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Mathematical Modeling of Two-dimensional Unsteady Flow in Growing Tumor

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Abstract

We investigate the problem of unsteady fluid flow in growing solid tumors. We develop a mathematical model for a growing tumor whose boundary is taken as a sphere, and the unsteady fluid flow within the tumor is assumed to be two dimensional with respect to the radial distance and the latitudinal angle in spherical coordinates. The expressions for the time, radial and latitudinal variations of the flow velocity, pressure, and the two investigated drug concentrations within the tumor were determined analytically. We calculated these quantities in the tumor as well as in a corresponding normal tissue. We find, in particular, that blood pressure in the tumor would be higher than that in the normal tissue, and there could be blood flow circulation in the tumor. For a given spatial location in the tumor, the amount of drug delivered to the growing tumor decreases first with time, but then the rate of decrease reduces with further increase in time. The Therapeutic Index, which is a measure of the efficiency of drug delivery in the tumor in the biomedical science, is determined for different values of the parameters and discussed in the absence or presence of the drugs' interactions which may exist in the presence of the two drugs in the tumor. The main results of our model agree with the available experiments.

Keywords: Tumor; Brain tumor; Spherical tumor; Drug concentration; Fluid flow; Drug delivery; Solid tumor

MSC 2010: 92C10, 76Zxx, 92Bxx, 76S99

1. Introduction

Cancer is the second leading cause of death in the American continent (Jain 2005). The most major treatment is surgical removal of the tumor, but there could be residual tumor cells and the re-growth of these tumor cells, a is very common occurance. 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. As can be indicated from the medical and experimental observations, 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 transportation to the affected area and drug change or reaction at the tumor site. Many drugs cannot be delivered to their targets because of the observed transportation limitations. 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 fluid transport in the tumors (Baxter and Jain, 1989, 1990, 1991; Saltzman and Radomsky, 1991; Tan et al., 2003; Soltani and Chen, 2011; Stylianopoulos and Jain, 2013; Zhan and Xu, 2013; Sefidgar et al., 2014; Sriraman et al., 2014).

The above studies as well as additional ones (Wang and Li, 1998; Byrne and Preziosi, 2003; Teo et al., 2005; Zhao et al., 2007) have been mostly about solid tumors in the brain. 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 reduces the negative effects of malignant tumors.

Very recently Riahi and Roy (2014) developed a one dimensional mathematical model of a stationary brain tumor, and they considered steady state features of the fluid flow within the non-growing tumor, which was assumed to be only in one-dimensional direction of the radial distance from the center of the tumor to a location within the tumor. The authors determined the radial velocity and the pressure as functions of the distance from the center of tumor, and, in addition, the radial variations of a drug concentration in the presence or absence of another drug within the systems. However, it should be noted that purely one-dimensional dependence of the flow quantities and the drug concentration as considered in Riahi and Roy (2014) is rather too simplistic and not realistic in the biomedical applications. In addition, the authors ignored the singularity at the center of the tumor that existed in their equation for the pressure, which cannot be justified in general. Earlier Roy and Riahi (2013) considered the same one-dimensional case and did some time-dependent computation, but again the model was too idealistic and incomplete as in their work in (2014).

The present investigation develops a two-dimensional unsteady model by significantly extending the one-dimensional work of Riahi and Roy (2013), where the velocity vector is considered to have, in general, two components along with 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. In addition, we apply the proper mathematical method of approach to take into account effectively for the singularity effect that exists at the center of tumor for the governing equations for the pressure and the drug concentrations. This is the first theoretical investigation of its kind to probe a for such new mathematical model in order 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 results 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 due to Riahi and Roy (2013). 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 the 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 applied mathematical 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.

2. Governing system

We consider a tumor in the shape of a sphere with radius $R`$ ($t`$) and a spherical coordinate system whose origin lies at the center of tumor, with the radial $r`$-axis positively outward from the origin and latitudinal angle $\theta$, which is measured with respect to the polar axis of the sphere. Here $t`$ is a time variable. Figure 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 xoy-plane are also shown.

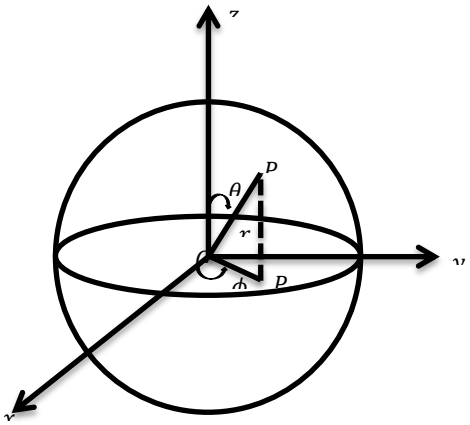

Figure 1. Geometry of the spherical tumor and coordinate system.

