Mathematical Modeling of Chemotherapy Strategies in Vascular Tumor Growth using Nanoparticles

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ABSTRACT

Drug release kinetics at the tumor site is an important aspect of chemotherapy. Nanoscale devices carrying chemotherapeutic drugs could extravasate from blood vessels and even diffuse through the tissue and enter tumor cells. Drug delivery through Nanoparticles (particles between 10 nm and 1000 nm in size) presents significant potential advantages over traditional delivery via bolus injection. It is expected that chemotherapy involving nanotechnology will be more effective in targeting malignant cells and sparing healthy tissue.

In this paper, we have developed a mathematical model that describes the drug delivery in a vascular tumor using the Nanoparticles on the order of 10 nm and 100 nm.
Keywords: Nanotechnology, drug delivery.

INTRODUCTION

Nanotechnology is the frontier research area of the twenty first century. In recent years, we have gained a better understanding of the mechanism responsible for cell recognition, transport of biological molecules across membranes and the mechanisms that regulate cell function. The concurrent progress and sophistication of organic synthetic chemistry, has sparked optimism for the development of 'intelligent medicines" (i.e. drugs that are actively directed to the target cell, actively translocated across the membrane, and specifically intervene with a particular function in the cell). One area where nanoscale work is well underway is within the field of drug delivery. In drug delivery, nanoparticles are fabricated in order to entrap and deliver specific pharmaceutical agents to various locations in the body.

Traditional drug delivery methods include oral and intravenous routes of administration. Oral delivery via tablets or capsules is largely inefficient due to exposure of the pharmaceutical agent to the metabolic processes of the body. Therefore a larger than necessary dose is often required and the maximum effectiveness of the drug is limited. Traditional intravenous (IV) administration is much more problematic. Specificity for IV injectable drugs is often low, necessitating large amounts of a drug to be injected into a patient, creating a high concentration of the drug in the blood stream that could potentially lead to toxic side effects. Nanoparticle drug delivery provides a more efficient, less risky solution to many drug delivery challenges. Nanoparticles are generally defined as particles between 10 nm and 1000 nm in size. Applications of nanotechnologies in medicines are especially promising in the longer term. These can be expected to enable drug delivery targeted at specific sites in the body so that, chemotherapy is less invasive.

There are numerous models that describe the tumor behavior. Anderson and Chaplain [1] presented both continuous and discrete mathematical models, which described the formation of capillary sprout network in response to chemical stimuli (tumor angiogenic factor, TAF) supplied by a tumor. S.R. McDougall et al. [2] generated theoretical capillary networks using the discrete mathematical model of Anderson and Chaplain [1]. Byrne et al. [3] described the growth of Non-necrotic tumors in the presence and absence of inhibitors. Shangbin Cui and A. Friedman [4] also studied the model of Necrotic tumor growth. Later Zheng et al. [5] presented a full nonlinear, two-dimensional simulation, showing the potential of virtual cancer simulator. Sinek et al. [6] developed a model for two-dimensional chemotherapy simulations that demonstrate fundamental transport and tumor response limitations involving nanoparticles.

Although the clinical arsenal in treating tumor has been greatly extended in recent years with the application of new drugs and therapeutic modalities, the three basic approaches continue to be surgical resection, radiation, and chemotherapy. A significance proportion of research is focused on improving the efficacy of chemotherapy and the drug release kinetics at the tumor site is an important aspect of chemotherapy [7]. In this paper, we have proposed a mathematical model that describes the nanodrug delivery in a vascular tumor using the nanoparticles on the order of 10 nm and 100 nm.

MATHEMATICAL FORMULATION

Over the past two decades, tumor growth has been fertile for mathematical modeling and many models have appeared in this era. Treating the tumor as a growing spherical mass, with radial symmetry [4], a one-space-dimensional model is used to describe the tumor response to the Nanodrug delivery. The tumor consists of a spherical core of dead cells (necrotic core) and a spherical shell of life-proliferating cells surrounding the core (non-necrotic shell). The non-necrotic region receives its blood supply through a developed network of capillary

vessels (vascularized tumor). The blood supply provides the non-necrotic region with nutrients. Across the micro-vascular wall, the transport of molecules is mainly due to convection while diffusion is also important. Convection depends on the nutrient concentration in the blood stream, while the diffusion is proportional to the difference of the vascular and interstitial concentration [6]. We assume that 1-10 nm particles convect from the vasculature, diffuse through the tumor interstitial, and enter cancer cells just as do nutrients or drug molecules, and so the net local rate of chemotherapeutic nanodrug delivery from the neo-vasculature and uptake by the tumor cells as [6]

$$S = \nu_1\left(\frac{s_v - s}{n_v}\right)\delta - \eta\frac{s}{n_v}.$$

where

$s =$ local chemotherapeutic carrier concentration.

