

APPLICATION OF THE PHENOMENON OF RESONANCE OF A RADIO- FREQUENCY FIELD WITH FLUCTUATION-ROTATIONAL MOTION IN MAGNETIC HYPERTHERMIA

A. Ugulava, G. Mchedlishvili , O. Kharshiladze

I. Javakhishvili Tbilisi State University, Georgia, Tbilisi, 0179, I. Chavchavadze Ave. 3.

Abstract

A characteristic feature of most magnetic materials is that they have a hysteresis cycle. The energy of an alternating magnetic field, supplied to the nanoparticles during repeated passage of the hysteresis cycle by the magnetic field, is converted into heat in the environment. This is the usual mechanism of heating a malignant tumor in hyperthermia. In this paper, we consider the possibility of heating a part of the body under the resonant action of a radio-frequency field, where the resonant frequency is due to the flow of root-mean-square fluctuations of angular variables (rotational diffusion) that is cyclic motion. This method of heating the tumor area is different from those commonly used in magnetic hyperthermia. It is shown that by a selection of the parameters of the resonant field, it is possible to achieve an increase in tumor temperature by 6 degrees (sufficient for the destruction of malignant cells) in 27 minutes.

Key words: magnetic hyperthermia, nanoparticles, fluctuation-dissipation theory.

Corresponding author: Giorgi Mchedlishvili, email: mchedluka@yahoo.com

1. Introduction

Magnetic fluids are attracting attention in various branches of biomedicine and particularly in hyperthermia. Magnetic hyperthermia is a progressive method of cancer treatment [1-13]. The essence of this method is that magnetic particles of nanometer sizes (nanoparticles) coated with special bioactive layers are injected into the area where cancer cells are diagnosed. Thanks to the coatings, nanoparticles are captured by these cells. Then the tumor area is placed in an alternating magnetic field, in which the nanoparticles are heated and warm the tumor cells that have captured them. If the cell temperature exceeds 42°C , diseased cells die. Healthy cells at this temperature remain intact. Magnetic nanoparticles in this role in hyperthermia were first used by Gilchrist et al. [4] (Gilchrist *at all*), which has led to the development of a variety of cancer treatments using the nanoparticles mentioned above.

Magnetic nanoparticles, being inside the tumor as part of a suspension, create conditions for the absorption of the energy of an alternating magnetic field. A characteristic feature of most magnetic materials is that they have a hysteresis cycle. The energy of an alternating magnetic field, supplied to nanoparticles during repeated passage of the hysteresis loop, is converted into heat in the environment. This is the mechanism of tumor heating in hyperthermia.

In this work, to heat the tumor, it is proposed to use a different, in particular, resonant, method of exposing a system of nanoparticles to an alternating field. The root-mean-square fluctuation of the angular variables, due to their cyclic nature of change, at large times becomes a periodic function of the frequency proportional to the rate of Brownian relaxation. It is assumed that

the radio frequency field is in resonance with this frequency. The absorbed power of the radio frequency field converted into heat is calculated using the fluctuation-dissipation theorem.

2. Anisotropy energy of nanoparticles.

In ferromagnetic crystals, there are interactions that can orient the magnetization vector along the directions of the crystallographic axes. These axes are called the easy axes, and the energy associated with these interactions is called the magnetic anisotropy energy. For example, cobalt may have a hexagonal crystallographic structure. The cobalt hexagonal axis is the easy magnetization axis (uniaxial crystal). In this case, the magnetic anisotropy energy density is presented in the form [14]

$$U_A = K_1^* \sin^2 \zeta + K_2^* \sin^4 \zeta \quad (1)$$

where $\zeta = \psi - \theta$ is the angle between the magnetization vector and the easy magnetization axis (Fig.1). At room temperature - $K_1^* = 4,1 \cdot 10^5 \text{ J/m}^3$, $K_2^* = 1,0 \cdot 10^5 \text{ J/m}^3$.

