Mathematical Models and Methods in Applied Sciences Vol. 12, No. 7 (2002)

HYPERBOLIC MODELS FOR CHEMOSENSITIVE MOVEMENT

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Chemosensitive movement describes the active orientation of individuals on chemical signals. In cases of cellular slime molds or flagellated bacteria, chemosensitive movement leads to aggregations and pattern formation. The classical mathematical model to describe chemosensitive movement is the diffusion based Patlak-Keller-Segel model. It suffers from the drawback of infinite propagation speeds. The relevant model parameters (motility and chemo-sensitivity) are related to population statistics. Hyperbolic models respect finite propagation speeds and the relevant model parameters (turning rate, distribution of new chosen velocities) are based on the individual movement patterns of the species at hand. In this article hyperbolic models (in 1-D) and a transport model (in n-D) for chemosensitive movement are discussed and compared to the classical model. For the hyperbolic and transport models the following topics are reviewed: parabolic limit (which in some cases leads to the Patlak-Keller-Segel model), local and global existence, asymptotic behavior and moment closure. The moment closure approach leads to models based on Cattaneo's law of heat conduction (telegraph equation).

Keywords: Chemosensitive movement, chemotaxis, transport equations, Keller-Segel model, telegraph equation, parabolic limit, moment closure

1. Introduction

Transport equations are very well suited to model movement of populations of unicellular organisms like bacteria or amoeba. In particular, flagellated bacteria show a characteristic movement pattern of *runs* and *tumbles* ([8]), which can be modeled by a *velocity jump process*, hence *transport equation* ([87]). Transport models are favorable to related diffusion based models in that they account for finite propagation speed. Moreover, the relevant model parameters (like turning rate, turning distribution) can be measured from individual movement patterns of members of the population at hand. If the cells adapt their movement according to a chemical signal, the adaptation is called *chemosensitive movement*. Linear transport models can be extended in a straightforward way to cover this effect.

As we will see later, the long time asymptotics of a typical transport model is described by a related diffusion based model. The two competing model classes; diffusion based and transport models, show the same results asymptotically. This explains the success of diffusion based models in this field (see e.g. Murray [62]).

Transport equations for biological applications are closely related to transport models in a physical context, like neutron transport, semiconductor theory, radiation transport or the Boltzmann equation. The functional analytical properties differ in that in a biological context there is one preserved quantity; the total population size, whereas typical collision events of gas molecules respect mass, momentum and energy conservation. This is reflected in the fact the kernel of the corresponding turning operator is one dimensional in a biological context and (typically) 5 dimensional in physical applications. Since, in the case studied here, the set of possible velocities V is *a-priori* bounded (bacteria or slime molds can not move arbitrarily fast), we can extend some of the theories from physics, which are limited by unbounded velocities. (e.g. moment closure approximations, Section 5).

It is a great challenge to the live sciences to understand the response of individuals and communities to external stimuli. All species recognize signals from their surrounding environment and they adapt their behavior accordingly. Examples are orientation toward light sources, the avoidance of harmful substances, foraging strategies, aggregational tendencies in amoeba and strategies to find a sexual partner. Many of the responses to different stimuli have been measured experimentally, which leads to a good understanding of the biological phenomenon. The experiments can roughly be classified into two classes: (i) measurements of individual behavior and (ii) measurements of population behavior. Of course the behavior of a population is determined by the individual behavior of its members. It is far from obvious how the individual behavior affects the collective behavior. Indeed this question is one of the leading questions for mathematical biology today. Mathematical modeling provides an excellent tool to connect the individual behavior to the collective behavior. This will be demonstrate in context of chemosensitive movement.

Originally, the effect of chemosensitive movement was classified into two classes; *chemotaxis* and *chemokinesis*. We discuss the differences of chemotaxis and chemokinesis in Section 2. For chemotaxis and chemokinesis a mathematical discipline on its own has evolved. Starting with the *Patlak-Keller-Segel* model (PKS), which is based on Brownian motion, results on aggregation and finite time blow-up have been achieved. We summarize known results for the PKS model and for alternative models in this Introduction.

Whereas the PKS model is based on diffusion, another class of models is based on correlated random walk assumptions, which lead to nonlinear transport equations. The main part of this text focuses on transport models for chemosensitive movement. Two methods will be presented which allow the reduction of the transport equations to simpler models. From a multi scale analysis we obtain diffusion based models. We will explain that transport models are based on the individual movement behavior whereas diffusion models are population models. The question of individual versus collective translates into the connection of transport models to diffusion based models.

Another technique to reduce a full kinetic transport model is the moment closure method. The moment closure leads to hyperbolic sub-models. In the two-moment case the reduced models depend on Cattaneo's law of heat conduction. We will illustrate the moment closure method in Section 5.

The topics chosen for presentation here are subject to my own preferences. I include a number of references which enable the reader to find more information on all the topics which are only briefly discussed here.

In Section 2, the biology of chemosensitive movement is explained and the classical PKS-model is introduced. In Section 3, a hyperbolic model for chemosensitive movement in one space dimension will be presented, which is based on a correlated, biased random walk. Section 4 gives a complete picture of transport models for chemosensitive movement and it illustrates the *parabolic scaling.* The classical PKS-model appears in appropriately chosen limits. In Section 5 we discuss the moment closure approach and we derive a Cattaneo model for chemosensitive movement. Before we consider chemosensitive movement, we recall some known facts about transport equations:

1.1. *Velocity Jump Processes and Transport Equations*

As observed in experiments with (see e.g. Adler [1], Dahlquist, Lovely, Koshland [18], or Berg and Brown [9]), bacteria have a characteristic movement behavior. They move in a certain direction with an almost constant speed (run). Suddenly they stop and choose a new direction (tumble) to continue movement. The tumbling intervals are short compared to the mean run times. This type of individual movement pattern can be modeled by a stochastic process which is called a *velocity jump process* (see Stroock [87]). The characteristic parameters are mean runtime, turning distribution and mean speed. Stroock showed how a transport equation (see (1.1) below) for the spatial distribution of one particle can be derived from such a velocity jump process.

