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Tumor Growth Modeling from the Perspective of Multiphase Porous Media Mechanics

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Abstract: Multiphase porous media mechanics is used for modeling tumor growth, using governing equations obtained via the Thermodynamically Constrained Averaging Theory (TCAT). This approach incorporates the interaction of more phases than legacy tumor growth models. The tumor is treated as a multiphase system composed of an extracellular matrix, tumor cells which may become necrotic depending on nutrient level and pressure, healthy cells and an interstitial fluid which transports nutrients. The governing equations are numerically solved within a Finite Element framework for predicting the growth rate of the tumor mass, and of its individual components, as a function of the initial tumor-to-healthy cell ratio, nutrient concentration, and mechanical strain. Preliminary results are shown.

Keywords: TCAT, porous media mechanics, tumor growth, necrosis, Finite Elements.

Nomenclature

Roman letters

b	exponent in the pressure-saturations relationship
c^g	nutrient concentration in liquid (kg/m^3)
c^g_{crit}	critical nutrient concentration in liquid for growth
c^g_{env}	reference nutrient concentration in the environment
$D^{\overline{gl}}_{eff}$	effective diffusion coefficient
H	Heaviside step function

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$\mathbf{k}^{\alpha s}$	absolute permeability tensor of the phase α
k_{rel}^{α}	relative permeability
$\overset{l\to t}{M}_{growth}$	rate of growth term due to transfer of mass from fluid to tumor
$\overset{gl\to t}{M}$	nutrient consumption rate from liquid to tumor
p^{α}	pressure in the phase α
$\varepsilon^t r^{Nt}$	reaction term in the tumor cells phase: generation of necrotic cells
S^{α}	saturation degree of the phaseα
$\mathbf{t}_{eff}^{s}$	effective stress in the solid
$\mathbf{v}^{\alpha}$	velocity of the phaseα

Greek letters

a_{α}	adhesion
γ_{growth}^{t}	growth coefficient
$\gamma_{necrosis}^{t}$	necrosis coefficient
γ^{g}	nutrient consumption
ε	porosity
ε^{α}	volume fraction of the phase α
μ^{α}	dynamic viscosityof the phase α
ρ^{α}	density of the phase α
σ_c	coefficient in the pressure-saturations relationship
$\omega^{N\bar{t}}$	mass fraction of necrotic cells in the tumor cells phase

Subscripts and superscripts

crit	critical value for growth
g	nutrient
h	host cell phase
l	interstitial fluid
necr	critical value for the effect of pressure on the cell death rate
s	solid
t	tumor cell phase
α	phase indicator with α=*t,h,l,* or *s*

1 Introduction

Every year around 12 million new cases of cancer are diagnosed worldwide. With a continuously aging world population, a surge in cancer incidence is anticipated. Clearly treatment optimization is critical for improving the prognosis and quality of

life, and for minimizing the economic impact. Patient-specific, multiscale computational models can help in predicting tumor proliferation and response to different therapeutic regimens, and thus would offer an ideal prognostic tool. Our aim is to advance in this direction.

We focus on solid tumors which can be considered as a multiphase system comprising different, interrelated compartments with specific biological and biomechanical properties. These would include a tumor region, composed of necrotic and/or quickly dividing neoplastic living cells; a healthy tissue region; an extracellular compartment for the tumor and for the healthy tissue; a fluid compartment, which permeates the extracellular matrix; and a vascular compartment. These phases are closely connected in space, over multiple scales.

Different computational models for predicting tumor initiation and proliferation have been proposed in recent years; see for excellent overviews: Araujo and McElwain (2009), Quaranta et al. (2005), Roose et al. (2007), Zaman (2007) and Lowengrub et al. (2010). Three main approaches can be identified: i) discrete, single cell models; ii) continuum models; and iii) hybrid models. Discrete models are mostly based on cellular automata, generally limited to a small number of tumor cells. Therefore they can only capture the early initiation and growth of malignancy. Further, subdomains are not representative of the whole domain (Perfahl et al., 2011). Differently, continuous models describe the interacting fields by means of differential equations and can be effective in analyzing the long term development of larger tumor masses. Finally, hybrid models combine elements of both approaches and, to be effective, require a combination of 'mature' models of the discrete and continuum types. We limit ourselves to continuum models.

A novel mathematical approach is proposed based on the Thermodynamically Constrained Averaging Theory (TCAT). This is a framework recently established for the analysis of continuum and porous media, which is consistent over multiple scales. TCAT (Gray and Miller, 2005, and Gray et al., 2012) provides a rigorous yet flexible method for developing multiphase, continuum models at any scale of interest. Many natural and engineered systems are characteristically multiphase, meaning that two or more fluid and solid phases occupy a shared domain. More recently, biological tissues also have been treated as continuum, multiphase systems.

We describe avascular tumor growth with TCAT and solve the resulting balance equations numerically with the Finite Element Method. There are four coupled mass balance equations and a linear (negligible advective nonlinearity) momentum balance equation to be solved simultaneously; the chosen staggered scheme conserves the coupled nature of the problem. The presentation of the model is followed by results of modeling tumor growth of spheroids and a tumor cord and the development of necrotic regions due to nutrient deficiency and/or to the pressure

excess.

