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Two dimensional mathematical model of fluid flow in a growing solid tumor

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TWO DIMENSIONAL MATHEMATICAL MODEL OF FLUID FLOW IN A GROWING SOLID TUMOR

A Thesis

by

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ABSTRACT

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We investigate the problem of steady and unsteady fluid flow in a growing solid tumor. We develop a mathematical model for the two dimensional fluid flow in a spherical tumor where the spatial variations of the interstitial velocity, interstitial pressure and the drug concentration within the tumor are, in general, with respect to the radial distance and the latitudinal angle in the spherical coordinates. The expressions for radial and latitudinal variations of the interstitial velocity, interstitial pressure, and the two investigated drug concentrations were determined analytically. We calculated these quantities in the tumor as well as in a corresponding normal tissue. Depending on the types of the two considered drug concentrations, we determine the results about efficiency and the way drug delivery in the tumor takes place in absence or presence of the drugs' interactions that could be significant in the presence of the two drugs in the tumor.

DEDICATION

I dedicate my thesis work, firstly to God who has given me the strength and wisdom to accomplish this goal, to my parents who made many sacrifices so that I could get to where I am today, to my husband who has given me unconditional support and motivation, to my brothers and sister so that I could be a role model in their life, and to my daughter that in hopes that one day she can read this thesis and see what her mother accomplished. Thank you all for so much help. I love you.

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The work contained in this thesis would not have been possible without the assistance, encouragement, and mentoring of many stunning individuals. I am extremely grateful to my exceptional thesis advisers, Dr. Daniel Riahi and Dr. Ranadhir Roy who have mentored me throughout my graduate studies. I have learned tremendously from both of you. I also would like to thank Dr. Qiao, and all the GAANN Fellowship Committee for choosing me to be part of such a great fellowship, and allowing me to earn my master's degree here at the University of Texas Pan American. I want to thank Dr. Maruno and Dr. Pierce for introducing me to applied mathematics and interdisciplinary research, this incredible field that has numerous areas of study. As well as all the mathematics department faculty and staff for all the hard work they do to make this department such a success.

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CHAPTER I

INTRODUCTION

Cancer is the second leading cause of death in the American continent [6] . The most major treatment is surgical removal of the tumor, but there will be residual tumor cells and the re-growth of these tumor cells, which is very common. In order to prevent the reoccurrence of tumor cells anticancer drugs are prescribed. Hence the successful cure is an efficient distribution of anticancer drugs within targeted areas after surgery. The drugs' most noticeable limitation is their inability to reach the targeted area.The two most important considerations in effective cancer treatment, from a mathematical point of view, are drug transport to the affected area and drug change or reaction at the tumor site. Many drugs cannot be delivered to their targets because of transport limitations. Most of the human cancers are solid in nature and highly heterogeneous tumors, and current chemotherapy depends on the adequate delivery of therapeutic agents in tumor sites. An important process in drug delivery is an inward convection and diffusion of the injected drug concentration in the presence or absence of another drug concentration within the solid tumor system. Some investigated numerical simulations have provided some understanding of the mechanisms of the interstitial fluid transport [1, 2, 3]; [11];[13]; [12]. The above studies as well as additional ones[15, 14, 16] have been mostly about solid tumors. Despite many experimental or computational investigations on the tumors that have been carried out in the past including those referred to here, there is still little information available about the mechanism that operates for drug interactions when more than one drug concentrations are transported in the patient's body to effectively reduce the negative effects of malignant tumors. In a study by Dr. Riahi and Dr. Roy they developed a one dimensional mathematical model of a stationary brain tumor by approximating its shape by a sphere, and they

considered steady state features of the fluid flow within the non-growing tumor. The flow is assumed to be only in the one-dimensional direction of the radial distance within the spherical tumor [9]. Such steady state features of the flow quantities, which can be considered as time averages of the flow quantities, are reasonable as leading first approximation under the assumption that the rate of the growth of the tumor is sufficiently small. The authors determined interstitial velocity and pressure as functions of distance from the center of tumor, and, in addition, the radial variations of a drug concentration in presence or absence of another drug within such systems. However, it should be noted that even though the structures of many tumors are approximately close to that of a sphere, the purely one-dimensional dependence of the flow quantities and the drug concentration on the radial variable as well as consideration of only radial velocity as considered in [9] is more mathematical and less realistic in the biomedical applications. In another work by Dr. Riahi and Dr. Roy they considered the same one-dimensional problem and did some time dependent computation, but again the model was too idealistic as in the work in [10].

The present investigation extends the one-dimensional work due to [10] to more realistic two-dimensional unsteady cases for growing tumors, where the interstitial velocity vector is considered to have, in general, two components along radial and latitudinal direction, and all the dependent variables for the flow velocity, pressure and drug concentrations are assumed to depend on time as well as on both radial and latitudinal variables. This is a first type of theoretical investigation to obtain information about the mechanism of the drug delivery and drug interactions in the growing tumor system and drug dependence on more precise locations in the tumor. Furthermore, our present work can help to improve understanding of the drug transport mechanisms in the growing solid tumors which can consequently help to improve drug delivery schemes to such tumors. We found a number of interesting results that cannot be detected by a one-dimensional model of the type used in [10]. For example, we detected existence of blood flow circulation in the tumor, and the amount of drug delivered to the tumor was found to decrease as tumor grows in time, but then the rate of decrease reduces as time goes on. We also determined the efficiency of the drug delivery in the growing tumor system in the absence or presence of another drug delivery in the system.

Such results can provide some understanding of the cause for the decrease or increase of the drug effectiveness within the patient's body which can be useful as further guiding tools for the specialists and doctors to improve chances for the patient's health recovery.

1.1 MATHEMATICAL FORMULATION

First, will assume we are working with a homogeneous tumor of size 1cm. Let us consider a spherical tumor with radius $R'(t')$ and a spherical coordinate system whose origin lies at the center of tumor, with radial r'- axis positively outward from the origin and latitudinal angle θ , which is measured with respect to the polar axis of the sphere. Here t' is the time variable. Figure 1.1 presents a spherical tumor whose center is at the origin O of the shown three-dimensional coordinate system, where a point P on the surface boundary of the tumor and its vertical projection on the $x-y$ plane are also shown. The non-dimensional radius and the radial coordinate of the spherical tumor are designated by R and r, respectively, and the latitudinal and azimuthal angles of the spherical coordinates are designated by θ and ϕ, respectively.

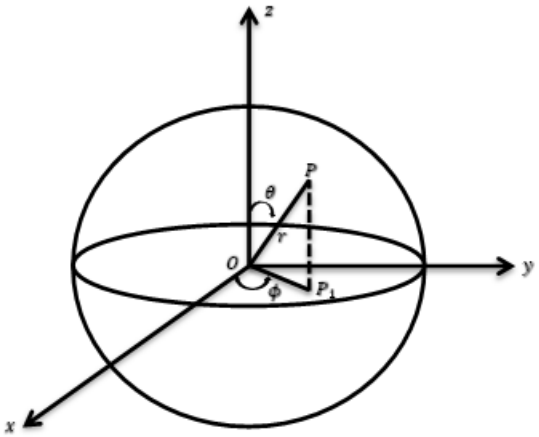

Figure 1.1: Spherical Tumor Representation

We assume that growth rate of the tumor is small and positive $(0 < \frac{\partial R'}{\partial t'} << 1)$. We consider the governing equations for the fluid flow in the tumor or the corresponding normal tissue [13, 12], which basically are the Darcy Momentum equation, the mass continuity equation in the presence

sinks and sources, which is appropriate for the interstitial fluid [1] and the sources and sinks part is based on the Starling's law and the fluid productions by cells due to metabolism [13], and the equations for the concentrations of two drugs. These equations and the necessary boundary conditions, which turn out to be needed in the present analytical procedure, are given below.

$$\left(\frac{\mu}{k}\right) u' = \nabla P' \tag{1.1}$$

$$\nabla u' = a_1 - a_2 P' \tag{1.2}$$

$$\left(\frac{\partial}{\partial t'} + u'\nabla\right) C_1 = D_1 \nabla^2 C_1 - a_3 C_1 - a_4 C_2 \tag{1.3}$$

$$\left(\frac{\partial}{\partial t'} + u'\nabla\right) C_2 = D_2 \nabla^2 C_2 - a_5 C_1 - a_6 C_2 \tag{1.4}$$

$$P' = P'_B, \quad C_i = C'_{B_i} \quad \text{at} \quad r' = R'(t'), \quad \text{for} \quad (i = 1,2) \tag{1.5}$$

Where u' is the interstitial fluid velocity vector, P' is the interstitial pressure, P'_B is a nonzero quantity, which can be a constant for a function of θ, μ is dynamic viscosity, k is permeability, a_1 and a_2 are constants whose expressions are given in [13] with a_1 due to hydraulic conductivity K_v of the macro-vascular wall, vascular pressure, osmotic reflection coefficient for the plasma protein, osmotic pressures of the plasma and interstitial pressures and exchange area $\frac{S}{V}$ of the blood vessels per unit volume of tissues and $a_2 = K_v\left(\frac{S}{V}\right)$. In addition, C_i where $(i = 1,2)$ are the concentrations of two drugs with diffusion coefficients D_i, C'_{Bi} are constants, and $a_i (i = 3,,6)$ represent source or sink terms in the concentration equations, which can be due to presence of either one or two drugs. As explained in [13], such source and sink terms can be due to chemical elimination by the drug degradation in the cavity or by metabolic reactions in the tumor and normal tissues as well as drug gain from the blood capillaries in the tumor or tissue.

