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Effective interface conditions for a model of tumour invasion through a membrane

Giorgia Ciavolella¹²³ Noemi David¹⁴ Alexandre Poulain¹

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Abstract

Motivated by biological applications on tumour invasion through thin membranes, we study a porous-medium type equation where the density of the cell population evolves under Darcy's law, assuming continuity of both the density and flux velocity on the thin membrane which separates two domains. The drastically different scales and mobility rates between the membrane and the adjacent tissues lead to consider the limit as the thickness of the membrane approaches zero. We are interested in recovering the *effective interface problem* and the transmission conditions on the limiting zero-thickness surface, formally derived by Chaplain *et al.* (2019), which are compatible with nonlinear generalized Kedem-Katchalsky ones. Our analysis relies on *a priori* estimates and compactness arguments as well as on the construction of a suitable extension operator which allows to deal with the degeneracy of the mobility rate in the membrane, as its thickness tends to zero.

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1 Introduction

We consider a model of cell movement through a membrane where the density population $u = u(t, x)$ is driven by porous medium dynamics. We assume the domain to be an open and bounded set $\Omega \subset \mathbb{R}^3$ which is divided into three open subdomains, $\Omega_{i,\varepsilon}$ for $i = 1, 2, 3$, where $\varepsilon > 0$ is the thickness of the intermediate membrane, $\Omega_{2,\varepsilon}$, see Figure 1. In the three domains, the cells are moving with different constant mobilities, $\mu_{i,\varepsilon}$, for $i = 1, 2, 3$, and they are allowed to cross the adjacent boundaries of these domains which are $\Gamma_{1,2,\varepsilon}$ (between $\Omega_{1,\varepsilon}$ and $\Omega_{2,\varepsilon}$) and $\Gamma_{2,3,\varepsilon}$ (between $\Omega_{2,\varepsilon}$ and $\Omega_{3,\varepsilon}$). The system reads as

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$$\left\{ \begin{array}{ll} \partial_t u_{i,\varepsilon} - \mu_{i,\varepsilon} \nabla \cdot (u_{i,\varepsilon} \nabla p_{i,\varepsilon}) = u_{i,\varepsilon} G(p_{i,\varepsilon}) & \text{in } (0, T) \times \Omega_{i,\varepsilon}, \quad i = 1, 2, 3, \\ \mu_{i,\varepsilon} u_{i,\varepsilon} \nabla p_{i,\varepsilon} \cdot \mathbf{n}_{i,i+1} = \mu_{i+1,\varepsilon} u_{i+1,\varepsilon} \nabla p_{i+1,\varepsilon} \cdot \mathbf{n}_{i,i+1} & \text{on } (0, T) \times \Gamma_{i,i+1,\varepsilon}, \quad i = 1, 2, \\ u_{i,\varepsilon} = u_{i+1,\varepsilon} & \text{on } (0, T) \times \Gamma_{i,i+1,\varepsilon}, \quad i = 1, 2, \\ u_{i,\varepsilon} = 0 & \text{on } (0, T) \times \partial\Omega. \end{array} \right. \quad (1)$$

We denote by $p_{i,\varepsilon}$ the density-dependent pressure, which is given by the following power law

$$p_{i,\varepsilon} = u_{i,\varepsilon}^\gamma, \quad \text{with } \gamma > 1.$$

In this paper, we are interested in studying the convergence of System (1) as $\varepsilon \rightarrow 0$. When the thickness of the thin layer decreases to zero, the membrane collapses to a limiting interface, $\tilde{\Gamma}_{1,3}$, which separates two domains denoted by $\tilde{\Omega}_1$ and $\tilde{\Omega}_3$, see Figure 1. We derive in a rigorous way the *effective problem* (2), and in particular, the transmission conditions on the limit density, \tilde{u} , across the effective interface. Assuming that the diffusion coefficients satisfy $\mu_{i,\varepsilon} > 0$ for $i = 1, 3$ and

$$\lim_{\varepsilon \rightarrow 0} \mu_{1,\varepsilon} = \tilde{\mu}_1 \in (0, +\infty), \quad \lim_{\varepsilon \rightarrow 0} \frac{\mu_{2,\varepsilon}}{\varepsilon} = \tilde{\mu}_{1,3} \in (0, +\infty), \quad \lim_{\varepsilon \rightarrow 0} \mu_{3,\varepsilon} = \tilde{\mu}_3 \in (0, +\infty),$$

we prove that Problem (1) converges to the following system

$$\left\{ \begin{array}{ll} \partial_t \tilde{u}_i - \tilde{\mu}_i \nabla \cdot (\tilde{u}_i \nabla \tilde{p}_i) = \tilde{u}_i G(\tilde{p}_i) & \text{in } (0, T) \times \tilde{\Omega}_i, \quad i = 1, 3, \\ \tilde{\mu}_{1,3} \llbracket \Pi \rrbracket = \tilde{\mu}_1 \tilde{u}_1 \nabla \tilde{p}_1 \cdot \tilde{\mathbf{n}}_{1,3} = \tilde{\mu}_3 \tilde{u}_3 \nabla \tilde{p}_3 \cdot \tilde{\mathbf{n}}_{1,3} & \text{on } (0, T) \times \tilde{\Gamma}_{1,3}, \\ \tilde{u} = 0 & \text{on } (0, T) \times \partial\Omega, \end{array} \right. \quad (2)$$

where Π satisfies $\Pi'(u) = up'(u)$, namely

$$\Pi(u) := \frac{\gamma}{\gamma+1} u^{\gamma+1}.$$

We use the symbol $\llbracket (\cdot) \rrbracket$ to denote the jump across the interface $\tilde{\Gamma}_{1,3}$, *i.e.*

$$\llbracket \Pi \rrbracket := \frac{\gamma}{\gamma+1} (\tilde{u}^{\gamma+1})_3 - \frac{\gamma}{\gamma+1} (\tilde{u}^{\gamma+1})_1, \quad (3)$$

where the subscript indicates that (\cdot) is evaluated as the limit to a point of the interface coming from the subdomain $\tilde{\Omega}_1$, $\tilde{\Omega}_3$, respectively.

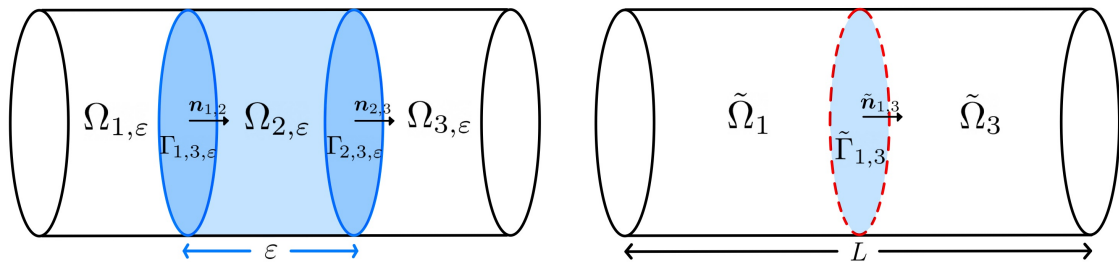


Figure 1: We represent here the bounded cylindrical domain Ω of length L . On the left, we can see the subdomains $\Omega_{i,\varepsilon}$ with related outward normals. The membrane $\Omega_{2,\varepsilon}$ of thickness $\varepsilon > 0$ is delimited by $\Gamma_{i,i+1,\varepsilon} = \{x_3 = \pm\varepsilon/2\} \cap \Omega$ which are symmetric with respect to the effective interface, $\tilde{\Gamma}_{1,3} = \{x_3 = 0\} \cap \Omega$. On the right, we represent the limit domain as $\varepsilon \rightarrow 0$. The effective interface, $\tilde{\Gamma}_{1,3}$, separates the two limit domains, $\tilde{\Omega}_1, \tilde{\Omega}_3$.

Motivations and previous works. Nowadays, a huge literature can be found on the mathematical modeling of tumour growth [6, 13, 16, 24, 26, 28, 32], on a domain $\Omega \subseteq \mathbb{R}^d$ (with $d = 2, 3$ for *in vitro* experiments, $d = 3$ for *in vivo* tumours). Studying tumour's evolution, a crucial and challenging scenario is represented by cancer cells invasion through thin membranes. In particular, one of the most difficult barriers for the cells to cross is the *basement membrane*. This kind of membrane separates the epithelial tissue from the connective one, providing a barrier that isolates malignant cells from the surrounding environment. At the early stage, cancer cells proliferate locally in the epithelial tissue originating a carcinoma *in situ*. Unfortunately, cancer cells could mutate and acquire the ability to migrate by producing *matrix metalloproteinases* (MMPs), specific enzymes which degrade the basement membrane. A specific study can be done on the relation between MMP and their inhibitors as in Bresch *et al.* [31]. Instead, we are interested in modeling cancer transition from *in situ* stage to the invasive phase.

Since in biological systems the membrane is often much smaller than the size of the other components, it is then convenient and reasonable to approximate the membrane as a zero-thickness one, as done in [10, 14], differently from [31]. In particular, it is possible to mathematically describe cancer invasion through a zero thickness interface considering a limiting problem defined on two domains. The system is then closed by *transmission conditions* on the effective interface which generalise the classical Kedem-Katchalsky conditions. The latter were first formulated in [18] and are used to describe different diffusive phenomena, such as, for instance, the transport of molecules through the cell/nucleus membrane [9, 12, 34], solutes absorption processes through the arterial wall [30], the transfer of chemicals through thin biological membranes [8], or the transfer of ions through the interface between two different materials [2].

For these reasons, studying the convergence as the thickness of the membrane tends to zero represents a relevant and interesting problem both from a biological and mathematical point of view. In the literature, this limit has been studied in different fields of applications other than tumour invasion, such as, for instance, thermal, electric or magnetic conductivity, [21, 33], or transport of drugs and ions through an heterogeneous layer, [25]. Physical, cellular and ecological applications characterised the bulk-surface model and the dynamical boundary value problem, derived in [22] in the context of boundary adsorption-desorption of diffusive substances between a bulk (body) and a surface. Another class of limiting systems is offered by [20], in the case in which the diffusion in the thin membrane is not as small as its thickness. Again,

this has a very large application field, from thermal barrier coatings (TBCs) for turbine engine blades to the spreading of animal species, from commercial pathways accelerating epidemics to cell membrane.

As it is now well-established, see for instance [7], living tissues behave like compressible fluids. Therefore, in the last decades, mathematical models have been more and more focusing on the fluid mechanical aspects of tissue and tumour development, see for instance [3, 6, 7, 10, 16, 26]. Tissue cells move through a porous embedding, such as the extra-cellular matrix (ECM). This nonlinear and degenerate diffusion process is well captured by filtration-type equations like the following, rather than the classical heat equation,

$$\partial_t u + \nabla \cdot (u\mathbf{v}) = F(u), \quad \text{for } t > 0, x \in \Omega. \quad (4)$$

Here $F(u)$ represents a generic density-dependent reaction term and the model is closed with the velocity field equation

$$\mathbf{v} := -\mu \nabla p, \quad (5)$$

and a density-dependent law of state for the pressure $p := f(u)$. The function $\mu = \mu(t, x) \geq 0$ represents the cell mobility coefficient and the velocity field equation corresponds to the Darcy law of fluid mechanics. This relation between the velocity of the cells and the pressure gradient reflects the tendency of the cells to move away from regions of high compression.

Our model is based on the one by Chaplain *et al.* [10], where the authors formally recover the *effective interface problem*, analogous to System (2), as the limit of a transmission problem, (or *thin layer problem*) *cf.* System (1), when the thickness of the membrane converges to zero. They also validate through numerical simulations the equivalence between the two models. When shrinking the membrane $\Omega_{2,\varepsilon}$ to an infinitesimal region, $\tilde{\Gamma}_{1,3}$, (*i.e.* when passing to the limit $\varepsilon \rightarrow 0$, where ε is proportional to the thickness of the membrane), it is important to guarantee that the effect of the thin membrane on the cell invasion remains preserved. To this end, it is essential to make the following assumption on the mobility coefficient of the subdomain $\Omega_{2,\varepsilon}$,

$$\mu_{2,\varepsilon} \xrightarrow{\varepsilon \rightarrow 0} 0 \quad \text{such that} \quad \frac{\mu_{2,\varepsilon}}{\varepsilon} \xrightarrow{\varepsilon \rightarrow 0} \tilde{\mu}_{1,3}.$$

This condition implies that, when shrinking the pores of the membrane, the local permeability of the layer decreases to zero proportionally with respect to the local shrinkage. The function $\tilde{\mu}_{1,3}$ represents the *effective permeability coefficient* of the limiting interface $\tilde{\Gamma}_{1,3}$, *i.e.* the permeability of the zero-thickness membrane. We refer the reader to [10, Remark 2.4] for the derivation of the analogous assumption in the case of a fluid flowing through a porous medium. In [10], the authors derive the effective transmission conditions on the limiting interface, $\tilde{\Gamma}_{1,3}$, which relates the jump of the quantity $\Pi := \Pi(u)$, defined by $\Pi'(u) = uf'(u)$ and the normal flux across the interface, namely

$$\tilde{\mu}_{1,3}[\Pi] = \tilde{\mu}_i \tilde{u}_i \nabla f(\tilde{u}_i) \cdot \tilde{\mathbf{n}}_{1,3} = \tilde{\mu}_i \nabla \Pi(\tilde{u}_i) \cdot \tilde{\mathbf{n}}_{1,3}, \quad \text{for } i = 1, 3 \quad \text{on } \tilde{\Gamma}_{1,3}. \quad ^1$$

These conditions turns out to be the well-known Kedem-Katchalsky interface conditions when $f(u) := \ln(u)$, for which $\Pi(u) = u + C$, $C \in \mathbb{R}$, *i.e.* the linear diffusion case.

