

# Magnetic Targeted Drug Delivery to the Human Eye Retina: an Optimization Methodology

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**Abstract**—We present a new optimization method for permanent magnet systems aimed for magnetic targeted drug delivery. On the example of a human eye, a special attention is paid to the challenging situation, where the placement of magnets in close vicinity of the targeted area is impossible. In this paper we demonstrate how a system of magnets can be optimized to provide the maximal magnitude of the magnetic field gradient with a prescribed orientation in an extended area (vitreous body). The presented methodology is applicable for all tasks involving a magnetic targeted drug delivery to biological objects.

**Keywords**—nanoparticles, drug delivery, magnetism, permanent magnets, eye, retina

## I. INTRODUCTION

MAGNETIC nanoparticles are widely employed in numerous applications of modern biotechnology, including hyperthermia, magnetic resonance imaging and genetic engineering. One of the most prominent approaches in medical applications is the use of ferrofluid particles as drug carriers [1], [2], [3]. Such a particle comprises a magnetic core (usually iron oxide for a trouble-free ability of absorption by a human body) covered by a shell preventing the particle aggregation and containing the corresponding medical component. Significant efforts in this approach are devoted to the development of a magnetic system which produces a magnetic drag force with the maximal magnitude and prescribed orientation (see, e.g., [4]).

This development should take into account some specific properties ([5], [6], [7], [8]) of biological objects under study. In particular, the diameter of ferrofluid particles has to be much less than the typical size of a blood cell, i.e. about  $5 \mu\text{m}$ . This requirement determines the upper boundary of the magnetic moment of a ferrofluid particle, posing strong demands for the strength of the magnetic field gradient to be provided by a targeting magnetic system, e.g. by a system of permanent magnets.

Another important challenge in magnetic drug delivery occurs when the placement of magnetic system in close proximity to the object is complicated or even impossible. For example, many eye diseases require the drug delivery directly to the retina. In frames of non-invasive treatment, the medical agent is deposited on the outer part of the eye. The following penetration of nanoparticles in the direction to the retina is caused by the magnetic field gradient. It means that the movement of nanoparticles through the whole volume of the vitreous body has to be controlled by the external magnetic field only. This restriction implies the development of a magnetic system which produces magnetic drug force with the maximal magnitude and the prescribed orientation in an extended area, located at the prescribed minimal distance from this system.

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The presented study is devoted to the optimization of a permanent magnet system for the targeted drug delivery, which should satisfy the following three requirements: (i) the placement of magnets in close vicinity to the targeted area is impossible; (ii) the magnitude of the magnetic drag force in the extended area in question should be as large as possible and (iii) the direction of this drag force in the mentioned area should be as close as possible to the desired one.

## II. THEORETICAL BACKGROUND

Magnetic drag force acting on a particle with the magnetic moment  $\vec{\mu}$  in the magnetic field  $\vec{B}$  is derived by the gradient of its magnetic free energy  $G$  [9]:

$$\vec{F}_m = -\nabla G = \nabla(\vec{B} \cdot \vec{\mu}). \quad (1)$$

Particles in this study are considered to be in a superparamagnetic state [10], thus having a constant magnetization and the magnetic moment magnitude  $\mu$ . They can freely rotate in the carrier liquid, so that in sufficiently strong external field ( $\mu B \gg kT$ ) their moment direction always coincides with the direction of this field. If we write the particle moment as  $\vec{\mu} = \mu \vec{e}_B$  with the unit vector  $\vec{e}_B \parallel \vec{B}$ , Eq. (1) can be rewritten in the following way:

$$\vec{F}_m = \nabla(\mu \vec{B} \cdot \vec{e}_B) = \mu \nabla(\vec{B} \cdot \vec{e}_B) = \mu \nabla B. \quad (2)$$

This expression demonstrates, that the magnetic drag force in the approximation described above ( $\mu B \gg kT$ ) is proportional to and directed along the gradient of the magnetic field *magnitude*. Taking into account that for all common magnet systems their magnetic field decreases with increasing the distance to the magnet(s), the field gradient is always directed towards the magnetic system (for some sophisticated designs it is possible to produce field gradients directed away from the magnets, but only in a very small region and with magnitudes which make this design of a purely academic interest [11]).

