

Universal lower bound on the free-energy cost of molecular measurementsSuman G. Das,¹ Madan Rao,¹ and Garud Iyengar²¹*Simons Centre for the Study of Living Machines, National Centre for Biological Sciences (TIFR), GKVK Campus, Bellary Road, Bangalore 560065, India*²*Industrial Engineering and Operations Research, Columbia University, New York, New York 10027, USA*

(Received 26 August 2016; published 15 June 2017)

The living cell uses a variety of molecular receptors to read and process chemical signals that vary in space and time. We model the dynamics of such molecular level measurements as Markov processes in steady state, with a coupling between the receptor and the signal. We prove *exactly* that, when the signal dynamics is not perturbed by the receptors, the free energy consumed by the measurement process is lower bounded by a quantity proportional to the mutual information. Our result is completely independent of the receptor architecture and dependent on signal properties alone, and therefore holds as a general principle for molecular information processing.

DOI: [10.1103/PhysRevE.95.062410](https://doi.org/10.1103/PhysRevE.95.062410)**I. INTRODUCTION**

Sensing and processing information about the environment and the internal state is essential for the growth and sustenance of living cells. In this cellular context, information is chemical (in the form of ligands) and is sensed by molecular receptors at the cell surface. Examples of information processing arise in antigen-TCR [1], ECM-integrin [2,3], pathogen-antibody [4,5] interactions, and a variety of other contexts [6–8]. Given the limited supply of resources, we expect this sensing and information transmission to be *efficient* in an appropriate sense. Understanding the fundamental limits on sensing is relevant not only for understanding biochemical sensors in the cellular context, but also for engineering low power nanosensors [9]. Drawing on the connections between information and thermodynamics, several groups have considered the intrinsic costs associated with sensing.

Shannon [10] provided the foundation for the theory of information and communication. This theory was concerned with sensing an input random variable X via an information channel with the output being a random variable Y . Shannon quantified the information in X by the entropy $H(X) = -\sum_x p(x) \ln p(x)$, which is precisely the generalized nonequilibrium entropy of a nonequilibrium system described by X . The average uncertainty in X given the observation Y is quantified by the conditional entropy $H(X|Y) = -\sum_{x,y} p(x,y) \ln p(x|y)$, and the difference $I(X,Y) = H(X) - H(X|Y)$ is called the mutual information.

The thermodynamics of information processing [6,11–18] seeks to understand the relationship between information, energy flow, and useful work. A bipartite Markov chain model involving two coupled random variables (X,Y) has emerged as the canonical model for studying the thermodynamics of information [13,14]. For such systems, information flow [13,15] or learning rate ℓ_Y [14] has been proposed as a metric for the performance of the sensor Y . Introducing learning rate ℓ_Y allows one to write a more general form of the second law of stochastic thermodynamics, which explains the entropy production by Maxwell’s demon without introducing “erasures.” Further, since learning rate ℓ_Y is bounded by the rate of entropy production at the sensor, it appears to be an appropriate thermodynamic quantity for measuring sensing quality.

However, a recent paper [18] argues that the learning rate ℓ_Y is not a good substitute of mutual information, nor does it necessarily capture the essential qualities of sensor performance. In [18] it is shown that the learning rate ℓ_Y quantifies the rate at which Y learns about the current value of X as time progresses; specifically $\ell_Y = \frac{d}{d\tau} I(X_t, Y_{t+\tau})|_{\tau=0}$. Consequently, ℓ_Y is not necessarily closely related to the steady state information $I(X;Y)$. For two-state networks, the learning rate and mutual information behave in a similar manner. However, in complex networks, the similarity between learning rate and mutual information breaks down. In [18] the authors discuss a specific example of a unidirectional network where the mutual information saturates to a finite value but the learning rate vanishes in the limit of a large number of states. In steady state, information flow is perhaps best interpreted as the rate of transitions in the sensor state needed to maintain a certain level of mutual information, and not necessarily as a measure of the quality of sensor performance [18]. To summarize, while the learning rate ℓ_Y is clearly related to a thermodynamic quantity, its usefulness in quantifying sensor efficiency is unclear.

Thus, in order to understand the fundamental limits on information and sensing, we need to relate the “cost” of generating steady state mutual information $I(X,Y)$ to relevant thermodynamic quantities. Free-energy consumption appears a natural candidate for such a cost, as has been established in specific models of ligand-receptor binding involved in simplified signaling cascades [19]. But does this extend to arbitrary complex signaling networks? Indeed, what are the conditions under which such a general proposition might hold? We show that in unidirectional bipartite Markov chain models of signaling, i.e., models where the signal is unperturbed by the receptor, the free-energy consumption in the sensors is bounded below by a term proportional to the product of mutual information and a time scale of signal dynamics. Thus, it follows that it is impossible to have signal reception when the free-energy consumption rate is zero. Further, for a class of signal network topologies called *one-hop networks*, we prove a tighter lower bound. This is a first step toward establishing a thermodynamic metric for the physical cost of information processing. We also discuss information processing using a time series of receptor states. We show that in order to account for the free-energy cost of the information in a time series of re-

ceptor states, one must account for both the cost of information acquisition and the cost of maintaining memory. Disregarding the cost of memory leads to the erroneous conclusion that information can be obtained at zero entropy rate.

II. THE MODEL

Let X_n denote the location and concentration of all ligands (signals), and Y_n , the internal states of all receptors at time instants n . We assume that the $\{(X_n, Y_n) : n \geq 1\}$ is a time-stationary bipartite Markov process [13,14,16,20], i.e., the individual processes $\mathbb{X} = \{X_n : n \geq 1\}$ and $\mathbb{Y} = \{Y_n : n \geq 1\}$ do not change state simultaneously. The absolute time between epochs is considered to be so short that the probability of simultaneous transitions is negligible.

