Accuracy and Gain in Biological Receptors:
Constraints from Intrinsic Noise

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Building on the classic work by Berg and Purcell [1], we derive fundamental limits on the measurement accuracy of biological receptors from a statistical mechanics point of view. We extend these results to multiple receptors functioning cooperatively as a switch, demonstrating the trade-off between the measurement accuracy and the gain of the switch.

I. INTRODUCTION

Ensuring the proper execution of the chain of events involved in the construction of macromolecules inside the cell is central to all biological functions: growth, differentiation and generating the specialized properties of cells. Networks of biochemical reactions play an important role in this regard, from the control of gene expression to regulating a cell’s response to external cues. A common feature of these biochemical networks is the ability to operate in the presence of small numbers of crucial molecules, such as enzymes controlling reaction rates. In this regime, fluctuations in the numbers of these molecules are significant. Yet, the output of the network, appropriately defined, appears to be “robust” to such fluctuations [2, 3]. Hence, recent efforts in understanding cellular mechanisms have focused on elucidating network “topologies” - sequences of biochemical reactions involving extensive feedback loops - that ensure robustness of the output to noise at input and/or during intermediate steps.

Furthermore, given the size and complexity of these networks and the lack of complete data to characterize them, it has proven useful to modularize complete networks into functional subnetworks, or motifs, in an effort to deduce the structure and function of partially known networks [6]. A common control motif is the biochemical switch [4]. Switches allow the cell to perform thresholding operations, converting graded signals into an all-or-none response. Their use by the cell is ubiquitous, from the level of gene expression [5] - for example, in activating the successive classes of genes that generate the proteins comprising the flagellum in E. coli in the requisite time-dependent manner [7] - to behavioral response of the cell - for example, in determining the direction of rotation of the flagellum in response to attractants/repellents in the environment [8].

In this work, we focus on the class of biological switches involving the binding of a substrate to a receptor molecule, either intra- or extracellularly. Furthermore, we consider the generic case where the rate of substrate-receptor binding is diffusion-limited: binding occurs when a diffusing substrate molecule comes within range of chemical interaction with the receptor. Fluctuations in the substrate concentration due to Brownian motion as well as thermal noise leading to fluctuations in binding/unbinding rates pose limits on the accuracy with which biological receptors can measure concentrations and respond accordingly. While in principle receptors (or a cascade of biochemical reactions triggered by a receptor) can provide large amplification of the input signal, there is a trade-off between gain and accuracy of switching in the presence of intrinsically noisy input. Knowledge of the properties of the input noise may help elucidate, or at least constrain, the underlying mechanisms involved in signal detection and response when, as in many well-studied examples in biology [10–13], the performance of the system is “optimal.”

The limit set by noise on the measurement of concentration of attractant/repellent molecules by surface receptors in E. coli was first addressed in a classic paper by Berg and Purcell [1]. Drawing on the analogy between diffusion and electrostatics, and given certain assumptions about the details of the microscopic binding kinetics, they determined the lower limit on the accuracy of this measurement in the presence of noise due to the discrete arrival of substrate molecules at the receptors. By comparing with available

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experimental results, they pointed out that remarkably, the cell’s chemotactic response is as sensitive as this limit allows.

In this work, we revisit the Berg-Purcell analysis from statistical mechanics considerations. In doing so, we generalize this classic result to intra- as well as extracellular signaling. Our goal is to present a detailed derivation of the main results, as well as pedagogical explanations of the physics concepts that may not be familiar to nonexperts. Finally, we examine the physical limit to the measurement of concentration by a cluster of receptors functioning cooperatively as a switch.

II. REVIEW OF BERG-PURCELL RESULTS

A. The “perfect” device

The original Berg-Purcell result was concerned with chemotaxis in bacteria, such as E. coli, which is a biased random walk of “runs” punctuated by “tumbles”. Each bacterium has four to six flagella: CCW rotation of the motor apparatus at the base of each flagellum allows the flagella to bundle up and act as a single propeller, leading to running motion of the cell. CW rotation of one or more flagella leads to the flying apart of the bundle, resulting in tumbling which allows a new, perhaps more favorable direction of motion to be randomly selected. It should be emphasized that although these external signaling molecules are potentially food, the receptors involved in the sensing mechanism are distinct from those involved in their transport into the cell to be metabolized. The external signal is converted via an intracellular network of biochemical reactions into an internal signal, namely the phosphorylated form of the protein CheY, which in turn binds to the motor assembly and biases its direction of rotation, thereby modulating the mean runtime. Hence, chemotaxis provides an example of both intra- and extracellular signaling.

The classical analysis of bacterial chemotaxis by Berg and Purcell provided a simple estimate and an intuitive picture of the noise in “measuring” chemical concentrations. They begin by considering the hypothetical “concentration-measuring” device, which is able to exactly count the number of substrate molecules in a volume $V \sim a^3$, determined by its effective size. The mean number of molecules that such a measurement would reveal is $N \sim ca^3$; however, any single measurement is subject to fluctuations given by $\sqrt{N}$, consistent with Poisson statistics for the arrival of particles. The device can beat down this measurement error by integrating the concentration field for some time $\tau$. The number of independent measurements it can make in that time is $N_{\text{meas}} \sim \tau/\tau_D$, where $\tau_D$ is how long it takes for diffusion to refresh the particles in a volume $V$. Hence, the relative accuracy in the estimate of $N$, and in measuring the concentration $\bar{c}$ itself, is reduced by a factor of $\sqrt{N_{\text{meas}}}$:

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

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 $a \sim 1 \mu m$. 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. In either case, they were the first to point out that the measurement of chemoattractant concentration by a single-celled organism is limited by statistical fluctuations, and that the least fractional error attainable is set by the physics of diffusion.

