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Fundamental mathematical model shows that applied electrical field enhances chemotherapy delivery to tumors

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ABSTRACT

Biobarriers imposed by the tumor microenvironment create a challenge to deliver chemotherapeutics effectively. Electric fields can be used to overcome these biobarriers in the form of electrochemotherapy, or by applying an electric field to tissue after chemotherapy has been delivered systemically. A fundamental understanding of the underlying physical phenomena governing tumor response to an applied electrical field is lacking. Building upon the work of Pascal et al. [1], a mathematical model that predicts the fraction of tumor killed due to a direct current (DC) applied electrical field and chemotherapy is developed here for tumor tissue surrounding a single, straight, cylindrical blood vessel. Results show the typical values of various parameters related to properties of the electrical field, tumor tissue and chemotherapy drug that have the most significant influence on the fraction of tumor killed. We show that the applied electrical field enhances tumor death due to chemotherapy and that the direction and magnitude of the applied electrical field have a significant impact on the fraction of tumor killed.

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1. Introduction and motivation

The second leading cause of death in the United States is cancer, accounting for approximately 25% of deaths. Therefore, discovering ways to more effectively deliver treatment to patients is critically important. Penetration of anti-cancer drugs into tumor cells has been studied by many researchers [2,3] but with a focus on the molecular mechanisms of the tumor resistance to chemotherapy. An often overlooked aspect hindering treatment is the tumor microenvironment which can have a significant influence on the drug distribution within the tumor [4,5]. Therapies such as electrochemotherapy can have a positive impact on tumor response to chemotherapy by overcoming barriers created by the microenvironment [4,6] Electrochemotherapy has been shown experimentally to improve tumor response due to enhancements in drug perfusion and cellular uptake [7,8]. This therapy involves administering chemotherapy to the patient intravenously then applying an electrical field to the tumor area [9]. Despite recent advances in the development of electrical field-based devices to treat cancer, it remains too expensive to be accessible to many patients. Thus, deepening the understanding of the effects of electrical fields on chemotherapy delivery to tumors can potentially lead to affordable, easy to operate electric-based devices.

There have been many experimental and clinical studies on electrochemotherapy, but not a concerted effort in mathematical/computational modeling [8]. The modeling that has been done has focused on electrical field distributions within tumors [9], and optimization of electrode distance and shape [10]. Therefore, research studying the effect of the field on tumor response has yet to be addressed. Electric fields have been shown to improve cellular uptake of anti cancer drugs with low uptake rates, such as bleomycin. Most devices used to deliver hyperthermia to tumors use applied alternating current (AC) electrical fields to generate heat. It has been shown experimentally that when only electrical fields are applied to tumors after chemotherapy is administered (electrochemotherapy), the tumor cells uptake more drug compared to traditional, systemic delivery [10,11]. Mathematical/computational modeling can help guide these experiments and treatment protocols. The small amount of modeling research in this area has been centered around studying electrical field distributions within tumors [10,12] and optimization of electrode distance and shape for the cumbersome technologies that are currently available with no focus on *tumor response* to these electrical fields [12–16].

Electrochemotherapy is not only toxic to tumor cells but can also have a vascular disrupting effect on the tumor microenvironment, thus inhibiting delivery of nutrients to the tumor which can lead to necrosis. Researchers have also studied the interactions of low frequency fields with growing cells experimentally and theoretically [17]. Stewart et al. (2005) [18] observed arrested cancer cell development by applying a uniform electric field of 2 V/cm intensity at

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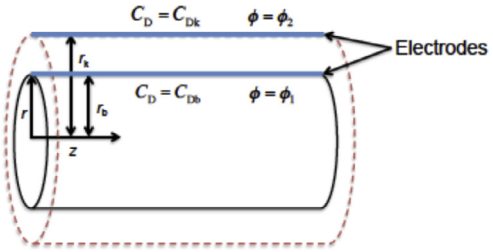

Fig. 1. Illustration of the system under study. Diffusion of chemotherapy drug from a single, straight cylindrical blood vessel under the influence of electrophoresis.

frequencies of 100–300 kHz. Gowrishankar et al. (2003) [19] presented a theoretical model describing a transport lattice method for modeling single and multiple cell systems with irregular shapes. The model results investigated tissue-level electrical field effects in organisms by using a multicellular model. In 2005, Cucullo et al. [20] described the effect of low frequency (<75 Hz) and low intensity (<8.5 V/cm) on cellular functions and cell proliferation. It has been observed that low frequencies and intensities of alternating current (AC) can impact cell proliferation without any influence to cell existence, but higher AC frequencies and intensities can cause cell apoptosis. In 2007, Kirson et al. [17] demonstrated the inhibitory effect of low frequency and low intensity electrical fields on tumor growth by in vivo treatment of tumors in animals.

Here, building directly upon the work of Pascal et al. [1], we develop a mathematical model that predicts the fraction of tumor killed due to an applied DC electrical field and chemotherapy. We quantify the effect of a direct current (DC) applied electrical field on tumor response by computing the fraction of tumor killed from a mathematical model describing transport of the drug from a single, straight cylindrical blood vessel and compare it to results in which no field is applied.

