Nonlinear Hyperbolic Systems and Transport Equations in Mathematical Biology

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Abstract: The standard models for groups of interacting and moving individuals, (from cell biology to vertebrate population dynamics) are reaction-diffusion models. They base on Brownian motion, which is characterized by one single parameter (diffusion coefficient). In particular for moving bacteria and (slime mold) amoebae, detailed information on individual movement behavior is available (speed, run times, turn angle distributions). If such information is entered into models for populations, then reaction-transport equations or hyperbolic equations (telegraph equations, damped wave equations) result.

The goal of this review is to present some basic applications of transport equations and hyperbolic systems and to illustrate the connections between transport equations, hyperbolic models, and reaction-diffusion equations. Applied to chemosensitive movement (chemotaxis) functional estimates for the nonlinearities in the classical chemotaxis model (Patlak-Keller-Segel) can be derived, based on the individual behavior of cells and attractants.

While reporting on traveling front problems, models with quiescent states, and epidemic modeling in passing, a detailed review is given on two methods of reduction for transport equations. First the construction of parabolic limits (diffusion limits) for linear and non-linear transport equations and then a moment closure method based on energy minimization principles. Closure methods are studied for moment systems of any order, the lowest non-trivial case (two-moment closure) leads to Cattaneo systems.

Keywords: Chemotaxis, transport equations, hyperbolic systems, Keller-Segel model, telegraph equation, parabolic limit, moment closure

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1 Introduction

Hyperbolic models and transport equations are used in Mathematical Biology to model movement and growth of populations. For example certain bacteria (like *Escherichia coli* or *Salmonella typhimurium*) show a very characteristic movement pattern. Periods of straight runs alternate with periods of random rotations which lead to reorientation of the cells ([4]). This behavior can be modeled by a *velocity jump process*, which in a continuum formulation leads to a *transport equation* ([65]).

Transport models in one space dimension can be seen as hyperbolic systems. Moreover, in any space dimension, moment closure methods lead from transport models to hyperbolic systems. In contrast to diffusion based models, transport models and hyperbolic systems do not show the unwanted effect of infinitely fast propagation. Transport equations are based on detailed information on turning rate, turning distribution and mean speed. The relevant parameters can be extracted from the measurements of individual paths.

Transport models for biological applications are closely related to transport models in Physics, like semiconductor [49], radiation [50], and neutron transport [42], as well as to thermodynamics [51] and the Boltzmann equation [7], [3]. In typical physical applications the directional changes of the individual particles are driven by collisions. These collisions usually conserve mass, momentum and energy, and hence the collision operator has a five-dimensional null space. In a biological context only the total particle mass is conserved. Otherwise the directional changes have to be treated as spontaneous (without collisions), and they do not necessarily preserve energy or momentum. Hence the turning operator has a one-dimensional null space. This difference becomes important if one uses functional analytic properties of the operators involved (like spectral properties, stability, parabolic scaling limits, asymptotic behavior etc.).

All moving species orient their movement on external information. For bacteria the only source of information comes via their cell surface receptors which collect information mainly on chemical cues. In chemotaxis, for example, cells move towards high concentrations of a chemical attractant. Experiments on chemotaxis measure either the behavior of the population as a whole, e.g. in terms of densities (e.g. Woodward *et al.* [67]) or the paths of individuals are followed with a video apparatus (Ford *et al.* [15]). Of course the behavior of the population results from the movement of its members. Mathematical modeling provides a way to relate the individual and collective movement parameters, e.g. by forming parabolic limits.

The first mathematical model for chemotaxis is the *Patlak-Keller-Segel* model (PKS), which is based on Brownian motion. It is known that the PKS model shows all kinds of different patterns, e.g. standing waves, aggregation, finite time blow-up, or spinodal decomposition patterns ([48]).

In this article we review hyperbolic models and transport equations together with their application to chemotaxis. We compare the resulting chemotaxis models to the standard PKS-type models and we show that in certain situations they have advantages while in others they are equally applicable. Before describing non-linear chemotaxis models we first recall simpler linear cases.

1.1 Correlated random walk in one-dimension

Movement in one space dimension with constant speed γ and constant turning rate μ can be described by a correlated random walk. The total population density $u(t,x)$ is split as $u = u^+ + u^-$ into densities for right/left moving part of the population, u^+, u^-, respectively. These are the variables of the Goldstein-Kac model for correlated random walk ([19], [44]).

$$u_t^+ + \gamma u_x^+ = -\mu u^+ + \frac{\mu}{2}(u^+ + u^-), \qquad u_t^- - \gamma u_x^- = -\mu u^- + \frac{\mu}{2}(u^+ + u^-). \quad (1)$$

This system can be transformed to an equivalent system for the total population density u and the population flux $v = \gamma(u^+ - u^-)$:

$$u_t + v_x = 0, \qquad v_t + \gamma^2 u_x = -\mu v. \quad (2)$$

By eliminating the variable v (*Kac' trick*) one obtains a telegraph equation or damped wave equation.

$$\frac{1}{\mu} u_{tt} + u_t = \frac{\gamma^2}{\mu} u_{xx}. \quad (3)$$

Note that the transition from (1) to (3) (which can be generalized to systems with several dependent variables in any space dimension) is not completely invertible ([24]).

If we let the parameters μ and γ go to infinity such that the quotient γ^2/μ converges to a number $D > 0$ then we formally obtain the parabolic limit $u_t = D u_{xx}$. Notice that in this linear case the transition is equivalent to a scaling of space and time $\tau = \varepsilon^2 t$ and $\xi = \varepsilon x$ with μ and γ held constant.

