THE DIFFUSION LIMIT OF TRANSPORT EQUATIONS II: CHEMOTAXIS EQUATIONS

HANS G. OTHMER* AND THOMAS HILLEN†

Key words. aggregation, chemotaxis equations, diffusion approximation, velocity jump processes, transport equations

Abstract.

In this paper we use the diffusion-limit expansion of transport equations developed earlier [23] to study the limiting equation under a variety of external biases imposed on the motion. When applied to chemotaxis or chemokinesis, these biases produce modification of the turning rate, the movement speed or the preferred direction of movement. Depending on the strength of the bias, it leads to anisotropic diffusion, to a drift term in the flux or to both, in the parabolic limit. We show that the classical chemotaxis equation - which we call the Patlak-Keller-Segel-Alt (PKSA) equation - only arises when the bias is sufficiently small. Using this general framework, we derive phenomenological models for chemotaxis of flagellated bacteria, of slime molds and of myxobacteria. We also show that certain results derived earlier for one-dimensional motion can easily be generalized to two- or three-dimensional motion as well.

1. Introduction.

The linear transport equation

$$\frac{\partial}{\partial t}p(x,v,t) + v\cdot\nabla p(x,v,t) = -\lambda p(x,v,t) + \int_V \lambda\, T(v,v')p(x,v',t)dv', \tag{1.1}$$

in which $p(x,v,t)$ represents the density of particles at spatial position $x \in \mathbb{R}^n$ moving with velocity $v \in V \subset \mathbb{R}^n$ at time $t \geq 0$, arises when the movement of biological organisms is modeled by a velocity-jump process [38]. Here the turning rate λ may be space- or velocity-dependent, but in other contexts it may also depend on internal variables that evolve in space and time, in which case (1.1) must be generalized. The turning kernel or turn angle distribution $T(v,v')$ gives the probability of a velocity jump from v' to v if a jump occurs: in general it may also be space-dependent or depend on internal variables. In the present formulation we assume that the 'decision' to turn as reflected in λ is not coupled to the 'choice' of direction, but in general it may be. When (1.1) is applied to the bacterium *E.coli*, the kernel T includes a bias, as described later, and the turning frequency must depend on the extracellular signal, as transduced through the signal transduction and motor control system. When (1.1) is applied to amoeboid cells such as *Dictyostelium discoideum* (Dd), which use both run length control and modulation of the turning kernel [15], both the kernel and the turning rate depend indirectly on the extracellular distribution of the signaling chemical.

In a previous paper [23] we analyzed the pure diffusion limit of (1.1), in which both the turning rate and the turning kernel are constant. Under some mild restrictions on the turning kernel T, the turning operator $\mathcal{T}$ (defined as the integral operator whose kernel is T) is positive in a suitable sense. The positivity guarantees that the turning operator has a single, dominant zero eigenvalue and the diffusion limit of the jump process exists. By employing the pseudo-inverse $\mathcal{F}$ of the operator $\mathcal{L}$ defined by the right-hand side of (1.1), we were able to (i) systematize the construction of the diffusion tensor, (ii) obtain a number of equivalent conditions on the turn angle distribution under which the diffusion matrix is a scalar multiple of the identity, (iii) show that in this case the diffusion constant depends on the second eigenvalue of the turning operator, and (iv) prove an estimate on the accuracy of the diffusion approximation and provide an algorithm for constructing solutions of arbitrary order in the perturbation parameter. In this paper we analyze the effect of external fields on the parabolic limit, and show how the classical chemotaxis equations arise under suitable conditions on the magnitude of the bias. In the following subsection we briefly describe various types of taxes that have been identified and discuss some of the previous mathematical models that lead to diffusion descriptions of these processes. We use the telegraph process and the resulting telegraph equation to illustrate the velocity jump process in one space dimension, and discuss conditions under which it leads to localization or aggregation in space. The remaining sections are devoted to

* Department of Mathematics, University of Minnnesota, Minneapolis, MN 55455 (`othmer @math.umn.edu`). This author's research was supported in part by NIH Grant #GM 29123 and by NSF Grant #DMS 9805494.

† Biomathematik, Universität Tübingen, Auf der Morgenstelle 10, D-72076 Tübingen (`hillen @uni-tuebingen.de`). This author's research was supported by the *DFG Schwerpunkt: ANumE.*

the analysis of the effects of bias in the turning rate or the turning kernel in any number of space dimensions. We consider several examples, some to illustrate the theory, and others related to specific examples. We give prototype models for chemotaxis of bacteria, of slime molds and of myxobacteria. One result of our analysis is to show that results previously derived for one space dimension [45, 17] can be extended to two or three dimensions with only minor changes. We also show how nonlocal dependence on the external signal can arise.

1.1. Chemotaxis. A variety of mechanisms have evolved by which living systems sense the environment in which they reside and respond to signals they detect, often by changing their patterns of movement. The movement response can entail changing the speed of movement and the frequency of turning, which is called *kinesis*, it may involve directed movement, which is called *taxis*, or it may involve a combination of these. Taxes and kineses may be characterized as positive or negative, depending on whether they lead to accumulation at high or low points of the external stimulus that triggers the motion. A variety of both modes are known, including responses to gradients of oxygen and other chemicals, gradients of adhesion to the substrate, and others. Tactic and kinetic responses both involve the detection of the external signal, and transduction of this signal into an internal signal that triggers the response. An important aspect of both modes of response from the modeling and analysis standpoint is whether or not the individual merely detects the signal or alters it as well. In the former case individuals simply respond to the spatio-temporal distribution of the signal, but when the individual produces or degrades the signal there is coupling between the local density of individuals and the evolution of the signal. An example of the latter occurs in Dd, where individuals aggregate in response to a signal from 'organizers' and relay the signal as well.

A major theoretical problem in the analysis of cell movement is whether, and if so how, cells can extract directional information from an extracellular field. The motion of flagellated bacteria such as *E. coli* has been studied for several decades and much is known about how they sense and process environmental signals [4, 3]. *E. coli* alternates two basic behavioral modes, a more or less linear motion called a run, and a highly erratic motion called tumbling, which produces little translocation but reorients the cell. During a run the bacteria move at approximately constant speed in the most recently chosen direction. Run times are typically much longer than the time spent tumbling, and when bacteria move in a favorable direction (*i.e.*, either in the direction of foodstuffs or away from harmful substances) the run times are increased further. In addition, these bacteria adapt to constant signal levels, and in effect only alter the run length in response to changes in extracellular signals. These bacteria are too small to detect spatial differences in the concentration of an attractant on the scale of a cell length, and during a tumble they simply choose a new direction essentially at random, although it has some bias in the direction of the preceding run [4, 3]. The effect of alternating these two modes of behavior, and in particular, of increasing the run length when moving in a favorable direction, is that a bacterium executes a three-dimensional random walk with drift in a favorable direction, when observed on a sufficiently long time scale [3, 32]. A model for signal transduction and adaptation in this system is given in [51], but at present such detailed models have not been incorporated into a description of population-level behavior. A phenomenological model that incorporates certain aspects of signal transduction is discussed later.

It is conceivable that larger amoeboid cells such as leukocytes or the cellular slime mold Dd are able to extract directional information from the extracellular field, with or without moving. In the case of Dd, the signal is cyclic AMP (cAMP), and since the cAMP distribution is a scalar field, directional information can only be obtained from this field by *effectively* taking measurements at two points in space. Experimental studies of Dd motion in a steady cAMP gradient show that cells combine taxis and kinesis, in that they move slightly faster when traveling up the gradient, they correct the direction of travel to approach the gradient direction, and they decrease the turning rate [15]. Fisher *et al.* [15] suggest that directional information is obtained by extension of pseudopods bearing cAMP receptors, and that sensing the temporal change experienced by a receptor is equivalent to sensing the spatial gradient. However Dd cells contain a cAMP-degrading enzyme on their surface, and it has been shown that as a result, the cAMP concentration increases in all directions normal to the cell surface [12]. Furthermore, more recent experiments show that cells in a steady gradient can polarize in the direction of the gradient without extending pseudopods [42]. Thus cells must rely entirely on differences in the signal across the cell body for orientation. A mechanism for how this might be done is suggested in [12, 9].

In the absence of an external signal, the movement of organisms released at a point in a uniform environment

can often be described as an uncorrelated, unbiased random walk of noninteracting particles on a sufficiently long time scale. In an appropriate continuum limit the cell density N, measured in units of cells/L^n, where L denotes length and n=1, 2 or 3, satisfies the diffusion equation

$$\frac{\partial N}{\partial t} = D\Delta N.$$

The cell flux is given by $j = -D\nabla N$, and if we define the average cell velocity u at time t at position x via the relation $j(x,t) = N(x,t)u(x,t)$, then we see that for pure diffusive spread

$$u = -D\frac{\nabla N}{N} = -D\nabla \ln N.$$

The simplest phenomenological description of chemotactic cell motion in the presence of an attractant or repellent is obtained by adding a directed component to the diffusive flux to obtain

$$j = -D\nabla N + Nu_c$$

where u_c is the macroscopic chemotactic velocity. The taxis is positive or negative according as u_c is parallel or anti-parallel to the direction of increase of the chemotactic substance. The resulting evolution equation is

$$\frac{\partial N}{\partial \tau} = \nabla \cdot (D\nabla N - Nu_c), \tag{1.2}$$

and this is called a chemotaxis equation. One often postulates a constitutive relation for the chemotactic velocity of the form

$$u_c = \chi(S)\nabla S, \tag{1.3}$$

where S is the concentration of the chemotactic substance and the function $\chi(S)$ is called the *chemotactic sensitivity*. When $\chi > 0$ the tactic component of the flux is in the direction of ∇S and the taxis is positive. With this postulate (1.2) can be written in the form

$$\frac{\partial N}{\partial \tau} = \nabla \cdot (D\nabla N - N\chi(S)\nabla S). \tag{1.4}$$

We call an equation of this type a classical chemotaxis equation, or as in [23], a PKSA equation (Patlak [44], Keller-Segel [30], Alt [1]). To obtain a complete model for the dynamics of a population and of the signal, the chemotaxis equation (1.4) has to be supplemented by another equation for the signal distribution. For that we assume that the signal diffuses with constant D_S and that production, degradation and consumption of the signal is described by a function $f(N,S)$. Then the equation for S is

$$\frac{\partial S}{\partial \tau} = D_S\Delta S + f(N,S). \tag{1.5}$$

We call the system (1.4), (1.5) a chemotaxis or PKSA system. The mathematical analysis of PKSA systems has grown rapidly in the last decade, and much is known about local and global existence and finite time blow up (see e.g. [27, 21, 35, 40, 6, 18, 24] and references therein).

A significant question in using equations such as (1.4) to describe chemotaxis is how one justifies the constitutive assumption (1.3), and in particular, how one incorporates microscopic responses of individual cells into population-level functions such as the chemotactic sensitivity χ. A number of phenomenological approaches to the derivation of the chemotactic sensitivity or chemotactic velocity have been taken. For example, Keller and Segel [30] postulated that the chemotactic velocity is given by (1.3) and in [31], related the chemotactic sensitivity to the frequency of reversals of a particle moving along the real line. Segel [48] incorporated receptor dynamics into the Keller-Segel model, and Pate and Othmer [43] derived the velocity in terms of forces exerted by the cell. Starting from Newton's law for the motion of a point particle, neglecting inertial effects, and assuming that the motive force exerted by a cell is a function of the attractant concentration, they showed how the chemotactic

sensitivity is related to the rate of change of the force with attractant concentration. In this formulation the dependence of the flux on the gradient of the attractant arises from the difference in the force exerted in different directions due to different attractant concentrations. Experimental support for the last approach comes from work of Varnum-Finney *et al.* [54], who show that in Dd as many pseudopods are produced down-gradient as up, but those up-gradient are more successful in generating cell movement.

