Development of a Diffusion-Based Mathematical Model for Predicting Chemotherapy Effects

Zhihui Wang, Romica Kerketta, Yao-Li Chuang, and Vittorio Cristini

***Abstract*—Mathematical modeling of drug transport can complement current experimental and clinical investigations to understand drug resistance mechanisms, which eventually will help to develop patient-specific chemotherapy treatments. In this paper, we present a general time- and space-dependent mathematical model based on diffusion theory for predicting chemotherapy outcome. This model has two important parameters: the blood volume fraction and radius of blood vessels divided by drug diffusion penetration length. Model analysis finds that a larger ratio of the radius of blood vessel to diffusion penetration length resulted in to a larger fraction of tumor killed, thereby leading to a better treatment outcome. Clinical translation of the model can help quantify and predict the optimal dosage size and frequency of chemotherapy for individual patients.**

I. Introduction

Colorectal cancer (CRC) is one of the most common malignancies in the world; while metastatic CRC patients are routinely administered with chemotherapy, the five-year survival rate remains low [1]. It is helpful to predict and monitor each individual patient's tumor response to chemotherapy drugs, in the hope that if the treatments are ineffective, they can be aborted in time to avoid accumulation of toxicity in the body as well as to mitigate patient expenses. However, current methods for predicting chemotherapy outcome primarily rely on data gathered through *in vitro* monolayer cell-culture experiments [2]. Such methods underestimate the influences of drug and microenvironmental factors (e.g., oxygen and nutrient gradients) on drug transport. For example, for a chemotherapeutic agent to successfully reach the tumor site, it has to first reach the blood vessels of the tumor through the circulatory system, cross the blood vessel walls, and traverse through the tumor interstitium [3]. Moreover, many studies have highlighted the role of tumor microenvironment and blood supply in drug resistance to chemotherapy [4-6]. Taken together, in order to predict the effects of a specific chemotherapy treatment, it is required to (1) study the delivery of chemotherapeutic agents percolating into the tumor and (2) take into account the effect of the three-dimensional tumor microenvironment *in vivo* on drug supply.

We have been studying how a tumor's biophysical properties affect drug transport using a combined mathematical modeling and experimental/clinical approach [7-11]. Specifically, we developed and validated a mechanistic steady-state model for predicting the fraction of tumor killed (f_{kill}) by chemotherapy in patients with CRC metastatic to liver [10]. More recently, we developed a time-dependent model based on first-principles of cell biophysics that successfully predicted *in vitro* tumor cellular response to a variety of drugs via two drug delivery methods, free drugs and targeted nanodrugs, across different types of cancers [9]. We found that the targeted nanodrug method is more effective in delivering drugs than the free-drug method and overcomes drug resistance due to improved cellular uptake rates of drug. In this paper, we further extend the time-dependent diffusion-based model [9] by accounting for spatial dependence, in order to develop a more clinically relevant mathematical model for predicting tumor response to chemotherapy. Parameter perturbation analysis of the model finds that a larger ratio of r_{b} (blood vessel radius) to L (diffusion penetration length) leads to a higher f_{kill}, indicating a better treatment effect.

II. Methods

A. Mathematical Model

We extend the previously developed time-dependent diffusion-based model [9] by introducing the space factor into the model:

$$\frac{\partial \sigma}{\partial t} = D\nabla^2\sigma - \lambda_{\text{u}}\rho\sigma\,, \qquad (1)$$

$$\frac{\partial \rho}{\partial t} = -\lambda_{\text{u}}\lambda_{\text{k}}\rho(\mathbf{x},t)\int_0^t \sigma(\mathbf{x},\tau)\,\rho(\mathbf{x},\tau)\,\mathrm{d}\tau\,, \qquad (2)$$

where $\sigma(\mathbf{x},t)$ and $\rho(\mathbf{x},t)$ are the drug concentration and the volume fraction of tumor cells, respectively, both dependent on time and space; D is the diffusivity of the drug, λ_u the per-volume cellular uptake rate of drug, and λ_k the death rate of tumor cells due to drug uptake.

