J. Math. Biol. (2000) 40: 97–135

Journal of Mathematical Biology

A generalized transport model for biased cell migration in an anisotropic environment

Richard B. Dickinson

Department of Chemical Engineering, University of Florida, Gainesville, FL 32601, USA. e-mail: dickinso@che.ufl.edu

Received: 8 April 1999

Abstract. A generalized transport model is derived for cell migration in an anisotropic environment and is applied to the specific cases of biased cell migration in a gradient of a stimulus (*taxis*; *e.g.*, *chemotaxis* or *haptotaxis*) or along an axis of anisotropy (*e.g.*, *contact guidance*). The model accounts for spatial or directional dependence of cell speed and cell turning behavior to predict a constitutive cell flux equation with drift velocity and diffusivity tensor (termed *random motility tensor*) that are explicit functions of the parameters of the underlying random walk model. This model provides the connection between cell locomotion and the resulting persistent random walk behavior to the observed cell migration on longer time scales, thus it provides a framework for interpreting cell migration data in terms of underlying motility mechanisms.

Key words: Cell migration – Chemotaxis – Haptotaxis – Contact guidance – Random

1. Introduction

The active migration of blood and tissue cells is essential to a number of physiological processes such as wound healing, inflammation, metastasis, and embryogenesis. A salient feature of the blood and tissue cell locomotion (and that of and some amoebae) is a polarized morphology as illustrated in Fig. 1A. Locomotion requires the coordination of several complex physicochemical processes to yield a displacement in the direction of cell polarity. Typically, a crawling tissue cell extends pseudopods from the leading edge which subsequently adhere the

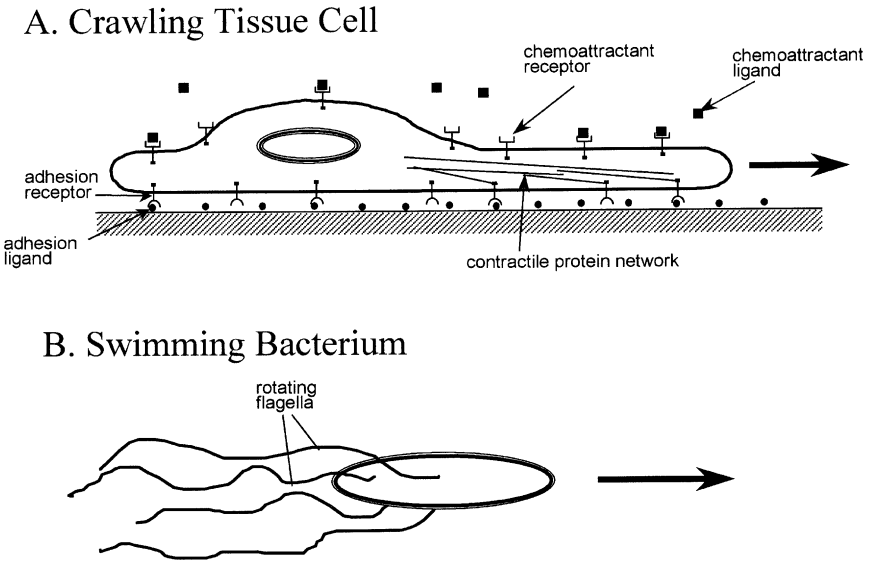

Fig. 1. Cell locomotion. **A** A schematic of a blood or tissue cell crawling on a surface. Pseudopods extend from the leading edge, adhere to the substratum via the binding of cell surface receptors to adhesion ligands, and contract to pull the cell in the direction of polarity. Pseudopodial extension and contraction may be mediated by binding of chemotactic receptors to chemoattractant ligands. **B** A schematic of a swimming bacterium. During a "run", the flagella align and rotate to propel the cell in the direction of cell polarity until the next "tumble", where the flagella rotation direction is reversed causing them to slay and the cell to rotate in place for a short time before the subsequent run. Although not shown, receptor binding to chemoattractants may also mediate the average time length of a run.

surrounding substratum and contract to pull the cell forward (see Fig. 1A). The contractile force is generated in an intracellular contractile protein network and is transmitted to the substratum via bound adhesion receptors, which create a cross-membrane linkage between extracellular adhesion molecules and the cell cytoskeleton. The extension and retraction of pseudopods may be stimulated by the binding of another class of cell surface receptors to soluble extracellular molecules known as chemoattractants (For reviews of tissue cell motility, see, e.g., Trinkaus (1984) and Lauffenburger (1991)).

The motility mechanisms of a swimming bacterium such as *Escherishia coli* differ from those of blood and tissue cells (Berg and Brown, 1972). The path of a swimming *E. coli* bacterium is a sequence of "runs" and "tumbles". As illustrated in Fig. 1B, the rotation of several coiled filaments on the cell surface, called *flagella*, propels the cell through a liquid medium. During a run the flagella align for efficient swimming in the direction of the cell polarity. However, during

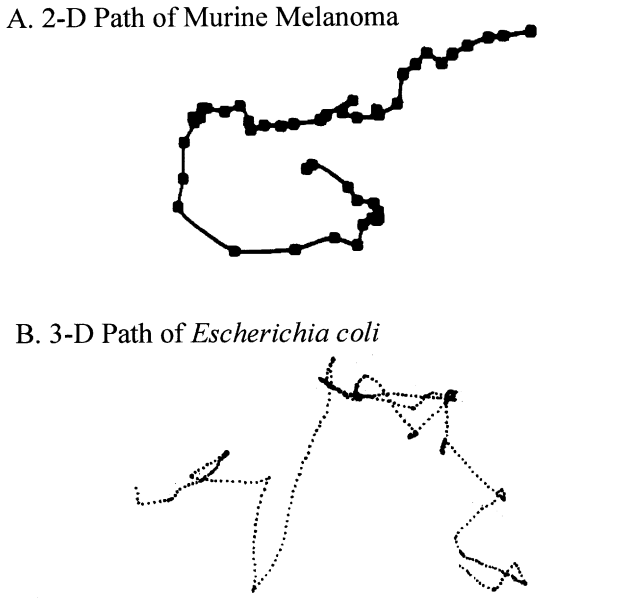

Fig. 2. Cell trajectories showing discrete and continuous cell turning. **A** The path of a K1735 murine melanoma cell on a surface coated with adhesion ligands (from Dickinson and Tranquillo (1993b)). Notice that cell turning results primarily from the accumulation of small changes in the movement direction between time points. **B** Two-dimensional projection of the path of an Escherichia coli bacterium swimming in three dimensions in water (from Berg and Brown (1972)). In this case, cell turning results primarily from discrete changes in orientation direction.

a tumble, the rotation direction of the flagella is reversed, splaying the flagella in various directions, which results in a change in orientation before the subsequent run. Bacterial motility may also be mediated by receptor binding to chemoattractants, which alters the frequency of tumbles when the cell is exposed to an increasing concentration of chemoattractant (Berg and Brown 1972).

Although the short term result of both general types of motility is locomotion in the direction of the cell's polarity, cumulative changes in the direction of motion on a longer time scale lead to a meandering path, which has often been modeled as a persistent random walk (Furth 1920; Gail and Boone 1970; Hall 1977; Dunn, 1983). Depending on the type of cell and its environment, this meandering path results from both continuous and discrete changes in cell orientation, as shown in Fig. 2, which compares paths of a crawling tumor cell and a swimming bacterium. On a time scale much longer than the characteristic time of directional persistence, cell migration can be modeled as a spatial diffusion process (Furth 1920; Gail and Boone 1970; Keller and Segel 1971). Following the time scale classifications used in

Dickinson and Tranquillo (1995), we label these three time scales in this paper as *locomotion*, *translocation*, and *migration*, respectively. On the shortest time scale of *locomotion*, the cell's dynamic motility machinery propel the cell forward. However, fluctuations in velocity and turning on the *locomotion* time scale lead to the meandering path observed on the time scale of *translocation*. These random changes in orientation on the *translocation* time scale ultimately lead to the diffusive behavior observed on the time scale of *migration*.

In an isotropic environment, the correlated random walk behavior is termed *random motility*. The rate of cell dispersal by random motility can be quantified by the *random motility coefficient*, μ (Keller and Segel 1971), analogous to the diffusion coefficient for molecular diffusion. However, the presence of a directional cue such as a concentration gradient of chemoattractant or adhesion ligands, or a structural cue such as aligned grooves etched into a surface (Matthes and Gruler 1988; Dunn and Brown 1986) or aligned fibrils in a collagen matrix (Dunn and Ebendal 1978; Dickinson et al. 1993), may cause cells to exhibit a net directional bias in their motion. (Hereafter, for generality, the factor affecting the motility is be referred to as the *stimulus*, which may be spatially non-uniform or directionally anisotropic.) A unidirectional migration bias in the direction of a gradient of a stimulus is generally known as *taxis* (Tranquillo and Alt 1990) (*e.g.*, *chemotaxis* for a response to a chemoattractant concentration gradient, *haptotaxis* for a response to a adhesion ligand concentration gradient, *galvanotaxis* for a response in gradient of electrical potential, *etc.*), and the unidirectional bias in migration can be quantified by the drift velocity vector, V (Keller and Segel 1971). A number of different modifications of the cell path have been suggested to contribute to the net taxis drift velocity (Tranquillo and Alt 1990). These include a bias in turning toward the gradient direction, a response known as *tropotaxis*; a directionally-dependent cell speed or random turning frequency, termed *orthotaxis* and *klinotaxis*, respectively; or a dependence of cell speed or turning frequency on the magnitude of the stimulus, termed *orthokinesis* and *klinokinesis*, respectively. The migration bias due to *orthokinesis* and *klinokinesis* does not result from the directional anisotropy of the stimulus, *per se*, rather from a dependence of the random walk behavior on cell position due to the non-uniform distribution of the stimulus (Wilkinson 1988).

A bi-directional cell migration bias along an axis of structural anisotropy is known as *contact guidance*, and can be characterized by a directionally-dependent random motility coefficient (Dickinson et al. 1993). For example, the rate of dispersion of migrating fibroblasts in gels of aligned collagen fibrils was shown to by greater along the axis of

fiber alignment, and lower in the orthogonal direction, and this bias increased with increasing degree of fiber alignment (Dickinson et al. 1993). Hence, in an anisotropic environment, directionally-dependent cell dispersal is more generally characterized by a *random motility tensor*, M (Dickinson and Tranquillo 1995).

V and M appear in a constitutive flux equation for the diffusive motion of cells of the form

$$J_c = -M\partial_r c(r, t) + Vc(r, t) \tag{1.1}$$

where is $c(r, t)$ is the concentration of cells at position, r, at time, t. (In this paper, we adopt the notation that all vectors are considered column vectors and transposes of vectors are row vectors. Hence, for two vectors v and w, $v^T w$ is the dot product (a scalar), and vw^T is the dyad product (a tensor), upon applying normal matrix multiplication. The partial with respect to a vector can be represented as a column vector; *e.g.*, if $r \equiv [x \;\; y \;\; z]^T$ and $v \equiv [v_x \;\; v_y \;\; v_z]^T$ then $\partial_r \equiv [\partial_x \;\; \partial_y \;\; \partial_z]^T$ such that $\partial_r c = [\partial_x c \;\; \partial_y c \;\; \partial_z c]^T$, $\partial_r^2 c \equiv \partial_r^T \partial_r c = \partial_x^2 c + \partial_y^2 c + \partial_z^2 c$, and $\partial_r^T v = \partial_x v_x + \partial_y v_y + \partial_z v_z$.) Neglecting changes in concentration due to cell growth or death, a population balance yields the continuity equation

$$\partial_t c = -\partial_r^T J_c = \partial_r^T M \partial_r c(r, t) + \partial_r^T V c(r, t). \tag{1.2}$$

Because of the exact analogy between the concentration of non-interacting cells and the probability density function, $p(r, t)$, of the position of one cell, $c(r, t)$ and $p(r, t)$ are interchangeable in Eqs. (1.1–2).

A central goal in modeling cell movement is to predict cell migration behavior, reflected in Eqs. (1.1–2), based on a mechanistic understanding of the processes involved in cell locomotion. This requires derivation of the governing equations for cell migration in terms of parameters which reflect cell movement on the shorter time scales, as has been done previously for migration in response to a concentration gradient of chemoattractant (chemotaxis) (Keller and Segel 1971; Alt 1980; Rivero et al. 1989) or of adhesion molecules (haptotaxis) (Dickinson and Tranquillo 1993a, 1995). Each of these models develops a reasonable method to relate the physicochemical motility mechanisms in the presence of a stimulus to the persistent random walk behavior, then derives a cell flux expression of the form of Eq. (1.1), which is valid for a time scale much longer than the characteristic time of directional persistence. The derived forms of V and M depend on the number of dimensions (one, two, or three) in which the cell is confined to move, on whether discrete or continuous turning is assumed, and on the assumed dependence of the parameters in the underlying persistent random walk model on the magnitude of the stimulus and the

steepness of the gradient. However, the mathematical similarity of the approaches and the resulting constitutive equation suggest these models may be special cases of the long-time-scale approximation of a more general persistent random walk model in an anisotropic environment. The purpose of this manuscript is to derive Eq. (1.2) for biased cell migration in a general anisotropic environment, allowing for both discrete and continuous turning and a generalized dependence of cell velocity and turning on cell position and orientation. As is demonstrated below, many of the previous cell migration models are are special cases of the more general model derived here.

After derivation of the general model in Sect. 2, the simplest case of migration in an isotropic environment is examined in Sect. 3. In Sect. 4, the first order biased response to a general anisotropy is determined, then applied to the specific cases of taxis and contact guidance in Sects. 5 and 6, respectively.

