Ligand-concentration sensitivity of a multi-state receptor

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Biological sensory systems generally operate out of equilibrium, which often leads to improved performance. Here, we study the sensitivity of ligand concentration for a general receptor model, which is generally in the non-equilibrium stationary state, in the framework of a stochastic diffusion equation. We derived a general formula of the maximum sensitivity. Specifically, we find that any non-equilibrium receptor dynamics does not improve the sensitivity according to the laws of physics. The seminal work by Berg and Purcell [1] proved that the sensitivity of receptors detecting diffusing ligands is limited universally by the Berg-Purcell limit [Biophys. J., 1977], regardless of whether the receptor is in an equilibrium or non-equilibrium state.

FIG. 1. An example of the transition networks of a receptor (M = 5 and R = 6). Ligands are represented by green circles and receptor states as square boxes. A subset of the states generates signals indicating ligand concentrations.

by

\[
\frac{dc}{dt} = D\nabla^2 c - \delta^{(3d)}(x) \frac{d}{dt} \sum_m l_m n_m, \tag{2}
\]

where \(n_m(t)\) is the fraction of the \(m\)-th receptor state (0 \(\leq n_m(t) \leq 1\)), and \(k_r\) is the rate constant of the \(r\)-th reaction. \(k_r\) depends on the ligand concentration, \(c(x = 0, t)\), at the receptor site if \(r\) is a ligand-binding reaction (i.e., \(l_\beta(r) - l_\alpha(r) > 0\)). \(\delta^{(3d)}(x)\) represents the three-dimensional Dirac delta function.

Suppose that the system is in a steady state specified by \(c(x, t) = \bar{c}\) and \(n_m = \bar{n}_m\). \(\bar{n}_m\) is determined explicitly as a function of rate constants as \(\bar{n}_m(\bar{c})\) by solving [3], where the ligand-concentration dependence enters implicitly through \(\bar{k}_r = k_r|_{c=\bar{c}}\). By linearizing the system around the steady state and including stochastic fluctuations [24], we obtain the following Langevin equations:

\[
\frac{dc}{dt} = D\nabla^2 c - \delta^{(3d)}(x) \frac{d}{dt} \sum_m l_m \delta n_m - \nabla \cdot J, \tag{4}
\]

Here, \(\bar{k}_r \equiv \partial k_r(c)/\partial c|_{c=\bar{c}}\) is nonzero only when the \(r\)-th reaction is a ligand-binding reaction. \(\xi_r\) represents the

\[
\frac{dn_m}{dt} = \sum_r \nu_{m,r} (\bar{k}_r \delta n_\alpha(r) + \bar{k}_r' \bar{n}_\alpha(r) \delta c(x = 0, t)) + \sum_r \nu_{m,r} \xi_r. \tag{5}
\]
noise associated with the $r$-th reaction, satisfying
\[ \langle \xi_r(t) \xi_r(t') \rangle = \delta_{r,r'} \tilde{k}_r \tilde{n}_{\alpha(r)} \delta(t-t'), \]
and $J(t,x) = (J_x, J_y, J_z)$ is the diffusional noise, satisfying
\[ \langle J_i(t,x) J_j(t',x') \rangle = 2 D \bar{c} \delta_{ij} \delta(t-t') \delta^{(3)}(x-x'). \]
The term $-\nabla \cdot J$ in (4) and (7) can be derived by regarding the diffusional process as a special type of “reaction”, where a molecule at a site (in the three dimensional space) is “produced” from one located at a neighboring site, and by using van Kampen’s size expansion (see also [20]).

