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ON SOME MODELS DESCRIBING CELLULAR MOVEMENT: THE MACROSCOPIC SCALE

C. MORALES-RODRIGO

Departamento de Ecuaciones Diferenciales y Análisis Numérico
Universidad de Sevilla

cristianm@us.es

Abstract

Along this work we will consider several models of partial differential equations that describe cellular movement. We will introduce some mathematical techniques in order to describe the behaviour of the solutions of these models.

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1 Introduction

One of the most important characteristics of living systems is their interaction with the environment in which they reside. Frequently, the way of interaction involves movement towards or away from an external stimulus or signal and such a response to the stimulus is called *taxis*. The process which leads to taxis is very complex but, basically, it is divided in three steps. In the first step, the cell detects the extracellular signal by specific receptors on its surface. Then the cell processes the signal and, finally, the cell alters its motile behaviour. Depending on the nature of the signal we have different kinds of taxis (see for instance [36]), for example aerotaxis, chemotaxis, galvanotaxis, haptotaxis, phototaxis, etc.

The following question arises: how this phenomenon can be described with mathematical terminology? The answer to this question is not simple but surely involves different scales, subcellular, cellular or mesoscopic and macroscopic and each of them can be described in a continuous or discrete setting. Another subsequent question are which is the relationship between different scales or

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how the individual behaviour influences the collective one. These questions, although important are not addressed here. We will just focus on a particular kind of continuous models concerning the motion of cells at the macroscopic scale.

Along this work, we will assume that the organisms respond to the spatial gradient of the stimulus. Moreover, we will suppose that the organisms also move without any preferable direction, see [35] for a justification. In some cases we will add a term which describes the process of birth and death of the organisms. To be more precise, throughout this work, the equation that describes the motion of the organisms is given by

$$u_t = \underbrace{\Delta u}_{Diffusion} \pm \underbrace{\nabla \cdot (\phi(u,v)\nabla v)}_{Taxis} + \underbrace{f(u,v)}_{Reaction} \tag{1}$$

where $f : [0,+\infty)^2 \to \mathbb{R}$, $\phi : [0,+\infty)^2 \to \mathbb{R}$ and u, v denote the concentration of organisms and the stimulus or signal density respectively.

While, in general, the taxis term leads to aggregation, the diffusive term always has a dispersive effect. Therefore, there is a competition between the taxis term and the diffusive one and three different regimes are possible:

- The diffusive dominant regime. This means that the diffusive term is dominant and the effect of the taxis can be ignored for large times. Consequently, as time goes to infinity, the solution to (1), if exists and is unique, behaves like the solution to the heat equation with the reaction term $f(u,v)$.
- The taxis dominant regime. Here, the taxis term is strong enough to generates singularities either in finite time or infinite time.
- The equilibrium or transition regime.

In the next Sections we will deal with various models related to (1) that serve to illustrate diffusive dominant, taxis dominant and the equilibrium regimes.

In the sequel, C denotes a generic positive constant.

2 Chemorepulsion

Probably one of the most famous models in mathematical biology is the Keller-Segel system. Such a model was proposed in [27] in order to describe a very particular stage in the life of many species of cellular slime molds, the aggregative stage. At this stage, the amoebas *begin to aggregate in a number of "collecting points" or centers. At each center a slug forms, migrates and eventually forms a multicellular fruiting body* ([27] p. 399). The aggregation is induced by the presence of a chemical substance produced by some of the amoebae. This particular case of taxis, induced by a chemical, is called chemotaxis. We will make some comments about the Keller-Segel system in the last Section. In this Section we assume that the cells produce a chemical and the chemical acts as a repellent. So, the cells escape from the chemical moving away from its gradient. Here, we study the following model that was proposed in [40]:

$$\begin{cases} u_t = \underbrace{\Delta u}_{Diffusion} + \underbrace{\nabla \cdot (u \nabla v)}_{Chemotaxis} & \text{in} \quad \Omega \times (0,T), \\ v_t = \underbrace{D\,\Delta v}_{Diffusion} - \underbrace{\beta v}_{Decay} + \underbrace{u}_{Production} & \text{in} \quad \Omega \times (0,T), \\ \\ \dfrac{\partial u}{\partial n} = \dfrac{\partial v}{\partial n} = 0 & \text{on} \quad \partial\Omega \times (0,T), \\ (u,v)(x,0) = (u_0,v_0)(x) & \text{in} \quad \Omega, \end{cases} \tag{2}$$

where Ω is an open bounded subset of $\mathbb{R}^N$ with smooth boundary $\partial\Omega$, n denotes the outward unit normal vector to $\partial\Omega$ and D and β are positive real numbers.

Our first step is to show that (2) admits a unique positive local in time solution. This is proved with help of the abstract theory for quasilinear parabolic problems presented in [2].

Théorème 1 *Let $p > N$ be given and consider the initial condition $(u_0, v_0) \in W^{1,p}(\Omega; \mathbb{R}^2)$ with $u_0, v_0 \geq 0$. Then (2) has a unique local in time classical solution*

$$(u,v) \in \mathcal{C}(\overline{\Omega} \times [0, T_{max}); \mathbb{R}^2) \cap \mathcal{C}^{\infty}(\overline{\Omega} \times (0, T_{max}); \mathbb{R}^2),$$

with $u(x,t), v(x,t) \geq 0$ for each $(x,t) \in \overline{\Omega} \times [0, T_{max})$; T_{max} denotes the maximal existence time. Moreover, if there exists a function $w : (0,+\infty) \mapsto (0,+\infty)$ such that, for each $T > 0$,

$$\|(u(t), v(t))\|_\infty \leq w(T), \quad 0 < t < min\{T, T_{max}\}, \tag{3}$$

then $T_{max} = +\infty$.

At this point we must wonder if the solution provided by the previous theorem is global in time or not, that is, whether $T_{max} = +\infty$ or $T_{max} < +\infty$. Notice that the physical interpretation of (2) suggests that $T_{max} = +\infty$. Therefore we should try to prove (3) and, to this aim, we use a recursive argument.

A first attempt, not the best one, can be the following: We integrate in the space variable the u-equation of (2) and we get

$$\frac{d}{dt} \int_\Omega u = 0, \tag{4}$$

which implies

$$\|u(t)\|_1 = \|u_0\|_1, \quad 0 < t < T_{max}. \tag{5}$$

A direct consequence of (5) is that, for every measurable set $E \subset \Omega$ with positive Lebesgue measure we have

$$\liminf_{t \to T_{max}^-} \left(\sup_{x \in E} u(x,t) \right) < +\infty.$$

So, the set of blow-up points for u has zero Lebesgue measure. Now, from the uniformly L^1-bound (5) coming from the u-equation we can use parabolic regularity theory in the v-equation to get uniform bounds for v:

Lemme 2 *Assume that* $0 < t_0 < T_{max}$ *and* $1 \le \gamma < N$. *Let us set* $\gamma^* = N\gamma/(N-\gamma)$. *If* $\|u(t)\|_\gamma \le C_1$ *for all* $t \in [t_0, T_{max})$ *then for each* $p \in [1, \gamma^*)$ *there exists* C_2 *depending on* N, C_1 *and* p *such that*

$$\|v(t)\|_{W^{1,p}} \le C_2, \;\; t \in [t_0, T_{max}).$$

The proof of this Lemma can be obtained from the representation by linear semigroups of the v-equation; see for instance [25, Lemma 4.1].

As we see, in this procedure we are regarding the system (2) as a set of separated equations. For example, if $N \ge 2$ we cannot obtain uniform bounds of $\|v(t)\|_{W^{1,2}}$. Moreover, the bounds for v depend strongly on the dimension N. We should use, if it is possible, the intrinsic properties of the system and deal with the full system simultaneously. The idea is to capture properly the taxis term of the u-equation from the v-equation. In a formal way, we proceed as follows.