1.2 The Linear Transport Equation

We denote the population density at time $t \geq 0$, position $x \in \mathbb{R}^n$, and velocity $v \in V \subset \mathbb{R}^n$ with $p(t,x,v)$. We assume that the set of possible velocities $V \subset \mathbb{R}^n$ is bounded and symmetric (i.e. $v \in V \Rightarrow -v \in V$). Then the linear transport model, which is based on a velocity jump process (see e.g. Stroock [65] or Othmer *et al.* [53]) reads

$$\frac{\partial}{\partial t}p(t,x,v) + v \cdot \nabla p(t,x,v) = -\mu p(t,x,v) + \mu \int T(v,v')p(t,x,v')dv'. \quad (4)$$

Here μ is the turning rate or turning frequency, and $\tau = 1/\mu$ is the mean run time. The kernel $T(v,v')$ describes the probability for the new velocity v given the previous velocity v', hence $\int T(v,v')dv = 1$.

The one dimensional Goldstein-Kac model (1) occurs as a special case in one space dimension if we study (4) with $v \in \{\pm\gamma\}$ and $T(v,v') \equiv 1/2$.

1.3 Models with Reaction

Reaction diffusion equations are the standard models for spread in space and interaction of particles, e.g. density-dependent birth and death processes (e.g. Murray [52]). If the diffusion process is replaced by a more detailed transport process, then reaction transport models result.

$$p_t + v \cdot \nabla p = -\mu p + \mu \int T(v,v')p(t,x,v')dv' + F[p], \quad (5)$$

where the functional $F[p]$ describes the growth dynamics (see [23]).

Whereas in earlier papers on reaction transport equations (and on correlated random walk models with reactions) the nonlinearity has not been further specified, later, with respect to ecological modeling, a clear distinction between production and removal events has been made. If, for example, the newly produced individuals have a uniform distribution of velocities, then the nonlinearity has the form

$$F[p] = \frac{1}{|V|}b(m^0)m^0 - g(m^0)p,$$

with non-negative rates $b(m^0), g(m^0)$. The total population density is denoted as

$$m^0(t,x) = \int_V p(t,x,v)\,dv \quad (6)$$

(we will use m^j for moments later). This model preserves positivity. In the isotropic case, where the non-linearity depends only on m^0, $F[p] = f(m^0)$,

positivity can no longer be guaranteed if f changes sign. For isotropic and non-isotropic models boundary value and spectral problems have been studied in [24]. The traveling front problems in the case of one space dimension (which covers also the case of Cattaneo systems in any space dimension) have been studied in a sequence of papers, where [25] gives the most detailed analysis. For the stability of hyperbolic fronts see also [18]. Schwetlick [61, 62] has obtained rather general results on the minimal propagation speed in reaction transport equations (which depends on space dimension in a natural way) and on the existence of fronts.

1.4 Resting states

In reaction diffusion equations and related semilinear transport equations the transport and the interaction processes run parallel. However, in many realistic situations they alternate, either periodically or with random transitions. Periodically alternating actions lead to non-autonomous problems ([29]) while random transitions lead to a new class of reaction diffusion or transport systems. Typical examples are systems derived from the Fisher equation ([47], [28])

$$\begin{aligned} v_t &= D\Delta v - \gamma_2 v + \gamma_1 w \\ w_t &= f(w) - \gamma_1 w + \gamma_2 v \end{aligned} \tag{7}$$

with $f(w) = w(1-w)$, describing a moving state v and an interacting state w. This system is essentially equivalent to a formal wave equation with nonlinear diffusion and with viscous damping (with $\tau = 1/(\gamma_1 + \gamma_2)$ and $\rho_i = \tau\gamma_i$)

$$\begin{aligned} \tau w_{tt} &+ (1 - \tau f'(w))w_t - \tau D\Delta w_t \\ &= \rho_1 D\Delta w + \rho_2 f(w) - \tau D\Delta f(w). \end{aligned} \tag{8}$$

In this equation again a "parabolic limit" $\tau \to 0$ can be taken which results in another rescaled Fisher equation.

The wave operator in this problem, i.e., $w_{tt} - \rho_1 D\Delta w + \tau D\Delta f(w)$, shows a transition from hyperbolic to elliptic for large τ. Models of this form also play a role in the theory of infectious diseases, where the moving and sedentary states correspond to long range and short range infections [26]. These phenomena and connections suggest to study transport equations with sedentary states in general [33]. The spectral theory as developed in Section 3 carries over to transport equations with resting phases and diffusion limits can be studied in that framework [33]. It turns out that a spatially dependent stopping rate $\gamma_2(x)$ leads, in the parabolic limit, to a drift term proportional to

$\nabla\gamma_2(x)$. This describes a net drift towards favorable habitats (rich nutrition or shelter).

In general it can be stated that introducing a resting state into a given dynamics tends to remove oscillations, quite in contrast to a delay which (together with negative feedback) tends to enhance oscillatory behavior, see a forthcoming paper [27].

2 Models for Chemotaxis

If the movement of a population or an individual is biased by a chemical signal the response is termed *chemotaxis* (or more generally *chemosensitive movement*). Models for chemotaxis have been successfully applied to bacteria, slime molds, skin pigmentation patterns, leukocytes and many other examples.

As mentioned in the introduction the first model for chemosensitive movement has been developed by Patlak [57] and Keller and Segel [45]. Patlak's model is based on a detailed random walk description [57].

The Keller-Segel model in its general form consists of four coupled reaction diffusion equations. In most cases it is reduced to two essential variables, the population density $u(t,x)$ and the concentration of a chemical signal $v(t,x)$. The Keller-Segel model reads

$$\begin{aligned} u_t &= \nabla(k_1(u,v)\nabla u - k_2(u,v)\nabla v) \\ v_t &= k_c\Delta v - k_3(v)v + uf(v). \end{aligned} \tag{9}$$

This system has been studied on unbounded and on bounded domains with various boundary conditions (Dirichlet, Neumann, mixed). In two survey articles, Horstmann [39, 40] gives an ample review of the many now available analytical results, in particular on blow-up in finite time. In the case of constant coefficient functions k_1, k_2, k_3, and f it is known that the qualitative behavior strongly depends on the space dimension. In 1-D the system has globally existing solutions. The 2-D case in ambiguous and thresholds have been found. If the total initial mass exceeds its threshold, then the solution blows up in finite time. If the initial mass is below this threshold, then the solution exists globally in time.