By applying the Fourier transform to Eqns. (4) and (5), we obtain
\[ -i \omega \sum_{m'} (\delta_{m,m'} - l_m / \tau_c) \tilde{n}_{m'} - \sum_r \nu_{m,r} \tilde{k}_r \tilde{n}_{\alpha(r)} = \sum_r \nu_{m,r} [\tilde{k}_r \tilde{n}_{\alpha(r)}] \tilde{J} + J_r, \]
where
\[ \tau_c(\omega) \equiv \frac{1}{\bar{c}} \int \frac{d^3k}{(2\pi)^3} \frac{1}{-i\omega + Dk^2} \approx \frac{\Lambda}{2\pi^2 D\bar{c}}; \]
\[ \tilde{J}(\omega) \equiv \int \frac{d^3k}{(2\pi)^3} \frac{-i \omega \tilde{J}}{-i \omega + D k^2}. \]
In [9], we have evaluated the integral at low frequency ($\omega \ll D \Lambda^2$) by introducing a UV cutoff, $\Lambda$, corresponding to the inverse of the receptor size as in [2]. $\tau_c$ represents the time-scale associated with ligand molecules diffusing around the receptor. $\tilde{J}$ represents the effective diffusional noise “felt” by the receptor, satisfying when $\omega \ll D \Lambda^2$,\n\[ \langle \tilde{J}(\omega) \tilde{J}(\omega') \rangle \approx 2\pi (2\tau_c \pi^2) \delta(\omega + \omega'), \]
where we used [7] and [9].

For ligand-concentration sensitivity, a relevant object is the spectral density, $S_{mm'}(\omega)$, defined as $\langle \delta n_m(\omega) \tilde{n}_{m'}(\omega') \rangle = 2\pi S_{mm'}(\omega) \delta(\omega + \omega')$. Although we can straightforwardly compute this from [8], the analytic computation is difficult for general receptor dynamics. For our purpose, we need only the long-term behavior (i.e., $S_{mm'}(\omega = 0)$), which can be determined indirectly, as shown below.

In the low-frequency region, by dropping the terms proportional to $\omega$, (8) can be simplified as
\[ -\sum_r \nu_{m,r} \tilde{k}_r \tilde{n}_{\alpha(r)} \approx \sum_r \nu_{m,r} (\tilde{k}_r \tilde{n}_{\alpha(r)} \tilde{J} + J_r). \]
In contrast to [8], it is no longer possible to invert the left-hand side of (12), because the coefficient matrix, $\nu_{m,r} \tilde{k}_r$, on the left-hand side is rank-deficient due to the conservation $\sum_m \frac{d}{dt} \bar{n}_m = 0$. One naive way to avoid this difficulty is to eliminate one of the $M$ variables by using $\tilde{n}_{m} = -\sum_{m' \neq m} \tilde{n}_{m'}$ and express (12) in terms of the remaining $M - 1$ variables. However, this asymmetric treatment of variables is inconvenient for the derivation of general formulas.

A key step in our approach is to make use of the following relationships satisfied by $\frac{\partial \tilde{n}_m}{\partial \bar{c}}$ and $\frac{\partial \tilde{n}_m}{\partial k_r}$,
\[ -\sum_r \nu_{m,r} \tilde{k}_r \frac{\partial \tilde{n}_{\alpha(r)}}{\partial \bar{c}} = \sum_r \nu_{m,r} \tilde{k}_r \tilde{n}_{\alpha(r)}; \]
\[ -\sum_r \nu_{m,r} \tilde{k}_r \frac{\partial \tilde{n}_{\alpha(r)}}{\partial k_r} = \nu_{m,r} \tilde{n}_{\alpha(r)}; \]
which can be easily obtained from [3]. The comparison of the coefficients in (12) and (13) implies that (12) can be expressed as
\[ \tilde{n}_{m} \approx \omega \tilde{n}_{m} \tilde{J} + \frac{1}{\nu_{m,r}} \frac{\partial \tilde{n}_m}{\partial \bar{c}} \tilde{J} + \sum_r \nu_{m,r} \tilde{J} (\Delta c)^2. \]
See the Appendix for a more rigorous derivation of (14). The physical meaning of the step from (12) to (14) is that, the low-frequency fluctuations $\delta n_{\alpha}(\omega \approx 0)$ can be determined from the dependences of the steady state on external parameters, $\bar{c}$ and $k_r$. We call the derivatives $\frac{\partial \tilde{n}_m}{\partial \bar{c}}$ and $\frac{\partial \tilde{n}_m}{\partial k_r}$ the susceptibilities of the steady states to $\bar{c}$ and $k_r$, respectively.

