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ON THE CLOSURE OF MASS BALANCE MODELS FOR TUMOR GROWTH

D. AMBROSI* and L. PREZIOSI†

Dipartimento di Matematica, Politecnico di Torino,
Corso Duca degli Abruzzi 24, I-10129 Torino, Italy
* *ambrosi@calvino.polito.it*
† *preziosi@polito.it*

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Mass balance equations typically adopted to describe tumor growth are to be closed by introducing a suitable velocity field. The first part of this paper is devoted to a critical review of some approaches devised to this aim in the relevant literature. In the second part we start from the observation that the phenomenological description of a tumor spheroid suggests to model it as a growing and deformable porous material. The concept of volume fraction and the essentials of the mechanics of multicomponent continua are then introduced and applied to the problem at hand. The system of equations regulating such a system is stated and its validity is then discussed at the light of numerical simulations.

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AMS Subject Classification: 92C10

1. Introduction

When considering the problem to describe tumor growth in terms of balance equations, the very first difficulty that is encountered is the necessity to take into account a quite large number of cell types as well as biological effects. Cells and chemical factors that typically play a non-negligible role are alive tumor cells, dead cells, endothelial cells, nutrient factors, angiogenic factors, growth factors, and so on. The rather complicated biological scenario is probably the reason that has been leading researchers to concentrate their efforts on modelling the complex interactions occurring between the many biological actors, while describing the motion of the cells in quite a simple manner. The usual approach is to write down a set of balance equations, one for each constituent, where source and sink terms account for many biological mechanisms. As a first step one should clarify which is the quantity to be balanced. In a continuum description, the "number of cells" of a given species is probably not a suitable candidate: it seems more appropriate to

introduce the *volume fraction* concept, straightforwardly inherited from the theory of multicomponent continua, so that "balance equations" for the components are to be read as "mass balance equations". Such a set of equations obviously calls for velocity (or displacement) fields that are to be enforced somehow. We call this the *closure problem.*

The first aim of this paper is to review critically the more or less tacit assumptions that lead to descriptions of cell motion as is currently done in the literature. In fact, when describing the growth of spherically symmetric multicell spheroids made of a single type of cells at a constant density (see Chaplain & Preziosi[6] and references therein) the closure is dictated by geometrical constraints. Otherwise, when dealing with several types of cells, nonhomogeneous spheroids or three-dimensional problems, some closure assumptions are usually invoked,[2,9,16,19] but we argue that more physical arguments should be addressed.

In this paper a multiphase mechanical framework is introduced as a background for the deduction of tumour growth models. The main idea is that multicell spheroids can be modelled as ensembles of deformable balloons in contact, the extracellular space being filled by the organic liquid and, in a more refined description, by the extracellular matrix. A biphasic model of this type has been recently proposed by Byrne & Preziosi[4]; here a more general theoretical framework is introduced leading, for instance, to a triphasic description including the extracellular matrix.

The emphasis of this paper is on the motion of cells due to their mutual mechanical interactions or because of external mechanical solicitations. The random motion of the cells as well as external factors possibly stimulating it, like chemotaxis and haptotaxis, are not of concern: the interested reader is referred to the review article by Othmer and Stevens.[21]

The introduction of a mechanical framework allows in principle to deal with several important problems such as the description of the stress field inside the growing spheroid and at the interface with the external tissues, which is related to compression, necrosis, collapse, or rupture of the surrounding tissues due to the uncontrolled growth of tumor.[12] Vice versa, a basis is given to understand how the stress due to solicitations exerted by external tissues can interfere with tumor growth. Last, but not least, in this framework it is possible to recover some of the simpler models adopted in the literature while clarifying the underlying assumptions.

The paper is organized as follows: Sec. 2 outlines some of the approaches that are currently encountered in the literature, in Sec. 3 we introduce a heuristic model for cell-to-cell interactions which includes some of the closures that are used in the relevant literature. In Sec. 4 the tumor is modelled as a growing and deformable porous material. In Sec. 5 the results of a simulation based on the model deduced in the preceding section are discussed. In the last section the presence of an extracellular network is included in the description, obtaining a model that includes the simpler ones as a particular case.

2. Potential Flow Closure

Most of the models used to describe tumor growth are based on balance equations for the cell mass $\rho_j\phi_j$, where ρ_j is the constant density of a single cell (e.g. the density of water) and $\phi_j(\mathbf{x},t)$ is the volume fraction occupied by the cells of the jth type over the total volume at point $\mathbf{x}$ at time t. The basis of this concept is that we are considering the continuum not in its real state (at a cellular level at any spatial point there can only be a cell or not), but as a mixture: at *every* point of the mixture there is a fraction ϕ_j of the jth constituent. The interested reader can find a detailed discussion of this concept in the first chapter of the book by Bear & Bachmat.[1]

Generally speaking (see Chaplain & Preziosi[6] for more details), mass balance equations read

$$\rho_j\left[\frac{\partial\phi_j}{\partial t}+\nabla\cdot(\phi_j\mathbf{v}_j)\right]=\rho_j\Gamma_j\,,\quad j=1,\ldots,n\,, \tag{2.1}$$

where $\mathbf{v}_j(\mathbf{x},t)$ is the velocity of the cells of jth type and Γ_j is the corresponding generation/death rate. In some cases the random motility of cells is also taken into account by a diffusion term, which is not included in the present description. Usually, both these terms depend on the concentration u_i of some chemicals, e.g. nutrients, oxygen, chemoattractants, which, in turn, satisfy advection–diffusion equations

$$\frac{\partial u_i}{\partial t}+\nabla\cdot(u_i\mathbf{v})=\nabla\cdot(Q_i\nabla u_i)+G_i-D_iu_i\,,\quad i=1,\ldots,m\,, \tag{2.2}$$

where Q_i is the diffusion coefficient, $\mathbf{v}(\mathbf{x},t)$ is the advective velocity (e.g. the velocity of the extracellular liquid in which the constituents are soluted), G_i is the production term and D_i the degradation/uptake coefficient.

