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A MULTIPHASE CAHN–HILLIARD–DARCY MODEL FOR TUMOUR GROWTH WITH NECROSIS

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We derive a Cahn–Hilliard–Darcy model to describe multiphase tumour growth taking interactions with multiple chemical species into account as well as the simultaneous occurrence of proliferating, quiescent and necrotic regions. A multitude of phenomena such as nutrient diffusion and consumption, angiogenesis, hypoxia, blood vessel growth, and inhibition by toxic agents, which are released for example by the necrotic cells, are included. A new feature of the modelling approach is that a volume-averaged velocity is used, which dramatically simplifies the resulting equations. With the help of formally matched asymptotic analysis we develop new sharp interface models. Finite element numerical computations are performed and in particular the effects of necrosis on tumour growth is investigated numerically. In particular, for certain modelling choices we obtain some form of focal and patchy necrotic growth that have been observed in experiments.

Keywords: Multiphase tumour growth; phase field model; Darcy flow; necrosis; cellular adhesion; matched asymptotic expansions; finite element computations.

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1. Introduction

The morphological evolution of cancer cells, driven by chemical and biological mechanisms, is still poorly understood even in the simplest case of avascular tumour growth. It is well-known that in the avascular stage, initially homogeneous tumour cells will eventually develop heterogeneity in their growth behaviour. For example, quiescent cells appear when the tumour reaches a diffusion-limited size, where levels of nutrients, such as oxygen, are too low to support cell proliferation, and necrotic cells develop when the nutrient density drops further. It is expected that angiogenic factors are secreted by the quiescent tumour cells to induce the development of a capillary network towards the tumour and deliver much required nutrients for proliferation⁶². But it has also been observed (experimentally⁵⁵ and in numerical simulations^{12,14}) that the tumour exhibits morphological instabilities, driven by a combination of chemotactic gradients and inhomogeneous proliferation, which allows the interior tumour cells to access nutrients by increasing the surface area of the tumour interface.

In this paper, we propose a multi-component diffuse interface model for modelling heterogeneous tumour growth. We consider L types of cells, with M chemical species. Similar in spirit to Ref. 3 (see also Refs. 5, 22, 61), we model each of the L different cell types as inertia-less fluids, and each of the M chemical species can freely diffuse and may be subject to additional mechanisms such as chemotaxis and active transport. In the diffuse interface methodology, interfaces between different components are modelled as thin transition layers, in which the macroscopically distinct components are allowed to mix microscopically. This is in contrast to the sharp interface approach, where the interfaces are modelled as idealised moving hypersurfaces. The treatment of cells as viscous inertia-less fluids naturally leads to a notion of an averaged velocity for the fluid mixture, and we will use a volume-averaged velocity, which is also considered in Refs. 1, 27.

From basic conservation laws, we will derive the following multi-component model:

$$\operatorname{div} \bar{v} = \mathbf{1} \cdot \mathbf{U}(\boldsymbol{\varphi}, \boldsymbol{\sigma}), \quad (1.1a)$$

$$\bar{v} = -K \nabla p + K (\nabla \boldsymbol{\varphi})^\top (\boldsymbol{\mu} - \mathbf{N}_{,\boldsymbol{\varphi}}(\boldsymbol{\varphi}, \boldsymbol{\sigma})), \quad (1.1b)$$

$$\partial_t \boldsymbol{\varphi} + \operatorname{div} (\boldsymbol{\varphi} \otimes \bar{v}) = \operatorname{div} (\underline{\underline{C}}(\boldsymbol{\varphi}, \boldsymbol{\sigma}) \nabla \boldsymbol{\mu}) + \mathbf{U}(\boldsymbol{\varphi}, \boldsymbol{\sigma}), \quad (1.1c)$$

$$\boldsymbol{\mu} = -\beta \varepsilon \Delta \boldsymbol{\varphi} + \beta \varepsilon^{-1} \Psi_{,\boldsymbol{\varphi}}(\boldsymbol{\varphi}) + \mathbf{N}_{,\boldsymbol{\varphi}}(\boldsymbol{\varphi}, \boldsymbol{\sigma}), \quad (1.1d)$$

$$\partial_t \boldsymbol{\sigma} + \operatorname{div} (\boldsymbol{\sigma} \otimes \bar{v}) = \operatorname{div} (\underline{\underline{D}}(\boldsymbol{\varphi}, \boldsymbol{\sigma}) \nabla \mathbf{N}_{,\boldsymbol{\sigma}}(\boldsymbol{\varphi}, \boldsymbol{\sigma})) + \mathbf{S}(\boldsymbol{\varphi}, \boldsymbol{\sigma}), \quad (1.1e)$$

for a vector $\boldsymbol{\varphi} = (\varphi_1, \dots, \varphi_L)^\top$ of volume fractions, i.e., $\sum_{i=1}^L \varphi_i = 1$ and $\varphi_i \geq 0$ for $1 \leq i \leq L$, where φ_i represents the volume fraction of the i th cell type, and for a vector $\boldsymbol{\sigma} = (\sigma_1, \dots, \sigma_M)^\top$, with σ_j representing the density of the j th chemical species. The velocity \bar{v} is the volume-averaged velocity, p is the pressure, $\boldsymbol{\mu} = (\mu_1, \dots, \mu_L)^\top$ is the vector of chemical potentials associated to $\boldsymbol{\varphi}$, and $\mathbf{N}_{,\boldsymbol{\varphi}} \in \mathbb{R}^L$ and $\mathbf{N}_{,\boldsymbol{\sigma}} \in \mathbb{R}^M$ denote the partial derivatives of the chemical free energy density N with respect to $\boldsymbol{\varphi}$ and

σ , respectively.

The system (1.1) can be seen as the multi-component variant of the Cahn–Hilliard–Darcy system derived in Ref. 27. Equation (1.1e) can be viewed as a convection-reaction-diffusion system with a vector of source terms $\mathbf{S} \in \mathbb{R}^M$, where for vectors $\mathbf{a} \in \mathbb{R}^k$ and $\mathbf{b} \in \mathbb{R}^l$, the tensor product $\mathbf{a} \otimes \mathbf{b} \in \mathbb{R}^{k \times l}$ is defined as $(\mathbf{a} \otimes \mathbf{b})_{ij} = a_i b_j$ for $1 \leq i \leq k$ and $1 \leq j \leq l$. The positive semi-definite mobility tensor $\underline{D}(\varphi, \sigma)$ can be taken as a second order tensor in $\mathbb{R}^{M \times M}$, or even as a fourth order tensor in $\mathbb{R}^{M \times d \times M \times d}$, where d is the spatial dimension.

Equations (1.1c) and (1.1d) constitute a multi-component convective Cahn–Hilliard system with a vector of source terms $\mathbf{U} \in \mathbb{R}^L$ and a mobility tensor $\underline{C}(\varphi, \sigma)$, which we take to be either a second order tensor in $\mathbb{R}^{L \times L}$ or a fourth order tensor in $\mathbb{R}^{L \times d \times L \times d}$. Furthermore, we ask that $\sum_{i=1}^L \underline{C}_{ij} = 0$ in the former case and $\sum_{i=1}^L \underline{C}_{imjl} = 0$ in the latter case for any $1 \leq j \leq L$ and $1 \leq m, l \leq d$. These conditions ensure that $\sum_{i=1}^L \varphi_i(t) = 1$ for $t > 0$ if $\sum_{i=1}^L \varphi_i(0) = 1$. One example of such a second order mobility tensor is $\underline{C}_{ij}(\varphi, \sigma) = m_i(\varphi_i)(\delta_{ij} - m_j(\varphi_j) / \sum_{k=1}^L m_k(\varphi_k))$ for $1 \leq i, j \leq L$ and so-called bare mobilities $m_i(\varphi_i)$, see Ref. 19. The vector $\Psi_{,\varphi}$ is the vector of partial derivatives of a multi-well potential Ψ with L equal minima at the points \mathbf{e}_l , $l = 1, \dots, L$, where \mathbf{e}_l is the l th unit vector in \mathbb{R}^L .

Equation (1.1b) is a generalised Darcy’s law (with permeability $K > 0$) relating the volume-averaged velocity \bar{v} and the pressure p , while in equation (1.1a), $\mathbf{1} = (1, \dots, 1)^T \in \mathbb{R}^L$ and $\mathbf{1} \cdot \mathbf{U}$ is the sum of the components of the vector of source terms \mathbf{U} in (1.1c), and (1.1a) relates the gain or loss of volume from the vector of source terms \mathbf{U} to the changes of mass balance.

Lastly, $\beta > 0$ and $\varepsilon > 0$ are parameters related to the surface tension and the interfacial thickness, respectively. In fact, associated with (1.1) is the free energy

$$\mathcal{E}(\varphi, \sigma) = \int_{\Omega} \frac{\beta \varepsilon}{2} \sum_{i=1}^L |\nabla \varphi_i|^2 + \frac{\beta}{\varepsilon} \Psi(\varphi) + N(\varphi, \sigma) d\mathcal{L}^d, \quad (1.2)$$

where $d\mathcal{L}^d$ denotes integration with respect to the d dimensional Lebesgue measure. The first two terms in the integral account for the interfacial energy (and by extension the adhesive properties of the different cell types), and the last term accounts for the free energy of the chemical species and their interaction with the cells.

We focus on a special case with $L = 3$ and $M = 1$, so that we have three cell types; host cells (φ_1), proliferating tumour cells (φ_2) and necrotic tumour cells (φ_3), along with one chemical species (σ) acting as nutrient, for example oxygen. Then, (1.1e) becomes a scalar equation, with a scalar mobility function $D(\varphi, \sigma)$, and a scalar source function $S(\varphi, \sigma)$. In this setting, one can consider a chemical free energy density of the form

$$N(\varphi, \sigma) = \frac{\chi_{\sigma}}{2} |\sigma|^2 - \chi_{\varphi} \sigma \varphi_2 - \chi_n f(\sigma) \varphi_3, \quad (1.3)$$

where $\chi_{\sigma} > 0, \chi_{\varphi}, \chi_n \geq 0$ are constants and $f : [0, \infty) \rightarrow [0, \infty)$ is a monotonically decreasing function such that $f(s) = 0$ for $s \geq c_{*} > 0$. The first term of (1.3) will lead to diffusion of the nutrient, and the second term models the chemotaxis

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mechanism that drives the proliferating tumour cells to regions of high nutrient, which was similarly considered in Refs. 12, 13, 27, 36. The third term shows that it is energetically favourable to be in the necrotic phase when the nutrient density is below c_* . Indeed, when $\sigma < c_*$, $f(\sigma)$ is positive, and so the term $-\chi_n f(\sigma)\varphi_3$ is negative when $\varphi_3 = 1$. Overall we obtain from (1.1) the three-component model

$$\operatorname{div} \vec{v} = \mathbf{1} \cdot \mathbf{U}(\varphi, \sigma), \quad \vec{v} = -K \nabla p + K (\nabla \varphi)^\top (\boldsymbol{\mu} - \mathbf{N}_{,\varphi}(\varphi, \sigma)), \quad (1.4a)$$

$$\partial_t \varphi + \operatorname{div}(\varphi \otimes \vec{v}) = \operatorname{div}(\underline{\underline{C}}(\varphi, \sigma) \nabla \boldsymbol{\mu}) + \mathbf{U}(\varphi, \sigma), \quad (1.4b)$$

$$\boldsymbol{\mu} = -\beta \varepsilon \Delta \varphi + \beta \varepsilon^{-1} \Psi_{,\varphi}(\varphi) + \mathbf{N}_{,\varphi}(\varphi, \sigma), \quad (1.4c)$$

$$\partial_t \sigma + \operatorname{div}(\sigma \vec{v}) = \operatorname{div}(D(\varphi, \sigma) \nabla (\chi_\sigma \sigma - \chi_\varphi \varphi_2 - \chi_n f'(\sigma) \varphi_3)) + S(\varphi, \sigma), \quad (1.4d)$$

$$\mathbf{N}_{,\varphi}(\varphi, \sigma) = (0, -\chi_\varphi \sigma, -\chi_n f(\sigma))^\top. \quad (1.4e)$$

Similar to Ref. 27, we define

$$\lambda = \frac{\chi_\varphi}{\chi_\sigma}, \quad \theta = \frac{\chi_n}{\chi_\sigma}, \quad d(\varphi, \sigma) = D(\varphi, \sigma) \chi_\sigma, \quad (1.5)$$

so that (1.4d) becomes

$$\partial_t \sigma + \operatorname{div}(\sigma \vec{v}) = \operatorname{div}(d(\varphi, \sigma) \nabla (\sigma - \lambda \varphi_2 - \theta f'(\sigma) \varphi_3)) + S(\varphi, \sigma), \quad (1.6)$$

which allows us to decouple the chemotaxis mechanism that was appearing in (1.4c) and (1.4d). We point out that it is possible to neglect the effects of fluid flow by sending $K \rightarrow 0$ in the case $\mathbf{1} \cdot \mathbf{U} = 0$. By Darcy's law and $\operatorname{div} \vec{v} = 0$, we obtain $\vec{v} \rightarrow \vec{0}$ as $K \rightarrow 0$, and the above system (1.4) with source terms satisfying $\mathbf{1} \cdot \mathbf{U}(\varphi, \sigma) = 0$ transforms into

$$\partial_t \varphi = \operatorname{div}(\underline{\underline{C}}(\varphi, \sigma) \nabla \boldsymbol{\mu}) + \mathbf{U}(\varphi, \sigma),$$

$$\boldsymbol{\mu} = -\beta \varepsilon \Delta \varphi + \beta \varepsilon^{-1} \Psi_{,\varphi}(\varphi) + \mathbf{N}_{,\varphi}(\varphi, \sigma),$$

$$\partial_t \sigma = \operatorname{div}(D(\varphi, \sigma) \nabla (\chi_\sigma \sigma - \chi_\varphi \varphi_2 - \chi_n f'(\sigma) \varphi_3)) + S(\varphi, \sigma).$$

It is noteworthy to point out that the condition $\mathbf{1} \cdot \mathbf{U}(\varphi, \sigma) = 0$ for the above reduced model is rather restrictive. Although our diffuse interface model is derived from balance laws and is thermodynamically consistent, the choices of source terms $\mathbf{U}(\varphi, \sigma)$, $S(\varphi, \sigma)$, as well as the chemical free energy $N(\varphi, \sigma)$ in the later sections are phenomenological rather than derived from a macroscopic limit of cellular dynamics. Thus, when one considers using the reduced model with no velocity, the modification of the vector $\mathbf{U}(\varphi, \sigma)$ so that $\mathbf{1} \cdot \mathbf{U}(\varphi, \sigma) = 0$ introduces artificial terms which may not have biological relevance. In Sec. 4 below we detail a comparison between the case $K > 0$ (Darcy flow) and $K = 0$ (velocity is neglected) for a specific setting involving necrotic cells, and the simulations demonstrate that the full Darcy model yields more realistic results than the reduced model.

In our choice of the adhesion energy in (1.2), the presence of a multi-well potential $\Psi(\varphi)$ leads to the development of large regions of individual cell-phases separated by thin interfacial layers. Biologically, this means that the interfaces between the heterogeneous growth regions within the tumour are energetic, and one

may view the tumour as a cluster consisting of $L-1$ distinct types of cells each with their own interfacial energy. This is in contrast to the usual intuition where the tumour contains the same type of cells exhibiting heterogeneity in growth behaviour due to environmental influences. The latter can also be treated within a multiphase framework by choosing a different interfacial energy, which we will briefly outline below. For general $L \geq 2$ and $M \geq 1$, let φ_1 denote the volume fraction of the host cells, and $\varphi_T = 1 - \varphi_1 = \sum_{i=2}^L \varphi_i$ is the total volume fraction of the tumour cells exhibiting $(L-1)$ -types of growth behaviour. Then, consider the interfacial energy:

$$E(\boldsymbol{\varphi}) = \int_{\Omega} \frac{\beta\varepsilon}{2} \left| \sum_{i=2}^L \nabla \varphi_i \right|^2 + \frac{\beta}{\varepsilon} W \left(\sum_{i=2}^L \varphi_i \right) d\mathcal{L}^d, \quad (1.7)$$

where W is a scalar potential with equal minima at 0 and 1. Note that (1.7) can be viewed as a function of φ_T , i.e., $E(\boldsymbol{\varphi}) = \hat{E}(\varphi_T) = \int_{\Omega} \frac{\beta\varepsilon}{2} |\nabla \varphi_T|^2 + \frac{\beta}{\varepsilon} W(\varphi_T) d\mathcal{L}^d$, and it is energetically favourable to have $\varphi_T = 0$ (representing the host tissues) or $\varphi_T = 1$ (representing the tumour as a whole). It holds that the first variation of E with respect to φ_i , $2 \leq i \leq L$, satisfies

$$\frac{\delta E}{\delta \varphi_i} = \frac{\delta \hat{E}}{\delta \varphi_T} = -\beta\varepsilon \Delta \varphi_T + \beta\varepsilon^{-1} W'(\varphi_T) =: \mu_T,$$

and so, if the chemical free energy density N is independent of $\boldsymbol{\varphi}$, the corresponding equations for the chemical potentials for the tumour phases now read as

$$\mu_1 = 0, \quad \mu_i = -\beta\varepsilon \Delta \varphi_T + \beta\varepsilon^{-1} W'(\varphi_T) = \mu_T \text{ for } 2 \leq i \leq L.$$

Then, choosing a second order mobility tensor $\underline{C}(\boldsymbol{\varphi}, \boldsymbol{\sigma})$ such that $\sum_{j=2}^L \underline{C}_{ij}(\boldsymbol{\varphi}, \boldsymbol{\sigma}) = M(\varphi_i)$, for $2 \leq i \leq L$, and $\sum_{j=2}^L \underline{C}_{1j}(\boldsymbol{\varphi}, \boldsymbol{\sigma}) = -\sum_{j=2}^L M(\varphi_j)$ for a non-negative mobility function $M(\cdot)$, the equations for φ_i take the form

$$\partial_t \varphi_i + \operatorname{div}(\varphi_i \vec{v}) = \operatorname{div}(M(\varphi_i) \nabla \mu_T) + U_i(\boldsymbol{\varphi}, \boldsymbol{\sigma}), \quad 2 \leq i \leq L,$$

which resemble the system of equations studied in Refs. 10, 11, 23, 65, 67. Note in particular that only μ_T is needed to drive the evolution of φ_i , $2 \leq i \leq L$. However, the mathematical treatment of these types of models is difficult due to the fact that the equation for φ_i is now a transport equation with a high order source term $\operatorname{div}(M(\varphi_i) \nabla \mu_T)$, and the natural energy identity of the model does not appear to yield useful a priori estimates for φ_i . In the case that the mobility M is a constant (which considerably simplifies some of the equations), the existence of a weak solution for the model of Ref. 11 has been studied by Dai et al. in Ref. 17. Hence, we argue that the consideration of a multi-well potential as in (1.2), although it leads to a vectorial Cahn–Hilliard system, may yield a mathematical model that is further amenable to analytical and numerical investigations, see for example Ref. 24.

The specific forms of the source terms $\mathbf{U}(\boldsymbol{\varphi}, \boldsymbol{\sigma})$ and $\mathbf{S}(\boldsymbol{\varphi}, \boldsymbol{\sigma})$ will depend on the specific situation we want to model. In our numerical investigations, we will primarily focus on a three-component model consisting of host cells (φ_1), proliferating

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tumour cells (φ_2) and necrotic cells (φ_3) in the presence of a quasi-static nutrient (σ), i.e., $L = 3$ and $M = 1$. Of biological relevance are the following choices:

$$S(\varphi, \sigma) = -\mathcal{C}\varphi_2\sigma, \quad (1.8a)$$

$$\mathbf{U}_A(\varphi, \sigma) = (0, \varphi_2(\mathcal{P}\sigma - \mathcal{A}), \mathcal{A}\varphi_2 - D_N\varphi_3)^\top, \quad (1.8b)$$

$$\mathbf{U}_B(\varphi, \sigma) = (-\varphi_2\mathcal{P}\sigma, \varphi_2(\mathcal{P}\sigma - \mathcal{A}), \mathcal{A}\varphi_2 - D_N\varphi_3)^\top, \quad (1.8c)$$

$$\mathbf{U}_C(\varphi, \sigma) = (0, \frac{1}{\varepsilon}\varphi_2^2(1 - \varphi_2)^2(\mathcal{P}\sigma - \mathcal{A}), \frac{1}{\varepsilon}\varphi_3^2(1 - \varphi_3)^2(\mathcal{A} - D_N))^\top. \quad (1.8d)$$

The source term (1.8a) models the consumption of nutrients by the proliferating cells at a constant rate $\mathcal{C} > 0$. The choice (1.8b) models the proliferation of tumour cells at a constant rate $\mathcal{P} > 0$ by consuming the nutrient, the apoptosis of the tumour cells at a constant rate $\mathcal{A} \geq 0$, which can be considered as a source term for the necrotic cells, and we assume that the necrotic cells degrade at constant rate $D_N \geq 0$. Meanwhile, in (1.8c), any mass gain for the proliferating tumour equals the mass loss by the host cells, and vice versa for the necrotic and proliferating cells. In (1.8d), the functions $\varphi_2^2(1 - \varphi_2)^2$ and $\varphi_3^2(1 - \varphi_3)^2$ are zero except near the vicinity of the interfacial layers. The scaling with ε^{-1} is chosen similarly as in Ref. 37, which allows the source terms to influence the evolution of the interfaces, see Sec. 3.4 below for more details.

In (1.1), the parameter ε is related to the thickness of the interfacial layers, and hence it is natural to ask if a sharp interface model will emerge in the limit $\varepsilon \rightarrow 0$. Due to the multi-component nature of (1.1), the sharp interface model consists of equations posed on time-dependent regions $\Omega_i = \{\varphi_i = 1\}$ for $1 \leq i \leq L$ and on the free boundaries $\Gamma_{ij} = \partial\Omega_i \cap \partial\Omega_j$ for $1 \leq i < j \leq L$. We refer the reader to Sec. 3 below for the multi-component sharp interface limit of (1.1), which is too complex to state here.

Instead, we consider the system (1.4) with a quasi-static nutrient (neglecting the left-hand side of (1.4d)), $\chi_\varphi = \chi_n = 0$ (so that $\mathbf{N}_{,\varphi}(\varphi, \sigma) = \mathbf{0}$), $D(\varphi, \sigma) = 1$, a mobility tensor $\underline{\underline{C}}(\varphi, \sigma) = (\delta_{ij} - \frac{1}{3})_{i,j=1}^3$, and the source term $S(\varphi, \sigma) = -\mathcal{C}\varphi_2\sigma$. Then, (1.4) simplifies to

$$\operatorname{div} \bar{v} = \mathbf{1} \cdot \mathbf{U}(\varphi, \sigma), \quad \bar{v} = -K\nabla p + K(\nabla\varphi)^\top \boldsymbol{\mu}, \quad (1.9a)$$

$$\partial_t \varphi_1 + \operatorname{div}(\varphi_1 \bar{v}) = \Delta y + U_1(\varphi, \sigma), \quad (1.9b)$$

$$\partial_t \varphi_2 + \operatorname{div}(\varphi_2 \bar{v}) = \Delta z + U_2(\varphi, \sigma), \quad (1.9c)$$

$$\partial_t \varphi_3 + \operatorname{div}(\varphi_3 \bar{v}) = -\Delta(y + z) + U_3(\varphi, \sigma), \quad (1.9d)$$

$$\mu_k = -\beta\varepsilon\Delta\varphi_k + \beta\varepsilon^{-1}\Psi_{,\varphi_k}(\varphi), \quad k = 1, 2, 3, \quad (1.9e)$$

$$0 = \Delta\sigma - \mathcal{C}\varphi_2\sigma, \quad (1.9f)$$

where $\mathbf{U} = (U_1, U_2, U_3)^\top$,

$$3y = (\mu_1 - \mu_2) + (\mu_1 - \mu_3), \quad 3z = -(\mu_1 - \mu_2) + (\mu_2 - \mu_3).$$

Note that $3(y + z) = (\mu_1 - \mu_3) + (\mu_2 - \mu_3)$, and hence diffusion is governed by the difference of chemical potentials, see also Ref. 7. Let us denote $\Omega_H = \{\varphi_1 = 1, \varphi_2 =$

$\varphi_3 = 0\}$, $\Omega_P = \{\varphi_2 = 1, \varphi_1 = \varphi_3 = 0\}$, $\Omega_N = \{\varphi_3 = 1, \varphi_1 = \varphi_2 = 0\}$ as the regions of host cells, proliferating tumour and necrotic cells, respectively, along with interfaces $\Gamma_{PN} = \partial\Omega_P \cap \partial\Omega_N$ and $\Gamma_{HP} = \partial\Omega_H \cap \partial\Omega_P$. We also consider the setting where the host cells do not share a boundary with the necrotic cells, i.e., $\Gamma_{HN} = \emptyset$. This makes sense biologically as the tumour cells display necrotic growth only when the level of nutrient in the surrounding drops below a critical threshold. As the host cells consume considerably less nutrient than the tumour cells, the nutrient level in the vicinity of the host cells is plentiful and we expect that necrotic cells do not develop there. Then, the sharp interface limit of (1.9) reads as (see Sec. 3.4 for a derivation)

$$\begin{cases} -\Delta y = U_1(\varphi, \sigma) - (\mathbf{1} \cdot \mathbf{U}(\varphi, \sigma))\varphi_1, \\ -\Delta z = U_2(\varphi, \sigma) - (\mathbf{1} \cdot \mathbf{U}(\varphi, \sigma))\varphi_2, \\ -K\Delta p = \mathbf{1} \cdot \mathbf{U}(\varphi, \sigma), \end{cases} \quad \text{in } \Omega_H \cup \Omega_P \cup \Omega_N, \quad (1.10a)$$

$$\Delta\sigma = \begin{cases} 0 & \text{in } \Omega_H \cup \Omega_N, \\ \mathcal{C}\sigma & \text{in } \Omega_P, \end{cases} \quad (1.10b)$$

$$[y] = [z] = [\sigma] = [\nabla\sigma] \cdot \vec{\nu} = [\nabla p] \cdot \vec{\nu} = 0 \quad \text{on } \Gamma_{PN} \cup \Gamma_{HP}, \quad (1.10c)$$

$$\begin{cases} [p]_N^P = \beta\gamma_{PN}\kappa = 2y - z, \\ -\mathcal{V} + K\nabla p \cdot \vec{\nu} = [\nabla z]_N^P \cdot \vec{\nu}, \\ 0 = [\nabla y]_N^P \cdot \vec{\nu}, \end{cases} \quad \text{on } \Gamma_{PN}, \quad (1.10d)$$

$$\begin{cases} [p]_P^H = \beta\gamma_{HP}\kappa = y - z, \\ -\mathcal{V} + K\nabla p \cdot \vec{\nu} = [\nabla y]_P^H \cdot \vec{\nu} = -[\nabla z]_P^H \cdot \vec{\nu}, \end{cases} \quad \text{on } \Gamma_{HP}. \quad (1.10e)$$

In the above $\vec{\nu}$ denotes the unit normal on Γ_{PN} pointing into Ω_P or the unit normal on Γ_{HP} pointing into Ω_H , κ is the mean curvature, γ_{PN} and γ_{HP} are positive constants related the potential Ψ , \mathcal{V} denotes the normal velocity of Γ_{PN} or Γ_{HP} , and $[\cdot]$ denotes the jump across the interfaces. Let us point out that for the choice (1.8b) of $\mathbf{U}(\varphi, \sigma)$, equation (1.10a) becomes

$$-\Delta y = 0 \quad \text{in } \Omega_H \cup \Omega_P \cup \Omega_N, \quad -\Delta z = \begin{cases} 0 & \text{in } \Omega_H \cup \Omega_N, \\ -\mathcal{A} & \text{in } \Omega_P, \end{cases} \quad -K\Delta p = \begin{cases} 0 & \text{in } \Omega_H, \\ \mathcal{P}\sigma & \text{in } \Omega_P, \\ -D_N & \text{in } \Omega_N, \end{cases}$$

and for the choice (1.8c) of $\mathbf{U}(\varphi, \sigma)$, equation (1.10a) becomes

$$-\Delta y = \begin{cases} -\mathcal{P}\sigma & \text{in } \Omega_P, \\ 0 & \text{in } \Omega_H \cup \Omega_N, \end{cases} \quad -\Delta z = \begin{cases} \mathcal{P}\sigma - \mathcal{A} & \text{in } \Omega_P, \\ 0 & \text{in } \Omega_H \cup \Omega_N, \end{cases} \quad -K\Delta p = \begin{cases} 0 & \text{in } \Omega_H \cup \Omega_P, \\ -D_N & \text{in } \Omega_N. \end{cases}$$

Note that the overall gain or loss in mass is reflected in the equation for p , compare for instance with Sec. 4.6 of Ref. 13.