Two major approaches have been used to relate the chemotactic velocity or sensitivity to a microscopic description of movement. In the first one begins with a lattice walk or space-jump process, either in discrete or continuous time, and postulates how the transition probabilities depend on the external signal. For a discrete time walk the chemotaxis equation is derived in the diffusion limit of this process, by letting the space step size h and the time step δt go to zero in such a way that the ratio $h^2/\delta t$ is a constant, namely D. A more general approach leads to a renewal equation, from which a partial differential equation is obtained by particular choices of the jump kernel and the waiting time distribution [38]. Another method, based on a continuous time reinforced random walk in which the walker modifies the transition probabilities of an interval for successive crossings, is developed in [40] for a single tactic substance, and in [41] for multiple substances.

However, an alternative stochastic process that may provide a more accurate representation of the motion of cells than the space-jump process is the velocity-jump process [38]. In this process the velocity, rather than the spatial position, changes by random jumps, and the probability density evolves according to (1.1). The prototypical organisms whose motion can be described as a velocity jump process are the flagellated bacteria such as *E. coli.*. The earliest derivation of the chemotactic sensitivity from a velocity jump process was done by Patlak [44], who used kinetic theory arguments to express u_c in terms of averages of the velocities and run times of individual cells. His formulation also led to a variable diffusion coefficient. Stroock [52] rigorously derived the corresponding backward transport equation from a one particle random walk and suggested possible applications to chemotaxis. Keller [29] also proposed the use of transport models to describe the phenomenon of bacterial aggregation. Alt [1, 2] derives equation (1.4) from a transport equation using a model for the motion of crawling cells and a number of specific assumptions. One aim of the work reported here is to generalize his results.

1.2. Aggregation and the parabolic limit in one space dimension. Organisms modulate their patterns of movement in response to external signals in order to move toward favorable environments or away from unfavorable ones. This is manifested at the population level by the development of nonuniform spatial distributions of the population density, and an important mathematical problem is to understand when the chemotaxis equations predict such solutions. Our main objective in this paper is to show how external biases affect the structure of the resulting chemotaxis equations for general turning operators, but we first wish to illustrate both the reduction to a parabolic equation and conditions on the turning rate and kernel that produce non constant solutions in the simplest possible context: the one-dimensional telegraph process. When the speed is constant the resulting model was first analyzed by Goldstein[20], and subsequently by many others [28, 34, 49, 38, 45, 26].

Suppose that the underlying space is one-dimensional, that a particle travels with speed $s^{\pm}(x)$ that depends on x and its direction of travel, and that at random instants of time it reverses direction. Assume that the "velocity-reversing" process is a Poisson process with intensities $\lambda^{\pm}$ that may depend on x and on the direction of travel. Let $p^{\pm}(x,t)$ be the probability density of particles that are at (x,t) and are moving to the right $(+)$ and left $(-)$. Then $p^{\pm}(x,t)$ satisfy the equations

$$\begin{aligned} \frac{\partial p^+}{\partial t} + \frac{\partial (s^+ p^+)}{\partial x} &= -\lambda^+ p^+ + \lambda^- p^- \\ \frac{\partial p^-}{\partial t} - \frac{\partial (s^- p^-)}{\partial x} &= \quad \lambda^+ p^+ - \lambda^- p^-. \end{aligned} \tag{1.6}$$

These equations are obtained from (1.1) when there are only two velocities and the speed and turning rate are functions of x and the direction of travel.

The probability density that a particle is at (x,t) is $p(x,t) \equiv p^+(x,t) + p^-(x,t)$, and the probability flux is

$j \equiv (s^+p^+ - s^-p^-)$. These quantities satisfy the equations

$$\frac{\partial p}{\partial t} + \frac{\partial j}{\partial x} = 0 \tag{1.7}$$

$$\frac{\partial j}{\partial t} + (\lambda^+ + \lambda^-)j = -s^+ \frac{\partial}{\partial x}(s^+p^+) - s^- \frac{\partial}{\partial x}(s^-p^-) + (\lambda^- s^+ - \lambda^+ s^-)p \tag{1.8}$$

and the initial conditions $p(x,0) = p_0(x)$, $j(x,0) = j_0(x)$, where p_0 and j_0 are determined from the initial distribution of p^+ and p^-.

To illustrate how variable speeds and turning rates affect the existence of nonuniform steady states, which can be interpreted as aggregations, consider the system (1.7-1.8) on the interval (0,1) and impose homogeneous Neumann (no-flux) boundary conditions at both ends [39]. We first suppose that λ is constant and determine under what conditions, if any, these equations have time-independent, non-constant solutions for $p^\pm$. Under steady state conditions the first equation implies that j is a constant, and the boundary conditions imply that $j \equiv 0$. Therefore $s^+p^+ = s^-p^-$, and the second equation reduces to

$$\frac{\partial}{\partial x}(s^+p^+) = \lambda s^+p^+ \left(\frac{s^+ - s^-}{s^+s^-}\right). \tag{1.9}$$

The solution of this equation is

$$p^+(x) = \frac{s^+(0)p^+(0)}{s^+(x)} e^{\lambda \int_0^x \frac{s^+ - s^-}{s^+s^-} d\xi} \equiv p^+(0)F^+(x),$$

and therefore the condition of vanishing flux gives p^- as

$$p^-(x) = \frac{s^+(0)p^+(0)}{s^-(x)} e^{\lambda \int_0^x \frac{s^+ - s^-}{s^+s^-} d\xi} \equiv p^+(0)F^-(x).$$

It follows that $p(x) \equiv p^+(x) + p^-(x)$ is given by

$$p(x) = \alpha \left(\frac{1}{s^+(x)} + \frac{1}{s^-(x)}\right) e^{\lambda \int_0^x \frac{s^+ - s^-}{s^+s^-} d\xi}, \tag{1.10}$$

wherein α is a constant given by

$$\alpha = \frac{Ns^+(0)}{\int_0^1 (F^+(\xi) + F^-(\xi))d\xi}$$

and N is the total number of cells in the unit interval. From this one can determine how the distribution of $s^\pm$ affects the distribution of p. In particular, if $s^\pm$ are not constant then $p^\pm$ and p are also non-constant. This is most easily seen if $s^+(x) = s^-(x)$, for then it follows directly from (1.10) that cells accumulate at the minima of the speed distribution. In any case, this simple model shows that cells can aggregate in a time-independent gradient by only modifying their speed, a process called orthokinesis. The case in which the velocities $s^\pm$ in system (1.7) depend on the signal distribution S has been considered in [25], where the local and global existence of solutions is established using the vanishing viscosity method.

It is also easy to see that particles cannot accumulate if the speed is symmetric and constant, but the turning rate λ is symmetric and a function of x, *i.e.* if only local information is used to determine the rate of turning. When the speed is symmetric and constant but the turning rates are biased, the time-independent solution of (1.7-1.8) is given by $j \equiv 0$ and

$$\log p(x) = \log p(0) + \frac{1}{s}\int_0^x (\lambda^- - \lambda^+)d\xi,$$

where the constant $\log p(0)$ is determined by N. Clearly $p(x)$ is identically $p(0)$ when $\lambda^- \equiv \lambda^+$. In the bacterial system described earlier the speed is essentially constant, but the turning rate depends on the history of exposure to the attractant or repellent, and hence on the path of the bacterium. In this case $\lambda^- \neq \lambda^+$ by virtue of the different history of a particle moving up-gradient as compared with one moving down-gradient. By formally ignoring the time derivative of j in (1.8), or more precisely, considering the limit $s, \lambda \to \infty, s^2/2\lambda \equiv D = \text{constant}$, the diffusion coefficient, one sees that in this case the chemotactic velocity is given by

$$u_c = -\frac{s\lambda^+ - \lambda^-}{2\lambda} \equiv -\frac{s\lambda_1}{\lambda}.$$

The random and directed components of motion will be of the same order only if either $\lambda_1 \sim \mathcal{O}(\sqrt{\lambda})$ or $\lambda_1 \sim \mathcal{O}(s)$. This case is studied in detail in [45, 26].

When both the speed and the turning rate are constant the system reduces to the telegraph equation

$$\frac{\partial^2 p}{\partial t^2} + 2\lambda \frac{\partial p}{\partial t} = s^2 \frac{\partial^2 p}{\partial x^2} \tag{1.11}$$

and the diffusion equation results either by taking the limit $\lambda \to \infty, s \to \infty$ with $s^2/2\lambda \equiv D$ constant as above, or by rescaling space and time appropriately, as in [23]. However, as we will show elsewhere, the stochastic telegraph process in higher space dimensions does not lead to the corresponding telegraph equation, even in the form of a system similar to (1.7), and thus the conclusions reached for one space dimension may not carry over directly to higher dimensions.

2. A brief summary of [23]. To make this paper self-contained we recall some results presented in [23]. We consider $\Omega = \mathbb{R}^n$ and we suppose that the velocities lie in a compact set $V \subset \mathbb{R}^n$ and that V is symmetric with respect to the origin, which is no restriction for the applications to chemotaxis equations. In many applications it is assumed that the kernel T is symmetric or that it is continuous (see e.g. [1]). We can relax these conditions with very little effort and still obtain a parabolic equation in the diffusion limit. Unless stated otherwise, we assume that λ is constant.

Let $\mathcal{K}$ denote the cone of nonnegative functions in $L^2(V)$, and for fixed (x,t) define an integral operator $\mathcal{T}$ and its adjoint $\mathcal{T}^*$ by

$$\mathcal{T}\, p = \int_V T(v,v')p(x,v',t)dv', \qquad \mathcal{T}^*\, p = \int_V T(v',v)p(x,v',t)dv'. \tag{2.1}$$

We impose the following conditions on the kernel and the integral operator.

(T1) $T(v,v') \geq 0, \quad \int_V T(v,v')dv = 1, \quad$ and $\quad \int_V \int_V T^2(v,v')dv'dv < \infty.$
(T2) *There are functions* $u_0, \phi,$ *and* $\psi \in \mathcal{K}$ *with* $u_0 \not\equiv 0$ *and* $\phi, \psi \neq 0$ *a.e. such that for all* $(v,v') \in V \times V$

$$u_0(v)\phi(v') \leq T(v',v) \leq u_0(v)\psi(v'). \tag{2.2}$$

(T3) $\|\mathcal{T}\|_{\langle 1\rangle^\perp} < 1$, where $\langle 1\rangle^\perp$ is the orthogonal complement in $L^2(V)$ of the span of 1.
(T4) $\int_V T(v,v')dv' = 1.$

We define the turning operator

$$\mathcal{L}p(v) = -\lambda p(v) + \lambda \mathcal{T}\, p(v), \tag{2.3}$$

acting in $L^2(V)$, and then have the following conclusions concerning its spectral properties [23].

Theorem 2.1. *Assume* (T1)-(T4)*; then*

1. 0 *is a simple eigenvalue of* $\mathcal{L}$ *and the corresponding eigenfunction is* $\phi(v) \equiv 1$.

