A two species hyperbolic-parabolic model of tissue growth

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Abstract

Models of tissue growth are now well established, in particular in relation to their applications to cancer. They describe the dynamics of cells subject to motion resulting from a pressure gradient generated by the death and birth of cells, itself controlled primarily by pressure through contact inhibition. In the compressible regime we consider, when pressure results from the cell densities and when two different populations of cells are considered, a specific difficulty arises from the hyperbolic character of the equation for each cell density, and to the parabolic aspect of the equation for the total cell density. For that reason, few a priori estimates are available and discontinuities may occur. Therefore the existence of solutions is a difficult problem.

Here, we establish the existence of weak solutions to the model with two cell populations which react similarly to the pressure in terms of their motion but undergo different growth/death rates. In opposition to the method used in the recent paper [16], our strategy is to ignore compactness on the cell densities and to prove strong compactness on the pressure gradient. We improve known results in two directions; we obtain new estimates, we treat higher dimension than 1 and we deal with singularities resulting from vacuum.

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Introduction

The topic of modeling tissue growth has recently progressed with various inputs from physics and mechanics [29, 13, 19, 30]. Models are now used for image-based prediction of cancer growth [9, 31].

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They describe the dynamics of cell number density subject to motion resulting from a pressure gradient generated by the death and birth of cells, itself controlled primarily by pressure through contact inhibition. In the compressible regime, pressure results from a combination of the cell densities and controls both the motion through Darcy's law and birth and death of cells according to a finding in [12] and commonly used since then. Models with a single type of cells have been studied recently by many authors, as well as their incompressible limit [28, 27, 21, 22, 25]. More general formalisms using incompressibility conditions also occur in two phase flows, and they appear, e.g., in oil recovery [1, 2] where each phase has its own pressure. Models may also contain several "phases", and have also been widely established and studied [14, 32, 15, 20, 6]. For instance, a specific question is to understand when segregation occurs [5, 16].

Here, we consider the following compressible two cell population model, that we state in the full space for the sake of simplicity,

$$\begin{cases} \partial_t n_1 - \operatorname{div}[n_1 \nabla p] = n_1 F_1(p) + n_2 G_1(p), \qquad x \in \mathbb{R}^d,\ t \geq 0, \\ \partial_t n_2 - \operatorname{div}[n_2 \nabla p] = n_1 F_2(p) + n_2 G_2(p), \end{cases} \tag{1}$$

with

$$n := n_1 + n_2, \qquad p = n^\gamma, \quad \gamma > 1. \tag{2}$$

We assume that there is a value $P_H > 0$ (the name homeostatic pressure was coined in [30]) such that the smooth functions F_i, G_i, describing the division/death rates of cells, satisfy the properties

$$F(p) := F_1(p) + F_2(p) \leq 0, \qquad G(p) := G_1(p) + G_2(p) \leq 0, \qquad \forall p \geq P_H. \tag{3}$$

We also assume that the initial data n_1^0, n_2^0, $n^0 = n_1^0 + n_2^0$ satisfy

$$n_1^0 \geq 0, \qquad n_2^0 \geq 0, \qquad p^0 := (n_1^0 + n_2^0)^\gamma \leq P_H, \tag{4}$$

$$n^0(1 + |x|^2 + |\ln(n^0)|) \in L^1(\mathbb{R}^d), \tag{5}$$

$$\nabla p^0 \in L^2(\mathbb{R}^d), \qquad \Delta p^0 \in \mathcal{M}_{loc}(\mathbb{R}^d), \qquad \left(\Delta p^0\right)_- \in L^2_{loc}(\mathbb{R}^d), \tag{6}$$

where $\mathcal{M}_{loc}(\mathbb{R}^d)$ refers to the vector space of locally bounded measures. At some point, we will also need the restrictions that γ is large enough when $d \geq 5$ and that near $p = 0$ some cancelation occurs, namely

$$\gamma > 2 - \frac{4}{d}, \qquad \sup_{0 \leq p \leq P_H} \frac{|F(p) - G(p)|^2}{p^{1/\gamma}} \leq C_H. \tag{7}$$

In words, the total proliferation rates of cells n_1 and n_2 are the same when $p \approx 0$.

A specific difficulty arises from the hyperbolic character of the equation for each cell density n_i, and to the parabolic aspect of the total cell density n. For example, it is known that solutions n_1, n_2 may have discontinuities. For that reason, the existence of solutions is a difficult problem by lack of strong a priori estimates. Also we cannot hope for strong solutions in general. Here, we establish the existence of weak solutions. In opposition to the method used in the recent paper [16], our strategy is to ignore compactness on the cell densities and to prove strong compactness on the pressure gradient. Therefore, we improve known results in two directions; we treat higher dimension than 1 as in [16] and we deal with vacuum while [6] only considers uniformly positive and smooth solutions.

Theorem 1 (A priori estimates) *With the assumptions (3)–(6), the following estimates hold true for all $T > 0$ with constants $C(T)$ which only depend on the bounds in the above assumptions*

$$n(x,t) \geq 0, \qquad \int_{\mathbb{R}^d} n(x,t)\, dx \leq Ce^{Ct}, \qquad p(x,t) \leq P_H, \tag{8}$$

$$\int_0^T \int_{\mathbb{R}^d} \frac{|\nabla p|^2}{p^{1-1/\gamma}}\, dxdt \leq C(T). \tag{9}$$

Assuming also (7), we have for $t \in (0,T)$, and with $\phi(\cdot) \in C^2_{\text{Comp}}(\mathbb{R}^d)$ a localizing function,

$$\int_{\mathbb{R}^d} |\Delta p(t)|_-^2 \phi(x)\, dx \leq C(T), \qquad \int_0^T \int_{\mathbb{R}^d} |\Delta p(t)|_-^3 \phi(x)\, dxdt \leq C(T), \tag{10}$$

$$\int_{\mathbb{R}^d} |\Delta p(x,t)|\, \phi(x)\, dx \leq C(T). \tag{11}$$

Since our framework includes the Barenblatt solutions, see [33], we know that these estimates are sharp in the sense that Δp may be a singular measure supported by the free boundary. Note that p being bounded, the estimate (9) also gives an $L^2_{t,x}$ bound on ∇p. Another a priori estimate is also available, which we do not use in the subsequent results, and that we postpone to the Appendix.

