magnetic moment energy in the constant geomagnetic field.

It turns out that explicitly taking into account the elasticity of the medium enables one to describe a nonlinear stochastic rotational motion of magnetosomes. It may be used to explain the peculiarities of magnetoreception of weak and hyperweak MFs. The nonlinear dynamics of oscillating magnetic particles in the ELF MFs has not been studied in detail yet.

This article considers the dynamics of a magnetite particle embedded in the cytoskeleton. The latter consists of a 3D net of protein fibers (actin filaments, intermediate filaments, and microtubules) of 6 to 25 nm in diameter. The ends of these fibers may be attached to the membrane surface and to various cell organelles. In [6] the fibers were assumed to be attached also to a magnetosome surface. The fibers fix the position of the magnetosome and constrain its rotation to some extent. Unlike [6], where the magnetosome's magnetic moment followed the direction of the MF, we consider the other case when the fibers prevent the magnetosome from orienting along the MF. In this case, on average with time, the vectors of the magnetic moment and the MF are oppositely directed and the stationary orientation of the magnetosome generally does not follow the constant MF direction. The balance of the elastic and magnetic torques determines the orientation now. The torque $\boldsymbol{m}$ affecting a particle with the magnetic moment $\boldsymbol{\mu}$ in an MF $\boldsymbol{H}$ equals $\boldsymbol{m} = \boldsymbol{\mu} \times \boldsymbol{H}$. Here, putting aside the 3D character of the magnetosome rotations, we consider the motion of a magnetosome in the plane of two vectors: the unit vector $\boldsymbol{n}$ of the x-axis, with which the vector of magnetosome's magnetic moment coincides in the absence of the MF (equilibrium position, $\varphi = 0$), and the MF vector $\boldsymbol{H}$. Then, the Langevin equation for rotational oscillations of the particle is as follows:

$$I\ddot{\varphi} + \gamma\dot{\varphi} + k\varphi = -\mu H(t)\sin(\varphi - \varphi_0) + \xi'(t), \qquad \omega_0 = \sqrt{k/I}\,, \tag{1}$$

where φ is the angular displacement, I is the moment of inertia of the particle, γ is the dissipation coefficient, k is the coefficient of mechanical elasticity resulting from the bending of the cytoskeleton fibers, $\xi'(t)$ is a stochastic torque with the correlation function $\langle \xi'(t)\xi'(t+\Delta t)\rangle = 2\gamma\kappa T\delta(\Delta t)$, while ω_0 is the eigenfrequency, and φ_0 is the MF direction. We assume the quantity of fibers fastening the magnetosome to the cytoskeleton may vary from particle to particle and a significant number of magnetosomes are mobile enough to markedly change their orientation in the geomagnetic field. This means that the mechanical elasticity due to the bending of the fibers is of the same order as or less than the magnetic elasticity $k \lesssim \mu H \approx 24\kappa T$. For magnetite Fe_3O_4 particles with the bulk density $\rho \approx 5.2\,\mathrm{g/cm^3}$ and radius $r \sim 10^{-5}\,\mathrm{cm}$, for which $I = 8\pi\rho r^5/15$, we derive a value ω_0 on the order of $10^6\,\mathrm{rad/s}$. A resonance, however, is not possible since the inertia forces are much less than viscous forces: $I\omega_0 \ll \gamma$. This follows from the relation $\gamma \sim 4\pi\eta r^3$ [16], in which the viscosity factor η is taken to be that of water $10^{-2}\,\mathrm{g\,cm^{-1}\,s^{-1}}$. Hereafter, the inertia term in the equation of motion may be ignored.

