Simulation of the role of the anti-angiogenic therapy in fluid flow behavior and macromolecule transport into a heterogeneous solid tumor

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ABSTRACT

The present study develops a numerical approach based on the mathematical models governing the behavior of fluid flow and drug transport in tumors to investigate the delivery of a macromolecule under the effect of the vascular normalization into a non-uniform tumor, including different parts of a real solid tumor. In this study, different tumor sizes in the range of $0.23 \le R_{eq} \le 2.79\,\mathrm{cm}$ are considered. The area under the curves of the drug average distribution and its deviation in the tumor site over time is studied as the amount of drug delivered and the uniformity of delivered drug to assess the quality of drug delivery. Results show that before and after normalization, the behaviors of interstitial fluid flow and the distribution of therapeutic agent concentration depend on tumor size. Normalization in all sizes reduces the interstitial fluid pressure, which this pressure drop increases as the tumor size reduces. Normalization improves antibody concentration distribution at different times depending on tumor size. However, from the point of view of the average spatiotemporal criterion, vascular normalization improves macromolecule delivery into the tumor site in $0.46 \le R_{eq} \le 0.93\,\mathrm{cm}$ by increasing the distribution uniformity. This research, by discussing the mechanisms affecting normalization efficiency, can provide insights for in vivo and in vitro studies that address the combination of anti-angiogenic therapy and chemotherapy.

KEYWORDS

Fluid flow, Drug transport, Non-uniform tumor, Vascular normalization, Combo-therapy.

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1. Introduction

According to the importance of cancer understanding, many researchers from various disciplines study this issue from different points of view. In this way, mathematical modeling does have a great contribution to these studies.

The abnormal structure of the tumor microvascular network is one of the limits of efficient chemotherapy as a treatment method for cancer. Therefore, numerical investigation of the drug delivery into the solid tumor coincides with the anti-angiogenesis seems essential. Jain et al. [1] examined the interstitial fluid pressure and velocity (IFP and IFV) in the homogeneous tumor due to the vascular normalization induced by anti-angiogenic therapy in a basic mathematical study.

In the present numerical study, a more accurate survey is done about the drug delivery into the solid tumor by considering the vascular normalization function by applying both fluid flow and solute transport analyses to the model and exerting the non-uniform real image-based tumor. Moreover, drug delivery quality is marked not only by the quantity of carried drug into the tumor but also by the less variation in drug distribution.

2. Materials and Methods

Governing equations, meshed view of the computational domain, and boundary conditions are discussed below to demonstrate the methodology of this study.

2.1 Governing Equations

The mathematical statements of interstitial fluid flow and drug transport describe the model of this problem. Interstitial fluid flow is defined by [2];

$$\vec{V}_i = -k\nabla P_i \tag{1}$$

$$\nabla.\vec{V}_i = \phi_B - \phi_L \tag{2}$$

In the above equations $\vec{V}_i$, k, P_i, ϕ_B, and ϕ_L show IFV, hydraulic conductivity of the interstitium, IFP, the fluid flow rate per unit volume from the blood vessels to the interstitium and vice versa, and the fluid flow rate per unit volume from the interstitium to lymphatic vessels, respectively.

Equations (3) and (4) explain the drug transport behavior [2]. In which C_i, $\vec{J}$, φ_B, φ_L, and D_{eff} illustrate the drug concentration, drug mass flux, rate of the drug transport per unit volume from blood vessels to the interstitium, rate of the drug transport per unit volume from the interstitium into the lymphatic system, and the effective diffusion coefficient, respectively.

$$\frac{\partial C_i}{\partial t} = -\nabla.\vec{J} + \varphi_B - \varphi_L \tag{3}$$

$$\vec{J} = -D_{eff}\nabla C_i + \vec{V}_i C_i \tag{4}$$

2.2 Meshed Geometry of Computational Domain and Boundary Conditions

Figure 1 shows the cross-sectional view of the geometric model with the generated grid. Boundary conditions (BCs) are shown in this figure.

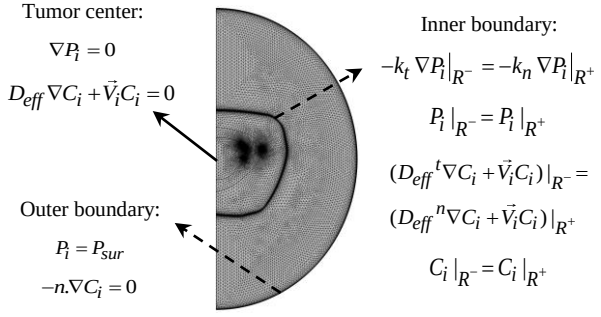


Figure 1. Meshed view of the computational field and BCs.

