Numerical Simulation of Avascular Tumor Growth

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Abstract. A mathematical and numerical model for the description of different aspects of microtumor development is presented. The model is based in the solution of a system of partial differential equations describing an avascular tumor growth. A detailed second-order numeric algorithm for solving this system is described. Parameters are swiped to cover a range of feasible physiological values. While previous published works used a single set of parameters values, here we present a wide range of feasible solutions for tumor growth, covering a more realistic scenario. The model is validated by experimental data obtained with a multicellular spheroid model, a specific type of in vitro biological model which is at present considered to be optimum for the study of complex aspects of avascular microtumor physiology. Moreover, a dynamical analysis and local behaviour of the system is presented, showing chaotic situations for particular sets of parameter values at some fixed points. Further biological experiments related to those specific points may give potentially interesting results.

1. Introduction
The mathematics dedicated to the resolution of oncology problems, called “oncology mathematics”, is considered a new specialty in the interdisciplinary sciences and it is based in the utilization of mathematical methods and models for the description and prediction of morphologic and physiologic aspects of tumor development [1, 2]. Over the last 10 years increasingly complex mathematical models of cancerous growth have been developed, especially on solid tumors, in which growth primarily comes from cellular proliferation [3]. Many of these models have the potential of being used in order to check the efficacy and efficiency of different therapeutic strategies. Particularly, Ward’s models [4–6] describe the growth or regression of an avascular microtumor versus the nutrient and/or drug concentration present in the medium. These models can be applied to and validated by the biological model of multicellular spheroids.

The multicellular spheroid model is at present considered an optimum in vitro model to study complex aspects of tumor physiology, especially those related to therapeutic strategies that cannot be adequately faced by other simpler in vitro models. This kind of model represents an intermediate level of complexity between in vitro monolayer cell cultures and in vivo solid tumors [7]. It consists in a three-dimensional culture of tumor cells grouped in spheroids growing in suspension in an aqueous medium. As the spheroid grows up to a diameter of few millimeters, it develops three different inner layers: a necrotic core of dead cells, an intermediate region of quiescent viable cells and an external rim of viable cells in active proliferation.
Ward’s mathematical models apply to this kind of microtumors, and are based on a system of nonlinear partial differential equations which assume the existence of a continuum of cells in two possible states: alive or dead. According to the concentration of a generic nutrient, the living cell may reproduce or die. Besides, the external drug application can be modeled as the presence of a material able to diffuse to the spheroid interior and to kill cells with linear or Michaelis-Menten kinetics. The division or death of cells implies the expansion or contraction of the tumor volume, respectively, with the consequent generation of an associated velocity field.

The aim of this study is to present a mathematical model and its corresponding numerical simulations extending results previously published by Ward [4–6]. Our final goal will be to use this model for predicting the outcome of different therapy strategies against avascular microtumors and micrometastasis.

2. Model equations
The model equations were first presented in [4] and have basically three unknowns:

- number of living cells \( n \);
- local growth velocity \( v \);
- nutrient concentration \( c \).

These three unknowns depend on time and space with the following equations:

\[
\frac{\partial n}{\partial t} + \nabla \cdot (vn) = [k_m(c) - k_d(c)]n \tag{1}
\]

\[
\nabla \cdot v = k_m(c)nV_L - k_d(c)n(V_L - V_D) \tag{2}
\]

\[
\frac{\partial c}{\partial t} + \nabla \cdot (vc) = \nabla \cdot (D \nabla c) - [\beta k_m(c) + \gamma(c)]n \tag{3}
\]

where \( k_m \) and \( k_d \) are the mitosis and cellular death ratios respectively. \( V_L \) and \( V_D \) represent the living and dead cell volume, \( \gamma \) represents the nutrient consumption rate of a cell in interphase and \( \beta(c) \) represents the nutrient consumption rate of a cell in mitosis.

\[
k_m(c) = \frac{A c^{m_1}}{c_0^{m_1} + c^{m_1}}
\]

\[
k_d(c) = B \left(1 - \frac{\sigma c^{m_2}}{c_d^{m_2} + c^{m_2}}\right)
\]

where \( c_0 \) is the critical concentration for cell proliferation, \( c_d \) the critical concentration for cell survival and the basal rate of cell death without nutrient limitations.

