NUMERICAL APPROACH FOR AN APPLICATION OF MAGNETIC DRUG TARGETING IN CANCER THERAPY

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Cancer patients often present with localized disease. Yet, surgical eradication or radiation treatment is not always possible or meaningful. Site-directed drug targeting is one way of local or regional antitumor treatment. Magnetically controlled drug targeting is one of the various possibilities of drug targeting. This technology is based on binding established anticancer drugs with ferrofluids that concentrate the drug in the area of interest (tumor site) by means of magnetic fields. Then, the drug desorbs from the ferrofluid and enfolds its mechanism of action.

1. INTRODUCTION

Cancer is characterized by a reduction or loss of cellular control and normal maturation mechanisms. Its features include excessive cell growth, undifferentiated cells and tissues, and the ability to grow into neighboring tissues and to metastasize. The choice of treatment includes the total excision of tumor tissue and possibly part of the adjacent tissues, combination chemotherapy, immunotherapy, radiation treatment, and a combination of these. Since complete eradication of cancer cells is imperative for successful treatment, total excision is the treatment of choice if applicable. However, depending on the location and the involvement of the tumor with surrounding tissues, surgery may not always be possible. Under such circumstances radio or chemotherapy becomes necessary. However, severe complications with these treatments have been reported. Therefore, the development of techniques that could selectively deliver drug molecules to the diseased site, without a concurrent increase in its level in the healthy tissues of the organism, is currently one of the most active areas of cancer research. This overview focuses on the fundamentals of drug targeting with particular emphasis on magnetically controlled anticancer chemotherapy [1, 2].

Drug targeting is a principle by which the distribution of drug in the organism is maneuvered in a manner such that its major fraction interacts exclusively with the target tissue at the cellular or subcellular level. Theoretically,
selective or targeted drug delivery systems can improve the outcome of chemotherapy by one or more of the following processes:

- by allowing the maximum fraction of the delivered drug molecule to react exclusively with the cancer cells without adverse effects to the normal cells;
- by allowing preferential distribution of drug to the cancer cells.

Magnetic drug targeting allows the concentration of drugs at a defined target site generally and, importantly, away from the reticular endothelial system (RES) with the aid of a magnetic field. Typically, the intended drug and a suitable magnetically active component are formulated into a pharmacologically stable formulation. Typically, this compound is injected through the artery supplying the tumor tissue in the presence of an external magnetic field with sufficient field strength and gradient to retain the carrier at the target site.

The development of magnetically responsive microspheres has brought an additional driving force into play. Particles that are bound to magnetic fluids can be used to remove cells and molecules by applying magnetic fields and—in vivo—to concentrate drugs at anatomical sites with restricted access. These possibilities form the basis for well-established biomedical applications in protein and cell separation. Additional modifications of the magnetic particles with monoclonal antibodies, lectins, peptides, or hormones make these applications more efficient and also highly specific. A combination of these two advantages makes the magnetic microspheres application so successful in molecular and cell biology, advancing both basic science and clinical practice [3].

In other words, technically, it is difficult to build up sufficient field strength that focuses on a small area and is able to counteract the linear blood-flow rates in the tissue (0.10 cm/s in arteries and 0.005 cm/s in capillaries), so that to effectively retain the magnetic drug carrier, magnetic forces must be high enough to reach that goal. Even with stronger magnets, one important problem remains and must be overcome [1].

Intense efforts are also ongoing in the development of biocompatible magnetic carriers for the directed transport and controlled release of drugs or radionuclides for use as sources of local temperature increase (hyperthermia) and for local contrast enhancement in MR imaging [4]. Recently, the principle of magnetic manipulation has been applied to concentrating magnetic drug carriers in definite regions, provided that the carriers can be transported to the target site.

This model example demonstrates a simple setup to investigate an external magnetic field and its interaction with blood flow with a magnetic carrier substance. The model treats the liquid as a continuum, which is a good first step. The equations and theory are based on the Maxwell’s equation and Navier-Stokes equations. For a representative geometry (blood vessel), the model solves the
Maxwell equations for a static magnetic field. The resulting magnetic field is coupled to a fluid flow problem described by the Navier Stokes equations. By adding a magnetic volume force, which stems from the solution to magnetic field problem, to the Navier Stokes equations, you can study the ferrohydrodynamics of the blood.

2. MODEL DEFINITION

A simple geometric representation of a blood vessel and a permanent magnet is made by making a 2D assumption. A blood vessel is fed with a liquid (blood) from the left in Fig. 1. The velocity and pressure field is calculated in the blood stream. The magnetic field (magnetic vector potential) that is generated by the permanent magnet is calculated. This magnetic field generates a magnetic volume force that affects the flow field in the blood vessel.

For the magnetostatic problem, the solver resolve a problem with perpendicular currents that are zero, and that reduces the Maxwell equations to:

$$\text{rot}\left(\frac{1}{\mu_0 \mu_r} \text{rot} A - M\right) = 0.$$  \hspace{1cm} (1)

An arcus tangent expression with two material parameters $\alpha$ and $\beta$ can characterize the induced magnetization $\mathbf{M}(x, y) = (M_x, M_y)$ of a ferrofluid according to [5].
\[ M_x = \alpha \tan \left( \frac{\beta}{\mu_0 \mu_r} \frac{\partial A_z}{\partial y} \right) \]
\[ M_y = \alpha \tan \left( -\frac{\beta}{\mu_0 \mu_r} \frac{\partial A_z}{\partial x} \right) \]  

Along a system boundary reasonably far away from the magnet it can apply a magnetic insulation boundary condition, \( A_z = 0 \).

