Chemical Sensing by Nonequilibrium Cooperative Receptors

Monica Skoge, Sahin Naqvi, Yigal Meir, and Ned S. Wingreen

Phys. Rev. Lett. **110**, 248102 — Published 11 June 2013

DOI: 10.1103/PhysRevLett.110.248102

Chemical sensing by nonequilibrium cooperative receptors

Monica Skoge,[1] Sahin Naqvi,[2,*] Yigal Meir,[3] and Ned S. Wingreen[2]

[1] *Department of Biology, University of California San Diego, San Diego, CA 92037*
[2] *Department of Molecular Biology, Princeton University, Princeton, NJ 08544*
[3] *Department of Physics, Ben-Gurion University, Beer Sheva, Israel 84105*

Cooperativity arising from local interactions in equilibrium receptor systems provides gain, but does not increase sensory performance, as measured by the signal-to-noise ratio (SNR) due to a fundamental tradeoff between gain and intrinsic noise. Here we allow sensing to be a nonequilibrium process and show that energy dissipation cannot circumvent the fundamental tradeoff, so that SNR is still optimal for independent receptors. For systems requiring high gain, nonequilibrium 2D-coupled receptors maximize SNR, revealing a new design principle for biological sensors.

Biological systems generally operate out of equilibrium, using free-energy dissipation to drive metabolic reactions, perform mechanical work via molecular motors, communicate over large distances via action potentials, and much more. In cellular information processing, free-energy dissipation plays essential roles in adaptation [1], time-averaging [2], and the sensitivity of chemical switches [3], and can overcome equilibrium physical limits to performance [4, 5]. The best-known example of the latter is kinetic proofreading [4], in which the specificity of interaction between an enzyme and two competing substrates can exceed the equilibrium limit set by the ratio of their binding affinities. Previously, we identified a tradeoff between gain and intrinsic noise for equilibrium *locally* coupled receptor systems, limiting their ability to sense weak signals, as measured by the signal-to-noise ratio (SNR) [6]. Can free-energy dissipation also help circumvent this tradeoff and thereby increase sensory performance?

In what follows, we answer this question generally for 1D- and 2D-coupled receptor systems by optimizing the SNR over the full, nonequilibrium parameter space of these systems, subject only to constraints of lattice symmetry and locality of interactions. Compared to equilibrium, these systems gain additional parameters related to cyclic fluxes, which enable novel behavior. Our main results are: (a) even for nonequilibrium the SNR is optimal for independent receptors compared to coupled receptors, and (b) when gain (and hence cooperativity) is required, nonequilibrium can improve SNR for 2D-coupled receptors, but not for 1D-coupled receptors. The first result is an extension of our previous equilibrium observations, showing that nonequilibrium can at best modestly alter the tradeoff between gain and intrinsic noise due to interaction-mediated slowing down. To understand the second, surprising result we map the dynamics of cooperative receptors onto simpler 1-step processes, and uncover an optimal design principle for biological sensors with high gain.

A classic problem facing the cell, originally posed by Berg and Purcell [7], is the estimation of external ligand concentration via cell-surface receptors in the presence of stochastic fluctuations. Here, we consider a variant of this problem motivated by *E. coli*'s strategy of sensing small *changes* in chemotactic ligand concentration using strongly-coupled chemoreceptors. Following our previous framework [6], we study the linear response of the average total activity $A \in [0, N]$ of N coupled receptors to a small relative change in ligand concentration $\Delta \log([\mathrm{L}])$, time-averaged over a period τ_{avg} (*e.g.* set by the turnover time of the response regulator CheY-P in *E. coli*) that is long. The sensing performance of the cell is governed by the signal-to-noise ratio per receptor [6]

$$\mathrm{SNR}(\tau_{\mathrm{avg}}) \equiv \frac{(\Delta A)^2}{N\sigma^2(\tau_{\mathrm{avg}})}, \tag{1}$$

where $\Delta A \sim \Delta \log([\mathrm{L}])$ is the resulting change in average activity and $\sigma^2(\tau_{\mathrm{avg}})$ is the long-time-averaged variance of activity, which decreases as $\sim 1/\tau_{\mathrm{avg}}$ as $\tau_{\mathrm{avg}} \to \infty$.