First, if we multiply the u-equation by $\log u$ and we integrate respect to the space variable, we get:

$$\int_\Omega u_t \log u = -\int_\Omega \frac{|\nabla u|^2}{u} - \int_\Omega \nabla u \cdot \nabla v$$

and, by (4), we deduce that

$$\frac{d}{dt} \int_\Omega u \log u = -\int_\Omega \frac{|\nabla u|^2}{u} - \int_\Omega \nabla u \cdot \nabla v. \tag{6}$$

On the other hand, multiplying the v-equation by $-\Delta v$ and integrating with respect to space, we obtain:

$$\frac{d}{dt} \int_\Omega |\nabla v|^2 = -D \int_\Omega |\Delta v|^2 - \beta \int_\Omega |\nabla v|^2 + \int_\Omega \nabla u \cdot \nabla v. \tag{7}$$

Finally, by adding (6) and (7), we have that

$$\frac{d}{dt} F(u(t), v(t)) = -D(u(t), v(t)) \le 0, \tag{8}$$

where

$$F(u,v) := \int_\Omega u \log u + \frac{1}{2} \int_\Omega |\nabla v|^2,$$

$$D(u,v) := \int_\Omega \frac{|\nabla u|^2}{u} + D\int_\Omega |\Delta v|^2 + \beta \int_\Omega |\nabla v|^2.$$

Observe that it is possible to control the negative part of $s \log s$, thanks to the boundedness of the domain Ω. Therefore, there exists a constant $C > 0$ such that

$$-C \leq F(u(t), v(t)), \quad t \in [0, T_{max}). \tag{9}$$

This, together with (8), has various important consequences for the associated system (2). Frequently, when the systems under consideration stem from phenomena in physics, the functional F is called the *entropy* and the functional D is called the *entropy production*. In mathematical terminology, F a Lyapunov functional.

The first consequence that we get uniform bounds for u and v independently of the dimension. By a simple integration of (8) in the time variable, taking into account the regularity of the initial data we get that

$$-C \leq F(u(t), v(t)) \leq F(u_0, v_0) < +\infty, \quad t \in [0, T_{max}). \tag{10}$$

We also have

$$\int_0^t D(u(s), v(s))ds \leq F(u_0, v_0) + C, \quad t \in [0, T_{max}). \tag{11}$$

The second consequence is that the information provided by the Lyapunov functional F can be used to determine the long time behaviour of (2).

Let us summarize. Our goal is to show that the solution of (2) is global in time and we are trying to find bounds uniform in time in the L^∞-norm for u and v. To this aim, we have introduced the Lyapunov functional associated to (2).

At this point, since the results depend on the dimension, we distinguish between $N \leq 2$ and the higher dimensional case.

2.1 The Case $N \leq 2$

Here, it is possible to derive uniform L^p-bounds for every p. This is done by multiplying the u-equation by $(p+1)u^p$, integrating in the space variable and using the uniform bound

$$\int_0^t \int_\Omega |\Delta v|^2 < +\infty, \quad t \in [0, T_{max}),$$

as well as the Gagliardo-Nirenberg inequality. After that, we can adapt the Moser iteration method (see for instance [1]) or the De Giorgi method (see for instance [6, 8]) to get uniform L^∞ estimates for u.

We skip the details of the estimates, since we consider more interesting to show how to use the functional F in order to infer the long time behaviour of (2). In particular, we will show that u tends to the mean value

$$\overline{u} := \frac{1}{|\Omega|}\int_\Omega u = \frac{1}{|\Omega|}\int_\Omega u_0,$$

where $|\Omega|$ stands for the N-dimensional Legesgue measure of Ω. Moreover, we will also derive the rate of convergence to the mean value of u.

To be more precise, we have the following:

Théorème 3 *Assume that $N \leq 2$. If (u_0, v_0) satisfies the hypotheses of Theorem 1, then*

$$\|u(\cdot,t) - \overline{u}\|_1^2 \leq Ce^{-\alpha t},$$

where the constants C, $\alpha > 0$ can be computed explicitly.

Dèmonstration. It is convenient to use a slight modification of the Lyapunov functional F. The functional

$$G(u,v) := \int_\Omega u \log(u/\overline{u}) + \frac{1}{2}\int_\Omega |\nabla v|^2$$

also satisfies

$$\frac{d}{dt}G(u(t),v(t)) = -D(u(t),v(t)). \tag{12}$$

From the Jensen inequality with the probability measure $d\mu = dx/|\Omega|$ we readily see that $G(u,v) \geq 0$. Assume for the moment that there exists a constant $\alpha > 0$ such that

$$\alpha G(u,v) \leq D(u,v). \tag{13}$$

Then, from (12) we deduce that

$$0 \leq G(u(t),v(t)) \leq G(u_0,v_0)e^{-\alpha t}.$$

Therefore, we get that the Lyapunov functional G decays exponentially to zero. In particular, we have

$$\int_\Omega u \log(u/\overline{u}) \leq G(u_0,v_0)e^{-\alpha t}.$$

Finally, using the Cziszar-Kullback inequality (see [4])

$$\frac{1}{2\overline{u}}\|u-\overline{u}\|_1^2 \leq \int_\Omega u\log(u/\overline{u}),$$

we conclude the proof.

It only remains to prove (13). We know that, for any $r \geq 0$,

$$r\log r + r - 1 \leq (r-1)^2.$$

Let us set $r = u/\overline{u}$. By the Poincare-Wirtinger inequality and (5), we have:

$$\begin{aligned}
\int_\Omega u \log(u/\overline{u}) &= \overline{u} \int_\Omega r \log r + \overline{u} \int_\Omega (r-1) \\
&\leq \overline{u} \int_\Omega (r-1)^2 \\
&= \frac{1}{\overline{u}} \int_\Omega (u-\overline{u})^2 \\
&\leq \frac{C}{\overline{u}} \left(\int_\Omega |\nabla u| \right)^2 \\
&= \frac{4C}{\overline{u}} \left(\int_\Omega |u^{1/2} \nabla u^{1/2}| \right)^2 \\
&\leq \frac{4C}{\overline{u}} \left(\int_\Omega u \right) \left(\int_\Omega |\nabla u^{1/2}|^2 \right) \\
&= |\Omega| C \int_\Omega u^{-1} |\nabla u|^2.
\end{aligned}$$

Therefore, $\alpha G(u, v) \leq D(u, v)$ with

$$\alpha = \min \left\{ 2\beta, \frac{1}{|\Omega| C_{pw}} \right\}.$$

□

Before ending this case, let us give an additional explanation of the fact that u converges asymptotically in time towards its mean value. Observe that, for any k, the couple $(k, k/\beta)$ is a solution to

$$\left\{ \begin{array}{lll}
-\Delta u + \nabla \cdot (u \nabla v) = 0 & \text{in} & \Omega, \\
-D\Delta v + \beta v = u & \text{in} & \Omega, \\
\\
\dfrac{\partial u}{\partial n} = \dfrac{\partial v}{\partial n} = 0 & \text{on} & \partial\Omega.
\end{array} \right. \tag{14}$$

The conservation of the L^1-norm of the solution along time can be used to select the constant k:

$$k|\Omega| = \|u(t)\|_1 = \|u_0\|_1$$

for all t. Therefore, $\overline{u}$ is a solution to the setady state problem associated to (2).

2.2 The higher dimensional case

Unfortunately, for $N \geq 3$ it is not known whether the estimates provided by the Lyapunov F are enough to show the existence of global regular solutions, independently of the size of (u_0, v_0). However, the bounds given by the functional F suggest the existence of global L^1-solutions.

In this case we use the compactness method. The idea is to introduce a regularization $(2)_\epsilon$ of (2) and to pass to the limit as $\epsilon \to 0^+$ to get a solution of (2). For this purpose, we need proper bounds of the solution of $(2)_\epsilon$ independently of $\epsilon > 0$. The perturbation we will introduce is based on the *volume filling effect*, a property that was identified in [19, 20] and can be used to prevent the overcrowding of cells.

