Derivation of a Hele-Shaw type system from a cell model with active motion

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Abstract

We formulate a Hele-Shaw type free boundary problem for a tumor growing under the combined effects of pressure forces, cell multiplication and active motion, the latter being the novelty of the present paper. This new ingredient is considered here as a standard diffusion process. The free boundary model is derived from a description at the cell level using the asymptotic of a stiff pressure limit.

Compared to the case when active motion is neglected, the pressure satisfies the same complementarity Hele-Shaw type formula. However, the cell density is smoother (Lipschitz continuous), while there is a deep change in the free boundary velocity, which is no longer given by the gradient of the pressure, because a region, with limited population but diffusing with long range, can prepare the tumor invasion.

Key-words: Tumor growth; Hele-Shaw equation; porous medium equation; free boundary problems.
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1 Introduction

Among the several models now available to deal with cancer development, there is a class, initiated in the 70's by Greenspan [18], that considers that cancerous cells multiplication is limited by nutrients (glucosis, oxygen) brought by blood vessels. Models of this class rely on two kinds of descriptions; either they describe the dynamics of cell population density [6] or they consider the 'geometric' motion of the tumor through a free boundary problem; see [13, 14, 16, 19] and the references therein. In the latter kind of models the stability or instability of the free boundary is an important issue that has attracted attention, [10, 16].

The first stage, where growth is limited by nutrients, lasts until the tumor reaches the size of $\approx$ 1mm; then, lack of food leads to cell necrosis which triggers neovasculatures development [9] that supply the tumor with enough nourishment. This has motivated a new generation of models where growth

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is limited by the competition for space [5], turning the modeling effort towards mechanical concepts, considering tissues as multiphasic fluids (the phases could be intersticial water, healthy and tumor cells, extra-cellular matrix ...) [2, 7, 8, 21, 23]. This point of view is now sustained by experimental evidence [22]. The term 'homeostatic pressure', coined recently, denotes the lower pressure that prevents cell multiplication by contact inhibition.

In a recent paper [20] the authors explain how asymptotic analysis can link the two main approaches, cell density models and free boundary models (of Hele-Shaw type), in the context of fluid mechanics for the simplest cell population density model, proposed in [7], in which the cell population density evolves under pressure forces and cell multiplication. The principle of the derivation is to use the stiff limit in the pressure law of state, as treated in several papers; see for instance [3, 17] and the references therein. The stiff law of state is usually accepted in the biophysical literature and means that there is a maximal compaction level [10]. In [15], the results of agent based models are compared to a Hele-Shaw flow.

Besides mechanical motion induced by pressure, for some types of cancer cells it is important to take into account active motion; see [4, 15, 24]. In the present paper we extend the asymptotic analysis of [20] to a model that includes such an ingredient. We examine the specific form of the Hele-Shaw limit and draw qualitative conclusions on the behaviour of the solutions in terms of regularity and free boundary velocity.

2 Notations and main result

Our model of tumor growth incorporates active motion of cells thanks to a diffusion term,

$$\partial_t n_k - \operatorname{div}\big(n_k \nabla p_k\big) - \nu \Delta n_k = n_k G\big(p_k\big), \qquad (x,t) \in Q := \mathbb{R}^d \times (0,\infty). \tag{2.1}$$

The variable n_k represents the density of tumor cells, and the variable p_k the pressure, which is considered to be given by a homogeneous law (written with a specific coefficient so as to simplify notations later on)

$$p_k(n) = \frac{k}{k-1} n^{k-1}. \tag{2.2}$$

Hence, we are dealing with a porous medium type equation; see [26] for a general reference on such problems. We complement this system with a family of initial conditions that is supposed to satisfy (uniformly in k)

$$\begin{cases} n_k(x,0) = n_k^{\text{ini}}(x) > 0, \qquad n_k^{\text{ini}} \in L^1(\mathbb{R}^d) \cap L^\infty(\mathbb{R}^d), \\ p_k^{\text{ini}} := \frac{k}{k-1}(n_k^{\text{ini}})^{k-1} \le P_M. \end{cases} \tag{2.3}$$

In a purely mechanical view, the pressure-limited growth is described by the function G, which satisfies

$$G'(\cdot) < 0 \qquad \text{and} \qquad G(P_M) = 0, \tag{2.4}$$

for some $P_M > 0$, usually called the homeostatic pressure; see [7, 22].

Many authors use another type of models, namely free boundary problems on the tumor region $\Omega(t)$. Our purpose is to make a rigorous derivation of one of such models from (2.1), (2.2). As it is wellkown, for $\nu = 0$ this is possible in the asymptotics k large. This is connected, in fluid mechanics, to the Hele-Shaw equations; a complete proof of the derivation is provided in [20]. Typically the limit of the cell density is an indicator function for each time $t > 0$, $n_\infty = \mathbb{1}_{\Omega(t)}$, if this is initially true, and the problem is reduced to describing the velocity of the boundary $\partial\Omega(t)$.

Our aim is to understand what is the effect of including active motion, that is, $\nu > 0$. We will show that both the densities and the pressures have limits, n_∞ and p_∞, as $k \to \infty$ that satisfy

$$\partial_t n_\infty - \operatorname{div}\big(n_\infty \nabla p_\infty\big) - \nu \Delta n_\infty = n_\infty G\big(p_\infty\big). \tag{2.5}$$

Compared with the case $\nu = 0$ considered in [20], a first major difference is that now the cell density n_k is smooth and positive, since equation (2.1) is non-degenerate when $\nu > 0$. Is that translated into more regularity for the limit density? We will show that this is indeed the case. Though the limit density satisfies

$$0 \le n_\infty \le 1,$$

it is not an indicator function any more, and its time derivate $\partial_t n_\infty$ is a function, while it is only a measure when $\nu = 0$. As for the pressure, we will establish that we still have

$$n_\infty = 1 \text{ in } \Omega(t) = \{p_\infty(t) > 0\},$$

or in other words $p_\infty \in P_\infty(n_\infty)$, with P_∞ the limiting monotone graph

$$P_\infty(n) = \begin{cases} 0, & 0 \le n < 1, \\ [0, \infty), & n = 1. \end{cases} \tag{2.6}$$

Furthermore, multiplying equation (2.1) by $p'_k(n_k)$ leads to

$$\partial_t p_k - n_k p'_k(n_k) \Delta p_k - |\nabla p_k|^2 - \nu \Delta p_k = n_k p'_k(n_k) G\big(p_k\big) - \nu p''_k(n_k) |\nabla n_k|^2,$$

and for the special case $p_k = \frac{k}{k-1} n_k^{k-1}$ at hand we find

$$\partial_t p_k - (k-1) p_k \Delta p_k - |\nabla p_k|^2 - \nu \Delta p_k = (k-1) p_k G\big(p_k\big) - \nu \frac{(k-2) \nabla p_k \cdot \nabla n_k}{n_k}. \tag{2.7}$$

Therefore, the 'complementarity relation'

$$-\, p_\infty \Delta p_\infty = p_\infty G\big(p_\infty\big) - \nu \frac{\nabla p_\infty \cdot \nabla n_\infty}{n_\infty}, \tag{2.8}$$

is expected in the limit. However, ∇p_∞ vanishes unless $p_\infty > 0$, in which case $n_\infty = 1$, therefore $\nabla n_\infty = 0$. Thus, the equation on p_∞ ignores the additional term coming from active motion and reduces to the same Hele-Shaw equation (also called *complementarity relation*) for the pressure that holds when $\nu = 0$, namely

$$p_\infty \left(\Delta p_\infty + G\big(p_\infty\big) \right) = 0. \tag{2.9}$$

Let us remark that this similar complementary relation does not mean that active motion has no effect in the limit. Though the pressure equation is the same one as for the case $\nu = 0$, the free boundary $\partial\Omega(t)$ is not expected to move with the usual Hele-Shaw rule $V = -\nabla p_\infty$, but with a faster one; see Section 7 for a discussion on the speed of the free boundary.

