DISCRETE AND CONTINUOUS
DYNAMICAL SYSTEMS SERIES B
Volume **18**, Number **4**, June **2013**

doi:10.3934/dcdsb.2013.18.847

pp. **847–863**

MODELING CHEMOTAXIS FROM L^2–CLOSURE MOMENTS IN KINETIC THEORY OF ACTIVE PARTICLES

Nicola Bellomo*, Abdelghani Bellouquid†
Juanjo Nieto‡ and Juan Soler‡

*Department of Mathematica Sciences, Politecnico di Torino, Italy
†University Cadi Ayyad, Ecole Nationale des Sciences Appliquées, Safi, Maroc
‡Departamento de Matemática Aplicada, Universidad de Granada, Spain

Abstract. This paper deals with the derivation of macroscopic tissue models from the underlying description delivered by a class of equations modeling binary mixtures of multi-cellular systems by methods of the kinetic theory for active particles. Cellular interactions generate both modification of biological functions and proliferative-destructive events. The analysis refers to a suitable hyperbolic approximation to show how the macroscopic tissue behavior can be described from the underlying cellular description. The approach is specifically focused on the modeling of chemotaxis phenomena by the Keller–Segel approximation.

1. **Introduction.** The derivation of biological tissue models at the macroscopic scale has bee arguably introduced by the pioneering paper by Othmer, Dunbar and Alt [46]. Subsequently, several papers have contributed to further development of this research line which consists in deriving microscopic models for multi-cellular systems derived by methods of the generalized kinetic theory. Among others [2, 7, 14, 15, 19, 22, 25, 30, 38, 39, 47], and several others as reported in the survey [4].

The derivation is based on suitable development of asymptotic methods, somehow analogous to those of the classical kinetic theory, which amount to expanding the distribution function in terms of a small dimensionless parameter related to the intermolecular distances (the space-scale dimensionless parameter); this approach is equivalent to the connections between the biological constants. The limit is singular and the convergence properties can be proved under suitable technical assumptions.

This present paper develops a different approach based on the closure of moment equations. This closure problem is well known in transport theory. Most authors use ad hoc arguments or projection methods to close the moment system, see among others [49, 51]. This approach was applied to Boltzmann equations by the theory of Extended Thermodynamics, e.g. Muller and Ruggeri [44]. The physical entropy is maximized under the constraint of fixed first m-moments. One assumes that the $(m+1)$-moments of the minimizer approximates the $(m+1)$-st moments of the true solution, that gives the desired closure. It appears that theories for a large number of moments can approximate steep gradients and shocks [44]. The most important

2010 *Mathematics Subject Classification.* 35Q92, 92C17, 35K57.

Key words and phrases. Living systems, cancer cells, chemotaxis, kinetic theory, multi-cellular systems, closure method, Keller–Segel.

The first author is partially supported by MIUR, Italian Minister for University and Research. The second author is supported by Hassan II Academy of Sciences and Technology (Morocco).

first-moment approximations to the Boltzmann equation are the Euler equations [6] and the Navier-Stokes equations.

Further developments are due to Ringhofer et al. [51] for moment systems for the semiconductor Boltzmann models by using orthogonal projections of expansions in terms of Hermite polynomials. The closed system forms a Galerkin approximation to the transport equation. A numerical method is developed and by appropriate scaling of space and time, error estimates are proved. The expansion by Hermite polynomials together with an orthogonal projection is equivalent to Levermore's procedure of moment closure [41] as well as to entropy maximization used in Extended Thermodynamics.

A method to close the moment equations, which is based on a minimization principle by Hillen [28], is proposed in this paper for a binary mixture of cell populations to obtain a mixed hyperbolic–hyperbolic macroscopic model. Two different approaches are presented based on the assumptions that populations are involved in some (linear or nonlinear) hyperbolic processes.

The second approach consists in using the first one to derive diffusion processes for both population, in particular the classical Keller–Segel [32, 33, 34, 35] model, the parabolic–eliptic Keller–Segel model, the drift optimal Keller–Segel model [3], and a chemotaxis model with saturated chemotaxis flux (see the survey [29] for more general frameworks). More precisely, following [28] we present an L^2–moment closure procedure for mixture of two populations. Specifically, we focus on the simplest nontrivial case, namely the second–moment closure for both population.

The contents of this paper is of interest in the modeling of biological tissues, cancer angiogenesis phenomena [1, 23], pattern formation in populations of slime molds, swarming, and chemotaxis in different contexts [16, 19, 21, 26, 36, 37, 42, 43, 50, 53]. The guiding principle consists in starting with microscopic models from kinetic theory of active particles and then in deriving macroscopic hyperbolic models by a minimization principles. Subsequently, different variants of the Keller–Segel model are deduced by different scale regimes.

The underlying description at the cell scale is delivered by the so called kinetic theory active particles, which applies to large systems of interacting entities, called *active particles*, whose microscopic state 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. Interactions not only modify the microscopic state, but may also generate proliferative and/or destructive phenomena. The theory and specific models are reported in the book [11], and in various papers related to applications, among several ones [9, 10, 5, 12]. 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,?.

This paper is organized as follows. Section 2 presents a description of the equations of the kinetic theory that describe multi-cellular systems and a derivation of hyperbolic equations by using a closure moment in the case of absence of biological interaction. Section 3 generalizes the description to active particles including interactions modifying the biological functions expressed by cells and proliferative or destructive events. Section 4 deals with the derivation of different variants of the Keller–Segel model (classical Keller–Segel model, parabolic–elliptic model, the drift optimal Keller–Segel model, and a chemotaxis model with saturated chemotaxis flux) thought different macroscopic scalings. Finally, Section 5 proposes some research perspectives with special attention to growth and invasion phenomena.

2. **Linear transport models with stochastic velocity jump perturbation.** This section presents the derivation, by moment closure, of linear transport models of multi-cellular systems of a binary mixture of cells whose state, called *microscopic state*, is denoted by the variable $\{x\,,v\,,u\}$, where $\{x,v\}$ are, respectively, position and velocity of the cell, while $u \in D_u \subseteq \mathbb{R}$ is the ***biological function*** expressed by each population regarded as a module [24]. The collective description is encoded in the statistical distribution functions $f_i = f_i(t,x,v,u)$, for $i = 1,2$, which is called ***generalized distribution function***. Weighted moments provide, under suitable integrability properties, the calculation of macroscopic variables. More precisely, let us consider the following class of equations:

$$\begin{cases} \big(\partial_t + v\cdot\nabla_x\big) f_1 = \nu_1\,\mathcal{L}_1(f_1), \\ \\ \big(\tau\partial_t + v\cdot\nabla_x\big) f_2 = \nu_2\mathcal{L}_2(f_2), \end{cases} \tag{1}$$

where $f = \{f_1, f_2\}$, while the operator $\mathcal{L}_i(f_i)$ models the dynamics of biological organisms by a velocity-jump process, and is defined as follows:

$$\mathcal{L}_i(f) = \int_V \Big[T_i(v^*,v) f(t,x,v^*,u) - T_i(v,v^*) f(t,x,v,u)\Big]\, dv^*\,, \tag{2}$$

for $i = 1,2$, where $T_i(v,v^*)$ is the probability kernel for the new velocity $v \in V$ assuming that the previous velocity was v^*. The operators T_i may depend on f_1 and f_2; in fact, we will assume that T_1 depends on the population f_2.

