An Energy-Accuracy Tradeoff for Nonequilibrium Receptors

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Summary

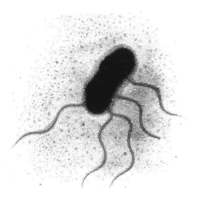
We explore the application of large deviation theory and stochastic thermodynamics to biophysical sensors

- We derive two theoretical bounds on the uncertainty of a sensor modeled as a continuous-time Markov process, in different limits of what is observable about the process
  - First inequality: detailed observations of the process $\Longrightarrow$ no advantage to adding more states/nonequilibrium.
  - Second inequality: estimation based on coarse-grained observable related to occupancy time in a set of states $\Longrightarrow$ estimation accuracy can be improved by driving the network out of equilibrium and adding more states.
- We verified our bounds using numerical simulations and optimization, and observe that nonuniform ring networks saturate the numerically optimal uncertainty curves as a function of energy consumption.

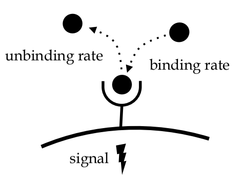
Background

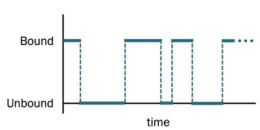
How do cells measure external concentrations and infer information about their environment?

- Surface receptors: ligand binds to receptor → intracellular response → behavioral response
- Receptor system has a history of study by physicists interested in the fundamental limits on sensing ability
- Often modeled with continuous-time Markov chains



Adler, Julius. Chemotaxis in *Escherichia coli*. In *Sensory Receptors*, Cold Spring Harbor Symp. Quant. Biol. *30*, (1965).





Berg-Purcell limit (1977)

- 2-state single receptor model, estimation based on fraction of time bound

$$uncertainty: \frac{\langle(\delta c)^2\rangle}{c^2} = \frac{2}{\underbrace{4Dsc}_{\text{rate of particle capture}}\underbrace{(1-\overline{p})}_{\text{probability receptor unoccupied}}T} = \frac{2}{\overline{N}}$$

$\overline{N}$: *Expected number of binding events in time* T

We are interested in:

How the *observability* and *network size* affects the estimation uncertainty

Tradeoffs between **energy**, **estimation accuracy**, and **speed**.

We derive two bounds on the uncertainty by violating the Berg-Purcell assumptions in more general cases

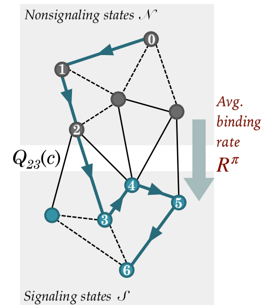
Ideal Observer: Observation of a Markov Trajectory

- Calculate the **Fisher Information** for the observed Markov chain trajectory with respect to the signal c

Q_{ij} : *transition rates*
π_i : *steady state density*

$$J_c = J_c^0 + T\sum_{\substack{i,j\\ i\neq j}} \pi_i Q_{ij}\left[\partial_c \log Q_{ij}\right]^2 \quad \textit{i,j index all states}$$

$$J_c^0 = \sum_{x_0} \pi_{x_0}\left[\partial_c \log \pi_{x_0}\right]^2 \quad \textit{"single shot" Fisher information}$$



solid edges $\Longrightarrow$ *transition rates* $\sim c$

- **Cramér-Rao bound** gives fundamental limit on the precision with which the signal can be estimated based on the observations

Assume:

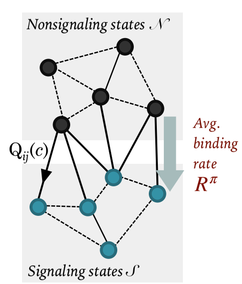
States are divided into two groups, signaling ($\mathcal{S}$) and non-signaling ($\mathcal{N}$)
"Binding transitions" ($\mathcal{N}\to\mathcal{S}$) are linearly related to signal c

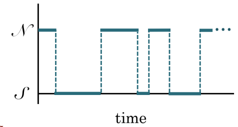
$$\frac{\langle(\delta\hat{c})^2\rangle}{c^2} \geq \frac{1}{J_c c^2} = \frac{1}{TR^\pi} = \frac{1}{\overline{N}}.$$