We model receptor cooperativity using a general Ising-type framework with *local* receptor-receptor interactions. By varying the coupling strength J, our model encompasses independent receptors ($J = 0$), receptors near a critical point (intermediate $J \approx J_c$), as well as allosteric Monod-Wyman-Changeaux (MWC) receptors [8] (large J). This last regime has had much success explaining steady-state signal amplification by bacterial chemoreceptors. Importantly, finite J intrinsically slows down the rate of receptor switching, thereby limiting noise reduction via time-averaging [6]. Indeed, this slowing down is most dramatic in the strongly-coupled (large J) limit and corresponds to the very slow switching of a ferromagnet below the transition temperature – a process generally considered too slow to be relevant for magnets, but required for signaling by MWC systems. The previous successful applications of the MWC model to bacterial chemoreceptors motivate our question whether nonequilibrium can counteract the slowing down of receptor switching and increase sensory performance.

Specifically, we consider four-state receptors, which can bind/unbind ligand with rates $\{k\}$ and switch conformations between active and inactive states with rates $\{w\}$, as shown schematically in Fig. 1(A). As allosteric coupling between receptors is mediated via the conformational degrees-of-freedom as opposed to the occupancy

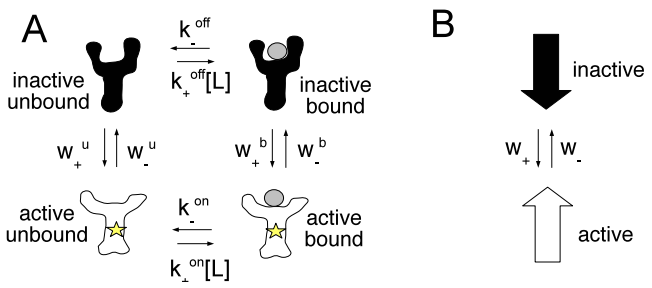

FIG. 1. **Single receptor. (A)** Schematic diagram of interconversion among the four states of a single receptor: inactive/unbound, inactive/bound, active/bound, and active/unbound. **(B)** In the limit of fast ligand binding and unbinding, the receptor dynamics reduces to switching between two states, active and inactive.

1D Neighbors	$\Delta\epsilon$
$++$	$-4J+f+\gamma_{f2}$
$-+$	f
$--$	$4J+f+\gamma_{f2}$
2D Neighbors	$\Delta\epsilon$
$++++$	$-8J+f+\gamma_{f4}$
$-+++$	$-4J-\gamma_J+f+\gamma_{f3}$
$--++$	f
$---+$	$4J+\gamma_J+f+\gamma_{f3}$
$----$	$8J+f+\gamma_{f4}$

TABLE I. Energy change $\Delta\epsilon$ upon switching conformation from inactive to active with a given configuration of nearest neighbors.

of binding pockets, we let the switching rates $\{w\}$ depend on the conformation/activity (but not the occupancy) of neighboring receptors, while keeping the binding/unbinding rates $\{k\}$ independent of neighboring receptors. Conformational switching rates $\{w\}$ ($\leq 10^4$/s for large-scale rearrangements [9]) are typically slower than the binding/unbinding rates $\{k\}$ ($\approx 10^5$/s for bacterial chemoreceptors [10]), and, therefore, many individual binding/unbinding events contribute to an effective field f that biases receptor activity via the differences in ligand affinity between the active and inactive states. In this fast binding limit, the dynamics of four-state receptors can be reduced to that of effective two-state receptors, as shown schematically in Fig. 1(B), with changes in ligand concentration implying changes in the field f. Consequently, we can write the signal ΔA in Eq. (1) as

$$\Delta A = \frac{1}{4} R \Delta f, \tag{2}$$

where we define the response $R \equiv 4dA/df$ and the gain $R/N \in [1, N]$ is the amplification of changes in activity relative to independent receptors due to receptor-receptor interactions. In what follows, we deal exclusively with coupled two-state receptors and optimize $\mathrm{SNR}/[\tau_{\mathrm{avg}}(\Delta f)^2]$ to focus on the benefits of nonequilibrium for receptor cooperativity [11]. (For a full discussion of the role of nonequilibrium in determining the sensitivity of the four-state receptor, see [12].)

