



Limits of Sensing Temporal Concentration Changes by Single Cells

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Berg and Purcell [Biophys. J. **20**, 193 (1977)] calculated how the accuracy of concentration sensing by single-celled organisms is limited by noise from the small number of counted molecules. Here we generalize their results to the sensing of concentration ramps, which is often the biologically relevant situation (e.g., during bacterial chemotaxis). We calculate lower bounds on the uncertainty of ramp sensing by three measurement devices: a single receptor, an absorbing sphere, and a monitoring sphere. We contrast two strategies, simple linear regression of the input signal versus maximum likelihood estimation, and show that the latter can be twice as accurate as the former. Finally, we consider biological implementations of these two strategies, and identify possible signatures that maximum likelihood estimation is implemented by real biological systems.

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Cells are able to sense concentration gradients with high accuracy. Large eukaryotic cells such as the amoeba *Dictyostelium discoideum* and the budding yeast *Saccharomyces cerevisiae* can sense very shallow spatial gradients by comparing concentrations across their lengths [1]. By contrast, small motile bacteria such as *Escherichia coli* detect spatial gradients indirectly by measuring concentration ramps (temporal concentration changes) as they swim [2], and can respond to concentrations as low as 3.2 nM—about three molecules per cell volume [3]. The noise arising from the small number of detected molecules sets a fundamental physical limit on the accuracy of concentration sensing, as originally shown in the seminal work of Berg and Purcell [4,5]. This approach was recently extended to derive a fundamental bound on the accuracy of direct spatial gradient sensing [6]. However, no theory exists for the physical limit of ramp sensing, which is what bacteria actually do when they chemotact. In this Letter, we present such a theory for different measurement devices, from a single receptor to an entire cell. We contrast two strategies: linear regression (LR) of the input signal (in line with Berg and Purcell) and maximum likelihood estimation (MLE) [7,8], a method from statistics to optimally fit a model to data, revealing an up to twofold advantage for the latter. Finally, we introduce a biochemical signaling network, similar to the *E. coli* chemotaxis system, that outputs an estimate of the ramp rate. Consistent with the derived theoretical bounds, we find that a mechanism emulating MLE yields twofold higher accuracy than one emulating LR. However, this improved performance has a cost: either storage of signaling proteins near the receptors or irreversibility of the receptor cycle with concomitant energy consumption.

Sensing small numbers of molecules implies relative noise $\sim n^{-1/2}$, where n is the number of detected mole-

cules. Berg and Purcell (BP) calculated how this noise affects the accuracy of concentration sensing [4]. They considered three types of measurement devices: a single receptor, a perfectly absorbing sphere, and a perfectly monitoring sphere. Following their approach, we investigate ramp sensing by these three devices when presented with a concentration $c(t) = c_0 + c_1 t$, as schematized in Fig. 1.

A single receptor [Fig. 1(a)] binds particles at rate $k_+ c(t)$ and unbinds them at rate k_- . Following BP, we assume that

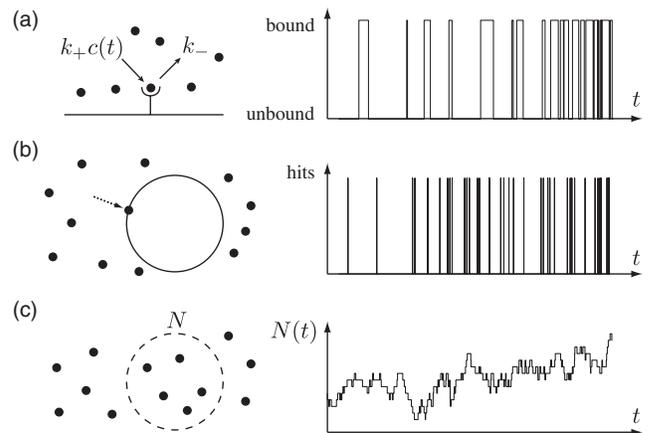


FIG. 1. Schematic of measurement devices and corresponding time traces for linearly increasing concentration $c(t) = c_0 + c_1 t$. (a) Left: a single receptor binds a particle at rate $k_+ c(t)$, and releases it at rate k_- . Right: the binary time series of receptor occupancy is depicted as a telegraph process. (b) Left: particles are incident on an absorbing sphere with average flux $4\pi D a c(t)$. Right: sequence of times when a particle hits the sphere. (c) Left: a monitoring sphere counts the number of particles inside its volume without hindering their diffusion. Right: number $N(t)$ of particles inside the sphere as a function of time.