2. Derivation of general model

2.1. Generalized persistent random walk model

As depicted in Fig. 3, the relevant stochastic vector quantities which describe the cell path are position vector, $r(t)$, and the direction of cell orientation, $\Theta(t)$ (a unit vector in the direction of cell polarity). While $r(t)$ is a continuous function of time, both discrete and continuous transitions in $\Theta(t)$ are allowed, which accounts for the possibility of both discrete and continuous cell turning. For example, for blood and tissue cell locomotion, discrete turning may correspond to a spontaneous discrete re-polarization of the cell to a new direction. For a swimming bacterium, discrete turning would correspond to a tumble and initiation of a run in a new direction. In either case, the time required to complete the discrete turn is assumed negligibly small compared to the time between discrete turns. During locomotion, fluctuations in the forces on the cell will lead to fluctuations in the cell's translational velocity and in the rate of continuous changes in the cell polarity (hereafter termed "rotational velocity", although changes in polarity do not require the assumption of rigid body rotation). If the fluctuations in cell translational velocity and rotational velocity are uncorrelated with each other and relax quickly relative to the time required for significant changes in $r(t)$ and $\Theta(t)$, then $r(t)$ and $\Theta(t)$ can be approximated as a coupled stochastic process on the time scale of translocation, with $r(t)$ and $\Theta(t)$ being stochastic variables (Dickinson and Tranquillo, 1995). The time evolution of the joint probability

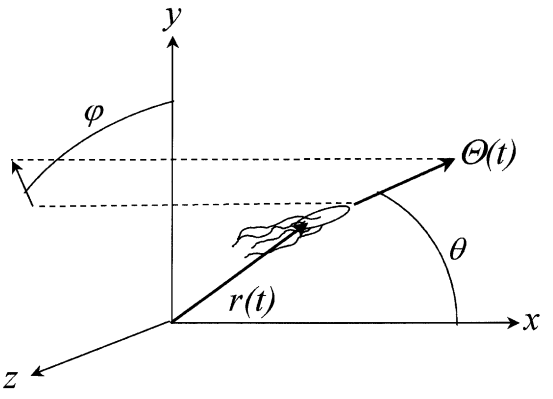

Fig. 3. The relevant coordinate system for three-dimensional cell motion. At time, t, the cell has position vector, $r(t) = [xyz]^T$, and orientation vector, $\Theta(t) = [\cos\theta \sin\theta \cos\varphi \sin\theta \sin\varphi]^T$. In the spherical coordinate system, θ is the angle between Θ and the x-axis, and φ is angle between the projection of Θ in the y-z-plane and the y-axis. ($0 \leqq \theta \leqq$; $0 \leqq \varphi \leqq 2\pi$). Similarly, for a cell moving only in two dimensions (e.g. on a surface), $r(t) = [xy]^T$, and $\theta(t) = [\cos\theta \sin\theta]^T$ with $0 \leqq \theta \leqq 2\pi$.

density, $p(\Theta, r, t)$, is governed by the continuity equation,

$$\partial_t p(\Theta, r, t) = L(\Theta, r, t)\ p(\Theta, r, t) + L_r(\Theta, r, t)\ p(\Theta, r, t), \qquad (2.1)$$

where $L(\Theta, r, t)$ and $L_r(\Theta, r, t)$ are linear operators that account for changes in $p(\Theta, r, t)$ due to turning (changes in the direction of polarity) and due to translation (changes in position), respectively. The *translation operator*, $L_r(\Theta, r, t)$, acts on functions of r, and is defined by

$$L_r(\Theta, r, t)\, f(r) \equiv -\partial_r^T [v(\Theta, r, t) f(r) - B(\Theta, r, t)\partial_r f(r)], \qquad (2.2)$$

where $v(\Theta, r, t)$ is the mean velocity of a cell moving in direction Θ, and $B(\Theta, r, t)$ is a diffusion tensor resulting from fluctuations in the cell velocity that lead to a dispersal in cell position. In other words, Eq. (2.2) accounts for the deterministic and stochastic motion of a cell with a *given* orientation, Θ, with $v(\Theta, r, t)$ accounting for the deterministic motion and $B(\Theta, r, t)$ accounting for the dispersion effect of short-time-scale velocity fluctuations. For example, a swimming bacterium on a *run* may have fluctuations in cell speed that lead to a spreading distribution of possible positions over the time of the run, even though the orientation is fixed. Only if the motion is completely deterministic ($B = 0$) will the cell position over the time of the run be completely specified by the mean cell speed. The diffusion tensor, B, reflects this spreading distribution. As shown below, B is distinguished from the random motility tensor, M, which accounts also for changes in Θ that lead to cell dispersion on a longer time scale.

If $\{r(t), \Theta(t)\}$ is a Markov process (an assumption made in the sections to follow but not necessary to the results in this section), then the *turning operator*, $L(\Theta, r, t)$, acts on functions of Θ, and has general form

$$L(\Theta, r, t) f(\Theta) \equiv -\partial_\Theta^T[(\omega(\Theta, r, t) \times \Theta) f(\Theta) - D(\Theta, r, t)\partial_\Theta f(\Theta)] + \int d\Theta' [\Omega(\Theta, \Theta'; r, t) f(\Theta') - \Omega(\Theta', \Theta; r, t) f(\Theta)], \tag{2.3}$$

where $\omega(\Theta, r, t)$ and $D(\Theta, r, t)$ are the *rotational drift velocity vector* and *rotational diffusion tensor*, respectively, and $\Omega(\Theta, \Theta'; r, t)$ is the probability per unit time of a discrete reorientation of the cell polarity from direction Θ' to new direction Θ. The first term in Eq. 2.3 accounts for continuous changes in $\Theta(t)$, and the second term accounts for discrete changes.

Eqs. (2.1–3) allow for a general dependence of the coefficients, v, B, ω, D, and Ω, on (Θ, r, t). In many applications, this dependence is attributed to the position and orientation in a gradient field of a stimulus. For example, a bacterium undergoing chemotaxis in a gradient of chemoattractant may have the velocity and turning frequency that depend on magnitude of chemoattractant concentration, $\varrho(r, t)$, as well as its perceived temporal gradient (Berg and Brown 1972, Alt 1980, Alt 1981), given by

$$D_t \varrho(r, t) \equiv \partial_t \varrho(r, t) + v^T \partial_r \varrho(r, t). \tag{2.4}$$

If $\varrho(r, t)$ is a known function of (r, t) such that $\partial_t \varrho(r, t)$ and $\partial_r \varrho(r, t)$ are known, then $v(\varrho(r, t), D_t \varrho(r, t))$ is an implicit function of (Θ, r, t) and can be simply written as $v(\Theta, r, t)$. Likewise, all other coefficients in Eqs. (2.1–3) that depend on $(\varrho(r, t), D_t \varrho(r, t))$ can be written as explicit functions of (Θ, r, t). In other applications, such as contact guidance, v, B, ω, D, and Ω may be explicit functions Θ because of a directionally anisotropic property the cell's environment.

In the following section, we examine the asymptotic behavior of Eq. (2.1) to derive a diffusion equation of the form of Eq. (1.2). First, we consider the case where the parameters v, B, ω, and Ω are not explicit functions of time. The time-inhomogeneous case is deferred to Sect. 2.4 where it is shown that the same resulting diffusion equation holds as long as the parameters vary slowly in time relative to the relaxation time of Θ.

2.2. Diffusion approximation

To describe cell motion on the time scale of migration, we seek an approximate equation of the form in Eq. 2.1, which governs the

probability density of $r(t)$ alone, i.e. $p(r, t) \equiv \int d\Theta p(\Theta, r, t)$, and is valid for times much larger than the characteristic relaxation time of $\Theta(t)$. On this time scale, deviations of $p(\Theta, r, t)$ from $p(r, t)\, p_s(\Theta; r)$ relax quickly, where $p_s(\Theta; r)$ is the pseudo-stationary density of Θ for fixed r, defined by the solution to

$$L(\Theta, r, t)\, p_s(\Theta; r) = 0. \tag{2.5}$$

Our approach is to apply an adiabatic elimination of fast variables procedure with projection operator formalism developed in Kubo et al. (1991) and Gardiner (1983).

Let T_0 be the time scale on which cell migration is observed, assumed much longer than the relaxation time of Θ as measured by λ_1, the least negative eigenvalue of L. Let $\eta \equiv T_0/(-\lambda_1)$ then be a large parameter that reflects the disparity in time scales ($\eta \gg 1$). Also, we choose the relevant length scale, R_0, such that $v(\Theta, r) \sim R_0/T_0$. We further assume that the contribution of short time scale velocity fluctuations is small relative to deterministic motion, such that $v(\Theta, r)$ $R_0 \sim \gamma B(\Theta, r)$, where γ is also a large parameter. We now introduce dimensionless time and position, which are scaled with respect to T_0 and R_0, respectively, and are again denoted as t and x. Eq. (2.1) is now scaled with respect to T_0 and R_0 and rewritten in dimensionless form as

$$\partial_t p(\Theta, r, t) = \eta L(\Theta, r)\ p(\Theta, r, t) + L_r(\Theta, r)\ p(\Theta, r, t), \tag{2.6}$$

where dimensionless $L(\Theta, r)$ is defined as in Eq. (2.3), and now

$$L_r(\Theta, r) f(r) \equiv\ -\partial_r^T [v(\Theta, r) f(r)] + \gamma^{-1} \partial_r^T [B(\Theta, r)\ \partial_r f(r)]. \tag{2.7}$$

The analysis to follow assumes that all terms in Eqs. (2.6–7) have been scaled appropriately to be proportional to the powers of η and γ^{-1} as shown. This assumption also requires that $v(\Theta, r)$ and $B(\Theta, r)$ are sufficiently weak functions of r such that dimensionless $\partial_r^T v(\Theta, r)$ and $\partial_r^T B(\Theta, r)$ are $O(1)$.

We now examine the asymptotic behavior of Eq. (2.4) based on the above assumptions. Let $\bar{f}(r)$ be the pseudo-stationary mean of any function $f(\Theta, r)$ under the pseudo-stationary density, $p_s(\Theta; r)$; *i.e.*,

$$\bar{f}(r) \equiv \int d\Theta' f(\Theta', r)\, p_s(\Theta'; r). \tag{2.8}$$

The *translation operator*, $L_r(\Theta, r)$, is divided into components $\bar{L}_r(r)$ and $L_r'(\Theta, r)$, corresponding to the mean and the fluctuations of the translational motion respectively; *i.e.*, $L_r(\Theta, r) = \bar{L}_r(r) + L_r'(\Theta, r)$, where

$$\bar{L}_r(r) f(r) \equiv\ -\partial_r^T [\bar{v}(r) f(r)] + \gamma^{-1} \partial_r^T [\bar{B}(r) \partial_r f(r)] \tag{2.9}$$

and

$$L_r'(\Theta, r) f(r) \equiv -\partial_r^T[(v(\Theta, r) - \bar{v}(r)) f(r)] + \gamma^{-1}\partial_r^T[(B(\Theta, r) - \bar{B}(r))\partial_r f(r)]. \tag{2.10}$$

Let P be a projection operator that projects any function, $f(\Theta, r, t)$, into the subset of functions proportional to $p_s(\Theta; r)$; *i.e.*,

$$Pf(\Theta, r, t) \equiv p_s(\Theta; r) \int d\Theta' f(\Theta', r, t). \tag{2.11}$$

Defining $\psi(\Theta, r, t) \equiv Pp(\Theta, r, t) = p_s(\Theta, r) p(r, t)$ and $\psi'(\Theta, r, t) \equiv (1 - P) p(\Theta, r, t)$, then operating on Eq. (2.6) by P and $(1 - P)$, respectively, yields

$$\partial_t \psi = P(\eta L + L_r' + \bar{L}_r)(\psi + \psi') = PL_r'\psi' + P\bar{L}_r\psi \tag{2.12}$$

$$\partial_t \psi' = (1 - P)(\eta L + L_r' + \bar{L}_r)(\psi + \psi') = [\eta L + (1 - P)(L_r' + \bar{L}_r)]\psi' + (1 - P)(L_r' + \bar{L}_r)\psi, \tag{2.13}$$

where we have noted that $PL = LP = 0$, $PL_r'P = 0$, and $P\bar{L}_r(1 - P) = 0$. Solving Eq. (2.13) to $O(\eta^{-1})$ for ψ' provides

$$\psi' = -\eta^{-1} L^{-1}(1 - P)(L_r' + \bar{L}_r)\psi + O(\eta^{-2}), \tag{2.14}$$

which is substituted into Eq. 2.12 to give

$$\partial_t \psi = \bar{L}_r \psi - \eta^{-1} PL_r' L^{-1}(1 - P)(L_r' + \bar{L}_r)\psi + O(\eta^{-2}). \tag{2.15}$$

Upon dividing through Eq. (2.15) by $p_s(\Theta; r)$, we have

$$\partial_t p(r, t) = \bar{L}_r p(r, t) - \eta^{-1} \int d\Theta' L_r' L^{-1}(1 - P)(L_r' + \bar{L}_r) p_s(\Theta'; r) p(r, t) + O(\eta^{-2}). \tag{2.16}$$

We now wish to represent the right hand side of Eq. (2.16) in terms of the conditional probability, $p(\Theta, \tau | \Theta_0, 0; r)$, which is the probability density of the cell having orientation, Θ, at time, τ, given a specified initial orientation, Θ_0, at time zero (for fixed r). Because $p(\Theta, \tau | \Theta_0, 0; r)$ is the solution to

$$\partial_\tau p(\Theta, \tau | \Theta_0, 0; r) = Lp(\Theta, \tau | \Theta_0, 0; r), \tag{2.17}$$

we can formally write any function, $f(\Theta, \tau; r)$, as

$$f(\Theta, \tau; r) = e^{L\tau} f(\Theta_0, 0; r) = \int d\Theta_0 \, p(\Theta, \tau | \Theta_0, 0; r) f(\Theta_0; r), \tag{2.18}$$

and because

$$L^{-1}(1-P) = -\int_0^\infty d\tau e^{L\tau}, \tag{2.19}$$

we have

$$L^{-1}(1-P)f(\Theta_0, 0; r) = -\int d\Theta_0 \int_0^\infty d\tau p(\Theta, \tau|\Theta_0, 0; r) f(\Theta_0, 0; r). \tag{2.20}$$

Substituting $f(\Theta_0, 0; r) = (L_r'(\Theta_0; r) + \bar{L}_r) p_s(\Theta_0; r) p(r, t)$ as the initial condition and combining Eq. (2.20) with Eq. (2.16), we have

$$\partial_t p(r, t) = \bar{L}_r p(r, t) + \frac{1}{\eta} \int d\Theta \int d\Theta_0 \int_0^\infty d\tau L_r'(\Theta, r) p(\Theta, \tau|\Theta_0, 0; r)$$
$$(L_r'(\Theta_0, r) + \bar{L}_r) p_s(\Theta_0; r) p(r, t) + O(\eta^{-2}). \tag{2.21}$$

2.3. *Generalized diffusion equation*

Eq. (2.21) is recognizable as a diffusion equation when written as

$$\partial_t p(r, t) = -\partial_r^T [V(r) p(r, t)] + \partial_r^T [M(r) \partial_r p(r, t)]$$
$$+ O(\eta^{-2}) + O(\gamma^{-1}\eta^{-1}). \tag{2.22}$$

where the $O(\gamma^{-1}\eta^{-1})$ results from the $O(\gamma^{-1})$ term in Eq. (2.10). Here, $M(r)$ and $V(r)$ are the *random motility tensor* and *drift velocity vector*, respectively, given by

$$M(r) \equiv \int d\Theta_0 \Delta(\Theta_0; r) \Gamma(\Theta_0; r)^T + \gamma^{-1} \bar{B}(r), \tag{2.23}$$

$$V(r) \equiv \bar{v}(r) - \int d\Theta_0 \Delta(\Theta_0; r) \partial_r^T \Gamma(\Theta_0; r). \tag{2.24}$$

The vectors, $\Gamma(\Theta_0; r)$ and $\Delta(\Theta_0; r)$, which appear in Eqs. (2.23–4), have physical significance related to the persistent motion of the cell with given initial orientation, Θ_0. $\Gamma(\Theta_0; r)$ is labeled the *directionally weighted velocity* and is defined by

$$\Gamma(\Theta_0; r) \equiv v(\Theta_0, r) p_s(\Theta_0; r). \tag{2.25}$$

$\Delta(\Theta_0; r)$ is labeled the *persistence displacement*, defined by

$$\Delta(\Theta_0; r) \equiv \eta^{-1} \int_0^\infty d\tau \int d\Theta [v(\Theta, r) - \bar{v}(r)] p(\Theta, \tau|\Theta_0, 0; r), \tag{2.26}$$

and can be interpreted as is the mean displacement relative to expected position, $\bar{v}(r)t$, due to persistence of a cell with initial direction Θ_0.