In this paper, we provide a rigorous proof to the derivation of these limiting transmission conditions, for a particular choice of the pressure law. To the best of our knowledge, this question has not been addressed before in the literature for a non-linear and degenerate model such as System (1). Although our system falls into the class of models formulated by Chaplain *et al.*, we consider a less general case, making some choices on the quantities of interest. First of all,

¹This equation is reported in [10, Proposition 3.1], where we adapted the notation to that of our paper.

for the sake of simplicity, we assume the mobility coefficients $\mu_{i,\varepsilon}$ to be positive constants, hence they do not depend on time and space as in [10]. We take a reaction term of the form $uG(p)$, where G is a pressure-penalized growth rate. Moreover, we take a power-law as pressure law of state, *i.e.* $p = u^\gamma$, with $\gamma \geq 1$. Hence, our model turns out to be in fact a porous medium type model, since Equations (4, 5) read as follows

$$\partial_t u - \frac{\gamma}{\gamma + 1} \Delta u^{\gamma+1} = uG(p), \quad \text{for } t > 0, x \in \Omega.$$

The nonlinearity and the degeneracy of the porous medium equation (PME) bring several additional difficulties to its analysis compared to its linear and non-degenerate counterpart. In particular, the main challenge is represented by the emergence of a free boundary, which separates the region where $u > 0$ from the region of vacuum. On this interface the equation degenerates, affecting the control and the regularity of the main quantities. For example, it is well-known that the density can develop jumps singularities, therefore preventing any control of the gradient in L^2 , opposite to the case of linear diffusion. On the other hand, using the fundamental change of variables of the PME, $p = u^\gamma$, and studying the equation on the pressure rather than the equation on the density, turns out to be very useful when searching for better regularity of the gradient. Nevertheless, since the pressure presents "corners" at the free boundary, it is not possible to bound its laplacian in L^2 (uniformly on the entire domain).

For these reasons, we could not straightforwardly apply some of the methods previously used in the literature in the case of linear diffusion. For instance, the result in [5] is based on proving H^2 -*a priori* bounds, which do not hold in our case. The authors consider elliptic equations in a domain divided into three subdomains, each one contained into the interior of the other. The coefficients of the second-order terms are assumed to be piecewise continuous with jumps along the interior interfaces. Then, the authors study the limit as the thickness of the interior reinforcement tends to zero. In [33], Sanchez-Palencia studies the same problem in the particular case of a lense-shaped region, I_ε , which shrinks to a smooth surface in the limit, facing also the parabolic case. The approach is based on H^1 -*a priori* estimates, namely the L^2 -boundedness of the gradient of the unknown. Considering the variational formulation of the problem, the author is able to pass to the limit upon applying an extension operator. In fact, if the mobility coefficient in I_ε converges to zero proportionally with respect to ε , it is only possible to establish uniform bounds outside of I_ε . The extension operator allows to "truncate" the solution and then "extend" it into I_ε reflecting its profile from outside. Therefore, making use of the uniform control outside of the ε -thickness layer, the author is able to pass to the limit in the variational formulation. Let us also mention that, in the literature, one can find different methods and strategies for reaction-diffusion problems with a thin layer. For instance, in [25], the authors develop a multiscale method which combines classical compactness results based on *a priori estimates* and weak-strong two-scale convergence results in order to be able to pass to the limit in a thin heterogeneous membrane.

The passage at the limit allows to infer the existence of weak solutions for the effective Problem (2). In the case of linear diffusion, the existence of global weak solutions for the effective problem with the Kedem-Katchalsky conditions is provided by [11]. In particular, the authors prove it under weaker hypothesis such as L^1 initial data and reaction terms with sub-quadratic growth in an L^1 -setting.

Outline of the paper. The paper is organised as follows. In Section 2, we introduce the assumptions and notations, including the definition of weak solution of the original problem, System (1). In Section 3, *a priori* estimates that will be useful to pass to the limit are proven.

Section 4 is devoted to prove the convergence of Problem (1), following the method introduced in [33] for the (non-degenerate) elliptic and parabolic cases. The argument relies on recovering

the L^2 -boundedness (uniform with respect to ε) of the velocity field, in our case, the pressure gradient. As one may expect, since the permeability of the membrane, $\mu_{2,\varepsilon}$, tends to zero proportionally with respect to ε , it is only possible to establish a uniform bound outside of $\Omega_{2,\varepsilon}$. For this reason, following [33], we introduce an extension operator (Subsection 4.1) and apply it to the pressure in order to extend the H^1 -uniform bounds in the whole space $\Omega \setminus \tilde{\Gamma}_{1,3}$, hence proving compactness results. We remark that the main difference between the strategy in [33] and our adaptation, is given by the fact that due to the non-linearity of the equation, we have to infer strong compactness of the pressure (and consequently of the density) in order to pass to the limit in the variational formulation. For this reason, we also need the L^1 -boundedness of the time derivative, hence obtaining compactness with a standard Sobolev's embedding argument. Moreover, since the solution to the limit Problem (2) will present discontinuities at the effective interface, we need to build proper test functions which belong to $H^1(\Omega \setminus \tilde{\Gamma}_{1,3})$ that are zero on $\partial\Omega$ and are discontinuous across $\tilde{\Gamma}_{1,3}$, (Subsection 4.2).

Finally, using the compactness obtained thanks to the extension operator, we are able to prove the convergence of a solution to Problem (1) to a couple (\tilde{u}, \tilde{p}) which satisfies Problem (2) in a weak sense, therefore inferring the existence of a solution of the effective problem, as stated in the following theorem.

Theorem 1.1 (Convergence to the effective problem). *The solution of Problem (1) converges to a solution (\tilde{u}, \tilde{p}) of Problem (2) in the following weak sense*

$$\begin{aligned} & - \int_0^T \int_{\Omega} \tilde{u} \partial_t w + \tilde{\mu}_1 \int_0^T \int_{\tilde{\Omega}_1} \tilde{u} \nabla \tilde{p} \cdot \nabla w + \tilde{\mu}_3 \int_0^T \int_{\tilde{\Omega}_3} \tilde{u} \nabla \tilde{p} \cdot \nabla w \\ & + \tilde{\mu}_{1,3} \int_0^T \int_{\tilde{\Gamma}_{1,3}} \llbracket \Pi \rrbracket (w|_{x_3=0^+} - w|_{x_3=0^-}) = \int_0^T \int_{\Omega} \tilde{u} G(\tilde{p}) w + \int_{\Omega} \tilde{u}^0 w^0, \end{aligned} \quad (6)$$

for all test functions $w(t, x)$ with a proper regularity and $w(T, x) = 0$, a.e. in Ω (defined in Theorem 4.3), and with

$$\llbracket \Pi \rrbracket := \frac{\gamma}{\gamma + 1} (\tilde{u}^{\gamma+1})|_{x_3=0^+} - \frac{\gamma}{\gamma + 1} (\tilde{u}^{\gamma+1})|_{x_3=0^-},$$

and $(\cdot)|_{x_3=0^\pm} = \mathcal{T}(\cdot)$, with \mathcal{T} the trace operator defined in Section 2.

Section 5 concludes the paper and provides some research perspectives.

2 Assumptions and notations

Here, we detail the problem setting and assumptions. For the sake of simplicity, we consider as domain $\Omega \subset \mathbb{R}^3$ a cylinder with axis x_3 , see Figure 1. Let us notice that it is possible to take a more general domain $\hat{\Omega}$ defining a proper diffeomorphism $F : \hat{\Omega} \rightarrow \Omega$. Therefore, the results of this work extend to more general domains as long as the existence of the map F can be proved (this implies that $\hat{\Omega}$ is a connected open subset of \mathbb{R}^d and has a smooth boundary). We also want to emphasize the fact that our proofs hold in a 2D domain considering three rectangular subdomains. We introduce

$$u_\varepsilon := \begin{cases} u_{1,\varepsilon}, & \text{in } \Omega_{1,\varepsilon}, \\ u_{2,\varepsilon}, & \text{in } \Omega_{2,\varepsilon}, \\ u_{3,\varepsilon}, & \text{in } \Omega_{3,\varepsilon}, \end{cases} \quad p_\varepsilon := \begin{cases} p_{1,\varepsilon}, & \text{in } \Omega_{1,\varepsilon}, \\ p_{2,\varepsilon}, & \text{in } \Omega_{2,\varepsilon}, \\ p_{3,\varepsilon}, & \text{in } \Omega_{3,\varepsilon}. \end{cases}$$

We define the interfaces between the domains $\Omega_{i,\varepsilon}$ and $\Omega_{i+1,\varepsilon}$ for $i = 1, 2$, as

$$\Gamma_{i,i+1,\varepsilon} = \partial\Omega_{i,\varepsilon} \cap \partial\Omega_{i+1,\varepsilon}.$$

We denote with $\mathbf{n}_{i,i+1}$ the outward normal to $\Gamma_{i,i+1,\varepsilon}$ with respect to $\Omega_{i,\varepsilon}$, for $i = 1, 2$. Let us notice that $\mathbf{n}_{i,i+1} = -\mathbf{n}_{i+1,i}$.

We call \mathcal{T} the bounded linear trace operator, [4],

$$\mathcal{T} : W^{k,p}(\Omega \setminus \tilde{\Gamma}_{1,3}) \longrightarrow W^{k-\frac{1}{p},p}(\partial\Omega \cup \tilde{\Gamma}_{1,3}) \subset L^p(\partial\Omega \cup \tilde{\Gamma}_{1,3}), \quad \text{for } 1 \leq p \leq +\infty, \quad k > \frac{1}{p}.$$

Given $z \in W^{k,p}(\Omega \setminus \tilde{\Gamma}_{1,3})$, we denote $z|_{\partial\Omega \cup \tilde{\Gamma}_{1,3}} := \mathcal{T}z \in W^{k-\frac{1}{p},p}(\partial\Omega \cup \tilde{\Gamma}_{1,3})$ and the following continuity property holds

$$\|\mathcal{T}z\|_{W^{k-\frac{1}{p},p}(\partial\Omega \cup \tilde{\Gamma}_{1,3})} \leq C\|z\|_{W^{k,p}(\Omega \setminus \tilde{\Gamma}_{1,3})}.$$

We make the following assumptions on the initial data: there exists a positive constant p_H , such that

$$0 \leq p_\varepsilon^0 \leq p_H, \quad 0 \leq u_\varepsilon^0 \leq p_H^{1/\gamma} =: u_H, \quad (\text{A-data1})$$

$$\Delta((u_{i,\varepsilon}^0)^{\gamma+1}) \in L^1(\Omega_{i,\varepsilon}), \quad \text{for } i = 1, 2, 3. \quad (\text{A-data2})$$

Moreover, we assume that there exists a function $\tilde{u}_0 \in L^1_+(\Omega)$ such that

$$\|u_\varepsilon^0 - \tilde{u}_0\|_{L^1(\Omega)} \longrightarrow 0, \quad \text{as } \varepsilon \rightarrow 0. \quad (\text{A-data3})$$

The growth rate $G(\cdot)$ satisfies

$$G(0) = G_M > 0, \quad G'(\cdot) < 0, \quad G(p_H) = 0. \quad (\text{A-G})$$

The value p_H , called *homeostatic pressure*, represents the lowest level of pressure that prevents cell multiplication due to contact-inhibition.

We assume that the diffusion coefficients satisfy $\mu_{i,\varepsilon} > 0$ for $i = 1, 3$ and

$$\lim_{\varepsilon \rightarrow 0} \mu_{1,\varepsilon} = \tilde{\mu}_1 > 0, \quad \lim_{\varepsilon \rightarrow 0} \frac{\mu_{2,\varepsilon}}{\varepsilon} = \tilde{\mu}_{1,3} > 0, \quad \lim_{\varepsilon \rightarrow 0} \mu_{3,\varepsilon} = \tilde{\mu}_3 > 0. \quad (7)$$

Notations. For all $T > 0$, we denote $\Omega_T := (0, T) \times \Omega$. We use the abbreviated form $u_\varepsilon := u_\varepsilon(t) := u_\varepsilon(t, x)$. From now on, we use C to indicate a generic positive constant independent of ε that may change from line to line. Moreover, we denote

$$\text{sign}_+(w) = \mathbb{1}_{\{w>0\}}, \quad \text{sign}_-(w) = -\mathbb{1}_{\{w<0\}},$$

and

$$\text{sign}(w) = \text{sign}_+(w) + \text{sign}_-(w).$$

We also define the positive and negative part of w as follows

$$|w|_+ := \begin{cases} w, & \text{for } w > 0, \\ 0, & \text{for } w \leq 0, \end{cases} \quad \text{and} \quad |w|_- := \begin{cases} -w, & \text{for } w < 0, \\ 0, & \text{for } w \geq 0. \end{cases}$$

Now, let us write the variational formulation of Problem (1).

