Phenomenological approach to eukaryotic chemotactic efficiency

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Eukaryotic cells are capable of detecting small chemical gradients for a wide range of background concentrations. Ultimately, fluctuations place a limit on gradient sensing and recent work has focused on the role of stochastic receptor occupancy as one possible limiting factor. Here, we use a phenomenological approach to add spontaneous motility fluctuations to receptor noise and predict the directional statistics of eukaryotic chemotaxis. Specifically, an Itô diffusion equation with direction-dependent multiplicative noise is developed and analytically studied. We show that our approach can naturally accommodate recent experimental data for the chemotaxis of the social amoeba *Dictyostelium*.

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I. INTRODUCTION

During chemotaxis, cells direct their movement by sensing chemical gradients. Chemotaxis plays an important role in various biological processes including fertilization, neuronal development, wound healing, and cancer metastasis [1,2]. Unlike prokaryotes, eukaryotic cells use a spatial measurement of the asymmetric distribution of bound receptors following the external gradient. These bound receptors trigger the activation of intracellular signaling pathways, eventually leading to the generation of directional movement. Interestingly, eukaryotic cells are able to direct their motion in shallow gradients. For example, the social amoeba *Dictyostelium discoideum* is observed to crawl up a chemoattractant gradient when the front-back difference in the concentration is around 1% [3,4]. Furthermore, the cells respond even when the average local concentration is well below the dissociation constant K_d. These findings have led to significant interest from the biophysics community in understanding the effect of noise on chemotaxis [5–12].

Studies to date have mainly focused on fluctuations in gradient sensing arising, for example, from stochastic receptor dynamics [6,10]. However, there are other sources of noise as is evidenced by the fact that cells move *randomly* in the absence of directional information [13,14]. The simplest approach to adding random motility to directional bias is to assume that the cell executes Brownian motion in a deterministic periodic potential [15]; however, this approach fails to take into account uncertainties in evaluating gradient steepness and direction. Thus, what is needed is a new model of directed cell motility that takes into account both sources of fluctuations. Such a model should be able to relate the relative importance of gradient-determination noise versus motility noise to testable predictions for the behavior of chemotactic cells. Here, we propose a phenomenological stochastic differential equation (SDE) model for this purpose and compare its predictions with the available data. As we will see, our approach naturally accounts for the unusual shape of the directional probability distribution for chemotaxing cells.

II. MODEL

In our model, the cellular surface takes a circular geometry where N independent receptors are uniformly distributed (Fig. 1). We divide the surface into M sectors such that the local ligand concentration near each sector is constant, while the number of receptors in each sector $N_m=N/M$ is large enough for the continuous approximation. For *Dictyostelium*, a typical value is $N=60\,000$, and one may choose $M=300$ and $N_m=200$. We define the gradient steepness parameter as $p=(L/C_0)(dC/dr)$, where C_0 is the average local ligand concentration across the cell length L. Then, the local concentration at the m_{th} sector with angular position φ_m is given by $C_m=C_0[1+\frac{p}{2}\cos(\varphi_m-\phi)]$, where ϕ specifies the gradient direction. The time for receptor decorrelation is dominated by the individual receptor rate $\tau_m=(k_-+k_+C_m)^{-1}$, which is typically faster than the process by which motion can be mechanically altered [16]. This allows us to use the white-noise approximation in which the number of occupied receptors is $Y_m=\langle Y_m\rangle+\eta_m=N_mC_m/(C_m+K_d)+\eta_m$ for $m=1,\ldots,M$, with $\langle\eta_m(t)\eta_n(s)\rangle\approx N_mC_mK_d/(C_m+K_d)^2\delta(t-s)\delta_{mn}$ [7,17]. Thus, the receptor signal is decomposed into M independent Gaussian random variables.

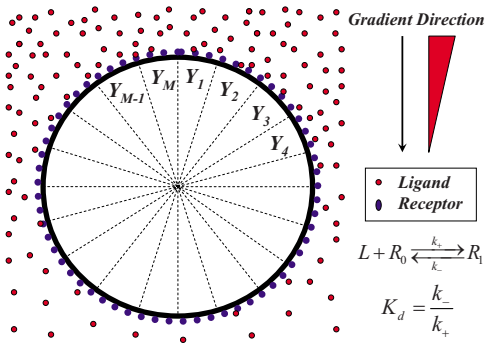

FIG. 1. (Color online) Schematic representation of our model. The forward rate k_+ and backward rate k_- determine the transition between the unoccupied R_0 and occupied R_1 states. The dissociation constant K_d is the ligand concentration at which half the receptors are bound in equilibrium.

