J. Math. Biology 9, 147–177 (1980)

Journal of
Mathematical
Biology

Biased Random Walk Models for Chemotaxis and Related Diffusion Approximations

Wolgang Alt

Institut für Angewandte Mathematik, Im Neuenheimer Feld 294, D-6900 Heidelberg, Federal Republic of Germany

Summary. Stochastic models of biased random walk are discussed, which describe the behavior of chemosensitive cells like bacteria or leukocytes in the gradient of a chemotactic factor. In particular the turning frequency and turn angle distributions are derived from certain biological hypotheses on the background of related experimental observations. Under suitable assumptions it is shown that solutions of the underlying differential-integral equation approximately satisfy the well-known Patlak–Keller–Segel diffusion equation, whose coefficients can be expressed in terms of the microscopic parameters. By an appropriate energy functional a precise error estimation of the diffusion approximation is given within the framework of singular perturbation theory.

Key words: Chemotaxis — Biased random walk — Diffusion equations — Singular perturbation.

1. Introduction

The phenomenon of chemotaxis, that is, the preferred movement and orientation of sensitive organisms or cells along the gradient of a chemical substance, is mathematically described by

i) stochastic processes for the position and moving direction of each individual, compare Boyarsky and Noble [9], Nossal and Weiss [26, 29], Stroock [40], and by

ii) partial differential equations for the density and the mean flux of a whole population, compare Keller and Segel [17, 38].

The underlying stochastic models are based on quantitative observations, performed in experiments with bacteria by Berg and Brown [6] or MacNab and Koshland [22], for example, and with leukocytes by Ramsey [36], Peterson and Noble [35], Zigmond and Hirsch [44] or Nossal and Zigmond [30, 42], for example. The statistics for the turning frequency and the turn angle distributions of these cells have been evaluated and built into the constituting equations, see [13, 14, 21, 23, 29, 37].

0303-6812/80/0009/0147/$06.20

If both distributions are locally isotropic, the result is a random walk model for the cell locomotion describing the effect of chemokinesis. If however one or both probability distributions are biased in the direction of a chemical gradient, this leads to a biased random walk model describing the effect of chemotaxis, see Sections 2, 3 and 8 below.

The first problem of interest for theoretical biologists is the way in which the turning frequency and turn angle distributions of a chemosensitive cell are correlated to intracellular events controlling the locomotion and to the mechanisms of receptors sensing the concentration of a surrounding chemotactic factor, compare [7, 11, 18, 27, 31, 43].

Section 4 of this paper is intended to contribute to this discussion by proposing simple hypotheses for a biochemical control mechanism of locomotion, and by showing how to deduce from these a quantitative expression of the turning frequency, see (4.8).

Moreover, in Section 5 we briefly discuss a model of the turn angle distribution for migrating cells (like leukocytes or amoebae) based on the hypothesis that cells discover preferred directions by 'testing' protrusions of their plasma membrane (cf. [2, 12]), see (5.5).

The second problem essential for an application of these theoretical models is to show how these hypotheses on 'microscopic' characteristics of cell behavior influence the mean orientation of cells with respect to the chemotactic gradient (see Section 8, I) and the accumulation at regions of high chemoattractant concentration (Section 8, II).

Therefore one tries to construct approximate evolution equations for the density and the mean direction of moving individuals. In the case of one dimension, Keller [16] and Segel [37, 38] gave several derivations of a diffusion equation for the density, and expressed the coefficients, namely the motility μ and the chemotaxis coefficient χ, in terms of the turning frequency.

The main object of this paper is to give a derivation of this diffusion equation (8.13) in the general case of n dimensions, based on the more refined stochastic model (3.1), (3.2), including approximate expressions for the mean orientation as well as for the mean run length of moving cells (8.17).

Prepared by Sections 6 and 7, where the properties of the underlying differential integral equation are analyzed, in Section 8 we investigate smallness conditions on various parameters (mean run length or time, turning strength, cf. (8.18)) under which a diffusion approximation to the biased random walk model is valid.

As a first step we suppose an *a priori* boundedness assumption (8.3) for the solutions, independent of the small parameters (quasi steady state hypothesis), and show that these solutions must approximately satisfy the so-called Patlak–Keller–Segel diffusion equation (8.13). In a former paper [34], Patlak already deduced this equation under similar (partly more general and partly more restricted) hypotheses with the aid of a formal Taylor expansion and by rather complicated arguments,

using explicit calculations for different dimensions $n = 3, 2, 1$. The first part of Section 8 may be viewed as a simplified version of Patlak's argument.

In order to give a precise mathematical justification for the validity of this diffusion approximation we use a singular perturbation approach to prove (Section 9) that indeed the probability density $\bar{\sigma}(t, x, \theta)$ of individuals moving at time t and position x in direction θ can be written as

$$\bar{\sigma}(\cdot, \theta) = \frac{1}{|S|}(u^0 + nw^0 \cdot \theta) + \text{smaller terms}, \tag{1.1}$$

where u^0 exactly satisfies the diffusion equation (8.13) with mean flux cw^0. The choice of suitable L^2-energy functionals enables us to prove a global error estimate for all time (Theorems 1 and 2 in Section 9).

The general asymptotic analysis developed by Kurtz [19] and Papanicolaou [32, 33] can, in principle, be applied here; however, under the same assumptions it would give error estimates, which hold only for finite time intervals and would be of the same order as the w^0-term in (1.1), see Theorem 2 in [32]. Thus, compared with this general approach, we obtain more detailed information about the special stochastic process describing chemotaxis by the application of an appropriate energy estimation method.

2. General Hypotheses on the Type of Locomotion

Consider the locomotion of individuals, moving independently of each other in the following way:

a) The motion of each individual or of a well defined observable part of it (the nucleus of a cell, for instance) is piecewise linear, where the (mean) speed of such a linear 'run' or 'step' equals $c(t, x)$, depending on time t and position x of the individual.
b) An individual, running in direction θ at (t, x) with run time τ, counted from the beginning of the run, stops at (t, x) with a given probability $\beta(t, x, \theta, \tau)$ per unit time.
c) If an individual stops a run with direction θ at (t, x), then after a negligibly short time ('twiddling' of bacteria, 'reorientation' of leukocytes) it chooses a new direction η of motion with a given probability $k(t, x, \theta; \eta)$.

These model assumptions reflect the observed flagellant motion of many bacteria in a liquid, see for example [6, 22]. They also can be regarded as an appropriate model to describe the locomotion of certain types of cells migrating on a surface in almost straight track segments of varying lengths. For leukocytes compare Peterson and Noble [35], Allan and Wilkinson [3] or Zigmond [41], Figure 1, for mouse fibroblasts see Albrecht–Buehler [1], Figure 2. A more detailed investigation of the hypotheses (a)–(c) is given in Sections 4 and 5.

3. Modelling Equations

The constitutive equations describing the stochastic model in Section 2 can be written down easily, provided the density $\sigma(t, x, \theta, \tau)$ of individuals, moving at

(t, x) in direction θ and having started their run a time τ ago, is a smooth function of its variables. Then with the aid of Gauss' theorem applied to suitable test domains one concludes from (a)–(c) the following *differential-integral-system* for σ:

$$\partial_t\sigma(\cdot, \theta, \tau) + \partial_\tau\sigma(\cdot, \theta, \tau) + \theta\cdot\nabla_x(c\sigma(\cdot, \theta, \tau)) = -(\beta\sigma)(\cdot, \theta, \tau) \quad \text{for } \tau > 0, \theta \in S, \tag{3.1}$$

and

$$\sigma(\cdot, \eta, 0) = \int_0^\infty\int_S (\beta\sigma)(\cdot, \theta, \tau)k(\cdot, \theta; \eta)\, d\theta\, d\tau \quad \text{for each } \eta \in S. \tag{3.2}$$

Here $S = S^{n-1}$ denotes the unit sphere in n-dimensional space ($n = 1, 2, 3$) and $d\theta$ the surface measure on S. The dot denotes dependence on (t, x), the time and space variables.

The left hand side of (3.1) expresses the total temporal change of σ along a run in direction θ at (t, x) with speed $c = c(t, x)$. It equals the loss of those individuals which stop their run per unit time with 'stopping' or 'turning' frequency $\beta(t, x, \theta, \tau)$. These immediately turn into a new direction η along the turn angle distribution

$$\eta \mapsto k(t, x, \theta; \eta).$$

This gives the integral relation (3.2) for the density $\sigma(t, x, \eta, 0)$ of individuals starting a new run in direction η at (t, x).

Usual experiments and observations are performed in a bounded region $\Omega \subset \mathbb{R}^n$, $n = 2$ or 3, with piecewise smooth boundary, which cannot be crossed by individuals of the population.

Suppose then (as a most simple model assumption) that an individual running in direction θ and reaching a boundary point x continues its run in the *reflected direction*

$$\phi_x(\theta) = \theta - 2(\theta\cdot\nu_x)\nu_x, \tag{3.3}$$

where ν_x denotes the outer normal to Ω at x.

The equations (3.1), (3.2) for points (t, x) with $x \in \Omega$ then have to be supplemented by the *boundary condition*

$$\sigma(t, x, \theta, \tau) = \sigma(t, x, \phi_x(\theta), \tau) \tag{3.4}$$

for all t, θ and τ and $x \in \overset{\circ}{\partial}\Omega = \{x \in \partial\Omega, \nu_x \text{ exists}\}$.

Remark. If β is independent of the run time τ, then the system (3.1), (3.2) for the time-space-velocity density

$$\bar{\sigma}(t, x, \theta) := \int_0^\infty \sigma(t, x, \theta, \tau)\, d\tau \tag{3.5}$$

directly gives the *differential integral equation*

$$\partial_t\bar{\sigma}(\cdot, \theta) + \theta\cdot\nabla_x(c\bar{\sigma}(\cdot, \theta)) = -(\beta\bar{\sigma})(\cdot, \theta) + \int_S (\beta\bar{\sigma})(\cdot, \eta)k(\cdot, \eta; \theta)\, d\eta. \tag{3.6}$$

This is just the forward equation for the probability density of the stochastic process constructed by Stroock [40]. And in the case $n = 1$ it represents the basic equations, from which Keller [16] and Segel [37, 38] derived their approximating diffusion equations.

The first problem is to obtain values for the turning frequency β. In Figure 1 (Fig. 6 of [6]), Berg and Brown plotted the amount of observed run lengths exceeding a time τ using a logarithmic scale.

