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Original Research Paper

The effect of red blood cell motion and deformation on nanoparticle delivery to tumor

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ABSTRACT

The aim of this study is to evaluate the effect of movement and deformation of red blood cells on therapeutic nanoparticle delivery to tumor tissue through the pores on its vasculature wall. For this purpose, nanoparticle-blood flow through a segment of tumor microvascular is numerically studied. Blood is modeled as a mixture of plasma as a continuous fluid and red blood cell as an elastic solid by using coupled fluid structure interaction method. Lagrangian approach is used for tracking nanoparticles in the tumor microvessel, and effective forces from the fluid are applied to the particles. The effect of pore size and tumor interstitial fluid pressure on the deformation of red blood cell in the vicinity of the pore and on the particle delivery is studied. It is shown that by increasing the pore size and decreasing the interstitial fluid pressure, the amount of deformation of the cell and nanoparticle delivery are increased. The effect of transient motion and deformation of red blood cells on the amount of particles delivered to the tumor is investigated and it is shown that by approaching the cell to the pore, the particle delivery initially increases and then decreases.

1. Introduction

Transmission of food and drug to tissues is done in capillaries. These vessels' wall is composed of a layer of endothelial cells. Sometimes, two adjacent endothelial cells create a pore. These pores are the reason of the permeability of capillary wall. The tumor vascular permeability due to their larger capillary pores is more. Nanotechnology developments brought the idea to use pharmaceutical nanoparticles, which are larger than the size of normal tissue capillary pores and smaller than the size of cancer tissue capillary pore [1,2]. Some researchers experimentally and numerically investigated nanoparticle delivery to the tumor.

Kong et al. [3] investigated the effect of particle size on nanoparticle uptake by the tumor under normothermic and mild hyperthermic conditions. Their experiments were done on human ovarian carcinoma xenograft which is grown in mice window chamber. They showed hyperthermia increases the capillary pore size and so the particle uptake increases. Lammers et al. [4] investigated the effects of radiotherapy and hyperthermia on pharmaceutical nanoparticle delivery to the different tumors based on the syngeneic Dunning rat prostate model. They found that radiotherapy reduces the interstitial fluid pressure and thus increases drug delivery. Mishra et al. [5] proposed a mathematical model to describe the drug distribution in the tumor tissue and studied the effect of particle size.

There are two methods for modeling the capillary membrane; the first method is the modeling of membrane as a permeable wall with specific permeability. Penetration of nanoparticles through a permeable wall is studied numerically by some researchers, for example Hajmohammadi et al. [6] investigated heat transfer and hydrodynamics of nanofluid flow over a permeable flat plate. By assuming equilibrium for two phases, they wrote equations for mixture and by using similarity transformed equations to ordinary equations and then numerically solved them. They examined the effect of nanoparticle type, volume fraction and permeability parameters on heat transfer and flow parameters. Akbar [7] studied the effect of magnetic field on ferromagnetic carbon nanotube particles suspended copper- water nanofluid flow through composite stenosed arteries with permeable wall under various conditions with the exact solution of governing equation. The second method is the use of capillary wall nature which has pores that open to the tissue. Podduturi et al. [8] for the first time used this method for modeling the capillary wall. They investigated drug delivery to tumors under the different conditions by considering blood as non-Newtonian fluid. The particle movement in their model was due to pressure driven flow and Brownian motion. They studied the effect of pore size, interstitial fluid pressure, and etc. on

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Nomenclature

CBP	capillary blood pressure, mmHg
d	nanoparticle diameter, m
D	cylinder diameter, m
D_p	pore diameter, m
E	elastic module, Pa
$\vec{F}_B$	Brownian force per unit mass, N kg^{-1}
$\vec{F}_L$	Saffman's lift force per unit mass, N kg^{-1}
$\vec{F}_P$	the force due to pressure gradient, N kg^{-1}
$\vec{F}_V$	virtual mass force, N kg^{-1}
IFP	interstitial fluid pressure, mmHg
K	stiffness matrix, N m^{-1}
L	cylinder length, m
L_0	the distance of red blood cell from inlet, m
M	mass matrix, kg
p	pressure, Pa
po	Poisson's ratio
t	time, s
$\vec{u}$	velocity vector, m s^{-1}
U_{in}	velocity inlet, m s^{-1}
x	nodal acceleration vector, m
$\ddot{x}$	nodal displacement vector, m s^{-2}

Greek symbols

μ	viscosity, Pa s
ρ	density, kg m^{-3}

the particle uptake. Barisam and Shams [9] used this method for modeling the capillary wall. They considered all possible effective forces applied to nanoparticles in these conditions and examined drug delivery to cancer tissue and developed a correlation for the amount of nanoparticles delivered to the tumor tissue in term of the net filtration pressure, pore size, fluid viscosity near the pore and capillary fluid flow velocity and the size of the capillary and pore size distribution.

