Thermodynamics of Statistical Inference by Cells

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The deep connection between thermodynamics, computation, and information is now well established both theoretically and experimentally. Here, we extend these ideas to show that thermodynamics also places fundamental constraints on statistical estimation and learning. To do so, we investigate the constraints placed by (nonequilibrium) thermodynamics on the ability of biochemical signaling networks to estimate the concentration of an external signal. We show that accuracy is limited by energy consumption, suggesting that there are fundamental thermodynamic constraints on statistical inference.

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Cells often perform complex computations in response to external signals. These computations are implemented using elaborate biochemical networks that may operate out of equilibrium and consume energy [1–7]. Given that energetic costs place important constraints on the design of physical computing devices [8] and neural computing architectures [9], one may conjecture that thermodynamic constraints also influence the design of cellular information processing networks. This raises interesting questions about the relationship between the information processing capabilities of biochemical networks and energy consumption [10–14]. Indeed, we will show that thermodynamics places fundamental constraints on the ability of biochemical networks to perform statistical inference. More generally, statistical inference is intimately tied to the manipulation of information and hence offers a rich setting to study the relationship between information and thermodynamics [15–19].

In order for a cell to formulate an appropriate response to an environmental signal, it must first estimate the concentration of an external signaling molecule using membrane bound receptors [1–6,20]. The biophysics and biochemistry of cellular receptors is highly variable. Whereas some simple receptor proteins behave like two-state systems (i.e., unbound and ligand bound) with dynamics obeying detailed balance [21], other receptors, such as G-protein coupled receptors, can actively consume energy as they cycle through multiple states. This naturally raises questions about how energy consumption by cellular receptors affects their ability to perform statistical inference. Here, we address these questions by analyzing the accuracy of statistical inference (i.e., learning) as a function of energy consumption in a simple but biophysically realistic model. We show that learning more accurately always requires expending more energy, suggesting that the accuracy of a statistical estimator is fundamentally constrained by thermodynamics.

Cells estimate the concentration of an external ligand using ligand-specific receptors expressed on the cell surface. A ligand (usually a small molecule), at a concentration c in the environment, binds the receptor at a concentration-dependent rate, k_+c, and unbinds at a concentration-independent rate, k_- [1] [see Fig. 1(a)]. Upon ligand binding, the receptor protein undergoes conformational changes or chemical modifications that alter its activity, sending a signal that the ligand is bound to downstream portions of the biochemical network. During a time interval T, the receptor can undergo multiple stochastic transitions between the unbound nonsignaling state and the bound signaling states. This information is contained in the time series of signaling and nonsignaling intervals [see Fig. 1(b)].

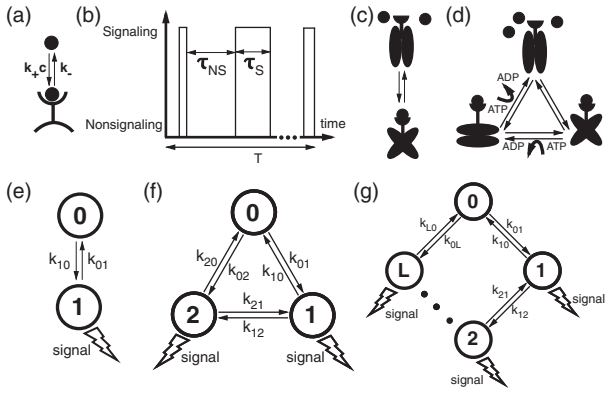

FIG. 1. Schematic of a cell receptor and our model of a receptor. (a) A chemical ligand at concentration c binds to the receptor at rate k_+c and unbinds at rate k_-. (b) Example time series of a receptor binding. While unbound, the receptor is in a nonsignaling state, but upon ligand binding it transitions to a signaling state. After a long time T, the receptor has a series of nonsignaling times τ_{NS} and signaling times τ_S from which to estimate the concentration. (c) Two-state and (d) three-state biochemical models of a receptor. Upon ligand binding the receptor undergoes a physical change (represented as a conformational change) that transmits signals to the downstream biochemical network. (e) Two-state, (f) three-state, and (g) L-state Markov models of a receptor, where the chain of states $3, 4, \ldots, L-1$ has been suppressed.

