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# MAGNETIC TARGETED DRUG DELIVERY USING FOCUSED MAGNET

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A special focused magnet, designed for magnetic targeted drug delivery, was constructed. Calculations of the adhesion condition for a magnetic fluid drop in a magnetic field with the obtained design have shown that the constructed focused magnet generates a sufficient magnetic force for capturing a magnetic drop on the vessel wall.

**Introduction.** Guided transport of biologically active substances to the target organ allows to create an optimum therapeutic concentration of the drug in the desired part of the organism, while keeping the total injected dose low [1–3]. The use of a biocompatible magnetic fluid as a potential drug carrier appears to be a promising technique. Due to their superparamagnetic properties, the magnetic fluid drops can be precisely transported, positioned and controlled in desirable parts of blood vessels or hollow organs with the help of an external magnetic field. The motion of a magnetic drop within the body is controlled by the combination of a magnetic force and a hemodynamic drag force due to the blood flow. In order to effectively overcome the influence of the blood flow, the magnetic force must be larger than the drag force. The conditions for holding a magnetic fluid drop on a blood vessel wall were investigated by Voltairas *et al.* [4]. In this work the non-uniformity of the considered magnetic field was higher only close to the magnetic pole, and this fact was regarded as a major technical problem that has to be solved in order the drug targeting remains essentially non-invasive. The aim of our work was to construct a focused magnet, which enables to achieve a maximal magnetic force in deep position, to map its magnetic field and to find the adhesion condition for a magnetic fluid drop in the magnetic field with the obtained design.

**1. The theoretical model.** In [4] Voltairas *et al.* presented a self-consistent ferrohydrodynamic theory of magnetic drug targeting and examined a model case to account for adhesion. They obtained an upper bound of the mean blood flow velocity as a function of the applied magnetic field, which was considered to be induced by a point source located outside the body at $x = -\delta, y = 0, z = \zeta$, $(\delta, \zeta > 0)$ and had the form

$$\mathbf{H} = \frac{m(\mathbf{r} + \delta\hat{\mathbf{e}}_x - \zeta\hat{\mathbf{e}}_z)}{(r^2 + \delta^2 + \zeta^2 + 2\delta x - 2\zeta z)^{3/2}}, \tag{1}$$

where $m$ is the magnetic dipole moment. The magnetic point source was oriented at an angle

$$\omega = \arcsin\left(\frac{\zeta}{\delta}\right) \tag{2}$$

with respect to the $x$-axis. The found adhesion condition in the dimensionless form reads

$$\frac{1}{\mathrm{B_m}} = \frac{\chi}{4S_0}\int\int_{S_1}(h^2 + h_n^2)\mathrm{d}S, \tag{3}$$

where

$$\mathrm{B_m} = \frac{\mu_0 H_0^2 R}{\gamma} \tag{4}$$

is the magnetic Bond number with $R$ being the radius of the magnetic drop and

$$h = \frac{H}{H_0}, \quad h_n = \frac{H_n}{H_0}, \quad H_0 = \frac{m}{\delta^3}, \quad S_0 = 2\pi R^2, \tag{5}$$

with $H_n = \hat{\mathbf{n}} \cdot \mathbf{H}$. An additional global condition, taking into account the deformation of the magnetic drop due to the blood flow, was derived in the form

$$V_\mathrm{m} = \frac{\chi}{2\beta S_0}\int\int_{S_1}[(h^2 - (1+2\chi)h_n^2)\hat{n}_z + 2\chi(1+\chi)h_n h_z]\mathrm{d}S, \tag{6}$$

where

$$V_\mathrm{m} = \frac{\eta_2 u_0}{\mu_0 H_0^2 R} \tag{7}$$

is the dimensionless velocity and

$$\beta = \frac{\gamma_v - 1}{\gamma_v + 1}, \quad \gamma_v = \frac{\eta_2}{\eta_1}, \quad h_z = \frac{H_z}{H_0}. \tag{8}$$

Here $\eta_2$ is the blood viscosity, $\eta_1$ is the viscosity of magnetic drug and $u_0$ is the mean blood flow velocity.

Thus, instead of one adhesion condition, Voltairas *et al.* [4] obtained two Eqs. (3) and (6) and the dependence of the blood flow velocity on the applied magnetic field was parameterized as

$$\mathrm{B_m} = \mathrm{B_m}(R/\delta, \chi, \omega) \tag{9}$$

and

$$V_\mathrm{m} = V_\mathrm{m}(R/\delta, \chi, \omega, \gamma_v). \tag{10}$$

The obtained law $V_\mathrm{m} = V_\mathrm{m}(\mathrm{B_m})$ gives an upper bound of the mean blood flow velocity, at which the applied magnetic field is able to capture a magnetic drug drop on the blood vessel wall.