For each $\epsilon > 0$ we consider the following perturbation of (2):

$$\begin{cases} u_t^\epsilon = \Delta u^\epsilon + \nabla \cdot (u^\epsilon(1-\epsilon u^\epsilon)\nabla v^\epsilon) & \text{in } \Omega \times (0,T), \\ v_t^\epsilon = D\Delta v^\epsilon - \beta v^\epsilon + u^\epsilon & \text{in } \Omega \times (0,T), \\ \dfrac{\partial u^\epsilon}{\partial n} = \dfrac{\partial v^\epsilon}{\partial n} = 0 & \text{on } \partial\Omega \times (0,T), \\ (u^\epsilon, v^\epsilon)(x,0) = (u_0, v_0)(x) & \text{in } \Omega. \end{cases} \tag{15}$$

Observe that (2) is obtained by taking $\epsilon = 0$ in (15). Moreover, since the function $f(s) = s(1-\epsilon s)$ vanishes at 0 and at $1/\epsilon$ then, if $0 \le u_0^\epsilon, v_0^\epsilon \le 1/\epsilon$ we have

$$0 \le u^\epsilon, v^\epsilon \le 1/\epsilon.$$

The last assertion is a consequence of [2, Theorem 15.1] when we rewrite the u^ϵ-equation in terms of the new variable $z^\epsilon = 1/\epsilon - u^\epsilon$. Using the results of [2], we can also deduce, if $(u_0^\epsilon, v_0^\epsilon) \in W^{1,p}(\Omega; \mathbb{R}^2)$ and $p > N$, the existence and uniqueness of a unique regular solution to (15) for sufficiently small $\epsilon > 0$.

Next we turn to present an estimate of the solutions (u^ϵ, v^ϵ) that is uniform with respect to ϵ:

Lemme 4 *For any sufficiently small $\epsilon > 0$ and any $t \ge 0$, the solution (u^ϵ, v^ϵ) to (15) satisfies*

$$\int_\Omega \left(u^\epsilon |\log u^\epsilon| + \frac{|\nabla v^\epsilon|^2}{2} \right)(t) + \\ + \int_0^t \int_\Omega \left(\frac{|\nabla u^\epsilon|^2}{u^\epsilon} + D|\Delta v^\epsilon|^2 + \beta |\nabla v^\epsilon|^2 \right) \le C_0,$$

where C_0 depends only on Ω and $F(u_0, v_0)$.

We skip the proof of this lemma and we present without proof the results for $N = 3$ and $N = 4$ that can be inferred:

Théorème 5 *Let $N = 3$. If u_0 and v_0 are non-negative functions in $W^{1,p_0}(\Omega)$ for some $p_0 > 3$, then there exists a global weak solution (u, v) to (2) which also satisfies*

$$(u, v) \in L^{5/4}(0, T; W^{1,5/4}(\Omega; \mathbb{R}^2))$$

for any $T > 0$. Moreover, we have

$$\lim_{t \to +\infty} \int_\Omega (u(x,t) - \overline{u}) \; \phi(x) \; dx = 0 \quad \forall \phi \in L^\infty(\Omega) \tag{16}$$

and

$$\lim_{t \to +\infty} \|v(\cdot, t) - \overline{v}\|_2 = 0, \tag{17}$$

where $\overline{v}$ denotes the mean value of v.

Théorème 6 *Let $N = 4$. If u_0 and v_0 are non-negative functions in $W^{1,p_0}(\Omega)$ for some $p_0 > 4$, then there exists a global weak solution (u, v) to (2). Moreover we also have (16) and (17).*

Let us point out that the previous existence results do not seem to extend to space dimensions $N \geq 5$ since, for these N, we cannot ensure that $u\nabla v \in L^1(\Omega \times (0,T); \mathbb{R}^N)$ for all $T > 0$. In fact, if $N = 4$ we have $u\nabla v \in L^1(\Omega \times (0,T); \mathbb{R}^N)$ and no more than this and we have to apply the Dunford-Pettis Theorem (see [3]) as well as the Vitali convergence Theorem (see [14]) in the compactness method.

The proofs that have been omitted here can be found in [7].

3 Invasion

In the previous Section, the signal or stimulus diffuses in the environment. However there are cases in which the stimulus is strictly localized; for example, this explains the behavior of the ants, which follow trails left by predecessors, myxobacteria (see [36]); this is also the situation in cell invasion phenomena. The cell invasion into the surrounded extracellular matrix is a process that is present in various biological phenomena like wound healing, tumor invasion or morphogenesis.

Along this Section, we will deal with a model related to tumor invasion that covers the models proposed in [5, 37]. It is assumed that the tumoral cells produce proteolytic enzymes which degrade the extracellular matrix. Then, the tumoral cells move towards the gradient of the matrix. Such a movement is called *haptotaxis*. The model has three main variables, u (the concentration of cancer cells), v (the extracellular matrix distribution) and m (the concentration of proteolytic enzymes) and is the following:

$$\begin{cases} u_t = \underbrace{\rho\Delta u}_{Diffusion} - \underbrace{\nabla \cdot (u\chi(v)\nabla v)}_{Haptotaxis} + \underbrace{\mu u(1-u-v)}_{Proliferation} & \text{in } \Omega \times (0,T), \\ v_t = -\underbrace{\gamma m v}_{Degradation} & \text{in } \Omega \times (0,T), \\ m_t = \underbrace{\Delta m}_{Diffusion} - \underbrace{\beta m}_{Decay} + \underbrace{\alpha u g(v)}_{Production} & \text{in } \Omega \times (0,T), \\ \rho\dfrac{\partial u}{\partial n} - u\chi(v)\dfrac{\partial v}{\partial n} = \dfrac{\partial m}{\partial n} = 0 & \text{on } \partial\Omega \times (0,T), \\ (u,v,m)(x,0) = (u_0, v_0, m_0)(x) & \text{in } \Omega. \end{cases} \tag{18}$$

Here, $\Omega \subset \mathbb{R}^N$ is again a bounded regular domain, $g, \chi \in \mathcal{C}^2([0,+\infty))$ with $g(s), \chi(s) \geq 0$ for all $s \geq 0$, $\mu \geq 0$ and $\alpha, \beta, \gamma, \rho$ are positive constants.

In order to elucidate the behaviour of (18), let us simplify the equations. Later on, we will deal with the full system. Dividing the m-equation by β we get:

$$\beta^{-1} m_t = \beta^{-1}\Delta m - m + \frac{\alpha}{\beta} u g(v).$$

Next, we observe that if the production and decay rates of the proteolytic enzymes, denoted by α and β respectively, are much greater than the motility, that is $\alpha \gg 1, \beta \gg 1$, then, heuristically, we can claim that

$$m \simeq \frac{\alpha}{\beta} u g(v).$$

Now, let us replace m by this function in the v-equation. Assuming that the proliferation term in (18) is of the form $\mu u(1-u)$, we get:

$$\begin{cases} u_t = \nabla \cdot (\rho \nabla u - u\chi(v)\nabla v) + \mu u(1-u) & \text{in } \Omega \times (0,T), \\ v_t = -\dfrac{\gamma\alpha}{\beta} v u g(v) & \text{in } \Omega \times (0,T), \\ \dfrac{\partial u}{\partial n} - u\chi(v)\dfrac{\partial v}{\partial n} = 0 & \text{on } \partial\Omega \times (0,T), \\ (u,v)(x,0) = (u_0, v_0)(x) & \text{in } \Omega. \end{cases} \tag{19}$$

Let us now suppose that $\rho = \frac{\gamma\alpha}{\beta} = 1$ (because the values of the constants play no role in the proofs). Moreover, for simplicity, let us also assume that $\chi(v) = 1$ and $g(v) = v^{\beta-1}$ for some $\beta \geq 1$. Then we have from (19):

$$\begin{cases} u_t = \nabla \cdot (\nabla u - u\nabla v) + \mu u(1-u) & \text{in } \Omega \times (0,T), \\ v_t = -uv^{\beta} & \text{in } \Omega \times (0,T), \\ \dfrac{\partial u}{\partial n} - u\dfrac{\partial v}{\partial n} = 0 & \text{on } \partial\Omega \times (0,T), \\ (u,v)(x,0) = (u_0, v_0)(x) & \text{in } \Omega. \end{cases} \tag{20}$$

The lack of an operator acting in the space variables has two important consequences in the v-equation. The first one is that there is not space regularization for v and this makes appear in some sense a hyperbolic structure. This can be seen by solving the v-equation. For instance, if $\beta = 1$,

$$v(x,t) = v_0(x) e^{-\int_0^t u(x,s)ds}$$

and, if $v_0(\cdot) \in L^1(\Omega)$, we have $v(\cdot,t) \in L^1(\Omega)$ and not more than this for all $t > 0$. The second consequence is that the speed of propagation in the v-equation is zero. This means that, if $v_0(x_0) = 0$ for some $x_0 \in \Omega$, then $v(x_0,t) = 0$ for all $t > 0$.