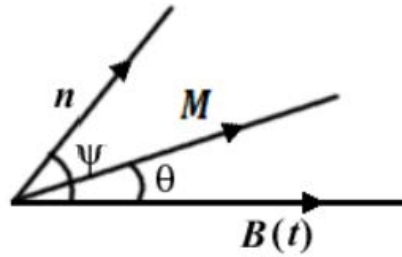


Fig.1. Directions of magnetic field vector $B(t)$, saturation magnetization M , and anisotropy axis n for uniaxial crystal.

Iron, unlike cobalt, is a cubic crystal. The easy magnetization axes of iron coincide with the edges of the cube. The energy density of the magnetic anisotropy of an iron crystal at an arbitrary value of the magnetization vector M_s (saturation magnetization) is usually expressed using direction cosines $-q_x, q_y, q_z$ (Fig .2) satisfying the condition $q_x^2 + q_y^2 + q_z^2 = 1$. In this case, the anisotropy energy density has the form [14]

$$U_A^{Fe} = K_1(q_x^2 q_y^2 + q_x^2 q_z^2 + q_y^2 q_z^2) + K_2 q_x^2 q_y^2 q_z^2, \quad (2)$$

where $q_i = \cos \alpha_i = \frac{M_s^i}{|M_s|}$, ($i = x, y, z$) are direction cosines, $K_1 = 4,2 \cdot 10^4 \text{ J/m}^3$, $K_2 = 1,5 \cdot 10^4 \text{ J/m}^3$ are the anisotropy density coefficients.

The magnetic moment of the nanoparticle is $\mu = M_s V_m \text{ A} \cdot \text{m}^2$, where V_m is the “magnetic” volume of the nanoparticle. As we can see, the anisotropy energy density of iron is an order of magnitude less than that of cobalt ($K_{1,2} < K_{1,2}^*$) and therefore it is less efficient.

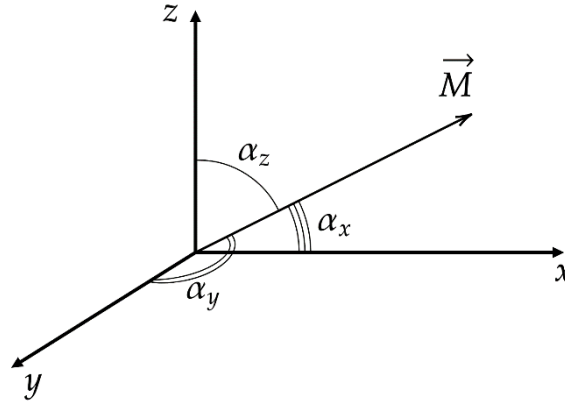


Fig.2. The orientation of the magnetization vector in space, expressed in terms of direction cosines.

As you know, iron is easily oxidized. One of the iron oxides is magnetite Fe_3O_4 , or, more precisely, $-FeO \cdot Fe_2O_3$ which is a ferrimagnet (ferrite). It has the cubic crystallographic structure of the spinel mineral [14]. Magnetite is the only biologically compatible material that is used in hyperthermia [15, 16]. The value of saturation magnetization of magnetite $M_s = 4,8 \cdot 10^5 \text{ A/m}$ is much less than for iron.

As follows from the expressions for the anisotropy energies (2), the directions of the anisotropy axes correspond to the energy minima. There is one minimum for cobalt, and three for iron and magnetite. It is obvious that the same axes determine the equilibrium directions of the magnetic moment of nanoparticles (the magnetization vector). A sufficiently strong thermal motion can disturb the equilibrium state, pushing the magnetization out of the equilibrium state. Formula of the characteristic time τ_r of thermal motions of the magnetic moment of uniaxial nanoparticles (the time spent to overcome the energy barrier ΔE (Fig.3)) was derived by Neel in the form