The set of possible velocities is denoted by V, where $V \subset \mathbb{R}^3$, and it is assumed that V is bounded and radial symmetric. In particular, we consider velocity jump process with fixed speed s, but any direction, i.e. $V = s\,\mathbb{S}^{d-1}$. This corresponds to the assumption that any individual of the population chooses any direction with bounded velocity. Finally, ν_1 and ν_2 represent the interaction rates of the mechanical interactions.

The dimensionless constant $\tau \in (0,1)$ indicates that the spatial spread of the first population f_1 and the second f_2 are on different time scales. The case of $\tau = 0$ corresponds to a steady state assumption for the second distribution.

The derivation of macroscopic equations for linear transport models subject to the aforesaid stochastic perturbation has been studied by Othmer and Hillen [30, 47] for cells, where the microscopic state is simply defined by position and velocity. Here the activity variable is introduced and is heterogeneously distributed, however the model is such that interactions do not modify such distribution.

Bearing all above in mind, it can be shown how the moment closure method can be used to derive macroscopic equations. By multiplying (1) with powers of v and integrating them, an infinite sequence of equations for the v–moments of f_1, f_2 will be obtained, where the $(m+1)$-st moments appears in the equation for the m-st moments. Therefore, an approximation of the the $(m+1)$-st moment is needed to close the equation for the m-moment. Calculations can be done under the following assumption concerning the turning operators $\mathcal{L}_i$ for $i = 1,2$.

Assumption H.1. *The turning operators $\mathcal{L}_1$ and $\mathcal{L}_2$ are assumed to satisfy the following equalities:*

$$\int_V T_i(v,v^\star)\, dv^\star = 1, \qquad i = 1,2, \tag{3}$$

and

$$\int_V v\,\mathcal{L}_i(g(v))\, dv = -\int_V v\, g(v)\, dv, \quad i = 1,2. \tag{4}$$

Assumption H.2. *The set $D_u \subset \mathbb{R}$ of possible biological functions is bounded.*

Remark 1. Assumption H.1 implies the following equality

$$\int_V \mathcal{L}_i(g(v))\,dv = 0, \qquad i = 1, 2, \tag{5}$$

which ensures conservation of the number of cells.

A general model for probability kernels with relaxation in time can be considered as follows:

$$T_i(v, v^*) = \frac{1}{|V|} \quad i = 1, 2.$$

Therefore:

$$\mathcal{L}_i(g) = \frac{1}{|V|}\int_V g(v)\,dv - g(v), \qquad i = 1, 2,$$

which satisfies Assumptions H.1. and H.2.

Let $f = \{f_1, f_2\}$ be a solution to the model (1) and let us define the first two moments:

$$n(t,x) = \int_{D_u}\int_V f_1\,dv\,du, \quad n(t,x)\,U(t,x) = \int_{D_u}\int_V v\,f_1\,dv\,du, \tag{6}$$

corresponding to the first equation and

$$S(t,x) = \int_{D_u}\int_V f_2\,dv\,du, \quad S(t,x)\,U_S(t,x) = \int_{D_u}\int_V v\,f_2\,dv\,du, \tag{7}$$

for the second one. To derive the equations for the moments in (6) we multiply the first equation of (1) by 1 and v and integrate over V and D_u to obtain the following conservation laws:

$$\begin{cases} \partial_t n + \mathrm{div}_x\,(n\,U) = 0, \\ \\ \partial_t(n\,U) + \mathrm{Div}_x(P(f_1)) = -\nu_1\,n\,U, \end{cases} \tag{8}$$

where Div_x stands for the divergence operator at each row, and $P(f_1)$ stands for the pressure tensor:

$$P(f_1) = (P)_{ij}(f_1) = \int_{D_u}\int_V v_i v_j f_1(t,x,v,u)\,dv\,du.$$

This system of two–moment equations (8) can be closed by looking for an appropriate expression of $P(f_1)$. The approach consists in deriving a function $a(t,x,v,u)$, which minimizes the $L^2(V \times D_u)$ norm under the constraint that it has the same first two moments, n and $n\,U$, as f_1. Once this function a has been found, we replace $P(f_1)$ by $P(a)$.

Let us introduce Lagrangian multipliers β_1 and $\vec{\beta}_2 = (\beta_2^1, ...\beta_2^n)$, respectively scalar and vector, and define the following operator:

$$\begin{aligned} H(a) \;&=\; \frac{1}{2}\int_{D_u}\int_V a^2(t,x,v,u)\,dv\,du - \beta_1\left(\int_{D_u}\int_V a(t,x,v,u)\,dv\,du - n(t,x)\right) \\ &-\; \vec{\beta}_2\cdot\left(\int_{D_u}\int_V v\,a(t,x,v,u)\,dv\,du - n(t,x)U(t,x)\right). \end{aligned}$$

The Euler–Lagrange equation (first variation) of $H(a)$ reads $a = \beta_1 + \vec{\beta}_2 \cdot v$. We use the constraints to determine β_1 and $\vec{\beta}_2$. From (6) one gets easily

$$\beta_1 = \frac{n}{|V||D_u|}. \tag{9}$$

Noting that

$$\int_V v_i v_j \, dv = \frac{s^{d+1}|\mathbb{S}^{d-1}|}{d} = \frac{|V|s^2}{d}\delta_{ij}, \tag{10}$$

yields

$$n(t,x)U(t,x) = \int_{D_u}\int_V v\, a(t,x,v,u)\, dv\, du = \vec{\beta}_2 |V||D_u|\frac{s^2}{d}, \tag{11}$$

which implies

$$\vec{\beta}_2 = \frac{d}{|D_u||V|\, s^2} n(t,x)U(t,x),$$

and therefore

$$a(t,x,v,u) = \frac{1}{|D_u|\,|V|}\left(n(t,x) + \frac{d}{s^2}\, n(t,x)\, U(t,x)\cdot v\right). \tag{12}$$

Then, the derivation of the moment closure can be pursued by considering the second moment of the minimizer a:

$$P(a) = \int_{D_u}\int_V v \otimes v\, a(t,x,v,u)\, dv\, du = \frac{s^2}{d}\, n(t,x) I.$$

Finally the two-moment equations (8) for the minimizer becomes

$$\begin{cases} \partial_t n + \operatorname{div}_x (n\, U) = 0, \\ \\ \partial_t (n\, U) + \dfrac{s^2}{d}\nabla_x n = -\nu_1\, n\, U. \end{cases} \tag{13}$$

