A MATHEMATICAL MODEL OF VASCULAR TUMOR WITH CHEMOTHERAPY DRUG CONCENTRATION AT NANO-SCALE

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ABSTRACT: In this work we consider a model that represents the procedure for tumor treatment, which includes tumor cell density, blood plasma concentration and chemotherapy drug concentration at nano-scale. We modeled the problem in the form of partial differential equations. We find that the blood plasma concentration in the tumor cell density. Graphically, we present the effects of blood plasma concentration and chemotherapy drug concentration on tumor cells concentration with respect to time and radius of the tumor through mathematical analysis.

1. INTRODUCTION

Cancer is a complex disease caused by genetics instability and accumulation of multiple molecular alterations. Current diagnostic and prognostic classifications do not reflect the whole clinical heterogeneity of tumors and are insufficient to make predictions for outcome. Most current anticancer agents do not greatly differentiate between cancerous and normal cells, leading to systematic toxicity and adverse effects.

Consequently, systematic applications of these drugs often cause severe side effects in other tissues (bone-marrow suppression, cardimyopathy and neurotoxicity), which greatly limits the maximal allowable dose of the drug. In addition, rapid limitation and wide-spread distribution into non-targeted organs and tissues require the administration of a drug in large quantities, which is not economical and often complicated owing to non-specific toxicity. Nanotechnology offers a more targeted approach and could thus provide significant benefits to cancer patients. In fact, the use of Nanoparticals for drug delivery and targeting is likely one of the most exciting and clinically important applications of cancer Nanotechnology.

Nanotechnology is a multidisciplinary field, which covers a vast and diverse array of devices derived from Engineering, biology, Physics and Chemistry. These devices include Nanovectors for the targeted delivery of anticancer drugs and imaging contrast agents. Nanowires and Nanocantiliver arrays are among the leading approaches under development for the early detection of precancerous and malignant lesions from biological fluid these and other Nanodevices can provide essential breakthroughs in the fight of cancers. The emergence of Nanotechnology is likely to have a significant impact on drug delivery sector, affecting just about every route of administration from
oral to inject-able, according to specialist market research firm Nanomarkets. For injectable drugs Nanotechnology is already generating new dosage forms that are easier to administer, most pleasant for the patients receive and confer a competitive advantage in the market place. Nanotechnology is also opening up new opportunities in implantable delivery systems, which are often preferable to the use of injectable drugs because the latter frequently display first-order kinetics (the blood concentration goes up rapidly, but drops exponentially over time). This rapid rise may cause difficulties with toxicity, and drug efficacy can diminish as the drug concentration falls below the targeted range.

In contrast, implantable time release systems may help minimize peak plasma levels and reduce the risk of adverse reactions, allow for the predictable and extended duration of action, reduce the frequency of re-dosing and improve patient acceptance and compliance. The scientists claims several advantages over existing system, including no requirement to open the blood brain barrier, the ability to deliver potentially any drug, whether hydrophilic or hydrophobic, and no need to modify the drug itself, which may effect its activity. Nanomarket believes that not only will the Nano enabled drug delivery market be one of the first true Nanomedicines markets to evolve, but as it does so, the revenues from Nanoenabled drug delivery systems will be quite large.


In a different phenomena with blood plasma, Leonard A. et al., (1997) tested the hypothesis that dietary linoleic acid intake controls the arterial blood plasma linoleic acid concentration and the rates of tumor growth and linoleic acid metabolism in vivo. Ahrearn T. S. et al., (2004), considered a pharmacokinetics models describing such tissue properties relies to time. When direct measurement is not possible bi-exponential decay has been applied using data from healthy volunteers. This work investigates, by simulation, the magnitude of errors resulting from this definition with respect to normal variation in renal function and for cases with renal impairment.
In this work we combine these two phenomena by introducing the new very important factor blood plasma concentration in nanodrug delivery in vascular tumor using the nano particles. Blood plasma is the liquid component of blood, consisting of around half of the total blood volume. Without plasma, blood cells would have no medium to travel on as they moved through the body, and plasma also performs a number of other useful functions in the body.

