

ONE-COMPONENT SPHERICALLY SYMMETRIC MODEL OF A NON-NECROTIC TUMOR GROWTH

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Abstract. A spherically symmetric model for a non-necrotic vascularized tumor, proposed several years ago by Byrne and Chaplain (1995) [9], was reviewed and extended. The nutrient and inhibitor concentrations are satisfying reaction-diffusion equations, and the tumor radius is determined from a very simple integro-differential equation obtained from the balance of cell proliferation and cell death. The free inhibitor model is extended assuming a space dependence for the nutrient concentration in the vasculature (two distinct regions are considered, one near the surface with a higher concentration, and the rest of the tumor). It is a very simple generalization, which is taking into account a higher tumor angiogenesis factor near the tumor surface. The stationary state of this improved model is carefully investigated.

Key words: nonlinear equations, tumor growth, carcinogenesis.

INTRODUCTION

The carcinogenesis is a very complex, multistage phenomenon, involving the space and time evolution of a large number of variables, each with a specific activity and strongly interacting between them [6], [7]. Therefore, the mathematical modeling of a tumor evolution is a challenging problem at the frontier of applied mathematics and biology. In each stage specific variables are characterizing the processes taking place in the tumor region and specific mathematical modes are used to describe the tumor evolution. This approach allows us to identify the main processes characteristic for the respective stage, and to introduce proper variables to describe them.

In the present paper we shall concentrate on the last stage, when the tumor has become a macroscopic object (of volume V and a smooth surface Σ) of more or less spherical form. The various models developed to describe the tumor growth are formulated as initial value problem for partial differential equations (linear, or nonlinear), with the tumor surface as a free boundary. A lot of models, of various

Received: December 2007;
in final form March 2009.

degree of generality, have been proposed in the last decades. They include avascular models [1–4, 8, 18, 20–22], characterized by the direct diffusion of nutrients and wastes to and from surrounding tissues. Generally, they lead asymptotically to a dormant, but viable steady state.

But a vascular tumor with a proximal host vasculature may become vascularized as a result of the emission of tumor angiogenesis factors (TAF) and by stimulating the neighboring capillaries to form sprouts which are migrating towards and into the tumor. In this way the tumor receives supplemental nourishment by blood-tissue transfer. This revolutionary idea that tumor growth is angiogenesis dependent was first proposed in the seminal paper of Folkman in 1971 [13], but more than 10 years elapsed until the idea was accepted by the biomedical research community [14]. Now the angiogenic therapy is considered one of the most powerful modality of cancer treatment. Mathematical models, including the principal biological interactions that contribute to the vascularization of cancerous tissues, have been devised by several authors (see [5, 19, 21] and references therein). A *minimal* model including five principal species (endothelial cells, tumor angiogenic factors, the extracellular matrix-fibronectin, the proteases, and inhibitors) is discussed in [19]. But, to combine these models with those describing tumor growth is an extremely difficult mathematical problem and very successful results have been obtained until now. Therefore, several authors did overcome this difficulty by simply introducing supplementary terms describing the nutrient transfer between the vasculature and the tissue [9, 10, 15]. This point of view is also adopted in the present paper.

Further more elaborated models are taking into account the existence of different types of cancerous cells inside the tumor (usually three types: proliferating, quiescent and dead cells) [16, 17]. Their concentrations are satisfying a coupled set of reaction-diffusion equations, with coefficients depending on the nutrient (eventually inhibitor) concentration. The problem is highly nonlinear as the nutrient concentration satisfies a diffusion equation, and the tumor surface is time dependent.

In the following, we are discussing and extending a very simple model, proposed several years ago by Byrne and Chaplain [9]. It is a spherically symmetric model of a vascularized non-necrotic tumor. The initial model of Byrne and Chaplain is extended assuming that near the tumor boundary, in a layer of given thickness, the nutrient concentration in the vasculature is greater than in the rest of the tumor. The governing equations for the nutrient and inhibitors concentrations, together with the equation giving the time evolution of the tumor radius, are written down in the next section. In the third section the steady state solution of the inhibitor free model is carefully investigated. A few comments and remarks on the new results are given in the final section.

