

Theoretical analysis of magnetic particle trajectory in high-current pulsed quadrupole: implications for magnetic cell separation, drug targeting, and gene therapy

A. KRAFČÍK, M. BABINCOVÁ, P. BABINEC*

Department of Nuclear Physics and Biophysics, Comenius University, Mlynská dolina F1, 842 48 Bratislava, Slovak Republic

A novel magnetic cell, drug, or gene targeting system utilizing high gradient magnetic separation principles was proposed and analyzed theoretically. The system is based on four wires carrying high electric current for a short time, creating a quadrupolar magnetic field with high intensity and gradient. Analyzing trajectories of magnetic nanoparticles as well as microparticles we have found that the mean capture time is sufficiently short, and the biomedical applications of such a system are feasible.

(Received December 17, 2008; accepted March 19, 2009)

Keywords: Magnetic separation, Drug targeting, Gene therapy, Pulsed quadrupolar magnet, Magnetic particles

1. Introduction

Magnetic drug delivery by particulate carriers is a very efficient method of delivering a drug to localized disease site. Magnetic drug transport technique is based on the fact that the drug can be either encapsulated into a magnetic microsphere (or nanosphere) or conjugated on the surface of the micro/nanosphere. When the magnetic carrier is intravenously administered, the accumulation takes place within area to which the magnetic field is applied. The accumulation of the carrier at the target site allows them to deliver the drug locally. Efficiency of accumulation of magnetic carrier on physiological carrier depends on physiological parameters, eg. particle size, surface characteristic, field strength, and blood flow rate. The magnetic field helps to extravasate the magnetic carrier into the targeted area. Very high concentration of chemotherapeutic agents can be achieved near the target site without any toxic effect to normal surrounding tissue or to whole body. It is thus possible to replace large amounts of drug targeted magnetically to localized disease site, reaching effective and up to several fold increased drug levels [1-8].

The two key magnetic components of such systems are the magnetic particles used in the separation of the biological entities, and the magnetic field used to separate them. Such a field is usually generated by the presence of permanent magnets, while some devices use electromagnets to achieve the same aim — the generation of a static magnetic field with a significant field gradient, within the target volume. Simple magnet blocks typically generate field gradients in the order of $1\text{--}6\text{ Tm}^{-1}$ across the diameter of standard 15–50 ml laboratory test tubes. High-gradient magnet separators [9] generate field gradients that are significantly higher than this, through the use of

optimally designed magnetic circuits. Across 15–50 ml test tubes, such systems may generate gradients ranging from 10 to 100 Tm^{-1} .

A laboratory prototype of a flow cell sorter based on magnetic quadrupole field was built and evaluated already ten years ago [10]. The magnetic force acting on magnetically labeled cells in such a field has a ‘centrifugal’ character which provides a basis for the design of a continuous separation process. The sorter was tested on a model cell system of human peripheral lymphocytes labeled with magnetic colloid.

Pulsed magnetic quadrupole lenses have been developed for focusing high energetic heavy ion beams [11, 12]. Pulsed beam guidance elements have been used so far to solve crucial problems of accelerator physics. Such problems are for instance the extraction of ion beams out of synchrotrons by kicker magnets, or strong final focusing achieved by plasma lenses. For accelerators, operated in a single-shot mode, however, ion beams in principle could be guided by pulsed devices exclusively. Quadrupole lenses, used most frequently in accelerator technology, can be built by an arrangement of four electric conductors parallel to the optic axis [13]. A strong electric current flowing through neighbouring conductors in opposite directions will produce such a magnetic field distribution of fourfold symmetry.