In Hillen and Othmer [42,70] the transport model (1.1) has been studied systematically with respect to different forms of biases; possible limit equations (of PKS-type) and relations between the relevant parameters have been considered. Let $p(t,x,v)$ denote the population density at time $t \geq 0$ at spatial position $x \in \mathbb{R}^n$ with velocity $v \in \mathbb{R}^n$. Most important are space dimensions of $n = 1,2,3$, the theory, however, works for all $n \in \mathbb{N}$. We assume that individuals choose any direction with bounded velocity. We denote the set of possible velocities as V, where we assume $V \subset \mathbb{R}^n$ 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 [87] or Othmer *et al.* [69]) reads

$$\frac{\partial}{\partial t} p(t,x,v) + v \cdot \nabla p(t,x,v) = -\mu p(t,x,v) + \mu \int T(v,v') p(t,x,v') dv', \qquad (1.1)$$

where μ is the turning rate or turning frequency, hence $\tau = \frac{1}{\mu}$ is the mean run time and $T(v,v')$ is the probability kernel for the new velocity v given the previous velocity was v'. Of course

$$\int T(v,v')dv = 1$$

to ensure particle conservation.

From a mathematical point of view the use of transport models for populations is not rigorously justified. The transport model has been derived for a one-particle distribution function (Stroock [87]). If individuals move independently, transport models are still suitable. If, however, there are correlations between individuals, which might come from birth-death interactions or from alignment or chemosensitive movement, then the verification of transport models from stochastic processes, even in 1-D, has still to be carried out mathematically. This is an ongoing field of mathematical research. The same holds for diffusion based models.

In a special case of movement in one space dimension, with constant speed γ and constant turning rate μ we obtain the Goldstein-Kac model for correlated random walk ([30], [51]). It is assumed that the total population density $u(t,x)$ can be split into densities for right/left moving part of the population, $u^{\pm}$, respectively. Of course $u = u^+ + u^-$. The Goldstein-Kac model for this correlated random walk reads:

$$\begin{array}{rcl} u_t^+ + \gamma u_x^+ & = & \frac{\mu}{2}(u^- - u^+) \\ u_t^- - \gamma u_x^- & = & \frac{\mu}{2}(u^+ - u^-), \end{array} \tag{1.2}$$

where lower case indices denote partial derivatives with respect to that variable. This model is a special case of (1.1) for two velocities $v \in \{\pm\gamma\}$ in one space dimension and with $T(v,v') \equiv \frac{1}{2}$.

In terms of the total population density u and the population flow $v = u^+ - u^-$, system (1.2) is equivalent to

$$\begin{array}{rcl} u_t + \gamma v_x & = & 0 \\ v_t + \gamma u_x & = & -\mu v. \end{array} \tag{1.3}$$

Using *Kac's trick* we obtain an equation for u alone: Differentiate the first equation with respect to time and the second equation with respect to space and eliminate the v-variable. Then u satisfies a *telegraph equation*

$$\frac{1}{\mu}u_{tt} + u_t = \frac{\gamma^2}{\mu}u_{xx}. \tag{1.4}$$

A diffusion equation $u_t = Du_{xx}$ follows formally by considering a limit of high turning rates $\mu \to \infty$ and large speed $\gamma \to \infty$ in such a way that

$$D = \lim \frac{\gamma^2}{\mu} < \infty.$$

This special scaling is called a *parabolic limit.* It can be shown that a time and space scaling of $\tau = \varepsilon^2 t$ and $\xi = \varepsilon x$ with fixed γ, μ leads to the same limit for $\varepsilon \to 0$ ([42]).

To model birth and death processes for a randomly spreading population usually reaction-diffusion models are studied (see e.g. Murray [62]). Similarly for transport models we obtain *reaction-transport models.* Depending on the situation at hand reactions may depend on the actual velocity of the particles, hence a nonlinear reaction-transport equation reads ([35])

$$p_t + v \cdot \nabla p = -\mu p + \mu \int T(v,v')p(t,x,v')dv' + f(v,p,m^0), \tag{1.5}$$

where the total population density is denoted as

$$m^0(t,x) = \int_V p(t,x,v)\,dv. \tag{1.6}$$

Reaction-transport models of this form have been studied by Hadeler [36,37] and by Schwetlick [80,81]. In [41] we assume that individuals give birth at rest only. In the parabolic limit a reaction-diffusion model follows with effective birth and death rates.

2. Chemosensitive Movement

The movement behavior of most species is guided by external signals: amoeba move along chemical gradients, insects orient towards light sources, the smell of a sexual partner makes it favorable to choose a certain direction. Some species are able to extract directed information from their surrounding (e.g. gradient of a chemical) others are too small to sense chemical gradients and they turn more often, when they move in an unfavorable direction. Both behaviors lead to orientation towards the source of a chemical, but the mechanisms have been distinguished into chemotaxis – for directed movement – and chemokinesis – for undirected movement – (see [4], p.516). If the movement is towards or away from the source of stimulus we call it *positive or negative bias*, respectively.

The distinction of chemotaxis versus chemokinesis is not at all straightforward and we denote responses to chemical stimuli in general by *chemosensitive movement.* This includes chemokinesis, chemotaxis and responses to non-local information as well. Some of the most studied species for chemosensitive movement are bacteria (e.g. *E. coli*), slime molds (e.g. *Dictyostelium discoideum*), or leukocytes.

2.1. *The Classical Patlak-Keller-Segel Model*

The earliest model for chemosensitive movement has been developed by Patlak [74] and Keller and Segel [53]. Here we give a brief derivation of the PKS model. We assume that in the absence of any external signal the spread of a population density $u(t,x)$ is described by the diffusion equation

$$u_t = d\Delta u, \tag{2.7}$$

where $d > 0$ is the diffusion constant. We define the net flux as $j = -d\nabla u$. If there is some external signal S we just assume that it results in a *chemotactic velocity* β.

Then the flux is

$$j = -d\nabla u + \beta u.$$

To be more specific, we assume that the chemotactic velocity β has the direction of the gradient ∇S and that the *sensitivity* χ to the gradient depends on the signal concentration $S(t,x)$. Then

$$\beta = \chi(S)\nabla S.$$

We use this modified flux in (2.7) to obtain the *parabolic chemotaxis equation*

$$u_t = \nabla(d\nabla u - \chi(S)\nabla S u). \tag{2.8}$$

If $\chi(S)$ is positive, which means that the chemotactic velocity is in direction of the gradient, we call it *positive bias*, whereas $\chi < 0$ is called *negative bias*.