$$\tau_r = \tau_T \exp (\Delta E / kT), \quad \Delta E \geq KV_m. \quad (3)$$

The coefficient τ_T in front of the exponent in formula (3) depends on many parameters - temperature, saturation magnetization, energy barrier value, etc. However, for simplicity τ_T is often assumed to be a constant quantity having the value in the interval $10^{-9} \div 10^{-13} \text{ s}$. Here we will try to obtain a criterion for overcoming the barrier for cubic crystals using an approach similar to that developed by Néel. In the case of cubic crystals, on the path of rotation of the magnetization vector (Fig. 2), directions of "attraction" appear along three mutually perpendicular directions of the anisotropy axes in the form of two wells and a barrier between them (Fig. 3). Expressions similar to (3) for the times of overcoming the barriers by thermal fluctuations for these three directions will naturally look the same. They determine the time τ_r the system of magnetite nanoparticles to be in equilibrium state (free rotation). At sufficiently high temperatures, the time taken to overcome the barrier τ_r becomes less than the time Δt of the experiment $\tau_r \ll \Delta t$, the magnetization will be able to freely move from one well to another (Fig. 3) and the system comes into a super-paramagnetic state. In the opposite limiting case $\tau_r \gg \Delta t$, the magnetization vector will not have time to overcome the barrier and will remain blocked in the well. Note that the role of the time of the experiment in hyperthermia is played by the duration of the treatment procedure.

In Neel's theory, the condition $\tau_r = \Delta t$ determines the blocking temperature T_b , below which the magnetization is in the blocked state of the anisotropy energy well, and above which it is in the super-paramagnetic state. In hyperthermia, temperature is not the same control parameter at the disposal of the researcher (the attending physician) as it is in physical experiments. Therefore, the blocking process will be considered similarly, according to the same condition $\Delta t = \tau_r$, but not in terms of temperature, but in terms of the volume of the nanoparticle.

And so, we write an equation for determining the value of the critical volume V_c - an analogue of the blocking temperature T_b . Suppose that $T = 310^0$ and $\tau_T = 10^{-9}$ s, then from relation (3) we easily obtain an equation for determining the value V_c -

$$\Delta t = 10^{-9} \exp(1,1 \cdot 10^{25} V_c) . \quad (4)$$

If we further assume that $\Delta t = 600$ s, then from (4) we get

$$V_c \approx 2,6 \cdot 10^{-24} m^3 \quad (d_c = 16 nm). \quad (5)$$

Note that the maximum single-domain size of magnetite nanoparticles [17] is $d_{max} = 128 nm$.

Let us consider two limiting cases: 1) case of large volumes of nanoparticles $V \gg V_c$ and 2) case of small ones - $V \ll V_c$. In case 1) the magnetization, blocked along one of the directions of the anisotropy axes, performs Brownian motion together with the nanoparticle, and in case 2) it rotates freely, regardless of the nanoparticle that performs Brownian motion (both translational and rotational). In case 1) nanoparticles come in motion under the influence of an alternating field, as well as random collisions of liquid molecules. In case 2), the external alternating field is unable to influence the rotational fluctuation of particles in a liquid, and therefore below we will consider only case 1).

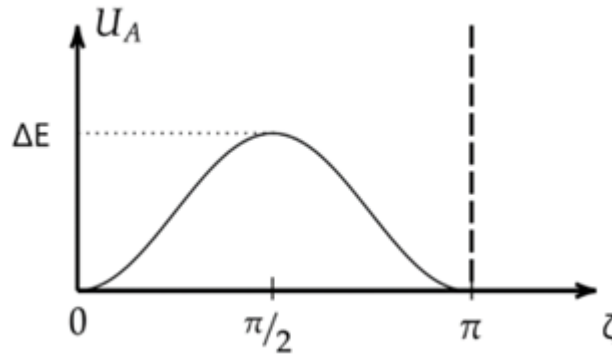


Fig.3. Anisotropy energy of a uniaxial nanoparticle as a function of the angle ζ

3. Equations of rotational motion of magnetic suspension nanoparticles

The dynamics of magnetic nanoparticles, as is known, is described by two angular variables θ and ψ (Fig.1). However, in 1) case of nanoparticles with a volume greater than the critical one $V \gg V_c$, when the magnetization rests on the bottom of one of the wells, the value $\psi - \theta$ is conserved during motion, and the motion of the magnetization can be described by one angular variable θ .

The equations of motion of the angular variable θ of the suspension nanoparticle is:

$$\ddot{\theta} + \frac{2}{\tau_s} \dot{\theta} + \frac{\mu B(t) \cos \theta}{I} = \frac{N(t)}{I}, \quad (6)$$

where

$$B(t) = b e^{-\gamma|t|} \cos \omega t$$

is the magnetic induction of the alternating field, b - amplitude, ω - frequency, γ - frequency broadening of the field.