Next, we follow the same steps in the previous Section in order to analyze (20). The next result provides global existence and uniqueness for (20) in 2-dimensional domains:

Théorème 7 *Assume that $0 < l < 1$ and $\Omega \subset \mathbb{R}^2$ is a bounded domain with $\mathcal{C}^{2+l}$ boundary $\partial\Omega$. If $(u_0, w_0) \in \mathcal{C}^{2+l}(\overline{\Omega}; \mathbb{R}^2)$, $u_0 \geq 0$, $v_0 > 0$, $u_0 \not\equiv 0$ and the compatibility condition*

$$\frac{\partial u_0}{\partial n} = u_0 \frac{\partial v_0}{\partial n} \quad \text{on } \partial\Omega$$

is satisfied, then (20) has a unique global positive solution defined on $[0,+\infty)$ and $(u,v) \in \mathcal{C}^{2+l,1+l/2}(\overline{\Omega \times [0,T]}; \mathbb{R}^2)$, for all $T > 0$.

The proof can be carried out as follows. First, we establish local existence of a solution; this is done in a similar way as in [38, 39]. The main difficulty to overcome with respect to these papers is that we use different boundary conditions. Then, in order to obtain global existence, suitable estimates of the solutions are obtained. However, in contrast with the previous Section, the lack of spatial regularization effect for v demands tedious estimates. As in the previous Section, a Lyapunov function

$$F(u,w) = \int_\Omega u(\log u - 1) + \frac{1}{2}\int_\Omega v^{-\beta}|\nabla v|^2$$

associated to (20) plays an important role. For $\mu = 0$, that is, without proliferation, such a Lyapunov function was first introduced in [9], although some ideas had already been given in [39].

Now, we will focus on the long time behavior of the solutions to (20). As we have seen in the previous Section, the solutions to the stationary problem associated to (20) are candidate to be the limit of the solutions as time goes to infinity.

Théorème 8 *The positive solutions (u,v) to the stationary problem associated to (20) with $v \in W^{1,\infty}(\Omega)$ are given by*

$$\begin{aligned} (u^*,v^*) &= (0,\widetilde{v}), & \widetilde{v} &\in \mathcal{P}_2, \\ (u^*,v^*) &= (1,0), & &\text{if } \mu > 0, \\ (u^*,v^*) &= (k,0), & &\text{if } \mu = 0, \end{aligned}$$

where $k > 0$ and $\mathcal{P}_2 = \{z \in W^{1,\infty}(\Omega) : \; z \geq 0, \; z \not\equiv 0\}$.

Let us stress that $uv = 0$ does not imply that either $u \equiv 0$ or $v \equiv 0$. Notice that functions with disjoints supports satisfy $uv = 0$.

The basic idea in the proof of this result is to rewrite the system for the new variable $z = ue^{-v}$ and then to apply the strong maximum principle and the Hopf Lemma (see for instance [17, Lemma 3.4,Theorem 3.5]) to deduce that either $z \equiv 0$ or $z(x) > 0$ for all $x \in \overline{\Omega}$.

By the results of the previous Section we can expect that the solutions $(1,0)$ or $(k,0)$ are globally asymptotically stable and the solutions $(0,\widetilde{v})$ are unstable. In fact, it is just this what happens. However, the rate of convergence is known to be exponential only when $\beta = 1$. Thus, we distinguish the cases $\beta = 1$ and $\beta > 1$.

The case $\beta = 1$ **-** We prove the following:

Théorème 9 *Under the hypotheses of Theorem 7 we have:*

$$\|u(\cdot,t) - u_\mu\|_2 \leq Ce^{-\theta t}, \qquad \|v(\cdot,t)\|_\infty \leq Ce^{-\theta' t}, \tag{21}$$

where θ, θ' are positive constants and

$$u_\mu := \begin{cases} \dfrac{1}{|\Omega|}\displaystyle\int_\Omega u_0 & \text{if } \mu = 0, \\ 1 & \text{if } \mu > 0. \end{cases} \tag{22}$$

Dèmonstration. Again, the proof relies on the properties of a Lyapunov function F. In this case, we have

$$\frac{d}{dt}F(u,v) = -D(u,v),$$

where

$$F(u,v) = \int_\Omega u(\log u - 1) + 1 + \frac{1}{2}\int_\Omega v^{-1}|\nabla v|^2\,,$$

$$D(u,v) = \int_\Omega \frac{|\nabla u|^2}{u} + \frac{1}{2}\int_\Omega \left(uv^{-1}|\nabla v|^2 + \mu u(u-1)\log u\right).$$

The first step is to prove the exponential decay of F. For this purpose, it is enough to prove that $D(u,v) \geq \alpha F(u,v)$ for some $\alpha > 0$ and, to get this inequality, it is convenient to establish that u is separated from zero:

Lemme 10 *Under the hypotheses of Theorem 7, if* $\min_{x\in\overline{\Omega}} u_0(x) \geq \rho_0 > 0$ *for some* $\rho_0 > 0$ *then* $\min_{x\in\overline{\Omega}} u(x,t) \geq \rho$ *for some* $\rho > 0$.

We skip the proof. Let us point out that, if $\min_{x\in\overline{\Omega}} u_0(x) = 0$ but $u_0 \not\equiv 0$ then, by the strong maximum principle, for $\tau > 0$ we have $\min_{x\in\overline{\Omega}} u(x,\tau) > 0$. Consequently, in this case we can repeat our arguments taking as new initial time $\tau > 0$.

By the previous lemma and the inequality $\log s \leq s - 1$, we obtain

$$\begin{aligned} D(u,v) &\geq \frac{\rho}{2}\int_\Omega v^{-1}|\nabla v|^2 + \mu\rho(u-1)\log u \\ &\geq \frac{\rho}{2}\int_\Omega v^{-1}|\nabla v|^2 + \mu\rho(u(\log u - 1) + 1) \geq \gamma F(u(t),v(t)), \end{aligned}$$

where $\gamma = \min\{\rho, \mu\rho\}$. Therefore, $F(u(t),v(t)) \leq F(u_0,v_0)e^{-\gamma t}$ and, in particular, we have

$$\int_\Omega C_v^{-1}|\nabla v|^2 \leq \int_\Omega \frac{|\nabla v|^2}{v} \leq F(u_0,v_0)e^{-\gamma t} \tag{23}$$

where $C_v > 0$ is any positive constant such that $v \leq v_0 \leq C_v$. Next, we multiply the u-equation by $u - u_\mu$ and we integrate in the space variable. From the uniform bounds in time of $u(\cdot,t)$ in the L^∞-norm, (23) and the Poincare-Wirtinger inequality, we get:

$$\begin{aligned} \frac{d}{dt}\int_\Omega (u-u_\mu)^2 &= -2\int_\Omega |\nabla u|^2 + 2\int_\Omega u\nabla u\cdot\nabla v - 2\mu\int_\Omega u(u-u_\mu)^2 \\ &\leq (\epsilon C - 2)\int_\Omega |\nabla u|^2 + C(\epsilon)\int_\Omega |\nabla v|^2 - 2\mu\rho\int_\Omega (u-u_\mu)^2 \qquad (24) \\ &\leq C(\epsilon)C_v F(u_0,v_0)e^{-\gamma t} - C(\mu)\int_\Omega (u-u_\mu)^2, \end{aligned}$$

where

$$C(\mu) = \begin{cases} 2\mu\rho & \text{if } \mu > 0, \\ \frac{2-C\epsilon}{C_{pw}} & \text{if } \mu = 0. \end{cases}$$