Remark 2.1. Note that if the velocity field is solenoidal, Eq. (2.2) can be rewritten as

$$\frac{\partial u_i}{\partial t}+\mathbf{v}\cdot\nabla u_i=\nabla\cdot(Q_i\nabla u_i)+G_i-D_iu_i\,.$$

This assumption is often encountered in the literature, probably motivated by the incompressibility property of liquids. This assumption is plain for one-constituent continua, but it is no longer true when a liquid is one of the components of a mixture. In fact cells and liquid concentrations are defined at any $\mathbf{x}$, they are *co-present* in a description of a tumor like the one at hand. This means that some average has been tacitly operated on the dependent variables so that some obvious property holding in bulk, that is when only liquid matter is considered, are no longer true. This issue will be discussed in more detail in Remark 4.1.

The above arguments yield models that call for the specification of $\mathbf{v}_j$, Q_j, G_j, D_j and Γ_j in terms of the state variables. The scalar quantities have to be constitutively specified and verified on the basis of phenomenological observation. A

most difficult point consists of defining how cells move, i.e. linking the drift velocities $\mathbf{v}_1, \ldots, \mathbf{v}_n$ to the state variables $\phi_1, \ldots, \phi_n$, and $u_1, \ldots, u_m$. The velocity fields $\mathbf{v}_j$ can be provided constitutively in terms of the other variables or are to be found as solutions of supplementary differential equations (*momentum equations*). We call this step of the modelling procedure the *closure* problem. In the following, the direct influence of chemical factors on cell motion, e.g. chemotaxis and haptotaxis, will be neglected and the attention will be focused on the motion of cells generated by cell duplication or death. In this respect, only chemical factors which influence growth will be considered, e.g. growth promoting factors, growth inhibitory factors and nutrients.

Referring to Chaplain & Preziosi[6] for a review, we notice that most of the papers dealing with avascular growth of multicell spheroids work under the following hypotheses, even though they are not always explicitly stated:

(1) There is just one kind of cells, e.g. tumor cells;
(2) The tumor cells occupy a constant volume fraction $\bar{\phi}_T$, e.g. they are packed in the space as a bunch of rigid spheres in the close packing configuration;
(3) There is a symmetry condition which reduces the number of space variables to one and the velocity vector to a scalar, e.g. in spherical symmetry $\mathbf{v}_T = v_T(r)\mathbf{e}_r$ where $\mathbf{e}_r$ is the unit vector pointing into the radial direction;
(4) The convection of chemical factors and nutrients is negligible.

The introduction of the assumptions above into the evolution Eq. (2.1) yields, in spherical coordinates

$$\frac{1}{r^2}\frac{\partial}{\partial r}(r^2 v_T) = \frac{\Gamma_T(\mathbf{u})}{\bar{\phi}_T}\,, \quad \text{with} \quad \bar{\phi}_T = \text{const.}\,, \tag{2.3}$$

where $\mathbf{u} = (u_1, \ldots, u_n)$ and Γ_T depends on the different chemical factors and nutrients influencing the evolution, which assuming negligible drift evolve according to

$$\frac{\partial u_i}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 Q_i \frac{\partial u_i}{\partial r}\right) + G_i(\mathbf{u}) - D_i(\mathbf{u})u_i\,, \quad i = 1, \ldots, m\,. \tag{2.4}$$

After specifying the production and destruction terms in (2.4), the system of equations has to be supplemented by proper initial and boundary conditions. Equation (2.3) can then be integrated to write the velocity v_T in terms of the densities of nutrients and chemical factors. In particular, it can be used to determine how the tumor grows. In fact, the border of the tumor $R(t)$ moves with the tumor cells lying at the surface, i.e. with velocity

$$\frac{dR}{dt}(t) = v_T(R(t))\,. \tag{2.5}$$

The integration of Eq. (2.3) evaluated in $R(t)$ then gives

$$\frac{1}{3}\frac{dR^3}{dt}(t) = \frac{1}{\bar{\phi}_T}\int_0^{R(t)} \Gamma_T(\mathbf{u}(r,t))r^2 dr\,. \tag{2.6}$$

Therefore, thanks to the quite strong assumptions 1–4, the growth rate of the tumor mass is immediately provided by a simple ODE of geometric nature, thus skipping every difficulty related to determining the displacement of the cells in terms of the other unknowns. As we will show, this procedure works just in this particular case: more general problems need more assumptions.

When there are several cell types, such a simple geometric argument does not work any more even in the simple axisymmetric case. If the cells of the jth kind occupy a volume ratio ϕ_j, condition 2 in this context reads:

$$\sum_{j=1}^{n} \phi_j(r,t) = \Phi\,, \tag{2.7}$$

where Φ is a constant. Even in the one-dimensional case, one then has $n+1$ equations (n mass balance equations plus Eq. (2.7)) and $2n$ unknowns ϕ_j, v_j. In order to have a closed set of equations, a relation between the (scalar) velocities for cells of every type is needed. For instance, the assumption

$$v_j = \alpha_j v\,, \tag{2.8}$$

with α_j given, would allow to write

$$\frac{\partial \phi_j}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}(r^2 \phi_j \alpha_j v) = \Gamma_j(\phi, \mathbf{u})\,, \quad j = 1, \ldots, n\,, \tag{2.9}$$

where $\phi = (\phi_1, \ldots, \phi_n)$, which together with Eqs. (2.2) and (2.7) constitutes a set of $n+m+1$ equations in the same number of unknowns ϕ_j, u_i, W. It has to be noticed, however, that determining the coefficients α_j can be very hard. The most common assumption, named in mixture theory the "constrained mixture assumption", is to set $\alpha_j = 1$, for every j, so that all the constituents move with the same velocity and then they do not undergo any relative motion or friction. A similar approach is used by Ward and King who considered the evolution of live and dead cells,[22] added necrotic materials as a macromolecule produced by the dead cells,[23] and considered living cells, re-usable material deriving from cell death, and waste products.[24]

