PDE models for chemotactic movements

Parabolic, hyperbolic and kinetic

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Abstract

Modeling the movement of cells (bacteria, amoeba) is a long standing subject and Partial Differential equations have been used several times. The most classical and successful system was proposed by Patlak [55] and Keller & Segel [39] and is formed of parabolic or elliptic equations coupled through a drift term. This model exhibits a very deep mathematical structure because smooth solutions exist for small initial norm (in the appropriate space) and blow-up for large norms. This reflects experiments on bacteria like *Escherichia Coli* or amoeba like *Dictyostelium Discoïdeum* exhibiting pointwise concentrations.

For human endothelial cells, several experiments show the formation of networks that can be interpreted as the initiation of angiogenesis. To recover such patterns a hydrodynamical model seems better adapted.

The two systems can be unified by a kinetic approach that was proposed for *Escherichia Coli*, based on more precise experiments showing a movement by 'jump and tumble'. This nonlinear kinetic model is interesting by itself and the existence theory is not complete. It is also interesting from a scaling point of view; in a diffusion limit one recovers the Keller-Segel model and in a hydrodynamical limit one recovers the model proposed for human endothelial cells.

We also mention the mathematical interest of a analyzing another degenerate parabolic

system (exhibiting different properties) proposed to describe the angiogenesis phenomena i.e. the formation of capillary blood vessels.

Key words. Chemotaxis, angiogenesis, degenerate parabolic equations, kinetic equations, global weak solutions, blow-up.
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Contents

1 Introduction

This paper is concerned by the description of mathematical theory for some examples of chemotaxis process. *Chemotaxis* is a biological phenomenon describing the change of motion when a population formed of individuals (such as amoebae, bacteria, endothelial cells etc.) reacts in response (*taxis*) to an external chemical stimulus spread in the environment where they reside. As a consequence, the population changes its movement toward (*positive chemotaxis*) a higher concentration of the chemical substance. A possible fascinating issue of a positive chemotactical movement is the aggregation of the organisms involved to form a more complex organism or body. Various biological issues and mathematical questions around cell motion can also be

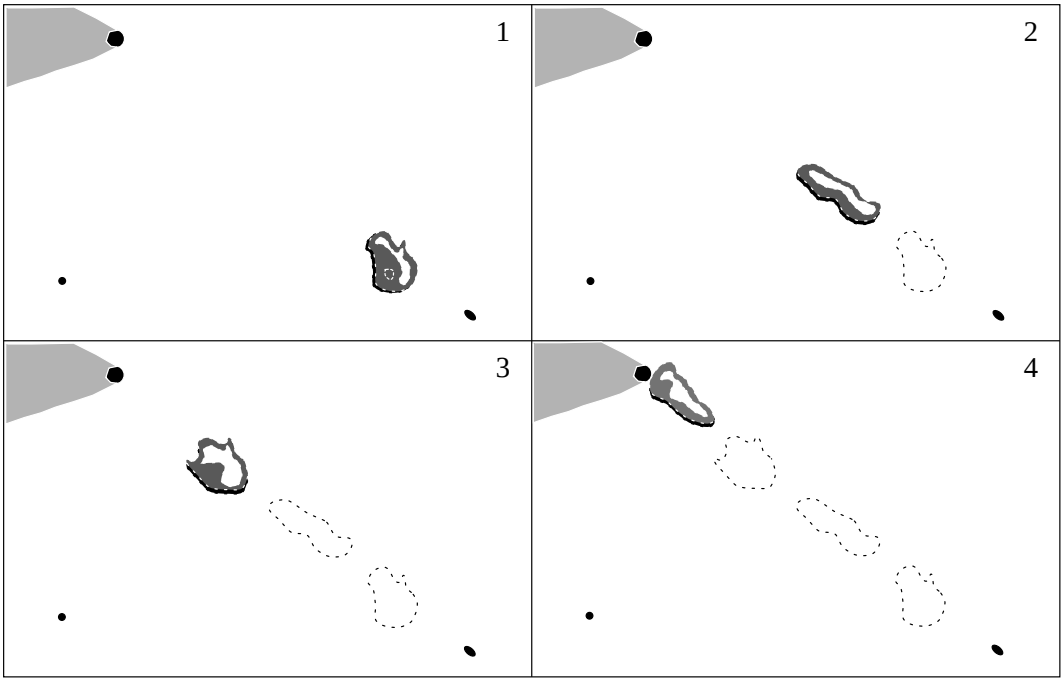

Figure 1: Motion of amoeba Dictyostelium Discoïdeum in reaction to a chemoattractant emitted from the dark point at the upper left corner.

found in the Lecture Notes in Biomathematics edited by Alt and Hoffmannn [2].

When a population density is involved in a chemotaxis process, a first level of description has been considered from a Partial Differential Equation viewpoint; the full population at the *macroscopic* level is described by a coupled system on its density and the chemoattractant concentration. The most famous being Patlak, Keller & Segel model ([55, 39]) which is formed of parabolic or elliptic equations coupled through a drift term. This model is very successful for describing the aggregation of the population in a single point (*chemotactic collapse* in the terminology of [32]). For this reason it has given rise to an important literature and we refer to the survey [35] for complements. Here we will give a very simplified account on the status of the Patlak, Keller-Segel system.

More recently, experiments with human endothelial cells on matrigel have been realized. Their movements lead to the formation of networks that are interpreted as the beginning of a vasculature ([59, 28]). This phenomenon is important since it is responsible for angiogenesis, a major factor for the growth of tumors [14, 44]. These structures cannot be explained by the above

parabolic models which generically lead to pointwise blow-up, but are recovered by numerical experiments on hyperbolic models. This also represent a recent tendency in the literature to use hyperbolic equations to describe intermediate regimes at the macroscopic level rather than parabolic equations, see for instance [20] and the references therein.

Another class of models has been proposed which consider a more local (say individual) or *mesoscopic* level. This approach involves kinetic (Boltzmann type) equations with nonlinear scattering kernels which are based upon a detailed knowledge of the motion at the cell level. *Escherichia Coli* bacterium for instance is known to move with a sequence of runs and tumbles, see [1, 54, 53, 62, 13] and the references therein. The advantage of the kinetic model is that, not only it provides a better detailed description of the movement, but also unifies the two macroscopic models by asymptotic derivations using either a *diffusion* or a *hydrodynamic* scale.

For simplicity, we always present the models in the case of the full space $\mathbb{R}^d$ (although experiments are always on dishes), and we always consider the simplest models (although many more complexity in the reactions are needed for most of the experiments), and we always take the coefficients equal to one as much as this is possible by choosing the correct scales (in other words we only keep the lowest numbers of parameters).

For chemotaxis we borrow our presentation from the paper [17].

2 The Patlak/Keller-Segel system for chemotaxis

2.1 Existence and blow-up

The simpler model proposed for describing the chemotactic motion takes only into account the density $n(t,x)$ of cells and the chemoattractant concentration $c(t,x)$ assuming that the cells emit directly the chemoattractant which is immediately diffused. Then we arrive to the following parabolic-elliptic system

$$\left\{\begin{array}{l} \frac{\partial}{\partial t} n = \Delta n - \chi \nabla \cdot [n \nabla c], \quad t > 0,\ x \in \mathbb{R}^d, \\ \\ -\Delta c = n, \quad t > 0,\ x \in \mathbb{R}^d, \\ \\ n(0,x) = n_0(x) \geq 0, \qquad x \in \mathbb{R}^d. \end{array}\right. \tag{1}$$

where the *chemotactic sensitivity* function χ is constant with respect to the chemical density c. Notice that with the ad hoc decay conditions at infinity on n and c, the chemical concentration

gradient can be represented exactly by

$$\nabla c(t,x) = \int_{\mathbb{R}^d} \nabla E_d(x-y) n(t,y) dy, \tag{2}$$

where E_d is the fundamental solution of the Laplacian in $\mathbb{R}^d$, a formula that can be used directly in the equation on n. The validity of (1) in the framework of chemotaxis is supported by some experiments on the *Escherichia Coli* bacterium (see [11], [6] and the references therein), even if this model does not seem to reproduce some of the observed chemotactic movement ([11]). Moreover, system (1) has other interesting physical interpretations. For example it arises in astrophysics and in statistical mechanics (see [7], [8], [9] and the references therein). System (1) was extensively studied by many authors and a huge quantity of mathematical results on the existence of global in time solutions and on the blow-up of local in time solutions, have been produced. We refer to [35] for a quite complete bibliography. Let us just mention that system (1) has a conserved energy (see for example [10], [27] and [34]) given by

$$\frac{d}{dt} \int \Big\{ n(\ln n - 1) - \frac{\chi}{2} |\nabla c|^2 \Big\} dx = - \int n |\nabla (\ln n - \chi c)|^2 dx \leq 0.$$