2 Materials and Methods

2.1 The physical Model

The tumor model here refers to the avascular stage where the tumor has not yet developed its own vasculature. The model consists of four phases: one solid and three fluids. The cells maintain tissue integrity by cell to cell contact, and the extracellular matrix (ECM) acts as a scaffold to give the tissue more structure and rigidity. The ECM components of a tissue will be treated as a single solid phase (s). The three fluid phases are the host tissue (h) composed of healthy cells, the tumor tissue able to proliferate (t) composed of living and death tumor cells, and the interstitial fluid (l) which carries dissolved nutrient to the cells and provides a medium for intercellular signaling molecules to travel between cells. The interstitial fluid is very different from blood, composed primarily of water and is assumed to be incompressible. The necrotic areas develop because the tumor receives its nutrition via diffusion from the outside, and once the tumor is larger than the diffusion distance (about 100 μm) necrosis occurs beyond this distance from the outer rim or the vessel wall.

2.2 The Mathematical Model

When modeling flow and transport in systems involving more than one phase, one must consider the desired length scale in order to derive the relevant conservation equations. The smallest scale at which the continuum hypothesis holds is called the microscale or pore scale. At the microscale, a single (continuum) point contains a large number of cells and/or molecules such that properties such as density, temperature, and pressure of a phase are all defined. At the microscale the well-known, classical conservation equations and thermodynamic expressions are written. However, the domains of interest are too large for the system to be modeled at the microscale. Alternatively, multiphase domains may be too complex to resolve certain variables (frequently velocities) at the microscale across the entire domain. Thus, many porous media models are formulated at a larger scale, called the macroscale. The Thermodynamically Constrained Averaging Theory uses averaging theorems to formally and consistently convert microscale equations to the macroscale. These averaging theorems convert averages of microscale derivatives into derivatives of macroscale averages and share some features of the well-known transport and divergence theorems. The development of the balance equations is a rather lengthy procedure and the reader is referred to Shelton (2011) and Sciumè et al (2012) for a detailed discussion and the statement of the constitutive forms. The governing

and constitutive equations of the model are given in the Appendix. The numerical solution of the model and the computational strategy are discussed next.

2.3 The numerical model

The weak form of the governing equations is obtained by applying the standard Galerkin procedure. The equations are then discretized in space by means of the finite element method (Lewis and Schrefler, 1998). Integration in the time domain is carried out with the generalized mid-point rule where an implicit procedure is used. Within each time step the equations are linearized by means of the Newton-Raphson method. The primary variables chosen are the saturation degree of the tumor cells phase S^t, the saturation degree of the host cells phase S^h, the interstitial fluid pressure p^l, the ECM velocity $\mathbf{v^s}$ and the mass concentration of nutrient in the interstitial fluid phase c^g.

For the solution of the equations a staggered scheme is adopted with iterations within each time step to preserve the coupled nature of the system. The convergence of such staggered schemes has been documented by Turska et al., (1994). In particular for the iteration convergence within each time step, a lower limit of $\Delta t/h^2$ has to be observed. A similar limit is also met in the numerical solution of Poisson type equations (Murthy et al., 1989). Both situations apply here.

Three computational units are used in the staggered scheme as shown in Figure 1: the first is for the nutrient mass concentration c^g; the second to compute S^t, S^h and p^l; and the third to obtain the solid velocity vector. Once convergence is achieved within a time step the procedure can march forward.

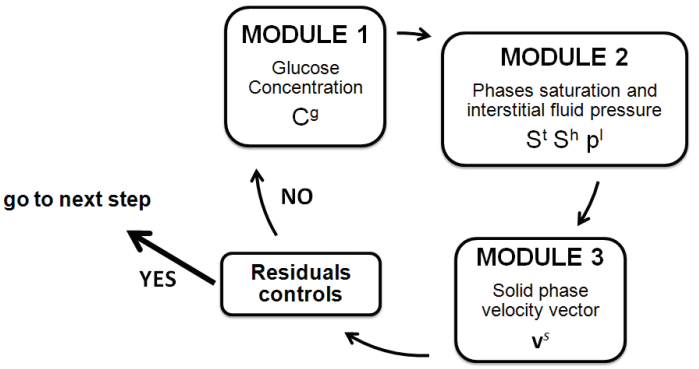


Figure 1: Solution strategy implemented in Cast3M

Note that there is a striking analogy between this model and the three fluids model

of concrete at high temperature (Gawin et al., 2002) and concrete at early ages (Gawin et al., 2006). In all three cases we have one solid phase and three fluid phases together with reactions and mass exchanges. The procedure has hence been implemented in the code CAST3M (http://www-cast3m.cea.fr) of the French Atomic Energy Commission taking advantage of the fact that recently the first author had implemented in the same code our model for young concrete (Gawinet al., 2006) and previously the procedure for concrete at high temperature had also been implemented there (Dal Pont et al., 2007).

