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A three-dimensional two phase method for predicting drug delivery to tumor

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ABSTRACT

This study aims to numerically investigate drug delivery to the tumor through the pores in its microvascular wall. A segment of tumor capillaries is modeled as a rigid cylinder with a single pore. Blood flow with nanoparticles is examined by Eulerian–Lagrangian approach in which the blood and particles are modeled as continuous phase and discrete phase, respectively. For investigating of nanoparticle-blood flow, a model is used in which almost all possible effective forces on the motion of particles are considered and blood flow are modeled as a combination of a non-Newtonian core region and Newtonian peripheral region. At the core region, it is considered that the blood flow behaves as non-Newtonian power law model. The effect of different controllable parameters on the particle delivery is investigated and the effectiveness of each of these parameters is discussed and compared with each other. Finally, a correlation was developed for the nanoparticle delivery.

1. Introduction

Tumors are abnormal masses of tissues in the body with special features. Some tumors can damage the surrounding tissues; these tumors are synonymous with cancer which is a name for more than 100 different diseases. Currently, cancer is treated by surgery, targeted radiation, employing cytotoxic agents, etc. With the exception of surgery, other therapies commonly involve the delivery of therapeutic agents to cancer cells. The goal of chemotherapy is the delivery of cytotoxic agents into tumor cells. For cancer treatment, the concentrations of these agents in every tumor cells must be higher than a therapeutic level. Most anticancer drugs are toxic, so that the dose administered is restricted by normal tissue tolerance [1]. On the other hand, intercellular clefts between the endothelial cells of capillary wall are responsible for material exchange between capillary blood and interstitial fluid, But the area of capillary wall occupied by the intercellular clefts is very small [2]. These two factors lower the penetration of nanoparticles to tumors. The inadequate delivery of therapeutic agents because of the difficulty to cross the microvascular wall leads to the frequently low therapeutic index [3]. Therefore, many studies have focused to recognize the ways to enhance drug delivery to tumor cells.

Larger pore cutoff size in tumors capillary leads to the greater absorption of nanoparticles. However, the high interstitial fluid pressure of tumors reduces drug delivery [1]. Therefore, the recognition of factors affecting the uptake of nanoparticles and the effect of each of them on the amount of delivered drug to tumor is necessary for the design of drug delivery systems.

Some researchers have experimentally investigated the effect of various parameters on the delivery of nanoparticles to tumors. Kong et al. [3] studied the effect of particle diameter and mild hyperthermia on the nanoparticle uptake by the tumor. They also investigated the effect of different hyperthermia conditions and different temperatures on the nanoparticle uptake by the tumor [4]. Li et al. [5] investigated hyperthermia conditions required to improve the permeability of tumor capillary. They observed intercellular cleft up to 10 μm induced by hyperthermia. Lammers et al. [6] studied the Effects of radiotherapy and hyperthermia on the drug delivery to the tumor. They concluded that radiotherapy improves the nanoparticle delivery to the tumor by several mechanisms such as decreasing the interstitial fluid pressure, reducing tumor cell density, etc. They also found that the effect of hyperthermia on the enhancement of drug delivery dependents on drug delivery systems.

Some researchers have numerically or mathematically studied drug delivery to tumors. Weinberg et al. [7] modeled drug delivery in the cancer therapy using one-dimensional and three-dimensional simulations. They reported that the model provided the feasible estimation of drug distribution dynamics following placement of an intratumoral chemotherapeutic implant. Some researchers investigated targeted drug delivery by the external factors [8–11]. Jackson and Byrne [12] presented a mathematical model consisting of a set of partial differential equations governing the concentration of drug in the tumor. They reported that their model can describe the reduction in the volume of a vascular tumor in response to specific chemotherapeutic administration

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strategies. Mishra et al. [13] developed a mathematical model to describe drug concentration in the tumor cell and illustrated tumor's response to the different size of chemotherapeutic particles. For modeling drug delivery to the tumor, Podduturi et al. [14] considered a segment of tumor capillaries as a rigid cylinder with a single pore. In their model, nanoparticle movement is due to a pressure driven flow over imposed Brownian motion. They investigated the effect of pore size, nanoparticles' size and concentration, interstitial fluid pressure, and capillary blood pressure on the particle uptake.

In the present study, geometry similar to reference [14] is used to model a segment of tumor microvascular. Eulerian–Lagrangian two-phase model is used to simulate blood–nanoparticle two-phase flow. Blood is considered as a non-Newtonian Power law fluid at the core region and a fluid with constant viscosity at the peripheral region. In this study, in addition to the effect of parameters which are studied by Podduturi et al. [14], the effect of net filtration pressure, velocity inlet, capillary diameter and minimum viscosity on the particle delivery is investigated and the extent of effectiveness of each of these parameters is discussed and compared. Regarding to the role of each parameter on the particle delivery, a correlation is developed for the particle delivery. This information provides a clear understanding of how the drug is delivered to the tumor tissue, which can be useful for the design of optimal drug delivery systems.