The non-dimensional radius and the radial coordinate of the spherical tumor are designated by R and r, respectively, while the latitudinal and azimuthal angles of the spherical coordinates are designated by θ and ϕ, respectively.

We assume that the growth rate of the tumor is small and positive ($0<\partial R` /\partial t`<<1$). We consider the governing equations for the fluid flow in the tumor or the corresponding normal tissue (Tan et al., 2003; Soltani and Chen, 2011), which basically are the Darcy-momentum equation, the mass continuity equation in the presence of sinks and sources, that may be appropriate for the fluid in the tumor (Baxter and Jain, 1989) and the sources and sinks part is based on the Starling's law and the fluid productions by cells due to metabolism (Tan et al., 2003), and the equations for the concentrations of two drugs. These governing equations with the necessary boundary conditions, which turn out to be needed in the present analytical procedure, are given below

$$(\mu/k)\mathbf{u}` = -\nabla P`, \tag{1a}$$

$$\nabla.\mathbf{u}` = a_1 - a_2 P`, \tag{1b}$$

$$(\partial/\partial t` + \mathbf{u}`.\nabla)C_1 = D_1\nabla^2 C_1 - a_3 C_1 - a_4 C_2, \tag{1c}$$

$$(\partial/\partial t` + \mathbf{u}`.\nabla)C_2 = D_2 \nabla^2 C_2 - a_5 C_1 - a_6 C_2, \tag{1d}$$

$$P` = P_B`,\ C_i = C_{Bi}` \text{ at } r` = R`(t`),\ (i=1, 2), \tag{1e}$$

where $\mathbf{u}`$ is the fluid velocity vector in the tumor, $P`$ is the associated pressure, $P_B`$ is a non-zero quantity, which can be a constant for a function of θ, μ is dynamic viscosity, k the permeability, a_1 and a_2 constants whose expressions are given in Tan et al. (2003). The C_i (i=1, 2) are the concentrations of the two drugs with diffusion coefficients D_i, $C_{Bi}`$ constants, and a_i (i = 3, …, 6) represent source or sink terms in the concentration equations, which can be due to the presence of either one or two drugs and, in general, can be variable (Jackiewicz et al., 2009). As explained in Tan et al. (2003), such source and sink terms may undergo 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. Following the best known model for the volume of a tumor as a function of the time variable (Steel, 1977; Kansal, et al., 2000), we derive the following model for the time-dependent radius of the slowly growing tumor as

$$R`(t`) = R_0\, exp\{\varepsilon[1-exp(-\varepsilon\alpha` t`)]\}, \tag{1f}$$

where ε is a small parameter ($\varepsilon<<1$) of the order of magnitude of the relative growth rate of the tumor, R_0 is the constant radius of the tumor in the absence of its growth and $\alpha`$ 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 $(1/R`)\partial R` /\partial t` = o(\varepsilon)<<1$.

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 azimuthal direction of the spherical coordinate system. We make the governing system (1) dimensionless by using length scale R_0, time scale $R_0^2/(\varepsilon\nu)$, where $\nu\equiv\mu/\rho$ is kinematic viscosity and ρ is fluid density, velocity scale ν/R_0 and pressure scale $\nu^2\rho/k$, so that the dimensional forms of the variables and R are related to their non-dimensional counterpart by

$$(r`, t`, \mathbf{u}`, P`, R`)=\{R_0\, r, [R_0^2/(\varepsilon\nu)]t, (\nu/R_0)\mathbf{u}, (\nu^2\rho/k)P, R_0\, R\}. \quad (2)$$