The different signs in the two terms allow for a complex behaviour as it is expressed in the

Theorem 2.1 *(Existence for the chemotaxis system (1)) Assume $d \geq 2$ and consider some $n_0 \in L^1(\mathbb{R}^d)$ such that $n_0 \geq 0$. There exists a constant $K_*(\chi, d)$ such that if $\|n_0\|_{L^{\frac{d}{2}}(\mathbb{R}^d)} \leq K_*$, then system (1) has a global (in time) weak solution (n, c) such that for all $t > 0$, $n(t)$ is nonnegative and*

$$\int_{\mathbb{R}^d} n(t,x) dx = \int_{\mathbb{R}^d} n_0(x) dx, \qquad \|n(t)\|_{L^p(\mathbb{R}^d)} \leq \|n_0\|_{L^p(\mathbb{R}^d)}\ , \quad \max\{1; \frac{d}{2} - 1\} \leq p \leq \frac{d}{2},$$

and

$$\|n(t)\|_{L^p(\mathbb{R}^d)} \leq C(t, K_0, \|n_0\|_{L^p(\mathbb{R}^d)}) \qquad \frac{d}{2} < p \leq \infty.$$

Theorem 2.2 *(Blow-up for chemotaxis system (1)). For $d \geq 3$, assume that*

$$\int_{\mathbb{R}^d} \frac{|x|^2}{2} n_0(x) dx \leq C_* \, \big(\int_{\mathbb{R}^d} n_0(x) dx \big)^{\frac{d}{d-2}} \tag{3}$$

for some constant $C_* = C_*(\chi, d) > 0$, and for $d = 2$, assume that $\int_{\mathbb{R}^d} \frac{|x|^2}{2} n_0(x) dx$ is finite and that $\int_{\mathbb{R}^d} n_0 \geq K^*(\chi, d = 2) = \frac{8\pi}{\chi}$. Then, the chemotaxis system (1) has no global smooth solution with fast decay.

Remark 2.3 *In dimensions $d \geq 3$, the assumption (3) is incompatible with the smallness assumption on $\|n_0\|_{L^{\frac{d}{2}}(\mathbb{R}^d)}$ of Theorem 2.1 in view of the classical inequality*

$$\big(\int_{\mathbb{R}^d} n_0(x) dx \big)^d \leq C \, \big(\int_{\mathbb{R}^d} \frac{|x|^2}{2} n_0(x) dx \big)^{d-2} \, \|n_0\|^2_{L^{\frac{d}{2}}(\mathbb{R}^d)}.$$

It can be derived just dividing this integral in two integrals for $|x| \leq R$ (and use Hölder inequality) and $|x| \geq R$ (and use $|x|^2 \geq R^2$) and optimizing the result in R. In three dimensions, it is an open question to replace assumption (3) by "$\|n_0\|_{L^{\frac{d}{2}}(\mathbb{R}^d)}$ large enough" (without second x-moment), as it is suggested in two dimensions and for radial solutions by the result of [32] (see also [60]).

Remark 2.4 *In dimension 2, it is proved recently that the constant $K_*(\chi, 2) = \frac{8\pi}{\chi}$ in [21]. The method differs slightly from that derived in [37] (and that we present below) which gives $K_*(\chi, 2) = \frac{4\pi(1.86225)}{\chi}$, after estimating the corresponding Gagliardo-Nirenberg-Sobolev constant $C_{\rm gns} = \frac{1}{\pi(1.86225)}$ following [64]. Therefore the threshold for blow-up or existence of classical solutions is exactly $\frac{8\pi}{\chi}$. The corresponding result in a bounded domain was proved in [27].*

These results are proved, as stated here in [17]. They are classical except the propagation of L^p norms under the only assumption $\|n_0\|_{L^{\frac{d}{2}}(\mathbb{R}^d)} \leq K_0$. We recall that the basic argument for existence is due to [37] who also proved that blow-up may occur in two space dimensions for large initial data. This result was extended to dimensions $d \geq 3$ in the case of radial symmetric solutions by Nagai [50] who shows that blow-up may arise whatever the initial mass is, depending on the x momentum of order d of n_0. Actually, the radial case is better understood and, in two space dimensions for large mass M (larger than the corresponding K_0 in Theorem 2.1), the type of blow-up has been specified. In [32] the authors proved that *chemotactic collapse* i.e. pointwise concentration as a Dirac mass occurs, more precisely, we have the following

Theorem 2.5 *(Chemotactic collapse for system (1)). For $d = 2$ and radial solutions to (1), assume that $\int_{\mathbb{R}^2} n_0(x)dx > K_0(\chi, d = 2) = \frac{8\pi}{\chi}$. Then there is a finite time T^* such that*

$$n(t, x) \underset{t \to T^*}{\rightharpoonup} \frac{8\pi}{\chi}\delta(x = 0) + Rem(x),$$

where the remainder $Rem(x)$ is a L^1 function that can be explicitly computed

Even in the non-radial case, blow-up and chemotactic collapse in two space dimensions are very close: indeed from the argument in [37], blow-up can occur only if solutions lose equicontinuity in L^1. In [60] and the references therein, the concentration measures that can appear in finite time are characterized. In three dimensions, the extreme complexity of the behavior appears in the numerous blow-up modalities described in [10].

Besides aggregation of cells, another important subject that motivated the derivation of system (1), is the travelling waves solutions. Additional and very specific nonlinearities (sensitivity

factor $\chi = \frac{1}{c}$ for instance) can lead to travelling waves [61] , [63]. Another biochemical explanation is proposed in [11] in order to obtain swarm rings , namely the attractant (aspartate, $c(t,x)$ with previous notation) is produced by cells themselves when consuming succinate ($f(t,x)$ below). The proposed model is

$$\begin{cases} \frac{\partial}{\partial t} n - \Delta n + \mathrm{div}(n \nabla c) = 0, \\ \\ \frac{\partial}{\partial t} c - \Delta c = n\ f, \\ \\ \frac{\partial}{\partial t} f - \beta \Delta f = -\gamma\ f\ n. \end{cases} \tag{4}$$

The pattern formations in such more elaborate systems can be much more involved than those in (1). The chemical reactions can create spiral waves that themselves induce waves on the cell density n (see [45, 49]).

2.2 A priori estimates for small initial data

We indicate here the main argument leading to global existence. It was given in [37] as well as a proof of blow-up for large data. We depart from the equation (1). We arrive directly, after multiplication by $n^{p-1}p$, to

$$\begin{array}{ll} \frac{d}{dt} \int_{\mathbb{R}^d} n^p + 4\frac{p-1}{p} \int_{\mathbb{R}^d} |\nabla n^{p/2}|^2 & = \chi \int_{\mathbb{R}^d} \nabla n^p \cdot \nabla c \\ & = \chi \int_{\mathbb{R}^d} n^{p+1}. \end{array} \tag{5}$$

In order to estimate the L^{p+1} norm of n, we use standard interpolation and the Gagliardo-Nirenberg-Sobolev inequality (see [23]) on the function $u(x) = n^{p/2}$. Hence, in space dimension $d > 2$ we get for any $p \geq \frac{d}{2} - 1$ (so that : $\frac{d}{2} \leq p+1 \leq \frac{dp}{d-2}$)

$$\int_{\mathbb{R}^d} n^{p+1} \leq C_{\mathrm{gns}}(d,p) \|\nabla n^{p/2}\|^2_{L^2(\mathbb{R}^d)}\ \|n\|_{L^{\frac{d}{2}}(\mathbb{R}^d)}\ . \tag{6}$$