The Navier Stokes equations describe the time-dependent mass and momentum balances for an incompressible flow:

\[
\frac{\rho \partial \mathbf{u}}{\partial t} - \nabla \eta (\nabla \mathbf{u} + (\nabla \mathbf{u})^T) + \rho (\mathbf{u} \cdot \nabla \mathbf{u}) + \nabla p = \mathbf{F};
\]

\[
\nabla \cdot \mathbf{u} = 0,
\]

where \( \eta \) denotes the dynamic viscosity [kg/(ms)], \( \mathbf{u} \) the velocity vector [m/s], \( \rho \) the density of the fluid [kg/m³], and \( p \) the pressure [N/m²], \( \mathbf{F} \) is a volume force [N/m³].

With the assumption that the magnetic nanoparticles in the fluid do not interact, the magnetic force \( \mathbf{F} = (F_x, F_y) \) on the ferrofluid for relatively weak fields is proportional to the magnetization according to [6]:

\[
F_x = M_x \frac{\partial^2 A_z}{\partial x \partial y};
\]
\[
F_y = M_y \frac{\partial^2 A_z}{\partial y \partial x}.
\]  

On the vessel walls, apply no-slip conditions, \( u = v = 0 \). At the outlet you can set an outlet pressure condition, \( p = 0 \). At the inlet boundary, specify a parabolic flow profile on the \( x \)-velocity according to \( 4v_0 s (1-s) \), where \( s \) is a boundary segment length parameter that goes from 0 to 1 along the inlet boundary segment and \( v_0 \) the maximum velocity. To emulate the heart beat, the mean \( x \)-velocity \( v \) follows a sinusoidal expression in time and \( y \)-velocity \( u \) is zero.

\[
u = \frac{v_0}{4} s (1-s) \left( \gamma \sin(\omega t) + \sqrt{\sin^2(\omega t)} \right)
\]

Selecting the angular velocity \( \omega \) to \( 2\pi \) results in a heart beat rate of 60 beats per minute.
3. RESULTS AND SIMULATION

First we consider a magnetization of the permanent magnet $M_s = 25 \text{ kA/m}$. Fig. 2 shows a detail from the plot of the magnetic field strength. It is easy to see that the strength of the $B$-field is strongest inside the magnet. The figure does not show field strengths above 0.17 Vs/m² in order to see the low-level variations in the surrounding tissue and vessels. The geometrical form of the magnet generates strong fields just outside of the rounded off corners. Sharper corners generate even stronger local fields.

Fig. 2 – Contour lines of the magnetic vector potential at $M_s = 25 \text{ kA/m}$.

Figures 3–6 shows the velocity field in four cases: Fig. 3 – $M_s = 25 \text{ kA/m}$, Fig. 4 – $M_s = 50 \text{ kA/m}$, Fig. 5 – $M_s = 75 \text{ kA/m}$, Fig. 6 – $M_s = 100 \text{ kA/m}$ at a heart beat where there is a maximum mean throughput through the vessel. At the left end there is a parabolic laminar flow profile. In the experiments show in Fig. 4 and Fig. 5 certain points near the disturbances are exposed to a larger flow rate per unit area (close to the gray areas), whereas some parts are less exposed (black areas near vessel wall).
Fig. 3 – Velocity field at maximum blood throughput \((t = 0.25)\) in the case of \(M_s = 25\) kA/m (maximum velocity 0.375 m/s).

Fig. 4 – Velocity field at maximum blood throughput \((t = 0.25)\) in the case of \(M_s = 50\) kA/m (maximum velocity 0.669 m/s).
One can notice that the flow field is disturbed in the vicinity of the magnet (Figs. 4, 5) and in the Fig. 3 this phenomena does not appear because the magnetization of the magnet is too low.

Fig. 5 – Velocity field at maximum blood throughput ($t = 0.25$) in the case of $M_s = 75$ kA/m (maximum velocity 0.830 m/s).

Fig. 6 – Velocity field at maximum blood throughput ($t = 0.25$) in the case of $M_s = 100$ kA/m (maximum velocity 1.25 m/s).
In the experiment illustrated in Fig. 6 can be noticed a skin effect that can perturb to much the movement of the magnetic particles. The desorption sustained over more than 24 hours and by magnetic fields of several hundred kA/m could determine the ferrofluids carrier that be retained within capillaries [1].

Figures 7–10 reveals the velocity field between two heart beats, where the net throughput is zero. It shows that the blood is not at rest but rather agitated in local eddies by the magnetic forces on the fluid.

**Fig. 7** – Velocity field at zero blood throughput \((t = 1)\) in the case of \(M_s = 25\) kA/m.

**Fig. 8** – Velocity field at zero blood throughput \((t = 1)\) in the case \(M_s = 50\) kA/m.
In some medical reports it was demonstrated that magnetic targeted carriers did not redistribute after removal of the magnetic field and high density particles were found in the interstitium and occasionally intraarterially [1, 7].

**Fig. 9** — Velocity field at zero blood throughput \( t = 1 \) in the case \( M_s = 75 \text{ kA/m} \).

**Fig. 10** — Velocity field at zero blood throughput \( t = 1 \) in the case \( M_s = 100 \text{ kA/m} \).
4. CONCLUSION

Magnetic drug targeting is a means of holding the chemotherapeutic agent at the desired site of activity, thus increasing efficacy and diminishing systemic toxicity. Direction and magnitude reflect the inhomogeneous character of the magnetic field, which is of key importance for magnetic drug targeting. If the particles are too small, the external magnetic field might not provide sufficient attraction so that the particles are drawn into the tumor. The optimal value for the magnetization is between 50–75 kA/m, because, in the case of using a 100 kA/m, a skin effect may appear which implies that the magnetic drug targeting is useless.

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REFERENCES