A TRANSPORT MODEL FOR DRUG TARGETTING WITH NANO PARTICLES

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Abstract: Magnetic drug targeting of tumors situated in the cavity of the human body is difficult because the magnetic gradients decrease rapidly with the distance from the magnets. A mathematical model for targeted drug delivery using magnetic particles is developed. The model is used to track particles in a vessel network and Magnetic field design is discussed. Nanomaterials are at the leading edge of the rapidly developing field of nanotechnology. Magnetic nanoparticles for cancer therapy and diagnosis have been developed on the basis of their unique physico-chemical properties not present in other materials. In this review we concentrate on the physical principles of magnetic drug targeting and biomedical applications of this technique. An analytical model is developed for the purpose of magnetic targeting into the lung using a quadrapole magnet.

Keywords: Magnetic Targeting, drug delivery, nano particles, mathematical modelling and magnetic particles.

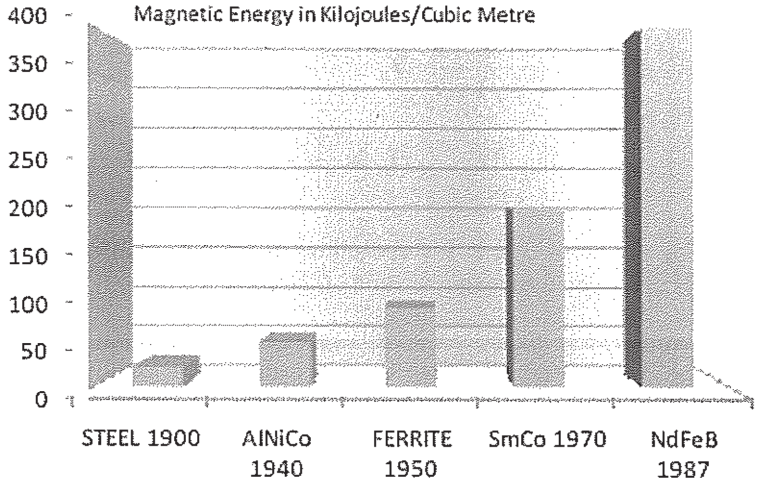
1. INTRODUCTION

One of the most promising fields of research lying on the border of medicine, biology, physics, chemistry, and engineering – "nanomedicine", according to the definition given by USA National Institutes of Health is based on the applications of nanotechnology for treatment, diagnosis, monitoring, and control of biological systems. In the forefront of this field is research into the rational delivery and targeting of pharmaceutical, therapeutic, and diagnostic agents. The oldest and still most vivid subfield is applications of magnetic nanoparticles (MNs) in biology and medicine. Multifunctional MNs which are the topic of this review have diverse potential applications in many biological and medical applications such as cell separation, drug targeting, electromagnetic hyperthermia, magnetic resonance contrast enhancement.

2. SOURCES OF MAGNETIC FIELD

Permanent magnets are made from "hard" ferromagnetic materials which are designed to stay magnetized, while "soft" ferromagnetic materials like soft iron are attracted to a magnet but do not tend to stay magnetized. Human tissues have a very low level of susceptibility to static magnetic fields, there is no direct scientific evidence showing a health hazard associated with exposure to these fields. The most commonly used ceramic, or ferrite, magnets are made of a sintered composite of powdered iron oxide and barium/strontium carbonate ceramic, noncorroding, but brittle and must be treated like other ceramics. The field of magnetic research has been revolutionarily changed by the introduction of rare-earth magnets. Permanent magnets made from alloys of rare earth elements are substantially stronger than ferrite or alnico magnets. The magnetic field typically produced by rare-earth magnets can be in excess of 120 mT, whereas ferrite or ceramic magnets typically exhibit fields of 50 to 100 mT.

Comparison of Magnetic Energy of most commonly used permanent magnets



3. MAGNETIC DRUG TARGETING

The major problems of chemotherapeutics come essentially from the relative lack of specificity derived from their systemic bio distribution and the subsequent side effects provoked by the drug attacking both healthy and target cells. There are several forces acting on magnetic particles in viscous environment and magnetic field, such as magnetic force due to all field sources. Stokes viscous drag force, inertia, buoyancy and gravity, thermal kinetics (Brownian motion), and of course particle fluid interactions and interparticle effects like magnetic dipole interactions, electric double layer interactions. Given the considerations mentioned before, we can predict the trajectory of motion of magnetic particle in magnetic field and viscous fluid ambient using Newton's law:

$$m_p \frac{d\mathbf{v}_p}{dt} = \mathbf{F}_m + \mathbf{F}_s,$$

where mp and vp are the mass and velocity of the particle, and Fm and Fs are the magnetic and Stoke's drag forces, respectively. Force acting on the dipole is given by

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

where μ is permeability of fluid ambient, mp,eff is "effective"dipole moment of the particle, which depends on externally applied magnetic field intensity Ha at the center of particle, where the dipole moment is localized. According to the magnetization model of particles based on self demagnetization and magnetic saturation developed by Furlani group the effective dipole moment can be expressed as