3 Results

We focus on tumor growth, its validation with experimental results and on necrosis due to nutrient deficiency and/or to the pressure excess. As the predominant nutrient we use glucose. These are preliminary results, and we consider a rigid extracellular matrix.

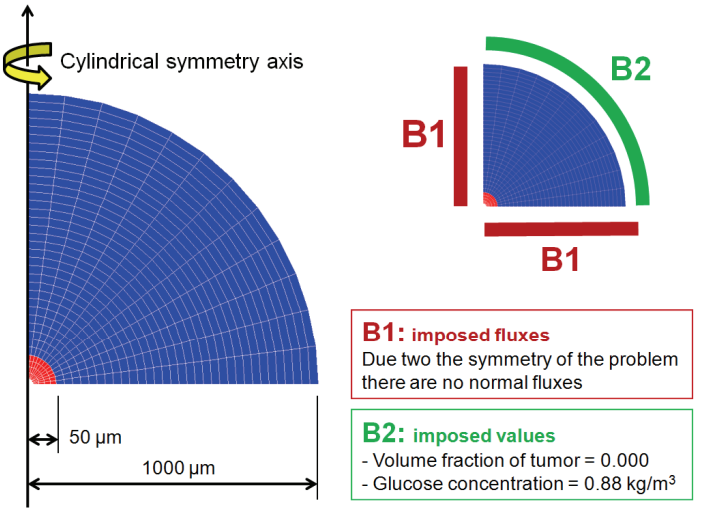
First we investigate the growth of a tumor spheroid *in vitro*, where only tumor cells in a rigid ECM are considered. During the growth of the spheroid the cells consume nutrient due to their metabolism. Therefore when the spheroid increases its radius, gradients in concentration of nutrient develop from the periphery to the center of the spheroid. A decrease of nutrients at the center causes necrosis to start once the nutrient concentration is below a critical value. The glucose deficiency is here the main indicator of cells necrosis.

For simplicity consider a quarter sphere with cylindrical symmetry. The geometry as well as the initial and boundary conditions are shown in Figure 2. The reference pressure is the atmospheric one. The parameters used for the numerical simulation are summarized in Table 1.

Table 1: Solution strategy implemented in Cast3M

PARAMETER	SYMBOL	VALUE	UNIT
Volume fraction of ECM	ε^s	0,1	
Density of the phases	ρ^α	1000	Kg/m^3
Diffusion coefficient of glucose	D_g	5.0e-10	m^2/s
Permeability for the tumor cells' phase	k^{ts}	1.0e-19	m^2
Adhesion of tumor cells	a_t	2.e6	Pa/m
Coeff. γ_{growth} for the growth function	γ_{growth}	1.00	Kg/(m^3* sec)
Critical value of glucose concentration	c^g_{crit}	0,86	Kg/m^3

The numerical results are compared in Figure 3 with those obtained in different in vitro experiments (Yuhas et al.,1977, Chignola et al., 1995, Chignola et al., 2000).



Initial conditions	ε^s	ε^t	ε^h	p^l	c^g
Red zone	0.10	0.05	0.00	0.00	0.880
Blu zone	0.10	0.00	0.00	0.00	0.880

Figure 2: Geometry of the finite element mesh (left), initial conditions and boundary conditions (right)

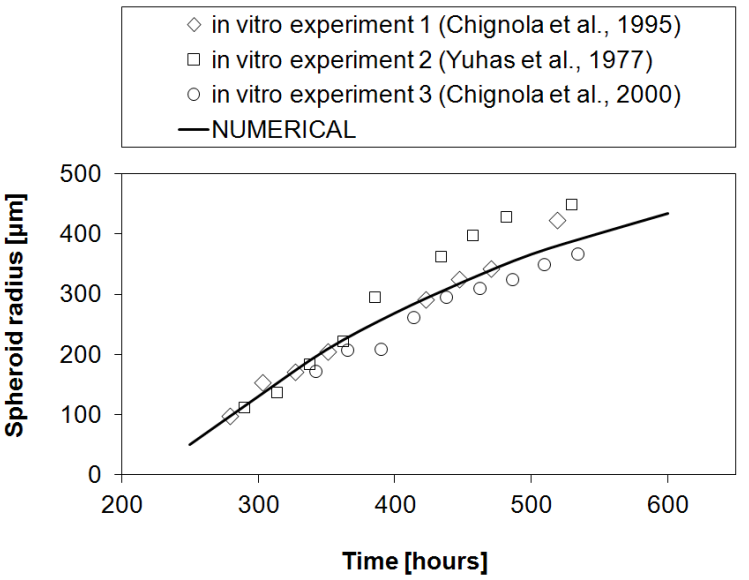


Figure 3: Numerical result compared with different in vitro experiments (symbols)