The idea of this work is to study the dynamics of a magnetosome predominantly oriented in a direction opposite to that of a constant MF: $\varphi_0 = \pi$. The potential energy of a magnetosome in terms of μH in the absence of ac MF,

$$U = \cos(\varphi) + \frac{a}{2}\varphi^2, \qquad a = \frac{k}{\mu H}\,,$$

is shown in fig. 1. As is seen, for not too large angles at $a < 1$ there are two stable equilibrium positions $\varphi = \varphi_\pm$ and the unstable one $\varphi = 0$. Within each of the wells of this double-well potential, the motion of the magnetosome demonstrates no peculiarities. This sort of motion has been repeatedly considered in the literature. At the same time, due to thermal disturbances, the transitions appear from well to well even with no ac MF signal. Given that, the stochastic rotation of the particle takes place with considerable angular displacements. A deterministic

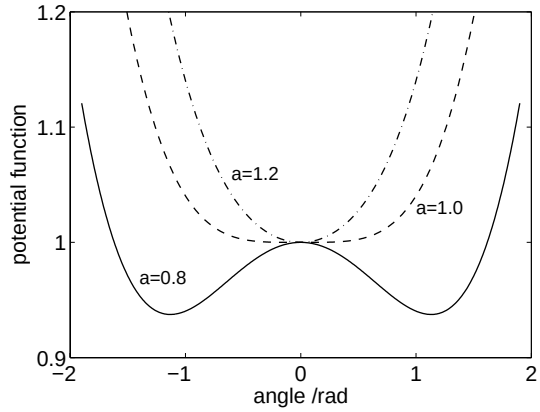

Fig. 1 – Potential function of a magnetosome at different values of the elastic parameter a.

external force, the ac MF in our case, causes such transitions to be somewhat ordered, the maximum order being at the optimal level of the noise. It is essentially the phenomenon of the so-called stochastic resonance (SR) first introduced in [17] to explain some geophysical processes.

So far, the probable manifestation of the SR in the dynamics of magnetosomes has not been investigated. Consider the joint influence of a magnetic signal $h\sin(\Omega t)$ and a random torque $\xi'(t)$ on a magnetosome. The equation of motion takes the form $\gamma\dot{\varphi} - \mu H\sin(\varphi) + k\varphi - \mu h\sin(\Omega t) = \xi'(t)$. With the designations

$$h' \equiv \frac{h}{H}\,, \qquad \beta \equiv \frac{\gamma\Omega}{\mu H}\,, \qquad \tau \equiv \frac{\mu H}{\gamma}t\,, \qquad D \equiv \frac{2\kappa T}{\mu H} \tag{2}$$

the equation is reduced to

$$\dot{\varphi} + \partial_\varphi U(\varphi,\tau) = \sqrt{D}\xi(\tau), \tag{3}$$

$$U(\varphi,\tau) = \cos(\varphi) + \frac{a}{2}\varphi^2 - \varphi h'\sin(\beta\tau). \tag{4}$$

Here $U(\varphi,\tau)$ is the potential in the combined ac/dc MF, $\xi(\tau)$ is the centered Gaussian process of unit variance (the identity $\delta(\alpha t) = \delta(t)/|\alpha|$ is used).

Several SR theories are known; we use the results of [18], where the general expression has been derived for the power spectrum of the oscillations of a bistable system agitated by regular and random signals. The signal-to-noise ratio is determined as the ratio of the spectrum amplitude at the frequency of the regular signal, to the level of noise at the same frequency. For the system (3) with a general double-well potential the signal-to-noise ratio equals

$$R_{\rm sn} = \sqrt{|U''(0)|U''(\varphi_\pm)}\,\frac{U_1^2}{D^2}\exp\left[-2U_0/D\right], \tag{5}$$

where U_0 and U_1 are the height and modulation amplitude of the potential barrier, and U'' is the curvature of the potential at the respective equilibrium points. The function (5) attains its maximum at the optimal level of noise $D = U_0$. This means there is an interval in the value of D, where the signal-to-noise ratio unexpectedly increases along with increasing noise power: it is the signature of SR.

