Relevance of intracellular polarity to accuracy of eukaryotic chemotaxis

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Abstract

Eukaryotic chemotaxis is usually mediated by intracellular signals that tend to localize at the front or back of the cell. Such intracellular polarities frequently require no extracellular guidance cues, indicating that spontaneous polarization occurs in the signal network. Spontaneous polarization activity is considered relevant to the persistent motions in random cell migrations and chemotaxis. In this study, we propose a theoretical model that connects spontaneous intracellular polarity and motile ability in a chemoattractant solution. We demonstrate that the intracellular polarity can enhance the accuracy of chemotaxis. Chemotactic accuracy should also depend on chemoattractant concentration through the concentration-dependent correlation time in the polarity direction. Both the polarity correlation time and the chemotactic accuracy depend on the degree of responsiveness to the chemical gradient. We show that optimally accurate chemotaxis occurs at an intermediate responsiveness of intracellular polarity. Experimentally, we find that the persistence time of randomly migrating Dictyostelium cells depends on the chemoattractant concentration, as predicted by our theory. At the optimum responsiveness, this ameboid cell can enhance its chemotactic accuracy tenfold.

Keywords: Dictyostelium, cell movement, cell polarity

(Some figures may appear in colour only in the online journal)

1. Introduction

Cell polarity maintains cell orientation by anisotropic distribution of particular factors. As such, it is an essential feature of many cells and tissues [1]. For example, budding yeasts retain memory of the original junction with their mother cell [1]. As another example, epithelial cells retain their apical and basal sides to establish and maintain sheet structures [1]. Single migrating cells such as cellular slime mold Dictyostelium discoideum, mammalian leukocytes and neurons migrate in response to extracellular chemical guidance cues. This directional cell migration is called chemotaxis. Establishment and control of cell polarity is particularly important in eukaryotic chemotaxis in developmental processes, wound healing and immunological responses [2]. Thus, it is natural to question how cell polarity contributes to chemotaxis.

Dictyostelium cell is a well-studied model organism for investigating eukaryotic chemotaxis. Its chemotaxis signaling pathways have been well characterized [3], and its spontaneous and chemotactic migration have been extensively investigated [4–10]. These studies have revealed high chemotactic accuracy of Dictyostelium cells even in shallow chemical gradients and low chemoattractant concentrations.
The experimentally determined chemotactic accuracy is higher than expected, assuming that the cell estimates the gradient direction as efficiently as possible. If we quantify the accuracy of chemotaxis by the chemotaxis index ($C_I$), which quantifies the chemotactic accuracy as the cosine of the angle between the direction of the guidance cue and the migration trajectory, the maximum likelihood estimation of the direction of orientation [11] yield a CI of $C_I \approx 0.023$ for the cell\textsuperscript{6}. However, Fisher’s seminal experiment [4] yielded a CI of $C_I \approx 0.12$ in a chemical gradient of $-25 \text{nM m}^{-1}$.

As in many chemotactic eukaryotic cells, Dictystelium cells spontaneously polarize and migrate in random directions in the absence of extracellular cues. This polarity manifests as self-organization in signaling systems [12–15], polarized structures in the cytoskeletal network, and localization of subcellular organelles. To distinguish these polarities from specific cell-shapes and anisotropy in external environments, we collectively label them as ‘internal polarity’. Spontaneous internal polarity in the absence of extracellular inhomogeneity implies a spontaneous breakdown of the isotropy or rotational symmetry. Such spontaneous violation of a continuous symmetry can be illustrated by a state point in the bottom of a potential shaped like a Mexican hat, as illustrated in the right panel of figure 1(a). This symmetry breaking is accompanied by a memory effect associated with a slowly-changing directional parameter. In other words, in the asymmetric state, cells maintain their current directions. By contrast, in the symmetric state, directional information rapidly dissipates (see figure 1(a) left). Asymmetric polarity is considered to underlie the persistence of cell migration over a characteristic period of time, called the persistence time. The persistence time of Dictystelium cells ranges from 200 to 600 s, depending on the chemoattractant concentration (figure 2(b)), much longer than the time constant of the chemoattractant–receptor reaction ($\sim 1 \text{s}$).

Such intracellular polarities are essential to high chemotactic accuracy. Under shallow gradients, activities in the signal transduction network are modulated by spatial small differences in the probability of membrane-association of chemoligand, which induces gradient responses. When a chemoattractant is homogeneously distributed in space, the distribution of receptor occupancy along the cell periphery fluctuates due to its inherent stochasticity. Similar to external gradients, these spatial fluctuations can also drive cells to orientate in different directions [16]. In fact, it has been reported that a short chemoattractant stimulus of 1 s, which is similar to the time constant of receptor–ligand reaction [17], can modulate the state in the signaling pathway of gradient sensing in Dictystelium cell [18]. Therefore, directional cell

\textsuperscript{6} The maximum likelihood estimation assumes Dictystelium cells with 80 000 receptors on the cell surface, dissociation constant $K_d = 180 \text{ nM}$ of the chemo-ligand (cAMP) and its receptors, and 1% gradient ($25 \text{ nM mm}^{-1}$ for cell length of $10 \mu m$) with average chemoattractant concentration $C_0 = 0.25 \text{nM}$. 

\textbf{Figure 1.} Theoretical chemotaxis model with internal polarity and directional sensing. (a) Spontaneous rotational symmetry breaking. (b) Schematic of signaling processing in eukaryotic chemotaxis. (c) Schematic of the presented model.
migration under gradients is expected to have a connection to random cell migration under uniform conditions.

Several theoretical models have been proposed to describe random cell migration with persistence in the absence of gradients [6, 8, 9]. Directional cell migrations under gradients have been also studied theoretically [16, 19–24]. Lauffenburger studied the high chemotactic accuracy in a shallow chemical gradient using a probabilistic model in which ligand–receptor binding exhibited a thermal fluctuation, and concluded that receptor occupancy measurements must be averaged in time for a few minutes to explain the accuracy of chemotactic orientation of leukocytes [25]. He and his coworkers also showed that the orientation bias in chemotactic cell migration is affected by the persistence, based on a stochastic model of the motility [16]. Gruler analyzed the statistics for random, chemotactic and electrotactic cell migrations from a unified view in terms of the symmetry of external environment [26]. Gruler et al also

**Figure 2.** Persistent cell migration in Dictyostelium cells under spatially and temporally uniform chemoattractant concentration. (a) Auto-correlation functions of the direction of cell migration. Red points indicate the auto-correlation function obtained experimentally. Here, error bars indicate the SEM. Solid lines are the fitted curves of equation (2). (b) Persistence time of cell migration as a function of average ligand concentration. The correlation times of migrating directions (red squares) and velocity vectors (green circles) were experimentally obtained. The solid line indicates equation (5), fitted to the data indicated by the red squares. The fitting parameters are obtained as $f_0 \sim 0.0539 \text{ rad s}^{-1}$ and $D_{\text{diff}} \sim 0.00163 \text{ rad s}^{-1}$. The numbers of cells for individual conditions are $N = 42$ (0 M), 36 (100 pM), 27 (1 nM), 38 (10 nM), 38 (100 nM), and 38 (1 μM).
proposed a stochastic model in which time evolutions of migration speed and direction were given independently of each other, and showed that the migration direction was influenced by both the stochastic noise and deterministic driving force to the external directional cues [22, 23]. Recently, optimal estimations of gradient direction from a ligand distribution on cell surface have been studied based on the ideas of statistics such as maximum likelihood estimation and Bayesian statistics [11, 27–29]. The ideas that cells infer the gradient information have been incorporated into stochastic models of directional cell migration [24, 30]. The link between spontaneous polarization and directional sensing has also been investigated to study the chemosensory mechanism to detect shallow gradients [31–34]. So far, however, the connection between random and directional migrations in the absence and presence of gradients, respectively, are not fully addressed. Therefore, in this paper, we propose a theoretical model to connect the two aspects, random cell migrations in uniform chemoattractant conditions and chemotaxis in shallow gradients. This connection allows us to understand how symmetry breaking contributes to chemotaxis in shallow chemical gradients.

