A stochastic Keller-Segel model of chemotaxis

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Abstract

We introduce stochastic models of chemotaxis generalizing the deterministic Keller-Segel model. These models include fluctuations which are important in systems with small particle numbers or close to a critical point. Following Dean's approach, we derive the exact kinetic equation satisfied by the density distribution of cells. In the mean field limit where statistical correlations between cells are neglected, we recover the Keller-Segel model governing the smooth density field. We also consider hydrodynamic and kinetic models of chemotaxis that take into account the inertia of the particles and lead to a delay in the adjustment of the velocity of cells with the chemotactic gradient. We make the connection with the Cattaneo model of chemotaxis and the telegraph equation.

1 Introduction

In biology, many organisms (bacteria, amoebae, cells,...) or social insects (like ants, swarms,...) interact through the process of chemotaxis [1, 2, 3]. Chemotaxis is a long-range interaction that accounts for the orientation of individuals along chemical signals that they produce themselves. Famous examples of biological species experiencing chemotaxis are the slime mold amoebae Dictyostelium discoideum, the flagellated bacteria Salmonella typhimurium and Es*cherichia coli*, the human endothelial cells etc. When the interaction is attractive, chemotaxis is responsible for the self-organization of the system into coherent structures such as peaks, clusters, aggregates, fruiting bodies, periodic patterns, spirals, rings, spots, honeycomb patterns, stripes or even filaments. This spontaneous organization has been observed in several experiments [4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16] and numerical simulations [17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33]. Chemotactic attraction is therefore a leading mechanism to account for the morphogenesis and self-organization of biological systems. For example, it has been advocated to explain aggregation patterns in bacteria, tissue organization during embryonic growth, cell guidance, fish skin pigmentation patterning, angiogenesis in tumour progression and wound healing, formation of plaques in Alzheimer's disease, dynamics of blood vessel formation etc [24, 34]. It is fascinating to realize that the self-organization of chemotactic species in biology shares some analogies with the selforganization of galaxies in astrophysics and large-scale vortices (like Jupiter's great red spot) in

two-dimensional turbulence ¹. A first successful model of chemotactic aggregation is provided by the Keller-Segel (KS) model [41] introduced in 1970. The standard KS model can be written as

$$\frac{\partial \rho}{\partial t} = \nabla \cdot (D_* \nabla \rho - \chi \rho \nabla c), \tag{1}$$

$$\frac{\partial c}{\partial t} = D_c \Delta c - kc + h\rho.$$
⁽²⁾

It consists in two coupled differential equations that govern the evolution of the density of cells (or other biological entities) $\rho(\mathbf{r}, t)$ and the evolution of the secreted chemical $c(\mathbf{r}, t)$. The first equation (1) is a drift-diffusion equation. The cells diffuse with a diffusion coefficient D_* and they also move in a direction of a gradient of the chemical (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 coefficient χ can be positive or negative. In the first case (chemoattraction), the particles climb the chemical gradient and form clusters. In the second case (chemorepulsion), they descend the chemical gradient and repell each other. In that case, the chemical acts like a poison. The second equation (2) in the KS model is a reaction-diffusion equation. The chemical is produced by the bacteria with a rate h and is degraded with a rate k. It also diffuses with a diffusion coefficient D_c . When chemotactic attraction prevails over diffusion, the KS model describes a *chemotactic collapse* leading to aggregates or Dirac peaks. There is a vast literature on this subject. We refer to Perthame [42] for numerous references in applied mathematics and to Chavanis [43] for additional references in physics.

The first equation of the KS model can be interpeted as a mean-field Smoluchowski equation describing a system of Brownian particles in interaction. On the other hand, in the limit of large diffusivity of the chemical, we can make a quasi-stationary approximation $\partial c/\partial t \simeq 0$ in the second equation and obtain the screened Poisson equation. We are led therefore to the simplified Keller-Segel model

$$\frac{\partial \rho}{\partial t} = \nabla \cdot (D_* \nabla \rho - \chi \rho \nabla c), \tag{3}$$

$$\Delta c - k_0^2 c = -\lambda \rho, \tag{4}$$

where we have set $k_0^2 = k/D_c$ and $\lambda = h/D_c$. In the absence of degradation of the chemical $(k_0 = 0)$, the field equation (4) reduces to the Poisson equation $\Delta c = -\lambda \rho$ (see [44] and Appendix C of [32] for a precise justification of these approximations). In that case, the Keller-Segel (KS) model becomes isomorphic to the Smoluchowski-Poisson (SP) system

$$\frac{\partial \rho}{\partial t} = \nabla \cdot \left[\frac{1}{\xi} \left(\frac{k_B T}{m} \nabla \rho + \rho \nabla \Phi \right) \right],\tag{5}$$

$$\Delta \Phi = S_d G \rho, \tag{6}$$

¹These analogies are intrinsically due to the long-range attractive nature of the interaction. In particular, selfgravitating systems, 2D vortices and chemotactic species interact through a field produced by the distribution of particles via a Poisson equation (or its generalizations). Furthermore, the process of self-organization is described by relatively similar relaxation equations corresponding to nonlinear mean field Fokker-Planck equations [35]. Therefore, self-gravitating systems, 2D vortices and chemotactic species share many analogies despite their very different physical nature. These striking analogies have been emphasized by the author in several papers [36, 37, 38, 39, 40, 35].

describing a system of overdamped self-gravitating Brownian particles in the mean field approximation [45, 25, 28, 30, 46, 31, 47, 43, 48, 49]. We have the correspondences: $D_* = k_B T / \xi m$, $\chi = 1/\xi$, $c = -\Phi$, $\lambda = S_d G$. In particular, the concentration of the secreted chemical $c(\mathbf{r}, t) = -\Phi(\mathbf{r}, t)$ in biology plays the role of the gravitational potential (with the opposite sign) in astrophysics². More generally, when we consider a system of Brownian particles interacting via an arbitrary binary potential $u(\mathbf{r} - \mathbf{r}')$ and make a mean-field approximation [53, 54, 55], we obtain the mean-field Smoluchowski equation

$$\frac{\partial \rho}{\partial t} = \nabla \cdot \left[\frac{1}{\xi} \left(\frac{k_B T}{m} \nabla \rho + \rho \nabla \Phi \right) \right],\tag{7}$$

$$\Phi(\mathbf{r},t) = \int \rho(\mathbf{r}',t) u(\mathbf{r}-\mathbf{r}') \, d\mathbf{r}'.$$
(8)

The main difference between models (1)-(2) and (7)-(8) comes from the equation for the field $c(\mathbf{r}, t)$ or $\Phi(\mathbf{r}, t)$. Equation (2) is non-markovian since the concentration of the chemical $c(\mathbf{r}, t)$ at time t depends on the concentration of the bacteria and of the chemical at earlier times. By contrast, Eq. (8) is markovian since the potential $\Phi(\mathbf{r}, t)$ is assumed to be instantaneously produced by the distribution of particles.

