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Mathematical modelling for trajectories of magnetic nanoparticles in a blood vessel under magnetic field

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ABSTRACT

A mathematical model is developed to describe the trajectories of a cluster of magnetic nanoparticles in a blood vessel for the application of magnetic drug targeting (MDT). The magnetic nanoparticles are injected into a blood vessel upstream from a malignant tissue and are captured at the tumour site with help of an applied magnetic field. The applied field is produced by a rare earth cylindrical magnet positioned outside the body. All forces expected to significantly affect the transport of nanoparticles were incorporated, including magnetization force, drag force and buoyancy force. The results show that particles are slow down and captured under the influence of magnetic force, which is responsible to attract the magnetic particles towards the magnet. It is optimized that all particles are captured either before or at the centre of the magnet ($z \leq 0$) when blood vessel is very close proximity to the magnet ($d = 2.5$ cm). However, as the distance between blood vessel and magnet (d) increases (above 4.5 cm), the magnetic nanoparticles particles become free and they flow away down the blood vessel. Further, the present model results are validated by the simulations performed using the finite element based COMSOL software.

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1. Introduction

The delivery of anticancer agents to the specific target sites with minimum side effects is an important challenge in chemo, radio and gene-therapy. Magnetic Drug Targeting (MDT) is one of the promising methods for effective targeting and delivery of drugs to a specific target with aid of a local magnetic field [1,2]. In this method, magnetic carrier particles loaded with drug molecules are injected into the microvasculature upstream from the malignant tissue and attracted towards the targeted region in the body with help of a local magnetic field [3–6]. MDT is growing due to speedy progress in the growth of functionalized magnetic nanoparticles, which are used for chemo, radio, and gene-therapy at a tumour site [7,8]. It is also shown by various studies that MDT is relatively safe and effective method for targeting drugs to a specific site [9–11].

Previous work on magnetic particles transport in the vasculature for MDT is summarized in many review papers [12–14]. Kingsley et al. [15] examined the development of nanoparticles based targeted drug delivery systems in detail. The magnetite (Fe_3O_4) nanoparticles are generally used in targeted drug delivery systems because of their biocompatibility and large magnetization [16]. A detail discussion on the current and future prospective of the targeted drug targeting through the blood stream by magnetic drug carriers was presented by Yokoyama [17]. Lubbe et al. [10] also elaborated the details of the usage of magnetic nanoparticles as a carrier in medical applications through a review article. A two-dimensional mathematical model for magnetic particle transport as a drug carrier has been developed by Aviles et al. [18] at the carotid bifurcation region. Shaw et al. [19] presented a model to achieve high concentration of drug at the targeted region in the impermeable micro-vessel by assuming blood as Herschel–Bulkley fluid. Ritter et al. [20] studied the targeted of drug by the magnetic carrier at a specific site by employing high gradient magnetic separation technique using FEMLAB simulations. Rotariu and Strachan [21] evaluated the targeting of magnetic nanoparticles at the tumour site located deep inside the body through computational simulations. Furlani and Furlani [22] presented an analytic model for transport and capture of therapeutic magnetic nanoparticles in the human microvasculature for targeted drug delivery applications. Design of an effective MDT system requires research in three main areas: synthesis of composite drug and magnetic particles, real-time imaging of magnetic particles as they move through the blood stream, and development of technology to steer the particles through the circulatory system and hold them at the correct location [23]. The current work focuses on the second and third area of research in the field of magnetic drug targeting.

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In the present work, a mathematical model is developed to describe the trajectories of a cluster of magnetic nanoparticles in a blood vessel with the aid of a local magnetic field applied through a cylindrical magnet positioned outside the body. The magnetic nanoparticles are flowing along the axis of blood vessel and magnetic field is applied perpendicular to the direction of the blood flow. The mathematical equations used in the model are solved using classical fourth order Runge–Kutta method to predict the magnetic particle trajectories within a blood vessel. The model is also used to optimize the position of outside magnet for magnetic particle capture at the tumour site for effective drug targeting.

2. Description and mathematical formulation

The present model is developed to predict the transport and capture of magnetic nanoparticles under the influence of magnetic field. The magnetic nanoparticles are injected into the blood vessel and their flow within blood (in the direction of z axis along the axis of blood vessel) is targeted by applying an external magnetic field. The magnetic field is applied by a rare-earth cylindrical magnet positioned outside the body. The magnet is assumed to be infinite extent and oriented to the perpendicular direction of the blood flow (x direction). The schematic diagram of magnetic particle transport in a blood vessel is depicted in Fig. 1. The blood vessel is assumed to be a cylindrical tube with laminar flow of magnetic particles within blood parallel to its axis.

2.1. Mathematical formulation

The transport of magnetic nanoparticles in the vascular system is governed by a number of forces [24], however, in the present study, we considered the dominant magnetic, drag and buoyancy forces and a steady flow analysis is implemented.