We consider the two-dimensional axisymmetric case of the flow system where the spatial variation is along the latitudinal and radial directions, and the velocity vector has non-zero components along the latitudinal and radial directions. The flow system is axisymmetric with respect to the azimutal direction of the spherical coordinate system. The expression for the time-dependent radius of the tumor for the steady case is considered to be in the form

$$R'(t') = R_0 \exp\left\{\varepsilon\left[1-\exp(-\alpha' t')\right]\right\} \tag{1.6}$$

Similarly we have, the time-dependent radius for the tumor for the unsteady case,

$$R'(t') = R_0 \exp\left\{\varepsilon\left[1-\exp(-\varepsilon\alpha' t')\right]\right\} \tag{1.7}$$

where ε is a small parameter ($\varepsilon << 1$) representing the order of magnitude of the relative growth rate of the tumor, R_0 is the constant radius of tumor in the absence of its growth and α' is a constant quantity per unit time whose value can affect the relative growth rate. We have assumed that the tumor grows slowly in time, so that $\left(\frac{1}{R'}\right)\frac{\partial R'}{\partial t'} = o(\varepsilon) << 1$.We make the governing system 1.1-1.5 dimensionless by using length scale R_0, time scale $\frac{R_0^2}{\nu}$ for steady case and $\frac{R_0^2}{\varepsilon\nu}$ for unsteady case, where $\nu \equiv \frac{\mu}{\rho}$ is kinematic viscosity and ρ is fluid density, velocity scale $\frac{\nu}{R_0}$ and pressure scale $\frac{\nu^2\rho}{k}$, so that the dimensional forms of the variables and R are related to their non-dimensional counterpart by

$$\left(r',t',\mathbf{u}',P',R'\right) = \left[R_0 r, \left(\frac{R_0^2}{\nu}\right)t, \left(\frac{\nu}{R_0}\right)\mathbf{u}, \left(\frac{\nu^2\rho}{k}\right)P, R_o R\right] \tag{1.8}$$

$$\left(r',t',\mathbf{u}',P',R'\right) = \left[R_0 r, \left(\frac{R_0^2}{\varepsilon\nu}\right)t, \left(\frac{\nu}{R_0}\right)\mathbf{u}, \left(\frac{\nu^2\rho}{k}\right)P, R_o R\right] \tag{1.9}$$

where equation 1.8 is for steady part and equation 1.9 for unsteady part. We then apply a perturbation expansion in powers of small ε by assuming that the growth rate of increase of the tumor with respect to time is sufficiently small and write it in the form

$$\begin{aligned}(\mathbf{u},P,C_1,C_2,R) = [\mathbf{u}_0(r,\theta),P_0(r,\theta),C_{10}(r,\theta),C_{20}(r,\theta),1] + \\ \varepsilon\left[\mathbf{u}_1(r,\theta),P_1(r,\theta),C_{11}(r,\theta),C_{21}(r,\theta),1\right]\left[1-\exp(-\alpha t)\right] + o(\varepsilon^2)\end{aligned} \tag{1.10}$$

$$(\mathbf{u},P,C_1,C_2,R) = [\mathbf{u}_s(r,\theta),P_s(r,\theta),C_{1s}(r,\theta),C_{2s}(r,\theta),1] + \varepsilon\,[\mathbf{u}_u(r,\theta),P_u(r,\theta),C_{1u}(r,\theta),C_{2u}(r,\theta),1]\,[1-\exp(-\alpha t)] + o(\varepsilon^2) \quad (1.11)$$

where $\alpha = \alpha' \frac{R_0^2}{\nu}$ is a non-dimensional constant, and the subscript "s" and "u" refer to the leading order steady part and the unsteady part, respectively, for each dependent variable.

CHAPTER II

STEADY CASE

In this section, since we assume that the growth rate of the tumor is small ($\varepsilon << 1$) due to the slow time scale for such growth, we analyze and determine the solutions for the steady state parts of the flow quantities. Thus, we first consider 1.11 to the lowest order in ε, and use 1.11 together with 1.9 in 1.1–1.5 to find the following simplified non-dimensional axisymmetric form of the system in the spherical coordinates.

$$\frac{\partial P_s}{\partial r} = u_s \tag{2.1}$$

$$\left(\frac{1}{r}\right)\left(\frac{\partial P_s}{\partial \theta}\right) = v_s \tag{2.2}$$

$$\left[\left(\frac{\partial}{\partial r}\right)\left(r^2\sin(\theta)u_s\right) + \left(\frac{\partial}{\partial \theta}\right)\left(r\sin(\theta)v_s\right)\right] = b_1 - b_2 P_s \tag{2.3}$$

$$u_s\frac{\partial C_1}{\partial r} + \frac{v_s}{r}\frac{\partial C_{1s}}{\partial \theta} = L_1\left\{\left[\left(\frac{1}{r^2}\right)\left(\frac{\partial}{\partial r}\right)\left(r^2\frac{\partial C_{1s}}{\partial r}\right)\right] + \frac{1}{r^2\sin\theta}\left(\frac{\partial}{\partial \theta}\right)\left[\sin\theta\left(\frac{\partial}{\partial \theta}\right)\right]C_{1s}\right\} - \hat{b}_3 C_{1s} - \hat{b}_4 C_{2s} \tag{2.4}$$

$$u_s\frac{\partial C_2}{\partial r} + \frac{v_s}{r}\frac{\partial C_{2s}}{\partial \theta} = L_2\left\{\left[\left(\frac{1}{r^2}\right)\left(\frac{\partial}{\partial r}\right)\left(r^2\frac{\partial C_{2s}}{\partial r}\right)\right] + \frac{1}{r^2\sin\theta}\left(\frac{\partial}{\partial \theta}\right)\left[\sin\theta\left(\frac{\partial}{\partial \theta}\right)\right]C_{2s}\right\} - \hat{b}_5 C_{2s} - \hat{b}_6 C_{2s} \tag{2.5}$$

$$P_s = \hat{P}_B, \quad C_{is} = C_{Bi} \quad \text{at} \quad r = 1, \quad (i = 1,2), \tag{2.6}$$

where u_s is the steady part of the radial component of the velocity, v_s is the steady part of the latitudinal component of $\mathbf{u}, L_1 = \frac{D_1}{v}$ and$L_2 = \frac{D_2}{v}$ are the non-dimensional diffusion parameters for the two drug concentrations, and C_{1s} and C_{2s} the leading steady parts of the two drug concentrations, respectively, $b_1 = a_1\frac{R_0^2}{v}, b_2 = a_2 v\frac{R_0^2}{k}, \hat{b}_i = a_i\frac{R_0^2}{v}$ for $i = 3,4,5,6$, $\hat{P}_B = P'_B\frac{k}{\rho v^2}$ and C_{Bi} are the boundary conditions for leading parts of the drug concentrations. Using 2.1 and 3.2 in 3.3, we found the

equation for the steady part of the interstitial pressure which can be simplified to the form

$$\frac{1}{r^2}\frac{\partial}{\partial r}r^2\frac{\partial P_s}{\partial r}+\frac{\cot\theta}{r^2}\frac{\partial P_s}{\partial \theta}+\frac{1}{r}\frac{\partial^2 P_s}{\partial \theta^2}=b_1-b_2P_s \tag{2.7}$$

This equation admits solutions of the form

$$P_s(r,\theta)=S(r)+t(r)\cos\theta \tag{2.8}$$

where the unknown functions S and T need to be determined. Now, use 2.8 in 2.7, we find the following equations for these functions

$$\frac{d^2S}{dr^2}+\frac{2}{r}\frac{dS}{dr}+b_2S=b_1 \tag{2.9}$$

$$\frac{d^2T}{dr^2}+\frac{2}{r}\frac{dT}{dr}+\left[b_2-\frac{2}{r^2}\right]T=0 \tag{2.10}$$