Note that in deriving Eq. (2.22), we have not required that $\{r(t), \Theta(t)\}$ be a Markov process nor that L be of the form in Eq. (2.3). The requirements on L in deriving Eq. (2.22) are only that it is a linear operator on functions of Θ, that its eigenvalues are non-positive, and that a non-trivial solution to $Lp_s(\Theta; r) = 0$ exists.

2.4. *Time-inhomogeneous case*

We now drop the assumption that coefficients, v, B, ω, and D, are independent of time to derive a more general form of Eq. (2.22). However, these parameters are assumed to evolve on a time scale much slower than the relaxation time of Θ. To remove the explicit dependence of the coefficients on time, t is replaced in L and L_r with a new variable, t_1, which is defined as simply $t_1 = t$; *i.e.* t_1 is a process with deterministic velocity equal to one. The joint probability, $p(\Theta, r, t_1, t)$ is then governed by

$$\partial_t p(\Theta, r, t_1, t) = \eta L(\Theta, r, t_1) p(\Theta, r, t_1, t) + L_r(\Theta, r, t_1) p(\Theta, r, t_1, t) - \partial_{t_1} p(\Theta, r, t_1, t). \quad (2.27)$$

Now define $L'_r(\Theta, r, t_1)$ and $\bar{L}_r(r, t_1)$ as in Eqs. (2.9–10), but with dependence now on (r, t_1) instead of only on (r). Let L_1 be a new operator defined by

$$L_1(r, t_1) \equiv \bar{L}_r(r, t_1) f(r, t_1) - \partial_{t_1} f(r, t_1). \quad (2.28)$$

From here, the asymptotic analysis proceeds as above with the derivation of Eq. (2.21) for the time-homogeneous case, only (r) is now replaced with (r, t_1), and $L_r(r)$ is replaced with $L_1(r, t_1)$. The resulting analog to Eq. (2.21) is

$$\partial_t p(r, t_1, t) = \bar{L}_1(r, t_1) p(r, t_1, t) + \frac{1}{\eta} \int d\Theta \int d\Theta_0 \int_0^\infty d\tau \times L'_r(\Theta, r, t_1) p(\Theta, \tau | \Theta_0, 0; r, t_1) (L'_r(\Theta_0, r, t_1) + \bar{L}_r(r, t_1)) p_s(\Theta_0; r, t_1) p(r, t_1, t) + O(\eta^{-2}). \quad (2.29)$$

(Note that $\bar{L}_r$ instead of L_1 appears in the integral in Eq. (2.29) because $(1 - P)\partial_{t_1} P = 0$ [cf. Eq. (2.15)].) Reverting back to the time-

inhomogenous form by eliminating t_1 in terms of t, we have

$$\partial_t p(r,t) = \bar{L}_r(r,t)\,p(r,t) + \frac{1}{\eta}\int d\Theta \int d\Theta_0 \int_0^\infty d\tau\, L'_r(\Theta, r, t)\, p(\Theta, \tau|\Theta_0, 0; r, t)$$
$$\times (L'_r(\Theta_0, r, t) + \bar{L}_r(r,t))\, p_s(\Theta_0; r, t)\, p(r,t) + O(\eta^{-2}). \qquad (2.30)$$

Eq. (2.30) is identical to Eq. (2.21), except for the explicit time-dependence of v, B, ω, D, and Ω appearing in the operators L, L'_r, and $\bar{L}_r$. The resulting diffusion equation is

$$\partial_t p(r,t) = -\partial_r^T [V(r,t)\,p(r,t)] + \partial_r^T [M(r,t)\partial_r p(r,t)]$$
$$+ O(\eta^{-2}) + O(\gamma^{-1}\eta^{-1}). \qquad (2.31)$$

where $M(r,t)$ and $V(r,t)$ are defined as in Eqs. (2.23–4), except that $\Gamma(\Theta_0; r, t)$ and $\Delta(\Theta_0; r, t)$ are now explicit functions of time. The conclusion is that the time-inhomogenous case requires no special consideration, as long as stimulus field varies slowly relative the relaxation time of Θ. Hereafter, the possible dependence of the various parameters on time is not shown explicitly, but is implied.

2.5. Examples

To illustrate were cell path modifications contribute to the net drift velocity, we examine three special cases as examples. (Hereafter, the equations are re-scaled to remove the explicit dependence on η and γ.)

Example 1. Let L and therefore $p_s(\Theta)$ be independent of r and let $v(\Theta, r)$ be given by $v(\Theta, r) = S(r)\Theta$, where $S(r)$ is the cell speed. In this case, Eq. (2.23) simplifies to

$$M(r) = S(r)^2 T + \bar{B}(r) \qquad (2.32)$$

where T is the *directional persistence tensor* (Dickinson and Tranquillo, 1995), which reflects the mean time of directional persistence in any direction relative to the mean direction, $\bar{\Theta} \equiv \int d\Theta_0 \Theta_0 p_s(\Theta_0)$, and is given by

$$T \equiv \int_0^\infty d\tau \int d\Theta_0 \int d\Theta (\Theta - \bar{\Theta})\Theta_0^T\, p(\Theta, \tau|\Theta_0, 0)\, p_s(\Theta_0)$$
$$\equiv \int_0^\infty d\tau \langle \Theta(\tau), \Theta(0)\rangle. \qquad (2.33)$$

Here $\langle \Theta(\tau), \Theta(0) \rangle$ is the *directional autocorrelation tensor*, defined by

$$\langle \Theta(\tau), \Theta(0) \rangle \equiv \int d\Theta_0 \int d\Theta (\Theta - \bar{\Theta}) \Theta_0^T p(\Theta, \tau | \Theta_0, 0) p_s(\Theta_0). \tag{2.34}$$

The drift velocity in this case is

$$V(r) = S(r)\bar{\Theta} - S(r) T \partial_r S(r). \tag{2.35}$$

In this case, a *directional orientation bias* reflected in non-zero $\bar{\Theta}$ and a dependence of cell speed on position contributes to the net drift velocity. The former is consistent with the definition of *taxis*, and the latter is consistent with the definition of *orthokinesis*. As shown in the sections to follow, the directional orientation bias can result from a bias in the direction of turning (*tropotaxis*) or a direction-dependent frequency of turning (*klinotaxis*), both of which may result in a directionally non-uniform $p_s(\Theta; r)$.

Example 2. Let L be defined such that $p_s(\Theta; r)$ is a directionally uniform distribution (*i.e.* $p_s(\Theta; r)$ is a constant, $p_s^{(0)}$, which is independent of Θ as well as r), making $\bar{\Theta} = 0$. Let $v(\Theta)$ be independent of r but depend on Θ in the form of $v(\Theta) = S\Theta + v'(\Theta)$, where $v'(\Theta)$ represents the additional cell velocity attributed to a dependence of velocity on the direction of cell polarity in an anisotropic environment. The drift velocity is then

$$V(r) = \overline{v'} = \int d\Theta' v'(\Theta') p_s^{(0)}. \tag{2.36}$$

Although there is no bias in directional orientation in this case, the dependence of cell velocity on the direction of orientation (*orthotaxis*), reflected in $\bar{v}'$, can lead to a separate contribution to V.

Example 3. Let $v(\Theta)$ be independent of r, but let $p_s(\Theta; r)$ depend on r as well as on Θ. In this case, Eq. (2.24) reduces to

$$V(r) = \bar{v}(r) - \langle \Delta(\Theta) v^T(\Theta) \partial_r \ln p_s(\Theta; r) > . \tag{2.37}$$

Here, cell speed is independent of position, but the dependence of $p_s(\Theta; r)$ on position contributes to the total drift velocity. This contribution results from a dependence of turning behavior on the position of the cell in the anisotropic environment, hence on the magnitude of the stimulus, which is consistent with the definition of *klinokinesis*. Note, however, that the second term in Eq. (2.37) can only contribute to $V(r)$ when $p_s(\Theta; r)$ is not a uniform distribution, for which $p_s(\Theta; r)$ would be a constant, p_{s0}, thus independent of both r and Θ.

2.6. *Fourier expansions*

Explicit expressions for $M(r)$ and $V(r)$ require solutions to Eq. (2.5) and Eq. (2.17) for the probability densities, $p_s(\Theta_0; r)$ and $p(\Theta, \tau|\Theta_0, 0; r)$, respectively, with initial condition, $p(\Theta, 0|\Theta_0, 0; r) = \delta(\Theta - \Theta_0)$, for the latter. In the specific cases of the following sections, these solutions are obtained by expanding all functions of Θ into Fourier series of orthonormal circular or spherical harmonic functions, written generally as $\{\Psi_\mu(\Theta)\}$. For two-dimensional motion, $\Theta = [\cos\theta \ \sin\theta]^T$ and the $\{\Psi_\mu(\Theta)\}$ are $\{\frac{1}{\sqrt{2\pi}} e^{im\theta}\}$, with $-\infty < m < \infty$. For three-dimensional motion, $\Theta = [\cos\theta \ \sin\theta\cos\varphi \ \sin\Theta\sin\varphi]^T$, $\{\Psi_\mu(\Theta)\}$ are the spherical harmonics, $\{Y^l_m(\Theta, \varphi)\}$, given by

$$Y^l_m(\theta, \varphi) = \left[\frac{(2m+1)}{4\pi}\frac{(m-|l|)!}{(m+|l|)!}\right]^{1/2} P^{|l|}_m(\cos\theta)\, e^{il\varphi}, \tag{2.38}$$

where $0 \leqq m < \infty$, $-m \leqq l \leqq m$, and $\{P^l_m\}$ are the associated Legendre functions. In general, all functions of Θ are expanded as a Fourier series: $f(\Theta) = \sum_\mu f_\mu \Psi_\mu(\Theta)$ with the Fourier coefficients given by $f_\mu = \int d\Theta' \Psi^*_\mu(\Theta') f(\Theta')$. Furthermore, the conditional probability, $p(\Theta, \tau|\Theta_0, 0; r)$, is doubly expanded as

$$p(\Theta, \tau|\Theta_0, 0; r) = \sum_\mu \sum_\nu p_{\mu,\nu}(\tau; r)\, \Psi_\mu(\Theta)\, \Psi_\nu(\Theta_0)^*. \tag{2.39}$$

Transformation of Eq. (2.17) provides the governing equations for the coefficients, $p_{\mu,\nu}(\tau; r)$:

$$d_\tau p_{\mu,\nu}(\tau; r) = \sum_\kappa {}_\mu\lambda_\kappa(r)\, p_{\kappa,\nu}(\tau; r) \tag{2.40}$$

where the coefficients $\{{}_\mu\lambda_\kappa(r)\}$ are defined by

$${}_\mu\lambda_\kappa(r) \equiv \int \Psi_\mu(\Theta')^* L(\Theta, r) \Psi_\kappa(\Theta'). \tag{2.41}$$

Transformation of the initial condition, $p(\Theta, 0|\Theta_0, 0; r) = \delta(\Theta - \Theta_0)$, implies that the initial condition for Eq. (2.40) is $p_{\mu,\nu}(0; r) = \delta_{\mu,\nu}$, where $\delta_{\mu,\nu}$ is the Kronecker delta. Also, the stationary probability density, $p_s(\Theta; r)$, is expanded as

$$p_s(\Theta; r) = \sum_\mu p_{s,\mu}(r)\, \Psi_\mu(\Theta). \tag{2.42}$$

Note that

$$p_s(\Theta; r) = \lim_{\tau\to\infty} \int d\Theta_0\, p(\Theta, \tau|\Theta_0, 0; r), \tag{2.43}$$

which, from Eq. (2.39), implies

$$p_{s,\mu}(r) = \lim_{\tau \to \infty} p_{\mu,0}(\tau; r)\Psi_0. \tag{2.44}$$

From Eqs. (2.23–4), the migration parameters, $M(r)$ and $V(r)$, can be written in terms of the Fourier coefficients of Δ, Γ and B, as

$$M(r) = \sum_{\mu} \Delta_{\mu}(r)^* \Gamma_{\mu}(r)^T + B_{\mu}(r)^* p_{s,\mu}(r) \tag{2.45}$$

and

$$V(r) = \Psi^{-1}_0 \Gamma_0(r) - \sum_{\mu} \Delta_{\mu}(r)^* \partial_r^T \Gamma_{\mu}(r), \tag{2.46}$$

respectively, with $\Delta_{\mu}(r)$ and $\Gamma_{\mu}(r)$ given by

$$\Delta_{\mu}(r) = \sum_{\nu} v_{\nu}(r) \int_0^{\infty} d\tau \left[p_{\nu,\mu}(\tau; r)^* - \delta_{\mu,0} \Psi_0^{-1} p_{s,\nu}(r)^* \right] \tag{2.47}$$

and

$$\begin{aligned} \Gamma_{\mu}(r) &= \int d\Theta' \Psi_{\mu}(\Theta')^* v(\Theta', r) p_s(\Theta'; r) \\ &= \sum_{\nu} p_{s,\nu}(r) \int d\Theta' \Psi_{\mu}(\Theta')^* v(\Theta', r) \Psi_{\nu}(\Theta'), \end{aligned} \tag{2.48}$$

respectively. The primary benefit of representing M and V in this form is that now only the coefficients $\{p_{\mu,\nu}(\tau)\}$ are required, which can be obtained by solving Eq. (2.40).

In the following section, these general results are first applied to examine cell migration in an isotropic environment, where the analysis is greatly simplified by the fact that $\{\Psi_{\mu}\}$ are eigenfunctions of L, which uncouples the infinite set of differential equations represented in Eq. (2.40). In the later sections, the more complex cases of taxis and contact guidance are addressed, where we apply a small bias approximation to find first-order corrections of solution for an isotropic environment.

