

Physical limits to biochemical signaling

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Abstract

Many crucial biological processes operate with surprisingly small numbers of molecules, and there is renewed interest in analyzing the impact of noise associated with these small numbers. Twenty-five years ago, Berg and Purcell showed that bacterial chemotaxis, where a single celled organism must respond to small changes in concentration of chemicals outside the cell, is limited directly by molecule counting noise, and that aspects of the bacteria's behavioral and computational strategies must be chosen to minimize the effects of this noise [1]. Here we revisit and generalize their arguments to estimate the physical limits to signaling processes within the cell, and argue that recent experiments are consistent with performance approaching these limits.

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I. INTRODUCTION

A striking fact about biological systems is that single molecular events can have macroscopic consequences. The most famous example is of course the storage of genetic information in a single molecule of DNA, so that changes in the structure of this single molecule (mutations) can have effects on animal behavior and body plan from generation to generation [2]. But there also are examples where the dynamics of individual molecular interactions can influence behavior on much shorter time scales. Thus we (and other animals) can see when a single molecule of rhodopsin in the rod cells of the retina absorbs a photon [3], and some animals can smell a single molecule of airborne odorant [4]. Even if a single molecular event does not generate a specific behavior, it may still be that the reliability of behavior is limited by inevitable fluctuations associated with counting random molecular events. Thus the visual system has a regime where perception is limited by photon shot noise [5,6], and the reliability with which bacteria can swim up a chemical gradient appears to be limited by noise in the measurement of the gradient itself [1]. It is an open question whether biochemical signaling systems within cells operate close to the corresponding counting noise limits.

The classical analysis of bacterial chemotaxis by Berg and Purcell provided a simple estimate and a clear intuitive picture of the noise in ‘measuring’ chemical concentrations. Their argument was that if we have a sensor with linear dimensions a , we expect to count an average of $\bar{N} \sim \bar{c}a^3$ molecules when the mean concentration is \bar{c} . Each such measurement, however, is associated with a noise $\delta N_1 \sim \sqrt{\bar{N}}$. A volume with linear dimension a can be cleared by diffusion in a time $\tau_D \sim a^2/D$, so if we are willing to integrate over a time τ we should be able to make $N_{\text{meas}} \sim \tau/\tau_D$ independent measurements, reducing the noise in our estimate of N by a factor of $\sqrt{N_{\text{meas}}}$. The result is that our fractional accuracy in measuring N , and hence in measuring the concentration c itself, is given by

$$\frac{\delta c}{\bar{c}} = \frac{\delta N}{\bar{N}} = \frac{1}{\sqrt{\bar{N}N_{\text{meas}}}} = \frac{1}{\sqrt{Da\bar{c}\tau}}. \quad (1)$$

A crucial claim of Berg and Purcell is that this result applies when the sensor is a single receptor molecule, so that a is of molecular dimensions, as well as when the sensor is the whole cell, so that $a \sim 1 \mu\text{m}$. In particular, imagine a cell of radius R which has receptor molecules of size a on its surface. With just one receptor the limiting concentration resolution must be $\delta c/c \sim (Da\bar{c}\tau)^{-1/2}$, and if N_r receptors are distributed sparsely over the cell surface we expect that they provide independent measurements, improving the resolution to $\delta c/c \sim (DN_r a\bar{c}\tau)^{-1/2}$. But as N_r increases to the point where $N_r a \sim R$, this must saturate at $\delta c/c \sim (DR\bar{c}\tau)^{-1/2}$, presumably because of correlations among the concentration signals sensed by the different receptors.

The discussion by Berg and Purcell makes use of several special assumptions which we suspect are not required, and this leads to some clear questions:

- For interactions of a substrate with a single receptor, does Eq. (1) provide a general limit to sensitivity, independent of molecular details?
- Can we understand explicitly how correlations among nearby receptors result in a limit like Eq. (1), but with a reflecting the size of the receptor cluster?
- Do the spatial correlations among nearby receptors have an analog in the time domain, so that there is a minimum averaging time required for noise reduction to be effective?

