Physical Limits on Cellular Sensing of Spatial Gradients

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Many eukaryotic cells are able to detect chemical gradients by directly measuring spatial concentration differences. The precision of such gradient sensing is limited by fluctuations in the binding of diffusing particles to specific receptors on the cell surface. Here, we explore the physical limits of the spatial sensing mechanism by modeling the chemotactic cell as an Ising spin chain subject to a spatially varying field. Our results demonstrate that the accuracy to sense the gradient direction not only increases dramatically with the cell size but also can be improved significantly by introducing receptor cooperativity. Thus, receptor coupling may open the possibility for small bacteria to perform spatial measurements of gradients, as supported by a recent experimental finding.

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Cells often direct their motion under the guidance of chemical gradients. This is essential for critical biological functions including neuronal development, wound repair, and cancer spreading [1]. To detect gradients, small organisms like bacterial cells usually employ a temporal sensing strategy by measuring and comparing concentration signals over time along their swimming tracks [2]. In contrast, eukaryotic cells are sufficiently large to implement a spatial sensing mechanism, as they can measure the concentration differences across their cell bodies. Measurements for both strategies are accomplished by specific cell-surface receptors which diffusing chemical particles (ligands) can bind to. Spatial sensing among eukaryotes exhibits a remarkable sensitivity to gradients of merely 1%–2% across the cell [3–5]. Given the dynamic fluctuations in ligand-receptor interaction, the receptor signal is inherently noisy, as demonstrated by single-cell imaging experiments [6]. This naturally raises a question concerning the reliability of spatial gradient sensing.

In analyzing bacterial chemotaxis, Berg and Purcell showed that the minimal uncertainty of concentration sensing is set by the diffusion of ligand particles [7]. This work has been extended to include ligand-receptor binding effects and possible receptor cooperativity [8–13]. Instead of measuring the mean concentration, the spatial sensing program concerns the acquisition of information regarding the asymmetry in space (the gradient steepness and direction). Still, the accuracy of gradient measurements must be limited by physical laws governing ligand diffusion and stochastic receptor-ligand dynamics. Previous studies on gradient sensing limits are either based on idealized mechanisms in absence of kinetics [11], or restricted to one-dimensional simplifications in which sensing is a *discrete* choice [13], or rely on heuristic signal transduction models [14]. Thus, the precise attainable accuracy remains unknown for directional sensing. In this Letter, we address this problem more generally using a statistical mechanical approach, where we view the surface receptors as a (possibly coupled) spin chain and treat the chemical gradient as a perturbation field. By calculating the system's partition function, we are able to derive the gradient sensing limits both for independent receptors and for receptors exhibiting cooperativity. Our results indicate that the spatial sensing strategy may not be exclusive to large eukaryotic cells, but also be applicable to some small bacteria [15], especially with the aid of receptor cooperativity.

We consider a circular cell with diameter L immersed in a chemoattractant gradient (Fig. 1) and suppose that there are N receptors distributed at equally spaced intervals on the cell perimeter [16]. The angular coordinates of these receptors are indicated by $\varphi_n = 2\pi n/N$ for $n = 1, \ldots, N$. For analytical convenience, we assume that the gradient field takes an exponential profile, as was recently realized in experiments utilizing the social amoeba *Dictyostelium* [5,17]. The local concentration at the nth receptor is $C_n = C_0 \exp[\frac{p}{2}\cos(\varphi_n - \phi)]$, where C_0 is the background con-

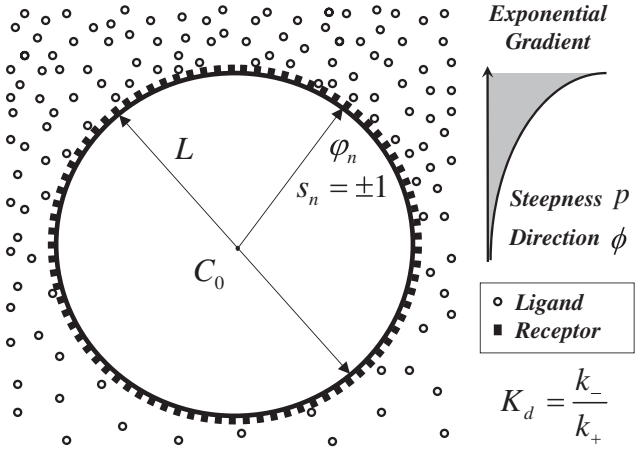

FIG. 1. Schematic representation of our model: a circular cell, covered with receptors, is placed in an exponential gradient. The forward and backward rates $k_\pm$ control the transition between the bound and unbound states for the receptors.