In the previous studies, the dispersion of noise term in the stochastic models has been assumed as a phenomenological fitting parameter [22–24]. However, the strengths of stochastic fluctuations in receptor occupancy depend on the chemoattractant concentration. Consequently, the random cell migration can also depend on this concentration. Therefore, we first study the dependence of random cell migration with the spontaneous internal polarity on the chemoattractant concentration. We found that the persistence time of migration direction increases with the concentration of spatially uniform chemoattractant, which agreed with our experimental result. We then introduce directional bias by applying an external gradient. Considering that the internal polarity responsible for the persistence time is equally applicable to chemotaxis, we demonstrate that cell polarity enhances the chemotactic accuracy. Finally, we determine the model parameters by comparing our theoretical results with experimental data of randomly migrating Dictyostelium cells in a uniform condition. We show that cell polarity can account for the high accuracy of chemotaxis exhibited by Dictyostelium cells as shown in the Fisher’s study [4].

2. Materials and methods

2.1. Mathematical model

We consider a spontaneously maintained internal polarity in the intracellular process (figure 1(b)). The cells migrate in the direction of the internal polarity, which is subject to change by intra- and extra-cellular perturbations (figure 1(c)). The intra-cellular perturbation originates from stochastic variation of signal reactions and other intracellular processes, which introduces randomness to the polarity direction, leading to random cell migration. For the extra-cellular perturbation, we consider the bias of chemoattractant gradients, and the random variation due to the stochastic binding between receptors and chemoattractant ligands. Cells sense the gradient through the inference process of external gradients that exerts the effective bias on the direction of motion. Here, we denote the bias by a non-dimensional parameter $A$ (figure 1(c)). For simplicity, we assume that the magnitude of the internal polarity and the migration speed are constant.

The time-evolution of the polarity direction is given by

$$\frac{d}{dt} \theta_y(t) = -S \sin \theta_y(t) + \xi_y(t),$$

(1)

where $\theta_y(t)$ is the angle between the directions of the internal polarity and chemical gradient at the time $t$. The first term on the right hand side of equation (1) describes the deterministic driving force which orients the internal polarity into the gradient direction. The coefficient $S$ indicates the strength of the driving force, and $\sin \theta_y(t)$ is the first term in the Fourier series that satisfies the symmetry with respect to $\theta_y(t) \rightarrow \theta_y(t) + 2\pi$ and $\theta_y(t) \rightarrow -\theta_y(t)$. The second term $\xi_y(t)$ describes the stochastic variation in the intra- and extra-cellular perturbations; $\xi_y(t) = \xi_{y, \text{int}}(t) + \xi_{y, \text{ext}}(t)$. The terms $\xi_{y, \text{int}}(t)$ and $\xi_{y, \text{ext}}(t)$ are given as the white Gaussian noises satisfying $\langle \xi_{y, \text{int}}(t) \rangle = 0$ and $\langle \xi_{y, \text{ext}}(t) \xi_{y, \text{ext}}(t') \rangle = 2D^* S \delta(t - t')$ with the magnitudes $D^*$ (rad$^2$/s$^{-1}$) of the dispersion. Here, the superscript * is int or ext. The extra-cellular noise term $\xi_{y, \text{ext}}(t)$ describes the stochastic variation in the number of ligand–receptor complex. Thus, its dispersion $D_{y, \text{ext}}^*$ depends on the chemoattractant concentration. The intra-cellular noise term $\xi_{y, \text{int}}$ describes the fluctuation in the chemotactic signal reactions. For simplicity we consider that the dispersion $D_{y, \text{int}}^*$ is independent of the chemoattractant concentration. The total dispersion is given by the sum of these dispersions as $D = D_{y, \text{int}}^* + D_{y, \text{ext}}^*$. The intrinsic property of the cell, $D_{y, \text{int}}^*$, is independent from the extracellular perturbation, $S$ and $D_{y, \text{ext}}^*$. Dynamics and statistics of the direction $\theta_y(t)$ of the internal polarity and migration are determined by all these properties as a consequence of equation (1). In particular, the persistence of the direction $\theta_y(t)$ depends on both $D_{y, \text{int}}^*$ and $D_{y, \text{ext}}^*$ as briefly explained in section 1. More rigorous formulation of equation (1) and the relation between the coefficients and physical parameters are shown in appendix A.1.

In [20, 23], equation (1) is derived by the symmetry argument as in the present paper. In [21, 22], the dependence of the driving force $S$ in equation (1) on the extracellular chemoattractant concentration was taken into account. In these works [20–23], the dispersion of noise term $\xi_y(t)$ is characterized by a phenomenological parameter independent of the chemoattractant concentration. Here, for the noise term, we explicitly consider the noise contribution in the stochastic process between ligand and receptor. As a result, the dependence on the chemoattractant concentration naturally appears. We introduce this dependence with an intuitive consideration in section 3.1 and with the mathematical derivation in appendix A.1.
2.2. Cell motility assay

*D. discoideum* AX2 cells (wild type) were starved by suspension in development buffer (DB: 5 mM Na phosphate buffer, 2 mM MgSO4, 0.2 mM CaCl2, pH 6.3) for 1 h and were then pulsed with 10 nM cAMP at 6 min intervals for up to 3.5 h at 21 °C, resulting in elongated cells with chemotactic competency [35]. The prepared cells were settled on a glass dish (IWAKI) at cell density ×10^5 cell ml⁻¹ to preclude explicit cell–cell interactions, containing DB supplemented with a given concentration of cAMP and 2 mM dithiothreitol (DTT, Sigma) was added to inhibit phosphodiesterase in order to keep the cAMP concentration in the medium. Cells were incubated under these conditions for 20 min. Phase-contrast imaging was performed using an inverted microscope (TiE, Nikon) with a 40× phase-contrast objective, equipped with an EMCCD camera (iXon+, Andor). Images of cells were taken every second for 30 min. To obtain the trajectories of cell area centroids, the cell periphery of individual cells was detected by enhancing the image contrast using the function histeq in Matlab 7.6 (mathworks) and then thresholded. All trajectories analyzed were longer than 5 min. The cell velocity \( v_n \) in frame \( n \) was obtained as \( v_n = r_{n+1} - r_n \), where \( r_n \) denotes the centroid trajectory. The migration direction \( \theta_n \) at frame \( n \) was defined as \( v_n = v_n(\cos \theta, \sin \theta) \), where \( v_n \) is the speed. The temporal autocorrelation function of the migration direction, \( C(n) \), given by, \( C(n) = \langle \cos(\theta_n - \theta_0) \rangle \) was calculated for individual cells. Then, the average autocorrelation functions were obtained by taking the averages over ensembles, as shown in figure 2(a) (red points). The autocorrelation functions (red points) exhibits delta-function like behavior at \( n = 0 \), indicating the presence of a time scale much shorter than 1 s and/or an uncorrelated noise due to the measurement error including image processing. Because the cell velocity \( v_n \) was obtained by one-step difference of centroid positions, the velocities in subsequent two steps exhibit anti-correlation. Thus, the sudden drops in the values at \( n = 1 \) are artifacts of data analysis. Therefore, we considered the autocorrelation function from \( n = 2 \) to 200 s to determine the characteristic time. Then, equation (2) was used for the fitting using the function isqcurevfit of Matlab 7.6 (mathworks). The fitted line was indicated by black lines in figure 2(a). The numbers of cells for individual conditions were shown in the legend of figure 2.