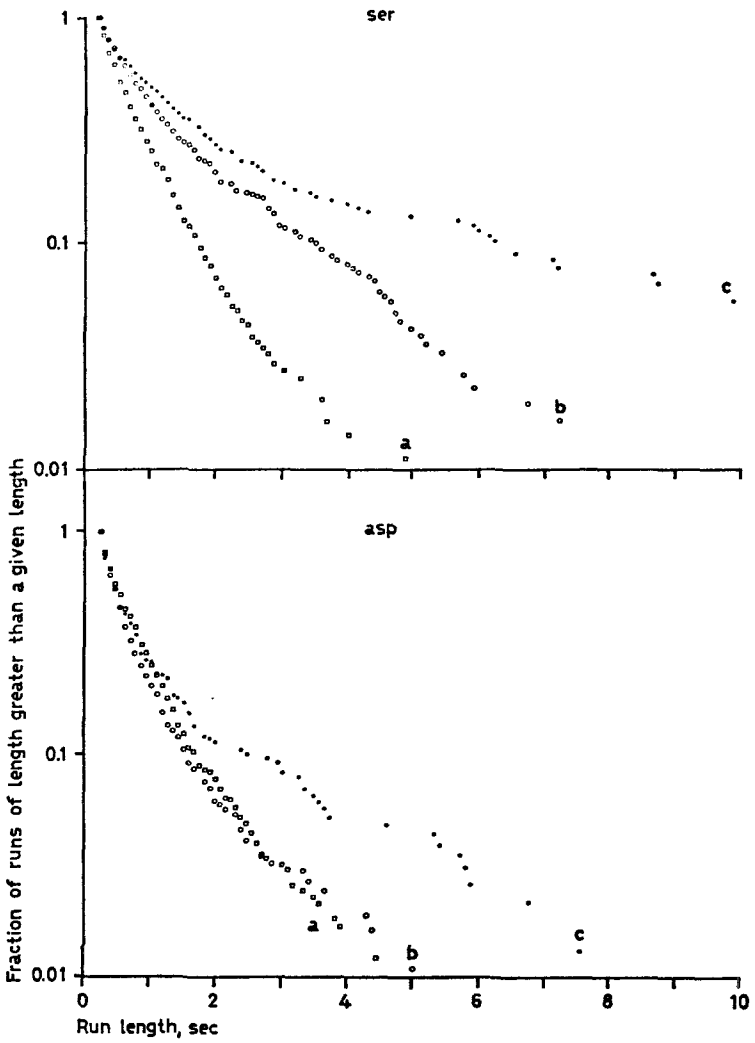


Fig. 1. The data from the serine (*top*) and the aspartate (*bottom*) experiments plotted as the logarithm of the fractional number of runs of length greater than a given length. a = Runs in the control experiments; b = runs down the gradient; c = runs up the gradient. From H. C. Berg and D. A. Brown [6], Figure 6

The probability distribution $q_{t,x,\theta}(\tau)$ of individuals, starting a run at (t, x) in direction θ and running at least for a time τ, can be calculated from the backward equation to (3.1) as

$$q_{t,x,\theta}(\tau) = \exp\left(-\int_0^\tau \beta(t + s, x + \zeta_{t,x,\theta}(s), \theta, s)\, ds\right), \tag{3.7}$$

where $\zeta_{t,x,\theta}(s)$ denotes the vector which the individual runs from point x in the time interval $[t, t + s]$, $\zeta_{t,x,\theta}(s) = cs\theta$ for constant speed c. (For bounded regions, $x + \zeta_{t,x,\theta}(s)$ describes the successively reflected path.)

The measurements of bacteria in Figure 1 to a certain extent agree with this exponential q-distribution. In an isotropic medium the stopping frequency β is nearly constant and independent of θ, whereas in media with a given concentration gradient $\nabla_x \rho$ of a chemotactic factor (ρ) the value of β has to be smaller (especially for τ about 5–7 s), if the sensed gradient $\theta \cdot \nabla_x \rho$ is essentially positive, and larger, if it is negative.

A simple functional dependence

$$\beta(t, x) = \beta_0(\rho(t, x)), \tag{3.8}$$

meaning that each cell is able to sense only the chemotactic factor concentration at some time and position, would lead to a contradiction, as Segel [37] has already pointed out. He therefore postulated as a 'simplest' realistic theoretical model a dependence of the form (see Eq. (45) in [38]):

$$\beta(t, x, \theta) = \beta_0(\rho(t, x), D^\theta \rho(t, x)), \qquad D^\theta \rho \coloneqq \partial_t \rho + c\theta \cdot \nabla_x \rho, \tag{3.9}$$

describing a 'differentially' sensitive receptor mechanism in the moving cells. Compare the related experiments [8, 22].

Previously Keller [16], Eq. (17), modelled such a mechanism by postulating a 'memory' time T such that the turning frequency (for constant c) is given by

$$\beta(t, x, \theta) = \beta_0(\rho(t, x), \rho(t - T, x - Tc\theta)). \tag{3.10}$$

In both models the important question remains how the postulated changes in the amount of bounded ρ-receptors at the cell surface regulate the turning frequency β of its locomotive apparatus. Obviously the regulation occurs during the run of the cells. Thus, in order to build into a mathematical model various (up to now mostly hypothetical) biochemical or biophysical concepts about the run control mechanism, the more detailed system (3.1), (3.2), where β also depends on τ, seems to be suitable. We will discuss this in the next section.

4. A Biochemical Model of Run Length Control

Suppose the locomotion mechanism of a cell is controlled by some internal chemical activator a (for example Ca^{++}) in such a way that the cell continues its run as long as the concentration of a is above (below) a certain critical level a^* and that during locomotion (rotating flagella of certain bacteria, extending leading pseudopods of leukocytes or amoebae) this activator is decreased (increased) with rate λ.

If during a run some receptor-sensor-mechanism at the cell membrane regulates the additional generation (production or influx) of the activator, this will lead to change of the run length. As a conceivable model we assume that

the fast binding of an extracellular diffusing chemotactic factor with concentraction ρ induces a momentary portion of bounded receptor sites $b = b(\rho)$, (4.1)

an enzyme system e (at the bottom of the receptor) instantaneously is switched into an active state e^* with association constant $A = A(b(\rho))$ depending on the receptor state, (4.2)

the active enzyme e^* converts a substrate s into the activator a (or induces an active transport of extracellular substance s to become intracellular a) along the simple reaction scheme

$$s + e^* \underset{k_{-1}}{\overset{k_1}{\leftrightarrows}} \kappa \underset{k_2}{\overset{k_{-2}}{\leftrightarrows}} a + e, \tag{4.3}$$

being fast compared with averaged run time $\bar{\tau}$ of a cell, $k_{\pm i} \gg 1/\bar{\tau}$.

Then with $K = k_{-1}k_2/k_1k_{-2}$ the quasi steady state kinetics can be written in the following system of equations:

$$a = \frac{\pi}{K} s \quad \text{with } \pi := \frac{e^*}{e} = A(b(\rho)) \tag{4.4}$$

$$(a + s)^{\cdot} = -\lambda.$$

To complete the model of run length control, suppose that

by reaching the critical a-level a^*, the locomotion of the cell stops for a short time, small compared with $\bar{\tau}$ (a bacterium tumbles by opposite rotation of the flagellar bundle, a leukocyte or amoeba stops the elongation of the leading pseudopod and begins the protrusion of a new one), and (4.5)

that during such a *tumble* or *reorientation* phase the a-level at the (new) locomotion system in the cell is raised from a^* to a new value a_0 according to a Poisson distribution $1/\mu_0 \exp(-(a_0 - a^*)/\mu_0)$, (reflecting observations of Berg and Brown [6], that the duration of the tumble phase for bacteria is exponentially distributed). The factor μ_0 expresses the 'mean locomotive activation' of a cell at the beginning of a new run phase, see Figure 2. (4.6)

If the chemotactic factor ρ is also chemokinetic, the value μ_0 depends on ρ, for example via the same receptor mechanism $\mu_0 = \mu_0(\rho) = M(b(\rho))$. A similar dependence is conceivable for the critical value $a^* = a^*(\rho)$, the consumption rate $\lambda = \lambda(\rho)$, and also for the displacement speed $c = c(\rho)$.

From (4.4) it follows that if the activator level of a cell at the beginning of a run in

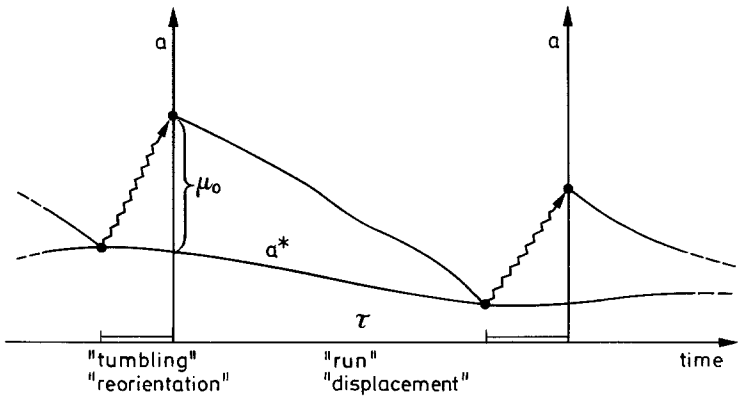


Fig. 2

direction θ at (t_0, x_0) has the value $a_0 > a_0^*$, it will reach the critical value a_τ^* after a time τ, iff

$$a_\tau^*\left(1 + \frac{K}{\pi_\tau}\right) = a_0\left(1 + \frac{K}{\pi_0}\right) - \int_0^\tau \lambda_r \, dr,$$

where we have used the notation

$$a_\tau^* := a^*(\rho(t_0 + \tau, x_0 + \zeta_{t_0,x_0,\theta}(\tau))), \pi_\tau \text{ and } \lambda_\tau$$

analogously. This implies

$$a_0 - a_0^* = \frac{\pi_0}{K + \pi_0}\int_0^\tau \left\{\lambda_r + \left(a^* \frac{K + \pi}{\pi}\right)_r^{\cdot}\right\} dr. \tag{4.7}$$

Since according to (4.6) the distribution of run lengths exceeding this value τ is

$$q_{t_0,x_0,\theta}(\tau) = \exp\left(-\frac{a_0 - a_0^*}{\mu_0}\right),$$

the identities (3.7) and (4.7) give the following expression for the *turning frequency* during a run phase:

$$\beta(\cdot, \theta, \tau) = \left(\frac{\pi}{\mu_0(K + \pi)}\right)_{\theta,\tau} \cdot \left(\lambda + \left(a^* \frac{K + \pi}{\pi}\right)' \cdot D^\theta \rho\right), \tag{4.8}$$

where the first factor

$$\phi_{\theta,\tau}(t, x) := \phi(\rho(t - \tau, x + \zeta_{t,x,\theta}(-\tau)))$$

counts the chemoeffector concentration at the beginning of the run, while the coefficient functions in the second factor are evaluated at the momentary concentration $\rho = \rho(t, x)$.

The expression (4.8) based on the hypotheses (4.1)–(4.3), (4.5) and (4.6) explains the behavior observed in the mentioned experiments (Fig. 1): the turning frequency β is diminished proportional to the sensed gradient $D^\theta\rho$ during a run, if for example the critical level $a^*(\rho)$ decreases with increasing concentration ρ or the receptor-effector kinetics $\pi(\rho)$ is monotone increasing.

For migrating cells like leukocytes or amoebae the mechanism controlling the duration of a displacement and the maintenance of a polarity in the moving direction seems to be connected with the process of discovering preferable directions during reorientation (see the next section and [43]).

Nevertheless the control model above, by identifying the activator $\boldsymbol{a}$ with some regulatory substance (Ca^{++} or cAMP for example) which induces or maintains an intracellular filamentous system, can describe this effect in a simplified manner, compare also [11, 39].

More detailed models have been developed to describe the sensory control of bacterial locomotion and chemotaxis, see for instance [7, 18, 31]. If again $\boldsymbol{a}$ denotes the intracellular Ca^{++}-level and a^* is considered as an upper threshold initiating clockwise rotation of flagella [31], then the hypotheses above can serve as a simple switching model neglecting the phenomenon of sensory adaptation.

Other more realistic biochemical models as in [7] or [18] could be built into the same framework by enlarging the number of control variables or by altering their functional dependence. For example an adaptation behavior of the threshold a^* (in analogy to the 'adaptation reservoir' in [7]) can reproduce the observed asymmetry of the turning frequency $\beta(\cdot, \theta, \tau)$ depending on the sign of $D^\theta\rho$. Compare [8], [27] and [37].

5. Reorientation of Turn Angle Distributions

Statistics for the change of direction during the tumble phase of bacteria [6] show a symmetric distribution of new directions η around the former one θ (see Fig. 3a):

$$k(\cdot, \theta; \eta) = h(\cdot, |\eta - \theta|), \tag{5.1}$$

where $|\eta - \theta|$ may denote the distance of points η, θ on the unit sphere (or their space angle, for example).

Contrary to that, cells creeping on a surface by adhesion have been observed to change their direction asymmetrically in preference for directions up the chemotactic gradient, for leukocytes compare Nossal and Zigmond [30], Figure 2.

