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Regularity and stability in a strongly degenerate nonlinear diffusion and haptotaxis model of cancer invasion

Benoît Perthame* Chiara Villa†

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Abstract

We consider a mathematical model of cancer cell invasion of the extracellular matrix (ECM), comprising a strongly degenerate parabolic partial differential equation for the cell volume fraction, coupled with an ordinary differential equation for the ECM volume fraction. The model captures the intricate link between the dynamics of invading cancer cells and the surrounding ECM. First, migrating cells undergo haptotaxis, i.e., movement up ECM density gradients. Secondly, cancer cells degrade the ECM fibers by means of membrane-bound proteases. Finally, their migration speed is modulated by the ECM pore sizes, resulting in the saturation or even interruption of cell motility both at high and low ECM densities. The inclusion of the physical limits of cell migration results in two regimes of degeneracy of the nonlinear diffusion and haptotaxis terms.

We devise specific estimates that are compatible with the strong degeneracy of the equation, focusing on the vacuum present at low ECM densities. Based on these regularity results, and associated local compactness, we prove stability of weak solutions with respect to perturbations on bounded initial data.

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1 Introduction

We begin with a short summary of the biological phenomena motivating the form of the equation and of the analytical efforts made for more approachable versions of the model.

Biological context. Migrating cells typically move following environmental clues. Notably, they may have the ability to sense environmental gradients resulting in directed movement, for instance, down density-dependent pressure gradients or up gradients of chemical concentrations (e.g., oxygen, growth factors, etc), phenomenon known as chemotaxis. Empirical evidence also indicates the tendency of migrating cells to move by haptotaxis [3], that is up density gradients of the extracellular matrix (ECM) – i.e., the network consisting of extracellular macromolecules and elastic fibers providing cells

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with structural support. Haptotaxis-driven motion is particularly interesting in the context of cancer invasion, as invading cells may themselves create ECM gradients [14] by degrading the ECM fibers by means of diffusive or membrane-bound proteases [9].

Independently of the environmental clues directing cell migration, the density of the ECM plays an important role in modulating the speed at which cells can migrate through 3D tissues [23]. On one hand, invading cells rely on the presence of ECM fibers to form focal adhesions and exert traction forces boosting them forward, and thus a lower ECM density may hinder this process. On the other hand, a denser ECM is characterised by smaller pore sizes that may slow down cell migration, by friction, or impede it altogether if the pore size is smaller than the diameter of the cell nucleus. Indeed, the proteolytic degradation of ECM fibers by cancer cells may help them achieve the optimal environmental set up for fast invasion [9].

State of the art. A wide range of mathematical models have been proposed in the study of cancer invasion, see [16] and references therein, many of which comprise a system of partial differential equations (PDEs) for the cancer cell and ECM densities, building on the framework first proposed in [1, 14]. PDE models including haptotaxis have sparked the interest of the mathematical community, as the resulting system is not of the standard parabolic type [20] due to the nonlinear negative feedback induced by ECM degradation, and their analytical study can be more demanding than that of the classical Keller-Segel model for chemotaxis due to the non-diffusive nature of the ECM [4].

In the case of diffusive proteases, many results on global existence, boundedness and large time behaviour of the solution to the model comprising linear (or nonlinear) diffusion and haptotaxis have been obtained, following the initial results in [20, 21]. These include model extensions featuring chemotaxis and ECM remodelling, building on the framework proposed by Chaplain and Lolas [5], as well as parabolic-elliptic variants under quasi-stationary assumptions on protease dynamics, and two-species models. We refer the interested reader to [4, 6, 22] for an exhaustive summary of rigorous analytical results obtained up to 2022, noting that the relevant literature has since expanded [7, 11, 12].

On the contrary, very few works have investigated the well-posedness of models solely considering membrane-bound proteases as in [14], which lacks the additional regularity introduced by the protease diffusivity, mainly by Zhigun and coworkers [25, 26, 24]. In these papers, the authors prove global existence of weak solutions in haptotaxis-driven cancer invasion models, with carefully defined diffusion and haptotactic coefficients to avoid blow up of solutions in finite time typical of Chaplain-Lolas inspired models [17, 19]. Interestingly, they focus on parabolic PDEs presenting a degeneracy of the diffusion in the absence of ECM density, although this degeneracy does not impact haptotaxis.

The modulation of the speed of cell migration by the ECM pore size – or, under isotropic assumptions, the ECM density or volume fraction – has been well characterised by Preziosi and coworkers [2, 10, 15]. The resulting function modelling the ECM density-dependent saturation of cell migration speed may result in the degeneracy of the overall velocity [13], both at low and high ECM density. The well-posedness of PDE models implementing such a degeneracy resulting from the physical limits of cell migration is yet to be addressed and motivates the present work.

Paper content. We present, in Section 2, a strongly degenerate nonlinear diffusion and haptotaxis model of cancer invasion, focusing on membrane-bound proteases, that accounts for the ECM density-dependent saturation of the overall cell migration speed. In Section 3, we devise specific estimates compatible with the degeneracy of the equation. Based on the regularity provided by these estimates, we obtain some local compactness results in Section 4 and prove stability of weak solutions with respect to perturbations of bounded initial data, in Section 5. We conclude with a brief discussion in Section 6.

2 The model

Consider a population of cancer cells invading the surrounding tissue. For the purpose of our work, we here only take into account the role played by the ECM in this process, i.e. we ignore other cell populations and abiotic factors for simplicity. Cells are assumed to proliferate in the limits imposed by the availability of free space, and die due to compression in the lack of it. Spatial movement of cells is assumed to be driven by haptotaxis and cell density-induced pressure gradients, i.e. cells move up ECM density gradients and down cell density gradients, within the physical limits imposed by ECM pore sizes. Finally, cancer cells are assumed to have the ability to degrade the ECM and increase the availability of free space to move and proliferate in.

