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On the measurements of magnetic nanoparticle concentration in a biological medium using a superconducting quantum magnetometer

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Magnetic nano-particles are used in medicine both as medical means, and for the transport of medicines in the pathological area of an organism. Simultaneous influence on these particles of ultrasonic radiation and a constant magnetic field allows summarising a magnetic field of an nano-particles ensemble to the value, sufficient for its registration by the remote magnetic detector. The parity connecting the measured magnetic flux of the nano-particles with parameters of the particles, ultrasound, and the measuring system using as the magnetic detector superconducting quantum magnetometer is received. Calculations have shown, that such a system can measure a concentration of the nano-particles in colloidal solution, modeling the biological medium, in the unattainable earlier dynamic range of values (from 1 vol % to 10^{-7} vol %).

Keywords: superconducting quantum magnetometer, biological medium, magnetic nanoparticles, ultrasound radiation, colloidal solution.

1. Introduction

In recent years, a problem has arisen of detecting magnetic nanoparticles (MNPs) in a biological medium (BM). MNPs can be both an integral part of biological objects or artificially introduced into the biological medium in order to use their specific properties for medicinal purposes. An example of their first case is the biogenic magnetite present in the organisms of birds and humans [1]. The second case of MNP in the form of magnetite is used, in particular, for used drug delivery to the pathological region of the human body [2–4]. Moreover, there is the task of determining the concentration of MNP in the target area of the biological medium. Currently, to solve this problem, the most commonly used method is magnetic resonance imaging (MRI) [5]. The presence of the magnetic field of MNPs in BM is determined in this method by monitoring the energy states of hydrogen atoms as an intermediate substance. Therefore, the MRI method is not direct and limited both in the top allowable level and in the accuracy of MNPs concentration measurements. We propose an alternative way for measuring the concentration of MNPs in BM using the acousto-magnetic method (AMM) of exposure to BM with MNPs. A new method for measuring the concentration of MNP is direct, and according to our estimates, it free from the limitations of MRI. The AMM involves excitation with the help of ultrasound radiation (USR) of the MNP vibrations in the target region of the medium, placed in an external uniform constant magnetic field H_d. Vibrations of the ensemble of oriented (polarized) particles in the field of H_d leading to the appearance in the surrounding space of an alternating magnetic field of H_a with a frequency of USR. The magnetic flux of this field depends on the concentration of MNPs in the studied region and can be measured by a highly sensitive detector located outside this region. As such a detector, one can use a superconducting quantum magnetometer (SQM), which, as is known, has the highest sensitivity and dynamic measurement range among the known types of magnetometers [6–8]. Model experiments using USR confirm the fundamental possibility of implementing the AMM [9]. To assess the achievable characteristics of the AMM in model experiments, it is necessary to obtain the calculated relationships between the physical parameters of the USR, MNP, biological medium, magnetic detector, and MNP concentration in the studied liquid medium. The aim of the present work is to obtain the indicated relations, to compare the calculated characteristics with the results of model experiments, and also to estimate the range of measured concentrations of MNPs by the AMM using a superconducting quantum magnetometer as an MNP detector.

2. Model measuring system with an AMM

Figure 1 shows a diagram of the measuring system with an AMM. The scheme consists of three the blocks (A, B, C), allowing to determine the concentration of MNPs in a vessel with a model biological substance (BS). Block A represents a model biological medium with an MNP affected by a constant magnetic field H_d and ultrasonic radiation (US). As a result, the US MNP vibrations generate an alternating magnetic field H_a, depending on the concentration of the MNP in the BS region. Block B is a highly sensitive device for measuring the field H_a. Block C is H_a value a recorder.

