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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 uses 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 [18] 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 [12]. This toxicity

Key words and phrases. Avascular tumor growth. Multiscale models. Cell cycle modeling. Fluid dynamics.

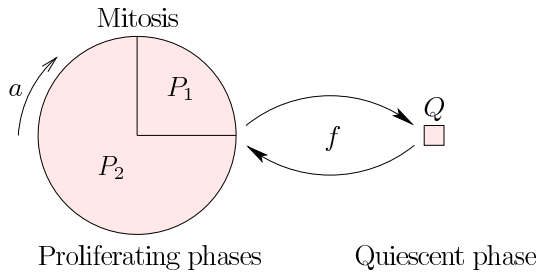

FIGURE 1. Scheme of the simplified cell-cycle used in this paper and presented in [18].

may harm cancer or healthy cells and favor tumoral invasion. Finally, it is known that cellular adhesion has an influence on tumor growth [4, 3].

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 [1, 17]. 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. Yet a precise description at the cellular level is possible [8, 10].

Continuous models compute the evolution of cellular densities or of the boundary of the tumor (when strong geometrical assumptions apply) [9]. 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 [11] or mass-balance equations [2]. Some of these models are accounting for complex phenomena like contact inhibition [20] or cellular adhesion [6]. In this paper, we present a model of this kind, where mass flow is obtained through a viscoelastic description of the tumor mass and describing the mechanical behavior of the healthy tissues, the interstitial liquid and the cancer cells in a compact way. 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 healthy 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 [18] for a detailed presentation.

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

$$S + L + \int_a (P_1 + P_2)\, da + Q = N_0. \tag{1}$$

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 (proportional to the concentration of protons). We also consider that the cellular division generates a movement described by a macroscopic velocity denoted by $\mathbf{v}(t,\mathbf{x})$. In this model, we assume that the movement is passive as it is only caused by the increase of volume due to the mitosis. With this assumption, the various species are transported at the same velocity $\mathbf{v}$. However, the species do not have the same mechanical behavior as the rheological properties depend on cellular densities as shown in Eq. (13) and (14).

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 instantly 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

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

where f_{AS} is the function giving the rate of apoptosis for healthy cells. It has the form of a boolean function (with a value of 1 if the environmental conditions are favorable and 0 otherwise)

$$f_{A_S} = \mathbf{1}_{\{C<\tau_{0,S} \text{ or } \Sigma_p>K_S \text{ or } H>H_{0,S}\}}, \tag{3}$$

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:

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

with a ranging from 0 to a_{max,P_1}. The function f_{A_P} 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:

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

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

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

which describes the mitosis and

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

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

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

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

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

with the same notation as above.

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

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

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 and assumption (1) leads to

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

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:

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

where ν denotes the viscosity of the surrounding liquid like for emulsions. The phenomenological constitutive law for the stress (see [16] for instance) is

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

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 nonlinear terms $\mathbf{v} \cdot \nabla \sigma - (\nabla \mathbf{v})^t \sigma - \sigma \nabla \mathbf{v}$ as the velocities considered are small. The relaxation time τ is given by

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

and the function β by

$$\beta(\tau) = \beta_0 + \tau \beta_\infty. \tag{15}$$

Then, the limit $\tau \to 0$ 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 $\tau \to \infty$, 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. In this work, we have only considered a very limited aspect of cellular adhesion (passive adhesion) as a complete description is out of reach. For a more complete description one can see [19, 14]. In Eq. (14), the expression for τ is rather simple but could be complexified

once more biological insight becomes available on the mechanical behavior of cells. Of course, we have no microscopic justification of such a law. The goal is to have a qualitatively correct behavior of the properties described above.

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. Let us denote by O the domain corresponding to oxygen sources (for instance blood vessels). In this domain the concentration of oxygen is fixed. This leads to the equation

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

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

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

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

For this matter, we have adapted the model from [11].

3. **Numerical results.** In this section, we present some numerical results of our model.

To discretize the mass-balance equations (4), (5), (9), (10), we have used a combination of a WENO [15] and an exponential scheme as described in [5]. For Eq. (12), (13) and (11), we adapt the scheme described in [7]. The viscosity ν in Eq. (12) is taken equal to 0.1 [7].