In contrast, multi-component models obtained from a degenerate interfacial energy such as (1.7) have simpler sharp interface limits. Due to the fact that (1.7) is a

function only of φ_T , the asymptotic analysis leads to a sharp interface limit which is defined on two time-dependent regions $\Omega_T = \{\varphi_T = 1\}$ (tumour) and $\Omega_H = \Omega \setminus \Omega_T$ (host), and one free boundary $\Gamma = \partial\Omega_T$. In particular, differentiation between the different types of tumour cells is based on the local density of nutrients^{48,49,50,68}, unlike in (1.10) where an evolution law for the interface Γ_{PN} between the proliferating and necrotic cells is stated. We refer the reader also to Sec. 3.5 below for the sharp interface limit of a model with degenerate interfacial energy.

Let us now give a non-exhaustive comparison between the multi-component diffuse interface models in the literature and the model (1.1) we propose in this work.

Interfacial energy/cellular adhesion. In Refs. 10, 11, 23, 45, 46, 65, 67, it is assumed that the different types of tumour cells prefer to adhere to one another instead of the host cells, and thus the degenerate interfacial energy density (1.7) is considered. This is in contrast to Ref. 54 and our present work, where the adhesive properties of cells with different growth behaviour are distinct and the total energy (1.2) is considered. Furthermore, we point out that the model of Ref. 66 can be seen as a two-phase model (tumour and host cells), which uses an interfacial energy similar to (1.7). But they use a non-conserved phase field equation of Allen–Cahn type, rather than a Cahn–Hilliard equation, to describe the tumour evolution.

Mixture velocity. In Refs. 10, 11, 23, 54, 65, 67 a mass-averaged velocity is used instead of the volume-averaged velocity considered in our present approach and also in Ref. 60. Meanwhile, in Refs. 45, 46 the velocities of the cell components are assumed to be negligible.

Source terms. Aside from mitosis proportional to the local density of nutrients, and constant apoptosis for the tumour cells, certain sink terms for one cell type become source terms for another, for example the term $\mathcal{A}\varphi_2$ in (1.8b). It is commonly assumed that the host cells are homeostatic^{10,11,23,67,65}, and so the source term for the host cells is zero. In Refs. 45, 46, where quiescent cells are also considered, a two-sided exchange between the proliferating cells and the quiescent cells, and a one-sided exchange from quiescent cells to necrotic cells based on local nutrient concentration are included. However, to the best of our knowledge, source terms of the form (1.8d) have not yet been considered in the multi-component setting.

Sharp interface limit. Out of the aforementioned references, it appears that only Ref. 65 state a sharp interface limit for a multi-component diffuse interface model with degenerate interfacial energy (1.7). For a two-phase setting we refer the reader to Refs. 12, 27.

The remainder of this paper is organised as follows: In Sec. 2 we derive the diffuse interface model (1.1) from thermodynamic principles. In Sec. 3 we perform

a formal asymptotic analysis to derive the sharp interface limit. In Sec. 4 we present some numerical simulations for the three-component tumour model derived in this paper.

2. Model derivation

In this section, we derive (1.1) from balance laws and ensure thermodynamic consistency by choosing appropriate constitutive assumptions. Since a similar procedure is used for the two-phase setting and is presented in great detail in Ref. 27, we only briefly outline the procedure. In an open, bounded domain $\Omega \subset \mathbb{R}^d$, $d = 1, 2, 3$, we consider a mixture that consists of $L \geq 2$ cell components. Denoting the actual mass of matter per volume in the mixture of the i th component as ρ_i , and the constant mass density of a pure component i as $\bar{\rho}_i$, we define the volume fraction of the i th component as the ratio $\varphi_i := \rho_i/\bar{\rho}_i$ for $1 \leq i \leq L$. The vector of volume fractions $\boldsymbol{\varphi} = (\varphi_1, \dots, \varphi_L)^\top \in \mathbb{R}^L$ plays a crucial role in our model (1.1) where it identifies which cell-phases we are at a particular point in the domain Ω .

Physically, we expect $\rho_i \in [0, \bar{\rho}_i]$ and so $\varphi_i \in [0, 1]$. Assuming no external volume compartment exists besides the aforementioned L components, we necessarily have that $\varphi_1 + \dots + \varphi_L = \sum_{i=1}^L \varphi_i = 1$. Each of the cell component is transported by its individual velocity, which we denote by \vec{v}_{φ_i} for the i th component, and we define the mixture velocity as the volume-averaged velocity

$$\vec{v} = \sum_{i=1}^L \varphi_i \vec{v}_{\varphi_i}. \quad (2.1)$$

Lastly, in addition to the cells, we allow for the presence of $M \geq 1$ chemical species in Ω , whose densities we summarise as a vector $\boldsymbol{\sigma} = (\sigma_1, \dots, \sigma_M)^\top \in \mathbb{R}^M$.

2.1. Balance laws

The mass balances for the i th cell component and the j th chemical species read as

$$\partial_t \rho_i + \operatorname{div}(\rho_i \vec{v}_{\varphi_i}) = \mathcal{U}_i, \quad i = 1, \dots, L, \quad (2.2a)$$

$$\partial_t \sigma_j + \operatorname{div}(\sigma_j \vec{v}) + \operatorname{div} \vec{J}_{\sigma_j} = S_j, \quad j = 1, \dots, M, \quad (2.2b)$$

where \mathcal{U}_i denotes a source/sink term for the i th component, S_j denotes a source/sink term for the j th chemical species, $\sigma_j \vec{v}$ models the transport by the volume-averaged velocity and \vec{J}_{σ_j} accounts for other transport mechanisms.

Dividing (2.2a) by $\bar{\rho}_i$ and using the relation $\varphi_i = \rho_i/\bar{\rho}_i$ leads to an equation for φ_i involving the individual velocities \vec{v}_{φ_i} . Upon summing and using $\sum_{i=1}^L \varphi_i = 1$ and (2.1) leads to the mass balance

$$\operatorname{div} \vec{v} = \sum_{i=1}^L \operatorname{div}(\varphi_i \vec{v}_{\varphi_i}) = \sum_{i=1}^L \frac{\mathcal{U}_i}{\bar{\rho}_i}. \quad (2.3)$$

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It is however more convenient to have an equation for φ_i in terms of the volume-averaged velocity \bar{v} , thus, introducing the fluxes

$$\bar{J}_{\varphi_i} = \rho_i(\bar{v}_{\varphi_i} - \bar{v}), \quad i = 1, \dots, L, \quad (2.4)$$

leads to

$$\partial_t \varphi_i + \frac{1}{\bar{\rho}_i} \operatorname{div} \bar{J}_{\varphi_i} + \operatorname{div}(\varphi_i \bar{v}) = \frac{\mathcal{U}_i}{\bar{\rho}_i}, \quad i = 1, \dots, L. \quad (2.5)$$

As a further consequence of the condition $\sum_{i=1}^L \varphi_i = 1$, after dividing (2.4) by $\bar{\rho}_i$, summing and using (2.1) we find that necessarily

$$\sum_{i=1}^L \frac{1}{\bar{\rho}_i} \bar{J}_{\varphi_i} = \sum_{i=1}^L \varphi_i (\bar{v}_{\varphi_i} - \bar{v}) = \bar{v} - \bar{v} = \bar{0} \quad (2.6)$$

has to hold. For a more compact presentation, we introduce

$$\begin{aligned} \mathbf{U} &= (\bar{\rho}_1^{-1} \mathcal{U}_1, \dots, \bar{\rho}_L^{-1} \mathcal{U}_L)^\top \in \mathbb{R}^L, & \mathbf{S} &= (S_1, \dots, S_M)^\top \in \mathbb{R}^M, \\ \underline{\underline{K}}_\varphi^\top &= (\bar{\rho}_1^{-1} \bar{J}_{\varphi_1}, \dots, \bar{\rho}_L^{-1} \bar{J}_{\varphi_L}) \in \mathbb{R}^{d \times L}, & \underline{\underline{K}}_\sigma^\top &= (\bar{J}_{\sigma_1}, \dots, \bar{J}_{\sigma_M}) \in \mathbb{R}^{d \times M}, \end{aligned} \quad (2.7)$$

i.e., the l th row of $\underline{\underline{K}}_\varphi$ is the flux $\bar{\rho}_l^{-1} \bar{J}_{\varphi_l} \in \mathbb{R}^d$ and the l th row of $\underline{\underline{K}}_\sigma$ is the flux $\bar{J}_{\sigma_l} \in \mathbb{R}^d$. We recall that the divergence applied to a second order tensor $\underline{\underline{A}} \in \mathbb{R}^{k \times l}$ results in a vector in \mathbb{R}^k whose i th component is the divergence of $(A_{ij})_{j=1}^l$, that is, $(\operatorname{div} \underline{\underline{A}})_i = \sum_{j=1}^l \partial_{x_j} A_{ij}$. Then, (2.3), (2.5), and (2.2b) can be compactly summarised as

$$\operatorname{div} \bar{v} = \mathbf{1} \cdot \mathbf{U}, \quad (2.8a)$$

$$\partial_t \varphi + \operatorname{div}(\varphi \otimes \bar{v}) + \operatorname{div} \underline{\underline{K}}_\varphi = \mathbf{U}, \quad (2.8b)$$

$$\partial_t \sigma + \operatorname{div}(\sigma \otimes \bar{v}) + \operatorname{div} \underline{\underline{K}}_\sigma = \mathbf{S}, \quad (2.8c)$$

respectively, where $\mathbf{1} = (1, \dots, 1)^\top \in \mathbb{R}^L$.

2.2. Energy inequality

To derive the appropriate constitutive assumptions for the fluxes $\underline{\underline{K}}_\varphi, \underline{\underline{K}}_\sigma$ so that the model is thermodynamically consistent, we employ an energetic approach. To account for the condition $\sum_{i=1}^L \varphi_i = 1$, we introduce for $L \in \mathbb{N}$, $L \geq 2$,

$$\operatorname{HG} = \left\{ \boldsymbol{\phi} = (\phi_1, \dots, \phi_L)^\top \in \mathbb{R}^L : \sum_{i=1}^L \phi_i = 1 \right\}, \quad \operatorname{G} = \{ \boldsymbol{\phi} \in \operatorname{HG} : \phi_i \geq 0 \forall i \}. \quad (2.9)$$

The latter is also known as the Gibbs simplex. The corresponding tangent space $T_{\boldsymbol{\phi}} \operatorname{HG}$ can be identified as the space

$$T_{\boldsymbol{\phi}} \operatorname{HG} \cong \operatorname{TG} = \left\{ \boldsymbol{\psi} \in \mathbb{R}^L : \sum_{i=1}^L \psi_i = 0 \right\}. \quad (2.10)$$

We postulate a general free energy of Ginzburg–Landau form, i.e.,

$$\mathcal{E}(\boldsymbol{\varphi}, \boldsymbol{\sigma}) = \int_{\Omega} e(\boldsymbol{\varphi}, \nabla \boldsymbol{\varphi}, \boldsymbol{\sigma}) d\mathcal{L}^d = \int_{\Omega} A\Psi(\boldsymbol{\varphi}) + Ba(\boldsymbol{\varphi}, \nabla \boldsymbol{\varphi}) + N(\boldsymbol{\varphi}, \boldsymbol{\sigma}) d\mathcal{L}^d, \quad (2.11)$$

where $\boldsymbol{\varphi} = (\varphi_1, \dots, \varphi_L)^\top \in G$, $\boldsymbol{\sigma} = (\sigma_1, \dots, \sigma_M)^\top$ and $\nabla \boldsymbol{\varphi} = (\partial_{x_k} \varphi_i)_{1 \leq i \leq L, 1 \leq k \leq d}$. Here $A, B > 0$ are constants, $a : G \times (\text{TG})^d \rightarrow \mathbb{R}$ is a smooth gradient energy density and $\Psi : G \rightarrow \mathbb{R}_{\geq 0}$ is a smooth multi-well potential with exactly L equal minima at the points \mathbf{e}_l , $l = 1, \dots, L$, where $\mathbf{e}_l = (\delta_{lm})_{m=1}^L$ is the l th unit vector in \mathbb{R}^L . In particular, the minima of Ψ are the corners of the Gibbs simplex G . The first two terms in the integral in (2.11) account for interfacial energy and unmixing tendencies, and the term $N(\boldsymbol{\varphi}, \boldsymbol{\sigma})$ accounts for the chemical energy of the species and any energy contributions resulting from the interactions between the cells and the chemical species.

Recalling the vector $\mathbf{1} = (1, \dots, 1)^\top \in \mathbb{R}^L$, we now introduce the projection operator \mathbb{P} to the tangent space TG as follows:

$$\mathbb{P}\mathbf{f} = \mathbf{f} - \frac{1}{L}(\mathbf{1} \cdot \mathbf{f})\mathbf{1} \quad (2.12)$$

for a vector $\mathbf{f} \in \mathbb{R}^L$. For a second order tensor $\underline{\underline{A}} \in \mathbb{R}^{L \times d}$ we define the (i, j) th component of its projection to be

$$(\mathbb{P}\underline{\underline{A}})_{ij} = A_{ij} - \frac{1}{L} \sum_{k=1}^L A_{kj}.$$

We now derive a diffuse interface model based on a dissipation inequality for the balance laws in (2.8). We point out that balance laws with source terms have been used similarly by Gurtin in Refs. 33, 34 and Podio-Guidugli in Ref. 58 to derive phase field and Cahn–Hilliard type equations. These authors used the second law of thermodynamics which in an isothermal situation is formulated as a free energy inequality.

The second law of thermodynamics in the isothermal situation requires that for all volumes $V(t) \subset \Omega$, which are transported with the fluid velocity, the following inequality has to hold (see Refs. 33, 34, 58 and Chap. 62 of Ref. 35)

$$\frac{d}{dt} \int_{V(t)} e(\boldsymbol{\varphi}, \nabla \boldsymbol{\varphi}, \boldsymbol{\sigma}) d\mathcal{L}^d \leq - \int_{\partial V(t)} \bar{\mathbf{J}}_e \cdot \bar{\boldsymbol{\nu}} d\mathcal{H}^{d-1} + \int_{V(t)} (\mathbf{c}_\varphi + c_v \mathbf{1}) \cdot \mathbf{U} + \mathbf{c}_\sigma \cdot \mathbf{S} d\mathcal{L}^d,$$

where $d\mathcal{H}^{d-1}$ denotes integration with respect to the $d - 1$ dimensional Hausdorff measure, $\bar{\boldsymbol{\nu}}$ is the outer unit normal to $\partial V(t)$, $\bar{\mathbf{J}}_e$ is an energy flux yet to be specified, and we have postulated that the source terms \mathbf{U} and \mathbf{S} carry with them a supply of energy described by

$$\int_{V(t)} (\mathbf{c}_\varphi + c_v \mathbf{1}) \cdot \mathbf{U} + \mathbf{c}_\sigma \cdot \mathbf{S} d\mathcal{L}^d, \quad (2.13)$$

for some $\mathbf{c}_\varphi \in \text{TG}$, $c_v \in \mathbb{R}$ and $\mathbf{c}_\sigma \in \mathbb{R}^M$ yet to be determined.

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Applying the transport theorem and the divergence theorem, we obtain the following local form

$$\partial_t e + \operatorname{div}(e\vec{v}) + \operatorname{div}\vec{J}_e - (\mathbf{c}_\varphi + c_v \mathbf{1}) \cdot \mathbf{U} - \mathbf{c}_\sigma \cdot \mathbf{S} \leq 0. \quad (2.14)$$

We now use the Lagrange multiplier method of Liu and Müller (see Sec. 2.2 of Ref. 1 and Chap. 7 of Ref. 47). Let $\lambda_\varphi \in \operatorname{TG}$, $\lambda_\sigma \in \mathbb{R}^M$ and $\lambda_v \in \mathbb{R}$ denote the Lagrange multipliers for the equations in (2.8b), (2.8c) and (2.8a), respectively. Then, we require that the following inequality holds for arbitrary $\varphi \in \operatorname{G}$, $\partial_t \varphi \in \operatorname{TG}$, $\nabla \varphi \in (\operatorname{TG})^d$, $\sigma, \partial_t \sigma \in \mathbb{R}^M$, $\nabla \sigma \in \mathbb{R}^{M \times d}$, $\vec{v} \in \mathbb{R}^d$, $\mathbf{U} \in \mathbb{R}^L$, and $\mathbf{S} \in \mathbb{R}^M$:

$$\begin{aligned} -\mathcal{D} &= \partial_t e + \vec{v} \cdot \nabla e + e \operatorname{div} \vec{v} + \operatorname{div} \vec{J}_e - (\mathbf{c}_\varphi + c_v \mathbf{1}) \cdot \mathbf{U} - \mathbf{c}_\sigma \cdot \mathbf{S} \\ &\quad - \lambda_\varphi \cdot (\partial_t \varphi + (\nabla \varphi) \vec{v} + (\operatorname{div} \vec{v}) \varphi + \operatorname{div} \underline{\underline{K}}_\varphi - \mathbf{U}) \\ &\quad - \lambda_\sigma \cdot (\partial_t \sigma + (\nabla \sigma) \vec{v} + (\operatorname{div} \vec{v}) \sigma + \operatorname{div} \underline{\underline{K}}_\sigma - \mathbf{S}) \\ &\quad - \lambda_v (\operatorname{div} \vec{v} - \mathbf{1} \cdot \mathbf{U}) \leq 0. \end{aligned} \quad (2.15)$$

Using the identities

$$[(\nabla \varphi) \vec{v}]_i = \sum_{k=1}^d \partial_{x_k} \varphi_i v_k, \quad \partial_t^\bullet \varphi = \partial_t \varphi + (\nabla \varphi) \vec{v}, \quad \partial_t^\bullet f = \partial_t f + \vec{v} \cdot \nabla f,$$

$$\lambda \cdot \operatorname{div}(\varphi \otimes \vec{v}) = \lambda \cdot (\nabla \varphi) \vec{v} + (\lambda \cdot \varphi) \operatorname{div} \vec{v}, \quad \operatorname{div}(\underline{\underline{K}}^\top \lambda) = \underline{\underline{K}} : \nabla \lambda + (\operatorname{div} \underline{\underline{K}}) \cdot \lambda,$$

where for two tensors $\underline{\underline{A}}$ and $\underline{\underline{B}}$, the product $\underline{\underline{A}} : \underline{\underline{B}}$ is defined as $\underline{\underline{A}} : \underline{\underline{B}} = \operatorname{tr}(\underline{\underline{A}}^\top \underline{\underline{B}})$, we arrive at

$$\begin{aligned} -\mathcal{D} &= \operatorname{div}(\vec{J}_e - \underline{\underline{K}}_\varphi^\top \lambda_\varphi - \underline{\underline{K}}_\sigma^\top \lambda_\sigma) + (Ba_{,\varphi} + A\Psi_{,\varphi} + N_{,\varphi} - \lambda_\varphi) \cdot \partial_t^\bullet \varphi \\ &\quad + (N_{,\sigma} - \lambda_\sigma) \cdot \partial_t^\bullet \sigma + \mathbf{U} \cdot (\lambda_\varphi - \mathbf{c}_\varphi + (\lambda_v - c_v) \mathbf{1}) + \mathbf{S} \cdot (\lambda_\sigma - \mathbf{c}_\sigma) \\ &\quad + B \sum_{i=1}^L \sum_{k=1}^d (a_{,\partial_k \varphi_i}) [\partial_t^\bullet \partial_{x_k} \varphi_i] + (\operatorname{div} \vec{v})(e - \lambda_\varphi \cdot \varphi - \lambda_\sigma \cdot \sigma - \lambda_v) \\ &\quad + \underline{\underline{K}}_\varphi : \nabla \lambda_\varphi + \underline{\underline{K}}_\sigma : \nabla \lambda_\sigma, \end{aligned} \quad (2.16)$$

where $a_{,\partial_k \varphi_i} := \frac{\partial a}{\partial (\partial_k \varphi_i)} = (a_{,\nabla \varphi})_{ik}$,

$$\mathbf{N}_{,\varphi} = \left(\frac{\partial N}{\partial \varphi_1}, \dots, \frac{\partial N}{\partial \varphi_L} \right)^\top \in \mathbb{R}^L, \quad \mathbf{N}_{,\sigma} = \left(\frac{\partial N}{\partial \sigma_1}, \dots, \frac{\partial N}{\partial \sigma_M} \right)^\top \in \mathbb{R}^M.$$

A short calculation with the product rule shows that

$$\begin{aligned} &\sum_{i=1}^L \sum_{k=1}^d (a_{,\partial_k \varphi_i}) [\partial_t^\bullet \partial_{x_k} \varphi_i] \\ &= \operatorname{div}((a_{,\nabla \varphi})^\top \partial_t \varphi) - \operatorname{div}(a_{,\nabla \varphi}) \cdot \partial_t^\bullet \varphi + \vec{v} \cdot \operatorname{div}((\nabla \varphi)^\top (a_{,\nabla \varphi})). \end{aligned}$$

Applying the product rule on the term involving $\operatorname{div} \vec{v}$ we get

$$\begin{aligned} (\operatorname{div} \vec{v})(e - \lambda_\varphi \cdot \varphi - \lambda_\sigma \cdot \sigma - \lambda_v) &= \operatorname{div}((e - \lambda_\varphi \cdot \varphi - \lambda_\sigma \cdot \sigma - \lambda_v) \vec{v}) \\ &\quad - \vec{v} \cdot \nabla(e - \lambda_\varphi \cdot \varphi - \lambda_\sigma \cdot \sigma - \lambda_v). \end{aligned}$$

Thus, substituting the above into the expression (2.16) we obtain

$$\begin{aligned}
 -\mathcal{D} &= \operatorname{div} \left(\vec{J}_e - \underline{\underline{K}}_\varphi^\top \lambda_\varphi - \underline{\underline{K}}_\sigma^\top \lambda_\sigma + B(a, \nabla \varphi)^\top \partial_t \varphi + (e - \lambda_\varphi \cdot \varphi - \lambda_\sigma \cdot \sigma - \lambda_v) \vec{v} \right) \\
 &\quad - \vec{v} \cdot \left[\nabla (e - \lambda_\varphi \cdot \varphi - \lambda_\sigma \cdot \sigma - \lambda_v) - B \operatorname{div} ((\nabla \varphi)^\top (a, \nabla \varphi)) \right] \\
 &\quad + (Ba, \varphi - B \operatorname{div} (a, \nabla \varphi) + A \Psi_{, \varphi} + N_{, \varphi} - \lambda_\varphi) \cdot \partial_t^\bullet \varphi + (N_{, \sigma} - \lambda_\sigma) \cdot \partial_t^\bullet \sigma \\
 &\quad + \mathbf{U} \cdot (\lambda_\varphi - c_\varphi + (\lambda_v - c_v) \mathbf{1}) + \mathbf{S} \cdot (\lambda_\sigma - c_\sigma) + \underline{\underline{K}}_\varphi : \nabla \lambda_\varphi + \underline{\underline{K}}_\sigma : \nabla \lambda_\sigma.
 \end{aligned} \tag{2.17}$$