As a consequence of the estimates in Theorem 1, we establish the following stability result

Theorem 2 (Stability of weak solutions) *Assume (3) and (7) and that the family of initial data satisfies, with uniform bounds, the assumptions (4)–(6). Then, the corresponding weak solutions n_i^ε, with the above bounds true, satisfy after extraction of subsequences,*

$$n_i^\varepsilon \rightharpoonup n_i, \quad \text{in } L^\infty\big((0,T)\times\mathbb{R}^d\big) - w*, \qquad i = 1,\, 2,$$

$$n^\varepsilon \to n, \qquad p^\varepsilon \to p, \quad \text{in } L^q\big((0,T)\times\mathbb{R}^d\big),\ 1 \leq q < \infty,$$

$$\nabla p^\varepsilon \to \nabla p, \quad \text{in } L^2\big((0,T)\times\mathbb{R}^d\big)$$

and n_1, n_2, p satisfy, in the weak sense, the system (1)–(2) with initial data n_1^0, n_2^0.

Finally, these two results lead us to the existence theorem, which is the main result of the current paper.

Theorem 3 (Existence of weak solutions) *With the assumptions of Theorem 2, there exists a weak solution $n_1, n_2, p \in L^\infty((0,T)\times\mathbb{R}^d)$ to the system (1)–(2), i.e., for $i = 1,\, 2$*

$$\int_0^T \int_{\mathbb{R}^d} \left[-n_i \partial_t \psi + n_i \nabla p . \nabla \psi - \big(n_1 F_i(p) + n_2 G_i(p)\big)\psi\right] dxdt = \int_{\mathbb{R}^d} n_i^0 \psi(0)\, dx \tag{12}$$

holds for all $\psi \in C^1_{\text{Comp}}(\mathbb{R}\times\mathbb{R}^d)$ and relations (2) hold a.e. in $(0,T)\times\mathbb{R}^d$.

The main observation is that, while our problem is of hyperbolic nature, we can take advantage of informations coming from the parabolic equation on n

$$\partial_t n - \text{div}[n\nabla p] = n_1 F(p) + n_2 G(p) =: nR(c_1, c_2, p), \qquad x \in \mathbb{R}^d,\ t \geq 0, \tag{13}$$

where, following [16], we define

$$c_i = \frac{n_i}{n} \leq 1 \quad \text{and} \quad c_i(x,t) = 0 \ \text{ when } \ n(x,t) = 0,$$

$$R = c_1 F(p) + c_2 G(p) \in L^\infty. \tag{14}$$

Next, multiplying equation (13) with $p'(n)$, we compute that p satisfies

$$\partial_t p - |\nabla p|^2 - \gamma p \Delta p = \gamma p R. \tag{15}$$

It is also useful for later purpose to state the equation for the c_i's

$$\partial_t c_i - \nabla p . \nabla c_i = c_1 F_i(p) + c_2 G_i(p) - c_i R. \tag{16}$$

To obtain the equation for c_i we multiply the equation for n_i with $1/n$ and add it to the equation for n multiplied by $-n_i/n^2$. Indeed, observe that

$$-\frac{1}{n}\text{div}[n_i \nabla p] + \frac{n_i}{n^2}\text{div}[n\nabla p] = -\frac{1}{n}\nabla n_i . \nabla p - \frac{n_i}{n}\Delta p + \frac{n_i}{n^2}\nabla n . \nabla p + \frac{n_i}{n^2} n \Delta p = -\nabla(\frac{1}{n} n_i) . \nabla p$$

and the remaining terms are immediate.

The rest of the paper is devoted to the proofs of these three theorems which we perform in the three next sections. Some remarks and open problems are commented in the conclusion.

1 Proof of Theorem 1

The first estimates come from the balance law expressed by the equation (1) and from the maximum principle for equation (15). One easily gets, by integrating (13) over $\mathbb{R}^d$ and using the Gronwall inequality, that

$$\int_{\mathbb{R}^d} n(t,x)\, dx \leq \int_{\mathbb{R}^d} n^0(x)\, dx \exp(t\|R\|_\infty). \tag{17}$$

To show the uniform bound on p we multiply (15) with $(p - P_H)_+$. Observe that for any $\eta \in C^2$ it holds $\Delta \eta(p) = \Delta p \eta'(p) + \eta''(p)|\nabla p|^2$, which allows us to handle the highest order term with $\eta'(p) = p(p - P_H)_+$. Thus we get

$$\frac{1}{2}\partial_t (p - P_H)_+^2 + [\gamma \eta''(p) - (p - P_H)_+]|\nabla p|^2 - \gamma \Delta \eta(p) = \gamma p (p - P_H)_+ R(p). \tag{18}$$

We integrate over $\mathbb{R}^d$ and observe that as $\gamma > 1$, thus $\gamma \eta''(p) - (p - P_H)_+ \geq 0$ and

$$\frac{1}{2}\frac{d}{dt}\int_{\mathbb{R}^d} (p - P_H)_+^2\, dx \leq \gamma \int_{\mathbb{R}^d} p(p - P_H)_+ R(p) \leq 0, \tag{19}$$

where the last inequality follows from (3) and (4).

