Modeling Growth Saturation in Avascular Tumors

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Abstract—We comment on a commonly used oxygen diffusion boundary condition in tumor models. The Dirichlet boundary condition at the tumor boundary is unrealistic since it implies that the surrounding tissue is not affected by the presence of the neoplasm. We build an alternative model, which does not assume constant oxygen concentration at the interface and, therefore, predicts lower oxygen tension in the outer layer of the tumor and hence decreased proliferation. This seemingly minor change to the model has consequences on the cell population dynamics and offers a simple alternative to current explanations of the often described phenomenon of growth saturation.

I. INTRODUCTION

In the early phases of tumor development most tumors growing in vivo develop as avascular cell clusters, relying on diffusion from the neighboring healthy vascularized tissue for the supply of oxygen and nutrients and the removal of wastes. Often, these tumors do not grow beyond a certain size and can stay dormant for many years.

The paper of Ward and King [1] analyzes growth saturation and presents a model, which can account for this phenomenon. Their model assumes that nutrients diffuse and are consumed by the cells, which proliferate or die depending on the availability of resources (oxygen, glucose, etc.). The model is defined only inside the tumor and assumes constant nutrient concentration at the tumor boundary. The analysis of Ward and King demonstrates that based on these assumptions, growth saturation is only possible if the necrotic material is transported outside of the tumor. This model is representative of many others, in the sense that it assumes a direct influence of nutrient availability on the proliferative strength of the tumor cells. It is also common to assume constant oxygen levels at the tumor boundary [2], [3], [4]. There are also several models, which do not assume constant concentration at the border [5], [6], [7]. However, the consequences of this choice have not been discussed.

In this short paper we analyze the significance of the mentioned boundary condition for qualitative and quantitative studies alike. Based on a simple model, which does not treat the concentration at the boundary as constant, we identified an alternative reason for growth saturation.

II. METHODS

For our analysis we use a simple model of tumor growth, which includes oxygen transport and production/consumption as well as proliferation-based growth and elastic tissue response. The oxygen concentration in the tissue obeys a reaction-diffusion equation of the form

$$\frac{dc}{dt} = \nabla^2 c + D_1 \left( R^+ (c) - R^- (c) \right),$$

where $c$ is the concentration, $D_1$ is the diffusion coefficient, $R^+ (c)$ is the source term, which depends on the vasculature and blood flow, and $R^- (c)$ is the consumption of oxygen by the cells. For the consumption we take a logistic term $R^- (c) = R_{sat} \frac{c}{c + c_{1/2}}$, where $c_{1/2}$ is the concentration at which the reaction term reaches half maximum and $p$ controls the shape of $R^- (c)$. This reflects that the consumption is bounded by the amount of oxygen available but also reaches a maximum if oxygen is unlimited. The delivery of oxygen depends on the partial pressure difference between the blood and the tissue. It increases in hypoxic areas, while in regions with high concentrations, only little oxygen is delivered. Therefore, outside the tumor we assume a constant source with a linear term, which penalizes deviations from the optimal concentration (i.e. $R^+ (c) = R_0 - R_p (c - c_0)$).

Since we focus on avascular tumors, the source term inside the tumor is zero. More advanced models are discussed elsewhere [4].

As in our previous paper [4], we treat cell proliferation macroscopically using an elastic growth model. We assume the growth rate to be zero for $c < c_{1/2}$ while increasing linearly to a maximum at $c = c_{BC}$. For simplicity we set the displacement boundary condition to zero.

The parameters have been taken from the literature where available. The diffusion constant in tissue is approximately $D_1 = 2.4 \times 10^{-5}$ cm$^2$/s [8]. Based on estimates of oxygen partial pressure in the human breast, we set the oxygen to $c_{BC} = 2.5 \times 10^{-3}$ cm$^{-3}$/O$_2$ [9] at the far boundary. Since this is the preferred concentration, we set $c_0 = c_{BC}$. The saturation consumption must be $R_{sat} = R_0 \frac{c_{1/2}}{c_{BC} + c_{1/2}}$ in order to balance the source when there is no tumor. The reaction term depends largely on the tissue and varying conditions such as altitude, physical activity etc. Under resting the zero order reaction term has been estimated to be $R_0 = 1.7 \times 10^{-4}$ cm$^{-3}$/O$_2$ [8]. Other parameters, such as $c_{1/2}$ and $R_p$ can only be guessed. For lack of better information we set $p = 1$, $c_{1/2} = t_d = 0.6c_{BC}$, $R_p = 2 \times 10^{-2}$ s$^{-1}$.

We solve the model equations in polar coordinates for the spherically symmetric case using Galerkin finite element methods. The domain is described by the tumor interface position $r = r_I$ and the far boundary position $r = r_{MAX}$. We assume the growth to be much slower than oxygen transport and elastic response. Therefore, these processes can be treated in a quasi-static manner, i.e. in order to compute...
the current growth rate we use the static solution from Eq. 1 for the current domain description.

III. RESULTS

The Dirichlet boundary condition at the tumor surface can be enforced in our framework by an infinite diffusion constant $D_i$ or an infinite linear source coefficient $R_p$ outside the tumor. While such settings are of course hardly realistic, they allow to study the effects of applying Dirichlet boundary conditions to the tumour growth problem. The results in this section are shown for the default parameters mentioned above - and for the case when either $D_i$ or $R_p$ is increased by a factor of 100.

In Fig. 1 the evolution of the tumor volume is plotted against time. The shape of the curves (first exponential, then linear and finally saturation) is reminiscent of the result in Ward and King [1]. Note that although we have not assumed any volume loss due to necrosis, the growth curve does reach a saturation value. In Fig. 2 the oxygen concentration profile of a tumor with a diameter of 1mm is shown for different parameter settings. The figure illustrates the effect of increasing $D_i$ or $R_p$ in the healthy tissue and demonstrates that the actual oxygen tension can be significantly reduced at the tumor boundary. In Fig. 3 the reaction terms are depicted. The effect of increasing $R_p$ is to raise the source by $R_p(c_0-c)$, which in the case where $R_p$ is a factor 100 higher leads to a significantly larger source close to the tumor.

IV. DISCUSSION

Using a simple model we have shown that volume loss and transport of cell debris across the tumor boundary is not necessary to explain growth saturation. While we do not want to suggest that there is no volume loss due to apoptosis or necrosis, these results might suggest that its influence has been eventually overestimated in the past. Especially removal of necrotic (vs. apoptotic) cells might be slower than implied, since the resulting cell debris must be ingested by neutrophils and macrophages.

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REFERENCES