The behavior of the coupled two-state receptor system is completely determined by the conformational switching rates $\{w\}$, and thus we seek to optimize these rates to maximize SNR, without imposing the equilibrium constraint of detailed balance. As a simple multiplicative increase of all rates can trivially decrease the correlation time, thereby decreasing noise and increasing SNR, we constrain the sum of forward and backward rates for conformational switching to be $w_+ + w_- = \alpha$, where α is the intrinsic switching rate (with units of inverse time) [13].

In this case, the rates $\{w\}$ can be expressed in the form of heat-bath kinetics

$$w_\pm = \frac{\alpha}{1+e^{\pm\Delta\epsilon}}, \tag{3}$$

where $\Delta\epsilon$ is an effective energy change upon switching conformation from inactive to active [14].

1D receptors. We first consider a 1D chain of N receptors. For the 1D-chain, there is only one nonequilibrium degree-of-freedom $\gamma_{f2} \equiv \Delta G/2$, which we define in terms of the thermodynamic driving force ΔG of the 4-cycle shown in Fig. 2(A): For any cycle in a nonequilibrium steady-state system, the thermodynamic driving force ΔG is related to the ratio of the cycle fluxes, $j_{\mathrm{CW}}/j_{\mathrm{CCW}}$, in the clockwise versus counterclockwise directions, or equivalently, the ratio of the product of rate constants going clockwise around the loop to that going counterclockwise, according to [15, 16]

$$e^{-\Delta G} = \frac{j_{\mathrm{CW}}}{j_{\mathrm{CCW}}} = \frac{w_1 w_2 w_3 w_4}{w_{-1} w_{-2} w_{-3} w_{-4}}, \tag{4}$$

In equilibrium, these products are equal so that $\Delta G = 0$. Therefore, the ΔG's for cycles in reaction space provide a useful basis for parameterization of the nonequilibrium behavior. The energy dissipation rate attributable to a given cycle is the product of ΔG and the net cycle flux $j_{\mathrm{CW}} - j_{\mathrm{CCW}}$ (in analogy to power being the product of voltage and current in electrical circuits [15]).

The switching rates $\{w\}$ from Eq. (3) are parameterized in Table I in terms of γ_{f2} and the equilibrium Ising parameters [17]: the coupling strength J and the field f. The nonequilibrium parameter γ_{f2} behaves as an additional field present only when nearest neighbors match each other's activity. As expected, the model reduces in equilibrium ($\gamma_{f2} = 0$) to the 1D Ising model with heat bath kinetics [17].

For a 1D-chain with $N = 9$, we globally searched the J, f, γ_{f2} parameter space to maximize the SNR numerically utilizing the nonequilibrium FDT [12, 18]. We found that SNR is globally optimal for independent re-