3. Cell migration in an isotropic environment

In this section, the random motility tensor, M, as defined in Eq. (2.23) and evaluated in Eq. (2.45), is determined for cell migration in a two- or three-dimensional isotropic environment. Let $L^{(0)}$ be $L(\Theta; r)$ [defined

in Eq. (2.3)] for an isotropic environment, with the general form

$$L^{(0)}p(\Theta) = D_\theta^{(0)}\partial_\Theta^2 p(\Theta) + \int d\Theta, [\Omega^{(0)}(\Theta, \Theta')p(\Theta') - (\Omega^{(0)}(\Theta', \Theta)p(\Theta)], \tag{3.1}$$

where $D_\theta^{(0)}$ and $\Omega^{(0)}(\Theta, \Theta')$ are the rotational diffusion coefficient (scalar) and random turning kernel, respectively, in the isotropic environment. Assuming random turning is symmetric about the direction of cell polarity then $\Omega^{(0)}(\Theta', \Theta) = \Omega^{(0)}(\Theta, \Theta')$, which implies $\Omega^{(0)}\ (\Theta, \Theta')$ can be expanded as

$$\Omega^{(0)}(\Theta, \Theta') = \sum_\mu \Omega_\mu \Psi_\mu(\Theta')^* \Psi_\mu(\Theta) = \sum_\mu \Omega_\mu \Psi_\mu(\Theta')^* \Psi_\mu(\Theta)^*. \tag{3.2}$$

Because $\{\Psi_\mu\}$ are eigenfunctions of $L^{(0)}$ with eigenvalues obtained from

$$\lambda_\mu^{(0)} = \int d\Theta' \Psi_\mu(\Theta')^* L^{(0)} \Psi_\mu(\Theta'), \tag{3.3}$$

the coefficients ${}_\kappa\lambda_\mu$ are equal to $\delta_{\mu,\kappa}\lambda_\mu^{(0)}$.

3.1. Two-dimensional isotropic migration

For two-dimensional movement, Eq. (3.1) becomes

$$L^{(0)}p(\theta) = D_\theta^{(0)}\partial_\theta^2 p(\theta) + \int_0^{2\pi} d\theta'[\Omega^{(0)}(\theta, \theta')p(\theta') - \Omega^{(0)}(\theta', \theta)p(\theta)], \tag{3.4}$$

and the turning kernel, $\Omega^{(0)}(\theta, \theta')$, can be expanded as

$$\Omega^{(0)}(\theta, \theta') = \sum_{m=-\infty}^{\infty} \Omega_m \mathrm{e}^{-im(\theta' - \theta)}\ , \tag{3.5}$$

with $\Omega_m = \Omega_{-m}$ because of symmetry in turning about Θ. From Eq. (3.3), the eigenvalues of $L^{(0)}$ are

$$\lambda_m^{(0)} = -m^2 D_\theta^{(0)} - (\Omega_0 - \Omega_m). \tag{3.6}$$

The solution to Eq. (2.40) is simply

$$p_{m,n}^{(0)}(\tau) = \delta_{m,n}\mathrm{e}^{\lambda_m^{(0)}\tau}, \tag{3.7}$$

and because $\lambda_0^{(0)} = 0$ and $p_{s,m}^{(0)} = \lim_{\tau\to\infty} p_{m,0}(\tau)\Psi_0$, then $p_{s,m}^{(0)} = \delta_{m,0}\frac{1}{\sqrt{2\pi}}$.

Furthermore, because $v(\theta, r) = S^{(0)}\Theta$ in an isotropic environment, the Fourier coefficients of $v(\theta)$ can be written as $v_m^{(0)} = S^{(0)}\Theta_m$ where

$\{\Theta_m\}$ are the moments of Θ, given by

$$\Theta_m \equiv \int_0^{2\pi} d\theta \frac{1}{\sqrt{2\pi}} e^{-im\theta} \begin{bmatrix} \cos\theta \\ \sin\theta \end{bmatrix} = \sqrt{\frac{\pi}{2}} \left(\delta_{m,-1} \begin{bmatrix} 1 \\ i \end{bmatrix} + \delta_{m,1} \begin{bmatrix} 1 \\ -i \end{bmatrix} \right). \tag{3.8}$$

This implies that the only non-zero coefficients $\Gamma_m^{(0)}$ from Eq. (2.48) are

$$\Gamma_{\pm 1}^{(0)} = \frac{S^{(0)}}{2\pi} \Theta_{\pm 1}. \tag{3.9}$$

It can be shown immediately from Eq. (2.46) that because $\Gamma_0^{(0)} = 0$, then $V = 0$, and from Eq. (3.8) that $\bar{\Theta} = 0$, implying there is no drift velocity nor directional orientation bias in an isotropic environment. Upon integrating Eq. (2.47) and applying Eqs. (3.7–8), the only non-zero expansion coefficients of $\Delta(\Theta)$ are

$$\Delta_{\pm 1}^{(0)} = \frac{S^{(0)}}{-\lambda_1^{(0)}} \Theta_{\pm 1}. \tag{3.10}$$

Finally, if fluctuations in cell velocity on the time scale of locomotion reflected in B are assumed to occur only in the direction of cell polarity, then $B^{(0)}(\Theta) = b^{(0)} \Theta \Theta^T$ such that

$$B_m^{(0)} \equiv \int_0^{2\pi} d\theta \, \Psi_0 B^{(0)}(\theta) = b^{(0)} \sqrt{\frac{\pi}{2}} \left(\delta_{m,0} I_2 + \delta_{m,-2} \begin{bmatrix} 1 & i \\ i & -1 \end{bmatrix} + \delta_{m,2} \begin{bmatrix} 1 & -i \\ -i & -1 \end{bmatrix} \right), \tag{3.11}$$

where I_2 is the two-dimensional identity tensor.

Combining the above terms with Eq. (2.45) provides:

$$\begin{aligned} M^{(0)} &= \Delta_{-1}^{(0)} * \Gamma_{-1}^{(0)} + \Delta_1^{(0)} * \Gamma_1^{(0)} + B_0^{(0)} p_{s,0} \\ &= \frac{1}{2} \left(\frac{S^{(0)^2}}{D_\theta^{(0)} + (\Omega_0 - \Omega_1)} + b^{(0)} \right) I_2 \equiv \mu I_2, \end{aligned} \tag{3.12}$$

where μ is the random motility coefficient (a scalar). This result is similar to that derived previously by Dickinson and Tranquillo (1995), which also accounted for velocity fluctuations (leading to the $b^{(0)}$ contribution), but did not account for discrete turning. The inclusion of discrete turning in the underlying random walk model results in the additional $(\Omega_0 - \Omega_1)$ term in the denominator, effectively decreasing the random motility coefficient. Physically, Ω_0 is the overall frequency of discrete turns, and $\Omega_1/\Omega_0 = \langle \cos(\theta - \theta') \rangle$ reflects the average magnitude of the discrete turns.

The directional persistence tensor for the isotropic environment, $T^{(0)}$ [c.f. Eq. (2.33)], can also be found by applying Eqs. (2.34) and (3.7). In terms of the expansion coefficients, Θ_m, the autocorrelation function of Θ is

$$\langle \Theta(\tau), \Theta(0) \rangle = \int d\Theta' \sum_m \Theta_m^* \Psi_m(\Theta')^* \, \mathrm{e}^{\lambda_m^{(0)}\tau} \Theta'^T p_s^{(0)}$$

$$= \frac{1}{2\pi} \sum_m \Theta_m^* \Theta_m^T \mathrm{e}^{\lambda_m^{(0)}\tau} = \frac{1}{2} \mathrm{e}^{\lambda_1^{(0)}\tau} I_2, \tag{3.13}$$

therefore

$$T^{(0)} = \int d\tau \frac{1}{2} \mathrm{e}^{\lambda_m^{(0)}\tau} I_2 = \frac{1}{2} [D_\theta^{(0)} + (\Omega_0 - \Omega_1)]^{-1} I_2. \tag{3.14}$$

By combining the above, we see that $M^{(0)} = S^{(0)^2} T^{(0)} + \frac{1}{2} b^{(0)} I_2$.

3.2. Three-dimensional isotropic migration

For three-dimensional cell movement in an isotropic environment, $L^{(0)}$ has the form

$$L^{(0)} p(\theta, \varphi) = D_\theta^{(0)} \frac{1}{\sin^2 \theta} \partial_\varphi^2 \, p(\theta, \varphi) + \frac{1}{\sin \theta} \partial_\theta [D_\theta^{(0)} \sin \theta \, \partial_\theta p(\theta, \varphi)]$$

$$+ \int_0^{2\pi} d\varphi' \int_0^{\pi} d\theta' \sin \theta' [\Omega^{(0)}(\theta', \varphi', \theta, \varphi) p(\theta', \varphi')$$

$$- \Omega^{(0)}(\theta, \varphi, \theta', \varphi') p(\theta, \varphi)], \tag{3.15}$$

where we have noted that the rotational diffusion tensor is isotropic with respect to turning direction, such that $D_\varphi^{(0)} = D_\theta^{(0)}$. Also, because of turning symmetry, the turning kernel, $\Omega^{(0)}(\theta', \varphi', \theta, \varphi)$, can be expanded as

$$\Omega^{(0)}(\theta', \varphi', \theta, \varphi) = \sum_{m=0}^{\infty} \sum_{l=-m}^{m} \Omega_m \, Y_m^{-l}(\theta', \varphi') \, Y_m^l(\theta, \varphi). \tag{3.16}$$

The eigenvalues of three-dimensional $L^{(0)}$ are then

$$\lambda_m^{(0)} = -m(m+1) D_\theta^{(0)} - (\Omega_0 - \Omega_m). \tag{3.17}$$

The normalization condition requires $p_s^{(0)} = Y_0^{0^2} = 1/4\pi$, such that $p_{s,m}^{l^{(0)}} = \delta_{m,0}\delta_{l,0}\,1/\sqrt{4\pi}$. Also, the modes of Θ are

$$\Theta_m^l \equiv \int_0^{2\pi} d\varphi \int_0^{\pi} d\theta \sin\theta\, Y_m^{-l}(\theta, \varphi) \begin{bmatrix} \cos\theta \\ \sin\theta\cos\varphi \\ \sin\theta\sin\varphi \end{bmatrix}$$

$$= \delta_{m,1}\sqrt{\frac{2\pi}{3}} \left(\delta_{l,0} \begin{bmatrix} \sqrt{2} \\ 0 \\ 0 \end{bmatrix} + \delta_{l,1} \begin{bmatrix} 0 \\ 1 \\ -i \end{bmatrix} + \delta_{l,-1} \begin{bmatrix} 0 \\ 1 \\ i \end{bmatrix} \right). \tag{3.18}$$

Eqs. (2.47–8) and (3.18) imply that the non-zero expansion coefficients of $\Gamma_m^{l(0)}$ and $\Delta_m^{l(0)}$ are

$$\Gamma_1^{l^{(0)}} = \frac{S^{(0)}}{4\pi}\Theta_1^l \tag{3.19}$$

$$\Delta_1^{l^{(0)}} = \frac{S^{(0)}}{2D_\theta^{(0)} + (\Omega_0 - \Omega_1)}\Theta_1^l \tag{3.20}$$

for $l = \{-1, 0, 1\}$. Also, if $B^{(0)}(\Theta) = b^{(0)}\Theta\Theta^T$, then

$$B_0^{(0)} = \int_0^{2\pi} d\varphi \int_0^{\pi} d\theta \sin\theta\, \Psi_0\, b^{(0)}\Theta\Theta^T = \frac{2\sqrt{\pi}}{3} b^{(0)} I_3 \tag{3.21}$$

Combining the above into Eq. 2.41, we have

$$M^{(0)} = \frac{1}{3}\left(\frac{S^{(0)^2}}{2D_\theta^{(0)} + (\Omega_0 - \Omega_1)} + b^{(0)} \right) I_3 \equiv \mu I_3 . \tag{3.22}$$

The only differences between this result and the two-dimensional motility tensor are pre-factor of $\frac{1}{3}$ instead of $\frac{1}{2}$, and $2D_\theta^{(0)}$ instead of $D_\theta^{(0)}$ in the denominator. These differences result from the additional degree of freedom in translation and rotation, respectively.

Eq. (3.22) is a generalization of results derived previously by others. For example, for the special case with negligible fluctuations in translational and rotational velocities on the time scale of locomotion such that $b^{(0)}$ and $D_\theta^{(0)}$ are zero, this result reduces to $M^{(0)} = (1/3)S^{(0)^2}/(\Omega_0 - \Omega_1)I_3$, which is equivalent to the well-known result for the random motility coefficient derived by Lovely and Dahlquist (1975). In the more general model presented here, the effect of small fluctuations in cell orientation and speed during a run are now also accounted for in $D_\theta^{(0)}$ and $b^{(0)}$, respectively.

Proceeding as in the two-dimensional case [Eqs. (3.13–4)], the directional autocorrelation function and directional persistence tensor for the three-dimensional isotropic environment are

$$\langle \Theta(\tau), \Theta(0) \rangle = \tfrac{1}{3} \mathrm{e}^{[-2D_\theta^{(0)} - (\Omega_0 - \Omega_1)]\tau} I_3 \tag{3.23}$$

and

$$T^{(0)} = \tfrac{1}{3} [2D_\theta^{(0)} + (\Omega_0 - \Omega_1)]^{-1} I_3 \ , \tag{3.24}$$

respectively.

These results indicate that for two- or three-dimensional migration ($n_d = 2$ or 3), the general result is $M = S^{(0)^2} T^{(0)} + 1/n_d \, b^{(0)} I_{n_d}$, where the tensor $T^{(0)}$ is given by Eq. (3.14) or Eq. (3.24) respectively [see also Eq. (2.32)]. If fluctuations in cell speed are negligible ($b^{(0)} = 0$), and defining the *directional persistence time*, P_t as the scalar trace of $T^{(0)}$, then we have the well-known result $\mu = 1/n_d \, S^{(0)^2} P_t$ (Dunn, 1983). However, the more general form of the directional persistence time derived here accounts for both discrete and continuous random turning and velocity fluctuations.

Another definition of directional persistence time proposed by Alt (1990) is

$$P \equiv \frac{\int_0^\infty d\tau\tau \langle v(\Theta(\tau))^T v(\Theta(0)) \rangle}{\int_0^\infty d\tau \langle v(\Theta(\tau))^T v(\Theta(0)) \rangle}. \tag{3.25}$$

However, because $\langle v(\Theta(\tau))^T v(\Theta(0)) \rangle = S^{(0)^2} \mathrm{e}^{\lambda_1^{(0)}\tau}$, both definitions of directional persistence time yield the same result in this case.

These results for migration in an isotropic environment serve as a basis for the following sections where M and V are derived for an anisotropic environment.