Definition 2.1 (Definition of weak solutions). Given $\varepsilon > 0$, a weak solution to Problem (1) is given by $u_\varepsilon, p_\varepsilon \in L^1(0, T; L^\infty(\Omega))$ such that $\nabla p_\varepsilon \in L^2(\Omega_T)$ and

$$-\int_0^T \int_\Omega u_\varepsilon \partial_t \psi + \sum_{i=1}^3 \mu_{i,\varepsilon} \int_0^T \int_{\Omega_{i,\varepsilon}} u_{i,\varepsilon} \nabla p_{i,\varepsilon} \cdot \nabla \psi = \int_0^T \int_\Omega u_\varepsilon G(p_\varepsilon) \psi + \int_\Omega u_\varepsilon^0 \psi(0, x), \quad (8)$$

for all test functions $\psi \in H^1(0, T; H_0^1(\Omega))$ such that $\psi(T, x) = 0$ a.e. in Ω .

Remark 2.2. The existence of such solutions can be proved by a straightforward application of standard techniques for nonlinear parabolic equations (see, for instance, [36]).

3 A priori estimates

We show that the main quantities satisfy some uniform *a priori* estimates which will later allow us to prove strong compactness and pass to the limit.

Lemma 3.1 (A priori estimates). *Given the assumptions in Section 2, let $(u_\varepsilon, p_\varepsilon)$ be the solution of Problem (1). The following properties hold uniformly with respect to ε .*

- (i) $0 \leq u_\varepsilon \leq u_H$ and $0 \leq p_\varepsilon \leq p_H$,
- (ii) $u_\varepsilon, p_\varepsilon \in L^\infty(0, T; L^p(\Omega))$, for $1 \leq p < \infty$,
- (iii) $\partial_t u_\varepsilon, \partial_t p_\varepsilon \in L^\infty(0, T; L^1(\Omega))$,
- (iv) $\nabla p_\varepsilon \in L^2(0, T; L^2(\Omega \setminus \Omega_{2,\varepsilon}))$.

Proof. Let us recall the equation satisfied by u_ε on $\Omega_{i,\varepsilon}$, namely

$$\partial_t u_{i,\varepsilon} - \mu_{i,\varepsilon} \nabla \cdot (u_{i,\varepsilon} \nabla u_{i,\varepsilon}^\gamma) = u_{i,\varepsilon} G(p_{i,\varepsilon}). \quad (9)$$

(i) $0 \leq u_\varepsilon \leq u_H$, $0 \leq p_\varepsilon \leq p_H$. The L^∞ -bounds of the density and the pressure are a straight-forward consequence of the comparison principle applied to Equation (9), which can be rewritten as

$$\partial_t u_{i,\varepsilon} - \frac{\gamma}{\gamma+1} \mu_{i,\varepsilon} \Delta u_{i,\varepsilon}^{\gamma+1} = u_{i,\varepsilon} G(p_{i,\varepsilon}). \quad (10)$$

Indeed, summing up Equations (10) for $i = 1, 2, 3$, we obtain

$$\sum_{i=1}^3 \partial_t u_{i,\varepsilon} - \frac{\gamma}{\gamma+1} \sum_{i=1}^3 \mu_{i,\varepsilon} \Delta u_{i,\varepsilon}^{\gamma+1} = \sum_{i=1}^3 u_{i,\varepsilon} G(p_{i,\varepsilon}). \quad (11)$$

Then, we also have

$$\sum_{i=1}^3 \partial_t (u_H - u_{i,\varepsilon}) = \frac{\gamma}{\gamma+1} \sum_{i=1}^3 \mu_{i,\varepsilon} \Delta (u_H^{\gamma+1} - u_{i,\varepsilon}^{\gamma+1}) + \sum_{i=1}^3 (u_H - u_{i,\varepsilon}) G(p_{i,\varepsilon}) - u_H \sum_{i=1}^3 G(p_{i,\varepsilon}).$$

If we multiply by $\text{sign}_-(u_H - u_{i,\varepsilon})$, thanks to Kato's inequality, we infer that

$$\begin{aligned} \sum_{i=1}^3 \partial_t (u_H - u_{i,\varepsilon})_- &\leq \sum_{i=1}^3 \left[\frac{\gamma}{\gamma+1} \mu_{i,\varepsilon} \Delta (u_H^{\gamma+1} - u_{i,\varepsilon}^{\gamma+1})_- + (u_H - u_{i,\varepsilon})_- G(p_{i,\varepsilon}) \right. \\ &\quad \left. - u_H G(p_{i,\varepsilon}) \text{sign}_-(u_H - u_{i,\varepsilon}) \right] \\ &\leq \sum_{i=1}^3 \left[\frac{\gamma}{\gamma+1} \mu_{i,\varepsilon} \Delta (u_H^{\gamma+1} - u_{i,\varepsilon}^{\gamma+1})_- + (u_H - u_{i,\varepsilon})_- G(p_{i,\varepsilon}) \right], \end{aligned} \quad (12)$$

where we have used the assumption (A-G). We integrate over the domain Ω . Thanks to the boundary conditions in System (1), *i.e.* the density and flux continuity across the interfaces, and

the homogeneous Dirichlet conditions on $\partial\Omega$, we gain

$$\begin{aligned}
& \sum_{i=1}^3 \int_{\Omega_{i,\varepsilon}} \mu_{i,\varepsilon} \Delta (u_H^{\gamma+1} - u_{i,\varepsilon}^{\gamma+1})_- \\
&= \sum_{i=1}^2 \int_{\Gamma_{i,i+1,\varepsilon}} \left[\mu_i \nabla (u_H^{\gamma+1} - u_{i,\varepsilon}^{\gamma+1})_- - \mu_{i+1,\varepsilon} \nabla (u_H^{\gamma+1} - u_{i+1,\varepsilon}^{\gamma+1})_- \right] \cdot \mathbf{n}_{i,i+1} \\
&= \sum_{i=1}^2 \left[\int_{\Gamma_{i,i+1,\varepsilon} \cap \{u_H < u_{i,\varepsilon}\}} \mu_i \nabla u_{i,\varepsilon}^{\gamma+1} \cdot \mathbf{n}_{i,i+1} - \int_{\Gamma_{i,i+1,\varepsilon} \cap \{u_H < u_{i+1,\varepsilon}\}} \mu_{i+1,\varepsilon} \nabla u_{i+1,\varepsilon}^{\gamma+1} \cdot \mathbf{n}_{i,i+1} \right] \\
&= \sum_{i=1}^2 \int_{\Gamma_{i,i+1,\varepsilon} \cap \{u_H < u_{i,\varepsilon}\}} \left[\mu_i \nabla u_{i,\varepsilon}^{\gamma+1} - \mu_{i+1,\varepsilon} \nabla u_{i+1,\varepsilon}^{\gamma+1} \right] \cdot \mathbf{n}_{i,i+1} \\
&= 0.
\end{aligned}$$

Hence, from Equation (12), we find

$$\frac{d}{dt} \sum_{i=1}^3 \int_{\Omega_{i,\varepsilon}} (u_H - u_{i,\varepsilon})_- \leq G_M \sum_{i=1}^3 \int_{\Omega_{i,\varepsilon}} (u_H - u_{i,\varepsilon})_-.$$

Finally, Gronwall's lemma and hypothesis (A-data1) on $u_{i,\varepsilon}^0$ imply

$$\sum_{i=1}^3 \int_{\Omega_{i,\varepsilon}} (u_H - u_{i,\varepsilon})_- \leq e^{G_M t} \sum_{i=1}^3 \int_{\Omega_{i,\varepsilon}} (u_H - u_{i,\varepsilon}^0)_- = 0.$$

We then conclude the boundedness of $u_{i,\varepsilon}$ by u_H for all $i = 1, 2, 3$. From the relation $p_\varepsilon = u_\varepsilon^\gamma$, we conclude the boundedness of p_ε .

(ii) $\mathbf{u}_\varepsilon \in L^\infty(\mathbf{0}, T; L^p(\Omega))$. Integrating Equation (9) in space and taking the sum over all i we find

$$\frac{d}{dt} \sum_{i=1}^3 \int_{\Omega_{i,\varepsilon}} u_{i,\varepsilon} - \sum_{i=1}^3 \int_{\Omega_{i,\varepsilon}} \mu_{i,\varepsilon} \nabla \cdot (u_{i,\varepsilon} \nabla p_{i,\varepsilon}) = \sum_{i=1}^3 \int_{\Omega_{i,\varepsilon}} u_{i,\varepsilon} G(p_{i,\varepsilon}).$$

By the boundary and the interface conditions in System (1), upon integrating by parts the second integral turns out to be zero. In fact, we obtain

$$\begin{aligned}
\sum_{i=1}^3 \int_{\Omega_{i,\varepsilon}} \mu_{i,\varepsilon} \nabla \cdot (u_{i,\varepsilon} \nabla p_{i,\varepsilon}) &= \int_{\Gamma_{1,2,\varepsilon}} \mu_{1,\varepsilon} u_{1,\varepsilon} \nabla p_{1,\varepsilon} \cdot \mathbf{n}_{1,2} + \int_{\Gamma_{1,2,\varepsilon}} \mu_{2,\varepsilon} u_{2,\varepsilon} \nabla p_{2,\varepsilon} \cdot \mathbf{n}_{2,1} \\
&\quad + \int_{\Gamma_{2,3,\varepsilon}} \mu_{2,\varepsilon} u_{2,\varepsilon} \nabla p_{2,\varepsilon} \cdot \mathbf{n}_{2,3} + \int_{\Gamma_{2,3,\varepsilon}} \mu_{3,\varepsilon} u_{3,\varepsilon} \nabla p_{3,\varepsilon} \cdot \mathbf{n}_{3,2},
\end{aligned}$$

which vanishes thanks to the continuity condition on the flux, and the fact that $\mathbf{n}_{i,i+1} = -\mathbf{n}_{i+1,i}$, for $i = 1, 2$.

Thanks to the assumptions on G , cf. Equation (A-G), we find

$$\frac{d}{dt} \sum_{i=1}^3 \int_{\Omega_{i,\varepsilon}} u_{i,\varepsilon} \leq G_M \sum_{i=1}^3 \int_{\Omega_{i,\varepsilon}} u_{i,\varepsilon},$$

and applying Gronwall's inequality, we obtain

$$\sum_{i=1}^3 \int_{\Omega_{i,\varepsilon}} u_{i,\varepsilon}(t) \leq e^{G_M t} \sum_{i=1}^3 \int_{\Omega_{i,\varepsilon}} u_{i,\varepsilon}^0.$$

Thanks to the L^1 initial bound, we obtain $u_\varepsilon \in L^\infty(0, T; L^1(\Omega))$.

Then, since $p_\varepsilon = p_\varepsilon^{(\gamma-1)/\gamma} u_\varepsilon \leq p_H^{(\gamma-1)/\gamma} u_\varepsilon$, we conclude that $p_\varepsilon \in L^\infty(0, T; L^1(\Omega))$. Let us notice that since u_ε and p_ε are uniformly bounded in L^∞ , then $u_\varepsilon, p_\varepsilon \in L^\infty(0, T; L^p(\Omega))$, for all $1 \leq p \leq +\infty$.

(iii) $\partial_t u_\varepsilon, \partial_t p_\varepsilon \in L^\infty(0, T; L^1(\Omega))$. We derive Equation (10) with respect to time to obtain

$$\partial_t(\partial_t u_{i,\varepsilon}) = \mu_{i,\varepsilon} \gamma \Delta(p_{i,\varepsilon} \partial_t u_{i,\varepsilon}) + \partial_t u_{i,\varepsilon} G(p_{i,\varepsilon}) + u_{i,\varepsilon} G'(p_{i,\varepsilon}) \partial_t p_{i,\varepsilon}.$$

Upon multiplying by $\text{sign}(\partial_t u_{i,\varepsilon})$ and using Kato's inequality, we have

$$\partial_t(|\partial_t u_{i,\varepsilon}|) \leq \mu_{i,\varepsilon} \gamma \Delta(p_{i,\varepsilon} |\partial_t u_{i,\varepsilon}|) + |\partial_t u_{i,\varepsilon}| G(p_{i,\varepsilon}) + u_{i,\varepsilon} G'(p_{i,\varepsilon}) |\partial_t p_{i,\varepsilon}|,$$

since $u_{i,\varepsilon}$ and $p_{i,\varepsilon}$ are both nonnegative and $\partial_t p_{i,\varepsilon} = \gamma u_{i,\varepsilon}^{\gamma-1} \partial_t u_{i,\varepsilon}$. We integrate over $\Omega_{i,\varepsilon}$ and we sum over $i = 1, 2, 3$, namely

$$\frac{d}{dt} \sum_{i=1}^3 \int_{\Omega_{i,\varepsilon}} |\partial_t u_{i,\varepsilon}| \leq \underbrace{\gamma \sum_{i=1}^3 \mu_{i,\varepsilon} \int_{\Omega_{i,\varepsilon}} \Delta(p_{i,\varepsilon} |\partial_t u_{i,\varepsilon}|)}_{\mathcal{J}} + G_M \int_{\Omega_{i,\varepsilon}} |\partial_t u_{i,\varepsilon}|, \quad (13)$$

where we use that $G' \leq 0$.