The transition rates from state (α, i) to (β, j)

$$w_{ij}^{\alpha\beta} = \mathbb{P}(X_{t+1} = \beta, Y_{t+1} = j \mid X_t = \alpha, Y_t = i)$$

are given by

$$\begin{aligned} w_{ij}^{\alpha\beta} &= w^{\alpha\beta} && \text{if } i = j \text{ and } \alpha \neq \beta \\ &= w_{ij}^{\alpha} && \text{if } i \neq j \text{ and } \alpha = \beta \\ &= 0 && \text{if } i \neq j \text{ and } \alpha \neq \beta \\ &= \bar{w}_i^{\alpha} && \text{if } \alpha = \beta \text{ and } i = j. \end{aligned} \quad (1)$$

Note that $\bar{w}_i^{\alpha} = 1 - \sum_{\beta \neq \alpha} w^{\alpha\beta} - \sum_{j \neq i} w_{ij}^{\alpha}$. Our results remain valid in the continuous time limit when the rates are scaled as $w\tau$ with $\tau \rightarrow 0$.

The bipartite Markov chain defined in (1) is unidirectional, where the transitions of the signal state X do *not* depend on the receptor state Y ; however, the transitions of the receptor state Y *do* depend on the signal state X . This is a natural model for measurement—the external signal remains unperturbed by the measurement. The underlying assumption here is that the signal and receptor are embedded in different physical environments (Fig. 1), and that their transition probabilities are *not* governed by a joint Hamiltonian. Let

$$P_i^{\alpha} = \mathbb{P}(X_t = \alpha, Y_t = i) \quad (2)$$

denote the steady state probability distribution of the Markov process (X, Y) . Then the steady state mutual information I_{ss} between the signal \mathbb{X} and the receptor \mathbb{Y} [21] is defined as

$$I_{ss} = \sum_{\alpha, i} P_i^{\alpha} \log \left(\frac{P_i^{\alpha}}{P^{\alpha} P_i} \right), \quad (3)$$

where P_i^{α} denotes the stationary distribution of the bipartite Markov chain (\mathbb{X}, \mathbb{Y}) , $P^{\alpha} = \sum_i P_i^{\alpha}$ is the marginal distribution of the signal state, and $P_i = \sum_{\alpha} P_i^{\alpha}$ is the marginal distribution of the receptor state. We use the natural logarithm here and elsewhere in the article. Note that $I_{ss} = 0$ if, and only if, the signal state X_t is independent of the receptor state Y_t in steady state, i.e., $P_i^{\alpha} = P^{\alpha} P_i$. In this work we seek to establish a lower bound on the free-energy consumption in the sensors in terms of the steady state mutual information I_{ss} . We focus on the steady state mutual information, since otherwise, there could be entropy generation independent of information sensing. Note that the quantity of interest in [13–15] is the information flow or learning rate which was shown in [18] to be related to the rate at which the information in Y grows, and as such is not the same as the steady state mutual information.

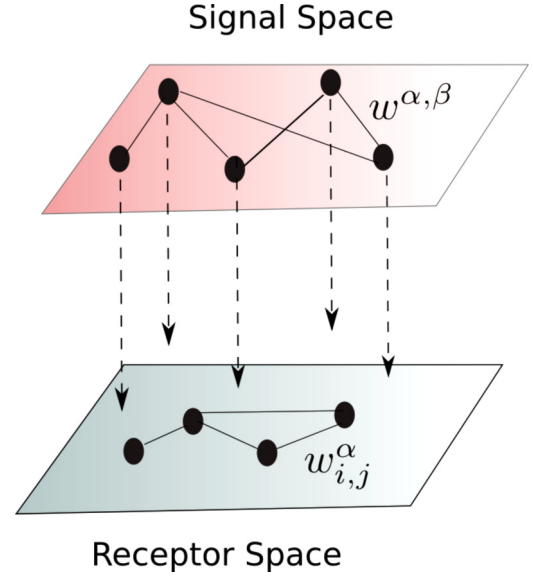


FIG. 1. The signal and receptor state spaces are embedded in their physical environments (upper and lower boxes, respectively). The signal transition rates $w^{\alpha, \beta}$ are independent of the receptor, while the receptor transition rates $w_{i, j}^{\alpha}$ depend on the current signal state.

We establish a lower bound on the free-energy consumption in terms of the mutual information I_{ss} and a quantity that is a function of a *graph* associated with signal dynamics. Let N denote the cardinality of the set $\{\alpha : P^{\alpha} > 0\}$ of signal states with positive steady state probability. Define a graph \mathcal{N} on N nodes as follows: For all $\alpha \neq \beta \in \{1, \dots, N\}$, add a directed arc (α, β) from α to β if $w^{\alpha, \beta} > 0$. Let $w^{\min} = \min\{w^{\alpha\beta} : (\alpha, \beta) \in \mathcal{N}\}$, $w^{\max} = \max\{w^{\alpha\beta}\}$, $P^{\min} = \min_{\alpha} \{P^{\alpha}\}$ and d^{\max} is the largest out-degree of \mathcal{N} . For nodes $\alpha \neq \beta$, let $l^{\alpha\beta}$ denote the length of the shortest directed path from α to β , and let $\Delta = \max_{\alpha, \beta} \{l^{\alpha\beta}\}$ denote the diameter of \mathcal{N} .

So far, we have only described the signal and receptor in purely mathematical terms. However, these signal and receptor processes are embedded in their respective *physical* environments, where states correspond to positional or conformational states of molecules, or concentrations. From the Schnakenberg network theory [22], it follows that the thermodynamic entropy rate $\dot{\sigma}$ of these mesoscopic thermal systems is given by

$$\dot{\sigma} = \underbrace{\sum_{\alpha\beta} P^{\alpha} w^{\alpha\beta} \log \frac{w^{\alpha\beta}}{w^{\beta\alpha}}}_{\dot{\sigma}_x} + \underbrace{\sum_{\alpha ij} P_i^{\alpha} w_{ij}^{\alpha} \log \frac{w_{ij}^{\alpha}}{w_{ji}^{\alpha}}}_{\dot{\sigma}_y}, \quad (4)$$

where $\dot{\sigma}_x$ is the steady state entropy rate of the physically independent signal process, and is thus the free energy consumed in generating the signal alone. The second term $\dot{\sigma}_y$ is the rate of free-energy consumption associated with the measurement process.

III. UNIVERSAL ENTROPY BOUND ON MUTUAL INFORMATION

Our main result is as follows.

