

Multiphase Models of Tumor Growth: General Framework and Particular Cases

Luigi Preziosi and Luigi Graziano

Dipartimento di Matematica, Politecnico di Torino

Abstract. The avascular tumor is regarded as a mixture of $N + 1$ components. A general multiphase model is deduced and then specialized to the biphasic and triphasic case including the presence of extracellular liquid and extracellular matrix.

1 Introduction

Recently a mathematical description of avascular tumor as a biphasic system has been proposed [2], [3], [5], [6], [10], [13]. This approach starts from the observation that multicell spheroids are basically made of two constituents: a solid skeleton constituted by an ensemble of sticky cells and by an organic liquid filling the extracellular space, which is used by the cells to grow. To complete the picture chemical factors and nutrients diffuse in the extracellular liquid, being absorbed or produced by the tumor cells. More precisely, the multicell spheroid is modeled as a saturated porous medium, with the additional characteristic, common to all organic tissues, that the porous structure is alive and deformable. In fact, its constituent (the cells) move, duplicate and die, originating deformation and volumetric growth of the tumor.

The main advantage of the introduction of such a mechanical framework consists in the ability to deal with stresses, with their influence on the evolution of the system [11], and with the mechanical interactions with the surrounding tissues [4], [7].

The models proposed in [3], [5] are based on the constitutive assumption that the ensemble of cells behaves as a “viscous growing fluid”, so that one does not need to describe the deformations of the material with respect to some reference configuration, but only to deal with their rates. In this respect, it is possible to use an Eulerian framework and the mathematical description of the “growing fluid” just involves an additional source of mass.

An additional problem occurs in describing the multicellular spheroid as a solid, e.g. a growing elastic material. In this case the knowledge of deformation is required to define a mechanical response. The question in this case is: “Deformation with respect to what?”.

This problem was studied in [1], [12] using the notion of multiple natural configurations. In these papers the volumetric growth of a continuous medium is approached using a description that splits growth and mechanical response into two separate contributions. In particular, Ambrosi and Mollica [1] specifically refer to tumor growth taking also into account the fact that

mitosis and apoptosis strongly depend upon the availability of nutrients and that stresses influence growth.

In the present paper we consider the tumor as a mixture of $N + 1$ constituents and deduce a general multiphase model. Specializing the model, we first draw a relation between the biphasic models dealing with chemotaxis as a force and the many biomathematical models which adopt the chemotactic closure of the mass balance equation. We then apply the general model to the biphasic and the thiphasic cases, considering the presence of the extracellular matrix.

2 Multiphase Models

Consider the tumor as made of $N + 1$ different constituents. To achieve the aim of this section, it will not be necessary to specify precisely the type of constituents involved. One can then generally write the well known equations (see [2] and reference therein)

$$\begin{cases} \frac{\partial}{\partial t} \phi_i + \nabla \cdot (\phi_i \mathbf{v}_i) = \Gamma_i, \\ \rho_i \phi_i \left(\frac{\partial}{\partial t} \mathbf{v}_i + \mathbf{v}_i \cdot \nabla \mathbf{v}_i \right) = \nabla \cdot \mathbf{T}_i + \mathbf{b}_i + \mathbf{m}_i^\sigma, \end{cases} \quad (1)$$

for $i = 0, \dots, N$, where ϕ_i is the volume ratio of the i -th constituent, \mathbf{m}_i^σ is the interaction force with the other constituents and \mathbf{b}_i are the body forces, e.g., chemotaxis.

In many biological phenomena as those dealt with in this article, inertial terms can be neglected and the main contribution to the interfacial forces can be assumed to be proportional to the velocity difference between the constituents

$$\mathbf{m}_i^\sigma = \mathbf{m}_i^0 - \sum_{j=0, j \neq i}^N M_{ij} (\mathbf{v}_i - \mathbf{v}_j),$$

with and $M_{ij} = M_{ji} > 0$. The coefficients M_{ij} are related to the relative permeabilities. One can then rewrite the momentum equations as

$$\mathbf{B}_i - \sum_{j=0, j \neq i}^N M_{ij} (\mathbf{v}_i - \mathbf{v}_j) = \mathbf{0}, \quad i = 0, \dots, N,$$

where $\mathbf{B}_i = \nabla \cdot \mathbf{T}_i + \mathbf{b}_i + \mathbf{m}_i^0$. It is useful to separate one contribution from the others and write

$$\mathbf{B}_i + M_{i0} \mathbf{v}_0 - \left(M_{i0} + \sum_{j=1, j \neq i}^N M_{ij} \right) \mathbf{v}_i - \sum_{j=1, j \neq i}^N M_{ij} \mathbf{v}_j = \mathbf{0}, \quad i = 1, \dots, N. \quad (2)$$