In the same way, to close the first two moments of the second population, one derives a function $b(t,x,v,u)$, which minimizes the $L^2(V \times D_u)$ norm under the constraint that $b(t,x,v,u)$ has the same first two moments, S and $S\, U_S$, as f_2. One has analogously

$$b(t,x,v,u) = \frac{1}{|D_u|\,|V|}\left(S(t,x) + \frac{d}{s^2}\, S(t,x)\, U_S(t,x)\cdot v\right), \tag{14}$$

and finally obtains the following macroscopic model:

$$\begin{cases} \partial_t n + \operatorname{div}_x (n\, U) = 0, \\ \\ \partial_t (n\, U) + \frac{s^2}{d}\nabla_x n = -\nu_1 n\, U, \\ \\ \tau\partial_t S + \operatorname{div}_x (S\, U_S) = 0, \\ \\ \tau\partial_t (S\, U_S) + \frac{s^2}{d}\nabla_x S = -\nu_2 S\, U_S. \end{cases} \tag{15}$$

Remark 2. The second variation of H is $\delta^2 H(a) = 1 > 0$, then the extremum $a(t,x,v,u)$ is a minimum and the same holds true for $b(t,x,v,u)$.

The error which appears during this approximation can be controlled for long times as in [28]. Moreover following [28] one proves that the $L_2(V \times D_u)$-norm satisfies an H-Theorem, i.e., it is an entropy for equation (1):

$$\partial_t \int_{V\times D_u} (f_1^2(t,x,v,u) + f_2^2(t,x,v,u))dvdu + \mathrm{div}_x \int_{V\times D_u} v(f_1^2 + f_2^2)dvdu \leq 0.$$

Remark 3. The minimizer $(a(t,x,v,u), b(t,x,v,u))$ given by (12)-(14) is the first nontrivial approximation to $(f_1(t,x,v,u), f_2(t,x,v,u))$ in the following sense: if we only fix the first moments n and S for the two populations f_1 and f_2, then minimizing the $L^2(V \times D_u)$ norm will lead to

$$a(t,x,v,u) = \frac{1}{|V||D_u|} n(t,x), \quad b(t,x,v,u) = \frac{1}{|V||D_u|} S(t,x).$$

Then a and b are respectively the projection of f_1 and f_2 onto the space of functions constant in v, u, and the corresponding moment closure is simply $\partial_t n = \partial_t S = 0$.

3. **Binary mixture with progression and proliferative and destructive interactions.** Let us consider, referring to [4], a binary mixture of cells where the output of interactions includes progression of the activity variable and proliferative or destructive events. Each population is regarded as a module [24], namely a functional subsystem characterized by a different activity variable. More precisely, we consider the following class of equations modeling the dynamics of $f = \{f_1, f_2\}$:

$$\begin{cases} \big(\partial_t + v\cdot\nabla_x\big) f_1 = \nu_1\, \mathcal{L}_1(f_1) + \mathcal{G}_1[f,f] + \mathcal{I}_1[f,f], \\ \big(\tau\partial_t + v\cdot\nabla_x\big) f_2 = \nu_2 \mathcal{L}_2(f_2) + \mathcal{G}_2[f,f] + \mathcal{I}_2[f,f]\,, \end{cases} \tag{16}$$

where the operator $\mathcal{L}_i(f_i)$ has been already described in Section 2. Moreover

• The operators $\mathcal{G}_i$, describe the gain–loss balance of active particles (cells, chemoattractant, molecules, etc.) in state u, in each population, due to conservative encounters, namely those which modify only the biological state:

$$\begin{aligned} \mathcal{G}_i[f,f](t,x,v,u) &= \sum_{j=1}^{2} \mathcal{G}_{ij}[f,f](t,x,v,u) \\ &= \sum_{j=1}^{2} \int_{D_u\times\Lambda} \eta_{ij} w_{ij}(x,x^*) \mathcal{B}_{ij}(u_* \to u | u_*, u^*) \\ &\times \quad f_i(t,x,v,u_*)\, f_j(t,x^*,v,u^*)\, dx^*\, du_* du^* \\ &- \quad f_i(t,x,v,u) \int_{\Lambda} \eta_{ij} w_{ij}(x,x^*)\, f_j(t,x^*,v,u^*)\, dx^* du^*\,, \end{aligned} \tag{17}$$

where Ω is the interaction domain and $\Lambda = D_u \times \Omega$. The kernel $\mathcal{B}_{ij}$ models the transition probability density of an individual with state u_* into the state u, after interaction with some individual with state u^*, $w_{ij}(x,x^*)$ is a normalized (with respect to space integration over Ω) weight function that accounts the distance and distribution that weaken the intensity of the interaction.

• The terms η_{ij} denote the biological interaction rates related to interactions that modify the biological state of the interacting individuals for each population.

• The operators $\mathcal{I}_i$, which describe proliferative/destructive interactions, are defined as follows:

$$\begin{aligned}\mathcal{I}_i[f,f](t,x,v,u) &= \sum_{j=1}^{2}\mathcal{I}_{ij}[f,f](t,x,v,u)\\ &= f_i(t,x,v,u)\sum_{j=1}^{2}\int_\Lambda w_{ij}(x,x^*)\,\eta_{ij}p_{ij}(u,u^*)\\ &\times\ f_j(t,x,v,u^*)\,dx^*\,du^*\,,\end{aligned}\tag{18}$$

where p_{ij} is the proliferative/destructive rate of particles into state u of subsystem i, after inetraction with particles with state u^* of subsystem j.

Different closures will be treated in the following subsections thus obtaining different macroscopic models.

3.1. **Closure for nonlinear binary mixture.** Let us now consider, referring to Eq. (16), the equations for the first moments n, nU, S and SU_S which, instead of (8) and the corresponding for the second population, now becomes

$$\begin{cases}\partial_t n + \mathrm{div}_x\,(n\,U) = \psi(f,f) = \displaystyle\int_{D_u}\int_V \mathcal{I}_1[f,f]\,dv\,du,\\ \partial_t(n\,U) + \mathrm{Div}_x\,(P(f_1)) = \phi(f,f) = -\nu_1 nU + \displaystyle\int_{D_u}\int_V v\mathcal{I}_1[f,f]\,dv\,du,\\ \tau\partial_t S + \mathrm{div}_x\,(S\,U_S) = \Gamma(f,f) = \displaystyle\int_{D_u}\int_V \mathcal{I}_2[f,f]\,dv\,du,\\ \tau\partial_t(S\,U_S) + \mathrm{Div}_x\,(P(f_2)) = \delta(f,f) = -\nu_2 SU_S + \displaystyle\int_{D_u}\int_V v\mathcal{I}_2[f,f]dvdu.\end{cases}\tag{19}$$

The minimization of the $L^2(V\times D_u)$–norm with the same constraints as in the previous sections can be used to find an appropriate expression not only for the pressure tensors $P(f_i)$, but also for ψ, ϕ, Γ, and δ. Let us write the result in the following Lemma.

