Initial/boundary-value problems of tumor growth within a host tissue

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Abstract This paper concerns multiphase models of tumor growth in interaction with a surrounding tissue, taking into account also the interplay with diffusible nutrients feeding the cells. Models specialize in nonlinear systems of possibly degenerate parabolic equations, which include phenomenological terms related to specific cell functions. The paper discusses general modeling guidelines for such terms, as well as for initial and boundary conditions, aiming at both biological consistency and mathematical robustness of the resulting problems. Particularly, it addresses some qualitative properties such as a priori non-negativity, boundedness, and uniqueness of the solutions. Existence of the solutions is studied in the one-dimensional time-independent case.

Keywords Multiphase models · Nonlinear (degenerate) diffusion · A priori estimates

Mathematics Subject Classification (2000) 35B45 · 35Q92 · 92B05

During the preparation of this work, the author was funded by a post-doctoral research scholarship “Compagnia di San Paolo” awarded by the National Institute for Advanced Mathematics “F. Severi” (INdAM, Italy).

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1 Mixture-theory equations for tumor growth

1.1 Mixture-theory-based models

The interest toward mathematical modeling of tumor growth rose considerably in the last decades, to such an extent that it has now become one of the most studied topics in mathematical biology. Early mathematical models (Byrne 2003; Byrne and Chaplain 1995, 1996) considered tumors as ensembles of only one type of cells. Growth was described under the main assumption of constant cell density, by relating the volume variation of the tumor mass to birth and death of cells triggered by nutrient supply. In most cases simple in vitro geometries were considered, such as spheroids, and qualitative analyses of the resulting free boundary problems were detailed (Bueno et al. 2005, 2008; Chen and Friedman 2003; Cui and Friedman 2001; Friedman 2009; Friedman and Hu 2007; Friedman and Reitich 1999).

However, the biological literature pointed out soon that tumors should be regarded more properly as ensembles of different interacting components, e.g., normal and abnormal cells, intercellular fluid, extracellular matrix. This aspect is taken into account by modeling tumors as multiphase materials by methods of mixture theory, see for instance (Byrne and Preziosi 2003). In mixture theory one introduces a few volume ratios \( \phi_\alpha \), where the index \( \alpha \) labels the components of the mixture, expressing the percent amount of the constituents. Each volume ratio is supposed to satisfy \( 0 \leq \phi_\alpha \leq 1 \), with a possible further condition \( \sum_\alpha \phi_\alpha = 1 \), called saturation constraint, if one assumes that no voids are left within the mixture. Mass balance equations are written for the constituents under the assumption of same density:

\[
\frac{\partial \phi_\alpha}{\partial t} + \nabla \cdot (\phi_\alpha \mathbf{v}_\alpha) = \Gamma_\alpha,
\]  

(1)

where \( \mathbf{v}_\alpha \) and \( \Gamma_\alpha \) are the velocity and the source/sink term of the constituent \( \alpha \), respectively.

A first class of multiphase models is obtained from Eq. 1 via suitable closure relations relating the velocities to the volume ratios of the constituents (Ambrosi and Preziosi 2002). A very common assumption is that all cell populations share the same velocity, while non-cellular components have their own. Then geometrical considerations, for instance some symmetries, may determine kinematically the velocities of some constituents, as it happens in Bertuzzi et al. (2005a) where the cylindrical symmetry of tumor cords developing along a blood vessel is used to deduce the velocity of the cells. The model presented in that paper combines ideas coming from mixture theory with free boundary issues. Particularly, it includes dynamical constraints on the nutrient distribution across the tumor mass for modeling the formation of an outer necrotic shell of dead cells at the periphery of the tumor cord.

A second class of multiphase models is obtained by joining to Eq. 1 some stress balance equations for the constituents of the mixture, in which inertial effects are neglected:

\[
- \nabla \cdot (\phi_\alpha \mathbf{T}_\alpha) + \phi_\alpha \nabla p = \mathbf{m}_\alpha.
\]  

(2)
Here $T_\alpha$, $m_\alpha$ are the excess stress tensor and the resultant of the external actions on the constituent $\alpha$, respectively, whereas $p$ is the intercellular fluid pressure. Equation 2 is used to derive the velocities $v_\alpha$ from mechanical arguments on the internal and external stress sustained by the constituents. For instance, assuming that the external actions $m_\alpha$ can be expressed as viscous frictions, thus involving only the relative velocity of pairs of constituents, one gets (possibly generalized) Darcy’s laws that can be plugged into Eq. 1. Considering in particular a sub-mixture of two cell populations, namely tumor cells labeled with $\alpha = T$ and healthy host cells labeled with $\alpha = H$, which share the same mechanical properties, and assuming that the extracellular matrix only acts as a rigid non-remodeling scaffold providing them with a support for their movement, the following equations are obtained (Preziosi and Tosin 2009):

$$\frac{\partial \phi_\alpha}{\partial t} - \nabla \cdot \left[ \phi_\alpha^2 K_{\alpha m} \nabla (\phi \Sigma(\phi)) \right] = \Gamma_\alpha,$$

where $\phi := \phi_T + \phi_H$ is the overall volume ratio of the cellular matter, $\Sigma = \Sigma(\phi)$ is the intercellular stress, such that

$$T_T = T_H = -\Sigma(\phi)I,$$

and finally $K_{\alpha m}$ is the motility tensor of the cell population $\alpha$ within the extracellular matrix.

The source/sink terms $\Gamma_\alpha$ model proliferation or death of cells, taking into account both natural processes linked to the vital cell cycle and the availability of nutrient. Hence they depend on the cell volume ratios $\phi_T$, $\phi_H$ and on the nutrient concentration $c$, which entails $\Gamma_\alpha = \Gamma_\alpha(\phi_T, \phi_H, c)$. This introduces the new variable $c$, for which an evolution equation, usually of reaction-diffusion type, is supplied:

$$\frac{\partial c}{\partial t} - \nabla \cdot (D \nabla c) = \sum_{\alpha = T, H} Q_\alpha(\phi_\alpha, c),$$

where $D$ is the diffusivity tensor and $Q_\alpha$ models the absorption of nutrient by the cells of the population $\alpha$. The tensor $D$ may be taken independent of $c$, and also of the cell volume ratios $\phi_\alpha$, because nutrient molecules are not regarded as a part of the mixture, i.e., they are assumed to diffuse through the mixture without occupying space. Equation 5 features then a linear diffusion. In addition, the functions $Q_\alpha$ are sometimes linear in $c$, hence Eq. 5 turns out to be, in most cases, a linear model for the nutrient concentration. However, the simultaneous dependence of the functions $\Gamma_\alpha$, $Q_\alpha$ on both $\phi_\alpha$, $c$ makes Eqs. 3, 5 ultimately coupled.

Technical simplifications in Eqs. 3, 5 may involve the assumption of homogeneous isotropic motility of the cells in the extracellular matrix, as well as homogeneous isotropic diffusion of the nutrient through the mixture. These imply $K_{\alpha m} = \kappa_{\alpha m}I$ in Eq. 3 and $D = D_{I}$ in Eq. 5, for positive constants $\kappa_{\alpha m}$, $D$. In addition, invoking the hypothesis of same mechanical properties for tumor and host cells, one may set $\kappa_{Tm} = \kappa_{Hm} =: \kappa_m > 0$, which, as pointed out in Preziosi and Tosin (2009), is a
good approximation at least in the initial stages of the development of a tumor, when contact inhibition among cells is more influential than differences in their motility.

1.2 Cell segregation

An interesting case is when tumor and host cells remain segregated, i.e., the spatial domain \( \Omega \subseteq \mathbb{R}^d \) of the problem can be split at each time in two (open) sub-domains \( \Omega_T(t), \Omega_H(t) \) such that \( \Omega_T(t) \cup \Omega_H(t) = \Omega \) and \( \Omega_T(t) \cap \Omega_H(t) = \emptyset \) (Fig. 1). In practice, each sub-domain contains a mixture of extracellular fluid, extracellular matrix, and just one type of cells obeying the following balance equation:

\[
\frac{\partial \phi_\alpha}{\partial t} - \kappa_m \nabla \cdot [\phi_\alpha \nabla (\phi_\alpha \Sigma(\phi_\alpha))] = \Gamma_\alpha(\phi_\alpha, c), \tag{6}
\]

each volume ratio \( \phi_\alpha \) being defined only in the corresponding domain \( \Omega_\alpha \). Equation 6 is derived from Eq. 3 noticing that \( \phi \equiv \phi_\alpha \) in \( \Omega_\alpha \) owing to segregation. The two mixtures interact at the interface \( S(t) := \partial \Omega_T(t) \cap \partial \Omega_H(t) \) separating the sub-domains, hence each \( \phi_\alpha \) solves in principle a free boundary problem because \( S(t) \) is not fixed. However, it is possible to supplement Eq. 6 with proper conditions on \( S(t) \) so as to reformulate it globally in \( \Omega \). Proceeding in a formal fashion, we integrate Eq. 6 on \( \Omega_\alpha(t) \) up to a certain final time \( T_{\text{max}} > 0 \), then we apply Gauss’ Theorem to the divergence term at the left-hand side and sum over \( \alpha \) to discover:

\[
\sum_{\alpha=T, H} \left( \int_0^{T_{\text{max}}} \int_{\Omega_\alpha(t)} \frac{\partial \phi_\alpha}{\partial t} \, dx \, dt - \kappa_m \int_0^{T_{\text{max}}} \int_{\partial \Omega_\alpha(t) \setminus S(t)} \phi_\alpha \nabla (\phi_\alpha \Sigma(\phi_\alpha)) \cdot \mathbf{n} \, d\sigma \, dt \right)
\]

\[
+ \kappa_m \int_0^{T_{\text{max}}} \int_{S(t)} [\phi_T \nabla (\phi_T \Sigma(\phi_T)) - \phi_H \nabla (\phi_H \Sigma(\phi_H))] \cdot \mathbf{n} \, d\sigma \, dt
\]

\[
= \sum_{\alpha=T, H} \int_0^{T_{\text{max}}} \int_{\Omega_\alpha(t)} \Gamma_\alpha(\phi_\alpha, c) \, dx \, dt,
\]
where $d\sigma$ is the $(d-1)$-dimensional Hausdorff measure in $\mathbb{R}^d$ and $n$ is the outward normal unit vector to the boundary on which integration is performed. In particular, along $S(t)$ it denotes the outward normal unit vector to $\Omega_H(t)$, so that the analogous vector for $\Omega_T(t)$ is $-n$ (but, of course, the opposite convention may also be adopted).

Next we reintroduce the function $\phi : [0, T_{\text{max}}] \times \Omega \rightarrow \mathbb{R}$:

$$\phi(t, x) = \begin{cases} \phi_T(t, x) & \text{if } x \in \Omega_T(t) \\ \phi_H(t, x) & \text{if } x \in \Omega_H(t) \end{cases}, \quad t \in [0, T_{\text{max}}],$$

and use $\bigcup_\alpha \Omega_\alpha(t) = \Omega, \bigcup_\alpha \partial \Omega_\alpha(t) \setminus S(t) = \partial \Omega$ to obtain

$$\begin{align*}
&\int_0^{T_{\text{max}}} \int_\Omega \frac{\partial \phi}{\partial t} \, dx \, dt - \kappa_m \int_0^{T_{\text{max}}} \int_{\partial \Omega} \phi \nabla (\phi \Sigma(\phi)) \cdot n \, d\sigma \, dt \\
&+ \kappa_m \int_0^{T_{\text{max}}} \int_{S(t)} \left[ \phi \nabla (\phi \Sigma(\phi)) \right] \cdot n \, d\sigma \, dt = \int_0^{T_{\text{max}}} \int_{\Omega} \Gamma(t, x, \phi, c) \, dx \, dt, \quad (7)
\end{align*}$$

where we have defined

$$\Gamma(t, x, \phi, c) := \sum_{\alpha = T, H} \Gamma_\alpha(\phi_\alpha, c) \mathbb{1}_{\Omega_\alpha(t)}(x). \quad (8)$$

In formulas 7, 8, $[\cdot]$ denotes jump across $S(t)$ whereas $\mathbb{1}_{\Omega_\alpha(t)}$ is the indicator function of the set $\Omega_\alpha(t)$. If we reapply Gauss’ Theorem to the second term at the left-hand side, we can regard Eq. 7 as the integral version of the differential equation

$$\frac{\partial \phi}{\partial t} - \kappa_m \nabla \cdot [\phi \nabla (\phi \Sigma(\phi))] = \Gamma(t, x, \phi, c) \quad (9)$$

provided $\kappa_m \left[ \phi \nabla (\phi \Sigma(\phi)) \right] \cdot n = 0$ on $S(t)$ at each time. With this condition, Eq. 9 is equivalent to Eq. 6 on either sub-domain $\Omega_\alpha(t)$, being at the same time posed globally in $\Omega$. We will come back later (cf. Sect. 3.2) to the significance of such an interface condition from the modeling viewpoint.

By comparing Eq. 9 with the standard mass balance equation of continuum mechanics we infer that the velocity $v$ of the cellular matter is

$$v = -\kappa_m \nabla (\phi \Sigma(\phi)). \quad (10)$$

Furthermore, by defining

$$\Phi'(s) := s(s \Sigma(s))' \quad (11)$$
we notice that Eq. 9 can be rewritten in the form of nonlinear diffusion:

$$\frac{\partial \phi}{\partial t} - \kappa_m \Delta \Phi(\phi) = \Gamma(t, x, \phi, c).$$

(12)

Conversely, Eq. 5 is naturally defined on the whole $\Omega$: segregation is for cells, not for nutrient. Nevertheless, coherently with the segregation assumption, we redefine the right-hand side as

$$Q(t, x, \phi, c) := \sum_{\alpha=I, H} Q_\alpha(\phi, c) \mathbb{I}_{\Omega_\alpha(t)}(x)$$

and write

$$\frac{\partial c}{\partial t} - D \Delta c = Q(t, x, \phi, c).$$

(13)

1.3 Aims and scope

This paper is concerned with mathematical models of tumor growth of the kind outlined above, with a twofold goal. On the one hand, to discuss biologically consistent modeling lines for the phenomenological terms of the equations (namely, the functions $\Sigma$, $\Gamma$, and $Q$), as well as suitable boundary, interface, and initial conditions. On the other hand, to obtain qualitative results, such as a priori non-negativity, boundedness, and uniqueness of the solution, along with continuous dependence estimates, which support modeling with mathematical rigor. For this reason, the paper is ideally divided in two parts.

The first part, encompassing Sects. 2, 3, is especially devoted to modeling. Particularly, Sect. 2 surveys the most popular models proposed in the literature for $\Sigma$, $\Gamma$, and $Q$. Inspired by them, it fixes some modeling assumptions which will be used throughout the subsequent sections. Section 3 discusses boundary, interface, and initial conditions needed to formulate mathematical problems, with special emphasis on the use of the former for simulating the surrounding environment e.g., a nearby vasculature.

