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MULTISCALE BIOLOGICAL TISSUE MODELS
AND FLUX-LIMITED CHEMOTAXIS FOR
MULTICELLULAR GROWING SYSTEMS

NICOLA BELLOMO

Department of Mathematics, Politecnico Torino,
Corso Duca degli Abruzzi 24, 10129 Torino, Italy
nicola.bellomo@polito.it

ABDELGHANI BELLOUQUID

University Cadi Ayyad, Ecole Nationale des
Sciences Appliquées, Safi, Maroc
bellouquid@gmail.com

JUAN NIETO* and JUAN SOLER†

University of Granada, Departamento de Matemática Aplicada,
18071 Granada, Spain
*jjmnieto@ugr.es
†jsoler@ugr.es

This paper deals with the derivation of macroscopic tissue models from the underlying description delivered by a class of equations that models binary mixtures of multicellular systems by methods of the kinetic theory for active particles. Cellular interactions generate both modification of the biological functions and proliferative and destructive events. The asymptotic analysis deals with suitable parabolic and hyperbolic limits, and is specifically focused on the modeling of the chemotaxis phenomena.

Keywords: Living systems; kinetic theory; multicellular systems; chemotaxis; asymptotic limits; hyperbolic limits; diffusion limits.

1. Introduction

This paper deals with the derivation of macroscopic models of biological tissues from the underlying description that is offered by the kinetic theory for active particles KTAP,[13] for short, and focuses on the asymptotic limit for macroscopic models that we have considered to be a mixture of two populations of cells. Different combinations of parabolic and hyperbolic scales are used, according to the dispersive or

non-dispersive nature of the population under consideration. The methodological approach can easily be generalized to more than two populations. Two different approaches have been considered and are supported by the assumptions that both populations are involved in some (linear or nonlinear) diffusion processes or, in a different context, that the dynamics of at least one of the populations is dominated by the hyperbolic behavior, where diffusion does not have any, even negative, role on preserving singular structures or patterns.

Our analysis is quite general, in the sense that it could be applied to different species, but for some aspects can be considered as a good example of the interactions of a population with a chemical attractant: chemotaxis. As is well known, chemotaxis consists of the characteristic, movement or, orientation of a population (bacteria, cell or other single or multicellular organisms) along a chemical concentration gradient either towards or away from the chemical stimulus (signals). Typical examples are bacteria swimming to find food, the movement of sperm towards the egg during fertilization, migration of lymphocytes, and cancer metastasis.[1,33,34,57] A wide literature on the biological basis of the chemotaxis in different contexts has been documented in review paper.[42]

Let us briefly comment on some issues involved in modeling chemotaxis phenomena that are at present being discussed in the scientific community and on which this paper tries to offer some insight:

(1) Several papers have been proposed in the literature based on suitable hypothesis on the static or dynamic nature of the chemical signal. In our opinion, stationary models (usually called parabolic−elliptic Keller−Segel models[19,32]) for the chemical population only seem to be justified from a mathematical point of view and provide a kind of hydrodynamical approach to these phenomena. The time-spatial model detects chemoattractant waves coming from a particular direction going towards, and interacting with the population, which is in continuous movement. It should be noted that this mechanism might not reach a static gradient. On the other hand, if we are dealing with an isolated system, the propagation of the chemical substances could reasonably be represented by a diffusion process which would induce a parabolic (diffusion) scale in our kinetic approach. However, a different choice of the model (such as hyperbolic or nonlinear parabolic) as well as a more refined choice of scale can be considered in a more complex scenario.

(2) Depending on the type of organism, on their ability to move (which is, for example, different in a bacteria or in a cell) and on the interaction with the multiple protein molecule signals that they could detect, some small fluctuations might appear in the trajectory of the population towards the path defined by the chemoattractants. It is also of interest to point out that, in many of the approaches that describe the transport of a population, it is not clear how the trajectory of the population is explicitly captured in the model, in correlation with the signal pathway. This transport term is usually assumed linear in the concentration gradient of chemoattractants and is denoted by S, i.e. of type $\mathrm{div}_{\mathbf{x}}(n\nabla_{\mathbf{x}}S)$, where n is the density of the

population and $\mathbf{x}$ the space variable.[19,20,32] However, this approach is not optimal in the optimal transportation sense and, accordingly, it is only valid for very small values of $|\nabla_{\mathbf{x}} S|$, which is not the general case.

(3) Another aspect involved in modeling these phenomena, which is also of great interest in relation to the previous point, is to obtain an answer to the following question: *Does the population (cells or bacteria) move by (linear) diffusion?*

Although linear diffusion (terms of heat or Fokker−Planck type) usually has infinite speed of propagation, it has been taken as a prototype to describe the movement of biological populations. However, in some cases, linear diffusion contributes with an excess of diffusion that destroys the dynamics of the systems and it has a crucial aspect of the phenomena in chemotaxis pattern formation. It does not seem reasonable to think that this kind of population can move in a Gaussian manner, while experiments[23,31] have proved that, on the contrary, the propagation is made by fronts and singularities that are certainly far from that of linear diffusion models. Because of this evidence, this modeling of the dynamics has been assumed, but with some doubts, by the scientific community, which has tried to use alternative mechanisms, such as the hyperbolic Cattaneo approach,[25] which was finally proved to violate the second principle of thermodynamics.[56] Recently, different ideas have appeared in order to understand more clearly the population propagation, based mainly on nonlinear diffusion or on hyperbolic models that allow front propagations, periodic solutions, breathing modes, singularities, and so on to be transported and preserved. One of the approaches consists in changing the classical diffusion term Δn by a power law diffusion of a porous medium or nonlinear mean field Fokker−Planck[28−30] type $\mathrm{div}_{\mathbf{x}}(n^m \nabla_{\mathbf{x}} n)$. However, in this case the velocity at which the system propagates the structures (fronts, patterns or singularities) of the population is not an intrinsic property of the population; it actually depends on the initial conditions. Many of the properties of the classical porous media equation are involved in this new approach.[58]

Another point of view consists in modifying the model by introducing a nonlinear limited flux of the type

$$\mathrm{div}_{\mathbf{x}}\left(n \frac{\nabla_{\mathbf{x}} n}{\sqrt{n^2 + \frac{\nu^2}{c^2}|\nabla_{\mathbf{x}} n|^2}}\right)$$

instead of linear diffusion, ν being the kinematic viscosity and c the maximum speed of propagation. The motivation behind this approach was first given by Rosenau[54,55] and then derived by Brenier[20] by means of a Monge−Kantorovich mass transport theory. The introduction of this type of term can also be motivated by the assumption that particles do not move (diffuse) arbitrarily in the space but, on the contrary, through some privileged curves such as the border of cells. The analysis of systems with limited flux[4−8] as well as some extensions to biological context (transport of morphogens) has been recently explored.[2] This flux limited argument

shows that the non-physical diffusion is eliminated and the population moves with a finite speed of propagation, c, which is one of the intrinsic characteristics. As a consequence, the system behaves more as a hyperbolic system than the usual linear diffusive (Fokker−Planck) system and we obtain the preservation during the time evolution of the dynamical structures: propagation fronts, biological responses or stable patterns. It is also possible, in the same term, to combine the flux limited with a porous media type term,[3]

$$\operatorname{div}_{\mathbf{x}} \left(n^m \frac{\nabla_{\mathbf{x}} n}{\sqrt{n^2 + \frac{\nu^2}{c^2}|\nabla_{\mathbf{x}} n|^2}} \right),$$

where new phenomena can be modeled. The idea of replacing the diffusion effects with a purely hyperbolic model for the cells or bacteria while keeping the parabolic process for the chemoattractant, will also be analyzed later.

In order to anticipate some of our final results, let us here introduce the following macroscopic model for the density and chemoattractant. This model collects two of the innovating improved terms, with respect to the classical Keller−Segel model, and consists of the choice of a limited flux and of the optimal transport of the population n according to the chemical signal S

$$\begin{cases} \partial_t n = \operatorname{div}_{\mathbf{x}} \left(D_n \frac{n\nabla_{\mathbf{x}} n}{\sqrt{n^2 + \frac{D_n^2}{c^2}|\nabla_{\mathbf{x}} n|^2}} - n\chi \frac{\nabla_{\mathbf{x}} S}{\sqrt{1 + |\nabla_{\mathbf{x}} S|^2}} \right) + H_2(n, S), \\ \partial_t S = \operatorname{div}_{\mathbf{x}}(D_S \cdot \nabla_{\mathbf{x}} S) + H_1(n, S), \end{cases} \quad (1.1)$$

where $H_i(n, S)$, $i = 1, 2$ describes the interactions between the populations and the remaining parameters and functions are related to the inner properties of the species, as will be explained later. It should be pointed out that both modifications are motivated by optimal transportation criteria[20] that are essential from a qualitative point of view, for instance, for the propagation of singular fronts.

The aim of this paper is to deduce, from basic principles, macroscopic models generated by the interaction of several populations for which chemotaxis is a particular situation. The improvements and new issues involved in modeling these phenomena are motivated by the optimal transportation criteria which is important to incorporate qualitative properties of the system under consideration. The idea is to start with microscopic models deduced from the kinetic theory and then derive macroscopic models at parabolic−parabolic and/or hyperbolic−parabolic scales. To this aim, KTAP methods deal with large systems of interacting entities (cells), according to the following main principles:

(i) The microscopic state of the interacting cells, called *active particles*, is characterized not only by position and velocity, but also by an additional microscopic state, called *activity*, which represents the biological functions expressed at a cellular level.

(ii) Microscopic interactions not only modify the microscopic state, but may also generate proliferative and/or destructive phenomena.

Focusing on the mathematical models of multicellular systems derived according to the KTAP method, the book[18] and the survey[14] report on the application of the theory to model complex systems in biology, while different models in life sciences are presented in the survey.[13]

The dynamics of the overall system is described by an evolution equation for the distribution function over the microscopic state of the particles (cells, bacteria, morphogens,...). Asymptotic methods amount to expanding the distribution function in terms of a small dimensionless parameter related to the intermolecular distances (the space-scale dimensionless parameter), which is equivalent to the connections between the biological constants. The limit is singular and the convergence properties can be proved under suitable technical assumptions. In the previous papers, biological systems were considered in which the interactions do not follow classical mechanical rules, and biological activity may play a relevant role in determining the dynamics.

An example that motivates the role of the activation variables can be found in the study and modeling the cellular growth. One of the approaches adopted in the literature to model cellular growth consists in adapting the experimental results to the growth of a radial ball in a linear heat equation. However, where is biology in this approach? External agents, such as insulin, are involved in the activation of biological variables, which trigger the pathway of the TOR protein, which in turn plays a central role in cellular growth. Therefore, modeling on the basis of first principles, as far as possible, could contribute to incorporate the correct biological inputs in the macroscopic context. This is a crucial aspect in our approach to the modeling of living systems, where the active particles that compose their matter have the ability to subtract mass, information or energy from the environment for their own benefit, including proliferative and/or destructive events. Proliferation is in fact generally obtained using the energy of other living entities which are destroyed.

In recent years, the analysis of the applicability of this procedure to different systems has reached an important stage of development in the so-called parabolic and hyperbolic limits or equivalently low and high field limits. The parabolic (low field) limit of kinetic equations leads to a drift−diffusion type system (or reaction−diffusion system) in which the diffusion processes dominate the behavior of the solutions. The specialized literature offers a number of recent contributions concerning various limits for parabolic diffusive models of the mathematical kinetic theory.[38,53]

When dealing with cell interactions, the authors do not believe that the diffusive (parabolic) limit is the most appropriate approach, while diffusion seems to be more correct for the case of the concurrence of a chemical process or in a surrounding fluid with a precise viscosity. On the other hand, in the hyperbolic (high field) limit the influence of the diffusion terms is of lower (or equal) order of magnitude compared with other convective or interaction terms and the aim is to derive hyperbolic

macroscopic models.[21,36,37] Therefore, different macroscopic models are obtained in agreement with different scaling assumptions, see Ref. 52.