Guided by various reports about the surface activities of such cells during locomotion (cf. [2, 10, 39]) let us consider the following model for reorientation of migrating cells: Assume that

(5.2) there are active protrusions ('pilot' pseudopods [12]) on the cell surface, which occur symmetrically with respect to the direction θ of the preceding cell displacement according to the probability distribution

$$\eta \mapsto h(\cdot, |\eta - \theta|),$$

the 'testing' protrusions enlarging with (mean) speed $c_0 = c_0(\rho)$ in direction η bear fast binding ρ-specific receptors with the effect that an increase (decrease) of the portion $b = b_\eta(\rho)$ of bound receptors during protrusion increases (decreases) the probability for extending an (afterwards leading) pseudopod in this direction (for example by stabilization of a filamentous system at this region), (5.3)

the density or affinity of ρ-receptors for the testing protrusions is symmetric with respect to θ, (5.4)

$$b'_\eta(\rho) \sim p(\rho, |\eta - \theta|).$$

Now the change of bound receptor sites during a relatively short protrusion period of mean length $\delta_0 < \bar{\tau}$ is proportional to $\delta_0 \cdot b'_\eta(\rho) \cdot D_0^\eta \rho$, where

$$D_0^\eta \rho := \partial_t \rho + c_0 \eta \cdot \nabla_x \rho$$

denotes the chemotactic gradient along a testing protrusion in direction η.

Then (5.2)–(5.4) lead to the model hypothesis, that the probability $k(\cdot, \theta; \eta)$ for a switch from direction θ to direction η is proportional to

$$h(\cdot, |\eta - \theta|) \cdot (1 + \delta_0 p(\rho, |\eta - \theta|) D_0^\eta \rho).$$

After normalization[1] to a probability measure, one gets the following expression for the *turn angle distribution*:

$$\begin{aligned} k(\cdot, \theta; \eta) = h(\cdot, |\eta - \theta|)(1 &+ \delta_0(p(\cdot, |\eta - \theta|) - \bar{p})\partial_t \rho \\ &+ \delta_0 c_0 (p(\cdot, |\eta - \theta|)\eta - \bar{p}\psi^p \theta) \cdot \nabla_x \rho), \end{aligned} \tag{5.5}$$

where h, c_0 and p are evaluated at the momentary concentration level ρ, where with $\mathbb{1} := (1, 0, \cdots, 0) \in S$

$$\bar{p} := \int_S (h \cdot p)(\cdot, |\eta - \mathbb{1}|)\, d\eta \tag{5.6}$$

describes the 'mean protrusion sensitivity' over the whole cell surface and where the so-called 'forward index' of this protrusion sensitivity

$$\psi^p := \frac{1}{\bar{p}} \int_S (h \cdot p)(\cdot, |\eta - \mathbb{1}|)\eta_1\, d\eta \tag{5.7}$$

with $-1 \leqslant \psi^p < 1$ is positive (negative) if the majority of ρ-receptors of a turning cell lies on the anterior (posterior) part of its membrane surface.

Clearly one has to suppose that the bracket in (5.5) stays positive. But this will be fulfilled if $\delta_0 c_0 \bar{p}$ and δ_0 are relatively small. Compare assumption (8.12).

With suitable choices of h and p it is possible to reproduce the measured data in [30], at least qualitatively. This and a comparison with the turn angle model of Nossal [26] can be found in [4].

---

[1] Linearized with respect to $(\delta_0 D_0^\eta \rho)$, which is justified for small δ_0, see (8.18).

6. Scaling of the Differential-Integral System

Let T and X denote the size of 'macroscopic' time and space variables determined by the experimental situation, for example T is the time during which changes in density or orientation of individuals are observed and X is the diameter of the region Ω, for example in the Zigmond bridge assay [42] one can choose $T \sim 60$ min and $X \sim 100\,\mu$.

Further, suppose that ρ is already dimensionless, which means that it stands for ρ/ρ_0, where ρ_0 for example is an averaged value of ρ in Ω. This includes, that the receptor kinetics $\pi(\rho)$, $\mu_0(\rho)$ etc. in (4.8) and the sensitivity-distribution $p = p(\rho, \cdot)$ in (5.5) are measured relative to this averaged value ρ_0 and thus are dimensionless.

For the homogeneous distribution $\rho \equiv 1$ the turning frequency is constant $\beta = \boldsymbol{\beta}$, and eq. (3.1) implies, that the mean run time τ_0 of individuals is $\tau_0 = 1/\boldsymbol{\beta}$. In the following we will consider situations, where the *mean run time is relatively small*:

$$\varepsilon := \frac{\tau_0}{T} \ll 1, \tag{6.1}$$

an assumption, which is fulfilled in most chemotaxis assays. (For the Zigmond bridge a value $\tau_0 \sim$ 1–5 min gives $\varepsilon \sim 0.02$–0.1.)

Passing over to dimensionless variables t/T, x/X, τ/τ_0 and dimensionless quantities cT/X, c_0T/X, $\lambda \cdot \tau_0$, Eq. (3.1) reads, again using the old notations,

$$\partial_t \sigma + \varepsilon(\partial_t \sigma + \theta \cdot \nabla_x(c\sigma)) = -\beta_\varepsilon \sigma, \quad \text{for } \tau > 0, \tag{6.2}$$

where, based on the model assumptions of Section 4,

$$\begin{aligned} \beta_\varepsilon(\cdot, \theta, \tau) &= \left(\frac{\pi}{u_0(K+\pi)}\right)_{\theta, \varepsilon\tau} \cdot \left(\lambda + \varepsilon\left(a^* \frac{K+\pi}{\pi}\right)' \cdot D^\theta \rho\right) \\ &= \beta_0\left(1 - \varepsilon\left(\frac{\chi_0}{\beta_0} + \tau\chi_1\right) D^\theta \rho + (\varepsilon c)^2 0(\tau(1+\tau))\right) \end{aligned} \tag{6.3}$$

with

$$\begin{aligned} \beta_0 &= \frac{\lambda}{\mu_0} \frac{\pi}{K+\pi}, \\ \chi_0 &= -\frac{\pi}{\mu_0(K+\pi)} \left(a^* \frac{K+\pi}{\pi}\right)', \\ \chi_1 &= -\frac{\pi}{\mu_0(K+\pi)} \left(\mu_0 \frac{K+\pi}{\pi}\right)', \end{aligned} \tag{6.4}$$

all coefficients depending on the momentary chemotactic concentration ρ. A discussion of these coefficients and a comparison with former models is postponed until Section 8.

Note that $\chi_1 = (\ln \beta_0)'$ provided λ is independent of ρ.

Similarly replacing $\delta = (\delta_0/T)\bar{p}$, Eq. (3.2) can be written in the form

$$\sigma(\cdot, \blacksquare, 0) = T_\delta\left(\int_0^\infty (\beta_\varepsilon\sigma)(\cdot, \blacksquare, \tau)\, d\tau\right) \tag{6.5}$$

where the *turn angle operator* on the sphere S is

$$T_\delta\phi(\eta) = \int_S \phi(\theta)k_\delta(\cdot, \theta; \eta)\, d\theta,$$

with kernel, according to the model assumptions of Section 5,

$$k_\delta(\cdot, \theta; \eta) = h(\cdot, |\eta - \theta|)\left(1 + \delta\left(\frac{p(\cdot, |\theta - \eta|)}{\bar{p}} - 1\right)\delta_t\rho + \delta c_0\left(\frac{p(\cdot, |\theta - \eta|)}{\bar{p}}\eta - \psi^p\theta\right)\nabla_x\rho\right).$$

Since the τ-dependence of σ usually cannot be measured experimentally, we are interested in an approximate equation for the density $\bar{\sigma}$ defined in (3.5):

Proposition 1. *If σ is a solution of system* (6.2), (6.5), *then the density $\bar{\sigma}$ defined in* (3.5) *satisfies the differential integral equation*

$$\varepsilon(\partial_t\bar{\sigma} + \theta\cdot\nabla_x(c\bar{\sigma})) = -\beta_0(id - T_\delta)\left(\left(1 - \frac{\varepsilon}{\beta_0}\tilde{\chi}D^\eta\rho\right)\bar{\sigma} - \varepsilon\chi_1 D^\eta\rho\left(\sigma^{(1)} - \frac{1}{\beta_0}\bar{\sigma}\right) + (\varepsilon c)^2\sigma_\varepsilon\right) \tag{6.6}$$

with

$$\tilde{\chi} = \chi_0 + \chi_1, \tag{6.7}$$

$$\sigma_\varepsilon = \frac{1}{\beta_0 c^2}\chi_0\chi_1(D^\eta\rho)^2\sigma^{(1)} + \left[\frac{1}{2c^2}(\chi_2(D^\eta\rho)^2 + \chi_1(D^\eta)^2\rho) + 0(\varepsilon c)\right]\sigma^{(2)} + \varepsilon c0(\sigma^{(3)}), \tag{6.8}$$

and χ_2 defined in (6.13). *Here*

$$\sigma^{(\nu)}(\cdot, \theta) := \int_0^\infty \tau^\nu\sigma(\cdot, \theta, \tau)\, d\tau, \quad \nu \geqslant 1, \tag{6.9}$$

denotes the ν-th τ-moment, for which the following differential equations, resp. inequalities, hold:

$$\varepsilon(\partial_t\sigma^{(\nu)} + \theta\cdot\nabla_x(c\sigma^{(\nu)})) \begin{cases} = -\beta_0\left(1 - \varepsilon\dfrac{\chi_0}{\beta_0}D^\theta\rho\right)\sigma^{(\nu)} + \nu\sigma^{(\nu-1)} \\ \quad + \varepsilon\beta_0\chi_1 D^\theta\rho\sigma^{(\nu+1)} + (\varepsilon c)^2 0(\sigma^{(\nu)} + \sigma^{(\nu+2)}) \\ = -\beta_0\sigma^{(\nu)} + \nu\sigma^{(\nu-1)} + \varepsilon c0(\sigma^{(\nu)} + \sigma^{(\nu+1)}) \\ \leqslant -\beta_*\sigma^{(\nu)} + \nu\sigma^{(\nu-1)}, \end{cases} \tag{6.10}$$

with $\beta_* = \inf\beta_\varepsilon > 0$ and the notation $\sigma^{(0)} := \bar{\sigma}$.

We note that the mean running time of individuals currently moving in direction θ is given by

$$\bar{\tau}(\cdot, \theta) = \frac{\sigma^{(1)}(\cdot, \theta)}{\bar{\sigma}(\cdot, \theta)} \tau_0. \tag{6.11}$$

In Section 8 we will show that under certain conditions the last two terms in the bracket on the right hand side of (6.6) remain small compared to the first one. Thus up to a small error the differential integral equation (6.6) corresponds to (3.6) with the modified turning frequency

$$\beta(\cdot, \theta) = \frac{1}{\varepsilon}\left(\beta_\varepsilon(\cdot, \theta, 0) + \frac{1}{\beta_0}\partial_\tau\beta_\varepsilon(\cdot, \theta, 0)\right). \tag{6.12}$$

This means that a τ-linear change of the turning frequency has an additive effect on the averaged turning frequency $\beta(\cdot, \theta)$, which determines the evolution of the density $\bar{\sigma}$. This effect is just reflected in the additive formula (6.7) for $\tilde{\chi}$.

