Supplementary Material

1 Model derivation

Let us consider a simple system model made by a monolayer of epithelial cells immersed in a large bath. The wounded epithelial layer is considered as biphasic mixture: a diffuse interface separates the wound, i.e a liquid phase with volume fraction $\phi_l = \phi_l(\mathbf{x}, t)$, from the healthy surrounding epithelial tissue, i.e. a cellular phase describing with volume fraction $\phi_c = \phi_c(\mathbf{x}, t) = 1 - \phi_l$.

We assume that the mixture is saturated, i.e. $\phi_c + \phi_l = 1$ and that the two phases have approximately the same density as water γ. Thus, we enforce the mass balance equation for each phase as:

$$\frac{\partial \phi_i}{\partial t} + \nabla \cdot (\phi_i \boldsymbol{u}_i) = \frac{\Gamma_i}{\gamma}, \qquad i = \{c, l\} \tag{S.1}$$

where $\mathbf{u}_i$ and Γ_i represent the convective velocity and the source term of the i-th phase, respectively. We define the mixture velocity as the volume-averaged velocity, i.e. $\mathbf{u} = \phi_c \mathbf{u}_c + \phi_l \mathbf{u}_l$, and the relative velocity between the phases as $\mathbf{w} = \mathbf{u}_l - \mathbf{u}_c$. The incompressibility condition imposes $\nabla \cdot \mathbf{u} = 0$. By combining the latter relations with the saturation constraint, the following expression for the single phase velocities as function of $\mathbf{u}$ and $\mathbf{w}$ is trivially obtained:

$$\mathbf{u}_l = \mathbf{u} + \mathbf{w}(1 - \phi_l), \tag{S.2a}$$

$$\mathbf{u}_c = \mathbf{u} - \phi_l \mathbf{w}. \tag{S.2b}$$

Then, substituting Equation (S.2) into Equation (S.1) and exploiting the incompressibility constrain, we

write the mass balances for the cellular phase:

$$-\frac{\partial \phi_c}{\partial t} - \mathbf{u} \cdot \nabla \phi_c = -\frac{\Gamma_c}{\gamma} - \nabla \cdot (\phi_l \phi_c \mathbf{w}), \tag{S.3}$$

and for the liquid phase:

$$\frac{\partial \phi_l}{\partial t} + \mathbf{u} \cdot \nabla \phi_l = -\frac{\Gamma_c}{\gamma} - \nabla \cdot (\phi_l \phi_c \mathbf{w}), \tag{S.4}$$

where in the last equation we prescribe that the mixture is not growing, i.e. $\Gamma_l = -\Gamma_c$. We then introduce a phase-field variable $\phi = \phi_l - \phi_c$, defined as the difference between the liquid phase and the cellular phase, such that $\phi = \{1\}$ in the wound area and $\phi = \{-1\}$ on the healthy tissue. By summing Equation (S.4) and Equation (S.3) we obtain the following mass balance for ϕ:

$$\frac{\partial \phi}{\partial t} + \mathbf{u} \cdot \nabla \phi = -2\Gamma - 2\nabla \cdot (\phi_l \phi_c \mathbf{w}) \tag{S.5}$$

where $\Gamma = \Gamma_c/\gamma$. Here we observe that the left-hand-side of Equation (S.5) correspond to a material derivative, that we denote from now on with the following notation:

$$\overset{\bullet}{\phi} = \frac{\partial \phi}{\partial t} + \mathbf{u} \cdot \nabla \phi.$$

Considering the tissue as a highly viscous mixture that is not subjected to bulk forces, we adopt a diffuse interface approach to find a thermodinamically consistent expression for the mass and energy fluxes. First, we introduce the following Landau free energy for the binary mixture:

$$F(\phi, \nabla\phi) = \int_\Omega f(\phi, \nabla\phi)\, d\Omega = \int_\Omega \Big(\frac{\beta}{\epsilon}\Psi(\phi) + \frac{\beta\epsilon}{2}|\nabla\phi|^2 \Big)\, d\Omega, \tag{S.6}$$

where Ω represents the whole domain containing the wound and the surrounding healthy tissue. We observe that the energy density in the integral contained in Equation (S.6) accounts for both the local interaction among cells within the single phase, through $\frac{\beta}{\epsilon}\Psi(\phi)$, and a short-range nonlocal interaction expressed by the gradient dependence [1, 2]. In physical terms, the parameter β plays the role of a surface tension at the wound edge, while ϵ is proportional to the thickness of the interface separating the two pure phases. We further impose a double-well form for the cell-cell interaction potential by setting $\Psi(\phi) = \frac{1}{4}(1-\phi^2)^2$, so that its minima correspond to the pure phases. This choice is a widely

employed approximation of the logarithmic dependence for the mixture entropy, that enables significant simplifications in the numerical discretization.

