A universal lower bound on the free energy cost of molecular measurements

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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.

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In the natural world, the processing of chemical information (ligands) is carried out by molecular receptors that operate within a prescribed physical milieu. Examples of information processing involving ligand-receptor interactions arise in a variety of contexts such as antigen-TCR [2], ECM-integrin [3, 4], pathogen-antibody [5, 6] interactions, and a variety of other contexts [7]. Thermodynamics of information processing [7, 8, 10–15], seek to understand information flows in cell-signaling networks, through which biomolecules learn about and respond to changes in their environment [14, 15]. Given the wide variety of signaling modalities, it is useful to have a general framework to study the nonequilibrium dynamics of information flows [10, 11, 16].

Shannon [17] proposed mutual information between the source (or signal) and the receptor as an appropriate measure of information, and the objective in signal processing is to optimize (minimize for rate distortion, and maximize for transmission) mutual information (or information rate) under suitable constraints or costs [18]. In the biological context, it is clear that the fixed costs should include the cost of synthesizing proteins that participate in signaling networks. However in addition, there should be a cost for the dynamics of information sensing, and it would be desirable to have a universal measure of this dynamic cost. The natural candidate for such a cost is the rate of free energy consumption. Specific models of ligand-receptor binding in simplified signaling cascades have established free energy as the cost for transmitting distortion, and maximize for transmission) mutual information (or information rate) under suitable constraints or costs [19]. But does this assertion extend to arbitrary complex signaling networks? Indeed, what are the conditions under which such a general proposition might hold? We focus our attention on Markov models of signaling, and prove that, when the signal is unperturbed by the receptor, it is impossible to have signal reception when the free energy consumption rate is zero. This establishes unequivocally that the rate of free energy consumption rate is a universal metric for the physical cost of information processing without signal perturbation. We establish this by demonstrating an exact general lower bound on the free energy consumption rate in terms of the mutual information and the time-scale of signal dynamics. For a class of signal network topologies called one-hop networks, we prove a tighter lower bound.

In this ligand-receptor binding context, let \( X \) denote the location and concentration of all ligands (signals), and \( Y \), the location and internal states of all receptors. Let \( \mathbb{X} = \{X_n : n \geq 1\} \) and \( \mathbb{Y} = \{Y_n : n \geq 1\} \) denote the time series of the signal and receptor states, respectively. We assume that the \( (\mathbb{X}, \mathbb{Y}) \) is a time-stationary bipartite Markov chain [10, 11, 13, 20], i.e. the individual chains \( \mathbb{X} \) and \( \mathbb{Y} \) do not change state simultaneously. This is not a significant restriction, since the probability of simultaneous transitions is always negligible in the continuous time limit. We assume that the transition probability

\[
w_{ij}^{\alpha,\beta} = \mathbb{P}(X_{n+1} = \beta, Y_{n+1} = j \mid X_n = \alpha, Y_n = i)
\]

is given by

\[
w_{ij}^{\alpha,\beta} = w^{\alpha,\beta} \text{ if } i = j \text{ and } \alpha \neq \beta \\
= w^\alpha \text{ if } i \neq j \text{ and } \alpha = \beta \\
= 0 \text{ if } i \neq j \text{ and } \alpha \neq \beta
\]

(1)

For notational convenience, we define \( w_{i,i}^\alpha = w_{i,i}^{\alpha,\alpha} = 0 \). Note that transitions of the signal \( X_n \) do not depend on the receptor state \( Y_n \); however, the transitions of the receptor state \( Y_n \) do depend on the signal state \( X_n \). 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 \( H(X,Y) \). We introduce the notation \((\alpha, \beta)\) to denote an outgoing edge from \( \alpha \) to \( \beta \) when \( w^{\alpha,\beta} > 0 \). Let \( \mathcal{N}_+ = \{(\alpha, \beta) : P^\alpha w^{\alpha,\beta} > 0\} \) denote the set of outgoing arcs in the signal network with positive probability, \( w_{\min} = \min \{w^{\alpha,\beta} : (\alpha, \beta) \in \mathcal{N}_+\} \), \( w_{\max} = \max \{w^{\alpha,\beta}\} \), \( P_{\min} = \min \{P^\alpha\} \) and \( d_{\max} \) is the largest out-degree in the graph. For any two states \( \alpha \neq \beta \) of the \( X \) Markov Chain, we denote the shortest directed path between them as \( l^{\alpha,\beta} \), and the diameter of the Markov chain is \( \Delta = \max_{\alpha,\beta} \{l^{\alpha,\beta}\} \).