Depending on the species at hand, the external signal is produced by the individuals and decays, which is described by a nonlinear function $f(S,u)$. We assume that the spatial spread of the external signal is driven by diffusion. Then the full system for u and S reads

$$\begin{aligned} u_t &= \nabla(d\nabla u - u\chi(S)\nabla S), \\ \tau S_t &= \alpha\Delta S + f(S,u). \end{aligned} \tag{2.9}$$

The time constant $0 \leq \tau \leq 1$ indicates that the spatial spread of the organisms u and the signal S are on different time scales. The case of $\tau = 0$ corresponds to a quasi-steady state assumption for the signal distribution.

This system has first been derived by Patlak [74] from a position jump process. Since the early work of Patlak is difficult to read, model (2.9) has become well known as the Keller-Segel model for chemotaxis. Here we presented the derivation of Keller and Segel [53] for (2.9).

The PKS model has been used in many applications to study aggregation or pattern formation (see e.g. Murray [62], Okubo [68], Keller and Segel [54]). The model has been criticized, though. First, the movement process of the population is modeled by diffusion. However, 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 is not a Brownian motion, it is a velocity jump process, as described earlier. Second, the diffusion terms in (2.9) allow for infinite fast propagation of information, which is an undesired property. Finally, the relevant parameters like diffusion constants d, α 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. Tranquillo [4], Segel [82] or Ford [27]). In this context, it is useful to study alternative models, like hyperbolic equations and transport models (see the following sections).

As we have shown in [42] the parabolic system (2.9) describes the long time asymptotics of solutions of transport models ([61], [42]). This means that if we wait long enough the description of an experiment with (2.9) is as good as a description with a transport model. This explains the success of parabolic models so far.

2.2. *Theoretical Results on the PKS Model*

Since the PKS model is designed to describe the behavior of bacteria and bacteria aggregates, the question arises whether or not this model is able to show aggregation. Intensive theoretical research uncovered exact conditions for aggregations and for blow up (see e.g. Childress and Percus [17,16], Jäger and Luckhaus [49], Nagai [63], Gajewski and Zacharias [28], Senba [83], Rascle and Ziti [77], Herrero and Velazquez [39,38], Othmer and Stevens [72] or Levine and Sleeman [57]). Following the definitions given in Othmer and Stevens, *aggregation* denotes a global existing solution which has a unique global maximum, whereas *blow up* denotes a solution with a maximum that grows to infinity in finite time. After blow up has occurred the model is no longer appropriate. That is the reason that several authors denote the blow up scenario with *chemotactic collapse*.

The possibility of blow-up has been shown to depend strongly on space dimension. For $\chi = const.$ and linear reproduction, $f(u,S) = \gamma u - \delta S$, finite time blow-up never occurs in 1-D (unless there is no diffusion of the attractant, S), but can always occur in n-D for $n \geq 3$. The 2-D case is ambiguous and thresholds θ_{rad} for radially symmetric solutions and $\theta_{\text{dom}} = \theta_{\text{rad}}/2$ for solutions in smooth domains have been found. If the initial distribution exceeds its threshold, then the solution blows up in finite time. When the initial mass is below its threshold, the solution exists globally. An interior blow up point is supported by a mass of exactly θ_{rad}, a boundary blow up has half of this mass. Horstmann considers the case, where the total mass is in-between these thresholds. He shows that in these cases blow up occurs only at the boundary [48,47]. Senba and Suzuki [84] consider stationary solutions and they use the above thresholds to estimate the number of blow-up points. The number of possible blow-up points is limited by the total mass divided by θ_{dom}.

Global existence below these thresholds has been proven using a Lyapunov functional in Gajewski, Zacharias [28], Nagai, Senba and Yoshida [66] and Biler [10]. The Lyapunov technique has been generalized to obtain similar thresholds for chemotactic sensitivities $\chi(S)$ given by a primitive $\phi(S) = \int \chi(S)$ which is *strictly sub-linear* (see [11]). This includes functional forms of $\phi(S) = \log S, \phi(S) = S^p$, for $0 < p < 1$ or equally bounded functions $\phi(S)$ (see Nagai *et al.* [67,64,65], Biler [11]). Post [76] considers chemotactic velocities with saturation in S and linear in u. Using a modification of the Lyapunov function from [28], global existence of solutions was shown. Horstmann [46] gave sufficient conditions for reaction-diffusion systems in general, such that a Lyapunov function of the above form exists.

A version of the PKS model, that allows for global existence in any space dimension, has been discussed in [43]. There we assume that the individuals sense the local cell density (e.g. E.coli releases a *quorum sensing molecule*), and the chemotactic sensitivity is reduced or vanishes at high population densities.

3. Hyperbolic Models in 1-D

It is fairly useful to study models for chemosensitive movement in one space dimension first. This provides good insights into basic phenomena, which also become important in 2 or 3 dimensions. Furthermore, some experimental situations can be formally reduced to a one dimensional problem, e.g. experiments in a cylindrical test chamber where the medium is homogeneous in each cross section (see Chen, Ford, Cummings [14]).

Due to recent experiments by e.g. Soll and Wessels [86] or Fisher *et al.* [24] and others [55,8] it turned out that, in general, the speed and the turning rates of individuals depend not only on the magnitude of an external signal $S(t,x)$ but on temporal and spatial variations $S_t(t,x)$ and $S_x(t,x)$ as well. Depending on the situation at hand, the signal can be produced and decay in time. This will be described by a function $f(S, u^+ + u^-)$. Then a modification of the Goldstein-Kac model (1.2) gives the following hyperbolic model for chemosensitive movement in one space dimension:

$$\begin{aligned} u_t^+ + (\gamma(S,S_t,S_x)u^+)_x &= -\mu^+(S,S_t,S_x)u^+ + \mu^-(S,S_t,S_x)u^-, \\ u_t^- - (\gamma(S,S_t,S_x)u^-)_x &= \mu^+(S,S_t,S_x)u^+ - \mu^-(S,S_t,S_x)u^-, \\ \tau S_t &= \alpha S_{xx} + f(S, u^+ + u^-)\ ,\ \tau \geq 0, \\ u^\pm(0,.) = u_0^\pm, \qquad & S(0,.) = S_0. \end{aligned} \tag{3.10}$$

Here the rates $\mu^\pm$ are turning rates, whereas in (1.2) μ is a stopping rate and each direction will be chosen with probability of 0.5.