Lemma 3.1. *Let $f=\binom{a}{b}$ be given by (12)–(14), then the following equalities*

$$\begin{aligned}\psi(f,f)=\tilde\psi(n,nU,S,SU_S) &= \alpha_{11}\Big(H_{11}(n,n)+\frac{d}{s^2}H_{11}(nU,nU)\Big)\\ &\quad+\alpha_{12}\Big(H_{12}(n,S)+\frac{d}{s^2}H_{12}(nU,SU_S)\Big),\end{aligned}\tag{20}$$

$$\begin{aligned}\phi(f,f)=\tilde\phi(n,nU,S,SU_S) &= \alpha_{11}\Big(H_{11}(n,nU)+H_{11}(nU,n)\Big)\\ &\quad+\alpha_{12}\Big(H_{12}(nU,S)+H_{12}(n,SU_S)\Big),\end{aligned}\tag{21}$$

$$\Gamma(f,f) = \tilde{\Gamma}(n, nU, S, SU_S) = \alpha_{21}\left(H_{21}(S,n) + \frac{d}{s^2}H_{21}(SU_S, nU)\right) + \alpha_{22}\left(H_{22}(S,S) + \frac{d}{s^2}H_{22}(SU_S, SU_S)\right), \quad (22)$$

$$\delta(f,f) = \tilde{\delta}(n, S, nU, SU_S) = \alpha_{21}\left(H_{21}(S,nU) + H_{21}(SU_S, n)\right) \alpha_{22}\left(H_{22}(S,SU_S) + H_{22}(SU_S, S)\right), \quad (23)$$

hold true, where for any scalar or vector h, k, the operators H_{ij} are given by

$$H_{ij}(h,k) = \frac{h(t,x)}{|D_u|^2|V|} \cdot \int_\Omega w_{ij}(x,x^*)\, k(t,x^*)\, dx^*, \quad (24)$$

and the coefficients α_{ij} are simply defined as follows:

$$\alpha_{ij} = \int_{D_u \times D_u} p_{ij}(u,u^*)\, du\, du^*. \quad (25)$$

Proof. It is an straightforward computation by using (18) and (10). □

The application of Lemma 3.1, yields the following nonlinear coupled hyperbolic model:

$$\begin{cases} \partial_t n + \mathrm{div}_x\,(n\,U) = \tilde{\psi}(n, nU, S, SU_S), \\ \partial_t(n\,U) + \dfrac{s^2}{d}\nabla_x n = -\nu_1 nU + \tilde{\phi}(n, nU, S, SU_S), \\ \tau\partial_t S + \mathrm{div}_x\,(S\,U_S) = \tilde{\Gamma}(n, nU, S, SU_S), \\ \tau\partial_t(S\,U_S) + \dfrac{s^2}{d}\nabla_x S = -\nu_2 SU_S + \tilde{\delta}(n, nU, S, SU_S), \end{cases} \quad (26)$$

where $\tilde{\psi}(n, nU, S, SU_S)$, $\tilde{\phi}(n, nU, S, SU_S)$, $\tilde{\Gamma}(n, nU, S, SU_S)$, and $\tilde{\delta}(n, nU, S, SU_S)$ are given in (20), (21), (22), and (23).

3.2. **The binary mixture chemosensitive movement.** Chemotaxis bacteria can significantly change their movement in response to external stimuli. Hence, we modify the turning operator to derive a model for chemosensitive movement. More precisely, it is assumed that turning operator depends on the velocity v, on the concentration of the external signal S, and on its gradient $\nabla_x S$.

Let us consider the model defined by choosing T_1 as follows:

$$T_1[f_2](v,v^*) = \frac{1}{|V|}\left(1 - \frac{d}{s^2} v \cdot \alpha\left(\langle f_2\rangle\right)\right), \quad (27)$$

where α is a vector function, and $\langle\cdot\rangle$ stands for the (v,u)–mean of a function, i.e.,

$$\langle g\rangle = \int_{D_u}\int_V g(t,x,v,u)\, dv\, du, \qquad g \in L^2(V \times D_u).$$

It is easy to see that the kernel T_1 satisfies (3) and the operator $\mathcal{L}_1(f_1)$, can be computed as follows

$$\mathcal{L}_1[f_2](f_1) = \left(\frac{1}{|V|}\int_V f_1(v)\, dv - f_1\right) - \frac{d}{s^2}\left(\frac{1}{|V|}\int_V v f_1(v)\, dv - v\, f_1\right) \cdot \alpha\left(\langle f_2\rangle\right),$$

but now, assumption (4) becomes

$$\int_V v\mathcal{L}_1[f_2](f_1)\,dv = -\int_V vf_1\,dv + \frac{d}{s^2}\int_V v\otimes vf_1\,dv\cdot\alpha(\langle f_2\rangle). \tag{28}$$

In particular by integrating (28) over u, and using (10), one computes (28) for the minimizer $f = \binom{a}{b}$ given by (12)-(14), to get:

$$\int_{D_u}\int_V v\mathcal{L}_1[b](a)\,dv\,du = -n\,U + n\,\alpha(S).$$

Therefore, for $\alpha(S) = \alpha_1(S)\nabla_x S$, one again derives the corresponding hyperbolic system for chemosensitive, coupled with the concentration equation for S:

$$\begin{cases} \partial_t n + \operatorname{div}_x(n\,U) = \tilde{\psi}(n, nU, S, SU_S), \\ \partial_t(n\,U) + \dfrac{s^2}{d}\nabla_x n = -\nu_1\big(n\,U - n\alpha_1(S)\nabla_x S\big) + \tilde{\phi}(n, nU, S, SU_S), \\ \tau\partial_t S + \operatorname{div}_x(S\,U_S) = \tilde{\Gamma}(n, nU, S, SU_S), \\ \tau\partial_t(S\,U_S) + \dfrac{s^2}{d}\nabla_x S = -\nu_2 SU_S + \tilde{\delta}(n, nU, S, SU_S). \end{cases} \tag{29}$$

Remark 4. The first two equations of this model were already obtained in [3] by asymptotic analysis. In absence of biological activity and interaction, Filbert, Perthame [22] and Hillen [28] derived, respectively, the first two equations for $(n, n\,U)$ by asymptotic analysis and moment closure.