Theorem 1. For arbitrary signal and network topologies,

$$I_{ss} \leq c \dot{\sigma}_y / w^{\min}, \quad (5)$$

where $c = 4\Delta \log(2)N^2 \left(\frac{d^{\max} w^{\max}}{w^{\min}}\right)^{2\Delta}$ is a constant that only depends on signal parameters, and is *independent of receptor parameters*.

While our results seem superficially analogous to the results in [23], we address a very distinct problem here. Unlike [23], we are interested in the entropy production associated with dynamics that *do not change the joint distribution*—the free-energy consumption is associated with the fact that receptors are able to *infer* the microscopic signal states, *without affecting it*.

To establish our result, we first prove the following lemmas, which we will combine finally to prove Eq. (5).

Lemma 1.

$$\dot{\sigma}_y \geq P^{\min} w^{\min} \sum_{(\alpha, \beta) \in \mathcal{N}} D(P(\cdot|\alpha) \| P(\cdot|\beta)). \quad (6)$$

Proof. We start our proof by noting that

$$\begin{aligned} & \sum_{\alpha ij} P_i^\alpha w_{ij}^\alpha \log \frac{P_i^\alpha w_{ij}^\alpha}{P_j^\alpha w_{ji}^\alpha} \\ &= \frac{1}{2} \sum_{ij\alpha} (P_i^\alpha w_{ij}^\alpha - P_j^\alpha w_{ji}^\alpha) \log \frac{P_i^\alpha w_{ij}^\alpha}{P_j^\alpha w_{ji}^\alpha} \geq 0. \end{aligned} \quad (7)$$

Then,

$$\begin{aligned} \dot{\sigma}_y &= \sum_{\alpha ij} P_i^\alpha w_{ij}^\alpha \log \frac{w_{ij}^\alpha}{w_{ji}^\alpha} \\ &\geq - \sum_{\alpha ij} P_i^\alpha w_{ij}^\alpha \log \frac{P_i^\alpha}{P_j^\alpha} \end{aligned} \quad (8a)$$

$$= \sum_{\alpha \beta i} P_i^\alpha w^{\alpha\beta} \log \frac{P_i^\alpha}{P_i^\beta} \quad (8b)$$

$$\begin{aligned} &= \sum_{\alpha\beta} w^{\alpha\beta} \sum_i P_i^\alpha \log \frac{P_i^\alpha}{P_i^\beta} \\ &= \sum_{\alpha, \beta} P^\alpha w^{\alpha, \beta} \sum_i P(i|\alpha) \log \frac{P(i|\alpha)}{P(i|\beta)} \end{aligned} \quad (8c)$$

$$\geq P^{\min} w^{\min} \sum_{(\alpha\beta) \in \mathcal{N}} D(P(\cdot|\alpha) \| P(\cdot|\beta)), \quad (8d)$$

where (8a) follows from (7), (8b) follows from the fact that the Shannon entropy of the whole system is constant, (8c) follows from the fact that $\sum P^\alpha w^{\alpha, \beta} \log \frac{P^\alpha}{P^\beta} = 0$ because the signal is in steady state, (8d) follows the definition of w^{\min} ,

and $D(p\|q)$ denotes the Kullback-Leibler divergence between p and q [21]. The expression on the right side of (8a) has been defined as the learning rate ℓ_y in some previous works [13–15]. Our main result (5) gives, as a corollary, a lower bound on ℓ_y in terms of the mutual information I_{ss} .

We now introduce new notation to improve the clarity of our exposition. Let $\pi_\alpha(\cdot) = P(\cdot|\alpha)$ denote the conditional distribution of the receptor state i given that the signal state is α . We remove from consideration any signal state i such that $P_i = \sum_\alpha P^\alpha \pi_\alpha(i) = 0$ since the conditional probability $\pi_\alpha(i) = 0$ for all α , and thus, state i is not informative about the signal state. Define the norm $\|x\| = \sqrt{\sum_i x_i^2 / P_i}$. In Lemma 2 we establish that

$$\sum_{(\alpha, \beta) \in \mathcal{N}} D(\pi_\alpha \| \pi_\beta) \geq \frac{P^{\min}}{2} \sum_{(\alpha, \beta) \in \mathcal{N}_+} \|\pi_\alpha - \pi_\beta\|^2,$$

and in Lemma 3 we establish that

$$I_{ss} \leq 2 \log(2) \Delta \sum_{(\alpha, \beta) \in \mathcal{N}} \|\pi_\alpha - \pi_\beta\|^2.$$

The result follows by establishing a bound on P^{\min} .

Lemma 2. The sum

$$\sum_{(\alpha, \beta) \in \mathcal{N}} D(\pi_\alpha \| \pi_\beta) \geq \frac{P^{\min}}{2} \sum_{(\alpha, \beta) \in \mathcal{N}_+} \|\pi_\alpha - \pi_\beta\|^2. \quad (9)$$

Proof. We first establish that $\gamma_{\max} = \max_{\alpha i} \frac{|\pi_\alpha(i) - P_i|}{P_i} \leq \frac{1}{P^{\min}} - 1$. Note that $P^{\min} \leq \frac{1}{2}$, therefore $\frac{1}{P^{\min}} - 1 \geq 1$. Also, $P_i = \sum_\beta P^\beta \pi_\beta(i) \geq P^\alpha \pi_\alpha(i) \geq P^{\min} \pi_\alpha(i)$ implies that $\pi_\alpha(i) / P_i \leq \frac{1}{P^{\min}}$. Thus, it follows that

$$\begin{aligned} \frac{|\pi_\alpha(i) - P_i|}{P_i} &\leq \max \left\{ 1 - \frac{\pi_\alpha(i)}{P_i}, \frac{\pi_\alpha(i)}{P_i} - 1 \right\} \\ &\leq \max \left\{ 1, \frac{1}{P^{\min}} - 1 \right\} = \frac{1}{P^{\min}} - 1. \end{aligned}$$

