Multiphase modeling of tumor growth and extracellular matrix interaction: Mathematical tools and applications

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Abstract

In a multiphase modeling framework tumors are described as a mixture of tumor and host cells within a porous structure constituted by a remodeling extracellular matrix (ECM), which is wet by a physiological extracellular fluid. The main focus of the model presented in this article is the description of the mechanical interactions of the growing tumor with the host tissue, their influence on tumor growth, and the attachment/detachment mechanisms between cells and ECM. Starting from some recent experimental evidences, the model proposes to address the interaction forces involving the extracellular matrix via some concepts deriving from viscoplasticity. Then it is applied to describe the growth of tumor cords and the formation of fibrosis.

1 Introduction

As recently reviewed in [6], the first models dealing with avascular tumor growth worked under the hypothesis that the tumor is made by only one type of cells having a constant density. In the last few years it became evident that this description was insufficient and multiphase models started being developed [5, 15, 16, 17, 18, 22, 23, 24] (see also the review articles [8] and [25]). This new setting allows to describe density variation within the tumor and the host tissue, to evaluate the evolution of stresses and to take into account the mechanical interactions among the constituents, e.g., cells and extracellular matrix, and between tissues.

For instance, Chaplain *et al.* [20] developed a model accounting for contact inhibition of growth and showed how a misperception of the local compression state of the tissue, and consequently also of the stress exerted on a cell, can generate by itself a clonal advantage on the surrounding cells leading to the replacement and the invasion of the healthy tissue by the tumor. In addition to biomechanical effects, the model also considers the effect of a stress-dependent production of extracellular matrix (ECM) and of matrix degrading enzymes (MDEs). Frank *et al.* [22, 23] developed instead a model of ductal carcinoma, in which all constituents, solid and liquid, move with the same velocity. The model also includes the mechanical interaction with the duct walls. Breward *et al.* [14, 16] deduced a one-dimensional multiphase model to describe vascular tumor growth and tumor vessel interaction.

Still within the multiphase modeling framework, here we aim at describing soft tissues as mainly constituted by ECM and cells. The former will be schematized as a network of fibrous material, the latter as an ensemble of sticky and highly deformable baloons living in it. More specifically, we will focus on a mixture of four constituents: tumor and host cells within a porous structure represented by the extracellular matrix, which is wet by a physiological extracellular fluid. We will take into account tumor growth, ECM remodeling and mechanical interaction with the host tissue. Generalizations to more cell populations or to more ECM constituents will also be discussed.

The main focus of the article is on the interaction forces between cells and ECM, starting from the experimental evidences presented in Baumgartner *et al.* [11], in Canetta *et al.* [19], and in Sun *et al.* [32]. These papers, in fact, study in detail the attachment/detachment properties of the adhesion sites on the cell membrane.

For instance, in [11] the described test consists in gluing a functionalized microsphere at the tip of an AFM cantilever (atomic force microscopy). After putting the microsphere in contact with the cell and allowing enough time to attach well, the cantilever is pulled away at a constant speed (in the range 0.2–4 μm/sec). Adhesion gives rise to the measurement of a stretching force and a characteristic jump indicating the rupture of an adhesive bond. Actually, since a sphere binds to many receptors, it is common to experience multiple unbinding events occurring at different instants during the single experiment.

Transferring this concept to the macroscopic scale, one may infer that if the pressure acting on a cell is not strong enough, then the cell moves together with the ECM: They can deform but adhesion sites are not broken. On the other hand, if an ensemble of cells is subject to a sufficiently high tension or shear, then some bonds break and new ones may form. This occurs in particular during growth, when the duplicating cell needs to displace its neighbors to make room for its sister cells. Such a qualitative description calls for a modeling of cell-ECM interaction forces involving viscoplastic phenomena.

We will then first deduce a general multiphase model, and next we will simplify it in view of the observation that the interactions with the liquid are much weaker than those involving cells and ECM. More specifically, the simplification consists in that the equations describing the evolution of the interstitial pressure and of the liquid flow can be solved after solving those related to the solid constituents, i.e., cells and ECM, which in turn do not depend directly on the liquid and pressure evolution.

The model is then specialized to two cases: in the first one the tumor grows in a rigid non-remodeling ECM around one or more vessels from which the necessary nutrients diffuse out; in the second one growth is coupled to ECM remodeling. One of the by-product of the latter model is the possibility to describe the formation of fibrotic tissues, namely tissues stiffer than normal that can be felt with a self-test.

Specifically, the paper develops as follows. In the section following this Introduction the general multiphase model is developed, focusing first on the constitutive modeling of the interaction forces and then on that of the stress tensor. A simplified model is subsequently deduced under the observation that the interactions with the liquid are negligible if compared, for instance, with cell-ECM interactions. The inclusion of diffusion of nutrients and chemical factors relevant for growth is also described. Finally, the third section describes the two applications mentioned above, and the fourth draws some conclusions and briefly sketches research perspectives.

2 Multiphase modeling

Soft tissues are made of several cell populations living within a porous structure, the extracellular matrix, which is wet by a physiological extracellular fluid. In principle, such a physical system is a rather complicated mixture of many different interacting components; however, aiming at focusing on the main ingredients of a mathematical model of tumor growth, we restrict the number of state variables according to the following assumptions:

Assumption 2.1 (Cell populations)**.** We account for two cell populations, namely *tumor cells* and *normal cells* belonging to the host tissue. We denote by ϕ_t, $\phi_h \in [0, 1]$ their volume ratios, respectively.

Assumption 2.2 (Extracellular matrix)**.** We consider the ECM as a whole without distinguishing its components (collagen, elastin, fibronectin, and so on), though we are aware that they contribute differently to the mechanical and adhesive properties of the matrix and have different production and degradation mechanisms. We denote by $\phi_m \in [0, 1]$ the ECM volume ratio.

Assumption 2.3 (Extracellular fluid)**.** We assume that the extracellular fluid, whose volume ratio is denoted by $\phi_\ell \in [0, 1]$, fills all interstices of the mixture, so that no empty space is left within the latter (*saturated mixture*).

We simply remark that the inclusion of other cell populations as well as of more ECM components is a purely technical matter, which does not affect the basic ideas underlying the mathematical modeling of the system. We briefly discuss this topic in Remark 2.4 at the end of the next subsection and refer the interested reader to [10] for more details.

2.1 Basic equations

Let us introduce the index set $\mathcal{C} = \{t, h, m, \ell\}$ to identify the components of the mixture; if $\alpha, \beta \in \mathcal{C}$, it will be sometimes useful in the sequel to use the notations $\mathcal{C}_\alpha$, $\mathcal{C}_{\alpha,\beta}$ to denote the index sets $\mathcal{C} \setminus \{\alpha\}$, $\mathcal{C} \setminus \{\alpha, \beta\}$, respectively. In addition, whenever necessary we will use the letter d for the spatial dimension ($d = 1, 2, 3$ from the physical point of view).

The saturation constraint claimed by Assumption 2.3 implies

$$\sum_{\alpha\in\mathcal{C}} \phi_\alpha = 1; \tag{2.1}$$

on the other hand, for each of the above state variables one can write a mass balance equation of the form

$$\frac{\partial \phi_\alpha}{\partial t} + \nabla \cdot (\phi_\alpha \mathbf{v}_\alpha) = \Gamma_\alpha, \qquad (\alpha \in \mathcal{C}) \tag{2.2}$$

where $\mathbf{v}_\alpha \in \mathbb{R}^d$, $\Gamma_\alpha \in \mathbb{R}$ are the velocity and the source/sink term of the constituent α, respectively. Equation (2.2) implicitly assumes that all constituents of the mixture have the same (constant) mass density ρ, which equals that of the physiological fluid. Summing Eq. (2.2) over α and taking Eq. (2.1) into account yields

$$\nabla \cdot \left(\sum_{\alpha\in\mathcal{C}} \phi_\alpha \mathbf{v}_\alpha \right) = \sum_{\alpha\in\mathcal{C}} \Gamma_\alpha; \tag{2.3}$$

if in addition the mixture is *closed*, so that mass exchanges occur only among its constituents, then

$$\sum_{\alpha\in\mathcal{C}} \Gamma_\alpha = 0 \tag{2.4}$$

and Eq. (2.3) rewrites as

$$\nabla \cdot \left(\sum_{\alpha\in\mathcal{C}} \phi_\alpha \mathbf{v}_\alpha \right) = 0. \tag{2.5}$$

Eqs. (2.3), (2.5) are differential versions of the algebraic saturation constraint (2.1). Following a popular custom in mixture theory, we can define the *composite velocity* $\mathbf{v}_c$ of the mixture as the weighted average of the velocities of the constituents:

$$\mathbf{v}_c = \sum_{\alpha\in\mathcal{C}} \phi_\alpha \mathbf{v}_\alpha, \tag{2.6}$$

so that for a closed mixture it follows from Eq. (2.5) that $\nabla \cdot \mathbf{v}_c = 0$. This result can be regarded as the counterpart of the incompressibility constraint for a classical continuum; notice, however, that in spite of the assumption of constant density for each constituent one is not allowed here to conclude on the solenoidality of any of the vectors $\mathbf{v}_\alpha$. Furthermore, we remark that sometimes Eq. (2.4) cannot even be imposed, whence one definitely loses the solenoidality of the composite velocity itself. This is, for instance, the case when external mass sources/sinks are introduced to describe inflow or outflow processes related to a homogenized vascular or lymphatic structure within the mixture (Breward *et al.* [14, 16], Franks and King [24]).

In multiphase models velocity fields are determined by taking into account the mechanical response of the constituents to the mutual interactions. Specifically, in describing growth phenomena the inertial effects are negligible, therefore the corresponding terms can be dropped in the momentum equations. By consequence the latter read

$$-\nabla \cdot (\phi_\alpha \mathbb{T}_\alpha) + \phi_\alpha \nabla p = \mathbf{m}_\alpha, \qquad (\alpha \in \mathcal{C}) \tag{2.7}$$

where:

- $p \in \mathbb{R}$ is introduced as a Lagrange multiplier due to the saturation constraint (2.1) and is then classically identified with the *interstitial pressure* of the extracellular fluid;
- $\mathbb{T}_\alpha \in \mathbb{R}^{d\times d}$ is the so-called *excess stress tensor* of the constituent α, accounting for the characteristic internal stress of the latter;
- $\mathbf{m}_\alpha \in \mathbb{R}^d$ is the resultant of the forces acting on the constituent α due to the interactions with the other components of the mixture.