The same methodological approach has been developed over the last decade to derive macroscopic equations from the underlying microscopic models for multi-cellular systems derived from the methods of the generalized kinetic theory. Although the literature on this topic is not as vast as that of classical particles, several interesting contributions[10−12,26,27,35,43,48,50] have been developed after the pioneering paper by Othmer, Dunbar and Alt.[49]

This paper is organized as follows. Section 2 deals with the description of the class of equations of the KTAP method that describe multicellular systems where interactions modify the biological functions expressed by cells, and proliferative or destructive events. Section 3 deals with the definition of parabolic scalings derived from the asymptotic analysis in the limit of the macroscopic equation. Section 4 deals with mixed parabolic and hyperbolic scaling, again focusing on the derivation of macroscopic biological phenomena. Various examples are reported in both Secs. 3 and 4.

2. A General Mathematical Framework

Let us consider a physical system constituted by a large number of cells that interact in the environment of a vertebrate. The physical variable used to describe the state of each cell, called *microscopic state*, is denoted by the variable $\{t, \mathbf{x}, \mathbf{v}, u\}$, where $\{\mathbf{x}, \mathbf{v}\}$ is the *mechanical microscopic state*, identified by position and velocity, and $u \in D_u \subseteq \mathbb{R}$ is the *biological function* expressed by each population regarded as a module,[41] and t is the time.

Specifically, let us consider a binary mixture, where the statistical collective description is encoded in the statistical distribution functions $f_i = f_i(t, \mathbf{x}, \mathbf{v}, u)$, for $i = 1, 2$, which is called *generalized distribution function*. Weighted moments provide, under suitable integrability properties, the calculation of macroscopic variables.

Modeling the evolution of the distribution function can be obtained by the KTAP method. In detail, the evolution of $f = (f_1, f_2)$ can be modeled for a system of two populations, as follows:

$$\begin{cases} (\partial_t + \mathbf{v} \cdot \nabla_{\mathbf{x}})f_1 = \nu_1 \mathcal{L}_1(f_1) + \eta_1 \mathcal{G}_1[f, f] + \mu_1 \mathcal{I}_1[f, f], \\ (\partial_t + \mathbf{v} \cdot \nabla_{\mathbf{x}})f_2 = \nu_2 \mathcal{L}_2(f_2) + \eta_2 \mathcal{G}_2[f, f] + \mu_2 \mathcal{I}_2[f, f], \end{cases} \quad (2.1)$$

where

- The operator $\mathcal{L}_i(f_i)$ that models the dynamics of biological organisms by a velocity-jump process is defined as follows:

$$\mathcal{L}_i(f) = \int_V [T_i(\mathbf{v}, \mathbf{v}^*)f(t, \mathbf{x}, \mathbf{v}^*, u) - T_i(\mathbf{v}^*, \mathbf{v})f(t, \mathbf{x}, \mathbf{v}, u)]d\mathbf{v}^*,$$

  for $i = 1, 2$, where $T_i(\mathbf{v}, \mathbf{v}^*)$ is the probability kernel over the new velocity $\mathbf{v} \in V$, assuming that the previous velocity was $\mathbf{v}^*$. This corresponds to the assumption

that any individual of the population chooses any direction with bounded velocity. Specifically, the set of possible velocities is denoted by V, where $V \subset \mathbb{R}^3$; moreover, it is assumed that V is bounded and spherically symmetric (i.e. $\mathbf{v} \in V \Rightarrow -\mathbf{v} \in V$). The operators T_i may depend on f_1 and f_2; moreover, ν_1 and ν_2 represent the interaction rates of the mechanical interactions.

- η_1 and η_2 denote the biological interaction rates related to interactions that modify the biological state of the individuals for each population.
- The operators $\mathcal{G}_i$ are defined as follows:

$$\mathcal{G}_i[f, f](t, \mathbf{x}, \mathbf{v}, u) = \sum_{j=1}^{2} \mathcal{G}_{ij}[f, f](t, \mathbf{x}, \mathbf{v}, u),$$

where

$$\mathcal{G}_{ij} = \int_{\Gamma} w_{ij}(\mathbf{x}, \mathbf{x}^*) \mathcal{B}_{ij}(u_* \rightarrow u | u_*, u^*) f_i(t, \mathbf{x}, \mathbf{v}, u_*) f_j(t, \mathbf{x}^*, \mathbf{v}, u^*) d\mathbf{x}^* \, du_* du^*$$
$$- f_i(t, \mathbf{x}, \mathbf{v}, u) \int_{\Lambda} w_{ij}(\mathbf{x}, \mathbf{x}^*) f_j(t, \mathbf{x}^*, \mathbf{v}, u^*) d\mathbf{x}^* du^*,$$

and $\Gamma = D_u \times D_u \times \Omega$ and $\Lambda = D_u \times \Omega$, where Ω is the spatial interaction domain. The operators $\mathcal{G}_{ij}$ describe the gain–loss balance of individuals (cells, chemoattractants, molecules, etc.) in state u, in each population, due to conservative encounters, namely those which modify the biological state without generating proliferation or destruction phenomena. The kernel $\mathcal{B}_{ij}$ models the transition probability density of the individual with state u_* into the individual with state u, after interaction with the individual with state u^*, $w_{ij}(\mathbf{x}, \mathbf{x}^*)$ is a normalized (with respect to space integration over Ω) weight function that accounts for the distance and distribution that weakens the intensity of the interaction.

- $\mathcal{I}_i$ corresponds to proliferative/destructive interactions (in the absence of proliferation, due to genetic mutations into a population different from that of the interacting individuals). This operator is defined as follows:

$$\mathcal{I}_i[f, f](t, \mathbf{x}, \mathbf{v}, u) = \sum_{j=1}^{2} \mathcal{I}_{ij}[f, f](t, \mathbf{x}, \mathbf{v}, u),$$

where

$$\mathcal{I}_{ij}(f, f) = f_i(t, \mathbf{x}, \mathbf{v}, u) \int_{\Lambda} w_{ij}(\mathbf{x}, \mathbf{x}^*) p_{ij}(u, u^*) f_j(t, \mathbf{x}^*, \mathbf{v}, u^*) d\mathbf{x}^* du^*.$$

Remark 2.1. The distribution function $f_i(t, \mathbf{x}, \mathbf{v}, u)$ refers to the *test* individual, while interactions occur between pairs of a *test* and a *field* individual $f_j(t, \mathbf{x}^*, \mathbf{v}, u^*)$ that generate proliferative or destructive outputs; and between a *candidate* $f_j(t, \mathbf{x}, \mathbf{v}, u^*)$ and *field* individual with mutation of the state of the candidate individual into the state of the test individual.[15]

Remark 2.2. The above modeling approach is based on the assumption that interactions occur, and are weighted, within the action domain Ω of the test individual. In particular, the term $\mathcal{B}_{ij}(u_* \to u|u_*, u^*)$ has the structure of a probability density with respect to the output u for any input variable.

Remark 2.3. The assumption that the microscopic state u is a scalar variable can be technically related to the theory of modules by Hartwell.[41] It has been proposed in Ref. 15 that modules are identified by the biological functions they express, which corresponds to refer the collective behavior of the population to one biological function only. Accordingly, the denomination of *functional subsystems* has been proposed.

3. The Parabolic–Parabolic Limit: Linear Turning Operators

In this section different possibilities, which could appear when dealing with parabolic hydrodynamical limits for both populations, are introduced. These limits depend on the scaling choice for the biological constants. First the basis of the kinetic approach to this microscopic model is given; then, based on the identification in the limit of the moments of the solutions, the different limit cases can be deduced. Finally, several examples motivated in the choice of the transport and interactions operators involved in our general kinetic model are reported.

3.1. *The kinetic model*

The purpose of this section is to derive macroscopic models (as for example those of chemotaxis) from the kinetic model (2.1). These macroscopic equations can be obtained in the regime $\nu_1 \leq \nu_2$ and also in the regime where the biological parameters are small with respect to mechanical ones. After a dimensionless of the system is obtained, see Ref. 12, a small parameter ε can be chosen such that

$$\nu_1 = \frac{1}{\varepsilon^p}, \quad \nu_2 = \frac{1}{\varepsilon}, \quad p \geq 1$$

and

$$\eta_1 = \eta_2 = \varepsilon^q, \quad \mu_1 = \varepsilon^{r_1}, \quad \mu_2 = \varepsilon^{r_2},$$

where $q \geq 1$, and r_1, r_2 are non-negative constants.

Then, the model (2.1) can be written in the following form:

$$\begin{cases} (\varepsilon\partial_t + \mathbf{v}\cdot\nabla_{\mathbf{x}})f_1^\varepsilon = \dfrac{1}{\varepsilon^p}\mathcal{L}_1(f_1^\varepsilon) + \varepsilon^q\mathcal{G}_1[f^\varepsilon, f^\varepsilon] + \varepsilon^{q+r_1}\mathcal{I}_1[f^\varepsilon, f^\varepsilon], \\[2mm] (\varepsilon\partial_t + \mathbf{v}\cdot\nabla_{\mathbf{x}})f_2^\varepsilon = \dfrac{1}{\varepsilon}\mathcal{L}_2[f_1^\varepsilon](f_2^\varepsilon) + \varepsilon^q\mathcal{G}_2[f^\varepsilon, f^\varepsilon] + \varepsilon^{q+r_2}\mathcal{I}_2[f^\varepsilon, f^\varepsilon], \end{cases} \tag{3.1}$$

where we assume that the turning operator $\mathcal{L}_2[f_1]$ can be written as follows:

$$\mathcal{L}_2[f_1](g) = \mathcal{L}_2^0(g) + \varepsilon\mathcal{L}_2^1[f_1](g), \tag{3.2}$$

and where $\mathcal{L}_2^i$ for $i = 0, 1$ are given by

$$\mathcal{L}_2^i(g) = \int_V [T_2^i g(t, \mathbf{x}, \mathbf{v}^*, u) - T_2^{i\,*} g(t, \mathbf{x}, \mathbf{v}, u)] d\mathbf{v}^*, \tag{3.3}$$

where $T_2^{i\,*} = T_2^i(\mathbf{v}^*, \mathbf{v})$.

The dependence on f_1 of the operator $\mathcal{L}_2[f_1]$ stems from $\mathcal{L}_2^1$. We assume that $\mathcal{L}_2^0$ is independent of f_1. A nonlinear choice leading to limited flux operators will be introduced in the last section of this paper.

Let us first state some assumptions on the turning operator $\mathcal{L}_i$ $(i = 1, 2)$.

Assumption H.3.1. We assume that the turning operators $\mathcal{L}_1$ and $\mathcal{L}_2$ satisfy

$$\int_V \mathcal{L}_1(g) d\mathbf{v} = \int_V \mathcal{L}_2^0(g) d\mathbf{v} = \int_V \mathcal{L}_2^1[f_1](g) d\mathbf{v} = 0. \tag{3.4}$$

Some definitions and assumptions are necessary to develop the asymptotic analysis leading to the derivation of macroscopic models. In the following, the integral with respect to the variable $\mathbf{v}$ will be denoted by $\langle \cdot \rangle$.

Assumption H.3.2. There exists a bounded velocity distribution $M_i(\mathbf{v}) > 0$, $i = 1, 2$ independent of $t, \mathbf{x}$, such that the detailed balance

$$T_1(\mathbf{v}, \mathbf{v}^*) M_1(\mathbf{v}^*) = T_1(\mathbf{v}^*, \mathbf{v}) M_1(\mathbf{v})$$

and

$$T_2^0(\mathbf{v}, \mathbf{v}^*) M_2(\mathbf{v}^*) = T_2^0(\mathbf{v}^*, \mathbf{v}) M_2(\mathbf{v})$$

holds. Moreover, the flow produced by these equilibrium distributions vanishes, and M_i are normalized, i.e. $\langle \mathbf{v} M_i(\mathbf{v}) \rangle = 0$ and $\langle M_i(\mathbf{v}) \rangle = 1$.

Also, the kernels $T_1(\mathbf{v}, \mathbf{v}^*)$ and $T_2^0(\mathbf{v}, \mathbf{v}^*)$ are bounded, and there exists a constant $\sigma_i > 0$, $i = 1, 2$, such that

$$T_1(\mathbf{v}, \mathbf{v}^*) \geq \sigma_1 M_1(\mathbf{v}), \quad T_2^0(\mathbf{v}, \mathbf{v}^*) \geq \sigma_2 M_2(\mathbf{v}),$$

for all $(\mathbf{v}, \mathbf{v}^*) \in V \times V$, $\mathbf{x} \in \Omega$ and $t > 0$.