Notice that $\Omega(t)$ coincides almost everywhere with the set where $\varrho_\infty(t) = 1$. Indeed, on the one hand, by the definition of the graph P_∞ we have $\Omega(t) \subset \{x;\ \varrho_\infty(x,t) = 1\}$; on the other hand, if

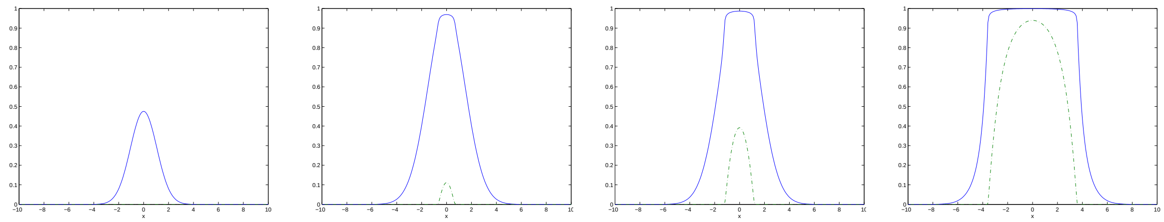

Figure 1: First steps of the initiation of the free boundary. Results obtained thanks to a discretization of the system (2.1)–(2.2) with $k = 100$ and $\nu = 0.5$. The density n is plotted in solid line whereas the pressure p is represented in dashed line. The pressure p has the same shape as in the classical Hele-Shaw system with growth. However the density n is smoother.

we had $p_\infty = 0$ and $\varrho_\infty = 1$ in some set with positive measure, then ϱ_∞ would continue to grow (exponentially) there, which is a contradiction. Therefore, $\Omega(t)$ may be regarded as the *tumor*, while the regions where $0 < \varrho_\infty < 1$ (mushy regions, in the literature of phase-changes) correspond to *precancer* cells.

The above heuristic discussion can be made rigorous.

Theorem 2.1 *Let $T > 0$ and $Q_T = \mathbb{R}^d \times (0,T)$. Assume* (2.3), (2.4), *and that the initial data are subsolutions to the stationary equation, that is $-\mathrm{div}\big(n_k^{\mathrm{ini}} \nabla p_k^{\mathrm{ini}}\big) - \nu \Delta n_k^{\mathrm{ini}} \le n_k^{\mathrm{ini}} G\big(p_k^{\mathrm{ini}}\big)$. Consider a weak solution (n_k, p_k) of* (2.1)–(2.2)*. Up to extraction of a subsequence, $(n_k)_k$, $(p_k)_k$ converge strongly in $L^p(Q_T)$, $1 \le p < \infty$, to limits*

$$n_\infty \in C\big([0,\infty); L^1(\mathbb{R}^d)\big) \cap L^\infty((0,T); H^1(\mathbb{R}^d)), \qquad p_\infty \in L^\infty((0,T); H^1(\mathbb{R}^d)),$$

such that $0 \le n_\infty \le 1$, $n_\infty(0) = n^{\mathrm{ini}}$, $0 \le p_\infty \le P_M$, $p_\infty \in P_\infty(n_\infty)$, where P_∞ is the Hele-Shaw monotone graph given in (2.6)*. Moreover, the pair (n_∞, p_∞) satisfies both* (2.5) *and the Hele-Shaw type equation*

$$\partial_t n_\infty - \Delta p_\infty - \nu \Delta n_\infty = n_\infty G\big(p_\infty\big), \tag{2.10}$$

and also the complementarity relation (2.9) *for almost every $t > 0$. All three equations hold in the weak sense. The time derivatives of the limit functions satisfy*

$$\partial_t n_\infty,\ \partial_t p_\infty \in \mathcal{M}^1(Q_T), \qquad \partial_t n_\infty,\ \partial_t p_\infty \ge 0.$$

Here $\mathcal{M}^1$ denotes the Banach space of bounded measures, endowed with its weak topology.

To illustrate this behaviour, we present numerical results obtained thanks to a discretization with finite volumes of system (2.1)–(2.2) in the case $k = 100$, $\nu = 0.5$ and with $G(p) = 1 - p$. We display in Figure 1 the first steps of the formation of a tumor which is initially given by a small bump. The shape of the pressure p at the place where $n = 1$ is similar to the one observed for the classical Hele-Shaw system (see e.g. [20]). But a major difference is that, as expected, the population density n is smooth. This effect is in accordance with the observation that different imaging procedures can give different tumor contours.

The hypothesis that the initial data are subsolutions to the stationary problem, which is rather strong, can be removed. However, it has the advantage of allowing a simple presentation of the limiting process. Therefore, we have chosen to keep it in a first stage, postponing the long and technical argument for regularizing effects and time compactness allowing to drop it to Section 8.

The rest of the paper is organized as follows. We begin in Section 3 with some uniform (in k) a priori estimates which are necessary for strong compactness. Then, in Section 4 we prove the main statements in Theorem 2.1. The most delicate part, establishing (2.9), is postponed to Section 5. After proving uniqueness for the limit problem in Section 6, we devote Section 7 to discuss further regularity issues and the speed of the boundary of the tumor zone. We end with Section 8, whose aim is to weaken the assumptions on the initial data, as explained above.

3 Estimates

To begin with, we gather in the following statement all the a priori estimates that we need later on.

Lemma 3.1 *With the assumptions and notations in Theorem 2.1, the weak solution (n_k, p_k) of (2.1)–(2.2) satisfies*

$$0 \le n_k \le \Big(\frac{k-1}{k} P_M\Big)^{1/(k-1)} \underset{k\to\infty}{\longrightarrow} 1, \qquad 0 \le p_k \le P_M,$$

$$\int_{\mathbb{R}^d} n_k(t) \le e^{G(0)t} \int_{\mathbb{R}^d} n^{\text{ini}}, \qquad \int_{\mathbb{R}^d} p_k(t) \le C e^{G(0)t} \int_{\mathbb{R}^d} n^{\text{ini}}.$$

with C a constant independent of k. Furthermore, there exists a uniform (with respect to k) nonnegative constant $C = C\Big(T, \|n^{\text{ini}}\|_{L^1(\mathbb{R}^d)\cap L^\infty(\mathbb{R}^d)}\Big)$ such that

$$\int_{\mathbb{R}^d} \Big(\nu|\nabla n_k|^2 + k n_k^{k-1}|\nabla n_k|^2 + |\nabla p_k|^2\Big)(t) \le C \quad \text{for all } t \in (0,T). \tag{3.1}$$

Finally,

$$\partial_t n_k, \partial_t p_k \ge 0, \quad \partial_t n_k \text{ is bounded in } L^\infty((0,T); L^1(\mathbb{R}^d)), \quad \partial_t p_k \text{ is bounded in } L^1(Q_T).$$

Proof. *Estimates on n_k and p_k.* The $L^\infty(Q)$ bounds are a consequence of standard comparison arguments for (2.1) and (2.7). The $L^\infty((0,T); L^1(\mathbb{R}^d))$ bound for n_k can be obtained by integrating (2.1) over $\mathbb{R}^d$ and then using (2.4). The $L^\infty((0,T); L^1(\mathbb{R}^d))$ bound for p_k now follows from the relation between p_k and n_k.