We obtained the trajectories of cell centroids at 1 s intervals for longer than 5 min up to 30 min. The velocity vector of the area centroid of cells, \( \mathbf{v}(t) = v(\cos \theta(t), \sin \theta(t)) \), was determined, from which we calculated the temporal autocorrelation function \( C(t) \) of the migration direction \( \theta(t) \), given by \( C(t) = \langle \cos(\theta(t) - \theta(0)) \rangle \) as above. figure 2(a) plots \( C(t) \) at different cAMP concentrations. The correlation function \( C(t) \) can be fitted by a sum of two exponential functions given by

\[
C(t) = C_1 e^{-t/\tau_1} + C_2 e^{-t/\tau_2} . \tag{2}
\]

The time constants \( \tau_1 \) and \( \tau_2 \) (\( \tau_1 < \tau_2 \)) obtained by the curve fitting showed a dependence on cAMP concentration. The time constant \( \tau_1 \) is within ranges of about 10–20 s and \( \tau_2 \) is in several hundreds of seconds. The shorter time constant \( \tau_1 \) is considered to characterize rapid deformations in the cell shape, whereas the longer one \( \tau_2 \) quantifies the persistence time in the migration direction. Since the time scale of the persistence is the focus of this paper, we plot \( \tau_2 \) as the correlation time in figure 2(b). We note that the correlation times of the centroid velocity \( v(t) \) and the direction \( \theta(t) \) essentially correspond with each other (figure 2(b)). This indicates that the constant speed approximation used in equation (A.3) is valid in this time scale.

3. Results and discussion

3.1. Random cell migration under uniform conditions

We first consider cell migration under uniform conditions without gradients of chemoattractant. In this case, the time-evolution of polarity direction \( \theta(t) \) is given by equation (1) with \( S = 0 \). In the absence of extra-cellular perturbation, the total noise strength is \( D = D^{int} \). When the cell is exposed to a spatially uniform chemoattractant, the stochastic binding of receptors and chemoattractant ligands is another noise contribution, \( D^{ext} \). The information of the binding states at a particular time decays exponentially with time constant \( \tau_R \). Here, \( \tau_R \) is the correlation time of the receptor state, given by [24]

\[
\tau_R(C_0) = \frac{1}{k_d + k_a C_0} = \frac{1}{k_d \left( 1 + K^{-1}_d C_0 \right)} , \tag{3}
\]

where \( k_d \) and \( k_a \) are the dissociation and association rates, respectively, \( C_0 \) is the chemoattractant concentration, and \( K_d = k_d/k_a \) is the dissociation constant. The strength of noise applied during time interval \( \tau_R \) is proportional to \( f_q \tau_R \), where \( f_q \) is the responsiveness that characterizes the response to the extra-cellular perturbation. The number of independent such noise per unit time is estimated as \( N \sim 1/\tau_R \). Thus, the dispersion of the extracellular-noise contribution \( D^{ext} \) through receptors is estimated by taking the average over \( N \) independent noises as \( D^{ext} \sim \left( f_q \tau_R N \right)^2 / N = f_q^2 \tau_R \). By a detailed calculation of \( D^{ext} \) shown in appendix (equations (A.7), (A.9) and (A.10)), we have the similar expression with the numerical factor 1/2 as

\[
D^{ext} = \frac{f_q^2 \tau_R}{2} . \tag{4}
\]

The direction of cell migration is determined by the direction of internal polarity, which shows stochastic fluctuation as a result of intra- and extra-cellular perturbations, as explained above. With the increase in total dispersion, \( D = D^{int} + D^{ext} \), the correlation time \( \tau_c \) of the migration direction decreases. Considering that the angular diffusion constant \( D \) has an inverse time unit, the correlation time \( \tau_c \) is given by \( \tau_c = D^{-1} \). (For a detailed derivation of this relation, see section appendix A.3). Thus, from equations (3) and (4),
the correlation time $\tau_c$ is given by

$$\tau_c(C_0) = \left( D^{\text{ext.}} + D^{\text{int.}} \right)^{-1}$$

$$= \left( \frac{f_q^2}{2k_d (1 + K_d^{-1} C_0)} + D^{\text{int.}} \right)^{-1}. \quad (5)$$

This equality indicates that the motile behavior of cells depends upon chemoattractant concentration, even if the chemoattractant is homogeneously distributed in space. When the chemoattractant concentration $C_0$ is much smaller than the dissociation constant $K_d$, $C_0 \ll K_d$, the correlation time $\tau_c(C_0)$ is approximately constant with respect to $C_0$. When the concentration is comparable to or larger than the dissociation constant, i.e., $C_0 \geq K_d$, but $C_0 \lesssim K_d f_q^2 (2k_d D^{\text{int.}})^{-1}$, equation (5) indicates that $\tau_c(C_0)$ increases with $C_0$ (figure 2(b), blue solid line). When $C_0 \gg K_d f_q^2 (2k_d D^{\text{int.}})^{-1}$, $\tau_c(C_0)$ is approximately constant and given by $\tau_c = (D^{\text{int.}})^{-1}$. Altogether, our theory indicates that the correlation time $\tau_c$ shows an increase with the concentration $C_0$ at $C_0 \sim K_d$. By fitting equation (5) to the measured concentration dependence of the correlation time, and knowing the values of the receptor parameters, we can estimate the values of parameters $f_q$ and $D^{\text{int.}}$. To perform this, since we focus on the time scale of the persistence here, we compare $\tau_s$ with the correlation time $\tau_c$ in equation (5).

### 3.2. The effect of internal polarity on the gradient response and chemotactic accuracy

In the presence of chemoattractant gradients, cells perform gradient sensing, and orient their internal polarity in the direction of the gradient. The quality of the gradient sensing may depend on the stochasticity in the receptor states. When the noise increases or decreases relative to the signal strength, the accuracy of gradient sensing may decrease or increase, respectively [36, 37]. Thus, the effective gradient information, quantified by the bias $A$, may decrease if the stochastic noise increases. The bias $A$ also depends on the chemoattractant concentration and the steepness of the gradient. The dependence of $A$ on the gradient information and ligand–receptor reaction can be explicitly derived by considering the gradient sensing process (see equation (A.25) for detail).

The response of cells to gradient perturbations should depend on the responsiveness $f_q$. As $f_q$ increases, the chemoattractant gradient should exert greater effect. Thus, the driving force $S$ exerted on the internal polarity depends on both the bias and the responsiveness, which may be expressed as

$$S = \frac{f_q A}{2}. \quad (6)$$

A more detailed derivation is given in appendix A.1.

