Estimation of macromolecular drug diffusivities in solid tumors

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Abstract

To effectively deliver drugs to all tumor regions is one of the most current important research issues at present. Unfortunately, some of measurements of transport properties were infeasible to obtain at present technology and some of experimental trails involved complicated tumor microenvironments that were hard to analyze. Therefore, the main purpose of this study is to use an optimization scheme to seek for optimal macromolecular speed at blood vessel surface and diffusivity. With integrating experimental information on dextran covalently linked to a fluorophore in tumors, optimization scheme, mathematical modeling and numerical modeling, an estimation scheme is proposed to predict several parameters of interest in tumour region.

One-dimensional transient solute transport equation coupled with experimental pharmacokinetics data is used in the study. The governing equation, which is derived from cylindrical coordinate, includes convection and diffusion modes of transport. Results show that comparably convection plays a rather significant role in solid tumor than diffusion for larger size of macromolecules and in optimization process to obtain solutions of diffusivities and drifting velocities, although it is still weak. The computational results show in accordance with figure 6 of Dreher et al's paper.

Keywords: Transport Phenomena, Diffusion, Convection, Pharmacokinetics, Numerical Simulations.

1. Introduction

The neoplastic vasculature of solid tumors has significant impact on the distribution of anticancer drugs. Investigation of drug transport phenomena within tumors is motivated by the desire to understand macromolecular drugs in the cancer treatment. In this study, we utilized, analyzed and compared experimental data published by Dreher et al [1] recently.

The inability to deliver adequate quantities of macromolecular drugs to all area

of solid tumors depends on many factors [2]. One of them is due to high interstitial fluid pressure within solid tumors and it is a well recognized phenomenon. To effectively deliver drugs to all tumorous regions is the most current important research topic at present [3, 4]. Most of research groups presented studies which usually focused on experimental measurements and trials to obtain transport properties which are used for analysis and treatment strategies. However, some of measurements were infeasible to obtain at present technology and some of experimental trails involved complicated tumor microenvironments that were hard to analyze. Therefore, the use of mathematical modeling and numerical modeling to assist obtaining transport properties of interested domain can help us reduced cost of experimental procedures, predicting and accelerating outcome of results that are the objective of this paper.

Rakesh K. Jain and his associates [5] used their mathematical model to gain insights of IFP and macromolecular transport in tumors. And they confirmed in two years later after their mathematical predictions that “IFP is relatively uniform throughout the tumor and decreases precipitously in the tumor margin. Because fluid convection or bulk flows, requires pressure gradients. It indicated that convection would be negligible throughout the tumor”.

The elevated interstitial fluid pressure (IFP) that contributes to a barrier to drug transport to the tumor region is one of factors in solid tumors. Many research groups propose and suggest novel treatment strategies to overcome this issue. Recent reviews [4] said that anticancer drugs distribute within tumors they form gradients from tumor blood vessels that change with time as the drug is cleared from the body. The permeability of vessel walls influences drug penetration, but is thought to be insignificant in many tumors where blood-vessel fenestrations have been observed. Drugs penetrate normal tissues by both diffusion and convection, with a net flow of fluid from blood vessels balanced by resorption into lymphatics. However tumors often lack functional lymphatics [4], which can lead to increased levels of IFP in tumors which in turn are likely to reduce convection and thereby inhibit the distribution of macromolecules.

It is now well established that elevated interstitial fluid pressure (IFP) exists in many solid tumors. As early as 1950, Young *et al.* [6] had already reported the hydrostatic pressure of tumors is often increased. In 1987, Jain hypothesized that the osmotic pressure in tumors must be high and that the high IFP is a barrier for efficient drug delivery [7, 8]. Although mathematical modeling was present at that time, it was

simple without incorporating pharmacokinetics data from experiments. So we assume that the magnitude of interstitial fluid velocity (IFV) moving out of vascular vessels toward tumor regions is inversely decreasing as distance increases. The value of fluid velocity at the periphery, for a tumor of 1 cm radius is about 0.1~ 0.2 μm/s, however the value of convective velocity inside the tumor is not known.

