Macroscopic Taxis Equations from Cell-based Models

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Cell movement is an essential process at various stages in the life cycle of most organisms. Motile organisms sense their environment and can respond to it either by directed movement toward or away from a signal, which is called *taxis*, or by changing their speed of movement and/or frequency of turning, which is called *kinesis*, but for simplicity we denote both as taxis. Let Ω be a compact subset of $\mathbb{R}^N$ with smooth boundary. The classical Patlak-Keller-Segel chemotaxis equations, which govern the evolution of the macroscopic "particle" density n and the "signal" density S, are

$$\frac{\partial n}{\partial t} = \nabla \cdot (\nabla n - n\chi \nabla S) \tag{1}$$
$$\frac{\partial S}{\partial t} = D\Delta S + f(n,S)$$

in Ω, with homogeneous Neumann data on the boundary. Here χ is the chemotactic sensitivity coefficient. These equations have been studied intensively over the last thirty years, and a great deal is known about the existence and uniqueness of solutions for specific forms of χ and f [4]. However, except in examples described later, little is known about how an individual-based description of signal transduction and movement translates into the chemotactic sensitivity. Until recently these coefficients were either simply postulated or derived from experimental population-level statistics of movement.

Many bacteria, such as *Escherichia coli* and *Proteus mirabilis*, use a "run-and-tumble" strategy for movement, and in this case χ can be expressed in terms of microscopic properties of individual cells. This case is treated in detail in [1, 2], where we describe the movement of cells using a velocity-jump process [5], and incorporate internal state variables of individual cells into the governing transport equation. Thus suppose that the internal variables $\mathbf{y} \in Y \subset \mathbb{R}^m$ involved in signal transduction and control of movement evolve according the equations

$$\frac{d\mathbf{y}}{dt} = \mathbf{f}(\mathbf{y}, \hat{S})$$

where $\hat{S}$ is some functional of the external signal and $f(\cdot, \hat{S}) : Y \to \mathbb{R}^m$. Inclusion of internal state variables in the velocity-jump process leads to the equation

$$\frac{\partial p}{\partial t} + \nabla_{\mathbf{x}} \cdot \mathbf{v}p + \nabla_{\mathbf{y}} \cdot \mathbf{f}p = -\lambda(\mathbf{y})p + \int_V \lambda(\mathbf{y})T(\mathbf{v}, \mathbf{v}', \mathbf{y})p(\mathbf{x}, \mathbf{v}', \mathbf{y}, t)\mathrm{d}\mathbf{v}' \tag{2}$$

where $p(\mathbf{x}, \mathbf{v}, \mathbf{y}, t)$ is the density of cells with internal state $\mathbf{y}$ at position $\mathbf{x}$, moving with velocity $\mathbf{v} \in V \subset \mathbb{R}^N$ at time $t \geq 0$. Here we assume that the random velocity changes are the result of

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a Poisson process of intensity $\lambda(\mathbf{y})$, and the kernel $T(\mathbf{v}, \mathbf{v}', \mathbf{y})$ gives the probability of a change in velocity from $\mathbf{v}'$ to $\mathbf{v}$, given that a reorientation occurs. The kernel T is non-negative and satisfies the normalization condition $\int_V T(\mathbf{v}, \mathbf{v}', \mathbf{y})\mathrm{d}\mathbf{v} = 1$. To connect this with the chemotaxis equation (1), one has to derive an evolution equation for the macroscopic density

$$n(\mathbf{x}, t) = \int_Y \int_V p(\mathbf{x}, \mathbf{v}, \mathbf{y}, t)\mathrm{d}\mathbf{v}\mathrm{d}\mathbf{y} \tag{3}$$

of individuals and formulate the evolution equation for the extracellular signal. This has been carried out in detail for a simplified description of the internal dynamics where $\mathbf{y} = (y_1, y_2)^T$ evolves according to

$$\frac{dy_1}{d\tau} = \frac{g(S(\tau)) - (y_1 + y_2)}{\tau_e}, \qquad \frac{dy_2}{d\tau} = \frac{g(S(\tau)) - y_2}{\tau_a}, \qquad \text{and} \qquad \lambda(\mathbf{y}) = \lambda_0 - by_1.$$

Here the first equation captures the rapidly-varying excitation step, whereas the second reflects the slower adaptation step. Clearly y_1 adapts perfectly to any signal, and thus it is used to modulate the turning rate as indicated. The reduction of (2) to the form (1) is done by an asymptotic analysis on suitable space and time scales, with the result that n evolves according to

$$\frac{\partial n}{\partial t} = \nabla \cdot \left(\frac{s^2}{N\lambda_0} \nabla n - n \cdot g'(S(\mathbf{x})) \frac{bs^2\tau_a}{N\lambda_0(1 + \lambda_0\tau_a)(1 + \lambda_0\tau_e)} \nabla S \right)$$

where S is a time-independent signal field. Therefore the chemotactic sensitivity is given by

$$\chi = g'(S(\mathbf{x})) \frac{bs^2\tau_a}{N\lambda_0(1 + \lambda_0\tau_a)(1 + \lambda_0\tau_e)}.$$

This incorporates the microscopic cell speed s, the sensitivity of the turning rate to the internal variable y_1, and the excitation and adaptation time scales τ_e and τ_a; for details of the derivation see [2].