Before passing to the next estimate, on $|\nabla p|^2$, let us observe that the second moment of n is bounded. Indeed, multiplying (13) with $x^2\Phi_L$, where $\Phi_L(|x|)$ is a radially symmetric smooth function, which vanishes outside the ball of radius $L+1$, equals to 1 on the ball of radius L, with $\nabla\Phi_L$ and $\Delta\Phi_L$ bounded uniformly in L; and integrating by parts over $\mathbb{R}^d$ gives

$$\frac{d}{dt}\int_{\mathbb{R}^d} x^2 n\Phi_L\,dx + \frac{\gamma}{\gamma+1}\int_{\mathbb{R}^d} n^{\gamma+1}(x^2\Delta\Phi_L + 4x\nabla\Phi_L + 2\Phi_L)\,dx = \int_{\mathbb{R}^d} x^2 nR\Phi_L\,dx. \tag{20}$$

Since $n^\gamma \le P_H$, we can furthermore obtain

$$\frac{d}{dt}\int_{\mathbb{R}^d} x^2 n\Phi_L\,dx \le C\int_{\mathbb{R}^d} x^2 n\Phi_L\,dx + \int_{\mathbb{R}^d} n\Phi_L\,dx + \int_{\{L\le|x|\le L+1\}} nx|\nabla\Phi_L|\,dx + \int_{\{L\le|x|\le L+1\}} nx^2|\Delta\Phi_L|\,dx, \tag{21}$$

where the constant C depends on $\|R\|_\infty$, γ and P_H. As $n\in L^1$, we can claim that the second term on the right-hand side is bounded. For the moment let us assume that n vanishes sufficiently fast at infinity, what we will prove later. Then, by the Lebesgue dominated convergence theorem we can pass to the limit in terms containing Φ_L and using that n vanishes for large x and both $\nabla\Phi_L$ and $\Delta\Phi_L$ are uniformly bounded, we show that the last two terms on the right-hand side vanish. We complete the estimate by applying the Gronwall inequality.

The estimate (9) comes from the entropy relation. We multiply (13) with $\Phi_L \ln n$, where Φ_L is the same truncation function as above, integrate over $\mathbb{R}^d$, and find

$$\begin{aligned}\frac{d}{dt}\int_{\mathbb{R}^d} n(\ln(n)-1)\Phi_L\,dx + \frac{1}{\gamma}\int_{\mathbb{R}^d} p^{-1+1/\gamma}|\nabla p|^2\Phi_L\,dx\\ -\frac{1}{\gamma-1}\int_{\{L\le|x|\le L+1\}} p^{1-\frac{1}{\gamma}}(\ln(p)-1)\Delta\Phi_L\,dx = \int_{\mathbb{R}^d} n\ln(n)\,R\Phi_L\,dx.\end{aligned} \tag{22}$$

It is easy to observe that if the function n, and thus also p vanishes sufficiently fast, then again the integral over the annulus vanishes as $L\to\infty$ and we conclude (9). For that purpose we recall also that a control of the second moment in x is used here to control the negative values of $n\ln(n)$. Indeed, observe that

$$\int_{\mathbb{R}^d} n|\ln(n)|\,dx = \int_{\mathbb{R}^d} n\ln(n)\,dx - \int_{\{x\in\mathbb{R}^d: n<1\}} n\ln(n)\,dx \le \int_{\mathbb{R}^d} n\ln(n)\,dx + 2\int_{\mathbb{R}^d} n|x|^2\,dx + c. \tag{23}$$

And the above inequality allows us to get

$$\int_{\mathbb{R}^d} n|\ln(n)|\,dx \le \|R\|_\infty\int_0^T\int_{\mathbb{R}^d} n|\ln(n)| + 2\int_{\mathbb{R}^d} n|x|^2 + \int_{\mathbb{R}^d} n\,dx + \int_{\mathbb{R}^d} n^0(\ln(n^0)-n^0)\,dx + c. \tag{24}$$

We complete the estimate (9) using the Gronwall lemma.

Finally, the fundamental estimates (10) come from Aronson and Benilan's method [4, 33] for the porous media equation with several adaptations. Firstly, and this s a new feature here, we weaken their estimate to L^2 rather than L^∞. Secondly, we need to localize the estimate in space. Thirdly, we adapt the functional under consideration using also the idea from [28], and we do not work directly with Δp but with

$$w = \Delta p + R, \qquad \partial_t p = |\nabla p|^2 + \gamma p w.$$

We compute

$$\begin{aligned}\partial_t \Delta p &= 2(\partial_{ij}p)^2 + 2\nabla p \nabla \Delta p + \gamma \Delta(pw),\\ \partial_t R &= R_{c_1}\partial_t c_1 + R_{c_2}\partial_t c_2 + R_p \partial_t p \\ &= F(p)[\nabla c_1.\nabla p + \xi_1] + G(p)[\nabla c_2.\nabla p + \xi_2] + R_p[|\nabla p|^2 + \gamma pw]\end{aligned} \tag{25}$$

where

$$\xi_i := c_1 F_i(p) + c_2 G_i(p) + c_i R, \qquad i = 1,\, 2,$$

are the right-hand sides from equations (16). Therefore, since $c_1 + c_2 = 1$, we find

$$\partial_t w = 2(\partial_{ij}p)^2 + 2\nabla p \nabla \Delta p + \gamma \Delta(pw) + [F(p) - G(p)]\nabla c_1.\nabla p + R_p[|\nabla p|^2 + \gamma pw] + Bdd_1$$

with "Bdd" terms which are bounded in L^∞,

$$Bdd_1 := F(p)\xi_1 + G(p)\xi_2,$$

but this may change from line to line. Since

$$\nabla p.\nabla \Delta p = \nabla p.\nabla(w - R) = \nabla p.\nabla w - \mathrm{div}(R\nabla p) + R(w - R)$$

this is also

$$\begin{aligned}\partial_t w \geq\ & \frac{2}{d}(\Delta p)^2 + 2\nabla p \nabla w - 2\mathrm{div}(R\nabla p) + 2R(w - R) + \gamma \Delta(pw)\\ &+ [F(p) - G(p)]\nabla c_1.\nabla p + R_p[|\nabla p|^2 + \gamma pw] + Bdd_1.\end{aligned} \tag{26}$$

The negative part, that we denote by $|w|_-$, therefore satisfies, with $sgn_- := 1\!\!1_{\{w<0\}}$,

$$\begin{aligned}\partial_t |w|_- \leq & -\frac{2}{d}|w|_-^2 + 2\nabla p \nabla |w|_- + 2sgn_- \mathrm{div}(R\nabla p) + 2(1 - \frac{2}{d})R|w|_- + \gamma \Delta(p|w|_-)\\ & - sgn_-[F(p) - G(p)]\nabla c_1.\nabla p - sgn_- R_p |\nabla p|^2 + \gamma R_p p |w|_- + Bdd\end{aligned} \tag{27}$$

using that $-\frac{2}{d}(w - R)^2 = -\frac{2}{d}w^2 + \frac{4}{d}Rw - \frac{2}{d}R^2$, where the last term we include within bounded terms that we still gather in Bdd.