More in detail, in the theory of deformable porous media the excess stress tensor $\mathbb{T}_\ell$ of the fluid is usually neglected in order to get Darcy-like laws (see Section 2.2). Consequently, the corresponding momentum equation (2.7) for $\alpha = \ell$ simplifies as

$$\phi_\ell \nabla p = \mathbf{m}_\ell. \tag{2.8}$$

Remark 2.4. In order to take more cell populations into account it is technically sufficient to allow the index α in Eqs. (2.2), (2.7) to range in a larger index set $\mathcal{C}$. Similarily if some of the components of the ECM need to be distinguished explicitly. However, as far as this second case is concerned we remark that ECM fibers are usually so tangled that it is reasonable to invoke the *constrained mixture hypothesis*, which amounts in essence to assuming that all ECM constituents move with the same velocity $\mathbf{v}_m$. This way all mass balance equations for the components of the ECM are featured by $\mathbf{v}_m$, and no extra momentum equation is needed besides

$$-\nabla \cdot (\phi_m \mathbb{T}_m) + \phi_m \nabla p = \mathbf{m}_m. \tag{2.9}$$

Of course, all consituents of the ECM contribute to the excess stress tensor $\mathbb{T}_m$ according to their relative proportions, and $\mathbf{m}_m$ accounts for all interactions involving all ECM constituents and cell populations [10].

2.2 Interaction forces

The interaction forces $\mathbf{m}_\alpha$ appearing in Eq. (2.7) can be specialized, according to their definition, as

$$\mathbf{m}_\alpha = \sum_{\beta \in \mathcal{C}_\alpha} \mathbf{m}_{\alpha\beta},$$

where $\mathbf{m}_{\alpha\beta}$ represents the external force exerted on the constituent α by the constituent β. Clearly, we must have $\beta \neq \alpha$ because internal forces of the constituent α are accounted for by the stress tensor $\mathbb{T}_\alpha$.

In mixture theory one proves that the sum of the $\mathbf{m}_\alpha$'s equals the global momentum transfer due to mass exchanges produced by phase transitions among the components. In biological phenomena, however, such a momentum transfer is very small compared to the magnitude of the interaction forces (see [30]), hence one can say that the $\mathbf{m}_\alpha$'s sum to zero, as it is not surprising because they act as internal forces among the constituents:

$$\sum_{\alpha \in \mathcal{C}} \mathbf{m}_\alpha = 0. \tag{2.10}$$

Here we further reinforce this condition assuming, consistently with an *action-reaction principle*, that

$$\mathbf{m}_{\alpha\beta} = -\mathbf{m}_{\beta\alpha}, \qquad \forall\, \alpha,\, \beta \in \mathcal{C},\, \alpha \neq \beta. \tag{2.11}$$

Let us now fix $\alpha = \ell$ and focus on the interaction forces between the extracellular fluid and the other constituents of the mixture. Darcy-like laws are obtained by taking $\mathbf{m}_{\ell\beta}$ proportional to the relative velocity between the fluid and the constituent β via a positive definite matrix $\mathbb{M}_{\ell\beta} \in \mathbb{R}^{d\times d}$, i.e.,

$$\mathbf{m}_{\ell\beta} = \mathbb{M}_{\ell\beta}(\mathbf{v}_\beta - \mathbf{v}_\ell). \tag{2.12}$$

It is worth pointing out that $\mathbb{M}_{\ell\beta}$ depends in general in a nonlinear way on the volume ratios ϕ_ℓ, ϕ_β of the interacting constituents. Also notice that here and throughout the paper $\mathbb{I} \in \mathbb{R}^{d\times d}$ will denote the identity matrix. From Eq. (2.12) we deduce

$$\mathbf{m}_\ell = \sum_{\beta\in\mathcal{C}_\ell} \mathbb{M}_{\ell\beta}(\mathbf{v}_\beta - \mathbf{v}_\ell) = \sum_{\beta\in\mathcal{C}_\ell} \mathbb{M}_{\ell\beta}\mathbf{v}_\beta - \mathbb{M}_\ell \mathbf{v}_\ell, \tag{2.13}$$

where we have denoted $\mathbb{M}_\ell := \sum_{\beta\in\mathcal{C}_\ell} \mathbb{M}_{\ell\beta}$ for brevity; inserting then Eq. (2.13) into Eq. (2.8) we get the (generalized) *Darcy law*

$$\sum_{\beta\in\mathcal{C}_\ell} \mathbb{M}_{\ell\beta}(\mathbf{v}_\beta - \mathbf{v}_\ell) = \phi_\ell \nabla p \tag{2.14}$$

relating the relative motion of the fluid within the mixture to the local pressure gradient. Since each $\mathbb{M}_{\ell\beta}$, $\beta \in \mathcal{C}_\ell$, is positive definite, so is also $\mathbb{M}_\ell$, and therefore invertible. From Eq. (2.14) we obtain then

$$\mathbf{v}_\ell = \mathbb{M}_\ell^{-1}\left(\sum_{\beta\in\mathcal{C}_\ell} \mathbb{M}_{\ell\beta}\mathbf{v}_\beta - \phi_\ell \nabla p\right); \tag{2.15}$$

considering moreover that $\phi_\ell = 1 - \sum_{\beta\in\mathcal{C}_\ell} \phi_\beta$ (cf. Eq. (2.1)), we see that Eq. (2.15) allows to represent the velocity of the extracellular fluid in terms of the volume ratios and velocities of the remaining components of the mixture, along with the interstitial pressure p. Substituting now this expression of $\mathbf{v}_\ell$ into Eq. (2.3) we find, after some standard algebra,

$$\nabla\cdot\left(\phi_\ell^2 \mathbb{M}_\ell^{-1}\nabla p\right) = \nabla\cdot\left(\sum_{\beta\in\mathcal{C}_\ell}\left(\phi_\ell \mathbb{M}_\ell^{-1}\mathbb{M}_{\ell\beta} + \phi_\beta \mathbb{I}\right)\mathbf{v}_\beta\right) - \sum_{\beta\in\mathcal{C}} \Gamma_\beta. \tag{2.16}$$

In the case that condition (2.4) holds, the second term at the right-hand side of Eq. (2.16) drops and one simply obtains an equation for p, formally independent of any unknown quantity linked to the extracellular fluid.

Let us consider now the interaction forces $\mathbf{m}_{th} = -\mathbf{m}_{ht}$ among cell populations. Since cellular mechanical properties are virtually not influenced by the progession state, we assume that all cells respond in the same way to the compression of the other surrounding cells, independently of the specific population they belong to. From the mechanical point of view this corresponds to regarding tumor and host cells as a unique population with the same excess stress tensor, henceforth denoted by $\mathbb{T}_\phi$:

$$\mathbb{T}_\phi := \mathbb{T}_t = \mathbb{T}_h; \tag{2.17}$$

then tumor cells press host cells with a stress proportional to $\nabla\cdot(\phi_t \mathbb{T}_\phi)$, and at the same time are pressed by the latter with a stress proportional to $\nabla\cdot(\phi_h \mathbb{T}_\phi)$. In view of an integral balance law, these contributions have to be multiplied by the volume ratio of the population they act upon, with reference to the overall cellular component of the mixture. Defining $\phi := \phi_t + \phi_h$, the net interaction force $\mathbf{m}_{th}$ is consequently given by

$$\mathbf{m}_{th} = \frac{\phi_t}{\phi}\nabla\cdot(\phi_h \mathbb{T}_\phi) - \frac{\phi_h}{\phi}\nabla\cdot(\phi_t \mathbb{T}_\phi), \tag{2.18}$$

so that, owing to Eqs. (2.7), (2.12), the momentum equations for the cell populations specialize as

$$-\frac{\phi_\alpha}{\phi}\nabla\cdot(\phi\mathbb{T}_\phi)+\phi_\alpha\nabla p=\mathbf{m}_{\alpha m}-\mathbb{M}_{\ell\alpha}(\mathbf{v}_\alpha-\mathbf{v}_\ell),\qquad(\alpha=t,\,h). \tag{2.19}$$

Summing Eq. (2.19) for $\alpha=t,h$ gives the force balance equation for the ensemble of cells without distinguishing tumor and host cells and assuming that they respond in the same way to compression.

Finally, we consider the interaction forces $\mathbf{m}_{\alpha m}$ between cells and ECM. We observe that in principle they depend on the volume ratios of both the ECM constituents and the cells, and consequently also on the portion of 'free' space ϕ_ℓ filled by the extracellular fluid (recall the saturation constraint (2.1)); in particular, they become very large when $\phi_\ell\to 0$, due to the lack of available space. In addition, it is known that there is an optimal concentration of ECM favoring cell motility, which then decreases as the ECM content becomes both smaller and larger, respectively, because of the lack of substrate to move on in the first case, and of the increased number of adhesive links in the second case. The observation that cells hardly move when there is too little or too much extracellular matrix can be rendered by saying that $\mathbf{m}_{\alpha m}$, $\alpha\in\mathcal{C}_{m,\ell}$, increase for both small and large ϕ_m.

As a first approximation, one can still mimic Eq. (2.12) and assume $\mathbf{m}_{\alpha m}$ to be proportional to the relative velocity $\mathbf{v}_m-\mathbf{v}_\alpha$, which amounts in essence to envisaging a viscous friction between cells and ECM. Introducing new positive definite matrices $\mathbb{M}_{\alpha m}\in\mathbb{R}^{d\times d}$ for $\alpha=t$, h one then has

$$\mathbf{m}_{\alpha m}=\mathbb{M}_{\alpha m}(\mathbf{v}_m-\mathbf{v}_\alpha), \tag{2.20}$$

where the $\mathbb{M}_{\alpha m}$'s depend in turn non-linearly on the volume ratio ϕ_m and possibly also on ϕ_α.