It is important to note that the Keller-Segel model is a mean field model which ignores fluctuations. This implicitly assumes that the number of cells $N \to +\infty$ and that we are far from a critical point [56]. Now, in biology, the number of particles in the system can be relatively small. Furthermore, from the statistical physics viewpoint, it is natural to investigate the role of fluctuations during chemotaxis. In order to go beyond the mean field approximation, some authors [17, 57, 58, 32] have proposed to return to a corpuscular description of the dynamics and to describe the motion of the particles (chemotactic species or "active" walkers) by Ncoupled stochastic Langevin equations of the form

$$\frac{d\mathbf{r}_i}{dt} = \chi \nabla c_d(\mathbf{r}_i(t), t) + \sqrt{2D_*} \mathbf{R}_i(t), \tag{9}$$

$$\frac{\partial c_d}{\partial t} = D_c \Delta c_d - kc_d + h \sum_{i=1}^N \delta(\mathbf{r} - \mathbf{r}_i(t)), \qquad (10)$$

where $\mathbf{r}_i(t)$ denote the positions of the particles, $c_d(\mathbf{r}, t)$ is the exact field of secreted chemical and $\mathbf{R}_i(t)$ is a white noise satisfying $\langle \mathbf{R}_i(t) \rangle = \mathbf{0}$ and $\langle R_{i,\alpha}(t)R_{j,\beta}(t') \rangle = \delta_{ij}\delta_{\alpha\beta}\delta(t-t')$ where i = 1, ..., N refer the the particles and $\alpha = 1, ..., d$ to the dimensions of space. Note that the motion of cells is treated on an individual basis but the chemical signals are treated in the continuum limit. This separation of scales appears to be reasonable in most applications. In the mean field approximation, these stochastic equations lead to the KS model (1)- $(2)^3$. When the reaction-diffusion equation (10) is replaced by a Markovian equation of the form

$$\Delta c_d - k_0^2 c_d = -\lambda \sum_{i=1}^N \delta(\mathbf{r} - \mathbf{r}_i(t)), \qquad (11)$$

²One great achievement of Keller & Segel [41] was to interpret slime mold aggregation as a manifestation of a fundamental instability in a uniform distribution of amoebae and acrasin (chemoattractant). As noticed in [50, 51], this instability is closely related to the Jeans gravitational instability in astrophysics [52].

³Stevens [57] gives the first rigorous derivation (in the mathematical sense) of the KS model from an interacting stochastic many-particle system where the interaction between the particles is rescaled in a moderate way as the population size N tends to infinity.

we obtain a simplified model of chemotaxis that leads to the simplified KS model (3)-(4) in the mean field approximation. More generally, for Brownian particles interacting via a binary potential of interaction $u(\mathbf{r} - \mathbf{r}')$, one obtains the stochastic model

$$\frac{d\mathbf{r}_i}{dt} = -\frac{1}{\xi} \nabla \Phi_d(\mathbf{r}_i(t), t) + \sqrt{\frac{2k_B T}{\xi m}} \mathbf{R}_i(t),$$
(12)

$$\Phi_d(\mathbf{r},t) = \sum_{i=1}^N m \ u(\mathbf{r} - \mathbf{r}_i(t)), \tag{13}$$

considered in [59, 60, 61, 53, 62, 54, 55, 47, 56]. In the mean field approximation [53, 54, 55], these equations yield the mean-field Smoluchowski equation (7)-(8).

In systems with weak long-range interactions, the mean field approximation is expected to become exact in a proper thermodynamic limit $N \to +\infty$ such that the strength of the potential scales like 1/N while the volume V remains of order unity [54]. In the context of chemotaxis, the differences between mean field and non mean field models have been discussed by Grima [34] who showed situations where the mean field approximation fails to predict the width of the aggregate sizes. In particular, the disagreement is very severe close to the critical point where we know that mean field approximation breaks down in general [63]. This is because the fluctuations become very important so that it is not possible to neglect the twobody correlation function anymore [56]. On the other hand, the mean field approximation assumes that the number of particles $N \gg 1$. In stellar systems and plasmas, this is always the case. However, for biological systems, the number of interacting bacteria or cells is frequently less than a few thousands so that finite N effects and statistical fluctuations are important. In view of these remarks, it is highly desirable to obtain stochastic kinetic equations that take into account fluctuations and that go beyond the deterministic mean field Keller-Segel model. Such equations are discussed in the present paper. In the first part of the paper (Sec. 2), following Dean's approach [60], we derive the exact kinetic equation satisfied by the density distribution of chemotactic species. This equation takes into account stochastic fluctuations and memory effects present in the field equation for the secreted chemical. If we average over the noise, we recover the hierarchy of kinetic equations discussed by Newman & Grima [58]. If we make a mean-field approximation, we recover the Keller-Segel model [41]. Therefore, this exact stochastic kinetic equation generalizes several models introduced in the chemotactic literature. We also propose a simplified kinetic equation for a coarse-grained density field (instead of a sum of δ -functions) keeping track of fluctuations. This equation (31)-(32) could be of practical interest in chemotaxis. In the second part of the paper (Secs. 3 to 6), we note that the Keller-Segel model is a parabolic model which neglects the inertia of the particles and which assumes an instantaneous adjustment of the velocity with the chemotactic gradient. We consider hyperbolic models that generalize this parabolic model. We first consider the Cattaneo model of chemotaxis [26] which consists in introducing a delay in the establishment of the current (Sec. 3). Then, we consider hydrodynamic models including a friction force (Sec. 4). Using a semi-linear approximation, we show that the Cattaneo model can be recovered from these hydrodynamic equations [56]. In Sec. 5, we generalize these models so as to take into account fluctuations. This leads to stochastic hyperbolic models of chemotaxis which generalize the ordinary deterministic parabolic Keller-Segel model. Finally, in Sec. 6, we develop a kinetic theory of chemotactic species in phase space taking into account the inertia of the particles and the discrete nature of the system. We derive stochastic kinetic equations that should improve the description of the cells' motion. The link with the parabolic and hyperbolic models is also discussed.

This paper adapts the results of [56] to the context of chemotaxis with complements and amplification. Although these different stochastic equations (in particular the parabolic ones) are well-known in statistical physics [59, 60, 61, 62, 56] their application to the context of chemotaxis, proposed in [56], is new and is an important contribution of the present paper.

2 The stochastic Keller-Segel model

In this section, we introduce a stochastic model of chemotaxis, generalizing the Keller-Segel model, by taking into account fluctuations. Let us first derive the exact kinetic equation satisfied by the density distribution of cells whose dynamics is described by the coupled stochastic Langevin equations (9)-(10). We follow Dean's approach [60]. The exact density field, expressed in terms of δ -functions, can be written

$$\rho_d(\mathbf{r},t) = \sum_{i=1}^N \rho_i(\mathbf{r},t) = \sum_{i=1}^N \delta(\mathbf{r} - \mathbf{r}_i(t)).$$
(14)

For any function $F(\mathbf{r})$, we have $F(\mathbf{r}_i(t)) = \int \rho_i(\mathbf{r}, t) F(\mathbf{r}) d\mathbf{r}$. Now, using Ito's calculus [64], one has

$$\frac{dF(\mathbf{r}_i)}{dt} = \int \rho_i(\mathbf{r}, t) \left[\chi \nabla F(\mathbf{r}) \cdot \nabla c_d(\mathbf{r}, t) + \sqrt{2D_*} \nabla F(\mathbf{r}) \cdot \mathbf{R}_i(t) + D_* \Delta F(\mathbf{r}) \right] d\mathbf{r}.$$
 (15)

Integrating by parts, we obtain

$$\frac{dF(\mathbf{r}_i)}{dt} = \int F(\mathbf{r}) \left[-\chi \nabla \cdot (\rho_i(\mathbf{r}, t) \nabla c_d(\mathbf{r}, t)) - \sqrt{2D_*} \nabla \cdot (\rho_i(\mathbf{r}, t) \mathbf{R}_i(t)) + D_* \Delta \rho_i(\mathbf{r}, t) \right] d\mathbf{r}.$$
(16)