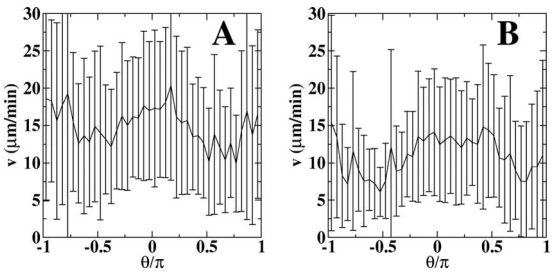

FIG. 2. The average cell speed in the experiments of Ref. [4] as a function of angle for (A) $p=5\%$ and (B) $p=10\%$. For each gradient steepness, the speed was computed by tracking the position of the centroid of 30–40 cells during 8 min. For more experimental details, see Ref. [4].

The simplest estimate a cell can make of the gradient is obtained by the following statistic: $Z=\Sigma_{m=1}^{M} Y_m \cos\varphi_m + i\Sigma_{m=1}^{M} Y_m \sin\varphi_m \equiv z_1 + iz_2$. When M is large, one can evaluate Z via replacing the sum with an integral. For small gradients ($p<10\%$), the integrand can be expanded around p and we find

$$\langle Z\rangle \approx \frac{pNC_0K_d e^{i\phi}}{4(C_0+K_d)^2} + \mathcal{O}(p^3) \equiv \nu e^{i\phi} + \mathcal{O}(p^3), \tag{1}$$

$$\langle z_{1,2}^2\rangle \approx \frac{NC_0K_d}{2(C_0+K_d)^2} + \mathcal{O}(p^2) \equiv \sigma^2 + \mathcal{O}(p^2). \tag{2}$$

It is easy to check that z_1 and z_2 are uncorrelated Gaussian random variables, with different means but with the same variance. This implies that Z is a complex Gaussian variable which can be written in polar coordinates as $Z=\rho e^{i\psi}$. Here, ρ measures the degree of asymmetry in the ligand-bound receptor distribution, while the phase ψ estimates the gradient direction ϕ. Mathematically, ρ follows the Rice distribution and ψ takes a symmetric unimodal circular distribution [18]. It was found that for large signal-to-noise ratio ($\mathrm{SNR}=\nu/\sigma \gtrsim 3$) both ρ and ψ are asymptotically Gaussian [18]. Thus, $\rho \approx \nu + \eta_\rho$ with $\langle \eta_\rho(t)\eta_\rho(s)\rangle = \sigma^2\delta(t-s)$, and $\psi \approx \phi + \eta_\psi$ with $\langle \eta_\psi(t)\eta_\psi(s)\rangle = (\sigma^2/\nu^2)\delta(t-s)$. As an orthogonal transformation from the Cartesian coordinates, η_ρ is independent of η_ψ. For typical *Dictyostelium* values we find that $\mathrm{SNR}>3$, consistent with the Gaussian approximation.

Cellular motion can be decomposed into two stochastic processes: speed and direction. Recent experimental data in *Dictyostelium* [4] show that the average speed is roughly identical for all directions. In these experiments, cells were exposed to stable exponential chemoattractant profiles using microfluidic devices. The centroid of each cell in the field of view was automatically tracked every 5 s for 100 frames. Cells that moved the furthest without colliding with another cell were chosen for the data analysis. 10–25 such cells were collected in each experiment, giving thousands of data points for each particular gradient. The average speed as a function of the angle is plotted in Fig. 2 for two different gradient steepnesses. From this figure, we can conclude that any possible correlation between angle and speed is smaller than can be obtained from the data. Thus, we restrict ourselves to the directional process, parametrized by the migration angle $\theta(t)$, by assuming a uniform migration speed.