Let $L_1 = \mathcal{L}_1$ and $L_2 = \mathcal{L}_2^0$. Assumption H.3.2 yields the proof of the following lemma (see Ref. 9):

Lemma 3.1. *Suppose that Assumptions* H.3.1 *and* H.3.2 *hold. Then, the following properties of the operators L_1 and L_2 hold:*

(i) *For $f \in L^2$, the equation $L_i(g) = f$, $i = 1, 2$, has a unique solution $g \in L^2(V, \frac{d\mathbf{v}}{M_i})$, which satisfies*

$$\langle g \rangle = \int_V g(\mathbf{v}) d\mathbf{v} = 0 \quad \text{if and only if} \quad \langle f \rangle = \int_V f(\mathbf{v}) d\mathbf{v} = 0.$$

(ii) *The operator L_i is self-adjoint in the space $L^2(V, \frac{d\mathbf{v}}{M_i})$.*

(iii) *The equation $L_i(g) = \mathbf{v}M_i(\mathbf{v})$, $i = 1, 2$, has a unique solution that we call $\theta_i(\mathbf{v})$.*
(iv) *The kernel of L_i is $N(L_i) = \text{vect}(M_i(\mathbf{v}))$, $i = 1, 2$.*

We will first derive the general form of the velocity of the first population in terms of the operator $\mathcal{L}_2^1[f_1]$, without a detailed specification as to how it depends on the other population, and thereby we will derive the equation at the macroscopic level from the model at the microscopic scale.

3.2. *The hydrodynamic limit*

The limit $\varepsilon \to 0$ is formally developed, in this subsection, for (3.1). The resulting macroscopic model depends on the properties of the turning operators. The strategy to derive the macroscopic model consists of the following steps:

Step 1. Multiplying the first equation of (3.1) by ε^p and letting ε go to zero, yields $\mathcal{L}_1(f_1^0) = 0$. Therefore, one deduces, by Lemma 3.1(iv) that there exists a function S, independent of $\mathbf{v}$, such that

$$f_1^0(t, \mathbf{x}, \mathbf{v}, u) = S(t, \mathbf{x}, u)M_1(\mathbf{v}). \tag{3.5}$$

By multiplying the second equation of (3.1) by ε, using (3.2), and letting ε go to zero, yields $\mathcal{L}_2^0(f_2^0) = 0$. Moreover, analogous reasonings yield

$$f_2^0(t, \mathbf{x}, \mathbf{v}, u) = n(t, \mathbf{x}, u)M_2(\mathbf{v}). \tag{3.6}$$

Step 2. Integration of the first and second equations in (3.1) over $\mathbf{v}$ and using (3.4) yields:

$$\partial_t \langle f_1^\varepsilon \rangle + \frac{1}{\varepsilon} \langle \mathbf{v} \cdot \nabla_\mathbf{x} f_1^\varepsilon \rangle = \varepsilon^{q-1} \langle \mathcal{G}_1[f^\varepsilon, f^\varepsilon] \rangle + \varepsilon^{q+r_1-1} \langle \mathcal{I}_1[f^\varepsilon, f^\varepsilon] \rangle \tag{3.7}$$

and

$$\partial_t \langle f_2^\varepsilon \rangle + \frac{1}{\varepsilon} \langle \mathbf{v} \cdot \nabla_\mathbf{x} f_2^\varepsilon \rangle = \varepsilon^{q-1} \langle \mathcal{G}_2[f^\varepsilon, f^\varepsilon] \rangle + \varepsilon^{q+r_2-1} \langle \mathcal{I}_2[f^\varepsilon, f^\varepsilon] \rangle. \tag{3.8}$$

The asymptotic limit of $\frac{1}{\varepsilon} \langle \mathbf{v} \cdot \nabla_\mathbf{x} f_i^\varepsilon \rangle$, $i = 1, 2$, needs to be estimated to recover the limit in (3.7) and (3.8). Moreover, let us consider the identity

$$\frac{1}{\varepsilon} \langle \mathbf{v} \cdot \nabla_\mathbf{x} f_i^\varepsilon \rangle = \text{div}_\mathbf{x} \left\langle \frac{M_i(\mathbf{v}) \mathbf{v} f_i^\varepsilon}{\varepsilon M_i(\mathbf{v})} \right\rangle = \text{div}_\mathbf{x} \left\langle \frac{1}{\varepsilon} \theta_i(\mathbf{v}) \mathcal{L}_i(f_i^\varepsilon) \frac{1}{M_i(\mathbf{v})} \right\rangle, \quad i = 1, 2,$$

where functions θ_i are given by Lemma 3.1; and using the identities

$$\frac{1}{\varepsilon} \mathcal{L}_1(f_1^\varepsilon) = \varepsilon^p \partial_t f_1^\varepsilon + \varepsilon^{p-1} \mathbf{v} \cdot \nabla_\mathbf{x} f_1^\varepsilon - \varepsilon^{p-1+q} \mathcal{G}_1[f^\varepsilon, f^\varepsilon] - \varepsilon^{q+r_1+p-1} \mathcal{I}_1[f^\varepsilon, f^\varepsilon]$$

and

$$\frac{1}{\varepsilon} \mathcal{L}_2^0(f_2^\varepsilon) = \varepsilon \partial_t f_2^\varepsilon + \mathbf{v} \cdot \nabla_\mathbf{x} f_2^\varepsilon - \mathcal{L}_2^1[f_1^\varepsilon](f_2^\varepsilon) - \varepsilon^q \mathcal{G}_2[f^\varepsilon, f^\varepsilon] - \varepsilon^{q+r_2} \mathcal{I}_2[f^\varepsilon, f^\varepsilon]$$

and the properties that $\mathcal{L}_2^0$ and $\mathcal{L}_1$ are self-adjoint operators, one deduces that

$$\frac{1}{\varepsilon}\langle \mathbf{v} \cdot \nabla_{\mathbf{x}} f_1^{\varepsilon}\rangle \rightarrow \mathrm{div}_{\mathbf{x}}\langle \theta_1(\mathbf{v} \cdot \nabla_{\mathbf{x}})S\rangle, \quad \text{if } p = 1, \text{ or } 0 \text{ if } p > 1,$$

and

$$\frac{1}{\varepsilon}\langle \mathbf{v} \cdot \nabla_{\mathbf{x}} f_2^{\varepsilon}\rangle \rightarrow \mathrm{div}_{\mathbf{x}}\langle \theta_2(\mathbf{v} \cdot \nabla_{\mathbf{x}}n)\rangle - \mathrm{div}_{\mathbf{x}}\left\langle \frac{\theta_2}{M_2(\mathbf{v})}\mathcal{L}_2^1[M_1 S](M_2 n)\right\rangle.$$

The asymptotic quadratic terms of (3.7) and (3.8) converge, for $i = 1, 2$, to the following functionals:

$$G_i(n, S)(t, \mathbf{x}, u) = \left\langle \mathcal{G}_i\left[\begin{pmatrix} M_1 S \\ M_2 n \end{pmatrix}, \begin{pmatrix} M_1 S \\ M_2 n \end{pmatrix}\right]\right\rangle$$

and

$$I_i(n, S)(t, \mathbf{x}, u) = \left\langle \mathcal{I}_i\left[\begin{pmatrix} M_1 S \\ M_2 n \end{pmatrix}, \begin{pmatrix} M_1 S \\ M_2 n \end{pmatrix}\right]\right\rangle.$$

Therefore, we can derive macroscopic models by taking limits in (3.7) and (3.8).

Some assumptions on the kernels $T_1(\mathbf{v}, \mathbf{v}^*)$, $T_2^0(\mathbf{v}, \mathbf{v}^*)$ and $T_2^1[f_1]$ are needed to develop the convergence analysis leading to the derivation of macroscopic models.

Assumption H.3.3. There exists C_i, $i = 1, 2, 3$ independent of t, $\mathbf{x}$, and $\mathbf{v}$ such that:

$$T_1(\mathbf{v}, \mathbf{v}^*) \leq C_1 M_1(\mathbf{v}), \quad T_2^0(\mathbf{v}, \mathbf{v}^*) \leq C_2 M_2(\mathbf{v}), \quad |T_2^1[f_1]| \leq C_3|f_1|.$$

To pass to the limit it is sufficient to assume pointwise convergence together with a global L^m bound of f_i^{ε} (see Ref. 12 for details). This result can be stated as follows.

Theorem 3.1. *Let $f_i^{\varepsilon}(t, \mathbf{x}, \mathbf{v}, u)$ be a sequence of solutions to the scaled kinetic system (3.1), which verifies Assumptions H.3.1−H.3.3 such that f_i^{ε} converges a.e. in $[0, \infty) \times \Omega \times V \times D_u$ to a function f_i^0 as ε goes to zero and*

$$\sup_{t \geq 0} \int_{\Omega} \int_V \int_{D_u} |f_i^{\varepsilon}(t, \mathbf{x}, \mathbf{v}, u)|^m \, du \, d\mathbf{v} \, d\mathbf{x} \leq C < \infty \tag{3.9}$$

for some positive constants $C > 0$ and $m > 2$. Moreover, it is assumed that the probability kernels $\mathcal{B}_{ij}$ are bounded functions and that the weight functions w_{ij} and p_{ij} have finite integrals. It follows that the asymptotic limits f_i^0 have the form (3.5)−(3.6) where n, S are the weak solutions of the following equation (that depends on the values of p, q, r_1 and r_2)

$$\partial_t S - \delta_{p,1} \mathrm{div}_{\mathbf{x}}(D_S \cdot \nabla_{\mathbf{x}} S) = \delta_{q,1} G_1(n, S) + \delta_{q,1} \delta_{r_1,0} I_1(n, S),$$
$$\partial_t n + \mathrm{div}_{\mathbf{x}}(n\, \alpha(S) - D_n \cdot \nabla_{\mathbf{x}} n) = \delta_{q,1} G_2(n, S) + \delta_{q,1} \delta_{r_2,0} I_2(n, S),$$

where $\delta_{a,b}$ stands for the Kronecker delta and D_n, D_S and $\alpha(S)$ are given by

$$D_S = -\int_V \mathbf{v} \otimes \theta_1(\mathbf{v}) d\mathbf{v}, \quad D_n = -\int_V \mathbf{v} \otimes \theta_2(\mathbf{v}) d\mathbf{v} \tag{3.10}$$

and

$$\alpha(S) = -\int_V \frac{\theta_2(\mathbf{v})}{M_2(\mathbf{v})} \mathcal{L}_2^1[M_1 S](M_2)(\mathbf{v})d\mathbf{v}. \tag{3.11}$$

Remark 3.1. The matrices D_n and D_S are symmetric and positive definite according to a standard result in the theory of diffusion limits (see Ref. 9 for a proof).

Remark 3.2. In general D_n and D_S are not isotropic (there are not scalar factor of the identity matrix). An example where the tensors D_n and D_S are isotropic will be given in Sec. 3.3.1.

The approach we have developed is quite general. Some more specific examples are now given.

3.3. *Examples for linear turning kernels*

Specific models for turning kernels and compute explicit formulas for the macroscopic transport coefficients are analyzed in this subsection.

3.3.1. *Example I: A general model for kernels with relaxation in time*

Let us first consider the following task for the probability kernels:

$$T_1(\mathbf{v}, \mathbf{v}^*) = \sigma_1 M_1(\mathbf{v}), \quad T_2^0(\mathbf{v}, \mathbf{v}^*) = \sigma_2 M_2(\mathbf{v}), \quad \sigma_1, \sigma_2 > 0.$$

Consequently, the leading turning operators $\mathcal{L}_1$ and $\mathcal{L}_2^0$ become relaxation operators:

$$\mathcal{L}_1(g) = -\sigma_1(g - \langle g \rangle M_1), \quad \mathcal{L}_2^0(g) = -\sigma_2(g - \langle g \rangle M_2).$$

In particular, θ_1 and θ_2 are given by

$$\theta_1(\mathbf{v}) = -\frac{1}{\sigma_1} \mathbf{v} M_1(\mathbf{v}), \quad \theta_2(\mathbf{v}) = -\frac{1}{\sigma_2} \mathbf{v} M_2(\mathbf{v}).$$

Moreover

$$\alpha(S) = \frac{1}{\sigma_2} \int_V \mathbf{v} \mathcal{L}_2^1[M_1 S](M_2)(\mathbf{v})d\mathbf{v}, \tag{3.12}$$

while the diffusion tensors D_n and D_S are given by

$$D_S = \frac{1}{\sigma_1} \int_V \mathbf{v} \otimes \mathbf{v} M_1(\mathbf{v})d\mathbf{v}, \quad D_n = \frac{1}{\sigma_2} \int_V \mathbf{v} \otimes \mathbf{v} M_2(\mathbf{v})d\mathbf{v}.$$

If rotational invariance of the equilibrium distribution, namely $M_i = M_i(|\mathbf{v}|)$ is assumed, the isotropic tensors D_n and D_S are given by:

$$D_S = \left(\frac{1}{3\sigma_1} \int_V |\mathbf{v}|^2 M_1(\mathbf{v})d\mathbf{v}\right)I, \quad D_n = \left(\frac{1}{3\sigma_2} \int_V |\mathbf{v}|^2 M_2(\mathbf{v})d\mathbf{v}\right)I.$$

3.3.2. *Some fundamentals of chemotaxis*

The mathematical study of chemotaxis started with the work of Patlak[51] and was boosted by the papers of Keller and Segel, where they introduced a model to study the aggregation of Dictyostelium discoideum due to an attractive chemical substance[44] and made some further comments and studies.[45,46] We refer to Ref. 47 for a review about the first years of research on the Keller−Segel model.