The blow-up solutions of the system (9) show the existence of a very strong instability and a large aggregational force. In certain situations, however, it is desirable to obtain stable aggregation patterns, which do not blow up in finite time. There are various mechanisms which prevent blow up. These can be classified as follows:

1. *Saturation effects* in $k_2(u,v)$ occur very naturally if cell surface receptor kinetics is taken into account. Chemotaxis models with saturation effects have been studied analytically and have been used in many applications (Othmer and Stevens [55], Biler [5], Rivero *et al.* [59], Ford *et al.* [17]).

2. A *volume filling* effect was introduced by Hillen and Painter [35, 56]. Here it is assumed that particles have a finite volume and that cells cannot move into regions which are already filled by other cells. A simple version of the volume filling method leads to a term $k_2(u,v) = \chi u(1-u)$. It was shown analytically that this form of k_2 leads to globally existing solutions in all space dimensions.

3. *Quorum sensing* occurs if the cells release an extra chemical which is repulsive to other cells [35]. The resulting equation has two competing drift terms, chemotactic attraction and quorum sensing repulsion. It is an open mathematical problem to find general conditions such that solutions blow up, or exist globally.

4. Also a *finite sampling radius* leads to global existence, at least in 2-D, as was shown by Hillen and Schmeiser [37]. Here it is assumed that individuals measure the chemical substance on a disc with non-vanishing radius (e.g. measurement around the cell surface membrane).

2.1 Hyperbolic Chemotaxis Models in 1-D

Here we describe a hyperbolic model for chemotaxis in one space dimension and outline the basic properties and results which are known to date. The one dimensional model is applicable to data which have been collected in highly symmetric "one–dimensional" experiments (e.g. Chen, Ford Cummings [9], or Rivero [59]). Moreover, the study of the one–dimensional model provides good insights into the analytical tools, which are important in 2 or 3 dimensions as well.

In experiments of Soll and Wessels [64], Fisher *et al.* [14], and others it turns out that the speed and the turning rates of individuals do not depend only on the concentration of the external signal $S(t,x)$ but also on temporal and spatial variations $S_t(t,x)$ and $S_x(t,x)$. The Goldstein-Kac model (1) is easily extended to include chemotaxis effects:

$$\begin{aligned} u_t^+ + (\gamma(S,S_t,S_x)u^+)_x &= -\mu^+(S,S_t,S_x)u^+ + \mu^-(S,S_t,S_x)u^-, \\ u_t^- - (\gamma(S,S_t,S_x)u^-)_x &= \mu^+(S,S_t,S_x)u^+ - \mu^-(S,S_t,S_x)u^-, \\ \tau S_t &= \alpha S_{xx} + f(S,u^+ + u^-)\ ,\ \tau \geq 0, \\ u^\pm(0,.) = u_0^\pm, &\qquad S(0,.) = S_0. \end{aligned} \tag{10}$$

In this notation the rates $\mu^{\pm}$ are turning rates, whereas in (1) μ is a stopping rate and each direction will be chosen with probability of $1/2$. The function $f(S, u^+ + u^-)$ describes production and decay of the external signal. System (10) requires additional assumptions to ensure a well defined Cauchy problem, which does not allow for backward diffusion (for example through the dependence on S_x). A possible set of sufficient conditions is given in [36] or in [41].

Special cases of (10) were studied or applied by Segel [63], Rivero *et al.* [59], Greenberg and Alt [21], and Chen *et al.* [9, 8].

In [38] local and global existence of solutions has been proven for the case of constant speed and for turning rates depending on S and S_x. In [36] global in time existence for $\gamma = \gamma(S)$ has been shown, where the signal distribution was assumed to be in quasi-equilibrium ($\tau = 0$). The results of [38] and [36] have been extended recently in [41] to include S_t and S_{xx} dependence in the turning rates and $\tau \neq 0$ for the case studied in [36].

2.2 The Parabolic Limit in 1-D

In this section we recall some of the results from [38], in particular the scaling analysis which leads to a parabolic limit. Basically there are two effects leading to chemotactic aggregation. Either particles slow down at high concentration levels, or they turn less often if they move up a gradient. Either effect is sufficient to produce aggregation.

To do the formal asymptotics we reformulate (10) in terms of the total density $u = u^+ + u^-$ and the difference $q = u^+ - u^-$:

$$\begin{aligned} u_t + (\gamma q)_x &= 0, \\ q_t + (\gamma u)_x &= -(\mu^+ - \mu^-)u + (\mu^+ + \mu^-)q, \\ \tau S_t &= \alpha S_{xx} + f(S, u). \end{aligned} \tag{11}$$

Similar to the analysis of the linear model (1), we can derive a telegraph equation.

$$u_{tt} + h u_t - (\gamma(\gamma u)_x)_x - (\gamma(\mu^+ - \mu^-)_x + h_x q = 0, \tag{12}$$

with an auxiliary function

$$h(x,t) := \mu^+(S, S_t, S_x) + \mu^-(S, S_t, S_x) - \frac{\gamma_t(S, S_t, S_x)}{\gamma(S, S_t, S_x)}. \tag{13}$$

We require that h does not depend explicitly on the space variable x. This restriction on $\mu^{\pm}, \gamma$ is true for many applications. We give examples later.

We introduce a small scaling parameter $\varepsilon > 0$ as

$$\gamma = \frac{\gamma_0}{\varepsilon}, \quad \text{and} \quad \mu^{\pm} = \frac{\mu_0^{\pm}}{\varepsilon^2}, \tag{14}$$

where γ_0 and $\mu_0^{\pm}$ are of order 1 with respect to ε. In this scaling we find that

$$h(t) = \frac{h_0(t)}{\varepsilon^2}, \quad \text{with} \quad h_0 = \mu_0^+ + \mu_0^- - \varepsilon^2 \frac{\gamma_{0,t}}{\gamma_0} \tag{15}$$

and for $\varepsilon \to 0$ we obtain

$$D = \lim_{\varepsilon \to 0} \frac{\gamma^2}{h(t)} = \frac{\gamma_0^2}{\mu_0^+ + \mu_0^-}. \tag{16}$$

If we scale the corresponding telegraph equation accordingly then we obtain for $\varepsilon \to 0$ the parabolic limit equation

$$u_t = \left(Du_x - u\Phi\right)_x, \tag{17}$$

with a diffusion coefficient given by (16) and the *chemotactic velocity* Φ given by

$$\Phi = -\frac{\gamma_0}{\mu_0^+ + \mu_0^-} \left(\gamma_{0,x} + \lim_{\varepsilon \to 0} \frac{1}{\varepsilon}(\mu_0^+ - \mu_0^-)\right). \tag{18}$$

A special case of this relation was derived and used in Rivero *et al.* [59] and Segel [63].