We reorganize this inequality as (here the parameter $\alpha > 0$ can be chosen as small as we wish)

$$\begin{aligned}\partial_t |w|_- \leq & -(\frac{2}{d} - \alpha)|w|_-^2 + 2\nabla p \nabla |w|_- + \gamma \Delta(p|w|_-) + 2sgn_- \mathrm{div}(R\nabla p)\\ & - sgn_-[F(p) - G(p)]\nabla c_1.\nabla p - sgn_- R_p |\nabla p|^2 + Bdd\ .\end{aligned}$$

Notice that, above, we have applied the Young inequality to the terms $2(1 - \frac{2}{d})R|w|_-$ and $\gamma R_p p |w|_-$, that is

$$2R|w|_-(1 - \frac{2}{d}) \leq \frac{\alpha}{2}|w|_-^2 + c(\alpha)R^2, \qquad R_p \gamma p |w|_- \leq \frac{\alpha}{2}|w|_-^2 + c(\alpha)|R_p \gamma p|^2,$$

and thus the term Bdd is given by

$$Bdd := F(p)\xi_1 + G(p)\xi_2 - \frac{2}{d}R^2 + c(\alpha)(R^2 + |\gamma R_p p|^2).$$

We need to localize and use a nonnegative, compactly supported, smooth test function Φ to compute

$$\frac{d}{dt}\int_{\mathbb{R}^d} \frac{|w|_-^2}{2}\Phi \; dx \leq I + II. \tag{28}$$

The terms II are those with $\nabla\Phi$ which are certainly better because they contain one less derivative in the unknowns.

For the difficult term we have, after several integrations by parts, in particular to eliminate derivatives in c_1 which are the worse,

$$\begin{aligned}
I \leq & -(\frac{2}{d}-\alpha)\int_{\mathbb{R}^d}\Phi|w|_-^3\,dx - \int_{\mathbb{R}^d}\Phi|w|_-^2\Delta p\,dx - \gamma\int_{\mathbb{R}^d}\Phi p|\nabla|w|_-|^2\,dx + \frac{\gamma}{2}\int_{\mathbb{R}^d}\Phi|w|_-^2\Delta p\,dx \\
& - 2\int_{\mathbb{R}^d}\Phi R\nabla|w|_-.\nabla p\,dx + \int_{\mathbb{R}^d}\Phi c_1[F(p)-G(p)]|w|_-\Delta p\,dx \\
& + \int_{\mathbb{R}^d}\Phi c_1[F(p)-G(p)]\nabla|w|_-.\nabla p\,dx + C\int_{\mathbb{R}^d}\Phi|w|_-|\nabla p|^2\,dx + \int_{\mathbb{R}^d}\Phi|w|_- Bdd\,dx\,.
\end{aligned} \tag{29}$$

where C is constant which here takes into account $c_1(F'-G')$ as well as R_p and which is changing from line to line below.

The linear and quadratic terms in $|w|_-$ are not a problem because the dominant term contains a cubic power of $|w|_-$. We observe about the third-power terms that

$$\int_{\mathbb{R}^d}\Phi|w|_-^2\Delta p\,dx = \int_{\mathbb{R}^d}\Phi|w|_-^2(w-R)\,dx = -\int_{\mathbb{R}^d}\Phi|w|_-^3\,dx - \int_{\mathbb{R}^d}\Phi|w|_-^2 R\,dx.$$

Because $R = G(p)+c_1[F(p)-G(p)]$, we also have

$$\begin{aligned}
I \leq & -(\frac{\gamma}{2}+\frac{2}{d}-1-\alpha)\int_{\mathbb{R}^d}\Phi|w|_-^3\,dx - \gamma\int_{\mathbb{R}^d}\Phi p|\nabla|w|_-|^2\,dx \\
& - 2\int_{\mathbb{R}^d}\Phi G\nabla|w|_-\nabla p\,dx + \int_{\mathbb{R}^d}\Phi c_1[F(p)-G(p)]|w|_-\Delta p\,dx \\
& - \int_{\mathbb{R}^d}\Phi c_1[F(p)-G(p)]\nabla|w|_-.\nabla p\,dx + C\int_{\mathbb{R}^d}\Phi|w|_-|\nabla p|^2\,dx \\
& + (1-\frac{\gamma}{2})\int_{\mathbb{R}^d}\Phi|w|_-^2 R\,dx + \int_{\mathbb{R}^d}\Phi|w|_- Bdd\,dx\,,
\end{aligned} \tag{30}$$

it holds

$$\int_{\mathbb{R}^d}\Phi c_1[F(p)-G(p)]|w|_-\Delta p\,dx = -\int_{\mathbb{R}^d}\Phi c_1[F(p)-G(p)]|w|_-^2\,dx - \int_{\mathbb{R}^d}\Phi c_1[F(p)-G(p)]|w|_- R\,dx$$

and estimating further (the second term of the above we include already in $\int_{\mathbb{R}^d}\Phi|w|_- Bdd\,dx$),

$$\begin{aligned}
I \leq & -(\frac{\gamma}{2}+\frac{2}{d}-1-\alpha)\int_{\mathbb{R}^d}\Phi|w|_-^3\,dx - \gamma\int_{\mathbb{R}^d}\Phi p|\nabla|w|_-|^2\,dx \\
& + 2\int_{\mathbb{R}^d}\Phi G|w|_-\Delta p\,dx + 2\int_{\mathbb{R}^d}\Phi G'(p)|w|_-|\nabla p|^2\,dx \\
& + \frac{1}{2}\int_{\mathbb{R}^d}\Phi p c_1^2|\nabla|w|_-|^2\,dx + \frac{1}{2}\int_{\mathbb{R}^d}\Phi\frac{[F(p)-G(p)]^2}{p}|\nabla p|^2\,dx + C\int_{\mathbb{R}^d}\Phi|w|_-|\nabla p|^2\,dx \\
& + (1-\frac{\gamma}{2})\int_{\mathbb{R}^d}\Phi|w|_-^2 R\,dx - \int_{\mathbb{R}^d}\Phi c_1[F(p)-G(p)]|w|_-^2\,dx + \int_{\mathbb{R}^d}\Phi|w|_- Bdd\,dx\,.
\end{aligned} \tag{31}$$

