Possible Registration of Magnetic Particles in Biological Objects

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Abstract. The possibility of non-invasive detection of magnetic particles in biological objects using magnetic field sensors of various types is investigated. Estimates of the threshold sensitivity of the sensors and the maximum distance at which the sensor can detect magnetic particles are made. It is shown that magnetite particles with a concentration of \(\sim 10^{-9}\) vol.\%, superparamagnetic particles and catalytic particles of the composition "iron in carbon nanotubes" can be fixed by SQUID or combined magnetic field sensors with operating temperatures \(\sim 4\) K at a distance of \(\leq 0.1\) m. It is noted that magnetic field sensors with ultra-low threshold sensitivity values \((\leq 10^{-10}\) T) may be promising for non-invasive control of organs, implants, prostheses and other elements of biological systems.

1. Introduction
The vital process of the body is accompanied by the flow of very weak electric currents (biocurrents) caused by electrical activity mainly of muscles, nerves and cells inside them. These currents induce magnetic fields \(B\) of the order \(\sim 10^{-15} - 10^{-12}\) T. Weak magnetic fields in the human body can also be generated by ferromagnetic particles that are captured or deliberately injected into it. In an external magnetic field, ferromagnetic particles magnetize and cause non-uniform magnetic susceptibility of biological tissues. It is obvious that the magnetic fields coming from both biological objects and ferromagnetic particles in them are very weak and their values are near the magnetic vacuum boundary \(B \sim 10^{-17}\) T. For non-invasive registration of such an ultra-weak magnetic field, it is necessary to use a magnetic field sensor (MFS) with a very low threshold sensitivity \(\delta B\) \cite{1}, i.e. having a high resolution. Particular attention should be paid to methods and tools of detecting micron submicron and nano-sized magnetic particles (MP). Such particles are widely used in medical practice, for example, to: improving contrast, magnetic resonance imaging (MRI), diagnosis and treatment of oncological diseases, targeted drug delivery to certain organs, etc.

In particular, spherical MP coated with active substances are used to isolate DNA and RNA from biological materials. In this case, the nucleic acid is stored with MP much longer than in their absence.
[2]. Superparamagnetic particles ranging in size from 400 nm to 600 nm with a concentration of 5 mg/ml facilitate the separation of serum albumin (BSA) from aqueous dispersion [3]. A new method of non-invasive diagnostics based on magnetic particles is also actively developing. The so-called magnetic-particle imaging (MPI) is similar to MRI [3]. However, the useful signal comes directly from magnetic particles. In this case, the magnetization of the magnetic particles in MPI is more than ten million times greater than the magnetization of the medium in the MRI method. Therefore, the MPI requires a magnetic field of only a few mT, while the MRI uses a magnetic field of several T. Carbon nanotubes (CNT) and nanomaterials based on them can work as containers for the delivery of MP. Indeed, CNT may contain catalytic ferromagnetic (iron, nickel, etc.) or other magnetic particles encapsulated in them. Three-dimensional (3D) composite nanomaterials containing the BSA matrix and a CNT fillers are promising for use in various bioresorbable implants, for example, in bone or cartilage tissues, and their aqueous suspensions, so-called bio-solders, are suitable for laser welding of biological tissues [4-6]. Of course, the CNT implant located inside the human body, should be controlled non-invasively. CNT ends usually contain catalytic ferromagnetic or superparamagnetic nanoparticles, so they can be represented as MP. Therefore, the use MFS of very low threshold sensitivity for non-destructive testing of biological objects in which CNT is included is actual. For example, such control will allow non-invasive assessment of the state of an implant or a seam obtained by laser welding of biological tissues.

In this paper, we offer estimates of the maximum distance within which the magnetic field sensor can detect magnetic particles.