The second part, encompassing Sects. 4–6, is targeted at analytical issues. Specifically, Sect. 4 is a preliminary technical one, introducing the main notations and recalling the essential theoretical background. Subsequently, Sects. 5, 6 approach the time-dependent and time-independent problems, respectively, establishing a priori estimates on their solutions. Existence of solutions is also explicitly addressed in the one-dimensional stationary case.

Finally, Sect. 7 sketches some research perspectives on recent multiphase models of tumor growth incorporating explicitly the attachment/detachment of cells to/from the extracellular matrix.

The paper is equipped with two Appendices, which contribute to make it as self-contained as possible. Appendix A concerns the handling of the nonlinearities in the equations of the models. Appendix B further extends the theory to other kinds of
boundary conditions, partly different from those discussed in Sect. 3, relevant for applications.

2 Constitutive assumptions

2.1 The cell stress function

The function $\Sigma$ expresses the internal stress to each cell population. As already mentioned, the Cauchy excess stress tensors are given by $T_T = T_H = -\Sigma(\phi)I$, hence $\Sigma$ acts as an intercellular pressure depending on the local cell packing.

For theoretic purposes, in the sequel it will be more customary to deal with the so-called constitutive function $\Phi$, defined by Eq. 11, rather than with $\Sigma$ itself, although it is obviously possible to switch at any time to either function via the above-mentioned relationship.

Diffusion problems are well-known to be ill-posed if the diffusion coefficient is negative, therefore a very basic requirement in our case is that $\Phi'$ be nonnegative. A more complete characterization is provided by the following assumption:

\[(H1) \quad \Phi : \mathbb{R} \to \mathbb{R} \text{ is smooth, strictly increasing, and normalized in such a way that } \Phi(0) = 0.\]

Strict monotonicity of the constitutive function is classically required in the theory of nonlinear parabolic equations (Vázquez 2007). Notice that if $\Phi$ is strictly increasing then $\Phi'$ cannot vanish but possibly at the origin (indeed $\Phi'(0) = 0$ is forced by Eq. 11 if $(s \Sigma(s))'$ is not infinite in $s = 0$), therefore $\Phi'(s) > 0$ for all $s \neq 0$ and $\Phi$ is invertible. We anticipate that we will use invertibility in Sect. 6 for the existence theory of the solutions to the stationary problem.

Many models in the literature assume that $\Sigma$ grows steeply as cells get highly packed. For example, in Tosin et al. (2006) a particular instance of the following function is proposed (Fig. 2, left):

$$\Sigma(s) = as + b\left[(s - \phi_*)^+\right]^n,$$

Fig. 2 From left to right, the intercellular stress functions 14, 15, 16
where \( a, b \) are positive constants with \( b \gg a, n \geq 1 \) is integer, \( \phi_\ast \in (0, 1) \) is the close-packing cell volume ratio, and \((\cdot)^+\) denotes the positive part of its argument. In practice, such a \( \Sigma \) is a physiological pressure for normally packed cells, which rapidly increases as soon as the tissue becomes overly dense. Function 14 is smooth for \( n > 1 \) and piecewise smooth for \( n = 1 \), and the corresponding constitutive function \( \Phi \):

\[
\Phi(s) = \frac{2}{3}as^3 + b[(s - \phi_\ast)^+]^n \left\{ s^2 - \frac{s(s - \phi_\ast)^+}{n + 1} + \frac{[(s - \phi_\ast)^+]^2}{(n + 1)(n + 2)} \right\}
\]

fulfills hypothesis (H1).

Other authors use (Manoussaki 2003; Murray 2003) (Fig. 2, center)

\[
\Sigma(s) = \frac{\tau s}{1 + \lambda s^2},
\]

\( \lambda, \tau > 0 \), which grows again linearly for small \( s \) (physiological pressure) but then reproduces a release of the stress after the maximum \( \tau/(2\sqrt{\lambda}) \) attained for \( s = 1/\sqrt{\lambda} \). This should model a saturation effect due to that at high densities all cells are not able to push. It is interesting to note that such a behavior is opposite to the one assumed by Eq. 14, nevertheless from Eq. 11 it can be easily computed

\[
\Phi(s) = \frac{\tau}{\lambda} \left( \frac{\arctan(\sqrt{\lambda}s)}{\sqrt{\lambda}} - \frac{s}{1 + \lambda s^2} \right),
\]

which complies in turn with hypothesis (H1).

In the previous two examples it results \( \Sigma(s) \geq 0 \) for all \( s \geq 0 \), but this is not strictly necessary for hypothesis (H1) to be satisfied: even if \( \Sigma(s) < 0 \) for some \( s \geq 0 \) one might get \( \Phi'(s) > 0 \) for all \( s \neq 0 \). As recalled in Ambrosi and Preziosi (2002) and Byrne and Preziosi (2003), negative values of the stress model adhesive intercellular forces, which compete with the repulsive ones because cells, unless too packed, like to stick together to form multicellular aggregates. This behavior is reproduced, for instance, by the function \( \Sigma \) proposed in Tosin (2008) (Fig. 2, right):

\[
\Sigma(s) = \begin{cases} \frac{1}{s} \log \left| \frac{s}{\phi_\ast} \right| & \text{if } n = 1 \\ \frac{n}{n - 1} \cdot \frac{|s|^{n-1} - \phi_\ast^{n-1}}{s} & \text{if } n > 1, \end{cases}
\]

where now \( \phi_\ast \) denotes the stress-free volume ratio corresponding to unstressed tissue (i.e., \( \Sigma(\phi_\ast) = 0 \)). Notice that \( \Sigma(s) \leq 0 \) for \( |s| \leq \phi_\ast \), with \( \Sigma(s) \to -\infty \) for \( |s| \to 0 \). The resulting constitutive function:

\[
\Phi(s) = |s|^{n-1}s
\]

is strictly increasing for all \( n \geq 1 \) and turns Eq. 12 into the porous medium equation with nonlinear forcing term. Function 16 somehow summarizes qualitatively the
trends of the functions 14, 15 at large volume ratios, indeed for 1 ≤ n ≤ 2 it is bounded from above and, if n < 2, tends to zero when s → +∞ (saturation effect), whereas for n > 2 it grows unboundedly and more and more steeply as n increases.

In De Angelis and Preziosi (2000) the authors introduce the idea, next borrowed by a few other papers (Ambrosi and Preziosi 2002; Byrne and Preziosi 2003; Chaplain et al. 2006), that the cell stress blows up when φ approaches a maximum allowed volume ratio φ_{max} ∈ (0, 1], which corresponds to an asymptote of the function Σ for s = φ_{max} (Fig 3, left):

\[ \Sigma(s) = p(\phi_{\text{max}} - \phi_*) - \frac{s - \phi_*}{|s|(\phi_{\text{max}} - s)}, \] 

where p > 0 is a constant coefficient and φ_* denotes again the stress-free volume ratio. Notice that, Σ being infinite at φ_{max}, Φ’ is also infinite, which violates hypothesis (H1). However, strict monotonicity of Φ on (−∞, φ_{max}) is preserved by function 17, while in general it fails on [0, φ_{max}) with the function proposed in Ambrosi and Preziosi (2002) and Byrne and Preziosi (2003) (Fig. 3, right). The latter is such that Σ(s) ≤ 0 for φ_* ≤ s ≤ φ_2 with a local minimum at s = φ_1 ∈ (φ_*, φ_2) in order to take into account cell adhesiveness at low volume ratios, then Σ(s) > 0 for φ_2 < s < φ_{max} with Σ(s) → +∞ when s → φ_{max} to reproduce cell repulsion. In addition, they set Σ(s) = 0 for 0 ≤ s ≤ φ_* to model that far apart cells ignore each other. We refer the reader to Byrne and Preziosi (2003) for the analytical expression of such a Σ. In Chaplain et al. (2006) the adhesion region is instead eliminated by taking φ_* ≡ φ_2 and setting Σ ≡ 0 before φ_* in practice, the resulting function is the positive part of function 17, which restores the monotonicity (however not strict) of Φ before φ_{max}.

It can be argued that condition Σ(s) → +∞ for s → φ_{max} is mainly intended to enforce the bound φ ≤ φ_{max} on the solution to Eq. 9, trusting to the physical intuition that a strong, infinite in the limit, intercellular pressure prevents cells from packing too much. Nevertheless, we will prove that this is not necessary to achieve the proper upper bound on φ.

Before concluding the discussion on the constitutive function, we introduce a condition that will play a fundamental role in the forthcoming theory (cf. also Fadimba and Sharpley 1995; Laurençot and Wrzosek 2005):
Definition 1 We say that a function $f : \mathbb{R} \to \mathbb{R}$ is \textit{$\Phi$-Lipschitz continuous} in an interval $I \subseteq \mathbb{R}$, with constant $\text{Lip}_\Phi(f) > 0$, if

$$|f(s_2) - f(s_1)|^2 \leq \text{Lip}_\Phi(f) (\Phi(s_2) - \Phi(s_1)) (s_2 - s_1), \quad \forall s_1, s_2 \in I.$$ 

Notice that the right-hand side is nonnegative because $\Phi$ is increasing.

2.2 The growth term

The function $\Gamma$ expresses proliferation or death of cells in connection with the availability of nutrient. The basic principles inspiring the modeling of $\Gamma$ are usually that few cells proliferate less than many cells, that proliferation stops when cells fill all the available space, and that cells need a minimum amount of nutrient to survive.

For instance, in Breward et al. (2002) they use

$$\Gamma(\phi, c) = \phi(1 - \phi)(c - S_0 c_1 + S_1 c - \phi S_2 + S_3 c),$$

where the first term at the right-hand side is the cell growth due to mitosis (fostered by the availability of nutrient), the second term is the cell death (enhanced by the lack of nutrient), and $S_0, \ldots, S_4 > 0$ are parameters. Notice that cell growth is zero whenever $\phi = 0$ (no cells) or $\phi = 1$ (cells occupy the whole space, recall the saturation constraint) and that nutrient chemistry reminds of the Michaelis–Menten kinetic.

A simpler form of $\Gamma$, including an explicit nutrient threshold triggering the switch between cell proliferation and death, is that proposed in Tosin (2008):

$$\Gamma(\phi, c) = \gamma \phi(1 - \phi)(c - c_*)$$

where $\gamma, c_* > 0$ are parameters. In this case, for $\phi \in [0, 1]$ it results $\Gamma > 0$ if $c > c_*$, $\Gamma < 0$ if $c < c_*$, hence $\Gamma$ acts as a source or a sink, respectively, according to the values taken by $c$. A more elaborated expression, allowing for different cell duplication and death rates, is

$$\Gamma(\phi, c) = \gamma_1 \phi(1 - \phi)(c - c_*)^+ - \gamma_2 \phi(c - c_*)^-,$$  \hspace{1cm} (18)

where $(\cdot)^+, (\cdot)^-$ denote positive and negative parts of their arguments and $\gamma_1, \gamma_2 > 0$ are parameters.

In Astanin and Preziosi (2009) and Astanin and Tosin (2007) proliferation and death of cells are linked to energy arguments, specifically ATP consumption through nutrient oxidation along the cell cycle, and the following form of $\Gamma$ is proposed:

$$\Gamma(\phi, c) = \frac{k \ln 2}{Q_M^0} \phi(f(\phi)g(c) - \hat{\theta})^+ - \frac{k \ln 2}{\hat{\theta} \tau_{1/2}} \phi(f(\phi)g(c) - \hat{\theta})^-,$$  \hspace{1cm} (19)

where $k, \hat{\theta}, Q_M^0, \tau_{1/2} > 0$ are the reaction rate of oxidation, the total rate of ATP consumption, the average cost of the full cell cycle, and the half-life of dying cells,
respectively. The function $f$ (of $\phi$ alone) is introduced to inhibit proliferation (namely, ATP production) in overly dense tissues, whereas the function $g$ (of $c$ alone) defines the effectiveness of the oxidative process in terms of nutrient supply. In more detail, $f$ vanishes when $\phi$ attains the maximum threshold $\phi_{\text{max}}$ and $g$ increases with $c$. Examples of such functions are $f(\phi) = \phi_{\text{max}} - \phi$, $g(c) = c$.

In Chaplain et al. (2006) and Preziosi and Tosin (2009) it is suggested that cell duplication and death may occur on a stress-induced basis, depending on the level of compression felt from the surrounding tissue:

$$\Gamma_\alpha(\phi, c) = \gamma_\alpha \phi \left( \Sigma_\alpha^* - \Sigma(\phi) \right) \left( \frac{c}{c_*} - 1 \right) - \delta_\alpha \phi \left( \Sigma(\phi) - \Sigma_{\alpha}^{**} \right),$$

$H$ being (possibly a mollification of) the Heaviside function and $\Sigma_{\alpha}^* \leq \Sigma_{\alpha}^{**}$ two stress thresholds. When the actual stress acting on the cells is above the first threshold proliferation is inhibited. If the stress further grows above the second threshold then cell apoptosis is triggered. Since the sensitivity to the stress affects the way in which a cell runs through its vital cycle, which is what mainly breaks down when mutations change a normal cell into an abnormal one, the thresholds $\Sigma_{\alpha}^*$, $\Sigma_{\alpha}^{**}$ are expected to be different for tumor and host cells, in particular $\Sigma_{T}^{**} > \Sigma_{H}^{**}$ (Chaplain et al. 2006).

Inspired by the examples above, we see that a convenient structure of the growth terms is

$$\Gamma_\alpha(\phi, c) = \sum_{\nu=p,d} \gamma_\alpha^\nu f_\alpha^\nu(\phi) g_\alpha^\nu(c) - \delta_\phi,$$

which allows one to account for possible differences in the mechanisms of proliferation ($\nu = p$) and death ($\nu = d$) of tumor and host cells, as depicted for instance by Eqs. 18, 20. In more detail, the coefficients $\gamma_\alpha^\nu$ are specific proliferation and death rates for tumor and host cells. The terms $f_\alpha^\nu(\phi) g_\alpha^\nu(c)$ refer to joint stress-nutrient induced proliferation and apoptosis, under the assumption that the cell stress is directly determined by the volume ratio $\phi$. Finally, the term $-\delta_\phi$ accounts for natural cell apoptosis without influence from the distribution of nutrient, the coefficient $\delta$ being the same for both cell populations.