And this also holds true in dimension $d = 2$ for $p > 0$.
Inserting this inequality in the right hand side of (5), we find, for all p such that $\max\{1; \frac{d}{2} - 1\} \leq p < \infty$,

$$\frac{d}{dt} \int_{\mathbb{R}^d} n^p \leq (p-1) \|\nabla n^{p/2}\|^2_{L^2(\mathbb{R}^d)} \left[\chi C_{\mathrm{gns}}(d,p) \|n\|_{L^{\frac{d}{2}}(\mathbb{R}^d)} - \frac{4}{p} \right]\ . \tag{7}$$

In dimension $d = 2$, (7) means that if the initial mass $\int n_0$ is sufficiently small, then the $\|n(t)\|_{L^p(\mathbb{R}^2)}$ norm (for the same p) decreases for all times $t \geq 0$. More precisely, the threshold for these a priori bounds is

$$\int_{\mathbb{R}^2} n_0 < \frac{4}{\chi C_{\mathrm{gns}}(d=2, p=1)} = \frac{4\pi(1.86225)}{\chi},$$

as announced in Remark 2.4. Notice also that the equality can be obtained using an estimate on the "entropy" $n \ln_+(n)$ in place of n^p (which amounts to use $p = 1$ in the above calculation).

In dimension $d > 2$ and for $p = \frac{d}{2}$, the inequality (7) gives us that whenever we have initially

$$\chi C_{\rm gns}(d,p)\|n_0\|_{L^{\frac{d}{2}}(\mathbb{R}^d)} - \frac{8}{d} \leq 0 \ , \tag{8}$$

the $\|n(t)\|_{L^{\frac{d}{2}}(\mathbb{R}^d)}$ norm decreases for all times $t \geq 0$. As a consequence, whenever (8) holds true, all the $\|n(t)\|_{L^p(\mathbb{R}^d)}$ norms, with $\max\{1; \frac{d}{2} - 1\} \leq p \leq \frac{d}{2}$, decrease for all times $t \geq 0$.

We refer to [17] for more details about the proof and especially for the propagation of L^p bounds with a smallness assumption independent of p and for the proof of existence based on a regularized system satisfying the same estimates. We also refer to [21] for a proof of the optimal critical mass in two dimensions.

2.3 Blow-up

In this subsection, we give a proof of Theorem 2.2. Here we use the standard quantity

$$I(t) = \int_{\mathbb{R}^d} \frac{|x|^2}{2} n(t,x)dx,$$

and the formula (2), since we deal with a smooth solution (n, c) of (1) with fast decay at infinity. Hence

$$\nabla c(t,x) = -\lambda_d \int_{\mathbb{R}^d} \frac{x-y}{|x-y|^d} n(t,y)dy, \qquad \lambda_d > 0.$$

Next, we denote by $M = \int_{\mathbb{R}^d} n_0(x)dx$. Using mass conservation, $M = \int_{\mathbb{R}^d} n(t,x)dx$, and following [51, 50, 30, 9], we compute for $d \geq 3$

$$\begin{aligned}
\tfrac{d}{dt} I(t) &= d \textstyle\int_{\mathbb{R}^d} n_0(x)dx + \chi \int_{\mathbb{R}^d} n(t,x)\ x \cdot \nabla c(t,x)\ dx \\
&= dM - \lambda_d \chi \textstyle\int_{\mathbb{R}^d \times \mathbb{R}^d} n(t,x)n(t,y) \frac{x\cdot(x-y)}{|x-y|^d}\ dxdy \\
&= dM - \tfrac{\lambda_d}{2} \chi \textstyle\int_{\mathbb{R}^d \times \mathbb{R}^d} n(t,x)n(t,y) \frac{1}{|x-y|^{d-2}}\ dxdy \\
&\leq dM - \tfrac{\lambda_d}{2R^{d-2}} \chi \textstyle\int_{|x-y|\leq R} n(t,x)n(t,y)\ dxdy \\
&= dM - \tfrac{\lambda_d \chi}{2R^{d-2}} M^2 + \tfrac{\lambda_d}{2R^{d-2}} \chi \textstyle\int_{|x-y|\geq R} n(t,x)n(t,y)\ dxdy \\
&\leq dM - \tfrac{\lambda_d \chi}{2R^{d-2}} M^2 + \tfrac{\lambda_d}{2R^d} \chi \textstyle\int_{\mathbb{R}^d \times \mathbb{R}^d} n(t,x)n(t,y)|x-y|^2\ dxdy \\
&\leq dM - \tfrac{\lambda_d \chi}{2R^{d-2}} M^2 + \tfrac{2\lambda_d}{R^d} \chi M \textstyle\int_{\mathbb{R}^d} |x|^2 n(t,x)\ dx = dM - \tfrac{\lambda_d \chi}{2R^{d-2}} M^2 + \tfrac{4\lambda_d}{R^d} \chi M\ I(t).
\end{aligned}$$

Choosing $R = \mu M^{\frac{1}{d-2}}$ with μ small enough we find

$$\frac{d}{dt} I(t) \leq M \left[\frac{C}{M^{\frac{d}{d-2}}} I(t) - 1 \right].$$

When the second x momentum of n_0, $I(0)$, is too small compared to $M^{\frac{d}{d-2}}$, then $I(t)$ decreases for all times and

$$\frac{d}{dt} I(t) \leq M \left[\frac{C}{M^{\frac{d}{d-2}}} I(0) - 1 \right] < 0 \quad \forall t \geq 0.$$

This leads to a contradiction after the time $T^* = I(0) M^{-1} \left[1 - \frac{C}{M^{\frac{d}{d-2}}} I(0) \right]^{-1}$ since $I(t)$ cannot be negative for smooth solutions.

For $d = 2$, the situation is simpler because we arrive directly at the identity

$$\frac{d}{dt} I(t) = 2M - \frac{\lambda_d}{2} \chi \int_{\mathbb{R}^d \times \mathbb{R}^d} n(t,x) n(t,y) \, dxdy = 2M - \frac{\lambda_d}{2} \chi M^2,$$

with $\lambda_d = \frac{\pi}{2}$, which leads directly to the same contradiction as before after the time

$$T^* = I(0) M^{-1} [\frac{\pi}{4} \chi M - 2]^{-1} \, .$$

This leads to the blow-up condition $M > \frac{8\pi}{\chi}$.

2.4 Radially symmetric solutions

In this Section, we come back on the result of [31], [32], Theorem 2.5, that expresses the type of blow-up as a *chemotactic collapse* for radial solutions in two dimensions. We explain why, for radially symmetric solutions, the system can be simplified and we prove a blow-up result which is close to exhibit the shape of the chemotactic collapse solution.

Radially symmetric solutions to system (1) in d dimensions are reduced to the system on $n(t,r)$, $c(t,r)$, where we set $r = |x|$,

$$\left\{ \begin{array}{rl} \frac{\partial}{\partial t}(r^{d-1} \, n) \; - (r^{d-1} n')' + \chi (r^{d-1} n c')' & = 0, \quad t \geq 0, \quad r \geq 0, \\ -(r^{d-1} c')' & = r^{d-1} n, \\ n'(t, r=0) = c(t, r=0) & = 0. \end{array} \right. \tag{9}$$

where $'$ stands for $\frac{\partial}{\partial r}$ and initial data have to be specified. We introduce the quantity

$$M(t,r) = \int_0^r \sigma^{d-1} n(t,\sigma) d\sigma = -r^{d-1} c'(t,r),$$

and equation (9) can be reduced to a single equation. Indeed it is equivalent to

$$\left\{ \begin{array}{rl} M'(r) & = r^{d-1} n(r), \\ \frac{\partial}{\partial t} M(t,r) - r^{d-1} (\frac{M'}{r^{d-1}})' - \frac{\chi}{r^{d-1}} M' \, M & = 0. \end{array} \right. \tag{10}$$

where we have deleted the argument (t, r) when not necessary.