We arrive at the final form, using the constant C_H in (7),

$$
\begin{aligned}
I \leq &-(\frac{\gamma}{2}+\frac{2}{d}-1-\alpha)\int_{\mathbb{R}^d}\Phi|w|_-^3\,dx-(\gamma-\frac{1}{2})\int_{\mathbb{R}^d}\Phi p|\nabla|w|_-|^2\,dx \\
&+C\int_{\mathbb{R}^d}\Phi|w|_-^2\,dx+\frac{C_H}{2}\int_{\mathbb{R}^d}\Phi\frac{|\nabla p|^2}{p^{1-1/\gamma}}\,dx+C\int_{\mathbb{R}^d}\Phi|w|_-|\nabla p|^2\,dx+\int_{\mathbb{R}^d}\Phi|w|_-Bdd\,dx\,.
\end{aligned}
\tag{32}
$$

where a constant C standing next to the integral $\int_{\mathbb{R}^d}\Phi|w|_-|\nabla p|^2\,dx$ takes into account also $2G'$. The first two terms on the right-hand side are the "good terms". Indeed, they have a good sign, unless $\gamma > 2(1-\frac{2}{d})$, which is automatically satisfied as we assume $\gamma > 1$ in $d \leq 4$ and in higher dimensions implies higher requirement of the exponent γ as stated in (7). The difficult term is at the highest order

$$
\int_{\mathbb{R}^d}\Phi|w|_-|\nabla p|^2\,dx=-\int_{\mathbb{R}^d}\Phi[\nabla|w|_-p\nabla p+|w|_-p\Delta p]\,dx. \tag{33}
$$

which is under control. Indeed,

$$
\int_{\mathbb{R}^d}\Phi\nabla|w|_-p\nabla p\,dx\leq(\gamma-\frac{1}{2})\int_{\mathbb{R}^d}\Phi p|\nabla|w|_-|^2\,dx+c(\gamma)\int_{\mathbb{R}^d}\Phi p|\nabla p|^2\,dx.
$$

Here, the first term on the right hand side just cancels the second "good term"and the second is bounded.

For the second term of the right-hand side of (33) we have

$$
\int_{\mathbb{R}^d}\Phi|w|_-p\Delta p\,dx=\int_{\mathbb{R}^d}\Phi|w|_-p(w-R)\,dx=-\int_{\mathbb{R}^d}\Phi|w|_-^2p\,dx+\int_{\mathbb{R}^d}\Phi|w|_-pR\,dx
$$

where both these terms are under control to give the final estimate

$$
I\leq-(\frac{\gamma}{2}+\frac{2}{d}-1-\alpha)\int_{\mathbb{R}^d}\Phi|w|_-^3\,dx+C. \tag{34}
$$

The terms containing gradient of Φ are collected in II

$$
\begin{aligned}
II=&\int_{\mathbb{R}^d}\nabla p|w|_-^2\nabla\Phi\,dx-\gamma\int_{\mathbb{R}^d}\nabla p|w|_-^2\nabla\Phi\,dx-\gamma\int_{\mathbb{R}^d}p\nabla(|w|_-^2)\nabla\Phi\,dx-2\int_{\mathbb{R}^d}R\nabla p|w|_-\nabla\Phi\,dx \\
&+\int_{\mathbb{R}^d}[F(p)-G(p)]c_1\nabla p|w|_-\nabla\Phi\,dx+2\int_{\mathbb{R}^d}\nabla\Phi G|w|_-\nabla p\,dx-\int_{\mathbb{R}^d}\nabla\Phi|w|_-p\nabla p\,dx
\end{aligned}
\tag{35}
$$

and they all do not bring additional difficulties.

Therefore, using the inequality (28) and the negative sign in the right hand side of (34), we obtain the a priori estimates announced in (10). The L^1 bound for Δp in (11) is a simple consequence because $\int\Phi\Delta p dx$ is bounded, therefore $\int\Phi|\Delta p|_+dx$ is controlled by $\int\Phi|\Delta p|_-dx$ which itself is controlled thanks to (10).

2 Proof of Theorem 2

The goal here is to explain the main compactness argument which is used to pass to the limit in an approximate sequence. As in [16], the compactness in time is a major issue.

Weak convergence of the quantities n_i^ε follows from the bound in L^∞. The strong convergence of p^ε follows from compactness by Sobolev injections. Indeed, on the one hand, we control $\int_0^T \int_{\mathbb{R}^d} |\nabla p^\varepsilon|^2 dxdt$ from (9) because the pressure is bounded by P_H. On the other hand, we may win time compactness by the Lions-Aubin Lemma using equation (15), which also reads

$$\partial_t p^\varepsilon = (\gamma - 1)|\nabla p^\varepsilon|^2 + \frac{\gamma}{2}\Delta p^{\varepsilon 2} + \gamma p^\varepsilon R^\varepsilon, \tag{36}$$

and the space compactness on p^ε together with the known bounds provide time compactness. Therefore the expression $n^\varepsilon = (p^\varepsilon)^{1/\gamma}$ shows that we may also extract a sub-sequence of n^ε which converges.

The strong compactness for ∇p^ε is more involved. It mainly relies on the second estimate (10) which provides the space compactness, still by the Sobolev embedding theorems. Indeed, the control in L^1_{loc} of Δp^ε is enough for compactness of ∇p^ε, a fact which can be inferred from the representation formula for the solution of the Laplace equation.

For time compactness of ∇p^ε, we write, using (36),

$$\partial_t \nabla p^\varepsilon = \nabla\big[(\gamma - 1)|\nabla p^\varepsilon|^2 + \gamma p^\varepsilon R^\varepsilon\big] + \frac{\gamma}{2}\nabla\Delta p^{\varepsilon 2}.$$

Again, we know the local space compactness of ∇p^ε from the previous paragraph, the right hand side is a sum of space derivatives of bounded functions, therefore we may apply the Lions-Aubin compactness argument and find that ∇p^ε is compact in space and time.