3.3. **A chemotaxis model with density control.** A chemotaxis model with density control mechanism is introduced and investigated in [48]. The density control leads to the effect that at high population densities, the chemotaxis is turned off and pure diffusion dominates. Solutions exist globally and no blow-up occurs. The model in [48] can be constructed from a binary mixture model (16) via a corresponding hyperbolic approximation. We consider

$$T_1[f_2] = \frac{1}{|V|}\left(1 - \frac{d}{s^2}\gamma(\langle f_1\rangle)v\cdot\alpha\left(\langle f_2\rangle\right)\right), \tag{30}$$

where $\gamma(n)$ is a density dependent sensitivity. It is assumed to have a zero at some $n^* > 0$ and $\gamma(n) > 0$ for $n \in (0, n^*)$. A standard example for γ is $\gamma(n) = 1 - n$. Therefore, the operator $\mathcal{L}_1(f_1)$, can be computed as follows:

$$\mathcal{L}_1[f_2](f_1) = \frac{1}{|V|}\int_V f_1(v)\,dv - f_1(v) - \frac{d}{s^2}\left(\frac{1}{|V|}\int_V vf_1(v)\,dv - v\,f_1\right)\cdot\gamma(\langle f_1\rangle)\alpha\left(\langle f_2\rangle\right).$$

It is easy to check that $\mathcal{L}_1[f_2](f_1)$ satisfies (3), instead of (4), and that one has the following:

$$\int_{D_u}\int_V v\mathcal{L}_1[b](a)\,dv\,du = -n\,U + n\,\alpha(S)\gamma(n).$$

Therefore, for $\alpha(S) = \alpha_1(S)\nabla_x S$, the corresponding hyperbolic system for chemosensitive movement with density control, coupled with the concentration equation

for S is derived:

$$\begin{cases} \partial_t n + \operatorname{div}_x (n\,U) = \tilde{\psi}(n, nU, S, SU_S), \\ \partial_t (n\,U) + \dfrac{s^2}{d}\nabla_x n = -\nu_1 n\,U + \nu_1\alpha_1 n\gamma(n)\nabla_x S + \tilde{\phi}(n, nU, S), \\ \tau\partial_t S + \operatorname{div}_x (S\,U_S) = \tilde{\Gamma}(n, nUS, SU_S), \\ \tau\partial_t (S\,U_S) + \dfrac{s^2}{d}\nabla_x S = -\nu_2 SU_S + \tilde{\delta}(n, nU, S, SU_S). \end{cases} \tag{31}$$

4. **On the derivation of Keller–Segel models.** The time and space dynamics of a cell population under chemoattractant action can be described by phenomenological PDE models at a macroscopic level, as a coupled system of equations for the chemosensitive cell density $n = n(t, x)$ and the chemoattractant concentration $S = S(t, x)$, for $x \in \Omega \subset R^d$. The model by Patlak [49], and Keller-Segel model [32, 34] is the most important approach, which stated by a parabolic or elliptic equations coupled through a drift term. This model is successful to describe the aggregation of the population at a single point (chemotactic collapse in the terminology of [27]). Solutions show a blow up, however not fully realistic, that has attracted applied mathematicians as documented in the survey [31]. The parabolic Keller–Segel model (PKS) model is as follows:

$$\begin{cases} \partial_t n = \operatorname{div}_x(D_n\nabla_x n - n\chi(S)\nabla_x S) + f(n, S), \\ \tau\partial_t S - D_S\Delta S = g(n, S), \end{cases} \tag{32}$$

where $D_S > 0$ and the positive definite tensor D_n model the diffusivity of the chemoattractant and the cells, respectively, and $\chi(S)$ is the chemotactic sensitivity. The functions $f(n, S)$, and $g(n, S)$ model the source terms.

The PKS model has been used in many applications to study aggregation or pattern formation (see e.g. Murray [45]). However, the literature also reports about various criticisms. For instance, the movement of the population is modeled by diffusion. On the other hand, for bacteria, it is known that they move along straight lines, suddenly stop to choose a new direction, and then continue moving in the new direction. This appears to be a velocity jump process analogous to that described earlier, rather than a Brownian motion. Moreover, the diffusion terms in (32) allow a propagation of information with infinite speed and blow up of solutions, which constitute an undesired property. In fact, specific studies look for finite propagation speeds [13]. Finally, the relevant parameters like diffusion constants D_n, D_S and chemotactic sensitivity χ are not directly related to the individual movement pattern of the species. They can be measured only indirectly (see e.g. [52]).

Within this context, it is useful to study alternative models, like hyperbolic equations and transport models. Moreover, the challenging problem consists in deriving macroscopic models form the underlying description at the microscopic scale. This challenging target was pursued in [3] by asymptotic methods, while this research line continued in this section by the moment closure method presented in the preceding sections. It will be shown, in the following subsections, how the method leads to new models.

4.1. **Derivation of the classical Keller–Segel model.** Let consider the macroscopic model (29) and consider some specific regimes to derive Keller–Segel type models.

4.1.1. *Full Keller–Segel regime.* Consider the following regime of coefficients

$$\nu_1,\ \nu_2,\ \text{and } s\to\infty,\quad \frac{s^2}{\nu_1 d}\to D_n,\quad \frac{s^2}{\nu_2 d}\to D_S \tag{33}$$

and divide the second equation of (29) by ν_1, it yields

$$\frac{1}{\nu_1}\,\partial_t(n\,U)+\frac{s^2}{d\nu_1}\,\nabla_x n=-n\,U+\alpha_1 n\,\nabla_{\mathbf{x}}\,S+\frac{1}{\nu_1}\,\tilde{\phi}(n,n\,U,S,SU_S).$$

Taking limits (33) yields

$$-\,n\,U+\alpha_1 n\,\nabla_{\mathbf{x}}\,S=D_n\,\nabla_x n. \tag{34}$$

Therefore the first equation of (29) can be written as

$$\partial_t n=\mathrm{div}_x(D_n\nabla_x n-n\,\chi(S)\nabla_x S)+f(n,S), \tag{35}$$

with

$$\chi(S)=\alpha_1(S), \tag{36}$$

while by (20), one has

$$f(n,S)\quad=\quad\alpha_{11}H_{11}(n,n)+\alpha_{12}H_{12}(n,S). \tag{37}$$

In the same way, dividing the fourth equation of (29) by ν_2 and taking limits yields

$$-\,S\,U_S=D_S\,\nabla_x S. \tag{38}$$

Therefore the third equation of (29) writes

$$\tau\partial_t S=D_S\Delta S+g(n,S), \tag{39}$$

where

$$g(n,S)=\alpha_{21}H_{21}(S,n)+\alpha_{22}H_{22}(S,S). \tag{40}$$

Then, system (35)–(39) is derived, which corresponds to the Keller–Segel model (32)

$$\begin{cases}\partial_t n=\mathrm{div}_x(D_n\nabla_x n-n\chi(S)\nabla_x S)+f(n,S),\\[2ex] \tau\partial_t S-D_S\Delta S=g(n,S),\end{cases} \tag{41}$$

where f and g, are given respectively by (37) and (40).

