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A viscoelastic model for avascular tumor growth

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Abstract

In this article, we present a new continuous model for tumor growth . This model describes the evolution of three components: sane tissue, cancer cells and extracellular medium. In order to render correctly the cellular division, this model use a discrete description of the cell cycle (the set of steps a cell has to undergo in order to divide). To account for cellular adhesion and the mechanics which may influence the growth, we assume a viscoelastic mechanical behavior. This model extends the one presented in [4] with a more realistic description of the forces that drive the movement.

1 Introduction

In a sketchy way, a tumor arises after several mutations of cells that have made them less sensible to anti-growth factors or lack of nutrients, for instance. This may lead to uncontrolled division of these cells.

In order to divide, a cell needs nutrients (such as oxygen), which is obtained from its close environment in the avascular phase. As the tumor grows, some cells do not get any more enough nutrient and turn to a quiescent state where they no longer divide waiting for the environment to become favorable again. Therefore, for a realistic description of cancer growth, one has to describe the evolution of the concentration of nutrients. Tumor cells have also the ability to produce their energy from glucose, whose production lowers the pH of the medium. This toxicity may harm cancer or healthy cells and favor tumoral invasion. Finally, it is known that cellular adhesion has an influence on tumor growth [2].

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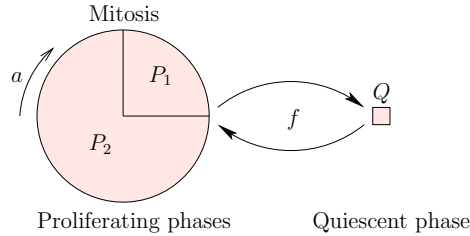


Figure 1: Scheme of the simplified cell-cycle used in this paper and presented in [4].

There are many mathematical models describing solid tumor growth. Roughly they can be divided in two classes. In discrete models, one describes the evolution of cells individually. In this class, we find for instance cellular automata or agent-based models. These approaches are very efficient to describe the cell-scale aspects of tumor growth, they are computationally expensive, which makes them difficult to use for a large number of cells. Furthermore, it is also difficult to account for the mechanical effects (cell-to-cell mechanical interaction) influencing tumor growth.

Continuous models compute the evolution of cellular densities or of the boundary of the tumor (when strong geometrical assumptions apply)[3]. They are much less expensive to discretize but, as they deal with averages over a large number of cells, they can not always account correctly for the microscopic or genetic aspects of tumor growth. Most of these models are based on partial differential equations, such as reaction-diffusion equations or advection equations [1]. In this paper, we present a model of this kind, where mass flow is obtained through a viscoelastic description of the tumor mass. The outline of this paper is the following one. In Sec. 2, we present the mathematical model and in Sec. 3, we show a numerical experiment performed with this model.

2 Description of the model

Our aim is to describe the evolution in time of the density (number of cells per unit volume) of few cellular species. The density of sane tissue at time t in the location \mathbf{x} will be denoted by $S(t, \mathbf{x})$, the density of extra-cellular medium or interstitial liquid by $L(t, \mathbf{x})$. Cancer cells are described by their densities in each of the two proliferation phases $P_1(t, a, \mathbf{x})$, $P_2(t, a, \mathbf{x})$ and quiescent phase $Q(t, \mathbf{x})$ respectively. The proliferation phases are age-structured as shown in Fig. 1. We refer the reader to [4] for a detailed presentation.

We assume that the total number of species is constant per unit volume, *i.e.*

$$S + L + \int_a (P_1 + P_2) da + Q = N_0. \quad (1)$$

In the sequel, we will take $N_0 = 1$.

We denote by $C(t, \mathbf{x})$ the concentration of nutrients and $H(t, \mathbf{x})$ the acidity. We also consider that the cellular division generates a movement described by a macroscopic velocity denoted by $\mathbf{v}(t, \mathbf{x})$.

We make the following biological assumptions:

- Healthy cells may die if the concentration of nutrient is too low or if the total cell density is too high or if the acidity is high enough. We neglect division of these cells.
- Cancer cells may die for the same reasons than healthy cells but they are more resistant to harsh conditions. (Therefore the corresponding survival thresholds will be less restrictive.)
- Proliferating cells undergo division. If the environment is not favorable enough (in term of hypoxia, overpopulation and acidity) they become quiescent and stop dividing.
- Dead cells are metabolized and are accounted for in the extracellular phase.

2.1 Equation for the populations of cells

In order to obtain the equations giving the evolution of cellular densities, we use the mass-balance principle for every specie. The equation for the healthy cells is

$$\partial_t S + \nabla \cdot (\mathbf{v}S) = -\alpha_S f_{AS} S, \quad (2)$$

where f_{AS} is the function giving the rate of apoptosis for healthy cells. It has the form

$$f_{AS} = \mathbf{1}_{\{C < \tau_{0,S} \text{ or } \Sigma_p > K_S \text{ or } H > H_{0,S}\}}, \quad (3)$$

where Σ_p is the indicator for overpopulation and is computed as $\Sigma_p = S + \int_0^{a_{max,P_1}} P_1(a) da + \int_0^{a_{max,P_2}} P_2(a) da + Q$. We have denoted by $\tau_{0,S}$, K_S and $H_{0,S}$ the thresholds for hypoxia, overpopulation and toxicity respectively.

