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Mathematical models for cellular aggregation: the chemotactic instability and clustering formation

Tesi di Laurea Magistrale in Fisica Matematica

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Contents

Abstract

In this thesis we present a mathematical formulation of the interaction between microorganisms such as bacteria or amoebae and chemicals, often produced by the organisms themselves. This interaction is called chemotaxis and leads to cellular aggregation. We derive some models to describe chemotaxis. The first is the pioneristic Keller-Segel parabolic-parabolic model and it is derived by two different frameworks: a macroscopic perspective and a microscopic perspective, in which we start with a stochastic differential equation and we perform a mean-field approximation. This parabolic model may be generalized by the introduction of a degenerate diffusion parameter, which depends on the density itself via a power law. Then we derive a model for chemotaxis based on Cattaneo's law of heat propagation with finite speed, which is a hyperbolic model. The last model proposed here is a hydrodynamic model, which takes into account the inertia of the system by a friction force. In the limit of strong friction, the model reduces to the parabolic model, whereas in the limit of weak friction, we recover a hyperbolic model. Finally, we analyze the instability condition, which is the condition that leads to aggregation, and we describe the different kinds of aggregates we may obtain: the parabolic models lead to clusters or peaks whereas the hyperbolic models lead to the formation of network patterns or filaments. Moreover, we discuss the analogy between bacterial colonies and self gravitating systems by comparing the chemotactic collapse and the gravitational collapse (Jeans instability).

Key words: chemotaxis, parabolic model, mean-field approximation, degenerate diffusivity, Cattaneo's law, hydrodynamic model, friction force, spectral analysis, clusters, network patterns, Jeans instability

Introduction

The term *chemotaxis* frequently occurs in biology and refers to the phenomenon of chemically directed movement. Consider, for example, a species with a densely crowded population. In a diffusion process, the population will spread outward in space. By contrast, chemotaxis is the opposite effect in which the species is attracted towards a higher (or lower) chemical concentration; we talk about chemo-attraction, and respectively about chemo-repulsion.

Chemotaxis is important in animals and insects ecology because a large number of them rely on an acute sense of smell for conveying information between members of the species. Chemicals which are involved in these processes are called *pheromones*; one of the simplest and most important consequence of pheromones release (other than territorial demarcation) is the directed movement it can generate in a population. Furthermore, chemotaxis may be crucial in some biological processes. We give just a couple of example: when a bacterial infection invades the body it may be attacked by movement of cells towards the source as a result of chemotaxis; moreover, convincing evidence suggests that leukocyte cells in the blood move towards a region of bacterial inflammation, to counter it, by moving up a chemical gradient caused by the infection. The most prominent examples of chemotactic species which we can find in literature are the slime mold *Dictyostelium discoideum*, which moves towards higher concentration of cAMP, or flagellated bacteria like *Salmonella typhimurium*, which reacts to aspartate (see [7]).

Besides, it is important to study the mathematical models which describe the chemosensitive movement because the chemotactic phenomenon explains the spontaneous self-organization of biological cells (bacteria, amoebae, endothelial cells, ...) due to the long-range attraction of a chemical, often produced by the organisms themselves, and the formation of cellular aggregates or patterns (connected to morphogenesis).

The classical mathematical model for chemotaxis is the Keller-Segel model (see [14]), sometimes called Patlak-Keller-Segel model from a previous article by Patlak (see [17]), which consists of a system of two coupled parabolic equations, for the time variation of the organism density and of the chemical concentration. The former is represented by a drift-diffusion equation: there is a diffusion term, which mod-

els the erratic motion of the particles (like in Brownian theory), and a drift term, which is responsible of a systematic motion along the gradient of concentration of the secreted chemical. On the other hand, the evolution of the secreted chemical is described by a diffusion equation involving terms of source and degradation. If there is chemo-attraction, the Keller-Segel model is able to reproduce the chemotactic aggregation (collapse) of biological populations when the attractive drift term overcomes the diffusive term. As we will show, this is similar to the gravitational collapse of self-gravitating Brownian particles. This parabolic model leads to the formation of Dirac peaks or, in a regularized version, of smoother density profiles (round clusters), as one may find in [6].

However, recent experiments of in vitro formation of blood vessels show that cells randomly spread on a gel matrix autonomously organize to form a connected vascular network that is interpreted as the beginning of a vasculature ([8]). These networks cannot be explained by parabolic models, because they lead to pointwise blow-up. In fact, they can be recovered by *hyperbolic models*. There are mainly two kinds of hyperbolic models discussed in literature: a *Cattaneo type model* for chemotaxis ([7]), which is the result of the application of Cattaneo's law of heat propagation to the chemotaxis problem and which respects finite propagation speeds, and a hydrodynamic model ([6] and [4]), which considers a barotropic fluid with a certain equation of state $p = p(\rho)$.

The purpose of this thesis is to derive (from a macroscopic and a microscopic point of view) the models used to describe the chemotaxis, and to study the instability conditions of the homogeneous steady state. As the instability of the uniform equilibrium state is strictly connected to cellular aggregation, we would like to discuss and analyze the differences between the instability (and consequently between the clustering formation) of the parabolic models and of the hyperbolic ones.

In the first chapter we focus on the pioneristic Keller-Segel model. Firstly, we derive the two parabolic equations via the local balance equations and the constitutive relations for the fluxes, as Keller and Segel did in their first article which dates back to 1970. Secondly, we propose a kinetic derivation of the same model, starting from a microscopic description of the dynamics of the biological populations (namely, we introduce two stochastic differential equations for the motion of the individual microorganism and chemical). By performing a mean-field approximation, and by applying arguments from stochastic calculus, we recover the same parabolic-parabolic system as before. We conclude the first chapter with some generalizations of the parabolic model for chemotaxis. It is of particular interest a parabolic model where the diffusivity parameters are not constant but depend on the density itself, for instance via a power law ([21]). In this way, we may obtain parabolic models for chemotaxis with

degenerate diffusivities; they are called porous medium equations and they have recently been studied, since systems of this kind account for finite speed of propagation but they still remain parabolic.
In the second chapter we turn our attention on hyperbolic models. We first recall some tools of Cattaneo's theory of heat propagation, which is a modification of Fourier's law of heat conduction and it is used to describe heat propagation with finite speed. Then, we present a Cattaneo type model for chemotaxis, which is characterized by the introduction of a small delay time in the response of the microorganism. This model consists of two coupled equations, where the first one is now a hyperbolic equation whereas the second one, for the chemical, remains unchanged: indeed the system is sometimes called hyperbolic-parabolic. Secondly, we show a hydrodynamic model for chemotaxis. Following the standard Eulerian description, it describes the rate of change of the organism density and velocity, together with the chemical concentration. It involves a friction force, which has the role of taking into account the inertia of the system. We show that in the limit of strong friction we recover the Keller-Segel parabolic model, whereas in the limit of weak friction we reduce to a hyperbolic model, similar to the Cattaneo type model. As we did in chapter 1, in order to derive the hydrodynamic model, we start from two stochastic equations and, through a mean-field approximation, we obtain the corresponding Fokker-Planck equations. By taking the successive moments of these generalized Fokker-Planck equations and using a local thermodynamic equilibrium condition, we derive the hyperbolic system which describes chemotaxis from a hydrodynamic point of view.
Finally, in the third chapter, we perform a linear stability analysis of the uniform state of the systems. Specifically, we study the stability of an infinite and homogeneous distribution of particles against the "chemotactic collapse". In the first section of the chapter we focus on the Keller Segel model and we use spectral analysis tools to obtain a condition for the instability of the system. As we will show in detail, the diffusivity parameter and the chemical degradation rate increase the stability, whereas the chemosensitivity and the chemical production lead to aggregation. In the second section of the chapter, we consider the hydrodynamic model. First of all, we underline the similarities between this model and the Euler-Poisson system used to describe the dynamics of self-gravitating particles. There is indeed an analogy between the chemotactic collapse in biology and the gravitational collapse in astrophysics. Then we look for the instability conditions for two simplified hydrodynamic models. We neglect the time variation of the chemical concentration c and, for a first moment we also ignore the chemical degradation rate. The model found out is called Newtonian model. In a second moment, we consider the chemical degradation which leads to a shielding of the interaction (Yunkawa model). We remark that numerical simulations

may be performed to show the network patterns formation which we get if we consider hyperbolic models instead of parabolic ones.

Introduzione

Il termine *chemiotassi* compare frequentemente in biologia e si riferisce al fenomeno di movimento direzionato chimicamente. Si consideri, per esempio, una specie con una popolazione densamente fitta. In un processo di diffusione, la popolazione si spargerà verso l'esterno nello spazio. Al contrario, la chemiotassi è l'effetto opposto, nel quale la specie viene attratta verso una concentrazione chimica più alta (o più bassa); parleremo di chemio-attrazione e, rispettivamente, di chemio-repulsione.
La chemiotassi risulta importante nello studio della vita di animali ed insetti in quanto un grande numero di essi fa affidamento su un acuto senso dell'olfatto per trasmettere informazioni tra i membri della propria specie. Gli agenti chimici coinvolti in questi processi sono chiamati *ferormoni*; una delle più semplici ed importanti conseguenze del rilascio dei ferormoni è (oltre la demarcazione territoriale) il movimento direzionato che ciò può generare nella popolazione. Per di più, la chemiotassi può essere cruciale in alcuni processi biologici. Diamo solo qualche esempio: quando un'infezione batterica invade il nostro corpo, essa può essere attaccata dal movimento di cellule verso la sorgente, e ciò è un risultato della chemiotassi; inoltre, prove convincenti suggeriscono che le cellule dei leucociti nel sangue si muovano verso la regione dell'infiammazione batterica, per contrastarla, salendo lungo un gradiente chimico crescente, causato dall'infezione. I maggiori esempi di speci chemiotattiche che possiamo trovare in letteratura sono la muffa *Discotelium discoideum*, che si muove verso una più alta concentrazione di cAMP, e batteri flagellati come la *Salmonella typhimurium* che reagisce all'aspartato (vedi [7]).
Inoltre, è importante studiare i modelli matematici che descrivono il movimento chemosensitivo perché il fenomeno chemiotattico spiega la auto-organizzazione spontanea di cellule biologiche (batteri, amebe, cellule endoteliali, ...) a causa dell'attrazione ad ampio raggio operata da un agente chimico, spesso prodotto dall'organismo stesso, e la formazione di aggregati cellulari o pattern (collegati al fenomeno della morfogenesi).
Il modello matematico classico per la chemiotassi è il modello di Keller-Segel (vedi [14]), talvolta chiamato modello di Patlak-Keller-Segel, da un precedente articolo di Patlak (vedi [17]), che consiste in un sistema di due equationi paraboliche accoppiate,