In the following, we are going to derive an explicit expression for the material derivative of the energy in Equation (S.6) with respect to the time. Exploiting the Reynolds theorem and the divergence theorem, we get:

$$\frac{d\,F}{d\,t} = \int_\Omega \Big(\frac{\partial f}{\partial \phi}\dot{\phi} + \frac{\partial f}{\partial \nabla \phi}\dot{\nabla}\phi + f(\nabla \cdot \mathbf{u}) \Big)\, d\Omega, \tag{S.7}$$

that combined with Equation (S.6) gives:

$$\frac{d\,F}{d\,t} = \int_\Omega \Big(\frac{\beta}{\epsilon}\Psi'(\phi)\dot{\phi} + \epsilon\beta\nabla\phi\cdot\dot{\nabla}\phi + \underbrace{\Big(\frac{\beta}{\epsilon}\Psi(\phi) + \frac{\beta\epsilon}{2}|\nabla\phi|^2 \Big)}_{f}(\nabla\cdot\mathbf{u}) \Big)\, d\Omega. \tag{S.8}$$

Proceeding as in [3], we employ the following identities:

$$\nabla\mathbf{u} : (\nabla\phi\otimes\nabla\phi) = \nabla\cdot\big[(\nabla\phi\otimes\nabla\phi)\cdot\mathbf{u}\big] - \mathbf{u}\cdot\big[\nabla\cdot(\nabla\phi\otimes\nabla\phi)\big], \tag{S.9a}$$

$$\frac{1}{2}\nabla(|\nabla\phi|^2) = \nabla\cdot(\nabla\phi\otimes\nabla\phi) - \Delta\phi\nabla\phi, \tag{S.9b}$$

$$\frac{\partial\phi}{\partial t}\nabla\phi = \dot{\phi}\nabla\phi - (\nabla\phi\cdot\mathbf{u})\nabla\phi = \dot{\phi}\nabla\phi - (\nabla\phi\otimes\nabla\phi)\cdot\mathbf{u}, \tag{S.9c}$$

$$\nabla\phi\cdot\dot{\nabla}\phi = \nabla\cdot(\dot{\phi}\nabla\phi) - \dot{\phi}\nabla\cdot(\nabla\phi) - (\nabla\phi\otimes\nabla\phi) : \nabla\mathbf{u}, \tag{S.9d}$$

from which we obtain:

$$\nabla\phi\cdot\dot{\nabla}\phi = \nabla\cdot\left(\frac{\partial\phi}{\partial t}\nabla\phi\right) - \dot{\phi}\Delta\phi + \mathbf{u}\cdot\left[\frac{1}{2}\nabla|\nabla\phi|^2 + \Delta\phi\nabla\phi\right]. \tag{S.10}$$

By substituting Equation (S.10) into Equation (S.8) we get:

$$\begin{aligned}\frac{d\,F}{d\,t} = \int_\Omega \Bigg\{ &\dot{\phi}\left(\frac{\beta}{\epsilon}\Psi'(\phi) - \beta\epsilon\Delta\phi\right) + \nabla\cdot\left(\epsilon\beta\frac{\partial\phi}{\partial t}\nabla\phi + f\mathbf{u}\right) \\ &+\mathbf{u}\cdot\left[\nabla\left(\frac{\beta\epsilon}{2}|\nabla\phi|^2 - f\right) + \beta\epsilon\Delta\phi\nabla\phi\right]\Bigg\}\, d\Omega.\end{aligned} \tag{S.11}$$

We now have to impose thermodynamic consistency of the phase-field model [4, 5].

The second law of thermodynamics in the isothermal condition imposes the following inequality to

hold

$$\frac{d\,F}{d\,t} + \int_{\partial\Omega} \mathcal{J}_e \cdot \mathbf{n}\, d\gamma - \int_{\Omega} c_e \Gamma_e \, d\Omega \leq 0, \tag{S.12}$$

where $\mathcal{J}_e$ is the energy flux, $\mathbf{n}$ is the outward unit normal of $\partial\Omega$ and $c_e\Gamma_e$ is an energy source term. Substituting (S.11) into (S.12) and applying the Reynolds transport theorem and the divergence theorem, we get the following local form of (S.12)

$$\begin{aligned}
&\dot{\phi}\left(\frac{\beta}{\epsilon}\Psi'(\phi) - \beta\epsilon\Delta\phi\right) + \nabla\cdot\left(\epsilon\beta\frac{\partial\phi}{\partial t}\nabla\phi + f\mathbf{u}\right) + \mathbf{u}\cdot\left[\nabla\left(\frac{\beta\epsilon}{2}|\nabla\phi|^2 - f\right) + \beta\epsilon\Delta\phi\nabla\phi\right] \\
&+ \nabla\cdot\mathcal{J}_e - c_e\Gamma_e \\
&- \lambda_p(\nabla\cdot\mathbf{u}) \\
&- \lambda_\mu(\dot{\phi} + 2\Gamma + 2\nabla\cdot(\phi_l\phi_c\mathbf{w})) \leq 0,
\end{aligned} \tag{S.13}$$

where we enforce the incompressibility and the mass balance constraints (from Eq. (S.5)) by using the Lagrangian multipliers λ_p and λ_μ, respectively. After trivial manipulations, (S.13) can be written as

$$\begin{aligned}
&\dot{\phi}\left(\frac{\beta}{\epsilon}\Psi'(\phi) - \epsilon\beta\Delta\phi - \lambda_\mu\right) \\
&+ \nabla\cdot\left(\mathcal{J}_e - \lambda_p\mathbf{u} + \epsilon\beta\frac{\partial\phi}{\partial t}\nabla\phi + f\mathbf{u}\right) - c_e\Gamma_e - 2\lambda_\mu\Gamma \\
&- 2\lambda_\mu\nabla\cdot(\phi_l\phi_c\mathbf{w}) + \mathbf{u}\cdot\left[\nabla\left(\lambda_p + \frac{\beta\epsilon}{2}|\nabla\phi|^2 - f\right) + \beta\epsilon\Delta\phi\nabla\phi\right] \leq 0.
\end{aligned} \tag{S.14}$$