centration, p denotes the gradient steepness, and ϕ indicates the gradient direction. By its definition, $p \equiv \frac{L}{C_0}|\vec{\nabla}C|$ quantifies the percentage concentration change across the cell length L. Like a spin in physics, each receptor switches between two states: either active ($s_n = +1$) or inactive (-1). For independent receptors, a receptor is activated only if it is bound by a ligand and inactive otherwise. Let the energy associated with the state $s_n = +1$ (or -1) be $-\varepsilon_n$ (or $+\varepsilon_n$) in units of the thermal energy k_BT. Then the "on" probability of the nth spin is given by the Boltzmann distribution: $P_{\text{on}} = e^{\varepsilon_n}/(e^{\varepsilon_n} + e^{-\varepsilon_n})$. For simple receptor-ligand kinetics (Fig. 1), we have $P_{\text{on}} = C_n/(C_n + K_d)$ in chemical equilibrium where $K_d = k_-/k_+$ is the dissociation constant. Thus, the free energy is given by:

$$\varepsilon_n = \frac{1}{2}\ln\frac{C_n}{K_d} = \frac{1}{2}\ln\frac{C_0}{K_d} + \frac{p}{4}\cos(\varphi_n - \phi) \equiv \alpha_0 + h_n. \quad (1)$$

We define three statistical quantities $(z_0, z_1, z_2) \equiv (\sum_n s_n, \frac{1}{2}\sum_n s_n \cos\varphi_n, \frac{1}{2}\sum_n s_n \sin\varphi_n)$, where z_0 is a measure of the overall receptor activity and where z_1 and z_2 measure the asymmetry in the receptor states. Using the transformation $(\alpha_1, \alpha_2) \equiv (p\cos\phi, p\sin\phi)$, we can write the system's Hamiltonian as $\mathcal{H}_N\{s_n\} = -\sum_n \varepsilon_n s_n = -\alpha_0 z_0 - (\alpha_1 z_1 + \alpha_2 z_2)/2$ and compute its logarithm partition function as follows:

$$\ln\mathcal{Q}_N = \ln\prod_{n=1}^{N}(e^{\varepsilon_n} + e^{-\varepsilon_n}) = \sum_{n=1}^{N}\ln[2\cosh(\alpha_0 + h_n)]$$
$$= N\ln(2\cosh\alpha_0) + \frac{Np^2}{64\cosh^2\alpha_0} + \mathcal{O}(p^4), \quad (2)$$

where in the last step the summand is expanded in powers of p and the sum is replaced by an integral over $[0, 2\pi]$.

The partition function contains all the thermodynamic information we need to infer the gradient parameters p and ϕ, or alternatively, the transformed parameters α_1 and α_2. Since $p^2 = \alpha_1^2 + \alpha_2^2$, we have by Eq. (2):

$$E[z_{1,2}] = 2\frac{\partial\ln\mathcal{Q}_N}{\partial\alpha_{1,2}} = \frac{\alpha_{1,2}NC_0K_d}{4(C_0 + K_d)^2} + \mathcal{O}(p^3), \quad (3)$$

$$\text{Var}[z_{1,2}] = 4\frac{\partial^2\ln\mathcal{Q}_N}{\partial\alpha_{1,2}^2} = \frac{NC_0K_d}{2(C_0 + K_d)^2} + \mathcal{O}(p^2). \quad (4)$$