This paper adopts some of experimental results treated as an input data to the simulator and it produces the results of interests. Implicitly, this paper is a semi-experimental analysis paper to predict the macromolecular drug diffusivity in solid tumor and further describe the drug transport in solid tumors.

2. Material and methods

A graphical model used in the study is shown in Fig. 1. It represents a schematic cross-section view of the domain of interest: drug particles transport through a blood vessel's porous wall into solid tumor region. Vascular compartment of blood vessel is a region containing dynamic drug intensity as regarded as an input transient data, which is a given experimental data, to the governing equation in numerical calculation. The extravascular compartment is the region outside of the blood vessel's wall to the distance of 35 μm away from the vessel wall. Cylindrical coordinate system is used in the study and a positive normal vector is pointing outward of blood vessel wall.

To effectively deliver anticancer therapeutic agents to solid tumor must rely on drug carriers. Macromolecular drug carriers are an attractive alternative drug delivery method because they appear to target tumors and have limited toxicity in normal tissues. Dextrin of different sizes of particles is used in the study. We used dextrans with molecular weights from 3.3 kDa to 2 MDa, as dextran covalently linked to a fluorophore was administered in tumors experimentally.

According to Fick's first law and solute particle drift, the total flux density (or fluence rate) is the sum of both terms which is described as

$$j_s = -D\frac{\partial C}{\partial r} + r_f u C \qquad (1)$$

where r_f is the retardation factor (it indicates the ratio of drug particles' velocity to fluid velocity and usually it is 1.0), u is the drug particles' drifting velocity at blood vessel wall, C is the concentration of drug, D is the diffusivity of macromolecular drug in solid tumor (assumed constant in the study) and r is radial position in cylindrical coordinate.

With the theory of continuity equation ($\frac{\partial C}{\partial t} = -\nabla \sqcup j_s$) and conservation of mass in extravasculation and applying the equation 1, we are able to generate Fick's second

law, which the governing equation is expressed as

$$\frac{\partial C}{\partial t} = D\left(\frac{1}{r}\frac{\partial C}{\partial r} + \frac{\partial^2 C}{\partial r^2}\right) - \frac{uC}{r} - \frac{\partial (uC)}{\partial r} \tag{2}$$

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The concentration of drug in solid tumor depends on the intensity of drug carried in blood vessel which is the driving force of the distribution of drug dose in solid tumor. In experimental setup, the administration of the macromolecules was modeled as a bolus injection into a central blood compartment that was allowed to exchange with both normal and tumor extravascular compartment and to be eliminated. Therefore we used vascular pharmacokinetics (figure 4.A of the paper [1]) as boundary condition to the equation 2 and assumed zero concentration at the other end of boundary condition.

$$C(r,t) = \begin{Bmatrix} C(t), & r = r_v \\ 0, & r = L \end{Bmatrix} \tag{3}$$

where r_v is the radius of blood vessel and L is the location at the other end which is far away from the blood vessel. *C(t)* is the driving force of drug penetrating from vascular compartment into solid tumor. The initial condition is zero concentration in the domain of interest.

$C(r) = 0$ when t = 0, at any location in the domain. (4)

The simulator of the system equations is capable of predicting solute transport which includes two mass transfer modes: diffusion and convection.

To calculate the equation 2 with supplementary equations 3 and 4, the finite difference method is used for the non-dimensional form of equation 2. The Crank-Nicolson method is used for transient and diffusion terms of equation 2. Both terms basically adopt central difference method which is the second order accuracy. Convective terms of the equation 2 involving velocity are treated with upwind numerical method which is the first order accuracy method. The drug sifting velocity is assumed to be inversely decreased with increasing r value (i.e. away from vessel wall) as indicated below,

$$u(r) = \frac{r_w}{r} u_w \tag{5}$$

where u_w is the drug particles shifting velocity at vessel wall (r_w).

