Supporting Information: Thermodynamics of Statistical Inference by Cells

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Contents

NOTATION

Here we provide more details of the results in the main text. First, we outline our notation. The time dependent probability of state i is $p_i = p_i(t)$, while the steady state probability of state i is p_i^{ss}. The Laplace transformed probability of state i is $P_i(s)$. The rate to go from state i to state j is k_{ij}. The probability to transition from state i to state j is q_{ij}. The time it takes to transition from state i to j is τ_{ij}. The first passage time is given by $f(t)$ while the Laplace transformed first passage time is $F(s)$. The lifetime of state i is ρ_i.

DETAILED DERIVATION OF GENERAL UNCERTAINTY

Here we derive formulas for the accuracy of statistical inference when the activated signaling states continuously produce signals. Following Berg and Purcell [1], we will measure the accuracy of a receptor by the "uncertainty" of the concentration estimate:

$$\text{uncertainty} := \frac{\langle (\delta c)^2 \rangle}{\bar{c}^2} \tag{1}$$

where $\bar{c}$ is the mean and $\langle (\delta c)^2 \rangle$ is the variance of the estimated concentration.

Let us consider the case where activated signaling states produce downstream signaling molecules at a rate α. We will define $\overline{\tau}_S$ as the mean lifetime of the signaling states and $\overline{\tau}_{NS}$ as the mean non-signaling time. Then, we know that the mean number of signaling molecules $\overline{u}$ produced after a time T is given by

$$\overline{u} = \alpha T \left(\frac{\overline{\tau}_S}{\overline{\tau}_S + \overline{\tau}_{NS}} \right) \equiv \alpha T \bar{\phi} \tag{2}$$

This follows by noting that $\bar{\phi}$ is just the fraction of time the receptor is in the signaling states. Notice that by definition, α and T are independent of the concentration c. The signaling time $\overline{\tau}_S$, can in principle depend on concentration, and for L signaling states is given by

$$\overline{\tau}_S = \sum_{i=1}^{L} p_{0i} \tau_{i0} \tag{3}$$

where p_{0i} is the probability to transition from state 0 to state i, and τ_{i0} is the mean time to return from state i to state 0. Since we assume the receiving state is strongly biased (i.e. k_{01} is much larger than any other rate k_{0i} from non-signaling, 0, to signaling state i), then the derivative of the signaling time with respect to concentration is:

$$\frac{d\overline{\tau}_S}{dc} = -\sum_{i=2}^{L} \frac{k_{0i}}{k_{01}} \left(\tau_{10} + \tau_{i0} \right) \tag{4}$$

Since this is by assumption small, we will approximate $\overline{\tau}_S$ as independent of concentration, and thus all the concentration dependence comes from $\overline{\tau}_{NS}$. Thus, using the usual error-propagation formulas one has

$$\frac{\delta u}{\overline{u}} = -\frac{d\overline{\tau}_{NS}}{dc} \frac{1}{\overline{\tau}_S + \overline{\tau}_{NS}} \delta c \tag{5}$$

which gives the uncertainty for the concentration:

$$\frac{\langle (\delta c)^2 \rangle}{\overline{c}^2} = \left(\overline{c} \frac{d\overline{\tau}_{NS}}{dc} \right)^{-2} \left(\overline{\tau}_{NS} + \overline{\tau}_S \right)^2 \frac{\langle (\delta u)^2 \rangle}{\overline{u}^2} \tag{6}$$

The formula above reduces the problem to calculating the uncertainty in the number of signaling molecules produced in a time T. To calculate this, notice that $\overline{u}$ comes from on average $\overline{N} = T/(\overline{\tau}_S + \overline{\tau}_{NS})$ independent binding cycles (state 0 to state 1 transition). Thus, the variance in the fraction of time bound during a time T will just be $\overline{N}^{-1}$ times the variance in a single binding cycle. In particular, the coefficient of variation in a single cycle is given by

$$\frac{\delta \phi}{\overline{\phi}} = \frac{\overline{\tau}_{NS}}{\overline{\tau}_S + \overline{\tau}_{NS}} \left[\left(\frac{\delta \tau_S}{\overline{\tau}_S} \right) - \left(\frac{\delta \tau_{NS}}{\overline{\tau}_{NS}} \right) \right] \tag{7}$$