In addition, one can check that $\text{Cov}[z_1, z_2] = 0$. Thus, for small p, the joint probability density of z_1 and z_2 is

$$f(z_{1,2}|\alpha_{1,2}) \approx \frac{1}{2\pi\sigma^2}\exp\left[-\frac{(z_1 - \mu\alpha_1)^2 + (z_2 - \mu\alpha_2)^2}{2\sigma^2}\right],$$

with $\mu \equiv NC_0K_d/[4(C_0 + K_d)^2]$ and $\sigma^2 = 2\mu$ [17]. It is easy to show that the maximum likelihood estimator (MLE) [18] of $\alpha_{1,2}$ is $\hat{\alpha}_{1,2} = z_{1,2}/\mu$. As an orthogonal transformation, the MLEs of p and ϕ are given by $\hat{p} = \sqrt{\hat{\alpha}_1^2 + \hat{\alpha}_1^2} = \mu^{-1}\sqrt{z_1^2 + z_2^2}$ and $\hat{\phi} = \arctan(\hat{\alpha}_2/\hat{\alpha}_1) = \arctan(z_2/z_1)$, respectively. By the properties of the MLE, both $\hat{p}$ and $\hat{\phi}$ tend to be unbiased and normal in the large N limit, i.e., $\hat{p} \xrightarrow{d} \mathcal{N}(p, \sigma_p^2)$ and $\hat{\phi} \xrightarrow{d} \mathcal{N}(\phi, \sigma_\phi^2)$, where "$\xrightarrow{d}$" denotes convergence in distribution. The asymptotic variances σ_p^2 and σ_ϕ^2 can be derived from the Fisher information matrix [18], which is diagonal here since p and ϕ are independent. Thus, we have

$$\sigma_p^2 = 1/E[(\partial_p \ln f)^2] = \frac{\sigma^2}{\mu^2} = \frac{2}{\mu} = \frac{8(C_0 + K_d)^2}{NK_dC_0}, \quad (5)$$

$$\sigma_\phi^2 = 1/E[(\partial_\phi \ln f)^2] = \frac{\sigma^2}{\mu^2p^2} = \frac{2}{\mu p^2} = \frac{\sigma_p^2}{p^2}. \quad (6)$$

According to the Cramér-Rao inequality, σ_p^2 and σ_ϕ^2 set the lowest uncertainties of gradient measurements from an instantaneous sampling of the receptor states [18]. The analytical approximation of each variance is plotted as a function of the background concentration C_0 [Fig. 2(a)] and the gradient steepness p [Fig. 2(b)], which agrees well with the sample variance of $\hat{p}$ or $\hat{\phi}$ numerically obtained from our Monte Carlo simulations. We can see that both σ_p^2 and σ_ϕ^2 reach a minimum at $C_0 = K_d$ [Fig. 2(a)], while only the error in direction estimation depends on the gradient steepness (i.e., $\sigma_\phi^2 \sim p^{-2}$) as shown in Fig. 2(b). Since the gradient steepness increases with the cell size (i.e., $p \sim L$), larger cells are able to sense the gradient direction with higher accuracy.

The above results are derived from a single snapshot of the system. If the cell integrates receptor signals over some time interval $\mathcal{T}$, then averaging over multiple measurements can appreciably reduce the errors of gradient sensing. However, the capacity of such averaging is limited by the expected time it takes for every independent measurement. As shown in [4,9], the time to complete a single measurement is roughly twice the system's correlation time τ, resulting from the diffusion and binding of ligands. So the number of independent measurements that a cell can make within $\mathcal{T}$ is roughly $\mathcal{T}/(2\tau)$, which leads to a corresponding reduction of measurement uncertainties. The correlation time can be decomposed as $\tau = \tau_{\text{rec}} + \tau_{\text{diff}}$, where $\tau_{\text{rec}} = 1/(k_- + C_0k_+)$ is the time scale of receptor-ligand reaction and τ_{diff} describes the diffusive transport time of ligands. Let $\eta \equiv \tau_{\text{diff}}/\tau_{\text{rec}}$, then the measurement is reaction limited if $\eta \ll 1$ and diffusion limited if $\eta \gg 1$ [19]. From the above arguments we find that averaging signals over $\mathcal{T}$ yields a lower uncertainty,

$$\sigma_{p,\mathcal{T}}^2 \simeq \frac{2\tau}{\mathcal{T}}\sigma_p^2 = \frac{4\tau_{\text{rec}}(1+\eta)}{\mu\mathcal{T}} = \frac{16(1+\eta)}{N\mathcal{T}k_-}\left(1 + \frac{K_d}{C_0}\right). \quad (7)$$