Now we show that the term \mathcal{J} vanishes. Integration by parts yields

$$\mathcal{J} = \sum_{i=1}^2 \int_{\Gamma_{i,i+1,\varepsilon}} \mu_{i,\varepsilon} \nabla(p_{i,\varepsilon} |\partial_t u_{i,\varepsilon}|) \cdot \mathbf{n}_{i,i+1} + \sum_{i=1}^2 \int_{\Gamma_{i,i+1,\varepsilon}} \mu_{i+1,\varepsilon} \nabla(p_{i+1,\varepsilon} |\partial_t u_{i+1,\varepsilon}|) \cdot \mathbf{n}_{i+1,i}.$$

For the sake of simplicity, we denote $\mathbf{n} := \mathbf{n}_{i,i+1}$. Let us recall that, by definition, $\mathbf{n}_{i+1,i} = -\mathbf{n}$. We have

$$\begin{aligned} \mathcal{J} &= \sum_{i=1}^2 \int_{\Gamma_{i,i+1,\varepsilon}} (\mu_{i,\varepsilon} \nabla(p_{i,\varepsilon} |\partial_t u_{i,\varepsilon}|) - \mu_{i+1,\varepsilon} \nabla(p_{i+1,\varepsilon} |\partial_t u_{i+1,\varepsilon}|)) \cdot \mathbf{n} \\ &= \underbrace{\sum_{i=1}^2 \int_{\Gamma_{i,i+1,\varepsilon}} |\partial_t u_{i,\varepsilon}| \mu_{i,\varepsilon} \nabla p_{i,\varepsilon} \cdot \mathbf{n} - |\partial_t u_{i+1,\varepsilon}| \mu_{i+1,\varepsilon} \nabla p_{i+1,\varepsilon} \cdot \mathbf{n}}_{\mathcal{J}_1} \\ &\quad + \underbrace{\sum_{i=1}^2 \int_{\Gamma_{i,i+1,\varepsilon}} \mu_{i,\varepsilon} p_{i,\varepsilon} \nabla |\partial_t u_{i,\varepsilon}| \cdot \mathbf{n} - \mu_{i+1,\varepsilon} p_{i+1,\varepsilon} \nabla |\partial_t u_{i+1,\varepsilon}| \cdot \mathbf{n}}_{\mathcal{J}_2}. \end{aligned}$$

Let us recall the membrane conditions of Problem (1), namely

$$\mu_{i,\varepsilon} u_{i,\varepsilon} \nabla p_{i,\varepsilon} \cdot \mathbf{n} = \mu_{i+1,\varepsilon} u_{i+1,\varepsilon} \nabla p_{i+1,\varepsilon} \cdot \mathbf{n}, \quad (14)$$

$$u_{i,\varepsilon} = u_{i+1,\varepsilon}, \quad (15)$$

on $(0, T) \times \Gamma_{i,i+1,\varepsilon}$, for $i = 1, 2$. From Equation (15), it is immediate to infer

$$\partial_t u_{i,\varepsilon} = \partial_t u_{i+1,\varepsilon}, \quad \text{on } (0, T) \times \Gamma_{i,i+1,\varepsilon}, \quad (16)$$

since

$$u_{i,\varepsilon}(t+h) - u_{i,\varepsilon}(t) = u_{i+1,\varepsilon}(t+h) - u_{i+1,\varepsilon}(t),$$

on $\Gamma_{i,i+1,\varepsilon}$ for all $h > 0$ such that $t + h \in (0, T)$.

Combing Equation (15) and Equation (14) we get

$$\mu_{i,\varepsilon} \nabla p_{i,\varepsilon} \cdot \mathbf{n} = \mu_{i+1,\varepsilon} \nabla p_{i+1,\varepsilon} \cdot \mathbf{n} \quad \text{on } (0, T) \times \Gamma_{i,i+1,\varepsilon}. \quad (17)$$

Moreover, Equation (14) also implies

$$\mu_{i,\varepsilon} p_{i,\varepsilon} \nabla u_{i,\varepsilon} \cdot \mathbf{n} = \mu_{i+1,\varepsilon} p_{i+1,\varepsilon} \nabla u_{i+1,\varepsilon} \cdot \mathbf{n} \quad \text{on } (0, T) \times \Gamma_{i,i+1,\varepsilon}, \quad (18)$$

which, combined with Equation (15) gives also

$$\mu_{i,\varepsilon} \nabla u_{i,\varepsilon} \cdot \mathbf{n} = \mu_{i+1,\varepsilon} \nabla u_{i+1,\varepsilon} \cdot \mathbf{n} \quad \text{on } (0, T) \times \Gamma_{i,i+1,\varepsilon}. \quad (19)$$

Now we may come back to the computation of the term \mathcal{J} . By Equations (16), and (17) we directly infer that \mathcal{J}_1 vanishes.

We rewrite the term \mathcal{J}_2 as

$$\begin{aligned} & \sum_{i=1}^2 \int_{\Gamma_{i,i+1,\varepsilon}} \mu_{i,\varepsilon} p_{i,\varepsilon} \operatorname{sign}(\partial_t u_{i,\varepsilon}) \partial_t (\nabla u_{i,\varepsilon} \cdot \mathbf{n}) - \mu_{i+1,\varepsilon} p_{i+1,\varepsilon} \operatorname{sign}(\partial_t u_{i+1,\varepsilon}) \partial_t (\nabla u_{i+1,\varepsilon} \cdot \mathbf{n}) \\ &= \underbrace{\sum_{i=1}^2 \int_{\Gamma_{i,i+1,\varepsilon}} \operatorname{sign}(\partial_t u_{i,\varepsilon}) \partial_t (\mu_{i,\varepsilon} p_{i,\varepsilon} \nabla u_{i,\varepsilon} \cdot \mathbf{n} - \mu_{i+1,\varepsilon} p_{i+1,\varepsilon} \nabla u_{i+1,\varepsilon} \cdot \mathbf{n})}_{\mathcal{J}_{2,1}} \\ & \quad - \underbrace{\sum_{i=1}^2 \int_{\Gamma_{i,i+1,\varepsilon}} |\partial_t p_{i,\varepsilon}| (\mu_{i,\varepsilon} \nabla u_{i,\varepsilon} \cdot \mathbf{n} - \mu_{i+1,\varepsilon} \nabla u_{i+1,\varepsilon} \cdot \mathbf{n})}_{\mathcal{J}_{2,2}}, \end{aligned}$$

where we used Equation (16), which also implies $\partial_t p_{i,\varepsilon} = \partial_t p_{i+1,\varepsilon}$ on $(0, T) \times \Gamma_{i,i+1,\varepsilon}$, for $i = 1, 2$. The terms $\mathcal{J}_{2,1}$ and $\mathcal{J}_{2,2}$ vanish thanks to Equation (18) and Equation (19), respectively.

Hence, from Equation (13), we finally have

$$\frac{d}{dt} \sum_{i=1}^3 \int_{\Omega_{i,\varepsilon}} |\partial_t u_{i,\varepsilon}| \leq G_M \sum_{i=1}^3 \int_{\Omega_{i,\varepsilon}} |\partial_t u_{i,\varepsilon}|,$$

and, using Gronwall's inequality, we obtain

$$\sum_{i=1}^3 \int_{\Omega_{i,\varepsilon}} |\partial_t u_{i,\varepsilon}(t)| \leq e^{G_M t} \sum_{i=1}^3 \int_{\Omega_{i,\varepsilon}} |(\partial_t u_{i,\varepsilon})^0|.$$

Thanks to the assumptions on the initial data, *cf.* Equation (A-data2), we conclude.

(iv) $p_\varepsilon \in L^2(0, T; H^1(\Omega \setminus \Omega_{2,\varepsilon}))$. As known, in the context of a filtration equation, we can recover the pressure equation upon multiplying the equation on $u_{i,\varepsilon}$, *cf.* System (1), by $p'(u_{i,\varepsilon}) = \gamma u_{i,\varepsilon}^{\gamma-1}$. Therefore, we obtain

$$\partial_t p_{i,\varepsilon} - \gamma \mu_{i,\varepsilon} p_{i,\varepsilon} \Delta p_{i,\varepsilon} = \mu_{i,\varepsilon} |\nabla p_{i,\varepsilon}|^2 + \gamma p_{i,\varepsilon} G(p_{i,\varepsilon}). \quad (20)$$

Studying the equation on p_ε rather than the equation on u_ε turns out to be very useful in order to prove compactness, since, as it is well-know for the porous medium equation (PME), the gradient of the pressure can be easily bounded in L^2 , while the density solution of the PME can develop jump singularities on the free boundary, [35].

We integrate Equation (20) on each $\Omega_{i,\varepsilon}$, and we sum over all i to obtain

$$\sum_{i=1}^3 \int_{\Omega_{i,\varepsilon}} \partial_t p_{i,\varepsilon} = \sum_{i=1}^3 \left(\gamma \mu_{i,\varepsilon} \int_{\Omega_{i,\varepsilon}} p_{i,\varepsilon} \Delta p_{i,\varepsilon} + \int_{\Omega_{i,\varepsilon}} \mu_{i,\varepsilon} |\nabla p_{i,\varepsilon}|^2 + \gamma \int_{\Omega_{i,\varepsilon}} p_{i,\varepsilon} G(p_{i,\varepsilon}) \right). \quad (21)$$

Integration by parts yields

$$\begin{aligned} \sum_{i=1}^3 \mu_{i,\varepsilon} \int_{\Omega_{i,\varepsilon}} p_{i,\varepsilon} \Delta p_{i,\varepsilon} &= - \sum_{i=1}^3 \mu_{i,\varepsilon} \int_{\Omega_{i,\varepsilon}} |\nabla p_{i,\varepsilon}|^2 + \sum_{i=1}^2 \int_{\Gamma_{i,i+1,\varepsilon}} \mu_{i,\varepsilon} p_{i,\varepsilon} \nabla p_{i,\varepsilon} \cdot \mathbf{n}_{i,i+1} \\ &\quad + \sum_{i=1}^2 \int_{\Gamma_{i,i+1,\varepsilon}} \mu_{i+1,\varepsilon} p_{i+1,\varepsilon} \nabla p_{i+1,\varepsilon} \cdot \mathbf{n}_{i+1,i} \\ &= - \sum_{i=1}^3 \mu_{i,\varepsilon} \int_{\Omega_{i,\varepsilon}} |\nabla p_{i,\varepsilon}|^2, \end{aligned}$$

since we have homogeneous Dirichlet boundary conditions on $\partial\Omega$ and the flux continuity conditions (17).

Hence, from Equation (21), we have

$$\sum_{i=1}^3 \int_{\Omega_{i,\varepsilon}} \partial_t p_{i,\varepsilon} = \sum_{i=1}^3 \mu_{i,\varepsilon} \left((1 - \gamma) \int_{\Omega_{i,\varepsilon}} |\nabla p_{i,\varepsilon}|^2 + \gamma \int_{\Omega_{i,\varepsilon}} p_{i,\varepsilon} G(p_{i,\varepsilon}) \right). \quad (22)$$

We integrate over time and we deduce that

$$\sum_{i=1}^3 \left(\int_{\Omega_{i,\varepsilon}} p_{i,\varepsilon}(T) - \int_{\Omega_{i,\varepsilon}} p_{i,\varepsilon}^0 + \mu_{i,\varepsilon} (\gamma - 1) \int_0^T \int_{\Omega_{i,\varepsilon}} |\nabla p_{i,\varepsilon}|^2 \right) = \sum_{i=1}^3 \gamma \int_0^T \int_{\Omega_{i,\varepsilon}} p_{i,\varepsilon} G(p_{i,\varepsilon}). \quad (23)$$

Finally, we conclude that

$$\sum_{i=1}^3 \int_0^T \int_{\Omega_{i,\varepsilon}} \mu_{i,\varepsilon} |\nabla p_{i,\varepsilon}|^2 \leq \sum_{i=1}^3 \frac{\gamma}{\gamma - 1} \int_0^T \int_{\Omega_{i,\varepsilon}} p_{i,\varepsilon} G(p_{i,\varepsilon}) + \frac{1}{\gamma - 1} \int_{\Omega_{i,\varepsilon}} p_{i,\varepsilon}^0, \quad (24)$$

Since we have already proved that $p_{i,\varepsilon}$ is bounded in $L^\infty(\Omega_T)$ and by assumption G is continuous, we finally find that

$$\sum_{i=1}^3 \mu_{i,\varepsilon} \int_0^T \int_{\Omega_{i,\varepsilon}} |\nabla p_{i,\varepsilon}|^2 \leq C, \quad (25)$$

where C denotes a constant independent of ε . Since both $\mu_{1,\varepsilon}$ and $\mu_{3,\varepsilon}$ are bounded from below away from zero, we conclude that the uniform bound holds in $\Omega \setminus \Omega_{2,\varepsilon}$. \square

Remark 3.2. Let us also notice that, differently from [33], where the author studies the linear and uniformly parabolic case, proving weak compactness is not enough. Indeed, due to the presence of the nonlinear term $u \nabla p$, it is necessary to infer strong compactness of u . For this reason, the L^1 -uniform estimate on the time derivative proven in Lemma 3.1 is fundamental.