For the tumor cells in phase P_1 , the equation is:

$$\partial_t P_1 + \partial_a P_1 + \nabla \cdot (\mathbf{v}P_1) = -\alpha_P f_{AP} P_1, \quad (4)$$

with a ranging from 0 to a_{max,P_1} . The function f_{AP} describing apoptosis has the same expression as Eq. (3) with different (less restrictive) parameters ($\tau_{0,P} < \tau_{0,S}$, $K_P > K_S$ and $H_{0,P} < H_{0,S}$). The equation for cells in phase P_2 is similar:

$$\partial_t P_2 + \partial_a P_2 + \nabla \cdot (\mathbf{v}P_2) = -\alpha_P f_{AP} P_2, \quad (5)$$

for $a = 0$ to a_{max,P_2} . The boundary conditions accounting for the transition between phases in Fig. 1 are:

$$P_1(a = 0) = 2P_2(a_{max,P_2}), \quad (6)$$

which describes the mitosis and

$$P_2(a = 0) = f_Q P_1(a_{max,P_1}) + \left[\frac{d}{dt} f_Q \right]^+ Q(t^-), \quad (7)$$

where f_Q is the boolean function checking the environmental factors for a cell to go or come back from the quiescent state:

$$f_Q = 1 - \mathbf{1}_{\{C < \tau_Q \text{ or } \Sigma_p > K_Q \text{ or } H < H_{0,Q}\}}, \quad (8)$$

where again the thresholds are different of those of apoptosis: $\tau_{0,P} < \tau_{0,S} < \tau_Q$, $K_P > K_S > K_Q$ and $H_Q < H_{0,P} < H_{0,S}$. That means that if the environmental conditions are not favorable, then the proliferating cells go into quiescent state and if they become even worse, cells undergo apoptosis.

The equation for the quiescent cells is

$$\partial_t Q + \nabla \cdot (\mathbf{v}Q) = (1 - f)P_1(a = a_{max,P_1}) - \left[\frac{d}{dt} f_Q \right]^+ Q(t^-) - \alpha_P f_{AP} Q \quad (9)$$

with the same notation as above.

We still have to deal with the extra-cellular phase L :

$$\begin{aligned} \partial_t L + \nabla \cdot (\mathbf{v}L) = & \alpha_S f_{AS} S + \int_0^{a_{max,P_1}} \alpha_P f_{AP} P_1 \\ & + \int_0^{a_{max,P_2}} \alpha_P f_{AP} P_2 + \alpha_p f_{AQ} Q \end{aligned} \quad (10)$$

where we have added every source terms coming from the different equations (2), (4), (5) and (9) in order to ensure conservation (1). This means from the biological point of view that every waste produced by the death of any kind of cells enter the extracellular medium.

Collecting the equations leads to

$$\nabla \cdot \mathbf{v} = P_2(a = a_{max,P_2}). \quad (11)$$

2.2 Equation on the velocity

Eq. (11) is not sufficient to determine the velocity \mathbf{v} . The medium is described as being a viscoelastic material: the relation between the stress, pressure and velocity is:

$$\nabla \cdot \sigma - \nabla p = -\nu \Delta \mathbf{v}, \quad (12)$$

where ν denotes the viscosity of the surrounding liquid like for emulsions. The constitutive law for the stress is

$$\partial_t \sigma + \mathbf{v} \cdot \nabla \sigma - \nabla \mathbf{v}^t \sigma - \sigma \nabla \mathbf{v} + \frac{1}{\tau} \sigma = \frac{\beta(\tau)}{\tau} D(\mathbf{v}), \quad (13)$$

where $D(\mathbf{v}) = \frac{\nabla\mathbf{v} + (\nabla\mathbf{v})^t}{2}$ and $\beta(\tau)$ is a function describing the rheological properties of the tissue. In this paper, we neglect the terms $\mathbf{v} \cdot \nabla\sigma - (\nabla\mathbf{v})^t\sigma - \sigma\nabla\mathbf{v}$. The relaxation time τ is given by

$$\tau = (1 - L) + \frac{1 - L}{1 - S}, \quad (14)$$

and the function β by

$$\beta(\tau) = \beta_0 + \tau\beta_\infty. \quad (15)$$

Then, the limit $\tau \rightarrow 0$ leads to $\sigma = \beta(0)D(\mathbf{v})$, which describes the behavior of a Newtonian liquid (*i.e.* the extracellular medium L is liquid). When $\tau \rightarrow \infty$, we obtain $\partial_t\sigma = \beta_\infty D(\mathbf{v})$, which is the law for linear elasticity *i.e.* healthy tissue is considered as elastic. Cell-to-cell adhesion is weaker for cancer cells than for healthy ones and therefore we consider their behavior as being viscoelastic.