$s_v =$ chemotherapeutic carrier concentration in vasculature.

$n_v =$ nutrient and chemotherapeutic carrier concentration in the vasculature.

$\eta =$ rate of drug loss due to decay, cellular uptake and metabolism.

$\nu_1 =$ transfer coefficient from the vasculature.

$\delta =$ indicator function of vasculature (1 where it exists, 0 otherwise).

Consider a spherically symmetric tumor of radius $R(t)$. The local volume changes accompanying cell proliferation and death produce cell movement. So we associate a local cell velocity $u(r,t)$ with cell movement.

The governing equation for drug $N(r,t)$ concentration is given by

$$\frac{\partial N}{\partial t} = D\nabla^2 N + \nu_1\left(\frac{s_v - s}{n_v}\right)\delta - \eta N. \quad \text{where} \quad N = \frac{s}{n_v}$$

In spherically symmetric co-ordinates,

$$\frac{\partial N}{\partial t} = \frac{D}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial N}{\partial r}\right) + \nu_1\left(N_B(t) - N\right)\delta - \eta N. \tag{1}$$

Where $N_B(t) = \frac{s_v}{n_v} =$ the prescribed drug concentration in the tumor vasculature.

$D =$ diffusion coefficient of the drug in the tumor tissue.

$r =$ radial distance from the center of the 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 given by

$$\nabla \cdot u = \lambda_M N - \lambda_D. \quad \text{Or}$$

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 u\right) = \lambda_M N - \lambda_D. \tag{2}$$

where λ_D is the death rate of tumor cells due to apoptosis.

To assess the tumor's response to the chemotherapeutic treatment via nanoparticles, it will be necessary to follow the evolution of tumor volume(= $\frac{4}{3}\pi R^3$, for radial symmetry), or the tumor radius $R(t)$.

Under radial symmetry, the tumor expands at a rate which is equal to the radial component of the velocity there, i.e.

$$\frac{dR}{dt} = u(R(t),t). \tag{3}$$

The initial and boundary conditions are,

$$R(0) = R_0,\ N(r,0) = 0,\ \frac{\partial N(0,t)}{\partial r} = 0,\ N(R(t),t) = N_R(t),\ u(0,t) = 0.$$

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.

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

$$\bar{u} = \frac{u}{L\lambda_M},\ \bar{r} = \frac{r}{L},\ \bar{\eta} = \frac{\eta L^2}{D},\ \bar{\nu}_1 = \frac{\nu_1 L^2}{D},\ \zeta = \frac{L^2\lambda_M}{D},\ \bar{t} = \lambda_M t,\ \bar{\lambda}_D = \frac{\lambda_D}{\lambda_M}.$$

Where $\lambda_M =$ characteristic tumor cell mitosis rate.

$D =$ characteristic diffusion constant.

$L =$ characteristic diffusion length.

Dropping the bars, the governing equations transform to give

$$\zeta\frac{\partial N}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial N}{\partial r}\right) + \nu_1\left(N_B(t) - N\right)\delta - \eta N. \tag{4}$$

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 u\right) = N - \lambda_D. \tag{5}$$

$$\frac{dR}{dt} = u(R(t),t). \tag{6}$$

$$R(0) = 1,\ N(r,0) = 0,\ \frac{\partial N(0,t)}{\partial r} = 0,\ N(R(t),t) = N_R(t),\ u(0,t) = 0.$$

Since there are two time-scales:

(1) The tumor growth (λ_M) time-scale (i.e. per day).

(2) The drug-diffusion (L^2/D) time-scale (i.e. minutes).

So $\zeta = \frac{\lambda_M L^2}{D} << 1$.

To leading order with $\zeta = 0$, we get,

$$N(r,t) = \left(N_R(t) - \frac{\psi N_B(t)}{\chi^2}\right)\frac{R(t)\sinh\chi r}{r\sinh\chi R(t)} + \frac{\psi N_B(t)}{\chi^2}. \tag{7}$$

where $\psi = \nu_1\delta$, $\chi^2 = \nu_1\delta + \eta$.