per l'evoluzione temporale della densità dell'organismo e della concentrazione chimica. La prima è rappresentata da un'equazione di diffusione-trasporto: è presente un termine diffusivo che modella il moto casuale delle particelle (come nella teoria Browniana), e un termine di trasporto, che è responsabile del moto sistematico lungo il gradiente della concentrazione dell'agente chimico secreto. D'altra parte, l'evoluzione dell'agente chimico secreto è descritta da un'equazione di diffusione che coinvolge anche termini di produzione e di degradazione. Se c'è chemio-attrazione, il modello di Keller-Segel è in grado di riprodurre l'aggregazione chemiotattica (collasso) di popolazioni biologiche, quando il termine attrattivo di trasporto supera il termine diffusivo. Come mostreremo, questo processo è simile al collasso gravitazionale di particelle Browniane auto-gravitanti. Questo modello parabolico porta alla formazione di picchi di Dirac o, in una versione regolarizzata, a profili di densità più continui (aggregati circolari), come si può trovare in [6].
D'altra parte, recenti esperimenti di formazione in vitro di vasi sanguigni mostrano che cellule sparse casualmente su una matrice di gel si organizzano autonomamente per formare una rete vascolare connessa che viene interpretata come l'inizio di una vascolarizzazione ([8]). Questi reticoli non possono essere spiegati dai modelli parabolici, dato che essi conducono ad un'aggregazione puntuale. Invece, essi possono essere ritrovati da *modelli iperbolici*. Ci sono principalmente due tipi di modelli iperbolici discussi in letteratura: un *modello di tipo Cattaneo* per la chemiotassi ([7]), che è il risultato dell'applicazione della legge di Cattaneo per la propagazione del calore al problema della chemiotassi e che rispetta finite velocità di propagazione, e un *modello idrodinamico* ([6] and [4]), che considera un fluido barotropico con una certa equazione di stato $p = p(\rho)$.
Lo scopo di questa tesi è derivare (da un punto di vista macroscopico e microscopico) i modelli usati per descrivere la chemiotassi, e di studiare le condizioni di instabilità dello stato di equilibrio omogeneo. Siccome l'instabilità dello stato di equilibrio uniforme è strettamente connessa all'aggregazione cellulare, ci proponiamo di discutere e analizzare le differenze tra le instabilità (e conseguentemente tra le formazioni di aggregati) per quanto riguarda i modelli parabolici e quelli iperbolici.
Nel primo capitolo ci focalizziamo sul modello pioneristico di Keller-Segel. Per prima cosa, deriviamo le due equazioni paraboliche tramite le equazioni di bilancio locali e le relazioni costitutive per i flussi, come fecero Keller e Segel nel loro primo articolo, che risale al 1970. In secondo luogo, proponiamo una derivazione cinetica dello stesso modello, partendo da una descrizione microscopica della dinamica delle popolazioni biologiche (ossia, introduciamo due equazioni differenziali stocastiche per il moto dei singoli micro-organismi e agenti chimici). Attuando un'approssimazione di campo medio, e utilizzando ragionamenti di calcolo stocastico, ritroviamo lo stesso

modello parabolico-parabolico di prima. Concludiamo il primo capitolo con alcune generalizzazioni del modello parabolico per la chemiotassi. È di particolare interesse un modello parabolico in cui i parametri diffusivi non sono costanti ma dipendono dalla densità stessa, per esempio tramite una legge potenza ([21]). In questo modo possiamo ottenere modelli parabolici per la chemiotassi con diffusività degeneri; sono chiamate equazioni del mezzo poroso e sono state recentemente studiate poiché sistemi di questo tipo sono responsabili di una velocità finita di propagazione ma rimangono comunque parabolici.

Nel secondo capitolo, spostiamo la nostra attenzione sui modelli iperbolici. Richiamiamo innanzi tutto alcune nozioni della teoria di Cattaneo sulla conduzione del calore, che è una modifica della legge di Fourier sulla propagazione del calore e viene usata per descrivere la diffusione con velocità finita. Quindi, presentiamo un modello di tipo Cattaneo per la chemiotassi, che è caratterizzato dall'introduzione di un piccolo tempo di ritardo nella risposta del micro-organismo. Questo modello consta di due equazioni accoppiate, dove la prima è ora un'equazione iperbolica, mentre la seconda, per l'agente chimico, è rimasta invariata: infatti il sistema viene talvolta chiamato iperbolico-parabolico. Nella seconda parte del capitolo, mostriamo un modello idrodinamico per la chemiotassi. Seguendo la classica descrizione Euleriana, esso descrive il cambiamento della densità e della velocità dell'organismo, insieme alla concentrazione chimica. Coinvolge una forza di attrito, che ha la funzione di tenere conto dell'inerzia del sistema. Mostriamo che, prendendo il limite per un forte attrito, ritroviamo il modello parabolico di Keller-Segel, mentre nel limite per un debole attrito ci riduciamo ad un modello iperbolico, simile al modello di tipo Cattaneo. Come abbiamo fatto nel capitolo 1, per derivare il modello idrodinamico partiamo da due equazioni stocastiche e, tramite una approssimazione di campo medio, otteniamo le corrispondenti equazioni di Fokker-Planck. Prendendo i momenti successivi di queste equazioni di Fokker-Planck generalizzate, e usando una condizione di locale equilibrio termodinamico, deriviamo il sistema iperbolico che descrive la chemiotassi da un punto di vista idrodinamico.

Infine, nel terzo capitolo, eseguiamo una analisi lineare della stabilità dello stato uniforme dei sistemi. Specificamente, studiamo la stabilità di una distribuzione di particelle finita e omogenea contro il "collasso chemiotattico". Nella prima sezione del capitolo, ci focalizziamo sul modello di Keller-Segel e usiamo strumenti dell'analisi spettrale per ottenere una condizione per l'instabilità del sistema. Come mostreremo in dettaglio, il parametro di diffusività e il tasso di degradazione chimica stabilizzano il sistema, mentre la chemosensitività e la produzione di agenti chimici portano ad una maggiore aggregazione. Nella seconda sezione del capitolo, consideriamo il modello idrodinamico. Prima di tutto, sottolineiamo le analogie tra questo modello e il sistema

di Eulero-Poisson usato per descrivere la dinamica di particelle autogravitanti. C'è infatti una similarità tra il collasso chemiotattico in biologia e il collasso gravitazionale in astrofisica. Quindi cerchiamo le condizioni di instabilità per due modelli idrodinamici semplificati. Trascuriamo la variazione temporale della concentrazione chimica e, in un primo momento, ignoriamo anche il tasso di degradazione dell'agente chimico. Il modello trovato viene denominato modello Newtoniano. In un secondo momento, consideriamo la degradazione chimica, che porta ad una schermatura dell'interazione (modello di Yunkawa). Osserviamo che simulazioni numeriche possono essere svolte per mostrare la formazione di reticolati che si ottengono se consideriamo modelli iperbolici anziché parabolici.

Chapter 1

The Keller-Segel model for chemotaxis

The first mathematical approach to analyze chemotactic movement was by Keller and Segel in their article *Initiation of slime mold aggregation viewed as an instability* [14]. They observed the morphogenetic development of many species of slime molds (Acrasiales) and they tried to work out a mathematical model which was in accordance with the observations. In that paper, they derived the model through a macroscopic point of view: they examined the motion of the amoeba (*Dictyostelium discoideum*) and of the chemical (*Acrasin*) in their entirety, by indicating them with smooth functions, having the meaning of concentrations.
In this chapter, we are going to derive the Keller-Segel model for the chemotactic response, firstly using the same approach as in [14], secondly via a stochastic method. In order to do that, we will introduce the *random walk* concept, which describes the motion of a single particle in a diffusive context (that is, without chemo-attraction); subsequently we add the chemotactic term, which has the function of convecting the random motion to a certain "point" (where the concentration of the chemical is higher for chemo-attraction, or lower in the case of chemo-repulsion); finally we will make a mean-field approximation to get the macroscopic model. The results turn out to be the same: a system of two coupled parabolic PDEs. We will call it "parabolic-parabolic" model.

1.1 Formulation of the model: general integral and local balance laws

In the following, we will consider two spatial dimensions, x and y. All the results derived are still valid also in $\mathbb{R}^3$, but we restrict our analysis in two space dimensions

for mathematical reasons (in two spatial dimensions it is easier to study the solutions of the equations). We will indicate with the continuous functions $\rho(x, y, t)$ and $c(x, y, t)$ the concentration of the amoeba and the chemical, respectively. Our goal is to build a system of two partial differential equations which may be an accurate description of the motion of the two species.
Actually, in the real phenomenon, the amoeba produces Acrasin and Acrasinase, which are respectively the chemical which attracts the amoeba and the enzyme which destroys the Acrasin. As in every enzyme reaction, the two species are connecting to each other and form a complex enzyme+substrate, which is very unstable and decays quite quickly to the enzyme plus some products. The chemical reaction is the following, where the concentration of the enzyme is η and the complex concentration is C:

$$c + \eta \rightleftharpoons C \to \eta + product$$

Since at the beginning we have both Acrasin and Acrasinase, whereas at the end of the reaction we get just Acrasinase (plus some products), the result of the interaction between the chemical c and the enzyme is the "death" of the chemical species. As in this thesis we are not mainly interested in the chemical reaction, but we focus our attention on mathematical models, we are going to neglect the Acrasinase equation (and with it we do not consider either the complex enzyme+substrate), but we have a function $\ell(c)$ which indicates the average degradation of the chemical, and we know they are due to the interaction with the enzyme. In this way, we work only with two equations, for the amoeba and for the chemical, instead of four.
We now make the following assumptions:

1. The Acrasin is produced at a rate $h(c)$ by the amoeba;

2. The Acrasin is degraded at a rate $\ell(c)$, proportional to itself (and to the enzyme which we no longer consider);

3. The birth and death of the amoeba are not taken into account, as they happen at a rate considerably smaller than the time of the movement; here it would be interesting the analysis of this phenomenon with a different time scale, for example with the relaxation time as a new time scale (cfr chapter 2);

4. The Acrasin is moving in a diffusive way, with a diffusion mobility D_c;

5. The changes in the concentration of the amoeba are the results of an oriented chemotactic motion in the direction of a positive "gradient" of Acrasin and a random motion (analogous to a diffusion way, with a mobility D_ρ).

Our aim here is interpreting the five conditions above to work out the equations for ρ and c.

Henceforth, let A be an arbitrary, fixed, bounded and regular region of the (x, y) plane where the amoeba are located; S is its boundary. Let us suppose A to be sufficiently smooth to apply the divergence theorem. The general integral balance laws read as follows:

$$\frac{d}{dt}\int_A \rho \, dxdy = \int_A Q^{(\rho)} \, dxdy - \int_S \vec{J}^{(\rho)} \cdot \vec{n} \, ds \tag{1.1}$$

$$\frac{d}{dt}\int_A c \, dxdy = \int_A Q^{(c)} \, dxdy - \int_S \vec{J}^{(c)} \cdot \vec{n} \, ds \tag{1.2}$$

where, as usual, $\vec{J}^{\rho}$ and $\vec{J}^{c}$ are the (constitutive) amoeba and chemical fluxes, whereas Q^{ρ} and Q^{c} represent the amoeba and chemical supplies, and $\vec{n}$ is the outward unit normal vector to S.

We are now interested in the local forms of (1.1) and (1.2); the derivative of local forms rests upon suitable assumptions on the smoothness of the fields ρ, c, $\vec{J}^{\rho}$, $\vec{J}^{c}$, Q^{ρ} and Q^{c}. In order to put the derivative inside the integral, we use a reduction of the classical transport theorem, so we have:

$$\frac{d}{dt}\int_A \rho \, dxdy = \int_A \frac{\partial}{\partial t}\rho \, dxdy \tag{1.3}$$

and the same for c.

The use of the Gauss divergence theorem yields:

$$\int_S \vec{J} \cdot \vec{n} \, ds = \int_A \nabla \cdot \vec{J} \, dxdy \tag{1.4}$$

for both $\vec{J}^{\rho}$ and $\vec{J}^{c}$.