For the *proof* of (6.6) integrate Eq. (6.2) with respect to τ, use (6.5) and the exponential decay of σ for $\tau \to \infty$. The remaining terms can be expanded in powers of εc, regarding that (6.3) implies

$$\partial_\tau\beta_\varepsilon(\cdot, \theta, 0) = -\varepsilon\beta_0\left(1 - \varepsilon\frac{\chi_0}{\beta_0} D^\theta\rho\right)\chi_1 D^\theta\rho$$

and

$$\partial_\tau^2\beta_\varepsilon(\cdot, \theta, 0) = \varepsilon^2\beta_0\left(1 - \varepsilon\frac{\chi_0}{\beta_0} D^\theta\rho\right)(\chi_2(D^\theta\rho)^2 + \chi_1(D^\theta)^2\rho)$$

with

$$\chi_2 = -\frac{\pi}{\mu_0(K + \pi)}\left(\mu_0\frac{K + \pi}{\pi}\right)'' + 2\chi_1^2. \tag{6.13}$$

This gives the estimate (6.8).

Similarly the inequalities (6.10) follow, if (6.2) is multiplied by τ^ν and then integrated.

If the region Ω is bounded, with the assumptions in Section 3, then the boundary condition (3.4) clearly induces the same reflection condition for the integrated densities

$$\sigma^{(\nu)}(t, x, \cdot)\circ\phi_x = \sigma^{(\nu)}(t, x, \cdot) \quad \forall t > 0, x \in \mathring{\partial}\Omega, \nu \geqslant 0. \tag{6.14}$$

Given initial values $\bar{\sigma}(0, x, \theta)$ and $\sigma^{(1)}(0, x, \theta)$ as well as estimates for $\sigma^{(\nu)}(0, \cdot)$, $\nu = 2, 3$, then the evolution of a related solution $\bar{\sigma}$ of the initial-boundary-value problem (6.6), (6.14) (accompanied by the differential inequalities (6.10) for $\sigma^{(\nu)}$, $\nu \geqslant 1$) essentially depends on the smallness of ε compared with the size of the mean speed c and on the properties of the 'turning operator'

$$B := (id - T_\delta)\left(1 - \frac{\varepsilon}{\beta_0}\tilde{\chi} D^\theta\rho\right), \tag{6.15}$$

regarded for example as a compact operator on the Hilbert space $L^2(S)$ of square integrable functions on the sphere S, for each fixed (t, x).

7. Properties of the Turning Operator

Since $k_\delta(\cdot, \theta; \blacksquare)$ is a probability kernel, one has

$$\int_S (id - T_\delta)\phi = 0 \quad \text{for all } \phi \in L^2(S),\ \delta \geqslant 0.$$

Thus the turning operator B defined in (6.15) has the property

$$B: L^2(S) \to [\text{const}]^\perp = \{\phi \in L^2(S): \int_S \phi = 0\}.$$

This degeneracy of the turning operator actually leads (by averaging Eq. (6.6) over S) to the *first conservation law*

$$\partial_t \bar{u} + \nabla_x \cdot (c\bar{w}) = 0 \tag{7.1}$$

for the *density*

$$\bar{u}(t, x) = \int_S \bar{\sigma}(t, x, \theta)\, d\theta$$

and the *mean direction*

$$\bar{w}(t, x) = \int_S \bar{\sigma}(t, x, \theta)\theta\, d\theta.$$

We note an analogy to the derivation of hydrodynamical conservation laws from the Boltzmann equation. However, while the linearized Boltzmann operator B degenerates on a five-dimensional subspace of $L^2(\mathbb{R}^n)$, see, e.g. Nishida [25], the main symmetric part $(id - T_0)$ of the turning operator is positive definite on $[\text{const}]^\perp$ and T_0 has an eigenfunction system identical to the Fourier series system in the case $n = 2$:

Lemma. *Suppose the unbiased turn angle distribution h is continuous, then the compact symmetric operator*

$$T_0\phi(\eta) := \int_S \phi(\theta)h(\cdot, |\eta - \theta|)\, d\theta$$

has a complete set $\{\phi_j, j \geqslant 0\}$ of orthogonal eigenfunctions in $L^2(S)$ with eigenvalues $\psi_\nu \in \mathbb{R}$, where we can choose

$$\phi_0(\theta) = \frac{1}{|S|} \qquad \text{with eigenvalue } \psi_0 = 1,$$

$$\phi_j(\theta) = \frac{n}{|S|}\theta_j \quad \text{with eigenvalue } \psi := \psi_1 = \int_S h(\cdot, |\eta - \mathbb{1}|)\eta_1\, d\eta, \tag{7.2}$$

called the 'forward index' of protrusion activity[2] *in analogy with* (5.7). *For $n \geqslant 2$ the*

[2] Compare Patlak [34], (30), where ψ is called the 'coefficient of persistence of direction', identical with the 'mean cosine' [21].

'θ-quadratic' eigenfunctions $\phi_{n+1}, \ldots, \phi_{2n+n(n-1)/2}$ can be chosen to span the eigenspace

$$\left\{\left(\theta_i\theta_j - \frac{1}{n}\,\delta_{ij}\right), \quad i,j = 1, \ldots, n\right\}$$

with eigenvalue

$$\psi_2 = 1 - n\int_S h(\cdot, |\eta - \mathbb{1}|)\eta_n^2\, d\eta. \tag{7.3}$$

Moreover we have $|\psi_\nu| < 1$ for all $\nu \geqslant 1$, $n \geqslant 2$, and id-T_0 is positive definite on $[\phi_0]^\perp$. Finally each function $\phi \in L^2(S)$ can uniquely be written

$$\phi(\theta) = \frac{1}{|S|}\left(u + nw\cdot\theta + n\frac{n+2}{2}\sum_{i,j=1}^{n} z_{ij}\theta_i\theta_j\right) + \hat{\phi}(\theta) \tag{7.4}$$

briefly $\phi = [u, w, z; \hat{\phi}]$, where

$$u = \int_S \phi, \qquad w = \int_S \phi(\theta)\theta\, d\theta$$

and

$$z_{ij} = \int_S \phi(\theta)\left(\theta_i\theta_j - \frac{1}{n}\,\delta_{ij}\right) d\theta,$$

satisfying the conditions

$$z_{ij} = z_{ji} \quad \text{and} \quad \sum_{i=1}^{n} z_{ii} = 0, \tag{7.5}$$

and where $\hat{\phi}$ is orthogonal to all functions which are at most quadratic in θ.

The lemma similarly holds for the compact symmetric operator

$$T^p\phi(\eta) := \frac{1}{p}\int_S \phi(\theta)(hp)(\cdot, |\eta - \theta|)\, d\theta. \tag{7.6}$$

Its first two eigenvalues are $\psi_0^p = 1$ and $\psi_1^p = \psi^p$, which was already defined in (5.7). With this notation and with the hypotheses on T_δ we easily deduce the following

Representation of the Turning Operator in (6.15)

$$\begin{aligned} B = {} & id - T_0 - \nabla\rho\cdot\left(\delta c_0(\theta T^p - \psi^p T_0\theta) + \varepsilon\frac{\tilde{\chi}}{\beta_0}\, c(id - T_0)\theta\right) \\ & + \delta c_0\nabla\rho\cdot(\theta T^p - \psi^p T_0\theta)\varepsilon\frac{\tilde{\chi}}{\beta_0}\, c\nabla\rho\cdot\theta \\ & - \partial_t\rho\left(\delta(T^p - T_0)\left(1 - \varepsilon\frac{\tilde{\chi}}{\beta_0}\, c\nabla\rho\cdot\theta\right) + \varepsilon\frac{\tilde{\chi}}{\beta_0}\,(id - T_\delta)\right), \end{aligned} \tag{7.7}$$

where we obviously use θ to denote the related (vector valued) multiplication operator in $L^2(S)$, see the remarks at the beginning of the Appendix.

Thus the chemotactic gradient induces a nonsymmetric deformation of the main part $id - T_0$ of B, wherein the most important $\nabla\rho$-linear term appears as the sum of two effects: a direct alteration of the turn angle distribution by the operator T^p and an indirect modification consisting in a suppression of turns for cells migrating in the gradient direction. This additive influence of both effects appears later on in the formula (8.16) for the chemotaxis coefficient χ.

8. Smallness of Parameters and Formal Derivation of the Diffusion Equation

According to the turn angle distributions measured for bacteria [6], Figure 3a, and leukocytes [30], Figure 3b, we suppose that the higher eigenvalues of T_0 satisfy

$$1 - \psi_\nu \geqslant \tilde{\zeta} > 0 \quad \text{with some fixed } \tilde{\zeta} \text{ (not small) } \forall \nu \geqslant 2, \tag{8.1}$$

but we allow (contrary to the assumption in [34]) that the forward index ψ can be closer to 1. While three-dimensional bacterial locomotion typically shows $\psi \sim 0.3$, for the two-dimensional movement of leukocytes values $\psi \sim 0.85$ can be computed from Figure 3b below, see also [13].

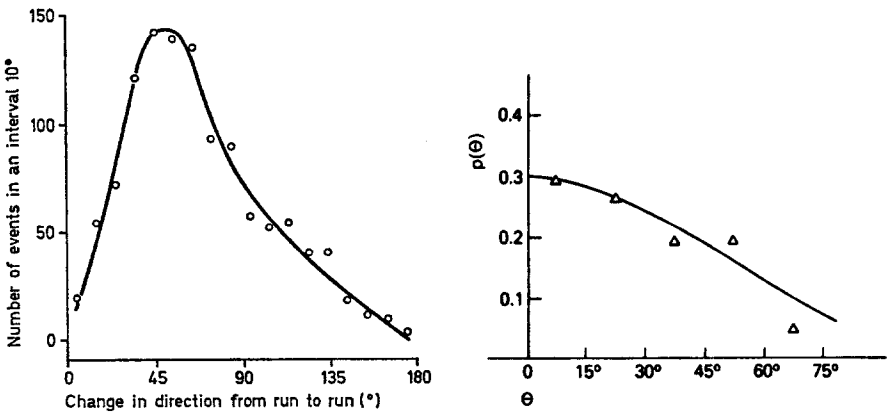
Furthermore we are particularly interested in such experiments for which the speed of each individual is large compared with the ratio X/T. (Usually leukocytes move with a speed of about $c \sim$ 10–20 μ/min, compared with $X/T \sim 1.5$ μ/min.)

Then introducing quantities ζ and α with

$$(1 - \psi) \sim \zeta \quad \text{and} \quad \frac{1}{c} \sim \alpha \tag{8.2}$$

we are interested in how the solutions of Eq. (6.6) depend on the smallness of the four parameters ε (mean run time), δ (protrusion sensitivity), ζ (turning strength) and α (inverse cell speed).