The ordinary differential equations 2.9 and 2.10 have the so-called regular singular points at the center of the tumor ($r=0$), and, hence, the well known method of Frobenius can be used to determine their solutions [17]. This method represents a power series solution for the dependent variable satisfying the respective differential equation. Applying the method of Frobenius for 2.9 and 2.10, we find the solutions for $S(r)$ and $T(r)$ and, hence for $P_s(r,\theta)$. Due to the result that the coefficients in the power series representations of the solutions for S and T are found to be proportional to the b_2 or its positive-integer powers, and b_2 is generally quite small of $O(10^{-7})$ in biomedical applications (see Table 1 in the next section), the very good approximated solution for $P_s(r,\theta)$ is given by

$$P_s(r,\theta)=e_0\left[1-\left(\frac{b_2}{6}\right)r^2+\left(\frac{b_2^2}{120}\right)r^4\right]+e_1\left[r-\left(\frac{b_2}{10}\right)r^3+\left(\frac{b_2^2}{280}\right)r^5\right]\cos\theta \tag{2.11}$$

where the constants e_0 and e_1 to be determined by the boundary condition $\hat{P}_B$ on the outer surface of the solid tumor for P_s. In the simplest form the interstitial pressure boundary condition at $r=1$ can be a constant. However, in more realistic cases, one can expect that the value of the interstitial pressure on the surface of the spherical type tumor to vary also with respect to the latitudinal angle θ or at least in a weak manner. In the present analytical study we consider the case where

$$\hat{P}_B=P_B(1+\delta\cos\theta) \tag{2.12}$$

Here δ is a sufficiently small constant parameter ($\delta << 1$).

2.1 RESULTS

We calculated the main quantities, which are the velocity, pressure and the concentrations of two drugs, by using the prescribed numerical values for the non-dimensional constant coefficients $b_i(i = 1, ..., 6)$ and for the non-dimensional parameters L_i, and we evaluated the arbitrary constants$e_i(i = 1, ..., 5)$ in the solutions 2.12, (9a-b), (10) and (12a-d) by using the boundary values P_B and $C_{Bi}(i = 1, 2)$. These numerical values were chosen based on the dimensional values of the corresponding quantities, which were collected mainly from the relevant literatures on biomedical applications [7, 13, 12]. The nondimensional values of the constant coefficients $b_i \quad (i = 1, \cdots, 6)$, the boundary values P_B, $C_{Bi}(i = 1, 2)$ and the diffusion parameters $L_i(i = 1, 2)$ are given in Table 2.1.

Quantities	Tumor Values	Normal Tissue Values	Cavity Values
b_1	$-2.218032(10^{-7})$	$-2.98848(10^{-5})$	
b_2	$4.22(10^{-7})$	$0.54(10^{-7})$	
b_3	1.662	0.212	0.212
b_4	0.016662	0.00212	0.00212
b_5	1.662	0.212	0.212
b_6	1.01662	0.00212	0.00212
C_{B1}	0.1	0.1	0.1
C_{B2}	0.1	0.1	0.1
L_1	$1.4175(10^{-5})$	$0.525(10^{-6})$	$0.3003(10^{-5})$
L_2	$1.4175(10^{-8})$	$0.525(10^{-8})$	$0.3003(10^{-8})$
P_B	$1.02(10^3)$	$1.02(10^3)$	$1.02(10^3)$
T_1	0.1	0.1	0.1
T_1	0.1	0.1	0.1

Table 2.1: Non-dimensional values of the quantities used for calculation

For the two drug concentrations we chose Etanidazole, which is used for cancer patients to regulate the level of oxygen concentration in the tissue in order for delivery of radiotherapy can be applicable to destroy the malignant cells, and Cisplatin which is a kind of chemotherapy drug. Figure 2.1 presents interstitial pressure versus the radial variable for the case where the surface boundary of the pressure is a constant $(\delta = 0)$ and for both tumor and normal tissue.

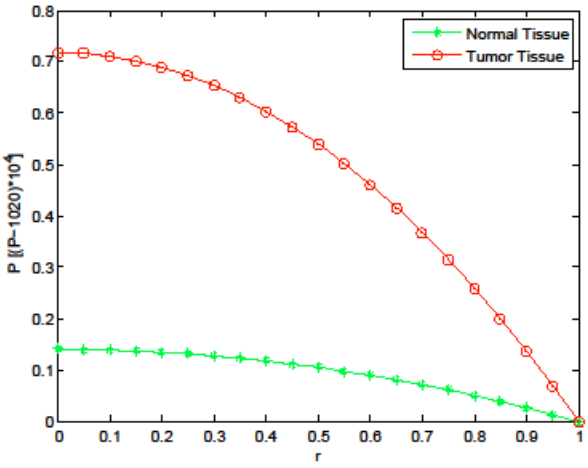

Figure 2.1: Interstitial pressure versus Radial variable

It can be seen from this figure that interstitial pressure increases with decreasing the radial variable, and it has a maximum at the center of both tumor and normal tissue, which is consistent if no flow activity can be apparent at the center of tumor or normal tissue. In addition, the interstitial pressure in the tumor is higher than that in the normal tissue, which is an indication of extra problem due to presence of tumor. The magnitude of the rate of change of the pressure is found to decreases with decreasing the radial variable for both cases of tumor and normal tissue. Figure 2.2 presents radial velocity of the flow versus the radial variable for both tumor and normal tissue and for the case where the surface boundary of the interstitial pressure is constant.

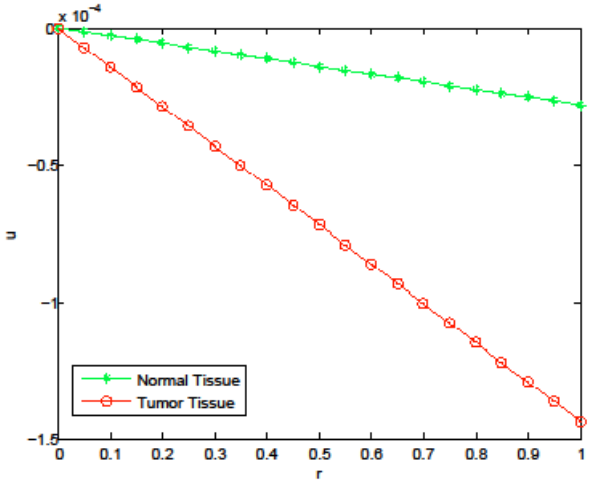

Figure 2.2: Radial component of instertitial velocity versus Radial variable

As can been seen from this figure, $u < 0$ which is due to the fact that flow enters into the tumor or tissue from the boundary surface. The velocity profile appears to be linear in the domain for $r(0 < r < 1)$, and its magnitude for tumor is higher than that for the tissue. It is also seen that $|u_o| \to 0$ as$r \to 0$ which is reasonable since the high interstitial pressure at the center put the motion into rest there.

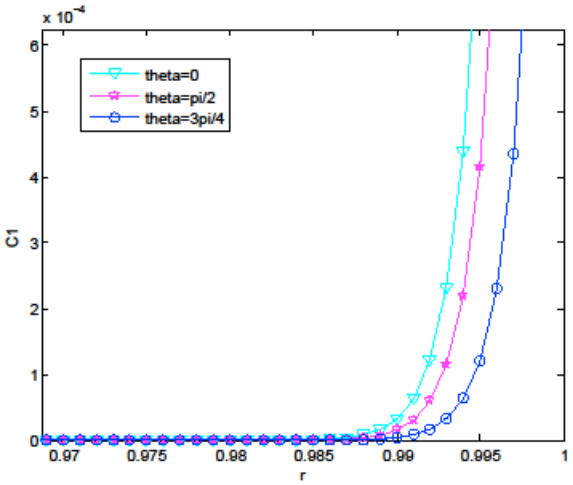

Figure 2.3: Etanidazole concentration in tumor versus radial variable

Figure 2.3 presents etanidazole drug transport in tumor versus radial variable for several values of the latitudinal angle θ and in the absence of another drug transport. It can be seen from this figure that amount of transported drug decreases with decreasing the radial variable and the amount is zero at the center of tumor. This result indicates that etanidazole is consumed entirely by the tumor. It is also apparent from this figure that the transported drug at high latitude domain is higher that either in mid- or low-latitude domain. The rate of change of the concentration with respect to the radial variable decreases with decreasing the radial variable, which is consistent due to the fact that the amount of drug delivery is less in the regions closer to the center of tumor. Figure 2.4 presents etanidazole concentration in normal tissue versus radial variable and for several values of the latitudinal angle.