If Φ has the form $\Phi(S, S_x) = \chi(S)S_x$ then (17) is the classical chemotaxis model with *chemotactic sensitivity* $\chi(S)$.

The chemotactic velocity (18) consists of two terms which can be interpreted independently:

1. Assume for now that $\gamma = \gamma(S) \geq 0$ and that the difference $\mu_0^+ - \mu_0^-$ is of order ε^κ, for $\varepsilon \to 0$, with some $\kappa > 1$. Then $\mu^+ - \mu^- = O(\varepsilon^{\kappa-2})$ and

$$\Phi = -\frac{\gamma_0}{\mu_0^+ + \mu_0^-} \gamma_0' S_x. \tag{19}$$

The limiting equation for chemosensitive movement (10) reads

$$u_t = \left(\frac{\gamma_0}{\mu_0^+ + \mu_0^-} \left(\gamma_0 u_x + \gamma_0' S_x u\right)\right)_x. \tag{20}$$

In case that the population slows down at high concentrations of S, $\gamma'(S) < 0$, a net flow of the population in the direction of higher concentrations of S occurs. This flow stabilizes aggregations.

If $\gamma'(S) > 0$, i.e. if particles accelerate at high concentrations of S, then the population will spread out.

2. If we assume that $\gamma = const.$ then the first term in (18) vanishes and the chemotactic velocity is given by the difference in the turning rates. We assume that this difference can be expanded as

$$\mu^+ - \mu^- = \varepsilon^{-1}\varphi_1 + \varphi_2,$$

with functions $\varphi_1(S, S_t, S_x), \varphi_2(S, S_t, S_x)$. Hence the rescaled turning rates satisfy $\mu_0^+ - \mu_0^- = \varepsilon\varphi_1 + \varepsilon^2\varphi_2$. and the chemotactic velocity reads

$$\Phi = -\frac{\gamma_0}{\mu_0^+ + \mu_0^-}\varphi_1.$$

For a linear function $\varphi_1 = \varphi_0(S)S_x$ a PKS model is obtained

$$u_t = \left(\frac{\gamma_0^2}{\mu_0^+ + \mu_0^-}u_x + \frac{\gamma_0}{\mu_0^+ + \mu_0^-}\varphi_0(S)S_x u\right)_x. \tag{21}$$

The sign of the difference in turning rates determines the aggregation behavior.

If $S_x > 0$ and $\varphi_0 < 0$, then the part of the population moving up the gradient, turns less often than the population moving downwards. This behavior has been observed in bacteria.

If $S_x > 0$ and $\varphi_0 > 0$, then the population moving up the gradient, turns more often than the population moving downwards. Such behavior would destabilize aggregation.

Hence two effects lead to positive bias: When moving upward a signal gradient, individuals slow down, they lower their turning rate, or both. These effects have also been found by Schnitzer [60] in a similar one-dimensional hyperbolic model for bacterial movement, where memory effects have been included.

3 Transport Models

There is a rich literature on transport models applied to populations. We refer to the articles W. Alt [1, 2], Othmer, Dunbar and Alt [53], Chen *et al.* [9], Dickinson and Tranquillo [12], Dickinson [11], and Hillen and Othmer [34, 54].

In [34, 54] a general theory has been developed to obtain the parabolic limit (diffusion limit) for a general transport equation which describes movement of populations. We present the basic result in the following subsections.

In the case of chemosensitive movement in (4) the turning rate μ and the velocity distribution kernel $T(v,v')$ depend on the signal distribution $S(t,x)$, on its gradient $\nabla S(t,x)$, or on other properties of S (e.g. non-local dependence can be included).

$$\mu = \mu(S, \nabla S, \ldots), \quad T(v,v') = T(v,v',S,\nabla S,\ldots) \tag{22}$$

3.1 Basic Assumptions (T1)-(T4)

We consider (4) on $\Omega = \mathbb{R}^n$. We assume that $V \subset \mathbb{R}^n$ is compact and symmetric such that $v \in V$ implies $-v \in V$. Let $\mathcal{K}$ denote the cone of non-negative functions in $L^2(V)$. We define the following operators on $L^2(V)$:

$$\begin{aligned} \mathcal{T}\,p(v) &= \int_V T(v,v')p(v')dv', \qquad \mathcal{T}^*\,p(v) = \int_V T(v',v)p(v')dv', \\ \mathcal{L} &= -\mu(I-\mathcal{T}), \end{aligned}$$

where I denotes the identity. For the kernel T we assume:

(T1) $T(v,v') \geq 0, \quad \int T(v,v')dv = 1, \quad$ and $\quad \int\int T^2(v,v')dv'dv < \infty.$

(T2) There exists some $u_0 \in \mathcal{K}$ with $u_0 \not\equiv 0$, some integer N and a constant $\rho > 0$ such that for all $(v,v') \in V \times V$

$$u_0(v) \leq \; T^N(v',v) \; \leq \rho u_0(v),$$

where the N-th iterate of T is

$$T^N(v,v') := \int \ldots \int T(v,w_1)T(w_1,w_2)\cdots T(w_{N-1},v')dw_1 \ldots dw_{N-1}.$$

(T3) $\|\mathcal{T}\|_{\langle 1\rangle^\perp} < 1$, where $\langle 1\rangle^\perp$ denotes the orthogonal complement of the subspace $\langle 1\rangle \subset L^2(V)$ of functions constant in v.