From Theorem 3 in [24] we have

$$\begin{aligned} & \frac{1}{2} \sum_{\nu=1}^{\infty} \sum_i \frac{(p_i - q_i)^2}{p_i + (2^\nu - 1)q_i} \leq D(P \| Q) \\ & \leq \log(2) \sum_{\nu=1}^{\infty} \sum_i \frac{(p_i - q_i)^2}{p_i + (2^\nu - 1)q_i}. \end{aligned} \quad (10)$$

Now turning to the sum of relative entropy across arcs in the graph \mathcal{N} ,

$$\begin{aligned} \sum_{(\alpha, \beta) \in \mathcal{N}_+} D(\pi_\alpha \| \pi_\beta) &\geq \frac{1}{2} \sum_{(\alpha, \beta) \in \mathcal{N}_+} \sum_i \sum_{\nu \geq 1} \frac{(\pi_{\alpha, i} - \pi_{\beta, i})^2}{\pi_{\alpha, i} + (2^\nu - 1)\pi_{\beta, i}} \\ &= \frac{1}{2} \sum_{(\alpha, \beta) \in \mathcal{N}_+} \sum_i \sum_{\nu \geq 1} \frac{(\pi_{\alpha, i} - \pi_{\beta, i})^2}{2^\nu P_i + [(\pi_{\alpha, i} - P_i) + (2^\nu - 1)(\pi_{\beta, i} - P_i)]} \\ &= \frac{1}{2} \sum_{(\alpha, \beta) \in \mathcal{N}_+} \sum_i \sum_{\nu \geq 1} \frac{2^{-\nu} (\pi_{\alpha, i} - \pi_{\beta, i})^2}{P_i} \frac{1}{1 + \left[2^{-\nu} \frac{(\pi_{\alpha, i} - P_i)}{P_i} + (1 - 2^{-\nu}) \frac{(\pi_{\beta, i} - P_i)}{P_i} \right]} \\ &\geq \frac{1}{2(1 + \gamma_{\max})} \sum_{(\alpha, \beta) \in \mathcal{N}_+} \sum_i \frac{(\pi_{\alpha, i} - \pi_{\beta, i})^2}{P_i} \sum_{\nu \geq 1} 2^{-\nu} \geq \frac{P^{\min}}{2} \sum_{(\alpha, \beta) \in \mathcal{N}_+} \|\pi_\alpha - \pi_\beta\|^2, \end{aligned} \quad (11)$$

where the second inequality follows from the fact that $\frac{(\pi_{\alpha,i} - P_i)}{P_i} \leq \frac{|\pi_{\alpha,i} - P_i|}{P_i} \leq \gamma_{\max}$, and the last inequality from $\gamma_{\max} \leq 1/P^{\min} + 1$, as proved above. ■

Lemma 3. The steady state mutual information is as follows:

$$I_{ss} \leq 2 \log(2) \Delta \sum_{(\alpha, \beta) \in \mathcal{N}} \|\pi_{\alpha} - \pi_{\beta}\|^2. \quad (12)$$

Proof. Let $\pi = \sum_{\alpha} P^{\alpha} \pi_{\alpha}$ denote the marginal distribution of the receptor states. Then we have that

$$\begin{aligned} I_{ss} &= \sum_{\alpha} P^{\alpha} \sum_i P(i|\alpha) \log \frac{P(i|\alpha)}{P_i} \\ &= \sum_{\alpha} P^{\alpha} D(\pi_{\alpha} \| \pi) \\ &\leq \log(2) \sum_{\alpha} P^{\alpha} \sum_i \sum_{\nu \geq 1} \frac{[\pi_{\alpha}(i) - \pi(i)]^2}{\pi_{\alpha}(i) + (2^{\nu} - 1)\pi(i)} \\ &\leq \log(2) \sum_{\alpha} P^{\alpha} \sum_i \frac{[\pi_{\alpha}(i) - \pi(i)]^2}{P_i} \sum_{\nu \geq 1} \frac{1}{2^{\nu} - 1} \\ &\leq \log(2) \sum_{\alpha} P^{\alpha} \sum_i \frac{[\pi_{\alpha}(i) - \pi(i)]^2}{\pi(i)} \left(1 + \sum_{\nu \geq 1} 2^{-\nu}\right) \\ &= 2 \log(2) \sum_{\alpha} P^{\alpha} \sum_i \frac{[\pi_{\alpha}(i) - \pi(i)]^2}{\pi(i)} \\ &= 2 \log(2) \sum_{\alpha} P^{\alpha} \|\pi_{\alpha} - \pi\|^2, \\ &\leq 2 \log(2) \sum_{\alpha\beta} P^{\alpha} P^{\beta} \|\pi_{\alpha} - \pi_{\beta}\|^2 \\ &\leq 2 \log(2) \max_{\alpha\beta} \|\pi_{\alpha} - \pi_{\beta}\|^2, \end{aligned}$$

where the first inequality follows from the second inequality in (10), the third inequality follows from $\frac{1}{2^{\nu+1}-1} < 2^{-\nu}$ for $\nu \geq 1$, and the fourth inequality from the convexity of the square of a norm, and the fact that $\pi = \sum_{\beta} P^{\beta} \pi_{\beta}$.

Fix α and β . Let $(\alpha_1 = \alpha, \dots, \alpha_m = \beta)$ denote a directed path connecting α and β in \mathcal{N} . By triangle inequality and the convexity of the norm it follows that

$$\begin{aligned} \|\pi_{\alpha_m} - \pi_{\alpha_1}\|^2 &\leq \left(\sum_{k=1}^{m-1} \|\pi_{\alpha_k} - \pi_{\alpha_{k+1}}\| \right)^2 \\ &\leq (m-1) \sum_{1 \leq k \leq m} \|\pi_{\alpha_k} - \pi_{\alpha_{k+1}}\|^2 \\ &< \Delta \sum_{(\alpha, \beta) \in \mathcal{N}} \|\pi_{\alpha} - \pi_{\beta}\|^2. \end{aligned} \quad (13)$$

The last step in the proof is to establish a bound on P^{\min} in terms of the signal network parameters. ■

Lemma 4. The minimum probability P^{\min} of any signal state satisfies

$$\frac{1}{P^{\min}} \leq N \left(\frac{d^{\max} w^{\max}}{w^{\min}} \right)^{\Delta}.$$

Proof. Let α^{\max} denote a state such that $P^{\alpha^{\max}} = \max_{\alpha} \{P^{\alpha}\}$. Then $P^{\alpha^{\max}} \geq \frac{1}{N}$, where N denotes the number of signal states; thus, $1/P^{\alpha^{\max}} \leq N$. Fix a state β . Let $(\alpha_1 = \alpha^{\max}, \alpha_2, \dots, \alpha_m = \beta)$ denote the shortest path from α^* to β . Such a path always exists, because the diameter $\Delta < \infty$.