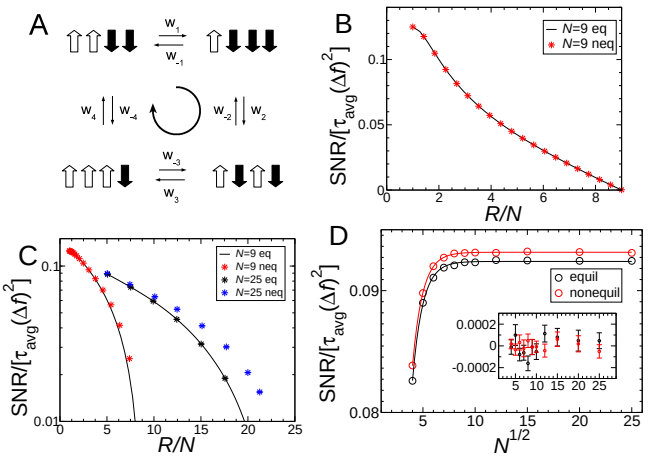

FIG. 2. **1D- and 2D-coupled receptors.** **(A)** Schematic diagram of 4-state cycle for a chain of 1D-coupled receptors. White-up and black-down arrows denote active and inactive receptors, respectively. Optimal SNR/$[\tau_{\rm avg}(\Delta f)^2]$ as a function of gain R/N for **(B)** 1D- and **(C)** 2D-coupled receptors for equilibrium (black) and nonequilibrium (red $N = 9$ and blue $N = 25$). **(D)** SNR/$[\tau_{\rm avg}(\Delta f)^2]$ as a function of linear system size $N^{1/2}$ for gain $R/N = 5$ for equilibrium (black) and nonequilibrium with $\gamma_J = -0.5$ (red). Error bars show standard errors of the mean and curves are exponential fits. The inset shows the residuals from the fits.

ceptors, as shown in Fig. 2(B). Moreover, even for a specified gain, nonequilibrium offers no advantage.

2D receptors. Can nonequilibrium improve SNR in higher dimensions? For a 2D square lattice with nearest-neighbor interactions and four-fold symmetry [19], there are three nonequilibrium degrees-of-freedom, which we define as γ_{f3}, γ_{f4}, and γ_J. As in 1D, we define these nonequilibrium parameters in terms of the driving forces for 2D versions of the cycle shown in Fig. 2(A) [12]. The 2D switching rates $\{w\}$ from Eq. (3) are given in Table I. Like γ_{f2} of the 1D model, the nonequilibrium parameters γ_{f3} and γ_{f4} behave as additional fields specific for the states with three and four activity-matched nearest neighbors, respectively. The third nonequilibrium parameter γ_J behaves as an additional coupling strength for states with exactly three matched nearest neighbors.

For 2D receptors, a global search of the 5-dimensional $J, f, \gamma_{f3}, \gamma_{f4}, \gamma_J$ parameter space reveals, once again, that SNR is maximal for independent equilibrium receptors. However, unlike 1D, for a specified gain $R/N > 1$, nonequilibrium does increase the SNR relative to nonequilibrium, as shown in Fig. 2(C), via an "antiferromagnetic" pseudo-coupling $\gamma_J < 0$. Though modest, this improvement is not simply a finite-size effect and persists in the limit $N \to \infty$, as shown in Fig. 2(D) with $\gamma_J = -0.5$ chosen for convenience (since γ_J is not optimal this provides a lower bound on the increase in SNR achievable by nonequilibrium).

Why does nonequilibrium improve SNR for 2D-coupled receptors (but not 1D-coupled receptors)? For a fixed gain R/N, optimizing SNR is equivalent to minimizing the noise $\sigma^2(\tau_{\rm avg})$. We find that nonequilibrium does not decrease the steady-state variance ("snapshot noise") [12], and therefore it must decrease the correlation time of the noise τ_c, making time-averaging more effective. In the high-gain regime, the steady-state distribution of activity $p(A)$ is strongly peaked at the fully active/inactive states and the correlation time is approximately the mean-first-passage-time (MFPT) to switch from fully inactive/active to half-maximal activity. As shown in Fig. 3(A), the SNR for nonequilibrium optima depends linearly on the inverse MFPT as the nonequilibrium parameter γ_J is varied, showing that nonequilibrium indeed improves SNR by minimizing MFPT.

Activity as a reaction coordinate. To better understand how nonequilibrium decreases MFPT at high gain, we map the dynamics of our coupled receptor systems with their N-dimensional state space onto a single dimension, a suitable reaction coordinate, which we take to be the normalized and symmetrized total activity $a \equiv 2A/N - 1$. The dynamics then takes the form of an analytically tractable 1-step process [20], as shown schematically in the inset to Fig. 3(B). For the forward and backward rates $w^n_\pm$, we take the trajectory-averaged transition rates from simulations of the dynamics in the full state space. This mapping to a 1-step process preserves the dynamics surprisingly well, specifically capturing the SNR as a function of gain as shown in Fig. 3(B) for both 1D- and 2D-coupled receptors.