The approach presented above is also no longer possible in multi-dimensional problems. In fact, even for a single kind of cell with constant volume ratio, Eq. (2.3) becomes

$$\nabla \cdot \mathbf{v}_T = \frac{\Gamma_T(\mathbf{u})}{\bar{\phi}_T}\,, \tag{2.10}$$

which just provides a constraint on $\mathbf{v}_T$. The simplest possible assumption for closing the problem is that the motion of the cells is a potential flow

$$\mathbf{v}_T = \nabla \Psi\,, \tag{2.11}$$

where Ψ is a scalar function that, thanks to (2.10) satisfies

$$\nabla^2 \Psi = \frac{\Gamma_T(\mathbf{u})}{\bar{\phi}_T}\,. \tag{2.12}$$

We call the models obtained using this assumption *potential flow models*.

Similarly to what has been postulated in Eq. (2.8), for cells of several types, the potential flow assumption (2.11) can be generalized to

$$\mathbf{v}_j = \alpha_j \nabla \Psi \,, \tag{2.13}$$

with α_j given. In this case the system of Eq. (2.1) can be rewritten as

$$\frac{\partial \phi_j}{\partial t} + \nabla \cdot (\phi_j \alpha_j \nabla \Psi) = \Gamma_j(\phi, \mathbf{u}) \,, \quad j = 1, \ldots, n \,. \tag{2.14}$$

Again, Eqs. (2.14) with (2.2) and (2.7) constitute a set of $n + m + 1$ equations in the $n + m + 1$ unknowns ϕ_j, u_i, Ψ.

3. A Heuristic Argument for Cell-to-Cell Interaction

In this section we heuristically introduce a kind of cell-to-cell interaction that occurs in a tumor spheroid which reduces to the models illustrated above in some particular cases. A more solid basis for the conjecture done here will be given in Sec. 6. For the sake of simplicity we start considering a single species of cell, characterized by the volume fraction ϕ. When denoting by $\Sigma(\phi)$ the action of the surrounding cells depending only on their own density, one can phenomenologically assume that

$$\mathbf{v} = -K \nabla \Sigma \,, \tag{3.1}$$

where K is a motility coefficient possibly depending on the density of fibronectin or on the existence of an extracellular matrix to crawl upon. Equation (3.1) can be used to close the basic mass balance Eq. (2.1) obtaining

$$\frac{\partial \phi}{\partial t} - \nabla \cdot [\phi K \Sigma'(\phi) \nabla \phi] = \Gamma \,. \tag{3.2}$$

This approach has been used in De Angelis & Preziosi.[7] A qualitative characterization of Σ based on biological observations is sketched in Fig. 1. The threshold value $\bar{\phi}$, which might be called *natural* or *undeformed* state, corresponds to the density of cells such that no action is exerted on the neighbors. For larger volume ratio,

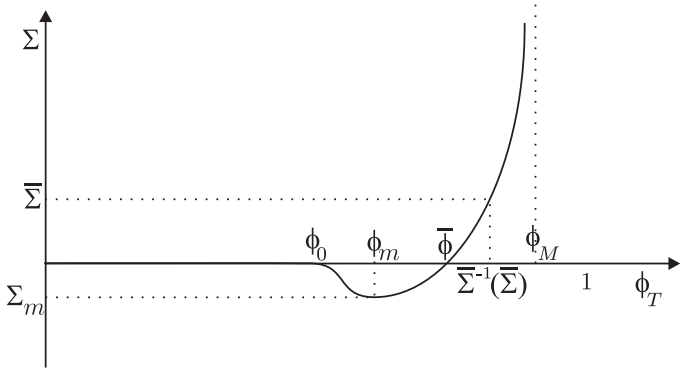

Fig. 1. Stress and deformation.

the cells are compressed and $\Sigma' > 0$, corresponding to an increasing repulsive force. However, there exists a maximum volume ratio ϕ_M, at most equal to one, that can be achieved by compressing the multicell spheroid. Hence, Σ has a vertical asymptote in ϕ_M. To characterize the behavior for $\phi < \bar{\phi}$, we recall that cells like to stick together. This is achieved through the expression of proper cell membrane receptors which link cells together to form multicell spheroids. This means that if cells are pull apart they feel an adhesion-type force and $\Sigma < 0$. The value ϕ_0 corresponds to the range of the short-range interaction, and Σ_m is related to the force needed to separate two attached cells.

A different evolution in time of the solution occurs depending on the sign of Σ'. If $\phi > \phi_m$, Eq. (3.2) is the standard (nonlinear) heat equation, when Σ' becomes negative, the equation becomes formally analogous to a backward heat equation.