A more accurate modeling of the attachment/detachment process occurring between cells and ECM calls however for an alternative form of the interaction terms $\mathbf{m}_{\alpha m}$. In particular, on the basis of the experiments performed by Baumgartner *et al.* [11], Canetta *et al.* [19], and Sun *et al.* [32], it can be inferred that to each cell population α there corresponds a minimal threshold $\sigma_{\alpha m}$ of the strength of the interaction force with the extracellular matrix causing the detachment. If $|\mathbf{m}_{\alpha m}|<\sigma_{\alpha m}$ then the interaction is not strong enough and cells remain attached to the ECM; conversely, if $|\mathbf{m}_{\alpha m}|\geq\sigma_{\alpha m}$ they detach and in this case, following some guidelines of visco-plasticity, we can recover the idea of proportionality of the force in excess to the relative velocity $\mathbf{v}_m-\mathbf{v}_\alpha$. This is mathematically expressed by

$$\mathbb{M}_{\alpha m}(\mathbf{v}_m-\mathbf{v}_\alpha)=\begin{cases}0 & \text{if } |\mathbf{m}_{\alpha m}|<\sigma_{\alpha m}\\ (|\mathbf{m}_{\alpha m}|-\sigma_{\alpha m})\,\dfrac{\mathbf{m}_{\alpha m}}{|\mathbf{m}_{\alpha m}|} & \text{if } |\mathbf{m}_{\alpha m}|\geq\sigma_{\alpha m}\end{cases} \tag{2.21}$$

or, in a more compact form,

$$\mathbb{M}_{\alpha m}(\mathbf{v}_m-\mathbf{v}_\alpha)=\left(1-\frac{\sigma_{\alpha m}}{|\mathbf{m}_{\alpha m}|}\right)^+\mathbf{m}_{\alpha m}, \tag{2.22}$$

where $(\cdot)^+$ denotes the positive part of the expression in parenthesis. This relation defines implicitly $\mathbf{m}_{\alpha m}$ in terms of the relative velocity $\mathbf{v}_m-\mathbf{v}_\alpha$; notice however that, unlike the previous viscous case (cf. Eq. (2.20)), such a definition is univocal only for $|\mathbf{m}_{\alpha m}|\geq\sigma_{\alpha m}$, when Eq. (2.22) yields indeed

$$\mathbf{m}_{\alpha m}=\left(1+\frac{\sigma_{\alpha m}}{|\mathbb{M}_{\alpha m}(\mathbf{v}_m-\mathbf{v}_\alpha)|}\right)\mathbb{M}_{\alpha m}(\mathbf{v}_m-\mathbf{v}_\alpha). \tag{2.23}$$

In particular, it can be observed that Eq. (2.20) is recovered from Eq. (2.22) or Eq. (2.23) in the limit case $\sigma_{\alpha m}=0$. We remark that $\sigma_{\alpha m}$ is a function of the ECM volume ratio, $\sigma_{\alpha m}=\sigma_{\alpha m}(\phi_m)$, as the number of adhesion bonds depends on the density of ECM.

Eqs. (2.15), (2.19), and (2.22) allow in principle to express the velocity fields $\mathbf{v}_\ell$, $\mathbf{v}_t$, $\mathbf{v}_h$ in terms of the internal and external stress on the corresponding components of the mixture, as well as of the velocity $\mathbf{v}_m$ of the extracellular matrix.

Concerning the latter, we remark that its momentum equation can be straightforwardly replaced by the analogous equation for the whole mixture, which is obtained summing Eqs. (2.7) over $\alpha \in \mathcal{C}$ while taking Eqs. (2.1) and (2.10) into account

$$-\nabla \cdot (\phi \mathbb{T}_\phi + \phi_m \mathbb{T}_m) + \nabla p = 0. \tag{2.24}$$

2.3 Stress tensors

As usual, the momentum equations above call for the specification of the constitutive laws describing the response of the cells and the extracellular matrix to stress. However, unlike the inert matter dealt with by classical continuum mechanics, living materials continuously change, indeed ECM is frequently remodeled and cells undergo proliferation and death processes during their evolution. There is then a conceptual difficulty in describing tumors as solid masses, for this would force to identify a relationship between stress and deformation. This ultimately requires a reference configuration, and therefore a Lagrangian treatment of the system. Such a key issue has been recently addressed for tumor and tissue growth in several papers (see e.g., [1, 2, 4, 26, 27, 31]) resorting to the evolving natural configuration idea and will not be investigated in detail here.

Of course, the basic question is to understand whether cells and ECM behave like solids, like (possibily visco-elastic) liquids, or like visco-plastic bodies. In this respect, some tests on the mechanical properties of the ECM constituents such as elastin and collagen suggest that in the absence of remodeling the latter can be regarded as elastic compressible materials with different elastic features. More difficult is to establish from both the conceptual and the experimental point of view whether the ensemble of cells behaves like a solid or a liquid, how important visco-elastic effects are, if and when plastic deformation occurs, and so on.

Clearly, the above-mentioned problem of the reference configuration is circumvented if tumor cells are modeled as a fluid, for in such a case it is possible to look at them from the Eulerian point of view and to describe cell stress in terms of volume ratios and deformation rates. In this paper we confine ourselves to this kind of constitutive equations, following the most popular custom in multiphase models of tumor growth. We just remark here that actually the ensemble of cells is most likely to not behave like a liquid; however, in this modeling approach the 'cellular liquid' lives within a solid structure given by the extracellular matrix, so that finally the whole mixture would behave like a visco-elastic solid.

The easiest constitutive equation for the cellular matter is

$$\mathbb{T}_\phi = -\Sigma(\phi)\mathbb{I}, \tag{2.25}$$

where $\Sigma : [0, 1] \to \mathbb{R}$ is a nonlinear pressure-like function depending on the overall cell volume ratio $\phi = \phi_t + \phi_h$, whose positive values indicate compression. Eq. (2.25) refers essentially to an elastic fluid; as a possible extension one might want to consider a viscous contribution of the form

$$\mathbb{T}_\phi = 2\mu \mathbb{D}_\phi + (-\Sigma(\phi) + \lambda \nabla \cdot \mathbf{v}_\phi)\mathbb{I}, \qquad \mu,\, \lambda > 0$$

where $\mathbb{D}_\phi = \mathrm{Sym}(\nabla \mathbf{v}_\phi)$ is the deformation rate tensor based on the 'reduced' composite velocity $\mathbf{v}_\phi = \phi_t \mathbf{v}_t + \phi_h \mathbf{v}_h$ in the sense that it is restricted to the cellular component only. Nevertheless, we refrain from dealing with visco-elastic constitutive relations since, despite their importance in accounting for mechanical properties of tissues, visco-elastic behaviors are less influential on cell growth phenomena. Indeed, the characteristic time of the viscous response of biological tissues is of the order of tens of seconds, thus by far much lower than that needed for cell duplication, which ranges instead from nearly one day up to several days (see e.g., Forgacs *et al.* [21]).

As a further hint toward intercellular stress modeling, we simply mention that in principle the same argument used in Section 2.2 to describe the adhesive mechanism occurring between cells and ECM, which from the physical point of view involves integrins, may be reproposed for cell-cell interaction, even if the latter involves different proteins such as cadherins. However we refrain here from doing that, referring instead to [4] for more details on more complex constitutive relations.

2.4 Reduced equations

In the momentum equations (2.7) it is often useful to distinguish the contributions of the terms related to the pressure gradient and to the interaction with the extracellular fluid, namely ∇p and $\mathbf{m}_{\alpha\ell}$ for $\alpha \in \mathcal{C}_\ell$, from those related to the interaction between tumor and host cells and between cells and ECM, i.e., $\mathbf{m}_{\alpha\beta}$ for $\alpha \in \mathcal{C}_\ell$, $\beta \in \mathcal{C}_{\alpha,\ell}$. In most cases one can assume that the magnitudes of the former are negligible with respect to those of the latter:

$$\phi_\alpha |\nabla p|,\ |\mathbf{m}_{\alpha\ell}| = o\left(|\nabla \cdot (\phi_\alpha \mathbb{T}_\alpha)|,\ |\mathbf{m}_{\alpha\beta}|\right), \qquad (\alpha \in \mathcal{C}_\ell,\ \beta \in \mathcal{C}_{\alpha,\ell}) \tag{2.26}$$

so that the main momentum balance reduces to

$$-\nabla \cdot (\phi_\alpha \mathbb{T}_\alpha) = \sum_{\beta \in \mathcal{C}_{\alpha,\ell}} \mathbf{m}_{\alpha\beta}, \qquad (\alpha \in \mathcal{C}_\ell). \tag{2.27}$$

This assumption has several interesting implications on the resulting mathematical models.

First of all, it should be noticed that now Eqs. (2.15) and (2.16) live in principle a life apart, since their integration is a by-product of the solutions of the other equations of the model. This is certainly true for a closed mixture in view of condition (2.4); depending on the specific form of the source/sink terms Γ_α, the same possibly applies also to other types of mixtures. Therefore one might recover *a posteriori* the interstitial pressure p and the velocity $\mathbf{v}_\ell$ of the extracellular fluid, after solving the coupled system of Eqs. (2.2), (2.27) for $\alpha \in \mathcal{C}_\ell$. Regarding the latter, we specifically observe that Eqs. (2.19) become

$$-\frac{\phi_\alpha}{\phi} \nabla \cdot (\phi \mathbb{T}_\phi) = \mathbf{m}_{\alpha m}, \qquad (\alpha = t,\ h) \tag{2.28}$$

while summing Eq. (2.27) over $\alpha \in \mathcal{C}_\ell$ and recalling (2.11) yields

$$\nabla \cdot (\phi \mathbb{T}_\phi + \phi_m \mathbb{T}_m) = 0, \tag{2.29}$$

which represents the reduced counterpart of the momentum balance equation (2.24) for the whole mixture.

Secondly, in this reduced framework Eqs.(2.20), (2.22) can be effectively used to obtain explicit expressions of the velocities $\mathbf{v}_t$, $\mathbf{v}_h$ in terms of the velocity $\mathbf{v}_m$ and the internal stress of the cellular matter: thanks to Eq. (2.28), if we define $\mathbb{K}_{\alpha m} = \mathbb{M}_{\alpha m}^{-1}$ we have indeed

$$\mathbf{v}_\alpha - \mathbf{v}_m = \frac{\phi_\alpha}{\phi} \mathbb{K}_{\alpha m} \nabla \cdot (\phi \mathbb{T}_\phi), \qquad (\alpha = t,\ h) \tag{2.30}$$

in case of viscous friction between cells and ECM (cf. Eq. (2.20)), or

$$\mathbf{v}_\alpha - \mathbf{v}_m = \left(\frac{\phi_\alpha}{\phi} - \frac{\sigma_{\alpha m}}{|\nabla \cdot (\phi \mathbb{T}_\phi)|} \right)^+ \mathbb{K}_{\alpha m} \nabla \cdot (\phi \mathbb{T}_\phi), \qquad (\alpha = t,\ h) \tag{2.31}$$

if a more sophisticated visco-plastic interaction is accounted for. Again, we notice that Eq. (2.30) is a special case of Eq. (2.31) with $\sigma_{\alpha m} = 0$.

2.5 Advection and diffusion of chemicals

A crucial role in tumor growth is played by all chemicals, namely nutrients, growth factors, chemotactic factors, and so on, dissolved in the liquid component. They diffuse and are advected through the mixture by the extracellular fluid; in addition, they are either absorbed or produced by the cells, that make use of them in order to carry out some vital functions such as proliferation, growth or intercellular communication.

For the sake of simplicity, let us focus on just one species of chemical, and let us denote by $c_\alpha \in \mathbb{R}$, $\alpha \in \mathcal{C}$, its concentration per unit volume within the constituent α of the mixture. The

generalization of the result we are going to state to more chemical species is straightforward, requiring in essence the same ideas up to some more complicated mathematical notation.