Their original model consists in an advection-diffusion system of two coupled parabolic equations:

$$\begin{cases} \partial_t n = \text{div}_{\mathbf{x}}(D_n \nabla_{\mathbf{x}} n - \chi n \nabla_{\mathbf{x}} S) + H(n, S), \\ \partial_t S = D_S \Delta S + K(n, S), \end{cases} \tag{3.13}$$

where $n = n(t, \mathbf{x})$ is the cell density at position $\mathbf{x}$ and time t, and $S = S(t, \mathbf{x})$ is the density of the chemoattractant. The positive-definite terms D_S and D_n are the diffusivity of the chemoattractant and of the cells, respectively, while $\chi \geq 0$ is the chemotactic sensitivity. As we will see later, in a more general framework in which diffusions are not isotropic, D_S and D_n could be positive-definite matrices.

We will examine several forms for the dependence of the kernel on S and its gradient, some of which lead to the classical systems such as the Keller−Segel chemotaxis model. Our approach gives the derivation of the evolution equation (linear Fokker−Planck) for S, while nonlinear cases will be analyzed at the end of the paper.

Let us briefly comment on the main aspects of model (3.13) in order to clearly understand its derivation from a microscopic approach and how to improve or incorporate some new fundamental aspects of chemotaxis:

- It is reasonable, in a preliminary approach, assuming that the chemical population undergoes a linear diffusion process; in general the substance S does not only diffuse in the substrate, but it can also be produced by bacteria themselves.
- The role of the functions $H(n, S)$ and $K(n, S)$ in (3.13) consists in modeling the interaction between both quantities. For example, the Slime Mold Amoebae produce themselves the chemoattractant when it is lacking nourishment.
- It is not completely clear how the term $\text{div}_{\mathbf{x}}(\chi n \nabla_{\mathbf{x}} S)$ induces *per se* the *optimal* movement of the cells towards the pathway determined by the chemoattractant. Then, in our opinion, this term could be modified in a fashion that the flux density of particles is optimized along the trajectory induced by the chemoattractant, namely by minimizing the functional

$$\int \chi n \, dS = \int \chi n \sqrt{1 + |\nabla_{\mathbf{x}} S|^2} dx$$

with respect to S, where dS is the measure of the curve defined by S. This approach provides an alternative term in the corresponding Euler–Lagrange equation of type

$$\text{div}_{\mathbf{x}} \left(\chi n \frac{\nabla_{\mathbf{x}} S}{\sqrt{1 + |\nabla_{\mathbf{x}} S|^2}} \right). \tag{3.14}$$

Of course this term coincides with $\mathrm{div}_{\mathbf{x}}(\chi n \nabla_{\mathbf{x}} S)$ when $|\nabla_{\mathbf{x}} S|$ is very small. However, if $|\nabla_{\mathbf{x}} S| \sim 0$, comparing this scale with the remaining scales of the problem is necessary.

• As we mentioned in the Introduction, it does not seem realistic to think that cells or bacteria move simply by (linear Fokker–Planck) diffusion, $\mathrm{div}_{\mathbf{x}}(D_n \nabla_{\mathbf{x}} n)$. Other possibilities to modify this approach based on incorporating real phenomena related with cell or bacteria motion (cilium activation or elasticity properties of the membrane, among others) can be considered. For instance, considering a nonlinear limited flux that allows a richer and more realistic dynamics: finite speed of propagation c, preservation of fronts in the evolution, or formation of biological patterns. This is represented by terms of the type

$$\mathrm{div}_{\mathbf{x}}\left(D_n n \frac{\nabla_{\mathbf{x}} n}{\sqrt{n^2 + \frac{D_n^2}{c^2}|\nabla_{\mathbf{x}} n|^2}} \right).$$

We investigate, in the following examples, how the classical chemotaxis equations (3.13), which describe the population-level response to external chemical signals, can be obtained from the microscopic description delivered by model (2.1), as well as some more precise approaches to the several phenomena described in the previous items.

3.3.3. *Example II*: *Classical Keller–Segel type models*

The relaxation kernels presented in Sec. 3.3.1, together with the choice

$$T_2^1[f_1] = K_{\frac{f_1}{M_1}}(\mathbf{v}, \mathbf{v}^*) \cdot \nabla_{\mathbf{x}} \frac{f_1}{M_1},$$

where $K_{\frac{f_1}{M_1}}(\mathbf{v}, \mathbf{v}^*)$ is a vector-valued function, leads to the model

$$\mathcal{L}_2^1[M_1 S](M_2) = h(v, S) \cdot \nabla_{\mathbf{x}} S,$$

where

$$h(v, S) = \int_V (K_S(\mathbf{v}, \mathbf{v}^*)M_2(\mathbf{v}^*) - K_S(\mathbf{v}^*, \mathbf{v})M_2(\mathbf{v}))d\mathbf{v}^*.$$

Finally, the function $\alpha(S)$ in (3.12) is given by

$$\alpha(S) = \chi(S) \cdot \nabla_{\mathbf{x}} S,$$

where the chemotactic sensitivity $\chi(S)$ is given by the matrix

$$\chi(S) = \frac{1}{\sigma_2} \int_V \mathbf{v} \otimes h(\mathbf{v}, S)d\mathbf{v}. \tag{3.15}$$

Therefore, the drift term $\mathrm{div}_{\mathbf{x}}(n\alpha(S))$ that appears in the macroscopic case stated by Theorem 3.1 becomes:

$$\mathrm{div}_{\mathbf{x}}(n\alpha(S)) = \mathrm{div}_{\mathbf{x}}(n\chi(S) \cdot \nabla_{\mathbf{x}} S),$$

which gives a Keller–Segel type model (3.13) in the case $p = 1$ of Theorem 3.1.

3.3.4. *Example III: Optimal drift following the chemoattractant*

If we combine the relaxation kernels presented in Sec. 3.3.1 with the following choice for T_2^1:

$$T_2^1[f_1] = K_{\frac{f_1}{M_1}}(\mathbf{v}, \mathbf{v}^*) \cdot \frac{\nabla_{\mathbf{x}} \frac{f_1}{M_1}}{\sqrt{1 + |\nabla_{\mathbf{x}} \frac{f_1}{M_1}|^2}}, \tag{3.16}$$

then, the drift term $\text{div}_{\mathbf{x}}(n\alpha(S))$ that appears in the macroscopic cases defined in Theorem 3.1 becomes

$$\text{div}_{\mathbf{x}}(n\alpha(S)) = \text{div}_{\mathbf{x}}\left(n\chi(S) \cdot \frac{\nabla_{\mathbf{x}}S}{\sqrt{1 + |\nabla_{\mathbf{x}}S|^2}}\right),$$

where the chemotactic sensitivity $\chi(S)$ is given by the matrix (3.15), and, in general, is not constant. This corresponds to the optimal drift term (3.14) presented in Sec. 3.3.2 as a modification of the Keller−Segel model (3.13).

The model deduced in Sec. 3.3.3 could be a reasonable simplification of this one when $|\nabla_{\mathbf{x}}S| \sim 0$, but it is not, in general, a good simplification since the trajectories can develop, for example, spiral patterns.

Similar type of turning operators, addressed to find a flux limited Keller−Segel model as a parabolic limit of a kinetic description, can also be found in Ref. 22. In that paper the authors introduce a flux-limited operator of type $\nabla_{\mathbf{x}}S/|\nabla_{\mathbf{x}}S|$ with a multiplicative factor in terms of the time derivative of S trying to model the microscopic features that stem from the response of a bacterium to a change in the environment.

Constructing turning operator, that lead to deduce nonlinear flux-limited terms as they were described in the Introduction, requires a different approach. Some nonlinear turning operators, obtained from first principles of the flux-limited system, are deduced in the last section for the hyperbolic−parabolic limit, according to an appropriate choice of the operator $\mathcal{L}_2$. This choice depends of both populations on the drift−diffusion type models analyzed in this section.

4. Binary Mixtures and Mixed Scalings: Flux-Limited Systems

Let us now consider again the class of equations derived in Sec. 2, which acts as a fundamental paradigm for the derivation of various models of interest in biology and life sciences as documented in the book[18] and in papers.[16,17,15]

The asymptotic analysis developed in the preceding section was based on the assumption of the *parabolic scaling* (3.1) for both populations. The limit gives rise to a system of coupled equations which includes a diffusion term for both populations. Assuming that the second population (cells or bacteria in the example of chemotaxis) has no diffusive behavior, the derivation of macroscopic equations requires *hyperbolic scaling* for this population. Bearing this in mind, let us now consider system (2.1)

with a parabolic scaling for the first population, but with a hyperbolic one for the second one:

$$(\varepsilon\partial_t + \mathbf{v}\cdot\nabla_{\mathbf{x}})f_1^\varepsilon = \frac{1}{\varepsilon^p}\mathcal{L}_1(f_1^\varepsilon) + \varepsilon^q\mathcal{G}_1[f^\varepsilon,f^\varepsilon] + \varepsilon^{q+r_1}\mathcal{I}_1[f^\varepsilon,f^\varepsilon], \qquad (4.1)$$

$$\varepsilon(\partial_t + \mathbf{v}\cdot\nabla_{\mathbf{x}})f_2^\varepsilon = \mathcal{L}_2[f_1^\varepsilon](f_2^\varepsilon) + \varepsilon^q\mathcal{G}_2[f^\varepsilon,f^\varepsilon] + \varepsilon^{q+r_2}\mathcal{I}_2[f^\varepsilon,f^\varepsilon], \qquad (4.2)$$

where $p, q \geq 1$, $r_1, r_2 \geq 0$, and ε is a small parameter that is allowed to tend to zero. We refer to Ref. 12 for more details about the hyperbolic scaling.

4.1. *The parabolic limit for the first specie*

The limit $\varepsilon \to 0$ of (4.1) is analyzed in this subsection, as in Sec. 3.2. Macroscopic models are obtained depending on the turning operator $\mathcal{L}_1$.

Considering that the scaling for the first Eq. (4.1), that corresponds to the chemical substance, is exactly that of Sec. 3.1, the hypothesis on $\mathcal{L}_1$ and the passage to the limit follow the same guidelines. This approach yields:

$$\partial_t S = \delta_{p,1}\operatorname{div}_{\mathbf{x}}(D_S\cdot\nabla_{\mathbf{x}}S) + \delta_{q,1}\left\langle\mathcal{G}_1\left[\begin{pmatrix}M_1S\\f_2^0\end{pmatrix},\begin{pmatrix}M_1S\\f_2^0\end{pmatrix}\right]\right\rangle$$

$$+ \delta_{q,1},\delta_{r_1,0}\left\langle\mathcal{I}_1\left[\begin{pmatrix}M_1S\\f_2^0\end{pmatrix},\begin{pmatrix}M_1S\\f_2^0\end{pmatrix}\right]\right\rangle,$$

where $\delta_{a,b}$ stands for the Kronecker delta and f_2^0 will be given by the limit of f_2^ε, to be determined.