## 2. The manufacturing of the focused magnet.

*2.1. Theoretical background.* To achieve a proper non-uniform magnetic field, able to localize a magnetic drop inside the body, two types of magnets could be used – permanent magnets or electromagnets. Permanent magnets generate magnetic fields, which are rather weak for trapping magnetic drops in a bulk vessel. Electromagnets generate stronger magnetic fields, however, they need an outer source of electrical current and they produce the Joule heat. Our aim was to develop an arrangement of permanent magnets, which could generate a higher

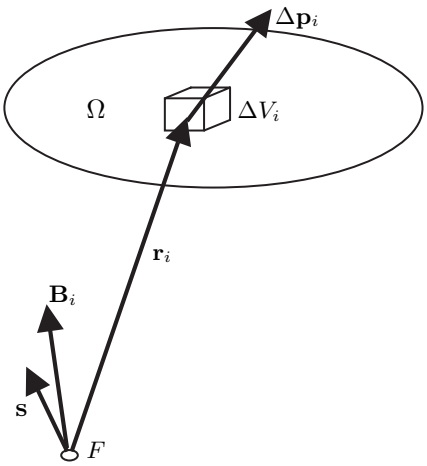


*Fig. 1.* Illustration of the studied problem: $\Omega$ – closed part of space with a permanent magnet; $\mathbf{B}_i$ – magnetic induction generated by magnetic moment $\Delta\mathbf{p}_i = \mathbf{M}(r_i)\Delta V_i$.

induction and gradient of magnetic field than classical magnets with simple geometry. The first step in manufacturing such focused magnet was a theoretical optimization of the magnetic field generated by a permanent magnet.

Let us consider a closed part of space $\Omega$ with a permanent magnet or a frame of permanent magnets. The magnitude of magnetization $\mathbf{M}$ is given by the properties of the used material. Our question is: at which orientation of the magnetization in $\Omega$ will the maximal projection of induction $\mathbf{B}$ into direction $\mathbf{s}$ at point $F$ (Fig. 1) be achieved?

The volume $\Omega$ can be divided into elements $\Delta V_i$ with position vectors $\mathbf{r}_i$, starting at point $F$. The magnetic induction $\mathbf{B}$ at point $F$ is then the sum of contributions $\Delta\mathbf{B}_i$ generated by magnetic moments $\Delta\mathbf{p}_i = \mathbf{M}(r_i)\Delta V_i$. The radial, tangential and azimuthal components of contribution $\Delta\mathbf{B}_i$ are

$$\Delta B_{i,r} = \frac{\Delta p_i}{r^3} \cdot 2\cos\alpha_i, \tag{11}$$

$$\Delta B_{i,\Theta} = \frac{\Delta p_i}{r^3} \cdot \sin(-\alpha_i), \tag{12}$$

$$\Delta B_{i,\varphi} = 0, \tag{13}$$

respectively, where $\alpha_i$ is the angle between $\Delta\mathbf{p}_i$ and $\mathbf{r}_i$. The projection $\Delta B_{i,s}$ of vector $\Delta\mathbf{B}_i$ into direction $\mathbf{s}$ is the sum of projections of its components. The projection of the radial component is $\Delta B_{i,r} \cdot \cos\upsilon_i$, where $\upsilon_i$ is the angle between $\mathbf{s}$ and $\mathbf{r}_i$. The projection of the tangential component at fixed $\alpha_i$ and $\upsilon_i$ is maximal, if vectors $\mathbf{s}$, $\Delta\mathbf{p}_i$ and $\mathbf{r}_i$ lie in the same plane and the azimuthal angle of vectors $\mathbf{s}$ and $\Delta\mathbf{p}_i$, with respect to positional vector $\mathbf{r}_i$, is equal to $\pi$. Then this projection is equal to $\Delta B_{i,\Theta} \cdot \sin(-\upsilon_i)$ and

$$\Delta B_{i,s} = \Delta B_{i,r} \cdot \cos\upsilon_i + \Delta B_{i,\Theta} \cdot \sin(-\upsilon_i). \tag{14}$$

Using Eqs. (11) and (12), the projection $\Delta B_{i,s}$ can be expressed as

$$\Delta B_{i,s} = \frac{\Delta p_i}{r_i^3}(2\cos\alpha_i \cdot \cos\upsilon_i + \sin\alpha_i \cdot \sin\upsilon_i). \tag{15}$$