Finally, if we can establish Eq. (1) or its generalizations as a real limit on sensitivity for any signaling process, we would like to know if cells actually operate near this limit.

In most cases that we know about, biochemical signaling molecules are thought to interact with their receptors through some kinetic process which leads to the establishment of equilibrium between bound and unbound states. If this is the case, we can view the fluctuations in occupancy of a binding site as an example of thermal noise, and we can use the fluctuation–dissipation theorem rather than tracing through the consequences of different microscopic hypotheses about the nature of the interaction between signaling molecules and their targets. We begin with a simple example, to show that we can recover conventional

results.

II. BINDING TO A SINGLE RECEPTOR

Consider a binding site for signaling molecules, and let the fractional occupancy of the site be n . If we do not worry about the discreteness of this one site, or about the fluctuations in concentration c of the signaling molecule, we can write a kinetic equation

$$\frac{dn(t)}{dt} = k_+c[1 - n(t)] - k_-n(t). \quad (2)$$

This describes the kinetics whereby the system comes to equilibrium, and the free energy F associated with binding is determined by detailed balance,

$$\frac{k_+c}{k_-} = \exp\left(\frac{F}{k_B T}\right). \quad (3)$$

If we imagine that thermal fluctuations can lead to small changes in the rate constants, we can linearize Eq. (2) to obtain

$$\frac{d\delta n}{dt} = -(k_+c + k_-)\delta n + c(1 - \bar{n})\delta k_+ - \bar{n}\delta k_-. \quad (4)$$

But from Eq. (3) we have

$$\frac{\delta k_+}{k_+} - \frac{\delta k_-}{k_-} = \frac{\delta F}{k_B T}. \quad (5)$$

Applying this constraint to Eq. (4) we find that the individual rate constant fluctuations cancel and all that remains is the fluctuation in the thermodynamic binding energy δF :

$$\frac{d\delta n}{dt} = -(k_+c + k_-)\delta n + k_+c(1 - \bar{n})\frac{\delta F}{k_B T}. \quad (6)$$

Fourier transforming,

$$\delta n(t) = \int \frac{d\omega}{2\pi} \exp(-i\omega t) \delta \tilde{n}(\omega), \quad (7)$$

we can solve Eq. (6) to find the frequency dependent susceptibility of the coordinate n to its conjugate force F ,

$$\frac{\delta\tilde{n}(\omega)}{\delta\tilde{F}(\omega)} = \frac{1}{k_B T} \frac{k_+ c(1 - \bar{n})}{-i\omega + (k_+ c + k_-)} \quad (8)$$

Now we can compute the power spectrum of fluctuations in the occupancy n using the fluctuation–dissipation theorem:

$$\langle \delta n(t) \delta n(t') \rangle = \int \frac{d\omega}{2\pi} \exp[-i\omega(t - t')] S_n(\omega) \quad (9)$$

$$S_n(\omega) = \frac{2k_B T}{\omega} \Im \left[\frac{\delta\tilde{n}(\omega)}{\delta\tilde{F}(\omega)} \right] \quad (10)$$

$$= \frac{2k_+ c(1 - \bar{n})}{\omega^2 + (k_+ c + k_-)^2}. \quad (11)$$

It is convenient to rewrite this as

$$S_n(\omega) = \langle (\delta n)^2 \rangle \frac{2\tau_c}{1 + (\omega\tau_c)^2}, \quad (12)$$

where the total variance is

$$\langle (\delta n)^2 \rangle = \int \frac{d\omega}{2\pi} S_n(\omega) = k_B T \left. \frac{\delta\tilde{n}(\omega)}{\delta\tilde{F}(\omega)} \right|_{\omega=0} \quad (13)$$

$$= \frac{k_+ c(1 - \bar{n})}{k_+ c + k_-} \quad (14)$$

$$= \bar{n}(1 - \bar{n}), \quad (15)$$

and the correlation time is given by

$$\tau_c = \frac{1}{k_+ c + k_-}. \quad (16)$$

This is the usual result for switching in a Markovian way between two states; here it follows from the ‘macroscopic’ kinetic equations, plus the fact that binding is an equilibrium process.