2. Theoretical modelling

2.1. Magnetic force

We suppose magnetic force acting on a magnetic nanoparticle according effective dipole moment method in which a magnetic particle is replaced by an “equivalent”

point dipole with a moment $\mathbf{m}_{p,\text{eff}}$. In this framework the force affecting on the particle is given by [14]

$$\mathbf{F}_m = \mu (\mathbf{m}_{p,\text{eff}} \cdot \nabla) \mathbf{H}_a, \quad (1)$$

where μ is the permeability of ambient of the particle, $\mathbf{m}_{p,\text{eff}}$ is “effective” dipole moment of the particle, which depends on $\mathbf{H}_a$, the externally applied magnetic field intensity at the center of the particle - in the place of equivalent point dipole location. The magnetic force on particles is a function of the external magnetic field gradient and the magnetization of the particle. Before saturation, particles are linearly magnetized with their magnetic moment magnitude increasing in the direction of the external field. Beyond the saturation point, magnitude of the moment tends to a constant value. Furlani developed magnetization model of the particles based on self-demagnetization and magnetic saturation [15]. In this model,

$$\mathbf{m}_{p,\text{eff}} = V_p f(H_a) \mathbf{H}_a \quad (2)$$

we consider magnetic nanoparticle with radius R_p and volume V_p , and function

$$f(H_a) = \begin{cases} \frac{3(\chi_p - \chi_f)}{(\chi_p - \chi_f) + 3}, & H_a < \left(\frac{(\chi_p - \chi_f) + 3}{3\chi_p} \right) M_{sp} \\ M_{sp}/H_a, & H_a \geq \left(\frac{(\chi_p - \chi_f) + 3}{3\chi_p} \right) M_{sp} \end{cases} \quad (3)$$

where χ_p and χ_f are the magnetic susceptibilities of the particle and ambient fluid, respectively, M_{sp} is the saturation magnetization of the particle, and $H_a = |\mathbf{H}_a|$.

We assume that the fluid is nonmagnetic ($\chi_f = 0$) and the susceptibility of magnetic particles is $\chi_p \approx 1$, what is in the case of water or air as fluid ambient and magnetite (Fe_3O_4) as particles (almost) accomplished. In this case

$$f(H_a) = \begin{cases} 3, & H_a < M_{sp}/3 \\ M_{sp}/H_a, & H_a \geq M_{sp}/3 \end{cases} \quad (4)$$

Below, we use for description of magnetic field flux density (B), which is in dependence with field intensity (H) by relation

$$\mathbf{H}_a = \frac{\mathbf{B}}{\mu}. \quad (5)$$

2.1.1. Magnetic field created by ideal wire quadrupole

According to Biot – Savart law flux density B of magnetic field of four ideal parallel infinite electric wires arranged in edges of square, driven by electric current I flowing through neighbouring conductors in opposite direction, can be describe in the plane perpendicular to the conductors by

$$\begin{aligned} B_x(x, y) &= \frac{\mu I}{2\pi} \left(+\frac{y}{(a-x)^2 + y^2} - \frac{y-a}{x^2 + (a-y)^2} + \right. \\ &\quad \left. +\frac{y}{(a+x)^2 + y^2} - \frac{y+a}{x^2 + (a+y)^2} \right) \\ B_y(x, y) &= \frac{\mu I}{2\pi} \left(-\frac{x-a}{(a-x)^2 + y^2} + \frac{x}{x^2 + (a-y)^2} - \right. \\ &\quad \left. -\frac{x+a}{(a+x)^2 + y^2} + \frac{x}{x^2 + (a+y)^2} \right) \\ B_z(x, y) &= 0 \end{aligned} \quad (6)$$

which is the superposition of magnetic flux densities formed by this four single conductors, and where a is the distance of the wires from the longitudinal axis of this quadrupole.

In these terms, magnetic force acting on magnetic nanoparticle in the field of ideal wire quadrupole can be obtained by combination of expressions (1), (2) and (4)-(6).

2.2. Stokes drag force

In our model we regard in addition to magnetic force a fluidic force acting on moving particle in ambient fluid. It is predicted using the Stokes' law for the drag on a sphere in uniform flow,

$$\mathbf{F}_f = -6\pi\eta R_p (\mathbf{v}_p - \mathbf{v}_f) \quad (7)$$

where η and $\mathbf{v}_f$ are the viscosity and the velocity of the fluid, respectively, and R_p and $\mathbf{v}_p$ are the radius and the velocity of the particle. In our case we consider that fluid is not moving, i.e. $\mathbf{v}_p = 0 \text{ m.s}^{-1}$.