2.3. Constitutive assumptions and the general model

We define the vector of chemical potentials $\boldsymbol{\mu}$ to be

$$\boldsymbol{\mu} = Ba, \varphi(\varphi, \nabla \varphi) - B \operatorname{div} (a, \nabla \varphi(\varphi, \nabla \varphi)) + A \Psi_{, \varphi}(\varphi) + N_{, \varphi}(\varphi, \sigma), \tag{2.18}$$

and by the definition (2.12) of the projection operator \mathbb{P} , we have

$$(\boldsymbol{\mu} - \lambda_\varphi) \cdot \partial_t^\bullet \varphi = \mathbb{P}(\boldsymbol{\mu} - \lambda_\varphi) \cdot \partial_t^\bullet \varphi + \frac{1}{L} ((\boldsymbol{\mu} - \lambda_\varphi) \cdot \mathbf{1}) \mathbf{1} \cdot \partial_t^\bullet \varphi = \mathbb{P}(\boldsymbol{\mu} - \lambda_\varphi) \cdot \partial_t^\bullet \varphi$$

as $\partial_t^\bullet \varphi \in \operatorname{TG}$ and $\partial_t^\bullet \varphi \cdot \mathbf{1} = 0$. Furthermore, from (2.6) we find that $\underline{\underline{K}}_\varphi : \nabla \lambda_\varphi = \underline{\underline{K}}_\varphi : \nabla (\mathbb{P} \lambda_\varphi)$, and so (2.17) can be simplified to

$$\begin{aligned}
 -\mathcal{D} &= \operatorname{div} \left(\vec{J}_e - \underline{\underline{K}}_\varphi^\top \lambda_\varphi - \underline{\underline{K}}_\sigma^\top \lambda_\sigma + B(a, \nabla \varphi)^\top \partial_t \varphi + (e - \lambda_\varphi \cdot \varphi - \lambda_\sigma \cdot \sigma - \lambda_v) \vec{v} \right) \\
 &\quad + \underline{\underline{K}}_\varphi : \nabla (\mathbb{P} \lambda_\varphi) + \underline{\underline{K}}_\sigma : \nabla \lambda_\sigma + \mathbb{P}(\boldsymbol{\mu} - \lambda_\varphi) \cdot \partial_t^\bullet \varphi \\
 &\quad + (N_{, \sigma} - \lambda_\sigma) \cdot \partial_t^\bullet \sigma + \mathbf{U} \cdot (\lambda_\varphi - c_\varphi + (\lambda_v - c_v) \mathbf{1}) + \mathbf{S} \cdot (\lambda_\sigma - c_\sigma) \\
 &\quad - \vec{v} \cdot \left[\nabla (e - \lambda_\varphi \cdot \varphi - \lambda_\sigma \cdot \sigma - \lambda_v) - B \operatorname{div} ((\nabla \varphi)^\top (a, \nabla \varphi)) \right].
 \end{aligned} \tag{2.19}$$

Based on (2.19) we make the following constitutive assumptions,

$$\vec{J}_e = \underline{\underline{K}}_\varphi^\top \lambda_\varphi + \underline{\underline{K}}_\sigma^\top \lambda_\sigma - B(a, \nabla \varphi(\varphi, \nabla \varphi))^\top \partial_t \varphi \tag{2.20a}$$

$$- (e(\varphi, \nabla \varphi, \sigma) - \lambda_\varphi \cdot \varphi - \lambda_\sigma \cdot \sigma - \lambda_v) \vec{v},$$

$$c_\sigma = \lambda_\sigma = N_{, \sigma}(\varphi, \sigma), \quad c_\varphi = \lambda_\varphi, \quad \lambda_\varphi = \mathbb{P} \boldsymbol{\mu}, \quad c_v = \lambda_v, \tag{2.20b}$$

$$\underline{\underline{K}}_\sigma = -\underline{\underline{D}}(\varphi, \sigma) \nabla N_{, \sigma}(\varphi, \sigma), \quad \underline{\underline{K}}_\varphi = -\underline{\underline{C}}(\varphi, \sigma) \nabla (\mathbb{P} \boldsymbol{\mu}), \tag{2.20c}$$

where $\underline{\underline{C}}(\varphi, \sigma) \in \mathbb{R}^{L \times L}$ and $\underline{\underline{D}}(\varphi, \sigma) \in \mathbb{R}^{M \times M}$ are non-negative second order mobility tensors such that

$$\sum_{i=1}^L \underline{\underline{C}}_{ik}(\varphi, \sigma) = 0 \quad \text{for all } \varphi \in G, \sigma \in \mathbb{R}^M, \text{ and } 1 \leq k \leq L. \tag{2.21}$$

Here, by a non-negative second order tensor $\underline{\underline{A}} \in \mathbb{R}^{L \times L}$, we mean that for all $\mathbf{b} \in \mathbb{R}^L$, $\mathbf{b} \cdot \underline{\underline{A}} \mathbf{b} \geq 0$ and $\mathbf{b} \cdot \underline{\underline{A}} \mathbf{b} = 0$ if and only if $\mathbf{b} = \mathbf{0}$. Recalling the definition of $\underline{\underline{K}}_\varphi$ and $\underline{\underline{K}}_\sigma$ from (2.7), we see that for $1 \leq m \leq d$, the m th component of the fluxes \vec{J}_{φ_i} and \vec{J}_{σ_j} are given as

$$\begin{aligned}
 \frac{1}{\rho_i} (\vec{J}_{\varphi_i})_m &= - \sum_{k=1}^L \underline{\underline{C}}_{ik}(\varphi, \sigma) \partial_{x_m} (\mathbb{P} \boldsymbol{\mu})_k, \\
 (\vec{J}_{\sigma_j})_m &= - \sum_{k=1}^M \underline{\underline{D}}_{jk}(\varphi, \sigma) \partial_{x_m} \left(\frac{\partial N}{\partial \sigma_k} \right).
 \end{aligned}$$

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Then, the constraint (2.6) requires

$$\sum_{i=1}^L \sum_{k=1}^L \underline{\underline{C}}_{ik}(\varphi, \sigma) \partial_{x_m} (\mathbb{P}\boldsymbol{\mu})_k = 0 \quad \forall 1 \leq m \leq d, \quad (2.22)$$

which is satisfied when the constitutive assumption (2.21) is considered. We point out that one may take $\underline{\underline{D}}(\varphi, \sigma) \in \mathbb{R}^{M \times d \times M \times d}$ as a non-negative fourth order mobility tensor, that is, $\underline{\underline{D}}\underline{\underline{A}} : \underline{\underline{A}} \geq 0$ and $\underline{\underline{D}}\underline{\underline{A}} : \underline{\underline{A}} = 0$ if and only if $\underline{\underline{A}} = \underline{\underline{0}}$ for any second order tensors $\underline{\underline{A}} \in \mathbb{R}^{M \times d}$. If we also consider $\underline{\underline{C}}(\varphi, \sigma) \in \mathbb{R}^{L \times d \times L \times d}$ as a fourth order tensor, then (2.21) becomes

$$\sum_{i=1}^L \underline{\underline{C}}_{imkl}(\varphi, \sigma) = 0 \quad \text{for all } \varphi \in G, \sigma \in \mathbb{R}^M, \text{ and } 1 \leq m, l \leq d, 1 \leq k \leq L, \quad (2.23)$$

and for $1 \leq m \leq d$, the m th component of the fluxes \vec{J}_{φ_i} and \vec{J}_{σ_j} are given as

$$\begin{aligned} \frac{1}{\rho_i} (\vec{J}_{\varphi_i})_m &= - \sum_{k=1}^L \sum_{l=1}^d \underline{\underline{C}}_{imkl}(\varphi, \sigma) \partial_{x_l} (\mathbb{P}\boldsymbol{\mu})_k, \\ (\vec{J}_{\sigma_j})_m &= - \sum_{k=1}^M \sum_{l=1}^d \underline{\underline{D}}_{jmkl}(\varphi, \sigma) \partial_{x_l} \left(\frac{\partial N}{\partial \sigma_k} \right). \end{aligned}$$

Note that, from (2.19) and the arbitrariness of \mathbf{U} , we require the prefactor $\boldsymbol{\lambda}_\varphi - \mathbf{c}_\varphi + (\lambda_v - c_v)\mathbf{1}$ to vanish. Since $\boldsymbol{\lambda}_\varphi, \mathbf{c}_\varphi \in \text{TG}$ and the vector $(\lambda_v - c_v)\mathbf{1}$ is orthogonal to TG this leads to the consideration $\boldsymbol{\lambda}_\varphi = \mathbf{c}_\varphi$ and $\lambda_v = c_v$ in (2.20b). We introduce a pressure-like function p and choose

$$\begin{aligned} \lambda_v &= p - Ba(\varphi, \nabla\varphi) - A\Psi(\varphi) + e(\varphi, \nabla\varphi, \sigma) - \mathbb{P}\boldsymbol{\mu} \cdot \varphi - \mathbf{N}_{,\sigma}(\varphi, \sigma) \cdot \sigma \\ &= p + N(\varphi, \sigma) - \mathbb{P}\boldsymbol{\mu} \cdot \varphi - \mathbf{N}_{,\sigma}(\varphi, \sigma) \cdot \sigma. \end{aligned} \quad (2.24)$$

and, for a positive constant K ,

$$\begin{aligned} \vec{v} &= K \left(\nabla(e(\varphi, \nabla\varphi, \sigma) - \mathbb{P}\boldsymbol{\mu} \cdot \varphi - \mathbf{N}_{,\sigma}(\varphi, \sigma) \cdot \sigma - \lambda_v) - B \operatorname{div}((\nabla\varphi)^\top a_{,\nabla\varphi}(\varphi, \nabla\varphi)) \right) \\ &= K \left(\nabla(-p + Ba(\varphi, \nabla\varphi) + A\Psi(\varphi)) - B \operatorname{div}((\nabla\varphi)^\top a_{,\nabla\varphi}(\varphi, \nabla\varphi)) \right). \end{aligned} \quad (2.25)$$

We can further simplify (2.25) with the identity (dropping the dependence on $(\varphi, \nabla\varphi)$ of $a_{,\varphi}$ and $a_{,\nabla\varphi}$):

$$\nabla(a(\varphi, \nabla\varphi)) = (\nabla\varphi)^\top a_{,\varphi} + \operatorname{div}((\nabla\varphi)^\top a_{,\nabla\varphi}) - (\nabla\varphi)^\top \operatorname{div}(a_{,\nabla\varphi}),$$

and hence, (2.25) becomes

$$\vec{v} = -K \nabla p + K (\nabla\varphi)^\top (\boldsymbol{\mu} - \mathbf{N}_{,\varphi}(\varphi, \sigma)). \quad (2.26)$$

Thus, the model equations are

$$\operatorname{div} \vec{v} = \mathbf{1} \cdot \mathbf{U}(\varphi, \sigma), \quad (2.27a)$$

$$\vec{v} = -K \nabla p + K (\nabla\varphi)^\top (\boldsymbol{\mu} - \mathbf{N}_{,\varphi}(\varphi, \sigma)), \quad (2.27b)$$

$$\partial_t \varphi + \operatorname{div}(\varphi \otimes \vec{v}) = \operatorname{div}(\underline{\underline{C}}(\varphi, \sigma) \nabla(\mathbb{P}\boldsymbol{\mu})) + \mathbf{U}(\varphi, \sigma), \quad (2.27c)$$

$$\boldsymbol{\mu} - \mathbf{N}_{,\varphi}(\varphi, \sigma) = Ba_{,\varphi}(\varphi, \nabla\varphi) - B \operatorname{div}(a_{,\nabla\varphi}(\varphi, \nabla\varphi)) + A\Psi_{,\varphi}(\varphi), \quad (2.27d)$$

$$\partial_t \sigma + \operatorname{div}(\sigma \otimes \vec{v}) = \operatorname{div}(\underline{\underline{D}}(\varphi, \sigma) \nabla \mathbf{N}_{,\sigma}(\varphi, \sigma)) + \mathbf{S}(\varphi, \sigma), \quad (2.27e)$$

where

$$\mathbf{U} = (\bar{\rho}_1^{-1}\mathcal{U}_1, \dots, \bar{\rho}_L^{-1}\mathcal{U}_L)^\top \in \mathbb{R}^L, \quad \mathbf{1} \cdot \mathbf{U} = \sum_{i=1}^L \frac{\mathcal{U}_i}{\bar{\rho}_i}, \quad \mathbf{S} = (S_1, \dots, S_M)^\top \in \mathbb{R}^M.$$

In fact, one observes that the constitutive choices above lead to the expression

$$-\mathcal{D} = -\underline{\underline{C}}(\varphi, \boldsymbol{\sigma}) \nabla(\mathbb{P}\boldsymbol{\mu}) : \nabla(\mathbb{P}\boldsymbol{\mu}) - \underline{\underline{D}}(\varphi, \boldsymbol{\sigma}) \nabla N_{,\boldsymbol{\sigma}}(\varphi, \boldsymbol{\sigma}) : \nabla N_{,\boldsymbol{\sigma}}(\varphi, \boldsymbol{\sigma}) - \frac{|\bar{v}|^2}{K}.$$

Then substituting into (2.15) and integrating over Ω , using (2.8a), (2.8b) and (2.8c) to simplify then yields the energy identity:

$$\begin{aligned} & \frac{d}{dt} \int_{\Omega} e(\varphi, \nabla \varphi, \boldsymbol{\sigma}) d\mathcal{L}^d + \mathcal{D} + \int_{\partial\Omega} (e(\varphi, \nabla \varphi, \boldsymbol{\sigma}) \bar{v} + \bar{J}_e) \cdot \bar{v} d\mathcal{H}^{d-1} \\ & = \int_{\Omega} (\mathbb{P}\boldsymbol{\mu} + \lambda_v \mathbf{1}) \cdot \mathbf{U}(\varphi, \boldsymbol{\sigma}) + N_{,\boldsymbol{\sigma}}(\varphi, \boldsymbol{\sigma}) \cdot \mathbf{S}(\varphi, \boldsymbol{\sigma}) d\mathcal{L}^d. \end{aligned} \quad (2.28)$$

By substituting the expressions for \bar{J}_e , \mathcal{D} , and λ_v into the above, we can formulate the above energy identity as follows.

Theorem 2.1. *A sufficiently smooth solution to (2.27) fulfills*

$$\begin{aligned} & \frac{d}{dt} \mathcal{E}(\varphi, \boldsymbol{\sigma}) \\ & = \frac{d}{dt} \int_{\Omega} (A\Psi(\varphi) + Ba(\varphi, \nabla \varphi) + N(\varphi, \boldsymbol{\sigma})) d\mathcal{L}^d \\ & = - \int_{\Omega} \underline{\underline{C}}(\varphi, \boldsymbol{\sigma}) \nabla(\mathbb{P}\boldsymbol{\mu}) : \nabla(\mathbb{P}\boldsymbol{\mu}) + \underline{\underline{D}}(\varphi, \boldsymbol{\sigma}) \nabla N_{,\boldsymbol{\sigma}}(\varphi, \boldsymbol{\sigma}) : \nabla N_{,\boldsymbol{\sigma}}(\varphi, \boldsymbol{\sigma}) + \frac{|\bar{v}|^2}{K} d\mathcal{L}^d \\ & \quad + \int_{\Omega} \mathbf{S}(\varphi, \boldsymbol{\sigma}) \cdot N_{,\boldsymbol{\sigma}}(\varphi, \boldsymbol{\sigma}) + \mathbf{U}(\varphi, \boldsymbol{\sigma}) \cdot \mathbb{P}\boldsymbol{\mu} d\mathcal{L}^d \\ & \quad + \int_{\Omega} (\mathbf{1} \cdot \mathbf{U}(\varphi, \boldsymbol{\sigma})) (p - \varphi \cdot \mathbb{P}\boldsymbol{\mu} - \boldsymbol{\sigma} \cdot N_{,\boldsymbol{\sigma}}(\varphi, \boldsymbol{\sigma}) + N(\varphi, \boldsymbol{\sigma})) d\mathcal{L}^d \\ & \quad + \int_{\partial\Omega} \underline{\underline{C}}(\varphi, \boldsymbol{\sigma}) \nabla(\mathbb{P}\boldsymbol{\mu}) : (\mathbb{P}\boldsymbol{\mu} \otimes \bar{v}) + BPa_{,\nabla\varphi}(\varphi, \nabla \varphi) : (\partial_t \varphi \otimes \bar{v}) d\mathcal{H}^{d-1} \\ & \quad + \int_{\partial\Omega} \underline{\underline{D}}(\varphi, \boldsymbol{\sigma}) \nabla N_{,\boldsymbol{\sigma}}(\varphi, \boldsymbol{\sigma}) : (N_{,\boldsymbol{\sigma}}(\varphi, \boldsymbol{\sigma}) \otimes \bar{v}) + (N(\varphi, \boldsymbol{\sigma}) + p) \bar{v} \cdot \bar{v} d\mathcal{H}^{d-1}. \end{aligned}$$

Remark 2.1. It follows from Theorem 2.1 that, under the boundary conditions

$$\begin{aligned} & (\underline{\underline{C}}(\varphi, \boldsymbol{\sigma}) \nabla(\mathbb{P}\boldsymbol{\mu})) \bar{v} = \vec{0}, \quad (\underline{\underline{D}}(\varphi, \boldsymbol{\sigma}) \nabla N_{,\boldsymbol{\sigma}}(\varphi, \boldsymbol{\sigma})) \bar{v} = \vec{0}, \\ & (Pa_{,\nabla\varphi}(\varphi, \nabla \varphi)) \bar{v} = \vec{0}, \quad \bar{v} \cdot \bar{v} = 0 \end{aligned}$$

on $\partial\Omega$, and in the absence of source terms $\mathbf{S}(\varphi, \boldsymbol{\sigma}) = \vec{0}$ and $\mathbf{U}(\varphi, \boldsymbol{\sigma}) = \vec{0}$, the total free energy $\mathcal{E}(\varphi, \boldsymbol{\sigma})$ is non-increasing in time.

2.4. Specific models

2.4.1. Zero velocity and zero excess of total mass

Assuming zero excess of total mass, i.e., $\mathbf{1} \cdot \mathbf{U} = \sum_{i=1}^L \bar{\rho}_i^{-1} \mathcal{U}_i = 0$, we obtain from (2.27a) that $\operatorname{div} \bar{v} = 0$. Then, sending $K \rightarrow 0$ in (2.27b) formally implies that $\bar{v} \rightarrow \vec{0}$,

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see also Sec. 6 of Ref. 26 for a rigorous treatment in the two-component case. Then (2.27), with source terms satisfying $\mathbf{1} \cdot \mathbf{U} = 0$, can be reduced to

$$\partial_t \varphi = \operatorname{div}(\underline{\underline{C}}(\varphi, \sigma) \nabla(\mathbb{P}\mu)) + \mathbf{U}(\varphi, \sigma), \quad (2.29a)$$

$$\mu = Ba_{,\varphi}(\varphi, \nabla\varphi) - B \operatorname{div}(a_{,\nabla\varphi}(\varphi, \nabla\varphi)) + A\Psi_{,\varphi}(\varphi) + N_{,\varphi}(\varphi, \sigma), \quad (2.29b)$$

$$\partial_t \sigma = \operatorname{div}(\underline{\underline{D}}(\varphi, \sigma) \nabla N_{,\sigma}(\varphi, \sigma)) + \mathbf{S}(\varphi, \sigma), \quad (2.29c)$$

which can be seen as the multiphase analogue of the model considered in Sec. 2.4.3 of Ref. 27. Note that due to the condition $\mathbf{1} \cdot \mathbf{U} = 0$ and (2.21) (for second order tensors) or (2.23) (for fourth order tensors), we necessarily have that $\varphi(t) \in G$ for all $t > 0$ if the initial condition φ_0 for φ belongs to G .

2.4.2. Choices for the Ginzburg–Landau energy

Typical choices for the gradient part of the free energy are the following

$$a(\boldsymbol{\eta}, \nabla\varphi) = \sum_{i=1}^L \frac{1}{2} |\nabla\varphi_i|^2, \text{ or } a(\boldsymbol{\eta}, \nabla\varphi) = \sum_{1 \leq i < j \leq L} \frac{1}{2} \beta_{ij}^2 |\eta_i \nabla\varphi_j - \eta_j \nabla\varphi_i|^2,$$

where the constants β_{ij} , $1 \leq i < j \leq L$ are referred to as the gradient energy coefficient of phases i and j (see Refs. 25, 30). For the potential part, we may consider the following

$$\Psi(\varphi) = k_B \theta \sum_{i=1}^L \varphi_i \ln \varphi_i - \frac{1}{2} \varphi \cdot \underline{\underline{W}} \varphi,$$

where k_B denotes the Boltzmann constant, θ is the absolute temperature, and $\underline{\underline{W}} = (w_{ij})_{1 \leq i, j \leq L}$ is a symmetric $L \times L$ matrix with zeros on the diagonal and positive definite on TG. For example, the choice $\underline{\underline{W}} = \underline{\underline{I}} - \mathbf{1} \otimes \mathbf{1}$, where $\underline{\underline{I}}$ is the identity matrix, is used in Refs. 6, 30, 53. One can check that $\zeta \cdot (\underline{\underline{I}} - \mathbf{1} \otimes \mathbf{1}) \zeta = |\zeta|^2$ for any $\zeta \in \text{TG}$. We can also consider obstacle potentials that penalise the order parameter φ from straying out of the set G :

$$\Psi(\varphi) = I_G(\varphi) - \frac{1}{2} \varphi \cdot \underline{\underline{W}} \varphi, \quad I_G(\mathbf{y}) = \begin{cases} 0 & \text{for } \mathbf{y} \in G, \\ \infty & \text{otherwise.} \end{cases} \quad (2.30)$$

Let us also mention potentials of polynomial type, which generalise the quartic double-well potential $(1-y^2)^2$ commonly used in two-phase diffuse interface models. One example is

$$\Psi(\varphi) = \sum_{1 \leq i < j \leq L} \alpha_{ij} \varphi_i^2 \varphi_j^2,$$

where α_{ij} are positive constants²⁹.

2.5. Degenerate Ginzburg–Landau energy

We may consider a Ginzburg–Landau-type energy of the form

$$\mathcal{E}(\boldsymbol{\varphi}, \boldsymbol{\sigma}) = \int_{\Omega} \frac{B}{2} \left| \sum_{i=2}^k \nabla \varphi_i \right|^2 + AW \left(\sum_{i=2}^k \varphi_i \right) + N(\boldsymbol{\varphi}, \boldsymbol{\sigma}) d\mathcal{L}^d,$$

for some $2 \leq k \leq L$, i.e., $\mathcal{E}(\boldsymbol{\varphi}, \boldsymbol{\sigma})$ can be independent of φ_1 and φ_j for any $j > k$, and W is a scalar potential with equal minima at 0 and 1. In the simplest setting $L = 2$ and if the chemical free energy density N is independent of $\boldsymbol{\varphi}$, we obtain from (2.27d) that

$$\mu_1 = 0, \quad \mu_2 = -B\Delta\varphi_2 + AW'(\varphi_2).$$

Together with a mobility tensor $\underline{\underline{C}}(\boldsymbol{\varphi}, \boldsymbol{\sigma}) \in \mathbb{R}^{2 \times 2}$ such that $\underline{\underline{C}}_{22}(\boldsymbol{\varphi}, \boldsymbol{\sigma}) = -\underline{\underline{C}}_{21}(\boldsymbol{\varphi}, \boldsymbol{\sigma}) = m(\varphi_2)$ for some mobility function m , we obtain from (2.27c)

$$\begin{aligned} \partial_t \varphi_1 + \operatorname{div}(\varphi_1 \bar{v}) &= -\operatorname{div}(m(\varphi_2) \nabla \mu_2) + \bar{\rho}_1^{-1} \mathcal{U}_1, \\ \partial_t \varphi_2 + \operatorname{div}(\varphi_2 \bar{v}) &= \operatorname{div}(m(\varphi_2) \nabla \mu_2) + \bar{\rho}_2^{-1} \mathcal{U}_2. \end{aligned}$$

This yields a Cahn–Hilliard type equation for φ_2 , while for φ_1 we have a transport equation with source terms $\bar{\rho}_1^{-1} \mathcal{U}_1$ and $\operatorname{div}(m(\varphi_2) \nabla \mu_2)$. This is similar to the situations encountered in Refs. 10, 11, 17, 23, 65, 67.

2.6. Mobility tensor

We consider second order mobility tensors $\underline{\underline{C}}(\boldsymbol{\varphi}, \boldsymbol{\sigma})$ which fulfill (2.21). For future analysis and numerical implementations, it is advantageous to consider a mobility that is symmetric and positive semi-definite on TG, see for instance Refs. 4, 19. In most cases $\underline{\underline{C}}(\boldsymbol{\varphi}, \boldsymbol{\sigma})$ is expected to mainly depend on $\boldsymbol{\varphi}$ and our standard choice will be independent of $\boldsymbol{\sigma}$ and of the form

$$\underline{\underline{C}}_{ij}(\boldsymbol{\varphi}) = m_i(\varphi_i) \left(\delta_{ij} - m_j(\varphi_j) \left(\sum_{k=1}^L m_k(\varphi_k) \right)^{-1} \right) \text{ for } 1 \leq i, j \leq L, \quad (2.31)$$

where $m_i(\varphi_i) \geq 0$, $1 \leq i \leq L$, are the so-called bare mobilities. Here, we assume that the vector $(m_1(\varphi_1), \dots, m_L(\varphi_L))^{\top}$ is not identically zero on the Gibbs simplex, so that the reciprocal of the sum $\sum_{k=1}^L m_k(\varphi_k)$ is well-defined. Summing over $1 \leq i \leq L$ in (2.31) shows that (2.21) is satisfied. Furthermore, for any $\boldsymbol{\zeta} \in \mathbb{R}^L$, we have (for notational convenience we write m_i for $m_i(\varphi_i)$) the relations

$$\begin{aligned} \sum_{i=1}^L m_i |\zeta_i|^2 \sum_{j=1}^L m_j &= \sum_{i=1}^L m_i^2 |\zeta_i|^2 + \sum_{1 \leq i < j \leq L} m_i m_j (|\zeta_i|^2 + |\zeta_j|^2), \\ \left(\sum_{i=1}^L m_i \zeta_i \right)^2 &= \sum_{i=1}^L m_i^2 |\zeta_i|^2 + 2 \sum_{1 \leq i < j \leq L} m_i m_j \zeta_i \zeta_j, \end{aligned}$$

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so that

$$\begin{aligned}
 \left(\sum_{j=1}^L m_j \right) (\zeta \cdot \underline{\underline{C}}(\varphi) \zeta) &= \sum_{i=1}^L m_i |\zeta_i|^2 \sum_{j=1}^L m_j - \left(\sum_{i=1}^L m_i \zeta_i \right)^2 \\
 &= \sum_{1 \leq i < j \leq L} m_i m_j (|\zeta_i|^2 + |\zeta_j|^2 - 2\zeta_i \zeta_j) \\
 &= \sum_{1 \leq i < j \leq L} m_i m_j (\zeta_i - \zeta_j)^2 \geq 0.
 \end{aligned}$$

In particular, for any $\varphi \in G$, $\underline{\underline{C}}(\varphi)$ is positive semi-definite.