To pass to the limit in the equations is now easy. All the nonlinear terms, that are

$$n_i^\varepsilon \nabla p^\varepsilon, \qquad n_i^\varepsilon F_j(p^\varepsilon), \qquad n_i^\varepsilon G_j(p^\varepsilon),$$

have limits as products of weak limits of n_i^ε by strong limits of p^ε and ∇p^ε. This completes the proof of Theorem 2. □

At this stage, let us point out that our strategy differs deeply from that in [16] based on BV estimates for the quantities c_i^ε in one dimension. This estimate is somehow sharp since examples with discontinuities on the n_i^ε are known. Also the method for time compactness is very different since [16] use a control of the Wasserstein distance.

3 Proof of Theorem 3

We already have a priori estimates and a weak sequential stability result, thus to complete the existence proof we need to construct an approximate system compatible with these estimates. We do that in two steps. Firstly, we make positive the initial data and prove a control from below by a (small) Gaussian. Secondly, we introduce a uniform parabolic regularization.

First step. A regularized problem with a positive control from below. We show that the function

$$\underline{n}(t,x) = \underline{c}\exp\left(-\frac{|x|^2}{2} - ct\right) \tag{37}$$

is a subsolution to equation (13) if we choose c sufficiently large. Since $\partial_t \underline{n} = -c\underline{n}$, $\nabla \underline{n} = -x\underline{n}$ and $\Delta \underline{n} = d\underline{n} + |x|^2 \underline{n}$, we may insert (37) into the equation for n and as we search for a subsolution, we change equality to inequality. We obtain

$$-c\underline{n} - \gamma(\gamma+1)\underline{n}^{\gamma+1}|x|^2 + \gamma\underline{n}^{\gamma+1} - R\underline{n} \le 0 \tag{38}$$

which holds true choosing c large enough so that the inequality is satisfied

$$-c - \gamma(\gamma+1)\left[\exp\left(-\frac{|x|^2}{2} - ct\right)\right]^\gamma |x|^2 + \gamma\left[\exp\left(-\frac{|x|^2}{2} - ct\right)\right]^\gamma + \|R\|_\infty \le 0. \tag{39}$$

It is now a matter of standard estimates, [33], to obtain that if we start with the specific initial condition larger than n^0, we will call it $n^0_\delta := n^0 + \delta\exp(\frac{-|x|^2}{2})$, with $\delta > 0$, then the solution to the problem will be larger than the subsolution $\underline{n}$ given by (37) with c large enough.

Thus our first approximation step is to replace an initial data n^0 by n^0_δ as it is introduced above. In a consequence the corresponding solution n_δ, as well as p_δ are locally bounded away from zero, we call these bounds $\underline{n}_\delta$ and $\underline{p}_\delta$. The solution has a regularity $L^q(0,T;W^{2,q}_{loc}(\mathbb{R}^d))$, see [33] for details and the method in [6].

Note that an analogue maximum estimate can be proven to provide a bound from above and justify that n vanishes at infinity, what we announced earlier.

Second step. A uniformly parabolic approximation. We consider the system of equations, which consists of a parabolic equation for n and hyperbolic equations for c_1 and c_2. Thus we construct a parabolic approximation of the equation for c_i, $i = 1, 2$. Let $\varepsilon > 0$,

$$\partial_t c_i^\varepsilon - \nabla p^\varepsilon.\nabla c_i^\varepsilon - \varepsilon\,\mathrm{div}[p^\varepsilon \nabla c_i^\varepsilon] = c_1^\varepsilon F_i(p^\varepsilon) + c_2^\varepsilon G_i(p^\varepsilon) - c_i^\varepsilon R(p^\varepsilon). \tag{40}$$

Note that all the quantities are for simplicity labelled only with ε, but they depend both on ε and δ, i.e. $p^\varepsilon := p^{\varepsilon,\delta}$ as well as the other quantities. We proceed now as follows: We solve a parabolic system consisting of (13) and (40) with initial data p^0_δ and $\frac{n^0_{i,\delta}}{n^0_\delta}$, completed with the relation $p^\varepsilon = (n^\varepsilon)^\gamma$. The equations (40) allow to observe the crucial property, which c_i possessed and which was the only information on these quantities used in a priori estimates. Indeed, adding the equations on c_i^ε, we keep the fundamental relationship $c_1^\varepsilon + c_2^\varepsilon \equiv 1$ thanks to the definition of R in (14), since initially $c_1^\varepsilon + c_2^\varepsilon = 1$. Finally, with the fully parabolic framework at hand, it is in the folklore of the domain to obtain the existence of the coupled problem between n^ε and c_i^ε.

Next, we notice that all the a priori bounds used to pass to the limit are true. Multiplying with $c_i^\varepsilon |w^\varepsilon|_- \Phi$ and integrating over $(0,T)\times\mathbb{R}^d$ gives

$$\begin{aligned}\int_{\mathbb{R}^d} |c_i^\varepsilon|^2 |w^\varepsilon|_- \Phi\,dx &+ \int_0^T\int_{\mathbb{R}^d} \nabla p^\varepsilon.\nabla c_i^\varepsilon c_i^\varepsilon |w^\varepsilon|_- \Phi\,dxdt \\ &+ \varepsilon\left[\int_0^T\int_{\mathbb{R}^d} p^\varepsilon|\nabla c_i^\varepsilon|^2|w^\varepsilon|_-\Phi\,dxdt + \int_0^T\int_{\mathbb{R}^d} p^\varepsilon \nabla c_i^\varepsilon \nabla|w^\varepsilon|_-\Phi\,dxdt\right] \\ &= \int_0^T\int_{\mathbb{R}^d} [c_1^\varepsilon F_i(p^\varepsilon) + c_2^\varepsilon G_i(p^\varepsilon) + c_i^\varepsilon R(p^\varepsilon)]|w^\varepsilon|_- c_i^\varepsilon \Phi\,dxdt + \int_{\mathbb{R}^d} |c_i^\varepsilon(0)|^2 |w^\varepsilon|_-\Phi\,dx.\end{aligned} \tag{41}$$