Optimization scheme to seek for optimal macromolecular speed at blood vessel surface and diffusivity is described in figure 2. Before optimization process starts, a

pre-process logical search shown in table 1 for suitable ranges of those two properties is performed. With initial values of diffusivity and velocity at vessel wall, coupled with experimental data in vascular and extravascular compartments, we obtained optimal solutions for diffusivity and velocity for different size of macromolecules according to the criterion. The comparison criterion used for the scheme is:

$$\frac{\sum_{i \in S} \frac{\left| I_{i,\exp} - I_{i,est} \right|}{I_{i,est}}}{num(S)} \qquad (6)$$

where set *S* is defined as all selected data points for the period of 30 minutes. In this study, we take a data point at each minute. $I_{i,\exp}$ is the extravascular intensity at the i^{th} minute from experiment shown in figure 4.a of [1]. $I_{i,est}$ is the estimated intensity at the i^{th} minute from computer calculation which the estimated intensity is the average of all location points within 35μm zone of extravascular compartment. The interval distance among the location points is 1μm. Num(*S*) means total number of data points in the set *S*. Therefore, we used the 30 minutes time period for the comparison. At every one minute interval we compared the experimental data and estimated data as described by the criterion. The optimal solution reaches when the comparison criterion value is less than 7%. Therefore iteration stops.

3. Results

The initial guess on drifting velocity at vessel wall is 0.1μm /s. It is based on Jain's paper [15, 16] that the value of fluid velocity at the periphery, for a tumor of 1 cm radius is about 0.1~ 0.2 μm/s, however the value of convective velocity inside the tumor is not known. The try-and-error logical search for optimal diffusivities and drug particles velocities for different sizes of macromolecular drug are shown in table 1. We ran several cases of simulations according to experimental results. Following the rule of the larger size of macromolecules, the more difficult particles can penetrate into tumor interstitium. The purpose of this search is to first establish ranges of diffusivities and velocities for all macromolecular sizes. It lets us to search optimal values on a smaller range of each macromolecular drug in optimization with less computational time. To illustrate our calculated results, we compared them with experimental results and showed them at different sizes of macromolecules in figures 3 and 4.

Figure 3 shows comparison of experimental and simulation results with various

apparent diffusivities and particles drifting velocities by convection for extravascular accumulation of dextran with 3.3kDa molecular weight. The unit of diffusivities is cm^2/s and that for macromolecular particles shifting speed is μm/s. The cases of simulating transport parameters for this macromolecular drug are ({diffusivity, drug particles shifting speed}) {$1.0*10^{-6}$, 0.0}, {$1.0*10^{-7}$, 0.0}, {$1.0*10^{-6}$, 0.01}, {$1.0*10^{-6}$, 0.05}, {$7.0*10^{-7}$, 0.05}, {$5.0*10^{-7}$, 0.05} and {$5.0*10^{-7}$, 0.08}.

Figure 4 shows comparison of experimental and simulation results with various apparent diffusivities and particles drifting velocities by convection for extravascular accumulation of dextran with 2M Da molecular weights. The unit of diffusivities is cm^2/s and that for macromolecular particles shifting speed is μm/s. The cases of simulating transport parameters for this macromolecular drug are ({diffusivity, drug particles drifting speed}) {$1.0*10^{-9}$, 0.0}, {$1.0*10^{-10}$, 0.0}, {$5.0*10^{-11}$, 0.0}, {$5.0*10^{-11}$, 0.001}, and {$5.0*10^{-11}$, 0.0011}.

After optimization scheme shown in figure 2, we obtained optimal diffusivities and drug particles drifting velocity at vessel wall. According to the resultant figures in the journal paper, we presented our numerical results in the same figure format that drug intensity as a function of the distance from vessel wall and time. Compared our calculated results in figures 5.a and 5.b with figure 6 in the journal paper [1], they have shown in a good agreement of different sizes of macromolecules. Thus this provides one of verification in our calculations. Figure 5 shows penetration of macromolecules ((a) 3.3kDa and (b) 2MDa) into tumor interstitium from the vascular surface with optimal values for apparent diffusivities and convective drifting particle velocities. Zero distance was defined as the vascular compartment, and every distance greater than zero was defined in extravascular compartment.

