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A New Physical Method of Localization of Nanomechanical Action of Magnetic Nanoparticles Controlled by Low-Frequency Magnetic Field on Mechanically Sensitive Biochemical Systems

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Abstract

Magnetic/superparamagnetic nanoparticles (**MNPs**) controlled by an external magnetic field (**MF**) have a great potential for various biomedical applications. The MNPs make it possible to provide selective nanomechanical impact at the level of individual molecules of the intended type by means of their magnetomechanical actuation in the low-frequency MF. However, the MNPs introduced into the bloodstream can accumulate in many organs, creating the hazard of unexpected side effects that may occur when activating alternating MF is turned on. In this paper, we propose a new physical method and technology of localization of the MNP impact on the biochemical system, by creating a static gradient localizing MF with a field free point near the center of the magnetic system. Under these conditions, the activating alternating MF stimulates only those MNPs that are in the vicinity of the field free point. Far from it, where the localizing MF is higher than the stimulating alternating MF, the MNPs are "frozen" in static field and are not affected by the weaker activating alternating MF. The shape and size of the impact localization region are studied depending on the characteristics of the localizing and activating MF.

Keywords

Magnetic nanoparticles; non-heating low-frequency magnetic field; localization; magnetomechanical impact.

Introduction

Magnetic nanoparticles (**MNPs**) have long been used as contrast agents in magnetic resonance imaging [1–3] and in anticancer magnetic hyperthermia (**MHT**) [4–7]. The latter is based on the fact that in the radiofrequency (100–700 kHz) magnetic field, MNPs are capable of releasing heat intensively, which leads to the induction of apoptosis and the subsequent ablation of malignant cells. However, the potential of using MNPs in biomedicine is incomparably larger than these two applications. The MNPs are promising in targeted drug delivery technologies as transducers of an external magnetic field that controls the movement of containers with a therapeutic agent into the desired area or triggers a controlled drug release with a given rate [8–11].

In the last decade, a new magnetomechanical approach to control the behavior of MNPs for innovative biomedical technologies has emerged. It uses the conversion of the magnetic field energy to the mechanical motion of single-domain MNPs and is referred to as magnetomechanical activation (**MMA**) [12–15]. For the MMA, a non-heating low-frequency alternating magnetic field (**AMF**) with a frequency of 1–1000 Hz is used, which causes the oscillating translational or rotational motion of the MNPs. The motion of particles can be used for nanoscale deformation of biologically and chemically active macromolecular structures, such as, membranes and enzymes. As a rule, for this purpose, the MNPs are functionalized with the help of molecular-specific ligands. A number of experimental studies have shown that within the MMA, the functionalized MNPs can be

used to control the vital activity of cells in tissue engineering [12,16–18], as well as drugless cancer therapy [19–24] by direct nanomagnetomechanical cell destruction without the use of either chemo- or radiotherapy. However, because of poorly developed theoretical basis, most of the works do not have good physical justification with respect to the choice of parameters of the magnetic field and are of search character.

In a number of works of Golovin et al. attempts have been made to develop the theoretical basis of the MMA [25–28]. For instance, in [26], a characteristic frequency was found theoretically, connecting the main parameters of the MNP, alternating magnetic field and viscous medium according to the following expression $\omega_c = \mu\mu_0 H_a / 6\eta V_{HD}$, where μ is the magnetic moment of the MNP, μ_0 is the magnetic constant, H_a is the AMF amplitude, η is surrounding medium viscosity, V_{HD} is a hydrodynamic volume of the particle. If low-frequency AMF is below ω_c, functionalized MNPs with a radius of the magnetic core more than some critical (~ 5–10 nm for different magnetic materials) blocking Néel relaxation, perform oscillational-rotational movements with a sweep close to 180°, deforming the associated macromolecules. The force generated by MNPs is sufficient to change the state of such macromolecular structures as micellar/vesicular nanocontainers and cytoplasmic cell membranes. In addition, nanoscale deformations of enzymes, membrane receptors, and ion channels can change their activity [29] due to changes in angles and interatomic distances in their active centers. Experimental studies confirm the main conclusions of theoretical studies [30–32].

The success of *in vitro* experiments stimulate the testing of MMA *in vivo* for various purposes. The technological platform based on MMA makes it possible to selectively influence artificial nanocontainers for the purpose of targeted delivery and controlled release of medicines, drugless oncotherapy, regenerative medicine, and unlike the heat field in MHT, the nanomechanical action of the MNPs does not spread spontaneously in the volume of tissue due to thermal conductivity, but it is localized at the molecular or nano-scale. For *in vivo* purposes, functionalized MNPs are usually administered intravenously, since this is the only way to ensure their successful delivery to the target tissue in the internal organs and anchoring on the targeted cell type or even molecular groups. The problem is that a significant quantity of particles are captured by the liver, kidneys, spleen, i.e. chemical modification and vectorization is not enough for the macroscopic localization of the MNPs distribution. Thus, to various extent, all tissues covered by external activating AMF, in which the MNPs were accumulated, are subjected to nanomechanical impact. This creates the risk of side effects.