2.7. Reduction to a two-component tumour model

We assume that the domain Ω consists of proliferating tumour tissue and host tissue in the presence of a chemical species acting as a nutrient for the tumour. Let $L = 2$ and $M = 1$, and set

$$\begin{aligned}
 \tilde{\varphi} &= \varphi_2 - \varphi_1, \quad \tilde{\Psi}(\tilde{\varphi}) = \Psi\left(\frac{1}{2}(1 - \tilde{\varphi}), \frac{1}{2}(1 + \tilde{\varphi})\right), \\
 \tilde{\mu} &= \frac{1}{2}(\mu_2 - \mu_1), \quad a(\boldsymbol{\eta}, \nabla \varphi) = |\nabla \varphi_1|^2 + |\nabla \varphi_2|^2, \\
 \tilde{N}(\tilde{\varphi}, \sigma) &= N\left(\frac{1}{2}(1 - \tilde{\varphi}), \frac{1}{2}(1 + \tilde{\varphi}), \sigma\right), \\
 \tilde{S}(\tilde{\varphi}, \sigma) &= S\left(\frac{1}{2}(1 - \tilde{\varphi}), \frac{1}{2}(1 + \tilde{\varphi}), \sigma\right), \\
 \tilde{\mathcal{U}}_i(\tilde{\varphi}, \sigma) &= \mathcal{U}_i\left(\frac{1}{2}(1 - \tilde{\varphi}), \frac{1}{2}(1 + \tilde{\varphi}), \sigma\right) \text{ for } i = 1, 2,
 \end{aligned} \tag{2.32}$$

together with a scalar mobility

$$D\left(\frac{1}{2}(1 - \tilde{\varphi}), \frac{1}{2}(1 + \tilde{\varphi}), \sigma\right) = n(\tilde{\varphi}), \tag{2.33}$$

which we here assume to be independent of σ , for the nutrient equation and a second order mobility tensor $\underline{\underline{C}}(\varphi)$ of the form (2.31) with bare mobilities $m_1(\varphi_1)$ and $m_2(\varphi_2)$. With the help of (2.31) the entries of $\underline{\underline{C}}(\varphi)$ can be computed as

$$\underline{\underline{C}}_{11}(\varphi) = \underline{\underline{C}}_{22}(\varphi) = -\underline{\underline{C}}_{12}(\varphi) = -\underline{\underline{C}}_{21}(\varphi) = \frac{m_1(\varphi_1)m_2(\varphi_2)}{m_1(\varphi_1) + m_2(\varphi_2)}.$$

Then, upon defining a non-negative scalar mobility m that is a function of $\tilde{\varphi}$ as

$$m(\tilde{\varphi}) = \frac{4m_1\left(\frac{1-\tilde{\varphi}}{2}\right)m_2\left(\frac{1+\tilde{\varphi}}{2}\right)}{m_1\left(\frac{1-\tilde{\varphi}}{2}\right) + m_2\left(\frac{1+\tilde{\varphi}}{2}\right)} \Rightarrow \underline{\underline{C}}(\varphi) = \frac{1}{4} \begin{pmatrix} m(\tilde{\varphi}) & -m(\tilde{\varphi}) \\ -m(\tilde{\varphi}) & m(\tilde{\varphi}) \end{pmatrix} \in \mathbb{R}^{2 \times 2}, \tag{2.34}$$

it can be shown that (2.27) becomes

$$\operatorname{div} \tilde{v} = \bar{\rho}_1^{-1} \tilde{\mathcal{U}}_1(\tilde{\varphi}, \sigma) + \bar{\rho}_2^{-1} \tilde{\mathcal{U}}_2(\tilde{\varphi}, \sigma), \tag{2.35a}$$

$$\tilde{v} = -K \nabla p + K(\tilde{\mu} - \tilde{N}_{,\tilde{\varphi}}(\tilde{\varphi}, \sigma)) \nabla \tilde{\varphi}, \tag{2.35b}$$

$$\partial_t \tilde{\varphi} + \operatorname{div}(\tilde{\varphi} \tilde{v}) = \operatorname{div}(m(\tilde{\varphi}) \nabla \tilde{\mu}) + \bar{\rho}_2^{-1} \tilde{\mathcal{U}}_2(\tilde{\varphi}, \sigma) - \bar{\rho}_1^{-1} \tilde{\mathcal{U}}_1(\tilde{\varphi}, \sigma), \tag{2.35c}$$

$$\tilde{\mu} = A \tilde{\Psi}'(\tilde{\varphi}) - B \Delta \tilde{\varphi} + \tilde{N}_{,\tilde{\varphi}}(\tilde{\varphi}, \sigma), \tag{2.35d}$$

$$\partial_t \sigma + \operatorname{div}(\sigma \tilde{v}) = \operatorname{div}(n(\tilde{\varphi}) \nabla \tilde{N}_{,\sigma}) + \tilde{S}(\tilde{\varphi}, \sigma), \tag{2.35e}$$

which coincides with Equ. (2.25) of Ref. 27. We refer the reader to Ref. 27 for a detailed comparison between (2.35) with other two-component phase field models of tumour growth in the literature.

2.8. Tumour with quiescent and necrotic cells

In this section, we give some examples of source terms for the case where a tumour exhibits a quiescent region and a necrotic region. Let $L = 4$ and denote the volume fractions of the host tissue, proliferating tumour cells, quiescent tumour cells and necrotic tumour cells by φ_H , φ_P , φ_Q , and φ_N , respectively, i.e., $\boldsymbol{\varphi} = (\varphi_H, \varphi_P, \varphi_Q, \varphi_N)^\top$.

We assume matched densities $\bar{\rho}_H = \bar{\rho}_P = \bar{\rho}_Q = \bar{\rho}_N = 1$, and that there are two chemical species $M = 2$ present in the domain. The first is a nutrient whose density is denoted as σ_{nu} , and is only consumed by the proliferating and quiescent tumour cells, and the second is a toxic intracellular agent, whose density is denoted as σ_{tx} , so that $\boldsymbol{\sigma} = (\sigma_{nu}, \sigma_{tx})^\top$. During necrosis, the cell membrane loses its integrity and toxic agents from the former intracellular compartment flow outwards. We assume that these toxic agents act as growth inhibitors on the surrounding living cells and degrade at a constant rate. Furthermore, we denote by σ_{pq}^* , σ_{qn}^* , $\sigma_{tx}^* > 0$ the critical thresholds such that

- if $\sigma_{qn}^* < \sigma_{nu} < \sigma_{pq}^*$, then the proliferating tumour cells will turn quiescent,
- if $\sigma_{nu} < \sigma_{qn}^*$, then the quiescent tumour cells will undergo necrosis,
- if $\sigma_{tx} \geq \sigma_{tx}^*$, then the toxic agents start to inhibit the growth of the living cells.

For a compact presentation, unless stated explicitly, in the following the consumption rates $\mathcal{C}_P, \mathcal{C}_Q$, the release rate \mathcal{R}_{tx} , the degradation rates $\mathcal{D}_{tx}, \mathcal{D}_N$, the proliferation rate \mathcal{P} , the apoptosis rates $\mathcal{A}_H, \mathcal{A}_P, \mathcal{A}_Q$, the inhibition rate \mathcal{A}_{tx} , and the conversion rates $\mathcal{T}_{pq}, \mathcal{T}_{qp}, \mathcal{T}_{qn}$ are taken to be non-negative constants. For the source/sink terms $S_j(\boldsymbol{\varphi}, \boldsymbol{\sigma})$, $j \in \{nu, tx\}$, we consider

$$S_{nu}(\boldsymbol{\varphi}, \boldsymbol{\sigma}) = - \underbrace{\sigma_{nu}\varphi_P\mathcal{C}_P}_{\text{consumption by proliferating cells}} - \underbrace{\sigma_{nu}\varphi_Q\mathcal{C}_Q}_{\text{consumption by quiescent cells}}, \quad S_{tx}(\boldsymbol{\varphi}, \boldsymbol{\sigma}) = \underbrace{\varphi_N\mathcal{R}_{tx}}_{\text{release by necrotic cells}} - \underbrace{\mathcal{D}_{tx}\sigma_{tx}}_{\text{degradation}}.$$

We consider the following free energy density $N(\boldsymbol{\varphi}, \boldsymbol{\sigma})$:

$$N(\boldsymbol{\varphi}, \boldsymbol{\sigma}) = \frac{D_{nu}}{2} |\sigma_{nu}|^2 + \frac{D_{tx}}{2} |\sigma_{tx}|^2 - \chi_{nu}\sigma_{nu}\varphi_P, \quad (2.36)$$

where $D_{nu}, D_{tx} > 0$ denote parameters related to the diffusivity of the nutrient and of the toxic agent, respectively, and $\chi_{nu} \geq 0$ can be viewed as a parameter for transport mechanisms such as chemotaxis and active transport. Neglecting the toxic agent, the above form for the free energy density N is similar to the one chosen in Refs. 27, 36. In particular, the first two terms of N lead to diffusion of the nutrient and toxic agent, respectively, while the third term of N will give rise to transport

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mechanisms that drive the proliferating tumour cells to the regions of high nutrient, and also drive the nutrient to the proliferating tumour cells, see Ref. 27 for more details regarding the effects of the third term.

Then, computing $N_{,\sigma}(\varphi, \sigma)$ and considering $\underline{D}(\varphi, \sigma)$ to be the second order identity tensor $\underline{I} \in \mathbb{R}^{2 \times 2}$, (2.27e) becomes

$$\partial_t \sigma_{nu} + \operatorname{div}(\sigma_{nu} \vec{v}) = \operatorname{div}(D_{nu} \nabla \sigma_{nu} - \chi_{nu} \nabla \varphi_P) - \sigma_{nu} (\varphi_P \mathcal{C}_P + \varphi_Q \mathcal{C}_Q), \quad (2.37a)$$

$$\partial_t \sigma_{tx} + \operatorname{div}(\sigma_{tx} \vec{v}) = \operatorname{div}(D_{tx} \nabla \sigma_{tx}) + \varphi_N \mathcal{R}_{tx} - \mathcal{D}_{tx} \sigma_{tx}. \quad (2.37b)$$

Denoting by $(f)^+ = \max(0, f)$ the positive part of a function f , for the source terms $\mathcal{U}_H, \mathcal{U}_P, \mathcal{U}_Q, \mathcal{U}_N$, we consider

$$\begin{aligned} \mathcal{U}_H(\varphi, \sigma) &= \underbrace{-\varphi_H \mathcal{A}_{tx} (\sigma_{tx} - \sigma_{tx}^*)^+}_{\text{inhibition by toxic agents}} - \underbrace{\varphi_H \mathcal{A}_H}_{\text{apoptosis of host tissue}}, \\ \mathcal{U}_P(\varphi, \sigma) &= \underbrace{\varphi_P \mathcal{P} \sigma_{nu}}_{\text{growth due to nutrient consumption}} - \underbrace{\varphi_P \mathcal{A}_{tx} (\sigma_{tx} - \sigma_{tx}^*)^+}_{\text{inhibition by toxic agents}} - \underbrace{\varphi_P \mathcal{A}_P}_{\text{apoptosis of proliferating cells}} \\ &\quad + \underbrace{\varphi_Q \mathcal{T}_{qp} (\sigma_{nu} - \sigma_{pq}^*)^+}_{\text{transition from quiescent to proliferating cells}} - \underbrace{\varphi_P \mathcal{T}_{pq} (\sigma_{pq}^* - \sigma_{nu})^+}_{\text{transition from proliferating to quiescent cells}}, \\ \mathcal{U}_Q(\varphi, \sigma) &= -\underbrace{\varphi_Q \mathcal{A}_{tx} (\sigma_{tx} - \sigma_{tx}^*)^+}_{\text{inhibition by toxic agents}} - \underbrace{\varphi_Q \mathcal{A}_Q}_{\text{apoptosis of quiescent cells}} - \underbrace{\varphi_Q \mathcal{T}_{qn} (\sigma_{qn}^* - \sigma_{nu})^+}_{\text{transition from quiescent to necrotic cells}} \\ &\quad - \underbrace{\varphi_Q \mathcal{T}_{qp} (\sigma_{nu} - \sigma_{pq}^*)^+}_{\text{transition from quiescent to proliferating cells}} + \underbrace{\varphi_P \mathcal{T}_{pq} (\sigma_{pq}^* - \sigma_{nu})^+}_{\text{transition from proliferating to quiescent cells}}, \\ \mathcal{U}_N(\varphi, \sigma) &= \underbrace{\varphi_P \mathcal{A}_P + \varphi_Q \mathcal{A}_Q}_{\text{apoptosis of proliferating and quiescent cells}} + \underbrace{\varphi_Q \mathcal{T}_{qn} (\sigma_{qn}^* - \sigma_{nu})^+}_{\text{transition from quiescent to necrotic cells}} - \underbrace{\mathcal{D}_N \varphi_N}_{\text{degradation}}. \end{aligned}$$

In the above choice, we cover apoptosis and inhibition by toxic agents affecting all living cells, the two-sided transition between proliferating and quiescent cells when σ_{nu} is in the vicinity of the critical threshold σ_{pq}^* and the one-sided transition from quiescent cells to necrotic cells when σ_{nu} falls below σ_{qn}^* .

In practice, on the timescale considered, \mathcal{A}_H is small and will often be neglected. A unique feature of the necrotic core is reflected in the second term of \mathcal{U}_N , which describes a spontaneous degradation of the necrotic core. Physiologically, one would expect that the remains of the necrotic cells are slowly processed by specialised cells, leaving only extracellular liquid behind. Since we do not account for a pure liquid phase in our systems, we obtain a local mass defect due to the disintegration of the necrotic core. For the source terms discussed above, the equation (2.3) for equal densities $\bar{\rho}_H = \bar{\rho}_P = \bar{\rho}_Q = \bar{\rho}_N = 1$ then becomes

$$\operatorname{div} \vec{v} = \varphi_P \mathcal{P} \sigma_{nu} - \varphi_H \mathcal{A}_H - \mathcal{A}_{tx} (1 - \varphi_N) (\sigma_{tx} - \sigma_{tx}^*)^+ - \mathcal{D}_N \varphi_N,$$

and the disintegration of the necrotic core leads to a sink term for the divergence of the volume-averaged velocity field. Hence one could argue that there are two effects resulting from the existence of a necrotic core which could possibly limit the uncontrolled growth of the tumour colony. On the one hand we have the obvious growth inhibition due to the toxic agents, whereas on the other hand the degradation of the necrotic core draws the growing periphery of the tumour back towards the tumour centre. We indeed observe this behaviour in our numerical simulations in Sec. 4.2.4.

2.9. Blood vessels and angiogenic factors

We can introduce angiogenic factors into the system by considering two additional chemical species: blood vessels whose density is denoted as b and an angiogenic factor whose concentration is denoted as a . Accounting for the additional chemical species, we now have $\boldsymbol{\sigma} = (\sigma_{nu}, \sigma_{tx}, a, b)^\top$. We assume that

- the blood vessels offer a supply of nutrient $\sigma_{\text{Sup}} \geq 0$ at a constant rate $\mathcal{B}_{nu} \geq 0$, which leads to the modification

$$S_{nu}(\boldsymbol{\varphi}, \boldsymbol{\sigma}) = \underbrace{\mathcal{B}_{nu} b (\sigma_{\text{Sup}} - \sigma_{nu})}_{\substack{\text{nutrient supply} \\ \text{from blood vessels}}} - \sigma_{nu} (\varphi_P \mathcal{C}_P + \varphi_Q \mathcal{C}_Q).$$

The new term $\mathcal{B}_{nu} b (\sigma_{\text{Sup}} - \sigma_{nu})$ in S_{nu} models the situation where if the nutrient concentration is below σ_{Sup} , then additional nutrient is supplied by the blood vessels at a rate \mathcal{B}_{nu} . However, if $\sigma_{nu} \geq \sigma_{\text{Sup}}$, then the nutrient diffuses into the blood vessels and is transported away from the cells.

- The blood vessels are capable of removing the toxic agents released by the necrotic cells at a constant rate $\mathcal{B}_{tx} \geq 0$, which leads to the modification

$$S_{tx}(\boldsymbol{\varphi}, \boldsymbol{\sigma}) = \varphi_N \mathcal{R}_{tx} - \mathcal{D}_{tx} \sigma_{tx} - \underbrace{\mathcal{B}_{tx} \sigma_{tx} b}_{\substack{\text{removal by} \\ \text{blood vessels}}}.$$

- The angiogenic factor is a chemical species that is released by the quiescent tumour cells at a constant rate $\mathcal{R}_{ang} \geq 0$ due to the lack of nutrient in their surroundings, and it degrades at a constant rate $\mathcal{D}_{ang} \geq 0$. This leads to

$$S_a(\boldsymbol{\varphi}, \boldsymbol{\sigma}) = \underbrace{\varphi_Q \mathcal{R}_{ang}}_{\substack{\text{release by} \\ \text{quiescent cells}}} - \underbrace{\mathcal{D}_{ang} a}_{\text{degradation}}.$$

In our model, tumour cells become quiescent as a consequence of a lack of nutrient. Therefore it makes sense to assume that the cells, which are in most need of a reliable vascularisation, are secreting factors which induce the necessary blood vessel growth. This assumption has already been suggested in Refs. 8, 16. A very important example for tumour nutrient is

oxygen. It is well known that a lack of this nutrient, hypoxia, is an important stimulus for angiogenesis⁶².

- Meanwhile, the angiogenic factor induces angiogenesis and consequently the vessel density around the badly supplied tumour cells increases at a constant rate $\mathcal{G}_{bv} \geq 0$. There are two ways in which the blood vessels can degrade. The first is a natural process which occurs at a constant rate $\mathcal{D}_{bv} \geq 0$, and the second is through the overexposure of the toxic agent. That is, the blood vessels degrade at a constant rate \mathcal{D}_{bv} when the concentration of the toxic agent σ_{tx} is higher than the critical value σ_{tx}^* . These considerations lead to

$$S_b(\varphi, \sigma) = \underbrace{\mathcal{G}_{bv}ab}_{\text{vessel growth due to angiogenic factors}} - \underbrace{\mathcal{D}_{bv}b}_{\text{natural degradation}} - \underbrace{\mathcal{D}_{bv}(\sigma_{tx} - \sigma_{tx}^*)^+}_{\text{degradation due to toxic agents}}b.$$

Similar to Sec. 2.8, for the choice of the free energy density $N(\varphi, \sigma)$, we consider

$$N(\varphi, \sigma) = \frac{D_{nu}}{2} |\sigma_{nu}|^2 + \frac{D_{bv}}{2} |b|^2 + \frac{D_{ang}}{2} |a|^2 + \frac{D_{tx}}{2} |\sigma_{tx}|^2 - \chi_{nu} \sigma_{nu} \varphi_P. \quad (2.38)$$

The difference between (2.36) and (2.38) is the addition of the terms $\frac{D_{bv}}{2} |b|^2 + \frac{D_{ang}}{2} |a|^2$ to model the diffusion of the blood vessel density and the angiogenic factor, respectively. Computing $N_{,\sigma}(\varphi, \sigma)$ and taking $\underline{D}(\varphi, \sigma)$ as the identity tensor in $\mathbb{R}^{4 \times 4}$, we arrive at the following system for the chemical species:

$$\begin{aligned} \partial_t \sigma_{nu} + \operatorname{div}(\sigma_{nu} \bar{v}) &= \operatorname{div}(D_{nu} \nabla \sigma_{nu} - \chi_{nu} \nabla \varphi_P) + \mathcal{B}_{nu} b (\sigma_{Sup} - \sigma_{nu}) \\ &\quad - \sigma_{nu} (\varphi_P \mathcal{C}_P + \varphi_Q \mathcal{C}_Q), \end{aligned} \quad (2.39a)$$

$$\partial_t \sigma_{tx} + \operatorname{div}(\sigma_{tx} \bar{v}) = \operatorname{div}(D_{tx} \nabla \sigma_{tx}) + \varphi_N \mathcal{R}_{tx} - \mathcal{D}_{tx} \sigma_{tx} - \mathcal{B}_{tx} \sigma_{tx} b, \quad (2.39b)$$

$$\partial_t b + \operatorname{div}(b \bar{v}) = \operatorname{div}(D_{bv} \nabla b) + \mathcal{G}_{bv} ab - \mathcal{D}_{bv} b (1 + (\sigma_{tx} - \sigma_{tx}^*)^+), \quad (2.39c)$$

$$\partial_t a + \operatorname{div}(a \bar{v}) = \operatorname{div}(D_{ang} \nabla a) + \varphi_Q \mathcal{R}_{ang} - \mathcal{D}_{ang} a. \quad (2.39d)$$

We expect that $D_{bv} = 0$ in practice, however choosing D_{bv} to be positive is beneficial for the analytical and numerical treatment of the equations.

An alternative way to model angiogenesis is as follows. One could fix the blood vessel density on the boundary of the domain and assume that blood vessel growth is governed by chemotaxis towards the angiogenic factor, meaning that blood vessels are drawn towards regions with a high concentration of angiogenic factors. In this case, we neglect the first term of S_b , leading to

$$S_b(\varphi, \sigma) = -\mathcal{D}_{bv} b - \mathcal{D}_{bv} (\sigma_{tx} - \sigma_{tx}^*)^+ b.$$

If we consider the free energy density N as in (2.38), with its partial derivative with respect to the vector σ given as

$$N_{,\sigma}(\varphi, \sigma) = (D_{nu} \sigma_{nu} + \chi_{nu} \varphi_P, D_{bv} b, D_{ang} a, D_{tx} \sigma_{tx})^\top \in \mathbb{R}^4,$$

then we may consider a second order mobility tensor $\underline{\underline{D}}(\boldsymbol{\varphi}, \boldsymbol{\sigma}) \in \mathbb{R}^{4 \times 4}$ of the form

$$[\underline{\underline{D}}(\boldsymbol{\varphi}, \boldsymbol{\sigma})]_{ij} = \begin{cases} 1 & \text{if } i = j, \\ -\frac{\chi_{\text{ang}}}{D_{\text{ang}}} b & \text{if } i = 2, j = 3, \\ 0 & \text{otherwise,} \end{cases}$$

where $\chi_{\text{ang}} \geq 0$ is a chemotactic sensitivity to the angiogenic factor. Then, upon computing $\underline{\underline{D}}(\boldsymbol{\varphi}, \boldsymbol{\sigma}) \nabla \mathbf{N}_{,\sigma}(\boldsymbol{\varphi}, \boldsymbol{\sigma})$, this yields the following convection-reaction-diffusion system for the blood vessel density and the angiogenic factor:

$$\begin{aligned} \partial_t b + \operatorname{div}(b\bar{v}) &= \operatorname{div}(D_{\text{bv}} \nabla b - \chi_{\text{ang}} b \nabla a) - \mathcal{D}_{\text{bv}} b - \mathcal{D}_{\text{bv}} (\sigma_{tx} - \sigma_{tx}^*)^+ b, \\ \partial_t a + \operatorname{div}(a\bar{v}) &= \operatorname{div}(D_{\text{ang}} \nabla a) + \varphi_Q \mathcal{R}_{\text{ang}} - \mathcal{D}_{\text{ang}} a. \end{aligned}$$

The term $-\operatorname{div}(\chi_{\text{ang}} b \nabla a)$ in the equation for b can also be found in the classical models for chemotaxis (see for example Refs. 38, 39, 40, 41). We remark that the above modelling approach is different to that in Ref. 23 (see also Sec. 5.12 of Ref. 13), which utilises a random walk model for angiogenesis.

