J. Math. Biol. (2009) 58:625–656
DOI 10.1007/s00285-008-0218-7

Mathematical Biology

Multiphase modelling of tumour growth and extracellular matrix interaction: mathematical tools and applications

Luigi Preziosi · Andrea Tosin

Received: 20 June 2007 / Revised: 2 January 2008 / Published online: 14 October 2008

Abstract Resorting to a multiphase modelling framework, tumours are described here as a mixture of tumour and host cells within a porous structure constituted by a remodelling extracellular matrix (ECM), which is wet by a physiological extracellular fluid. The model presented in this article focuses mainly on the description of mechanical interactions of the growing tumour with the host tissue, their influence on tumour growth, and the attachment/detachment mechanisms between cells and ECM. Starting from some recent experimental evidences, we propose to describe the interaction forces involving the extracellular matrix via some concepts coming from viscoplasticity. We then apply the model to the description of the growth of tumour cords and the formation of fibrosis.

Mathematics Subject Classification (2000) 92C10 · 92C50

1 Introduction

As recently reviewed in [6], the first models dealing with avascular tumour growth worked under the hypothesis that the tumour is made by only one type of cells having a constant density [31]. In the last few years, it became evident that such a description

Electronic supplementary material The online version of this article (doi:10.1007/s00285-008-0218-7) contains supplementary material, which is available to authorized users.

L. Preziosi (✉) · A. Tosin
Department of Mathematics, Politecnico di Torino,
Corso Duca degli Abruzzi 24, 10129 Torino, Italy
e-mail: luigi.preziosi@polito.it

A. Tosin
e-mail: andrea.tosin@polito.it

was insufficient, and multiphase models started being developed [5,16–19,26–28] (see also the review articles [8], [30]). This description allows to consider density variation within the tumour and the host tissue, to evaluate the evolution of stresses, and to take into account mechanical interactions among the constituents, e.g., cells and extracellular matrix, and among tissues.

For instance, Chaplain et al. [21] developed a model accounting for contact inhibition of growth and showed how a misperception of the compression state of the local tissue, hence of the subsequent stress which is 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 tumour. In addition to bio-mechanical effects, the model also takes into account the effect of the stress-dependent production of extracellular matrix (ECM) and of matrix degrading enzymes (MDEs). Franks et al. [26,27] developed 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. [15,17] deduced a one-dimensional multiphase model to describe vascular tumour growth and tumour vessel interaction.

Still within the multiphase modelling framework, here we want to describe soft tissues as mainly made of ECM and cells. The former will be schematised as a network of fibrous material, the latter as an ensemble of sticky and highly deformable balloons living in it. More specifically, we will focus on a mixture of four constituents: tumour and host cells, within a porous structure constituted by the extracellular matrix, which is wet by a physiological extracellular fluid. We will take account of tumour growth, ECM remodelling 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. [20], and in Sun et al. [47]. The above papers, in fact, study in detail the attachment/detachment properties of the adhesion sites on the cell membrane. In [11] the described test consists in gluing a functionalised microsphere at the tip of an atomic force microscopy (AFM) cantilever. 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/s). 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 binding sites, it is common to experience multiple unbinding events occurring at different instants during a 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. It 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 neighbours to make room for its sister cells. The qualitative description above calls for a description of the interaction forces involving the extracellular matrix that includes viscoplastic phenomena.

We will first deduce a general multiphase model, and then simplify it considerably in view of the observation that the interactions with the liquid are much weaker than those involving cells and ECM. Specifically, the simplification consists in that the

equations describing the evolution of the interstitial pressure and of the liquid flow can be possibly solved after solving those related to the solid constituents, i.e., cells and ECM, that do not depend directly on the liquid and pressure evolution. We will then specialise the model to two cases study: In the former the tumour grows in a rigid non-remodelling ECM around one or more vessels from which the necessary nutrients diffuse out, in the latter growth is accompanied by ECM remodelling. One of the by-products of the second case is the possibility to describe the formation of fibrotic tissues, namely tissues stiffer than normal that can be felt with a self-test.

In more detail, the paper develops as follows. After this introduction, in Sect. 2 the general multiphase model is developed, focusing first on the constitutive modelling of the interaction forces and then on that of the stress tensor. A simplified model is deduced under the observation and hypothesis that interactions with the liquid are negligible, if compared, for instance, with cell–ECM interactions. The inclusion of the diffusion of nutrients and chemicals relevant for growth is also described. Section 3 details the two aforementioned applications, and Sect. 4 finally draws conclusions and sketches some research perspectives.

2 Multiphase modelling

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, this system is a rather complicated mixture of many different interacting components. However, aiming at focusing on the main ingredients of a mathematical model of tumour 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 *tumour cells* and *normal healthy cells* belonging to the host tissue. We denote by $\phi_t,\ \phi_h \in [0,\ 1]$ 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 modelling of the system. We briefly discuss this topic in Remark 2.4 at the end of the next section, 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 $\mathcal{C}\backslash\{\alpha\}, \mathcal{C}\backslash\{\alpha,\ \beta\}$, 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

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

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

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

Following a popular custom in mixture theory, we define the *composite velocity* $\mathbf{v}_c$ of the mixture as the weighted average of the velocities of the constituents:

$$\mathbf{v}_c = \sum_{\alpha\in\mathcal{C}} \phi_\alpha \mathbf{v}_\alpha. \tag{2.4}$$

In addition, we introduce the notation

$$\Gamma_c = \sum_{\alpha\in\mathcal{C}} \Gamma_\alpha, \tag{2.5}$$

so that Eq. 2.3 becomes

$$\nabla \cdot \mathbf{v}_c = \Gamma_c. \tag{2.6}$$

Equations 2.3 and 2.6 are differential versions of the algebraic saturation constraint 2.1. If it is possible to assume that the mixture is *closed*, as in the avascular case, or

for in vitro experiments, so that mass exchanges occur only among its constituents, then condition

$$\Gamma_c = 0 \tag{2.7}$$

applies, whence $\nabla \cdot \mathbf{v}_c = 0$. 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 $\mathbf{v}_\alpha$.

On the other hand, we remark that in many cases one cannot assume condition 2.7. This is, for instance, the case when external mass sources/sinks are introduced to describe inflow or outflow processes related to a homogenised vascular or lymphatic structure within the mixture (Breward et al. [15,17], Franks and King [28]). In this case, the solenoidality of the composite velocity is definitely lost, hence in the vascular case Eq. 2.6 must be adopted.

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

$$-\nabla \cdot (\phi_\alpha \mathbb{T}_\alpha) + \phi_\alpha \nabla p = \mathbf{m}_\alpha, \qquad (\alpha \in \mathcal{C}) \tag{2.8}$$

where

(i) $p \in \mathbb{R}$ 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;
(ii) $\mathbb{T}_\alpha \in \mathbb{R}^{d\times d}$ is the so-called *excess stress tensor* of the constituent α, accounting for the characteristic internal stress of the latter;
(iii) $\mathbf{m}_\alpha \in \mathbb{R}^d$ is the resultant of the forces acting on the constituent α due to the interactions with the other components of the mixture.

More specifically, 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 [49]. This procedure is justified by the fact that Brinkman-like effects have not been pointed out yet. Consequently, the corresponding momentum equation 2.8 for $\alpha = \ell$ simplifies as

$$\phi_\ell \nabla p = \mathbf{m}_\ell. \tag{2.9}$$

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 and 2.8 to range in a larger index set $\mathcal{C}$. Similarly, 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 fibres 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

$$-\nabla\cdot(\phi_m\mathbb{T}_m)+\phi_m\nabla p=\mathbf{m}_m. \tag{2.10}$$

Of course, all constituents 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. 2.8 can be specialised, 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 [45]), hence one can say that the $\mathbf{m}_\alpha$'s sum to zero. This is actually not surprising, for they act as internal forces among the constituents:

$$\sum_{\alpha\in\mathcal{C}}\mathbf{m}_\alpha=0. \tag{2.11}$$

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

$$\mathbf{m}_{\alpha\beta}=-\mathbf{m}_{\beta\alpha},\quad\forall\,\alpha,\ \beta\in\mathcal{C},\ \alpha\neq\beta. \tag{2.12}$$

Let us now fix $\alpha=\ell$ and focus first 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.,

$$\mathbf{m}_{\ell\beta}=\mathbb{M}_{\ell\beta}(\mathbf{v}_\beta-\mathbf{v}_\ell). \tag{2.13}$$

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.

From Eq. 2.13 we deduce

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

where we have denoted $\mathbb{M}_\ell := \sum_{\beta\in\mathcal{C}_\ell} \mathbb{M}_{\ell\beta}$ for the sake of brevity. Inserting Eq. 2.14 into Eq. 2.9 we get then the (generalised) *Darcy law*

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

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 $\mathbb{M}_\ell$, thus invertible. From Eq. 2.15 we obtain then

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

Considering moreover that $\phi_\ell = 1 - \sum_{\beta\in\mathcal{C}_\ell} \phi_\beta$ (cf. Eq. 2.1), we see that Eq. 2.16 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,

$$\nabla\cdot\left(\phi_\ell^2\mathbb{M}_\ell^{-1}\nabla p\right) = \nabla\cdot\left(\sum_{\beta\in\mathcal{C}_\ell}\left(\phi_\ell\mathbb{M}_\ell^{-1}\mathbb{M}_{\ell\beta} + \phi_\beta\mathbb{I}\right)\mathbf{v}_\beta\right) - \sum_{\beta\in\mathcal{C}}\Gamma_\beta, \tag{2.17}$$

where $\mathbb{I} \in \mathbb{R}^{d\times d}$ denotes the identity matrix. In case that condition 2.7 holds, the second term at the right-hand side of Eq. 2.17 drops and one simply obtains an equation for p, formally independent of any unknown quantity linked to the flow of the extracellular fluid.