Noting that the signaling and non-signaling events are independent, we get

$$\frac{\langle (\delta u)^2 \rangle}{\overline{u}^2} = \frac{1}{\overline{N}} \left(\frac{\overline{\tau}_{NS}}{\overline{\tau}_S + \overline{\tau}_{NS}} \right)^2 \left[\frac{\langle (\delta \tau_{NS})^2 \rangle}{\overline{\tau}_{NS}^2} + \frac{\langle (\delta \tau_S)^2 \rangle}{\overline{\tau}_S^2} \right] \tag{8}$$

Plugging this expressions into (6) gives

$$\frac{\langle (\delta c)^2 \rangle}{\overline{c}^2} = \frac{1}{\overline{N}} \left(\overline{c} \frac{d \log \left(\overline{\tau}_{NS} \right)}{dc} \right)^{-2} \left[\frac{\langle (\delta \tau_{NS})^2 \rangle}{\overline{\tau}_{NS}^2} + \frac{\langle (\delta \tau_S)^2 \rangle}{\overline{\tau}_S^2} \right] \tag{9}$$

Therefore the complicated response of a receptor is reduced to its mean and variance of the time in both the signaling and non-signaling states. In this paper, we will examine the case where there is a single non-signaling state (0) and there are L signaling states arranged in a ring. In this case, the above expression simplifies to (leading order k_{0L}/k_{01}):

$$\frac{\langle (\delta c)^2 \rangle}{\overline{c}^2} = \frac{1}{\overline{N}} \left[1 + \frac{\langle (\delta \tau_S)^2 \rangle}{\overline{\tau}_S^2} \right] \tag{10}$$

For a two state process as considered by Mora and Wingreen [2], there is only the receiving state and one signaling state. These are just Poisson processes which each have an uncertainty of 1 and we recover the Berg and Purcell [1] limit

$$\frac{\langle (\delta c)^2 \rangle}{\overline{c}^2} = \frac{2}{\overline{N}} \tag{11}$$

GENERAL FIRST PASSAGE TIME

We need to calculate the first passage properties of the Markov chain, specifically the mean and variance of the first passage time. This can be calculated as follows [3, 4]. The master equation that we want to solve is $\frac{dp}{dt} = Kp(t)$.

First apply the Laplace transform

$$P_i(s) = \int_0^\infty p_i(t) e^{-st} dt \tag{12}$$

which leads to the master equation

$$(s - K)\, P(s) = p(t = 0) \tag{13}$$

with K the matrix of transitions for the full system but with the transition rates leaving the absorbing states set to zero.

The first passage time to return to state 0 is

$$f(t) = \frac{dp_0(t)}{dt} \tag{14}$$

$$F(s) = sP_0(s) \tag{15}$$

For our purposes, we only need the mean and variance of the first passage time. This is easily obtained by the uncentered moments

$$M^{(m)} = \int_0^\infty t^m f(t) = (-1)^m \left. \frac{d^m F(s)}{ds^m} \right|_{s=0} \tag{16}$$

where $m = 1$ is the mean and $m = 2$ is the uncentered second moment.

In general we know that τ_x, the spent in state x, is drawn from a mixture where it can switch to states $j = 1, 2, ...$ The variance of mixtures is $X = \sum_i w_i X_i$, where w_i are arbitrary weights and X_i are random variables drawn from distributions with mean μ_i and variance σ_i. Combining equations we get:

$$\mathrm{Var(X)} = \sum_i w_i \left[(\mu_i - \mu)^2 + \sigma_i^2 \right] \tag{17}$$

with $\mu = \sum_i w_i \mu_i$.

We can get the time spent in state x, τ_x, by using the variance mixture formula combined with $\overline{\tau}_{ix}$ and $\mathrm{Var}(\tau_{ix})$, respectively the mean and variance first passage time of starting in state i and ending in state x. This gives us

$$\overline{\tau}_x = \sum_i q_{xi} \overline{\tau}_{ix} \tag{18}$$

$$q_{xi} = \frac{k_{xi}}{\sum_j k_{xj}} = k_{xi} \rho_x \tag{19}$$

$$\rho_x = \left(\sum_j k_{xj} \right)^{-1} \tag{20}$$

$$\mathrm{Var}(\tau_x) = \sum_i q_{xi} Var(\tau_{ix}) + \sum_i q_{xi} \left(\overline{\tau}_{ix} - \sum_k q_{xk} \overline{\tau}_{kx} \right)^2 \tag{21}$$

where q_{xi} is the probability of transitioning from state x to state i, k_{xi} is the rate to go from state x to state i, and ρ_x is the lifetime of state x.

