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Image-based numerical model for drug delivery to solid tumors

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ABSTRACT: Mathematical models and numerical simulations along with clinical studies can help provide better understanding of drug delivery mechanisms, increase the efficacy of therapy, and demonstrate the effect of various physiological parameters on tumor behavior. The main objective of this study is to use a multiscale model based on mathematical modeling and computational fluid dynamics to evaluate drug delivery to a solid tumor and to predict treatment efficacy. A more-realistic physiological model of the tumor compared to the previous models is examined by obtaining the capillary-network's geometry from an image, as well as by considering the necrotic area and cellular uptake. Fluid flow modeling and drug delivery simulation are then performed for the interstitium. The fraction of killed cells is obtained approximately 69.03% after the cancerous tissue is treated with doxorubicin. Results also demonstrate that the drug concentration in the necrotic area is very low; only a small amount of the drug penetrates into the necrotic area by diffusion. The findings of this study may help researchers better understand the mechanism of drug delivery to solid tumors, —a necessary step in overcoming the micro-environmental barriers of tumors that impede treatment efficacy.

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1. Introduction

Due to the high mortality rates associated with cancerous tumors, many researchers are focused on finding methods and tools for early detection and effective treatment. Developing a mathematical model to properly predict treatment, improve and optimize it, and provide new therapies can help personalize treatment, increase patients' longevity, and enhance their quality of life.

The effectiveness of chemotherapy depends on the spatial-temporal distribution of the drug in the tumor, which itself depends on the characteristics of the tumor microenvironment, as well as the drug. Recently, Computational Fluid Dynamics (CFD) have generated a new field based on personalized clinical features employing computational modeling of drug delivery to solid tumors by combining patient characteristics with medical imaging data. For example, recently, Moradi Kashkoli et al. [1] examined the distribution of the drug using a finite element method, taking into account an image of a vascularized tumor.

In this study, by using mathematical modeling and computational fluid dynamics, employing an image of vascularized tumor, and also making the tumor physiology more realistic (considering drug binding to the cell, cellular uptake, and the presence of necrotic core in the tumor), the model for drug delivery to solid tumors is developed

2. Material and Methods

Delivery of chemotherapy drugs to tumor cells involves injection and transport through the circulatory system, leakage from the tumor microvessels, interstitial transport to tumor cells, binding to the cells, and eventually entering the cell space (Fig. 1(a)). The compartment model of the present study is also illustrated in Fig. 1(b).

2.1. Governing equations

The equations governing the present problem include: interstitial fluid flow, drug transport, and effectiveness of chemotherapy equations as follows

- Interstitial fluid flow [1]:

$$\nabla \cdot v_i = \phi_B - \phi_L \tag{1}$$

$$v_i = -\kappa \nabla P_i \tag{2}$$

in which κ is the interstitium's hydraulic conductivity, vi is Interstitial Fluid Velocity (*IFV*), Pi is Interstitial Fluid Pressure (*IFP*), ϕB is the fluid flow rate from capillary network to the interstitium and ϕL is the fluid flow rate from tissue to the lymphatic system.

- Drug transport [1]:

$$\frac{\partial C_F}{\partial t} = -\nabla \cdot (v_i C_F) + \nabla \cdot (D_{eff} \nabla C_F) - \frac{1}{\varphi} K_{ON} C_{rec} C_F + K_{OFF} C_B + (\Phi_B - \Phi_L) \tag{3}$$

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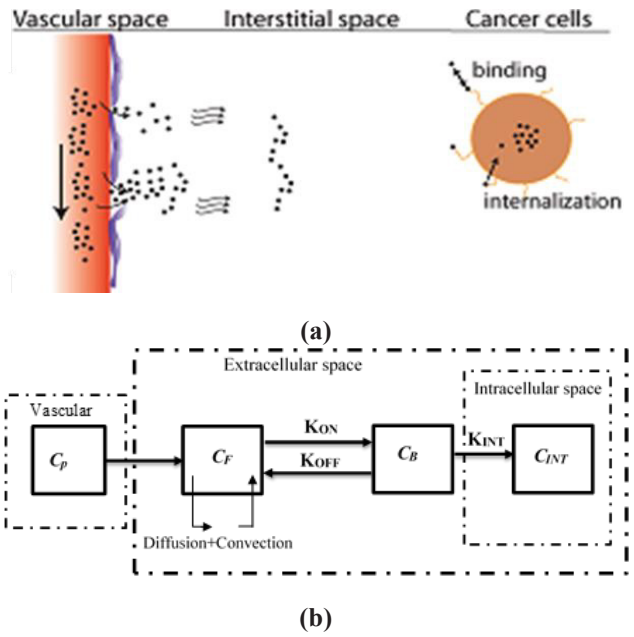

Table 1. The optimization results for the proposed cycle

$$\frac{\partial C_F}{\partial t} = -\nabla \cdot (v_i\ C_F) + \nabla \cdot (D_{eff} \nabla C_F) \tag{4}$$

$$-\frac{1}{\varphi} K_{ON}\ C_{rec} C_F + K_{OFF} C_B + (\Phi_B - \Phi_L) \tag{5}$$

in which C_F, C_B, and C_{INT} are respectively the concentration of free, bound and internalized drugs. Crec represents the drug concentration at the cell-surface receptors and Deff indicates effective diffusion coefficient. K_{ON}, K_{OFF}, and K_{INT} are the constants for binding, unbinding, and internalization, respectively. *ΦB* and *ΦL* are the rate of solute transport from capillaries to interstitium and from interstitium to the lymphatic system, respectively.

