COMSOL MULTIPHYSICS®

Magnetic Drug Targeting in Cancer Therapy

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Introduction

Current research on methods to target chemotherapy drugs in the human body includes the investigation of bio-compatible magnetic nanocarrier systems. For example, magnetic liquids such as ferrofluids can play an important role as drug carriers in the human body (Ref. 1). As such, they can be used for drug targeting in modern locoregional cancer treatment. A remaining challenge for this medical application is the choice of clinical setting. Important parameters are optimal adjustment of the external magnetic field and the choice of ferrofluid properties.

Avoiding damage to healthy human cells from chemotherapy drugs imposes an upper limit in the treatment dose. This limit impedes the chances of successful treatment of the tumor cells. One objective of modern cancer research is therefore to concentrate chemotherapy drugs locally on tumor tissue and to weaken the global exposure to the organism.

This model of the ferrohydrodynamics of blood demonstrates a simple setup for investigating an external magnetic field and its interaction with blood flow containing a magnetic carrier substance. The model treats the liquid as a continuum, which is a good first step. You can extend this model by particle tracing, making it a multiscale model. The equations and theory are based on Maxwell's equations and the Navier-Stokes equations. You first solve Maxwell's equations in the full modeling domain formed by permanent-magnet, blood-vessel, tissue, and air domains. A magnetic volume force then couples the resulting magnetic field to a fluid-flow problem in the blood-vessel domain described by the Navier-Stokes equations.

Model Definition[1]

The model geometry represents a blood vessel, a permanent magnet, surrounding tissue, and air in 2D. Blood feeds into the vessel from the left in Figure 1. The velocity and pressure fields are calculated in the blood stream. COMSOL Multiphysics computes the magnetic field (magnetic vector potential) generated by the permanent

1. This model was provided by Dr. Daniel J. Strauss, The Institute for New Materials, Inc., www.inm-gmbh.de.

magnet. This magnetic field generates a magnetic volume force that affects the flow field in the blood vessel.

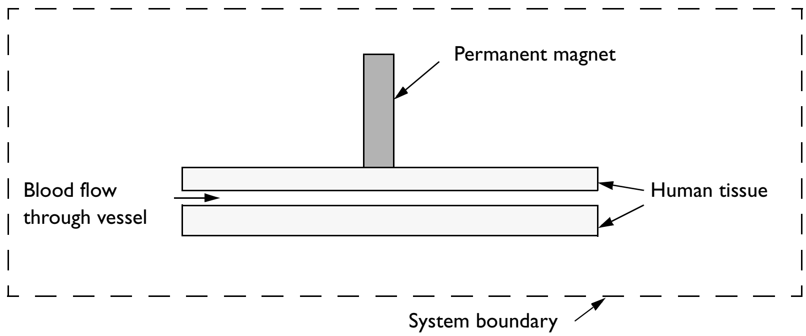

Figure 1: Geometric representation of the model.

MAGNETOSTATIC EQUATIONS

Because the magnetic part of this problem is static, Maxwell-Ampere's law for the magnetic field $\mathbf{H}$ (A/m) and the current density $\mathbf{J}$ (A/m^2) applies:

$$\nabla \times \mathbf{H} = \mathbf{J} \tag{1}$$

Furthermore, Gauss' law for the magnetic flux density $\mathbf{B}$ (Vs/m^2) states that

$$\nabla \cdot \mathbf{B} = 0\,. \tag{2}$$

The constitutive equations describing the relation between $\mathbf{B}$ and $\mathbf{H}$ in the different parts of the modeling domain read:

$$\mathbf{B} = \begin{cases} \mu_0 \mu_{r,\,\mathrm{mag}} \mathbf{H} + \mathbf{B}_{\mathrm{rem}} & \text{permanent magnet} \\ \mu_0(\mathbf{H} + \mathbf{M}_{\mathrm{ff}}(\mathbf{H})) & \text{blood stream} \\ \mu_0 \mathbf{H} & \text{tissue and air} \end{cases} \tag{3}$$

Here μ_0 is the magnetic permeability of vacuum (Vs/(A·m)); μ_r is the relative magnetic permeability of the permanent magnet (dimensionless); $\mathbf{B}_{\mathrm{rem}}$ is the remanent magnetic flux (A/m); and $\mathbf{M}_{\mathrm{ff}}$ is the magnetization vector in the blood stream (A/m), which is a function of the magnetic field, $\mathbf{H}$.