Let us temporarily suppose that cells have perfect knowledge about the gradient direction ϕ. In general, the equation of $\theta(t)$ can be written as $d\theta/dt = G(\rho,\theta-\phi)+\eta_0$ along with $\langle \eta_0(t)\eta_0(s)\rangle = \sigma_0^2\delta(t-s)$. The incorporation of the gradient-independent noise η_0 above allows the cell to perform a random walk in the absence of any gradient. Note that unlike a recent study of random motility [13], we do not include colored noise in our model. The function $G(\rho,\theta)$ must exhibit the following symmetry properties [15]: (1) 2π periodicity, $G(\rho,\theta\pm 2n\pi)=G(\rho,\theta)$ for any integer n; (2) polar symmetry, $G(\rho,\theta\pm\pi)=-G(\rho,\theta)$, because the system's polarity will be reversed under the reversal of gradient direction; and (3) reflection symmetry, $G(\rho,-\theta)=-G(\rho,\theta)$, i.e., cells cannot distinguish between left and right with respect to the direction ϕ. The simplest form obeying these requirements is $G(\rho,\theta-\phi)=-\beta(\rho)\sin(\theta-\phi)$. Of course, cells have only imperfect knowledge of the gradient direction. The phase variable ψ in our model serves as an unbiased estimator of ϕ for the cell. Thus, we arrive at the phenomenological Langevin equation

$$d\theta/dt = -\beta(\rho)\sin(\theta-\psi) + \eta_0. \tag{3}$$

This phenomenological equation describes a chemotactic cell trying to align its movement with the estimated gradient direction ψ. The first term describes a gradient-dependent restoring force which steers the cell toward the gradient direction and which contains gradient-dependent fluctuations (arising from receptor-ligand dynamics and downstream pathways), while the second term represents gradient-independent noise in the random motility machinery.

Without loss of generality, we will set $\phi=0$. In the small noise limit we can perform a Taylor expansion $d\theta/dt \approx -\beta(\nu)\sin\theta + \beta'(\nu)\sin\theta\,\eta_\rho + \beta(\nu)\cos\theta\,\eta_\psi + \eta_0 = -\beta(\nu)\sin\theta + \eta_{tot}$, where the variance of the total noise is

$$\langle \eta_{tot}^2\rangle \equiv \sigma_{tot}^2 = [\sigma\beta'(\nu)\sin\theta]^2 + [\sigma\beta_{-1}(\nu)\cos\theta]^2 + \sigma_0^2, \tag{4}$$

with $\beta'(\nu)=\partial\beta(x)/\partial x|_{x=\nu}$ and $\beta_{-1}(\nu)=\beta(\nu)/\nu$. The first term in Eq. (4) describes the fluctuations arising from ρ, the amplitude of the gradient estimate, while the second term describes the fluctuations in ψ, the direction of the gradient estimate. Both of them vary with the instantaneous direction of motion $\theta(t)$ and therefore are multiplicative fluctuations. Since the cell responds to noise at its current position, the multiplicative noise is defined with the Itô prescription. From the previous expression it is clear that the ultimate directional dependence in σ_{tot}^2 relies on the sign of $\beta'(\nu)-\beta_{-1}(\nu)$. To capture possible nonlinear input-output characteristics of downstream pathways, we assume that $\beta(\nu)$ has a power-law functional form, i.e., $\beta(\nu)=a\nu^b$. We can distinguish between two qualitatively different cases. In the first, $b>1$, the total variance is of the "sin θ" type, $\sigma_{tot}^2=\sigma_0^2+(\sigma\beta_{-1})^2+(\beta'^2-\beta_{-1}^2)(\sigma\sin\theta)^2$, and is maximal at $\theta=\pi/2$; in the second, $b<1$, the variance is described by a "cos θ" type and is maximal at $\theta=0$. In the special case

