Singular solutions of partial differential equations modelling chemotactic aggregation

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Abstract. This paper reviews several mathematical results for partial differential equations modelling chemotaxis. In particular, questions like singularity formation for the Keller–Segel model and continuation of the solutions beyond the blow-up time will be discussed. Some of the open problems that remain for the Keller–Segel model as well as some new mathematical problems arising in the study of chemotaxis problems will be discussed.

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1. Introduction

There are several relevant biological phenomena that involve the type of cell interaction that is known as chemotaxis. This word denotes the capability of many cells to react to chemical stimuli and move towards an increasing or decreasing chemical gradient. Chemotaxis plays a relevant role in biological processes like embryogenesis, angiogenesis or others.

A particular biological process that has deserved considerable attention by biologists, mathematicians and physicists is the phenomenon of chemotactic aggregation. Several unicellular organisms, like Dictyostelium discoideum and Myxococcus xanthus under conditions of environmental stress begin a complex cascade of chemical processes having as a major consequence the release away from the cell of a chemical substance that has chemoattractant properties in the cells themselves. As a consequence, cells begin to approach to each other. This yields to the formation of dense cellular aggregates where the cells usually begin a differentiation process and as a final result the formation of a fruiting body containing cell sporae that remain in such dormant state until they find suitable environmental conditions where they can proliferate again. From the biological point of view an appealing feature of these social organisms is that they expend part of their life cycle as unicellular organisms and the other part as multicellular organisms.

The details of the phenomenon of chemotactic aggregation change very much from organism to organism. On the other hand, even during the simplest stages of the

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process it is possible to observe many interesting patterns like spiral waves, cell stream formation and others. Nevertheless, in spite of the complexity of this biological process, some of the main features of the problem are simple enough to motivate several mathematicians to derive models that could amount at least for some of the most important features of the phenomenon.

2. The Keller–Segel model

The earliest attempt to describe chemotactic aggregation using a system of partial differential equations was the Keller–Segel model that was introduced in [33]. The authors of this model introduced a continuum description of the aggregation process for Dictyostelium discoideum (from now on Dd) containing some of the biological knowledge that had been gained from the experiments made in previous decades. The book [7] contains a great part of the information available on this biological problem at the time of the formulation of the Keller–Segel model.

In a typical aggregation experiments made with Dd many individual amoebae are distributed in the basement of a Petri dish and covered by a liquid layer. Under suitable conditions the cells begin emitting chemical pulses that trigger the aggregation process.

The Keller–Segel model describes this process assuming that there are only two relevant variables in the problem, namely the cell concentration n and the chemical concentration of the substance that propagates the signals between the cells that will be denoted as c. Both concentrations are understood to be measured for unit of surface in the basis of the Petri dish. The chemical substance propagating the chemical signals in the case of Dd was identified in the late 60s and it turns out to be the chemical known as cAMP. The functions are assumed to be during the aggregation process functions of the position in the Petri dish x as well as the time t, i.e.,

$$n = n(x, t),$$
$$c = c(x, t).$$

The validity of this description requires to measure the functions n and c in a length scale larger than the typical distance between cells that is of the order of some hundreds of microns. Under this assumption it is natural to write the following continuity equations for the densities n and c:

$$\frac{\partial n}{\partial t} + \nabla \cdot (j_n) = 0, \tag{1}$$
$$\frac{\partial c}{\partial t} + \nabla \cdot (j_c) = f(n, c), \tag{2}$$

where j_n, j_c are the cell fluxes and chemical fluxes respectively. The function $f(n, c)$ describes the production of chemical by the cells as well as the decay of the concentration of c due to its interaction with the substances placed in the extracellular matrix.

It is implicitly assumed in (1) that processes like mitosis or cell death do not play any relevant role. This assumption is reasonable because such processes take place in a time scale much longer than the one related to chemotactic aggregation.

In order to complete model it remains to prescribe the functions j_n, j_c, $f(n, c)$. Concerning the chemical fluxes the most natural assumption is to assume that the chemical diffuses according to the classical Fick's law:

$$j_c = -D_c \nabla c \tag{3}$$

where D_c is the diffusion coefficient for the chemical.