In this paper, we have one non-signaling state and the other L states are signaling. Therefore, we will let state 0 be the absorbing state, and it can initially transition to state 1 and state L. The above equations then simplify to

$$\overline{\tau_0} = q_{01} \overline{\tau}_{10} + q_{0L} \overline{\tau}_{L0} \tag{22}$$

$$\mathrm{Var}(\tau_0) = q_{01} Var(\tau_{10}) + q_{0L} Var(\tau_{L0}) + 2 q_{01} q_{0L} \left(\overline{\tau}_{10} - \overline{\tau}_{L0} \right)^2 \tag{23}$$

$$q_{0L} = 1 - q_{01} \tag{24}$$

FIRST PASSAGE TIME: 2 SIGNALING STATES

Here we calculate the mean and variance of the first passage time to return to state 0 from either state 1 or 2. The master equation that we need to solve is $\frac{dp}{dt} = Kp(t)$. The matrix rates are:

$$K_{ij} = \begin{cases} k_{10} & \text{for } i = 0 \text{ and } j = 1 \\ k_{12} & \text{for } i = 2 \text{ and } j = 1 \\ k_{20} & \text{for } i = 0 \text{ and } j = 2 \\ k_{21} & \text{for } i = 1 \text{ and } j = 2 \\ -(k_{10} + k_{12}) & \text{for } i = 1 \text{ and } j = 1 \\ -(k_{20} + k_{21}) & \text{for } i = 2 \text{ and } j = 2 \\ 0 & \text{everywhere else} \end{cases} \tag{25}$$

While the initial conditions are set by the rates k_{01} and k_{02}, for the purposes of the first passage time calculation, the rates from 0 to 1 (k_{01}) and from 0 to 2 (k_{02}) are both set to zero, $k_{01} = k_{02} = 0$.

The Laplace transform for the initial condition of starting in state 1 is:

$$F(s) = sP_0(s) = k_{10}P_1 + k_{20}P_2 \tag{26}$$

with

$$P_1 = \left[\Gamma_1 - \frac{k_{12}k_{21}}{\Gamma_2}\right]^{-1} \tag{27}$$

$$P_2 = \frac{k_{12}}{\Gamma_2}P_1 \tag{28}$$

$$\Gamma_i = s + \rho_i^{-1} \tag{29}$$

We can obtain mean and variance from

$$\overline{\tau} = -\left.\frac{dF}{ds}\right|_{s=0} \tag{30}$$

$$\mathrm{Var}(\tau) = \left.\frac{d^2F}{ds^2}\right|_{s=0} - \overline{\tau}^2 \tag{31}$$

The mean and variance of the first passage time from starting in either state 1 or state 2 is:

$$\overline{\tau}_{10} = \rho_1\frac{1 + k_{12}\rho_2}{1 - k_{12}k_{21}\rho_1\rho_2} = \frac{k_{12} + k_{20} + k_{21}}{\xi} \tag{32}$$

$$\overline{\tau}_{20} = \rho_2\frac{1 + k_{21}\rho_1}{1 - k_{12}k_{21}\rho_1\rho_2} = \frac{k_{10} + k_{12} + k_{21}}{\xi} \tag{33}$$

$$\mathrm{Var}(\tau_{10}) = \tau_{10}^2\left[1 + 2\rho_2^2\frac{k_{12}\left(k_{10} - k_{20}\right)}{(1 + k_{12}\rho_2)^2}\right] = \tau_{10}^2 + 2\frac{k_{12}(k_{10} - k_{20})}{\xi^2} \tag{34}$$

$$\mathrm{Var}(\tau_{20}) = \tau_{20}^2\left[1 + 2\rho_1^2\frac{k_{21}\left(k_{20} - k_{10}\right)}{(1 + k_{21}\rho_1)^2}\right] = \tau_{20}^2 - 2\frac{k_{21}(k_{10} - k_{20})}{\xi^2} \tag{35}$$

$$\xi = k_{10}k_{20} + k_{10}k_{21} + k_{12}k_{20} \tag{36}$$

where the second equality holds as long as $\xi \neq 0$.