Some technical requirements on the previous terms are now stated, taking into account a generic maximum volume ratio $\phi_{\text{max}} \in (0, 1]$ allowed for cell packing:\footnote{If $\phi_{\text{max}} < 1$ then $1 - \phi_{\text{max}}$ is the constant volume ratio of the rigid non-remodeling extracellular matrix, and $\phi_{\ell} := \phi_{\text{max}} - \phi$ the volume ratio of the extracellular fluid (not explicitly modeled) filling the interstices within the mixture to enforce the saturation constraint.}

(H2) $\gamma_\alpha^p, \delta > 0$, $\gamma_\alpha^d < 0$

(H3) $f_\alpha^\nu(\cdot)$-Lipschitz continuous and nonnegative in $[0, \phi_{\text{max}}]$

(H3.1) $f_\alpha^p(\cdot) \geq 0$ in $(-\infty, 0)$, $f_\alpha^p(\cdot) \leq 0$ in $(\phi_{\text{max}}, +\infty)$, $f_\alpha^p(0) = f_\alpha^p(\phi_{\text{max}}) = 0$

(H3.2) $f_\alpha^d(\cdot) \leq 0$ in $(-\infty, 0)$, $f_\alpha^d(\cdot) \geq 0$ in $(\phi_{\text{max}}, +\infty)$, $f_\alpha^d(0) = 0$

(H4) $g_\alpha^\nu$ Lipschitz continuous and nonnegative in $\mathbb{R}$. 

\[ \gamma_\alpha^p, \delta > 0, \gamma_\alpha^d < 0 \]

\[ (H3) \quad f_\alpha^\nu(\cdot) \text{-Lipschitz continuous and nonnegative in } [0, \phi_{\text{max}}] \]

\[ (H3.1) \quad f_\alpha^p(\cdot) \geq 0 \text{ in } (-\infty, 0), f_\alpha^p(\cdot) \leq 0 \text{ in } (\phi_{\text{max}}, +\infty), f_\alpha^p(0) = f_\alpha^p(\phi_{\text{max}}) = 0 \]

\[ (H3.2) \quad f_\alpha^d(\cdot) \leq 0 \text{ in } (-\infty, 0), f_\alpha^d(\cdot) \geq 0 \text{ in } (\phi_{\text{max}}, +\infty), f_\alpha^d(0) = 0 \]

\[ (H4) \quad g_\alpha^\nu \text{ Lipschitz continuous and nonnegative in } \mathbb{R}. \]
Although not explicitly required, we incidentally notice that further assumptions may be suggested by physical considerations. For instance, nutrient-induced proliferation $g^p_\alpha$ may be non-decreasing and nutrient-induced death $g^d_\alpha$ non-increasing.

2.3 The absorption term

The function $Q$ describes the uptake of nutrient by cells. A common and simple prototype of this term is (see e.g., Anderson and Chaplain 1998; Byrne and Preziosi 2003; Tosin 2008)

$$Q(\phi, c) = -\lambda \phi c,$$

where $\lambda > 0$ is a parameter. This form translates the basic principle that the absorption of nutrient depends simultaneously on the number of cells present in the domain and on the quantity of nutrient available to them, including that few cells uptake, on the whole, few nutrient even if the latter is abundantly supplied, and, conversely, that few nutrient can poorly feed a large cell population. More general absorption terms are introduced in the series of papers (Bertuzzi et al. 2005a,b,c, 2007b):

$$Q(\phi, c) = -\phi \psi(c),$$

where $\psi$ is then suggested to be of Michaelis-Menten type (cf. also Breward et al. 2002; Manoussaki 2003). This allows the authors to generalize $Q$ to the case of multiple species of nutrients, including in $\psi$ the dependence on the various concentrations (Bertuzzi et al. 2007a).

In Astanin and Tosin (2007) the absorption term is directly linked to the chemical mechanisms internal to the cells responsible for proliferation and death, and the following form of $Q$ is proposed:

$$Q(\phi, c) = -\lambda \phi f(\phi) g(c),$$

where $\lambda > 0$ is the oxygen uptake rate and the functions $f$, $g$ are the same as in Eq. 19.

In view of these examples, and of possible differences in the consumption of nutrient by normal and abnormal cells, we refer to the following structure of the absorption term:

$$Q_\alpha(\phi, c) = -\lambda_\alpha h_\alpha(\phi) q_\alpha(c).$$

Here, $\lambda_\alpha$ is the specific absorption rate of the cell population $\alpha$ while the function $h_\alpha$ accounts for cell-dependent uptake dynamics, which may differ for cancer and host cells because of different internal chemistry. Finally, $q_\alpha$ is the chemical consumption rate of nutrient, which instead is much likely to be the same for tumor and host cells as it depends essentially on the chemical properties of the environment and of the nutrient itself rather than on cell genetics.
Some technical assumptions on these terms are in order, namely:

(H5) $\lambda_\alpha > 0$
(H6) $h_\alpha \Phi$-Lipschitz continuous and nonnegative in $\mathbb{R}$
(H7) $q_\alpha$ locally bounded and nonnegative in $[0, +\infty)$
  (H7.1) $q_\alpha(0) = 0$, $q_\alpha \leq 0$ in $(-\infty, 0)$
  (H7.2) $q_\alpha$ nondecreasing in $[0, +\infty)$.

Again, additional assumptions, not strictly needed for theoretic issues, may be welcome for physical consistency. For instance, one may require the cell-dependent absorption rate to vanish when no cells are present, i.e., $h_\alpha(0) = 0$. We anticipate that we will actually use this assumption when addressing the existence of stationary solutions.

3 Boundary, interface, and initial conditions

3.1 Boundary conditions

The parabolic character of Eqs. 12, 13 calls for conditions on the whole boundary $\partial \Omega \times (0, T_{\text{max}}]$ in order to properly define the corresponding mathematical problems. The most common boundary conditions in tumor growth problems refer to characteristic values of some quantities at the periphery of the cell tissue (Dirichlet conditions) or to their fluxes across the external shell of the portion of tissue under consideration (Neumann or Robin conditions). Often boundary conditions account for interactions of the cell aggregate with the outer environment (not explicitly modeled).

Let us consider, at first, the chemicals nourishing the cells. Nutrient is supplied to the cells by the external environment e.g., by a nearby vasculature, whence, dissolved in the extracellular fluid, it diffuses through the cell tissue. The presence of the vasculature can be modeled as a boundary condition for Eq. 13: one identifies a portion of the boundary, say $\partial_b \Omega$ the subscript $b$ standing for “blood”, with a blood vessel, whence the nutrient carried by blood flows into the tissue. One has therefore a condition on the normal flux $-D \nabla c \cdot n$, $n$ being the outward normal unit vector to $\partial_b \Omega$. This may be either a Neumann condition, if the flux is given, or a Robin condition, if the flux is expressed in terms of $c$ itself, for instance as $\eta(c - c_b)$ where $\eta$, $c_b > 0$ are parameters. Such a condition implies that the flow of nutrient across the vessel wall depends on the quantity of nutrient already present in the tissue, with respect to a characteristic threshold $c_b$. In more detail, if the concentration $c$ equals the characteristic concentration $c_b$ then there is no flux, while if $c < c_b$ then the nutrient flows from the blood to the tissue. Conversely, if $c > c_b$ then the nutrient flows from the tissue to the blood, namely blood carries away the nutrient in excess. However, this situation is not expected to happen because blood is the only source of nutrient in this model. The parameter $c_b$ can be identified with the average physiological concentration of nutrient in the blood, whereas $\eta$ is a characteristic speed of filtration through the vessel wall. We point out that Robin’s is the biologically most appropriate condition to be imposed at the vessel wall, see Keener and Sneyd (1998) and Truskey et al. (2009), and in this respect Neumann condition should be regarded as a zeroth-order approximation. For this reason, we ultimately set
\[-D \nabla c \cdot \mathbf{n} = \eta (c - c_b) \quad \text{on } \partial_b \Omega \times (0, T_{\text{max}}].\]

In the remaining portion of the boundary, say \(\partial_f \Omega\) the subscript \(f\) standing for “far” (in the sense that this boundary is far from the vasculature where tumor growth mainly takes place), one might prescribe the concentration \(c_b\) for conveying the idea that the quantity of nutrient is there the average physiological one in healthy tissues:

\[c = c_b \quad \text{on } \partial_f \Omega \times (0, T_{\text{max}}].\]

which is a Dirichlet boundary condition.

We suppose \(\partial_b \Omega \cup \partial_f \Omega = \partial \Omega\), \(\text{Int }\partial_b \Omega \cap \text{Int }\partial_f \Omega = \emptyset\) for consistency (cf. Fig. 1) but we do not exclude that either \(\partial_f \Omega\) or \(\partial_b \Omega\) is empty, if for instance the vasculature fully surrounds the cellular tissue \((\partial_f \Omega = \emptyset, \partial \Omega \equiv \partial_b \Omega)\) or if one is concerned with avascular tumors \((\partial_b \Omega = \emptyset, \partial \Omega \equiv \partial_f \Omega)\).

**Remark 1** In the formulation of the model it is implicitly assumed that blood vessels are not displaced by the growing tumor mass; in other words, that the boundary \(\partial_b \Omega\) is fixed. Actually blood vessels, especially those crossing the frontier between tumor and host tissues, are pushed by duplicating cells in order to make room for new cells. However, the assumption of fixed \(\partial_b \Omega\) seems to be an acceptable one for reducing the technical complexity of the mathematical description.

Concerning the cells, since we are considering in situ tumor growth, it is reasonable to assume that they do not penetrate the vasculature, which corresponds to no flux across the boundary \(\partial_b \Omega\):

\[\kappa_m \nabla \Phi(\phi) \cdot \mathbf{n} = 0 \quad \text{on } \partial_b \Omega \times (0, T_{\text{max}}].\]

Recalling Eq. 10, this condition can be rewritten as \(\phi \mathbf{v} \cdot \mathbf{n} = 0\), which says that the normal component of the velocity of the cells vanishes at the blood vessel. Cells neither cross the vessel wall nor detach from it, but they can slide along the vessel because no restriction is imposed on the tangential component of their velocity. Instead, at the far boundary \(\partial_f \Omega\) the tissue can be assumed to withstand a given stress due, for instance, to it being confined by bones, or even to be stress-free, if the domain \(\Omega\) is so large that the main dynamics are expected to occur near the vasculature. According to Eq. 4, the normal stress of both tumor and host cells at the boundary is given by

\[(T_{\alpha} \mathbf{n}) \cdot \mathbf{n} = -\Sigma \mathbf{n} \cdot \mathbf{n} = -\Sigma,\]

hence the aforesaid condition on \(\partial_f \Omega\) takes the form

\[\Sigma(\phi) = \sigma_* \quad \text{on } \partial_f \Omega \times (0, T_{\text{max}}]. \tag{21}\]

where \(\sigma_* \geq 0\) is a prescribed stress threshold. Since the intercellular stress is, by assumption, a function of the cell volume ratio, Eq. 21 can be ultimately reformulated as a Dirichlet boundary condition for \(\phi\):
Fig. 4  Left blood vessels and far boundaries are among the edges of Ω. Right blood vessels are internal holes to Ω, whereas the far boundary coincides with the outer edges of Ω

\[ \phi = \phi_* \in (0, \phi_{\text{max}}) \text{ on } \partial_f \Omega \times (0, T_{\text{max}}). \]

especially when \( \Sigma \) is one-to-one (like in the majority of the examples discussed in Sect. 2.1). In this case, \( \phi_* \) is the cell volume ratio such that \( \Sigma(\phi_*) = \sigma_* \).

Boundary conditions outlined here are mainly indicative, and may be detailed more precisely for specific domains Ω. In particular, the boundaries \( \partial_b \Omega, \partial_f \Omega \) need not be connected, especially when several blood vessels are present (in which case \( \partial_b \Omega \) will be presumably the union of several connected components). As an example, one may consider the applications illustrated in Preziosi and Tosin (2009), which deal with two-dimensional tumor growth in a rectangular domain Ω. In some cases, blood vessels coincide with one or more (not necessarily adjacent) edges of Ω, the remaining ones forming instead \( \partial_f \Omega \) (Fig. 4, left). In other cases, all of the outer edges of Ω define \( \partial_f \Omega \), whereas blood vessels are circular holes within the rectangle. The union of their circumferences is then \( \partial_b \Omega \), which plays the role of an internal boundary to Ω (Fig. 4, right).

3.2 Interface conditions

The interface \( S(t) \) separating the two sub-domains \( \Omega_T(t), \Omega_H(t) \) is a material one for the cells, meaning that the latter cannot detach from it on either side. This entails the continuity of their normal velocity across \( S(t) \), i.e., recalling Eq. 10,

\[ [v \cdot n] = -\kappa_m [\nabla (\phi \Sigma(\phi))] \cdot n = 0, \quad \forall t \in (0, T_{\text{max}}]. \]  (22)

In addition, classical theory of continuum mechanics requires the continuity of the stress of the interfacing materials:

\[ \phi \Sigma(\phi) n = 0, \quad \forall t \in (0, T_{\text{max}}]. \]  (23)

For a continuous stress function \( \Sigma \), this is fulfilled if \( [\phi] = 0 \), which, coupled with Eq. 22, yields \( \kappa_m [\phi \nabla (\phi \Sigma(\phi))] \cdot n = 0 \). Hence the condition necessary for the validity of Eq. 9 on \( \Omega \) is compatible with the standard interface conditions of continuum mechanics. Owing to this argument, we ultimately impose
\[ \kappa_m [\phi \nabla (\phi \Sigma (\phi))] \cdot \mathbf{n} = 0 \text{ on } S(t), t \in (0, T_{\text{max}}], \]

because it is this interface condition which is really needed in our problem.

As far as the motion of the interface is concerned, an evolution equation for \( S \) has to be provided. Since, as stated above, the latter is a material surface for the cells, the usual condition is that its points are transported by the velocity field of the cellular matter:

\[
\frac{dx}{dt} \cdot \mathbf{n} = v_{|S} \cdot \mathbf{n}, \quad \forall x \in S(t).
\]

Several analytical and numerical methods can be used to implement such a condition e.g., the level set or the immersed boundary methods. We refrain from dwelling too much on this aspect of the problem, which is beyond the scope of the present paper. Instead, we will provide general results independent of the specific interface-tracking technique, cf. Theorems 2, 4.

**Remark 2** Although the interface condition 23 is widely applied in the literature on tumor growth modeling, cf. e.g., Cristini and Lowengrub (2010), Kim et al. (2011) and Roose et al. (2007), it is worth pointing out that the normal stress may also be discontinuous across \( S(t) \) if the intercellular interaction happens to be unbalanced on either side of the material boundary. This is, for instance, the case when one accounts explicitly for adhesion among cancer cells, which can be modeled as a surface-tension like jump at the tumor-host interface linked to the mean curvature of the latter, cf. e.g., Byrne and Drasdo (2009) and Macklin et al. (2009). However, in the present context we avoid dealing with this specific problem, also in view of the tacit assumption that the composition of the mixture is the same in the whole domain \( \Omega \).