Denoting by

$$M_i = M_{i0} + \sum_{j=1, j \neq i}^N M_{ij}, \quad i = 1, \dots, N,$$

one can rewrite (2) as a system of equations in the unknowns \mathbf{v}_i

$$M_i \mathbf{v}_i - \sum_{j=1, j \neq i}^N M_{ij} \mathbf{v}_j = \mathbf{B}_i + M_{i0} \mathbf{v}_0, \quad i = 1, \dots, N. \quad (3)$$

It is evident that the matrix $\tilde{\mathbf{M}}$ of the coefficients of $\mathbf{v}_k, k \neq 0$, in the system (3) is diagonally dominated. One can then explicitly write

$$\mathbf{v}_i = \sum_{j=1}^N \tilde{M}_{ij}^{-1} (\mathbf{B}_j + M_{j0} \mathbf{v}_0), \quad i = 1, \dots, N.$$

Thanks to the symmetry of the system (3) with respect to $\mathbf{v}_k, k = 0, \dots, N$, one can prove that

$$\sum_{j=1}^N \tilde{M}_{ij}^{-1} M_{j0} = 1.$$

The system (1) then simplifies to

$$\begin{cases} \frac{\partial}{\partial t} \phi_0 + \nabla \cdot (\phi_0 \mathbf{v}_0) = \Gamma_0, \\ \frac{\partial}{\partial t} \phi_i + \nabla \cdot \left[\phi_i \left(\mathbf{v}_0 + \sum_{j=1}^N \tilde{M}_{ij}^{-1} \mathbf{B}_j \right) \right] = \Gamma_i, \quad i = 1, \dots, N, \\ \nabla \cdot \mathbf{T}_0 + \mathbf{b}_0 + \mathbf{m}_0^g = \mathbf{0} \end{cases} \quad (4)$$

If the mixture is closed (that is, if all constituents are taken into account) then $\sum_{i=0}^N \Gamma_i = 0$, and, under the saturation assumption $\sum_{i=0}^N \phi_i = 1$, the first equation of the system (4) can then be replaced by

$$\nabla \cdot \left(\sum_{i=0}^N \phi_i \mathbf{v}_i \right) = 0, \quad (5)$$

or

$$\nabla \cdot \left(\mathbf{v}_0 + \sum_{i=1}^N \phi_i \sum_{j=1}^N \tilde{M}_{ij}^{-1} \mathbf{B}_j \right) = 0. \quad (6)$$

3 Chemotactic Force and Chemotactic Velocity

For a general biphasic mixture, $\tilde{M}_{11}^{-1} = 1/M_{01}$ and Eq.(4) writes

$$\begin{cases} \frac{\partial}{\partial t}\phi_0 + \nabla \cdot (\phi_0 \mathbf{v}_0) = \Gamma_0, \\ \frac{\partial}{\partial t}\phi_1 + \nabla \cdot \left[\phi_1 \left(\mathbf{v}_0 + \frac{1}{M_{01}} \mathbf{B}_1 \right) \right] = \Gamma_1, \\ \nabla \cdot \mathbf{T}_0 + \mathbf{b}_0 + \mathbf{m}_0^g = \mathbf{0}. \end{cases} \quad (7)$$

Consider the simplest situation of a cell population living in a rigid environment, for instance a multicell spheroid made of a single type of cells proliferating in a rigid extracellular matrix. The rigidity of the environment implies that $\mathbf{v}_0 = \mathbf{0}$ and that the stress \mathbf{T}_0 takes the role of an unknown reaction. In this case, Eq.(7) writes as

$$\begin{cases} \frac{\partial}{\partial t}\phi_0 = \Gamma_0, \\ \frac{\partial}{\partial t}\phi_T + \nabla \cdot \left[\frac{\phi_T}{M_{0T}} (\nabla \cdot \mathbf{T}_T + \mathbf{b}_T) \right] = \Gamma_T. \end{cases} \quad (8)$$

