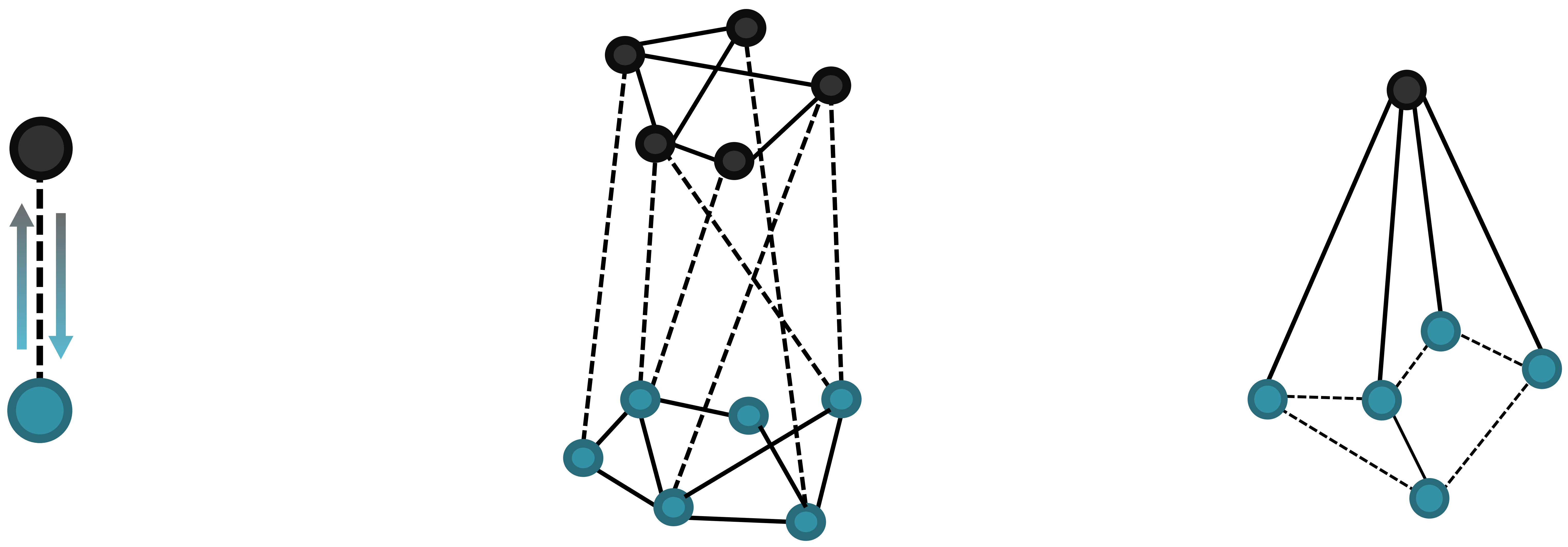


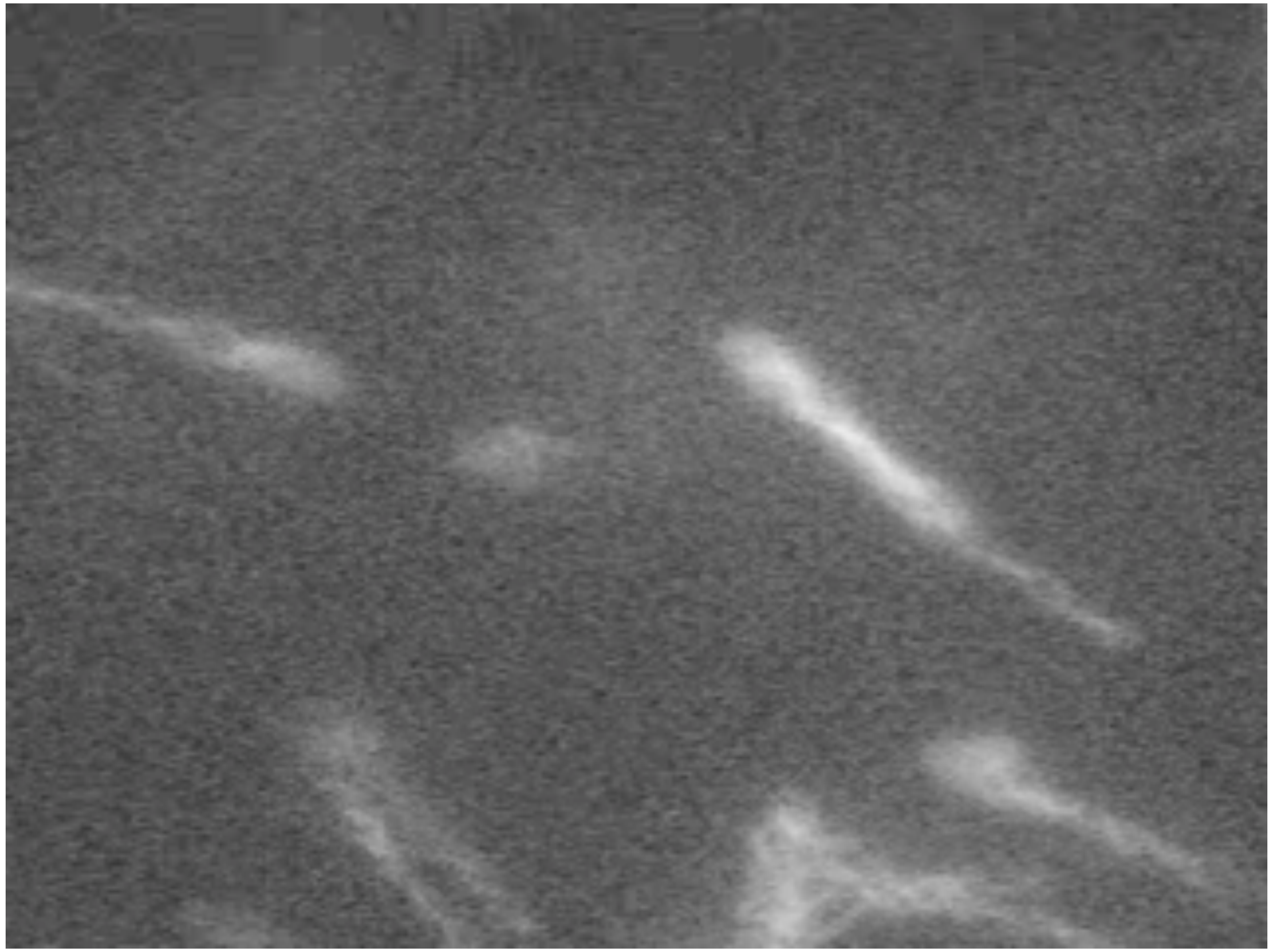
An Energy–Accuracy Tradeoff for Nonequilibrium Receptors

Sarah Harvey, Subhaneil Lahiri, Surya Ganguli

Department of Applied Physics, Stanford University

BIRS workshop 20w5074: Mathematical Models in Biology: from Information Theory to Thermodynamics

Cells Perform Interesting Sensing Tasks



Fluorescently-labeled swimming Escherichia coli cells showing their flagellar bundles (video from Howard C. Berg Lab)

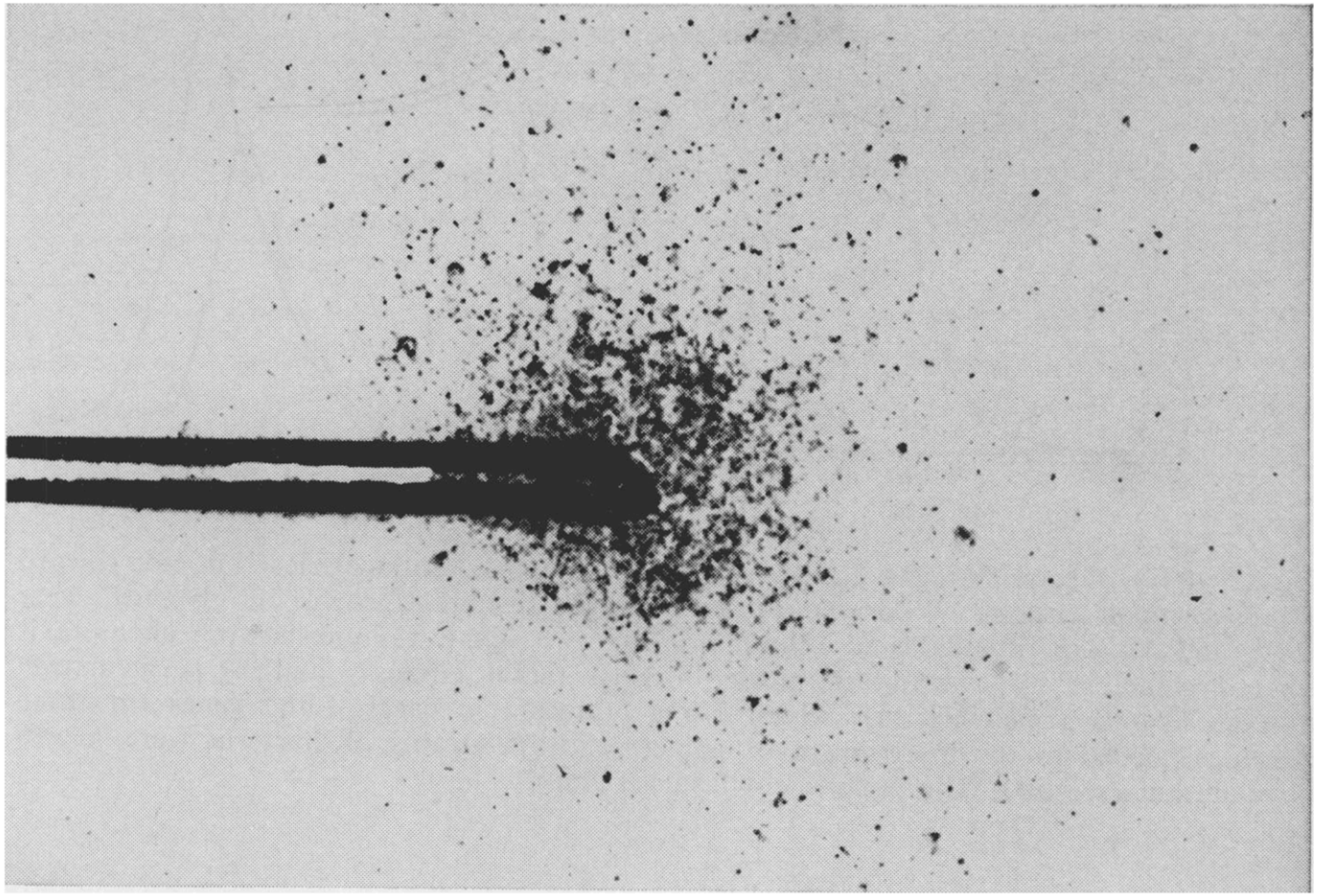


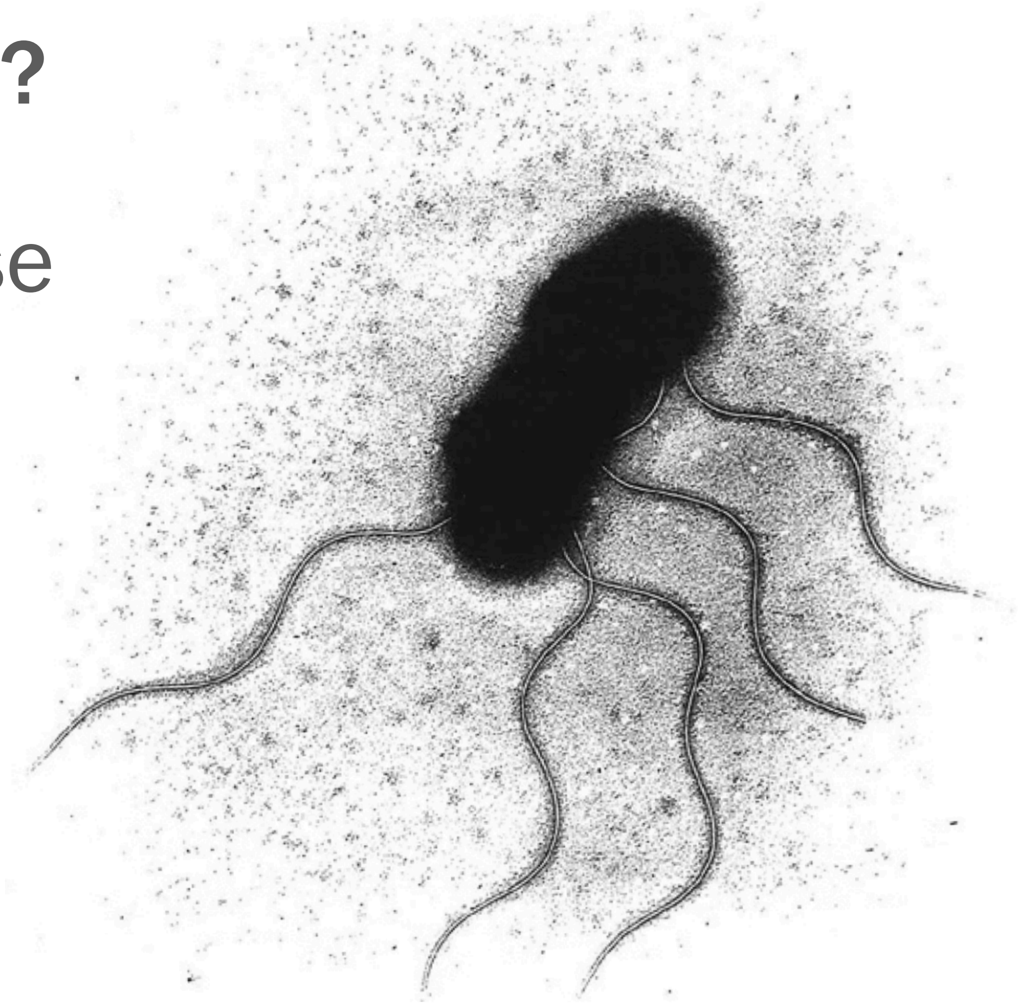
Fig. 1. Photomicrograph showing attraction of *Escherichia coli* bacteria to aspartate. The capillary tube (diameter, ~ 25 microns) contained aspartate at a concentration of $2 \times 10^{-3} M$. [Photomicrograph by Scott W. Ramsey; dark-field photography]

http://www.rowland.harvard.edu/labs/bacteria/movies/ecoli.php

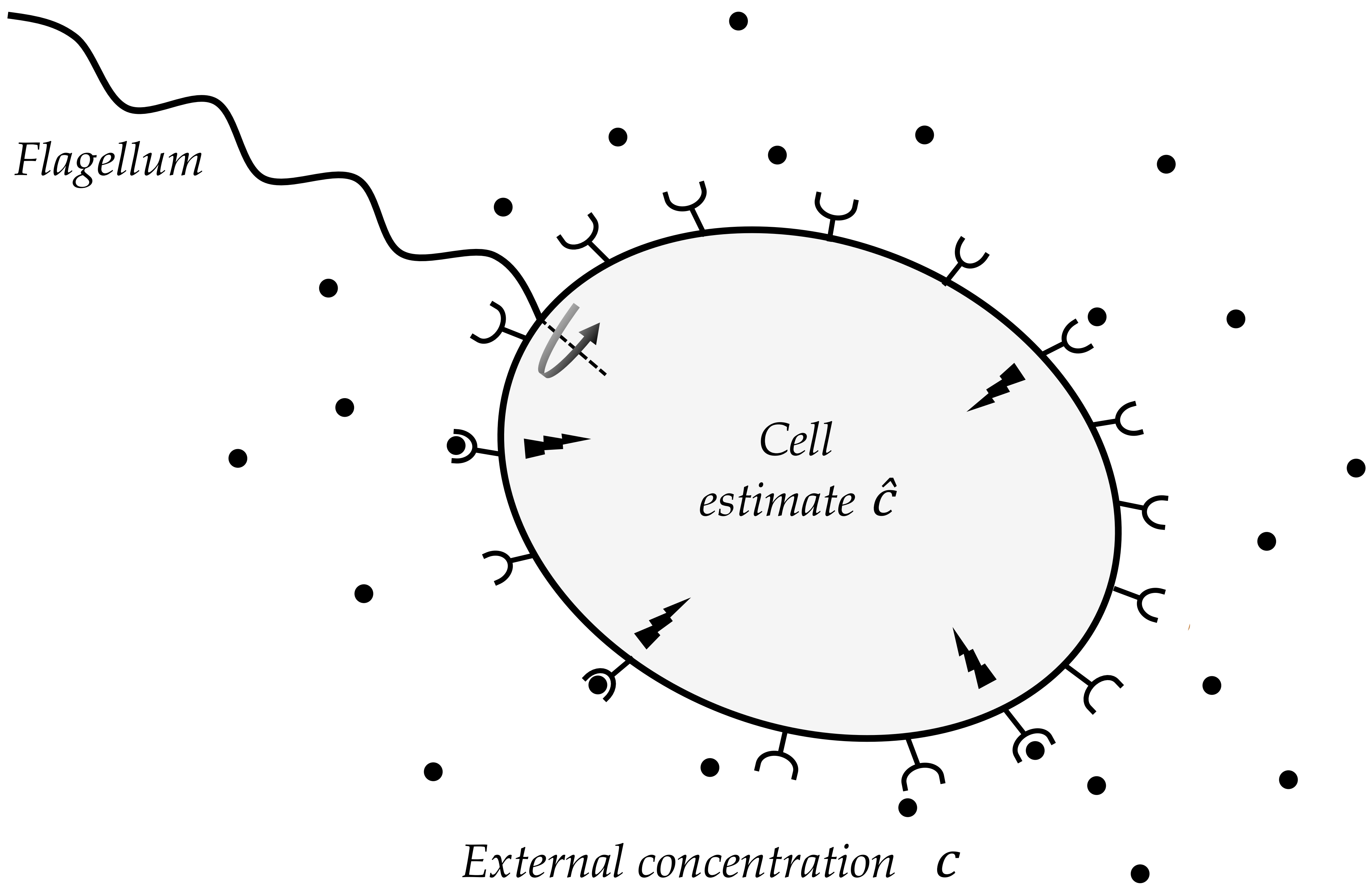
Reproduced from Adler, J. *Science* 26 Dec 1969: Vol. 166, Issue 3913, pp. 1588-1597

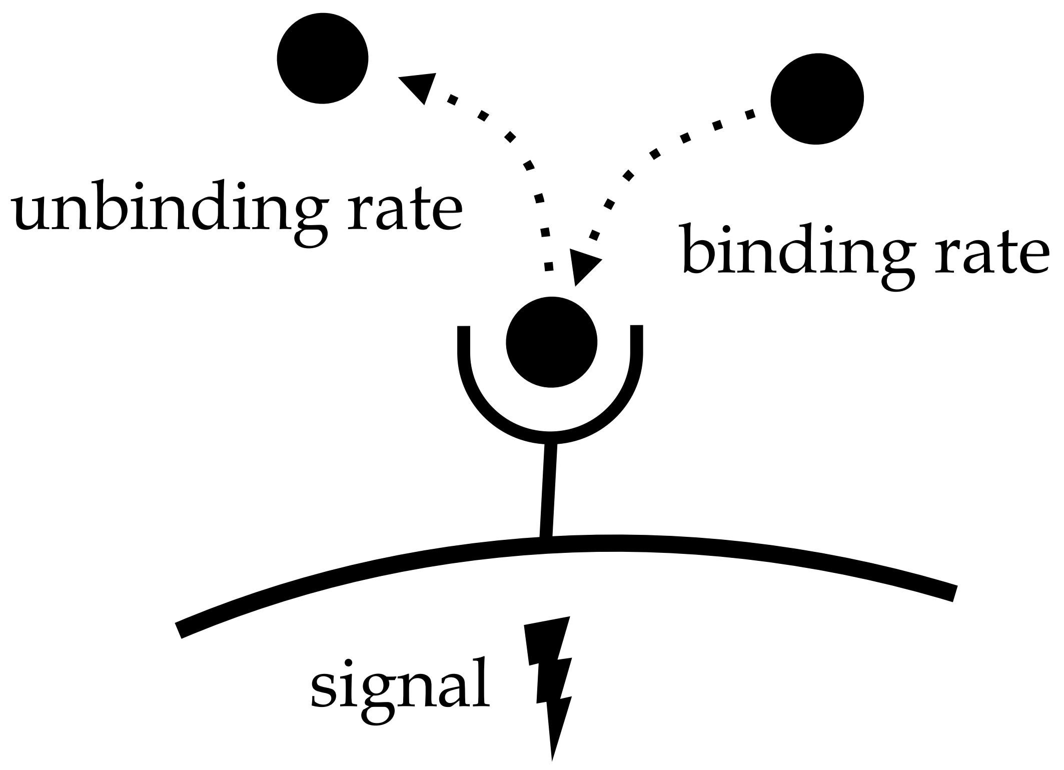
The Cell as a Chemosensation Device

- **How do cells measure external concentrations and infer information about their environment?**
  - **Surface receptors:** ligand binds to receptor → intracellular response → behavioral response
  - 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).