Furthermore, we mention that another phenomenon affecting dramatically the dynamics of tumor invasion, hence the conditions to be imposed at the interface \( S(t) \), is tumor acidification triggered by cell hypoxia (lack of oxygen). As described in Smallbone et al. (2005), this causes the diffusion of hydrogen ions through the tumor periphery into the adjacent normal tissue, which leads to death of healthy cells due to their lower resistance to acidic pH. Tumor invasion is thus enhanced by a combined chemo-mechanical effect at the interface \( S(t) \), whose modeling requires nontrivial modifications of condition 23.

### 3.3 Initial conditions

The initial distributions of cells and nutrient in \( \Omega \) are described by two functions \( \phi_0, c_0 : \Omega \to \mathbb{R} \), which should not exceed the expected physiological ranges. Therefore:

**\( \text{(H8)} \)** \( 0 \leq \phi_0 \leq \phi_{\text{max}}, 0 \leq c_0 \leq c_b \) in \( \Omega \).

In particular, as observed in Sect. 3.1, nutrient concentration is expected to stay below the average physiological value \( c_b \) because, in the present context, blood is the only source of nutrient, which is then consumed by cells.
4 Notations and theoretic background

In this section we prepare to tackle the analysis of the above-discussed models. We fix the main notations and quickly recall some essential technical material.

**Domain.** The spatial domain is an open and bounded set \( \Omega \subset \mathbb{R}^d \) (physically \( d = 1, 2, 3 \)) with smooth boundary \( \partial \Omega \). We use \( \sigma \) for the coordinate along \( \partial \Omega \) and \( d\sigma \) for the \((d - 1)\)-dimensional Hausdorff measure in \( \mathbb{R}^d \). The time interval of interest is \( [0, T_{\text{max}}] \), with finite final time \( T_{\text{max}} > 0 \). We denote by \( Q_{T_{\text{max}}} \) the cylinder \( \Omega \times (0, T_{\text{max}}] \subset \mathbb{R}^{d+1} \).

**Functions.** In general, we regard \( \phi, c \) as functions parameterized by time. Particularly, when we want to emphasize the dependence on \( t \) we write \( \phi(t), c(t) \) for the functions of \( x \) defined as \( (\phi(t))(x) = \phi(t, x), (c(t))(x) = c(t, x) \).

We will occasionally denote the time derivative by the subscript \( t \) for short (e.g., \( \phi_t \), \( c_t \)). We write \( \text{Lip}(u) \) for the Lipschitz constant of a function \( u \), and \( u^+, u^- \) for its positive and negative part: \( u^+ := \max\{u, 0\}, u^- := \max\{0, -u\} \).

**Function spaces.** \( L^2(\Omega) \) is the usual Hilbert space of square-integrable functions in \( \Omega \), endowed with the norm

\[
\|u\|_0 := \left( \int_\Omega |u(x)|^2 \, dx \right)^{1/2}.
\]

We will also use a weaker \( L^2 \) norm denoted by \( \| \cdot \|_0 \) (cf. Appendix A).

\( H^1(\Omega) \) is the Sobolev space of \( L^2 \) functions with square-integrable (weak) derivatives in \( \Omega \), endowed with the norm

\[
\|u\|_1 := \left( \|u\|_0^2 + \|\nabla u\|_0^2 \right)^{1/2}.
\]

For \( u \in H^1(\Omega) \), Stampacchia’s Theorem asserts that \( u^+, u^- \in H^1(\Omega) \) as well, with \( \nabla u^+ = \nabla u 1_{\{u > 0\}}, \nabla u^- = -\nabla u 1_{\{u < 0\}} \).

\( H^1_{0,B}(\Omega) \) is the space of \( H^1 \) functions whose trace vanishes on \( B \subseteq \partial \Omega \). The \( L^2 \) norm of the trace along \( B \) is

\[
\|u\|_{0,B} := \left( \int_B |u|^2 \, d\sigma \right)^{1/2}.
\]

We will deal, in particular, with the case \( B = \partial_b \Omega \).
\(L^2(0, T_{\text{max}}; H^1(\Omega))\) is the space of functions of \(t\), valued in \(H^1(\Omega)\), which are square-integrable in the interval \([0, T_{\text{max}}]\), endowed with the norm

\[
\|u\|_{L^2_t H^1_x} := \left( \int_0^{T_{\text{max}}} \|u(t)\|_1^2 \, dt \right)^{1/2}.
\]

The spaces \(L^2(0, T_{\text{max}}; L^2(\Omega)), L^2(0, T_{\text{max}}; H^1_{0,\partial \Omega}(\Omega))\) are defined analogously, and their respective norms denoted similarly. In particular, in the former we will use the norm

\[
\|u\|_{L^2_t L^2_x} := \left( \int_0^{T_{\text{max}}} \|u(t)\|_0^2 \, dt \right)^{1/2},
\]

\(\cdot \|_0\) being defined in Appendix A.

We introduce the following shorthand notations:

- \(\mathbb{V}_{T_{\text{max}}} := L^2(0, T_{\text{max}}; H^1(\Omega)) \times L^2(0, T_{\text{max}}; H^1(\Omega))\)
- \(\mathbb{V} := H^1(\Omega) \times H^1(\Omega)\)
- \(V_f := H^1_{0,\partial \Omega}(\Omega)\)
- \(V'_f\) for the dual space of \(V_f\).

We use the symbol \(\langle \cdot, \cdot \rangle\) for the duality pairing between \(V_f\) and \(V'_f\). Given \(u \in L^2(0, T_{\text{max}}; V_f)\) with \(u_t \in L^2(0, T_{\text{max}}; V'_f)\), it results

\[
\langle u_t(t), u(t) \rangle = \frac{1}{2} \frac{d}{dt} \|u(t)\|_0^2.
\]

We use the abbreviation “a.e.” for properties which hold “almost everywhere” with respect to the Lebesgue measure.

If \(I \subseteq \mathbb{R}\) is an interval, \(C^0(I)\) is the space of continuous functions in \(I\), endowed with the norm

\[
\|u\|_\infty := \sup_{x \in I} |u(x)|.
\]

Estimates and constants. We write

\[
a \lesssim b \quad \text{to mean} \quad \exists C > 0 : a \leq Cb,
\]

the constant \(C\) being understood to be independent of both \(a\) and \(b\), when the specific value of \(C\) is unimportant. In this case, \(C\) may vary from line to line within the same computation without explicit notice.
Inequalities.
- Cauchy’s (or Young’s): for all \( a, b \in \mathbb{R} \), \( ab \leq \frac{e \varepsilon}{2} \frac{a^2}{2} + \frac{b^2}{2} \varepsilon \) with arbitrary \( \varepsilon > 0 \).
- Poincaré’s: if \( u \in H^1_{0,B}(\Omega) \) then \( \|u\|_0 \lesssim \|\nabla u\|_0 \). The constant involved in this estimate, denoted by \( C_p \), depends in general on \( \Omega \) and \( B \).
- Cauchy-Schwartz’s: \( |\int_{\Omega} u(x)v(x) \, dx| \leq \|u\|_0 \|v\|_0 \) for all \( u, v \in L^2(\Omega) \).

Remark 3 When applied to a function, the operator \(|\cdot|\) is the classical absolute value. When applied to a subset of \( \mathbb{R}^d \), it denotes instead the Lebesgue measure of that subset.

5 The time-dependent problem

In this section we consider the initial/boundary-value problem

\[
\begin{align*}
\partial_t \phi - \kappa_m \Delta \Phi(\phi) &= \Gamma(t, x, \phi, c) \quad \text{in } \{\Omega_T(t), \Omega_H(t)\} \\
\partial_t c - D\Delta c &= Q(t, x, \phi, c) \quad \text{in } Q_{T_{\max}} \\
\kappa_m \nabla \Phi(\phi) \cdot n &= 0, \\
\phi &= \phi^*, c = c_b \quad \text{on } \partial_f \Omega \times (0, T_{\max}] \\
\phi(0) &= \phi_0, c(0) = c_0 \quad \text{in } \Omega
\end{align*}
\]

along with the series of hypotheses (H1)–(H8), and we look for estimates of non-negativity, boundedness, uniqueness, and continuous dependence on the data of the functions \( \phi, c \). We assume that solutions exist to this problem, in the suitable sense specified below. Notice that, in (24), the interface condition has been conveniently rewritten in terms of \( \nabla \Phi(\phi) \) using Eq. 11.

Definition 2 (Weak solutions for the time-dependent problem) A weak solution to Problem 24 is a pair \((\phi, c) \in V_{T_{\max}}\) such that:

(i) \( \phi_t, c_t \in L^2(0, T_{\max}; V_f') \)

(ii) \( \Phi(\phi) \in L^2(0, T_{\max}; H^1(\Omega)) \)

(iii) \( \phi = \phi^*, c = c_b \) on \( \partial_f \Omega \times (0, T_{\max}] \) in the trace sense

(iv) \( \phi(0) = \phi_0 \in L^2(\Omega), c(0) = c_0 \in L^2(\Omega) \)

which satisfies

\[
\langle \phi_t, v_1 \rangle + \langle c_t, v_2 \rangle + \int_{\Omega} (\kappa_m \nabla \Phi(\phi) \cdot \nabla v_1 + D\nabla c \cdot \nabla v_2) \, dx + \eta \int_{\partial_b \Omega} (c - c_b) v_2 \, d\sigma
\]

\[
= \sum_{\alpha=T, H} \int_{\Omega_{\alpha}(t)} \left( \sum_{v=p, d} \gamma \nu_{\alpha} \nu_{\alpha}(\phi) g_{\alpha}(c) v_1 - \delta \phi v_1 - \lambda_{\alpha} h_{\alpha}(\phi) q_{\alpha}(c) v_2 \right) \, dx
\]

for all \( v_1, v_2 \in V_f \) and a.e. \( t \in [0, T_{\max}] \).
5.1 Non-negativity and boundedness of the solution

**Theorem 1** Any weak solution \((\phi, \, c) \in \nabla T_{\text{max}}\) to Problem 24 satisfies

\[
0 \leq \phi(t, \, x) \leq \phi_{\text{max}}, \quad 0 \leq c(t, \, x) \leq c_b \quad \text{for a.e.} \ (x, \, t) \in Q_{T_{\text{max}}}.
\]

**Proof** First we establish that \(\phi, \, c\) are a.e. nonnegative by showing \(\phi^-, \, c^- = 0\) a.e. in \(Q_{T_{\text{max}}}\). Choosing \(v_1 = \phi^-(t), \, v_2 = c^-(t)\) as test functions in Eq. 25 reveals

\[
-\frac{1}{2} \frac{d}{dt} \left( \|\phi^-(t)\|_0^2 + \|c^-(t)\|_0^2 \right) - \kappa_m \int_{\Omega} \Phi'(\phi^-)|\nabla \phi^-|^2 \, dx - D\|\nabla c^-(t)\|_0^2
\]

\[
- \eta \|c^-(t)\|_0^2 - \eta c_b \int_{\partial_b \Omega} c^- \, d\sigma
\]

\[
= \sum_{\alpha=T, \, H_{\Omega_a(t)}} \int \left( \sum_{v=p, \, d} \gamma_v f_v^\alpha (-\phi^-)g_v^\alpha(c)\phi^- + \delta(\phi^-)^2 - \lambda\alpha h_\alpha(\phi)q_\alpha (-c^-)c^- \right) \, dx.
\]

Because of hypotheses (H2)–(H7), the right-hand side is nonnegative for a.e. \(t \in [0, \, T_{\text{max}}]\). Integrating from 0 to \(t \leq T_{\text{max}}\) and using \(\phi_0, \, c_0^- = 0\) (hypothesis (H8)) we get then

\[
\|\phi^-(t)\|_0^2 + \|c^-(t)\|_0^2 + 2\kappa_m \int_0^t \int_{\Omega} \Phi'(\phi^-)|\nabla \phi^-|^2 \, dx \, d\tau
\]

\[
+ 2D \int_0^t \|\nabla c^-(t)\|_0^2 \, d\tau + 2\eta \int_0^t \|c^-(t)\|_0^2 - \eta c_b \int_{\partial_b \Omega} c^- \, d\sigma \leq 0
\]

for all \(t \in [0, \, T_{\text{max}}]\), whence \(\phi^-, \, c^- = 0\) a.e. in \(Q_{T_{\text{max}}}\) due to the non-negativity of each term at the left-hand side (use hypothesis (H1) for the term containing \(\Phi'\)).

Next we claim \((\phi - \phi_{\text{max}})^+ = (c - c_b)^+ = 0\) a.e. in \(Q_{T_{\text{max}}}\), which amounts to \(\phi \leq \phi_{\text{max}}, \, c \leq c_b\). Let \(\tilde{\phi} := (\phi - \phi_{\text{max}})^+, \, \tilde{c} := (c - c_b)^+\) for brevity. Taking \(v_1 = \tilde{\phi}(t), \, v_2 = \tilde{c}(t)\) as test functions in Eq. 25 yields

\[
\frac{1}{2} \frac{d}{dt} \left( \|\tilde{\phi}(t)\|_0^2 + \|\tilde{c}(t)\|_0^2 \right) + \kappa_m \int_{\Omega} \Phi'(\phi_{\text{max}} + \tilde{\phi})|\nabla \tilde{\phi}|^2 \, dx + D\|\nabla \tilde{c}(t)\|_0^2 + \eta \|\tilde{c}(t)\|_0^2
\]

\[
= \sum_{\alpha=T, \, H_{\Omega_a(t)}} \int \left( \sum_{v=p, \, d} \gamma_v f_v^\alpha (\phi_{\text{max}} + \tilde{\phi})g_v^\alpha(c)\tilde{\phi} - \delta(\phi_{\text{max}} + \tilde{\phi})\tilde{\phi} - \lambda\alpha h_\alpha(\phi)q_\alpha (c_b + \tilde{\phi})\tilde{c} \right) \, dx,
\]

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the right-hand side being this time nonpositive for a.e. $t \in [0, T_{\text{max}}]$. Integrating in time and using now $\tilde{\phi}(0) = \tilde{c}(0) = 0$ we obtain

$$
\|\tilde{\phi}(t)\|_0^2 + \|\tilde{c}(t)\|_0^2 + 2\kappa m \int_0^t \int_\Omega \Phi'(\phi^* + \tilde{\phi})|\nabla \tilde{\phi}|^2 \, dx \, d\tau + 2D \int_0^t \|\nabla \tilde{c}(\tau)\|_0^2 \, d\tau + 2\eta \int_0^t \|\tilde{c}(\tau)\|_{0, \partial \Omega}^2 \, d\tau \leq 0
$$

for all $t \in [0, T_{\text{max}}]$, whence the claim follows by arguing like in the previous point.

