Numerical Simulation of Magnetic Drug Targeting with Flow – Structural Interaction in an Arterial Branching Region of Interest

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Abstract: We report a numerical study on the blood – magnetic carrier aggregate flow in an external magnetic field, for applications such as magnetic drug targeting. The arterial system morphology is complex and patient-related therefore more realistic numerical simulations request medical image-based reconstruction to generate computational domains. Simpleware package is used to generate the computational domain that comprises a segment of the cardiac arterial tree – vessels and embedding muscular mass – and a permanent magnet that produces the magnetic field. The numerical simulation, under pulsating flow conditions, was solved by COMSOL. The fluid (blood) is assumed Newtonian, its flow is incompressible, laminar. The artery wall and cardiac muscle are hyperelastic media. The magnetic field is produced by a permanent magnet, embedded in the muscular volume. Numerical simulation results unveil the complex field-flow-structural interactions that occur in this problem.

Keywords: magnetic drug targeting, blood flow, medical imaging reconstruction, numerical simulation, magnetic field – flow – structural interactions.

1. Introduction

Magnetic drug targeting (MDT) is considered as a unique opportunity to treat malignant tumors locoregionally without systemic toxicity [1]. In MDT, an external magnetic field is focused on a particular region of interest to retain magnetic nanoparticles (ferrofluids) that, conveyed by the blood flow, carry the chemotherapeutic agents bound to them to desired targets (*e.g.*, tumors) for specific delivery. Furthermore, it may be possible to use magnetic particles as a "carrier system" for a variety of anticancer agents, *e.g.,* radionuclides, cancer-specific antibodies, and genes [2]. MDT is a complex process, where several phenomena concur: the pulsating blood flow that conveys the ferrofluid mix, its action on the vessels and muscular volume, and the interaction with an external magnetic field (due to the magnetization of the magnetic nanoparticles) aimed at prolonging the time of residence of the magnetizable drug carriers conveyed by the blood stream in the region of interest.

This study is concerned with the field - flow - structure interactions in a notional numerical model for MDT. The mathematical modeling difficulty of the MDT problem is enhanced by the complex geometry of the anatomic region on interest. Therefore MDT studies were conducted on simplified models, *e.g.* [3]. However, recently, modern software packages that may be used to generate more realistic computational domains obtained out of medical, patient-related images are available [4]. In this study, we used Simpleware [5] to process MRI images of a set of arteries to generate a more realistic computational domain for investigating and predicting the hemodynamic flow interaction with a stationary magnetic field generated by a permanent magnet trough an arterial tree embedded in a deformable muscular volume. The multiphysics mathematical model of this flow-field-structural interaction is implemented and solved for in COMSOL [6].

The study may be used in the MDT optimization and planning, for vascular surgery training, planning and intervention, for atherosclerosis genesis etc.

2. A More Realistic Computational Domain Obtained out of Medical Images

Realistic computational domains are crucial for generating physically meaningful results to medical physics problems. A straightforward solution to this issue may be found by using modern CT/MRI scanners that provide patient

related image sets, and software packages for segmenting out the anatomic regions of interest.

Figure 1 shows a dataset of 2D scans, in Digital Imaging and Communications in Medicine (DICOM) format, that provide the information needed to generate the arterial tree in our study. Next, we outline the steps from the raw, DICOM data to the computational domain used in the numerical simulation.

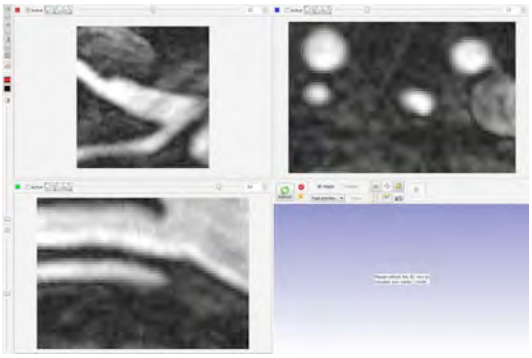


Figure 1. The MRI patient acquired datasets.

