Published in final edited form as:

Phys Biol. ; 11(6): 065004. doi:10.1088/1478-3975/11/6/065004.

A tumor growth model with deformable ECM

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Abstract

Existing tumor growth models based on fluid analogy for the cells do not generally include the extracellular matrix (ECM), or if present, take it as rigid. The three-fluid model originally proposed by the authors and comprising tumor cells (TC), host cells (HC), interstitial fluid (IF) and an ECM, considered up to now only a rigid ECM in the applications. This limitation is here relaxed and the deformability of the ECM is investigated in detail. The ECM is modeled as a porous solid matrix with Green-elastic and elasto-visco-plastic material behavior within a large strain approach. Jauman and Truesdell objective stress measures are adopted together with the deformation rate tensor. Numerical results are first compared with those of a reference experiment of a multicellular tumor spheroid (MTS) growing *in vitro*, then three different tumor cases are studied: growth of an MTS in a decellularized ECM, growth of a spheroid in the presence of host cells and growth of a melanoma. The influence of the stiffness of the ECM is evidenced and comparison with the case of a rigid ECM is made. The processes in a deformable ECM are more rapid than in a rigid ECM and the obtained growth pattern differs. The reasons for this are due to the changes in porosity induced by the tumor growth. These changes are inhibited in a rigid ECM. This enhanced computational model emphasizes the importance of properly characterizing the biomechanical behavior of the malignant mass in all its components to correctly predict its temporal and spatial pattern evolution.

Keywords

porous media mechanics; multiphase systems; finite deformations; Finite Element Method; tumor spheroid; melanoma

1. Introduction

Cells, including tumor cells (TC) produce their own extracellular matrix (ECM) or grow within an existing one [1]. The ECM is a mesh-like structure formed by collagen and elastin

families of proteins and is the structural component of the cell microenvironment. The voids of the ECM where the cells migrate and/or are attached and the interstitial fluid flows, will be referred to as pores. ECM is seldom taken into account in tumor growth models where a solid phase is often missing. In fact from review papers of numerical models for tumor growth such as Roose *et al* [2], Lowengrub *et al* [3], Deisboeck *et al* [4], and Sciumè *et al* [5], it appears clearly that in the realm of a continuum approach the vast majority of models describe the malignant mass (TC), the host cells (HC) and the interstitial fluid (IF) as homogeneous, viscous fluids and employ reaction–diffusion–advection equations for predicting the distribution and transport of nutrients. If an ECM is present, it is generally taken as rigid with a few exceptions discussed below. In the more recent models the interfaces, if present, are obtained by means of Cahn–Hilliard equations [5].

Fewer models treat the tumor as a (porous) solid. In this case there are a few bi-phasic solid–liquid models, a pure solid model without IF of Ambrosi and Preziosi [6] and a much more complete model [7] developed within the thermodynamically constrained averaging theory (TCAT) [8–10].

Within the bi-phasic solid–liquid models, Ehlers *et al* [11] investigate avascular tumor growth in the framework of the theory of porous media which is a mixture theory. The tumor is treated as a biphasic medium where living TC and ECM are lumped together in the solid phase; IF, necrotic debris and cell precursors make up the single fluid phase. An example is shown for a finite element simulation of finite 3D growth of a tumor spheroid. The IF permeates the whole domain and there are no interfaces. Earlier bi-phasic models with a solid matrix can be found for instance in Preziosi and Farina [12], Samtinoranont *et al* [13], and Araujo and McElwain [14].

Shelton [7] has developed the governing equations within TCAT of a most comprehensive model where viable TC, necrotic TC (NTC) and host tissue with their respective ECMs are treated as solids which are permeated by a nutrient carrying IF, and by blood. With the cell populations in separate domains, interfaces exist from the beginning and move as the tumor changes size or necrotizes. These interfaces have to be traced with a large strain analysis, and appropriate constitutive relationships are needed. The numerical implementation is still pending and invasion, often observed in tumor growth may become a problem.

Starting from geomechanics, we have developed a model for tumor growth [15, 16] where healthy cells, TC, both viable and NTC, and IF are fluids while the ECM, either rigid or deformable, is the scaffold. This is de facto a multiphase flow model in a porous solid (ECM). The importance of this model in transport oncophysics is discussed by Ferrari in [17] together with other problems of (nano) medical mechanics. This model does not need interface tracking; they arise naturally from the solution of an initial-boundary value problem that must be comprised of the mass balance equations of all phases involved [5]. Another model without interface tracking is that of Narayanan *et al* [18], where the free energy rates associated with biochemical dynamics and mechanics of tumors are investigated. The model is derived within the theory of mixtures involving coupled reaction–transport equations for the concentration of cells, of the ECM, of oxygen and glucose, and a quasi-static balance of momentum equation that governs the mechanics of the tumor. IF is

not taken into account. Interfaces are determined by simply observing the resulting concentrations. The model does not invoke the flow in a porous media analogy. Within the theory of mixtures Oden *et al* [19] develop a general model containing hyper elastic solid phases. As an example they derive governing equations for the case of Araujo and McElwain [14].

In the applications by Sciumè *et al* [15, 16] the ECM was taken as rigid. This limitation is now relaxed and the deformability of the ECM is investigated in detail. We consider Green-elastic and elasto-visco-plastic material behavior within a large strain approach. The Jauman and Truesdell objective stress measures are adopted together with the deformation rate tensor.

The outline of the paper is as follows: the general mathematical formulation of the model and the constitutive equations for fluids and the ECM are described in section 2.

Comparison with experimental results of a multicellular tumor spheroid (MTS) growing *in vitro* and three examples of biological relevance are presented in section 3: the first one refers to growth of an MTS in a decellularized ECM, the second with the growth of a spheroid in the presence of host cells and the third with the growth of a melanoma.

Conclusions and perspectives of the presented multiphase model follow in section 4.

2. The multiphase tumor growth model

The adopted tumor growth model is now summarized following [20]. Tumors are modeled at the macroscopic scale, since the domain of interest is too large and the phase distributions too complex for modeling at the microscale. The TCAT approach [8, 9] is used to transform known microscale relations to mathematically and physically consistent macroscale relations. The macroscale relations are adequate for describing the tumor behavior while filtering out high frequency spatial variability. The governing equations of the model are closed by introducing constitutive relations into the macroscale equations.

The multiphase system is comprised of the following phases: (i) TC, which partition into living cells (LTC) and NTC; (ii) HC; (iii) ECM; and (iv) IF; see [16, 20]. The ECM is a porous solid, while all other phases are fluids. The TC may become necrotic upon exposure to low nutrient concentrations or excessive mechanical pressure. The IF, transporting nutrients, is a mixture of water and biomolecules, such as nutrients, oxygen and waste products. In the following mass and momentum balance equations, α denotes a generic phase, t the TC, h the HC, s the solid phase (ECM), and l the IF.

The representative elementary volume of the multiphase system is depicted in the inset of figure 1 which shows an outline of the different stages of the modeling process.

A short overview of the mathematical model is given next; additional details are available in [16, 20]. We use both vectorial and indicial notation where convenient.

2.1. General governing equations

The ECM has porosity ε , so that the volume fraction of the solid phase is $\varepsilon^s = 1 - \varepsilon$. The rest of the volume is occupied by TC (ε^t); HC (ε^h); and IF (ε^l). The volume fractions for all phases add up to unity:

$$\varepsilon^s + \varepsilon^h + \varepsilon^t + \varepsilon^l = 1 \quad (1)$$

The saturation degree of a fluid phase α is: $S^\alpha = \varepsilon^\alpha / \varepsilon$. Using porosity, ε , and volume fraction, ε^α , (1) yields:

$$S^h + S^t + S^l = 1 \quad (2)$$

Having three fluids with different pressures we define [5, 20] the following differential pressures (called capillary pressures in geomechanics):

$$\begin{aligned} p^{hl} &= p^h - p^l \\ p^{tl} &= p^t - p^l \\ p^{th} &= p^t - p^h \end{aligned} \quad (3)$$

We infer that in the t - h - l system the sum of the t - h and h - l pressure differences is equal to the t - l pressure difference:

$$\begin{aligned} p^{th} + p^{hl} &= (p^t - p^h) + (p^h - p^l) \\ &= p^t - p^l \\ &= p^{tl} \end{aligned} \quad (4)$$

Different from the previous versions of the model [16, 20] the primary variables of the model here are: differential pressures p^{hl} and p^{th} , IF pressure (IFP) p^l , nutrient mass fraction ω^{nl} , and displacement u^s of the solid phase (ECM). The choice of pressures and differential pressures instead of saturations is due to the form of the solid stress tensor equations (12) and (13) and was already successfully applied in [21] and in successive models [22] This allows for the discontinuity of phases' saturation degrees at interfaces between tissues with different ECM scaffolds even if the pressure fields are continuous across those interfaces.

The macroscopic mass and momentum balance equations of phases and species have been derived in [16] and are not repeated here. Their transformation to take into account the new primary variables is rather lengthy and is shown in appendix A. The final form of the governing equations shown below are obtained from the general forms (see appendix A) by introducing some simplifications and closure relationships (e.g. a Fickian type equation for diffusion of species, a generalized Darcy's equation for flow of the fluid phases, etc).

The mass balance equation of the ECM is:

$$\frac{\partial \varepsilon}{\partial t} = \nabla \cdot \mathbf{v}^s + \frac{(1-\varepsilon)}{\rho^s} \frac{\partial \rho^s}{\partial t} - \nabla \cdot (\varepsilon \mathbf{v}^s) \quad (5)$$

The mass balance equation of TCs reads:

$$\begin{aligned} & \left[\frac{\varepsilon S^t}{K_T} + \frac{S^t(1-\varepsilon)}{K_S} \left(S^t + p^{th} \frac{\partial S^t}{\partial p^{th}} \right) + \varepsilon \frac{\partial S^t}{\partial p^{th}} \right] \frac{\partial p^{th}}{\partial t} \\ & + \left[\frac{\varepsilon S^t}{K_T} + \frac{S^t(1-\varepsilon)}{K_S} \left(1 - S^l - p^{hl} \frac{\partial S^l}{\partial p^{hl}} \right) \right] \frac{\partial p^{hl}}{\partial t} \\ & + \left[\frac{\varepsilon S^t}{K_T} + \frac{S^t(1-\varepsilon)}{K_S} \right] \frac{\partial p^l}{\partial t} \\ & = \nabla \cdot \left[\frac{k_{rel}^t \mathbf{k}}{\mu^t} \cdot \nabla (p^l + p^{hl} + p^{th}) \right] \\ & - S^t \left(\mathbf{1} : \mathbf{d}^s \right) - \nabla S^t \cdot (\varepsilon \mathbf{v}^s) + \frac{1}{\rho^t} \overset{l \rightarrow t}{M} \end{aligned} \quad (6)$$

The mass balance equation of HCs reads:

$$\begin{aligned} & \left[\frac{S^h(1-\varepsilon)}{K_S} \left(S^t + p^{th} \frac{\partial S^t}{\partial p^{th}} \right) - \varepsilon \frac{\partial S^t}{\partial p^{th}} \right] \frac{\partial p^{th}}{\partial t} \\ & + \left[\frac{\varepsilon S^h}{K_H} + \frac{S^h(1-\varepsilon)}{K_S} \left(1 - S^l - p^{hl} \frac{\partial S^l}{\partial p^{hl}} \right) - \varepsilon \frac{\partial S^l}{\partial p^{hl}} \right] \\ & \times \frac{\partial p^{hl}}{\partial t} + \left[\frac{\varepsilon S^h}{K_H} + \frac{S^h(1-\varepsilon)}{K_S} \right] \frac{\partial p^l}{\partial t} \\ & = \nabla \cdot \left[\frac{k_{rel}^h \mathbf{k}}{\mu^h} \cdot \nabla (p^l + p^{hl}) \right] \\ & - S^h \left(\mathbf{1} : \mathbf{d}^s \right) - \nabla S^h \cdot (\varepsilon \mathbf{v}^s) \end{aligned} \quad (7)$$

The mass balance equation of IF reads:

$$\begin{aligned} & \frac{S^l(1-\varepsilon)}{K_S} \left(p^{th} \frac{\partial S^t}{\partial p^{th}} + S^t \right) \frac{\partial p^{th}}{\partial t} \\ & + \left[\frac{S^l(1-\varepsilon)}{K_S} \left(1 - p^{hl} \frac{\partial S^l}{\partial p^{hl}} - S^l \right) + \varepsilon \frac{\partial S^l}{\partial p^{hl}} \right] \frac{\partial p^{hl}}{\partial t} \\ & + \left(\frac{S^l(1-\varepsilon)}{K_S} + \frac{\varepsilon S^l}{K_L} \right) \frac{\partial p^l}{\partial t} = \nabla \cdot \left[\frac{k_{rel}^l \mathbf{k}}{\mu^l} \cdot \nabla p^l \right] \\ & - S^l \left(\mathbf{1} : \mathbf{d}^s \right) - \nabla S^l \cdot (\varepsilon \mathbf{v}^s) - \frac{1}{\rho^t} \overset{l \rightarrow t}{M} \end{aligned} \quad (8)$$

where μ^a is dynamic viscosity, k_{rel}^a is relative permeability, ρ^a is density, and p^a is pressure of phase a ($a = h, l$ and t). Also, $\mathbf{d}^s$ is the Eulerian rate of strain tensor, $\mathbf{k}$ the intrinsic permeability tensor of the ECM, and $\overset{l \rightarrow t}{M}$ is an inter-phase exchange of mass between the phases l and t , and represents the mass of IF which becomes a tumor due to cell growth. K_I is the compressibility of phase I (with $I = S, T, H$ and L). For all other terms refer to the nomenclature.