4. Cell migration in an anisotropic environment

$M(r)$ and $V(r)$ are evaluated in an anisotropic environment by assigning a *bias parameter*, ε, to reflect the magnitude of the cell response to the anisotropy. The turning operator, $L(\Theta, r)$ can then be expanded in powers of ε, *i.e.*,

$$L(\Theta, r) = L^{(0)}(r) + \varepsilon L^{(1)}(\Theta, r) + \varepsilon^2 L^{(2)}(\Theta, r) + \ \dots \ , \tag{4.1}$$

where $L^{(0)}(r)$ has the same form as in the previous section, but evaluated at the stimulus field encountered at position r. Similarly, the coefficients, $\{{}_\nu\lambda_\mu(r)\}$ can be expanded as

$${}_\nu\lambda_\mu(r) = {}_\nu\lambda_\mu^{(0)}(r) + \varepsilon_\nu\lambda_\mu^{(1)}(r) + \varepsilon^2 \, {}_\nu\lambda_\mu^{(2)}(r) + \ \dots \tag{4.2}$$

where

$$ {}_{\nu}\lambda_{\mu}^{(j)}(r) \equiv \int d\Theta' \Psi_{\nu}(\Theta')^* L^{(j)}(\Theta', r) \Psi_{\mu}(\Theta'). \tag{4.3} $$

For two-dimensional cell motion, these coefficients are

$$ {}_{n}\lambda_{m}^{(j)}(r) = \frac{1}{2\pi} \int_0^{2\pi} d\theta' \, \mathrm{e}^{-in\theta'} L^{(j)}(\theta', r) \mathrm{e}^{im\theta'}, \tag{4.4} $$

and for three-dimensional motion, they are

$$ {}_{n}^{k}\lambda_{m}^{l(j)}(r) = \int_0^{2\pi} d\varphi' \int_0^{\pi} d\theta' \sin\theta' \; Y_n^{-k}(\theta', \varphi') L^{(j)}(\theta', \varphi', r) \, Y_m^l(\theta', \varphi'). \tag{4.5} $$

Recall that $\{\Psi_{\mu}(\Theta)\}$ are eigenfunctions of $L^{(0)}$ with eigenvalues, $\lambda_{\mu}^{(0)}(r)$, such that ${}_{\nu}\lambda_{\mu}^{(0)}(r) = \delta_{\mu,\nu}\lambda_{\mu}^{(0)}(r)$. (Hereafter, to simplify notation, the dependence of the Fourier coefficients and eigenvalues on r is not shown explicitly.)

Our goal is to find a first-order approximation for the biased migration response by determining $M(r)$ and $V(r)$ to first-order of ε, although this procedure can be used to sequentially determine terms of higher order of ε, too. The coefficients v_{μ}, B_{μ}, Δ_{μ}, Γ_{μ}, and $p_{s,\mu}$ are now general functions of r. We proceed by expanding these coefficients into powers of ε then substituting these series into Eqs. (2.45) and (2.46). The results are

$$ \begin{aligned} M(r) = M^{(0)}(r) &+ \sum_{\mu} \varepsilon \left[\Delta_{\mu}^{(1)^*} \Gamma_{\mu}^{(0)} + \Delta_{\mu}^{(0)^*} \Gamma_{\mu}^{(1)} \right] \\ &+ \Psi_0 \varepsilon B_0^{(1)} + \varepsilon \sum_{\mu} B_{\mu}^{(0)} p_{s,\mu}^{(1)} + O(\varepsilon^2) \end{aligned} \tag{4.6} $$

$$ \begin{aligned} V(r) = \Psi^{-1}{}_0 \varepsilon \Gamma_0^{(1)} &- \sum_{\mu} \Delta_{\mu}^{(0)^*} \partial_r \Gamma_{\mu}^{(0)} - \varepsilon \sum_{\mu} \left[\Delta_{\mu}^{(1)^*} \partial_r \Gamma_{\mu}^{(0)} \right. \\ &\left. + \Delta_{\mu}^{(0)^*} \partial_r \Gamma_{\mu}^{(1)} \right] + O(\varepsilon^2). \end{aligned} \tag{4.7} $$

Note that if the bias parameter, ε, is proportional to the magnitude of a gradient of a stimulus, $\varrho(r)$, (*e.g.*, chemoattractant concentration), then $\partial_r = d\varrho/dr \, \partial_{\varrho}$ is $O(\varepsilon)$ which makes the final term in Eq. (4.7) also $O(\varepsilon^2)$.

To obtain the perturbation coefficients of Γ_{μ} and Δ_{μ}, the coefficients, $p_{\mu,\nu}(\tau)$, are solved by expanding in the form $p_{\mu,\nu} = p_{\mu,\nu}^{(0)} + \varepsilon p_{\mu,\nu}^{(1)} + \ldots$, substituting the expansions of $p_{\mu,\nu}$ and ${}_{\nu}\lambda_{\mu}$ into Eq. (2.40), collecting terms of equal order of ε, then sequentially solving the

resulting ordinary differential equations for increasing orders of ε. To lower order, we have

$$p^{(0)}_{\mu,\nu}(\tau) = \delta_{\mu,\nu} e^{\lambda^{(0)}_\mu \tau}. \tag{4.8}$$

Upon substitution of $p^{(0)}_{\mu,\nu}(\tau)$ into Eq. (2.40), the differential equation for first-order terms becomes

$$d_\tau p^{(1)}_{\mu,\nu}(\tau) = {}_\mu\lambda^{(1)}_\nu e^{\lambda^{(0)}_\nu \tau} + \lambda^{(0)}_\mu p^{(1)}_{\mu,\nu}(\tau), \tag{4.9}$$

which, for $\lambda^{(0)}_\nu \neq \lambda^{(0)}_\mu$, has the solution

$$p^{(1)}_{\mu,\nu}(\tau) = \frac{{}_\mu\lambda^{(1)}_\nu}{\lambda^{(0)}_\nu - \lambda^{(0)}_\mu}\left(e^{\lambda^{(0)}_\nu \tau} - e^{\lambda^{(0)}_\mu \tau}\right), \tag{4.10}$$

and, for $\lambda^{(0)}_\nu = \lambda^{(0)}_\mu$, has the solution

$$p^{(1)}_{\mu,\nu}(\tau) = {}_\mu\lambda^{(1)}_\nu \tau e^{\lambda^{(0)}_\mu \tau}. \tag{4.11}$$

From Eqs. (4.8) and (4.11), the zeroth and first-order coefficients of $p_s(\Theta)$ are, for $\mu \neq 0$,

$$p^{(0)}_{s,\mu} = 0 \tag{4.12}$$

$$p^{(1)}_{s,\mu} = \lim_{\tau\to\infty} p^{(1)}_{\mu,0}(\tau)\Psi_0 = \Psi_0 \frac{{}_\mu\lambda^{(1)}_0}{-\lambda^{(0)}_\mu}, \tag{4.13}$$

and for $\mu = 0$,

$$p^{(0)}_{s,0} = \Psi_0. \tag{4.14}$$

The Fourier coefficients, v_μ, B_μ, Δ_μ and Γ_μ are now expanded into powers of ε. From Eq. 2.47, the first two terms of Δ_μ, are

$$\Delta^{(0)}_\mu = \frac{S^{(0)}}{-\lambda^{(0)}_\mu}\Theta_\mu \tag{4.15}$$

$$\Delta^{(1)}_\mu = \frac{v^{(1)}_\mu}{-\lambda^{(0)}_\mu} + \sum_\nu S^{(0)}\Theta_\nu\left(c_{\nu,\mu}\frac{{}_\nu\lambda^{(1)*}_\mu}{(\lambda^{(0)}_\mu)^2} + (1-c_{\nu,\mu})\frac{{}_\nu\lambda^{(1)*}_\mu}{\lambda^{(0)}_\nu - \lambda^{(0)}_\mu}\left(\frac{1}{\lambda^{(0)}_\nu} - \frac{1}{\lambda^{(0)}_\mu}\right)\right), \tag{4.16}$$

where $c_{\nu,\mu} = 1$ if $\lambda^{(0)}_\nu = \lambda^{(0)}_\mu$, otherwise, $c_{\nu,\mu} = 0$. From Eq. (2.48), the zero and first-order terms of Γ_μ are

$$\Gamma^{(0)}_\mu = \Psi^2_0 S^{(0)}\Theta_\mu \tag{4.17}$$

$$\Gamma^{(1)}_\mu = \Psi^2_0 v^{(1)}_\mu + S^{(0)}\sum_\nu \Psi_0 \frac{{}_\nu\lambda^{(1)}_0}{-\lambda^{(0)}_\nu}\int d\Theta' \Psi_\mu(\Theta')^* \Theta' \Psi_\nu(\Theta'). \tag{4.18}$$

We can reduce Eqs. (4.16) & (4.18) further by taking advantage of the results in the previous section for the isotropic environment. For two-dimensional motion, we found that the only non-zero coefficients of $\Delta_m^{(0)}$ and $\Gamma_m^{(0)}$ were for $m = \pm 1$. This implies only $\Delta_{\pm 1}^{(1)}$ and $\Gamma_{\pm 1}^{(1)}$ are needed to evaluate Eqs. (4.16–7). From Eqs. (4.16) and (4.18), these coefficients are

$$\Delta_{\pm 1}^{(1)} = \frac{v_{\pm 1}^{(1)}}{-\lambda_1^{(0)}} + \frac{S^{(0)}}{(\lambda_1^{(0)})^2}\left({}_{-1}\lambda_{\pm 1}^{(1)*}\Theta_{-1} + {}_{1}\lambda_{\pm 1}^{(1)*}\Theta_1\right) \tag{4.19}$$

$$\Gamma_{\pm 1}^{(1)} = \frac{1}{2\pi}\left(v_{\pm 1}^{(1)} + \frac{{}_{\pm 2}\lambda_0^{(1)}}{-\lambda_2^{(0)}} S^{(0)}\Theta_{\mp 1}\right). \tag{4.20}$$

We also found in the previous section that $\lambda_m^{(0)} = \lambda_{-m}^{(0)}$, $\Delta_1^{(0)} = \Delta_{-1}^{(0)*}$ and $\Gamma_1^{(0)} = \Gamma_{-1}^{(0)*}$. Noting that $v_1^{(1)} = v_{-1}^{(1)*}$ and ${}_n\lambda_m^{(1)} = {}_{-n}\lambda_{-m}^{(1)*}$, which imply $\Delta_1^{(1)} = \Delta_{-1}^{(1)*}$ and $\Gamma_1^{(1)} = \Gamma_{-1}^{(1)*}$, we have $\Delta_1^{(1)*}\Gamma_1^{(0)T} + \Delta_{-1}^{(1)*}\Gamma_{-1}^{(0)T} = 2\Re(\Delta_1^{(1)*}\Gamma_1^{(0)T})$ and $\Delta_1^{(0)*}\Gamma_1^{(1)T} + \Delta_{-1}^{(0)*}\Gamma_{-1}^{(1)T} = 2\Re\{\Delta_1^{(0)*}\Gamma_1^{(1)T}\}$. Therefore, combining the above into Eq. (4.6) yields the first-order correction to the random motility tensor for two-dimensional motion in a general anisotropic environment:

$$\begin{aligned} M = M^{(0)} &+ \varepsilon\frac{1}{2\pi}\frac{S^{(0)}}{-\lambda_1^{(0)}} 2\Re\left\{\Theta_{-1}v_1^{(1)T} + v_{-1}^{(1)}\Theta_1{}^T + S^{(0)}\frac{{}_2\lambda_0^{(1)}}{-\lambda_2^{(0)}}\Theta_{-1}\Theta_{-1}^T\right. \\ &\left. + \frac{{}_1\lambda_1^{(1)}}{-\lambda_1^{(0)}}\Theta_{-1}\Theta_1^T + \frac{{}_{-1}\lambda_1^{(1)}}{-\lambda_1^{(0)}}\Theta_1\Theta_1^T\right\} \\ &+ \varepsilon\frac{1}{\sqrt{2\pi}}\left(B_0^{(1)} + 2\Re\left\{B_2^{(0)}\frac{{}_2\lambda_0^{(1)}}{-\lambda_2^{(0)}}\right\}\right) + O(\varepsilon^2), \end{aligned} \tag{4.21}$$

where $M^{(0)}$ is given by Eq. (3.12).

Evaluation of $V(r)$ requires $\Gamma_0^{(1)}$, which, from Eq. (4.18), is

$$\Gamma_0^{(1)} = \frac{1}{2\pi}\left(v_0^{(1)} + S^{(0)}2\Re\left\{\frac{{}_1\lambda_0{}^{(1)}}{-\lambda_1^{(0)}}\Theta_{-1}\right\}\right). \tag{4.22}$$

Introducing Eq. (4.22) into Eq. (4.7) yields

$$\begin{aligned} V(r) = &\frac{1}{\sqrt{2\pi}}\varepsilon\left(v_0^{(1)} + 2S^{(0)}\Re\left\{\frac{{}_1\lambda_0^{(1)}}{-\lambda_1^{(0)}}\Theta_{-1}\right\}\right) \\ &- \frac{1}{2}\frac{S^{(0)}}{-\lambda_1^{(0)}}\partial_r S^{(0)} - 2\varepsilon\Re\{\Delta_{-1}^{(1)}\partial_r\Gamma_1^{(0)} + \Delta_{-1}^{(0)}\partial_r\Gamma_1^{(1)}\} + O(\varepsilon^2), \end{aligned} \tag{4.23}$$

where, again, the final term is $O(\varepsilon^2)$ if ∂_r is $O(\varepsilon)$.