4 Limit $\varepsilon \rightarrow 0$

We have now the *a priori* tools to face the limit $\varepsilon \rightarrow 0$. We need to construct an extension operator with the aim of controlling uniformly, with respect to ε , the pressure gradient in $L^2(\Omega)$. Indeed, from (25), we see that one cannot find a uniform bound for $\|\nabla p_{2,\varepsilon}\|_{L^2(\Omega_{2,\varepsilon})}$. The blow-up of Estimate (25) for $i = 2$, is in fact the main challenge in order to find compactness on Ω . To this end, following [33], we introduce in Subsection 4.1 an extension operator which projects the points of $\Omega_{1,\varepsilon} \cup \Omega_{3,\varepsilon}$ inside $\Omega_{2,\varepsilon}$. Then, introducing proper test functions such that the variational formulation for $\varepsilon > 0$ in (8) and $\varepsilon \rightarrow 0$ in (6) are well-defined, we can pass to the limit (Subsection 4.2).

4.1 Extension operator and compactness

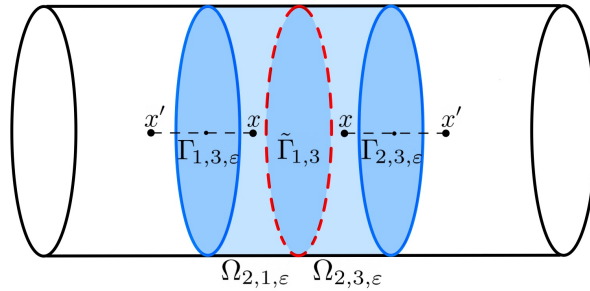


Figure 2: Representation of the spatial symmetry used in the definition of the extension operator, cf. Equation (26) and of the two subdomains of $\Omega_{2,1,\varepsilon}$ and $\Omega_{2,3,\varepsilon}$.

As mentioned above, in order to be able to pass to the limit $\varepsilon \rightarrow 0$, we first need to define the following extension operator

$$\mathcal{P}_\varepsilon : L^q(0, T; W^{1,p}(\Omega \setminus \Omega_{2,\varepsilon})) \rightarrow L^q(0, T; W^{1,p}(\Omega \setminus \tilde{\Gamma}_{1,3})), \quad \text{for } 1 \leq p, q \leq +\infty,$$

as follows for a general function $z \in L^q(0, T; W^{1,p}(\Omega \setminus \Omega_{2,\varepsilon}))$,

$$\mathcal{P}_\varepsilon(z(t, x)) = \begin{cases} z(t, x), & \text{if } x \in \Omega_{1,\varepsilon} \cup \Omega_{3,\varepsilon}, \\ z(t, x'), & \text{if } x \in \Omega_{2,\varepsilon}, \end{cases} \quad (26)$$

where x' is the symmetric of x with respect to $\Gamma_{1,2,\varepsilon}$ (or $\Gamma_{2,3,\varepsilon}$) if $x \in \Omega_{2,1,\varepsilon}$ (respectively $x \in \Omega_{2,3,\varepsilon}$), as illustrated in Figure 2. It can be easily seen that the function $g : x \rightarrow x'$ for $x \in \Omega_{2,\varepsilon}$ and its inverse have uniformly bounded first derivatives. Hence, we infer that \mathcal{P}_ε is linear and bounded, *i.e.*

$$\|\mathcal{P}_\varepsilon(z)\|_{L^q(0,T;W^{1,p}(\Omega \setminus \tilde{\Gamma}_{1,3}))} \leq C, \quad \forall z \in L^q(0, T; W^{1,p}(\Omega \setminus \Omega_{2,\varepsilon})).$$

Since the previous bound is uniform in ε , we obtain that \mathcal{P}_ε remains bounded even in the limit $\varepsilon \rightarrow 0$. Let us notice that the extension operator is well defined also from $L^1((0, T) \times (\Omega \setminus \Omega_{2,\varepsilon}))$ into $L^1((0, T) \times (\Omega \setminus \tilde{\Gamma}_{1,3}))$. Hence, we can apply it also on u_ε and $\partial_t p_\varepsilon$.

Remark 4.1. Thanks to the properties of the extension operator, the estimates stated in Lemma 3.1 hold true also upon applying $\mathcal{P}_\varepsilon(\cdot)$ on $p_\varepsilon, u_\varepsilon$, and $\partial_t p_\varepsilon$, namely

$$\begin{aligned} 0 &\leq \mathcal{P}_\varepsilon(p_\varepsilon) \leq p_H, & 0 &\leq \mathcal{P}_\varepsilon(u_\varepsilon) \leq u_H, \\ \partial_t \mathcal{P}_\varepsilon(p_\varepsilon) &\in L^\infty(0, T; L^1(\Omega \setminus \tilde{\Gamma}_{1,3})), \\ \nabla \mathcal{P}_\varepsilon(p_\varepsilon) &\in L^2(0, T; L^2(\Omega \setminus \tilde{\Gamma}_{1,3})). \end{aligned}$$

Lemma 4.2 (Compactness of the extension operator). *Let $(u_\varepsilon, p_\varepsilon)$ be the solution of Problem (1). There exists a couple (\tilde{u}, \tilde{p}) with*

$$\tilde{u} \in L^\infty(0, T; L^\infty(\Omega \setminus \tilde{\Gamma}_{1,3})), \quad \tilde{p} \in L^2(0, T; H^1(\Omega \setminus \tilde{\Gamma}_{1,3})) \cap L^\infty(0, T; L^\infty(\Omega \setminus \tilde{\Gamma}_{1,3})),$$

such that, up to a subsequence, it holds

- (i) $\mathcal{P}_\varepsilon(p_\varepsilon) \rightarrow \tilde{p}$ strongly in $L^p(0, T; L^p(\Omega \setminus \tilde{\Gamma}_{1,3}))$, for $1 \leq p < +\infty$,
- (ii) $\mathcal{P}_\varepsilon(u_\varepsilon) \rightarrow \tilde{u}$ strongly in $L^p(0, T; L^p(\Omega \setminus \tilde{\Gamma}_{1,3}))$, for $1 \leq p < +\infty$,
- (iii) $\nabla \mathcal{P}_\varepsilon(p_\varepsilon) \rightharpoonup \nabla \tilde{p}$ weakly in $L^2(0, T; L^2(\Omega \setminus \tilde{\Gamma}_{1,3}))$.

Proof. (i). Since both $\partial_t \mathcal{P}_\varepsilon(p_\varepsilon)$ and $\nabla \mathcal{P}_\varepsilon(p_\varepsilon)$ are bounded in $L^1(0, T; L^1(\Omega \setminus \tilde{\Gamma}_{1,3}))$ uniformly with respect to ε , we infer the strong compactness of $\mathcal{P}_\varepsilon(p_\varepsilon)$ in $L^1(0, T; L^1(\Omega \setminus \tilde{\Gamma}_{1,3}))$. Let us also notice that since both u_ε and p_ε are uniformly bounded in $L^\infty(0, T; L^\infty(\Omega \setminus \tilde{\Gamma}_{1,3}))$ then the strong convergence holds in any $L^p(0, T; L^p(\Omega \setminus \tilde{\Gamma}_{1,3}))$ with $1 \leq p < \infty$.

(ii). From (i), we can extract a subsequence of $\mathcal{P}_\varepsilon(p_\varepsilon)$ which converges almost everywhere. Then, remembering that $u_\varepsilon = p_\varepsilon^{1/\gamma}$, with $\gamma > 1$ fixed, we have convergence of $\mathcal{P}_\varepsilon(u_\varepsilon)$ almost everywhere. Thanks to the uniform L^∞ -bound of $\mathcal{P}_\varepsilon(u_\varepsilon)$, Lebesgue's theorem implies the statement. Let us point out that, in particular, the L^∞ -uniform bound is also valid in the limit.

(iii). The uniform boundedness of $\nabla \mathcal{P}_\varepsilon(p_\varepsilon)$ in $L^2(0, T; L^2(\Omega \setminus \tilde{\Gamma}_{1,3}))$ immediately implies weak convergence up to a subsequence. □

4.2 Test function space and passage to the limit $\varepsilon \rightarrow 0$

Since in the limit we expect a discontinuity of the density on $\tilde{\Gamma}_{1,3}$, we need to define a suitable space of test functions. Therefore we construct the space E^* as follows. Let us consider a function $\zeta \in \mathcal{D}(\Omega)$ (i.e. $C_c^\infty(\Omega)$). For any $\varepsilon > 0$ small enough, we build the function $v_\varepsilon = \mathcal{P}_\varepsilon(\zeta)$, using the extension operator previously defined. The space of all finite (and therefore well-defined) linear combinations of these functions v_ε is called $E^* \subset H^1(\Omega \setminus \tilde{\Gamma}_{1,3})$. We stress that the functions of E^* are discontinuous on $\tilde{\Gamma}_{1,3}$.

In the weak formulation of the limit problem (6), we will make use of piece-wise C^∞ -test functions (discontinuous on $\tilde{\Gamma}_{1,3}$) of the type $w(t, x) = \varphi(t)v(x)$, where $\varphi \in C^1([0, T])$ with $\varphi(T) = 0$ and $v \in E^*$. Therefore, w belongs to $C^1([0, T]; E^*)$. On the other hand, in the variational formulation (8), i.e. for $\varepsilon > 0$, $H^1(0, T; H_0^1(\Omega))$ test functions are required. Thus, in order to study the limit $\varepsilon \rightarrow 0$, we need to introduce a proper sequence of test functions depending on ε that converges to w . To this end, we define the operator $L_\varepsilon : C^1([0, T]; E^*) \rightarrow H^1(0, T; H_0^1(\Omega))$ such that

$$L_\varepsilon(w) \rightarrow w, \quad \text{uniformly as } \varepsilon \rightarrow 0, \quad \forall w \in C^1([0, T]; E^*).$$

In this way, $L_\varepsilon(w)$ belongs to $H^1(0, T; H_0^1(\Omega))$, therefore, it can be used as test function in the formulation (8).

Following Sanchez-Palancia, [33], for all $t \in [0, T]$ and $x = (x_1, x_2, x_3) \in \Omega$, we define

$$L_\varepsilon(w(t, x)) = \begin{cases} w(t, x), & \text{if } x \notin \Omega_{2\varepsilon}, \\ \frac{1}{2} \left[w\left(t, x_1, x_2, \frac{\varepsilon}{2}\right) + w\left(t, x_1, x_2, -\frac{\varepsilon}{2}\right) \right] \\ \quad + \left[w\left(t, x_1, x_2, \frac{\varepsilon}{2}\right) - w\left(t, x_1, x_2, -\frac{\varepsilon}{2}\right) \right] \frac{x_3}{\varepsilon}, & \text{otherwise.} \end{cases}$$

It can be easily verified that L_ε is linear with respect to x_3 in $\Omega_{2\varepsilon}$ and is continuous on $\partial\Omega_{2\varepsilon}$. Let us notice that it holds

$$\left| \frac{\partial L_\varepsilon(w)}{\partial x_3} \right| \leq \frac{C}{\varepsilon}. \quad (27)$$

Furthermore, thanks to the mean value theorem, the partial derivatives of L_ε with respect to x_1 and x_2 are bounded by a constant (independent of ε),

$$\left| \frac{\partial L_\varepsilon(w)}{\partial x_1} \right| \leq C, \quad \left| \frac{\partial L_\varepsilon(w)}{\partial x_2} \right| \leq C,$$

and since the measure of $\Omega_{2\varepsilon}$ is proportional to ε , we have

$$\int_0^T \int_{\Omega_{2\varepsilon}} \left| \frac{\partial L_\varepsilon(w)}{\partial x_1} \right|^2 + \left| \frac{\partial L_\varepsilon(w)}{\partial x_2} \right|^2 \leq C\varepsilon. \quad (28)$$

Given $w \in C^1([0, T]; E^*)$, we take $L_\varepsilon(w)$ as a test function in the variational formulation of the problem, *i.e.* Equation (8), and we have

$$\begin{aligned} - \int_0^T \int_{\Omega} u_\varepsilon \partial_t L_\varepsilon(w) + \sum_{i=1}^3 \mu_{i,\varepsilon} \int_0^T \int_{\Omega_{i,\varepsilon}} u_{i,\varepsilon} \nabla p_{i,\varepsilon} \cdot \nabla L_\varepsilon(w) \\ = \int_0^T \int_{\Omega} u_\varepsilon G(p_\varepsilon) L_\varepsilon(w) + \int_{\Omega} u_\varepsilon^0 L_\varepsilon(w^0). \end{aligned} \quad (29)$$

Thanks to the *a priori* estimates already proven, *cf.* Lemma 3.1, Remark 4.1 and the convergence result on the extension operator, *cf.* Lemma 4.2, we are now able to pass to the limit $\varepsilon \rightarrow 0$ and recover the effective interface problem.