In two dimensions, steady states solutions can be further derived from this system and are given by (just differentiate the second equation of (10) to see it)

$$r\bar{M}' - 2\bar{M} + \frac{\chi}{2}\bar{M}^2 = 0, \quad M(0) = 0.$$

One readily checks that there is a non trivial solution only in the case of a special relation between χ and the total mass, namely $M(\infty) = \bar{M}^\infty$ with,

$$4 \, \chi \, \bar{M}^\infty = 1,$$

$$\bar{M}_\lambda(r) = \frac{\bar{M}^\infty}{1 + \lambda r^{-2}}.$$

Notice that the above equality is equivalent to the threshold for blow-up in Theorems 2.2 and 2.1 because $M(\infty)$ differs from the total mass of n by a factor 2π.

This solution may serve to give a hint on the behavior of generic radially symmetric solutions and especially to understand why a singularity can arise only at the origin.

Theorem 2.6 *Assume that in the 2d radial case, we have*

$$4 \, \chi \, M(\infty) < 1, \qquad M(t=0,r) \leq \bar{M}_{\lambda^0}(r),$$

for some $\lambda^0 > 0$ (notice that $\bar{M}^\infty > M(\infty)$). Then the solution to (10) satisfies

$$M(t,r) \to 0 \quad as \; t \to \infty \quad locally \; uniformly,$$

and thus $n(t)$ in (9) vanishes in $L^1(\mathbb{R}^2)$ locally.

Theorem 2.7 *In the 2d radial case, when we have*

$$4 \, \chi \, M(\infty) > 1, \qquad M(t=0) \geq \frac{M(\infty)}{1 + \lambda^0 r^{-2}},$$

for some $\lambda^0 > 0$. Then the solution to (9) blows up in finite time.

This Theorem expresses that, in the blow-up result proved in Theorem 2.2, the limitation on the second moment is in fact useless in the radially symmetric case. The proof we propose here uses a comparison argument with sub or supersolutions in the spirit of [37].

Proof of Theorem 2.6. Being given χ, $M(\infty)$ and $\bar{M}^\infty > M(\infty)$, we may always choose a $\bar{\chi} > \chi$ which satisfies $4\bar{\chi}\bar{M}^\infty = 1$. Then we consider the function

$$\bar{N}(t,r) = \inf(M(\infty), \bar{M}_{\lambda(t)}(r)), \quad \lambda(t) = \lambda^0 + 2(\bar{M}^\infty - M(\infty))(\bar{\chi} - \chi)t,$$

and we claim it is a supersolution to (10) (with $d = 2$). Indeed, we have

$$\frac{\partial}{\partial t}\bar{N} = -\bar{N}\,\frac{r^{-2}}{1+\lambda r^{-2}}\,\frac{d}{dt}\lambda(t) \qquad or\ 0,$$

$$\bar{N}' = 2\bar{N}\frac{\lambda r^{-3}}{1+\lambda r^{-2}} \qquad or \quad 0.$$

Therefore, we first compute the radius $R(t)$ such that for $r > R(t)$ the infimum of $\bar{N}$ is attained by $M(\infty)$. It is given by

$$\lambda(t)R(t)^{-2} = \frac{\bar{M}^\infty - M(\infty)}{M(\infty)},$$

and for $r \le R(t)$, we have

$$\begin{aligned}
\tfrac{\partial}{\partial t}\bar{N} - r(\tfrac{\bar{N}'}{r})' - \tfrac{\chi}{r}\bar{N}'\,\bar{N} &= \bar{N}\,\tfrac{r^{-2}}{1+\lambda r^{-2}}[-\tfrac{d}{dt}\lambda(t) + 2\bar{M}^\infty(\bar{\chi}-\chi)\tfrac{\lambda r^{-2}}{1+\lambda r^{-2}}] \\
&\ge \bar{N}\,\tfrac{r^{-2}}{1+\lambda r^{-2}}[-\tfrac{d}{dt}\lambda(t) + 2\bar{M}^\infty(\bar{\chi}-\chi)\tfrac{\lambda R(t)^{-2}}{1+\lambda R(t)^{-2}}] \\
&= \bar{N}\,\tfrac{r^{-2}}{1+\lambda r^{-2}}[-\tfrac{d}{dt}\lambda(t) + 2(\bar{M}^\infty - M(\infty))(\bar{\chi}-\chi)] \\
&= 0.
\end{aligned}$$

But the infimum of two solutions is a supersolution and thus $\bar{N}$ is indeed a supersolution to (10).

By the comparison principle, we deduce that the solution (10) satisfies $M(t,r) \le \bar{N}(t,r)$. We conclude the proof just noticing that $R(t) \to \infty$ and for a given interval $r \in (0,R)$ we therefore have for t large enough $M(t,r) \le \bar{M}^\infty/(1+\lambda(t)R^2) \to 0$. □

Proof of Theorem 2.7. We follow the same lines as before and first choose a $\bar{M}^\infty < M(\infty)$ and a $\bar{\chi} < \chi$ which satisfy $4\bar{\chi}\bar{M}^\infty = 1$. We consider the function

$$\bar{N}(t,r) = \sup(\frac{M(\infty)}{1+\lambda^0 r^{-2}}, \bar{M}_{\lambda(t)}(r)),$$

and we argue in two steps; i) $\lambda(t) = \lambda^0 e^{-\alpha t}$ for $t < t_1$ large enough, ii) $\lambda(t) = \lambda(t_1) - t + t_1$ for $t_1 < t < t_2 = t_1 + \lambda(t_1)$ the first time where $\lambda(t)$ vanishes, and also we decrease slightly the

value of $\bar{M}^\infty$ during this step.

We will prove that $\bar{N}$ is a subsolution as the supremum of two subsolutions and this concludes the proof because we deduce that $M(t) \geq \bar{N}(t)$ and thus $M(t_2, 0) > 0$ which is impossible for smooth solutions.

To prove that $\bar{N}$ is a subsolution, we first notice that $\frac{M(\infty)}{1+\lambda^0 r^{-2}}$ is a subsolution to (10) because it is an increasing function and a solution for $\bar{\chi} < \chi$. Secondly, we consider $t < t_1$ and we have to prove that $\bar{M}_{\lambda(t)}(r))$ is a subsolution only in an interval $r \leq (t)R$ where it is attained by the sup i.e.

$$\frac{M(\infty)}{1+\lambda^0 R(t)^{-2}} = \frac{\bar{M}^\infty}{1+\lambda(t)R(t)^{-2}}.$$

Notice that $R(t) \leq R_0$ with $\frac{M(\infty)}{1+\lambda^0 R(t)^{-2}} = \bar{M}^\infty$. Then, we compute

$$\begin{aligned}
\tfrac{\partial}{\partial t}\bar{N} - r(\tfrac{\bar{N}'}{r})' - \tfrac{\chi}{r}\bar{N}'\,\bar{N} &= \bar{N}\,\tfrac{r^{-2}}{1+\lambda r^{-2}}[-\tfrac{d}{dt}\lambda(t) + 2\bar{M}^\infty(\bar{\chi}-\chi)\tfrac{\lambda r^{-2}}{1+\lambda r^{-2}}] \\
&\leq \bar{N}\,\tfrac{r^{-2}}{1+\lambda r^{-2}}[-\tfrac{d}{dt}\lambda(t) + 2\bar{M}^\infty(\bar{\chi}-\chi)\tfrac{\lambda R_0^{-2}}{1+\lambda R_0^{-2}}] \\
&\leq \bar{N}\,\tfrac{r^{-2}}{1+\lambda r^{-2}}[-\tfrac{d}{dt}\lambda(t) + 2\bar{M}^\infty(\bar{\chi}-\chi)\lambda R_0^{-2}] \\
&= 0.
\end{aligned}$$

choosing

$$\frac{d}{dt}\lambda(t) = -2\bar{M}^\infty(\chi-\bar{\chi})R_0^{-2}\,\lambda(t), \quad \alpha = 2\bar{M}^\infty(\chi-\bar{\chi})R_0^{-2}.$$

In a third step, we choose t_1 large enough so that $\lambda(t_1)$ is as small as necessary and choose,

$$\lambda(t) = \lambda(t_1) - t + t_1, \qquad \bar{M}^\infty(t) = \bar{M}^\infty(1-2(t-t_1)),$$

for $t_1 < t < t_2$ with t_2 the time where $\lambda(t_2)$ vanishes which can be chosen as close as we wish to t_1 by choosing t_1 large. This can be achieved by keeping the corresponding $\bar{\chi}(t) \leq \chi$. Then we have

$$\begin{aligned}
\tfrac{\partial}{\partial t}\bar{N} - r(\tfrac{\bar{N}'}{r})' - \tfrac{\chi}{r}\bar{N}'\,\bar{N} &\leq \bar{N}[-\tfrac{r^{-2}}{1+\lambda r^{-2}}\tfrac{d}{dt}\lambda(t) + \tfrac{d}{dt}\bar{M}^\infty(t)/\bar{M}^\infty(t)] \\
&\leq 0,
\end{aligned}$$

as long as $t < t_2$ is close enough to t_1 which is exactly what we want. We have obtained again a subsolution which concludes the proof of Theorem 2.7.