This inherent feature introduces the important limitation for the drug targeting into the eye, for which permanent magnets should be placed around the head. Namely, the placement of magnets in front of the eye - i.e., within the closest possible distance to achieve the largest field gradient - would lead to the pulling of magnetic particles out of the eye due to the direction of the gradient of the magnetic field magnitude.

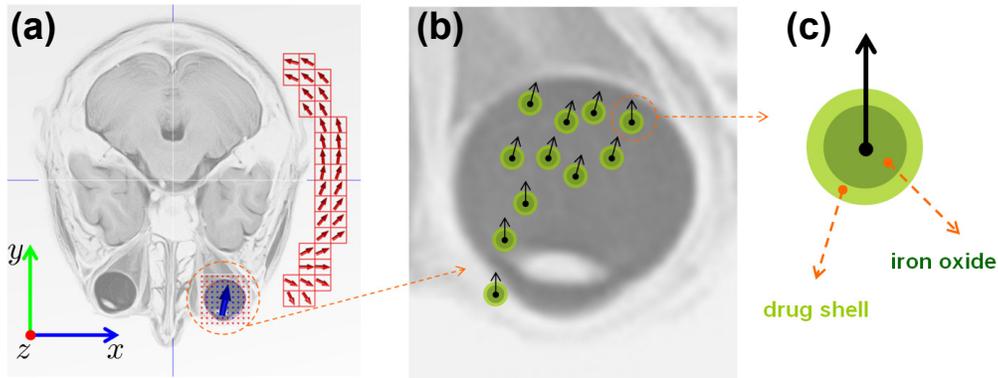


Fig. 1. (a) Example of a system of permanent magnets around a human head with red arrows showing magnetization directions of Nd-Fe-B magnets after the optimization (coordinate system used in the paper is also shown); blue arrow corresponds to the desirable direction of the magnetic drag force from the front surface of the eye to the retina. (b) Schematic representation of magnetic nanoparticles in the vitreous body of the eye. (c) Scheme of a magnetic particle with a drug shell used in the magnetic targeted drug delivery.

The obvious decision to put a large magnet behind the head would provide the desirable direction of  $\nabla B$ , but the large distance between the magnet and the eye would make the field gradient very small (due to the fast decrease of the magnetic field with distance). Hence we are facing a problem to design a system of magnets which would provide an optimal compromise between (i) the achievement of the largest possible value of  $\|\nabla B\|$  and (ii) the proximity of its direction to the 'ideal' gradient alignment towards the eye retina. In this paper, we first describe an algorithm, which allows to perform the corresponding optimization, and then analyze the results obtained with this method.

### III. OPTIMIZATION PROCEDURE

To achieve the desired goal, we optimize a permanent magnet system consisted of a large number of magnets positioned on a prescribed grid [12]. In our approach, the magnetization orientations of these magnets are determined according to the optimization criteria outlined above, which include the maximization of the magnetic field gradient, whereby its direction in an extended area (vitreous body in our case) is prescribed.

An example of such a permanent magnet system is shown on Fig. 1(a). The system consists of commercially available cubical Nd-Fe-B magnets with the saturation magnetization 1.3 T placed around a human head. The size of magnets is 1 cm and, if it is not stated otherwise, they are arranged in one layer in the  $xy$ -plane. The task of the optimization procedure is to maximize the projection of the magnetic drag force on the desired direction of the drug targeting  $\vec{n}$  in the volume of vitreous body of the (left) eye by determining the optimal directions of magnetization for every cubical magnet. Desirable direction of the magnetic force  $\vec{n}$  is shown in Fig. 1(a) by the blue arrow pointing from the outer part of the eye to the retina.

To formally define the function to be optimized, the volume of the vitreous body is divided into regularly placed points, where magnetic field produced by permanent magnets and corresponding magnetic field gradient are calculated. Magnetic field of every Nd-Fe-B magnet is computed in the point (or

spherical) dipole approximation which is completely sufficient taking into account the cubical (i.e., nearly isotropic) shape of magnets and the relatively large distances between the magnets and the eye. The calculation of the corresponding magnetic field gradient is consistently performed in the same approximation on the same grid.