5.2 Estimates on the solution and uniqueness

**Theorem 2** Let $(\phi_i, c_i) \in V_{T_{\text{max}}}, i = 1, 2$, be two weak solutions of Problem 24 with initial conditions $(\phi_{i,0}, c_{i,0}) \in L^2(\Omega) \times L^2(\Omega)$. Then the following estimate holds:

$$
\|\phi_2 - \phi_1\|_{L^2_t L^2_\Omega}^2 + \int_0^{T_{\text{max}}} \int_\Omega (\Phi(\phi_2) - \Phi(\phi_1)) (\phi_2 - \phi_1) \, dx \, dt \\
+ \|c_2 - c_1\|_{L^2_t H^1_\Omega}^2 + \int_0^{T_{\text{max}}} \|c_2(t) - c_1(t)\|_{0, \partial \Omega}^2 \, dt \\
\lesssim \|\phi_{2,0} - \phi_{1,0}\|_0^2 + \|c_{2,0} - c_{1,0}\|_0^2 + \sum_{\alpha=T, H} \int_0^{T_{\text{max}}} |\Omega_{2,\alpha}(t) \triangle \Omega_{1,\alpha}(t)| \, dt. \quad (26)
$$

where $\Omega_{i,\alpha}(t)$ is, at time $t$, the sub-domain of the cell population $\alpha$ corresponding to the solution $i$, and $\triangle$ denotes the symmetric difference of two sets.

In particular, for a prescribed initial condition $(\phi_0, c_0)$, the solution is determined univocally by the evolving shape of the sub-domains $\Omega_T(t), \Omega_H(t)$, in the sense that if $\Omega_{1,\alpha}(t) = \Omega_{2,\alpha}(t)$ for a.e. $t \in [0, T_{\text{max}}]$ and both $\alpha = T, H$ then $(\phi_1, c_1) = (\phi_2, c_2)$.

**Proof** It is sufficient to prove the estimate 26, for then uniqueness of the solution easily follows out of it with $\phi_{1,0} = \phi_{2,0}, c_{1,0} = c_{2,0}$, and $\Omega_{1,\alpha}(t) = \Omega_{2,\alpha}(t)$ for a.e. $t$.

For all $v_1, v_2 \in V_f$, the difference $(\phi_2 - \phi_1, c_2 - c_1)$ of the two given solutions satisfies
\[ ((\phi_2 - \phi_1)_t, v_1) + ((c_2 - c_1)_t, v_2) + \int_\Omega (\kappa_m \nabla (\Phi(\phi_2) - \Phi(\phi_1)) \cdot \nabla v_1 \]
\[ + D (c_2 - c_1) \cdot \nabla v_2) \, dx + \eta \int_{\partial_s \Omega} (c_2 - c_1) v_2 \, d\sigma \]
\[ = \sum_{\alpha = T, H} \int_\Omega \left( \sum_{v = p, d} \gamma_{\alpha}^v \{ [f_{\alpha}^v(\phi_2) - f_{\alpha}^v(\phi_1)] g_{\alpha}^v(c_2) + f_{\alpha}^v(\phi_1)[g_{\alpha}^v(c_2) - g_{\alpha}^v(c_1)] \} v_1 \right. \]
\[ - \delta (\phi_2 - \phi_1) v_1 - \lambda_\alpha (h_\alpha(\phi_2) - h_\alpha(\phi_1)) q_\alpha(c_2) v_2 \]
\[ - \lambda_\alpha h_\alpha(\phi_1) (q_\alpha(c_2) - q_\alpha(c_1)) v_2 \left( \mathbb{1}_{\Omega_2,\alpha(t)} - \mathbb{1}_{\Omega_1,\alpha(t)} \right) dx \]
\[ + \sum_{\alpha = T, H} \int_\Omega \left( \sum_{v = p, d} \gamma_{\alpha}^v f_{\alpha}^v(\phi_1) g_{\alpha}^v(c_1) v_1 - \delta_1 v_1 \right. \]
\[ - \lambda_\alpha h_\alpha(\phi_1) (q_\alpha(c_2) - q_\alpha(c_1)) v_2 \left( \mathbb{1}_{\Omega_2,\alpha(t)} - \mathbb{1}_{\Omega_1,\alpha(t)} \right) dx, \tag{27} \]

whence, choosing the test functions \( v_1 = \mathcal{P}(\phi_2 - \phi_1), v_2 = c_2 - c_1 \) and using Eq. 45 (cf. Appendix A), we rewrite the left-hand side as

\[ \text{l.h.s of (27)} = \frac{1}{2} \frac{d}{dt} \left( \| (\phi_2 - \phi_1)(t) \|_0^2 + \| (c_2 - c_1)(t) \|_0^2 \right) \]
\[ + \kappa_m \int_\Omega (\Phi(\phi_2) - \Phi(\phi_1)) (\phi_2 - \phi_1) \, dx \]
\[ + D \| \nabla (c_2 - c_1)(t) \|_0^2 + \eta \| (c_2 - c_1)(t) \|_{\partial_s \Omega}^2. \tag{28} \]

As for the right-hand side, Cauchy-Schwartz’s inequality for the standard inner product in \( L^2(\Omega) \), along with the boundedness of \( f_{\alpha}^v, \ldots, q_\alpha \) in the ranges of \( \phi, c \) (recall Theorem 1), allows us to bound it from above as

\[ \text{r.h.s of (27)} \leq \sum_{\alpha = T, H} \| \gamma_{\alpha}^v \| \| g_{\alpha}^v \|_{\infty} \| f_{\alpha}^v(\phi_2) - f_{\alpha}^v(\phi_1) \|_0 \]
\[ + \| f_{\alpha}^v \| \| g_{\alpha}^v(c_2) - g_{\alpha}^v(c_1) \|_0 \| \mathcal{P}(\phi_2 - \phi_1)(t) \|_0 \]
\[ - \delta \| (\phi_2 - \phi_1)(t) \|_0^2 \]
\[ + \sum_{\alpha = T, H} \lambda_\alpha \| q_\alpha \|_{\infty} \| h_\alpha(\phi_2) - h_\alpha(\phi_1) \|_0 \| (c_2 - c_1)(t) \|_0 \]
\[ + \sum_{\alpha=T,H} \left( \sum_{v=p,d} |\gamma_v^\alpha| \|f_v^\alpha\|_\infty \|g_v^\alpha\|_\infty + \delta \phi_{\text{max}} \right) \|\mathcal{P}(\phi_2 - \phi_1)(t)\|_0 \\
+ \lambda_\alpha \|h_\alpha\|_\infty \|q_\alpha\|_\infty \|(c_2 - c_1)(t)\|_0 \right) |\Omega_{2,\alpha}(t)\triangle\Omega_{1,\alpha}(t)|^{\frac{1}{2}} \]

where we have further used that \(-\lambda_\alpha h_\alpha(\phi_1)(q_\alpha(c_2) - q_\alpha(c_1))(c_2 - c_1) \leq 0\) a.e. in \(Q_{T_{\text{max}}}\) because \(q_\alpha\) is nondecreasing (hypothesis (H7.2)) and that, by definition of symmetric difference, it results \(|\Omega_{2,\alpha}(t) - \Omega_{1,\alpha}(t)| = |\Omega_{2,\alpha}(t)\triangle\Omega_{1,\alpha}(t)|\). Since \(f_v^\alpha, h_\alpha\) are \(\Phi\)-Lipschitz continuous, it results

\[
\|f_v^\alpha(\phi_2) - f_v^\alpha(\phi_1)\|_0^2, \|h_\alpha(\phi_2) - h_\alpha(\phi_1)\|_0^2 \lesssim \int_\Omega (\Phi(\phi_2) - \Phi(\phi_1))(\phi_2 - \phi_1) \, dx.
\]

Combing this with the Lipschitz continuity of the \(g_v^{\nu}\)'s (hypothesis (H4)), Cauchy's inequality, and the fact that \(\|\mathcal{P} \cdot \|_0 \lesssim \| \cdot \|_0\) (cf. Appendix A), after some algebraic manipulations we arrive at

r.h.s. of (27) \(\lesssim \epsilon \int_\Omega (\Phi(\phi_2) - \Phi(\phi_1))(\phi_2 - \phi_1) \, dx\)

\[
+ \left(1 + \frac{1}{\epsilon}\right) \left(\|\phi_2 - \phi_1(t)\|_0^2 + \|(c_2 - c_1)(t)\|_0^2\right) \\
+ \sum_{\alpha=T,H} |\Omega_{2,\alpha}(t)\triangle\Omega_{1,\alpha}(t)|.
\]

(29)

where \(\epsilon > 0\) is arbitrary. From Eqs. 28, 29 we deduce then that there exists \(C > 0\) such that

\[
\frac{1}{2} \frac{d}{dt} \left(\|\phi_2 - \phi_1(t)\|_0^2 + \|(c_2 - c_1)(t)\|_0^2\right) \\
+ (\kappa_m - \epsilon C) \int_\Omega (\Phi(\phi_2) - \Phi(\phi_1))(\phi_2 - \phi_1) \, dx + D \|\nabla(c_2 - c_1)(t)\|_0^2 \\
+ \eta \|(c_2 - c_1)(t)\|_{0,\partial b,\Omega}^2 \\
\leq C \left[ \left(1 + \frac{1}{\epsilon}\right) \left(\|\phi_2 - \phi_1(t)\|_0^2 + \|(c_2 - c_1)(t)\|_0^2\right) \right.
\left. + \sum_{\alpha=T,H} |\Omega_{2,\alpha}(t)\triangle\Omega_{1,\alpha}(t)| \right]
\]
for a.e. $t \in [0, T_{\text{max}}]$. Particularly, it is possible to choose $\epsilon$ so small that $\kappa_m - \epsilon C > 0$, whence, invoking Gronwall’s inequality,

$$
\| (\phi_2 - \phi_1)(t) \|^2_0 + \| (c_2 - c_1)(t) \|^2_0
$$

$$
+ 2(\kappa_m - \epsilon C) \int_0^t \int_{\Omega} (\Phi(\phi_2) - \Phi(\phi_1))(\phi_2 - \phi_1) \, dx \, d\tau
$$

$$
+ 2D \int_0^t \| \nabla (c_2 - c_1)(\tau) \|^2_0 \, d\tau + 2\eta \int_0^t \| (c_2 - c_1)(\tau) \|^2_{0, \partial_b \Omega} \, d\tau
$$

$$
\leq e^{C \left( 1 + \frac{1}{\epsilon} \right) T_{\text{max}}} \left( \| \phi_{2,0} - \phi_{1,0} \|^2_0 + \| c_{2,0} - c_{1,0} \|^2_0 
$$

$$
+ C \sum_{\alpha=T, H}^{T_{\text{max}}} \int_0^T |\Omega_{2,\alpha}(t) \triangle \Omega_{1,\alpha}(t)| \, dt \right)
$$

for all $t \in [0, T_{\text{max}}]$. At this point it suffices to observe that each term at the left-hand side, being nonnegative, is singularly bounded from above by the right-hand side. Integrating the first twos on $[0, T_{\text{max}}]$ and evaluating the remaining ones for $t = T_{\text{max}}$ gives the thesis.\qed

It is worth pointing out that Theorem 2 gives an estimate on the solution to Problem 24 independent of the specific method used to track the time evolution of the interface $S$ (cf. also Sect. 3.2). Upon adopting a particular front-tracking technique, estimate 26 can be further specialized by linking the “geometric” term $|\Omega_{2,\alpha}(t) \triangle \Omega_{1,\alpha}(t)|$ to the difference of the solutions $(\phi_2 - \phi_1, c_2 - c_1)$.

## 6 The stationary problem

In this section we turn our attention to the stationary problem

\[
\begin{aligned}
-\kappa_m \Delta \phi &= \Gamma(x, \phi, c) \quad \text{in } \Omega_T, \Omega_H \\
-D \Delta c &= Q(x, \phi, c) \quad \text{in } \Omega \\
\kappa_m \nabla \phi \cdot n &= 0, \quad -D \nabla c \cdot n = \eta(c - c_b) \quad \text{on } \partial_b \Omega \\
\phi &= \phi^*, \quad c = c_b \quad \text{on } \partial_f \Omega \\
\kappa_m \nabla \phi \cdot n &= 0 \quad \text{on } S
\end{aligned}
\]

which describes the equilibrium configurations of the model for large times. The asymptotic stability of constant steady states for a reaction-diffusion system sharing some analogies with Problem 30 has been addressed in Di Francesco and Twarogowska (2011).

Heuristically, the solution of Problem 30 is what the solution of the time-dependent Problem 24 tends to for $t \to +\infty$. Making this limit rigorous with the appropriate
concept of convergence is beyond the scope of this work, therefore we will be satisfied with the above intuitive interpretation.

In Problem 30 the state variables depend on space only: \( \phi = \phi(x), \ c = c(x) \). The sub-domains \( \Omega_T, \ \Omega_H \) are fixed, their interface being \( S \).

We assume that solutions exist to Problem 30 in the following sense:

**Definition 3** (Weak solutions to the stationary problem) A weak solution to Problem 30 is a pair \((\phi, c)\) \(\in V\) such that:

(i) \( \Phi(\phi) \in H^1(\Omega) \)

(ii) \( \phi = \phi_v, \ c = cb \) on \( \partial_b\Omega \) in the trace sense

which satisfies

\[
\int_{\Omega} (\kappa_m \nabla \Phi(\phi) \cdot \nabla v_1 + D \nabla c \cdot \nabla v_2) \, dx + \eta \int_{\partial_b\Omega} (c - cb)v_2 \, d\sigma = \sum_{\alpha=T,H} \left( \int_{\Omega_\alpha} \left( \sum_{v=p,d} \gamma_v f_v(\phi_s)g_v(c)v_1 - \delta \phi v_1 - \lambda_{\alpha}(\phi)q_{\alpha}(c)v_2 \right) \, dx \right)
\]

for all \( v_1, v_2 \in V_f \).

6.1 Non-negativity, boundedness, and uniqueness of the solution

The same arguments used in the proof of Theorem 1 work here in a similar way to prove that:

**Theorem 3** Any weak solution \((\phi, c)\) \(\in V\) to Problem 30 satisfies

\[ 0 \leq \phi(x) \leq \phi_{\max}, \ 0 \leq c(x) \leq cb \text{ for a.e. } x \in \Omega. \]

As far as the uniqueness of the solution is concerned, the equilibrium shape of the sub-domains \( \Omega_T, \ \Omega_H \) plays again a major role. However, in the stationary case it is not sufficient by itself and additional conditions on the parameters of the model have to be taken into account. This is expressed by the following result:

**Theorem 4** There exists a constant \( C > 0 \), depending only on the coefficients \( \gamma_v, \lambda_{\alpha} \) and on the functions \( f_v, g_v, h_{\alpha}, q_{\alpha} \), such that if \( C \) is sufficiently small then the shape of the sub-domains \( \Omega_T, \ \Omega_H \) determines univocally the solution \((\phi, c)\) \(\in V\) to Problem 30.