2.10. Three phase model with necrotic cells

In Sec. 4, we perform numerical simulations of a three-component model, similar to (1.4), consisting of host, proliferating and necrotic cells, along with a single nutrient $\sigma = \sigma_{nu}$. Neglecting the quiescent cells (φ_Q) and the toxic intracellular agent (σ_{tx}), as well as the apoptosis of host cells ($\mathcal{A}_H = 0$), the source terms from Sec. 2.8 now become

$$\mathcal{U}_H(\boldsymbol{\varphi}, \boldsymbol{\sigma}) = 0, \quad \mathcal{U}_P(\boldsymbol{\varphi}, \boldsymbol{\sigma}) = \varphi_P(\mathcal{P}\sigma - \mathcal{A}_P), \quad \mathcal{U}_N(\boldsymbol{\varphi}, \boldsymbol{\sigma}) = \mathcal{A}_P \varphi_P - \mathcal{D}_N \varphi_N,$$

where the mass lost by the proliferating cells through apoptosis is equal to the mass gained by the necrotic cells. In the case of equal densities $\bar{\rho}_H = \bar{\rho}_P = \bar{\rho}_N = 1$, this yields the vector \mathbf{U}_A in (1.8b). Alternatively, we can consider source terms of the form

$$\begin{aligned} \mathcal{U}_H(\boldsymbol{\varphi}, \boldsymbol{\sigma}) &= 0, \\ \mathcal{U}_P(\boldsymbol{\varphi}, \boldsymbol{\sigma}) &= \varepsilon^{-1} F(\varphi_P) (\mathcal{P}\sigma - \mathcal{A}), \\ \mathcal{U}_N(\boldsymbol{\varphi}, \boldsymbol{\sigma}) &= \varepsilon^{-1} F(\varphi_N) (\mathcal{A} - \mathcal{D}_N), \end{aligned} \tag{2.40}$$

where F is a non-negative function satisfying $F(0) = F(1) = 0$, $F'(0) = F'(1) = 0$, and $\varepsilon > 0$ is a parameter measuring the thickness of the interfacial layers (recall (1.2)). One such example is $F(s) = s^2(1-s)^2$, which in the case of equal densities $\bar{\rho}_H = \bar{\rho}_P = \bar{\rho}_N = 1$ leads to the vector \mathbf{U}_C in (1.8d). These source terms are chosen in the spirit of Ref. 37 (see also Sec. 3.3.2 of Ref. 27), where we note that $\varphi_i^2(1-\varphi_i)^2$ is non-zero only near the vicinity of the interfacial layers, while the scaling with $\frac{1}{\varepsilon}$ and the specific properties of F ensure that these source terms only appear in the equation of motion for the interfaces when we consider the sharp interface limit $\varepsilon \rightarrow 0$.

3. Sharp interface asymptotics

One advantage of the diffuse interface methodology is that certain classical models using a free boundary description can be recovered in the limit of vanishing interfacial thickness $\varepsilon \rightarrow 0$. This is especially important for our present application to the study of tumours as many of the earlier works model the growth of a tumour via a free boundary problem (for example Refs. 15, 20 where a necrotic core is present). In this section, we perform a formally matched asymptotic analysis in the small parameter ε for (2.27) to identify new free boundary problems. We stress that although the method presented below is formal in nature, the formal identification of sharp interface limits for diffuse interface models in great generality can be obtained rather effortlessly. In contrast, rigorous results so far in the literature for Cahn–Hilliard(–Darcy) systems^{2,9,21,51} only deal with the case when source terms are absent and the generalisation to the case with source terms is still open.

We make the following assumptions for this section:

1. $A = \frac{\beta}{\varepsilon}$ and $B = \beta\varepsilon$ for positive constants β and ε .
2. The mass exchange terms $\mathbf{U} \in \mathbb{R}^L$ and $\mathbf{S} \in \mathbb{R}^M$ depend only on $\varphi \in \mathbb{R}^L$ and $\boldsymbol{\sigma} \in \mathbb{R}^M$, and not on any derivatives.
3. The mobility tensor $\underline{\underline{D}}(\varphi, \boldsymbol{\sigma}) \in \mathbb{R}^{M \times d \times M \times d}$ is a strictly positive and smooth fourth order tensor for all $\varphi \in \mathbb{G}$ and $\boldsymbol{\sigma} \in \mathbb{R}^M$. Here by a strictly positive fourth order tensor $\underline{\underline{A}}$ we mean $\mathbf{t} : (\underline{\underline{A}}\mathbf{t}) > 0$ for all second order tensors $\mathbf{t} \in \mathbb{R}^{M \times d}$, $\mathbf{t} \neq \mathbf{0}$, and $\mathbf{t} : (\underline{\underline{A}}\mathbf{t}) = 0 \Leftrightarrow \mathbf{t} = \mathbf{0}$.
4. $\Psi : \mathbb{G} \rightarrow \mathbb{R}_{\geq 0}$ is a smooth multi-well potential with L equal minima at the points \mathbf{e}_l satisfying $\Psi(\mathbf{e}_l) = 0$ for $1 \leq l \leq L$. Furthermore, we assume that there exist constants c_1, c_2, c_3 and $p \geq 2$ such that

$$c_1 |\varphi|^p \leq \Psi(\varphi) \leq c_2 |\varphi|^p \quad \text{for } |\varphi| \geq c_3.$$

5. We choose the gradient energy as

$$a(\boldsymbol{\eta}, \nabla \varphi) = \frac{1}{2} \sum_{i=1}^L |\nabla \varphi_i|^2 = \frac{1}{2} \sum_{i=1}^L \sum_{k=1}^d |\partial_{x_k} \varphi_i|^2 = \frac{1}{2} (\nabla \varphi : \nabla \varphi).$$

6. The mobility tensor $\underline{\underline{C}}(\varphi, \boldsymbol{\sigma}) \in \mathbb{R}^{L \times d \times L \times d}$ for all $\varphi \in \mathbb{G}$ and $\boldsymbol{\sigma} \in \mathbb{R}^M$ is a smooth fourth order tensor such that (2.21) is satisfied and also fulfils $\underline{\underline{C}}(\varphi, \boldsymbol{\sigma})(\mathbf{a} \otimes \vec{\mathbf{b}}) : (\mathbf{a} \otimes \vec{\mathbf{b}}) > 0$ for all $\mathbf{0} \neq \mathbf{a} \in \{\mathbf{1}\}^\perp$ and $\vec{\mathbf{0}} \neq \vec{\mathbf{b}} \in \mathbb{R}^d$.
7. For small ε , we assume that the domain Ω can be divided into L open subdomains $\Omega_i(\varepsilon)$, $1 \leq i \leq L$, separated by interfaces $\Gamma_{ij}(\varepsilon)$, $1 \leq i < j \leq L$ that do not intersect with each other or with the boundary $\partial\Omega$.
8. We assume that there is a family $(\vec{v}_\varepsilon, p_\varepsilon, \boldsymbol{\varphi}_\varepsilon, \boldsymbol{\sigma}_\varepsilon, \boldsymbol{\mu}_\varepsilon)_{\varepsilon>0}$ of solutions to (2.27), which are sufficiently smooth and have an asymptotic expansion in ε in the bulk regions away from the interfaces $\{\Gamma_{ij}(\varepsilon)\}_{1 \leq i < j \leq L}$ (the outer expansion), and another expansion in the interfacial regions close to the interfaces (the inner expansion).

Remark 3.1. In the above assumption, for a domain $\Omega \subset \mathbb{R}^d$, $d = 2, 3$, we exclude the possibility of triple junction points in \mathbb{R}^2 and triple junction lines or quadruple junction points in \mathbb{R}^3 . Although the method of formally matched asymptotic analysis is able to derive certain boundary/angle conditions for the interfaces Γ_{ij} at such a triple junction, as the case of junctions is not so relevant for tumour growth we will omit the analysis and refer the reader to Refs. 6, 7, 28, 29, 52.

With the above assumptions, (2.27) becomes

$$\operatorname{div} \bar{v} = \mathbf{1} \cdot \mathbf{U}(\varphi, \sigma), \quad (3.1a)$$

$$\bar{v} = -K \nabla p + K (\nabla \varphi)^\top (\boldsymbol{\mu} - \mathbf{N}_{,\varphi}(\varphi, \sigma)), \quad (3.1b)$$

$$\partial_t \varphi + \operatorname{div}(\varphi \otimes \bar{v}) = \operatorname{div}(\underline{\underline{C}}(\varphi, \sigma) \nabla (\mathbb{P} \boldsymbol{\mu})) + \mathbf{U}(\varphi, \sigma), \quad (3.1c)$$

$$\mathbb{P} \boldsymbol{\mu} = -\beta \varepsilon \Delta \varphi + \beta \varepsilon^{-1} \mathbb{P}(\Psi_{,\varphi}(\varphi) + \mathbf{N}_{,\varphi}(\varphi, \sigma)), \quad (3.1d)$$

$$\partial_t \sigma + \operatorname{div}(\sigma \otimes \bar{v}) = \operatorname{div}(\underline{\underline{D}}(\varphi, \sigma) \nabla \mathbf{N}_{,\sigma}(\varphi, \sigma)) + \mathbf{S}(\varphi, \sigma). \quad (3.1e)$$

Heuristically, when ε is small, the potential term $\frac{1}{\varepsilon} \Psi(\varphi)$ will force φ to take values equal to the minima of Ψ , thereby partitioning the domain Ω into L subdomains $\Omega_i := \{\varphi \approx e_i\}$ for $1 \leq i \leq L$. The interfacial region where the value of φ is away from the minima of Ψ has a thickness scaling with ε , and thus in the limit $\varepsilon \rightarrow 0$ we obtain moving hypersurfaces Γ_{ij} , $1 \leq i < j \leq L$, separating the domains Ω_i and Ω_j . The idea of the matched asymptotic analysis is to plug the outer and inner expansions in the model equations and solve them order by order, and in addition, we have to define a suitable region where these expansions should match up. It will turn out that the outer expansions lead to equations satisfied in the bulk domains Ω_i , $1 \leq i \leq L$, and the inner expansions lead to boundary conditions on Γ_{ij} , $1 \leq i < j \leq L$.

We will use the following notation: $(3.1a)_O^\alpha$ and $(3.1a)_I^\alpha$ denote the terms resulting from the order α outer and inner expansions of (3.1a), respectively. For convenience, we will denote $\mathbf{N}_{,\sigma}(\varphi, \sigma)$ by the variable $\boldsymbol{\theta}$.

3.1. Outer expansions

We assume that for $f_\varepsilon \in \{\bar{v}_\varepsilon, \varphi_\varepsilon, \sigma_\varepsilon, \boldsymbol{\mu}_\varepsilon, p_\varepsilon, \boldsymbol{\theta}_\varepsilon\}$, the following outer expansions hold:

$$f_\varepsilon = f_0 + \varepsilon f_1 + \varepsilon^2 f_2 + \dots,$$

where to ensure that the constraint $\varphi_\varepsilon \in \mathbf{G}$ is satisfied, we additionally assume that

$$\varphi_0 \in \mathbf{G}, \quad \varphi_k \in \mathbf{TG} \quad \forall k \geq 1.$$

Note that we can relate the expansions for $\boldsymbol{\theta}_\varepsilon$ by means of Taylor's expansion:

$$\boldsymbol{\theta}_0 = \mathbf{N}_{,\sigma}(\varphi_0, \sigma_0), \quad \boldsymbol{\theta}_1 = \mathbf{N}_{,\sigma\varphi}(\varphi_0, \sigma_0) \varphi_1 + \mathbf{N}_{,\sigma\sigma}(\varphi_0, \sigma_0) \sigma_1, \quad \dots \quad (3.2)$$

To leading order $(3.1d)_O^{-1}$ we have

$$\mathbb{P} \Psi_{,\varphi}(\varphi_0) = \Psi_{,\varphi}(\varphi_0) - \frac{1}{L} \sum_{i=1}^L \frac{\partial \Psi}{\partial \varphi_i}(\varphi_0) \mathbf{1} = \vec{0}. \quad (3.3)$$

The stable solutions to (3.3) are the minima of Ψ , that is, $\varphi_0 = \mathbf{e}_i$, $1 \leq i \leq L$. Thus, to leading order the domain Ω is partitioned into L regions corresponding to the stable minima of Ψ . We define

$$\Omega_i = \{\bar{x} \in \Omega : \varphi_0(\bar{x}) = \mathbf{e}_i\} \quad \text{for } 1 \leq i \leq L.$$

Since $\nabla \varphi_0 = \underline{\underline{0}} \in \mathbb{R}^{L \times d}$ is the zero tensor in the bulk regions Ω_i , $1 \leq i \leq L$, we obtain from (3.1a), (3.1b), (3.1c) and (3.1e) to zeroth order in each bulk region:

$$\operatorname{div} \bar{v}_0 = \mathbf{1} \cdot \mathbf{U}(\varphi_0, \boldsymbol{\sigma}_0), \quad (3.4a)$$

$$\bar{v}_0 = -K \nabla p_0, \quad (3.4b)$$

$$-\operatorname{div}(\underline{\underline{C}}(\varphi_0, \boldsymbol{\sigma}_0) \nabla(\mathbb{P}\boldsymbol{\mu}_0)) = \mathbf{U}(\varphi_0, \boldsymbol{\sigma}_0) - (\mathbf{1} \cdot \mathbf{U}(\varphi_0, \boldsymbol{\sigma}_0)) \varphi_0, \quad (3.4c)$$

$$\partial_t \boldsymbol{\sigma}_0 + \operatorname{div}(\boldsymbol{\sigma}_0 \otimes \bar{v}_0) = \operatorname{div}(\underline{\underline{D}}(\varphi_0, \boldsymbol{\sigma}_0) \nabla \mathbf{N}_{,\sigma}(\varphi_0, \boldsymbol{\sigma}_0)) + \mathbf{S}(\varphi_0, \boldsymbol{\sigma}_0). \quad (3.4d)$$

At this stage we are missing the boundary conditions for the above partial differential equations. These boundary conditions will be derived below.

3.2. Inner expansions and matching conditions

In this section we fix $1 \leq i < j \leq L$ and construct a solution that makes a transition from Ω_i to Ω_j across a smoothly evolving hypersurface $\Gamma = \Gamma_{ij}$ moving with normal velocity \mathcal{V} . Let $d(\bar{x})$ denote the signed distance function to Γ , and set $z = \frac{d}{\varepsilon}$ as the rescaled distance variable. Here we use the convention that $d(\bar{x}) < 0$ in Ω_i and $d(\bar{x}) > 0$ in Ω_j . Thus the gradient ∇d points from Ω_i to Ω_j and we may use ∇d on Γ as a unit normal $\bar{\nu}$.

Let $g(t, s)$ denote a parameterisation of Γ by arclength s , and in a tubular neighbourhood of Γ , for smooth functions $f(\bar{x})$, we have

$$f(\bar{x}) = f(g(t, s) + \varepsilon z \bar{\nu}(g(t, s))) =: F(t, s, z).$$

In this new (t, s, z) -coordinate system, the following change of variables apply^{1,31}:

$$\partial_t f = -\frac{1}{\varepsilon} \mathcal{V} \partial_z F + \text{h.o.t.}, \quad \nabla_x f = \frac{1}{\varepsilon} \partial_z F \bar{\nu} + \nabla_\Gamma F + \text{h.o.t.},$$

where $\nabla_\Gamma h$ denotes the surface gradient of h on Γ and h.o.t. denotes higher order terms with respect to ε . In particular, we have

$$\Delta f = \operatorname{div}_x(\nabla_x f) = \frac{1}{\varepsilon^2} \partial_{zz} F + \frac{1}{\varepsilon} \underbrace{\operatorname{div}_\Gamma(\partial_z F \bar{\nu})}_{=-\kappa \partial_z F} + \text{h.o.t.},$$

where $\kappa = -\operatorname{div}_\Gamma \bar{\nu}$ is the mean curvature of Γ . Moreover, if \mathbf{f} is a vector-valued function with $\mathbf{F}(t, s, z) = \mathbf{f}(t, \bar{x})$ for \bar{x} in a tubular neighbourhood of Γ , then we obtain

$$\begin{aligned} \partial_t \mathbf{f} &= -\frac{1}{\varepsilon} \mathcal{V} \partial_z \mathbf{F} + \text{h.o.t.}, \quad \nabla_x \mathbf{f} = \frac{1}{\varepsilon} \partial_z \mathbf{F} \otimes \bar{\nu} + \nabla_\Gamma \mathbf{F} + \text{h.o.t.}, \\ \operatorname{div}_x \mathbf{f} &= \frac{1}{\varepsilon} \partial_z \mathbf{F} \cdot \bar{\nu} + \operatorname{div}_\Gamma \mathbf{F} + \text{h.o.t.} \end{aligned}$$

We denote the variables $\varphi_\varepsilon, \vec{v}_\varepsilon, p_\varepsilon, \boldsymbol{\mu}_\varepsilon, \boldsymbol{\sigma}_\varepsilon, \boldsymbol{\theta}_\varepsilon$ in the new coordinate system by $\Phi_\varepsilon, \vec{V}_\varepsilon, P_\varepsilon, \Upsilon_\varepsilon, \Sigma_\varepsilon, \Theta_\varepsilon$, respectively. We further assume that they have the following inner expansions:

$$F_\varepsilon(t, s, z) = F_0(t, s, z) + \varepsilon F_1(t, s, z) + \varepsilon^2 F_2(t, s, z) + \dots,$$

for $F_\varepsilon \in \{\Phi_\varepsilon, \vec{V}_\varepsilon, P_\varepsilon, \Upsilon_\varepsilon, \Sigma_\varepsilon, \Theta_\varepsilon\}$ such that

$$\Phi_0 \in G, \quad \Phi_k \in TG \quad \forall k \geq 1.$$

to ensure that the constraint $\varphi_\varepsilon \in G$ is satisfied. Analogous to (3.2), by Taylor's expansion, we have

$$\Theta_0 = N_{,\sigma}(\Phi_0, \Sigma_0), \quad \Theta_1 = N_{,\sigma\varphi}(\Phi_0, \Sigma_0)\Phi_1 + N_{,\sigma\sigma}(\Phi_0, \Sigma_0)\Sigma_1, \quad \dots \quad (3.5)$$

In order to match the inner expansions valid in the interfacial region to the outer expansions of Sec. 3.1, we employ the matching conditions³¹:

$$\lim_{z \rightarrow \pm l} F_0(t, s, z) = f_0^\pm(t, \vec{x}), \quad (3.6)$$

$$\lim_{z \rightarrow \pm l} \partial_z F_0(t, s, z) = 0, \quad (3.7)$$

$$\lim_{z \rightarrow \pm l} \partial_z F_1(t, s, z) = \nabla f_0^\pm(t, \vec{x}) \cdot \vec{\nu}, \quad (3.8)$$

where $f_0^\pm(t, \vec{x}) = \lim_{\delta \rightarrow 0} f_0(t, \vec{x} \pm \delta \vec{\nu}(\vec{x}))$ for $\vec{x} \in \Gamma$ and $\delta > 0$. Here we use the convention that for a vectorial quantity \mathbf{f}_0 , the right hand side of (3.8) reads as $(\nabla \mathbf{f}_0^\pm) \cdot \vec{\nu}$. Moreover, we use the following notation: Let $\delta > 0$ and for $\vec{x} \in \Gamma$ with $x - \delta \vec{\nu}(\vec{x}) \in \Omega_i$ and $x + \delta \vec{\nu}(\vec{x}) \in \Omega_j$, we denote the jump of a scalar quantity f across the interface by

$$[f]_i^j = \lim_{\delta \rightarrow 0} (f(t, \vec{x} + \delta \vec{\nu}(\vec{x})) - f(t, \vec{x} - \delta \vec{\nu}(\vec{x}))). \quad (3.9)$$

For a vectorial quantity $\mathbf{f} \in \mathbb{R}^k$, we define

$$[\mathbf{f}]_i^j = \lim_{\delta \rightarrow 0} (\mathbf{f}(t, \vec{x} + \delta \vec{\nu}(\vec{x})) - \mathbf{f}(t, \vec{x} - \delta \vec{\nu}(\vec{x}))) = ([f_1]_i^j, \dots, [f_k]_i^j)^\top.$$

It will be useful to compute the expansion for the term $\text{div}(\underline{\underline{D}}(\varphi, \boldsymbol{\sigma}) \nabla N_{,\sigma}(\varphi, \boldsymbol{\sigma}))$ as follows: For fixed $1 \leq l, n \leq d$ and $1 \leq k, m \leq M$, we find from the above change of variables formula

$$\begin{aligned} \partial_{x_l} \left((\underline{\underline{D}}(\varphi, \boldsymbol{\sigma}))_{klmn} \partial_{x_n} \theta_m \right) &= \frac{1}{\varepsilon} \partial_z \left((\underline{\underline{D}}(\Phi, \Sigma))_{klmn} \left(\frac{1}{\varepsilon} \partial_z \Theta_m \nu_n + \underline{D}_n \Theta_m \right) \right) \nu_l \\ &\quad + \underline{D}_l \left((\underline{\underline{D}}(\Phi, \Sigma))_{klmn} \left(\frac{1}{\varepsilon} \partial_z \Theta_m \nu_n + \underline{D}_l \Theta_m \right) \right) + \text{h.o.t.}, \end{aligned}$$

where \underline{D}_n denotes the n th component of the surface gradient, i.e., $\nabla_\Gamma f = (\underline{D}_1 f, \dots, \underline{D}_d f)^\top$. Plugging in the expansion (where we use $\Theta_{m,q}$ to denote the q th term of the inner expansion for the m th component of Θ) and using Taylor's

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theorem we have

$$\begin{aligned}
 & \partial_{x_i} \left((\underline{\underline{D}}(\varphi, \sigma))_{klmn} \partial_{x_n} \theta_m \right) \\
 &= \frac{1}{\varepsilon^2} \partial_z \left((\underline{\underline{D}}(\Phi_0, \Sigma_0))_{klmn} \partial_z \Theta_{m,0} \right) \nu_l \nu_n + \frac{1}{\varepsilon} \partial_z \left((\underline{\underline{D}}(\Phi_0, \Sigma_0))_{klmn} \partial_z \Theta_{m,1} \right) \nu_l \nu_n \\
 &+ \frac{1}{\varepsilon} \left[\partial_z \left((\underline{\underline{D}}(\Phi_0, \Sigma_0))_{klmn} \underline{D}_n \Theta_{m,0} \nu_l \right) + \underline{D}_l \left((\underline{\underline{D}}(\Phi_0, \Sigma_0))_{klmn} \partial_z \Theta_{m,0} \nu_n \right) \right] \\
 &+ \frac{1}{\varepsilon} \partial_z \left(\left(\sum_{s=1}^L \frac{\partial(\underline{\underline{D}}(t, \mathbf{w}))_{klmn}}{\partial t_s} \Phi_{s,1} + \sum_{s=1}^M \frac{\partial(\underline{\underline{D}}(t, \mathbf{w}))_{klmn}}{\partial w_s} \Sigma_{s,1} \right) (\partial_z \Theta_{m,0} \nu_n) \right) \nu_l \\
 &+ \text{h.o.t.},
 \end{aligned} \tag{3.10}$$

where we evaluate the last term at $\mathbf{t} = \Phi_0$ and $\mathbf{w} = \Sigma_0$. Using that

$$\operatorname{div}(\underline{\underline{D}}(\varphi, \sigma) \nabla N_{,\sigma}(\varphi, \sigma)) = \left(\sum_{l,n=1}^d \sum_{m=1}^M \partial_{x_l} \left((\underline{\underline{D}}(\varphi, \sigma))_{klmn} \partial_{x_n} \theta_m \right) \right)_{1 \leq k \leq L},$$

we obtain the expansion for the term $\operatorname{div}(\underline{\underline{D}}(\varphi, \sigma) \nabla N_{,\sigma}(\varphi, \sigma))$. One can also derive a similar expansion for $\operatorname{div}(\underline{\underline{C}}(\varphi, \sigma) \nabla(\mathbb{P}\mu))$.