Because drug diffusion occurs much faster than the process of cell death, Eq. 1 can be reasonably solved at the steady state, i.e., $\partial\sigma/\partial t = 0$. The nondimensionalized forms of Eqs. 1 and 2 can then be described as:

$$\nabla'^2\sigma' - \rho'\sigma' = 0\,, \qquad (3)$$

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Z. W., R. K., Y.-L. Chuang, and V. C. are with the Department of Pathology, University of New Mexico, Albuquerque, NM 87131 USA (corresponding author, phone: 505-272-3291; fax: 505-272-5186; e-mail: ZWang@salud.unm.edu, VCristini@salud.unm.edu).

V. C. is also with the Department of Chemical and Nuclear Engineering and Center for Biomedical Engineering, University of New Mexico, Albuquerque, NM 87131, USA; and Department of Mathematics, Faculty of Science, King Abdulaziz University, Jeddah 21589, Saudi Arabia.

$$\frac{\partial \rho'}{\partial t'} = -\rho'(\mathbf{x}', t')\int_0^{t'} \sigma'(\mathbf{x}', \tau)\rho'(\mathbf{x}', \tau)\,\mathrm{d}\tau \,, \quad (4)$$

where $\mathbf{x}' = \mathbf{x}/L$, with $L = \sqrt{D/(\rho_0 \lambda_u)}$ (the effective diffusion penetration length of the drug [12]), and $t' = (\lambda_k \lambda_u \rho_0 \sigma_0)^{1/2} t$ are the dimensionless space and time coordinates; the dimensionless drug concentration is defined as $\sigma' = \sigma/\sigma_0$, and the tumor volume fraction is made dimensionless by $\rho' = \rho/\rho_0$.

B. Parameter Estimation against Patient Data

We consider a cylindrically symmetric domain surrounding a blood vessel (**Fig. 1**). The inner cylinder has a radius r_b/L in dimensionless unit, representing the blood vessel at the center of the domain. We also hypothesize that the substrate supply for any location in a tissue is supported by the closest blood vessel, and thus estimate that $r_b/(L \cdot BVF^{1/2})$ is the radius of the influenced tissue volume of the vessel, where BVF (i.e., blood volume fraction) is < 1. The influenced tissue volume refers to a specific block of tissue that relies on this blood vessel for supply of oxygen and other essential chemicals.

We obtain parameter values for r_b and L from a CRC patient data set containing 27 cases. As demonstrated in [10], the predicted f_{kill} for each patient is described as a function of parameters, r_b, BVF, and L (diffusion penetration length), all of which can be directly measured from histopathology or imaging data. A least-squares fitting was performed to the measured f_{kill} and BVF. This resulted in estimates of two parameters, r_b and L, which produced the best fit. **Figure 2** shows a comparison of the predictions with the direct measurements of f_{kill} (see [10] for how to measure f_{kill} from patient histopathology imaging data). The radius of the blood vessels r_b = 15.83 μm obtained from this fitting was consistent with published data [13] and also with our histopathology measurements. The diffusion penetration length (L) from regression analysis is 155.06 μm. Using *Mathematica*, statistically significant P values were obtained from nonlinear regression analysis for both r_b and L. (**Fig. 2**, inset).