Fisher et al [4] specifies the accuracy $\kappa$ by the sharpness of the distribution $P(\theta_i)$ of migration directions $\theta_i$, defined by $P(\theta_i) \propto \exp (\kappa \cos \theta_i)$. The CI is $\kappa = \langle \cos \theta_i \rangle$ with the statistical average $\langle \cdot \rangle$ according to the distribution $P(\theta_i)$. When the chemotactic accuracy $\kappa$ is small, the CI is roughly $\kappa/2$ [4]. $\kappa$ is also expected to be proportional to the driving force $S$. Furthermore, $\kappa$ should improve as the stochastic perturbations $D^{\text{ext.}} + D^{\text{int.}}$ decrease, or conversely, as the correlation time $\tau_c$ increases. These conditions are satisfied if $\kappa$ takes the form

$$\kappa = \tau_c S = \frac{A}{f_q k_d (1 + K_d^{-1} C_0)^{-1} + 2f_q^{-1} D^{\text{int.}}}. \quad (7)$$

Details are provided in appendix A.4.

To see the significance of the internal polarity on the chemotactic accuracy, we consider the amplification ratio $r$ given by the ratio between the chemotactic accuracy $\kappa$ with and without internal polarity. Here, the accuracy $\kappa$ without internal polarity is given by the bias $A$. (We can see this fact by comparing (A.4) and (A.17) in appendix for small $A$.) This ratio $r = \kappa/A$ quantifies the extent to which the internal polarity enhances the chemotactic accuracy. From equation (7), the amplification ratio $r$ is obtained as

$$r = \frac{1}{f_q \tau_R + 2f_q^{-1} D^{\text{int.}}}, \quad (8)$$

which depends on both $D^{\text{int.}}$ and $C_0$ through $\tau_R$. In figure 3(a), the amplification ratio $r$ is plotted as a function of $f_q$ and $D^{\text{int.}}$ in the low concentration limit $C_0 \sim 0$, i.e. $\tau_R = 1$ s. To remove the dependences on $D^{\text{int.}}$ and $C_0$, we study the scaled amplification ratio $\hat{r}$ given by

$$\hat{r} \equiv \frac{r}{\sqrt{1/(8\tauRD^{\text{int.}})}} = \frac{2}{\hat{f}_q + \hat{f}_q^{-1}}, \quad (9)$$

which depends only on the scaled responsiveness $\hat{f}_q = f_q / \sqrt{2D^{\text{int.}}/\tau_R}$. Figure 3(b) plots the rescaled amplification ratio $\hat{r}$ as a function of the rescaled responsiveness $\hat{f}_q$. From this figure, we observe that the amplification is maximized ($\hat{r} \equiv 1$) at $\hat{f}_q = 1$. These results suggest that, for a given value of $D^{\text{int.}}$, there exists an optimum responsiveness $f_q$ that maximizes the chemotactic accuracy. This maximum accuracy is achieved when the external and intrinsic perturbations are balanced. If the responsiveness $f_q$ is small, the correlation time $\tau_c$ in equation (5) is almost independent of $f_q$, because the dispersion is dominated by the intrinsic stochastic perturbation $D^{\text{int.}}$. Simultaneously, the external driving force $S$ in equation (6) is strengthened as $f_q$ increases. Therefore, for small responsiveness $f_q$, the accuracy $\kappa$ increases proportionally to the responsiveness $f_q$. Conversely, if the responsiveness $f_q$ is large, the correlation time $\tau_c$ is dominated by extrinsic stochastic perturbations as $\tau_c \propto f_q^{-2}$ in equation (5). In this case, the accuracy $\kappa$ in equation (7) decreases in proportion to $f_q^{-1}$.

### 3.3. Optimality of Dictyostelium chemotaxis

In this subsection, we study the influence of internal polarity on chemotaxis based on the values of the parameters $f_q$ and $D^{\text{int.}}$ of Dictyostelium cells. To determine these values, we
The effect of internal polarity on chemotactic accuracy. (a) The amplification ratio $r$ is given by equation (8) in the low concentration limit $C_0 \to 0$ for $k_d = 1$ s$^{-1}$. The red circle indicates the parameters of Dictyostelium cells, namely, $f_q \sim 0.0539$ rad s$^{-1}$ and $D_{\text{int}} \sim 0.00163$ rad$^2$ s$^{-1}$. (b) The scaled amplification ratio $\hat{r}$ given by equation (9). Horizontal axis is the dimensionless responsiveness $\hat{f}_q = f_q/\sqrt{2D_{\text{int}}/\tau_R}$. The dimensionless responsiveness for the given parameters, estimated from the correlation time of spontaneous migration (see equations (10) and (11)), is about 0.997 in the low average concentration limit $C_0 \to 0$, 0.705 at $C_0 = 180$ nM, and 0.301 at $C_0 = 1800$ nM.

We next study the dependence of chemotactic accuracy $\kappa$ and chemotaxis index CI on the chemoattractant concentration $C_0$. As shown in figure 4(b), both the accuracy and dynamic range of chemotaxis, given by equation (7) (red solid line), are larger in the presence of internal polarity than those in the absence of the polarity (blue broken line). Together, these results indicate that internal polarity contributes not only to chemotactic accuracy but also to the dynamic range of chemotaxis. Figure 4(c) shows the dependence of the CI on the concentration $C_0$. The stochastic signal processing and transduction during chemotactic signaling has been investigated theoretically [36] and experimentally [37]. These previous studies showed that the relationship between chemotactic accuracy and extracellular cAMP concentration mirrors the signal-to-noise ratio at the level of the second messenger [36, 37]. Therefore, here, we also take into account the intracellular noise in the second messenger reaction to the bias $A$ (see equations (A.25) – (A.27) in appendix for details), and investigate its effect. The resultant chemotactic accuracy $\kappa$ and CI as functions of cAMP concentration are shown in figure 4(d) and 4(e) (red solid lines), respectively. Those peak concentrations are lower than the case without the second messenger reaction shown in figure 4(b), (c). Again, both the accuracy and dynamic range of chemotaxis are improved by internal polarity. Comparing figure 4(d) with figure 4(b), we find that the accuracy $\kappa$ in the high concentration region $C_0 \gtrsim K_d$ is reduced by stochasticity in the second messenger reaction. The slope at the higher concentration $C_0 > K_d$ becomes steeper than that at $C_0 \lesssim K_d$ as shown in figure 4(d) (red solid lines), which agrees with the experimental result by Fisher et al [4]. Thus, the present theoretical result reproduces the ligand concentration of the highest chemotactic accuracy and the dynamic range of chemotaxis as shown in the Fisher’s result [4] by taking into account the second messenger reaction and adjusting the parameter values.