The direct solution of equation (6), due to the presence of random functions in them, is not possible. We study this equation, which contains a random force on the right side, using the Langevin method [18]. We multiply both parts of this equation by a variable θ and after simple mathematical transformations, we average the resulting equation over time τ_c according to the rule

$$\overline{L(t)} = \frac{1}{t} \int_0^t L(x) dx, \quad t \gg \tau_c,$$

where as usual $\tau_c \approx 10^{-13}$ s. Then, using the law of equipartition of energy over degrees of freedom $\frac{I}{2} \overline{\dot{\theta}^2} = \frac{kT}{2}$ and the correlation properties of the random function

$$\overline{\theta N(\theta)} = \bar{\theta} \cdot \overline{N(\theta)} = 0, \quad \overline{N(\theta)} = 0, \quad (7)$$

we get the following equation of the rms fluctuation $\overline{\theta^2}$

$$\ddot{\overline{\theta^2}} + \frac{2}{\tau_s} \dot{\overline{\theta^2}} + \frac{2\mu b}{I} \cdot \overline{\theta \cos \theta} \cdot e^{-\gamma t} \cos \omega t = \frac{2kT}{I}. \quad (8)$$

Note that here we have introduced a new, "good" variable - $\overline{\theta^2}$, which at this and subsequent stages of system dynamics will play the role of a dynamic variable. As can be seen from equation (8), the equation of fluctuations is similar to the equation of motion of some imaginary particle under the influence of a force that depends on an alternating field and temperature - the fluctuation moves like a particle. However, due to the last term on the left side of the equation, it is not a closed equation with respect to $\overline{\theta^2}$ and is an integral-differential equation of the complex form.

Since the moment of inertia is a small quantity, the inertial term can be neglected in the last equation ($\ddot{\overline{\theta^2}} \rightarrow 0$). Then from eq. (8) we get

$$\dot{\overline{\theta^2}} = \frac{1}{\tau_B} (1 - \varepsilon \cdot \overline{\theta \cos \theta} \cdot e^{-\gamma t} \cos \omega t), \quad (9)$$

where $\frac{1}{\tau_B} = \frac{kT}{3V\eta}$ is the rate of Brownian relaxation (rotational diffusion), $\varepsilon = \frac{\mu b}{kT}$ is a small interaction parameter.

Consider case 1) $V > V_m > V_c$, when the magnetization moves along with the nanoparticle. Suppose $V_m = 10^{-23} \text{ m}^3$, $V = 2 \cdot 10^{-23}$ and $b = 2 \cdot 10^{-4} \text{ Tesla}$. Then for the rate of Brownian relaxation we obtain $\frac{1}{\tau_B} = 0,2 \cdot 10^5 \text{ s}^{-1}$, and a small parameter $\varepsilon = 0,2$.

The solution of equation (9) can be presented as a series in powers of ε

$$\overline{\theta^2} \approx [\overline{\theta^2}]^{(0)} + \varepsilon [\overline{\theta^2}]^{(1)} + \dots, \quad (10)$$

where $[\overline{\theta^2}]^{(0)}$ is the zero order solution and $[\overline{\theta^2}]^{(1)}$ is the first order correction, which are solutions of the following equations:

$$\frac{d[\overline{\theta^2}]^{(0)}}{dt} = \frac{1}{\tau_B} \quad (11)$$

$$\frac{d[\overline{\theta^2}]^{(1)}}{dt} = -\frac{1}{\tau_B} \overline{\theta \cos \theta}^{(0)} e^{-\gamma t} \cos \omega t. \quad (12)$$

Here, the dash above the terms with index (0) means averaging over the unperturbed motion.

Solution of equation (11) - $[\overline{\theta^2}]^{(0)} = \frac{t}{\tau_B} = \frac{kT}{3V\eta} t$ is a rotational analogue of the well-known Einstein formula for Brownian translational motion ($\overline{x^2} = \frac{kT}{3\pi r\eta} t$, where r is the radius of the particle). As you can see, at short times $\frac{t}{\tau_B} \ll 1$ they do not qualitatively differ from each other. However, since the variable θ , in contrast to the coordinate x , is a cyclic variable, the "thermodynamic" variable $[\overline{\theta^2}]^{(0)}$ must also satisfy a similar condition of cyclicity (periodicity). This, in turn, at large times $\frac{t}{\tau_B} \gg 1$ leads to a qualitative difference between these two types of Brownian motion.