Estimates on the time derivatives. We introduce the quantity

$$\Sigma(n_k) = n_k^k + \nu n_k, \qquad \Sigma'(n_k) = k n_k^{k-1} + \nu. \tag{3.2}$$

The density equation (2.1) is rewritten in terms of this new variable as

$$\partial_t n_k - \Delta\Sigma(n_k) = n_k G(p_k). \tag{3.3}$$

Using the notation $\Sigma_k = \Sigma(n_k)$ and multiplying the above equation by $\Sigma'(n_k)$, we get

$$\partial_t \Sigma_k - \Sigma_k' \Delta\Sigma_k = n_k \Sigma_k' G\big(p_k\big). \tag{3.4}$$

Let $w_k = \partial_t \Sigma(n_k)$. Notice that $\text{sign}\,(\partial_t n_k) = \text{sign}\,(w_k)$. A straightforward computation yields

$$\partial_t w_k - \Sigma_k' \Delta w_k = \partial_t n_k \Sigma_k'' \big(\Delta \Sigma_k + n_k G(p_k)\big) + \partial_t n_k \Sigma_k' G(p_k) + \partial_t n_k \Sigma_k' k n_k^{k-1} G'(p_k).$$

By using that $w_k = \Sigma_k' \partial_t n_k$ and $\Sigma'(n_k) \geq \nu > 0$, the right hand side of the above equation can be written in a more handful way as

$$\partial_t w_k - \Sigma_k' \Delta w_k = w_k \Big(\frac{\Sigma_k''}{\Sigma_k'} \big(\Delta \Sigma_k + n_k G(p_k)\big) + G(p_k) + k n_k^{k-1} G'(p_k) \Big).$$

Since this equation preserves positivity and $\text{sign}\,(w_k(0)) = \text{sign}\,(\partial_t n_k^{\text{ini}}) \geq 0$, we conclude that $w_k \geq 0$, that is, $\partial_t n_k \geq 0$. The relation between p_k and n_k then immediately yields $\partial_t p_k \geq 0$.

Now that we know that the time derivatives have a sign, bounds for them follow easily. Indeed, using (2.1), we get

$$\|\partial_t n_k(t)\|_{L^1(\mathbb{R}^d)} = \frac{d}{dt} \int_{\mathbb{R}^d} n_k(t) \leq G(0) \|n_k(t)\|_{L^1(\mathbb{R}^d)}.$$

This gives the bound on $\partial_t n_k$ in $L^\infty([0,T]; L^1(\mathbb{R}^d))$. For $\partial_t p_k$ we write

$$\|\partial_t p_k\|_{L^1(Q_T)} = \int_0^T \frac{d}{dt} \left(\int_{\mathbb{R}^d} p_k(t) \right) dt \leq \int_{\mathbb{R}^d} p_k(T).$$

This last expression is uniformly bounded in k.

Estimates on the gradients. We multiply equation (2.1) by n_k, integrate over $\mathbb{R}^d$ and use integration by parts for the diffusion terms,

$$\int_{\mathbb{R}^d} (n_k \partial_t n_k)(t) + \int_{\mathbb{R}^d} \big(k n_k^{k-1} |\nabla n_k|^2 + \nu |\nabla n_k|^2\big)(t) = \int_{\mathbb{R}^d} (n_k^2 G(p_k))(t) \leq G(0) \int_{\mathbb{R}^d} n_k^2(t).$$

Since both n_k and $\partial_t n_k$ are nonnegative, we immediately obtain the estimate on the first two terms in (3.1). On the other hand, integrating equation (2.7), we deduce

$$\begin{aligned} \int_{\mathbb{R}^d} \partial_t p_k(t) + (k-2) \int_{\mathbb{R}^d} \big(|\nabla p_k|^2 + \nu k n_k^{k-3} |\nabla n_k|^2\big)(t) &= (k-1) \int_{\mathbb{R}^d} (p_k G(p_k))(t) \\ &\leq (k-1) G(0) \int_{\mathbb{R}^d} p_k(t). \end{aligned}$$

Since $\partial_t p_k \geq 0$, we easily obtain the L^2 bound on ∇p_k in (3.1). □

4 Proof of Theorem 2.1

In this section we prove all the statements in Theorem 2.1 except the one concerning the complementarity relation for the pressure, equation (2.9), whose proof is postponed to the next section.

Strong convergence and bounds. Since the families n_k and p_k are bounded in $W^{1,1}_{\text{loc}}(Q)$, we have strong convergence in L^1_{loc} both for n_k and p_k. To pass from local convergence to convergence in $L^1(Q_T)$, we need to prove that the mass in an initial strip $t \in [0, 1/R]$ and in the tails $|x| > R$ is uniformly (in k)

small if R is large enough. The control on the initial strip is immediate using our uniform, in k and t, bounds for $\|n_k(t)\|_{L^1(\mathbb{R}^d)}$ and $\|p_k(t)\|_{L^1(\mathbb{R}^d)}$. The tails for the densities n_k are controlled using the equation, pretty in the same way as it was done for the case $\nu = 0$; see [20] for the details. The control on the tails of the pressures p_k then follows from the relation between p_k and n_k. Strong convergence in $L^p(Q_T)$ for $1 < p < \infty$ is now a consequence of the uniform bounds for n_k and p_k.

Thanks to the a priori estimates proved above, we also have that $(\nabla n_k)_k$ and $(\nabla p_k)_k$ converge weakly in $L^2(Q_T)$, and

$$0 \le n_\infty \le 1, \quad n_\infty,\ p_\infty \in L^\infty((0,T);H^1(\mathbb{R}^d)), \quad \partial_t n_\infty,\ \partial_t p_\infty \in \mathcal{M}^1(Q_T), \quad \partial_t n_\infty,\ \partial_t p_\infty \ge 0.$$

Identification of the limit. To establish equation (2.5) in the distributional sense, we just pass to the limit, by weak-strong convergence, in equation (2.1) . On the other hand, using the definition of p_k in (2.2), we have

$$n_k p_k = \frac{k}{k-1} n_k^k = \Big(1 - \frac{1}{k}\Big)^{1/(k-1)} p_k^{k/(k-1)} \underset{k\to\infty}{\longrightarrow} p_\infty.$$

Taking the limit $k \to \infty$, we deduce the monotone graph property

$$p_\infty(1 - n_\infty) = 0. \tag{4.1}$$

In order to show the equivalence of (2.10) and (2.5), we need to prove that $\nabla p_\infty = n_\infty \nabla p_\infty$. This es seen to be equivalent to $p_\infty \nabla n_\infty = 0$ by applying Leibniz's rule in $H^1(\mathbb{R}^d)$ to (4.1). To prove the latter identity, we first write

$$p_k \nabla n_k = \frac{k}{k-1} n_k^k \nabla n_k = \frac{\sqrt{k}}{k-1} n_k^{(k+1)/2} \big(\sqrt{k}\, n_k^{(k-1)/2} \nabla n_k\big).$$

¿From estimate (3.1), the term between parentheses is uniformly bounded in $L^2(Q_T)$ and since $(n_k)_k$ is uniformly (in k) bounded in $L^\infty(Q_T)$, we conclude that

$$\lim_{k\to\infty} \|p_k \nabla n_k\|_{L^2(Q_T)} = 0.$$

We deduce then from the strong convergence of $(p_k)_k$ and the weak convergence of $(\nabla n_k)_k$ that

$$p_\infty \nabla n_\infty = 0, \tag{4.2}$$

as desired.