Upon defining introducing the following notation

$$\mu := \frac{\beta}{\epsilon}\Psi'(\phi) - \epsilon\beta\Delta\phi$$

where the new variable μ behaves as a chemical potential, (S.14) drives to the constitutive assumptions

$$\mathcal{J}_e = \lambda_p\mathbf{u} - \epsilon\beta\frac{\partial\phi}{\partial t}\nabla\phi - f\mathbf{u}, \tag{S.15a}$$

$$c_e = \lambda_\mu = \mu, \tag{S.15b}$$

$$\Gamma_e = -2\Gamma. \tag{S.15c}$$

We then introduce a pressure-like function p such that

$$\lambda_p + \frac{\beta\epsilon}{2}|\nabla\phi|^2 - f = p - f_L\phi - \frac{\beta}{\epsilon}\Psi(\phi), \tag{S.16}$$

where the term f_L represents the force per unit length exerted by the cellular lamellipodia in the crawling mechanism. Thus, by substituting (S.16) into (S.14) and exploiting the constitutive assumptions in (S.15), we have the following dissipation function

$$\mathcal{D}_{iss} := -2\mu\nabla\cdot(\phi_1\phi_2\mathbf{w}) + \mathbf{u}\cdot\Big[\nabla p - \mu\nabla\phi - f_L\nabla\phi\Big]. \tag{S.17}$$

For our purposes we now introduce the Rayleighian functional $\mathcal{R}$ defined as

$$\mathcal{R} := \mathcal{W} + \mathcal{D}_{iss}, \tag{S.18}$$

where we assume the following explicit form for work done by the dissipative forces acting on the system per unit of time

$$\mathcal{W} := \nu||\mathcal{D}(\mathbf{u})||^2 + \frac{1}{2}\eta||\mathbf{u}||^2 + \phi_l^2\phi_c^2\frac{1}{M}||\mathbf{w}||^2, \tag{S.19}$$

where $\mathcal{D}(\mathbf{u})$ denotes the symmetric part of the velocity tensor gradient, ν represents the viscosity of the mixture due to the presence of homophilic interaction among cells within the tissue generating a non-negligible drag [6, 7], η the friction coefficient of the mixture over the substrate, and M the mobility coefficient of the two phases. We assumed the friction between the epithelial monolayer and the substrate as a fluid-solid interaction, having the same physical characteristics of the wetting of a liquid film on a solid surface [8].

Finally, extending the original framework proposed by Onsager [9], we propose a maximum dissipation principle to model the closure dynamics as a macroscopic collective behavior of the cells driven by thermodynamically-consistent evolution of near-equilibrium state variables, accounting for both microscopic active phenomena and dissipation mechanisms.

Thus, we enforce the maximum dissipation principle by requiring that the mixture evolves at the stationary point of the Rayleghian with respect to the mixture and relative velocities, [10]. From the condition $\delta\mathcal{R}/\delta\mathbf{w} = 0$ we get:

$$\phi_l \phi_c \mathbf{w} = -M \nabla \mu, \tag{S.20}$$

stating that the relative velocity between the phases follows the gradient of the chemical potential. From the condition $\delta \mathcal{R}/\delta \mathbf{u} = 0$, we finally get:

$$-2\nu \nabla \cdot \mathcal{D}(\mathbf{u}) + \eta \mathbf{u} = -\nabla p + \mu \nabla \phi + f_L \nabla \phi, \tag{S.21}$$

that is a Darcy-Brinkman equation with Korteweg forces driven by the chemical potential μ and by the crawling potential f_L.

1.1 Main assumption underlying the model derivation

In this part we summarize the main hypotheses underlying the model derivation proposed above.
First and foremost is the assumption that **the wounded epithelium behaves as a mixture**

- which is biphasic, saturated and incompressible;
- which is not growing;
- which is highly viscous mixture that is not subjected to bulk forces;
- whose phases has approximately the same density of the water (γ) and are separated by a diffuse interface.

From a thermodynamics perspective, the mixture is characterized by

- a Landau free energy in the form stated in (S.6) with a double-well form for the cell-cell interaction potential;
- a dissipation due to three main contribution: friction between the mixture and the substrate, friction within the single pure phase and friction at the interface between the two phases.

Lastly, we assume the mixture to evolve according to the maximum dissipation principle.

2 Sharp interface asymptotics

In this Section, we perform a formal asymptotic analysis on the model (1-4) in the limit of zero thickness interface, i.e. taking $\epsilon \to 0$. Following [3, 11–15], we consider the following assumptions:

- for small ϵ the domain Ω can be divided into two distinct open subdomains Ω^+ and Ω^-, referred as bulk regions in the following. They are separated by an interface $\Sigma(\epsilon)$ which is considered sufficiently far from the boundary $\partial\Omega$;
- there exists a family of solutions (ϕ_ϵ, μ_ϵ, $\mathbf{v}_\epsilon$, p_ϵ) for the System (1-4), that are sufficiently smooth and admit an asymptotic expansion in the parameter ϵ in the bulk regions away from the interface (outer expansion), and another expansion in the interfacial region close to $\Sigma(\epsilon)$ (inner expansion);
- the zero-level sets of ϕ_ϵ converge to a hypersurface Σ_0.

We now perform the outer and inner expansion for the dimensional model. For the sake of notation compactness, in the following we denote by $(N)^\alpha_\beta$ the outer ($\beta = O$) and inner ($\beta = I$) expansions of Equation(N) at the order ϵ^α.