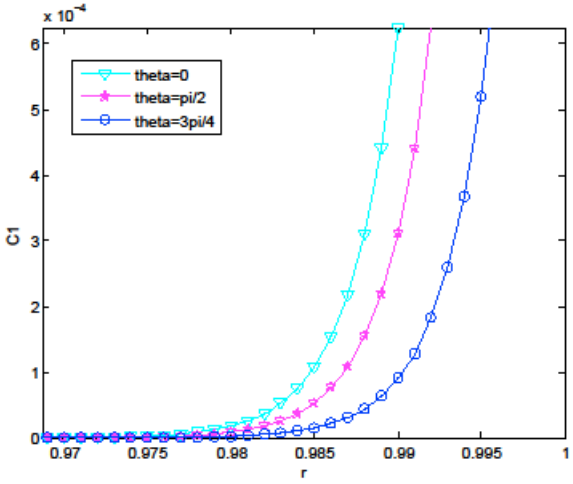

Figure 2.4: Etanidazole concentration in normal tissue versus radial variable

As in the case of tumor the amount of transported drug decreases with decreasing the radial variable and the amount diminishes to zero at the center of the tissue. In addition, the amount transported in the tissue in high latitude region is higher than those transported in the mid- or low-latitude region, and the rate of decrease of the drug reduces as it approaches the center. However, a comparison of our calculated data for tumor and normal tissue indicate that the amount transported by this drug is lower in the normal tissue than in the tumor, which may be contributed to

the complexity of the tumor structure absorbing higher amount of such drug than in normal tissue. Figures 2.5 and 2.6 present respectively drug concentrations of cisplatin in tumor and normal tissue versus radial variable and for several values of the latitudinal angle. It can be seen from these figures that amount of concentration diminishes quickly as it approaches center of the tissue. The amount of delivery of cisplatin in high latitude is higher than those in mid or low latitude.

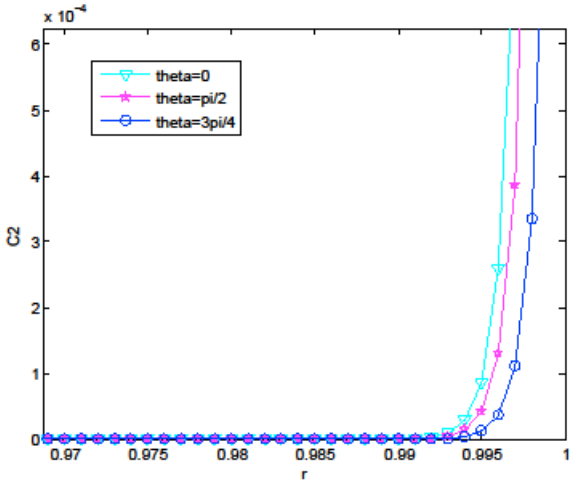

Figure 2.5: Cisplatin concentration in tumor versus radial variable

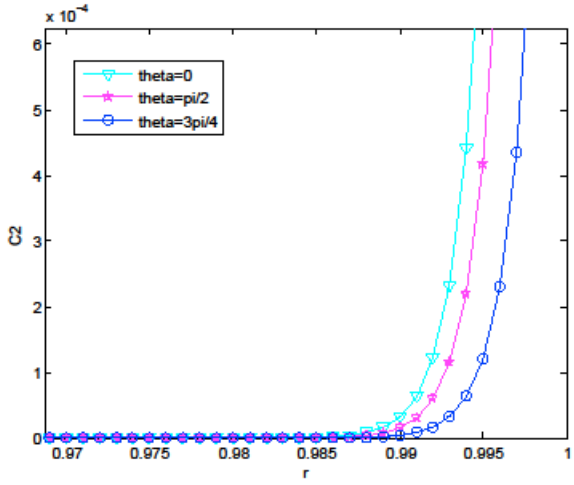

Figure 2.6: Cisplatin concentration in normal tissue versus radial variable

Also closer inspection of our calculated data indicated that the amount of cisplatin concentration in the normal tissue is higher than the one in the tumor, which indicated that the amount of drug consumed by either tumor or normal tissue depends on the type of drug concentration in such tissues. The results based on the generated data for the cisplatin concentration in each of the two tissues indicated that the amount of cisplatin drug in the normal tissue is higher than that in the tumor. Hence, the factors that can affect the amount of drug concentration in a tissue depends not only on the type of drug but also on the competing effect of the drug type versus tissue type. A comparison with the generated data for the etanidazole transport in each of the two tissues indicated that for the tumor amount of cisplatin concentration is less than that of etanidazole, while in the normal tissue amount of cisplatin concentration is higher than that of etanidazole, and so the result is based on the dominating effect of higher diffusivity of the drug as well as the structure of the type of tissue which is consumed by the drug. Figures 2.7 and 2.8 present respectively interstitial pressure versus the radial variable for tumor and the normal tissue and for the latitudinal angle $\theta = \frac{\pi}{2}$.

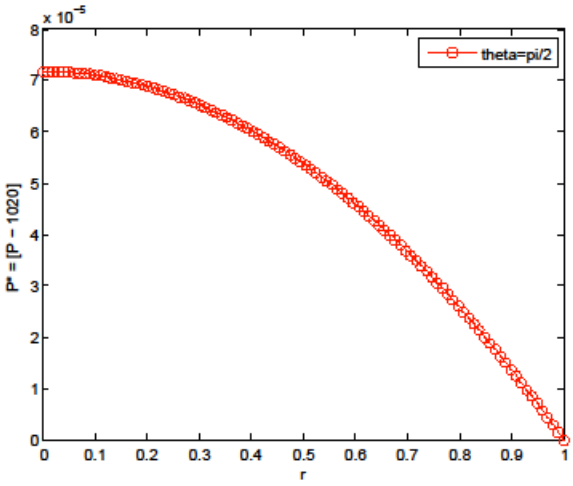

Figure 2.7: Interstitial pressure versus radial variable in the case of tumor tissue and latitudinal angle $\theta = \frac{\pi}{2}$

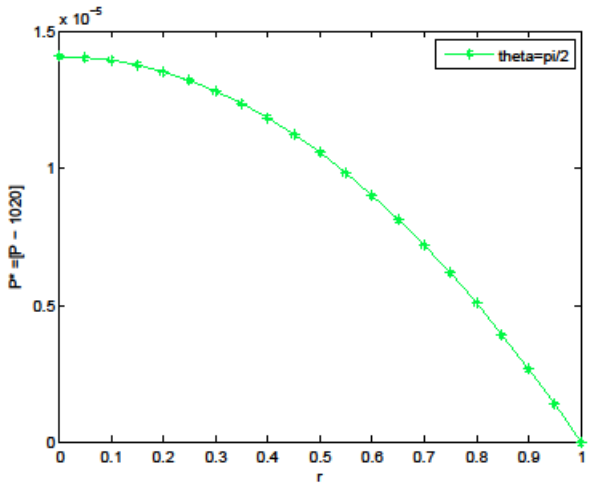

Figure 2.8: Interstitial pressure versus radial variable in the case of normal tissue and latitudinal angle $\theta = \frac{\pi}{2}$

It can be seen from these figures that the pressure increases as the radius decreases leaving maximum pressure at the center of tumor or tissue. The value of the pressure in the tumor is higher than that in the tissue, and, in addition, the radial rate of change of the pressure in the tumor is higher than the corresponding one in the tissue. Our results for both interstitial pressure and velocity that we described so far agree qualitatively with the available experimental results [5, 1, 4, 8].Figure 2.9 presents interstitial pressure versus radial variable for normal tissue at$\theta = 0$.

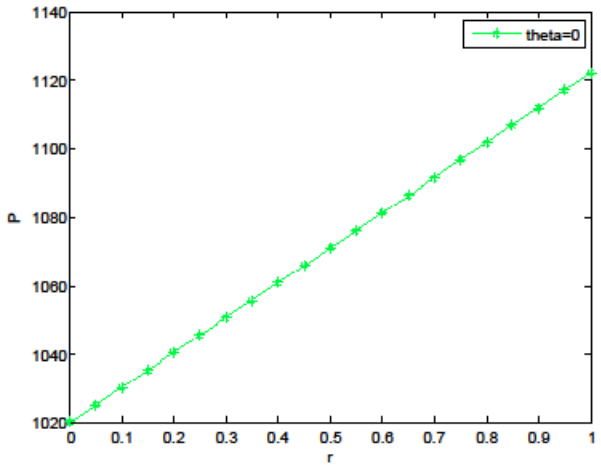

Figure 2.9: Interstitial pressure versus radial variable in the case of normal tissue and latitudinal angle $\theta = 0$

Here the value of the blood pressure decreases with decreasing the radial distance from the center, and value of the pressure is non-zero at the center. Our additional collected data for blood pressure at other values of latitudinal angle, such as $\theta = \frac{3\pi}{4}$, indicated that interstitial blood pressure can decrease (or increase) with decreasing the value of the radial variable for tumor (or normal tissue). So these results indicate that depending on the internal blood flow direction and intensity, blood pressure may increase or decrease with respect to r. Figures 2.10 and 2.11 present, respectively, interstitial radial velocity versus radial variable for tumor and normal tissue at latitudinal angle $\theta = 0$.

