Spatio-Temporal Tumor Model for Analysis and Mechanism of Action of Intracellular Drug Accumulation

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ABSTRACT

We have developed a one-dimensional tumor simulator to describe the biodistribution of chemotherapeutic drugs to a tumoral lesion and the tumor cell's response to therapy. A three-compartment model is used for drug dynamics within the tumor. The first compartment represents the extracellular space in which cell move, the second corresponds to the intracellular fluid space (including cell membrane) which is in direct equilibrium with the extracellular space, and the third is a non-exchangeable compartment that represents sequestered drug which is trapped in the nucleus to damage the cellular DNA directly triggering cell death. The analytical and numerical techniques (Finite Element Method) are used to describe the tumor's response to therapy and the effect of parameter variation on the drug concentration profiles in three compartments.

Keywords: Tumor, Drug accumulation, Finite Element Method.

1. INTRODUCTION

Cancer is an important societal and scientific problem. Vast sums of human and material resources are spent in attempts to understand its root causes and to develop successful treatments and prevention strategies [1]. A major cause of the failure of chemotherapeutic treatments for cancer is the development of resistance to drugs. One of the major challenges that prevent most patients from benefiting from chemotherapy is the presence of tumor cell mechanism that causes drug resistance. A tumor may evolve mechanisms to avoid damage by chemotherapeutic agents via the acquisition of mutations that confer a drug-resistant status. Jackson et al. [3] proposed a promising two-step approach that is designed to minimize systemic drug toxicity while maximizing activity in tumors employs monoclonal antibody enzyme conjugates for the activation of anti-cancer prodrugs.

In this paper, we have proposed a spatio-temporal model that describes tumor response to sequestered, intracellular drug treatment and also analyze the biodistribution of the drug and to measure its influence on a growing population of tumor cells by Finite Element Method using Matlab.

2. MATHEMATICAL FORMULATION

The tumor is viewed as a densely packed, radially-symmetric sphere of radius $R(t)$ containing a rapidly dividing population $p(r,t)$ (cells per mm^3) that is highly susceptible to the drug. Cell movement is produced by the local volume changes that accompany cell proliferation and death. It is convenient to associate with such movement a local cell velocity $\upsilon(r,t)$. The spheroid expands or shrinks at a rate, which depends upon the tumor volume, the latter term being modified by the presence of the drug. It is assumed that the spatially dependent variables depend only on the radial distance from the center of the tumor [4].

A three-compartment model is taken into account for drug dynamics within the tumor. The first compartment represents the extracellular space in which cells move, the second compartment corresponds to the intracellular fluid space (including the cell membrane), which is in direct equilibrium with the extracellular space, and the third is a non-exchangeable compartment that represents sequestered drug which is trapped, perhaps in the nucleus, where it begins to damage the cellular DNA directly triggering cell death. The drug concentrations in extracellular space, intracellular fluid space and in the nucleus are represented by N_1, N_2 and N_3 respectively.

As in [5], the governing equations for drug concentrations in three compartments and the tumor population by applying the conservation of mass as follows:

$$\frac{\partial N_1}{\partial t} + \nabla \cdot (\upsilon N_1) = \nabla \cdot (D \nabla N_1) + \nu_1 (N_B(t) - N_1) - \mu_{12} N_1 + \mu_{21} N_2. \quad (1)$$

$$\frac{\partial N_2}{\partial t} + \nabla \cdot (\upsilon N_2) = \mu_{12} N_1 - \mu_{21} N_2 - \mu_{23} N_2. \quad (2)$$

$$\frac{\partial N_3}{\partial t} + \nabla \cdot (\upsilon N_3) = \mu_{23} N_2. \quad (3)$$

In equation (1), D is the diffusion coefficient of the drug in the tumor tissue. The function $N_B(t)$ is the prescribed

drug concentration in the tumor vasculature and ν_1 represents capillary permeability-surface area product per unit volume, which is the rate coefficient of blood-tissue transfer, which is assumed constant. μ_{12} and μ_{21} are compartmental transfer coefficients representing the rate of flow from the extracellular compartment and to the intracellular compartment and vice-versa. μ_{23} is the rate of drug transfer from the cystosol to internal organelles.