Defining a magnetic vector potential $\mathbf{A}$ such that

$$\mathbf{B} = \nabla \times \mathbf{A}, \qquad \nabla \cdot \mathbf{A} = 0\,, \tag{4}$$

you finally, by substitution in Equation 1 through Equation 3, arrive at the following vector equation to solve:

$$\nabla \times \left(\frac{1}{\mu}\nabla \times \mathbf{A} - \mathbf{M}\right) = \mathbf{J}$$

Simplifying to a 2D problem with no perpendicular currents, this equation reduces to

$$\nabla \times \left(\frac{1}{\mu_0}\nabla \times \mathbf{A} - \mathbf{M}\right) = \mathbf{0}\,. \tag{5}$$

Note that this equation assumes that the magnetic vector potential has a nonzero component only perpendicularly to the plane, $\mathbf{A} = (0, 0, A_z)$.

An arc tangent expression with two material parameters α (A/m) and β (m/A) characterizes the induced magnetization $\mathbf{M}_{\text{ff}}(x, y) = (M_{\text{ffx}}, M_{\text{ffy}})$ of a ferrofluid (Ref. 2):

$$M_x = \alpha \operatorname{atan}\left(\frac{\beta}{\mu_0}\frac{\partial A_z}{\partial y}\right)$$

$$M_y = \alpha \operatorname{atan}\left(\frac{\beta}{\mu_0}\frac{\partial A_z}{\partial x}\right)$$

For the magnetic fields of interest, it is possible to linearize these expressions to obtain

$$\begin{aligned} M_x &= \frac{\chi}{\mu_0}\frac{\partial A_z}{\partial y} \\ M_y &= -\frac{\chi}{\mu_0}\frac{\partial A_z}{\partial x} \end{aligned} \tag{6}$$

where $\chi = \alpha\beta$ is the magnetic susceptibility.

Boundary Conditions

Along a system boundary reasonably far away from the magnet (see Figure 1) you can apply a magnetic insulation boundary condition, $A_z = 0$.

FLUID FLOW EQUATIONS

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

$$\rho\frac{\partial \mathbf{u}}{\partial t} - \nabla \cdot \eta(\nabla \mathbf{u} + (\nabla \mathbf{u})^T) + \rho \mathbf{u} \cdot \nabla \mathbf{u} + \nabla p = \mathbf{F} \qquad (7)$$

$$\nabla \cdot \mathbf{u} = 0$$

where η denotes the dynamic viscosity (kg/(m·s)), $\mathbf{u}$ the velocity (m/s), ρ the fluid density (kg/m^3), p the pressure (N/m^2), and $\mathbf{F}$ a volume force (N/m^3).

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 given by $\mathbf{F} = |\mathbf{M}|\nabla|\mathbf{H}|$. Using Equation 3, Equation 4, and Equation 6 then leads to the expressions

$$F_x = \frac{\chi}{\mu_0\mu_r^2}\left(\frac{\partial A_z}{\partial x}\frac{\partial^2 A_z}{\partial x^2} + \frac{\partial A_z}{\partial y}\frac{\partial^2 A_z}{\partial x \partial y}\right)$$

$$F_y = \frac{\chi}{\mu_0\mu_r^2}\left(\frac{\partial A_z}{\partial x}\frac{\partial^2 A_z}{\partial x \partial y} + \frac{\partial A_z}{\partial y}\frac{\partial^2 A_z}{\partial y^2}\right)$$

To get the final expression for the volume force in the blood stream, multiply these expressions by the ferrofluid mass fraction, k_{ff}.

Boundary Conditions

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 normal inflow velocity according to $4U_\mathrm{m}s(1-s)$, where s is a boundary segment length parameter that goes from 0 to 1 along the inlet boundary segment and U_m is the maximal flow velocity. To emulate the heart beat, the inflow velocity follows a sinusoidal expression in time:

$$U_0 = 2U_\mathrm{m}s(1-s)(\sin(\omega t) + \sqrt{\sin(\omega t)^2})$$

Selecting the angular velocity ω to be 2π rad/s gives a heart beat rate of 60 beats per minute. Figure 2 displays the resulting expression (normalized to unity).