The physical approaches to the macroscopic impact localization are usually based on the localization of MNPs themselves through a gradient magnetic field created by a sharpened pole of a permanent magnet or electromagnet [33]. However, such localization methods are effective only when MNPs are concentrated in thin limbs, other appendages of the body of small laboratory animals or superficial regions. Focusing of the MNPs in the deep tissues is a very challenging task [34, 35]. Another method of concentrating MNPs in the desired region is described in [36] and it is based on alignment of the magnetic moments of rod-like MNPs in the direction of magnetic field and subsequent pushing of the MNPs by rapidly switching the direction of the magnetic field. The application of such an approach in a living organism can be associated with certain difficulties, since viscous biological structures will prevent the translational movement of the MNPs. In addition, when moving the MNPs in various areas of a living organism, the viscosity will be different, which will lead to their uneven, non-synchronous movement and, leading to MNPs deconcentration.

In connection with the foregoing, the purpose of this research is to develop new physical method and technology for the macroscopic localization of the nanoscale effect of the MNPs, to determine the optimal configuration of the electromagnetic coil system that provides the best spatial resolution, to analyze the dependence of the geometric dimensions of the localization region on the parameters of the localizing magnetic system creating a gradient magnetic field , and to assess the maximum scanning speed of a mechanically sensitive biochemical system.

Methods and approaches

A new method for localizing the nanomechanical action consists in generation of an additional localizing gradient field H_{gr} with a field free point near the center of the magnetic system (Fig. 1). The main idea is that under the influence of an external AMF with an amplitude H_a on MNPs in such a magnetic field system, there exists a region of space with linear size $L \approx 2H_a / \mathrm{grad}(H_{gr})$, in which the MNPs can perform oscillational-rotational motions under the action of an external activating AMF (Fig. 1), nanomechanically affecting associated molecules. Outside this region,

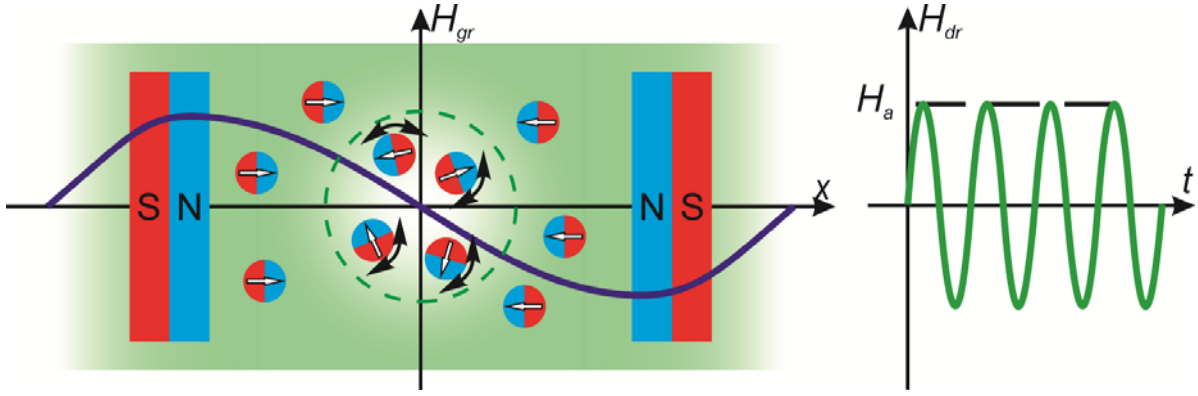

Fig. 1. A diagram illustrating the method developed. The localizing gradient field H_{gr} (on the left) selects the region (green dashed line), outside which MNPs are "frozen" under the action of the activating AMF H_{dr}

the total magnetic field will not change its direction when the magnitude and direction of the activating AMF are changed. Thus, the MNPs will be "frozen" in the constant gradient field H_{gr}, ensuring that cells and tissues outside the impact region are not subjected to unintended effects of the oscillational-rotational motion of the MNPs.