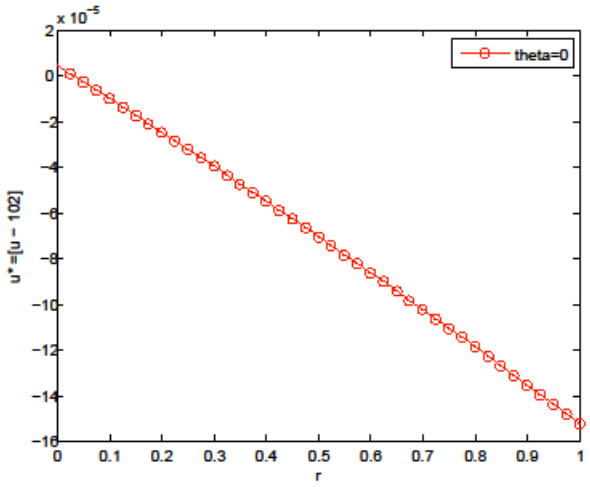

Figure 2.10: Radial Component of interstitial velocity versus radial variable in the case of tumor tissue and latitudinal angle $\theta = 0$

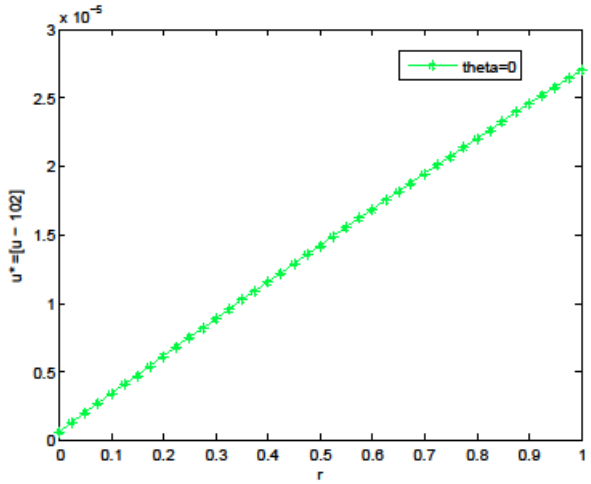

Figure 2.11: Radial Component of interstitial velocity versus radial variable in the case of normal tissue and latitudinal angle $\theta = 0$

It can be seen from these figures that radial velocity is positive and non-zero at the center in both tumor and normal tissue, but it decreases with increasing r in the tumor and increases with r in the normal tissue. Our additional generated data for the radial velocity at different values of the

latitudinal angle, such as $\theta = \frac{3\pi}{4}$, indicated different direction and sign and variation with respect to r, which are indication of existence of blood flow circulation within tumor and to less intensity in the normal tissue.

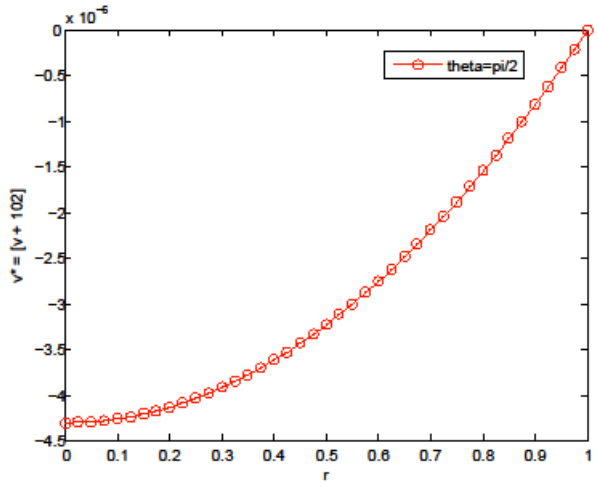

Figure 2.12: Latitudinal component of interstitial velocity versus radial variable in the case of tumor tissue and for the latitudinal angle$\theta = \frac{\pi}{2}$

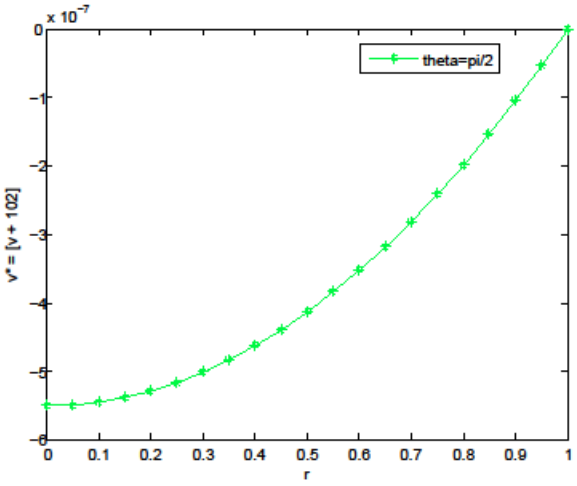

Figure 2.13: Latitudinal component of interstitial velocity versus radial variable in the case of normal tissue and for the latitudinal angle $\theta = \frac{\pi}{2}$

Figures 2.12 and 2.13 present, respectively, the latitudinal component of the blood velocity versus the radial variable in tumor and normal tissue at $\theta = \frac{\pi}{2}$. It can be seen from these figures that latitudinal velocity is negative and its magnitude increases with decreasing the radial variable. The magnitude of the latitudinal velocity is slightly higher in the tumor than in the normal tissue. We also calculated the concentrations of drugs when both drugs are present and some of our results for such case are shown in Figures 15-18. These figures present respectively concentrations of etanidazole (figures 2.14 and 2.15) and cisplatin (figures 2.16 and 2.17) versus the radial variable and the cases of tumor and normal tissue. It can be seen from these figures that both concentrations again deccrease with decreasing the radial variable and the value and the radial rate of change of each concentration is highest in the normal tissue and lowest in the tumor. Similar to the case in the absence of drug interaction presented in figures 2.3–2.6, we can see from figures 2.14–2.17 that the radial rate of change of each of these concentrations is higher close to the spherical boundary.

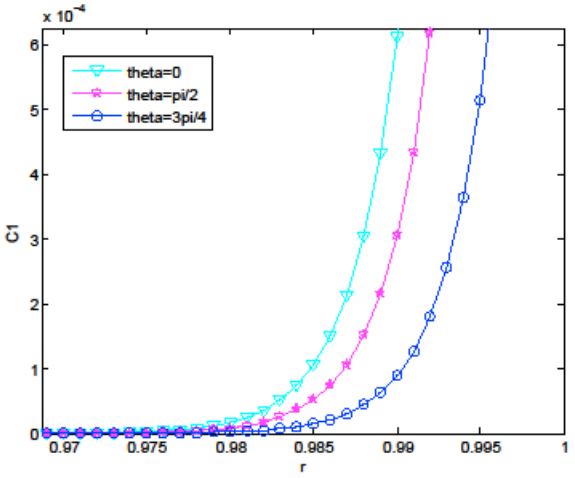

Figure 2.14: Etanidazole concentration versus radial variable in tumor tissue in the presence of cisplatin concentration and for several values of the latitudinal angle

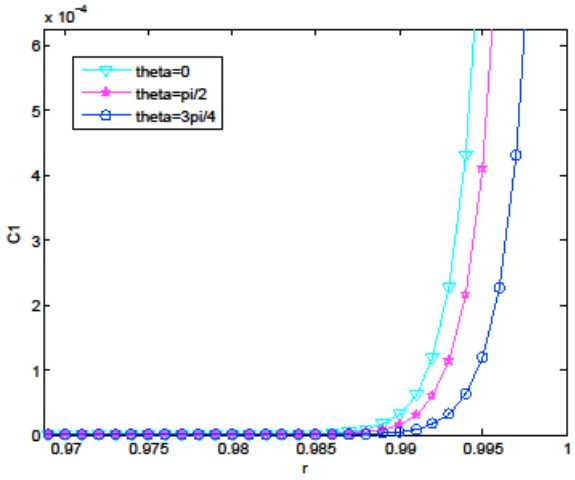

Figure 2.15: Etanidazole concentration versus radial variable in normal tissue in the presence of cisplatin concentration and for several values of the latitudinal angle

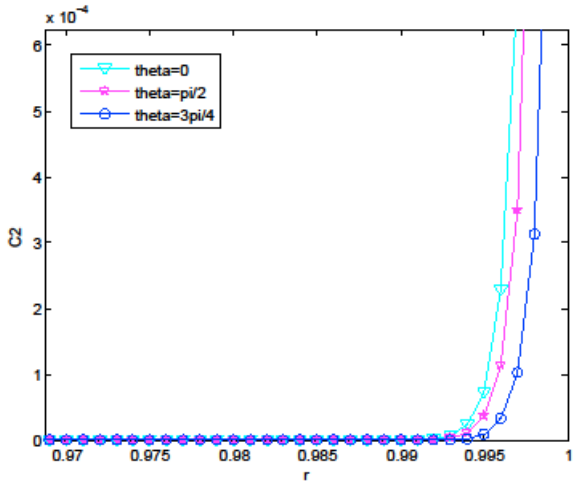

Figure 2.16: Cisplatin concentration versus radial variable in tumor in the presence of etanidazole concentration and for several values of the latitudinal angle