To obtain a zeroth order approximation we make the following



a b

Fig. 3. a from H. C. Berg and D. A. Brown [6]; b from R. Nossal [30]

Boundness Assumption. *Suppose* $\bar{\sigma}, \sigma^{(\nu)}, \nu \geqslant 1$, *solutions of* (6.6), (6.10), *together with their derivatives are bounded uniformly in the four parameters above.* (8.3)

Then the w-component of Eq. (6.6) can be written in the following way, using the eigenfunction representation of $\bar{\sigma} = [\bar{u}, \bar{w}, \bar{z}; \hat{\sigma}]$ in (7.4), formula (7.7) and the Appendix (10.5):

$$(1 - \psi)\bar{w} = \frac{1}{n}(1 - \psi)\left(\varepsilon c \frac{\tilde{\chi}}{\beta_0} + \delta c_0 \tilde{\psi}\right)\bar{u}\nabla\rho - \frac{\varepsilon}{\beta_0}\left(\frac{1}{n}\nabla(c\bar{u}) + \partial_t \bar{w}\right)$$

$$- \delta c_0(\psi^p\psi - \psi_2^g)P_{\nabla\rho}\bar{z} - \frac{\varepsilon}{\beta_0}P_{\nabla}(c\bar{z}) + R_w + 0(\varepsilon^2 c^2) \tag{8.4}$$

provided the natural condition

$$1 - \psi^p \leqslant 1 - \psi \tag{8.5}$$

holds, which roughly means that if the protrusion activity is concentrated in the front region of the cell, the same is true for the protrusion sensitivity. This implies the boundedness of

$$\tilde{\psi} := \frac{1 - \psi^p\psi}{1 - \psi} = 1 + \psi\frac{1 - \psi^p}{1 - \psi}. \tag{8.6}$$

The last term in (8.4) arises from the two remainder terms in (6.6), since Eq. (6.10) involves the approximate relation

$$\sigma^{(\nu)} = \frac{\nu!}{\beta_0 \nu}\bar{\sigma} + 0(\varepsilon c), \quad \nu \geqslant 1. \tag{8.7}$$

Now (8.4) has the consequence that generally $(1 - \psi)\bar{w}$ is of the same order as $(\varepsilon c + \zeta\delta c_0)$. On the other hand Eq. (7.1) and the boundedness of $\partial_t \bar{u}$ generally (i.e. in case of a nonlinear ρ-gradient) requires $\bar{w} = 0(\alpha)$, so that it is reasonable to assume that the parameters are related as follows:

$$\varepsilon c \leqslant \zeta\alpha \quad \text{and} \quad \delta c_0 \leqslant \alpha. \tag{8.8}$$

A similar analysis of the z- and $\hat{\phi}$-component of Eq. (6.6) yields, since the protrusion speed c_0 usually exceeds the displacement speed c,

$$\bar{z} = 0(\alpha^2) \quad \text{and} \quad \hat{\sigma} = 0(\alpha^3), \tag{8.9}$$

more precisely

$$\bar{z} = z[\bar{u}, \bar{w}] + 0(\alpha^4) \quad \text{with } z[u, w] \tag{8.10}$$

as in (10.7). Inserting this in (8.4) and using (10.4) we obtain an

Approximate equation for the mean direction

$$\bar{w} = \frac{1}{n}\left(\varepsilon c \frac{\tilde{\chi}}{\beta_0} + \delta c_0 \tilde{\psi}\right)\bar{u}\nabla\rho - \frac{\varepsilon}{n(1 - \psi)\beta_0}\nabla(c\bar{u})$$

$$- \frac{(\delta c_0)^2}{(n + 2)(1 - \psi)}\psi^p(\psi^p\psi - \psi_2^g)\left(|\nabla\rho|^2\bar{w} + \left(1 - \frac{2}{n}\right)(\nabla\rho \cdot \bar{w})\nabla\rho\right)$$

$$+ 0(\zeta\alpha^2 + \alpha^3). \tag{8.11}$$

First consider the case $\alpha^2 \ll \zeta$, which implies that the third term in (8.11), being of order $0(\alpha^3/\zeta)$, can be neglected. Insertion of $\bar{w}$ into the conservation law (7.1) then results in the well-known (Patlak–)Keller–Segel diffusion equation for $\bar{u}$. The assumptions on the parameters can be summarized as follows:

Hypotheses relating the size of parameters

$$\frac{\varepsilon}{\zeta},\ \delta,\ \delta\frac{c_0}{c} \leqslant \alpha^2 \ll 1 \tag{8.12}$$

$$1 - \psi^p \leqslant \zeta \quad \text{and} \quad 1 - \psi_v \sim 1 \quad \text{for } v \geqslant 2.$$

Proposition 2 (Patlak–Keller–Segel diffusion equation). *Assume that* $\bar{\sigma}$, $\sigma^{(v)}$, *solutions of system* (6.6), (6.10), *together with their derivatives are bounded independently of* α, *where* α, ε, δ *and* ζ *with* $\alpha^2 \ll \zeta$ *fulfil the hypotheses* (8.12). *Then the* density $\bar{u}$ *solves the scaled diffusion equation*

$$\partial_t u = \nabla_x\left(\frac{\mu}{c}\nabla_x(cu) - \chi u \nabla_x \rho\right) \tag{8.13}$$

up to an error of order $0(\zeta\alpha + \alpha^2/\zeta)$, *the* mean flux *being* (*approximately*)

$$c\bar{w} = \chi_c \bar{u}\nabla_x\rho - \mu\nabla_x\bar{u}, \qquad \chi_c := \chi - \mu\frac{c'}{c}, \tag{8.14}$$

where the motility *is*

$$\mu = \frac{\varepsilon c^2}{n(1-\psi)\beta_0} \quad \textit{with } \beta_0 = \frac{\lambda}{\mu_0}\frac{\pi}{K+\pi} \tag{8.15}$$

and the chemotaxis coefficient *is*

$$\chi = \frac{1}{n}\varepsilon c^2\left(\frac{\tilde{\chi}}{\beta_0} + \frac{\delta c_0}{\varepsilon c}\tilde{\psi}\right) \quad \textit{with } \tilde{\psi} \textit{ as in } (8.6) \tag{8.16}$$

and

$$\tilde{\chi} = \frac{\beta_0'}{\beta_0} - \left(\frac{a^*}{\mu_0}\right)',$$

provided λ *is independent of* ρ.

Furthermore the mean running time *defined in* (6.11) satisfies

$$\bar{\tau} = \frac{1}{\beta_0}\tau_0 + 0(\zeta\alpha). \tag{8.17}$$

Additional Remark (Modified diffusion equation). In the case $\zeta \leqslant \alpha^2$ the approximate equation (8.11) gives, instead of (8.14), the following approximation of the mean flux

$$c\bar{w} \cong \chi^\kappa \bar{u}\nabla_x\rho - \frac{\mu^\kappa}{c}(id - P_\kappa)(\nabla_x(c\bar{u})), \tag{8.14$'$}$$

where

$$\mu^\kappa = \mu/(1 + \kappa|\nabla\rho|^2), \qquad \chi^\kappa = \chi/\left(1 + 2\frac{n-1}{n}\kappa|\nabla\rho|^2\right)$$

and

$$P_\kappa v = \frac{(n-2)\kappa}{n + 2(n-1)\kappa|\nabla\rho|^2}(v\cdot\nabla\rho)\nabla\rho,$$

a projector in gradient direction, with

$$\kappa = \frac{1}{n+2}\frac{(\delta_0 c_0)^2}{1-\psi}\psi^p(\psi^p\psi - \psi_2^p) \leqslant \alpha^2/\zeta.$$

Inserting (8.14)′ in (7.1) yields a 'modified' Patlak–Keller–Segel equation, in which the motility and the chemotaxis coefficient are decreased if $\kappa|\nabla\rho|^2$ is large, see also [29]. (For $n \geqslant 3$ the diffusion matrix is anisotropic so that the motility in gradient direction is slightly reduced compared with orthogonal directions.) This shows that a locomotive behavior with small turn angles (such that $1 - \psi \leqslant \alpha^2$) and corresponding small step lengths and high speed does not lead to an improvement of the chemotactic effect.

Interpretation of the Parameter Assumptions (8.18)

The hypotheses (8.12) are fulfilled if (expressed in terms of *unscaled* parameters)

1) the speed of cell displacements and of testing protrusions is relatively large

$$c_0 \gtrsim c \gg \frac{X}{T},$$

and

2) the mean turning frequency is relatively small

$$\bar\tau \cong \frac{\tau_0}{\beta_0} \ll T,$$

such that

3) the product of mean step length $\bar\tau c$ and speed c remains bounded by

$$(\bar\tau c)c \leqslant (1-\psi)\frac{X^2}{T},$$

the quotient (up to a constant) just being the motility

$$\mu = \frac{1}{n}\frac{(\bar\tau c)c}{(1-\psi)X^2/T},$$

and

4) the ratio of mean protrusion length $\delta_0 c_0$ and mean step length $\bar\tau c$ remains bounded

$$(1-\psi)\frac{\delta_0 c_0}{\bar\tau c} \leqslant 1,$$

the chemotaxis coefficient just being

$$\chi = \mu(1-\psi)\left(\tilde\chi + \bar p\,\frac{\delta_0 c_0}{\bar\tau c}\tilde\psi\right).$$

In experimental situations the chemotactic effect due to a concentration gradient $\nabla\rho$ can be tested in various ways:

I. Mean Chemotropism Index

Suppose that the change in cell density can be neglected at least for a certain time, as it is the case for many experiments observing the individual cell paths [3, 14, 23]. Then under the hypotheses of Proposition 2 the '*chemotactic velocity*'

$$v = \frac{\text{mean flux}}{\text{density}}$$

can be approximated from (8.14) as

$$v \cong \frac{c\bar{w}}{\bar{u}} \cong \chi_c \nabla\rho. \tag{8.19}$$

Now the *mean chemotropism index* of individuals (that is the distance they move in direction of the gradient compared with the absolute path length after sufficiently many turns), using formula (4) in [30], can approximately be written as the quotient of chemotactic speed, i.e. the $\nabla\rho$-component of v, and the mean cell speed c:

$$\overline{CI} \cong \frac{v \cdot \nabla\rho}{c|\nabla\rho|}.$$

From (8.16) and (8.19) this can be computed in terms of unscaled parameters as

$$\overline{CI} \cong \frac{1}{n}\left[\left(\frac{\beta_0'}{\beta_0} - \frac{1}{1-\psi}\frac{c'}{c} - \left(\frac{a^*}{\mu_0}\right)'\right)\bar{\tau}c + \frac{1-\psi^p\psi}{1-\psi}\bar{p}\delta_0 c_0\right]|\nabla\rho|. \tag{8.20}$$

The approximation is valid for small $\bar{\tau}c|\nabla\rho|$ and small $\delta_0 c_0|\nabla\rho|$ in accordance with (8.18) and the scaling procedure in Section 6, this means, for relatively small changes of chemoattractant concentration over distances lying in the range of a mean cell displacement and of a mean protrusion length.

A similar assumption appears in the one-dimensional derivations of (8.13) by Keller [16] and Segel [37] and is fulfilled in most chemotactic gradient assays. Compare, for example, [42] with about 1–10% concentration difference over 10 μm.

The chemotropism index $\overline{CI}$ in (8.20) is the sum of two terms:

a) The first term is proportional to the maximal ρ-change over a mean cell displacement, with a proportion factor which is positive at some ρ-level if

a_1) the mean (random locomotive) turning frequency $\beta_0 = \beta_0(\rho)$ increases with ρ or

a_2) the mean displacement speed $c = c(\rho)$ decreases with increasing ρ,

both (a_1) and (a_2) imply a reduction of the motility μ (8.15) for increasing ρ-values, or

a_3) the critical activator level $a^* = a^*(\rho)$, responsible for the intracellular run control (cf. Fig. 2), related to the mean locomotive activation $\mu_0 = \mu_0(\rho)$ decreases with increasing ρ-values.

Hence a positive contribution to the chemotropism index is achieved, if ρ-specific receptors on the cell membrane regulate, in a way described in (a_1)–(a_3), one of

these locomotion control parameters, which can be related to the Ca^{++} level, the polymerization and stabilization of microfilaments and microtubuli or the membrane adhesion to the underlying surface or tissue. See the remarks following (4.8).

b) The second term in $\overline{CI}$ is proportional to the maximal ρ-change over a cell protrusion of mean length, with a proportion factor determined by the mean protrusion sensitivity $\bar{p}$ (5.6) and by the way in which the inducing ρ-receptors on active protrusions are distributed over the cell membrane, described by the value of ψ^p (5.7).

In the usual case that the protrusion activity is stronger on advancing parts of a migrating cell ($\psi > 0$) the chemotropism index turns out to be larger if the main part of free ρ-receptors are placed at the flanks in front. For a more detailed discussion compare [4].

II. Chemotactic Accumulation

A chemotactically sensitive cell population, if observed for longer times in a stationary gradient, accumulates in regions of high ρ-values (in vivo: leukocytes at infectious tissue parts [20], in vitro: migrating cells in the lower part of the Boyden filter [24] or bacteria in a densiometric assay [28]). Either the cell density grows exponentially (at least for some time) in those regions or it reaches a final distribution u_∞ which is a stable steady state solution of the diffusion equation (8.13).