The changes in tumor cell density assume a monoclonal tumor population as follows:

$$\frac{\partial p}{\partial t} + \nabla \cdot (\upsilon p) = D_P \Delta p + \lambda_M \frac{N_3}{N_0} p - \lambda_D p. \quad (4)$$

where λ_D is a death term by apoptosis that depends on the local levels of chemotherapeutic agent (e.g. nanoparticles, drug molecules) [2]. It is assumed that the tumor tissue is saturated with growth factors, and that nutrient availability limits cell proliferation, therefore the fraction of cycling cell is taken into account by $\frac{N_3}{N_0}$, where N_3 will not exceed N_0. λ_M is the cell mitosis rate and D_p is the assumed constant random motility coefficient of the tumor cells.

Tumor cell proliferation leads to motion of the cells and growth of the overall tumor. It is assumed that cell mass density is uniform in the tumor, the local specific mass growth rate is the divergence of the tumor cell's velocity field 'u' and is given by

$$\nabla \cdot \upsilon = \lambda_M \frac{N_3}{N_0} - \lambda_D. \quad (5)$$

In order to access the tumor's response to the chemotherapeutic treatment, it will be necessary to follow the evolution of the tumor volume ($= \left(4/3\right)\pi R^3$, for radial symmetry), or equivalently the tumor $R(t)$ [4].

$$\frac{dR}{dt} = \upsilon(R(t), t). \quad (6)$$

The initial and boundary conditions are

$$R(0) = R_0, \qquad p(r,0) = p_0(r), \qquad N_i(r,0) = 0, \quad i = 1,2,3$$

$$N_B(0) = N_0, \qquad \upsilon(0,t) = 0, \qquad \frac{\partial p}{\partial r}(0,t) = 0,$$

$$N_1(R(t),t) = N_R(t). \quad (7)$$

R_0 is the initial tumor cell radius and by symmetry, at $r = 0$, there is no amount of drug and the local velocity is zero. $N_R(t)$ is the drug concentration on the tumor boundary (i.e. in the surrounding normal tissue). the parameter values μ_{12}, μ_{21} and μ_{23} indicate that the drug leaves (or re-enters) the extracellular space far more slowly than it enters organelles. However, the drug re-entered the intracellular space may be enhanced due to over expression of P-glycoprotein drug efflux pumps. So, we take μ_{12}, μ_{21} and μ_{23} as variable parameters.

3. NON-DIMENSIONALIZATION

We rescale the mathematical model in the following manner, denoting non-dimensional variables with bars:

$$\bar{\upsilon} = \frac{\upsilon}{R_0 \lambda_M}, \qquad \bar{r} = \frac{r}{R_0}, \qquad \bar{\mu}_j = \frac{\mu_j}{\lambda_M}, \; j = 1,2,3,$$

$$\bar{N}_i = \frac{N_i}{N_0}, i = 1,2,3 \; \bar{\nu}_1 = \frac{\nu_1 {R_0}^2}{D}, \qquad \bar{t} = \lambda_M t,$$

$$\chi = \frac{{R_0}^2 \lambda_M}{D}, \; \phi = \frac{D_P}{\lambda_M {R_0}^2}, \; \bar{p} = \frac{p}{p_0}.$$

Dropping the bars, the governing equations transform to give

$$\chi\left\{\frac{\partial N_1}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \upsilon N_1\right)\right\} = \quad (8)$$

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial N_1}{\partial r}\right) + \nu_1 (N_B(t) - N_1) - \chi \mu_{12} N_1 + \chi \mu_{21} N_2.$$

$$\frac{\partial N_2}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \upsilon N_2\right) = \mu_{12} N_1 - \mu_{21} N_2 - \mu_{23} N_2. \quad (9)$$

$$\frac{\partial N_3}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}\left(r_2 \upsilon N_3\right) = \mu_{23} N_2. \quad (10)$$

$$\frac{\partial p}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \upsilon p\right) = \phi \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial p}{\partial r}\right) + N_3 p - \lambda_D p. \quad (11)$$

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \upsilon\right) = N_3 - \lambda_D. \quad (12)$$

$$\upsilon(0,t) = 0, \qquad R(0) = 1, \qquad N_i(r,0) = 0,$$

$$i = 1,2,3.$$

$$N_1(R(t),t) = N_R(t), \qquad \frac{dR(t)}{dt} = u(R(t),t). \quad (13)$$

Since there are two time-scales:

(1) The tumor growth $\left(\lambda_M\right)$ time-scale (i.e. per day).

(2) The drug-diffusion $\left(\frac{{R_0}^2}{D}\right)$ time-scale (i.e. minutes).