For three-dimensional biased migration, the coefficients of Δ_1^l and Γ_1^l are similarly evaluated from Eqs. (76) and (78) to be

$$\Delta_1^{l\,(1)} = \frac{v_1^{l\,(1)}}{-\lambda_1^{(0)}} + \frac{S^{(0)}}{(\lambda_1^{(0)})^2}({}_1^0\lambda_1^{l\,(1)^*}\Theta_1^0 + {}_1^1\lambda_1^{l\,(1)^*}\Theta_1^1 + {}_1^{-1}\lambda_1^{l\,(1)^*}\Theta^{-1}{}_1^1) \tag{4.24}$$

for $l = -1, 0, 1$, and

$$\Gamma_1^{0(1)} = \frac{1}{4\pi}v_1^{0(1)} + S^{(0)}\left(\sqrt{\frac{4}{5}}\frac{{}_2^0\lambda_0^{0(1)}}{-\lambda_2^{(0)}}\Theta_1^0 + \sqrt{\frac{3}{5}}\frac{{}_2^1\lambda_0^{0(1)}}{-\lambda_2^{(0)}}\Theta^{-1}{}_1^1 + \sqrt{\frac{3}{5}}\frac{{}_2^{-1}\lambda_0^{0(1)}}{-\lambda_2^{(0)}}\Theta_1^1\right) \tag{4.25}$$

$$\Gamma^{\pm 1}{}_1^{(1)} = \frac{1}{4\pi}v^{\pm 1}{}_1^{(1)} + S^{(0)}\left(\sqrt{\frac{6}{5}}\frac{{}_2^{\pm 2}\lambda_0^{0(1)}}{-\lambda_2^{(0)}}\Theta_1^0 - \sqrt{\frac{1}{5}}\frac{{}_2^0\lambda_0^{0(1)}}{-\lambda_2^{(0)}}\Theta^{\pm 1}{}_1^1 + \sqrt{\frac{3}{5}}\frac{{}_2^{\pm 1}\lambda_0^{0(1)}}{-\lambda_2^{(0)}}\Theta^0{}_1^1\right). \tag{4.26}$$

Combining these coefficients into Eq. (4.6) and noting that $\Theta^{\pm 1}{}_1^1[\Theta_1^0]^T = \Theta_1^0[\Theta^{\pm 1}{}_1^1]^T = 0$ yield the general first-order correction for M in an anisotropic environment:

$$\begin{aligned} M = M^{(0)} &+ \frac{\varepsilon}{4\pi}\frac{S^{(0)}}{-\lambda_1^{(0)}}\Bigg(\Theta_1^0[v_1^{0(1)}]^T + v_1^{0(1)}[\Theta_1^0]^T \\ &+ S^{(0)}\left[\frac{2}{\sqrt{5}}\frac{{}_2^0\lambda_0^{0(1)}}{-\lambda_2^{(0)}} + \frac{{}_1^0\lambda_1^{0(1)}}{-\lambda_1^{(0)}}\right]\Theta_1^0[\Theta_1^0]^T \\ &+ 2\Re\{\Theta^{-1}{}_1^1 v_1^{1(1)^T} + v^{-1}{}_1^{1(1)}[\Theta_1^1]^T\} \\ &+ 2S^{(0)}\Re\left\{\left[\sqrt{\frac{6}{5}}\frac{{}_2^{-2}\lambda_0^{0(1)}}{-\lambda_2^{(0)}} + \frac{{}_1^{-1}\lambda_1^{1(1)}}{-\lambda_1^{(0)}}\right]\Theta_1^1[\Theta_1^1]^T \right. \\ &\left. + S^{(0)}\left[\frac{{}_1^1\lambda_1^{1(1)}}{-\lambda_1^{(0)}} - \sqrt{\frac{1}{5}}\frac{{}_2^0\lambda_0^{0(1)}}{-\lambda_2^{(0)}}\right]\Theta^{-1}{}_1^1[\Theta_1^1]^T\right\}\Bigg) \\ &+ \frac{\varepsilon}{\sqrt{4\pi}}\left(B_0^{0(1)} + B_2^{0(0)}\frac{{}_2^0\lambda_0^{0(1)}}{-\lambda_2^{(0)}}\right) + O(\varepsilon^2). \end{aligned} \tag{4.27}$$

Evaluation of the three-dimensional drift velocity requires

$$\Gamma_0^{(1)} = \frac{1}{4\pi}\left(v_0^{(1)} + S^{(0)}\frac{{}_1^0\lambda_0^{0(1)}}{-\lambda_0^{(0)}}\Theta_1^0 + S^{(0)}2\Re\left\{\frac{{}_1^1\lambda_0^{0(1)}}{-\lambda_1^{(0)}}\Theta^{-1}{}_1^1\right\}\right), \tag{4.28}$$

which, combined with Eq. (4.7), yields

$$V(r) = \frac{1}{\sqrt{4\pi}}\varepsilon\left(v_0^{0^{(1)}} + S^{(0)}\frac{{}_1^0\lambda_1^{0^{(1)}}}{-\lambda_0^{(0)}}\Theta_1^{0^{(0)}} + S^{(0)}2\Re\left\{\frac{{}_1^1\lambda_1^{1^{(1)}}}{-\lambda_1^{(0)}}\Theta^{-1}_1\right\}\right)$$

$$-\frac{1}{3}\frac{S^{(0)}}{-\lambda_1^{(0)}}\partial_r S^{(0)} - \varepsilon[\Delta_1^{0^{(1)}}\partial_r\Gamma_1^{0^{(0)}} + \Delta_1^{0^{(0)}}\partial_r\Gamma_1^{0^{(1)}}]$$

$$-2\varepsilon\Re\{\Delta_{-1}^{(1)}\partial_r\Gamma_1^{1^{(0)}} + \Delta_{-1}^{(0)}\partial_r\Gamma_1^{1^{(1)}}\} + O(\varepsilon^2). \tag{4.29}$$

To this point, no assumptions have been made as to the type or the directionality of the anisotropic stimulus. However, the small bias approximation provides equations for first-order corrections in M and V which only require the Fourier coefficients of $B^{(1)}$ and $v^{(1)}$ and determination of the coefficients, ${}_\nu\lambda_\mu$, appearing in Eqs. (4.21), (4.23), (4.27), and (4.29). As shown in the following sections, these coefficients can be evaluated if the dependence of $L^{(1)}$ on Θ is known. In the cases to follow, we propose appropriate forms for these dependencies for two- and three-dimensional taxis and contact guidance in the anisotropic environment.

5. Biased cell migration by taxis

In this section, the above general results are applied to the specific case of biased cell migration by taxis in a spatial gradient of a stimulus. Let ε reflect the magnitude of the response, assumed to be proportional to the steepness of the gradient, and assign the x-direction as the gradient direction. In this case, we assume v, B, Ω, and L depend on both Θ and x.

5.1. Two-dimensional taxis

For two-dimensional migration, $L(\theta, x)$ is assumed to have the form

$$L(\theta, x)f(\theta) \equiv -\partial_\theta[\omega_\theta(\theta, x)f(\theta) - D_\theta(\theta, x)\partial_\theta f(\theta)]$$

$$+\int_0^{2\pi} d\theta'[\Omega(\theta, \theta'; x)f(\theta') - \Omega(\theta', \theta; x)f(\theta)], \tag{5.1}$$

where $\omega_\theta(\theta, x)$ and $D_\theta(\theta, x)$ are the rotational drift velocity (scalar) and rotational diffusion coefficient, respectively. The θ-dependence of

ω_θ, D_θ, B, and v are approximated by expanding in the various parameters terms of ε:

$$\omega_\theta(\theta, x) = -\omega_\theta^{(1)}(x)\varepsilon\sin\theta + O(\varepsilon^2) \tag{5.2}$$

$$D_\theta(\theta, x) = D_\theta^{(0)}(x) + D_\theta^{(1)}(x)\varepsilon\cos\theta + O(\varepsilon^2) \tag{5.3}$$

$$B(\theta, x) = (b^{(0)}(x) + b^{(1)}(x)\varepsilon\cos\theta)\Theta\Theta^T + O(\varepsilon^2) \tag{5.4}$$

$$v(\theta, x) = (S^{(0)}(x) + S^{(1)}(x)\varepsilon\cos\theta)\Theta + O(\varepsilon^2). \tag{5.5}$$

To simplify the analysis somewhat, we have again assumed in Eqs. (5.4–5) that the cell velocity is confined to the direction of cell orientation, thus allowing v and B to have only components proportional to the vector Θ and the dyadic $\Theta\Theta^T$, respectively. The $\cos\theta$ and $\sin\theta$ dependencies result from the parameter being symmetric functions ($f(\theta) = f(-\theta)$) or anti- symmetric functions ($f(\theta) = -f(-\theta)$) of θ, respectively, about the gradient direction, $\theta = 0$. Furthermore, $\Omega(\theta, \theta')$ is assumed to have the form

$$\Omega(\theta, \theta'; x) = \Omega^{(0)}(\theta, \theta')(1 + \varepsilon[\alpha(x)\cos\theta - \beta(x)\cos\theta']) + O(\varepsilon^2), \tag{5.6}$$

where $\Omega^{(0)}(\theta, \theta')$ is given by Eq. (3.5). The factor $\alpha(x)\cos\theta$ reflects the enhanced probability of turning to new direction with a component in the gradient direction, and $\beta(x)\cos\theta'$ reflects the decreased probability of turning from a direction with a component in the gradient direction.

Introducing the above expansions into Eq. (5.1), and collecting terms of $O(\varepsilon)$, we find

$$\begin{aligned} L^{(1)}f(\theta) = {} & \partial_\theta[\omega_\theta^{(1)}(x)\sin\theta f(\theta)] + \partial_\theta[D_\theta^{(1)}(x)\cos\theta\partial_\theta f(\theta)] \\ & + \int_0^{2\pi} d\theta'\,[\Omega^{(0)}(\theta, \theta'; x)(\alpha(x)\cos\theta - \beta(x)\cos\theta')f(\theta') \\ & - \Omega^{(0)}(\theta', \theta)(\alpha(x)\cos\theta' - \beta(x)\cos\theta)f(\theta)]. \end{aligned} \tag{5.7}$$

Determination of $M(x)$ and $V(x)$ now only requires evaluating the various necessary coefficients which appear in Eqs. (4.21) and (4.23). Upon applying Eq. (4.4), we find ${}_2\lambda_0^{(1)} = {}_1\lambda_1^{(1)} = {}_{-1}\lambda_1^{(1)} = 0$. Also, by transforming the first-order terms in Eqs. (5.4–5), one finds

$$v_{\pm 1}^{(1)} = \frac{1}{\sqrt{2\pi}} S^{(1)} \int_0^{2\pi} d\theta e^{\mp i\theta}\cos\theta\Theta = 0,$$

and

$$B_0^{(1)} = \frac{1}{\sqrt{2\pi}} b^{(1)} \int_0^{2\pi} d\theta\cos\theta\,\Theta\Theta^T = 0.$$

These imply that there is no first-order dependence of M on ε; *i.e.*, $M(x) = M^{(0)}(x) + O(\varepsilon^2)$. Evaluation of $V(x)$ requires

$$v_0^{(1)} \equiv \frac{1}{\sqrt{2\pi}} \int_0^{2\pi} d\theta S^{(1)}(x) \cos\theta' \Theta' = \sqrt{\frac{\pi}{2}} S^{(1)}(x) \begin{bmatrix} 1 \\ 0 \end{bmatrix} \tag{5.8}$$

and

$${}_1\lambda_0^{(1)} \equiv \frac{1}{2\pi} \int_0^{2\pi} d\theta \mathrm{e}^{-i\theta} L^{(1)} 1 = \frac{1}{2} [\omega_\theta^{(1)} + (\Omega_0 - \Omega_1)(\alpha + \beta)], \tag{5.9}$$

which, from Eq. (4.23), yield

$$V(x) = \frac{1}{2} \left(\varepsilon S^{(1)} + \varepsilon S^{(0)} \frac{\omega_\theta^{(1)} + (\Omega_0 - \Omega_1)(\alpha + \beta)}{D_\theta^{(0)} + (\Omega_0 - \Omega_1)} + \frac{S^{(0)}}{D_\theta^{(0)} + (\Omega_0 - \Omega_1)} \partial_x S^{(0)} \right) \begin{bmatrix} 1 \\ 0 \end{bmatrix} + O(\varepsilon^2), \tag{5.10}$$

where we use the fact that $\partial_x = O(\varepsilon)$ in a gradient of a stimulus, such that the last term in Eq. (4.23) is $O(\varepsilon^2)$.

The terms in Eq. (5.10) show the contributions to the drift velocity from the various cell path modifications. The first term with $S^{(1)}$ results from the enhanced cell speed of the cell when moving in the gradient direction and a corresponding decrease in the opposite direction, consistent with the definition of *orthotaxis*. The second term results from the directional orientation bias (*i.e.*, non-uniform $p_s(\theta)$), which results from both continuous and discrete biased turning toward the gradient direction, reflected in $\omega_\theta^{(1)}$ and α, respectively. This response is consistent with the definition of *tropotaxis*. Non-uniform $p_s(\theta)$ also results from a directional dependence on turning frequency, consistent with *klinotaxis*, and reflected in the parameter, β. The final contribution results from a dependence of the cell speed on the position, therefore is consistent with *orthokinesis*.

For a cell with only continuous turning, Eq. (5.10) reduces to

$$V(x) = \frac{1}{2} \left(\varepsilon S^{(1)} + \varepsilon S^{(0)} \frac{\omega_\theta^{(1)}}{D_\theta^{(0)}} + \frac{S^{(0)}}{D_\theta^{(0)}} \partial_x S^{(0)} \right) \begin{bmatrix} 1 \\ 0 \end{bmatrix} + O(\varepsilon^2), \tag{5.11}$$

which is the result derived previously in Dickinson and Tranquillo (1995). For a cell with only discrete turning, Eq. (5.10) becomes

$$V(x) = \frac{1}{2} \left(\varepsilon S^{(1)} + \varepsilon S^{(0)} (\alpha + \beta) + \frac{S^{(0)}}{\Omega_0 - \Omega_1} \partial_x S^{(0)} \right) \begin{bmatrix} 1 \\ 0 \end{bmatrix} + O(\varepsilon^2). \tag{5.12}$$

5.2. *Three-dimensional taxis*

The three-dimensional analog to Eq. (5.1) can be expressed in spherical coordinates as

$$\begin{aligned} L(\theta, x) f(\theta, \varphi) \equiv \frac{D_\varphi(\theta, x)}{\sin^2\theta} \partial_\varphi^2 f(\theta, \varphi) - \frac{1}{\sin\theta} \partial_\theta [\omega_\theta(\theta, x) \sin\theta f(\theta, \varphi) \\ - D_\theta(\theta, x) \sin\theta \partial_\theta f(\theta, \varphi)] \\ + \int_0^{2\pi} d\varphi' \int_0^{\pi} d\theta' \sin\theta' (\Omega(\theta, \varphi, \theta', \varphi'; r) f(\theta', \varphi') \\ - \Omega(\theta', \varphi', \theta, \varphi; r) f(\theta, \varphi)) \end{aligned} \tag{5.13}$$

where $D_\varphi(\theta, r)$ is the rotational diffusion coefficient in the φ-direction, $\omega_\theta(\theta, r)$ is again the rotational drift velocity (scalar) in the θ-direction, and $D_\theta(\theta, r)$ is the rotational diffusion coefficient in the θ-direction. Axial symmetry is assumed around the x-axis (gradient direction), such that the coefficients are independent of φ and the rotational drift velocity in the φ direction, ω_φ, is equal to zero.

