Numerical Investigation of Critical Factors for Spatial and Temporal Responses of Macromolecular Carriers in Tumor Tissues

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Abstract

Cancer is the leading cause of death in the modern society. The conventional treatment includes the injection of anticancer therapeutic agent to tumor tissues. The efficacy of the treatment depends on the delivery of the drug in the interstitium. The substances that could improve the delivery process can be employed as drug carriers. Macromolecules or nanoparticles that can target at tumor tissues and contain limited toxicity to normal tissues are particularly suitable for serving as carriers. These carriers can be conjugated to flurophores and tracked using optical microscopy to provide spatial and temporal distribution of the drug. In this work, we investigated bio-distribution responses of dextrans with molecular weight ranging from 10 k-Da to 2 M-Da. Factors such as carrier molecular weight and diffusion of carriers were quantitatively studied through computer simulations. The temporal and accumulated distribution of dextrans were investigated to evaluate therapeutic effects under different conditions.

Keywords: drug carrier concentration, simulation model, pharmacokinetics

Introduction

The concentration of drug carrier can indicate the presence of anti-cancer drug in tumor tissues. Provided such information, researchers and physicians can customize the physical properties of these carriers to achieve a desired concentration distribution for therapeutic purposes. In practice, this can be accomplished by tagging the drug molecules and tracking them via imaging methods. Although relevant experimental investigations have demonstrated the feasibility in a laboratory setting, it remains of great difficulty to estimate the drug concentration in clinics. The instantaneous and accumulated concentration distributions are essential to the effects of the treatment. By establishing a computer simulation model that can provide a reasonable prognosis of each drug under various circumstances, the treatment plan can be administered accordingly. Thus, the objective of this paper is to provide a simulation model that can calculate the concentration distribution and accumulation of drug carriers subject to different physiological conditions in tumor tissues.

Method

System Architecture

The simulation geometry consists of a three-dimensional square array of arterial and venous capillaries, which are arranged in square areas alternately. The two-dimensional cross-sectional view of the distribution of these capillaries is illustrated in Fig 1. (a). Because the flow pattern is symmetric, its study can thus be represented by a single square area due to the periodic arrangement.

A schematic of the simulation cell is given in Fig 1. (b). Here, the vascular hydrostatic pressures immediately next to the arterial capillary and venous capillaries are denoted by P_a (mmHg) and P_v (mmHg), respectively. The other parameters to be considered are hydraulic conductivity of tissue k (μm ^{2}/mmHg-s), diffusion coefficient of the drug carrier in the tumor tissue D (μm ^{2}/ s), the elimination half-life time of particles in arterial and venous capillaries λ (s), and the average vascular distance G (μm).

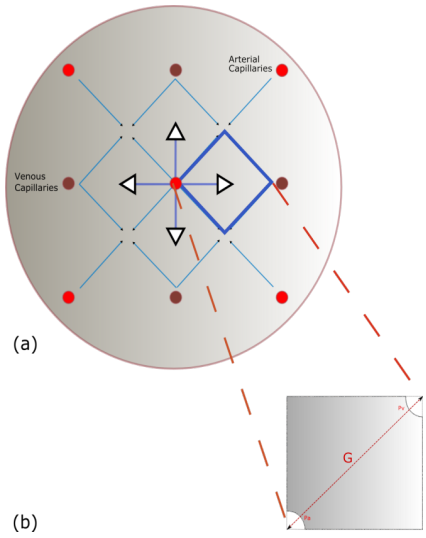


Figure 1. The simulation system model.

Proposed Method

The transport of molecules is driven by diffusion and convection effects. The diffusion effect is caused by concentration gradient, while the convection effect is caused by pressure gradient. The simulation procedures are shown in Fig 2., including the determination of the pressure and velocity field, and the computation of concentration field.