The effect of internal polarity on chemotaxis can be characterized by the amplification ratio $r$ introduced in...
Chemotactic accuracy. (a) Stationary distribution of the migration direction $P_s(\theta_s)$ with $\theta_s = 0$ in the absence of cell polarity (blue broken line) and $\theta_s = \theta$ with cell polarity (red solid line). Parameters are: $f_p \sim 0.0539 \text{ rad s}^{-1}$, $D_{\text{int}} \sim 0.00163 \text{ rad s}^{-1}$ (obtained for Dictyostelium cells as equations (10) and (11)), $N = 80,000$, and $k_2 = 1 \text{ s}^{-1}$. For the average chemoattractant concentration $C_0$, we set $K_0 C_0 \to 0$. We chose the bias $A$ to be 0.1. (b) and (c). (b) The accuracy of chemotaxis $\kappa$ and (c) the chemotaxis index $C_I$ plotted as functions of average chemoattractant concentration $C_0$. At all concentrations, the gradient steepness is $p = 0.01$. The chemotactic accuracy $\kappa$ in (7) and chemotaxis index $C_I$ in (A.18) achieved with internal polarity are indicated by the red solid lines, while those without internal polarity (calculated from equation (A.5); $\kappa = A$) are indicated by the blue broken lines. The bias $A$ was determined from equation (A.25) together with equation (A.27). Parameters are the same as (a). (d) and (e). (d) The effect of intracellular noise in the second messenger reaction in (d) the accuracy of chemotaxis $\kappa$ and (e) the chemotaxis index $C_I$, as functions of ligand concentration. The bias $A$ was determined from equation (A.25) together with equation (A.26). For red solid and blue broken lines, $X = 200,000$ and the other parameters are the same as (a). For green dotted lines, $N = 250$ and $X = 200,000$, and for purple dashed–dotted lines, $N = 80,000$ and $X = 1250$, and the other parameters are the same as above for both.
equation (8). The ratio $r$ depends on the values of $f_q$ and $D^{\text{int}}$, as shown in figure 3(a). For the values of $f_q$ and $D^{\text{int}}$ of Dictyostelium cells, indicated by the red circle in figure 3(a), the amplification factor is $r \approx 8.74$. The scaled amplification ratio $\hat{r}$ given by equation (9) depends only on the scaled responsiveness $\hat{f}_q$ as explained above. The scaled responsiveness of Dictyostelium cells is estimated as $\hat{f}_q \sim 0.997$, 0.705, and 0.301 for $C_0 \to 0$, $C_0 = K_d = 180$ nM, and $C_0 = 10 \times K_d = 1800$ nM, respectively (see figure 3(b), broken lines). For $C_0 \ll K_d$, the responsiveness is distributed around the maximum amplification ratio, indicating that the responsiveness parameter $f_q$ of Dictyostelium cells is almost optimal in this concentration range.

3.4. Discussion

3.4.1. Chemotaxis ability of mutant cells. The reduced chemotactic ability of mutant cells has been extensively studied. From our proposed theory, we can identify an aspect of the chemotaxis impaired by mutation. In equation (7), the mutable parameters are the bias $A$, the responsiveness $f_q$ and the internal noise $D^{\text{int}}$. A mutation can cause a reduction in the bias $A$, an increase in the internal noise $D^{\text{int}}$, and/or a decline in the responsiveness $f_q$. Since an optimal $f_q$ exists in Dictyostelium wild type cells (see figure 3), decreasing the responsiveness $f_q$ will cause a decrease in chemotactic ability. Among these three parameters, $f_q$ and $D^{\text{int}}$ affect the correlation time $\tau_c$ of random cell migration in isotropic conditions. By studying the dependence of this time constant $\tau_c$ on the chemoattractant concentration, we can identify which of $f_q$ or $D^{\text{int}}$ is modulated. We also notice that amplification ratio $r$ is insensitive to change of responsiveness $f_q$ around its optimal value (see equation (9) and figure 3(b)). Hence, the chemotactic accuracy of Dictyostelium cells should not be sensitive to small changes in the responsiveness $f_q$.

The directional correlation of random cell migration is characterized by 'persistence', denoted by $P$, defined as the ratio of net displacement to total path length in a given time interval (it is also called 'directionality'). Note that $P$ depends on the observational time interval $t$, and is independent of cell migration speed. $P$ and $\tau_c$ are related as follows; in the absence of a chemoattractant gradient, the persistence $P$ is almost 1 when $t \ll \tau_c$. When $t \approx \tau_c$, it becomes proportional to the square root of the correlation time; that is, $P \sim \sqrt{\tau_c/t}$. In the presence of a chemoattractant gradient, $P \sim 1$ when $t \ll \tau_c$, $P \sim \sqrt{\tau_c/t}$ when $\tau_c \ll t \ll \tau_A$, and $P \sim CI$ when $t \approx \tau_A$, and $P \sim CI$ when $t \approx \tau_A$. Here, $\tau_A$ is the time scale over which the directional motion induced by the gradient bias $CI \times \nu(t)$ dominates the diffusion length by randomness in the cell migration, given by $\nu(t) \sqrt{\tau_c/t}$. Thus, $\tau_A$ is given by $\nu(t) \sim CI^{-2} \tau_c$.

The chemotactic ability of PI3K mutant of Dictyostelium cells has been studied in [38, 39]. PI3K is involved in the self-organization of the phosphatidylinositol lipids signaling system [13, 14], and is a candidate constituent of the internal cell polarity. In addition, PI3K is activated by RasG [3]. RasG is involved in one of the parallel chemotactic signaling pathways in Dictyostelium cells [3]. Therefore, we expect that $D^{\text{int}}$ is increased and $f_q$ is decreased in the PI3K mutant. This may lead to lowering both the chemotactic accuracy in shallow gradients, as shown by equation (9), and the persistence $P$, regardless of whether chemoattractant is present. These speculations have been verified by experimental observation [38, 39].

If the ability to detect and respond to the chemoattractant gradient are intact (i.e. the bias $A$ and responsiveness $f_q$ are intact), equation (7) predicts that the ratio of CI to the square of the persistence, i.e., $CI/P^2$, is approximately constant, with $P$ defined in the interval $\tau_c \ll t \ll \tau_A$. This tendency has indeed been verified in Phosphatase and Tensin Homolog (PTEN) mutant cells, in which $CI/P^2$ was similar to that of wild type cells (using data reported in [40]). PTEN is also involved in the self-organization of the phosphatidylinositol lipid signaling system [13, 14]. This suggests that the loss of PTEN activity amplifies the intrinsic fluctuations $D^{\text{int}}$ of the polarity, while little affecting $A$ and $f_q$. In support of this idea, lateral pseudopod formation is enhanced in PTEN mutant cells [40]. However, our assumption that the migration and polarity directions are linked may not be valid for PTEN mutants. If this assumption is removed, the chemotaxis accuracy and persistence decrease.

The synergistic effect of several chemotaxis pathway has been studied in [41]. Simultaneous inhibition of both PI3K and sGC pathways induces a dramatic reduction in chemotactic ability $CI$ and persistence $P$, while inhibitions of either pathway cause a mild reduction, indicating the pathways exert a synergistic effect. Although variations arise in both chemotactic ability and persistence, their ratios $CI/P^2$ in the mutation and inhibition experiments of [41] appear to be almost constant. This might indicate that neither gradient detection ability $A$ nor responsiveness $f_q$ are strongly affected by the mutation, and that the sGC pathway is involved in stabilizing the internal polarity $D^{\text{int}}$ via synergistic effects with the PI3K pathway.

3.4.2. Other contributions relevant to chemotactic accuracy.

Several factors that may reduce chemotactic accuracy have been excluded from the model. The experimental accuracy of chemotaxis obtained by Fisher et al [4] is smaller than that obtained in our theory (see figure 4(d)), indicating that some of these factors are significant.