On substituting (7) in (5) and integrating subject to $u(0,t) = 0$ gives the expression for velocity in the tumor.

$$u(r,t)=\frac{R(t)}{\chi^2}\left(N_R(t)-\frac{\psi N_B(t)}{\chi^2}\right)\frac{r\chi\cosh\chi r-\sinh\chi r}{r^2\sinh\chi R(t)}+\left(\frac{\psi N_B(t)}{\chi^2}-\lambda_D\right)\frac{r}{3}. \quad (8)$$

On substituting (8) in (6) gives

$$\frac{dR}{dt}=\frac{1}{R(t)\chi^2}\left(N_R(t)-\frac{\psi N_B(t)}{\chi^2}\right)\frac{R\chi\cosh\chi R-\sinh\chi R}{\sinh\chi R(t)}+\left(\frac{\psi N_B(t)}{\chi^2}-\lambda_D\right)\frac{R(t)}{3}. \quad (9)$$

The blood clearance data for many chemotherapeutic agents following a bolus injection can be fit with an exponential or biexponential function [6, 10], so we consider,

$$N_B(t)=Ae^{-\xi_1 t}+Be^{-\xi_2 t}.$$

$$N_R(t)=1-\left(Ae^{-\xi_1 t}+Be^{-\xi_2 t}\right).$$

In the case of 100 nm particles, they are too bulky to diffuse. It is assumed that 100 nm drug particles once extravasated, they provide a constant source of drug along the vasculature. So in this case, the net local rate of chemotherapeutic nanodrug delivery from the neo-vasculature and uptake by the tumor cells as [6]

$S=\nu_2\delta-\eta\frac{s}{n_v}$. where ν_2 = constant flux of drug molecules into the tissue.

So the governing equations for 100 nm particles are as follows:

$$\frac{\partial N}{\partial t}=\frac{D}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial N}{\partial r}\right)+\nu_2\delta-\eta\frac{s}{n_v}. \quad (10)$$

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2u\right)=\lambda_M N-\lambda_D. \quad (11) \text{ and}$$

$$\frac{dR}{dt}=u(R(t),t) \quad (12)$$

The initial and boundary conditions are

$$\frac{\partial N(0,t)}{\partial r}=0,\ N(r,0)=0,\ u(0,t)=0.$$

After non-dimensionalization we get the transformed equations similar to (4), (5) and (6),

$$\frac{\partial N}{\partial t}=\frac{D}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial N}{\partial r}\right)+\nu_2\delta-\eta N.$$

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2u\right)=N-\lambda_D. \quad \text{and} \quad \frac{dR}{dt}=u(R(t),t)$$

On solving we get,

$$N(r,t)=\left(N_R(t)-\frac{\nu_2\delta}{\eta}\right)\frac{R(t)\sinh\left(\alpha r\sqrt{\zeta}\right)}{r\sinh\left(\alpha R\sqrt{\zeta}\right)}+\frac{\nu_2\delta}{\eta}.$$

$$u(r,t)=\left(N_R(t)-\frac{\nu_2\delta}{\eta}\right)\frac{R(t)}{\zeta\alpha^2r^2}\left[\frac{\alpha r\sqrt{\zeta}\cosh\left(\alpha r\sqrt{\zeta}\right)-\sinh\left(\alpha r\sqrt{\zeta}\right)}{\sinh\left(\alpha R\sqrt{\zeta}\right)}\right]+\left(\frac{\nu_2\delta}{\eta}-\lambda_D\right)\frac{r}{3}.$$

$$\frac{dR}{dt}=\left(N_R(t)-\frac{\nu_2\delta}{\eta}\right)\frac{1}{\zeta\alpha^2R(t)}\left[\frac{R(t)\alpha\sqrt{\zeta}\cosh\left(\alpha R\sqrt{\zeta}\right)}{\sinh\left(\alpha R\sqrt{\zeta}\right)}-1\right]+\left(\frac{\nu_2\delta}{\eta}-\lambda_D\right)\frac{R(t)}{3}.$$

where α is positive real number. The expression for $N_R(t)$ is same as described previously. The parameter values are presented in table 1.

RESULTS AND DISCUSSION

In this paper, we have developed a mathematical model that illustrates the chemotherapy strategies in spherically-symmetric tumor. A system of partial differential equations is used to describe the drug concentration in the tumor cell, the cell movement whose divergence defines the local specific mass growth rate and the expression for the radius of the tumor cell. The analytical and numerical techniques are used to illustrate the tumor's response to various chemotherapeutic strategies (i.e. for 10nm and 100nm).

Long time response:

As $t\to\infty$, $N_B(t)\to 0$, $N_R(t)\to 0$.

In case of 1-10 nm particles, $N(r,t)\to 0$,

$u\to-\frac{\lambda_D r}{3}$, $\frac{dR}{dt}\to-\frac{\lambda_D R}{3}$.