We now want to apply a perturbation expansion in powers of small ε ($\varepsilon<<1$) by assuming that the growth rate of increase of the tumor's radius with respect to time is small. This implies that we can apply a Taylor series expansion for $R(t)$ about $R=1$ and keep only the leading order terms up to the second order in ε, this gives

$$R(t)=1+\varepsilon[1-\exp(-\alpha t)]+o(\varepsilon^2), \quad (3a)$$

where $\alpha=\alpha`\, R_0^2/\nu$ is a non-dimensional constant. As can be seen from (1a), (1e) and (3a), the boundary conditions for the dependent variables at $r=R$ can be in terms of the steady part and unsteady part. The form of (3a) then dictates that the solution for the time dependent parts of the dependent variables should be of the form of the unsteady part for R given in (3a). Hence, applying the perturbation expansion in powers of ε of the dependent variables, R can be in the form

$$(\mathbf{u}, P, C_1, C_2, R) = [\mathbf{u}_s(r, \theta), P_s(r, \theta), C_{1s}(r, \theta), C_{2s}(r, \theta), 1] + \varepsilon[\mathbf{u}_u(r, \theta), P_u(r, \theta), C_{1u}(r, \theta), C_{2u}(r, \theta), 1][1-\exp(-\alpha t)] + o(\varepsilon^2), \quad (3b)$$

where the subscript "*s*" and "*u*" refer to the leading order steady part and the unsteady part, respectively, for each dependent variable.

3. Analysis and solutions for steady parts

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, then to the leading order approximation, which corresponds to the lowest order in ε ($\varepsilon<<1$) in (3), we analyze and determine the solutions for the steady state parts of the flow quantities. Thus, we set $\varepsilon=0$ in (3) and then use (3) together with (2) in (1) to find the following simplified non-dimensional form of the axisymmetric system in the spherical coordinates that will be investigated in the first part of this paper:

$$-\partial P_s/\partial r = u_s, \quad (4a)$$

$$-(1/r)(\partial P_s/\partial\theta) = v_s, \tag{4b}$$

$$[(\partial/\partial r)(r^2 \sin\theta\, u_s)+(\partial/\partial\theta)(r \sin\theta\, v_s)]=b_1 - b_2 P_s, \tag{4c}$$

$$u_s\partial C_1/\partial r +(v_s/r)(\partial C_{1s}/\partial\theta = L_1 \{[(1/r^2)(\partial/\partial r)(r^2 \partial C_{1s}/\partial r)] + [1/(r^2\sin\theta)] (\partial/\partial\theta)[\sin\theta(\partial/\partial\theta)]C_{1s}\} -\hat{b_3} C_{1s} - \hat{b_4} C_{2s}, \tag{4d}$$

$$u_s\partial C_{2s}/\partial r +(v_s/r)(\partial C_{2s}/\partial\theta = L_2\{[(1/r^2)(\partial/\partial r)(r^2 \partial C_{2s}/\partial r)]+[1/(r^2\sin\theta)](\partial/\partial\theta)[\sin\theta(\partial/\partial\theta)]C_{2s}\} -\hat{b_5} C_{1s} - \hat{b_6} C_{2s}, \tag{4e}$$

$$P_s=\hat{P_B}, C_{is} = C_{Bi} \text{ at } r=1, (i=1, 2), \tag{4f}$$

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 **u**, P_s is the steady part of the pressure, $L_1 = D_1/\nu$ and $L_2 = D_2/\nu$ are the non-dimensional diffusion parameters for the two drug concentrations, and C_{1s} and C_{2s} are the leading steady parts of the two concentrations, respectively, $b_1=a_1 R_0^2/\nu$, $\hat{b_i} = a_i R_0^2/\nu$ (i =3, 4, 5, 6), $b_2 = a_2\nu R_0^2/k$, $\hat{P_B} = P_B` k/(\rho\nu^2)$ and C_{Bi} are the boundary conditions for the leading parts of the concentrations.

Using (4a-b) in (4c), we found the equation for the steady part of the fluid pressure which simplified to the form

$$(1/r^2)(\partial/\partial r)(r^2\partial P_s/\partial r)+(\cot\theta/r^2)(\partial P_s/\partial\theta)+(1/r)(\partial^2 P_s/\partial\theta^2)=-b_1+b_2P_s. \tag{5}$$

This is a second order linear partial differential equation for P_s in r and θ whose coefficients depend on the r and θ and, thus, are variable. We have searched for the solution of (5) using analytical approaches and the successful one was detected to be based on a new mathematical procedure, which can be classified as a type of the method of separation of variables. We assume $P_s = S(r)+T(r)Q(\theta)$, where S, T and Q are unknown functions. We use such a form for P_s in (5) and found the equation for S separates from that for TQ. The resulting ordinary differential equation for S is then given below by (7a). For the remaining equation for TQ, we divide the equation by $Q(\theta)$ and simplify the resulting equation. We find that it leads to an ordinary differential equation for T but with r- and θ-dependent coefficient for T. Since the solution for T should depend only on r, we need to assume that the θ-dependent part of this coefficient is a constant. This leads to a linear ordinary differential equation for Q in θ whose solution is found to be cosθ. Thus, the equation (5) admits solution in the form