2. Mathematical Method

Murray J. D. et al., (2002) formulated the problem as a density equation, which can be expressed as follows:

The rate of change of tumor cell population = the diffusion (motility) of tumor cells + the net proliferation of tumor cells + blood plasma concentration of tumor cells – loss of tumor cells due to chemotherapy drug concentration.

Or mathematically,

\[
\frac{\partial T}{\partial t} = \frac{D}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial T}{\partial r} \right) + \rho T + \beta b_p - kOT. \tag{1}
\]

Consider a spherical symmetric tumor of radius \(R(t)\). In which \(T(r, t)\) designates the tumor cell concentration at \(r\) radial distance from the origin at time \(t\), \(b_p\) is the blood plasma concentration, \(\beta\) is the transfer constant, \(\rho\) is the proliferation rate of tumor cells, \(k\) is chemotherapy drug concentration and \(D\) is the diffusion coefficient representing the active motility of cells.

The equation for drug concentration \(O(r, t)\) in spherical co-ordinates system is below:

\[
\frac{\partial O}{\partial t} = \frac{D_o}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial O}{\partial r} \right) + v\delta - \eta \frac{c}{c_v} \tag{2}
\]

where

\[
O = \frac{c}{c_v}.
\]

Where \(D_o\) represent the diffusion coefficient of the drug in the tumor tissue and \(r\) is the radial distance from the center of the tumor, \(c\) represent is local chemotherapeutic carrier concentration, \(c_v\) represent the nutrient and chemotherapeutic carrier concentration in vasculature, \(\eta\) represent drug loss due to decay rate, \(v\) represent the transfer coefficient from the vasculature and \(\delta\) represent the indicator function of vasculature (1 where it exists, 0 otherwise).
We suppose that the cell mass concentration is uniform in the tumor, the local specific mass growth rate is the divergence of tumor cell’s velocity field $\omega$.

$$\frac{1}{r^2} \frac{\partial}{\partial r} (r^2 \omega) = \rho O - \rho_d - k OT. \quad (3)$$

Where $\rho_d$ is the death rate of tumor cells due to apoptosis. Let the radial symmetrical tumor expands at a rate, which is equal to the radial component of velocity there, i.e.

$$\frac{dR}{dt} = \omega(R(t), t). \quad (4)$$

The tumor surface is a moving boundary. The initial and boundary conditions are,

$$R(0) = R_0, \quad O(r, t) = 0, \quad T(R(t), t) = p\theta, \quad \frac{\partial T(0, t)}{\partial r} = \frac{\partial O(0, t)}{\partial r} = 0$$

$$O(R(t), t) = O_K(t), \quad \omega(0, t) = 0,$$  

where $\theta$ is the cells concentration.

$R_0$ is the initial tumor cell radius and by symmetry, at $r = 0$, there is no amount of drug and local velocity is zero. $O_K(t)$ is the drug concentration on the tumor boundary.

Non-dimensionalization

$$\hat{\omega} = \frac{\omega}{R_0 \rho}, \quad \hat{r} = \frac{r}{R_0}, \quad \hat{\eta} = \frac{\eta R_0^2}{D_0}, \quad \hat{\nu} = \frac{v R_0^2}{D_0}$$

$$\chi = \frac{\rho R_0^2}{D_0}, \quad \hat{\rho} = \rho t, \quad \hat{\rho}_d = \frac{\rho_d}{\rho}, \quad \hat{k} = \frac{k R_0^2}{D_0}$$

Dropping the caps and then we get the equations in the form of

$$\chi \frac{\partial T}{\partial t} = \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial T}{\partial r} \right) + \rho T - \beta b_p - k OT$$  

$$\frac{\partial O}{\partial t} = \frac{D_0}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial T}{\partial r} \right) + \nu \delta - \eta O$$  

$$\frac{1}{r^2} \frac{\partial}{\partial r} (r^2 \omega) = O - \rho_d - k OT$$
The initial and boundary conditions are:

\[ R(0) = R_0, \quad O(r, t) = 0, \quad T(R(t), t) = \rho \theta, \quad \frac{\partial T(0, t)}{\partial r} = \frac{\partial O(0, t)}{\partial r} = 0 \]

\[ O(R(t), t) = O_R(t), \quad \omega(0, t) = 0. \]  