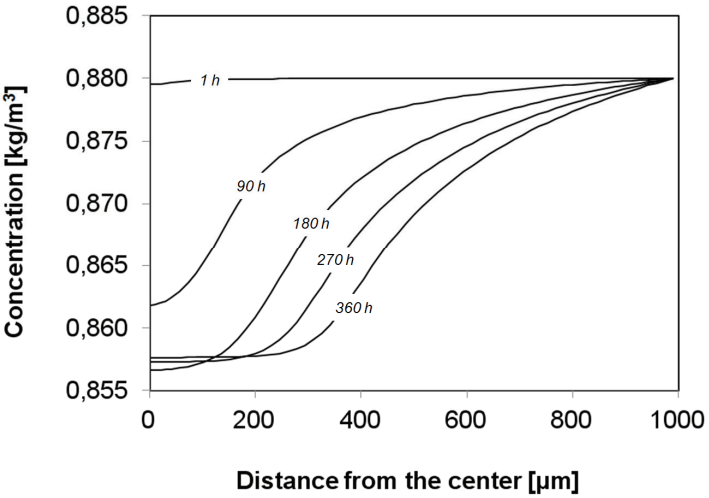


Figure 4: Glucose concentration during 360 hours

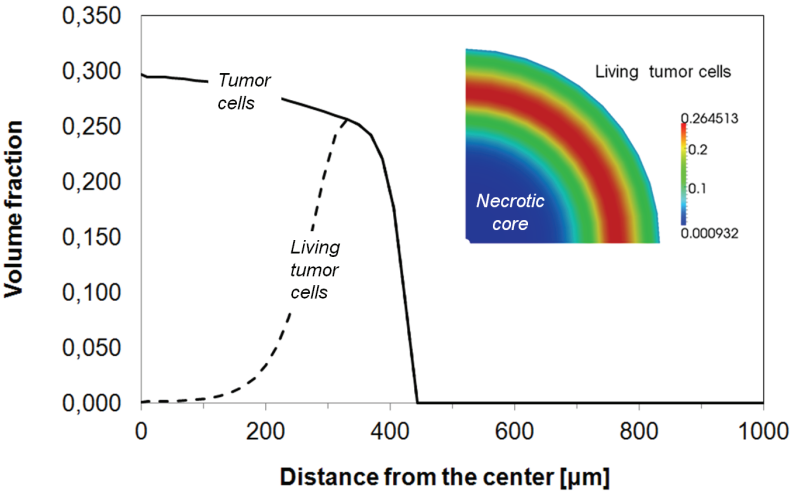


Figure 5: Necrotic and living tumor cells at 360 hours

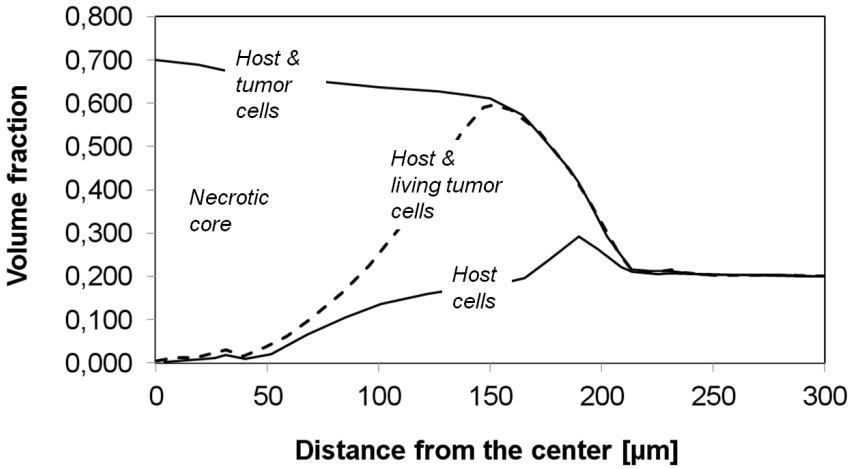


Figure 6: Volume fractions of the cell populations after 240 hours

Figure 4 shows that the glucose concentration decreases at the center due to its consumption. Note its progressive slight later increase due to gradient driven continued diffusion to the center.

Figure 5 shows the volume fractions of the tumor cells and of the living tumor cells at 360 hours. The difference between the continuous line and the dashed line is the volume fraction of the dead tumor cells (i.e. the necrotic core of the spheroid).

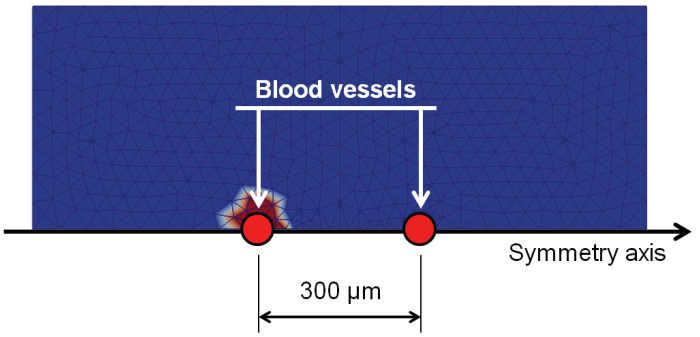
The second example is similar to the previous one, but in this case the population of host cells is also considered.