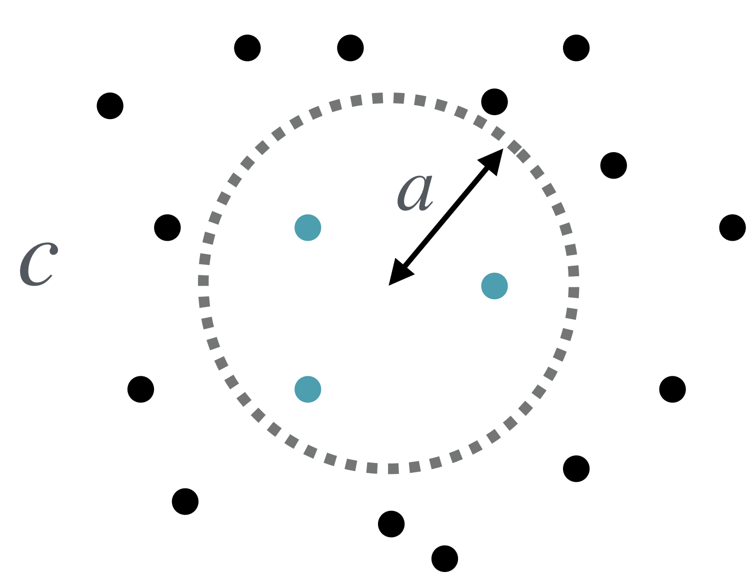
Receptor protein methylation level ↔ internal representation of concentration

Crucial for adaptation

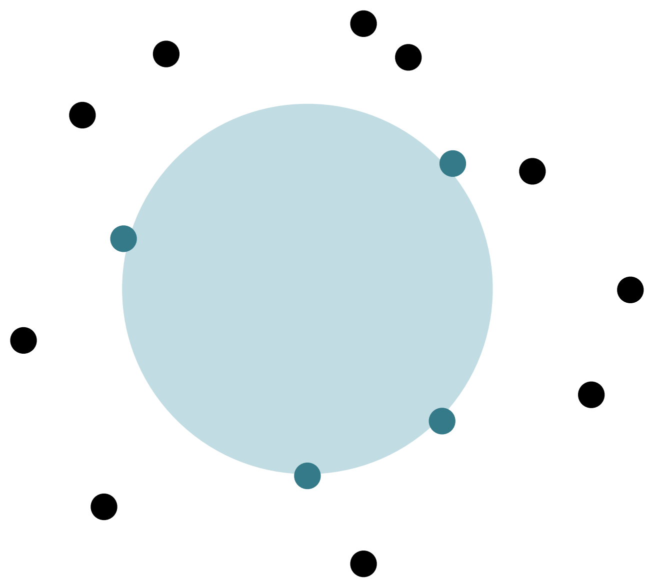
Lan, G., & Tu, Y. (2016). Information processing in bacteria: memory, computation, and statistical physics: a key issues review. Reports on Progress in Physics, 79(5), 052601.

Berg-Purcell Limit (1977)

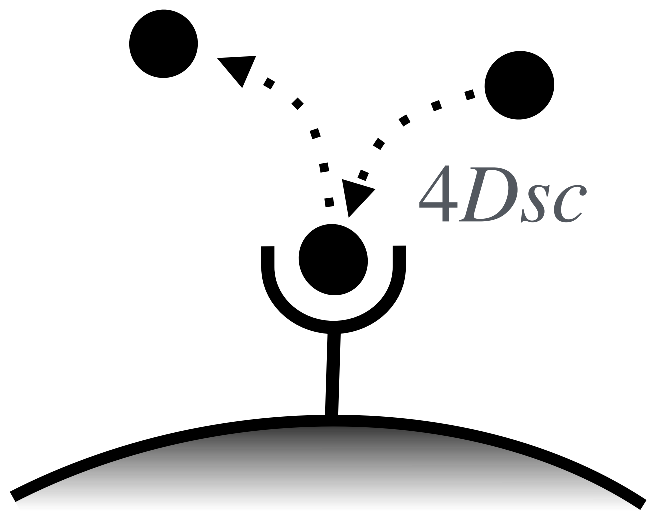
- Used diffusive transport and low Reynolds number mechanics to develop theories about the physical limits of bacterial chemoreception in various ideal cases
- 2-state single receptor model, estimation based on fraction of time bound



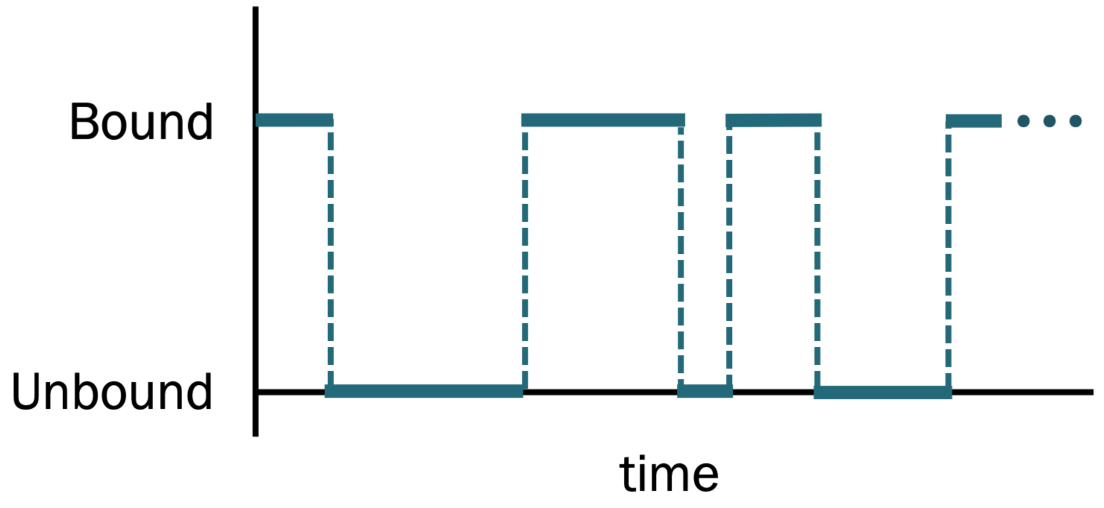
Integrating sphere

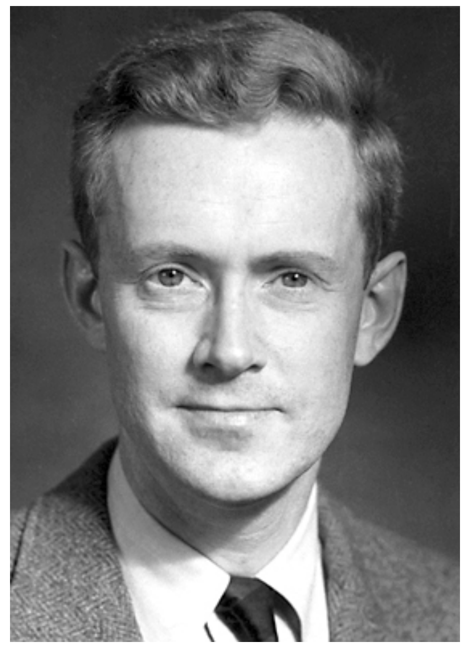


Perfect absorption

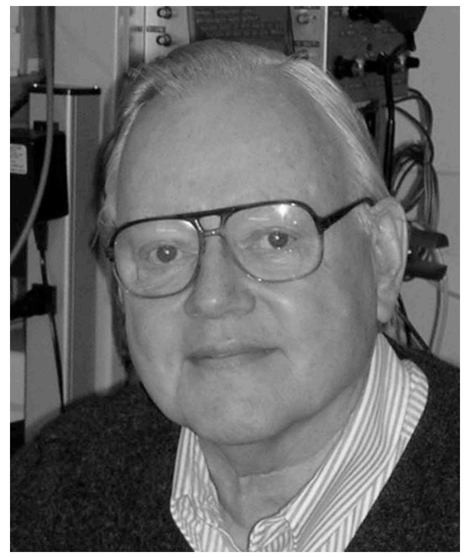


Single receptor





Edward Purcell



Howard Berg

$$uncertainty \equiv \frac{\langle(\delta c)^2\rangle}{c^2}$$

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

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

How to surpass? Violate assumptions made

Berg, H. C., & Purcell, E. M. (1977). Physics of chemoreception. *Biophysical journal*, *20*(2), 193–219.

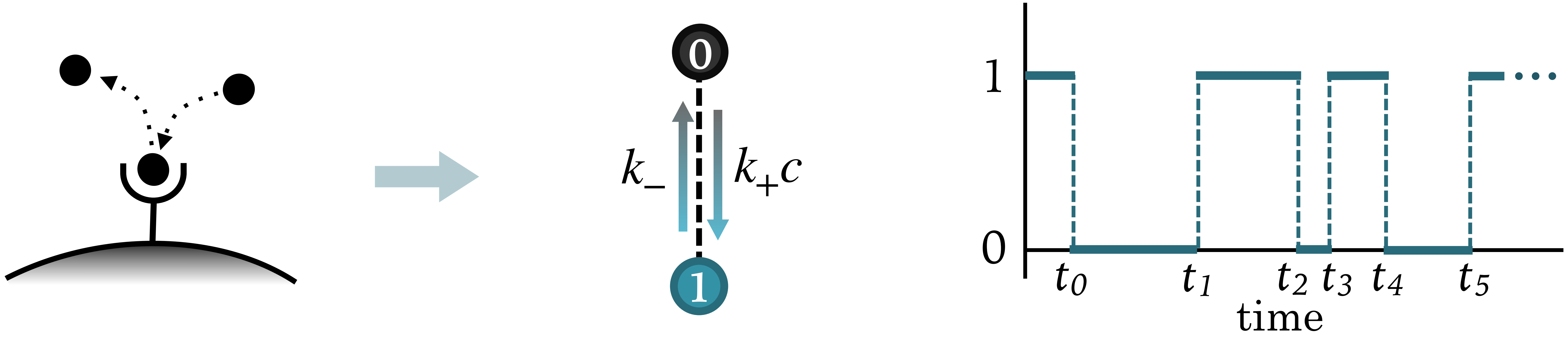
Surpassing the Berg-Purcell Limit

1. Change observable

- ➤ Endres and Wingreen (2009): Maximum likelihood and the single receptor
  - ➤ Applied Maximum likelihood estimation to a single, two-state receptor binding/unbinding **time series**
  - ➤ Showed you can do better than the Berg-Purcell bound with:

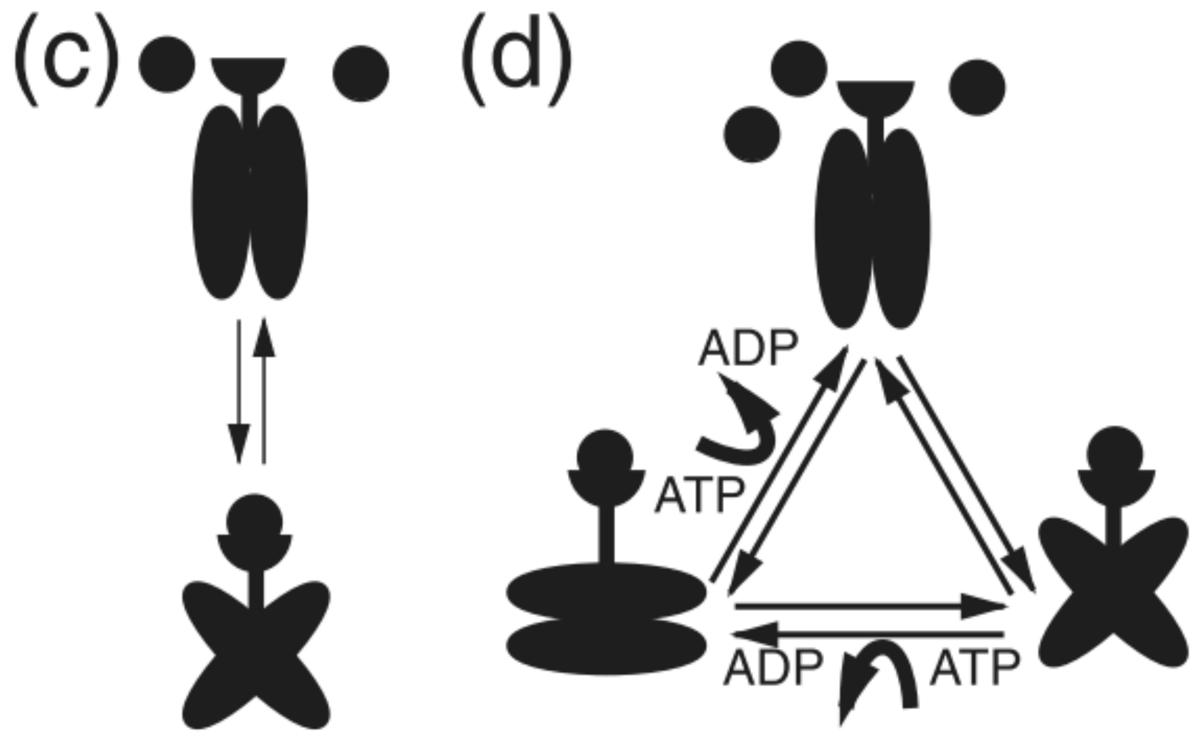
$$c_{ML} = \frac{N}{T_u k_+} \qquad \frac{\langle (\delta c_{ML})^2 \rangle}{c^2} = \frac{1}{\overline{N}}$$

Intuition: only the unbound intervals contain information about c



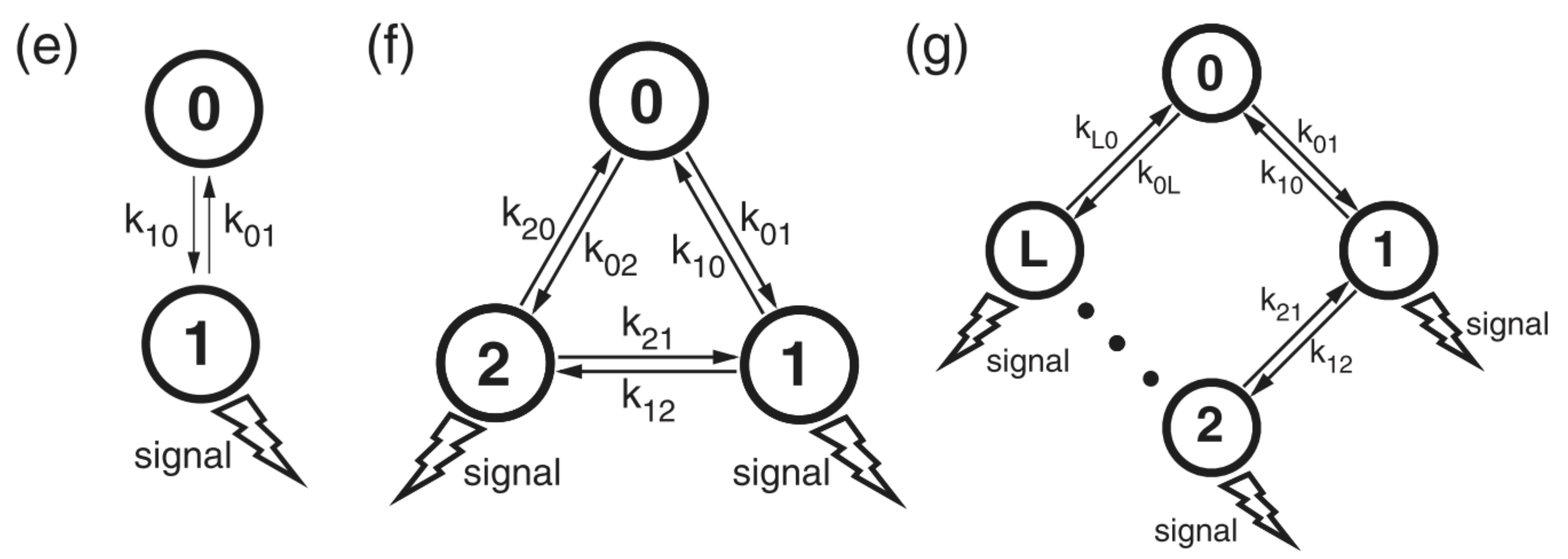
Endres, R. G. & Wingreen, N. S. (2009). Maximum Likelihood and the Single Receptor. Phys Rev Lett. 2009 Oct 9;103(15):15810.