Let $\psi(t, \mathbf{x}) \geq 0$ and $\varphi(t, \mathbf{x}) \geq 0$ respectively denote the volume fraction of a population of cancer cells and that of the ECM components at time $t \in \mathbb{R}_{\geq 0}$ and spatial position $\mathbf{x} \in \Omega \subseteq \mathbb{R}^d$ ($d = 1, 2, 3$). Then $\psi(t, \mathbf{x})$ and $\varphi(t, \mathbf{x})$ satisfy the following system of PDEs for $t > 0$ and $\mathbf{x} \in \Omega$

$$\begin{cases} \partial_t \psi + \nabla \cdot [\psi \mathbf{V}(\psi, \varphi)] = \psi R(\psi, \varphi), \\ \partial_t \varphi = -\gamma \varphi \psi. \end{cases} \quad (1)$$

The second term on the left-hand-side of Eq. (1)₁ models cell motion with velocity \mathbf{V} given by

$$\mathbf{V}(\psi, \varphi) := S(\varphi) (\alpha \nabla \varphi - D \nabla \psi), \quad (2)$$

with haptotactic coefficient $\alpha > 0$, nonlinear diffusion coefficient $D > 0$ and where $S(\varphi)$ models the modulation of the motility of cancer cells according to healthy tissue permeability, and is therefore a function of the local ECM volume fraction. Building on the work presented in [10, 13], we take

$$S(\varphi) := \varphi(1 - \varphi), \quad (3)$$

capturing the saturation of cell motility when the ECM volume fraction is too low (i.e. cells lack proper structural support of ECM fibers to move quickly) or too high (i.e. cells are slowed down by the physical constraints imposed by small ECM pores). The term on the right-hand-side of Eq. (1)₁ models cell proliferation and death at a net rate $R(\psi, \varphi)$ which, following classical volume exclusion assumptions [1, 5, 14], we take to be an increasing function of the available space, i.e.

$$R(\psi, \varphi) := R_0 (1 - \varphi - \psi), \quad (4)$$

where $R_0 > 0$ is the maximum net proliferation rate. Finally, Eq. (1)₂ models ECM degradation by cancer cells at a rate $\gamma > 0$.

System (1) is complemented with the initial conditions

$$\psi(0, \mathbf{x}) = \psi^0(\mathbf{x}) \quad \text{and} \quad \varphi(0, \mathbf{x}) = \varphi^0(\mathbf{x}), \quad (5)$$

which are assumed to satisfy the following properties:

$$0 \leq \varphi^0(\mathbf{x}) \leq 1, \quad \int_{\Omega} \varphi^0(\mathbf{x}) \, d\mathbf{x} < \infty, \quad 0 \leq \psi^0(\mathbf{x}), \quad \int_{\Omega} \left(1 + \frac{|\mathbf{x}|^2}{2} + \psi^0(\mathbf{x})\right) \psi^0(\mathbf{x}) \, d\mathbf{x} < \infty. \quad (6)$$

After initial regularity estimates in Section 3.1, we proceed with the additional stronger assumptions

$$0 \leq \varphi^0(\mathbf{x}) \leq \frac{2}{3}, \quad |\nabla \sqrt{\varphi^0}| \in L^2(\Omega). \quad (7)$$

In the following we take $\Omega \equiv \mathbb{R}^d$, but analogous results can be obtained for $\Omega \subset \mathbb{R}^d$ complementing (1)₁ with no-flux boundary conditions on $\partial\Omega$.

3 Regularity estimates

3.1 Regularity results for $\varphi^0 \leq 1$

Proposition 1 (Elementary a priori estimates) *Let $\Omega \equiv \mathbb{R}^d$, and let $\psi \geq 0$ and $\varphi \geq 0$ be solutions of (1) and definitions (2)-(4), complemented with initial conditions $\psi(0, \mathbf{x}) = \psi^0(\mathbf{x})$ and $\varphi(0, \mathbf{x}) = \varphi^0(\mathbf{x})$ satisfying assumptions (6). Then for all $t \in [0, \infty)$ and $\mathbf{x} \in \Omega$ we have that*

$$\varphi(t, \mathbf{x}) \leq \varphi^0(\mathbf{x}). \quad (8)$$

In addition, we have the following estimates for all $T > 0$:

$$\psi \in L^\infty((0, T); L^1(\Omega) \cap L^2(\Omega)), \quad (9)$$

$$\frac{|\mathbf{x}|^2}{2} \psi \in L^\infty((0, T); L^1(\Omega)), \quad (10)$$

$$\psi |\ln(\psi)| \in L^\infty((0, T); L^1(\Omega)), \quad (11)$$

$$\psi \in L^3((0, T) \times \Omega), \quad (12)$$

$$\psi \varphi (1 - \varphi) |\alpha \nabla \varphi - D \nabla \psi|^2 \in L^1((0, T) \times \Omega). \quad (13)$$

Proof.

Step 1. Upper bound on φ . The bound (8) on φ comes directly from integrating Eq. (1)₂ and using the non-negativity of ψ , yielding that φ can only decrease in time. Therefore $\varphi \in L^\infty((0, \infty) \times \Omega)$, as in estimate (9).