The tumor is surrounded by the cells comprising the host tissue. Consequently, for the spheroid to increase its radius, it has to push against the host cells or invade the host tissue that occupies most of the ECM free space. The nutrient supply is more difficult due to the presence of the host cells that reduce the effective diffusivity. The geometry, the initial conditions and the boundary conditions are analogous to the previous example; but in this case in the blue zone of Figure 2 the host cell phase is present with a volume fraction equal to 0.2. The adhesion of the host cells a_h is assumed equal to that of the tumor cells a_t. In Figure 6 the volume fractions of the host cell phase, of the host cell phase plus that of the tumor cell phase and of the host cell phase plus that of the living tumor cell phase are plotted. Figure 6 shows the interaction between the two cell populations: the tumor spheroid due to its growth pushes the host cell population and partly invades its space. In this case both cell populations have the same adhesion. If the adhesion of the host cells is lower , the growing tumor cells completely displace the host cells, while

with higher adhesion the invasion in the host cell space is more important. This is analyzed in more detail in Sciumè et al. (2012). Similar to Figure 5 the difference between the continuous line "host & tumor cells" and the dashed line is the volume fraction of the dead tumor cells.

Next case we simulate the growth of a tumor in the direct vicinity of the capillary blood vessels. The region near the blood vessel is favorable for tumor growth because the blood delivers nutrients to tumor cells. Therefore, in this case the tumor develops along the vessels and, in contrast to the first two cases, necrosis doesnot occur on the center of the tumor, but in the zones distant from the vessels.

Consider two capillary vessels with the tumor only on the left vessel as shown in Figure 7. The distance between the two vessels is 300 μm.



Initial conditions	ε^s	ε^t	ε^h	p^l	c^g
Red zone	0.20	0.05	0.00	0.00	0.880
Blu zone	0.20	0.00	0.00	0.00	0.880

Figure 7: Geometry and initial conditions of the third case

Only the tumor cell population and a rigid ECM are considered. A constant value of the glucose concentration c^g = 0.880 kg/m^3, is imposed at the surface of the capillary vessels. The boundary conditions for the third case are reported in Figure 8.

The example shows how a tumor can develop from vessel to vessel due to vascularization of the organ tissue (see Figure 9).

A 3-D solution of this case depicts the development of the tumor along the vessels as shown in Figure 10. This typical configuration is called a *tumor cord*.

Figure 11 shows the decrease of the glucose concentration in the extracellular

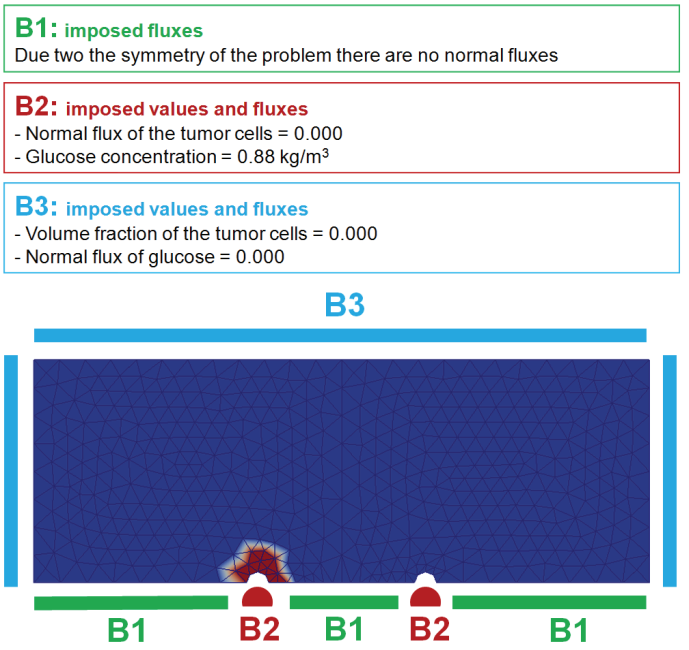


Figure 8: Boundary conditions of the third case

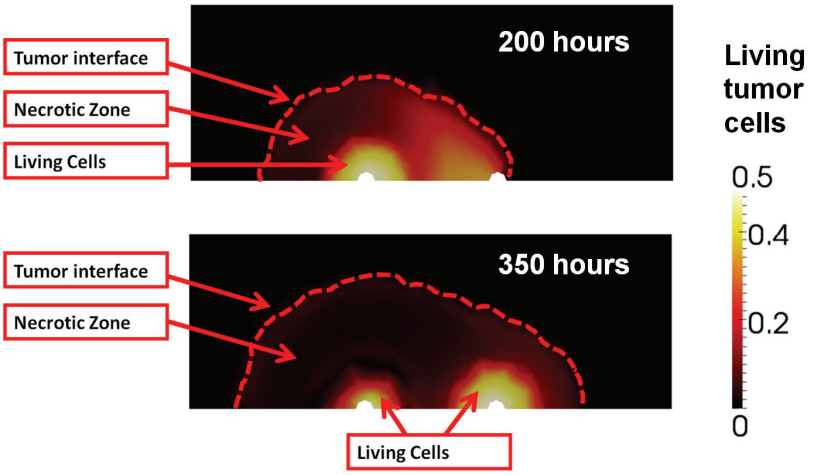


Figure 9: 2-D solution: living tumor cells at 200 hours and 350 hours.