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After a time T, the cell converts this time series into an estimate for the external concentration. A longer time series T always gives a better estimate for the concentration; however, the cell needs to make a decision in a finite time, so we consider T to be fixed to a large but finite value. In principle, the estimate for the concentration could be computed using one of many different statistics that can be obtained from this time series (e.g., average bound time, average unbound time, etc.). Each of the resulting estimators for the external ligand concentration has a different accuracy. Following Berg and Purcell (BP) [1], we measure the accuracy of an estimator for the concentration using its "uncertainty," defined as

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

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

Several methods have been proposed for how a cell may estimate the concentration of the external signaling molecule. In their pioneering paper, Berg and Purcell suggested estimating the concentration using the average time the receptor was bound during the time T [1]. They showed that the minimal uncertainty a receptor could achieve with this estimator was

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

where $\bar{N}$ is the expected number of binding events during the time interval T. For 30 years, many thought that the BP estimator placed a fundamental limit on the accuracy of a cellular receptor. However, in 2009, Endres and Wingreen [3] showed that a cell using maximum likelihood estimation (MLE) based on the average nonsignaling time could reduce its uncertainty by half to

$$\frac{\langle (\delta c)^2 \rangle}{\bar{c}^2} = \frac{1}{\bar{N}}. \tag{3}$$

However, the increased accuracy of MLE comes at an energetic cost. Previous work [5] established that BP sets a limit for the best possible estimator in equilibrium, implying that any receptor that performs MLE must operate out of equilibrium and consume energy.

In order to study the relationship between thermodynamics and the accuracy of statistical estimators, we introduce a new family of biophysically inspired cellular receptors that interpolate between BP and MLE. In our model, receptors can actively consume energy by operating out of equilibrium [for example, by hydrolyzing adenosine triphosphate (ATP)]. Using this family of models, we show that there is a direct connection between the energy consumed by a receptor and the uncertainty of the resulting estimator. We find that in order to learn more information (decrease its uncertainty), the receptor must always expend more energy (increase entropy production). Note that, in this Letter, we restrict ourselves to modeling the receptor and ignore the downstream signaling network that converts the signal from the receptor into a cellular response [10,13]. Thus, the energies computed here represent lower bounds on the total energy consumed by the statistical estimation network.

Figure 1(c) shows the simple two-state receptor considered by BP. The binding of an external ligand to the receptor induces a change in the receptor from a nonsignaling state to a signaling state [see Fig. 1(b)]. The dynamics of this simple two-state receptor always obey detailed balance. Thus, in order to model nonequilibrium receptors, we must consider receptors with more than two states. Figure 1(d) shows a receptor with three states: one nonsignaling state to which ligands can bind and two signaling states to which ligands cannot bind. With this extra state, the dynamics of the receptor can break detailed balance by coupling the conformational change in the receptor to another reaction such as the hydrolosis of ATP. In particular, by consuming energy it is possible to drive the system preferentially through a series of state changes [22] [for example, clockwise in Figs. 1(f) and 1(g)]. This results in a nonzero probability flux through the state space and positive entropy production.

In order to relate the thermodynamic properties of these receptors to their ability to perform statistical inferences, it is useful to represent receptors as Markov chains. For example, the two-state receptor shown in Fig. 1(c) can be represented as a two-state Markov chain with a state 0 corresponding to the unbound nonsignaling state and state 1 corresponding to the signaling state [see Fig. 1(e)]. We choose the transition rates between states in the Markov chain to be identical to the transition rates between conformations of the receptor. The three-state receptor can also be modeled as a three-state Markov chain with a ring structure, with state 0 once again corresponding to the unbound, nonsignaling state [Fig. 1(f)]. In this more abstract notation, it is easy to generalize the three-state receptor considered above to a receptor with $L+1$ states [see Fig. 1(g)]: L of these states are signaling states that cannot bind the ligand, while the remaining state, 0, corresponds to the nonsignaling state that can bind ligands. For ease of analysis, in this Letter, we consider receptors arranged in a ring only. However, our model is a good approximation for more complicated receptors with multiple pathways, so long as the receptor has a single path (for example, of length L^*) that dominates the probability flux; see [23] for details. In that case, the complicated receptor reduces to a single ring of length L^*.