$$P_s(r, \theta) = S(r)+T(r)\cos\theta, \tag{6}$$

where the unknown functions S and T need to be determined. Using (6) in (5), we obtain the following equations for these functions

$$(d^2S/dr^2)+(2/r)(dS/dr)-b_2S=-b_1, \quad (7a)$$

$$(d^2T/d\,r^2)+(2/r)(dT/d\,r)+[-b_2+2/(r^2)]T=0. \quad (7b)$$

The ordinary differential equations (7a-b) 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 (Zill, 2013). This method represents a power series solution for the dependent variable satisfying the respective differential equation. Applying the method of Frobenius for (7a-b), 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 all proportional to the coefficient b_2 or its positive-integer powers, and since b_2 is generally quite small of $O(10^{-7})$ or smaller as evidenced in the experimental and biomedical applications (Tan et al., 2003), a very good approximated solution for $P_s(r, \theta)$ is then given by

$$P_s(r, \theta) = e_0\,[1+(b_2/6)r^2+(b_2^2/120)r^4]+e_1\,[r+(b_2/10)r^3+(b_2^2/280)r^5]\cos\theta, \quad (8a)$$

where the constants e_0 and e_1 are to be determined by the boundary condition $P_B^{\wedge}$ on the outer surface of the solid tumor for P_s.

In the simplest form the fluid pressure boundary condition for the steady part at r=1 can be a constant. However, in more realistic cases, one may expect that the value of the pressure at 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 accordance with the solution for the pressure in the form (6) and for the present analytical study we consider the pressure condition on the boundary to be a weakly varying function with respect to θ in the form

$$P_B^{\wedge}=P_B\,(1+\delta\cos\theta). \quad (8b)$$

Here δ is a sufficiently small constant parameter (δ<<1). Using (8b) in (8a), we find

$$e_0=[P_B-(b_1/b_2)]/[1+(b_2/6)+(b_2^2/120)],\ e_1=\delta P_B/[1+(b_2/10)+(b_2^2/280)]. \quad (8c)$$

Using (8a-c) in (4a-b), we find the following expressions for the radial and latitudinal components of the flow velocity:

$$u_s(r, \theta) =e_0\,[(b_2/3)r+(b_2^2/30)r^3]+e_1\,[1+(3\,b_2/10)r^2+(5\,b_2^2/280)r^4]\cos\theta, \quad (9a)$$

$$v_s(r, \theta)=e_1\,[-1-(b_2/10)r^2-(b_2^2/280)]\sin\theta. \quad (9b)$$

Next, we consider the equations (4d-e) for the drug concentrations. Using (9a-b) in these equations and to the leading order in δ, the equations (4d-e) become linear partial

differential equations with coefficients that can vary with respect to r and θ. Following our mathematical method of approach for finding the analytical solution that we applied for the equation (5) for P_s, which turned out to be under the category of the method based on the separation of variables, we apply a similar approach by considering the solutions for C_1 and C_2 to be in the form

$$(C_{1s}, C_{2s})=[C_3(r), C_5(r)]\cos\theta+[C_4(r), C_6(r)], \tag{10}$$

where C_i (i=3, 4, 5, 6) are unknown functions of r. Using (10) in (4d-e), following similar approach to that of the equation (5) for P_s and simplifying to the leading order terms in δ (δ<<1), we find the following ordinary differential equations for C_i (i=3, 4, 5, 6):

$$(-u_2 r + u_3 r^3) DC_3 = L_1 [(2/r)D + D^2 - (2/r^2) - (b_3^\wedge)]C_3 - b_4^\wedge C_5, \tag{11a}$$

$$(-u_2 r + u_3 r^3) DC_4 = L_1 [(2/r)D + D^2 - b_3^\wedge]C_4 - b_4^\wedge C_6, \tag{11b}$$

$$(-u_2 r + u_3 r^3) DC_5 = L_2 [(2/r)D + D^2 - (2/r^2) - b_6^\wedge]C_5 - b_5^\wedge C_3, \tag{11c}$$

$$(-u_2 r + u_3 r^3) DC_6 = \mathrm{L}\,[(2/r)D + D^2 - b_6^\wedge]C_6 - b_5^\wedge C_4, \tag{11d}$$

where $D \equiv (\partial/\partial r)$ and

$$(u_2, u_3) \equiv (-1, b_2/10)(b_2/3)[P_B - (b_1/b_2)]/[1 + (b_2/6) + (b_2^2/120)]. \tag{11e}$$