Let us consider now the interaction forces $\mathbf{m}_{th} = -\mathbf{m}_{ht}$ among cell populations. We assume that cellular mechanical properties are at most only slightly influenced by the progression state. Hence, it might be reasonable to suppose that the response of a cell to the compression by other surrounding cells is independent of the specific pushing cell population. Experimental investigations on the validity of this hypothesis would be desirable. From the mechanical point of view, this corresponds to regarding tumour and host cells as a unique population with the same excess stress tensor, henceforth denoted by $\mathbb{T}_\phi$:

$$\mathbb{T}_\phi := \mathbb{T}_t = \mathbb{T}_h. \tag{2.18}$$

Tumour cells press host cells with a force proportional to $\nabla\cdot\left(\phi_t\mathbb{T}_\phi\right)$, and at the same time are pressed by the latter with a force proportional to $\nabla\cdot\left(\phi_h\mathbb{T}_\phi\right)$. 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

$$\phi := \phi_t + \phi_h, \tag{2.19}$$

the net interaction force $\mathbf{m}_{th}$ is consequently given by

$$\mathbf{m}_{th} = \frac{\phi_t}{\phi}\nabla\cdot\left(\phi_h\mathbb{T}_\phi\right) - \frac{\phi_h}{\phi}\nabla\cdot\left(\phi_t\mathbb{T}_\phi\right), \tag{2.20}$$

so that, owing to Eqs. 2.8 and 2.13, the momentum equations for the cell populations specialise as

$$-\frac{\phi_\alpha}{\phi}\nabla\cdot\left(\phi\mathbb{T}_\phi\right) + \phi_\alpha\nabla p = \mathbf{m}_{\alpha m} - \mathbb{M}_{\ell\alpha}(\mathbf{v}_\alpha - \mathbf{v}_\ell), \qquad (\alpha = t,\ h). \tag{2.21}$$

Summing Eq. 2.21 for $\alpha = t,\ h$ gives the force balance equation for the ensemble of cells, without distinguishing tumour 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 [23,24,43] that there is an optimal concentration of ECM favouring cell motility, which then decreases as the ECM content becomes both smaller and larger. This is due to the lack of substrate to move on and to the increased number of adhesive links, respectively. The observation that cells hardly move when there is too few or too much extracellular matrix can be rendered by saying that $\mathbf{m}_{\alpha m}$'s, $\alpha \in \mathcal{C}_{m,\ell}$, increase for both small and large ϕ_m.

As a first approximation, one can still mimic Eq. 2.13 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

$$\mathbf{m}_{\alpha m} = \mathbb{M}_{\alpha m}(\mathbf{v}_m - \mathbf{v}_\alpha), \tag{2.22}$$

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

A more accurate modelling 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. [20], and Sun et al. [47], 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 viscoplasticity, 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

$$\mathbb{M}_{\alpha m}(\mathbf{v}_m - \mathbf{v}_\alpha) = \begin{cases} 0 & \text{if } |\mathbf{m}_{\alpha m}| < \sigma_{\alpha m} \\ (|\mathbf{m}_{\alpha m}| - \sigma_{\alpha m}) \dfrac{\mathbf{m}_{\alpha m}}{|\mathbf{m}_{\alpha m}|} & \text{if } |\mathbf{m}_{\alpha m}| \geq \sigma_{\alpha m} \end{cases} \tag{2.23}$$

or, in a more compact form, by

$$\mathbb{M}_{\alpha m}(\mathbf{v}_m - \mathbf{v}_\alpha) = \left(1 - \frac{\sigma_{\alpha m}}{|\mathbf{m}_{\alpha m}|}\right)^+ \mathbf{m}_{\alpha m}, \tag{2.24}$$

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. 2.22), such a definition is univocal only for $|\mathbf{m}_{\alpha m}| \geq \sigma_{\alpha m}$, when Eq. 2.24 yields indeed

$$\mathbf{m}_{\alpha m} = \left(1 + \frac{\sigma_{\alpha m}}{|\mathbb{M}_{\alpha m}(\mathbf{v}_m - \mathbf{v}_\alpha)|}\right) \mathbb{M}_{\alpha m}(\mathbf{v}_m - \mathbf{v}_\alpha). \tag{2.25}$$

In particular, it can be observed that Eqs. 2.22 is recovered from 2.24 or Eq. 2.25 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.

Equations 2.16, 2.21, and 2.24 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. 2.8 over $\alpha \in \mathcal{C}$ while taking Eqs. 2.1 and 2.11 into account:

$$-\nabla \cdot \left(\phi \mathbb{T}_\phi + \phi_m \mathbb{T}_m\right) + \nabla p = 0. \tag{2.26}$$

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 remodelled and cells undergo proliferation and death processes during their evolution. There is then a conceptual difficulty in describing tumours 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 tumour and tissue growth in several papers (see e.g., [1–4,33,34,46]),

resorting to the idea of evolving natural configuration, and will not be investigated in detail here.

Of course, the basic question is to understand whether cells and ECM behave like solids, like (possibly viscoelastic) liquids, or like viscoplastic bodies. In this respect, some tests on the mechanical properties of ECM constituents such as elastin and collagen suggest that in the absence of remodelling the latter can be regarded as elastic compressible materials with different elastic features [12,29,32,41]. 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 viscoelastic effects are, if and when plastic deformation occurs, and so on.

Clearly, the above-mentioned problem of the reference configuration is circumvented if tumour cells are modelled 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 tumour growth. We simply remark here that actually the ensemble of cells is most likely not to behave like a liquid. However, even using the just stated constitutive model, the 'cellular liquid' lives within a solid structure given by the extracellular matrix, so that finally the whole mixture would behave like a viscoelastic solid.

The easiest constitutive equation for the cellular matter is

$$\mathbb{T}_\phi = -\Sigma(\phi)\mathbb{I}, \tag{2.27}$$

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. Equation 2.27 refers essentially to an elastic fluid. As a possible extension, one might want to consider a viscous contribution of the form

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

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 viscoelastic constitutive relations since, despite their importance in accounting for mechanical properties of tissues, viscoelastic behaviours 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. [25]). For this reason, viscoelastic effects fade away by the time a cell duplicates.

As a further hint toward intercellular stress modelling, we simply mention that in principle the same argument used in Sect. 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 from doing that here, and refer instead to [4] for additional details on more complex constitutive relations.

2.4 Reduced equations

In the momentum equations 2.8 it is often useful to distinguish the contributions of the terms related to the pressure gradient and to the interaction with the extracellular fluid. In most cases one can assume that the magnitudes of the interaction forces involving the liquid $\mathbf{m}_{\alpha\ell}$ and ∇p for $\alpha \in \mathcal{C}_\ell$ are negligible with respect to those related to the interaction among cells and between cells and ECM, i.e., $\mathbf{m}_{\alpha\beta}$ for $\alpha \in \mathcal{C}_\ell$, $\beta \in \mathcal{C}_{\alpha,\ell}$:

$$\phi_\alpha |\nabla p|,\ |\mathbf{m}_{\alpha\ell}| = o\left(|\nabla \cdot (\phi_\alpha \mathbb{T}_\alpha)|,\ |\mathbf{m}_{\alpha\beta}|\right), \qquad (\alpha \in \mathcal{C}_\ell,\ \beta \in \mathcal{C}_{\alpha,\ell}), \tag{2.28}$$

so that the main momentum balance reduces to

$$-\nabla \cdot (\phi_\alpha \mathbb{T}_\alpha) = \sum_{\beta \in \mathcal{C}_{\alpha,\ell}} \mathbf{m}_{\alpha\beta}, \qquad (\alpha \in \mathcal{C}_\ell). \tag{2.29}$$

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

First of all, it should be noticed that now Eqs. 2.16 and 2.17 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 2.7. 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 and 2.29 for $\alpha \in \mathcal{C}_\ell$. Regarding the latter, we specifically observe that Eqs. 2.21 become

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

while summing Eq. 2.29 over $\alpha \in \mathcal{C}_\ell$ and recalling 2.12 yields

$$\nabla \cdot \left(\phi \mathbb{T}_\phi + \phi_m \mathbb{T}_m\right) = 0, \tag{2.31}$$

which represents the reduced counterpart of the momentum balance equation 2.26 for the whole mixture.