To obtain the maximum feasible accuracy, we assumed that all 80 000 receptors are located at the periphery of the cell. However, in reality, the receptors in the vicinity of the vertical point cannot contribute to determining the migration direction. This effect reduces the effective number of receptors and hence decreases the chemotactic accuracy. In the same way, when the number $X$ of second messengers is reduced, the accuracy also decreases. As an extreme example, we consider the cases when $N = 250$ for the receptors (green dotted lines) and $X = 1250$ for the second messengers (purple...
dashed–dotted lines) as shown in figures 4(d), (e). In both cases, the accuracy is predicted to be decreased. We showed more detailed dependence of the accuracy $\kappa$ and index $\text{CI}$ on $N$ and $X$ in figure A.2 in Appendix.

Spatial and temporal stochastic variations in the distribution of receptors and intracellular signaling molecules may also affect the dispersion in the chemotactic accuracy. For example, we have neglected the correlations in the spatial density fluctuations of receptors and the activated second messengers at different times and positions along the cell membrane (see appendix A.5 for details). However, these spatiotemporal stochastic fluctuations and correlations are expected because the receptors and activated second messengers can diffuse. In addition, the activation time is also subject to stochastic delays. An intriguing future problem is to theoretically investigate the consequences of spatial and temporal correlations on the density fluctuations of activated second messengers. Such studies might elucidate how cells overcome these noises.

We also postulated that the migration direction $\theta_m$ adiabatically follows the polarity direction $\theta_p$ on the time scale of interest. However, $\theta_m$ may deviate from $\theta_p$ over time scales exceeding the correlation time of polarity direction. These deviations, which would further contribute to fluctuations in the motile direction, are observed in cell deformation processes. Previously, we have reported that cell deformation can alter the gradient sensing ability, with subsequent effect on the probability distribution of chemotactic migration directions [29, 30]. Therefore, the temporal fluctuations observed in Dictyostelium cells may also affect the dispersion of motile directions.

3.4.3. Cell polarity and gradient-sensing response. In our previous study [42], polarized responses of membrane phosphatidylinositol 3, 4, 5-trisphosphate (PIP3) in a single cell to paired cAMP pulses of 1 s with an interval of 75 s exhibited no correlation in orientations of the responses. In this study, spatially uniform stimuli under flows were used. Refractory behavior was also reported for repeated transient stimuli [42, 43]. Therefore, the characteristic time in the direction of the polarity in the level of this signaling reaction can be less than 75 s, indicating that the polarity of the signaling alone may not be sufficient to explain the persistence in the cell migration with the characteristic time of $\sim$300 s. It was also reported that for repeated gradient stimuli the membrane concentration of PIP3 showed polarized responses [44], although the inter stimuli interval were not clearly indicated in the paper. Although the polarized directions were not completely oriented to the gradient direction, the variation of the direction in individual cells was smaller than the variation in the population [44]. This result was interpreted that cells possess their own intrinsic polarities, which can be modulated by the external gradient stimuli. Together with our previous study [42], the responses of PIP3 to gradient stimuli might be affected by some polarities other than the PIP3 itself, which might have characteristic times longer than that of the PIP3 polarity. If several different polarities are present in cells, it takes time for those polarities to be reoriented to the external gradients, which are longer than the intrinsic characteristic times of those polarities. Thus, within those time constants, the polarities should have correlation in the direction of migration and internal polarity used in the present theory.

Extension of our theory to incorporate multiple polarities is straightforward. Whether all possible polarities contribute efficient gradient sensing is an interesting future problem.

4. Conclusion and outlook

4.1. Conclusion

In this paper, we developed a theory of chemotactic cell migration that demonstrates the connection between cell intrinsic polarity and chemotactic accuracy. The time-evolution of the direction of the polarity is described by a stochastic differential equation (1), which consists of the deterministic driving force due to the guidance cue and stochastic noise due to both intra- and extra-cellular perturbations. We connected their coefficients with the physical quantities on chemical environment and signal processing by examining the statistics of chemo-ligand and receptors as a source of external perturbation. Based on this theory, firstly, we demonstrated that the direction of polarity persists over a correlation time that is predicted to increase as the chemoattractant concentration is increased (equation (5)). Next, we theoretically derived the chemotactic accuracy as a function of both the bias due to the guidance cue and the correlation time of polarity direction (equation (7)). The results indicated that the accuracy can be improved by the presence of intracellular polarity. Furthermore, the analysis of chemotactic accuracy suggests that accuracy is maximized at some optimal responsiveness to extracellular perturbations (equation (9)). To obtain the model parameters, we studied the correlation time of random cell migration in cell tracking analysis of Dictyostelium cells. The persistence time depended on the chemoattractant concentration as predicted. From the fitted parameters (10) and (11), we inferred that polarized Dictyostelium cells can respond optimally to a chemical gradient as shown in figure 3(b). Chemotactic accuracy was almost nine times larger than can be achieved by non-polarized gradient sensing. Using the obtained parameter values, we show that polarity also improves the dynamic range of chemotaxis. We conclude that cell polarity established spontaneously in the absence of external guidance cues plays a pivotal role in efficient chemotaxis. This conclusion is consistent with the recent numerical study based on a detailed mathematical model [45].

4.2. Outlook

The present model, which incorporates internal polarity and gradient sensing, is applicable to several different cases, including chemotaxis with cell shape deformation. In particular, slight deviations of the motile direction distribution
from the normal circular distribution can be explained by the present model, provided that the process of cell deformation and the influence of cell shape on the gradient sensing are included [30]. The current model can be used to study chemotaxis towards time-varying gradients, such as chemottractant waves. By introducing cell–cell interactions into the model, the collective chemotaxis of cell populations could also be investigated. The connection between microscopic models based on signal reaction kinetics [13, 14, 32, 33] and macroscopic models, such as our present theory, is an intriguing future topic.

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Appendix A. Details of the mathematical model

A.1. Mathematical modeling of internal polarity

We consider the spontaneous formation of the internal polarity \( q = (q_x, q_y) \), incorporating gradient sensing and internal and external perturbations. The simplest evolution equation that describes such internal polarity \( q = (q_x, q_y) \) is given by [30]

\[
\frac{d}{dt}q = I_q (1 - |q|^2)q + \Xi^{\text{int}}(t) + \Xi^{\text{ext}}(t) . \tag{A.1}
\]

The first term on the right hand side describes the formation of polarity. In particular, by the first part \( I_q q \) of this term, the isotropy of \( q \) is spontaneously broken. The same formulation has been proposed for an active Brownian particle with energy supply [47, 48]. The other part \(-I_q |q|^2 q\) is the lowest order term for preventing the divergence of \( q \) [46]. In this article, we assume \( I_q \to \infty \) for further simplicity, so that the internal polarity \( q \) is reduced to \( q(t) = (\cos \theta_q(t) \sin \theta_q(t)) \) with \( |q| = 1 \). The second term \( \Xi^{\text{int}}(t) \) describes the internal noise, assumed as Gaussian white noise with \( \langle \Xi^{\text{int}} \rangle = 0 \), and

\[
\langle \Xi^{\text{int}}(t)\Xi^{\text{int}}(t') \rangle = 2D^{\text{int}} \delta(t-t') . \tag{A.2}
\]

The last term \( \Xi^{\text{ext}}(t) \equiv f_q e(t) \) describes the gradient sensing with responsiveness \( f_q \). The unit vector \( e(t) \) specifies the inferred direction of the external gradient, \( \phi(t) \), i.e. \( e(t) = (\sin \phi(t), \cos \phi(t)) \). Here, we consider that the cell estimates the extracellular gradient direction from the distribution of its chemotactrant-occupied receptors or activated second messengers (see appendix A.5). In this paper, we consider cell motions in the time scale longer than the persistence time of cell migration. On these time scales, the velocity \( v \) of the cell immediately follows the internal polarity as

\[
v = v_0 q , \tag{A.3}
\]

where the migration speed \( v_0 \) is assumed constant as previously reported [24].