The same order of magnitude of the size of the capillaries and red blood cells leads to intense deformation of the cell. This deformation affects the blood flow and creates a difference between the blood flow in the microvessels and the other vessels. Experimental and numerical studies about blood flow through microvessels have been done by many researchers.

Tsukada et al. [10] studied the deformation of red blood cells in a microchannel experimentally. They studied the effect of the velocity of red blood cells on their deformation. Jeong et al. [11] measured red blood cell velocity and deformation in rat mesenteric capillaries in vivo. Hosseini and Feng [12] used the particle-based method for two-dimensional simulation of the motion and deformation of red blood cells. Shi et al. [13] investigated the deformation of red blood cells under different initial conditions with the help of three-dimensional transient numerical simulations.

In the present study, transient delivery of nanoparticles to the tumor is examined by considering blood as a mixture of plasma and elastic red blood cells. The effect of pore size and tumor interstitial fluid pressure on particle delivery is studied. The influence of motion and the deformation of red blood cell due to the presence of the pore on nanoparticle delivery to the tumor is investigated.

2. Material and methods

2.1. Geometry

Fig. 1 shows the schematic of the problem geometry. Geometry of the problem similar to the Ref. [8] is a rigid cylinder with dimensions of $L = 10$ μm and $D = 9.3$ μm and with a single pore on its wall. Inside the tube, a red blood cell as its steady state shape coaxial with tube is initially located at a distance of $L_0 = 3.45$ μm from the inlet. Pore location is at $(L/2, 0, D/2)$.

The steady state shape of red blood cell is obtained by performing a simulation of plasma and red blood cell flow through a long tube at the same velocity and diameter. In this simulation, the red blood cell is initially as its static shape with Cross section profile as follows [14]:

$$\bar{x} = 0.5(1 - \bar{y}^2)^{0.5}(c_0 + c_2\bar{y}^2 + c_4\bar{y}^4) \quad (1)$$

where $\bar{x}$ and $\bar{y}$ are longitudinal and transverse coordinates which are normalized by red blood cell radius (3.91 μm). c_0, c_2 and c_4 are 0.207, 2.002 and −1.122, respectively [14,15].

2.2. Governing equations

In this study, for modeling of blood flow as a mixture of plasma and red blood cells, coupled fluid structure interaction method is used. The problem is divided into two fluid and structure subproblems.

In the structural subproblem, since the red blood cell is under time- varying stress, so transient dynamic analysis is required. In this work, the transient motion and deformation of red blood cell is modeled as an elastic structure. The governing equation of motion of any nodes in the structure is as follows:

$$M\ddot{x} + Kx = P(t) \quad (2)$$

where $\ddot{x}$, x and P are nodal acceleration, displacement and temporal force vectors, respectively. M and K are the mass and stiffness matrices, respectively which are written as follows:

$$M = \rho_{RBC}\int_{\forall} N^T N d\forall \quad (3)$$

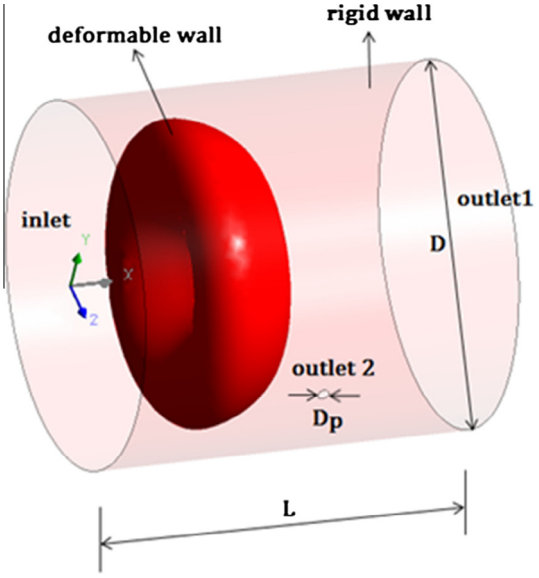

Fig. 1. The geometry of the problem.