We now notice that equations (11a-d) are basically of the sort of equations containing regular singular point at r=0, and so we apply again the method of Frobenius to find the solutions for these equations (11a-d). First for the case of zero interaction between the two drugs, we have to set $b_4^\wedge = b_5^\wedge = 0$ and then rescale $b_i^\wedge = b_i / r^2$ (i=3, 6), where b_i are constants. The above rescaling y was based on the observation that the sources can be variable (Jackiewicz et al., 2009), and it is found that such rescaling could be reasonable to obtain the only possible non-trivial analytical solutions whose results agree qualitatively with the experimental observations (Tan et al., 2003). Similar to the reasoning described before to find the solutions for S and T and consequently for P_s in (8a), the solutions for C_{is} (i=3, 4, 5, 6) are then determined as given below

$$\begin{aligned} &C_3(r) = 2 e_2 r^{L3} (1 + L_4 r^2), \\ &L_3 \equiv [-L_1 + (9 L_1^2 + 4 b_3 L_1)^{0.5}]/(2 L_1), \\ &L_4 \equiv -u_2 L_3 / [L_1 (L_3 + 2)(L_3 + 3) - (2L_1 + b_3)], \end{aligned} \tag{12a}$$

$$\begin{aligned} &C_4(r) = 2 e_3 r^{L5} (1 + L_6 r^2), \\ &L_5 \equiv [-L_1 + (L_1^2 + 4 L_1 b_3)^{0.5}]/(2 L_1), \\ &L_6 \equiv -u_2 L_5 / [L_1 (L_5 + 2)(L_5 + 3) - b_3], \end{aligned} \tag{12b}$$

$$C_5(r)=2\, e_4\, r^{L7}\,(1+ L_8\, r^2),$$
$$L_7 \equiv[-L_2 +(9\, L_2^{\,2} +4\, L_2\, b_6\,)^{05}]/(2\, L_2\,),$$
$$L_8 \equiv -u_2\, L_7\, /[L_2\,(L_7 +2)(L_7 +3)- (2\, L_2 +b_6\,)], \qquad (12c)$$

$$C_6(r\,)=2\, e_5\, r^{L9}\,(1+L_{10}\, r^2),$$
$$L_9 \equiv[-L_2 +(L_2^{\,2} +4\, L_2\, b_6\,)^{0.5}\,]/(2\, L_2),$$
$$L_{10} \equiv -u_2\, L_9\, /[L_2\,(L_9 +2)(L_9 +3)-b_6\,]. \qquad (12d)$$

Using (12a-d) in (10), we find the solution for the drug concentrations C_1 and C_2.in the absence of interactions between them.

Next, for the case of non-zero interactions between the two drugs, we need to consider non-zero values for $b_4^{\wedge}$ and $b_5^{\wedge}$, and following the same arguments made earlier for rescaling $b_3^{\wedge}$ and $b_6^{\wedge}$, we rescale $b_4^{\wedge} = b_4\, r^{-2+L3-L7}$ and $b_5^{\wedge} = b_5\, r^{-2+L9-L5}$, where b_i (i=4, 5) are given constants. Using these in (11a-d), we find that the same solutions given by (12a-d) are valid, provided we replace b_3 and b_6 in the expressions for these solutions by ($b_3 + b_4$) and [$b_6 + b_5\,(e_5\,/e_3$)], respectively.

4. Analysis and solutions for unsteady parts

Using (2) and (3b) in (1a)-(1e), 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, which we assume to have the same spherical boundary as in the case of tumor, we find the following equations and boundary conditions at the order ε for the unsteady parts of the dependent variables:

$$-\partial P_u/\partial r = u_u, \qquad (13a)$$

$$-(1/r)(\partial P_u/\partial\theta) = v_u, \qquad (13b)$$

$$[1/(r^2\sin\theta)][(\partial/\partial r)(r^2\sin\theta\, u_u)+(\partial/\partial\theta)(r\sin\theta\, v_u)] = -b_2\, P_u, \qquad (13c)$$

$$u_s\partial C_{1u}/\partial r + u_u\partial C_{1s}/\partial r + (v_s/r)\partial C_{1u}/\partial\theta + v_u\partial C_{1s}/\partial r$$
$$= L_1\{(1/r^2)(\partial/\partial r)(r^2\partial/\partial r)+[1/(r^2\sin\theta)]\,(\partial/\partial\theta)(\sin\theta\partial/\partial\theta)\}C_{1u}$$
$$-b_3{\wedge}\, C_{1u} - b_4{\wedge}\, C_{2u}, \qquad (13d)$$