Thus, plugging (1.3) and (1.4) into (1.1) and (1.2), we obtain:

$$\int_A \left[\frac{\partial}{\partial t}\rho - Q^{(\rho)} + \nabla \cdot \vec{J}^{(\rho)}\right] \, dxdy = 0 \tag{1.5}$$

$$\int_A \left[\frac{\partial}{\partial t}c - Q^{(c)} + \nabla \cdot \vec{J}^{(c)}\right] \, dxdy = 0 \tag{1.6}$$

In view of the arbitrary choice of the region A, by applying standard arguments, we recover:

$$\begin{aligned} \frac{\partial}{\partial t}\rho - Q^{(\rho)} + \nabla \cdot \vec{J}^{(\rho)} &= 0 \\ \frac{\partial}{\partial t}c - Q^{(c)} + \nabla \cdot \vec{J}^{(c)} &= 0 \end{aligned} \tag{1.7}$$

which are called *local balance equations* or (for $Q^{\rho} = Q^{c} = 0$) *local conservation laws*. By the assumptions 1 to 5 made above, both fluxes are of diffusive type. Hence we

can characterize them through the following flux gradient type constitutive relations:

$$\begin{aligned} \vec{J}^{(\rho)} &= -D_\rho \nabla \rho + \chi \nabla c \\ \vec{J}^{(c)} &= -D_c \nabla c \end{aligned} \tag{1.8}$$

where the (non negative) density and chemical mobilities D_ρ and D_c are supposed to be constant. Indeed they might depend on ρ and c respectively.
The non negative function χ is not a constant, except for some simple cases, and it is called the *chemotactic sensitivity*. Very often, it is proportional to the amoeba concentration ρ. Thus the simplest chemotactic function may be given by $\chi(\rho) = \chi_0 \rho$.
We note that the amoeba flux is made up by two terms, the first proportional to the amoeba gradient itself, which will be the cause of the diffusive term in the final equation, and the second proportional to the Acrasin gradient, which is responsible of the chemotactic motion. We write a plus sign in the latter because we have attraction; in the case of repulsion (the chemical acts as a poison), we would have got a minus sign.
For our previous assumptions, we ignore the amoeba supply, so: $Q^{(\rho)} = 0$. On the other hand, the effects of production and degradation for the chemical cannot be neglected, thus we set: $Q^{(c)} = \rho h(c) - c\ell(c)$. As argued before, the rate of birth of Acrasin is proportional to the concentration of amoeba and the rate of death is proportional to the concentration of the chemical itself.
Putting everything together, and plugging the constitutive relations (1.8) into the local balance equations (1.7), we finally obtain the following system of two partial differential equations:

$$\begin{aligned} \frac{\partial \rho}{\partial t} &= D_\rho \Delta \rho - \nabla \cdot (\chi \nabla c) \\ \frac{\partial c}{\partial t} &= D_c \Delta c - c\ell(c) + \rho h(c) \end{aligned} \tag{1.9}$$

In literature, (1.9) is known as the Keller-Segel model (KS model) and represents the pioneristic and yet most general model for the chemotaxis.
The first equation is a **drift-diffusion** equation: the cells diffuse with a diffusion coefficient D_ρ and they also move in the direction of a gradient of c (chemotactic drift). The chemotactic sensitivity χ is a measure of the strength of the influence of the chemical gradient on the flow of cells.
The second equation in the KS model is a **reaction-diffusion** equation. The chemical c is produced by the bacteria with a rate h and it is degradated with a rate ℓ. It also diffuses with a diffusion coefficient D_c. We remark that $h(c)$ and $\ell(c)$ are positive functions of c.
Once we have given suitable initial conditions $\rho(0)$ and $c(0)$, and boundary conditions

(homogeneous Neumann) the system (1.9) can theoretically be solved to give ρ and c at any later times.
It is more interesting, and even easier, to analyze the stability of the uniform steady state of this system. This is strictly connected to aggregation phenomena, which are observed in the slime mold life cycle. When the chemotactic attraction prevails over diffusion, the KS model accounts for a chemotactic collapse leading to aggregations on Dirac peaks. There is a great amount of literature on this issue. We mainly refer to Hillen ([11]) and Chavanis ([6]). The stability analysis tool will be discussed in detail in Chapter 3.
In the following section we are going to derive this same model by a stochastic and microscopic approach.

1.2 Stochastic Derivation of the model

Within the microscopic framework, we interpret the movement of species populations as a consequence of microscopic irregular movement of single members of the considered population that results in a macroscopic regular behaviour of the whole population. This leads to a parabolic limit, which is the same we have worked out in the previous section by combining balance and constitutive equations.
In this section, we follow the procedures as in [13] and in [19], and we always refer to them for further proofs or calculations. We will use some probability tools, such as **Brownian motion** and **Ito's formula**, which are not defined in this thesis. Hereafter, we employ standard probability notations. For a probability background which could be useful (and sufficient) to understand everything in this section see e.g. [18].
Although in the first section we have looked at a binary system constituted by amoeba and acrasin, because Keller and Segel in their first article [14] based their results on observations made upon those species, we now refer to *bacteria* to indicate the motile microorganisms, whose density is still labelled ρ, and to a general *chemical* to indicate the chemical species, produced by the bacteria themselves (the chemical concentration is always c).
We consider a system with N particles, which is divided into two subpopulations: the bacteria and the particles of a chemical substance, produced by the bacteria themselves, denoted by S_ρ and S_c respectively. Let the particles be numbered consecutively and let $P_N^k(t)$ be the position of the kth particle at time t. We now may define the following measure valued empirical processes:

$$S_{N_\rho} = \frac{1}{N} \sum_{k \in S_\rho(t,N)} \delta_{P_N^k(t)}$$

$$S_{N_c} = \frac{1}{N} \sum_{k \in S_c(t,N)} \delta_{P_N^k(t)}$$

Where δ_x denotes the Dirac measure in $x \in \mathbb{R}^3$. We now may generalize our analysis in three spatial dimensions.

Our aim is to show that, for large N, the empirical processes converge to the solution of the initial value problem related to the previous chemotaxis system.

We define the functions $\hat{S}_{N_r}$, with $r = \rho, c$ as a smoothed version of the empirical processes S_{N_r} defined above. We just need to think to them as a convolution with some probability densities $W_N(x)$ and $\hat{W}_N(x)$.

$$\hat{S}_{N_r}(t,x) = (S_{N_r}(t) * W_N * \hat{W}_N)(x)$$

where the exact construction of $W_N(x)$ and $\hat{W}_N(x)$ may be found in [19]. This is a really tricky procedure to get continuous and differentiable functions with the same behavior as the empirical processes above. The functions which describe the dynamics of the particles depend on these smoothed version of the processes.

Moreover, following the same scheme as in [13] and [19], the chemotactic KS equations may be rigorously derived from an interacting stochastic many particle system, where the interaction between the particles is rescaled in a moderate way, as the population size grows, i.e. as $N \longrightarrow \infty$.

For each particle in the many-particle system, the motion through the space is described by a stochastic differential equation. For $k \in S_\rho(t,N)$:

$$dP_N^k(t) = \chi_N(t, P_N^k(t)) \nabla \hat{S}_{N_c}(t, P_N^k(t))\, dt + \sqrt{2D_\rho}\, dW^k(t) \tag{1.10}$$

On the other hand, for $k \in S_c(t,N)$:

$$dP_N^k(t) = \sqrt{2D_c}\, dW^k(t) \tag{1.11}$$

We are now going to explain each term in the equations (1.10) and (1.11).

First of all, we say that the processes $W^k(t)$ are independent standard Brownian motions. In the SDE for the position of the chemical ((1.11)) we only have the brownian term, and no drift term; because of that, since the brownian motion is a not oriented behaviour, without any preferred direction, very similar to heat diffusion phenomena, we can say the chemical motion is just diffusive, without any interaction with other particles. Instead, the dt term in the SDE (1.10) is a deterministic term, which means a motion oriented towards a certain direction (where the chemical gradient is higher, in this case). This term is called *chemotactic drift* and it is the result of the chemoattraction experienced by the bacteria ρ due to the presence of the chemical. This term is indeed proportional to the chemical gradient $\nabla \hat{S}_{N_c}$. Thus, for the bacteria motion, we can argue it is the combination of diffusion (given by the $dW^k(t)$ term)

and chemo-attraction (given by the dt term).
D_ρ and D_c are constants and they are the diffusion parameters; the function χ is the chemotactic function and in this section it is considered as a function of both the bacteria and the chemicals: $\chi = \chi(\hat{S}_{N_\rho}, \hat{S}_{N_c})$.
Let us first write the stochastic differential equations above in the integral form:

$$P_N^k(t) = \int_0^t \chi_N(\tau, \cdot)\nabla \hat{S}_{N_c}(\tau, \cdot)\, d\tau + \int_0^t \sqrt{2D_\rho}\, dW^k(\tau) \tag{1.12}$$

$$P_N^k(t) = \int_0^t \sqrt{2D_c}\, dW^k(\tau) \tag{1.13}$$

For births and deaths of chemical particles, we make the same assumptions as before, which, in the microscopic view, translate into the following statement.
Each single particle $k \in S_\rho(t, N)$ at position P_N^k can produce a particle $k^* \in S_c(t, N)$ at P_N^k with intensity $h_N(t, P_N^k)$ where $h_N(t, x) = h(\hat{S}_{N_\rho}, \hat{S}_{N_c})$. In a similar way, a particle $k \in S_c$ at position $P_N^k(t)$ at time t may die with intensity $\ell_N(t, P_N^k(t))$, with $\ell_N(t, x) = \ell(\hat{S}_{N_\rho}, \hat{S}_{N_c})$. These processes mark the instants when the kth particle gives birth to another one or dies.
We are now ready to apply **Ito's Lemma** to the SDEs (1.12)-(1.13), using a function $f(t, x) \in C_b^2(\mathbb{R}^+ \times \mathbb{R}^2)$, where C_b^2 denotes the set of twice continuously differentiable functions, bounded together with their derivatives. Thus we find:

$$\begin{aligned}
&\left\langle S_{N_\rho}(t), f(t, \cdot)\right\rangle = \frac{1}{N} \sum_{k \in S_\rho(t,N)} f(t, P_N^k(t)) = \left\langle S_{N_\rho}(0), f(0, \cdot)\right\rangle + \\
&+ \int_0^t \langle S_{N_\rho}(\tau), \chi_N(\tau, \cdot)\nabla \hat{S}_{N_c}(\tau, \cdot) \cdot \nabla f(\tau, \cdot) + D_\rho\, \Delta f(\tau, \cdot) + \frac{\partial}{\partial \tau} f(\tau, \cdot)\rangle\, d\tau + \\
&+ \frac{1}{N} \int_0^t \sum_{k \in S_\rho(t,N)} \sqrt{2D_\rho}\, \nabla f(\tau, P_N^k(\tau)) \cdot dW^k(\tau)
\end{aligned} \tag{1.14}$$

and:

$$\begin{aligned}
&\langle S_{N_c}(t), f(t, \cdot)\rangle = \frac{1}{N} \sum_{k \in S_c(t,N)} f(t, P_N^k(t)) = \langle S_{N_c}(0), f(0, \cdot)\rangle + \\
&+ \frac{1}{N} \int_0^t \sum_{k \in S_c(t,N)} \sqrt{2D_c}\, \nabla f(\tau, P_N^k(\tau)) \cdot dW^k(\tau) + \\
&+ \frac{1}{N} \int_0^t \sum_{k \in S_\rho(t,N)} f(\tau, P_N^k(\tau)) h_N^{k*}(d\tau) - \frac{1}{N} \int_0^t \sum_{k \in S_c(t,N)} f(\tau, P_N^k(\tau) \ell_N^{k*}(d\tau)
\end{aligned} \tag{1.15}$$

when we have taken into account the definition of δ_x (this distribution acts on $f \in C_b^k$ in the following way: $\langle \delta_x, f(t, \cdot)\rangle = f(t, x)$) and the effects of single birth and deaths. The first remark we can do now is that the stochastic integrals

$$\int_0^t \sum_{k \in S_\rho(t,N)} \sqrt{2D_\rho}\, \nabla f(\tau, P_N^k(\tau)) \cdot dW^k(\tau)$$

and

$$\int_0^t \sum_{k \in S_c(t,N)} \sqrt{2D_c}\, \nabla f(\tau, P_N^k(\tau)) \cdot dW^k(\tau)$$

are **martingales** with respect to the natural filtration $\{\mathcal{F}_t\}$, generated by the processes $t \longmapsto (P_N^k(t), 1_{S_r(N,t)}(k))\mathbf{I}_N^k(t)$, for $r = \rho, c$, where $\mathbf{I}_N^k$ is the indicator function of the lifetime of the kth particle. Thus we can assume their **quadratic variation** to be 0 as $N \longrightarrow \infty$.

