Derivation and application of effective interface conditions for continuum mechanical models of cell invasion through thin membranes *

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February 2, 2019

Abstract

We consider a continuum mechanical model of cell invasion through thin membranes, which consists of a transmission problem for a system of nonlinear partial differential equations for the cell volume fraction complemented with continuity of stresses and mass flux across the surfaces of the membranes. We reduce the original problem to a limiting transmission problem whereby each thin membrane is replaced by an effective interface, and we develop a formal asymptotic method that enables us to derive a set of biophysically consistent transmission conditions to close the limiting problem. The formal results obtained are validated via numerical simulations showing that the relative error between the solutions to the original transmission problem and the solutions to the limiting problem vanishes when the thickness of the membranes tends to zero. In order to illustrate the potential application of our effective interface conditions, we employ the limiting transmission problem to mathematically describe cancer cell invasion through the basement membrane and, in particular, to model the metastatic spread of ovarian carcinoma.

1 Introduction

Biological background Cell migration is crucial to maintain normal homeostasis [44] and sustain many physiological and pathological processes [23, 38, 46, 48]. During migration phenomena, cells encounter a variety of barriers encompassing other cells, cell-cell junctions, and extracellular matrices (ECMs) of different densities and compositions [38].

One of the most difficult barrier for the cells to cross is the basement membrane. This is a thin, dense and highly cross-linked sheet-like network of ECM macromolecules that underlies, amongst others, all epithelial and endothelial layers [36, 38]. With its pore size being in the order of 50 nm, only small molecules such as nutrients (*e.g.* oxygen and glucose) and other chemical factors are able to passively diffuse across the basement membrane [36, 59]. Nonetheless, such a structural barrier is crossed daily by billions of cells in healthy tissues in the course of normal immune cell trafficking [32], epithelial-to-mesenchymal transition [62], collective cell migration [23, 46, 48], and tissue development and morphogenesis [63]. Recent empirical studies [38, 64] suggest

*This work was partially supported by the MIUR grant "Dipartimenti di Eccellenza 2018-2022", by the INDAM grant "Progetto Giovani GNFM 2018" and by the EPSRC grant no. EP/N014642/1.

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that during these physiological processes cells can invade the basement membrane and other thin ECM barriers in a variety of ways, including either active removal (*e.g.* through invadopodia breaching and barrier disruption mediated by the down-regulation of adhesion receptors) or structural remodelling leading to the creation of gaps in the barrier, or even physiological enlargement of preexisting openings that facilitate, for instance, leukocyte trafficking in the vasculature [52].

Similar mechanisms of cell invasion are likely to be activated in pathological conditions, including fibrotic diseases (most commonly affecting the lungs or kidneys), inflammatory diseases, arteriosclerosis and neoplastic processes [38]. In particular, many types of tumours originate and develop in body regions that are separated from the surrounding environment by the basement membrane. This is, for instance, the case of breast tumours (ductal carcinoma) [17], ovary tumours [3], and exocrine or endocrine pancreatic tumours [12]. During the first stages of cancer progression, non-invasive dysplastic cells proliferate locally and form a carcinoma *in situ*. At some later stage of tumour development, such a localised cancer lesion may acquire the capacity to invade the adjacent tissues by perforating the basement membrane, thus becoming an invasive carcinoma [16, 60]. The transition from carcinoma *in situ* to invasive carcinoma is sustained by the ability of cancer cells to produce matrix metalloproteinases (MMPs). These are enzymes capable of digesting the collagen fibers that constitute the extracellular environment and the basement membrane [33, 64]. The MMPs' action widens the pores of the fibre networks and enable cancer cells to spread from the primary site to the surrounding tissues. Notably, experimental studies on cancer cell mobility in MMP-degradable collagen lattices and nondegradable substrates of various porosity have revealed the existence of an ECM critical pore size below which cancer cell migration is entirely hampered in the absence of MMP secretion. Such a critical pore size was termed "the physical limit of migration" [64].

Mathematical modelling background Despite our growing knowledge about the underpinnings of cell invasion during physiological and pathological processes [23, 31, 38, 59, 64, 65], a number of key aspects still remain unclear. This is mainly due to the difficulty of examining *in vivo* the interactions occurring between cells and the basement membrane or other ECM barriers during cellular invasion, as well as to the wide range of diverse mechanisms that cells can use to cross different extracellular structures [38]. As a consequence of our partial understanding of this complex biological phenomenon, there has been little prior work on the mathematical modelling of cell invasion through thin membranes. In fact, classical mathematical models of tumour growth [6, 22, 51, 57] and cell migration on two-dimensional flat substrates [18] do not take into account the effects of cell invasion through ECM barriers nor the transition from carcinomas *in situ* to invasive tumours.

Only more recently physiological and pathological processes involving the migration of single cells in the presence of obstacles or barriers have been mathematically described by means of discrete models [28, 34, 47], and different aspects of tumour growth in confined environments have been investigated *in silico* using both discrete and hybrid models [29, 39, 40]. These models can be easily tailored to capture fine details of the changes in cell-cell and cell-ECM adhesion properties observed during cell migration. However, their computational cost can become prohibitive for large cell numbers. Therefore, to model cell migration through the basement membrane and other thin ECM barriers at the scale of larger portions of tissues, it is desirable to use continuum models, which offer the possibility to carry out efficient numerical simulations for large cell numbers that are biologically and clinically relevant.

In this regard, focussing on breast cancer, which originates in the epithelial lining of the milk ducts, Ribba *et al.* [58] have proposed a mathematical model of cancer cell invasion whereby the basement membrane of the ducts is explicitly represented as a weakly permeable thin region. Although it has provided some interesting biological insights, such a modelling approach could become computationally inefficient in the presence of multiple thin membranes, as they would still be modelled as finite regions. Moreover, Gallinato *et al.* [25] have proposed a mixture model of breast cancer cell invasion whereby the presence of the basement membrane of the milk ducts is taken into account by imposing nonlinear Kedem-Katchalsky interface conditions [13, 20, 21, 37, 41, 54] at

the interface between the tumour and the host region. In the setting of Gallinato *et al.* [25], such transmission conditions lead the normal velocity of the cells and the cell volume fraction to be continuous across the basement membrane, which is not necessarily the case. Finally, Arduino & Preziosi [7] and Giverso *et al.* [27] have presented a number of multiphase models of cancer cell migration and invasion through the ECM. In agreement with the biological experiments of Wolf *et al.* [64], in these models the cellular mobility vanishes when the ECM pore size decreases below a certain critical value. These models effectively capture the fact that the ECM critical pore size is relative to the geometrical and mechanical characteristics of the cells (*e.g.* the size and elasticity of the nucleus, the stiffness of the nuclear membrane, cellular adhesion and traction), and they have been proven useful to study cancer cell invasion in cases where the morphological characteristics of the ECM are spatially heterogeneous, or even discontinuous. However, such models do not apply to biological scenarios where ECM regions with different mechanical and structural properties (*i.e.* different cell mobilities) are separated by thin membranes.

Contents of the paper In this paper, we consider a continuum mechanical model of cell movement and cellular proliferation in a spatial domain that is divided into subdomains by one or multiple thin membranes. The model is formulated in terms of a transmission problem defined by a system of nonlinear partial differential equations for the cell volume fraction complemented with mass-continuity and stress-continuity conditions on the interfaces between the membranes and the rest of the domain.

Nonlinear partial differential equations describing reaction-diffusion processes and transport phenomena in spatial domains that comprise different parts separated by thin layers (*i.e.* films or membranes) arise in the mathematical modelling of various chemical, physical and biological systems [1, 2, 4, 5, 9, 10, 11, 14, 15, 19, 24, 26, 30, 35, 43, 45, 50, 49, 55, 56]. Due to the analytical and numerical challenges posed by the presence of such layers [8], it is often convenient to approximate the original problem by an equivalent transmission problem whereby each thin layer is replaced by an effective interface. The equivalent problem is then closed by imposing appropriate transmission conditions on the effective interfaces.

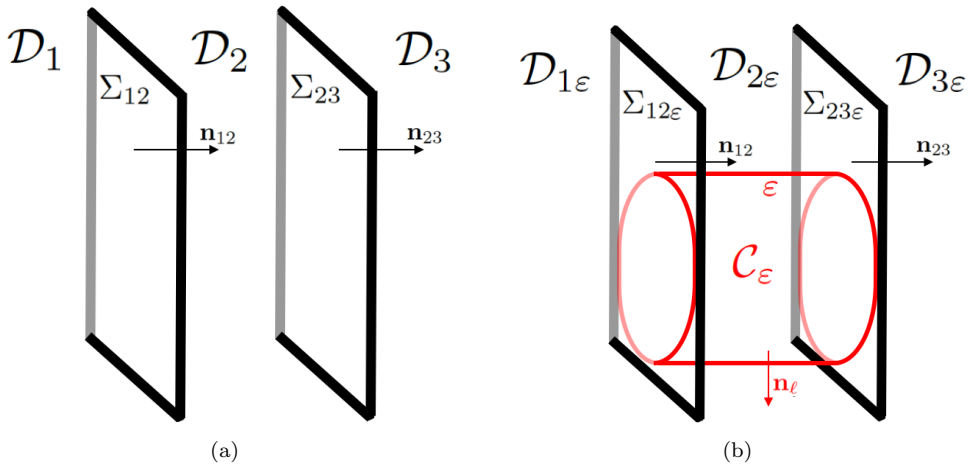
In this spirit, we develop a formal procedure to derive a set of biophysically consistent interface conditions to close the limiting problem. Specifically, we find that the mass flux across the effective interfaces must be continuous, as one would expect, and proportional to the jump of a term linked to the cell pressure. The biophysical interest lies in the fact that this proportionality coefficient can be related to the size of the pores of the thin membrane, as well as to the geometrical and mechanical characteristics of the cells as in [7, 27, 28]. This makes the limiting transmission problem suitable for providing a possible macroscopic description of cell invasion through thin membranes that takes explicitly into account cell microscopic characteristics, such as the mechanical constraints imposed by the cell nuclear envelope and the solid material surrounded by it [64].

The transmission condition identified by the limiting procedure can be regarded as a nonlinear generalisation of the classical Kedem-Katchalsky interface condition, as it reduces to it for a peculiar (logarithmic) choice of the constitutive relation between the cell pressure and the cell volume fraction. In contrast to other nonlinear Kedem-Katchalsky interface conditions that have been previously employed to model cell invasion through the basement membrane [25], our transmission condition allows the cell volume fraction to be discontinuous across the equivalent interface, while ensuring mass conservation.

The remainder of the paper is organised as follows. In Section 2, we present the original transmission problem and we introduce the related limiting problem. In Section 3, we formally derive a set of effective interface conditions to close the limiting problem. In Section 4, we present sample numerical solutions that illustrate the formal results established in Section 3 and show their application potential. In particular, we use the limiting transmission problem to describe cancer cell invasion through the basement membrane and to model the metastatic spread of ovarian carcinoma. Section 5 concludes the paper and provides a brief overview of possible research perspectives.

2 Statement of the problem

We consider a population of cells moving through a region of space that is filled with a porous embedding medium, *e.g.* the ECM. Mathematically, we identify such a region with a simply-connected spatial domain $\mathcal{D} \subset \mathbb{R}^d$, with $d = 1, 2, 3$. Focussing on the biological scenario where the spatial domain is divided into two regions separated by a porous membrane, we let the domain $\mathcal{D}$ consist of three subdomains represented by the open sets $\mathcal{D}_1$, $\mathcal{D}_2$ and $\mathcal{D}_3$, as in the scheme depicted in Fig. 1(a) for a three-dimensional case. The subdomain $\mathcal{D}_2$ represents the porous membrane, and the interfaces between the membrane and the subdomains $\mathcal{D}_1$ and $\mathcal{D}_3$ are denoted by Σ_{12} and Σ_{23}, respectively.



(a) (b)

Figure 1: **Spatial domain and notation. (a)** Scheme of the spatial domain in a three-dimensional case and related notation. **(b)** Scheme of the spatial domain in a three-dimensional case and related notation used in the proof of Propositions 1 and 2.

We model the cell volume fraction at position $\mathbf{x} \in \mathcal{D}$ and time $t \geq 0$ by means of the function $\rho(t, \mathbf{x}) \geq 0$. The evolution of the cell volume fraction is governed by the mass balance equation

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \, \mathbf{v}) = \Gamma, \quad (t, \mathbf{x}) \in \mathbb{R}_+ \times \mathcal{D} \tag{1}$$

complemented with the momentum-related equation

$$\mathbf{v} := -\mu \, \nabla p. \tag{2}$$

In Eq. (1), the net growth rate Γ depends on the cell volume fraction ρ, that is, $\Gamma(t, \mathbf{x}) \equiv \Gamma(\rho(t, \mathbf{x}))$. If necessary, one can let the net growth rate depend also on the concentration of some chemical factors, such as nutrients and growth factors. In Eq. (2) the function $\mu(t, \mathbf{x}) \geq 0$ stands for the cell mobility coefficient and the function p represents the cell pressure, which depends on the cell volume fraction, *i.e.* $p(t, \mathbf{x}) \equiv p(\rho(t, \mathbf{x}))$. In analogy with the classical Darcy's law for fluids, Eq. (2) models the tendency of cells to move towards regions where they feel less compressed. It is important to stress the fact that we let the cell mobility coefficient be a function of both t and $\mathbf{x}$. This is to take into account the heterogeneous composition of the spatial domain $\mathcal{D}$ and the biological notion that the mobility of cells in the embedding medium, especially within the membrane, can vary

considerably across space and time. Variability of the cell mobility can be due both to local variations in the micro-structure of the ECM and to spatio-temporal changes in the concentration of MMPs. Therefore, one may let the function μ depend explicitly on the local concentration of MMPs and then couple Eqs. (1) and (2) with a conservation equation for the MMP concentration, as we will do in Section 4.