$$u_s\,\partial C_{2u}/\partial r + u_u\,\partial C_{2s}/\partial r + (v_s/r)\partial C_{2u}/\partial\theta + v_u\partial C_{2s}/\partial r$$
$$= L_2\,\{(1/r^2)(\partial/\partial r)(r^2\,\partial/\partial r)+[1/(r^2\sin\theta)]\,(\partial/\partial\theta)(\sin\theta\partial/\partial\theta)\}C_{2u}$$
$$-b_5{\wedge}\, C_{1u} - b_6{\wedge}\, C_{2u}, \qquad (13e)$$

$$P_u + \partial P_s/\partial r = C_{1u} + \partial C_{1s}/\partial r = C_{2u} + \partial C_{1s}/\partial r = 0 \text{ at } r = 1. \qquad (13f)$$

Similar to the procedure and the mathematical method described in detail in section 3 for the steady parts, we also are able to obtain the solutions for the unsteady parts of the dependent variables, which are too lengthy and will not be given here. We then use these solutions as well as the solutions for the steady parts of the dependent variables given in the section 3 in (3b) to find the results for the total quantities which we refer to for P, u, v, C_1 and C_2. The results for the total quantities are then presented and discussed in the next section 5.

5. Results and discussion

We calculated the main quantities in (3), the velocity, the pressure and the concentrations for 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 necessary constants such as the arbitrary constants e_i (i=0, 1, 2, 3, 4, 5) in the steady parts of the solutions (8a), (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 relevant literatures on biomedical applications (Jain and Baxter, 1988; Boucher and Jain, 1992; Zhang, Luck, Dewhirst and Yuen, 2000; Tan et al., 2003; Soltani and Chen, 2011). The non-dimensional values of the constant coefficients b_i (i=1, …, 6), the boundary values P_B , C_{Bi} (i=1, 2) and the diffusion parameters L_i (i=1, 2) are given in Table 1.

Table 1. Non-dimensional values of the quantities that are used in the calculation

Quantities	Tumor values	Normal tissue values
b_1	$2.218032(10^{-7})$	$2.92248(10^{-5})$
b_2	$4.22(10^{-7})$	$0.54\ (10^{-7})$
b_3	1.662	0.212
b_4	0.01662	0.00212
b_5	1.662	0.212
b_6	0.01662	0.00212
C_{B1}	0.01	0.01
C_{B2}	0.01	0.01
L_1	$1.4175(10^{-6})$	$0.525(10^{-6})$
L_2	$1.4175(10^{-8})$	$0.525(10^{-8})$
P_B	0.25	0.25

The value of the constants α and ε given in (3b) are set, respectively as 1 and 0.1. For the two drug concentrations we chose etanidazole, which is used for cancer patients to regulate the level of oxygen concentration in the tissue so that radiotherapy would be applicable to destroy the malignant cells, and cisplatin which is a kind of chemotherapy drug.

Figure 2 presents the fluid pressure versus the radial variable for the case where the latitudinal angle is $\pi/2$ and for both tumor and normal tissue.

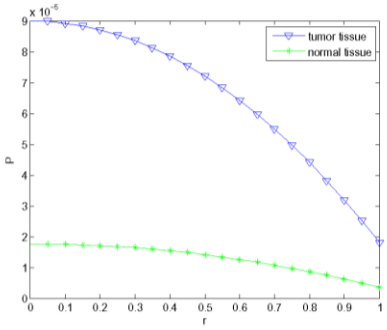

Figure 2. Pressure versus r for tumor and normal tissue with $\theta=\pi/2$

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

Figure 3 presents the radial velocity of the flow versus the radial variable for both tumor and normal tissue and for $\theta = \pi/2$.

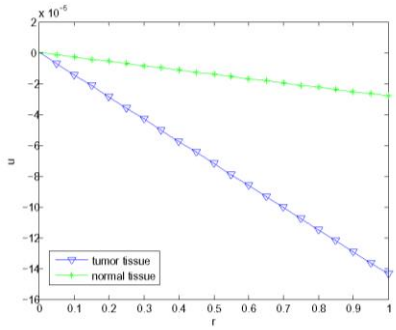

Figure 3. Radial velocity versus r for tumor and normal tissue with $\theta = \pi/2$

As can be seen from this figure, $u < 0$ which is due to the fact that the 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 $|u_0|\rightarrow 0$ as $r\rightarrow 0$ which is reasonable since the high 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 of the latitudinal angle such as $\theta = 3\pi/4$ and

found that the magnitude of the latitudinal velocity is higher as compared to the corresponding magnitude for $\theta = \pi/2$.