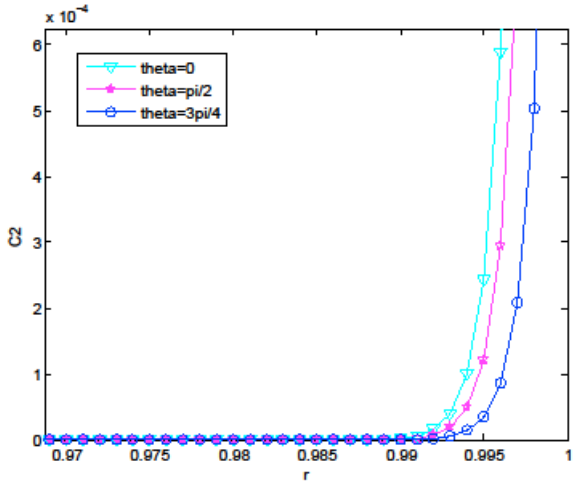

Figure 2.17: Cisplatin concentration versus radial variable in normal tissue in the presence of etanidazole concentration and for several values of the latitudinal angle

An inspection of our generated data for both drugs and in the presence of drug interactions indicated that the amount of etanidazole concentration in tumor is higher than that in normal tissue, while the amount of cisplatin in the normal tissue is higher than that in the tumor. In addition, concentration of etanidazole in both tissue is higher than that of cisplatin. Comparing the generated data for the results in figures 2.14 – 2.17 in the presence of drug interactions to those for the results in figures 2.3–2.6 in the absence of such interactions, we find that the values of the concentrations is each tissue are less in the presence of drug interactions as compare to those in the absence of such interactions. This result indicates that in the actual drug delivery mechanism to the patients, these can be a case where providing a secondary drug to the patient could adversely affect the transport of the primary drug to the patient's tumor thereby could adversely affect the patient's health conditions. We should also refer to the efficacy of a drug delivery system [13] that for a given radius it can depend, in particular, on the ratio of the values of the concentration for the tumor to that for the normal tissue. This ratio referred to as Therapeutic Index (TI) in relevant biomedical literature [13]. So, TI is a measure of the efficiency of the drug delivery, so that a higher value of TI indicates that higher amount of drug delivers to the tumor than to the normal tissue. In our results based on our

generated data for TI in the cases of etanidazole or cisplatin delivery, we conclude that drug delivery is more efficient in the tumor system if a second drug delivery also takes place simultaneously in the same tumor system. In the case of etanidazole, TI increases with decreasing the radial distance from the center, and it also increases with the latitudinal angle. However, in the case of cisplatin, TI increases with radial distance from the center and decreases with increasing the latitudinal angle. In addition, TI is much higher for etnidazole as compare to the case of cisplatin implying that etanidazole delivery is much more efficient which is due to its higher diffusivity parameter L_1 as compared to L_2. Hence, value of the diffusivity coefficient for each drug can be an important factor for the efficiency of the corresponding drug delivery in the tumor.

CHAPTER III

UNSTEADY CASE

Using 1.9 and 1.11 in 1.1-1.5, considering the non-dimensional system to the first order in ε and applying a Taylor series expansion about $r = 1$ for the boundary conditions at the outer surface of the tumor or normal tissue, we find the following equations and boundary conditions for the unsteady parts of the dependent variables:

$$\frac{\partial P_u}{\partial r} = u_u \tag{3.1}$$

$$\left(\frac{1}{r}\right)\left(\frac{\partial P_u}{\partial \theta}\right) = v_u \tag{3.2}$$

$$\left(\frac{1}{r^2 \sin\theta}\right)\left[\left(\frac{\partial}{\partial r}\right)\left(r^2 \sin\theta u_u\right) + \left(\frac{\partial}{\partial \theta}\right)\left(r \sin\theta v_u\right)\right] = -b_2 P_u \tag{3.3}$$

$$u_s \frac{\partial C_{1u}}{\partial r} + u_u \frac{\partial C_{1s}}{\partial r} + \frac{v_s}{r}\frac{\partial C_{1u}}{\partial \theta} + v_u \frac{\partial C_{1s}}{\partial r} = L_1\left\{\left[\left(\frac{1}{r^2}\right)\left(\frac{\partial}{\partial r}\right)\left(r^2 \frac{\partial}{\partial r}\right)\right] + \left[\frac{1}{r^2 \sin\theta}\right]\left(\frac{\partial}{\partial \theta}\right)\left[\sin\theta\left(\frac{\partial}{\partial \theta}\right)\right] C_{1u}\right\} - \hat{b}_3 C_{1u} - \hat{b}_4 C_{2u} \tag{3.4}$$

$$u_s \frac{\partial C_{2u}}{\partial r} + u_u \frac{\partial C_{2s}}{\partial r} + \frac{v_s}{r}\frac{\partial C_{2u}}{\partial \theta} + v_u \frac{\partial C_{2s}}{\partial r} = L_1\left\{\left[\left(\frac{1}{r^2}\right)\left(\frac{\partial}{\partial r}\right)\left(r^2 \frac{\partial}{\partial r}\right)\right] + \left[\frac{1}{r^2 \sin\theta}\right]\left(\frac{\partial}{\partial \theta}\right)\left[\sin\theta\left(\frac{\partial}{\partial \theta}\right)\right] C_{2u}\right\} - \hat{b}_5 C_{2u} - \hat{b}_6 C_{2u} \tag{3.5}$$

$$P_u + \frac{P_s}{\partial r} = C_{1u} + \frac{\partial C_{1s}}{\partial r} = C_{2u} + \frac{\partial C_{1s}}{\partial r} = 0 \quad r = 1 \tag{3.6}$$

Similar to the procedure and the method described in the previous section, we obtain the the solutions for the unsteady parts, which are lengthy and will not be given here. We then use these results as well as the solutions for the steady parts given in Chapter II to find the results for the total quantities.

3.1 RESULTS

In this section we will discuss the results obtained for the unsteady case. From figure 3.1 we have interstitial pressure versus the radial variable for the case where the latitudinal angle is $\frac{\pi}{2}$ and for both tumor and normal tissue. It can be seen from this figure that interstitial pressure increases with decreasing the radial variable, and it has a maximum at the center of both tumor and normal tissue, which indicates as if no significant radial flow can exist very close to the center of tumor or normal tissue. In addition, the interstitial pressure in the tumor is higher than that in the normal tissue, which is an indication of extra problem due to presence of tumor. The magnitude of the rate of change of the pressure is found to decreases with decreasing the radial variable for both cases of tumor and normal tissue. We also generated the results for the interstitial pressure versus r but for different values of the latitudinal angle such as $\theta = \frac{3\pi}{4}$ and find similar behavior as in the case of $\theta = \frac{\pi}{2}$ but with smaller values for both cases in the tumor and in the normal tissue.

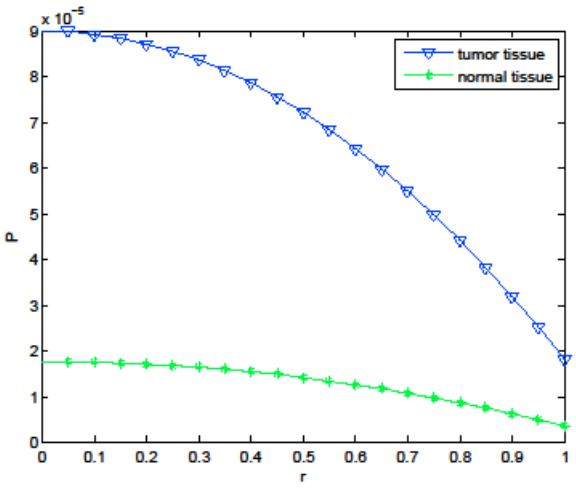

Figure 3.1: Interstitial pressure versus r for tumor and normal tissue with $\theta = \frac{\pi}{2}$

Figure 3.2 presents radial velocity of the flow versus the radial variable for both tumor and normal tissue and for $\theta = \frac{\pi}{2}$. As can been seen from this figure,$u < 0$ which is due to the fact that flow enters into the tumor or normal tissue from the boundary surface. The velocity profile appears

to be linear in the domain for r $(0 < r < 1)$, and its magnitude for tumor is higher than that for the tissue. It is also seen that $|u_0| \to 0$ as $r \to 0$ which is reasonable since the high interstitial pressure at the center put the motion into rest there. We also generated data for the radial velocity versus radial variable and for different values if the latitudinal angle such $\theta = \frac{3\pi}{4}$ and found that the magnitude of the latitudinal velocity is higher as compare to the corresponding magnitude for$\theta = \frac{\pi}{2}$.