Summing equations (6)–(8), using the constraint equations on volume fractions and saturation, equations (1) and (2) gives (see appendix A):

$$\begin{aligned}
& \left[\frac{\varepsilon S^t}{K_T} + \frac{1-\varepsilon}{K_S} \left(S^t + p^{th} \frac{\partial S^t}{\partial p^{th}} \right) \right] \frac{\partial p^{th}}{\partial t} \\
& + \left[\frac{\varepsilon S^t}{K_T} + \frac{\varepsilon S^h}{K_H} + \frac{1-\varepsilon}{K_S} \left(1 - S^l - p^{hl} \frac{\partial S^l}{\partial p^{hl}} \right) \right] \frac{\partial p^{hl}}{\partial t} \\
& + \left(\frac{\varepsilon S^t}{K_T} + \frac{\varepsilon S^h}{K_H} + \frac{\varepsilon S^l}{K_L} + \frac{1-\varepsilon}{K_S} \right) \frac{\partial p^l}{\partial t} \\
& = \nabla \cdot \left[\frac{k_{rel}^t \mathbf{k}}{\mu^t} \cdot \nabla p^{th} \right] \\
& + \nabla \cdot \left[\left(\frac{k_{rel}^t \mathbf{k}}{\mu^t} + \frac{k_{rel}^h \mathbf{k}}{\mu^h} \right) \cdot \nabla p^{hl} \right] \\
& + \nabla \cdot \left[\left(\frac{k_{rel}^t \mathbf{k}}{\mu^t} + \frac{k_{rel}^h \mathbf{k}}{\mu^h} + \frac{k_{rel}^l \mathbf{k}}{\mu^l} \right) \cdot \nabla p^l \right] \\
& - \left(\mathbf{1} : \mathbf{d}^s \right) + \frac{\rho^l - \rho^t}{\rho^t \rho^l} \overset{l \rightarrow t}{M}
\end{aligned} \tag{9}$$

Equations (6), (7) and (9) which incorporate equation (5) are three of the governing equations of the model.

The tumor phase t comprises an NTC with mass fraction ω^{Nt} and a growing phase with LTC whose mass fraction is $1 - \omega^{Nt}$; the summation of the conservation equation for each of these two mass fractions gives equation (6) [16]. Assuming that there is no diffusion of either necrotic or living cells and that there is no exchange of the NTC with other phases, the mass fraction of the NTC is given by:

$$\frac{\partial \omega^{Nt}}{\partial t} = \frac{1}{\varepsilon S^t \rho^t} \left[\varepsilon^t r^{Nt} - \left(\omega^{Nt} \overset{l \rightarrow t}{M} \right) - \left(\varepsilon S^t \rho^t \mathbf{v}^t \right) \cdot \nabla \omega^{Nt} \right] \tag{10}$$

where $\mathbf{v}^t$ is the velocity of the TC (LTC and NTC move with the same velocity) and $\varepsilon^t r^{Nt}$ is the death rate of TC, i.e. the rate of generation of NTC. Unlike a mass exchange term between phases, $\overset{l \rightarrow t}{M}$ in equation (6), the reaction term $\varepsilon^t r^{Nt}$ is an intra-phase exchange term.

The mass balance equation of the nutrient reads:

$$\begin{aligned}
& \varepsilon S^l \frac{\partial \omega^{nl}}{\partial t} - \nabla \cdot \left(\varepsilon S^l D_{eff}^{nl} \nabla \omega^{nl} \right) \\
& = \frac{1}{\rho^t} \left(\omega^{nl} \overset{l \rightarrow t}{M} - \overset{nl \rightarrow t}{M} \right) \\
& - \varepsilon S^l \mathbf{v}^l \cdot \nabla \omega^{nl}
\end{aligned} \tag{11}$$

where D_{eff}^{nl} is the effective diffusivity of the nutrient species in the extracellular space and $\overset{nl \rightarrow t}{M}$ is the mass of nutrient consumed by TC via metabolism and growth. Equation (11) is another governing equation of the model.

The effective stress tensor, $\bar{\mathbf{t}}_{eff}^s$, in the sense of porous media mechanics is

$$\bar{\mathbf{t}}_{eff}^s = \bar{\mathbf{t}}^s + \bar{\alpha} p^s \mathbf{1} \quad (12)$$

where $\mathbf{1}$ is the unit tensor, $\bar{\mathbf{t}}^s$ is the total stress tensor in the solid phase, $\bar{\alpha}$ is the Biot's coefficient ($\bar{\alpha} = 1 - K/K_s$, with K compressibility of the unsaturated ECM). In the modeled problem, K/K_s tends to zero hence we can assume a Biot's coefficient equal to 1. The solid pressure p^s is given as [23]:

$$\begin{aligned} p^s &= S^h p^h + S^t p^t + S^l p^l \\ &= p^l + (1 - S^l) p^{hl} + S^t p^{th} \end{aligned} \quad (13)$$

where the Bishop parameter of each fluid phase (solid surface fraction in contact with the phase) has been taken equal to its own degree of saturation.

The last governing equation of the model is the linear momentum balance of the solid phase expressed in rate form [24]:

$$\nabla \cdot \left(\frac{\partial \bar{\mathbf{t}}_{eff}^s}{\partial t} - \bar{\alpha} \frac{\partial p^s}{\partial t} \mathbf{1} \right) = 0, \quad (14)$$

where the interaction between the solid and the three fluid phases is accounted for through the effective stress principle, equation (12).

2.2. Solid phase behavior

Since an ECM is present in the model its configuration is used as reference configuration whereby the velocities of the fluid are relative to the ECM which is described in a Lagrangian system. This is customary in multiphase flow models within deforming porous media [24].

A large deformation regime is assumed for the ECM (solid phase). As far as the stress and strain measures are concerned, objectivity (invariance with respect to coordinate transformations, particularly rotations) and work-conjugacy (which guarantees energy consistency, i.e. correct expressions for the second-order energy increment) should be conserved. The satisfaction of the second requirement guarantees that of the first, but not the opposite. Among the several objective stress rates [25, 26] we have taken two options: the Jaumann stress rate and the Truesdell stress rate.

The Jaumann stress rate is used as a corotational measure associated with the Eulerian strain

rate tensor $\bar{\mathbf{d}}^s$ within an updated Lagrangian approach with sufficiently small load increments [24]. The deformation is in fact described by the velocity gradient tensor

$\bar{\mathbf{L}}^s = \nabla \bar{\mathbf{v}}^s = \bar{\mathbf{d}}^s + \bar{\mathbf{w}}^s$, where the symmetric part $\bar{\mathbf{d}}^s$ is the Eulerian strain rate tensor:

$$d_{ij}^s = \frac{1}{2} \left(\frac{\partial v_i}{\partial x_j} + \frac{\partial v_j}{\partial x_i} \right) \quad (15)$$

and the skew-symmetric one, $\overline{\mathbf{w}}^s$, the spin tensor:

$$w_{ij}^s = \frac{1}{2} \left(\frac{\partial v_i}{\partial x_j} - \frac{\partial v_j}{\partial x_i} \right) \quad (16)$$

If the strain increments are kept small during each step, the spin tensor $\overline{\mathbf{w}}^s$ accurately approximates the local angular velocity $\overline{\boldsymbol{\Theta}}^s$, and gives the Jaumann stress rate as (omitting the double overbar):

$$\overset{J}{\dot{\mathbf{t}}}^s = \dot{\mathbf{t}}^s - \mathbf{t}_{kj}^s w_{ik}^s + \mathbf{t}_{ik}^s w_{jk}^s \quad (17)$$

where the superior dot indicates $\partial/\partial t$. True work-conjugacy can be recovered by adding a volumetric correction term to the tangential stiffness moduli [25, 26]. For our problems this is not necessary because we do not consider high compressibility or large rotations.

The objective Truesdell rate of Cauchy stress is:

$$\overset{T}{\dot{\mathbf{t}}}^s = \dot{\mathbf{t}}^s - \mathbf{t}_{kj}^s \frac{\partial v_i}{\partial x_k} - \mathbf{t}_{ik}^s \frac{\partial v_j}{\partial x_k} + \mathbf{t}_{ij}^s \frac{\partial v_k}{\partial x_k} \quad (18)$$

which is work conjugate with the Green-Lagrange strain measure. For a sufficiently small loading step (or increment), one may use the deformation rate tensor (or velocity strain) as above or the increment representing the linearized strain increment from the initial (stressed and deformed) state in the step, i.e. the last converged solution:

$$\Delta E_{ij}^s = d_{ij}^s \Delta t \quad (19)$$

The adoption of the objective Truesdell rate of Cauchy gives a symmetric tangent stiffness matrix while the Jaumann rate of Cauchy stress would yield a non-symmetric tangent stiffness matrix. In case of elasticity the non-symmetry terms are small compared to the elastic modulus, but in the case of plasticity they become not negligible (Cheng and Tsui, [27]).

2.3. Constitutive relationships

The constitutive equations for growth, necrosis, and nutrient consumption are given in [16, 20] and are not repeated here. Attention is focused on the fluids, needed in appendix A for the derivation of the governing equations, and the solid part behavior, the main focus of this paper.

2.3.1. Fluid phases—The constitutive relationships for the fluid phases have been extensively dealt with in [20, 28] and only the most important ones are listed here. The differential pressure-saturation relationships are:

$$\begin{aligned} S^l &= 1 - \left[\frac{2}{\pi} \arctan \left(\frac{p^{hl}}{a} \right) \right] \\ S^h + S^l &= 1 - S^t \\ &= 1 - \left[\frac{2}{\pi} \arctan \left(\frac{\sigma_{hl} p^{th}}{\sigma_{th} a} \right) \right] \end{aligned} \quad (20)$$

where σ_{ij} is the interfacial tension between fluid phases i and j , and a is a constant parameter related to ECM porosity. Equation (20) express the fact that the interfaces between phases are also capable of sustaining a jump in pressure between phases. This difference in pressures can be attributed to the curvature of the interface between fluid phases and to the interfacial tension and is not linked to flow.

Interaction forces are in play when there is flow: the different velocities of the different phases set up resistance forces between the phases. The resistance tensor that accounts for the frictional interactions between phases in the generalized Darcy law contained in equations (6), (7), and (9) is:

$$(\mathbf{R}^\alpha)^{-1} = \frac{k_{rel}^\alpha \mathbf{k}}{\mu^\alpha (\varepsilon^\alpha)^2} \quad (\alpha = h, t, l) \quad (21)$$

with:

$$\mu^\alpha = \frac{\mu_0^\alpha}{(1 - \xi) \left\langle 1 - \frac{\psi_\alpha}{|\nabla p^\alpha|} \right\rangle} + \xi \quad (\alpha = h, t) \quad (22)$$

for HC and TC, allowing us to model adhesion [20]. μ^α is the dynamic viscosity for large value of $|\nabla p^\alpha|$ (nominally for $|\nabla p^\alpha| \rightarrow \infty$, ξ is a constant parameter (in the examples it is set equal to 0.1), and ψ_α is the adhesion threshold of the phase α (Pa/m); in the examples in section 3 TCs and HCs are assumed to be not-adhesive ($\psi_t = \psi_h = 0$). This formulation considers that the dynamic viscosity decreases substantially when the magnitude of the gradient exceeds the threshold of cell adherence; cells in fact mutually adhere firmly until a certain value of the local pressure gradient is reached, causing them to start moving. Finally, diffusion of the chemical species dissolved in the IF follows Fick's law [16, 20].

2.3.2. Solid phase—The solid behavior is either Green-elastic where the elastic coefficients are derived from the strain energy function or elasto-visco-plastic in which the stress–strain relation is defined incrementally. The absence of a potential in the second case requires the adoption of objective stress rates mentioned above. Elasto-visco-plasticity has been chosen as the model in the future, along with a remodeling of the ECM, see also Preziosi *et al* [29]. We describe here the elasto-visco-plastic model in some detail. It considers over stresses and was introduced by Perzyna [30, 31].