Then, using $dF(\mathbf{r}_i)/dt = \int \partial_t \rho_i(\mathbf{r}, t) F(\mathbf{r}) d\mathbf{r}$ and comparing with Eq. (16), we get (using the fact that F is an arbitrary function)

$$\frac{\partial \rho_i}{\partial t} = -\chi \nabla \cdot \left(\rho_i(\mathbf{r}, t) \nabla c_d(\mathbf{r}, t)\right) - \sqrt{2D_*} \nabla \cdot \left(\rho_i(\mathbf{r}, t) \mathbf{R}_i(t)\right) + D_* \Delta \rho_i(\mathbf{r}, t).$$
(17)

Summing this relation over the i, we finally obtain

$$\frac{\partial \rho_d}{\partial t}(\mathbf{r},t) = D_* \Delta \rho_d(\mathbf{r},t) - \chi \nabla \cdot (\rho_d(\mathbf{r},t) \nabla c_d(\mathbf{r},t)) - \sqrt{2D_*} \sum_{i=1}^N \nabla \cdot (\rho_i(\mathbf{r},t) \mathbf{R}_i(t)).$$
(18)

Now, the last term can be rewritten [60]:

$$-\sum_{i=1}^{N} \nabla \cdot (\rho_i(\mathbf{r}, t) \mathbf{R}_i(t)) = \nabla \cdot (\rho_d^{1/2}(\mathbf{r}, t) \mathbf{R}(\mathbf{r}, t)),$$
(19)

where $\mathbf{R}(\mathbf{r},t)$ is a Gaussian random field such that $\langle \mathbf{R}(\mathbf{r},t) \rangle = \mathbf{0}$ and $\langle R_{\alpha}(\mathbf{r},t)R_{\beta}(\mathbf{r}',t') \rangle = \delta_{\alpha\beta}\delta(\mathbf{r}-\mathbf{r}')\delta(t-t')$. Therefore, the system of equations satisfied by the exact density field expressed in terms of δ -functions is

$$\frac{\partial \rho_d}{\partial t}(\mathbf{r},t) = D_* \Delta \rho_d(\mathbf{r},t) - \chi \nabla \cdot \left(\rho_d(\mathbf{r},t) \nabla c_d(\mathbf{r},t)\right) + \nabla \cdot \left(\sqrt{2D_*\rho_d(\mathbf{r},t)} \mathbf{R}(\mathbf{r},t)\right),$$
(20)

$$\frac{\partial c_d}{\partial t} = D_c \Delta c_d(\mathbf{r}, t) - k c_d(\mathbf{r}, t) + h \rho_d(\mathbf{r}, t).$$
(21)

The first and third terms in the r.h.s. of Eq. (20) correspond to a pure Brownian motion and the second term takes into account chemotaxis, i.e the attraction or repulsion of the cells by the chemical. As noted by Dean [60], the noise in Eq. (20) appears not additively but multiplicatively.

Integrating Eq. (10), the concentration of the chemical can be expressed in terms of the cell paths as [58]:

$$c_d(\mathbf{r},t) = h \int d\mathbf{r}' \int_0^t dt' G(\mathbf{r} - \mathbf{r}', t - t') \sum_{i=1}^N \delta(\mathbf{r}' - \mathbf{r}_i(t')), \qquad (22)$$

where the Green function for the chemical diffusion equation is given by

$$G(\mathbf{r},t) = (4\pi D_c t)^{-d/2} \exp\left[-\frac{r^2}{4D_c t} - kt\right].$$
 (23)

The gradient of the concentration field is

$$\nabla c_d(\mathbf{r}, t) = h \int d\mathbf{r}' \int_0^t dt' \nabla G(\mathbf{r} - \mathbf{r}', t - t') \rho_d(\mathbf{r}', t').$$
(24)

Substituting Eq. (24) in Eq. (20), we obtain

$$\frac{\partial \rho_d}{\partial t}(\mathbf{r},t) = D_* \Delta \rho_d(\mathbf{r},t) - \chi h \nabla \cdot \left[\rho_d(\mathbf{r},t) \nabla \int d\mathbf{r}' \int_0^t dt' G(\mathbf{r}-\mathbf{r}',t-t') \rho_d(\mathbf{r}',t') \right] + \nabla \cdot \left(\sqrt{2D_*\rho_d(\mathbf{r},t)} \mathbf{R}(\mathbf{r},t) \right).$$
(25)

If we average over the noise and introduce the smooth density $\rho(\mathbf{r}, t) = \langle \rho_d(\mathbf{r}, t) \rangle$, we recover Eq. (9) of Newman & Grima [58]:

$$\frac{\partial \rho}{\partial t}(\mathbf{r},t) = D_* \Delta \rho(\mathbf{r},t) - \chi h \nabla \cdot \int d\mathbf{r}' \int_0^t dt' [\nabla G(\mathbf{r}-\mathbf{r}',t-t')] \langle \rho_d(\mathbf{r},t) \rho_d(\mathbf{r}',t') \rangle.$$
(26)

If we make a mean field approximation $\langle \rho_d(\mathbf{r}, t) \rho_d(\mathbf{r}', t') \rangle \simeq \rho(\mathbf{r}, t) \rho(\mathbf{r}', t')$ in Eq. (26), we recover the Keller-Segel model [41]:

$$\frac{\partial \rho}{\partial t}(\mathbf{r},t) = D_* \Delta \rho(\mathbf{r},t) - \chi \nabla \cdot (\rho(\mathbf{r},t) \nabla c(\mathbf{r},t)), \qquad (27)$$

with

$$c(\mathbf{r},t) = h \int d\mathbf{r}' \int_0^t dt' G(\mathbf{r} - \mathbf{r}', t - t') \rho(\mathbf{r}', t').$$
(28)

Given the definition of the Green function G, the smooth concentration $c(\mathbf{r}, t)$ is solution of the reaction-diffusion equation

$$\frac{\partial c}{\partial t} = D_c \Delta c - kc + h\rho.$$
⁽²⁹⁾

We also note, for future reference, that the steady solutions of the KS model (27) correspond to a mean field Boltzmann-like distribution

$$\rho = A e^{c/T_{eff}},\tag{30}$$

where $T_{eff} = D_*/\chi$ is an effective temperature given by an Einstein relation.

Grima [34] has shown that the mean field approximation may lead to wrong results if we are close to a critical point or if the number of particles is not large enough. Therefore, it may be useful to have a more general model than the Keller-Segel model (1)-(2) which keeps track of fluctuations. Equations (20)-(21) are exact and contain the same information as the *N*-body stochastic Langevin equations (9)-(10). They are not very useful for practical purposes since they govern the evolution of a density field which is expressed as a sum of δ -functions. It is easier to directly solve the equivalent *N*-body stochastic Langevin equations (9)-(10). However, using phenomenological arguments like those described in [62, 56], we can consider a spatio-temporal coarse-grained distribution $\overline{\rho}(\mathbf{r}, t)$ which smoothes out the exact density field $\rho_d(\mathbf{r}, t)$ while keeping track of fluctuations. We also assume that the spatio-temporal window is sufficiently small so that we can make the approximation $\overline{\rho}^{(2)}(\mathbf{r}, \mathbf{r}', t) \simeq \overline{\rho}(\mathbf{r}, t)\overline{\rho}(\mathbf{r}', t)$. In that case, we obtain the stochastic Keller-Segel model for the coarse-grained distribution

$$\frac{\partial \overline{\rho}}{\partial t}(\mathbf{r},t) = D_* \Delta \overline{\rho}(\mathbf{r},t) - \chi \nabla \cdot \left(\overline{\rho}(\mathbf{r},t) \nabla \overline{c}(\mathbf{r},t)\right) + \nabla \cdot \left(\sqrt{2D_* \overline{\rho}(\mathbf{r},t)} \mathbf{R}(\mathbf{r},t)\right), \tag{31}$$

$$\frac{\partial \overline{c}}{\partial t} = D_c \Delta \overline{c} - k \overline{c} + h \overline{\rho}, \qquad (32)$$

generalizing the deterministic Keller-Segel model (1)-(2). This equation is one of the most important result of this paper. As shown in Appendix B of [56], the form of the noise term in Eq. (31) can be obtained from the general theory of fluctuations developed in Landau & Lifshitz [65]. This provides another, direct, justification of the stochastic Eq. (31). As shown in [56], the mean field approximation breaks down close to a critical point because the twobody correlation function diverges. In that case, it may be more relevant to use the stochastic Keller-Segel model (31)-(32) including fluctuations instead of the deterministic Keller-Segel model (1)-(2).