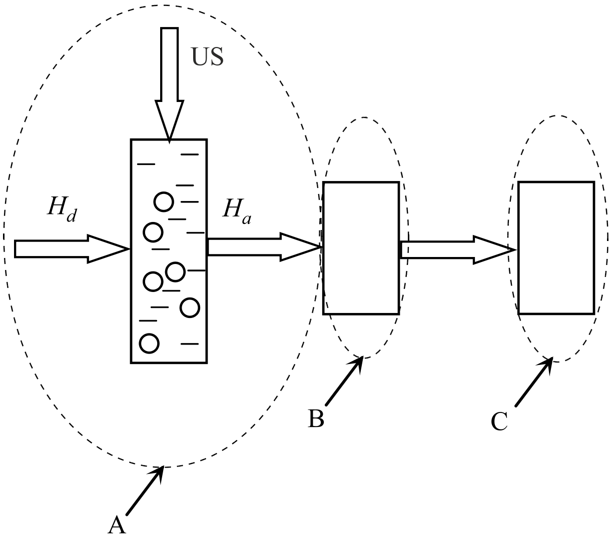

Fig. 1. Diagram of the model measuring system: A — signal generation containing the object of study, B — measuring block, C — recording block. H_d is a constant homogeneous magnetic field; H_a is an alternating inhomogeneous magnetic field, originated from particle vibrations induced by USR.

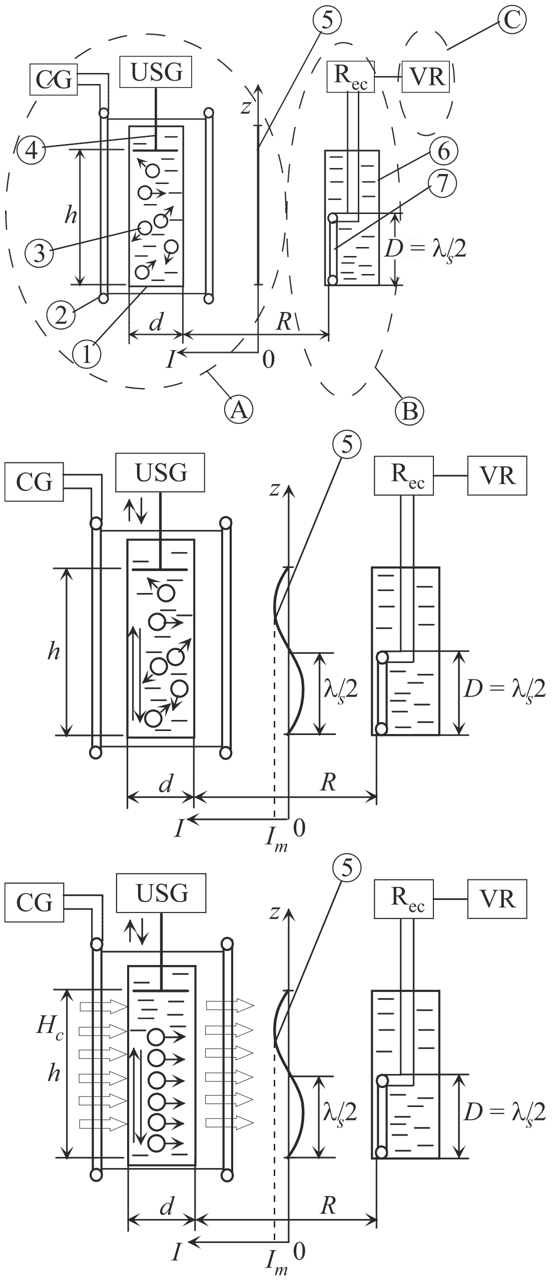

Fig. 2. Diagrams of a measuring system for determining the concentration of MNPs in a model colloidal solution in three states: (a) state before switching on constant magnetic field H_d and ultrasound, (b) state after switching on only ultrasound along the longitudinal axis z of the vessel with MNP, (c) state after switching on a constant magnetic field and ultrasound, 1 — a cylindrical vessel with a diameter of d, 2 — Helmholtz coils, 3 — a magnetic nanoparticle, 4 — sound conductor, 5 — distribution of the amplitude of a standing ultrasound wave along the vessel longitudinal axis z, 6 — SQM cryostat, 7 — receiving coil (antenna) of the SQM magnetic flux transformer (to simplify the circuit, an interferometer is not shown).