(T4) $\int_V T(v,v')dv' = 1.$

Under these assumptions the turning operator $\mathcal{L}$ has the following Krein-Rutman properties:

Theorem 1 *Assume* (T1)-(T4). *Then*

1. *0 is a simple eigenvalue of $\mathcal{L}$ with eigenfunction $\phi(v) \equiv 1$.*
2. *There exists an orthogonal decomposition $L^2(V) = \langle 1\rangle \oplus \langle 1\rangle^\perp$ and for all $\psi \in \langle 1\rangle^\perp$ we have*

$$\int \psi \mathcal{L}\psi dv \leq -\nu_2 \|\psi\|^2_{L^2(V)}, \quad \textit{with} \quad \nu_2 \equiv \mu(1 - \|\mathcal{T}\|_{\langle 1\rangle^\perp}).$$

3. *Each eigenvalue* $\lambda \neq 0$ *satisfies* $-2\mu < Re\ \lambda \leq -\nu_2 < 0$, *and there is no other positive eigenfunction.*

4. $\|\mathcal{L}\|_{\mathcal{L}(L^2(V),L^2(V))} \leq 2\mu$.

5. $\mathcal{L}$ *restricted to* $\langle 1\rangle^\perp \subset L^2(V)$ *has a linear inverse* $\mathcal{F}$ *with norm*

$$\|\mathcal{F}\|_{\mathcal{L}(\langle 1\rangle^\perp,\langle 1\rangle^\perp)} \leq \frac{1}{\nu_2}.$$

This theorem can be proven along the following lines, see [34]. From (T1) it follows that $\mathcal{T}$ and $\mathcal{T}^*$ are compact Hilbert-Schmidt operators. Assumption (T2) ensures that $\mathcal{T}$ is u_0-positive in the sense of Krasnoselskii [46], hence there exists a unique positive eigenfunction $\phi(v) = 1$. From (T4) we obtain the orthogonal decomposition of $L^2(V)$. The assumption (T3) is essential. It ensures that the turning operator is dissipative.

Assumption (T2) is general enough to include turn-angle distributions, which are zero for larger turn-angles. If, for example, individuals choose new velocities in an arc of 45° compared to the previous velocity, then the iterate $\mathcal{T}^4$ would be u_0 positive.

3.2 Parabolic Scaling

On typical experimental time periods (3 h *E.coli*) bacteria show many turns per unit of time. We can identify three times scales the *mean run time* of about 1 sec, *drift-time scale* of about 100 turns and the *diffusion-time scale* of about 10000 individual turns. To reflect these scalings in the model we choose the *parabolic scaling* with a small ε ($\varepsilon = 0.01$ for the example above).

$$\tau = \varepsilon^2 t \quad \text{and} \quad \xi = \varepsilon x. \tag{23}$$

We rescale equation (4), which gives

$$\varepsilon^2 p_\tau + \varepsilon v \cdot \nabla_\xi p = \mathcal{L}p. \tag{24}$$

For $k > 2$ we consider an expansion of p:

$$p(\tau,\xi,v) = \sum_{i=0}^{k} p_i(\tau,\xi,v)\varepsilon^i + p_{k+1}(\tau,\xi,v)\varepsilon^{k+1}.$$

If we collect terms of equal order in ε we get:

$$\begin{aligned} \varepsilon^0 &: \quad 0 = \mathcal{L}p_0, \\ \varepsilon^1 &: \quad v \cdot \nabla p_0 = \mathcal{L}p_1, \\ \varepsilon^2 &: \quad p_{0\tau} + v \cdot \nabla p_1 = \mathcal{L}p_2, \end{aligned} \tag{25}$$

where the subscript ξ on the nabla operator has been omitted. We use the spectral properties of $\mathcal{L}$ (Theorem 1). The order one equation gives $p_0 = p_0(\tau, \xi)$. Hence p_0 is independent of $v \in V$. Since V is assumed to be symmetric, the solvability condition $\int v \cdot \nabla p_0 dv = 0$ of the ε^1-equation is satisfied. Hence $p_1 = \mathcal{F}(v \cdot \nabla p_0)$, where $\mathcal{F}$ is the pseudo-inverse of $\mathcal{L}$ restricted to the space $\langle 1 \rangle^\perp$, as defined in Theorem 1. The solvability condition for the ε^2-equation reads

$$\int_V p_{0\tau} + v \cdot \nabla p_1 \, dv = 0.$$

Using the representation of p_1 from above, a diffusion equation for p_0 is obtained

$$p_{0,\tau} = \nabla \cdot D \nabla p_0, \qquad p_0(\xi, 0) = \int_V p(\xi, v, 0) dv, \tag{26}$$

$$\text{with diffusion tensor} \qquad D \equiv -\frac{1}{\omega} \int_V v \mathcal{F} v^T \, dv. \tag{27}$$

The procedure can be continued to higher orders in ε and, as has been shown in [34], the residuum of this approximation can be controlled:

Theorem 2 *By induction a sequence of functions p_j can be constructed such that the sums $q_k := \sum_{j=0}^k \varepsilon^j p_j$ have the following property: For each $\vartheta > 0$ there is a constant $C_\vartheta > 0$ such that*

$$\|p(x, ., t) - q_k(x, ., t)\|_{L^2(V)} \leq C_\vartheta \, \varepsilon^{k+1}$$

for all $\vartheta/\varepsilon^2 < t < \infty$ and each $x \in \Omega$.

Hence the asymptotic behavior of solutions of (4) is described by the diffusion equation in (26). The proof of this result uses an induction argument. In particular property (T3) is important to show that the limiting equation in (26) is parabolic.

3.3 The Diffusion Tensor D

In this section we derive conditions for the diffusion tensor in (27) to be isotropic, i.e., to be a scalar multiple of the identity. We define the *expected velocity*

$$\bar{v}(v) \equiv \int T(v, v') v' dv'. \tag{28}$$

It follows from (T1) that $\int_V \bar{v}(v) dv = 0$. Moreover, if V is symmetric with respect to $SO(n)$, then there exists a constant K_V such that

$$\int_V v v^T dv = K_V I$$

(which can be seen by applying the left hand side onto two test-vectors and using the divergence theorem). In the case of $V = sS^{n-1}$ we have $K_V = \omega_0 s^2/n$.