B. The chemical receptor

Bacteria do not sample the external concentration field through volume-sampling, as just described. Instead, this is accomplished through binding of the attractant/repellent molecules to surface receptors, with the average receptor occupancy giving the external concentration. The motion of substrate molecules is
governed by the diffusion equation
\[ \frac{\partial c}{\partial t} = D \nabla^2 c, \] (2)
whose steady state solution in spherical polar coordinates is given by
\[ c(r) = C_1/r + C_2 \] (3)
where \( C_2 = \pi \) is the concentration at “infinity” [26], measured in units of number of particles per unit volume. \( C_1 \) is determined from boundary conditions: assuming the receptor to be a perfect absorber of spherical radius \( a \) (with the coordinate origin centered at the receptor), \( C_1 = -a \pi \) satisfying \( c = 0 \) at the receptor surface. At equilibrium, the probability of a substrate molecule binding to the receptor is given by \( \pi \). If the average time a particle remains bound to the receptor is \( \tau_b \), detailed balance requires:
\[ \frac{\pi}{\tau_b} = (1 - \pi) J_{in} \] (4)
where \( J_{in} = 4 \pi a D \pi \) is the inward flux of particles to the receptor. The receptor is able to sample the concentration at intervals given by the correlation time, \( \tau_c \), of the binding/unbinding process
\[ \tau_c^{-1} = \tau_b^{-1} + J_{in} = \pi/J_{in}, \] (5)
where the last equality follows from detailed balance. Hence, if the receptor measures for a time \( \tau \), there can be maximum of \( N = 2 \tau/\tau_c \) independent binding events. The probability of \( n_\tau \) binding events in time \( \tau \) is given by the binomial distribution with mean and variance equal to \( \pi \) and \( (\delta \pi)^2 = (n_\tau - \pi)^2 = N(\pi(1 - \pi)) \), respectively. \( \pi \) is the mean fractional occupancy of the receptor at equilibrium, or equivalently, the probability that the receptor is bound. The receptor approximates \( \pi \) by measuring \( n_\tau \) and constructing \( n_\tau/N \). The expected error in this measurement is
\[ \frac{(\delta \pi)^2}{\pi(1 - \pi)} = \frac{1}{J_{in}(1 - \pi)/\tau}. \] (6)
To relate this to the expected error in measuring \( \pi \), we note that
\[ \pi = \frac{\pi}{\pi + c_{1/2}}, \] (7)
where \( c_{1/2} = (4 \pi D a \tau_b)^{-1} \) is the dissociation constant for the binding of the substrate to the receptor. Hence,
\[ \frac{(\delta \pi)^2}{\pi} = \left( \frac{\partial \pi}{\partial \pi} \right)^2 (\delta \pi)^2, \] (8)
and, the fractional error in measuring \( \pi \) is
\[ \frac{(\delta \pi)^2}{\pi^2} = \frac{2}{J_{in}(1 - \pi)/\tau}, \] (9)
\[ = \frac{1}{2 \pi a \tau (1 - \pi)/\tau}. \] (10)

Using arguments similar to those given here, Berg and Purcell’s classical work gives the accuracy limit of the perfect “\( \pi \)-measuring” device, as well as a receptor making this measurement through binding/unbinding to the substrate. Several remarks are in order:

(i) This fractional error is simply the inverse of the square-root of the total number of “new” molecules that the receptor has counted in time \( \tau \). The total number of particles “absorbed” by the receptor this time, \( J_{in}\tau \), times the probability that the receptor is unbound, \( (1 - \pi) \), equals the number of “new” particles that the receptor encounters in the time interval, \( \tau \). However, unlike the perfect hypothetical device, this number depends on the details of measurement procedure, namely the dissociation constant of the reaction kinetics (through \( \pi \)).
(ii) The treatment of the receptor surface as a perfectly absorbing boundary in determining the diffusive flux to the receptor is not consistent with a non-zero probability of unbinding.

Below, within the framework of statistical mechanics, we show that both limits given by Eqs. 1 and 10 are obtained simultaneously as contributions to the overall measurement accuracy. Furthermore, extension of these results to multiple receptors, which is achieved by analogy with electrostatics in the original Berg-Purcell work, proceeds in a straight-forward way within the same framework.

The cornerstone of our analysis is the fluctuation–dissipation theorem, which we review for the general audience in the next section.

III. STATISTICAL MECHANICS TREATMENT

A. Fluctuation-dissipation theorem

The fluctuation–dissipation theorem is perhaps best motivated in the context of Brownian motion, which has become the canonical example of a random process. The Langevin formulation of this process amounts to Newton’s second law for the position, $X(t)$, of a Brownian particle of mass $M$ in thermal equilibrium with a particle bath. The total force due to particle collisions is taken to be the sum of a dissipative force, proportional to the velocity of the Brownian particle, and a fluctuating (or “complementary” [14]) force, $f(t)$, with zero average. For generality, and later extension to chemical kinetics, we also include a restoring force due to a harmonic potential (Fig. 1)

$$M \frac{d^2X}{dt^2} = -kX - \gamma \frac{dX}{dt} + f(t).$$  \hspace{1cm} (11)

The dissipative and fluctuating forces are related through the fluctuation–dissipation theorem, and intuitively, this is a consequence of the fact that both forces arise due to collisions with the particle bath

$$\langle f(t)f(t+\tau) \rangle = 2k_BT\gamma \delta(\tau).$$  \hspace{1cm} (12)

$k_B$ is the Boltzmann constant, $\gamma$ is the damping coefficient for the Brownian particle interacting with the bath, $T$ is the temperature, $k$ is the “spring” constant, and brackets denote ensemble averaging.