The same methods can be used in the more general case where the concentration is allowed to fluctuate. Now we write

$$\frac{dn(t)}{dt} = k_+ c(\vec{x}_0, t)[1 - n(t)] - k_- n(t), \quad (17)$$

where the receptor is located at \vec{x}_0 , and

$$\frac{\partial c(\vec{x}, t)}{\partial t} = D \nabla^2 c(\vec{x}, t) - \delta(\vec{x} - \vec{x}_0) \frac{dn(t)}{dt}. \quad (18)$$

Following the same steps as above, we find the linear response function

$$\frac{\delta\tilde{n}(\omega)}{\delta\tilde{F}(\omega)} = \frac{k_+c(1-\bar{n})}{k_B T} \frac{1}{-i\omega[1+\Sigma(\omega)]+(k_+\bar{c}+k_-)} \quad (19)$$

$$\Sigma(\omega) = k_+(1-\bar{n}) \int \frac{d^3k}{(2\pi)^3} \frac{1}{-i\omega + Dk^2} \quad (20)$$

The “self-energy” $\Sigma(\omega)$ is ultraviolet divergent, which can be traced to the delta function in Eq. (18); we have assumed that the receptor is infinitely small. A more realistic treatment would give the receptor a finite size, which is equivalent to cutting off the k integrals at some (large) $\Lambda \sim \pi/a$, with a the linear dimension of the receptor. If we imagine mechanisms which read out the receptor occupancy and average over a time τ long compared to the correlation time τ_c of the noise, then the relevant quantity is the low frequency limit of the noise spectrum. Hence,

$$\Sigma(\omega \ll D/a^2) \approx \Sigma(0) = \frac{k_+(1-\bar{n})}{2\pi Da}, \quad (21)$$

and

$$\frac{\delta\tilde{n}(\omega)}{\delta\tilde{F}(\omega)} = \frac{k_+\bar{c}(1-\bar{n})}{k_B T} \left[-i\omega \left(1 + \frac{k_+(1-\bar{n})}{2\pi Da} \right) + (k_+\bar{c} + k_-) \right]^{-1}, \quad (22)$$

where \bar{c} is the mean concentration. Applying the fluctuation–dissipation theorem once again we find the spectral density of occupancy fluctuations,

$$S_n(\omega) \approx 2k_+\bar{c}(1-\bar{n}) \frac{1+\Sigma(0)}{\omega^2(1+\Sigma(0))^2 + (k_+\bar{c}+k_-)^2}. \quad (23)$$

We note that the total variance in occupancy is unchanged since this is an equilibrium property of the system while coupling to concentration fluctuations serves only to change the kinetics.

Coupling to concentration fluctuations does serve to renormalize the correlation time of the noise,

$$\tau_c \rightarrow \tau_c[1 + \Sigma(0)]. \quad (24)$$

The new τ_c can be written as

$$\tau_c = \frac{1 - \bar{n}}{k_-} + \frac{\bar{n}(1 - \bar{n})}{2\pi Da\bar{c}}, \quad (25)$$

so there is a lower bound on τ_c , independent of the kinetic parameters k_{\pm} ,

$$\tau_c > \frac{\bar{n}(1 - \bar{n})}{2\pi Da\bar{c}}. \quad (26)$$

Again, the relevant quantity is the low frequency limit of the noise spectrum,

$$S_n(\omega = 0) = 2k_+\bar{c}(1 - \bar{n}) \cdot \frac{1 + \Sigma(0)}{(k_+\bar{c} + k_-)^2} \quad (27)$$

$$= \frac{2\bar{n}(1 - \bar{n})}{k_+\bar{c} + k_-} + \frac{[\bar{n}(1 - \bar{n})]^2}{\pi Da\bar{c}}. \quad (28)$$