2.1. Initial and boundary conditions
Initial conditions are given by:

\[
S(0) = \frac{3}{\sqrt{4\pi}} \frac{V_L}{V_L}, \quad n(0, r) = \frac{1}{V_L}, \quad c(0, r) = c_0 \tag{4}
\]

where the initial state of the tumor, represented by \( S(0) \), is a single cell submerged in a given nutrient concentration, and \( c_0 \) is the nutrient concentration where the spheroid is immersed. The boundary conditions used are:

\[
\frac{\partial S}{\partial t} = v(t, S(t)), \quad c(t, S(t)) = c_0 \tag{5}
\]

\[
\frac{\partial c(t, 0)}{\partial r} = 0, \quad v(t, 0) = 0 \tag{6}
\]
where the first boundary condition in the first equation implies that the boundary of the spheroid moves with the local velocity.

3. System non-dimensionalization
In order to solve the model presented in section 2, we applied non-dimensionalization under a quasi-stable approximation. We will denote a non-dimensional variable with a hat. The non-dimensionalization and the spherical symmetry leads to the following equation system:

\[
\frac{\partial \hat{n}}{\partial t} + \hat{v} \frac{\partial \hat{n}}{\partial \hat{r}} = [a(\hat{c}) - b(\hat{c})\hat{n}]\hat{n}
\]

\[
\frac{1}{\hat{r}^2} \frac{\partial (\hat{r}^2 \hat{v})}{\partial \hat{r}} = b(\hat{c})\hat{n}
\]

\[
\frac{1}{\hat{r}^2} \left( \frac{\partial}{\partial \hat{r}} \left( \hat{r}^2 \frac{\partial \hat{c}}{\partial \hat{r}} \right) \right) = k(\hat{c})\hat{n}
\]

where

\[
\hat{k}_m(\hat{c}) = \frac{\hat{c}^{m_1}}{\hat{c}^{m_1} + \hat{c}^{m_2}}, \quad \hat{k}_d(\hat{c}) = \frac{B}{A} \left( 1 - \sigma \frac{\hat{c}^{m_2}}{\hat{c}^{m_1} + \hat{c}^{m_2}} \right)
\]

\[
a(\hat{c}) = \hat{k}_m(\hat{c}) - \hat{k}_d(\hat{c})
\]

\[
b(\hat{c}) = \hat{k}_m(\hat{c}) - (1 - \delta)\hat{k}_d(\hat{c}) = a(\hat{c}) + \delta \hat{k}_d(\hat{c})
\]

\[
k(\hat{c}) = \beta \hat{k}_m(\hat{c}) + \hat{c} \hat{c}
\]

where \( \delta = V_D/V_L \in [0, 1] \), \( \beta = r_0^2 \beta A/DV_L c_0 \) and \( \hat{c}(\hat{c}) = r_0^2 \gamma(c)/DV_L c_0 \). \( a(\hat{c}) \) represents the rate of cell population growth, \( b(\hat{c}) \) the rate of volume growth and \( k(\hat{c}) \) is proportional to the nutrient consumption of the system.

4. Local behaviour of the model
If we insert equation 2 in the non-dimensionalized dynamical equations 1 and 3, we eliminate the divergence terms and \( n \times m_i = m_i = 1, A = 1 \) and \( c_i = c \), we arrive to the following system:

\[
\frac{\partial n}{\partial t} = -n^2 \left( \frac{c}{c + d} - (1 - \delta)(1 - \sigma) \frac{c}{c + d} \right) + n \left( 1 + \sigma \frac{c}{c + d} - 1 \right)
\]

\[
\frac{\partial c}{\partial t} = -c n \left( \frac{c}{c + d} - (1 - \delta)(1 - \sigma) \frac{c}{c + d} - c \beta \frac{c}{c + d} - c \gamma \right)
\]

By searching fixed points in the phase space \( (n, c) \), we find a trivial solution at \( (n, c = 0) \). Since \( c = 0 \), there are no cells in the system, so we obtain a constant behavior.

On the other hand, we find two more solutions, \( (n^+, c^+) \) and \( (n^-, c^-) \), corresponding to two non-trivial fixed points:

\[
n_{\pm} = \frac{\sigma c_{\pm} - d}{c_{\pm} - (1 - \delta)(d + c_{\pm}(1 - \sigma))}
\]

\[
c_{\pm} = (\beta + \gamma - d(1 - \delta))^{\pm} \sqrt{(\beta + \gamma - d(1 - \delta))^2 - 4d(\delta + (1 - \delta)\sigma)} / \left( -2(\delta + (1 - \delta)\sigma) \right)
\]
Taking $\sigma = 0.9$, $\delta = 0.5$ and $d = 0.1$, we move the parameters $\beta$ and $\gamma$ to start the analysis of the local dynamics.