It is worth pointing out that in the present context chemicals are not regarded as components of the mixture; however, the concentration c_α has to be related to the volume ratio ϕ_α occupied by the constituent in which it is present, so that finally the relevant entities for an overall balance over the whole mixture are the *reduced* (or *weighted*) *concentrations* $C_\alpha = \phi_\alpha c_\alpha$. For these quantities one can write the following set of reaction-advection-diffusion equations:

$$\frac{\partial}{\partial t}(\phi_\alpha c_\alpha) + \nabla \cdot (\phi_\alpha c_\alpha \mathbf{v}_\alpha) = \nabla \cdot (\mathbb{D}_\alpha \nabla c_\alpha) + \gamma_\alpha - \delta_\alpha c_\alpha, \qquad (\alpha \in \mathcal{C}) \tag{2.32}$$

where

- $\mathbb{D}_\alpha = \mathbb{D}_\alpha(\phi_\alpha)$ is the *effective diffusion tensor* characteristic of the constituent α, which accounts for diffusion of the chemical in the constituent α due to Brownian motion as well as for molecules dispersion due to the porous structure of the mixture;
- $\gamma_\alpha > 0$ is the production/source term in the constituent α, which may either depend or not on the other state variables of the system (including e.g., the volume ratios ϕ_t, ϕ_h of the cells) according to the specific production mechanisms of the chemical at hand. For instance, nutrients like oxygen and growth activators/inhibitors are usually not produced by the components of the mixture but are delivered from outside, while chemotactic factors are released by the cells during their motion to trigger intercellular signaling (Lanza *et al.* [28]);
- $\delta_\alpha > 0$ is the degradation/uptake rate, linked either to the solubility of the chemical in the constituent α or to its absorption by the latter.

Assuming that the concentrations c_α are the same in all constituents and dropping therefore the subscript α, we can sum Eqs. (2.32) over $\alpha \in \mathcal{C}$ to get an equation satisfied by c over the whole mixture. Recalling in particular the saturation constraint (2.1) and the definition of the composite velocity (2.6) we get

$$\frac{\partial c}{\partial t} + \nabla \cdot (c\mathbf{v}_c) = \nabla \cdot (\mathbb{D}\nabla c) + \gamma - \delta c, \tag{2.33}$$

where we have let $\mathbb{D} := \sum_{\alpha\in\mathcal{C}} \mathbb{D}_\alpha$, $\gamma := \sum_{\alpha\in\mathcal{C}} \gamma_\alpha$, and $\delta := \sum_{\alpha\in\mathcal{C}} \delta_\alpha$. Specifically, we observe that for closed mixtures the composite velocity is solenoidal, hence in such a case the advection term at the left-hand side of Eq. (2.33) gives rise to pure transport: $\nabla \cdot (c\mathbf{v}_c) = \mathbf{v}_c \cdot \nabla c$.

Eqs. (2.33) can be further manipulated for those chemicals for which homogeneous and isotropic diffusion dominates over advection. Specifically, the advection term $\nabla \cdot (c\mathbf{v}_c)$ can be dropped and the evolution of the concentration c can be duly described by the following reaction-diffusion equation:

$$\frac{\partial c}{\partial t} = D\Delta c + \gamma - \delta c\,, \tag{2.34}$$

which is the one classically used in many models but requires the validity of the assumptions above.

3 Tumor growth in a rigid ECM

Probably the most simplifying hypothesis to generate specific models of tumor growth from the general theory developed in the previous section is to consider the ECM as a rigid scaffold, within which cells and extracellular fluid move and evolve in time. From the macroscopic point of view, this implies that the whole tissue behaves like a rigid porous medium: any possible external action on it is sustained by the extracellular matrix, while cells and extracellular fluid in the core of the tissue withstand no external stress imposed on the mixture from its boundary.

Specifically, since possible rigid motions of the ECM are irrelevant in the study of growth processes, it is not restrictive to assume

$$\mathbf{v}_m \equiv 0\,. \tag{3.1}$$

In view of this, no momentum equation for the extracellular matrix is needed, and the stress tensor $\mathbb{T}_m$ has to be regarded formally as a Lagrange multiplier to satisfy the constraint (3.1). The relevant mass and momentum balance equations for the component of the mixture turn out to be then

$$\frac{\partial \phi_\alpha}{\partial t} + \nabla \cdot (\phi_\alpha \mathbf{v}_\alpha) = \Gamma_\alpha, \tag{3.2}$$

$$-\frac{\phi_\alpha}{\phi}\nabla \cdot (\phi \mathbb{T}_\phi) = \mathbf{m}_{\alpha m}, \tag{3.3}$$

$$\frac{\partial \phi_m}{\partial t} = \Gamma_m \tag{3.4}$$

for $\alpha = t,\, h$. Notice in particular that, owing to Eqs. (2.31) (or Eq. (2.30) in the special case $\sigma_{\alpha m} = 0$) and (3.1), the cell momentum equation (3.3) along with the constitutive relation (2.25) yields

$$\mathbf{v}_\alpha = -\left(\frac{\phi_\alpha}{\phi} - \frac{\sigma_{\alpha m}}{|\nabla(\phi\Sigma(\phi))|}\right)^+ \mathbb{K}_{\alpha m}\nabla(\phi\Sigma(\phi)). \tag{3.5}$$

Substituting this into Eq. (3.2) we get a pair of single equations for the cellular component:

$$\frac{\partial \phi_\alpha}{\partial t} - \nabla \cdot \left(\phi_\alpha \left(\frac{\phi_\alpha}{\phi} - \frac{\sigma_{\alpha m}}{|\nabla(\phi\Sigma(\phi))|}\right)^+ \mathbb{K}_{\alpha m}\nabla(\phi\Sigma(\phi))\right) = \Gamma_\alpha, \qquad (\alpha = t,\, h), \tag{3.6}$$

which in case of viscous friction between cells and ECM (formally $\sigma_{\alpha m} = 0$) specializes as

$$\frac{\partial \phi_\alpha}{\partial t} - \nabla \cdot \left(\frac{\phi_\alpha^2}{\phi}\mathbb{K}_{\alpha m}\nabla(\phi\Sigma(\phi))\right) = \Gamma_\alpha, \qquad (\alpha = t,\, h). \tag{3.7}$$

It is worth mentioning that when the two cell populations occupy different spatial regions and are not mixed, Eqs. (3.5) and (3.6) can be further simplified because in each region only one population is found and therefore $\phi = \phi_\alpha$. Specifically, consider the situation in which a spatial region $Q \subset \mathbb{R}^d$ can be initially divided into two sub-regions $\Omega_t(0)$ and $\Omega_h(0)$, such that $\Omega_t(0) \cup \Omega_h(0) = Q$, occupied by tumor and by healthy host cells respectively, i.e. $\phi_t = 0$ in $\Omega_h(0)$ and viceversa. As we will see, the model is such that the tumor cells will be always confined into $\Omega_t(t)$ and the host population always in Ω_h(t). However, the two cell populations interact by exerting mutual stresses on the $(d-1)$-dimensional interface $S(t) = \Omega_t(t) \cap \Omega_h(t)$ separating their respective domains. It is plain that $\Omega_t(t)$ and $\Omega_h(t)$, as well as the interface $S(t)$, evolve geometrically in time according to the growth of the tumor mass within the surrounding tissue. By pushing normal cells away to gain space for growing, tumor cells compress the region $\Omega_h(t)$ and simultaneously enlarge $\Omega_t(t)$; conversely, when they die for an insufficient delivery of nutrient $\Omega_t(t)$ locally shrinks and correspondingly $\Omega_h(t)$ expands.

One then has

$$\frac{\partial \phi_\alpha}{\partial t} - \nabla \cdot (\phi_\alpha \mathcal{I}[\phi_\alpha,\, \nabla\phi_\alpha;\, \sigma_{\alpha m}]\mathbb{K}_{\alpha m}\nabla(\phi_\alpha\Sigma(\phi_\alpha))) = \Gamma_\alpha \quad \text{in } \Omega_\alpha(t) \qquad (\alpha = t,\, h), \tag{3.8}$$

where

$$\mathcal{I}[\phi_\alpha,\, \nabla\phi_\alpha;\, \sigma_{\alpha m}] := \left(1 - \frac{\sigma_{\alpha m}}{|\nabla(\phi_\alpha\Sigma(\phi_\alpha))|}\right)^+. \tag{3.9}$$

The interface $S(t)$ between $\Omega_t(t)$ and $\Omega_h(t)$ moves with the velocity of the constituents on the two sides, that must be the same, i.e.,

$$[\![\mathcal{I}[\phi_\alpha,\, \nabla\phi_\alpha;\, \sigma_{\alpha m}]\mathbb{K}_{\alpha m}\nabla(\phi_\alpha\Sigma(\phi_\alpha)) \cdot \mathbf{n}]\!] = 0, \tag{3.10}$$

where $\mathbf{n}$ is the unit normal to the interface and $[\![\cdot]\!]$ denotes the jump across it. Hence,

$$\frac{d\mathbf{x}(t)}{dt} \cdot \mathbf{n} = \mathbf{v}(\mathbf{x}(t),\, t) \cdot \mathbf{n}, \qquad \forall\, \mathbf{x} \in S(t) \tag{3.11}$$

where for instance

$$\mathbf{v} = -\mathcal{I}[\phi_t,\, \nabla\phi_t\,;\sigma_{tm}]\mathbb{K}_{tm}\nabla(\phi_t\Sigma(\phi_t)). \tag{3.12}$$

In addition, on the interface $S(t)$ continuity of cell stress and of nutrient flux in the normal direction has to be imposed according to the classical theory of continuum mechanics:

$$[\![\mathbb{T}_\phi \mathbf{n}]\!] = 0, \qquad [\![\nabla c]\!] \cdot \mathbf{n} = 0. \tag{3.13}$$

Recalling Eq. (2.25), we see that the continuity of the normal cell stress is actually equivalent to $[\![\phi\Sigma(\phi)]\!] = 0$ and, if one assumes that $\phi\Sigma(\phi)$ is a continuous monotone function of ϕ, further to

$$[\![\phi]\!] = 0 \tag{3.14}$$

namely to the continuity of the cell volume ratio across $S(t)$, i.e., $\phi_t = \phi_h$ on $S(t)$.