The estimated transport properties are shown in table 2. Table 2 illustrates optimized parameters of convective particles drifting velocity and diffusivity, and optimization calculation properties for different size of macromolecules. The optimal solutions of diffusivity and drifting velocity for each size of macromolecules are highlighted on two columns in the table. It showed ({diffusivity, drug particles drifting speed}) {0.1, $4.8*10^{-7}$} for 3.3-kDa macromolecules, {0.01, $6.4*10^{-8}$} for 10-kDa macromolecules, {0.0023, $5.0*10^{-9}$} for 70-kDa macromolecules and {0.00085, $1.0*10^{-10}$} for 2-MDa macromolecules.

4. Discussion and conclusion

For the molecular weight of 3.3kDa drug, the region near capillary vessels the diffusion plays a more significant role than the convection as shown in figure 3. The convection contributes to an increase in overall distributions. That means it helps drug particles in penetrating into tumor interstitium however, the strength of convection remains weak in solid tumors.

For the large size of macromolecular drug of 2M Da shown in figure 4, drug diffusion into tumor interstitium from vascular compartment is very weak. Comparably convection plays a rather significant role in solid tumor than diffusion for larger size of macromolecules, although it is still weak. This phenomenon also clearly is showed in figure 5.b that the inability to penetrate deep into tumor interstitium for large size of macromolecules. The distribution of the drug particles are within 5 μm of distance away from blood vessel. In other words, most particles still closely contact with blood vessel.

The strength of convection is very weak in the study; however it is significant in optimization process to obtain solutions of diffusivities and drifting velocities as indicated in figures 3 and 4. From our study, the estimated macromolecular diffusivities of dextrans in solid tumors indicate smaller values than those diffusivities in normal tissue. The extracellular matrix (ECM) may contribute to the drug resistance of a solid tumor by preventing the penetration of therapeutic agents.

References

[1] Matthew R. Dreher , Wenge Liu , Charles R. Michelich , Mark W. Dewhirst ,Fan Yuan , Ashutosh Chilkoti, “Tumor Vascular Permeability, Accumulation, and Penetration of Macromolecular Drug Carriers”, *Journal of the National Cancer Institute*, **98**, No. 5, 335-344, 2006

[2] Dai Fukumura and Rakesh K. Jain, Tumor Microenvironment Abnormalities: Causes, Consequences, and Strategies to Normalize, *Journal of Cellular Biochemistry* 101:937–949, 2007.

[3] Heldin, C. H., Rubin, K., Pietras, K. & Ostman, A. High interstitial fluid pressure — an obstacle in cancer therapy. *Nature Rev. Cancer* **4**, 806–813, 2004.

[4] Andrew I. Minchinton and Ian F. Tannock, Drug Penetration in Solid Tumors. *Nature Reviews* **6**, 583-592, 2006.

[5] Rakesh K. Jain, Ricky T. Tong, and Lance L. Munn, Effect of Vascular Normalization by Antiangiogenic Therapy on Interstitial Hypertension, Peritumor Edema, and Lymphatic Metastasis: Insights from a Mathematical Model, *Cancer Res*, **67**: (6). March 15, 2007

[6] Young, J. S. *et al.* The significance of the tissue pressure of normal testicular and of neoplastic (Brown–Pearce carcinoma) tissue in the rabbit. *J. Pathol. Bacteriol.* **62**, 313–333, 1950.

[7] Jain, R. K. Transport of molecules across tumor vasculature. *Cancer Metastasis Rev.* **6**, 559–593, 1987.

[8] Jain, R. K. Transport of molecules in the tumor interstitium: a review. *Cancer Res.* **47**, 3039–3051, 1987.