Let

\[
P^\alpha_i = \mathbb{P}(X_n = \alpha, Y_n = i)
\]

(2)
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 $w^{\alpha}_{i,j}$ depend on the current signal state.

denote the steady state probability distribution of the Markov chain $\{(X_n, Y_n) : n \geq 1\}$, where $x \log x = 0$, when $x = 0$. We ask if it is possible to perform measurement without consuming free energy. Since non-steady states are out of equilibrium and generate entropy, we focus on measurement in steady state, and define the steady state mutual information $I_{ss}$ between the signal $X$ and the receptor $Y$ in the usual way [18]:

$$I_{ss} = \sum_{\alpha,i} P^{\alpha}_{i} \log \left( \frac{P^{\alpha}_{i}}{P^{\alpha} P_{i}} \right),$$

where $P^{\alpha}$ denotes the stationary distribution of the bipartite Markov chain $(X, Y)$, $P^{\alpha} = \sum_{i} P^{\alpha}_{i}$ is the marginal distribution of the signal state, and $P_{i} = \sum_{\alpha} P^{\alpha}_{i}$ is the marginal distribution of the receptor state. Note that $I_{ss} = 0$ iff the signal state $X_n$ is independent of the receptor state $Y_n$ in steady state, i.e. $P^{\alpha}_{i} = P^{\alpha} P_{i}$.

So far, we have only described the signal and receptor in purely information-theoretic terms. However these processes are embedded in their respective physical environments where states would correspond to positional or conformational states of molecules, or concentrations. The thermodynamic entropy rate $\dot{\sigma}$ of these mesoscopic thermal systems can be formally described by the Schnakenberg network theory [21]. In our case,

$$\dot{\sigma} = \sum_{\alpha,\beta} P^{\alpha} w^{\alpha,\beta} \log \frac{w^{\alpha,\beta}}{w^{\beta,\alpha}} + \sum_{\alpha,i,j} P^{\alpha}_{i} w^{\alpha}_{i,j} \log \frac{w^{\alpha}_{i,j}}{w^{\alpha}_{j,i}}.$$  

The first term is the steady state entropy rate of the physically independent signal process, and is thus the free energy consumed in generating the signal alone. Therefore, the second term $\dot{\sigma}_y$ can be unambiguously identified as rate of free energy consumption associated with the measurement process.

We establish that, for arbitrary signal and network topologies,

$$I_{ss} \leq c \dot{\sigma}_y$$

where $c = \frac{4 \Delta \log(2) N^2}{w^{\min}_{\alpha}} \left( \frac{w^{\max}_{\alpha} w^{\max}_{\beta}}{w^{\min}_{\alpha}} \right)^{2 \Delta}$ is a constant independent of receptor parameters and dependent on the signal parameters alone.

While our results seem superficially analogous to the results in [22], we address a very distinct problem here. In contrast to [22], 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.

We start our proof by noting that

\[
\sum_{\alpha, i,j} P^{\alpha}_{i} w_{i,j}^{\alpha} \log \frac{P^{\alpha}_{i} w_{i,j}^{\alpha}}{P^{\alpha}_{j} w_{j,i}^{\alpha}} = \frac{1}{2} \sum_{i,j,\alpha} (P^{\alpha}_{i} w_{i,j}^{\alpha} - P^{\alpha}_{j} w_{j,i}^{\alpha}) \log \frac{P^{\alpha}_{i} w_{i,j}^{\alpha}}{P^{\alpha}_{j} w_{j,i}^{\alpha}} \geq 0. \tag{6}
\]

Then,

\[
\dot{\sigma}_{y} = \sum_{\alpha, i,j} P^{\alpha}_{i} w_{i,j}^{\alpha} \log \frac{w_{i,j}^{\alpha}}{w_{j,i}^{\alpha}}
\geq - \sum_{\alpha, i,j} P^{\alpha}_{i} w_{i,j}^{\alpha} \log \frac{P^{\alpha}_{j}}{P^{\alpha}_{i}} \tag{7a}
= \sum_{\alpha,\beta,i,j} P^{\alpha}_{i} w^{\alpha,\beta} \log \frac{P^{\alpha}_{i}}{P^{\beta}_{i}} \tag{7b}
= \sum_{\alpha,\beta} w^{\alpha,\beta} \sum_{i} P^{\alpha}_{i} \log \frac{P^{\alpha}_{i}}{P^{\beta}_{i}}
= \sum_{\alpha,\beta} P^{\alpha}_{i} w^{\alpha,\beta} \sum_{i} P(i|\alpha) \log \frac{P(i|\alpha)}{P(i|\beta)} \tag{7c}
\geq P^{\min}_{\alpha} w^{\min}_{\alpha} \sum_{(\alpha,\beta)\in N_{+}} D(P(\cdot|\alpha)\|P(\cdot|\beta)), \tag{7d}
\]