It is also very important to take into account fluctuations when the system can be found in several metastable states. If we introduce the coarse-grained free energy functional

$$F_{c.g.}[\overline{\rho},\overline{c}] = \frac{D_*}{\chi} \int \overline{\rho} \ln \overline{\rho} \, d\mathbf{r} + \frac{1}{2h} \int \left[D_c (\nabla \overline{c})^2 + k\overline{c}^2 \right] \, d\mathbf{r} - \int \overline{\rho} \, \overline{c} \, d\mathbf{r}, \tag{33}$$

we can write the stochastic equation (31) in the form

$$\frac{\partial \overline{\rho}}{\partial t} = \nabla \cdot \left[\chi \overline{\rho}(\mathbf{r}, t) \nabla \frac{\delta F_{c.g.}}{\delta \overline{\rho}} \right] + \nabla \cdot \left(\sqrt{2D_* \overline{\rho}(\mathbf{r}, t)} \mathbf{R}(\mathbf{r}, t) \right).$$
(34)

This equation can be viewed as a Langevin equation for the field $\overline{\rho}(\mathbf{r}, t)$. The evolution of the probability of the density distribution $W[\overline{\rho}, t]$ is governed by a Fokker-Planck equation of the form

$$\frac{\partial W[\overline{\rho}, t]}{\partial t} = -\int \frac{\delta}{\delta \overline{\rho}(\mathbf{r}, t)} \left\{ \nabla \cdot \overline{\rho}(\mathbf{r}, t) \nabla \left[D_* \frac{\delta}{\delta \overline{\rho}} + \chi \frac{\delta F_{c.g.}}{\delta \overline{\rho}} \right] W[\overline{\rho}, t] \right\} d\mathbf{r}.$$
(35)

At equilibrium, we have $W[\overline{\rho}] \propto e^{-F_{c.g.}[\overline{\rho}]/T_{eff}-\alpha\int \overline{\rho} d\mathbf{r}}$ with $F_{c.g.}[\overline{\rho}] = \frac{D_*}{\chi} \int \overline{\rho} \ln \overline{\rho} d\mathbf{r} - \frac{1}{2} \int \overline{\rho} \ \overline{c} d\mathbf{r}$ (we have substituted Eq. (32) with $\partial \overline{c}/\partial t = 0$ in Eq. (33)). For $N \to +\infty$, the equilibrium distribution $W[\overline{\rho}]$ is strongly peaked around the global minimum of $F_{c.g.}[\overline{\rho}]$ at fixed mass $M = \int \overline{\rho} d\mathbf{r}$. However, the system can remain trapped in a metastable state (local minimum of $F_{c.g.}[\overline{\rho}]$ for a very long time which becomes infinite at the thermodynamic limit $N \to +\infty$. Let us be more precise. If we ignore the noise term, Eq. (34) reduces to

$$\frac{\partial \overline{\rho}}{\partial t} = \nabla \cdot \left[\chi \overline{\rho}(\mathbf{r}, t) \nabla \frac{\delta F_{c.g.}}{\delta \overline{\rho}} \right], \tag{36}$$

which is the deterministic Keller-Segel model (27). This equation satisfies an H-theorem

$$\dot{F} = -\int \frac{1}{\chi\rho} \left(D_* \nabla \overline{\rho} - \chi \overline{\rho} \nabla \overline{c} \right)^2 \, d\mathbf{r} - \frac{1}{h} \int \left(D_c \Delta \overline{c} - k\overline{c} + h\overline{\rho} \right)^2 \, d\mathbf{r} \le 0, \tag{37}$$

with $\dot{F} = 0$ iff the distribution is given by Eq. (30). Therefore, a steady state is stable iff it is a (local) minimum of free energy at fixed mass. Assuming that the free energy is bounded from below, we know from Lyapunov's direct method that the system will relax towards a steady state that is a minimum (global or local) of the free energy functional $F_{c.g.}[\overline{\rho}]$ at fixed mass (maxima or saddle points of free energy are linearly dynamically unstable with respect to mean field Fokker-Planck equations [35]). If the free energy admits several local minima, the selection of the steady state will depend on a notion of *basin of attraction*. Without noise, the system remains on a minimum of free energy forever. Now, in the presence of noise, the fluctuations can induce dynamical phase transitions from one minimum to the other. We should therefore see the system "jump" between different states. Thus, accounting correctly for fluctuations is very important when there exists metastable states. The probability of transition scales as $e^{-\Delta F/T_{eff}}$ where ΔF is the barrier of free energy between two minima. Therefore, on an infinite time, the system will explore all the minima and will spend most time in the global minimum. This will be the case only if N is not too large. Indeed, for systems with long-range interactions, the barrier of free energy ΔF scales like N so that the probability of escape from a local minimum is very small and behaves like e^{-N} . Therefore, even if the global minimum is in principle the most probable state, metastable states are highly robust in practice since their lifetime scales like e^N . They are thus fully relevant for $N \gg 1$: metastable states are in practice "stable states". These interesting features (basin of attraction, dynamical phase transitions, metastability,...) would be interesting to study in more detail in the case of chemotaxis. The study of the stochastic Keller-Segel model will be considered in future publications.

3 The Cattaneo model of chemotaxis

The general Keller-Segel (GKS) model [41] can be written as

$$\xi \frac{\partial \rho}{\partial t} = \nabla \cdot (D_2(\rho, c) \nabla \rho - D_1(\rho, c) \nabla c), \qquad (38)$$

$$\frac{\partial c}{\partial t} = D_c \Delta c - k(c)c + h(c)\rho, \qquad (39)$$

where $D_1 = D_1(\rho, c)$ and $D_2 = D_2(\rho, c)$ can both depend on the concentration of the cells and of the chemical. This takes into account microscopic constraints, like close-packing effects, that can hinder the movement of cells and lead to nonlinear diffusion and nonlinear mobility. The GKS model (38)-(39) can be viewed as a *nonlinear mean field Fokker-Planck equation* associated with a notion of effective generalized thermodynamics [35]. The first equation can be written in the form of a continuity equation $\partial_t \rho = -\nabla \cdot \mathbf{J}$ with a current

$$\mathbf{J} = -\frac{1}{\xi} \left(D_2(\rho, c) \nabla \rho - D_1(\rho, c) \nabla c \right).$$
(40)