A straightforward calculation shows that for the architectures in Fig. 1 [24], the uncertainty of an estimate for the concentration is given by [3]

$$\frac{\langle (\delta c)^2 \rangle}{\bar{c}^2} = \frac{1}{\bar{N}} \left[1 + \frac{\langle (\delta \tau_S)^2 \rangle}{\bar{\tau}_S^2} \right] \equiv \frac{\mathcal{E}}{\bar{N}}, \tag{4}$$

where N is the number of binding events, $\bar{\tau}_S$ is the mean time spent in the signaling state after binding a ligand, and $\langle(\delta\tau_S)^2\rangle$ is the variance of the time spent in the signaling states. In the second equality, we have defined the coefficient $\mathcal{E}$ which measures the accuracy of an estimator, e.g., $\mathcal{E}=2$ for the Berg-Purcell limit and $\mathcal{E}=1$ for MLE. For a given estimator (i.e., a specific architecture and a set of rates $\vec{k}$), we can calculate the mean and the variance of the signaling time by a first passage calculation similar to that in [24,25].

Here we provide some intuition for Eq. (4). Notice that all the information about the ligand concentration is contained in the event of a ligand binding to the receptor, and the unbinding of the ligand, or the exiting of the signaling state, is independent of concentration. Thus, any variation in the duration of the signaling state adds additional noise to the estimate but does not contain any more information about the concentration. Therefore, the optimal estimator is one where the signaling intervals are completely deterministic and $\langle(\delta\tau_S)^2\rangle=0$. Comparing Eqs. (4) and (3), we see that this corresponds to MLE. This is consistent with the well-known fact that MLE is the optimal unbiased estimator for large sample sizes. When the durations of the signaling times are exponentially distributed, like for a two-state receptor $\langle(\delta\tau_S)^2\rangle=\bar{\tau}_S^2$, then Eq. (4) reduces to the BP result given in Eq. (2). Finally, in all cases, the uncertainty scales inversely with the average number of binding events $\bar{N}$ during the time interval T. This scaling law follows from the central limit theorem by treating each binding event as an independent sample of the concentration.

The Markov representation allows us to calculate the energy consumption using ideas from nonequilibrium statistical physics. We focus on long time intervals, $T\gg 1$, with many binding events, where the receptor dynamics can be modeled by nonequilibrium steady states (NESS). The entropy production of the Markov process is the energy per unit time (power) required to maintain this NESS, and, therefore, calculating the entropy production is equivalent to calculating the energy consumed by the biochemical network [10,22]. The entropy production is given by [26]

$$e_p=\sum_{i=0}^{L}\sum_{j\neq i}^{L}p_i^{ss}k_{ij}\ln\frac{k_{ij}}{k_{ji}}, \tag{5}$$

with p_i^{ss} is the steady state probability of state i, k_{ij} is the transition rate from state i to state j, and we have set $k_BT=1$ [24]. For the architectures where the Markov process forms a ring, the entropy production simplifies to

$$e_p=(p_0^{ss}k_{01}-p_1^{ss}k_{10})\ln\frac{k_{01}k_{12}\ldots k_{L0}}{k_{0L}k_{10}\ldots k_{L,L-1}}=J\ln\gamma, \tag{6}$$

where J is the net flux around the ring and $\ln\gamma$ is the free energy per cycle [22,24]. For later reference, the total energy released in ATP hydrolysis is approximately $20\,k_BT$ at room temperature [27]. We note that previous work investigating tradeoffs between accuracy and energy in Markov chains used a nonthermodynamically feasible energy [28].

Our goal is to find the best performing estimator for a given receptor architecture and entropy production (energy consumption) rate. However, there are several biological constraints that need to be considered when optimizing over choices of kinetic parameters. First, the rate at which a chemical ligand binds to a receptor is set by diffusion limited binding [1] and hence k_{01} is not controlled by the cell. Therefore, we set $k_{01}=1$ and do not optimize over this rate. Second, a receptor needs to be specific. In principle, both "correct" ligands (i.e., the ligands the receptor has evolved to detect) and "wrong" ligands (any other chemical) can bind the receptor. However, nonspecific ligands quickly unbind and cause the receptor to switch back to the nonsignaling state. Thus, the specificity of a receptor is set by the mean duration of the signaling state in the presence of the correct ligand, $\bar{\tau}_S$. This is incorporated by requiring a small nonspecific binding rate ($k_{0L}=\epsilon\ll 1=k_{01}$) and we do not optimize over k_{0L}. Lastly, since any statistical estimator is always improved with more samples, to fairly compare different families of estimates, we will fix the sampling rate, $\bar{n}=\bar{N}/T$, where $\bar{N}$ is the expected number of samples and T is the signal integration time. By fixing the nonspecific binding rate (k_{0L}) to be small [24], this implies $\bar{\tau}_S\approx\bar{n}^{-1}-1$. But since we are also fixing the sampling rate, $\bar{n}$, this fixes $\bar{\tau}_S$. In summary, our goal is to find the global minima for uncertainty, given the above constraints.