Time continuity and initial trace. Time continuity for the limit density n_∞ follows from the monotonicity and the equation, as in the case $\nu = 0$. Once we have continuity, the identification of the initial trace will follow from the equation for n_k, letting first $k \to \infty$ and then $t \to 0$; see [20] for the details.

Remark. Since $p_\infty \ge 0$, (4.2) implies that

$$\nabla p_\infty \cdot \nabla n_\infty = 0. \tag{4.3}$$

5 The equation on p_∞

In this section we give a rigorous derivation of equation (2.9), which is the most delicate point in the proof of Theorem 2.1.

(i) Our first goal is to establish that, in the weak sense,

$$p_\infty \Delta p_\infty + p_\infty G(p_\infty) \le 0. \tag{5.1}$$

Thanks to (4.2) and (4.3), this is equivalent to proving that

$$p_\infty \Delta\big(p_\infty + \nu n_\infty\big) + p_\infty G(p_\infty) \le 0. \tag{5.2}$$

In order to prove the latter inequality, we follow an idea of [20] and use a time regularization method *à la Steklov*. To this aim, we introduce a regularizing kernel $\omega_\varepsilon(t) \ge 0$ with compact support of length ε.

Let $n_{k,\varepsilon} = n_k * \omega_\varepsilon$. ¿From equation (2.1), we deduce

$$\partial_t n_{k,\varepsilon} - \Delta \omega_\varepsilon * (n_k^k + \nu n_k) = (n_k G(p_k)) * \omega_\varepsilon. \tag{5.3}$$

Then, for fixed $\varepsilon > 0$, $\Delta\omega_\varepsilon * (n_k^k + \nu n_k)$ is bounded in $L^q(Q_T)$ for all $q \ge 1$. Thus, we can extract a subsequence such that $(\nabla\omega_\varepsilon * (n_k^k + \nu n_k))_k$ converges strongly in $L^2(Q_T)$. Since we have strong convergence of $(n_k^k + \nu n_k)_k$ towards $p_\infty + \nu n_\infty$, we deduce that the strong limit of $(\nabla\omega_\varepsilon * (n_k^k + \nu n_k))_k$ is equal to $\nabla\omega_\varepsilon * (p_\infty + \nu n_\infty)$.

Multiplying equation (5.3) by p_k, we have

$$p_k \partial_t n_{k,\varepsilon} = p_k \Delta\big(n_k^k * \omega_\varepsilon + \nu n_{k,\varepsilon}\big) + p_k\big((n_k G(p_k)) * \omega_\varepsilon\big).$$

We can pass to the limit $k \to \infty$ to get

$$\lim_{k\to\infty} p_k \partial_t n_{k,\varepsilon} = p_\infty \Delta\big(\omega_\varepsilon * (p_\infty + \nu n_\infty)\big) + p_\infty\big((n_\infty G(p_\infty)) * \omega_\varepsilon\big).$$

To determine the sign, we decompose the left hand side term, divided by the harmless factor $k/(k-1)$, as

$$\int_{\mathbb{R}} n_k^{k-1}(t) \partial_t n_k(s) \omega_\varepsilon(t-s)\, ds = \underbrace{\int_{\mathbb{R}} n_k^{k-1}(s) \partial_t n_k(s) \omega_\varepsilon(t-s)\, ds}_{\mathcal{A}_k} + \underbrace{\int_{\mathbb{R}} (n_k^{k-1}(t) - n_k^{k-1}(s)) \partial_t n_k(s) \omega_\varepsilon(t-s)\, ds}_{\mathcal{B}_k}.$$

On the one hand we have

$$\mathcal{A}_k = \frac{1}{k} \int_{\mathbb{R}} \partial_t n^k(s) \omega_\varepsilon(t-s)\, ds \to 0 \quad \text{ when } k \to \infty.$$

As for $\mathcal{B}_k$, we recall that $\partial_t n_k \ge 0$ provided $\partial_t n^{\mathrm{ini}} \ge 0$; see Lemma 3.1. Thus, for $s > t$ we have $n_k^{k-1}(t) - n_k^{k-1}(s) \le 0$. Then, choosing ω_ε such that $\operatorname{supp} \omega_\varepsilon \subset \mathbb{R}_-$, we deduce that $\mathcal{B}_k \le 0$, which yields

$$p_\infty \Delta\big(\omega_\varepsilon * (p_\infty + \nu n_\infty)\big) + p_\infty\big(n_\infty G(p_\infty) * \omega_\varepsilon\big) \le 0.$$

It remains to pass to the limit $\varepsilon \to 0$ in the regularization process. We can pass to the limit in the weak formulation since we already know that $\nabla p_\infty \in L^2(Q_T)$. Then, using (4.1), we get the inequality (5.2) and thus (5.1).

(ii) Our second purpose is to establish the other inequality, namely

$$p_\infty \Delta p_\infty + p_\infty G(p_\infty) \geq 0. \tag{5.4}$$

To prove it, we multiply equation (2.7) by a nonnegative test function $\phi(x,t)$ and integrate, and obtain

$$\iint_{Q_T} \phi\big(p_k \Delta p_k + p_k G(p_k) - \nu \frac{k-2}{k-1} \frac{\nabla p_k \cdot \nabla n_k}{n_k}\big) = \frac{1}{k-1} \iint_{Q_T} \left(\phi\big(\partial_t p_k - |\nabla p_k|^2\big) + \nu \nabla\phi \cdot \nabla p_k\right).$$

¿From the proved bounds, the right hand side of the above equation converges to 0 as $k \to \infty$. We can use integration by parts and rewrite the left hand side as

$$\iint_{Q_T} \left(\phi p_k G(p_k) - p_k \nabla\phi \cdot \nabla p_k - \phi |\nabla p_k|^2 - \phi\nu \frac{k(k-2)}{k-1} n_k^{k-3} |\nabla n_k|^2\right).$$

Since the last term is nonpositive, we obtain that

$$\liminf_{k\to\infty} \iint_{Q_T} \left(\phi p_k G(p_k) - p_k \nabla\phi \cdot \nabla p_k - \phi |\nabla p_k|^2\right) \geq 0.$$

¿From weak-strong convergence in products, or convexity inequalities in the weak limit, we finally conclude

$$\iint_{Q_T} \left(\phi p_\infty G(p_\infty) - p_\infty \nabla\phi \cdot \nabla p_\infty - \phi |\nabla p_\infty|^2\right) \geq 0.$$

This is the weak formulation of (5.4).

Remark. A careful inspection of the proof of (5.4) shows that (2.8) holds if and only if ∇p_k converges strongly in $L^2(Q_T)$ and $k n_k^{k-3} |\nabla n_k|^2$ converges weakly to 0 locally in $L^1(Q)$. Since we have proved (2.8), we conclude that we have the two mentioned convergence results.

6 Uniqueness for the limit model

In this section we prove that the limit problem (2.10) admits at most one solution. We will adapt Hilbert's duality method in the spirit of [12, 20].