Figures 2(a)–2(c) show a more detailed diagram of an experimental measuring system to determine the concentration (K) of MNPs (3) in a model colloidal solution located in a cylindrical vessel (1) with a diameter d. Block A contains a direct current generator CG, which feeds Helmholtz coils (2), creating a constant magnetic field H_d in the region of the vessel (1) with a colloidal solution of MNPs (3). In addition, this block posses an ultrasound generator (USG) that transmits acoustic vibrations into the solution using a sound waveguide (4). Block B consists of a liquid helium cryostat (6), with a superconducting quantum magnetometer (SQM) detector (7) based on a superconducting quantum interferometer (SQI) equipped by a superconducting magnetic flux transformer, as well as an electric signal interferometer amplifier (R_{ec}). The detector in the form of a single-turn antenna of the magnetometer is placed close to in the vessel with the solution at a distance R. Block C is a recorder (VR) of the electric voltage at the output of the amplifier of the interferometer, which is proportional to the concentration of the MNPs in the solution. Figures 2(a)–2(c) also illustrate a change in the physical state of the measuring system after sequentially turning on the ultrasound and the field H_d.

Figure 2(a) shows the initial state of the measuring system with random moments of the MNP in the absence of a field ($H_d = 0$) and ultrasound (power of ultrasound $I = 0$). The random heat states of the MNPs magnetic moment directions shown by the arrows of the particles does not create the resulting magnetic field in the SQM region. The voltage on the VR recorder is zero. Figure 2(b) shows the situation when the ultrasound is turned on and its amplitude is I_m. A standing wave, along the axis z of the vessel, is established since the ultrasound wave propagating along the axis of the vessel is reflected from its bottom [10]. The distance from the ultrasound source to the bottom is selected so that one or more wavelengths λ_s fit on it. One of the possible distributions of the power amplitude I_m of the ultrasound along z is shown in Fig. 2(b) as the dependence $I_m(z)$. In this case, in one part of the vessel axis $\delta z = \lambda_s/2$, the solution is compressed with MNPs, and in the other part, corresponding to a half-wave of the opposite sign is tensed. Harmonic vibrations of MNPs arise with magnetic moments randomly distributed in space with ultrasound frequency f. Such vibrations of the MNPs also do not create the resulting magnetic field and the voltage at the recorder remains equal to zero. Figure 2(c) shows the situation when, in addition to ultrasound, a constant magnetic field H_d, perpendicular to the axis of the vessel and the plane of the SQM antenna, is turned on. This field orientates (polarizes) the magnetic moments of all MNPs along its direction, similar to the rotation in a magnetic compass. The resulting total magnetic moment of all the MNPs arises along the direction of polarization. The longitudinal oscillations of this total moment, directed perpendicular to the plane of the SQM antenna, create an alternating magnetic field and an alternating magnetic flux Φ_a through the antenna in the space near the vessel. When the diameter D of the antenna is equal to $\lambda_s/2$, as shown in Fig. 2(c), the maximum magnetic coupling of the alternating magnetic flux with the SQM antenna is achieved [10]:

$$D \le \lambda_s/2 = v_s/(2f), \qquad (1)$$

where λ_s, v_s are the wavelength of sound and the velocity of sound in solution, respectively. This provides high sensitivity for magnetic measurements. The advantage of measuring an alternating rather than a constant magnetic field is the high noise immunity of these measurements, occurring at a fixed frequency of ultrasound because this facilitates the selection of a useful signal against the background of inevitable surrounding electromagnetic interference with a wide range of frequencies. For the indicated scheme of the measuring device, the expression for the amplitude of the excited variable magnetic flux Φ_a can be represented as:

$$\Phi_a = B_c \delta S \approx B_c(\lambda_s/2)A/2, \qquad (2)$$

where B_c, is the magnitude of the magnetic induction component of the particle flux Φ_a, perpendicular to the plane of the SQM antenna, created by all polarized MNPs of the solution column section with a height $\lambda_s/2$ at the antenna location; the change in the area occupied by magnetic field lines δS is of magnetic waves of MNPs passing through the antenna $A/2$ is, due to their movement under the action of ultrasound relative to the antenna; the average value of compression (expansion) of a portion of a solution column with a height $\lambda_s/2$ with an amplitude of compression (expansion) equal to A. The amplitude (A) is associated with the parameters of ultrasound and a liquid medium [11]:

$$A = [2I/(\rho v_s)]^{0.5}/(2\pi f), \qquad (3)$$

where I, ρ, v_s are, respectively, the ultrasound power, the density of the solution, and the velocity of sound in the solution. The value of B_c is determined by the number N of MNP in the section of the solution column with a height $\lambda_s/2$, the magnetic moment M_0 of each of them and the distance R to the SQM antenna:

$$B_c = \mu_0 N H_c \approx \mu_0 N[M_0/(2\pi R^3)], \qquad (4)$$

where $H_c = 2M_0/(4\pi R^3)$ is the magnetic field strength generated by one MNP at a distance R. Formula (4) is applicable if the diameter of the vessel d with the solution is substantially less than the distance R and all MNPs have the same magnetic moment M_0. In turn, the magnetic moment of the MNP can be expressed through its parameters:

$$M_0 = J_0 V_0, \qquad (5)$$

where J_0 and V_0 are the specific magnetization and volume of one MNP.

The volume concentration K of the MNPs in the test volume V of the solution is expressed by the formula:

$$K = NV_0/V. \qquad (6)$$

In turn:

$$V \approx \lambda_s d^2/2. \qquad (7)$$

Express the value of N using formulas (6), (7):

$$N \approx K\lambda_s d^2/(2V_0). \qquad (8)$$

After substituting (8) and (5) in (4) we get:

$$B_c \approx \mu_0 J_0 \lambda_s d^2 K/(4\pi R^3) \qquad (9)$$

Substituting (9) and (3) in (2), taking into account the relationship between the ultrasound wavelength and its frequency ($\lambda_s = v_s/f$), we obtain:

$$\Phi_a \approx [\mu_0 J_0 v_s^{1,5} d^2 (2I_m)^{0,5}/(32\pi^2 \rho^{0,5} R^3)] (K/f^3). \qquad (10)$$

Table 1. The values of the parameters included in formula (10)

μ_0, G/m	J_0, A/m	v_s, m/s	d, m	I_m, W/m^2	ρ, kg/m^3	R, m	K	f, Hz
$4\pi\cdot10^{-7}$	$4.7\cdot10^5$	1500	0.015	10^3	10^3	0.01	0.01	$2\cdot10^4$

The main advantage of formula (10) is the possibility of a fairly simple determination of the volume concentration K of MNPs in a given region of the model solution, measuring the magnetic flux Φ_a with the specified known parameters of the measuring device and the colloidal solution. This formula also shows strong dependences of the flux on the ultrasound frequency f and the distance R between the receiving coil of the magnetometer and the vessel with the solution. It can be expected that the same strong dependences will exist during field measurements of the magnetic flux generated by MNPs introduced into a living organism when using AMM with ultrasound to determine their local concentration.

3. Verification of the main equation

To verify the relation (10), it was measured the alternating voltage with an amplitude U_m on an induction coil with a diameter equal to the diameter D of the SQM receiving coil, used in the model system instead of the SQM detector.

The instantaneous value of the alternating magnetic flux ϕ through the coil can be represented in the form $\phi = \Phi_a \sin(2\pi f t)$, t is time. According to the Faraday law, the voltage u on the coil is equal to:

$$u = (d\phi/dt)w = \Phi_a 2\pi f w \cos(2\pi f t), \qquad (11)$$

where $U_m = 2\pi f \Phi_a w$, w is the number of turns of the induction coil ($w = 2600$). The values of the parameters embedded in formula (10) are shown in Table 1.