Second, in this reduced framework Eqs. 2.22 and 2.24 can be effectively used to obtain explicit expressions for the velocities $\mathbf{v}_t$, $\mathbf{v}_h$ in terms of the velocity $\mathbf{v}_m$ and of the internal stress of the cellular matter. Thanks to Eq. 2.30, if we define $\mathbb{K}_{\alpha m} := \mathbb{M}_{\alpha m}^{-1}$ we have indeed

$$\mathbf{v}_\alpha - \mathbf{v}_m = \frac{\phi_\alpha}{\phi} \mathbb{K}_{\alpha m} \nabla \cdot \left(\phi \mathbb{T}_\phi\right), \qquad (\alpha = t,\ h) \tag{2.32}$$

in case of viscous friction between cells and ECM (cf. Eq. 2.22), or

$$\mathbf{v}_\alpha - \mathbf{v}_m = \left(\frac{\phi_\alpha}{\phi} - \frac{\sigma_{\alpha m}}{|\nabla \cdot \left(\phi \mathbb{T}_\phi\right)|}\right)^+ \mathbb{K}_{\alpha m} \nabla \cdot \left(\phi \mathbb{T}_\phi\right), \qquad (\alpha = t,\ h) \tag{2.33}$$

if a more sophisticated viscoplastic interaction is accounted for. Again, we notice that Eq. 2.32 is a special case of Eq. 2.33 with $\sigma_{\alpha m} = 0$.

2.5 Advection and diffusion of chemicals

A crucial role in tumour 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 generalisation 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

$$\frac{\partial}{\partial t}(\phi_\alpha c_\alpha) + \nabla \cdot (\phi_\alpha c_\alpha \mathbf{v}_\alpha) = \nabla \cdot (\mathbb{D}_\alpha \nabla c_\alpha) + \gamma_\alpha - \delta_\alpha c_\alpha, \qquad (\alpha \in \mathcal{C}) \quad (2.34)$$

where

(i) $\mathbb{D}_\alpha = \mathbb{D}_\alpha(\phi_\alpha)$ 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;

(ii) $\gamma_\alpha > 0$ 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 signalling (Lanza et al. [38]);

(iii) $\delta_\alpha > 0$ is the degradation/uptake rate, linked either to the solubility of the chemical in the constituent α or to its absorption by the latter. Notice that δ_α might in turn depend on the volume ratio ϕ_α, especially when it represents an absorption rate. Conversely, when it plays the role of a degradation rate, it is usually assimilated to a constant related to the characteristic degradation time of the chemical at hand.

Under the assumption that the concentrations c_α are the same in all constituents, i.e., $c_\alpha \equiv c$, we can sum Eqs. 2.34 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 2.4 we find

$$\frac{\partial c}{\partial t} + \nabla \cdot (c\mathbf{v}_c) = \nabla \cdot (\mathbb{D}\nabla c) + \gamma - \delta c, \tag{2.35}$$

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 divergence-free, hence in such a case the advection term at the left-hand side of Eq. 2.35 gives rise to pure transport $\nabla \cdot (c\mathbf{v}_c) = \mathbf{v}_c \cdot \nabla c$.

We remark that in most cases the assumption above is only a first order approximation. Indeed, taking the concentration of chemicals independent of the constituents of the mixture in which they are microscopically diffusing may not be satisfactory, particularly for chemicals with high molecular weight, such as drugs, or showing different affinities with the various components of the mixture.

Equation 2.35 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:

$$\frac{\partial c}{\partial t} = D\Delta c + \gamma - \delta c, \tag{2.36}$$

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

3 Tumour growth in a rigid ECM

Probably the most simplifying hypothesis to generate specific models of tumour 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 stand 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 components

of the mixture turn out to be then

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

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

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

for $\alpha = t,\ h$. Notice in particular that, owing to Eqs. 2.33 (or Eq. 2.32 in the special case $\sigma_{\alpha m} = 0$) and 3.1, the cell momentum equation 3.3 along with the constitutive relation 2.27 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:

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

which in case of viscous friction between cells and ECM (formally $\sigma_{\alpha m} = 0$) specialise 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 if the two cell populations occupy different regions of space and are not mixed, then Eqs. 3.5 and 3.6 can be further simplified because in each region only one population is found, hence $\phi = \phi_\alpha$. Specifically, consider the situation in which a spatial region $Q \subset \mathbb{R}^d$ can be initially divided into two subregions $\Omega_t(0)$ and $\Omega_h(0)$, such that $\Omega_t(0) \cup \Omega_h(0) = Q$, occupied by tumour and by healthy host cells, respectively. Then $\phi_t = 0$ in $\Omega_h(0)$ and $\phi_h = 0$ in $\Omega_t(0)$. As we will see, the model is such that the tumour 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 tumour mass within the surrounding tissue. By pushing normal cells away to gain space for growing, tumour 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. We refer the reader to Appendix A for a short discussion of the method used in addressing the simulation of such a system.

One then has

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

where

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

The velocity of the cells on the two sides of the interface $S(t)$ must be the same, i.e.,

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

where $\mathbf{n}$ is the normal to the interface and $[\![\cdot]\!]$ denotes the jump across it. The interface $S(t)$, which is a material surface for the cellular matter, moves then with their common velocity:

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

where, for instance,

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

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

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

Recalling Eq. 2.27, 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 $S(t)$. Finally, continuity of the concentration c is imposed:

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

3.1 Tumour cords

As a first application we consider the case of a capillary surrounded by a tissue within which an aggregate of tumour 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 tumour tends to develop along the blood vessel, giving rise to a structure called *tumour cord* due to its particular spatial geometry.

In the specialised literature, the papers by Bertuzzi et al. [13,14] have originated a relevant thread of mathematical models of tumour 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 tumour 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 analysed from the qualitative point of view in [48].

The whole system is regarded as a saturated mixture of cells, extracellular fluid and extracellular matrix, the latter being a rigid non-remodelling 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 tumour 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 $\Omega_h(t)$.

As a sample case, we assume, like in [21], that tumour cells and normal cells only differ in the mechanism that regulates their proliferation and death. This is a good approximation in the initial stages of tumour growth, when contact inhibition is more important than differences in motility like those considered in [22]. From the modelling point of view, the consequence is that in Eq. 3.8 we take $\sigma_{tm} = \sigma_{hm} =: \sigma_m$, $\mathbb{K}_{tm} = \mathbb{K}_{hm} =: K_m\mathbb{I}$ for a positive parameter K_m, though at later stages these parameters may be different for different clones, and phenomena like mesenchymal transition, differential motility, and formation of metastasis come into play.

Regarding the source/sink terms Γ_α, we consider that in $\Omega_t(t)$ tumour cells are mainly concerned with proliferation or death on the basis of the local availability of oxygen. In addition, following [21], we want to include also phenomena like contact inhibition of growth, as well as the development of hyperplasia as a consequence of the loss of tissue compression responsiveness by the cells. In more detail, Chaplain et al. [21] focus on a characterization of normal and abnormal cells based on the ability of the cells themselves to sense the stress exerted 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 neighbourhood. In case of excess of stress, normal cells enter a quiescent survival state, whence they possibly reactivate 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 characterising 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 tumours. 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:

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

$\gamma_t > 0$ is the growth rate of tumour cells, and $c_0 > 0$ represents the critical threshold in the nutrient concentration below which cells starve and die and above which they instead duplicate if they feel to be not too compressed, i.e., if $\Sigma(\phi_t) < \Sigma_t^*$. The last two terms in parenthesis in Eq. 3.16 are related to apoptosis. Specifically, the first one reflects the fact that high compression levels, like those produced by growing tumour cells, may induce apoptosis (see e.g., Ambrosi and Mollica [2,3]). Hence, $\bar{\Sigma}_t > 0$ represents the maximum stress that tumour cells can sustain without undergoing apoptosis, and $\delta_t > 0$ is the stress-induced apoptotic rate. Finally, δ_t' is the physiological apoptotic rate.

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

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

A similar equation can be set in $\Omega_h(t)$ 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 $\alpha = t,\, h$.

Finally, we join to Eq. 3.8 the diffusion of the nutrient in the tissue

$$\frac{\partial c}{\partial t} = D\Delta c - (\beta_t \phi_t + \beta_h \phi_h)c \tag{3.19}$$

where $\beta_t,\, \beta_h > 0$ are phenomenological parameters related to the nutrient uptake rate by tumour and host cells. Notice that Eq. 3.19 is a particular case of Eq. 2.36 with $\gamma = 0$ (i.e., no production of oxygen by the cells) and $\delta = \beta_t \phi_t + \delta_h \phi_h$ (i.e., $\delta = \delta_t + \delta_h$ with $\delta_\alpha = \beta_\alpha \phi_\alpha$, $\alpha = t,\, h$).

In addition to the interface conditions 3.10, 3.13, 3.14, 3.15, and to the evolution equation for the moving interface 3.11, the model 3.6 has 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 cells. In view of Eq. 3.5 this amounts to

$$-\mathcal{I}(\phi;\ \sigma_m)K_m\nabla(\phi\Sigma(\phi))\cdot\mathbf{n}=0. \tag{3.20}$$

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.

(ii) The part of the outer boundaries 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 tumour 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 tumour mass, initially located at the intersection between two capillaries coinciding with the bottom and the left edge of the domain Q (Fig. 1a), grows along them. In the first stages, the host tissue is well nourished by the capillaries (Fig. 1b) but when the tumour cord starts growing an hypoxic region forms. In particular, cells closer to the capillaries have enough nutrient and proliferate, while those farther away starve because of the lack of oxygen due to the eagerness of tumour cells (Fig. 1d). The balance between these tendencies results in that away from the propagating fronts the thickness of the cord is nearly constant and steady, whereas its heads move forward as they are mostly made of proliferating cells. Notice that the largest densities of cells are, in fact, at the heads and at the capillary junction (Fig. 1c). In principle, a similar situation could be reproduced in vitro by allowing nutrients to diffuse only through part of the boundary of, say, a Petri dish, or by growing cells around cylindrical porous membranes mimicking the capillaries, immersed in a three-dimensional gel.