The fluctuation of the square of the angle θ is a periodic function

$$[\overline{\theta^2}]^{(0)}(t + \tau_0) = [\overline{\theta^2}]^{(0)}(t) \quad (13)$$

where τ_0 is the period of the fluctuation. It is natural to assume that the fluctuation $\overline{\theta^2}$ follows the corresponding variable θ . Then, since the phase period of rotation θ (based on the form of the anisotropy energy function (1)) is π , the period of fluctuation $\overline{\theta^2}$ will also be equal π (Fig. 3). During the time τ_0 the value of the fluctuation will reach its maximum value, $[\overline{\theta^2}]^{(0)}(\tau_0) = \pi^2$, and the role of the period of movement is played by $\tau_0 = \pi \tau_B$.

It follows from all the abovesaid that at large times $t \gg \tau_0$, the flow of fluctuations, which initially has a chaotic character, acquires the character of a regular (periodic) movement - order emerges from chaos. The energy expended to maintain this motion is taken from the base fluid by means of a random force $N(t)$.

Taking into account the periodicity condition (13), the solution of the first of equations (11), can be written as a function

$$[\overline{\theta^2}]^{(0)}(t) = \pi^2 |t/\tau_0 - n|, \quad (14)$$

$$n\pi \leq t/\tau_0 < (n+1)\pi, \quad n = 0, \pm 1, \pm 2, \dots,$$

the graph of which has a "sawtooth" shape (Fig.4).

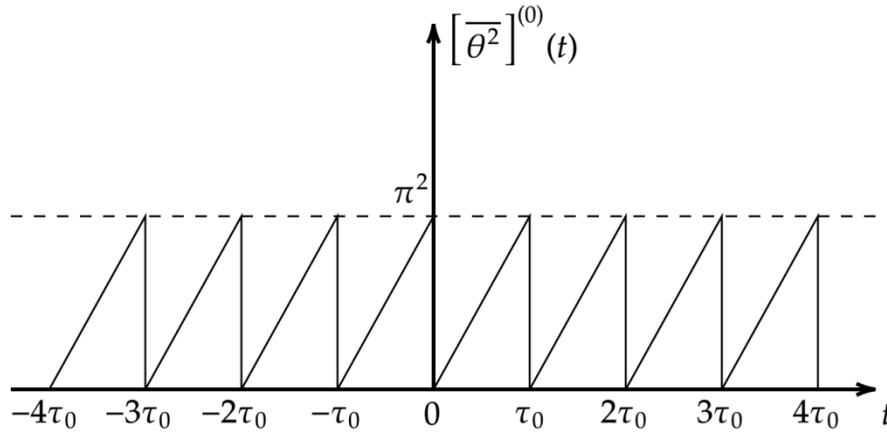


Fig.4. Fluctuation $[\theta^2]^{(0)}(t)$ - function of time t .

Expanding the “sawtooth” function (14) into a Fourier series [19], we can determine the spectral composition of fluctuations of the periodic motion of the magnetic moment

$$[\theta^2]^{(0)}(t) = \pi^2 \left[\frac{1}{2} - \frac{1}{\pi} \left(\frac{\sin \omega_0 t}{1} + \frac{\sin 2\omega_0 t}{2} + \dots + \frac{\sin n\omega_0 t}{n} + \dots \right) \right], \quad (15)$$

where $\omega_0 = 2\pi/\tau_0 = 2/\tau_B \approx 0,4 \cdot 10^5 \text{ s}^{-1}$ is the fundamental one, which plays the role of the natural frequency of the medium.