More generally, the linear response of a system, $X(t)$, to small external perturbations from equilibrium ($\langle X(t) \rangle = 0$), can be obtained from the thermodynamically conjugate force, $F(t)$, through the generalized susceptibility, $\alpha(t)$,

$$X(t) = \int_0^\infty \alpha(t') F(t-t')dt'.$$  \hspace{1cm} (13)

Working in Fourier space, where

$$\alpha(\omega) = \int_0^\infty \alpha(t) e^{i\omega t} dt.$$  \hspace{1cm} (14)

by applying a small external force, whose Fourier spectrum, $F(\omega)$, we control, and measuring the linear response of the system, $X(\omega)$, we can find the susceptibility, $\alpha(\omega) = X(\omega)/F(\omega)$. The fluctuation–dissipation theorem relates the imaginary part of the susceptibility, which is proportional to the rate at which work done by external forces is dissipated as heat, to the Fourier transform of the mean-square fluctuation of the coordinate, $X$, for the closed system in thermal equilibrium [15]

$$S_X(\omega) = \frac{2k_BT}{\omega} \Im[\alpha(\omega)].$$  \hspace{1cm} (15)

The power spectrum, $S_X(\omega)$, is related to the correlation function according to the Weiner-Klinchine theorem (for a stationary random variable)

$$\langle X(t)X(t+\tau) \rangle = \int_{-\infty}^{\infty} \frac{d\omega}{2\pi} S_X(\omega)e^{-i\omega\tau}.$$  \hspace{1cm} (16)
TABLE I: The response of a chemical system at equilibrium to thermal fluctuations is directly analogous to that of the familiar mass-spring system in contact with a particle bath, in the limit that the inertial term, \( M \ddot{X} \), can be neglected (valid for \( k/M \ll \frac{\gamma^2}{4} \)).

While the total variance is obtained from the equal time correlation function, if in measuring the linear response, \( X(t) \), we average for a time \( \tau \) (filtering out frequencies greater than \( \tau^{-1} \))

\[
Y(t) = \frac{1}{\tau} \int_{t-\tau/2}^{t+\tau/2} X(t')dt',
\]

then, for \( \tau \gg 1 \)

\[
\langle [Y(t)]^2 \rangle \approx S_X(0)/\tau.
\]

Hence, for progressively longer time intervals \( \tau \), the standard deviation of the fluctuations seen through this averaging filter goes down in proportion to \( 1/\sqrt{\tau} \). This is the continuous time version of the familiar notion that by making many independent discrete measurements of a quantity, the standard deviation is reduced by \( 1/\sqrt{N_{\text{meas}}} \) [13].

The Langevin description of the dynamics of a Brownian particle in a harmonic potential contains the essential features for understanding the role of fluctuations on the reaction kinetics of biomolecules (Table 1). In a chemical system, the “coordinates” are the concentrations of the interacting species, or equivalently the fractional occupancy of receptors, the phenomenological “equations of motion” are the chemical kinetics, and the thermodynamically conjugate “forces” are the free-energy differences among the species [16]. We begin with a simple example, to show that we can recover conventional results.

**B. Single receptor**

Our starting point is the set of macroscopic equations for the binding of a diffusing substrate \( C \) to a spherical receptor of radius \( a \)

\[
n_t = k_+ (1 - n) c - k_- n,
\]

\[
c_t = D \nabla^2 c - n, \frac{\delta(r-a)}{4\pi a^2},
\]

where

\[
\int_0^\infty \delta(r-a)4\pi r^2 dr = 4\pi a^2.
\]

\( n(t) \) is the probability that the receptor is bound; \( k_+ \) and \( k_- \) are the forward/reverse reaction rates for binding of \( C \) to the receptor; \( c(r,t) \) is the spherically symmetric solution to the diffusion equation, satisfying the appropriate boundary conditions, with dimensions of number of particles per unit volume; \( D \) is the diffusion constant. At steady state,

\[
\pi = \frac{k_+ \pi}{k_+ c + k_-}.
\]
Note that at thermal equilibrium, the rates satisfy
\[
\frac{k_+ \tau}{k_-} = e^{-\beta \Delta F},
\] (23)
where \(\beta = k_B T\), and \(\Delta F = F_b - F_{ub}\) is the difference in free energy between the bound and unbound states. These energy states are subject to thermal fluctuations, leading to fluctuations, \(\delta F(t)\), in the energy difference and in turn to fluctuating rates consistent with
\[
\frac{\delta k_+}{k_+} - \frac{\delta k_-}{k_-} = \beta \delta F.
\] (24)

Reaction rate fluctuations will drive fluctuations in the fractional receptor occupancy, and hence fluctuations in the substrate concentration. The linear response of the system is obtained from the linearized equations:
\[
\delta n_t = -(k_+ \tau + k_-) \delta n + k_+ (1 - \bar{n}) \delta c(a,t) + k_+ (1 - \bar{n}) \tau \beta \delta F,
\] (25)
\[
\delta c_t = D \nabla^2 \delta c - \delta n_t - \frac{1}{4\pi a^2} \delta (r - a).
\] (26)
where
\[
n(t) = \bar{n} + \delta n(t),
\] (27)
\[
c(r,t) = \bar{c}(r) + \delta c(r,t).
\] (28)

Rewriting Eq. 26 in Fourier space, and noting that
\[
\int d^3 r \delta(r - a) e^{-i \vec{k} \cdot \vec{r}} = \frac{4\pi a}{k} \sin ak,
\] (29)
we find
\[
\delta c(k,\omega) = -i\omega \delta n(\omega) \frac{\sin ak}{ak} \frac{1}{Dk^2 + i\omega},
\] (30)
from which we obtain
\[
\delta c(r,\omega) = \frac{i\omega \delta n(\omega)}{2\pi^2 a^2} \int_0^\infty \sin ak \sin kr \frac{dk}{Dk^2 + i\omega}.
\] (31)
At the receptor surface \(r = a\),
\[
\delta c(a,\omega) = \frac{i\omega \delta n(\omega)}{2\pi^2 a^2} I(\omega; a, D),
\] (32)
where the integral \(I(\omega; a, D)\) is given by
\[
I(\omega; a, D) = \int_0^\infty \frac{\sin^2 ak}{Dk^2 + i\omega} dk = \frac{\pi}{4(\omega D)^{1/2}} \left( -1 + \cosh 2a \left( \frac{i\omega}{D} \right)^{1/2} - \sinh 2a \left( \frac{i\omega}{D} \right)^{1/2} \right).
\] (33)
For \(2a \left( \frac{1}{D} \right)^{1/2} \ll 1\) (valid in the limit \(\omega \to 0\)), we have
\[
\delta c(a,\omega) \approx -\frac{i\omega \delta n(\omega)}{4\pi a D}.
\] (34)