Theorem 6.1 *Let $T > 0$, $\nu > 0$. There is a unique pair (n,p) of functions in $L^\infty([0,T]; L^1(\mathbb{R}^d) \cap L^\infty(\mathbb{R}^d))$, $n \in C([0,T]; L^1(\mathbb{R}^d))$, $n(0) = n^{\text{ini}}$, $p \in P_\infty(n)$, satisfying* (2.10) *in the sense of distributions and such that ∇n, $\nabla p \in L^2(Q_T)$, $\partial_t n$, $\partial_t p \in \mathcal{M}^1(Q_T)$.*

Proof. Let us consider two solutions (n_1, p_1) and (n_2, p_2). Then for any test function ϕ with $\phi \in W^{2,2}(Q_T)$ and $\partial_t \phi \in L^2(Q_T)$, we have

$$\iint_{Q_T} \Big((n_1 - n_2)\partial_t \phi + (p_1 - p_2 + \nu(n_1 - n_2))\Delta\phi + \big(n_1 G(p_1) - n_2 G(p_2)\big)\phi\Big) = 0, \tag{6.1}$$

which can be rewritten as

$$\iint_{Q_T} \big(\nu(n_1 - n_2) + p_1 - p_2\big)\big(A\partial_t\phi + \Delta\phi + AG(p_1)\phi - B\phi\big) = 0, \tag{6.2}$$

where

$$0 \le A = \frac{n_1 - n_2}{\nu(n_1 - n_2) + p_1 - p_2} \le \frac{1}{\nu},$$
$$0 \le B = -n_2 \frac{G(p_1) - G(p_2)}{\nu(n_1 - n_2) + p_1 - p_2} \le \kappa,$$

for some nonnegative constant κ. To arrive to these bounds on A we set $A = 0$ when $n_1 = n_2$, even if $p_1 = p_2$. Since A can vanish, we use a smoothing argument by introducing the regularizing sequences $(A_n)_n$, $(B_n)_n$ and $(G_{1,n})_n$ such that

$$\begin{aligned}
&\|A - A_n\|_{L^2(Q_T)} < \alpha/n, && 1/n < A_n \le 1, && \\
&\|B - B_n\|_{L^2(Q_T)} < \beta/n, && 0 \le B_n \le \beta_2, && \|\partial_t B_n\|_{L^1(Q_T)} \le \beta_3, \\
&\|G_{1,n} - G(p_1)\|_{L^2(Q_T)} \le \delta/n, && |G_{1,n}| < \delta_2, && \|\nabla G_{1,n}\|_{L^2(Q_T)} \le \delta_3,
\end{aligned}$$

for some nonnegative constants α, β, β_2, β_3, δ, δ_2, δ_3.

Given any arbitrary smooth function ψ compactly supported, we consider the solution ϕ_n of the backward heat equation

$$\begin{cases} \partial_t\phi_n + \dfrac{1}{A_n}\Delta\phi_n + G_{1,n}\phi_n - \dfrac{B_n}{A_n}\phi_n = \psi & \text{in } Q_T, \\ \phi_n(T) = 0. \end{cases} \tag{6.3}$$

The coefficient $1/A_n$ is continuous, positive and bounded below away from zero. Then the equation satisfied by ϕ_n is parabolic. Hence ϕ_n is smooth and since ψ is compactly supported, we have that ϕ_n, $\Delta\phi_n$ and therefore $\partial_t\phi_n$ are L^2-integrable. Therefore, we can use ϕ_n as a test function in (6.2). Then, by the definition of A, we have

$$\iint_{Q_T} (n_1 - n_2)\psi = \iint_{Q_T} \big(\nu(n_1 - n_2) + p_1 - p_2\big)A\psi.$$

Inserting (6.3) and substracting (6.2), we obtain

$$\iint_{Q_T} (n_1 - n_2)\psi = I_{1n} + I_{2n} + I_{3n},$$

where

$$\begin{aligned}
I_{1n} &= \iint_{Q_T} \big(\nu(n_1 - n_2) + p_1 - p_2\big)\Big(\big(\frac{A}{A_n} - 1\big)\big(\Delta\phi_n - C_n\phi_n\big)\Big), \\
I_{2n} &= \iint_{Q_T} \big(\nu(n_1 - n_2) + p_1 - p_2\big)(B - B_n)\phi_n, \\
I_{3n} &= \iint_{Q_T} (n_1 - n_2)\big(G_{1,n} - G(p_1)\big)\phi_n.
\end{aligned}$$

The convergence towards 0 of the terms $I_{in},\ i = 1, 2, 3$ is now a consequence on some estimates on the test functions ϕ_n which are gathered in Lemma 6.2 below. Indeed, applying the mentioned estimates and Cauchy-Schwarz inequality we have

$$\begin{aligned} &I_{1n} \le K\|(A - A_n)/\sqrt{A_n}\|_{L^2(Q_T)} \le K\sqrt{n}\|A - A_n\|_{L^2(Q_T)} \le K\alpha/\sqrt{n},\\ &I_{2n} \le K\|B - B_n\|_{L^2(Q_T)} \le K\gamma/n,\\ &I_{3n} \le K\delta/n, \end{aligned}$$

(in all the computations, K denotes various nonnegative constants). Then letting $n \to \infty$, we conclude that

$$\iint_{Q_T} (n_1 - n_2)\psi = 0,$$

for any smooth function ψ compactly supported, hence $n_1 = n_2$. It is then obvious, thanks to (6.1), that $p_1 = p_2$. □

Lemma 6.2 *Under the assumptions of Theorem 6.1, we have the uniform bounds, only depending on T and ψ,*

$$\|\phi_n\|_{L^\infty(Q_T)} \le \kappa_1, \quad \sup_{0\le t\le T} \|\nabla\phi_n(t)\|_{L^2(\mathbb{R}^d)} \le \kappa_2, \quad \|1/\sqrt{A_n}(\Delta\phi_n - B_n\phi_n)\|_{L^2(Q_T)} \le \kappa_3.$$

Proof. The first bound is a consequence of the maximum principle for (6.3). Then, multiplying (6.3) by $\Delta\phi_n - B_n\phi_n$ and integrating on $\mathbb{R}^d$, we get

$$\begin{aligned} &-\frac{1}{2}\frac{d}{dt}\int_{\mathbb{R}^d} |\nabla\phi_n(t)|^2 - \frac{1}{2}\frac{d}{dt}\int_{\mathbb{R}^d} B_n\phi_n^2(t) + \int_{\mathbb{R}^d} \frac{1}{A_n}|\Delta\phi_n - B_n\phi_n|^2(t) + \frac{1}{2}\int_{R^d} (\partial_t B_n\phi_n^2)(t),\\ &= \int_{\mathbb{R}^d} \Big(G_{1,n}|\nabla\phi_n|^2 + \phi_n\nabla\phi_n \cdot \nabla G_{1,n} + B_nG_{1,n}\phi_n^2 + (\Delta\psi - B_n\psi)\phi_n\Big)(t). \end{aligned}$$

After an integration in time on $[t, T]$, we deduce

$$\frac{1}{2}\|\nabla\phi_n(t)\|_{L^2(\mathbb{R}^d)} + \int_t^T \int_{\mathbb{R}^d} \frac{1}{A_n}|\Delta\phi_n - B_n\phi_n|^2 \le K\Big(1 - t + \int_t^T \|\nabla\phi_n(s)\|_{L^2(\mathbb{R}^d)}\, ds\Big),$$

where we use the bounds on $\nabla G_{1,n}$ and $\partial_t B_n$ by construction of the regularization. We conclude by applying Gronwall's Lemma. □

7 Further regularity and velocity of the free boundary

Remember that both p_∞ and n_∞ belong to $H^1(\mathbb{R}^d)$ for almost every $t > 0$. This regularity cannot be improved, because there are jumps in the gradients of both p_∞ and n_∞ at the free boundary. As a consequence, their laplacians are not functions, but measures. However, these singularities cancel in the combination $\Sigma_\infty = p_\infty + \nu n_\infty$, as we will see now.

