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Simulations of magnetic capturing of drug carriers in the brain vascular system

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ABSTRACT

The present paper reports on numerical simulations of blood flow and magnetic drug carrier distributions in a complex brain vascular system. The blood is represented as a non-Newtonian fluid by the generalised power law. The Lagrangian tracking of the double-layer spherical particles is performed to estimate particle deposition under influence of imposed magnetic field gradients across arterial walls. Two situations are considered: neutral (magnetic field off) and active control (magnetic field on) case. The double-layer spherical particles that mimic a real medical drug are characterised by two characteristic diameters - the outer one and the inner one of the magnetic core. A numerical mesh of the brain vascular system consisting of multi-branching arteries is generated from raw MRI scan images of a patient. The blood is supplied through four main inlet arteries and the entire vascular system includes more than 30 outlets, which are modelled by Murray's law. The no-slip boundary condition is applied for velocity components along the smooth and rigid arterial walls. Numerical simulations revealed detailed insights into blood flow patterns, wall-shear-stress and local particle deposition efficiency along arterial walls. It is demonstrated that magnetically targeted drug delivery significantly increased the particle capturing efficiency in the pre-defined regions. This feature can be potentially useful for localised, non-invasive treatment of brain tumours.

1. Introduction

Magnetic Drug Targeting (MDT) is a medical technique based on a relatively simple concept of attaching a therapeutic drug to a small magnetic carrier, which makes it possible to precisely deliver medical drug to the desired location by specifically designed external magnetic field gradients. This localised medical drug delivery enables a significant local increase of the medical drug in regions affected by disease and at the same time reduces the total amount of supplied medical drug. This leads to a significant reduction of the always present negative side-effects of aggressive medical treatments. Experimental studies on animals and pre-clinical studies on human patients demonstrated potentials of this approach as shown in Lübbe et al. (1996a,b), Arnold and Parak (2006), Torchilin (2006).

Numerical modelling and simulations can provide important insights needed for further advancement and optimisation of the MDT technique – especially in obtaining detailed predictions of local distributions of medical drugs along arterial walls for different sets of the working parameters that include a characteristic particle diameter and different orientations and strengths of an externally imposed magnetic field. In our previous studies we addressed numerical simulations of the MDT technique in simplified and realistic arterial bifurcations (carotid artery, coronary arteries), Kenjereš (2008), Haverkort et al. (2009a,b), Kenjereš and Cohen Stuart (2009) and Cohen Stuart et al. (2011). The magnetic drug was simplified to a finite-size spherical particle with uniform properties. In the present study, we are extending these simulations to a real-patient brain vascular system. A brain vascular system is a rather complex network of multi-branching arteries. Particular challenge lies in specific anatomic uniqueness of each individual patient that must be included in order to achieve optimised drug delivery. This includes not only the specific geometry of the brain vascular system, but also specific blood flow rates imposed by heartbeats. In addition, a more realistic representation of the multi-layer structure of particles is introduced. It contains a magnetic core and a coated layer of chemotherapeutical drug. The inner magnetic diameter is used in calculating the magnetisation force and the outer diameter is used for the drag force. The transport of the different classes of the finite-size particles is calculated by time-integration of the particle force balance equation,

2. Mathematical model

The mathematical model consists of conservative equations for mass and momentum for description of the continuous phase (blood), whereas the discrete phase (the finite size/mass particles) is traced in a Lagrangian framework.

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Nomenclature

C_d	drag coefficient (–)
D_p	particle diameter (m)
D_m	magnetic core diameter (m)
m_p	particle mass (kg)
n_i	total number of particles at the inlet (–)
n_{wall}	total number of particles at the wall (–)
p	pressure (Pa)
u_i	velocity vector (m/s)
v_p	particle velocity (m/s)
V_p	particle volume (m^3)
V_m	magnetic core volume (m^3)
Re	Reynolds number (–)
Re_p	particle Reynolds number (–)
St	Stokes number (–)
M_{sat}	saturation magnetisation (A/m)
$\vec{F}_d$	drag force (N)
$\vec{F}_m$	magnetisation force (N)
$\vec{F}_v$	added mass force (N)
$\vec{M}$	magnetisation (A/m)
$\vec{H}$	auxiliary magnetic field (A/m)
$\vec{B}$	imposed magnetic field (T)