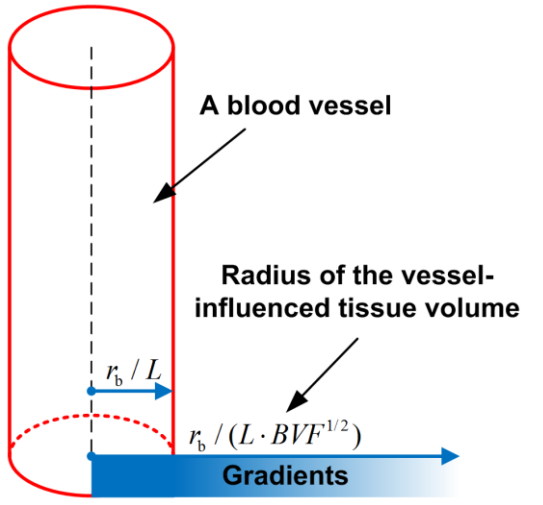

Fig. 1. Model domain hypothesis. By diffusion, a blood vessel supplies substrates to the tissue volume cylindrically surrounding the vessel. We hypothesize that at each location inside the tissue, the substrate supply is supported by the closest blood vessel. Thus, the tissue influenced by the blood vessel can be estimated to be between a cylinder of radius $r_b/(L \cdot BVF^{1/2})$ in dimensionless unit and the vessel itself with radius r_b/L in dimensionless unit.

III. Results

We performed a parameter perturbation study and simulated the model (Eqs. 3 and 4) in a cylindrically symmetric domain surrounding a blood vessel (**Fig. 1**) to examine the impact of each model parameter on the fraction of tumor killed f_{kill}. Standard model parameter values were set as follows: L = 155.1 μm and r_b = 15.8 μm, giving r_b/L = 0.1; BVF was set to be 0.054, i.e., the mean of the measured BVF values. For each parameter, we created 11 variations, through a range of +/-50% of the parameter's standard value and with a 10.0% variation interval. Note that a 50% variation has been assumed as reasonable in systems modeling analysis [14-16]. Accordingly, this generated a total of (11 × 11 =) 121 parameter variation pairs, covering a wider range of parameter space.

Figure 3 shows the simulation results of f_{kill} from changing BVF and r_b/L, at t = 3 dimensionless time units. We find that smaller r_b/L and greater BVF values lead to larger f_{kill} and thus increased treatment effects. This is because that in our simulations, the domain size (i.e., the

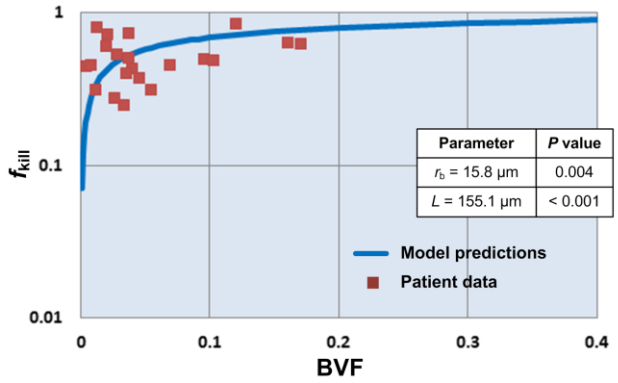

Fig. 2. Model fitting to patient data and comparison of model predictions with the patient data. Symbols: measurements with standard deviations from histopathology images of the patients with CRC metastatic to liver; each point represents an individual patient. Dark blue: least-square fit; coefficient of determination R^2 = 0.86. Inset: parameter values obtained from the fit.