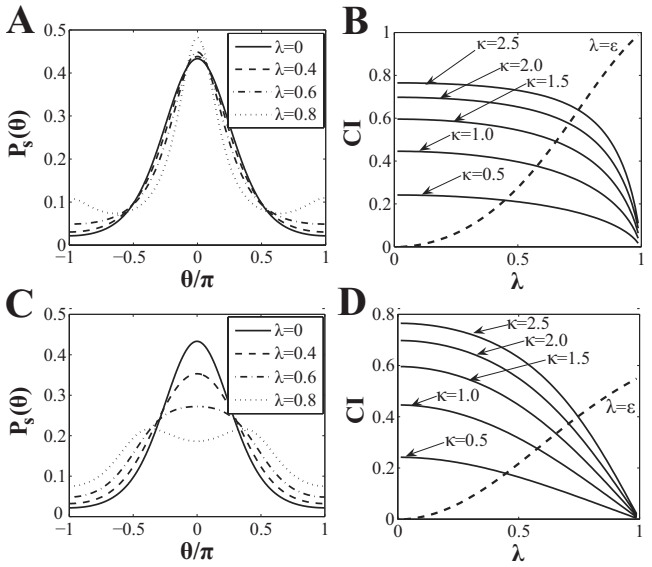

FIG. 3. The stationary distribution $P_s(\theta|\phi=0;\kappa=1.5,\lambda)$ for (A) $b>1$ and (C) $b<1$ as a function of the parameter λ representing the ratio of direction-dependent noise to maximal total variance. The CI vs λ for (B) $b>1$ and (D) $b<1$, with the dashed lines indicating where the bifurcation occurs.

$b=1$, the total variance is reduced to $\sigma_{tot}^2=\sigma_0^2+a^2\sigma^2$ with no directional dependence.

III. RESULTS

We first study the case of $b>1$ where the restoring force is ultrasensitive to the input signal. Define the direction-independent noise $\sigma_\perp^2=\sigma_0^2+(\sigma\beta_{-1})^2$ and the direction-dependent noise $\sigma_\parallel^2=(\beta'^2-\beta_{-1}^2)\sigma^2$. Then the previous Langevin equation can be approximated as the Itô SDE,

$$\frac{d\theta}{dt}=-\beta(\nu)\sin\theta+\sqrt{(\sigma_\parallel\sin\theta)^2+\sigma_\perp^2}\,\eta(t), \tag{5}$$

where $\eta(t)$ is white noise. One can solve the associated Fokker-Planck equation on the interval $[-\pi,\pi]$ by imposing periodic boundary conditions [19]. The stationary distribution reads

$$P_s(\theta)=\frac{\Omega\exp\left[\kappa\frac{1-\lambda^2}{\lambda}\operatorname{arctanh}(\lambda\cos\theta)\right]}{1-(\lambda\cos\theta)^2}, \tag{6}$$

where $\kappa=2\beta/\sigma_\perp^2$ is a parameter that compares the direction-biased force with the direction-independent noise and where $\lambda=\sigma_\parallel/\sqrt{\sigma_\parallel^2+\sigma_\perp^2}$ is the ratio of the direction-dependent and maximal total variance. The normalization parameter Ω can be determined numerically. For a vanishing λ, we recover the circular normal (CN) distribution: $\lim_{\lambda\to 0}P_s(\theta;\kappa,\lambda)=\exp(\kappa\cos\theta)/[2\pi I_0(\kappa)]$. For large λ, our stationary distribution will appreciably deviate from the CN distribution with a sharper peak at $\theta=0$ and heavier tails near $\theta=\pm\pi$ [see Fig. 3(A)]. A physical interpretation of this leptokurtic feature can be given by realizing that the first term in the Langevin equation [Eq. (3)] functions as a restoring force. Contrary to the CN case, the amplitude of this force, $\beta(\rho)$, is taken from a distribution. Thus, large values can occur and correspond to large restoring forces which lead to a sharper peak in $P_s(\theta)$. Using the same argument, one can see that the occurrence of small values in this distribution is responsible for the heavy tails in $P_s(\theta)$.