2. Calculation technique

We calculated the maximum possible distance from an MFS with threshold sensitivity \( \delta B \) to a material containing MPs with different parameters. In the calculation, we assumed MPs to be spheres with diameter \( D \) and magnetization \( J \). Let the external background magnetic field, e.g., the Earth’s magnetic field \( B_0 \), be directed along the \( z \) symmetry axis. Under the action of field \( B_0 \), the vectors \( J \) align parallel to the \( z \) axis; at \( B_0 = 0 \), the vectors \( J \) of individual particles are randomly oriented. In this case, the magnetic moment of an individual MP is equal to

\[
M = \frac{\pi}{6} D^3 J
\]

We assume MPs to occupy a spatial region (magnetic region) with characteristic linear dimension \( \Delta \), which is much smaller than distance \( l \) from an MP to MFS and have concentration \( n \). Then, the total magnetic moment \( M_\Sigma \) is

\[
M_\Sigma = \frac{\pi}{6} D^3 : \frac{\pi}{6} \Delta^3 n = \frac{J n \pi^2 (D\Delta)^3}{36}
\]

This total magnetic moment induces the magnetic field

\[
B = \mu_0 M_\Sigma \frac{\sqrt{1+3\cos^2\varphi}}{l^3}
\]

near the sensor, where \( \mu_0 = 1.256 \cdot 10^6 \text{ H/m} \) is the magnetic constant, \( \varphi \) is the angle between the \( z \) axis (the direction of MP magnetization and the Earth’s magnetic field) and the measurement line, i.e., the magnetic region–MFS direction.

In Eq. (3), the coefficient \( \sqrt{1+3\cos^2\varphi} \) takes maximum value (2) when the MP magnetic moment is directed along the measurement line and minimum value (1) when the MP magnetic moment is perpendicular to the measurement line. Therefore, hereinafter we assume this coefficient to be 1.5. Obviously, if the MFS has threshold sensitivity \( \delta B \), then it can detect the magnetic field from a source when the inequality \( B \geq \delta B \) is valid. Taking this condition into account, we obtain from (1) – (3)
In experiments, the specific remnant magnetization of an MP $J_0 = J/\rho$ is usually measured, where $\rho$ is the MP material density. In this case, formula (4) takes the form

$$I \approx 0.01 \cdot D \cdot \Delta \cdot \sqrt{\frac{J_0}{\delta B}}$$  \hspace{1cm} (4)$$

In Eqs. (1) – (5), all the parameters are taken in the SI units.

3. Results

The value $\delta B$, included in (4) and (5), is the threshold sensitivity of MFS and the maximum distance $l_{max}$ within which the MP registration will be possible depends on its value significantly. Consider the question of estimating of $\delta B$ for MFS, where the magnetically sensitive element is a structure with a magnetically resistive properties. In particular, spintronics structures [10] serve as magnetically sensitive elements in combined magnetic field sensors (CMFS) or in a commercial sensor HMC1001.

As usual, such an element in the form of resistor, is included in one of the arms of the measuring bridge “Wheatstone”. From this resistor the signal goes to the input of the amplifier (Fig.1).

The full signal $V_i$, at the input of the amplifier in the mode of a given current $I$ and a given voltage $V_i$, respectively, will have values:

$$V_i = I \Delta R + e_R + e_A,$$  \hspace{1cm} (6)$$

$$V_i = V_i \Delta R / R + e_R + e_A,$$  \hspace{1cm} (7)$$

where $\Delta R$ – change $R$ due to measured magnetic field. For full equivalent noise voltage $e_R$ allowed:

$$<e_R^2> + <e_A^2>.$$  \hspace{1cm} (8)$$

Therefore, the signal-to-noise ratio will be:

$$\eta = \frac{V_i}{(<e_R^2> + <e_A^2>)^{1/2}} = \frac{IR\beta \delta B}{(<e_R^2> + <e_A^2>)^{1/2}}$$  \hspace{1cm} (9)$$

where $\beta = \frac{\Delta R}{RB}$ – magnetoresistive sensor sensitivity.

The minimum value of the magnetic field is determined from (8), equivalent to the noise that the sensor can detect:

$$\delta B_{\text{min}} = \eta_{\text{min}} \frac{(<e_R^2> + <e_A^2>)^{1/2}}{I_{\text{max}} R \beta_{\text{max}}}$$  \hspace{1cm} (10)$$