On the other hand, the Keller–Segel model assumes that the cell motions are the superposition of two effects, namely a random motility and a drift towards the regions having a larger concentration of chemical due to the effect of the chemotaxis. In the case of amoeba-like cells like Dd it is experimentally observed that the cells, that move by means of the expansion and retraction of pseudopods, have some kind of random component in their motion resembling, in a suitable length scale the motion of a brownian particle. On the other hand, it is experimentally observed that the drifting motion of the cells is, on average, proportional to the gradient of chemical concentration. These features make reasonable to assume that the random motility follows the standard Fick's law for diffusive processes and that the drifting motion yields an additional cell flux proportional to $n\nabla c$. The closure relation for the cell flux then becomes

$$j_n = -D_n \nabla n + \chi n \nabla c, \tag{4}$$

where D_n is the diffusion coefficient for the cells and χ will be termed as chemotactic sensitivity.

Finally, in order to determine the function $f(n, c)$ there are two features that it is important to take into account. The molecules of cAMP degrade with a characteristic life-time, due to their interaction with the molecules of the extracellular membrane. On the other hand, the production of chemical for unit of area is proportional to the cell concentration n if the chemical production of each cell it is assumed to be approximately independent from the others. Under these assumptions the formula for $f(n, c)$ would be

$$f(n, c) = \alpha n - \beta c \tag{5}$$

with $\alpha > 0$, $\beta > 0$.

Combining the equations (1)–(5) the following system of equations follows:

$$\frac{\partial n}{\partial t} = D_n \Delta n - \chi \nabla \cdot (n \nabla c), \tag{6}$$

$$\frac{\partial c}{\partial t} = D_c \Delta c + \alpha n - \beta c. \tag{7}$$

The system (6), (7) is a particular case of classical Keller–Segel model that was introduced in [33]. Using a suitable set of dimensionless variables, it is possible to

reduce (6), (7) to the analysis of the particular case:

$$\frac{\partial n}{\partial t} = \Delta n - \chi \nabla \cdot (n \nabla c), \tag{8}$$

$$\frac{\partial c}{\partial t} = L \Delta c + n - \beta c. \tag{9}$$

This system is usually solved in a domain $\Omega \subset I\!R^2$ for positive times $t > 0$ with suitable initial data $n(x, 0) = n_0(x) \geq 0, c(x, 0) = c_0(x) \geq 0$ and zero flux boundary conditions:

$$\frac{\partial n}{\partial \nu} - \chi n \frac{\partial c}{\partial \nu} = 0, \quad \frac{\partial c}{\partial \nu} = 0, \quad x \in \partial\Omega, \quad t > 0 \tag{10}$$

where ν is the outer normal at the boundary $\partial\Omega$. Notice that, under these boundary conditions, the total number of cells $\int_\Omega n_0(x)\, dx \equiv N_0$ is conserved during the evolution of the system. In several of the discussions below it will be assumed that N_0 is a real number of order one, something that at a first glance might look strange for a number that denotes the rather large number of cells contained in Ω. However, this is due only to the fact that in the formulation (8), (9) dimensionless variables have been used. A number N_0 of order one for the solutions of the system (8), (9) is in reality a huge number of cells if the dimensional form of the equations (6), (7) is used.

The problem (8), (9) turned out to be a source of interesting mathematical problems. From the mathematical point of view the most interesting feature of the system (8), (9) is the nonlinear term $\chi \nabla \cdot (n \nabla c)$. If the chemotactic interaction between cells is chemoattractive, i.e. if $\chi > 0$, this term yields singularity formation in finite time. The peculiar form of this nonlinear term is a rather common feature of the chemotaxis models. The study of the consequences of this term in the dynamics of the solutions of (8), (9) has led to the development of several mathematical tools by different authors.

3. Singularity formation in chemotaxis models

Childress suggested that the solutions of (6), (7) could generate singularities and that the process of chemotactic aggregation could be thought as the formation of a singularity (cf. [13]). The first rigorous proof of blow-up in a chemotaxis model was obtained by Jäger and Luckhaus in [31]. These authors took advantage of the fact that the diffusion coefficient for the chemical D_c is much larger than the diffusion coefficient D_n for the cells. In that particular limit the system of equations (8), (9) with nonzero flux boundary conditions can be reduced to the simpler problem

$$\frac{\partial n}{\partial t} = \Delta n - \chi \nabla \cdot (n \nabla c), \tag{11}$$

$$0 = L \Delta c + n - \bar{n}, \tag{12}$$

where $\bar{n} = \frac{1}{|\Omega|} \int_\Omega n\, dx$. Notice that in order to solve (11), (12) only the initial data $n(x, 0) = n_0(x)$ must be prescribed.

Jäger and Luckhaus obtained two basic results for the solutions of (11), (12) that established the basic framework for many of the subsequent researches in this type of problems. They proved that the solutions of (11), (12) with N_0 small are globally bounded. On the other hand, [31] contains also a large class of radial initial data $n_0(x)$ for which the corresponding solution of (11), (12) becomes unbounded in finite time, or using the standard terminology used by the partial differential community, the solutions of (11), (12) blow up in finite time for suitable initial data.