4.1.2. *Keller–Segel without source term regime.* If we consider the same regime that in section 4.1.1 and neglect the proliferative/destructive biological interactions given by (25), i.e.

$$\nu_1,\ \nu_2,\ \text{and } s\to\infty,\quad \frac{s^2}{\nu_1 d}\to D_n,\quad \frac{s^2}{\nu_2 d}\to D_S,\quad \alpha_{ij}\to 0$$

then $f(n,S)=g(n,S)=0$, while the following Keller–Segel model without source term is obtained

$$\begin{cases}\partial_t n=\mathrm{div}_x(D_n\nabla_x n-n\chi(S)\nabla_x S),\\[2ex] \tau\partial_t S-D_S\Delta S=0.\end{cases} \tag{42}$$

Remark 5. Some experimental setups for bacteria are designed for shallow gradients (see e.g. Chen et al. [17]). Patlak [49] derived the classical PKS-model for chemosensitive movement under the assumption, that on an average distance traveled by particles between turns, the change in particle distribution: $\nabla_x n$ is small.

Remark 6. The prototype chemotaxis model (16) with (30) leads to the well-known Keller–Segel model in two steps: First closure of the first three moment equations to get the hyperbolic approximations (29), and then passing to the parabolic limit for fast speeds and large turning rates.

As shown by Bellomo et al. [3], Patlak [49], and Hillen [28], one can directly scale the transport model (16) to derive the parabolic limit (42).

4.1.3. *Parabolic–elliptic Keller–Segel model.* Now we consider a regime for which the equation for the chemoatractant becomes elliptic. We set

$$\nu_1,\ \nu_2,\ \text{and } s\to\infty,\quad \frac{s^2}{\nu_1 d}\to D_n,\quad \frac{s^2}{\nu_2 d}\to D_S,\quad \tau\to 0, \tag{43}$$

where the parameter τ can be regarded as a relaxation time scale such that $\frac{1}{\tau}$ is the rate towards equilibrium.

The difference with section 4.1.1 is that we let $\tau\to 0$, and we get $-D_S\Delta S = g(n,S)$, so that the following parabolic–elliptic Keller–Segel model is derived:

$$\begin{cases} \partial_t n = \operatorname{div}_x(D_n\nabla_x n - n\,\chi(S)\nabla_x S) + f(n,S), \\ \\ -D_S\Delta S = g(n,S). \end{cases} \tag{44}$$

Remark 7. This is the case where the chemical substance S relaxes so fast that it reaches its equilibrium instantaneously, i.e. $\tau\to 0$ and (41) is reduced to a parabolic–elliptic system, see [31]. It is also equivalent to say that this model has been studied in a molecular diffusion case. It is much faster (s very large) than that of cells (which are much larger objects), and the term $\partial_t S$ can be neglected.

4.1.4. *Parabolic–elliptic Keller–Segel model without source term.* We can finally consider the previous regime but also neglecting the biological interactions given by (25), i.e.

$$\nu_1,\ \nu_2,\ \text{and } s\to\infty,\quad \frac{s^2}{\nu_1 d}\to D_n,\quad \frac{s^2}{\nu_2 d}\to D_S,\quad \tau\to 0,\quad \alpha_{ij}\to 0. \tag{45}$$

This case corresponds to assuming that biological interaction are small enough, so that one has $f(n,S) = g(n,S) = 0$ and obtains the following parabolic-elliptic Keller–Segel model without source term:

$$\begin{cases} \partial_t n = \operatorname{div}_x(D_n\nabla_x n - n\chi(S)\nabla_x S), \\ \\ \Delta S = 0. \end{cases} \tag{46}$$

4.2. **Optimal drift following the chemoattractant.** It is not completely clear how the term $\operatorname{div}_x(\chi n\nabla_x S)$ induces *per se* the *optimal* movement of the cells towards the pathway determined by the chemoattractant. Then, 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

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

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

$$\mathrm{div}_x\left(\chi n\frac{\nabla_x S}{\sqrt{1+|\nabla_x S|^2}}\right). \tag{47}$$

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

This approach was successfully studied in [3] by using asymptotic limit of model (16), the following model was obtained:

$$\begin{cases} \partial_t n = \mathrm{div}_x\Big(D_n\nabla_x n - n\,\chi(S)\,\dfrac{\nabla_x S}{\sqrt{1+|\nabla_x S|^2}}\Big) + f(n,S), \\ \tau\partial_t S - D_S\,\Delta S = g(n,S). \end{cases} \tag{48}$$

More generally, one can consider a regularization of the PKS model, which is based on a fundamental biological property of the chemotactic flux function-its boundedness (this feature is almost always lost in weakly nonlinear, small gradients expansions, underlying the derivation of most continuum models). To derive the modified system we replace the linear chemotactic flux $\chi n\nabla_x S$ by a nonlinear saturated one, $\chi nQ(\nabla_x S)$, which is proportional to the magnitude of the chemoattractant gradient only when the latter is small and is bounded when the chemoattractant gradient tends to infinity. The regularized model then reads:

$$\begin{cases} \partial_t n = \nabla_x(D_n\nabla_x n - n\,\chi(S)\,Q(\nabla_x S)) + f(n,S), \\ \tau\partial_t S - D_S\Delta S = g(n,S), \end{cases} \tag{49}$$

where a smooth bounded chemotactic flux function $Q(x)=(Q_1(x),.....,D_d(x))$, and $x=(x_1,.....,x_d)^T$, satisfies the following properties:

$$Q(0)=0,\quad |Q_i|\le C_i,\quad \frac{\partial Q_i}{\partial x_i}>0,\quad i=1,....d, \tag{50}$$

where C_i are constants.

The synthesized form of the saturated flux is a Pade approximate which connects universal features present at both very small and very large gradients. There is a certain arbitrariness in the choice of the chemotactic flux function Q. A typical example of such function (see [18])

$$Q(\nabla_x S)=\begin{cases} \nabla_x S, \quad if \quad |\nabla_x S|\le x^\star, \\ \left(\dfrac{|\nabla_x S|-x^\star}{\sqrt{1+|\nabla_x S-x^\star|^2}}+x^\star\right)\dfrac{\nabla_x S}{|\nabla_x S|}, \quad if \quad |\nabla_x S|>x^\star, \end{cases} \tag{51}$$

where $x^\star$ is a switching parameter, which defines a small gradient values, for which the system (49) reduces to the original PKS system (32) so that the effect of saturated chemotactic flux function is felt at large gradient regimes only. Note that when $x^\star=0$, the flux (51) becomes a mean curvature type function:

$$Q(\nabla_x S)=\frac{\nabla_x S}{\sqrt{1+|\nabla_x S|^2}}$$

and the model (49)-(51) become (48).

In the following we will derive the hyperbolic corresponding to model (49)-(50), and deduce the classical parabolic chemotaxis equations (49).