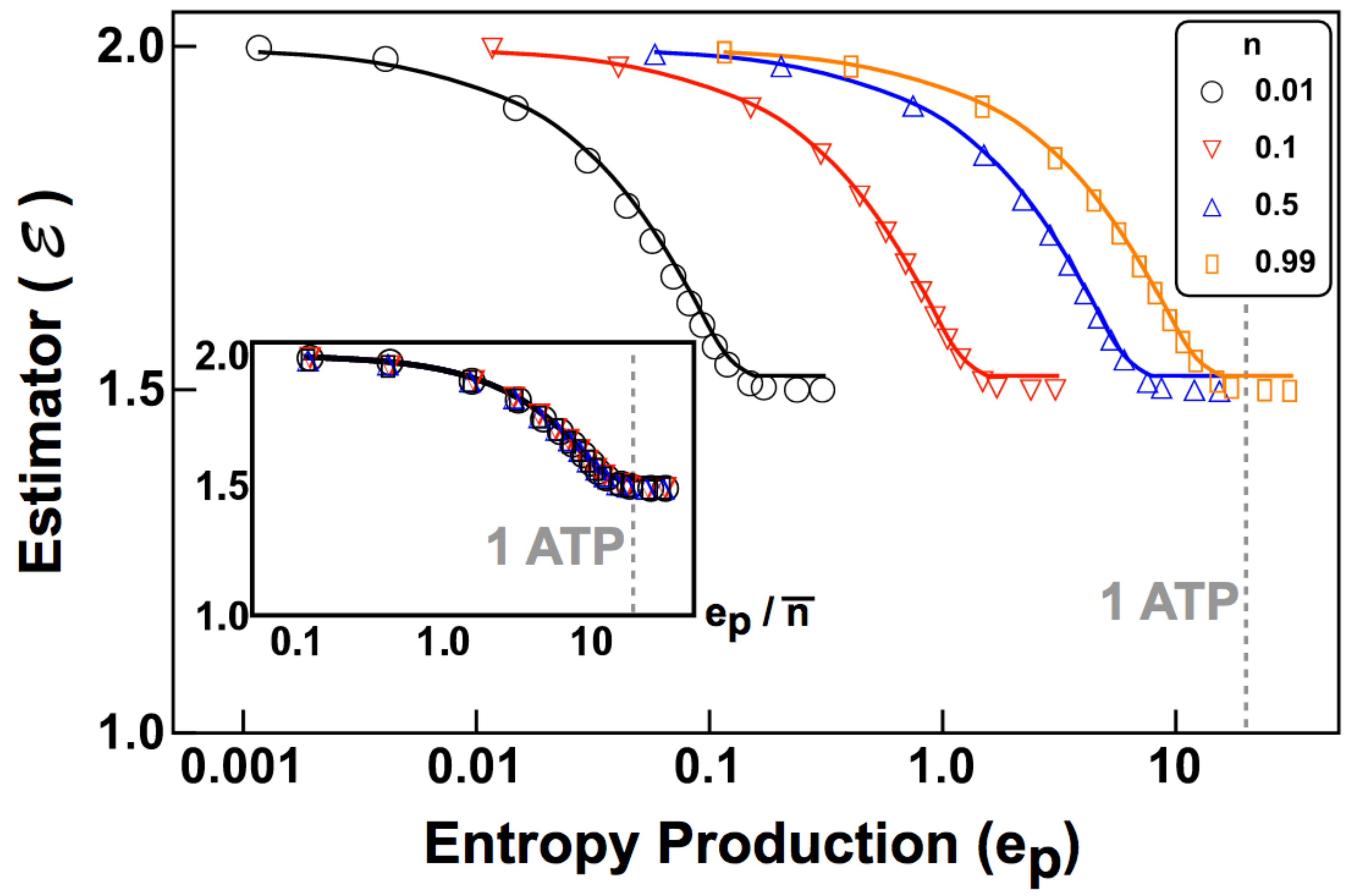
2. Drive sensing network out of equilibrium



- Lang et al (2014): What about complex networks that consume energy? What is the relationship between the estimation capability and the energy consumption?
  - For larger Markov networks constrained to be **rings**, showed:

"uncertainty": $$\frac{\langle(\delta\hat{c})^2\rangle}{c^2} = \frac{1}{\overline{N}}\left[1 + \frac{\langle(\delta\tau_S)^2\rangle}{\overline{\tau}_S}\right]$$ τ_S : *lifetime in signaling states*





observed numerically: **accuracy** limited by **entropy production**

Figures reproduced from: Lang, A. H., Fisher, C. K., Mora, T., & Mehta, P. (2014). Thermodynamics of Statistical Inference by Cells. Physical Review Letters, 113(14), 148103.

We are interested in:

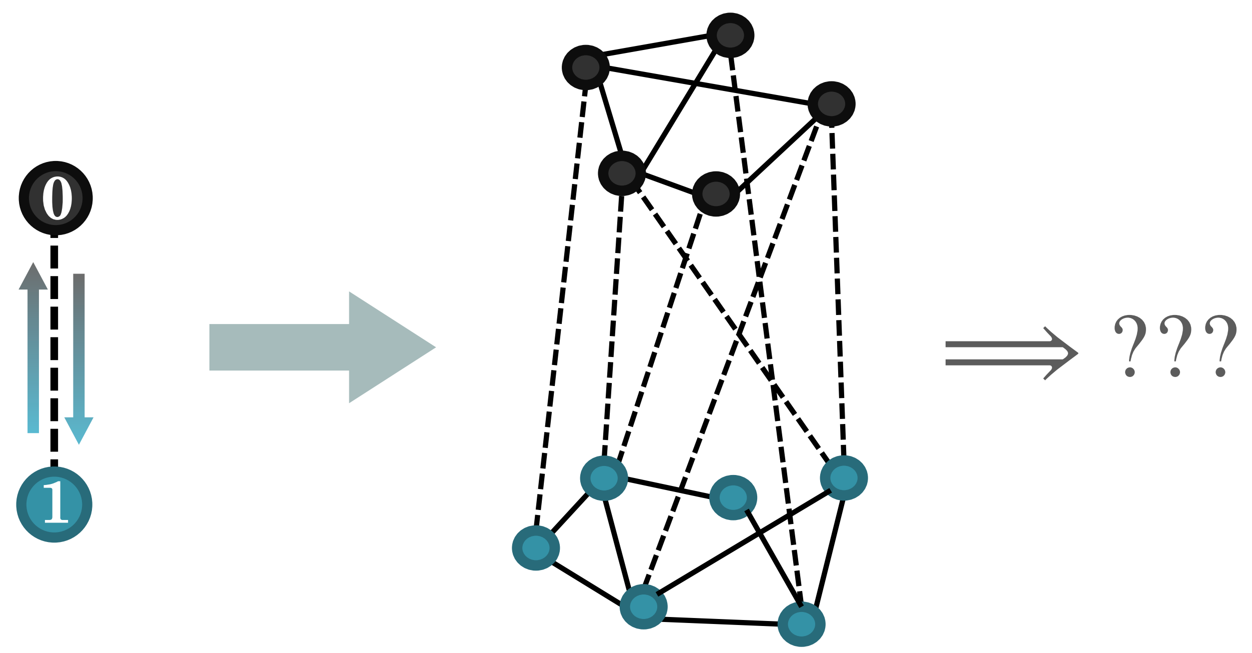
How the *observability of the process* affects the estimation uncertainty

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

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

0. Introduce some mathematical concepts and notations
1. Cramer-Rao bound for an observation of a general Markov trajectory

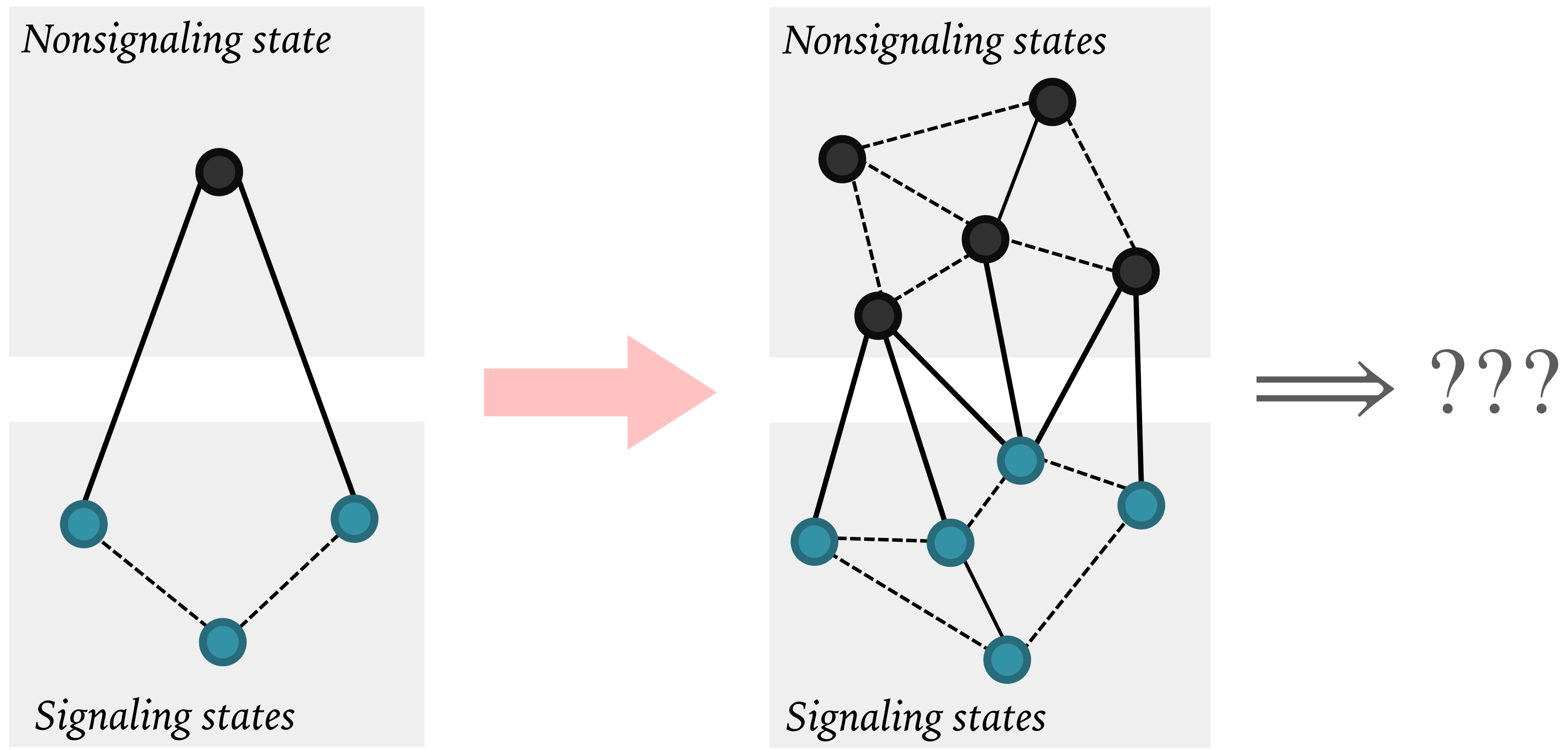
"ideal observer"



2. Bound on coarse-grained observations of Markov process

"simple observer"

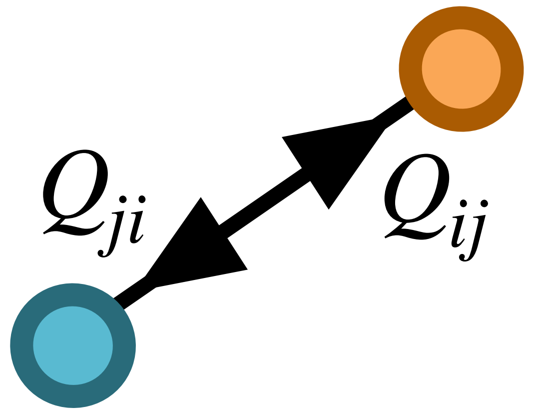
- *Stochastic thermodynamics*
- *Large deviation theory*



3. Numerical studies

Brief Review of Markov Chains

- Model the sensing device (receptor) as continuous-time Markov chain
  - System has discrete states ⟶ nodes on graph
  - Allowed transitions between states ⟶ edges



- Transitions between states i and j described by transition rate Q_{ij}

Probability density over states (p) is evolves according to the **master equation:** $\frac{dp_j(t)}{dt} = \sum_i \left[p_i(t)Q_{ij} - p_j(t)Q_{ji}\right]$

$$\frac{d\pi}{dt} = 0 \qquad \pi : \textit{steady state distribution}$$

Bracketed quantity is the mean current flowing from i to j: $j_{ij}^{p}(t) = p_i(t)Q_{ij} - p_j(t)Q_{ji}$

Flux between two states: $\phi_{ij} = p_i Q_{ij}, \quad j_{ij}^{p} = \phi_{ij} - \phi_{ji}$

In steady state: $\phi_{ij}^{\pi} \equiv \pi_i Q_{ij}\,, \quad j_{ij}^{\pi} = \phi_{ij}^{\pi} - \phi_{ji}^{\pi}$

Brief Review of Markov Chains

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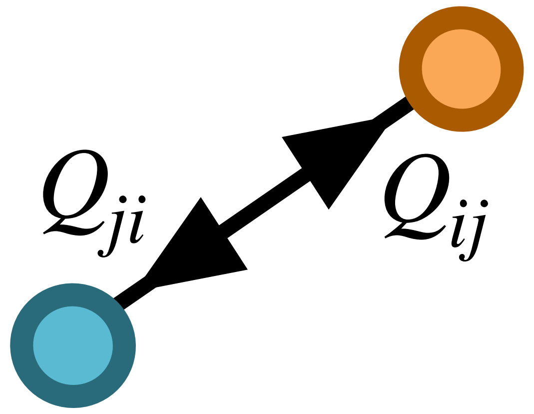

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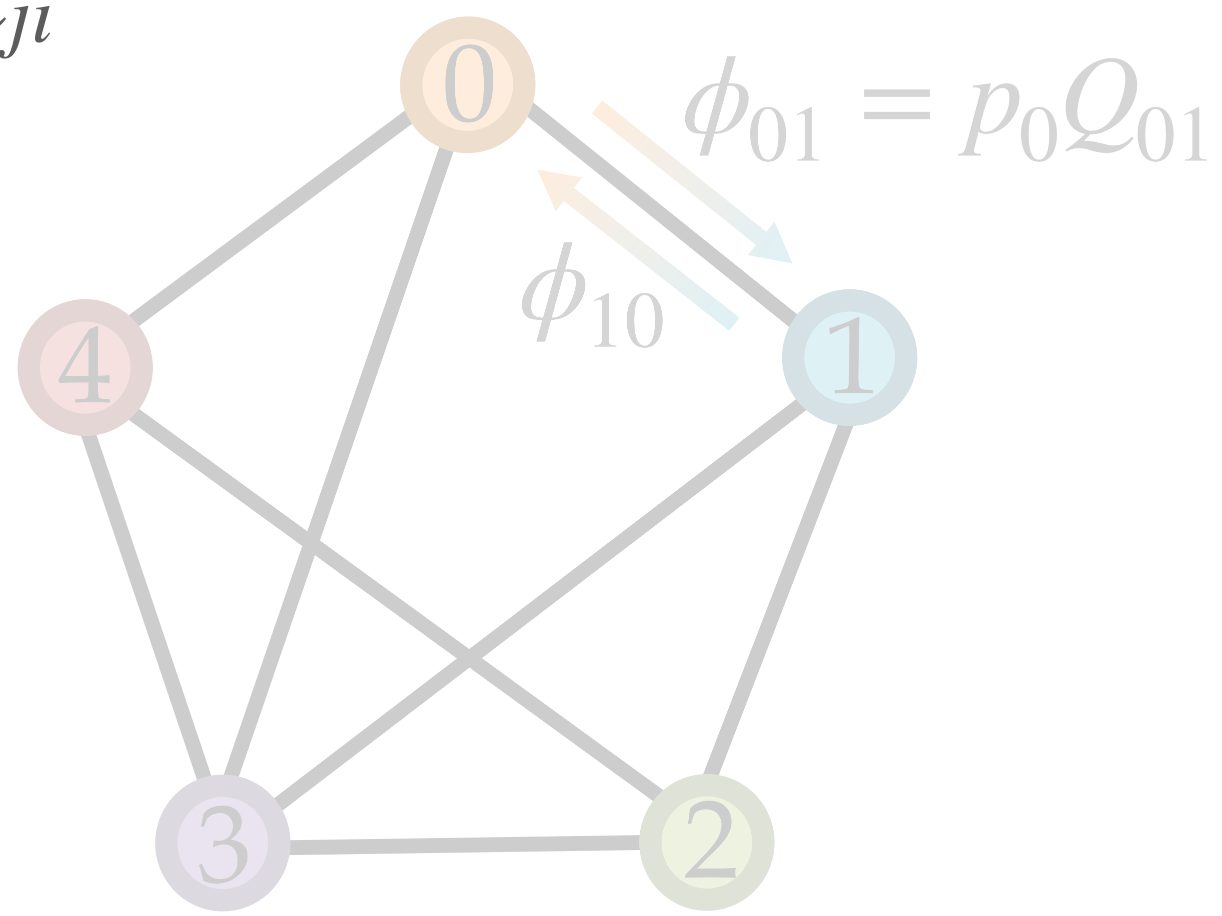

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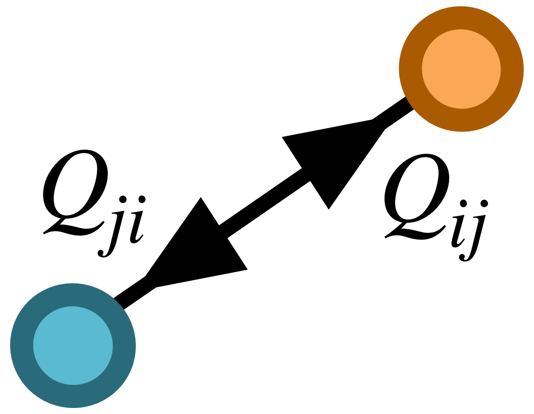