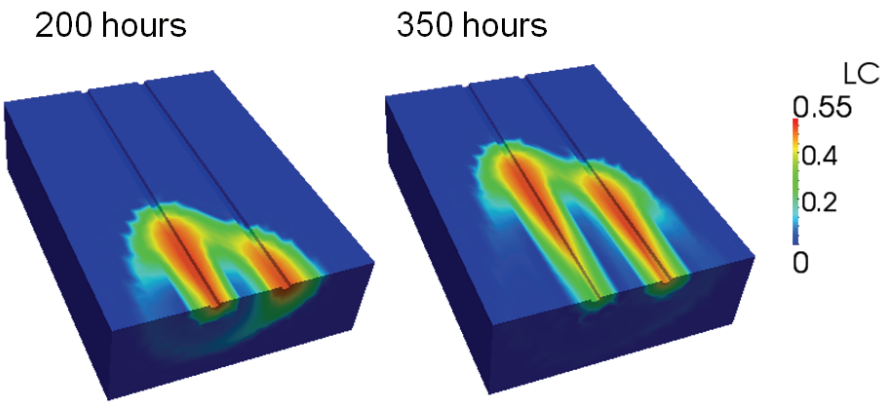


Figure 10: 3-D solution: living tumor cells at 200 hours and 350 hours.

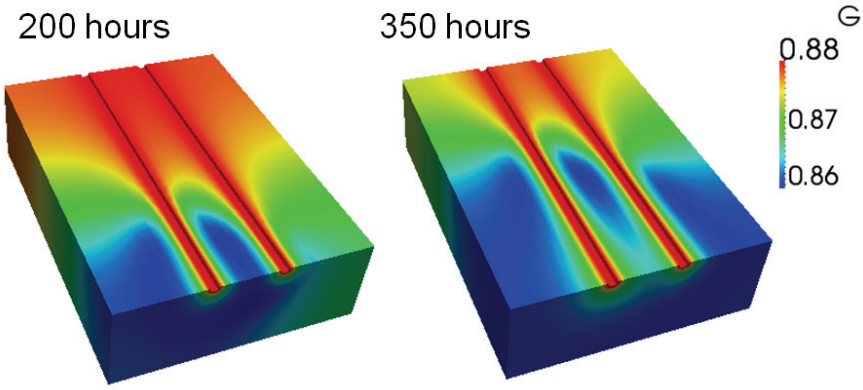


Figure 11: 3-D solution: glucose concentration at 200 hours and 350 hours.

spaces caused by the presence of the tumor. Note that sustained diffusion partly replenishes the nutrient level in the necrotic region because of lack of consumption (see Figure 11, at 350 hours, between the two cords). Note the left-right asymmetry.

4 Discussion

A tumor growth model based on multiphase porous media mechanics is presented. The governing differential equations have been obtained by means of the Thermodynamically Constrained Averaging Theory. These are mass balance equations for each phase, ageneralization of Darcy's law for the interstitial liquid and cell populations, and closure relations that allow for adhesion of the cell phases. The nutrient transport mass balance equation is a Fickian form. The solid deformation can consider an elasto-viscoplastic behavior.

We have modeled the growth behavior of a spheroid in vitro within a rigid ECM. The growth curve compares well with experiments and is compatible with Gompertzian growth pattern in exponents (Casey, 1934). Nutrient deficiency at the center of the growing spheroid causes the onset of necrosis and a typical ring of viable tumor cells is obtained as observed in experiments (Mueller-Klieser, 1986). The rate of growth function plays an important role in matching experimental data. This deserves further attention. In these preliminary calculations, we have used glucose as the prevalent nutrient. The role of other nutrients such as oxygen will be investigated because its deficiency seems to be more critical in triggering necrosis. Also, the role of products of metabolism such as ATP and lactate needs study. The introduction of a host cell population in the previous example has shown that the growing tumor mass invades and/or displaces the host cell population. The important factor hereis the adhesion of the respective cell populations. Also this aspect will be investigated further.

The modeling of the deformation of the ECM requires realistic boundary conditions which must consider a higher scale (megascopic level) than that at which the tumor is modeled (macroscopic level). This means that also the organ where the tumor grows has to be taken into account. This aspect is under investigation.

The case of the tumor cord shows how availability of a nutrient source, in this case a second blood vessel, attracts growing tumor cell population. Also the importance of three-dimensional modeling is recognized: only such allows the investigation of realistic in vivo situations. Clearly in this case also the host cell phase should be included. Its presence slows down the growth of the tumor as will be shown in Sciumé et al. (2012).

As far as the numerical aspects are concerned, the importance of the above mentioned lower limit of $\Delta t/h^2$ has to be assessed in more detail. Here the assessment

has been carried out with numerical experiments.