We begin by analyzing the three-state receptor [Fig. 1(f)]. Figure 2 shows the uncertainty as a function of entropy production for the optimal three-state receptor for four different choices of the ligand binding rate, $\bar{n}=\bar{N}/T$. To generate these plots, we have used an analytic ansatz [24] for the optimal parameters which we have checked using simulated annealing (with agreement within 1.25%). Notice that learning more accurately (reducing uncertainty) always increased energy consumption (entropy production). At low energy consumption, the receptor approaches the equilibrium BP limit ($\mathcal{E}=2$), while at high energy consumption (corresponding approximately to the energy of ATP hydrolysis) the optimal performance asymptotically approaches the infinite entropy production analytic limit of

$$\frac{\langle(\delta c)^2\rangle}{\bar{c}^2}\sim\frac{3}{2\bar{N}}. \tag{7}$$

One striking observation is that these curves exhibit a data collapse when plotted as a function of the energy consumption per ligand binding rate, $e_p/\bar{n}$. The inset of Fig. 2 shows the same curves as the main graph as a function of $e_p/\bar{n}$. Since each ligand binding event can be viewed as an independent sample of the external

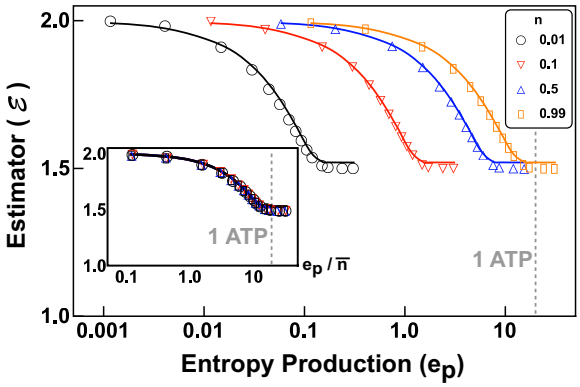

FIG. 2 (color online). Two signaling state estimator performance. For varying sampling rate $\bar{n} = \bar{N}/T$, the plot shows estimator performance ($\mathcal{E}$) versus entropy production (e_p, with units of $k_B T = 1$). The symbols represent results from simulated annealing, where $k_{01} = 1$ and $k_{02} = \epsilon = 10^{-3}$, while the other four rates are optimized. The continuous lines represent our *ansatz* [24] for the global minima. At high entropy production, the estimators asymptotically approach 1.5. The inset shows the data collapse when the estimator performance ($\mathcal{E}$) is plotted versus entropy production per sampling rate ($e_p/\bar{n}$). The vertical dashed line corresponds to the approximate energy released by hydrolysis of a single ATP.

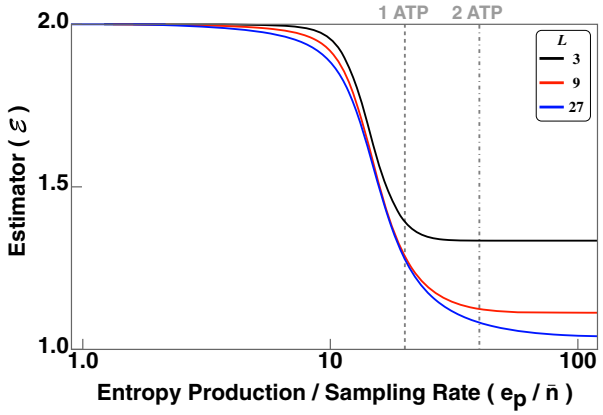

FIG. 3 (color online). Illustrative example of L signaling state estimator performance. For a varying number of signaling states L, the plot shows estimator performance ($\mathcal{E}$) versus energy consumption ($e_p/\bar{n}$). For an increasing L, at high energy consumption the estimator approaches the maximum likelihood limit of 1. The following parameters are fixed at $\bar{n} = 0.99$, $k_{01} = 1$, $k_{0L} = 10^{-3}$, $\alpha = k_{10}/b = 10^{-3}$, and $\omega = k_{L0}/f = 1$, while b was varied to keep $\bar{n}$ fixed and $\theta = f/b$ was varied to change the estimator and the energy consumption. These parameters were chosen for convenience and are not global optima. The vertical lines correspond to the approximate energy released by hydrolysis of a single ATP (dashes) or two ATPs (dot dashes).

concentration, this data collapse suggests that the natural variable linking thermodynamics and inference is the energy per independent sample consumed in constructing an estimator.