The total solid strain is considered as a sum of the elastic part and the visco-plastic part:

$$\bar{\mathbf{e}}^s = \bar{\mathbf{e}}_{el}^s + \bar{\mathbf{e}}_{vp}^s \quad (23)$$

The relationship between the effective stress for the solid and the elastic strain is:

$$\dot{\bar{\mathbf{t}}}_{eff}^s = \mathbf{D}_s : \dot{\bar{\mathbf{e}}}_{el}^s = \mathbf{D}_s : \left(\dot{\bar{\mathbf{e}}}^s - \dot{\bar{\mathbf{e}}}_{vp}^s \right) \quad (24)$$

where $\mathbf{D}_s$ is the tangent matrix containing the mechanical properties of the solid skeleton.

For visco-plastic analysis the constitutive tangent matrix $\mathbf{D}_s$ should be such that all materials' symmetries are preserved, in accordance with the associative character of the model. The matrix will generally depend on the current state variables and on the direction of loading.

The elastic range is defined as the set of all possible absolute values of the effective stress that are less than or equal to the frictional constant $t_{eff,y}^s$, i.e. the yield limit (this value allows us to define the boundary of elastic domain). Until the absolute value of the effective stress is contained in the elastic range, the rate of change of the visco-plastic strain is zero while beyond this limit it is different from zero. These values are defined by the constitutive flow rule that for classical viscoplasticity is obtained from rate-independent plasticity by replacing the consistency parameter $\gamma > 0$ with the constitutive equation:

$$\gamma = \frac{\left\langle f \left(\bar{\mathbf{t}}_{eff}^s \right) \right\rangle}{f_0 \eta} \quad \eta \in (0, \infty). \quad (25)$$

$$f \left(\bar{\mathbf{t}}_{eff}^s \right) = \left\| \bar{\mathbf{t}}_{eff}^s \right\| - t_{eff,y}^s \quad (26)$$

is called the yield condition or loading function, η is the viscosity, f_0 is a reference fixed value making $f \left(\bar{\mathbf{t}}_{eff}^s \right) / f_0$ dimensionless [32].

Then the flow rule defining the rate of change of viscoplastic strain, is:

$$\dot{\bar{\mathbf{e}}}_{vp}^s = \frac{\left\langle f \left(\bar{\mathbf{t}}_{eff}^s \right) \right\rangle}{f_0 \eta} \frac{\partial f \left(\bar{\mathbf{t}}_{eff}^s \right)}{\partial \bar{\mathbf{t}}_{eff}^s} \quad (27)$$

The two equations (25) and (26) are the visco-plastic constitutive equations of the Perzyna type [31]. The linear isotropic hardening model of Perzyna is obtained taking into account an internal variable λ with an evolutionary equation:

$$\dot{\lambda} = \|\dot{\mathbf{e}}_{vp}^s\| \geq 0 \quad (28)$$

and by modifying the yield condition with the isotropic hardening modulus H as:

$$f\left(\bar{\mathbf{t}}_{eff}^s, \lambda\right) = \|\bar{\mathbf{t}}_{eff}^s\| - \left(\bar{\mathbf{t}}_{eff,y}^s + H\lambda\right) \quad (29)$$

In this case the elastic range is obviously time-dependent.

The classical model of viscoplasticity used to describe the ECM behavior is obtained by introducing the von Mises yield condition:

$$f\left(\bar{\mathbf{t}}_{eff}^s, \lambda\right) = \|\text{dev}\left[\bar{\mathbf{t}}_{eff}^s\right]\| - \sqrt{\frac{2}{3}}\left(\bar{\mathbf{t}}_{eff,y}^s + H\lambda\right) \quad (30)$$

where $\text{dev}\left[\bar{\mathbf{t}}_{eff}^s\right] = \bar{\mathbf{t}}_{eff}^s - \frac{1}{3}\left(\text{tr}\left[\bar{\mathbf{t}}_{eff}^s\right]\right)\mathbf{1}$ is the deviatoric part of the effective stress, $\mathbf{1}$ the second order identity tensor, and the equivalent visco-plastic strain as an internal variable:

$$\dot{\lambda} = \sqrt{\frac{2}{3}}\gamma \quad (31)$$

The algorithm used to model the constitutive behavior above is the ‘radial return mapping algorithm’ of Simo and Hughes [31] and has been implemented in the finite elements code CAST3M (www-cast3m.cea.fr) together with our model.

An overview of the finite element implementation and solution process is given in appendix B.

3. Model validation and numerical examples

In this section the model is used first to simulate an MTS growing *in vitro*. The numerical results are compared with those of a reference experiment (Chignola *et al* 2000 [33]). Then three cases of biological interest are modeled, focusing on the impact of ECM deformability on tumor growth: the first one deals with growth of an MTS in a decellularized ECM, the second one with the growth of an MTS within a host tissue and the third one with growth of a melanoma.

3.1. MTS growth *in vitro*: comparison with experimental data

The model is validated with respect to the experiment by Chignola *et al* 2000 [33] and the results are shown in figure 2. This case has been modeled already in Sciumè *et al* [16] with a rigid ECM, thus for boundary and initial conditions the reader is referred to [16]. Here a deformable ECM is assumed. As better explained in the following example, the overall growth rate increases with the decrease of the ECM stiffness; consequently to fit the model to experimental data, in this validation case the value of γ_{growth}^t (parameter which governs TCs growth rate) is lower than that used in [16] while other parameters are unchanged. The input parameters are listed in table 1.

Comparison with experimental results in figure 2 shows that the presented model is able to simulate well the growth of the MTS during the initial (exponential) growth phase and the following linear one. The saturation part is only partly captured. To capture this part the introduction of lysis will be needed as shown by preliminary runs.

3.2. MTS growth in a decellularized ECM

As shown in Mishra *et al* [1] TC can be grown successfully in decellularized organs. This allows us to mimic the *in vivo* environment and has been done successfully for an *ex vivo* 3D lung model where it was possible to grow perfusable lung nodules [1].

As an example for an *ex vivo* experiment we show a multicellular tumor spheroid which grows in a deformable ECM. The simulations are limited to the avascular stage. Since decellularized ECM is a rather deformable scaffold, we show the influence of the stiffness of the ECM on the growth by comparing the solution between a rigid and a deformable ECM. Since in the examples we put main emphasis on the influence of deformation, the effects of cell pressure in the growth function and the rate of TC death have here been neglected.

The geometry of the problem is simulated with a sphere segment in axisymmetric conditions with a radius of 1000 μm . The MTS is composed of three phases: (i) the solid phase ECM (which fills the whole domain), (ii) the fluid phase of LTC and later on of NTC and (iii) the IF phase. At the initial time instant the three phases coexist in the red area with a radius of 30 μm shown in figure 3, whereas the rest of the sphere segment represents the cell culture medium surrounding the MTS and the ECM with a radius up to 1000 μm . The initial IFP is zero Pa in the entire domain and the atmospheric pressure is taken as the reference pressure. The initial volume fraction of TCs is 0.02 and of the ECM in the domain 0.2, hence the initial porosity is 0.8.

Boundary conditions are imposed as indicated in figure 3. To allow IF flux at the outer boundary the IFP is fixed there to zero Pa. Due to the symmetry of the problem there is no flux normal to the radius of the sphere segment. Oxygen is the sole nutrient species and its mass fraction is fixed to $\omega_{env}^{nl} = 4.2 \cdot 10^{-6}$ at the outer boundary and throughout the computational domain at initial time (see table 2). This mass fraction of oxygen corresponds to the average of the dissolved oxygen in the plasma of a healthy individual.

All model parameters are listed in tables 3–5 classified by type. The critical value of the oxygen mass fraction which controls TC growth rate and induces necrosis is $\omega_{crit}^{nl}=1 \cdot 10^{-6}$ (the used constitutive equations for growth and necrosis are reported in [16]). This critical threshold has been chosen in accordance with the experiments of Walenta *et al* [34].

Coefficients γ_{growth}^{nl} and γ_0^{nl} control the TCs uptake of oxygen (see the constitutive equation reported [16]); they allow modeling consumption due to TCs growth and their metabolism, and with the chosen values an oxygen consumption rate in accordance with experimental observations of Mueller-Klieser *et al* [35] is obtained. The oxygen diffusion coefficient in the IF, D_0^{nl} , has been taken from [36].

Recently we have included the effect of fluid–fluid interfacial tension taking into account explicitly HC–IF, σ_{hl} , TC–HC, σ_{th} , and TC–IF interfacial tensions, σ_{tl} [20]. The values of interfacial tensions in table 3 have been chosen respecting order of magnitude of experimental measurements [37, 38].

Finite displacements and a Lagrangian updated formulation together with the objective Truesdell rate of Cauchy stress, see section 2.2, are adopted for the simulation. Figure 4(a) shows the displacements field in radial direction due to the deformability of the ECM. The Young modulus for the deformable ECM is $E = 2.0 \cdot 10^2$ Pa, whereas it takes a large value for the rigid ECM simulation shown later on for comparison. The constitutive behavior of the deformable ECM is elastic until the yield limit, after that the behavior becomes viscoplastic. The equivalent viscoplastic strains (equation 31) are shown in figure 4(b). The viscoplastic parameters for the Perzyna type model (see section 2.3.2) are described in table 5.

The reason for the significantly different behavior between a deformable and a rigid ECM lies in the porosity. In a deformable ECM the growing tumor is able to increase the available pore space in the region where growth happens, while in the outer space the porosity of the ECM slightly decreases. This is shown in figure 4(c) for the final stage of the simulation.

Figure 5(a) shows the volume fractions of tumor cells for deformable ECM (dashed lines) and rigid ECM (solid lines). The volume fraction of the TCs in the deformable ECM differs from that in the rigid ECM because growth is faster in the first case. The outer radius of MTS (the radius for which the volume fraction is zero) is larger in the deformable ECM; the overall volume of the ECM increases creating more pore space while in the rigid ECM the sphere volume is fixed.

The pressure of the IF is plotted in figure 5(b) versus the radius for the deformable (dashed lines) and rigid ECM (solid lines). In both cases at the beginning IFP gradient remains zero so that no additional IF from the surroundings is needed because the TCs increase density without lateral expansion. In case of rigid ECM, the IFP gradient is zero for a longer time than for the deformable ECM. After this first growth stage, the MTS increases its radius hence the IFP in the MTS core decreases. When the MTS increases its volume the IF flows inward, respecting the constraint $S^t + S^l = 1$. The processes in a deformable ECM are more rapid than in a rigid ECM: the front of the IFP and of the tumor mass fraction move faster towards the outside border (see figure 5(b)). In figure 5(d) it can be seen that the radius of

the tumor in a deformable ECM increases faster than in a rigid ECM where in this case the radial solid stresses are higher up to 45%. An initial exponential growth followed by a linear phase can be seen. However without lysis the tumor growth curves do not saturate. Figure 5(c) shows the evolution of the oxygen mass fraction in deformable and rigid ECM (dashed and solid lines respectively). The oxygen decreases from the original mass fraction of $4.2 \cdot 10^{-6}$ because of its consumption made by living TC. Oxygen is the sole nutrient species considered here. Once the oxygen concentration decreases below the critical value fixed in table 3 cell necrosis begins.

3.3. MTS growing in host tissue

For comparison we show the behavior of a case similar to that in figure 3 but this time the available space filled also with healthy cells, see figure 6(a). Boundary and initial conditions are similar to those of the previous case. Only HCs with an initial volume fraction of 0.45 in the orange zone are added, and their volume fraction is prescribed in the green boundary ($\epsilon^h = 0.45$ in B2). The domain is smaller because the outer region in this case is less important: what matters is the presence of a host tissue. Again results for a deformable and a rigid ECM are compared.

Even if in this case differences between deformable and rigid cases are less relevant, as in the previous example where with rigid ECM the growth rate is slower than in that with deformable ECM. In fact in the latter the pressure of the tumor phase leads not only to TC infiltration but also to the increase of ECM porosity (i.e. the available space for TCs) as already observed in figure 4.

The volume fractions of the TC are depicted in figure 6(c): the growth is much slower than in the absence of a healthy tissue. The same is true for the radius of the MTS, shown in figure 6(b). Here the same remark about the influence of lysis as in the previous example applies. The evolution of the IFP is shown in figure 6(d).

In the panel's figures dashed lines refer to the case with deformable ECM while solid lines refer to the case with rigid ECM.

3.4. Melanoma growth

Cutaneous melanoma is the most dangerous form of skin cancer. It arises in the melanocytes, the specialized melanin producing cells, which are scattered along the epidermis-dermis border. It is recalled that the outer structure of skin has a layered structure where three compartments can be evidenced: the epidermis, an outer epithelium of stratified cells; the dermis, an intermediate cushion of vascularized connective tissue; and the hypodermis, the lowermost layer made of loose tissue and adipose cells [39]. The dermis is separated from the epidermis by the basement membrane or basal laminae, a tough sheet of ECM. Two well defined clinical stages characterize the progression of a melanoma: first there is radial expansion in the epidermis; then the tumor may switch to vertical growth penetrating the basement membrane. This penetration and angiogenesis occur generally in parallel and are hallmarks of malignant invasion. Intense angiogenesis requires ECM remodeling [40]. Two continuum mechanics models for the growth of melanoma, related to

the approach chosen in this paper are briefly discussed. Eikenberry *et al* [40] examine tumor invasion in a cylindrical section of the skin. The model variables are the densities of TC, HC, endothelial cells, necrotic debris, basement membrane, tumor angiogenic factor (TFA) and partial pressure of oxygen. Cell motility is described by Fick's law (diffusion) and cancer cell motility depends additionally on contact with other cancer cells and oxygen concentration. Oxygen is the limiting nutrient and diffuses into the skin. Insufficient oxygen concentration causes cancer cell death. Cancer cells produce TFA; endothelial cells migrate into the system in response to TFA, degrade the basement membrane and form the neovasculature. The patterns of invasion are studied and the model is then extended to include cellular immune response, metastatic spread and surgical treatment. No tissue mechanics or flow aspects are included in the model.