MODEL PRESENTATION

One considers a spherically symmetric tumor of radius $R(t)$ containing only proliferating cells. Since their density is constant, they will not play any role in the tumor evolution, which is determined only by the feeding mechanism involving nutrients and inhibitors. We shall consider only one kind of nutrients and inhibitors and denote their concentrations by $c(r,t)$ and $\beta(r,t)$ respectively. One assumes that the nutrient concentration satisfies the equation

$$\frac{\partial c}{\partial t} = \frac{D_1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial c}{\partial r} \right) + \Gamma (c_B - c) - \lambda c - g_1(c, \beta) \quad (1)$$

The first term in the right-hand-side (rhs) describes the nutrient diffusion in the tumor (D_1 diffusion parameter assumed constant). The second describes the nourishment by blood-tissue transfer, Γ being the rate of blood-tissue transfer per length unit and c_B the nutrient concentration in the vasculature. As discussed in the introduction such a term is the expression and a final result of the angiogenesis process through which the tumor generates its own vasculature. The next term describes the nutrient consumption at the rate λc . The presence of the inhibitor acts as a new sink for the nutrient and is described by the term $g_1(c, \beta)$ in the rhs of (1). For $\Gamma = 0$ we get the avascular case, and for $g_1 = 0$ an inhibitor free model. The model is describing a non-necrotic tumor, but it can easily be extended to a necrotic one, assuming that such a situation appears when the nutrient concentration in the center of the tumor decreases below a certain value c_N [10], when necrosis of proliferating cells starts to occur.

Usually the parameters D_1 , Γ , c_B , λ are assumed constant in the tumor region, but this assumption can be enlarged considering reasonable and simple spatial expressions for some of them. Such a dependence could take into account more realistic situations as nonuniformities in the tumor region, or a higher tumor vasculature near the surface. More correctly, some of these parameters start to be time-dependent and should be considered as dynamical variables. In the present paper we shall vary only c_B , reflecting a larger nutrient flux in a thin shell near the tumor surface. More reasonable assumption, such as taking into account also a variable rate of blood-tissue transfer, is under investigation and the results will be presented elsewhere. The following expression for c_B will be considered

$$c_B = \begin{cases} c_B(1 + \Delta), & R(1 - \delta) < r < R \\ c_B, & 0 < r < R(1 - \delta) \end{cases} \quad (2)$$

As the inhibitor is concerned, its concentration $\beta(r,t)$ satisfies also a reaction-diffusion equation

$$\frac{\partial \beta}{\partial t} = \frac{D_2}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial \beta}{\partial r} \right) - g_2(c, \beta) \quad (3)$$

where D_2 is the diffusion constant for the inhibitor fluid inside the tumor (usually $D_2 < D_1$) and all the inhibitor sinks are included in $g_2(c, \beta)$, whose form depends on the scenario by which the inhibitor is delivered and acts on the tumor.

In the case of a single species of cancerous cells inside the tumor, in order to calculate the time evolution of its radius it is necessary to give an expression for the cell proliferation rate. Denoting by $S(c, \beta)$ the cell proliferating rate at a point inside the tumor, the mass conservation applied to a spherical tumor (for an incompressible fluid mass conservation implies volume conservation) yields the following partial differential equations describing time evolution of the tumor radius $R(t)$

$$R^2 \frac{dR}{dt} = \int_0^{R(t)} S(c(r, t), \beta(r, t)) r^2 dr \quad (4)$$

Several expressions can be used for $S(c, \beta)$, each of them expressing the balance between the creation and death of cells.

In the absence of inhibitors the simplest expression is

$$S(c) = s(c - \bar{c}), \quad c > \bar{c} \quad (5)$$

where s and \bar{c} are constant. Here sc is the birth rate, proportional to the nutrient concentration, and $s\bar{c}$ a constant death rate of the cells inside the tumor. Another expression is a logistic one

$$S(c) = sc \left(1 - \frac{c}{\hat{c}} \right), \quad c < \hat{c} \quad (5')$$

In the presence of inhibitors, the expression (5) can be completed with a similar linear term in β

$$S(c, \beta) = s(c - \bar{c})(\bar{\beta} - \beta), \quad c > \bar{c}, \beta < \bar{\beta} \quad (6)$$

To complete the previous description of the model we have to give explicit expressions for the functions g_1 and g_2 . Experimental information about the inhibitor action is very limited, and insufficient to determine these expressions, so we start with the simplest situations. Several scenarios are possible and the simplest ones are listed below:

- inhibitor free case:

$$\beta = 0, \quad g_1 = g_2 = 0, \quad S = s(c - \bar{c}) \quad (7-a)$$

inhibitor affects cell proliferation, but not the nutrient concentration:

$$g_1 = 0, \quad g_2 = \gamma_2 \beta, \quad S = s(c - \bar{c})(\bar{\beta} - \beta) \quad (7-b)$$

inhibitor affects nutrient concentration, but not the cell proliferation:

$$g_1 = \gamma_1 \beta, \quad g_2 = \gamma_2 \beta, \quad S = s(c - \bar{c}) \quad (7-c)$$

inhibitor affects both the nutrient concentration and the cell proliferation:

$$g_1 = \gamma_1 \beta, \quad g_2 = \gamma_2 \beta, \quad S = s(c - \bar{c})(\bar{\beta} - \beta) \quad (7-d)$$

The linear expressions of g_1 and g_2 mentioned above will keep the linear character of the diffusion-reaction equations (1) and (3), which is a great advantage for solving them.

In order to complete the model formulation we have to specify the boundary and initial conditions. The boundary conditions write

$$\begin{aligned} \frac{\partial c(r=0,t)}{\partial r} = 0 \quad \frac{\partial \beta(r=0,t)}{\partial r} = 0 \\ c(R(t)) = c_R \quad \beta(R(t)) = \beta_R \end{aligned} \quad (8)$$

where c_R and β_R are usually assumed constant.

The initial conditions are

$$\begin{aligned} c(r, t=0) = c_0(r), \quad \beta(r, t=0) = \beta_0(r) \\ R(t=0) = R_0 \end{aligned} \quad (9)$$

with $c_0(r)$, $\beta_0(r)$, R_0 given.

It is very important to realize that two-time scales are present in the time evolution of a tumor. First there is a diffusion time $\tau_D = \frac{L^2}{D}$, where L is a typical length, τ_D being of order of minutes, and the second time T related to the growth rate of the tumor, being of order of days. Therefore, $\varepsilon = \tau_D/T$ is a small quantity. It is convenient to rescale the quantities and introduce dimensionless variables and parameters:

$$\begin{aligned} \bar{r} = \frac{r}{R_0}, \quad \bar{t} = \frac{t}{T} \\ \bar{c}(\bar{r}, \bar{t}) = \frac{c(r,t)}{C}, \quad \bar{\beta}(\bar{r}, \bar{t}) = \frac{\beta(r,t)}{B}, \quad \bar{R}(\bar{t}) = \frac{R(t)}{R_0} \\ \bar{D} = \frac{D_2}{D_1}, \quad \bar{\Gamma} = \frac{\Gamma R_0^2}{D_1}, \quad \bar{\lambda} = \frac{\lambda R_0^2}{D_1} \\ \bar{\gamma}_1 = \frac{\gamma_1 R_0^2 B}{D_1 C}, \quad \bar{\gamma}_2 = \frac{\gamma_2 R_0^2}{D_2}, \quad \bar{S}(\bar{c}, \bar{\beta}) = TS(c, \beta) \end{aligned} \quad (10)$$

where C and B are typical nutrient and inhibitor concentrations. Dropping the bars, the equations describing the tumor growth are:

$$\begin{aligned}\varepsilon \frac{\partial c}{\partial t} &= \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial c}{\partial r} \right) + \Gamma(c_B - c) - \lambda c - \gamma_1 \beta \\ \varepsilon \frac{\partial \beta}{\partial t} &= \frac{D}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial \beta}{\partial r} \right) - \gamma_2 \beta \\ R^2 \frac{dR}{dt} &= s \int_0^{R_0(t)} (c - \bar{c})(\bar{\beta} - \beta) r^2 dr\end{aligned}\quad (11)$$

subjected to the boundary conditions:

$$\begin{aligned}\frac{\partial c(0,t)}{\partial t} &= 0, & \frac{\partial \beta(0,t)}{\partial t} &= 0 \\ c(R(t)) &= c_R, & \beta(R(t)) &= \beta_R\end{aligned}\quad (12)$$

and the initial conditions

$$c(r,0) = c_0(r), \quad \beta(r,0) = \beta_0(r), \quad R(0) = 1 \quad (13)$$

Numerical solutions of (11) were discussed in [9]. In the next section we discuss only the inhibitor free case ($\beta \equiv 0$), and because $\varepsilon \ll 1$ we consider first the stationary situation $\left(\frac{\partial c}{\partial t} = 0 \right)$, but with c_B given by (2).