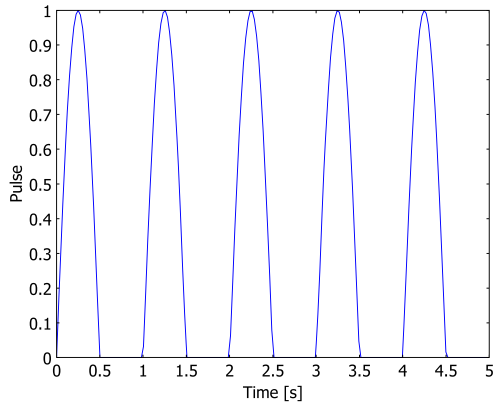

Figure 2: Simulated heart beat.

Model Data

Table 1 lists the relevant material properties for the model.

TABLE 1: MODEL DATA

QUANTITY	DESCRIPTION	VALUE
$\mu_{r,mag}$	Relative permeability, magnet	$5\cdot10^3$
B_{rem}	Remanent flux density, magnet	0.5 T
α	Ferrofluid magnetization-curve parameter	10^{-4} A/m
β	Ferrofluid magnetization-curve parameter	$3\cdot10^{-5}$ (A/m)$^{-1}$
ρ	Density, blood	1000 kg/m^3
η	Dynamic viscosity, blood	$5\cdot10^{-3}$ kg/(m·s)

Results

Figure 3 shows a detail from the plot of the magnetic field strength. The highest B-field strength clearly occurs inside the magnet. To see the low-level variations in the surrounding tissue and vessels, the plot does not show magnetic flux densities above 0.17 T. The geometric form of the magnet generates strong fields just outside of the rounded corners. Sharper corners generate even stronger local fields.

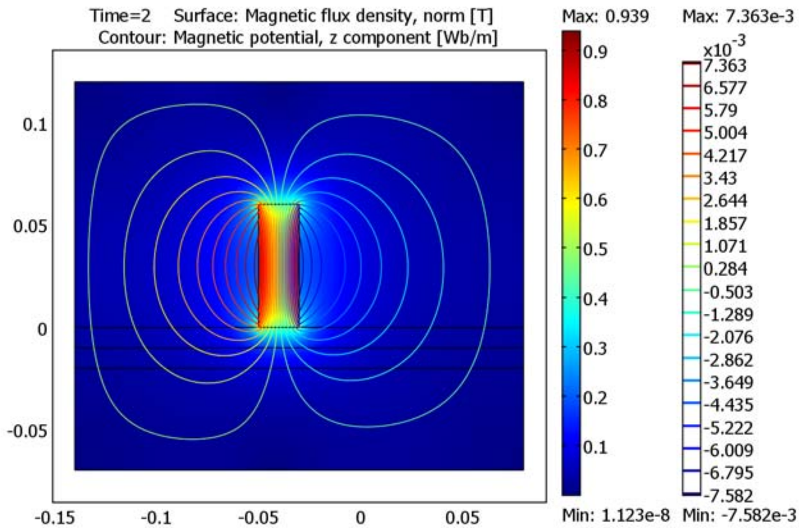

Figure 3: Magnetic vector potential and magnetic flux density, B field (white areas surpass the plot color range).

Figure 4 shows the velocity field at a heart beat where there is a maximum mean throughput in the vessel. At the left end there is a parabolic laminar flow profile.

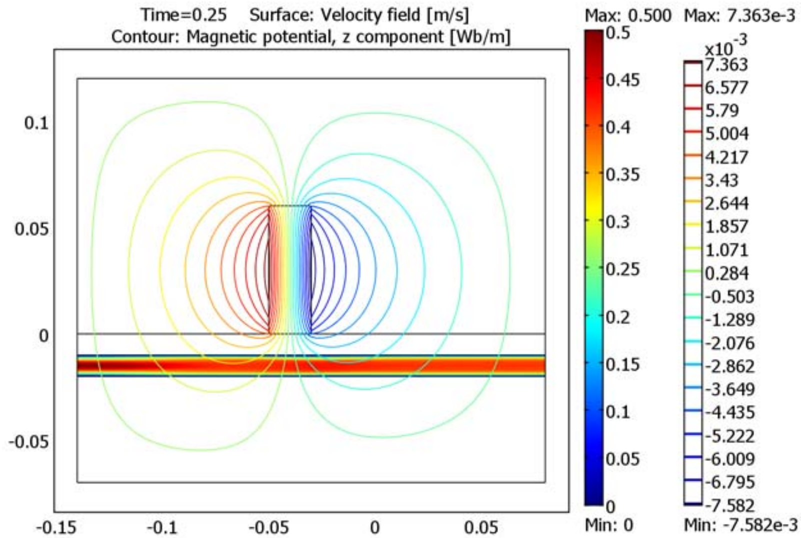

Figure 4: Velocity field at maximum blood throughput (t = 0.25).