The blood domain is isolated from the imported image set using a segmetation tool (*e.g.*, the *floodfill filter* [5]). The *Dilate* and *Erode* morphological tools and *Inversion* boolean operations were then used to obtain the arterial tree. The final 3D solid models were adjusted with smoothing filters (binarisation and recursive gaussian filters), and resampled to produce a reasonable, manageable computational domain. Figure 2 outlines the main phases of this process.

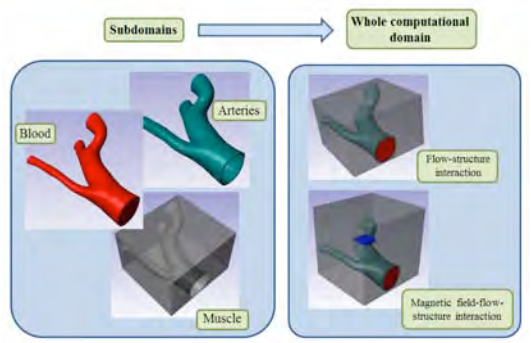


Figure 2. Obtaining a more realistic computational domain out of a DICOM dataset.

The MDT numerical simulation requires a computational domain made of arteries, the blood stream, and the surrounding tissue. When the magnetic field problem is studied, a supplementary subdomain may add up to "contain" the magnetic field problem.

The solid volumes are then meshed (ScanFE, the Simpleware's volumetric meshing module). This step closes the computational domain issue. At this point, the FEM mesh is available for export to Comsol Multiphysics [6].

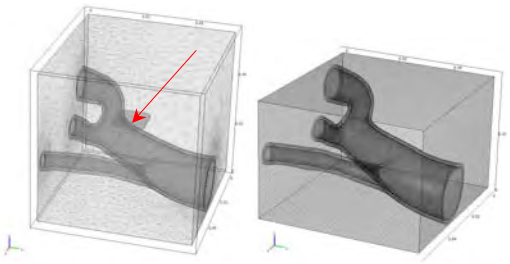


Figure 3. The FEM meshes of the computational domains – with (left) and without (right) the magnet.

3. The Mathematical Model of the MDT

The mathematical model accounts for the MDT magnetic field problem, the hemodynamic arterial flow, and the structural reaction of the vessels and the embedding muscular mass. The arteries interact with the surrounding muscular tissue: they expand when the blood is advected, and constricts after the blood is ejected.

In MDT, the drug carriers are ligand coated ferromagnetic nanoparticles. If uniformly and finely distributed in the blood stream, the blood – carrier mix behaves as a ferromagnetic fluid. Therefore in an external magnetic field magnetization body forces are produced. Their action may result in secondary flows – in the off phase of the pulsating arterial flow – through which the magnetized carriers are conveyed to the vessel walls to be further diffused in the targeted tissue. The flow – vessels and muscular tissue is assumed one-way: the vessels and the muscle deforms under the flow-induced stress, but they do not act upon the flow.

3.1 The Magnetic Field

In our notional model, the magnetic field is produced by a permanent magnet, conveniently embedded in the muscular volume. Maxwell's

equations that apply are then

Ampere's law

$$\nabla \times \mathbf{H} = 0, \quad (1)$$

Magnetic flux law

$$\nabla \cdot \mathbf{B} = 0, \quad (2)$$

The constitutive law

the magnet

$$\mathbf{B} = \mu_0 \mu_{r,mag} \mathbf{H} + \mathbf{B}_{rem}, \quad (3.a)$$

the aggregate, blood-carrier fluid

$$\mathbf{B} = \mu_0 \left[\mathbf{H} + \mathbf{M}_{ff}(\mathbf{H}) \right], \quad (3.b)$$

the arterial walls and surrounding tissue

$$\mathbf{B} = \mu_0 \mathbf{H}, \quad (3.c)$$

Here, μ_0 is the magnetic permeability of air; μ_r is the relative magnetic permeability of the permanent magnet; **H** is the magnetic field strength; **B** is the magnetic flux density; $\mathbf{B}_{rem}$ is the remanent magnetic flux density; and $\mathbf{M}_{ff}$ is the magnetization of the super-paramagnetic aggregate stream, which is a function of **H**.