From continuum mechanics, one has that mass flux must be continuous across the interfaces Σ_{12} and Σ_{23}. Furthermore, since we focus on the case where inertia can be neglected, stresses must also be continuous across both interfaces. Within the framework of Eqs. (1) and (2), such continuity conditions translate into the following interface conditions:

$$[\![\rho\,\mathbf{v}\cdot\mathbf{n}_{ij}]\!] = 0 \ \text{ on } \Sigma_{ij} \ \text{ with } \ i=1,2 \ \text{ and } \ j=i+1, \tag{3}$$

and

$$[\![p]\!] = 0 \ \text{ on } \Sigma_{ij} \ \text{ with } \ i=1,2 \ \text{ and } \ j=i+1. \tag{4}$$

In Eqs. (3) and (4), the notation $[\![(\cdot)]\!]$ represents the jump across the interface Σ_{ij}, *i.e.*

$$[\![(\cdot)]\!] := (\cdot)_j - (\cdot)_i$$

with the subscript i indicating that $(\cdot)$ is evaluated as the limit to a point of the interface coming from the subdomain $\mathcal{D}_i$. Moreover, as shown in Fig. 1(a), we denote by $\mathbf{n}_{ij}$ the unit vector normal to the interface Σ_{ij} that points towards the subdomain $\mathcal{D}_j$. Substituting the expression (2) for the velocity field $\mathbf{v}$ into the flux-continuity condition (3) yields

$$[\![\mu\,\rho\,\nabla p\cdot\mathbf{n}_{ij}]\!] = 0 \ \text{ on } \Sigma_{ij} \ \text{ with } \ i=1,2 \ \text{ and } \ j=i+1. \tag{5}$$

In order to close the transmission problem defined by Eqs. (1) and (2) complemented with the interface conditions (4) and (5), in addition to prescribing suitable boundary conditions on the outer boundaries (*i.e.* the non-interfacing parts of the boundaries of the three spatial subdomains) and suitable initial conditions, one should specify a barotropic relation $p(\rho)$.

Remark 1. *In the case where the pressure p is a continuous function of the cell volume fraction ρ, the stress-continuity condition* (4) *implies that also ρ is continuous across the interfaces Σ_{12} and Σ_{23}, that is,*

$$[\![\rho]\!] = 0 \ \text{ on } \Sigma_{ij} \ \text{ with } \ i=1,2 \ \text{ and } \ j=i+1.$$

Hence, the flux-continuity conditions (3) *or* (5) *read as*

$$[\![\mathbf{v}\cdot\mathbf{n}_{ij}]\!] = 0 \quad \text{or} \quad [\![\mu\,\nabla p\cdot\mathbf{n}_{ij}]\!] = 0 \ \text{ on } \Sigma_{ij} \ \text{ with } \ i=1,2 \ \text{ and } \ j=i+1.$$

In general, the three subdomains can differ in their biophysical properties. As a result, the mobility coefficient and the net growth rate can become discontinuous across the interfaces Σ_{12} and Σ_{23}. In this case, denoting by $\rho_i(t,\mathbf{x}) \geq 0$, $\mu_i(t,\mathbf{x}) \geq 0$ and $\Gamma_i(t,\mathbf{x}) \equiv \Gamma_i(\rho_i(t,\mathbf{x}))$ the restrictions to the subdomain $\mathcal{D}_i$ of the functions that represent the local cell volume fraction, the mobility coefficient and the net growth rate, respectively, we can rewrite the problem defined by Eqs. (1) and (2) complemented with the interface conditions (4) and (5) as

$$\begin{cases} \dfrac{\partial \rho_i}{\partial t} - \nabla\cdot(\mu_i\,\rho_i\,\nabla p) = \Gamma_i(\rho_i) & \text{in } \mathcal{D}_i, \quad i=1,2,3, \\ \mu_i\,\rho_i\,\nabla p\cdot\mathbf{n}_{ij} = \mu_j\,\rho_j\,\nabla p\cdot\mathbf{n}_{ij} & \text{on } \Sigma_{ij}, \quad i=1,2, \quad j=i+1, \\ [\![p]\!] = 0 & \text{on } \Sigma_{ij}, \quad i=1,2, \quad j=i+1. \end{cases} \tag{6}$$

In this paper, we make the following assumptions:

Assumption 1. *The cell mobility coefficient μ_i is continuous in both arguments.*

Assumption 2. *The net growth rate Γ_i is a bounded function of ρ_i.*

Assumption 3. *The pressure p is a continuously differentiable function of the cell volume fraction.*

In most biologically relevant scenarios arising in the study of cell invasion through the basement membrane and other ECM barriers, the thickness of the membrane or the barrier is much smaller than the characteristic size $L > 0$ of the spatial domain. In order to translate this biological observation into mathematical terms, we define the thickness of the membrane represented by the subdomain $\mathcal{D}_2$ as

$$\varepsilon := \max_{\hat{\mathbf{x}}_{12} \in \Sigma_{12}} \left\{ \min\{a > 0 : \hat{\mathbf{x}}_{12} + a\, \mathbf{n}_{12} \in \Sigma_{23}\} \right\} \tag{7}$$

and we assume $\varepsilon \ll L$. In the biological scenarios corresponding to the assumption $\varepsilon \ll L$, one typically wishes to:

i) replace the subdomain $\mathcal{D}_2$ with an effective interface, which is obtained from the actual interfaces Σ_{12} and Σ_{23} by letting $\varepsilon \to 0$;

ii) find biophysically consistent transmission conditions to impose on the effective interface in the asymptotic regime.

With these goals in mind, we rewrite the transmission problem (6) as

$$\mathcal{P}_\varepsilon \equiv \begin{cases} \dfrac{\partial \rho_{i\varepsilon}}{\partial t} - \nabla \cdot (\mu_{i\varepsilon}\, \rho_{i\varepsilon}\, \nabla p_\varepsilon) = \Gamma_{i\varepsilon} & \text{in } \mathcal{D}_{i\varepsilon}, \quad i = 1,2,3, \\ \mu_{i\varepsilon}\, \rho_{i\varepsilon}\, \nabla p_\varepsilon \cdot \mathbf{n}_{ij} = \mu_{j\varepsilon}\, \rho_{j\varepsilon}\, \nabla p_\varepsilon \cdot \mathbf{n}_{ij} & \text{on } \Sigma_{ij\varepsilon}, \quad i = 1,2, \quad j = i+1, \\ [\![p_\varepsilon]\!] = 0 & \text{on } \Sigma_{ij\varepsilon}, \quad i = 1,2, \quad j = i+1, \end{cases} \tag{8}$$

while the limiting transmission problem whereby the subdomain $\mathcal{D}_2$ is replaced by an effective interface reads as

$$\mathcal{P}_0 \equiv \begin{cases} \dfrac{\partial \tilde{\rho}_i}{\partial t} - \nabla \cdot (\tilde{\mu}_i\, \tilde{\rho}_i\, \nabla \tilde{p}) = \tilde{\Gamma}_i & \text{in } \tilde{\mathcal{D}}_i, \quad i = 1,3, \\ \text{transmission conditions} & \text{on } \tilde{\Sigma}_{13}, \end{cases} \tag{9}$$

where

$$\tilde{\mathcal{D}}_1 = \lim_{\varepsilon \to 0} \mathcal{D}_{1\varepsilon}, \quad \tilde{\mathcal{D}}_3 = \lim_{\varepsilon \to 0} \mathcal{D}_{3\varepsilon}, \quad \tilde{\Sigma}_{13} = \lim_{\varepsilon \to 0} \Sigma_{12\varepsilon} = \lim_{\varepsilon \to 0} \Sigma_{23\varepsilon}, \tag{10}$$

while

$$\tilde{\rho}_1 = \lim_{\varepsilon \to 0} \rho_{1\varepsilon}, \quad \tilde{\rho}_3 = \lim_{\varepsilon \to 0} \rho_{3\varepsilon}, \quad \tilde{p} = \lim_{\varepsilon \to 0} p_\varepsilon \tag{11}$$

and

$$\tilde{\mu}_i = \lim_{\varepsilon \to 0} \mu_{i\varepsilon}, \quad \tilde{\Gamma}_i = \lim_{\varepsilon \to 0} \Gamma_{i\varepsilon}, \quad i = 1,3. \tag{12}$$

Remark 2. *In the remainder of the paper, we will refer to the transmission problem $\mathcal{P}_\varepsilon$ defined by the system of equations* (8)*, or equivalently by the system of equations* (6)*, as the "thin layer problem", and to the limiting transmission problem $\mathcal{P}_0$ defined by the system of equations* (9) *along with the appropriate transmission conditions as the "effective interface problem".*

The next section will be devoted to derive the transmission conditions that are necessary to complete the effective interface problem $\mathcal{P}_0$. A crucial role will be played by the ratio $\mu_{2\varepsilon}/\varepsilon$. In particular, from the mathematical point of view, we will need $\varepsilon \to 0$ and $\mu_{2\varepsilon} \to 0$ in such a way that the existing relationships between the biophysical characteristics of the thin membrane and the mechanical and geometrical properties of the cells remain intact across the effective interface $\tilde{\Sigma}_{13}$. To this end, we will assume

$$\frac{\mu_{2\varepsilon}}{\varepsilon} \xrightarrow[\varepsilon\to 0]{\mu_{2\varepsilon}\to 0} \tilde{\mu}_{13} \quad \text{with} \quad 0 < \tilde{\mu}_{13}(t,\mathbf{x}) < \infty \quad \text{for all} \quad (t,\mathbf{x}) \in \mathbb{R}_+ \times \tilde{\Sigma}_{13}. \tag{13}$$

The function $\tilde{\mu}_{13}(t,\mathbf{x})$ can be seen as the "effective mobility coefficient" of the cells through the thin membrane represented by the effective interface $\tilde{\Sigma}_{13}$ (*vid.* Remark 3 below). The rationale behind the assumption (13) is that for the effective interface $\tilde{\Sigma}_{13}$ (*i.e.* an infinitesimal region) to have an effect on cell invasion analogous to that of the actual thin membrane represented by the subdomain $\mathcal{D}_{2\varepsilon}$ (*i.e.* a finite region), the mobility coefficient $\mu_{2\varepsilon}$ and the thickness of the membrane ε should tend to zero at the same rate. In other words, the effective interface should be obtained by virtually shrinking the pores of the membrane in such a way as to cause a reduction in the local permeability that is proportional to the local shrinkage. This guarantees that the cell mobility along the effective interface faithfully approximates the cell mobility throughout the actual thin membrane.

Remark 3. *By analogy, consider a liquid flowing through a layer of porous material with unitary cross-sectional area. The liquid flux Q can be computed using the classical Darcy's law as*

$$Q = -\frac{\kappa}{\nu}\frac{\Delta P}{\Delta x},$$

where ΔP is the pressure drop between the ends of the layer, Δx stands for the thickness of the layer, κ represents the hydraulic permeability of the material and ν is the dynamic viscosity of the liquid. We can draw a conceptual analogy between the biological problem at hand and the case of the liquid by noting that the above equation can be rewritten in the alternative form

$$Q = -\frac{1}{\nu}\frac{\kappa}{\Delta x}\Delta P = -\frac{\tilde{\kappa}}{\nu}\Delta P \quad \textit{with} \quad \tilde{\kappa} := \frac{\kappa}{\Delta x},$$

where $\tilde{\kappa}$ represents an "effective permeability" of the porous layer in the case where the layer is thin.

3 Formal derivation of the interface conditions for the effective transmission problem

In this section, we formally derive the transmission conditions required to complete the effective transmission problem $\mathcal{P}_0$ defined by the system of equations (9). In summary, letting $\varepsilon \to 0$ in the thin layer problem $\mathcal{P}_\varepsilon$ defined by the system of equations (8), we first show that the mass flux across the effective interface $\tilde{\Sigma}_{13}$ is continuous (*vid.* Proposition 1). Moreover, letting $\varepsilon \to 0$ and $\mu_{2\varepsilon} \to 0$ in the thin layer problem $\mathcal{P}_\varepsilon$ in such a way that the condition (13) is met, we find an additional transmission condition that establishes a relationship between the mass flux across the effective interface $\tilde{\Sigma}_{13}$ and the effective cell mobility coefficient $\tilde{\mu}_{13}(t,\mathbf{x})$ (*vid.* Proposition 2).

Proposition 1. *Under Assumptions 1-3, if the solutions to the thin layer problem* (8) *are such that $\rho_{i\varepsilon}(\cdot,\mathbf{x}) \in C^1(\mathcal{D}_{i\varepsilon})$ for $i = 1,2,3$, then the following transmission condition formally applies to the effective interface problem* (9)

$$\tilde{\mu}_1\,\tilde{\rho}_1\,\nabla\tilde{p}\cdot\tilde{\mathbf{n}}_{13} = \tilde{\mu}_3\,\tilde{\rho}_3\,\nabla\tilde{p}\cdot\tilde{\mathbf{n}}_{13} \qquad \text{on } \tilde{\Sigma}_{13}, \tag{14}$$

with $\tilde{\mathbf{n}}_{13}$ being the unit vector normal to the interface $\tilde{\Sigma}_{13}$ that points towards the subdomain $\tilde{\mathcal{D}}_3$.