Theorem 4.3. *For all test functions of the form $w(t, x) := \varphi(t)v(x)$ with $\varphi \in C^1([0, T])$ and $v \in E^*$, the limit couple (\tilde{u}, \tilde{p}) of Lemma 4.2 satisfies the following equation*

$$\begin{aligned} - \int_0^T \int_{\Omega} \tilde{u} \partial_t w + \tilde{\mu}_1 \int_0^T \int_{\tilde{\Omega}_1} \tilde{u} \nabla \tilde{p} \cdot \nabla w + \tilde{\mu}_3 \int_0^T \int_{\tilde{\Omega}_3} \tilde{u} \nabla \tilde{p} \cdot \nabla w \\ + \tilde{\mu}_{1,3} \int_0^T \int_{\tilde{\Gamma}_{1,3}} \llbracket \Pi \rrbracket (w|_{x_3=0^+} - w|_{x_3=0^-}) = \int_0^T \int_{\Omega} \tilde{u} G(\tilde{p}) w + \int_{\Omega} \tilde{u}^0 w^0, \end{aligned}$$

where

$$\llbracket \Pi \rrbracket := \frac{\gamma}{\gamma+1} (\tilde{u}^{\gamma+1})|_{x_3=0^+} - \frac{\gamma}{\gamma+1} (\tilde{u}^{\gamma+1})|_{x_3=0^-},$$

and $(\cdot)|_{x_3=0^\pm} = \mathcal{T}(\cdot)$, with \mathcal{T} the trace operator defined in Section 2.

Proof. We may pass to the limit in Equation (29), computing each term individually.

Step 1. Time derivative integral. We split the first integral into two parts

$$-\int_0^T \int_{\Omega} u_{\varepsilon} \partial_t L_{\varepsilon}(w) = -\underbrace{\int_0^T \int_{\Omega_{1,\varepsilon} \cup \Omega_{3,\varepsilon}} u_{\varepsilon} \partial_t L_{\varepsilon}(w)}_{\mathcal{I}_1} - \underbrace{\int_0^T \int_{\Omega_{2,\varepsilon}} u_{\varepsilon} \partial_t L_{\varepsilon}(w)}_{\mathcal{I}_2}.$$

Since outside of $\Omega_{2,\varepsilon}$ the extension operator coincides with the identity, and $L_{\varepsilon}(w) = w$, we have

$$\mathcal{I}_1 = -\int_0^T \int_{\Omega_{1,\varepsilon} \cup \Omega_{3,\varepsilon}} \mathcal{P}_{\varepsilon}(u_{\varepsilon}) \partial_t w = -\int_0^T \int_{\Omega} \mathcal{P}_{\varepsilon}(u_{\varepsilon}) \partial_t w + \int_0^T \int_{\Omega_{2,\varepsilon}} \mathcal{P}_{\varepsilon}(u_{\varepsilon}) \partial_t w.$$

Thanks to Remark 4.1, we know that the last integral converges to zero, since both $\mathcal{P}_{\varepsilon}(u_{\varepsilon})$ and $\partial_t w$ are bounded in L^2 and the measure of $\Omega_{2,\varepsilon}$ tends to zero as $\varepsilon \rightarrow 0$. Then, by Lemma 4.2, we have

$$-\int_0^T \int_{\Omega} \mathcal{P}_{\varepsilon}(u_{\varepsilon}) \partial_t w \longrightarrow -\int_0^T \int_{\Omega} \tilde{u} \partial_t w, \quad \text{as } \varepsilon \rightarrow 0,$$

where we used the weak convergence of $\mathcal{P}_{\varepsilon}(u_{\varepsilon})$ to \tilde{u} in $L^2(0, T; L^2(\Omega \setminus \tilde{\Gamma}_{1,3}))$. The term \mathcal{I}_2 vanishes in the limit, since both u_{ε} and $\partial_t L_{\varepsilon}(w)$ are bounded in L^2 uniformly with respect to ε . Hence, we finally have

$$-\int_0^T \int_{\Omega} u_{\varepsilon} \partial_t L_{\varepsilon}(w) \longrightarrow -\int_0^T \int_{\Omega} \tilde{u} \partial_t w, \quad \text{as } \varepsilon \rightarrow 0. \quad (30)$$

Step 2. Reaction integral. We use the same argument for the reaction term, namely

$$\int_0^T \int_{\Omega} u_{\varepsilon} G(p_{\varepsilon}) L_{\varepsilon}(w) = \underbrace{\int_0^T \int_{\Omega_{1,\varepsilon} \cup \Omega_{3,\varepsilon}} u_{\varepsilon} G(p_{\varepsilon}) L_{\varepsilon}(w)}_{\mathcal{K}_1} + \underbrace{\int_0^T \int_{\Omega_{2,\varepsilon}} u_{\varepsilon} G(p_{\varepsilon}) L_{\varepsilon}(w)}_{\mathcal{K}_2}.$$

Using again the convergence result on the extension operator, cf. Lemma 4.2, we obtain

$$\mathcal{K}_1 = \int_0^T \int_{\Omega_{1,\varepsilon} \cup \Omega_{3,\varepsilon}} \mathcal{P}_{\varepsilon}(u_{\varepsilon}) G(\mathcal{P}_{\varepsilon}(p_{\varepsilon})) w \longrightarrow \int_0^T \int_{\Omega} \tilde{u} G(\tilde{p}) w, \quad \text{as } \varepsilon \rightarrow 0,$$

since both $\mathcal{P}_{\varepsilon}(u_{\varepsilon})$ and $G(\mathcal{P}_{\varepsilon}(p_{\varepsilon}))$ converge strongly in $L^2(0, T; L^2(\Omega \setminus \tilde{\Gamma}_{1,3}))$. Arguing as before, it is immediate to see that \mathcal{K}_2 vanishes in the limit. Hence

$$\int_0^T \int_{\Omega} u_{\varepsilon} G(p_{\varepsilon}) L_{\varepsilon}(w) \longrightarrow \int_0^T \int_{\Omega} \tilde{u} G(\tilde{p}) w, \quad \text{as } \varepsilon \rightarrow 0. \quad (31)$$

Step 3. Initial data integral. From (A-data3), it is easy to see that

$$\int_{\Omega} u_{\varepsilon}^0 L_{\varepsilon}(w^0) \longrightarrow \int_{\Omega} \tilde{u}^0 w^0, \quad \text{as } \varepsilon \rightarrow 0. \quad (32)$$

Step 4. Divergence integral. Now it remains to treat the divergence term in Equation (29), from which we recover the effective interface conditions at the limit.

Since the extension operator $\mathcal{P}_{\varepsilon}$ is in fact the identity operator on $\Omega \setminus \Omega_{2,\varepsilon}$, we can write

$$\begin{aligned} & \sum_{i=1}^3 \mu_{i,\varepsilon} \int_0^T \int_{\Omega_{i,\varepsilon}} u_{i,\varepsilon} \nabla p_{i,\varepsilon} \cdot \nabla L_{\varepsilon}(w) \\ &= \underbrace{\sum_{i=1,3} \mu_{i,\varepsilon} \int_0^T \int_{\Omega_{i,\varepsilon}} \mathcal{P}_{\varepsilon}(u_{i,\varepsilon}) \nabla \mathcal{P}_{\varepsilon}(p_{i,\varepsilon}) \cdot \nabla w}_{\mathcal{H}_1} + \underbrace{\mu_{2,\varepsilon} \int_0^T \int_{\Omega_{2,\varepsilon}} u_{2,\varepsilon} \nabla p_{2,\varepsilon} \cdot \nabla L_{\varepsilon}(w)}_{\mathcal{H}_2}. \end{aligned} \quad (33)$$

We treat the two terms separately. Since we want to use the weak convergence of $\nabla \mathcal{P}_\varepsilon(p_\varepsilon)$ in $L^2(0, T; L^2(\Omega \setminus \tilde{\Gamma}_{1,3}))$ (together with the strong convergence of $\mathcal{P}_\varepsilon(u_\varepsilon)$ in $L^2(0, T; L^2(\Omega \setminus \tilde{\Gamma}_{1,3}))$) we need to write the term \mathcal{H}_1 as an integral over Ω . To this end, let $\bar{\mu}_\varepsilon := \bar{\mu}_\varepsilon(x)$ be a function defined as follows

$$\bar{\mu}_\varepsilon(x) := \begin{cases} \mu_{1,\varepsilon} & \text{for } x \in \Omega_{1,\varepsilon}, \\ 0 & \text{for } x \in \Omega_{2,\varepsilon}, \\ \mu_{3,\varepsilon} & \text{for } x \in \Omega_{3,\varepsilon}. \end{cases}$$

Then, we can write

$$\mathcal{H}_1 = \int_0^T \int_\Omega \bar{\mu}_\varepsilon \mathcal{P}_\varepsilon(u_\varepsilon) \nabla \mathcal{P}_\varepsilon(p_\varepsilon) \cdot \nabla w.$$

Let us notice that as ε goes to 0, $\bar{\mu}_\varepsilon$ converges to $\tilde{\mu}_1$ in $\tilde{\Omega}_1$ and $\tilde{\mu}_3$ in $\tilde{\Omega}_3$. Therefore, by Lemma 4.2, we infer

$$\mathcal{H}_1 \longrightarrow \tilde{\mu}_1 \int_{\tilde{\Omega}_1} \tilde{u} \nabla \tilde{p} \cdot \nabla w + \tilde{\mu}_3 \int_{\tilde{\Omega}_3} \tilde{u} \nabla \tilde{p} \cdot \nabla w, \quad \text{as } \varepsilon \rightarrow 0. \quad (34)$$

Now we treat the term \mathcal{H}_2 , which can be written as

$$\begin{aligned} \mathcal{H}_2 &= \mu_{2,\varepsilon} \int_0^T \int_{\Omega_{2,\varepsilon}} u_{2,\varepsilon} \nabla p_{2,\varepsilon} \cdot \nabla L_\varepsilon(w) \\ &= \mu_{2,\varepsilon} \int_0^T \int_{\Omega_{2,\varepsilon}} \left(u_{2,\varepsilon} \frac{\partial p_{2,\varepsilon}}{\partial x_1} \frac{\partial L_\varepsilon(w)}{\partial x_1} + u_{2,\varepsilon} \frac{\partial p_{2,\varepsilon}}{\partial x_2} \frac{\partial L_\varepsilon(w)}{\partial x_2} \right) + \mu_{2,\varepsilon} \int_0^T \int_{\Omega_{2,\varepsilon}} u_{2,\varepsilon} \frac{\partial p_{2,\varepsilon}}{\partial x_3} \frac{\partial L_\varepsilon(w)}{\partial x_3}. \end{aligned}$$

By the Cauchy-Schwarz inequality, the a priori estimate (25), and Equation (28), we have

$$\begin{aligned} &\mu_{2,\varepsilon} \int_0^T \int_{\Omega_{2,\varepsilon}} u_{2,\varepsilon} \frac{\partial p_{2,\varepsilon}}{\partial x_1} \frac{\partial L_\varepsilon(w)}{\partial x_1} + u_{2,\varepsilon} \frac{\partial p_{2,\varepsilon}}{\partial x_2} \frac{\partial L_\varepsilon(w)}{\partial x_2} \\ &\leq \mu_{2,\varepsilon}^{1/2} \|u_{2,\varepsilon}\|_{L^\infty((0,T) \times \Omega_{2,\varepsilon})} \left(\left\| \mu_{2,\varepsilon}^{1/2} \frac{\partial p_{2,\varepsilon}}{\partial x_1} \right\|_{L^2((0,T) \times \Omega_{2,\varepsilon})} \left\| \frac{\partial L_\varepsilon(w)}{\partial x_1} \right\|_{L^2((0,T) \times \Omega_{2,\varepsilon})} \right) \\ &\quad + \mu_{2,\varepsilon}^{1/2} \|u_{2,\varepsilon}\|_{L^\infty((0,T) \times \Omega_{2,\varepsilon})} \left(\left\| \mu_{2,\varepsilon}^{1/2} \frac{\partial p_{2,\varepsilon}}{\partial x_2} \right\|_{L^2((0,T) \times \Omega_{2,\varepsilon})} \left\| \frac{\partial L_\varepsilon(w)}{\partial x_2} \right\|_{L^2((0,T) \times \Omega_{2,\varepsilon})} \right) \\ &\leq C \mu_{2,\varepsilon}^{1/2} \varepsilon^{1/2} \rightarrow 0. \end{aligned}$$