2.3 Nutrients and acidity

The oxygen (or nutrient) is consumed by cancer and healthy cells. As proliferating cells consume much more oxygen, their consumption rate is much higher than the one of quiescent or healthy cells. This leads to the equation

$$\begin{cases} -\nabla \cdot (D \nabla C) = -\alpha_C \left(\int_0^{a_{max,P_1}} P_1(a) da + \int_0^{a_{max,P_2}} P_2(a) da \right) C \\ \quad -\alpha_S S - \alpha_Q Q - \Gamma_C C \text{ on } \Omega/O, \\ C = C_0 \text{ on } \partial\Omega, \\ C = C_{max} \text{ on } O, \end{cases} \quad (16)$$

where we have made the stationary assumption because the diffusion time-scale of oxygen is much lower than the time-scale of cellular division.

The acidity is produced by the cancer cells and is transported by the blood vessels:

$$\begin{cases} -\nabla \cdot (D \nabla H) = \alpha_H^P \left(\int_0^{a_{max,P_1}} P_1(a) da + \int_0^{a_{max,P_2}} P_2(a) da \right) + \alpha_H^Q Q - \alpha_H^B \mathbf{1}_O H, \\ H = H_0 \text{ on } \partial\Omega. \end{cases} \quad (17)$$

3 Numerical result

In this section, we present some numerical results of our model. In this numerical experiment, the focus is on the effect of mechanical stress on the shape of the tumor.

The initial tumor is a sphere, the oxygen distribution is isotropic. Hence, with a constant stress in absence of instabilities, the spheroid should keep its spherical form through the computations. In our case, the healthy tissue is softer in a strip around the x axis. This is achieved by changing the density of

sane tissue and liquid according to

$$S = 0.99(1 - N) \times \begin{cases} \frac{1}{2} & \text{if } |x - \frac{L}{2}| < 5\delta x \\ 1 & \text{otherwise,} \end{cases}$$

N being the total density of cancer cells and $L = 1 - N - S$.

The oxygen source is represented by the domain $O = \{|\mathbf{x}| > \frac{L}{2} - 4\delta x\}$, on this domain, we set $C = 0.1$.

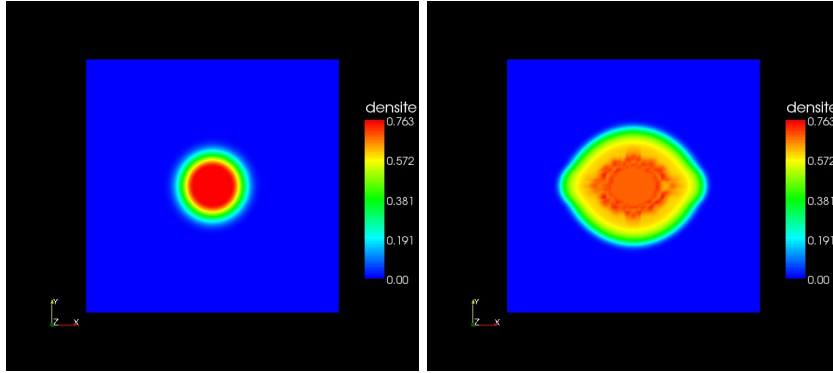


Figure 2: Evolution of a spheroid when the mechanical stress is not isotropic.

With an isotropic stress (or a simpler model as [4]), the tumor would have stayed disc-shaped. The kind of shape obtained in this run is observed in *in-vitro* experiments. Detailed comparison will be discussed in forthcoming work.

4 Conclusion

In this paper, we have presented a mathematical model for avascular tumor growth. The movement of the species obeys to a force balance equation of viscoelastic type. The model accounts, the same time, for microscopic (cell-cycle) and macroscopic (cellular-adhesion, mechanical effects) aspects of the tumoral growth.

This model was initially described to study avascular growth. Yet, through the domain O appearing in Eq. (16) and (17), a coupling could be made with a model describing the evolution of the density of blood vessels during the process of angiogenesis.

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References

- [1] D. Ambrosi and L. Preziosi. On the closure of mass balance models for tumor growth. *Math. Models Methods Appl. Sci.*, 12(5):737–754, 2002.
- [2] R.C. Bast, D.W. Kufe, R.E. Pollock, R.R. Weichselbaum, and J.F. Holland. *Cancer Medicine*. BC Decker Inc, Canada, 2000.
- [3] Avner Friedman. A hierarchy of cancer models and their mathematical challenges. *Discrete Contin. Dyn. Syst. Ser. B*, 4(1):147–159, 2004. Mathematical models in cancer (Nashville, TN, 2002).
- [4] B. Ribba, O. Saut, T. Colin, D. Bresch, E. Grenier, and J.P. Boissel. A multiscale mathematical model of avascular tumor growth to investigate the therapeutic benefit of anti-invasive agents. *J. Theoret. Biol.*, 243(4):532–541, 2006.