Proof. Consider an open cylinder-like region $\mathcal{C}_\varepsilon \subset \mathcal{D}_{2\varepsilon}$ of height ε and radius $r_\varepsilon \leq \varepsilon$, with axis parallel to the normal to the interfaces $\Sigma_{12\varepsilon}$ and $\Sigma_{23\varepsilon}$ and bases lying on $\Sigma_{12\varepsilon}$ and $\Sigma_{23\varepsilon}$ [*vid.* Fig. 1(b)]. Furthermore, let $\Sigma_{\ell\varepsilon}$ denote the lateral surface of $\mathcal{C}_\varepsilon$ and use the notation $\mathbf{n}_\ell$ for the outward unit vector normal to $\Sigma_{\ell\varepsilon}$. Finally, let $\partial\mathcal{C}_\varepsilon$ denote the border of $\mathcal{C}_\varepsilon$ and $\mathbf{n}$ be the unit outward normal vector to $\partial\mathcal{C}_\varepsilon$.

In the framework of the thin layer problem $\mathcal{P}_\varepsilon$ defined by the system of equations (8), the integral mass balance equation for the number of cells in the cylinder-like region $\mathcal{C}_\varepsilon$ reads as

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_{\mathcal{C}_\varepsilon} \rho_{2\varepsilon}\,\mathrm{d}V = \int_{\partial\mathcal{C}_\varepsilon} \mu_{2\varepsilon}\,\rho_{2\varepsilon}\,\nabla p_\varepsilon \cdot \mathbf{n}\,\mathrm{d}\Sigma + \int_{\mathcal{C}_\varepsilon} \Gamma_{2\varepsilon}\,\mathrm{d}V\,, \tag{15}$$

with

$$\begin{aligned}\int_{\partial\mathcal{C}_\varepsilon} \mu_{2\varepsilon}\,\rho_{2\varepsilon}\,\nabla p_\varepsilon \cdot \mathbf{n}\,\mathrm{d}\Sigma \;=\; &-\int_{\partial\mathcal{C}_\varepsilon\cap\Sigma_{12\varepsilon}} \mu_{2\varepsilon}\,\rho_{2\varepsilon}\,\nabla p_\varepsilon \cdot \mathbf{n}_{12}\,\mathrm{d}\Sigma\\ &+\int_{\partial\mathcal{C}_\varepsilon\cap\Sigma_{23\varepsilon}} \mu_{2\varepsilon}\,\rho_{2\varepsilon}\,\nabla p_\varepsilon \cdot \mathbf{n}_{23}\,\mathrm{d}\Sigma\\ &+\int_{\Sigma_{\ell\varepsilon}} \mu_{2\varepsilon}\,\rho_{2\varepsilon}\,\nabla p_\varepsilon \cdot \mathbf{n}_\ell\,\mathrm{d}\Sigma\,.\end{aligned} \tag{16}$$

Moreover, using the continuity of the mass flux across the interfaces $\Sigma_{12\varepsilon}$ and $\Sigma_{23\varepsilon}$, one can rewrite the first and the second terms on the right-hand side of Eq. (16) as

$$\int_{\partial\mathcal{C}_\varepsilon\cap\Sigma_{12\varepsilon}} \mu_{2\varepsilon}\,\rho_{2\varepsilon}\,\nabla p_\varepsilon \cdot \mathbf{n}_{12}\,\mathrm{d}\Sigma = \int_{\partial\mathcal{C}_\varepsilon\cap\Sigma_{12\varepsilon}} \mu_{1\varepsilon}\,\rho_{1\varepsilon}\,\nabla p_\varepsilon \cdot \mathbf{n}_{12}\,\mathrm{d}\Sigma$$

$$\int_{\partial\mathcal{C}_\varepsilon\cap\Sigma_{23\varepsilon}} \mu_{2\varepsilon}\,\rho_{2\varepsilon}\,\nabla p_\varepsilon \cdot \mathbf{n}_{23}\,\mathrm{d}\Sigma = \int_{\partial\mathcal{C}_\varepsilon\cap\Sigma_{23\varepsilon}} \mu_{3\varepsilon}\,\rho_{3\varepsilon}\,\nabla p_\varepsilon \cdot \mathbf{n}_{23}\,\mathrm{d}\Sigma$$

and, in so doing, obtain

$$\begin{aligned}\int_{\partial\mathcal{C}_\varepsilon} \mu_{2\varepsilon}\,\rho_{2\varepsilon}\,\nabla p_\varepsilon \cdot \mathbf{n}\,\mathrm{d}\Sigma \;=\; &-\int_{\partial\mathcal{C}_\varepsilon\cap\Sigma_{12\varepsilon}} \mu_{1\varepsilon}\,\rho_{1\varepsilon}\,\nabla p_\varepsilon \cdot \mathbf{n}_{12}\,\mathrm{d}\Sigma\\ &+\int_{\partial\mathcal{C}_\varepsilon\cap\Sigma_{23\varepsilon}} \mu_{3\varepsilon}\,\rho_{3\varepsilon}\,\nabla p_\varepsilon \cdot \mathbf{n}_{23}\,\mathrm{d}\Sigma\\ &+\int_{\Sigma_{\ell\varepsilon}} \mu_{2\varepsilon}\,\rho_{2\varepsilon}\,\nabla p_\varepsilon \cdot \mathbf{n}_\ell\,\mathrm{d}\Sigma\,.\end{aligned} \tag{17}$$

Substituting Eq. (17) into Eq. (15) and rearranging terms gives

$$\begin{aligned}\int_{\mathcal{C}_\varepsilon} \left(\frac{\partial\rho_{2\varepsilon}}{\partial t} - \Gamma_{2\varepsilon}\right)\mathrm{d}V \;=\; &-\int_{\partial\mathcal{C}_\varepsilon\cap\Sigma_{12\varepsilon}} \mu_{1\varepsilon}\,\rho_{1\varepsilon}\,\nabla p_\varepsilon \cdot \mathbf{n}_{12}\,\mathrm{d}\Sigma\\ &+\int_{\partial\mathcal{C}_\varepsilon\cap\Sigma_{23\varepsilon}} \mu_{3\varepsilon}\,\rho_{3\varepsilon}\,\nabla p_\varepsilon \cdot \mathbf{n}_{23}\,\mathrm{d}\Sigma\\ &+\int_{\Sigma_{\ell\varepsilon}} \mu_{2\varepsilon}\,\rho_{2\varepsilon}\,\nabla p_\varepsilon \cdot \mathbf{n}_\ell\,\mathrm{d}\Sigma\,.\end{aligned}$$

Under Assumptions 1-3, if $\rho_{1\varepsilon}(t,\mathbf{x})$ and $\rho_{3\varepsilon}(t,\mathbf{x})$ are continuously differentiable functions of $\mathbf{x}$, then the integrands in the first and the second term on the right-hand side of the above equation are continuous functions

of $\mathbf{x}$. Therefore, we can use the first mean value theorem for integrals and, dividing both sides of the resulting equation by $|\partial\mathcal{C}_\varepsilon \cap \Sigma_{12\varepsilon}| > 0$, find that

$$\begin{aligned}\frac{1}{|\partial\mathcal{C}_\varepsilon \cap \Sigma_{12\varepsilon}|}\int_{\mathcal{C}_\varepsilon}\left(\frac{\partial\rho_{2\varepsilon}}{\partial t}-\Gamma_{2\varepsilon}\right)\mathrm{d}V &= -\Big(\mu_{1\varepsilon}\,\rho_{1\varepsilon}\,\nabla p_\varepsilon\cdot\mathbf{n}_{12}\Big)\Big|_{\mathbf{x}=\hat{\mathbf{x}}_{12\varepsilon}}\\ &\quad+\frac{|\partial\mathcal{C}_\varepsilon\cap\Sigma_{23\varepsilon}|}{|\partial\mathcal{C}_\varepsilon\cap\Sigma_{12\varepsilon}|}\Big(\mu_{3\varepsilon}\,\rho_{3\varepsilon}\,\nabla p_\varepsilon\cdot\mathbf{n}_{23}\Big)\Big|_{\mathbf{x}=\hat{\mathbf{x}}_{23\varepsilon}}\\ &\quad+\frac{1}{|\partial\mathcal{C}_\varepsilon\cap\Sigma_{12\varepsilon}|}\int_{\Sigma_{\ell\varepsilon}}\mu_{2\varepsilon}\,\rho_{2\varepsilon}\,\nabla p_\varepsilon\cdot\mathbf{n}_\ell\,\mathrm{d}\Sigma\,,\end{aligned}\tag{18}$$

where the points $\hat{\mathbf{x}}_{12\varepsilon}$ and $\hat{\mathbf{x}}_{23\varepsilon}$ belong, respectively, to the surfaces $\partial\mathcal{C}_\varepsilon\cap\Sigma_{12\varepsilon}$ and $\partial\mathcal{C}_\varepsilon\cap\Sigma_{23\varepsilon}$. When $\varepsilon\to 0$, the left-hand side and the last term on the right-hand side of Eq. (18) formally vanish. Moreover,

$$\frac{|\partial\mathcal{C}_\varepsilon\cap\Sigma_{23\varepsilon}|}{|\partial\mathcal{C}_\varepsilon\cap\Sigma_{12\varepsilon}|}\xrightarrow[\varepsilon\to 0]{}1.\tag{19}$$

Hence, if

$$\rho_{1\varepsilon}\to\tilde{\rho}_1,\quad \rho_{3\varepsilon}\to\tilde{\rho}_3\quad\text{and}\quad p_\varepsilon\to\tilde{p}\quad\text{as }\varepsilon\to 0,$$

letting $\varepsilon\to 0$ in Eq. (18), and recalling the limits given by equations (10) and (12), we formally achieve the transmission condition

$$\tilde{\mu}_1\,\tilde{\rho}_1\,\nabla\tilde{p}\cdot\tilde{\mathbf{n}}_{13}=\tilde{\mu}_3\,\tilde{\rho}_3\,\nabla\tilde{p}\cdot\tilde{\mathbf{n}}_{13}\qquad\text{on }\tilde{\Sigma}_{13},$$

where $\tilde{\mathbf{n}}_{13}$ is the unit vector normal to the effective interface $\tilde{\Sigma}_{13}$ that points towards the subdomain $\tilde{\mathcal{D}}_3$. Noting that $\mathcal{C}_\varepsilon$ can be chosen arbitrarily, from the above transmission condition we obtain the flux-continuity condition (14). □

Proposition 2. *Under Assumptions 1-3 and assumption* (13)*, if the solutions to the thin layer problem* (8) *are such that* $\rho_{i\varepsilon}(\cdot,\mathbf{x})\in C^1(\mathcal{D}_{i\varepsilon})$ *for* $i=1,2,3$*, then the following transmission condition formally applies to the effective interface problem* (9)

$$\tilde{\mu}_{13}\,[\![\Pi]\!]=\tilde{\mu}_1\,\tilde{\rho}_1\,\nabla\tilde{p}\cdot\tilde{\mathbf{n}}_{13}=\tilde{\mu}_3\,\tilde{\rho}_3\,\nabla\tilde{p}\cdot\tilde{\mathbf{n}}_{13}\qquad\textit{on }\tilde{\Sigma}_{13},\tag{20}$$

where Π *is defined according to the equation*

$$\nabla\Pi=\tilde{\rho}\,\nabla\tilde{p},\tag{21}$$

and $\tilde{\mathbf{n}}_{13}$ *is the unit vector normal to the interface* $\tilde{\Sigma}_{13}$ *that points towards the subdomain* $\tilde{\mathcal{D}}_3$*.*

Proof. Here we use the same notation as in the proof of Proposition 1. The continuity of the mass flux across the interface $\Sigma_{12\varepsilon}$ implies that

$$\int_{\partial\mathcal{C}_\varepsilon\cap\Sigma_{12\varepsilon}}\mu_{2\varepsilon}\,\rho_{2\varepsilon}\,\nabla p_\varepsilon\cdot\mathbf{n}_{12}\,\mathrm{d}\Sigma=\int_{\partial\mathcal{C}_\varepsilon\cap\Sigma_{12\varepsilon}}\mu_{1\varepsilon}\,\rho_{1\varepsilon}\,\nabla p_\varepsilon\cdot\mathbf{n}_{12}\,\mathrm{d}\Sigma.$$

Substituting the above equation into the first term on the right-hand side of Eq. (16) yields

$$\begin{aligned}\int_{\partial\mathcal{C}_\varepsilon}\mu_{2\varepsilon}\,\rho_{2\varepsilon}\,\nabla p_\varepsilon\cdot\mathbf{n}\,\mathrm{d}\Sigma &= -\int_{\partial\mathcal{C}_\varepsilon\cap\Sigma_{12\varepsilon}}\mu_{1\varepsilon}\,\rho_{1\varepsilon}\,\nabla p_\varepsilon\cdot\mathbf{n}_{12}\,\mathrm{d}\Sigma\\ &\quad+\int_{\partial\mathcal{C}_\varepsilon\cap\Sigma_{23\varepsilon}}\mu_{2\varepsilon}\,\rho_{2\varepsilon}\,\nabla p_\varepsilon\cdot\mathbf{n}_{23}\,\mathrm{d}\Sigma\\ &\quad+\int_{\Sigma_{\ell\varepsilon}}\mu_{2\varepsilon}\,\rho_{2\varepsilon}\,\nabla p_\varepsilon\cdot\mathbf{n}_\ell\,\mathrm{d}\Sigma\,.\end{aligned}\tag{22}$$