From (24), we easily get the result. □

The case $\beta > 1$ **-** We now have:

Théorème 11 *Under the hypotheses of Theorem 7, if t is sufficiently large, then*

$$\|u(\cdot,t) - u_\mu\|_2 \leq C(\|v_0\|_\infty^{1-\beta}\rho(\beta-1)t)^{\frac{1}{2(1-\beta)}} \tag{25}$$

$$\|v(\cdot,t)\|_\infty \leq (\|v_0\|_\infty^{1-\beta} + \rho(\beta-1)t)^{\frac{1}{1-\beta}}. \tag{26}$$

Dèmonstration. On one hand, we know that

$$\int_0^t \int_\Omega uv^{-1}|\nabla v|^2 \leq C. \tag{27}$$

On the other hand, solving the v-equation we have that

$$v(x,t) = \left(v_0(x)^{1-\beta} + (\beta-1)\int_0^t u(x,s)ds\right)^{\frac{1}{1-\beta}}.$$

This equality, together with Lemma 10, implies (26). As a consequence

$$u(x,t)v(x,t)^{-1} \geq \rho(\|v_0\|_\infty^{1-\beta} + \rho(\beta-1)t)^{\frac{1}{\beta-1}}.$$

Now, putting the above estimate in (27), we obtain

$$\int_0^t \rho(\|v_0\|_\infty^{1-\beta} + \rho(\beta-1)s)^{\frac{1}{\beta-1}} \int_\Omega |\nabla v|^2 \leq C. \tag{28}$$

Taking into account this decay property of the gradient, we can use an argument similar to the one used in the case $\beta = 1$ to conclude the proof. □

Now, we study the full system (18). This has an advantage with respect to (20) because the m-equation induces regularity in the component v. Accordingly, in this case we can also deal with 3-dimensional domains. We will assume in fact that $N = 3$ in the rest of the Section.

Let us introduce some spaces. Let $p \in (1,\infty)$ and let us define the operator

$$A_p u := -\Delta u + \beta u$$

with domain

$$D(A_p) := \left\{u \in W^{2,p}(\Omega) : \ \frac{\partial u}{\partial n} = 0 \text{ on } \partial\Omega\right\}.$$

Since $Re\ \sigma(A_p) \geq \beta > 0$, where $\sigma(A_p)$ stands for the spectrum of A_p, we can also introduce the fractional powers A_p^ν for all $\nu > 0$ (see [18, Chapter 1, Section 4]) . Let us set

$$X_p^\nu := D(A_p^\nu).$$

In the next result, the local existence and the continuous dependence of the solution respect to the initial data are analyzed:

Théorème 12 *Let* $\nu \in \left(\frac{1}{2} + \frac{3}{2p}, 1\right)$ *and* $p \in (3, 6)$. *Suppose that the initial data satisfies*

$$\mathbf{x_0} := (u_0, v_0, m_0) \in H^1(\Omega) \times W^{1,\infty}(\Omega) \times X_p^\nu := \mathbf{Y}.$$

Then there exists $\tau(\|\mathbf{x_0}\|_{\mathbf{Y}})$ *such that the problem (18) has a unique solution*

$$\begin{array}{ll} u & \in \mathcal{C}\left([0,\tau]; H^1(\Omega)\right) \cap \mathcal{C}^1\left((0,\tau); W^{1,\infty}(\Omega)\right), \\ v & \in \mathcal{C}\left([0,\tau]; W^{1,\infty}(\Omega)\right) \cap \mathcal{C}^1\left((0,\tau); W^{1,\infty}(\Omega)\right), \\ m & \in \mathcal{C}\left([0,\tau]; X_p^\nu\right) \cap \mathcal{C}^1\left((0,\tau); X_p^\nu\right) \cap \mathcal{C}\left((0,\tau); W^{2,p}(\Omega)\right). \end{array} \tag{29}$$

Moreover, the solution depends continuously on the initial data. Finally, if $u_0(x), v_0(x), m_0(x) \geq 0$ *then* $u(x,t), v(x,t), m(x,t) \geq 0$ *for all* $(x,t) \in \Omega \times (0,\tau]$.

In order to show that $T_{max} = +\infty$, where T_{max} denotes the maximal interval of existence, we have just to check that, for all $T > 0$ such that the solution exists in $[0,T)$, one has $(u,v,m) \in X_T \times Y_T \times Z_T$ and

$$\|(u,v,m)\|_{X_T \times Y_T \times Z_T} \leq C(T) < +\infty, \tag{30}$$

where

$$\begin{array}{ll} X_T & := L^\infty\left(0,T; H^1(\Omega)\right), \\ Y_T & := L^\infty\left(0,T; W^{1,\infty}(\Omega)\right), \\ Z_T & := L^\infty\left(0,T; X_p^\nu\right). \end{array}$$

At this time, let us explain why the estimate (30) is enough to obtain global existence and also uniqueness. The argument is as follows.

First, we apply Theorem 12. This gives us a solution up to a time $t_1 > 0$; then, we can apply again the Theorem 12 with initial data

$$(u_0, v_0, m_0) = (u(\cdot, t_1), v(\cdot, t_1), m(\cdot, t_1)).$$

Therefore, recursively we have an increasing sequence of times t_k, $k \in \mathbb{N}$ and, thanks to (30) it can be assumed that $t_k \to +\infty$. This argument leads to the existence of solution in $[0,T]$ for all $T > 0$.

It should be stressed that, a priori, we do not have uniqueness of solution on $[0,T]$ for any given $T > 0$ because Theorem 12 assures uniqueness just for T small. However, this difficulty can be solved as follows.

Let $\mathbf{u_1}, \mathbf{u_2}$ two solutions of (18). We define the set $\mathcal{A}$ by

$$\mathcal{A} := \{t \in [0,T] : \ \mathbf{u_1}(\cdot,t) \neq \mathbf{u_2}(\cdot,t) \text{ in } \mathbf{Y}\}.$$

Assume that $\mathcal{A} \neq \varnothing$; then there exists $t^* = \inf A$ and $t^* > 0$, by Theorem 12. Hence, $t^* - \epsilon \notin A$, for all $\epsilon > 0$. Now, applying Theorem 12 at time $t^* - \epsilon$ and taking into account that the maximal existence and uniqueness time is bounded from below, we obtain that $\mathbf{u_1}(\cdot, t) = \mathbf{u_2}(\cdot, t)$ for all $t \in [0, t^*+k]$ for some $k > 0$, contradicting the Definition of t^*. Therefore, $A = \varnothing$ and the uniqueness result follows.

We skip the proof of (30), that it is based on the Gagliardo-Nirenberg inequality (see for instance [18, Chapter 1, Section 6]) and a parabolic regularity result (Lemma 2).

Our next step is to study the long time behavior of the solutions. In this part of the Section, we will focus on the cases $g(s) = 1$ and $g(s) = s$, that correspond to the models proposed in [5] and [37] respectively. Clearly, the simplified system suggests the result. Unfortunately, we cannot argue as previously for the long time behaviour due to the lack of a Lyapunov function for (18). However, if we examine carefully the proof of Theorem 9 we notice that two estimates were crucial in the proof. The first one is the separation from zero of u and the second one is the exponential decay of the gradient of v to zero.

Lemme 13 *Under the hypotheses of Theorem 12, if* $\min_{x\in\overline{\Omega}} u_0(x) \geq \rho_0 > 0$ *for some* $\rho_0 > 0$, $\|v_0\|_\infty < 1$ *and* $\mu > 0$, *then* $\min_{x\in\overline{\Omega}} u(x,t) \geq \rho$ *for some* $\rho > 0$.

Lemme 14 *Let* $\tau > 0$, $v_0 > 0$. *Assume that*

$$m(x,t) \geq \delta > 0, \;\; \forall t \geq \tau. \tag{31}$$

Then, for all $t \geq \tau$, *we have*

$$\int_\Omega |\nabla v(t)|^2 \leq Ce^{-kt}, \tag{32}$$

for all $0 < k < \delta$.