The optimizing condition for $\Delta B_{i,s}$ reads

$$\frac{\mathrm{d}(\Delta B_{i,s})}{\mathrm{d}(\alpha_i)} = 0, \tag{16}$$

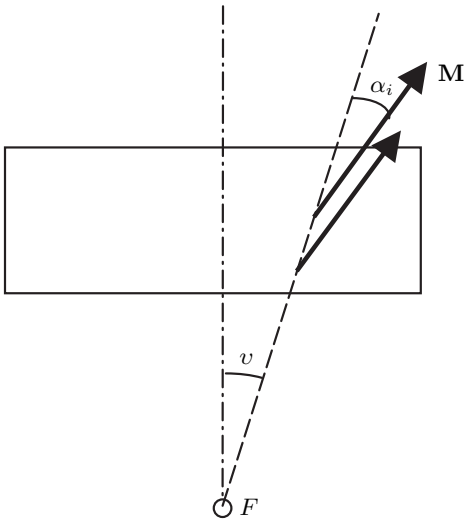


*Fig. 2.* The magnetic focusing, corresponding to the condition $\tan\alpha = 1/2\tan\upsilon$.

that yields

$$-2\sin\alpha_i \cdot \cos\upsilon_i + \cos\alpha_i \cdot \sin\upsilon_i = 0. \tag{17}$$

Thus, the angle $\alpha_i$ is optimal if

$$\tan\alpha_i = \frac{1}{2}\tan\upsilon_i. \tag{18}$$

This condition determines the direction of the lines of force of the magnetic field generated by a fictive dipole of direction $\mathbf{s}$, located at point $F$. If condition Eq. (18) is accomplished in all volume elements of $\Omega$, then the sum of their contributions will be optimal, too. Now we can summarize: if the magnetization of permanent magnet (a system of permanent magnets) is parallel to the lines of force of a dipole of direction $\mathbf{s}$, localized at point $F$, then the projection of the magnetic induction generated by this magnet into direction $s$ at point $F$ will be optimal.

*2.2. Construction of the focused magnet.* The principle of magnetic focusing, consisting in fulfilment of condition Eq. (18), is presented in Fig. 2 for the simple case of prism. It is evident that the manufacturing of such magnet from one piece would be very problematic. Nevertheless, some approach, which implements the principle at least in a reasonable approximation, should be viable.

We could apply the information that the direction of magnetization is parallel to the straight lines passing the focus (see Fig. 2). It means that the magnet could be composed of pyramids with peaks in focus $F$; the direction of the magnetization in the pyramids should be parallel – satisfying approximately the condition given by Eq. (18).

Following the above mentioned considerations and taking into account the technological simplicity, we proposed the construction of a compound focused magnet. Its cross-section is schematically presented in Fig. 3. Using a computer model, in which the magnetic field and its gradient for different focus distances were calculated, the parameters of the focused magnet were compared with a prism magnet. The found results are illustrated in Fig. 4.

The original FeNdB magnet had a form of rectangular prism ($40\times40\times10$ mm), the preferred direction of magnetization was perpendicular to its greatest side. Prior to magnetization, the magnet was cut into six prisms by an electro-spark cutter, according to the scheme shown in Fig. 3. Moreover, each prism was shaped

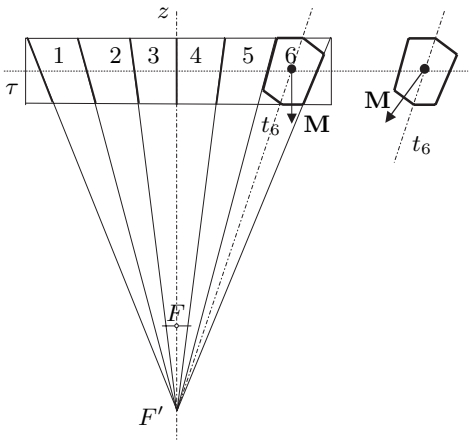


*Fig. 3.* The crossed-section of the focused magnet.