In case of 100 nm particles, $N(r,t)\to\frac{\nu_2\delta}{\eta}$.

$$u\to-\left(\lambda_D-\frac{\nu_2\delta}{\eta}\right)\frac{r}{3}-\frac{\nu_2\delta}{\eta}\frac{R(t)}{\zeta\alpha^2r^2}\left(\frac{r\alpha\cosh\left(\alpha r\sqrt{\zeta}\right)-\sinh\left(\alpha r\sqrt{\zeta}\right)}{\sinh\left(\alpha R\sqrt{\zeta}\right)}\right).$$

$$\frac{dR}{dt}\to-\left(\lambda_D-\frac{\nu_2\delta}{\eta}\right)\frac{R(t)}{3}+\frac{\nu_2\delta}{\eta}\frac{D}{\zeta\alpha^2R(t)}\left(1-\frac{R\alpha\sqrt{\zeta}\cosh\left(\alpha R\sqrt{\zeta}\right)}{\sinh\left(\alpha R\sqrt{\zeta}\right)}\right).$$

These results imply that after a long time, the drug concentration in tumor cells in case of 10 nm particles becomes zero while the concentration of 100 nm particles is not equal to zero. It satisfies the fact that 100 nm drug particles works as a constant supply of drug in the tumor cell [6].

It also predicts the exponential reduction of the tumor as a long time response to the treatment in both cases (i.e. 10 nm and 100 nm). It is cleared through the Figure 1 and Figure 2.

Figure 3 shows that the reduction of tumor radius in case of chemotherapy through 100nm particles is more in comparison to 10nm drug particles. This satisfies the fact that chemotherapy through 100nm particles is more beneficial than the drug therapy through 10nm particles.

The uptake of the drug by tumor cells is shown in Figure 4 for two different initial doses (6 mg/kg and 12 mg/kg) at time zero and the total accumulation within the tumor cells is plotted for the first two hr. post treatment. This shows that the drug concentration in tumor cell increases linearly with the increase of initial doses which is consistent with the result of Jackson [8].

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Table 1

Parameter	Value	Unit
η	1	$\min^{-1}$
ν_1	0.025	$\min^{-1}$
ν_2	0.015	$\min^{-1}$
D	10^{-5}	$cm^2/\sec$
λ_M	0.3	day^{-1}
L	250	μm
λ_D	2.1	day^{-1}
A	0.69	--
B	0.24	--
ξ_1	0.015	$\sec^{-1}$
ξ_2	0.00056	$\sec^{-1}$

The above parameter values are taken from the literature [6, 8].

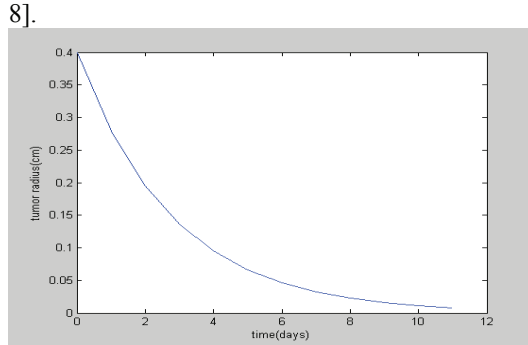

Figure 1: For 10nm

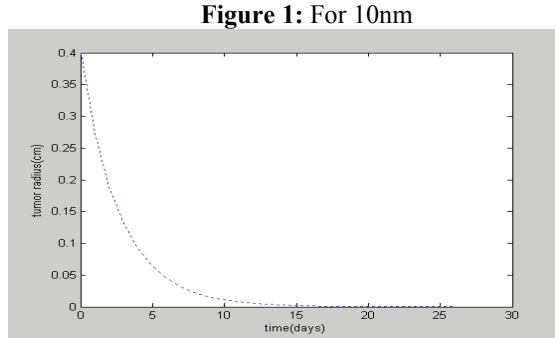

Figure 2 : For 100nm

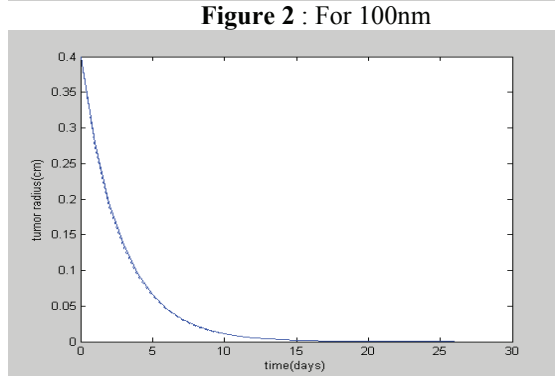

Figure 3: Solid line for 10nm and dotted line for 100nm

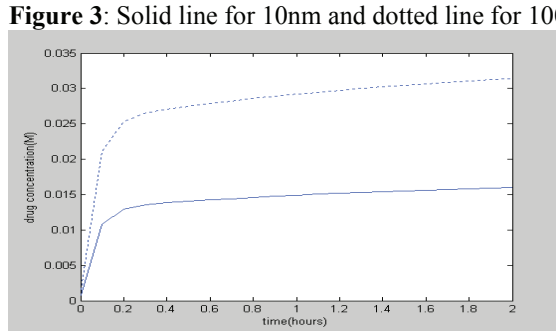

Figure 4: For 10nm, solid line for 6mg/kg and dotted line for 12mg/kg as initial doses.