4. The radio frequency field power absorbed by the suspension. Magnetic hyperthermia

To calculate the absorbed power of the radio frequency field by the suspension, we use the fluctuation-dissipation theorem. This theorem connects such seemingly different characteristics of a physical system as fluctuations in the interaction energy and dissipation energy (the energy of an external source absorbed and converted into heat). The fluctuation-dissipation theorem was proved by G. Collen and T. Walton and was presented in the form [20, 21]

$$Q(\omega) = \frac{\pi\omega}{\hbar} \tanh \frac{\hbar\omega}{2kT} \cdot G(\omega), \quad (16)$$

where $Q(\omega)$ is the absorbed energy per unit time, $G(\omega)$ is the Fourier component of the fluctuation correlation function (power spectral density). In the high-temperature limiting case (in the classical limit) $kT \gg \hbar\omega$ fluctuation-dissipation theorem (16) takes the form

$$Q(\omega) = \frac{\pi\omega^2}{2kT} \cdot G(\omega). \quad (17)$$

To calculate the absorbed power $Q(\omega_0)$ at the resonant frequency, we use the classical form (17) of the fluctuation-dissipation theorem.

In our case, when the interaction of an external alternating field with magnetic nanoparticles is given in the form

$$H_{int} = -\mu B(t) \cos \theta, \quad (18)$$

the correlation function and the power spectral density have the following form, respectively

$$G(\tau) = \overline{H_{int}(t)H_{int}(t+\tau)}^{(0)} \quad (19)$$

$$G(\omega) = \frac{1}{2\pi} \int_{-\infty}^{\infty} G(\tau) \sin \omega \tau d\tau. \quad (20)$$

As is known, the correlation function depends only on $\tau \neq 0$, but does not depend on the choice of t . Assuming in (19) $t=0$, and also using the expression of the magnetic induction $B(t)$ of the alternating field (6), we obtain

$$G(\tau) = \mu^2 b^2 F(\tau) e^{-\gamma|\tau|} \cos \omega \tau \quad (21)$$

where

$$F(\tau) = [\overline{\cos \theta(0) \cos \theta(\tau)}]^{(0)}. \quad (22)$$

Note that in order to calculate the correlation function (22), it is sufficient to consider only the zero order approximation of the perturbation theory (11, 14). Thus, the application of the fluctuation-dissipation theorem makes it possible to calculate the absorbed power without calculating the perturbation theory corrections and without solving the complex integral-differential equation (12).

It is easy to see from the expansion of $[\overline{\theta^2}]^{(0)}(t)$ in series (15) that the fundamental (first) harmonic, with which the alternating field has a resonant connection, has the form

$$[\overline{\theta^2}(t)]_{\omega \approx \omega_0}^{(0)} = -\pi \sin \omega_0 t. \quad (23)$$

As can be seen from (22), in the limit, $\tau \rightarrow 0$ the correlative function $F(\tau \rightarrow 0)$ coincides with the root mean square value of the random function $\cos \theta$. In the spectrum of the rms value of the function, $[\overline{\cos^2 \theta(t)}]^{(0)}$ we find the harmonic at the frequency ω_0

$$\begin{aligned} [F(t, \tau = 0)]_{\omega \approx \omega_0} &= [\overline{\cos^2 \theta(t)}]_{\omega \approx \omega_0}^{(0)} = \\ &= [\overline{(1 - \theta^2(t) + \dots)(1 - \theta^2(t) + \dots)}]_{\omega \approx \omega_0}^{(0)} = -2 [\overline{\theta^2(t)}]_{\omega \approx \omega_0}^{(0)}. \end{aligned} \quad (24)$$

Then, taking into account (23), we obtain that the resonant components of the functions $F(t)$ and $G(\tau)$

$$[F(t, \tau = 0)]_{\omega \approx \omega_0} = 2\pi \sin \omega_0 t, \quad (25)$$

$$[G(t = 0, \tau)]_{\omega \approx \omega_0} = 2\pi(\mu b)^2 e^{-\gamma|\tau|} \sin \omega_0 \tau \cos \omega \tau. \quad (26)$$

To find the power spectral density at the frequency ω_0 by integrating (20) taking into account (26) with respect to the variable τ within $-1/\gamma \ll \tau \ll 1/\gamma$, passing to the limit $\gamma \rightarrow 0$ and neglecting non-resonant terms, we obtain

$$G(\omega_0) = (\mu b)^2 \int_{-\infty}^{\infty} e^{-\gamma|\tau|} \sin \omega_0 \tau \sin \omega \tau d\tau \approx \frac{1}{2} (\mu b)^2 \frac{\gamma}{\Delta^2 + \gamma^2}, \quad (27)$$

where $\Delta = \omega - \omega_0$.