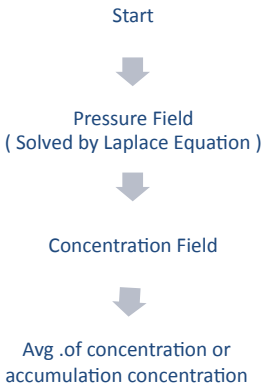


Figure 2. The simulation flowchart

Assuming incompressible fluid, the continuity equation can be written as

$$\nabla \cdot \vec{v} = 0, \tag{1}$$

where $\vec{v} \equiv (v_x, v_y)$ is the velocity vector (μm /s), and v_x and v_y are the velocity along the x and y directions, respectively. The velocity distribution can be obtained by applying Darcy's Law as

$$v_x = -k\frac{\partial P}{\partial x},\ v_y = -k\frac{\partial P}{\partial y}, \tag{2}$$

Where k (μm ^{2}/mmHg-s) is hydraulic conductivity and P (mmHg) is the pressure. Combining Eqs. (1) and (2), the pressure field will satisfy

$$k\left(\frac{\partial^2 P}{\partial x^2} + \frac{\partial^2 P}{\partial y^2}\right) + \left(\frac{\partial k}{\partial x}\frac{\partial P}{\partial x} + \frac{\partial k}{\partial y}\frac{\partial P}{\partial y}\right) = 0, \tag{3}$$

where k (μm ^{2}/mmHg-s) is hydraulic conductivity.

Subsequent to solving the pressure and velocity fields from Eqs. (3) and (2), we can determine the concentration distribution of drug carrier by use of

$$\frac{\partial C}{\partial t} = D\left(\frac{\partial^2 C}{\partial x^2} + \frac{\partial^2 C}{\partial y^2}\right) - \left(v_x\frac{\partial C}{\partial x} + v_y\frac{\partial C}{\partial y}\right) - R \tag{4}$$

where R is the reaction rate and C is the concentration of drug carrier in tumor tissues.

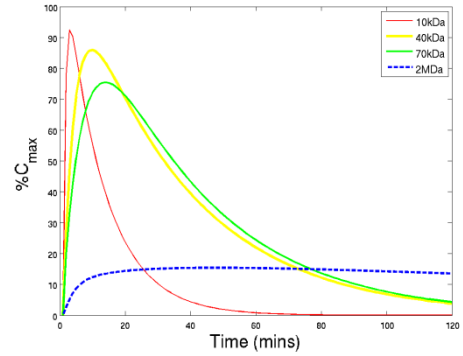
Results

In this paper, we chose the dextran as the drug carrier, whose characteristics are listed in Table 1, and investigated its concentration distribution in tumor tissues. The molecular weights of the dextran are 10 k-Da, 40 k-Da, 70 k-Da, and 2 M-Da, and the capillary distances are set as 100, 200, to 500 μm, respectively. The results of average concentration in tumor tissue corresponding to parameters mentioned above are shown in Fig 3.

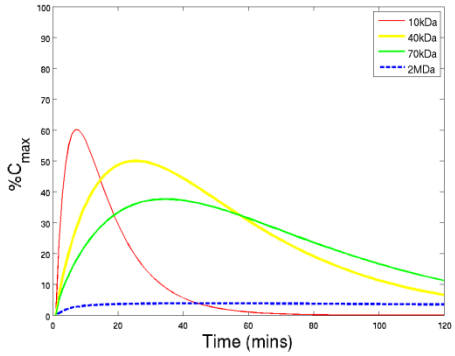
The other part of results is about the accumulation of concentration in tumor tissue. In this part of simulation, we also set different capillary distances as 100 μm, 200 μm, and 500 μm, and molecular weights of the dextran is 70 k-Da. We record the accumulation of concentration values corresponding to time every 10 minutes in totally 120 minutes. The results are showed in Fig. 4.