2. *There is a decomposition* $L^2(V) = \langle 1\rangle \oplus \langle 1\rangle^\perp$ *and for all* $\psi \in \langle 1\rangle^\perp$

$$\int_V \psi \mathcal{L}\psi dv \leq -\mu_2 \|\psi\|^2_{L^2(V)}, \quad \text{where} \quad \mu_2 \equiv \lambda(1 - \|\mathcal{T}\|_{\langle 1\rangle^\perp}). \tag{2.4}$$

3. *All nonzero eigenvalues* μ *satisfy* $-2\lambda < Re\ \mu \leq -\mu_2 < 0$*, and to within scalar multiples there is no other positive eigenfunction.*
4. $\|\mathcal{L}\|_{\mathbf{L}(L^2(V),L^2(V))} \leq 2\lambda$.
5. $\mathcal{L}$ *restricted to* $\langle 1\rangle^\perp \subset L^2(V)$ *has a linear inverse* $\mathcal{F}$ *with norm*

$$\|\mathcal{F}\|_{\mathbf{L}(\langle 1\rangle^\perp,\langle 1\rangle^\perp)} \leq \frac{1}{\mu_2}. \tag{2.5}$$

Remark 2.1. *It turns out that in many applications* e.g.*, for symmetric turning kernel* $T(v,v') = t(|v-v'|)$ *the constant* μ_2 *given in (2.4) is the negative of the second eigenvalue of the turning operator* $\mathcal{L}$*. It defines the width of the spectral gap and determines the dissipative character of the turning process. If 1 is not a simple eigenvalue of* $\mathcal{T}$ *then the coordinate projections are eigenfunctions of* $\mathcal{T}$ *and the kernel of* $\mathcal{L}$ *is n+1-dimensional. In this case the hyperbolic or streaming character of the transport process dominates and we can no longer expect to obtain a diffusion limit.*

2.1. The Diffusion Limit. As we showed in [23], transport equations such as (1.1) can lead to diffusion equations if time and space are scaled as $\tau = \epsilon^2 t$ and $\xi = \epsilon x$, where ϵ is a small dimensionless parameter. Strictly speaking, these variables should be written as $\tau = \epsilon^2\gamma_1 t$ and $\xi = \epsilon\gamma_2 x$, where γ_1 and γ_2 are dimensional variables of order one, as is clear from the analysis in [23], but we ignore this detail.

The transport equation (1.1) in the new variables reads

$$\epsilon^2 \frac{\partial p}{\partial \tau} + \epsilon v \cdot \nabla_\xi p = -\lambda p + \lambda \int_V T(v,v')p(\xi,v',\tau)dv', \tag{2.6}$$

Here the subscript on ∇, which we drop hereafter, indicates differentiation with respect to the scaled space variable. In view of the space and time scalings chosen, we assume that $\lambda \sim \mathcal{O}(1)$. Since $\int_V T(v,v')dv = 1$, it follows that the right-hand side of (2.6) is $\mathcal{O}(1)$ compared with the left-hand side, whatever the magnitude of p. As was shown in [23], this leads to a diffusion equation for the lowest order term p_0 of an outer expansion, which we write as

$$p(\xi,v,\tau) = \sum_{i=0}^{k} p_i(\xi,v,\tau)\epsilon^i + \epsilon^{k+1}p_{k+1}(\xi,v,\tau). \tag{2.7}$$

In [23] we also proved an approximation result, for any order in ϵ, that provides a bound on the difference between the solution of the transport equation and an expansion derived from the solution of the associated parabolic diffusion equation. Here we give the result for a second-order approximation, which illustrates the essential idea of the construction.

Theorem 2.2. *Assume* (T1)-(T4)*. We consider a second order regular expansion in* ϵ*:*

$$q_2(\xi,v,\tau) = p_0(\xi,\tau) + \epsilon p_1(\xi,v,\tau) + \epsilon^2 p_2(\xi,v,\tau),$$

where p_0 *solves the parabolic limit equation*

$$\frac{\partial p_0}{\partial \tau} - \nabla \cdot \big(D\nabla p_0\big) = 0, \qquad p_0(\xi,0) = \int_V p(\xi,v,0)dv \tag{2.8}$$

with diffusion tensor [1]

$$D = -\frac{1}{\omega}\int_V v\mathcal{F}v dv. \tag{2.9}$$

[1] Throughout we use the terminology 'diffusion tensor' and diffusion matrix' interchangeably, since the latter is just the representation of the former with respect a specific basis.

In addition, the higher-order corrections are given by

$$p_1 = \mathcal{F}(v \cdot \nabla p_0), \qquad p_2 = \mathcal{F}(p_{0,\tau} + v \cdot \nabla \mathcal{F} v \cdot \nabla p_0),$$

where $\mathcal{F}$ is the pseudo inverse defined in Theorem 2.1 and $\omega = |V|$. Then for each $\vartheta > 0$ there exists a constant $C > 0$ such that for each $\vartheta/\epsilon^2 < t < \infty$ and each $x \in \mathbb{R}^n$

$$\|p(x,.,t) - q_2(\epsilon x,.,\epsilon^2 t)\|_{L^2(V)} \leq C\,\epsilon^3,^2$$

and the constant C depends on μ_2, V, D, and ϑ.

In general the approximate solution depends only on the solution of the limiting parabolic equation, and therefore it cannot be uniformly valid in time (*cf.* [23]).

Finally, we recall some of the results concerning the structure of the diffusion tensor. The simplest example occurs if $V = sS^{n-1}$ and $T(v,v') = \frac{1}{\omega}$, *i.e.* , when the speed is constant and the outgoing directions are uniformly distributed on S^{n-1}. In that case $\mathcal{F} = -\lambda^{-1}$ and

$$D = \frac{1}{\omega}\int_V \frac{vv}{\lambda} dv = \frac{s^2}{\lambda n} I.$$

Necessary and sufficient conditions for the isotropy of D can also be given in general. To state these we assume that the set of velocities V is symmetric with respect to $SO(n)$. Then there is a constant $K_V > 0$ such that

$$\int_V vv\, dv = K_V I. \tag{2.10}$$

Consider the following properties:

(St 1): *There exists an orthonormal basis (ONB) $\{e_1, \ldots, e_n\}$ of $\mathbb{R}^n$ such that the coordinate mappings $\phi_i : V \to \mathbb{R}$ given by $\phi_i(v) = v_i$ are eigenfunctions of $\mathcal{L}$ with eigenvalue $\mu \in (-2\lambda, 0)$, for $1 \leq i \leq n$.*

(St 2): *The expected velocity*

$$\bar{v}(v) \equiv \int_V T(v,v')v'dv' \quad \textit{satisfies} \quad \bar{v}(v) \parallel v \quad \textit{and} \quad \frac{\bar{v}(v)\cdot v}{v^2} = \gamma \tag{2.11}$$

for all $v \in V$ and a constant $\gamma \in (-1,1)$. We call γ the adjoint persistence.

(St 3): *There is a constant $d > 0$ such that the diffusion matrix has the representation*

$$D = d\, I.$$

Theorem 2.3. *Assume* (T1)-(T4) *and assume that V is symmetric with respect to $SO(n)$; then we have*

$$\text{(St 1)} \quad \Longleftrightarrow \quad \text{(St 2)} \quad \Longrightarrow \quad \text{(St 3)}.$$

The constants μ, γ and d are related as follows.

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

If T also satisfies the condition

(T5): *There is a matrix M such that $\bar{v}(v) = Mv$ for all $v \in V$*

then all three statements are equivalent.

[2] In [23] this estimate appears with the L^2-norm squared, but it is clear from the proof that there should be no square.

3. The general setup for signal-dependent turning rates and turning kernels. In this section we determine the parabolic limit equation when the turn angle distribution T and the turning rate λ depend on a given external signal field $S(\xi,\tau)$. However, to simplify the notation we write $T = T(v,v',\hat{S})$ and $\lambda(v,\hat{S})$ to indicate that T and λ depend on the function S rather than on the density $S(\xi,\tau)$ only at (ξ,τ). In particular, T and λ may depend on both S and ∇S, or they may have nonlocal dependence on S. We begin with (2.6) and construct the evolution equation for the first term of the regular perturbation expansion given in (2.7). As we shall see, how the effect of the external field enters into the limit equations depends on the magnitude of the perturbation relative to the unperturbed problem, and therefore we write the turning kernel and the turning rate in the form

$$T(v,v',\hat{S}) = T_0(v,v') + \epsilon^k T_1(v,v',\hat{S}) \tag{3.1}$$

$$\lambda(v,\hat{S}) = \lambda_0 + \epsilon^l \lambda_1(v,\hat{S}) \tag{3.2}$$

Here k,l are non-negative integers, both T_1 and λ_1 are assumed to be $\mathcal{O}(1)$, and λ_0 is assumed to be a constant. One could also introduce a series for the signal-dependent term, but as we will see, we can identify the dominant effects using the above form with k and l either 0 or 1.

In any case we assume that the unperturbed kernel $T_0(v,v')$ satisfies conditions (T1)–(T4). The assumptions for T_1 are different in the cases $k=0$ and $k=1$, and will be given in the corresponding subsection. The only assumptions needed on λ_1 are that it is continuous in its arguments and $\mathcal{O}(1)$. For most purposes the velocity-dependence of the turning rate is in fact dependence on the direction of travel, and in particular, is related to the dependence on ∇S, *e.g.,* via $(v/|v|)\cdot\nabla S$.

We begin with the general form of the scaled transport equation (2.6), which now takes the form

$$\epsilon^2 \frac{\partial p}{\partial \tau} + \epsilon v\cdot\nabla p = \mathcal{L}_0 p - \epsilon^l \lambda_1 p + \epsilon^k \lambda_0 \int_V T_1(v,v',\hat{S}) p(\xi,v',\tau)\,dv' \tag{3.3}$$
$$+\epsilon^l \int_V \lambda_1(v',\hat{S}) T_0(v,v') p(\xi,v',\tau)\,dv' + \epsilon^{k+l}\int_V \lambda_1(v',\hat{S}) T_1(v,v',\hat{S}) p(\xi,v',\tau)\,dv'$$

Here and hereafter $\mathcal{L}_0$ denotes the integral operator defined in (2.3) wherein $\lambda=\lambda_0$ and $T=T_0$. The fact that the perturbation in the turning rate appears under the integral sign reflects the assumption that the turning rate depends on the velocity (and in most cases on *both* the speed and direction) before a turn.

The assumption of the regular perturbation expansion (2.7) to order k for p leads to the following system of equations

$$\epsilon^0: \qquad \mathcal{L}p_0 = 0 \tag{3.4}$$

$$\epsilon^1: \qquad \mathcal{L}p_1 = \mathcal{R}_0(p_0) \tag{3.5}$$

$$\epsilon^2: \qquad \mathcal{L}p_2 = \mathcal{R}_1(p_0,p_1) \tag{3.6}$$

$$\vdots$$

$$\epsilon^i: \qquad \mathcal{L}p_i = \mathcal{R}_i(p_{i-2},p_{i-1}), \quad 3\le i\le k. \tag{3.7}$$

Here the linear operator $\mathcal{L}$ can be written as $\mathcal{L}=\mathcal{L}_0+\mathcal{L}_1$, either when $T_1=\lambda_1=0$, which is the case treated earlier, or when the perturbation is non-zero and its magnitude is $\mathcal{O}(1)$ *i.e.*, $k=0$ in (3.1). If the perturbation is $\mathcal{O}(\epsilon)$ then $\mathcal{L}=\mathcal{L}_0$. The functions $\mathcal{R}_i$ on the right-hand side of these equations are linear, and the pseudo-inverse of $\mathcal{L}$ is also. To simplify the presentation of the analysis we first consider separately perturbations of the turning kernel (Section 4) and the turning rate (Section 5), and then we combine the two in Section 6.