Finally, from (6), (11), and (14), we obtain
\[ S_{m,m'}(\omega = 0) = 2\tau_c \bar{c}^2 \frac{\partial \tilde{n}_m}{\partial \bar{c}} \frac{\partial \tilde{n}_{m'}}{\partial \bar{c}} + s_{m,m'}^{\text{reac}}, \]
where
\[ s_{m,m'}^{\text{reac}} \equiv \sum_r \tilde{k}_r \frac{\partial \tilde{n}_{\alpha(r)}}{\partial \bar{c}} \frac{\partial \tilde{n}_{m'}}{\partial k_r} \]
represents the contribution from the reaction noises, $\xi_r$.

Similar to [2] [3] [9] [11], we assume that the cell “averages” the receptor states over a long-term period, $T$, and quantify the sensitivity of ligand concentration, $\Delta c$, based on the signal-to-noise ratio (SNR). Therefore, we analyze the time-averaged fluctuations
\[ \delta N_m \equiv \frac{1}{T} \int dt \, \bar{n}_m(t), \]
and the variances
\[ C_{m,m'} \equiv \langle \delta N_m \delta N_{m'} \rangle = \frac{1}{T} S_{m,m'}(\omega = 0). \]
Suppose that a subset of receptor states (active states), $M_a \subset \{1, \ldots, M\}$, generates signals indicating the ligand concentration. The maximum SNR is then given by
\[ SNR = \sum_{m,m' \in M_a} \frac{\partial \tilde{n}_m}{\partial \bar{c}} (C^{-1})_{m,m'} \frac{\partial \tilde{n}_{m'}}{\partial \bar{c}} (\Delta c)^2. \]
The maximum sensitivity (or resolution) can be estimated from the point at which the SNR equals one, which leads to
\[
\left(\frac{\Delta c}{c}\right)^2 = \frac{1}{T F^2} \sum_{m,m' \in M_a} \frac{\partial n_{m'}}{\partial c} S_{m,m'}^{-1} \frac{\partial n_m}{\partial c}.
\] 
(20)

By plugging (15) into (20) with some matrix manipulation, the maximum sensitivity becomes
\[
\left(\frac{\Delta c}{c}\right)^2 = \frac{2\tau_c}{T} + \frac{1}{T F^2} \sum_{m,m' \in M_a} \frac{\partial n_{m'}}{\partial c} (S_{\text{reac}})^{-1} m_m \frac{\partial n_m'}{\partial c}.
\] 
(21)

The first term is the same as the BP limit, and the receptor kinetics enters into the second term, which is positive-definite, because $S_{\text{reac}}$ is a covariance matrix. Therefore, we have proven that the sensitivity is bounded by the BP limit, regardless of whether the receptor dynamics is in an equilibrium state or a non-equilibrium state.

If, as is usually assumed, all ligand-binding rates are proportional to $c$, the second term in (21) can be written as
\[
\frac{1}{T} \sum_{r,r' \in \text{l.b.}} \sum_{m,m' \in M_a} k_r \frac{\partial n_{m'}}{\partial c} (S_{\text{reac}})^{-1} m_m k_r' \frac{\partial n_m'}{\partial c},
\] 
(22)

where the summation of reactions, $r, r'$, runs over all ligand-binding reactions (l.b.). By utilizing a technique developed in [25–27], the denominator in (22) can be determined from the state-transition network of the receptor dynamics and expressed as a rational function of rate constants, $k_r$ (see Appendix for details). Such an explicit formula for arbitrary single-receptor dynamics does not exist in the literature. This enables us to evaluate the sensitivity systematically, even for receptors with complex dynamics.