Moreover, for the limiting behavior of of (1.14) and (1.15), we assume, for $r = \rho, c$:

$$\lim_{N \longrightarrow \infty} S_{N_r}(t) = S_r(t)$$

where the distribution $S_r(t)$ has the smooth density $r(t, \cdot)$ with respect to the Lebesgue measure. Let $\rho_0(\cdot)$ and $c_0(\cdot)$ be the densities of $S_\rho(0)$ and $S_c(0)$ respectively. Since, in the sense of the distribution measures

$$\lim_{N \longrightarrow \infty} W_N = \lim_{N \longrightarrow \infty} \hat{W}_N = \delta_0$$

it follows that

$$\lim_{N \longrightarrow \infty} \hat{S}_{N_r}(t, \cdot) = r(t, \cdot)$$

and also

$$\lim_{N \longrightarrow \infty} \nabla \hat{S}_{N_r}(t, \cdot) = \nabla r(t, \cdot)$$

Finally, when we consider the definitions of the birth and death functions, we need to remember they were functions of two arguments: $h_N(t, P_N^k(t))$ and $\ell_N(t, P_N^k(t))$. We have defined the "stared" functions used in the integrals above as the following equality holds:

$$h_N^{k*}(dt) = h_N(t, P_N^k(t))dt$$

And an analogous one for ℓ_N^{k*}.

So, taking the limit for $N \longrightarrow \infty$ in 1.14 and 1.15, at least formally we obtain:

$$\begin{aligned} \langle \rho(t, \cdot), f(t, \cdot) \rangle = \langle \rho_0(\cdot), f(0, \cdot) \rangle + \int_0^t \langle \rho(\tau, \cdot), \chi_\infty(\tau, \cdot) \nabla c(\tau, \cdot) \cdot \nabla f(\tau, \cdot) \rangle d\tau + \\ + \int_0^t \langle \rho(\tau, \cdot), D_\rho \Delta f(\tau, \cdot) + \frac{\partial}{\partial \tau} f(\tau, \cdot) \rangle d\tau \end{aligned} \tag{1.16}$$

$$\begin{aligned} \langle c(t, \cdot), f(t, \cdot) \rangle = \langle c_0(\cdot), f(0, \cdot) \rangle + \\ + \int_0^t \langle c(\tau, \cdot), D_c \Delta f(\tau, \cdot) + \frac{\partial}{\partial \tau} f(\tau, \cdot) - \ell_\infty(\tau, \cdot) f(\tau, \cdot) \rangle d\tau + \\ + \int_0^t \langle \rho(\tau, \cdot), h_\infty(\tau, \cdot) f(\tau, \cdot) \rangle d\tau \end{aligned} \tag{1.17}$$

where $\chi_\infty(t, \cdot) = \chi(\rho(t, \cdot), c(t, \cdot))$ and likewise for h_∞ and ℓ_∞. Now, using an integration by parts, deriving both sides with respect to t and applying the Fundamental

Theorem of Integral Calculus, we easily get the following system of parabolic differential equations:

$$\begin{aligned} \frac{\partial \rho}{\partial t} &= \nabla \cdot (D_\rho \nabla \rho - \chi(\rho, c)\rho \nabla c) \\ \frac{\partial c}{\partial t} &= D_c \Delta c - c\ell(\rho, c) + \rho h(\rho, c) \end{aligned} \tag{1.18}$$

As we have changed the notation used in [19] in order to make them uniform with the ones used in the previous section, we can see that (1.18) is closely related to the KS system (1.9) worked out in section 1.1 with the macroscopic approach. In this case, we have chosen more general functions χ, h, ℓ, which depend not only upon one variable, but they are function of both (ρ, c). Moreover, we see that in the chemotactic drift in (1.18) we have an extra factor ρ. This is because, very often, the chemotactic function χ is proportional to the concentration of the bacteria ρ. We can then argue that in the previous system (1.9), the part of the chemotactic drift proportional to the concentration ρ is included inside the function χ itself.
This is only an heuristic derivation. In this section we have made some assumptions without proving them, together with some intuitive calculation which were not formally proved. We believe that we have given anyway a fairly simple idea of the stochastic derivation of the Keller-Segel model and about how from microscopic assumptions we can reach a continuum model, through the distribution theory and Ito's calculus. For a more detailed derivation, we refer to sections 5-9 of [19].

1.3 A more general parabolic model for chemotaxis

We saw in the past two sections how to derive the Keller-Segel model for chemotaxis. We also noticed that with the two derivations we get slightly different results regarding the chemotactic function χ. Here we present the most general parabolic model which describes chemosensitive movement, proposed in [12] by Hillen and Painter. Following their scheme, we show that under particular values given to the parameters, we are able to reduce to the pioneristic model (1.9) derived in [14].
The most general model for chemotaxis reads as follows:

$$\begin{aligned} \frac{\partial \rho}{\partial t} &= \nabla \cdot (k_1(\rho, c)\nabla \rho - k_2(\rho, c)\rho \nabla c) + k_3(\rho, c) \\ \frac{\partial c}{\partial t} &= \nabla \cdot (D_c \nabla c) + k_4(\rho, c)\rho - k_5(\rho, c)c \end{aligned} \tag{1.19}$$

We can make these remarks:

- The chemotactic function χ is here represented by $k_2(\rho, c)\rho$; that means the chemotactic drift is proportional to the concentration of the motile organism ρ. For positive valued functions k_2, we have attraction, otherwise we have repulsion (the chemical acts like a poison).

- The function $k_1(\rho, c)$ is the diffusion coefficient for ρ. In the previous models it was a constant D_ρ; here we show it could be a non negative function of (ρ, c).

- The function $k_3(\rho, c)$ represents the average births and deaths of the organism, previously neglected because they happen in a time scale larger than the chemosensitive movement.

- The function $k_4(\rho, c)$ represents the source of chemicals (indeed it is proportional to ρ, because the organisms produce chemicals). On the other hand, $k_5(\rho, c)$ is the rate of consumption of chemicals: both functions are positive valued.

If we fix $k_1 = D_\rho$, $k_2 = \chi_0$, $k_3 = 0$, $k_4 = h(c)$ and $k_5 = \ell(c)$, then the system (2.8) reduces to the system (1.9) worked out before.
Before concluding the chapter, it is worth to underline an additional remark, regarding the chemical diffusivity D_c.
Even this diffusivity, likewise the cells mobility D_ρ, may not be a constant, but a positive valued function of c. For instance, we may consider the case when $D_c = D_0 c^n$, $n \geq 1$. The equation we obtain for the chemical time variation reads as follows:

$$\frac{\partial c}{\partial t} = \nabla \cdot (D_0 c^n \nabla c) + k_4(\rho, c)\rho - k_5(\rho, c)c \tag{1.20}$$

which is no longer a semi-linear reaction-diffusion equation. In literature it is known as **porous medium equation** (PME) and it is a diffusion equation where the diffusivity depends upon the chemical itself. It has been studied by lots of authors in the latest years and the most famous book about the results on this topic (existence of solutions, uniqueness, regularity, etc.) is [21] by Juan Luis Vazquez.
This nonlinear diffusion equation consists of a **degenerate** diffusive mobility depending upon the chemical concentration itself in a power form.
Roughly speaking, the main difference between a linear diffusion and a nonlinear (*quasi-linear*) diffusion (PME) is the fact that the solution of this nonlinear diffusion equation shows a finite speed of propagation, whereas the solution of a linear diffusion equation admits an infinite speed of propagation. Because of that, some authors have recently tried to perform and then to analyze mathematical models for chemotaxis which have the feature of degenerate diffusivity (for both the chemical and the bacteria) dependent on the chemical and bacteria densities. In this way, we get a system of two coupled parabolic equations which are both of a porous medium type (e.g. see

[2]).
In the next chapter, we will first introduce a Cattaneo type model for chemotaxis. The aim of this model, as we will see, is to avoid the paradox of infinite speed of propagation predicted by KS model, by turning the first parabolic equation (for ρ) into a hyperbolic equation. Using a density-dependent sensitivity $D_\rho = D_0\rho^n$ might be an other way to escape the infinite-speed paradox, still working with a parabolic-parabolic model.

Chapter 2

Alternative mathematical models for chemotaxis

In the first chapter we introduced the classical mathematical model for the chemotaxis, which dates back to 1970. Here we propose two possible recent modifications to that model, with the the aim of making the model more and more realistic towards the applications.

The first one is called the **Cattaneo type model**. It is derived following the same guide lines of Cattaneo's law of heat propagation (see e.g. [3], an article by Cattaneo from 1948). He modified the diffusion equation by the introduction of a delay time in the constitutive response. In this way, the delayed model allows the temperature to travel as a wave rather than simply by diffusion, thus overcoming the paradox of infinite speed of propagation typical of the standard Fourier's law for heat conduction. Thus, following [20] and [15], we will briefly address the Cattaneo's hyperbolic heat theory and then we apply the same ideas within the KS model (see e.g. [7]), in order to develop a hyperbolic-parabolic system of equations more general than (1.18), which incorporates second sound type effects for the density ρ (even preserving the KS reaction diffusion equation for c).

Successively, we provide a second modification within the stochastic derivation, following the scheme proposed by Chavanis and Sire in [6]. They are the first to propose a hydrodynamic model for chemotaxis; moreover, they introduce a strategic friction term in the stochastic equation and, again through a mean field approximation, they come to a continuum model. The interesting thing, which will be detaily analyzed in the last section of this chapter, is that both models (the Cattaneo type model and the hydrodynamic model with the presence of a friction force) come out to be hyperbolic, while we saw in chapter 1 that the Keller-Segel model was a parabolic-parabolic model.

This fact produce a change in the stability of the system, which we will analyze in the

next chapter. There, we will also state why these new hyperbolic models are more realistic than the parabolic one.

2.1 Cattaneo type models for chemotaxis

2.1.1 Cattaneo's Theory of heat propagation

Let us first make a step back and have a brief look at how the Cattaneo's theory of heat propagation in spatially unbounded regions was born.
For sake of simplicity, in this section we will work in only one spatial dimension. Of course, every result could be intuitively generalized to more than one spatial dimensions.
The classical 1D heat equation, with absence of heat supplies, is:

$$\frac{\partial \theta}{\partial t} = D\frac{\partial^2 \theta}{\partial x^2} \tag{2.1}$$

where $\theta = \theta(t, x)$ is the absolute temperature and D is the constant and positive thermal diffusivity.
The equation (2.1), for the initial condition $\theta(x, 0) = k\delta_0(x)$, where $k > 0$ $\delta_0(x)$ is the Delta of Dirac measure centered in the origin, easily yields to the instantaneous solution ([20]):

$$\theta(t, x) = \frac{A}{\sqrt{t}} e^{-\frac{x^2}{4Dt}}$$

where A is a constant which depends on the initial condition. We observe that this solution predicts infinite speed of propagation. At time $t = 0$, we have temperature $\theta = 0$ everywhere but in a point (which might be called the source of heat) and our solution implies $\theta \neq 0 \; \forall x \in \mathbb{R}$, if $t > 0$.
In order to overcome infinite speed of propagation, in [3] was proposed the following hyperbolic model for thermal diffusion. Let us note that the diffusion equation (2.1) is a combination of the local conservation law:

$$\frac{\partial \theta}{\partial t} = -\frac{\partial J}{\partial x} \tag{2.2}$$

with a flux gradient constitutive law for the heat flux vector $J(t, x)$:

$$J(t, x) = -D\frac{\partial \theta}{\partial x}(t, x) \tag{2.3}$$

This last equation is known as Fourier's Law for heat conduction. Cattaneo's theory acts properly on this. He introduces a small delay time in the response of the temperature: thus the heat flux does not depend istantaneously on the temperature

gradient, but there is a short timelag τ before this effect is felt, as experimentally observed. So the new constitutive law becomes:

$$J(t+\tau, x) = -D\frac{\partial \theta}{\partial x}(t, x) \tag{2.4}$$

where the parameter $\tau > 0$ plays the role of a thermal relaxation time.
If we expand the LHS of (2.4) as a Taylor series in t, and we neglect the second and higher order terms, we easily get the rate-type equation:

$$J(t, x) + \tau\frac{\partial J}{\partial t}(t, x) = -D\frac{\partial \theta}{\partial x}(t, x) \tag{2.5}$$