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

we consider magnetic particle with radius *Rp* and volume *Vp*, and a function

$$f(H_a) = \begin{cases} \dfrac{3(\chi_p - \chi_f)}{(\chi_p - \chi_f) + 3} & H_a < \dfrac{(\chi_p - \chi_f) + 3}{3\chi_p} M_{sp} \\ M_{sp}/\mathrm{H}_a & H_a \geq \dfrac{(\chi_p - \chi_f) + 3}{3\chi_p} M_{sp} \end{cases} \quad (|\chi_f| << 1),$$

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

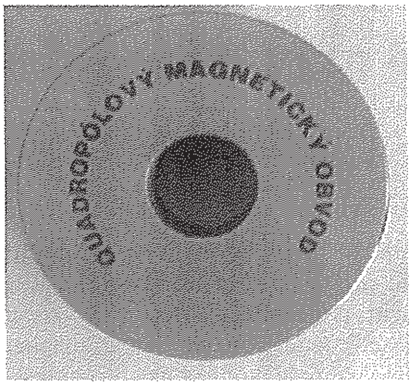
We assume nonmagnetic fluid $(\chi_f \approx 0)$ and high susceptibility of magnetic particles, i.e. $\chi_p > 1$, which is in the case of water or air as fluid ambient, and magnetite
(Fe_3O_4) as particles accomplished; hence

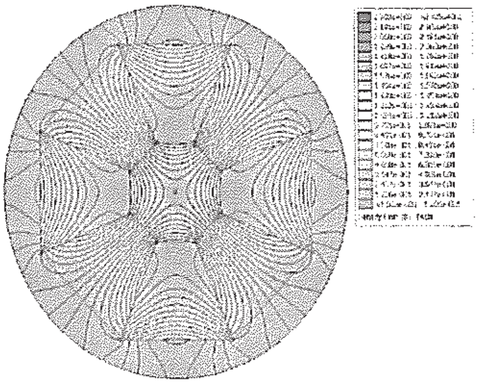
$$f(B) = \begin{cases} 3 & B/\mu < M_{sp}/3 \\ M_{sp}\,\mu/B & B/\mu \geq M_{sp}/3 \end{cases},$$

where *B* is magnetic flux density of external field and is valid:$B/\mu = H_a$.

As an illustration the trajectory of magnetite particles in the magnetic field of permanent quadrupole was modeled as magnetostatic problem by finite element method (FEM). [1]

Permanent Quadrupole realized as an Octapolar Magnet, and its flux density obtained from FEMM Model





Magnetostatic problems are those in which the fields are time-independent. In this case, the field intensity (H) and flux density (B) must obey equations

$$\nabla X H = J,$$

$$\nabla . B = 0,$$

with a constitutive relationship between B and H for each material

$$B = \mu H$$

If a material is nonlinear $\mu = B / H(B)$

$B = \nabla x A$

Then the first equation can be rewritten as:

$$\nabla \times \left(\frac{1}{\mu(\mathrm{B})} \nabla \times \mathrm{A} \right) = \mathrm{J} \cdot$$

$$-\nabla \cdot \left(\frac{1}{\mu} \nabla \right) \mathrm{A} = \mathrm{J} ,$$

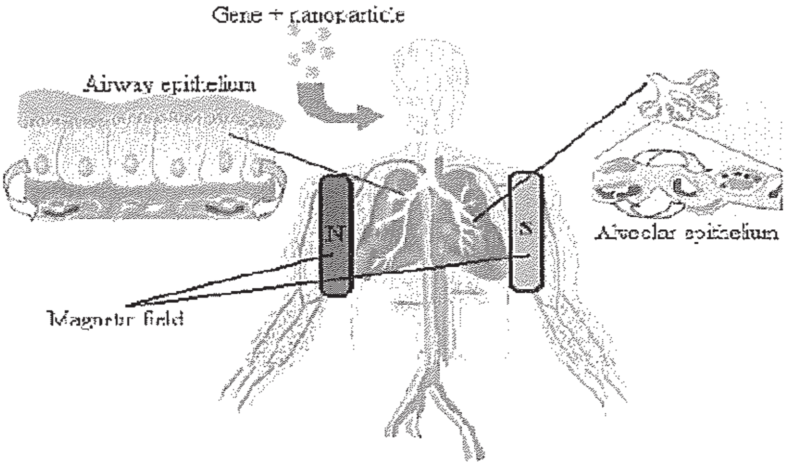
Flux density is defined in x–y plane, i.e. z-coordinate is regarded as magnetic flux density, B_z, equals to zero, which means that magnetic vector potential is equal to A = $(0,0, A)$.