As an illustration, we first examine a simple receptor model studied by Bialek and Setayeshgar in [2]. In this model, the receptor has two states: a ligand-unbound ($m = 1$) and ligand-bound state ($m = 2$). The receptor dynamics is described by
\[
\frac{d}{dt} \begin{pmatrix} n_1 \\ n_2 \end{pmatrix} = \begin{pmatrix} -k_1 & k_{-1} \\ k_1 & -k_{-1} \end{pmatrix} \begin{pmatrix} n_1 \\ n_2 \end{pmatrix},
\] 
(23)

with $k_1 = k'_c$. We assume that the cell “estimates” the ligand concentration from $n_2$ (i.e., $M_a = \{2\}$). Note that the resulting sensitivity is the same for $M_a = \{1\}$, because $\delta n_1 = -\delta n_2$. The maximum sensitivity [21] becomes
\[
\left(\frac{\Delta c}{c}\right)^2 = \frac{2\tau_c}{T} + \frac{1}{T} \frac{2(k_1 + k_{-1})}{k_1 k_{-1}},
\] 
(24)

which agrees exactly with the result derived from the FDT in [2]. We note that, although the approach based on the FDT gives only the sum of the two terms in (21), our method determines them separately, which makes clear the physical origins of these two terms: the contribution from the effective diffusional noise, $J$, and from the reaction noises, $\xi$, respectively.

For more nontrivial and biologically relevant receptor dynamics, we consider a kinetic proofreading model [28] and compare this model with the reversible-reaction analogue (Fig. 2). The kinetic proofreading model was originally proposed to explain the ability of T-cell receptors to discriminate foreign antigens from self-antigens based on relatively small differences in ligand affinities. Similar to the kinetic proofreading model of DNA synthesis [21], this model utilizes multiple irreversible steps, resulting in large differences in the production of active states depending on affinity. We remark that we here examine the sensitivity to a single ligand concentration. For a receptor model interacting with spurious ligands, see [14].

In the kinetic proofreading model, the bare receptor binds with a ligand molecule (with rate $k_1 = k'_c$), and the ligand-bound state is then phosphorylated up to $M - 2$ times (with rate $k_p$, for each modification). The phosphorylated states revert to the unbound state with transition rate $k_{-1}$. By contrast, the reversible model consists of a ligand-binding reaction (with rate $k_1 = k'_c$), $M - 2$ forward reactions (with rate $k_p$), and $M - 1$ backward reactions (with rate $k_{-1}$).

We assume that only the final state is active and sends signals indicating ligand concentrations (i.e., $M_a = \{M\}$). Introducing the dimensionless parameters $\kappa_1, \kappa_{-1}$ as
\[ k_1 = \kappa_1 k_p, \quad k_{-1} = \kappa_{-1} k_p, \] 
(25)

we can express the maximum sensitivity, (21), in the following form:
\[
\left(\frac{\Delta c}{c}\right)^2 = \frac{2\tau_c}{T} + \frac{F_M(\kappa_1, \kappa_{-1})}{k_p T},
\] 
(26)

where $F_M$ is a dimensionless factor that depends on $\kappa_1, \kappa_{-1}$ (see the Appendix for the explicit expression of $F_M$).