Figure 4 presents the latitudinal component of the velocity of the flow versus the radial variable for both tumor and normal tissue at $\theta = \pi/2$. It can be seen from this figure that the 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 radial variable. These results for the radial and latitudinal velocity components indicate that the flow is mainly rotational and circulatory around the center of either tumor or normal tissue. We also generated data for the latitudinal velocity versus the radial variable and for different values of the latitudinal angle such as $\theta = 3\pi/4$ and found that magnitude of velocity component reduces as compared to the corresponding value for $\theta = \pi/2$.

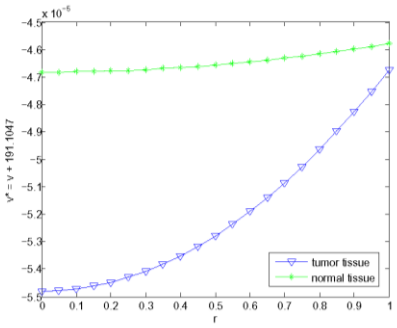

Figure 4. Latitudinal velocity versus *r* for tumor and normal tissue at θ=π/2

Figure 5 presents etanidazole drug transport in tumor versus the radial variable for several values of the latitudinal angle θ and in the absence of another drug transport.

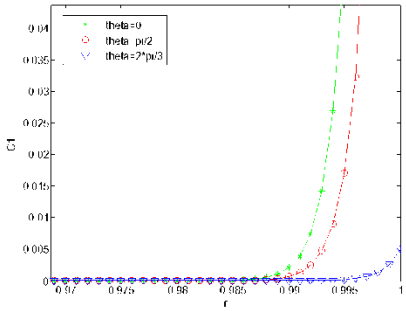

Figure 5. Etanidazole concentration in tumor versus *r* in the absence of the other drug concentration and for several values of $\theta = 0, \pi/2$ & $2\pi/3$

It can be seen from this figure that the amount of transported drug decreases quickly with decreasing radial variables and the amount is zero at the center of tumor. This result, which also agrees with the biomedical evidence (Soltani and Chen, 2011), 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 a 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 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 radial variable and the amount diminishes to zero at the center of the tissue. In addition, the amount transported in the normal tissue in a 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 due contributed to the complexity of the tumor structure absorbing higher amount of drug than normal tissue.

Figures 6 presents drug concentration of cisplatin in tumor versus radial variable and for several values of the latitudinal angle.

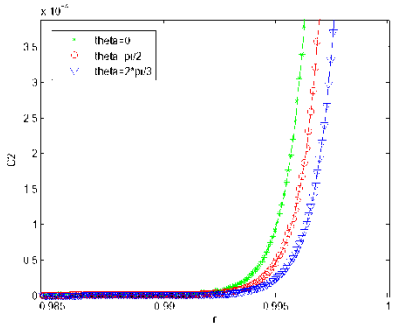

Figure 6. The same as in figure 5 but for cisplatin concentration

It can be seen from this figure, as well as from our additional generated data for the corresponding normal tissue that the amount of concentration diminishes quickly as it approaches the 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 generated 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 depend 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 the amount of cisplatin concentration is less than that of etanidazole, while in the normal tissue the 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 7-9 present respectively 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 $\theta = 3\pi/4$ in the case of Figure 7 and $\theta = \pi/2$ in the cases of Figures 8-9. It can be seen from Figure 7 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 t. The results shown in Figure 9 indicate that the latitudinal velocity is negative, so that the latitudinal flow is toward tumor's South-pole, and the magnitude of v decreases with increasing t. Our additional generated data for these quantities at different values of latitudinal angle such as $\theta = \pi/2$ for pressure and $\theta = 3\pi/4$ in the cases of the velocity components indicate similar behavior but with higher value of the magnitude of pressure and lower values of the magnitudes of both $\theta = 3\pi/4$. 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.