So $\chi = \frac{\lambda_M {R_0}^2}{D} << 1$

To the leading order with $\chi = 0$, the equation (8) becomes,

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$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial N_1}{\partial r}\right)+\nu_1\left(N_B(t)-N_1\right)=0. \quad (14)$$

On solving we get,

$$N_1(r,t)=\left(N_R(t)-N_B(t)\right)\frac{R(t)\sinh\xi r}{r\sinh\xi R(t)}+N_B(t). \quad (15)$$

where $\xi=\sqrt{\nu_1}$.

A tri-exponential decline function based on a three-compartment model is used to describe the drug concentration $N_B(t)$ in the tumor vasculature [5].

$$\frac{N_B(t)}{N_0}=Ae^{-\xi_1 t}+Be^{-\xi_2 t}+(1-A-B)e^{-\xi_3 t}.$$

where N_0 is the concentration of drug in the plasma at time zero or the dose of drug administered divided by the plasma volume [20]. The drug concentration in the normal tissue, $N_R(t)$, is assumed of the form as follows:

$$\frac{N_R(t)}{N_0}=C\left(e^{-\xi_2 t}+e^{-\xi_3 t}-e^{-\xi_1 t}\right).$$

Since the tumor surface is a moving boundary, so we transform the region $\{0\le r\le R(t)\}$ into the fixed region $\{0\le\zeta\le 1\}$ by $\zeta=\zeta(r,t)=\frac{r}{R(t)}$ and set

$$\tilde{N}_i(\zeta,t)=N_i(r,t), i=1,2,3,\ \tilde{\upsilon}(\zeta,t)=\frac{\upsilon(r,t)}{R(t)}. \quad (16)$$

Dropping the tildes of $\tilde{N}_i(\zeta,t)$ and $\tilde{\upsilon}(\zeta,t)$ for notations convenience, the equation (9), (10), (12) and (15) becomes,

$$N_1(\zeta,t)=\left(N_R(t)-N_B(t)\right)\frac{\sinh(\xi R(t)\zeta)}{\zeta\sinh(\xi R(t))}+N_B(t). \quad (17)$$

$$\frac{\partial N_2}{\partial t}+\left[\upsilon(\zeta,t)-\zeta\upsilon(1,t)\right]\frac{\partial N_2}{\partial\zeta}= \quad (18)$$
$$\mu_{12}N_1-(\mu_{21}+\mu_{23}+N_3-\lambda_D)N_2.$$

$$\frac{\partial N_3}{\partial t}+\left[\upsilon(\zeta,t)-\zeta\upsilon(1,t)\right]\frac{\partial N_3}{\partial\zeta}= \quad (19)$$
$$\mu_{23}N_2-(N_3-\lambda_D)N_3.$$

$$\frac{1}{\zeta^2}\frac{\partial}{\partial\zeta}\left(\zeta^2\upsilon(\zeta,t)\right)=N_3-\lambda_D. \quad (20)$$

and $$\frac{dR(t)}{dt}=R(t)\upsilon(1,t). \quad (21)$$

For $\zeta=0,1,$ we have $\left[\upsilon(\zeta,t)-\zeta\upsilon(1,t)\right]=0.$

We have solved the equations (17)-(19) by Finite Element Method using Matlab.

4. RESULTS AND DISCUSSION

The spatio-temporal dynamics of drug concentrations in three compartments and the effect of different parameters are studied using Finite Element Method (with 100 elements) and simulated using Matlab.

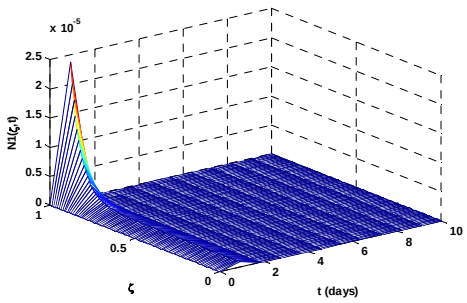

Figure 1.

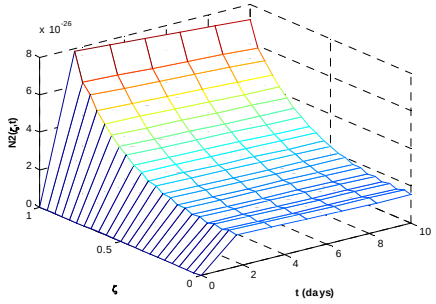

Figure 2.