Similarly, Fourier transforming Eq. 25
\[
i\omega \delta n(\omega) = -(k_+ \tau + k_-) \delta n(\omega) + k_+ (1 - \bar{n}) \delta c(a,\omega) + k_+ (1 - \bar{n}) \tau \beta \delta F(\omega),
\] (35)
and using Eq. 34, we find
\[ i\omega \left( 1 + \frac{k_+(1-\pi)}{4\pi a D} \right) + k_+ \tau + k_- \] \delta n(\omega) = k_+(1-\pi) \tau \beta \delta F(\omega). \tag{36} \]

The thermodynamically conjugate “force” to the receptor occupancy, \( \delta n \), is the change in free energy, \( \delta F \); hence, the susceptibility, \( \alpha(\omega) \), is given by
\[ \alpha(\omega) = \frac{k_+(1-\pi) \beta \tau}{k_+ \tau + k_- + i\omega \left( 1 + \frac{k_+(1-\pi)}{4\pi a D} \right)} \tag{37} \]

The power spectrum of the fluctuations in the receptor binding occupancy is obtained from the fluctuation-dissipation theorem:
\[ S_n(\omega) = \frac{2}{\beta\omega} \Im \left\{ \alpha(\omega) \right\}, \tag{38} \]
\[ = \frac{2 k_+ \tau (1-\pi) \left[ 1 + \frac{k_+(1-\pi)}{4\pi a D} \right]}{(k_+ \tau + k_-)^2 + \omega^2 \left[ 1 + \frac{k_+(1-\pi)}{4\pi a D} \right]^2}. \tag{39} \]

If the receptor occupancy is averaged over a time \( \tau \gg \tau_c \), then the variance of this averaged quantity is the power contained in \( \omega \in (0, \Delta \omega) \),
\[ \overline{(\delta n)^2} \approx S_n(0)/\tau = \left[ \pi (1-\pi) \right]^2 \left[ \frac{2}{k_+ \tau (1-\pi) \tau} + \frac{1}{2\pi Da\tau} \right], \tag{40} \]
where \( \Delta \omega = \pi/\tau \). Note that the limit \( \omega \to 0 \) of the power spectrum considered here justifies the approximation leading to Eq. 34.

Equivalently, the power spectrum of the conjugate force, \( S_F(\omega) \), can be obtained from \( \alpha(\omega) \equiv \alpha(\omega)^{-1} \), which is related to that of the power spectrum of the effective concentration according to
\[ S_c(\omega) = (\beta\tau)^2 S_F(\omega). \tag{41} \]

Again, taking the relevant zero-frequency limit, we find the fractional accuracy with which the concentration can be measured is
\[ \frac{\overline{(\delta c)^2}}{\bar c^2} \approx \frac{2}{k_+ \tau (1-\pi) \tau} + \frac{1}{2\pi Da\tau}. \tag{42} \]

We note that the first term depends explicitly on the reaction kinetics, while the second term presents a lower bound that depends on the diffusion constant, linear dimension of the receptor, and substrate concentration only. If the binding rate, \( k_+ \tau \), is taken to be the diffusion-limited rate, then the first term reduces to the Berg-Purcell result given by Eq. 10. At the same time, we have retrieved the lower limit to the measurement accuracy of the “perfect” device, given by the second term.

C. Multiple receptors

To extend the above calculation to a collection of receptors, we approximate each receptor as a sphere of radius \( b \), located at \( \vec{x}_i = \vec{x}_i, i = 1, \ldots, N_r \). As before, the linearized equations governing fluctuations from equilibrium are given by:
\[ \delta n_{i,t} = -(k_+ \tau + k_-) \delta n_i + k_+(1-\pi_i) \delta c_i + k_+(1-\pi_i) \tau \beta \delta F_i, \tag{43} \]
where \( \delta c_i = \delta c(\vec{x}_i, t) \), and
\[ \delta c_t = D \nabla^2 \delta c - \sum_{i=1}^{N_r} \frac{\delta (|\vec{x} - \vec{x}_i| - b)}{4\pi b^2} \delta n_{i,t}, \tag{44} \]
with changes in the receptor occupancy acting as sources/sinks for diffusion of the substrate. Rewriting the above in Fourier space

\[ \delta c(\vec{k}, \omega) = -\frac{i\omega}{Dk^2 + i\omega} \sin \frac{kb}{kb} \sum_{i=1}^{N_r} \delta n_i(\omega) e^{i\vec{k} \cdot \vec{x}_i}, \]  

(45)

and taking the inverse Fourier transform, we find

\[ \delta c(\vec{x}, \omega) = -\frac{i\omega}{2\pi^2 b} \sum_{i=1}^{N_r} \delta n_i(\omega) \frac{1}{|\vec{x} - \vec{x}_i|} \int_0^\infty \frac{dk}{Dk^2 + i\omega} \sin \frac{kb}{kb} |\vec{x} - \vec{x}_i| \]  

(46)

Setting \( \eta \equiv |\vec{x} - \vec{x}_i| \), the integral is given by [18]

\[ \int_0^\infty \frac{dk}{Dk^2 + i\omega} = \frac{\pi}{4\omega^2 (-iD/\omega)^{3/2}}, \]

\[ \sinh \left( \frac{\eta - b}{\sqrt{\omega D}} \right) - \sin \left( \frac{\eta + b}{\sqrt{\omega D}} \right) + 2 \sin \left( \eta \frac{\sqrt{\omega D}}{\sqrt{\delta n}} \right) \sinh \left( b \frac{\sqrt{\omega D}}{\sqrt{\delta n}} \right) \]  

(47)

Using this result, in the limit \( 2\eta (\omega/D)^{1/2} \ll 1 \) (valid as \( \omega \to 0 \)), Eq. 46 can be approximated as

\[ \delta c(\vec{x}_i, \omega) = -\frac{i\omega}{4\pi Db} \delta n_i(\omega) - \frac{i\omega}{4\pi D} \sum_{j \neq i} \delta n_j(\omega) \frac{1}{|\vec{x}_i - \vec{x}_j|}, \]  