For small background concentrations ($C_0 \ll K_d$), $\tau_{\text{diff}} = N/(2\pi LDK_d)$ where D denotes the ligand diffusion coefficient [7,9,19], and the uncertainty reduces to $\sigma_{p,\mathcal{T}}^2 \simeq 16/(N\mathcal{T}C_0k_+) + 8/(\pi\mathcal{T}DLC_0)$. This expression resembles the result derived for the one-dimensional case [13] and contains two terms: the first one is determined by the

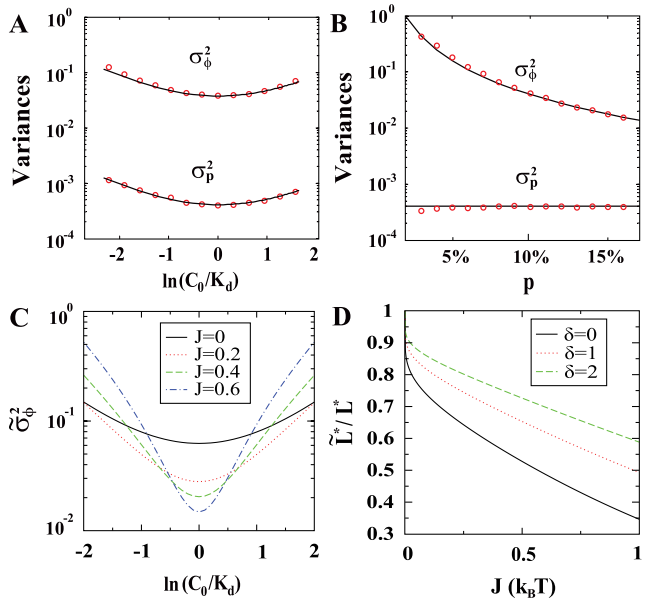

FIG. 2 (color online). (a) The uncertainties σ_p^2 and σ_ϕ^2 versus $\ln(C_0/K_d)$ under a gradient of steepness $p = 10\%$; (b) σ_p^2 and σ_ϕ^2 versus p for fixed background concentrations $C_0 = K_d$. In both (a) and (b), the solid lines represent our analytical expressions while the symbols correspond to the sample variances of $\hat{p}$ and $\hat{\phi}$ computed based on 5000 independent Monte Carlo realizations of 80 000 receptors. (c) $\tilde{\sigma}_\phi^2$ as a function of $\ln(C_0/K_d)$ for different values of the cooperativity strength J, under a gradient of steepness $p = 8\%$ and using $N = 80\,000$. (d) The critical cell size below which spatial gradient sensing is ineffective, normalized by the critical cell size in the absence of cooperativity, as a function of J.

chemical kinetics, and the second one, up to a geometric constant, is exactly the Berg-Purcell limit [7,11]. We shall have similar results for the direction inference, since $\sigma_{\phi,\mathcal{T}}^2 = \sigma_{p,\mathcal{T}}^2/p^2$. For typical eukaryotic cells, it has been estimated [9,19] that $\eta \ll 1$, which implies $\sigma_{\phi,\mathcal{T}}^2 \simeq 16(1 + K_d/C_0)/(Np^2\mathcal{T}k_-) \sim 1/(Np^2)$. Assuming that the number of receptors in our model scales with the cell size as $N = N_0 L^\delta$ with $0 \le \delta \le 2$, we find $\sigma_{\phi,\mathcal{T}}^2 \sim L^{-(2+\delta)}$. For comparison, the Berg-Purcell analysis considered only the mean concentration measurement, with a limit that scales as $\sigma_{c,\mathcal{T}}^2 \sim L^{-1}$ [7]. Our results thus indicate that directional sensing is much more sensitive to the cell size.