Step 2. L^1 , L^2 and L^3 bounds on ψ , the energy and initial gradients control. Integrating Eq. (1)₁, in space and time, and applying the Gronwall lemma we obtain

$$\int_{\Omega} \psi(t, \mathbf{x}) \, d\mathbf{x} \leq \int_{\Omega} \psi^0(\mathbf{x}) \, d\mathbf{x} e^{R_0 t}$$

which yields $\psi \in L^\infty((0, T); L^1(\Omega))$ thanks to (6). The same integration, knowing (9), yields

$$R_0 \int_0^T \int_{\Omega} \psi(t, \mathbf{x})^2 \, d\mathbf{x} \leq C_1(T) \quad (14)$$

for some constant $C_1(T)$, i.e. $\psi \in L^2((0, T) \times \Omega)$ as $R_0 > 0$. Since the problem has gradient flow structure we use the energy

$$\begin{aligned} \frac{d}{dt} \int_{\Omega} \psi \left(\frac{D}{2} \psi - \alpha \varphi \right) \, d\mathbf{x} &= \int_{\Omega} [\partial_t \psi (D \psi - \alpha \varphi) - \alpha \psi \partial_t \varphi] \, d\mathbf{x} \\ &= - \int_{\Omega} \psi \varphi (1 - \varphi) |\alpha \nabla \varphi - D \nabla \psi|^2 \, d\mathbf{x} + \int_{\Omega} \psi R (D \psi - \alpha \varphi) \, d\mathbf{x} + \int_{\Omega} \alpha \gamma \psi^2 \varphi \, d\mathbf{x}. \end{aligned}$$

From this, using definition (4) for R and the bound (8) with assumption (6) on φ^0 , some simple algebra leads to

$$\frac{d}{dt} \int_{\Omega} \psi \left(\frac{D}{2} \psi - \alpha \varphi \right) \, d\mathbf{x} \leq C_2 \int_{\Omega} \psi \left(\frac{D}{2} \psi - \alpha \varphi \right) \, d\mathbf{x} + \alpha (C_2 + R_0) \int_{\Omega} \psi \, d\mathbf{x},$$

where $C_2 := \frac{2}{D} (DR_0 + \alpha R_0 + \alpha\gamma)$. Then, using (9), assumption (6) and the Gronwall lemma, we conclude that

$$\int_{\Omega} \psi(t, \mathbf{x}) \left(\frac{D}{2} \psi(t, \mathbf{x}) - \alpha \varphi(t, \mathbf{x}) \right) d\mathbf{x} \leq C_3(t) \quad (15)$$

for some constant $C_3(t)$. From the same equality for the energy, integrating in time for $T \in [0, T]$ and using (15), we obtain

$$DR_0 \int_0^T \int_{\Omega} \psi(t, \mathbf{x})^3 d\mathbf{x} dt \leq C_4(T) \quad \text{and} \quad \int_{\Omega} \psi \varphi (1 - \varphi) |\alpha \nabla \varphi - D \nabla \psi|^2 d\mathbf{x} dt \leq C_5(T),$$

i.e. respectively estimates (12), since $D, R_0 > 0$, and (13). From (15) and (9) we also have

$$\sup_{t \leq T} \int_{\Omega} \psi(t, \mathbf{x})^2 d\mathbf{x} \leq C_6(T),$$

i.e. $\psi \in L^\infty((0, T); L^1(\Omega))$. This concludes estimate (9).

Step 3. The second moment. Then, the second moment can be estimated as

$$\begin{aligned} \frac{d}{dt} \int_{\Omega} \frac{|\mathbf{x}|^2}{2} \psi(t, \mathbf{x}) d\mathbf{x} &= \int_{\Omega} |\mathbf{x}| \psi \varphi (1 - \varphi) |\alpha \nabla \varphi - D \nabla \psi| d\mathbf{x} + \int_{\Omega} \frac{|\mathbf{x}|^2}{2} \psi R_0 (1 - \psi - \varphi) d\mathbf{x} \\ &\leq \sqrt{\int_{\Omega} |\mathbf{x}|^2 \psi \varphi (1 - \varphi) d\mathbf{x}} \sqrt{\int_{\Omega} \psi \varphi (1 - \varphi) |\alpha \nabla \varphi - D \nabla \psi|^2 d\mathbf{x}} + \int_{\Omega} \frac{|\mathbf{x}|^2}{2} \psi R_0 d\mathbf{x} \\ &\leq \int_{\Omega} \frac{|\mathbf{x}|^2}{2} \psi \varphi (1 - \varphi) d\mathbf{x} + \frac{1}{2} \int_{\Omega} \psi \varphi (1 - \varphi) |\alpha \nabla \varphi - D \nabla \psi|^2 d\mathbf{x} + \int_{\Omega} \frac{|\mathbf{x}|^2}{2} \psi R_0 d\mathbf{x}, \end{aligned}$$

where we applied the Cauchy-Schwarz and the AM-GM inequalities to the first term. From this, thanks to the Gronwall lemma, estimate (13) and assumption (6), we conclude (10).

Step 4. The entropy. Following the strategy presented in [8], we obtain (11) as a consequence of (13) and (10) by writing

$$\int_{\Omega} \psi |\ln(\psi)| d\mathbf{x} = \int_{\psi > 1} \psi |\ln(\psi)| d\mathbf{x} + \int_{1 \geq \psi \geq e^{-|\mathbf{x}|^2}} \psi |\ln(\psi)| d\mathbf{x} + \int_{\psi < e^{-|\mathbf{x}|^2}} \psi |\ln(\psi)| d\mathbf{x}.$$