4. Perturbations of the turning kernel. First we assume that $\lambda_1=0$, and we show that either the diffusion matrix is perturbed or a taxis term arises, depending on the magnitude of the perturbation of T_0.

4.1. Order one perturbations. When $k=0$ the turn angle distribution has the form

$$T(v,v',\hat{S}) = T_0(v,v') + T_1(v,v',\hat{S}).$$

and the equations (3.4)-(3.7) are identical in structure to those considered in [23], except that here

$$\mathcal{L}p = \mathcal{L}_0 p + \lambda_0 \int_V T_1(v, v', \hat{S}) p(\xi, v', \tau) dv'. \tag{4.1}$$

To apply the general theory we assume (T1)-(T4) for both T and T_0 and the corresponding turning operators. Since T_0 is already assumed to satisfy (T1)-(T4) we have to state additional assumptions on T_1. To satisfy condition (T1) for $T = T_0 + T_1$ we assume for T_1:

$$(\mathbf{T_1 1}) \qquad \begin{aligned} &T_1(.,.,\hat{S}) \in L^2(V \times V), \quad \int T_1(v, v', \hat{S}) dv = 0 \\ &|T_1(v, v', \hat{S})| \leq T_0(v, v', \hat{S}) \quad \forall \ \ (v, v') \in V \times V. \end{aligned}$$

Condition (T2) for T follows from condition (T2) for T_0 and from the above assumption $(T_1 1)$. To satisfy (T3) and (T4) we assume that

$$(\mathbf{T_1 3}) \qquad \|\mathcal{T}_1\|_{\langle 1 \rangle^\perp} < 1 - \|\mathcal{T}_0\|_{\langle 1 \rangle^\perp},$$

and

$$(\mathbf{T_1 4}) \quad \int_V T_1(v, v', \hat{S}) dv' = 0.$$

Then the parabolic limit equation for the first order term $p_0(\xi, \tau)$ is given by

$$\frac{\partial p_0}{\partial \tau} = \nabla \cdot D \nabla p_0, \qquad p_0(\xi, 0) = \int_V p(\xi, v, 0) dv, \tag{4.2}$$

where the diffusion tensor is

$$D = -\frac{1}{\omega} \int_V v \mathcal{F} v \ dv,$$

and the pseudo-inverse is

$$\mathcal{F} := \left((\mathcal{L}_0 + \lambda_0 \mathcal{T}_1)|_{\langle 1 \rangle^\perp} \right)^{-1}.$$

Because the perturbation of T_0 perturbs $\mathcal{L}_0$, there is no taxis term in the limiting parabolic equation. Explicit computation of the diffusion matrix D depends on whether or not the inverse $\mathcal{F}$ can be computed explicitly. Fortunately this can be done for some nontrivial choices of T_0 and T_1.

For example suppose that T_0 represents a uniform redistribution of velocities $v \in V = sS^{n-1}$, and consider a perturbation of the form $T_1 = v \cdot M(\hat{S}) v'$, where M is a matrix-valued function of $S, \nabla S$ or other characteristics of S. This perturbation biases the outgoing direction in proportion to the incoming velocity stretched and rotated in an $\hat{S}$-dependent manner by M. In this case assumptions $(T_1 1)$ and $(T_1 3)$ require that

$$\|M(\hat{S})\|_\infty \leq \frac{1}{s^2} \min(1, \omega^{-1}). \tag{4.3}$$

This implies a fact that we will use later, namely that

$$\frac{n}{\omega s^2} \notin \sigma(M), \tag{4.4}$$

where $\sigma(M)$ denotes the spectrum of M. Since $\int_V (v \cdot M v') dv = \int_V (v \cdot M v') dv' = 0$ conditions $(T_1 1)$ and $(T_1 4)$ are satisfied. Clearly we could replace v and v' in T_1 by functions $f(v)$ and $g(v')$ that have zero mean without altering this conclusion.

According to Theorem 2.3, the diffusion matrix D corresponding to this T is isotropic only if $\bar{v}(v)$ and v are collinear for each $v \in V$. We have

$$\bar{v}(v) = \int_V \frac{1}{\omega} v' dv' + \int_V (v \cdot Mv')v' dv' = \frac{\omega s^2}{n} vM,$$

and therefore $\bar{v}(v) \parallel v$ with a constant value of $\bar{v}(v) \cdot v$ for all $v \in V$ only if M is a scalar multiple of the identity.

Suppose that this is not the case; then D is not a scalar matrix, and we compute it as follows. For a given $\psi \in \mathbb{R}^n$ we have $z(v) = \mathcal{F}(v \cdot \psi)$ and $z(v) \in \langle 1 \rangle^\perp$ if and only if

$$\mathcal{L}_0 z(v) + \lambda_0 \int_V (v \cdot Mv')z(v')dv' = v \cdot \psi \quad \text{and} \quad \int_V z(v')dv' = 0.$$

Therefore

$$z(v) = -\frac{1}{\lambda_0} v \cdot \psi + v \cdot Mz_1, \quad \text{with} \quad z_1 = \int_V v' z(v')dv'. \tag{4.5}$$

We multiply this equation by v and integrate to obtain

$$\left(I - \frac{\omega s^2}{n} M \right) z_1 = -\frac{\omega s^2}{\lambda_0 n} \psi.$$

In view of the assumption (4.4) the matrix on the left hand side is invertible, and using (4.5) we obtain

$$z(v) = -\frac{v}{\lambda_0} \cdot \left(I + \frac{\omega s^2}{n} M \left(I - \frac{\omega s^2}{n} M \right)^{-1} \right) \psi. \tag{4.6}$$

This gives the explicit representation of $\mathcal{F}(v \cdot \psi)$ and from this we can calculate the diffusion matrix:

$$D\psi = -\frac{1}{\omega} \int_V v z(v) dv = \frac{s^2}{\lambda_0 n} \left(I + \frac{\omega s^2}{n} M \left(I - \frac{\omega s^2}{n} M \right)^{-1} \right) \psi.$$

Hence the anisotropic diffusion tensor is

$$D = \frac{s^2}{\lambda_0 n} \left(I + \frac{\omega s^2}{n} M \left(I - \frac{\omega s^2}{n} M \right)^{-1} \right). \tag{4.7}$$

Note that D is symmetric if and only if M is symmetric.

Remark 4.1. *In [23] we showed that a normal operator $\mathcal{T}$ gives rise to a spectral representation of $\mathcal{L}$ and of $\mathcal{F}$ as well. This provides an alternate way to calculate the diffusion matrix. One expects that if M in the foregoing is normal then so is $\mathcal{T}_1$, and this is proven in the following lemma.*

Lemma 4.1. *Let $SO(n)$ denote the orthogonal group in n dimensions. If V is $SO(n)$-invariant and if $M \in \mathbb{R}^{n \times n}$ is normal, then the operator $\mathcal{T}_1$ with kernel $v \cdot Mv'$ is a normal operator on $L^2(V)$.*

Proof. For $\mathcal{T}_1$ to be normal we require

$$\int_V T(v, v'')T(v', v'')dv'' = \int_V T(v'', v)T(v'', v')dv'', \quad \forall\, (v, v') \in V \times V,$$

Here this condition can be transformed into the condition that for all $(v, v') \in V \times V$

$$\int_V v \cdot Mv''\; v' \cdot Mv''\; dv'' = \int_V v \cdot M^* v''\; v' \cdot M^* v''\; dv''. \tag{4.8}$$

Since M is assumed to be normal and M has real entries there is an $\Omega \in SO(n)$ such that $M^* = M\Omega$. We use this in (4.8) and substitute $w = \Omega v''$. Then the right hand side of (4.8) equals

$$\int_V v \cdot Mw\, v' \cdot Mw \det(\Omega^{-1})\, dw.$$

Since Ω is orthogonal, its determinant is ± 1. For $+1$ (4.8) is valid, and for -1 we substitute $y = -w$ and again observe that (4.8) indeed is true. □

In particular, we consider a system of individuals which show a certain direction of anisotropy $b \in \mathbb{R}^n$. This applies, for example, to a stream of elongated bacteria such as myxobacteria that is oriented in the direction b. The following turning kernel describes a tendency toward alignment in the the direction of the stream.

$$T_1 = \kappa(v \cdot b)(v' \cdot b), \qquad |b| = 1.$$

If the actual direction v' is in the direction b or $-b$, then there is an increased probability to choose a new velocity v in the direction b or $-b$, respectively. When moving in the direction of the stream this kernel reflects a tendency to move forward or backward of magnitude $\sim \kappa s^2$. In the notation used above we have $M = \kappa bb$ and condition (4.3) reads in this case

$$\kappa \leq \frac{1}{s^2} \min\,(1, \omega^{-1}).$$

The corresponding diffusion matrix is

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

The diffusivity in the direction b or $-b$ is enhanced, whereas it has the value $s^2/\lambda_0 n$ in the orthogonal direction, as in the unbiased case.

Remark 4.2. *We can summarize the results for an order one perturbation of T_0 as follows. Due to the fact that the organisms sense and respond to the external field, we obtain an anisotropic diffusion tensor D. However, there is no taxis component in the diffusion approximation, and as we observed earlier, because the evolution equation for p_0 has the form (4.2), there are no nonconstant steady state solutions under Neumann boundary conditions in this case. Thus, if the effect of the external field is of the same order as the reorientation in the absence of the external field, there is no taxis and no steady-state aggregation. The secondary restrictions on the magnitude of the perturbation, as reflected in (4.3), are essential. Without these a sufficiently large perturbation would destroy the ellipticity of the space operator in the limiting equation, and the diffusion limit would not be valid. It is not known what the appropriate form of the limiting equation is when (4.3) is not satisfied. One possibility is that the evolution from general initial data never relaxes to the parabolic regime. This could occur, for example, if the convection in v-space is on the same or a faster time scale than relaxation of the velocity changes. In those cases the turning operator loses its dissipative character.*

As we will see in the following section, a weaker perturbation leads to a taxis component in the evolution equation for p_0.

4.2. $\mathcal{O}(\epsilon)$ perturbations. Next we consider $\mathcal{O}(\epsilon)$ perturbations to T_0, *i.e.,* $k = 1$ in (3.1). In this case $\mathcal{L} = \mathcal{L}_0$ and the only assumptions on T_1 are that this perturbation gives rise to a well defined Cauchy problem and that the total particle mass is preserved. To satisfy (T1) for the perturbed kernel we assume that for each $\hat{S}$

$$(\mathbf{T_1 1'}) \qquad T_1(.,.,\hat{S}) \in L^2(V \times V) \text{ and } \int T_1(v, v', \hat{S})dv = 0.$$

We first derive the general form of the chemotactic velocity in terms of properties of the bias $\mathcal{T}_1$ of the turning operator, without a detailed specification as to how $\mathcal{T}_1$ depends on the external signal, and thereby show how to derive the chemotaxis equation (1.2) from the microscopic model of the motion. We then examine several forms

for the dependence of the kernel on S and its gradient, some of which lead to the classical PKSA equation, and others which lead to more general equations.