where (7a) follows from (6), (7b) follows from the fact that the Shannon entropy of the whole system is constant, (7c) follows from the fact that \( \sum P_{i} w^{\alpha,\beta} \log \frac{P^{\alpha}_{i}}{P^{\beta}_{i}} = 0 \) because the signal is in steady state, (7d) follows the definition of \( w^{\min} \), and \( D(p\|q) \) denotes the Kullback-Leibler (K-L) divergence between \( p \) and \( q \) [18]. The expression in (7a) [http://evolution.haifa.ac.il/index.php/people/311-eyal-privman-ph-d] has been named learning rate and information flow in some previous works [10, 12]; here we provide a rigorous information-theoretic bound for this in terms of the mutual information, \( I_{ss} \).

In [23] we lower bound the sum of divergences

\[
\sum_{(\alpha,\beta)\in N_{+}} D(P(\cdot|\alpha)\|P(\cdot|\beta)) \geq \frac{1}{2} P^{\min}_{\alpha} \sum_{(\alpha,\beta)\in N_{+}} \sum_{i} \left( \frac{P(i|\alpha) - P(i|\beta)}{P_{i}} \right)^{2},
\]

in terms of a sum over \( \chi \)-squared distances between the conditional probabilities of the receptor states. We also prove there that \( I_{ss} \leq \Delta \sum_{(\alpha,\beta)\in N_{+}} \sum_{i} \left( \frac{P(i|\alpha) - P(i|\beta)}{P_{i}} \right)^{2} \), and \( 1/P^{\min} \leq N \left( \frac{w^{\max}}{w^{\min}} \right)^{\Delta} \). Combining these, we have our main result [5], \( I_{ss} \leq c \delta_{y} \).

From this general result, many corollaries follow. For instance, since \( I_{ss} \geq 0 \), it follows that \( 0 = \delta_{y} \geq \frac{1}{2} I_{ss} \) implies that \( I_{ss} = 0 \), i.e. \( X_{n} \) is independent of \( Y_{n} \) for all \( n \). In [23] we show that when \( \delta_{y} = 0 \), the set of variables \( \{X_{nk} : k = 1, \ldots, K \geq 0\} \) is independent of \( Y_{n} \) for any choice of \( K \) and \( n_{k} \geq 0 \). This shows that if any signal is unperturbed by the receptor, the receptor system must produce entropy in order to have any information about the signal. Also, \( \delta_{y} = I_{ss} = 0 \) implies that (7a) has to be an equality, which holds iff the conditional detailed balance

\[
P^{\alpha}_{i} = \frac{w_{i,j}^{\alpha}}{w_{j,i}^{\alpha}} \tag{8}
\]
of a ligand, i.e. \( w \) receptor unbinds at the rate \( X \) conformation change into the bound configuration, in the absence of ligand, \( Y \in \{0, 1\} \). This implies that \( I \) is saturates (it cannot be greater than \( \log(2) \), which is the Shannon entropy) whereas the entropy \( \sigma \) upper bound is approached only close to \( \dot{\sigma} \). Since \( \dot{\sigma} \) 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 \([13]\). Since \( \dot{\sigma} \) as opposed to \( \sigma \) analytical bounds from (5), which are clearly validated. The circles represent \( \dot{\sigma} \), which diverge with increasing \( w_m \), as opposed to \( I_{ss} \) (boxes) which saturate at large \( w_m \).

We also prove an additive bound for the entropy rate. We call a set \( C \) a cover for the signal states if for all \( \alpha \) there exists \( \beta_\alpha \in C \) such that \( (\alpha, \beta_\alpha) \in C \). Let \( C_{\min} \) be any minimum cover, and let \( n_c = |C_{\min}| \). We prove \([23]\) that \( I_{ss} \leq \log(n_c) + \frac{\sigma_u}{w_{\text{min}}} \). Thus, it follows that \( I_{ss} \leq \min \{ c\dot{\sigma}_y, \frac{\sigma_u}{w_{\text{min}}} + \log(n_c) \} \), with the multiplicative bound being tight when \( \dot{\sigma}_y \approx 0 \) and the additive bound being tight when \( \frac{\sigma_u}{w_{\text{min}}} \gg 1 \). For a one-hop network with \( n_c = 1 \), we have \( I_{ss} \leq \frac{\sigma_u}{w_{\text{min}}} \).