FIRST PASSAGE TIME: L SIGNALING STATES

Derivation

Here we calculate the mean and variance of the first passage time in a $L+1$ state chain. The master equation that we need to solve is $\frac{dp}{dt} = Kp(t)$. The matrix is indexed from 0 to L and the rates are:

$$K_{ij} = \begin{cases} k_{10} & \text{for } i = 0 \text{ and } j = 1 \\ k_{L0} & \text{for } i = 0 \text{ and } j = L \\ f & \text{for } i = j+1 \text{ and } 1 < j < L \\ b & \text{for } i = j-1 \text{ and } 1 < j < L \\ -(f + k_{10}) & \text{for } i = 1 \text{ and } j = 1 \\ -(f + b) & \text{for } i = j \text{ and } 1 < j < L \\ -(k_{L0} + b) & \text{for } i = L \text{ and } j = L \\ 0 & \text{everywhere else} \end{cases} \tag{37}$$

While the initial conditions are set by the rates k_{01} and k_{0L}, for the purposes of the first passage time calculation, the rates from 0 to 1 (k_{01}) and from 0 to L (k_{0L}) are both set to zero, $k_{01} = k_{0L} = 0$.

For later convenience we define the following ratio of rates:

$$\theta = \frac{f}{b} \tag{38}$$

$$\alpha = \frac{k_{10}}{b} \tag{39}$$

$$\omega = \frac{k_{L0}}{f} \tag{40}$$

We can use a transfer matrix to find a general solution (for non-degenerate eigenvales, i.e. $\theta \neq 1$) to the state probability as

$$P_i(s) = C_+ \lambda_+^{i-1} + C_- \lambda_-^{i-1} \tag{41}$$

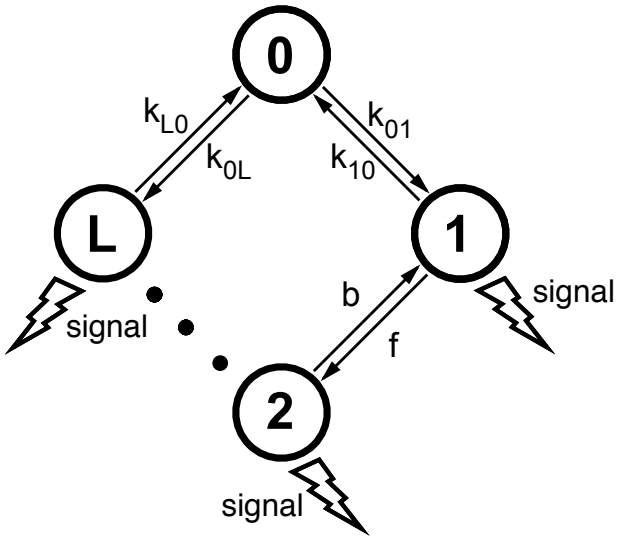

FIG. 1: Simplified rate structure considered for L signaling states first passage time calculation. The rates k_{01}, k_{10}, k_{L0}, k_{0L} are unconstrained, while the remaining forward rates are equal, $f = k_{12} = k_{23} = \ldots = k_{L-1,L}$ and the remaining backward rates are equal, $b = k_{21} = k_{32} = \ldots = k_{L,L-1}$.

Solving for the the expressions $1 < i < L$ leads to

$$\lambda_\pm = \frac{1}{2b}\left(s+f+b \pm \sqrt{(s+f+b)^2-4fb}\right) \tag{42}$$
$$= \frac{1}{2}\left(\sigma \pm \sqrt{\sigma^2-4\theta}\right) = \frac{1}{2}\left(\sigma \pm \psi\right) \tag{43}$$
$$\sigma = \frac{s}{b}+\theta+1 \tag{44}$$
$$\psi = \sqrt{\sigma^2-4\theta} \tag{45}$$

With the initial condition of starting in P_1, the boundary equations for P_1 and P_L are:

$$(\sigma+\alpha-1)\left(C_+ + C_-\right) = 1/b + \left(C_+\lambda_+ + C_-\lambda_-\right) \tag{46}$$
$$\left(\sigma+(\omega-1)\theta\right)\left(C_+\lambda_+^{L-1} + C_-\lambda_-^{L-1}\right) = \theta\left(C_+\lambda_+^{L-2} + C_-\lambda_-^{L-2}\right) \tag{47}$$

Solving these equations gives

$$C_- = -C_+\Lambda^L M \tag{48}$$
$$C_+ = \frac{1}{b\left[\lambda_- + \alpha - 1 - (\lambda_+ + \alpha - 1)\Lambda^L M\right]} \tag{49}$$
$$\Lambda = \frac{\lambda_+}{\lambda_-} \tag{50}$$
$$M = \frac{1+(\omega-1)\lambda_-}{1+(\omega-1)\lambda_+} \tag{51}$$

And then the probabilities are

$$P_1(s) = C_+\left(1-\Lambda^L M\right) \tag{52}$$
$$P_L(s) = C_+\lambda_+^{L-1}\left(1-\Lambda M\right) \tag{53}$$