After solution we get

\[ T(r, t) = \left( T_R(t) - \frac{\beta b_p}{(\rho - kO)} \right) \frac{R(t) \sinh(\beta r)}{r} + \frac{\beta b_p}{(\rho - kO)}, \]

\[ O(r, t) = \left( O_R(t) - \frac{\nu \delta}{\eta} \right) \frac{R(t) \sinh(\alpha r \sqrt{\chi})}{r \sinh(\alpha R(t) \sqrt{\chi})} + \frac{\nu \delta}{\eta}, \]

\[ \omega(r, t) = \left( O_R(t) - \frac{\nu \delta}{\eta} \right) \frac{R(t)}{\chi \alpha^2 E(t)} \left[ \frac{\alpha R(t) \sqrt{\chi} \cosh(\alpha R(t) \sqrt{\chi}) - \sinh(\alpha R(t) \sqrt{\chi})}{\sinh(\alpha R(t) \sqrt{\chi})} \right] + \left( \frac{\nu \delta}{\eta} - \rho_d \right) \frac{R(t)}{3}, \]

Parameter Estimations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \chi )</td>
<td>( 4.8 \times 10^4 ) cm s/s</td>
</tr>
<tr>
<td>( \eta )</td>
<td>1/min.</td>
</tr>
<tr>
<td>( v )</td>
<td>0.015/min.</td>
</tr>
<tr>
<td>( D_o )</td>
<td>( 10^{-5} )</td>
</tr>
<tr>
<td>( \rho )</td>
<td>0.3/day</td>
</tr>
<tr>
<td>( \rho_d )</td>
<td>2.1/day</td>
</tr>
<tr>
<td>( R_o )</td>
<td>4</td>
</tr>
<tr>
<td>( \theta )</td>
<td>( 10^6 ) cells/mm³</td>
</tr>
<tr>
<td>( b_p )</td>
<td>0.5 mM. l⁻¹</td>
</tr>
<tr>
<td>( B )</td>
<td>0.1 per min.</td>
</tr>
<tr>
<td>( \alpha )</td>
<td>10.54092553</td>
</tr>
<tr>
<td>( D )</td>
<td>10⁻¹⁰</td>
</tr>
</tbody>
</table>
3. Results

Here we developed a mathematical model for the chemotherapy strategies in spherically symmetric tumor with blood plasma. The numerical procedure used to approximate the system of partial differential equations, being approximate using the MATLAB 6.0, to solve the partial differential equation.

Figure 1

Figure 1 represents the evolution of equation (1) which tumor cell concentration with the radius \( r = 0 \) to \( 1 \) and the time \( t = 0 \) to \( 10 \) hr directions. We see that the tumor cell concentration is linear growth with respect to time. It is 4.5 (approx.) after 10 hr.

Figure 2
Equation (11) is mathematical solution of equation (1) for tumor cell density. Figure 2 represents the evolution of equation (11) which tumor cell concentration with the radius ($r = 0$ to $1$) and the time ($t = 0$ to $10$ hr) directions. We see that the tumor cell concentration is linear growth with respect to time. It is 4.5 (approx.) after 10 hr.

4. DISCUSSION

We consider a mathematical model for drug accumulation with blood plasma concentration in a spherical tumor at nano-scale. The work of blood plasma here is to give a medium to blood cells to move through out the organ. The mathematical model is formulated in non-linear system of partial differential equations. We numerically and analytically solve the system for tumor cell concentration which shows the same results in Fig. 1 and 2. After going through this study we reached the decision that, after some time in the case of 10 nm particles the drug concentration in tumor cell becomes zero, on the other hand the drug concentration for the 100 nm particles is not going to be zero. This implies that particles with the range of 1-10 nm do not give constant supply for long time, so for the long time constant supply of drug we need at least the particles with the range of 100-1000 nm. Good penetration of drugs into tumor cells will greatly improve the efficacy of chemotherapy in cancer treatment. We hope that the modeling framework that we have developed and our findings lead to several possibilities for extended studies.

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