As far as AMF impact localization region (**LR**) position in space is fully specified by field free point coordinates proposed physical localization method involves control over LR positioning. This possibility can be employed by creating additional homogeneous magnetic fields that change the position of the field free point, for example by means of Helmholtz coils (Fig. 2). In such case displacing magnetic field magnitude can be easily tuned by changing coil current. Assuming three orthogonal pairs of coils

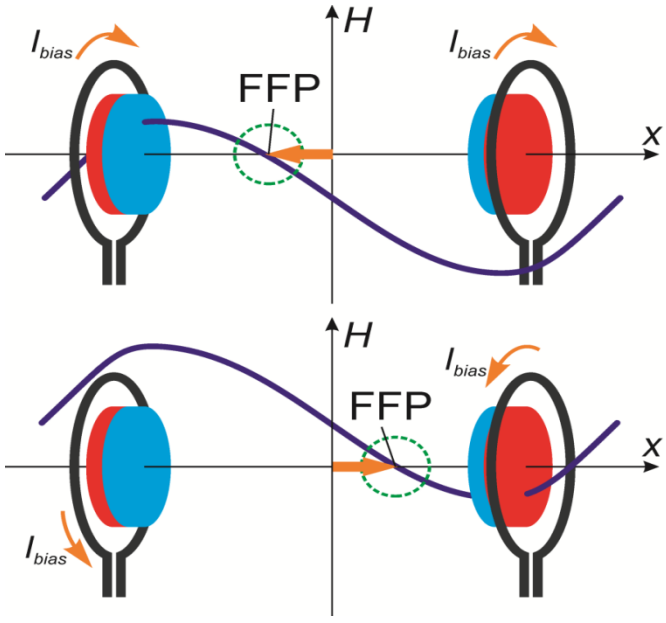

Fig. 2. Displacement of the field free point (FFP) using additional homogeneous field

proposed method creates opportunity for consequent step-by-step scanning of desired region with custom 3D shape.

In order to study the LR size dependence on configuration of the localizing system, three types of model systems that create a constant gradient magnetic field with a field free point using electromagnetic coils were considered:

i) a pair of coils arranged in the Maxwell system;

ii) two orthogonally placed pairs of coils arranged in the Maxwell system;

iii) a pair of concentric coils.

To compare the LR sizes, we selected the following coil parameters: the coil cross section was 5×5 mm^2, the average radius was 15 mm, except for the case of a pair of concentric coils, where the radii were 10 and 20 mm, and the number of turns was 25. The current in the pair of coils i) and iii) was chosen to be 10 A for definiteness, and in two pairs of coils ii) equal to 5 A, to equal electric power of the systems. The control AMF was chosen equal to 0.8 kA/m (~ 1 mT) for definiteness.

In addition, a localizing system consisting of a pair of permanent magnets was examined to determine whether it could be used for simple demonstration experiments. The main parameter of permanent magnets is remnant magnetization, it was chosen equal to 1.2 T, which corresponds to the most common NdFeB magnets.

In this paper, the finite element method was used to model the distribution of the magnetic field.

Results

1. Determination of the optimal configuration of the localizing system

As a result of gradient magnetic field distribution calculation for three model systems described above, the following dimensions of the AMF localization region were found:

i) $1.05 \times 2.04 \times 2.04$ mm^3;
ii) $1.4 \times 1.4 \times 7.5$ mm^3;
iii) $2.77 \times 3.06 \times 3.06$ mm^3.

These findings indicate that under identical conditions the geometry of a pair of Maxwell coils allows obtaining a higher level of localization in comparison with two pairs of coils and a pair of concentric coils. The larger size of the impact LR created by the two pairs of coils is due to the fact that the second pair introduces a magnetic field component directed opposite to the field vectors of the first pair of coils, thereby weakening the gradient of the first pair of coils.

2. Determination of achievable sizes of the localization region using permanent magnets

Proceeding from the obtained distributions of the static gradient MF, the LR dimensions of the AMF action with amplitude of 8 kA/m (~ 10 mT) were determined for the distances between magnets lying in the range from 40 to 90 mm with 10 mm increment. The data obtained is presented in Table 1.

In cross section LR shape is close to ellipse, in three-dimensional space it is ellipsoid-like figure which eccentricity varies depending on the distance between the magnets.

3. Estimation of the maximum scanning speed of a mechanically sensitive biochemical system

Let us estimate the maximum speed of sequential exposure of the target areas of the mechanically sensitive biochemical system by changing the position of the field free point. Suppose, for simplicity, that to change the state of the biochemical system in the region of the action, it is necessary to act by AMF for some number of field periods, while the needed to change position of the field free point can be neglected in comparison with the time of continuous exposure of the LR to the AMF. Then the maximum scanning speed of the mechanically sensitive biochemical system can be expressed approximately as $V_{loc} f / N_{eff}$. Here, the minimum exposure time is assumed to be equal to N_{eff} / f, where N_{eff} is the number of AMF periods leading to perceptible biological response, V_{loc} is the volume of AMF impact LR, and f is the AMF frequency.