Calculations similar to those in the proof of Proposition 1 give

$$\begin{aligned}\frac{1}{|\partial\mathcal{C}_\varepsilon\cap\Sigma_{12\varepsilon}|}\int_{\mathcal{C}_\varepsilon}\left(\frac{\partial\rho_{2\varepsilon}}{\partial t}-\Gamma_{2\varepsilon}\right)\mathrm{d}V &= -\Big(\mu_{1\varepsilon}\,\rho_{1\varepsilon}\nabla p_\varepsilon\cdot\mathbf{n}_{12}\Big)\Big|_{\mathbf{x}=\hat{\mathbf{x}}_{12\varepsilon}}\\ &\quad+\frac{|\partial\mathcal{C}_\varepsilon\cap\Sigma_{23\varepsilon}|}{|\partial\mathcal{C}_\varepsilon\cap\Sigma_{12\varepsilon}|}\Big(\mu_{2\varepsilon}\,\rho_{2\varepsilon}\,\nabla p_\varepsilon\cdot\mathbf{n}_{23}\Big)\Big|_{\mathbf{x}=\hat{\mathbf{x}}_{23\varepsilon}}\\ &\quad+\frac{1}{|\partial\mathcal{C}_\varepsilon\cap\Sigma_{12\varepsilon}|}\int_{\Sigma_{\ell\varepsilon}}\mu_{2\varepsilon}\,\rho_{2\varepsilon}\,\nabla p_\varepsilon\cdot\mathbf{n}_\ell\,\mathrm{d}\Sigma\,,\end{aligned}\tag{23}$$

where the points $\hat{\mathbf{x}}_{12\varepsilon}$ and $\hat{\mathbf{x}}_{23\varepsilon}$ belong, respectively, to the surfaces $\partial\mathcal{C}_\varepsilon\cap\Sigma_{12\varepsilon}$ and $\partial\mathcal{C}_\varepsilon\cap\Sigma_{23\varepsilon}$. Defining Π according to Eq. (21) and substituting $\nabla\Pi$ into the second term on the right-hand side of Eq. (23) yields

$$\begin{aligned}\frac{1}{|\partial\mathcal{C}_\varepsilon\cap\Sigma_{12\varepsilon}|}\int_{\mathcal{C}_\varepsilon}\left(\frac{\partial\rho_{2\varepsilon}}{\partial t}-\Gamma_{2\varepsilon}\right)\mathrm{d}V &= -\Big(\mu_{1\varepsilon}\,\rho_{1\varepsilon}\,\nabla p_\varepsilon\cdot\mathbf{n}_{12}\Big)\Big|_{\mathbf{x}=\hat{\mathbf{x}}_{12\varepsilon}}\\ &\quad+\frac{|\partial\mathcal{C}_\varepsilon\cap\Sigma_{23\varepsilon}|}{|\partial\mathcal{C}_\varepsilon\cap\Sigma_{12\varepsilon}|}\Big(\mu_{2\varepsilon}\,\nabla\Pi\cdot\mathbf{n}_{23}\Big)\Big|_{\mathbf{x}=\hat{\mathbf{x}}_{23\varepsilon}}\\ &\quad+\frac{1}{|\partial\mathcal{C}_\varepsilon\cap\Sigma_{12\varepsilon}|}\int_{\Sigma_{\ell\varepsilon}}\mu_{2\varepsilon}\,\rho_{2\varepsilon}\,\nabla p_\varepsilon\cdot\mathbf{n}_\ell\,\mathrm{d}\Sigma\,.\end{aligned}\tag{24}$$

For ε sufficiently small the normal derivative $\nabla\Pi(t,\hat{\mathbf{x}}_{23\varepsilon})\cdot\mathbf{n}_{23}$ can be approximated as

$$\nabla\Pi(t,\hat{\mathbf{x}}_{23\varepsilon})\cdot\mathbf{n}_{23}\approx\frac{\Pi(t,\hat{\mathbf{x}}_{23\varepsilon})-\Pi(t,\hat{\mathbf{x}}_{23\varepsilon}-\varepsilon\,\mathbf{n}_{23})}{\varepsilon}.\tag{25}$$

Using the approximation (25) we rewrite Eq. (24) in the following approximate form

$$\begin{aligned}\frac{1}{|\partial\mathcal{C}_\varepsilon\cap\Sigma_{12\varepsilon}|}\int_{\mathcal{C}_\varepsilon}\left(\frac{\partial\rho_{2\varepsilon}}{\partial t}-\Gamma_{2\varepsilon}\right)\mathrm{d}V &\approx \frac{1}{|\partial\mathcal{C}_\varepsilon\cap\Sigma_{12\varepsilon}|}\int_{\Sigma_{\ell\varepsilon}}\mu_{2\varepsilon}\,\rho_{2\varepsilon}\,\nabla p_\varepsilon\cdot\mathbf{n}_\ell\,\mathrm{d}\Sigma\\ &\quad-\Big(\mu_{1\varepsilon}\,\rho_{1\varepsilon}\nabla p_\varepsilon\cdot\mathbf{n}_{12}\Big)\Big|_{\mathbf{x}=\hat{\mathbf{x}}_{12\varepsilon}}\\ &\quad+\frac{|\partial\mathcal{C}_\varepsilon\cap\Sigma_{23\varepsilon}|}{|\partial\mathcal{C}_\varepsilon\cap\Sigma_{12\varepsilon}|}\,\frac{\mu_{2\varepsilon}(t,\hat{\mathbf{x}}_{23\varepsilon})}{\varepsilon}\\ &\quad\times\Big(\Pi(t,\hat{\mathbf{x}}_{23\varepsilon})-\Pi(t,\hat{\mathbf{x}}_{23\varepsilon}-\varepsilon\mathbf{n})\Big).\end{aligned}\tag{26}$$

Both the left-hand side and the first term on the right-hand side of Eq. (26) formally vanish when $\varepsilon\to 0$. Moreover, recalling the asymptotic relation (19) and noting that

$$\lim_{\varepsilon\to0}\hat{\mathbf{x}}_{12\varepsilon}=\lim_{\varepsilon\to0}\hat{\mathbf{x}}_{23\varepsilon}=\tilde{\mathbf{x}}_{13}\tag{27}$$

for some $\tilde{\mathbf{x}}_{13}\in\tilde{\Sigma}_{13}$, under assumption (13) we have that

$$\frac{\mu_{2\varepsilon}(t,\hat{\mathbf{x}}_{23\varepsilon})}{\varepsilon}\xrightarrow[\varepsilon\to0]{\mu_{2\varepsilon}(t,\hat{\mathbf{x}}_{23\varepsilon})\to0}\tilde{\mu}_{13}(t,\tilde{\mathbf{x}}_{13})\quad\text{with}\quad 0<\tilde{\mu}_{13}(t,\tilde{\mathbf{x}}_{13})<\infty,\qquad\text{for all } t\in\mathbb{R}_+.$$

Therefore, if

$$\rho_{1\varepsilon}\to\tilde{\rho}_1,\quad \rho_{3\varepsilon}\to\tilde{\rho}_3\quad\text{and}\quad p_\varepsilon\to\tilde{p}\quad\text{as }\varepsilon\to0,$$

letting both $\varepsilon\to0$ and $\mu_{2\varepsilon}(t,\hat{\mathbf{x}}_{23\varepsilon})\to0$ in such a way that assumption (13) is verified, from Eq. (26) we formally achieve the transmission condition

$$\tilde{\mu}_{13}\,[\![\Pi]\!]=\tilde{\mu}_1\,\tilde{\rho}_1\nabla\tilde{p}\cdot\tilde{\mathbf{n}}_{13}\qquad\text{on }\tilde{\Sigma}_{13},\tag{28}$$

where $\tilde{\mathbf{n}}_{13}$ is the unit vector normal to the effective interface $\tilde{\Sigma}_{13}$ that points towards the subdomain $\tilde{\mathcal{D}}_3$ and $\tilde{\mathbf{x}}_{13} \in \tilde{\Sigma}_{13}$. Moreover, combining the transmission condition (28) with the flux continuity condition (14) we find the transmission condition

$$\tilde{\mu}_{13}\,[\![\Pi]\!] = \tilde{\mu}_3\,\tilde{\rho}_3 \nabla\tilde{p}\,\cdot\,\tilde{\mathbf{n}}_{13} \qquad \text{on } \tilde{\Sigma}_{13}. \tag{29}$$

Finally, using the fact that $\mathcal{C}_\varepsilon$ can be chosen arbitrarily, from the transmission conditions (28) and (29) we obtain the transmission condition (20). □

Remark 4. *If the cell pressure is given by the barotropic relation*

$$p(\rho) := P \ln(\rho/\rho_0),$$

with P and ρ_0 being positive real numbers, then the partial differential equation for $\rho_{i\varepsilon}$ in the system of equations (8) *becomes a weakly nonlinear reaction-diffusion equation (*i.e. *with nonlinearity only in the reaction term) and*

$$\Pi = P\,\rho + C, \quad C \in \mathbb{R}.$$

A similar barotropic relation has been previously used, for instance, by Tang et al. [61]. In this case, the interface condition (20) *reduces to the classical Kedem-Katchalsky interface condition,* i.e.

$$\tilde{\mu}_{13}\,(\tilde{\rho}_3 - \tilde{\rho}_1) = \tilde{\mu}_1\,\nabla\tilde{\rho}_1 \cdot \tilde{\mathbf{n}}_{13} = \tilde{\mu}_3\,\nabla\tilde{\rho}_3 \cdot \tilde{\mathbf{n}}_{13}, \qquad \textit{on } \tilde{\Sigma}_{13}.$$

Taken together, the formal results established by Propositions 1 and 2 allow us to complete the effective interface problem $\mathcal{P}_0$ given by the system of equations (9) as follows

$$\mathcal{P}_0 \equiv \begin{cases} \dfrac{\partial\tilde{\rho}_1}{\partial t} - \nabla\cdot(\tilde{\mu}_1\,\tilde{\rho}_1\,\nabla\tilde{p}) = \tilde{\Gamma}_1 & \text{in } \tilde{\mathcal{D}}_1, \\ \dfrac{\partial\tilde{\rho}_3}{\partial t} - \nabla\cdot(\tilde{\mu}_3\,\tilde{\rho}_3\,\nabla\tilde{p}) = \tilde{\Gamma}_3 & \text{in } \tilde{\mathcal{D}}_3, \\ \tilde{\mu}_{13}[\![\Pi]\!] = \tilde{\mu}_1\,\tilde{\rho}_1\,\nabla\tilde{p}\cdot\tilde{\mathbf{n}}_{13} = \tilde{\mu}_3\,\tilde{\rho}_3\,\nabla\tilde{p}\cdot\tilde{\mathbf{n}}_{13} & \text{on } \tilde{\Sigma}_{13}. \end{cases} \tag{30}$$

Remark 5. *If $\tilde{\mu}_{13} \equiv 0$ then the thin membrane represented by the effective interface $\tilde{\Sigma}_{13}$ is impermeable and we recover no-flux boundary conditions on both sides of $\tilde{\Sigma}_{13}$, i.e. the cells in each subdomain are compartmentalised and cannot invade the other subdomain.*

4 Numerical results

The numerical solutions presented in this section illustrate the formal results established by Propositions 1 and 2, and show the potential application of these results.

In Section 4.1, we construct numerical solutions of a one-dimensional version of the thin layer problem $\mathcal{P}_\varepsilon$ for decreasing values of ε, and we compare the numerical solutions obtained with the numerical solutions of the corresponding effective interface problem $\mathcal{P}_0$. We show that the relative error between the numerical solutions to the two transmission problems tends to zero as $\varepsilon \to 0$.

In Section 4.2, we consider a two-dimensional model of cancer cell invasion through basement membrane. We assume the subdomains $\mathcal{D}_{1\varepsilon}$ and $\mathcal{D}_{3\varepsilon}$ to be initially occupied by cancer cells and healthy cells, respectively, and we let the subdomain $\mathcal{D}_{2\varepsilon}$ represent the basement membrane, which we assume to have thickness ε. The corresponding effective interface problem is such that the subdomains $\tilde{\mathcal{D}}_1$ and $\tilde{\mathcal{D}}_3$ are initially occupied by

cancer cells and healthy cells, respectively, and the basement membrane is represented by the effective interface $\tilde{\Sigma}_{13}$. Moreover, we assume the basement membrane to be partially damaged and thus permeable to cancer cells. We present a sample of numerical results indicating that the effective interface problem provides a good approximation of the original transmission problem for membranes of sufficiently small thickness.

In Section 4.3, we apply the results established by Proposition 1 and Proposition 2 to the mathematical modelling of cell invasion dynamics in ovarian carcinoma. Our numerical results show that a mathematical model relying on the interface conditions derived in Section 3 can qualitatively reproduce the key steps of the complex process leading ovarian cancer cells to spread through nearby normal tissues.

The numerical solutions presented here were obtained using the finite element software (FEM) COMSOL Multiphysics®, with the parallel sparse direct solver MUMPS. The method for constructing numerical solutions is based on the backward differentiation formula with an adaptive time-step. Computations were carried out with a refined mesh in the region about the interface.