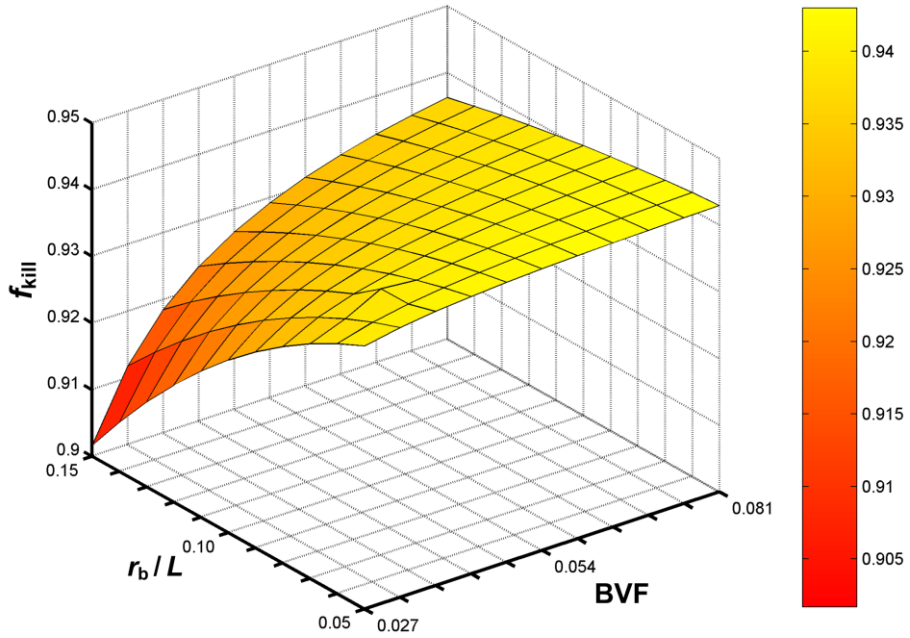

Fig. 3. The effects of combinatorial change in BVF and r_b / L on the fraction of tumor killed f_{kill}.

radius of the outer cylinder) was determined by $r_b / (L \cdot BVF^{1/2})$. Thus, a larger r_b / L or a smaller BVF represented a larger tissue volume relying on the modeled blood vessel for drug transport, and hence would require a longer time to achieve the same f_{kill}.

IV. Discussion

In clinical practice, robust biomarkers have long been used to evaluate and predict chemotherapy outcomes in patients, but our modeling-based approach presented here provides a simpler way to achieve this, possibly at a much earlier stage in the course of treatment. Our approach not only helps to predict the tumor's response to drugs before the start of the treatment (accordingly, lowering the cost and toxicity that the patients might be exposed to), but also provides a quantitative understanding of the biophysical barriers that are responsible for the resistance of cancer cells to chemotherapy. In this study, the model specifically demonstrates that biophysical barriers, especially drug diffusion gradients in the microenvironment *in vivo*, are significant factors in determining the efficacy of drug delivery, and thus should be considered as equally important as the underlying intrinsic genetic/molecular and cellular programs in understanding chemotherapy resistance.

As demonstrated, blood volume fraction (BVF) for each patient can be used in the mathematical model for the prediction of treatment outcome. It is particularly noteworthy that this parameter can be easily measured from histology images or directly assessed from CT scans (i.e., using the easy-to-obtain CT scans data to quantify BVF; see [10] for an example on predicting chemotherapy outcome based on standard contrast CT imaging data). Accordingly, for each individual patient, an optimal treatment strategy specific to this patient, including dosage and dosing schedule, can be developed prior to the actual treatment. Model analysis shown in **Fig. 3** suggests a strategy to improve treatment outcome. That is, to increase BVF (which, in turn, leads to an increase in f_{kill}), we can promote angiogenesis first at the target tumor site before actual chemotherapy treatment. However, we note here that this strategy is contrary to the concept of current anti-angiogenesis therapy [17]. This model can be used alone to predict the fraction of tumor killed or in combination with other methods such as the apparent diffusion coefficient from diffusion weighted-MRI in predicting tumor size at a future time point.

With necessary modifications, the model concept presented here can be applied to the evaluation of other treatment methods *in vivo*, such as nanoparticles and immunotherapy. In future development, additional layers of complexity including other factors or biophysical barriers, such as hypoxia and acidic extracellular pH, effect of cell-cell and cell-matrix interactions, and effect of chemotherapy on the tumor vasculature will be added to the model to improve the model's predictive power.

V. Conclusion

We present a mathematical model to predict time- and space-dependent tumor response to chemotherapy. The model has been validated with clinical CRC patient data. We find that the diffusion-related parameters had a significant impact on the amount of drug delivered to the tumor, suggesting clinical applications of the model.

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