2.5 Non radial blow-up

Very little is known on the blow-up modalities for non radially symmetric blow-up. A first question is the condition for blow-up itself; indeed it is not clear if the condition of a finite second x-moment is needed. It is striking that this condition is not necessary in the radial

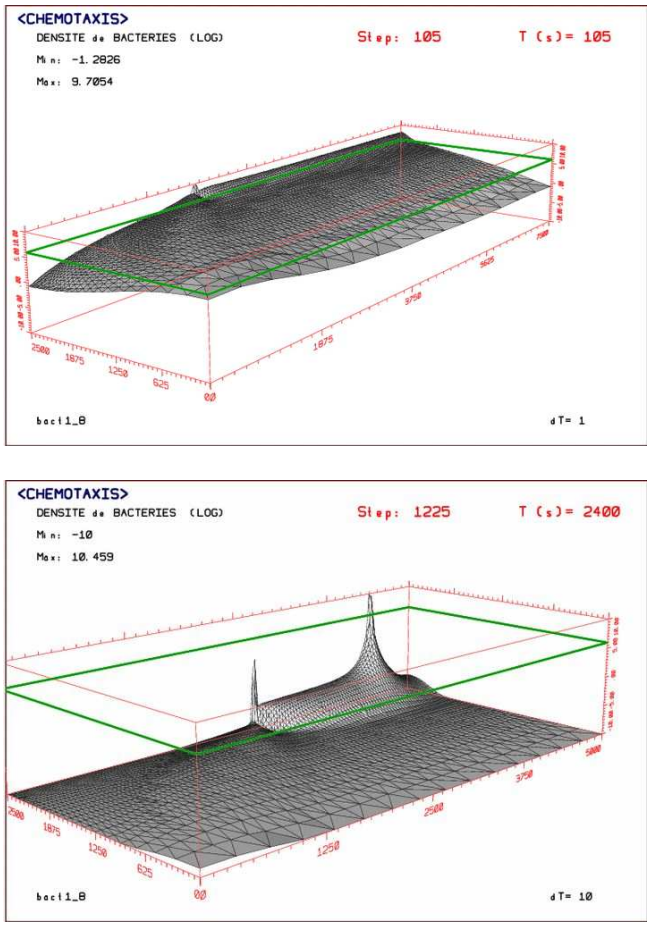

Figure 2: Chemotactic collapse for Keller-Segel model (1) set in a rectangle. This is log scale. (Courtesy of A. Marrocco)

case (see Theorem 2.5). Computations were performed on rectangular domains by Marrocco [47] which show that the blow-up does not occur at the barycenter of the rectangle (see Figure 2). It seems that a singularity (corner) in the concentration is responsible for the singularity formation rather than a mere concentration of n at large values of c. It is also shown that the limitation of the chemoattractant production in the equation on c in (1) leads to a smooth solution that converges in long time to a Dirac mass at the center. Other numerical experiments in three dimensions can be found in [6] which share the same conclusions as in [47], namely the pointwise blow-up follows a first high concentration regime on higher dimensions structures.

3 Initiation of angiogenesis

Very recently, several experiments with human endothelial cells on matrigel were performed. Their movements lead to the formation of networks that are interpreted by biologists as the beginning of a vasculature (see Figure 3 and similar experimental results in [59, 28]). This phenomenon is important since it is responsible for angiogenesis, a major factor for the growth of tumors [14, 44] (see also Section 4). These structures cannot be explained by the Patlak/Keller-Segel parabolic model (or the variants) which generically lead to pointwise blow-up. As shown in [59, 28, 24] they can be recovered by numerical experiments on the following hyperbolic model proposed in [59, 28]

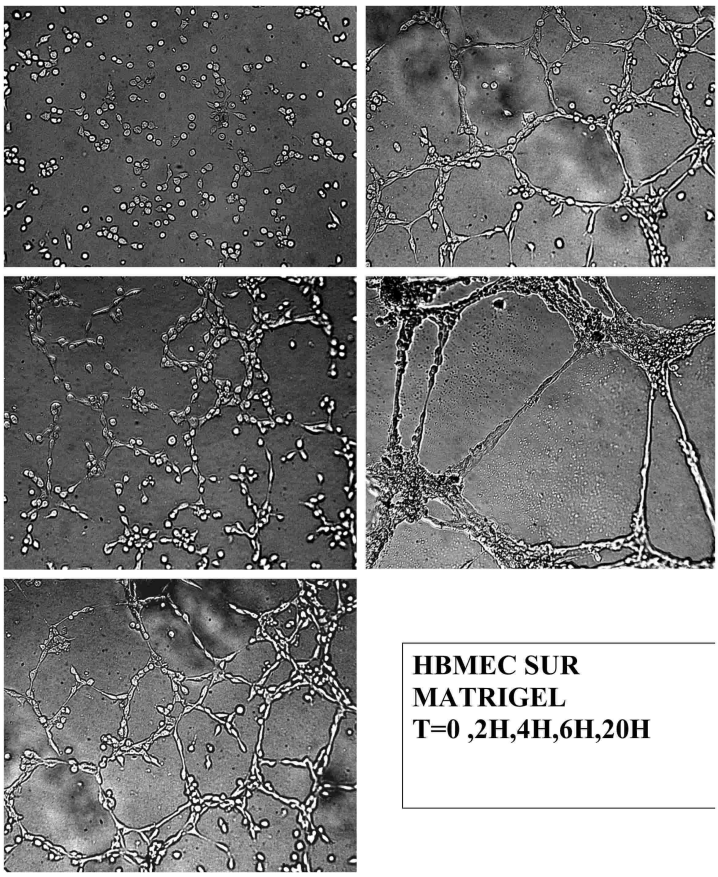

Figure 3: Experiment on the formation of network (courtesy of M. Mirshahi)

$$\begin{cases} \dfrac{\partial n}{\partial t} + \operatorname{div}(n\ u) = 0, \\ \dfrac{\partial (nu)}{\partial t} + \operatorname{div}(n\, u \otimes u) + \nabla \vartheta(n) = n \nabla c - \tau_0 n u, \\ \dfrac{\partial c}{\partial t} - \Delta c + \tau_1 c = n(t,x). \end{cases} \tag{11}$$

This model has proven to be successful to describe qualitatively network formations similar to what is observed experimentally. Notice that it does not differ so much from the Patlak/Keller-Segel model and the main difference is the so-called *persistance* term

$$\frac{\partial (nu)}{\partial t} + \operatorname{div} n\, u \otimes u.$$

If this term was neglected, then, following the derivation of Darcy equations from the compressible gas dynamics system, the momentum equation would reduce to the explicit form of the velocity field

$$\tau_0 n u = n \nabla c - \nabla \vartheta(n).$$

And inserting this in the continuity equation for n, we find nothing but a version of P/K-S model (1) with variable coefficients.

System (11) can be considered as classical hydrodynamic with an isentropic (also called barotropic) pressure law (the term $\vartheta(n)$) in the momentum equation. The force term ∇c is also present in gravitational models (arising in astrophysics) and the main difference with (1) is mainly the equation on the concentration c which is no longer mere diffusion. Numerical simulations performed in [59, 28, 24] confirm the network formation for high enough initial cell densities. Of course this model does not take into account the deformation of cells which can be observed in Figure 3 and which seems important in the pattern observed after some time. Notice also that for bovin endothelial cells (which are much larger), another explanation has been provided based on the elasticity of the support by [46] and similar networking can also be found in coupling the continuity equation on n to an elasticity model for the velocity.