diffusion is fast enough that the receptor never rebinds the same particle. An ideal observer has access to the binary time series $s(t)$ of receptor occupancy between $-T/2$ and $T/2$, which can be described by a telegraph process. The lengths of bound and unbound intervals have exponential distributions with means $1/k_-$ and $1/k_+c$, respectively. Throughout, we assume that the ramp is shallow, $c_1T \ll c_0$, and that the observation time is long compared to receptor kinetics, $T \gg 1/k_-, 1/k_+c$. In BP, the true concentration c is estimated from the fraction of time the receptor is bound, $\bar{s} = \frac{1}{T} \int_{-T/2}^{T/2} dt s(t)$, which is equal to the equilibrium occupancy in the limit of large times (but with $c_1T \ll c_0$):

$$\bar{s} \approx \langle s \rangle = k_+c / (k_- + k_+c), \quad (1)$$

where $\langle \cdot \rangle$ represents an ensemble average. Following a similar strategy, we can estimate the ramp rate by performing the linear regression of $s(t)$ to $s_0 + s_1t$:

$$s_0 = \frac{1}{T} \int_{-T/2}^{T/2} dt s(t), \quad s_1 = \frac{12}{T^3} \int_{-T/2}^{T/2} dt ts(t), \quad (2)$$

from which the concentration and the ramp rate are estimated using (1) as

$$c_0^{\text{LR}} := \frac{k_-}{k_+} \frac{s_0}{1 - s_0}, \quad c_1^{\text{LR}} := c_0^{\text{LR}} \frac{s_1}{s_0(1 - s_0)}. \quad (3)$$

The uncertainties of these estimates can be calculated from the time correlations of receptor occupancy [9], yielding

$$\frac{\langle (\delta c_0^{\text{LR}})^2 \rangle}{c_0^2} = \frac{2}{n}, \quad \frac{\langle (\delta c_1^{\text{LR}})^2 \rangle}{(c_0/T)^2} = \frac{24}{n}, \quad (4)$$

where n is the total number of binding events in the time T . Note that the result for c_0 is precisely that of BP [4,8].

In [8], it was shown that the accuracy of concentration sensing could be improved using maximum likelihood estimation. In this scheme, the parameters of the model are chosen to maximize the probability (“likelihood”) that the observed data were generated by the model. Can we also improve the accuracy of ramp sensing over LR by using this method? The time trace $s(t)$ can be characterized by the series of binding (t_i^+) and subsequent unbinding (t_i^-) times, $i = 1, \dots, n$. The likelihood of the data within our model is [8]

$$P = e^{-k_-T_b} e^{-k_+ \sum_i \int_{t_i^-}^{t_i^+} dt c(t)} k_-^n \prod_{i=1}^n k_+ c(t_i^+), \quad (5)$$

where T_b is the *total* bound time over time T . The concentration and the ramp rate, c_0 and c_1 , are the model parameters. Given the times of the events, the likelihood is maximized with respect to c_0 and c_1 by solving $\partial P / \partial c_0 = 0$ and $\partial P / \partial c_1 = 0$, from which the maximum likelihood estimate ($c_0^{\text{MLE}}, c_1^{\text{MLE}}$) is obtained. In general, these equations have no simple solution, but we can obtain the average behavior by exploiting the fact that binding and unbinding are fast with respect to concentration changes, i.e., that the receptor remains adiabatically in equilibrium with the concentration $c(t)$. We can thus simplify the sum

and product in (5):

$$\sum_{i=1}^n \int_{t_i^-}^{t_i^+} dt c(t) \approx \int_{-T/2}^{T/2} dt [1 - \langle s(t) \rangle] c(t), \quad (6)$$

$$\sum_{i=1}^n \log c(t_i^+) \approx \int_{-T/2}^{T/2} dt k_- \langle s(t) \rangle \log c(t), \quad (7)$$

where $\langle s(t) \rangle$ is the equilibrium occupancy at time t , given by (1) with $c = \tilde{c}_0 + \tilde{c}_1t$, where \tilde{c}_0 and \tilde{c}_1 are the *true* parameters that generated the data. Applying this approximation to $\partial P / \partial c_0, \partial P / \partial c_1$, we confirm that $c_0^{\text{MLE}} = \tilde{c}_0$ and $c_1^{\text{MLE}} = \tilde{c}_1$ for $T \rightarrow \infty$ [9]. For finite times, the errors in $c_0^{\text{MLE}}, c_1^{\text{MLE}}$ can be estimated by the Cramér-Rao bound [10], which states that the variance of parameter estimates exceeds the inverse of the Fisher information, and approaches equality in the limit of long time series:

$$\langle \delta \mathbf{c}^T \delta \mathbf{c} \rangle \geq -[\partial_{\mathbf{c}}^T \partial_{\mathbf{c}} \log P]^{-1}, \quad (8)$$

where $\delta \mathbf{c} = (c_0^{\text{MLE}} - \tilde{c}_0, c_1^{\text{MLE}} - \tilde{c}_1)$ and $\partial_{\mathbf{c}} = (\partial / \partial c_0, \partial / \partial c_1)$. Again we can use the adiabatic approximation to compute the Hessian of the log-likelihood on the right-hand side of (8), to obtain

$$\frac{\langle (\delta c_0^{\text{MLE}})^2 \rangle}{c_0^2} = \frac{1}{n}, \quad \frac{\langle (\delta c_1^{\text{MLE}})^2 \rangle}{(c_0/T)^2} = \frac{12}{n}. \quad (9)$$

These variances are half the ones obtained from LR (4). The first result for constant concentrations is that of [8]. As observed there, the LR estimate weighs bound and unbound intervals equally and adds the uncertainties from both. In contrast, the maximum likelihood estimate relies only on unbound interval durations since these carry all the information about the concentration. Furthermore, LR requires finite bound intervals, during which the receptor is blocked and cannot serve as a detector, while in MLE, particles can be released instantly.

We now turn to ramp sensing by an entire cell, starting with the case of an idealized absorbing sphere [Fig. 1(b)]. An ideal observer witnesses a time series of absorption events, described by the instantaneous current $I(t) = \sum_{i=1}^n \delta(t - t_i)$, where $\delta(t)$ is the Dirac delta function and $\{t_i\}$ are the absorption times. The average current of molecules impinging on the sphere is given by $\langle I(t) \rangle = 4\pi D a c(t)$, where D is the diffusivity, a the sphere radius, and $c(t)$ the concentration far from the sphere [4]. Applying the same methods used for the single receptor, we calculated the uncertainty of ramp sensing for linear regression of $I(t)$ as well as for MLE [9]. We found no difference between the two strategies, which both yield the same uncertainties as in (9), with n now the total number of molecules absorbed during time T : $n \approx 4\pi D a c_0 T$. For a monitoring sphere [Fig. 1(c)], molecules are free to diffuse into and out of the sphere, and the observer records the number $N(t)$ of particles inside the sphere as a function of time. On average, this number is $\langle N(t) \rangle = (4/3)\pi a^3 c(t)$. Performing a linear regression of $N(t)$ to $N_0 + N_1t$, one can estimate the concentration and the ramp rate through $c_0^{\text{LR}} := 3N_0/4\pi a^3$ and $c_1^{\text{LR}} := 3N_1/4\pi a^3$. Following [4],

the uncertainty of these estimates can be calculated from the time autocorrelation of $N(t)$ [9], yielding

$$\frac{\langle(\delta c_0)^2\rangle}{c_0^2} = \frac{3}{5\pi Dac_0T}, \quad \frac{\langle(\delta c_1)^2\rangle}{(c_0/T)^2} = \frac{36}{5\pi Dac_0T}. \quad (10)$$

The first result was obtained in [4]. Maximum likelihood is difficult to implement in the context of the monitoring sphere because it requires a sum over all possible histories of particles exiting and returning to the sphere. Thus, whether the LR result can be improved upon remains an open question.

Maximum likelihood estimation is in general the optimal way to sense ramps and provides a twofold improvement over simple linear regression in the case of the single receptor. Could MLE be implemented in biological systems? To address this question, we now introduce a simple, deterministic biochemical network (Fig. 2) that can approach the optimal performance limit set by MLE. The same network implements either LR or MLE depending on the receptor signaling mechanism: LR is implemented if each receptor signals continuously while a particle is bound; MLE is implemented if each receptor signals with a fixed-size burst upon binding a particle, and then releases the particle rapidly. The first case corresponds to integrating the fraction of time the receptor is bound, while the second corresponds to counting binding events. Accordingly, we will show that the shot noise (Poisson noise) due to the stochastic nature of binding and unbinding is twice as large in the first case as in the second. Let $u(t)$ be the receptor activity: for continuous signaling, this activity is simply proportional to receptor occupancy: $u(t) = \alpha s(t)$,