Differentiating with respect to x both sides of (2.5) and plugging the result for $\frac{\partial J}{\partial x}$ into the conservation law (2.2), we have:

$$\frac{\partial \theta}{\partial t} - \tau\frac{\partial^2 J}{\partial x \partial t} = D\frac{\partial^2 \theta}{\partial x^2} \tag{2.6}$$

Finally, if we identify again $\frac{\partial J}{\partial x}$ with $-\frac{\partial \theta}{\partial t}$, we arrive at the modified heat propagation equation according to Cattaneo:

$$\frac{\partial \theta}{\partial t} + \tau\frac{\partial^2 \theta}{\partial t^2} = D\frac{\partial^2 \theta}{\partial x^2} \tag{2.7}$$

This equation, which is of second order in time, is hyperbolic, and it is analogous to the telegrapher's equation, which takes into account memory effects. As we can see in chapter 1.2 of [20], its characteristic curves may be interpreted as thermal waves propagating with finite speeds given by $\pm\sqrt{\frac{D}{\tau}}$.
It is worth to observe that when we write the Fourier's Law (2.3) for the entropy flux given by $\frac{J}{\theta}$, we recover a nonlinear degenerate parabolic equation, known in literature as a Porous Medium Equation with exponent 2 (already mentioned at the end of chapter 1). We remember that such equations exhibit the remarkable mathematical property of finite wave speed propagation (see [21] by Vazquez). In this way, the classification of the partial differential equation does not change (it is still parabolic), but the paradox of an infinite speed is nevertheless overcome. This could be another interesting issue to be addressed also in the context of cells in a chemosensitive movement, as we have seen in the most recent research about PME models for chemotaxis ([21] and [2]).

2.1.2 Cattaneo's Law into Keller-Segel model

Now, following the scheme proposed by Dolak and Hillen in [7], we apply a 3D Cattaneo type correction to the KS model for a chemosensitive movement. For sake of

generality, we start with the parabolic model:

$$\begin{aligned} \frac{\partial \rho}{\partial t} &= \nabla \cdot (k_1(\rho, c)\nabla\rho - k_2(\rho, c)\rho\nabla c) + k_3(\rho, c) \\ \frac{\partial c}{\partial t} &= D_c\Delta c + k_4(\rho, c)\rho - k_5(\rho, c)c \end{aligned} \tag{2.8}$$

Our aim is to turn the parabolic equation which describe the movement of the motile organism into a hyperbolic one. The motivation will be carefully explained in chapter 3, where we will analyze in detail the instability of the various models, together with the prediction of pattern formation or blow-ups. We can anyway give a brief idea: by introducing a small delay time, we take into account the visco-elastic properties of the medium where the motion happens.

The bacteria flux in the Keller-Segel model may be given by:

$$\vec{J}^{(\rho)}(t, \vec{x}) = -k_1(\rho, c)\nabla\rho + k_2(\rho, c)\rho\nabla c \tag{2.9}$$

where, for sake of simplicity, we have omitted the $(t, \vec{x})$ dependences.

As before, we assume that the flux is not istantaneously equal to the right hand side of (2.9), but it may relaxe to it within a time constant $\tau > 0$. Again, we perform a first order Taylor expansion of the LHS in order to get a new rate type equation for the flux $\vec{J}^{(\rho)}$. Thus, the alternative Cattaneo model for chemotaxis reads:

$$\begin{aligned} &\frac{\partial \rho}{\partial t} + \nabla \cdot \vec{J}^{\rho} = k_3(\rho, c) \\ &\tau\frac{\partial \vec{J}^{\rho}}{\partial t} + \vec{J}^{\rho} = -k_1(\rho, c)\nabla\rho + k_2(\rho, c)\rho\nabla c \\ &\frac{\partial c}{\partial t} = D_c\Delta c + k_4(\rho, c)\rho - k_5(\rho, c)c \end{aligned} \tag{2.10}$$

We observe that the equation of the chemical is just the same as in chapter one. On the other hand, the equation of the bacteria is quite changed: it is introduced a delay time in the response to the chemical gradient. We thus expect that the pioneristic Keller-Segel model and this new Cattaneo model share the same asymptotic behavior, that is in a long time scale both modellings show the same results. However, for short time ranges, we expect a better description from the Cattaneo model, due to the presence of a small relaxation time.

In [10] we can find an interesting derivation of a Cattaneo-type model for chemosensitive movement, based on a moment closure procedure of a kinetic equation. It is a microscopic-stochastic approach, and in that the relevant parameters (diffusion constant D_ρ, chemotactic function χ, delay time τ) are directly related to the movement characteristics of the individual microorganisms (turning rate μ and velocity distribution T). We are not interested here in analyzing in detail this approach.

We would rather focus on the hydrodynamic model for describing chemotaxis, first proposed by Chavanis and Sire in 2007.

2.2 Hydrodynamic model and friction forces

In this section, we introduce a hydrodynamic model for chemotaxis, in which the flux of particles is considered as a fluid (having a mass flux, given by $\rho\vec{v}$). We will derive the hydrodynamic model as a limit of a kinetic model, following [4] and [6]. We observe that the hydrodynamic model is hyperbolic and may be suitably comparable with the Euler's model for barotropic fluids. In a second moment, we introduce a friction force (by a term labeled with $-\xi\vec{v}$), and we formulate a model which takes into account also the inertia of the system. Finally, we show how this model, in the limit of strong friction ($\xi \longrightarrow +\infty$), reduces to the primitive Keller-Segel (parabolic) model; on the other hand, in the limit of weak friction ($\xi \longrightarrow 0$), it reduces to the hydrodynamic hyperbolic model.

We start with a slightly different parabolic-parabolic model for chemotaxis.

$$\begin{aligned} \frac{\partial \rho}{\partial t} &= \nabla \cdot (\nabla p(\rho) - \chi(\rho, c)\rho \nabla c) \\ \frac{\partial c}{\partial t} &= D_c \Delta c - c\ell(\rho, c) + \rho h(\rho, c) \end{aligned} \tag{2.11}$$

The first equation is still a drift-diffusion equation, as in (1.18), but now the cells flux term $D_\rho \nabla \rho$ is replaced by a more general "pressure term" $\nabla p(\rho)$, taking into account the barotropic state equation $p = p(\rho)$ for compressible fluids.

As we will show in chapter 3, the parabolic Keller-Segel model (1.18) is able to predict Dirac peaks (clusters), whereas the new model predicts smoother density profiles (aggregates). The dynamical evolution of the regularized model (2.11) generically leads to the formation of a high number of round aggregates which progressively merge until one final big aggregate remains.

However, recent experiments of *in vitro* formation of blood vessels show that cells randomly spread on a gel matrix autonomously form a connected vascular network that is interpreted as the beginning of a vasculature. This phenomenon is responsible of angiogenesis, a major actor for the growth of tumors; therefore, here is one of the main reason why it is so important to propose and then study new and more realistic mathematical models which describe chemotaxis in order to account for the formation of complex network patterns like filaments rather than only peaks or aggregates. Meanwhile these networks cannot be explained via the parabolic models like (1.18) or (2.11); but they can be recovered via **hyperbolic-parabolic** equations of the form:

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \vec{v}) = 0 \tag{2.12}$$

$$\frac{\partial \vec{v}}{\partial t} + (\vec{v} \cdot \nabla)\vec{v} = -\frac{1}{\rho}\nabla p + \nabla c \tag{2.13}$$

$$\frac{\partial c}{\partial t} = D_c \Delta c - \ell(c)c + h(c)\rho \tag{2.14}$$

There are striking similarities between the evolutionary system of hydrodynamic equations above and the so-called Euler-Poisson hyperbolic-elliptic system, used to describe large scale structures in the universe. Our system reduces to the Euler-Poisson system whenever the parabolic equation (2.14) reduces to the stationary elliptic form:

$$h\rho + \Delta c = 0$$

where $h = 4\pi G$; G is the gravitational constant and c plays the role of self-gravity potential. Note that the degradation rate ℓ in the E-P equations may be substituted by $\Lambda > 0$, the cosmological constant.

There is indeed an interesting analogy between the chemotactic collapse in bio-medical settings and the gravitational collapse of a self gravitating gas cloud of the interstellar matter in astrophysics. This may be an other interesting issue to debate (cellular aggregation versus stellar formation, see [5]).

As before, $\rho(\vec{r}, t)$ is the density and $\vec{v}(\vec{r}, t)$ is a smooth velocity. As a hydrodynamic system, we have used the density dependent pressure term $-\nabla p$: it can take into account the fact that the cells do not interpenetrate (as they are considered in a single-fluid approach).

We propose a kinetic derivation of hyperbolic models of this type starting from a microscopic description of the dynamic of the biological population. The closed set of hydrodynamic equations we will derive is as follows:

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \vec{v}) = 0 \tag{2.15}$$

$$\frac{\partial \vec{v}}{\partial t} + (\vec{v} \cdot \nabla)\vec{v} = -\frac{1}{\rho}\nabla p + \nabla c - \xi \vec{v} \tag{2.16}$$

$$\frac{\partial c}{\partial t} = D_c \Delta c - \ell(c)c + h(c)\rho \tag{2.17}$$

It involves a friction term $-\xi\vec{v}$: the minus sign explain it is in opposition to the destabilizing chemotactic drift ∇c. It is easy to see that, for $\xi = 0$, we recover the hyberbolic model (2.12)-(2.14), which is the hydrodynamic alternative to the Cattaneo model for chemotaxis proposed in section 2.1. On the other hand, let us analyze what happens in the limit of strong friction, when $\xi \longrightarrow +\infty$.

Let us start with equation (2.16) and multiply both sides by $\frac{\rho}{\xi}$. We obtain:

$$\frac{\rho}{\xi}\left[\frac{\partial \vec{v}}{\partial t} + (\vec{v} \cdot \nabla)\vec{v}\right] = -\rho\vec{v} + \frac{1}{\xi}(-\nabla p + \rho \nabla c) \tag{2.18}$$

We know $\xi \longrightarrow +\infty$, so we can neglect the left hand side of (2.18) (acceleration terms). Thus we may isolate the term $\rho\vec{v}$ to be inserted in (2.15) to get:

$$\frac{\partial \rho}{\partial t} + \nabla \cdot \left[\frac{1}{\xi}(-\nabla p + \rho \nabla c)\right] = 0 \tag{2.19}$$

We need to remember the pressure is density dependent through the state equation $p = p(\rho)$, where $p(\rho)$ is of class C^1 with $p'(\rho) > 0$, as experimentally required. So, we can write $p'(\rho)\nabla\rho$ in place of $\nabla p(\rho)$. Thus, if we fix the chemotactic constant $\chi_0 = \frac{1}{\xi}$, and the diffusive parameter $D_\rho = \frac{1}{\xi}p'(\rho)$, we recover:

$$\frac{\partial \rho}{\partial t} = \nabla \cdot (D_\rho \nabla \rho) - \nabla \cdot (\chi_0 \rho \nabla c) \tag{2.20}$$

which, together with the equation (2.17) which is unchanged, represents the Keller-Segel parabolic model presented in chapter 1, where the first term of the RHS of (2.20) is the diffusion term and the second one is the chemotactic drift. In conclusion, we can say that in the limit of strong friction, the hydrodynamic hyperbolic model which takes into account inertial terms and a friction force reduces to the classical parabolic model.