Segel [82] has considered a hyperbolic model of type (3.10) without the equation for S. He studied a given increasing attractant concentration and constant particle speed γ, constant turning rate μ^-, and μ^+ depending on the gradient of S in characteristic direction. The external stimulus S is assumed to decay with a constant rate. His model has been used by Rivero *et al.* [78] to describe experiments with flagellated bacteria and with *leukocytes*. Greenberg and Alt [32] consider the special case of (3.10), where the speed is constant, with special choice of the turning rates, and f is linear. They pose the problem of existence of solutions for their hyperbolic model and use it to motivate a non local PKS model. The hyperbolic model proposed in (3.10) allows more general dependencies in the turning rates and the velocity, and it compares with the experiments of Soll ([85]). Chen *et al.* [15,14] considered a model of the above type to describe experimental data for the movement of *E. coli* bacteria. In their model the bacterial speed is close to constant and the turning frequency depends on the temporal gradient of the external signal. Consequently, the bacteria "feel" spatial gradients by moving through them. The model is put into relation with a one dimensional projection of a 3-D model by Alt [3], which we discuss later. The connection of the hyperbolic model (3.10) to the PKS model ([53]) opens a wide field of interesting questions concerning scaling and modeling of crucial parameters. Some of them have been answered in [42,70]. For the special case of constant speed and for turning rates depending on S and S_x we have proven local and global existence of solutions in L^∞ in [45]. To achieve an abstract existence result for dependence on S_t a more detailed analysis is required. Without S_t dependence the preservation of total population size is sufficient to show existence of weak solutions in L^∞. To control S_t stronger pre-assumptions are required. If the speed depends on S or its gradients we expect the formation of steep gradients. This case has been considered in [44]. There we showed global in time existence for $\gamma = \gamma(S)$, where we assumed that the signal distribution is in quasi-equilibrium ($\tau = 0$). Then, with a vanishing-viscosity method we obtain local and global existence.

3.1. *The Parabolic Limit in 1-D*

In this section we consider the parabolic limit for the hyperbolic model for chemosensitive movement (3.10). The mathematical details are presented in [45]. One first derives an equivalent system for $u = u^+ + u^-$ and $v = u^+ - u^-$. From this a general telegraph equation (1.4) can be derived. The resulting telegraph equation is independent of v only if we assume that the auxiliary function

$$h(t) := \mu^+(S, S_t, S_x) + \mu^-(S, S_t, S_x) - \frac{\gamma_t(S, S_t, S_x)}{\gamma(S, S_t, S_x)} \tag{3.11}$$

does not depend on the spatial position x. Of course this is a restriction to the parameters $\mu^\pm, \gamma$ which, however, is satisfied for many examples. We give examples in the next subsection.

Since here γ and $\mu^\pm$ are functions of $S(t,x)$ we can not just pass to the limit of $\gamma, \mu^\pm \to \infty$. We introduce an additional dimensionless small parameter $\varepsilon > 0$ and set

$$\gamma = \frac{\gamma_0}{\varepsilon}, \quad \text{and} \quad \mu^\pm = \frac{\mu_0^\pm}{\varepsilon^2}, \tag{3.12}$$

where γ_0 and $\mu_0^\pm$ are of order 1 with respect to ε. Then the auxiliary function h scales as

$$h(t) = \frac{h_0(t)}{\varepsilon^2}, \qquad \text{with} \quad h_0 = \mu_0^+ + \mu_0^- - \varepsilon^2 \frac{\gamma_{0,t}}{\gamma_0} \tag{3.13}$$

and for $\varepsilon \to 0$ we obtain

$$D = \lim_{\varepsilon \to 0} \frac{\gamma^2}{h(t)} = \frac{\gamma_0^2}{\mu_0^+ + \mu_0^-}. \tag{3.14}$$

We introduce this scaling in the corresponding telegraph equation (see [45] for details) and for $\varepsilon \to 0$ we formally obtain the following limit equation of PKS type:

$$u_t = \left(D u_x - \chi u S_x\right)_x,$$

with a diffusion parameter given by (3.14) and chemotactic sensitivity χ given by

$$\chi S_x = -\frac{\gamma_0}{\mu_0^+ + \mu_0^-} \left(\gamma_{0,x} + \lim_{\varepsilon \to 0} \frac{1}{\varepsilon} (\mu_0^+ - \mu_0^-) \right). \tag{3.15}$$

This relation in a special case has also been found by Rivero *et al.* [78] and Segel [82].

Since the chemotactic sensitivity consists of two terms, we can identify two effects which lead to positive or negative biases.

1. We consider $\gamma = \gamma(S) \geq 0$ and we assume, 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

   $$\chi S_x = -\frac{\gamma_0}{\mu_0^+ + \mu_0^-}\gamma_0' S_x \tag{3.16}$$

   and the limiting equation for chemosensitive movement reads

   $$u_t = \left(\frac{\gamma_0}{\mu_0^+ + \mu_0^-}\left(\gamma_0 u_x + \gamma_0' S_x u\right)\right)_x . \tag{3.17}$$

   If $\gamma'(S) < 0$, which means that the population slows down at high concentrations of S, then a net flow of the population in the direction of higher concentrations of S follows, which is a positive bias.

   If $\gamma'(S) > 0$, which means that higher concentrations of S enhance the speed, then the population has a stronger tendency to spread out, as compared to simple diffusion. This causes a negative bias. Hence the population glides in the direction of decreasing concentrations of S.

2. Now we assume that $\gamma = const.$ and that the difference in turning has an expansion as

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

   with appropriate functions $\varphi_1(S, S_t, S_x), \varphi_2(S, S_t, S_x)$. This means $\mu_0^+ - \mu_0^- = \varepsilon\varphi_1 + \varepsilon^2\varphi_2$. Then the chemotactic sensitivity is given by

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

   Moreover, if we assume linearity in S_x, e.g. $\varphi_1 = \varphi_0(S)S_x$ then a PKS model follows

   $$u_t = \left(\frac{\gamma_0^2}{\mu_0^+ + \mu_0^-}u_x + \frac{\gamma_0}{\mu_0^+ + \mu_0^-}\varphi_0(S)S_x u\right)_x . \tag{3.18}$$

   Here, the swarming or aggregation behavior depends exactly on the sign of the difference between the turning frequencies.