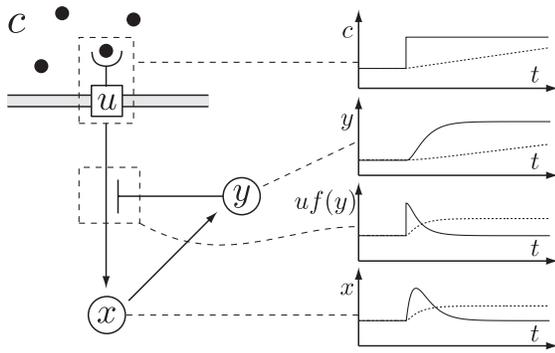


FIG. 2. Biochemical network for measuring concentration ramps. Binding of ligand to the receptor increases its activity u and causes species x to be produced. This production is downregulated by a feedback factor y which is itself catalyzed by x . Right: average network response to a step function in the concentration, $c(t) = c_0 + \Delta c\theta(t - t_0)$ (solid curves) and to a ramp, $c(t) = c_0 + c_1(t - t_0)\theta(t - t_0)$ (dotted curves). In response to the step function, the network adapts precisely and x decays back to its original value after an initial increase. In response to a ramp, x shifts by an amount proportional to the ramp rate. The quantitative ability of the network to sense such ramps depends on whether receptors signal continuously or in a discrete burst upon ligand binding.

whereas for burst signaling, $u(t)$ is a series of fixed-size bursts at the times of binding: $u(t) = \beta \sum_i^n \delta(t - t_i^+)$. Without loss of generality, we set $\alpha = k_-$ and $\beta = 1$ so that $\langle u(t) \rangle$ is equal to the mean rate of binding events in both cases, $\langle u(t) \rangle = k_- k_+ c(t) / [k_- + k_+ c(t)]$. For averaging times much longer than $1/k_-$ and $1/k_+ c$, we can approximate the fluctuations of $u(t)$ by Gaussian white noise, $u(t) = \langle u(t) \rangle + \delta u(t)$, where $\langle \delta u(t) \delta u(t') \rangle = g \langle u(t) \rangle \delta(t - t') / [1 + k_+ c(t) / k_-]^2$, with $g = 2$ for continuous signaling, and $g = 1 + (k_+ c / k_-)^2$ for fixed-size burst signaling [9]. For rapid unbinding, $k_- \rightarrow +\infty$, we recover the same twofold difference as between (4) and (9), and for the same reason: in the case of continuous signaling, noise from the stochasticity of bound intervals adds to the noise from random arrivals.

To extract the ramp rate from receptor activity requires a network that “takes the derivative” of its input signal. An example is the *E. coli* chemotaxis system, which relies on precise adaptation via integral feedback [11]. A minimal deterministic version of such a network is schematized in Fig. 2 and described by the following differential equations:

$$\frac{dx}{dt} = k_x [uf(y) - x], \quad \frac{dy}{dt} = k_y (x - 1), \quad (11)$$

where for simplicity $u(t)$ is the activity of a single receptor and x is the concentration of signaling molecules it produces. $f(y)$ is a monotonically decreasing function regulating the production of x . The role of y is similar to that of the receptor methylation level in *E. coli*: y precisely adapts the production rate of signaling molecules so that the steady-state value of x does not depend on the external ligand concentration. This property is illustrated by the graphs on the right side of Fig. 2, which show how the network responds to a sudden change in ligand concentration (solid curves). While the network output x is insensitive to the absolute concentration, it responds to steady ramps (dotted curves). When the input varies slowly in time, $\langle u(t) \rangle = u_0 + u_1 t$ (with $u_1 \ll u_0 k_x, u_0 k_y$), the system responds by shifting x away from 1 so that the change in $y(t)$ tracks the change in $u(t)$:

$$\langle x(t) \rangle = 1 + \gamma \frac{u_1}{k_y u_0}, \quad \langle y(t) \rangle = y_0 - \gamma^2 \frac{u_1}{k_y u_0} - \gamma \frac{u_1}{u_0} t, \quad (12)$$

with $u_0 f(y_0) = 1$ and $\gamma = -f(y_0) / f'(y_0)$. Thus, y provides a readout of the absolute concentration to leading order via $u_0 = 1/f(y)$, and x provides a readout of the ramp rate through $u_1 = k_y u_0 (x - 1) / \gamma$. The accuracy of these readouts is limited by the ligand binding shot noise $\delta u(t)$. The effect of noise can be calculated by expanding the solution of (11) linearly around its average [9]:

$$\begin{bmatrix} \delta x(t) \\ \delta y(t) \end{bmatrix} := \begin{bmatrix} x(t) - \langle x(t) \rangle \\ y(t) - \langle y(t) \rangle \end{bmatrix} = \int_{-\infty}^t dt' \mathbf{K}(t - t') \delta u(t')$$

with $\mathbf{K}(t) = \frac{k_x}{u_0} e^{-k_x t/2} \begin{bmatrix} \cosh(\omega t) - \frac{k_x}{2\omega} \sinh(\omega t) \\ \frac{k_y}{\omega} \sinh(\omega t) \end{bmatrix}$,

where $\omega^2 = k_x^2/4 - k_x k_y/\gamma$ (ω can be imaginary). From (12), we deduce the uncertainties of c_0 and c_1 :

$$\frac{\langle(\delta c_0)^2\rangle}{c_0^2} = \frac{gk_y/\gamma}{2u_0}, \quad \frac{\langle(\delta c_1)^2\rangle}{(c_0 k_y/\gamma)^2} = \frac{gk_x}{2u_0}. \quad (13)$$

For a fixed k_y , the optimal value of k_x is the smallest one with a nonoscillating response kernel $\mathbf{K}(t)$: $k_x = 4k_y/\gamma$. Systems with oscillating kernels are undesirable because they detect oscillations rather than ramps. For $k_x = 4k_y/\gamma$, our results are consistent with those of Eqs. (4) and (9), namely, uncertainties inversely proportional to the number of binding events, if we interpret $\gamma/k_y \rightarrow T$ as the effective time of measurement and u_0 as the rate of binding events. The factor g reflects the difference between the two mechanisms of receptor signaling.

Despite its simplicity, our biochemical model may help analyze features of real biological systems. There are two separate aspects to the model: on the input side, different mechanisms of receptor signaling—continuous signaling (LR) versus burst signaling (MLE)—affect readout accuracy; on the output side, integral feedback provides a natural readout for sensing ramps.

Many receptors, including the well-studied chemotaxis receptors of *E. coli*, signal continuously rather than in bursts, and therefore do not employ MLE. In practice, how could cells implement MLE? Receptors could signal continuously following a binding event but with a narrowly peaked distribution of durations. Our results can easily be extended to an arbitrary distribution of bound interval durations τ_b , yielding $g = 1 + \langle(\delta\tau_b)^2\rangle/\langle\tau_b\rangle^2$ [9]: the more peaked the distribution of τ_b , the less noisy the readout. For equilibrium binding or unbinding, we find $g \geq 2$ [9], with an irreversible binding cycle driven by energy dissipation required to achieve $g < 2$. Interestingly, there are examples of such irreversible cycles in ligand-gated ion channels [12], where ions play the role of our output signal x . In these ion channels, peaked open-time distributions are interpreted as evidence that time reversibility is broken and energy is being consumed [13]. We speculate that the role of this irreversibility may be to reduce the variance of bursts, thereby increasing the accuracy of concentration or ramp sensing. Relatedly, a multiplicity of irreversible steps in rhodopsin signaling has been shown to explain the reproducibility of single-photon responses in rod cells [14].

As for the mechanism of ramp sensing, the integral feedback system underlying *E. coli* chemotaxis is similar to our simple model. However, the receptor methylation level, which plays the same role as y in our model, adjusts the binding/unbinding rates k_+/k_- so that $k_- \approx k_+c$, rather than adjusting the production rate $k_x f(y)u$ as in (11). In *E. coli*, receptors increase their gain by responding cooperatively [15], and $k_- \approx k_+c$ is required to maximize this gain, which precludes the limit $k_- \ll k_+c$ required for

MLE. Moreover, k_+ is physically limited by diffusion and receptor size, and should optimally be kept near the diffusion limit to maximize the number of binding events. It is worth noting that in *E. coli*, the methylation and demethylation processes responsible for integral feedback are themselves subject to noise, giving rise to additional, dominant fluctuations [16]. For a receptor signaling in bursts, integral feedback could act by adjusting the number of released molecules upon binding if the receptor stores molecules, or the mean bound duration $\langle\tau_b\rangle$ if signaling is continuous, or the channel conductivity in ligand-gated ion channels. We hope that our analysis will suggest experiments for testing these scenarios.

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