To calculate the absorbed power, we apply the classical form of the fluctuation-dissipation theorem (17). Taking into account (17, 26), we finally obtain that, the absorbed power:

$$Q(\omega_0) = \frac{\pi \omega_0^2}{4 kT} (\mu b)^2 \frac{\gamma}{\Delta^2 + \gamma^2}. \quad (28)$$

Using the numerical data given in the text, and also assuming:

$$\Delta = 0, \omega_0 = 0,4 \cdot 10^5 \text{ rad/s}, \quad \gamma = 5 \text{ rad/s}, \quad T = 310^0 K, \quad \mu \approx 4,8 \cdot 10^{-18} \text{ A} \cdot \text{m}^2,$$

the power absorbed at the frequency ω_0 from (28) we obtain

$$Q(\omega_0) \approx 5,4 \cdot 10^{-14} \text{ W}. \quad (29)$$

To heat up a suspension consisting of a system of nanoparticles with a mass M_p and a liquid with a mass $M_d \approx 2M_p$, by ΔT degrees will take time

$$\Delta t = (C_p M_p + C_d M_d) \frac{\Delta T}{Q} = M_p (C_p + 2C_d) \frac{\Delta T}{Q}. \quad (30)$$

where C_p and C_d are the heat capacities of nanoparticles and liquid, respectively.

The mass of one magnetite molecule is $m_{Fe_3O_4} \approx 3,8 \cdot 10^{-25} \text{ kg}$. If a magnetite nanoparticle contains $n \approx 10^5$ number of molecules, then the mass of one nanoparticle will be $M_n \approx n \cdot m_{Fe_3O_4}$. The mass of the powder consisting of $N \approx 10^4$ magnetite nanoparticles will be $M_p \approx N \cdot n \cdot m_{Fe_3O_4} = 3,8 \cdot 10^{-16} \text{ kg}$. Substituting in (30) the values of the masses, the heat capacities of iron $C_p = 0,4 \cdot 10^3 \text{ J/kg} \cdot K$ and water $C_d = 4,2 \cdot 10^3 \text{ J/kg} \cdot K$, $\Delta T = 6^0 K$, we get $\Delta t = 370 \text{ s} \approx 6 \text{ min}$.

Using this data, we obtain that a very commonly used characteristic of the process of magnetic hyperthermia (SAR), $SAR = \frac{Q}{M_p} = 0,1 \frac{W}{g}$. Note that both the warm-up time Δt per ΔT degree and the SAR have practical values.

The method of suspension heating proposed by us allows us to expand the range of parameters used for this purpose of the radio-frequency field in hyperthermia: decrease the frequency from several hundred kilohertz to tens of kilohertz, and amplitude - from hundreds of gauss to several gauss.

5. Conclusion

An experimental method of cancer treatment - the method of magnetic hyperthermia is based on the heating of magnetite nanoparticles and the cancer cells captured by nanoparticles, which formed a suspension, by an alternating electromagnetic field. Dynamics of magnetic nanoparticles in suspension at times longer than the characteristic time of τ_0 collision of the molecules of the base fluid (blood) is described by changing the root-mean-square fluctuation of the angular variables. The dynamics of this fluctuation, which is a rotational Brownian motion, at times exceeding the Brownian relaxation time $t \gg \tau_B \gg \tau_0$, acquires a periodic character with a complex spectral composition. The fundamental frequency of this spectrum is of the order of the reciprocal of the Brownian relaxation time. $\omega_0 \sim 1/\tau_B$. With the help of a radio-frequency field, which is in resonance with the main component of this spectrum, it is possible to heat up nanoparticles together with diseased cells and liquid. This is the proposed method for heating a suspension of magnetic

nanoparticles, the use of which will make it possible to expand the range of characteristics used in hyperthermia of an alternating field, both in frequency and amplitude.