2.3. Equations of motion

The differential equations governing the motion of a spherical particle subjected to the magnetic and Stokes forces is given by

$$\begin{aligned} m \frac{d^2 x}{dt^2} &= F_{mx} + F_{fx} \\ m \frac{d^2 y}{dt^2} &= F_{my} + F_{fy} \end{aligned} \quad (8)$$

where m is the mass of the particle.

3. Results and discussion

The behavior of a fine magnetic particle inside the quadrupolar magnetic field created by wires carrying currents, with magnetic flux density lines and flux density B of magnetic field shown in Fig. 1, is determined by the balance between magnetic and Stokes drag forces that are exerted on the particle (Eq. 10). The theoretical model described in the previous sections was numerically implemented in order to obtain particle trajectories. Differential equations were solved using Matlab's ODE15s solver. The standard solver was not effective, due

to stiffness [19] of the solved problem. We have analyzed motion of nanoparticles with radius of 50 nm, which are often used in magnetic drug targeting, as well as microparticles with radius 10 μm , often used for magnetic separation purposes or vein embolization.

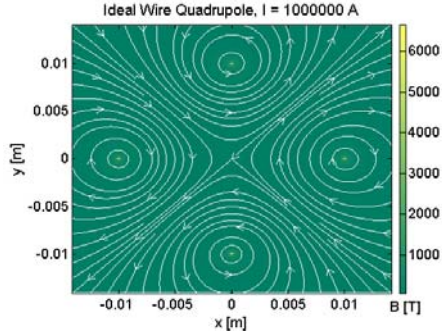


Fig. 1. Magnetic flux density lines and flux density B of magnetic field of ideal wire quadrupole with current 10^6 A in transversal plane.

In Fig. 2 are shown snapshots of trajectories of the 100 + 100 magnetite particles of both sizes in the field of ideal wire quadrupole with current 10^6 A in water in different times. Computation of trajectory for each particle was stopped after it reached the distance 1 cm from the center. The larger microparticles were captured very easily in about 0.5 ms. The majority of smaller nanoparticles were captured after few seconds.