If we average for a time τ , then the root-mean-square error in our estimate of n will be

$$\delta n_{\text{rms}} = \sqrt{S_n(0) \cdot \frac{1}{\tau}}, \quad (29)$$

and we see that this noise level has a minimum value independent of the kinetic parameters k_{\pm} ,

$$\delta n_{\text{rms}} > \frac{\bar{n}(1 - \bar{n})}{\sqrt{\pi Da\bar{c}\tau}}. \quad (30)$$

To relate these results back to the discussion by Berg and Purcell, we note that an overall change in concentration is equivalent to a change in F by an amount equal to the change in chemical potential, so that $\Delta c/\bar{c} \equiv \Delta F/k_B T$. This means that there is an effective spectral density of noise in measuring c given by

$$S_c^{\text{eff}}(\omega) = \left(\frac{\bar{c}}{k_B T}\right)^2 S_F(\omega), \quad (31)$$

where the ‘noise force’ spectrum $S_F(\omega)$ is given by the fluctuation–dissipation theorem as

$$S_F(\omega) = \left| \frac{\delta \tilde{n}(\omega)}{\delta \tilde{F}(\omega)} \right|^{-2} S_n(\omega) = -\frac{2k_B T}{\omega} \Im \left[\frac{\delta \tilde{F}(\omega)}{\delta \tilde{n}(\omega)} \right]. \quad (32)$$

In the present case we find that

$$S_c^{\text{eff}}(\omega) = \frac{2\bar{c}^2}{k_+\bar{c}(1 - \bar{n})} \left[1 + \frac{k_+(1 - \bar{n})}{2\pi Da} \right]. \quad (33)$$

As before, the accuracy of a measurement which integrates for a time τ is set by

$$\delta c_{\text{rms}} = \sqrt{S_c^{\text{eff}}(0) \cdot \frac{1}{\tau}}, \quad (34)$$

and we find again a lower bound which is determined only by the physics of diffusion,

$$\frac{\delta c_{\text{rms}}}{\bar{c}} > \frac{1}{\sqrt{\pi D a \bar{c} \tau}}. \quad (35)$$

Note that this is (up to a factor of $\sqrt{\pi}$) exactly the Berg–Purcell result in Eq. (1).

III. BINDING TO MULTIPLE RECEPTORS

To complete the derivation of Berg and Purcell’s original results, we consider a collection of m receptor sites at positions \vec{x}_μ :

$$\frac{dn_\mu(t)}{dt} = k_+ c(\vec{x}_\mu, t) [1 - n_\mu(t)] - k_- n_\mu(t) \quad (36)$$

$$\frac{\partial c(\vec{x}, t)}{\partial t} = D \nabla^2 c(\vec{x}, t) - \sum_{i=1}^N \delta(\vec{x} - \vec{x}_i) \frac{dn_i(t)}{dt}. \quad (37)$$

From Eq. 37, we can write

$$\delta c(\vec{x}_\nu, \omega) = \frac{i\omega\Lambda}{2\pi^2 D} \delta \tilde{n}_\nu(\omega) + \frac{i\omega}{2\pi^2} \sum_{\mu \neq \nu}^m \frac{\delta \tilde{n}_\mu(\omega)}{|\vec{x} - \vec{x}_\mu|} \int_0^\infty \frac{k \sin(k |\vec{x} - \vec{x}_\mu|)}{-i\omega + Dk^2} dk, \quad (38)$$

where Λ is the cut-off wave number; as before, the cut-off arises to regulate the delta function in Eq. 37, and is related to the size of the individual receptor. In the limit $(\omega/D)^{1/2} \ll 1$, we have

$$\delta c(\vec{x}_\nu, \omega) = \frac{i\omega\Lambda}{2\pi^2 D} \delta \tilde{n}_\nu(\omega) + \frac{i\omega}{4\pi D} \sum_{\mu \neq \nu}^m \frac{\delta \tilde{n}_\mu(\omega)}{|\vec{x} - \vec{x}_i|}, \quad (39)$$