**Proof** Proceeding like in the proof of Theorem 2, we now estimate

\[
(k_m - C) \int_{\Omega} (\Phi(\phi_2) - \Phi(\phi_1)) (\phi_2 - \phi_1) \, dx + (\delta - C) \|\phi_2 - \phi_1\|_0^2 \\
+ D \frac{C_p^2}{1 + C_p^2} \|c_2 - c_1\|^2 + \eta \|c_2 - c_1\|_{0, \partial_b\Omega}^2 \leq \sum_{\alpha=T,H} |\Omega_{2,\alpha} \triangle \Omega_{1,\alpha}|.
\]
where $C > 0$ is a suitable constant (see Remark 4 below). If it is “sufficiently” small, in the sense that

$$C < \min \left\{ \kappa_m, \delta, \frac{D}{C_p^2} \right\},$$

then all of the terms at the left-hand side are nonnegative. Consequently, the estimate above shows that, for a given steady configuration of the tumor and host tissues (i.e., $\Omega_{1,\alpha} = \Omega_{2,\alpha}$ for both $\alpha = T, H$), there is at most one solution $(\phi, c)$ to the problem.

**Remark 4** For the sake of definiteness, we record that a possible constant $C$ for Theorem 4 is

$$C = \frac{1}{2} \max \left\{ \sum_{\alpha = T, H} \left( \sum_{\nu = p, d} \gamma^v_{\alpha} \text{Lip} \phi(f^\nu_{\alpha}) \|g^v_{\alpha}\|_{\infty} + \lambda_{\alpha} \text{Lip} \phi(h^\alpha_{\alpha}) \|q_{\alpha}\|_{\infty} \right), \right.$$  
$$\sum_{\alpha = T, H} \left( \sum_{\nu = p, d} \gamma^v_{\alpha} \|f^\nu_{\alpha}\|_{\infty} \text{Lip}^2(g^v_{\alpha}) + \lambda_{\alpha} \|q_{\alpha}\|_{\infty} \right), \right.$$  
$$C_p^2 \sum_{\alpha = T, H} \sum_{\nu = p, d} \gamma^\nu_{\alpha} \left( \|f^\nu_{\alpha}\|_{\infty} + \|g^\nu_{\alpha}\|_{\infty} \right) \right\}.$$  

6.2 Existence of the solution

We complete our analysis of model 30 by outlining the theory of the existence of solutions. We confine ourselves to the one-dimensional setting, taking as reference domain the dimensionless interval $I = (0, 1)$. In particular, $x = 0$ will be the vascular boundary and $x = 1$ the far boundary.

The case $d = 1$ allows us to rely on two basic tools, which are not available in higher dimensions: on the one hand the Sobolev embedding $C^0(\bar{I}) \subset H^1(I)$, on the other hand Morrey’s inequality $\|u\|_{\infty} \lesssim \|u\|_1$ for $u \in H^1(I)$. Extending the theory to the case $d > 1$ is likely to require partly different tools, which is at present beyond the scope of the work.

The one-dimensional problem is written as

$$\begin{align*}
-\kappa_m \phi_{xx} &= \Gamma(x, \phi, c) \quad \text{in } (0, S), (S, 1) \\
-Dc_{xx} &= Q(x, \phi, c) \quad \text{in } I \\
\kappa_m \phi_{x}(0) &= 0, \\
\phi_{x}(1) &= \phi_{x}, \\
\kappa_m \left[ \phi_{x} \right] &= 0
\end{align*}$$

in (32)

where $S \in \bar{I}$ is the location of the point interface between tumor and host cells. In particular, $\Omega_T = (0, S)$ and $\Omega_H = (S, 1)$. By adapting Definition 3 to the
present context, a weak solution to Problem 32 is a pair \((\phi, c) \in V\), such that \(\Phi(\phi) \in H^1(I), \phi(1) = \phi_a, c(1) = c_b\), which satisfies

\[
\int_0^1 (\kappa_m \Phi(\phi)_x v_{1x} + Dc_x v_{2x}) \, dx + \eta (c(0) - c_b) v_2(0) = \sum_{\alpha=T, H} \int_{\Omega_\alpha} \left( \sum_{\nu=p, d} \gamma^\nu_{\alpha} f^\nu_{\alpha}(\phi) g^\nu_{\alpha}(c) v_1 - \delta \phi v_1 - \lambda_{\alpha} h_{\alpha}(\phi) q_{\alpha}(c) v_2 \right) \, dx
\]

for all \(v_1, v_2 \in V_f\).

For the subsequent theory, it is useful to introduce the inverse \(\Phi^{-1}\) of the constitutive function. Owing to hypothesis (H1), \(\Phi^{-1}\) is continuous and strictly increasing, with \(\Phi^{-1}(0) = 0, \Phi^{-1}(s) < 0\) for \(s < 0\), and \(\Phi^{-1}(s) > 0\) for \(s > 0\). It is also smooth on \((-\infty, 0)\) and \((0, +\infty)\), however \(\lim_{s \to 0} (\Phi^{-1})'(s) = +\infty\) because of the degeneracy of \(\Phi'\) at the origin.

In order to prove the existence of stationary solutions we resort to a splitting method, which consists in approaching the two differential equations of Problem 32 separately, assuming that the main unknown is either \(\phi\) or \(c\) and that the other function is known.

**Theorem 5** Assume \(h_{\alpha}(0) = 0\). There exists a constant \(C > 0\), depending only on the parameters \(\kappa_m, \gamma^\nu_{\alpha}, \delta, \phi_{\text{max}}\) and on the functions \(\Phi, f^\nu_{\alpha}, g^\nu_{\alpha}\), such that if \(C\) is sufficiently small then Problem 32 admits a weak solution \((\phi, c) \in V\).

**Proof** We preliminarily define the sets

\[
V := \{ f \in L^2(I) : 0 \leq f \leq \phi_{\text{max}} \text{ a.e. in } I \}
\]

\[
U := \{ f \in L^2(I) : 0 \leq f \leq c_b \text{ a.e. in } I \}.
\]

Let us begin by considering the problem

\[
\begin{aligned}
-Dc_{xx} &= Q(x, \varphi, c) \quad \text{in } I \\
Dc_x(0) &= \eta(c(0) - c_b) \\
c(1) &= c_b,
\end{aligned}
\]

(34)

where \(\varphi \in V\) is given. We associate with it an auxiliary problem in which the function \(q_{\alpha}\) is replaced by \(\tilde{q}_{\alpha} = q_{\alpha} \mathbb{1}_{[0, +\infty)}\). The corresponding weak formulation is obtained from Eq. 33 by letting \(v_1 = 0\) and writing \(\tilde{q}_{\alpha}\) in place of \(q_{\alpha}\): find \(c \in H^1(I)\), with \(c(1) = c_b\), such that

\[
D \int_0^1 c_x v_x \, dx + \eta(c(0) - c_b) v(0) = -\sum_{\alpha=T, H} \int_{\Omega_\alpha} \lambda_{\alpha} h_{\alpha}(\varphi) \tilde{q}_{\alpha}(c) v \, dx
\]

(35)

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for all $v \in V_f$. By introducing the antiderivative $\tilde{Q}_\alpha$ of $\tilde{q}_\alpha$ vanishing in zero, we can view Eq. 35 as the Euler-Lagrange equation for the functional

$$J_1(c) = \frac{D}{2} \int_0^1 c_x^2 \, dx + \frac{\eta}{2} (c(0) - c_b)^2 + \sum_{\alpha = T, H} \int_{\Omega_\alpha} \lambda_\alpha h_\alpha(\varphi) \tilde{Q}_\alpha(c) \, dx$$

over the class of admissible functions $A_1 = \{ c \in H^1(I) : c(1) = c_b \}$. Thus we can seek our solution $c$ as a minimizing point of $J_1$ on $A_1$.

Since $\tilde{q}_\alpha(s) = 0$ for $s < 0$ and $\tilde{q}_\alpha(s) = q_\alpha(s) \geq 0$ for $s \geq 0$, we have $\tilde{Q}_\alpha(s) \geq 0$ for all $s \in \mathbb{R}$. Using further that $\lambda_\alpha$ and $h_\alpha$ are nonnegative we obtain $J_1(c) \geq D/2 \| c_x \|^2_{L^2}$, which implies that $J_1$ is coercive. Therefore any minimizing sequence $\{ c_k \}_{k=1}^\infty \subseteq A_1$ is bounded in $H^1(I)$ and, upon passing to a subsequence, we can assume that it converges weakly to some $\tilde{c} \in H^1(I)$. But $c_k - c_b \in V_f$ all $k$ and $V_f$ is a weakly closed subspace of $H^1(I)$ (in view of Mazur’s Theorem, as it is closed), thus we deduce more precisely $\tilde{c} - c_b \in V_f$, i.e., $\tilde{c}(1) = c_b$ and ultimately $\tilde{c} \in A_1$.

Considering that $J_1$ is of the form $\int_0^1 L_1(c_x, c, x) \, dx$ for the Lagrangian

$$L_1(p, z, x) = \frac{D}{2} p^2 - \eta(z - c_b)p + \sum_{\alpha = T, H} \lambda_\alpha(x) h_\alpha(\varphi(x)) \tilde{Q}_\alpha(z) 1_{\Omega_\alpha}(x),$$

which is smooth and convex in $p$ for all $z \in \mathbb{R}$ and all $x \in I$, we deduce that $J_1$ is sequentially weakly lower semicontinuous on $H^1(I)$. Thus $\tilde{c}$ is a minimizing point of $J_1$, i.e., a solution to our auxiliary problem.

Mimicking the computations of the proof of Theorem 3 with $v_1 = 0$ reveals that, for any fixed $\varphi \in \mathcal{V}$, all solutions to the auxiliary problem range in $[0, c_b]$. Hence we conclude $0 \leq \tilde{c}(x) \leq c_b$ for all $x \in I$, and consequently that $\tilde{c}$ solves also Problem 34 because the latter and the auxiliary problem coincide for $c \in [0, c_b]$. Notice that $\tilde{c} \in \mathcal{U}$.

We show now that the solutions to Problem 34 depend continuously on $\varphi$. Let $c_1$, $c_2$ be two solutions corresponding to $\varphi_1$, $\varphi_2 \in \mathcal{V}$, respectively, then for all $v \in V_f$ the difference $c_2 - c_1$ satisfies

$$D \int_0^1 (c_2 - c_1)xv_x \, dx + \eta \left( c_2(0) - c_1(0) \right) v(0)$$

$$= - \sum_{\alpha = T, H} \int_{\Omega_\alpha} \lambda_\alpha \left( (h_\alpha(\varphi_2) - h_\alpha(\varphi_1)) q_\alpha(c_2) + h_\alpha(\varphi_1)(q_\alpha(c_2) - q_\alpha(c_1)) \right) v \, dx.$$

We choose $v = c_2 - c_1$ and observe that $-\lambda_\alpha h_\alpha(\varphi_1)(q_\alpha(c_2) - q_\alpha(c_1))(c_2 - c_1) \leq 0$ in $\Omega_\alpha$ (hypothesis (H7.2)), whence
\[
D \| (c_2 - c_1)_x \|_0^2 + \eta \left( (c_2(0) - c_1(0))^2 \right)
\]
\[
\leq \sum_{\alpha = T, H} \lambda_\alpha q_\alpha (c_2) | h_\alpha (\varphi_2) - h_\alpha (\varphi_1) | \cdot | c_2 - c_1 | dx
\]
\[
\leq \frac{1}{2} \sum_{\alpha = T, H} \lambda_\alpha \| q_\alpha \|_\infty \left( \frac{1}{\epsilon} \| h_\alpha (\varphi_2) - h_\alpha (\varphi_1) \|_0^2 + \epsilon \| c_2 - c_1 \|_0^2 \right).
\]

Now we recall, from hypothesis (H6), that \( h_\alpha \) is \( \Phi \)-Lipschitz continuous, whence
\[
\| h_\alpha (\varphi_2) - h_\alpha (\varphi_1) \|_0^2 \leq \text{Lip}_{\Phi (h_\alpha)} \int_0^1 (\Phi (\varphi_2) - \Phi (\varphi_1)) (\varphi_2 - \varphi_1) \, dx
\]
\[
\lesssim \| \varphi_2 - \varphi_1 \|_0^2.
\]

Thus the previous computation can be continued by asserting that there exists \( C > 0 \) such that
\[
\frac{D - \epsilon CC_P^2}{1 + C_P^2} \| c_2 - c_1 \|_1^2 + \eta \left( (c_2(0) - c_1(0))^2 \right) \leq \frac{C}{\epsilon} \| \varphi_2 - \varphi_1 \|_0^2,
\] (36)

where we also applied Poincaré’s inequality to \( c_2 - c_1 \in V_f \). Choosing \( \epsilon > 0 \) so small that \( D - \epsilon CC_P^2 > 0 \), we get from Eq. 36 the desired continuity estimate. In particular, for \( \varphi_1 = \varphi_2 \) we obtain the uniqueness of the solution to Problem 34.

The foregoing results enable us to define the operator \( \mathcal{S}_1 : \mathcal{V} \rightarrow \mathcal{U} \) such that \( \mathcal{S}_1 (\varphi) = c \). From the continuity estimate 36 we deduce that \( \mathcal{S}_1 \) is Lipschitz continuous on \( \mathcal{V} \) and, with a little more work, that it is also compact. To see this, we observe first of all that the assumption \( h_\alpha (0) = 0 \) implies \( \mathcal{S}_1 (0) = c_b \) (i.e., the unique solution to Problem 34 for \( \varphi = 0 \) is \( c = c_b \)), then we choose \( \varphi_1 = \varphi_2 = 0 \) in Eq. 36 and drop the subindex 2 to obtain
\[
\| \mathcal{S}_1 (\varphi) - c_b \|_1^2 \lesssim \| \varphi \|_0^2.
\]

We take now \( \{ \varphi_k \}_{k=1}^\infty \subseteq \mathcal{V} \) and notice that, in view of the latter estimate, the sequence \( \{ \mathcal{S}_1 (\varphi_k) - c_b \}_{k=1}^\infty \) is bounded in \( H^1 (I) \). Owing to Rellich’s Theorem, we can therefore assume, upon passing to a subsequence, that \( \mathcal{S}_1 (\varphi_k) - c_b \) converges in \( L^2 (I) \) as \( k \to \infty \), i.e., that the sequence \( \{ \mathcal{S}_1 (\varphi_k) \}_{k=1}^\infty \subseteq \mathcal{U} \) is convergent, which proves the compactness of \( \mathcal{S}_1 \).