The first equation describes the deposition or degradation of the extracellular matrix. If the body force is a chemotactic force, $\mathbf{b}_T = \chi(\phi_T)\nabla u$, where u is the concentration of a given chemical factor, and the stress tensor is isotropic, $\mathbf{T}_T = -\Sigma(\phi_T)\mathbf{I}$, then (8)₂ rewrites as

$$\frac{\partial \phi_T}{\partial t} + \nabla \cdot \left(\frac{\chi(\phi_T)}{M_{0T}} \phi_T \nabla u \right) = \nabla \cdot \left(\frac{\Sigma'(\phi_T) \phi_T}{M_{0T}} \nabla \phi_T \right) + \Gamma_T, \quad (9)$$

where Σ' is the derivative of Σ with respect to the volume ratio ϕ_T .

In the particular case of negligible stress exerted by tumor cells, one has the classical chemotactic models

$$\frac{\partial \phi_T}{\partial t} + \nabla \cdot \left(\frac{\chi(\phi_T)}{M_{0T}} \phi_T \nabla u \right) = \Gamma_T.$$

In this deduction, however, chemotaxis is conceived as a force balanced by the drag force exerted by the substratum, since

$$\chi(\phi_T)\nabla u - M_{0T}\mathbf{v}_T = \mathbf{0} \Rightarrow \mathbf{v}_T = \frac{\chi(\phi_T)}{M_{0T}}\nabla u,$$

and not as a convenient closure of the mass balance equation. A number of additional hypothesis then allows to find a bridge between this general procedure and the classical model.

In addition, Eq.(9) takes into account of the fact that cells can not overcrowd a certain region of space. If the function Σ has some physically plausible properties (increasing, convex, blowing up at a finite value of the volume

ratio) then the blow-up of the solution is avoided. This procedure then justifies a way of refining the classical chemotactic models to models giving rise to well-behaved solutions. It is true that viscous effects should also be taken into account which would improve the stability properties of the solution.

4 One Constituent in a Saturating Liquid Environment

Consider the multicell spheroid as made of a single type of cells embedded in a liquid environment. Assuming saturation implies that $\phi_T + \phi_\ell = 1$ and $\mathbf{B}_i = -\phi_i \nabla P + \nabla \cdot \mathbf{T}'_i + \mathbf{b}_i, i = T, \ell$. Recalling that $\tilde{M}_{\ell\ell}^{-1} = 1/M_{\ell T}$ and replacing (7)₂ with (6), one can write

$$\begin{cases} \frac{\partial}{\partial t} \phi_T + \nabla \cdot (\phi_T \mathbf{v}_T) = \Gamma_T, \\ \nabla \cdot \left(\mathbf{v}_T + \frac{1}{M_{T\ell}} \phi_\ell \mathbf{B}_\ell \right) = 0, \\ -\phi_T \nabla P + \nabla \cdot \mathbf{T}'_T + \mathbf{b}_T - M_{\ell T} (\mathbf{v}_T - \mathbf{v}_\ell) = \mathbf{0}, \end{cases} \quad (10)$$

where \mathbf{T}'_T is the excess stress of the solid constituent.

In the simplest case

$$\mathbf{B}_\ell = -\phi_\ell \nabla P \quad (11)$$

where P is the extracellular liquid pressure. Specializing the constitutive equation for \mathbf{T}'_T , one has the models deduced in [2], [3], [5], [6].

In one-dimensional problems, (10)₂ implies that cells move up the pressure gradient, while the extracellular liquid moves in the opposite direction. This is in agreement with the results by Dorie et al. [8].