Actually, some different "hyperbolic" hypotheses on the operator $\mathcal{L}_2[f_1^\varepsilon]$ are required to establish the behavior of the second specie and its macroscopical limit. In fact, we have different ways to proceed depending on the expected result. In the next subsections we will see how different hypotheses produce different descriptions of the macroscopic behavior.

4.2. *Parabolic−hyperbolic description: Integral coupling*

We assume that the turning operator $\mathcal{L}_2[f_1^\varepsilon]$ is decomposed as in (3.2) and verifies (3.3), meanwhile condition (3.4) and Assumption H.3.2 are replaced by the following hyperbolic assumptions (see Ref. 12 for more details).

Assumption H.4.1. The turning operator $\mathcal{L}_2[f_1^\varepsilon] = \mathcal{L}_2^0 + \varepsilon\mathcal{L}_2^1[f_1^\varepsilon]$ satisfies

$$\int_V \mathcal{L}_2^0(g)d\mathbf{v} = \int_V \mathcal{L}_2^1[f_1](g)d\mathbf{v} = 0, \qquad (4.3)$$

$$\int_V \mathbf{v}\mathcal{L}_2^0(g)d\mathbf{v} = 0. \qquad (4.4)$$

Assumption H.4.2. For any $n \in [0, +\infty)$ and $U \in \mathbb{R}^n$, there exists a unique function $M_{n,U} \in L^1(V, (1 + |\mathbf{v}|)d\mathbf{v})$ such that

$$\mathcal{L}_2^0(M_{n,U}) = 0, \quad \int_V M_{n,U}(v)d\mathbf{v} = n, \quad \int_V \mathbf{v} M_{n,U}(\mathbf{v})d\mathbf{v} = nU. \quad (4.5)$$

Then, we let ε go to zero in Eq. (4.2). This yields $\mathcal{L}_2^0(f_2^0) = 0$. Therefore, as a consequence, there exist $n \geq 0$ and $U \in \mathbb{R}^n$ (depending on $(t, \mathbf{x}, u)$), namely the macroscopic density and velocity associated to function f_2^0, such that $f_2^0 = M_{n,U}$.

The next step consists in determining the macroscopic dynamics for n and U and the coupling with the macroscopic density S. To do that, we integrate (4.2) over $\mathbf{v}$ and use (4.3) to obtain

$$\partial_t \langle f_2^\varepsilon \rangle + \langle \mathbf{v} \cdot \nabla_\mathbf{x} f_2^\varepsilon \rangle = \varepsilon^{q-1} \langle \mathcal{G}_2[f^\varepsilon, f^\varepsilon] \rangle + \varepsilon^{q-1+r_2} \langle \mathcal{I}_2[f^\varepsilon, f^\varepsilon] \rangle.$$

By letting $\varepsilon \to 0$, we find that the function n satisfies the following conservation law

$$\frac{\partial n}{\partial t} + \mathrm{div}_\mathbf{x}(nU) = \delta_{q,1} \langle \mathcal{G}_2[f^0, f^0] \rangle + \delta_{q,1} \delta_{r_2,0} \langle \mathcal{I}_2[f^0, f^0] \rangle$$

at the equilibrium, where

$$f^0 = (M_1(\mathbf{v})S, M_{n,U}). \quad (4.6)$$

In the same way, multiplying (4.2) by $\mathbf{v}$, integrating over $\mathbf{v}$, and using (4.4) yields

$$\partial_t \langle \mathbf{v} f_2^\varepsilon \rangle + \mathrm{Div}_\mathbf{x} \langle \mathbf{v} \otimes \mathbf{v} f_2^\varepsilon \rangle = \langle \mathbf{v} \mathcal{L}_2^1[f_1^\varepsilon](f_2^\varepsilon) \rangle$$
$$+ \varepsilon^{q-1} \langle \mathbf{v} \mathcal{G}_2[f^\varepsilon, f^\varepsilon] \rangle + \varepsilon^{q-1+r_2} \langle \mathbf{v} \mathcal{I}_2[f^\varepsilon, f^\varepsilon] \rangle.$$

Letting again $\varepsilon \to 0$, the limit equation for the momentum is rapidly obtained:

$$\frac{\partial(nU)}{\partial t} + \mathrm{Div}(nU \otimes U + \mathbb{P}) = \langle \mathbf{v} \mathcal{L}_2^1[M_2 S](M_{n,U}) \rangle$$
$$+ \delta_{q,1} \langle \mathbf{v} \mathcal{G}_2[f^0, f^0] \rangle + \delta_{q,1} \delta_{r_2,0} \langle \mathbf{v} \mathcal{I}_2[f^0, f^0] \rangle,$$

where f^0 is defined by (4.6) and the pressure tensor is, as usual, given by

$$\mathbb{P} = \int_V (\mathbf{v} - U) \otimes (\mathbf{v} - U) M_{n,U} d\mathbf{v}. \quad (4.7)$$

Therefore, the model at the macroscopic scale is obtained as follows:

$$\begin{cases} \partial_t S = \delta_{p,1} \mathrm{div}_\mathbf{x}(D_S \cdot \nabla_\mathbf{x} S) + \delta_{q,1} \langle \mathcal{G}_1[f^0, f^0] \rangle + \delta_{q,1} \delta_{r_1,0} \langle \mathcal{I}_1[f^0, f^0] \rangle, \\ \partial_t n + \mathrm{div}_\mathbf{x}(nU) = \delta_{q,1} \langle \mathcal{G}_2[f^0, f^0] \rangle + \delta_{q,1} \delta_{r_2,0} \langle \mathcal{I}_2[f^0, f^0] \rangle, \\ \partial_t(n\,U) + \mathrm{Div}(nU \otimes U + \mathbb{P}) \\ \quad = \langle \mathbf{v} \mathcal{L}_2^1[M_1\,S](M_{n,U}) \rangle + \delta_{q,1} \langle \mathbf{v} \mathcal{G}_2[f^0, f^0] \rangle + \delta_{q,1} \delta_{r_2,0} \langle \mathbf{v} \mathcal{I}_2[f^0, f^0] \rangle. \end{cases} \quad (4.8)$$

This result can be summarized in the following theorem.

Theorem 4.1. *Let $f_i^\varepsilon(t, \mathbf{x}, \mathbf{v}, u)$ be a sequence of solutions to the scaled kinetic system* (4.1)−(4.2) *with $\mathcal{L}_1$ verifying Assumptions* H.3.1−H.3.3 *and $\mathcal{L}_2$ verifying*

Assumptions H.4.1 *and* H.4.2. *Assume that* f_i^ε *verifies* (3.9) *and converges a.e. in* $[0, \infty) \times \Omega \times V \times D_u$ *to a function* f_i^0 *as* ε *goes to zero. Moreover, it is assumed that the probability kernels* $\mathcal{B}_{ij}$ *are bounded functions and that the weight functions* w_{ij} *and* p_{ij} *have finite integrals. Then, the asymptotic limit is given by* (4.6) *where S, n and U are the weak solutions of* (4.7)−(4.8).

Remark 4.1. Note that the influence of the population S on the velocity U is given by an integral source term. Moreover, even if we take $\mathcal{L}_2^1 = 0$, the other integral terms give an analogous coupling once $q = 1$.

Remark 4.2. Note that system (4.8) is not closed in general. Some examples where system (4.8) is closed are as follows.

4.3. *Examples from parabolic−hyperbolic coupling*

Let us anticipate here the following macroscopic models, which is a particular case of the next general result.

4.3.1. *Recovering Cattaneo system*

The linear Cattaneo system has the following form:

$$\begin{cases} \partial_t n + \operatorname{div}_\mathbf{x}(nU) = 0, \\ \tau \partial_t(nU) + d\nabla_\mathbf{x} n = -nU. \end{cases} \tag{4.9}$$

The linear Cattaneo system (4.9) can be seen as a generalization of a correlated random walk.[39] Therefore, $n(t, \mathbf{x})$ is the population density and $n(t, \mathbf{x})U(t, \mathbf{x})$ is the population flux. The constant d and the time constant τ are positive. The Cattaneo law, namely the second equation in (4.9), was introduced by Cattaneo[25] to describe heat transport with finite speed. This property justified the extensive use in biology of the Cattaneo model until Rubin[56] proved that the system violates the second principle of the thermodynamics.

Let us now define the operators $\mathcal{L}_2^0(f)$ and T_2^1 in the kinetic formulation leading through the parabolic−hyperbolic limit to the Cattaneo system. Consider the case where the set for velocity is the sphere of radius $r > 0$, $V = r\mathbb{S}^{d-1}$. Let us take a kernel $T_2^0(\mathbf{v}, \mathbf{v}^*)$ in the form $T_2^0(\mathbf{v}, \mathbf{v}^*) = \lambda + \beta\, \mathbf{v} \cdot \mathbf{v}^*$, so that the operator $\mathcal{L}_2^0(f)$ can be computed as follows:

$$\mathcal{L}_2^0(f) = \lambda|V|\left(\frac{n}{|V|}\left(1 + \frac{\beta}{\lambda}\, \mathbf{v} \cdot U\right) - f(\mathbf{v})\right). \tag{4.10}$$

Then $\mathcal{L}_2^0(f)$, with $\beta r^2 = \lambda n$ verifies Assumptions H.4.1 and H.4.2 for a function $M_{n,U}(\mathbf{v})$ given by

$$M_{n,U}(\mathbf{v}) = \frac{n}{|V|}\left(1 + \frac{\beta}{\lambda}\mathbf{v} \cdot U\right) = \frac{n}{|V|}\left(1 + \frac{d}{r^2}\, \mathbf{v} \cdot U\right) \tag{4.11}$$

and $\mathcal{L}_2^0(f)$ is the relaxation operator

$$\mathcal{L}_2^0(f) = \lambda |V|(M_{n,U}(\mathbf{v}) - f(\mathbf{v})). \qquad (4.12)$$

Then, the pressure tensor $\mathbb{P}$ defined in (4.7) associated with $M_{n,U}(\mathbf{v})$ is given by

$$\mathbb{P} = \frac{r^2}{d} n\mathbb{I} - nU \otimes U.$$

Let us now take first a kernel $T_2^1(\mathbf{v}, \mathbf{v}^*)$ independent of f_1

$$T_2^1(\mathbf{v}, \mathbf{v}^*) = \frac{\alpha_1}{|V|} \qquad (4.13)$$

such that the operator $\mathcal{L}_2^1(f)$ satisfies (4.3) and can be computed as follows:

$$\mathcal{L}_2^1[f_1](f_2) = \alpha_1 \left(\frac{n}{|V|} - f_2 \right) \qquad (4.14)$$

and

$$\int_V \mathbf{v}\mathcal{L}_2^1[M_2 S](M_{n,U})d\mathbf{v} = -\alpha_1 nU. \qquad (4.15)$$