Tissue mechanic effects on the contrary are included in Ciarletta *et al* [39] who address radial growth of a primary melanoma within the multiphase theory of mixtures. In particular loss of adhesiveness and of anchorage between the melanoma cells and the basal laminae is investigated with a three component mixture: IF, melanoma cells and elastic substrate (hyperelastic nearly incompressible solid medium undergoing finite deformations). An advection-diffusion equation is used for the nutrient transport. Cell to cell interactions are described by an elastic fluid model of Darcy type while the connection between melanocytes and basal laminae is of visco-plastic type. The alterations in the keratinocytes–melanocytes interactions during the radial growth phase are then modeled through a four component mixture model comprising IF, two cellular phases made of keratinocytes and melanoma cells and the elastic phase representing the basal laminae. The examples involving surface spreading at the level of the basal epidermis are two-dimensional.

3.4.1. General description and hypothesis of a modeled case—The following example of evolution of a melanoma during the avasculare stage shares some aspects with that in [40]; we consider a similar geometry with the skin made of an epidermal zone of 185 μm (EZ); a basement membrane of 30 μm (MZ), and a dermal zone of 585 μm (DZ) (see figure 7). A different volume fraction of ECM is assumed for each of the three discretized zones according to their different nature ($\varepsilon_{EZ}^s = 0.2$ for the EZ, $\varepsilon_{MZ}^s = 0.3$ for the MZ and $\varepsilon_{DZ}^s = 0.1$ for the DZ).

If a unique differential pressure saturation relationship (p-s) is used for the whole domain the saturation degree of fluid phases is continuous across the interface between zones, but the differences in porosity leads to volume fractions discontinuity across EZ–MZ and MZ–DZ interfaces.

The pressure-based formulation adopted here has the advantage of allowing discontinuities between saturation degrees of fluid phases without jump conditions (across interfaces between zones with unequal p-s relationships), while the pressures fields are continuous. Since EZ, MZ and DZ have their own porous microstructure, generally a p-s constitutive model must be specified for each zone; this leads to discontinuities of the saturation degrees of fluids at interfaces between zones and consequently impacts also on discontinuities between volume fractions.

A different volume fraction of the solid phase corresponds to a different stiffness of the solid skeleton. In the example we perform two simulations assuming two different values of the averaged Young's modulus of epidermis' scaffold E_{EZ} . E_{EZ} is considered as the reference Young's modulus and those of the two other zones are assumed to be related to volume fractions of their own ECM as follows:

$$E_{MZ} = \frac{\varepsilon_{MZ}^s}{\varepsilon_{EZ}^s} E_{EZ} \quad E_{DZ} = \frac{\varepsilon_{DZ}^s}{\varepsilon_{EZ}^s} E_{EZ} \quad (32)$$

A unique Poisson's ratio equal to 0.4 is used for the EZ, MZ and DZ.

The intrinsic permeability k and the parameter a (coefficient of equation (20)) of MZ and DZ, are obtained from those of EZ assuming the following dependence on the ratio between porosities of the zones:

$$k_{MZ} = \left(\frac{1 - \varepsilon_{MZ}^s}{1 - \varepsilon_{EZ}^s} \right)^{n_k} k_{EZ} \quad k_{DZ} = \left(\frac{1 - \varepsilon_{DZ}^s}{1 - \varepsilon_{EZ}^s} \right)^{n_k} k_{EZ} \quad (33)$$

$$a_{MZ} = \left(\frac{1 - \varepsilon_{MZ}^s}{1 - \varepsilon_{EZ}^s} \right)^{n_a} a_{EZ} \quad a_{DZ} = \left(\frac{1 - \varepsilon_{DZ}^s}{1 - \varepsilon_{EZ}^s} \right)^{n_a} a_{EZ} \quad (34)$$

with $n_k = 3$ and $n_a = 1$. Considering the assumed porosities, one can observe that $a_{MZ} > a_{EZ}$ and $a_{DZ} > a_{EZ}$: at the same pressure the saturation degrees of cells are higher/lower in MZ / DZ than in EZ.

Note that if EZ, MZ and DZ have the same porosity, equations (33) and (34) give for MZ and DZ the same parameters as for EZ; hence only quantitative differences between porosities of the different zones can be taken into account. A more sophisticated approach would also include the dependence on the averaged radius of the porous network of the zone, r_{IZ} , as follows:

$$p_{IZ} = \left[\left(\frac{1 - \varepsilon_{IZ}^s}{1 - \varepsilon_{EZ}^s} \right)^{n_p} + F(r_{IZ}/r_{EZ}) \right] p_{EZ} \quad (35)$$

where p_{IZ} is a generic parameter of the i -zone and F is a function of the ratio r_{IZ}/r_{EZ} , with $F(1) = 0$.

The parameters related to cells lines and oxygen diffusion are those of the previous example (tables 3 and 4), while in table 6 the parameters related to the ECM structure are specified for each of the two simulated cases.

3.4.2. Finite element mesh, initial and boundary conditions—The problem of figure 7 presents cylindrical symmetry and the domain is discretized by 3720 plane four node elements. The boundary conditions are described in figure 8.

The system is comprised of four phases: (i) TC; (ii) HC; (iii) ECM; and (iv) IF. In the whole discretized domain the initial IFP), p^l , is set equal to 0 Pa, while the HC-IF difference pressure, p^{hl} , is set equal to 719 Pa, which correspond to a saturation degree of IF, in EP, MZ and DZ equal to 0.44, 0.40, 0.48 respectively. At time $t = 0$ h, all four phases coexist in the purple region shown in figure 8 (it has a radius of $40 \mu\text{m}$), while in the remaining regions of the domain no TCs are present. Within the purple region, the initial saturation degree of the TC is set to 0.125, corresponding to $p^{th} \approx 59$ Pa. Oxygen is here the sole nutrient species, and in the whole domain its mass fraction is initially set equal to $4.2 \cdot 10^{-6}$, which corresponds to the average of the dissolved oxygen in the plasma of a healthy individual. The initial conditions are summarized in table 7.

At the upper boundary (B1), there are no fluxes of phases and species or applied forces. At the right boundary (B2) the primary variables p^l , p^{hl} , p^{th} and u_r are fixed in time (Dirichlet boundary conditions) and zero flux is imposed for oxygen. At the lower boundary (B3), the primary variables p^l , p^{hl} , p^{th} and u_z are fixed in time (see figure 8).

In [40] atmospheric oxygen provided by the skin surface is considered, and this improves TCs growth. In our multiphase model oxygen is assumed to be the main chemical species that impacts on growth and necrosis and is the only one considered explicitly. However, also other nutrient species (dissolved in IF) not explicitly considered in the model, impact on cells metabolism and growth (e.g. glucose) but these are not provided by skin surface from the atmosphere but only from vasculature. For this reason the choice has been here to consider only oxygen provided by the vascular bed; hence, the mass fraction of oxygen, ω^{nl} , is fixed in B3 (it is set to $4.2 \cdot 10^{-6}$). This does not preclude that a more complex formulation including effects of other nutrient species may also include oxygen provided by skin.

The boundary conditions at the z axis are assumed respecting cylindrical symmetry.

3.4.3. Results—Figure 9 shows volume fractions of TCs at one and two weeks for the two modeled cases. In case 1 the growing TCs deform the ECM of EZ, MZ and DZ importantly and make a ‘hill’ on the skin surface. This does not happen in the second modeled case due to the significant stiffness of ECM. The influence of the basement membrane is evident in both cases: at the beginning the tumor grows almost as a semi-sphere (see results at one week); then, when the membrane is reached, the growth pattern changes in a more complex configuration. This is due to intrinsic permeability assumed to be smaller in MZ. In the two cases, differences in the stiffness of ECMs lead to alterations in the obtained growth patterns (compare figures 9(a) and (b)). These differences increase significantly if we further reduce the stiffness of ECMs in case 1. On the other hand, if we consider case 2, increasing the stiffness of ECMs does not lead to great changes in the obtained growth pattern: this means that the set of parameters used in case 2 leads to a solution which tends to that of a rigid ECM.

TCs consume oxygen due to growth and to their metabolism. Oxygen consumption leads to a decrease of its mass fraction in the tumor area (see figure 10). Experimentally severe hypoxia induces quiescence of TCs and when sustained also necrosis; this behavior is successfully modeled as depicted in figure 11.

Figure 12 shows the volume fraction of HCs after two weeks of growth for the two modeled cases. The figure clearly shows discontinuities of volume fractions across EZ–MZ and MZ–DZ interfaces related to the different nature of the three considered zones.

The presented case refers to the initial stage of a malignant melanoma growth. Even if we have not yet exhaustively validated the presented multiphase model with respect to experiments, the numerical results are qualitatively similar (see figure 13) to an *in vivo* tissue section of [41].

4. Discussion and conclusions

The limitation of a rigid ECM has been relaxed in our model for tumor growth and the influence of the stiffness of the ECM on the growth pattern investigated in detail. For this purpose the ECM has been modeled as a porous solid matrix with Green-elastic and elasto-visco-plastic material behavior within a large strain approach. The Jauman and Truesdell objective stress measures are adopted together with the deformation rate tensor. An updated Lagrangian formulation has been used for the numerical simulation. First the model has been validated with respect to experimental data. The presented model is able to simulate well tumor growth of MTS during the initial (exponential) growth phase and the following linear one. The saturation part is only partly captured. Lysis will be necessary to follow this part, as shown by preliminary runs. This will be dealt with in a subsequent paper where also the influence of lysis on the outflow from the tumor mass will be evidenced. Three cases of tumor growth have then been investigated. The first one deals with a multicellular tumor spheroid which grows in a deformable decellularized ECM. The simulations have been limited to the avascular stage. Since decellularized ECM is a rather deformable scaffold, we have shown the influence of the stiffness of the ECM on the growth by comparing the solution between a rigid and a deformable ECM. The processes in a deformable ECM are more rapid than in a rigid ECM: the front of IFP and of tumor mass fraction move faster towards the outside border of the domain and the effective volume of the tumor in a deformable ECM increases faster. The reason for the significantly different behavior between a deformable and a rigid ECM lies in the porosity. In a deformable ECM the growing tumor is able to increase the available pore space in the region where growth happens, while in the outer space not occupied by the tumor, porosity of the ECM decreases slightly due to the deformation pattern.

As a second example we have shown the behavior of a similar case as before but with the available space also filled with HC. The investigated domain is smaller because the outer region in this case is less important: what matters is the presence of a host tissue. Again the comparison of results for a deformable and a rigid ECM show that the assumption of a rigid ECM slows the processes down even if the effect is less pronounced. Compared to the previous case the growth is much slower than in the absence of a healthy tissue. The same is true for the effective volume of the tumor.

The third example dealt with the evolution of a melanoma during the avascular stage. The system comprises TC, HC, an ECM, IF and includes a stiffer basement membrane made of ECM. Two cases with different values of the stiffness of the ECM have been solved. In the

case of lower stiffness the growing TCs deform the ECM in an appreciable manner and produce a slight elevation on the skin surface. This does not happen for significantly larger stiffness of the ECM. The influence of the basement membrane is evident in both cases: in the epidermis the tumor grows almost as a semi-sphere; then, when the membrane is attained, the growth pattern changes in a more complex configuration. The discontinuities of volume fractions across the interfaces are related to the different nature of the three considered zones: epidermis, basement membrane and dermis.

Differences in the stiffness of the ECMs lead to changes in the obtained growth pattern. These differences increase significantly if the stiffness of the ECMs is further reduced. On the other hand increasing the stiffness of the ECMs in the second case does not produce great changes in the obtained growth pattern which indicates that the set of parameters used in this case leads to a solution similar to that of a rigid ECM. Experimentally severe hypoxia induces quiescence of TCs and when sustained, also necrosis; this behavior has also been successfully modeled.

It becomes clear from the investigations the importance of properly characterizing the biomechanical behavior of the malignant mass in all its components to correctly predict its temporal and spatial pattern evolution.

Acknowledgments

GS, RS and BS acknowledge partial support from the Strategic Research Project ‘Algorithms and Architectures for Computational Science and Engineering’—AACSE (STPD08JA32—2008) of the University of Padova (Italy); PD and MF acknowledge partial support from the National Institutes of Health (USA) (NIH) grants U54CA143837 and U54CA151668. MF acknowledges the Ernest Cockrell Jr Distinguished Endowed Chair.