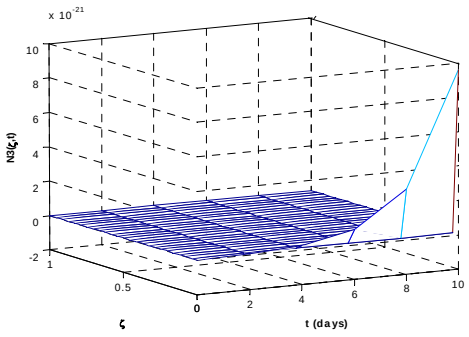

Figure 3.

Figure (1), (2) and (3) show the profiles of different drug concentrations in three compartments. From figure (1) and (2), we can see that as the time increases, the drug concentration decreases in the extracellular space and the intracellular fluid space but there is an increase or we can say that there is an accumulation of drug in the third non-exchangeable compartment that represents sequestered drug which is trapped in the nucleus.

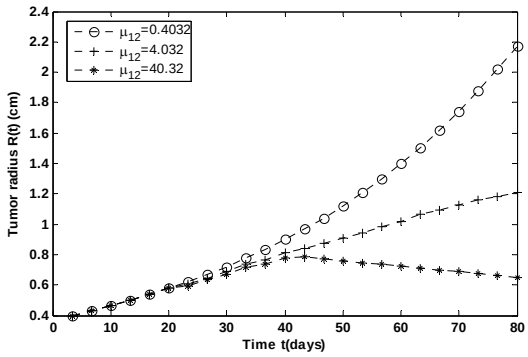

Figure 4.

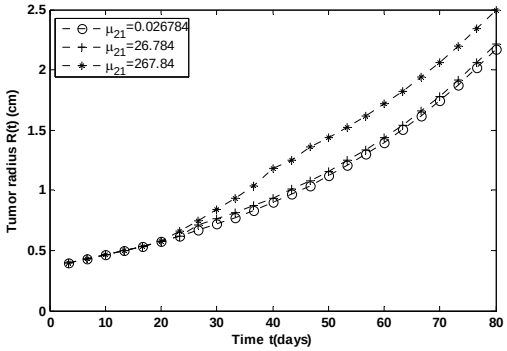

Figure 5.

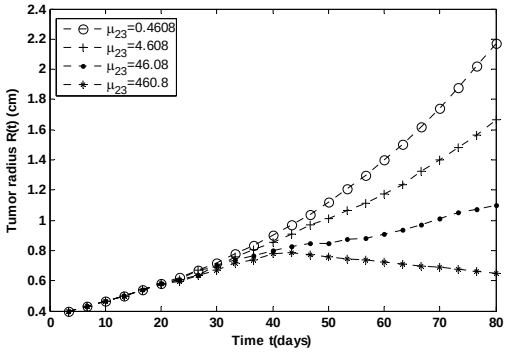

Figure 6.

Figures (4), (5) and (6) represent the effect of various transfer coefficients $(\mu_{12}, \mu_{21}, \mu_{23})$ on the tumor growth. From figure (4), it is clear that the tumor growth is greatly affected by a small change in the cellular permeability μ_{12}. So it is the most important cause of drug accumulation, which further induces drug resistance, which is consistent with the result of Tao [6]. Figure (5) shows that μ_{21} (drug efflux rate) has a small effect on the tumor growth if $\mu_{21} \prec 26.784$ and has a large effect if $\mu_{21} \succ 200$ i.e. μ_{21} is very large. Also figure (6) shows that drug sequestration rate μ_{23} has a small effect on the long time response of tumor growth if $\mu_{23} \succ 46.08$ and has a large effect if $\mu_{23} \prec 40$. The baseline parameter values (non-dimensionalized) used are $\mu_{12} = 0.4032$, $\mu_{21} = 0.026784$ and $\mu_{23} = 460.8$ for the typical parameter values given in [5].

From above, it is clear that cellular permeability μ_{12} has more influence on the model in comparison to drug efflux rate μ_{21} and the drug sequestration rate μ_{23}. Also it is found from the simulation of the model that there is no significant reduction in the tumor radius if we increase the initial doses of the drug to the tumor. It satisfies the fact that there is no benefit of giving large initial doses to the patient in comparison to the required dose (because its transfer to intracellular fluid space depends upon the parameter μ_{12}). However the multiple round treatments is a better option to provide more drug inside the tumor to control its growth.

5. REFERENCES

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