Figures 2 and 3 look at the formation of tumour cords around three capillary sections. In particular, Fig. 2 describes the evolution of the cell volume ratio and Fig. 3 that of the oxygen concentration. The tumour starts growing from the capillary on the right, keeping initially an almost circular shape (Fig. 2a). It can be noticed that, during growth, host cells on the left of the domain are still well nourished, as they do not consume much oxygen, while those on the top-right corner are in hypoxia (Fig. 3a). Before reaching the limit radius, characterised by balance between proliferation and death of cells, the tumour boundary approaches another capillary, and some cells begin to grow toward it (Fig. 2b, c). Upon reaching it (Fig. 2d), the tumour coopts the other

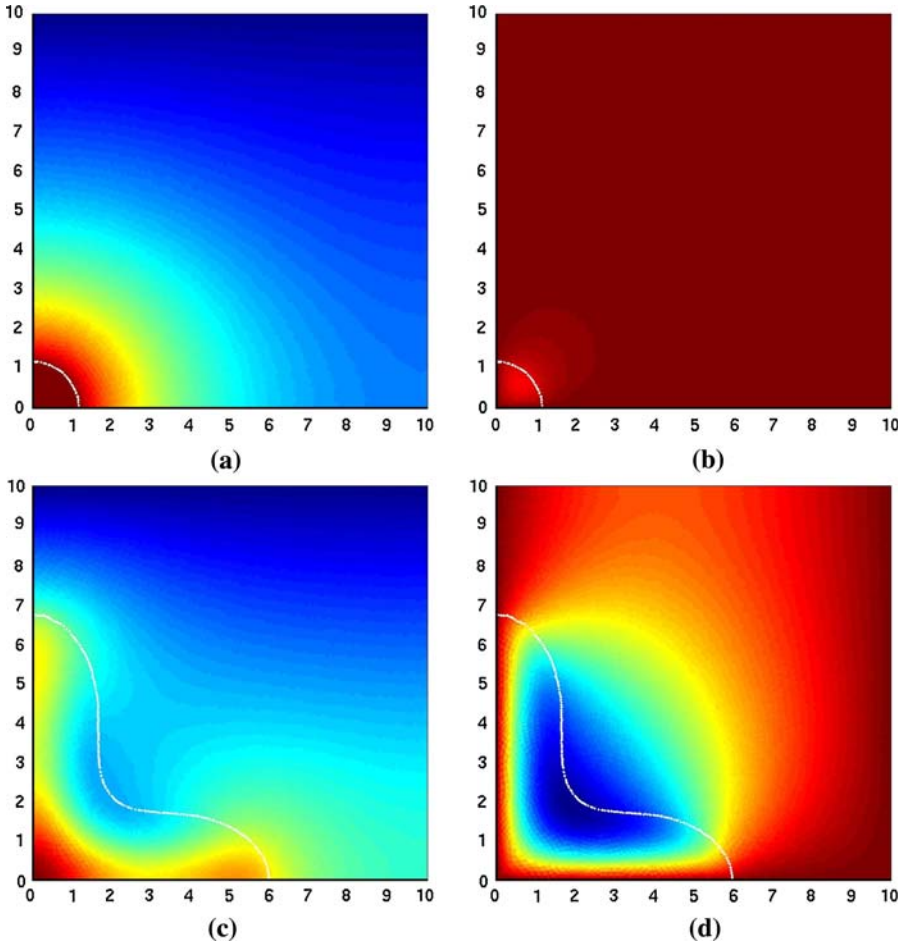

Fig. 1 Evolution of the cell volume ratio (*left*) and of the nutrient concentration (*right*) along two capillaries coinciding with the horizontal and vertical axes $y = 0$ and $x = 0$, respectively (thicker edges of the domain). The *white line* defines the interface $S(t)$. Values range in the interval $[0.75,\ 0.77]$ for the cell volume ratio, and in the interval $[0.66,\ 1]$ for the nutrient concentration

vessel, forming a tumour cord whose profile reminds the number 8 (Fig. 2e). The same does not happen for the lower vessel, because it is too far.

Figures 4 and 5 repeat the same simulation for closer vessels. In this case, also the third vessel is coopted (Fig. 4d), and the tumour is eventually all vascularised.

More details on the simulations can be obtained looking at the Supplemental material.

3.2 ECM remodelling and fibrosis

As a second example, following [21] and [30], we want to describe by the general modelling framework derived in the previous sections the formation of a fibrotic

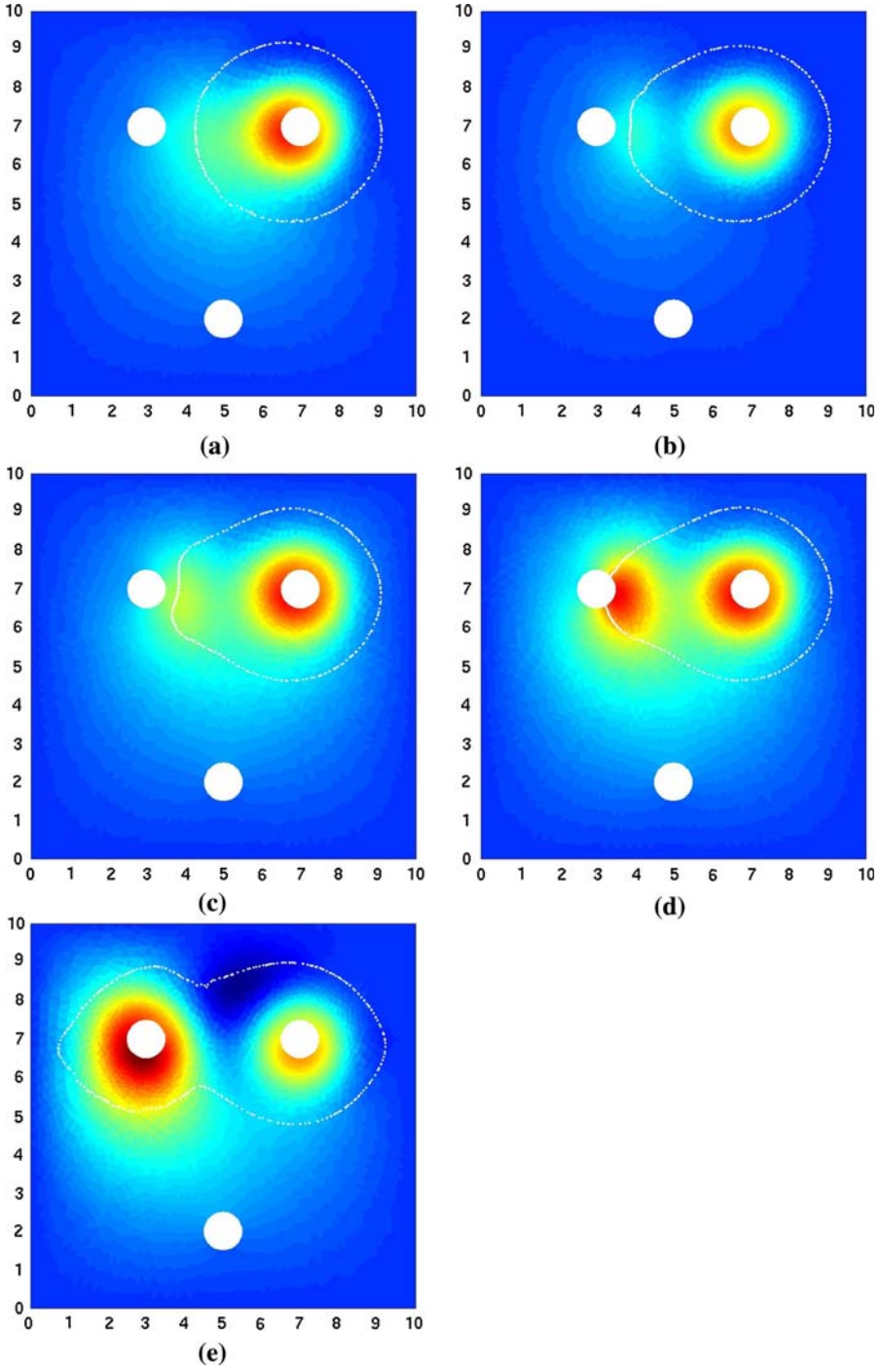

Fig. 2 Evolution of the cell volume ratio around three blood vessels at successive time instants. The *white line* defines the interface $S(t)$. Values range in the interval $[0.75,\ 0.77]$