For an $\mathcal{O}(\epsilon)$ perturbation it follows as in [23] that $p_0 = p_0(\xi, \tau)$. The $\mathcal{O}(\epsilon)$ equation now reads

$$\mathcal{L}_0 p_1 = (v \cdot \nabla - \lambda_0 \beta_1(v)) p_0, \tag{4.9}$$

where the directional distributions β_i, are defined as

$$\beta_i(v) = \int_V T_i(v, v') dv' \tag{4.10}$$

for $i = 0, 1$. The distribution β_0 gives the total probability of an outgoing direction v for all incoming velocities v', whereas the $\mathcal{O}(\epsilon)$ shift in the outgoing velocity distribution is given by the *directional bias* β_1. The average directional bias is

$$\int_V \beta_1(v) dv = 0$$

by virtue of condition $(T_1 1')$ and Fubini's theorem. The solvability condition is satisfied, because

$$\int (v \cdot \nabla p_0) dv = 0,$$

and therefore p_1 is given by

$$p_1 = \mathcal{F}_0(v \cdot \nabla p_0) - \lambda_0 \mathcal{F}_0(\beta_1(v) p_0).$$

Here $\mathcal{F}_0$ denotes the pseudo inverse of $\mathcal{L}_0$.

The evolution equation for p_2 reads

$$\epsilon^2 : \qquad \mathcal{L}_0 p_2 = \frac{\partial p_0}{\partial \tau} + v \cdot \nabla p_1 - \lambda_0 \int_V T_1(v, v', \hat{S}) p_1(v') dv'.$$

The solvability condition is

$$0 = \int_V \Big(\frac{\partial p_0}{\partial \tau} + (v \cdot \nabla) \mathcal{F}_0(v \cdot \nabla p_0) - \lambda_0 (v \cdot \nabla) \mathcal{F}_0(\beta_1(v) p_0 \Big) dv$$
$$- \lambda_0 \int_V \int_V T_1(v, v', \hat{S}) p_1(v') dv' dv.$$

and the last term vanishes because of assumption $(T_1 1')$. If we define the *chemotactic velocity* as

$$u_c \equiv -\frac{\lambda_0}{\omega} \int_V v \mathcal{F}_0 \beta_1(v) dv = -\frac{\lambda_0}{\omega} \int_V \int_V v \mathcal{F}_0 T_1(v, v', \hat{S}) dv' dv, \tag{4.11}$$

then the solvability condition leads to an equation equivalent to (1.2), namely

$$\frac{\partial p_0}{\partial \tau} = \nabla \cdot (D \nabla p_0 - u_c p_0), \tag{4.12}$$

where as before $D = -\omega^{-1} \int_V v \mathcal{F}_0 v dv$ and u_c depends on $\hat{S}$. The macroscopic chemotactic velocity defined by (4.11) is simply the first moment of the directional bias distribution transformed by the pseudo inverse $\mathcal{F}_0$, and as such, represents an average velocity formed by weighting the microscopic velocities by the transform of the directional bias. Note that if we were to impose condition $(T_1 4)$ on T_1, the chemotactic velocity would vanish. Thus the 'reversibility' imposed on the unbiased turning operator precludes chemotaxis if imposed on the $\mathcal{O}(\epsilon)$ bias of the turning operator.

4.2.1. T_1 linear in ∇S: The PKSA equation. Thus far a general dependence on S in the kernel T_1 is admissible, but to obtain the classical chemotaxis equation we must specify both T_0 and how T_1 depends on the external signal. As we have seen before, the case $T_0 = 1/\omega$ and $V = sS^{n-1}$ is simplest, since we know $\mathcal{F}_0$ explicitly, and in this case the diffusion matrix and the chemotactic velocity are given by

$$D = \frac{s^2}{\lambda_0 n} I$$

$$u_c = \frac{1}{\omega}\int_V v\beta_1(v)dv = \frac{1}{\omega}\int_V vT_1(v,v',\hat{S})dv'dv.$$

Since the pseudo inverse is simply multiplication by $-\lambda_0^{-1}$ for this choice of T_0, the macroscopic chemotactic velocity defined by (4.11) is proportional to the first moment of the directional bias distribution. A necessary condition to obtain the PKSA equation is that T_1 depends linearly on ∇S, in the form $T_1 = Q_1(v,v',S)\cdot\nabla S$, where $Q_1(v,v',S)$ is a vector valued function of v, v' and S that satisfies

$$\int_V Q_1(v,v',S)dv = 0. \tag{4.13}$$

In this case the directional bias (4.10) is given by

$$\beta_1(v) = \int_V Q_1(v,v',S)dv'\cdot\nabla S \equiv q_1(v,S)\cdot\nabla S. \tag{4.14}$$

The vector $q_1(v,S)$ is the average velocity in the direction of v, taken over a uniform distribution of incoming velocities. The chemotactic velocity can now be written as the linear transformation of ∇S given by

$$u_c(S,\nabla S) = \chi(S)\nabla S, \tag{4.15}$$

where the chemotactic sensitivity is given by the matrix

$$\chi(S) \equiv \frac{1}{\omega}\int_V\int_V vQ_1(v,v',S)dv'dv = \frac{1}{\omega}\int_V vq_1(v,S)dv. \tag{4.16}$$

It is clear that this may or may not reduce to a scalar sensitivity, even though the diffusion process generated by T_0 is isotropic.

In particular, suppose that Q_1 has the form

$$Q_1(v,v',S) = k_1(v',S)v \tag{4.17}$$

for a positive scalar function k_1 in the foregoing analysis. Then whenever v is in the direction of ∇S (i.e.$\nabla S\cdot v > 0$) the term T_1 increases the probability of choosing v as the new direction compared to T_0 alone. If v and ∇S are opposite this probability is reduced compared with that for no bias. Here $q_1 = (\int_V k_1(v',S)dv')v \equiv k(S)v$, and the chemotactic sensitivity matrix reduces to the scalar chemotactic sensitivity

$$\chi(S) = k(S)\frac{s^2}{\omega n} = \frac{\lambda_0 k(S)}{\omega}D.$$

The parabolic limit equation now reads

$$\frac{\partial p_0}{\partial\tau} = \nabla\cdot\left(D\nabla p_0 - p_0\chi(S)\nabla S\right), \tag{4.18}$$

which is of the PKSA form. Any other combination of kernels T_0 that generate isotropic diffusion and perturbations of the form $k(S)v\cdot\nabla S$ will also lead to the PKSA equation. In particular, the kernel T_0 may incorporate persistence.

The same analysis can be carried through for a general kernel T_0, the only change being that the chemotactic sensitivity now becomes

$$\chi(S) \equiv -\frac{\lambda_0}{\omega}\int_V v\mathcal{F}_0 q_1(v,S)dv. \tag{4.19}$$

4.2.2. Other linear and nonlinear perturbations. Similarly, other more general forms than (4.17) for the dependence of the perturbation on S and the incoming and outgoing velocities are possible, and in the following we consider several examples for T_0 general.

a) A first generalization of (4.17) is to allow dependence of k_1 on $|v - v'|$ as well as S. Thus suppose that $V = sS^{n-1}$ and that

$$T_1 = h_1(|v - v'|, S)(v \cdot \nabla S) \tag{4.20}$$

for a positive kernel h_1, where in order to satisfy $(T_1 1')$, we must require

$$\int_V v h_1(|v - v'|, S) dv = 0.$$

The function h_1 depends on the magnitude of the turn, and thus reflects the ability of the organism to turn in response to the gradient. One expects that it is non-increasing in the first argument.

The effective velocity (4.14) has the form $q_1(v, S) = a_1(S)v$, where

$$a_1(S) = \int_V h_1(|v - v'|, S) dv',$$

and therefore the chemotactic velocity u_c is

$$u_c(S) = \lambda_0 a_1(S) D \nabla S,$$

where the diffusion matrix D appears explicitly. Thus the chemotactic sensitivity is

$$\chi(S) = \lambda_0 a_1(S) D \tag{4.21}$$

and the transformation properties of the chemotactic matrix are the same as those of the diffusion tensor. In particular, when D is a multiple of the identity this leads to the PKSA equation.

b) The preceding examples reflect a bias based on the angle between the outgoing direction and the gradient direction, and reflects a choice based on the relative advantage of new directions of travel. Of course, the bias could also be based on the alignment between the gradient and the incoming direction, in which case we set $T_1 = h_2(v, v', S)(v' \cdot \nabla S)$. where as usual, h_2 has zero mean over V. Now the chemotactic velocity is linear in ∇S and the chemotactic sensitivity is given by

$$\chi(S) = \frac{1}{\omega} \int_V \int \lambda_0 v \mathcal{F} h_2(v, v', S) v' \, dv dv'. \tag{4.22}$$

In particular, if T_0 is general, and

$$T_1 = a_2(S) \frac{n}{\omega} \frac{v \cdot v'}{s^2} (v' \cdot \nabla S).$$

then h_2 certainly has zero mean, because $\int_V v \cdot v' dv = 0$. For this T_1 the probability of choosing a new direction v is increased relative to the unbiased turning if that direction satisfies $sgn(v \cdot v') = sgn(v' \cdot \nabla S)$, and decreased otherwise. In other words, if the incoming direction is up-gradient any direction in the half-space $v \cdot v' > 0$ has an increased likelihood relative to the unbiased turning. Here the effective velocity is again proportional to v

$$q_1(v) = \int_V a_2(S) \frac{n}{\omega} \frac{v \cdot v'}{s^2} v' dv' = a_2(S) v,$$

the chemotactic velocity is $u_c = \lambda_0 a_2(S) D \nabla S$, and the resulting parabolic limit reads

$$\frac{\partial p_0}{\partial \tau} = \nabla \cdot D(\nabla p_0 - \lambda_0 a_2(S) \nabla S \, p_0).$$

Again, for scalar D this is the PKSA equation.

c) In the foregoing the perturbations are all linear in the gradient of the external signal, but there is no *a priori* reason to restrict attention to this case. The final example shows how nonlinear dependence on the gradient can arise very naturally.

Let T_0 be a general kernel and suppose that T_1 depends on the angle

$$\theta = \arccos\left(\frac{v\cdot\nabla S}{|v||\nabla S|}\right).$$

In this case it is more appropriate to consider an expansion in Legendre polynomials $P_j(cos\theta)$, rather than assuming a Fourier expansion of T_1 in θ. We assume for some $J\in\mathbb{N}, J>0$ that

$$T_1(v,v',\hat{S}) = \sum_{j=0}^{J} a_j(S)P_j(cos\theta).$$

The chemotactic velocity is given by

$$u_c = -\frac{\lambda_0}{\omega}\int_V\int_V v\mathcal{F}_0\sum_{j=0}^{J} a_j(S)P_j\left(\frac{v\cdot\nabla S}{|v||\nabla S|}\right)dvdv',$$

which is clearly nonlinear in ∇S. In the particular case $V = sS^{n-1}, T_0 = 1/\omega$, the pseudo inverse $\mathcal{F}_0$ is multiplication with $-\lambda_0^{-1}$. Since the V domain is symmetric, all integrals involving odd powers of v vanish, and it follows that u_c is a polynomial in ∇S of highest order J (resp., $J-1$) for J odd (resp., even).