5 Conclusions

We have modeled tumor growth in an ECM in the absence or presence of a host cell population. The model equations are based on a TCAT formulation that ensures consistency of the model dynamics and thermodynamics across length scales. The nutrient is transported by the interstitial fluid which also yields the water needed for cell growth. The availability of nutrient influences the growth pattern, while its deficiency causes the development of a region of necrotic cells. Also the role of the pressure on cell death is included in the model. The results and the comparison with experimental data show that the adoption of multiphase porous media mechanics is an appropriate tool for effective modeling of the complicated evolution of a tumor and the development of a necrotic phase. The numerical model will now be extensively validated with in vitro experiments and then applied to patient specific cases. Glioblastom a multiforme (GBM) will be considered as a reference tumor for the in vitro experiments and model validation, calibration and refinement. The preliminary results are promising towards the development of patient-specific, multiscale computational models to predict tumor proliferation and response to therapeutic regimens.

Appendix: Balance and Constitutive Equations

The multiphase model of a cancer tumor requires conservation and constitutive equations appropriate for each phase and accounting for interphase processes. Elements of those equations are provided here.

The ECM (s) is treated as a porous solid with a volume fraction $\varepsilon^s = 1 - \varepsilon$, where ε is the porosity. The rest of the volume is occupied by the three fluid phases: the tumor cells (ε^t); the healthy cells (ε^h); and the interstitial fluid (ε^l). The volume fractions for all phases sum to 1

$$\varepsilon^s + \varepsilon^h + \varepsilon^t + \varepsilon^l = 1 \tag{1}$$

From the definition of porosity and volume fractions the saturation degrees of the three fluid phases can be defined as: $S^\alpha = \varepsilon^\alpha / \varepsilon$. For sake of simplicity we assume that the densities of the phases are constant and equal (close to that of water):

$$\rho^s = \rho^h = \rho^t = \rho^l = \rho = const \tag{2}$$

The primary variables chosen are the saturation degree of the tumor cells phase S^t, the saturation degree of the host cells phase S^h, the interstitial fluid pressure p^l,

the ECM velocity $\mathbf{v^s}$ and the mass concentration of nutrient in the interstitial fluid phase c^g.

The mass balance equations of the solid is

$$\frac{\partial\left(1-\varepsilon\right)}{\partial t}+\nabla\cdot\left[\left(1-\varepsilon\right)\mathbf{v}^s\right]=0 \tag{3}$$

where $\mathbf{v}^s$ is the solid phase velocity.

The mass balance equations of the tumor cell phase (t), the host cell phase (h) and interstitial fluid (l) are respectively

$$\frac{\partial\left(\varepsilon S^t\right)}{\partial t}+\nabla\cdot\left(\varepsilon S^t\mathbf{v}^s\right)-\nabla\cdot\left(\frac{k^t_{rel}\mathbf{k}^{ts}}{\mu^t}\nabla p^t\right)=\frac{1}{\rho}\overset{l\rightarrow t}{\underset{growth}{M}} \tag{4}$$

$$\frac{\partial\left(\varepsilon S^h\right)}{\partial t}+\nabla\cdot\left(\varepsilon S^h\mathbf{v}^s\right)-\nabla\cdot\left(\frac{k^h_{rel}\mathbf{k}^{hs}}{\mu^h}\nabla p^h\right)=0 \tag{5}$$

$$\frac{\partial\left(\varepsilon S^l\right)}{\partial t}+\nabla\cdot\left(\varepsilon S^l\mathbf{v}^s\right)-\nabla\cdot\left(\frac{k^l_{rel}\mathbf{k}^{ls}}{\mu^l}\nabla p^l\right)=-\frac{1}{\rho}\overset{l\rightarrow t}{\underset{growth}{M}} \tag{6}$$

where μ^α is the dynamic viscosity, k^α_{rel} is the relative permeability which takes care of the presence of the other two fluid phases (Sciumè et al., 2012), $\mathbf{k}^{\alpha s}$ is the absolute permeability, p^α is the pressure and ρ is the common density. The intrinsic permeability tensor $\mathbf{k}^{ls}$ of the interstitial fluid phase is constant and isotropic. Experimental evidence confirms that cells would stay in contact with the ECM if the mechanical pressure gradients exerted over the cell phase are smaller than a critical value (Baumgartner et al. 2000, Shiang et al. 2010). For this reason, for the healthy and tumor cells the intrinsic permeability tensors (i.e. $\mathbf{k}^{hs}$ and $\mathbf{k}^{ts}$) are isotropic but not constant, and are computed using the following equation

$$\mathbf{k}^{\alpha s}=\max\left(\tilde{\mathbf{k}}^{\alpha s}\left\langle 1-\frac{a_\alpha}{|\nabla p^\alpha|}\right\rangle_+,\frac{\tilde{\mathbf{k}}^{\alpha s}}{100}\right)\quad(\alpha=h,t) \tag{7}$$

where a_α is the adhesion. This represents the fact that if cells adhere firmly to the ECM, the phase permeability within the ECM is reduced. The minimum value of the permeability (set equal to $\tilde{\mathbf{k}}^{\alpha s}/100$) eliminates the indeterminacy in the case $|\nabla p^\alpha|<a_\alpha$, contained in the approach of Preziosi and Tosin (2009).