(48)

where we have used \( b \leq \eta \). Then, Eq. 43 becomes

\[ i\omega \delta n_i = -\left[ k_+ \pi + k_- + \frac{i\omega k_+(1 - \pi_i)}{4\pi Db} \right] \delta n_i - \frac{i\omega k_+(1 - \pi_i)}{4\pi D} \sum_{j \neq i} \delta n_j \frac{1}{|\vec{x}_j - \vec{x}_i|} + k_+(1 - \pi_i) \beta \delta F_i \]

(49)

Assuming \( \pi_i = \pi = k_+ \pi/(k_+ \pi + k_-) \), independent of the receptor site, and treating the fluctuations, \( \delta F_i \), in the mean-field approximation

\[ \delta F(\omega) = \frac{1}{m} \sum_{i=1}^{N_r} \delta F_i(\omega), \]  

(50)

we find,

\[ i\omega \delta N = -\left[ k_+ \pi + k_- + \frac{i\omega k_+(1 - \pi)}{4\pi Db} \right] \delta N + \sum_{j=1}^{N_r} \frac{1}{|\vec{x}_j - \vec{x}_i|} \left[ k_+ (1 - \pi) \frac{1}{4\pi D} \sum_{j \neq i} \sum_{(j \neq i)} \delta n_j \frac{1}{|\vec{x}_j - \vec{x}_i|} \right], \]

(51)

where we have defined \( \delta N(\omega) = \sum_{i=1}^{N_r} \delta n_i(\omega) \). We now restrict attention to receptor cluster geometries where the innermost sum is independent of \( \vec{x}_i \). This is true exactly for (i) receptors equally spaced on a circular ring, as with the FlIM subunits of the C-ring of the flagellar motor in \( E. coli \) (see Figure 2), as well as for (ii) receptors uniformly tessellating the surface of a sphere. Furthermore, it is also true on average for receptors distributed according to the uniform random distribution on the cluster (ring, sphere, etc.). Then,

\[ \sum_{i=1}^{N_r} \sum_{j \neq i} \frac{1}{|\vec{x}_j - \vec{x}_i|} = \frac{1}{2\pi} \sum_{j=2}^{N_r} \frac{1}{|\vec{x}_j - \vec{x}_1|}, \]

(52)

\[ = \frac{1}{\sqrt{2}a} \sum_{j=2}^{N_r} \frac{1}{\sqrt{1 - \cos \theta_j}}, \]

(53)
where \( a \) is the cluster radius, and \( \theta_j \) is the angular coordinate of the \( j^{th} \) receptor (with \( \theta_1 = 0 \)). Defining,

\[
\nu(N_r) \equiv \frac{1}{\sqrt{2}} \sum_{j=2}^{N_r} \frac{1}{\sqrt{1 - \cos \theta_j}}.
\]  

(54)

Eq. 51 becomes

\[
i\omega \delta N = - \left[ k_+ \bar{c} + k_- + \frac{i\omega k_+ (1 - \pi)}{4\pi D} \left( \frac{1}{b} + \frac{\nu(N_r)}{a} \right) \right] \delta N + N_r k_+ (1 - \pi) \beta \bar{c} \delta F.
\]  

(55)

With regularly distributed receptors on ring or spherical cluster geometries, \( \nu(N_r) \) must be evaluated numerically, and results are shown in Figures 3 and 4. For randomly distributed receptors on a ring, we define the continuous, random variable

\[
y = \frac{1}{\sqrt{1 - \cos \theta}},
\]  

(56)

where \( \theta \) has a uniform random distribution on \([0, \pi]\). Then, \( \nu(N_r) \) can be approximated as

\[
\nu(N_r) \approx \frac{1}{\sqrt{2}} (N_r - 1) \bar{y}.
\]  

(57)

With \( p(\theta) = \frac{1}{\pi} \), we have

\[
p(y) = \frac{2}{\pi y^3 \sqrt{1 - (1 - 1/y^2)^2}}.
\]  

(58)

and,

\[
\bar{y} = \int_{y_{\text{min}}}^{y_{\text{max}}} y p(y) \, dy = \frac{1}{\pi} \ln \left( 2y + \sqrt{4y^2 - 2} \right)|_{y_{\text{min}}}^{y_{\text{max}}}
\]  

(59)

where \((y_{\text{min}}, y_{\text{max}}) = \left( \frac{1}{\sqrt{2}}, \frac{1}{\sqrt{2}} \frac{a}{b} \right)\). For \( a \gg b \),

\[
\nu(N_r) \approx \frac{1}{\pi} \ln \left( \frac{2a}{b} - \frac{b}{2a} \right) (N_r - 1).
\]  

(60)

Similarly, for receptors distributed uniformly randomly on the surface of sphere of radius \( a \), using \( p(\cos \theta) = \frac{1}{2} \) we find

\[
\nu(N_r) \approx \left( 1 - \frac{b}{a} \right) (N_r - 1),
\]  

(61)

in agreement with numerical evaluations (see Figures 3 and 4). Supported by these results, we approximate \( \nu(N_r) \approx g_0 N_r \) for \( N_r \gg 1 \), where \( g_0 \) is a geometrical constant. The upper bound on \( g_0 \) is obtained for randomly distributed receptors: for a spherical cluster, \( g_0 \sim 1 \), and for a ring cluster, for example with \( 2a \sim 45 \text{ nm} \) and \( 2b \sim 4 \text{ nm} \), we also have \( g_0 \sim 1 \).