2.1 Outer expansion

The physical fields f in the *outer expansions* are written as regular perturbative series $f_\epsilon \in \{\mathbf{u}_\epsilon, p_\epsilon, \phi_\epsilon, \mu_\epsilon\}$, as follows:

$$f_\epsilon = f_0 + \epsilon f_1 + \epsilon^2 f_2 + O\big(\epsilon^3\big)\,.$$

We then substitute the outer expansions in the governing Equations (1-4) and we proceed by separating the contributions at the leading orders in ϵ.

Leading Order. The leading order $(\text{S.2})^{-1}_O$ is given by:

$$\Psi'(\phi_0) = 0, \tag{S.22}$$

whose solutions correspond to the minima of the double-well potential, $\phi_0 = \pm 1$. Hence, we identify:

$$\Omega^+ = \{x \in \Omega : \phi_0(x) = +1\}\,, \qquad \Omega^- = \{x \in \Omega : \phi_0(x) = -1\},$$

as the two external subdomains representing the wound and the healthy tissue, respectively. The leading order contributions $(\text{S.3})^0_O$ is:

$$-2\nu\nabla\cdot\mathcal{D}(\mathbf{u}_0)+\eta\mathbf{u}_0=-\nabla p_0+(\mu_0+f_L)\nabla\phi_0, \tag{S.23}$$

while for $(\text{S.1})^0_O$ is:

$$\frac{\partial\phi_0}{\partial t}+\mathbf{u}_0\cdot\nabla(\phi_0)=-\Gamma+M\Delta(\mu_0). \tag{S.24}$$

Since from Equation (S.2) we get $\nabla\phi_0=0$ on $\Omega^+\cup\Omega^-$, the latter equations simplify as:

$$-2\nu\nabla\cdot\mathcal{D}(\mathbf{u}_0)+\eta\mathbf{u}_0=-\nabla p_0, \tag{S.25}$$

$$M\Delta(\mu_0)=\Gamma, \tag{S.26}$$

where in the bulk regions we are allowed to neglect the time derivative contribution. Finally, $(\text{S.4})^0_O$ gives:

$$\nabla\cdot\mathbf{u}_0=0. \tag{S.27}$$

2.2 Inner expansion and matching conditions

Parameterization of the interface and inner scaled variables. Let us now denote by Σ_0 the limiting surface of the zero level sets of the variable ϕ. In order to study the asymptotic behaviour across the interface separating Ω^+ from Ω^- we introduce a curvilinear coordinate system. Hence, we define the *signed distance function* $r(x)$ to Σ_0, assuming that $r(x)<0$ away from the wound and $r(x)>0$ within the wound. Following the above convention, we notice that $\mathbf{n}=\nabla r$ points from the intact portion of the domain to the wounded one. We further introduce the new coordinates:

- the rescaled distance $z=\frac{r}{\epsilon}$;
- the arc-length coordinate s.

Hence, in a neighborhood of the interface Σ_0, we have:

$$\mathbf{x}(s,r;t)=R(s;t)+r\mathbf{n}(R(s;t)), \tag{S.28}$$

where $R(s;t)$ denotes a parametrization of the interface by the arc-length s, so that for sufficiently smooth functions $f(\mathbf{x};t)$ the following mapping holds:

$$f(\mathbf{x};t) = f(R(s;t) + \epsilon z \mathbf{n}(R(s;t))) := F(s,z;t).$$

In the following, we adopt the new notation $\{\Phi, \Xi, \mathbf{U}, P\}$ for the set of unknowns expressed w.r.t. the new curvilinear coordinate system. Thus, similarly to what was done for the *outer regions*, here we introduce the *inner expansions*:

$$\Phi(t;s,z) = \Phi_0(t;s,z) + \epsilon\Phi_1(t;s,z) + \epsilon^2\Phi_2(t;s,z) + h.o.t,$$

$$\Xi(t;s,z) = \Xi_0(t;s,z) + \epsilon\Xi_1(t;s,z) + \epsilon^2\Xi_2(t;s,z) + h.o.t.,$$

$$\mathbf{U}(t;s,z) = \mathbf{U}_0(t;s,z) + \epsilon\mathbf{U}_1(t;s,z) + \epsilon^2\mathbf{U}_2(t;s,z) + h.o.t.,$$

$$P(t;s,z) = P_0(t;s,z) + \epsilon P_1(t;s,z) + \epsilon^2 P_2(t;s,z) + h.o.t.$$

We start the inner expansion by rescaling the corresponding differential operators in the curvilinear coordinate system defined above.

From (S.28) we have:

$$\frac{d\mathbf{x}}{dr} = \mathbf{n}(R(s,t)),$$

$$\frac{d\mathbf{x}}{ds} = \frac{dR(s,t)}{ds} + \frac{r d(\mathbf{n}(R(s,t)))}{ds} = \mathbf{t} - r\kappa\mathbf{t} = (1 - r\kappa)\mathbf{t} = (1 - \epsilon z\kappa)\mathbf{t}.$$