Substituting this values into (10), $\Phi_a \approx 10^{-11}$ Wb was obtained, which corresponds to about 10^4 Φ_0, where Φ_0 is the magnetic flux quantum. According to (11), $U_m \approx 3\cdot10^{-3}$ V, which is close to the experimentally obtained amplitude of the voltage across the coil, equal to $1.4\cdot10^{-3}$ V [9]. Since the values of the ultrasound frequency and the number of turns in the coil were known, the obtained voltage value close to the calculated one confirms the correctness of the calculation of the magnetic flux Φ_a through the SQM antenna. In this experiment, the model colloidal solution consisted of a mixture of oleic acid and kerosene in a ratio of 1:2. Magnetic nanoparticles were of iron oxide Fe_3O_4 as fraction of larger particles of magnetic toner for laser printers [12, 13]. For the polarization of nanoparticles, a constant magnetic field of H_d of about 100 Oe was used. In superconducting magnetometers, a magnetic flux transformer serves to transfer it to a small-sized quantum interferometer. A correctly made flux transformer can transfer up to half of the magnetic flux measured by the receiving coil to the interferometer. At the same time, it is known [7] that an interferometer can measure a magnetic flux of 10^{-5} Φ_0 and even less, where Φ_0 is a quantum of magnetic flux, which corresponds to a flux of 10^{-20} Wb. This value is nine orders of magnitude (a billion times) less than the magnetic flux Φ_a measured in the experiment described above at an MNP concentration of 10^{-2}. Hence, use SQM with a dynamic range of measurements near 10^7 [7], used for measurement of makes it possible concentration by an acousto-magnetic method makes it possible to define concentrations in very wide range: from 10^{-2} to 10^{-9} (from 1 vol % to 10^{-7} vol %). This, in turn, means that this method allows the measurement of any concentrations of MNP required for medical applications ($K = 10^{-4}$–10^{-6}, which corresponds to 10^{-2}–10^{-4} vol %).

4. Conclusions

It was analyzed an application of superconducting quantum magnetometer to measure an alternating magnetic flux excited by vibrations of magnetic nanoparticles under the combined effect of a constant magnetic field and ultrasonic radiation (ultrasound) applied on a colloidal solution simulating a biological medium.

Equation (10) for a dependence of a magnitude of the excited alternating magnetic flux on the parameters of magnetic nanoparticles, ultrasound, model biological substance, and a measuring system is obtained.

The obtained equation was verified using a model experiment replacing the SQM by an induction copper coil. It's obvious that the measuring system with SQM makes it possible to register MNPs concentrations of Fe_3O_4 at any range required for medicine.

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Про вимірювання концентрації магнітних наночастинок у біологічному середовищі за допомогою надпровідного квантового магнітометра

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Магнітні наночастинки використовуються в медицині як лікувальний засіб та для транспортування ліків у патологічну область організму. Одночасний вплив на ці частинки ультразвукового випромінювання та постійного магнітного поля дозволяє збільшити магнітне поле наночастинок до величини, яка достатня для реєстрації віддаленим магнітним детектором. Отримано співвідношення, що зв'язує вимірюваний магнітний потік наночастинок з параметрами самих частинок, ультразвуку та вимірювальної системи, що використовує надпровідний квантовий магнітометр як магнітний детектор. Розрахунки показали, що така система може вимірювати концентрацію наночастинок у колоїдному розчині, який моделює біологічне середовище, у недосяжному раніше динамічному діапазоні значень (від 1 об. % до 10^{-7} об. %).

Ключові слова: надпровідний квантовий магнітометр, біологічне середовище, магнітні наночастинки, ультразвукове випромінювання, колоїдний розчин.