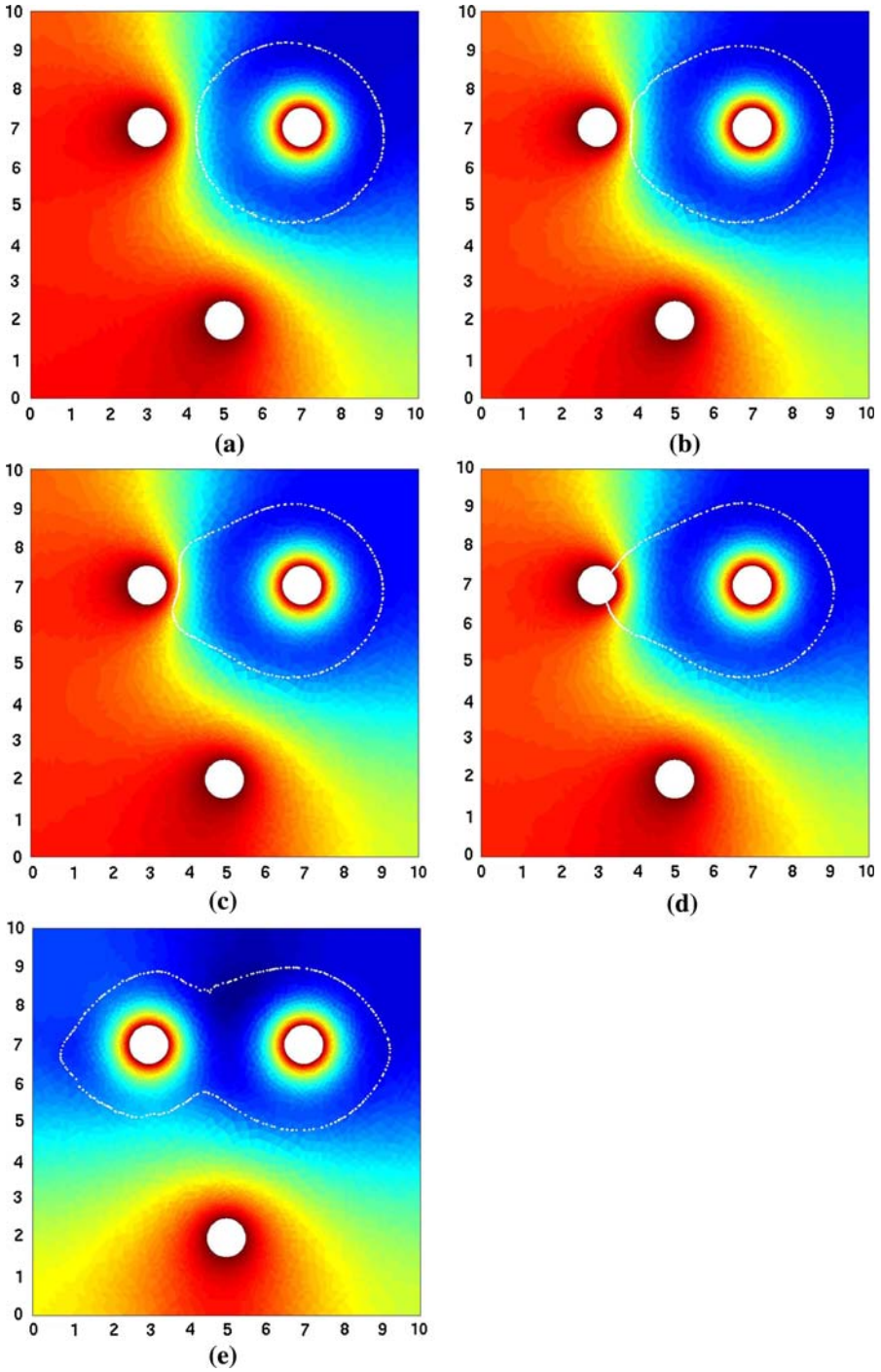

Fig. 3 Evolution of the nutrient concentration around three blood vessels at successive time instants. The *white line* defines the interface $S(t)$. Values range in the interval [0.53, 1]

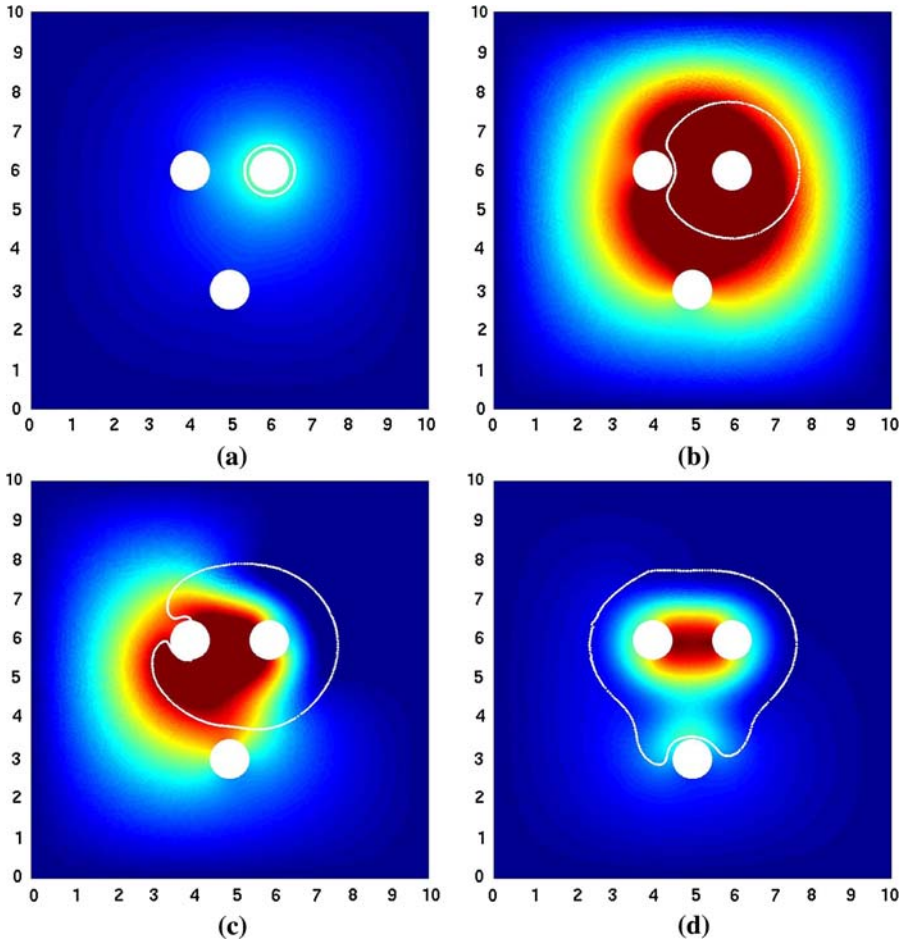

Fig. 4 Evolution of the cell volume ratio around three blood vessels at successive time instants. Vessels are now closer than in Fig. 2. The *white line* defines the interface $S(t)$. Values range in the interval [0.75, 0.77]

tumour [36,37,39,40,42]. In order to do that, we need to account for continuous production of matrix degrading enzymes (MDEs) and remodelling of (rigid) extracellular matrix by both normal and tumour cells. Since the amount of ECM present in the tissue plays a leading role in determining the overall stress on the cells, 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 cells and ECM:

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

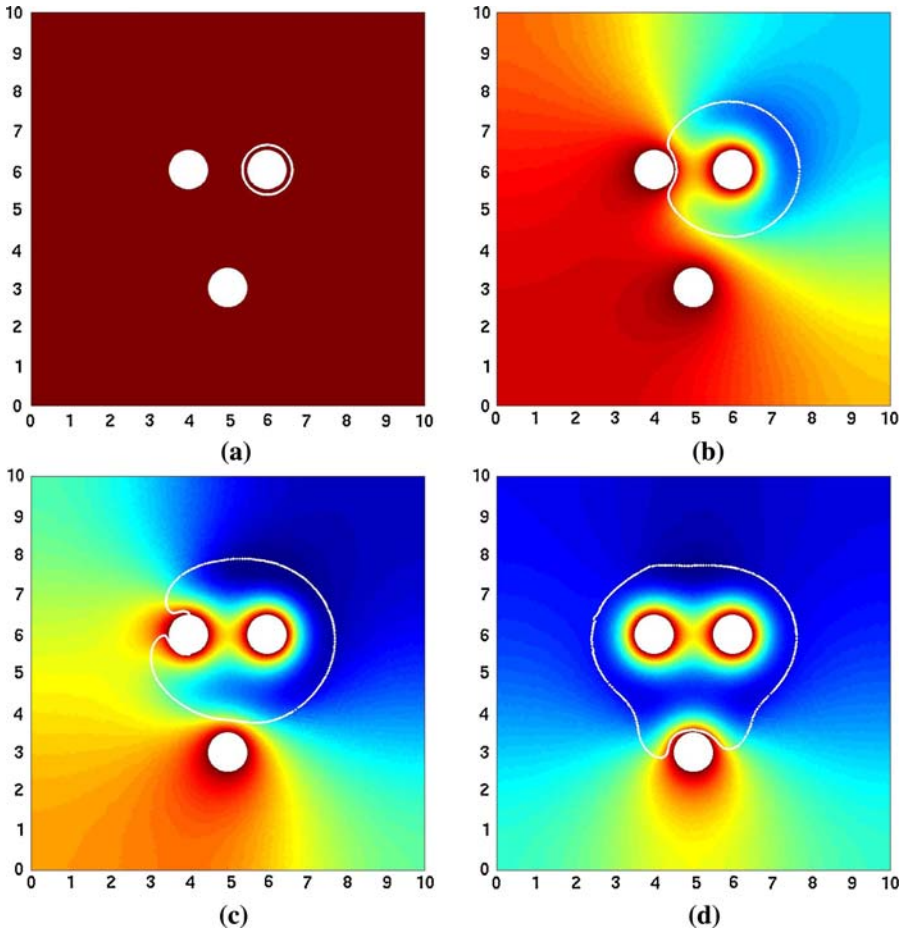

Fig. 5 Evolution of the nutrient concentration around three blood vessels at successive time instants. Vessels are now closer than in Fig. 3. The *white line* defines the interface $S(t)$. Values range in the interval $[0.71,\ 1]$

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 [21] 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 stand 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 increases indefinitely 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 generalisation of Eq. 2.27 (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 ratios) 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, which take natural death and stress-dependent duplication of cells into account:

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

In Eq. 3.25, 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 switch 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 $\Sigma \le \Sigma_\alpha$ and progressively inhibited for $\Sigma > \Sigma_\alpha$. Different sensitivity of tumour and host cells to mechanical cues, and in particular misperception of compression by the former, is translated in the present context as $\psi_t \ge \psi_h$. Finally, we assume the same reproduction and death rates $\gamma_\alpha,\ \delta_\alpha > 0$ for both cell populations, meaning that only stress perception is different between them.