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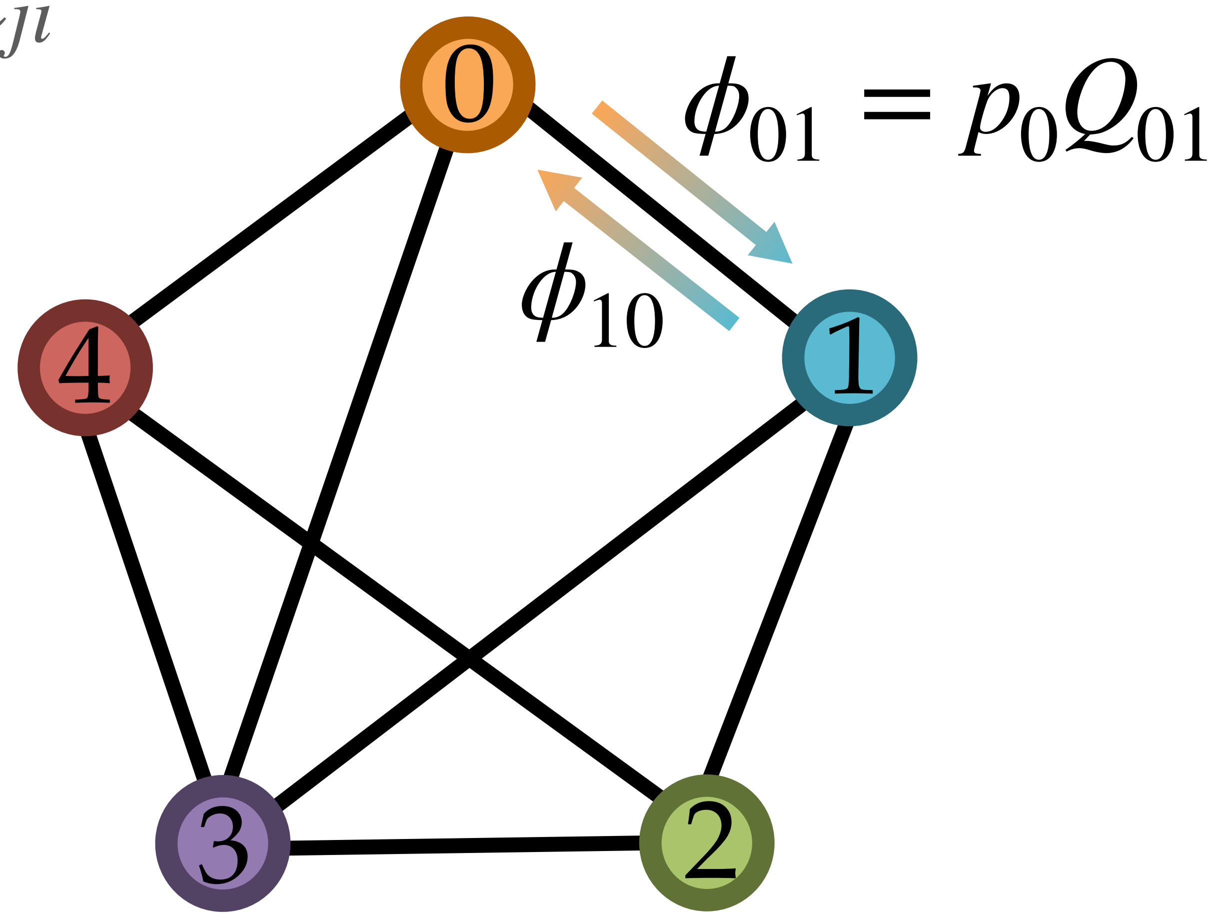

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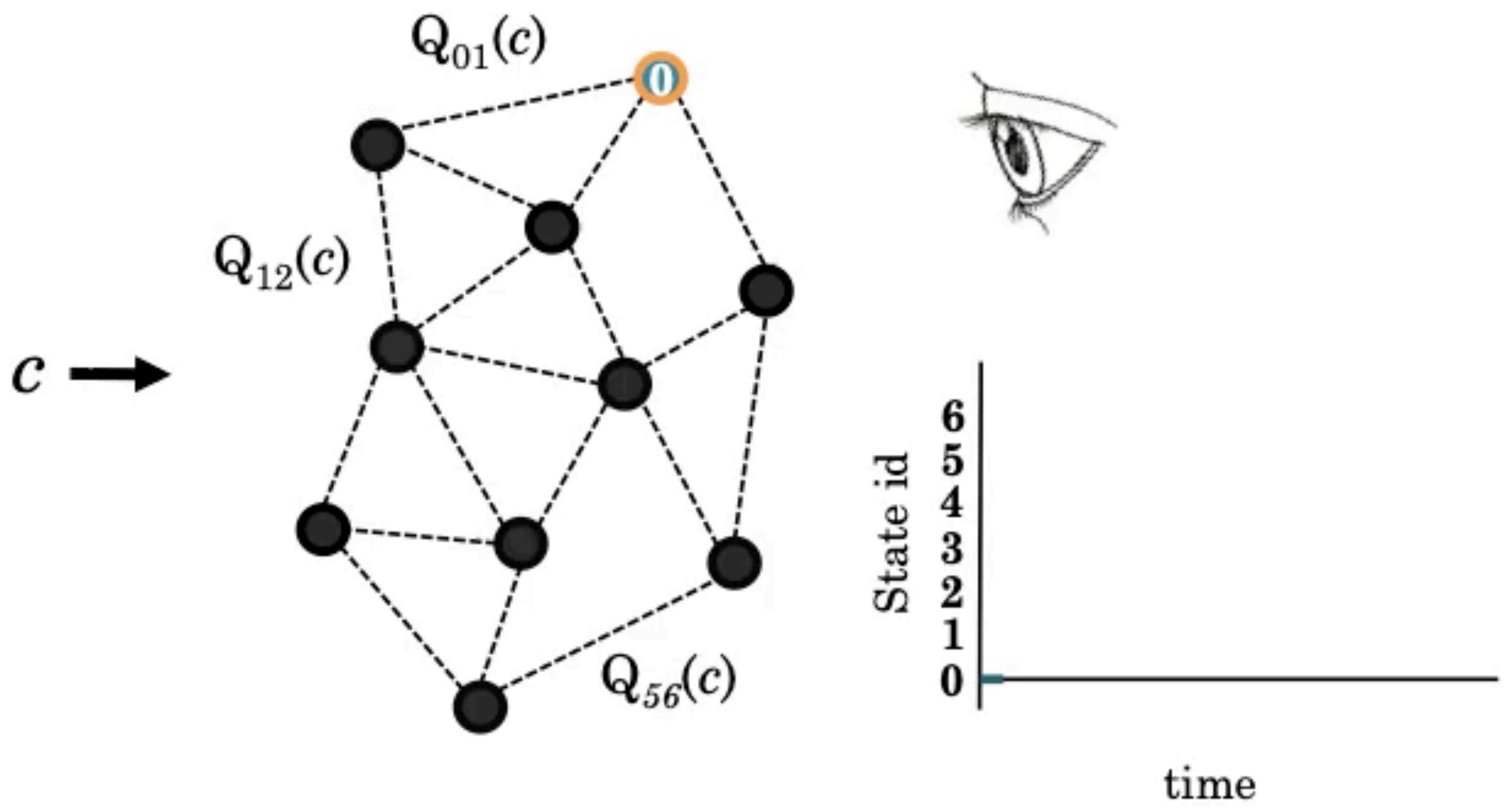
1. Ideal Observer: Observation of a Markov Trajectory

➤ **A general sensing problem:**

Signal is transmitted through a physical channel modeled as a continuous time Markov process

Ideal ‘observer’ records system’s entire state trajectory and transition times for a finite amount of time



Q_{ij} : *transition rates*

What is the best possible estimate the observer can make of the signal c ?

1. Ideal Observer: Observation of a Markov Trajectory

- Calculate the Fisher Information for the observed trajectory with respect to the signal c
- Cramér-Rao bound gives fundamental limit on the precision with which the signal can be estimated based on the observations

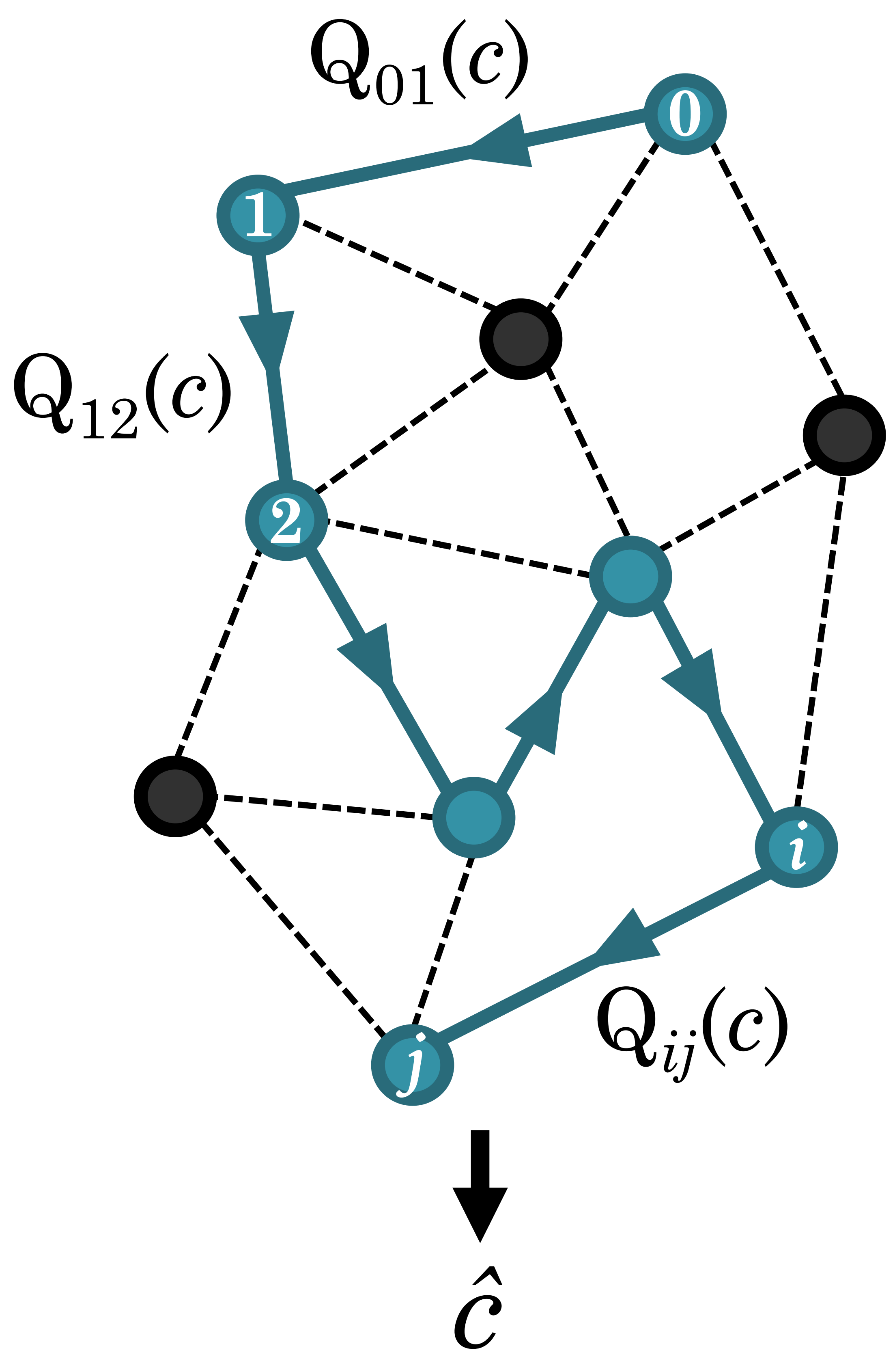
Plan: Write the probability of a trajectory in discrete time, calculate Fisher Information matrix, then take time steps → 0

Probability of a trajectory from a state x_0 at $t = 0$ to state x_n at $t = n\Delta t$:

$$\mathbb{P}(x_0 \dots x_n) = \pi_{x_0} M_{x_0 x_1} M_{x_1 x_2} \dots M_{x_{n-1} x_n}$$

M : *discrete time transition matrix*

$$M = e^{Q\Delta t} = I + Q\Delta t + \dots$$



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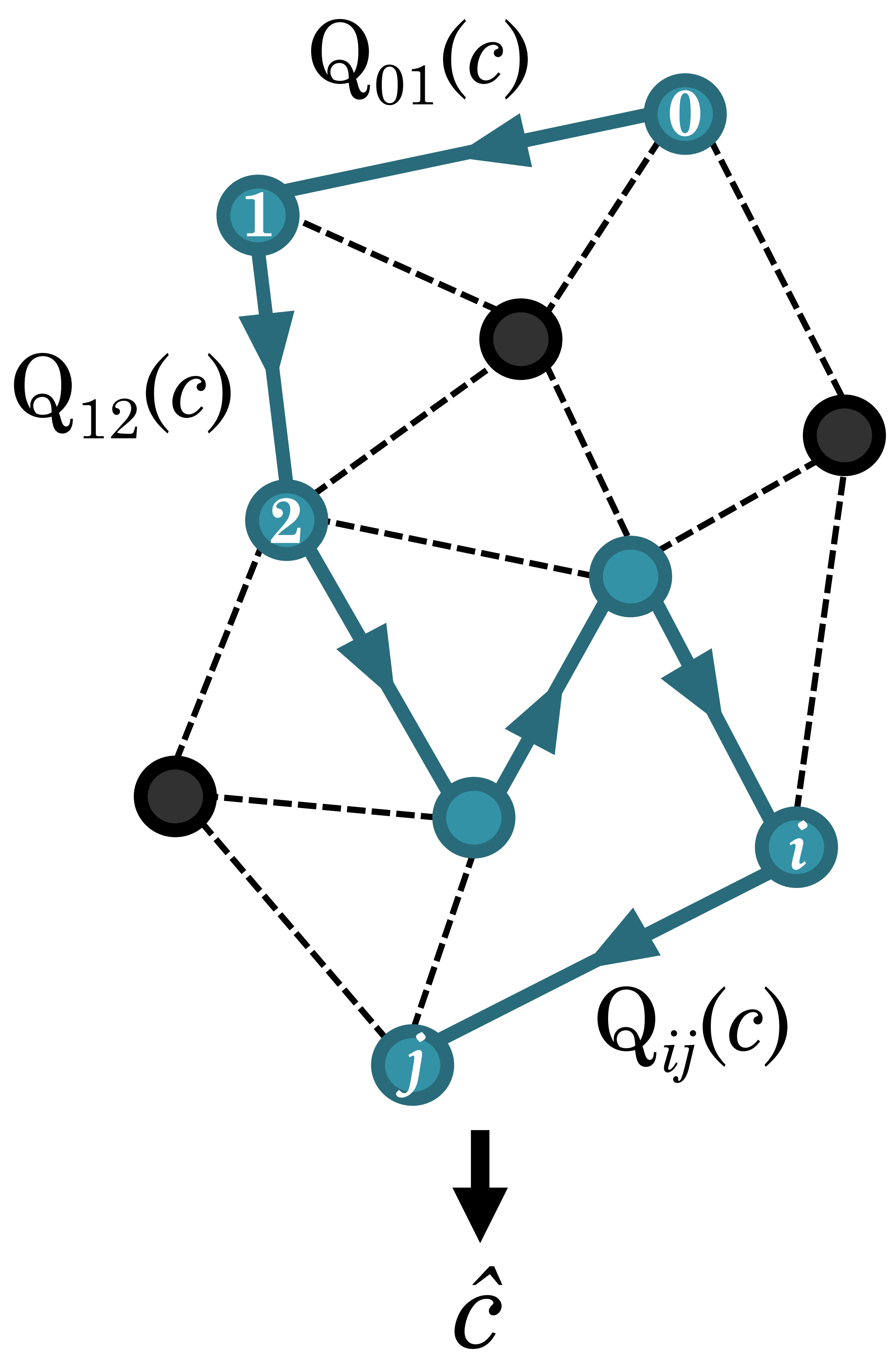

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1. Ideal Observer: Observation of a Markov Trajectory

Fisher Information:

$$\rightarrow J_c = \sum_{x_0,\ldots,x_n} \overbrace{(\pi_{x_0} M_{x_0x_1} \ldots M_{x_{n-1}x_n})}^{\mathbb{P}(x_0 \ldots x_n)} \left[\frac{\partial}{\partial c} \log(\pi_{i_0} M_{x_0x_1} \ldots M_{x_{n-1}x_n})\right]^2$$

After substituting $M = I + Q\Delta t$ and taking $\Delta t \rightarrow 0$ with fixed $T = n\Delta t$, we find:

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

i,j index all states

with

$$J_c^0 = \sum_{x_0} \pi_{x_0} \left[\partial_c \log \pi_{x_0}\right]^2$$

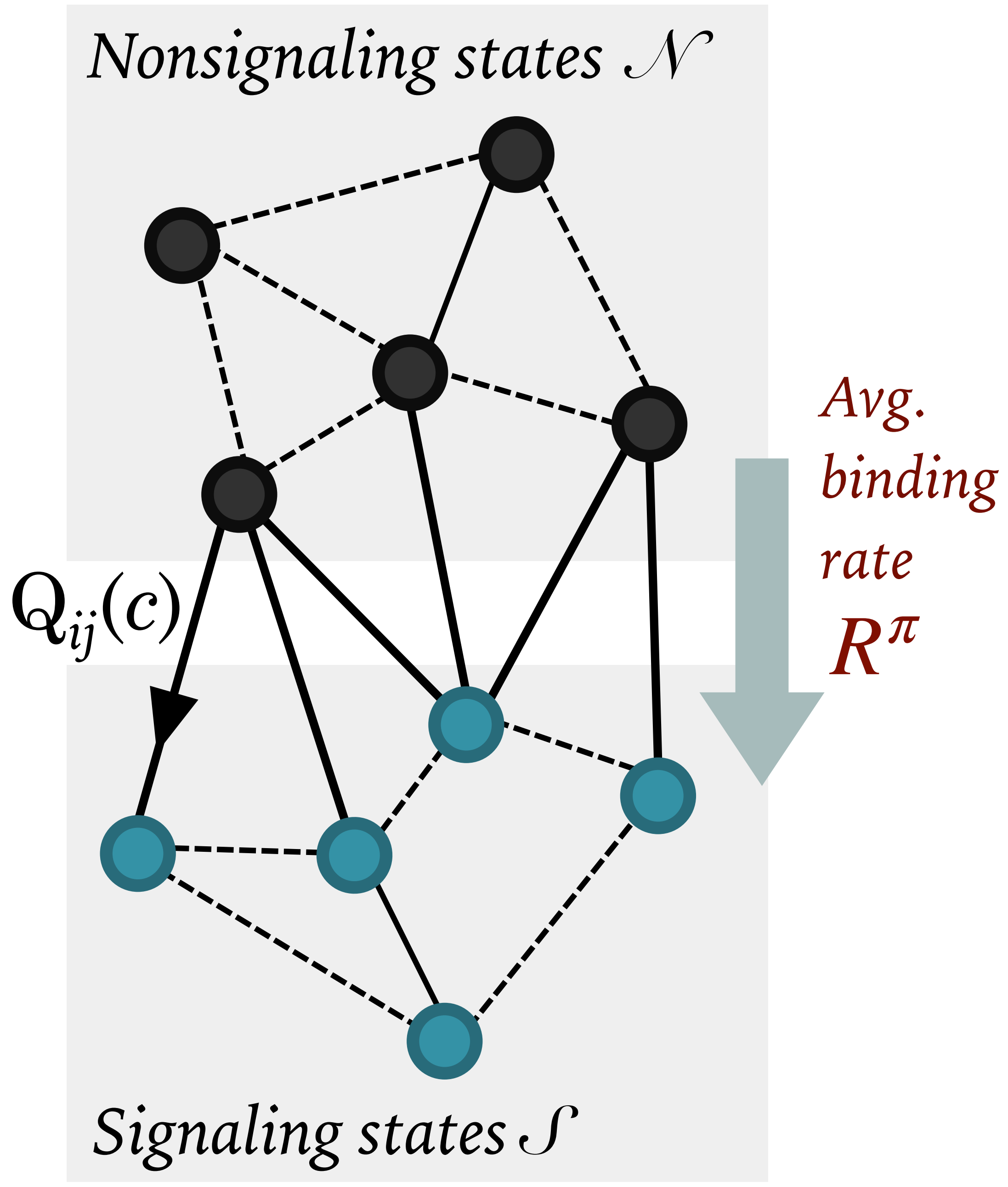
"single shot" Fisher information

Q_{ij} : *transition rates*

π_i : *steady state density*

Make some assumptions which are well suited for cellular sensing problem

- ➤ 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



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

Fisher Information simplifies to

$$J_c = \underbrace{J_c^0}_{\text{F.I. of single observation}} + \frac{T}{c^2} \underbrace{\sum_{\substack{i \in \mathcal{S} \\ j \in \mathcal{N}}} \pi_i Q_{ij}}_{\text{Avg. Binding rate } R^\pi}$$