Notice that the global existence result in [31] implies that there exists a threshold for the number of cells N_0, below which the solutions of (11), (12) do not exhibit singularities in finite time. There have been several researches trying to compute the value of such threshold number. In the case of radial solutions, it was proved by Nagai (cf. [37]) that the smallest number of cells needed to have blow up in finite time is $8\pi/\chi$. In nonradial cases the threshold for the mass is $4\pi/\chi$ (cf. [6], [16]).

4. Chemotactic aggregation

The blow up results mentioned in the previous section do not imply that the solutions of the system (11), (12) develop a Dirac mass in a finite time. The onset of such Dirac mass at the time of formation of the singularity $t = T$ seems the most natural outcome, as the previous discussion concerning the existence of a threshold for the number of cells needed to create a singularity suggests. However, the derivation of such conclusion is not so obvious. Indeed, a possibility that cannot be excluded in principle is the formation of a singularity where the number of cells contained in a small ball near the point where the singularity appears would oscillate infinitely often without converging to any number. Another possibility that is not easy to rule out in nonradial cases is the existence of a family of balls containing a large fraction of the total number of cells whose diameter decreases to zero as $t \to T^-$ and whose centers move erratically by the domain Ω.

We will denote as chemotactic aggregation the formation of a Dirac mass at a finite time $t = T < \infty$. In [17] was obtained a class of solutions yielding chemotactic aggregation. Moreover, for such a solutions there was a detailed description of the asymptotic behaviour of the solutions near the singularity. These solutions satisfy

$$n(\cdot, t) \rightharpoonup \frac{8\pi}{\chi}\delta(\cdot) + f(\cdot) \quad \text{as } t \to T^-, \tag{13}$$

where

$$f(x) \sim \frac{8e^{-(\gamma+2)}}{|x|^2} e^{-2\sqrt{|\log(|x|)|}}(1 + o(1)) \quad \text{as } |x| \to 0, \tag{14}$$

γ being the classical Euler constant. Moreover:

$$n(x,t) \sim \frac{8}{(T-t)(\varepsilon(|\log(T-t)|))^2} \frac{1}{\left(1 + \frac{|x|^2}{(T-t)(\varepsilon(|\log(T-t)|))^2}\right)^2} \quad \text{as } t \to T^- \tag{15}$$

for $|x| \leq C\sqrt{T-t}\varepsilon(|\log(T-t)|)$, where

$$\varepsilon(\tau) \sim 2e^{-\frac{2+\gamma}{2}} e^{-\sqrt{\frac{\tau}{2}}} \left(1 + O\left(\frac{\log(\tau)}{\sqrt{\tau}}\right)\right) \quad \text{as } \tau \to \infty. \tag{16}$$

It is interesting to point out that these solutions are not self-similar solutions in the sense that such term is usually understood. The most common meaning that it is given to the term self-similar solutions is the one of solutions that are invariant by a group of symmetries, and most often by a group of rescalings. If the term $\overline{n}$ that gives a low order contribution is ignored in the equations (11), (12) the resulting equations are invariant under the rescaling group:

$$x \to \lambda x, \quad t \to \lambda^2 t, \quad n \to \frac{1}{\lambda^2} n, \quad c \to c, \tag{17}$$

where λ is an arbitrary positive number. It can be shown that at least in the radial two dimensional case there are not self-similar solutions of (11), (12), even if the term $\overline{n}$ is neglected (cf. [20]). On the other hand, it is not hard to see that solutions with the asymptotics (15) are not invariant under the rescaling group (17) due to the presence of the terms $e^{-\sqrt{\frac{|\log(T-t)|}{2}}}$ in (16) that are not power laws. More precisely

$$(T-t)^a \ll e^{-\sqrt{\frac{|\log(T-t)|}{2}}} \ll 1 \quad \text{as } t \to T^-$$

for any $a > 0$. In the terminology of applied mathematicians such terms are often called "logarithmic corrections", even if they are not strictly logarithmic functions.