The expansions in Eqs. (5.2–6) are again applied to determine $L^{(1)}$, along with following expansion for $D_\varphi(\theta, x)$:

$$D_\varphi(\theta, x) = D_\theta^{(0)}(x) + D_\varphi^{(1)}(x) \varepsilon \cos\theta + O(\varepsilon^2) \tag{5.14}$$

(recalling $D_\varphi^{(0)} = D_\theta^{(0)}$), to obtain

$$\begin{aligned} L^{(1)}(\theta, x) f(\theta, \varphi) \equiv \frac{D_\varphi^{(1)}(x) \cos\theta}{\sin^2\theta} \partial_\varphi^2 f(\theta, \varphi) + \frac{1}{\sin\theta} \partial_\theta [\omega_\theta^{(1)}(x) \sin\theta f(\theta, \varphi) \\ + D_\theta^{(1)}(x) \cos\theta \sin\theta \partial_\theta f(\theta, \varphi)] \\ + \int_0^{2\pi} d\varphi' \int_0^{\pi} d\theta' \sin\theta' (\Omega^{(0)}(\theta, \varphi, \theta', \varphi'; x) \\ \times [\alpha(x) \cos\theta - \beta(x) \cos\theta'] f(\theta', \varphi') \\ - \Omega^{(0)}(\theta', \varphi', \theta, \varphi; x) \\ \times [\alpha(x) \cos\theta' - \beta(x) \cos\theta] f(\theta, \varphi) \Big) \end{aligned} \tag{5.15}$$

$M(x)$ and $V(x)$ are determined from Eqs. (4.27) and (4.29). In this case, ${}^{\pm 1}v_1^{(1)}$, $v_1^{0(1)}$, $B_0^{0(1)}$, ${}_2^0\lambda_0^{0(1)}$, ${}_2^{-2}\lambda_0^{2(1)}$, ${}_1^{\pm 1}\lambda_1^{1(1)}$ are all found to be 0, therefore, for three-dimensional migration, we again have $M(x) = M^{(0)}(x) +$

$O(\varepsilon^2)$, where $M^{(0)}$ is given in Eq. (3.22). Evaluation of V requires

$$v_0^{0^{(1)}} = \frac{1}{\sqrt{4\pi}} \int_0^{2\pi} d\varphi' \int_0^{\pi} d\theta \sin\theta \, \mathrm{S}^{(1)} \cos\theta\Theta = \frac{\sqrt{4\pi}}{3} S^{(1)} \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix} \tag{5.16}$$

and

$$\begin{aligned} {}_1^0\lambda_0^{0^{(1)}} &= \int_0^{2\pi} d\varphi' \int_0^{\pi} d\theta' \sin\theta' \, Y_1^0(\theta', \varphi') L^{(1)} \frac{1}{\sqrt{4\pi}} \\ &= \frac{1}{3}[\omega_\theta^{(1)} + (\Omega_0 - \Omega_1)(\alpha + \beta)]. \end{aligned} \tag{5.17}$$

Combining the above into Eq. (4.29) yields

$$\begin{aligned} V(x) = \frac{1}{3} \Bigg(& \varepsilon S^{(1)} + \varepsilon S^{(0)} \frac{\omega_\theta^{(1)} + (\Omega_0 - \Omega_1)(\alpha + \beta)}{2D_\theta^{(0)} + (\Omega_0 - \Omega_1)} \\ & + \frac{S^{(0)}}{2D_\theta^{(0)} + (\Omega_0 - \Omega_1)} \partial_x S^{(0)} \Bigg) \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix} + O(\varepsilon^2). \end{aligned} \tag{5.18}$$

If the cell only undergoes only continuous turning, this reduces to

$$V(x) = \frac{1}{3} \left(\varepsilon S^{(1)} + \varepsilon S^{(0)} \frac{\omega_\theta^{(1)}}{2D_\theta^{(0)}} + \frac{S^{(0)}}{2D_\theta^{(0)}} \partial_x S^{(0)} \right) \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix} + O(\varepsilon^2). \tag{5.19}$$

For a cell with only discrete turning, Eq. (5.18) reduces to

$$V(x) = \frac{1}{3} \left(\varepsilon S^{(1)} + \varepsilon S^{(0)} (\alpha + \beta) + \frac{S^{(0)}}{(\Omega_0 - \Omega_1)} \partial_x S^{(0)} \right) \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix} + O(\varepsilon^2). \tag{5.20}$$

The expression for three-dimensional drift velocity is very similar to that for the two dimensional drift velocity, with the primary differences being the factor of 1/3 instead of 1/2 and a factor of 2 preceding $D_\theta^{(0)}$. These factors again result from the additional degree of freedom for translation and rotation, respectively, for cell movement in three dimensions. As seen in the following section, this similarity between two and three dimensional cell flux expressions is not as apparent for contact guidance.

6. Biased cell migration by contact guidance

6.1. Two-dimensional contact guidance

In this section, M and V are derived for cell migration by contact guidance. Here L is assumed to depend only on Θ, not r (the anisotropy is assumed uniform with respect to position).

For two-dimensional contact guidance, L is assumed to have the form

$$L(\theta)f(\theta) \equiv -\partial_\theta\Big[\omega_\theta(\theta)f(\theta) - D_\theta(\theta)\partial_\theta f(\theta)\Big] + \int_0^{2\pi} d\theta' \,[\Omega(\theta,\theta')f(\theta') - \Omega(\theta',\theta)f(\theta)]. \tag{6.1}$$

As in the previous section, the θ-dependence of ω_θ, D, B, and v are approximated by expanding in terms of ε, which now reflects the magnitude of influence of the structural anisotropy on cell movement. Based on the bi-directional symmetry, the following expansions are applied for small ε:

$$w_\theta(\theta) = -w_\theta^{(1)}\varepsilon\sin 2\theta + O(\varepsilon^2) \tag{6.2}$$

$$D_\theta(\theta) = D_\theta^{(0)} + D_\theta^{(1)}\varepsilon\cos 2\theta + O(\varepsilon^2) \tag{6.3}$$

$$B(\theta) = (b^{(0)} + b^{(1)}\varepsilon\cos 2\theta)\Theta\Theta^T + O(\varepsilon^2) \tag{6.4}$$

$$v(\theta) = (S^{(0)} + S^{(1)}\varepsilon\cos 2\theta)\Theta + O(\varepsilon^2). \tag{6.5}$$

Also, we give $\Omega(\theta,\theta')$ the form

$$\Omega(\theta,\theta') = \Omega^{(0)}(\theta,\theta')[1 + \varepsilon(\alpha\cos 2\theta - \beta\cos 2\theta')] + O(\varepsilon^2), \tag{6.6}$$

where α and β are defined as in the previous section, reflecting the increased probability of turning toward the axis of anisotropy, and decreased probability of turning away from the axis of anisotropy, respectively. Introducing Eqs. (6.2–6) into Eq. (6.1) provides $L^{(1)}$:

$$L^{(1)}(\theta)f(\theta) = \partial_\theta(\omega_\theta^{(1)}\sin 2\theta f(\theta) + D_\theta^{(1)}\cos 2\theta\,\partial_\theta f(\Theta)) + \int_0^{2\pi} d\theta' \,[\Omega^{(0)}(\theta,\theta')(\alpha\cos 2\theta - \beta\cos 2\theta')f(\theta') - \Omega^{(0)}(\theta',\theta)(\alpha\cos 2\theta' - \beta\cos 2\theta)f(\theta)]. \tag{6.7}$$

In contrast to the results for taxis in the previous section, a number of terms contribute to $M^{(1)}$. The non-zero coefficients ${}_n\lambda_m$ appearing in

Eq. (4.21) are

$$ {}_2\lambda_0^{(1)} \equiv \frac{1}{2\pi}\int_0^{2\pi} d\theta \mathrm{e}^{-2i\theta} L^{(1)}[1] = \frac{1}{2}[2\omega_\theta^{(1)} + (\Omega_0 - \Omega_2)(\alpha + \beta)] \tag{6.8} $$

$$ {}_{-1}\lambda_1^{(1)} \equiv \frac{1}{2\pi}\int_0^{2\pi} d\theta \mathrm{e}^{i\theta} L^{(1)} \mathrm{e}^{i\theta} $$

$$ = \frac{1}{2}[\omega_\theta^{(1)} + D_\theta^{(1)} + \beta(\Omega_0 - \Omega_1) + \alpha(\Omega_1 - \Omega_2)]. \tag{6.9} $$

Also, $v_1^{(1)}$, $B_2^{(0)}$ and $B_0^{(0)}$ are non-zero, and given by

$$ v_1^{(1)} = \int_0^{2\pi} d\theta S^{(1)} \mathrm{e}^{-i\theta} \cos 2\theta = \frac{1}{2}\sqrt{\frac{\pi}{2}}\, S^{(1)} \begin{bmatrix} 1 \\ i \end{bmatrix}, \tag{6.10} $$

$$ B_2^{(0)} \equiv \frac{1}{\sqrt{2\pi}}\int_0^{2\pi} d\theta \mathrm{e}^{-2i\theta} b^{(0)} \Theta\Theta^T = \frac{1}{2}\sqrt{\frac{\pi}{2}}\, b^{(0)} \begin{bmatrix} 1 & -i \\ -i & -1 \end{bmatrix}, \tag{6.11} $$

and

$$ B_0^{(1)} \equiv \frac{1}{\sqrt{2\pi}}\int_0^{2\pi} d\theta b^{(1)} \cos 2\theta \Theta\Theta^T = \frac{1}{2}\sqrt{\frac{\pi}{2}}\, b^{(1)} \begin{bmatrix} 1 & -i \\ -i & -1 \end{bmatrix}. \tag{6.12} $$

Upon combining the above into Eq. (4.21), the first-order corrections to the xx- and yy-components of the random motility tensor become

$$ M_{xx}^{(1)} = -M_{yy}^{(1)} = \frac{1}{2}\frac{S^{(0)}}{D_\theta^{(0)} + \Omega_0 - \Omega_1}\left(S^{(1)} + S^{(0)} \frac{2\omega_\theta^{(1)} + (\Omega_0 - \Omega_2)(\alpha + \beta)}{4D_\theta^{(0)} + \Omega_0 - \Omega_2} \right. $$

$$ \left. + S^{(0)} \frac{\omega_\theta^{(1)} + D_\theta^{(1)} + \beta(\Omega_0 - \Omega_1) + \alpha(\Omega_1 - \Omega_2)}{D_\theta^{(0)} + \Omega_0 - \Omega_1} \right) $$

$$ + \frac{1}{2}b^{(1)} + \frac{1}{2}b^{(0)} \frac{2\omega_\theta^{(1)} + (\Omega_0 - \Omega_2)(\alpha + \beta)}{4D_\theta^{(0)} + \Omega_0 - \Omega_2}. \tag{6.13} $$

This result shows that, in the presence of the bi-directional anisotropic environment, the xx-component of the random motility coefficient is increased and the yy-component is correspondingly decreased by a number of cell path modifications: Enhanced cell speed when moving along the axis of anisotropy, reflected in $S^{(1)}$, increases M along this axis. Because of the analogy to *orthotaxis*, this effect is labeled *ortho-guidance*. Preferential turning toward the axis of anisotropy, reflected in parameters $\omega_\theta^{(1)}$ and α, also contributes the enhanced diffusive flux in this direction. This effect is analogous to *tropotaxis*, hence it is labeled *tropo-guidance*. Finally, a dependence of cell turning frequency on the

movement direction also contributes, reflected in parameters $D_\theta^{(1)}$ and β. Because of the analogy to *klinotaxis*, this effect is labeled *klino-guidance*.

For a cell moving only with continuous turns, Eq. (6.13) reduces to

$$M_{xx}^{(1)} = -M_{yy}^{(1)} = \frac{1}{2}\frac{S^{(0)}}{D_\theta^{(0)}}\left(S^{(1)} + \frac{S^{(0)}}{D_\theta^{(0)}}\left(\frac{3}{2}\omega_\theta^{(1)} + D_\theta^{(1)}\right)\right) + \frac{1}{2}b^{(1)} + \frac{1}{2}b^{(0)}\frac{\omega_\theta^{(1)}}{2D_\theta^{(0)}}, \tag{6.14}$$

which was derived previously using a different approach for two dimensional contact guidance (Dickinson, 1997). For a cell moving with only discrete turns, Eq. (6.13) becomes

$$M_{xx}^{(1)} = -M_{yy}^{(1)} = \frac{1}{2}\frac{S^{(0)}}{\Omega_0 - \Omega_1}\left(S^{(1)} + S^{(0)}\left[\alpha\left(1 + \frac{\Omega_1 - \Omega_2}{\Omega_0 - \Omega_1}\right) + 2\beta\right]\right) + \frac{1}{2}b^{(1)} + \frac{1}{2}b^{(0)}(\alpha + \beta). \tag{6.15}$$

6.2. Three-dimensional contact guidance

For three dimensional contact guidance, we again apply the expansions in Eqs. (6.2–6), to find

$$\begin{aligned} L^{(1)}(\theta)\,\mathrm{f}(\theta,\varphi) \equiv{}& \frac{D_\varphi^{(1)}\cos 2\theta}{\sin^2\theta}\partial^2 f(\theta,\varphi) \\ &+ \frac{1}{\sin\theta}\partial_\theta[\omega_\theta^{(1)}\sin 2\theta f(\theta,\varphi) + D_\theta^{(1)}\cos 2\theta \sin\theta\partial_\theta f(\theta,\varphi)] \\ &+ \int_0^{2\pi} d\varphi' \int_0^{\pi} d\theta' \sin\theta' (\Omega^{(0)}(\theta,\varphi,\theta',\varphi') \\ &\times [\alpha\cos 2\theta - \beta\cos 2\theta'] f(\theta',\varphi') \\ &- \Omega^{(0)}(\theta',\varphi',\theta,\varphi)[\alpha\cos 2\theta' - \beta\cos 2\theta] f(\theta,\varphi)). \end{aligned} \tag{6.16}$$

The non-zero coefficients $\{{}_n^k\lambda_m^{l^{(1)}}\}$ in Eq. (4.27) are obtained from Eq. (4.5) to find:

$${}_1^0\lambda_1^{0^{(1)}} = \frac{4}{5}\omega_\theta^{(1)} + \frac{6}{5}D_\theta^{(1)} + \frac{1}{5}\alpha(\Omega_1 - \Omega_2) + \frac{1}{3}\alpha(\Omega_0 - \Omega_2) + \frac{1}{5}\beta(\Omega_0 - \Omega_1), \tag{6.17}$$

$$
{}_1^1\lambda_1^{1^{(1)}} = \frac{1}{2} D_\varphi^{(1)} - \frac{4}{5}\omega_\theta^{(1)} - \frac{1}{10} D_\theta^{(1)} - \frac{3}{5}\alpha(\Omega_1 - \Omega_2)
$$

$$
+ \frac{1}{3}\alpha(\Omega_0 - \Omega_2) - \frac{3}{5}\beta(\Omega_0 - \Omega_1), \tag{6.18}
$$

and

$$
{}_2^0\lambda_0^{0^{(1)}} = \frac{4}{\sqrt{5}}\left(\omega_\theta^{(1)} + \frac{1}{3}(\alpha + \beta)(\Omega_0 - \Omega_2)\right). \tag{6.19}
$$

Also required are

$$
v_1^{0^{(1)}} \equiv \int_0^{2\pi} d\varphi \int_0^{\pi} d\theta \sin\theta Y_1^0(\theta, \varphi) S^{(1)} \cos 2\theta\Theta
$$

$$
= \frac{S^{(1)}}{5}\sqrt{\frac{2\pi}{3}} \begin{bmatrix} \sqrt{2} \\ 0 \\ 0 \end{bmatrix} \tag{6.20}
$$

and

$$
v^{\pm\, {}_1^1(1)} \equiv \int_0^{2\pi} d\varphi \int_0^{\pi} d\theta \sin\theta\, Y^{-1}{}_1^1(\theta, \varphi) S^{(1)} \cos 2\theta\Theta
$$

$$
= -\frac{3S^{(1)}}{5}\sqrt{\frac{2\pi}{3}} \begin{bmatrix} 0 \\ 1 \\ \mp i \end{bmatrix}. \tag{6.21}
$$