   If $S_x > 0$ and $\varphi_0 < 0$, then the right moving population, which is moving up the gradient, turns less often than the left moving one, which is moving down the gradient. This is the basic behavior also observed in experiments with bacteria.

   If $S_x > 0$ and $\varphi_0 > 0$, then the right moving population, which is moving up the gradient again, turns more often than the left moving one. This behavior enhances the spreading out of the total population.

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 [79] in a similar one-dimensional hyperbolic model for bacterial movement, where memory effects have been included.

4. Transport Models

In Stroock [87] and in Keller [52] a transport equation has first been proposed for bacterial chemotaxis. Soll and Voss (in [86]) showed how the movement rules of "run" and "tumble" can also be applied to movement behavior of slime mold amoeba like *Dictyostelium discoideum.* W. Alt studied a transport equation for amoeba-chemotaxis in two papers [2,3]. He assumed specific movement and signal detection rules and he used the run length as another state variable. In the case of constant run length the model of Stroock or Keller follows from Alt's transport equation. Alt uses singular perturbation methods to derive a diffusion equation of PKS-type. In Othmer, Dunbar and Alt [69] different forms of random movement for biological species are compared; position jump processes, velocity jump processes and diffusion models. Chen *et al.* [15] study perturbation expansions and projections of Alt's equation, which reduce to a special case of the one dimensional hyperbolic model for chemosensitive movement discussed above (3.10). Grünbaum [33] generalized Stroock's model to incorporate internal dynamics. Then the chemical network of signal recognition, transduction pathway and adaptation processes can be incorporated into the model. His analysis is based on specific scaling assumptions, but the mathematical methods need further justifications. An overview of results and known facts related to internal dynamics and chemical pathways is presented in a survey article of Othmer and Schaap [71]. Dickinson and Tranquillo [21] and Dickinson [20] study perturbation expansions of a stochastic velocity jump process with external bias due to chemotaxis. We will compare their results to the results of [42,70] later in a discussion section.

The diffusion approximation of transport models is a well known technique in many physical applications. We will summerize known results from neutron transport, kinetic theory of gases, radiation transport and stochastic processes in Section 4.5. For a detailed comparison it is better to first present the methods we used in [42,70].

In the case of chemosensitive movement in (1.1) the turning rate μ and the velocity distribution kernel $T(v,v')$ may depend on the signal distribution $S(t,x)$, its gradient $\nabla S(t,x)$ or on other properties of S (e.g. non-local dependence can be included).

$$\mu = \mu(S, \nabla S, \ldots), \quad T(v,v') = T(v,v',S,\nabla S,\ldots) \tag{4.19}$$

There are many experimental data available, where the dependence of turning rates μ and velocity distribution T on concentrations, spatial gradients or temporal variations have been measured (e.g. Berg and Brown [8], Soll and Wessels [85,86], Fisher, Merkl, Gerisch [24], Tani and Naitoh [88], Vicker [89], Macnab [58] to name but a few).

See also the Dicty-home-page: `http://dicty.cmb.nwu.edu/dicty/dicty.html`.

In [42,70] we consider general transport models for chemosensitive movement based on (1.1) and (4.19). A theory has been derived to generate a diffusion limit from a multi-scale analysis, which generalized the work of Alt [2,3]. The long time asymptotics of solutions of the transport model for chemosensitive movement are given in certain situations by a PKS-model. With this analysis a very natural connection of the parameters of the transport model (turning rate μ, velocity distribution T) to the parameters of the PKS-model (motility d, chemotactic sensitivity χ) has been found. We recall the main results of [42,70] here:

4.1. *Basic Assumptions (T1)-(T4)*

In [42] the linear transport equation (1.1) is considered in $\Omega = \mathbb{R}^n$. It is assumed that the set of velocities $V \subset \mathbb{R}^n$ is compact and symmetric such that $v \in V$ implies $-v \in V$. Let $\mathcal{K}$ denote the cone of non-negative functions in $L^2(V)$. Define the following operators on $L^2(V)$:

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

where I denotes the identity. We state the following assumptions on the kernel T.

(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 exist 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

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

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

The turning operator has the following properties:

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

1. 0 *is a simple eigenvalue of* $\mathcal{L}$ *with eigenfunction* $\phi(v) \equiv 1$.
2. *There exist 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*

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

The proof is given in [42]. In (T1) we state 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 [56]. There exists a unique positive eigenfunction $\phi(v) = 1$. The assumption (T2) allows us 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. With assumption (T4) we obtain the orthogonal decomposition of $L^2(V)$. Property (T3) represents the dissipative character of the transport model and this condition becomes important to show that the limit equation, which we will derive, indeed is parabolic.

4.2. *The Parabolic Scaling*

For some species (e.g. for *E.coli*) it appears that per unit of time there are many directional changes with a small net displacement. This behavior can be classified into three time scales: the *mean run time* $1/\mu$, the *drift-time scale* of about 100 individual turns and a *diffusion-time scale* of about 10000 individual turns. These scales can be modeled using the *parabolic scaling*

$$\tau = \varepsilon^2 t \quad \text{and} \quad \xi = \varepsilon x \tag{4.20}$$

for a small parameter ε ($\sim 10^{-2}$). We transform equation (1.1) accordingly, which gives

$$\varepsilon^2 p_\tau + \varepsilon v \cdot \nabla_\xi p = \mathcal{L}p. \tag{4.21}$$

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

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

We collect terms of equal order in ε:

$$\begin{aligned} \varepsilon^0 : &\qquad 0 = \mathcal{L}p_0, \\ \varepsilon^1 : &\qquad v \cdot \nabla p_0 = \mathcal{L}p_1, \\ \varepsilon^2 : &\qquad p_{0\tau} + v \cdot \nabla p_1 = \mathcal{L}p_2, \end{aligned} \tag{4.22}$$

where we omitted the subscript ξ on the nabla operator. We use the spectral properties of $\mathcal{L}$, as summarized in Theorem 1. It follows from the order one equation that $p_0 = p_0(\tau, \xi)$. 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