The computation of this logarithmic corrective term is the main technical difficulty solved in [17]. The key idea used in that paper was to derive first an approximation of the solution near the blow-up time using the so-called "matched asymptotic expansions". Such expansions are a heuristic, non fully mathematically rigorous procedure of deriving approximated formulae for the solutions different types of equations that contain large or small parameters. These methods are widely used in many fields applied mathematics, often combined with numerical simulations that provide an independent test of their validity. The basic idea of this method consists in to compute perturbative series for the solutions of the equations under consideration by simpler equations, something that is possible due to the presence of large or small parameters in the problem. However, such approximations of the solutions often lose their validity in some regions of the space because the form of the obtained solutions determines that some of the terms that had been previously ignored become important in some particular areas of the space of parameters. The solutions are then analysed in these specific regions introducing suitable rescalings and changes of variables that are often suggested by the form of the approximate solutions previously computed. The resulting equations can then be also analysed in a perturbative manner and in this way the form of the solutions in such new variables can be obtained too. In order to assert the validity of the obtained formula it remains to check that both obtained approximated

solutions agree in a region of common validity. This agreement is usually termed as "matching".

In the study of (11), (12) the small parameter is the distance between the time variable and the blow-up time, i.e. $(T-t)$. The analysis of the solutions was made decomposing the space of independent variables (x,t) in three different regions, namely:

$$\begin{aligned} &\text{(A)} \quad |x| \ll \sqrt{T-t}, \\ &\text{(B)} \quad |x| \approx \sqrt{T-t}, \\ &\text{(C)} \quad |x| \gg \sqrt{T-t}. \end{aligned}$$

The onset of the parabolic rescaling $\sqrt{T-t}$ it is very natural due to the parabolic character of the system (11), (12). In each of these regions these equations can be approximated to the leading order by a different type of equation whose solution can be obtained in an explicit manner. More precisely, the derived solutions solve a nonlinear ordinary differential equation in the region (A), a linear parabolic equation that reduces to the heat equation in the region (B), and a quasilinear hyperbolic equation in the region (C). The corrective term $e^{-\sqrt{\frac{|\log(T-t)|}{2}}}$ was obtained setting that the width of the region where the aggregating mass is concentrated is an unknown function $\varepsilon(t)$ whose precise form is computed matching the solutions obtained in the regions (A) and (B). Such matching condition provides an integro-differential equation for $\varepsilon(t)$ that allows to compute the "logarithmic correction" $e^{-\sqrt{\frac{|\log(T-t)|}{2}}}$. The details of this formal computation can be found in [18] and also in [45], [46].

The rigorous construction of the solutions whose formal description is given above was made reducing the problem to the one of finding the zeroes of a finite dimensional problem. This was achieved choosing an initial class of initial data depending on a finite number of parameters and showing that the choice of such parameters that solves a suitable equation provide some initial data whose corresponding solution blows up at the time $t = T$ with the asymptotic behaviour computed in an heuristic manner before. The details of the argument can be found in [17]. A crucial point in the argument is to use the formal asymptotics of the solutions as a guide to derive suitable "a priori" estimates for the solutions of (11), (12). This argument have been used in the construction of solutions with a prescribed blow-up behaviour in many other problems (cf. for instance [3], [10]).

All the previous analysis was made for the simplified version of the Keller–Segel model introduced by Jäger and Luckhaus. Nevertheless, the same results can be obtained for the whole Keller–Segel system (8), (9) (cf. [22]). Some technical difficulties arise due to the fact that for radial solutions it is possible to reduce (11), (12) to the study of a scalar equation. Such reduction is not possible in the case of the whole system (8), (9).

It is worth mentioning that this study provides a simple formula, originally derived in [13], relating the different parameters from the Keller–Segel model and the number

of aggregating cells. Indeed, rewriting (13) with the original dimensional variables it follows that the number of cells aggregating for the solutions of (8), (9) is

$$N_{\text{aggr.cells}} = \frac{8\pi D_c D_n}{\alpha \chi}.$$

5. Some analogies between chemotactic aggregation and the melting of ice balls

It is interesting to remark that the same type of "logarithmic correction" that has been described above (cf. (15)) appears in other problem that at a first glance looks rather different from the problem of chemotactic aggregation. Suppose that one tries to describe the size of a melting ice cylinder immersed in a big reservoir of water. One usual way of describing such process is by means of the so-called Stefan problem. In the resulting model it is assumed that the heat transfer in both the ice and the water follows the classical Fourier's law. Therefore, in both phases the temperature satisfies a heat equation. On the other hand, in the interface separating both phases the temperature takes a constant value that is the melting temperature of the water at the value of the pressure that the experiment is made. This assumption is not completely true if surface tension effects are taken into account, but these effects are relevant only for very small radii of the cylinder and therefore they can be ignored during most of the process. Moreover, we will assume also that the heat conductivity of the ice is much higher than the one of the ice, since this makes the problem easier to analyse and it does not change the final conclusions. A final feature that must be incorporated in the model is the fact that the melting of a given volume of ice requires to provide to it the amount of energy known as latent heat. The mathematical formulation of this condition provides an equation for the motion of the interface separating the ice and the liquid water. The resulting model, in dimensionless units and in the radial case is the following:

$$\frac{\partial \theta}{\partial t} = \Delta \theta \quad x \in I R^2, \quad |x| > R(t), \quad t > 0, \tag{18}$$

$$\theta = \theta_m, \quad |x| = R(t), \quad t > 0, \tag{19}$$

$$\dot{R}(t) = -\frac{\partial \theta}{\partial r}(R(t), t), \tag{20}$$

where $\theta(x, t)$ is the temperature of the liquid water. In absence of undercooled water we must assume that $\theta(x, 0) = \theta_0(x) \geq 0$.

This problem has classical solutions for a large class of initial data $\theta_0(x)$. Let us suppose also that $\theta_0(x) \to \theta_\infty > 0$ as $|x| \to \infty$. It might be seen that for such data the radius of the ice ball $R(t)$ decreases and eventually disappears in finite time. At such time a singularity arises for this free boundary problem.

As in the case of the Keller–Segel model there are not self-similar solutions describing this singularity. A description of this singularity using formal asymptotic

expansions was obtained in [39]. It turns out that the radius of such balls near the time $t = T$ for the vanishing of the spheres is given by:

$$R(t) \sim C\sqrt{T-t}e^{-\frac{\sqrt{2}}{2}|\log(T-t)|^{\frac{1}{2}}} \quad \text{as } t \to T$$

Asymptotic expansions for the solutions of the same problem in the non radial case were obtained in [19]. For these solutions the interface behaves asymptotically as an ellipsoidal cylinder near the time of the vanishing of the ice.

6. Some results for the Jäger–Luckhaus model in three dimensions

There are biological situations where it makes sense to analyse the three dimensional version of the Keller–Segel. A relevant example is the study of the aggregates of the bacteria E.coli.

From the mathematical point of view the type of singularities arising for the Keller–Segel model are very different in the three dimensional case and in the two dimensional case. It is possible to construct singular solutions blowing up in a line, just adding an additional dimension to the solution behaving as in (13)–(15). On the other hand, in three dimensions there exist radial self-similar solutions that yield singularities in a finite time without mass aggregation. On the other hand in three dimensions there exist a mechanism of chemotactic aggregation that is rather different from the one previously described for the two dimensional case. Such aggregation mechanism is driven by the first order terms in (11), except for a small boundary layer where the diffusive term Δc becomes essential. For these solutions the mass is concentrated as $t \to T^-$ in a layer placed at a distance of order $(T-t)^{1/3}$. The detailed description of such solutions can be found in [9], [20], [21].

7. On the continuation of the solutions beyond the blow-up Time

In the last decade several models have been suggested in order to describe the effects that could stop the aggregation process in different organisms. Several biochemical processes that could stop the aggregation of E. coli if the cell density reach high values were described in [8]. Another partial differential equations that stop cell aggregation were considered in [25], [46], [47]). It was assumed in [25] that the cell velocity vanishes for high cell concentrations. In [46] was assumed also that the cell velocity decreases also with the velocity for high values of the concentration. More precisely, the model studied in [46], [47] was the following:

$$\frac{\partial n}{\partial t} = \Delta n - \nabla \cdot (g_\varepsilon(n)\nabla c), \tag{21}$$

$$0 = \Delta c + n, \tag{22}$$

where

$$g_\varepsilon(n) = \frac{1}{\varepsilon} Q(\varepsilon n), \quad \varepsilon > 0, \tag{23}$$

and Q is an increasing function satisfying

$$Q(s) \sim s - \alpha s^2 \quad \text{as } s \to 0,$$
$$Q(s) \sim L > 0 \quad \text{as } s \to \infty.$$