4.2.1. *Different regimes for the optimal drift.* This subsection focuses on how the classical chemotaxis equations (49), which describe the population-level response to external chemical signals, can be obtained from the microscopic description delivered by model (16), as well as some more precise approaches to the several phenomena described in the previous items. If we combine the relaxation kernels presented in (27) with

$$\alpha(\langle f_2\rangle) = \alpha_1(\langle f_2\rangle)Q(\nabla_x\langle f_2\rangle), \tag{52}$$

where Q satisfies (50).

The term $(n\,\alpha(S))$ that appears in the macroscopic cases defined in (29) becomes: $n\,\alpha(S) = n\,\alpha_1(S)Q(\nabla_x S)$, and the corresponding hyperbolic model writes:

$$\begin{cases} \partial_t n + \operatorname{div}_x(n\,U) = \tilde{\psi}(n, n\,U, S, S\,U_S), \\ \partial_t(n\,U) + \dfrac{s^2}{d}\nabla_x n = -\nu_1 n\,U + \nu_1\alpha_1\,n\,Q(\nabla_x S) + \tilde{\phi}(n, n\,U, S, S\,U_S), \\ \tau\partial_t S + \operatorname{div}(S\,U_S) = \tilde{\Gamma}(n, nU, S, SU_S), \\ \tau\partial_t(S\,U_S) + \dfrac{s^2}{d}\nabla_x S = -\nu_2 S U_S + \tilde{\delta}(n, nU, S, S\,U_S). \end{cases} \tag{53}$$

A Keller–Segel model (49) can be obtained from a binary mixture (16), by dividing the second equation of (53) by ν_1:

$$\frac{1}{\nu_1}\partial_t(n\,U) + \frac{s^2}{d\nu_1}\nabla_x n = -n\,U + \alpha_1 n\,Q(\nabla_x S) + \frac{1}{\nu_1}\,\tilde{\phi}(n, nU, S, SU_S),$$

and by taking a limit (33), which yields

$$-\,n\,U + \alpha_1 n\,Q(\nabla_x S) = D_n\nabla_x n, \tag{54}$$

while the first equation of (53) gives

$$\partial_t n = \nabla_x(D_n\nabla_x n - n\,\chi(S)Q(\nabla_x S)) + f(n, S),$$

with $f(n, S)$ is given by (37). The same arguments can be applied to the second population by taking a limit (33) to obtain finally (49), where $g(n, S)$ is given by (40).

As before, if we consider now the regime (43), one obtains in this case the following Parabolic-Elliptic Keller–Segel model:

$$\begin{cases} \partial_t n = \operatorname{div}_x(D_n\nabla_x n - n\,\chi(S)Q(\nabla_x S)) + f(n, S), \\ -D_S\Delta S = g(n, S). \end{cases} \tag{55}$$

Finally, regime (45) give rise to $f(n, S) = g(n, S) = 0$, and the following model is obtained:

$$\begin{cases} \partial_t n = \operatorname{div}_x(D_n\nabla_x n - n\,\chi(S)Q(\nabla_x S)), \\ \Delta S = 0. \end{cases} \tag{56}$$

5. **Perspectives.** A methodological approach to derive macroscopic models of biological tissues from the underlying description at the microscopic scale delivered by the kinetic theory for active particle, was proposed in this paper. A binary mixture was considered and the closure method gave a hyperbolic model.

The approach was mainly focused on the derivation of various types models for chemosensitive movement, in particular the Keller–Segel models, which incorporates flux limited terms. It can be specifically applied to model different types of biological

phenomena, where pattern formation occurs, ranging from angiogenesis [23], to different types of vascular morphogenesis [26, 54, 55].

These applications should take into account that biological systems evolve in time. Accordingly, the structure and properties of macroscopic models of biological tissues should take into account this evolution that may include Darwinian selection [5, 8]. Possibly, the approach should link the dynamics at the cellular scale to that of tissues toward the identification of the asymptotic regimes that determine the properties of macroscopic models. This is a challenging, however difficult, perspective very important in cancer modeling [20]. The contents of this paper aims at contributing to this specific issue based on a methodological approach that can be hopefully extended to the derivation of macro-scale models concerning biological phenomena different from those treated in this present paper.

Focusing on analytic problems the new class of flux limited models deserve further analysis, to be viewed as research perspectives, on the qualitative properties of the solutions to initial and initial-boundary value problems to propagation of chaos [40].

REFERENCES

[1] A. R. A. Anderson and V. Quaranta, *Integrative mathematical oncology*, Nature Reviews - Cancer, **8** (2008), 227–234.

[2] N. Bellomo, A. Bellouquid, J. Nieto and J. Soler, *Complexity and mathematical tools toward the modelling of multicellular growing systems*, Math. Comput. Modelling., **51** (2010), 441–451.

[3] N. Bellomo, A. Bellouquid, J. Nieto and J. Soler, *Multiscale biological tissue models and flux–limited chemotaxis for multicellular growing systems*, Math. Models Methods Appl. Sci., **20** (2010), 1–29.

[4] N. Bellomo, A. Bellouquid, J. Nieto and J. Soler, *On the asymptotic theory from microscopic to macroscopic growing tissue models: An overview with perspectives*, Math. Models Methods Appl. Sci., **22** (2012), 1130001 (37 pages).

[5] N. Bellomo and B. Carbonaro, *Towards a mathematical theory of living systems focusing on developmental biology and evolution: A review and perspectives*, Physics of Life Reviews, **8** (2011), 1–18.

[6] A. Bellouquid, *On the asymptotic analysis of kinetic models towards the compressible Euler and acoustic equations*, Math. Models Methods Appl. Sci., **14** (2004), 853–882.

[7] A. Bellouquid and E. De Angelis, *From kinetic models of multicellular growing systems to macroscopic biological tissue models*, Nonlinear Analysis: Real World. Appl., **12** (2011), 1111–1122.

[8] A. Bellouquid, E. De Angelis and D. Knopoff, *From the modeling of the immune hallmarks of cancer to a black swan in biology*, Math. Models Methods Appl. Sci., **23** (2013).

[9] 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.

[10] 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.

[11] A. Bellouquid and M. Delitala, "Mathematical Modeling of Complex Biological Systems. A Kinetic Theory Approach," Birkäuser, Boston, 2006.

[12] C. Cattani and A. Ciancio, *Separable transition density in the hybrid model for tumor-immune system competition*, Comp. Math. Meth. in Medicine, Article ID 610126, (2012).

[13] F. Cerreti, B. Perthame, C. Schmeiser, M. Tang and V. Vauchelet, *Waves for the hyperbolic Keller–Segel model*, Math. Models Methods Appl. Sci., **21** (2011), 825–842.

[14] 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.

[15] 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.