From the current balance for the state α_1 , we have

$$\begin{aligned} \frac{1}{P^{\alpha_m}} &= \frac{\sum_{\gamma} w^{\alpha_m \gamma}}{\sum_{\gamma'} P^{\gamma'} w^{\gamma' \alpha_m}} \leq \frac{d^{\max} w^{\max}}{P^{\alpha_{m-1}} w^{\alpha_{m-1}, \alpha_m}} \\ &\leq \frac{d^{\max} w^{\max}}{w^{\min}} \frac{1}{P^{\alpha_{m-1}}} \leq \left(\frac{d^{\max} w^{\max}}{w^{\min}} \right)^{\Delta} \frac{1}{P^{\max}} \end{aligned} \quad (14)$$

$$\leq N \left(\frac{d^{\max} w^{\max}}{w^{\min}} \right)^{\Delta}, \quad (15)$$

where the first inequality follows from the fact that $\sum_{\gamma} w^{\alpha_m \gamma} \leq d^{\max} w^{\max}$, and that $\sum_{\gamma'} P^{\gamma'} w^{\gamma' \alpha_m} \geq P^{\alpha_{m-1}} w^{\alpha_{m-1}, \alpha_m}$, the second inequality follows from the fact that $w^{\min} \leq w^{\alpha_{m-1}, \alpha_m}$, (14) follows from iterating the inequality until we reach $\alpha_1 = \alpha^*$, and the fact that $m-1 \leq \Delta$, and the last inequality follows from $\frac{1}{P^{\max}} \leq N$. ■

Theorem 1 implies several corollaries.

Corollary 1. (a) Suppose the receptor entropy rate $\dot{\sigma}_y = 0$. Then the steady state mutual information $I_{ss} = 0$.

(b) The receptor entropy rate $\dot{\sigma}_y = 0$ if, and only if, the conditional detailed balance

$$\frac{P_i^{\alpha}}{P_j^{\alpha}} = \frac{w_{j,i}^{\alpha}}{w_{i,j}^{\alpha}} \quad (16)$$

holds, i.e., the ratio of the forward and backward transition rates of the receptor are unaffected by the signal; the signal dynamics affects only the absolute time scale of the receptor [16].

Proof. (a) follows $0 = \dot{\sigma}_y \geq \frac{1}{c} I_{ss} \geq 0$. (b) is established as follows. $\dot{\sigma}_y = I_{ss} = 0$ implies that (8a) has to be an equality. Thus, (16) holds. Since $\dot{\sigma}_y = \frac{1}{2} \sum_{i,j,\alpha} (P_i^{\alpha} w_{i,j}^{\alpha} - P_j^{\alpha} w_{j,i}^{\alpha}) \log \frac{w_{i,j}^{\alpha}}{w_{j,i}^{\alpha}}$, (16) implies that $\dot{\sigma}_y = 0$. ■

When $I_{ss} = 0$, X_t is independent of Y_t for all n . However, Y_t may still have information about the past or future signal states X_m , $m \neq n$. In the following section, we show that when $\dot{\sigma}_y = 0$, the entire set of variables $\{X_{n_k} : k = 1, \dots, K \geq 0\}$ is independent of Y_t for any choice of K and $n_k \geq 0$. This shows that when the receptor does not perturb the signal, the receptor system must produce entropy in order to get any information about the signal.

In the rest of this section, we establish an additive bound for the entropy rate. We call C a cover of \mathcal{N} , if for all α there exists $\beta_{\alpha} \in C$ such that $(\alpha, \beta_{\alpha}) \in \mathcal{N}$.

Theorem 2. Let n_c denote the size of any minimum cover for the graph \mathcal{N} . Then

$$I_{ss} \leq \frac{\dot{\sigma}_y}{w^{\min}} + \log(n_c). \quad (17)$$

Proof. Mutual information $I_{ss} \leq \sum_{\alpha,i} P_i^\alpha \log \left(\frac{P(i|\alpha)}{Q_i} \right)$ for any distribution Q [21]. Define $Q = \frac{1}{n_c} \sum_{\beta \in C_{\min}} P(\cdot|\beta)$, where C_{\min} is any minimum cover for \mathcal{N} . Then

$$\begin{aligned} I_{ss} &\leq \sum_{\alpha,i} P(i|\alpha) \log \frac{P(i|\alpha)}{\sum_{\beta \in C_{\min}} \frac{P(i|\beta)}{n_c}} \\ &= \sum_{\alpha,i} P(i|\alpha) \log \frac{P(i|\alpha)}{\sum_{\beta \in C_{\min}} P(i|\beta)} + \log(n_c) \\ &\leq \sum_{\alpha} P^\alpha \sum_i P(i|\alpha) \log \frac{P(i|\alpha)}{P(i|\beta_\alpha)} + \log(n_c) \\ &= \sum_{\alpha} P^\alpha D(P(\cdot|\alpha) || P(\cdot|\beta_\alpha)) + \log(n_c) \\ &\leq \max_{\alpha, \beta \in \mathcal{N}} D(P(\cdot|\alpha) || P(\cdot|\beta)) + \log(n_c) \\ &\leq \frac{\dot{\sigma}_y}{w_{\min}} + \log(n_c), \end{aligned}$$

where $\beta_\alpha \in C_{\min}$ is any state such that $(\alpha, \beta_\alpha) \in \mathcal{N}$. The last inequality follows from (8c). ■

Thus, it follows that $I_{ss} \leq \min \{c \frac{\dot{\sigma}_y}{w_{\min}}, \frac{\sigma_y}{w_{\min}} + \log(n_c)\}$. It is clear that $c > 1/w_{\min}$, and grows exponentially with the diameter Δ . Thus, when $\log(n_c)$ is small compared to $\frac{\dot{\sigma}_y}{w_{\min}}$, the second bound is tighter. In particular, for networks where there exists a state which can be reached from any other state in *one hop*, $n_c = 1$; thus, the second bound is always smaller than the first one, and $I_{ss} \leq \frac{\dot{\sigma}_y}{w_{\min}}$. A fully connected network is an example of a one-hop network.