3.2.1. Expansions to leading order

To leading order $(3.1d)_I^{-1}$ we obtain

$$\mathbf{0} = -\partial_z(\partial_z \Phi_0 \otimes \bar{\nu}) \cdot \bar{\nu} + \mathbb{P}\Psi_{,\varphi}(\Phi_0) = -\partial_{zz} \Phi_0 + \Psi_{,\varphi}(\Phi_0) - \frac{1}{L}(\Psi_{,\varphi}(\Phi_0) \cdot \mathbf{1})\mathbf{1}. \tag{3.11}$$

This is a second order differential equation for $\Phi_0(t, s, \cdot)$, and for each s we solve the above ordinary differential equation (in z) with the boundary conditions

$$\lim_{z \rightarrow \infty} \Phi_0(t, s, z) = \mathbf{e}_j, \quad \lim_{z \rightarrow -\infty} \Phi_0(t, s, z) = \mathbf{e}_i, \tag{3.12}$$

which then yields a vector-valued function that connects \mathbf{e}_i to \mathbf{e}_j and hence the values of the phase fields in Ω_i and Ω_j . By the assumptions satisfied by Ψ listed at the start of this section, it is shown by Sternberg in Lemma, p. 801 of Ref. 64 that for any $\mathbf{u} \in \mathbf{G}$, there exists a curve $\gamma_{\mathbf{u}} : [-1, 1] \rightarrow \mathbf{G}$ such that $\gamma_{\mathbf{u}}(-1) = \mathbf{e}_i$ and $\gamma_{\mathbf{u}}(1) = \mathbf{u}$ and the Lipschitz continuous function

$$q(\mathbf{u}) = \int_{-1}^1 \sqrt{\Psi(\gamma_{\mathbf{u}}(t))} |\gamma'_{\mathbf{u}}(t)| dt \quad \text{satisfies} \quad |\nabla q(\mathbf{u})| = \sqrt{\Psi(\mathbf{u})} \quad \text{for a.e. } \mathbf{u} \in \mathbf{G}.$$

Let us define $\beta : (-\infty, \infty) \rightarrow (-1, 1)$ as the monotone solution of

$$\beta'(z) = \frac{\sqrt{2\Psi(\gamma_{\mathbf{e}_j}(\beta(z)))}}{|\gamma'_{\mathbf{e}_j}(\beta(z))|}, \quad \beta(0) = 0$$

and then set

$$\bar{\Phi}(z) = \gamma_{\mathbf{e}_j}(\beta(z)).$$

Then, it holds that $|\overline{\Phi}'(z)| = \sqrt{2\Psi(\overline{\Phi}(z))}$ and

$$\begin{aligned} \sqrt{2}q(e_j) &= \sqrt{2} \int_{-\infty}^{\infty} \sqrt{\Psi(\gamma_{e_j}(\beta(z)))} |\gamma'_{e_j}(\beta(z))| \beta'(z) dz \\ &= 2 \int_{-\infty}^{\infty} \Psi(\overline{\Phi}(z)) dz = \int_{-\infty}^{\infty} \Psi(\overline{\Phi}(z)) + \frac{1}{2} |\overline{\Phi}'(z)|^2 dz. \end{aligned} \quad (3.13)$$

It follows that $\overline{\Phi}$ is a candidate solution to the following problem

$$\inf_{\zeta \in G, \zeta(-\infty)=e_i, \zeta(\infty)=e_j} \int_{-\infty}^{\infty} \Psi(\zeta(\tau)) + \frac{1}{2} |\zeta'(\tau)|^2 d\tau.$$

Computing its Euler–Lagrange equations (subject to the constraint $\zeta \in G$, which leads to the presence of the projection operator \mathbb{P} below) yields that

$$\overline{\Phi}''(z) = \mathbb{P}\Psi_{,\varphi}(\overline{\Phi}(z)) = \Psi_{,\varphi}(\overline{\Phi}(z)) - \frac{1}{L}(\Psi_{,\varphi}(\overline{\Phi}(z)) \cdot \mathbf{1})\mathbf{1},$$

and if we consider

$$\Phi_0(t, s, z) = \overline{\Phi}(z),$$

then $\Phi_0(z)$ satisfies (3.11) and (3.12). Furthermore, multiplying (3.11) with $\Phi'_0 \in \text{TG}$, integrating with respect to z and applying the matching condition (3.6) to Φ_0 , leads to the so-called equipartition of energy:

$$\Psi(\Phi_0(z)) = \frac{1}{2} |\Phi'_0(z)|^2 \quad \forall z \in \mathbb{R},$$

and we define the surface energy γ_{ij} to be

$$\gamma_{ij} = \sqrt{2}q(e_j) = \int_{-\infty}^{\infty} \Psi(\Phi_0(z)) + \frac{1}{2} |\Phi'_0(z)|^2 dz = \int_{-\infty}^{\infty} |\Phi'_0(z)|^2 dz. \quad (3.14)$$

Next, $(3.1a)_I^{-1}$ gives

$$\partial_z \vec{V}_0 \cdot \vec{\nu} = \partial_z (\vec{V}_0 \cdot \vec{\nu}) = 0. \quad (3.15)$$

Integrating with respect to z and using the matching condition (3.6) applied to \vec{v}_0 leads to

$$[\vec{v}_0]_i^j \cdot \vec{\nu} = 0. \quad (3.16)$$

From $(3.1e)_I^{-2}$ and (3.10) we have for each $k = 1, \dots, M$,

$$\sum_{l,n=1}^d \sum_{m=1}^M \partial_z ((\underline{\underline{D}}(\Phi_0, \Sigma_0))_{klmn} \partial_z \Theta_{m,0}) \nu_l \nu_n = 0. \quad (3.17)$$

Multiplying by $\Theta_{k,0}$ and summing from $k = 1$ to M and then integrating with respect to z , we obtain from integration by parts and the matching condition (3.7) applied to Θ_0 that

$$\begin{aligned} 0 &= - \sum_{k,m=1}^M \sum_{l,n=1}^d \int_{-\infty}^{\infty} (\underline{\underline{D}}(\Phi_0, \Sigma_0))_{klmn} \partial_z \Theta_{m,0} \nu_n \partial_z \Theta_{k,0} \nu_l dz \\ &= - \int_{-\infty}^{\infty} (\underline{\underline{D}}(\Phi_0, \Sigma_0)) (\partial_z \Theta_0 \otimes \vec{\nu}) : (\partial_z \Theta_0 \otimes \vec{\nu}) dz. \end{aligned}$$

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The strict positivity of \underline{D} yields

$$\partial_z \Theta_0(t, s, z) = \vec{0} \in \mathbb{R}^M \quad \forall z \in \mathbb{R}, \quad (3.18)$$

i.e., Θ_0 is independent of z . Moreover, integrating (3.18) with respect to z and using the matching condition (3.6) applied to Θ_0 gives

$$[\theta_0]_i^j = [N_{,\sigma}(\varphi_0, \sigma_0)]_i^j = \vec{0} \in \mathbb{R}^M. \quad (3.19)$$

Meanwhile, from (3.1c) $_I^{-2}$, we have for each $k = 1, \dots, L$,

$$\sum_{l,n=1}^d \sum_{m=1}^L \partial_z \left((\underline{C}(\Phi_0, \Sigma_0))_{klmn} \partial_z \mathbb{P}\Upsilon_{m,0} \right) \nu_l \nu_m = 0. \quad (3.20)$$

Multiplying by $\mathbb{P}\Upsilon_{k,0} \in \text{TG}$ and summing from $k = 1$ to L , an analysis similar to the above for Θ_0 using the assumptions on \underline{C} yields that

$$\partial_z \mathbb{P}\Upsilon_0(t, s, z) = \vec{0} \in \mathbb{R}^L \quad \forall z \in \mathbb{R} \quad \Rightarrow \quad [\mathbb{P}\mu_0]_i^j = \vec{0} \in \mathbb{R}^L. \quad (3.21)$$

Lastly, (3.1b) $_I^{-1}$ yields

$$\vec{0} = -\partial_z P_0 \vec{\nu} + (\Phi'_0 \cdot (\Upsilon_0 - N_{,\varphi}(\Phi_0, \Sigma_0))) \vec{\nu}. \quad (3.22)$$

Taking the scalar product with $\vec{\nu}$ and then integrating with respect to z leads to

$$\begin{aligned} [p_0]_i^j &= \int_{-\infty}^{\infty} \Phi'_0 \cdot (\Upsilon_0 - N_{,\varphi}(\Phi_0, \Sigma_0)) dz \\ &= \int_{-\infty}^{\infty} \Phi'_0 \cdot (\mathbb{P}\Upsilon_0 - N_{,\varphi}(\Phi_0, \Sigma_0)) dz, \end{aligned} \quad (3.23)$$

where we used the matching condition (3.6) applied to P_0 and the fact that $\Phi'_0 \in \text{TG}$ and so $\Phi'_0 \cdot \Upsilon_0 = \Phi'_0 \cdot \mathbb{P}\Upsilon_0$. Thanks to the fact that $\mathbb{P}\Upsilon_0$ is independent of z , we find that

$$\int_{-\infty}^{\infty} \Phi'_0 \cdot \mathbb{P}\Upsilon_0 dz = \int_{-\infty}^{\infty} \partial_z (\mathbb{P}\Upsilon_0 \cdot \Phi_0) dz = [\mathbb{P}\mu_0 \cdot \varphi_0]_i^j. \quad (3.24)$$

Recalling $\Theta_0 = N_{,\sigma}(\Phi_0, \Sigma_0)$ from (3.5), we have

$$\begin{aligned} \int_{-\infty}^{\infty} \Phi'_0 \cdot N_{,\varphi}(\Phi_0, \Sigma_0) dz &= [N(\Phi_0, \Sigma_0)]_i^j - \int_{-\infty}^{\infty} \partial_z \Sigma_0 \cdot \Theta_0 dz \\ &= [N(\varphi_0, \sigma_0)]_i^j - [\sigma_0]_i^j \cdot N_{,\sigma}(\varphi_0, \sigma_0), \end{aligned} \quad (3.25)$$

and so (3.23) becomes

$$[p_0 - \mathbb{P}\mu_0 \cdot \varphi_0 - N(\varphi_0, \sigma_0) + N_{,\sigma}(\varphi_0, \sigma_0) \cdot \sigma_0]_i^j = 0. \quad (3.26)$$

3.2.2. Expansions to first order

To first order, we find from (3.1d)⁰

$$\mathbb{P}\Upsilon_0 = \beta \mathbb{P}\Psi_{,\varphi\varphi}(\Phi_0)\Phi_1 + \mathbb{P}N_{,\varphi}(\Phi_0, \Sigma_0) - \beta \partial_{zz}\Phi_1 - \beta \operatorname{div}_\Gamma(\Phi'_0 \otimes \bar{\nu}), \quad (3.27)$$

where we used that Φ_0 is only a function of z and so $\nabla_\Gamma \Phi_0 = \underline{0}$ is the zero tensor. As $\Phi'_0 \in \operatorname{TG}$, $\mathbb{P}\mathbf{f} \cdot \Phi'_0 = \mathbf{f} \cdot \Phi'_0$, and hence after multiplying (3.27) with Φ'_0 and integrating over z we obtain

$$\begin{aligned} & \int_{-\infty}^{\infty} \frac{1}{\beta} (\mathbb{P}\Upsilon_0 - N_{,\varphi}(\Phi_0, \Sigma_0)) \cdot \Phi'_0 dz \\ &= \int_{-\infty}^{\infty} (\Psi_{,\varphi\varphi}(\Phi_0)\Phi_1) \cdot \Phi'_0 - \partial_{zz}\Phi_1 \cdot \Phi'_0 + \kappa |\Phi'_0|^2 dz, \end{aligned} \quad (3.28)$$

where $\kappa = -\operatorname{div}_\Gamma \bar{\nu}$ is the mean curvature of Γ and we have used that $\operatorname{div}_\Gamma(\Phi'_0 \otimes \bar{\nu}) = \Phi'_0 \operatorname{div}_\Gamma \bar{\nu} = -\kappa \Phi'_0$. Due to the symmetry of the tensor $\Psi_{,\varphi\varphi}$ it holds that

$$(\Psi_{,\varphi\varphi}(\Phi_0))\Phi_1 \cdot \Phi'_0 = (\Psi_{,\varphi\varphi}(\Phi_0))\Phi'_0 \cdot \Phi_1 = \partial_z(\Psi_{,\varphi}(\Phi_0)) \cdot \Phi_1. \quad (3.29)$$

Then by integrating by parts we obtain from (3.11) and the matching conditions (3.6), (3.7) applied to Φ_0 that

$$\begin{aligned} \int_{-\infty}^{\infty} \partial_z(\Psi_{,\varphi}(\Phi_0)) \cdot \Phi_1 - \partial_{zz}\Phi_1 \cdot \Phi'_0 dz &= \int_{-\infty}^{\infty} (\Psi_{,\varphi}(\Phi_0) - \Phi''_0) \cdot \partial_z \Phi_1 dz \\ &+ [\Psi_{,\varphi}(\Phi_0) \cdot \Phi_1 + \Phi'_0 \cdot \partial_z \Phi_1]_{z=-\infty}^{z=\infty} = 0. \end{aligned}$$

Using (3.14), (3.24), and (3.25), we obtain from (3.28) the following solvability condition for Φ_1 :

$$\beta \gamma_{ij} \kappa = [\mathbb{P}\mu_0 \cdot \varphi_0]_i^j - [N(\varphi_0, \sigma_0)]_i^j + [\sigma_0]_i^j \cdot N_{,\sigma}(\varphi_0, \sigma_0) = [p_0]_i^j. \quad (3.30)$$

Next, thanks to the fact that $\partial_z \mathbb{P}\Upsilon_0 = \bar{0}$, to first order we obtain from (3.1c)_I⁻¹

$$-\mathcal{V}\Phi'_0 + \partial_z(\Phi_0(\bar{v}_0 \cdot \bar{\nu})) = \partial_z \left((\underline{\underline{C}}(\Phi_0, \Sigma_0)) [(\partial_z \mathbb{P}\Upsilon_1 \otimes \bar{\nu}) + \nabla_\Gamma \mathbb{P}\Upsilon_0] \right) \bar{\nu}. \quad (3.31)$$

We note that by the matching condition (3.8) applied to $\mathbb{P}\Upsilon_1$, we have $\lim_{z \rightarrow \pm\infty} \partial_z \mathbb{P}\Upsilon_1 \otimes \bar{\nu} = \nabla(\mathbb{P}\mu_0^\pm) \bar{\nu}$, and hence

$$(\partial_z \mathbb{P}\Upsilon_1 \otimes \bar{\nu}) + \nabla_\Gamma \mathbb{P}\Upsilon_0 \rightarrow \begin{cases} \nabla \mathbb{P}\mu_0^+ & \text{for } z \rightarrow \infty, \\ \nabla \mathbb{P}\mu_0^- & \text{for } z \rightarrow -\infty. \end{cases}$$

From (3.15), $\bar{v}_0 \cdot \bar{\nu}$ is independent of z , so integrating (3.31) with respect to z and applying the matching condition (3.6) to Φ_0 and (3.8) to $\partial_z \mathbb{P}\Upsilon_1$ gives

$$(-\mathcal{V} + \bar{v}_0 \cdot \bar{\nu}) [\varphi_0]_i^j = [(\underline{\underline{C}}(\varphi_0, \sigma_0)) \nabla(\mathbb{P}\mu_0)]_i^j \bar{\nu}. \quad (3.32)$$

Similar, thanks to the fact that $\partial_z \Theta_0 = \bar{0}$, we obtain from (3.1e)_I⁻¹

$$-\mathcal{V}\partial_z \Sigma_0 + \partial_z(\Sigma_0(\bar{v}_0 \cdot \bar{\nu})) = \partial_z \left((\underline{\underline{D}}(\Phi_0, \Sigma_0)) [(\partial_z \Theta_1 \otimes \bar{\nu}) + \nabla_\Gamma \Theta_0] \right) \bar{\nu}, \quad (3.33)$$

and upon integrating with respect to z we obtain

$$(-\mathcal{V} + \bar{v}_0 \cdot \bar{\nu}) [\sigma_0]_i^j = [(\underline{\underline{D}}(\varphi_0, \sigma_0)) \nabla N_{,\sigma}(\varphi_0, \sigma_0)]_i^j \bar{\nu}. \quad (3.34)$$

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In summary, we obtain the following sharp interface model: In the bulk domains $\Omega_k = \{\varphi_0 = \mathbf{e}_k\}$, $1 \leq k \leq L$,

$$\operatorname{div} \bar{v}_0 = \mathbf{1} \cdot \mathbf{U}(\varphi_0, \sigma_0), \quad (3.35a)$$

$$\bar{v}_0 = -K \nabla p_0, \quad (3.35b)$$

$$-\operatorname{div} (\underline{\underline{C}}(\varphi_0, \sigma_0) \nabla (\mathbb{P} \mu_0)) = \mathbf{U}(\varphi_0, \sigma_0) - \mathbf{1} \cdot \mathbf{U}(\varphi_0, \sigma_0) \varphi_0, \quad (3.35c)$$

$$\partial_t \sigma_0 + \operatorname{div} (\sigma_0 \otimes \bar{v}_0) = \operatorname{div} (\underline{\underline{D}}(\varphi_0, \sigma_0) \nabla \mathbf{N}_{,\sigma}(\varphi_0, \sigma_0)) + \mathcal{S}(\varphi_0, \sigma_0), \quad (3.35d)$$

and on the free boundaries $\Gamma_{ij} = \partial\Omega_i \cap \partial\Omega_j$, $1 \leq i < j \leq L$, with unit normal $\bar{\nu}$ pointing from Ω_i to Ω_j ,

$$[\bar{v}_0]_i^j \cdot \bar{\nu} = 0, \quad [p_0]_i^j = \beta \gamma_{ij} \kappa, \quad (3.36a)$$

$$[\mathbb{P} \mu_0]_i^j = \bar{0}, \quad (3.36b)$$

$$[\mathbf{N}_{,\sigma}(\varphi_0, \sigma_0)]_i^j = \bar{0}, \quad (3.36c)$$

$$\beta \gamma_{ij} \kappa = [\mathbb{P} \mu_0 \cdot \varphi_0 - N(\varphi_0, \sigma_0) + \sigma_0 \cdot \mathbf{N}_{,\sigma}(\varphi_0, \sigma_0)]_i^j, \quad (3.36d)$$

$$(-\mathcal{V} + \bar{v}_0 \cdot \bar{\nu}) (\mathbf{e}_j - \mathbf{e}_i) = [\underline{\underline{C}}(\varphi_0, \sigma_0) \nabla (\mathbb{P} \mu_0)]_i^j \bar{\nu}, \quad (3.36e)$$

$$(-\mathcal{V} + \bar{v}_0 \cdot \bar{\nu}) [\sigma_0]_i^j = [\underline{\underline{D}}(\varphi_0, \sigma_0) \nabla \mathbf{N}_{,\sigma}(\varphi_0, \sigma_0)]_i^j \bar{\nu}, \quad (3.36f)$$

where the surface energy γ_{ij} is defined in (3.14).

3.3. Sharp interface limit for a two-component tumour model

We now sketch the argument to recover the sharp interface model (3.49) of Ref. 27 from (3.35)-(3.36) for a two-component model of host cells and tumour cells, along with a single nutrient species, recall also Sec. 2.7. Dropping the subscript 0 from (3.35)-(3.36), we consider (2.32) with

$$N(\varphi, \sigma) = \frac{\chi_\sigma}{2} |\sigma|^2 + 2\chi_\varphi \sigma \varphi_1, \quad \Psi(\varphi) = 4\varphi_1^2 \varphi_2^2 \quad \Rightarrow \quad \tilde{\Psi}(\tilde{\varphi}) = \frac{1}{4} (1 - \tilde{\varphi}^2)^2,$$

along with the scalar mobility (2.33), and the second order mobility tensor defined in (2.34). Setting $\Omega_H = \Omega_1 = \{\varphi = (1, 0)^\top\} = \{\tilde{\varphi} = -1\}$ and $\Omega_T = \Omega_2 = \{\varphi = (0, 1)^\top\} = \{\tilde{\varphi} = 1\}$, we obtain

$$\bar{v} = -K \nabla p, \quad \operatorname{div} \bar{v} = \bar{\rho}_1^{-1} \tilde{\mathcal{U}}_1(\tilde{\varphi}, \sigma) + \bar{\rho}_2^{-1} \tilde{\mathcal{U}}_2(\tilde{\varphi}, \sigma) \quad \text{in } \Omega_H \cup \Omega_T, \quad (3.37a)$$

$$\partial_t \sigma + \operatorname{div} (\sigma \bar{v}) = \chi_\sigma \operatorname{div} (n(\tilde{\varphi}) \nabla \sigma) + \tilde{\mathcal{S}}(\tilde{\varphi}, \sigma) \quad \text{in } \Omega_H \cup \Omega_T, \quad (3.37b)$$

$$m(+1) \Delta \mu = 2\bar{\rho}_1^{-1} \tilde{\mathcal{U}}_1(+1, \sigma) \quad \text{in } \Omega_T, \quad (3.37c)$$

$$-m(-1) \Delta \mu = 2\bar{\rho}_2^{-1} \tilde{\mathcal{U}}_2(-1, \sigma) \quad \text{in } \Omega_H. \quad (3.37d)$$

To obtain the free boundary conditions on $\Gamma = \Gamma_{12}$, let $\bar{\Phi}(z)$ denote the solution to (3.11) that connects $(0, 1)^\top$ to $(1, 0)^\top$, and let $\phi = \bar{\Phi}_2 - \bar{\Phi}_1$ denote the difference between the second and first components of $\bar{\Phi}$. Then, it holds that $\bar{\Phi}_1 = \frac{1-\phi}{2}$ and $\bar{\Phi}_2 = \frac{1+\phi}{2}$ with $\lim_{z \rightarrow -\infty} \phi(z) = -1$ and $\lim_{z \rightarrow +\infty} \phi(z) = 1$. We now derive the ODE

which is satisfied by ϕ . Taking the difference between the second and first components of (3.11) (noting that the last term on the right-hand side of (3.11) will not contribute to this difference), it holds that ϕ satisfies

$$-\phi''(z) + \phi^3(z) - \phi(z) = -\phi''(z) + \tilde{\Psi}'(\phi(z)) = 0.$$

The unique solution ϕ to the above ODE with the boundary conditions $\lim_{z \rightarrow \pm\infty} \phi(z) = \pm 1$ and satisfying $\phi(0) = 0$ is the function $\phi(z) = \tanh(z/\sqrt{2})$. With the help of (3.14), we compute the surface energy $\gamma = \gamma_{12}$ to be

$$\gamma = \int_{-\infty}^{\infty} 2\Psi(\bar{\Phi}(z)) dz = \int_{-\infty}^{\infty} 2\tilde{\Psi}(\phi(z)) dz = \int_{-1}^1 \sqrt{2\tilde{\Psi}(s)} ds = \frac{2\sqrt{2}}{3}.$$

We observe that the jump conditions (3.36c) and (3.36f) become

$$0 = [N, \sigma]_H^T \Rightarrow [\sigma]_H^T = 2\frac{\chi_\varphi}{\chi_\sigma}, \quad (-\mathcal{V} + \bar{v} \cdot \bar{v}) [\sigma]_H^T = 2\frac{\chi_\varphi}{\chi_\sigma} (-\mathcal{V} + \bar{v} \cdot \bar{v}) = \chi_\sigma [n(\tilde{\varphi}) \nabla \sigma]_H^T \cdot \bar{v},$$

respectively, and a short computation shows that

$$[\mathbb{P}\boldsymbol{\mu} \cdot \boldsymbol{\varphi}]_H^T = \mu_2 - \mu_1 = 2\tilde{\mu}, \quad [-N(\boldsymbol{\varphi}, \sigma) + \sigma N, \sigma(\boldsymbol{\varphi}, \sigma)]_H^T = \frac{\chi_\sigma}{2} [|\sigma|^2]_H^T,$$

so that (3.36d) becomes $\beta\gamma\kappa = 2\tilde{\mu} + \frac{\chi_\sigma}{2} [|\sigma|^2]_H^T$. Furthermore, taking the difference between the second and first components of the free boundary conditions (3.36b) and (3.36e), the free boundary conditions on $\Gamma = \Gamma_{12}$ translates to

$$[\bar{v}]_H^T \cdot \bar{v} = 0, \quad [\tilde{\mu}]_H^T = 0, \quad [p]_H^T = \beta\gamma\kappa, \quad (3.38a)$$

$$[\sigma]_H^T = 2\frac{\chi_\varphi}{\chi_\sigma}, \quad \beta\gamma\kappa = 2\tilde{\mu} + \frac{\chi_\sigma}{2} [|\sigma|^2]_H^T, \quad (3.38b)$$

$$2(-\mathcal{V} + \bar{v} \cdot \bar{v}) = [m(\tilde{\varphi}) \nabla \mu]_H^T \cdot \bar{v}, \quad (-\mathcal{V} + \bar{v} \cdot \bar{v}) [\sigma]_H^T = \chi_\sigma [n(\tilde{\varphi}) \nabla \sigma]_H^T \cdot \bar{v}. \quad (3.38c)$$

The resulting sharp interface model coincides with Equ. (3.49) of Ref. 27.

3.4. Sharp interface limit for (1.9)

In this section, we derive the sharp interface limit of (1.9) from the general sharp interface model (3.35)-(3.36), where we again drop the subscript 0. Setting $L = 3$ and $M = 1$, and choosing (1.3) with $\chi_\sigma = 1$, $\chi_\varphi = \chi_n = 0$ and (2.31) with $m_i(s) = 1$, $1 \leq i \leq 3$, we have

$$N(\boldsymbol{\varphi}, \sigma) = \frac{1}{2} |\sigma|^2, \quad \underline{\underline{C}}(\boldsymbol{\varphi}) = \left(\delta_{ij} - \frac{1}{3} \right)_{i,j=1}^3, \quad S(\boldsymbol{\varphi}, \sigma) = -\mathcal{C}\varphi_2\sigma,$$

so that $N, \sigma(\boldsymbol{\varphi}, \sigma) = \sigma$ and $N, \boldsymbol{\varphi}(\boldsymbol{\varphi}, \sigma) = \bar{\mathbf{0}}$. Moreover, defining $\Omega_H = \{\boldsymbol{\varphi} = \mathbf{e}_1\}$, $\Omega_P = \{\boldsymbol{\varphi} = \mathbf{e}_2\}$ and $\Omega_N = \{\boldsymbol{\varphi} = \mathbf{e}_3\}$, with interfaces $\Gamma_{HP} = \partial\Omega_H \cap \partial\Omega_P$, $\Gamma_{PN} = \partial\Omega_P \cap \partial\Omega_N$, we assume, for the reason outlined in the introduction, that $\partial\Omega_H \cap \partial\Omega_N = \emptyset$. One can compute that $\underline{\underline{C}}(\boldsymbol{\varphi}) \nabla(\mathbb{P}\boldsymbol{\mu}) = \underline{\underline{C}}(\boldsymbol{\varphi}) \nabla\boldsymbol{\mu}$, and thus upon setting

$$y = \frac{1}{3} (2\mu_1 - \mu_2 - \mu_3), \quad z = \frac{1}{3} (-\mu_1 + 2\mu_2 - \mu_3),$$

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from (3.35c) and (3.35d) (recalling that σ evolves quasi-statically) we obtain the following outer equations:

$$\Delta\sigma = \begin{cases} 0 & \text{in } \Omega_H \cup \Omega_N, \\ \mathcal{C}\sigma & \text{in } \Omega_P, \end{cases}$$

$$\begin{cases} -\Delta y = U_1(\varphi, \sigma) - (\mathbf{1} \cdot \mathbf{U}(\varphi, \sigma))\varphi_1, \\ -\Delta z = U_2(\varphi, \sigma) - (\mathbf{1} \cdot \mathbf{U}(\varphi, \sigma))\varphi_2, \\ -K\Delta p = \mathbf{1} \cdot \mathbf{U}(\varphi, \sigma), \end{cases} \quad \text{in } \Omega_H \cup \Omega_P \cup \Omega_N.$$

Meanwhile, due to the fact that $N_{,\sigma}(\varphi, \sigma) = \sigma$ and $\mathbb{P}\boldsymbol{\mu} = (y, z, -(y+z))^\top$, we obtain from (3.36a), (3.36b), (3.36c) and (3.36f) that

$$[\nabla p] \cdot \vec{\nu} = [y] = [z] = [\sigma] = [\nabla\sigma] \cdot \vec{\nu} = 0 \text{ on } \Gamma_{PN} \cup \Gamma_{HP}.$$

Furthermore, (3.36d) and (3.36e) simplify to

$$\begin{aligned} [p]_N^P &= \beta\gamma_{PN}\kappa = \mathbb{P}\mu_2 - \mathbb{P}\mu_3 = 2y - z \text{ on } \Gamma_{PN}, \\ [p]_P^H &= \beta\gamma_{HP}\kappa = \mathbb{P}\mu_1 - \mathbb{P}\mu_2 = y - z \text{ on } \Gamma_{HP}, \\ -\mathcal{V} + K\nabla p \cdot \vec{\nu} &= [\nabla z]_N^P \cdot \vec{\nu}, \quad 0 = [\nabla y]_N^P \cdot \vec{\nu} \text{ on } \Gamma_{PN}, \\ -\mathcal{V} + K\nabla p \cdot \vec{\nu} &= [\nabla y]_P^H \cdot \vec{\nu}, \quad \mathcal{V} - K\nabla p \cdot \vec{\nu} = [\nabla z]_P^H \cdot \vec{\nu} \text{ on } \Gamma_{HP}. \end{aligned}$$

In the case where source terms of the form (1.8d) are considered, the asymptotic analysis requires a slight modification, which we will briefly sketch below. The multi-component system we study is given by

$$\operatorname{div} \vec{v} = \varepsilon^{-1}(\mathbf{1} \cdot \mathbf{U}(\varphi, \sigma)), \quad (3.39a)$$

$$\vec{v} = -K\nabla p + K(\nabla\varphi)^\top \boldsymbol{\mu}, \quad (3.39b)$$

$$\partial_t \varphi + (\nabla\varphi)\vec{v} = \operatorname{div}(\underline{\underline{C}}(\varphi, \sigma)\nabla(\mathbb{P}\boldsymbol{\mu})) + \varepsilon^{-1}(\mathbf{U}(\varphi, \sigma) - (\mathbf{1} \cdot \mathbf{U}(\varphi, \sigma))\varphi), \quad (3.39c)$$

$$\mathbb{P}\boldsymbol{\mu} = -\beta\varepsilon\Delta\varphi + \beta\varepsilon^{-1}\mathbb{P}\Psi_{,\varphi}(\varphi), \quad (3.39d)$$

$$0 = \Delta\sigma + S(\varphi, \sigma), \quad (3.39e)$$

where we now consider

$$\mathbf{U}(\varphi, \sigma) = (\bar{\rho}_1^{-1}\mathcal{U}_1(\varphi_1, \sigma), \dots, \bar{\rho}_L^{-1}\mathcal{U}_L(\varphi_L, \sigma))^\top, \quad \mathcal{U}_k(\varphi_k, \sigma) = \varphi_k^2(1 - \varphi_k)^2 F_k(\sigma)$$

with scalar functions F_k , $1 \leq k \leq L$. For example, we may choose $L = 3$, $\bar{\rho}_i = 1$ for $1 \leq i \leq 3$, and $F_1(s) = 0$, $F_2(s) = \mathcal{P}s - \mathcal{A}$, $F_3(s) = \mathcal{A} - D_N$ in order to match with (1.8d).