If we suppose that the gradient $\nabla\rho$ is tangential at the boundary of Ω, with the aid of a maximum principle we easily deduce from (8.13) and the reflection condition (3.4), which implies the Neumann boundary condition for $\bar{u}$, that

$$u_\infty = \text{const.} \exp \int_{\rho_0}^{\rho} \frac{\chi_c}{\mu} \quad \text{with } \chi_c \text{ as in (8.14)}, \tag{8.21}$$

where the constant is uniquely determined by the total (time invariant) cell mass in Ω.

A sufficient condition for (global) stability of u_∞ is the existence of a $\lambda_0 > 0$ such that

$$\int_\Omega (\lambda_0 - \tfrac{1}{2}\nabla(\chi_c \nabla\rho))v^2 \leqslant \int_\Omega \mu |\nabla v|^2 \tag{8.22}$$

for all smooth functions v on Ω with $\int_\Omega v = 0$. Under this condition each solution of (8.13) approaches u_∞ exponentially with an exponent at least λ_0. Large values of λ_0 correspond to high motility.

Then (8.21) means that the degree of final cell accumulation depends on the so-called *chemotactic sensitivity*

$$\hat{\chi} := \frac{\chi_c}{\mu} = (1 - \psi)\frac{\beta_0'}{\beta_0} - \frac{c'}{c} - (1 - \psi)\left(\frac{a^*}{\mu_0}\right)' + (1 - \psi^p\psi)\bar{p}\,\frac{\delta_0 c_0}{\bar{\tau} c}. \tag{8.23}$$

Note that the chemotropism index in (8.20) is given by

$$\overline{CI} = \frac{1}{n(1-\psi)}\,\hat{\chi}\,|\nabla\rho|.$$

The first two terms in $\hat{\chi}$ represent the well-known phenomenon of '*trapping by migration inhibition*': either by an *enhancement of the turning frequency*, compare (a_1) above, or by a *reduction of cell speed*, compare (a_2), the majority of cells are guided into regions of higher concentrations of the chemotactic factor.

While '*indirect*' *chemotaxis* due to a bias of step lengths is reflected in the third term of $\hat{\chi}$, compare the remarks in (a_3) above, the last term represents '*direct*' *chemotaxis* by preferred orientation of cells along the gradient, compare (b) above, [4] and [27].

Thus the expressions (8.20) and (8.23) for the chemotropism index and the chemotactic sensitivity show that various mechanisms can contribute to the observed phenomena of chemotaxis, and that along with the modelling hypotheses (Sections 2, 4 and 5) measured values of $\overline{CI}$ or $\hat{\chi}$ have to be composed from several 'microscopic' ρ-dose dependent parameter functions according to the special experiment.

Indeed recent observations suggest that one chemotactic factor can induce both responses: chemotaxis at temperate ρ-concentrations and migration inhibition at high ρ-concentrations. Compare Jungi [15].

We note that in one space dimension the diffusion approximation by Segel [38], Eqs. (48) and (49), can be reproduced by (8.13), if β_0 and c are constant, $\psi = -1$ and f_2 there (the derivative of β_0 in (3.9) with respect to the second variable) corresponds to the expression $(a^*/\mu_0)'$. Thus we have shown, that a 'differential' recognition of chemotactic factors, which was postulated (cf. [8]) and in an alternative way modelled by Segel [37], can be achieved by a simple biochemical model of run length control as in Section 4, and that the crucial control parameters inducing such a differential recognition are the 'mean activation' μ_0 at the beginning and the 'critical threshold' a^* at the end of each run. (This result is reflected also in the simple model by Keller [16], compare (3.10).)

If we consider the case $a^* \equiv 0$, Eq. (4.8) says that the turning frequency $\beta(\cdot, \theta, \tau) = (\beta_0)_{\theta,\tau}$ during the run of an individual only depends on the ρ-concentration at the moment of start. Assuming $p = 0$ and $c = \text{const}$ the diffusion equation (8.13) then reads

$$\partial_t u = \frac{\varepsilon c^2}{n}\,\nabla_x\left(\frac{1}{(1-\psi)\,\beta_0}\,\nabla_x u - \frac{\beta_0'}{\beta_0^2}\,u\nabla_x\rho\right). \tag{8.24}$$

Thus the so-called modified Fokker–Planck equation

$$\partial_t u = \Delta_x(\mu u) \tag{8.25}$$

discussed by Patlak [34], Eq. (40), can arise only in cases where the 'forward index' ψ of the turn angle distribution vanishes, for example if $h \equiv 1$. (Compare also Segel [38], Section 4.)

Patlak's previous derivation of a diffusion equation, (37) in [34], starts from similar hypotheses on the turning frequency β and the turn angle distribution k as in Sections 4 and 5 of this paper. His partly complicated arguments and computations (in case $n = 3$) are based on a 'quasi steady state' assumption analogous to that in Proposition 2 above. Written in our terminology Patlak *a priori* assumes

$$\bar{\sigma}(\cdot, \theta) \cong \frac{1}{|S|}(u + nw \cdot \theta). \tag{8.26}$$

Then with the aid of Taylor expansions he arrives at the same equation as (8.13), provided p and c are fixed constants. The argument in [34] leading from (3) to (17) does not carry through for the general case of variable c-distribution.

In the next section we present a precise mathematical justification of the diffusion approximation (8.13) by singular perturbation theory, mainly with the aim to establish (8.26) as an approximation *a posteriori*, at least up to some initial layer terms.

9. Approximation by Singular Perturbation Theory

The formal derivation of the Keller–Segel diffusion equation presented in Section 8 may be sufficient for experimental situations, in which the measurements mainly concern the cell density. However, in experiments measuring also the direction of cell movement (like on the Zigmond bridge [42]) one wants to have more information about the distribution $\bar{\sigma}(\cdot, \theta)$ of cells moving in different directions θ, in order to compare the theoretical expression with the correlated measured data (for example Fig. 4 below).

In this section a precise estimation of the difference between $\bar{\sigma}(\cdot, \theta)$ satisfying (6.6), (6.14) and the θ-linear approximation

$$\bar{\sigma}_0(\cdot, \theta) = \frac{1}{|S|}(u^0 + nw^0 \cdot \theta) \tag{9.1}$$

is outlined with the aid of singular perturbation theory, where

$$\begin{aligned} &u^0 \text{ exactly satisfies the diffusion equation (8.13) with smooth initial} \\ &\text{conditions } u^0(0, \cdot) = \bar{u}(0, \cdot) \text{ and with Neumann boundary condition on} \\ &\partial\Omega, \end{aligned} \tag{9.2}$$

and where the mean direction is given by

$$w^0 = \frac{\chi}{c} u^0 \nabla \rho - \frac{\mu}{c^2} \nabla(cu^0). \tag{9.3}$$

It turns out that (up to an exponentially decreasing initial layer term) $\bar{\sigma}$ differs from $\bar{\sigma}_0$ by an error term which in the L^2-mean is $0(\alpha^2/\zeta) = o(\alpha)$ for $\alpha \ll \zeta$. This estimate is globally valid for all positive times, provided the stability condition (8.22) holds, under which u^0 approaches the stable steady state u_∞ (8.21) for $t \to \infty$. Differentiation with respect to space variables gives similar estimates in higher Sobolev spaces, these yielding error estimates also in the supremum norm on Ω.

Proposition 3. (Construction of the approximating solution). *Suppose the hypotheses* (8.12) *with* $\alpha \ll \zeta$ *and let the approximating density* u^0 *and mean direction* w^0 *be given by* (9.2) *and* (9.3). *Define*

$$\sigma_0(\cdot, \theta) = \frac{1}{|S|}\left(u^0 + nw^0 \cdot \theta + n\frac{n+2}{2}\sum_{i,j=1}^{n} z_{ij}[u^0, w^0]\theta_i\theta_j\right) \tag{9.5}$$

with $z[u, w]$ *explicated in* (10.7),

$$\sigma_0^{(1)} = \sigma^{(1)}[u^0, w^0] \tag{9.6}$$

as in (10.6) *and*

$$\sigma_0^{(2)} = \frac{2}{\beta_0^2|S|}u^0. \tag{9.7}$$

Then the functions σ_0, $\sigma_0^{(1)}$ *and* $\sigma_0^{(2)}$ *satisfy Eq.* (6.6) *up to an error term*

$$R_0 = [0, 0(\alpha^3), 0(\alpha^4); 0(\alpha^4)]$$

and inequalities (6.10) *up to*

$$R_1 = 0(\alpha^2) \quad \text{and} \quad R_2 = 0(\alpha) \quad \text{for } \nu = 1 \text{ and } 2 \text{ respectively.}$$

Since the initial conditions for σ_0 generally differ from those for $\bar{\sigma}$, we have to find correcting terms:

Proposition 4 (Construction of initial layer terms). *After the usual time transformation* $\tilde{t} = t/\varepsilon$ *define*

$$s_0 = \frac{1}{|S|}u^{00} + \tilde{s}_0$$

with $\tilde{s}_0 = [0, w^{00}, \ldots]$ *by the following initial value problems*

$$\partial_{\tilde{t}}\tilde{s}_0 = -\beta_0(id - T_0)\tilde{s}_0, \qquad \tilde{s}_0 = \bar{\sigma} - \sigma_0 \quad \text{for } t = 0, \tag{9.8}$$

$$\partial_{\tilde{t}}u^{00} = -\varepsilon\nabla_x(cw^{00}), \qquad u^{00} = 0 \quad \text{for } t = 0. \tag{9.9}$$

Then the function $\tilde{s}_0(t/\varepsilon, \cdot)$ *approaches zero exponentially with exponent* $\sim\zeta/\varepsilon$; $s_0(t/\varepsilon, \cdot)$ *fulfills* (6.6) *up to an error term*

$$r_0(t, \cdot) = \left[0, 0\left(\zeta\alpha \exp\left(-\text{const}\,\frac{\zeta}{\varepsilon}t\right)\right) + \alpha 0(u^{00})\right],$$

and one has $u^{00}(\frac{t}{\varepsilon}, \cdot) = 0(\alpha^2)$, *provided* $\tilde{s}_0 = 0(\alpha)$ for $t = 0$.

Now define the error functions

$$\sigma_*(t, \cdot) = \bar{\sigma}(t, \cdot) - \sigma_0(t, \cdot) - s_0\left(\frac{t}{\varepsilon}, \cdot\right) \tag{9.10}$$

and

$$\sigma_*^{(\nu)} = \sigma^{(\nu)} - \sigma_0^{(\nu)}, \quad \nu = 1 \text{ and } 2.$$

The reflection condition (6.14) is satisfied also for these functions if we assume that the normal derivative of ρ fulfills

$$\partial_\nu \rho = 0 \quad \text{on } \partial\Omega, \tag{9.11}$$

since this implies (6.14) for σ_0, $\sigma_0^{(1)}$ and $\sigma_0^{(2)}$.