We observe that

$$\int_0^T\int_{\mathbb{R}^d}\nabla p^\varepsilon.\nabla c_i^\varepsilon c_i^\varepsilon|w^\varepsilon|_-\Phi\,dxdt=\frac12\int_0^T\int_{\mathbb{R}^d}\nabla p^\varepsilon.\nabla|c_i^\varepsilon|^2|w^\varepsilon|_-\Phi\,dxdt$$
$$=-\frac12\int_0^T\int_{\mathbb{R}^d}\Delta p^\varepsilon|c_i^\varepsilon|^2\Phi\,dxdt-\frac12\int_0^T\int_{\mathbb{R}^d}\nabla p^\varepsilon|c_i^\varepsilon|^2\nabla\Phi\,dxdt$$
$$-\frac12\int_0^T\int_{\mathbb{R}^d}\nabla p^\varepsilon|c_i^\varepsilon|^2\nabla|w^\varepsilon|_-\Phi\,dxdt. \tag{42}$$

Consequently, we find that

$$\varepsilon\left[\int_0^T\int_{\mathbb{R}^d}p^\varepsilon|\nabla c_i^\varepsilon|^2|w^\varepsilon|_-\Phi\,dxdt+\int_0^T\int_{\mathbb{R}^d}p^\varepsilon\nabla c_i^\varepsilon\nabla|w^\varepsilon|_-\Phi\,dxdt\right]$$
$$\le C\int_0^T\int_{\mathbb{R}^d}|\Delta p^\varepsilon|\Phi\,dxdt+C\int_0^T\int_{\mathbb{R}^d}|\nabla p^\varepsilon|\nabla\Phi\,dxdt+C\int_0^T\int_{\mathbb{R}^d}\nabla p^\varepsilon|c_i^\varepsilon|^2\nabla|w^\varepsilon|_-\Phi\,dxdt$$
$$+C\int_0^T\int_{\mathbb{R}^d}|w^\varepsilon|_-c_i^\varepsilon\Phi\,dxdt+\int_{\mathbb{R}^d}|c_i^\varepsilon(0)|^2|w^\varepsilon|_-\Phi\,dx. \tag{43}$$

Therefore the first integral on the right-hand side can be again estimated by

$$\int_0^T\int_{\mathbb{R}^d}|\Delta p^\varepsilon|\Phi\,dxdt\le\int_0^T\int_{\mathbb{R}^d}(|w^\varepsilon|_-+R)\Phi\,dxdt.$$

This approximation step will affect our a priori estimates on the level of using computations (25), as additional terms related with parabolic approximation, which are estimated above, will appear. Taking these into account, we may pass to the limit as in Section 2, first with $\varepsilon\to0$ and no major difficulty arises. Thus we obtain a limit system for n and c_i's, but still we lack the information whether the equations for n_i are satisfied in distributional sense. To recover this we multiply the equations for c_i^ε with n^ε and add the equation for n^ε multiplied with c_i^ε. Let us then define $n_i^\varepsilon:=c_i^\varepsilon n^\varepsilon$ and observe that this operation will lead us to equations for n_i^ε

$$\partial_t n_i^\varepsilon-\operatorname{div}[n_i^\varepsilon\nabla p^e]-\varepsilon\operatorname{div}[p^\varepsilon\nabla c_i^\varepsilon]n^\varepsilon=n_1^\varepsilon F_i(p^\varepsilon)+n_2^\varepsilon G_i(p^\varepsilon) \tag{44}$$

The only term that needs to be discussed is $\varepsilon\operatorname{div}[p^\varepsilon\nabla c_i^\varepsilon]n^\varepsilon$. To show that this term vanishes in a limit observe that

$$\int_{\mathbb{R}^d}\operatorname{div}[p^\varepsilon\nabla c_i^\varepsilon]n^\varepsilon\phi dx=-\int_{\mathbb{R}^d}p^\varepsilon\nabla c_i^\varepsilon.\nabla[(p^\varepsilon)^{\frac1\gamma}]\phi dx-\int_{\mathbb{R}^d}p^\varepsilon\nabla c_i^\varepsilon(p^\varepsilon)^{\frac1\gamma}\nabla\phi dx$$
$$=-\frac1\gamma\int_{\mathbb{R}^d}(p^\varepsilon)^{\frac1\gamma}\nabla p^\varepsilon.\nabla c_i^\varepsilon\phi dx-\int_{\mathbb{R}^d}(p^\varepsilon)^{\frac1\gamma+1}\nabla c_i^\varepsilon.\nabla\phi dx$$
$$=\frac1\gamma\int_{\mathbb{R}^d}(p^\varepsilon)^{\frac1\gamma}\Delta p^\varepsilon c_i^\varepsilon\phi dx+\frac1\gamma\int_{\mathbb{R}^d}\nabla((p^\varepsilon)^{\frac1\gamma}).\nabla p^\varepsilon c_i^\varepsilon\phi dx+\frac1\gamma\int_{\mathbb{R}^d}(p^\varepsilon)^{\frac1\gamma}\nabla p^\varepsilon c_i^\varepsilon\nabla\phi dx$$
$$+\int_{\mathbb{R}^d}(p^\varepsilon)^{\frac1\gamma+1}c_i^\varepsilon\Delta\phi dx+\int_{\mathbb{R}^d}\nabla[(p^\varepsilon)^{\frac1\gamma+1}]c_i^\varepsilon\nabla\phi dx. \tag{45}$$

Since p^ε and c_i^ε are bounded, then the first term on the right-hand side is bounded due to (11). The boundedness of the second term is provided by (9). For the third and fifth term we use Young's inequality and argue with boundedness of ∇p^ε in $L^2_{t,x}$. The fourth term is obvious. Thus after letting $\varepsilon\to0$ this error term will vanish. Finally we let $\delta\to0$ and complete the proof. □

4 Conclusion and perspectives

We have proposed a strategy to prove existence of weak solutions for a two species model of tumor invasion. It relies on the extension of the Aronson-Benilan regularizing effect for porous media equations which provides estimates of the Laplacian of the pressure. The most important limitation so far is a combined condition on the two bulk growth terms and it is an open question to remove it. A route in this direction could be to use the energy type estimate given in Theroem 4 in the appendix.