For a given spatial distribution of chemotactrant-occupied receptors, we consider the most probable estimate of the gradient direction, \( \phi \). The simplest probability distribution \( P(\phi) \) of the estimated direction for cells with circular shape is given by [29]

\[
P(\phi) = \frac{1}{2\pi} + \frac{A}{2\pi} \cos \phi , \tag{A.4}
\]

where the true gradient direction is \( \phi = 0 \). Here, \( A \) is the bias strength, which can be derived by considering the gradient sensing process, as shown in equation (A.25) of appendix A.5. Equation (A.4) is the first order approximation of the circular-normal distribution with respect to the bias strength \( A \). In the absence of internal polarity, the CI gained from directional inference alone is given as

\[
\text{CI} = \int_0^{2\pi} d\phi \cos \phi P(\phi) = A/2 . \tag{A.5}
\]

The characteristic time \( \tau_c \) in equation (3) is much smaller than the persistence time of 300 s [8] in the migrating direction. Thus, we assume that the characteristic time \( \tau_c \), during which the polarity direction persists, is also much longer than the correlation time \( \tau_c \) of the estimated direction. We consider the integral of the driving force over time interval \( \Delta t \gg \tau_c \), \( \Delta W^{\text{ext}} = \int_{t}^{t+\Delta t} \Xi^{\text{ext}}(s) ds \). Then, by the central limit theorem, \( \Delta W^{\text{ext}} \) follows the Gaussian distribution. The average and mean square displacement of \( \Delta W^{\text{ext}} \) are given by

\[
\langle \Delta W^{\text{ext}} \rangle = 0 , \tag{A.6}
\]

and

\[
\langle \Delta W^{\text{ext}} \rangle^2 = 2f^2 q \tau_c \Delta t . \tag{A.7}
\]

Equations (A.6) and (A.7) are derived from the second term on the right hand side of equation (A.4) and the first term up to \( O(A) \), respectively. The driving force \( S \) in equation (6) is given by the y-component of \( \langle \Delta W^{\text{ext}} \rangle \) in equation (A.6) divided by \( \Delta t \). Next, consider the change in the direction of internal polarity within \( \Delta t \), \( \Delta \theta_q = \theta_q(t+\Delta t) - \theta_q(t) \). From equation (A.1) with \( I_q \to \infty \), equations (A.2), (A.6), and (A.7), the moments of \( \Delta \theta_q \) up to \( O(\Delta t) \) are given by

\[
\langle \Delta \theta_q \rangle = -\frac{1}{2} f_q A \sin \theta_q(t) \Delta t , \tag{A.8}
\]

and

\[
\langle \Delta \theta_q \rangle^2 = \left( f^2 q \tau_c + 2D^{\text{int}} \right) \Delta t . \tag{A.9}
\]

Here, since \( \Delta \theta_q \) is the projection of the 2D vector \( \Delta q \) into 1D, the numerical factor 2 in equation (A.7) disappears in equation (A.9). In this way we obtain equation (1) and, using the Kramers–Moyal expansion with equations (A.8) and (A.9)
the Fokker–Planck equation
\[
\frac{\partial}{\partial t}P(\theta_q, t) = \frac{\partial}{\partial \theta_q} \left[ c_q(\theta_q)P(\theta_q, t) \right] + D \frac{\partial^2}{\partial \theta_q^2}P(\theta_q, t) \tag{A.10}
\]
where \(c_q(\theta_q) = (\alpha \sin \theta_q)/2\), and \(D\) is the diffusion constant
\(D = D^{\text{ext.}} + D^{\text{int.}}\), which consists of two independent disper-
sions \(D^{\text{ext.}} = f_q^2 \tau_R/2\) and \(D^{\text{int.}}\), respectively denoting the diffusion strengths introduced by external and internal perturbations.

Note that, in the main text, we began with equation (1), in which the directionality of the deterministic driving term is given by \(\sin \theta_q\) and the noise dispersion \(D\) is independent from the polarity direction \(\theta_q\). This equation is justified with the central limit theorem when the gradient strength \(A\) is sufficiently small, or up to \(O(A)\), as shown in equations (A.6) and (A.7). This approximation does not depend on particular gradient sensing mechanisms of cells excepting the case in which the second order term \(\cos(2\phi)\) is included in equation (A.4) up to \(O(A)\). In this exception, the noise dispersion \(D^{\text{ext.}}\) depends on the polarity direction \(\theta_q\) [30].

A.2. Propagation of noise in the linear cascade reaction

Here, we consider the contribution of the receptor noise to the downstream signals. Consider a linear signaling cascade, in which the activity of each reaction step is modulated by the one-upstream step. Then, the stochastic temporal evolutions of the small deviations \(\eta_i\) from their stationary average at each step are described by the following linearized Langevin equations [49]
\[
\tau_i \frac{d}{dt} \eta_i = -\eta_i + \eta_{i-1} + \xi_i(t) , \tag{A.11}
\]
where \(\tau_i\) is the time constant (given by the inverse depletion rate) for each reaction step, and the dimensionless quantity \(\eta_i\) includes signal amplification effects. The noise in the activated receptor is given by \(\eta_0\), with \(\langle \eta_0(t') \eta_0(t) \rangle = \sigma_0^2 \exp(-|t' - t|/\tau_0).\) The last term \(\xi_i\) denotes the noise in the \(i\)th signal transduction.

From equation (A.11), the autocorrelation function is given by
\[
\langle \eta_0(t') \eta_0(t) \rangle = \langle \eta_0(t') \eta_0(t) \rangle_0 + \Delta \tag{A.12}
\]
where the first term on the right hand side denotes the contribution of the noise in the receptor signal, \(\eta_0\), to the noise at the \(n\)th step of the signal cascade, given by
\[
\langle \eta_0(t') \eta_0(t) \rangle_0 = \sigma_0^2 \Lambda_n(t' - t) . \tag{A.13}
\]

The function \(\Lambda_n(\Delta t)\) describes the time-dependence of the receptor noise in \(\eta_0(t)\)
\[
\Lambda_n(\Delta t) = \sum_{i=1}^n \tau_R \prod_{j=1}^n \left( \frac{\tau_j^2}{\tau_j - \tau} \right) e^{-|\Delta t|/\tau_j} \tag{A.14}
\]
with \(\tau_0 \equiv \tau_R\). The second noise term \(\Delta\) on the right hand side of equation (A.12) is the contribution of the various noises in the signal cascade downstream of the receptor, \(\xi_i\). Since \(\Delta\) is included in \(D^{\text{int.}}\) but not in \(D^{\text{ext.}}\), we focus on the receptor noise given by equation (A.13).