Observe that, when $g(v) = 1$, Lemma 13 implies (31). Therefore, for $g(v) = 1$ we can repeat the arguments in the proof of Theorem 9 and obtain the following:

Théorème 15 *Assume that* $g(v) = 1$. *Under the hypotheses of Theorem 12, if* $\|v_0\|_\infty < 1$ *and* $\mu > 0$, *we have:*

$$\|u(\cdot,t) - u_\mu\|_2^2 \leq Ce^{-\theta t}, \;\; \|v(\cdot,t)\|_\infty \leq Ce^{-\delta t}, \;\; \left\| m(\cdot,t) - \frac{\alpha u_\mu}{\beta} \right\|_2^2 \leq Ce^{-\varrho t} \tag{33}$$

where $\theta, \delta, \varrho > 0$ *and* u_μ *is as in Theorem 9.*

In the case $g(v) = v$ we cannot ensure (32). In fact, we will see that it does not hold in general. It is also unclear how to get a decay of the gradient of v in the spirit of (28). In this case, we use a different argument that is similar to the one used in [15].

Thus, let us introduce

$$y(t) = \|u(\cdot,t) - u_\mu\|_2 \,.$$

We try to prove that $\lim_{t\to+\infty} y(t) = 0$. Notice that the inequality

$$\int_0^\infty y(s)\,ds < C \tag{34}$$

is not sufficient to claim that $y(t)$ goes to zero as time goes to infinity. We need an additional condition to control the oscillatory behavior of $y(t)$. For example, the condition

$$\lim_{t\to+\infty} \int_t^{t+1} |y_t(s)|\,ds = 0. \tag{35}$$

The last theorem of this Section is the following:

Théorème 16 *Let $g(v) = v$. Under the hypotheses of Theorem 12, we have:*

$$\lim_{t\to+\infty} \|u(\cdot,t) - u_\mu\|_2 = 0, \quad \lim_{t\to+\infty} \|v(\cdot,t)\|_\infty = 0, \quad \lim_{t\to+\infty} \|m(\cdot,t)\|_2 = 0. \tag{36}$$

For the proof, we first check that (34) and (35) holds. We omit the details, that can be found in [29].

Before the end of the Section, let us point out that the results of this Section can be found in the papers [28, 29]. See also [43, 44], where the authors prove the existence of a global in time solution for other models of invasion.

4 Angiogenesis

Angiogenesis is a physiological process involving the new vessels sprout from a pre-existing vasculature in response to chemical stimuli. Angiogenesis is a normal process in growth, development and wound healing. However, angiogenesis is also induced by tumoral cells. As a response to oxygen deprivation, tumoral cells secrete tumor angiogenic factors (TAF). These factors diffuse until they reach the endothelial cells that form the blood vessel wall. Then the factors attach to the endothelial cells and provoke, after a signalling cascade, the chemotactic migration of the endothelial cells towards the tumor. After that, the cells join together to form new capillaries. The interested reader can found more details about tumor-induced angiogenesis in [32] and the references therein.

The model that we will consider in this Section has two variables, namely u (the concentration of endothelial cells) and v (the concentration of TAF). Both populations live in a bounded domain $\Omega \subset \mathbb{R}^N$, $N \geq 1$, with regular boundary. Moreover,

$$\partial\Omega = \Gamma_0 \cup \Gamma_1,$$

where Γ_0 and Γ_1 are open and closed sets in the relative topology of $\partial\Omega$. We assume that Γ_0 is the tumor boundary and Γ_1 the blood vessel boundary, see Figure 1 for an example.

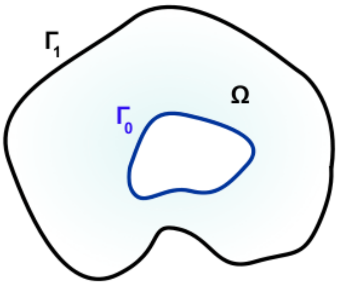

Figure 1 – Example of domain Ω.

We impose a homogeneous Neumann boundary condition for u on $\partial\Omega$ as well as for v on Γ_1. We also assume that there is a flux of TAF entering in the domain Ω through Γ_0 in a nonlinear way. This is the main difference here with respect to [12], where this term is linear. To fix ideas, we will assume that

$$\frac{\partial v}{\partial n} = \mu \frac{v}{1+v} \text{ on } \Gamma_0 \times (0,T)\,,$$

where $\mu \geq 0$ is a constant that measures the amount of TAF produced on the boundary of the tumor. Therefore, we consider the following parabolic problem

$$\begin{cases} u_t - \Delta u = -\mathrm{div}(V(u)\nabla v) + \lambda u - u^2 & \text{in } \Omega \times (0,T), \\ v_t - \Delta v = -v - cuv & \text{in } \Omega \times (0,T), \\ \dfrac{\partial u}{\partial n} = \dfrac{\partial v}{\partial n} = 0 & \text{on } \Gamma_1 \times (0,T), \\ \dfrac{\partial u}{\partial n} = 0, \quad \dfrac{\partial v}{\partial n} = \mu \dfrac{v}{1+v} & \text{on } \Gamma_0 \times (0,T), \\ u(x,0) = u_0(x), \quad v(x,0) = v_0(x) & \text{in } \Omega, \end{cases} \tag{37}$$

where $0 < T \leq +\infty$, $\lambda, \mu \geq 0$, $c > 0$ and the function

$$V \in \mathcal{C}^1(\mathbb{R}), \quad V > 0 \text{ in } (0,\infty) \text{ with } V(0) = 0; \tag{38}$$

and u_0 and v_0 are non-negative and non-trivial given functions.

Let us give a short explanation of the model. Endothelial cells diffuses, moves towards the gradient of TAF and reproduces following a logistic law. Here, V is the chemotactic response of the endothelial cells to the chemoatractant v. In this case the response depends on a nonlinear way on the density u. The TAF diffuses and either attach to the endothelial cells $-cuv$ or it is consumed $-v$.

As in the previous Sections, we will first present a local existence theorem whose proof relies on the abstract theory of semilinear parabolic problems.

Théorème 17 *Let us assume that* $p > N$*, (38) is satisfied and* $(u_0, v_0) \in (W^{1,p}(\Omega))^2$*, with* $u_0 \geq 0$*,* $v_0 \geq 0$ *a.e. in* Ω*. Then, (37) has a unique non-negative local in time classical solution*

$$(u, v) \in (\mathcal{C}([0, T_{max}); W^{1,p}(\Omega)) \cap \mathcal{C}^{2,1}(\overline{\Omega} \times (0, T_{max})))^2,$$

where T_{max} *denotes the maximal existence time. Moreover, if there exists a function* $w : (0, +\infty) \mapsto (0, +\infty)$ *such that, for each* $T > 0$*,*

$$\|(u(t), v(t))\|_\infty \leq w(T), \qquad 0 < t < \min\{T, T_{max}\}, \tag{39}$$

then $T_{max} = +\infty$*.*

For the global existence of a solution, we have to impose an additional assumption on V, for instance that V is bounded. In that case, we can prove the estimate (39) by a recursive procedure. The most technical part needs a regularity lemma like the one in the first Section (Lemma 2) for the v-equation:

Lemme 18 *Assume that* $0 < t_0 < T_{max}$ *and* $\gamma \in (1, \infty)$*. Let us set* $\gamma^* = N\gamma/(N-1)$*. If* $\|u(t)\|_\gamma \leq C_1$ *for all* $t \in [t_0, T_{max})$ *then for each* $p \in [1, \gamma^*)$ *there exists a constant* C_2*, depending on* N*,* C_1 *and* p*, such that*

$$\|v(t)\|_{W^{1,p}} \leq C_2, \quad t \in [t_0, T_{max}).$$

Next, we deal with the steady-state problem associated to (37). In previous Sections all the steady-states with positive components we have found were homogeneous in the space variable. Here, the nonlinearity on the boundary induces the presence of steady-states where none of the components satisfies this property.