So as T $\to$ large, we find: $J_c = \frac{T R^\pi}{c^2}$

The Cramér-Rao bound $\Longrightarrow$ the variance of an unbiased estimator of c is bounded by F.I. $\langle (\delta c)^2 \rangle \geq \frac{1}{J_c}$

which implies:

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

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

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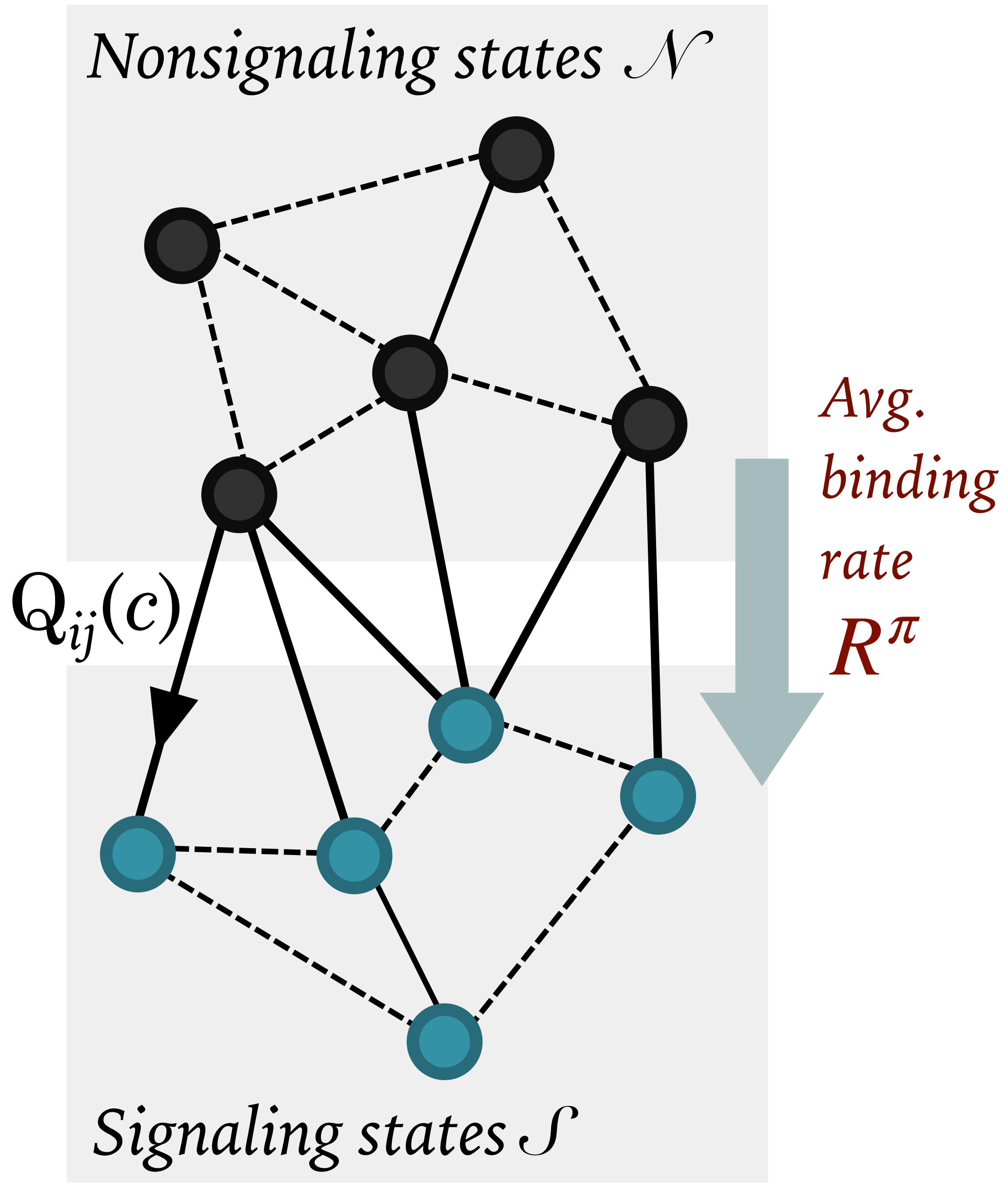
F.I. of single observation

So as T ⟶ large, we find: $\boxed{J_c = \frac{T R^\pi}{c^2}}$



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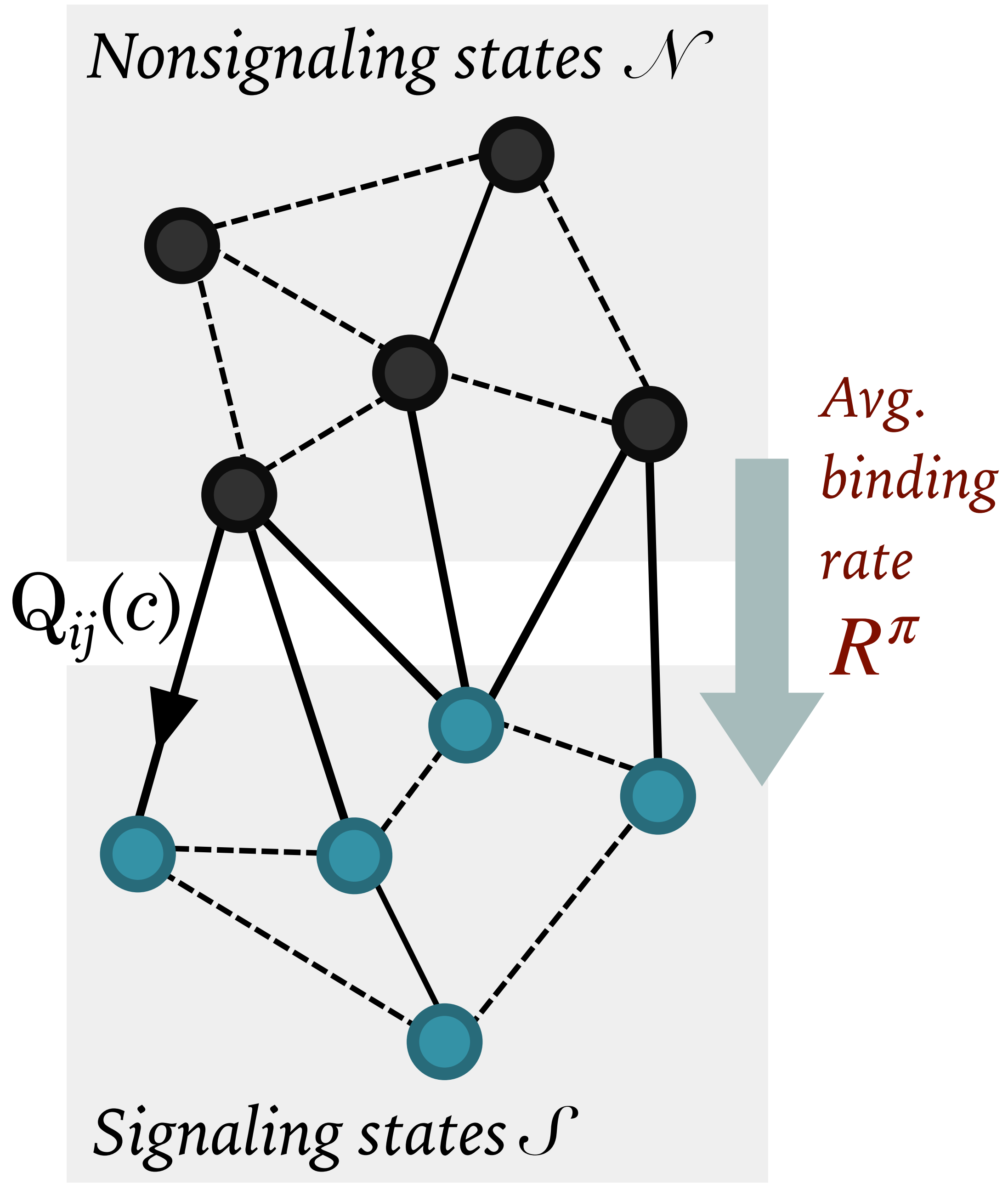

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which implies:

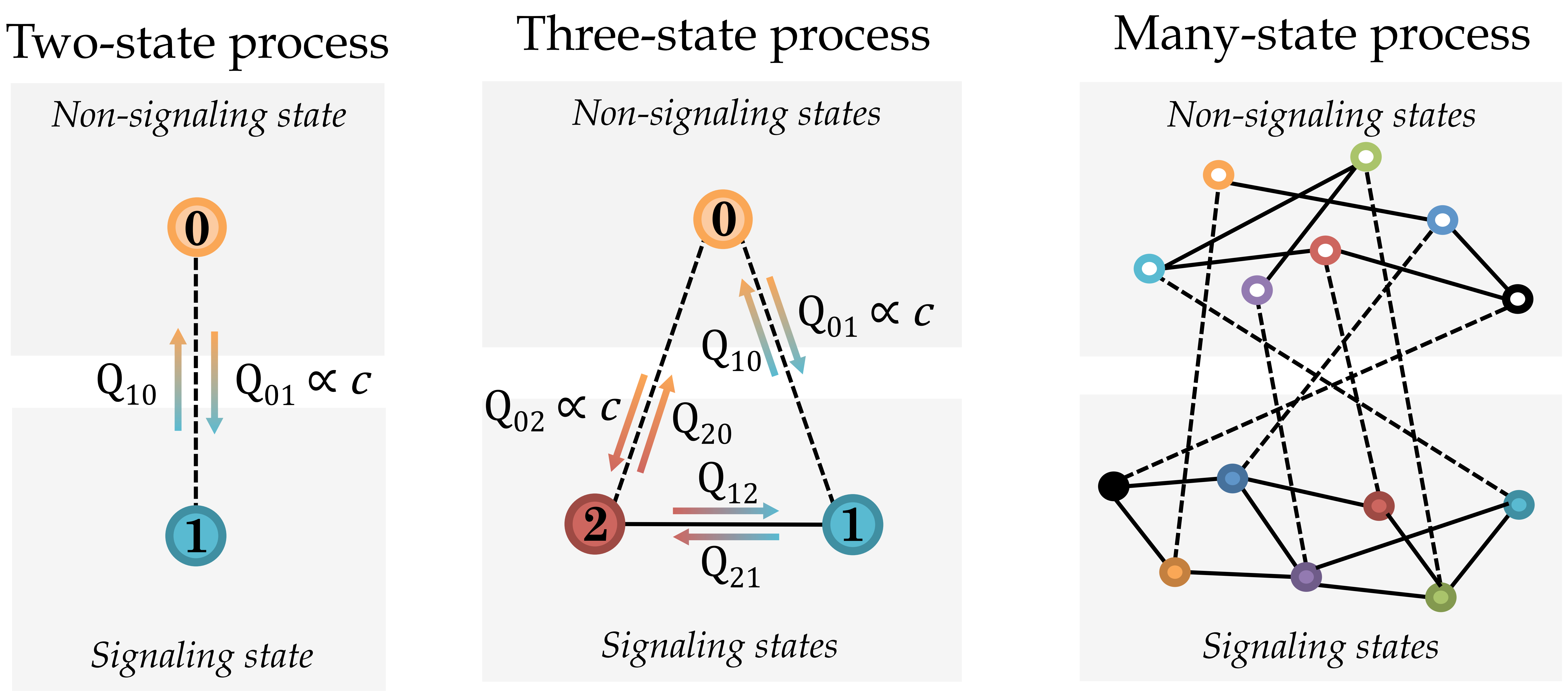
$$\frac{\langle(\delta\hat{c})^2\rangle}{c^2} \geq \frac{1}{J_c c^2} = \frac{1}{TR^\pi} = \frac{1}{\overline{N}}.$$

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

Generalizes Endres & Wingreen
no advantage to > 2 states

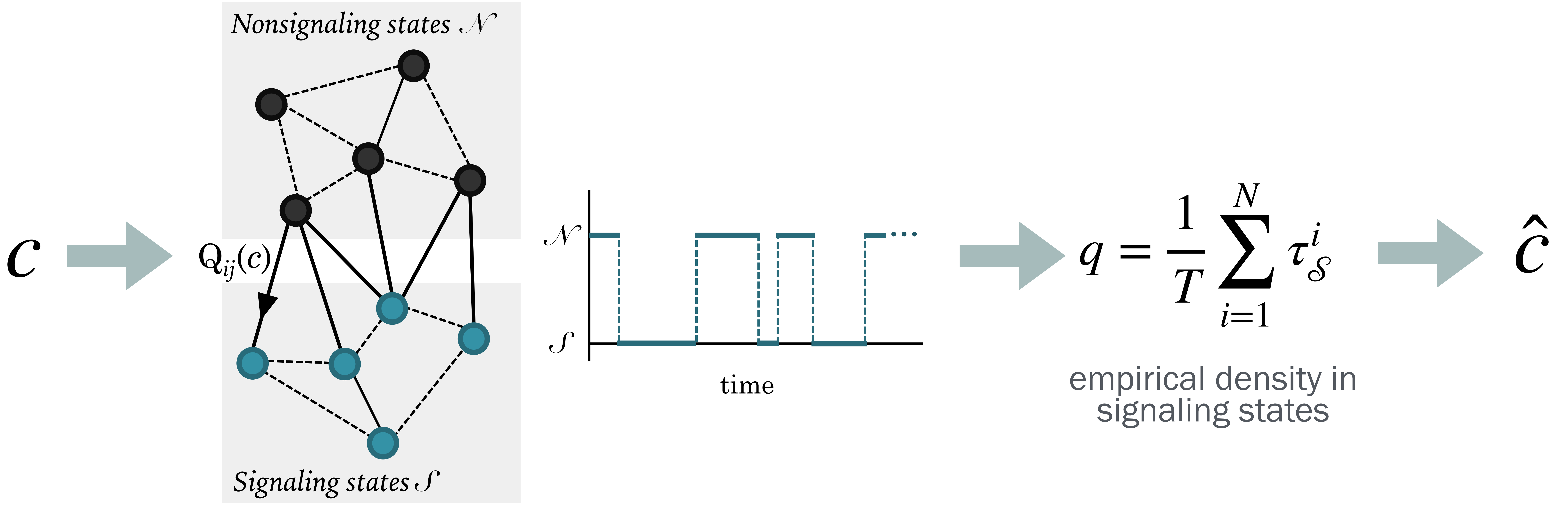
What Next?

- **What if we make more 'realistic' assumptions on the observability of the Markov process?**
  - Lang 2014 numerically observed that larger networks with the observability restricted to non-signaling/signaling can approach the Cramer-Rao result **only when driven out of equilibrium**



2. Coarse-Grained Observation

- **Coarse-grained scenario:** cell is not keeping track of the microscopic receptor transitions, rather estimation is based on fraction of time receptor spends in subset of states (same as Berg and Purcell)
- Assume network of arbitrary structure, but estimate is based on the density in the 'signaling states' $q = \sum_{i \in \mathcal{S}} p_i$
- *Is there an advantage to driving this sensor out of equilibrium?*

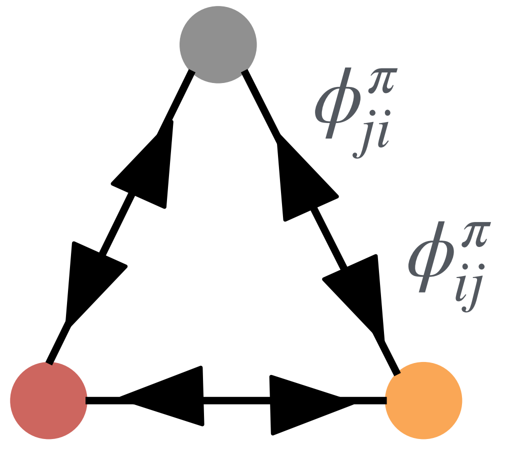


An ergodic Markov chain will relax to steady state distribution with $\frac{d\pi}{dt} = 0$

$$\pi : \frac{d\pi_j}{dt} = 0 \quad \forall j \qquad \Longrightarrow \frac{d\pi_j}{dt} = \sum_i \left[\pi_i(t) Q_{ij} - \pi_j(t) Q_{ji}\right] = 0$$

For more than two states, two ways to have $d\pi_i/dt = 0$

$\Longrightarrow$ **detailed balance, or 'equilibrium'** $j^{\pi}_{ij} = \underbrace{\pi_i(t) Q_{ij}}_{\phi^{\pi}_{ij}} - \underbrace{\pi_j(t) Q_{ji}}_{\phi^{\pi}_{ji}} = 0$ everywhere



OR

$\Longrightarrow$ **'nonequilibrium steady state':** Non-zero current loops which sum to zero

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

$j^{\pi}_{ij} = \pi_i(t) Q_{ij} - \pi_j(t) Q_{ji} \neq 0$ somewhere

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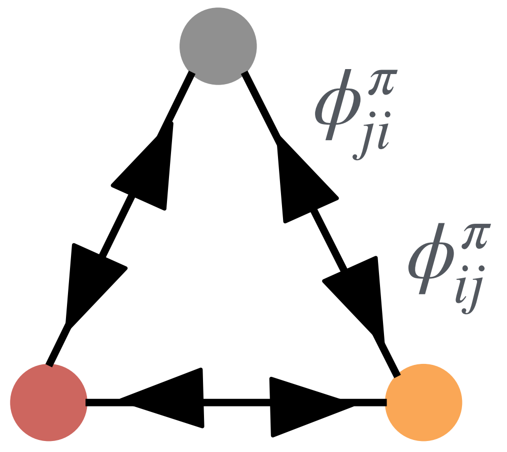