2. Materials and methods

2.1. Description of the system

To develop the mathematical model, we use an idealized description of the tumor tissue by studying the transport of a charged drug from a straight, cylindrical blood vessel (drug source), into the surrounding tumor tissue (Fig. 1). The drug will be transported out of the blood vessel through diffusive and electrophoretic processes a particular distance (i.e., the kill radius) before it is taken up by cells. Assumptions of our model include that electrophoretic and diffusive transport only occurs in the radial direction (i.e. $r_b/h \ll 1$). The convection due to the interstitial pressure in the tumor vasculature that causes low flow rates is neglected. Electrical potentials (ϕ) due to electrode placement are present on the blood vessel wall ($\phi = \phi_1$) and at the kill radius ($\phi = \phi_2$).

2.2. Theory and calculation

Here we present a mathematical model describing the transport of drug in a tumor under the influence of electrophoresis using continuum mechanics. First, we develop the equations governing electrical field transport. Next, using these results we develop the equations that describe the drug concentration distribution. Finally, we present the formulation of the fraction of tumor killed due to drug and the electric field as a function of relevant parameters of the system.

2.2.1. Electrostatics

The charged chemotherapy drug shown in Fig. 1 is under the influence of electrophoresis, or particle motion due to an applied electrical field, due to the electrodes present at the tumor blood vessel wall and kill radius, so the applied electrical field behavior is governed by the principle of conservation of charge. Under the assumption of negligible electroosmosis (i.e., the blood vessel wall is not charged) and solution electroneutrality, the applied electrical field potential is mathematically described by Laplace's equation [21]:

$$\nabla^2\phi = 0, \tag{1}$$

where ϕ is the electrical potential. Here we assume a long cylindrical blood vessel and tumor, so Eq. (1) can be simplified to (see Fig. 1):

$$\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial\phi}{\partial r}\right) = 0, \tag{2}$$

where r is the radial coordinate. In dimensionless form:

$$\frac{1}{\hat{r}}\frac{\partial}{\partial \hat{r}}\left(\hat{r}\frac{\partial\hat{\phi}}{\partial \hat{r}}\right) = 0, \tag{3}$$

where $\hat{r} = r/r_b$ and $\hat{\phi} = \phi/\phi_1$, where ϕ_1 is the electrical potential on the blood vessel wall ($r = r_b$), due to the electrode. Boundary conditions for Eq. (3) are a known electrical potential at the blood vessel wall ($r = r_b$) and an electric potential of zero at the kill radius ($r = r_k$), leading to the following expression for the electrostatic potential distribution,

$$\hat{\phi} = 1 + (\alpha - 1)\ln\left(\frac{\hat{r}}{\beta}\right), \tag{4}$$

where α is the electrical potential ratio, ϕ_2/ϕ_1 and β is r_k/r_b, the ratio between the kill and blood vessel radii. Eq. (4) will be used to aid in describing the concentration distribution of the chemotherapy in the tumor tissue surrounding the blood vessel in the following section.

2.2.2. Drug transport model

To describe the transport of chemotherapy from the blood vessel into the surrounding tumor tissue, we use the molar species continuity equation:

$$\frac{\partial C_D}{\partial t} = -\vec{\nabla}\cdot\vec{N}_D + R_D, \tag{5}$$

where C_D is the molar concentration of drug, t is time, $\vec{N}_D$ is the total molar drug flux and R_D describes the uptake of drug by the tumor cells. Under the assumption of no convection the total molar flux is equal to the summation of contributions due to diffusion and the applied electrical field:

$$\vec{N}_D = -D\vec{\nabla}C_D + zF\mu C_D\vec{\nabla}\phi, \tag{6}$$

where D is the drug diffusion coefficient, z is the charge number of the drug, F is Faraday's constant, or the charge of one mole of electrons [22]. To obtain a baseline, limiting case, we assume the drug uptake this is governed by first order kinetics. Future work will address the case in which the uptake rate is a function of the applied electrical field.

$$R_D = -\lambda C_D, \tag{7}$$

where λ is the cellular uptake rate of the drug. By combining Eqs. (1), (3), (4), and (6):

$$\frac{\partial C_D}{\partial t} = D\nabla^2 C_D - zF\mu\vec{\nabla}\cdot(C_D\vec{\nabla}\phi) - \lambda C_D. \tag{8}$$

Here the transport of chemotherapy is modeled under the assumptions of steady state and one dimensional, radial transport from the vessel, leading to,

$$\frac{D}{r}\frac{\partial}{\partial r}\left(r\frac{\partial C_D}{\partial r}\right) - zF\mu\frac{\partial\phi}{\partial r}\frac{\partial C_D}{\partial r} - \lambda C_D = 0, \tag{9}$$

In dimensionless form Eq. (9) becomes,

$$\frac{d^2\hat{C}_D}{d\hat{r}^2} - \frac{(1-p)}{\hat{r}}\frac{d\hat{C}_D}{d\hat{r}} - qC_D = 0, \tag{10}$$