STATIONARY SOLUTION

The equation (1) becomes $\left(\beta = 0, \frac{\partial c}{\partial t} = 0 \right)$

$$\frac{1}{r^2} \frac{d}{dr} \left(r^2 \frac{dc}{dr} \right) + \Gamma(c_B - c) - \lambda c = 0 \quad (14)$$

with the boundary conditions:

$$\frac{dc(0)}{dr} = 0, \quad c(R) = c_R \quad (15)$$

We shall consider first the situation when c_B is constant in the whole tumor volume. The solution is easily found to be:

$$c(r) = \frac{\Gamma c_B}{\Gamma + \lambda} + \left(c_R - \frac{\Gamma c_B}{\Gamma + \lambda} \right) \frac{R}{\sinh R\sqrt{\Gamma + \lambda}} \frac{\sinh r\sqrt{\Gamma + \lambda}}{r} \quad (16)$$

The stationary radius of the tumor is determined from (4) $\left(\frac{\partial R}{\partial t} = 0 \right)$

$$\int_0^R (c(r) - \bar{c}) r^2 dr = 0 \quad (17)$$

with $c(r)$ given by (16). The integration is straightforward and one obtains:

$$\frac{1}{3} \left(\bar{c} - \frac{\Gamma c_B}{\Gamma + \lambda} \right) \eta^2 = \left(c_R - \frac{\Gamma c_B}{\Gamma + \lambda} \right) \{ \eta \coth \eta - 1 \} \quad (18)$$

where we denoted:

$$\eta = R\sqrt{\Gamma + \lambda} \quad (19)$$

With the notation:

$$\Lambda = \frac{1}{3} \frac{\bar{c}(\Gamma + \lambda) - \Gamma c_B}{c_R(\Gamma + \lambda) - \Gamma c_B} \quad (20)$$

the equation (18) is transformed into:

$$F(\eta) = \frac{1}{\eta^2} (\eta \coth \eta - 1) = \Lambda \quad (21)$$

and the radius R is determined graphically for each value of Λ . In order to have a positive Λ the ratio $\frac{\Gamma}{\Gamma + \lambda} c_B$ must be smaller than \bar{c} and c_R . Also a reasonable assumption is $\bar{c} < c_R$, so the following inequalities have to be satisfied:

$$\frac{\Gamma}{\Gamma + \lambda} c_B < \bar{c} < c_R \quad (22)$$

Consequently, the parameter Λ satisfies:

$$0 < \Lambda < \frac{1}{3} \quad (22')$$

when the implicit equation (21) has a unique solution. Indeed it is easy to see that the function $F(\eta)$ is a monotonously decreasing function from $F(\eta=0) = \frac{1}{3}$ to $F(\eta \rightarrow \infty) \rightarrow 0$, so its intersection with the constant Λ gives a unique solution.

In Figure 1 this is represented for $\Lambda = 1/6$ and the solution is $\eta_e = 4.733$.

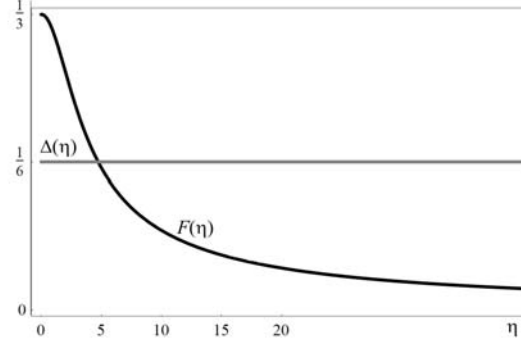


Fig. 1. Solution of equation (21) for $\Lambda = 1/6$.

Next we consider the situation when c_B is no more constant inside the tumor, but is defined on intervals as in relation (2), being greater in a layer of thickness δ near the tumor boundary. We keep in mind a situation when $\frac{\Gamma c_B}{\Gamma + \lambda}(1 + \Delta) > \bar{c}$. If this should happen in the whole tumor volume, according to the previous discussion, no stationary solution exists ($R \rightarrow \infty$). Then it is reasonable to suppose that a stationary solution exists if δ is smaller than a critical value δ_c , and we want to evaluate it.