We use the latter relations to derive the rescaled differential operators both for a generic scalar function F and for a generic vectorial function $\mathbf{F} = F_n\mathbf{n} + F_t\mathbf{t}$:

$$\partial_t f = -\frac{\mathcal{V}}{\epsilon}\partial_z F + h.o.t.,$$

$$\nabla_x f = \frac{1}{\epsilon}\mathbf{n}\partial_z F + \mathbf{t}\partial_s F + h.o.t.,$$

$$\nabla_x \cdot \mathbf{f} = \frac{1}{\epsilon}\mathbf{n}\cdot\partial_z\mathbf{f} + \mathbf{t}\cdot\partial_s\mathbf{f} = \frac{1}{\epsilon}\partial_z F_n + \partial_s F_s - \kappa F_n + h.o.t.,$$

$$\Delta f = \frac{1}{\epsilon^2}\partial_{zz}F - \frac{\kappa}{\epsilon}\partial_z F + \partial_{ss}F + h.o.t.,$$

where $\mathcal{V}$ and κ are the normal velocity and the curvature of the interface Σ_0, respectively. We notice that $-2\kappa = \Delta r$, thus adopting the convention that the curvature of the circle is positively defined. Moreover we adopt the following notation: let $\delta > 0$ and for $\mathbf{x}$ belonging to Σ_0 with $\mathbf{x} - \delta\mathbf{n} \in \Omega^-$ and $\mathbf{x} + \delta\mathbf{n} \in \Omega^+$, the jump of a function f across the interface is defined as:

$$[f]_-^+ := \lim_{\delta \searrow 0} f(t, \mathbf{x} + \delta\mathbf{n}) - \lim_{\delta \searrow 0} f(t, \mathbf{x} - \delta\mathbf{n}). \tag{S.29}$$

Matching conditions. Following [3], we state the matching conditions by assuming that the zero level set of ϕ_ϵ converges to the sharp interface Σ_0, which implies that:

$$\Phi_0(t, s, z = 0) = 0. \tag{S.30}$$

Furthermore, we assume that:

$$\Phi_\epsilon(t, s, z = +\infty) = +1, \qquad \Phi_\epsilon(t, s, z = -\infty) = -1. \tag{S.31}$$

Let $F(t, s, z)$ be the generic inner variable and f(**x**,t) the outer variable. In order to match the inner solution valid in the interfacial region with the outer solution, the following matching conditions are considered [16]:

$$\lim_{z \to \pm\infty} F_0(t, s, z) = f_0^\pm(t, \mathbf{x}), \tag{S.32}$$

$$\lim_{z \to \pm\infty} \partial_z F_0(t, s, z) = 0, \tag{S.33}$$

$$\lim_{z \to \pm\infty} \partial_z F_1(t, s, z) = \nabla f_0^\pm(t, \mathbf{x}) \cdot \mathbf{n}, \tag{S.34}$$

where $f_0^\pm(t, \mathbf{x})$:=$\lim_{\delta \searrow 0} f_0(t, \mathbf{x} \pm \delta\mathbf{n})$ for $\mathbf{x} \in \Sigma_0$.

Leading order inner expansion. Upon replacing the inner expansions and the new expressions for the differential operators in the System (1-4), we gather the leading order expansion of each equation with respect to ϵ. The leading order $(\text{S.2})_I^{-1}$ reads:

$$\Psi'(\Phi_0) - \partial_{zz}(\Phi_0) = 0. \tag{S.35}$$

From (S.30), we consider Φ_0 a function only of the variable z, i.e. independent from s and t. Thus,

Equation (S.35) gives:

$$\Psi'(\Phi_0) - \Phi_0'' = 0, \qquad \text{with} \qquad \Phi_0(0) = 0, \quad \Phi_0(\pm\infty) = \pm 1, \tag{S.36}$$

whose solution has the shape of an hyperbolic tangent:

$$\Phi_0(z) = \tanh\left(\frac{z}{\sqrt{2}}\right). \tag{S.37}$$

The leading order $(\text{S.4})_I^{-1}$ is

$$\mathbf{n} \cdot \partial_z(\mathbf{U}_0) = 0 \tag{S.38}$$

which integrated from $-\infty$ to $+\infty$ with respect to z becomes:

$$\int_{-\infty}^{+\infty} \mathbf{n} \cdot \partial_z(\mathbf{U}_0)\, dz = [\mathbf{n} \cdot \mathbf{U}_0]_{-\infty}^{+\infty} \tag{S.39}$$

and applying the matching condition (S.32) to $\mathbf{U}_0$ we obtain:

$$[\mathbf{u}_0]_-^+ \cdot \mathbf{n} = \mathbf{u}_0^+ \cdot \mathbf{n} - \mathbf{u}_0^- \cdot \mathbf{n} = 0. \tag{S.40}$$

Regarding the Cahn-Hilliard Equation, its leading order $(\text{S.1})_I^{-2}$ is:

$$\partial_{zz}\Xi_0 = 0, \tag{S.41}$$

which integrated with respect to dz and after applying the matching condition (S.33) becomes:

$$\partial_z\Xi_0 = 0. \tag{S.42}$$

Besides, integrating between $-\infty$ and $+\infty$ w.r.t. z we have:

$$\int_{-\infty}^{+\infty} \partial_z\Xi_0\, dz = [\Xi_0]_{-\infty}^{+\infty} = 0, \tag{S.43}$$

that turns into:

$$[\mu_0]_-^+ = 0, \tag{S.44}$$

upon the application of the matching condition (S.32) to Ξ_0. To conclude, from the leading order of the Darcy-Brinkman Equation we have $(\text{S.3})_I^{-2}$:

$$-\nu \mathbf{n} \partial_{zz}(U_{n,0}) = 0, \tag{S.45}$$

which, once integrated with respect to z and upon applying the matching condition (S.33), is equivalent to (S.38) and thus leads to (S.40).