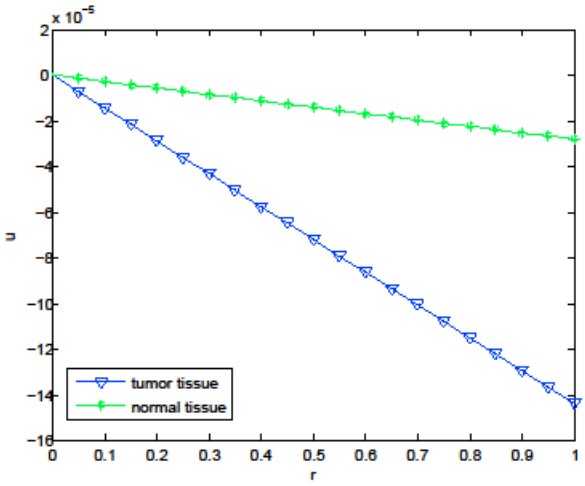

Figure 3.2: Radial velocity versus r for tumor and normal tissue with $\theta = \frac{\pi}{2}$

Figure 3.3 presents latitudinal component of velocity of the flow versus radial variable for both tumor and normal tissue at $\theta = \frac{\pi}{2}$. It can be seen from this figure that magnitude of the latitudinal velocity in the tumor is higher than the corresponding one in the normal tissue, and the value of the latitudinal velocity is negative and its magnitude increases with decreasing the radial variable. These results for the radial and latitudinal velocity components indicate that flow is mainly rotational and circulatory around the center of either tumor or normal tissue. We also generated data for the latitudinal velocity versus radial variable and for different values of the latitudinal angle such$\theta = \frac{3\pi}{4}$ and found that magnitude of such velocity component reduces as compared to the corresponding value for 1.

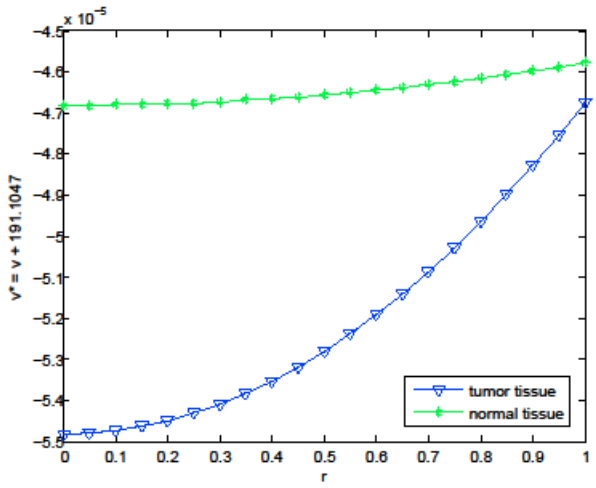

Figure 3.3: Latitudinal velocity versus r for tumor and normal tissue at $\theta = \frac{\pi}{2}$

Figure 3.4 presents etanidazole drug transport in tumor versus radial variable for several values of the latitudinal angle θ and in the absence of another drug transport.It can be seen from this figure that amount of transported drug decreases quickly with decreasing the radial variable and the amount is zero at the center of tumor. This result indicates that etanidazole is consumed mostly by the tumor near its boundary surface and not much is left to be transported more close to the center of the tumor. It is also apparent from this figure that the transported drug at high latitude domain is higher than either in mid- or low-latitude domain. The rate of change of the concentration with respect to the radial variable decreases with decreasing the radial variable, which is consistent due to the fact that the amount of drug delivery is less in the regions closer to the center of tumor. We also generated data for etanidazole concentration in normal tissue versus radial variable and for several values of the latitudinal angle. Again as in the case of tumor the amount of transported drug decreases quickly with decreasing the radial variable and the amount diminishes to zero at the center of the tissue. In addition, the amount transported in the tissue in high latitude region is higher than those transported in the mid- or low-latitude region, and the rate of decrease of the drug reduces as it approaches the center. However, a comparison of our calculated data for tumor and normal tissue indicated that the amount transported by this drug is lower in the normal tissue than

in the tumor, which may be contributed to the complexity of the tumor structure absorbing higher amount of such drug than in normal tissue.

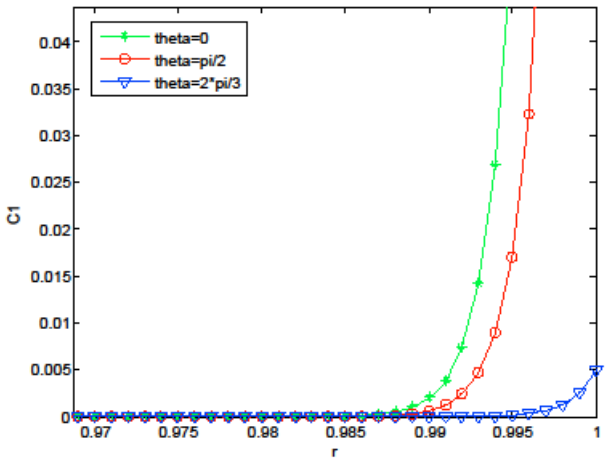

Figure 3.4: Etanidazole concentration in tumor versus r in the absence of other drug concentration and for several values of $\theta = 0, \frac{\pi}{2}$ and $\frac{2\pi}{3}$

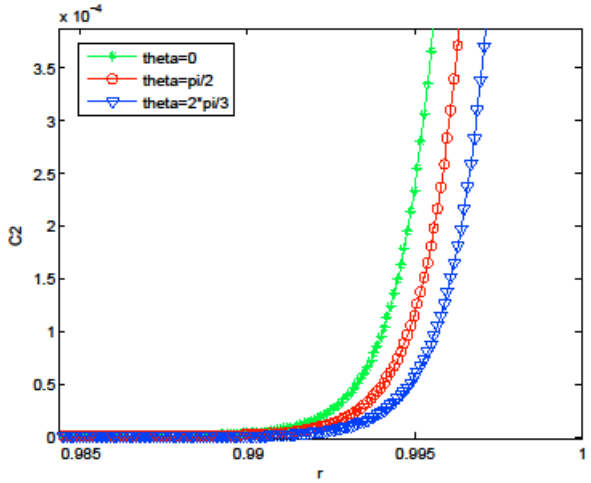

Figure 3.5: Cisplatin concentration in tumor versus r in the absence of other drug concentration and for several values of $\theta = 0, \frac{\pi}{2}$ and $\frac{2\pi}{3}$

It can be seen from these figure as well as from our additional generated data for the

corresponding normal tissue that amount of concentration diminishes quickly as it approaches center of the tumor tissue. The amount of delivery of cisplatin in high latitude is higher than those in mid or low latitude. Also closer inspection of our degenerated data indicated that the amount of cisplatin concentration in the normal tissue is higher than the one in the tumor, which indicated that the amount of drug consumed by either tumor or normal tissue depends on the type of drug concentration in such tissues. The results based on the generated data for the cisplatin concentration in each of the 2 tissues indicated that the amount of cisplatin drug in the normal tissue is higher than that in the tumor. Hence, the factors that can affect the amount of drug concentration in a tissue depends not only on the type of drug but also on the competing effect of the drug type versus tissue type. A comparison with the generated data for the etanidazole transport in each of the two tissues indicated that for the tumor amount of cisplatin concentration is less than that of etanidazole, while in the normal tissue amount of cisplatin concentration is higher than that of etanidazole, and so the result is based on the dominating effect of higher diffusivity of the drug as well as the structure of the type of tissue which is consumed by the drug.

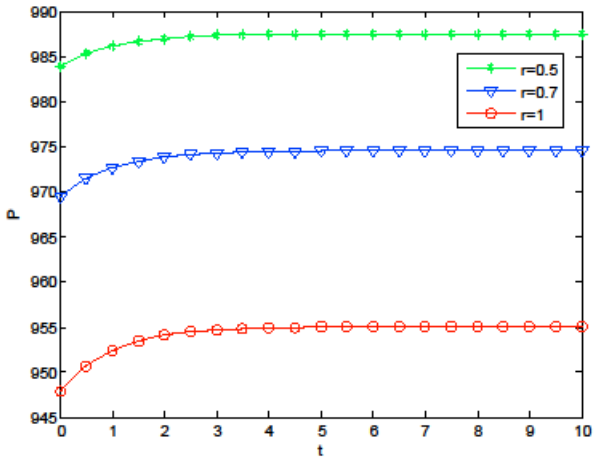

Figure 3.6: Interstitial pressure versus t for tumor at $\theta = \frac{3\pi}{4}$.