2.2.1 Derivation of the hydrodynamic equations

We shall introduce a model of chemotactic aggregation generalizing the Keller-Segel model (1.9). For biological systems, the number of constituents is not necessarily large so that it may be relevant to return to a "corpuscular" description of the system and introduce (as we have done in the stochastic derivation for the KS model in section 1.2) an equation of motion for each particle. We have seen that the motion of individuals might be described by a stochastic differential equation of the form:

$$\frac{dP_k}{dt} = \chi \nabla c + \sqrt{2D_\rho}\, W_k(t) \tag{2.21}$$

where the first term in the right hand side is the chemotactic drift to which the particles are submitted and the second term is a stochastic term (random). W_k, a standard Brownian motion, is the mathematical description of diffusion, the random motion that is observed for several biological organisms.
The number N is not necessarily large, so it may be of interest to treat the bacterial colony as a discrete system of particles. By contrast, the chemical that is secreted is usually described as a continuous field. Therefore, the evolution of the concentration of the chemical is governed by an equation of the form:

$$\frac{\partial c}{\partial t} = D_c \Delta c - \ell c + h \sum_{k \in S_{N_\rho}} \delta(P - P_k(t)) \tag{2.22}$$

Equations (2.21)-(2.22) have been studied a lot in literature and in the mean-field approximation they return the usual KS model. The computations are similar to those done in section 1.2, for more details you may see Appendix A of [6].
We shall now generalize the model in two respects. First of all, there exist biological

systems for which the inertia of the particles has to be taken into account. This "inertia" means they do not respond immediately to the chemotactic drift. We propose therefore to describe the motion of each individual particle by a stochastic equation of the form:

$$\begin{aligned} \frac{dP_k}{dt} &= \vec{v}_k \\ \frac{d\vec{v}_k}{dt} &= -\xi\vec{v}_k + \nabla c + \sqrt{2D}\, W_k(t) \end{aligned} \tag{2.23}$$

where the first term is a friction force, the second term is a force that models the chemotactic attraction due to the chemical c and the last term is a random force ($D > 0$ is constant). If we stop here our generalization and we pass to the hydrodynamic description, as we can see in Appendix A of [6], in the mean-field approximation we obtain the model (3.17)-(3.19) with a linear (isothermal) equation of state $p = \rho T = \frac{D\rho}{\xi}$.

Therefore, the second generalization we want to make is to consider a class of SDEs where the diffusion coefficient explicitly depends on the distribution function $f(\vec{r}, \vec{v}, t)$ of particles in phase space. Let us simplify the formalism and make a mean-field approximation since the start, in order to describe the motion of each individual of the biological population by a stochastic equation of the form:

$$\frac{d\vec{v}}{dt} = -\xi\vec{v} + \nabla S(c) + \sqrt{2D(f)}\, W(t) \tag{2.24}$$

where, as usual, $W(t)$ is a standard Brownian motion, responsible of the random diffusive motion, and, for sake of generality, we now have written the chemotactic force as the gradient of a function $S(c)$ of the concentration. The mean field force is determined by:

$$\frac{\partial c}{\partial t} = D_c\Delta c - \ell(c)c + h(c)\rho \tag{2.25}$$

where, because of the mean field approximation, the smooth local density of cells is $\rho(\vec{r}, t) = \langle\sum_i \delta(P - P_i(t)\rangle$ (the brackets denote an average).

So, our stochastic model is constituted by the equations (2.24)-(2.25). We shall now derive the hydrodynamic equations associated with that. Using standard methods of Brownian theory, we find that the evolution of the distribution function $f(\vec{r}, \vec{v}, t)$ of the system is described by a generalized mean field Fokker-Planck equation of the form

$$\frac{\partial f}{\partial t} + \vec{v}\cdot\frac{\partial f}{\partial \vec{r}} + \nabla S(c)\cdot\frac{\partial f}{\partial \vec{v}} = \frac{\partial}{\partial \vec{v}}\cdot\left[\frac{\partial}{\partial \vec{v}}(D(f)f) + \xi f\vec{v}\right] \tag{2.26}$$

In literature, lots of particular cases has been considered, such as when $D(f)$ is a power law or when $D(f) = Df[C(f)/f]'$, with $C(f)$ a convex function.

Our aim is now to derive the moments equations from the generalized nonlinear

Fokker-Planck (NFP) equation above. Let us firstly define the density and the local velocity by:

$$\begin{aligned} \rho &= \int f \, d\vec{v} \\ \rho\vec{u} &= \int f\vec{v} d\vec{v} \end{aligned} \tag{2.27}$$

Integrating (2.26) on velocity, we get the continuity equation:

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \vec{u}) = 0 \tag{2.28}$$

Next, multiplying (2.26) by $\vec{v}$ and integrating on velocity, we obtain

$$\frac{\partial}{\partial t}(\rho u_i) + \frac{\partial}{\partial x_j}(\rho u_i u_j) = -\frac{\partial (p\delta_{ij})}{\partial x_j} + \rho S'(c)\frac{\partial c}{\partial x_i} - \xi \rho u_i \tag{2.29}$$

where, using a condition of local thermodynamic equilibrium, we have defined the "pressure" tensor

$$P_{ij} = p(\rho)\delta_{ij} = \int f w_i w_j d\vec{v}$$

where $\vec{w} = \vec{v} - \vec{u}$ is the relative velocity. Using the continuity equation (2.28), the eq. (2.29) can be rewritten

$$\rho\left(\frac{\partial u_i}{\partial t} + u_j \frac{\partial u_i}{\partial x_j}\right) = -\frac{\partial (p\delta_{ij})}{\partial x_j} + \rho S'(c)\frac{\partial c}{\partial x_i} - \xi \rho u_i \tag{2.30}$$

Writing this last equation in vector form, and collecting the other constitutive equations, we obtain a hydrodynamic model of the form:

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \vec{u}) = 0 \tag{2.31}$$

$$\frac{\partial \vec{u}}{\partial t} + (\vec{u} \cdot \nabla)\vec{u} = -\frac{1}{\rho}\nabla p + \nabla S(c) - \xi \vec{u} \tag{2.32}$$

$$\frac{\partial c}{\partial t} = D_c \Delta c - \ell(c)c + h(c)\rho \tag{2.33}$$

In this way, equations (2.31)-(2.32) govern a damped barotropic Euler-type fluid in the presence of friction and chemotactic forces. They are interesting as they connect hyperbolic models to parabolic models, as we have seen at the beginning of the section. For $\xi = 0$ we recover the hyperbolic model (2.12)-(2.14). Alternatively, for $\xi \longrightarrow +\infty$, we can easily get the following expression for the velocity:

$$\vec{u} = -\frac{1}{\xi\rho}(\nabla p - \rho S'(c)\nabla c) + O(\xi^{-2})$$

. Substituting this drift term in the continuity equation (2.31), we obtain the drift-diffusion equation

$$\frac{\partial \rho}{\partial t} = \nabla \cdot \left[\frac{1}{\xi}(\nabla p - \rho S'(c)\nabla c)\right] \tag{2.34}$$

which is a generalization of the KS parabolic-parabolic model.

Chapter 3

Stability analysis: aggregation and pattern formation

In this chapter we shall devote our main attention to the aggregation process. Our basic point of view is to regard aggregation as a manifestation of instability in a uniform distribution of microorganisms and chemicals. We assume throughout a homogeneous population of cells. For instance, as noticed by Keller and Segel in [14], in the early life cycle of the amoebae, the properties of the cells are supposed to be such that a uniform distribution is stable. At some point in the life cycle of all cells, however, the characteristics of the individual cell change in such a way as to make a uniform distribution unstable. Any spontaneous perturbation can then trigger aggregation. We do not attempt to offer a physical explanation of the mechanisms for changes in the individual cell, but rather analyze the effects on a population of cells which result from such changes.

Instability of the kind we are going to consider have been studied since the 1950s and have received some attention as possible mechanisms for certain kind of structure or pattern formation in biological world (for example, **Turing instability**, see [16]).

In the first part of the chapter, we will focus on a spectral analysis for a general form of the KS parabolic-parabolic model. We will make a parallelism between instability and aggregation and we then analyze the instability condition as a solution of an eigenvalue problem. The scheme is the same as in [14] and [12], but, as we have chosen a general model, the computations and the notations are slightly different.

In the second part of the chapter, we will compare our results for the parabolic-parabolic model to other results regarding the hyperbolic and hydrodynamic models. Following [5], we will underline the similarities between the hydrodynamic model for chemotaxis and the Euler-Poisson model used to describe stellar aggragates in astrophysics. There is thus an analogy between the chemotactic collapse in biology and the gravitational collapse in astrophysics.

We will conclude with the differences between the instability in parabolic models, which leads to Dirac peaks or clusters (big aggregates), and that of hyperbolic/hydrodynamic models, which lead to formation of network patterns.

3.1 Spectral analysis for the Keller-Segel model

In our analysis, the system we will consider is the following:

$$\begin{aligned} \frac{\partial \rho}{\partial t} &= \nabla \cdot (D_\rho \nabla \rho - \chi(\rho, c)\rho \nabla c) \\ \frac{\partial c}{\partial t} &= \nabla \cdot (D_c \nabla c) + h(\rho, c)\rho - \ell(\rho, c)c \end{aligned} \tag{3.1}$$

where, again, D_ρ and D_c, the parameters of diffusivity, are positive constants, and we do not consider the effects of births or deaths for the bacteria ρ.
A uniform steady state for the system above arises when both the time and space derivatives of density ρ and concentration c are null. Thus we get a uniform (constant) state of equilibrium

$$(\rho_0, c_0)$$

such that they are related by:

$$h(\rho_0, c_0)\rho_0 = \ell(\rho_0, c_0)c_0 \tag{3.2}$$

Let us now look for solutions of (3.1) near to the equilibrium; that means we are looking for solution of the kind:

$$\begin{aligned} \rho(t, \vec{x}) &= \rho_0 + \delta\rho(t, \vec{x}) \\ c(t, \vec{x}) &= c_0 + \delta c(t, \vec{x}) \end{aligned} \tag{3.3}$$

where $\delta\rho$ and δc are small perturbations and they are time and space dependent. The time dependence of these solutions plays a key role in the instability analysis. If the solution increases as time increases, this means that, as time goes by, the solution is going further and further from the uniform state. Thus, the instability arises. On the other hand, as the solution decreases with time, then any random perturbation which occurs in the uniform state of equilibrium will eventually decay.
In order to abbreviate the notation, we will use $\chi_0 = \chi(\rho_0, c_0)$, $h_0 = h(\rho_0, c_0)$ and $\ell_0 = \ell(\rho_0, c_0)$.
Now, we want to put (3.3) into our system (3.1). In order to do that, we perform a Taylor expansion of the RHS of (3.1). That means we expand terms depending on ρ and c as follows:

$$F(\rho, c) = F(\rho_0, c_0) + \left(\frac{\partial F}{\partial \rho}\right)_{(\rho_0, c_0)} \delta\rho + \left(\frac{\partial F}{\partial c}\right)_{(\rho_0, c_0)} \delta c + \cdots \tag{3.4}$$

where, due to the smallness of $\delta\rho$ and δc, we can ignore higher order terms (denoted by $\cdots$). Thus, the linearized equations which result are:

$$\begin{aligned}\frac{\partial\delta\rho}{\partial t} &= \nabla\cdot(D_\rho\nabla\delta\rho - \chi_0\rho_0\nabla\delta c)\\ \frac{\partial\delta c}{\partial t} &= \nabla\cdot(D_c\nabla\delta c) + h_0\delta\rho + (h_\rho\delta\rho + h_c\delta c)\rho_0 - \ell_0\delta c - (\ell_\rho\delta\rho + \ell_c\delta c)c_0\end{aligned} \tag{3.5}$$

as ρ_0 and c_0 are constant. In the system above, we have indicated with h_ρ, h_c, ℓ_ρ and ℓ_c the partial derivatives $\frac{\partial h}{\partial\rho}$, $\frac{\partial h}{\partial c}$, $\frac{\partial\ell}{\partial\rho}$ and $\frac{\partial\ell}{\partial c}$, each evaluated in (ρ_0, c_0).
For simplicity of notations, let us call $\bar{h} = h_0 + h_\rho(\rho_0, c_0)\rho_0$ and $\bar{\ell} = \ell_0 + \ell_c(\rho_0, c_0)c_0$, in order to get the following Cramer system, linear in $\delta\rho$ and δc:

$$\begin{aligned}\frac{\partial\delta\rho}{\partial t} &= D_\rho\Delta\delta\rho - \chi_0\rho_0\Delta\delta c\\ \frac{\partial\delta c}{\partial t} &= D_c\Delta\delta c + (\bar{h} - c_0\ell_\rho(\rho_0, c_0))\delta\rho - (\bar{\ell} - \rho_0 h_c(\rho_0, c_0))\delta c\end{aligned} \tag{3.6}$$