The full Laplace transform F is:

$$F(s) = \frac{\alpha(1-\Lambda^L M) + \omega\theta\lambda_+^{L-1}(1-\Lambda M)}{\lambda_- + \alpha - 1 - (\lambda_+ + \alpha - 1)\Lambda^L M} \tag{54}$$

Results

To get the mean and variance of the first passage time, we need

$$\overline{\tau}_{10} = -\left.\frac{dF}{ds}\right|_{s=0} \tag{55}$$
$$\mathrm{Var}(\tau_{10}) = \left.\frac{d^2F}{ds^2}\right|_{s=0} - \overline{\tau}^2 \tag{56}$$

The mean return time to state 0 when starting in state 1 is:

$$\overline{\tau}_{10} = \frac{\overline{\tau}_{10,num}}{\overline{\tau}_{10,den}} \tag{57}$$
$$\overline{\tau}_{10,num} = (\omega L - \omega + 1)\theta^{L+1} - (\omega L + 1)\theta^L + (\omega - 1)\theta + 1 \tag{58}$$
$$\overline{\tau}_{10,den} = b\left[\theta - 1\right]\left[\omega\theta^{L+1} + \omega(\alpha-1)\theta^L + \alpha(1-\omega)\theta - \alpha\right] \tag{59}$$

The variance of the return time to state 0 when starting in state 1 is:

$$\begin{aligned}
\mathrm{Var}(\tau_{10}) &= \frac{\mathrm{Var}(\tau_{10})_{num}}{\mathrm{Var}(\tau_{10})_{den}} && (60)\\
\mathrm{Var}(\tau_{10})_{num} &= \theta^{2L+3}\left[\omega^2(L-1)+1\right] && (61)\\
&+ \theta^{2L+2}\left[\omega^2\left(L^2\alpha - L(3\alpha+1)+2\alpha-3\right)+2\omega((L-2)\alpha+1)+2\alpha-3\right]\\
&- \theta^{2L+1}\left[\omega^2\left(2L^2\alpha-4L\alpha+L+4\alpha-4\right)+\omega((4L-6)\alpha+4)+4\alpha-3\right]\\
&+ \theta^{2L}\left[\omega(\omega L+2)(L\alpha-\alpha+1)+2\alpha-1\right]\\
&+ \theta^{L+3}(\omega-1)\left[2(\omega-1)\alpha+3\omega L^2\alpha+L(\omega(4-5\alpha)+4\alpha)+2\right]\\
&+ \theta^{L+2}\left[-2\omega^2\left(3L^2\alpha+L(4-6\alpha)+\alpha-2\right)\right]\\
&+ \theta^{L+2}\left[\omega\left(9L^2\alpha+L(12-23\alpha)+8\alpha-6\right)+6(2L-1)\alpha+6\right]\\
&+ \theta^{L+1}\left[\omega\left(-9L^2\alpha+L(19\alpha-12)-6\alpha+6\right)\right]\\
&+ \theta^{L+1}\left[\omega^2(L-1)((3L-4)\alpha+4)+6(-2L\alpha+\alpha-1)\right]\\
&+ \theta^{L}\left[\alpha\left(3L^2\omega-5L\omega+4L+2\omega-2\right)+(4L-2)\omega+2\right]\\
&- \theta^3(\omega-1)^2(2\alpha-1)\\
&- \theta^2(\omega-1)(\omega+4\alpha-3)\\
&+ \theta(-2\omega-2\alpha+3)\\
&- 1\\
\mathrm{Var}(\tau_{10})_{den} &= b^2\left[\theta-1\right]^3\left[\omega\theta^{L+1}+\omega(\alpha-1)\theta^L+\alpha(1-\omega)\theta-\alpha\right]^2 && (62)
\end{aligned}$$

While the results here are for initial condition of being in state 1, one can easily find the results for the initial condition of state L if one makes the following substitutions $\theta \Leftrightarrow 1/\theta$, $b \Leftrightarrow f$, and $\alpha \Leftrightarrow \omega$.