Next to leading order expansion The next to leading order of the Cahn-Hilliard Equation $(\text{S.2})_I^0$ gives:

$$\Xi_0 = \frac{\beta}{\epsilon}\Psi'(\Phi_0 + \epsilon\Phi_1) - \beta\partial_{zz}(\Phi_1) + \beta\kappa\partial_z(\Phi_0). \tag{S.46}$$

Expanding the first derivative of the double-well potential $\Psi'(\Phi)$ in Taylor's series and considering the contribution at order $\mathcal{O}(1)$ only, we get:

$$\Xi_0 = \beta\Psi''(\Phi_0)\Phi_1 - \beta\partial_{zz}(\Phi_1) + \beta\kappa\partial_z(\Phi_0). \tag{S.47}$$

Multiplying the above equation by $\partial_z\Phi_0$ (i.e. by Φ_0') and integrating it with respect to z between $-\infty$ and $+\infty$ we have:

$$\int_{-\infty}^{+\infty} \Xi_0\Phi_0'\, dz = \beta\int_{-\infty}^{+\infty} ((\Psi'(\Phi_0))'\Phi_1\partial_{zz}(\Phi_1)\Phi_0' + \kappa(\Phi_0')^2)\, dz. \tag{S.48}$$

Focusing on the first two integrands at the r.h.s. and integrating by parts, we have:

$$\begin{aligned}\int_{-\infty}^{+\infty} ((\Psi'(\Phi_0))'\Phi_1 - \partial_{zz}(\Phi_1)\Phi_0')\, dz = \\ \left[\underbrace{\Psi'(\Phi_0)\Phi_1}_{(a)} - \underbrace{\partial_z\Phi_1\Phi_0'}_{(b)}\right]_{-\infty}^{+\infty} - \int_{-\infty}^{+\infty} \partial_z\Phi_1 \underbrace{(\Psi'(\Phi_0) - \Phi_0'')}_{(c)}\, dz.\end{aligned} \tag{S.49}$$

We notice that term (a) is null thanks to matching conditions (S.32) applied to Φ_0 and hen exploiting that $\Psi'(\pm 1) = 0$. Term (b) is null thanks to the matching condition (S.33), while term (c) is equal to zero thanks to Equation (S.35). Thus, we deduce that Equation (S.49) gives no contributions and

consequently, Equation (S.48) can be written as:

$$\int_{-\infty}^{+\infty} \Xi_0 \Phi_0' \, dz = \beta\kappa \int_{-\infty}^{+\infty} (\Phi_0')^2 \, dz. \tag{S.50}$$

Focusing on the l.h.s., from the expansion to the leading order (i.e from Equation (S.42)) since $\partial_z(\Xi_0) = 0$:

$$\Xi_0 \int_{-\infty}^{+\infty} \Phi_0' \, dz = \mu_0[\phi_0]_-^+ = 2\mu_0, \tag{S.51}$$

where the first equality of the chain is given by the application of the matching condition (S.32) to both the variables, while the second equality is given by the solution of Equation (S.22). Further considerations are needed to simplify the terms in the r.h.s. of Equation (S.50). Since $\Phi_0(z) = \tanh\big(z/\sqrt{2}\big)$, we have:

$$\begin{aligned}\int_{-\infty}^{+\infty} |(\Phi_0(z))'|^2 \, dz = \int_{-\infty}^{+\infty} \left(\frac{d}{dz}\tanh\left(\frac{z}{\sqrt{2}}\right)\right)^2 dz = \int_{-\infty}^{+\infty} \left(\frac{1}{\sqrt{2}}\mathrm{sech}^2\left(\frac{z}{\sqrt{2}}\right)\right)^2 dz \\ = \int_{-\infty}^{+\infty} \frac{1}{2}\mathrm{sech}^4\left(\frac{z}{\sqrt{2}}\right) dz = \frac{2\sqrt{2}}{3}.\end{aligned} \tag{S.52}$$

Thus, substituting (S.51) and (S.52) into (S.50), we obtain:

$$2\mu_0 = \beta\kappa\frac{2\sqrt{2}}{3}. \tag{S.53}$$

From the first order of the Cahn-Hilliard Equation $(\mathrm{S.1})_I^{-1}$ we have:

$$(-\mathcal{V} + U_{n,0})\, \partial_z \Phi_0 = M(\partial_{zz}\Xi_1 - \kappa\partial_z\Xi_0), \tag{S.54}$$

where we assume Γ and M to be $\mathcal{O}(1)$. Moreover, we notice that the last term on the r.h.s. is null thanks to Equation (S.42).

Integrating in the interval $(-\infty, +\infty)$ with respect to z, Equation (S.54) becomes:

$$\int_{-\infty}^{+\infty} (-\mathcal{V} + U_{n,0})\, \partial_z \Phi_0 \, dz = M \int_{-\infty}^{+\infty} \partial_{zz}\Xi_1 \, dz. \tag{S.55}$$