4.1 Numerical solutions to a one-dimensional problem illustrating the results of Propositions 1 and 2

In order to illustrate the formal results established by Propositions 1 and 2, we construct numerical solutions to a one-dimensional thin layer problem $\mathcal{P}_\varepsilon$ of mobility $\mu_{2\varepsilon} = \varepsilon\,\bar{\mu}_2$, where $\bar{\mu}_2 > 0$. We compare the solutions obtained for decreasing values of ε with the numerical solutions to the corresponding effective interface problem $\mathcal{P}_0$ of effective mobility $\tilde{\mu}_{13} = \mu_{2\varepsilon}/\varepsilon \equiv \bar{\mu}_2$. Throughout this section we make use of the notation $\mathbf{x} = x$.

For the solutions to the thin layer problem $\mathcal{P}_\varepsilon$ to converge to stationary profiles that are nonconstant in x, we consider a somehow artificial scenario whereby the cells proliferate according to a logistic law with intrinsic growth rate $r_1 > 0$ in the subdomain $\mathcal{D}_{1\varepsilon}$ whereas cell proliferation is balanced by natural death in the subdomains $\mathcal{D}_{2\varepsilon}$ and $\mathcal{D}_{3\varepsilon}$. Under these assumptions, denoting by $L > 0$ the thickness of the region represented by the subdomain $\mathcal{D}_{1\varepsilon}$, we introduce the nondimensionalised independent variables $\hat{t} = r_1\,t$ and $\hat{x} = x/L$ so that, dropping the carets from the nondimensionalised quantities, we have

$$\mathcal{D}_{1\varepsilon} := (-1, 0), \quad \mathcal{D}_{2\varepsilon} := (0, \varepsilon), \quad \mathcal{D}_{3\varepsilon} := (\varepsilon, 1)$$

and

$$\Gamma_{1\varepsilon}(\rho_{1\varepsilon}) := (1 - \rho_{1\varepsilon})\,\rho_{1\varepsilon}, \quad \Gamma_{2\varepsilon}(\rho_{2\varepsilon}) = \Gamma_{3\varepsilon}(\rho_{3\varepsilon}) \equiv 0.$$

We assume the cell mobility coefficients in the subdomains $\mathcal{D}_{1\varepsilon}$ and $\mathcal{D}_{3\varepsilon}$ to have the same constant value, *i.e.*

$$\mu_{1\varepsilon} = \mu_{3\varepsilon} \equiv \bar{\mu} \quad \text{with} \quad \bar{\mu} > 0.$$

Moreover, we make use of the following barotropic relation

$$p(\rho) := (\rho - \rho_0)_+ \quad \text{with} \quad \rho_0 > 0, \tag{31}$$

where $(\cdot)_+$ is the positive part of $(\cdot)$. We impose zero Neumann boundary condition on the left outer boundary and a Dirichlet boundary condition on the right outer boundary.

Similarly, for the effective interface problem $\mathcal{P}_0$ we assume

$$\tilde{\mathcal{D}}_1 := (-1, 0), \quad \tilde{\mathcal{D}}_3 := (0, 1)$$

$$\tilde{\Gamma}_1(\tilde{\rho}_1) := (1 - \tilde{\rho}_1)\,\tilde{\rho}_1, \quad \tilde{\Gamma}_3(\rho_3) := 0, \quad \tilde{\mu}_1 = \tilde{\mu}_3 \equiv \bar{\mu}, \quad \tilde{\mu}_{13}(\mathbf{x}) \equiv \bar{\mu}_2.$$

Furthermore, we use the barotropic relation (31). We impose zero Neumann boundary condition on the left outer boundary and a Dirichlet boundary condition on the right outer boundary.

To construct numerical solutions we choose

$$\rho_0 = 0.5, \quad \bar{\mu} = 0.5 \quad \text{and} \quad \bar{\mu}_2 = 0.1. \tag{32}$$

Moreover, we use the following initial conditions for the thin layer problem

$$\rho_{i\varepsilon}(0, x) = \rho_0 \quad \text{for all } x \in \mathcal{D}_{i\varepsilon}, \quad i = 1, 2, 3$$

and the following initial conditions for the effective interface problem

$$\tilde{\rho}_i(0, x) = \rho_0 \quad \text{for all } x \in \tilde{\mathcal{D}}_i, \quad i = 1, 3.$$

These initial conditions model a biological scenario where the cells are initially uniformly distributed in space at the stress-free state. For this choice of the initial conditions, the assumptions made on the net growth rates guarantee that the cell volume fractions are larger than ρ_0 in all subdomains for all $t > 0$. Hence, the pressure p defined by the barotropic relation (31) is continuously differentiable in all subdomains. Finally, since numerical solutions appear to be stationary at $t = 20$, we carry out computational simulations for $t \in [0, 20]$.

The results obtained are summarised by the plots in Fig. 2, which display the numerical solutions to the effective interface problem $\mathcal{P}_0$ and the numerical solutions to the thin layer problem $\mathcal{P}_\varepsilon$ for decreasing values of ε at $t = 20$. The curves in Fig. 2(a) indicate that the discrepancy between the numerical solutions to the thin layer problem and the numerical solutions to the effective interface problem decreases as ε tends to zero. This is more precisely quantified by the curves in Fig. 2(b), which display the relative error between the numerical solutions to the thin layer problem at $x = 0$ and the numerical solutions to the effective interface problem at $x = 0^-$ for $t = 20$ as a function of ε (blue line), as well as the relative error between the numerical solutions to the thin layer problem at $x = \varepsilon$ and the numerical solutions to the effective interface problem at $x = 0^+$ for $t = 20$ as a function of ε (red line). In agreement with the formal results established by Propositions 1 and 2, both relative errors tend to zero as $\varepsilon \to 0$. Taken together, the numerical results presented in this section illustrate how, under assumption (13), there is a good match between the numerical solutions to the original transmission problem with membrane thickness ε and mobility $\mu_{2\varepsilon}$ and the numerical solutions to the limiting transmission problem with effective mobility $\tilde{\mu}_{13}$. Hence, when the thickness of the membrane represented by the subdomain $\mathcal{D}_{2\varepsilon}$ is small, instead of solving the problem $\mathcal{P}_\varepsilon$ we can solve the approximate problem $\mathcal{P}_0$ with effective mobility coefficient $\tilde{\mu}_{13}$. The quality of the approximation is higher for membranes of smaller thickness.

4.2 Numerical simulation of cancer cell invasion through basement membrane

In this section, we compare the numerical solutions of a thin layer problem modelling a two-dimensional cell invasion problem with the numerical solutions of the corresponding effective interface problem. We consider a biological scenario whereby proliferating cancer cells invade a normal tissue composed of healthy cells in homeostatic equilibrium (*i.e.* cells for which proliferation is balanced by natural death) by squeezing through a damaged part of the basement membrane. Under this biological scenario, we choose the spatial domains schematised in Fig. 3 to carry out numerical simulations. For the thin layer problem [*vid.* Fig. 3(a)], we let the subdomains $\mathcal{D}_{1\varepsilon}$ and $\mathcal{D}_{3\varepsilon}$ be separated by the basement membrane of thickness ε, which is represented by the subdomain $\mathcal{D}_{2\varepsilon}$ with boundaries $\Sigma_{12\varepsilon}$ and $\Sigma_{23\varepsilon}$. We identify the part of the membrane that is damaged, and thus permeable to cancer cells, with a subset $\mathcal{D}_p \subset \overline{\mathcal{D}}_{2\varepsilon}$. Similarly, for the effective interface problem [*vid.* Fig. 3(b)], we let the subdomains $\tilde{\mathcal{D}}_1$ and $\tilde{\mathcal{D}}_3$ be separated by the effective interface $\tilde{\Sigma}_{13}$. In this case, the damaged part of the basement membrane is represented by a set $\tilde{\Sigma}_p \subset \tilde{\Sigma}_{13}$. We assume that cancer cells initially occupy only the region of space on the left of the membrane, while healthy cells reside in the remaining part of the spatial domain. As detailed in the next subsections, we use a level set method [53] in order to track the evolution of the region of space occupied by cancer cells. Throughout this section we make use of the notation $\mathbf{x} = (x, y)$.

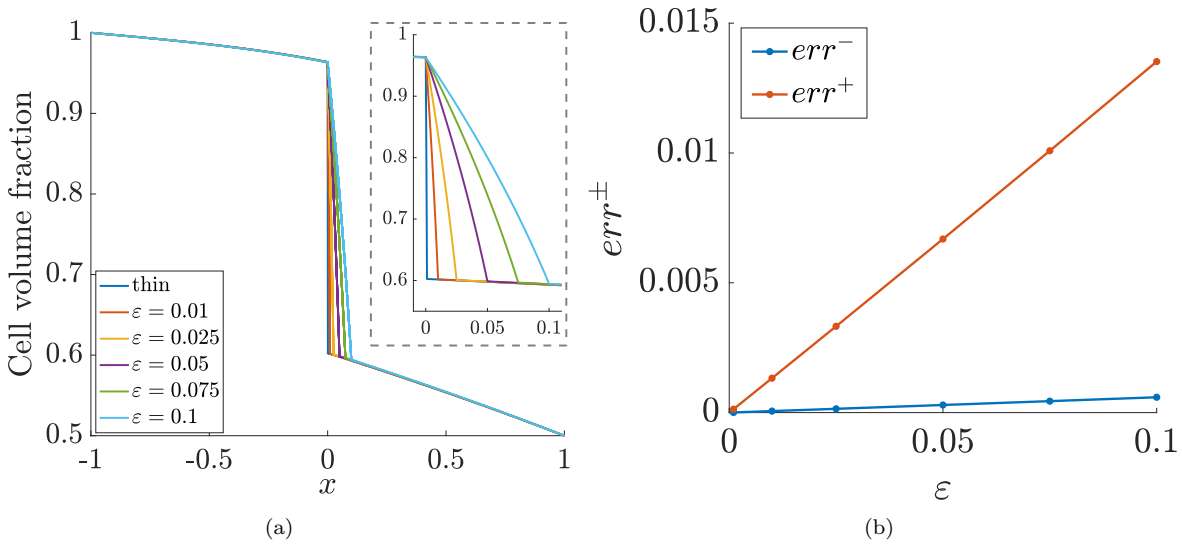


Figure 2: **Numerical solutions to a one-dimensional problem illustrating the results of Propositions 1 and 2. (a)** Comparison between the numerical solutions to the thin layer problem $\mathcal{P}_\varepsilon$ with thickness $\varepsilon = 0.01, 0.025, 0.05, 0.75, 0.1$ and mobility $\mu_{2\varepsilon} = \varepsilon\bar{\mu}_2$ and the numerical solutions to the corresponding effective interface problem $\mathcal{P}_0$ with effective mobility $\tilde{\mu}_{13} = \bar{\mu}_2$ at time $t = 20$. The time instant t is chosen such that the numerical solutions appear to be stationary at that time. **(b)** Relative error between the numerical solutions to the thin layer problem $\mathcal{P}_\varepsilon$ and the numerical solutions to the effective interface problem $\mathcal{P}_0$ as a function of ε at the time instant $t = 20$. The blue line displays the relative error $err^- = |\rho_{1\varepsilon}(20, 0) - \tilde{\rho}_1(20, 0^-)|/\tilde{\rho}_1(20, 0^-)$ while the red line displays the relative error $err^+ = |\rho_{3\varepsilon}(20, \varepsilon) - \tilde{\rho}_3(20, 0^+)|/\tilde{\rho}_3(20, 0^+)$.

4.2.1 Thin layer problem modelling cancer cell invasion through basement membrane

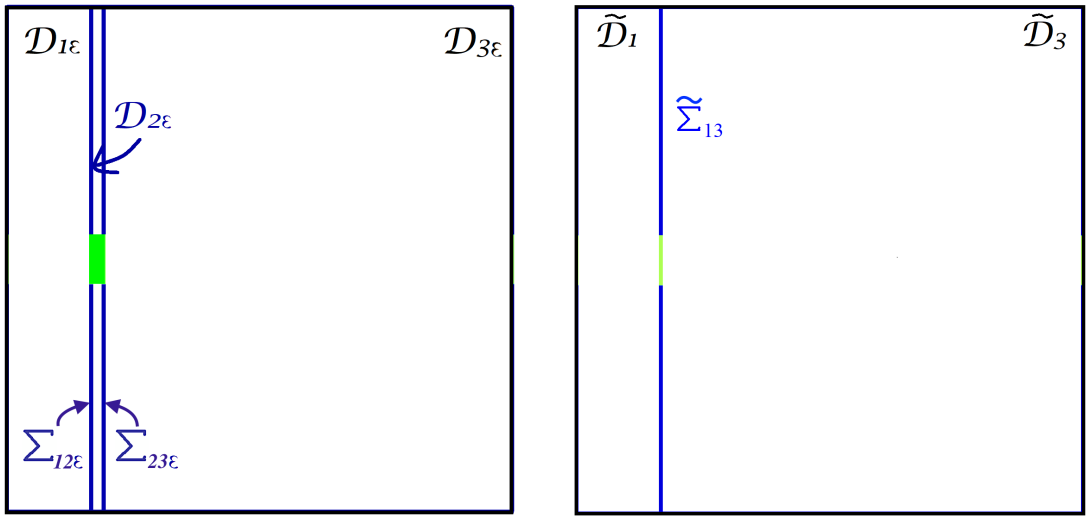
Let the function $\rho_{i\varepsilon}(t, \mathbf{x}) \geq 0$ model the cell volume fraction at position $\mathbf{x} \in \mathcal{D}_{i\varepsilon}$ and time $t \geq 0$. We describe the spatio-temporal evolution of the cells through the following system of equations

$$\begin{cases} \dfrac{\partial \rho_{i\varepsilon}}{\partial t} - \nabla \cdot (\mu_{i\varepsilon}\, \rho_{i\varepsilon}\, \nabla p_\varepsilon) = \Gamma_{i\varepsilon} & \text{in } \mathcal{D}_{i\varepsilon}, \quad i = 1, 2, 3, \\ \mu_{i\varepsilon}\, \rho_{i\varepsilon}\, \nabla p_\varepsilon \cdot \mathbf{n}_{ij} = \mu_{j\varepsilon}\, \rho_{j\varepsilon}\, \nabla p_\varepsilon \cdot \mathbf{n}_{ij} & \text{on } \Sigma_{ij\varepsilon}, \quad i = 1, 2, \quad j = i + 1, \\ [\![p_\varepsilon]\!] = 0 & \text{on } \Sigma_{ij\varepsilon}, \quad i = 1, 2, \quad j = i + 1. \end{cases} \tag{33}$$