Lemma 7.1 *With the assumptions of Theorem 2.1, the quantity Σ_∞ belongs to $L^2((0, T); H^2(\mathbb{R}^d))$ for all $T > 0$ and we have the estimate*

$$\iint_{Q_T} (\Delta\Sigma_\infty)^2 \le C(T).$$

Proof. We recall the definition of Σ_k in (3.2). Since $\nabla\Sigma_k = n_k\nabla p_k + \nu\nabla n_k$, estimate (3.1) yields that for all $0 < t \le T$,

$$\int_{\mathbb{R}^d} |\nabla\Sigma_k(t)|^2 \le C(T).$$

We now multiply the equation (3.4) by $\Delta\Sigma_k$, and integrate in Q_T, $0 < T < \infty$, to obtain, using that $\Sigma_k' > \nu$ and the fact that both n_k and $G(p_k)$ are nonnegative,

$$\iint_{Q_T} (\Delta\Sigma_k)^2 \le \frac{1}{2}\int_{\mathbb{R}^d} |\nabla\Sigma_k|^2(0) + C(T).$$

The result follows directly. $\square$

This implies in particular that in the limit $\Sigma_\infty(t) \in H^2(\mathbb{R}^d)$ for almost every $t > 0$. Hence, $\Sigma_\infty(t)$ is a continuous function for almost every $t > 0$. Let $t > 0$ be such that $\Sigma_\infty(t)$ is continuous. Since $n_\infty(t) = 1$, and hence continuous, in the interior of $\Omega(t)$, we have that $p_\infty(t)$ is also continuous in that set. On the other hand, $p_\infty(t) = 0$, in the exterior of $\Omega(t)$, and we conclude that $n_\infty(t)$ is continuous there. Therefore, the only possible points of discontinuity in space for both $n_\infty(t)$ and $p_\infty(t)$ are the ones lying at the boundary of $\Omega(t)$.

Let $\bar{x} \in \partial\Omega(t)$. Let $(x_n)_n \subset \mathrm{Int}(\Omega(t))$ and $(x_n')_n \subset \mathbb{R}^d \setminus \overline{\Omega(t)}$ be sequences converging to $\bar{x}$. The continuity of Σ_∞ implies then that

$$\nu \le \lim_{n\to\infty} \left(p_\infty(x_n,t) + \nu n_\infty(x_n,t)\right) = p_\infty(\bar{x},t) + \nu n_\infty(\bar{x},t) = \lim_{n\to\infty} \big(p_\infty(x_n',t) + \nu n_\infty(x_n',t)\big) \le \nu.$$

We conclude that

$$p_\infty(\bar{x},t) + \nu n_\infty(\bar{x},t) = \nu,$$

and hence that

$$p_\infty(\bar{x},t) = 0, \qquad n_\infty(\bar{x},t) = 1,$$

which implies in particular that both $n_\infty(t)$ and $p_\infty(t)$ are continuous in space for almost every $t > 0$.

A further consequence of the spatial regularity of Σ_∞ is that the size of the jump (downwards) of ∇p_∞ at the free boundary coincides with the size of the jump (upwards) of $\nu\nabla n_\infty$ there.

Concerning the time regularity, the limit equation for the density (3.3), now tells us that $\partial_t n_\infty \in L^2(Q_T)$. Hence $n_\infty \in H^1(Q_T)$. We do not have a similar property for the pressure (think of the situation when two tumors meet).

Our last goal is to derive formally an asymptotic value for the free boundary speed in a particular example. Let $\Omega(t)$ denote, as before, the space filled by the tumor at time t. We notice that n_∞ solves

$$\partial_t n_\infty = \nu\Delta n_\infty + G(0)n_\infty, \qquad x \in \mathbb{R}^d \setminus \Omega(t),\ t > 0,$$

with boundary conditions

$$n_\infty = 1, \quad \nu\partial_n n_\infty = \partial_n p_\infty, \qquad x \in \partial\Omega(t),\ t > 0.$$

If $\Omega(t)$ were known, the problem would be overdetermined. This is precisely what fixes the dynamics of the free boundary. Let us assume that the tumor is a ball centered at the origin,

$$\Omega(t) = \{x : p_\infty(x,t) > 0\} = \{x : n_\infty(x,t) = 1\} = B_{R(t)}(0).$$

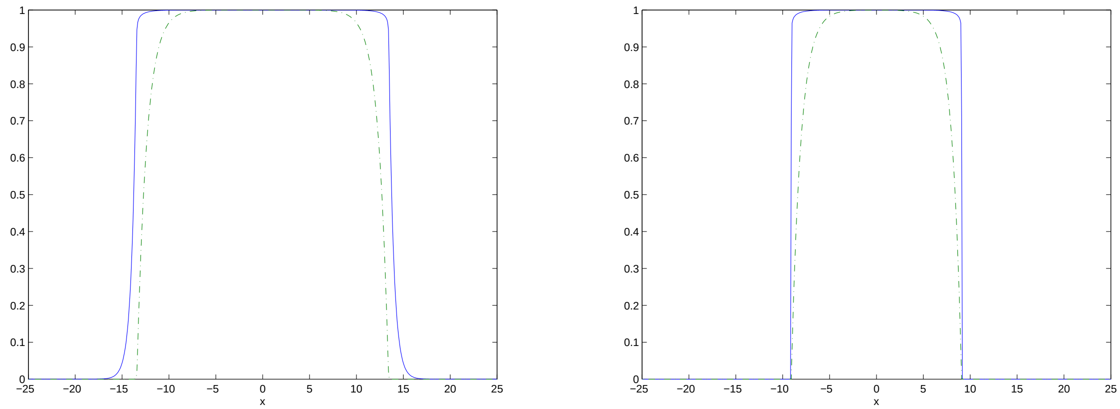

Figure 2: Shape of the traveling waves obtained thanks to a numerical discretization of the system (2.1)–(2.2) with $k = 100$ and $\nu = 0.5$ (left) or $\nu = 0$ (right) for the same initial data and the same final time. The density n is plotted in line whereas the pressure is represented in dashed line. We notice the regularity of n in the case $\nu = 0.5$, whereas it has a jump at the interface when $\nu = 0$. Also the free boundary moves faster when active motion is present.

We look for a solution which is spherically symmetric $n_\infty(r,t)$, $p_\infty(r,t)$. We set $\sigma = R'(t)$. In opposition to other models of tumor growth (see [25] for instance), here there are no radial solutions with constant speed. However, following [20] Appendix A, we expect our solution to behave for large times as a one dimensional traveling wave (with constant speed).