$\overline{N}$: *expected number of binding events*

no advantage to > 2 states

Simple Observer: Coarse-Grained Observation





$$q = \frac{1}{T}\sum_{i=1}^{N}\tau_{\mathcal{S}}^i \rightarrow \hat{c}$$

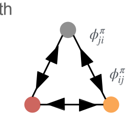
empirical density in signaling states

- **Is there an advantage to driving this sensor out of equilibrium?**

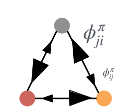
An ergodic Markov chain will relax to steady state distribution with

$$\frac{d\pi_j}{dt} = \sum_i \left[\pi_i(t)Q_{ij} - \pi_j(t)Q_{ji}\right] = 0$$

Detailed balance: $j_{ij}^\pi = \underbrace{\pi_i(t)Q_{ij}}_{\phi_{ij}^\pi} - \underbrace{\pi_j(t)Q_{ji}}_{\phi_{ji}^\pi} = 0$ everywhere



'Nonequilibrium steady state': Non-zero current loops



- Stochastic thermodynamics:

Mean entropy production rate of the system and its environment

$$\Sigma^\pi = \sum_{i<j} \overbrace{\left[\pi_i Q_{ij} - \pi_j Q_{ji}\right]}^{j_{ij}^\pi} \log\frac{\pi_i Q_{ij}}{\pi_j Q_{ji}}$$

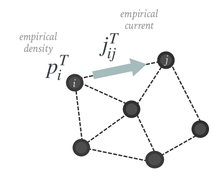
Measure of the time-reversal asymmetry of the process

Note: $\Sigma^\pi \geq 0$

- **Large deviation theory:** can study fluctuations in q using Level 2.5 LDT

Large, finite T: $P(p^T = p, j^T = j) \sim e^{-TI(p,j)}$

$I(p,j)$ **is a large deviation rate function with minimum at** $p=\pi$ **and** $j=j^\pi$



We want to study $I(q) = \inf_{p,j} I(p,j)$

and $\mathrm{var}(q) = \dfrac{1}{TI''(q^\pi)}$

Can bound as: $I(q) \leq I(p^*, j^*)$, as well as $I''(q)$ with intelligent guesses for p^* and j^* (see paper S.I.)

We find: $$\mathrm{var}(q) \geq \frac{8\left[q^\pi(1-q^\pi)\right]^2}{T\left[\Sigma^\pi + 4R^\pi\right]}.$$

Next: apply this relation to our cell sensing problem by relating q to c

Given some empirical density q, what signal c would make this typical?

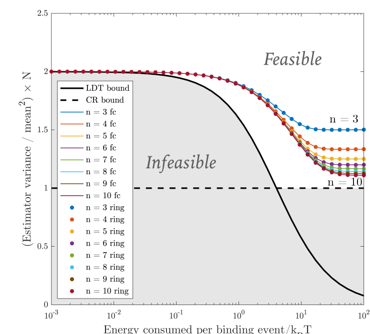
($q^\pi(c) = q$, solution is estimate $\hat{c}$)

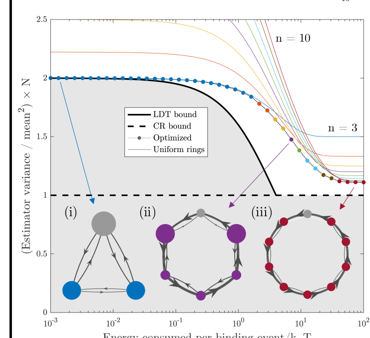
For networks with only one non-signaling state: $c\dfrac{dq^\pi}{dc} = q^\pi(1-q^\pi)$

$$\frac{\mathrm{var}(\hat{c})}{c^2} \geq \frac{8}{T\Sigma^\pi + 4\overline{N}}$$

- Numerical optimization of fully connected and ring-topology networks agree

Constrained to a particular energy consumption, we optimize an exact expression for $T \times \mathrm{var}(\hat{c})/c^2$ obtained by exactly contracting $I(p,j)$ to $I(q)$ to leading order





- Reducing uncertainty requires energy consumption and addition of states

Colored circles indicate the smallest number of states (using colormap from above) at a particular energy consumption level for which adding states (up to 10) would improve the uncertainty by less than 1%.

Colored lines show the performance of ring networks with uniform transition rates in each direction, which saturate the numerically optimal curve in the limit of large energy consumption.

[1] Berg, H. C., & Purcell, E. M. (1977). Physics of chemoreception. *Biophysical journal*, *20*(2), 193–219.
[2] Todd R. Gingrich, et. al. (2016). Dissipation bounds all steady state current fluctuations. Phys. Rev. Lett. 116, 120601.
[3] Seifert, U. (2019). From Stochastic Thermodynamics to Thermodynamic Inference. Annual Review of Condensed Matter Physics, 10(1), 171–192.
[4] Harvey, S., Lahiri, S., Ganguli, S. (2020). Universal energy accuracy tradeoffs in nonequilibrium cellular sensing. https://arxiv.org/abs/2002.10567

Acknowledgements
Stanford Graduate Fellowship | National Defense Science and Engineering Graduate Fellowship