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 \( w_{0,1}^{\alpha} = w_m \), 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 \( \dot{\sigma}_y = 0 \). The mutual information increases with \( w_m \) but quickly saturates (it cannot be greater than \( \log(2) \), which is 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 \( Y \) and \( X \) because when all the physical variables involved in the receptor process are taken into account, the problem reduces to our current formalism \([24]\).

To conclude, 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. A crucial feature of our model is that 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. This implies that \( I_{ss} \) can be considered a universally valid cost function for molecular measurements.

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. Our results can also be contrasted with the Monod-Wyman-Changeux (MWC) model [13, 26], where the combined system (signal and receptor) is in equilibrium and yet the mutual information is non-zero, because the MWC model allows the receptors to perturb the signal. In fact, we establish that entropy production in steady-state measurements is necessary if and only if the signal is unperturbed. This observation should be relevant to discussions on Maxwell’s Demon [28].

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 [16].

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SUPPLEMENTARY INFORMATION FOR “A UNIVERSAL LOWER BOUND ON THE FREE ENERGY COST OF MOLECULAR MEASUREMENTS”

PROOF OF THE INEQUALITIES

Recall that $P^\alpha$ denotes the stationary distribution of the signal network, and this is independent of its coupling the receptors. Suppose

$$ P_{\text{min}} = \min_{\alpha} \{P^\alpha\} > 0, $$

i.e. all signal states have strictly positive probability. Let $\pi_\alpha = P(\cdot \mid \alpha)$ denote the distribution of the receptor states when the signal state is $\alpha$, and let

$$ P_i = \sum_\alpha P^\alpha \pi_{\alpha,i} $$

denote the marginal distribution of the receptor states. We argue in the main text that $\min_i P_i > 0$. Define

$$ \gamma_{\text{max}} = \max_{\alpha,i} \frac{|\pi_{\alpha,i} - P_i|}{P_i}. $$

We first prove the following lemma:

**Lemma:** $\gamma_{\text{max}} \leq \frac{1}{P_{\text{min}}} - 1$.

To show this, consider the following two cases:

(i) $\pi_{\alpha,i} > P_i$. In this case

$$ \frac{|\pi_{\alpha,i} - P_i|}{P_i} = \frac{\pi_{\alpha,i} - P_i}{P_i} = \frac{\pi_{\alpha,i} - P_i}{P_i} \leq 1 - \frac{1}{P_{\text{min}}} - 1, $$

where the last inequality follows from the fact that $P_i = \sum_\beta P^\beta \pi_{\beta,i} \geq P^\alpha \pi_{\alpha,i} \geq P_{\text{min}} \pi_{\alpha,i}$.

(ii) $\pi_{\alpha,i} \leq P_i$. In this case,

$$ \frac{|\pi_{\alpha,i} - P_i|}{P_i} = \frac{P_i - \pi_{\alpha,i}}{P_i} = 1 - \frac{\pi_{\alpha,i}}{P_i} \leq 1. $$
Since $P_{\min} \leq \frac{1}{2}$, it follows that $\frac{1}{P_{\min}} - 1 \geq 1 - \pi_{\alpha,i}$. Thus it follows that $\gamma_{\max} \leq \frac{1}{P_{\min}} - 1$.

From Theorem 3 in [29] we have that

$$\frac{1}{2} \sum_{\nu=1}^{\infty} \sum_i \frac{(p_i - q_i)^2}{p_i + (2^\nu - 1)q_i} \leq D(P\|Q) \leq \log(2) \sum_{\nu=1}^{\infty} \sum_i \frac{(p_i - q_i)^2}{p_i + (2^\nu - 1)q_i}. \tag{9}$$

Thus, from the relation between mutual information $I_{ss}$ and the K-L divergence $D$,

$$I_{ss}(\lambda) \leq \log(2) \sum_\alpha P^\alpha \sum_i \sum_{\nu \geq 1} \frac{(\pi_{\alpha,i} - P_i)^2}{\pi_{\alpha,i} + (2^\nu - 1)P_i},$$

$$\leq \log(2) \sum_\alpha P^\alpha \sum_i \frac{(\pi_{\alpha,i} - P_i)^2}{P_i} \sum_{\nu \geq 1} \frac{1}{2^\nu - 1},$$

$$\leq \log(2) \sum_\alpha P^\alpha \sum_i \frac{(\pi_{\alpha,i} - P_i)^2}{P_i} \left(1 + \sum_{\nu \geq 1} 2^{-\nu}\right),$$

$$= 2 \log(2) \sum_\alpha P^\alpha \sum_i \frac{(\pi_{\alpha,i} - P_i)^2}{P_i}, \tag{10}$$

where the third inequality follows from $\frac{1}{2^\nu - 1} < 2^{-\nu}$ for $\nu \geq 1$.