and combining with Eq. 36 in Fourier space, we obtain

$$\begin{aligned} -i\omega \delta \tilde{N} = & - \left[(k_+ \bar{c} + k_-) - \frac{i\omega \Lambda k_+ (1 - \bar{n})}{2\pi^2 D} \right] \delta \tilde{N} \\ & + \frac{i\omega k_+ (1 - \bar{n})}{4\pi D} \sum_{\nu=1}^m \sum_{\mu \neq \nu} \delta \tilde{n}_\mu \frac{1}{|\vec{x}_\mu - \vec{x}_\nu|} + m k_+ \bar{c} (1 - \bar{n}) \left(\frac{\delta \tilde{F}}{k_B T} \right). \end{aligned} \quad (40)$$

where we have defined $\delta\tilde{N}(\omega) = \sum_{\mu=1}^m \delta n_{\mu}(\omega)$, and assumed the steady state fractional occupancies to be independent of the receptor site, $\bar{n}_{\mu} = \bar{n} = k_+\bar{c}/(k_+\bar{c} + k_-)$.

If we consider receptor cluster geometries such that the innermost sum is independent of \vec{x}_{ν} , we can write the sum as

$$\sum_{\nu=1}^m \sum_{\mu \neq \nu} \delta\tilde{n}_{\mu} \frac{1}{|\vec{x}_{\mu} - \vec{x}_{\nu}|} = \phi(m) \cdot \delta\tilde{N} \quad (41)$$

where

$$\phi(m) = \sum_{\mu=2}^m \frac{1}{|\vec{x}_{\mu} - \vec{x}_1|}. \quad (42)$$

From the fluctuation–dissipation theorem, we find the spectrum of $\delta\tilde{F}$ and convert that to an equivalent concentration error as in Eq. 33:

$$\frac{\delta c_{\text{rms}}}{\bar{c}} > \frac{1}{\sqrt{\pi D \bar{c} \tau}} \left(\frac{\Lambda}{m\pi} + \frac{\phi(m)}{2m} \right)^{1/2}. \quad (43)$$

For example, for receptors of radius b uniformly distributed around a ring of radius $a > b$, we have $\phi(m) = mg_0/a$, where g_0 is a geometric factor of order unity, and

$$\frac{\delta c_{\text{rms}}}{\bar{c}} > \frac{1}{\sqrt{\pi D \bar{c} \tau}} \left(\frac{1}{mb} + \frac{g_0}{2a} \right)^{1/2}. \quad (44)$$

In summary, we find that the simple formula in Eq. (1) really does provide a general limit on the precision of concentration measurements by sensors of linear dimension $\sim a$, at least in those cases where the interactions between the receptor and its ligand are passive. Further, there is a minimum level of receptor occupancy noise from Eq. (30), and a minimum correlation time from Eq. (26). Let us look at two examples to see how these limits compare with the performance of real cellular signaling mechanisms.

IV. PHYSICAL EXAMPLES

A. Regulation of gene expression in bacteria

Expression of genes is controlled in part by the occupancy of promoter sites adjacent to the regions of DNA which code for protein [7]. We thus can view gene expression as a readout

mechanism for sensing promoter site occupancy, or even as a sensor for the concentration of the transcription factor proteins which bind to the promoter site. In a bacterium like *E. coli*, transcription factors are present in $N_{\text{TF}} \sim 100$ copies in a cell of volume of $\sim 1 \mu\text{m}^3$ [8]. If the transcription factor is a repressor then gene expression levels are determined by $1 - n$, while if it is an activator then expression is related to n ; because $\delta n_{\text{rms}} \propto \bar{n}(1 - \bar{n})$ [Eq. (30)], fractional fluctuations in either $A = n$ or $A = 1 - n$ are determined by

$$\frac{\delta A}{\bar{A}} = (1 - \bar{A}) \frac{1}{\sqrt{\pi D a \bar{c} \tau}} \quad (45)$$

Direct measurements of diffusion constants for small proteins in the *E. Coli* cytoplasm yield $D \sim 3 \mu\text{m}^2/\text{s}$ [9]. A promoter site itself has linear dimensions $a \sim 3 \text{ nm}$, and putting these factors together we find the crucial combination of parameters $\pi D a \bar{c} \sim 3 \text{ s}^{-1}$. In particular this means that the fluctuations in occupancy of the promoter site, averaged over a time τ , are given by

$$\frac{\delta A}{\bar{A}} > (0.1) \cdot (1 - \bar{A}) \cdot \left(\frac{100}{N_{\text{TF}}}\right)^{1/2} \cdot \left(\frac{30 \text{ s}}{\tau}\right)^{1/2} \quad (46)$$