It seems interesting to understand the main difference between the parabolic system (1) and the hyperbolic system (11) from a microscopic point of view. This can sustain biological observations on the interactions of cells at the individual level while the above macroscopic pictures only deal with the population level.

As proposed in [24], a method to unify the parabolic P/K-S model (1) and the hyperbolic model (11), is to consider the phenomena from a kinetic perspective. It turns out that a kinetic

model was proposed based on observations on *Escherichia Coli*, in [1, 54]. We first present the kinetic model in a first subsection, with the existence theory and, in second and third subsections, we explain the derivation of the above macroscopic models. We refer to [30, 56] for a general mathematical theory for kinetic equations.

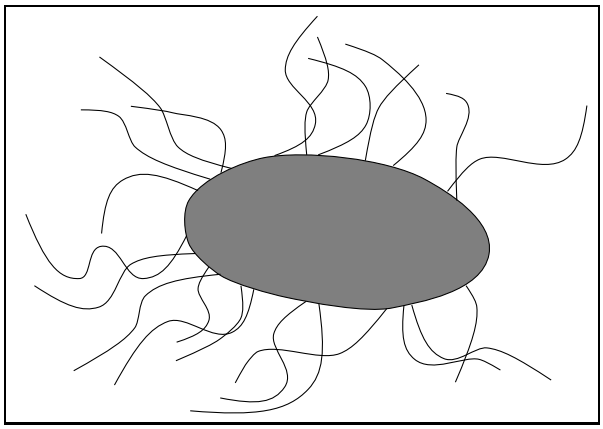

Figure 4: Bacterium Escherichia Coli is equipped with flagella. When rotated counterclockwise, the flagella act as a propellor resulting in a straight "run". When rotated clockwise they fly apart, resulting in a "tumble" which reorients the cell but causes nosignificant change in location.

3.1 Nonlinear scattering equation

Several experiments show that bacteria like *Escherichia Coli* move along straight lines, suddenly stop to choose a new direction and then continue moving in a new direction as the receptors of the cell saturate. This phenomenon, called run and tumble, can be modeled by a stochastic process called the velocity-jump process [1, 54, 53, 62]. At the level of the population this is

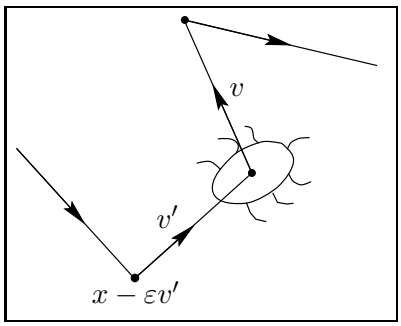

Figure 5: Run and tumble movement for E. Coli.

equivalent to writing a kinetic (or linear Boltzmann) type equation. In fact the model is similar to that of *scattering* for neutrons and is posed for $t \geq 0$, $x \in \mathbb{R}^d$, $\xi \in V \subset \mathbb{R}^d$ (again we choose this for the sake of simplicity and one can choose for instance V a ball of $\mathbb{R}^d$),

$$\begin{cases} \frac{\partial}{\partial t} f(t,x,\xi) + \xi \cdot \nabla_x f + \int_V \left[K(c;\xi,\xi') f(t,x,\xi) - K(c;\xi',\xi) f(t,x,\xi') \right] d\xi' = 0, \\ \\ f(t=0,x,\xi) = f_0(x,\xi) \geq 0, \qquad f_0 \in L^1(\mathbb{R}^d \times V). \end{cases} \tag{12}$$

The gradient term expresses the transport of organisms with their own velocity ξ and the function $K(c;\xi,\xi') \geq 0$ is called the turning rate or scattering kernel and may also depend on (t,x) through a nonlocal dependency upon c. It gives the rate $K(c;\xi',\xi)$ of organisms turning from velocity ξ' to ξ, and thus the rate $K(c;\xi,\xi')$ of organisms with velocity ξ that are substracted from the balance on $f(t,x,\xi)$. Several possible forms for this kernel can be found in [33]; here, and again for the sake of simplicity, we restrict ourselves to the case

$$\begin{cases} K(c;\xi,\xi') = k_-\big(c(t,x-\varepsilon\xi)\big) + k_+\big(c(t,x+\varepsilon\xi')\big), \\ \\ -\Delta c = n(t,x) := \int_V f(t,x,\xi) d\xi. \end{cases} \tag{13}$$

The k_- term expresses a delay ε in reaction time, while k_+ represent an (unphysical) knowledge of prefered directions (in the sense of higher chemoattractant concentration). Notice however that these models do not suppose a comparison between two values of the concentration $c(t,x)$, but only a biased turning rate according to the knowledge a single value $c(t, x \pm \varepsilon\xi)$. We will assume that

$$k_\pm \in C^1(\mathbb{R}^+;\mathbb{R}^+), \quad k_\pm(0) > 0, \quad 0 \leq k'_\pm \leq Q < \infty. \tag{14}$$

Also notice that, because of the diffusion equation on c, we arrive at a nonlinear *mean field equation* since the interaction is long range (see Subsection 3.3 for comments on this issue). This model shares many similarities with the gravitational Vlasov-Poisson equation (motion of self-attracting particles).

In terms of mathematical theory, this model is very interesting because of the lack of a priori estimates. The kernel being nonsymmetric in ξ and ξ', we have only at hand the two properties

$$f(t,x,\xi) \geq 0 \quad \forall t \geq 0, \qquad \text{(minimum principle)}, \tag{15}$$

$$\int_{\mathbb{R}^d \times V} f(t,x,\xi) dx\, d\xi = \int_{\mathbb{R}^d \times V} f_0(x,\xi) dx\, d\xi, \qquad \text{(mass conservation)}. \tag{16}$$

To go further in the linear case and derive L^p estimates on f for $p > 1$ is not so easy. Recently the entropy structure behind such general models which lacks a "detailed balance principle" was

understood by [48] (see also [33]). This involves specific cancellations that hold true for several linear equations arising in biology.

The existence theory for the nonlinear system (12)–(13) was settled in [13] (thus extending a result in [33] in the linear case) and yields the

Theorem 3.1 *In dimension $d = 3$, assume that V is bounded, that (14) holds and that $f_0 \in L^\infty(\mathbb{R}^d \times V)$, then there is a unique solution to the system (12)–(13), $f \in C\big([0,\infty); L^1(\mathbb{R}^d \times V)\big)$, moreover we have*

$$0 \le f(t,x,\xi) \le C(t),$$

$$\|\nabla c\|_{L^p(\mathbb{R}^d)} \le C(t), \qquad \frac{d}{d-1} < p \le \infty,$$

$$\|c\|_{L^p(\mathbb{R}^d)} \le C(t), \qquad d < p \le \infty.$$

for some increasing constant $C(t)$.

This result provides global strong solutions and therefore show a fundamental difference with the macroscopic model Patlak/Keller-Segel equation since we have seen that the latter exhibits blow-up. Several extensions of Theorem 3.1 have been obtained (see [36]) and the parabolic equation on c can be treated as well as specific dependency upon ∇c in k.

3.2 Diffusion limit

The classical field of application of the diffusion limits is to derive macroscopic equations like the heat equation from a scattering model. The regime of interest is when the scattering operator dominates transport and this leads to small velocities. Then a rescaling is introduced. Here it is natural to use the small time scale ε arising in (13). The diffusion scaling consists in considering

$$\begin{cases} \frac{\partial}{\partial t} f_\varepsilon(t,x,\xi) + \frac{\xi}{\varepsilon} \cdot \nabla_x f_\varepsilon + \frac{1}{\varepsilon^2} \int_V \left[K_\varepsilon(c_\varepsilon;\xi,\xi') f_\varepsilon(t,x,\xi) - K_\varepsilon(c_\varepsilon;\xi',\xi) f_\varepsilon(t,x,\xi') \right] d\xi' = 0, \\ \\ f_\varepsilon(t=0,x,\xi) = f_0(x,\xi) \ge 0. \end{cases} \tag{17}$$

The notation K_ε has only been used to put in evidence the dependency upon ε in the definition of K in (13).