We will next bound the $\chi^2$ distance $\sum_i \frac{(\pi_{\alpha,i} - P_i)^2}{P_i}$ in terms of the distance between neighboring nodes in the $N_+$ graph. Define the norm $\|x\| = \sqrt{\sum_i x_i^2}$. Let $(\alpha_1, \ldots, \alpha_m)$ denote a path in the graph $N_+$. By triangle inequality it follows that

$$\|\pi_{\alpha_m} - \pi_{\alpha_1}\|^2 \leq \left(\sum_{k=1}^{m-1} \|\pi_{\alpha_k} - \pi_{\alpha_{k+1}}\|\right)^2 \leq (m - 1) \max_{1 \leq k \leq m} \|\pi_{\alpha_k} - \pi_{\alpha_{k+1}}\|^2 < \Delta \sum_{(\alpha,\beta) \in N_+} \|\pi_{\alpha} - \pi_{\beta}\|^2$$

Thus,

$$\sum_\alpha P^\alpha \sum_i \frac{(\pi_{\alpha,i} - P_i)^2}{P_i} = \sum_\alpha P^\alpha \|\pi_{\alpha} - P\|^2$$

$$= \sum_\alpha P^\alpha \|\pi_{\alpha} - \sum_\gamma P^\gamma \pi_{\gamma}\|^2,$$

$$\leq \sum_\alpha \sum_\gamma P^\alpha P^\gamma \|\pi_{\alpha} - \pi_{\gamma}\|^2,$$

$$\leq \Delta \sum_{(\alpha,\beta) \in N_+} \|\pi_{\alpha} - \pi_{\beta}\|^2, \tag{11}$$

where the first inequality follows from the convexity of the $\chi^2$ distance.
Now turning to the sum of relative entropy across arcs in the graph $N_+$,

$$D_{\text{sum}}(\lambda) = \sum_{(\alpha, \beta) \in N_+} D(\pi_{\alpha} \| \pi_{\beta}),$$

$$\geq \frac{1}{2} \sum_{(\alpha, \beta) \in N_+} \sum_{i} \sum_{\nu \geq 1} \frac{(\pi_{\alpha,i} - \pi_{\beta,i})^2}{\pi_{\alpha,i} + (2^{\nu} - 1)\pi_{\beta,i}},$$

$$= \frac{1}{2} \sum_{(\alpha, \beta) \in N_+} \sum_{i} \sum_{\nu \geq 1} 2^{\nu} P_i + \left( (\pi_{\alpha,i} - P_i) + (2^{\nu} - 1)(\pi_{\beta,i} - P_i) \right),$$

$$= \frac{1}{2} \sum_{(\alpha, \beta) \in N_+} \sum_{i} \sum_{\nu \geq 1} 2^{-\nu} (\pi_{\alpha,i} - \pi_{\beta,i})^2 \frac{1}{P_i} \left( 1 + (2^{-\nu} (\pi_{\alpha,i} - P_i) + (1 - 2^{-\nu})(\pi_{\beta,i} - P_i)) \right),$$

$$\geq \frac{1}{2(1 + \gamma_{\text{max}})} \sum_{(\alpha, \beta) \in N_+} \sum_{i} \sum_{\nu \geq 1} 2^{-\nu} (\pi_{\alpha,i} - \pi_{\beta,i})^2 \frac{1}{P_i} \left( 1 + (2^{-\nu} (\pi_{\alpha,i} - P_i) + (1 - 2^{-\nu})(\pi_{\beta,i} - P_i)) \right),$$

$$= \frac{1}{2(1 + \gamma_{\text{max}})} \sum_{(\alpha, \beta) \in N_+} \|\pi_{\alpha} - \pi_{\beta}\|^2,$$

where the second inequality follows from the fact that

$$\frac{(\pi_{\alpha,i} - P_i)}{P_i} \leq \frac{|\pi_{\alpha,i} - P_i|}{P_i} \leq \gamma_{\text{max}}.$$

From [10], [11] and [12],

$$4\Delta(1 + \gamma_{\text{max}}) \log(2) D_{\text{sum}} = 2 \log(2) \Delta \sum_{(\alpha, \beta) \in N_+} \|x_{\alpha} - x_{\beta}\|^2 > I_{ss}.$$