We also confine to current density parallel to z-direction of coordinate system. In this simplification last equation leads to scalar elliptic partial differential equation

$$-\nabla \cdot \left(\frac{1}{\mu} \nabla A \right) = J ,$$

4. MATHEMATICAL MODEL

A planar model of permanent quadrupole represents the distribution of flux density in transversal plane of infinite long permanent magnets arranged to quadrupole with zero value of perpendicular component of flux density. The quadrupole consists of eight sphenoid blocks, in the section, of uniformly magnetized neodymium rare earth magnets with magnetic energy product 37 MG.Oe (megagauss-oersted; NdFeB N37) and with magnetization orientation revolved in 135° between adjacent blocks. The geometry of quadrupole is determined by the radii of inscribed and circumscribed circle, i.e. 1.4 and 4.5 cm in our case, respectively. The quadrupolar magnetic circuit for the purpose of magnetic targeting into lung is illustrated in the Figure given below:



In this model in addition to magnetic force, fluidic force acting on a moving particle in fluid medium is considered. Its magnitude is determined by Stokes' law for the drag on a sphere with radius *Rp* in uniform flow,

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

where η and V_f the viscosity and the velocity of the fluid, respectively, and V_p is the velocity of the particle. In this case the fluid ambient quiescent, i.e$V_f = 0$ m.s^{-1}

$$\frac{dx}{dt} = v_{p,x}$$

$$\frac{dy}{dt} = v_{p,y}$$

$$\frac{dv_{p,x}}{dt} = \frac{1}{m_p}\left\{\frac{V_p}{\mu} f\big(B(x,y)\big)\left[+ B_x(x,y)\frac{\partial B_x(x,y)}{\partial x} + \right.\right.$$
$$\left.\left. + B_y(x,y)\frac{\partial B_x(x,y)}{\partial y}\right] - 6\pi\eta R_p v_{p,x}\right\}$$

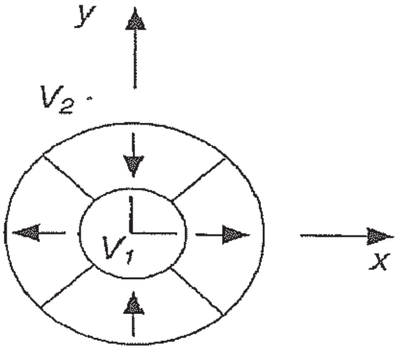
$$\frac{dv_{p,y}}{dt} = \frac{1}{m_p}\left\{\frac{V_p}{\mu} f\big(B(x,y)\big)\left[+ B_x(x,y)\frac{\partial B_y(x,y)}{\partial x} + \right.\right.$$
$$\left.\left. + B_y(x,y)\frac{\partial B_y(x,y)}{\partial y}\right] - 6\pi\eta R_p v_{p,y}\right\}$$

where $m_p = V_p \rho_p$ and $V_p = 4/3\Pi R^3_p$ are the mass and the volume of particle, respectively. The equation of the trajectory is obtained by solving the above system of equations. The flux density is obtained using the formula as given below:

$$B^{(2)}_{\phi}(r, \phi) = \mu_0 \sum_{i=1}^{L} i r^{-(i+1)} U^{(2)}_i(M_i, R_1, R_2, \mu) \sin(i\phi).$$

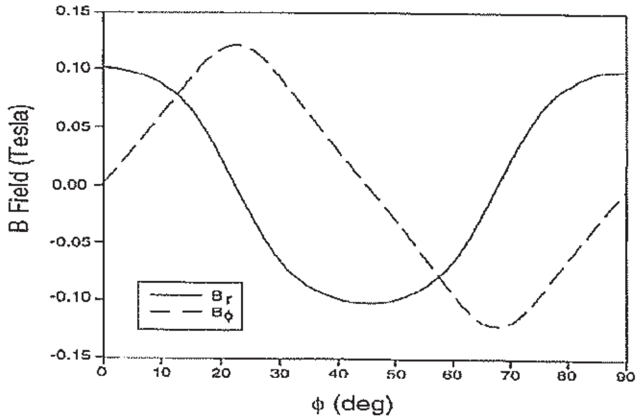
$$B^{(2)}_{r}(r, \phi) = \mu_0 \sum_{i=1}^{L} i r^{-(i+1)} U^{(2)}_i(M_i, R_1, R_2, \mu) \cos(i\phi)$$

GEOMETRY OF THE MODEL



We demonstrate the field solution via the analysis of magnetite (Fe3O4) particles, with density ρ_p = 5000 kg.m $^{-3}$ and a saturation magnetization M $_{sp}$ = 4.78 x 10^5 A.m^{-1} in the magnetic field created by quadrupole consisting of permanent NdFeB N37 magnets, which is represented by magnetic flux density lines and flux density *B* in the figure, in non-moving and nonmagnetic fluid, with viscosity equal to that of water or air, i.e. η = 1.003.x10–3 N.s.m-2 or η = 1.82.x10^{-5} N.s.m^{-2} respectively.

The components B_r and B_ϕ vs ϕ (r =12 mm



5. CONCLUSION

Functional magnetic nanoparticles offer improved spatio-temporal control over drug kinetics and distribution, thus opening the prospect of safer and more specific therapies. Capture time of magnetic particles in magnetic field of quadropole is increased by increasing magnetic flux density and field gradient by replacing permanent magnets by pulsed electromagnets. This analytical model will be highly useful in the development of new drug targeting apparatus and treatment.

6. REFERENCES

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