At each point inside the eye, the following variable is defined:

$$S_i = (\vec{n} \cdot \vec{\nabla} B_i) - \alpha_{\perp} (\vec{n}_{\perp} \cdot \vec{\nabla} B_i)^2 + \frac{a_{\text{exch}}}{8} \sum_{j \in n.n.(i)} (\vec{\nabla} B_i \cdot \vec{\nabla} B_j), \quad (3)$$

where  $i$  denotes a point inside the vitreous body ( $i = 1 \dots N_p$ ;  $N_p$  is the total number of considered points). First term is intended to align magnetic gradient vectors along the desirable direction  $\vec{n}$ . In general, this direction should point from the outer part of the eye to the retina; it can be adjusted depending on the exact location of the targeted area on the retina. The second term (note the minus sign) "punishes" configurations with magnetic gradient vectors having a component perpendicular ( $\vec{n}_{\perp}$ ) to  $\vec{n}$ . The last term forces the system to have a spatially uniform gradient configuration, being maximal if all gradient vectors inside the vitreous body are collinear. Coefficients  $\alpha_{\perp}$  and  $a_{\text{exch}}$  define the relative weights of various terms and has been varied in the ranges  $\alpha_{\perp} = 0 \dots 30$  and  $a_{\text{exch}} = 0 \dots 10$  to identify the best configuration of magnetic moments.

Summation of terms (3) over the points inside the vitreous body - blue dots in Fig. 1(a) gives the total optimization function

$$S = \sum_{i=1}^{N_p} S_i. \quad (4)$$

Other 'global' quantities of interest are the average projection of the magnetic field parallel to the desirable direction  $\vec{n}$  of the magnetic force

$$S_{\parallel} = \frac{1}{N_p} \sum_i (\vec{n} \cdot \vec{\nabla} B_i), \quad (5)$$

and the average projection on the corresponding perpendicular direction:

$$S_{\perp} = \frac{1}{N_p} \sum_i (\vec{n}_{\perp} \cdot \vec{\nabla} B_i), \quad (6)$$

These quantities describe the quality of the obtained moments configuration with respect to the desired spatial distribution of the magnetic drug force.

We start the optimization from the configuration where all magnetic moments of Nd-Fe-B cubes are directed along the  $y$ -axis. With the help of the steepest descent method with an adaptive step length, the value of  $S$  is maximized with respect to the orientations of magnetic moments constituting the system. Algorithm stops when the relative increase of the criterion (4) is less than 0.001 comparing to the previous step.

Result of the optimization described above is analyzed using the dependencies of the criteria (5) and (6) on both coefficients  $\alpha_{\perp}$  and  $a_{\text{exch}}$  mentioned above - see Fig. 2(a,b). For the optimal configuration of magnets, the average parallel gradient component (5) should be as large as possible, whereby the value of the average perpendicular component (6) should be kept at minimum.

#### IV. RESULTS

In this section we analyze the dependence of the achievable magnetic field gradient on various factors - position of the magnetic system with respect to the eye, size of the system in the  $xy$ -plane, number of magnetic layers in the  $z$ -direction etc.

##### *Effect of the azimuthal position of the magnetic system.*

The influence of this factor is closely related to the question debated in the Section II, *i.e.* the impact of the position of magnets on the magnitude and direction of the field gradient. In this simulation set, the  $90^{\circ}$ -sector consisting of about 35 magnets [see Fig. 3(a)] is placed at various positions around the head. The position of the sector center is defined by the angle  $\alpha$ . As mentioned in Sec.III, for each system position the optimization is carried out for the complete set of coefficients  $\{\alpha_{\perp}, a_{\text{exch}}\}$ , allowing to choose the best result based on the value of  $S_{\parallel}$ , but also taking into account the average direction of the field gradient and its uniformity. Fig. 2 shows an example of such an optimization for the  $90^{\circ}$ -sector of magnets positioned at  $\alpha = 0^{\circ}$ . Plots of the average parallel  $S_{\parallel}$  and perpendicular  $S_{\perp}$  projection of the field gradient on the desirable direction as functions of  $\{\alpha_{\perp}$  and  $a_{\text{exch}}\}$  allow to choose the optimized gradient configuration depending on specific treatment needs. For example (see Fig. 2(c)), there is a choice between the configuration with the lower gradient magnitude, but the better alignment along the desirable directions (upper panel) and the opposite situation (lower panel).