The solution of $c(r)$ in the two regions $0 \leq r \leq R(1-\delta)$ and $R(1-\delta) \leq r \leq R$ is easily found. In the first region, $0 < r < R(1-\delta)$ the solution is

$$c(r) = \frac{\Gamma c_B}{\Gamma + \lambda} + \kappa \frac{\sinh r\sqrt{\Gamma + \lambda}}{r} \quad (23)$$

It satisfies the boundary condition $\frac{dc(0)}{dr} = 0$.

In the second region, $R(1-\delta) \leq r \leq R$, we have

$$c(r) = \frac{\Gamma c_B (1 + \Delta)}{\Gamma + \lambda} + \frac{\kappa_1}{2} \frac{\exp(-r\sqrt{\Gamma + \lambda})}{r} + \frac{\kappa_2}{2} \frac{\exp(r\sqrt{\Gamma + \lambda})}{r} \quad (24)$$

Here $\kappa, \kappa_1, \kappa_2$ are integration constants which are determined from the boundary condition (15) and the continuity of $c(r)$ and its first derivative in the point $r = R(1-\delta)$. These boundary conditions lead to the following relations:

$$c_R - \frac{\Gamma c_B}{\Gamma + \lambda} (1 + \Delta) = \frac{1}{2R} \left[\kappa_1 \exp(-R\sqrt{\Gamma + \lambda}) + \kappa_2 \exp(R\sqrt{\Gamma + \lambda}) \right] \quad (25)$$

$$-\frac{1}{2}(\kappa + \kappa_1) \frac{e^{-R(1-\delta)\sqrt{\Gamma + \lambda}}}{R(1-\delta)} + \frac{1}{2}(\kappa - \kappa_2) \frac{e^{R(1-\delta)\sqrt{\Gamma + \lambda}}}{R(1-\delta)} = \frac{\Gamma c_B}{\Gamma + \lambda} \Delta \quad (26)$$

$$\begin{aligned} & \frac{1}{2}(\kappa + \kappa_1) \sqrt{\Gamma + \lambda} e^{-R(1-\delta)\sqrt{\Gamma + \lambda}} + \frac{1}{2}(\kappa - \kappa_2) \sqrt{\Gamma + \lambda} e^{R(1-\delta)\sqrt{\Gamma + \lambda}} = \\ & = -\frac{1}{2}(\kappa + \kappa_1) \frac{e^{-R(1-\delta)\sqrt{\Gamma + \lambda}}}{R(1-\delta)} + \frac{1}{2}(\kappa - \kappa_2) \frac{e^{R(1-\delta)\sqrt{\Gamma + \lambda}}}{R(1-\delta)} \end{aligned} \quad (27)$$

The system (25)–(27) is easily solvable and one obtains:

$$\begin{aligned} \kappa_1 &= -\kappa - \left[\eta(1-\delta) - 1 \right] \frac{\Gamma c_B}{(\Gamma + \lambda)^{3/2}} \Delta e^{\eta(1-\delta)} \\ \kappa_2 &= \kappa - \left[\eta(1-\delta) + 1 \right] \frac{\Gamma c_B}{(\Gamma + \lambda)^{3/2}} \Delta e^{-\eta(1-\delta)} \end{aligned} \quad (28)$$

$$c_R - \frac{\Gamma c_B}{\Gamma + \lambda} (1 + \Delta) = \kappa \sqrt{\Gamma + \lambda} \frac{\sinh \eta}{\eta} - \frac{\Gamma c_B}{\Gamma + \lambda} \Delta \left[(1-\delta) \cosh \delta \eta + \frac{\sinh \delta \eta}{\eta} \right]$$

where as before $\eta = R\sqrt{\Gamma + \lambda}$. The limit situations $\delta \rightarrow 0$ and $\delta \rightarrow 1$ are easily extracted from these expressions. For $\delta \rightarrow 0$ from the last equation (28) we get

$$c_R - \frac{\Gamma c_B}{\Gamma + \lambda} = \kappa \frac{\sinh \eta}{R},$$

while for $\delta \rightarrow 1$ the first region shrinks to zero and $\kappa_2 = -\kappa_1$ with κ_2 given by

$$c_R - \frac{\Gamma c_B}{\Gamma + \lambda} (1 + \Delta) = \kappa_2 \frac{\sinh \eta}{R}.$$

These are the expected results for c_B constant throughout the whole tumor volume.