Finally, the generalized susceptibility, \( \tilde{\alpha}(\omega) \)

\[
(\beta \bar{c})^2 \delta F(\omega) = \tilde{\alpha}(\omega) \delta N(\omega),
\]  

(62)

is obtained from Eq. 51 as

\[
\tilde{\alpha}(\omega) = \frac{\beta \bar{c}}{N_r k_+ (1 - \pi)} \left\{ k_+ \bar{c} + k_- + i\omega \left[ 1 + \frac{k_+ (1 - \pi)}{4\pi D} \left( \frac{1}{b} + \frac{\nu(N_r)}{a} \right) \right] \right\},
\]  

(63)
where $\tau \beta \delta F$ is the “effective” fluctuation in concentration. Again, using the fluctuation–dissipation theorem we find
\[
\frac{(\delta c)^2}{c^2} \approx \frac{2}{N_r k_B (1 - \pi/\tau) \tau} + \frac{1}{2\pi D \tau} \left( \frac{1}{N_r b} + \frac{g_0}{a} \right). \tag{64}
\]
For receptors uniformly populating the surface of the cluster (either regularly or randomly), as we have assumed above, we can distinguish two limiting cases where their distribution is (i) dense or (ii) sparse. In the first limiting case, $b$ and $a$ are related; for example, for a ring geometry, $N_r^{\text{max}} = \pi a$ with closest packing. In this limit, the relative accuracy with which concentration is measured is determined by the inverse of the linear dimension of the receptor cluster, $1/a$. In the second limiting case, with $g_0 \approx O(1)$ for various relevant geometries, the relative accuracy in measuring the concentration is dominated by $1/N_r b$ and improves with increasing $N_r$.

\section{Switching}

In this section, we consider a cluster of receptors acting as a switch: the cluster has a greater probability of being in one of two states based on its measurement of the concentration of a signaling molecule. A natural question is: how does the physical limit in measuring this concentration, addressed in the previous sections, constrain the accuracy of switching? Put differently, by observing the fraction of time the switch spends in one of its two states, how accurately can we infer the concentration of the signaling molecule?

Our description of the equilibrium thermodynamics of switching of the receptor cluster follows the application of the Monod-Wyman-Changeux (MWC) model [19] to the bacterial flagellar motor by Turner et al. [20]. The allosteric mechanism of this switch is not fully known and has been the subject of recent works [20–23]. The allosteric model adopted here is shown in Figure 5: The two states of the cluster are denoted by R (corresponding to CCW rotation of the flagellum leading to running motion) and T (corresponding to CW rotation of the flagellum leading to tumbling motion). R(n) and T(n) denote the cluster in running and tumbling states, respectively, with $n$ bound substrate molecules, where $n = 0, 1, \ldots, N_r$, and $N_r$ is the total number of binding sites. For the bacterial flagellar motor, the number of FliM molecules per C-ring, which acts as the switch, has been experimentally determined to be $N_r = 34$ [24]. We assume the binding and unbinding of the substrate to the receptor takes place at equilibrium. The free energy of each site in the R/T state is:
\[
F_{R,T} = \begin{cases} 
\frac{1}{N_r} F^0_{R,T} & \text{if unbound} \\
\frac{1}{N_r} F^0_{R,T} + \Delta F_{R,T} & \text{if bound}
\end{cases}
\tag{65}
\]
where $\Delta F_{R,T} = -k_B T \ln (c/K_{R,T})$ is the change in free energy of the cluster upon binding a single substrate molecule, $c$ is the substrate concentration, and $K_{R,T} = k_{R,T} / k_{T,R}$ denotes the dissociation constant in the R/T state, assumed to be different. The partition function for the receptor cluster can be written as:
\[
Z = \sum_{\text{states}} e^{-\beta F_{\text{state}}},
\tag{66}
\]
\[
e^{-\beta F^0_R} \sum_{n=0}^{N_r} \binom{N_r}{n} e^{-n\beta F_R} + e^{-\beta F^0_T} \sum_{n=0}^{N_r} \binom{N_r}{n} e^{-n\beta F_T},
\tag{67}
\]
\[
e^{-\beta F^0_R} \left(1 + \frac{c}{K_R}\right)^{N_r} + e^{-\beta F^0_T} \left(1 + \frac{c}{K_T}\right)^{N_r},
\tag{68}
\]
and the probability that the motor is in the state $T(n)$ with $n$ bound substrate molecules is given by
\[
p_T(n) = \binom{N_r}{i} \left(\frac{c}{K_T}\right)^n e^{-\beta F^0_T} Z.
\tag{69}
\]
Hence, the probability that the motor is in the state $T$ becomes
\[
p_T = \sum_{n=1}^{N_r} p_T(n) = \left[ 1 + \frac{1}{L} \left(1 + c/K_R\right)^{N_r} \right]^{-1},
\tag{70}
\]
where \( L \equiv \exp \left\{ -\beta (F^n_T - F^n_R) \right\} \).

To examine the kinetics of the transition between the two states of the cluster, we denote the transition rates to and from \( T(n) \) by \( k_f(n) \) and \( k_b(n) \), respectively. Following [20] we assume that the binding of each substrate molecule to the receptor cluster changes the activation energy for switching by a constant amount, given by \(-k_B T \ln \mu\) for the transition from \( R \) to \( T \), and by \(-k_B T \ln \nu\) for the transition from \( T \) to \( R \); then

\[
k_f(n) = k_f(0) \mu^n, \quad k_b(n) = k_b(0) \nu^n, \tag{71}
\]

where \( k_f, b(0) \) are the transition rates in the absence of bound substrate. Microscopic reversibility requires

\[
k_f(n) p_R(n) = k_b(n) p_T(n). \tag{72}
\]

Therefore, \( \mu \) and \( \nu \) are related as

\[
\frac{\mu}{K_R} = \frac{\nu}{K_T}. \tag{73}
\]

We further assume that the rate of binding/unbinding of ligand to the receptor cluster is faster than the rate of switching; hence, the equilibrium rates of switching can be obtained as averages with respect to the probabilities \( p_R, T(n) \):

\[
k_f = \frac{\sum_{n=0}^{N_r} k_f(n) p_R(n)}{\sum_{n=0}^{N_r} p_R(n)} = k_f(0) \left( \frac{1 + \mu c/K_R}{1 + c/K_R} \right)^{N_r}. \tag{74}
\]

Similarly,

\[
k_b = k_b(0) \left( \frac{1 + \nu c/K_T}{1 + c/K_T} \right)^{N_r} = k_b(0) \left( \frac{1 + \mu c/K_R}{1 + c/K_T} \right)^{N_r}, \tag{75}
\]

where in the last step we have used Eq. 74.