Therefore the macroscopic model (4.8) becomes

$$\begin{cases} \partial_t S = \delta_{p,1} \operatorname{div}_\mathbf{x}(D_S \cdot \nabla_\mathbf{x} S) + G_{\delta,q}(S,n), \\ \partial_t n + \operatorname{div}_\mathbf{x}(nU) = H_{\delta,q}[S,n,nU], \\ \partial_t(nU) + \dfrac{r^2}{d}\nabla_\mathbf{x} n = -\alpha_1 nU + K_{\delta,q}[S,n,nU], \end{cases}$$

where

$$G_{\delta,q}(S,n) = \delta_{q,1} \left\{ (\langle M_1(\mathbf{v})^2 \rangle \mathcal{G}_{11}\left[\binom{S}{n}, \binom{S}{n} \right] + \frac{1}{|V|}\mathcal{G}_{12}\left[\binom{S}{n}, \binom{S}{n} \right] \right\}$$

$$+ \delta_{q,1}\delta_{r_1,0} \left\{ \langle M_1(\mathbf{v})^2 \rangle \mathcal{I}_{11}\left[\binom{S}{n}, \binom{S}{n} \right] + \frac{1}{|V|}\mathcal{I}_{12}\left[\binom{S}{n}, \binom{S}{n} \right] \right\}$$

and

$$H_{\delta,q}(S,n,nU) = \frac{\delta_{q,1}}{|V|}\left(\mathcal{G}_{21}\left[\binom{S}{n}, \binom{S}{n} \right] + G(n) + \frac{d}{r^2}G(nU) \right)$$

$$+ \frac{\delta_{q,1}\delta_{r_2,0}}{|V|}\left(\mathcal{I}_{21}\left[\binom{S}{n}, \binom{S}{n} \right] + I(n) + \frac{d}{r^2}I(nU) \right),$$

$$K_{\delta,q}(S,n,nU) = \frac{\delta_{q,1}}{|V|}\left\{ \mathcal{G}_{21}\left[\binom{S}{\langle \mathbf{v} \otimes \mathbf{v} M_1(\mathbf{v}) \rangle \cdot nU}, \binom{S}{\langle \mathbf{v} \otimes \mathbf{v} M_1(\mathbf{v}) \rangle \cdot nU} \right]\right.$$

$$+ K(n,nU) + K(nU,n) \Big\}$$

$$+ \frac{\delta_{q,1}\delta_{r_2,0}}{|V|}\left\{ \frac{d}{r^2}\mathcal{I}_{21}\left[\binom{S}{\langle \mathbf{v} \otimes \mathbf{v} M_1(\mathbf{v}) \rangle \cdot nU}, \binom{S}{\langle \mathbf{v} \otimes \mathbf{v} M_1(\mathbf{v}) \rangle \cdot nU} \right]\right.$$

$$+ P(n,nU) \Big\},$$

where for any scalar or vector function h, the functions I and G are given by

$$G(h) = \mathcal{G}_{22}\left[\begin{pmatrix} \cdot \\ h \end{pmatrix}, \begin{pmatrix} \cdot \\ h \end{pmatrix}\right], \quad I(h) = \mathcal{I}_{22}\left[\begin{pmatrix} \cdot \\ h \end{pmatrix}, \begin{pmatrix} \cdot \\ h \end{pmatrix}\right],$$

and the vector functions $K(h, g)$ and $P(h, g)$ are given by

$$K(h,g) = \int_{\Gamma} w_{22}(\mathbf{x}, \mathbf{x}^*)\mathcal{B}_{22}(u_* \to u|u_*, u^*)h(t, \mathbf{x}, \mathbf{v}, u_*)g(t, \mathbf{x}^*, \mathbf{v}, u^*)d\mathbf{x}^* du_* du^*$$

$$- g(t, \mathbf{x}, \mathbf{v}, u)\int_{\Lambda} w_{22}(\mathbf{x}, \mathbf{x}^*)h(t, \mathbf{x}^*, \mathbf{v}, u^*)d\mathbf{x}^* du^*,$$

$$P(h,g) = g(t, \mathbf{x}, \mathbf{v}, u)\int_{\Lambda} w_{22}(\mathbf{x}, \mathbf{x}^*)p_{22}(u, u^*)h(t, \mathbf{x}, \mathbf{v}, u^*)d\mathbf{x}^* du^*$$

$$+ h(t, \mathbf{x}, \mathbf{v}, u)\int_{\Lambda} w_{22}(\mathbf{x}, \mathbf{x}^*)p_{22}(u, u^*)g(t, \mathbf{x}, \mathbf{v}, u^*)d\mathbf{x}^* du^*$$

for any vector or scalar function h and g.

Hence, the nonlinear Cattaneo system coupled with the concentration equation for S which has been studied qualitatively in Refs. 25 and 40 has been obtained, while for $q > 1$ the linear Cattaneo system (4.9) is deduced.

4.3.2. *A Cattaneo model for chemosensitive movement*

Chemotaxis, in the case of bacteria, can significantly change their movement in response to external stimuli. Hence, we modify the turning operator to derive a model for chemosensitive movement. The turning operator should depend on the velocity $\mathbf{v}$, on the concentration of the external signal S, and on its gradient $\nabla_{\mathbf{x}}S$.

Let us consider the model defined by (4.10) for $\mathcal{L}_2^0(f)$, and let us modify the choice of T_2^1 with respect to the previous example by using:

$$T_2^1[f_1^\epsilon] = \frac{1}{|V|}\left(\alpha_1 - \frac{d}{r^2}\mathbf{v} \cdot \alpha\left(\frac{1}{|V|}\left\langle\frac{f_1^\epsilon}{M_1}\right\rangle\right)\right), \tag{4.16}$$

where α_1 is a real number and α is a vector function.

Therefore, the operator $\mathcal{L}_2^1(f)$, can be computed as follows:

$$\mathcal{L}_2^1[f_1^\varepsilon](f_2^\varepsilon) = \alpha_1\left(\frac{n^\varepsilon}{|V|} - f_2^\varepsilon\right) - \frac{d}{r^2}\left(\frac{n^\varepsilon U^\varepsilon}{|V|} - \mathbf{v}f_2^\varepsilon\right) \cdot \alpha\left(\frac{1}{|V|}\left\langle\frac{f_1^\epsilon}{M_1}\right\rangle\right),$$

where n^ε and U^ε depend on f_2^ε and are given by

$$n^\varepsilon = \int_V f_2^\varepsilon(\mathbf{v})\,d\mathbf{v}, \quad n^\varepsilon U^\varepsilon = \int_V \mathbf{v}f_2^\varepsilon(\mathbf{v})d\mathbf{v}.$$

It is easy to check that $\mathcal{L}_2^1[f_1^\varepsilon](f_2^\varepsilon)$ satisfies (4.3) and that the coupling term in (4.8) can be written as follows:

$$\int_V \mathbf{v}\mathcal{L}_2^1[M_1 S](M_{n,U})d\mathbf{v} = \lim_{\varepsilon \to 0}\int_V \mathbf{v}\mathcal{L}_2^1[f_1^\varepsilon](f_2^\varepsilon)d\mathbf{v} = -\alpha_1 nU + n\alpha(S).$$

Therefore, for $\alpha(S) = \alpha_2 \nabla_{\mathbf{x}} S$, one again derives the corresponding Cattaneo system for chemosensitive movement with density control, coupled with the concentration equation for S

$$\begin{cases} \partial_t S = \delta_{p,1} \operatorname{div}_{\mathbf{x}}(D_S \cdot \nabla_{\mathbf{x}} S) + G_{\delta,q}(S, n), \\[2mm] \partial_t n + \operatorname{div}_{\mathbf{x}}(nU) = H_{\delta,q}[S, n, nU], \\[2mm] \partial_t(nU) + \dfrac{r^2}{d} \nabla_{\mathbf{x}} n = -\alpha_1 nU + \alpha_2 n \nabla_{\mathbf{x}} S + K_{\delta,q}[S, n, nU]. \end{cases}$$

A more realistic dependance on S can be taken into account by choosing $\alpha = \alpha(n, S)$. This is not possible with the choice of the kernel (4.16).

4.3.3. *Nonlinear operator $\mathcal{L}_2^1[f_1^\epsilon](f_2^\varepsilon)$ for chemosensitive movement*

Let us introduce a nonlinear turning operator, which depends nonlinearly on f. For instance, when only macroscopic quantities computed from the distribution function f are taken into account, a possible choice is the following:

$$\mathcal{L}_2^1[f_1^\epsilon](f_2^\epsilon) = \int_V H\left(\mathbf{v}, \mathbf{v}^*, U^\epsilon, \left\langle \frac{f_1^\epsilon}{M_1} \right\rangle\right) \nabla_{\mathbf{x}} \left\langle \frac{1}{|V|} \frac{f_1^\epsilon}{M_1} \right\rangle f_2^\epsilon(\mathbf{v}^*) d\mathbf{v}^*,$$

and assume that

$$H\left(\mathbf{v}, \mathbf{v}^*, U^\epsilon, \left\langle \frac{f_1^\epsilon}{M_1} \right\rangle\right) = \alpha\left(\frac{1}{|V|} \left\langle \frac{f_1^\epsilon}{M_1} \right\rangle\right) \mathbf{v} h(\mathbf{v})$$

with

$$\int_V h(\mathbf{v}) d\mathbf{v} = 1, \quad \int_V \mathbf{v} h(\mathbf{v}) d\mathbf{v} = 0, \quad \int_V \mathbf{v} \otimes \mathbf{v} h(\mathbf{v}) d\mathbf{v} = \beta I. \qquad (4.17)$$

Therefore $\mathcal{L}_2^1[f_1^\epsilon](f_2^\epsilon)$ is computed as follows:

$$\mathcal{L}_2^1[f_1^\epsilon](f_2^\epsilon) = \alpha\left(\frac{1}{|V|} \left\langle \frac{f_1^\epsilon}{M_1} \right\rangle\right) \mathbf{v} h(\mathbf{v}) \nabla_{\mathbf{x}} \left(\frac{1}{|V|} \left\langle \frac{f_1^\epsilon}{M_1} \right\rangle\right) n^\epsilon$$

which satisfies (4.3) and

$$\int_V \mathbf{v} \mathcal{L}_2^1[M_1 S](M_{n,U}) d\mathbf{v} = \lim_{\varepsilon \to 0} \int_V \mathbf{v} \mathcal{L}_2^1[f_1^\epsilon](f_2^\varepsilon) d\mathbf{v} = \beta n \alpha(S) \nabla_{\mathbf{x}}(S),$$

which is an example of nonlinear integral coupling in (4.8).

The dependence on n^ε in the kernel H can be introduced, however it makes the operator nonlinear and requires a more detailed analysis. This kind of nonlinearity will be developed in the last example of the paper.

4.4. *Pressureless hyperbolic description: Direct drift coupling*

In this section we try to obtain a model that in the limit preserves a drift term for the second population produced by the concentration gradient of the other population

(for example in chemical substance), but eliminating the diffusion effects. Instead of Assumptions H.4.1 and H.4.2, the following assumptions on the hyperbolic scaling are needed:

Assumption H.4.3. Assume that the turning operator $\mathcal{L}_2[f_1^\varepsilon]$ satisfies

$$\int_V \mathcal{L}_2[f_1^\varepsilon](g)d\mathbf{v} = 0, \tag{4.18}$$

$$\int_V \mathbf{v}\mathcal{L}_2[f_1^\varepsilon](g)d\mathbf{v} = \text{Const.}\left(\langle g\rangle\alpha\left(\frac{1}{|V|}\left\langle\frac{f_1^\varepsilon}{M_1}\right\rangle\right) - \langle\mathbf{v}g\rangle\right). \tag{4.19}$$

Remark 4.3. Actually, Assumption (4.19) have to be verified only after passing to the limit. A more explicit description of the kernel $\mathcal{L}_2$ is not needed. Some specific examples are reported in the next subsection.

Now we proceed as in the previous sections. Letting ε go to zero in Eq. (4.2) yields $\mathcal{L}_2[f_1^0](f_2^0) = 0$; therefore f_2^0 must be in the kernel of $\mathcal{L}_2[f_1^0]$. Then, we define $n := \langle f_2^0\rangle$ the limiting density of the second population and $j := \langle\mathbf{v}f_2^0\rangle$ its current. We integrate (4.2) over $\mathbf{v}$ and use (4.18) to obtain the evolution equation of n:

$$\partial_t\langle f_2^\varepsilon\rangle + \langle\mathbf{v}\cdot\nabla_\mathbf{x}f_2^\varepsilon\rangle = \varepsilon^{q-1}\langle\mathcal{G}_2[f^\varepsilon, f^\varepsilon]\rangle + \varepsilon^{q-1+r_2}\langle\mathcal{I}_2[f^\varepsilon, f^\varepsilon]\rangle.$$

Moreover, letting again $\varepsilon \to 0$ yields:

$$\frac{\partial n}{\partial t} + \text{div}_\mathbf{x}(j) = \delta_{q,1}\langle\mathcal{G}_2[f^0, f^0]\rangle + \delta_{q,1}\delta_{r_2,0}\langle\mathcal{I}_2[f^0, f^0]\rangle, \tag{4.20}$$

where $f^0 = (M_1(v)S, f_2^0)$. Here the main difference between Secs. 4.2 and 4.3 is defined. Now, instead of deriving the evolution of j by adding a solvability condition (4.4), it can be explicitly obtained as a function of S. To do that we multiply (4.2) by $\mathbf{v}$ and integrate over $\mathbf{v}$. This approach yields:

$$\langle\mathbf{v}\mathcal{L}_2[f_1^\varepsilon](f_2^\varepsilon)\rangle = \varepsilon\partial_t\langle\mathbf{v}f_2^\varepsilon\rangle + \varepsilon\,\text{Div}_\mathbf{x}\langle\mathbf{v}\otimes\mathbf{v}f_2^\varepsilon\rangle - \varepsilon^q\langle\mathbf{v}\mathcal{G}_2[f^\varepsilon, f^\varepsilon]\rangle$$

$$-\varepsilon^{q+r_2}\langle\mathbf{v}\mathcal{I}_2[f^\varepsilon, f^\varepsilon]\rangle.$$

Therefore, the term $\langle\mathbf{v}\mathcal{L}_2[f_1^\varepsilon](f_2^\varepsilon)\rangle$ is of order $\mathcal{O}(\varepsilon) + \mathcal{O}(\varepsilon^q)$ and then goes to zero. This fact combined with (4.19) produces

$$j = \lim_{\varepsilon\to 0}\langle\mathbf{v}f_2^\varepsilon\rangle = \lim_{\varepsilon\to 0}\left(\langle f_2^\varepsilon\rangle\alpha\left(\frac{1}{|V|}\left\langle\frac{f_1^\varepsilon}{M_1}\right\rangle\right)\right) = n\alpha(S). \tag{4.21}$$

Inserting this expression into (4.20) finally yields

$$\begin{cases} \partial_t S - \delta_{p,1}\,\text{div}_\mathbf{x}(D_S\cdot\nabla_\mathbf{x}S) = \delta_{q,1}\langle\mathcal{G}_1[f^0, f^0]\rangle + \delta_{q,1}\delta_{r_1,0}\langle\mathcal{I}_1[f^0, f^0]\rangle, \\ \partial_t n + \text{div}_\mathbf{x}(n\alpha(S)) = \delta_{q,1}\langle\mathcal{G}_2[f^0, f^0]\rangle + \delta_{q,1}\delta_{r_2,0}\langle\mathcal{I}_2[f^0, f^0]\rangle. \end{cases} \tag{4.22}$$

Therefore, the following theorem can be stated.