Concerning the extracellular matrix, we assume that it is globally remodelled by cells and degraded by MDEs, whose concentration is denoted by e, so that in 3.4 we specialise the right-hand side as

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

where $\mu_\alpha, \alpha = t,\ h$, is the possibly stress-dependent ECM production rate by the cell population α, and $\nu > 0$ the specific degradation rate by MDEs.

As usual, matrix degrading enzymes are not included among the components 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 with characteristic time $\tau > 0$, while production is operated by cells at possibly stress-dependent rates π_h, π_t.

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

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

No sort of nutrients are included in the dynamics of the system, since the focus is on the role of compression and stress on tumour 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 tumour originating from one of the two bones, ulna and radius, in the lower arm. As nutrients are not considered in this model and cells are assumed to be always abundantly nourished, no nutrient-limited dimension is observed. The tumour will then grow indefinitely. Looking closely at the line defining the interface between tumour and host tissue, one can notice the compression of the host tissue, while away from the interface the cell volume ratio is nearly constant (Fig. 6d).

Figure 7 focuses on the distribution of ECM, initially assumed homogeneous over the domain. The formation of extracellular matrix in excess to the physiological value closely follows the formation of the tumour. The amount of ECM increases in this numerical experiment from 20 to 30%. In the model, the ECM is supposed to be rigid. If this assumption is released, such an increase of ECM would cause an increase of almost one order of magnitude in tissue rigidity [30].

More simulations are given in the Supplemental material.

4 Possible theoretical and experimental developments

The mathematical model of a solid tumour illustrated in the present paper develops on the basis of three main observations. First, tumour cells duplicate in a tissue characterised by the presence of other host cells, a deformable extracellular matrix, and extracellular liquid. Second, during the evolution cells duplicate, reorganise and deform. Third, tumour cells are bound to the extracellular matrix through adhesion molecules, mainly integrins, that have a limited strength, which has been recently the aim of some experimental investigations. On the basis of these experimental evidences, it is proposed that there exists a threshold condition below which the ensemble of cells

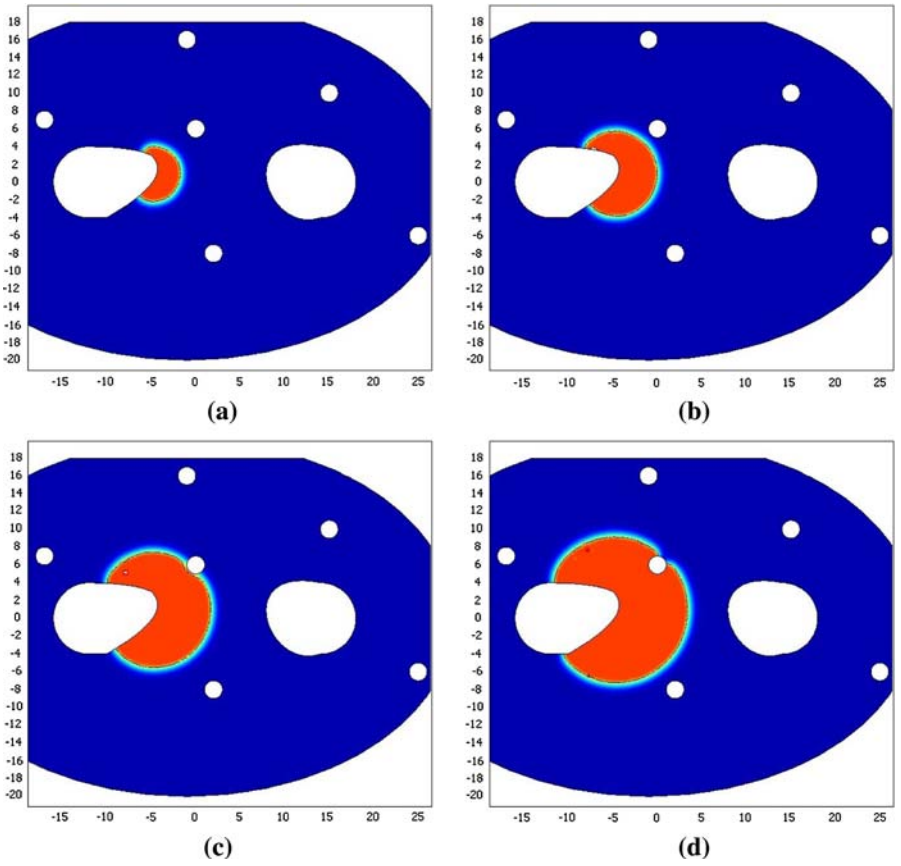

Fig. 6 Evolution of the cell volume ratio at successive time instants in the cross section of a lower arm. The *small circles* represent blood vessels, whereas the *bigger holes* in the domain correspond to the two bones in the arm, the ulna and the radius. Values range in the interval [0.5, 0.63]

stick to the extracellular matrix and move with it, and above which it partially detaches and features 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 generalised to even more complex configurations. As an example, one may detail the cell populations (endothelial cells, epithelial cells, fibroblasts, macrophages, lymphocytes), or distinguish different tumour clones characterised by relevant differences in their behaviour (for instance, to stay with the focus of this article, differences in cell–ECM adhesiveness), or 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 the generalisations above may give rise to interesting applications and deserve further studies. For instance, different cell adhesiveness will certainly influence the motion of cells, inducing differential motility and affecting the diffusion of tumour metastases. A similar problem is addressed in [22].

From the mechanical point of view, it would be interesting to extend the model presented here by including cell-to-cell adhesion mechanisms. In fact, using concepts

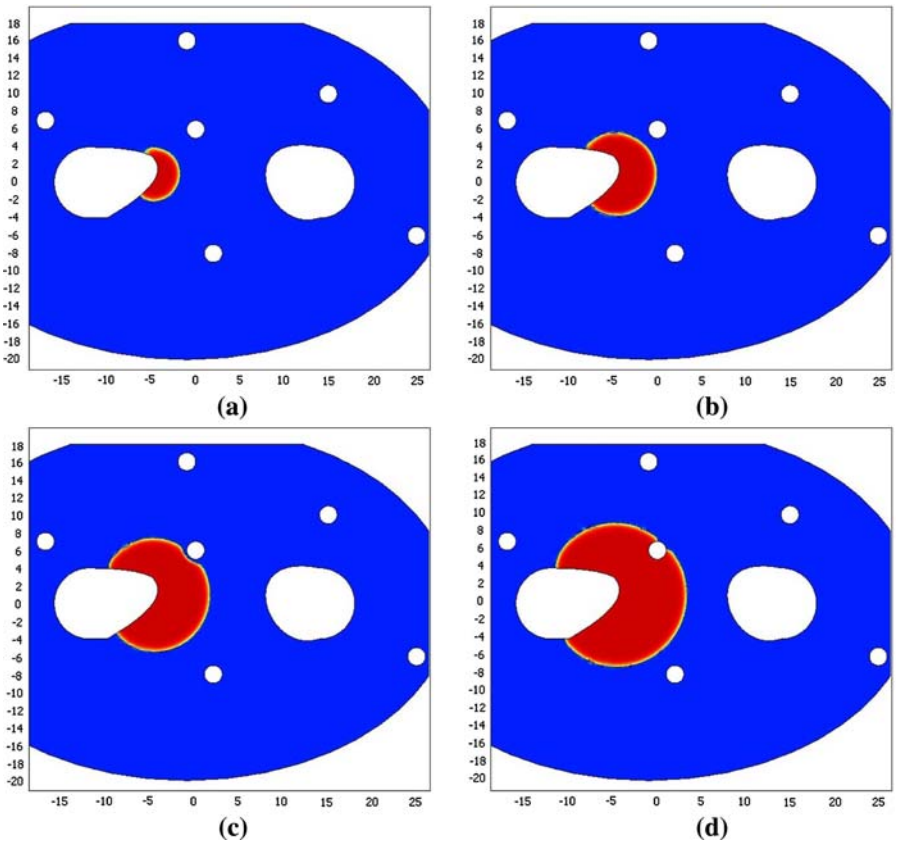

Fig. 7 Evolution of the ECM volume ratio at successive time instants in the cross section of a lower arm. The small circles represent blood vessels, whereas the bigger holes in the domain correspond to the two bones in the arm, the ulna and the radius. Values range in the interval [0.18, 0.31]

similar to that proposed here to describe cell–ECM adhesion, one can infer that if an ensemble of cells is subject to moderate stresses, then cells stay attached, may deform and recover all the deformation elastically (or viscoelastically). On the other hand, in case of sufficiently high tension or shear, some bonds 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 modelling of solid tumours, as well as of the concepts of evolving natural configurations [4].