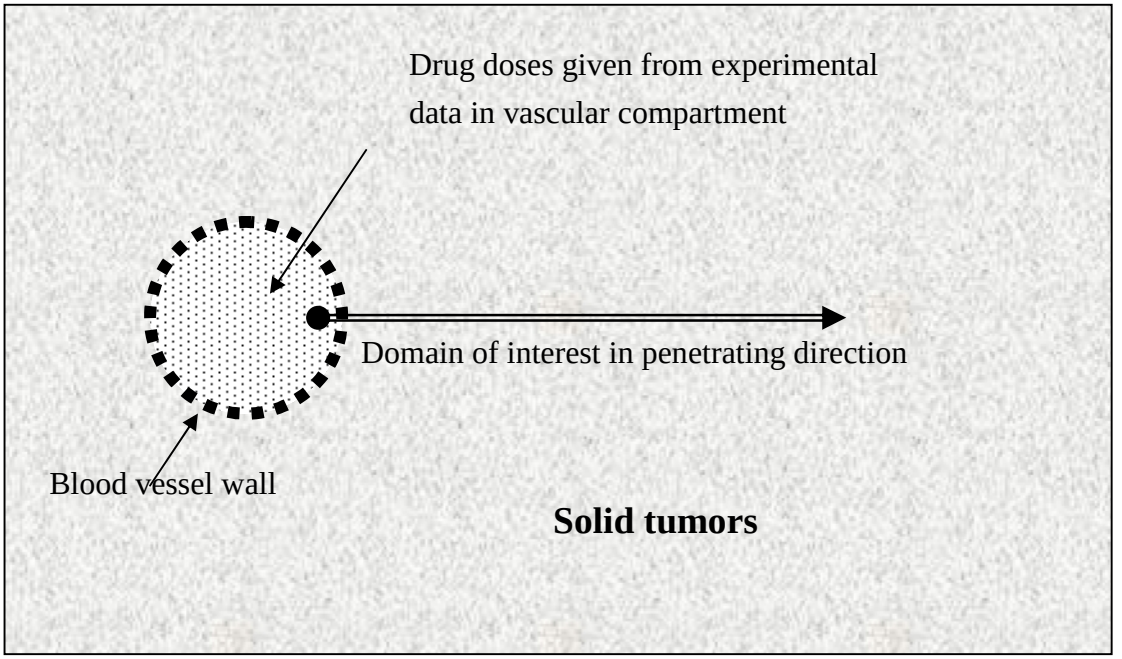


Figure 1. A schematic of macromolecular drug transport through a blood vessel's porous wall into solid tumor region. Cylindrical coordinate system is used in mathematical modeling.