The dynamics of 1-step processes are fully described by the steady-state probability distribution $p(a)$ and diffusion coefficient $D(a) \equiv (w^n_+ + w^{n+1}_-)(N\Delta a)^2/2$, where $\Delta a = 2/N$ is the spacing between states along the reaction coordinate. The relationship between MFPT, $p(a)$, and $D(a)$ has been calculated in Ref. [20] and in the continuum $N \to \infty$ limit is

$$\text{MFPT} = N^2 \int_{-1}^{0} da \frac{1}{D(a)p(a)} \int_{-1}^{a} da' p(a'). \qquad (5)$$

Using Eq. (5) we can ask what are the optimal $p(a)$ and $D(a)$ that minimizes MFPT for a certain gain. This question is only meaningful if the transition rates are constrained from diverging. For simplicity, we fix the total sum of transition rates $\sum_i (w^i_+ + w^i_-)$ or in the continuum limit the integral of $D(a)$ to be constant. The resulting optimal "potential", $-\log p(a)$, is shown in Fig. 3(C) (dashed curve) and consists of a flat barrier separating deep wells at the extreme activity states [12]. The deep wells make the first transition out of the fully active/inactive state rate limiting and ensure high gain. Subsequently, the flat potential gives a high probability for a fast direct switch to the opposite activity state. This mesa-like shape of the potential is also optimal when diffusion is held constant [12].

Strikingly, the optimal 1-step potential agrees almost precisely with the shape of the 2D nonequilibrium effective potential, as shown in Fig. 3(C). Comparison to the corresponding 2D equilibrium potential shows that nonequilibrium decreases MFPT by flattening the potential along the reaction coordinate. This insight also offers a simple explanation why there is no benefit of nonequilibrium in 1D: equilibrium 1D-coupled receptors already have a flat potential (green curve), as switching in 1D involves the unbiased diffusion of a single domain boundary separating active and inactive receptors.

What dimensionality of coupling yields the highest SNR, *i.e.* the fastest MFPT, for a fixed gain? In addition to the shape of the potential, the magnitude of the diffusion coefficient $D(a)$ is also important in determining MFPT. As shown in the inset to Fig. 3(D), 1D-coupled receptors have strikingly lower diffusion coefficient than receptors with higher-dimensional coupling. Diffusion along the reaction coordinate in 1D at high gain occurs exclusively via switching of one of the two receptors at the domain boundary. In contrast, multiple viable switching trajectories are possible in 2D. In the extreme case of all-to-all coupling, which can in principle be achieved by long-range interactions or a rapidly diffusable factor, any of the N receptors can always switch, thereby increasing the diffusion coefficient along the reaction coordinate. However, all-to-all coupling yields an unfavorable potential barrier of high curvature, as shown in Fig. 3(C). Consequently, nonequilibrium 2D-coupled receptors achieve the fastest switching in the high gain regime, as shown in Fig. 3(D), because they have the combined benefits of a relatively flat effective potential and a large diffusion coefficient.

To summarize, nonequilibrium cannot solve the problem of interaction-mediated slowing down inherent in cooperativity achieved via local receptor-receptor interactions. Hence, independent receptors maximize signal-to-noise ratio (SNR). However, nonequilibrium can increase SNR for a fixed gain by minimizing the mean-first-passage time (MFPT) of switching between extreme activity states. More generally, optimizing the tradeoff between cooperativity and interaction-mediated slowing down at fixed gain leads to a novel optimal-design principle for chemical sensing networks – namely bistable effective potentials with flat barriers separating deep wells. For sensing via coupled-receptor systems, we have found an unexpected near-optimality of nonequilibrium 2D-coupled receptors, which may offer insight into the organization of *E. coli* chemoreceptors.

This work was supported in part by National Science Foundation Grant PHY-0957573 and by the National Institutes of Health (www.nih.gov) Grant R01 GM082938.