Upon integrating between $-\infty$ and $+\infty$ with respect to z, exploiting (S.38) and applying the matching

condition (S.34) to the variable Ξ_1 we get:

$$2(-\mathcal{V} + u_{n,0}) = M[\nabla \mu_0]^+_- \cdot \mathbf{n}. \tag{S.56}$$

The first order of the mass balance equation $(4)^0_I$ is:

$$\mathbf{n} \cdot \partial_z(\mathbf{U}_1) + \mathbf{t}\partial_s(\mathbf{U}_0) = 0, \tag{S.57}$$

that is equivalent to:

$$\partial_z U_{n,1} - \kappa U_{n,0} + \partial_s U_{t,0} = 0. \tag{S.58}$$

To conclude, the next to leading of the Darcy-Brinkmann Equation $(S.3)^{-1}_I$ projected along the normal direction $\mathbf{n}$ and integrated between $-\infty$ and $+\infty$ with respect to z gives:

$$-\nu \int_{-\infty}^{+\infty} (\partial_{zz} U_{n,1} - \kappa \partial_z U_{n,0})\, dz = -\int_{-\infty}^{+\infty} \partial_z P_0\, dz + \int_{-\infty}^{+\infty} (\Xi_0 + f_L)\partial_z \Phi_0\, dz. \tag{S.59}$$

We can prove that the l.h.s. of the above equation gives no contribution; indeed we observe that, upon integration, it turns into:

$$-\nu[\partial_z U_{n,1} - \kappa U_{n,0}]^+_- \overset{(S.58)}{=} \nu[\partial_s U_{t,0}]^+_- = 0, \tag{S.60}$$

where the last equality is obtained thanks to the fact that the quantity $\partial_s(U_{t,0})$ is defined only on the interface so its jump across the interface is null. Thus, Equation (S.59) becomes:

$$[p_0]^+_- = 2(\mu_0 + f_L), \tag{S.61}$$

thanks to (S.42) and to the application of the matching condition (S.32). Finally, substituting (S.53) into Equation (S.61), we get:

$$[p_0]^+_- = \beta\kappa \frac{2\sqrt{2}}{3} + 2f_L. \tag{S.62}$$

3 Numerical discretization

Let consider a regular decomposition $\mathcal{T}_h$ of Ω_h, an approximation of the two-dimensional domain Ω, formed by non-overlapping triangles $\mathcal{K}_j$. We then introduce V_h and Q_h, the piece-wise finite element

spaces associated with $\mathcal{T}_h$ defined as follows:

$$V_h = \{\chi \in C^0(\bar{\Omega}) : \chi|_{\mathcal{K}_j} \in \mathbb{P}_b^1(\mathcal{K}_j) \quad \forall \mathcal{K}_j \in \mathcal{T}_h\} \subset H^1(\Omega),$$

$$Q_h = \{\chi \in C^0(\bar{\Omega}) : \chi|_{\mathcal{K}_j} \in \mathbb{P}^1(\mathcal{K}_j) \quad \forall \mathcal{K}_j \in \mathcal{T}_h\} \subset H^1(\Omega),$$

where $\mathbb{P}_b^1(\mathcal{K}_j)$ and $\mathbb{P}^1(\mathcal{K}_j)$ are the space of bubble polynomials of order one and the space of linear polynomials over $\mathcal{K}_j$, respectively. Beside the spatial decomposition, we introduce the partition of the time interval $[0, T]$ in N discrete sub-intervals $\Delta t = T/N$, thus defining the n-th simulation time-point $t_n = n\Delta t$ with $n = 0, .., N$.

Hence, given the discrete initial condition $(u_h^0, p_h^0, \phi_h^0, \mu_h^0) \in V_h^2 \times Q_h \times Q_h \times Q_h$ the fully discrete dimensionless problem reads as follows:

for $n = 1, ..., N$

find $(u_h^n, p_h^n, \phi_h^n, \mu_h^n) \in V_h^2 \times Q_h \times Q_h \times Q_h$

such that $\forall\, (v_h, q_h, \psi_h, w_h) \in V_h^2 \times Q_h \times Q_h \times Q_h$ *:*

$$\begin{cases} Da\left(\nabla u_h^n, \nabla v_h\right) + \left(u_h^n, v_h\right) - \left(p_h^n, \nabla \cdot v_h\right) - \left(\left(\mu_h^n + \bar{f}_L\right) \nabla \phi_h^{n-1}, v_h\right) = 0, \\ \left(\frac{\phi_h^n - \phi_h^{n-1}}{\Delta T}, \psi_h\right) + \left(u_h^n \cdot \nabla \phi_h^{n-1}, \psi_h\right) + \left(\bar{\Gamma}, \psi_h\right) + M\left(\nabla \mu_h^n, \nabla \psi_h\right) = 0, \\ \left(\mu_h^n, w_h\right) - \bar{\epsilon}\left(\nabla \phi_h^n, \nabla w_h\right) - \frac{1}{\bar{\epsilon}}\left(\Psi_1'\left(\phi_h^n\right), w_h\right) + \frac{1}{\bar{\epsilon}}\left(\Psi_2'\left(\phi_h^{n-1}\right), w_h\right) = 0, \\ \left(\nabla \cdot u_h^n, q_h\right) = 0, \end{cases} \tag{S.63}$$

where $(\cdot, \cdot)$ denotes the standard L^2 inner product over Ω_h. Moreover, we prescribe the concave-convex splitting for the derivative of the Cahn-Hilliard potential:

$$\Psi_1'(\phi_h^n) = (\phi_h^n)^3, \qquad \Psi_2'(\phi_h^{n-1}) = \phi_h^{n-1},$$

in order to ensure the gradient stability of the Cahn-Hilliard equation [17–20].

To conclude, the presence of different time-scales, dictated by the nature of the Cahn-Hilliard equation [21–23], requires particular attention to the choice of the time step. In our simulations, we set the amplitude of the n-th time-step as $\Delta t = t_f \cdot h_{\min}^2$, where with $h_{\min}$ we denote to the smallest edge length of the mesh cells and $t_f = 7 \cdot 10^7$ is a time step re-scaling factor.