References:

- [1] Q.A. Pankhurst, J. Connolly, S.K. Jones, J. Dobson. Applications of magnetic nanoparticles in biomedicine *J. Phys.D:Appl. Phys.* **36** (2003) R 167-R181.
- [2] Higer I. *In Vivo* applications of magnetic nanoparticles hyperthermia. *Int. J. Hyperthermia.* 2013; 29(8): 828-834.
- [3] Périto E.A., Hemery G., Sandre O., Ortega D., Garaio e., Plazaola F., Tran F.J., Fundamentals and advances in magnetic hyperthermia. *Applied Physics Reviews* 2015; 2(4): 1-35.
- [4] Gilchrist R, K. Medal R., Shorey W.D., Hanselman R.,C. Parrott J., Taylor C., B. Selective inductive heating of lymph nodes *Ann. Surg.* , 1957;**146**, 596-606.
- [5] P. Moroz, Jones S.K., Gray B.N. Status of Hyperthermia in the treatment advanced liver cancer. *J. Surg. Oncol.* 2001; **77**, 259-269.
- [6] A. Jordan, Scholz R., Wust P., Fahling H., Felix R. Magnetic fluid Hyperthermia (MFH) cancer treatment with AC magnetic field induced excitation of biocompatible super paramagnetic nanoparticles. *J.Magn. Magn. Mater.* 1999, 201, 413-419.
- [7] R.E. Rosensweig. Heating of a magnetic fluid with alternating magnetic field. *J. Magn. Magn. Mater.* 2002, **252**, 370-374.
- [8] P.C. Fannin, Charles S.W. Measurement of the Neel relaxation of magnetic particle in the frequency range 1kHz-160 MHz *J. Phys. D:Appl. Phys.* 1991, **24**, 76-77.
- [9] P.C. Fannin, Scaife B.K. Charles S.W. Relaxation and resonance in ferrofluids *J. Magn. Magn. Mater.* 1993, **122**, 159-63.
- [10] M. Hanson. The frequency dependence of the complex susceptibility of magnetic liquids. *J. Magn. magn. Mater.* 1991, **96**, 105-113.
- [11] Mullory M., Gogineli E., Gones G.C., Greer I., Simone C.B. Therapeutic hyperthermia: the old, the new and the upcoming. *Crit. Rev. Oncol. Hematol.* 2016,97, 56-64.
- [12] S.K. Jontes, Gray B.N., Burton M.A., Codde J.P., Street R. Evaluation of Ferromagnetic Materials for low frequency hysteresis heating of tumours. *Phys. Med. Biol.* 1992, 37, 293-299.
- [13] J. Carrey, B. Mehdaoui, M. Respaud, Simple models for dynamic hysteresis loop calculations of magnetic single-domain nanoparticles: Application to magnetic hyperthermia optimization. *Journal of Applied Physics* (2011), 109, 083921.
- [14] Ch. Kittel. *Introduction to Solid State Physics.* New-York, London. 1976.
- [15] S.L.Gawali, Shelar, S.B., Gupta, J., Barick, K.C., Hassan, P.A. Immobilization of protein on Fe_3O_4 nanoparticles for Magnetic Hyperthermia Application. *Int. J.Biol. macromol.* , (2021)166, 851-860.
- [16] A. Wlodarczyk, S. Gorgon, A. Rodon, K. Bajdak-Rusinek. Magnetite Nanoparticles in and Cancer Therapies: Challenges and perspectives. *Nanomaterials.* 12, 1807, (2022). <http://doi.org/103390/nano12111807>.
- [17] D. Leslie-Pelecky, R.D. Rieke. *Chem. Matter.* , (1996), **8**, 1770.
- [18] F. Schwabl. *Statistical Mechanics.* Springer -Verlag, Berlin,Heidelberg, New-York. 2006.
- [19] A. Korn, T. M. Korn. *Mathematical Handbook for Scientists and Engineers.* New York, Toronto, London. 1961.
- [20] L.D. Landau, E.M. Lifshits. *Statistical Physics.* Pergamon Press. 1966.
- [21] C.V. Heer. *Statistical Mechanics, Kinetic Theory and Stochastic Process.* New-York, London. 1972.