Finally, continuity of concentration is imposed:

$$[\![c]\!] = 0. \tag{3.15}$$

3.1 Tumor cords

As a first application we consider the case of a capillary surrounded by a tissue within which an aggregate of tumor cells has formed. The latter can survive and proliferate thanks to some nutrients (e.g., oxygen) carried by the blood, that penetrate from the vessel wall and diffuse into the tissue. For this reason, the tumor tends to develop along the blood vessel, giving rise to a structure called *tumor cord* due to its particular spatial geometry.

In the specialized literature, the papers by Bertuzzi and co-workers [12, 13] have originated a relevant thread of mathematical models of tumor cord growth. However, they use only partially the theory of multicomponent systems, relying mainly on some particular kinematic relations deduced under suitable assumptions on the geometry of the system (namely, cylindrical symmetry of the cord around the blood vessel). In this section, working under the hypothesis of rigid ECM, we want to apply instead the theory previously developed to deduce a multiphase model for the growth of a tumor cord in generic multidimensional domains, taking into account both the presence of several components in the system and their mutual mechanics. A minimal version of this model, focusing on two-dimensional development of a cord structure along the longitudinal axis of a blood vessel, is introduced and analyzed from the qualitative point of view in [33].

The whole system is regarded as a saturated mixture of cells, extracellular fluid and extracellular matrix, the latter being a rigid non-remodeling scaffold of zero velocity and constant volume ratio $\phi_m = 1 - \phi_*$, $\phi_* \in (0,\, 1)$. Equation (3.4) can therefore be disregarded in the present context.

Moreover, it is assumed that initially tumor cells and host cells occupy different spatial regions, which, as stated in the previous Section, causes the former to be always confined into $\Omega_t(t)$ and the latter into $\Omega_h(t)$.

Like in [20], we assume that tumor cells and normal cells only differ in the mechanism that regulates their proliferation and death. As a consequence, in Eq. (3.8) we take $\sigma_m := \sigma_{tm} = \sigma_{hm}$, $\mathbb{K}_{tm} = \mathbb{K}_{hm} = K_m\mathbb{I}$ for a positive parameter K_m.

Regarding the source/sink terms Γ_α, we consider that in $\Omega_t(t)$ tumor cells are mainly concerned with proliferation or death on the basis of the local oxygen concentration c. Following [20], we here want to include also phenomena like contact inhibition of growth and development of hyperplasia as a consequence of the loss of tissue compression responsiveness by the cells. More in detail, Chaplain and coworkers [20] focus on a characterization of normal and abnormal cells based on the ability of the cells themselves to sense the stress exterted by the surrounding environment. They assume that a correct detection of the compression state normally causes a cell to reproduce only

if it senses there is enough free space in its neighborhood; in case of excess of stress, normal cells enter a quiescent survival state, whence they possibly re-activate if, for instance, some surrounding cells die. Conversely, a misperception of the stress state, due to something wrong in the cascade of intracellular biochemical events characterizing the mechano-transduction pathway, may lead to cell replication even when there is actually insufficient free space for new cells. This mechanism, which is easily understood to give rise to hyperplasia, often underlies the formation and development of avascular tumors. Therefore we let

$$\Gamma_t = \Gamma_t(\phi_t, c) = \left[\gamma_t \left(\frac{c}{c_0} - 1\right) H(\Sigma_t^* - \Sigma(\phi_t)) - \delta_t H(\Sigma(\phi_t) - \bar{\Sigma}_t) - \delta_t'\right] \phi_t \quad \text{in } \Omega_t(t), \tag{3.16}$$

where H is the Heaviside function

$$H(s) = \begin{cases} 0 & \text{if } s \leq 0 \\ 1 & \text{if } s > 0, \end{cases} \tag{3.17}$$

$\gamma_t > 0$ is the growth rate and $c_0 > 0$ represents the critical threshold in the nutrient concentration, below which cells undergo starvation and die and above which cells duplicate if they feel to be not too compressed, i.e., $\Sigma(\phi_t) < \Sigma_t^*$. Regarding the apoptotic terms, the fist one reflects the fact that high compression levels, like those produced by growing tumor cells, may induce apoptosis (see e.g., Ambrosi and Mollica [2, 3]). Hence $\bar{\Sigma}_t > 0$ represents the maximum stress that tumor cells can sustain without undergoing apoptosis, $\delta_t > 0$ is the stress induced apoptotic rate and δ_t' is the physiological apoptotic rate.

If the function Σ is one-to-one in the range, and if $\bar{\phi}$ and ϕ_t^* denote respectively the values of ϕ_t such that $\Sigma(\bar{\phi}_t) = \bar{\Sigma}_t$ and $\Sigma(\phi_t^*) = \Sigma_t^*$, then Eq. (3.16) can be duly replaced by

$$\Gamma_t = \Gamma_t(\phi_t, c) = \left[\gamma \left(\frac{c}{c_0} - 1\right) H(\phi_t^* - \phi_t) - \delta_t H(\phi_t - \bar{\phi}_t) - \delta_t'\right] \phi_t \quad \text{in } \Omega_t(t)\,. \tag{3.18}$$

A similar equation can be set for the host tissue with t replaced by h.

An additional customary assumption on Σ is the existence of a value ϕ_0 such that $\Sigma(\phi_0) = 0$, identifying a stress-free state of the cells. For volume ratios lower than ϕ_0 the stress is negative, denoting tension in the cell population, while for volume ratios greater than ϕ_0 it is positive, denoting compression of the cell tissue. In view of this, the apoptosis threshold $\bar{\phi}_\alpha$ has to satisfy in particular $\bar{\phi}_\alpha > \phi_0$ for both $\alpha = t, h$.

Finally, we join to Eqs. (3.8) the diffusion in the tissue

$$\frac{\partial c}{\partial t} = D\Delta c - \beta_\alpha \phi_\alpha c, \quad \text{in } \Omega_\alpha(t), \tag{3.19}$$

where $\beta_\alpha > 0$, $\alpha = t, h$, are phenomenological parameters related to the nutrient uptake rate by the tumor and the host cells.

In addition to the interface conditions (3.10), $(3.13)_2$, (3.14), (3.15), and to the evolution equation for the moving interface (3.11), Eqs. (3.6) have to be supplemented by suitable boundary conditions. As their formal statement depends on the configuration of the system, we simply outline here, mainly at a qualitative level, the basic general ideas to be precisely formulated from time to time according to the specific geometrical setting at hand. In doing so, we denote by $\mathbf{n}$ any outward normal unit vector to be conveniently referred to the boundary under consideration.

(i) At the vessel wall we impose no detachment of both tumor and host cells; in view of Eq. (3.5) this amounts to

$$-\mathcal{I}[\phi_\alpha, \nabla\phi_\alpha; \sigma_{\alpha m}] K_m \nabla(\phi_\alpha \Sigma(\phi_\alpha)) \cdot \mathbf{n} = 0, \qquad (\alpha = t, h). \tag{3.20}$$

Concerning the nutrient, we prescribe a Dirichlet boundary condition of the form

$$c = c_b \tag{3.21}$$

where $c_b > 0$ denotes the characteristic oxygen concentration carried by the blood. If more than one vessel is present, then conditions (3.20), (3.21) have to be prescribed at each boundary representing a vessel wall.

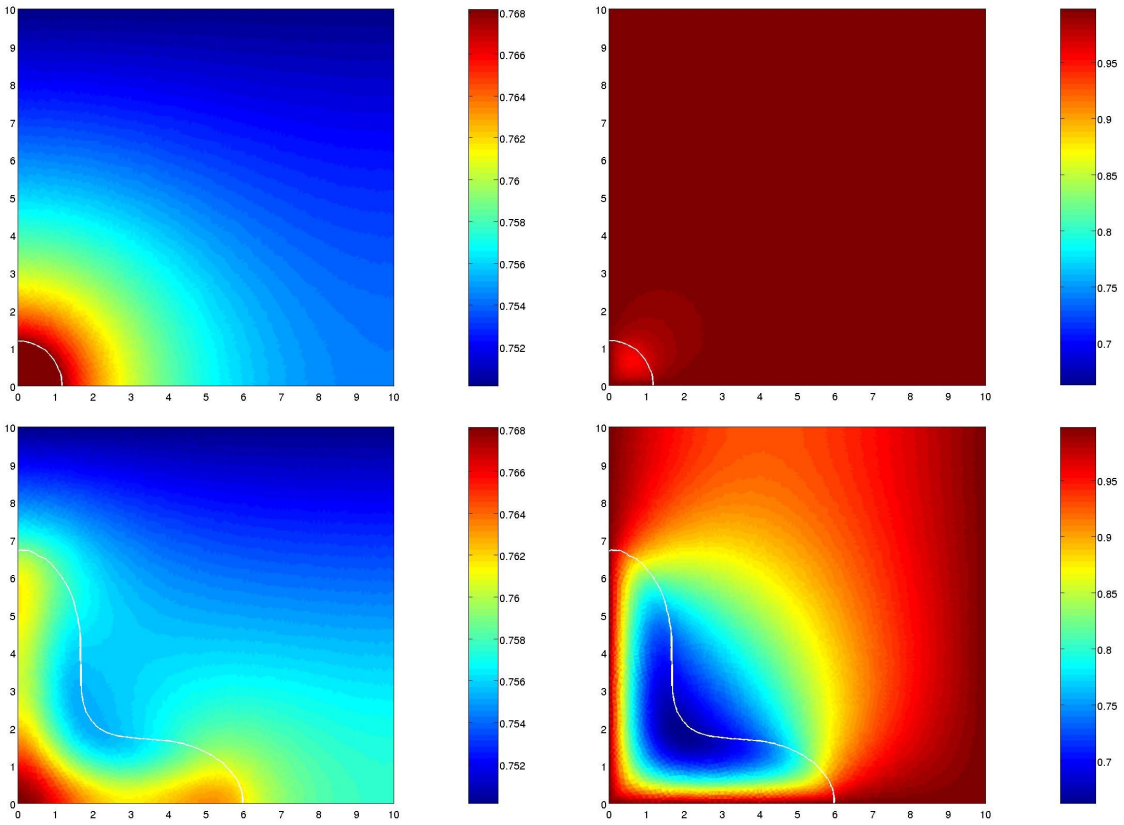

Figure 1: Evolution of cell density (left) and nutrient distribution (right) at $t = 100$ and 500 along two capillaries placed on the bottom and on the left side of the rectangle. The line defines the interface $S(t)$.