Theorem 4.2. *Let $f_i^\varepsilon(t, \mathbf{x}, \mathbf{v}, u)$ be a sequence of solutions to the scaled kinetic system (4.1)–(4.2) with $\mathcal{L}_1$ verifying Assumptions H.3.1–H.3.3 and $\mathcal{L}_2$ verifying*

Assumption H.4.3. *Assume that f_i^ε verifies the uniform bound* (3.9) *and converges a.e. in $[0, \infty) \times \Omega \times V \times D_u$ to some function f_i^0 as ε goes to 0. Moreover, it is assumed that the probability kernels $\mathcal{B}_{ij}$ are bounded functions and that the weight functions w_{ij} and p_{ij} have finite integrals. Then, the asymptotic limit verifies $f_1^0 = M_1 S$ and $\mathcal{L}_2[M_1 S](f_2^0) = 0$, where S and $n = \langle f_2^0 \rangle$ are the weak solutions of* (4.22).

4.5. *Pressureless hyperbolic examples*

4.5.1. *A direct drift coupling*

Let us show that a model whose limit preserves a drift term for the second population produced by the concentration gradient of the other population can be given. Specifically, an example which satisfies Assumption H.4.3 is given. Let $V \subset \mathbb{R}^d$ be a bounded domain. Consider the nonlinear turning operator given by

$$\mathcal{L}_2[f_1^\epsilon](f_2^\epsilon) = \int_V K\left(\mathbf{v}, \mathbf{v}^*, \left\langle \frac{f_1^\epsilon}{M_1} \right\rangle\right) f_2^\epsilon(\mathbf{v}^\star) \, d\mathbf{v}^* \tag{4.23}$$

with

$$K\left(\mathbf{v}, \mathbf{v}^*, \left\langle \frac{f_1^\epsilon}{M_1} \right\rangle\right) = \alpha\left(\frac{1}{|V|}\left\langle \frac{f_1^\epsilon}{M_1} \right\rangle\right) \mathbf{v} h(\mathbf{v}) - \mathbf{v}^* \mathbf{v} h(\mathbf{v}),$$

where h satisfies (4.17). Therefore $\mathcal{L}_2[f_1^\varepsilon](f_2^\varepsilon)$ is computed as follows:

$$\mathcal{L}_2[f_1^\varepsilon](f_2^\varepsilon) = \alpha\left(\frac{1}{|V|}\left\langle \frac{f_1^\epsilon}{M_1} \right\rangle\right) \mathbf{v} h(\mathbf{v}) n^\varepsilon - \mathbf{v} h(\mathbf{v}) j^\varepsilon,$$

where $j^\varepsilon := \langle \mathbf{v} f_2^\varepsilon \rangle$ is the current associated to the second population. Then, $\mathcal{L}_2[f_1^\varepsilon](f_2^\varepsilon)$ satisfies Assumption H.4.2 and

$$0 = \lim_{\varepsilon \to 0} \int_V \mathbf{v} \mathcal{L}_2[f_1^\varepsilon](f_2^\varepsilon) d\mathbf{v} = \beta\left(n\alpha(S) - \langle \mathbf{v} f_2^0 \rangle\right).$$

Here, again for an appropriate choice of $\alpha(S)$, the drift term $\text{div}_\mathbf{x}(n\alpha(S))$ appearing in the macroscopic system (4.22), can become the chemotactic sensitivity term of the Keller−Segel model (3.13). The next example introduces a kind of dependence on n^ε in the kernel K.

4.5.2. *Towards nonlinear diffusion: A flux-limited model for chemotaxis*

Let us briefly discuss how to modify the linear diffusion in order to incorporate optimal criteria for the population transport. To get an idea let us consider the very naive example of the heat equation for the evolution of a density of individuals in a population,

$$\partial_t n = \nu \Delta n. \tag{4.24}$$

We can rewrite (4.24) as follows:

$$\partial_t n = \text{div}_{\mathbf{x}}(n\nabla_{\mathbf{x}} \ln n) = \text{div}_{\mathbf{x}}(nv), \tag{4.25}$$

where $v = \nabla_{\mathbf{x}} \ln n$ is a microscopic velocity associated with individuals.

The heat equation, written as in (4.25), takes the form of a transport kinetic equation, in which the usual parabolic scale $(ht, h^2\mathbf{x})$ can be viewed as an implicit double (through the velocity) hyperbolic scale $(ht, h\mathbf{x})$. The velocity v is determined, again in a naive way, by both the Fisher entropy of the system, $F(n) = n\ln n$, and the density n,

$$\mathbf{v} = \nabla_{\mathbf{x}}\left(\frac{F(n)}{n}\right). \tag{4.26}$$

We consider modifying the form of the flux in (4.25), a new microscopic velocity, which is the above local velocity (4.26) averaged with respect to the line element associated with the motion of the particle. The velocity (4.26) (in the hyperbolic scale) is taken as the new unit to measure displacements, so that the new velocity is $\nabla_{\mathbf{v}}\sqrt{1 + |\mathbf{v}|^2}$. In this way the velocity can be considered as a measure of the relative entropy in terms of the particle concentration. We thus arrive at a flux limited equation,

$$\partial_t n = \nu \, \text{div}_{\mathbf{x}}\left(\frac{n\nabla_{\mathbf{x}} n}{\sqrt{n^2 + \frac{\nu^2}{c^2}|\nabla_{\mathbf{x}} n|^2}}\right), \tag{4.27}$$

where ν and c are parameters to be fixed; in particular, c represents the maximum macroscopic speed of propagation allowed.

The model was first deduced by Rosenau[55] from different points of view and then derived by Brenier[20] by means of a Monge−Kantorovich mass transport theory as a gradient flow of the Boltzmann entropy

$$\int_{\mathbb{R}^3} (\ln(n(\mathbf{x})) - 1)n(\mathbf{x})d\mathbf{x}$$

for the metrics corresponding to the cost function

$$k(z) = \begin{cases} c^2\left(1 - \sqrt{1 - \frac{|z|^2}{c^2}}\right), & \text{if } |z| \leq c, \\ +\infty, & \text{if } |z| > c. \end{cases}$$

In order to incorporate this kind of terms in the framework of our kinetic approach (2.1), and to obtain a macroscopic model for limited flux (1.1), we need to specify a nonlinear version of the operator $\mathcal{L}_2[f_1^\varepsilon](f_2^\varepsilon)$ given by (4.23), by introducing a dependence on $n^\epsilon = \langle f_2^\epsilon \rangle$. We proceed with an iterative argument which requires with assuming that the kinetic system admits a solution.

We develop this discussion at a formal level. Let $k \in \mathbb{N}$ and n_k^ε a given function. Then we define a sequence of operators

$$\mathcal{L}_{2,k+1}[f_1^\epsilon](f_2^\epsilon) = \int_V K\left(\mathbf{v}, \mathbf{v}^*, n_k^\epsilon, \left\langle \frac{f_1^\epsilon}{M_1} \right\rangle\right) f_2^\epsilon(\mathbf{v}^\star) d\mathbf{v}^*, \qquad (4.28)$$

where

$$K\left(\mathbf{v}, \mathbf{v}^*, n_k^\varepsilon, \left\langle \frac{f_1^\varepsilon}{M_1} \right\rangle\right) = \alpha\left(n_k^\varepsilon, \left\langle \frac{1}{|V|} \frac{f_1^\varepsilon}{M_1} \right\rangle\right) \mathbf{v}h(\mathbf{v}) - \mathbf{v}^* \mathbf{v}h(\mathbf{v})$$

and

$$\alpha\left(n_k^\varepsilon, \frac{1}{|V|} \left\langle \frac{f_1^\varepsilon}{M_1} \right\rangle\right) = \nu \frac{\nabla_\mathbf{x} n_k^\varepsilon}{\sqrt{(n_k^\varepsilon)^2 + \frac{\nu^2}{c^2}|\nabla_\mathbf{x} n_k^\varepsilon|^2}}$$

$$- \chi\left(\left\langle \frac{1}{|V|} \frac{f_1^\varepsilon}{M_1} \right\rangle\right) \frac{\nabla_\mathbf{x} \left\langle \frac{1}{|V|} \frac{f_1^\varepsilon}{M_1} \right\rangle}{\sqrt{1 + \left|\nabla_\mathbf{x} \left\langle \frac{1}{|V|} \frac{f_1^\varepsilon}{M_1} \right\rangle\right|^2}}.$$

The way by which the operator $\mathcal{L}_{2,k}$ is constructed implies that the hypothesis of Assumption H.4.2 holds. Denote by $f_{2,k+1}^\varepsilon$ the solution of the kinetic system $(4.1)-(4.2)$ associated to the above operator (4.28) and $n_{k+1}^\varepsilon = \langle f_{2,k+1}^\epsilon \rangle$. By an appropriate choice of the remainder of the operators involved in the linearized kinetic system $(4.1)-(4.2)$, the existence of solutions can be guaranteed for every k by taking the initial condition as $n_{k=0}^\varepsilon$ in order to initialize the sequence. The convergence of the sequence $\{f_{2,k}^\epsilon\}_k$ to a function f_2^ϵ, at least weakly in measure, can then be established. In this procedure for the sake of simplicity we have omitted the reference to the k-index for the other population f_1^ϵ.