STEADY STATE PROBABILITIES

In general, we are considering a Markov chain with $L+1$ nodes (labeled 0 to L). We have the master equation

$$\frac{dP(t)}{dt} = KP(t) \tag{63}$$

with K the matrix of transition rates. The rates are labeled as k_{ij} where i is the initial state and j is the final state. For later convenience, define the lifetime of a state as

$$\rho_i = \left(\sum_{j\neq i} k_{ij}\right)^{-1} \tag{64}$$

The steady state distributions are easily obtained by solving $Kp^{ss} = 0$. The solution can be written in a compact form [5] as

$$\begin{aligned}
P_i^{ss} &= \frac{z_i}{Z} && (65)\\
Z &= \sum_i z_i && (66)
\end{aligned}$$

and z_i is the matrix minor of K at (i,i) i.e. the determinant of K with the ith row and column removed.

For the two signaling state system we have that

$$p_0^{ss} = \frac{\rho_1^{-1}\rho_2^{-1} - k_{12}k_{21}}{Z} = \frac{k_{10}k_{20} + k_{10}k_{21} + k_{12}k_{20}}{Z} \tag{67}$$

$$p_1^{ss} = \frac{\rho_0^{-1}\rho_2^{-1} - k_{02}k_{20}}{Z} = \frac{k_{01}k_{20} + k_{01}k_{21} + k_{02}k_{21}}{Z} \tag{68}$$

$$p_2^{ss} = \frac{\rho_0^{-1}\rho_1^{-1} - k_{01}k_{10}}{Z} = \frac{k_{01}k_{12} + k_{02}k_{10} + k_{02}k_{12}}{Z} \tag{69}$$

$$Z = \sum_{i\neq j} \left(\rho_i^{-1}\rho_j^{-1} - k_{ij}k_{ji}\right) \tag{70}$$

For the L signaling state with the simplified rates, we will just present the result for state 0:

$$p_0^{ss} = \frac{p_{0,num}^{ss}}{p_{0,den}^{ss}} \tag{71}$$

$$p_{0,num}^{ss} = b(\theta-1)\left(\omega\theta^{L+1} + \omega(\alpha-1)\theta^L + \alpha(1-\omega)\theta - \alpha\right) \tag{72}$$

$$p_{0,den}^{ss} = -\alpha\epsilon + \alpha b + \alpha L\epsilon + \epsilon + 1 \tag{73}$$

$$+\ \theta\left(\alpha b\omega - 2\alpha b - \alpha L\epsilon + \omega - \epsilon - 1\right) \tag{74}$$

$$+\ \alpha b\theta^2\left(1-\omega\right) \tag{75}$$

$$+\ \theta^L\left(b\omega + \alpha\epsilon - L\omega - 1 - \epsilon - \alpha b\omega\right) \tag{76}$$

$$+\ \theta^{1+L}\left(\alpha b\omega - 2b\omega + L\omega - \omega + 1 + \epsilon\right) \tag{77}$$

$$+\ b\omega\theta^{L+2} \tag{78}$$

The rates from 0 to 1 is $k_{01} = 1$, from 1 to 0 is k_{10} (with $\alpha = k_{10}/b$), from 0 to L is $k_{0L} = \epsilon \ll 1$, and from L to 0 is k_{L0} (with $\omega = k_{L0}/f$). All other forward rates are f and backward rates are b and the ratio of rates is $\theta = f/b$.

AVERAGE SAMPLING RATE: $\overline{n}$

The average sampling rate is

$$\overline{n} = \frac{N}{T} = k_{01}p_0^{ss} \tag{79}$$

where N is the number of samples (i.e. number of binding events), T is the total integration time, k_{01} is the rate from state 0 to state 1, and p_0^{ss} is the steady state probability of being in state 0.

Since we are assuming that $k_{01} = 1$ and $k_{L0} = \epsilon \ll 1$, we have the mean signaling time becomes $\overline{\tau}_S \approx \tau_{10}$. With these rates we have

$$\overline{n} \approx \left(1 + \overline{\tau}_S\right)^{-1} \tag{80}$$

ENTROPY PRODUCTION: e_p

For a general Markov process with states labeled by i, steady state probabilities p_i^{ss}, and transition rate k_{ij} from state i to state j, the non-equilibrium steady state (NESS) entropy production [6, 7] is given by

$$e_p = \sum_{i=0}^{L}\sum_{j\neq i}^{L} p_i^{ss}k_{ij}\ln\frac{k_{ij}}{k_{ji}} \tag{81}$$

where the summation is over both i and j. Alternatively, the entropy production can be written as a sum over the flux between each connected node as

$$e_p = \sum_{i=0}^{L}\sum_{j>i}^{L}\left(p_i^{ss}k_{ij} - p_i^{ss}k_{ij}\right)\ln\frac{k_{ij}}{k_{ji}} \tag{82}$$

where now we have an unrestricted sum over i but a restricted sum over j.