Due to the parabolic nature of Eq. (3.2), one needs to give the boundary conditions on the border of the tumor. The natural ones involve the stress at the boundary. In the stress-free case, one has

$$\Sigma(\phi) = 0\,.$$

If at the boundary the tissues outside the multicell spheroid exert a stress $\bar{\Sigma} > 0$, then

$$\Sigma(\phi) = \bar{\Sigma}\,, \quad \text{or} \quad \phi = \Sigma^{-1}(\bar{\Sigma}) > \bar{\phi}\,.$$

The approach above can be generalized to more cell types assuming that Σ_j is a measure of the stress acting on the cells belonging of jth type:

$$\mathbf{v}_j = -K_j \nabla \Sigma_j\,, \tag{3.3}$$

where K_j is a motility coefficient which can differ from cell to cell. The concept of crowding may more likely involve all cells, independently of their type, that is the overall volume ratio, occupied by the cells

$$\sum_{j=1}^{n} \phi_j = 1 - \phi_\ell\,, \tag{3.4}$$

where ϕ_ℓ is the extracellular liquid volume ratio. Therefore $\Sigma_j = \Sigma_j(\phi_\ell)$, which can be used to close the mass balance Eq. (2.1), obtaining

$$\frac{\partial \phi_j}{\partial t} - \nabla \cdot [\phi_j K_j \Sigma_j'(\phi_\ell) \nabla \phi_\ell] = \Gamma_j\,, \quad j = 1, \ldots, n\,. \tag{3.5}$$

Heuristic arguments of this type lead to the set of reaction–diffusion equations defined on a domain with a moving boundary discussed by De Angelis and Preziosi.[7]

4. The Growing Porous Media Model

The determination of the movement due to the macroscopic growth of the tumor mass can be addressed on the basis of the deformable porous media theory (see for instance Sec. 1 of Rajagopal & Tao[20]), suitably adapted to the present biological

framework. As major difference with the approaches outlined in Sec. 1, a momentum equation is stated in order to provide the velocity field.

The ensemble of cells is assumed to live in a liquid environment in which some chemical factors diffuse. The multicell spheroid is then modelled as a living material characterized (as all organic tissues) by a porous structure permeated by an organic fluid. In addition, the porous structure is deformable and its constituent (the cells) undergo a relative motion because of growth, duplication and death, originating volumetric growth and deformation of the tumor.

For sake of simplicity no external sources of mass and momentum are considered, we will assume that the multicell spheroid is constituted by a single type of cells. Focusing on the evolution of tumor cells and of the extracellular liquid one can write the following system of equations

$$\frac{\partial \phi_T}{\partial t} + \nabla \cdot (\phi_T \mathbf{v}_T) = \Gamma_T \,, \tag{4.1}$$

$$\frac{\partial \phi_\ell}{\partial t} + \nabla \cdot (\phi_\ell \mathbf{v}_\ell) = \Gamma_\ell \,, \tag{4.2}$$

$$\rho_T \phi_T \left(\frac{\partial \mathbf{v}_T}{\partial t} + \mathbf{v}_T \cdot \nabla \mathbf{v}_T \right) - \nabla \cdot \mathbb{T}_T = \mathbf{m}_T \,, \tag{4.3}$$

$$\rho_\ell \phi_\ell \left(\frac{\partial \mathbf{v}_\ell}{\partial t} + \mathbf{v}_\ell \cdot \nabla \mathbf{v}_\ell \right) - \nabla \cdot \mathbb{T}_\ell = \mathbf{m}_\ell \,, \tag{4.4}$$

where Γ_T, Γ_ℓ are the production rates of cells and liquid, respectively, $\mathbb{T}_T, \mathbb{T}_\ell$ are the partial stress tensor of the tumor and liquid, respectively. The momentum supply $\mathbf{m}_\ell, \mathbf{m}_T$ of the ith constituent, contain both the drag due to the local interaction between the components and the Fickian diffusion of the single constituent. The saturation assumption states that the space is occupied by a tumor cell or by the extracellular liquid and reads

$$\phi_T + \phi_\ell = 1 \,. \tag{4.5}$$

As there are no external sources, the following conservation conditions for mass and momentum are to be satisfied:

$$\rho_T \Gamma_T + \rho_\ell \Gamma_\ell = 0 \,, \tag{4.6}$$

$$\mathbf{m}_T + \mathbf{m}_\ell + \rho_T \Gamma_T \mathbf{v}_T + \rho_\ell \Gamma_\ell \mathbf{v}_\ell = \mathbf{0} \,. \tag{4.7}$$

Remark 4.1. Referring to Remark 2.1, in the case of constant volume ratio of cells Eq. (4.2) can be rewritten as

$$\phi_\ell \nabla \cdot \mathbf{v}_\ell = \Gamma_\ell \,,$$

and therefore $\nabla \cdot \mathbf{v}_\ell \neq 0$ when tumor cells duplicate or die.

Summing up the mass balance Eqs. (4.1) and (4.2), and taking (4.5) into account gives

$$\nabla \cdot (\phi_T \mathbf{v}_T + \phi_\ell \mathbf{v}_\ell) = \Gamma_c \,, \tag{4.8}$$

where

$$\Gamma_c = \Gamma_T + \Gamma_\ell \,.$$

It can be noticed that, because of Eq. (4.6), the R.H.S. of Eq. (4.8) vanishes if $\rho_T = \rho_\ell$.

Adding up the two momentum equations in (4.3) and (4.4), after some algebra gives the momentum equation for the the multicellular spheroid, i.e. the mixture composed of the extracellular liquid and the cells

$$\rho_m \left(\frac{\partial \mathbf{v}_m}{\partial t} + \mathbf{v}_m \cdot \nabla \mathbf{v}_m \right) = \nabla \cdot \mathbb{T}_m \,, \tag{4.9}$$

where

$$\rho_m = \rho_T \phi_T + \rho_\ell \phi_\ell \,, \tag{4.10}$$

is the density of the mixture, and

$$\mathbf{v}_m = \frac{\rho_T \phi_T \mathbf{v}_T + \rho_\ell \phi_\ell \mathbf{v}_\ell}{\rho_m} \,, \tag{4.11}$$

is the mass average velocity, and $\mathbb{T}_m$ is the stress tensor of the mixture. The latter contains convective contributions that are not included in the barycentric momentum appearing on the left-hand side of Eq. (4.9).