The solutions of (23) are globally bounded for each $\varepsilon > 0$. On the other hand, the model (21)–(23) converges formally as $\varepsilon \to 0$ to the model

$$\frac{\partial n}{\partial t} = \Delta n - \nabla \cdot (n \nabla c), \tag{24}$$
$$0 = \Delta c + n, \tag{25}$$

that in two dimensions might yield chemotactic aggregation in finite time. It would be then natural try to understand the asymptotics of the solutions of (21)–(23) for arbitrary times as $\varepsilon \to 0$. Notice that the number of cells $\int_\Omega n\, dx$ remains constant for the solutions of (21)–(23). Therefore, even if the solutions of (21)–(23) become unbounded, the solutions of these equations should not become unbounded everywhere. The study of the dynamics of the solutions of (21)–(23) as $\varepsilon \to 0$ was made in [46], [47] using formal matched asymptotic expansions. The conclusion of such analysis was that it is possible to obtain asymptotic expansions valid in all the regions of the space for some solutions of (21)–(23) that behave asymptotically as $\varepsilon \to 0$ as

$$n(x,t) = \sum_{i=1}^{N} M_i(t) \delta(x - x_i(t)) + n_{\text{reg}}(x,t),$$

where $n_{\text{reg}}(x,t)$ is a bounded function. Moreover, the functions $M_i(t), x_i(t), n_{\text{reg}}(x,t)$ satisfy the following problem:

$$\frac{\partial n_{\text{reg}}}{\partial t} = \Delta n_{\text{reg}} + \sum_{j=1}^{N} \frac{M_j(t)}{2\pi} \frac{(x - x_j(t))}{|x - x_j(t)|^2} \cdot \nabla n_{\text{reg}} - \nabla (n_{\text{reg}} \nabla c_{\text{reg}}), \tag{26}$$

$$c_{\text{reg}} = -\frac{1}{2\pi} \int_{I R^2} \log(|x - y|) n_{\text{reg}}(y,t)\, dy, \tag{27}$$

$$\dot{x}_i(t) = \Gamma(M_i(t)) A_i(t), \quad i = 1, \ldots, N, \tag{28}$$

$$A_i(t) = -\sum_{j=1}^{N} \frac{M_j(t)}{2\pi} \frac{(x - x_j(t))}{|x - x_j(t)|^2} + \nabla c_{\text{reg}}(x_i(t), t), \tag{29}$$

$$\frac{dM_i(t)}{dt} = c_{\text{reg}}(x_i(t), t) M_i(t), \quad i = 1, \ldots, N, \tag{30}$$

where $\Gamma(\cdot)$ is a positive function defined for values of its argument larger than 8π.

The problem (26)–(30) can be considered as a moving boundary problem. These equations indicate that there exist solutions of (21)–(23) having some concentration regions where the cells accumulate and that interact between themselves and with the cells away from the aggregates.

The solvability of the problem (26)–(30) is not entirely obvious due to the motion of the points $x_i(t)$ as well as the presence of the terms $\frac{M_j(t)}{2\pi}\frac{(x-x_j(t))}{|x-x_j(t)|^2}\cdot\nabla n_{\text{reg}}$ in (26). The local well-posedness of (26)–(30) in Hölder spaces has been proved in [48].

In [47] has been obtained using matched asymptotic expansions a description of the way in which the saturation of the chemotactic attraction for high values of the concentration stops the aggregation process and yields the formation of a concentration region for the density.

8. Some open questions for the Keller–Segel model

In the last two decades there have been several relevant advances in the understanding of the Keller–Segel model. There are, however, still many unsolved questions that could pose challenging analysis problems. I will describe shortly some of the ones that in my opinion are more relevant.

Probably, the most important problem that remains in order to understand completely the blow-up for the Keller–Segel model is to show that for arbitrary two dimensional domains Ω and arbitrary initial data, all the blowing up solutions of (8), (9), (or the simplified version (11), (12)) converge locally near the blow-up to a Dirac mass.

A more ambitious version of this problem would be to show that all the solutions that blow up in finite time behave near the singularity as indicated in (13)–(15). Experts in blow-up would immediately argue here that, since the solutions with large amount of cells blow up and the solutions with a small number of cells do not blow-up, there exists a transition regime between the one associated to global existence and the one associated to blow-up in finite time. I think that the most spread opinion among the mathematicians working in the Keller–Segel model about this point is that the transition regime corresponds precisely to the solutions having a total number of cells of $8\pi/\chi$, and that this critical amount of cells should lead to the type of behaviour that it is usually known as "blow-up in infinity time" (cf. for instance [29]). This would mean that the solutions would be globally defined but the solutions of (8), (9), (or (11), (12)) should eventually approach to a Dirac mass as $t \to \infty$. The blow-up mechanism (13)–(15) might be obtained with any number of cells strictly greater $8\pi/\chi$ cells. For the critical number of cells, the description of the long time asymptotics as $t \to \infty$ has not been obtained even at the formal level.