Fig. 3(b) presents the magnetic field gradient distribution (after optimization of the permanent magnet system) for different values of the angle  $\alpha$ . The dependence of  $S_{\parallel}$  on the position of magnets is very strong, resulting in a difference of one order of magnitude between systems with  $\alpha = 22.5^{\circ}$  (side position) and  $\alpha = 90^{\circ}$  (symmetrical position behind the head). The field gradient direction in the vitreous body roughly follows the angle  $\alpha$ , so that the position of magnets in this system is the main factor controlling this direction.

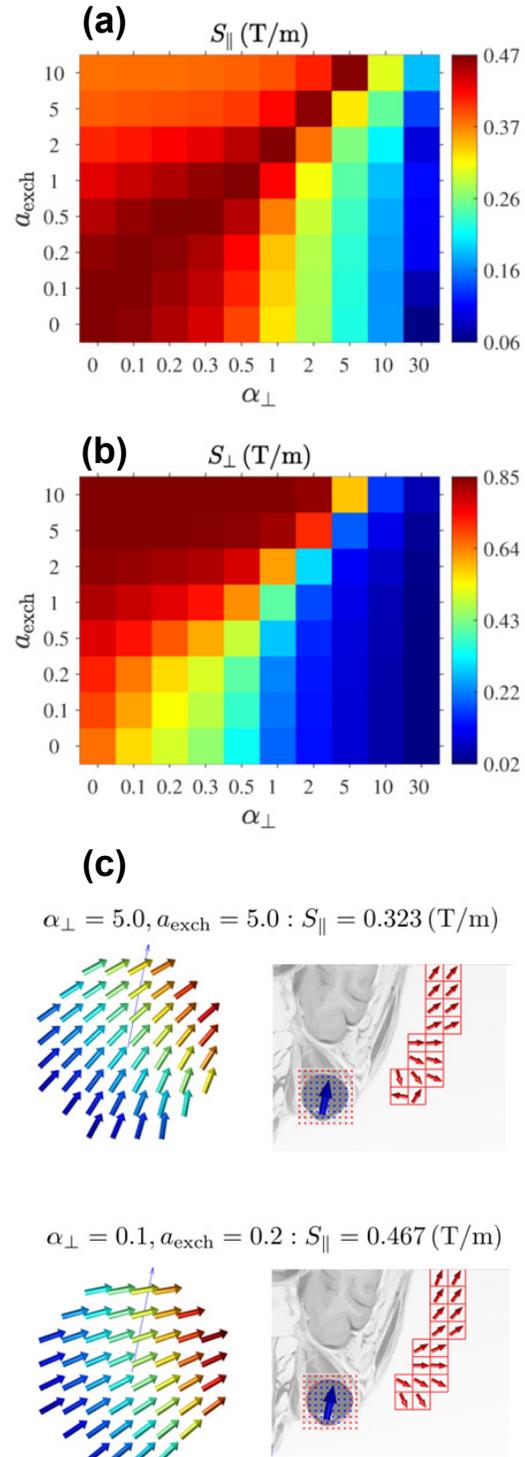


Fig. 2. (a),(b) Average parallel  $S_{\parallel}$  and perpendicular  $S_{\perp}$  projection of magnetic field gradient on the desirable direction of particle movement as function of  $\{\alpha_{\perp}, a_{\text{exch}}\}$ . Permanent magnet system consists of  $90^{\circ}$ -sector of magnets at  $\alpha = 0^{\circ}$ , where angle  $\alpha$  represents the position of the system around the head. (c) Magnetic field gradient distribution and part of the corresponding permanent magnet system for various values of  $\{\alpha_{\perp}, a_{\text{exch}}\}$ .