where $\beta = (\Delta R / R)B^{-1}$ – the maximum value of change in sensor resistance in a magnetic field. In (10) all noise values of the quantities considered in the 1 Hz frequency band are taken into account. Under the condition that in (9) the value $<e_R^2>$ is much smaller than $<e_A^2>$, the value $\delta B$ is approximately equal to $\delta B_{\text{min}} = 5 \cdot 10^{-8} \text{ T}$, where in the case of a GMR-based magnetoresistive sensor the following values are taken into account: $\eta_{\text{min}} \sim 1$, $<e_A^2> \sim 1 \text{ nV}$, $I_{\text{max}} \sim 1 \text{ mV}$, for $\beta_{\text{max}} \sim 20 \text{ T}^{-1}$. Obviously, when the noise voltage of the sensor is greater than the amplifier A, the value $\delta B$ will be even greater.
than the estimated value \(5 \cdot 10^{-8}\) T. For a commercial magnetoresistive sensor based on the structure of spintronics HMC1001 a low value \(\delta B = 3 \cdot 10^{-9}\) T is mainly achieved by high \(\beta_{\text{max}}\) [10]. Examples include sensors that operate at room temperature \(T \sim 300\) K.

With decreasing \(T\), the noise voltage decreases the coefficient \(\beta\) increases and the \(\delta B\) decreases. In particular, this happens in CMFS at low temperatures \(\leq 100\) K [8, 9]. In this case, the noise voltage on \(R\) is determined by thermal noise \((<e^2_0>)^{1/2} = (4kT R)^{1/2}\), and (9) takes the form:

\[
\delta B_N \sim \eta_{\text{min}} (4kT R)^{1/2},
\]

where \(k\) – Boltzmann constant, \(F\) – multiplication factor of the magnetic field, or, equivalently, the concentration factor of the magnetic field. At conclusion (10), the data obtained in [11] are taken into account: \(k = 1.38 \cdot 10^{-23}\) J/K, \(T = 67\) K, \(R = 1600\) Ohm, \(I_{\text{max}} = 10\) mA, \(\beta_{\text{max}} = 50\) T\(^{-1}\), \(F = 1000\). Then in the frequency band 1 Hz we get \(\delta B \approx 5 \cdot 10^{-15}\) T at \(T = 67\) K or \(\delta B \approx 1.3 \cdot 10^{-15}\) T at \(T = 4\) K. Indeed, the experiment recorded values [11]: \(\delta B \approx 30 \cdot 10^{-15}\) T at \(T = 67\) K, and \(\delta B \approx 7 \cdot 10^{-15}\) T at \(T = 4\) K.

It is clear that the experimental data and our estimates coincide in order, despite the fact that we did not take into account other types of possible noise in CMFS.

It is important to note that fact, that additional nanostructuring of the CMFS active band increases the coefficient \(F\) several times, therefore, according to (10), one can expect an even greater decrease in \(\delta B\).

We use the applied methodology for estimating the \(\delta B\) value for a superconducting quantum interference sensor (SQUID). For example, in a single-contact SQUID when measured in the 1 Hz frequency band, the magnetic flux threshold \(\delta \Phi\) can be expressed as [12]:

\[
\delta \Phi = L \sqrt{\frac{4kT R}{R}},
\]

where \(L\) – inductance of the superconducting ring, \(R\) – active resistance of a Josephson junction. In SQUID on the basis of high-temperature superconducting ceramics (HTSC) near the critical temperature \(T_c\), in the calculations it is necessary to take into account both magnetic and kinetic components of the inductance \(L\). In most cases, you can take the values: \(R \sim 5\) Ohm, \(T \sim 100\) K, \(L \sim 1\) nH, which implies the estimates \(\delta \Phi \sim 1.6 \cdot 10^4\phi_0\), and by \(T \sim 4\) K – \(\delta \Phi \sim 3.2 \cdot 10^3\phi_0\). Here \(\phi_0 = 2.07 \cdot 10^{-15}\) T•m\(^2\) is the magnetic flux quantum. Taking into account the area of the quantization circuit with a characteristic size of 1 mm, \(\delta B\) can be estimated at temperatures \(T \sim 100\) K and \(T \sim 4\) K, respectively, as \(\sim 40\) fT and \(\sim 5\) fT.

Table 1 shows the estimated threshold sensitivity \(\delta B\) of some magnetic field sensors. Numeric values are for \(T = 4\) K.

| Type of magnetic field sensor | \(\delta B\), fT |
|-----------------------------|----------------|
| HMC1001 [10]               | 10\(^9\)       |
| CMFS [11]                  | 1.3            |
| NS CMFS [13]               | 0.5            |
| SQUID [1]                  | 5              |

Equations (4) and (5) contain the concentration \(n\), that is, the amount of MP per unit volume of sample. In practice, however, often used the concentration value equal to the volume fraction of the MP in the material. Concentration is also used, which is the mass fraction of MP in the material. We recalculated the quantitative concentration \(n\) into fraction of the volume of MP in the total volume of sample \(C_v\).