Table 1. The parameters used in this paper

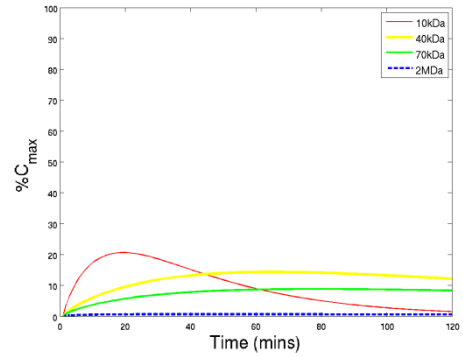
Parameters	Value		Ref.
The arterial capillary pressure (P_a)	17 mmHg		[3]
The venous capillary pressure (P_v)	17 mmHg		[3]
Hydraulic conductivity (k)	4.13 μm^{2}mmHg^{-1}s^{-1}		[5]
Diameter of vascular (Dia)	10 μm		[3]
The elimination half-life time of particles (λ)	10 k-Da	8.17 min	[1]
	40 k-Da	23.62 min	[1]
	70 k-Da	23.77 min	[1]
	2 M-Da	35.14 min	[1]
The diffusion coefficient (D)	10 k-Da	69.13 μm^{2}s^{-1}	[4]
	40 k-Da	14.23 μm^{2}s^{-1}	[4]
	70 k-Da	7.521 μm^{2}s^{-1}	[4]
	2 M-Da	0.1646 μm^{2}s^{-1}	[4]



(a) 100μm

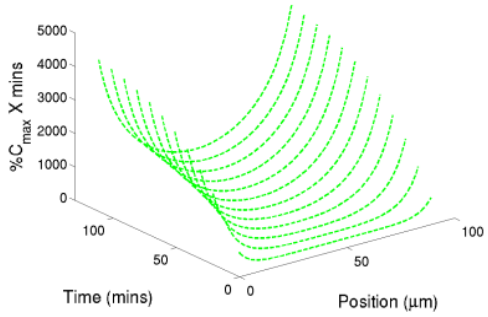


(b) 200μm

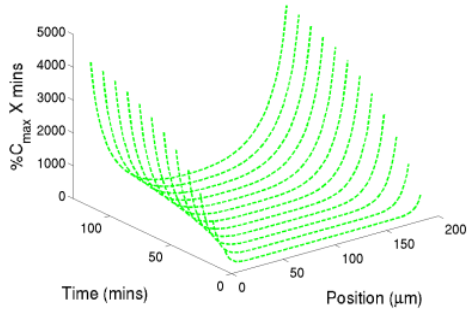


(c) 500 μm

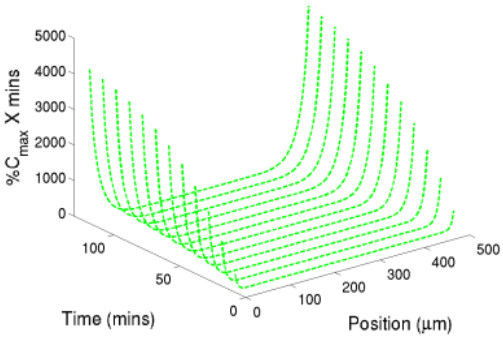
Figure 3. Simulation results about interstitial average concentration corresponded to time. Sub-figures (a), (b) and (c) correspond to capillary distances of 100, 200 and 500 μm, respectively.



(a) 100 μm



(b) 200μm



(c) 500 μm

Figure 4. Interstitial accumulated concentration corresponded to time after drug carrier injected. The accumulated concentration profiles in tumor tissues for 70 k-Da Dextran correspond to the vascular distance (a) 100, (b) 200 and (c) 500 μm, respectively. The accumulated concentration distributions were recorded every 10 minutes for 120 minutes.

Conclusion

The concentration field in different tissues can be simulated using the proposed model by assuming alternatively arranged capillaries. With the input of the corresponding parameters, the instantaneous and accumulated concentrations in tumor tissues can be determined. The model can be used to investigate factors pertinent to the interstitial concentration.

In the simulation, the concentration distribution of larger carrier of molecular weight 2 M-Da is lower than expected. Compared with Ref. [1], the delivery of dextran in 2MDa is also relatively small. The concentrations of carriers with molecular weight 40 and 70 k-Da are observed to be much higher than larger ones in this simulation.

Drug carrier transport depends on the joint effects of convection and diffusion. In general, the convection effects are more dominant for larger particles while diffusion effects tend to dictate the mass transfer of smaller particles [6]. The main driving force of delivery in interstitial region is diffusion effect, so the larger particles such as 2-MDa, which replies largely on convective effect, cannot transport well in tumor tissues. With the aid of these parameter simulation researchers can obtain a better estimation of the resulting concentration distribution, thereby allowing for a more precise prescription.

Acknowledgment

This work was supported in part by National Science Council under grant No. NSC 99-2221-E-002-043-MY3

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