Fixing $\beta = 0.05$, though in general for any value of this parameter, we find by varying $\gamma$ that the two fixed points define two branches, one stable and one unstable. If we set $\gamma$ greater than 0.38, both fixed points are real and, if we follow the evolution of the system into the phase space, we see that it falls into a stable solution. On the other side, if we set $\gamma$ smaller than 0.38, the fixed points become complex conjugates and the evolution of the system presents an oscillatory behaviour, typical of a Hopf bifurcation. Figure 1 shows a successive zooming of the solutions trajectory around the fixed points and reveals a chaotic behaviour.

![Figure 1](image_url)

**Figure 1.** Local behaviour for $n$ and $c$ with $\beta = 0.05$, $\sigma = 0.9$, $\delta = 0.5$, $d = 0.1$ and $\gamma = 0.3$. Zooming into the phase space of the solution shows chaotic behaviour.

5. Numerical Results

The computational model was written in C language and implemented on a Dual XEON class computer. The mesh used for solving the system was a 100-steps spatially contracting mesh, with $\lambda = 0.95$. The parametrization of different tumor growth velocities following [4] are shown in table 1.

**Table 1.** Parameter values for different tumor growth velocities.

| Parameter | Growth |
|-----------|--------|
|           | Normal | Slow | Fast |
| $\sigma$  | 0.9    |      |      |
| $\Delta$  | 0.5    |      |      |
| $\beta$   | 0.005  | 0.01 | 0.0025 |
| $cc$      | 0.1    | 0.2  | 0.05 |
| $cd$      | 0.05   | 0.1  | 0.025 |
| $m_1 = m_2$ | 1     |      |      |
| $B/A$     | 1      |      |      |
| $\Gamma$  | 0      |      |      |

Figure 2 shows the dimensionless tumor radius for three different parameter values. As it is stated in references [8, 10, 11], we can observe an initial period in which the growth rate increases; then, it slows down (although this is barely noticeable in the graph) and finally becomes constant.

For averaged parameter values, the velocity of tumor growth obtained is $2\mu$m/h. For other possible parameter values, we arrive to faster ($3\mu$m/h) or slower ($1\mu$m/h) tumor growth velocities.

5.1. Shrinking to a necrotic core

As stated in [12], if the natural death rate of living cells is larger than their proliferation rate, then the tumor shrinks to a necrotic core. Clearly, if $\sigma$ and $\delta$ are small enough, then this condition holds. This condition means that the maximum rate of cell death is larger than the maximum rate of cell proliferation; thus, we may expect that the living cells will eventually die. Under these assumptions, the numeric solution showed a decreasing tumor radius towards a necrotic core.
6. Discussion

Modeling cancer tumor evolution is a complex issue that has been explored in recent years resulting in the production of numerous mathematical models with different approaches. Many previously published tumor growth models represented the tumor as a mass of discrete inner layers separated by moving boundaries. More recent models, instead, were formulated in terms of a continuum of proliferating, quiescent or necrotic cells. These models seem to be in many cases numerically more efficient allowing finer mesh configurations and thus more accurate simulations of reality [13, 14]. Ward’s models are continuum models based in partial differential equations that describe the growth or regression of avascular microtumors responding to nutrient and/or drug concentration. Proliferation or death of tumor cells implies the expansion or contraction of tumor volume, respectively, with the consequent generation of an associated velocity field.

Solving the mathematical model results in one of three long-term possible solutions: the trivial solution (tumor death), the traveling wave solution (continuous tumor growth) and a sublinear growth case in which cells reach a pseudo-steady-state in the core. Recently, it has been proved theoretically that this model (implying a free boundary problem [15]) has a unique global solution [12]. Under restricted initial conditions and model parametrization, this global solution converges to a trivial steady-state solution of tumor death.

This kind of model can be applied to and validated by the biological model of multicellular spheroids, which is at present considered an optimum in vitro model to study complex aspects of avascular tumor development [16], and so are as well the responses to drug penetration and mechanisms of resistance to chemo or radiotherapy [17]. Multicellular spheroids also seem to be a good experimental approach in order to look for multiscale mathematical modeling that succeeds in relating macroscopic, mesoscopic and microscopic phenomena [18, 19].

In this paper, we extend the results previously presented by Ward [4–6], who used a single set of parameter values; thus, a single curve was calculated thereof. Here, we present a range of feasible solutions for tumor growth, depending on different possible biological responses corresponding to different tumor cell lines. This covers a more realistic scenario. We also analyze the local dynamics of the model, and found a chaotic behavior for same parameter values. This might represent an interesting issue for future studies and experimental validation.

Characterization of tumor growth kinetics in terms of clinically relevant parameters is
increasingly required for optimizing and personalizing treatments. The results of designing a numerical model that is robust in the parameter space of realistic physiological scenarios, and further validated with accurate experimental measurements, suggest its potential as a tool for analyzing different therapy strategies against avascular microtumors and micrometastasis.

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