A fundamental assumption in the use of velocity-jump processes to describe cell motion is that the jumps are instantaneous, and therefore the forces are Dirac distributions. This approximates the case in which very large forces act over very short time intervals, and even if one incorporates a resting or tumbling phase, as was done in [6, 1], the macroscopic description of motion is unchanged. This is appropriate for the analysis of bacterial motion (and other systems that use a "run-and-tumble" strategy), as summarized above, since there is no evidence that the signal affects the force generation mechanism itself.

However, the situation is very different when analyzing the movement of crawling cells such as leukocytes or fibroblasts, for here the control of the force-generation machinery is an essential component of the response. Therefore it is necessary to incorporate the force-generation machinery as part of the internal state, and as a first step we condense this all into a description of how the force exerted by a cell on its surroundings depends on the external signal. We denote the internal state by $\mathbf{y} \in \mathbb{Y}$, and the force per unit mass on the centroid of a cell by $\mathcal{F}(\mathbf{x}, \mathbf{v}, \mathbf{y})$. Here $\mathbb{Y}$ is a suitable, in general infinite-dimensional, Banach space. The internal state and velocity now evolve according to

$$\frac{\mathrm{d}\mathbf{y}}{\mathrm{d}t} = \mathcal{G}(\mathbf{y}, S), \qquad \frac{\mathrm{d}\mathbf{v}}{\mathrm{d}t} = \mathcal{F}(\mathbf{x}, \mathbf{v}, \mathbf{y}). \tag{4}$$

Here $\mathcal{G} : \mathbb{Y} \times \mathbb{S} \to \mathbb{Y}$ is a mapping between Banach spaces and $\mathcal{F} : \mathbb{R}^N \times \mathbb{R}^N \times \mathbb{Y} \to \mathbb{R}^N$ where $N = 1, 2$, or 3 is the dimension of the physical space. This generality is needed because the internal

state $\mathbf{y}$ can include quantities that depend on the location in the cell or on the membrane, and which may, for example, satisfy a reaction-diffusion equation or another evolution equation.

The cell is therefore described by the position and velocity of its centroid, and the internal state $\mathbf{y} \in \mathbb{Y}$. In some cases there is a projection $\mathcal{P} : \mathbb{Y} \to \mathbb{Z} \subset \mathbb{Y}$ from $\mathbb{Y}$ onto a suitable finite-dimensional subspace $\mathbb{Z}$, obtained for example by considering the first few modes in a suitable basis for $\mathbb{Y}$, such that

$$\mathcal{P}(\mathcal{G}(\mathbf{y}, S)) = \mathbf{G}(\mathbf{z}, S) \quad \text{and} \quad \mathcal{F}(\mathbf{x}, \mathbf{v}, \mathbf{y}) = \mathbf{F}(\mathbf{x}, \mathbf{v}, \mathbf{z}), \qquad \text{where} \quad \mathbf{z} \equiv \mathcal{P}\mathbf{y}.$$

Here $\mathbf{G}(\cdot, S) : \mathbb{Z} \to \mathbb{Z}$ and $\mathbf{F}(\cdot, \cdot, \cdot) : \mathbb{R}^N \times \mathbb{R}^N \times \mathbb{Z} \to \mathbb{R}^N$ are mappings between finite-dimensional spaces. The first equality defines the function $\mathbf{G}$, whereas $\mathbf{F}$ is explicitly given by the second equality when the reduction is possible. Given a suitable choice of the projection $\mathcal{P}$, one can reduce the infinite-dimensional system (4) to the set of ordinary differential equations for the evolution of the internal state of individual cells.

$$\frac{\mathrm{d}\mathbf{z}}{dt} = \mathbf{G}(\mathbf{z}, S) \qquad\qquad \frac{\mathrm{d}\mathbf{v}}{\mathrm{d}t} = \mathbf{F}(\mathbf{x}, \mathbf{v}, \mathbf{z}) \tag{5}$$

The transport equation (2) can now be written in the form

$$\frac{\partial p}{\partial t} + \nabla_{\mathbf{x}} \cdot \mathbf{v}p + \nabla_{\mathbf{v}} \cdot \mathbf{F}p + \nabla_{\mathbf{z}} \cdot \mathbf{G}p = -\lambda(\mathbf{z})p + \int_V \lambda(\mathbf{z})T(\mathbf{v}, \mathbf{v}', \mathbf{z})p(\mathbf{x}, \mathbf{v}', \mathbf{z}, t)\mathrm{d}\mathbf{v}'. \tag{6}$$

where here the right-hand side accounts for small random fluctuations of speed and direction.

In [3] we develop an infinite-dimensional model of the form (4) for a single cell and show that it can be reduced to a finite-dimensional version as given by (5). We show that the model for cell movement captures the essential features of movement in response to traveling waves of chemoattractant. Asymptotic analysis of the transport equation (6) then leads to a system of macroscopic hyperbolic equations, but it is not known if that system can in turn be reduced to (1). Details are given in [3].

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