Finally, the required Fourier coefficients for the contribution of the velocity fluctuations are

$$
B_0^{0^{(1)}} \equiv \int_0^{2\pi} d\varphi \int_0^{\pi} d\theta \sin\theta Y_0^0 b^{(1)} \cos 2\theta\Theta\Theta^T
$$

$$
= \sqrt{4\pi}\,\frac{1}{5}\, b^{(1)} \begin{bmatrix} 1/3 & 0 & 0 \\ 0 & -1 & 0 \\ 0 & 0 & -1 \end{bmatrix} \tag{6.22}
$$

$$
B_2^{0^{(0)}} \equiv \int_0^{2\pi} d\varphi \int_0^{\pi} d\theta \sin\theta Y_2^0 b^{(0)} \Theta\Theta^T
$$

$$
= \sqrt{4\pi}\frac{2}{3\sqrt{5}} b^{(1)} \begin{bmatrix} 1 & 0 & 0 \\ 0 & -1 & 0 \\ 0 & 0 & -1 \end{bmatrix}. \tag{6.23}
$$

Combining the above yields

$$M_{xx}^{(1)} = \frac{2}{15}S^{(0)}S^{(1)} + \frac{1}{3}S^{(0)^2} \times \left(\frac{\frac{4}{5}\omega_\theta^{(1)} + \frac{6}{5}D_\theta^{(1)} + \frac{1}{3}\alpha(\Omega_0 - \Omega_1) + \frac{8}{15}\alpha(\Omega_1 - \Omega_2) + \frac{1}{5}\beta(\Omega_0 - \Omega_1)}{2D_\theta^{(0)} + (\Omega_0 - \Omega_2)} + \frac{8}{5}\frac{\omega_\theta^{(1)} + \frac{1}{3}(\alpha + \beta)(\Omega_0 - \Omega_2)}{6D_\theta^{(0)} + (\Omega_0 - \Omega_2)} \right) + \frac{1}{15}b^{(1)} + \frac{4}{5}b^{(0)}\left(\frac{\omega_\theta^{(1)} + \frac{1}{3}(\alpha + \beta)(\Omega_0 - \Omega_2)}{6D_\theta^{(0)} + (\Omega_0 - \Omega_2)} \right) \tag{6.24}$$

and

$$M_{yy}^{(1)} = M_{zz}^{(1)} = -\frac{3}{15}S^{(0)}S^{(1)} + \frac{1}{3}S^{(0)^2} \times \left(\frac{\frac{1}{2}D_\varphi^{(1)} - \frac{4}{5}\omega_\theta^{(1)} - \frac{1}{10}D_\theta^{(1)} + \frac{1}{3}\alpha(\Omega_0 - \Omega_1) - \frac{4}{15}\alpha(\Omega_1 - \Omega_2) - \frac{3}{5}\beta(\Omega_0 - \Omega_1)}{2D_\theta^{(0)} + (\Omega_0 - \Omega_1)} - \frac{4}{5}\frac{\omega_\theta^{(1)} + \frac{1}{3}(\alpha + \beta)(\Omega_0 - \Omega_2)}{6D_\theta^{(0)} + (\Omega_0 - \Omega_2)} \right) - \frac{1}{5}b^{(1)} - \frac{4}{5}b^{(0)}\left(\frac{\omega_\theta^{(1)} + \frac{1}{3}(\alpha + \beta)(\Omega_0 - \Omega_2)}{6D_\theta^{(0)} + (\Omega_0 - \Omega_2)} \right). \tag{6.25}$$

In contrast to the result for three-dimensional taxis in the previous section, the expression for three-dimensional $M^{(1)}$ is more considerably complex than the corresponding term for two-dimensional migration. However, the ortho-guidance, tropo-guidance, and klino-guidance contributions are still be identifiable as for the two-dimensional case.

For a cell with only continuous turning, these expressions reduce to

$$M_{xx}^{(1)} = \frac{2}{15}S^{(0)}S^{(1)} + \frac{1}{3}\frac{S^{(0)2}}{D_\theta^{(0)}}\left(\frac{2}{3}\omega_\theta^{(1)} + \frac{13}{15}D_\theta^{(1)} \right) + \frac{1}{15}b^{(1)} + \frac{2}{15}b^{(0)}\left(\frac{\omega_\theta^{(1)}}{D_\theta^{(0)}} \right) \tag{6.26}$$

$$M_{yy}^{(1)} = M_{zz}^{(1)} = -\frac{3}{15}S^{(0)}S^{(1)} - \frac{1}{3}\frac{S^{(0)2}}{D_\theta^{(0)}}\left(\frac{8}{15}\omega_\theta^{(1)} + \frac{1}{15}D_\theta^{(1)} - \frac{1}{4}D_\varphi^{(1)} \right) - \frac{1}{5}b^{(1)} - \frac{2}{15}b^{(0)}\left(\frac{\omega_\theta^{(1)}}{D_\theta^{(0)}} \right). \tag{6.27}$$

And, for a cell with only discrete turning, Eqs. (6.24–25) reduce to

$$M_{xx}^{(1)} = \frac{2}{15}S^{(0)}S^{(1)} + \frac{1}{3}S^{(0)^2}\left(\frac{16}{15}\beta + \frac{1}{15}\alpha\left[8\frac{\Omega_1 - \Omega_2}{\Omega_0 - \Omega_1} + 11\right]\right) + \frac{1}{15}b^{(1)} + \frac{4}{15}b^{(1)}(\alpha + \beta) \tag{6.28}$$

$$M_{yy}^{(1)} = M_{zz}^{(1)} = -\frac{3}{15}S^{(0)}S^{(1)} - \frac{1}{3}S^{(0)^2}\left(\frac{13}{15}\beta + \frac{1}{15}\alpha\left[8\frac{\Omega_1 - \Omega_2}{\Omega_0 - \Omega_1} - 1\right]\right) - \frac{1}{5}b^{(1)} - \frac{4}{15}b^{(1)}(\alpha + \beta). \tag{6.29}$$

7. Discussion

The model presented here is a generalization of previous cell migration models by Keller and Segel (1971), Alt (1980), and Dickinson and Tranquillo (1995). A diffusion equation is derived from a generalized random walk model with a turning operator, L, that allows for both discrete and continuous transitions in cell orientation. The model also allows for a general dependence of cell velocity on cell orientation, cell position, and time, which allows the model to be applied to different types of anisotropic environment such as in a gradient of a stimulus (*taxis*) and in bi-directionally aligned substratum (*contact guidance*). This general dependence also allows determination of the relative contributions of the various path modifications, *tropotaxis*, *orthotaxis*, *orthokinesis*, *klinotaxis*, and *klinokinesis*, to the overall taxis drift velocity. Similarly, when applied to contact guidance, the analysis predicts previously undefined contributions to the preferential migration along an axis of anisotropy, including *ortho-guidance*, for a dependence of cell speed on the direction of cell polarity relative to the axis of anisotropy; *klino-guidance*, for a dependence of cell turning frequency on the direction of cell polarity; and *tropo-guidance* for preferential turning toward the axis of anisotropy. Although not shown in the examples provided, the model can also be applied in environment with multiple stimuli, where both guidance and taxis is present. Furthermore, it predicts of other interesting migration phenomena. For example, a gradient in *structural anisotropy* is predicted to result in a drift velocity when the cell velocity, $v(\Theta, \mathrm{r})$ or the orientation distribution, $p_s(\Theta; \mathrm{r})$, depend on position, r [c.f. Eqs. (2.24–5)].

In addition to the more general form of the turning operator, a primary difference between the underlying random walk model used here and the seminal model of Patlak (1953) is the assumption that the statistics of cell velocity and cell turning depend on the instantaneous

position of the cell, as was assumed by Alt (1980), rather than on the position of cell before of a step, as assumed by Patlak. Because cell locomotion depends primarily on encountered stimulus for a given cell position and orientation, this assumption is more appropriate for cell migration. This model can therefore be applied to any motion of a polarized object in an anisotropic environment where translation and turning depends on local conditions, such as that of many insects and other organisms.

In the examples given here, specific forms of the turning operator, L, were provided which corresponded to reasonable models for taxis and contact guidance. However, the general approach can be applied to any cell migration model where the appropriate form of L is known to $O(\varepsilon)$. The problem has been reduced to simply finding the coefficients $\{{}_{\nu}\lambda_{\mu}{}^{(0)}\}$. For example, for chemotaxis of *E. coli*, the turning frequency decreases when the cell is moving with a component of its velocity in the gradient direction, but does not modify its turning behavior when moving down-gradient (Berg and Brown 1972). In this case, the turning kernel, $\Omega(\Theta, \Theta')$ would simply have the form of Eq. (5.6) of for $0 \leqq \theta' < \pi/2$, but $\Omega(\Theta, \Theta') = \Omega^{(0)}(\Theta, \Theta')$ for $\pi/2 \leqq \theta' \leqq \pi$. Assuming no other contributing cell path modifications (*i.e.*, $S^{(1)} = \omega_{\theta}^{(1)} = \alpha = 0$), the result for the x-component of drift velocity is then simply $V(x) = \frac{1}{6}\varepsilon S^{(0)}\beta$. This example illustrates how simply the general model can be reduced and applied to specific cases.

In principle, all parameters in the resulting equations for M and V can be derived from an underlying mechanistic model of a single cell that can predict cell turning, cell speed and associated fluctuations as functions of the cell orientation, as has been developed previously for chemotaxis or haptotaxis (Tranquillo and Lauffenburger 1987; Dickinson and Tranquillo 1993a). This analysis therefore provides a framework to predict and interpret observed "macroscopic" cell migration behavior (*i.e.*, cell transport and cell movement statistics) by contact guidance or taxis in terms of the molecular and physical properties of a single moving cell.

Acknowledgments. This work has been supported in part by the NATO Fellowship Program and by a Biomedical Engineering Grant provided by the Whitaker Foundation. The author greatly appreciates helpful comments and suggestions from Wolfgang Alt, Universität Bonn, which have been incorporated into this manuscript.

References

Alt, W., Biased random walk models for chemotaxis and related diffusion approximations, J Math Biol 9(2), 147–77 (1980).

Alt, W., Singular perturbation of differential integral equations describing biased random walks, J. für die reine und angewandte Mathematik, 322: 14–41, (1981).

Alt, W. Correlation analysis of two-dimensional locomotion paths. In *Biological-Motion*. W. Alt and G. Hoffmann. Berlin, Springer-Verlag. 254–268 (1990).

Berg, H. C. and D. A. Brown Chemotaxis in *Escherishiacoli* analysed by three-dimensional tracking. Nature 239: 500–504 (1972).

Dickinson, R. B., S. Guido, and R. T. Tranquillo, Biased cell migration of fibroblasts exhibiting contact guidance in oriented collagen gels, Ann. Biomed. Eng. 22, 343–356 (1993).

Dickinson, R. B. and R. T. Tranquillo, A stochastic model for cell random motility and haptotaxis based on adhesion receptor fluctuations. J. Math. Biol. 31, 563–600 (1993a).

Dickinson, R. B. and R. T. Tranquillo. Optimal estimation of cell movement indices from the statistical analysis of cell tracking data. AICHE J. 39(12): 1995–2010 (1993).

Dickinson, R. B. and R. T. Tranquillo. Transport equations and cell movement indices based on single cell properties, SIAM J. Appl. Math. 55(5), 1419–54 (1995).

Dickinson, R. B. A model for cell migration by contact guidance. In *Dynamics of Cell and Tissue Motion*, W. Alt, A. Deutsch, G. Dunn, eds., Birkhäuser-Verlag, Basel. 149–155 (1997).

Dunn, G. A., Characterizing a kinesis response: time averaged measures of cell speed and directional persistence, Agents and Actions Suppl. 12, 14–33 (1983).

Dunn, G. A. and A. F. Brown. Alignment of fibroblasts on grooved surfaces described by a simple geometric transformation, J Cell Sci 83, 313–40 (1986).

Dunn, G. A. and T. Ebendal. Contact guidance on oriented collagen gels, Exp. Cell Res. 111, 475–9 (1978).

Furth, V. R. Die Brownische Bewegung bei Berücksichtigung einer Persistenz der Bewegungsrichtung. Mit Anwendungen auf die Bewegung lebender Infusorien. Zeit. f. Phys. 2: 244–256 (1920).

Gail, M. H. and C. W. Boone. The locomotion of mouse fibroblasts in tissue culture, Biophys J 10, 980–993 (1970).

Gardiner, C. W. Handbook of Stochastic Methods. Berlin Heidelberg, Springer-Verlag, (1983).

Guido, S. and R. T. Tranquillo. A methodology for the systematic and quantitative study of cell contact guidance in oriented collagen gels: Correlation of fibroblast orientation and gel birefringence, J Cell Sci 105, 317–331 (1993).

Hall, R. L. Amoeboid movement as a correlated walk. J. Math. Biol. 4: 327–335 (1977).

Lauffenburger, D. A. (1991). Models for receptor-mediated cell phenomena: adhesion and migration. Annu Rev Biophys Biophys Chem 20: 387–414.

Lovely, P. S. and F. W. Dahlquist Statistical Measures of Bacterial Motility and Chemotaxis. J Theor Biol 50: 477–496 (1975).

Keller, E. F. and L. A. Segel Model for chemotaxis. J. Theor. Biol. 30, 225–234 (1971).

Kubo, R., M. Toda, et al. (1991). Statistical Physics II: Nonequilibrium Statistical Mechanics. Berlin, Springer-Verlag.

Matthes, T. and H. Gruler. Analysis of cell locomotion. Contact guidance of human polymorphonuclear leukocytes, Eur Biophys J 15(6), 343–57 (1988).

Othmer, H. G., S. R. Dunbar and W. Alt. Models of dispersal in biological systems, J Math Biol 26(3), 263–98 (1988).

Patlak, C. S. Random walk with persistence and external bias. Bull. Math. Biophys. 15: 311–338 (1953).

Rivero, M. A., R. T. Tranquillo, H. M. Buettner and D. A. Lauffenburger. Transport models for chemotactic cell populations based on individual cell behavior. Chem. Eng. Sci. 44(12): 2881–2897. (1989).

Tranquillo, R. T. and W. Alt. Glossary of terms concerning oriented movement, In *BiologicalMotion*, W. Alt and G. Hoffman, ed., Springer-Verlag, Berlin. 510–17 (1990).

Tranquillo, R. T. and D. A. Lauffenburger. Stochastic model of leukocyte chemosensory movement, J Math Biol 25(3), 229–303 (1987).

Trinkaus, J. P. Cells Into Organs: The Forces that Shape the Embryo. Englewood Cliffs, NJ, Prentice-Hall, Inc. (1984).

Wilkinson, P. C. Chemotaxis and chemokinesis: confusion about definitions, J Immunol Methods 110(1), 143–9 (1988).