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

This leads, with use of the representation of p_1, to the following partial differential equation:

$$p_{0,\tau} = \nabla \cdot D \nabla p_0, \qquad p_0(\xi, 0) = \int_V p(\xi, v, 0) dv, \tag{4.23}$$

$$\text{with diffusion tensor} \qquad D \equiv -\frac{1}{\omega} \int_V v \mathcal{F} v^T \, dv. \tag{4.24}$$

The procedure can be continued to higher orders in ε and as shown in [42], the residuum of this approximation can be controlled:

Theorem 2 *Let* (T1)-(T4) *be true and let $\mathcal{F}$ denote the pseudo inverse from Theorem 1. For $k > 2$ we define a sequence of functions $p_0(\xi, \tau)$, $p_1(\xi, v, \tau)$, ..., $p_k(\xi, v, \tau)$ as follows:*

(*a*1) p_0 *solves the* **parabolic limit equation (4.23)**

(*a*2) *for each* $1 \leq j \leq k$ *let* $\int_V p_j(\xi, v, \tau) dv = 0$.

(*a*3) *for each* $2 \leq j \leq k$ *let* $\int_V v \, p_j(\xi, v, \tau) dv = 0$.

(*a*4) $p_1(\xi, v, \tau) := \mathcal{F}(v \cdot \nabla p_0(\xi, \tau))$.

(*a*5) $p_j(\xi, v, \tau) := \mathcal{F}(p_{j-2,\tau} + v \cdot \nabla p_{j-1})$, *für* $2 \leq j \leq k$.

Then for each $\vartheta > 0$ there is a constant $C_0 > 0$ with the property that the sum

$$q_k := \sum_{j=0}^{k} \varepsilon^j p_j$$

satisfies

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

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

Hence the asymptotic behavior of solutions of (1.1) is described by the diffusion equation in (a1). The proof of this result uses an induction argument. In particular property (T3) is important to show that the limit equation in (a1) is parabolic.

4.3. *The Diffusion Tensor D*

In (4.24) we found that in general diffusion is non isotropic, hence D is a tensor. We will show under which conditions this tensor is isotropic, i.e. it is a scalar multiple of the identity. We define the *expected velocity*

$$\bar{v}(v) \equiv \int T(v,v')v'dv'. \tag{4.25}$$

With assumption (T1) it follows that $\int_V \bar{v}(v)dv = 0$. Moreover, we assume that V is symmetric with respect to $SO(n)$. Then there exists a constant K_V such that

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

(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 $K_V = \omega_0 s^2/n$.

We compare three statements:

(S1): *There is an orthonormal basis* $\{e_1,\dots,e_n\}$ *of* $\mathbb{R}^n$ *such that for each* $i = 1,\dots,n$ *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*

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

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

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

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

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 proven in [42].

If T has the symmetric form of $T(v,v') = t(|v-v'|)$ then the diffusion limit is isotropic (see also Alt [2]). We will give an example for non-isotropic diffusion in the next setcion.

4.4. *Application to Chemosensitive Movement*

Let T_0 and μ_0 denote turning kernel and turning rate in absence of any chemical substance. In [70] 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 [70] and we prefer to 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: To get used to the method and the notations we start with a simple biased random walk without chemical signal. We assume that the probability of a change of velocity v' to v depends on the angle between these two velocities.

$$T_1(v,v') = \frac{1}{\omega}\left(1 + \frac{a}{s^2}(v \cdot v')\right) \quad \text{with} \quad a < n. \tag{4.26}$$

It is easy to check that the *expected velocity* is

$$\bar{v}(v) := \int v' T_1(v,v')dv' = \frac{a}{n}v. \tag{4.27}$$

The factor $\frac{a}{n} = \psi_d$ is denoted as persistence index (see Othmer *et al.* [69]). Theorem 3 applies and the first order approximation $p_0(\tau,\xi)$ fulfills the isotropic diffusion equation

$$\frac{\partial}{\partial \tau} p_0 = d\Delta p_0, \quad \text{with} \quad d = \frac{s^2}{\mu(n-a)}. \tag{4.28}$$

The case of $a = 0$ corresponds to random walk without persistence and the corresponding diffusion constant is

$$d = \frac{s^2}{\mu n}. \tag{4.29}$$

We have checked that a perturbation of lower order $T(v,v') = \frac{1}{\omega}(1 + \varepsilon\frac{a}{s^2}(v \cdot v'))$ does not affect the limit equation at all and (4.28) results with (4.29).

Now we consider chemosensitive movement. Note that Theorem 2 applies to Example 5, but not to the other following examples. Nevertheless, the formal derivation of the limit equation, as illustrated in (4.21)-(4.24) works for all of the following cases.

Example 2: Here we consider chemosensitive movement and we assume that an individual actively chooses directions upward chemical gradients (positive taxis). Then the angle of new velocity v and signal gradient ∇S is an important variable and we assume

$$T_2(v, v', S) = \frac{1}{\omega}(1 + \varepsilon a(S)(v \cdot \nabla S)). \tag{4.30}$$

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

$$\frac{\partial}{\partial \tau} p_0 = \nabla \Big(d \nabla p_0 - p_0 \chi(S) \nabla S \Big) \tag{4.31}$$

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 appears to be independent of signal gradients. But the turning rate increases if individuals move down the gradient and it decreases if they move upwards (chemokinesis). Hence we assume $T(v, v') = \frac{1}{\omega}$ and

$$\mu_2(S) = \mu_0(1 - \varepsilon b(S)(v \cdot \nabla S)). \tag{4.32}$$

Then a PKS-model follows

$$\frac{\partial}{\partial \tau} p_0 = \nabla \Big(d \nabla p_0 - \chi(S) p_0 \nabla S \Big) \tag{4.33}$$

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 ([27,26,25,12]). We illustrated the details in [70].

Example 4 (Amoeba): If we consider amoebae-chemotaxis we obtain both change of turning rate as in Example 3 and the active choice of preferred directions as modeled in Example 2. A combination of both

$$T_4(v, v') = T_2(v, v'), \qquad \mu_4(S) = \mu_2(S)$$

just leads to additional effects in the chemotaxis term

$$\chi(S) = \frac{s^2}{n}(a(S) + b(S)). \tag{4.34}$$

This case is also covered by the results of Patlak [74] and of Alt [2].