In order to clarify the general situation we formulate the following three properties.

(S1): *There is an orthonormal basis* $\{e_1, \ldots, e_n\}$ *of* $\mathbb{R}^n$ *such that for each* $i = 1, \ldots, n$ *the coordinate mappings* $\pi_i : V \to \mathbb{R}, \quad \pi_i(v) = v_i$ *are eigenfunctions of* $\mathcal{L}$ *with common eigenvalue* $\nu \in (-2\mu, 0)$.

(S2): *There is a constant* $\gamma \in (-1, 1)$ *such that for each* $v \in V$ *the expected velocity* $\bar{v}(v)$ *satisfies*

$$\bar{v}(v) \parallel v \qquad \textit{and} \qquad \frac{\bar{v}(v) \cdot v}{|\bar{v}(v)||v|} = \gamma.$$

(S3): *There is a constant* $d > 0$ *such that* $D = d\, I_n$.

Theorem 3 *Let* (T1)-(T4) *hold and assume that* V *is symmetric with respect to* $SO(n)$. *Then we have*

$$\text{(S1)} \quad \Longleftrightarrow \quad \text{(S2)} \quad \Longrightarrow \quad \text{(S3)}$$

whereby the constants ν, γ *and* d *are related as follows.*

$$\gamma = \frac{\nu + \mu}{\mu}, \qquad d = -\frac{K_V}{\omega\nu} = \frac{K_V}{\omega\mu(1-\gamma)}.$$

If T *also satisfies* **(T5):** *There is a matrix* M *such that* $\bar{v}(v) = Mv$ *for all* $v \in V$, *then all three statements are equivalent.*

This Theorem is proved in [34].

All statements are true if T has the symmetric form of $T(v, v') = t(|v - v'|)$ (see also Alt [1]). We will give an example for non-isotropic diffusion in the next section.

3.4 Application to Chemosensitive Movement

Let T_0 and μ_0 denote turning kernel and turning rate in absence of any chemical substance. In [54] we systematically study perturbations which come form chemical cues of the form

$$T(v, v', \hat{S}) = T_0(v, v') + \varepsilon^k \tilde{T}(v, v', \hat{S}), \quad \mu(v, \hat{S}) = \mu_0 + \varepsilon^l \tilde{\mu}(v, v', \hat{S}),$$

for $k = 0, 1$ and $l = 1$, where $\hat{S}$ denotes dependence on the function S and not only on the local value $S(t, x)$, e.g. dependence on $S(t, x), \nabla S(t, x), \int S(t, x)dx$

etc. are included. Perturbations of higher order $k, l \geq 2$ will not affect the parabolic limit equation. Perturbations of the turning rate μ_0 of order one ($l = 0$) do not fit into the framework developed here. But that case can be handled in the theory of moment closure as illustrated in Section 5. There, it is shown that also order one perturbations in the turning rate lead to PKS-type models.

We omit the most general formulations as stated in [54] and just give some illustrative examples, where the parabolic scaling applies. For all examples we restrict to fixed speed $|v| = s, V = sS^{n-1}$ and $\omega = |V|$.

Example 1: We assume that the probability of a change of velocity v' to v depends on the angle between these two velocities.

$$T_1(v, v') = \frac{1}{\omega}\left(1 + \frac{a}{s^2}(v \cdot v')\right) \quad \text{with} \quad a < n. \tag{29}$$

The *expected velocity* is $\bar{v}(v) = (a/n)v$. The factor $\frac{a}{n} = \psi_d$ is denoted as *persistence index* (see Othmer *et al.* [53]). Theorem 3 applies and the first order approximation $p_0(\tau, \xi)$ fulfills the isotropic diffusion equation

$$\frac{\partial}{\partial \tau} p_0 = d\Delta p_0, \quad \text{with} \quad d = \frac{s^2}{\mu(n-a)}. \tag{30}$$

The case $a = 0$ corresponds to random walk without directional persistence ($\psi_d = 0$) and the corresponding diffusion constant is $d = \frac{s^2}{\mu n}$.

Example 2: We assume that an individual actively chooses directions upward chemical gradients (positive taxis).

$$T_2(v, v', S) = \frac{1}{\omega}(1 + \varepsilon a(S)(v \cdot \nabla S)). \tag{31}$$

Passing to the limit of small ε leads to a PKS-type model

$$\frac{\partial}{\partial \tau} p_0 = \nabla\Big(d\nabla p_0 - p_0 \chi(S) \nabla S\Big) \tag{32}$$

with $d = \frac{s^2}{\mu n}$ and $\chi(S) = \frac{s^2}{n} a(S)$.

Example 3 (Bacteria): For bacterial chemotaxis the velocity distribution is constant $T(v, v') = \frac{1}{\omega}$ and the turning rate increases if individuals move down the gradient and it decreases if they move upwards (chemokinesis)

$$\mu_2(S) = \mu_0(1 - \varepsilon b(S)(v \cdot \nabla S)). \tag{33}$$

Then for $\varepsilon \to 0$ a PKS-model follows

$$\frac{\partial}{\partial \tau} p_0 = \nabla \Big(d \nabla p_0 - \chi(S) p_0 \nabla S \Big) \tag{34}$$

with $d = \frac{s^2}{\mu n}$ and $\chi(S) = \frac{s^2}{n} b(S)$. This example directly applies to the experiments of Ford *et al.* with *E. coli* bacteria ([16]). Further details are given in [54].

Example 4 (Amoeba): For modeling chemotaxis in amoebae we combine Examples 2 and 3, i.e., we put $T_4(v, v') = T_2(v, v')$, $\mu_4(S) = \mu_2(S)$. The scaling leads to additional effects in the chemotaxis term

$$\chi(S) = \frac{s^2}{n} (a(S) + b(S)). \tag{35}$$

This case is also covered by the results of Patlak [57] and of Alt [1].