2. Material and methods

2.1. Geometry

The model, similar to reference [14], consists of a cylinder with a single pore in its wall. The geometry of problem that is used for numerical simulation is shown in Fig. 1. The diameter and the length of the cylinder are 8 μm and 10 μm, respectively. Pore location is at (4, 0, 5) in micrometer.

2.2. Governing equations

The problem is modeled as laminar, steady state, incompressible and three-dimensional flow. Blood and nanoparticles are considered as continuous phase and discrete phase, respectively. Since the particles' volume fraction is low, the one-way coupling is used and the effect of particles on the continuous phase is not considered. The governing mass and momentum equations for continuous phase are written as follows:

$$\nabla.\left(\rho\vec{u}\right)=0 \tag{1}$$

$$\nabla.\left(\rho\vec{u}\,\vec{u}\right)=-\nabla p+\nabla.\left[\mu\left(\nabla\vec{u}+\nabla\vec{u}^{T}\right)\right] \tag{2}$$

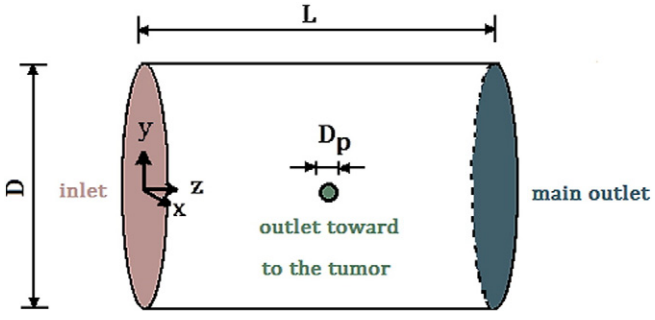

Fig. 1. The geometry of problem.

Table 1
Blood and particle properties [16,17].

Parameters	Value
$\rho_p(kg/m^3)$	1100
$\rho\ (kg/m^3)$	1060
n	0.708
k (mPa. s^n)	17
μ_{min} (Pa. s)	0.00319
μ_{max} (Pa. s)	0.02

Which $\vec{u}$ is velocity, p is pressure and μ is viscosity. Viscosity is given by the non-Newtonian power law model as follows [15]:

$$\mu=k\dot{\gamma}^{n-1} \tag{3}$$

Where k is the average viscosity of the fluid and n is the consistency index. The shear rate $\dot{\gamma}$ is given by

$$\dot{\gamma}=\nabla\vec{u}+\nabla\vec{u}^{T} \tag{4}$$

In this study if the calculated viscosity becomes less than the Predefined minimum value or greater than the Predefined maximum value, the calculated values will be replaced with the minimum or maximum one. All required parameters are given in Table 1.

According to the Newton's second law, equation of motion for particles is written as follows [18]:

$$\frac{d\vec{u}_p}{dt}=\vec{F}_D+\vec{F}_B+\vec{F}_L+\vec{F}_P+\vec{F}_V \tag{5}$$

Where $\vec{F}_D$ is drag force per unit mass, $\vec{F}_B$ is Brownian force, $\vec{F}_L$ is Saffman's lift force, $\vec{F}_P$ is contribution due to pressure gradient and $\vec{F}_V$ is virtual mass force. $\vec{F}_D$ is written as:

$$\vec{F}_D=C_D\left(\vec{u}-\vec{u}_p\right) \tag{6}$$

For submicron particles C_D is defined as follows [19]:

$$C_D=\frac{18\mu}{d^2\rho_p C_C} \tag{7}$$

C_C is the Cunningham correction to Stokes' drag law and is computed from:

$$C_c=1+\frac{2\lambda}{d}\left(1.257+0.4e^{\frac{-1.1d}{2\lambda}}\right) \tag{8}$$

Brownian force is modeled as Gaussian white noise with spectral intensity $S_{n,ij}$ given by Li and Ahmadi [20]:

$$\vec{F}_{B,i}=\zeta_i\sqrt{\frac{\pi S_0}{\Delta t}} \tag{9}$$

$$S_{n,ij}=S_0\delta_{ij} \tag{10}$$

Table 2
Grid-independency study results.

Number of cells	Pressure drop (Pa)
782,277	8.594
590,457	8.524
363,411	8.297
93,346	7.875