On the other hand, by Fubini's theorem, the following equality holds

$$\begin{aligned}
& \mu_{2,\varepsilon} \int_0^T \int_{\Omega_{2,\varepsilon}} u_{2,\varepsilon} \frac{\partial p_{2,\varepsilon}}{\partial x_3} \frac{\partial L_\varepsilon(w)}{\partial x_3} \\
&= \mu_{2,\varepsilon} \frac{\gamma}{\gamma+1} \int_0^T \int_{\Omega_{2,\varepsilon}} \frac{\partial u_{2,\varepsilon}^{\gamma+1}}{\partial x_3} \frac{\partial L_\varepsilon(w)}{\partial x_3} \\
&= \mu_{2,\varepsilon} \frac{\gamma}{\gamma+1} \int_0^T \int_{-\varepsilon/2}^{\varepsilon/2} \int_{\tilde{\Gamma}_{1,3}} \frac{\partial u_{2,\varepsilon}^{\gamma+1}}{\partial x_3} \frac{\partial L_\varepsilon(w)}{\partial x_3} d\sigma dx_3 \\
&= \mu_{2,\varepsilon} \frac{\gamma}{\gamma+1} \int_0^T \int_{-\varepsilon/2}^{\varepsilon/2} \int_{\tilde{\Gamma}_{1,3}} \frac{\partial u_{2,\varepsilon}^{\gamma+1}}{\partial x_3} \frac{w|_{x_3=\frac{\varepsilon}{2}} - w|_{x_3=-\frac{\varepsilon}{2}}}{\varepsilon} d\sigma dx_3 \\
&= \frac{\mu_{2,\varepsilon}}{\varepsilon} \frac{\gamma}{\gamma+1} \int_0^T \int_{\tilde{\Gamma}_{1,3}} \left(w|_{x_3=\frac{\varepsilon}{2}} - w|_{x_3=-\frac{\varepsilon}{2}} \right) \int_{-\varepsilon/2}^{\varepsilon/2} \frac{\partial u_{2,\varepsilon}^{\gamma+1}}{\partial x_3} dx_3 d\sigma \\
&= \frac{\mu_{2,\varepsilon}}{\varepsilon} \frac{\gamma}{\gamma+1} \int_0^T \int_{\tilde{\Gamma}_{1,3}} \left((u_{2,\varepsilon}^{\gamma+1})|_{x_3=\frac{\varepsilon}{2}} - (u_{2,\varepsilon}^{\gamma+1})|_{x_3=-\frac{\varepsilon}{2}} \right) \cdot \left(w|_{x_3=\frac{\varepsilon}{2}} - w|_{x_3=-\frac{\varepsilon}{2}} \right).
\end{aligned}$$

Therefore,

$$\lim_{\varepsilon \rightarrow 0} \mathcal{H}_2 = \lim_{\varepsilon \rightarrow 0} \frac{\mu_{2,\varepsilon}}{\varepsilon} \frac{\gamma}{\gamma+1} \int_0^T \int_{\tilde{\Gamma}_{1,3}} \left((u_{2,\varepsilon}^{\gamma+1})|_{x_3=\frac{\varepsilon}{2}} - (u_{2,\varepsilon}^{\gamma+1})|_{x_3=-\frac{\varepsilon}{2}} \right) \cdot \left(w|_{x_3=\frac{\varepsilon}{2}} - w|_{x_3=-\frac{\varepsilon}{2}} \right). \quad (35)$$

In order to conclude the proof, we state the following lemma, which is proven [below](#).

Lemma 4.4. *The following limit holds uniformly in $\tilde{\Gamma}_{1,3}$*

$$w|_{x_3=\frac{\varepsilon}{2}} - w|_{x_3=-\frac{\varepsilon}{2}} \longrightarrow w|_{x_3=0^+} - w|_{x_3=0^-}, \quad \text{as } \varepsilon \rightarrow 0. \quad (36)$$

Moreover,

$$\frac{\gamma}{\gamma+1} \left((u_{2,\varepsilon}^{\gamma+1})|_{x_3=\frac{\varepsilon}{2}} - (u_{2,\varepsilon}^{\gamma+1})|_{x_3=-\frac{\varepsilon}{2}} \right) \longrightarrow \frac{\gamma}{\gamma+1} \left((\tilde{u}^{\gamma+1})|_{x_3=0^+} - (\tilde{u}^{\gamma+1})|_{x_3=0^-} \right), \quad (37)$$

strongly in $L^2(0, T; L^2(\tilde{\Gamma}_{1,3}))$, as $\varepsilon \rightarrow 0$.

We may finally find the limit of the term \mathcal{H}_2 , using Assumption (7), and applying Lemma 4.4 to Equation (35)

$$\begin{aligned}
& \frac{\mu_{2,\varepsilon}}{\varepsilon} \frac{\gamma}{\gamma+1} \int_0^T \int_{\tilde{\Gamma}_{1,3}} \left((u_{2,\varepsilon}^{\gamma+1})|_{x_3=\frac{\varepsilon}{2}} - (u_{2,\varepsilon}^{\gamma+1})|_{x_3=-\frac{\varepsilon}{2}} \right) \cdot \left(w|_{x_3=\frac{\varepsilon}{2}} - w|_{x_3=-\frac{\varepsilon}{2}} \right) \\
& \longrightarrow \tilde{\mu}_{1,3} \frac{\gamma}{\gamma+1} \int_0^T \int_{\tilde{\Gamma}_{1,3}} \left((\tilde{u}^{\gamma+1})|_{x_3=0^+} - (\tilde{u}^{\gamma+1})|_{x_3=0^-} \right) \cdot \left(w|_{x_3=0^+} - w|_{x_3=0^-} \right),
\end{aligned}$$

as $\varepsilon \rightarrow 0$. Combining the above convergence to Equation (33) and Equation (34), we find the limit of the divergence term as ε goes to 0,

$$\begin{aligned}
& \sum_{i=1}^3 \mu_{i,\varepsilon} \int_0^T \int_{\Omega_{i,\varepsilon}} u_{i,\varepsilon} \nabla p_{i,\varepsilon} \cdot \nabla L_\varepsilon(w) \\
& \longrightarrow \tilde{\mu}_1 \int_0^T \int_{\tilde{\Omega}_1} \tilde{u} \nabla \tilde{p} \cdot \nabla w + \tilde{\mu}_3 \int_0^T \int_{\tilde{\Omega}_3} \tilde{u} \nabla \tilde{p} \cdot \nabla w \\
& \quad + \tilde{\mu}_{1,3} \frac{\gamma}{\gamma+1} \int_0^T \int_{\tilde{\Gamma}_{1,3}} \left((\tilde{u}^{\gamma+1})|_{x_3=0^+} - (\tilde{u}^{\gamma+1})|_{x_3=0^-} \right) \cdot \left(w|_{x_3=0^+} - w|_{x_3=0^-} \right),
\end{aligned}$$

which, together with Equations (29), (30), (31), and (32), concludes the proof. \square

We now turn to the proof of Lemma 4.4

Proof of Lemma 4.4. Since by definition $w(t, x) = \varphi(t)v(x)$, with $\varphi \in C^1([0, T])$ and $v \in E^*$, the uniform convergence in Equation (36) comes from the piece-wise differentiability of w .

A little bit trickier is the second convergence, *i.e.* Equation (37). We recall that on $\{x_3 = \pm\varepsilon/2\}$, $u_{2,\varepsilon}^{\gamma+1}$ coincides with $\mathcal{P}_\varepsilon(u_\varepsilon^{\gamma+1})$, since across the interfaces u_ε is continuous and $\mathcal{P}_\varepsilon(u_{i,\varepsilon}) = u_{i,\varepsilon}$, for $i = 1, 3$. Moreover, from (i) and (iv) in Remark 4.1, we infer that

$$\frac{\gamma}{\gamma+1} \nabla(\mathcal{P}_\varepsilon(u_\varepsilon^{\gamma+1})) = \mathcal{P}_\varepsilon(u_\varepsilon) \nabla \mathcal{P}_\varepsilon(p_\varepsilon) \in L^2(0, T; L^2(\Omega \setminus \tilde{\Gamma}_{1,3})),$$

hence

$$\|\mathcal{P}(u_\varepsilon^{\gamma+1})\|_{L^2(0,T;H^1(\Omega \setminus \tilde{\Gamma}_{1,3}))} \leq C.$$

Again from Remark 4.1, we know that

$$\|\partial_t(\mathcal{P}_\varepsilon(u_\varepsilon^{\gamma+1}))\|_{L^\infty(0,T;L^1(\Omega \setminus \tilde{\Gamma}_{1,3}))} \leq C.$$

Since we have the following embeddings

$$H^1(\Omega \setminus \tilde{\Gamma}_{1,3}) \subset\subset H^\beta(\Omega \setminus \tilde{\Gamma}_{1,3}) \subset L^1(\Omega \setminus \tilde{\Gamma}_{1,3}),$$

for every $\frac{1}{2} < \beta < 1$, upon applying Aubin-Lions lemma, [1, 23], we obtain

$$\mathcal{P}_\varepsilon(u_\varepsilon^{\gamma+1}) \longrightarrow \tilde{u}^{\gamma+1}, \quad \text{as } \varepsilon \rightarrow 0,$$

strongly in $L^2(0, T; H^\beta(\Omega \setminus \tilde{\Gamma}_{1,3}))$.

Thanks to the continuity of the trace operator $\mathcal{T} : H^\beta(\Omega \setminus \tilde{\Gamma}_{1,3}) \rightarrow L^2(\partial\Omega \cup \tilde{\Gamma}_{1,3})$, for $\frac{1}{2} < \beta < 1$, we finally recover that

$$\left\| \mathcal{P}_\varepsilon(u_\varepsilon^{\gamma+1})|_{x_3=0^\pm} - (\tilde{u}^{\gamma+1})|_{x_3=0^\pm} \right\|_{L^2(0,T;L^2(\tilde{\Gamma}_{1,3}))} \leq C \left\| \mathcal{P}_\varepsilon(u_\varepsilon^{\gamma+1}) - \tilde{u}^{\gamma+1} \right\|_{L^2(0,T;H^\beta(\Omega \setminus \tilde{\Gamma}_{1,3}))} \rightarrow 0, \quad (38)$$

as $\varepsilon \rightarrow 0$. We recall that the trace vanishes on the external boundary, $\partial\Omega$, therefore we only consider the $L^2(0, T; L^2(\tilde{\Gamma}_{1,3}))$ -norm. Recalling that L is the length of Ω , trivially, we find the following estimate

$$\begin{aligned} & \left\| \mathcal{P}_\varepsilon(u_\varepsilon^{\gamma+1})|_{x_3=\pm\varepsilon/2} - \mathcal{P}_\varepsilon(u_\varepsilon^{\gamma+1})|_{x_3=0^\pm} \right\|_{L^2(0,T;L^2(\tilde{\Gamma}_{1,3}))}^2 \\ &= \int_0^T \int_{\tilde{\Gamma}_{1,3}} \left(\int_0^{\pm\varepsilon/2} \frac{\partial \mathcal{P}_\varepsilon(u_\varepsilon^{\gamma+1})}{\partial x_3} \right)^2 \\ &= \int_0^T \int_{\tilde{\Gamma}_{1,3}} \left(\int_L \frac{\partial \mathcal{P}_\varepsilon(u_\varepsilon^{\gamma+1})}{\partial x_3} \mathbf{1}_{[0,\pm\varepsilon/2]}(x_3) \right)^2 \\ &\leq \int_0^T \int_{\tilde{\Gamma}_{1,3}} \left(\int_L \left(\frac{\partial \mathcal{P}_\varepsilon(u_\varepsilon^{\gamma+1})}{\partial x_3} \right)^2 \int_L (\mathbf{1}_{[0,\pm\varepsilon/2]}(x_3))^2 \right) \\ &\leq \frac{\varepsilon}{2} \|\nabla \mathcal{P}_\varepsilon(u_\varepsilon^{\gamma+1})\|_{L^2(0,T;L^2(\Omega \setminus \tilde{\Gamma}_{1,3}))} \\ &\leq \varepsilon C, \end{aligned}$$

and combing it with Equation (38), we finally obtain Equation (37). \square

Remark 4.5. Although not relevant from a biological point of view, let us point out that, in the case of dimension greater than 3, the analysis goes through without major changes. It is clear that the *a priori* estimates are not affected by the shape or the dimension of the domain (although some uniform constants C may depend on the dimension, this does not change the result in Lemma 3.1). The following methods, and in particular the definition of the extension operator and the functional space of test functions, clearly depends on the dimension, but the strategy is analogous for a d -dimensional cylinder with axis $\{x_1 = \dots = x_{d-1} = 0\}$.

5 Conclusions and perspectives

We proved the convergence of a continuous model of cell invasion through a membrane when its thickness is converging to zero, hence giving a rigorous derivation of the effective transmission conditions already conjectured in Chaplain *et al.*, [10]. Our strategy relies on the methods developed in [33], although we had to handle the difficulties coming from the nonlinearity and degeneracy of the system. We did not consider the case of non-constant mobilities, *i.e.* $\mu_{i,\varepsilon} := \mu_{i,\varepsilon}(t, x)$, which could bring additional challenges to the derivation of the *a priori estimates* and the compactness results. In particular, a very interesting direction both from the biological and mathematical point of view, could be coupling the system to an equation describing the evolution of the MMP concentration. In fact, as observed in [10], the permeability coefficient can depend on the local concentration of MMPs, since it indicates the level of "aggressiveness" at which the tumour is able to destroy the membrane and invade the tissue.