Quantities U_0 and others of the potential (4) have no exact analytical presentations. Here we derive them as series expansions over the parameter $1 - a$ that is assumed to be a small

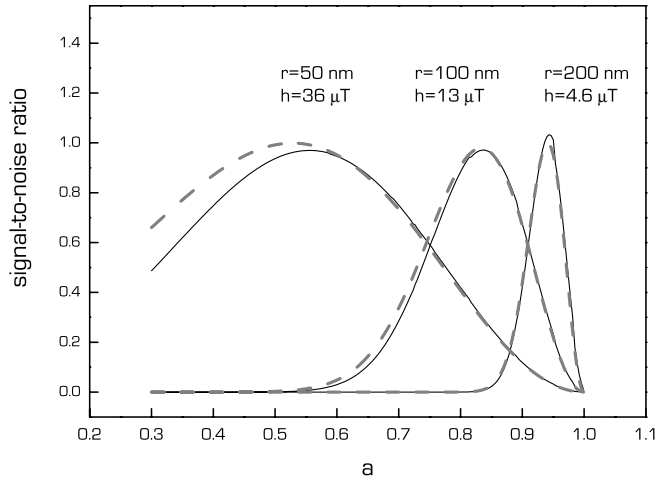

Fig. 2 – Signal-to-noise ratio $R_{\rm sn}$ in rotations of the magnetosomes of different radii and at different amplitudes of the ac MF; solid lines: numerical calculation of eqs. (5), (4); dashed lines: eq. (6).

parameter:

$$\varphi_+^2 = 6(1-a), \quad U_0 = \frac{3}{2}(1-a)^2, \quad U_1^2 = 6h'^2(1-a), \quad U''(0) = a-1, \quad U''(\varphi_+) = 2(1-a).$$

Substitution into (5) leads to the following expression for the signal-to-noise ratio:

$$R_{\rm sn} \approx \frac{6\sqrt{2}\,h'^2(1-a)^2}{D^2} \exp\left[-3(1-a)^2/D\right]. \tag{6}$$

This function is plotted in fig. 2 at various values of the ac MF $h' = h/H$ and noise parameter $D = 2\kappa T/\mu H = 3\kappa T/2\pi r^3 JH$, which depends on the size r of the magnetosome.

As is seen, there is a marked interval of the elasticity parameter $a = k/\mu H$, wherein the signal-to-noise ratio is close to unity. The 100 nm magnetosome fixed in the cytoskeleton with elasticity $a = 0.7$–$0.9\,\mu$H in the $13\,\mu$T ac MF and $46\,\mu$T geomagnetic field regularly turns at angles similar to those of the chaotic rotations. It is particularly evident for 50 nm particles; almost all of them are in the SR conditions. 200 nm particles make regular rotations at relatively small MFs $\approx 4.6\,\mu$T. Although in each of these cases there is no gain in the magnitude of the effective ac MF as compared to the case of a single-well motion, it is important that the rotation excursion is an order higher, about 2 rad. With such excursions it is easier to account for the influence of the rotations on biochemical processes.

In this regard, we note that proper MF $H \sim \mu/x^3$ produced by a 100 nm magnetosome is rather intense: it varies from about 200 mT on the magnetosome's surface to 0.2 mT at the distance $x \sim 10^{-4}$ cm. So, in a cell, metabolic reactions proceed in the mT-level MFs that are many times greater than the geomagnetic one, provided the cell contains a magnetosome. Such MFs can appreciably affect the rate of free-radical reactions [19].

Note that with a SR, the signal-to-noise ratio is enhanced because of the reduced coherence of the signal present in the spectrum of magnetosome oscillations as compared to the coherence of the ac MF signal. Therefore, the detection of a MF signal requires a discrimination system, probably a nonlinear system of biochemical reactions with the characteristic time $\sim 1/\Omega$ —which can "make a decision" as to whether a signal is present in the noise.

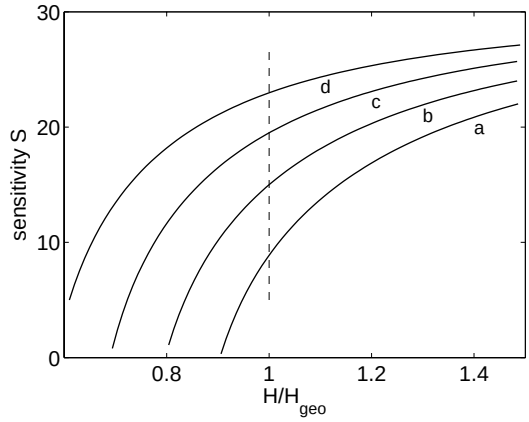

Fig. 3 – Sensitivity of the transition probability to MF variations: $k/\mu H_{\rm geo} = 0.8$ (a), 0.7 (b), 0.6 (c), 0.5 (d).