Greek symbols

ρ	fluid density (kg/m^3)
ρ_p	particle density (kg/m^3)
ρ_c	coated layer density (kg/m^3)
μ	fluid dynamic viscosity (m^2/s)
μ_0	magnetic permeability of the free space (H/m)
$\dot{\gamma}$	strain rate (1/s)
η	particle deposition efficiency (–)
ζ	local capture efficiency (–)
ϵ	characteristic sample distance (m)

2.1. Blood flow

The flow of an incompressible non-Newtonian fluid (blood) is described by conservation of momentum:

$$\frac{\partial \rho u_i}{\partial t} + u_j \frac{\partial \rho u_i}{\partial x_j} = -\frac{\partial p}{\partial x_i} + \frac{\partial}{\partial x_j}\left[\mu(\dot{\gamma})\left(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i}\right)\right] \quad (1)$$

and divergency-free velocity field condition ($\partial u_i/\partial x_i = 0$). The blood rheology (the shear-thinning behaviour due to the red blood cells aggregation and dispersion at low shear rates, which increase blood viscosity) is taken into account through a generalised power law, Ballyk et al. (1994):

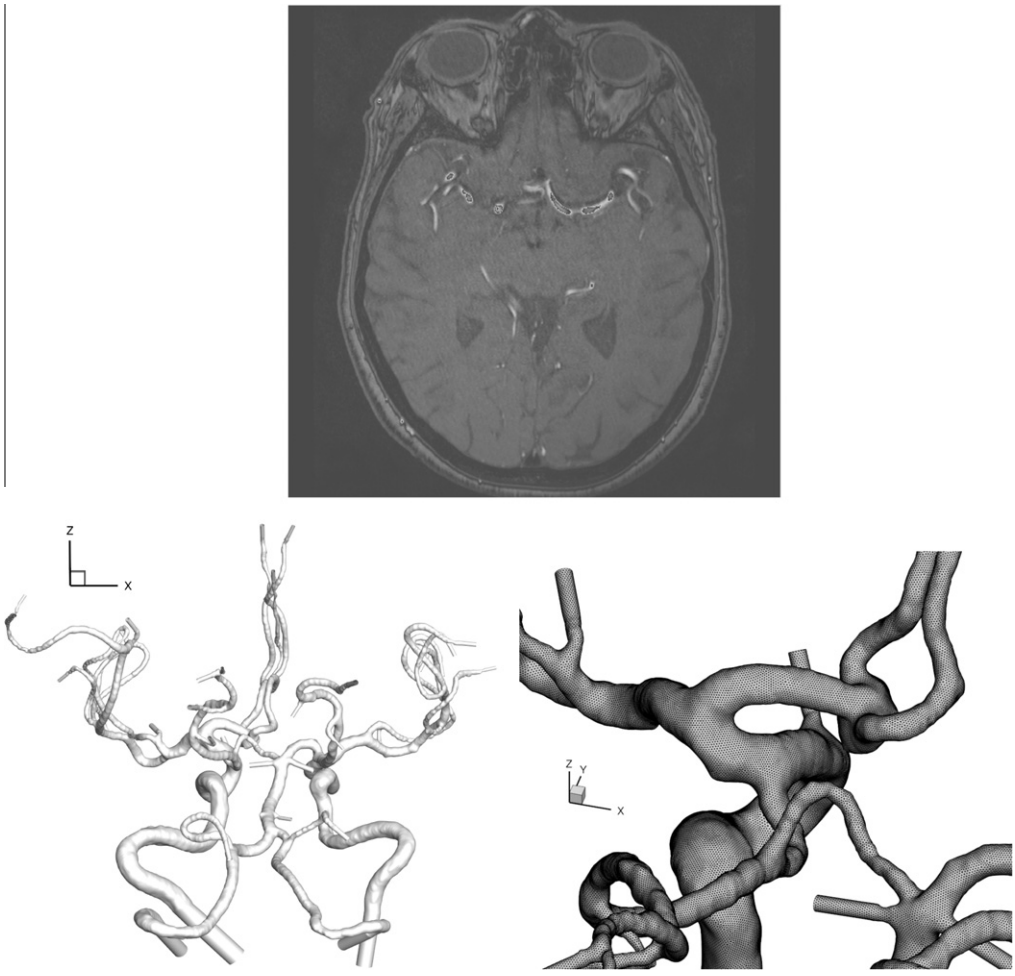

Fig. 1. Top-example of a raw MRI image with an enhanced contrast agent in the brain vascular system. White contrast indicates brain blood vessels in the particular horizontal slice. Bottom/left-reconstructed 3D geometry; Bottom/right-generated tetrahedral numerical mesh (a zoom-in).