Note that nanostructured CMFS (NS CMFS) and SQUID can have \(\delta B\) values of the same order. But, at the same time, since CMFS reacts to the magnitude of the magnetic induction, and SQUID to the...
magnetic flux, reducing the geometric dimensions of NS CMFS without degrading its threshold sensitivity is possible and for SQUID this procedure is impossible.

Figure 2 shows the dependences $l(C_v)$ for different values of the threshold sensitivity $\delta B$ for several types of MFS.

![Graph showing the dependence of $l(C_v)$ on $C_v$ for different values of $\delta B$.]

Here we used approximate values of the magnetite (FeO $\text{Fe}_2\text{O}_3$) MP parameters, which are promising for medical use [14]. You can see that the area for $\delta B$ overlaps the values shown in Table 1. Based on Figure 2, it can be concluded that the high resolution of the MFS ($10^{-14}$ T) provides the detection of material containing MP with dimensions $\sim 50$ nm and the concentration $C_v \sim 1$ vol.% at a sufficiently large distance $l$: $l_{\text{max}} \leq 1$ m. However, at small values $l$: $l_{\text{max}} \leq 1$ cm, it becomes possible to register these nanoparticles with very small $C_v \sim 10^{-9}$ vol.%. This level of MP registration will be available only in cases of using SQUIDs or CMFS [1,8,9,11-13], that require cryogenic cooling (operating temperature $\leq 77$ K). Unfortunately, both SQUIDs and CMFS are very complex and expensive systems.

Laser-pumped magnetometers based on nuclear magnetic resonance ($\delta B \leq 10^{-12}$ T) [15], and ferroprobes ($\delta B \leq 10^{-10}$ T) [16], can detected MP with $C_v \sim 1$ vol.% to $l_{\text{max}} \leq 0.1$ m.

Under the same conditions, commercial magnetoresistive sensors of the HMC1001 type can have $l_{\text{max}} \leq 0.01$ m [10].

It can be seen that listed magnetometers are significantly inferior to SQUID and CMFS in terms of $l_{\text{max}}$ values, however, they have an advantages over them in that they do not require cryogenic cooling and can operate at room temperature, in addition, they are not as complex and expensive systems as SQUIDs. Note that figure 2 shows the curves for MP with magnetite with certain parameters. MP based on hematite ($\text{Fe}_3\text{O}_4$) are also promising for medical use [17]. They have a lower specific magnetization than magnetite-based MP, but they are safer for use in the human body. For superparamagnetic particles with sizes $\leq 8$ nm and $C_v \leq 0.01$ vol.%, the value of $l_{\text{max}}$ does not exceed 0.01 m and they can be detected by only SQUID or CMFS. MPs of this type is often represented by catalytic iron particles formed at the ends of CNT. Therefore, in solid or liquid biocompatible nanomaterials containing CNT, these particles can be detected using the considered MFS. This will allow non-invasive monitoring of implants, artificial organs, prostheses and other elements formed on the basis of materials containing carbon nanotubes.

In this regard, a biocompatible nanocomposite BSA/CNT is the most affordable and has the prospects of large-scale application in medicine.

4. Conclusion
Investigated the possibility of non-invasive detection of magnetic particles in biological objects. It has been established that magnetite particles with a specific magnetization $50 \text{A} \times \text{m}^2/\text{kg}$ with characteristic sizes 50 nm and a concentration $C_v \sim 1 \text{vol.\%}$ can be detected by magnetoresistive magnetic field sensors at distances $\leq 0.1 \text{m}$. However, it is very likely that the same particles with a concentration up to $C_v \sim 10^{-9} \text{vol.\%}$ will be detected by SQUID magnetic field sensors or combined magnetic field sensors with operating temperatures $\sim 4 \text{K}$.

It is noted that superparamagnetic iron particles and carbon nanotubes containing catalytic iron particles can also be detected only by SQUID or combined magnetic field sensors. Thus, magnetic field sensors with a threshold sensitivity up to $10^{-10} \text{T}$ allow registering magnetic particles in biological objects and can be used for non-invasive control of organs, implants and prostheses.

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