Before presenting the numerical results, we estimate the two terms in (26) for acceptably accurate sensing.
in the two models. In the region of $\kappa M$ significantly as $\kappa$ increases, $O$ can become surface, which we assume to be $\sim 10^3$. Thus far, we have considered a single receptor. When $\kappa$ becomes larger (or the sensitivity becomes $\sim 10^3$), the behaviors differ qualitatively between the two models. While $F$ in the reversible model, an accurate sensing is possible over a wide range of $\kappa M$, $F$ might be larger in the reversible models, except for $\kappa M < 10^3$, deteriorating the sensitivity exponentially in $\kappa M$. Therefore, when $\kappa_1 < 1$, the dependence on $k_1$ diminishes along the long reaction chain, because a large factor, $\frac{1}{\kappa_1}$, is multiplied in each step toward the active state. By contrast, in the kinetic proofreading model, $\bar{n}_i/\bar{n}_i-1 = \frac{1}{\kappa_1}$ for $i = 3, ..., M$. Therefore, when $\kappa_1 < 1$, the dependence on $k_1$ is maintained along the reaction chain.

We note that, in the study of T-cell receptors in $\text{[25]}$, it is the susceptibility to the dissociation constant, $\partial \bar{n}_i/\partial \kappa_1$, that leads to T-cell receptor selectivity. However, what we have discussed here is the susceptibility to ligand concentration, $\partial \bar{n}_i/\partial \kappa_1$, which is relevant for the sensitivity to ligand concentration.

In summary, for precise sensing, the receptor does not allow many intermediate modification steps in the broad range of $\kappa_1$ in the reversible model. However, in the kinetic proofreading model, precise sensing is compatible with many internal states, as long as $\kappa_1 < 1$.

Thus far, we have considered a single receptor. When a cell has many independent receptors, the sensing accuracy of the entire cell is estimated by dividing $\bar{F}$ by the total number of receptors expressed on the cell surface, which we assume to be $\sim 10^4$. We estimate $\tau_c = 10^{-1} - 10^3$ sec, (we used $D = 10^{-1} - 10^3$ um$^2$/sec, a linear dimension of receptor $a \equiv \frac{A}{2} \sim 10^{-2}$um, and $\bar{c} = 10^2 - 10^4$ um$^{-2}$/sec), and the rate constant $k_p = 10^{-3} - 10^{-1}$ sec$^{-1}$ (see $\text{[29-31]}$ for this estimate). Using these values, while the first term in (26) is acceptably small for the integration times $T \sim 10^6$ and sec, the second term can become $O(1)$ only if $F_M < 10^3$. Therefore, in the following, we focus on the receptor-dependent part in (26), $F_M$.

Fig. 3 shows the numerical results of $F_{M-S}(\kappa_1, \kappa_1)$ in the two models. In the region of $\kappa_1 > 1$ (the upper-half region of Fig. 3) corresponding to rapid dissociation, the sensitivities in both models behave in a qualitatively similar way: $F_M$ is large, except for $\kappa_1 < 1$, and, as $\kappa_1$ increases, $F_M$ becomes larger (or the sensitivity becomes worse) rapidly. By contrast, in the region of $\kappa_1 < 1$, corresponding to slow dissociation, the behaviors differ qualitatively between the two models. While $F_M$ is large in the reversible models, $F_M$ does not depend significantly upon $\kappa_1$ and remains at a lower level in the kinetic proofreading model. Therefore, when $\kappa_1 < 1$ in the kinetic proofreading model, an accurate sensing is possible over a wide range of $\kappa_1$, or, equivalently, ligand-concentration, because $\kappa_1 = \frac{k_c}{k_p}$.

Next, we examine the dependence of $F_M$ on the length of the reaction chains, $M$ (see Fig. 4 (Left)). For simplicity of analysis, we set $\kappa_1 = 1$. From the analytical expression of $F_M$ in the Appendix, we can show that in both models, $F_M$ asymptotically approaches $F_M \sim 2\kappa^{-M-2}$ when $\kappa_1 \gg 1$, deteriorating the sensitivity exponentially as $M$ becomes large. However, when $\kappa_1 \ll 1$ and while $F_M \sim 2\kappa^{-M-3}$ is in the reversible model, which is again exponential in $M$, $F_M \sim M(M-1)/\kappa_1$ in the kinetic proofreading model, which depends on $M$ only algebraically. Therefore, when $\kappa_1 < 1$ and $M$ is large, the sensitivity is much higher in the kinetic proofreading model, compared with the reversible model. Note that in either model, for fixed $\kappa_1$, the sensitivity declines monotonically as $M$ increases.