In the outer expansions, we obtain (3.3) from (3.39d) $_O^{-1}$, which implies that $\varphi_0 = e_i$, $1 \leq i \leq L$. Then noting that the source term $\varepsilon^{-1}(\mathbf{U}(\varphi, \sigma) - (\mathbf{1} \cdot \mathbf{U}(\varphi, \sigma))\varphi)$ will not contribute to leading and first order, we obtain from the zeroth order expansions of (3.39a)-(3.39c), (3.39e) the outer equations

$$\operatorname{div} \vec{v}_0 = 0, \quad \vec{v}_0 = -K\nabla p_0, \quad \operatorname{div}(\underline{\underline{C}}(\varphi_0, \sigma_0)\nabla(\mathbb{P}\boldsymbol{\mu}_0)) = \vec{0}, \quad \Delta\sigma_0 = -S(\varphi_0, \sigma_0).$$

For the free boundary conditions on the interface Γ_{ij} , using the inner expansions, we recover (3.21) from (3.39c) $_I^{-2}$ and from (3.39d) $_I^{-1}$ we have similarly that Φ_0 is a function only in z connecting e_i to e_j . While the rest of the analysis is analogous, the only difference lies in (3.39a) $_I^{-1}$ and (3.39c) $_I^{-1}$ where now the source term enters. More precisely, from (3.39a) $_I^{-1}$ and (3.39c) $_I^{-1}$ we have

$$\partial_z \bar{V}_0 \cdot \bar{\nu} = \mathbf{1} \cdot \mathbf{U}(\Phi_0, \Sigma_0), \quad (3.40a)$$

$$\begin{aligned} (-\mathcal{V} + \bar{V}_0 \cdot \bar{\nu}) \Phi'_0 &= \partial_z \left(\underline{\underline{C}}(\Phi_0, \Sigma_0) \right) [(\partial_z \mathbb{P} \Upsilon_1 \otimes \bar{\nu}) + \nabla_{\Gamma} \mathbb{P} \Upsilon_0] \bar{\nu} \\ &+ \mathbf{U}(\Phi_0, \Sigma_0) - (\mathbf{1} \cdot \mathbf{U}(\Phi_0, \Sigma_0)) \Phi_0. \end{aligned} \quad (3.40b)$$

Using the fact that $\partial_z \Sigma_0 = 0$ (from (3.39e) $_I^{-2}$) and introducing the notation $\Phi_{0,k}$ as the k th component of the vector Φ_0 , we define

$$\begin{aligned} \delta &= (\delta_1, \dots, \delta_L)^\top, \quad \delta_k = \int_{\mathbb{R}} (\Phi_{0,k}(z))^2 (1 - \Phi_{0,k}(z))^2 dz, \\ \mathbf{H}(\sigma) &= (\delta_1 F_1(\sigma), \dots, \delta_L F_L(\sigma))^\top. \end{aligned}$$

Then, integrating (3.40a) and (3.40b) in z leads to

$$[\bar{v}_0]_i^j \cdot \bar{\nu} = \mathbf{1} \cdot \mathbf{H}(\sigma_0), \quad -\mathcal{V}(e_j - e_i) + [(\bar{v}_0 \cdot \bar{\nu}) \varphi_0]_i^j = [\underline{\underline{C}}(\varphi_0, \sigma_0) \nabla(\mathbb{P} \mu_0)]_i^j \bar{\nu} + \mathbf{H}(\sigma_0),$$

where we used (3.40a) and integration by parts to deduce that

$$\int_{\mathbb{R}} (\bar{V}_0 \cdot \bar{\nu}) \Phi'_0 + (\mathbf{1} \cdot \mathbf{U}(\Phi_0, \Sigma_0)) \Phi_0 dz = [(\bar{v}_0 \cdot \bar{\nu}) \varphi_0]_i^j.$$

Hence, the sharp interface limit of (3.39) is

$$\begin{aligned} -K \Delta p_0 &= 0, \quad \operatorname{div}(\underline{\underline{C}}(\varphi_0, \sigma_0) \nabla(\mathbb{P} \mu_0)) = \vec{0}, \quad -\Delta \sigma_0 = S(\varphi_0, \sigma_0) \text{ in } \Omega_k, \\ [\mathbb{P} \mu_0]_i^j &= \mathbf{0}, \quad [\sigma_0]_i^j = 0, \quad [\nabla \sigma_0]_i^j \cdot \bar{\nu} = 0, \quad \beta \gamma_{ij} \kappa = [\mathbb{P} \mu_0 \cdot \varphi_0]_i^j = [p_0]_i^j \text{ on } \Gamma_{ij}, \\ -\mathcal{V}(e_j - e_i) &+ [(\bar{v}_0 \cdot \bar{\nu}) \varphi_0]_i^j = [\underline{\underline{C}}(\varphi_0, \sigma_0) \nabla(\mathbb{P} \mu_0)]_i^j \bar{\nu} + \mathbf{H}(\sigma_0) \text{ on } \Gamma_{ij}, \\ [\bar{v}_0]_i^j \cdot \bar{\nu} &= \mathbf{1} \cdot \mathbf{H}(\sigma_0) \text{ on } \Gamma_{ij}, \end{aligned}$$

for $1 \leq k \leq L$ and $1 \leq i < j \leq L$. Let us point out that, in comparison to the sharp interface model (3.35)-(3.36), the source terms now appear in the free boundary conditions instead of in the bulk equations.

Remark 3.2. In our numerical investigations below, we will use an obstacle potential (2.30), and the asymptotic analysis for the obstacle potential will yield that the outer expansions φ_i for $i \geq 1$ are all zero. Hence, it is sufficient to consider source terms of the form (1.8d) with the prefactor $\varphi_i(1 - \varphi_i)$ instead of $\varphi_i^2(1 - \varphi_i)^2$, which will also lead to the same outer equations for the sharp interface limit, but in general, the prefactors δ_k will be different.

3.5. Sharp interface limit of a model with degenerate Ginzburg–Landau energy

In this section, we study a particular three-component model consisting of host cells (φ_1), proliferating cells (φ_2) and necrotic cells (φ_3) along with a quasi-static nutrient (σ), which is derived from a degenerate Ginzburg–Landau energy, similar to the discussions in Sec. 2.5. In particular, we have $L = 3$ and $M = 1$. We consider a total energy of the form

$$\mathcal{E}(\varphi, \sigma) = \int_{\Omega} \frac{\beta\varepsilon}{2} |\nabla\varphi_2|^2 + \frac{\beta}{\varepsilon} W(\varphi_2) + \frac{\chi\sigma}{2} |\sigma|^2 - \chi_{\varphi}\sigma\varphi_2 d\mathcal{L}^d, \quad (3.41)$$

where $W : \mathbb{R} \rightarrow \mathbb{R}$ is a potential with minima at 0 and 1. In the context of cellular adhesion, we assume that the host cells and necrotic cells prefer to adhere to each other rather than to the proliferating cells. Let us consider the bare mobilities $m_1(s) = 1 - s$, $m_2(s) = s$ and $m_3(s) = 1 - s$, and the second order tensor $\underline{\underline{C}}(\varphi) \in \mathbb{R}^{3 \times 3}$ with entries $\underline{\underline{C}}_{ij}(\varphi) = \frac{3}{2}m_i(\varphi_i) \left(\delta_{ij} - m_j(\varphi_j) \left(\sum_{k=1}^3 m_k(\varphi_k) \right)^{-1} \right)$, $1 \leq i, j \leq 3$. Then, for a vector of source terms \mathbf{U} such that $\mathbf{1} \cdot \mathbf{U} = 0$, the model (2.29) becomes

$$\partial_t \varphi = \operatorname{div}(\underline{\underline{C}}(\varphi) \nabla(\mathbb{P}\mu)) + \mathbf{U}(\varphi, \sigma), \quad (3.42a)$$

$$\mu_2 = -\beta\varepsilon\Delta\varphi_2 + \beta\varepsilon^{-1}W'(\varphi_2) - \chi_{\varphi}\sigma, \quad \mu_1 = \mu_3 = 0, \quad (3.42b)$$

$$\partial_t \sigma = \operatorname{div}(n(\varphi, \sigma) \nabla(\sigma - \lambda\varphi_2)) + S(\varphi, \sigma), \quad (3.42c)$$

where $n(\varphi, \sigma) = \underline{\underline{D}}(\varphi, \sigma)\chi_{\sigma}$, $\lambda = \chi_{\varphi}/\chi_{\sigma}$, and $\mu_1 = \mu_3 = 0$ precisely due to the fact that the energy (3.41) does not depend on φ_1 and φ_3 . Sending $\lambda \rightarrow 0$, and neglecting the left-hand side, as the nutrient evolves quasi-statically, and then considering a constant mobility $n(\varphi, \sigma) = 1$, leads to the phase field model

$$\partial_t \varphi_2 = \operatorname{div}(\underline{\underline{C}}_{22}(\varphi) \nabla\mu_2) + \bar{\rho}_2^{-1} \mathcal{U}_2(\varphi, \sigma), \quad (3.43a)$$

$$\partial_t \varphi_i = \operatorname{div}(\underline{\underline{C}}_{i2}(\varphi) \nabla\mu_2) + \bar{\rho}_i^{-1} \mathcal{U}_i(\varphi, \sigma), \quad i = 1, 3, \quad (3.43b)$$

$$\mu_2 = -\beta\varepsilon\Delta\varphi_2 + \beta\varepsilon^{-1}W'(\varphi_2) - \chi_{\varphi}\sigma, \quad (3.43c)$$

$$0 = \Delta\sigma + S(\varphi, \sigma). \quad (3.43d)$$

Note that by the relations $\mathbf{1} \cdot \mathbf{U} = \bar{\rho}_1^{-1} \mathcal{U}_1 + \bar{\rho}_2^{-1} \mathcal{U}_2 + \bar{\rho}_3^{-1} \mathcal{U}_3 = 0$, $\varphi_2 = 1 - \varphi_1 - \varphi_3$, and $\underline{\underline{C}}_{22}(\varphi) = -\underline{\underline{C}}_{12}(\varphi) - \underline{\underline{C}}_{32}(\varphi)$, equation (3.43a) can be written as

$$-\partial_t(\varphi_1 + \varphi_3) = -\operatorname{div}((\underline{\underline{C}}_{12} + \underline{\underline{C}}_{32})(\varphi) \nabla\mu_2) - (\bar{\rho}_1^{-1} \mathcal{U}_1 + \bar{\rho}_3^{-1} \mathcal{U}_3)(\varphi, \sigma),$$

which is the negative of the sum of (3.43b). As the minima of W are 0 and 1, we have that the leading order term $\varphi_{2,0} = 0$ or 1, which allows us to define the regions $\Omega_P = \{\varphi_{2,0} = 1\} = \{\varphi_{1,0} + \varphi_{3,0} = 0\}$ and $\Omega_P^c = \{\varphi_{2,0} = 0\} = \{\varphi_{1,0} + \varphi_{1,3} = 1\}$. Then, the following outer equations are derived:

$$\begin{aligned} 0 &= \Delta\sigma_0 + S(\varphi_0, \sigma_0) \text{ in } \Omega_P \cup \Omega_P^c, \\ -\Delta\mu_{2,0} &= \bar{\rho}_2^{-1} \mathcal{U}_2(\varphi_0, \sigma_0) = -(\bar{\rho}_1^{-1} \mathcal{U}_1 + \bar{\rho}_3^{-1} \mathcal{U}_3)(\varphi_0, \sigma_0) \text{ in } \Omega_P, \\ 0 &= \bar{\rho}_2^{-1} \mathcal{U}_2(\varphi_0, \sigma_0) = -(\bar{\rho}_1^{-1} \mathcal{U}_1 + \bar{\rho}_3^{-1} \mathcal{U}_3)(\varphi_0, \sigma_0) \text{ in } \Omega_P^c. \end{aligned}$$

Here we used that $\underline{C}_{22}(\varphi)$ is 1 in Ω_P and 0 in Ω_P^c , while $\underline{C}_{12}(\varphi)$, $\underline{C}_{32}(\varphi)$ are equal to $-\frac{1}{2}$ in Ω_P and 0 in Ω_P^c . Let $\Gamma = \partial\Omega_P$ denote the interface that is moving with normal velocity \mathcal{V} , and let $\vec{\nu}$ and κ denote the outward unit normal and mean curvature of Γ , respectively. Then, we obtain from the inner expansions the following set of equations

$$[\sigma_0] = 0, \quad [\nabla\sigma_0] \cdot \vec{\nu} = 0, \quad \mu_{2,0} = \beta\gamma\kappa - \chi_\varphi\sigma_0, \quad -\mathcal{V} = \nabla\mu_{2,0} \cdot \vec{\nu} \text{ on } \Gamma,$$

where γ is a positive constant defined by $\gamma = \int_0^1 \sqrt{2W(s)} ds$. In the case of equal densities $\bar{\rho}_1 = \bar{\rho}_2 = \bar{\rho}_3 = 1$, we now choose the source terms to be

$$S(\varphi, \sigma) = -\sigma, \quad \mathcal{U}_2(\varphi, \sigma) = \mathcal{P}\sigma\varphi_2, \quad \mathcal{U}_1(\varphi, \sigma) = \mathcal{U}_3(\varphi, \sigma) = -\frac{1}{2}\mathcal{P}\sigma\varphi_2,$$

for a positive constant \mathcal{P} , and define a pressure-like function $p = \mu_{2,0} + \chi_\varphi\sigma_0$, so that we have

$$\begin{aligned} \Delta\sigma_0 &= \sigma_0, \quad \Delta p = (\chi_\varphi - \mathcal{P})\sigma_0 \text{ in } \Omega_P, \quad \Delta\sigma_0 = \sigma_0 \text{ in } \Omega_P^c, \\ [\sigma_0] &= 0, \quad [\nabla\sigma_0] \cdot \vec{\nu} = 0, \quad p = \beta\gamma\kappa, \quad -\mathcal{V} = \nabla p \cdot \vec{\nu} - \chi_\varphi\nabla\sigma_0 \cdot \vec{\nu} \text{ on } \Gamma, \end{aligned}$$

which bears some similarities to the free boundary models studied in Refs. 12, 14, 20, 56.

4. Numerical approximation

In this section we propose a finite element approximation for the three-component model (1.4) with (1.6) and present several numerical simulations for it. In particular, we have $L = 3$ and $M = 1$ and consider the obstacle potential (2.30). For the mobility tensor $\underline{C}(\varphi)$ we choose (2.31) with

$$m_1(s) = 1 - s + \delta_C, \quad m_2(s) = s + \delta_C, \quad m_3(s) = s + \delta_C, \quad (4.1)$$

where $\delta_C = 10^{-6}$ is a regularisation parameter. Moreover, we consider (1.3) with $\chi_\sigma, \chi_\varphi > 0$ and $\chi_n = 0$, so that

$$\mathbf{N}_{,\varphi}(\sigma) = (0, -\chi_\varphi\sigma, 0)^\top. \quad (4.2)$$

Then, choosing a constant mobility $d(\varphi, \sigma) = 1$ in (1.6) we arrive at the nutrient equation

$$\partial_t\sigma + \operatorname{div}(\sigma\vec{v}) = \Delta\sigma - \lambda\Delta\varphi_2 + S(\varphi, \sigma).$$

In order to allow for the case $K = 0$, which means that we set the velocity to zero, we define

$$\widehat{\mathbf{U}}(\varphi, \sigma) = \begin{cases} \mathbf{U}(\varphi, \sigma) & \text{for } K > 0, \\ \mathbf{U}(\varphi, \sigma) - (\mathbf{1} \cdot \mathbf{U}(\varphi, \sigma))\varphi & \text{for } K = 0. \end{cases} \quad (4.3)$$

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Recalling (1.8a)-(1.8d), we consider

$$S(\boldsymbol{\varphi}, \sigma) = -\mathcal{C}\sigma\varphi_2, \tag{4.4a}$$

$$\mathbf{U}_A(\boldsymbol{\varphi}, \sigma) = (0, \varphi_2(\mathcal{P}\sigma - \mathcal{A}), \mathcal{A}\varphi_2 - D_N\varphi_3)^\top, \tag{4.4b}$$

$$\mathbf{U}_B(\boldsymbol{\varphi}, \sigma) = (-\varphi_2\mathcal{P}\sigma, \varphi_2(\mathcal{P}\sigma - \mathcal{A}), \mathcal{A}\varphi_2 - D_N\varphi_3)^\top, \tag{4.4c}$$

$$\mathbf{U}_C(\boldsymbol{\varphi}, \sigma) = (0, \varepsilon^{-1}\varphi_2(1 - \varphi_2)(\mathcal{P}\sigma - \mathcal{A}), \varepsilon^{-1}\varphi_3(1 - \varphi_3)(\mathcal{A} - D_N))^\top. \tag{4.4d}$$

Here we note that (4.4d) differs from (1.8d). In particular, we observe that for (4.4d) the function F in (2.40) is chosen as $F(s) = s(1 - s)$, rather than $F(s) = s^2(1 - s)^2$ as for (1.8d), which clearly does not satisfy the conditions stated below (2.40). However, we remark that the asymptotic analysis remains valid, see Remark 3.2.

4.1. Finite element approximation

Let \mathcal{T}_h be a regular triangulation of Ω into disjoint open simplices. Associated with \mathcal{T}_h is the piecewise linear finite element space

$$S_h = \left\{ \chi \in C^0(\overline{\Omega}) \mid \chi|_o \in P_1(o) \ \forall o \in \mathcal{T}_h \right\} \subset H^1(\Omega),$$

where we denote by $P_1(o)$ the set of all affine linear functions on o . Let $\mathbf{S}_h = [S_h]^L = S_h \times \cdots \times S_h$, and define

$$\mathbf{S}_h^+ = \{ \boldsymbol{\chi} \in \mathbf{S}_h^h : \boldsymbol{\chi} \geq \mathbf{0} \}.$$

Similar to Refs. 4, 53, we consider the splitting

$$\underline{\underline{\mathcal{W}}} \equiv \underline{\underline{\mathcal{W}}}^+ + \underline{\underline{\mathcal{W}}}^-,$$

where $\underline{\underline{\mathcal{W}}}^{+(-)}$ is symmetric and positive (negative) semi-definite, recall (2.30). Throughout we choose $\underline{\underline{\mathcal{W}}} = \underline{\underline{\mathbf{I}}} - \mathbf{1} \otimes \mathbf{1}$, and let $\underline{\underline{\mathcal{W}}}^- = -\frac{2}{3}\mathbf{1} \otimes \mathbf{1}$. We now introduce a finite element approximation of the model described above, in which we have taken homogeneous Neumann boundary conditions for $\boldsymbol{\varphi}$ and $\boldsymbol{\mu}$, and the Dirichlet boundary conditions $\sigma = \sigma_B \in \mathbb{R}$ and $p = 0$ on $\partial\Omega$. To this end, let $S_h^B = \{ \chi \in S_h \mid \chi = \sigma_B \text{ on } \partial\Omega \}$, as well as $S_h^0 = \{ \chi \in S_h \mid \chi = 0 \text{ on } \partial\Omega \}$. The numerical scheme is defined as follows: Find

$$(\boldsymbol{\varphi}_h^n, \boldsymbol{\mu}_h^n, \sigma_h^n, p_h^n) \in \mathbf{S}_h^+ \times \mathbf{S}_h \times S_h^B \times S_h^0$$

such that

$$\begin{aligned} & \frac{1}{\tau}(\varphi_h^n - \varphi_h^{n-1}, \boldsymbol{\eta}_h)_h + (\underline{\underline{C}}(\varphi_h^{n-1}) \nabla \boldsymbol{\mu}_h^n, \nabla \boldsymbol{\eta}_h)_h \\ &= (\widehat{\mathbf{U}}(\varphi_h^{n-1}, \sigma_h^{n-1}), \boldsymbol{\eta}_h)_h - ([\mathbf{1} \cdot \widehat{\mathbf{U}}(\varphi_h^{n-1}, \sigma_h^{n-1})] \varphi_h^{n-1}, \boldsymbol{\eta}_h)_h \\ & \quad + K((\nabla \varphi_h^{n-1})(\nabla p_h^{n-1} - (\nabla \varphi_h^{n-1})^\top (\boldsymbol{\mu}_h^{n-1} - \mathbf{N}_{,\varphi}(\sigma_h^{n-1}))), \boldsymbol{\eta}_h)_h, \end{aligned} \quad (4.5a)$$

$$\begin{aligned} & \beta \varepsilon (\nabla \varphi_h^n, \nabla (\boldsymbol{\zeta}_h - \varphi_h^n)) - (\beta \varepsilon^{-1} \underline{\underline{W}}^- \varphi_h^n + \boldsymbol{\mu}_h^n, \boldsymbol{\zeta}_h - \varphi_h^n)_h \\ & \geq \beta \varepsilon^{-1} (\underline{\underline{W}}^+ \varphi_h^{n-1}, \boldsymbol{\zeta}_h - \varphi_h^n)_h - (\mathbf{N}_{,\varphi}(\sigma_h^{n-1}), \boldsymbol{\zeta}_h - \varphi_h^n)_h, \end{aligned} \quad (4.5b)$$

$$\begin{aligned} & \frac{1}{\tau}(\sigma_h^n - \sigma_h^{n-1}, \chi_h)_h - K(\nabla \sigma_h^{n-1} \cdot (\nabla p_h^{n-1} - (\nabla \varphi_h^n)^\top (\boldsymbol{\mu}_h^n - \mathbf{N}_{,\varphi}(\sigma_h^{n-1}))), \chi_h)_h \\ & \quad + ([\mathbf{1} \cdot \widehat{\mathbf{U}}(\varphi_h^{n-1}, \sigma_h^{n-1})] \sigma_h^{n-1}, \chi_h)_h + (\nabla \sigma_h^n, \nabla \chi_h) - \lambda (\nabla \varphi_{2,h}^n, \nabla \chi_h) \\ & = -\mathcal{C}(\sigma_h^n \varphi_{2,h}^n, \chi_h)_h \end{aligned} \quad (4.5c)$$

$$(\nabla p_h^n, \nabla \chi_h) = ((\nabla \varphi_h^n)^\top (\boldsymbol{\mu}_h^n - \mathbf{N}_{,\varphi}(\sigma_h^n)), \nabla \chi_h)_h + \frac{1}{K}(\mathbf{1} \cdot \widehat{\mathbf{U}}(\varphi_h^n, \sigma_h^n), \chi_h)_h, \quad (4.5d)$$

holds for all $(\boldsymbol{\zeta}_h, \boldsymbol{\eta}_h, \chi_h) \in \mathbf{S}_h^+ \times \mathbf{S}_h \times S_h^0$, where τ denotes the time step size, (\cdot, \cdot) denotes the L^2 -inner product on Ω , $(\cdot, \cdot)_h$ is the usual mass lumped L^2 -inner product on Ω , and $\lambda = \frac{\chi_\varphi}{\chi_\sigma}$, recall (1.5). In the case $K = 0$ we simply neglect (4.5d) and do not compute for p_h^n . A quasi-static variant of the discrete nutrient equation (4.5c) is given by

$$(\nabla \sigma_h^n, \nabla \chi_h) - \lambda (\nabla \varphi_{2,h}^n, \nabla \chi_h) = -\mathcal{C}(\sigma_h^n \varphi_{2,h}^n, \chi_h)_h. \quad (4.6)$$

We implemented the scheme (4.5a)-(4.5d) with the help of the finite element toolbox ALBERTA⁶³. To increase computational efficiency, we employ adaptive meshes, which have a finer mesh size h_f within the diffuse interfacial regions and a coarser mesh size h_c away from them, see Ref. 53 for a more detailed description. Clearly, the system (4.5a)-(4.5d) decouples, and so we first solve the variational inequality (4.5a)-(4.5b) for $(\varphi_h^n, \boldsymbol{\mu}_h^n)$ with the projected block Gauss–Seidel algorithm from Ref. 53. Then we compute σ_h^n from (4.5c), or from (4.6), and finally p_h^n from (4.5d), where we employ the direct linear solver UMFPAK¹⁸. Finally, to increase the efficiency of the numerical computations in this paper, we exploit the symmetry of the problem and performed all computations only on a quarter of the desired domain Ω .