Since we are modeling our receptor as a ring, the entropy production simplifies to

$$e_p = (p_0^{ss} k_{01} - p_1^{ss} k_{10}) \ln \frac{k_{01} k_{12} \dots k_{L0}}{k_{0L} k_{10} \dots k_{L,L-1}} = J \ln \gamma \tag{83}$$

where the flux $J = p_0^{ss} k_{01} - p_1^{ss} k_{10}$ between each neighboring state is equal and the $\ln \gamma$ is the free energy difference of a cycle.

For 2 signaling states, the entropy production per sampling rate is given by:

$$\frac{e_p}{\overline{n}} = \left[1 + \frac{k_{10}}{k_{12}} + \frac{k_{10} k_{21}}{k_{12} k_{20}} \right]^{-1} \frac{\gamma - 1}{\gamma} \ln \gamma \tag{84}$$

$$\gamma = \frac{k_{01} k_{12} k_{20}}{k_{10} k_{21} k_{02}} \tag{85}$$

For the L signaling states arranged in a ring, the entropy production per sampling rate is given by:

$$\frac{e_p}{\overline{n}} = \left[1 + \frac{\alpha}{\omega} \theta^{-L} + \alpha \theta^{-1} \frac{1 - \theta^{1-L}}{1 - \theta^{-1}} \right]^{-1} \frac{\gamma - 1}{\gamma} \ln \gamma \tag{86}$$

$$\gamma = \frac{k_{01} \omega}{k_{0L} \alpha} \theta^L \tag{87}$$

where $\omega = k_{L0}/f$, $\alpha = k_{10}/b$, $\theta = f/b$, f is all the forward rates (except k_{01} and k_{L0}), and b is all the backward rates (except k_{10} and k_{0L}).

ANSATZ FOR 2 SIGNALING STATE RECEPTOR

Here are the details of the ansatz for the minimum uncertainty for the 2 signaling state system.

The rates are as follows:

- $k_{01} = 1$

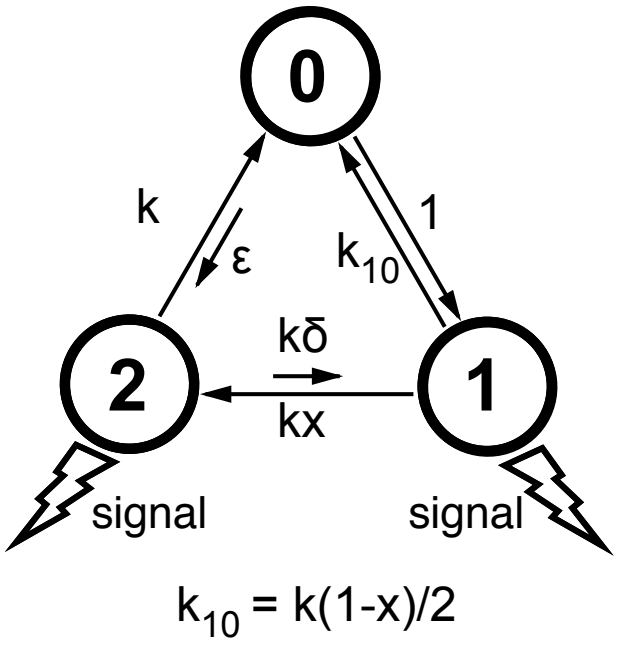

FIG. 2: Rate structure for ansatz of minimum uncertainty for the $L = 2$ signaling state system. The rates are as follows: $k_{01} = 1$, $k_{10} = \frac{k}{2}(1 - x)$, $k_{12} = kx$, $k_{21} = k\delta$, $k_{20} = k$, and $k_{02} = \epsilon$. The mean signaling time is set by k. The other rates are $\epsilon, \delta \ll 1$ and $0 < x < 1$.

- $k_{10} = \frac{k}{2}(1-x)$
- $k_{12} = kx$
- $k_{21} = k\delta$
- $k_{20} = k$
- $k_{02} = \epsilon$

where $\epsilon \ll 1$ (and in this paper $\epsilon = 10^{-3}$), $0 < x < 1$, $\delta \ll 1$ (and in this paper $\delta = 0.04$), and k is varied to fix the mean sampling rate $\overline{n}$.