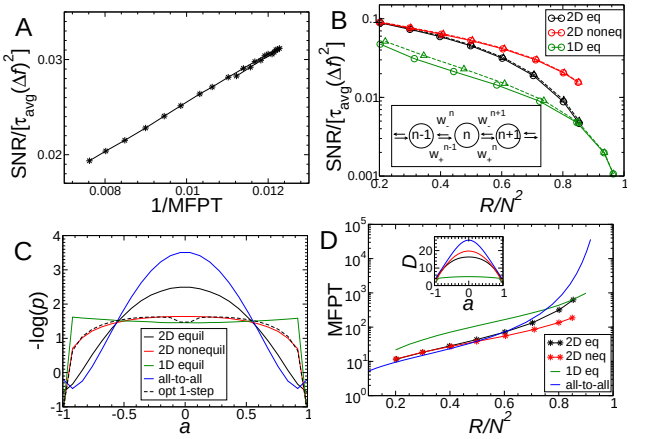

FIG. 3. **SNR, MFPT, and effective potentials at fixed gain.** **(A)** $\mathrm{SNR}/[\tau_{\mathrm{avg}}(\Delta f)^2]$ versus 1/MFPT for 2D-coupled receptors with $N = 25$ for gain $R/N = 0.7N$ as γ_J is increased from zero (starting at left). **(B)** $\mathrm{SNR}/[\tau_{\mathrm{avg}}(\Delta f)^2]$ versus normalized gain R/N^2 for 1D- and 2D-coupled receptors and their mappings to 1-step processes (dashed lines). Inset shows schematic of 1-step process with transition probabilities [20]. **(C)** "Potentials", $-\log p(a)$, as functions of normalized and symmetrized activity $a = 2A/N - 1$ for Ising lattices with $N = 25$ for gain $R/N = 0.7N$ and the optimal 1-step process (dashed curve). **(D)** MFPT as a function of R/N^2(=gain/N) for Ising lattices with $N = 25$. Inset shows the diffusion coefficients $D(a)$ for gain $R/N = 0.7N$.

* Present address: Department of Biology, MIT

[1] G. Lan, P. Sartori, S. Neumann, V. Sourjik, and Y. Tu, Nature Physics **8**, 422 (2012).
[2] P. Mehta and D. J. Schwab, Proc. Natl. Acad. Sci. USA **109**, 17978 (2012).
[3] H. Qian and T. Reluga, Phys. Rev. Lett. **94**, 28101 (2005).
[4] J. J. Hopfield, Proc. Natl. Acad. Sci. USA **71**, 4135 (1974).
[5] Y. Tu, Proc. Natl. Acad. Sci. USA **105**, 11737 (2008).
[6] M. Skoge, Y. Meir, and N. S. Wingreen, Phys. Rev. Lett. **107**, 178101 (2011).
[7] H. C. Berg and E. M. Purcell, Biophys. J. **20**, 193 (1977).
[8] J. Monod, J. Wyman, and J. P. Changeux, J. Mol. Biol. **12**, 88 (1965).
[9] R. G. Smock and L. M. Gierasch, Science **324**, 198 (2009).
[10] Assuming diffusion-limited binding [7] with diffusion coefficient $D = 400\mu^2/s$ and receptor size $s = 10$nm gives an association rate $k_+ = 4Ds = 3.9e9/[M]s$. For observed chemotactic ligand affinities of $\approx 20\mu M$ [21], the corresponding dissociation rates is $k_- = 7.7e4/s$.
[11] By restricting our analysis to coupled two-state receptors rather than four-state receptors, we neglect possible nonequilibrium coupling between ligand binding and receptor interactions.
[12] See supplementary information.
[13] We investigated letting $w_+ + w_- \leq \alpha$, but found SNR

was always optimal for equality.
[14] We work in units such that $k_B T = 1$, $\alpha = 1$ and $K^{\rm off} = 1$.
[15] T. L. Hill, *Free energy transduction in biology* (Academic Press, 1977).
[16] D. A. Beard and H. Qian, PLoS ONE **2**, e144 (2007).
[17] R. J. Glauber, J. Math. Phys. **4**, 294 (1963).
[18] M. Baiesi, C. Maes, and B. Wynants, Phys. Rev. Lett. **103**, 010602 (2009).
[19] For simplicity, we assume the same switching rates for the states with neighbors $++--$ or $+-+-$ around the cardinal directions.
[20] N. G. V. Kampen, *Stochastic processes in physics and chemistry, 3rd Ed.* (Academic Press, 1977).
[21] J. E. Keymer, R. G. Endres, M. Skoge, Y. Meir, and N. S. Wingreen, Proc. Natl. Acad. Sci. USA **103**, 1786 (2006).