Equations (4.8) and (4.9) can be considered instead of the mass balance for the liquid and the momentum balance for the solid. In addition, as the motion of cells and of the intercellular fluid is very slow, inertial terms can be neglected when compared to the stress terms. The system of evolution equations can then be written as

$$\frac{\partial \phi_T}{\partial t} + \nabla \cdot (\phi_T \mathbf{v}_T) = \Gamma_T \,, \tag{4.12}$$

$$\nabla \cdot (\phi_T \mathbf{v}_T + \phi_\ell \mathbf{v}_\ell) = \left(1 - \frac{\rho_T}{\rho_\ell} \right) \Gamma_T \,, \tag{4.13}$$

$$-\nabla \cdot \mathbb{T}_m = 0 \,, \tag{4.14}$$

$$-\nabla \cdot \mathbb{T}_\ell = \mathbf{m}_\ell \,, \tag{4.15}$$

$$\frac{\partial u_i}{\partial t} + \nabla \cdot (u_i \mathbf{v}_\ell) = \nabla \cdot (Q_i \nabla u_i) + G_i - D_i u_i \,, \quad i = 1, \ldots, m \,. \tag{4.16}$$

At this point one needs to deduce constitutive equations relating stresses ($\mathbb{T}_m$ and $\mathbb{T}_\ell$) and interaction forces ($\mathbf{m}_\ell$) to a suitable set of constitutive variables while the term Γ_T has to be determined on the basis of phenomenological observation on the duplication and death of tumor cells.

Regarding the constitutive equation for $\mathbb{T}_m$, the simplest assumption is that the state of stress of the multicell spheroid does not change when it undergoes a deformation which is locally volume preserving. This means that, for instance, if two cells switch place they do not tend to return to their original position, (as is

the case of an elastic solid) and the stress field is unmodified. It is however known that cells are subject to strong short range cell–cell interactions, which represent a resistance to their relative motion. Assuming also isotropy and absence of memory effects, a possible constitutive equation for the stress of the mixture accounting for the qualitative behavior outlined above is the following:

$$\mathbb{T}_m = -[P + \Sigma(\phi_T) - \lambda_T(\phi_T)\nabla \cdot \mathbf{v}_T]\mathbb{I} + \mu_T(\phi_T)(\nabla \mathbf{v}_T + (\nabla \mathbf{v}_T)^{\mathrm{T}}), \tag{4.17}$$

where Σ accounts for the elastic interaction of the cells and μ_T measures the resistance of the multicell spheroid to shear, which depends on the density of cells. This constitutive equation corresponds to an elastic viscous fluid subject to the kinematical constraint (4.8). The pressure of the mixture P is to be included to accomplish the saturation constraint (4.13). An example of a possible qualitative behavior of $\Sigma(\phi_T)$ is given in Fig. 1.

The momentum equation for the mixture is then

$$\nabla P + \Sigma'(\phi_T)\nabla\phi_T = \nabla[\lambda_T(\phi_T)\nabla \cdot \mathbf{v}_T] + \nabla \cdot [\mu_T(\phi_T)(\nabla \mathbf{v}_T + (\nabla \mathbf{v}_T)^{\mathrm{T}})], \tag{4.18}$$

where $\Sigma' = d\Sigma/d\phi_T$.

Considering the multicell spheroid as a growing and deformable porous medium filled by the extracellular liquid allows to work in the framework of Farina & Preziosi[11] and from the momentum equation for the liquid the following modified form of Darcy's law is deduced by proper assumptions

$$\phi_\ell(\mathbf{v}_\ell - \mathbf{v}_T) = -\frac{K_\ell}{\nabla P}, \tag{4.19}$$

where

$$K_\ell = \frac{K}{\mu_\ell(1-\gamma)}, \tag{4.20}$$

K is the permeability coefficient, μ_ℓ is the viscosity of the extracellular liquid, P is the pressure and

$$\gamma = \frac{K\Gamma_T}{2\mu_\ell\phi_\ell^2}, \tag{4.21}$$

is a dimensionless number which in biological applications is very small.

The model is then constituted of Eqs. (4.12), (4.13), (4.18), (4.19) and (4.16). A possible simplification occurs using (4.8) and (4.19) to determine explicitly

$$\mathbf{v}_\ell = \mathbf{v}_T - \frac{K_\ell}{(1-\phi_T)}\nabla P, \tag{4.22}$$

which can be substituted into the other equations.

Remark 4.2. In the one-dimensional case, Eq. (4.8) can be integrated to give (in the Cartesian case)

$$\phi_T v_T + \phi_\ell v_\ell = \text{const}. \tag{4.23}$$

For symmetry reasons in the center of the tumor both liquid and cell velocity vanish, so that the integration constant is zero. This allows to write explicitly

$$v_\ell = -\frac{\phi_T}{\phi_\ell} v_T \,,$$

which can be back substituted in Darcy's law (4.19) to get,

$$v_T = K_\ell \frac{\partial P}{\partial x} \,. \tag{4.24}$$

It is known that at the steady state the interstitial pressure is higher in the kernel of the tumor. According to Eq. (4.24) the cells move toward the center of the tumor while the extracellular liquid flows toward its border (see Fig. 2). The experiments discussed in Dorie *et al.*[8,9] show that a recirculation then forms: tumor cells starve near the center generating re-usable materials which flow to the border to feed new-born cells. This phenomenon is put in evidence in the simulation presented in the following section.