In order to analyze the expected asymptotic constant speed, we set $n_R(r - \sigma t) = n_\infty(r,t)$ and $p_R(r - \sigma t) = p_\infty(r,t)$. Introducing this ansatz in equation (2.10), we obtain

$$-\sigma n_R' = p_R'' + \frac{d-1}{r} p_R' + \nu n_R'' + \nu \frac{d-1}{r} n_R' + n_R G(p_R). \tag{7.1}$$

On $\mathbb{R}^d \setminus \Omega(t)$, we have $p_\infty = 0$. Then, integrating (7.1) in $(R(0), \infty)$, we get

$$\sigma n_R(R(0)) = -\nu n_R'(R(0)^+) + \nu(d-1) \int_{R(0)}^\infty \frac{n_R'}{r} dr + G(0) \int_{R(0)}^\infty n_R dr.$$

In a one dimensional setting ($d = 1$) and using the boundary relation at the interface of $\Omega(0)$, we deduce

$$\sigma = -p_R'(R(0)^-) + G(0) \int_{R(0)}^\infty n_R(r) dr. \tag{7.2}$$

We recall that for the Hele-Shaw model without active motion (i.e. $\nu = 0$), the traveling velocity is $\sigma_0 = -p_R'(R(0)^-)$. Since $n_R(R(0)) = 1$ and n_R is continuous and nonnegative, we have $\int_{R(0)}^\infty n_R(r)dr > 0$. Then we conclude from equation (7.2) that $\sigma > \sigma_0$.

We can do a more precise computation confirming the above statement for the one-dimensional case. From the complementarity relation (2.9), we have $-p_R'' = G(p_R)$ on $\Omega(0)$. Multiplying this latter equation by p_R' and integrating on $(0, R(0))$, we deduce

$$(p_R'(R(0)^-))^2 = 2 \int_0^{R(0)} p_R' G(p_R) dr.$$

In the center of the tumor, we expect a maximal packing of the cells. Therefore, we have the boundary conditions

$$\lim_{r\to 0} p_R(r) = P_M, \quad \lim_{r\to 0} p_R'(r) = 0.$$

Since $p_R'' = -G(p_R) \leq 0$, we deduce that $p_R' < 0$ and we can make the change of variable

$$(p_R'(R(0)^-))^2 = 2\int_0^{R(0)} p_R' G(p_R)\, dr = 2\int_0^{P_M} G(q)\, dq.$$

The quantity $\sigma_0 = \sqrt{2\int_0^{P_M} G(q)\, dq}$ is the traveling velocity for a tumor spheroid in the case $\nu = 0$; see Appendix A.1 of [20]. Combining this with (7.2), we deduce that the growth of the tumor is faster with active motion than in the case $\nu = 0$.

In Figure 2, we display numerical simulations obtained from a discretization with a finite volume scheme of system (2.1)–(2.2) for $k = 100$. The left picture presents the result for $\nu = 0.5$, and the right for $\nu = 0$ (i.e. without active motion). We use the growth function $G(p) = 1 - p$ and the results in both cases with the same initial data and at final time $t = 10$. We notice that in the case $\nu = 0.5$ the density function is smooth and the domain occupied by the tumor is larger than in the case without active motion, which suggests, as explained above, a faster invasion speed.

8 Generalization: regularizing effects and time compactness

As mentioned earlier, we can remove the assumption in Theorem 2.1 that the initial data are subsolutions to the stationary equation. This relies, as in [1, 11, 20] on a regularizing effect which, in turn gives an estimate on time derivatives.

Proposition 8.1 (Regularizing effects) *Under the assumptions* (2.3)–(2.4)*, and with the notations in Theorem 2.1, the weak solution* (n_k, p_k) *of* (2.1)–(2.2) *satisfies*

$$\partial_t \Sigma(n_k) \geq -\frac{K\Sigma(n_k)}{t}, \qquad \partial_t n_k \geq -\frac{K n_k}{t}\frac{\nu + \frac{k-1}{k}p_k}{\nu + (k-1)p_k}, \qquad t > 0, \tag{8.1}$$

for a sufficiently large nonnegative constant K*.*

In particular from the second inequality, in the limit $k \to \infty$ we recover that n_∞ does not decrease (in fact, it retains the value 1) when $p_\infty > 0$, and it holds in the distribution sense,

$$\partial_t n_\infty \geq -\frac{K n_\infty}{t} \mathbb{1}_{\{p_\infty = 0\}}.$$

This statement seems difficult to improve since, in the domain where $p_\infty = 0$, n_∞ satisfies the heat equation and this is the standard regularity inequality. Notice however, that, since $n_\infty(t) = 1$ in $\Omega(t) = \{\}$, this is enough to show that the pressure has the so called retention property: if is is positive at a certain point at some time, it stays positive at that point at any later time, which means that the tumor does not decrease. This in turn gives, using comparison for the elliptic equation $-\Delta p_\infty = G(p_\infty)$, that $\partial_t p_\infty \geq 0$ in the sense of distributions.

Proof of Proposition 8.1. To simplify notations, we omit the index k of all quantities in this proof. In order to avoid difficulties with the initial data in the comparison arguments that follow, we do all the computations for the approximate solution $(n_\varepsilon, p_\varepsilon)$ which corresponds to a lifted initial data $n_{k,\varepsilon}^{\text{ini}} = n_k^{\text{ini}} + \varepsilon$, $\varepsilon > 0$, and then recover the result for the original function by letting $\varepsilon \to 0$. No problem will arise with the logarithm, since $n > 0$ for all $t > 0$.

We introduce the quantity v defined by

$$v = \psi(n), \qquad \psi(n) = \nu \log n + \frac{k}{k-1} n^{k-1}.$$

Since for $n > 0$ the function ψ is invertible, we have $n = \psi^{-1}(v)$. Multiplying equation (3.3) by $\psi'(n)$, an easy computation shows that

$$\partial_t v = g(v)(\Delta v + \tilde{G}(v)) + |\nabla v|^2, \tag{8.2}$$

where $\tilde{G}(v) = G(p(\psi^{-1}(v)))$, with $p(n) = \frac{k}{k-1} n^{k-1}$, and

$$g(v) = \Sigma'(\psi^{-1}(v)) = \psi^{-1}(v)\psi'(\psi^{-1}(v)), \tag{8.3}$$

We can write equation (8.2) as

$$\partial_t v = g(v)w + |\nabla v|^2, \quad \text{with } w = \Delta v + \tilde{G}(v). \tag{8.4}$$

Since G is nonincreasing, we have $\tilde{G}' \leq 0$. Then, on the one hand, we have by multiplying (8.4) by $\tilde{G}'(v)$,

$$\begin{aligned}\partial_t(\tilde{G}(v)) &= \tilde{G}'(v)\partial_t v = \tilde{G}'(v)(g(v)w + |\nabla v|^2) \\ &\geq g(v)\tilde{G}'(v)w + 2\nabla(\tilde{G}(v)) \cdot \nabla v.\end{aligned}$$

On the other hand, we deduce from (8.4)

$$\begin{aligned}\partial_t(\Delta v) \quad &= g(v)\Delta w + 2\nabla(g(v)) \cdot \nabla w + \Delta(g(v))w + 2\nabla v \cdot \nabla(\Delta v) + 2\textstyle\sum_{i,j}(\partial_{x_i x_j} v)^2, \\ &\geq g(v)\Delta w + 2\nabla(g(v)) \cdot \nabla w + (g''(v)|\nabla v|^2 + g'(v)\Delta v)w + 2\nabla v \cdot \nabla(\Delta v) + \tfrac{2}{d}(\Delta v)^2.\end{aligned}$$

Combining the above inequalities we get

$$\partial_t w \geq g(v)\Delta w + 2\nabla(g(v) + v) \cdot \nabla w + g''(v)|\nabla v|^2 w + \big(g'(v)\Delta v + g(v)\tilde{G}'(v)\big)w + \frac{2}{d}(\Delta v)^2,$$

which can be rewritten as

$$\partial_t w \geq \mathcal{F}(w), \tag{8.5}$$

where we define the nonlinear operator

$$\begin{aligned}\mathcal{F}(w) = \quad & g(v)\Delta w + 2\nabla(g(v) + v) \cdot \nabla w + g''(v)|\nabla v|^2 w + \left(g'(v) + \frac{2}{d}\right) w^2 \\ & - \left(g'(v)\tilde{G}(v) - g(v)\tilde{G}'(v) + \frac{4}{d}\tilde{G}(v)\right) w.\end{aligned}$$

At this stage, we would like to observe that a major difference occurs with respect to [20]. For the coefficient of the linear term we get the lower bound $g'(v)\tilde{G}(v) - g(v)\tilde{G}'(v) + \frac{4}{d}\tilde{G}(v) \geq Cst > 0$, but nothing better, while in [20], the much larger lower bound $k\,Cst$ was used.