5 Two Constituents in a Rigid Environment

Let us now merge the previous cases considering the presence of both the extracellular matrix and the extracellular liquid. In this case, Eq.(4) writes

$$\begin{cases} \frac{\partial}{\partial t} \phi_0 + \nabla \cdot (\phi_0 \mathbf{v}_0) = \Gamma_0, \\ \frac{\partial}{\partial t} \phi_T + \nabla \cdot \left[\phi_T \left(\mathbf{v}_0 + \tilde{M}_{TT}^{-1} \mathbf{B}_T + \tilde{M}_{T\ell}^{-1} \mathbf{B}_\ell \right) \right] = \Gamma_T, \\ \frac{\partial}{\partial t} \phi_\ell + \nabla \cdot \left\{ \phi_\ell \left[\mathbf{v}_0 + \tilde{M}_{\ell\ell}^{-1} \mathbf{B}_\ell + \tilde{M}_{T\ell}^{-1} (\mathbf{B}_T) \right] \right\} = \Gamma_\ell, \\ \nabla \cdot \mathbf{T}_0 + \mathbf{b}_0 + \mathbf{m}_0^\sigma = \mathbf{0}, \end{cases} \quad (12)$$

where

$$\tilde{\mathbf{M}}^{-1} = \frac{1}{(M_{0T} + M_{T\ell}) M_{0\ell} + M_{0T} M_{T\ell}} \begin{pmatrix} M_{0\ell} + M_{T\ell} & M_{T\ell} \\ M_{T\ell} & M_{0T} + M_{T\ell} \end{pmatrix}$$

Considering the rigidity of the environment ($\mathbf{v}_0 = \mathbf{0}$) and (11), one can simplify (12) to

$$\begin{cases} \frac{\partial}{\partial t} \phi_0 = \Gamma_0 \\ \frac{\partial}{\partial t} \phi_T + \nabla \cdot \left[\phi_T \left(\tilde{M}_{TT}^{-1} \mathbf{B}_T - \tilde{M}_{T\ell}^{-1} \phi_\ell \nabla P \right) \right] = \Gamma_T \\ \nabla \cdot \left[(\phi_T \tilde{M}_{TT}^{-1} + \phi_\ell \tilde{M}_{T\ell}^{-1}) \mathbf{B}_T - (\phi_T \tilde{M}_{T\ell}^{-1} + \phi_\ell \tilde{M}_{\ell\ell}^{-1}) \phi_\ell \nabla P \right] = 0 \end{cases} \quad (13)$$

which can be solved after specializing the constitutive equation for the stress related to the tumor which is contained in \mathbf{B}_T . A further simplification can be obtained observing that M_{0T} is much larger than $M_{T\ell}$ and $M_{0\ell}$, as done in [2].

Acknowledgements. The authors gratefully acknowledge financial support from the European Community, through a Research Training Network Project (“Using Mathematical Modeling and Computer Simulation to Improve Cancer Treatment”) and the Italian Ministry of University and Scientific and Technological Research.

References

1. D. Ambrosi and F. Mollica, *Int. J. Eng. Sci.*, **40**, 1297–1316 (2002).
2. D. Ambrosi and L. Preziosi, *Math. Models Meth. Appl. Sciences*, **12**, 737–754 (2002).
3. H.M. Byrne, L. Preziosi, *IMA J. Math. Appl. Med. Biol.*, in press.
4. C.J.W. Beward, H.M. Byrne and C.E. Lewis, *J. Math. Biol.*, **45**, 125–152 (2002).
5. H.M. Byrne, J.R. King, D.L.S. McElwain and L. Preziosi, *Appl. Math. Lett.*, in press.
6. M.A.J. Chaplain and L. Preziosi, *Math. Models Meth. Appl. Sciences*, **13** (2003).
7. C.Y. Chen, H.M. Byrne and J.R. King, *J. Math. Biol.*, **43**, 191–220 (2001).
8. M.J. Dorie, R.F. Kallman, D.F. Rapacchietta, D. van Antwerp and Y.R. Huang, *Exp. Cell. Res.*, **141**, 201–209 (1982).
9. M.J. Dorie, R.F. Kallman and M.A. Coyne, *Exp. Cell. Res.* **166**, 370–378 (1986).
10. A. Farina and L. Preziosi, *Int. J. Nonlinear Mech.*, **37**, 485–491 (2001).
11. G. Helmlinger, P.A. Netti, H.C. Lichtenbeld, R.J. Melder and R.K. Jain, *Nature Biotech.*, **15**, 778–783 (1997).
12. J.D. Humphrey and K.R. Rajagopal, *Math. Models Meth. Appl. Sciences*, **12**, 407–430 (2002).
13. P.A. Netti, L.T. Baxter, Y. Boucher, R. Skalak & R.K. Jain, *AIChE J.*, **43**, 818–834 (1997).