Remark 4.3. Equation (4.24) is formally identical to Eq. (2.11) and, in the present context, it is supported by a more solid basis. However, we stress that these arguments cannot be generalized to the pluri-dimensional case, because even when $\Gamma_c = 0$, Eqs. (4.8) and (4.19) do not imply (2.11), as is argued in Landman & Please[16] and Please *et al.*[19] In this respect, we prefer to think of the Darcy's-type closure[2,13,19,14]

$$\mathbf{v}_T = \frac{K}{\mu} \nabla P \tag{4.25}$$

as a potential flow assumption or on the basis of the conjectures in Sec. 2. However, we remark that in Byrne & Chaplain,[2] Byrne[5] and McElwain & Pettet,[13] Eq. (4.25) is quoted with opposite sign, which is contrast with the mechanical description above and the results appearing in Dorie *et al.*[8,9] Such a discrepancy is actually uninfluent when dealing with 1D problems with constant ϕ_T and in fact, in spite of being mentioned, the Darcy's equation does not even appear in the final model by McElwain & Pettet.[13]

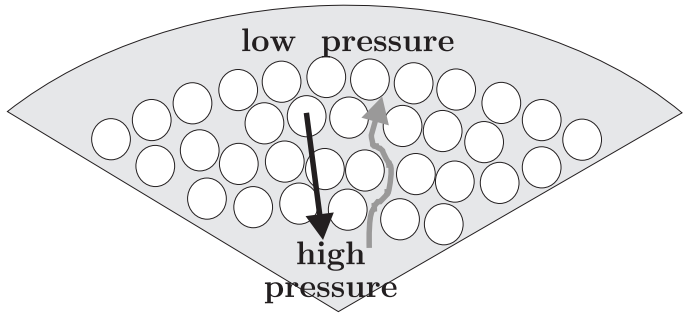

Fig. 2. Relative motion of cells and extracellular liquid in a tumor.

5. A Numerical Simulation

In this section we present the results of a simulation obtained using the model introduced in Sec. 4. Its aims are to demonstrate the ability of the model to account in a qualitatively correct way for the growth, the nonuniform character of compression, the flow of the interstitial liquid, the process of internalization of cells described in Remark 4.3 and the existence of a steady state. The simulation is performed for a single nutrient species, characterized by the concentration $n(\mathbf{x}, t)$, filtrating through the border of the tumor and consumed by tumor cells. Hence, consider Eq. (4.16) with $G = 0$, $D = \delta_n \phi_T$ and assume that the value of nutrient concentration at the border of the tumor is is $n_0 = \text{const}$. In addition, we consider the viscosity terms negligible ($\lambda_T = \mu_T = 0$), equal density ($\rho_T = \rho_\ell$), and use

$$K_\ell = K_0(1 - \phi_T)^{0.1}\,, \tag{5.1}$$

$$\Sigma = \begin{cases} \alpha \dfrac{(\phi_T - \phi_0)^2(\phi_T - \bar{\phi})}{\sqrt{1 - \phi_T}} & \text{if } \phi_T > \phi_0\,, \\ 0 & \text{otherwise}\,. \end{cases} \tag{5.2}$$

Finally

$$\Gamma_T = [\gamma(n - \bar{n})_+ - \delta]\phi_T\,, \tag{5.3}$$

where f_+ is the positive part of f and it is assumed that the tumor boundary is stress free. The influence of the stress on growth is considered in Byrne and Preziosi.[4]

Focusing on the evolution between the tumor midline and the border, three phases can be recognized during the evolution.

- Figure 3(a). The tumor is at an initial stage: its size is still small and all cells are able to duplicate because the level of nutrient is everywhere larger than $\hat{n}$. The maximum value of the volume ratio, and therefore the maximum stress, is in the center of the tumor. Tumor cells move from the center to the border of the tumor ($v_T \geq 0$ everywhere), while the liquid moves in the opposite direction ($v_\ell \leq 0$ everywhere).
- Figure 3(b). At this stage the tumor can be divided into three regions: a central one where the volume ratio of tumor cells is below the stress-free value $\bar{\phi}$ with a minimum in the center; an intermediate region where the volume ratio of tumor cells is above the stress-free value and increases till it reaches a maximum; a border region in which the volume ratio of tumor cells decreases. In the first two regions tumor cells move toward the center, while in the third one they move toward the boundary ($v_T \geq 0$), pushing forward the border of the tumor. The velocity of the fluid and cells vanishes where the volume ratio reaches its maximum. The last two regions can be identified with the proliferating region characterized by cells moving away from the point of maximum and organic liquid sucked toward it.