The three-state receptor is not able to reach the MLE limit of $\mathcal{E} = 1$ for any level of entropy production. To reach the MLE limit, we consider a receptor with $L + 1$ states, L of which are signaling states [see Fig. 1(g)]. This Markov chain has $2L$ independent parameters, which makes it hard to find the global optimum. For this reason, we analyzed a simplified, but still biophysically realistic, rate structure (without performing any optimization over parameters) where k_{01}, k_{0L}, k_{10}, k_{L0} can independently vary but all other forward rates are fixed to be identical, $k_{i,i+1} = f$ and all other backward rates chosen so that $k_{i+1,i} = b$, where $i = 1 \ldots L - 1$ [24]. Once again, for all choices of L, the optimal uncertainty exhibits a data collapse as a function of the energy consumption per ligand binding rate, $e_p/\bar{n}$ (see Fig. 3). At low energy consumption, the uncertainty approaches the BP limit ($\mathcal{E} = 2$), while at high energy consumption (corresponding approximately to the energy of ATP hydrolysis) asymptotically approaches the infinite entropy production analytic limit of

$$\frac{\langle (\delta c)^2 \rangle}{\bar{c}^2} \sim \left(1 + \frac{1}{L}\right) \frac{1}{\bar{N}}. \tag{8}$$

Thus, receptors with large energy consumption and many signaling states ($L \gg 1$) approach the MLE limit. In order to perfectly achieve the MLE limit, all backward rates b would need to be 0, leading to infinite entropy production. An interesting feature of these curves is that beyond some scale (which can be achieved by hydrolysis of only a few ATP), the marginal gain in improvement that results from consuming more energy becomes negligible. This is reminiscent of the recently found transition in kinetic proofreading where adding additional energy only marginally improves the error threshold [23,29]. It will be interesting to see if this is a generic feature of many biochemical information processing circuits.

In conclusion, by analyzing the ability of cells to estimate the concentration of an external chemical signal using nonequilibrium receptors, we have established an unexpected link between statistical inference and thermodynamics. Specifically, we found that the efficacy of an estimator for the concentration of a ligand depends on the energy consumed per independent sample by the receptor. Extrapolating this result suggests that there may be fundamental thermodynamic bounds on statistical inference. The trade-off between accuracy and energy is general and may be relevant for other signal transduction systems, such as gene regulation [30], light-activated proteins [31], or ligand-gated ion channels [32]. We note that following the tradition of Berg and Purcell, in this Letter we considered estimating a concentration only after a long time T. However, in many related cases, such as transcription [33], the speed is an important trade-off in addition to accuracy and energy consumption. In the context of phosphorelays, it is likely that the circuits can

respond quickly even for multistep cascades. For example, the four-stage phosphorelay utilized for phototransduction in the retina can still respond to stimuli in about half a second [34]. Nonetheless, understanding these trade-offs represents an important future research direction.

We conjecture that our observed scaling, $(e_p/\bar{n})$, reflects a general principle: the efficiency of a statistical estimator is limited by the energy consumed per sample during its construction. Of course, much more investigation is needed to see if this conjecture holds in general. In particular, it will be interesting to see if these results change for receptors modeled by heterogeneous Markov networks that are not strictly ringlike in nature. Recent work indicates that at large entropy production, the dynamics of such networks may be independent of details of the underlying topology, suggesting that our basic picture should hold even for more complicated nonequilibrium receptors [35]. An additional extension to our model would be to consider externally varying concentrations by implementing a sensory adaptive system as was done in recent papers [36,37]. These papers found that the accuracy and energy consumption of the sensory adaptive system depends on the time scale of external concentration fluctuations. Finally, it is well known that many receptors, such as G-protein coupled receptors, actively consume energy in order to operate. Our model presents one possible explanation for this observation. The energy consumption may help reduce noise in the downstream signal, allowing cells to more accurately determine external concentrations. Our model also shows that hydrolysis of only one or two ATP nearly achieves the theoretical minima of uncertainty. This may explain why cell sensors often require only a few phosphorylation sites.

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