It is important to note that the GKS model is a *parabolic* model like the usual heat diffusion equation. Like for the Fourier law of heat conduction, it is assumed that the current **J** is instantaneously equal to the right hand side of Eq. (40), that we shall call the "chemotactic gradient" for future reference. In the context of heat conduction, Cattaneo [66] has proposed a modification of Fourier's law in order to describe heat propagation with finite speed. In the context of chemotaxis, Dolak & Hillen [26] have introduced a Cattaneo model for chemosensitive movement. They assume that the current is not instantaneously equal to the chemotactic gradient but relaxes to it with a time constant $1/\tau$. Then, the corresponding Cattaneo model for chemosensitive movement reads

$$\frac{\partial \rho}{\partial t} + \nabla \cdot \mathbf{J} = 0, \tag{41}$$

$$\tau \frac{\partial \mathbf{J}}{\partial t} + \mathbf{J} = -\frac{1}{\xi} (D_2(\rho, c) \nabla \rho - D_1(\rho, c) \nabla c).$$
(42)

Taking the time derivative of Eq. (41) and using Eq. (42), we obtain the *hyperbolic* model

$$\tau \frac{\partial^2 \rho}{\partial t^2} + \frac{\partial \rho}{\partial t} = \frac{1}{\xi} \nabla \cdot (D_2(\rho, c) \nabla \rho - D_1(\rho, c) \nabla c).$$
(43)

This equation, which is second order in time, is analogous to the *telegraph equation* which generalizes the diffusion equation by introducing memory effects. For $\tau = 0$, we recover the GKS model (38)-(39) as a particular case.

4 Hydrodynamic models of chemotaxis

The parabolic Keller-Segel model [41] is able to reproduce the formation of clusters (clumps) resulting from chemotactic collapse. This can explain experiments on bacteria like *Escherichia coli* or amoebae like *Dictyostelium discoideum* exhibiting pointwise concentrations [4, 14, 9, 11, 5, 6, 7, 8]. Recently, several experiments with human endothelial cells have shown the formation of networks that can be interpreted as the initiation of a vasculature [10, 13, 27, 16, 15]. Cells randomly spread on a gel matrix autonomously organize to form a continuous multicellular network which can be described as a collection of nodes connected by chords [27]. This process takes place during the early stages of vasculogenesis in embryo development. These filaments are observed in the experiments of capillary blood vessel formation. These structures cannot be explained by the Keller-Segel parabolic model which generically leads to pointwise blow-up ⁴. In order to account for these filaments, hyperbolic models of chemotaxis have been introduced [27, 67, 38, 29, 50, 32, 68]. They have the form of damped hydrodynamic equations ⁵ taking

⁴In fact, some Keller-Segel models including cell kinetics can, under certain conditions, give rise to networklike patterns (see Fig. 12c of [24]).

⁵The type of hydrodynamic equations (44)-(45) including a long-range mean field interaction, a density dependent pressure and a friction force were introduced in Chavanis [69] (see also [36]) for Langevin particles in interaction and called the *damped Euler equations*. Their application to chemotaxis and gravity was mentioned. These equations can be derived from kinetic equations (nonlinear mean-field Fokker-Planck equations) by using a local thermodynamic equilibrium condition (L.T.E.) to close the hierarchy of hydrodynamic moments [69, 47, 32]. However, they remain heuristic because the L.T.E. approximation is not rigorously justified. By contrast, in the strong friction limit $\xi \to +\infty$, we can rigorously derive the GKS model (38)-(39), also called the *generalized Smoluchowski equation*, by using a Chapman-Enskog expansion [70] or a method of moments [71, 32, 35]. The model considered by Gamba *et al.* [27] (see also [67, 15, 29]) corresponds to $\xi = 0$ in Eq. (45). It can be derived in an asymptotic limit of kinetic equations of a different type (see [29] and Appendix D of [32]). In more recent papers [68], the aforementioned authors have also included a friction force in their model.

into account inertial effects :

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \mathbf{u}) = 0, \tag{44}$$

$$\frac{\partial}{\partial t}(\rho \mathbf{u}) + \nabla(\rho \mathbf{u} \otimes \mathbf{u}) = -D_2(\rho, c)\nabla\rho + D_1(\rho, c)\nabla c - \xi\rho \mathbf{u}.$$
(45)

Considering the momentum equation (45), the inertial term (l.h.s.) models cells directional persistence, i.e. the natural tendency of a particle to continue in a given direction in the absence of any interaction. When $D_2(\rho, c)$ depends only on the density, the first term on the r.h.s. can be interpreted as a barotropic pressure force $-\nabla p(\rho)$ (see [35] for different examples of equations of state). The pressure law is expected to be linear for low densities and to increase rapidly above a certain threshold $\sim \sigma_0$ in order to describe the fact that the cells do not interpenetrate. For example, in [69, 40, 32] we proposed to take $p(\rho) = -\sigma_0 T_{eff} \ln(1 - \rho/\sigma_0)$ which returns the "isothermal" equation of state $p = \rho T_{eff}$ for dilute systems $\rho \ll \sigma_0$ where the motion of an individual cell is not impeded by the other cells [25], and which diverges when the cells are compressed towards the maximum density $\rho \to \sigma_0$. Another possible equation of state is the polytropic one $p(\rho) = K \rho^{\gamma}$ [72, 32] taking into account anomalous transport (normal transport corresponds to the isothermal case $\gamma = 1$). The chemotactic response $D_1(\rho, c)$ of the bacterium to the chemical gradient (second term in the r.h.s. of Eq. (45)) can also depend on c and ρ so as to take into account anomalous reactivity (the normal case corresponds to $D_1(\rho, c) = \rho$ but the form $D_1(\rho, c) = \rho(1 - \rho/\sigma_0)$ has also been considered to take into account volume filling effects [24, 69, 40, 35]). Finally, the last term in the r.h.s. of Eq. (45) is a friction force that measures the importance of inertial effects. It parametrizes the tendency of the organisms to continue in a given direction. In this inertial model, the velocity of a particle takes a *finite* time ξ^{-1} to get aligned with the chemotactic gradient while in the Keller-Segel model, this alignement is assumed to be instantaneous (see below). The "delay" in the alignment of the velocity with the chemotactic gradient is similar to the idea that is at the heart of the Cattaneo model in Sec. 3.

If we neglect the friction force ($\xi = 0$) we recover the model introduced by Gamba *et al.* [27]. Alternatively, if we neglect the inertial term (l.h.s.) in Eq. (45) and substitute the resulting expression [69, 50, 32]:

$$\rho \mathbf{u} = -\frac{1}{\xi} \left(D_2(\rho, c) \nabla \rho - D_1(\rho, c) \nabla c \right), \tag{46}$$

in Eq. (44), we recover the GKS model. This is valid in a strong friction limit $\xi \to +\infty$. We can also obtain a more general model taking into account some memory effects. If we neglect only the nonlinear term $\nabla(\rho \mathbf{u} \otimes \mathbf{u})$ in Eq. (45), we obtain

$$\frac{\partial}{\partial t}(\rho \mathbf{u}) = -D_2(\rho, c)\nabla\rho + D_1(\rho, c)\nabla c - \xi\rho \mathbf{u}, \tag{47}$$

which is equivalent to the Cattaneo model (42) with $\tau = 1/\xi$. Taking the time derivative of Eq. (44) and substituting Eq. (47) in the resulting expression, we obtain a simplified hyperbolic model keeping track of memory effects

$$\frac{\partial^2 \rho}{\partial t^2} + \xi \frac{\partial \rho}{\partial t} = \nabla \cdot \left(D_2(\rho, c) \nabla \rho - D_1(\rho, c) \nabla c \right).$$
(48)

This provides a new justification (see also [56]) of the Cattaneo model of chemotaxis from the damped hydrodynamics equation (44)-(45). This can be viewed as a semi-linear hydrodynamic model since its derivation assumes that the nonlinear term $\nabla(\rho \mathbf{u} \otimes \mathbf{u})$ in Eq. (45) can be neglected while the full nonlinearities in the r.h.s. of Eq. (45) are taken into account.