From where does the discrepancy in performance between the two models originate? The sensitivity is determined form the ratio between the (squared) susceptibility, $(k_1 \partial \bar{n}_M/\partial k_1)^2$, and the fluctuation, $S_{M,M}^{\text{rev}}$ (see $\text{[22]}$). As shown in Fig. 4 (right), the value of $S_{M,M}^{\text{rev}}$ does not differ significantly between the two models. Therefore, the higher accuracy in the kinetic proofreading model essentially derives from its higher susceptibility, which can be understood as follows: In the reversible model, $\bar{n}_i/\bar{n}_i-1 = \frac{1}{\kappa_1}$ for $i = 3, ..., M$. Therefore, when $\kappa_1 < 1$, the dependence of $\bar{n}_M$ on $k_1$ diminishes along the long reaction chain, because a large factor, $\frac{1}{\kappa_1}$, is multiplied in each step toward the active state. By contrast, in the kinetic proofreading model, $\bar{n}_i/\bar{n}_i-1 = \frac{1}{\kappa_1}$ for $i = 3, ..., M-1$, which is not large when $\kappa_1 < 1$. Therefore, the dependence on $k_1$ is maintained along the reaction chain.

We note that, in the study of T-cell receptors in $\text{[25]}$, it is the susceptibility to the dissociation constant, $\partial \bar{n}_M/\partial k_1$, that leads to T-cell receptor selectivity. However, what we have discussed here is the susceptibility to ligand concentration, $\partial \bar{n}_M/\partial k_1$, which is relevant for the sensitivity to ligand concentration.

In summary, for precise sensing, the receptor does not allow many intermediate modification steps in the broad range of $\kappa_1$ in the reversible model. However, in the kinetic proofreading model, precise sensing is compatible with many internal states, as long as $\kappa_1 < 1$. 

![Fig. 3. The numerical result of $\log_{10} F_M$ for $M = 8$ in the kinetic proofreading model (left) and in the reversible model (right). Roughly, $F_M < 10^3$ is required for accurate estimation of ligand-concentration changes.](image1)

![Fig. 4. (Left) $F_M(1, \kappa_1)$ for $M = 6, 9, 12$ in the kinetic proofreading model (thick lines) and the reversible model (dashed lines). (Right) The thick and dashed lines represent the ratios $X_{\text{kin, proof}}/X_{\text{rev}}$, between the two models for $X = S_{M,M}^{\text{rev}}$ and $(k_1 \partial \bar{n}_M/\partial k_1)^2$, respectively.](image2)
serve as the basis for further research into more complex, realistic ligand-receptor dynamics investigations. For example, a potential generalization is the case where, in addition to the ligand the receptor estimates its concentration, the receptor is regulated by other (freely diffusing) ligand species. In this case, as shown in Appendix, $S_{\text{reac}}$ in [21] is replaced by

$$S_{m,m'}^{\text{reac}} \rightarrow S_{m,m'}^{\text{reac}} + \sum_i 2\tau_i \bar{c}_i^2 \left( \frac{\partial \bar{n}_m}{\partial \bar{c}_i} \right)^2,$$

where $i$ labels other ligand species with concentration $\bar{c}_i$ and diffusion constant $D_i$, and $\tau_i \equiv \frac{\Lambda}{2\pi^2 D_i \bar{c}_i}$. We can also investigate reacting ligands by replacing reaction-diffusion equations. Another biologically relevant and theoretically challenging extension involves dynamically interacting receptors, for example, through ligand-regulated oligomerizations, as in the epidermal growth factor (EGF) receptors [32]. We hope to report progress in these directions in the near future.

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