For the first term we have

$$\int_{\psi > 1} \psi |\ln(\psi)| d\mathbf{x} \leq \int_{\psi > 1} \psi^2 d\mathbf{x},$$

which is controlled thanks to (13). For the second term, $|\ln(\psi)|$ being decreasing, we have

$$\int_{1 \geq \psi \geq e^{-|\mathbf{x}|^2}} \psi |\ln(\psi)| d\mathbf{x} \leq \int_{1 \geq \psi \geq e^{-|\mathbf{x}|^2}} \psi(t, \mathbf{x}) |\mathbf{x}|^2 d\mathbf{x},$$

which is controlled thanks to (10). Finally, for the third term, the inequality $\psi |\ln(\psi)| \leq \sqrt{\psi}$ gives

$$\int_{\psi < e^{-|\mathbf{x}|^2}} \psi |\ln(\psi)| d\mathbf{x} \leq \int_{\psi < e^{-|\mathbf{x}|^2}} \sqrt{\psi} d\mathbf{x} \leq \int_{\psi < e^{-|\mathbf{x}|^2}} e^{-|\mathbf{x}|^2/2} d\mathbf{x},$$

which is also under control. Altogether we obtain (11). \square

3.2 Additional regularity results under assumptions (7)

Proposition 2 (Further estimates) *Let $\Omega \equiv \mathbb{R}^d$, and let ψ and φ be solutions of (1) and definitions (2)-(4), complemented with initial conditions $\psi(0, \mathbf{x}) = \psi^0(\mathbf{x})$ and $\varphi(0, \mathbf{x}) = \varphi^0(\mathbf{x})$ satisfying assumptions (6) and (7). We then have the following estimates for all $T > 0$:*

$$|\nabla\sqrt{\varphi}| \in L^\infty((0, T); L^2(\Omega)), \quad (16)$$

$$\varphi|\nabla\psi|^2 \in L^1((0, T) \times \Omega), \quad (17)$$

$$\psi|\nabla\sqrt{\varphi}|^2 \in L^1((0, T) \times \Omega), \quad (18)$$

$$\psi\varphi(1 - \varphi)|\nabla\psi|^2 \in L^1((0, T) \times \Omega). \quad (19)$$

Finally, we also have a bound for all $T > 0$

$$|\nabla(\varphi^{\frac{1}{2}}\psi)| \in L^2 + L^{\frac{3}{2}}((0, T) \times \Omega). \quad (20)$$

We cannot obtain compactness estimates on ψ because of the degeneracy when φ vanishes locally. This leads us to a gradient estimate on the quantity in (20) which vanishes with φ and is enough for our later purpose.

Proof.

Step 1. A stronger gradient control. We first write

$$\begin{aligned} \partial_t \left[\frac{|\nabla\varphi|^2}{2}(1 - \varphi) \right] &= (1 - \varphi)\nabla\varphi \cdot (\partial_t\nabla\varphi) - \frac{|\nabla\varphi|^2}{2}\partial_t\varphi \\ &= -\gamma(1 - \varphi) [\psi|\nabla\varphi|^2 + \varphi\nabla\varphi \cdot \nabla\psi] + \gamma\frac{|\nabla\varphi|^2}{2}\varphi\psi \\ &= -\gamma \left(1 - \frac{3}{2}\varphi \right) \psi|\nabla\varphi|^2 - \gamma(1 - \varphi)\varphi\nabla\varphi \cdot \nabla\psi \leq -\gamma(1 - \varphi)\varphi\nabla\varphi \cdot \nabla\psi, \end{aligned}$$

retrieving the inequality thanks to assumption (7) and the bound (8). Secondly, we use the entropy

$$\frac{d}{dt} \int_{\Omega} \psi \ln(\psi) \, d\mathbf{x} = \int_{\Omega} \nabla\psi \cdot [(1 - \varphi)\varphi(\alpha\nabla\varphi - D\nabla\psi)] + \int_{\Omega} \psi(1 + \ln(\psi))R_0(1 - \psi - \varphi),$$

and thus, combining these two equalities, obtain

$$\begin{aligned} &\frac{d}{dt} \int_{\Omega} \left[\frac{\alpha}{\gamma} \frac{|\nabla\varphi|^2}{2}(1 - \varphi) + \psi \ln(\psi) \right] d\mathbf{x} \\ &\leq \int_{\Omega} (1 - \varphi)\varphi [-\alpha\nabla\varphi \cdot \nabla\psi + \alpha\nabla\varphi \cdot \nabla\psi - D|\nabla\psi|^2] \, d\mathbf{x} + \int_{\Omega} \psi(1 + \ln(\psi))R_0(1 - \psi - \varphi) \, d\mathbf{x} \\ &\leq -D \int_{\Omega} (1 - \varphi)\varphi|\nabla\psi|^2 \, d\mathbf{x} + R_0 \int_{\Omega} [\psi + (1 - \varphi)\psi \ln(\psi) - \psi^2 - \psi^2 \ln(\psi) - \varphi\psi] \, d\mathbf{x} \\ &\leq -D \int_{\Omega} (1 - \varphi)\varphi|\nabla\psi|^2 \, d\mathbf{x} + R_0 \int_{\Omega} \psi \, d\mathbf{x} + R_0 \int_{\Omega} \psi \ln(\psi) \, d\mathbf{x} - R_0 \int_{\Omega} \psi^2 \ln(\psi) \, d\mathbf{x} \\ &\leq -D \int_{\Omega} (1 - \varphi)\varphi|\nabla\psi|^2 \, d\mathbf{x} + R_0 \int_{\Omega} \psi \, d\mathbf{x} + R_0 \int_{\psi \geq 1} \psi |\ln(\psi)| \, d\mathbf{x} + R_0 \int_{\psi < 1} \psi^2 |\ln(\psi)| \, d\mathbf{x} \\ &\leq -D \int_{\Omega} (1 - \varphi)\varphi|\nabla\psi|^2 \, d\mathbf{x} + R_0 \int_{\Omega} \psi \, d\mathbf{x} + R_0 \int_{\Omega} \psi |\ln(\psi)| \, d\mathbf{x}. \end{aligned}$$

Since the second and third terms are controlled by estimates (9) and (11) respectively, integrating in time we conclude

$$\frac{\alpha}{\gamma} \int_{\Omega} \frac{|\nabla\varphi|^2}{2} (1-\varphi) \, d\mathbf{x} \leq C_7(T), \quad D \int_0^T \int_{\Omega} (1-\varphi)\varphi |\nabla\psi|^2 \, d\mathbf{x}dt \leq C_8(T),$$

the latter corresponding to estimate (17) since $\alpha, \gamma, D > 0$.