5 Stochastic hydrodynamic models of chemotaxis

In this section, we generalize the previous hydrodynamic equations in order to take into account fluctuations. We restrict ourselves to the standard situation where $D_2 = \xi D_*$ and $D_1 = \rho$. The stochastic damped Euler equations generalizing Eqs. (44)-(45) can be written

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \mathbf{u}) = 0, \tag{49}$$

$$\frac{\partial}{\partial t}(\rho \mathbf{u}) + \nabla(\rho \mathbf{u} \otimes \mathbf{u}) = -\xi D_* \nabla \rho + \rho \nabla c - \xi \rho \mathbf{u} - \sqrt{2D_*\xi^2 \rho} \mathbf{R}(\mathbf{r}, t).$$
(50)

As shown in Appendix B of [56], the form of the noise in these equations can be obtained by applying the general theory of fluctuations developed by Landau & Lifshitz [65]. If we neglect the inertial term (l.h.s.) in Eq. (50) and substitute the resulting expression

$$\rho \mathbf{u} = -(D_* \nabla \rho - \chi \rho \nabla c) - \sqrt{2D_* \rho} \mathbf{R}(\mathbf{r}, t), \qquad (51)$$

where $\chi = 1/\xi$ in Eq. (49), we recover the stochastic Keller-Segel equation (31). This is valid in a strong friction limit $\xi \to +\infty$ with $\xi D_* \sim 1$. As in Sec. 4, we can obtain a more general model taking into account some memory effects. Indeed, if we neglect only the nonlinear term $\nabla(\rho \mathbf{u} \otimes \mathbf{u})$ in Eq. (50), we find

$$\chi \frac{\partial}{\partial t} (\rho \mathbf{u}) = -D_* \nabla \rho + \chi \rho \nabla c - \rho \mathbf{u} - \sqrt{2D_* \rho} \mathbf{R}(\mathbf{r}, t).$$
(52)

Taking the time derivative of Eq. (49) and substituting Eq. (52) in the resulting expression, we obtain the stochastic Cattaneo model of chemotaxis

$$\chi \frac{\partial^2 \rho}{\partial t^2} + \frac{\partial \rho}{\partial t} = \nabla \cdot (D_* \nabla \rho - \chi \rho \nabla c) + \nabla \cdot (\sqrt{2D_* \rho} \mathbf{R}).$$
(53)

6 Stochastic kinetic models of chemotaxis

In order to take into account fluctuations in a rigorous way, we must start from a microscopic description of the dynamics of the chemotactic species. In Sec. 2, we have considered an overdamped dynamics. However, according to recent observations in biology (as discussed in Sec. 4), it is important to take into account the inertia of the particles. A kinetic model of chemotaxis taking into account finite N effects and inertial effects has been proposed in Chavanis & Sire [32]. In the simplest case, the motion of the biological entities is described by N coupled stochastic Langevin equations of the form

$$\frac{d\mathbf{r}_i}{dt} = \mathbf{v}_i,\tag{54}$$

$$\frac{d\mathbf{v}_i}{dt} = -\xi \mathbf{v}_i + \nabla c_d(\mathbf{r}_i(t), t) + \sqrt{2D} \mathbf{R}_i(t),$$
(55)

$$\frac{\partial c_d}{\partial t} = D_c \Delta c_d - kc_d + h \sum_{i=1}^N \delta(\mathbf{r} - \mathbf{r}_i(t)),$$
(56)

where ξ is a friction coefficient and D a diffusion coefficient in velocity space. We can introduce an effective temperature T_{eff} through the Einstein relation $T_{eff} = D/\xi$ [32, 35]. The overdamped stochastic equations (9)-(10) can be recovered in a strong friction limit $\xi \to +\infty$, neglecting the inertial term in Eq. (55), and writing $\chi = 1/\xi$ and $D_* = D/\xi^2$. We now proceed in deriving the exact kinetic equation satisfied by the distribution function of cells whose dynamics is described by the coupled stochastic Langevin equations (54)-(56). The exact distribution function, expressed in terms of δ -functions, can be written

$$f_d(\mathbf{r}, \mathbf{v}, t) = \sum_{i=1}^N f_i(\mathbf{r}, \mathbf{v}, t) = \sum_{i=1}^N \delta(\mathbf{r} - \mathbf{r}_i(t))\delta(\mathbf{v} - \mathbf{v}_i(t)).$$
(57)

For any function $F(\mathbf{r}, \mathbf{v})$, we have $F(\mathbf{r}_i(t), \mathbf{v}_i(t)) = \int f_i(\mathbf{r}, \mathbf{v}, t) F(\mathbf{r}, \mathbf{v}) d\mathbf{r} d\mathbf{v}$. Now, using Ito's calculus, one has

$$\frac{dF(\mathbf{r}_{i},\mathbf{v}_{i})}{dt} = \int f_{i}(\mathbf{r},\mathbf{v},t) \left[\nabla_{\mathbf{r}}F(\mathbf{r},\mathbf{v})\cdot\mathbf{v} - \xi\nabla_{\mathbf{v}}F(\mathbf{r},\mathbf{v})\cdot\mathbf{v} + \nabla_{\mathbf{v}}F(\mathbf{r},\mathbf{v})\cdot\nabla c_{d}(\mathbf{r},t) + \sqrt{2D}\nabla_{\mathbf{v}}F(\mathbf{r},\mathbf{v})\cdot\mathbf{R}_{i}(t) + D\Delta_{\mathbf{v}}F(\mathbf{r},\mathbf{v}) \right] d\mathbf{r}d\mathbf{v}.$$
(58)

Integrating by parts, we obtain

$$\frac{dF(\mathbf{r}_{i},\mathbf{v}_{i})}{dt} = \int F(\mathbf{r},\mathbf{v}) \left[-\mathbf{v} \cdot \frac{\partial f_{i}}{\partial \mathbf{r}}(\mathbf{r},\mathbf{v},t) + \xi \frac{\partial}{\partial \mathbf{v}} \cdot (f_{i}(\mathbf{r},\mathbf{v},t)\mathbf{v}) - \nabla c_{d}(\mathbf{r},t) \cdot \frac{\partial f_{i}}{\partial \mathbf{v}}(\mathbf{r},\mathbf{v},t) - \sqrt{2D} \frac{\partial}{\partial \mathbf{v}} (f_{i}(\mathbf{r},\mathbf{v},t)\mathbf{R}_{i}(t)) + D\Delta_{\mathbf{v}}f_{i}(\mathbf{r},\mathbf{v},t) \right] d\mathbf{r}d\mathbf{v}.$$
 (59)

Then, using $dF(\mathbf{r}_i, \mathbf{v}_i)/dt = \int \partial_t f_i(\mathbf{r}, \mathbf{v}, t) F(\mathbf{r}, \mathbf{v}) d\mathbf{r} d\mathbf{v}$ and comparing with Eq. (59), we get

$$\frac{\partial f_i}{\partial t} + \mathbf{v} \cdot \frac{\partial f_i}{\partial \mathbf{r}} + \nabla c_d \cdot \frac{\partial f_i}{\partial \mathbf{v}} = \frac{\partial}{\partial \mathbf{v}} \cdot \left(D \frac{\partial f_i}{\partial \mathbf{v}} + \xi f_i \mathbf{v} \right) - \sqrt{2D} \frac{\partial}{\partial \mathbf{v}} \cdot \left(f_i \mathbf{R}_i \right).$$
(60)