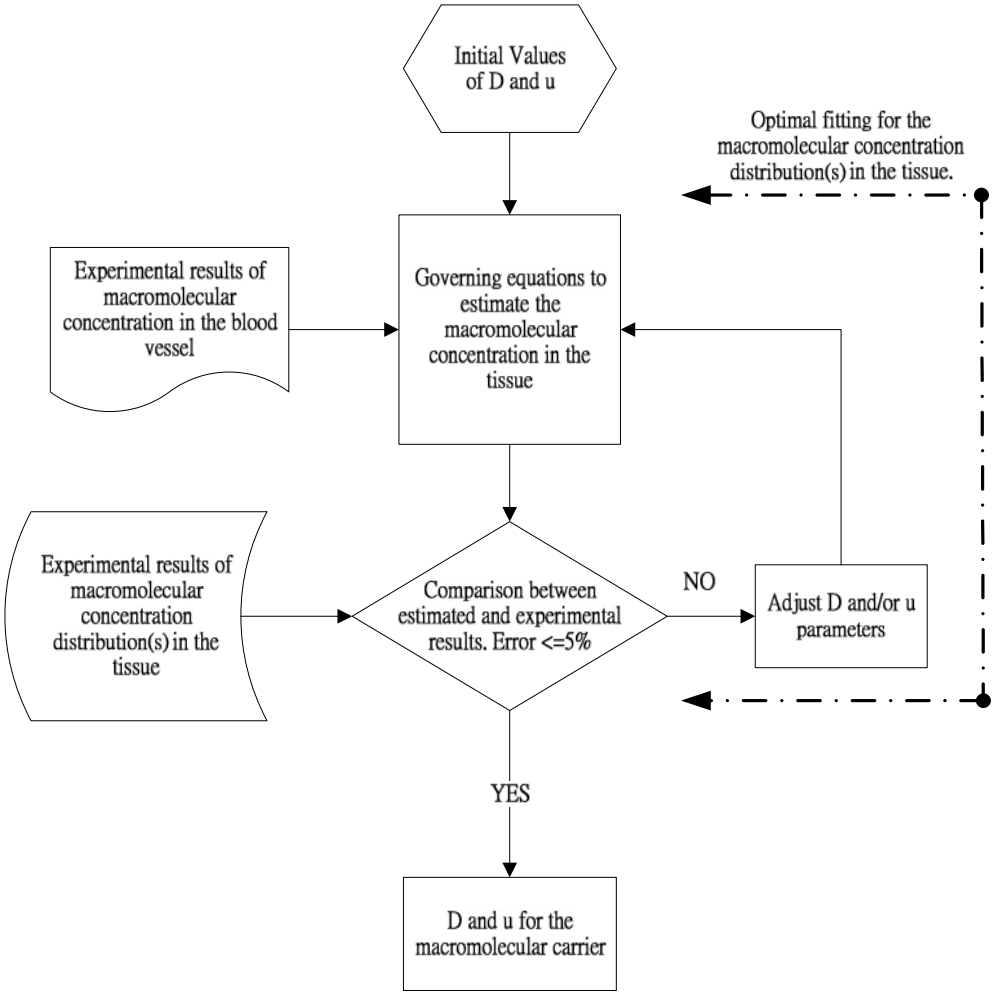


Figure 2. the flow chart of optimization to determine apparent macromolecular diffusivity (D) and particles drifting velocity (v) at vessel wall of the macromolecular drug. Given the initial D and v from logical searching table, optimization is done for each size of macromolecular drug particles.