Figure 5 reveals the velocity field between two heart beats, where the net throughput is zero.

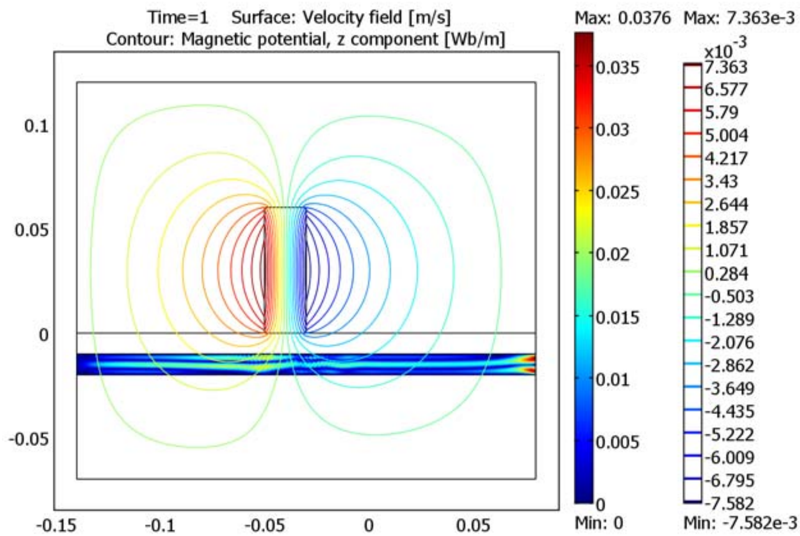

Figure 5: Velocity field at zero blood throughput (t = 1).

Modeling in COMSOL Multiphysics

EQUATIONS

To model Equation 5, use the Magnetostatics application mode in 2D. In the **Subdomain Settings** dialog box, choose the constitutive relation

$$\mathbf{B} = \mu_0\mu_r\mathbf{H} + \mathbf{B}_r$$

and make use of the fact that the remanent flux density $\mathbf{B}_r = \mu_0\chi\mathbf{M}$, where χ is the magnetic susceptibility.

STAGED SOLUTION

Because the magnetostatic problem is a stationary nonlinear problem that is independent of the fluid-flow problem, you need to solve that only once. You can therefore start by solving only Equation 5 with the stationary solver. Then proceed with solving only the fluid-flow problem, Equation 7, with the static magnetic potential as input. Solve the fluid-flow problem using the time-dependent solver. This strategy reduces RAM memory allocation and speeds up the solution.

SOLVER SETTINGS

The convergence tolerance for the time-stepping algorithm should only be based on the truly time-dependent equations. The continuity equation (second line in Equation 7) is stationary and describes the pressure distribution. Therefore, you can exclude p from the time-stepping tolerance checks. To do so, select **Exclude algebraic** in the **Error estimation strategy** list on the **Time Stepping** page of the **Solver Parameters** dialog box.

FINITE ELEMENT SHAPE FUNCTIONS

This problem includes second-order space derivatives of A in some coefficients. To get acceptable accuracy, use third-order Lagrange elements in the Magnetostatics application mode. The default setting in this application mode is second-order elements.

References

1. P.A. Voltairas, D.I. Fotiadis, and L.K. Michalis, "Hydrodynamics of Magnetic Drug Targeting," *J. Biomech.*, vol. 35, pp. 813–821, 2002.

2. C.M. Oldenburg, S.E. Borglin, and G.J. Moridis, "Numerical Simulation of Ferrofluid Flow for Subsurface Environmental Engineering Applications," *Transport in Porous Media*, vol. 38, pp. 319–344, 2000.

3. R.E. Rosensweig, *Ferrohydrodynamics*, Dover Publications, New York, 1997.