Appendix A: Derivation of the governing mass balance equations

The macroscopic governing equations have been derived by means of TCAT in [7, 16, 20] and then specialized for a chosen set of primary variables. We show here how the appropriate forms for a different set of primary variables including differential pressures instead of saturations, useful for addressing solid deformation, have been obtained. We start from the general form of the balance equations given in [16]. The balance equations not mentioned below do not change with respect to those of [16, 20].

The mass balance equation of the solid phase:

$$\frac{\partial [\rho^s (1 - \varepsilon)]}{\partial t} + \nabla \cdot [\rho^s (1 - \varepsilon) \mathbf{v}^s] = 0 \quad (\text{A.1})$$

is expanded by use of the product rule as:

$$\frac{(1 - \varepsilon)}{\rho^s} \frac{\partial \rho^s}{\partial t} - \frac{\partial \varepsilon}{\partial t} = - \frac{(1 - \varepsilon)}{\rho^s} \mathbf{v}^s \cdot \nabla \rho^s - \nabla \cdot \mathbf{v}^s + \nabla \cdot (\varepsilon \mathbf{v}^s) \quad (\text{A.2})$$

Neglecting the spatial gradients of the density, ρ^s , because of its small impact, the time derivative of porosity reads:

$$\frac{\partial \varepsilon}{\partial t} = \nabla \cdot \mathbf{v}^s + \frac{(1-\varepsilon)}{\rho^s} \frac{\partial \rho^s}{\partial t} - \nabla \cdot (\varepsilon \mathbf{v}^s) \quad (\text{A.3})$$

Derivation of governing equation (6)

The mass balance equation of the tumor cell phase (living + death cells) is:

$$\frac{\partial (\rho^t \varepsilon^t)}{\partial t} + \nabla \cdot (\rho^t \varepsilon^t \mathbf{v}^t) = \overset{l \rightarrow t}{M} \quad (\text{A.4})$$

Expanding equation (A.4) by the use of the product rule and introducing the saturation degree of TC gives:

$$\begin{aligned} & \frac{\varepsilon S^t}{\rho^t} \frac{\partial \rho^t}{\partial t} + \varepsilon \frac{\partial S^t}{\partial t} + S^t \frac{\partial \varepsilon}{\partial t} \\ &= -\nabla \cdot (\varepsilon S^t \mathbf{v}^t) \\ & - \frac{\varepsilon S^t}{\rho^t} \mathbf{v}^t \cdot \nabla \rho^t + \frac{1}{\rho^t} \overset{l \rightarrow t}{M} \end{aligned} \quad (\text{A.5})$$

Neglecting the spatial gradients of the density, ρ^t , and introducing equation (A.3) yields:

$$\begin{aligned} & \frac{\varepsilon S^t}{\rho^t} \frac{\partial \rho^t}{\partial t} + S^t \frac{(1-\varepsilon)}{\rho^s} \frac{\partial \rho^s}{\partial t} + \varepsilon \frac{\partial S^t}{\partial t} \\ &= S^t \nabla \cdot (\varepsilon \mathbf{v}^s) - S^t (\nabla \cdot \mathbf{v}^s) \\ & - \nabla \cdot (\varepsilon S^t \mathbf{v}^t) + \frac{1}{\rho^t} \overset{l \rightarrow t}{M} \end{aligned} \quad (\text{A.6})$$

$$\begin{aligned} & \frac{\varepsilon S^t}{\rho^t} \frac{\partial \rho^t}{\partial t} + S^t \frac{(1-\varepsilon)}{\rho^s} \frac{\partial \rho^s}{\partial t} + \varepsilon \frac{\partial S^t}{\partial t} \\ &= -\nabla \cdot \left[\varepsilon S^t (\mathbf{v}^t - \mathbf{v}^s) \right] \\ & - \nabla S^t \cdot (\varepsilon \mathbf{v}^s) - S^t (\nabla \cdot \mathbf{v}^s) + \frac{1}{\rho^t} \overset{l \rightarrow t}{M} \end{aligned} \quad (\text{A.7})$$

Equation of state for the tumor phase density, ρ^t , is approximated as dependent on its pressure alone:

$$\frac{1}{\rho^t} \frac{\partial \rho^t}{\partial p^t} = \frac{1}{K_T} \quad \text{and} \quad \frac{1}{\rho^t} \frac{\partial \rho^t}{\partial t} = \frac{1}{K_T} \frac{\partial p^t}{\partial t} \quad (\text{A.8})$$

From equation (4), taking into account the functional dependence in the pressure-saturation constitutive relationships equation (20) follows:

$$\frac{\partial p^t}{\partial t} = \frac{\partial p^l}{\partial t} + \frac{\partial p^{hl}}{\partial t} + \frac{\partial p^{th}}{\partial t} \quad (\text{A.9})$$

The density of the solid phase, ρ^s , depends of the other hand on the solid pressure p^s , equation (13) which acts normally to the fluid-solid interfaces:

$$\frac{1}{\rho^s} \frac{\partial \rho^s}{\partial \left(\sum_{f=t,h,l} \langle \mathbf{n}_s \cdot \mathbf{t}_s \cdot \mathbf{n}_s \rangle_{\Omega_{fs}, \Omega_{fs}} \right)} \simeq \frac{1}{\rho^s} \frac{\partial \rho^s}{\partial p^s} = \frac{1}{K_s} \quad (\text{A.10})$$

Hence, keeping in mind the chosen primary variables (p^l , p^{hl} , and p^{th}):

$$\begin{aligned} \frac{\partial p^s}{\partial t} = & \frac{\partial p^l}{\partial t} - p^{hl} \frac{\partial S^l}{\partial p^{hl}} \frac{\partial p^{hl}}{\partial t} + \frac{\partial p^{hl}}{\partial t} - S^l \frac{\partial p^{hl}}{\partial t} \\ & + p^{th} \frac{\partial S^t}{\partial p^{th}} \frac{\partial p^{th}}{\partial t} + S^t \frac{\partial p^{th}}{\partial t} \end{aligned} \quad (\text{A.11})$$

and equation (A.7) becomes:

$$\begin{aligned} & \frac{\varepsilon S^t}{K_T} \frac{\partial p^t}{\partial t} + \frac{S^t(1-\varepsilon)}{K_S} \frac{\partial p^s}{\partial t} + \varepsilon \frac{\partial S^t}{\partial t} \\ & = -\nabla \cdot \left[\varepsilon S^t \left(\mathbf{v}^t - \mathbf{v}^s \right) \right] - \nabla S^t \cdot \left(\varepsilon \mathbf{v}^s \right) \\ & - S^t \left(\nabla \cdot \mathbf{v}^s \right) + \frac{1}{\rho^t} \overset{l \rightarrow t}{M} \end{aligned} \quad (\text{A.12})$$

Introducing equations (A.9) and (A.11) in equation (A.12) and regrouping terms give:

$$\begin{aligned} & \left[\frac{\varepsilon S^t}{K_T} + \frac{S^t(1-\varepsilon)}{K_S} \left(S^t + p^{th} \frac{\partial S^t}{\partial p^{th}} \right) + \varepsilon \frac{\partial S^t}{\partial t} \right] \frac{\partial p^{th}}{\partial t} \\ & + \left[\frac{\varepsilon S^t}{K_T} + \frac{S^t(1-\varepsilon)}{K_S} \left(1 - S^l - p^{hl} \frac{\partial S^l}{\partial p^{hl}} \right) \right] \frac{\partial p^{hl}}{\partial t} \\ & + \left[\frac{\varepsilon S^t}{K_T} + \frac{S^t(1-\varepsilon)}{K_S} \right] \frac{\partial p^l}{\partial t} \\ & = -\nabla \cdot \left[\varepsilon S^t \left(\mathbf{v}^t - \mathbf{v}^s \right) \right] - \nabla S^t \cdot \left(\varepsilon \mathbf{v}^s \right) \\ & - S^t \left(\nabla \cdot \mathbf{v}^s \right) + \frac{1}{\rho^t} \overset{l \rightarrow t}{M} \end{aligned} \quad (\text{A.13})$$

Introducing the rate of strain tensor, $\mathbf{d}^s$, $\left(\nabla \cdot \mathbf{v}^s = \mathbf{1} : \mathbf{d}^s \right)$, and using a generalized Darcy equation to compute the relative velocity $\mathbf{v}^t - \mathbf{v}^s$, give equation (6):

$$\begin{aligned}
& \left[\frac{\varepsilon S^t}{K_T} + \frac{S^t(1-\varepsilon)}{K_S} \left(S^t + p^{th} \frac{\partial S^t}{\partial p^{th}} \right) + \varepsilon \frac{\partial S^t}{\partial p^{th}} \right] \frac{\partial p_c^{th}}{\partial t} \\
& + \left[\frac{\varepsilon S^t}{K_T} + \frac{S^t(1-\varepsilon)}{K_S} \left(1 - S^l - p^{hl} \frac{\partial S^l}{\partial p^{hl}} \right) \right] \frac{\partial p^{hl}}{\partial t} \\
& + \left[\frac{\varepsilon S^t}{K_T} + \frac{S^t(1-\varepsilon)}{K_S} \right] \frac{\partial p^l}{\partial t} \\
& = \nabla \cdot \left[\frac{k_{ce}^t}{\mu^t} \mathbf{k} \cdot \nabla (p^l + p^{hl} + p^{th}) \right] \\
& - S^t \left(\mathbf{1} : \mathbf{d}^s \right) - \nabla S^t \cdot \left(\varepsilon \mathbf{v}^s \right) + \frac{1}{\rho^t} \overset{l \rightarrow t}{M}
\end{aligned} \tag{A.14}$$

Derivation of governing equation (7)

The mass balance equation of the host cell phase reads:

$$\frac{\partial (\rho^h \varepsilon^h)}{\partial t} + \nabla \cdot (\rho^h \varepsilon^h \mathbf{v}^h) = 0 \tag{A.15}$$

Expanding equation (A.15) by the use of the product rule, introducing the saturation degree of host cells gives:

$$\begin{aligned}
& \frac{\varepsilon S^h}{\rho^h} \frac{\partial \rho^h}{\partial t} + \varepsilon \frac{\partial S^h}{\partial t} + S^h \frac{\partial \varepsilon}{\partial t} \\
& = - \nabla \cdot \left(\varepsilon S^h \mathbf{v}^h \right) \\
& - \frac{\varepsilon S^h}{\rho^h} \mathbf{v}^h \cdot \nabla \rho^h
\end{aligned} \tag{A.16}$$

Introducing equation (A.3) and neglecting the spatial gradients of the density, ρ^h , yields:

$$\begin{aligned}
& \frac{\varepsilon S^h}{\rho^h} \frac{\partial p^h}{\partial t} + S^h \frac{(1-\varepsilon)}{\rho^s} \frac{\partial \rho^s}{\partial t} + \varepsilon \frac{\partial S^h}{\partial t} \\
& = - \nabla \cdot \left[\varepsilon S^h \left(\mathbf{v}^h - \mathbf{v}^s \right) \right] \\
& - \nabla S^h \cdot \left(\varepsilon \mathbf{v}^s \right) - S^h \left(\nabla \cdot \mathbf{v}^s \right)
\end{aligned} \tag{A.17}$$

With an equation of state for the host phase density, ρ^h , similar to equation (A.8), but with bulk modulus K_H , taking into account:

$$\frac{\partial p^h}{\partial t} = \frac{\partial p^t}{\partial t} + \frac{\partial p^{hl}}{\partial t} \tag{A.18}$$

and introducing equation (A.10) and equation (A.11) and using the constraint (2), equation (A.17) becomes:

$$\begin{aligned}
& \frac{\varepsilon S^h}{K_H} \left(\frac{\partial p^l}{\partial t} + \frac{\partial p^{hl}}{\partial t} \right) + \frac{S^h(1-\varepsilon)}{K_S} \\
& \times \left(\frac{\partial p^l}{\partial t} - p^{hl} \frac{\partial S^l}{\partial p^{hl}} \frac{\partial p^{hl}}{\partial t} + \frac{\partial p^{hl}}{\partial t} \right. \\
& \left. - S^l \frac{\partial p^{hl}}{\partial t} + p^{th} \frac{\partial S^t}{\partial p^{th}} \frac{\partial p^{th}}{\partial t} + S^t \frac{\partial p^{th}}{\partial t} \right) \\
& - \varepsilon \frac{\partial S^t}{\partial p^{th}} \frac{\partial p^{th}}{\partial t} - \varepsilon \frac{\partial S^l}{\partial p^{hl}} \frac{\partial p^{hl}}{\partial t} \quad (A.19) \\
& = -\nabla \cdot \left[\varepsilon S^h \left(\mathbf{v}^h - \mathbf{v}^s \right) \right] \\
& - \nabla S^h \cdot \left(\varepsilon \mathbf{v}^s \right) - S^h \left(\nabla \cdot \mathbf{v}^s \right)
\end{aligned}$$