To estimate the maximum scanning speed, it was accepted that $N_{eff} = 100$, and the maximum frequency $f = 1000$ Hz, since at such a low frequency the common MNPs of biomedical use under biological conditions willsweep out the maximum angle during their oscillational-rotational movements, exerting a nanomechanical effect on the associated structures. Thus, the maximum scanning speed can be estimated as $10 V_{loc}$ per second, i.e. ~ 2.3 cm^3/s with the AMF impact localization volume ~ $4 \times 8 \times 8$ mm^3.

Table 1

The dimensions of the section of the localization region of the AMF with an amplitude of 8 kA/m as a function of the distance between the magnets with a remanent magnetization of 1.2 T

Distance between magnets, mm	Longitudinal dimension of LR, mm	Transverse dimension of LR, mm	Volume of LR, mm^3
40	1.56	3.02	14.23
50	2.48	4.90	59.54
60	3.80	7.80	231.19
70	5.92	12.02	855.32
80	8.54	19.10	3115.48
90	12.22	29.96	10968.70

Discussion

The method for AMF impact localization can be implemented both with the help of electromagnetic coils in various configurations and with the help of permanent magnets oriented by the same poles towards each other. However, the results obtained show that permanent magnets can be used successfully only for *in vitro* experiments or for small laboratory animals, since only for such a small volume, the size of the LR can be at the level of $4 \times 8 \times 8$ mm^3 for the AMF with an amplitude of 8 kA/m (~ 10 mT). Therefore, when scaling the presented approach to control the MNPs *in vivo* in the body of large mammals or humans, it will be impossible to achieve such values with the help of permanent magnets; to ensure the appropriate size of the impact LR it is necessary to use the Maxwell electromagnetic coils to create large gradients (> 5 T/m) at considerable distances ~ 0.5 m.

In addition, proceeding from the expression for the scanning speed for a mechanically sensitive biochemical system, it can be seen that in general scanning speed depends on the frequency and volume of the LR, i.e. the spatial localization degree. It is undesirable to choose the frequency of the AMF above 1000 Hz, since the MNPs motions become constrained

due to the increasing role of viscous forces, and the biochemical response in this case may weaken or disappear. Consequently, the scanning speed can be increased mainly by decreasing the gradient of the localizing field.

Thus, the transition to electromagnetic coils has one more advantage – the current variation makes it possible to dynamically change the gradient of the localizing MF, and, consequently, the size and volume of the LR.

One more point to highlight is deconcentration of MNPs which obviously will take place in gradient field. This problem affects only particles that are outside the LR because of their static orientation, while inside MNPs movement in one AMF halfcycle is nearly compensated by movement in the consequent one. The simple solution is periodic change of gradient field direction which will alter MNPs movement direction giving zero average particle displacement during number of gradient field cycles.

Conclusion

We proposed and developed new physical method and technology for non-heating low-frequency AMF impact localization on mechanically sensitive biochemical systems by their nanomagnetomechanical actuation and localization spot positioning allowing scanning of custom shape volume in three dimensional space. The mediators of this action – functionalized MNPs of 20–50 nm in size – perform oscillational-rotational motions when exposed to low-frequency AMF and induce deformations in associated macromolecules. By creating an additional gradient field H_{gr}, a region of local impact with linear dimensions $L \approx 2H_a/\mathrm{grad}(H_{gr})$ is distinguished.

It was found that the localizing magnetic system, built with Helmholtz coils, allows achieving a smaller size of the LR, i.e. a better spatial resolution, in comparison with arrangement consisting of a pair of concentric coils. In this case, one pair of coils allows achieving a greater spatial resolution, in comparison with two pairs of Helmholtz coils, creating a gradient field along two perpendicular directions.

The analysis of the AMF impact LR size using model system consisting of a pair of oppositely oriented permanent magnets showed that the linear dimensions of the localization spot vary squared with increasing distance between the magnets. It was found that permanent NdFeB magnets with a remanent magnetization of ~ 1.2 T can provide localization of the AMF action with an amplitude of 8 kA/m in the region of less than $4 \times 8 \times 8$ mm^3, which is sufficient for laboratory experiments *in vitro* or on small laboratory animals *in vivo*.

As follows from simple assumptions, it was established that the maximum scanning speed for sequential processing of the target area of the biochemical system is about $10V_{loc}$ per second, where V_{loc} is the volume of the localization region. For the simplest localization system using permanent magnets, the maximal scanning speed is ~ 2.3 cm^3/s.

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