When using the magnetic vector potential **A** (and the divergence free gauge condition)

$$\mathbf{B} = \nabla \times \mathbf{A}, \quad \nabla \cdot \mathbf{A} = 0, \quad (4)$$

the mathematical model for the magnetic field is

$$\nabla \times \left(\mu_0^{-1} \mu_r^{-1} \nabla \times \mathbf{A} \right) = 0. \quad (5)$$

Magnetic insulation ($\mathbf{n} \times \mathbf{A} = \mathbf{0}$) boundary conditions are set. Due attention is devoted to apply this condition far enough – while at a convenient distance in what concerns the size of the numerical model.

3.2 The Hemodynamic Model

The pulsating arterial flow is assumed incompressible, laminar; the fluid (blood) is newtonian, with constant properties; the aggregate blood and magnetic carrier is assumed super-paramagnetic, therefore mass transfer is not an issue. The arterial flow is governed by the momentum balance (Navier-Stokes) equation

$$\rho \left[\frac{\partial \mathbf{u}}{\partial t} + (\mathbf{u} \cdot \nabla)\mathbf{u} \right] = -\nabla \left[-p\mathbf{I} + \eta \left(\nabla \mathbf{u} + (\nabla \mathbf{u})^T \right) \right] + \mathbf{f}_{mg} \quad (6)$$

and by the mass conservation law

$$\nabla \cdot \mathbf{u} = 0. \quad (7)$$

Here **u** is the velocity field, p is pressure, ρ is the mass density, η is the dynamic viscosity, and **I** is the unity matrix.

The hydrodynamic problem is coupled to the magnetostatics problem through the magnetic body force $\mathbf{f}_{mg}$ due to the fluid magnetization under the influence of the magnetic field [7]

$$\mathbf{f}_{mg} = \mu_0 (\mathbf{M} \cdot \nabla)\mathbf{H}. \quad (8)$$

The boundary conditions (BC) that close the flow model are: no-slip velocity conditions at the walls; prescribed pressure conditions at the inlet and outlet cross sections to the vessels. The arterial structure belongs to the group of arteries that are known as *resistance vessels* [8]. Because the vessels here have relatively large cross sections, they oppose little resistance to the flow of blood. Therefore the pressure drop is small. In what follows we conjecture that the pressures at the inlet and outlet flow ports of the model vary synchronously.

3.2 The Structural Model for the Vessels Walls and Muscular Tissue

In this study we follow [9], which assumes a hyperelastic law for the artery wall and cardiac muscle, where the large displacement and the constitutive behavior of the materials imply a highly nonlinear behavior. The constitutive law is defined then based on a strain energy density function, W. The stress, S, is computed by derivating W with respect to Green-strains, E, so that $S = \partial W / \partial E$. The strain energy density model used here is neo-Hookean (isotropic model)

$$\overline{W} = \frac{1}{2} J^{-\frac{2}{3}} (I - \frac{1}{3} \overline{I}_1 \cdot C^{-1}) + \frac{1}{2} \kappa \cdot J(J-1) C^{-1}, \quad (9)$$

where $J = det(\mathbf{F})$ is the ratio between the current and the original volume; **F** is the deformation gradient; $C = \mathbf{F}^T \mathbf{F}$ is the right Cauchy-Green tensor – $I_1 = trace(C)$. The properties used in this study are available in [9].

4. Numerical Simulation

The mathematical model (5)-(9) was implemented in Comsol Multiphysics [6]. The following solution strategy was used: first, the magnetic field problem is solved for; next, we solve the hydrodynamic problem; in the last step, the structural model is solved for.