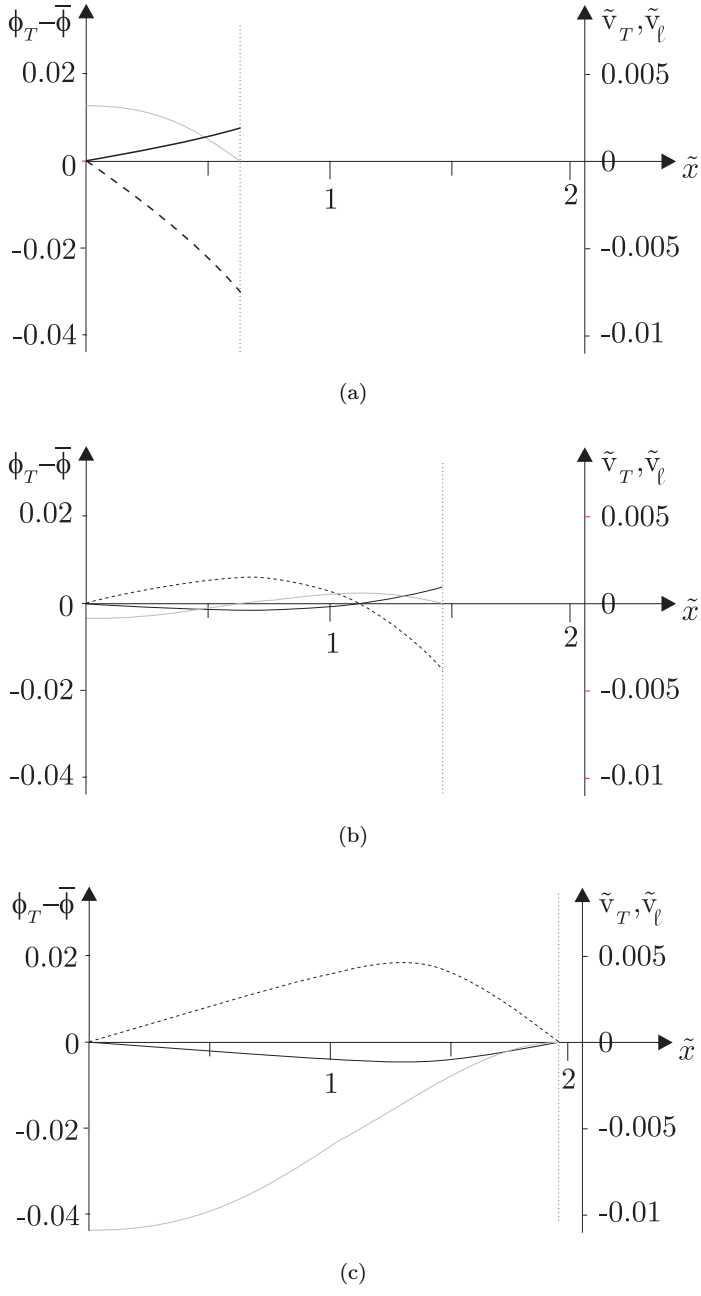

Fig. 3. Volume ratio (grey) and velocity of tumor cells (full) and of the liquid phase (dashed) at (a) $\tilde{t} = 500$ (a), (b) $\tilde{t} = 1000$ and (c) in the stationary configuration (c). The dotted vertical line shows the position of the tumor border while the axis on the left is the tumor centerline. The numerical simulation has been performed for equations written in non-dimensional form: the tumor has initial dimensionless radius 0.1 and dimensionless parameters are $\tilde{D} = K_0\alpha/Q = 0.1$, $\tilde{\gamma} = \gamma n_0/\delta_n = 0.01$, $\tilde{\delta} = \delta/\delta_n = 0.001$, $\phi_0 = 1/2$, $\bar{\phi} = 2/3$ and $\hat{n} = \bar{n}/n_0 = 0.5$.

- Figure 3(c). The tumor has reached the stationary configuration. The maximum volume ratio is achieved at the border, that does not move any more. Tumor cells, which are created in the outer region, move toward the center ($v_T \leq 0$ everywhere) where they do not find enough nutrient and die, the organic liquid moves in the opposite direction ($v_\ell \geq 0$ everywhere). This is in agreement with the phenomenon of internalization of cells mentioned in Dorie *et al.*[8,9]: tumor cells starve near the center generating re-usable materials which flow to the border to feed new-born cells.

6. Including the Extra-Cellular Matrix

The model described in the preceding section can be refined including the description of the presence of a rigid extracellular matrix influencing the movement of cells. The cells are then assumed to move according to the forces exerted on them, including both cell–cell and cell–matrix interactions. Though the extracellular matrix is actually deformable (see Holmes & Sleeman[15]), for sake of simplicity here it will be considered as a rigid net over which the cells crawl.

The ensemble of cells is described as a granular material infiltrating a porous structure, the network of pores being the extracellular matrix. Of course, this is not the real biological picture, as there are no channels in the matrix the cells move through. However, it is known that the cells exhibit a tendency to move along a network of macromolecules and the motion of the ensemble of cells along the "roads and crossings" of the extracellular matrix resembles the one of an ensemble of grains through a network of pores, of honey sliding down a net,[17] as depicted in Fig. 4. One can then describe the tumor as a binary (liquid–cells) saturated mixture constrained to move in a rigid porous medium. Assuming negligible inertia once more, the following set of equations can be written

$$\frac{\partial \phi_T}{\partial t} + \nabla \cdot (\phi_T \mathbf{v}_T) = \Gamma_T \,, \tag{6.1}$$

$$\frac{\partial \phi_\ell}{\partial t} + \nabla \cdot (\phi_\ell \mathbf{v}_\ell) = \Gamma_\ell \,, \tag{6.2}$$

$$\phi_T + \phi_\ell = 1 - \phi_e \,, \tag{6.3}$$

$$-\nabla \cdot \mathbb{T}_T = \mathbf{m}_T \,, \tag{6.4}$$

$$-\nabla \cdot \mathbb{T}_\ell = \mathbf{m}_\ell \,, \tag{6.5}$$

$$-\nabla \cdot \mathbb{T}_e = \mathbf{m}_e \,, \tag{6.6}$$

where the rigidity assumption of the extracellular matrix implies that its volume ratio $\phi_e(\mathbf{x})$ is constant in time and that the stress of the extracellular matrix balances the interfacial forces exerted by the other constituents. Mass exchange occurs between tumor and extracellular liquid only, so that Eq. (4.8) holds.

