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The effect of interstitial pressure on therapeutic agent transport: Coupling with the tumor blood and lymphatic vascular systems

Min Wu [a,1], Hermann B. Frieboes [b,1], Mark A.J. Chaplain [c], Steven R. McDougall [d], Vittorio Cristini [e,f], John S. Lowengrub [a,g,*]

[a] Department of Mathematics, University of California, Irvine, United States
[b] Department of Bioengineering and James Graham Brown Cancer Center, University of Louisville, Louisville, United States
[c] Division of Mathematics, University of Dundee, Dundee, Scotland, UK
[d] Institute of Petroleum Engineering, Heriot-Watt University, Edinburgh, Scotland, UK
[e] Department of Pathology, University of New Mexico, Albuquerque, United States
[f] Department of Chemical Engineering, University of New Mexico, Albuquerque, United States
[g] Department of Biomedical Engineering, University of California, Irvine, United States

HIGHLIGHTS

- We simulate tumor growth with both interstitial fluid flow and pressure.
- Chemotherapeutic agent uptake (AUC) is proportional to lymphatic resistance.
- Elevated interstitial hydraulic conductivity contributes to low agent AUC.
- Elevated vascular hydraulic conductivity has highest AUC when agent is less permeable.
- Normalization of both vasculature and interstitium is needed to optimize chemotherapy.

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ABSTRACT

Vascularized tumor growth is characterized by both abnormal interstitial fluid flow and the associated interstitial fluid pressure (IFP). Here, we study the effect that these conditions have on the transport of therapeutic agents during chemotherapy. We apply our recently developed vascular tumor growth model which couples a continuous growth component with a discrete angiogenesis model to show that hypertensive IFP is a physical barrier that may hinder vascular extravasation of agents through transvascular fluid flux convection, which drives the agents away from the tumor. This result is consistent with previous work using simpler models without blood flow or lymphatic drainage. We consider the vascular/interstitial/lymphatic fluid dynamics to show that tumors with larger lymphatic resistance increase the agent concentration more rapidly while also experiencing faster washout. In contrast, tumors with smaller lymphatic resistance accumulate less agents but are able to retain them for a longer time. The agent availability (area-under-the curve, or AUC) increases for less permeable agents as lymphatic resistance increases, and correspondingly decreases for more permeable agents. We also investigate the effect of vascular pathologies on agent transport. We show that elevated vascular hydraulic conductivity contributes to the highest AUC when the agent is less permeable, but to lower AUC when the agent is more permeable. We find that elevated interstitial hydraulic conductivity contributes to low AUC in general regardless of the transvascular agent transport capability. We also couple the agent transport with the tumor dynamics to simulate chemotherapy with the same vascularized tumor under different vascular pathologies. We show that tumors with an elevated interstitial hydraulic conductivity alone require the strongest dosage to shrink. We further show that tumors with elevated vascular hydraulic conductivity are more hypoxic during therapy and that the response slows down as the tumor shrinks due to the heterogeneity and low concentration of agents in the tumor interior compared with the cases where other pathological effects may combine to flatten the

* Corresponding author at: Department of Mathematics, University of California, Irvine, United States.
E-mail address: lowengrb@math.uci.edu (J.S. Lowengrub).
[1] Joint first authorship.

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IFP and thus reduce the heterogeneity. We conclude that dual normalizations of the microenvironment – both the vasculature and the interstitium – are needed to maximize the effects of chemotherapy, while normalization of only one of these may be insufficient to overcome the physical resistance and may thus lead to sub-optimal outcomes.

1. Introduction

Chemotherapy is a type of cancer treatment that targets cancer cells through the use of toxic agents, primarily drug molecules disrupting some aspect of cell division, such as DNA synthesis and function. Ideally, drug dosages should be sufficient to kill rapidly dividing tumor cells but not affect non-cancerous cells. Although isolated infusion is sometimes used to deliver a concentrated dosage more directly to specific tumor sites (Chreech et al., 1958; Noorda et al., 2007; McClaine et al., 2012), most drugs are delivered systemically as an oral or intravenous bolus. Tissues in the body that undergo cell proliferation under normal circumstances, such as cells in the digestive system, are also typically damaged by chemotherapeutic drugs. Consequently, the drug dose is usually the maximum tolerated dose (MTD) that prevents patient death but may be well below what is needed to eradicate all of the tumor cells. Diverse macromolecule agents (e.g., nanoparticle carriers as summarized in Jong and Borm, 2008) have been developed as vehicles to encapsulate drugs in order to achieve higher targeting efficacy while minimizing systemic toxicity. Nevertheless, both free drug and nanoparticles administered systematically suffer from impaired transport through tumor tissue due to the abnormal vascularization. Further, dosing schemes are crucial since the tumor response depends not only on the dynamics of the agents and the fluids that carry them but also on the complex physiology of the body systems and the local tumor tissue. Recent theoretical studies with the aid of mathematical modeling and computational simulation, coupled with the latest experimental technologies (e.g., intravital microscopy), have highlighted the complexity of chemotherapy delivery and uptake in live tumors (van de Ven et al., 2012, 2013).