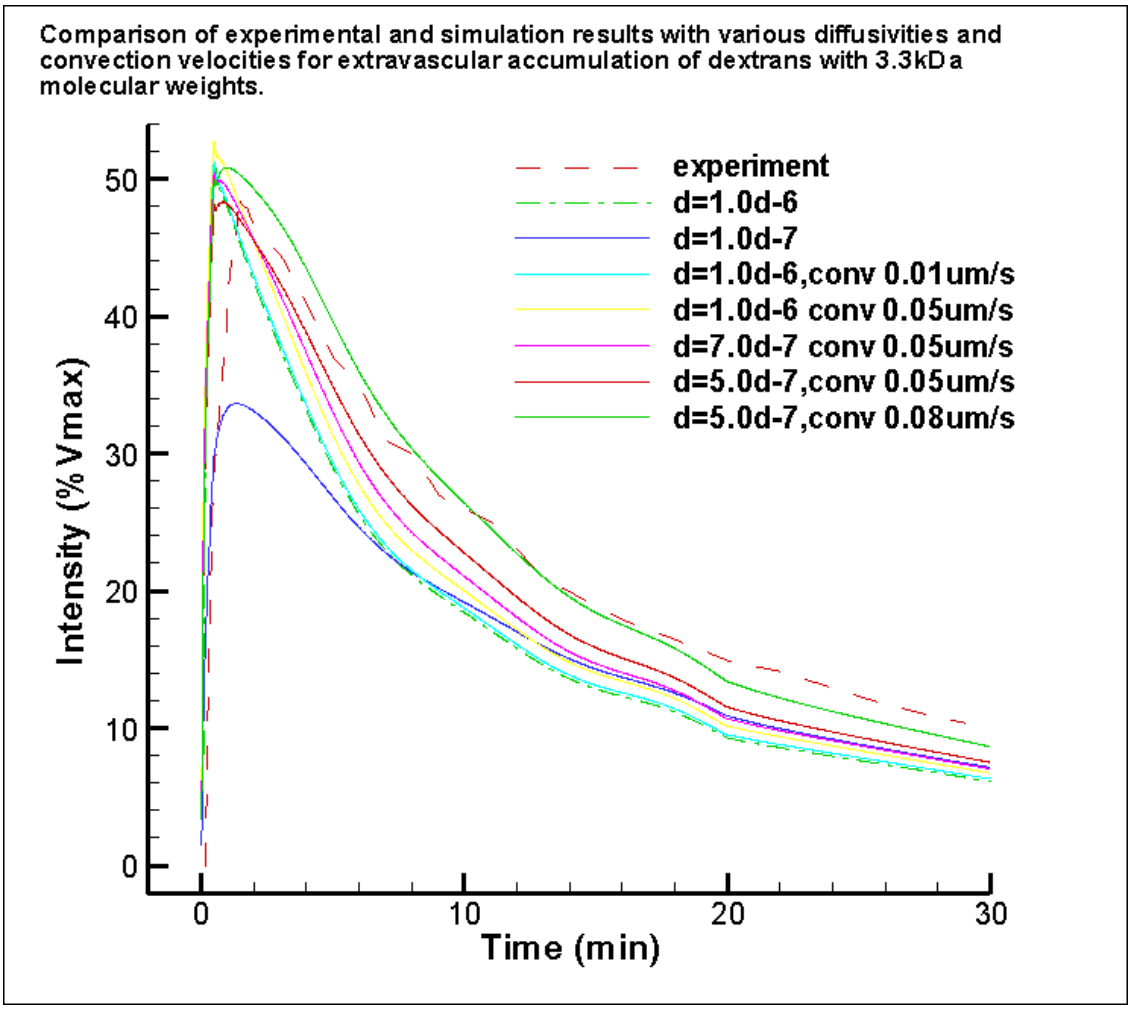


Figure 3. Comparison of experimental and simulation results with various apparent diffusivities and particles drifting velocity of convection for extravascular accumulation of dextran with 3.3kDa molecular weight.

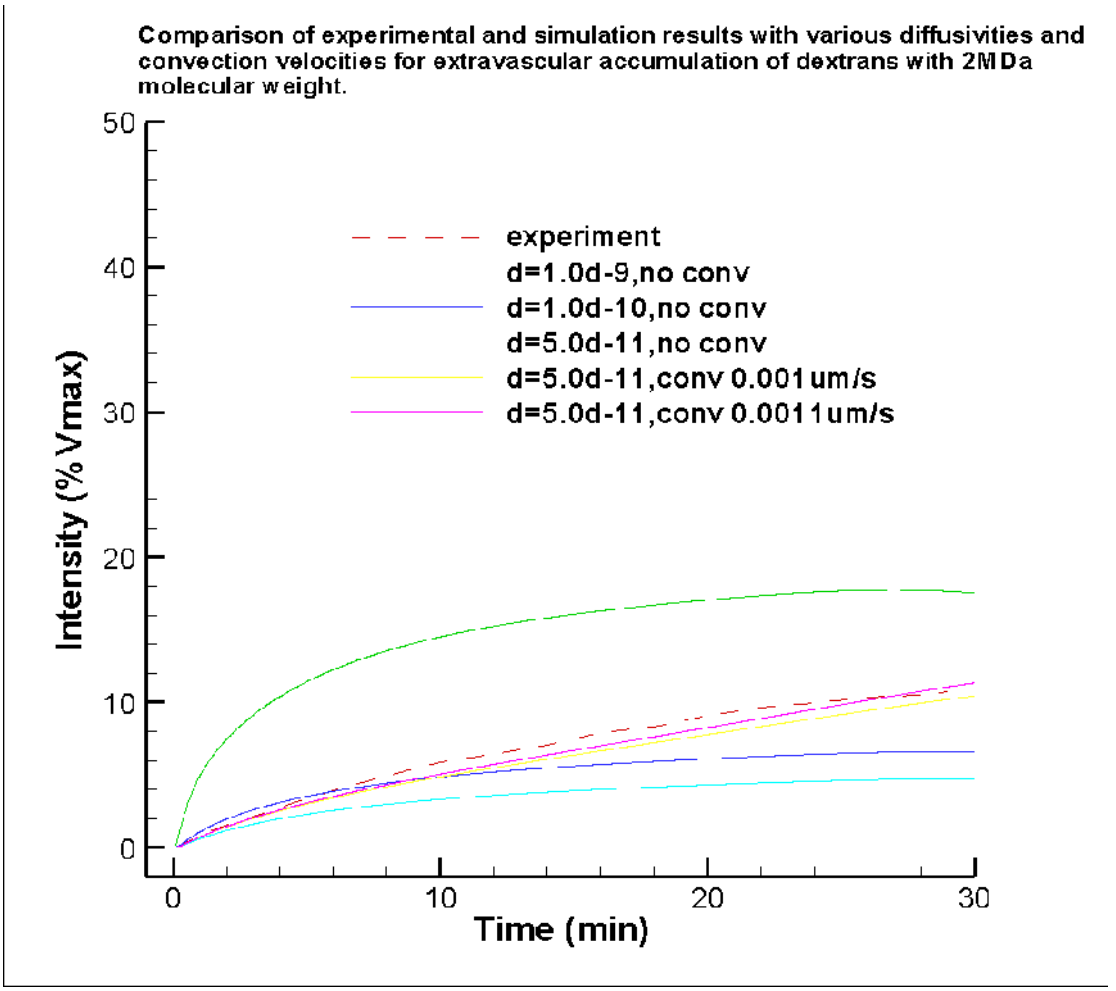
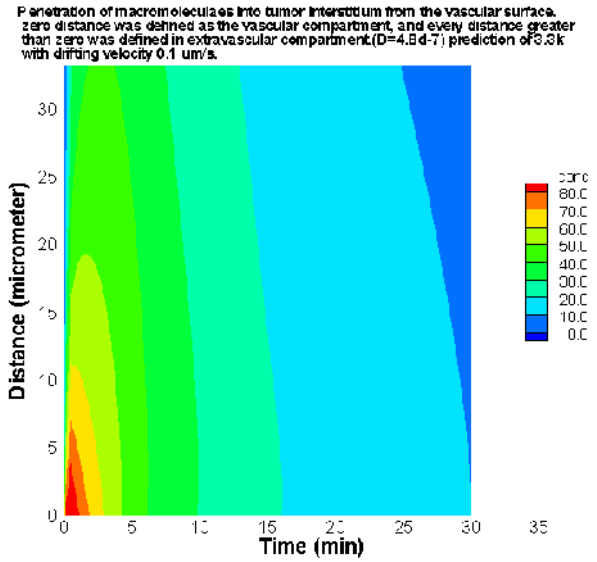