In the system of equations (33), the function $\varphi \equiv \varphi(t, \mathbf{x})$ is an auxiliary level set function that tracks the region of space occupied by cancer cells. At any time instant $t \geq 0$, if $\varphi(t, \mathbf{x}) > 0$ then the point $\mathbf{x}$ is occupied by cancer cells, whereas if $\varphi(t, \mathbf{x}) \leq 0$ then the point $\mathbf{x}$ is occupied by healthy cells. Hence, the zero level set of the function $\varphi(t, \mathbf{x})$ corresponds to the boundary of the tumour region at time t. The evolution of the function $\varphi(t, \mathbf{x})$ is governed by the following Hamilton-Jacobi equation [53]

$$\frac{\partial \varphi}{\partial t} + \mathbf{v} \cdot \nabla \varphi = 0 \ \text{ in } \ \mathcal{D}_{1\varepsilon} \cup \mathcal{D}_{2\varepsilon} \cup \mathcal{D}_{3\varepsilon} \quad \text{with } \ \mathbf{v} = -\mu_{i\varepsilon} \nabla p \ \text{ in } \ \mathcal{D}_{i\varepsilon} \tag{34}$$

for $i = 1, 2, 3$. We impose the continuity of the level set function φ across the interfaces $\Sigma_{12\varepsilon}$ and $\Sigma_{23\varepsilon}$. Notice that the transmission conditions $(33)_2$ ensure the continuity of the normal velocity across the interfaces $\Sigma_{12\varepsilon}$



(a) (b)

Figure 3: **Spatial domain used in the numerical simulation of cancer cell invasion through basement membrane. (a)** Spatial domain for the thin layer problem. The subdomains $\mathcal{D}_{1\varepsilon}$ and $\mathcal{D}_{3\varepsilon}$ are separated by the basement membrane of thickness ε, which is represented by the subdomain $\mathcal{D}_{2\varepsilon}$. The region highlighted in green (*i.e.* the set $\mathcal{D}_p \subset \overline{\mathcal{D}}_{2\varepsilon}$) is assumed to be damaged and thus permeable to cancer cells. **(b)** Spatial domain for the effective interface problem. The subdomains $\tilde{\mathcal{D}}_1$ and $\tilde{\mathcal{D}}_3$ are separated by the effective interface $\tilde{\Sigma}_{13}$. The region highlighted in green (*i.e.* the set $\tilde{\Sigma}_p \subset \tilde{\Sigma}_{13}$) is assumed to be damaged and thus permeable to cancer cells.

and $\Sigma_{23\varepsilon}$.

In order to construct numerical solutions for the thin layer problem (33), we focus on a biological scenario whereby cancer cells proliferate according to a logistic law with intrinsic growth rate $r > 0$ in the subdomains $\mathcal{D}_{1\varepsilon}$, $\mathcal{D}_{2\varepsilon}$ and $\mathcal{D}_{3\varepsilon}$. Under this assumption, denoting by $L > 0$ the thickness of the region represented by the subdomain $\mathcal{D}_{1\varepsilon}$, we introduce the nondimensionalised independent variables $\hat{t} = r\,t$ and $\hat{\mathbf{x}} = \mathbf{x}/L$ so that, dropping the carets from the nondimensionalised quantities, we have

$$\mathcal{D}_{1\varepsilon} := (-1, 0) \times (-3, 3), \quad \mathcal{D}_{2\varepsilon} := (0, \varepsilon) \times (-3, 3), \quad \mathcal{D}_3 := (\varepsilon, 5) \times (-3, 3)$$

and

$$\Gamma_{i\varepsilon}(\rho_{i\varepsilon}, \varphi) := (1 - \rho_{i\varepsilon})\, \rho_{i\varepsilon}\, H(\varphi), \quad \text{for} \quad i = 1, 2, 3.$$

In the definition of the net growth rate $\Gamma_{i\varepsilon}$, the term $H(\cdot)$ stands for the Heaviside step function. Moreover, we assume the cell mobility coefficients in the subdomains $\mathcal{D}_{1\varepsilon}$ and $\mathcal{D}_{3\varepsilon}$ to have the same constant value, *i.e.*

$$\mu_{1\varepsilon} = \mu_{3\varepsilon} \equiv \bar{\mu} \quad \text{with} \quad \bar{\mu} > 0,$$

and we define the mobility coefficient in the subdomain $\mathcal{D}_{2\varepsilon}$ as

$$\mu_{2\varepsilon}(\mathbf{x}) := \varepsilon\, \bar{\mu}_2\, \mathbf{1}_{\mathcal{D}_p}(\mathbf{x}) \quad \text{with} \quad \bar{\mu}_2 > 0$$

where the term $\mathbf{1}_{\mathcal{D}_p}(\mathbf{x})$ is a mollification of the indicator function of the set $\mathcal{D}_p \subset \overline{\mathcal{D}}_{2\varepsilon}$. Finally, we use the barotropic relation (31). We impose zero Neumann boundary condition both on the left outer boundary and

on the upper and lower boundaries, whereas a Dirichlet boundary condition is prescribed on the right outer boundary. We assume that the cells are uniformly distributed across the spatial domain at $t = 0$, that is, we impose the following initial conditions

$$\rho_{i\varepsilon}(0, \mathbf{x}) = \rho_0 > 0 \quad \text{for all } \mathbf{x} \in \mathcal{D}_{i\varepsilon}, \quad \text{with } \ i = 1, 2, 3.$$

We use the parameter values given by Eq. (32) and define $\varphi(0, x, \cdot) = -x$ so that $H(\varphi(0, x, y)) = 1$ only if $(x, y) \in \mathcal{D}_{1\varepsilon}$, *i.e.* we consider a biological scenario whereby cancer cells are initially confined to the subdomain $\mathcal{D}_{1\varepsilon}$ and healthy cells occupy the rest of the spatial domain.

4.2.2 Effective interface problem modelling cancer invasion through basement membrane

The effective interface problem corresponding to the thin layer problem (33) reads as

$$\begin{cases} \dfrac{\partial \tilde{\rho}_1}{\partial t} - \nabla \cdot (\tilde{\mu}_1 \, \tilde{\rho}_1 \, \nabla \tilde{p}) = \tilde{\Gamma}_1 & \text{in } \tilde{\mathcal{D}}_1, \\ \dfrac{\partial \tilde{\rho}_3}{\partial t} - \nabla \cdot (\tilde{\mu}_3 \, \tilde{\rho}_3 \, \nabla \tilde{p}) = \tilde{\Gamma}_3 & \text{in } \tilde{\mathcal{D}}_3, \\ \tilde{\mu}_{13} \, [\![\Pi]\!] = \tilde{\mu}_1 \, \tilde{\rho}_1 \, \nabla \tilde{p} \cdot \tilde{\mathbf{n}}_{13} = \tilde{\mu}_3 \, \tilde{\rho}_3 \, \nabla \tilde{p} \cdot \tilde{\mathbf{n}}_{13} & \text{on } \tilde{\Sigma}_{13}. \end{cases} \tag{35}$$

As for the thin layer problem, the function $\tilde{\varphi}(t, \mathbf{x})$ is the level set function tracking the region of space occupied by cancer cells, the evolution of which is governed by the following Hamilton-Jacobi equation [53]

$$\frac{\partial \tilde{\varphi}}{\partial t} + \mathbf{v} \cdot \nabla \tilde{\varphi} = 0 \ \text{ in } \ \tilde{\mathcal{D}}_1 \cup \tilde{\mathcal{D}}_3 \quad \text{with } \ \mathbf{v} = -\tilde{\mu}_i \nabla p \ \text{ in } \ \tilde{\mathcal{D}}_i \ \text{ for } \ i = 1, 3. \tag{36}$$

We impose the continuity of the level set function $\tilde{\varphi}$ across the interface $\tilde{\Sigma}_{13}$.

We use the barotropic relation (31). Moreover, we choose subdomains, net growth rates, parameter values, boundary conditions and initial conditions corresponding to those of the thin layer problem. In particular, we define

$$\tilde{\mathcal{D}}_1 := (-1, 0) \times (-3, 3), \quad \tilde{\mathcal{D}}_3 := (0, 5) \times (-3, 3),$$
$$\tilde{\Gamma}_1(\tilde{\rho}_1, \varphi) := (1 - \tilde{\rho}_1) \, \tilde{\rho}_1 \, H(\tilde{\varphi}), \quad \tilde{\Gamma}_3(\rho_3) := (1 - \tilde{\rho}_3) \, \tilde{\rho}_3 H(\tilde{\varphi}),$$

and

$$\tilde{\mu}_1 = \tilde{\mu}_3 \equiv \bar{\mu}, \quad \tilde{\mu}_{13} := \bar{\mu}_2 \, \mathbf{1}_{\tilde{\Sigma}_p}(\mathbf{x}).$$

Finally, we choose the following initial conditions

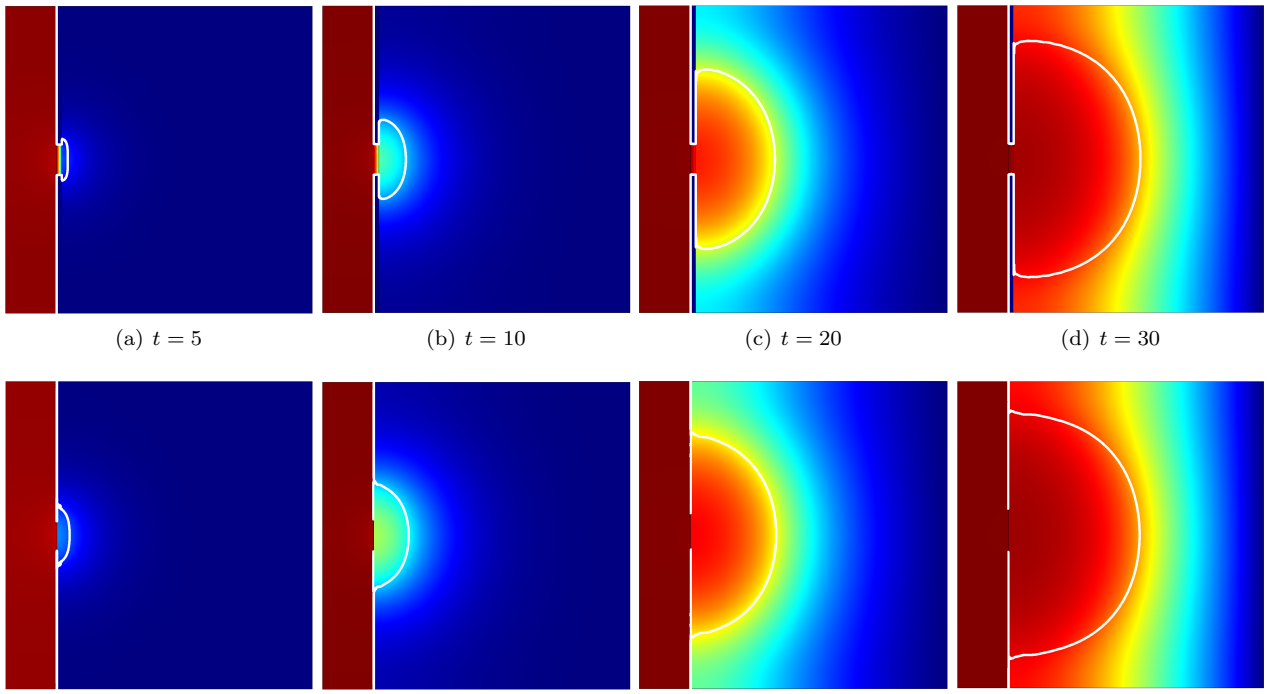
$$\tilde{\rho}_i(0, \mathbf{x}) = \rho_0 > 0 \quad \text{for all } \mathbf{x} \in \tilde{\mathcal{D}}_i, \quad \text{with } \ i = 1, 3, \tag{37}$$

and we define $\tilde{\varphi}(0, x, \cdot) = -x$ so that $H(\tilde{\varphi}(0, x, y)) = 1$ only if $(x, y) \in \tilde{\mathcal{D}}_1$.