Figures 3.6 present respectively interstitial pressure, radial velocity and latitudinal velocity versus the time variable for tumor for different values of the radial variable r and for the latitudinal

angle $\theta = \frac{3\pi}{4}$ in the case of figure and$\theta = \frac{\pi}{2}$ in cases of velocity components. It can be seen from Figure 3.6 that the pressure increases with time inside the tumor, which indicates that the interstitial pressure builds up with time in the growing tumor. The results shown in figures 8 indicate that the radial velocity is negative, so that the radial flow is toward the tumor's center, and the magnitude of u increases with time. Our additional generated data for these quantities at different values of latitudinal angle such as$\theta = \frac{\pi}{2}$ for pressure and $\theta = \frac{3\pi}{4}$ in the cases of the velocity components indicate similar behavior but with higher value of the magnitude of pressureand lower values of the magnitudes of both $\theta = \frac{3\pi}{4}$. Our additional generated data for the velocity components at several different values of r and θ indicate flow circulation in the tumor. In addition, our additional generated data for these quantities in the normal tissue case indicate that the magnitude of the pressure and the velocity components are higher in the tumor than in the normal tissue, but the qualitative features of the results in the normal tissue are similar to those in the tumor.

Figures 3.7 and 3.8 present respectively concentrations of entaidazole and cisplatin in the tumor versus time for several values of r and $\theta = \frac{\pi}{2}$. It can be seen from these figures that the drug concentrations appear to decrease with time in the tumor, but the rate of decrease reduces with increasing time. Our additional generated data for these drug concentrations in the normal tissue indicated similar results, but the values of the concentrations in the normal tissue are slightly less than the corresponding ones in the tumor. Also our additional generated data for these quantities at $\theta = \frac{3\pi}{4}$ indicate similar behavior but with small values of the magnitude of the quantities. We also calculated the concentrations of drugs when both drugs are present in both tumor and normal tissues. Our generated data indicated that both concentrations again decrease with decreasing the radial variable and the value and the radial rate of change of each concentration is highest in the normal tissue and lowest in the tumor. Similar to the results presented before for the case in the absence of drug interaction, we found that the radial rate of change of each of these concentrations is higher close to the spherical boundary. Also these drug concentrations decrease with increasing time in both tumor and normal tissue. Additional inspection of our generated data for both drugs and in the presence of drug interactions indicated that the amount of etanidazole concentration in

tumor is higher than that in normal tissue, while the amount of cisplatin in the normal tissue is higher than that in the tumor.

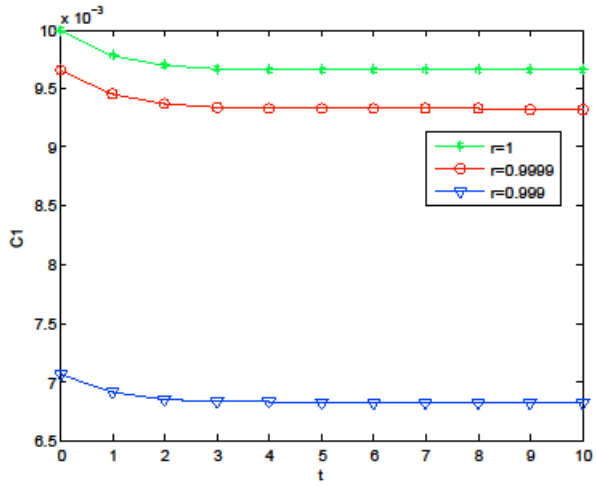

Figure 3.7: Etanidazole concentration in the tumor versus time at $\theta = \frac{\pi}{2}$.

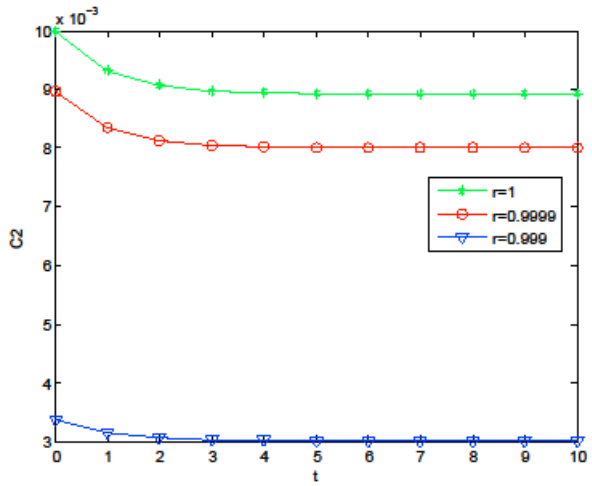

Figure 3.8: Cisplatin concentration in the tumor versus time at $\theta = \frac{\pi}{2}$.

In addition, concentration of etanidazole in both tissues is higher than that of cisplatin. We also find that the values of both concentrations in tumor are less in the presence of drug interactions, while values of these concentrations in the normal tissue are higher in the presence of

such interactions. This result indicates that in the actual drug delivery mechanism to the patients, these can be a case where providing a secondary drug to the patient could adversely affect the transport of the primary drug to the patient's tumor thereby could adversely affect the patient's health conditions. We should also refer to the efficacy of a drug delivery system (Tan et al. 2003) that for a given radius it can depend, in particular, on the ratio of the values of the concentration for the tumor to that for the normal tissue. This ratio referred to as Therapeutic Index (TI) in relevant biomedical literature [Tan et al., 2003]. So, TI is a measure of the efficiency of the drug delivery, so that a higher value of TI indicates that higher amount of drug delivers to the tumor than to the normal tissue. In our results based on our generated data for TI in the cases of etanidazole or cisplatin delivery, we conclude that drug delivery is more efficient in the tumor system if a second drug delivery does not takes place simultaneously in the same tumor system. In the case of etanidazolemor cisplatin, TI increases with decreasing the radial distance from the center, and it also increases with the latitudinal angle. In addition, TI is much higher for etnidazole as compare to the case of cisplatin implying that etanidazole delivery is much more efficient which is due to its higher diffusivity parameter L_1 as compared to L_2. Hence, value of the diffusivity coefficient for each drug can be an important facture for the efficiency of the corresponding drug delivery in the tumor.

CHAPTER IV

CONCLUSION

We investigated the problem of two-dimensional blood flow in a growing solid tumor by developing an analytical axisymmetric model for a spherical tumor or normal tissue under the assumption that the growth rate of the tumor is small but non-zero. We, thus, calculated the results for the main quantities such as interstitial pressure, interstitial radial and latitudinal components of blood flow velocity vector and concentrations of two different drugs in the present paper. We found that the interstitial blood pressure in the tumor is, in general, higher than that in the normal tissue, and the pressure increases with time in both tumor and normal tissue. The magnitude of the blood velocity vector was also found to be higher in the tumor than in the normal tissue, and it is found that the magnitude of the velocity vector decreases with increasing time in both tumor and normal tissue. Our results indicated, in general, presence of blood flow circulation in the tumor and to lesser intensity in the normal tissue. We also calculated the values of concentrations of two drugs (etanidazole and cisplatin) in the presence of both drugs and found, in particular, that both drug concentrations deccrease with increasing time but the rate of such decrease reducses with increasing time. The amount of etanidazole concentration at any internal location of tumor or normal tissue is found to be higher than the corresponding value of the cisplatin concentration. The amount of etanidazole or cisplatin concentration at any internal location of the tumor is found to be higher than the corresponding one in the normal tissue. The presence of both drugs that can produce interactive effects, can reduce the efficiency of the drug delivery in the tumor system, while the value of the therapeutic index is increased if only one drug is delivered. Also value of the diffusivity coefficient for a drug has important effect on the amount of the efficiency of the drug delivery in the

tumor system. The theoretical model developed and investigated here can be further extended and involved to apply to fully three dimensional solid tumors and normal tissues in terms of properties and geometrical configurations. Another extension can be to predict the effect that the rate of drug delivery to the tumor site can have on the tumor growth for the actual operating and drug conditions in the medical cases for the solid tumor patients.

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BIOGRAPHICAL SKETCH

Adriana Gracia was born in Pharr, Texas on April 23, 1991 and raised in Edinburg, TX. She is the oldest of four children born to her parents Mr. Rogelio Gracia Cantu and Mrs. Rosalva Gracia Perez. She is married to Mr. Erik Estrada and has a beautiful daughter named Analia. She received her B.S. in Mathematics with Applied Mathematics Concentration on December 2012 from The University of Texas-Pan American, and obtained her M.S. in Applied Mathematics on December 2014. For correspondence she may be reached at adrianagracia23@gmail.com or 10118 Cibolo Dr. Edinburg, TX 78542.