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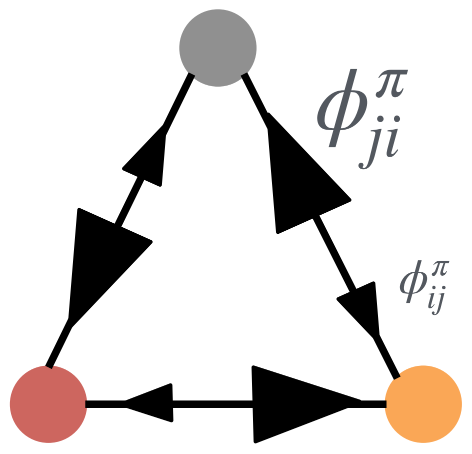


$$\sum_i \left[\pi_i(t) Q_{ij} - \pi_j(t) Q_{ji}\right] = 0$$

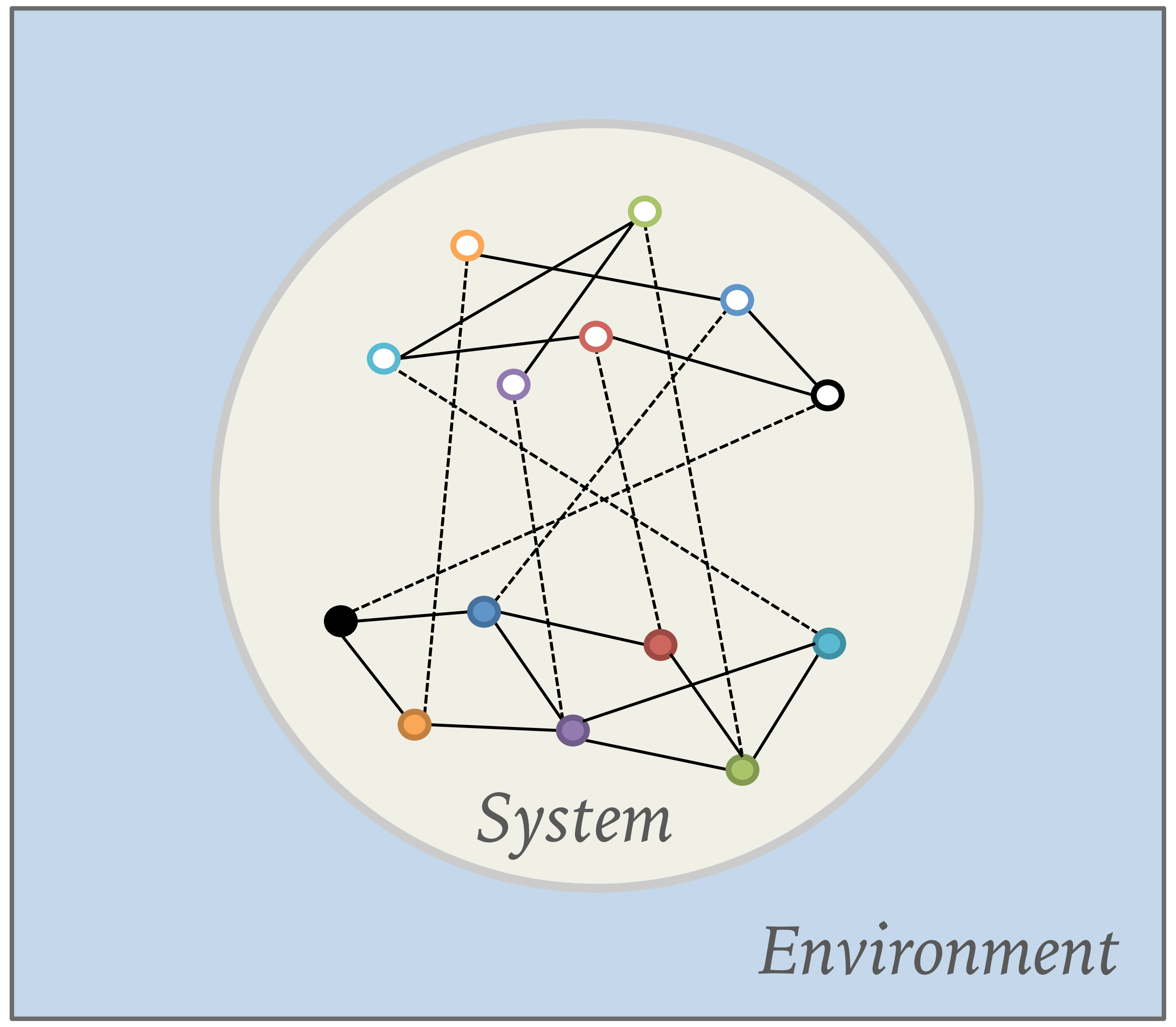
$$j^{\pi}_{ij} = \pi_i(t) Q_{ij} - \pi_j(t) Q_{ji} \neq 0 \quad \text{somewhere}$$

➤ **Local detailed balance:** energy change in system due to a transition in state space is balanced by corresponding change in energy of thermodynamic reservoir

$$\frac{Q_{ij}}{Q_{ji}} = \exp\left[-\Delta F_{ij} + W_{ij}\right]$$

equilibrium:

$$\frac{\pi_j}{\pi_i} = \frac{Q_{ij}}{Q_{ji}} = \exp[-\Delta F_{ij}]$$



$\Delta F_{ij} = F_j - F_i$ is the change in free energy of the system due to a transition from i to j

W is a work function driving the system out of equilibrium

The **mean entropy production rate** of the system and its environment in a nonequilibrium steady $\boldsymbol{\pi}$ is:

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

Measure of the time-reversal asymmetry of the process

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

See: Seifert, U. (2019). From Stochastic Thermodynamics to Thermodynamic Inference. Annual Review of Condensed Matter Physics, 10(1), 171–192.

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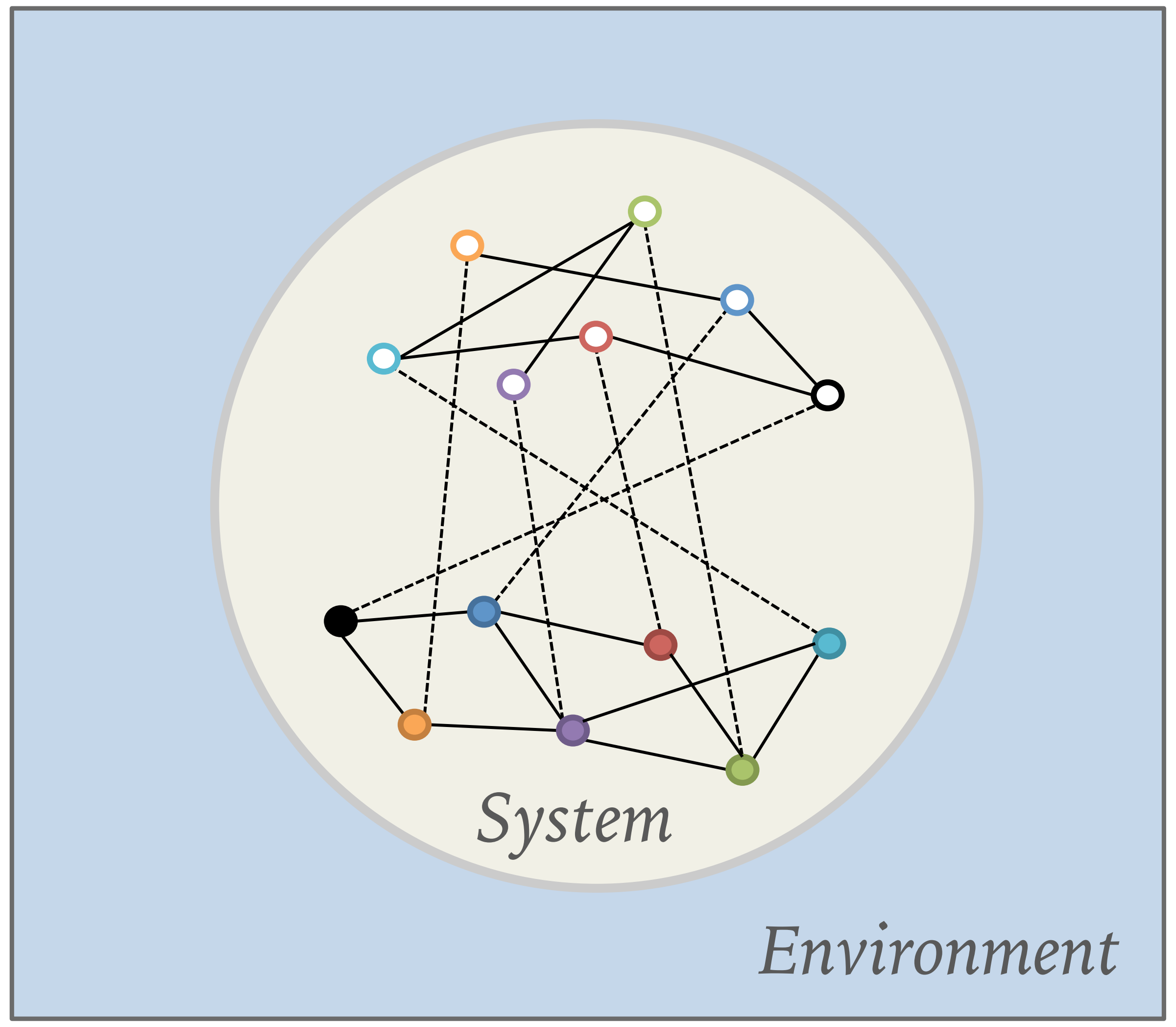

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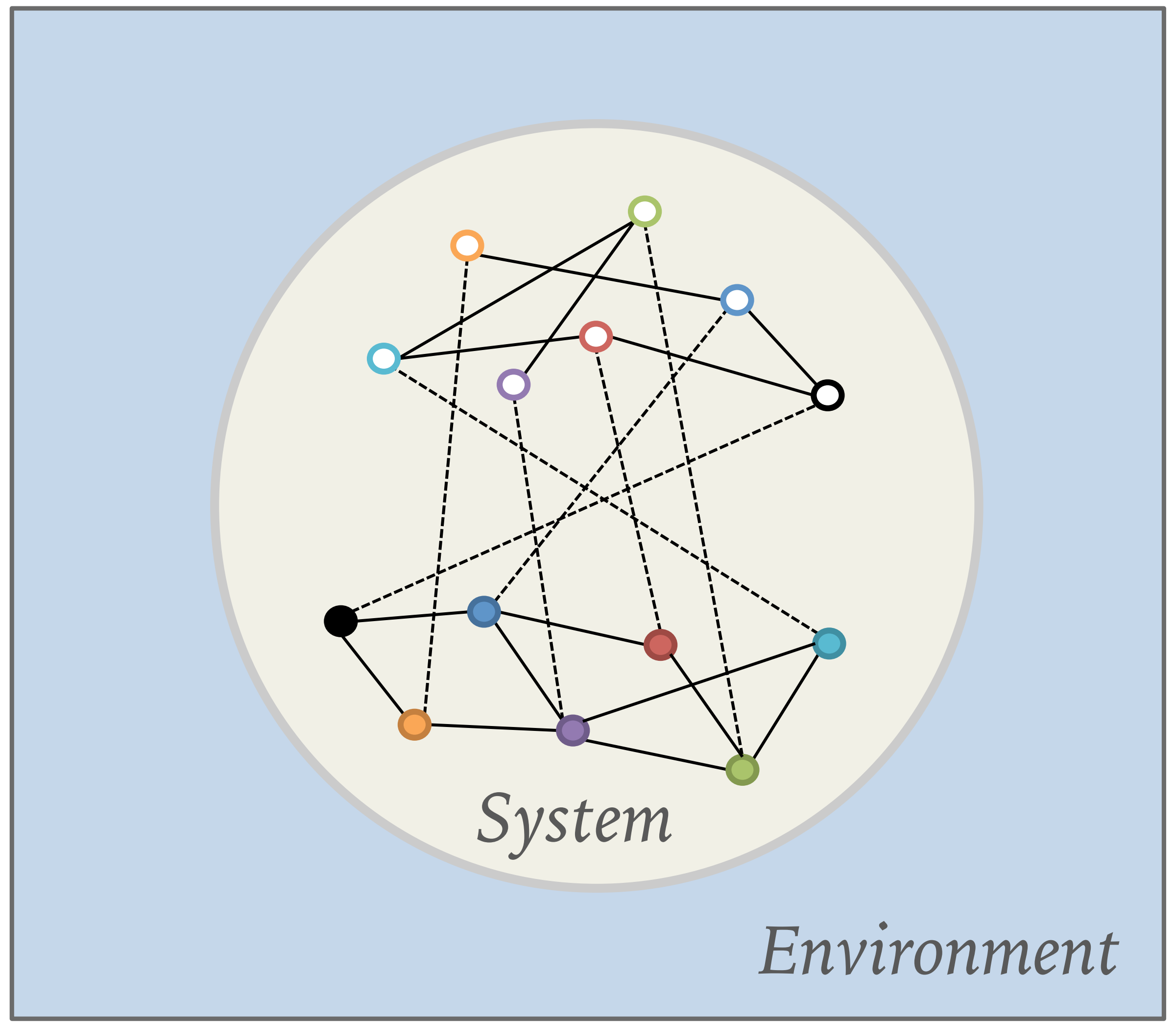

Is there a trade-off between ***entropy production*** *and measurement* ***precision*** *of the network?*

The **mean entropy production rate** of the system and its environment in a nonequilibrium steady $\boldsymbol{\pi}$ is:

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Large Deviation Theory Approach

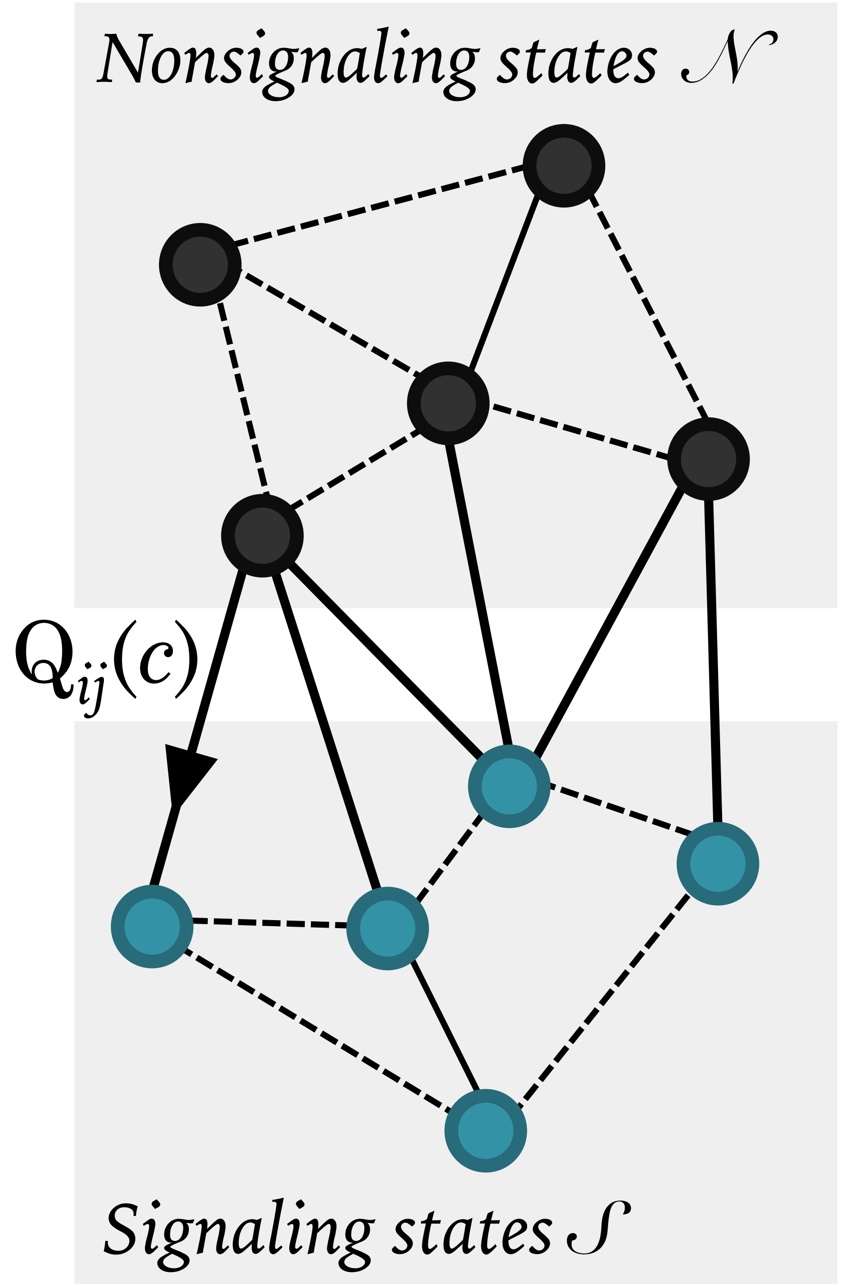
- In 2016, Gingrich et. al., used **large deviation theory** for Markov process currents to prove the previously conjectured **thermodynamic uncertainty relation** [1, 2]:

$$\epsilon_j^2 = \frac{\langle (\delta j)^2 \rangle}{j^{\pi\,2}} \geq \frac{2}{T\Sigma^\pi}$$

where Σ^π is the entropy production rate required

- We follow the same sort of program—bound the uncertainty of the concentration estimate under the coarse-grained measurement assumption

$$\frac{\langle (\delta \hat{c})^2 \rangle}{c^2} \geq ???$$

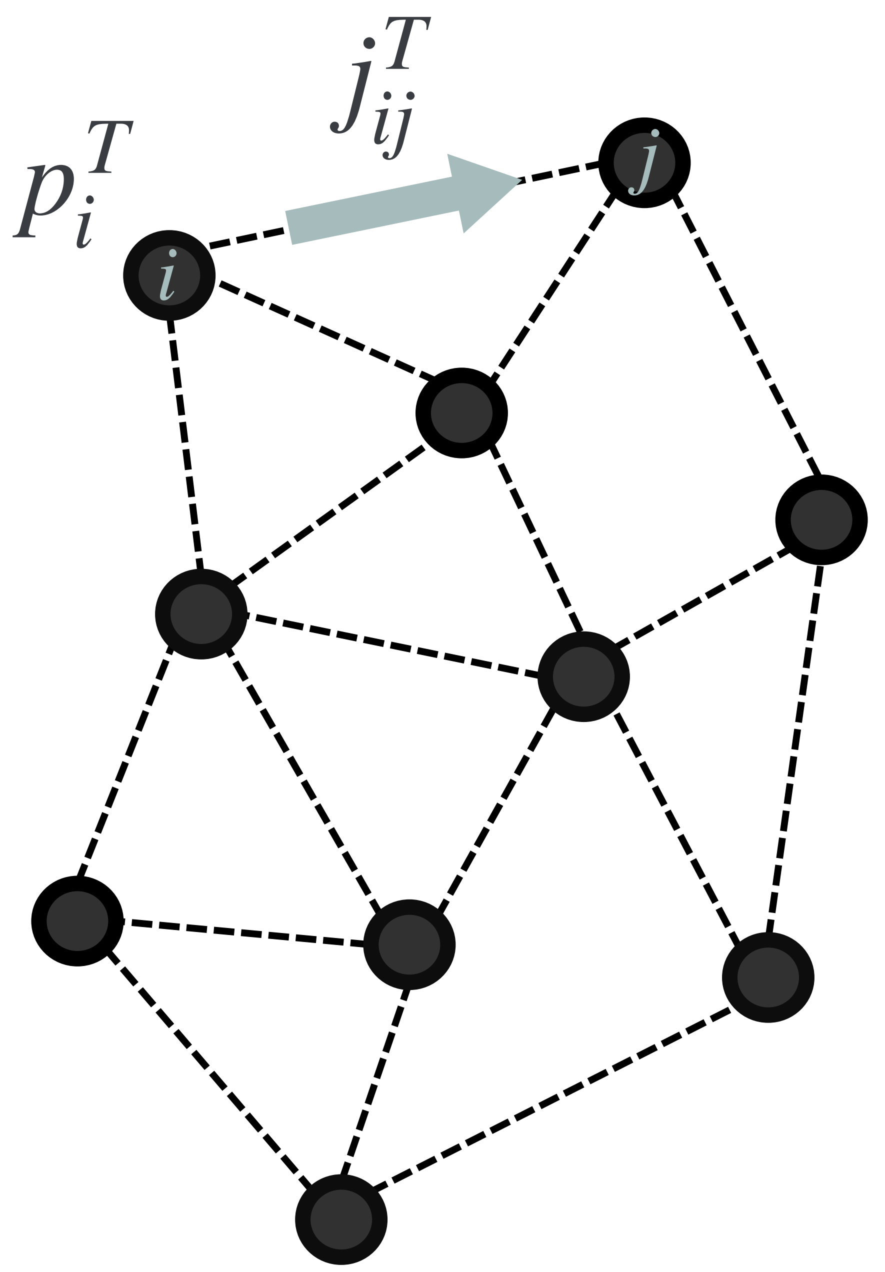


solid edges $\Longrightarrow$ *transition rates* $\sim c$

[1] Barato, A. C., & Seifert, U. (2015). Thermodynamic Uncertainty Relation for Biomolecular Processes. Physical Review Letters, 114(15), 158101.
[2] Todd R. Gingrich, Jordan M. Horowitz, Nikolay Perunov, and Jeremy L. England. (2016) Dissipation bounds all steady state current fluctuations. Phys. Rev. Lett. 116, 120601 .