Example 5 (non-isotropic diffusion): We assume that a stream of elongated bacteria such as myxobacteria is oriented in the direction $\eta \in \mathbb{R}^n$. To describe alignment toward this stream we choose the turning kernel

$$T_5 = \kappa (v \cdot \eta)(v' \cdot \eta), \qquad |\eta| = 1.$$

If the actual direction v' has a component in direction η (or $-\eta$), then this component is enhanced and the particle orients itself in direction η (or $-\eta$, respectively). If κ is small enough then the diffusion limit is

$$\frac{\partial}{\partial \tau} p_0 = \nabla \cdot D \nabla p_0$$

with non-isotropic diffusion

$$D(\xi, \tau) = \frac{s^2}{\mu n} \left(I + \frac{\omega s^2}{n} \kappa \eta \eta \left(I - \frac{\omega s^2}{n} \kappa \eta \eta \right)^{-1} \right).$$

The diffusivity in the direction η or $-\eta$ is enhanced, whereas it has the standard value $s^2/(\mu n)$ in the orthogonal direction.

Example 6 (non-local gradient): A non local gradient, which might be measured by amoeba along their surface, can be modeled by

$$\overset{\circ}{\nabla} S(x, t) = \frac{n}{\omega_0 R} \int_{S^{n-1}} \sigma \, S(x + R\sigma, t) \, d\sigma, \tag{36}$$

where $R > 0$ is the *effective sampling radius*. If $R \to 0$ then this expression approximates the local gradient ∇S. For chemosensitive movement we treat

the non-local gradient $\overset{\circ}{\nabla} S$ in exactly the same way as ∇S in the previous Examples 2,3 and 4.

Example 7 (directional derivative): Bacteria, for example, are too small to measure chemical gradients along their body axis. They move through a signal field and they measure the signal variation along their path. Hence the turning rate should depend on the directional derivative:

$$\partial_v S := S_t + v \cdot \nabla S.$$

In the parabolic scaling this law leads to $\partial_v S = \varepsilon^2 S_\tau + \varepsilon v \cdot \nabla_\xi S$. The time derivative is of lower order compared to the gradient term. To leading order we obtain the same limit as in Example 3.

4 The Moment Closure Method

One common approach in understanding the dynamic properties of reaction-transport equations and of Boltzmann equations are *moment methods* [51]. By multiplication of (4) with powers of v and integration, one can derive an infinite sequence of equations for the v-moments of p. In the equation for the n–th moment the $(n+1)$–st moment appears. To close the equations for the first n moments, one needs an approximation of the $(n+1)$–moment. This "closure problem" is well known and widely discussed in transport theory. Most authors use *ad hoc* arguments or regular expansions to close the moment system (see e.g. [20] or [10]). Here we present a theory for closing the moment equations which is based on a minimization principle.

For Boltzmann equations the closure problem has been treated in the theory of Extended Thermodynamics (see e.g. Müller and Ruggeri [51]). An entropy functional is maximized under the constraint of fixed first n moments. It is assumed that the $(n+1)$–st moment of the minimizer approximates the $(n+1)$–st moment of the true solution. This gives the desired closure. It appears that theories for a large number of moments are capable of approximating steep gradients and shocks [66].

For the transport equations for biological problems the negative $L^2(V)$-norm can be seen as an entropy as defined in thermodynamics (it satisfies an H-Theorem, equation (39)). We close the moment system by maximizing the negative L^2-norm (i.e. minimizing the L^2-norm) under the constraint of fixed first n-moments. This minimization flattens oscillations, high frequencies in space and time will be smoothed out and the global structure of the solution is emphasized. We present this procedure here to close the system for the first two moments (total population density and population flux). The closed

system is a *Cattaneo system*, which is well known in heat transport theory. In [32] we generalized this approach to close the moment system at any order. We will summarize some results in a later section. Finally we apply this method to the transport equation for chemosensitive movement.

4.1 A Minimization Principle

We demonstrate the moment closure method on the example of a velocity jump process with fixed speed, but variable direction (*Pearson walk* [58]). In this case $V = sS^{n-1}$ with $s > 0$ and $\omega = |V| = s^{n-1}\omega_0$, where $\omega_0 = |S^{n-1}|$. The turn angle distribution is assumed to be constant $T(v, v') = \frac{1}{\omega}$. As presented in [32], the method developed here can be generalized to more general kernels T and more general velocity sets V.

The initial value problem for the linear transport equation reads

$$p_t + v \cdot \nabla p = \mu \left(\frac{m^0}{\omega} - p \right), \tag{37}$$

$$p(0, x, v) = \varphi_0(x, v). \tag{38}$$

In [31] we proved the following H-Theorem:

Theorem 4

$$\frac{d}{dt}\|p(t, x, .)\|_2^2 + \partial_j \left(\int_V v^j \, p(t, x, .)^2 dv \right) \leq 0. \tag{39}$$

The velocity-moments of p are defined by m^α, where m^0 is defined by (6) and the higher moments of p are denoted by

$$m^i(t, x) = \int_V v^i p(t, x, v) \, dv, \qquad i = 1, \ldots, n \tag{40}$$

$$m^{ij}(t, x) = \int_V v^i v^j \, p(t, x, v) \, dv, \qquad i, j = 1, \ldots, n. \tag{41}$$

Note that m^0 is scalar, m^i is a vector and m^{ij} is a 2-tensor. We stress the usual summation convention on repeated indices.

To derive the equations for the first two moments m^0 and m^i we integrate (37) over V to obtain the conservation law

$$m_t^0 + \partial_j m^j = 0. \tag{42}$$

Multiplication of (37) with v^i and integration gives

$$m_t^i + \partial_j m^{ij} = -\mu m^i. \tag{43}$$

To close this system of two moment equations (42) and (43) we want to replace $m^{ij}(p)$. We derive a function $u_{\min}(t,x,v)$ which minimizes the $L^2(V)$ norm $\|u(t,x,.)\|_2^2$ under the constraint that $u_{\min}$ has the same first moments m^0 and m^i as p has. Once we have such a function $u_{\min}$ we replace $m^{ij}(p)$ by $m^{ij}(u_{\min})$.