The problem of studying the limit as ε vanishes is extremely classical and leads to a diffusion equation, see [4] for instance in the linear case. In case of the nonlinear model (12)–(13), it is proved ([13]) that, as $\varepsilon \to 0$,

$$f_\varepsilon(t,x,\xi) \to n(t,x),$$

$$c_\varepsilon(t,x) \to c(t,x), \qquad \nabla c_\varepsilon(t,x) \to \nabla c(t,x),$$

and that the Keller-Segel model holds in the limit

$$\begin{cases} \frac{\partial}{\partial t} n(t,x) + \operatorname{div}(\chi n \nabla c) &= \operatorname{div}(D \nabla n), \quad t \geq 0,\ x \in \mathbb{R}^d, \\ \\ -\Delta c &= n, \end{cases}$$

with transport coeficients given by

$$D(t,x) = \frac{1}{3|V|(\alpha_+ + \alpha_-)\psi(c)} \int_V |\xi|^2 \, d\xi, \qquad \chi(c) = \frac{\psi'(c)}{3\psi(c)} \int_V |\xi|^2 \, d\xi.$$

(in the case $k_+ = \alpha_+ \psi(c)$, $k_- = \alpha_- \psi(c)$).

This result expresses an interesting effect. The diffusion $D(c)$ only arises from the symmetric part of the turning kernel K (at zeroth order), while the drift (and thus the sensitivity $\chi(c)$) arises from the antisymmetric part at first order in ε. In other word the memory effect is fundamental to obtain the observed collective movement of cells. Notice also that drift terms in diffusion equations have been also considered in Degond *et al* [19, 52].

3.3 Hydrodynamic limit

The mere scattering model (12)–(13) does not allow to derive a correct hydrodynamical limit. Indeed local interactions (in the spirit of Boltzmann's binary collision operator) are needed for such a derivation. Such local interactions are not shown in the literature but several indications that they might hold are presently tested based on biochemical investigations. This pushed [24] to postulate a variant of the scattering equation where additionally to the chemattraction some local operator is introduced, thus arriving at a BGK type model. Those models have the advantage to avoid the physical description of the interactions since they only require to known the equilibrium state

$$\frac{n}{\vartheta^{d/2}(n)} F\left(\frac{\xi - u}{\vartheta^{1/2}(n)}\right),$$

where we use $V = \mathbb{R}^d$ because galilean invariance is fundamental in this approach. In order to fullfill basic conservation laws (number of cells and momentum) one assumes that

$$\int_{\mathbb{R}^d} F(\eta)\, d\eta = 1, \quad i.e. \quad \int_{\mathbb{R}^d} F\big(\frac{\xi - u}{\vartheta^{1/2}(n)}\big) d\xi = n,$$

$$\int_{\mathbb{R}^d} \eta F(\eta)\, d\eta = 0, \quad i.e. \quad \int_{\mathbb{R}^d} \xi F\big(\frac{\xi - u}{\vartheta^{1/2}(n)}\big) d\xi = nu.$$

We also need macroscopic notations

$$n_\varepsilon = \int_{\mathbb{R}^d} f_\varepsilon(t,x,\xi) d\xi, \qquad n_\varepsilon u_\varepsilon = \int_{\mathbb{R}^d} \xi f_\varepsilon(t,x,\xi) d\xi,$$

the quantity $u_\varepsilon(t,x)$ is therefore the average (bulk) velocity of the cells at time t and point x.

With these notations, the model proposed in [24] reads

$$\begin{array}{l} \frac{\partial}{\partial t} f_\varepsilon(t,x,\xi) + \xi \cdot \nabla_x f_\varepsilon \quad + \int_{\mathbb{R}^d} K_1(v,v',c) \cdot \nabla c\, f(v')\, dv' - \int_{\mathbb{R}^d} K_1(v',v,c) \cdot \nabla c\, dv'\, f(v). \\ \qquad\qquad + \frac{1}{\varepsilon}\big[f_\varepsilon - \frac{n}{\vartheta^{d/2}(n)} F\big(\frac{\xi - u}{\vartheta^{1/2}(n)}\big)\big] = 0. \end{array} \tag{18}$$

The scattering term has been modified to take into account only the antisymmetric part of K in (12) because the main collision operator (zeroth order part of K) has been replaced but the mere relaxation to an equilibrium F. The motivation behind this is that scattering models only describe interactions with an external medium (and thus is a linear operator). Here we wish to model local self interactions of cells and this requires a nonlinear operator. Finally, we have used a hyperbolic scale for the rescaling of (12) rather than a diffusion scale as was done in Section 3.2.

In the so-called hydrodynamic limit, i.e., $\varepsilon \to 0$ in (18), we then obtain the following model for the cell movements

$$\left\{ \begin{array}{l} \dfrac{\partial n}{\partial t} + \mathrm{div}(n\ u) = 0, \\ \\ \dfrac{\partial (nu)}{\partial t} + \mathrm{div}(n\, u \otimes u + n\vartheta(n) p) = n\, \vartheta^{(d+1)/2}(n)\ \chi(n,u,c) \nabla c, \end{array} \right. \tag{19}$$

still coupled with the concentration equation $-\Delta c = n$ (or whatever has been supposed for the production of c). The matrix χ is given by

$$\chi(n,u,S) = \int_{V \times V} (v - v') \otimes K_1(u + \vartheta^{1/2} v, u + \vartheta^{1/2} v', S) F(v')\, dv'\, dv.$$

This hyperbolic system has the same nature as that proposed in Section 3 for initiation of angiogenesis. It is therefore compatible with the idea that blood vessels formation is related with local interactions of cells at odds with the Keller-Segel model that describes long range interactions only. We refer to [24] for more details and variant models.

4 Angiogenesis

We consider here another kind of chemotaxis model (although we refer to it as the *angiogenesis* system) that has been much less studied than system (1), except in one space dimension. It is again a parabolic equation for the evolution of the density (of cells, or of new capillary vessels)

n coupled with a degenerate equation on the chemoattractant c and is written as the system

$$\begin{cases} \frac{\partial}{\partial t} n = \Delta n - \nabla \cdot [n\chi(c)\nabla c], \quad t > 0,\ x \in \mathbb{R}^d, \\ \\ \frac{\partial}{\partial t} c = -c^m\, n, \quad t > 0,\ x \in \mathbb{R}^d, \\ \\ n(0,x) = n_0(x) \geq 0, \qquad c(0,x) = c_0(x) \geq 0, \qquad x \in \mathbb{R}^d. \end{cases} \tag{20}$$

where m is a positive parameter ($m \geq 1$ in our results). In this case, the diffusion coefficient of the density n is still constant while the sensitivity function $\chi(c)$ is a given positive function on $\mathbb{R}_+$, generally chosen as a decreasing function since sensitivity is lower for higher concentrations of the chemical because of saturation effects. In particular, constant χ, $\chi(c) = c^{-\alpha}$, $0 < \alpha < 1$, and $\chi(c) = \frac{\beta}{\alpha+\beta c}$ with $\alpha, \beta > 0$, are allowed in the results presented below. The equation on c is just an ordinary differential equation, expressing the consumption of the chemical. Indeed, it is now clear that the asymptotic behavior of n depends strongly on the coupling effects of the dynamics of c and the chemotactic sensitivity $\chi(c)$ and that is the reason why systems of type (20) have been analyzed in [42], [53], [57], [58], [65]. Moreover, the omition of the diffusion of the chemical can be justified whenever the corresponding diffusion coefficient is small compared to the motility of the species of density n.

One more reason to consider system (20) is that it arises also in modeling the initiation of *angiogenesis*, a kind of chemotaxis process that occurs for example in the tumor growth ([14],[15], [16], [25], [44]). More specifically, angiogenesis is the formation of new capillary vessels from a pre-existing vascular network. The density n is the density of the new endothelial cells which form the lining of the different type of blood vessels. In the case of tumor growth, the chemical inducing the chemotactic movement of the endothelial cells toward the tumor is spread out by the tumor itself, in order to make up its own capillary network and to supply itself with the nourishment necessary for its development.