5. Perturbations of the turning rate. In this section we analyze the effect of perturbations in the turning rate for a fixed turning kernel T_0. We first consider an additive bias, and then show how the theoretical results apply to bacterial chemotaxis. We only consider the case of an $\mathcal{O}(\epsilon)$ additive perturbation, since an order one additive perturbation in the turning rate leads to an operator $\mathcal{L}$ whose spectral properties cannot be determined in general. In the case of an $\mathcal{O}(\epsilon)$ perturbation we have $\mathcal{L}=\mathcal{L}_0$, and we find that $\mathcal{R}_0$ in (3.5) is given by

$$\mathcal{R}_0(p_0) = v\cdot\nabla p_0 + \lambda_1(v,\hat{S})p_0 - \int_V \lambda_1(v',\hat{S})T_0(v,v')p_0(\xi,v',\tau)dv'. \tag{5.1}$$

Therefore $p_1 = \mathcal{F}_0(\mathcal{R}_0(p_0))$, and the $\mathcal{O}(\epsilon^2)$ equation becomes

$$\mathcal{L}_0 p_2 = \frac{\partial p_0}{\partial\tau} + \mathcal{R}_0(\mathcal{F}(\mathcal{R}_0(p_0))). \tag{5.2}$$

The solvability condition reads

$$\begin{aligned}\int_V \Bigg[\frac{\partial p_0}{\partial\tau} + \left(v\cdot\nabla + \lambda_1(v,\hat{S}) - \int_V \lambda_1(v',\hat{S})T_0(v,v')(\cdot)dv'\right)\cdot\\ \mathcal{F}_0\left(v\cdot\nabla + \lambda_1(v,\hat{S}) - \bar{\lambda}_1(v,\hat{S})\right)p_0(\xi,\tau)\Bigg]dv = 0\end{aligned} \tag{5.3}$$

where

$$\bar{\lambda}_1(v,\hat{S}) = \int_V \lambda_1(v',\hat{S})T_0(v,v')dv' \tag{5.4}$$

is the average bias, over all incoming velocities, of the rate of turning to v. Clearly $\int(\lambda_1-\bar{\lambda}_1)dv$ vanishes when λ_1 is independent of the velocity.

The solvability condition (5.3) can be written

$$\begin{aligned} 0 = \int_V \frac{\partial p_0}{\partial \tau} dv + \left(\nabla \cdot \int_V v \mathcal{F}_0 v dv \nabla \right) p_0 + \nabla \cdot \left(\int_V v \mathcal{F}_0 (\lambda_1 - \bar{\lambda}_1) dv \right) p_0 \\ + \Bigg[\int_V \lambda_1(v,\hat{S}) \mathcal{F}_0 \Big(v \cdot \nabla + \lambda_1(v,\hat{S}) - \bar{\lambda}_1(v,\hat{S}) \Big) dv \\ - \int_V \int \lambda_1(v',\hat{S}) T_0(v,v') \mathcal{F}_0 \Big(v' \cdot \nabla + \lambda_1(v',\hat{S}) - \bar{\lambda}_1(v',\hat{S}) \Big) dv' dv \Bigg] p_0, \end{aligned}$$

and it follows from condition (T1) for T_0 that the operator in square brackets is identically zero. Therefore the following parabolic limit equation remains

$$\frac{\partial p_0}{\partial \tau} = \nabla \cdot (D \nabla p_0 - u_c p_0). \tag{5.5}$$

As before the diffusion tensor is given by

$$D = -\frac{1}{\omega} \int_V v \mathcal{F}_0 v \, dv$$

and the chemotactic velocity is now given by

$$u_c = -\frac{1}{\omega} \int_V v \mathcal{F}_0 (\lambda_1(v,\hat{S}) - \bar{\lambda}_1(v,\hat{S})) dv.$$

For example, if $V = sS^{n-1}$ and $T_0 = \omega^{-1}$ the linear functional $\mathcal{F}_0$ is multiplication by $-\lambda_0^{-1}$. Hence $D = s^2/(\lambda_0 n)$ and $\bar{\lambda}_1(\hat{S}) = 1/\omega \int_V \lambda_1(v',\hat{S}) dv'$ does not depend on $v \in V$. Then the chemotactic velocity is

$$u_c(\hat{S}) = \frac{1}{\lambda_0 \omega} \int_V v \lambda_1(v,\hat{S}) dv,$$

which is proportional to the first moment of λ_1 with respect to v.

As a second example, suppose that

$$\lambda_1(v,\hat{S}) = \kappa(v,S) \cdot \nabla S,$$

whereupon

$$u_c(\hat{S}) = \chi(S) \cdot \nabla S,$$

with first moment

$$\chi(S) = \frac{1}{\lambda_0 \omega} \int_V v \kappa(v,S) dv. \tag{5.8}$$

Hence again we obtain the classical (PKSA) chemotaxis equation

$$\frac{\partial p_0}{\partial \tau} = \nabla \cdot \left(\frac{s^2}{\lambda_0 n} \nabla p_0 - p_0 \chi(S) \nabla S \right).$$

5.1. Application to bacterial chemotaxis. Ford and co-workers [17, 16] have studied bacterial chemotaxis using a *stopped flow diffusion chamber* (SFDC). In [17, 10] they use mathematical models based on transport equations and their diffusion limit to model the experiments and to identify the relevant parameters. The analysis is based on earlier work by Rivero *et al.* [45], in which taxis is described in one space dimension using experimental fits to the turning rate developed in [7]. Here we show that the general formulation developed above can be used directly in any number of space dimensions.

Berg and Brown [4] and Macnab [33] observed experimentally that the turning kernel for *E. coli* and *Salmonella typhimurium* only depends on the relative angle θ between the old and the new direction, where as usual

$$\theta = \arccos\left(\frac{v \cdot v'}{|v||v'|}\right).$$

Their results can be fit using

$$T(v, v') = \frac{f(\theta)}{2\pi \sin\theta}.$$

where f is a sixth-order polynomial that is nonnegative and satisfies $f(0) = f(\pi) = 0$ (cf eqn(40) of [10]), and normalized so that

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

The mean turning angle that emerges from the data is approximately 68 degrees, rather than the 90 degrees expected if the distribution of new directions is uniform on S^2.

Since T depends only on the angle θ, we can apply the conclusions in Remark 3.4 of [23]. In the notation used there we have $T(v, v') = h(\theta)$ with $h = f/(2\pi \sin)$. Since this kernel is symmetric the diffusion limit automatically is isotropic. The diffusion constant is given by

$$d := \frac{s^2}{n\lambda_0(1 - \psi_d)} \tag{5.9}$$

where the persistence ψ_d is

$$\psi_d = 2\pi \int_0^\pi h(\theta)\cos\theta \sin\theta d\theta = \int_0^\pi f(\theta)\cos\theta d\theta \tag{5.10}$$

(*cf.* [38] or eqn (3.26) in [23]). For $n = 1$ the above representation of the diffusion constant corresponds to eqn(17) in [16], where a one dimensional chemotaxis model was studied. Note that this representation breaks down when the persistence is large, and other scalings have to be introduced.

In the presence of a gradient of an extracellular signal $S(x, t)$, Block *et al.* [7] found that the experimental observations on tumbling in *E. coli* can be fit by assuming that tumbles are generated by a Poisson process whose intensity depends on the rate of change of the fraction

$$f = \frac{S}{K_D + S}$$

of occupied receptors. Here K_D is the dissociation constant for the attractant. For a swimming bacterium this leads to the expression

$$\lambda(x, v, t, \hat{S}) = \lambda_0 \exp\left(-\frac{c_1 K_D}{(K_D + S)^2}(S_t + v \cdot \nabla S)\right), \tag{5.11}$$

where λ_0 is the turning rate in the absence of the chemical signal and c_1 is the change in the turning rate per unit of change in df/dt. A similar relation was first derived by Nossal [36]. Rivero *et al.* [45] and Ford *et al.* [17] use this in one space dimension and derive expressions for the diffusion constant and the chemotactic sensitivity.

In the parabolic scaling used above ($\tau = \epsilon^2 t, \xi = \epsilon x$) we can expand this as a function of ϵ, and to first order we have

$$\begin{aligned}\lambda(\xi, v, \tau, \hat{S}) &= \lambda_0 \exp\left(-\frac{c_1 K_D}{(K_D + S)^2}\left(\epsilon^2 S_t + \epsilon v \cdot \nabla S\right)\right), \\ &= \lambda_0\left(1 - \epsilon\,\frac{c_1 K_D}{(K_D + S)^2}(v \cdot \nabla S) + O(\epsilon^2)\right).\end{aligned}$$

Therefore the chemotactic velocity is given by

$$u_c = \chi(S)\nabla S$$

and the chemotactic sensitivity is

$$\chi(S) = c_1 \frac{s^2}{n} \frac{K_D}{(K_D + S)^2}, \tag{5.12}$$

which corresponds to formula (15) in [16] when $n = 1$. Note that to lowest order in ϵ the local rate of change does not affect the chemotactic velocity; only the spatial gradient enters. This is of course based on the implicit assumption that the temporal derivatives are $\mathcal{O}(1)$ on the t scale.

Thus earlier results derived for one dimension can easily be extended to two or three dimensions and lead to the equation

$$\frac{\partial p_0}{\partial \tau} = \nabla \cdot (d\nabla p_0 - p_0 \chi(S)\nabla S),$$

with

$$d = \frac{s^2}{n\lambda_0(1-\psi_d)} \quad \text{and} \quad \chi(S) = \frac{c_1 s^2}{n} \frac{K_D}{(K_D + S)^2}.$$

The proportionality factors connecting $3D$ cell speed to one dimensional projections and other relations concerning the dimensionality of the equations are discussed in [11] and [23].

It should be noted that the chemotactic sensitivity does not involve the directional persistence, and that it vanishes when $c_1 = 0$, *i.e.* , when the turning rate does not depend on the change in occupancy of the receptors. In that case the taxis vanishes and there can be no aggregation. Said otherwise, this formulation is consistent with the experimental observation that no adaptation implies no aggregation [55]. A different phenomenological approach that incorporates adaptation is analyzed in [50].

6. Combination of the perturbations $\boldsymbol{\lambda = \lambda_0 + \epsilon\lambda_1}$ and $\boldsymbol{T = T_0 + \epsilon T_1}$. As we remarked in the introduction, the slime mold Dd uses both taxis and kinesis, in that they move slightly faster when traveling up the gradient, they correct the direction of travel to approach the gradient direction, and they decrease the turning rate. The first effect is small, and thus this system is an example of combined run length control and taxis.

When perturbations of both the turning rate and the turning kernel are admitted the scaled transport equation (3.3) has the form

$$\epsilon^2 \frac{\partial p}{\partial \tau} + \epsilon(v \cdot \nabla)p = \mathcal{L}_0 p + \epsilon \left(\lambda_1 p - \int_V \lambda_1(v', S) T_0(v, v') p(v', x, t) dv' \right)$$
$$-\epsilon\lambda_0 \int_V T_1(v, v', \hat{S}) p(v', x, t) dv' + \mathcal{O}(\epsilon^2).$$

The perturbations enter additively at order ϵ, and the order ϵ^2 term does not change the limiting equation. Hence we obtain

$$\frac{\partial p_0}{\partial \tau} = \nabla \cdot (D\nabla p_0 - u_c p_0),$$

where

$$D = -\frac{1}{\omega} \int_V v \mathcal{F}_0 v \, dv,$$

$$u_c = -\frac{\lambda_0}{\omega} \int_V v \mathcal{F}_0 \beta_1(v) dv - \frac{1}{\omega} \int_V v \mathcal{F}_0 (\lambda_1(v, \hat{S}) - \bar{\lambda}_1(v, \hat{S}) dv.$$

Here

$$\beta_1(v) = \int_V T_1(v, v', \hat{S}) dv' \quad \text{and} \quad \bar{\lambda}_1(v) = \int_V \lambda_1(v', S) T_0(v, v') dv'.$$

7. Inclusion of nonlocal sensing and birth-death processes.

7.1. Nonlocal dependence on the signal distribution. A long-standing question in chemotaxis is how small organisms such as bacteria or amoeboid cells extract directional information from a scalar extracellular field such as the concentration of an attractant. In the case of bacteria it is clear that the body length is too short to measure gradients along the body axis, whereas amoeba may be able to effectively measure and compare different concentrations on different sites on their cell surface. Related to this issue is the question of what the effective sampling volume is in which the signal is significant. This volume depends on how rapidly a receptor processes the signal [5]. For *E. coli* the off rate for the Tar receptor is 70 $\sec^{-1}$ [51], and thus the sampling volume is small, while in Dd the off rate is ~ 0.45 $\sec^{-1}$, and the effective sampling volume is many times the cell volume [39].