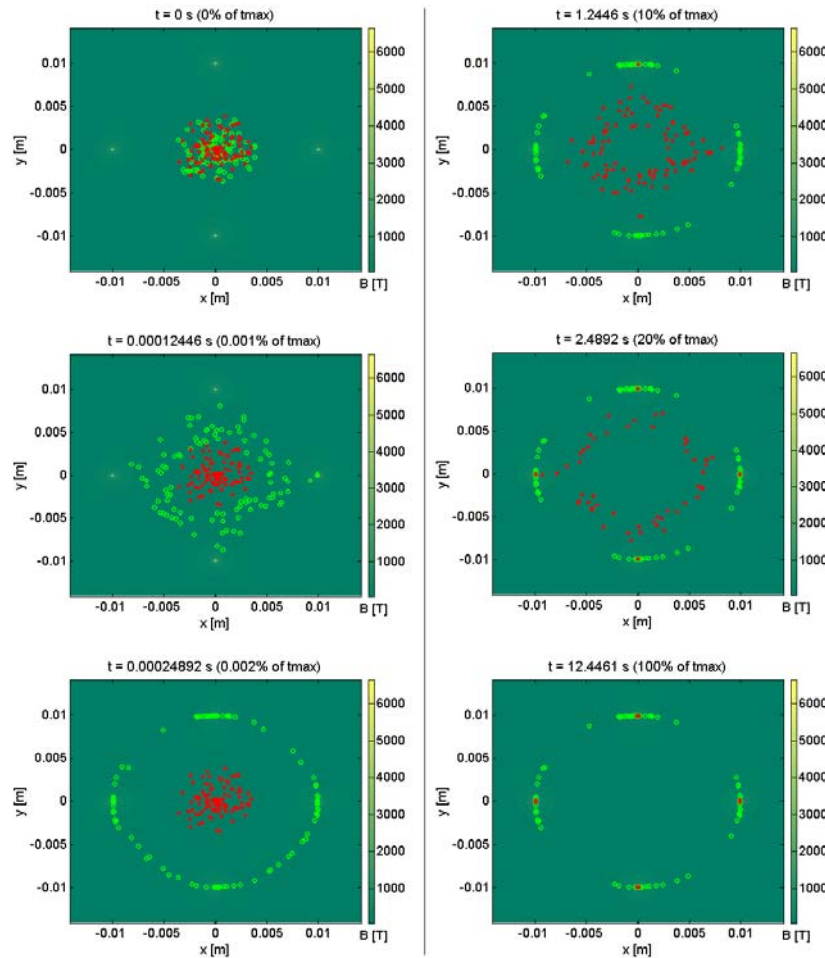


Fig. 2. Snapshots of trajectories of the magnetite particles with different sizes, the big one (green) with radius 10 μm and the small one (red) with radius 50 nm, in the field of ideal wire quadrupole with current 10^6 A in water, in different times, where t_{max} is time of the movement of the slowest particle. Computation of trajectory for each particle was stopped after it reached the distance 1 cm from the center. We consider saturation magnetization of magnetite particle $4.78 \cdot 10^5 \text{ A} \cdot \text{m}^{-1}$ and viscosity of water $1.003 \cdot 10^{-3} \text{ N} \cdot \text{s} \cdot \text{m}^{-2}$.

We were also interested in the dependence of mean capture time of the magnetite particles on their radius not only in the water but also in the air (Fig. 3), because recently very important experiments with magnetic gene targeting into the lung were made [20]. This is also important from the technological point of view, because magnetic filtration in high-gradient field is often used for air cleaning. As can be seen from Fig. 3, in the air the mean capture time for 50 nm magnetic nanoparticle is lower than 0.1 s, therefore very promising applications can be anticipated.

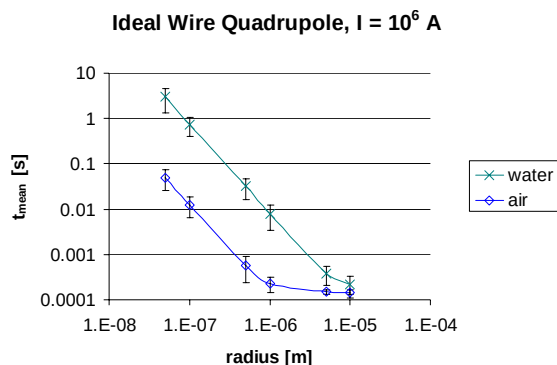


Fig. 3. Dependence of mean capture time of the magnetite particles on their radius (calculations were done for radii: 5×10^{-8} , 10^{-7} , 5×10^{-7} , 10^{-6} , 5×10^{-6} and 10^{-5} m) in the field of ideal wire quadrupole with current 10^6 A for two different fluid media: water (viscosity 1.003×10^{-3} N.s.m⁻²) and air (viscosity 1.82×10^{-5} N.s.m⁻²).

Finally, we have calculated dependence of the mean capture time of the magnetite particles on the current flowing through conductors for small (with radius 50 nm) and large (radius 50 μ m) particles in the water (Fig. 4). Our model is more appropriate for a larger particles, because for particles with size smaller than ~ 40 nm in the magnetic field smaller than 0.2 T Brownian motion is important part of their kinematics [21].

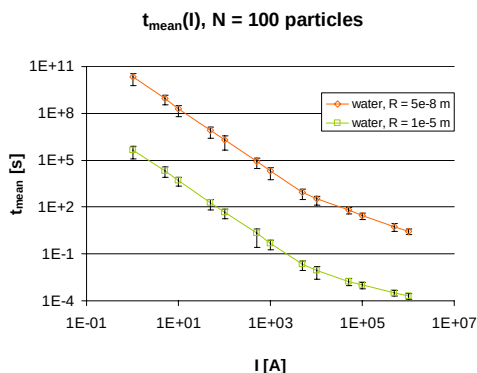


Fig. 4. Dependence of mean capture time of the magnetite particles on the current flowing through conductors for small (with radius 50 nm) and large (radius 50 μ m) particles in the water, in the field of ideal wire quadrupole.