For the ansatz, the mean, coefficient of variation, and entropy production simplifies to

$$\overline{\tau}_S \approx \frac{2}{k} \tag{88}$$

$$\frac{\langle(\delta\tau_S)^2\rangle}{\overline{\tau}_S^2} \approx 1 - \frac{x}{1+x} \tag{89}$$

$$\frac{e_p}{\overline{n}} \approx \left(1 + \frac{1-x}{2x}\right)^{-1} \frac{\gamma - 1}{\gamma} \ln\gamma \tag{90}$$

$$\gamma = \frac{2x}{\epsilon\delta(1-x)} \tag{91}$$

SIMULATED ANNEALING

Simulated annealing is a meta-heuristic algorithm for global optimization in which one uses the Metropolis algorithm to perform a random walk in parameter space while periodically lowering the temperature. We used a simulated annealing algorithm to search for the parameters of a model describing a receptor with 2 signaling states that minimizes a cost function given by

$$\text{cost} = \frac{\langle(\delta c)^2\rangle}{\bar{c}^2} + \lambda_{e_p}(\ln e_p - \ln\hat{e}_p)^2 - (\lambda_n\hat{n} - 1)\ln\overline{n} - (\lambda_n(1-\hat{n}) - 1)\ln(1-\overline{n}) \tag{92}$$

That is, we minimize the uncertainty of the resulting estimator ($\langle(\delta c)^2\rangle/\bar{c}^2$) subject to soft constraints on the energy production (e_p) and sampling rate ($\overline{n}$), which are constrained to $\hat{e}_p$ and $\hat{n}$, respectively. Here, λ_{e_p} and λ_n implement the constraints. We chose $\lambda_{e_p} = 20$ and $\lambda_n = 20/\max\{\hat{n}, 1-\hat{n}\}$.

Let Ω_1 denote a set of parameters describing a receptor with 2 signaling states (i.e. all of the various rate constants). A new set of trial parameters Ω_2 was generated in the following way: for each $k \in \Omega_1$ set the corresponding $k' \in \Omega_2$ to $\ln k' = \ln k + \eta$ where η is a random variable with from a Normal distribution centered at zero. The width of the Normal distribution was chosen adaptively so that approximately 25% of the steps were accepted. Making the random perturbations to the logarithm of the rate constants ensures that they are always positive. The trial move was accepted according to the Metropolis criterion with probability $\min[1, \exp((\text{cost}(\Omega_1) - \text{cost}(\Omega_2))/T)]$. The temperature T was initialized to $T = 10$ and adjusted by $T \leftarrow 0.95T$ every 2000 steps. The best solution obtained during the chain was stored in Ω_B, and the chain was re-initialized from $\Omega_1 = \Omega_B$ every 2000 steps to prevent the chain from getting stuck in a poor local minimum. This simulated annealing algorithm was run until convergence of $\langle(\delta c)^2\rangle/\bar{c}^2$, e_p and n.

SCALING WITH TEMPERATURE

In the main text, we worked in the units of $k_BT = 1$. However, here we examine the general temperature dependence. Experimentally, it is known that rates of biochemical reactions doubles for every 10 °C [8, 9]. Therefore, a general rate k at a temperature T (measured in degrees Celsius) is related to initial rate k_0 and initial temperature T_0 by:

$$k = k_0 2^{\frac{T-T_0}{10}} \tag{93}$$

Now we need to determine the general scaling of various entities in this paper, which is summarized below in terms of a general rate k:

- Mean signaling time, $\overline{\tau}_S \sim k^{-1}$
- Variance in signaling time, $\langle(\delta\tau_S)^2\rangle \sim k^{-2}$
- Coefficient of variation of signaling time, $\frac{\langle(\delta\tau_S)^2\rangle}{\overline{\tau}_S^2} \sim 1$
- Sampling rate, $\overline{n} \sim k$
- Uncertainity, $\frac{\langle(\delta c)^2\rangle}{\overline{c}^2} \sim k^{-1}$
- Entropy production, $e_p \sim k$

While increasing temperature increases both the mean and variance of the signaling time, since the estimator ($\mathcal{E} = 1 + \frac{\langle(\delta\tau_S)^2\rangle}{\overline{\tau}_S^2}$) only depends on the coefficient of variation of signaling time, the estimator is independent of temperature. The sampling rate $\overline{n}$ does increase with increasing temperature, and therefore increasing temperature decreases the uncertainty. However, this decrease in uncertainty costs energy. While the free energy per cycle ($\ln\gamma$) remains constant, the probability flux (J) is proportional to a rate, and since the entropy production is given by $e_p = J\ln\gamma$, we see that that decrease in uncertainty is directly related to the increase in entropy production.

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