A simple mathematical model that may capture the essence of both an effective sampling volume and a mechanism for extracting directional information is as follows. For simplicity we assume that a cell can be approximated as a sphere, and we denote its center by x and the effective sampling radius by R. Consider the quantity

$$\overset{\circ}{S}(x,t) = \frac{n}{\omega_0 R}\int_{S^{n-1}} \nu\, S(x+R\nu,t)\, d\nu, \tag{7.1}$$

where ν is the unit outer normal and ω_0 is the area of the unit (n-1)-sphere. The integral represents the dominant direction in the extracellular signal at a distance R from the center, which could be the cell radius, and hence if cells can 'compute' this integral they can extract directional information from a scalar extracellular field without measuring a gradient. Note that $\overset{\circ}{S}$ vanishes if S is spatially uniform, as it should. A simple mechanism by which cells could compute $\overset{\circ}{S}$ is to produce an intracellular signal in proportion to the number of receptors occupied and condition the response on the local level of this substance. A molecular mechanism based on a local activator and a long-range inhibitor or adaptation effector is currently under investigation [8].

As the sensing radius $R \to 0$ this expression approximates the local gradient of S, which can be seen as follows (we suppress the time dependence in the following calculation):

$$\begin{aligned}\overset{\circ}{S}(x) &= \frac{n}{\omega_0 R}\int_V \nu\left(S(x) + R(\nu\cdot\nabla)S(x) + \frac{R^2}{2}(\nu\cdot\nabla)(\nu\cdot\nabla)S(x) + \text{h.o.t.}\right) d\nu \\ &= \frac{n}{\omega_0 R}\left[\int_V \nu d\nu S(x) + R\int_V \nu\nu d\nu \nabla S(x) + \mathcal{O}(R^2)\right] \\ &= \nabla S(x) + \mathcal{O}(R).\end{aligned} \tag{7.2}$$

To derive chemotaxis equations we treat the non local 'gradient' $\overset{\circ}{S}$ in exactly the same way as we used ∇S in the previous sections. In particular for order ϵ-perturbations of the form

$$h_1(|v-v'|)(v\cdot\overset{\circ}{S}),$$

which is analogous to (4.20), we obtain the chemotaxis equation

$$\frac{\partial p_0}{\partial \tau} = \nabla\cdot(D\nabla p_0 - \chi(S)p_0\overset{\circ}{S}) \tag{7.3}$$

with $\chi(S)$ given by (4.21). This, combined with the signal equation (1.5), leads to an integro-differential model for chemotaxis. In addition, perturbations of the turning rate are given by replacing ∇S by $\overset{\circ}{S}$ in section 5. In particular

$$\lambda = \lambda_0 + \kappa\cdot\overset{\circ}{S}$$

leads to (7.3) with $\chi(S)$ given by (5.8).

In some cases an integro-differential equation for the species density such as (7.3) may be replaced by a fourth-order partial differential equation [37]. In the expansion (7.2), the R^2-term vanishes because it is odd in ν. Therefore the next correction to the gradient is the third derivative of S, which gives a fourth-order term in (7.3).

7.2. Incorporation of a Resting Phase in the Dynamics. The method developed here and in the companion paper [23] can also be applied when birth-death processes are present. Usually birth and movement are temporally distinct events, but many macroscopic models such as reaction diffusion models do not respect this distinction. It turns out, however, that an appropriate scaling leads to reaction-diffusion models with effective birth and death terms in the limit, and this gives some insight into the validity of such models when birth and death are incorporated. Here we summarize some of the main conclusions; details will be presented in [22].

We divide the total population density into a density $p(x,v,t)$ of individuals moving with velocity $v \in V$ and a density $r(x,t)$ for particles resting at $x \in \Omega$, as in [38]. The velocity set is assumed to be bounded and symmetric with respect to the origin, and to have measure $\omega = |V|$. We consider a model for (p,r) which is based on the following assumptions.

1. The pure movement process is a velocity jump process described by (1.1), where the kernel $T(v,v')$ satisfies the basic assumptions (T1)-(T4). We denote the turning operator as $\mathcal{L}_0 := -\lambda(I - \mathcal{T}_0)$ and note that Theorem 2.1 applies.
2. Individuals in motion stop at a rate $\alpha > 0$.
3. At rest particles give birth at a rate $m(N) \geq 0$, where $N(x,t) = \int_V p(x,t,v)dv + r(x,t)$.
4. Individuals at rest leave the rest state at a constant rate $\beta > 0$ and choose a velocity $v \in V$ from a uniform distribution on V.
5. Death occurs at the same rate $g(N) \geq 0$ for both moving and resting individuals. (In some situations one might suppose that the death rate at rest is higher due to predators).

The pure kinetic birth-death process without movement is denoted by $\dot{u} = f(u) \equiv m(u)u - g(u)u$ and the full model reads

$$\begin{aligned} \frac{\partial p}{\partial t} + v \cdot \nabla p &= \mathcal{L}_0 p - \alpha p + \frac{\beta}{\omega} r - g(N)p \\ \frac{\partial r}{\partial t} &= \alpha \textstyle\int_V p(x,v,t)dv - \beta r + m(N)r - g(N)r. \end{aligned} \tag{7.4}$$

To avoid boundary conditions we assume that the initial data has compact support on $\mathbb{R}^n$. Then the solutions will have compact support as long as they exist. Again we consider the parabolic scaling of $\tau = \epsilon^2 t, \xi = \epsilon x$, and in addition we assume that the interaction term scales as ϵ^2:

$$f(u) = \epsilon^2 \tilde{f}(u).$$

The asymptotic expansion procedure developed in [23] can now be applied here and the limit equation for the first order approximation N_0 of N reads

$$\frac{\partial N_0}{\partial t} = \nabla D_{\alpha,\beta} \nabla\, N_0 + \frac{\alpha}{\alpha+\beta} \tilde{m}(N_0)N_0 - \tilde{g}_0(N_0)N_0. \tag{7.5}$$

The diffusion tensor is now given by

$$D_{\alpha,\beta} := -\frac{\beta}{\omega(\alpha+\beta)} \int_V v\mathcal{F}_\alpha v\, dv = -\frac{1}{\omega}\left[\frac{\alpha^{-1}}{\alpha^{-1}+\beta^{-1}}\right] \int_V v\mathcal{F}_\alpha v\, dv \tag{7.6}$$

where $\mathcal{F}_\alpha$ denotes the pseudo inverse of $\mathcal{L}_\alpha$, defined by

$$\mathcal{L}_\alpha \psi(v) = -(\lambda+\alpha)\psi(v) + (\lambda+\alpha) \int_V \left(\frac{\lambda}{\lambda+\alpha} T(v,v') + \frac{\alpha}{(\lambda+\alpha)\omega} \right) \psi(v')\, dv'. \tag{7.7}$$

Note that according to (7.6), the diffusion tensor is proportional to the fraction of time spent in motion, and the birth-rate is proportional to the mean time spent in the resting state. Both are reduced from the value that applies when only one or the other state is present. This analysis shows that in appropriate scalings of space and time, birth terms can legitimately be included in a diffusion equation.

8. Discussion. We have shown that when there is bias in the turning characteristics of a velocity jump process, the asymptotic expansion of (1.1) can lead to either an anisotropic diffusion equation or a chemotaxis equation, depending on the type and strength of the bias. In many important cases we can relate the chemotactic velocity and the chemotactic sensitivity to more fundamental and observable characteristics of the motion reflected in the turning rate λ_1 and the kernel T_1. The problem of deriving diffusion approximations to various stochastic processes that model chemotaxis has been considered by a number of authors. Several approaches to the problem were discussed in [23], and others are discussed in the remainder of this section. We also indicate some generalizations of the present model.

The first systematic derivation of a chemotaxis equation from a velocity jump process is due to Patlak [44], who considers both internal and external biases in detail. A basic assumption in [44] is that the run length is *chosen and fixed* whenever the particle turns, and as a result his stochastic process is significantly different from the one studied here. The particle motion between turns is deterministic and thus, were the speed and run length constant, the process would be formally equivalent to a space jump process. In general one can show that his process leads to a renewal equation that generalizes the renewal equation (15) derived in [38], from which a diffusion equation is obtained by suitable choice of the waiting time and jump distributions. Patlak treats $\mathcal{O}\epsilon$ perturbations of a symmetric turning kernel T_0 and turning rate λ_0 (*cf.* eqns (7), (11) and (27) in [44]), a case we analyzed in section 6. A combination of these biases leads to additional drift terms in the parabolic limit equation.

Alt [1, 2] develops a model in which the run length is an explicit state variable, rather than a parameter in the equation, as in our analysis. This leads to a transport equation with the integral term in (1.1) replaced by a convective term in the run length time, and a separate renewal equation that governs how individuals that turn choose their direction and speed. If the stopping probability β in [1] is independent of the run time, integration over the run time leads to (1.1). The asymptotic expansion relays on four parameters whose relative orders of magnitude determine the asymptotic regime and thus the type of equation: the mean run time ϵ, the sensitivity for detecting chemotactic gradients by extending psuedopods δ (called the protrusion sensitivity in [1]), the turning strength $\zeta \equiv 1 - \psi_d$, where ψ_d is the persistence index, and the inverse cell speed α. Numerous distinct scalings of these parameters are possible, but two major cases are considered. The first limit, in which $\epsilon/\zeta, \delta, c_0\delta\alpha, \alpha^2 << 1$ corresponds to the case discussed in section 4.2. Assuming that $\zeta \sim \mathcal{O}(1)$ it leads to a PKSA equation if one also assumes that $c_0\delta\alpha \leq \mathcal{O}(\epsilon)$. The second case is somewhat special and corresponds in our notation to the case of $\|\mathcal{T}|_{\langle 1\rangle^\perp}\| = 1$. Then the turning operator degenerates and the kernel is no longer one dimensional. This case is not covered in our framework and Alt showed that the diffusion matrix is anisotropic in that special case. In the general case, the results in [1] depend on the fact that in a perturbation expansion with ϵ as the small parameter, the order one term T_0 in the expansion of $T(v, v')$ is symmetric and of the form $T_0(v, v') = t(|v - v'|)$. As we have seen, this always leads to an isotropic diffusion tensor in the parabolic limit.

One dimensional projections of Alt's model for weak chemotactic gradients are considered in [11]. The authors assume a kernel of the form $T(v, v') = t(|v - v'|)$, which leads to an isotropic diffusion limit, and that the turning rate is perturbed by a lower order term. As we showed in Section 5, our approach produces the chemotaxis equations in any space dimension directly. Schnitzer [47] allows for space-dependent particle speeds s and turning rates λ and considers different scenarios that lead to an additional drift term in the parabolic limit. In our notation, he assumes that the adjoint persistence γ is space dependent, which leads to a scalar diffusion parameter that is space-dependent. He considers perturbations $\lambda = \lambda_0 + \epsilon\lambda_1(v)$ of order ϵ where the perturbation depends on velocity.

Dickinson and Tranquillo [14] divide the movement process of amoeba and other organisms into three subprocesses, each characterized by a distinct time scale. The authors assume that reorientation arises from random forces on individuals and use stochastic differential equations with white noise for the velocity and position. Our results complement their's in that the underlying stochastic process is different in the two analyses.