4.2.3 Comparison between numerical solutions to the thin layer problem and numerical solutions to the effective interface problem

The results obtained are summarised by the plots in Fig. 4. The plots on the top line display the numerical solutions to the thin layer problem (33) with $\varepsilon = 0.1$ at different time instants. The numerical solutions to the effective interface problem (35) at the same time instants are displayed in the plots on the bottom line. The discrepancy between the solutions to the thin layer problem and the solutions to the effective interface

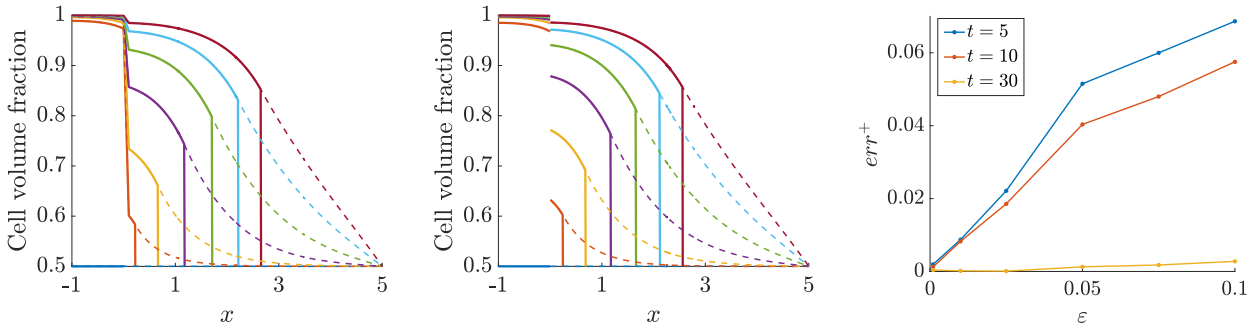
problem decays over time as the invasion front of cancer cells moves away from the basement membrane, which is represented either by the subdomain $\mathcal{D}_{2\varepsilon}$ or by the effective interface $\tilde{\Sigma}_{13}$. This is made clearer by the plots in Fig. 5(a) and Fig. 5(b). The curves in Fig. 5(a) summarise the spatio-temporal evolution of the volume fraction of cancer cells $\rho_{i\varepsilon}(t,x,0)\,H(\varphi(t,x,0))$ (solid lines) and the volume fraction of healthy cells $\rho_{i\varepsilon}(t,x,0)\,(1-H(\varphi(t,x,0)))$ (dashed lines) for the thin layer problem, with $i=1,2,3$. Similarly, the curves in Fig. 5(b) summarise the spatio-temporal evolution of the volume fraction of cancer cells $\tilde{\rho}_i(t,x,0)\,H(\tilde{\varphi}(t,x,0))$ (solid lines) and the volume fraction of healthy cells $\tilde{\rho}_i(t,x,0)\,(1-H(\tilde{\varphi}(t,x,0)))$ (dashed lines) for the effective interface problem, with $i=1,3$. Accordingly, the curves reported in Fig. 5(c) indicate that the relative error between the numerical solutions to the thin layer problem at the point $(\varepsilon,0)$ and the numerical solutions to the effective interface problem at the point $(0^+,0)$ decays over time. Notice that the relative error is larger for smaller time instants due to the fact that the initial conditions for the two problems are different. Moreover, in agreement with the formal results established by Propositions 1 and 2, the relative error tends to zero as $\varepsilon \to 0$. The relative error at the point $(0^-,0)$ is not reported as it was smaller than 5×10^{-3} for all $t>0$ and for all values of ε considered.



(a) $t=5$ (b) $t=10$ (c) $t=20$ (d) $t=30$

(e) $t=5$ (f) $t=10$ (g) $t=20$ (h) $t=30$

Figure 4: **Numerical simulation of cancer cell invasion through basement membrane. (a)-(d)** Numerical solutions to the thin layer problem (33) with $\varepsilon=0.1$. The different panels display the cell volume fractions $\rho_{1\varepsilon}(t,\mathbf{x})$, $\rho_{2\varepsilon}(t,\mathbf{x})$ and $\rho_{3\varepsilon}(t,\mathbf{x})$ at successive nondimensionalised time instants. **(e)-(h)** Numerical solutions to the effective interface problem (35). The different panels display the cell volume fractions $\tilde{\rho}_1(t,\mathbf{x})$ and $\tilde{\rho}_3(t,\mathbf{x})$ at successive nondimensionalised time instants. The colour scale ranges from blue (corresponding to the value 0.5) to red (corresponding to the value 1). The white curves are isolines that track the region of space occupied by cancer cells.



(a) $t = 0, 5, 10, 15, 20, 25, 30$ (b) $t = 0, 5, 10, 15, 20, 25, 30$ (c)

Figure 5: **Numerical simulation of cancer cell invasion through basement membrane. (a)** Spatio-temporal evolution of the volume fractions of cancer cells $\rho_{1\varepsilon}(t,x,0)\,H(\varphi(t,x,0))$, $\rho_{2\varepsilon}(t,x,0)\,H(\varphi(t,x,0))$ and $\rho_{3\varepsilon}(t,x,0)\,H(\varphi(t,x,0))$ (solid lines) and the volume fractions of healthy cells $\rho_{1\varepsilon}(t,x,0)\,(1-H(\varphi(t,x,0)))$, $\rho_{2\varepsilon}(t,x,0)\,(1-H(\varphi(t,x,0)))$ and $\rho_{3\varepsilon}(t,x,0)\,(1-H(\varphi(t,x,0)))$ (dashed lines) for the thin layer problem (33). **(b)** Spatio-temporal evolution of the volume fractions of cancer cells $\tilde{\rho}_1(t,x,0)\,H(\tilde{\varphi}(t,x,0))$ and $\tilde{\rho}_3(t,x,0)\,H(\tilde{\varphi}(t,x,0))$ (solid lines) and the volume fractions of healthy cells $\tilde{\rho}_1(t,x,0)\,(1-H(\tilde{\varphi}(t,x,0)))$ and $\tilde{\rho}_3(t,x,0)\,(1-H(\tilde{\varphi}(t,x,0)))$ (dashed lines) for the effective interface problem (35). **(c)** Relative error between the numerical solutions to the thin layer problem at the point $(\varepsilon,0)$ and the numerical solutions to the effective interface problem at the point $(0^+,0)$ (*i.e.* the quantity $err^+ = |\rho_{3\varepsilon}(t,\varepsilon,0) - \tilde{\rho}_3(t,0^+,0)|/\tilde{\rho}_3(t,0^+,0))$ as a function of ε, at time $t = 5$, $t = 10$ and $t = 30$.

4.3 Numerical simulation of ovarian cancer invasion

In this section, we apply the formal results established by Propositions 1 and 2 to the mathematical modelling of cell invasion dynamics in ovarian carcinoma. In particular, we simulate the metastatic journey of a cancer multicellular mass, from the initial growth inside the ovary to the invasion of the healthy tissue adjacent to the peritoneum. For the sake of brevity, in this section we will drop the tildes from all quantities.

4.3.1 Biological background

Ovarian carcinoma originates either on the surface of the ovary or in the fallopian tube. This type of cancer is known to invade the surrounding tissues and to metastasise both by direct extension and by cell detachment from the primary tumour [42]. The latter process of metastasis formation is peculiar to ovarian carcinoma and allows cancer cells to spread into the peritoneal cavity, to invade adjacent peritoneal tissues and, ultimately, to reach distant organs. Such a process encompasses multiple layers of complexity, which represents one of the main reasons why the metastatic behaviour of ovarian cancer cells remains poorly understood.

The detachment of ovarian cancer cells from the primary tumour starts with the destruction of the basement membrane underling the ovarian capsule (*i.e.* the ovarian surface epithelium) [3]. Cancer cells can subsequently break through the ovarian capsule as single cells or, more frequently, as spheroid-like aggregates. Such multicellular masses grow and passively move until they reach the walls of the peritoneal cavity – which represent the common site of disaggregation, dissemination and metastatic outgrowth for ovarian carcinoma [29].

The ovarian carcinoma cells that reach the walls of the cavity can attach to the mesothelial cells that constitute the peritoneal lining and, by secreting MMPs [42], they can degrade the basement membrane underling the

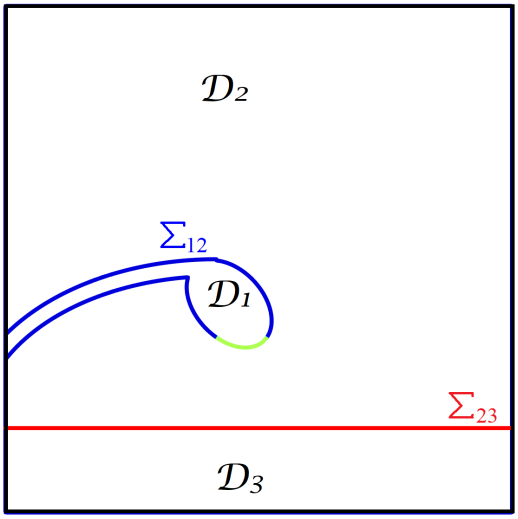


Figure 6: **Spatial domain used in the numerical simulation of ovarian cancer invasion.** The subdomain $\mathcal{D}_1$ corresponds to the ovary, the subdomain $\mathcal{D}_2$ represents the peritoneal cavity and the subdomain $\mathcal{D}_3$ stands for the healthy tissue adjacent to the peritoneum. The effective interfaces Σ_{12} and Σ_{23} represent, respectively, the ovarian capsule and the peritoneal lining. The part of the ovarian capsule highlighted in green (*i.e.* $\Sigma_p \subset \Sigma_{12}$) is assumed to be damaged and thus permeable to cancer cells.

mesothelium and cleave cell-cell adhesion molecules (*e.g.* N-cadherins) that hold mesothelial cells together [42]. This leads to the retraction of mesothelial cells at the cancer cells' attachment sites and brings about the formation of foci of invasion, which enable the ovarian cancer cells to invade the healthy tissue adjacent to the peritoneum and form secondary tumours [29].

4.3.2 Mathematical model

In adult human females, the ovarian capsule consists of a single layer of epithelial cells and the peritoneal lining is constituted by a monolayer of mesothelial cells [3]. Hence, the thickness of the ovarian capsule and the peritoneal lining is small compared to the characteristic size of the ovary and of the peritoneal cavity. For this reason, we represent both the ovarian capsule and the peritoneal lining, along with the underling basement membranes, as two thin porous membranes. Moreover, using the formal results established by Proposition 1 and Proposition 2, we model each thin porous membrane as an effective interface.

On the basis of these observations, considering a two-dimensional scenario, we represent the ovary, the peritoneal cavity and the healthy tissue adjacent to the peritoneum as three distinct spatial subdomains $\mathcal{D}_1$, $\mathcal{D}_2$ and $\mathcal{D}_3$ separated by the effective interfaces Σ_{12} (*i.e.* the ovarian capsule along with the underlying basement membrane) and Σ_{23} (*i.e.* the peritoneal lining along with the underlying basement membrane) – *cf.* respectively, the blue curve and the red line in Fig. 6. We focus on the biological scenario whereby there is a part of the ovarian capsule that is damaged and thus permeable to cancer cells. We identify such a region with a subset Σ_p of the effective interface Σ_{12} (*cf.* the green line in Fig. 6).

Letting the function $\rho_i(t, \mathbf{x}) \geq 0$ model the cell volume fraction at position $\mathbf{x} \in \mathcal{D}_i$ and time $t \geq 0$, we describe

the spatio-temporal evolution of the cells through the following system of equations

$$\begin{cases} \dfrac{\partial \rho_i}{\partial t} - \nabla \cdot (\mu_i \, \rho_i \, \nabla p) = \Gamma_i & \text{in } \mathcal{D}_i, \ i = 1, 2, 3, \\ \mu_{ij} [\![\Pi]\!] = \mu_i \rho_i \nabla p \cdot \mathbf{n}_{ij} = \mu_j \rho_j \nabla p \cdot \mathbf{n}_{ij} & \text{on } \Sigma_{ij}, \ i = 1, 2, \ j = i + 1. \end{cases} \tag{38}$$

Similarly to Section 4.2, the function $\varphi(t, \mathbf{x})$ is an auxiliary level set function that tracks the region of space occupied by ovarian cancer cells. At any time instant $t \geq 0$, if $\varphi(t, \mathbf{x}) > 0$ then the point $\mathbf{x}$ is occupied by cancer cells, whereas if $\varphi(t, \mathbf{x}) \leq 0$ then the point $\mathbf{x}$ is occupied by healthy cells. Hence, the zero level set of the function $\varphi(t, \mathbf{x})$ corresponds to the boundary of the tumour region at time t. The evolution of the function $\varphi(t, \mathbf{x})$ is governed by the following Hamilton-Jacobi equation [53]

$$\frac{\partial \varphi}{\partial t} + \mathbf{v} \cdot \nabla \varphi = 0 \,, \quad (t, \mathbf{x}) \in \mathbb{R}_+ \times \mathcal{D}_1 \cup \mathcal{D}_2 \cup \mathcal{D}_3 \quad \text{with} \ \ \mathbf{v} = -\mu_i \nabla p \ \ \text{in} \ \ \mathcal{D}_i, \tag{39}$$

for $i = 1, 2, 3$, and we impose the continuity of the function φ across the effective interfaces Σ_{12} and Σ_{23}.