(ii) The outer boundaries of Q not occupied by capillaries serve uniquely to confine geometrically the domain of the problem. We regard them as sufficiently far in the host tissue to be unaffected by the dynamics of the growing tumor cords; consequently, we prescribe there an unstressed cell field with zero flux of nutrient:

$$\Sigma(\phi) = 0, \qquad \nabla c \cdot \mathbf{n} = 0. \tag{3.22}$$

Figure 1 describes how a tumor mass, initially located at the intersection between two capillaries situated on the bottom and on the left side of the square Q, grows along them. In a first stage the host tissue is well nourished by the capillaries, but when the tumor cord starts growing an hypoxic region forms. In particular, the cells closer to the capillaries have enough nutrient and proliferate while those farther away starve because of lack of oxygen due to the eagerness of tumor cells. The balance between these two tendencies entails that away from the propagating fronts the thickness of the cord is nearly constant, while its head moves forward as it is mostly made of proliferating cells. The largest density of cells is, in fact, at the heads and at the capillary junction.

Figures 2 and 3 refer to the formation of tumor cords around three capillary sections. In particular, Figure 2 shows the evolution of the cell volume ratio and Figure 3 that of the oxygen concentration. The tumor starts growing from the capillary on the right and keeps an almost circular shape ($t = 300$). It can be noticed that during this initial growth the host cells located on the left of the domain are still well nourished, because they do not consume much oxygen, while those close to the top-right corner undergo hypoxia. Before reaching the limit radius, characterized by a balance between proliferation and death of cells, the tumor boundary approaches another

capillary, and some cells begin to grow toward it ($t = 600$). Upon reaching it ($t = 900$), it coopts the vessel forming a tumor cord whose external boundary shape recalls the number 8. The same does not happen for the lower vessel because it is too far.

Figures 4 and 5 refer to the same simulation but with closer vessels. In this case, also the third vessel is coopted, and eventually the tumor is fully vascularized.

More simulations are given in the Supplemental Material.

3.2 ECM remodeling and fibrosis

As a second example, following [20] and [25] we want to describe by the model above the formation of hyperplasia and fibrosis. In order to do that we take into account continuous production of matrix degrading enzymes and remodeling of (rigid) extracellular matrix by both normal and tumor cells. Moreover, the amount of ECM present in the tissue plays a leading role as a part of the surrounding environment in determining the overall stress on the cells, so that ECM evolution cannot definitely be disregarded in the present context. A massive production of abnormal ECM triggered by a large population of abnormal cells induces the formation of stiffer fibrotic tissue, whose dynamics is described as a by-product by the model.

A key parameter of the model is the overall volume ratio ψ occupied by all these components of the mixture:

$$\psi := \phi_h + \phi_t + \phi_m = 1 - \phi_\ell \,, \tag{3.23}$$

which indirectly measures the amount of free space locally available, and can therefore be used to account for the stress exerted by the environment on the cellular matter. In particular, the Authors of [20] use a stress-volume ratio relationship for the cells of the form

$$\Sigma(\psi) = E(1-\psi_0)\left(\frac{\psi-\psi_0}{1-\psi}\right)^+, \tag{3.24}$$

where $\psi_0 \in (0,\, 1)$ identifies the stress-free volume ratio ($\Sigma(\psi_0) = 0$) and E is a kind of Young modulus for moderate stress. Notice that $\Sigma(\psi) = 0$ for $\psi \in [0,\, \psi_0]$, meaning that in a diluted mixture cells neither get in touch with each other nor withstand external loads by the surrounding environment. On the contrary, $\Sigma(\psi) > 0$ for $\psi \in (\psi_0,\, 1)$ with $\Sigma \to +\infty$ when $\psi \to 1^-$, i.e., when $\phi_\ell \to 0^+$, hence for high packing levels cells experience compression which goes to infinity as the solid phase of the mixture tends to occupy the whole available space.

Equation (3.24) can be regarded to some extent as a generalization of Eq. (2.25) (where we recall that $\phi = \phi_h + \phi_t$) for a cell stress function depending also on the concentration of extracellular matrix. However, we point out that the dependence of the internal stress of a phase (in this case, the cellular phase) on one or more state variables related to other phases (here, the ECM volume ratio) is not common in classical mixture theory and need be quantified experimentally.

In this example we use Eq.(3.6) with the following source/sink terms taking into account natural death and stress-dependent duplication of cells:

$$\Gamma_\alpha = \Gamma_\alpha(\phi_\alpha,\, \psi) = \left[\gamma_\alpha H_\epsilon(\psi - \psi_\alpha) - \delta_\alpha\right]\phi_\alpha, \tag{3.25}$$

where H_ϵ is a continuous mollifier of the step function satisfying

$$H_\epsilon(s) = \begin{cases} 1 & \text{if } s \le 0 \\ 0 & \text{if } s > \epsilon. \end{cases} \tag{3.26}$$

The parameter $\epsilon > 0$ fixes the thickness of the transition between $H_\epsilon(s) = 1$ and $H_\epsilon(s) = 0$, hence it controls the rapidity of the on/off transition in cell reproduction. The threshold $\psi_\alpha > \psi_0$ determines instead the maximum packing level sustainable by the cells of the population α before sensing a reduction in the surrounding free space and eventually switching duplication off. Since the cell stress Σ (cf. Eq. (3.24)) is a monotonic function of the overall volume ratio ψ, this corresponds to saying that a stress threshold $\Sigma_\alpha > 0$ exists, with $\Sigma_\alpha = \Sigma(\psi_\alpha)$, such that cell

replication is promoted for $\Sigma \leq \Sigma_\alpha$ and progressively inhibited for $\Sigma > \Sigma_\alpha$. Different sensitivity of normal and abnormal cells to mechanical cues, and in particular misperception of compression by the latter, is translated in the present context by assuming $\psi_t \geq \psi_h$. Finally, reproduction and death rates γ_α, $\delta_\alpha > 0$ appearing in Eq. (3.25) can be taken equal for both cell populations, meaning that only stress perception is different between them.

Concerning the extracellular matrix, we assume that ECM is globally remodeled by cells and degraded by matrix degrading enzymes (MDEs), having concentration e, so that in Eq. (3.4) we use

$$\Gamma_m = \mu_t(\psi\Sigma(\psi))\phi_t + \mu_h(\psi\Sigma(\psi))\phi_h - \nu e\phi_m, \tag{3.27}$$

where μ_α is the possibly stress-dependent ECM production rate by the cell population α and $\nu > 0$ is a parameter.

As usual, matrix degrading enzymes are not included among the component of the mixture, but are regarded instead as macromolecules that diffuse in the extracellular fluid without occupying space. For them the following reaction-diffusion equation is proposed:

$$\frac{\partial e}{\partial t} = D\Delta e + \pi_h(\psi\Sigma(\psi))\phi_h + \pi_t(\psi\Sigma(\psi))\ phi_t - \frac{e}{\tau}, \tag{3.28}$$

where consumption is simply due to chemical decay and production is operated by cells at possibly stress-dependent rates π_h, π_t

Equations (3.8), (3.27), (3.28), along with Eqs. (3.24), (3.25), (3.26), completely define the mathematical model that we summarize here for the sake of completeness

$$\begin{cases} \dfrac{\partial \phi_t}{\partial t} &= \nabla \cdot \left(\phi_t \left(1 - \dfrac{\sigma_m}{|\nabla(\phi\Sigma(\phi))|} \right)^+ \mathbb{K}_m \nabla(\phi\Sigma(\phi)) \right) = \left[\gamma_t H_\epsilon(\psi_t^* - \psi_t) - \delta_t \right] \phi_t, \\ \dfrac{\partial \phi_h}{\partial t} &= \nabla \cdot \left(\phi_h \left(1 - \dfrac{\sigma_m}{|\nabla(\phi\Sigma(\phi))|} \right)^+ \mathbb{K}_m \nabla(\phi\Sigma(\phi)) \right) = \left[\gamma_h H_\epsilon(\psi_h^* - \psi_h) - \delta_h \right] \phi_h\,, \\ \dfrac{\partial \phi_m}{\partial t} &= \mu_t(\psi\Sigma(\psi))\phi_t + \mu_h(\psi\Sigma(\psi))\phi_h - \nu e\phi_m \\ \dfrac{\partial e}{\partial t} &= D\Delta e + \pi_h(\psi\Sigma(\psi))\phi_h + \pi_t(\psi\Sigma(\psi))\phi_t - \dfrac{e}{\tau}. \end{cases} \tag{3.29}$$

No sort of nutrients are included in the dynamics of the system, since in the present context the Authors of the model wanted to focus on the role of compression and stress on tumor invasion. From the physical point of view, this may correspond to the assumption that nutrients are always abundantly supplied to the cells according to their needs.

Figure 6 shows the evolution of a tumor starting from one of the two bones in the lower arm, also with the inclusion of some blood vessels. As nutrients are not considered in this model and it is assumed that cells have everything they need, no nutrient-limited dimension is observed: the tumor will grow indefinitely. By carefully looking at the line defining the interface between tumor and host tissue, one can notice the compression of the host tissue, while away from the interface the volume ratio is nearly constant. Figure 7 focuses instead on the evolution of ECM, which is assumed to be initially distributed homogeneously. The formation of extracellular matrix in excess to the physiological value closely follows the formation of the tumor. The amount of ECM increases in this numerical experiment from 20% to 30%. In the model the ECM is assumed rigid, but if this assumption is dropped such an increase in the ECM component would cause an increase of almost one order of magnitude in tissue rigidity [25].

More simulations are given in the Supplemental Material.

4 Final remarks and possible developments

The mathematical model of a solid tumor illustrated in the present paper develops on the basis of three main observations: First, tumor cells duplicate in a tissue characterized by the presence of

other host cells, of a deformable extracellular matrix and of extracellular liquid. Second, during the evolution cells duplicate, reorganize and deform. Third, tumor cells are bound to the extracellular matrix through adhesion molecules, mainly integrins, having a limited strength which has been recently the target of some experimental investigations. On the basis of these experimental evidences it is proposed that a threshold exists below which the ensemble of cells stick to the extracellular matrix and move with it, and above which it partially detaches and gets a relative motion with respect to the extracellular matrix. This new concept is embedded in a multiphase mathematical model with several constituents. Actually, the model can be easily generalized either to detail more cells populations (endothelial cells, epithelial cells, fibroblasts, macrophages, lymphocytes), or to distinguish among different tumor clones characterized by relevant differences in their behavior (for instance, to stay with the focus of this article, differences in cell-ECM adhesivity), or finally to include the different phases of the cell cycle, i.e. G_0, G_1, G_2, in view of the application of the model to the study of possible treatments. All these generalizations may give rise to interesting applications and deserve further studies.

From the mechanical point of view, it would be interesting to improve the present model by incorporating the cell-to-cell adhesion mechanisms. In fact, using concepts similar to the one used here to describe cell-ECM adhesion, one can infer that if an ensemble of cells is subject to moderate stresses, then cells remain attached, may deform and recover all the deformation elastically (or visco-elastically). On the other hand, in case of sufficiently high tension or shear some bonds might break and some others form. This kind of phenomenology suggests the existence of a yield stress, and therefore requires the use of a plastic (or viscoplastic) deformation formalism in the continuum modeling of solid tumors, as well as of the concepts of evolving natural configurations [4].