Apart from the negligible contribution related to mass exchange, the interaction forces $\mathbf{m}_i$ account for Fickian diffusion and for the drag forces exerted on the ith

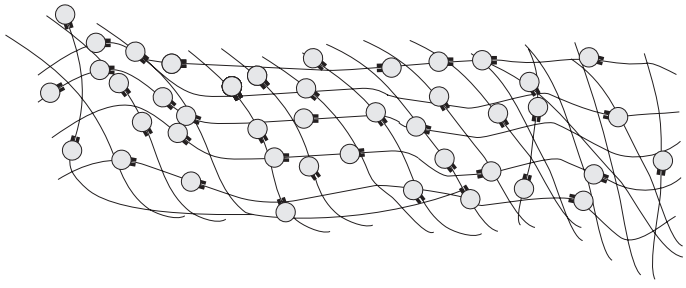

Fig. 4. Motion of the tumor cells on the extra-cellular matrix.

constituent by the other constituents. The latter can be taken to be proportional to the relative velocity between the constituents. Hence, one can write

$$\mathbf{m}_T = P\nabla\phi_T - \Lambda_T\mathbf{v}_T - \Lambda(\mathbf{v}_T - \mathbf{v}_\ell)\,, \tag{6.7}$$

$$\mathbf{m}_\ell = P\nabla\phi_\ell - \Lambda_\ell\mathbf{v}_\ell + \Lambda(\mathbf{v}_T - \mathbf{v}_\ell)\,, \tag{6.8}$$

$$\mathbf{m}_e = -\mathbf{m}_T - \mathbf{m}_\ell\,, \tag{6.9}$$

where the first term on the right-hand side is thermodynamically related to the saturation constraint (see Farina & Preziosi[10]).

Inspired by the analogy with the mechanical behavior of a system composed by an elastic and an ideal fluid, we assume the following constitutive equations for the partial stresses

$$\mathbb{T}_T = -\phi_T P\mathbb{I} - \Sigma_T(\phi_T)\mathbb{I}\,, \tag{6.10}$$

$$\mathbb{T}_\ell = -\phi_\ell P\mathbb{I}\,, \tag{6.11}$$

where P is the pressure of the mixture, i.e. the Lagrange multiplier that ensures the accomplishment of the constraint (6.3). The intercellular liquid is supposed to behave *in the mixture* as a perfect fluid, all the viscous contributions being included in the internal forces. Substituting the constitutive Eqs. (6.10) and (6.11) into the momentum equations, one gets

$$-\phi_T\nabla P = \Sigma_T'\nabla\phi_T = \Lambda(\mathbf{v}_T - \mathbf{v}_\ell) + \Lambda_T\mathbf{v}_T\,, \tag{6.12}$$

$$-\phi_\ell\nabla P = -\Lambda(\mathbf{v}_T - \mathbf{v}_\ell) + \Lambda_\ell\mathbf{v}_\ell\,. \tag{6.13}$$

Finally, Eqs. (6.12) and (6.13) are to be considered together with Eqs. (6.2) and (6.3). Possible simplifications of the problems, thanks to substitutions should be operated with care, neither to get a number of unknowns larger than the number of equations, nor to eliminate from the problem quantities that are typically invoked by boundary conditions.

Remark 6.1. A substantial simplification occurs if one neglects the presence of the extracellular liquid and drops the saturation constraint (6.3). In this case the

pressure term does not appear any more in the constitutive Eqs. (6.7)–(6.11) and one can write

$$\mathbf{m}_T = -\Lambda_T \mathbf{v}_T \quad \text{and} \quad \mathbb{T}_T = -\Sigma_T(\phi_T)\mathbb{I}\,, \tag{6.14}$$

with Σ_T taken positive in compression. Equation (6.4) then writes

$$\nabla\Sigma_T(\phi_T) + \Lambda_T \mathbf{v}_T = 0\,,$$

or

$$\mathbf{v}_T = -K_T \nabla\Sigma_T(\phi_T)\,,$$

with $K_T = 1/\Lambda_T$. This model corresponds to the slow motion of an elastic fluid with linear drag. The latter equation is formally identical to (3.1).

7. Conclusions

After discussing some methods that are typically adopted in the literature to close the mass balance equations to describe tumor growth, we have introduced a new modelling framework of mechanical description of the process. We started from the idea that multicell spheroids are made at least of two constituents: a solid skeleton constituted by an ensemble of sticky cells each of which can be schematized as an elastic membrane filled by organic fluid and organic liquid filling the extra-cellular space, which is used by the cells to grow. The correct mechanical framework for a system of this type is the theory of multicomponent continua; namely, we treat tumors as deformable porous media. The role of the extracellular matrix is also taken into account as a development of the basic model.

The introduction of such a mechanical framework allows to give a precise meaning to the concept of stress. This is essential for describing several phenomena involving the stress evolution inside the growing spheroid, at the interface with the external tissues, and the mechanical coupling between what happens inside and outside the growing tumor. This description allows in principle to determine how the tumor uncontrolled growth may cause compression, necrosis, collapse, or rupture of the surrounding tissues and, in particular, collapse of immature blood vessels and infiltration and rupture of ducts and capsules. In turn, the models allow to determine how the stresses inside the tumor related to the compression of the external tissues can interfere with tumor growth. Last, but not least, it gives a mechanical justification of Darcy's type closures.

However, we are conscious that this paper is just a first step in this direction. The most urgent necessity to proceed further is probably to determine experimentally some characterization of the mechanical behavior of multicellular spheroids, as it is usually done in biomechanics to study bones, articular cartilage and skin. Very few data are available in this respect, probably because mechanical experiments on ensemble of cells are much more difficult to carry out.

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