We can further explore the extrema and directionality of $P_s(\theta)$ by recalling that $\operatorname{arctanh}(x)=\frac{1}{2}\ln(\frac{1+x}{1-x})$ and setting $\epsilon\equiv\kappa(1-\lambda^2)/(2\lambda)=\lambda\beta(\nu)/\sigma_\parallel^2$, after which we obtain the alternative form $P_s(\theta)=\Omega(1+\lambda\cos\theta)^{\epsilon-1}/(1-\lambda\cos\theta)^{\epsilon+1}$. The solution of $\partial_\theta\ln P_s=0$ contains five possible roots in the interval $[-\pi,\pi]$: $\theta=0$, $\theta=\pm\pi$, and $\theta=\pm\arccos(-\epsilon/\lambda)$, which exist only if $\lambda>\epsilon$. As seen in Fig. 3(A), $P_s(\theta=\pm\pi)$ corresponds to global minima if $\lambda<\epsilon$, but become local maxima once $\lambda>\epsilon$, in which case the new global minima are located at $\theta=\pm\arccos(-\epsilon/\lambda)$. This change in extrema occurs at a critical point $\lambda_c=\epsilon$ (equivalent to $\sigma_\parallel^2=\beta$) where the direction-dependent noise becomes comparable to the magnitude of the restoring force. Direct numerical simulations of the full model described by Eq. (3) indicate that our analytical expression for $P_s(\theta)$ works well when SNR>3 and $\lambda<\epsilon$, justifying the Gaussian noise approximation.

As is common in the experimental literature, we can define an order parameter $\langle\cos\theta\rangle$, the chemotaxis index (CI), which is a measure of the directionality of the angular distribution. In Fig. 3(B), we plot the CI for different values of κ using our model. The dashed line in Fig. 3(B) corresponds to the CI with a value of κ that satisfies the critical condition $\lambda=\epsilon$ or equivalently $\kappa=2\lambda^2/(1-\lambda^2)$. To the right of this line the distribution shows a local maximum at $\pm\pi$. The slope of the CI is close to zero over a large range of values for λ. This can be understood by realizing that the negative effect of the heavy tails on the CI is partially compensated by the positive effect of a sharpened peak.

Next we look at the case of $b<1$. The corresponding stationary distribution is

$$P_s(\theta)=\frac{\Omega\exp\left[\kappa\frac{1-\lambda^2}{\lambda}\arctan(\lambda\cos\theta)\right]}{1+(\lambda\cos\theta)^2}, \tag{7}$$

with $\sigma_\perp^2=\sigma_0^2+(\sigma\beta')^2$ and $\sigma_\parallel^2=(\beta_{-1}^2-\beta'^2)\sigma^2$ in the definitions for κ and λ. The analysis proceeds as above and we only highlight the differences. The angle distribution exhibits not only heavy tails but also an obtuse peak for increasing values of λ [Fig. 3(C)]. This can be understood since in this case the noise in ψ, i.e., the second term in Eq. (4), dominates and reduces the accuracy in directionality. Due to the Gaussian approximation, the analytical probability distribution exhibits double peaks at $\theta=\pm\arccos(-\epsilon/\lambda)$ when $\lambda>\epsilon$ [20]. Also, the CI decays quickly with increasing λ even before the bifurcation [Fig. 3(D)], suggesting that cells should operate in a regime where $b\geq 1$. Finally, for $b=1$, the directional dependence in σ_{tot}^2 disappears and the stationary distribution reduces to the CN distribution with shape parameter $\tilde{\kappa}=2a\nu/(\sigma_0^2+a^2\sigma^2)$. Obviously, for larger values of the parameter a, the system is more sensitive to the gradient, and