The main novelty presented in this paper consists in the introduction of a simple way to model the fact that cells are attached to the extracellular matrix and that this adhesion force has a limited strength. Of course, some effort need to be done from the experimental point of view in order to measure and quantify the role of adhesion.

Some information can already be obtained from the works done by Baumgartner et al. [11], Canetta et al. [20], and Sun et al. [47]. Unfortunately, the difficulty in using these data consists in upscaling microscopic measurements to macroscopic scale, i.e., in transferring information obtained on single bonds to mechanical properties like

yield stress or elastic moduli. In addition, the experimental setups used in the above-mentioned papers can be classified as uniaxial tests. On the other hand, it would be desirable to have some data on the response to shear, possibly on ensembles of cells or on cells in ECM. In this respect, very recently Iordan et al. [35] tested the response of cell suspensions to shear using a classical plate-and-plate rheometer. Using Chinese hamster ovary cells, they proved the existence of a yield stress for volume ratios higher than $\phi = 0.4$. This is consistent with the concept proposed in this paper. Still more experiments in this direction are needed, also interfering with the adhesion molecules, for instance, modifying the anchorage mechanism, or using antibodies of the extracellular domain of the adhesion molecules. These experiments would be very important to understand the mechanics underlying the diffusion of metastases.

We have applied the model, which at a first glance may appear rather complex, to some test cases, showing its applicability also to non trivial two-dimensional geometries. In the first set of simulations, cells were virtually grown around capillaries which just act as sources of nutrients. It would be interesting to devise experiments in which nutrients can diffuse in the apparatus only from part of the domain, e.g., from one of its edges, or from two adjacent edges as in Fig. 1, or even from some sources placed inside the in vitro apparatus, in order to mimic situations like those presented in Figs. 2, 3, 4 and 5. For instance, one may put semi-permeable membranes, connected to proper reservoirs, in a collagen gel. Alternatively, one can use calcium alginate beads, that are widely employed for the slow release of water soluble chemicals and that can therefore be used as sources of nutrients.

In this respect, the model can be used to simulate many practical situations in which tissue and cell–ECM interactions play a relevant role. For instance, interesting situations to be addressed are, among others, vessel collapse due to tumour growth, capsule formation and degradation, tissue invasion related to changes in the adhesion mechanisms, cell compartmentalisation due to strong inhomogeneities in the ECM distribution or to the presence of porous membranes. Actually, this last phenomenon cannot be described by simple fluid-like models. In fact, if the cellular constituent is treated as a viscous fluid living in a porous ECM scaffold, sooner or later it will flow through it. On the contrary, taking adhesion and yield-like behaviours into account would allow to keep the ensemble of cells on one side of the membrane, or to describe the displacement of the membrane due to the growth of the cell mass within it, and eventually its rupture due to both mechanical pressure and chemical degradation.

Acknowledgements Partially supported by the European Community, through the Marie Curie Research Training Network Project HPRN-CT-2004-503661: Modelling, Mathematical Methods and Computer Simulation of tumour Growth and Therapy and by the Italian Ministry for University and Research, through a PRIN project on Modelli matematici di crescita e vascolarizzazione di tumori e tessuti biologici.

Appendix A: The level set method

In this appendix, we concisely report about a mathematical technique that can be profitably used to address numerically the equations of a multiphase model of tumour growth. In particular, we concentrate on the case in which two cell populations are

present, that remain segregated and interact through a material boundary $S(t)$, like in the applications discussed in this paper.

To be specific, let us consider the equation

$$\frac{\partial \phi_\alpha}{\partial t} + \nabla \cdot (\phi_\alpha \mathbf{v}_\alpha) = \Gamma_\alpha \quad \text{in } \Omega_\alpha(t) \qquad (\alpha = t,\ h), \tag{4.1}$$

where the velocity $\mathbf{v}_\alpha$ may be given, for instance, by Eq. 3.5. The subdomains $\Omega_t(t)$, $\Omega_h(t)$ evolve in time according to the mutual dynamics of tumour and host cells, however the model is conceived so that they never overlap, sharing only the boundary $S(t)$ which separates the tumour mass from the healthy host tissue (see e.g., Figs. 1, 2, 3, 4, and 5). As a consequence, it is unnecessary to explicitly distinguish between ϕ_t and ϕ_h: A single variable ϕ for the cell volume ratio is in principle sufficient to track the evolution in time and space of both cell populations, provided one is able to locate at each time the position of the interface $S(t)$. Analogously, the source/sink terms Γ_t, Γ_h can be merged into a unique term Γ defined as follows:

$$\Gamma = \Gamma_t \chi_{\Omega_t} + \Gamma_h \chi_{\Omega_h},$$

where χ_{Ω_t}, χ_{Ω_h} denote the indicator functions of the sets Ω_t, Ω_h, respectively:

$$\chi_{\Omega_\alpha(t)}(t,\ \mathbf{x}) = \begin{cases} 1 & \text{if } \mathbf{x} \in \Omega_\alpha(t) \text{ at time } t \\ 0 & \text{otherwise,} \end{cases} \qquad (\alpha = t,\ h).$$

The segregation of tumours and host cells has its mathematical counterpart in that locating the domain of the former allows to uniquely identify the domain of the latter.

In view of the discussion above, Eq. 4.1 rewrites formally as

$$\frac{\partial \phi}{\partial t} + \nabla \cdot (\phi \mathbf{v}) = \Gamma \quad \text{in } Q, \tag{4.2}$$

where $Q = \Omega_t \cup \Omega_h$ is a fixed in time domain and $\mathbf{v}$ is the velocity field of the cells in Q, described in a unified manner like the cell volume ratio ϕ. Notice that this is possible because, in view of Eq. 3.5, the velocity of each cell population is determined directly by the corresponding cell volume ratio.

Solving Eq. 4.2 requires to track simultaneously the evolution of the free boundary $S(t)$, which implicitly underlies the correct definition of the source/sink term Γ and has to be regarded to all purposes as a further unknown of the problem. In particular, it plays the role of a material surface for the cellular matter, meaning that it moves with the velocity $\mathbf{v}$ of the cells, which, owing to Eq. 3.10, must be the same on both sides of $S(t)$.

A suitable technique, which can be easily converted in a numerical method, to determine the motion of the interface $S(t)$ in connection with the overall dynamics of the system is the *Level Set Method*. The basic idea is to introduce a function

$$f = f(t,\ \mathbf{x}) : [0,\ +\infty) \times Q \to \mathbb{R},$$

called *level set function*, such that at time $t = 0$ its zero level set coincides with the initial configuration $S(0)$ of the free boundary (prescribed indeed as an initial condition of the problem):

$$S(0) = \{\mathbf{x} \in Q \,:\, f(0,\, \mathbf{x}) = 0\}.$$

In addition, $f(0,\, \mathbf{x})$ is required to change sign only once in Q, so that for instance $f(0,\, \mathbf{x}) < 0$ for $\mathbf{x} \in \Omega_t(0)$ and $f(0,\, \mathbf{x}) > 0$ for $\mathbf{x} \in \Omega_h(0)$ or vice versa. Finally, the evolution in time and space of f is described as a pure advection at the velocity $\mathbf{v}$ of the cells, hence the level set function satisfies the equation

$$\frac{\partial f}{\partial t} + \mathbf{v} \cdot \nabla f = 0. \tag{4.3}$$

At each time instant $t > 0$, the position of the interface $S(t)$ is determined by the zero level set of f:

$$S(t) = \{\mathbf{x} \in Q \,:\, f(t,\, \mathbf{x}) = 0\}.$$

Moreover, the tumour and host tissue domains are recovered respectively as

$$\Omega_t(t) = \{\mathbf{x} \in Q \,:\, f(t,\, \mathbf{x}) > 0\}, \qquad \Omega_h(t) = \{\mathbf{x} \in Q \,:\, f(t,\, \mathbf{x}) < 0\} \tag{4.4}$$

or vice versa, according to the initial form given to the level set function.

From Eq. 4.3 it is immediately seen that condition 3.11 governing the motion of $S(t)$ is satisfied. Furthermore, in view of Eq. 4.4, the level set function can be used to define the indicator functions of $\Omega_t(t)$ and $\Omega_h(t)$:

$$\chi_{\Omega_t(t)}(t,\, \mathbf{x}) = H(f(t,\, \mathbf{x})), \qquad \chi_{\Omega_h(t)}(t,\, \mathbf{x}) = H(-f(t,\, \mathbf{x})), \tag{4.5}$$

where $H(\cdot)$ is the Heaviside function:

$$H(s) = \begin{cases} 1 & \text{if } s > 0 \\ 0 & \text{if } s < 0. \end{cases}$$

By coupling Eqs. 4.2 and 4.3, along with Eq. 4.5, one gets the system

$$\begin{cases} \dfrac{\partial \phi}{\partial t} + \nabla \cdot (\phi \mathbf{v}) = \Gamma_t H(f) + \Gamma_h H(-f), \\ \dfrac{\partial f}{\partial t} + \mathbf{v} \cdot \nabla f = 0, \end{cases}$$

which can be regarded as a standard system of partial differential equations and solved by means of the most suitable numerical methods for hyperbolic and (possibly nonlinear) parabolic equations.