In Dictyostelium cells, the receptor time constant \(\tau_R\) is about 1 s, while the time constants \(\tau_i\) of cascade reactions \((i = 1, 2, \ldots, n)\) are comparable to or less than several seconds [50, 51]. On the other hand, the persistence time of the migration direction is about \(\tau_c \sim 300\) s. Because the time constants \(\tau_i\) \((i = 0, 1, 2, \ldots, n)\) are much smaller than \(\tau_c\), we can replace \(e^{-|\Delta t|/\tau_i}\) by \(2\tau_i \delta(\Delta t)\). Thus, we obtain
\[
\Lambda_n(\Delta t) = 2\tau_R \delta(\Delta t) \sim e^{-|\Delta t|/\tau_c} , \tag{A.15}
\]
and hence \(\langle \eta_0(t') \eta_0(t) \rangle = \langle \eta_0(t') \eta_0(t) \rangle_0\). Therefore, the time constant \(\tau_R(=\tau_0)\) can be used in equations (4) and (A.7). Intuitively, this argument implies that the time constant \(\tau_R\), considered as the interval of signaling events at the receptor, is not affected by the time delay between a particular signaling event and the resulting directional changes along the signaling cascades (figure A.1).

A.3. Cell motile behavior in the uniform chemoattractant solution

The persistence of migration direction is characterized by the autocorrelation function of the migration direction. In the presence of a uniform chemoattractant with \(C_0 > 0\) and \(A = 0\), the autocorrelation function of \(\bm{q}(t)\), \(C(t) = \langle \bm{q}(t) \cdot \bm{q}(0) \rangle = \langle \cos(\theta_q(t) - \theta_q(0)) \rangle\) is obtained from equation (A.10) with \(A = 0\) as
\[
C(t) = \int_0^{t+D} \cos \theta_q P(\theta_q, t|\theta_q = 0, t = 0) d\theta_q \tag{A.16}
\]
where the diffusion constant \(D = D^{\text{ext.}} + D^{\text{int.}}\). In this manner, we obtain the correlation time \(\tau_c\) in equation (5).

A.4. Stationary distribution of the migration direction and CI in a shallow chemical gradient

Solving equation (A.10), the stationary probability distribution \(P_s(\theta_q)\) of the polarity and migration direction \(\theta_q\) is given by
\[
\sum_{n=0}^{\infty} \frac{(-1)^n A_n}{n!} \prod_{i=1}^n (A_i - A_{i+1})P_s(\theta_q) = \prod_{i=1}^n (A_i - A_{i+1}) \tag{A.17}
\]
for arbitrary numbers \(A_i\) \((i = 0, 1, 2, \ldots, n)\).

Figure A.1. Propagation of time delay in the signal transduction cascade.
given by the circular normal distribution as
\[ P_{\theta}(\theta) = \frac{1}{I_0(\kappa)} \exp\left(\kappa \cos \theta\right), \quad (A.17) \]
where the accuracy \( \kappa \) is obtained from equation (7). Here, \( I_0(\kappa) \) is the modified Bessel function, defined as \( I_0(\kappa) = \int_0^\infty \exp(\kappa \cos \theta) d\theta \). Equation (A.17) is plotted as a function of migration direction in figure 4(a) (red solid line). The parameter values of a Dictyostelium cell are assumed as \( \kappa_0 = 1 \) s\(^{-1}\) and \( K_d = 180 \text{nM} \) and the parameter values (10) and (11).

\[ \text{CI} \equiv \int d\theta \cos \theta P_{\theta}(\theta) = \frac{d}{d\kappa} \log I_0(\kappa) \bigg|_{\kappa=(\hat{\kappa}/2D)} \quad (A.18) \]

The CI, given by equation (A.18), saturates at \( 1 \); that is, \( \text{CI} \sim 1 - (f_0 D) + 2f_0^{-1} D_{\text{eff}} y/(2A) \to 1 \) as \( A \to \infty \), whereas \( \text{CI} \sim \Lambda(2f_0 D_{\text{eff}} + f_0^{-1} D_{\text{eff}}) \sim \kappa/2 \) as \( A \to 0 \). Figure 4(c) plots the CI (A.18) with equations (A.25) and (A.27) (red solid line) as functions of chemotactic concentration assuming the average and the dispersion of \( x^* \) as

\[ \sigma^2(\theta) = \frac{C(\theta)K_d}{(C(\theta) + K_d)^2 r_0}, \quad (A.23) \]

where \( g_\lambda(\theta) = K_\lambda/(K_X + r^*_\lambda) \), \( r_{\lambda}(\theta) = (k_{\text{off}} C(\theta) + k_{\text{off}})^{-1} \), and \( \tau_{\lambda}(\theta) = (k_{\text{on}} C(\theta) + k_{\text{off}})^{-1} \). Using the average and dispersion of \( x^*(\theta) \), the distribution of \( \phi \) was evaluated up to the first order of \( p \) (see equation (A.4)) with

\[ A = \frac{1}{2} p^3/2 \mu^{1/2}, \quad (A.25) \]

and

\[ \mu^{-1} = 2 \left[ \frac{C_0 K_d + 1}{\pi C_0 K_X x_0} \right] ^2 \left[ \frac{K_d X + C_0 (X + n_0)}{C_0 + K_d} \right] ^2 + \frac{K_a K_d}{C_0 + K_d} \left[ \frac{K_X (C_0 + K_d)}{C_0 + K_d} \right] ^2 \left[ \frac{C_0 K_d N}{4 (C_0 + K_d)^2} \right] ^2. \quad (A.26) \]

Taking \( x_0 \to \infty \), followed by the limit \( k_{sp} \to \infty \) with fixed \( K_X \), we have \( \mu = \mu_{\text{theo.}} \) where

\[ \mu_{\text{theo.}} \equiv \frac{C_0 K_d N}{4 (C_0 + K_d)^2}. \quad (A.27) \]

This form of \( \mu_{\text{theo.}} \) is consistent with the result based on the most efficient estimation (maximum likelihood estimate without stochasticity in the second messenger reaction) [29]. We also note that, as \( C_0 \to \infty \), we have \( \mu \sim (\pi/2) K_X K_d^2 n_0 C_0^{-2}/(K_X + n_0)^2 \propto C_0^{-2} \). Thus, this function decays much faster than \( \mu_{\text{theo.}} \) derived from the most efficient estimate, which decreases as \( \propto C_0^{-1} \) as \( C_0 \to \infty \). Moreover, the coefficient is proportional to the second messenger concentration \( x_0 \). Therefore, consistent with a previous report [36], the activation of the second messenger becomes the bottleneck of the chemotactic signal processing at high chemotactic concentrations.

Figure A.2 shows the chemotactic accuracy in equation (7) and chemotaxis index given by equation (A.18) with equations (A.25) and (A.26) for several different numbers of receptors \( N \) and second messengers \( X \), with the experimental parameter values \( k_3 = 1 \) s\(^{-1}\) and \( K_d = 180 \text{nM} \) and the values of \( f_0 D_{\text{eff}} \) given by (10) and (11). As shown in figures A.2(a), the peak concentration of the accuracy increases and get close to the dissociation constant \( K_d \) when only the numbers \( N \) of receptors are reduced. If we also
reduce the numbers $X$ of second messengers, the peak concentration is decreased as shown in figures A.2(c). In each case of figures A.2(c), the peak concentration is lower than that of the red solid line in figure 4(d) and the purple dashed-dotted line in figure A.2(c).

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