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Implant-assisted magnetic drug targeting in permeable microvessels: Comparison of two-fluid statistical transport model with experiment

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ABSTRACT

In experiments and theoretical analyses, this study examines the capture efficiency (CE) of magnetic drug carrier particles (MDCPs) for implant-assisted magnetic drug targeting (IA-MDT) in microvessels. It also proposes a three-dimensional statistical transport model of MDCPs for IA-MDT in permeable microvessels, which describes blood flow by the two-fluid (Casson and Newtonian) model. The model accounts for the permeable effect of the microvessel wall and the coupling effect between the blood flow and tissue fluid flow. The MDCPs move randomly through the microvessel, and their transport state is described by the Boltzmann equation. The regulated changes and factors affecting the CE of the MDCPs in the assisted magnetic targeting were obtained by solving the theoretical model and by experimental testing. The CE was negatively correlated with the blood flow velocity, and positively correlated with the external magnetic field intensity and microvessel permeability. The predicted CEs of the MDCPs were consistent with the experimental results. Additionally, under the same external magnetic field, the predicted CE was 5–8% higher in the IA-MDT model than in the model ignoring the permeability effect of the microvessel wall.

1. Introduction

Magnetic drug targeting (MDT) is one of the most promising targeting technologies in the clinical treatment of tumors. Traditional MDT guides the magnetic drug carrier particles (MDCPs) to the focal area and captures them under an external magnetic field [1–3]. However, the magnetic field force is a sharply decreasing function of distance, and is easily dominated by the fluid power. To overcome these limitations, researchers have proposed implant-assisted magnetic drug targeting (IA-MDT). In this technique, the drug carrier particles are assisted by ferromagnetic wires or particles, which are implanted in advance. Under an external magnetic field, these ferromagnetic substances generate magnetism and strong additional magnetic field forces near the focal area, increasing the capture efficiency (CE) of the MDCPs near the local area. Aviles et al. [4,5] proposed high gradient magnetic separation for IA-MDT and established a theoretical model of the technique. They showed that when ferromagnetic particles are implanted as seeds in the presence of an external permanent magnet, the seeds become magnetized, improving the local magnetic field gradient. Seeding yields an obviously higher CE than when an external permanent magnet only is applied, proving the feasibility of IA-MDT. Implant stents for IA-MDT have been theoretically and experimentally studied by Avilés et al. [6] and Cregg et al. [7,8], who considered the modification of the magnetic field by MDCPs. They also reported obvious improvements in the CE. Cokelet [9] experimentally showed that microvessels comprise a core layer (which suspends the erythrocytes) and a peripheral layer of plasma. Hence, blood flow through microvessels can be treated by a two-fluid model. More specifically, the core region containing the erythrocytes behaves as a non-Newtonian fluid, whereas the plasma behaves as a Newtonian fluid. Kim et al. [10] investigated the viscosity and yield stress of blood in capillaries using a scanning capillary-tube rheometer. They calculated the viscosity and yield stress of the blood by the Casson and Herschel–Buckley models, and observed no significant difference between the model results. Lubbe et al. [1] pointed out that the fluid flow in tissues around tumor microvessels vitally affects the CE of the MDCPs in the microvessels. Furthermore, Gerber et al. [11–13] showed that when the diameter of the MDCPs is sufficiently small ($F_m D_p \le k_B T$), the magnetic drug targeting is significantly affected by the random motion of the MDCPs. The magnetic field forces in drug targeting technologies are tiny (commonly of the order of 10^{-2} pN). Hence, when the MDCPs are below 400 nm in diameter, their random motions need to be considered. Microvessels in tumor tissues are characterized by fast and irregular growth, discontinuity, lack of smooth muscle cells and pericytes. Endothelial cells have no tight junctions and are separated by large pore spaces [14]. Consequently, the microvessel walls of tumor

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tissues are more permeable than those of normal tissues. The theoretical IA-MDT model must then include the permeability effect of the microvessel wall.

The present article develops a theoretical model that can accurately describe the transport state of MDCPs for assisted magnetic targeting in microvessels. The model accounts for the non-Newtonian property of blood, the fluid flow state of the tissues and the random motion effects of the MDCPs. The theoretical model was verified in experiments of MDCPs in microvessels. The experiments were conducted in a custom-built device. The factors influencing the CE of the MDCPs, and their regulation, were predicted under feasible physiological conditions through numerical simulations of the theoretical model. The predicted results favorably compared with the experimental observations.

2. Theoretical model

2.1. Blood pressure equation of two-fluid model

Taylor et al. [15,16] experimentally showed that when blood flows through a microvessel, the erythrocytes are suspended within a core region while the plasma occupies a peripheral layer. Hence, for a more realistic description of blood flow, the blood can be treated as a two-fluid model consisting of a Casson fluid (the core region containing the erythrocytes) and a Newtonian fluid (the plasma in the peripheral layer). Hence, the blood flow in a permeable microvessel can be described as an axially symmetric, laminar, steady and fully developed flow. The theoretical model assumes that the external magnetic medium is set in the target area, and the target is centered in the microvessel, as shown in Fig. 1.