Empirical density: $p_i^T = \frac{1}{T}\int_0^T dt\, \delta_{x(t),i}$

Empirical current: $j_{ij}^T = \frac{[\#\,\text{transitions}\; i \to j] - [\#\,\text{transitions}\; j \to i]}{T}$



As $T \to \infty$, p_i^T and j_{ij}^T converge to their mean values, the steady state probabilities and currents:

$$\lim_{T\to\infty} p_i^T = \pi_i \quad \text{and} \quad \lim_{T\to\infty} j_{ij}^T = j_{ij}^\pi = \pi_i Q_{ij} - \pi_j Q_{ji}$$

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

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

Large Deviation Theory for Markov Chains

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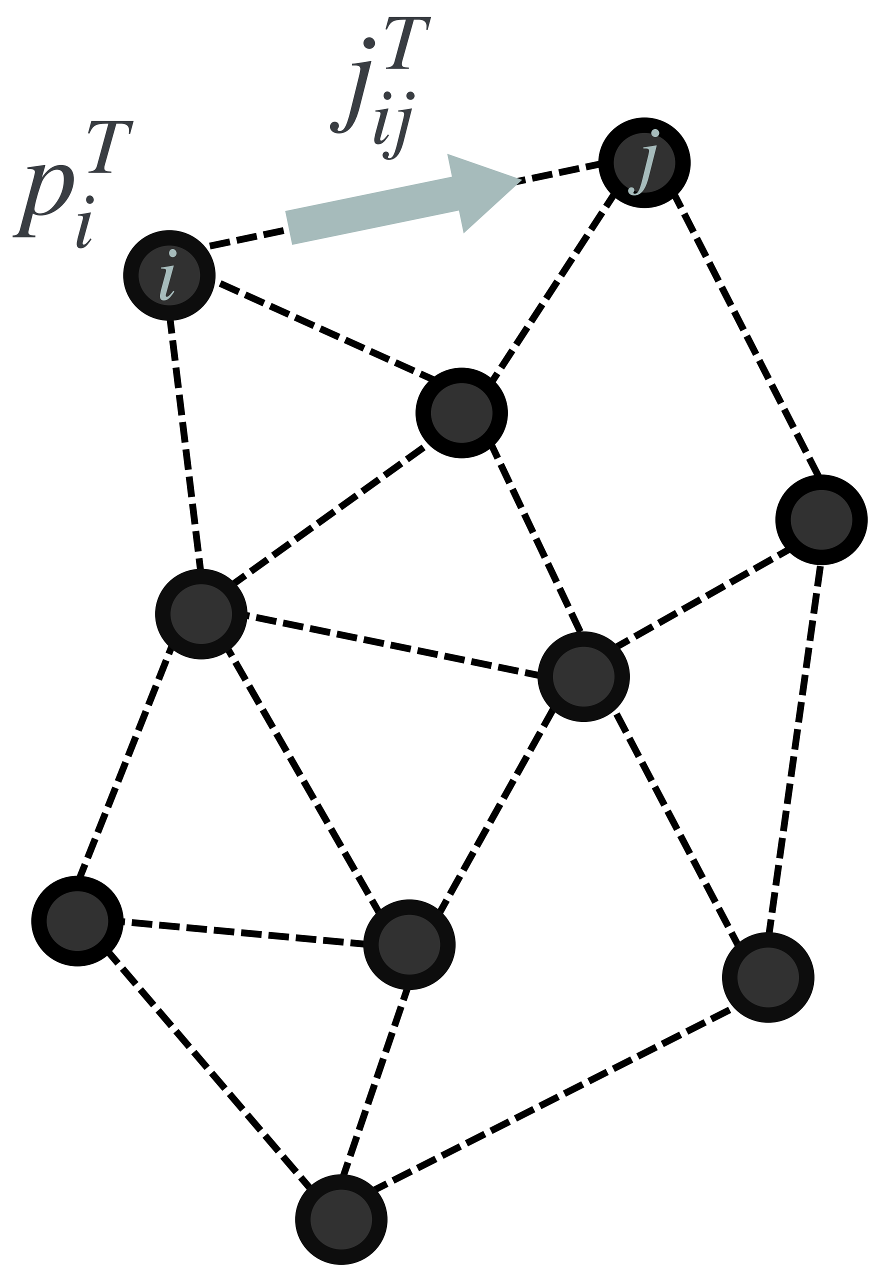

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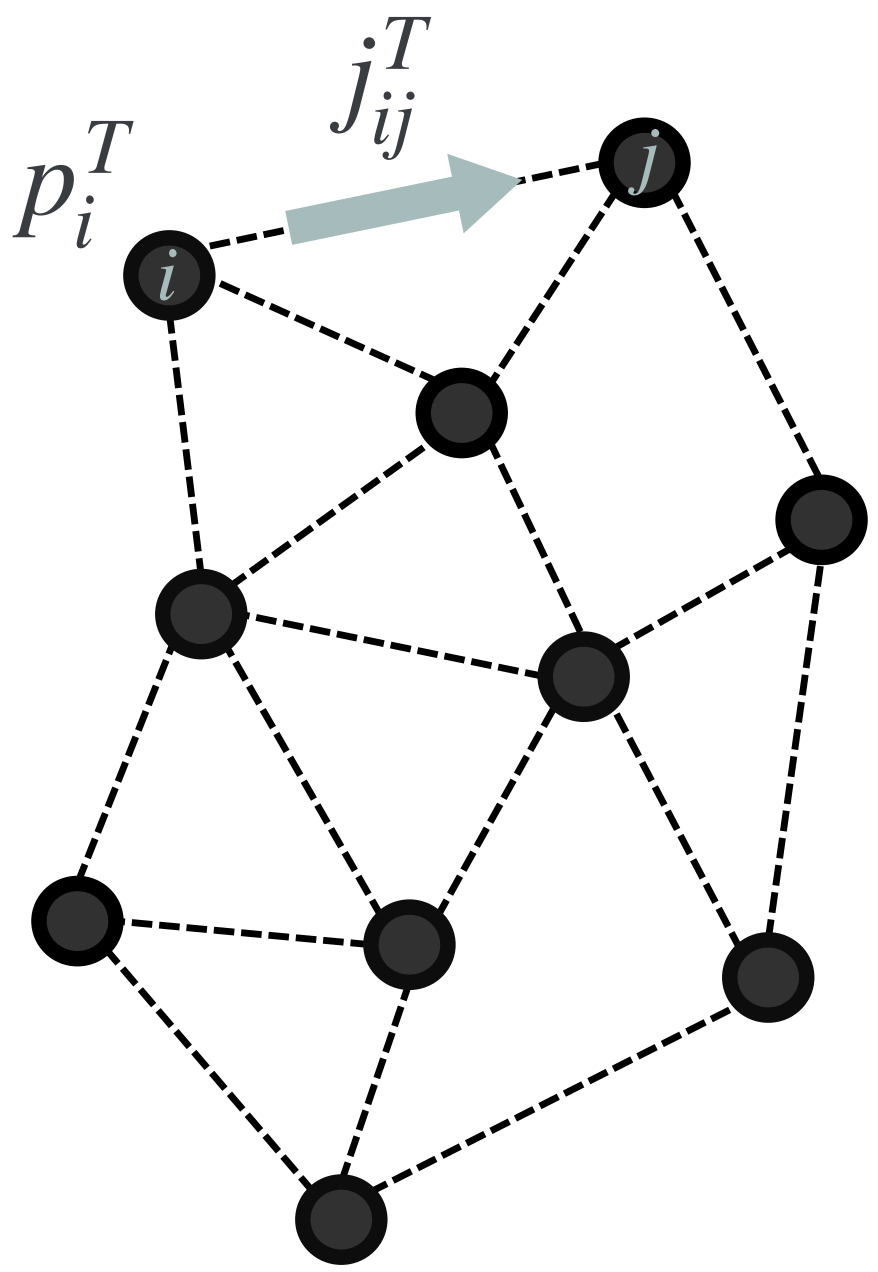
Large Deviation Theory for Markov Chains

"Level 2.5" large deviation theory:

$$I(p^T, j^T) = \sum_{i<j} \left[j_{ij}^T \left(\mathrm{arcsinh}\frac{j_{ij}^T}{a_{ij}^p} - \mathrm{arcsinh}\frac{j_{ij}^p}{a_{ij}^p}\right) - \sqrt{j_{ij}^{T\,2} + a_{ij}^{p\,2}} - \sqrt{j_{ij}^{p\,2} + a_{ij}^{p\,2}} \right].$$



See S.I. for a derivation

$$I(p^T, j^T) = \sum_{i<j} \Psi(j_{ij}^T, j_{ij}^p, a_{ij}^p)$$

$$j_{ij}^p = p_i^T Q_{ij} - p_j^T Q_{ji}$$

$$a_{ij} = 2\sqrt{p_i^T Q_{ij}\, p_j^T Q_{ji}}$$

Maes, C., & Netočný, K. (2008). Canonical structure of dynamical fluctuations in mesoscopic nonequilibrium steady states. EPL (Europhysics Letters), 82(3), 30003.
Bertini, L; Faggionato, A; Gabrielli, D. Large deviations of the empirical flow for continuous time Markov chains. Ann. Inst. H. Poincaré Probab. Statist. 51 (2015), no. 3, 867–900

Uncertainty Bound for Density in Subset of States

We want to study $I(q) = \inf_{p,j} I(p, j)$ where $q = \sum_{i \in \mathcal{S}} p_i,\ \sum_i p_i = 1$, $\sum_j j_{ij} = 0\ \forall i$

and $\mathrm{var}(q) = \dfrac{1}{T I''(q^\pi)}$

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

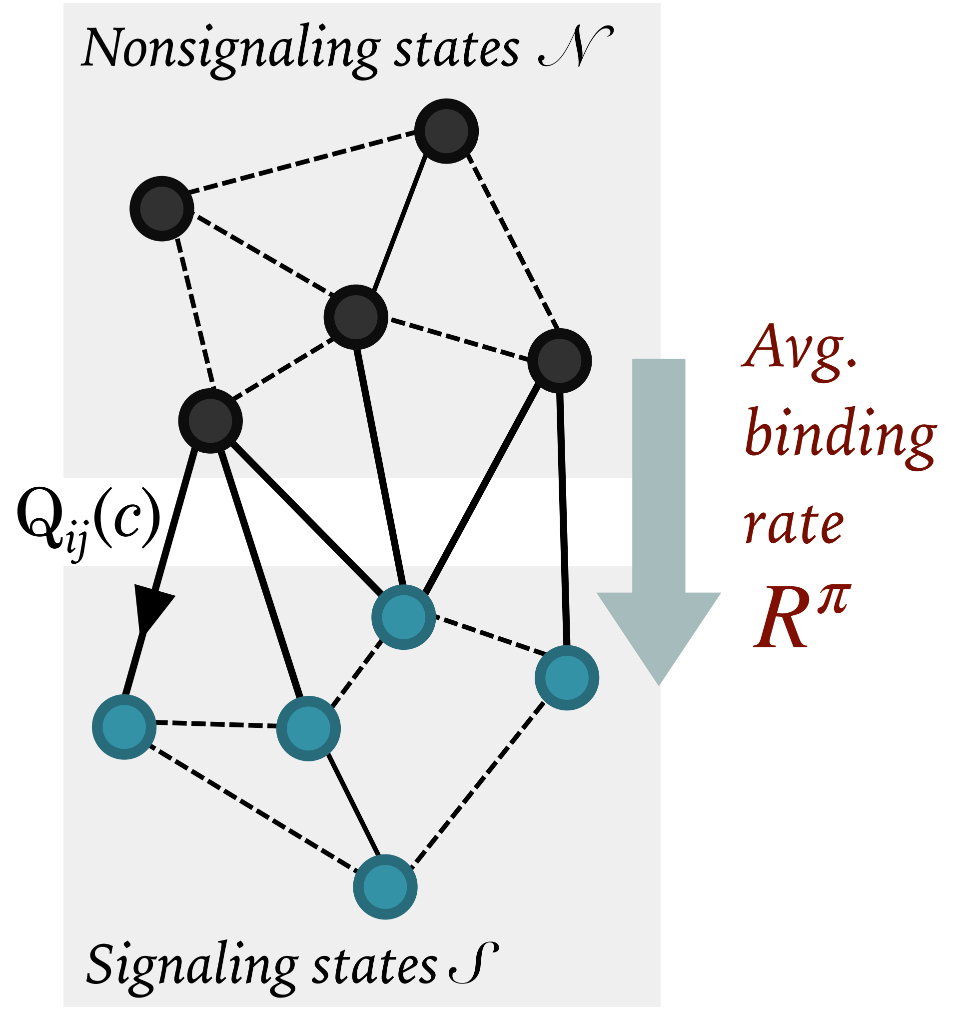
We find:

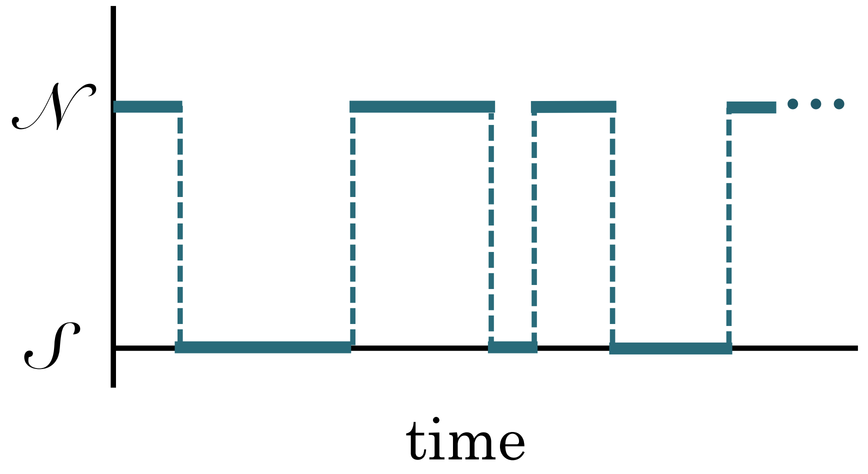
$$I''(q^\pi) \leq \frac{\Sigma^\pi + 4R^\pi}{8[q^\pi(1-q^\pi)]^2}.$$

which implies

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

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





$$q = \frac{1}{T}\sum_{i=1}^{N} \tau^i_{\mathcal{S}}$$

empirical density in signaling states

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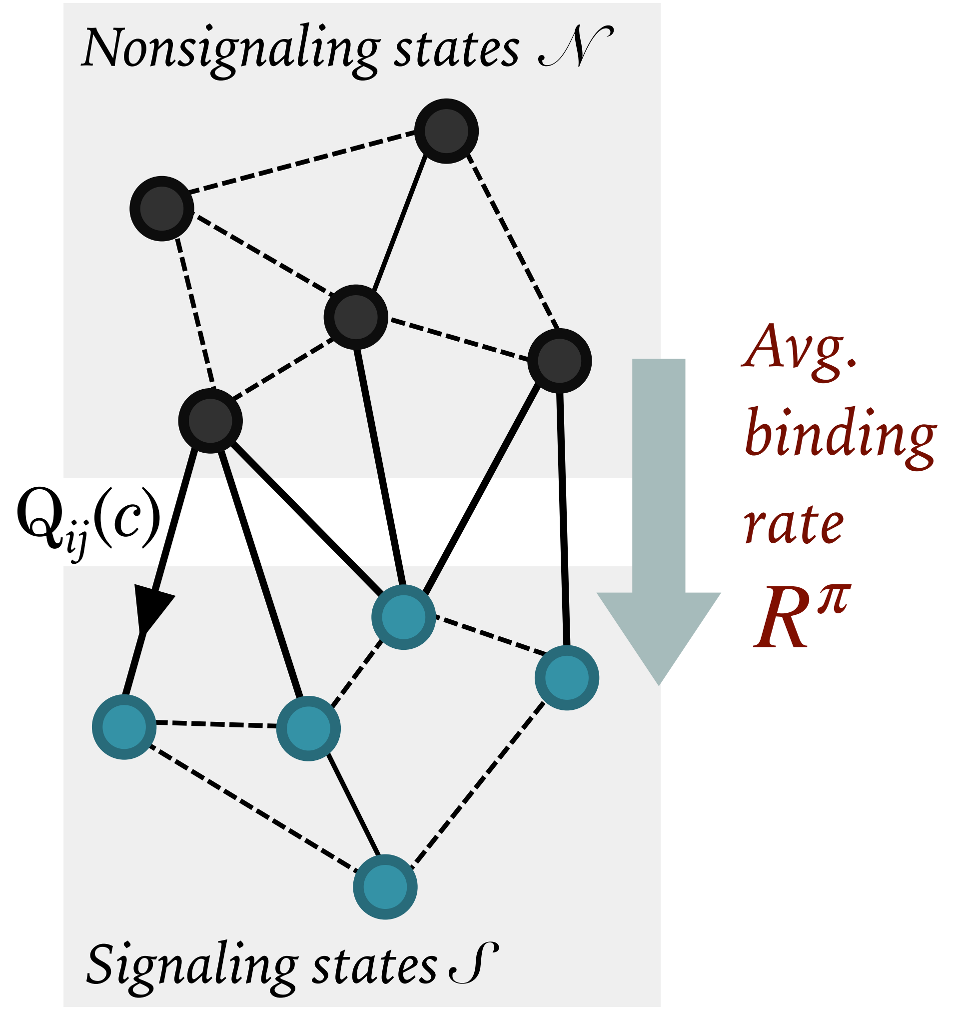