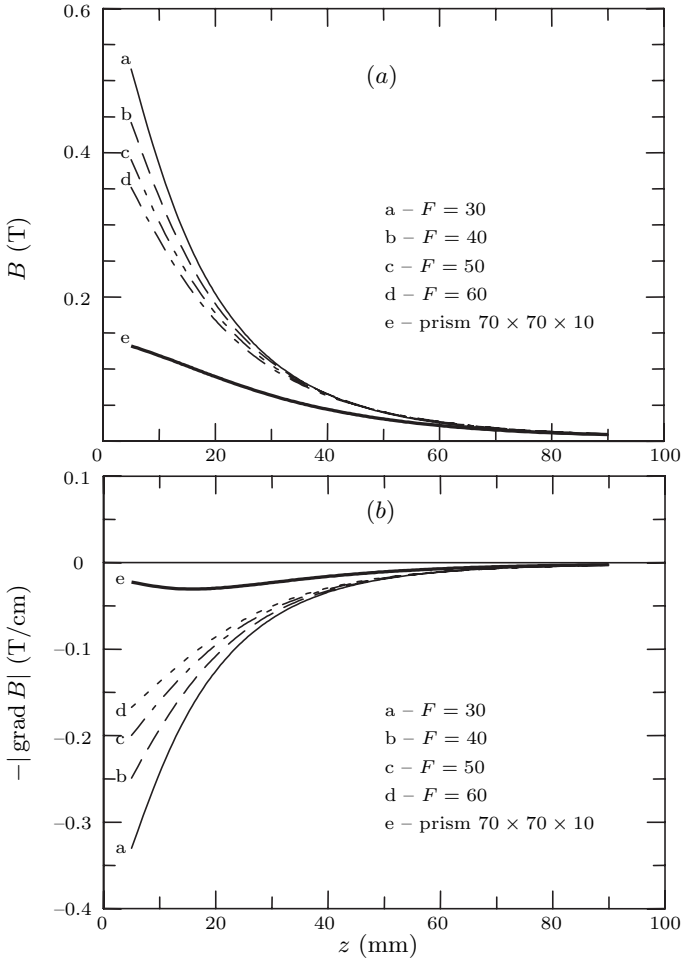


*Fig. 4.* (*a*) The magnetic field and (*b*) the magnetic field gradient calculated for the proposed focused permanent magnet NdFeB, comparison with the prism magnet. $F$ – focus distance of the proposed magnet in mm, $x = 0$, $y = 0$.

in such a way, that its cross-section became symmetric with regard to the axis, crossing its center of mass and peak $F'$. This modification is shown for prism No. 6. Then the prisms were rotated through 180° about the axes $t_i$, $i = 1 - 6$ and glued to their neighbours. The position of prism No. 6 after gluing is shown in the right margin of Fig. 3 – it occupies the same part of space but the direction of magnetization was changed due to rotation. After the gluing, the cutting procedure into six prisms followed, according to the same scheme. The only difference was that the glued magnet was turned through 90° about the $z$-axis before a new cutting, so a checkered structure of the magnet was obtained. The turning and gluing of the prisms were repeated and finally a compound intermediate magnet was obtained, with magnetization of each part directed into approximately one point on the $z$-axis. This point lies in the middle of the distance between the plane $\tau$ and peak $F'$ (in the plane $\tau$ the centers of mass of the parts of the compound magnet lie). Note that point $F$ lies approximately at 3/4 of the distance $\tau - F'$. After the second gluing the intermediate magnets were enclosed into a brass mantle and magnetized in an uniform magnetic field of 15 T. In such a way the focused magnet, designed for the magnetic targeted drug delivery, was obtained.

**3. Testing of the constructed focused magnet** The profile of the magnetic field of the constructed focused magnet is shown schematically in Fig. 5. In order to test the magnet ability to generate a strong magnetic field in deep position, the found profile of its magnetic field was used in a numerical calculation following the Voltairas *et al.* model. The aim was to find the parameters, for which the dependence $\mathrm{B_m}(V_\mathrm{m})$ fits the curves obtained in [4]. The best fit, obtained for the distance between the pole of the magnet and the vessel wall, being $1.5 - 2$ cm longer than that in [4], is presented in Fig. 6. So it can be said that using our specially focused magnet a stronger magnetic field can be induced in deep position that could enable the non-invasivity of the magnetic drug targeting procedure.