We have applied the model, which at the first glance appear rather complex, to some test cases, showing its applicability also to non trivial two-dimensional geometries. In this respect, the model can be used to simulate many practical situations in which tissue interaction and cell-ECM interaction play a relevant role. For instance, interesting situations that may be studied are vessel collapse due to tumor growth, capsule formation and degradation, cell compartimentalization due to strong inhomogeneities in the ECM distribution, or even tissue invasion related to changes in the adhesion mechanisms.

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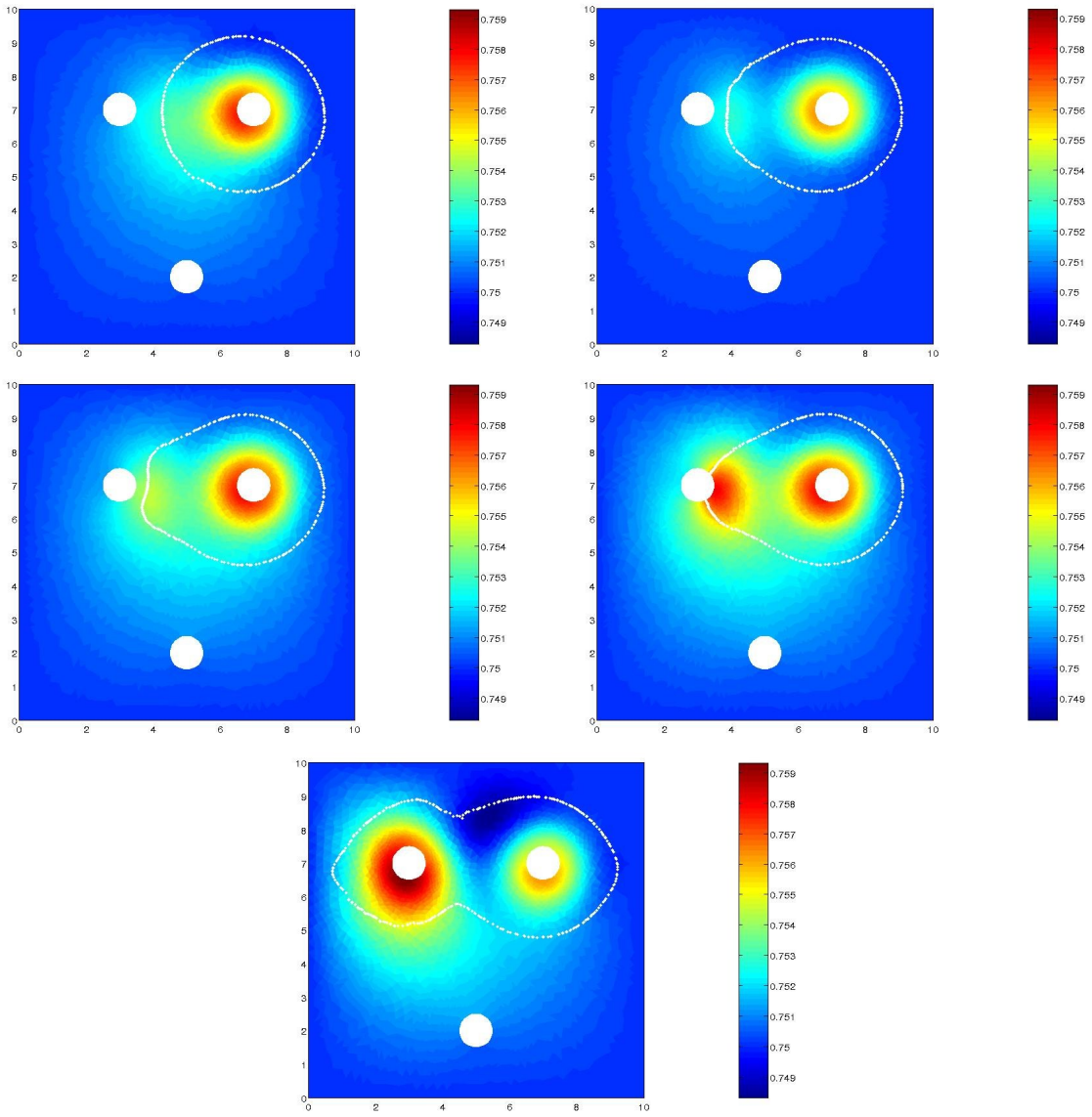

Figure 2: Evolution of cell volume ratio at $t = 300, 600, 900, 1050, 2800$ around three blood vessels. The line defines the interface $S(t)$.

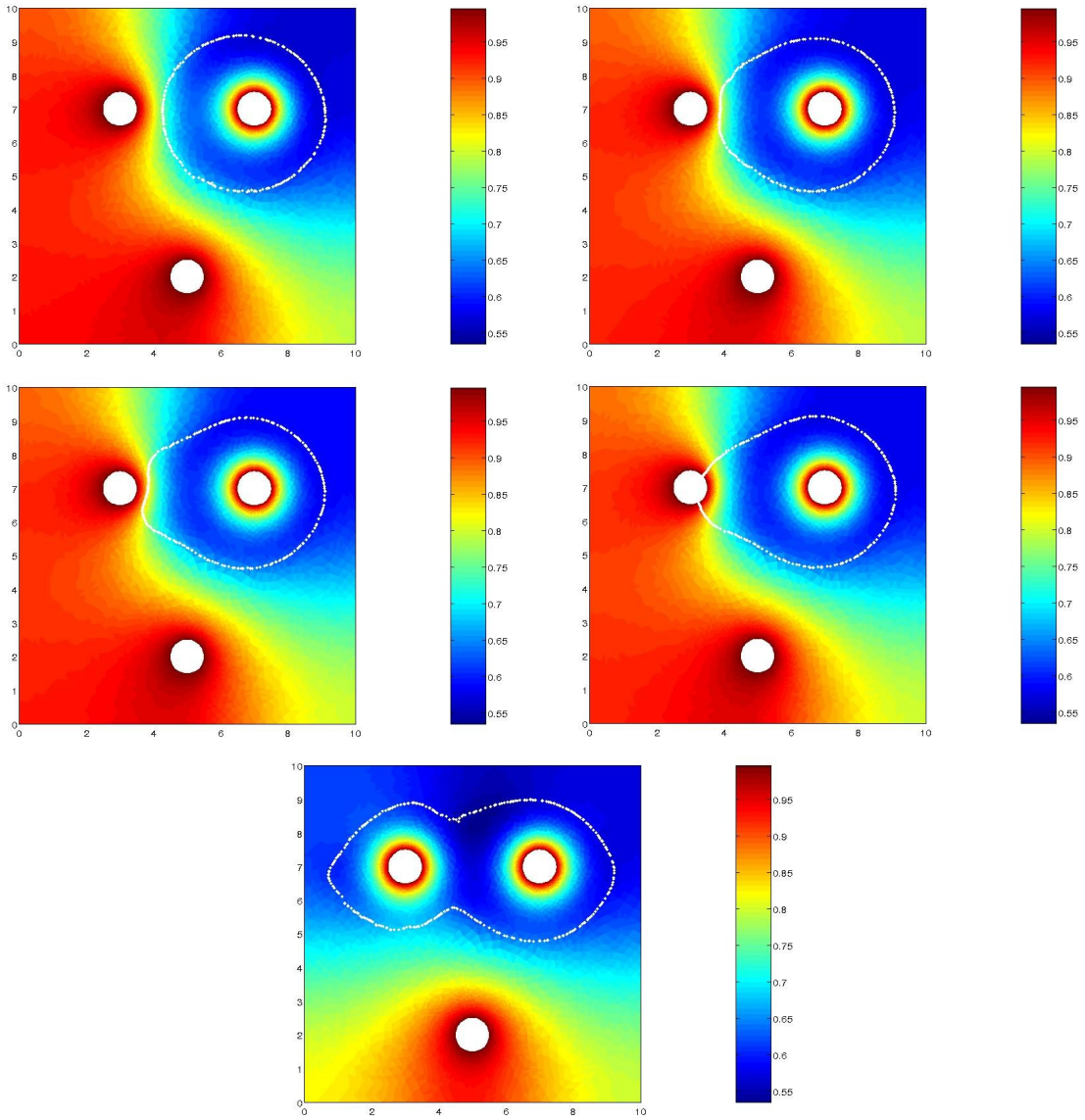

Figure 3: Evolution of nutrient distribution at $t = 300, 600, 900, 1050, 2800$ around three blood vessels. The line defines the interface $S(t)$.

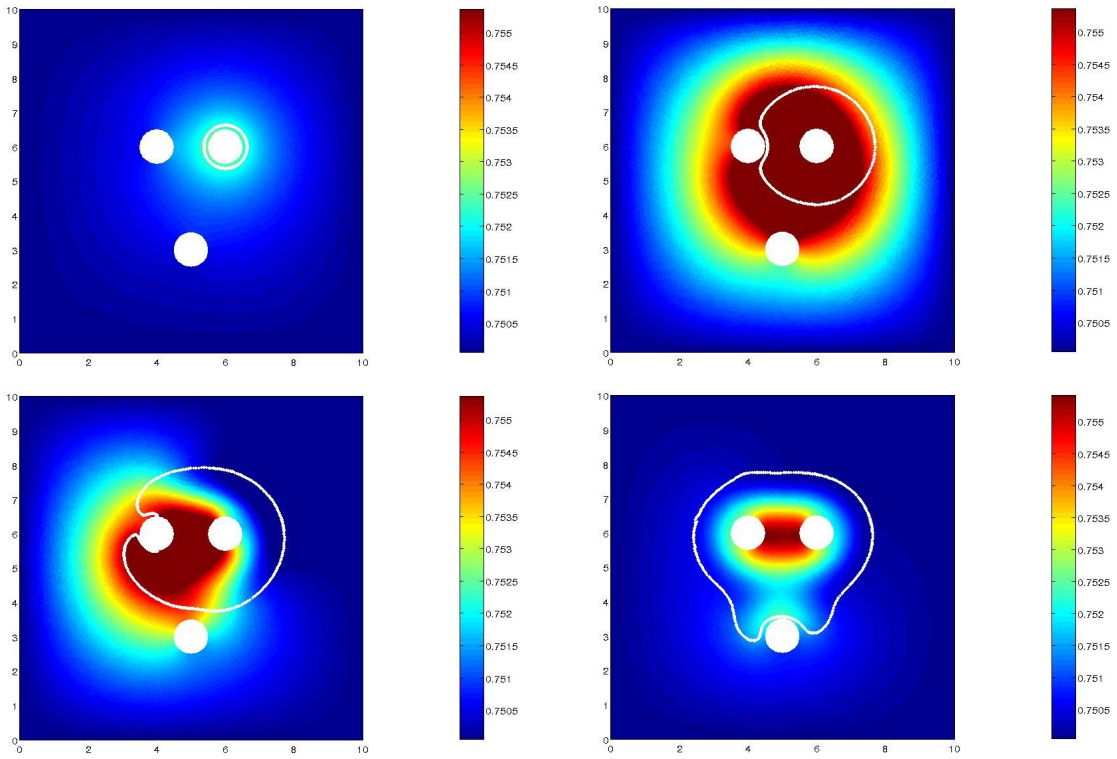

Figure 4: Evolution of cell volume ratio at $t = 10, 150, 300, 850$ around three blood vessels. The line defines the interface $S(t)$.