Step 2. Gradient estimate for $\sqrt{\varphi}$. Building on the ideas presented in [25, 26], at this stage we notice that $2\partial_t\sqrt{\varphi} = -\sqrt{\varphi}\psi$ and thus

$$\begin{aligned} \frac{d}{dt} \int_{\Omega} |\nabla\sqrt{\varphi}|^2 \, d\mathbf{x} &= 2 \int_{\Omega} \nabla\sqrt{\varphi} \cdot \nabla\partial_t\sqrt{\varphi} \, d\mathbf{x} = -\gamma \int_{\Omega} \nabla\sqrt{\varphi} \cdot \nabla(\sqrt{\varphi}\psi) \, d\mathbf{x} \\ &= -\gamma \int_{\Omega} [|\nabla\sqrt{\varphi}|^2\psi + \sqrt{\varphi}\nabla\sqrt{\varphi} \cdot \nabla\psi] \, d\mathbf{x} \\ &\leq -\gamma \int_{\Omega} |\nabla\sqrt{\varphi}|^2\psi \, d\mathbf{x} + \frac{\gamma}{2} \int_{\Omega} |\nabla\sqrt{\varphi}|^2 \, d\mathbf{x} + \frac{\gamma}{2} \int_{\Omega} \varphi |\nabla\psi|^2 \, d\mathbf{x} \\ &\leq -\gamma \int_{\Omega} |\nabla\sqrt{\varphi}|^2\psi \, d\mathbf{x} + \frac{\gamma}{2} \int_{\Omega} |\nabla\sqrt{\varphi}|^2 \, d\mathbf{x} + \frac{3\gamma}{2} \int_{\Omega} (1-\varphi)\varphi |\nabla\psi|^2 \, d\mathbf{x} \end{aligned}$$

where we have used the upper bound (8) under assumption (7) in the last step. Using the estimate (17) and the Gronwall lemma, we conclude that for $t \leq T$

$$\int_{\Omega} |\nabla\sqrt{\varphi}|^2 \, d\mathbf{x} \leq C_9(T), \quad \int_0^T \int_{\Omega} \psi |\nabla\sqrt{\varphi}|^2 \, d\mathbf{x}dt \leq C_{10}(T),$$

i.e. estimates (16) and (18). Moreover, using the second estimate we just obtained on (13) we have

$$\int_0^T \int_{\Omega} \psi\varphi(1-\varphi) |\nabla\psi|^2 \, d\mathbf{x}dt \leq C_{11}(T),$$

concluding (19).

Step 3. Gradient estimate for $\varphi^{\frac{1}{2}}\psi$. Finally, we expand

$$\nabla(\varphi^{\frac{1}{2}}\psi) = \varphi^{\frac{1}{2}}\nabla\psi + \psi^{\frac{1}{2}}\psi^{\frac{1}{2}}\nabla\sqrt{\varphi}.$$

The first term on the right belongs to $L^2((0, T) \times \Omega)$ thanks to (17). The second term belongs to $L^{\frac{3}{2}}((0, T) \times \Omega)$ given that

$$\int_0^T \int_{\Omega} \left| \psi^{\frac{1}{2}} \left(\psi^{\frac{1}{2}}\nabla\sqrt{\varphi} \right) \right|^{\frac{3}{2}} \, d\mathbf{x}dt \leq \left(\int_0^T \int_{\Omega} \psi^3 \, d\mathbf{x}dt \right)^{\frac{1}{4}} \left(\int_0^T \int_{\Omega} \varphi |\nabla\psi|^2 \, d\mathbf{x}dt \right)^{\frac{3}{4}},$$

obtained by applying the Hölder inequality (with $p = 4, q = 4/3$), is bounded thanks to (12) and (18).

□

4 Local compactness

Next, we require space and time compactness. Under the stronger assumption (7) on the upper bound of φ^0 , we obtained local compactness in space of $\sqrt{\varphi}$ from (16) (and of φ since $|\nabla\varphi|^2 = 4|\nabla\sqrt{\varphi}|^2\varphi$ is also bounded) and of $\varphi^{\frac{1}{2}}\psi$ from (20).

We now focus on time compactness. First of all, since $|\partial_t\sqrt{\varphi}| = \frac{\gamma}{2}\sqrt{\varphi}\psi$, from estimates (8) and (12) we conclude that

$$|\partial_t\sqrt{\varphi}| \in L^3((0, T) \times \Omega), \quad (21)$$

i.e., local time compactness for $\sqrt{\varphi}$ (and for φ , similarly as for space compactness).

Secondly, we use the Aubin-Lions-Simon lemma [18, Theorem 5] to gain time compactness of $\varphi^{\frac{1}{2}}\psi$. We combine the equations on φ and ψ in (1), to get

$$\partial_t(\varphi^{\frac{1}{2}}\psi) = -\nabla \cdot \left[\varphi^{\frac{1}{2}}\psi \mathbf{V} \right] + \psi \nabla \varphi^{\frac{1}{2}} \cdot \mathbf{V} + \psi \varphi^{\frac{1}{2}} R - \frac{\gamma}{2} \varphi^{\frac{1}{2}} \psi^2, \quad (22)$$

with $\mathbf{V} \equiv \mathbf{V}(\psi, \varphi)$ and $R \equiv R(\psi, \varphi)$ given by (2)-(4). From this, to apply the Aubin-Lions-Simon lemma, it remains to estimate the right-hand-side of Eq. (22) as the divergence of a term bounded in L^1_{loc} and other terms bounded in L^1_{loc} . To get this, we see that $\varphi^{\frac{1}{2}}\psi \mathbf{V}(\psi, \varphi) \in L^1((0, T) \times \Omega)$ from