Introducing the rate of strain tensor, $\bar{\mathbf{d}}^s$, $\left(\nabla \cdot \mathbf{v}^s = \mathbf{1} : \bar{\mathbf{d}}^s \right)$, using a generalized Darcy equation to compute the relative velocity $\mathbf{v}^h - \mathbf{v}^s$, gives equation (7):

$$\begin{aligned}
& \left[\frac{S^h(1-\varepsilon)}{K_S} \left(S^t + p^{th} \frac{\partial S^t}{\partial p^{th}} \right) - \varepsilon \frac{\partial S^t}{\partial p^{th}} \right] \frac{\partial p^{th}}{\partial S^t} \\
& + \left[\frac{\varepsilon S^h}{K_H} + \frac{S^h(1-\varepsilon)}{K_S} \left(1 - S^l - p^{hl} \frac{\partial S^l}{\partial p^{hl}} \right) \right. \\
& \left. - \varepsilon \frac{\partial S^l}{\partial p^{hl}} \right] \frac{\partial p^{hl}}{\partial S^h} \\
& + \left[\frac{\varepsilon S^h}{K_H} + \frac{S^h(1-\varepsilon)}{K_S} \right] \frac{\partial p^l}{\partial t} \quad (A.20) \\
& = \nabla \cdot \left(\frac{k_{rel}^h}{\mu^h} \cdot \nabla (p^l + p^{hl}) \right) \\
& - S^h \left(\mathbf{1} : \bar{\mathbf{d}}^s \right) - \nabla S^h \cdot \left(\varepsilon \mathbf{v}^s \right)
\end{aligned}$$

Derivation of governing equation (9)

The mass balance equation of the interstitial fluid phase:

$$\frac{\partial (\rho^l \varepsilon^l)}{\partial t} + \nabla \cdot (\rho^l \varepsilon^l \mathbf{v}^l) = - \frac{l \rightarrow t}{M} \quad (A.21)$$

becomes after introduction of the saturation degree of IF:

$$\begin{aligned}
& \frac{\varepsilon S^l}{\rho^l} \frac{\partial \rho^l}{\partial t} + \varepsilon \frac{\partial S^l}{\partial t} + S^l \frac{\partial \varepsilon}{\partial t} \\
& = -\nabla \cdot \left(\varepsilon S^l \mathbf{v}^l \right) \quad (A.22) \\
& - \frac{\varepsilon S^l}{\rho^l} \mathbf{v}^l \cdot \nabla \rho^l - \frac{1}{\rho^l} \frac{l \rightarrow t}{M}
\end{aligned}$$

Summing equation (A.22) with equations (A.5) and (A.16) gives:

$$\begin{aligned}
& \frac{\varepsilon S^t}{\rho^t} \frac{\partial \rho^t}{\partial t} + \frac{\varepsilon S^h}{\rho^h} \frac{\partial \rho^h}{\partial t} + \frac{\varepsilon S^l}{\rho^l} \frac{\partial \rho^l}{\partial t} \\
& + \varepsilon \left(\frac{\partial S^l}{\partial t} + \frac{\partial S^h}{\partial t} + \frac{\partial S^t}{\partial t} \right) \\
& + \left(S^t + S^h + S^l \right) \frac{\partial \varepsilon}{\partial t} = \\
& = -\nabla \cdot \left(\varepsilon S^l \mathbf{v}^l \right) - \frac{\varepsilon S^l}{\rho^l} \mathbf{v}^l \cdot \nabla \rho^l \\
& -\nabla \cdot \left(\varepsilon S^t \mathbf{v}^t \right) - \frac{\varepsilon S^t}{\rho^t} \mathbf{v}^t \cdot \nabla \rho^t \\
& -\nabla \cdot \left(\varepsilon S^h \mathbf{v}^h \right) - \frac{\varepsilon S^h}{\rho^h} \mathbf{v}^h \cdot \nabla \rho^h \\
& + \frac{\rho^l - \rho^t}{\rho^t \rho^l} \overset{l \rightarrow t}{M}
\end{aligned} \tag{A.23}$$

Taking into account the constraints on degrees of saturation and volume fractions, neglecting the spatial gradient of the densities and introducing equation (A.3) into equation (A.23) yields:

$$\begin{aligned}
& \frac{\varepsilon S^t}{\rho^t} \frac{\partial \rho^t}{\partial t} + \frac{\varepsilon S^h}{\rho^h} \frac{\partial \rho^h}{\partial t} + \frac{\varepsilon S^l}{\rho^l} \frac{\partial \rho^l}{\partial t} + \frac{(1-\varepsilon)}{\rho^s} \frac{\partial \rho^s}{\partial t} \\
& = -\nabla \cdot \left(\varepsilon S^l \mathbf{v}^l \right) - \nabla \cdot \left(\varepsilon S^t \mathbf{v}^t \right) \\
& -\nabla \cdot \left(\varepsilon S^h \mathbf{v}^h \right) - \nabla \cdot \left(\varepsilon \mathbf{v}^s \right) \\
& -\nabla \cdot \mathbf{v}^l + \frac{\rho^l - \rho^t}{\rho^t \rho^l} \overset{l \rightarrow t}{M}
\end{aligned} \tag{A.24}$$

Expanding $\nabla \cdot (\varepsilon \mathbf{v}^s)$ as $\nabla \cdot \left[\varepsilon (S^t + S^h + S^l) \mathbf{v}^s \right]$ gives an alternative form to equation (A.24):

$$\begin{aligned}
& \frac{\varepsilon S^t}{\rho^t} \frac{\partial \rho^t}{\partial t} + \frac{\varepsilon S^h}{\rho^h} \frac{\partial \rho^h}{\partial t} + \frac{\varepsilon S^l}{\rho^l} \frac{\partial \rho^l}{\partial t} + \frac{(1-\varepsilon)}{\rho^s} \frac{\partial \rho^s}{\partial t} \\
& = -\nabla \cdot \left[\varepsilon S^l (\mathbf{v}^l - \mathbf{v}^s) \right] \\
& -\nabla \cdot \left[\varepsilon S^t (\mathbf{v}^t - \mathbf{v}^s) \right] - \nabla \cdot \left[-\varepsilon S^h (\mathbf{v}^h - \mathbf{v}^s) \right] \\
& -\nabla \cdot \mathbf{v}^l + \frac{\rho^l - \rho^t}{\rho^t \rho^l} \overset{l \rightarrow t}{M}
\end{aligned} \tag{A.25}$$

We use an equation of state for the IF phase density, ρ^l , similar to equation (A.8), but with the bulk modulus K_L , introduce the other state equations for phase density and a generalized Darcy equation to obtain:

$$\begin{aligned}
& \frac{\varepsilon S^t}{K_T} \frac{\partial p^t}{\partial t} + \frac{\varepsilon S^h}{K_H} \frac{\partial p^h}{\partial t} + \frac{\varepsilon S^l}{K_L} \frac{\partial p^l}{\partial t} + \frac{1-\varepsilon}{K_S} \frac{\partial p^s}{\partial t} \\
& = \nabla \cdot \left[\frac{k_{rel}^t}{\mu^t} \mathbf{k} \cdot \nabla p^t \right] \\
& + \nabla \cdot \left[\frac{k_{rel}^h}{\mu^h} \mathbf{k} \cdot \nabla p^h \right] + \nabla \cdot \left[\frac{k_{rel}^l}{\mu^l} \mathbf{k} \cdot \nabla p^l \right] \\
& -\nabla \cdot \mathbf{v}^s + \frac{\rho^l - \rho^t}{\rho^t \rho^l} \overset{l \rightarrow t}{M}
\end{aligned} \tag{A.26}$$

Introducing equations (A.9), (A.11) and (A.18), rearranging to explicit the primary variables of the model, and introducing the stain rate tensor gives equation (9):

$$\begin{aligned}
 & \left[\frac{\varepsilon S^t}{K_T} + \frac{1-\varepsilon}{K_S} \left(S^t + p^{th} \frac{\partial S^t}{\partial p^{th}} \right) \right] \frac{\partial p^{th}}{\partial t} \\
 & + \left[\frac{\varepsilon S^t}{K_T} + \frac{\varepsilon S^h}{K_H} + \frac{1-\varepsilon}{K_S} \left(1 - S^l - p^{hl} \frac{\partial S^l}{\partial p^{hl}} \right) \right] \frac{\partial p^{hl}}{\partial t} \\
 & + \left(\frac{\varepsilon S^t}{K_T} + \frac{\varepsilon S^h}{K_H} + \frac{\varepsilon S^l}{K_L} + \frac{1-\varepsilon}{K_S} \right) \frac{\partial p^l}{\partial t} \\
 & = \nabla \cdot \left[\frac{k_{rel}^t \mathbf{k}}{\mu^t} \cdot \nabla p^{th} \right] \\
 & + \nabla \cdot \left[\left(\frac{k_{rel}^t \mathbf{k}}{\mu^t} + \frac{k_{rel}^h \mathbf{k}}{\mu^h} \right) \cdot \nabla p^{hl} \right] \\
 & + \nabla \cdot \left[\left(\frac{k_{rel}^t \mathbf{k}}{\mu^t} + \frac{k_{rel}^h \mathbf{k}}{\mu^h} + \frac{k_{rel}^l \mathbf{k}}{\mu^l} \right) \cdot \nabla p^l \right] \\
 & - \left(\mathbf{1} : \bar{\mathbf{d}}^s \right) + \frac{\rho^l - \rho^t}{\rho^t \rho^l} \frac{l \rightarrow t}{M}
 \end{aligned} \tag{A.27}$$

Appendix B: Numerical solution and computational procedure

The system of equations presented in the main text is solved by means of a partitioned approach within the framework of a staggered algorithm preserving the coupling nature of the multiphysics problem. The model is implemented in CAST3M (www-cast3m.cea.fr) where the mass balance equations are introduced in a slightly modified form. In further detail, we call $\bar{\mathbf{d}}_{sp}^s$ the elastic strain rate induced by the solid pressure:

$$\bar{\mathbf{d}}_{sp}^s = \frac{\bar{\alpha}}{3K} \frac{\partial p^s}{\partial t} \mathbf{1} \tag{B.1}$$

where K is the bulk modulus of the unsaturated ECM scaffold. Introduction of the rate of the solid pressure, equation (13) yields:

$$\begin{aligned}
 \mathbf{1} : \bar{\mathbf{d}}_{sp}^s &= \frac{\bar{\alpha}}{K} \left(S^t + p^{th} \frac{\partial S^t}{\partial p^{th}} \right) \frac{\partial p^{th}}{\partial t} \\
 &+ \frac{\bar{\alpha}}{K} \left(1 - S^l - p^{hl} \frac{\partial S^l}{\partial p^{hl}} \right) \frac{\partial p^{hl}}{\partial t} + \frac{\bar{\alpha}}{K} \frac{\partial p^l}{\partial t}
 \end{aligned} \tag{B.2}$$

We consider now, e.g. the mass balance equation of the tumor phase (equation (6)): by

adding and subtracting $S^t \left(\mathbf{1} : \bar{\mathbf{d}}_{sp}^s \right)$, moving the subtracted quantity to the *lhs*, and exploiting (B.2) this equation becomes:

$$\begin{aligned}
& \left[\frac{\varepsilon S^t}{K_T} + \left(\frac{S^t(1-\varepsilon)}{K_S} + \frac{S^t \alpha}{K} \right) \left(S^t + p^{th} \frac{\partial S^t}{\partial p^{th}} \right) \right. \\
& \left. + \varepsilon \frac{\partial S^t}{\partial p^{th}} \right] \frac{\partial p^{th}}{\partial t} \\
& + \left[\frac{\varepsilon S^t}{K_T} + \left(\frac{S^t(1-\varepsilon)}{K_S} + \frac{S^t \alpha}{K} \right) \right. \\
& \times \left(1 - S^l - p^{hl} \frac{\partial S^l}{\partial p^{hl}} \right) \left. \right] \frac{\partial p^{hl}}{\partial t} \\
& + \left[\frac{\varepsilon S^t}{K_T} + \frac{S^t(1-\varepsilon)}{K_S} + \frac{S^t \alpha}{K} \right] \frac{\partial p^l}{\partial t} \\
& = \nabla \cdot \left[\frac{k_{rel}^t}{\mu^t} \cdot \nabla (p^l + p^{hl} + p^{th}) \right] \\
& - S^t \left[\mathbf{1} : \left(\bar{\mathbf{d}}^s - \bar{\mathbf{d}}_{sp}^s \right) \right] \\
& - \nabla S^t \cdot \left(\varepsilon \mathbf{v}^s \right) + \frac{1}{\rho^t} \frac{d}{dt} M
\end{aligned} \tag{B.3}$$

The same is carried out for equations (7) and (9). In case of weakly compressible or incompressible phases this modified form enhances the efficiency of the adopted staggered procedure and stability of the solution as explained in [42].