The proposed primary mechanism of magnetobiological effects displays no frequency selectivity in the ELF range. Nonetheless, it allows one to verify it experimentally. Since the parameter $a = k/\mu H$ depends on the constant MF, the "resonance" on fig. 2 will show itself also as a "window" in the values of the constant MF when the effect is possible. Therefore, provided the MF signal transduction to the biochemical level is governed by a SR with magnetosomes of a certain size within limits of about 10–20%, it follows that the biological effect in the ac MF will take place only in a constant MF near the level $H \sim k/a\mu$. Indeed, when the MF decreases, the potential function transforms into a single-well one, and large rotational excursions are no longer possible. When the MF increases, the potential barrier grows and the magnetosome finally remains within one of the two wells. This case also rules out SR manifestation.

Apparently, for a portion of magnetosomes, large angular chaotic rotation takes place in the absence of an ac MF also. If some biochemical reaction depends on this rotation, it is evident that it must be sensitive to the condition of a "magnetic vacuum" $h \ll H \ll H_{\rm geo}$. Furthermore, the reaction must be sensitive to small variations of the constant MF, since the probability of transition W from well to well *exponentially* depends on the barrier height U_0. W is derived, for example, in [18]; it may be reduced to the approximate expression:

$$W = \frac{1}{2\pi}\sqrt{|U''(0)|U''(\varphi_\pm)}\exp\left[-2U_0/D\right] \approx \frac{\pi\sqrt{2}}{1-a}\exp\left[\frac{3(1-a)^2}{D}\right].$$

W is a function of the variables $a = k/\mu H$ and $D = 2\kappa T/\mu H$, and hence of H. The relative value of the changes in this probability at small variations of the constant MF, *i.e.*, the quantity

$$S = -\frac{1}{W}\frac{{\rm d}W}{{\rm d}(H/H_{\rm geo})}$$

is of interest. Since the probability drops with the growth of the barrier height, we use the minus sign to retain positive values for the sensitivity S. Shown in fig. 3 is the sensitivity S computed at several values of the elasticity of the bond between a magnetosome and cytoskeleton. It is seen that the sensitivity of the relative changes in the probability to MF variations near $H_{\rm geo}$ is equal to 10–20, in a wide range of the elasticity values. This means a 1% change in the MF causes 10–20% changes in the transition probability. Assuming 10%

changes to be biologically significant, we arrive at the limit of detectable values of the constant MF variations $\sim 0.005 H_{\rm geo}$ or $0.2\,\mu$T. This finding generally does not rule out the possibility of a biological system containing magnetosomes reacting to slow geomagnetic fluctuations.

The evaluation of the sensitivity is valid for the MF variations slow enough to provide the statistical equilibrium. The timescale of the variations should be larger than $1/W$. The solution of this inequality shows suitable range of elasticities that is wide enough to provide the equilibrium: $a \gtrsim 0.48$ for the usual frequencies of geomagnetic fluctuations $f \leq 0.01$ Hz.

Conclusions. – The proposed mechanism differs from the ferromagnetic transduction model [6] in the following ways: the mechanism I) is based on "double-well" non-linear dynamics and the SR phenomenon that makes thermal noise to contribute to MF perception; II) does not involve membrane channels; instead, the rate of intracellular free-radical biochemical reactions is assumed to be altered by changes in the mT-range magnetosome's MF; III) provides 10-fold better sensitivity to ac MFs, about $10\,\mu$T, than that derived in [6]; and IV) demonstrates, for the first time, the sensitivity to slow MF variations as small as of 200 nT per unit magnetosome.

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