An energy-accuracy tradeoff in subneuronal molecular sensing

Sarah Harvey, Subhaneil Lahiri, and Surya Ganguli

Remarkably, the human brain computes using only 20 watts of power, whereas modern supercomputers consume megawatts. To understand the unrivaled energy efficiency of neural computation, we need better theories governing energy-accuracy tradeoffs in subneuronal molecular dynamics and information processing, as dominant sources of neural energy dissipation originate in biomolecular processes.

Here, we focus on energy-accuracy tradeoffs in nonequilibrium molecular processes underlying neuronal signaling. We model a subneuronal signaling cascade as an arbitrary, physically realizable, continuous time Markov chain which can sense an external signal that modulates its transition rates. This framework is widely applicable to many scenarios in neuroscience, including the sensing of external neurotransmitters by synaptic spines, light by retinal opsins, or sound by cochlear hair cells.

We first derive fundamental limits on sensing accuracy by an ideal observer of the entire temporal trajectory of signaling states, by computing the Fisher information this trajectory has about the external signal. We find a simple formula for this information in terms of molecular fluxes. However, biologically plausible molecular observers cannot observe this trajectory and instead observe the time a signaling system spends in an active state. We next compute a lower bound on the accuracy of such plausible molecular observers in terms of the power consumed by the signaling system and the observation time. Our lower bounds, confirmed by numerical simulations, reveal that as power consumption becomes larger, even by a modest amount, a biologically plausible molecular observer can achieve accuracy comparable to that of the ideal observer. Moreover, as the power consumption is reduced, our bound indicates sensing accuracy will necessarily be lower. At zero power consumption, our bound matches the classical results of Berg and Purcell.

Overall, our work reveals fundamental limits on sensing accuracy given power consumption and observation time for any biophysical molecular signaling system.

Additional Detail

Significance: We are very excited about this work, as we have achieved a fundamental breakthrough in theoretically relating power dissipation to statistical inference for biochemical signaling networks. This relationship is intuitive and has been observed numerically [1], but here we are able to theoretically show that thermodynamics fundamentally limits statistical inference and learning. In doing so, we have brought together the diverse concepts of energy, sampling time and statistical estimation in a single theorem that applies to all physical sensing systems that can be modeled using Markovian dynamics. We believe this work will help elucidate the connections between computation, thermodynamics, and information for biological systems. We feel that these results could have a substantial impact on the thinking of theorists, as well as the design of future experiments in neuroscience and biophysics. Therefore, we have requested a talk as this work would be of interest to the Cosyne community.

Methods: We model the sensing system as an arbitrary finite continuous time Markov chain, as shown in fig. 1(a). The system is then separable into two sets of states, the states which trigger a downstream effect used to estimate the signal (signaling states) and those which have no effect (non-signaling states). We further assume that the parameter we desire to estimate, c, which could represent the external concentration of some ligand in an extracellular medium, modulates the transition rates between states in the arbitrary Markov chain. We first analyze the performance of an ideal observer that can see every transition and transition time (trajectory) of the chain during some interval Δt, and can use this information to make an estimate of c. We find a novel expression for the Fisher information

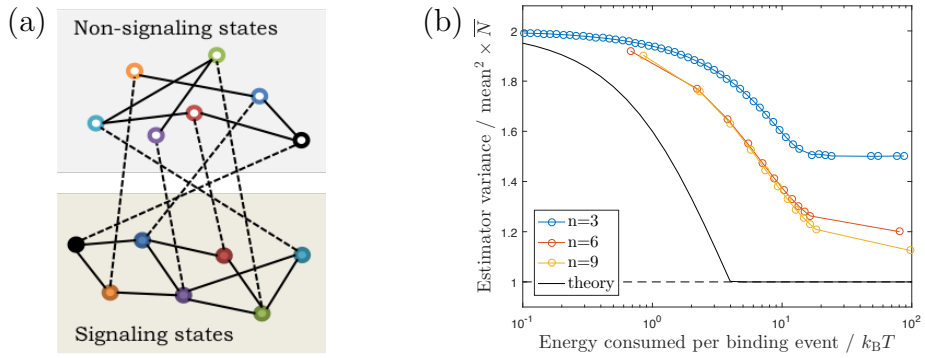

Figure 1: The tradeoff between energy dissipation and precision of concentration estimation. (a) The class of models for an arbitrary receptor. These include the set of arbitrary continuous time Markov processes which can be separated into states which, when occupied, transmit a signal to a downstream biochemical network, and non signaling states. In the ligand-receptor system, signaling states represent states in which the ligand has bound to the receptor, and the non signaling states represent unbound states. (b) Comparison between our theoretical bound and constrained numerical minimization of signal estimation error at fixed power consumption over molecular networks with n states.

that the distribution over trajectories has about the parameter of interest c to be simply:

$$J_c^{\text{traj}} = \frac{\Delta t\, \Phi_{NS\to S}}{c^2}. \tag{1}$$

where $\Phi_{NS\to S}$ is the flux from the non-signaling states to the signaling states, Δt is the total measurement time, and c is the estimation parameter. Applying the Cramér-Rao bound using (1), we find an expression for the estimation uncertainty, defined as the variance over the mean squared $\epsilon_c^2 \equiv \frac{\langle(\delta c)^2\rangle}{c^2}$:

$$\epsilon_c^2 \geq \frac{1}{\Delta t\, \Phi_{NS\to S}} = \frac{1}{\overline{N}}. \tag{2}$$

where $\overline{N}$ is the expected number of binding events in time Δt. This result agrees with the maximum likelihood result for a two state system found in [2], but applies more generally to *all* chains. This scenario, however, relies on an ideal readout that acts as an omniscient observer of the entire signaling trajectory, and it is unlikely that real biological read-out networks could accomplish this feat. Equation (2) also notably makes no mention of how power consumption might limit estimation accuracy.

We next consider the more biologically plausible scenario in which the signal estimation is based on the occupation time in the signaling states, not the entire Markovian trajectory. Using the formalism of large deviation theory similar to that of [3] (applied to empirical densities, rather than empirical currents), we find a tradeoff between the energy dissipation rate, or power consumption P, in the signaling network (defined as in [1]), the measurement time Δt and the estimation uncertainty ϵ_c^2 in terms of the trajectory Fisher information,

$$\epsilon_c^2 \geq \frac{8}{P\,\Delta t + 4 J_c^{\text{traj}}\, c^2}. \tag{3}$$

Here P is measured in units of k_BT, the energy scale of thermal fluctuations, making $P\Delta t$ dimensionless. Together, (2) and (3) yield a bound which reproduces the classic Berg-Purcell result of $\epsilon_c^2 \geq \frac{2}{\overline{N}}$ [4] as $P \to 0$ (thermodynamic equilibrium) and the Cramer-Rao bound for an ideal observer as P becomes large. This theoretical bound is supported by numerical calculations of the estimation uncertainty, as shown in fig. 1(b). In principle, all physical sensing systems that can be modeled as a continuous time Markov process are subject to our universal bound. Further exploration of our newly derived energy–accuracy tradeoff could yield insights into the mechanisms by which the brain and other biological sensing networks achieve such precise yet energy efficient computations.

[1] A. H. Lang et al. *Phys. Rev. Lett.* 113.14 (2014), p. 148103. **[2]** R. G. Endres and N. S. Wingreen. *Phys. Rev. Lett.* 103.15 (2009), p. 158101. **[3]** T. R. Gingrich et al. *Phys. Rev. Lett.* 116.12 (2016), p. 120601. **[4]** H. C. Berg and E. M. Purcell. English. *Biophys. J.* 20.2 (1977), pp. 193–219.