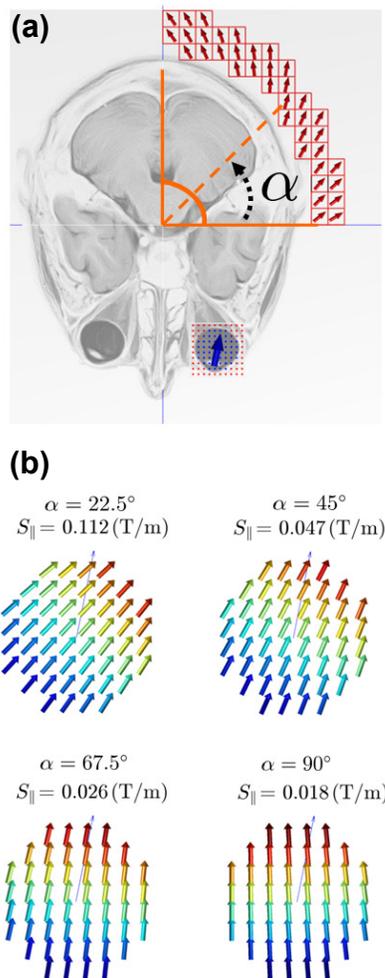


Fig. 3. (a) Optimized permanent magnet system consisting of the  $90^\circ$ -sector of magnets at  $\alpha = 45^\circ$ , where angle  $\alpha$  defines the azimuthal position of the system around the head. (b) Magnetic field gradient distribution in the vitreous body for various angles  $\alpha$ ; values of the average parallel projection  $S_{\parallel}$  of the field gradient on the desirable direction of particle movement are indicated in the legend.

The difficulty of achieving the best compromise between the gradient magnitude and its desired direction can be clearly seen in this example: e.g., magnets positioned behind the head easily align the gradient vectors along the desirable direction, but their magnitude does not achieve the technologically relevant values even with the use of the best permanent magnets available (Nd-Fe-B).

The distribution of the field gradient on all presented figures follows the same pattern (see also Fig. 6): its magnitude is significantly larger near the retina than at the outer eye part due to the fast decrease of the magnetic field with increasing the distance to permanent magnets. Under such conditions the nanoparticles will move slower at first, but as they penetrate deeper into the eye, their velocity will increase, reaching its maximum on the retina.

*Effect of additional sectors of permanent magnets.* Our simulations have shown that additional sectors of magnets placed around the head with the total azimuthal coverage up to  $270^\circ$  (excepting the  $90^\circ$ -sector in front of the eyes) lead

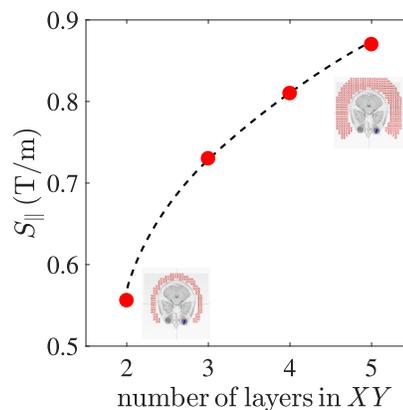


Fig. 4. Dependence of the average projection of the field gradient on the desirable direction on the number of permanent magnet layers in  $XY$ -plane. Dashed line is the guide for an eye.

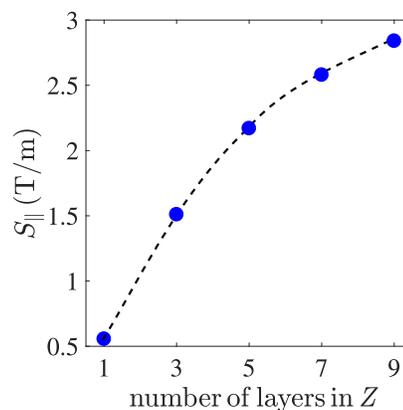


Fig. 5. Dependence of the average projection of the field gradient on the desirable direction  $S_{\parallel}$  on the number of magnet layers in  $z$ -direction. The number of magnet layers in the  $xy$ -plane is 2. Dashed line is the guide for an eye.

to  $\approx 10\%$  increase of  $S_{\parallel}$  (data not shown). Furthermore, the additional sectors of magnets placed on another side of the head (with the respect to the eye under treatment) allow to rotate the field gradient vectors towards the  $y$ -axis. This feature makes the system more flexible concerning the ability to adjust the field gradient direction.