4.2. Numerical simulations

In the following we present several numerical computations in two spatial dimensions for the scheme (4.5a)-(4.5b), (4.5d) and (4.6). We will fix the interfacial parameter to $\varepsilon = 0.05$ throughout, and employ a fine mesh size of $h_f = 0.02$, with $h_c = 8h_f$. For the uniform time step size we choose $\tau = 10^{-3}$. In order to define the initial data, we introduce the following functions. Given $R_2, R_3 > 0$, $\delta_2, \delta_3 \geq 0$ and $m_2, m_3 \in \mathbb{N}$,

we define

$$\tilde{R}_i(\bar{x}) = R_i + \delta_i \cos(m_i \theta), \quad \text{with } \theta = \tan^{-1} \left(\frac{x_2}{x_1} \right), \quad i = 2, 3. \quad (4.7)$$

Then we set

$$v_1(\bar{x}) = 1, \quad v_i(\bar{x}) = \begin{cases} 1 & \text{if } r(\bar{x}) - \tilde{R}_i(\bar{x}) \leq -\frac{\varepsilon\pi}{2}, \\ \frac{1}{2} - \frac{1}{2} \sin \left(\frac{r(\bar{x}) - \tilde{R}_i(\bar{x})}{\varepsilon} \right) & \text{if } |r(\bar{x}) - \tilde{R}_i(\bar{x})| < \frac{\varepsilon\pi}{2}, \\ 0 & \text{if } r(\bar{x}) - \tilde{R}_i(\bar{x}) \geq \frac{\varepsilon\pi}{2}, \end{cases} \quad i = 2, 3, \quad (4.8)$$

where $r(\bar{x}) = [\sum_{j=1}^d |x_j|^2]^{\frac{1}{2}}$. In line with the formally matched asymptotic analysis for phase field models with the double-obstacle potential, the interfacial thicknesses for v_2 and v_3 are equal to $\varepsilon\pi$, see for example Equ. (3.24) of Ref. 27. For the initial data φ_h^0 to (4.5a)-(4.5d) we set

$$(\varphi_h^0)_i(\bar{x}) = v_i(\bar{x}) \prod_{j=i+1}^3 (1 - v_j(\bar{x})), \quad i = 1, 2, 3, \quad (4.9)$$

see also Equ. (3.5) of Ref. 53. Unless otherwise stated, we use $R_2 = 2$, $R_3 = 1$ in (4.7) and choose

$$\delta_2 = 0.1, \quad m_2 = 2, \quad \delta_3 = 0.05, \quad m_3 = 6, \quad (4.10a)$$

$$\text{or } \delta_2 = 0.1, \quad m_2 = 6, \quad \delta_3 = 0.05, \quad m_3 = 4, \quad (4.10b)$$

$$\text{or } \delta_2 = 0.1, \quad m_2 = 2, \quad \delta_3 = 0. \quad (4.10c)$$

In addition, we set $p_h^0 = 0$ and $\sigma_h^0 = \sigma_B$. For the graphical representation of φ_h^n we will always plot the scalar quantity $(0, 1, 2)^\top \cdot \varphi_h^n$, which clearly takes on the values 0, 1, 2 in the host, proliferating and necrotic phases, respectively.

4.2.1. Simulation with the source term (4.4d)

In a first simulation, we investigate the radial growth of the tumour phases for the source term (4.4d) given sufficient nutrient. To this end, we let $\Omega = (-5, 5)^2$ and

$$\mathcal{A} = 0.5, \quad \beta = 0.1, \quad \mathcal{C} = 2, \quad \mathcal{P} = 0.5, \quad \lambda = \chi_\varphi = 0.1, \quad \mathcal{D}_N = 0.$$

For the values $\sigma_B = 5$ and $K = 0.01$ we start with the perturbed initial profiles defined by (4.10a) and (4.10b), respectively, and observe that in each case the initial perturbations get smoothed out, leading to a nearly radial growth. We show the corresponding simulations in Figs. 1 and 2. The smoothing of the perturbation is in contrast to the behaviour observed in the two-phase case (consisting of only host cells and proliferating tumour cells), where small perturbations from an initial radial setting lead to the development of long and thin protrusions^{12,27}. A linear stability analysis shows that the mechanism responsible for these morphological instabilities is the chemotaxis mechanism $\chi_\varphi > 0$. Thus, Figs. 1 and 2 seem to suggest that the presence of a (large) necrotic core suppresses morphological instabilities caused by the chemotaxis mechanism, leading to a more radial growth of the tumour.

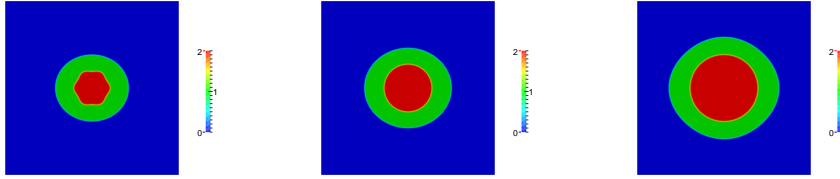


Fig. 1. ($\sigma_B = 5$, $K = 0.01$) The solution φ_h^n at times $t = 0, 2, 5$ for (4.4d) with initial profile (4.10a).

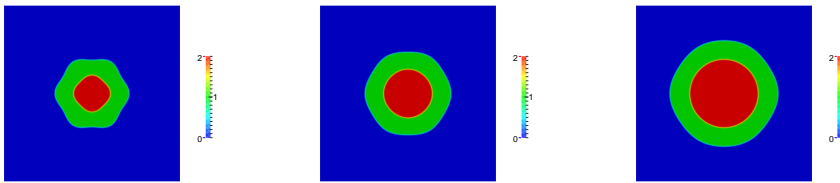


Fig. 2. ($\sigma_B = 5$, $K = 0.01$) The solution φ_h^n at times $t = 0, 2, 5$ for (4.4d) with initial profile (4.10b).

We point out that the tumours in Figs. 1 and 2 continue to grow in a more-or-less radially symmetric manner until the growing periphery is close to the boundary of the computational domain. Then, we stop the simulations once the proliferating tumour touches the external boundary.

In order to investigate the radial growth in more detail, and to study the dependence on the presence of the fluid flow and on the strength of the nutrient source, we repeat the simulations in Figs. 1 and 2 for circular initial data, and for different values of σ_B and K . In particular, we choose $\delta_2 = \delta_3 = 0$ in (4.7) and let $\sigma_B \in \{2, 5, 10\}$, with $K = 0$ or $K = 0.01$. Plots of the radii of the two interfacial layers over time for the different parameters can be seen in Fig. 3.

Looking at the results for $\sigma_B = 2$ in particular, we also investigate whether the two radii eventually meet. To this end, we repeat the simulations for a longer time. As observed in Fig. 4, in the absence of Darcy flow the inner radius indeed catches up with the outer radius. When Darcy flow is present, however, a constant minimum distance between the two radii is maintained throughout the evolution, compare also Figs. 2 and 3 of Ref. 65.

We show some snapshots of the two different evolutions in Fig. 5. In particular, Fig. 5 shows that the Darcy variant of the model yields what we consider is a more biologically realistic evolution of tumour growth than the variant without fluid velocity. We believe that in the absence of fluid flow, and the modification of the source term $\mathbf{U}(\varphi, \sigma)$ so that $\mathbf{1} \cdot \mathbf{U}(\varphi, \sigma) = 0$, introduce artificial non-biological effects and thus lead to the appearance of small colonies of proliferating cells between the host and the necrotic regions.

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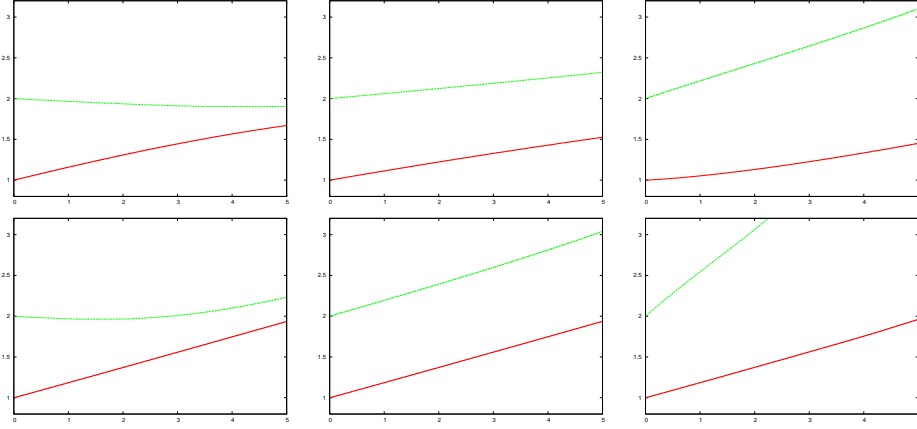


Fig. 3. A plot of the two radii over time for (4.4d). The above plots are without fluid flow, i.e., $K = 0$, for $\sigma_B = 2, 5, 10$. Below the same for $K = 0.01$.

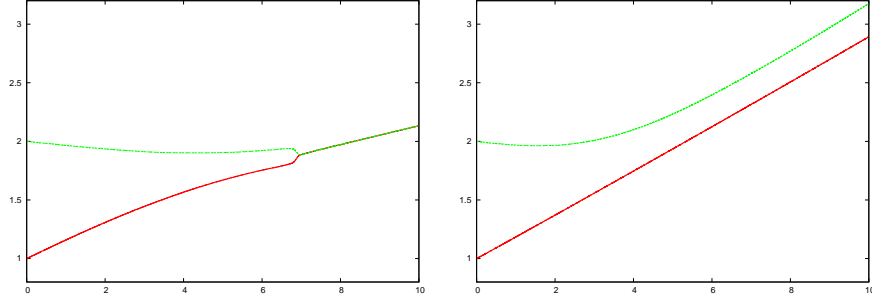


Fig. 4. A plot of the two radii over time for (4.4d) and $\sigma_B = 2$. The left plot is without fluid flow, i.e., $K = 0$, while the right plot is for $K = 0.01$.

4.2.2. Simulation with the source term (4.4b)

The same simulation as in Fig. 1, but now for the source term (4.4b) can be seen in Fig. 6. As a comparison we also show the evolution without the fluid flow, see Fig. 7. In this case we observe quite complex nucleation phenomena of the necrotic phase within the proliferating phase. We believe that the difference in behaviour can be attributed to the prefactor $\varepsilon^{-1}\varphi_i(1 - \varphi_i)$ in \mathbf{U}_C , and in light of the asymptotic analysis in Sec. 3.4, any effect of the source term \mathbf{U}_C is localised to the interfacial regions. Thus, we do not expect to observe nucleation-type effects in the bulk regions as the source terms are not active there. In contrast, inspecting the source term \mathbf{U}_A , in particular for the necrotic cells, we see that in the proliferating region $\Omega_P = \{\varphi_2 = 1\}$, the necrotic cells receive a constant source with magnitude $\mathcal{A} = 0.5$, which may explain the nucleation of necrotic cells in the proliferating region. Furthermore, a closer inspection of the corresponding plots for the nutrient in Figs. 6 and 7 shows

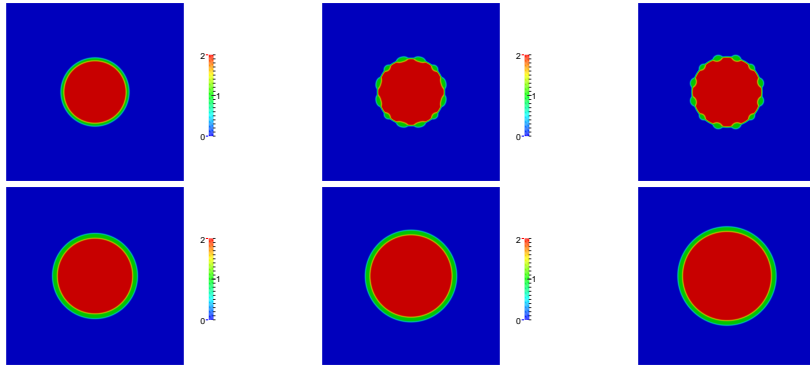


Fig. 5. The solution φ_h^n at times $t = 6, 7, 8$ for the two evolutions from Figure 4. Above for $K = 0$, below for $K = 0.01$.

that regions of lowest nutrient are those occupied by the necrotic cells.

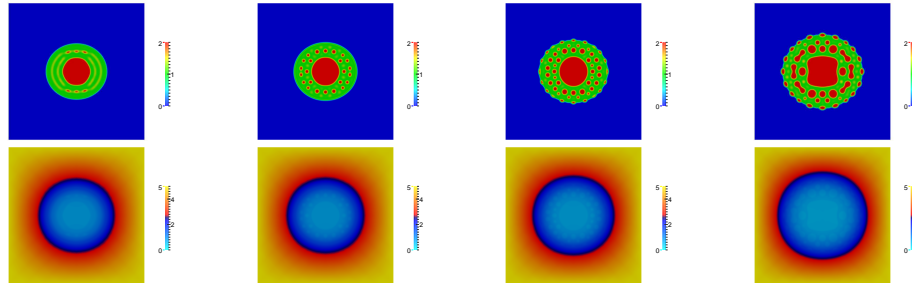


Fig. 6. ($\sigma_B = 5, K = 0.01$) The solution φ_h^n at times $t = 0.3, 0.5, 1, 2$ for (4.4b). Below we show plots of σ_h^n at the same times.

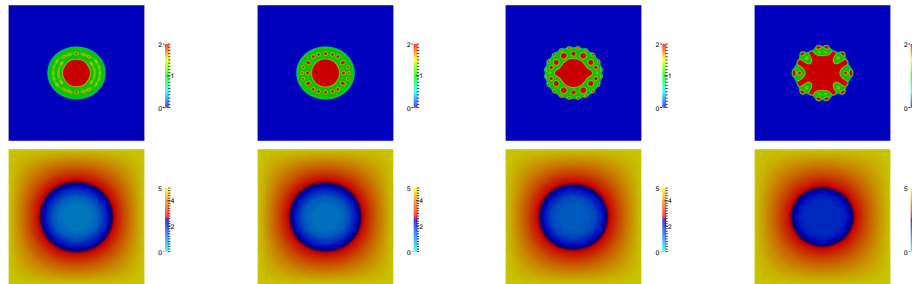


Fig. 7. ($\sigma_B = 5, K = 0$) The solution φ_h^n at times $t = 0.3, 0.5, 1, 2$ for (4.4b). Below we show plots of σ_h^n at the same times.

Finally, we consider a numerical simulation on the larger domain $\Omega = (-10, 10)^2$ for the source term (4.4b), with the parameters

$$\begin{aligned} \mathcal{A} &= 0, & \beta &= 0.1, & \mathcal{C} &= 2, & \mathcal{P} &= 0.1, & \lambda &= 0.02, \\ \chi_\varphi &= 5, & \mathcal{D}_N &= 0, & \sigma_B &= 1, & K &= 0.01. \end{aligned}$$

The evolution of the three phases is shown in Fig. 8, where we chose the initial radius $R_3 = 1$. It can be seen that both tumour phases grow, with some instabilities developing at the tumour/host cell interface. However, if the initial necrotic phase is smaller, it vanishes and the perturbations become more pronounced, see Fig. 9. In fact, towards the end the evolution in Fig. 9 becomes similar to Fig. 5 of Ref. 27. Let us also point out that the numerical simulations with the source term (4.4c)

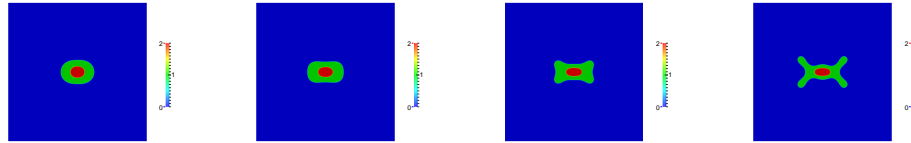


Fig. 8. The solution φ_h^n at times $t = 10, 15, 20, 25$ for (4.4b) with the perturbed initial data (4.10c) and $R_3 = 1$.

are almost identical to Figs. 8 and 9, and so we omit the results.

4.2.3. *Effects of necrotic degradation on invasive growth*

We also investigate the effects of a larger initial necrotic core on the evolution of the tumour. To this end, we repeat the computation in Fig. 8 for the initial radius $R_3 = 1.5$ for $\mathcal{D}_N \in \{0, 1, 5\}$. The three different evolutions can be seen in Fig. 10, where we observe that for positive values of \mathcal{D}_N , the necrotic core slowly disappears, and the subsequent evolution of the tumour is similar to that observed in Fig. 9. Meanwhile, in the case where the necrotic core does not degrade, upon comparing to Fig. 8, we can conclude that a large necrotic core seems to suppress or delay the development of protrusions and leads to a more compact growth.

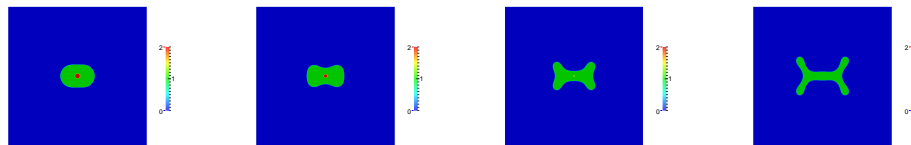


Fig. 9. The solution φ_h^n at times $t = 10, 15, 20, 25$ for (4.4b) with the perturbed initial data (4.10c) and $R_3 = 0.5$.

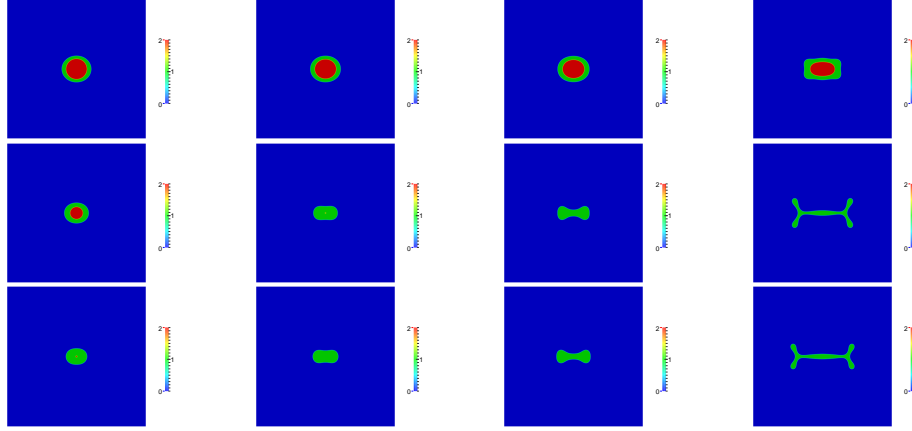


Fig. 10. The solution φ_h^n at times $t = 1, 5, 10, 25$ for (4.4b) with the perturbed initial data (4.10c) and $R_3 = 1.5$. The top row is for $\mathcal{D}_N = 0$, the middle row is for $\mathcal{D}_N = 1$, and the bottom row is for $\mathcal{D}_N = 5$.

4.2.4. Effects of necrotic degradation on the velocity field

We repeat the experiment in Fig. 8, but now for circular initial data, i.e. $\delta_2 = \delta_3 = 0$, and with $\chi_\varphi = \lambda = 0$ and $\mathcal{D}_N = 0.5$. In this setting, we expect to maintain radial symmetry as the tumour evolves, and due to the disintegration of the necrotic core, as mentioned at the end of Sec. 2.8, we expect to see that the growing tumour periphery is pulled back towards the centre as long as the necrotic core exists, and once the core has vanished, the growing periphery will move away from the centre.

In Fig. 11 we visualise the discrete velocity profile $\vec{v}_h^n \in [S_h]^2$, defined by

$$(\vec{v}_h^n, \vec{\chi}_h)_h = -K(\nabla p_h^n - (\nabla \varphi_h^n)^\top (\mu_h^n - \mathbf{N}_{,\varphi}(\sigma_h^n)), \vec{\chi}_h)_h \quad \forall \vec{\chi}_h \in [S_h]^2,$$

at different stages of the evolution, and we observe that the velocity points towards the origin when a necrotic core is present, with the magnitude decreasing as the core shrinks. When the core has disappeared, the velocity points outwards, but with a rather small magnitude. In Fig. 12 a plot of the radii of the necrotic core and the growing periphery over time is displayed, and it can be seen that the outer radius increases, albeit rather slowly, after the core has vanished. The observed behaviour of the cell velocity field is consistent with earlier numerical simulations (see Figs. 4b and 5b(ii) of Ref. 65).

4.2.5. Discussion of the numerical simulations

In the above numerical simulations, we obtained results that seem to be rather different compared to the literature. We believe that this is due to the nature of our multiphase model (in which a multi-well potential is used, as opposed to the degenerate Ginzburg–Landau variant used in Refs. 10, 11, 23, 45, 46, 65, 67) and the phenomenological modelling of the growth mechanisms.

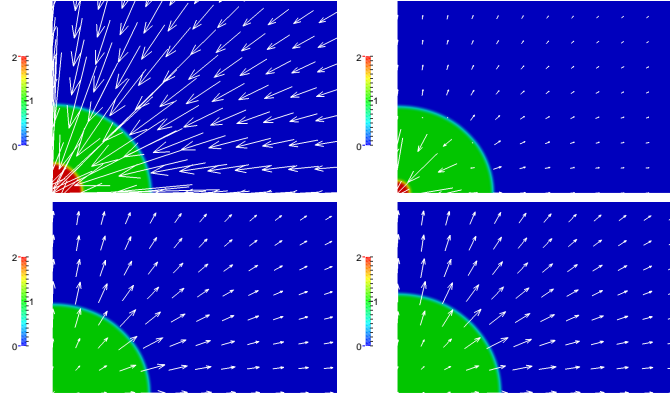


Fig. 11. The solution φ_h^n , and a visualisation of \bar{v}_h^n , at times $t = 2$ (top left), 5 (top right), 10 (bottom left), 30 (bottom right) for (4.4b) for the circular initial data (4.7) with $\delta_2 = \delta_3 = 0$.

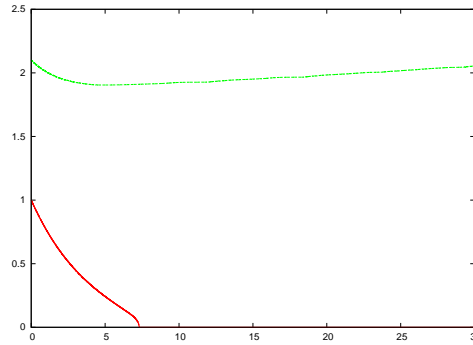


Fig. 12. A plot of the two radii over time for (4.4b).

While U_A and U_B are the natural generalisations of the source terms capturing proliferating and apoptosis from the two-phase setting in Refs. 12, 14, 27, we did not anticipate the development of necrotic phases in the proliferating region. Remarkably, these kinds of growth behaviours of the necrotic cells have in principle been observed in clinical research: In experimental gliomas in rats, multiple areas of focal necrosis were found in regions distant to any blood vessels (Figs. 1 and 3 of Ref. 43). Conventional renal cancer is known to develop focal and patchy necrosis⁴⁴. These results are concordant to the simulated tumour morphology in Fig. 6. Furthermore, in an experimental neurinoma in rats also finger-like growth of the necrotic core has been observed (Fig. 6b of Ref. 42). Our results seem to suggest that the presence of a necrotic core can inhibit invasive tumour growth. Despite the nucleation of necrotic cells within the tumour (Figs. 6 and 7), we point out that the overall tumour remains roughly spherical, and when the necrotic core is allowed to disintegrate, the loss of necrotic cells leads to a velocity field pointing towards the centre of the tumour

(Fig. 11) which has the effect of perturbing the tumour–host cell interface. Coupled with the chemotaxis mechanism, once the necrotic core has vanished, we expect that the tumour displays morphological instabilities as observed in the two-phase setting (Fig. 10). Therefore, based on our simulations, one might conclude that in a clinical setting, the presence of necrosis might be beneficial since it inhibits further tumour growth. However, for many common tumour entities, the opposite seems to be true, as the existence of necrotic components in a tumour are associated with a worsening of prognosis and reduced long-term survival^{32,57,59}. One explanation for this fact would be that aggressive, undifferentiated tumours tend to show a less controlled pattern of growth and therefore more often “outgrow” their own nutrient supply, consequently developing a necrotic core.

In contrast to the behaviour obtained with the source term U_A , we observed that the tumour with U_C as a source term evolves in a more-or-less radially symmetric manner despite initial perturbations of the interfaces, where one would expect to develop morphological instabilities in the two-phase setting (Figs. 1 and 2). The idea behind the source term U_C is rather recent³⁷ and seems to yield results in line with the current intuition regarding avascular tumour spheroids (Figs. 4 and 5). We believe that the idea behind U_C warrants further investigation, as it allows for the modelling assumption where the cells in the interior of the tumour are tightly packed so that only the cells near the periphery of the tumour region experience growth.

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