Denote by $\mathcal{L}_2[f_1^\varepsilon](f_2^\varepsilon)$ the limit as $k \to \infty$ of the set $\{\mathcal{L}_{2,k}\}_k$ which satisfies Assumption H.4.3. Thus $\mathcal{L}_2[f_1^\varepsilon](f_2^\varepsilon)$ is finally defined by

$$K\left(\mathbf{v}, \mathbf{v}^*, n^\varepsilon, \left\langle \frac{f_1^\varepsilon}{M_1} \right\rangle\right) = \alpha\left(n^\varepsilon, \left\langle \frac{1}{|V|} \frac{f_1^\varepsilon}{M_1} \right\rangle\right) \mathbf{v}h(\mathbf{v}) - \mathbf{v}^* \mathbf{v}h(\mathbf{v}).$$

Moreover, reasoning analogously to previous Sec. 4.5.1, we conclude that the limiting *nonlinear* current, instead on (4.21), is given by

$$j = \langle \mathbf{v} f_2^0 \rangle = n\alpha(n, S),$$

with

$$\alpha(n, S) = \nu \frac{\nabla_\mathbf{x} n}{\sqrt{n^2 + \frac{\nu^2}{c^2}|\nabla_\mathbf{x} n|^2}} - \chi(S) \frac{\nabla_\mathbf{x} S}{\sqrt{1 + |\nabla_\mathbf{x} S|^2}}.$$

Then, we can formally deduce that the limiting system verified by the macroscopic limiting quantities is (4.22) with $\alpha(S)$ replaced by $\alpha(n, S)$, i.e.

$$
\begin{cases}
\partial_t S = \delta_{p,1} \nabla_{\mathbf{x}}(D_S \cdot \nabla_{\mathbf{x}} S) + H_1[n, S], \\[2mm]
\partial_t n = \operatorname{div}_{\mathbf{x}}\left(\nu \, \dfrac{n \nabla_{\mathbf{x}} n}{\sqrt{n^2 + \frac{\nu^2}{c^2}|\nabla_{\mathbf{x}} n|^2}} - n\chi \, \dfrac{\nabla_{\mathbf{x}} S}{\sqrt{1 + |\nabla_{\mathbf{x}} S|^2}} \right) + H_1[n, S],
\end{cases}
\tag{4.29}
$$

with

$$
\begin{aligned}
H_1[n, S] &= \delta_{q,1}\langle \mathcal{G}_1[f^0, f^0]\rangle + \delta_{q,1}\delta_{r_1,0}\langle \mathcal{I}_1[f^0, f^0]\rangle, \\
H_2[n, S] &= \delta_{q,1}\langle \mathcal{G}_2[f^0, f^0]\rangle + \delta_{q,1}\delta_{r_2,0}\langle \mathcal{I}_2[f^0, f^0]\rangle,
\end{aligned}
$$

where $f^0 = (M_1 S, f_2^0)$. Then, (4.29) corresponds to the limited flux Keller−Segel model with optimal transport of the population n with respect to the chemical signal S, (1.1). The qualitative analysis of model (4.29) will be given in Ref. 24.

Acknowledgments

References

1. A. R. A. Anderson and V. Quaranta, Integrative mathematical oncology, *Nature Rev. Cancer* **8** (2008) 227−234.
2. F. Andreu, J. Calvo, J. M. Mazón and J. Soler, On a nonlinear flux-limited equation arising in the transport of morphogens, to appear in *Arch. Rational Mech. Anal.*
3. F. Andreu, V. Caselles, J. M. Mazón, J. Soler and M. Verbeni, Radially symmetric solutions of a tempered diffusion equation. The porous media-flux-limited case, preprint (2009).
4. F. Andreu, V. Caselles and J. M. Mazón, A strongly degenerate quasilinear equation: The parabolic case, *Arch. Rational Mech. Anal.* **176** (2005) 415−453.
5. F. Andreu, V. Caselles and J. M. Mazón, A strongly degenerate quasilinear elliptic equation, *Nonlinear Anal. TMA* **61** (2005) 637−669.
6. F. Andreu, V. Caselles and J. M. Mazón, The Cauchy problem for a strongly degenerate quasilinear equation, *J. Euro. Math. Soc.* **7** (2005) 361−393.
7. F. Andreu, V. Caselles and J. M. Mazón, Some regularity results on the "relativistic" heat equation, *J. Diff. Eqns.* **245** (2008) 3639−3663.
8. F. Andreu, V. Caselles, J. M. Mazón and S. Moll, Finite propagation speed for limited flux diffusion equations, *Arch. Rational Mech. Anal.* **182** (2006) 269−297.
9. N. Bellomo and A. Bellouquid, On the onset of nonlinearity for diffusion models of binary mixtures of biological materials by asymptotic analysis, *Int. J. Nonlinear Mech.* **41** (2006) 281−293.
10. N. Bellomo and A. Bellouquid, On the derivation of macroscopic tissue equations from hybrid models of the kinetic theory of multicellular growing systems — The effect of global equilibrium, *Nonlinear Anal. Hybrid Syst.* **3** (2009) 215−224.

11. N. Bellomo, A. Bellouquid and M. A. Herrero, From microscopic to macroscopic description of multicellular systems and biological growing tissues, *Comp. Math. Appl.* **53** (2007) 647−663.

12. N. Bellomo, A. Bellouquid, J. Nieto and J. Soler, Multicellular growing systems: Hyperbolic limits towards macroscopic description, *Math. Models Methods Appl. Sci.* **17** (2007) 1675−1693.

13. N. Bellomo, C. Bianca and M. Delitala, Complexity analysis and mathematical tools towards the modelling of living systems, *Phys. Life Rev.* **6** (2009) 144−176.

14. N. Bellomo and M. Delitala, From the mathematical kinetic, and stochastic game theory to modelling mutations, onset, progression and immune competition of cancer cells, *Phys. Life Rev.* **5** (2008) 183−206.

15. N. Bellomo and G. Forni, Complex multicellular systems and immune competition: New paradigms looking for a mathematical theory, *Current Top. Develop. Biol.* **81** (2008) 485−502.

16. A. Bellouquid and M. Delitala, Kinetic (cellular) models of cell progression and competition with the immune system, *Z. Agnew. Math. Phys.* **55** (2004) 295−317.

17. A. Bellouquid and M. Delitala, Mathematical models and tools of kinetic theory towards modelling complex biological systems, *Math. Models Methods Appl. Sci.* **15** (2005) 1639−1666.

18. A. Bellouquid and M. Delitala, *Mathematical Modeling of Complex Biological Systems. A Kinetic Theory Approach* (Birkhäuser, 2006).

19. A. Blanchet, J. Dolbeault, M. Escobedo and J. Fernández, Asymptotic behavior for small mass in the two-dimensional parabolic−elliptic Keller−Segel model, preprint.

20. Y. Brenier, Extended Monge−Kantorovich Theory, in *Optimal Transportation and Applications*, Lectures given at the C.I.M.E. Summer School help in Martina Franca, eds. L. A. Caffarelli and S. Salsa, Lecture Notes in Math., Vol. 1813 (Springer-Verlag, 2003), pp. 91−122.

21. L. Bonilla and J. Soler, High field limit for the Vlasov−Poisson−Fokker−Planck system: A comparison of different perturbation methods, *Math. Models Methods Appl. Sci.* **11** (2001) 1457−1681.

22. N. Bournaveas, A. Bugin, V. Calvez, B. Perthame, J. Saragosti and P. Silberzan, Mathematical description of bacterial travelling pulses, preprint (2010).

23. A. Callejo, E. Mollica, A. Bilioni, N. Gorfinkiel, C. Torroja, L. Doglio, J. Sierra, J. Ibenez and I. Guerrero, A cytoneme-mediated baso-lateral transport, controlled by Dispatched, iHog and Dally-like, operates in Hedgehog gradient formation, preprint.

24. J. Calvo, J. M. Mazón and J. Soler, Analysis of a nonlinear flux-limited system in chemotaxis, work in preparation.

25. C. Cattaneo, Sulla conduzione del calore, *Atti. del Sem. Mat. Univ. Modena* **3** (1948) 83−101.

26. F. A. Chalub, P. Markovich, B. Perthame and C. Schmeiser, Kinetic models for chemotaxis and their drift−diffusion limits, *Monatsh. Math.* **142** (2004) 123−141.

27. F. A. Chalub, Y. Dolak-Struss, P. Markowich, D. Oeltz, C. Schmeiser and A. Soref, Model hierarchies for cell aggregation by chemotaxis, *Math. Models Methods Appl. Sci.* **16** (2006) 1173−1198.

28. P. H. Chavanis, Jeans type instability for a chemotactic model of cellular aggregation, *Euro. Phys. J. B* **52** (2006) 433−443.

29. P. H. Chavanis, Nonlinear mean field Fokker−Planck equations. Application to the chemotaxis of biological populations, arXiv:0709.1829v1.

30. P. H. Chavanis and C. Sire, Jeans type analysis of chemotactic collapse, arXiv:0708.3163v1.

31. E. Dessaud, L. L. Yang, K. Hill, B. Cox, F. Ulloa, A. Ribeiro, A. Mynett, B. G. Novitch and J. Briscoe, Interpretation of the sonic hedgehog morphogen gradient by a temporal adaptation mechanism, *Nature* **450** (2007) 717−720.

32. J. Dolbeault and C. Schmeiser, The two-dimensional Keller−Segel model after blowup, *Disc. Cont. Dyn. Syst.* **25** (2009) 109−121.

33. J. Folkman and K. Kerbel, Clinical translation of angiogenesis inhibitors, *Nature Rev. Cancer* **2** (2002) 727−739.

34. J. Folkman, Role of angiogenesis in tumor growth and metastasis, *Sem. Oncol.* **29** (2002) 15−18.

35. F. Filbet, P. Laurençot and B. Perthame, Derivation of hyperbolic models for chemo-sensitive movement, *J. Math. Biol.* **50** (2005) 189−207.

36. T. Goudon, J. Nieto, J. Soler and F. Poupaud, Multidimensional high-field limit of the electrostatic Vlasov−Poisson−Fokker−Planck system, *J. Diff. Eqns.* **213** (2005) 418−442.

37. T. Goudon, J. Nieto, O. Sánchez and J. Soler, Vanishing viscosity regimes and non-standard shock relations for semiconductor superlattices models, preprint.

38. T. Goudon, O. Sánchez, J. Soler and L. L. Bonilla, Low-field limit for a nonlinear discrete drift−diffusion model arising in semiconductor superlattices theory, *SIAM J. Appl. Math.* **64** (2004) 1526−1549.

39. K. P. Hadeler, Reaction transport systems, in *Mathematics Inspired by Biology*, eds. V. Capasso and O. Diekmann, CIME Lectures 1997, Florence (Springer, 1998), p. 95.

40. T. Hillen, Qualitative analysis of semilinear Cattaneo systems, *Math. Models Methods Appl. Sci.* **8** (1998) 507−519.

41. H. L. Hartwell, J. J. Hopfield, S. Leibner and A. W. Murray, From molecular to modular cell biology, *Nature* **402** (1999) c47−c52.

42. M. A. Herrero, A. Köhn and J. M. Pérez-Pomares, Modelling vascular morphogenesis: Current view on blood vessels development, *Math. Models Methods Appl. Sci.* **19** (2009) 1483−1538.

43. T. Hillen and H. Othmer, The diffusion limit of transport equations derived from velo-city−jump processes, *SIAM J. Appl. Math.* **61** (2000) 751−775.

44. E. F. Keller and L. A. Segel, Initiation of slide mold aggregation viewed as an instability, *J. Theor. Biol.* **26** (1970) 399−415.

45. E. F. Keller and L. A. Segel, Model for chemotaxis, *J. Theor. Biol.* **30** (1971) 225−234.

46. E. F. Keller and L. A. Segel, Traveling bands of chemotactic bacteria: A theoretical analysis, *J. Theor. Biol.* **30** (1971) 235−248.

47. E. F. Keller, Assessing the Keller−Segel model: How has it fared?, in *Biological Growth and Spread*, Proc. Conf., Heidelberg, 1979 (Springer, 1980), pp. 379−387.

48. M. Lachowicz, Micro and meso scales of description corresponding to a model of tissue invasion by solid tumors, *Math. Models Methods Appl. Sci.* **15** (2005) 1667−1683.

49. H. G. Othmer, S. R. Dunbar and W. Alt, Models of dispersal in biological systems, *J. Math. Biol.* **26** (1988) 263−298.

50. H. G. Othmer and T. Hillen, The diffusion limit of transport equations II: Chemotaxis equations, *SIAM J. Appl. Math.* **62** (2002) 1222−1250.

51. C. S. Patlak, Random walk with persistant and external bias, *Bull. Math. Biophys.* **15** (1953) 311−338.

52. B. Perthame, Mathematical tools for kinetic equations, *Bull. Amer. Math. Soc.* **41** (2004) 205−244.

53. F. Poupaud and J. Soler, Parabolic limit and stability of the Vlasov−Poisson−Fokker−Planck system, *Math. Models Methods Appl. Sci.* **10** (2000) 1027−1045.

54. P. Rosenau, Free energy functionals at the high gradient limit, *Phys. Rev. A* **41** (1990) 2227−2230.

55. P. Rosenau, Tempered diffusion: A transport process with propagating front and inertial delay, *Phys. Rev. A* **46** (1992) 7371−7374.

56. M. B. Rubin, Hyperbolic heat conduction and the second law, *Int. J. Engrg. Sci.* **30** (1992) 1665−1676.

57. R. A. Weinberg, *The Biology of Cancer* (Taylor and Francis, 2007).

58. J. L. Vázquez, *The Porous Medium Equation. Mathematical Theory* (Oxford Univ. Press, 2006).