Our analysis above, which extends beyond the Berg-Purcell framework by providing a direct calculation of the directional sensing limit $\sigma_{\phi,\mathcal{T}}^2$, was carried out for independent (i.e., noncooperative) receptors, as is assumed to be the case for most eukaryotic cells that have been studied. It has been proposed that cooperativity can dampen the fluctuations in receptor signals and thus help concentration sensing to approach the physical limit of diffusive counting noise [10]. For spatial gradient sensing, we now ask about possible effects of receptor cooperativity as has been found in many bacterial cells [20–22]. Intuitively, short-range interactions make it possible for receptors to collectively respond and sharpen the asymmetry of receptor signals. It is natural to speculate that such enhanced sensitivity may set new and lower limits for directional sensing. To incorporate potential receptor cooperativity, we extend our model to include a nearest-neighbor interaction J (again, in units of k_BT). Now, the activity of a receptor, still represented by s_n, is determined not only by the local concentration but also by the states of its neighboring receptors. This means that an unbound receptor is not necessarily inactive, as it may have been affected by active receptors nearby.

Because the local concentration is identical for nearest-neighbor sites (i.e., $\varepsilon_n = \varepsilon_{n\pm1}$), the Hamiltonian of our Ising chain can be written in a symmetric form: $\tilde{\mathcal{H}}_N\{s_n\} = -\sum_{n=1}^{N}[Js_ns_{n+1} + \varepsilon_n(s_n + s_{n+1})/2]$, with the boundary condition $s_{N+1} = s_1$. The corresponding partition function is $\tilde{\mathcal{Q}}_N = \sum_{s_1}\cdots\sum_{s_N} e^{-(H_0+H_1)}$, where $H_0 \equiv -\sum_n[Js_ns_{n+1} + \alpha_0(s_n + s_{n+1})/2]$ represents the Hamiltonian of an isotropic reference system and where $H_1 \equiv -\sum_n s_n h_n = -\frac{p}{4}\sum_n s_n \cos(\varphi_n - \phi)$ results from the spatial heterogeneity in concentration. For small p, one can view H_1 as a perturbation to H_0. The partition function of the reference system, $\tilde{\mathcal{Q}}_N^{(0)} = \sum_{s_1}\cdots\sum_{s_N} e^{-H_0}$, is well known and exactly solvable by the transfer matrix method: $\tilde{\mathcal{Q}}_N^{(0)} = \lambda_+^N + \lambda_-^N$, with $\lambda_\pm = e^J\cosh\alpha_0 \pm \sqrt{e^{-2J} + e^{2J}\sinh^2\alpha_0}$ (see the supplementary material [23] for details). Thus, $\ln\tilde{\mathcal{Q}}_N^{(0)} \simeq N\ln\lambda_+$. The statistical perturbation theory inspires us to write $\tilde{\mathcal{Q}}_N = \tilde{\mathcal{Q}}_N^{(0)}\sum_{s_1}\cdots\sum_{s_N} e^{-H_0}e^{-H_1}/\tilde{\mathcal{Q}}_N^{(0)} = \tilde{\mathcal{Q}}_N^{(0)}\langle e^{-H_1}\rangle \simeq \lambda_+^N[1 + \frac{p}{4}\sum_n\langle s_n\rangle\cos\theta_n + \frac{p^2}{32}\sum_{n,m}\langle s_ns_m\rangle\cos\theta_n\cos\theta_m]$, where we denote $\theta_n \equiv \varphi_n - \phi$ for short and use $\langle\cdots\rangle$ to represent the expectation over the reference system. Because of isotropy, $\langle s_n\rangle$ is independent of its location (index n) and hence $\sum_n\langle s_n\rangle\cos\theta_n = \langle s_n\rangle\sum_n\cos\theta_n = 0$. With details provided in the supplementary material [23], we further calculate that $\sum_{n,m}\langle s_ns_m\rangle\cos\theta_n\cos\theta_m = \frac{N}{2}(1 + 2\xi)/(1 + e^{4J}\sinh^2\alpha_0)$, where $\xi \equiv [\ln(\lambda_+/\lambda_-)]^{-1}$ defines the correlation length of the classic Ising chain. Finally, the log-partition function of our model is found to be

$$\ln\widetilde{\mathcal{Q}}_N \simeq N\ln\lambda_+ + \frac{Np^2(1 + 2\xi)}{64(1 + e^{4J}\sinh^2\alpha_0)} + \mathcal{O}(p^3), \quad (8)$$