Since $D_{\text{sum}} \leq \frac{\sigma_a}{w_{\text{min}}}$, it follows that

$$I_{ss} \leq \frac{4 \log(2) \Delta \sigma_y}{P_{\text{min}} w}.$$

(13)

Now we bound $1/P_{\text{min}}$ above by parameters of the signal network. Let $a^*$ denote a state such that $P_{a^*} = \max_{\alpha} \{P_{\alpha}\}$. Then $P_{a^*} \geq \frac{1}{N}$, where $N$ denotes the number of signal states; thus, $1/P_{a^*} \leq N$. Fix a state $\beta$. Let $(\alpha_1 = \alpha^*, \alpha_2, \ldots, \alpha_m = \beta)$ denote the shortest path from $\alpha^*$ to $\beta$. Such a path always exists because the diameter $\Delta < \infty$. From the current balance for the state $\alpha_1$, we have

$$\frac{1}{P_{a_1}} = \sum_{y} \sum_{\gamma' \alpha_m} w_{\gamma' \alpha_m} \leq P_{a_{m-1}} \sum_{y} \sum_{\gamma' \alpha_m} \min_{u_{\gamma'} \alpha_m} \frac{1}{P_{a_{m-1}}} \leq \left( \frac{\min_{u_{\gamma'} \alpha_m}}{\min_{u_{\gamma'} \alpha_m}} \right) \frac{\Delta}{P^*} \leq N \left( \frac{\min_{u_{\gamma'} \alpha_m}}{\min_{u_{\gamma'} \alpha_m}} \right) \Delta.$$

(14)

where the first inequality follows from the fact that $\sum_y w_{\gamma' \alpha_m} \leq \min_{u_{\gamma'} \alpha_m}$, and that $\sum_y, P_{\gamma' \alpha_m} \geq P_{a_{m-1}} \sum_{y} \sum_{\gamma' \alpha_m}$, the second inequality follows from the fact that $u_{\gamma'} \alpha_m = \max_{u_{\gamma'} \alpha_{m-1}} \alpha_m$, (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 $\frac{1}{P^*} \leq N$. From [13] and [15], we get the main result of the article.
PROOF THAT \( \{X_{n_k} : k = 1, \ldots, K \geq 0\} \) IS INDEPENDENT OF \( Y_n \)

Let \( T = \{t_k : k = 1, \ldots, K\} \) denote a finite set of time epochs, and \( t \) an arbitrary time epoch. Then \( \dot{\sigma}_y = 0 \) implies that

\[
I(\{X_{t_k} : k = 1, \ldots, K\}; Y_t) = 0. \tag{16}
\]

This result is an extension of the result that \( \dot{\sigma}_y = 0 \) implies that \( I_{ss} = I(X_n; Y_n) = 0. \)

We have established that \( \dot{\sigma}_y = 0 \) implies that \( I_{ss} = 0, \) and consequently, \( X_n \) is independent of \( Y_n, \) or equivalently, \( P_{ij}^\alpha = P^\alpha P_j. \) We now establish that \( \dot{\sigma}_y = 0 \) also implies that the bipartite Markov chain \((X, Y)\) satisfies a certain conditional detail balance condition. When \( \dot{\sigma}_y = I_{ss} = 0, \) the inequality (9a) reduces to an equality. This happens if and only if

\[
\frac{P_{ij}^\alpha}{P_{ji}^\alpha} = \frac{w_{j,i}^\alpha}{w_{i,j}^\alpha}. \tag{17}
\]

We call this the conditional detailed balance condition. We first establish that (16) holds for \( T = \{t - 1\}. \)

\[
\mathbb{P}(X_{t-1} = \alpha, Y_t = i) = \sum_j \mathbb{P}(Y_{t-1} = j, X_{t-1} = \alpha) w_{j,i}^\alpha + \sum_\beta \mathbb{P}(Y_{t-1} = i, X_{t-1} = \beta) w_{i,j}^{\beta,\alpha}
\]

\[
+ \mathbb{P}(Y_{t-1} = i, X_{t-1} = \alpha) \bar{w}_{i}^\alpha
\]

\[
= P^\alpha \left( \sum_j P_j w_{j,i}^\alpha + \sum_\beta P_{ij} w_{i,j}^{\beta,\alpha} + P_i \bar{w}_{i}^\alpha \right) \tag{18a}
\]

\[
= P^\alpha \left( \sum_j P_{ij} w_{i,j}^\alpha + \sum_\beta P_{ji} w_{j,i}^{\beta,\alpha} + P_i \bar{w}_{i}^\alpha \right) \tag{18b}
\]