IV. INFORMATION TRANSMISSION AT ZERO ENTROPY RATE

We have established that $\dot{\sigma}_y = 0$ implies that $I_{ss} = 0$, and consequently, $P_i^\alpha = P^\alpha P_i$. In this section, we establish the following more general result.

Theorem 3. Suppose $\dot{\sigma}_y = 0$. Let $\mathcal{T} = \{t_k : k = 1, \dots, K\}$ denote any finite set of time epochs, $X_{\mathcal{T}} = \{X_{t_k} : k = 1, \dots, K\}$, and t an arbitrary time epoch. Then

$$I(X_{\mathcal{T}}; Y_t) = 0. \quad (18)$$

Proof. We first prove that $\mathbb{P}(X_{t-1} = \alpha, Y_t = i) = P^\alpha P_i$, i.e., X_{t-1} and Y_t are independent. Recall that $I_{ss} = 0$ implies that $\mathbb{P}(X_s = \alpha, Y_s = i) = P^\alpha P_i$ for all s . Thus, the Markov property implies that

$$\begin{aligned} \mathbb{P}(X_{t-1} = \alpha, Y_t = i) &= \sum_{j \neq i} \mathbb{P}(Y_{t-1} = j, X_{t-1} = \alpha) w_{ji}^\alpha \\ &\quad + \sum_{\beta \neq \alpha} \mathbb{P}(Y_{t-1} = i, X_{t-1} = \beta) w^{\beta\alpha} \\ &\quad + \mathbb{P}(Y_{t-1} = i, X_{t-1} = \alpha) \bar{w}_i^\alpha \\ &= P^\alpha \sum_{j \neq i} P_j w_{ji}^\alpha + P_i \sum_{\beta \neq \alpha} P^\beta w^{\beta\alpha} + P^\alpha P_i \bar{w}_i^\alpha. \end{aligned}$$

Next, we use the fact that $I_{ss} = 0$ implies conditional detailed balance (16), i.e., $P_i^\alpha w_{ij}^\alpha = P_j^\alpha w_{ji}^\alpha$, and the \mathbb{X} Markov chain is

in steady state, i.e., $\sum_{\beta \neq \alpha} P^\beta w^{\beta\alpha} = \sum_{\beta \neq \alpha} P^\alpha w^{\alpha\beta}$ to rewrite the first two terms as follows:

$$\begin{aligned} \mathbb{P}(X_{t-1} = \alpha, Y_t = i) &= P^\alpha \sum_{j \neq i} P_j w_{ij}^\alpha + P_i \sum_{\beta \neq \alpha} P^\beta w^{\alpha\beta} + P_i \bar{w}_i^\alpha \\ &= P^\alpha P_i \left(\sum_{j \neq i} w_{i,j}^\alpha \delta + \sum_{\beta} P_i w^{\alpha,\beta} \delta + P_i \bar{w}_i^\alpha \right) \\ &= P^\alpha P_i \left(\sum_j w_{i,j}^\alpha + \sum_{\beta} w^{\alpha,\beta} + \bar{w}_i^\alpha \right) \\ &= P^\alpha P_i. \end{aligned}$$

Define $u = \min \{ \{t_k : k = 1, \dots, K\}, t \}$, $v = \max \{ \{t_k : k = 1, \dots, K\}, t \}$. We abbreviate the sequence of random variables $(X_u, X_{u+1}, \dots, X_v)$ as X_u^v , the sequence of values $(\alpha_u, \alpha_{u+1}, \dots, \alpha_v)$ as α_u^v , and the probability $\mathbb{P}[(X_u^v, Y_t) = (\alpha_u^v, i_t)] = \mathbb{P}(\alpha_u^v, i_t)$. Then the Markov property implies that

$$\begin{aligned} \mathbb{P}(\alpha_u^v, i_t) &= \mathbb{P}(\alpha_{t+1}^v | \alpha_t) \mathbb{P}(\alpha_t^v, i_t) \\ &= \mathbb{P}(\alpha_{t+1}^v | \alpha_t) \sum_{i_u, \dots, i_{t-1}} \mathbb{P}(\alpha_u^t, i_u^t), \\ &= \mathbb{P}(\alpha_{t+1}^v | \alpha_t) \\ &\quad \times \sum_{i_u, \dots, i_{t-1}} \mathbb{P}(\alpha_u, i_u) \prod_{s=u+1}^t \mathbb{P}(\alpha_s, i_s | \alpha_{s-1}, i_{s-1}). \end{aligned}$$

From the structure of the bipartite Markov chain (\mathbb{X}, \mathbb{Y}) it follows that $\mathbb{P}(\alpha_{s+1} | \alpha_s, i_s) = \mathbb{P}(\alpha_{s+1} | \alpha_s)$, and $\mathbb{P}(i_{s+1} | \alpha_s, i_s, \alpha_{s+1}) = \mathbb{P}(\alpha_{s+1} | \alpha_s, i_s)$. Moreover, X_s is independent of Y_s , and X_{s+1} is independent of Y_s , and it follows that $\mathbb{P}(i_s, \alpha_s) = \mathbb{P}(i_s) \mathbb{P}(\alpha_s)$ and $\mathbb{P}(i_{s+1}, \alpha_s) = \mathbb{P}(i_{s+1}) \mathbb{P}(\alpha_s)$. Isolating the terms involving i_u we get

$$\begin{aligned} \sum_{i_u} \mathbb{P}(\alpha_u) \mathbb{P}(i_u) \mathbb{P}(\alpha_{u+1}, i_{u+1} | \alpha_u, i_u) &= \mathbb{P}(\alpha_u) \sum_{i_u} \mathbb{P}(i_u) \mathbb{P}(\alpha_{u+1} | \alpha_u, i_u) \mathbb{P}(i_{u+1} | \alpha_u, i_u) \\ &= \mathbb{P}(\alpha_u) \mathbb{P}(\alpha_{u+1} | \alpha_u) \sum_{i_u} \mathbb{P}(i_u) \mathbb{P}(\alpha_{u+1} | \alpha_u, i_u) \\ &= \mathbb{P}(\alpha_{u+1}, \alpha_u) \mathbb{P}(i_{u+1} | \alpha_u) \\ &= \mathbb{P}(\alpha_u | \alpha_{u+1}) \mathbb{P}(\alpha_{u+1}) \mathbb{P}(i_{u+1}). \end{aligned}$$