4 Sensitivity analysis

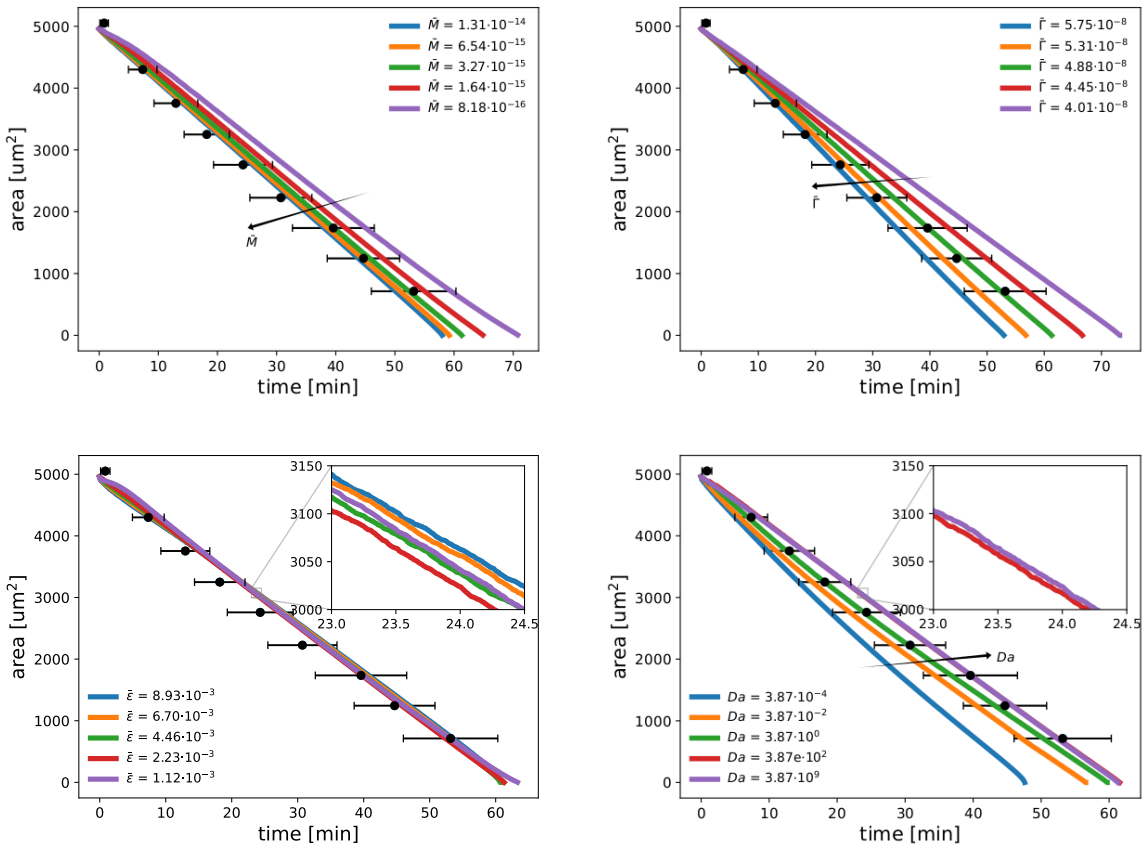

Figure S1: Sensitivity analysis performed on varying the dimensionless parameters of the model: the motility $\bar{M}$ (top left), the mass source $\bar{\Gamma}$ (top right), the interface amplitude $\bar{\epsilon}$ (bottom left) and the Darcy number Da (bottom right) for the square inset geometry. Where a clear trend is present, black arrows indicate the increase of the parameter.

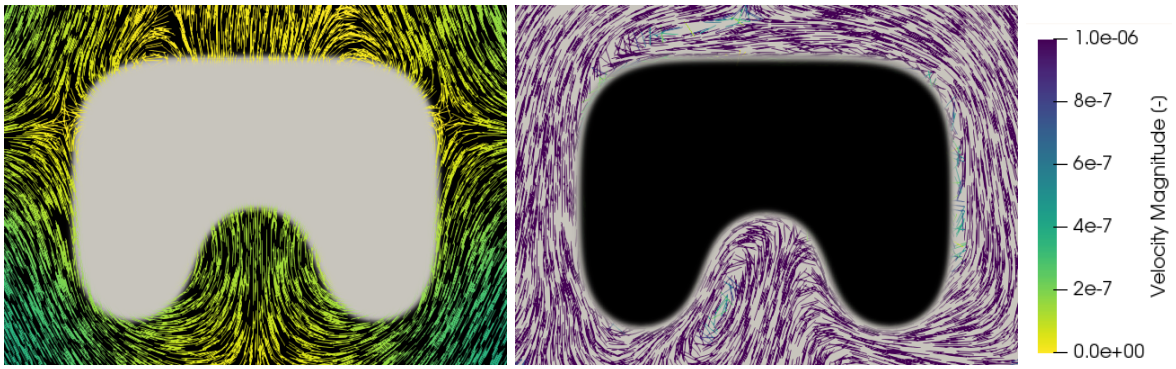

Figure S2: Zoomed snapshots of the velocity field in the healthy tissue surrounding the wound at $t = 3\,\text{min}$ for different values of the Darcy coefficient: $Da = 3.87 \cdot 10^{2}$ (left) and $Da = 3.87 \cdot 10^{-2}$ (right) for the square inset geometry.

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