From Propositions 3 and 4 we directly conclude that σ_* vanishes for $t = 0$ and together with $\sigma_*^{(1)}$ and $\sigma_*^{(2)}$ satisfies the differential equations

$$\varepsilon(\partial_t \sigma_* + \theta \cdot \nabla(c\sigma_*)) + \beta_0 B\sigma_* = R_0 + r_0 + \beta_0 \varepsilon c(id - T_\delta)\sigma_{**} \tag{9.12}$$

and

$$\begin{aligned} &\varepsilon(\partial_t \sigma_*^{(\nu)} + \theta \cdot \nabla(c\sigma_*^{(\nu)})) + (\beta_0 + 0(\zeta\alpha))\sigma_*^{(\nu)} \\ &\quad = \nu\sigma_*^{(\nu-1)} + 0(\zeta\alpha)\sigma^{(\nu+1)} + f^{(\nu)} \end{aligned} \tag{9.13}$$

for $\nu = 1$ and 2, where $f^{(1)} = R_1 + s_0$, $f^{(2)} = R_2$ and

$$\sigma_{**} = \frac{\chi_1}{c} D^\theta \rho\boldsymbol{\sigma} - \varepsilon c\sigma_\varepsilon^*$$

with σ_ε^* the same as (6.8), but with $\sigma^{(1)}$, $\sigma^{(2)}$ replaced by $\sigma_*^{(1)}$, $\sigma_*^{(2)}$, and with

$$\boldsymbol{\sigma} := \sigma_*^{(1)} - \frac{1}{\beta_0}\sigma_*.$$

Then Eqs. (9.12) and (9.13) for $\nu = 1$ imply that this difference fulfils

$$\begin{aligned} \varepsilon(\partial_t \boldsymbol{\sigma} + \theta \cdot \nabla(c\boldsymbol{\sigma})) + (\beta_0 + 0(\zeta\alpha))\boldsymbol{\sigma} &= B\sigma_* + R_1 - \frac{1}{\beta_0} R_0 \\ &\quad + s_0 - \frac{1}{\beta_0} r_0 + \zeta^2\alpha^2 0(\sigma_*^{(1)} + \sigma_*^{(2)} + \zeta\alpha\sigma^{(3)}). \end{aligned} \tag{9.14}$$

Now we define an appropriate L^2-energy functional

$$E_* = |\|\sigma_*\||^2 + \varepsilon c_1 \|\boldsymbol{\sigma}\|^2 + \varepsilon\alpha^2 c_2 \|\sigma_*^{(2)}\|^2 + \varepsilon\zeta\alpha^4 c_3 \|\sigma^{(3)}\|^2 \tag{9.15}$$

with

$$\|\phi(t, \cdot)\|^2 = \int_\Omega \int_S \phi^2(t, x, \theta)\, d\theta\, dx$$

and the weighted L^2-norm

$$|\|\phi(t, \cdot)\||^2 = \int_\Omega \int_S \exp\left(-\int_{\rho_0}^{\rho(t,x)} \hat{\chi}\right) \phi^2(t, x, \theta)\, d\theta\, dx,$$

where $\hat{\chi}$ was defined in (8.23). In case of a time independent ρ-distribution the weight equals $1/u_\infty$ up to a multiplicative constant, compare (8.21).

With this special choice of weight function and with suitable c_i's we are able to derive from Eqs. (9.12)–(9.14) and from boundary conditions (3.4) and (9.11)

the following differential inequality for E_* (the proof uses standard energy estimate techniques for hyperbolic equations, compare [5]):

$$\tfrac{1}{2}\, d_t E_* \leqslant (\sup |\partial_t \rho| + \zeta\alpha^2)\|u\|^2 + \|\tilde{s}_0(0, \cdot)\|_{H_1}^2\, e^{-\mathrm{const}(\zeta/\varepsilon)t} + 0(\alpha^4/\zeta^2), \tag{9.16}$$

where the last term depends on u^0 and its derivatives. This inequality then leads to the

Proposition 5 (Energy estimate). *Assume that the hypotheses* (8.12) *are fulfilled with* $\alpha \ll \zeta$ *and that the initial values satisfy*

$$\bar{\sigma}(0, \cdot) = \frac{1}{|S|}\,\bar{u}(0, \cdot) + 0(\alpha)$$

and

$$\bar{\tau}(0, \cdot) = \frac{1}{\beta_0}\,\tau_0 + 0(\alpha).$$

Then, for sufficiently small α, *there are constants* $c_i > 0$ *and a positive function* $\lambda_*(t) \geqslant \sup |\partial_t \rho(t, \cdot)| + \zeta\alpha^2$ *such that the energy functional* E_* *in* (9.15) *can be estimated by*

$$E_*(t) \leqslant \alpha^2 M_0^2(t) \exp\left(\int_0^t \lambda_*\right)\left(\alpha^2 + \frac{\alpha^2}{\zeta^2}\int_0^t \exp\left(-\int_0^s \lambda_*\right) M_1^2(s)\, ds\right), \tag{9.17}$$

where $M_0(t)$ *depends on the supremum of time and space derivatives of* $\rho(t, \cdot)$ *and* $M_1(t)$ *additionally on derivatives of the approximating solution* $u^0(t, \cdot)$ *in* (9.2).

Consider first the case, where the population really accumulates at regions of high chemoattractant concentration. Since (8.13) is linear in u, then one usually has exponential growth of u^0 (say in L^2-norm on Ω) at least for some time permitting the use of the model assumptions in Section 2. Thus $M_1(t) \sim \exp(\lambda t)$ with some $\lambda > 0$ and we conclude the

Theorem 1. *Suppose that the assumptions of proposition* 5 *hold and that the gradient* $\nabla\rho$ *and all coefficients depending on* ρ *are uniformly bounded. Let the approximating density* u^0 *in* (9.2) *together with its derivatives explode exponentially with factor* $\lambda > 0$. *Then for sufficiently small* α *and under the condition* $\sup |\partial_t \rho| \ll \lambda$ *the same explosion behavior holds for the 'true' solution* $\bar{\sigma}$ *of* (6.6) *and the difference to* $\bar{\sigma}_0$ *defined in* (9.1) *is of order* $o(\alpha) \exp(\lambda t)$ *up to an exponentially decreasing initial layer term. More precisely*

$$\|\bar{\sigma}(t, \cdot) - \bar{\sigma}_0(t, \cdot) - s_0\left(\frac{t}{\varepsilon}, \cdot\right)\|_{L^2(\Omega)} \leqslant \frac{\alpha^2}{\zeta} \exp(\lambda t),$$

being relatively small compared with the w^0*-term in* (9.1) (*since* $\alpha \ll \zeta$), *and*

$$\left\|\bar{\tau}(t, \cdot) - \frac{\tau_0}{\beta_0(\rho(t, \cdot))}\right\|_{L^2(\Omega)} \leqslant \alpha/\zeta^{3/2},$$

being small provided even $\alpha \ll \zeta^{3/2}$.

This result means that up to relatively small error terms (initial layer, terms of order $o(\alpha)$) the θ-linear distribution $\bar{\sigma}_0(\cdot, \theta)$ defined by (9.1)–(9.3) indeed describes the evolution of cells migrating in a relatively weak chemotactic gradient, and that in addition the mean run time $\bar{\tau}$ approximately equals τ_0/β_0 as expected.

A comparison with measurements of cell orientation with respect to a gradient on the Zigmond bridge [42] yields a rough correspondence between the theoretical cell distribution $\bar{\sigma}_0$ (which by (9.3), neglecting ∇u^0, is a cosine function of the angle between moving direction and gradient direction) and the measured values in Figure 4 (Fig. 8 of [42]).

The fact that the empiric distributions under certain circumstances are more concentrated around the gradient direction than the cosine-distribution, suggests that in these cases the θ-linear function $\bar{\sigma}_0$ has to be replaced by an approximation of higher order. Indeed the θ-quadratic distribution σ_0 in (9.5) serves as a better approximation. In order to realize this, a singular perturbation theory of higher order has to be used, compare [4] and [5].

It remains to consider the case where the approximating density u^0 approaches a stable steady state for $t \to \infty$, see (8.21). With the help of a Poincaré estimate and a suitably defined energy functional involving also the L^2-norms $\|\|\nabla_x \sigma\|\|$, $\|\|\partial_t \sigma\|\|$ and $\|\theta \cdot \nabla_x(c\sigma)\|$, the following result can be deduced (a proof is given in [5]):

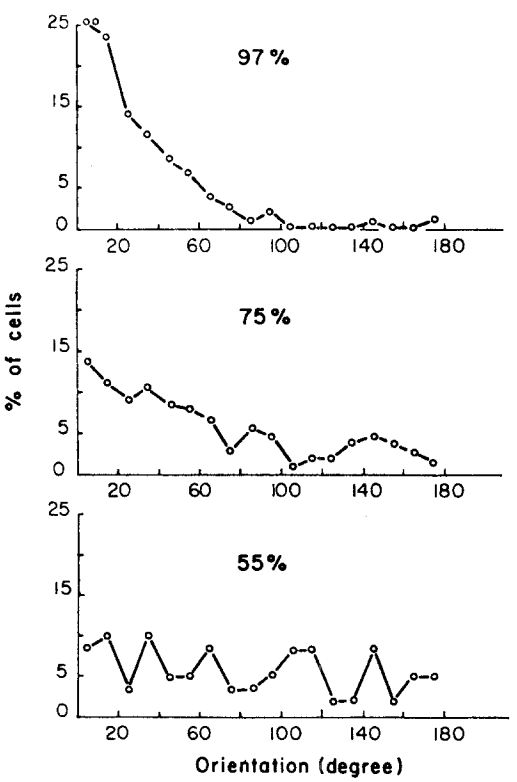


Fig. 4. Accuracy of orientation. Photographs of preparations with high (97%), medium (75%), or low (55%) percentages of cells oriented in gradient of FMMM were examined to determine the angle of deviation of each cell's orientation from the direct path to the well containing the higher concentration FMMM. Over 100 cells were examined for each level of orientation. The percentage of cells oriented in each 10° sector is plotted. From S. Zigmond [42]

Theorem 2. *Suppose that the assumptions of Proposition 5 are fulfilled, that the gradient $\nabla\rho$ and all coefficients depending on ρ are uniformly bounded on $\mathbb{R}_+ \times \bar{\Omega}$, and that for the bounded region Ω with piecewise smooth boundary the stability condition* (8.22) *is satisfied. Then the error between a solution $\bar{\sigma}$ of* (6.6) *and the constructed diffusion approximation $\bar{\sigma}_0$ in* (9.1) *remains small, for all time up to an initial layer:*

$$\|\bar{\sigma}(t, \cdot) - \bar{\sigma}_0(t, \cdot) - s_0\left(\frac{t}{\varepsilon}, \cdot\right)\|_{L^2(\Omega)} = o(\alpha), \quad t \geqslant 0.$$

In particular the steady state distribution u_∞ in (8.21) *approximates the final density of the cell population up to an error of order* $o(\alpha)$.

10. Appendix

For an investigation of the turning operator B in (7.7) we need a representation of the multiplication operator

$$M_\xi\phi(\theta) := (\xi\cdot\theta)\cdot\phi(\theta), \quad \phi \in L^2(S), \xi \in \mathbb{R}^n,$$

with respect to the eigenfunction system of T_0 described in the lemma of Section 7. Let $\phi = [u, w, z; \hat{\phi}]$ be as in (7.4), then an algebraic computation gives

$$M_\xi\phi = \left[\xi\cdot w, \frac{1}{n}u\xi + P_\xi z, \frac{2}{n+2}P_\xi^\tau w + \hat{P}_\xi\hat{\phi}; \hat{M}_\xi[0, 0, z; \hat{\phi}]\right], \tag{10.1}$$

where

$$(P_\xi z)_k = \xi_k z_{kk} + \sum_{l\neq k}\xi_l\frac{1}{2}\sum_{i\neq j}(\delta_{ik}\delta_{jl} + \delta_{il}\delta_{jk})z_{ij} \tag{10.2}$$

and the transposed operator is given by

$$(P_\xi^\tau w)_{ij} = \frac{1}{2}(\xi_i w_j + \xi_j w_i) - \frac{1}{n}\delta_{ij}\xi\cdot w. \tag{10.3}$$

The definitions of $\hat{P}_\xi$ and $\hat{M}_\xi$ are obvious and are not explicitely used in this paper. From (10.2) and (10.3) it follows

$$P_\xi P_\xi^\tau w = \frac{1}{2}|\xi|^2 w + \left(\frac{1}{2} - \frac{1}{n}\right)(\xi\cdot w)\xi. \tag{10.4}$$