4.1 Energy structure

When considering system (20) the situation differs from the Patlak/Keller-Segel system for chemotaxis (1), mainly because it comes with an energy structure such that

$$\tfrac{d}{dt}\mathcal{E}(t) \leq -\int_{\mathbb{R}^d} n\Big[|\nabla \ln(n)|^2 + \mu c^{m-1}|\nabla\Phi(c)|^2\Big]dx \leq 0\ , \tag{21}$$

where

$$\mathcal{E}(t) := \int_{R^d} [\frac{1}{2}|\nabla\Phi(c)|^2 + n\ln(n)]dx$$

and Φ and χ satisfy

$$\Phi'(c) = \sqrt{\frac{\chi}{c^m}}, \qquad \mu := \frac{1}{2}\inf_{c\geq 0}\{\frac{c\,\chi'}{\chi} + m\} > 0. \tag{22}$$

For initial data with finite energy and $m \geq 1$, (21) allows to prove the existence of weak solutions to (20) and the following result was proved in [16],

Theorem 4.1 *(Weak solutions for the angiogenesis system (20)) With the assumptions (22), $m \geq 1$ and $n_0 \in L^1 \cap L^\infty(\mathbb{R}^d)$, $c_0 \in L^\infty(\mathbb{R}^d)$, $n_0 \ln(1+|x|) \in L^1(\mathbb{R}^d)$ and $\mathcal{E}^0 < \infty$, there exists a weak solution to (20), such that $n \in C\Big(\mathbb{R}^+; L^1(\mathbb{R}^d)\Big)$, $c \in L^\infty(\mathbb{R}^+ \times \mathbb{R}^d)$ and*

$$n(t,x) \geq 0, \qquad \int_{\mathbb{R}^d} n(t,x)dx = \int_{\mathbb{R}^d} n_0(x)dx, \qquad 0 \leq c(t,x) \leq \|c_0\|_{L^\infty(\mathbb{R}^d)},$$

$$\int_{\mathbb{R}^d} |\nabla \Phi(c)|^2 \leq C(1+t)\ , \qquad \int_{\mathbb{R}^d} n(t,x)\ \big|\ln(1+|x|)\big|\ dx \leq C(1+t).$$

The main issue in proving this result comes from the definition of the nonlinear drift term $n\chi(c)\nabla c$. Thanks to the integrability provided by the energy dissipation in (21), we have

$$\int_0^\infty \int_{\mathbb{R}^d} n\ c^{m-1} |\nabla \Phi(c)|^2 < \infty.$$

And the drift term can also be written as

$$n\chi(c)\nabla c = n\sqrt{c\ \chi(c)}\ c^{\frac{m-1}{2}}\ \nabla \Phi(c).$$

And thus it is well defined in L^1, because

$$c\ \chi(c) \in L^\infty(\mathbb{R}^+ \times \mathbb{R}^d), \quad \sqrt{n} c^{(m-1)/2}\ \nabla \Phi(c) \in L^2(\mathbb{R}^+ \times \mathbb{R}^d)$$

and, by mass conservation, $\sqrt{n} \in L^\infty(\mathbb{R}^+; L^2(\mathbb{R}^d))$. The proof of the theorem therefore relies on finding an approximation scheme that preserves these a priori bounds. We refer to [16, 17] for this and for additional results.

4.2 L^p integrability for small data.

The energy exhibited in the previous subsection also provides equiintegrability for n, therefore solutions cannot exhibit concentrations, in opposition to Patlak/Keller-Segel model (1). But the question of propagation of smoothness of the solutions is still largely open and seems more difficult than for (1) by lack of regularizing effect on c.

Here we mention the following results in this direction that were obtained in [17]

Theorem 4.2 *(Strong solutions for the angiogenesis system (20)). Assume $d \geq 2$, $m \geq 1$ and χ a positive say continuous fonction on $\mathbb{R}^+$ (more generally χ can exhibit some singularities).*

Consider some $n_0 \in L^1(\mathbb{R}^d)$ *and* $c_0 \in L^\infty(\mathbb{R}^d)$ *such that* $n_0 \geq 0$ *and* $c_0 \geq 0$. *There exists a constant* $K_0(\chi, d, \|c_0\|_{L^\infty(\mathbb{R}^d)})$ *such that if* $\|n_0\|_{L^{\frac{d}{2}}(\mathbb{R}^d)} \leq K_0$, *then system (20) has a global (in time) weak solution* (n, c) *such that* $n \in L^\infty(\mathbb{R}^+, L^1 \cap L^{\frac{d}{2}}(\mathbb{R}^d))$, $c \in L^\infty(\mathbb{R}^+ \times \mathbb{R}^d)$ *and for any fixed* $\max\{1; \frac{d}{2} - 1\} \leq p^* < \infty$,

$$\|n(t)\|_{L^p(\mathbb{R}^d)} \leq C(t, K_0, p^*, \|n_0\|_{L^p(\mathbb{R}^d)}), \qquad \forall\ \max\{1; \frac{d}{2} - 1\} \leq p \leq p^*.$$

The derivation of an L^∞ bound for $n(t)$ is an open question as well as the relaxation of the smallness condition in dimension $d \geq 3$. However in two space dimensions we have the following result (still obtained in [17])

Theorem 4.3 *(Global* L^p *bound for the angiogenesis system (20) in two dimensions). Assume* $d = 2$, $m \geq 1$, χ *a positive say continuous fonction on* $\mathbb{R}^+$ *(more generally* χ *can be such that* K_1 *in the proof is finite) and* $\mu > 0$ *in (21). Consider some nonnegative initial data* (n_0, c_0) *with finite energy i.e.* $\mathcal{E}(0) < \infty$, *such that* $\ln(1 + |x|)n_0 \in L^1(\mathbb{R}^d)$ *and* $c_0 \in L^\infty(\mathbb{R}^d)$. *Then, there is a weak solution* (n, c) *of system (20) such that for any fixed* $1 \leq p^* < \infty$,

$$\|n(t)\|_{L^p(\mathbb{R}^d)} \leq C(t, p^*, \|n_0\|_{L^p(\mathbb{R}^d)}), \qquad \forall\ 1 \leq p \leq p^*\ .$$

We refer to [17] for the proof of these results, but we would like to mention the main tool to obtain L^p bounds. They rely on the equation on the ratio $\frac{n}{\phi(c)}$, where ϕ is defined by

$$\phi'(c) = \phi(c)\chi(c) \qquad c > 0, \qquad \phi(0) = 1.$$

One can directly derive from (20) the equation under a "symmetric form"

$$\frac{\partial}{\partial t}\left(\frac{n}{\phi(c)}\right) = \frac{1}{\phi(c)}\nabla \cdot \left[\phi(c)\nabla\left(\frac{n}{\phi(c)}\right)\right] + \left(\frac{n}{\phi(c)}\right)^2 \phi(c)\chi(c)\ c^m. \tag{23}$$

Actually, the change of variable $n \to \frac{n}{\phi}$ is the natural change of variable that puts the equation on n in divergence form and it is used by many authors, especially to prove the existence of classical solutions (see [25] for instance). Moreover, in terms of reinforced random walk, the function ϕ is the transition probability rate of n ([53], [44]), in terms of numerics such changes of variables are also fundamental to capture singularities ([47]).

From this form one can deduce the inequality

$$\frac{d}{dt}\int_{\mathbb{R}^d}\left(\frac{n}{\phi(c)}\right)^p \phi(c) = -4\frac{p-1}{p}\int_{\mathbb{R}^d}\phi(c)\left|\nabla\left(\frac{n}{\phi(c)}\right)^{p/2}\right|^2 + (p-1)\int_{\mathbb{R}^d}\phi^2(c)\chi(c)c^m\left(\frac{n}{\phi(c)}\right)^{p+1} \tag{24}$$

for all $1 \leq p \leq \infty$. It allows us to conclude the result using Gagliardo-Nirenberg-Sobolev inequality (see [23]) as in the chemotaxis case ([37]).

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