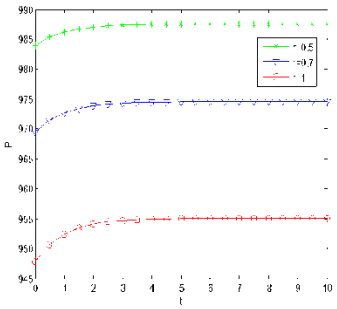

Figure 7. Pressure versus t for tumor at $\theta = 3\pi/4$

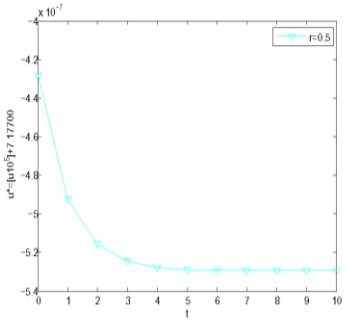

Figure 8. The same as in Figure 7 but for radial velocity

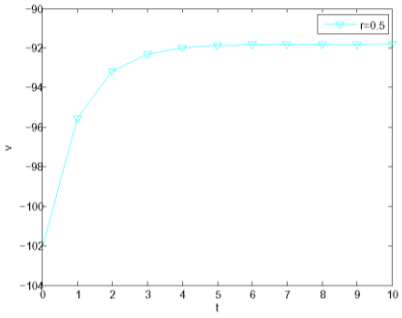

Figure 9. The same as in figure 7 but for latitudinal velocity

Our results for the pressure, the velocity and drug concentration that we described so far agree qualitatively with the available experimental results and biomedical evidence (Jain, 1987; Baxter and Jain, 1989; Boucher et al., 1990; Jain et al., 2007; Soltani and Chen, 2011).

Figures 10 and 11 present respectively concentrations of etanidazole and cisplatin in the tumor versus time for several values of r and $\theta = \pi/2$.

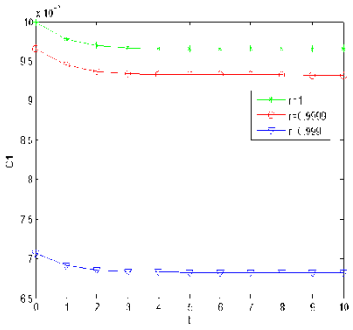

Figure 10. Etanidazole concentration in the tumor versus time at $\theta = \pi/2$

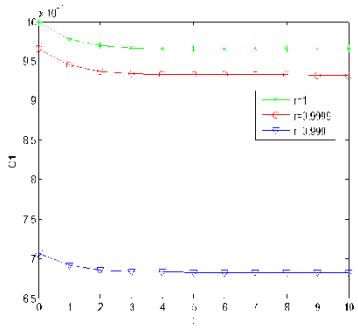

Figure 11. The same as in figure 10 but for cisplatin concentration

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 $\theta = 3\pi/4$ indicate similar behavior but with smaller 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 radial variable and the value and the radial rate of change of each concentration is higher in the normal tissue than 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 the tumor is higher than that in the 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 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, there 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 and 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 the Therapeutic Index (TI) can be found in the relevant biomedical literature (Tan et al., 2003). Thus, 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 etanidazole or cisplatin, the TI increases with decreasing radial distance from the center, and it also increases with the latitudinal angle. In addition, TI is much higher for etanidazole as compared 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 the diffusivity parameter L_2 for cisplatin. 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.

6. Conclusion

We have investigated the problem of fluid flow in a growing solid tumor by developing an axisymmetric mathematical model for an assumed 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 the fluid pressure, the radial and latitudinal components of the fluid flow velocity vector and the concentrations of two different drugs in the tumor or normal tissue. We found that the 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 fluid 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, the presence of fluid flow circulation in the tumor and to a lesser intensity in the normal tissue. The values of the drug concentration for either etanidazole or cisplatin decrease rapidly with decreasing radial distance from the center of the tissue, and the value of each drug concentration is very close to zero very near the center of either tumor or normal tissue. These results for the pressure, velocity and drug concentrations agree generally with the available experimental observations and biomedical data (Jain, 1987; Baxter and Jain, 1989; Boucher et al., 1990; Jain et al., 2007; Soltani and Chen, 2011).

Our additional new finding indicated that for a particular set of non-uniform boundary conditions for the pressure which led to smaller value of the pressure at the center of the tumor or normal tissue, the amount of drug concentration in the tumor or normal tissue can exdure more near the center of these tissues. This result may indicate a possible new procedure to improve the drug delivery to such tissues. We also calculated the values of

concentrations of two drugs in the presence of both drugs versus time and found, in particular, that both drug concentrations decrease with increasing time but the rate of such decrease reduces 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 drug concentrations 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 the value of the diffusivity coefficient for a drug has important complications on the efficiency of the drug delivery in the tumor system.

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

Acknowledgement

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