One can now combine the term $\mathbb{P}(\alpha_{u+1}) \mathbb{P}(i_{u+1})$ with the term $\mathbb{P}(\alpha_{u+2}, i_{u+2} | \alpha_{u+1}, i_{u+1})$, and sum over the index i_{u+1} , to get $\mathbb{P}(\alpha_{u+1} | \alpha_{u+2}) \mathbb{P}(\alpha_{u+2}) \mathbb{P}(i_{u+2})$. The procedure can be repeated to show that

$$\mathbb{P}(\alpha_u^v, i_t) = \mathbb{P}(i_t) \mathbb{P}(\alpha_{t+1}^v | \alpha_t) \mathbb{P}(\alpha_t) \prod_{s=u}^{t-1} \mathbb{P}(\alpha_s | \alpha_{s+1}).$$

Next, since \mathbb{X} is a Markov chain, it follows that for all t and k ,

$$\mathbb{P}(\alpha_t | \alpha_{t+1}, \dots, \alpha_{t+k}) = \mathbb{P}(\alpha_t | \alpha_{t+1}).$$

Thus, it follows that

$$\begin{aligned} & \mathbb{P}(\alpha_t) \prod_{s=u}^{t-1} \mathbb{P}(\alpha_s | \alpha_{s+1}) \\ &= \mathbb{P}(\alpha_t) \prod_{s=u}^{t-1} \mathbb{P}(\alpha_s | \alpha_{s+1}, \dots, \alpha_t) \\ &= \mathbb{P}(\alpha_u^t). \end{aligned}$$

Again, using the Markov property for \mathbb{X} , we get

$$\begin{aligned} \mathbb{P}(\alpha_u^v, i_t) &= \mathbb{P}(i_t) \mathbb{P}(\alpha_{t+1}^v | \alpha_t) \mathbb{P}(\alpha_t) \prod_{s=u}^{t-1} \mathbb{P}(\alpha_s | \alpha_{s+1}) \\ &= \mathbb{P}(i_t) \mathbb{P}(\alpha_{t+1}^v | \alpha_t) \mathbb{P}(\alpha_u^t) \\ &= \mathbb{P}(i_t) \mathbb{P}(\alpha_u^v). \end{aligned}$$

Thus, it follows that $I(X_u^v; Y_t) = 0$. Since $0 \leq I(X_T, Y_t) \leq I(X_u^v; Y_t) = 0$, we have that

$$I(X_T, Y_t) = 0. \quad \blacksquare$$

Given this result, it would be natural to ask whether $I(X_t, Y_T)$ is also zero for all $T = \{t_k : k = 1, \dots, K\}$ when $\dot{\sigma}_y = 0$. However, we argue that the roles of X and Y are *not* symmetric. This is because for $I(X_t, Y_T)$ to be relevant, one must have a perfect memory of the receptor states Y_T , and maintaining this memory consumes free energy.

Consider the four-state model described in Fig. 2 where $X_t \in \{0, 1\}$ and $Y_t \in \{0, 1\}$, with

$$\frac{w_{0,1}^0}{w_{1,0}^0} = \frac{w_{0,1}^1}{w_{1,0}^1} = c, \quad (19)$$

i.e., the transition rate of the receptor from 0 to 1 is always c times greater than the transition rate from 1 to 0, irrespective of the signal value. From Corollary 1 (b) it follows that $\dot{\sigma}_y = 0$, and consequently, $I_{ss} = 0$. Suppose $w_{1,0}^0 \gg w_{1,0}^1$, and consequently, $w_{0,1}^0 \gg w_{0,1}^1$, i.e., the rate of change of the receptor state between 0 and 1 is extremely fast when the signal state is 0, and very slow when the signal state is 1. Thus, if one has access to not just the receptor state Y_t at a single time instant but over a time series Y_T , fast jumps will indicate that the signal is 0, and vice versa. Thus, the mutual information $I(X_t, Y_T) > 0$.

Does this example violate the principle that no information is possible without free-energy consumption? In fact, not. Access to the time series Y_T implies perfect memory. Suppose a two-state receptor keeps a two-period memory. Then the $(Y_{t-1}, Y_t) = (0, 1)$ can transition to the state $(1, 1)$ and $(1, 0)$; however, when memory is perfect, the state $(1, 1)$ can never transition to the state $(0, 1)$. Thus, the Schnackenberg network theory [22] implies that the free energy consumed for maintaining perfect memory is infinite. Our results will continue to apply if one were to redefine the receptor state $\hat{Y}_t = (Y_{t-1}, Y_t)$, and set up the corresponding Markov chain. In this case, $\dot{\sigma}_y$ will account for *both* the free-energy consumption for sensing and maintaining memory.