*Increase of the system thickness in the  $xy$ -plane.* We have also performed a systematic study, adding layers of magnets in  $xy$ -plane to the systems shown in previous figures. Results of this addition for the system spanning the  $270^\circ$ -sector around the head are shown in Fig. 4. It has turned out that additional 3 layers in the  $xy$ -plane allow to increase the average gradient projection by approximately 60%. This increase can be explained as follows. By adding new in-plane magnet layers, the 'external' magnetic poles (i.e. magnetic poles located at the outer border of the magnetic system) are moved further away from the eye. These poles generate the field which is directed roughly opposite to the field generated by 'internal' poles. Thus by increasing the number of layers, the magnitude of the total field inside the eye increases and this field becomes more inhomogeneous. Both these features result in a significant increase of the magnitude of the total field gradient.

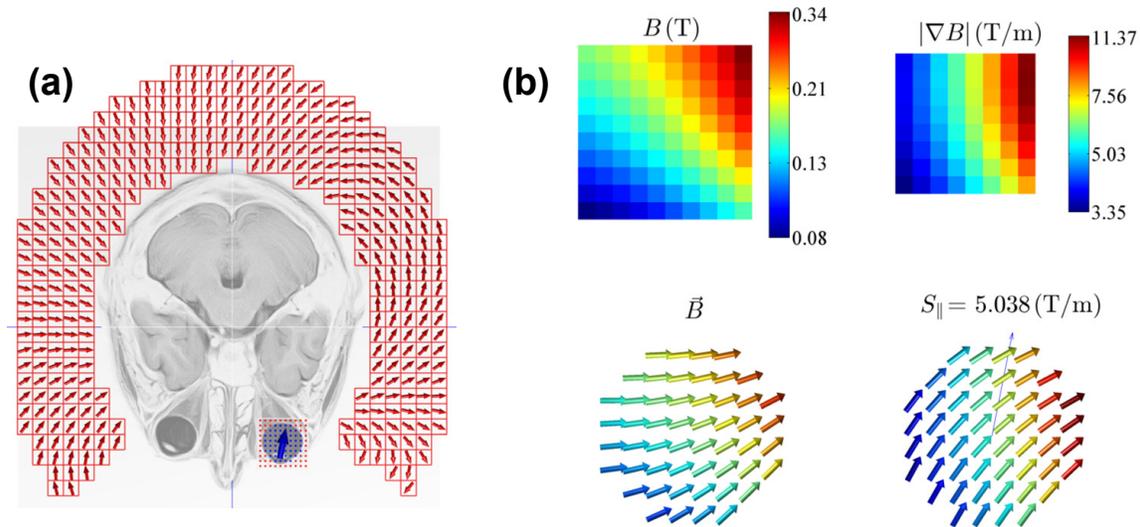


Fig. 6. (a) Optimized permanent magnet system consisted of 5 layers of permanent magnets in  $XY$ -plane and 9 layers in  $Z$ -direction. (b) Corresponding magnetic field and magnetic field gradient in the volume of vitreous body of the human eye.

*Transition to a 3D-system of magnets.* The most significant improvement was achieved by increasing the system size in  $z$ -direction. Keeping in mind that for practical applications the system design should be as simple as possible, we have extended the magnets of our system in  $z$ -direction, keeping the magnetization orientation of each magnet as it was for the system with the thickness (size in  $z$ -direction) of 1 cm. Symmetrical (relative to the plane  $z = 0$ ) addition of magnet layers with such magnetization distribution leads to the system consisting of rectangular rods with magnetizations lying in the  $xy$ -plane, i.e. perpendicular to the long side of rods.

Fig. 5 shows the simulated dependence of the average parallel gradient component  $S_{||}$  on the systems thickness, given as the number of magnet layer in the  $z$ -direction. This result shows that additional symmetrically placed 8 layers forming 9 cm long rods allow to increase the magnetic drag force in the desirable direction by more than 5 times in comparison to the 1 cm thick system. From the physical point of view, this large improvement is due to the increase of the effective system dimensionality, similar to the well known feature of electrostatic charge distributions, where the transition from the point-like charge to a linearly distributed charge and further to the charged plane leads to the much slower decrease of the generated field with the distance to the charged system.

We have checked by another set of simulations, that the usage of a more complex (truly 3D) distribution of magnetic moments, i.e. allowing non-zero components also along the  $z$ -axis lead only to a small improvement of the resulting gradient distribution. Taking into account that such systems are much more complicated in the practical realization, this additional complication is not meaningful.