\[
= P^\alpha P_i \left( \sum_j w_{i,j}^\alpha + \sum_\beta w_{j,i}^{\beta,\alpha} + \bar{w}_{i}^\alpha \right)
\]

\[
= P^\alpha P_i, \tag{18c}
\]

where (18a) follows from the fact that \( P_{ij}^\alpha = P^\alpha P_j, \) (18b) follows from conditional detail balance (17), and the fact that \( I_{ss} = 0 \) implies \( P_{ij}^\alpha = P^\alpha P_i, \) and (18c) follows from the fact \( \sum_{\beta,j} \mathbb{P}(X_{n+1} = \beta, Y_{n+1} = j, X_n = \alpha, Y_n = i) = 1. \)

Define \( t_{\min} = \min \{k : k = 1, \ldots, K\}, \) \( t_{\max} = \max \{k : k = 1, \ldots, K\}. \) Now, let us consider the joint probability distribution of the variables \((X_{t_{\max}}^{\alpha}, X_{t_{\max}-1}^{\alpha}, \ldots, X_{t_{\min}}^{\alpha}, Y_{t}). \) In what follows, we abbreviate the sequence of random variables \((X_{u}, X_{u-1}, \ldots, X_v)\) as \( X_{u}^{v}, \) the sequence of values \((\alpha_{u}, \alpha_{u-1}, \ldots, \alpha_v)\) as \( \alpha_{u}^{v}, \)
and the probability $\mathbb{P}((X_u, X_{u-1}, \ldots, X_v, Y_i) = (\alpha_u, \alpha_{u-1}, \ldots, \alpha_v, i_t)) = \mathbb{P}(\alpha^u, i_t)$. Then

$$
\mathbb{P}(\alpha^t_{\min}, i_t)
= \mathbb{P}(\alpha^t_{\min} \mid \alpha_t) \mathbb{P}(\alpha^t_{\min}, i_t)
= \mathbb{P}(\alpha^t_{\min} \mid \alpha_t) \sum_{\alpha_t} \mathbb{P}(\alpha^t_{\min}, i_t)
= \mathbb{P}(\alpha^t_{\min} \mid \alpha_t) \sum_{\alpha_t} \left( \prod_{\tau=t^\min}^{t-1} \mathbb{P}(\alpha_{\tau+1}, i_{\tau+1} \mid \alpha_{\tau}, i_{\tau}) \right) \mathbb{P}(\alpha^t_{\min}) \mathbb{P}(i_t)
= \mathbb{P}(\alpha^t_{\min} \mid \alpha_t) \cdot \sum_{\alpha_t} \left( \prod_{\tau=t^\min+1}^{t-1} \mathbb{P}(\alpha_{\tau+1}, i_{\tau+1} \mid \alpha_{\tau}, i_{\tau}) \right) \mathbb{P}(\alpha^t_{\min+1} \mid \alpha_t) \sum_{\alpha_t} \mathbb{P}(i_{t^\min+1} \mid \alpha_t, i_t) \mathbb{P}(\alpha^t_{\min}, i_t)
= \mathbb{P}(\alpha^t_{\min} \mid \alpha_t) \cdot \sum_{\alpha_t} \left( \prod_{\tau=t^\min+1}^{t-1} \mathbb{P}(\alpha_{\tau+1}, i_{\tau+1} \mid \alpha_{\tau}, i_{\tau}) \right) \mathbb{P}(\alpha^t_{\min+1} \mid \alpha_t) \mathbb{P}(\alpha^t_{\min}) \mathbb{P}(i_{t^\min+1} \mid \alpha_t) \mathbb{P}(i_t)
= \mathbb{P}(\alpha^t_{\min} \mid \alpha_t) \cdot \sum_{\alpha_t} \left( \prod_{\tau=t^\min+1}^{t-1} \mathbb{P}(\alpha_{\tau+1}, i_{\tau+1} \mid \alpha_{\tau}, i_{\tau}) \right) \mathbb{P}(\alpha^t_{\min+1}) \mathbb{P}(i_{t^\min+1})
$$

where (19a) and (19d) follow from the fact that $X_n$ and $Y_n$ are independent for all $n$, (19b) follows from the fact that $(X_n : n \geq 1)$ is a Markov chain, (19c) follows from the fact $X_t$ and $Y_{t+1}$ are independent (see [18]). Iterating the above construction, all the way through to $i_{t-1}$, we get

$$
\mathbb{P}(\alpha^t_{\min}, i_t) = \mathbb{P}(\alpha^t_{\min} \mid \alpha_t) \prod_{\tau=t^\min}^{t-1} \mathbb{P}(\alpha_{\tau} \mid \alpha_{\tau+1}) \cdot \mathbb{P}(i_{\tau})
$$