The value of η is determined from (17) with $c(r)$ given by (23) and (24). One obtains:

$$\begin{aligned} & \kappa \int_0^{R(1-\delta)} \sinh(r\sqrt{\Gamma + \lambda}) r dr + \frac{\kappa_1}{2} \int_{R(1-\delta)}^R e^{-r\sqrt{\Gamma + \lambda}} r dr + \frac{\kappa_2}{2} \int_{R(1-\delta)}^R e^{r\sqrt{\Gamma + \lambda}} r dr = \\ & = \frac{1}{3} \left[\bar{c} - \frac{\Gamma c_B}{\Gamma + \lambda} (1 + \Delta h(\delta)) \right] R^3 \end{aligned} \quad (29)$$

where we denoted $h(\delta) = 1 - (1 - \delta)^3$. The integrations are straightforward and using the expressions (28) for the coefficients κ_1 and κ_2 the final result writes

$$\begin{aligned} & \frac{1}{3} \left[\bar{c} - \frac{\Gamma c_B}{\Gamma + \lambda} (1 + \Delta \cdot h(\delta)) \right] = \\ & = \kappa \sqrt{\Gamma + \lambda} \frac{\sinh \eta}{\eta} F(\eta) - \frac{\Gamma c_B}{\Gamma + \lambda} \Delta \cdot g(\delta, \eta) \end{aligned} \quad (30)$$

where

$$g(\delta, \eta) = \frac{1}{\eta^2} \left[(1 - \delta) \eta \sinh \delta \eta + \delta \cosh \delta \eta - \frac{\sinh \delta \eta}{\eta} \right] \quad (31)$$

From the last equation (28) we get:

$$\kappa \sqrt{\Gamma + \lambda} \frac{\sinh \eta}{\eta} = c_R - \frac{\Gamma c_B}{\Gamma + \lambda} (1 - \Delta \cdot f(\delta, \eta)) \quad (32)$$

where:

$$f(\delta, \eta) = (1 - \delta) \cosh \delta \eta + \frac{\sinh \delta \eta}{\eta} - 1 \quad (33)$$

Introducing (32) into (30), after some algebraic manipulations we obtain:

$$F(\eta) = \Lambda(\delta, \Delta) + A(\delta, \Delta) G(\delta, \eta) \quad (34)$$

where we denoted:

$$\Lambda(\delta, \Delta) = \frac{1}{3} \frac{(\Gamma + \lambda) \bar{c} - \Gamma c_B (1 + \Delta h(\delta))}{(\Gamma + \lambda) c_R - \Gamma c_B (1 + \Delta h(\delta))} \quad (35)$$

$$A(\delta, \Delta) = \frac{\Gamma c_B \Delta}{(\Gamma + \lambda) c_R - \Gamma c_B (1 + \Delta h(\delta))} \quad (36)$$

$$G(\delta, \eta) = g(\delta, \eta) - [h(\delta) + f(\delta, \eta)] F(\eta) \quad (37)$$

The reason to introduce these quantities is that they have simple behaviors in the limit $\delta \rightarrow 0$ and $\delta \rightarrow 1$. It is easily seen that in the limit $\delta \rightarrow 0$ all the quantities $h(\delta), f(\delta, \eta), g(\delta, \eta), G(\delta, \eta)$ vanish, while in the limit $\delta \rightarrow 1$ only $G(\delta, \eta)$ vanishes and $h(\delta) \rightarrow 1$. Then in these limit cases the relation (34) transforms into the corresponding relation for a constant c_B in the whole tumor volume (see relation (21)). It is easily seen that, always, $\Lambda(\delta, \Delta) < \Lambda$, and

$$\lim_{\eta \rightarrow 0} f(\eta, \delta) = 0, \quad \lim_{\eta \rightarrow 0} G(\eta, \delta) = 0 \quad (38)$$