Theoretical modeling of chemotherapy usually relies on partial differential equation (PDEs) to describe the transport dynamics as well as the pharmacokinetics of therapeutic agents in time and space. Beginning with the vasculature, most studies have focused on the interaction between the vascular structure and blood flow, which contributes to the transport characteristics and agent availability through the vascular network as a closed system (e.g., McDougall et al., 2002; Stephanou et al., 2005; McDougall et al., 2006; Bartha and Rieger, 2006; Lee et al., 2006; Welter et al., 2008, 2009, 2010). However, fluids and substrates are exchanged through the vascular wall in the capillary regions. In the tumor interstitium, transport subject to interstitial fluid flow (IFF) has been investigated, where barriers due to lymphatic dysfunction as well as other common tumor pathologies (e.g., elevated vascular hydraulic conductivity and resultant attenuated transvascular osmotic pressure) were studied theoretically by Baxter and Jain (1989, 1990). These authors modeled the source of fluids and substrates through a vascular continuum and the effect of vascular flow was not considered. Recently, IFP, IFF and vascularized tumor growth were coupled dynamically in computational models by Cai et al. (2011), Wu et al. (2013), and Welter and Rieger (2013).

Pharmacokinetics and pharmacodynamics (PKPD) models, which combine reaction-diffusion PDEs that model the transport of chemotherapy agents in the tissue, and mass-action ordinary differential equations (ODEs) that model biochemical reactions in the cells, have been used to predict the tumor response to certain types of drug molecules (e.g., doxorubicin and cisplatin, see Jackson, 2003; Sanga et al., 2006, and Sinek et al., 2009), or to predict agent availability due to innovative transport modalities (e.g., nanoparticles or macrophages loaded with nanoparticles, see Sinek et al., 2004; Owen et al., 2004, respectively), as well as the resulting tumor response and therapy limitations (Frieboes et al., 2009; Sinek et al., 2009). Although most of these efforts are tied to angiogenesis models as the source of the agents, the extravasation is often assumed to be affected only by the transvascular concentration difference and the physical pressure from tumor cells outside the vasculature. The effects of convective transport by the interstitial fluid are usually not considered or are coupled with the tumor cell velocity (e.g., Jackson, 2003) instead of the IFF which can carry the agents through the interstitium.

Very recently, interstitial fluid flow and drug delivery have been investigated by Welter and Rieger (2013) in a 3-dimensional vascular tumor growth model using a continuum model for tumor cells and an arteriole-venous vascular network that accounted for drainage of interstitial fluid due to lymphatic function. Welter and Rieger (2013) found that the IFP, the IFF and the drug distributions are strongly heterogeneous due to the vascular architecture.

Here, we study the transport of therapeutic agents in a 2-dimensional interstitial continuum covered by a discrete tumor vasculature initially laid out as a rectangular grid to simulate the pre-existing capillary network. Unlike (Welter and Rieger, 2013) where the arterio-venous system is explicitly built, the capillaries considered here serve as both arterial and venous conduits since they are the smallest blood-carrying units in the tissue. Our approach builds on the tumor growth model developed in Macklin et al. (2009) and Wu et al. (2013), where we investigated the transcapillary and interstitial fluid dynamics during vascularized tumor growth coupled with the effect of blood and lymphatic vessel collapse. In particular, we investigated the effect of tumor vascular pathologies on the fluid flow across the tumor capillary bed, the lymphatic drainage and the IFP. Here, we focus on how the pathologies affect the transport of therapeutic agents during chemotherapy and the response of the tumor through the fluid flow. Considering the concentration of chemotherapy agents both in the vasculature and in the interstitium linked by the transcapillary fluid flux (modeled in Wu et al., 2013), as well as the loss of agents into the lymphatic system through the lymphatic fluid drainage (modeled in Wu et al., 2013), the model presented here can adapt to diverse delivery scenarios according to the specific agent characteristics and delivery protocols. In particular, we apply the model to study two injection schemes. The first, called “bolus injection,” applies to agents injected upstream of the tumor vasculature for a short period of time (e.g., 1–10 min). The second scheme, called “constant injection,” applies to agents injected upstream for a prolonged period of time ($\sim$100 min). We study the temporal and spatial distribution of agents in the vasculature and the interstitium together with the transcapillary concentration flux. We evaluate the efficiency of agent delivery while varying the functional lymphatic distribution and associated pathological factors. Finally, we assess the effects of chemotherapy on a growing tumor.

The outline of the paper is as follows. We present the mathematical models in Section 2, and describe the numerical