3. Numerical Results Validity

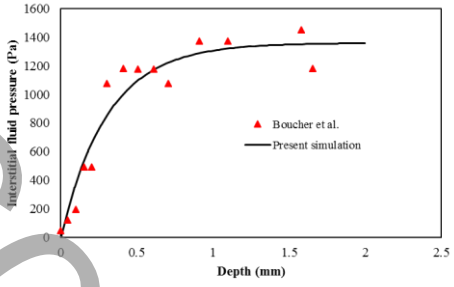
The interstitial fluid flow analysis is validated by comparing the results of the model of this study and those of experimental data [3]. Baxter and Jain's work [2] is simulated to investigate the reliability of drug transport analysis. Figure 2 demonstrates the comparison between the results of the current modeling and published ones [2, 3]. Good agreement shown in Figure 2 verifies the accuracy of the numerical method of this research.

4. Results and Discussion

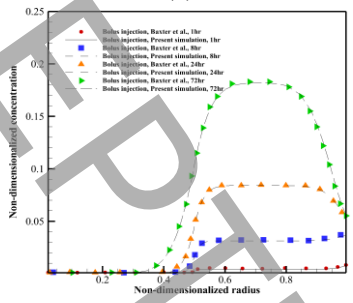
Figure 3 shows the non-dimensional IFP distribution in different tumor sizes under the influence of vascular normalization.

Normalization induced by anti-angiogenesis reduces the IFP, and this reduction enhances by decreasing the tumor size. In addition, normalization breaks the IFP behavior of uniform distribution throughout the tumor and makes the pressure gradient smoother in the tumor boundary by expanding it to the inner parts.

Regarding the area under the curves (AUC) of the average solute concentration distribution (ASCD) and deviation from it (DASCD) in the tumor during the time (Figure 4), it is found that the efficiency of normalization is in a certain range of tumor size.



(a)



(b)

Figure 2. Comparison between the results of the present research and literature ((a) [3] and (b) [2]).

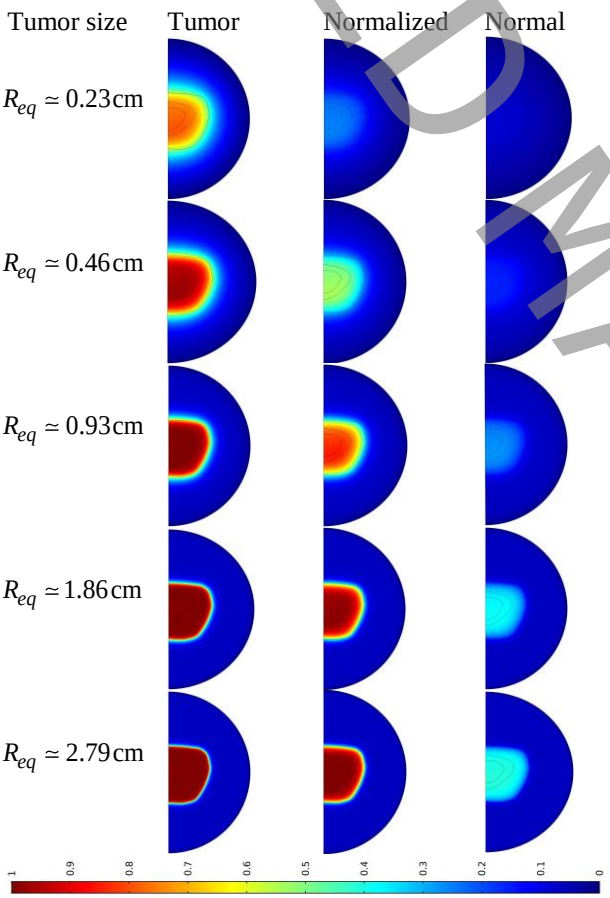


Figure 3. Non-dimensional IFP contour.

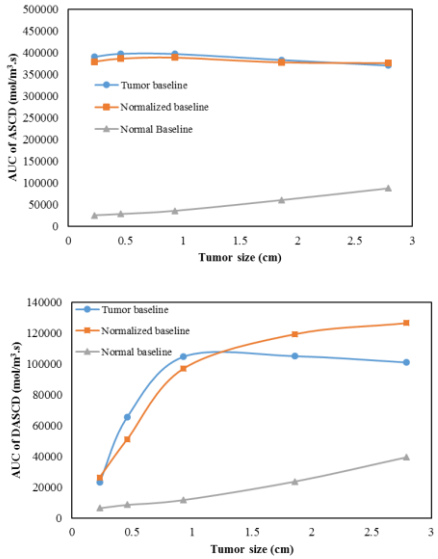


Figure 4. The AUCs of the ASCD and DASCD in the tumor site over the time.

5. Conclusion

In the present study, interstitial fluid flow and drug transport mathematical statements were introduced to the numerical model to investigate the drug delivery into the non-uniform solid tumor due to vascular normalization. According to the results, it is recognized that normalization improves the IFP and IFV specifications. Moreover, considering the drug transport model along with the fluid flow model show that to decide on whether normalization could be helpful or not, not only the tumor size but also the transport properties of tissue, drug type, and administration time should be noticed.

6. References

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