The blood flow is generated by a time dependent pressure gradient between the inlet

and the outlets of the arteries: p_1 = 13300 N/m^2; p_2 = 13290 N/m^2; p_3 = 13040 N/m^2; p_4 = 13040 N/m^2, $p_i = 1 + K\sin(t + 3/2)$, where K is a factor of order 10^{-1}.

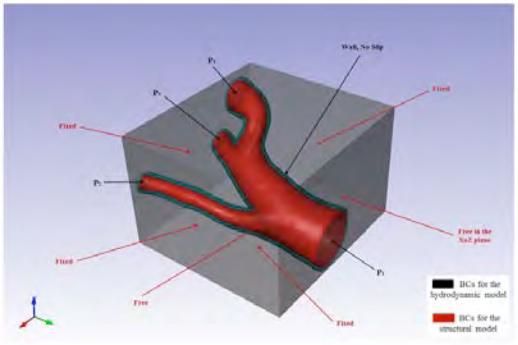
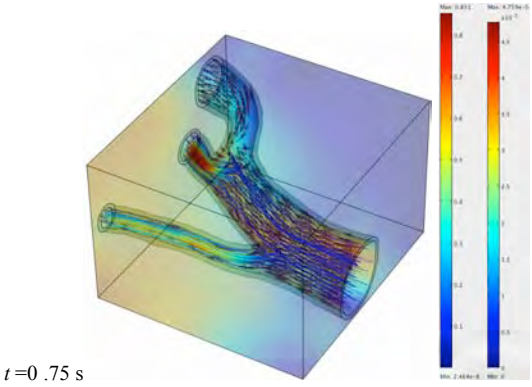


Figure 4. Boundary conditions for the hemodynamic and structural problems.

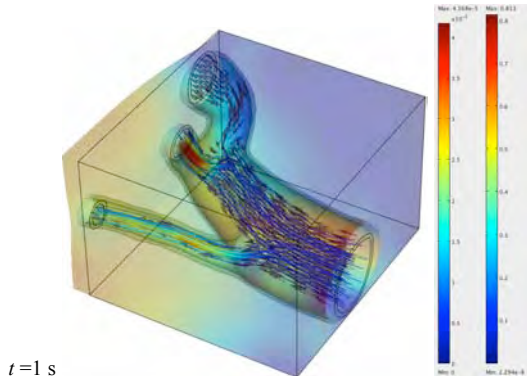
For the magnetic field solution phase, we used the segregated solver with FMGRES linear solver and Cholesky preconditioner. The hemodynamic problem was solved by using the BICGStab algorithm with geometric multigrid preconditioning.The structural model was solved for steady states, using a parametric solver that reads the pressure field at different moments, produced by the fluid dynamics analysis and previously stored on disk. The solver is PARDISO [6].

5. Results and Discussion

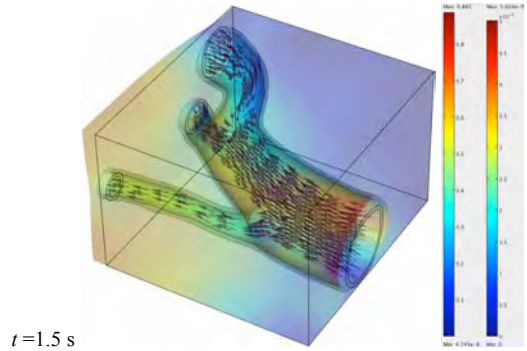
First, we investigate the blood flow without magnetic field interaction. The results are reported elsewhere [10]. Here we present the flow field (arrows and streamlines (tubes), and the deformation of the muscular volume and vessels walls under the pressure of the flow for several moments of the quasisteady flow regime.



t =0 .75 s



t =1 s



t =1.5 s

Figure 5. Flow-structure interactions – the deformations are amplified by a factor of 122.