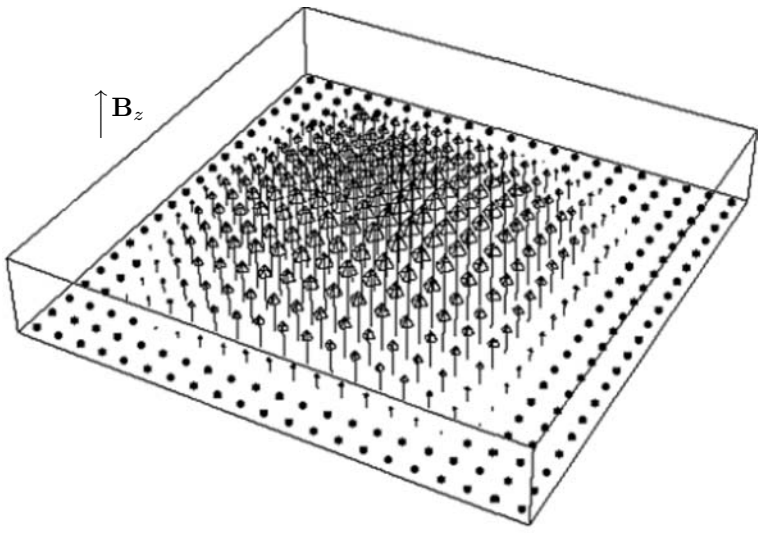


*Fig. 5.* Illustration of the profile of the magnetic field of the manufactured focused magnet.

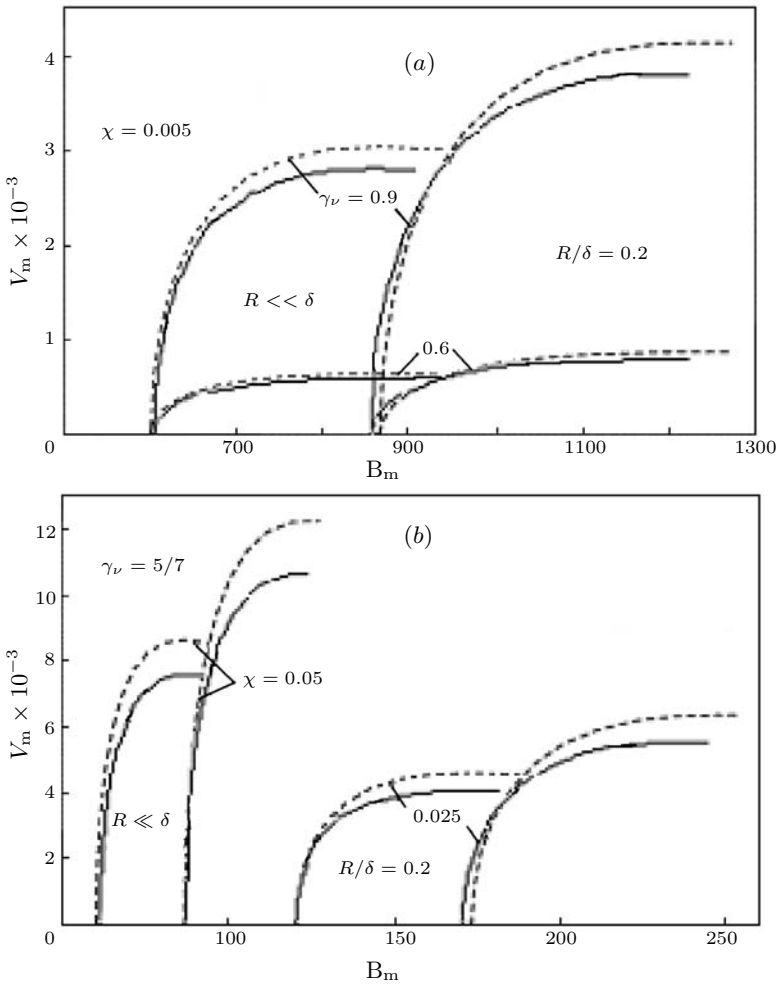


*Fig. 6.* Magnetic bond number $B_m$ vs. $V_m$ (*a*) for $\chi = 0.005$ and varying $\gamma_v$, and (*b*) for $\gamma_v = 0.5$ and varying $\chi$; $R/\delta = 0$ and $R/\delta = 0.2$ (- - - curves obtained by Voltairas *et al.* ; —— our fit).

**4. Conclusions.** A focused magnet consisting of 36 pyramid-shaped prisms was manufactured, which can generate a stronger magnetic field and a higher magnetic field gradient if compared to the classical prism. The magnetic field of the focused magnet was mapped and its profile was used in numerical calculations, yielding the upper bound of the mean blood flow velocity, at which the applied magnetic field is able to capture a magnetic drug drop on the blood vessel wall. The obtained results have verified the ability of the magnet to generate a sufficient magnetic force in deep position that could contribute to the non-invasivity of the magnetic drug targeting procedure.

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