A problem that could shed some light in the question of finding a complete classification of the singular behaviours for the Keller–Segel model is the study of the stability of the solutions of (11), (12) with the behaviour (13)–(15). In principle this

problem looks more amenable to analysis because it reduces to the study of a local problem. This stability study for these particular solutions has been made in [45] using formal computations linearizing formally around the solution obtained in [17]. This kind of linearization is customarily made by applied mathematicians working in problems that involve blow-up phenomena. Nevertheless, the study of such stability is more involved that in many of the blow-up problems so far considered due to the involved structure of boundary layers that is needed to describe the solution behaving as in (13)–(15). To prove in a fully rigorous manner that the solutions of (11), (12) with the behaviour (13)–(15) would require, most likely, to make fully rigorous the arguments in [45], something that would require to study in detail several parabolic problems described in [45]. A similar analysis challenge is the one posed by the proof in a fully rigorous manner of the results concerning "continuation beyond blow-up" mentioned in Section 7.

There is a huge wealth of problems associated to the study of the singularities for the Keller–Segel or the Jäger–Luckhaus problems in three spatial dimensions. As indicated in Section 6 in this case there are many more singular behaviours, whence a complete classification of blowing up solutions seems much harder. It is interesting to point out that the solutions of the Jäger–Luckhaus model blowing up in a line that are obtained adding an additional dimension to the solutions blowing up as in (13)–(15) seem to be unstable under nonconstant perturbations along that line, as the formal computations in [5] suggest.

Let us finally remark that there seem to be several analogies between the Keller–Segel model (or the Jäger–Luckhaus approximation) and the classical Stefan problem. This is particularly clear in the results mentioned in Section 5, but there are other points in the mathematical analysis of both problems where these analogies can be seen. It is not unlikely that the Stefan problem could be derived, at least formally, as a suitable asymptotic limit of the Keller–Segel model, in the same form as the Stefan problem and many other related free boundary problems can be derived from the so-called phase field limits. If the connection between these problems is found, it would be perhaps possible to explain the analogies found in Section 5. It would probably be possible also to use the large amount of information available for the Stefan problem in order to describe the behaviour of some class of initial data for the Keller–Segel model.

In this paper the description and stability of the steady states solutions of the Keller–Segel model has not been considered. There are several results concerning the structure of the steady states of this problem (cf. [40]). A detailed review of the different mathematical results available in the literature for the stationary and the evolutionary Keller–Segel model can be found in [27], [28].

9. Beyond the Keller–Segel model

All the previous discussion has focused exclusively in the study of the Keller–Segel model. As it was explained in Section 2 the Keller–Segel model is a continuous approximation of a rather complicated aggregation process. In recent decades the study of the process of chemotactic aggregation has developed in many more directions than in the study of this specific model. In this section, I will describe briefly some of this researches to illustrate the type of mathematical problems that have arisen in the study of this biological process.

One of the research directions that has deserved great attention and that was originated by the papers [1], [15], [38] is the study of kinetic or stochastic models describing the cell dynamics.

The idea underlying the stochastic models is to describe the dynamics of each individual cell using a stochastic differential equation. The information contained in the differential equation is that cells move in a rectilinear manner at constant speed during some time intervals. At the end of such intervals the direction of the velocity changes in a random manner. In order to obtain a chemotactic dynamics the models introduce some bias towards the regions having greater chemical concentration, something that can be made in several different ways. One possibility is to assume that the rate of change in the direction of motion is a function on the change of concentration of chemical. Another different possibility is to assume that the new direction of motion is biased towards the direction of largest chemical concentration. The first possibility is motivated by the well studied motion mechanism of E. coli that takes place by means of different types of discrete jumps in the space known as "runs" and "tumbles" (cf. the description in [4]). The second one can be thought as a reasonable approximation to the dynamics of amoebae-like cells like Dd. In order to avoid introducing in this model direct cell-cell interactions it must be assumed that the mean free path between jumps is much smaller than the cell distance. If it is assumed, in addition, that the characteristic distance for the chemical variation are much larger than the cell distance it might be seen that the particle distributions have small correlations and therefore they might be approximated as the product of one-particle distributions in the space of velocities and positions having the form $f(x, v, t)$. In all the mentioned asymptotic limits it is possible to approximate the evolution equation for the one-particle distribution function by means of the kinetic equation

$$f_t + v\nabla_x f = \int [T(x, v, w) f(x, w, t) - T(x, w, v) f(x, v, t)]\, dw. \tag{31}$$

The transition kernel $T(x, w, v)$ contains the bias towards higher concentrations, and therefore it depends in general in quantities like the chemical concentration, of its time or space derivatives.