- Effectiveness of chemotherapy [1]:

$$Fraction\ of\ \ Killed\ Cells = 1 - S_F = 1 - \exp(-\omega \cdot C_{INT}) \tag{6}$$

S_F is the ratio of remaining cells after chemotherapy, and ω is a constant which is determined for doxorubicin.

2.2. Geometric model and computational field

In this study, the image extracted from the study of Walter et al. [23] is used as input. After image processing, a 2D computational field considering a tumor with 1 cm diameter is examined. Fig. 2 shows the computational field considered in the simulation. The necrotic area is assumed at the center of the tumor as $R_n = 0.4R$.

3. Results and Discussion

Results of the *IFV* are shown in Fig. 3. The *IFV* in the tumor area has very small value and it is maximum at the outer border of the tumor. It should be noted that the *IFV* in the necrotic area is much lower than in other areas.

Fig. 2. Computational field considered in numerical simulation

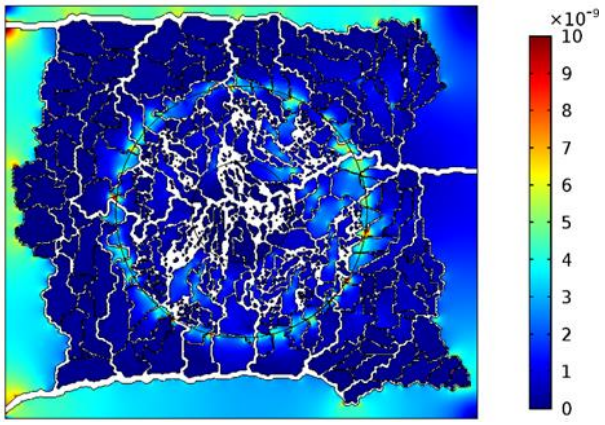

Fig. 3. Interstitial fluid velocity distribution (in m/s).

Spatial distribution of the non-dimensionalized state of different drug concentrations for the tumor and surrounding normal tissue is shown in Fig. 4 in 5 hours post-injection. The concentration in the necrotic area is so small that it can be generally neglected.

4. Validation of Numerical Results

The comparison between the result of this study and that of Stylianopoulos et al. [2] is performed based on the fraction of killed cancer cells parameters (Fig. 5). Different capillary networks and also differences in geometry due to the addition of necrotic core are caused such a result.

5. Conclusions

In this study, a computational model of drug delivery to solid tumors is developed, taking into account the capillary network obtained from the tumor image, the necrotic area in the geometry of tumor, as well as assuming real conditions. Findings of the current research are as follows:

- The *IFP* reaches maximum value in the tumor.
- The *IFV* is maximum at the border of the tumor and normal tissue.
- The complexity of capillary network is the main factor for the heterogeneous distribution of drug in the tumor.

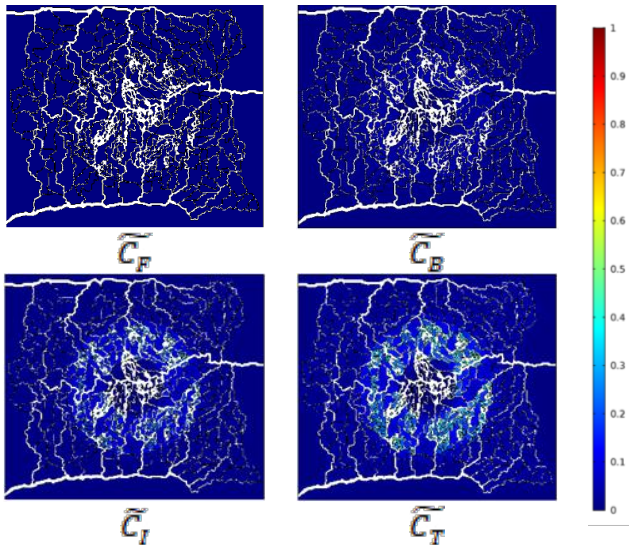

Fig. 4. Spatial distribution of different concentrations of drug for tumor and normal tissue in 5 hours post-injection

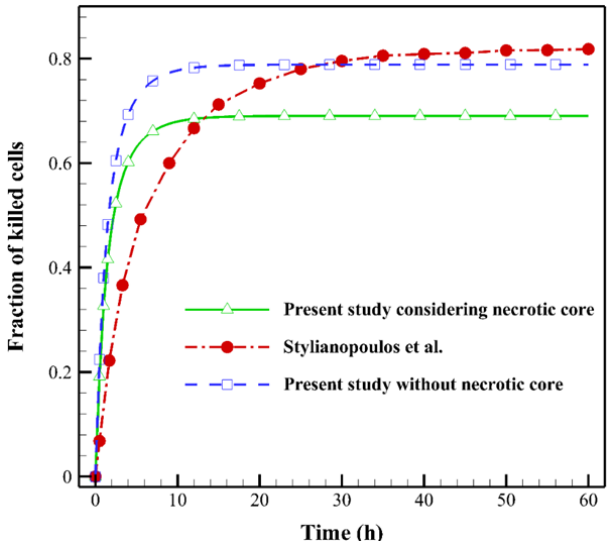

Fig. 5. Validation of results with previously published work using fraction of killed cancer cells over time

• After injection of drug, the concentration is gradually transferred from the free state to the bound and then the internalized state.

• By making the physiology of the tumor more realistic, the fraction of killed cancer cells in the tumor is about 69%.

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