The model outlines the influence of large displacements and for the hyperelastic behavior of the biological tissues. Fig. 5,c shows the total displacement at the peak load (after 1.5 s). The displacements are of the order of 10 μm, sustaining the validity of the one-way coupling.

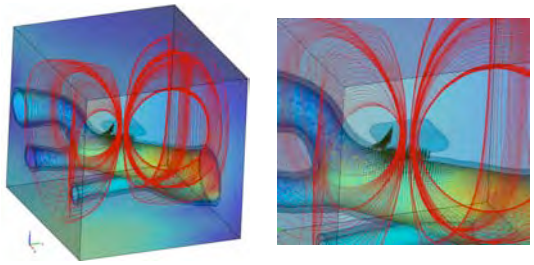


Figure 6. Magnetic field and magnetization forces.

Next, we consider the MDT model. The magnetic field produced by the permanent magnet is shown in Fig. 6, which presents also the magnetization body forces, at t = 10 s, eq. (8). Apparently, the targeting effect is localized.

The optimization of the magnet – position, size, shape, and magnetic properties – makes the object of future research. Figure 7 shows several instances of the flow (arrows) and muscular

mass and vessels deformation (boundary map).

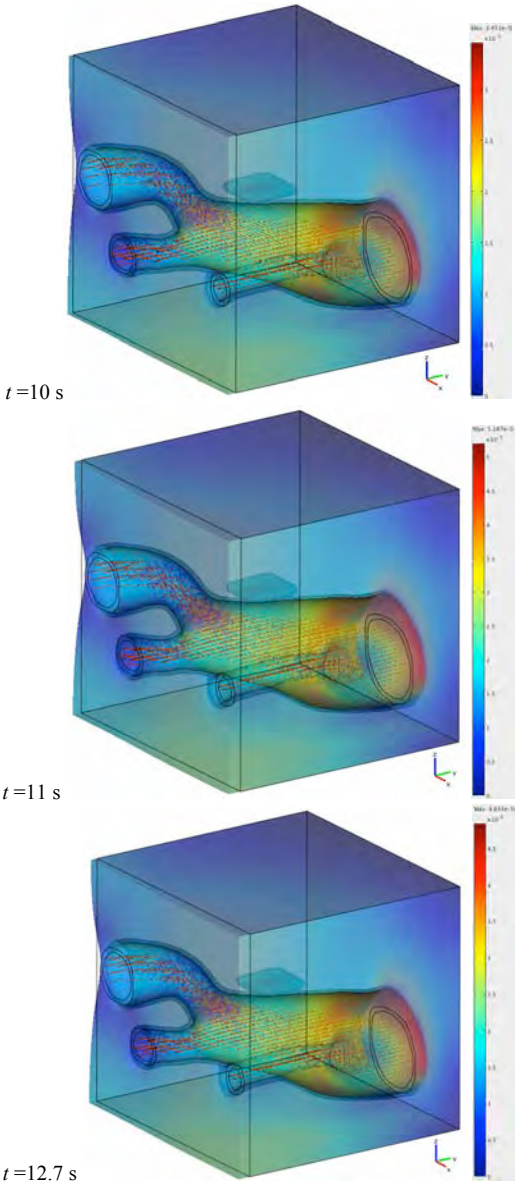


Figure 7. Flow-structure interactions in an external magnetic field – the deformations are amplified by a factor of 122.

The deformation is within the same range, the magnetic field has no substantial effect on it. The main effect is related to the blood flow. Here magnetic body forces (Fig. 6) drive the stream towards the region where the magnet is focused.

6. Conclusions

This paper presents a mathematical model and simulation results on the flow – structural interaction specific to magnetic drug targeting (MDT). The optimization of the magnetic field source – position, size, shape, and magnetic properties of the magnet – makes the object of future research. Here we are concerned on assessing the coherence and validity of the mathematical model in conjunction with the computational domain generated through medical image based reconstruction. The numerical simulation results may be helpful in developing and optimizing patient related magnetically targeted drug therapies.

9. References

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