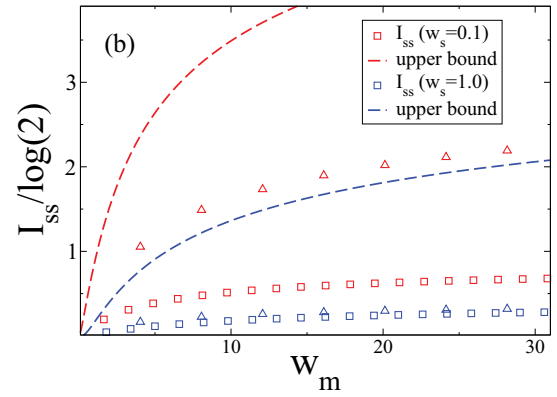
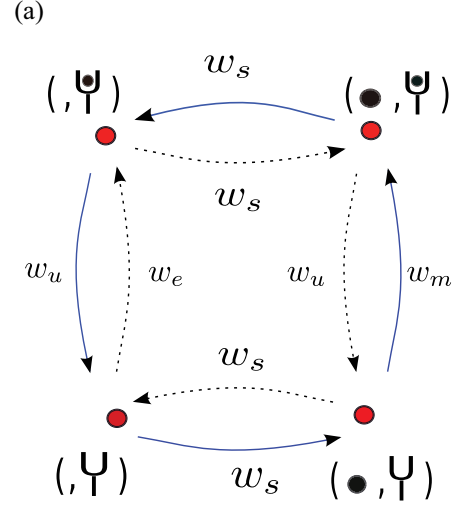


FIG. 2. (a) Single ligand-receptor binding model, with states (α, i) , where the first entry represents the absence (·) or presence (●) of a ligand, and the second entry represents whether the receptor is unbound (U) or bound. The arrows represent transitions with the rates written alongside. (b) For this model we have generated the data by numerically diagonalizing the transition matrix. The logarithm is in natural base. The parameters are $w_u = 1$, $w_e = 0.01$. The dotted lines are the analytical bounds from (5), which are clearly validated. The triangles represent $\dot{\sigma}_y$, which diverge with increasing w_m , as opposed to I_{ss} (boxes) which saturate at large w_m .

V. NUMERICAL RESULTS

We illustrate our result with a simple model of receptor-ligand binding. The signal $X \in \{0, 1\}$ corresponds to the absence or presence of a ligand at the receptor site, with $w^{01} = w^{10} = w_s$. The receptor state $Y \in \{0, 1\}$ corresponds to its unbound and bound configurations. The unbound receptor in the presence of a ligand, i.e., $X = 1$, binds at the rate $w_{0,1}^1 = w_m$, and for thermodynamic consistency, the rate of conformation change into the bound configuration in the absence of ligand, $w_{0,1}^0 = w_e > 0$. A bound receptor unbinds at the rate $w_{1,0}^1 = w_{1,0}^0 = w_u$. As we see in Fig. 2, the bound is numerically validated. The upper bound is approached only close to $\dot{\sigma}_y = 0$. This is not surprising since our bound (5) reduces to an equality only if conditional detailed balance is

satisfied, i.e., the entropy rate is zero. Thus at finite entropy rates, the inequality is strict. This is true for both the bounds.

The mutual information increases with w_m but quickly saturates since it cannot exceed $\log(2)$, the Shannon entropy of the signal, whereas the entropy rate continues to grow. I_{ss} is closer to the bound for the higher signal transition rate.

Note that in our analysis we did not consider the mutual information *rate* between \mathbb{Y} and \mathbb{X} because one then has to account for the free energy associated with maintaining memory.

VI. SUMMARY OF THEOREMS AND COROLLARIES

Sections III and IV contains a number of theorems and corollaries, which are the major results in this article. In this section, we summarize the key results. Definitions of all quantities are given in Sec. II.

Theorem 1.

$$I_{ss} \leq c \dot{\sigma}_y / w^{\min},$$

where the constant c depends on signal parameters alone [Eq. (5) in the main text].

Corollaries. (a) Suppose the receptor entropy rate $\dot{\sigma}_y = 0$. Then the steady state mutual information $I_{ss} = 0$. (b) The receptor entropy rate $\dot{\sigma}_y = 0$ if, and only if, the *conditional detailed balance*

$$\frac{P_i^\alpha}{P_j^\alpha} = \frac{w_{j,i}^\alpha}{w_{i,j}^\alpha}$$

holds, i.e., the ratio of the forward and backward transition rates of the receptor are unaffected by the signal.

Theorem 2.

$$I_{ss} \leq \frac{\dot{\sigma}_y}{w^{\min}} + \log(n_c), \quad (20)$$

where n_c is the size of the smallest subset of signal states that have incoming arcs from all signal states [Eq. (17) in the main text]. For networks with $n_c = 1$ (for example, a network which has a “reset” state where any state can collapse to), we have the tight bound $I_{ss} \leq \frac{\dot{\sigma}_y}{w^{\min}}$.

Theorem 3. Suppose $\dot{\sigma}_y = 0$. Let $\mathcal{T} = \{t_k : k = 1, \dots, K\}$ denote any finite set of time epochs, $X_{\mathcal{T}} = \{X_{t_k} : k = 1, \dots, K\}$,

and t an arbitrary time epoch. Then

$$I(X_{\mathcal{T}}; Y_t) = 0,$$

i.e., the receptor at any instant has no knowledge of the signal value at any set of points in time—past, present, or future. [Eq. (18) in main text]. This establishes that for unidirectionally coupled systems, *there is no measurement without free-energy consumption.*

VII. DISCUSSION

We consider the generic dynamics of how chemical information (ligand) represented as a Markov chain is read by sensors embedded, for instance, in the physical milieu of the cell. We focus on the setting where the signal and receptors are embedded in different physical environments, and therefore, the receptors cannot affect the signal dynamics. We show that the free-energy consumption rate of the receptors is bounded below by the mutual information times a constant (5) that depends only on properties of the signal dynamics, and is *independent of receptor architecture.*

Our results do *not* contradict the results of Bennett and others [25] that all computation can be done in a reversible manner (i.e., without generating entropy). This is because these computation models require intermediate steps where the input is first overwritten and then reconstructed [25], violating our assumption that the signal dynamics is unaffected by the receptor. In fact, we establish that information at zero entropy production is only possible if the receptors perturb the signal. This observation should be relevant to discussions on Maxwell’s demon [26].

Our study is relevant to a variety of contexts of cellular information processing involving the ligand-receptor interactions. Importantly, our work provides a metric for the cost of dynamics and implies that under the assumptions listed above, the dynamics of signal measurement should involve free-energy consumption at the scale of the measuring device, consistent with the proposal of active mechanics of signal processing [17].

ACKNOWLEDGMENT

G.I. thanks Simons Centre for the Study of Living Machines, the National Centre for Biological Sciences, TIFR, Bangalore for hospitality during a visit.

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