For general situations it turned out in [42],[70] that the diffusion limit is non isotropic. We give one example.

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 towards this stream we choose the turning kernel

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

If the actual direction v' is in the direction η or $-\eta$, then there is an increased probability to choose a new velocity v in the 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

$$D(\xi, \tau) = \frac{s^2}{\lambda_0 n} \left(I + \frac{\omega s^2}{n} \kappa \eta \eta \left(I - \frac{\omega s^2}{n} \kappa \eta \eta \right)^{-1} \right).$$

The diffusivity in the direction η or $-\eta$ is enhanced, whereas it has the standard value $s^2/(\lambda_0 n)$ 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

$$\overset{\circ}{S}(x,t) = \frac{n}{\omega_0 R} \int_{S^{n-1}} \sigma \, S(x + R\sigma, t) \, d\sigma, \tag{4.35}$$

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 $\overset{\circ}{S}$ in exactly the same way as we used ∇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 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.

4.5. *Discussion of Diffusion Limits*

The approximation of a transport equation with its diffusion limit is a classical method in many physical applications. This ranges from the kinetic theory of gases and thermodynamics over neutron transport theory to radiation transport models. We will discuss the literature concerned with biological applications. The results of Alt [2,3] , Schnitzer [79], Chen *et al.* [15], Othmer, Dunbar, Alt [69] and Grünbaum [33] have been mentioned in the introduction of this Section 4.

Dickinson and Tranquillo [21] and Dickinson [20] divide the movement process of the population into three subprocesses, each characterized by its own time scale. *Locomotion*, the fastest time scale, describes inter-cellular pathways; *translocation* is the scale of individual movement and the slowest time scale, *migration* characterizes the movement of the whole population. The authors consider a stochastic process which includes linear transport, reorientations, diffusion in velocity and rotations. They use the method of *adiabatic elimination of fast variables* (see Gardiner [29]) to derive the corresponding Smoluchovski equation. The Smoluchovski equation is a drift-diffusion model, which depends on the scaling parameter. The method of Dickinson *et al.* differs from our approach presented here in many ways. The adiabatic scaling corresponds in our notation to a choice of $\tilde{\tau} = \varepsilon t, \xi = \varepsilon x$, which leads to a diffusion limit depending on ε. If one scales the time variable of the drift-diffusion limit accordingly ($\tau = \varepsilon\tilde{\tau}$) then the diffusion limit follows. On the other hand, a perturbation expansion in $(\tilde{\tau}, \xi)$, as done here, would lead to an elliptic limit equation (see [42]). The connection of the adiabatic scaling to the parabolic scaling has to be checked in more detail. It turns out that both methods are present in different areas of physical applications (see e.g. [5]).

Bellomo considers Boltzmann equations for applications in biology, such as tumor growth and epidemiology [7].

From a mathematical point of view there are estimates for the accuracy of the diffusion approximation. First of all, in a paper by Papanicolaou [73] the diffusion approximation of the backward transport equation has been studied and estimates have been derived. Similar results have been derived by many authors for different applications and we found a good summary in Dautray and Lions [19]. In Dautray and Lions a singular perturbation method has been used, which is based on the parabolic scaling. Estimates of the accuracy of the diffusion approximation include the initial layer as well.

The discussion of diffusion limits is also well known in the field of stochastic processes. The central limit theorem and Donsker's theorem for martingales refer to the property that under certain conditions a stochastic process approximates Brownian motion (see Durrett [23] for details).

In all of the above studies it turned out that they are not directly applicable to problems which come from biology. In the case of Boltzmann equations there is conservation of mass, momentum and energy, whereas for populations we have, at most, conservation of the total particle number. This translates into different functional analytic properties of the turning operator. The kernel of the turning operator for the Boltzmann equation is five dimensional, which corresponds to the Maxwellian distributions. The kernel for biological applications is one dimensional, which corresponds to particle conservation. In neutron transport theory, or in radiation transport, most authors consider a symmetric kernel. In the case of chemosensitive movement however, we find an anisotropy in the direction of the signal gradient. Other authors assume a strictly positive turning kernel, which we relaxed into condition (T2).

Overall, we think that the set of conditions given above, (T1)-(T4), represents a quite general and sufficient set of conditions such that the diffusion limit for biological applications can be obtained in a clear and transparent way.

5. The Moment Closure Method

One common feature in understanding the dynamic properties of reaction-transport equations and of Boltzmann equations are *moment methods*. By multiplication of (1.1) with powers of v and integration, one can derive an infinite sequence of equations for the v-moments of p. As a matter of fact, 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. [31] or [19]). 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 [60]). An entropy functional is maximized under the constraint of fixed first n moments. One assumes 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 [90].

In a biological context, the negative $L^2(V)$-norm can be seen as an entropy as defined in thermodynamics. We close the moment system by 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 [41] 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.

5.1. *Cattaneo's Law*

The Cattaneo system has the following form

$$\begin{aligned} u_t + \nabla v &= 0 \\ \tau v_t + d\nabla u + v &= 0, \end{aligned} \tag{5.36}$$

where $u(t,x) \in \mathbb{R}$ and $v(t,x) \in \mathbb{R}^n$ are functions of space $x \in \Omega \subset \mathbb{R}^n$ and time

$t \geq 0$. The diffusion constant d and the time constant τ are positive. There are two interpretations of this system. First, it appears to describe heat transport with finite speed, or heat transport in media with memory ([50,34]). Then u is the temperature and v is the heat flux. Second, it can be seen as a generalization of a correlated random walk ([35]). Then u is the population density and v the population flux. The Cattaneo law (second equation in (5.36)) has been used by Cattaneo [13] to describe heat transport with finite speed. It has been known to Maxwell [59], who cast out the time derivative, because it "*... may be neglected, as the rate of conduction will rapidly establish itself.*" For $\tau = 0$ Cattaneo's law becomes Fourier's law. For $\tau \neq 0$ the flux is not directly proportional to the temperature gradient, it adapts with a time constant of τ. The Cattaneo system directly leads to a damped wave equation

$$\tau u_{tt} + u = D\Delta u,$$

which for $\tau \to 0$ formally converges to the heat equation (see the review article of Joseph and Preziosi [50] on heat transport or Hillen [40] on the Cattaneo system). It can also be motivated in terms of heat propagation in media with memory (Gurtin and Pipkin [34]), where the influence of the past decays exponentially. This property is important for biological species, since memory and adaptation effects play a role in many sensory processes. In [41] we showed that the Cattaneo law appears as a gradient flux of an exponentially weighted Dirichlet integral.