We turn now our attention to the problem
\[
\begin{align*}
-\kappa_m \Phi (\phi)_{xx} &= \Gamma (x, \phi, \theta) \quad \text{in} \ (0, S), 
\ k_{m} \Phi (\phi)_{x} (0) &= 0,
\phi (1) &= \phi_*,
\kappa_m [\Phi (\phi)_{x}] &= 0.
\end{align*}
\] (37)

where \( \theta \in \mathcal{U} \) is given. Again, we associate with it an auxiliary problem in which the functions \( f^p_\alpha, f^d_\alpha \) are replaced by \( \tilde{f}^p_\alpha = \mathbb{1}_{[0, \phi_{\text{max}}]}, \tilde{f}^d_\alpha = \mathbb{1}_{[0, +\infty)} \), respectively.

The weak formulation is recovered from Eq. 33 by letting \( v_2 = 0 \) and substituting conveniently the functions at the right-hand side: find \( \phi \in H^1(I) \), with \( \Phi(\phi) \in H^1(I) \) and \( \phi(1) = \phi_+ \), such that

\[
\kappa_m \int_0^1 \Phi(\phi)_x v_x \, dx = \sum_{\alpha=T, H} \int_{\Omega_\alpha} \left( \sum_{v=p, d} \gamma^v_\alpha \tilde{f}^v_\alpha(\phi) g^v_\alpha(\theta) - \delta \phi \right) v \, dx
\]

for all \( v \in V_f \). We set \( u := \Phi(\phi) \), whence \( \phi = \Phi^{-1}(u) \), so that this equation becomes

\[
\kappa_m \int_0^1 u_x v_x \, dx = \sum_{\alpha=T, H} \int_{\Omega_\alpha} \left( \sum_{v=p, d} \gamma^v_\alpha (\tilde{f}^v_\alpha \circ \Phi^{-1})(u) g^v_\alpha(\theta) - \delta \Phi^{-1}(u) \right) v \, dx \tag{38}
\]

for all \( v \in V_f \). If we introduce the antiderivatives \( \tilde{F}^v_\alpha, \Psi \) of \( \tilde{f}^v_\alpha \circ \Phi^{-1}, \Phi^{-1} \) vanishing in zero, we can regard Eq. 38 as the Euler-Lagrange equation for the functional

\[
J_2(u) = \frac{\kappa_m}{2} \int_0^1 u_x^2 \, dx - \sum_{\alpha=T, H} \int_{\Omega_\alpha} \left( \sum_{v=p, d} \gamma^v_\alpha \tilde{F}^v_\alpha(u) g^v_\alpha(\theta) - \delta \Psi(u) \right) \, dx
\]

over the class of admissible functions \( \mathcal{A}_2 = \{ u \in H^1(I) : u(1) = \Phi(\phi_+) \} \). Thus, again we can look for our solution \( u \) as a minimizing point of \( J_2 \) on \( \mathcal{A}_2 \).

Notice that \( \tilde{F}^p_\alpha(s) \leq \tilde{F}^p_\alpha(\Phi(\phi_{\text{max}})) \), and that \( \tilde{F}^d_\alpha(s), \Psi(s) \geq 0 \) for all \( s \in \mathbb{R} \). Therefore, recalling further that \( \gamma^d_\alpha < 0 \) (hypothesis (H2)), we have

\[
J_2(u) \geq \frac{\kappa_m}{2} \| u_x \|_0^2 - \sum_{\alpha=T, H} \gamma^p_\alpha \| g^p_\alpha \|_\infty \tilde{F}^p_\alpha(\Phi(\phi_{\text{max}})) |\Omega_\alpha|.
\]

\( J_2 \) is thus coercive, hence any minimizing sequence \( \{ u_k \}_{k=1}^\infty \subseteq \mathcal{A}_2 \) converges weakly (up to possibly passing to subsequences) to some \( \bar{u} \in H^1(I) \). Since \( u_k - \Phi(\phi_+) \in V_f \) and \( V_f \) is weakly closed in \( H^1(I) \), it results \( \bar{u} - \Phi(\phi_+) \in V_f \), that is \( \bar{u} \in \mathcal{A}_2 \). In addition, \( J_2 \) is in turn of the form \( \int_0^1 L_2(u_x, u, x) \, dx \) for the Lagrangian

\[
L_2(p, z, x) = \frac{\kappa_m}{2} p^2 - \sum_{\alpha=T, H} \left( \sum_{v=p, d} \gamma^v_\alpha \tilde{F}^v_\alpha(z) g^v_\alpha(\theta(x)) - \delta \Psi(z) \right) \mathbb{1}_{\Omega_\alpha}(x),
\]

which is smooth and convex in \( p \) for each \( z \in \mathbb{R}, x \in I \), hence \( J_2 \) is sequentially weakly lower semicontinuous on \( H^1(I) \). It follows that \( \bar{u} \) is a minimizing point for \( J_2 \) on \( \mathcal{A}_2 \), and consequently \( \Phi^{-1}(\bar{u}) \) is a weak solution to our auxiliary problem.
Mimic now the computations of the proof of Theorem 3 with \( v_2 = 0 \) to obtain that, for any fixed \( \theta \in \mathcal{U} \), all solutions to the auxiliary problem range in \([0, \Phi_{\text{max}}]\), whence \( 0 \leq \bar{\phi} \leq \Phi_{\text{max}} \) in \( \bar{I} \). But the auxiliary problem and Problem 37 coincide for \( \phi \in [0, \Phi_{\text{max}}] \), hence ultimately we have found a solution \( \bar{\phi} \in \mathcal{V} \) to Problem 37.

Next we show that, by introducing suitable constraints on the parameters, we can guarantee that \( \bar{\phi} \) be strictly positive in \( \bar{I} \). Let us pick \( v_1 = \Phi(\phi) - \Phi(\phi_\ast) \), \( v_2 = 0 \) as test functions in Eq. 33 to discover

\[
\kappa_m \int_0^1 \Phi(\phi)_x (\Phi(\phi) - \Phi(\phi_\ast))_x \, dx = \sum_{\alpha = T, H, \nu = p, d} \int_{\Omega_\alpha} \gamma^\nu_\alpha f^\nu_\alpha(\phi) g^\nu_\alpha(\phi)(\Phi(\phi) - \Phi(\phi_\ast)) \, dx \\
- \delta \int_0^1 \phi (\Phi(\phi) - \Phi(\phi_\ast)) \, dx.
\]

Noting that \( \Phi(\phi)_x = (\Phi(\phi) - \Phi(\phi_\ast))_x \) at the left-hand side and using the boundedness of \( f^\nu_\alpha, g^\nu_\alpha, \phi \) at the right-hand side, we estimate

\[
\| (\Phi(\phi) - \Phi(\phi_\ast))_x \|_0^2 \lesssim \| \Phi(\phi) - \Phi(\phi_\ast) \|_\infty.
\]

In addition, owing to Poincaré’s and Morrey’s inequalities,

\[
\| (\Phi(\phi) - \Phi(\phi_\ast))_x \|_0^2 \gtrsim \| \Phi(\phi) - \Phi(\phi_\ast) \|_1^2 \gtrsim \| \Phi(\phi) - \Phi(\phi_\ast) \|_\infty^2,
\]

hence finally there exists \( C_1 > 0 \) such that \( \| \Phi(\phi) - \Phi(\phi_\ast) \|_\infty \leq C_1 \), which indicates that \( \Phi(\phi(x)) \geq \Phi(\phi_\ast) - C_1 \) for all \( x \in \bar{I} \). For definiteness, we report the explicit expression of a possible constant \( C_1 \):

\[
C_1 = \frac{1 + C_2^2}{\kappa_m} \left( \sum_{\alpha = T, H, \nu = p, d} \gamma^\nu_\alpha \| f^\nu_\alpha \|_\infty \| g^\nu_\alpha \|_\infty |\Omega_\alpha| + \delta \Phi_{\text{max}} \right).
\]

We fix now \( \epsilon \in (0, \Phi_\ast) \) and observe that \( \phi \geq \epsilon \) if and only if \( \Phi(\phi) \geq \Phi(\epsilon) \), thus we can guarantee that \( \phi \) be strictly positive in \( \bar{I} \) if we require \( \Phi(\phi_\ast) - C_1 \geq \Phi(\epsilon) \), which implies the constraint

\[
C_1 \leq \Phi(\phi_\ast) - \Phi(\epsilon). \tag{39}
\]

Given this, any solution \( \phi \in \mathcal{V} \) to Problem 37 satisfies \( 0 < \epsilon \leq \phi \leq \Phi_{\text{max}} \) in \( \bar{I} \).

Finally we assert that, under condition 39, solutions to Problem 37 depend continuously on \( \theta \in \mathcal{U} \) in the norm \( \| \cdot \|_0 \). For this, let \( \phi_1, \phi_2 \) be two solutions corresponding to \( \theta_1, \theta_2 \in \mathcal{U} \), respectively, then for all \( v \in V_f \) their difference \( \phi_2 - \phi_1 \) solves
We choose \( v = \mathcal{P}(\phi_2 - \phi_1) \) (cf. Appendix A) and, mimicking the computations of Theorem 4, we find that there exists \( C_2 > 0 \) such that

\[
(\kappa_m - C_2) \int_0^1 (\Phi(\phi_2) - \Phi(\phi_1)) (\phi_2 - \phi_1) \, dx + (\delta - C_2)\|\phi_2 - \phi_1\|_0^2 \lesssim \|\theta_2 - \theta_1\|_0^2
\]

(for the sake of completeness, we point out that the constant \( C_2 \) is the same as the one appearing in Theorem 4, cf. also Remark 4). Assume

\[
C_2 \leq \min\{\kappa_m, \delta\},
\]

then, since \( |\Phi(\phi_2) - \Phi(\phi_1)| \geq (\min_{s \in [\epsilon, \phi_{\max}]} \Phi'(s)) |\phi_2 - \phi_1| \), it follows

\[
\min_{s \in [\epsilon, \phi_{\max}]} \Phi'(s)(\kappa_m - C_2)\|\phi_2 - \phi_1\|_0^2 + (\delta - C_2)\|\phi_2 - \phi_1\|_0^2 \lesssim \|\theta_2 - \theta_1\|_0^2.
\]

which yields the desired continuity estimate, together with uniqueness of the solution to Problem 37 when \( \theta_1 = \theta_2 \).

Define now \( C := \max\{C_1, C_2\} \) and impose

\[
C < \min\{\Phi(\phi_*) - \Phi(\epsilon), \kappa_m, \delta\},
\]

then Problem 37 admits a unique solution \( \phi \in \mathcal{V} \) for any given \( \theta \in \mathcal{U} \). Consequently, we are in a position to define the operator \( \mathcal{S}_2 : \mathcal{U} \rightarrow \mathcal{V} \) such that \( \mathcal{S}_2(\theta) = \phi \), which is Lipschitz continuous on \( \mathcal{U} \) in view of Eq. 40.

At last, we come back to the full Problem 32 in this way: we construct by composition the operator \( \mathcal{S} := \mathcal{S}_2 \circ \mathcal{S}_1 : \mathcal{V} \rightarrow \mathcal{V} \) such that \( \mathcal{S}(\phi) = \phi \). Since \( \mathcal{S}_1 \) is continuous and compact and \( \mathcal{S}_2 \) is continuous, \( \mathcal{S} \) is in turn continuous and compact; moreover, \( \mathcal{V} \) is convex and closed in \( L^2(I) \) (to see the latter property, use that convergence in \( L^2(I) \) implies pointwise convergence a.e. in \( I \) upon passing to subsequences). Schauder’s Fixed Point Theorem implies then that \( \mathcal{S} \) has a fixed point \( \phi \in \mathcal{V} \), hence the pair \( (\phi, c = \mathcal{S}_1(\phi)) \) is a weak solution to Problem 32 and we are done.

\[ \square \]

Remark 5 If, in addition to the hypotheses of Theorem 5, also the hypotheses of Theorem 4 hold true then the solution to Problem 32 is unique.
6.3 Further qualitative features of the stationary solutions

Some additional insights into the qualitative trends of the stationary solutions can be obtained by referring to specific applications of the models discussed in this paper. For instance, in Tosin (2008) the problem of the growth of tumor cord is specifically addressed, by means of mixture theory equations fitting the framework dealt with in the present work.

Tumor cords are nearly cylindrical arrangements of tumor cells developing along a blood vessel. They are composed by two main parts: the head, made by proliferating cells which penetrate the host environment, and the tail, which instead reaches a steady state due to a balance between stress and nutrient-limited growth. In such a context, the one-dimensional Problem 32 can be used to study the distribution of tumor cells and nutrient in a transversal section of the cord tail, given that, as shown in the already cited paper (Tosin 2008), the solution depends there only on the distance from the blood vessel.

In particular, the analysis is considerably simplified if one makes the ansatz \( \phi = \phi_h \) in the interval \((S, 1)\), which amounts to guessing the solution outside the tumor cord, assuming in particular that the host tissue, pushed at either side \( x = S \) (by the tumor tissue) and \( x = 1 \) (by e.g., a confining bone), reaches an equilibrium featuring a uniform distribution of the internal stress. Such a function \( \phi \) is indeed a solution to the first equation of Problem 32 if one sets e.g.,

\[
\gamma^p_H = \gamma^d_H = \delta = 0,
\]

corresponding to the approximation that host cells neither proliferate nor die during the time of observation of the system. In addition, by letting also

\[
\lambda_H = 0,
\]

which implies no nutrient consumption by host cells, it is readily seen that \( c = c_b \) is in turn a good ansatz for the nutrient distribution in \((S, 1)\). Due to the regularity of the solution \((\phi, c)\) in \( I \), the following conditions further apply at the interface \( S \):

\[
\phi(S) = \phi_h, \quad c(S) = c_b, \quad c_x(S) = 0
\]

so that finally the problem in the domain \((0, S)\) of the tumor tissue reads

\[
\begin{align*}
-\kappa_m \Phi(\phi)_{xx} &= \sum_{\nu=p,d} a^\nu \int_T^T(\phi)g_T^\nu(c) & \text{in } (0, S) \\
-Dc_{xx} &= -\lambda h_T(\phi)q_T(c) & \text{in } (0, S) \\
\kappa_m \Phi(\phi)_x(0) &= 0, \quad Dc_x(0) = \eta(c(0) - c_b) \\
\phi(S) &= \phi_h, \quad c(S) = c_b \\
\kappa_m \Phi(\phi)_x(S) &= 0, \quad c_x(S) = 0.
\end{align*}
\]
As an example, we may consider the following choices:

\[
\begin{align*}
\Phi(\phi) &= \phi^m \quad (m \text{ odd}) \\
\gamma_T^p &= -\gamma_T^d =: \gamma_T > 0 \\
f_T^p(\phi) &= f_T^d(\phi) = [\phi^n(\phi_{\text{max}} - \phi)]^+(n \text{ odd}) \\
g_T^p(c) &= (c - c_*)^+ \\
g_T^d(c) &= (c - c_*)^- \\
h_T(\phi) &= (\phi^n)^+ \quad (n \text{ odd}) \\
q_T(c) &= c,
\end{align*}
\]

whence we obtain the sample equations

\[
\begin{align*}
-\kappa_m (\phi^m)_{xx} &= \gamma_T [\phi^n(\phi_{\text{max}} - \phi)]^+(c - c_*) \\
-Dc_{xx} &= -\lambda_T (\phi^n)^+ c.
\end{align*}
\]

Notice that the requirement of odd exponents \(m, n\), as well as the use of the positive part on the terms containing \(\phi\) at the right-hand side, are practical ways of meeting hypotheses (H1), (H3), (H3.1), (H3.2), (H6) about the monotonicity of \(\Phi\) and the signs of \(f_T^p, f_T^d, h_T\) on \(R\).