The equilibrium constant for switching which describes the structural change leading to the transition between the \( R \) and \( T \) states is given by

\[
K_{eq} = \frac{p_T}{p_R} = \frac{k_f}{k_b} = L \left( \frac{1 + c/K_T}{1 + c/K_R} \right)^{N_r}, \tag{76}
\]

where \( p_{R,T} \) denotes the probability of finding the motor in the \( R/T \) state. \( L \) is the equilibrium constant in the absence of ligand (“allosteric constant” in the MWC model):

\[
L = \frac{p_T(0)}{p_R(0)} = \frac{k_f(0)}{k_b(0)}. \tag{77}
\]

In terms of the receptor binding occupancy in the \( R/T \) state, given by \( n_{R,T} \), we have

\[
\ln K_{eq} = \ln L + N_r \ln \frac{1 - n_R}{1 - n_T}. \tag{78}
\]

The dynamics of switching is given by

\[
\frac{dp_T}{dt} = k_f(1 - p_T) - k_b p_T, \tag{79}
\]

and linearizing about the equilibrium probability that the switch is in the \( T \) state, \( p_T(t) = \bar{p}_T + \delta p_T(t) \), we have

\[
\frac{d\delta p_T}{dt} = -(k_f + k_b) \delta p_T + k_f(1 - \bar{p}_T) \left( \frac{\delta k_f}{k_f} - \frac{\delta k_b}{k_b} \right). \tag{80}
\]

From Eq. 79, and setting \( \delta N_{R,T} = N_r \delta n_{R,T} \), the fluctuations in rate constants satisfy

\[
\frac{\delta k_f}{k_f} - \frac{\delta k_b}{k_b} = \beta \delta F + \left( \frac{\delta N_T}{1 - \bar{p}_T} - \frac{\delta N_R}{1 - \bar{p}_R} \right), \tag{81}
\]
where the first term is the contribution due to fluctuations in the free energy of the cluster in the two states in the absence of ligand, and the second term is the contribution due to fluctuations in the binding occupancy. Fourier transforming we obtain

\[ \delta p_T(\omega) = \alpha(\omega) \delta F(\omega), \]  

(83)

where

\[ \alpha(\omega) = \frac{\beta k_f (1 - p_T)}{k_f + k_b + i\omega} \left( 1 - \frac{\alpha R(\omega)}{\beta (1 - \pi_R)} + \frac{\alpha T(\omega)}{\beta (1 - \pi_T)} \right), \]

(84)

with \( \alpha_{R,T} \) obtained from Eq. 55:

\[ \alpha_{R,T} = \beta \pi N_r (1 - \pi_{R,T}) \left[ \tau + K_{R,T} + \frac{i\omega(1 - \pi_{R,T})}{4\pi D} \left( \frac{1}{b} + \frac{\nu(N_r)}{a} \right) \right]^{-1}. \]

(85)

Using the fluctuation-dissipation theorem we find

\[ \frac{(\delta p_T)^2}{\tau_s^2} \approx S_{p_T}(\omega = 0)/\tau, \]

\[ = 2p_T(1 - p_T) \frac{\tau_s}{\tau} \times \]

\[ \left[ 1 + N_r (\pi_T - \pi_R) + \frac{N_r}{4\pi D \tau_s} \left( \frac{1}{b} + \frac{\nu(N_r)}{a} \right) \left[ \bar{\pi}_T^2 (1 - \pi_T) - \bar{\pi}_R^2 (1 - \pi_R) \right] \right], \]

(86)

where \( \tau_s = (k_f + k_b)^{-1} \) is the correlation time of the switch, and \( \tau \) is the observation time. Similarly, we find

\[ \frac{(\delta c)^2}{\tau^2} \approx \frac{2}{\left[ 1 + N_r (\pi_T - \pi_R) \right]^2} \frac{1}{p_T(1 - p_T)} \frac{\tau_s}{\tau} \times \]

\[ \left[ 1 + N_r (\pi_T - \pi_R) + \frac{N_r}{4\pi D \tau_s} \left( \frac{1}{b} + \frac{\nu(N_r)}{a} \right) \left[ \bar{\pi}_T^2 (1 - \pi_T) - \bar{\pi}_R^2 (1 - \pi_R) \right] \right]. \]

(87)

To determine typical numerical values for this bound on the relative accuracy of measuring the concentration of CheY-P with \( \sim [25] \), we showed that if we neglect the intrinsic noise in the switching mechanism, the collection of receptors comprising the flagellar motor is able to measure the concentration of CheY-P with \( \sim 4\% \) accuracy in 2 sec at \( c = c_{1/2} \) where \( p_T(c) = 1/2 \). Here, we find that taking into account cooperative switching of the receptor, the performance of the motor is less accurate than this lower bound, with \( \sim 35\% \) accuracy in 2 sec.

The gain of the switch, defined as the slope of \( p_T(c) \) at \( c = c_{1/2} \), is a function of \( K_T \) and \( K_R \) at fixed \( L \). Keeping \( c_{1/2} \) fixed (chosen such that \( c_{1/2} = 3.1 \) \( \mu \text{M} \), consistent with recent experiments [8]), the gain increases with increasing \( K_R/K_T \) (dashed line in Figure 6). Increasing the gain by changing only the values of the substrate dissociation constants in the two states of the switch, in Figure 8 we show the corresponding decrease in (i) the maximum switching frequency and (ii) the relative accuracy in measuring \( c \). These results illustrate that additional gain is achieved at the cost of decrease in measurement accuracy or equivalently a longer measurement time.