We have also neglected that in the presence of the magnetic field, the magnetized particles in a fluid are attracted to each other by magnetic dipolar interaction, agglomerate and move as a cluster [22]. Nevertheless the total magnetic moment of such a cluster would be substantially higher than magnetic moment of individual particles and due to enhanced magnetic responsiveness they would move faster towards the attracting magnets.

3. Conclusions

A new possibility for a cell separation, drug targeting, and magnetofection utilizing high gradient quadrupolar magnetic field created by a short high current electric pulses has been described. Analyzing trajectories of magnetic nanoparticles as well as microparticles we have found that the mean capture time is sufficiently short, and the biomedical applications of such a system are feasible.

Acknowledgments

This work was supported by VEGA grant 1/0082/08 and Magseletofection project of 6. FP of EU under the contract No.: LSHB-CT-2006-019038.

References

- [1] M. Babincova, D. Leszczynska, P. Sourivong, P. Cicmanec, P. Babinec, J. Magn. Mater. **225**, 109 (2001).
- [2] M. Babincova, J. Novotny, J. Rosenecker, P. Babinec, Optoelectron. Adv. Mater. - Rapid Comm. **1**, 644 (2007).
- [3] M. Babincová, P. Cicmanec, V. Altanerová, C. Altaner, P. Babinec, Bioelectrochemistry **55**, 17 (2002).
- [4] M. Babincová, Bioelectrochem. Bioenerg **32**, 187 (1993).
- [5] I. Nedkov, J. Optoelectron. Adv. Mater. **9**, 24 (2007).
- [6] O. Rotariu, L. E. Udrea, N. J. Strachan, S. D. Heys, A. C. Schofield, F. J. Gilbert, V. Badescu, J. Optoelectron. Adv. Mater. **8**, 1758 (2006).
- [7] M. Babincová, V. Altanerová, C. Altaner, P. Cicmanec, P. Babinec, Med. Phys. **31**, 2219 (2004).
- [8] M. Babincová, V. Altanerová, C. Altaner, C. Bergemann, P. Babinec, IEEE Trans. NanoBioscience **7**, 15 (2007).
- [9] G. P. Hatch, R. E. Stelter, J. Magn. Mater. **225**, 262 (2001).
- [10] M. Zborovski, L. Sun, L. R. Moore, P. S. Williams, J. J. Chalmers, J. Magn. Mater. **194**, 224 (1999).
- [11] V. Chichkine, A. Winkler, K. H. Behr, H. Geissel, A. Kalimov, G. Li, G. Muenzenberg, C. Scheidenberger, H. Weick, H. Wollnik, IEEE Trans. Appl. Superconduct. **12**, 699 (2002).
- [12] W. Lou, D. Hartill, D. Rice, D. Rubin, Phys. Rev. **AB**

- 1, 022401 (1998).
- [13] M. Winkler, G. Li, C. Weil, H. Wollnik, P. Spiller, D. H. H. Hoffmann, A. Tauschwitz, Nucl. Inst. Phys. Res. A **344**, 455 (1994).
- [14] E. P. Furlani, K. C. Ng, Phys. Rev. E **73**, 061919 (2006).
- [18] E. P. Furlani, K. C. Ng, Phys. Rev. E **77**, 061914 (2008).
- [19] A. Biran, M. Breiner, Matlab 5 for Engineers, Boston, MA: Addison-Wesley, 1999.
- F. Wiekhorst, D. Eberbeck, I. Bittmann, C. Bergemann, T. Weyh, L. Trahms, J. Rosenecker, C. Rudolph, Nature Nanotechnol. **2**, 495 (2007).
- [21] O. Rotariu, G. Iacob, N.J.C. Strachan, H. Chiriac, Biotechnol. Prog. **20**, 299 (2004).
- [22] G. Iacob, O. Rotariu, N. J. C. Strachan, U. O. Hafeli, Biorheology **41**, 599 (2004).
- *Corresponding author: babinec@fmph.uniba.sk