We look for solutions to (3.6) of the form:

$$\begin{aligned}\delta\rho(t,\vec{x}) &= Ae^{\sigma t + \mathrm{i}\vec{k}\cdot\vec{x}}\\ \delta c(t,\vec{x})) &= Be^{\sigma t + \mathrm{i}\vec{k}\cdot\vec{x}}\end{aligned} \tag{3.7}$$

where the amplitudes A and B are constant real numbers, σ (real or complex) is the growth rate parameter, and $\vec{k}$ is a constant vector in $\mathbb{R}^3$. As usual, we have indicated with i the imaginary unity.
Substituting (3.7) into (3.6), we obtain:

$$\begin{aligned}&A(\sigma + k^2 D_\rho) - Bk^2\chi_0\rho_0 = 0\\ &A(c_0\ell_\rho(\rho_0, c_0) - \bar{h}) + B(\sigma + k^2 D_c + \bar{\ell} - \rho_0 h_c(\rho_0, c_0)) = 0\end{aligned} \tag{3.8}$$

where we have multiplied both sides for the exponential $e^{-\sigma t - \mathrm{i}\vec{k}\cdot\vec{x}}$ and we have labelled with k the modulus of the vector $\vec{k}$, that is the *wave-number* of the solution.
System (3.8) can be rewritten in a matrix form as follows:

$$\begin{pmatrix} \sigma + k^2 D_\rho & -k^2\chi_0\rho_0 \\ c_0\ell_\rho(\rho_0, c_0) - \bar{h} & \sigma + k^2 D_c + \bar{\ell} - \rho_0 h_c(\rho_0, c_0)\end{pmatrix}\begin{pmatrix} A \\ B\end{pmatrix} = \begin{pmatrix} 0 \\ 0\end{pmatrix} \tag{3.9}$$

Equation (3.9) for A and B have a non-trivial solution if and only if the determinant of the coefficients' matrix vanishes. Right for this reason, all this procedure is called spectral analysis: we have seen that all the problem reduces to an eigenvalue problem. It follows that:

$$\sigma^2 + \beta\sigma + \gamma = 0 \tag{3.10}$$

where:

$$\beta = k^2 D_\rho + k^2 D_c + \bar{\ell} - \rho_0 h_c(\rho_0, c_0) \tag{3.11}$$

$$\gamma = k^4 D_\rho D_c + k^2 D_\rho(\bar{\ell} - \rho_0 h_c(\rho_0, c_0)) + k^2 \chi_0 \rho_0 (c_0 \ell_\rho(\rho_0, c_0) - \bar{h}) \tag{3.12}$$

The first observation we make is that $\Delta > 0$, namely $\beta^2 > 4\gamma$. As a consequence, equation (3.10) has real roots. For elementary results of algebraic calculus, they will be both negative if and only if $\beta > 0$ and $\gamma > 0$. In our situation, these conditions translate into:

$$k^2 D_c + \bar{\ell} - \rho_0 h_c(\rho_0, c_0) > -k^2 D_\rho \tag{3.13}$$

$$k^2 D_c + \bar{\ell} - \rho_0 h_c(\rho_0, c_0) > \frac{\chi_0 \rho_0 (\bar{h} - c_0 \ell_\rho(\rho_0, c_0))}{D_\rho} \tag{3.14}$$

where, to find the second one, we have divided each term of γ by $k^2 D_\rho$.
Now it is worth to make a step back and remember that the functions ℓ and h, responsible of degradation and production of the chemical, were supposed to be just dependent on the chemical concentration c and not on the microorganisms density ρ. Once done this assumption, a consequence is that $\ell_\rho = 0$. Thus we are able to notice that the RHS of (3.14) is positive, whereas the RHS of (3.13) is negative, since all the parameters k, D_ρ, χ_0, ρ_0 and $\bar{h} = h_0$ are positive numbers. So, if condition (3.14) is satisfied, then also (3.13) will be satisfied. Thus, for a given value of k, the sole condition for stability (as we have seen, it corresponds to $\sigma < 0$) is:

$$D_\rho(k^2 D_c + \bar{\ell}) > \chi_0 \rho_0 h_0 + D_\rho \rho_0 h'(c_0) \tag{3.15}$$

where we have changed the partial derivative of h with the usual derivative, as we have argued that now we are considering h as a function of the only c.
Instability of the uniform state will occur if the LHS of (3.15) exceeds the RHS. This will first occur for disturbances associated with zero wave number $k = 0$. If we solve (3.10), we can also show that unstable disturbances with $k = 0$ always grow fastest. The final instability condition therefore reads:

$$\frac{\chi_0 \rho_0 h_0}{D_\rho \bar{\ell}} + \frac{\rho_0 h'(c_0)}{\bar{\ell}} > 1 \tag{3.16}$$

We have shown that instability commences at $k = 0$, that is at infinite wave-length (remember that k is the wave-number, so the wave-length is $\frac{2\pi}{k}$). It can be seen from (3.10) with $\sigma = 0$ and (3.12) that the stabilizing effect of bacteria diffusion and the destabilizing effect of chemotaxis both decrease with k but the ratio of the two effects is the unity. Equation (3.15) shows that the stabilizing effect of chemical diffusion also decrease as k decreases. In conclusion we can argue that perturbations

of infinite wave-length ($k = 0$) are most likely to grow because they are unaffected by the chemical diffusion (note that D_c does not appear in the instability condition).
It is interesting for further results to look at [12]. In this article, Hillen and Painter show eight different parabolic models for chemotaxis connected to different choices for the chemotactic function or the diffusivities. Then, they give conditions for instability for all of them in terms of the chemotactic parameter χ, the diffusivity D and other parameters which characterize their models. Moreover, they give the range for the wave-number k in order to get instability.

3.1.1 Physical meaning of the instability condition

We want to understand better the instability condition, by examining some of its qualitative features. Given an initial perturbation, there may be some factors which make it decay and some others which make it grow. As we can see in (3.16) there are two quite different independent sources of instability, given by the two terms of the LHS of the equation. We shall examine them separately.
The first term is of particular interest because it includes the chemotactic sensitivity χ. It is also the only term that remains when the chemical production is independent of the concentration ($h(c)$ is constant, so $h'(c) = 0\ \forall c$). To understand this term, suppose that a high concentration of bacteria and chemical momentarily appears at a point P. The greater is the rate production of the chemical at equilibrium $h(c_0)$, the more rapidly the chemical level is increased at this point even further. In addiction, a large value of χ will cause the microorganisms near P to be more strongly attracted by the relatively high concentration of chemical in P. On the other hand, a large value of D_ρ indicates a strong tendency to smooth out the local maximum in microorganisms concentration by diffusion. Similarly, a large value of the decay rate $\bar{\ell}$ will more effectively flatten out the local maximum for the chemical concentration. When the second term of (3.16), $\frac{\rho_0 h'(c_0)}{\bar{\ell}}$, is negligible compared to 1, it is thus the relative predominance of diffusion and chemical degradation on one hand, or chemotactic response and chemical production on the other, which determine the stability or instability of the uniform steady state. We have seen that the chemotactic response increases the instability and the aggregation, whereas the diffusion is a smoothing process, which increases the stability of the uniform state.
The second term illustrates an other mechanism for instability. The inequality $\rho_0 h'(c_0) > \bar{\ell}$ implies that a small increase in the chemical level cause an increase in the chemical output which outweighs its more rapid decay ([14]). This would lead immediately to an instability in the level of chemical. If there is no chemotaxis ($\chi = 0$), this would be the only mechanism in order to get instability. However, when $\chi = 0$, the microorganisms are not effected by the chemical concentration, so we are not able to

see cellular aggregation. It is only in virtue of a non vanishing chemotactic sensitivity χ that an instability in the chemical level can lead to a breakdown of the uniform concentration of the microorganisms.
In conclusion, we have shown theoretically that a homogeneous distribution of microorganisms which are moving according to a random-diffusive motion and to a chemotactic drift will become unstable if the cells suffer an increase in:

- their chemotactic sensitivity χ to a chemical gradient;
- their rate of chemical production h;
- the amount that a high ambient chemical level stimulates their rate of chemical production (derivative of h, evaluated in c_0).

Otherwise, there will be instability of the uniform distribution if the cells suffer a decrease in their diffusivity parameter D_ρ.
We have not mentioned the rate of degradation of the chemical ℓ since it is characteristic of the chemical and not of the cells which produce it.

3.2 Instability analysis for the hydrodynamic model

For the moment, we do not analyze the stability of the hyperbolic Cattaneo type model. That choice is because the hydrodynamic model proposed and derived in chapter 2, with the friction term, in the case when the friction coefficient ξ is closed to zero, reduces to a hyperbolic hydrodynamic model, whose behavior is barely the same as for the Cattaneo type model.
Let us start again reminding the hydrodynamic model derived in section 2.2, following [6]:

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \vec{u}) = 0 \tag{3.17}$$

$$\frac{\partial \vec{u}}{\partial t} + (\vec{u} \cdot \nabla)\vec{u} = -\frac{1}{\rho}\nabla p + \nabla c - \xi \vec{u} \tag{3.18}$$

$$\frac{\partial c}{\partial t} = -\ell(c)c + h(c)\rho + D_c \Delta c \tag{3.19}$$

Interestingly, this model of chemotaxis is similar to a model of self-gravitating particles described by the damped Euler-Poisson system:

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \vec{u}) = 0 \tag{3.20}$$

$$\frac{\partial \vec{u}}{\partial t} + (\vec{u} \cdot \nabla)\vec{u} = -\frac{1}{\rho}\nabla p + \nabla \Phi - \xi \vec{u} \tag{3.21}$$

$$\Delta \Phi = S_d G \rho \tag{3.22}$$

As we have done for the chemotaxis model, also for this system we can analyze the case when we have weak friction ($\xi = 0$) and when we have strong friction ($\xi \longrightarrow \infty$). For $\xi = 0$, the system (3.20)-(3.22) reduces to the barotropic Euler-Poisson system; for $\xi \longrightarrow \infty$, on the other hand, we obtain the generalized Smoluchowski-Poisson system:

$$\frac{\partial \rho}{\partial t} = \nabla \cdot \left[\frac{1}{\xi} (\nabla p - \rho \nabla \Phi) \right] \tag{3.23}$$

$$\Delta \Phi = S_d G \rho \tag{3.24}$$

In this analogy (see e.g. [5]) we observe that the concentration $-c(t,x)$ of the chemical plays the same role as the gravitational potential $\Phi(t,x)$. In biology, the interaction is mediated by a *material* substance (the secreted chemical) while the physical interpretation of the gravitational potential in astrophysics is more abstract.
The main difference between the chemotactic model (3.17)-(3.19) and the gravitational model (3.20)-(3.22) concerns the field equations (3.19) and (3.22). In astrophysics, the gravitational potential is determined istantaneously from the density of particles through the Poisson equation (3.22). In biology, the equation (3.19) determining the evolution of the chemical is more complex and it involves memory terms. The chemical diffuses with a diffusion coefficient D_c, is produced by the organisms at a rate h and is degraded at a rate ℓ. In this thesis, following the observation done by Chavanis and Sire in [5], we shall consider simplified models where the term $\frac{\partial c}{\partial t}$ can be neglected. This is valid in a limit of large diffusivity of the chemical ($D_c \longrightarrow \infty$).
In [5], we may also find that we can take the rate of chemical production and degradation as constants, and not dependent on the concentration c. Moreover, we first consider a model without chemical degradation ($\ell = 0$). Then, assuming $h = \lambda D_c$, and taking the limit $D_c \longrightarrow \infty$, we get:

$$\Delta c = -\lambda(\rho - \bar{\rho}) \tag{3.25}$$

where $\bar{\rho} = \frac{1}{V} \int \rho \, dx$ is the average value of the density which is a conserved quantity. In this case, the concentration is given by a Poisson equation. We refer to this model as "Newtonian model".
Then, we consider a case of finite degradation rate. Assuming $h = \lambda D_c$, $\ell = \ell_0^2 D_c$ and taking the limit $D_c \longrightarrow \infty$, one may get:

$$\Delta c - \ell_0^2 c = -\lambda \rho \tag{3.26}$$

If we formally take $\ell_0 = 0$, we obtain a Poisson equation similar to (3.22) where $-c(t,x)$ plays the role of $\Phi(t,x)$ and λ plays the role of the gravitational constant $S_d G$. However, equation (3.26) has been derived for $\ell_0 \neq 0$. This implies that the

interaction is shielded on a typical distance ℓ_0^{-1}. We shall refer to this model as "Yunkawa model", from the Yunkawa shielding in nuclear physics.
In this thesis, we shall not make the detailed computation for the linear stability analysis of the hydrodynamic model. Our aim is to give an idea of the differences between this model and the parabolic-parabolic model. As one can suppose, the scheme is similar to the one used for the KS model in section 3.1. We now give the main results and we always refer to [5] for further details.
We remind that our study concerns the stability of a uniform distribution against chemotactic collapse. This is similar to the classical Jeans stability analysis for the barotropic Euler-Poisson system. Indeed, the chemotactic collapse of biological populations is similar to the gravitational collapse in astrophysics (Jeans instability). There are, however, two main differences with the classical Jeans analysis. The first difference is the presence of a friction force $-\xi\vec{u}$ in the Euler equation. The second difference arises for the different nature of the field equations (3.19) and (3.22).
We recall (from [1]) that, in gravitational dynamics, an infinite and homogeneous distribution of matter with $\rho = const$ and $\vec{u} = 0$ is not a stationary solution of the barotropic Euler-Poisson system (3.20)-(3.22) because we cannot satisfy simultaneously the condition of hydrostatic equilibrium $\nabla p(\rho) + \rho\nabla\Phi = 0$ reducing to $\nabla\Phi = 0$ and the Poisson equation $\Delta\Phi = S_d G\rho \neq 0$. This leads to an inconsistency in the mathematical analysis when studying the linear dynamical stability of such a distribution: this is called the "**Jeans swindle**". By contrast, there is no "Jeans swindle" in the chemotactic problem. Indeed, an infinite and homogeneous distribution of cells is a steady state for the equations (3.17)-(3.19) corresponding to the condition $h\rho = \ell c$ (as before). For the "Newtoniam model" (3.25) this condition translates in $\rho = \bar{\rho}$; and for the "Yunkawa model" (3.26) it translates into $\ell_0^2 c = \lambda\rho$.
Following [5] of Chavanis and Sire, we restrict our analysis to the simplified models (3.25) and (3.26). In the Newtonian model, the only difference with the Jeans analysis is the presence of the friction force ξ. In the Yunkawa model, the differences with the Jaens analysis are due to the effects of the friction force ξ and of the shielding length ℓ_0^{-1} generated by the non-neglegible degradation of the chemical. In [5] is shown that the system is always stable for:

$$c_s \geq (c_s)_{crit} = \left(\frac{\lambda\bar{\rho}}{\ell_0^2}\right)^{1/2} \tag{3.27}$$

where $c_s = (\frac{dp}{d\rho})^{1/2}$ is the velocity of sound in the medium. We notice that, for specific equations of state $p = p(\rho)$, one can express the stability condition (3.27) in terms of the density of cells ρ.
Therefore, the system is stable if the velocity of sound is above a certain threshold value fixed by the shielding length ℓ_0^{-1}. By contrast, for $c_s < (c_s)_{crit}$, the system is

unstable for wave-numbers:

$$k \leq k_m = \sqrt{k_J^2 - \ell_0^2} \tag{3.28}$$

where $k_J = (\frac{\lambda\bar{\rho}}{c_s^2})^{1/2}$ is the Jeans wave-number.
In the Newtonian model, the condition $\ell_0 = 0$ implies $(c_s)_{crit} = +\infty$, so that the system is always unstable to perturbations with sufficiently large wavelengths $k < k_J$. It is worth to remark that the results are independent on ξ. The friction term only affects the evolution of the perturbations. As for the KS model, if $k \leq k_m(\ell_0)$, the perturbation grows exponentially rapidly (and notice again that k_m is function of the only ℓ_0). But one may define a friction-dependent wave-number $k_c(\ell_0, \xi)$ such that, for $k_m < k < k_c$, the perturbation is damped exponentially rapidly without oscillations, and for $k \geq k_c$ it presents damped oscillations. More precisely, the unstable modes have a growth rate which is dependent only on the shielding length, whereas the stable modes present damping rate and oscillation frequency which are functions of both ℓ_0 and ξ.
Owing to the above mentioned analogy between chemotaxis and gravity, this stability analysis also applies to self-gravitating Langevin particles, provided that we make the "Jeans swindle".
In conclusion, when the condition of instability found out above is fulfilled, the perturbation grows until the system can no longer be described by equilibrium or near equilibrium equations. Therefore, the next step is to study the chemotactic collapse in the nonlinear regime to see the formation of patterns like clusters or filaments.
A huge number of studies have considered the overdamped limit of the model (3.17)-(3.19) leading to the standard Keller-Segel model (1.9); of particular interest is the review given by Horstmann in [13]. For this parabolic-parabolic model, chemotactic collapse leads to the formation of round clusters. The evolution of a nonlinear cluster in the nonlinear regime can be studied by considering spherically symmetric solutions of the KS model. The standard Keller-Segel model leads to the formation of Dirac peaks (see [13]). In the regularized version (2.34), the Dirac peaks are replaced by smooth aggregates. These aggregates interact with each other and lead to a coarsening process where the number of clusters $N(t)$ decays with time as they collapse to each other. We espect that the decay of the number of clusters depends on the effective range of interaction mediated by the chemical ℓ_0^{-1} (shielding length). If the shielding length is small, the clusters do not "see" each other and the decay of $N(t)$ should be slowed down or even stopped ([5]). In that case, we obtain a quasi stationary state made of clusters separated from each other by a distance of the order of the shielding length ℓ_0^{-1}.
By contrast, if we take into account inertial effects, and we consider hyperbolic models instead of parabolic ones, the collection of isolated clusters is replaced by a network

pattern with nodes (clusters) separated by chords (see [8]). We notice that it is true for both the hydrodynamic model analyzed in detail in this chapter (3.17)-(3.19) and for the Cattaneo type model proposed in chapter 2. In this framework, the filaments between two nodes have the length of the order of ℓ_0^{-1}. Again, the number of nodes should decay with time. However, if the shielding length is small, the evolution is slowed down and we get a quasi equilibrium state with a filamentary structure corresponding to the initiation of a vasculature ([6]).

Chapter 4

Conclusions

In this thesis, we have derived the Keller-Segel model for chemotaxis. We have firstly focused our attention on the local balance equations, the constitutive relations for organism and chemical fluxes and we have thus worked out a parabolic-parabolic system of two coupled PDEs which describes the motion of microorganisms and chemicals while they interact with each other. The bacteria motion is not only of diffusive type, but it has a drift component, directed towards a higher concentration of the chemoattractant.
Secondly, we have considered the system not like a continuum, but as a union of a certain number of particles. For each of them, we have written a SDE which describes their motion. In this way, we have underlined the connection between the heat equation in the usual form and the heat equation in the stochastic form, using a standard Brownian motion, which has the meaning of random diffusion ([21]). Starting from the SDEs for a single particle of bacteria and chemical, we have performed a mean-field approximation. By applying elementary arguments of stochastic calculus, together with some notions of distribution theory and the fundamental theorem of integral calculus, we have arrived to the same result as before: a system of two coupled parabolic equations (a drift-diffusion equation and a reaction-diffusion equation) in the two variables ρ and c, the microorganism density and the chemical concentration, respectively.
We have ended the chapter 1 of this thesis with a generalization of the parabolic model derived in the first part. In particular, we have given attention to a parabolic model for chemotaxis where the diffusivity parameters depend upon the density or upon the concentration, in a power law. In this case, we would find a parabolic model called porous medium equation, which accounts a finite speed of propagation. Right in this direction, there could be a future work connected to this thesis: it may be interesting to look for a parabolic model for chemotaxis which takes into account the physics of the medium where the motion takes place. So two challenging open questions may be

whether it is possible to find out a chemotaxis model similar to the porous medium equation and how its solutions behave. One of the most recent papers working in this direction is [2].

In the second chapter we have turned our attention upon hyperbolic models for chemotaxis. The first introduced is a Cattaneo-type model, which has the peculiarity of the introduction of a delay time in the microorganism response. Secondly, we have referred to Chavanis and Sire (mainly, [6]) to present a hydrodynamic model for chemotaxis. Again, we have performed a mean-field approximation to derive the models by a stochastic point of view. We have arrived to a hydrodynamic model which takes into account the inertia of the system by a coefficient ξ. We have observed that in the limit of weak friction, we would recover a hydrodynamic hyperbolic model, whereas in the limit of strong friction we would get a parabolic model which is similar to the Keller-Segel model worked out in the first chapter.

A future work in this direction might be to follow Chavanis and Sire ideas and generalize their hydrodynamic model. Thus, a further generalization could be in the introduction of visco-elastic properties. The model proposed here takes into account just viscous properties (dissipative effects). But, for instance, the blood in microtubes has been observed to have some viscous properties and some elastic properties together. For this reason, it might be better described as a visco-elastic material. So, a more general model may put together dissipative effects (taken into account by Chavanis and Sire) and a delay time, typical of visco-elastic materials. Thus an interesting idea may be to build up a new model for chemotaxis which combines the Cattaneo type model and the hydrodynamic model introduced in this work.

In the third chapter we have started to talk about instability and cellular aggregation. This chapter is the *core* of the all thesis as our main purpose was to analyze the conditions for cellular aggregation in the models proposed. First of all, we have performed a **linear stability analysis** for the Keller-Segel model (spectral analysis), and we have found out the condition for instability. We have connected the instability of the uniform state to the aggregation, particularly to aggregation in Delta peaks. Then, we have stated that stability is caused by a large diffusivity parameter D_ρ and by a large chemical degradation rate ℓ, whereas aggregation happens due to a large chemical production h or to a large chemo-sensitivity χ. So, diffusion is a smoothing process, while chemotaxis leads to aggregates and to chemotactic collapse.

Secondly, we have presented again the hydrodynamic hyperbolic model and we have discussed the similarity with the Euler-Poisson system for self-gravitating bodies in astrophysics ([5]). We have briefly performed the same stability analysis as before and we have come to the instability condition and to the statement of the unstable wavenumbers, for two simplified models, the Newtonian model and the Yunkawa model.

We have remarked that the instability is independent of the inertia parameter ξ, which influences only the type of aggregation. Finally, we have shown the differences for the cellular aggregates caused by the instability of the parabolic systems (peaks or round aggregates) and of the hyperbolic systems (network patterns). The work may be completed in the future by some numerical simulations (which you may find in [7] and in [12] for Cattaneo type models and for parabolic models respectively). They might be really useful and they are motivated by recent experiments with human endothelial cells whose movements lead to the formation of complex network (interpreted as the beginning of a vasculature) which cannot be explained by parabolic models, but are recovered by numerical experiments on hyperbolic models.

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