Recent experiments [10] indicate that *E. Coli* achieves $\sim 10\%$ precision in control of gene expression at small values of \bar{A} . For this performance to be consistent with the physical limits, the transcription machinery must therefore integrate the promoter site occupancy for times of order one minute, even assuming that the translation from occupancy to expression level itself is noiseless. This integration can be provided by the lifetime of the mRNA transcripts themselves, which is $\sim 3 \text{ min}$ in prokaryotes [11].

B. Control of the flagellar motor by CheY

The output of bacterial chemotaxis is control of the flagellar rotary motor [12]. The phosphorylated form of the signaling protein CheY (CheY-P) binds to the motor and modulates the probability of clockwise versus counterclockwise rotation [13]. Recent measurements [14] show that the probability p of clockwise rotation depends very steeply on the concentration c of CheY-P,

$$p = \frac{c^h}{c^h + c_{1/2}^h}, \quad (47)$$

with $h \sim 10$ and $c_{1/2} \sim 3 \mu\text{M}$. Motors switch between clockwise and counterclockwise rotation as a simple random telegraph process, and for $c \approx c_{1/2}$ the switching frequency is $f \approx 1.5 \text{ s}^{-1}$. If we view the motor as a sensor for the internal messenger CheY, then the observed behavior of the motor determines an equivalent noise level of

$$\delta c_{rms} = \left(\frac{\partial p}{\partial c} \right)^{-1} \sqrt{p(1-p)} \cdot \left(\frac{\tau_0}{\tau} \right)^{1/2}, \quad (48)$$

where τ_0 is the correlation time of the motor state; for the simple telegraph model it can be shown that $\tau_0 = 2p(1-p)/f$. Using Eq. (47) we find

$$\frac{\delta c_{rms}}{c} = \frac{1}{h} \sqrt{\frac{2}{f\tau}}. \quad (49)$$

Thus, for $c \approx c_{1/2}$, a single motor provides a readout of CheY-P concentration accurate to $\sim 10\%$ within two seconds. Given the dimensions of the flagellar motor's C ring, $a \sim 45 \text{ nm}$, with $m \sim 34$ individual subunits to which the CheY-P molecules bind [15], from Eq. 44 we find

$$\frac{\delta c_{rms}}{c} \sim \frac{1}{22} \left(\frac{2 \text{ s}}{\tau} \right)^{1/2}, \quad (50)$$

where we have taken the size of the individual receptor binding site to be $b \sim 1 \text{ nm}$, and $D \sim 3 \mu\text{m}^2/\text{s}$ as above. Hence, the collection of receptors comprising the motor are able to measure the CheY-P concentration with $\sim 5\%$ precision within two seconds. This is in agreement with our earlier result obtained by observing the switching statistics of the motor to within a factor of two.

V. CONCLUDING REMARKS

In conclusion, we have derived from statistical mechanics considerations the physical limits to which biological sensors that rely on the binding of a diffusing substrate can measure its concentration. Our approach complements and extends the classic work by Berg and

Purcell. For a single receptor, we arrive at their earlier intuitive result, which states that the accuracy in measurement of concentration is limited by the noise associated with the arrival of discrete substrate molecules at the receptors. Our approach extends in a straightforward way to multiple receptors without relying on additional considerations; for this case, our result demonstrates more transparently the role of multiple receptors in improving the measurement accuracy, as well as the saturating limit in this improvement set by the receptor cluster size. Relevant internal or external signaling molecules are often present in low copy numbers, and their concentration in turn regulates downstream biochemical networks crucial to the cell's functions. For two experimentally well-studied examples, we show that the cell's performance is consistent with the counting noise limits in measuring the concentration of these signaling molecules.

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