The derivation of Cattaneo's model (refcattaneo), as presented in the next section, gives a new understanding of the role of the Cattaneo system in biological applications. Moreover, the relevant parameters are now related to the individual movement behavior of the underlying species.

5.2. *A Minimization Principle*

We consider a transport equation which corresponds to a velocity jump process with fixed speed, but variable direction (*Pearson walk* [75]). In this case $V = sS^{n-1}$ with $s > 0$ and we denote $\omega = |V| = s^{n-1}\omega_0$, where $\omega_0 = |S^{n-1}|$. The turn angle distribution is assumed to be constant $T(v, v') = \frac{1}{\omega}$. As presented in [41], the method developed here can be generalized to more general kernel T and more general velocity sets V. Here we illustrate the method on this particular case and we will apply it to a model for chemosensitive movement.

The initial value problem for the linear transport equation reads

$$p_t + v \cdot \nabla p = \mu \left(\frac{m^0}{\omega} - p \right), \tag{5.37}$$

$$p(0, x, v) = \varphi_0(x, v). \tag{5.38}$$

We will use the L^2-norm to carry out the moment closure. Hence, in this context it is natural to work in L^2 spaces. For other applications the L^1-theory is preferred, since the total particle number is preserved by the linear transport equation (see e.g. [6] for neutron transport). In [41] we proved the following H-Theorem:

Theorem 4

$$\frac{d}{dt}\|p(t,x,.)\|_2^2 + \partial_j \left(\int_V v^j\, p(t,x,.)^2 dv \right) \leq 0. \tag{5.39}$$

The velocity-moments of p are denoted by m^α, where m^0 is defined by (1.6) and the higher moments of p are denoted by

$$m^i(t,x) = \int_V v^i p(t,x,v)\, dv, \qquad i = 1, \dots, n \tag{5.40}$$

$$m^{ij}(t,x) = \int_V v^i v^j\, p(t,x,v)\, dv, \qquad i,j = 1, \dots, n. \tag{5.41}$$

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 (5.37) over V to obtain the conservation law

$$m_t^0 + \partial_j m^j = 0. \tag{5.42}$$

Multiplication of (5.37) with v^i and integration gives

$$m_t^i + \partial_j m^{ij} = -\mu m^i. \tag{5.43}$$

To close this system of two moment equations (5.42) and (5.43) 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. We showed in (5.39) that the negative of this norm is an entropy in the sense of thermodynamics. 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 $i = 1, \dots, n$ 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 [41] for details)

$$u_{\min}(t,x,v) = \frac{1}{\omega}\left(m^0(t,x) + \frac{n}{s^2}(v_i m^i(t,x)) \right). \tag{5.44}$$

Remark:

1. It turns out that $u_{\min}$ is the projection of p onto the linear subspace $\langle 1, v^1, \dots, v^n \rangle \subset L^2(V)$
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 (5.44). 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 with respect to every given level.

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

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

$$\begin{aligned} m^{ij}(u_{\min}) &= \int_V v^i v^j\, u_{\min}(t,x,v) dv \\ &= \frac{1}{\omega} \int_V v^i v^j\, m^0\, dv + \frac{n}{\omega s^2} \int_V v^i v^j v_k \, dv\, m^k \\ &= \frac{s^2}{n} m^0\, I, \end{aligned} \tag{5.45}$$

because the tensor $\int_V v^i v^j v_k\, dv$ vanishes due to symmetry of V.

We have chosen $u_{\min}$ such that $m^0(u) = m^0(p)$ and $m^i(u) = m^i(p)$. Now we close the system of the first two moments (5.42), (5.43) by assuming that $m^{ij}(u) \approx m^{ij}(p)$. Then, replacing m^{ij} in (5.43) together with (5.42) gives a linear Cattaneo system

$$\begin{aligned} M^0_t + \partial_j M^j &= 0, \\ M^i_t + \tfrac{s^2}{n} \partial_i M^0 &= -\mu M^i, \end{aligned} \tag{5.46}$$

with initial conditions

$$M^0(0,.) = m^0(0,.), \quad M^i(0,.) = m^i(0,.). \tag{5.47}$$

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 (5.46). 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 we define

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

and an energy

$$\mathsf{e}_s(r,q) := \frac{1}{2} \int_{\mathbb{R}^n} r^2 + \frac{n}{s^2}\, q^i q_i\, dx. \tag{5.48}$$

Then we proved in [41]

Theorem 5

$$\mathsf{e}_s(r(t,.), q(t,.)) \leq n b_n^2 \frac{s^2}{2\mu}\, \|\nabla_x m^0\|^2_{L^2([0,t]\times\mathbb{R}^n)}, \tag{5.49}$$

with an approporiate constant $b_n > 0$.

5.3. *A Chemotaxis Model with Density Control*

In [43] we studied a diffusion based model for chemosensitive movement where at high population densities the chemotaxis is turned off and pure diffusion dominates. Solutions exist globally and now blow-up occurs. The model of Hillen and Painter [43] can be constructed from a transport equation via a corresponding Cattaneo approximation. We 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*

$$\begin{aligned} M_t^0 + \partial_j M^j &= 0 \\ M_t^i + \tfrac{s^2}{n}\partial_i M^0 &= -\mu_0 \left(1 - \tfrac{n}{s^2}\beta(M^0)\chi(S)S_t\right) M^i + \beta(M^0)\chi(S)\, M^0\, \partial_i S. \end{aligned} \tag{5.50}$$

This model has been used in [22] to describe pattern formation in cellular slime molds and in bacteria. Moreover, a numerical scheme has been developed to solve (5.50).

5.4. *Higher Order Moment Closure*

The higher order moment closure requires severe bookkeeping of all the relevant tensor indices. Hence, we prefer to refer to [41] for details.

The H-Theorem (Theorem 4) of the previous section can be generalized to turning kernel 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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