$$\begin{aligned} \int_0^T \int_{\Omega} \varphi^{\frac{1}{2}}\psi |\mathbf{V}(\psi, \varphi)| \, d\mathbf{x}dt &= \int_0^T \int_{\Omega} \left(\varphi^{\frac{1}{2}}\varphi^{\frac{1}{2}}(1-\varphi)^{\frac{1}{2}}\psi^{\frac{1}{2}} \right) \left(\psi^{\frac{1}{2}}\varphi^{\frac{1}{2}}(1-\varphi)^{\frac{1}{2}}|\alpha\nabla\varphi - D\nabla\psi| \right) \, d\mathbf{x}dt \\ &\leq \left[\int_0^T \int_{\Omega} \psi\varphi^2(1-\varphi) \, d\mathbf{x}dt \int_0^T \int_{\Omega} \psi\varphi(1-\varphi) |\alpha\nabla\varphi - D\nabla\psi|^2 \, d\mathbf{x}dt \right]^{\frac{1}{2}} \end{aligned}$$

after using the Cauchy-Schwarz inequality. The first integral is bounded by (9) thanks to bound (8), and the second one is bounded by estimate (13). The second term on the right-hand side of Eq. (22) is bounded in L^1 since we have

$$\begin{aligned} \int_0^T \int_{\Omega} \psi |\nabla\varphi^{\frac{1}{2}} \cdot \mathbf{V}(\psi, \varphi)| \, d\mathbf{x}dt &= \int_0^T \int_{\Omega} |\nabla\sqrt{\varphi} \cdot [\psi\varphi(1-\varphi)(\alpha\nabla\varphi - D\nabla\psi)]| \, d\mathbf{x}dt \\ &\leq \left[\int_0^T \int_{\Omega} \varphi(1-\varphi)\psi |\nabla\sqrt{\varphi}|^2 \, d\mathbf{x}dt \int_0^T \int_{\Omega} \psi\varphi(1-\varphi) |\alpha\nabla\varphi - D\nabla\psi|^2 \, d\mathbf{x}dt \right]^{\frac{1}{2}}, \end{aligned}$$

again after using the Cauchy-Schwarz inequality. The first integral is bounded by estimate (18) thanks to bound (8) and under assumption (7). The second integral is bounded by estimate (13). Finally, the last two terms in Eq. (22) are bounded in L^1 thanks to (8) and (12).

5 Stability with respect to initial perturbations

We conclude by proving stability of weak solutions under initial perturbations, through the convergence of subsequences of solutions corresponding to initially perturbed data.

Definition 3 *We say that $\psi(t, \mathbf{x})$ and $\varphi(t, \mathbf{x})$, satisfying all properties of Propositions 1 and 2, are weak solutions of system (1) under initial conditions $\psi^0(\mathbf{x})$ and $\varphi^0(\mathbf{x})$ satisfying properties (6) if, for all $T > 0$ and all test functions $\chi(t, \mathbf{x}) \in C_c^\infty([0, T] \times \Omega)$ with $\chi(T, \mathbf{x}) \equiv 0$,*

$$-\int_0^T \int_{\Omega} \psi \partial_t \chi \, d\mathbf{x}dt = \int_{\Omega} \psi^0 \chi(0, \mathbf{x}) \, d\mathbf{x} + \int_0^T \int_{\Omega} \psi \nabla \chi \cdot \mathbf{V}(\psi, \varphi) \, d\mathbf{x}dt + \int_0^T \int_{\Omega} \chi \psi \bar{R}(\psi, \varphi) \, d\mathbf{x}dt$$

$$\varphi(t, x) = \varphi^0(x) - \gamma \int_0^t \varphi \psi(s, x) ds, \quad \forall t \geq 0, x \in \Omega,$$

where $\mathbf{V}(\psi, \varphi)$ and $\bar{R}(\psi, \varphi) \equiv R(\psi, \varphi)$ are given by (2)-(4).

It is necessary to introduce a possible weak limit \bar{R} because of the degeneracy of Eq. (1). For example, if $\varphi^0 \equiv 0$, then initial oscillations in ψ_ε^0 are not regularized and the weak limit of $\psi_\varepsilon R(\psi_\varepsilon, \varphi^0) = -R_0 \psi_\varepsilon^2$ will not be $-R_0 \psi^2$.

Theorem 4 (Weak limits of solutions) *Consider a family of initial data $\varphi_\varepsilon^0, \psi_\varepsilon^0$ which satisfies, uniformly in ε , the initial property (6), (7). Let $\varphi_\varepsilon, \psi_\varepsilon$ be the solutions of (1), in the sense of Definition 3, corresponding to initial conditions $\varphi_\varepsilon^0, \psi_\varepsilon^0$. Then we have that for all $T > 0$ and all balls $B \subset \Omega$,*

$$\begin{aligned} \varphi_\varepsilon(t, \mathbf{x}) &\rightarrow \varphi(t, \mathbf{x}) \quad \text{strongly in } L^p((0, T) \times B), \quad 1 \leq p < \infty, \\ \psi_\varepsilon &\rightharpoonup \psi \quad \text{weakly in } L^3((0, T) \times \Omega), \\ \varphi_\varepsilon^{\frac{1}{2}}(t, \mathbf{x}) \psi_\varepsilon(t, \mathbf{x}) &\rightarrow \varphi^{\frac{1}{2}} \psi \quad \text{strongly in } L^p((0, T) \times B), \quad 1 \leq p < 3, \\ \psi_\varepsilon &\rightarrow \psi \quad \text{a.e. in the set } \{\varphi > 0\}, \end{aligned}$$

and the limit functions φ, ψ satisfy Eq. (1) in the sense of Definition 3, with $\bar{R} = R$ on the set $\{\varphi > 0\}$. Moreover, if we also have $0 < \varphi^0 := w\text{-lim } \varphi_\varepsilon^0$, then

$$\psi_\varepsilon \rightarrow \psi \quad \text{strongly in } L^p((0, T) \times B), \quad 1 \leq p < 3,$$

and the limit functions φ, ψ satisfy Eq. (1) in the sense of Definition 3, with $\bar{R} \equiv R$ everywhere.