Next, we note that for all $t$ and $k$,

$$
\mathbb{P}(\alpha_t \mid \alpha_{t+1}, \ldots, \alpha_{t+k}) = \frac{\mathbb{P}(\alpha_t, \alpha_{t+1}, \ldots, \alpha_{t+k})}{\mathbb{P}(\alpha_{t+1}, \ldots, \alpha_{t+k})}
= \frac{\mathbb{P}(\alpha_t) \mathbb{P}(\alpha_{t+1} \mid \alpha_t) \prod_{\tau=t^\min+1}^{t^\min+k-1} \mathbb{P}(\alpha_{\tau+1} \mid \alpha_{\tau})}{\mathbb{P}(\alpha_{t+1}) \prod_{\tau=t^\min+1}^{t^\min+k-1} \mathbb{P}(\alpha_{\tau+1} \mid \alpha_{\tau})}
= \frac{\mathbb{P}(\alpha_t) \mathbb{P}(\alpha_{t+1} \mid \alpha_t)}{\mathbb{P}(\alpha_{t+1})}
= \mathbb{P}(\alpha_t \mid \alpha_{t+1}).
$$
Thus, it follows that
\[
\mathbb{P}(\alpha_t) \prod_{\tau=t}^{t-1} \mathbb{P}(\alpha_{\tau} | \alpha_{\tau+1}) = \mathbb{P}(\alpha_t) \prod_{\tau=t_1}^{t-1} \mathbb{P}(\alpha_{\tau+1} \ldots \alpha_t) = \mathbb{P}(\alpha_{t_1}, \ldots, \alpha_t)
\]
Combining this result with (20), and using the Markov property for \( \{X_n : n \geq 1\} \) we get
\[
\mathbb{P}(\alpha_{t_{\max}}, i_t) = \mathbb{P}(\alpha_{t_{\max}}) \mathbb{P}(i_t).
\] (21)
Thus, it follows that \( I(X_{t_{\min}}; Y_t) = 0 \). Since \( 0 \leq I(\{X_{t_k} : k = 1, \ldots, K\}; Y_t) \leq I(X_{t_{\max}}; \ldots, X_{t_{\min}}; Y_t) = 0 \), we have that
\[
I(\{X_{t_k} : k = 1, \ldots, K\}; Y_t) = 0.
\]

**PROOF OF THE ADDITIVE BOUND**

Mutual information satisfies the property that \( I_{ss} \leq \sum_{\alpha,i} P_i^\alpha \log \left( \frac{P(i|\alpha)}{Q_i} \right) \) for all distributions \( Q \). Then, considering \( Q = \frac{1}{n_c} \sum_{\beta \in C_{\min}} P(|\beta) \),

\[
I_{ss} \leq \sum_{\alpha,i} P(i|\alpha) \log \frac{P(i|\alpha)}{\sum_{\beta \in C_{\min}} P(i|\beta)} + \log(n_c)
\]
\[
= \sum_{\alpha,i} P(i|\alpha) \log \frac{P(i|\alpha)}{\sum_{\beta \in C_{\min}} P(i|\beta)} + \log(n_c)
\]
\[
\leq \sum_{\alpha} P^\alpha \sum_{i} P(i|\alpha) \log \frac{P(i|\alpha)}{P(i|\beta_{\alpha})} + \log(n_c)
\]
\[
= \sum_{\alpha} P^\alpha D(P(|\alpha||P(|\beta_{\alpha}))) + \log(n_c)
\]
\[
\leq \max_{\alpha,\beta \in \mathcal{N}_+} D(P(|\alpha||P(|\beta))) + \log(n_c)
\]
\[
\leq \sigma w + \log(n_c)
\]

where \( \beta_{\alpha} \in C_{\min} \) is any state such that \( (\alpha, \beta_{\alpha}) \in \mathcal{N}_+ \). The last inequality follows from Eq. (7c) in the main text.

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See Supplemental Material for detailed proof.

The choice of the rate as a metric for measurement would imply that the history of the receptor is accessible. If so, then the dynamics of the memory variables that record $Y$ may be subsumed within the receptor dynamics, and our results continue to hold for the combined memory-receptor process. In specific applications, it should be remembered that the true entropy rate is that of the combined process.

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