We introduce Lagrangian multipliers $\Lambda_0 \in \mathbb{R}$ and $\Lambda_i \in \mathbb{R}$ for $i = 1, \ldots, n$ and minimize

$$H(u) := \frac{1}{2}\int_V u^2 dv - \Lambda_0 \left(\int_V u dv - m^0\right) - \Lambda_i \left(\int_V v^i u dv - m^i\right).$$

We obtain an explicit representation of the minimizer (see [31] for details)

$$u_{\min}(t,x,v) = \frac{1}{\omega}\left(m^0(t,x) + \frac{n}{s^2}(v_i m^i(t,x))\right). \tag{44}$$

Remark:

1. It turns out that $u_{\min}$ is the projection of p onto the linear subspace $\langle 1, v^1, \ldots, v^n\rangle \subset L^2(V)$.

2. If we minimize the functional

$$H_a(u) := \frac{1}{2}\int_V (u-a)^2 dv - \Lambda_0 \left(\int_V u dv - m^0\right) - \Lambda_i \left(\int_V v^i u dv - m^i\right),$$

for some arbitrary $a \in \mathbb{R}$ with the same constraints as above we arrive at the same minimizer (44). For fixed $a \in \mathbb{R}$ the norm $\|u(t,x,.) - a\|_2$ is a measure of the oscillation around the level a. Hence, $u_{\min}$ minimizes oscillations.

3. The extremum $u_{\min}$ is indeed a minimum, since the second variation of H is $\delta^2 H(u) = 1 > 0$.

To derive the moment closure we consider the second moment of the minimizer $u_{\min}$:

$$m^{ij}(u_{\min}) = \frac{s^2}{n} m^0 \, I. \tag{45}$$

Now we close the system of the first two moments (42), (43) by assuming that $m^{ij}(u) \approx m^{ij}(p)$. Then, replacing m^{ij} in (43) together with (42) gives a linear Cattaneo system

$$\begin{aligned} M_t^0 + \partial_j M^j &= 0, \\ M_t^i + \tfrac{s^2}{n}\partial_i M^0 &= -\mu M^i, \end{aligned} \tag{46}$$

with initial conditions

$$M^0(0,.) = m^0(0,.), \quad M^i(0,.) = m^i(0,.). \tag{47}$$

We introduce capital letters to distinguish between the moments (m^0, m^i) of p and the solutions (M^0, M^i) of the Cattaneo system (46). Of course, if $m^{ij}(u) \neq m^{ij}(p)$ then $(M^0, M^i) \neq (m^0, m^i)$. The error which occurs in this approximation can be controlled. For that purpose we define

$$r := m^0 - M^0 \quad \text{and} \quad q^i := m^i - M^i,$$

and an energy

$$\mathsf{e}_s(r, q) := \frac{1}{2} \int_{\mathbb{R}^n} r^2 + \frac{n}{s^2}\, q^i q_i \, dx. \tag{48}$$

In [31] the following error estimate has been shown.

Theorem 5

$$\mathsf{e}_s(r(t,.), q(t,.)) \leq n b_n^2 \frac{s^2}{2\mu} \, \|\nabla_x m^0\|^2_{L^2([0,t]\times\mathbb{R}^n)}, \tag{49}$$

with an appropriate constant $b_n > 0$.

Cattaneo [6] used systems of the form (46) to model heat transport with finite speed. Then M^0 is the temperature and $(M^1, \ldots, M^n)$ the heat flux and the ratio $d = s^2/\mu n$ is the effective diffusion constant (see Joseph, Preziosi [43] or Gurtin, Pipkin [22] for the physical interpretations and [23], or [30] for biological interpretation).

The derivation of the Cattaneo model from a moment closure approach gives a new understanding of the role of the Cattaneo system in biological applications. The relevant parameters are related to the individual movement behavior of the underlying species.

4.2 A Chemotaxis Model with Density Control

Hillen and Painter [35] have studied a diffusion based model for chemosensitive movement where at high population densities the chemotaxis is turned off and pure diffusion dominates. This model can be constructed (from a transport equation) via a corresponding Cattaneo approximation. Solutions exist globally and now blow-up occurs. As an example consider a turning rate of the form

$$\mu(S, \delta_v S) := \mu_0 \left(1 - \frac{n}{s^2} \beta(m^0) \chi(S) \delta_v S\right),$$

where $\beta(m^0)$ is a density dependent sensitivity. The function β is assumed to have a zero at some $\bar{m}^0 > 0$ and $\beta(m) > 0$ for $0 < m < \bar{m}^0$. With turning

kernel $T(v,v') := \omega^{-1}\mu(S,\delta_{v'}S)$ the moment closure procedure leads to a *Cattaneo model for chemosensitive movement with density control*

$$\begin{aligned} M^0_t + \partial_j M^j &= 0 \\ M^i_t + \tfrac{s^2}{n}\partial_i M^0 &= -\mu_0\left(1 - \tfrac{n}{s^2}\beta(M^0)\chi(S)S_t\right)M^i + \beta(M^0)\chi(S)\,M^0\,\partial_i S. \end{aligned} \tag{50}$$

This model has been used in [13] to describe pattern formation in slime molds and in bacteria. Moreover, a numerical scheme has been developed to solve (50).

4.3 Higher Order Moment Closure

The higher order moment closure requires rigorous bookkeeping of all the relevant tensor indices which cannot be included here. We refer to [32] for details.

The H-Theorem (Theorem 4) of the previous section can be generalized to turning kernels T which satisfy the general assumptions $(T1) - (T4)$, defined above. The higher order moment closure can be derived in the framework of Lagrangian multipliers. It turns out that the steady states of the two moment closure (Cattaneo system) and of the three moment closure are determined by an elliptic equation (i.e., steady states of a corresponding diffusion problem). We conjecture that this is the case for all higher order moment closures.

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