The weak form of equations (6), (7), (9), (11) and (14) in their modified form as above is obtained by means of the standard Galerkin procedure and is then discretized in space by means of the finite element method [43]. The primary variables are expressed in terms of their nodal values as:

$$\begin{aligned}
p^{th}(t) & \cong \mathbf{N}_t \bar{\mathbf{P}}^{th}(t) \\
p^{hl}(t) & \cong \mathbf{N}_h \bar{\mathbf{P}}^{hl}(t) \\
p^l(t) & \cong \mathbf{N}_l \bar{\mathbf{P}}^l(t) \\
\omega^{nl}(t) & \cong \mathbf{N}_n \bar{\omega}^{nl}(t) \\
\mathbf{u}^s(t) & \cong \mathbf{N}_u \bar{\mathbf{u}}^s(t)
\end{aligned} \tag{B.4}$$

where $\bar{\omega}_i^{nl}(t)$, $\bar{\mathbf{P}}^{th}(t)$, $\bar{\mathbf{P}}^{hl}(t)$, $\bar{\mathbf{P}}^l(t)$, $\bar{\mathbf{u}}^s(t)$ are vectors of nodal values of the primary variables at time instant t , and $\mathbf{N}_n$, $\mathbf{N}_t$, $\mathbf{N}_h$, $\mathbf{N}_l$, and $\mathbf{N}_u$ are vectors/matrices of shape functions related to these variables.

Integration in the time domain is carried out by the finite difference method adopting a quasi-Crank–Nicolson scheme (θ -Wilson method with $\theta = 0.52$). Within each time step the equations are linearized by the Newton–Raphson method. For the numerical solution of the resulting system of equations, a staggered scheme is adopted with iterations within each time step to preserve the coupled nature of the system. The convergence properties of such staggered schemes have been investigated by Turska and Schrefler [44]. In particular, for the iteration convergence within each computational step a lower limit of $\Delta t/h^2$, function of the material properties, has to be observed; Δt is the time step and h the element size. The existence of this limit means that we cannot diminish the time step at will below a certain threshold without also decreasing the element size.

Three computational units are used in the staggered scheme: the first is for the nutrient mass fraction ω^{nl} , the second to compute p^{th} , p^{hl} and p^l , and the third is used to obtain the displacement vector $\mathbf{u}^s$. Within each iteration the mass fraction of NTC, ω^{Nt} , is updated using equation (10).

Taking into account the chosen staggered scheme, the final system of equations can be expressed in matrix form as follows, where some of the coupling terms have been placed in the source terms and are updated at each iteration:

$$\mathbf{C}_{ij}(\mathbf{x}) \frac{\partial \mathbf{x}}{\partial t} + \mathbf{K}_{ij}(\mathbf{x}) \mathbf{x} = \mathbf{f}_i(\mathbf{x}) \quad (\text{B.5})$$

with:

$$\begin{aligned} \mathbf{C}_{ij} &= \begin{pmatrix} \mathbf{C}_{nn} & 0 & 0 & 0 & 0 \\ 0 & \mathbf{C}_{tt} & \mathbf{C}_{th} & \mathbf{C}_{tl} & 0 \\ 0 & \mathbf{C}_{ht} & \mathbf{C}_{hh} & \mathbf{C}_{hl} & 0 \\ 0 & \mathbf{C}_{lt} & \mathbf{C}_{lh} & \mathbf{C}_{ll} & 0 \\ 0 & 0 & 0 & 0 & \mathbf{C}_{uu} \end{pmatrix} \\ \mathbf{K}_{ij} &= \begin{pmatrix} \mathbf{K}_{nn} & 0 & 0 & 0 & 0 \\ 0 & \mathbf{K}_{tt} & \mathbf{K}_{th} & \mathbf{K}_{tl} & 0 \\ 0 & \mathbf{K}_{ht} & \mathbf{K}_{hh} & \mathbf{K}_{hl} & 0 \\ 0 & \mathbf{K}_{lt} & \mathbf{K}_{lh} & \mathbf{K}_{ll} & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}, \quad (\text{B.6}) \\ \mathbf{f}_i &= \begin{pmatrix} \mathbf{f}_n \\ \mathbf{f}_t \\ \mathbf{f}_h \\ \mathbf{f}_l \\ \mathbf{f}_u \end{pmatrix} \end{aligned}$$

$$\text{where } \mathbf{x}^T = \left\{ \omega^{nl}, p^{th}, p^{hl}, p^l, \mathbf{u}^s \right\}$$

The modular computational structure allows more than one chemical species to be taken into account, simply by adding a computational unit (equivalent to the first one used for the nutrient) for each of the additional chemical species considered.

The nonlinear coefficient matrices $\mathbf{C}_{ij}(\mathbf{x})$, $\mathbf{K}_{ij}(\mathbf{x})$ and $\mathbf{f}_i(\mathbf{x})$ are given below.

$$\mathbf{C}_{nn} = \int_{\Omega} \mathbf{N}_n^T \left(\varepsilon S^l \mathbf{N}_n \right) d\Omega \quad (\text{B.7})$$

$$\mathbf{C}_{tt} = \int_{\Omega} \mathbf{N}_t^T \left[\frac{\varepsilon S^t}{K_T} \mathbf{N}_t + \left(\frac{S^t (1 - \varepsilon)}{K_S} + \frac{S^t \alpha}{K} \right) \times \left(S^t + p^{th} \frac{\partial S^t}{\partial p^{th}} \right) \mathbf{N}_t + \varepsilon \frac{\partial S^t}{\partial p^{th}} \mathbf{N}_t \right] d\Omega \quad (\text{B.8})$$

$$\mathbf{C}_{th} = \int_{\Omega} \mathbf{N}_t^T \left[\frac{\varepsilon S^t}{K_T} \mathbf{N}_h + \left(\frac{S^t(1-\varepsilon)}{K_S} + \frac{S^t \alpha}{K} \right) \left(1 - S^l - p^{hl} \frac{\partial S^l}{\partial p^{hl}} \right) \mathbf{N}_h \right] d\Omega \quad (\text{B.9})$$

$$\mathbf{C}_{tl} = \int_{\Omega} \mathbf{N}_t^T \left(\frac{\varepsilon S^t}{K_T} \mathbf{N}_l + \frac{S^t(1-\varepsilon)}{K_S} \mathbf{N}_l + \frac{S^t \alpha}{K} \mathbf{N}_l \right) d\Omega \quad (\text{B.10})$$

$$\mathbf{C}_{ht} = \int_{\Omega} \mathbf{N}_h^T \left[\left(\frac{S^h(1-\varepsilon)}{K_S} + \frac{S^h \alpha}{K} \right) \left(S^t + p^{th} \frac{\partial S^t}{\partial p^{th}} \right) \times \mathbf{N}_t - \varepsilon \frac{\partial S^t}{\partial p^{th}} \mathbf{N}_t \right] d\Omega \quad (\text{B.11})$$

$$\mathbf{C}_{hh} = \int_{\Omega} \mathbf{N}_h^T \left[\frac{\varepsilon S^h}{K_H} \mathbf{N}_h + \left(\frac{S^h(1-\varepsilon)}{K_S} + \frac{S^h \alpha}{K} \right) \times \left(1 - S^l - p^{hl} \frac{\partial S^l}{\partial p^{hl}} \right) \mathbf{N}_h - \varepsilon \frac{\partial S^l}{\partial p^{hl}} \mathbf{N}_h \right] d\Omega \quad (\text{B.12})$$

$$\mathbf{C}_{hl} = \int_{\Omega} \mathbf{N}_h^T \left(\frac{\varepsilon S^h}{K_H} \mathbf{N}_l + \frac{S^h(1-\varepsilon)}{K_S} \mathbf{N}_l + \frac{S^h \alpha}{K} \mathbf{N}_l \right) d\Omega \quad (\text{B.13})$$

$$\mathbf{C}_{lt} = \int_{\Omega} \mathbf{N}_l^T \left[\frac{\varepsilon S^t}{K_T} \mathbf{N}_t + \left(\frac{1-\varepsilon}{K_S} + \frac{\alpha}{K} \right) \left(S^t + p^{th} \frac{\partial S^t}{\partial p^{th}} \right) \mathbf{N}_t \right] d\Omega \quad (\text{B.14})$$

$$\mathbf{C}_{lh} = \int_{\Omega} \mathbf{N}_l^T \left[\frac{\varepsilon S^t}{K_T} \mathbf{N}_h + \frac{\varepsilon S^h}{K_H} \mathbf{N}_h + \left(\frac{1-\varepsilon}{K_S} + \frac{\alpha}{K} \right) \left(1 - S^l - p^{hl} \frac{\partial S^l}{\partial p^{hl}} \right) \mathbf{N}_h \right] d\Omega \quad (\text{B.15})$$

$$\mathbf{C}_{ll} = \int_{\Omega} \mathbf{N}_l^T \left(\frac{\varepsilon S^t}{K_T} \mathbf{N}_l + \frac{\varepsilon S^h}{K_H} \mathbf{N}_l + \frac{\varepsilon S^l}{K_L} \mathbf{N}_l + \frac{1-\varepsilon}{K_S} \mathbf{N}_l + \frac{\alpha}{K} \mathbf{N}_l \right) d\Omega \quad (\text{B.16})$$

$$(\mathbf{C}_{uu})_{ij} = - \int_{\Omega} \mathbf{B}^T \mathbf{D}_s \mathbf{B} d\Omega \quad (\text{B.17})$$

$$\mathbf{K}_{nn} = \int_{\Omega} (\nabla \mathbf{N}_n)^T \left(\varepsilon S^l D_{eff}^{nl} \nabla \mathbf{N}_n \right) d\Omega \quad (\text{B.18})$$

$$\mathbf{K}_{tt} = \int_{\Omega} (\nabla \mathbf{N}_t)^T \left(\frac{k_{rel}^t \mathbf{k}}{\mu^t} \nabla \mathbf{N}_t \right) d\Omega \quad (\text{B.19})$$

$$\mathbf{K}_{th} = \int_{\Omega} (\nabla \mathbf{N}_t)^T \left(\frac{k_{rel}^t \mathbf{k}}{\mu^t} \nabla \mathbf{N}_h \right) d\Omega \quad (\text{B.20})$$

$$\mathbf{K}_{tl} = \int_{\Omega} (\nabla \mathbf{N}_t)^T \left(\frac{k_{rel}^t \mathbf{k}}{\mu^t} \nabla \mathbf{N}_l \right) d\Omega \quad (\text{B.21})$$

$$\mathbf{K}_{ht} = 0 \quad (\text{B.22})$$

$$\mathbf{K}_{hh} = \int_{\Omega} (\nabla \mathbf{N}_h)^T \left(\frac{k_{rel}^h \mathbf{k}}{\mu^h} \nabla \mathbf{N}_h \right) d\Omega \quad (\text{B.23})$$

$$\mathbf{K}_{hl} = \int_{\Omega} (\nabla \mathbf{N}_h)^T \left(\frac{k_{rel}^h \mathbf{k}}{\mu^h} \nabla \mathbf{N}_l \right) d\Omega \quad (\text{B.24})$$

$$\mathbf{K}_{lt} = \int_{\Omega} (\nabla \mathbf{N}_l)^T \left(\frac{k_{rel}^t \mathbf{k}}{\mu^t} \nabla \mathbf{N}_t \right) d\Omega \quad (\text{B.25})$$

$$\mathbf{K}_{lh} = \int_{\Omega} (\nabla \mathbf{N}_l)^T \left(\frac{k_{rel}^t \mathbf{k}}{\mu^t} \nabla \mathbf{N}_h + \frac{k_{rel}^h \mathbf{k}}{\mu^h} \nabla \mathbf{N}_h \right) d\Omega \quad (\text{B.26})$$

$$\mathbf{K}_{ll} = \int_{\Omega} (\nabla \mathbf{N}_l)^T \left(\frac{k_{rel}^t \mathbf{k}}{\mu^t} \nabla \mathbf{N}_l + \frac{k_{rel}^h \mathbf{k}}{\mu^h} \nabla \mathbf{N}_l + \frac{k_{rel}^l \mathbf{k}}{\mu^l} \nabla \mathbf{N}_l \right) d\Omega \quad (\text{B.27})$$

$$\mathbf{f}_n = \int_{\Omega} \mathbf{N}_n^T \left(\frac{1}{\rho} \left(\omega^{\bar{n}l} \overset{l \rightarrow t}{M} - \overset{n \rightarrow t}{M} \right) - \varepsilon S^l \mathbf{v}^{\bar{l}} \cdot \nabla \omega^{\bar{n}l} \right) d\Omega \quad (\text{B.28})$$

$$\mathbf{f}_t = \int_{\Omega} \mathbf{N}_t^T \left\{ \frac{1}{\rho^t} \overset{l \rightarrow t}{M} - S^t \left[\mathbf{1} : \left(\bar{\mathbf{d}}^{\bar{s}} - \bar{\mathbf{d}}_{sp}^{\bar{s}} \right) \right] - \nabla S^t \cdot \left(\varepsilon \mathbf{v}^{\bar{s}} \right) \right\} d\Omega \quad (\text{B.29})$$

$$\mathbf{f}_h = \int_{\Omega} \mathbf{N}_h^T \left[-S^h \left[\mathbf{1} : \left(\bar{\mathbf{d}}^{\bar{s}} - \bar{\mathbf{d}}_{sp}^{\bar{s}} \right) \right] - \nabla S^h \cdot \left(\varepsilon \mathbf{v}^{\bar{s}} \right) \right] d\Omega \quad (\text{B.30})$$

$$\mathbf{f}_l = \int_{\Omega} \mathbf{N}_l^T \left[-\mathbf{1} : \left(\bar{\mathbf{d}}^{\bar{s}} - \bar{\mathbf{d}}_{sp}^{\bar{s}} \right) + \frac{\rho^l - \rho^t}{\rho^t \rho^l} \overset{l \rightarrow t}{M} \right] d\Omega \quad (\text{B.31})$$

$$\mathbf{f}_u = \int_{\Omega} \mathbf{B}^T \left(\mathbf{D}_s \bar{\mathbf{d}}_{\nu p}^{\bar{s}} \right) d\Omega + \int_{\Omega} \mathbf{B}^T \left(\mathbf{D}_s \bar{\mathbf{d}}_{sp}^{\bar{s}} \right) d\Omega \quad (\text{B.32})$$