Proof.

Step 1. Subsequence extraction and pointwise convergence. Thanks to the local compactness results proved in Section 4, we may extract a subsequence such that for all $T > 0$ and all balls $B \subset \Omega$,

$$\varphi_\varepsilon(t, \mathbf{x}) \rightarrow \varphi(t, \mathbf{x}) \quad \text{strongly in } L^p((0, T) \times B), \quad 1 \leq p < \infty \quad \text{and} \quad |\nabla \varphi| \in L^\infty((0, T); L^2(\Omega))$$

and this subsequence also converges almost everywhere. For ψ_ε , we cannot argue so simply. On the one hand, from the bound (12), we may extract another subsequence such that

$$\psi_\varepsilon \rightharpoonup \psi \quad \text{weakly in } L^3((0, T) \times \Omega).$$

On the other hand, the local compactness argument in Section 4, and the L^3 bound on ψ_ε , give the strong convergence

$$\varphi_\varepsilon^{\frac{1}{2}}(t, \mathbf{x}) \psi_\varepsilon(t, \mathbf{x}) \rightarrow \varphi^{\frac{1}{2}} \psi \quad \text{a.e. and thus strongly in } L^p((0, T) \times B), \quad 1 \leq p < 3,$$

and the weak convergence

$$\nabla(\varphi_\varepsilon^{\frac{1}{2}} \psi_\varepsilon) \rightharpoonup \nabla(\varphi^{\frac{1}{2}} \psi) \in L^{3/2}((0, T) \times B).$$

Notice that, by weak-strong convergence, we know indeed that the limit is $\varphi^{\frac{1}{2}} \psi$. Hence, in the set $\{\varphi(t, \mathbf{x}) > 0\}$ we also have the strong convergence

$$\psi_\varepsilon(t, \mathbf{x}) \rightarrow \psi(t, \mathbf{x}) \quad \text{strongly in } L^p((0, T) \times B \cap \{\varphi > 0\}), \quad 1 \leq p < 3,$$

again, by extraction of a subsequence that converges almost everywhere. Finally, if $0 < \varphi^0(\mathbf{x})$, then from Eq. (1)₂ (which holds in the limit again by weak-strong convergence, see Step 2) we see that we have $\varphi(t, \mathbf{x}) > 0$ for all $t \in [0, T]$ and thus conclude that ψ_ε converges almost everywhere and

$$\psi_\varepsilon(t, \mathbf{x}) \rightarrow \psi(t, \mathbf{x}) \quad \text{strongly in } L^p((0, T) \times B), \quad 1 \leq p < 3.$$

Step 2. Passing to the limit in Eq. (1). We now show that the limit functions φ, ψ satisfy Eq. (1) in the sense of Definition 3, by passing to the limit in the equation.

Multiplying both sides of the equations in system (1) for $\varphi_\varepsilon, \psi_\varepsilon$ by a test function $\chi(t, \mathbf{x}) \in C_c^\infty([0, T] \times \Omega)$ with $\chi(T, \mathbf{x}) \equiv 0$ and integrating by parts we obtain

$$-\int_0^T \int_\Omega \psi_\varepsilon \partial_t \chi \, d\mathbf{x} dt = \int_\Omega \psi_\varepsilon^0 \chi(0, \mathbf{x}) \, d\mathbf{x} + \int_0^T \int_\Omega \psi_\varepsilon \nabla \chi \cdot \mathbf{V}(\psi_\varepsilon, \varphi_\varepsilon) \, d\mathbf{x} dt + \int_0^T \int_\Omega \chi \psi_\varepsilon R(\psi_\varepsilon, \varphi_\varepsilon) \, d\mathbf{x} dt \quad (23)$$

and

$$\varphi_\varepsilon(t, x) = \varphi_\varepsilon^0(x) - \gamma \int_0^t \varphi_\varepsilon \psi_\varepsilon(s, x) ds, \quad \forall t \geq 0, x \in \Omega. \quad (24)$$

The convergence in Eq. (24) is straightforward given strong the convergence results of φ_ε and weak convergence of ψ_ε . In Eq. (23) the convergence is immediate for the time derivative and the initial data, but more delicate for the other terms, particularly for the drift term. We rewrite the second term on the right-hand-side of Eq. (23) as

$$\int_0^T \int_\Omega \psi_\varepsilon \nabla \chi \cdot \mathbf{V}(\psi_\varepsilon, \varphi_\varepsilon) \, d\mathbf{x} dt = \int_0^T \int_\Omega \underbrace{\alpha \psi_\varepsilon \varphi_\varepsilon (1 - \varphi_\varepsilon) \nabla \chi \cdot \nabla \varphi_\varepsilon}_{\mathcal{A}_\varepsilon} - D \underbrace{\psi_\varepsilon \varphi_\varepsilon (1 - \varphi_\varepsilon) \nabla \chi \cdot \nabla \psi_\varepsilon}_{\mathcal{B}_\varepsilon} \, d\mathbf{x} dt.$$

From the convergence results detailed in Step 1, the term \mathcal{A}_ε converges strongly to $\mathcal{A} = \psi \varphi (1 - \varphi) \nabla \chi \cdot \nabla \varphi$ because $\psi_\varepsilon \varphi_\varepsilon (1 - \varphi_\varepsilon)$ converges strongly in $L^p((0, T) \times B)$, $1 \leq p < 3$, while $\nabla \varphi_\varepsilon$ converges weakly in $L^2((0, T) \times B)$. For the other term, we write

$$\mathcal{B}_\varepsilon = (1 - \varphi_\varepsilon) \sqrt{\psi_\varepsilon \varphi_\varepsilon}^{\frac{1}{4}} \varphi_\varepsilon^{\frac{1}{4}} \sqrt{\psi_\varepsilon \varphi_\varepsilon} \nabla \chi \cdot \nabla \psi_\varepsilon.$$