Actually, the following series expansions for $\eta \ll 1$ exist:

$$\begin{aligned} f(\eta, \delta) &= \frac{\delta^2}{2} \left(1 - \frac{2\delta}{3} \right) \eta^2 + O(\eta^4) \\ G(\eta, \delta) &= \frac{1}{30} P_5(\delta) \eta^2 + O(\eta^4) \end{aligned} \quad (39)$$

where

$$P_5(\delta) = \delta^5 - 5\delta^4 + 9\delta^3 - 7\delta^2 + 2\delta \geq 0 \quad (40)$$

for $\delta \in [0, 1]$ ($P_5(0) = P_5(1) = 0$) and the right hand side of equation (34) is an increasing function of η for $\eta \ll 1$. As the asymptotic behavior of $G(\delta, \eta)$ is of the form $[1 - h(\delta)]/\eta$, the right hand side tends asymptotically ($\eta \rightarrow \infty$) to $\Lambda(\delta, \Delta)$. Therefore, a unique solution of (34) exists. As a numerical example we consider that $c_R : \bar{c} : \Gamma c_B / (\Gamma + \lambda)$ are proportional with 1:0.8:0.6 (these imply $\Lambda = 1/6$) and take $\Delta = 1/2.4$, $\delta = 0.2$. Then $\Lambda(\delta, \eta) = (4/7)\Lambda$, $A(\delta, \Delta) = 0.893$ and equation (34) is solved numerically (see Figure 2) giving $\eta_e(\delta, \Delta) = 6.581$.

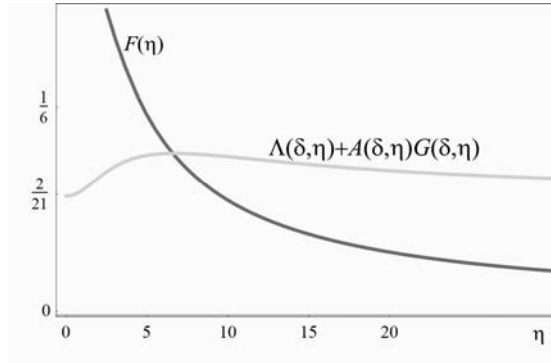


Fig. 2. Solution of equation (34) for $\delta = 0.2$, $\Lambda(\delta, \Delta) = 2/21$, and $A(\delta, \Delta) = 0.893$.

The necessary condition to have a stationary state of the tumor is now given by:

$$0 \leq \frac{(\Gamma + \lambda)\bar{c} - \Gamma c_B (1 + \Delta h(\delta))}{(\Gamma + \lambda)c_R - \Gamma c_B (1 + \Delta h(\delta))} \leq \frac{1}{3} \quad (41)$$

The tumor radius grows as $\Lambda(\delta, \Delta)$ decreases. The vanishing of the denominator in (41) sets a critical value of δ , and for $\delta > \delta_C$ no stationary state of the tumor is possible. The critical value of δ for which the solution tends to infinity is given by:

$$h(\delta_C) = \frac{(\Gamma + \lambda)\bar{c} - \Gamma c_B}{\Gamma c_B \Delta} \quad (42)$$

As we assumed $\bar{c} < \frac{\Gamma c_B}{\Gamma + \lambda}(1 + \Delta)$, denoting:

$$\Delta_0 = \frac{(\Gamma + \lambda)\bar{c} - \Gamma c_B}{\Gamma c_B} \quad (43)$$

the relation (41) becomes:

$$h(\delta_C) = \frac{\Delta_0}{\Delta} < 1 \quad (44)$$

Using the numerical values considered before, we have $\Delta_0 = 1/3$ and the critical value is $\delta_C = 0.415$. In other words if in the shell of volume $V[1 - (1 - \delta)^3] = 0.488V$ the nutrient concentration in the vasculature is increased by 41.66 %, the tumor radius increases from η_e to $\eta_e(\delta, \Delta)$, that is by ~ 1.4 times, reflecting the major effect of the nutrient concentration on the tumor stationary state dimensions.

CONCLUSIONS

In this paper the stationary state of a spherically symmetric vascular tumor was investigated. We considered a model in which the nutrient concentration in the vasculature near the tumor boundary, in a layer of thickness δ , is higher than in the rest of the tumor (relation (2)), reflecting a higher tumor angiogenesis factor in that region. We considered a situation when

$$\frac{\Gamma c_B}{\Gamma + \lambda} < \bar{c} < \frac{\Gamma c_B}{\Gamma + \lambda}(1 + \Delta)$$

which should correspond to a situation when no stationary solution exists if the nutrient concentration in the vasculature is $c_B(1 + \Delta)$ throughout the tumor volume. In the situation considered, a critical thickness δ_C was defined (see relation (39) or (41)) and a finite tumor radius exists if and only if $\delta < \delta_C$.