References

1. Ambrosi D, Guana F (2007) Stress modulated growth. Math Mech Solids 12(3):319–342
2. Ambrosi D, Mollica F (2002) On the mechanics of a growing tumor. Int J Eng Sci 40(12):1297–1316
3. Ambrosi D, Mollica F (2004) The role of stress in the growth of a multicell spheroid. J Math Biol 48(5):477–499
4. Ambrosi D, Preziosi L (2008) Cell adhesion mechanisms and elasto-viscoplastic mechanics of tumours. Biomech Model Mechanobiol (to appear)
5. Ambrosi D, Preziosi L (2002) On the closure of mass balance models for tumor growth. Math Models Methods Appl Sci 12(5):737–754
6. Araujo RP, McElwain DLS (2004) A history of the study of solid tumour growth: the contribution of mathematical modelling. Bull Math Biol 66(5):1039–1091
7. Araujo RP, McElwain DLS (2004) A linear-elastic model of anisotropic tumour growth. Eur J Appl Math 15(3):365–384
8. Araujo RP, McElwain DLS (2005) A mixture theory for the genesis of residual stresses in growing tissues. I. A general formulation. SIAM J Appl Math 65(4):1261–1284 (electronic)
9. Araujo RP, McElwain DLS (2005) A mixture theory for the genesis of residual stresses in growing tissues. II. Solutions to the biphasic equations for a multicell spheroid. SIAM J Appl Math 66(2):447–467 (electronic)
10. Astanin S, Preziosi L (2007) Multiphase models of tumour growth. In: Bellomo N, Chaplain M, De Angelis E (eds) Selected topics on cancer modelling: genesis—evolution—immune competition—therapy. Birkhäuser, Basel
11. Baumgartner W, Hinterdorfer P, Ness W, Raab A, Vestweber D, Schindler H, Drenckhahn D (2000) Cadherin interaction probed by atomic force microscopy. Proc Nat Acad Sci USA 97:4005–4010
12. Behravesh E, Timmer MD, Lemoine JJ, Liebschner MA, Mikos AG (2002) Evaluation of the in vitro degradation of macroporous hydrogels using gravimetry, confined compression testing, and micro-computed tomography. Biomacromolecules 3:1263–1270
13. Bertuzzi A, Fasano A, Gandolfi A (2004/2005) A free boundary problem with unilateral constraints describing the evolution of a tumor cord under the influence of cell killing agents. SIAM J Math Anal 36(3):882–915 (electronic)
14. Bertuzzi A, Fasano A, Gandolfi A (2005) A mathematical model for tumor cords incorporating the flow of interstitial fluid. Math Models Methods Appl Sci 15(11):1735–1777
15. Breward CJW, Byrne HM, Lewis CE (2001) Modelling the interactions between tumour cells and a blood vessel in a microenvironment within a vascular tumour. Eur J Appl Math 12(5):529–556
16. Breward CJW, Byrne HM, Lewis CE (2002) The role of cell–cell interactions in a two-phase model for avascular tumour growth. J Math Biol 45(2):125–152
17. Breward CJW, Byrne HM, Lewis CE (2003) A multiphase model describing vascular tumour growth. Bull Math Biol 65:609–640
18. Byrne HM, King JR, McElwain DLS, Preziosi L (2003) A two-phase model of solid tumour growth. Appl Math Lett 16(4):567–573
19. Byrne HM, Preziosi L (2004) Modeling solid tumor growth using the theory of mixtures. Math Med Biol 20:341–366
20. Canetta E, Leyrat A, Verdier C, Duperray A (2005) Measuring cell viscoelastic properties using a force-spectrometer: influence of the protein–cytoplasm interactions. Biorheology 42(5):321–333
21. Chaplain M, Graziano L, Preziosi L (2006) Mathematical modelling of the loss of tissue compression responsiveness and its role in solid tumour development. Math Med Biol 23:197–229
22. De Masi A, Luckhaus S, Presutti E (2007) Two scales hydrodynamic limit for a model of malignant tumour cells. Ann IHP Prob Stat 43(3):257–279
23. DiMilla PA, Kenneth B, Lauffenburger DA (1991) Mathematical model for the effects of adhesion and mechanics on cell migration speed. Biophys J 60(1):15–37
24. DiMilla PA, Stone JA, Quinn JA, Albelda SA, Lauffenburger DA (1993) Maximal migration of human smooth muscle cells fibronectin and type iv collagen occurs at an intermediate attachment strength. J Cell Biol 122:729–737
25. Forgacs G, Foty RA, Shafrir Y, Steinberg MS (1998) Viscoelastic properties of living embryonic tissues: a quantitative study. Biophys J 74:2227–2234
26. Franks SJ, Byrne HM, King JR, Underwood JCE, Lewis CE (2003) Modelling the early growth of ductal carcinoma in situ of the breast. J Math Biol 47(5):424–452

27. Franks SJ, Byrne HM, Mudhar HS, Underwood JCE, Lewis CE (2003) Mathematical modelling of comedo ductal carcinoma in situ of the breast. Math Med Biol 20:277–308
28. Franks SJ, King JR (2003) Interactions between a uniformly proliferating tumor and its surrounding. Uniform material properties. Math Med Biol 20:47–89
29. Fung YC (1993) Biomechanics: mechanical Properties of living tissues. Springer, Heidelberg
30. Graziano L, Preziosi L (2007) Mechanics in tumour growth. In: Mollica F, Preziosi L, Rajagopal KR (eds) Modeling of biological materials. Birkhäuser, Basel, pp 267–328
31. Greenspan HP (1976) On the growth and stability of cell-cultures and solid tumours. J Theor Biol 56:229–242
32. Gu WY, Yao H, Huang CY, Cheung HS (2003) New insight into deformation-dependent hydraulic permeability of gels and cartilage, and dynamic behavior of agarose gels in confined compression. J Biomech 36:593–598
33. Humphrey JD, Rajagopal KR (2002) A constrained mixture model for growth and remodeling of soft tissues. Math Mod Meth Appl Sci 12:407–430
34. Humphrey JD, Rajagopal KR (2003) A constrained mixture model for arterial adaptations to a sustained step-change in blood flow. Biomech Model Mechanobiol 2:109–126
35. Iordan A, Duperray A, Verdier C (2008) A fractal approach to the rheology of concentrated cell suspensions. Phys Rev E 77:011911
36. Iredale JP (2007) Models of liver fibrosis: exploring the dynamic nature of inflammationa and repair in a solid organ. J Clin Invest 117(3):539–548
37. Johnson PRA (2001) Two scales hydrodynamic limit for a model of malignant tumour cells. Clin Exp Pharm Physiol 28:233–236
38. Lanza V, Ambrosi D, Preziosi L (2006) Exogenous control of vascular network formation in vitro: a mathematical model. Netw Heterog Media 1(4):621–637 (electronic)
39. Liotta LA, Kohn EC (2007) The microenvironment of the tumor–host interface. Nature 411:375–379
40. Newby AC, Zaltsman AB (2000) Molecular mechanisms in intimal hyperplasia. J Pathol 190:300–309
41. Oxlund H, Andreassen TT (1980) The roles of hyaluronic acid, collagen and elastin in the mechanical properties of connective tissues. J Anat 131(4):611–620
42. Pujuguet PP, Hammann A, Moutet M, Samuel JL, Martin F, Martin M (1996) Expression of fibronectin eda+ and edb+ isoforms by human and experimental colorectal cancer. Am J Patho 148:579–592
43. Palecek SP, Loftus JC, Ginsberg MH, Lauffenburger DA, Horwitz AF (1997) Integrin-ligand binding properties govern cell migration speed through cell-substratum adhesiveness. Nature 385:537–540
44. Preziosi L (ed) (2003) Cancer modelling and simulation. Chapman & Hall/CRC Mathematical Biology and Medicine Series, Boca Raton/FL
45. Preziosi L, Farina A (2001) On Darcy's law for growing porous media. Int J Nonlinear Mech 37: 485–491
46. Rao IJ, Humphrey JD, Rajagopal KR (2003) Biological growth and remodeling: a uniaxial example with possible application to tendons and ligaments. CMES 4:439–455
47. Sun M, Graham JS, Hegedus B, Marga F, Zhang Y, Forgacs G, Grandbois M (2005) Multiple membrane tethers probed by atomic force microscopy. Biophys J 89:4320–4329
48. Tosin A (2008) Multiphase modeling and qualitative analysis of the growth of tumor cords. Netw Heterog Media 3:43–83
49. Truskey GA, Yuan F, Katz DF (2004) Transport phenomena in biological systems. Prentice Hall, Englewood Cliffs
50. Winters BS, Shepard SR, Foty RA (2005) Biophysical measurement of brain tumor cohesion. Int J Cancer 114:371–379