A question which we do not handle here is the strong compactness on the n_i^ε in the stability result of the approximation process. The bounds on Δp are too weak for the L^1 theory in [18] and are boarder line to apply the compactness theorems in [3, 7] which require that $D^2 p$ is a bounded measure.

The extension to more than two species, with the present strategy, requires combined conditions on the three growth terms which read, in the case of three species for instance, $c_1 F(p)+c_2 G(p)+c_3 H(p) \leq Cp^{1/\gamma}$ whenever the nonnegative c_i satisfy $c_1+c_2+c_3=1$. Then, the analysis goes through without major changes.

There are other questions which arise in this area and that we leave open. One of them concerns the 'incompressible limit' $\gamma \to \infty$ which has attracted much attention recently [28, 21, 17, 20, 22] because of its relation to congested traffic [24, 8, 25, 26]. Clearly the bounds provided here are not enough to investigate this question. However the one dimensional case is under investigation [10] based upon arguments from [16]. Another question is about different mobilities, see [23, 12, 11], where the parabolic aspects of the equation for $n = n_1 + n_2$ do not apply.

A Additional a priori bounds

Another remarkable estimate can be obtained for solutions of the system (1)–(2). We give it here for the sake of completeness. It can be interpreted as some kind of energy because the kinetic energy is given by $E_K = n\frac{|v|^2}{2} = p^{1/\gamma}\frac{|\nabla p|^2}{2}$.

Theorem 4 (Energy type a priori estimates) *With the assumptions (3)–(6), the following estimates hold true with constants $C(T)$ which only depend on the bounds in the above assumptions. For $\alpha_* = \frac{2}{\gamma}$, we control*

$$\int_0^T \int_{\mathbb{R}^d} \left[\operatorname{div}(p^{\frac{\alpha_*+1}{2}}\nabla p) - p^{\frac{\alpha_*+1}{2}}\frac{|\nabla p|^2}{2p}\right]^2 \leq C(T), \tag{46}$$

$$\int_{\mathbb{R}^d} p^{\alpha_*}\, |\nabla p(t)|^2\, dx \leq C(T) \qquad \forall t \in (0,T). \tag{47}$$

Proof. These two estimates, (46) and (47) come together and require some elaborate computations. We write

$$\partial_t \nabla p = \nabla[|\nabla p|^2 + \gamma p \Delta p + \gamma p R],$$

$$\partial_t \frac{|\nabla p|^2}{2} = \nabla p . \nabla[|\nabla p|^2 + \gamma p\Delta p + \gamma p R],$$

$$\partial_t p^\alpha \frac{|\nabla p|^2}{2} = p^\alpha \nabla p.\nabla[|\nabla p|^2 + \gamma p\Delta p + \gamma pR] + \alpha p^{\alpha-1}\frac{|\nabla p|^2}{2}[|\nabla p|^2 + \gamma p\Delta p + \gamma pR].$$

Therefore, we find

$$\frac{d}{dt}\int_{\mathbb{R}^d} p^\alpha \frac{|\nabla p|^2}{2} = \int_{\mathbb{R}^d}[-p^\alpha \Delta p - \alpha p^{\alpha-1}|\nabla p|^2 + \alpha p^{\alpha-1}\frac{|\nabla p|^2}{2}]\ [|\nabla p|^2 + \gamma p\Delta p + \gamma pR]$$

$$\frac{d}{dt}\int_{\mathbb{R}^d} p^\alpha \frac{|\nabla p|^2}{2} = \int_{\mathbb{R}^d}[-p^\alpha \Delta p - \alpha p^{\alpha-1}\frac{|\nabla p|^2}{2}]\ [|\nabla p|^2 + \gamma p\Delta p + \gamma pR]$$

but $p^\alpha \Delta p$ is not a good quantity. So the right-hand side has to be rewritten (divide it by γ)

$$-[p^{\frac{\alpha+1}{2}}\Delta p + \alpha p^{\frac{\alpha+1}{2}}\frac{|\nabla p|^2}{2p}]\ [p^{\frac{\alpha+1}{2}}\frac{|\nabla p|^2}{p\gamma} + p^{\frac{\alpha+1}{2}}\Delta p + p^{\frac{\alpha+1}{2}}R] =$$

$$-[\text{div}(p^{\frac{\alpha+1}{2}}\nabla p) - \frac{\alpha+1}{2}p^{\frac{\alpha+1}{2}}\frac{|\nabla p|^2}{p} + \alpha p^{\frac{\alpha+1}{2}}\frac{|\nabla p|^2}{2p}]\ [p^{\frac{\alpha+1}{2}}\frac{|\nabla p|^2}{p\gamma} - \frac{\alpha+1}{2}p^{\frac{\alpha+1}{2}}\frac{|\nabla p|^2}{p} + \text{div}(p^{\frac{\alpha+1}{2}}\nabla p) + p^{\frac{\alpha+1}{2}}R]$$

$$= -[\text{div}(p^{\frac{\alpha+1}{2}}\nabla p) - p^{\frac{\alpha+1}{2}}\frac{|\nabla p|^2}{2p}]\ [\text{div}(p^{\frac{\alpha+1}{2}}\nabla p) - p^{\frac{\alpha+1}{2}}\frac{|\nabla p|^2}{2p}(\alpha + 1 - \frac{2}{\gamma}) + p^{\frac{\alpha+1}{2}}R].$$

To create a negative square, we use the special value of α given by

$$\alpha_* = \frac{2}{\gamma}$$

and the right-hand side is controlled as $-[\text{div}(p^{\frac{\alpha+1}{2}}\nabla p) - p^{\frac{\alpha+1}{2}}\frac{|\nabla p|^2}{2p}]^2 + C\big|\text{div}(p^{\frac{\alpha+1}{2}}\nabla p) - p^{\frac{\alpha+1}{2}}\frac{|\nabla p|^2}{2p}\big|$.

Therefore, we obtain the inequalities (46) and (47). □

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