In a recent work [15], a formal derivation of the multi-species effective problem has been proposed. However, its rigorous proof remains an interesting and challenging open question. Indeed, introducing multiple species of cells, hence dealing with a cross-(nonlinear)-diffusion system, adds several challenges to the problem. As it is well-known, proving the existence of solutions to cross-diffusion systems with different mobilities is one of the most challenging and still open questions in the field. Nevertheless, even when dealing with the same constant mobility coefficients, the nature of the multi-species system (at least for dimension greater than one) usually requires strong compactness on the pressure gradient. We refer the reader to [17, 29] for existence results of the two-species model without membrane conditions.

Another direction of further investigation of the effective transmission problem (2) could be studying the so-called *incompressible limit*, namely the limit of the system as $\gamma \rightarrow \infty$. The study of this limit has a long history of applications to tumour growth models, and has attracted a lot of interest since it links density-based models to a geometrical (or free boundary) representation, *cf.* [19, 27].

Moreover, including the heterogeneity of the membrane in the model could not only be useful in order to improve the biological relevance of the model, but could bring interesting mathematical challenges, forcing to develop new methods or adapt already existent ones, [25], from the parabolic to the degenerate case.

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References

- [1] J.-P. Aubin. Un théorème de compacité. *C. R. Acad. Sci. Paris*, 256:5042–5044, 1963. ISSN 0001-4036. URL <https://gallica.bnf.fr/ark:/12148/bpt6k4006n/f1164.item>.
- [2] M. Bathory, M. Bulíček, and O. Souček. Existence and qualitative theory for nonlinear elliptic systems with a nonlinear interface condition used in electrochemistry. *Z. Angew. Math. Phys.*, 71(3):Paper No. 74, 24, 2020. ISSN 0044-2275. doi: 10.1007/s00033-020-01293-w. URL <https://doi-org.accesdistant.sorbonne-universite.fr/10.1007/s00033-020-01293-w>.
- [3] D. Bresch, T. Colin, E. Grenier, B. Ribba, and O. Saut. Computational modeling of solid tumor growth: the avascular stage. *SIAM J. Sci. Comput.*, 32(4):2321–2344, 2010. ISSN 1064-8275. doi: 10.1137/070708895. URL <https://doi.org/10.1137/070708895>.
- [4] H. Brezis. *Functional analysis, Sobolev spaces and partial differential equations*. Universitext. Springer, New York, 2011. ISBN 978-0-387-70913-0. URL <https://www.springer.com/gp/book/9780387709130>.
- [5] H. Brézis, L. A. Caffarelli, and A. Friedman. Reinforcement problems for elliptic equations and variational inequalities. *Ann. Mat. Pura Appl. (4)*, 123:219–246, 1980. ISSN 0003-4622. doi: 10.1007/BF01796546. URL <https://doi.org/10.1007/BF01796546>.
- [6] H. M. Byrne and M. A. J. Chaplain. Modelling the role of cell-cell adhesion in the growth and development of carcinomas. *Math. Comput. Modelling*, 24:1–17, 1996. ISSN 0895-7177. doi: [https://doi.org/10.1016/S0895-7177\(96\)00174-4](https://doi.org/10.1016/S0895-7177(96)00174-4). URL [https://doi.org/10.1016/S0895-7177\(96\)00174-4](https://doi.org/10.1016/S0895-7177(96)00174-4).
- [7] H. M. Byrne and D. Drasdo. Individual-based and continuum models of growing cell populations: a comparison. *J. Math. Biol.*, 58(4-5):657–687, 2009. ISSN 0303-6812. doi: 10.1007/s00285-008-0212-0. URL <https://doi.org/10.1007/s00285-008-0212-0>.
- [8] F. Calabrò and P. Zunino. Analysis of parabolic problems on partitioned domains with nonlinear conditions at the interface. Application to mass transfer through semi-permeable membranes. *Math. Models Methods Appl. Sci.*, 16(4):479–501, 2006. ISSN 0218-2025. doi: 10.1142/S0218202506001236. URL <https://doi.org/10.1142/S0218202506001236>.
- [9] A. Cangiani and R. Natalini. A spatial model of cellular molecular trafficking including active transport along microtubules. *J. Theoret. Biol.*, 267(4):614–625, 2010. ISSN 0022-5193. doi: 10.1016/j.jtbi.2010.08.017. URL <https://doi.org/10.1016/j.jtbi.2010.08.017>.
- [10] M. A. J. Chaplain, C. Giverso, T. Lorenzi, and L. Preziosi. Derivation and application of effective interface conditions for continuum mechanical models of cell invasion through thin membranes. *SIAM J. Appl. Math.*, 79(5):2011–2031, 2019. ISSN 0036-1399. doi: 10.1137/19M124263X. URL <https://doi.org/10.1137/19M124263X>.
- [11] G. Ciavolella and B. Perthame. Existence of a global weak solution for a reaction–diffusion problem with membrane conditions. *J. Evol. Equ.*, 2020. ISSN 1424-3202. doi: 10.1007/s00028-020-00633-7. URL <https://doi.org/10.1007/s00028-020-00633-7>.
- [12] L. Dimitrio. *Modelling nucleocytoplasmic transport with application to the intracellular dynamics of the tumor suppressor protein p53*. PhD thesis, Université Pierre et Marie

- Curie-Paris VI and Università degli Studi di Roma La Sapienza, 2012. URL <https://tel.archives-ouvertes.fr/tel-00769901/document>.
- [13] A. Friedman. Mathematical analysis and challenges arising from models of tumor growth. *Math. Models Methods Appl. Sci.*, 17(suppl.):1751–1772, 2007. ISSN 0218-2025. doi: 10.1142/S0218202507002467. URL <https://doi.org/10.1142/S0218202507002467>.
- [14] O. Gallinato, T. Colin, O. Saut, and C. Poignard. Tumor growth model of ductal carcinoma: from in situ phase to stroma invasion. *J. Theoret. Biol.*, 429:253–266, 2017. ISSN 0022-5193. doi: <https://doi.org/10.1016/j.jtbi.2017.06.022>. URL <https://doi.org/10.1016/j.jtbi.2017.06.022>.
- [15] C. Giverso, T. Lorenzi, and L. Preziosi. Effective interface conditions for continuum mechanical models describing the invasion of multiple cell populations through thin membranes. *preprint*, 2021. URL <https://arxiv.org/pdf/2104.12421.pdf>.
- [16] H. P. Greenspan. On the growth and stability of cell cultures and solid tumors. *J. Theoret. Biol.*, 56(1):229–242, 1976. ISSN 0022-5193. doi: 10.1016/S0022-5193(76)80054-9. URL [https://doi.org/10.1016/S0022-5193\(76\)80054-9](https://doi.org/10.1016/S0022-5193(76)80054-9).
- [17] P. Gwiazda, B. Perthame, and A. Świerczewska Gwiazda. A two-species hyperbolic-parabolic model of tissue growth. *Comm. Partial Differential Equations*, 44(12):1605–1618, 2019. ISSN 0360-5302. doi: 10.1080/03605302.2019.1650064. URL <https://doi.org/10.1080/03605302.2019.1650064>.
- [18] O. Kedem and A. Katchalsky. A physical interpretation of the phenomenological coefficients of membrane permeability. *J. Gen. Physiol.*, 45(1):143–179, 1961. doi: 10.1085/jgp.45.1.143. URL <https://doi.org/10.1085%2Fjgp.45.1.143>.
- [19] I. Kim and N. Požár. Porous medium equation to Hele-Shaw flow with general initial density. *Trans. Amer. Math. Soc.*, 370(2):873–909, 2018. ISSN 0002-9947. doi: 10.1090/tran/6969. URL <https://doi.org/10.1090/tran/6969>.
- [20] H. Li and X. Wang. Effective boundary conditions for the heat equation with interior inclusion. *Commun. Math. Res.*, 36(3):272–295, 2020. ISSN 1674-5647. doi: 10.4208/cmr.2020-0012. URL <https://doi.org/10.4208/cmr.2020-0012>.
- [21] J. Li, S. Rosencrans, X. Wang, and K. Zhang. Asymptotic analysis of a Dirichlet problem for the heat equation on a coated body. *Proc. Amer. Math. Soc.*, 137(5):1711–1721, 2009. ISSN 0002-9939. doi: 10.1090/S0002-9939-08-09766-9. URL <https://doi.org/10.1090/S0002-9939-08-09766-9>.
- [22] J. Li, L. Su, X. Wang, and Y. Wang. Bulk-Surface Coupling: Derivation of Two Models. *J. Diff. Eq.*, 289:1–34, 2021. ISSN 0022-0396. doi: <https://doi.org/10.1016/j.jde.2021.04.011>. URL <https://doi.org/10.1016/j.jde.2021.04.011>.
- [23] J.-L. Lions. Quelques méthodes de résolution des problèmes aux limites non linéaires. pages xx+554, 1969.
- [24] J. S. Lowengrub, H. B. Frieboes, F. Jin, Y.-L. Chuang, X. Li, P. Macklin, S. M. Wise, and V. Cristini. Nonlinear modelling of cancer: bridging the gap between cells and tumours. *Nonlinearity*, 23(1):R1–R91, 2010. ISSN 0951-7715. doi: 10.1088/0951-7715/23/1/001. URL <https://doi.org/10.1088/0951-7715/23/1/001>.

- [25] M. Neuss-Radu and W. Jäger. Effective transmission conditions for reaction-diffusion processes in domains separated by an interface. *SIAM J. Math. Anal.*, 39(3):687–720, 2007. ISSN 0036-1410. doi: 10.1137/060665452. URL <https://doi.org/10.1137/060665452>.
- [26] B. Perthame. Some mathematical models of tumor growth. *Université Pierre et Marie Curie-Paris*, 6, 2016. URL https://www.ljll.math.upmc.fr/perthame/cours_M2.pdf.
- [27] B. Perthame, F. Quirós, and J. L. Vázquez. The Hele-Shaw asymptotics for mechanical models of tumor growth. *Arch. Ration. Mech. Anal.*, 212(1):93–127, 2014. ISSN 0003-9527. doi: 10.1007/s00205-013-0704-y. URL <https://doi.org/10.1007/s00205-013-0704-y>.
- [28] L. Preziosi and A. Tosin. Multiphase modelling of tumour growth and extracellular matrix interaction: mathematical tools and applications. *J. Math. Biol.*, 58(4-5):625–656, 2009. ISSN 0303-6812. doi: 10.1007/s00285-008-0218-7. URL <https://doi.org/10.1007/s00285-008-0218-7>.
- [29] B. C. Price and X. Xu. Global existence theorem for a model governing the motion of two cell populations. *Kinet. Relat. Models*, 13(6):1175–1191, 2020. ISSN 1937-5093. doi: 10.3934/krm.2020042. URL <https://doi.org/10.3934/krm.2020042>.
- [30] A. Quarteroni, A. Veneziani, and P. Zunino. Mathematical and numerical modeling of solute dynamics in blood flow and arterial walls. *SIAM J. Numer. Anal.*, 39(5):1488–1511, 2001/02. ISSN 0036-1429. doi: 10.1137/S0036142900369714. URL <https://doi.org/10.1137/S0036142900369714>.
- [31] B. Ribba, O. Saut, T. Colin, D. Bresch, E. Grenier, and J. P. Boissel. A multiscale mathematical model of avascular tumor growth to investigate the therapeutic benefit of anti-invasive agents. *J. Theoret. Biol.*, 243(4):532–541, 2006. ISSN 0022-5193. doi: 10.1016/j.jtbi.2006.07.013. URL <https://doi.org/10.1016/j.jtbi.2006.07.013>.
- [32] T. Roose, S. J. Chapman, and P. K. Maini. Mathematical models of avascular tumor growth. *SIAM Rev.*, 49(2):179–208, 2007. ISSN 0036-1445. doi: 10.1137/S0036144504446291. URL <https://doi.org/10.1137/S0036144504446291>.
- [33] E. Sánchez-Palencia. Problèmes de perturbations liés aux phénomènes de conduction à travers des couches minces de grande résistivité. *J. Math. Pures Appl. (9)*, 53:251–269, 1974. ISSN 0021-7824.
- [34] A. Serafini. *Mathematical models for intracellular transport phenomena*. PhD thesis, Università degli Studi di Roma La Sapienza, 2007.
- [35] J. L. Vázquez. An introduction to the mathematical theory of the porous medium equation. In M. C. Delfour and G. Sabidussi, editors, *Shape Optimization and Free Boundaries*, pages 347–389. Springer Netherlands, Dordrecht, 1992. ISBN 978-94-011-2710-3. doi: 10.1007/978-94-011-2710-3_10. URL https://doi.org/10.1007/978-94-011-2710-3_10.
- [36] J. L. Vázquez. *The porous medium equation*. Oxford Mathematical Monographs. The Clarendon Press, Oxford University Press, Oxford, 2007. ISBN 978-0-19-856903-9; 0-19-856903-3. doi: 10.1093/acprof:oso/9780198569039.001.0001. URL <https://doi.org/10.1093/acprof:oso/9780198569039.001.0001>.