The analysis was done in the absence of inhibitors. The present study can be easily extended in several ways. As the equations (11) for the nutrient and inhibitor concentrations are linear, analytical solutions can be obtained. Looking for the stationary state we have:

$$\beta(r) = \beta_R \frac{R}{\sinh \gamma R} \frac{\sinh \gamma r}{r}, \quad \gamma^2 = \frac{\gamma_2}{D} \quad (45)$$

and the equation for $c(r)$ becomes a nonhomogeneous linear differential equation having the solution

$$c(r) = \frac{\Gamma c_B}{\Gamma + \lambda} + \left(c_R - \frac{\Gamma c_B}{\Gamma + \lambda} - A \beta_R \right) \frac{R}{\sinh R \sqrt{\Gamma + \lambda}} \frac{\sinh r \sqrt{\Gamma + \lambda}}{r} + A \beta(r) \quad (46)$$

Here

$$A = \frac{\gamma_1}{\gamma^2 - (\Gamma + \lambda)}$$

and can be a positive or negative quantity depending on γ^2 being greater or smaller than $(\Gamma + \lambda)$. The expression for the cell proliferating rate $S(c(r), \beta(r))$ is now completely determined adopting a certain scenario relative to the influence of inhibitors on the tumor evolution. If $S(c, \beta)$ is given by (6), the integral

$$\int_0^R (c(r) - \bar{c})(\bar{\beta} - \beta(r)) r^2 dr$$

can be computed, but the interpretation of the result needs further investigations. Work in this direction is underway.

The problem can be extended introducing more nutrient and inhibitor components. Then the equations (11) take matrix forms, but still they can be solved due to their linear character. The models will contain much more “characteristic constants”, and a careful analysis of the ratio of these constants is necessary. Results for a model with two nutrients (glucose and oxygen) in the presence of growth-inhibitory factors (chalcones) will be reported elsewhere.

The previous model may easily be developed to describe the situation when a necrotic core exists at the tumor center. A necrotic core starts to develop when the nutrient concentration diminishes below a certain value c_N , when the cancerous cells are insufficiently nourished to ensure their proliferation/survival. Denoting by r_n the inner radius where $c(r_n) = c_N$, the new equations describing the nutrient $c(r, t)$ and inhibitor $\beta(r, t)$ concentrations are [2, 10, 18]:

$$\begin{aligned}\varepsilon \frac{\partial c}{\partial t} &= \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial c}{\partial r} \right) + [\Gamma(c_B - c) - \lambda c - \gamma_1 \beta] H(r - r_n) \\ \varepsilon \frac{\partial \beta}{\partial t} &= \frac{D}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial \beta}{\partial r} \right) - \gamma_2 \beta H(r - r_n)\end{aligned}\quad (47)$$

where $H(x)$ is the Heaviside step function:

$$H(x) = \begin{cases} 1, & x > 0 \\ 0, & x < 0 \end{cases}$$

To these we have to add the balance equation governing the time evolution of tumor radius:

$$R^2 \frac{dR}{dt} = \int_0^R \{S(c, \beta) H(r - r_n) - N(c, \beta) H(r_n - r)\} r^2 dr \quad (48)$$

where $S(c, \beta)$ is the proliferating rate of the cancerous cells defined in the annulus $r_n < r < R$, and $N(c, \beta)$ is the cell loss rate due to necrosis and is restricted to nutrient depleted region $0 < r < r_n$. The model was numerically studied in [9].

But the main problem, which is still open, is the study of the time evolution of a tumor, starting from the partial differential equations (1) and (3) and the balance equation (4). Few exact results are known, and mainly one resorts to numerical simulations [9–12], [15–17], [23–26]. A careful analysis of the time evolution of the inhibitor free model is given in [11, 12]. One proves that

$$\liminf_{t \rightarrow \infty} R(t) > 0,$$

i.e. once engendered, the tumor persists in time even in a dormant state. If ε is sufficiently small, $R(t)$ reaches exponentially the steady state, which is globally asymptotically stable. But if ε is “somewhat large” the radius $R(t) \rightarrow \infty$. The analysis is more complicated for more complex models, and various asymptotic methods have to be used to get answers to these problems.

Acknowledgments. The authors are very indebted to the referee for valuable critical comments. This work is partially supported by the Ministry of Education and Research under the grant CEEEX-09-2005.

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