Following an idea of Crandall and Pierre [11], which generalizes the classical paper by Aronson and Bénilan [1], we use for (8.5) the subsolution $W = -h(v)/t$, where

$$h(r) = K\frac{\Sigma(\psi^{-1}(r))}{\Sigma'(\psi^{-1}(r))\psi^{-1}(r)}, \tag{8.6}$$

with K a nonnegative constant which we will chose large enough. In the particular case we have at hand, we obtain (denoting $v = \psi(n)$ as above)

$$g(v) = \nu + kn^{k-1}, \qquad g'(v) = \frac{k(k-1)n^{k-1}}{\nu + kn^{k-1}}, \qquad h(v) = K\frac{\nu + n^{k-1}}{\nu + kn^{k-1}}, \tag{8.7}$$

where we use the relation

$$(\psi^{-1})'(v) = \frac{1}{\psi'(n)} = \frac{n}{\nu + kn^{k-1}}.$$

With this definition for W, we have

$$\partial_t W = -\frac{h'(v)}{t}\partial_t v + \frac{1}{h(v)}W^2, \quad \nabla W = -\frac{h'(v)}{t}\nabla v, \quad \Delta W = -\frac{h'(v)}{t}\Delta v - \frac{h''(v)}{t}|\nabla v|^2.$$

Then, multiplying equation (8.4) by $-\frac{h'(v)}{t}$, we get

$$\partial_t W = g(v)\Delta W + \big(\frac{h''(v)}{t}g(v) - \frac{h'(v)}{t}\big)|\nabla v|^2 - \frac{h'(v)}{t}g(v)\tilde{G}(v) + \frac{1}{h(v)}W^2.$$

Using the definition of the operator $\mathcal{F}$ we obtain

$$\begin{aligned}\partial_t W = \;& \mathcal{F}(W) + \Big(\frac{1}{h(v)} - (g'(v) + \frac{2}{d})\Big)W^2 + \frac{|\nabla v|^2}{t}\big((gh)''(v) + h'(v)\big) \\ & + \big(g'(v)\tilde{G}(v) - g(v)\tilde{G}'(v) + \frac{4}{d}\tilde{G}(v)\big)W - \frac{h'(v)}{t}g(v)\tilde{G}(v).\end{aligned}$$

Recalling the expression $W = -h(v)/t$, we can rewrite this latter identity as

$$\begin{aligned}\partial_t W = \;& \mathcal{F}(W) + \Big(\frac{1}{h(v)} - \big(g'(v) + \frac{2}{d}\big)\Big)W^2 + \frac{|\nabla v|^2}{t}\big((gh)''(v) + h'(v)\big) \\ & -\frac{1}{t}\big((gh)'(v)\tilde{G}(v) - gh(v)\tilde{G}'(v) + \frac{4}{d}h(v)\tilde{G}(v)\big)\end{aligned} \tag{8.8}$$

We deduce from (8.7) after straightforward computations that

$$(gh)'(v) = K - h(v).$$

Then we have for any K,

$$(gh)''(v) + h'(v) = 0.$$

Actually, the function h defined in (8.6) has been chosen such that it satisfies this ODE. Moreover, since we have trivially from (8.7) that $h(v) \le K$ for $k \ge 1$, we deduce that $(gh)' \ge 0$. Then the term $(gh)'(v)\tilde{G}(v) - gh(v)\tilde{G}'(v) + \frac{4}{d}h(v)\tilde{G}(v)$ is positive.

Futhermore, we deduce from (8.7) that we can find K large enough independent of k such that

$$\frac{1}{h(v)} \leq g'(v) + \frac{2}{d}. \tag{8.9}$$

¿From these inequalities and the fact that $\tilde{G}' < 0$, we deduce from (8.8) that for all $t > 0$, $\partial_t W \leq \mathcal{F}(W)$. Applying the maximum principle, we finally obtain that $w \geq W$. This implies in particular, together with (8.4), that

$$\partial_t v = \psi'(n)\partial_t n \geq g(v)W = -\frac{K}{t}\frac{\Sigma(\psi^{-1}(v))}{\psi^{-1}(v)} = -\frac{K}{t}\frac{\Sigma(n)}{n}.$$

Therefore, using that $\psi'(n) = \frac{\Sigma'(n)}{n}$, see (8.3), we find

$$\partial_t(\Sigma(n)) \geq -\frac{K\Sigma(n)}{t}\frac{\Sigma'(n)}{\psi'(n)n} = -\frac{K\Sigma(n)}{t}.$$

This concludes the proof of the first inequality in (8.1). The inequality for n follows from the explicit formula for $n\Sigma'(n)/\Sigma(n)$ with $p_k = \frac{k}{k-1}n^{k-1}$.

□

The lower bound for $\partial_t n_k$ in (8.1) is enough to establish the complementarity relation (2.9), reasoning as in [20] to obtain one of the inequalities, and as in Section 5, paragraph (ii), to get the other one.

This result allows to recover time regularity for the quantities n_k and Σ_k. As it is standard, we use the identity $|\partial_t n_k| = \partial_t n_k + 2(\partial_t n_k)_-$, where we recall that $f_- = -\min\{f, 0\}$. Integrating on $\mathbb{R}^d$, we obtain then the estimate

$$\|\partial_t n_k(t)\|_{L^1(\mathbb{R}^d)} = \frac{d}{dt}\int_{\mathbb{R}^d} n_k(t) + 2\int_{\mathbb{R}^d} (\partial_t n_k(t))_- \leq \Big(G(0) + \frac{2K}{t}\Big)\int_{\mathbb{R}^d} n_k(t).$$

This gives a uniform bound in k on $\partial_t n_k$ in $L^\infty([\tau, T]; L^1(\mathbb{R}^d))$ for any $\tau,\ T > 0$. Using the same decomposition for $\partial_t \Sigma_k$, we get

$$\|\partial_t \Sigma_k(t)\|_{L^1(\mathbb{R}^d)} \leq \frac{d}{dt}\int_{\mathbb{R}^d} \Sigma_k(t) + \frac{2K}{t}\int_{\mathbb{R}^d} \Sigma_k(t).$$

Moreover, we recall that by definition we have $\Sigma_k = \nu n_k + \frac{k-1}{k} n_k p_k$. Since n_k and p_k are uniformly bounded in $L^\infty([0,T], L^1(\mathbb{R}^d)) \cap L^1(Q_T)$, we deduce that Σ_k is uniformly (in k) bounded in the same space. Then $\partial_t \Sigma_k$ is bounded uniformly in k in $L^1([\tau, T] \times \mathbb{R}^d)$ for any $\tau,\ T > 0$.

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