Because the blood flows slowly through the microvessel, its Reynolds number is very small. At sufficiently small Reynolds number, the inertia and the radial velocity can be ignored. In cylindrical coordinates, the Navier–Stokes equations of the Newtonian and Casson fluids in cylindrical coordinates then simplify to:

$$\frac{\partial}{\partial r}(r\tau_N) = r\frac{\partial p}{\partial x}, \quad R_C \le r \le R \tag{1}$$

$$\frac{\partial}{\partial r}(r\tau_C) = r\frac{\partial p}{\partial x}, \quad 0 \le r \le R_C \tag{2}$$

where

$$R_C = \xi R,\ \xi = 1-\delta,\ \delta = \frac{\Delta}{R}$$

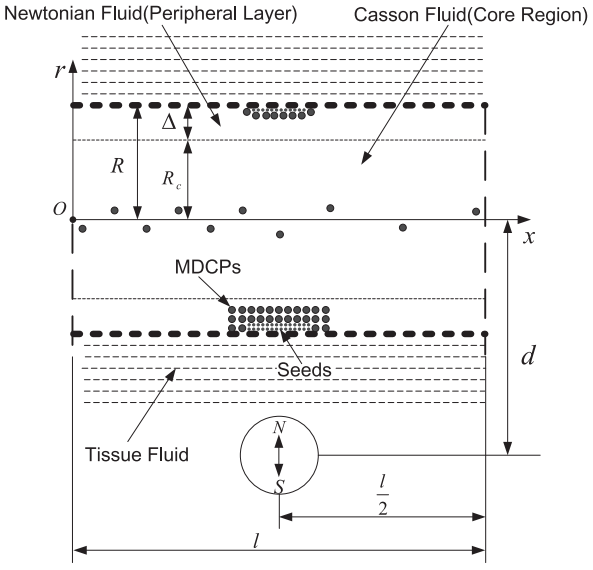

Fig. 1. Schematic of theoretical model.

Eqs. (1) and (2) are subjected to the following boundary conditions:

$$\left.\frac{\partial \mu_C}{\partial r}\right|_{r=0} = 0, \quad \tau_N|_{r=R_C} = \tau_C;$$
$$\mu_N|_{r=R_C} = \mu_C, \quad u_N|_{r=R} = 0. \tag{3}$$

Physically, Eq. (3) means that the velocities and shear stresses of the Newtonian and Casson fluids are continuous at the interface. Integrating Eqs. (1) and (2) with respect to r, and imposing the boundary condition (3), the velocities of the Newtonian and Casson fluids are respectively expressed as:

$$\mu_N = \frac{1}{4\eta_N}\frac{\partial p}{\partial x}(r^2 - R^2), \quad R_C \le r \le R \tag{4}$$

$$\mu_C = \frac{(\xi^2-1)R^2}{4\eta_N}\frac{\partial p}{\partial x} + F_1(r)\frac{\partial p}{\partial x}, \quad 0 \le r \le R_C \tag{5}$$

where the function $F_1(r)$ is defined as

$$F_1(r) = \int_r^{R_C} \frac{r}{2\eta_C} dr.$$

In the two-fluid model of a permeable microvessel, the blood pressure is governed by [17]

$$\left[\frac{(\xi^4-1)R^4}{8\eta_N} + 2G\right]\frac{\partial^2 p}{\partial x^2} + 2RK_p(p - p_i) = 0 \tag{6}$$

where G is defined as

$$G = \int_0^{R_c} rF_1(r)dr = -\frac{R_c^4}{16k^2}\left[1 + \frac{16}{7}\left(\frac{2\tau_0}{R_c\frac{\partial p}{\partial x}}\right)^{1/2} - \frac{4}{3}\left(\frac{2\tau_0}{R_c\frac{\partial p}{\partial x}}\right) + \frac{127}{21}\left(\frac{2\tau_0}{R_c\frac{\partial p}{\partial x}}\right)^4\right].$$

The boundary conditions of Eq. (6) are given by

$$p|_{x=0} = p_0 \quad \text{(Inlet pressure)} \tag{7}$$

$$p|_{x=l} = p_1 \quad \text{(Outlet pressure)} \tag{8}$$

2.2. Control equation of the tissue fluid pressure

Blood flow in permeable microvessels is characterized by fluid exchange between the blood in the microvessel and the fluid in the surrounding tissue. Therefore, the flow states of the blood and the tissue fluid are interactional, so the equations governing the blood pressure and the tissue fluid pressure need to be coupled to each other. The fluid flow in biological tissue is regarded as seepage flow in a porous medium, whose velocity satisfies Darcy's law. The tissue fluid pressure in cylindrical coordinates is then given as:

$$\frac{1}{r}\frac{\partial}{\partial r}\left[r\beta K_{pi}\frac{\partial p_i}{\partial r}\right] + \frac{\partial}{\partial x}\left[\beta K_{pi}\frac{\partial p_i}{\partial x}\right] = 0. \tag{9}$$

Experimentally, the factor βK has been determined as [18]

$$\beta K_{pi} = \alpha_0 p_i,\ \alpha_0 = 8.54 \times 10^{-16}\left(\frac{m^2}{(Pa)^2 \cdot S}\right).$$

The boundary conditions of Eq. (9) are as follows:

$$p_i(x, r)|_{(x^2+r^2)=\infty} = p_\infty, \left.\frac{\partial p_i(x, r)}{\partial x}\right|_{x=0} = 0, \left.\frac{\partial p_i(x, r)}{\partial x}\right|_{x=l} = 0 \tag{10}$$

Assuming that the fluid exchange between blood and biological tissue obeys the Starling Law [23], the following equation is satisfied in