A usually nontrivial task is checking the \(\Phi\)-Lipschitz continuity of the functions \(f_\alpha^v, h_\alpha\) on the basis of Definition 1. Following Laurençot and Wrzosek (2005), we discover that a sufficient condition, much simpler to verify, is

\[
(f_\alpha^v)' \Phi^{-1/2}, h_\alpha' \Phi^{-1/2} \in L^\infty(0, \phi_{\text{max}}),
\]

which, in the present case, entails the constraint

\[
m \leq 2(n - 1).
\]

It is worth pointing out that the latter gives rise to meaningful values of the exponent \(m\) only if \(n > 1\).

The theorems proved in the preceding sections guarantee the existence of a stationary solution \((\phi, c)\) describing the steady distribution of tumor cells and nutrient in the tail of the tumor cord, such that \(0 \leq \phi \leq \phi_{\text{max}}\) and \(0 \leq c \leq c_b\) in \((0, S)\). This solution is determined univocally by the location of the interface \(S\), which, in the present context, is representative of the thickness reached by the cord tail. Furthermore, by referring to the specific analysis developed in Tosin (2008), it is possible to deduce that:

(i) \( \phi \geq \phi_\ast \) in \((0, S)\)

(ii) \( c \) is non-increasing in \((0, S)\), with in particular \(c(0) \leq c_b\).

Recalling the ansatz formulated about \(\phi\) in \((S, 1)\), condition (i) implies that the tumor tissue is more compressed than the host at equilibrium, as a consequence of a more
intense proliferation of tumor cells. In this respect, condition (ii) is the natural consequence of the nutrient consumption operated by tumor cells for sustaining such a duplication activity.

7 Possible developments

In this paper we have addressed the mathematical formulation of initial and boundary-value problems for multiphase models of tumor growth, deduced from the framework developed in Preziosi and Tosin (2009). We have performed a qualitative analysis of both the time-dependent and the time-independent problems, mainly by means of $L^2$-$H^1$ estimates, establishing non-negativity, boundedness, uniqueness, and continuous dependence of the solution on the initial data. In the one-dimensional time-independent case we have also obtained the existence of the solution.

The analytical techniques used here may be profitably exploited to approach more advanced multiphase models, also fitting the framework presented in Preziosi and Tosin (2009), which incorporate a more accurate description of the interactions between the cells and the extracellular matrix. Based on phenomenological laboratory observations (Baumgartner et al. 2000; Canetta et al. 2005; Sun et al. 2005), they take into account the adhesion of the former to the latter by relating the cell-matrix stress $m_{am}$ (a component of the overall external stress $m_α$ included in Eq. 2) to the cell-matrix relative velocity $v_m - v_α$ as

$$v_m - v_α = K_{am} \left(1 - \frac{Σ_{am}}{|m_{am}|}\right)^+ m_{am}.$$  \(41\)

This formula says that if the magnitude of the stress $m_{am}$ is below some critical threshold $Σ_{am} > 0$ then there is no relative motion between the cells and the matrix, that is the former remain anchored to the latter. Conversely, if $|m_{am}|$ is above the threshold $Σ_{am}$ then the interaction stress $m_{am}$ is proportional to the relative velocity $v_m - v_α$, thus recovering a more classical viscous friction which, in particular, means that cells slide on the matrix with their own velocity. If Eq. 41 is used, with the additional assumption of motionless matrix ($v_m = 0$), then the equations ruling cell dynamics take the form

$$\frac{∂φ_α}{∂t} - \nabla \cdot \left[φ_α \mathcal{J}_α(φ_τ, φ_H, |∇φ|)K_{am} ∇(φ Σ(φ))\right] = Γ_α,$$  \(42\)

where

$$\mathcal{J}_α(φ_τ, φ_H, |∇φ|) = \left( \frac{φ_α}{φ} - \frac{Σ_{am}}{|∇(φ Σ(φ))|}\right)^+$$

translates the adhesion mechanisms discussed above. In particular, the velocity $v_α$ of the cells is

$$v_α = -\mathcal{J}_α K_{am} ∇(φ Σ(φ)).$$
hence if $|\nabla (\phi \Sigma (\phi))| < \Sigma_{am}$ then $v_\alpha = 0$ because $I_\alpha = 0$ (recall that $\phi_\alpha \leq \phi$ by definition) and the cells stay attached to the matrix, while if $|\nabla (\phi \Sigma (\phi))| > \Sigma_{am}$ the cells might detach from the matrix since one may have $I_\alpha > 0$.

Equation 42 can be regarded as a refined version of Eq. 3, which would be interesting to study in view of its physical significance, possibly adapting the techniques illustrated in this paper. Notice indeed that setting $\Sigma_\alpha m = 0$ for both $\alpha = T$ and $\alpha = H$, which amounts to assuming a purely viscous friction between the cells and the matrix without attachment/detachment, reduces Eq. 42 to Eq. 3, hence the latter turns out to be a particular case of the former. Additional mathematical difficulties need however to be overcome, especially the harder degeneracy of the differential operator in space caused by the term $I_\alpha$.

Acknowledgments The author wants to address special thanks to prof. Luigi Preziosi, who inspired this research line and kindly proofread the final version of the manuscript.

Appendix A: The Poisson solution operator

In this appendix we introduce a basic tool, inspired by Fadimba and Sharpley (1995); Laurençot and Wrzosek (2005), useful to handle the nonlinearity $\Phi$ of Eq. 12.

Consider the linear elliptic problem

$$\begin{cases} -\Delta u = f & \text{in } \Omega \\ \nabla u \cdot n = 0 & \text{on } \partial_b \Omega \\ u = 0 & \text{on } \partial_f \Omega \end{cases} \quad (43)$$

and assume $\partial_f \Omega \neq \emptyset$ (see Appendix B for the case $\partial_f \Omega = \emptyset$), $f \in L^2(\Omega)$. The classical weak formulation is:

$$\begin{align*}
\text{find } u \in V_f \text{ such that } \\
\int_\Omega \nabla u \cdot \nabla v \, dx = \int_\Omega f v \, dx, \quad \forall \, v \in V_f,
\end{align*} \quad (44)$$

which, owing to Lax-Milgram theory, yields a unique weak solution $u$ with $\|\nabla u\|_0 \lesssim \|f\|_0$.

Let us introduce the linear operator $\mathcal{P} : L^2(\Omega) \to L^2(\Omega)$, termed the Poisson solution operator, which associates with $f$ the solution $u = \mathcal{P} f$ to Problem 44 above. $\mathcal{P}$ is bounded, symmetric, and positive definite. Therefore, besides the standard inner product $(f, g) = \int_\Omega f(x) g(x) \, dx$, we can endow $L^2(\Omega)$ with an inner product induced by $\mathcal{P}$: $(f, g) := (\mathcal{P} f, g)$, with corresponding norm $\|f\|_\mathcal{P}^2 := (f, f) = (\mathcal{P} f, f)$. Using $\mathcal{P}$ we rewrite Eq. 44 as

$$\int_\Omega \nabla \mathcal{P} f \cdot \nabla v \, dx = \int_\Omega f v \, dx, \quad \forall \, f \in L^2(\Omega), \, v \in V_f, \quad (45)$$

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Fig. 5 The geometrical configuration of the domain $\Omega$ in the problem of a tumor mass surrounded by host tissue with no far boundary.

whence, letting $v = \mathcal{P} f \in V_f$, we see that $\|f\|_0 = \|\nabla \mathcal{P} f\|_0$. Thus the previous a priori estimate on $u$ implies $\|f\|_0 \lesssim \|f\|_0$. On the other hand, in view of Poincaré’s inequality, we also have $\|\mathcal{P} f\|_0 \lesssim \|\nabla \mathcal{P} f\|_0 = \|f\|_0$.

Given $u \in L^2(0, T_{\text{max}}; V_f)$ with $u_t \in L^2(0, T_{\text{max}}; V'_f)$, the duality pairing between $u_t(t) \in V'_f$ and $\mathcal{P} u(t) \in V_f$ yields, for a.e. $t$,

$$\langle u_t(t), \mathcal{P} u(t) \rangle = \frac{1}{2} \frac{d}{dt} \|u(t)\|_0^2.$$ 

Appendix B: Problems with no far boundary

The aim of this appendix is to extend the theory developed in Sect. 5 to problems in which there is actually no far boundary within the host environment, that is the whole tissue is surrounded by blood vessels ($\partial \Omega \equiv \partial_b \Omega, \partial_f \Omega = \emptyset$). For instance, this situation arises when studying the confinement of a tumor mass within a healthy tissue well supplied with blood by a nearby vasculature. In this case we can imagine that $\Omega_T(t) \subset \Omega$ at all times, with $\partial \Omega = \partial \Omega_H(t) \equiv \partial_b \Omega$ (Fig. 5). From the mathematical point of view, the main point is the disappearance of the Dirichlet boundary conditions, which forces one to modify the Poisson solution operator $\mathcal{P}$ introduced in Appendix A in order to deal with the new problem for $\phi$.

Specifically, in place of Problem 43 we consider (cf. also Fadimba and Sharpley 1995)

$$\begin{cases} -\Delta u = f - \langle f \rangle & \text{in } \Omega \\ \nabla u \cdot n = 0 & \text{on } \partial \Omega \\ \langle u \rangle = \langle f \rangle & \text{in } \Omega \end{cases}$$

for $f \in L^2(\Omega)$, where $\langle \cdot \rangle$ denotes average on $\Omega$:

$$\langle f \rangle := \frac{1}{|\Omega|} \int_{\Omega} f(x) \, dx.$$
The weak formulation is:

\[
\begin{align*}
\text{find } u \in H^1(\Omega) \text{ such that } \\
\int_{\Omega} \nabla u \cdot \nabla v \, dx + |\Omega| \langle u \rangle \langle v \rangle = \int_{\Omega} f v \, dx, \quad \forall \ v \in H^1(\Omega),
\end{align*}
\]

whence, owing to Lax-Milgram theory, we get a unique weak solution fulfilling \( \|u\|_1 \lesssim \|f\|_0 \). Setting \( u = \mathcal{P} f \), we observe from Eq. 46 that the operator \( \mathcal{P} \) satisfies now

\[
\int_{\Omega} \nabla \mathcal{P} f \cdot \nabla v \, dx + |\Omega| \langle \mathcal{P} f \rangle \langle v \rangle = \int_{\Omega} f v \, dx, \quad \forall \ f \in L^2(\Omega), \ v \in H^1(\Omega),
\]

therefore the inner product \( \langle \cdot, \cdot \rangle \) and the induced norm \( \| \cdot \|_0 \) take the following forms:

\[
\langle (f, g) \rangle = \int_{\Omega} \nabla \mathcal{P} f \cdot \nabla g \, dx + |\Omega| \langle \mathcal{P} f \rangle \langle g \rangle
\]

\[
\| f \|_0^2 = \| \nabla \mathcal{P} f \|_0^2 + |\Omega| \langle \mathcal{P} f \rangle^2 \times \| \mathcal{P} f \|_1^2.
\]

This essentially affects the estimates of Theorem 2 when dealing with

\[
\int_{\Omega} \nabla \Phi(\phi_2) - \Phi(\phi_1) \cdot \nabla \mathcal{P}(\phi_2 - \phi_1) \, dx
\]

\[
= \int_{\Omega} (\Phi(\phi_2) - \Phi(\phi_1))(\phi_2 - \phi_1) \, dx - |\Omega| \langle \Phi(\phi_2) - \Phi(\phi_1) \rangle \langle \mathcal{P}(\phi_2 - \phi_1) \rangle,
\]

because of the second term at the right-hand side which must be estimated. First we use Cauchy’s inequality to find

\[
\langle \Phi(\phi_2) - \Phi(\phi_1) \rangle \langle \mathcal{P}(\phi_2 - \phi_1) \rangle \leq \frac{\epsilon}{2} (\Phi(\phi_2) - \Phi(\phi_1))^2 + \frac{1}{2\epsilon} (\mathcal{P}(\phi_2 - \phi_1))^2.
\]

Next we employ Cauchy-Schwartz’s inequality and Lipschitz continuity of \( \Phi \) to discover

\[
\langle \Phi(\phi_2) - \Phi(\phi_1) \rangle^2 \leq \frac{1}{|\Omega|} \int_{\Omega} |\Phi(\phi_2) - \Phi(\phi_1)|^2 \, dx
\]

\[
\leq \frac{\text{Lip}(\Phi)}{|\Omega|} \int_{\Omega} (\Phi(\phi_2) - \Phi(\phi_1))(\phi_2 - \phi_1) \, dx,
\]

\[
\langle \mathcal{P}(\phi_2 - \phi_1)(t) \rangle^2 \leq \frac{1}{|\Omega|} \| \mathcal{P}(\phi_2 - \phi_1)(t) \|_0^2 \leq C \| (\phi_2 - \phi_1)(t) \|_0^2.
\]
whence
\[
\int_\Omega \nabla (\Phi(\phi_2) - \Phi(\phi_1)) \cdot \nabla \mathcal{P}(\phi_2 - \phi_1) \, dx \\
\geq \left( 1 - \frac{\epsilon \text{Lip}(\Phi)}{2|\Omega|} \right) \int_\Omega (\Phi(\phi_2) - \Phi(\phi_1))(\phi_2 - \phi_1) \, dx - \frac{C}{2\epsilon} \|\phi_2 - \phi_1(t)\|^2_0.
\]

Choosing \( \epsilon > 0 \) so small that \( \epsilon \text{Lip}(\Phi) < 2|\Omega| \), the terms at the right-hand side can be finally incorporated into the similar ones already present in the proof of Theorem 2.

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