The term $(1 - \varphi_\varepsilon) \sqrt{\psi_\varepsilon \varphi_\varepsilon}^{\frac{1}{4}}$ converges strongly in any $L^p((0, T) \times B)$, $1 \leq p < 6$, to $(1 - \varphi) \sqrt{\psi \varphi}^{\frac{1}{4}}$ using Step 1, while $\varphi_\varepsilon^{\frac{1}{4}} \sqrt{\psi_\varepsilon \varphi_\varepsilon} \nabla \chi \cdot \nabla \psi_\varepsilon$ is bounded in $L^2((0, T) \times B)$ thanks to (18), and thus converges weakly. To identify its limit we write it as

$$\varphi_\varepsilon^{\frac{1}{4}} \sqrt{\psi_\varepsilon \varphi_\varepsilon} \nabla \chi \cdot \nabla \psi_\varepsilon = \underbrace{\varphi_\varepsilon^{\frac{1}{4}} \sqrt{\psi_\varepsilon} \nabla \chi \cdot \nabla (\sqrt{\varphi_\varepsilon} \psi_\varepsilon)}_{\mathcal{C}_{1\varepsilon}} - \underbrace{\varphi_\varepsilon^{\frac{1}{4}} \psi_\varepsilon \sqrt{\psi_\varepsilon} \nabla \chi \cdot \nabla \sqrt{\varphi_\varepsilon}}_{\mathcal{C}_{2\varepsilon}}.$$

The term $\mathcal{C}_{1\varepsilon}$ converges because, as before, $\varphi_\varepsilon^{\frac{1}{4}} \sqrt{\psi_\varepsilon}$ converges strongly to $\varphi^{\frac{1}{4}} \sqrt{\psi}$ in any $L^p((0, T) \times B)$, $1 \leq p < 6$, while $\nabla \chi \cdot \nabla (\sqrt{\varphi_\varepsilon} \psi_\varepsilon)$ converges weakly in $L^{\frac{3}{2}}((0, T) \times B)$ to $\nabla \chi \cdot \nabla (\sqrt{\varphi} \psi)$. The term $\mathcal{C}_{2\varepsilon}$ converges because, as before, $\varphi_\varepsilon^{\frac{1}{4}} \psi_\varepsilon$ converges strongly to $\varphi^{\frac{1}{4}} \psi$ in any $L^p((0, T) \times B)$, $1 \leq p < 3$, while $\sqrt{\psi_\varepsilon} \nabla \chi \cdot \nabla \sqrt{\varphi_\varepsilon}$ converges weakly in $L^2((0, T) \times B)$ to $\sqrt{\psi} \nabla \chi \cdot \nabla \sqrt{\varphi}$.

Finally, if $0 < \varphi^0(\mathbf{x})$ we have strong convergence of ψ_ε and can pass to the limit also in the second term, concluding that the limit functions satisfy Eq. (1) in the sense of Definition 3, with $\bar{R} \equiv R$ everywhere. Otherwise, we can only conclude this with $\bar{R} = R$ on the set $\{\varphi > 0\}$. \square

6 Discussion

We focused on a strongly degenerate nonlinear diffusion and haptotaxis model of cancer invasion, implementing the ECM-dependent saturation of the speed of cell motion due to the physical limits of cell migration. The resulting equation for the cell volume fraction dynamics exhibits two regimes of degeneracy of the velocity, which can make it particularly challenging to obtain sufficient regularity results to investigate the well-posedness of the system. We here devised specific regularity estimates, in finite time, that are compatible with these degeneracies. After some regularity results under physical bounds on the initial ECM volume fraction φ_0 (i.e. $0 \leq \varphi_0 \leq 1$), within which both regimes of degeneracy may be encountered, we obtained additional regularity estimates under the stricter bounds $0 \leq \varphi_0 \leq \frac{2}{3}$, focusing on the vacuum observed at $\varphi = 0$. Based on these estimates and the associated local compactness results obtained, we proved the stability of – appropriately defined – weak solutions with respect to perturbations of the initial data. This confers robustness to the proposed cancer invasion model, despite the strong degeneracy. Moreover, the estimates derived in this work may also be useful to prove existence and uniqueness of solutions of the system, finalising the well-posedness of the model.

Indeed, we obtained the strongest results under the stricter bound on the initial ECM volume fraction $0 < \varphi_0 \leq \frac{2}{3}$. This is not an unreasonable assumption, given the physical meaning of the variable φ . On one hand, the ECM is a porous medium and in practice its volume fraction will not be close to 1. On the other hand, it is known that ECM is generally also present in the bulk of solid tumours, as captured by the strict positivity of φ . Nevertheless, the extension of the results presented in this work to the most general case with $0 \leq \varphi^0 \leq 1$ should still be pursued. This is particularly relevant in view of the fact that here we chose to define $S(\varphi)$, i.e. the modulation of the cell motility regulated by the ECM volume fraction, as a simplified version of the one derived in [10], i.e.

$$S(\varphi) = 4 \frac{[(\varphi - \varphi_{min})(\varphi_{th} - \varphi)]_+}{(\varphi_{th} - \varphi_{min})^2}.$$

Here, $\varphi_{min} > 0$ is the minimum ECM volume fraction below which cell movement through the ECM is hindered, and $\varphi_{th} > \varphi_0$ is a threshold ECM volume fraction above which cells can no longer pass through the ECM pores. Definition (3) consists in the specific case in which $\varphi_{min} = 0$ and $\varphi_{th} = 1$, but different values will be more biologically relevant, in which case the degeneracy will occur for intermediate values of φ .

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