Nomenclature

Roman letters

a	coefficient in the pressure-saturations relationship
C_{ij}	non linear coefficient of the discretized capacity matrix
$\bar{d}^\alpha$	rate of strain tensor
$\bar{D}_{eff}^{il}$	effective diffusion coefficient for the species i dissolved in the phase l
D_s	tangent matrix of the solid skeleton
$\bar{e}^s$	total strain tensor
$\bar{e}_{el}^s$	elastic strain tensor
$\bar{e}_{vp}^s$	visco-plastic strain tensor
f_v	discretized source term associated to the primary variable v
K_{ij}	non linear coefficient of the discretized conduction matrix
K_I	compressibility of the phase I ($I = S, T, H$ and L)
k	intrinsic permeability tensor of the ECM
k_{rel}^α	relative permeability of the phase α
N_v	vector of shape functions related to the primary variable v
p^α	pressure in the phase α
p^{ij}	pressure difference between fluid phases i and j
R^α	resistance tensor
S^α	saturation degree of the phase α
$\bar{t}_{eff}^s$	effective stress tensor of the solid phase s
$\bar{t}^s$	total stress tensor of the solid phase s
$\bar{t}_{eff,y}^s$	yield limit of the solid phase which defines the boundary of elastic domain
u^s	displacement vector of the solid phase s
$\bar{v}^\alpha$	velocity vector of the phase α
x	solution vector
Greek letters	
$\bar{\alpha}$	Biot's coefficient

γ_{growth}^t	growth coefficient
$\gamma_{necrosis}^t$	necrosis coefficient
$\overline{\gamma_{growth}^{nl}}$	nutrient consumption coefficient related to growth
$\overline{\gamma_0^{nl}}$	nutrient consumption coefficient not related to growth
ε	porosity
ε^a	volume fraction of the phase a
η	viscosity parameter of the solid phase
μ^a	dynamic viscosity of the phase a
ρ^a	density of the phase a
σ_{ij}	interfacial tension between fluid phases i and j
ψ^a	adhesion of the phase a
ω^{Nt}	mass fraction of necrotic cells in the tumor cells phase
$\overline{\omega^{nl}}$	nutrient mass fraction in the interstitial fluid
$\overline{\omega_{crit}^{nl}}$	critical nutrient mass fraction for growth
$\overline{\omega_{env}^{nl}}$	reference nutrient mass fraction in the environment
TCAT symbols	
$k_{\rightarrow\alpha}$	inter-phase mass transfer
M	
$\varepsilon_{\tau}^{\alpha,i\alpha}$	reaction term, i.e. intra-phase mass transfer
$k_{\rightarrow\alpha}$	inter-phase momentum transfer
T	
Subscripts and superscripts	
crit	critical value for growth
h	host cell phase
l	interstitial fluid
n	nutrient
s	solid
t	tumor cell phase
a	phase indicator with $a = t, h, l$ or s

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Figure 1.
Flow chart of the modeling process.

Figure 2.
Comparison between model results (solid line) and experimental data (circles) of Chignola *et al* [33].

Figure 3.
Geometry and boundary conditions for an MTS in a decellularized ECM.

Figure 4.

Results at the final stage of the analysis for the case with deformable ECM: (a) radial displacements field; (b) equivalent viscoplastic strain; (c) porosity distribution (porosity increases in the region occupied by the tumor).

Figure 5.

Volume fraction of (a) TCs; (b) IFP; and (c) mass fraction of oxygen at different times along the radius of the spheroid. (d) Radius of the MTS versus time. In the panel's figures the dashed lines refer to the case with deformable ECM while solid lines refer to the case with rigid ECM.

Figure 6. (a) Geometry and boundary conditions for an MTS in a host tissue. Results: (b) radius of the MTS versus time; (c) volume fraction of TCs; and (d) IFP at different times along the radius of the spheroid.

Figure 7.
Skin structure and geometry of the modeled case.

Figure 8.
Finite element mesh and boundary conditions.

Figure 9.
Volume fractions of TCs at one and two weeks for (a) case 1, and (b) case 2.

Figure 10.
Mass fraction of oxygen after two weeks for case 1.

Figure 11.
Volume fractions of LTCs at one and two weeks for (a) case 1, and (b) case 2.

Figure 12.
Volume fractions of HCs at two weeks for case 1 (right), and case 2 (left).

Figure 13. Paraffin-embedded tissue sections of (a) a melanocytic lesion [41] (*b.m.* is for basement membrane). (b) Numerical results (volume fraction of TCs) after two weeks of growth.

Table 1Input parameters used to simulate the experiment of Chignola *et al* [33].

Parameter	Symbol	Value	Unit
Young's modulus of ECM	E	500	Pa
Poisson's ratio of ECM	ν	0.4	—
Intrinsic permeability of ECM	k	$1.8 \cdot 10^{-15}$	m^2
Coefficient a in equation (20)	a	532	Pa
Density of phases ($\alpha = s, t$ and l)	ρ^α	1000	kg m^{-3}
Dynamic viscosity of IF equations (8)–(9)	μ^l	$1 \cdot 10^{-3}$	Pa·sec
Dynamic viscosity of TC equation (22)	μ_0^t	36	Pa·sec
Adhesion of TC in equation (22)	ψ^t	$1 \cdot 10^{-6}$	Pa m^{-1}
Critical mass fraction of oxygen [16, 20]	ω_{crit}^{nl}	$3.0 \cdot 10^{-6}$	—
Growth coefficient of tumor cells [16, 20]	γ_{growth}^t	$1.4 \cdot 10^{-2}$	$\text{kg}/(\text{m}^3 \cdot \text{s})$
Critical pressure for cell growth [20]	p_{crit}^t	1330	Pa
Necrosis coefficient [16, 20]	$\gamma_{necrosis}^t$	$1.6 \cdot 10^{-2}$	$\text{kg}/(\text{m}^3 \cdot \text{s})$
Cells pressure above which necrosis increases [20]	p_{necr}^t	930	Pa
Pressure dependent additional necrosis [20]	δ_a^t	$5 \cdot 10^{-4}$	—
Consumption related to growth [16, 20]	γ_{growth}^{nl}	$4 \cdot 10^{-4}$	$\text{kg}/(\text{m}^3 \cdot \text{s})$
Consumption related to metabolism [16, 20]	γ_0^{nl}	$6 \cdot 10^4$	$\text{kg}/(\text{m}^3 \cdot \text{s})$
TC-IF interfacial tension (equation (20))	σ_{tl}	72	mNm^{-1}
Diffusion coefficient of oxygen in interstitial fluid [16, 20]	D_0^{nl}	$3.2 \cdot 10^{-9}$	$\text{m}^2 \text{sec}^{-1}$
Normal mass fraction of oxygen in tissue [16, 20]	ω_{env}^{nl}	$7 \cdot 10^{-6}$	—

Table 2

Initial conditions.

Zone	p^l [Pa]	S^h [-]	S^l [-]	ω^{ml} [-]
Red zone (up to 30 μm)	0.0	0.0	0.022	$4.2 \cdot 10^{-6}$
Blue zone (up to 1000 μm)	0.0	0.0	0.0	$4.2 \cdot 10^{-6}$

Table 3

Parameters depending on cells' type and IF.

Parameter	Symbol	Value	Unit
Density of the three fluid phases ($a = h, t$ and l)	ρ^a	1000	kg m ⁻³
Dynamic viscosity of IF equations (8)–(9)	μ^l	$1 \cdot 10^{-2}$	Pa·sec
Dynamic viscosity of TC equation (22)	μ_0^t	20	Pa·sec
Dynamic viscosity of HC equation (22)	μ_0^h	20	Pa·sec
Adhesion of TC in equation (22)	ψ^t	0	Pa m ⁻¹
Adhesion of HC in equation (22)	ψ^h	0	Pa m ⁻¹
Critical mass fraction of oxygen [16, 20]	ω_{crit}^{nl}	$1.0 \cdot 10^{-6}$	—
Growth coefficient of tumor cells [16, 20]	γ_{growth}^t	$4 \cdot 10^{-2}$	kg/(m ³ · s)
Necrosis coefficient [16, 20]	$\gamma_{necrosis}^t$	$1 \cdot 10^{-2}$	kg/(m ³ · s)
Consumption related to growth [16, 20]	γ_{growth}^{nl}	$2 \cdot 10^{-4}$	kg/(m ³ · s)
Consumption related to metabolism [16, 20]	γ_0^{nl}	$3 \cdot 10^{-4}$	kg/(m ³ · s)
HC-IF interfacial tension (equation (20))	σ_{hl}	72	mN m ⁻¹
TC-HC interfacial tension (equation (20))	σ_{th}	36	mN m ⁻¹
TC-IF interfacial tension	σ_{tl}	108	mN m ⁻¹

Table 4

Parameters related to oxygen diffusion.

Parameter	Symbol	Value	Unit
Diffusion coefficient of oxygen in interstitial fluid [16, 20]	D_0^{nl}	$3.2 \cdot 10^{-9}$	$\text{m}^2 \text{sec}^{-1}$
Coefficient δ [16, 20]	δ	2	—
Normal mass fraction of oxygen in tissue [16, 20]	ω_{env}^{nl}	$4.2 \cdot 10^{-6}$	—

Table 5

Parameters depending on ECM type.

Parameter	Symbol	Value	Unit
Density of the solid phase	ρ^s	$1 \cdot 10^3$	kg m^{-3}
Poisson's ratio of the ECM	ν	0.4	—
Young's modulus of the ECM	E	$2 \cdot 10^2$	Pa
Volume fraction of ECM (initial)	ε^s	0.2	—
Coefficient a in equation (20)	a	590	Pa
Intrinsic permeability	k	$1.8 \cdot 10^{-15}$	m^2
Yield effective stress limit	$t_{\text{eff},y}^s$	$0.5 \cdot 10^1$	Pa
Viscosity	η	5	$\text{Pa} \cdot \text{sec}$
Hardening modulus	H	$1.0 \cdot 10^2$	Pa

Table 6

Parameters depending on ECM type.

Parameter	Symbol	Case 1	Case 2	Unit
Density of the solid phase	ρ^s	1000		kg m ⁻³
Poisson' ratio of the ECM	ν	0.4		—
Young's modulus of the ECM	E_{EZ}	$2 \cdot 10^2$	$2 \cdot 10^3$	Pa
	E_{MZ}	$3 \cdot 10^2$	$3 \cdot 10^3$	
	E_{DZ}	$1 \cdot 10^2$	$1 \cdot 10^3$	
	e_{EZ}^s	0.2		
Volume fraction of ECM	e_{MZ}^s	0.3		—
(initail)	e_{DZ}^s	0.1		—
Coefficient a in equation (20)	a_{EZ}	590		Pa
	a_{MZ}	516		
	a_{DZ}	664		
	k_{EZ}	$1.80 \cdot 10^{-15}$		
Intrinsic permeability	k_{MZ}	$1.21 \cdot 10^{-15}$		m ²
	k_{DZ}	$2.56 \cdot 10^{-15}$		

Table 7

Initial conditions.

Zone	p^l [Pa]	p^{hl} [Pa]	p^{th} [Pa]	S^h [-]	S^t [-]	ω^{nt} [-]
Initial tumor zone (epidermis)	0.0	719	59	0.435	0.125	$4.2 \cdot 10^{-6}$
Epidermal zone (EZ)	0.0	719	0.0	0.560	0.0	$4.2 \cdot 10^{-6}$
Membrane zone (MZ)	0.0	719	0.0	0.600	0.0	$4.2 \cdot 10^{-6}$
Dermal zone (DZ)	0.0	719	0.0	0.520	0.0	$4.2 \cdot 10^{-6}$