The steady states of (37) can be classified as follows:

- The trivial solution.
- Semi-trivial solutions i.e. couples (u, v) such that $u \equiv 0$ or $v \equiv 0$ but $(u, v) \not\equiv (0, 0)$.
- Solutions (u, v) such that $u \not\equiv 0$ and $v \not\equiv 0$, which are called *coexistence states.*

It is clear that the trivial solution exists for all $\lambda, \mu \geq 0$.

If the v-component of the steady-state is zero, then a semi-trivial positive solution exists if, and only if, $\lambda > 0$. In that case, it must be of the form $(\lambda, 0)$.

If the u-component is zero, then we must solve the nonlinear problem

$$\begin{cases} -\Delta v + v = 0 & \text{in } \Omega, \\ \dfrac{\partial v}{\partial n} = 0 & \text{on } \Gamma_1, \\ \dfrac{\partial v}{\partial n} = \mu \dfrac{v}{1+v} & \text{on } \Gamma_0. \end{cases} \tag{40}$$

This equation was analyzed in [42] when $\Gamma_1 = \emptyset$.

Lemme 19 *There exists a positive solution of (40) if, and only if,*

$$\mu > \mu_1 > 0,$$

where μ_1 is the principal eigenvalue of the linearization at zero of (40) i.e. the principal eigenvalue of

$$\begin{cases} -\Delta\psi + \psi = 0 & \textit{in } \Omega, \\ \dfrac{\partial\psi}{\partial n} = 0 & \textit{on } \Gamma_1, \\ \dfrac{\partial\psi}{\partial n} = \mu\psi & \textit{on } \Gamma_0. \end{cases}$$

Moreover, in such case, the positive solution is unique and will be denoted by θ_μ.

Hence, the couples $(0, \theta_\mu)$ for $\mu > \mu_1$ are the unique semi-trivial solutions for which the u-component is zero.

In the analysis of the existence of coexistence states of (37), we find two curves $\mu = F(\lambda)$ and $\lambda = \Lambda(\mu)$ that are crucial. Here, $F(\lambda)$ is the principal eigenvalue of the linearization of the stationary v-equation at $(\lambda, 0)$ i.e. the principal eigenvalue of

$$\begin{cases} -\Delta\psi + (1 + c\lambda)\psi = 0 & \text{in } \Omega, \\ \dfrac{\partial\psi}{\partial n} = 0 & \text{on } \Gamma_1, \\ \dfrac{\partial\psi}{\partial n} = \mu\psi & \text{on } \Gamma_0. \end{cases}$$

For each $\mu > \mu_1$, $\Lambda(\mu)$ is the principal eigenvalue of the linearization of the stationary u-equation at $(0, \theta_\mu)$ i.e. the principal eigenvalue of

$$\begin{cases} -\Delta\varphi + \operatorname{div}(V'(0)\theta_\mu\varphi) = \lambda\varphi & \text{in } \Omega, \\ \dfrac{\partial\varphi}{\partial n} = 0 & \text{on } \Gamma_0 \cup \Gamma_1, \end{cases}$$

and $\Lambda(\mu) = 0$ for $\mu \in [0, \mu_1)$.

The next theorem entails the existence of coexistence states for some range of the parameters λ, μ.

Théorème 20

1. *Assume that $V'(0) = 0$. Then, if*

$$\lambda > 0 \quad \textit{and} \quad \mu > F(\lambda), \tag{41}$$

   there exists at least one coexistence state.

2. *Assume that $V'(0) > 0$. Then, if*

$$(\lambda - \Lambda(\mu))(\mu - F(\lambda)) > 0. \tag{42}$$

   the same holds.

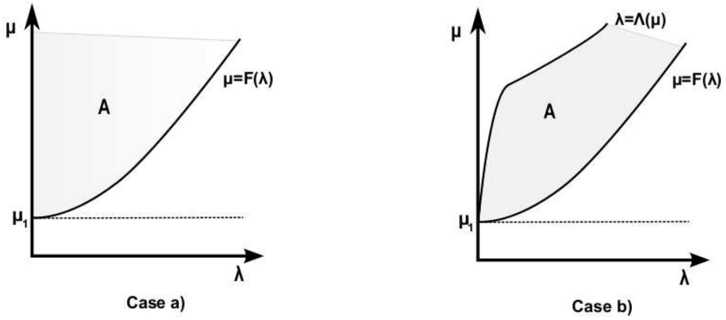

Figure 2 – Coexistence regions. Case a) $V'(0) = 0$ and Case b) $V'(0) > 0$.

In Figure 2 we have drawn the coexistence regions, denoted by A in both cases, $V'(0) = 0$ and $V'(0) > 0$.

The proof the previous theorem is based on well-known techniques in bifurcation theory. The main idea is to apply the Crandall-Rabinowitz Theorem [10] with λ as varying parameter to deduce that $(\lambda, u, v) = (\Lambda(\mu), 0, \theta_\mu)$ is a bifurcation point for the semi-trivial solution $(0, \theta_\mu)$. Then, we apply Theorem 4.1 of [31] and we get a continuum $\mathcal{C}^+$ of positive solutions emanating from the point $(\lambda, u, v) = (\Lambda(\mu), 0, \theta_\mu)$, such that $(\lambda_\infty, 0, 0) \in cl(\mathcal{C}^+)$, where λ_∞ satisfies $\mu = F(\lambda_\infty)$.

See Figure 3, where we have drawn the bifurcation diagrams in the cases $V'(0) = 0$ and $V'(0) > 0$.

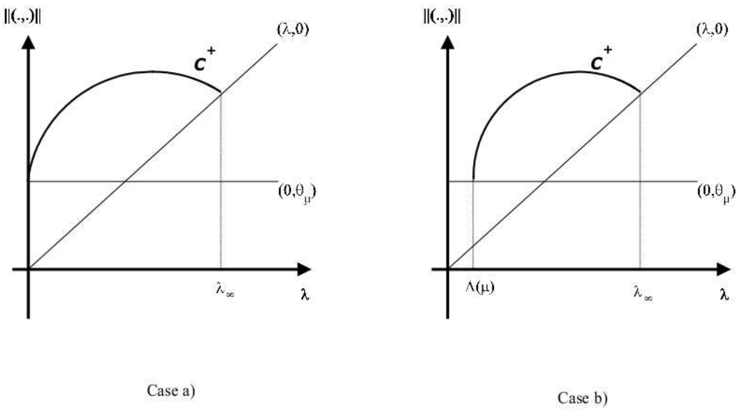

Figure 3 – Bifurcation diagrams. Case a) $V'(0) = 0$ and Case b) $V'(0) > 0$.

To end this Section, we will recall some results concerning the long time behavior of (37). We will assume that V is bounded and, therefore, the solutions are global in time. The first of these results asserts the exponential convergence of the v-component to zero whenever μ is sufficiently small:

Théorème 21 *There exists a decreasing function* $\alpha : [0, \mu_1) \mapsto (0, 1]$ *with the following property: if* $\gamma \in (1, +\infty)$, $\beta \in (1, 1 + 1/\gamma)$, $\mu \in [0, \mu_1)$ *and* $0 < \delta < \rho < \alpha(\mu)$, *there exists* $C > 0$ *such that the* v*-solution to (37) satisfies*

$$\|v(\cdot, t)\|_\gamma \leq Ce^{-\rho t}\|v_0\|_\gamma \quad \forall t > 0$$

and

$$\|v(\cdot, t)\|_{W^{\beta,\gamma}} \leq C(1 + t^{-\theta})e^{-\delta t}\|v_0\|_\gamma \quad \forall t > 0,$$

where $\theta = \theta(\beta) \in (0, 1)$.

Our next result shows the convergence of the u-component to zero for small μ and $\lambda = 0$.

Théorème 22 *Assume that* $\mu \in [0, \mu_1)$ *and* $\lambda = 0$. *Then*

$$\lim_{t \to +\infty} \|u(\cdot, t)\|_{W^{m,p}} = 0,$$

for any $m < 1$ *and any* $p \geq 2$.