Summarizing all possibilities for the performance improvement, we present our best result obtained on the system consisted of 5 layers of permanent magnets in  $xy$ -plane and 9 layers in  $z$ -direction (Fig. 6). The distribution of magnetization directions of permanent magnets after optimization has two

prominent features: in the region near the eye under treatment (left eye) it is highly nonuniform, but in the far-zone the angle between neighboring magnets does not exceed few degrees. This optimization results can be explained by different distances between corresponding magnets and the targeted area.

We emphasize, that for this optimal configuration the magnetic field in the vitreous body is highly inhomogeneous and lies in the range 0.1 – 0.3 T (in these fields superparamagnetic particles are nearly saturated, i.e. their moments are oriented almost along the field direction), providing high values of the field gradient. The average projection of this gradient on the desirable direction of the nanoparticles movement is  $\approx 5$  T/m, and the magnitude of the field gradient reaches  $\approx 10$  T/m.

Realization of the suggested design may encounter various technological difficulties. For example, in practice it might be easier to use the hexagonal-shaped rods (Fig. 7) with magnetic moments directed either along the diagonal of the hexagon or along the perpendiculars to the hexagon sides, instead of rectangular ones. Such rods with the discrete set of possible moment orientations (e.g. with  $30^\circ$  step) can be convenient building blocks for such a system due to the relative simplicity of their production and the system assembling. Our calculations (data not shown) validate that this discretization of magnetization directions has almost no influence on the achievable gradient projection.

Another construction option is the usage of cylindrical rods with the possibility to exactly imitate the suggested magnetization distribution. The decrease of the average gradient projection is proportional to the loss of magnetic material, but this scheme may be useful in the situations, where the prescribed magnetization distribution for magnets in the near-field zone should be exactly obeyed.

Next, we have studied the possibility to save magnetic material, removing the parts of the system with the largest distance to the corresponding eye. Fig. 7 demonstrates such

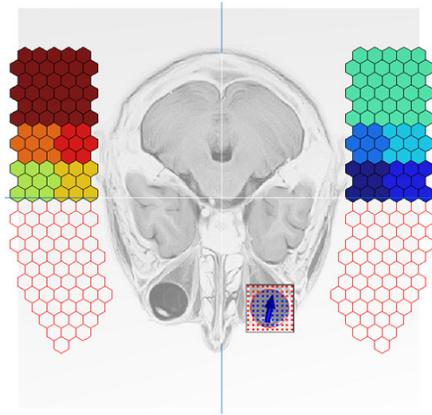


Fig. 7. Coarsening of magnets in the far zone: magnets represented by the same color may be replaced by large magnets with the uniform magnetization.

a system without a central sector of magnets in the region behind the head. We have found that the influence of this sector on the resulting gradient is weak; for example, removing the corresponding sector would save  $\approx 33\%$  of the magnetic material, at the same time leading only to the 6% loss of the magnetic drag force.

Finally, minor difference in magnetization directions between neighboring magnets in the far zone is a prerequisite for the coarsening of magnets in this area. The same Fig. 7 presents a possible option of such a coarsening. The corresponding simulations prove that the replacement of the fine magnetic structure in the colored regions by large magnets with the correspondingly averaged magnetic moment direction almost does not decrease the average gradient projection due to large distances to these regions.

## V. CONCLUSION

New methodology for designing magnetic drug targeting systems is suggested. This methodology is based on the modeling of magnetic field of permanent magnets and optimization of their placement and magnetic moment directions. Using our approach, the average projection on the desirable drug targeting direction (from the outer part of the eye to retina) of magnetic field gradient in the vitreous body for various configurations of permanent magnet placements is maximized achieving the value of 5 T/m.

It is demonstrated that the technologically more convenient magnetic system consisting of hexagonal-shaped rods with enlarged blocks in the far-field regions and without a central sector of magnets provides nearly the same magnetic field gradient.

Further optimization of the magnetic system is necessary based on the recommendations including the detailed characteristics of available permanent magnets (size, the possible directions of magnetizations, saturation magnetizations) and the desirable configuration of the magnetic force field in the vitreous body.

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