[16] M. A. J. Chaplain, M. Lachowicz, Z. Szyman'ska and D. Wrzosek, *Mathematical modelling of cancer invasion: The importance of cell-cell adhesion and cell-matrix adhesion* Math. Models Methods Appl. Sci., **21** (2011), 719–743.
[17] K. C. Chen, R. M. Ford and P. T. Cummings, *Perturbation expansion of Alt's cell balance equations reduces to Segel's 1d equation for shallow chemoattractant gradients*, SIAM J. Appl. Math., **59** (1999), 35–57.
[18] A. Chertock, A. Kurganov, X. Wang and Y. Wu, *On a chemotaxis model with saturated chemotactic flux*, Kinetic and Related Models., **5** (2012), 51–95.
[19] Y. Dolak and T. Hillen, *Cattaneo models for chemotaxis, numerical solution and pattern formation*, J. Math. Biol., **2** (2003), 153–170.
[20] A. D'Onofrio, P. Cerrai and A. Gandolfi, "New Challenges for Cancer Systems Biomedicine," SIMAI-Springer Series, Springer-Italia, 2012.
[21] H. Du, Z. Xu, J. D. Shrout and M. Alber, *Multiscale modeling of Pesudomonas Aeruginosa swarming*, Math. Models Methods Appl. Sci., **21** (2011), 939–954.
[22] F. Filbet, P. Laurençot and B. Perthame, *Derivation of hyperbolic models for chemosensitive movement*, J. Math. Biol., **50** (2005), 189–207.
[23] J. Folkman, *Role of angiogenesis in tumor growth and methastasis*, Seminar Oncology, **29** (2002), 15–18.
[24] H. L. Hartwell, J. J. Hopfield, S. Leibner and A. W. Murray, *From molecular to modular cell biology*, Nature, **402** (1999), c47–c52.
[25] J. Haskovec and C. Schmeiser, *Convergence of a stochastic particle approximation for measure solutions of the 2D Keller-Segel system*, Comm. Part. Diff. Eqs., **36** (2011), 940–960.
[26] M. A. Herrero, A. Köhn and J. M. Pérez-Pomares, *Modelling vascular morphogenesis: Current views on blood vessels development*, Math. Models Methods Appl. Sci., **19** (2009), 1483–1538.
[27] M. A. Herrero, E. Medina and J. J. L. Velázquez, *Finite-time aggregation into a single point in a reaction-diffusion system*, Nonlinearity, **10** (1997), 1739–1754.
[28] T. Hillen, *On the L^2-moment closure of transport equation: The Cattaneo approximation*, Disc. Cont. Dyn. Syst. B, **4** (2004), 961–982.
[29] T. Hillen and J. K. Painter, *A user's guide to PDE models for chemotaxis*, J. Math. Biol., **58** (2009), 183–217.
[30] T. Hillen and H. G. Othmer, *The diffusion limit of transport equations derived from velocity jump processes*, SIAM J. Appl. Math., **61** (2000), 751–775.
[31] D. Horstmann, *From 1970 until present: The Keller–Segel model in chemotaxis and its consequences: Jahresber I*, Deutsch. Math.-Verein, **105** (2003) 103–165.
[32] E. F. Keller and L. A. Segel, *Initiation od slide mold aggregation viewed as an instability*, J. Theor. Biol., **26** (1970), 399–415.
[33] E. F. Keller and L. A. Segel, *Model for chemotaxis*, J. Theor. Biol., **30** (1971), 225–234.
[34] E. F. Keller and L. A. Segel, *Traveling Bands of chemotactic Bacteria: A Theoretical Analysis*, J. Theor. Biol., **30** (1971), 235–248.
[35] E. F. Keller, *Assessing the Keller–Segel model: How has it fared? In biological growth and spread*, Proc. Conf. Math. Biol. Heidelberg, Springer, Berlin, (1980), 379–387.
[36] P. Koumoutsakos, B. Bayati, F. Milde and G. Tauriello, *Particle simulations of morphogenesis*, Math. Models Methods Appl. Sci., **21** (2011), 955–1006.
[37] R. Kowalczyck, *Preventing blow-up in a chemotaxis model*, J. Math. Anal. Appl., **305** (2005), 566–588.
[38] 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.
[39] M. Lachowicz, *Microscopic, mesoscopic and macroscopic descriptions of complex systems*, Probab. Eng. Mechanics, **26** (2011), 54–60.
[40] M. Lachowicz, *Individually-based Markov processes modeling nonlinear systems in mathematical biology*, Nonlinear Analysis: Real World Applications, **12** (2011), 2396–2407.
[41] C. D. Levermore, *Moment closure hierarchies for kinetic theories*, J. Stat. Phys., **83** (1996), 1021–1065.
[42] A. Marciniak-Czochra and M. Ptashnyk, *Derivation of a macroscopic receptor-based model using homogenization techniques*, SIAM J. Math. Analysis, **40** (2008), 215–237
[43] A. Marciniak-Czochra and M. Ptashnyk, *Boundedness of solutions of a haptotaxis model*, Math. Models Methods Appl. Sci., **20** (2010), 440–476.

[44] I. Muller and T. Ruggeri, "Rational Extended Thermodynamics," Springer, New, York, 2nd edition, 1998.
[45] J. D. Murray, "Mathematical Biology," Springer, Berlin, New York, 1989.
[46] H. G. Othmer, S. R. Dunbar and W. Alt, *Models of dispersal in biological systems*, J. Math. Biol., **26** (1988), 263–298.
[47] H. G. Othmer and T. Hillen, *The diffusion limit of transport equations II: Chemotaxis equations*, SIAM J. Appl. Math., **62** (2002), 1222–1250.
[48] K. Painter and T. Hillen, *Volume-filling and quorum-sensing in models for chemosensitive movement*, Canadian Appl. Math. Quart., **10** (2002), 501–543.
[49] C. S. Patlak, *Random walk with persistant and external bias*, Bull. Math. Biol., **15** (1953), 311–338.
[50] L. E. Payne and B. Straughan, *Decay for a Keller-Segel chemotaxis model*, Studies Appl. Math, **123** (2009), 337–360.
[51] C. Ringhofer, C. Schmeiser and A. Zwirchmayr, *Moment methods for the semiconductor Boltzmann equation on bounded position domains*, SIAM J. Num. Anal., **39** (2001), 1078–1095.
[52] L. A. Segel, *A theoretical study of receptor mechanisms in bacterial chemotaxis*, SIAM J. Appl. Math., **32** (1977), 653–665.
[53] M. A. Stolarska, K. I. M. Yangjin and H. G. Othmer, *Multi-scale models of cell and tissue dynamics*, Phil. Trans. Royal Society A: Math. Phys. Eng. Sci., **367** (2009), 3525–3553
[54] Y. Tao, *Global existence for a haptotaxis model of cancer invasion with tissue remodeling*, Nonlinear Analysis: RWA, **12** (2011), 418–435.
[55] R. A. Weinberg, "The Biology of Cancer," Garland Sciences - Taylor and Francis, New York, 2007.

Received March 2012; revised May 2012.

E-mail address: nicola.bellomo@polito.it
E-mail address: bellouquid@gmail.com
E-mail address: jjmnieto@ugr.es
E-mail address: jsoler@ugr.es