An analysis of the turning operator B in (7.7) then gives

$$\begin{aligned} B\phi = \Bigg[0, (1-\psi)w - \frac{1}{n}(1-\psi)\left(\varepsilon c\frac{\tilde{\chi}}{\beta_0} + \delta c_0\tilde{\psi}\right)u\nabla\rho \\ - \left(\varepsilon c\frac{\tilde{\chi}}{\beta_0}(1-\psi) + \delta c_0(\psi^p\psi - \psi_2^p)\right)P_{\nabla\rho}z + R_w, \\ (1-\psi_2)z - (1-\psi_2)\left(\varepsilon c\frac{\tilde{\chi}}{\beta_0} + \delta c_0\psi^p\right)\frac{2}{n+2}P_{\nabla\rho}^\tau w + R_z; \\ (id - T_0)\hat{\phi} + \hat{R}\Bigg] \end{aligned} \tag{10.5}$$

with

$$R_w = 0(\varepsilon\delta(c + c_0)u + (\zeta\varepsilon + \zeta\delta + \varepsilon c\delta c_0)|w| + \varepsilon\delta(c + c_0)|z| + \varepsilon c\delta c_0\|\hat{\phi}\|),$$
$$R_z = 0(\varepsilon c\delta c_0 u + \varepsilon\delta(c + c_0)|w| + (\varepsilon + \delta + \varepsilon c\delta c_0)|z| + (\varepsilon c + \delta c_0)\|\hat{\phi}\|)$$

and

$$\hat{R} = 0(\varepsilon c\delta c_0|w| + (\varepsilon c + \delta c_0)(|z| + \|\hat{\phi}\|)).$$

Using the assumption (8.3) for $\bar{\sigma}$ and $\sigma^{(v)}$ as well as the hypotheses (8.12), the z-component of Eq. (6.6) can be investigated in analogy to (8.4). Regarding that Eq. (6.10) even implies

$$\sigma^{(1)} = \sigma^{(1)}[\bar{u}, \bar{w}] + 0(\alpha^2)$$

with

$$\sigma^{(1)}[u, w] = \frac{1}{\beta_0|S|}\left(u + \theta\cdot\left[nw + \frac{1}{\beta_0}\varepsilon c(\chi_0 + 2\chi_1)u\nabla\rho - \varepsilon\cdot\nabla\left(\frac{c}{\beta_0}u\right)\right]\right), \tag{10.6}$$

we derive from (6.6), (6.8) and (10.5) the approximate relation

$$\bar{z} = z[\bar{u}, \bar{w}] + 0(\alpha^4)$$

with

$$\begin{aligned} n\frac{n+2}{2}\sum_{i,j=1}^{n} z_{ij}[u, w]\theta_i\theta_j &= n\left(\varepsilon c\frac{\tilde{\chi}}{\beta_0} + \delta c_0\psi^p\right)\left((\theta\cdot\nabla\rho)\theta\cdot w - \frac{1}{n}\nabla\rho\cdot w\right) \\ &+ \frac{n\varepsilon}{\beta_0(1-\psi_2)}\left(\theta\cdot\nabla(cw)\cdot\theta - \frac{1}{n}\nabla(cw)\right) \\ &- \left((\varepsilon c)^2 n\frac{n+2}{2\beta_0^2}(\chi_2 - 2\chi_1^2) + \varepsilon c\frac{\tilde{\chi}}{\beta_0}\delta c_0\psi^p\right)\left((\theta\cdot\nabla\rho)^2 - \frac{1}{n}|\nabla\rho|^2\right)u \\ &- (\varepsilon c)^2 n\frac{n+2}{2\beta_0^2}\chi_1\left(\theta\cdot\nabla^2\rho\cdot\theta - \frac{1}{n}\Delta\rho\right)u \\ &- (\varepsilon c)^2 n\frac{n+2}{2c\beta_0}\chi_1\left((\theta\cdot\nabla\rho)\theta\cdot\nabla\left(\frac{c}{\beta_0}u\right) - \frac{1}{n}\nabla\rho\cdot\nabla\left(\frac{c}{\beta_0}u\right)\right). \end{aligned} \tag{10.7}$$

This expression is used in (9.5) for the construction of an approximating solution within the framework of singular perturbation theory.

References

1. Albrecht-Buehler, G.: Phagokinetic tracks of 3T3 cells: Parallels between the orientation of track segments and of cellular structures which contain actin or tubulin. Cell **12**, 333–339 (1977)
2. Albrecht-Buehler, G.: The angular distribution of directional changes of guided 3T3 cells. J. Cell Biol. **80**, 53–60 (1979)
3. Allan, R. B., Wilkinson, P. C.: A visual analysis of chemotactic and chemokinetic locomotion of human neutrophil leukocytes. Exp. Cell Res. **111**, 191–203 (1978)
4. Alt, W.: Orientation of cells migrating in a chemotactic gradient. In: Proc. Conf. on Models of Biological Growth and Spread, Heidelberg, 1979 (to appear)

5. Alt, W.: Singular perturbation of differential integral equations describing biased random walks. Crelle J. Reine Angew. Math. (submitted)
6. Berg, H. C., Brown, D. A.: Chemotaxis in Escherichia coli analyzed by three-dimensional tracking. In: Antibiotics and Chemotherapy, Vol. 19, pp. 55–78. Basel: Karger, 1974
7. Berg, H. C, Tedesco, P. M.: Transient response to chemotactic stimuli in Escherichia coli. Proc. Nat. Acad. Sci. USA **72**, 3235–3239 (1975)
8. Brown, D. A., Berg H. C.: Temporal stimulation of chemotaxis in Escherichia coli. Proc. Nat. Acad. Sci. USA **71**, 1388–1392 (1974)
9. Boyarsky, A., Noble, P. B.: A Markov chain characterization of human neutrophil locomotion under neutral and chemotactic conditions. Can. J. Physiol. Pharmacology **55**, 1–6 (1977)
10. Dipasquale, A.: Locomotory activity of epithelial cells in culture. Exp. Cell Res. **94**, 191–215 (1975)
11. Gallin, J. I., Gallin, E. K., Malech, H. L., Cramer, E. B.: Structural and ionic events during leukocyte chemotaxis. In: Leukocyte chemotaxis (J. I. Gallin, P. G. Quie, eds.) pp. 123–141. New York: Raven Press, 1978
12. Gerisch, G., Hess, B., Malchow, D.: Cell communication and cyclic-AMP regulation during aggregation of the slime mold dictyostelium discoideum. In: Biochemistry of sensory functions (L. Jaenicke, ed.) pp. 279–298. Berlin, Heidelberg, New York: Springer Verlag, 1974
13. Hall, R. L.: Amoeboid movement as a correlated walk. J. math. Biol. **4**, 327–335 (1977)
14. Hall, R. L., Peterson, S. C.: Trajectories of human granulocytes. Biophys. J. **25**, 365–372 (1979)
15. Jungi, T. W.: Different concentrations of chemotactic factors can produce attraction or migration inhibition of leukocytes. Int. Archs. Allergy appl. Immun. **53**, 29–36 (1977)
16. Keller, E. F.: Mathematical aspects of bacterial chemotaxis. In: Antibiotics and Chemotherapy, Vol. 19, pp. 79–93. Basel: Karger, 1974
17. Keller, E. F., Segel, L. A.: Model for chemotaxis. J. theor. Biol. **30**, 225–234 (1971).
18. Koshland, D. E., jr.: A response regulator model in a simple sensory system. Science **196**, 1055–1063 (1977)
19. Kurtz, Th. G.: A limit theorem for perturbed operator semigroups with applications to random evolutions. J. Funct. Anal. **12**, 55–67 (1973)
20. Lauffenburger, D., Keller, K. H.: Effects of leukocyte random motility and chemotaxis in tissue inflammatory response. J. theor. Biol. **81**, 475–503 (1979)
21. Lovely, P. S., Dahlquist, F. W.: Statistical measures of bacterial motility and chemotaxis. J. theor. Biol. **50**, 477–496 (1975)
22. MacNab, R., Koshland, D. E., jr.: The gradient-sensing mechanism in bacterial chemotaxis. Proc. Nat. Acad. Sci. USA **69**, 2509–2512 (1972)
23. MacNab, R., Koshland, D. E., jr.: Persistence as a concept in the motility of chemotactic bacteria. J. Mechanochem. Cell Motility **2**, 141–148 (1973)
24. Maderazo, E. G., Woronick, Ch. L.: A modified micropore filter assay of human granulocyte leukotaxis. In: Leukocyte chemotaxis (J. I. Gallin, P. G. Quie, eds.) pp. 43–55. New York: Raven Press, 1978
25. Nishida, T.: Fluid dynamical limit of the nonlinear Boltzmann equation to the level of the compressible Euler equation. Commun. math. Phys. **61**, 119–148 (1978)
26. Nossal, R.: Directed cell locomotion arising from strongly biased turn angles. Math. Biosc. **31**, 121–129 (1976)
27. Nossal, R.: Mathematical theories of topotaxis. In: Proc. Conf. on Models of Biological Growth and Spread. Heidelberg, 1979 (to appear)
28. Nossal, R., Weiss, G. H.: Analysis of a densiometric assay for bacterial chemotaxis. J. theor. Biol. **41**, 143–147 (1973)
29. Nossal, R., Weiss, G. H.: A descriptive theory of cell migration on surfaces. J. theor. Biol. **47**, 103–113 (1974)
30. Nossal, R., Zigmond, S. H.: Chemotropism indices for polymorphonuclear leukocytes. Biophys. J. **16**, 1171–1182 (1976)

31. Ordal, G. W., Fields, R. B.: A biochemical mechanism for bacterial chemotaxis. J. theor. Biol. **68**, 491–500 (1977)
32. Papanicolaou, G. C.: Some probabilistic problems and methods in singular perturbations. Rocky Mount. J. Math. **6**, 653–674 (1976)
33. Papanicolaou, G. C.: Introduction to the asymptotic analysis of stochastic equations. In: Modern modeling of continuum phenomena. AMS Lectures in Appl. Math., Vol. 16 (R. C. DiPrima, ed.) pp. 109–147. Providence, 1977
34. Patlak, C. S.: Random walk with persistence and external bias. Bull. math. Biophys. **15**, 311–338 (1953)
35. Peterson, S. C., Noble, P. B.: A two-dimensional random-walk analysis of human granulocyte movement. Biophys. J. **12**, 1048–1055 (1972)
36. Ramsey, W. S.: Analysis of individual leukocyte behaviour during chemotaxis. Exp. Cell Res. **70**, 129–139 (1972)
37. Segel, L. A.: A theoretical study of receptor mechanisms in bacterial chemotaxis. SIAM J. Appl. Math. **32**, 653–665 (1977)
38. Segel, L. A.: Mathematical models for cellular behavior. In: A study in mathematical biology. MAA Studies in Math. Vol. 15 (S. Levin, ed.) pp. 156–190. Washington, 1978
39. Stossel, Th. P.: The mechanism of leukocyte locomotion. In: Leukocyte chemotaxis (J. I. Gallin, P. G. Quie, eds.) pp. 143–160. New York: Raven Press, 1978
40. Stroock, D. W.: Some stochastic processes which arise from a model of the motion of a bacterium. Zeitschr. Wahrsch.th. **28**, 305–315 (1974)
41. Zigmond, S. H.: Mechanisms of sensing chemical gradients by polymorphonuclear leukocytes. Nature **249**, 450–452 (1974)
42. Zigmond, S. H.: Ability of polymorphonuclear leukocytes to orient in gradients of chemotactic factors. J. Cell Biol. **75**, 606–616 (1977)
43. Zigmond, S. H.: Chemotaxis by polymorphonuclear leukocytes. J. Cell Biol. **77**, 269–287 (1978)
44. Zigmond, S. H., Hirsch, J. G.: Leukocyte locomotion and chemotaxis. J. Exp. Medicine **137**, 387–410 (1973)

Received August 15, 1979