Finally, the last theorem of this Section shows that, if we impose appropriate conditions on V at zero, μ is sufficiently small and $\lambda > 0$, the u-component converges to the constant function $u \equiv \lambda$:

Théorème 23 *Let* $\mu \in [0, \mu_1)$ *and assume that there exist* $C, \delta_0 > 0$ *and* $k > 1 + N/2$ *such that*

$$0 < V(s) < Cs^k \,, \qquad |V'(s)| \leq Cs^{k-1}$$

for all $s \in (0, \delta_0)$. *Then, there exists* $\theta > 0$ *such that*

$$\|u(\cdot, t) - \lambda\|_{W^{m,p}} \leq Ce^{-\theta t}\,,$$

for all $t \geq t_0 > 0$ *and any* $m < 1$, $p \geq 2$.

The results of this Section have been extracted from [11].

5 The Keller-Segel model

In this last Section we will say something about the Keller-Segel system, trying to cover situations that have not been considered yet. This system has been studied extensively in the literature, specially in the last years, see the review papers [21, 23, 24]. As we said in Section 2, the Keller-Segel system has been proposed to describe the aggregative stage of cellular slime molds. The model considers two variables u (concentration of cellular slime molds) and v (concentration of chemoattractant).

Under some assumptions, the following semi-stationary system is a good approximation:

$$\begin{cases} u_t = \nabla \cdot (\nabla u - \chi u \nabla v) & \text{in } \Omega \times (0,T), \\ 0 = \Delta v - \gamma v + \alpha u & \text{in } \Omega \times (0,T), \\ \dfrac{\partial u}{\partial n} = \dfrac{\partial v}{\partial n} = 0 & \text{on } \partial\Omega \times (0,T), \\ u(x,0) = u_0(x) & \text{in } \Omega, \end{cases} \tag{43}$$

where χ, α, γ are positive parameters. We will be concerned with blow-up phenomena for (43). The main ideas and arguments that we recall here have been taken from [33].

In [34] it is conjectured that blow-up may occur in finite time for u in a form of a Dirac delta function; such as phenomenon is known as chemotactic collapse. In [26] the authors showed in a 2-dimensional ball that it is certainly possible to choose radially symmetric initial data such that the blow-up of u occurs in finite time. In what follows, we assume that

- $\Omega = B_L \in \mathbb{R}^N$, $N \geq 2$, where B_L is an open ball of radius L with center at the origin.
- u_0 is radially symmetric.

Let us introduce

$$\theta = \frac{1}{\omega_N} \int_\Omega u_0 \,,$$

where ω_N is the area of the unit sphere S^{N-1} in $\mathbb{R}^N$. We define the following quantity

$$M_N(t) := \frac{1}{\omega_N} \int_\Omega u(x,t)|x|^N \,,$$

which is a measure of the concentration of the solution around the origin. If $M_N(t)$ is small, then the solution is concentrated at the origin and the smaller the quantity $M_N(t)$ is more concentrated is the solution around the origin. For $s \geq 0$, let us set

$$E_\theta(s) := 2N(N-1)\theta^{2/N} s^{(N-2)/N} - \frac{N}{2}\alpha\chi\theta^2 + \alpha\chi N L^{-N}\theta s + \alpha\chi\gamma R_\theta(s)$$

where

$$R_\theta(s) = \begin{cases} \frac{1}{e}\theta^{3/2} s^{1/2} & \text{if } N = 2, \\ \frac{N}{2(N-2)}\theta^{(2N-2)/N} s^{2/N} & \text{if } N \geq 3. \end{cases}$$

The idea for the blow-up analysis is to show that $M_N(t) \to 0$ as $t \to T_0^-$ for some $T_0 < +\infty$. For this purpose, it is enough to prove a differential inequality of the form

$$\frac{d}{dt} M_N(t) \leq E_\theta(M_N(t))$$

and pick the initial data $M_N(0)$ such that $E_\theta(M_N(0)) < 0$.

Théorème 24 *Let $N \geq 2$ and assume that $\alpha\chi\theta > 4$ when $N = 2$. Then there exists a positive constant $c(\theta)$ such that, if $0 < M_N(0) < c(\theta)$, then $T_{max} < +\infty$ and*

$$\lim_{t \to T_{max}^-} \|u(\cdot, t)\|_\infty = +\infty \,.$$

Moreover,

$$\lim_{t \to T_{max}^-} \|u(\cdot, t) \log u(\cdot, t)\|_1 = +\infty \,.$$

Of course, the last condition implies that u blows up in the L^p-norm for every $p > 1$.

Remarque 1 *If $T_{max} = T_0$ then the solution u forms a Dirac delta function at the origin as $t \to T_{max}^-$.*

Finally, to conclude this Section we will say something about the convergence to non-homogeneous setady states. This will be done for the fully parabolic Keller-Segel system.

Let $\Omega \subset \mathbb{R}^2$ be a regular domain. We consider the system

$$\begin{cases} U_t = \Delta U - \chi \nabla \cdot (U \nabla V) & \text{in } \Omega \times (0, T), \\ V_t = \alpha \Delta V - \beta V + \delta U & \text{in } \Omega \times (0, T), \\ \dfrac{\partial U}{\partial n} = \dfrac{\partial V}{\partial n} = 0 & \text{on } \partial\Omega \times (0, T), \\ (U, V)(x, 0) = (U_0, V_0)(x) & \text{in } \Omega, \end{cases}$$

where the initial data are non-negative. The change of variables

$$u = \frac{U}{\overline{U_0}}\,, \quad v = \chi(V - \overline{V})$$

leads to

$$\begin{cases} u_t = \Delta u - \nabla \cdot (u \nabla v) & \text{in } \Omega \times (0, T), \\ v_t = \alpha \Delta v - \beta v + \gamma(u - 1) & \text{in } \Omega \times (0, T), \\ \dfrac{\partial u}{\partial n} = \dfrac{\partial v}{\partial n} = 0 & \text{on } \partial\Omega \times (0, T), \\ (u, v)(x, 0) = (u_0, v_0)(x) & \text{in } \Omega, \end{cases} \tag{44}$$

where $\gamma = \chi\delta\overline{U}_0$, $u_0 = \frac{U_0}{\overline{U}_0}$ and $v_0 = \chi(V_0 - \overline{V}_0)$. It is clear that u_0 is positive; however, v_0 may be a sign changing function. The main tool for the analysis of (44) is the functional

$$F(u, v) = \int_\Omega \left(u \log u + \frac{1}{2\gamma}(\alpha|\nabla v|^2 + \beta v^2) - (u - 1)v \right),$$

that satisfies

$$\frac{d}{dt} F(u, v) = -D(u, v)\,,$$

where

$$D(u, v) = \frac{1}{\gamma} \int_\Omega (\partial_t v)^2 + \int_\Omega u |\nabla(\log u - v)|^2 \,.$$

Observe that F can be unbounded from below, due to the term $-\int_\Omega (u-1)v$. In fact, it is possible to choose initial data u_0, v_0 and parameters α, β and γ such that $F(u(t), v(t)) \to -\infty$ as $t \to T_{max}^-$, see [22].

In [16] it is proved by the compactness method that, when the solution does not blow up (in finite or infinite time), there are sequences $\{t_n\}$ such that $(u(t_n), v(t_n))$ converge to a solution of the steady-state problem. If there exists exactly one solution to the stationary problem, then this must happen for all sequences $\{t_n\}$.

However, the structure of the steady-state problem can be very complex and it is not excluded even the existence of a continuum of stationary solutions. Under the previous scenario, the convergence of the whole sequence to a solution of the stationary problem is a delicate question. Nowadays, it seems that the only tool available to handle this problem is the Łojasiewicz inequality. See [30] for a description in the finite dimensional framework and [41] for the infinite dimensional version. The Łojasiewicz inequality is used in [13] to prove convergence to a steady state. Unfortunately, the steady state can be the trivial one $(1, 0)$. To exclude this possibility it is enough to choose u_0 and v_0 such that the solution does not blow up and $F(u_0, v_0) < F(1, 0) = 0$; in view of the arguments in [16, Section 5], this is possible.

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