We make the prima facie assumption that the effective mobility coefficient μ_{12} is a given function of x and does not depend on t. On the other hand, on the basis of the biological facts discussed in Section 4.3.1, we let the effective mobility coefficient μ_{23} be a function of the local concentration of MMPs, $c(t, \mathbf{x}) \geq 0$, which can vary across space and time. In particular, using a modelling strategy similar to that proposed by Gallinato *et al.* [25] and Giverso *et al.* [27], we use the following definition

$$\mu_{23}(t, \mathbf{x}) := \bar{\mu}_{23} \frac{(A(t, \mathbf{x}) - A_0)_+}{B + (A(t, \mathbf{x}) - A_0)} \,, \tag{40}$$

where $\bar{\mu}_{23} > 0$ is the maximum mobility of ovarian cancer cells through the interface that models the peritoneal lining, the function $A(t, \mathbf{x}) > 0$ represents the average cross-section of the pores of the membrane at position $\mathbf{x} \in \Sigma_{23}$ and time $t \geq 0$, and the parameter $A_0 > 0$ stands for the critical value of the average pores' cross-section below which, according to the physical limit of migration [64], the membrane is completely impermeable to cancer cells. The evolution of the function $A(t, \mathbf{x})$ is governed by the following differential equation

$$\frac{\partial A}{\partial t} = \alpha \, (A_1 - A) + \beta \, c \qquad \text{on } \Sigma_{23}. \tag{41}$$

In Eq. (41), the parameter $A_1 > 0$, with $A_1 < A_0$, stands for the nondimensionalised average cross-section of the pores of the membrane in normal conditions (*i.e.* when $c \equiv 0$), α is the rate of remodelling of A to the normal value A_1, and $\beta > 0$ represents the rate at which MMPs increase the size of the pores of the membrane. Under the biologically realistic assumption that the process of pore cleavage and repairing is much faster than tumour expansion, we assume the average cross-section of the pores of the membrane to be in quasi-stationary equilibrium and rewrite Eq. (41) as

$$0 = \alpha \, (A_1 - A(t, \mathbf{x})) + \beta \, c(t, \mathbf{x}) \quad \Longrightarrow \quad A(t, \mathbf{x}) = A_1 + \frac{\beta}{\alpha} \, c(t, \mathbf{x}).$$

Substituting the above expression for $A(t, \mathbf{x})$ into the definition (40) and rearranging terms gives

$$\mu_{23}(t, \mathbf{x}) \equiv \mu_{23}(\hat{c}(t, \mathbf{x})) = \bar{\mu}_{23} \frac{(\hat{c}(t, \mathbf{x}) - 1)_+}{K_c + (\hat{c}(t, \mathbf{x}) - 1)} \,, \tag{42}$$

with

$$\hat{c}(t, \mathbf{x}) = \frac{\beta}{\alpha(A_0 - A_1)} \, c(t, \mathbf{x}) \quad \text{and} \quad K_c = \frac{B}{A_0 - A_1} \,.$$

In the reminder of this section, we will make use of the definition (42) and, with a slight abuse of notation, we will rename the rescaled concentration of MMPs $\hat{c}(t,\mathbf{x})$ to $c(t,\mathbf{x})$.

Denoting the restriction of the function c to the subdomain $\mathcal{D}_i$ by c_i, we describe the dynamics of the concentration of MMPs through the following system of equations

$$\begin{cases} \dfrac{\partial c_i}{\partial t} = \gamma_c\,\rho_i\,H(\varphi) + D_c\,\Delta c_i & \text{in } \mathcal{D}_i, \quad i=1,2,3, \\ D_c\,\nabla c_i\cdot\mathbf{n}_{ij} = D_c\,\nabla c_j\cdot\mathbf{n}_{ij} & \text{on } \Sigma_{ij}, \quad i=1,2, \quad j=i+1, \\ [\![c]\!] = 0 & \text{on } \Sigma_{ij}, \quad i=1,2, \quad j=i+1. \end{cases} \tag{43}$$

In the system of equations (43), the parameter $\gamma_c > 0$ stands for the rate at which cancer cells release MMPs and the parameter $D_c > 0$ is the diffusivity of MMPs. Notice that the transmission conditions in the system of equations (43) are such that the MMP concentration $c(t,\mathbf{x})$ and its flux are continuous across the effective interfaces Σ_{12} and Σ_{23}. This is because the size of the MMP molecules is smaller than the size of the pores of the membranes (*i.e.* the membranes are permeable to the MMP molecules). Alternatively, one could impose the classical Kedem-Katchalsky interface conditions on Σ_{12} and Σ_{23}.

4.3.3 Numerical solutions

In order to construct numerical solutions, we assume ovarian cancer cells to proliferate according to a logistic law with intrinsic growth rate $r > 0$ in all subdomains. Under this assumption, denoting by L the thickness of the region represented by the subdomain $\mathcal{D}_3$, we introduce the rescaled independent variables $\hat{t} = r\,t$ and $\hat{\mathbf{x}} = \mathbf{x}/L$ and then we drop the carets from the nondimensionalised quantities. We define

$$\Gamma_i(\rho_i,\varphi) := (1-\rho_i)\,\rho_i\,H(\varphi), \quad i=1,2,3$$

and we let the mobility coefficients in the three subdomains have the same constant value, *i.e.* we assume

$$\mu_1 = \mu_2 = \mu_3 \equiv \bar{\mu} \quad \text{with} \quad \bar{\mu} > 0.$$

We define the equivalent cell mobility coefficient μ_{12} as

$$\mu_{12}(\mathbf{x}) := \bar{\mu}_{12}\,\mathbf{1}_{\Sigma_p}(\mathbf{x}) \quad \text{with} \quad \bar{\mu}_{12} > 0, \tag{44}$$

where $\mathbf{1}_{\Sigma_p}(\mathbf{x})$ stands for a mollification of the indicator function of the set $\Sigma_p \subset \Sigma_{12}$. We use of the barotropic relation (31). Finally, we close the system of equations (38) and (43) coupled with Eq. (39) by imposing the following initial conditions

$$\rho_1(0,\mathbf{x}) \equiv \rho_0, \quad \rho_2(0,\mathbf{x}) \equiv \rho_0, \quad \rho_3(0,\mathbf{x}) \equiv \rho_0, \tag{45}$$

$$c(0,\mathbf{x}) \equiv 0, \quad \varphi(0,\mathbf{x}) = -1 + 2\,e^{\frac{|\mathbf{x}-\mathbf{x}_0|^2}{b}} \tag{46}$$

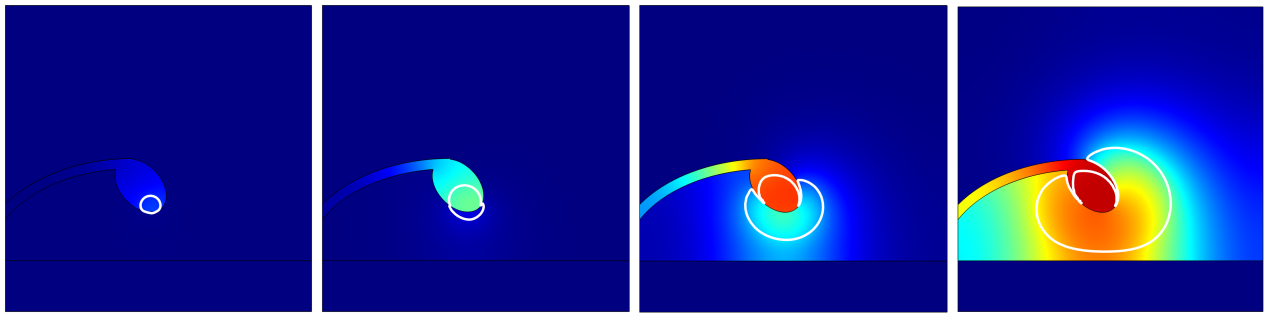
along with zero Neumann boundary conditions on the outer boundaries of the subdomains for all dependent variables. The initial conditions (45) model a biological scenario whereby cancer cells are initially confined to a circular region of the ovary centred at the point $\mathbf{x}_0$, while healthy cells occupy the rest of the spatial domain, and no MMPs are initially present.

We carry out numerical simulations using the following parameter values

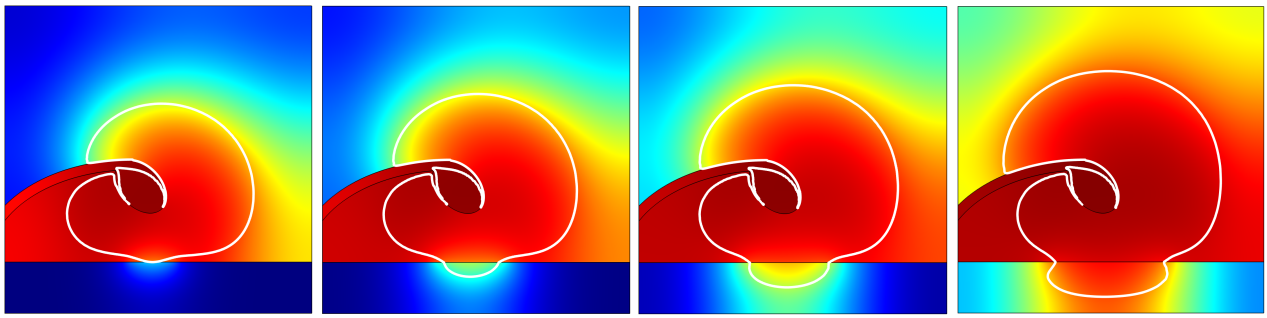
$$\rho_0 = 0.5, \quad \bar{\mu} = 0.5, \quad \bar{\mu}_{12} = 0.1, \quad \bar{\mu}_{23} = 1, \quad \mathbf{x}_0 = (-0.13, 1.04), \quad b = 0.01,$$

$$K_c = 0.2, \quad D_c = 0.005, \quad \gamma_c = 0.5.$$

As illustrated by the numerical results shown in Fig. 7, which display the cell volume fraction in the different subdomains along with the boundaries of the cancer multicellular mass (white lines), the mathematical model defined by the systems of equations (38) and (43) can qualitatively reproduce the salient steps of the metastatic journey undertaken by an ovarian cancer multicellular mass. In summary, cancer cells are initially confined



(a) $t = 4$ (b) $t = 8$ (c) $t = 14$ (d) $t = 20$



(e) $t = 28$ (f) $t = 30$ (g) $t = 32$ (h) $t = 36$

Figure 7: **Numerical simulation of ovarian cancer invasion.** Numerical solutions to the transmission problem defined by the system of equations (38) and (43) complemented with the initial conditions (45) and zero Neumann boundary conditions. The different panels display the cell volume fractions $\rho_1(t, \mathbf{x})$, $\rho_2(t, \mathbf{x})$ and $\rho_3(t, \mathbf{x})$ at successive nondimensionalised time instants. The colour scale ranges from blue (corresponding to the value 0.5) to red (corresponding to the value 1). The black lines highlight the boundaries of the subdomains $\mathcal{D}_1$, $\mathcal{D}_2$ and $\mathcal{D}_3$, as well as the effective interfaces Σ_{12} and Σ_{23}. The white curves are isolines that track the region of space occupied by the cancer multicellular mass.

to the ovary region $\mathcal{D}_1$ [*vid.* Fig. 7(a)], where they proliferate and grow into a multicellular mass. At later stages [*vid.* Figs. 7(b)-7(d)], cancer cells break through the damaged part of the ovarian capsule $\Sigma_p \subset \Sigma_{12}$ and spread across the peritoneal region $\mathcal{D}_2$, until they reach the peritoneal lining Σ_{23}. From there, secreting MMPs, cancer cells create one focus of invasion [*vid.* Fig. 7(e)], which enables the multicellular mass to squeeze through the peritoneal lining and form a secondary tumour in the healthy tissue adjacent to the peritoneum $\mathcal{D}_3$ – *vid.* Figs. 7(f)-7(h).

Notice that the plots in Figs. 7(e)-7(h) indicate that the size of the focus of invasion grows over time. This is due to the diffusion of MMPs secreted by cancer cells, which increase the local value of the effective mobility

coefficient $\mu_{23}(t, \mathbf{x})$ [*cf.* the definition (42)]. Moreover, throughout the simulations one can verify that the cell volume fractions can become discontinuous not only in the portions of the ovarian capsule and of the peritoneal lining that are impermeable, but also in the permeable part of the ovarian capsule and at the focus of invasion in the peritoneal lining.

5 Conclusions and research perspectives

Working in a continuum mechanics framework, we developed a formal asymptotic method to mathematically address biological problems of cell invasion through thin membranes (*i.e.* the basement membrane and other ECM barriers of small thickness). In particular, we showed how, starting from an original transmission problem in which thin membranes are represented as finite regions of small thickness, one can obtain a limiting transmission problem where each membrane is replaced by an effective interface, and we derived a set of biophysically consistent interface conditions to close the limiting problem.

The formal results obtained were validated via numerical simulations showing that the relative error between the solutions to the original transmission problem and the solutions to the limiting problem vanishes when the thickness of the membranes tends to zero. In order to illustrate the potential application of our effective interface conditions, we employed the limiting transmission problem to mathematically describe cancer cell invasion through the basement membrane and, in particular, to model the metastatic spread of ovarian carcinoma.

Our work can be extended both from the analytical perspective and from the modelling point of view. From the analytical perspective, it would be interesting to provide a rigorous proof of the formal results established by Propositions 1 and 2. From the modelling point of view, we would like to generalise the results presented in this paper to the case of multiple cell populations. Moreover, it would be interesting to understand how to develop further our formal method for deriving effective interface conditions to consider momentum-related equations different from Eq. (2).

Although the focus of this work has been on cancer invasion, cell penetration of thin membranes occurs also during development, immune surveillance and disease states other than cancer, such as fibrosis [59]. Hence, the effective interface conditions that we derived can find fruitful application in a variety of research fields in the biological and medical sciences, including developmental biology and immunology.

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