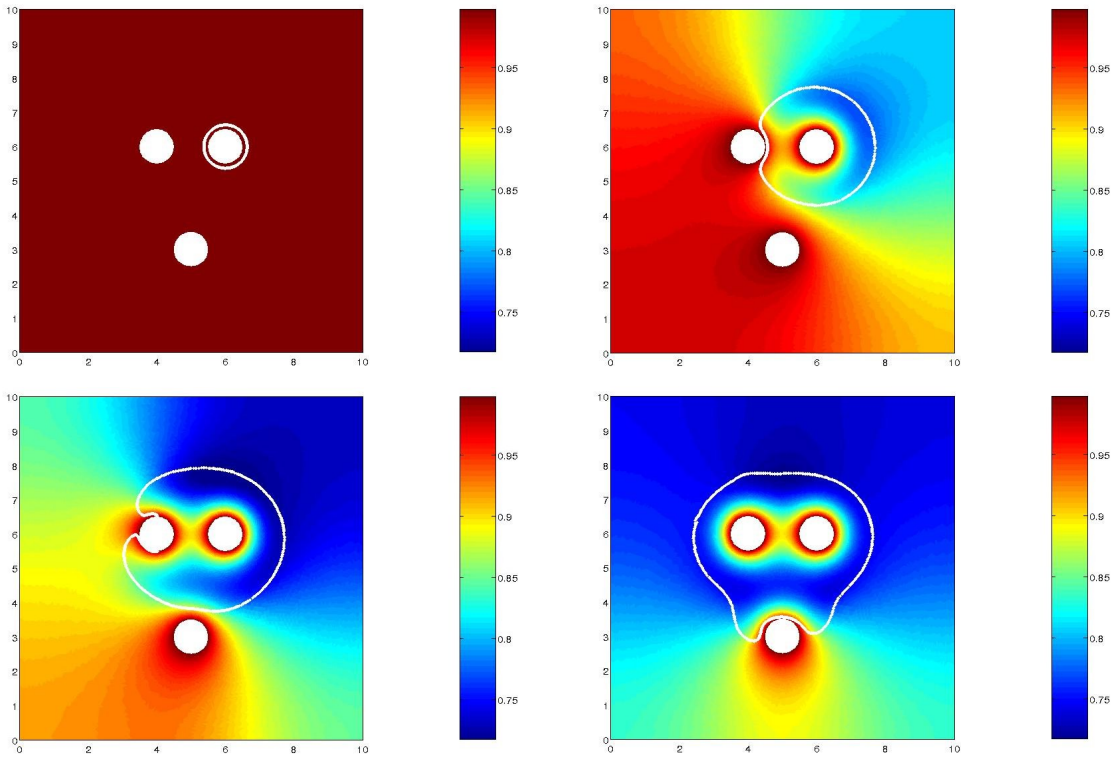

Figure 5: Evolution of nutrient distribution at $t = 10, 150, 300, 850$ around three blood vessels. The line defines the interface $S(t)$.

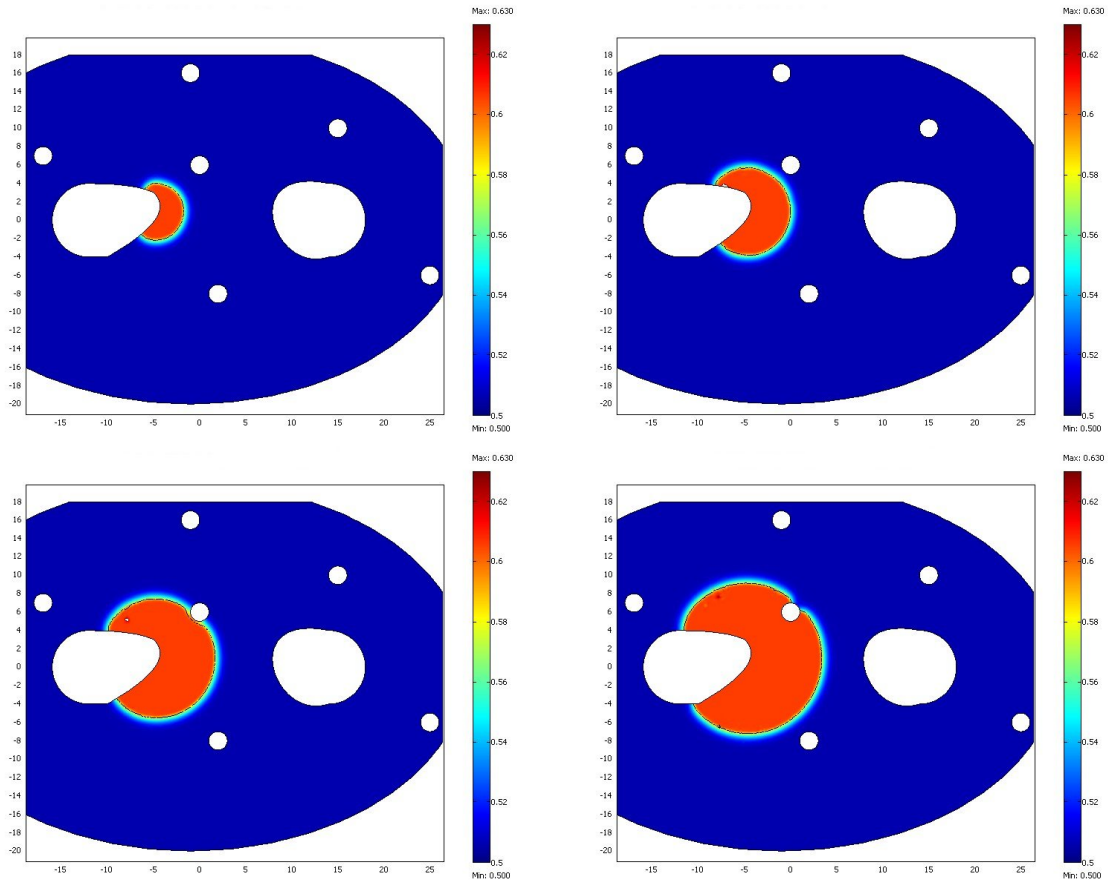

Figure 6: Evolution of cell volume ratio at $t = 30, 60, 90, 120$ in the cross section of a lower arm. The circles refer to vessels the bigger white correspond to the two bones in the arm, the ulna and the radius. The line defines the interface $S(t)$.

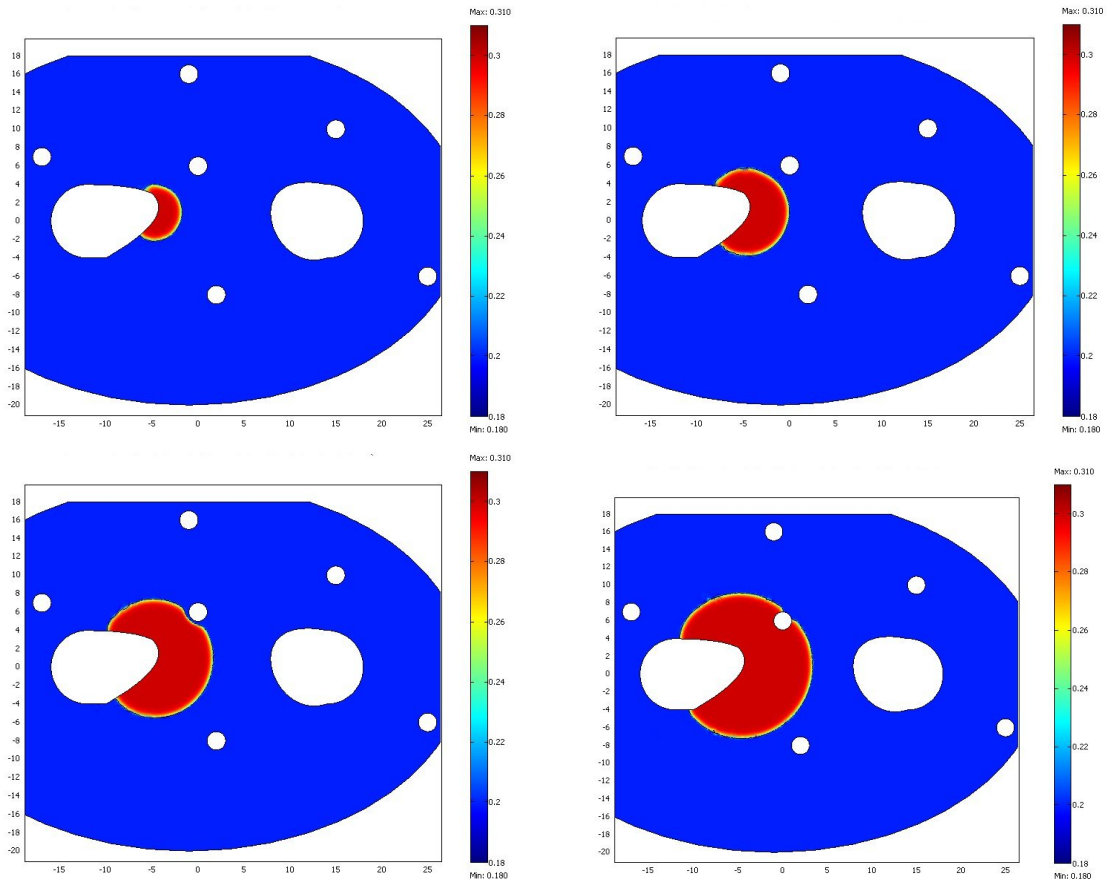

Figure 7: Evolution of the volume ratio occupied by the extracellular matrix at $t = 30, 60, 90, 120$ in the cross section of a lower arm. The circles refer to vessels the bigger white correspond to the two bones in the arm, the ulna and the radius. The line defines the interface $S(t)$.