Figure 4. Comparison of experimental and simulation results with various apparent diffusivities and particles drifting velocity of convection for extravascular accumulation of dextran with 2M Da molecular weight.

(a)



(b)

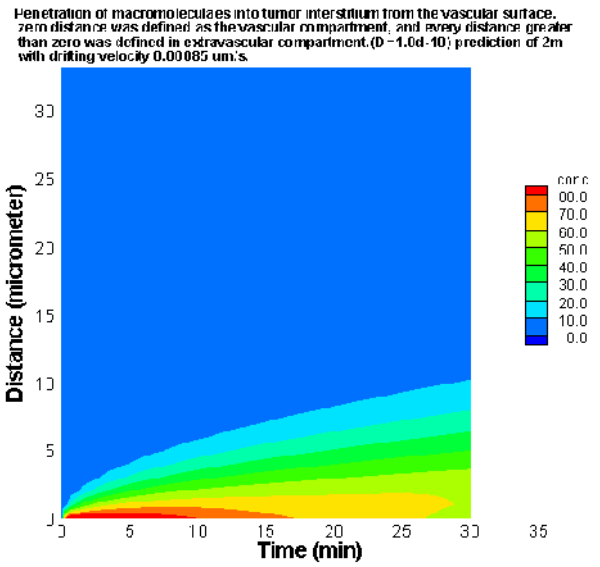


Figure 5. Penetration of macromolecules ((a) 3.3kDa and (b) 2MDa) into tumor interstitium from the vascular surface generated by computer simulation using optimal apparent diffusivities and convective drifting particle velocities. Zero distance was defined as the vascular compartment, and every distance greater than zero was defined in extravascular compartment.