Note that it is impossible to have precise values for the functions and parameters. Most of the quantities that we consider are taken in order to obtain behavior that are concordant to biological and medical values. A way to recover the information would be to use image-driven simulation in the spirit of [13].

3.1. **Heterogeneity of the medium.** 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 y axis. This is achieved by changing the density of healthy tissue and liquid according to

$$S = 0.99(1-N)\times\begin{cases}\frac{1}{2} \text{ if } |y-\frac{L}{2}| < 3.5\delta y \\ 1 \text{ otherwise,}\end{cases}$$

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

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

For comparison purposes, we have also plotted the contour of the tumoral density 0.3 as obtained from the same experimental conditions with a Newtonian model

based on [5] where the viscosity ν involved in the Stokes equation is given by the expression $\nu = 1 + S - L$ (with a simpler expression for the viscosity, the heterogeneity of the medium is not sensible).

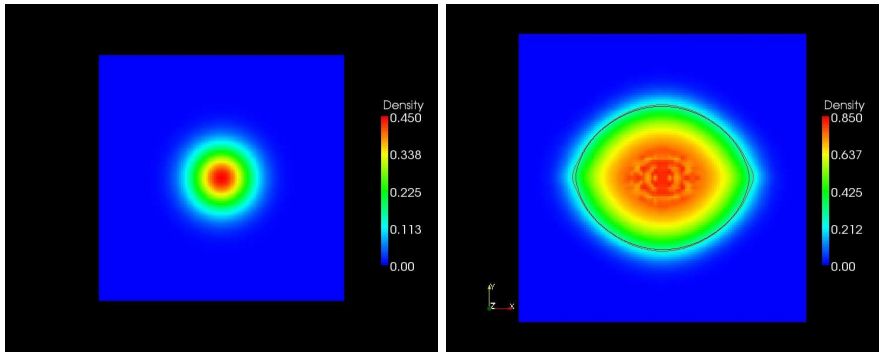

FIGURE 2. Evolution of a spheroid when the medium is mechanically heterogeneous. The contours corresponding to a density of 0.3 are shown in black (Newtonian model) and red (viscoelastic model).

With the viscoelastic model, a lemon-like shape is observed, whereas with a Newtonian model an ovoid is obtained. A detailed comparison (not presented here) shows that the main difference is indeed observed on the outer rim of the tumor. Even limited, this difference can eventually lead to bigger differences as the outer rim is composed of proliferating cells with exponential growth.

With an homogeneous medium (or a simpler model as [18]), 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.

3.2. **Influence of the stiffness of the external medium.** In this experiment, we consider the influence of the stiffness of the healthy tissue on the tumoral growth. The initial tumor is a spheroid. We plot the final tumoral density for two values ($\beta_\infty = 1$ and $\beta_\infty = 50$) of the parameter β_∞ in Eq. (15) on Fig. 3.

The experimental setup (oxygen sources,...) is the same as in the previous experiment.

For a lower stiffness the tumor is bigger as its growth is less restricted by the surrounding tissue. Let us also denote the necrotic core in the central part of the tumor, where nutrients are no longer available.

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 (limited 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.

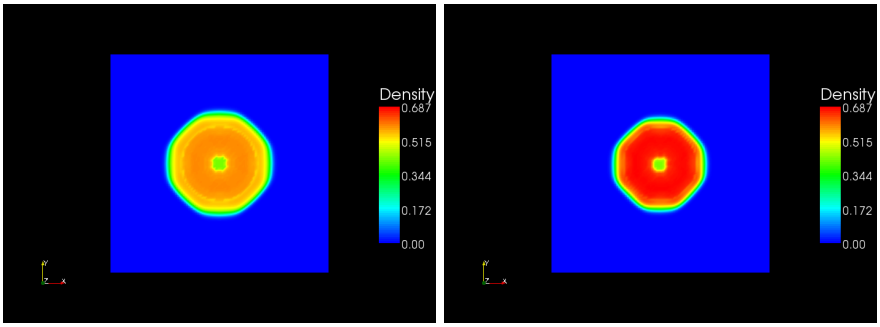

FIGURE 3. Evolution of a spheroid for two different stiffness of the healthy tissue (through different values of the parameter β_∞ in Eq. (15)).

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