Dickinson [13] considers a stochastic process which includes linear transport with spontaneous reorientations, diffusion in velocity, rotational drift and rotational diffusion. He uses the method of adiabatic elimination of fast variables (cf. [19]) to derive a corresponding Smoluchowski equation. However the analysis is based on what we called the hyperbolic scaling ($\hat{\tau} = \epsilon t, \xi = \epsilon x$) and it leads to a limit equation which still contains the scaling

parameter (ϵ in our notation). Here a simple rescaling apparently produces the correct result, but in general there is no guarantee that the matching is correct if one uses this procedure. Moreover the parabolic scaling which we use leads directly to an approximation theorem, as in Theorem 2.2.

To develop a complete model that includes detection of the external signal and its transduction into a response, it is necessary to incorporate a more detailed description of the signal transduction process. Detailed models for signal transduction are available for both *E. coli* and *Dictyostelium discoideum* [51, 53], and in the former case it is known how the motion is controlled by an intracellular control chemical [46]. A simplified form of signal transduction for haptotaxis is included in [14]. The incorporation of detailed models for signal transduction will shed further light on how the behavioral response of individuals is reflected in the macroscopic diffusion and chemotactic sensitivity parameters. As we noted earlier, incorporation of adaptation is essential in some applications.

REFERENCES

[1] W. Alt, *Biased random walk models for chemotaxis and related diffusion approximations*, J. of Math. Biol., 9 (1980), pp. 147–177.

[2] ———, *Singular perturbation of differential integral equations describing biased random walks*, J. für die reine und angewandte Mathematik, 322 (1981), pp. 15–41.

[3] H. Berg, *How bacteria swim*, Scientific American, 233 (1975), pp. 36–44.

[4] H. C. Berg and D. A. Brown, *Chemotaxis in* Escherichia coli *analysed by three-dimensional tracking*, Nature, 239 (1972), pp. 500–504.

[5] H. C. Berg and E. M. Purcell, *Physics of chemoreception*, Biophysical Journal, 20 (1977), pp. 193–219.

[6] P. Biler, *Local and global solvability of some parabolic systems modelling chemotaxis*, Advances in Math. Sci. and Appl., 8 (1998), pp. 715–743.

[7] S. M. Block, J. E. Segall, and H. C. Berg, *Adaptation kinetics in bacterial chemotaxis*, Journal of bacteriology, 154 (1983), pp. 312–323.

[8] D. Bottino, N. Edelson, and H. G. Othmer, *Sensing, orientation and polarization during chemotaxis in* Dictyostelium discoideum. In preparation, 2001.

[9] D. Bottino, O. Weiner, and H. G. Othmer, *A model for cell polarization.* In preparation.

[10] B. J. Brosilow, R. M. Ford, S. Sarman, and P. T. Cummings, *Numerical solution of transport equations for bacterial chemotaxis: Effects of discretization of directional motion*, SIAM J. Appl. Math, 56 (1996), pp. 1639–1663.

[11] K. C. Chen, R. M. Ford, and P. T. Cummings, *Perturbation expansion of Alt's cell balance equations reduces to Segel's 1D equation for shallow chemoattractant gradients*, SIAM J. Appl. Math., 59 (1998), pp. 35–57.

[12] J. Dallon and H. G. Othmer, *A continuum analysis of the chemotactic signal seen by* Dictyostelium discoideum, J. Theor. Biol., 194 (1998), pp. 461–483.

[13] R. B. Dickinson, *A generalized transport model for biased cell migration in an anisotropic environment*, J. Math. Biol., 40 (2000), pp. 97–135.

[14] R. B. Dickinson and R. T. Tranquillo, *Transport equations and indices for random and biased cell migration based on single cell properties*, SIAM J. Appl. Math., 55 (1995), pp. 1419–1454.

[15] P. R. Fisher, R. Merkl, and G. Gerisch, *Quantitative analysis of cell motility and chemotaxis in* Dictyostelium discoideum *by using an image processing system and a novel chemotaxis chamber providing stationary chemical gradients*, Journal of Cell Biology, 108 (1989), pp. 973–984.

[16] R. M. Ford and D. A. Lauffenburger, *Measurement of bacterial random motility and chemotaxis coefficients: II: Application of single-cell-based mathematical model*, Biotechnol. Bioeng., 37 (1991), pp. 661–672.

[17] R. M. Ford, B. R. Phillips, J. A. Quinn, and D. A. Lauffenburger, *Measurement of bacterial random motility and chemotaxis coefficients: I. stopped–flow diffusion chamber assay*, Biotechnol. Bioeng., 37 (1991), pp. 647–660.

[18] H. Gajewski and K. Zacharias, *Global behavior of a reaction-diffusion system modelling chemotaxis*, Math. Nachr., 159 (1998), pp. 77–114.

[19] C. W. Gardiner, *Handbook of Stochastic Methods*, Springer, Berlin, Heildeberg, 1983.

[20] S. Goldstein, *On diffusion by discontinuous movements and the telegraph equation*, Quart. J. Mech. Appl. Math., 4 (1951), pp. 129–156.

[21] M. Herrero and J. Velázquez, *Singularity patterns in a chemotaxis model*, Math. Annalen, 306 (1996), pp. 583–623.

[22] T. Hillen, *Transport Equations and Chemosensitive Movement*, 2001. Habilitation thesis.

[23] T. Hillen and H. G. Othmer, *The diffusion limit of transport equations derived from velocity jump processes*, SIAM JAM, 61 (2000), pp. 751–775.

[24] T. Hillen and K. Painter, *Global existence for a parabolic chemotaxis model with prevention of overcrowding*, Advance in Appl. Math., (2001). to appear.

[25] T. Hillen, C. Rohde, and F. Lutscher, *Existence of weak solutions for a hyperbolic model for chemosensitive movement*, J. Math. Ana. Appl., (2001). to appear.

[26] T. Hillen and A. Stevens, *Hyperbolic models for chemotaxis in 1-D*, Nonlinear Analysis: Real World Applications, 1 (2000), pp. 409–433.

[27] W. Jäger and S. Luckhaus, *On explosions of solutions to a system of partial differential equations modelling chemotaxis*, Trans. of the Am. Math. Society, 329 (1992), pp. 819–824.
[28] M. Kac, *A stochastic model related to the telegrapher's equation*, Rocky Mountain J. of Math., 3 (1974), pp. 497–509.
[29] E. Keller, *Mathematical aspects of bacterial chemotaxis*, Antibiotics and Chemotherapy, 19 (1974), pp. 79–93.
[30] E. F. Keller and L. A. Segel, *Initiation of slime mold aggregation viewed as an instability*, Journal of Theoretical Biology, 26 (1970), pp. 399–415.
[31] ———, *Model for chemotaxis*, J. Theor. Biology, 30 (1971), pp. 225–234.
[32] D. E. Koshland, *Bacterial Chemotaxis as a Model Behavior System*, Raven Pree, New York, NY, USA, 1980.
[33] R. M. Macnab, *Sensing the environment: Bacterial chemotaxis*, in Biological Regulation and Development, R. Goldberg, ed., New York, 1980, Plenum Press, pp. 377–412.
[34] H. McKean, *Chapman-Enskog-Hilbert expansions for a class of solutions of the telegraph equation*, J. of Math. Physics, 75 (1967), pp. 1–10.
[35] T. Nagai, T. Senba, and K. Yoshida, *Application of the Trudinger-Moser inequality to a parabolic system of chemotaxis*, Funkcialaj Ekvacioj, 40 (1997), pp. 411–433.
[36] R. Nossal, *Mathematical theories of topotaxis*, in Biological Growth and Spread, W. Jäger, H. Rost, and P. Tautu, eds., Springer-Verlag, New York, NY, USA, 1980, pp. 410–439.
[37] H. G. Othmer, *Interactions of Reaction and Diffusion in Open Systems*, PhD thesis, University of Minnesota, Minneapolis, Dec. 1969.
[38] H. G. Othmer, S. R. Dunbar, and W. Alt, *Models of dispersal in biological systems*, J. of Math. Biol., 26 (1988), pp. 263–298.
[39] H. G. Othmer and P. Schaap, *Oscillatory cAMP signaling in the development of* Dictyostelium discoideum, Comments on Theor. Biol., 5 (1998), pp. 175–282.
[40] H. G. Othmer and A. Stevens, *Aggregation, blowup and collapse: The ABC's of taxis in reinforced random walks*, SIAM J. Appl. Math., 57 (1997), pp. 1044–1081.
[41] K. J. Painter, P. K. Maini, and H. G. Othmer, *Development and applications of a model for cellular response to multiple chemotactic cues*, J. Math. Biol., 41 (2000), pp. 285–314.
[42] C. A. Parent and P. N. Devreotes, *A cell's sense of direction*, Science, 284 (1999), pp. 765–770.
[43] E. Pate and H. G. Othmer, *Differentiation, cell sorting and proportion regulation in the slug stage of* Dictyostelium discoideum, Journal of Theoretical Biology, 118 (1986), pp. 301–319.
[44] C. S. Patlak, *Random walk with persistence and external bias*, Bull. of Math. Biophys., 15 (1953), pp. 311–338.
[45] M. A. Rivero, R. T. Tranquillo, H. M. Buettner, and D. A. Lauffenburger, *Transport models for chemotactic cell populations based on individual cell behavior*, Chemical engineering science, 44 (1989), pp. 2881–2897.
[46] B. E. Scharf, K. A. Fahrner, L. Turner, and H. C. Berg, *Control of direction of flagellar rotation in bacterial chemotaxis*, Proceedings of the National Academy of Sciences of the United States of America, 95 (1998), pp. 201–206.
[47] M. J. Schnitzer, *Theory of continuum random walsk and applications to chemotaxis*, Phys. Rev. E, 48 (1993), pp. 2553–2568.
[48] L. A. Segel, *A theoretical study of receptor mechanisms in bacterial chemotaxis*, SIAM Journal on Applied Mathematics, 32 (1977), pp. 653–665.
[49] ———, *Mathematical models for cellular behavior*, in Studies in Mathematical Biology, S. A. Levin, ed., Washington, 1978, MAA, pp. 156–190.
[50] J. A. Sherratt, E. H. Sage, and J. D. Murray, *Chemical control of eukaryotic cell movement: A new model*, Journal of Theoretical Biology, 162 (1993), pp. 23–40.
[51] P. A. Spiro, J. S. Parkinson, and H. G. Othmer, *A model of excitation and adaptation in bacterial chemotaxis*, Proceedings of the National Academy of Sciences of the United States of America, 94 (1997), pp. 7263–7268.
[52] D. W. Stroock, *Some stochastic processes which arise from a model of the motion of a bacterium*, Probab. Theory and Related Fields, 28 (1974), pp. 305–315.
[53] Y. Tang and H. G. Othmer, *Excitation, oscillations and wave propagation in G–protein–based model of signal transduction in dictyostelium discoideum*, Phil. Trans. Roy. Soc. (London), B 349 (1995), pp. 179–195.
[54] B. J. Varnum-Finney, E. Voss, and D. R. Soll, *Frequency and orientation of pseudopod formation of* Dictyostelium discoideum *amebae chemotaxing in a spatial gradient: Further evidence for a temporal mechanism*, Cell Motility and the Cytoskeleton, 8 (1987), pp. 18–26.
[55] R. M. Weis and D. E. Koshland, *Reversible receptor methylation is essential for normal chemotaxis of* Escherichia coli *in gradients of aspartic acid*, Proc. Nat. Acad. Sci., 85 (1988), pp. 83–87.