$\overset{l\rightarrow t}{\underset{growth}{M}}$ is the rate of growth term adapted from Preziosi and Tosin (2009)

$$\overset{l\rightarrow t}{\underset{growth}{M}}=\left[\gamma_{growth}\left\langle\frac{c^g}{c^g_{crit}}-1\right\rangle_+H\left(p^t_{crit}-p^t\right)\right]\left(1-\omega^{N\bar{t}}\right)\varepsilon S^t \tag{8}$$

where the coefficient γ_{growth} takes into account both the effect of the nutrient uptake and of the consumption of water needed for cell growth; c^g_{crit} is the critical value of the nutrient concentration below which cell growth is inhibited. $\langle\rangle_+$ indicates the positive value of the argument of the Macaulay brackets, and H is the Heaviside function; p^t_{crit} is the critical pressure value above which there is no growth. $\omega^{N\bar{t}} = \frac{\varepsilon^{N\bar{t}}\rho^{N\bar{t}}}{\varepsilon^t\rho^t}$ is the mass fraction of necrotic cells in the tumor cells phase (t).

Assuming that: i) there is no diffusion of either necrotic or living cells; ii) there is no exchange of necrotic cells with other phases; the mass conservation equation for the necrotic portion of the tumor cells phase reads

$$\frac{\partial\left(\varepsilon^t\rho\,\omega^{N\bar{t}}\right)}{\partial t}+\nabla\cdot\left(\varepsilon^t\rho\,\omega^{N\bar{t}}\mathbf{v}^{\bar{t}}\right)-\varepsilon^t r^{Nt}=0 \tag{9}$$

in which $\varepsilon^t r^{Nt}$ is the rate of generation of necrotic cellsand $\mathbf{v}^{\bar{t}}$ is the velocity of the tumor cells phase. The previous hypothesis i) allows taking into account necrosis without the introduction of an additional primary variable, but simply considering $\omega^{N\bar{t}}$ as an internal variable of the model given by

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

Eqn (10) is obtained expanding eqn (9) by use of the product rule, and substituting in it the mass balance equation of the tumor cells phase. The rate of generation of necrotic cells is given by

$$\varepsilon^t r^{N^t}=-\left[\gamma^t_{necrosis}\left\langle\frac{c^g}{c^g_{crit}}-1\right\rangle_- -\delta^t_a H(p^t-p^t_{necr})\right](1-\omega^{N\bar{t}})\varepsilon S^t \tag{11}$$

where $\gamma^t_{necrosis}$ is the rate of cell death, $\langle\rangle_-$ is the negative part of the argument of the Macaulay brackets, p^t_{necr} is the pressure above which the tumor stress has effect on the cell death rate, and δ_a is the additional necrosis induced by a pressure excess.

The mass balance equation of the nutrient species in the interstitial fluid is

$$\frac{\partial\left(\varepsilon S^l c^g\right)}{\partial t}-\nabla\cdot\left(\varepsilon S^l D^{\overline{gl}}_{eff}\nabla c^g\right)=-\overset{gl\to t}{M} \tag{12}$$

where $D^{\overline{nl}}_{eff}$ is the effective diffusion coefficient depending on the available pore space, (Sciumè et al., 2012) and $\overset{gl\to t}{M}$ is the nutrient consumption rate. $\overset{gl\to t}{M}$ depends on the local nutrient availability (i.e. c^g) and is given as

$$\overset{gl\to t}{M}=\gamma^g\left(\frac{c^g}{c^g_{env}}\right)(1-\omega^{N\bar{t}})\varepsilon S^t \tag{13}$$

where γ^g is the maximum consumption of nutrient, c^g is the local mass concentration of nutrient (primary variable of the model) and c^g_{env} is a constant value and represents the environmental mass concentration of nutrient (in the vitro medium for a test *in vitro*, or in the blood plasma for a case *in vivo*).

A pressure difference is considered between the interstitial fluid phase and the two cells phases to preserve the immiscibility of the multi-phase system. The pressure in the tumor cells phase and in the host cells phase is given by the following constitutive equation

$$p^t = p^h = p^l + \sigma_c \tan\left[\frac{\pi}{2}\left(S^t + S^h\right)^b\right] \tag{14}$$

where σ_c and b are constants. The cells pressure essentially depends on the available pore space.

Finally the linear momentum balance equation of the solid phase in rate form reads as

$$\nabla \cdot \left(\frac{\partial \mathbf{t}^s_{eff}}{\partial t} - \frac{\partial p^s}{\partial t}\mathbf{1}\right) = 0 \tag{15}$$

where $\mathbf{t}^s_{eff}$ is the effective stress tensor in the solid and $\mathbf{1}$ is the unit tensor. The interaction between solid and the fluids, inclusive of the cell populations, has been accounted for through the effective stress principle (Gray and Schrefler, 2007).

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