V. CONCLUDING REMARKS
[26] $\bar{c}$ refers to the concentration far from the receptor, compared to the size of the receptor.
FIG. 1: For the mass-spring system immersed in a particle bath, measuring the linear response of the position, $X(t)$, to a known, small external force, $F_{\text{ext}}(t)$, determines the generalized susceptibility. From this, the fluctuation–dissipation theorem can be used to obtain the power spectrum of fluctuations in the closed system at equilibrium. These fluctuations pose a lower bound on the accuracy of any measurement of the position. If measurements are carried out on many identical mass-spring systems, the expected error is reduced by a factor of $1/\sqrt{N_{\text{meas}}}$. However, as $N_{\text{meas}}$ increases this improvement ceases to hold, as neighboring mass-spring systems become physically close enough to experience correlated fluctuations from collisions with the particle bath, as shown. These correlations have been experimentally measured for two optically trapped colloidal particles [17].
FIG. 2: Schematic representation of a cluster of $N_r$ receptors of size $b$, distributed uniformly on a ring of size $a$. For $a \gg b$, the relative accuracy in measurement of the substrate concentration improves as $1/\sqrt{N_r}$ until $N_r b \sim a$, at which point the binding/unbinding events of nearby receptors are no longer independent.
FIG. 3: Circular cluster of receptors with ring radius $a = 1$: The solid lines give the numerically evaluated sum, for uniformly randomly distributed receptors of radius $b = 0.005$ (black) and $b = 0.001$ (red), and regularly distributed receptors (blue). For randomly distributed receptors, the average of $\nu(N_r)$ is shown over 1000 realizations. The dashed lines show linear fits to the numerically evaluated sums, with slope given by $g_0 = 1.931 \pm 0.004$ (for $b = 0.005$) and $g_0 = 2.433 \pm 0.002$ (for $b = 0.001$). The theoretically predicted values of these slopes are 1.907 and 2.419, respectively. The linear fit to the sum for regularly distributed receptors yields $g_0 = 1.244$. 
FIG. 4: Spherical cluster of receptors with radius $a = 1$: The solid lines give the numerically evaluated sum, for uniformly randomly distributed receptors of radius $b = 0.005$ (black) and regularly distributed receptors (blue). For randomly distributed receptors, the average of $\nu(N_r)$ is shown over 1000 realizations. The algorithm for generating uniformly distributed receptors is based on minimization of the electrical potential due to $N$ equal charges. The dashed line shows the linear fit to the numerically evaluated sum, with slope given by $g_0 = 0.996 \pm 0.001$. The theoretically predicted value is 0.995.
FIG. 5: Allosteric model of a receptor cluster as a switch: the cluster is assumed to be in one of two states, R or T (corresponding to CCW or CW rotation in the case of the bacterial flagellar motor, for example, leading to running or tumbling motion of the cell, respectively). The cluster has $N_r$ identical substrate binding sites, with dissociation constants given by $K_R = k_R^-/k_R^+$ and $K_T = k_T^-/k_T^+$ for the cluster in the R and T states, assumed to be different. The transition rates between the two states depend on the number of bound receptors, $n$, with $\ln k_f(n)/k_b(n) = \ln L + n \ln K_R/K_T$, where $L = \exp\{ -\beta (F_0^T - F_0^R) \}$ is the equilibrium constant of the switch with no bound receptors. Given an ensemble of $M$ switches, $p_T(n, t)$ is the fraction of clusters with $n$ bound receptors in the T state at time $t$, and $[T(n, t)] = M p_T(n, t)$, with $d[T(n, t)]/dt = k_f^+ [T(n+1, t)] - (k_f^- + k_b^) [T(n, t)] + k_f^- [T(n-1, t)] + k_f(n) [T(n, t)] - k_b(n) [T(n, t)]$. We assume the vertical reactions proceed more rapidly than the horizontal ones; hence the equilibrium transition rates $k_{f,b}$ between $[R] = \sum_{n=0}^{N_r} [R(n)]$ and $[T] = \sum_{n=0}^{N_r} [T(n)]$ can be obtained as averages with respect to $p_T(n)$ and $p_R(n)$. 
FIG. 6: The tumbling bias, $p_T(c)$ (top) and switching frequency, $f(c)$ (measured in s$^{-1}$), are plotted as a function of $c = [\text{CheY-P}]$ (measured in $\mu$M) for the flagellar switch. The solid lines are obtained using numerical values for the physical parameters describing the switch given: $(K_R, K_T) = (4.4, 2) \mu$M, $L = 10^{-6}$, $\mu = 1.55$, $K_b(0) = 1800$ s$^{-1}$ and $N_r = 34$. For these values, the tumbling bias and switching frequency are in good agreement with recent experimental results (see Figure 3b of [8]). However, our choice of parameter values are not obtained from fits to these experimental results; rather, they are consistent with "typical" values of these parameters for the flagellar switch, as measured in [20, 21]. The dashed line denotes the tumbling bias for $(K_R, K_T) = (17, 4) \mu$M, with $L = 10^{-6}$. Note that with increasing $K_R/K_T$, the gain of the switch increases; for the parameter values giving the dashed line, the gain is in good agreement with the experimentally measured Hill coefficient of 10.3 [8].
FIG. 7: The relative accuracy in measuring concentration as a function of $c = [\text{CheY-P}]$ (measured in $\mu$M) from observing the flagellar switch for $\tau = 1$ s. The numerical values for the physical parameters are: $(K_R, K_T) = (4.4, 2)$ $\mu$M, $L = 10^{-6}$, $\mu = 1.55$ and $k_b(0) = 1800$ s$^{-1}$. For the geometrical parameters of the motor, we use $a = 22.5$ nm, $b = 2$ nm, $N_r = 34$ and $g_0 = 1$. The diffusion constant of the substrate is taken to be $D = 3$ $\mu$m/s$^2$. 
FIG. 8: The switching frequency, $f(c)$ (measured in s$^{-1}$) (top), and the relative accuracy in measuring concentration (bottom) are plotted as a function of $c = [\text{CheY-P}]$ (measured in µM) from observing the flagellar switch for $\tau = 1$ s. The numerical values for the physical parameters are: $(K_R, K_T) = (17, 4)$ µM, $L = 10^{-6}$, $\mu = 1.55$ and $k_b(0) = 1800$ s$^{-1}$. For the geometry of the motor, we use $a = 22.5$ nm, $b = 2$ nm, $N_r = 34$ and $g_0 = 1$. The diffusion constant of the substrate is taken to be $D = 3$ µm/s$^2$. 