In recent years there have been obtained several results proving that in some suitable asymptotic limits the solutions of (31) converge to the solutions of the Keller–Segel system (cf. [12], [23], [24], [30]). Readers familiar with gas-dynamics would

realize that the main assumption in these studies is that the mean free path between jumps is much smaller than the characteristic length associated to the chemical concentration. In all these studies the cell concentration is given by $n(x,t) = \int f(x,v,t)\,dv$. A more direct study of a system of stochastic differential equations that are coupled only through the concentration of the chemical was made in [42]. Nevertheless in this paper was also assumed that the distance between particles is small compared with the characteristic length associated to the chemical, and therefore the correlations between particle distributions are also small.

These results point out to some of the new possible directions for the development of the kinetic (or stochastic) theory of cell motion. Given the huge number of different situations that can arise in the study of cell interactions in biological situations it would be relevant to study the dynamics of stochastic equations in limits where the particle correlations could play a relevant role. The study of such problems, at least in biological problems is largely open.

On the other hand, all the studies of cell dynamics using stochastic or kinetic models described above assume that the cells are separated enough from each other to make cell-cell interaction effects negligible. However in many phenomena of chemotactic aggregation this hypothesis fails at least during some part of the process. For instance, in the case of Dd the cells become at some point a dense aggregate package. Even before reaching that state the cells distribute in some cell streams that cannot be described using a simple model as Keller–Segel, but that had been explained to be due to the instabilities of planar fronts for some more complicated reaction-diffusion systems (cf. [26]). Concerning the aggregate state there have been several attempts to model such cellular state by means of different approaches. I will not try to describe in detail all the results that have been obtained in this extensive research area, but I will mention a few results that could describe some of the main ideas that are been used to study this problem.

An approach that is rather popular in the field of mathematical biology is the use of cellular automata models, often in lattices, having a dynamic that mimics the laws of cell motion. Using this approach it is possible to obtain numerical simulations that very often resemble very much the patterns observed in biological systems. In the specific case of Dd the most remarkable results in this direction are those of [35]. These numerical simulations were able to reproduce the whole life cycle of Dd, including the aggregation, the formation of cell mounds, and the development of the fruiting body. The main difficulty with this approach is that the relation between the parameters in the cellular automata and the biochemical parameters is not an obvious one. On the other hand, the evolution rules that are used in the model are not true mechanical or chemical equations. In any case this approach is providing some insight in several biological problems about the type of interactions that must be taken into account to obtain some specific patterns.

There have been introduced in the literature several models that describe the mechanical interactions of a huge number of cells. One of the most recent papers in this direction, that is probably the one that includes the currently available information

about the mechanical interactions of the cells in a more careful manner is [14]. These results provide some interesting insights on the mechanics of dense cell aggregates. Nevertheless the mathematical object that a specialist in partial differential equations would like to have is a system of continuum equations for the cell aggregates, with a solid basis in physics and chemistry that could play a role in tissues analogous to the one played by the Navier–Stokes equations in fluid mechanics. Actually the Navier–Stokes equations have been used to model the evolution of cell aggregates (cf. [11]) and there has been obtained numerically good qualitative agreements with the experimentally observed patterns (cf. [41]). However, the mechanical properties of dense cell aggregates are most likely rather different from the properties of newtonian fluids.

I will mention shortly another problem related to the aggregation of Dd yielding also partial differential equations problems. This is the process of transmission of chemical signals between cells that yield the aggregation process. In the Keller–Segel model it is assumed that the production of chemical is proportional to the cell density and that the cell velocity is proportional to the concentration of chemical. However, this assumptions are just a simplification of a rather complex process. A more realistic picture of the production of chemical is provided by the theory of excitable systems. According to this picture the cells, upon the arrival of a diffusive chemical wave produce some additional chemical that compensates in this way the effect of its spontaneous degradation. After this production the cell enters in a refractory state lasting a few minutes during which the cell is unable to release chemical. There exists a huge mathematical theory for reaction-diffusion systems whose dynamics has these ingredients (cf. for instance [32]). Systems having such dynamics exhibit a large class of patterns, like travelling waves, spiral waves and several others. Actually, the chemical signalling in Dd aggregates was one of the problems that motivated the development of the theory of dynamical systems. In recent decades there have been several papers introducing models for the cell signalling process that include more detailed information about the biochemical processes taking place in the cell. Some of the most popular models are the ones in [36] and [43]. These models are reaction-diffusion models that are able to reproduce some of the features observed in the experiments that measure the chemical produced by cell aggregates (cf. [44]). Recently, in the article [34] several analytic formulae for magnitudes like the wave velocity, the chemical concentrations and other related quantities were computed using asymptotic methods.

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