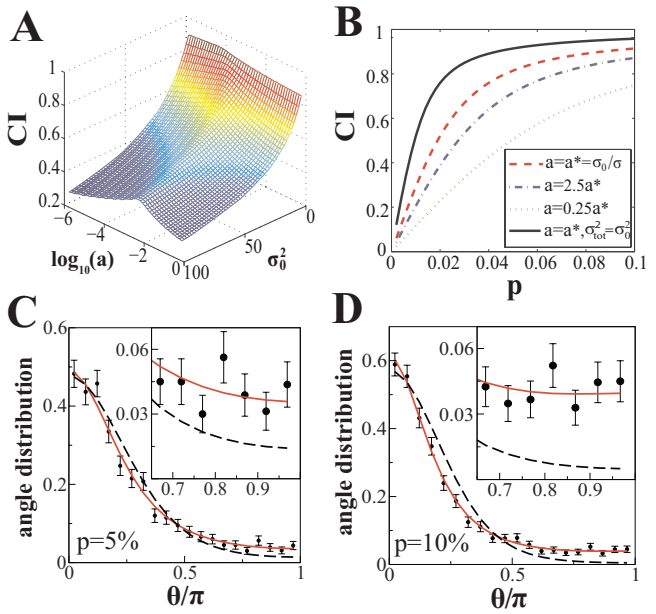

FIG. 4. (Color online) (A) CI maximized by choosing appropriate b for different values of a and σ_0^2, given $p=5\%$ and $C_0=K_d=30$ nM. (B) CI vs p for $C_0=K_d=30$ nM, $\sigma_0^2=2$, $b=1$, and $a=a^*$, $2.5a^*$, and $0.25a^*$. The solid line corresponds to a model neglecting receptor noise, i.e., $\sigma_{tot}^2=\sigma_0^2$. (C) Experimental direction distribution (symbols) for $p=5\%$, along with a fit using our model (solid line) and the CN distribution (dashed line). The error bars represent the standard deviation in the data set. The least-squares fitting parameters are $\lambda=0.5866$ and $\kappa=1.0222$. (D) Same as (C), but now for $p=10\%$ and with fitting parameters $\lambda=0.7566$ and $\kappa=1.8580$. The insets show the tails of the distributions.

more of the receptor noise is transmitted to the directional output.

For any given a and σ_0^2, there exists a unique value of b that maximizes the CI [Fig. 4(A)]. We found numerically that the combination of $a^*=\sigma_0/\sigma$ and $b^*=1$ optimizes the CI over the whole parameter space (a,b) given the level of σ_0. The optimal pair (a^*,b^*) corresponds to the ridge of the CI surface in Fig. 4(A). In summary, the exponent b is critical for the chemotactic responses. The optimal output requires $b=1$, while $b>1$ is suboptimal and $b<1$ leads to poor directionality. This can be understood by realizing that when the restoring force $\beta(\nu)$ is a nonlinear function (i.e., $b\neq 1$) of the receptor signal ν, the associated sensor noise is modulated to be direction dependent, which leads to heavy tails in the angle distribution (Fig. 3). In other words, there is a significant probability that cells may move in the wrong direction and the chemotactic performance is not optimal. An important implication of our model is that the CI is always lower than that predicted by models neglecting receptor noise [see Fig. 4(B)]. In fact, previous experimental data indicate that when the gradient steepness increases the saturating value of the CI is less than 1 [5,9]. This feature is not consistent with previous CN models but may be successfully explained by our $b>1$ model where the total noise σ_{tot}^2 becomes an increasing function of p.

We can compare our model to the results of recent experiments in which *Dictyostelium* cells were exposed to stable exponential chemoattractant profiles [4]. The data allow us to compute directional distributions for different gradient parameters. To eliminate the slight asymmetric bias introduced by the flow in the microfluidic chambers, we collected the data into 20 bins according to their absolute deviation from the gradient direction, $|\theta-\phi|$. The resulting distribution is shown as symbols for $p=5\%$ and $p=10\%$ in Figs. 4(C) and 4(D), respectively. We have also plotted as a solid line a least-squares fit to the data using our model [Eq. (6)]. Our fit captures well the heavy tails and the sharp peaks, features that the CN distribution—plotted as a dashed line—is unable to reproduce. A goodness of fit analysis using a Pearson's chi-square test revealed that the CN distribution is rejected at a significance level of less than 1%, while our model exhibits large p values [21]. The observed leptokurtic feature suggests that *Dictyostelium* cells are operating close to the optimal regime with the exponent b estimated as slightly larger than 1.

IV. DISCUSSION

A key assumption in our model is that the chemotaxing cell experiences a relatively stable gradient steepness ($p=$const) regardless of the cell's location or moving history. Thus, our model results can be directly compared to experiments in which the gradient is carefully quantified and controlled. If the gradient steepness is spatially varying, the chemotactic response would be heterogeneous in space, possibly obscuring the structure of the angular distribution.

Although we focus here on the role of receptor noise, it is easy to extend our model to include extra gradient-dependent fluctuations, by adding them to the magnitude of the restoring force $\beta(\rho)$. Such fluctuations might arise from noise in the downstream signal transduction pathways. Future work will track cells for longer periods of time and test for the presence of long-lived cell individuality and other fluctuations sources [22]. Should the data indicate such memory effects, our model could be extended to include quenched fluctuations in cell responses.

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