The motion of nanoparticles is governed by using the Newton's second law

$$m_p \frac{d\mathbf{v}_p}{dt} = \sum \mathbf{F}_{ext} \tag{1}$$

where m_p and $\mathbf{v}_p$ are the mass and velocity of the magnetic particle and $\sum \mathbf{F}_{ext}$ represents all the external forces exerted on the particle. The inertial term $m_p \frac{d\mathbf{v}_p}{dt}$ is very small, and could be ignored.

Then Eq. (1) becomes

$$\sum \mathbf{F}_{ext} = 0 \tag{2}$$

and

$$\sum \mathbf{F}_{ext} = \mathbf{F}_m + \mathbf{F}_f + \mathbf{F}_b \tag{3}$$

where $\mathbf{F}_m$,$\mathbf{F}_f$ and $\mathbf{F}_b$ are the magnetic, fluidic and buoyancy force considering the gravitational force, respectively. Furthermore, we have not included Brownian motion because it is negligible when particles are very small. The magnetic, fluidic and buoyancy forces experienced by the carrier particles in the blood vessel under the influence of external magnetic field are calculated as given below.

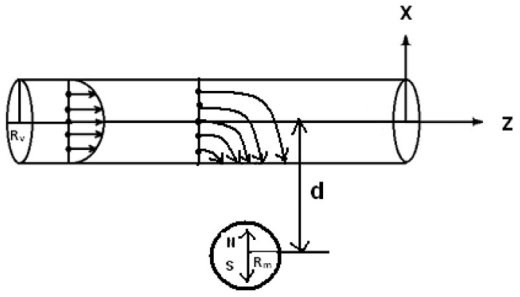

Fig. 1. Schematic diagram of the magnetic nanoparticles transport in a blood vessel. The cylindrical magnet is positioned outside the vessel to apply the magnetic field.

2.1.1. Magnetic force

If the magnetic particles are suspended in a fluid with permeability μ_f, the force experienced by the magnetic particles in an applied field $\mathbf{H}$ is [22] given as below,

$$\mathbf{F}_m = \mu_0 V_p \frac{3\chi_p}{(\chi_p + 3)} (\mathbf{H}\cdot\nabla)\mathbf{H} \tag{4}$$

where $V_p = \frac{4}{3}\pi R_p^3$ is the volume of the particle and χ_p is the susceptibility of the particle. $\mathbf{H}$ is the externally applied magnetic field.

Here, $\mu_0 = 4\pi \times 10^{-7}\, H/m$ is the permeability of free space.

We consider the motion in x–z plane and therefore, the magnetic force can be expressed as

$$\mathbf{F}_m = F_{mx}\hat{\mathbf{x}} + F_{mz}\hat{\mathbf{z}}$$

The magnetic force can be decomposed into its components form as

$$F_{mx}(x,z) = \mu_0 V_p \frac{3\chi_p}{(\chi_p + 3)}\left[H_x(x,z)\frac{\partial H_x(x,z)}{\partial x} + H_z(x,z)\frac{\partial H_x(x,z)}{\partial z}\right] \tag{5}$$

and

$$F_{mz}(x,z) = \mu_0 V_p \frac{3\chi_p}{(\chi_p + 3)}\left[H_x(x,z)\frac{\partial H_z(x,z)}{\partial x} + H_z(x,z)\frac{\partial H_z(x,z)}{\partial z}\right] \tag{6}$$

where $\mathbf{H}(x,z) = H_x(x,z)\hat{\mathbf{x}} + H_z(x,z)\hat{\mathbf{z}}$

The components of magnetic field for an infinite cylindrical magnet, which is magnetized perpendicular to its axis, can be represented inside the blood vessel as below [22].

Here,

$$H_x(x,z) = \frac{M_s R_m^2}{2}\frac{\left[(x+d)^2 - z^2\right]}{\left[(x+d)^2 + z^2\right]^2} \tag{7}$$

and

$$H_z(x,z) = \frac{M_s R_m^2}{2}\frac{2(x+d)z}{\left[(x+d)^2 + z^2\right]^2} \tag{8}$$

Here, M_s, R_m and d are the magnetization of the magnet, radius of the magnet and distance of magnetic nanoparticles from the centre of the magnet.

The partial derivatives of above these components of magnetic field w.r.t. x and z can be evaluated as

$$\frac{\partial H_x(x,z)}{\partial x} = -M_s R_m^2 \frac{(x+d)\left[(x+d)^2 - 3z^2\right]}{\left[(x+d)^2 + z^2\right]^3} \tag{9a}$$

$$\frac{\partial H_x(x,z)}{\partial z} = -M_s R_m^2 \frac{z\left[3(x+d)^2 - z^2\right]}{\left[(x+d)^2 + z^2\right]^3} \tag{9b}$$

$$\frac{\partial H_z(x,z)}{\partial x} = M_s R_m^2 \frac{z\left[z^2 - 3(x+d)^2\right]}{\left[(x+d)^2 + z^2\right]^3} \tag{9c}$$

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