Summing this relation over the i, we finally obtain

$$\frac{\partial f_d}{\partial t} + \mathbf{v} \cdot \frac{\partial f_d}{\partial \mathbf{r}} + \nabla c_d \cdot \frac{\partial f_d}{\partial \mathbf{v}} = \frac{\partial}{\partial \mathbf{v}} \cdot \left(D \frac{\partial f_d}{\partial \mathbf{v}} + \xi f_d \mathbf{v} \right) - \sqrt{2D} \sum_{i=1}^N \frac{\partial}{\partial \mathbf{v}} \cdot \left(f_i \mathbf{R}_i \right). \tag{61}$$

Now, proceeding like in [60], the last term can be rewritten:

$$-\sum_{i=1}^{N} \frac{\partial}{\partial \mathbf{v}} \cdot (f_i(\mathbf{r}, \mathbf{v}, t) \mathbf{R}_i(t)) = \frac{\partial}{\partial \mathbf{v}} \cdot (f_d^{1/2}(\mathbf{r}, \mathbf{v}, t) \mathbf{Q}(\mathbf{r}, \mathbf{v}, t)),$$
(62)

where $\mathbf{Q}(\mathbf{r}, \mathbf{v}, t)$ is a Gaussian random field such that $\langle \mathbf{Q}(\mathbf{r}, \mathbf{v}, t) \rangle = \mathbf{0}$ and $\langle Q_{\alpha}(\mathbf{r}, \mathbf{v}, t) Q_{\beta}(\mathbf{r}', \mathbf{v}', t') \rangle = \delta_{\alpha\beta} \delta(\mathbf{r} - \mathbf{r}') \delta(\mathbf{v} - \mathbf{v}') \delta(t - t')$. Therefore, the system of equations satisfied by the exact distribution function expressed in terms of δ -functions is

$$\frac{\partial f_d}{\partial t} + \mathbf{v} \cdot \frac{\partial f_d}{\partial \mathbf{r}} + \nabla c_d \cdot \frac{\partial f_d}{\partial \mathbf{v}} = \frac{\partial}{\partial \mathbf{v}} \cdot \left(D \frac{\partial f_d}{\partial \mathbf{v}} + \xi f_d \mathbf{v} \right) + \frac{\partial}{\partial \mathbf{v}} \cdot \left(\sqrt{2Df_d} \mathbf{Q}(\mathbf{r}, \mathbf{v}, t) \right), \tag{63}$$

$$\frac{\partial c_d}{\partial t} = D_c \Delta c_d - kc_d + h \int f_d(\mathbf{r}, \mathbf{v}, t) d\mathbf{v}.$$
(64)

This will be called the stochastic Kramers equation of chemotaxis for the exact distribution function. Using Eq. (24), it can be written

$$\frac{\partial f_d}{\partial t} + \mathbf{v} \cdot \frac{\partial f_d}{\partial \mathbf{r}} + h \int d\mathbf{r}' d\mathbf{v}' \int_0^t dt' \nabla G(\mathbf{r} - \mathbf{r}', t - t') f_d(\mathbf{r}', \mathbf{v}', t') \cdot \frac{\partial f_d}{\partial \mathbf{v}}(\mathbf{r}, \mathbf{v}, t) \\
= \frac{\partial}{\partial \mathbf{v}} \cdot \left(D \frac{\partial f}{\partial \mathbf{v}} + \xi f \mathbf{v} \right) + \frac{\partial}{\partial \mathbf{v}} \cdot \left(\sqrt{2Df_d} \mathbf{Q}(\mathbf{r}, \mathbf{v}, t) \right).$$
(65)

If we average over the noise and introduce the smooth distribution function $f(\mathbf{r}, \mathbf{v}, t) = \langle f_d(\mathbf{r}, \mathbf{v}, t) \rangle$, we recover Eq. (60) of Chavanis & Sire [32]:

$$\frac{\partial f}{\partial t} + \mathbf{v} \cdot \frac{\partial f}{\partial \mathbf{r}} + h \frac{\partial}{\partial \mathbf{v}} \cdot \int d\mathbf{r}' d\mathbf{v}' \int_0^t dt' \nabla G(\mathbf{r} - \mathbf{r}', t - t') \langle f_d(\mathbf{r}, \mathbf{v}, t) f_d(\mathbf{r}', \mathbf{v}', t') \rangle
= \frac{\partial}{\partial \mathbf{v}} \cdot \left(D \frac{\partial f}{\partial \mathbf{v}} + \xi f \mathbf{v} \right).$$
(66)

If we make a mean field approximation $\langle f_d(\mathbf{r}, \mathbf{v}, t) f_d(\mathbf{r}', \mathbf{v}', t') \rangle \simeq f(\mathbf{r}, \mathbf{v}, t) f(\mathbf{r}', \mathbf{v}', t')$, we recover Eqs. (66)-(68) of Chavanis & Sire [32]:

$$\frac{\partial f}{\partial t} + \mathbf{v} \cdot \frac{\partial f}{\partial \mathbf{r}} + \nabla c \cdot \frac{\partial f}{\partial \mathbf{v}} = \frac{\partial}{\partial \mathbf{v}} \cdot \left(D \frac{\partial f}{\partial \mathbf{v}} + \xi f \mathbf{v} \right),\tag{67}$$

$$\frac{\partial c}{\partial t} = D_c \Delta c - kc + h \int f(\mathbf{r}, \mathbf{v}, t) d\mathbf{v}.$$
(68)

This can be viewed as a mean field Kramers equation of chemotaxis in the same way that the Keller-Segel model can be viewed as a Smoluchowski equation of chemotaxis. In fact, the Keller-Segel model (1)-(2) can be recovered from Eqs. (67)-(68) in a strong friction limit $\xi \to +\infty$ by using a Chapman-Enskog expansion [70] or a method of moments [32]. Let us note, for future reference, that the steady solutions of the mean field Kramers equation of chemotaxis correspond to a mean field Maxwell-Boltzmann-like distribution

$$f = A' e^{-\beta(v^2/2 - c)},\tag{69}$$

where $\beta = 1/T_{eff}$ is the inverse effective temperature. If we integrate this distribution over the velocitities we recover the distribution (30) that is the steady solution of the Keller-Segel model (1)-(2).

As discussed in the Introduction, the mean field approximation may not always give a good description of the dynamics. On the other hand, Eqs. (63)-(64) for the distribution function expressed in terms of δ -functions are exact but they are too complicated for practical purposes because they contain exactly the same information as the *N*-body stochastic Langevin equations (54)-(56). Therefore, as in Sec. 2, we shall introduce a simplified kinetic equation for a coarse-grained distribution function $\overline{f}(\mathbf{r}, \mathbf{v}, t)$ which smoothes out the exact distribution function $f_d(\mathbf{r}, \mathbf{v}, t)$ while keeping track of fluctuations. We propose the simplified stochastic model

$$\frac{\partial \overline{f}}{\partial t} + \mathbf{v} \cdot \frac{\partial \overline{f}}{\partial \mathbf{r}} + \nabla \overline{c} \cdot \frac{\partial \overline{f}}{\partial \mathbf{v}} = \frac{\partial}{\partial \mathbf{v}} \cdot \left(D \frac{\partial \overline{f}}{\partial \mathbf{v}} + \xi \overline{f} \mathbf{v} \right) + \frac{\partial}{\partial \mathbf{v}} \cdot \left(\sqrt{2D\overline{f}} \mathbf{Q}(\mathbf{r}, \mathbf{v}, t) \right), \tag{70}$$

$$\frac{\partial \overline{c}}{\partial t} = D_c \Delta \overline{c} - k\overline{c} + h \int \overline{f}(\mathbf{r}, \mathbf{v}, t) d\mathbf{v}.$$
(71)

This model takes into account inertial effects and fluctuations so that it should provide a good description of the dynamics of chemotactic species. As shown in Appendix B of [56], the form of the noise in these equations can be obtained by applying the general theory of fluctuations developed by Landau & Lifshitz [65].