which reduces to Eq. (2) as $J \to 0$. Now we rewrite $\tilde{\mathcal{H}}_N = -J\sum_n s_ns_{n+1} - \alpha_0 z_0 - (\alpha_1 z_1 + \alpha_2 z_2)/2$, with the same notations for α_i and z_i, $i = 0, 1, 2$. As has been demonstrated before, the MLEs of α_1 and α_2 can be found from the joint Gaussian distribution of z_1 and z_2, except now we have to replace μ by $\tilde{\mu} \equiv \frac{1}{16}N(1 + 2\xi)/(1 + e^{4J}\sinh^2\alpha_0)$. So the MLEs of p and ϕ are given by $\tilde{p} = \tilde{\mu}^{-1}\sqrt{z_1^2 + z_2^2} \xrightarrow{d} \mathcal{N}(p, \tilde{\sigma}_p^2)$ and $\tilde{\phi} = \arctan(z_2/z_1) \xrightarrow{d} \mathcal{N}(\phi, \tilde{\sigma}_\phi^2)$. Similar

to Eqs. (5) and (6), their variances are $\tilde{\sigma}_p^2 = 2/\tilde{\mu}$ and $\tilde{\sigma}_\phi^2 = \tilde{\sigma}_p^2/p^2 = 2/(\tilde{\mu}p^2)$ [24]. We plot $\tilde{\sigma}_\phi^2$ as a function of $\ln(C_0/K_d)$ for different values of J in Fig. 2(c). Regardless of the receptor coupling strength, this error is minimal at $C_0 = K_d$ (or $\alpha_0 = 0$) where the correlation length becomes $\xi = 1/\ln(\coth J) \simeq \frac{1}{2}e^{2J}$ and $\tilde{\sigma}_\phi^2 \simeq 32/[Np^2(1 + e^{2J})] = \sigma_\phi^2/(1 + e^{2J})$.

Receptor cooperativity may help a smaller cell of diameter $\tilde{L}$ to reach the same level of directional sensing accuracy as achieved by a larger cell with diameter L but noncooperative receptors, i.e., $\tilde{\sigma}_\phi^2(\tilde{L}) = \sigma_\phi^2(L)$. By our previous scaling assumption, the receptor number of the smaller cell is $\tilde{N} = N(\tilde{L}/L)^\delta$. If L^* denotes a critical cell length below which spatial sensing is infeasible with independent receptors, then adding cooperativity will result in a smaller critical size, given by $\tilde{L}^* \simeq L^*(1 + e^{2J})^{-1/(2+\delta)}$ at $C_0 = K_d$. This is shown in Fig. 2(d) where we have plotted $\tilde{L}^*/L^*$ as a function of J for three different values of the scaling factor δ. As a specific example, we take $L^* = 8\ \mu$m which corresponds to the typical size of a *Dictyostelium* amoeba. For $J = 0.5$, the new critical cell length becomes $\tilde{L}^* \sim 4$–$6\ \mu$m, comparable to the size of many bacterial cells. It is worth remarking that although receptor interaction improves the precision of gradient sensing for C_0 close to K_d, it enlarges the errors when C_0 is far away from K_d [Fig. 2(c)]. Note that the receptor configuration tends to be homogeneous in both the large and small concentration extremes; i.e., it is dominated either by active receptors at $C_0 \gg K_d$ or by inactive receptors at $C_0 \ll K_d$. Cooperativity exaggerates such a tendency to reach an ordered phase, an effect which interferes with the cell's ability to extract information about the spatial heterogeneity from receptor states. Therefore, the improved accuracy at C_0 near K_d is accompanied by a narrowed range of background concentrations for which the cell can be sufficiently sensitive [Fig. 2(c)]. Such a tradeoff could be a limiting factor for the introduction of receptor coupling into the spatial sensing mechanism.

It is commonly believed that prokaryotic cells such as *E. coli* are too small to perform spatial measurements of chemical gradients. However, recent experimental observations show that at least one type of vibrioid bacteria (typical size $2 \times 6\ \mu$m) are able to spatially sense gradients along distances as short as $5\ \mu$m, and the proposed sensing system has two bipolar sensor regions containing receptor clusters [15]. Our calculations allow for the possibility that smaller organisms could employ the spatial sensing strategy with the aid of short-range receptor interactions. As spatial sensing is argued to be superior to temporal sensing for fast swimming bacteria [15,25], this possibility is of significant theoretical interest and remains a challenge for future empirical studies.

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