Let us try to make a connexion with the hydrodynamic equations introduced phenomenologically in Sec. 5. Taking the hydrodynamic moments of the stochastic Kramers equation (70) and proceeding as in [32], we obtain

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \mathbf{u}) = 0, \tag{72}$$

$$\frac{\partial}{\partial t}(\rho u_i) + \frac{\partial}{\partial x_j}(\rho u_i u_j) = -\frac{\partial P_{ij}}{\partial x_j} + \rho \frac{\partial c}{\partial x_i} - \xi \rho u_i - \int \sqrt{2Df} Q_i d\mathbf{v}, \tag{73}$$

where $\rho(\mathbf{r},t) = \int f d\mathbf{v}$ is the density, $\mathbf{u}(\mathbf{r},t) = (1/\rho) \int f \mathbf{v} d\mathbf{v}$ is the local velocity, $\mathbf{w} = \mathbf{v} - \mathbf{u}(\mathbf{r},t)$ is the relative velocity and $P_{ij} = \int f w_i w_j d\mathbf{v}$ is the pressure tensor. Defining $\mathbf{g}(\mathbf{r},t) \equiv \int \sqrt{2Df} \mathbf{Q} d\mathbf{v}$, it is clear that \mathbf{g} is a Gaussian noise and that its correlation function is

$$\langle g_i(\mathbf{r},t)g_j(\mathbf{r}',t')\rangle = 2D \int \sqrt{f(\mathbf{r},\mathbf{v},t)f(\mathbf{r}',\mathbf{v}',t')} \langle Q_i(\mathbf{r},\mathbf{v},t)Q_j(\mathbf{r}',\mathbf{v}',t')\rangle d\mathbf{v}d\mathbf{v}'$$

= $2D\delta_{ij}\delta(\mathbf{r}-\mathbf{r}')\delta(t-t')\int f(\mathbf{r},\mathbf{v},t)d\mathbf{v} = 2D\delta_{ij}\delta(\mathbf{r}-\mathbf{r}')\delta(t-t')\rho(\mathbf{r},t).$ (74)

Therefore, the equation for the momentum (73) can be rewritten

$$\frac{\partial}{\partial t}(\rho u_i) + \frac{\partial}{\partial x_j}(\rho u_i u_j) = -\frac{\partial P_{ij}}{\partial x_j} + \rho \frac{\partial c}{\partial x_i} - \xi \rho u_i - \sqrt{2D\rho}R_i(\mathbf{r}, t).$$
(75)

This equation is not closed since the pressure tensor depends on the next order moment of the velocity. If, following [32], we make a local thermodynamic equilibrium (L.T.E.) approximation $f_{LTE}(\mathbf{r}, \mathbf{v}, t) \simeq (\beta/2\pi)^{d/2} \rho(\mathbf{r}, t) e^{-\beta w^2/2}$ to compute the pressure tensor, we find that $P_{ij} \simeq T_{eff} \rho \delta_{ij}$. In that case, Eqs. (72) and (75) return the stochastic damped Euler equations (49)-(50). We recall, however, that there is no rigorous justification for this local thermodynamic equilibrium approximation. Therefore, it does not appear possible to rigorously derive the damped hydrodynamic equations (49)-(50) from the Kramers equation (70)-(71) by a systematic procedure. Alternatively, if we consider the strong friction limit $\xi \to +\infty$ for fixed β , implying $D = \xi/\beta \to +\infty$, the first term in the r.h.s. of Eq. (70) implies that $f(\mathbf{r}, \mathbf{v}, t) \simeq (\beta/2\pi)^{d/2} \rho(\mathbf{r}, t) e^{-\beta v^2/2} + O(1/\xi)$, $\mathbf{u} = O(1/\xi)$ and $P_{ij} = T_{eff} \rho \delta_{ij} + O(1/\xi)$ [32]. To leading order in $1/\xi$, Eq. (75) becomes

$$\rho \mathbf{u} \simeq -\frac{1}{\xi} \left(T_{eff} \nabla \rho - \rho \nabla c + \sqrt{2D\rho} \mathbf{R}(\mathbf{r}, t) \right).$$
(76)

Inserting Eq. (76) in the continuity equation (72) and recalling that $T_{eff} = D/\xi = \xi D_*$ and $\chi = 1/\xi$, we recover the stochastic Keller-Segel model (31)-(32). It is therefore possible to rigorously derive the stochastic Keller-Segel model (31)-(32) from the stochastic Kramers equation (70)-(71) in the strong friction limit $\xi \to +\infty$.

7 Conclusion

In this paper, we have derived generalized Keller-Segel models of chemotaxis taking into account fluctuations. This leads to stochastic kinetic equations instead of deterministic equations. Fluctuations become important close to a critical point [63, 34, 56], so it is valuable to have a model of chemotaxis going beyond the mean field approximation and taking into account fluctuations. The divergence of the spatial correlation function close to the critical point has been analyzed in detail in [56] for Brownian particles interacting through a binary potential. These particles are described by a stochastic Smoluchowski equation coupled to the markovian field equation (8). The general methods developed in [56] can be extended to the stochastic Keller-Segel model (31) coupled to the non-Markovian field equation (2). Accounting for fluctuations is also important when the number of particles N is small and when there exists several metastable states. In that case, fluctuations can trigger dynamical phase transitions from one state to the other.

We have also introduced kinetic models of chemotaxis in phase space taking into account inertial effects. In the strong friction limit, we recover the Keller-Segel model describing an overdamped dynamics. We have discussed the relation between the kinetic equations in phase space and the hydrodynamic equations introduced phenomenologically. Finally, we have shown how the Cattaneo model of chemotaxis [26] could be obtained from these hydrodynamic equations.

This paper and [56] are the first attempts to include fluctuations in the kinetic equations of chemotaxis (the main results were given in [56] and they have been discussed here specifically with more details and amplification). In view of the importance of the Keller-Segel model in biology, the stochastic equations that we propose can have a lot of applications and can open the way to many new investigations. Their detailed numerical and analytical study is therefore of considerable interest. We hope to come to these problems in future works.

Note added: Until now, fluctuations have been ignored by people working on chemotaxis. Therefore, Ref. [56] and the present paper are the first attempts to include fluctuations in the Keller-Segel model. However, after submission of these papers, a paper by Tailleur & Cates [arXiv:0803.1069] (now published as Phys. Rev. Lett. **100**, 218103 (2008)) came out on a related subject. These authors also consider the effect of fluctuations in the motion of bacteria. However, their goal is different. They are mainly interested in deriving transport coefficients from microscopic models, so they do not take into account the long-range interaction between bacteria due to chemotaxis. Alternatively, in our approach, the transport coefficients D_* and χ appearing in the Langevin equations are introduced phenomenologically but longrange interaction between bacteria due to chemotaxis is fully taken into account. Therefore, these two independent studies are complementary to each other.

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