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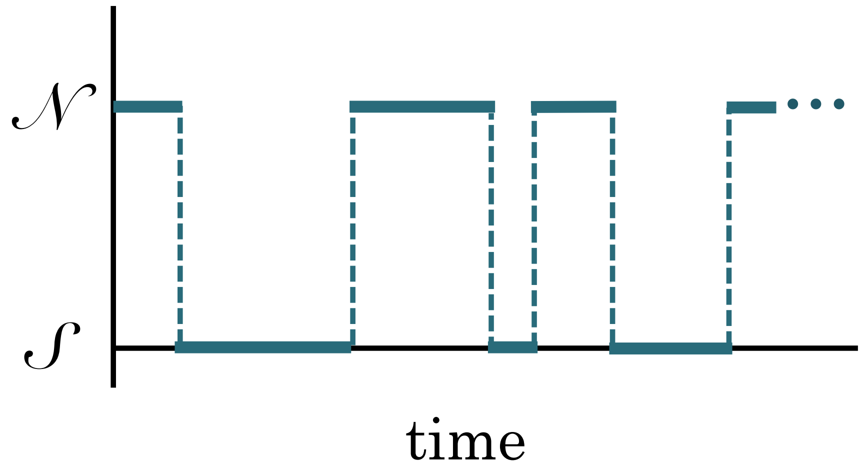

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empirical density in signaling states

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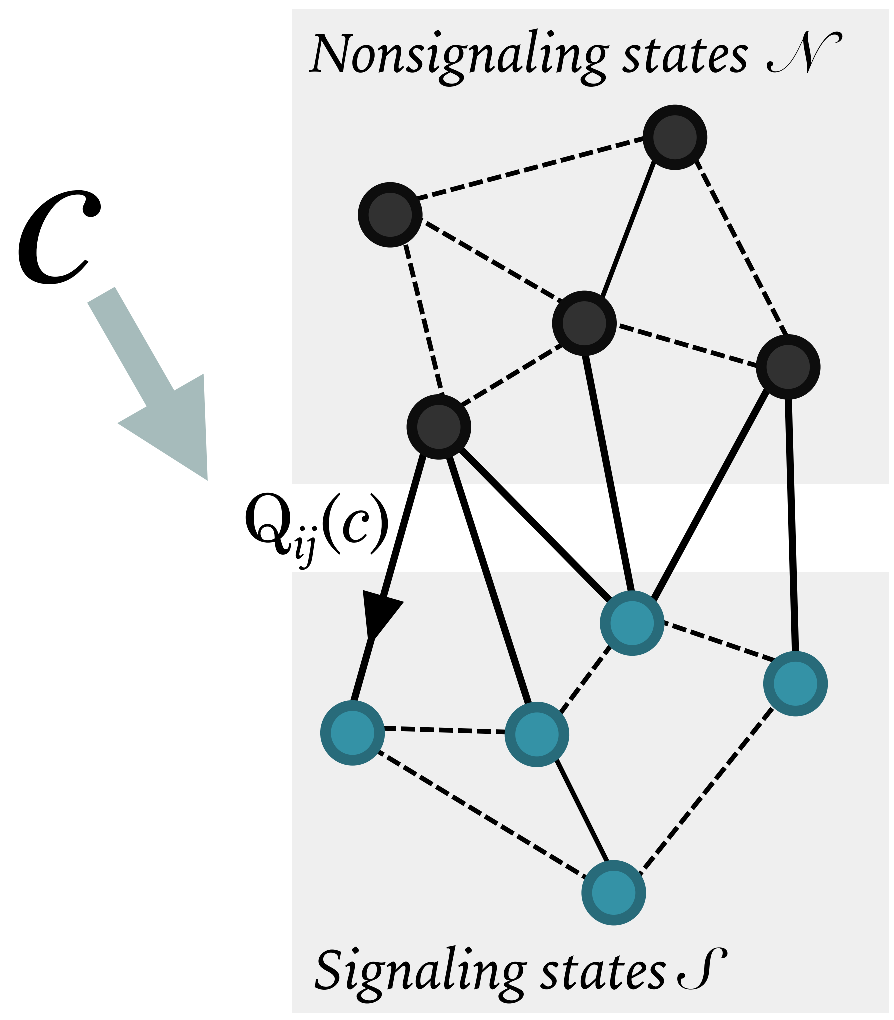
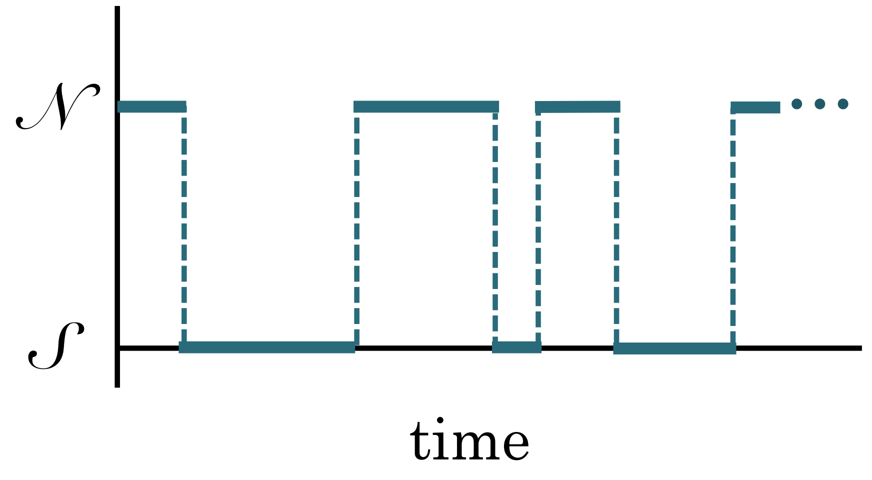
Relationship With Concentration Estimate

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

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

$$\frac{\mathrm{var}(\hat{c})}{c^2} = \left[c\frac{dq^\pi}{dc}\right]^{-2}\mathrm{var}(q)$$





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

empirical density in signaling states

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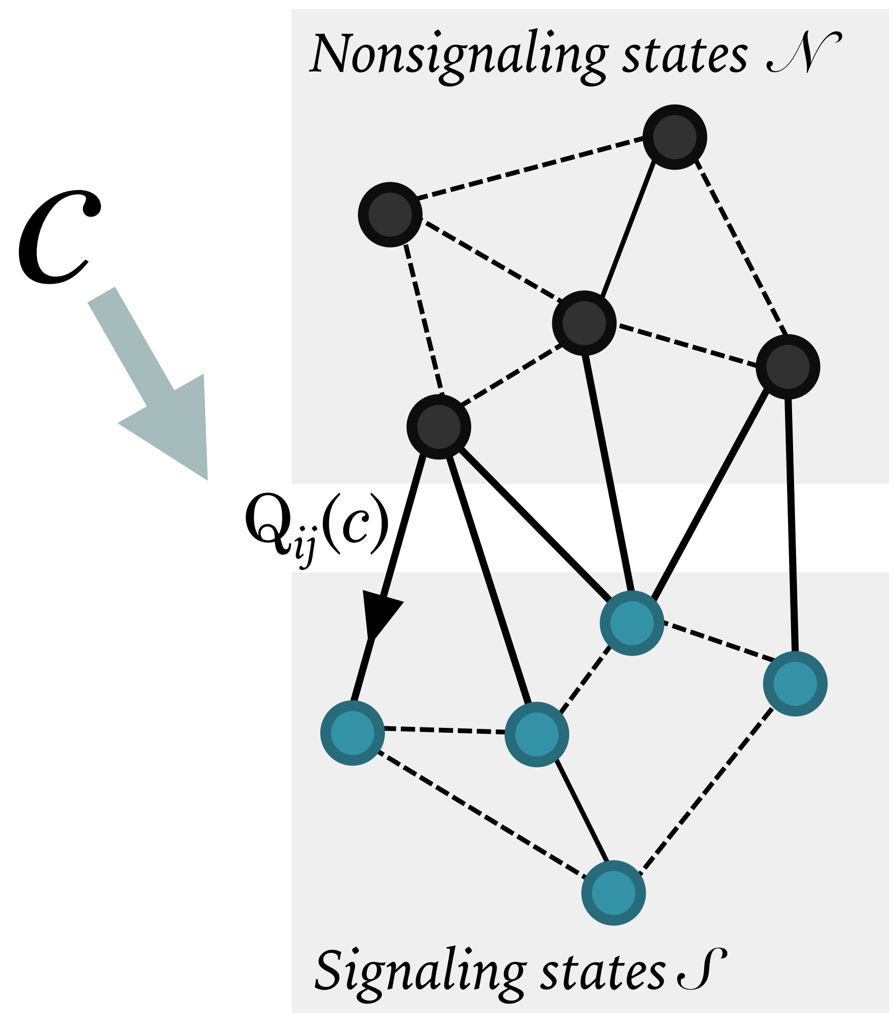
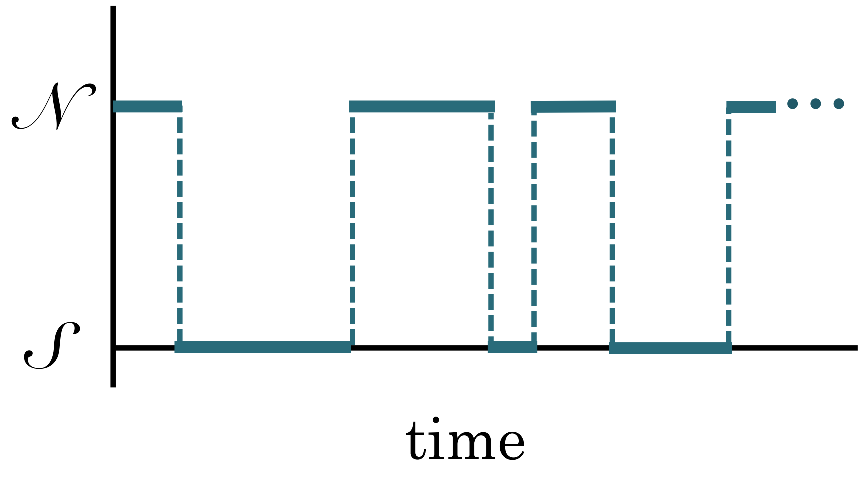
what is this?





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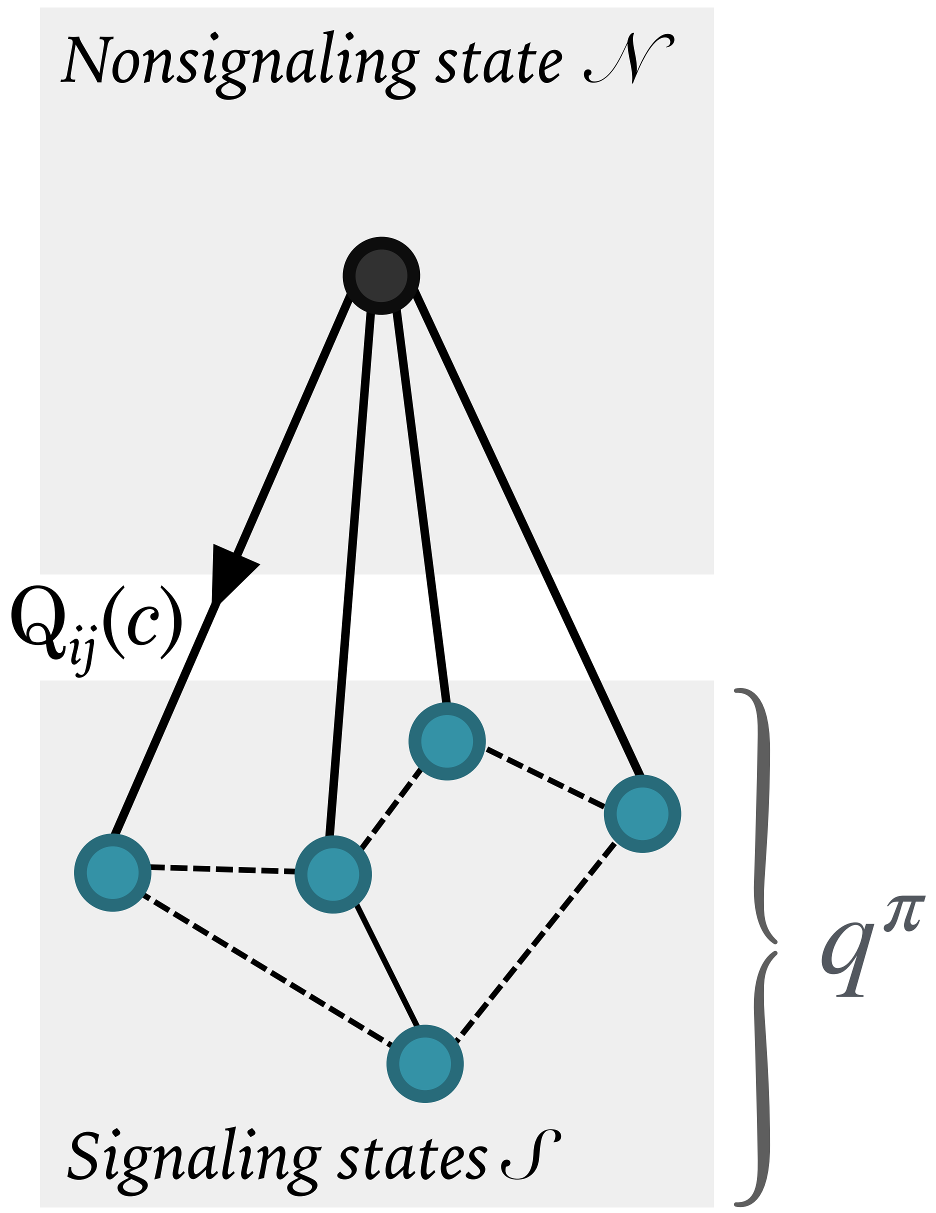
empirical density in signaling states

Relationship With Concentration Estimate

- As transition rates $Q_{ij}(c)$ are varied with c, steady state dist. π changes, determines $q^{\pi}(c) = \sum_{i \in \mathcal{S}} \pi_i(c)$



- What is $\dfrac{dq^{\pi}}{dc}$?

mean first passage times

use $$\frac{d\pi_k}{dc} = \sum_{i \neq k} \pi_i \frac{dQ_{ij}}{dc} (\overline{T}_{ik} - \overline{T}_{jk}) \pi_k$$ [1, 2]

- For networks with only one non-signaling state (c.f. Lang et. al., Berg Purcell), the Jacobian takes a simple form:

$$c \frac{dq^{\pi}}{dc} = q^{\pi}(1 - q^{\pi}) \implies q^{\pi}(c) = \frac{1}{1 + (K_d/c)}$$

K_d : dissociation constant

[1] G. Cho and C. Meyer, “Markov chain sensitivity measured by mean first passage times,” Linear Algebra Appl. 316 (2000)no. 1-3, 21–28
[2] Lahiri, S., & Ganguli, S. (n.d.). A memory frontier for complex synapses: Supplementary material.

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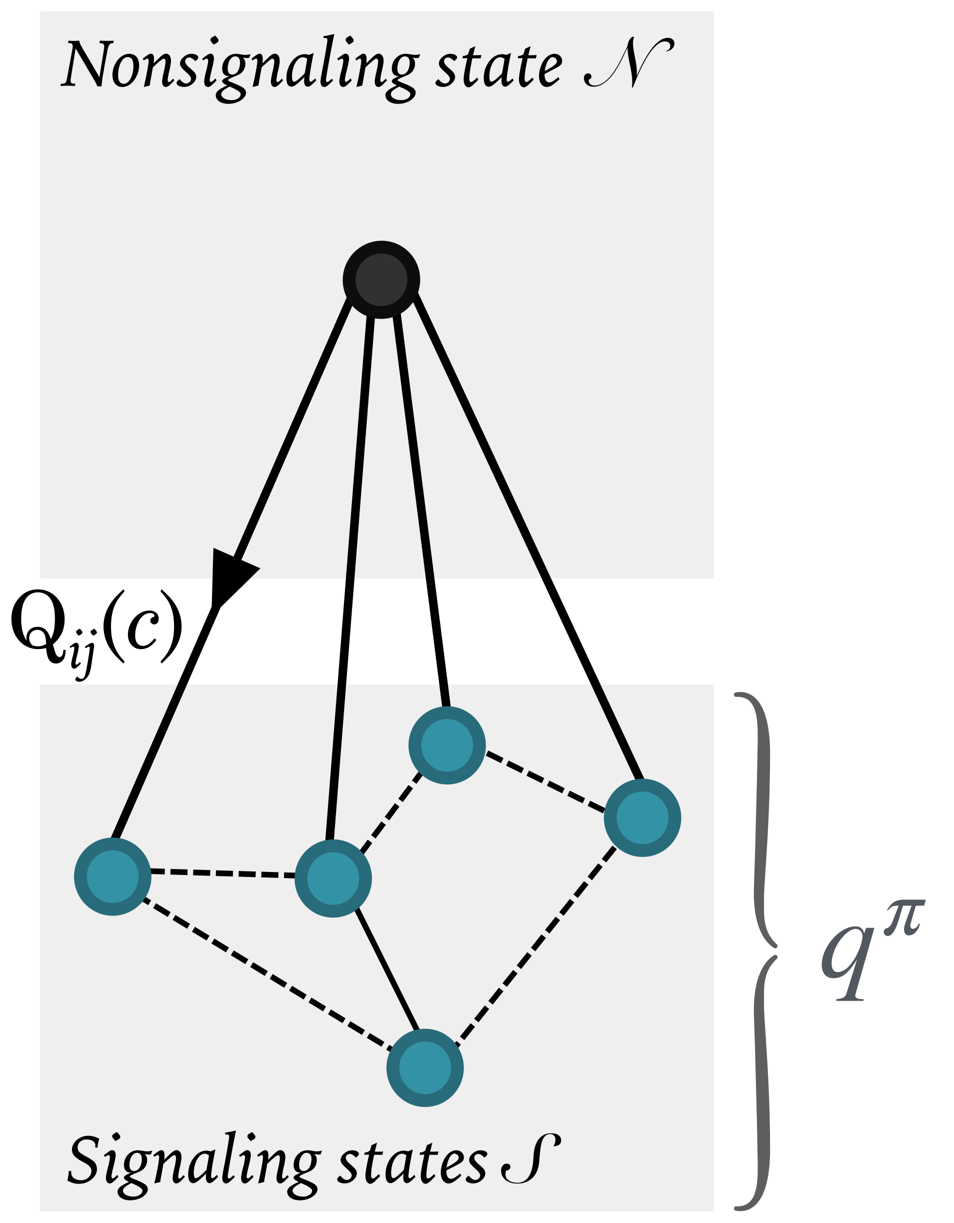

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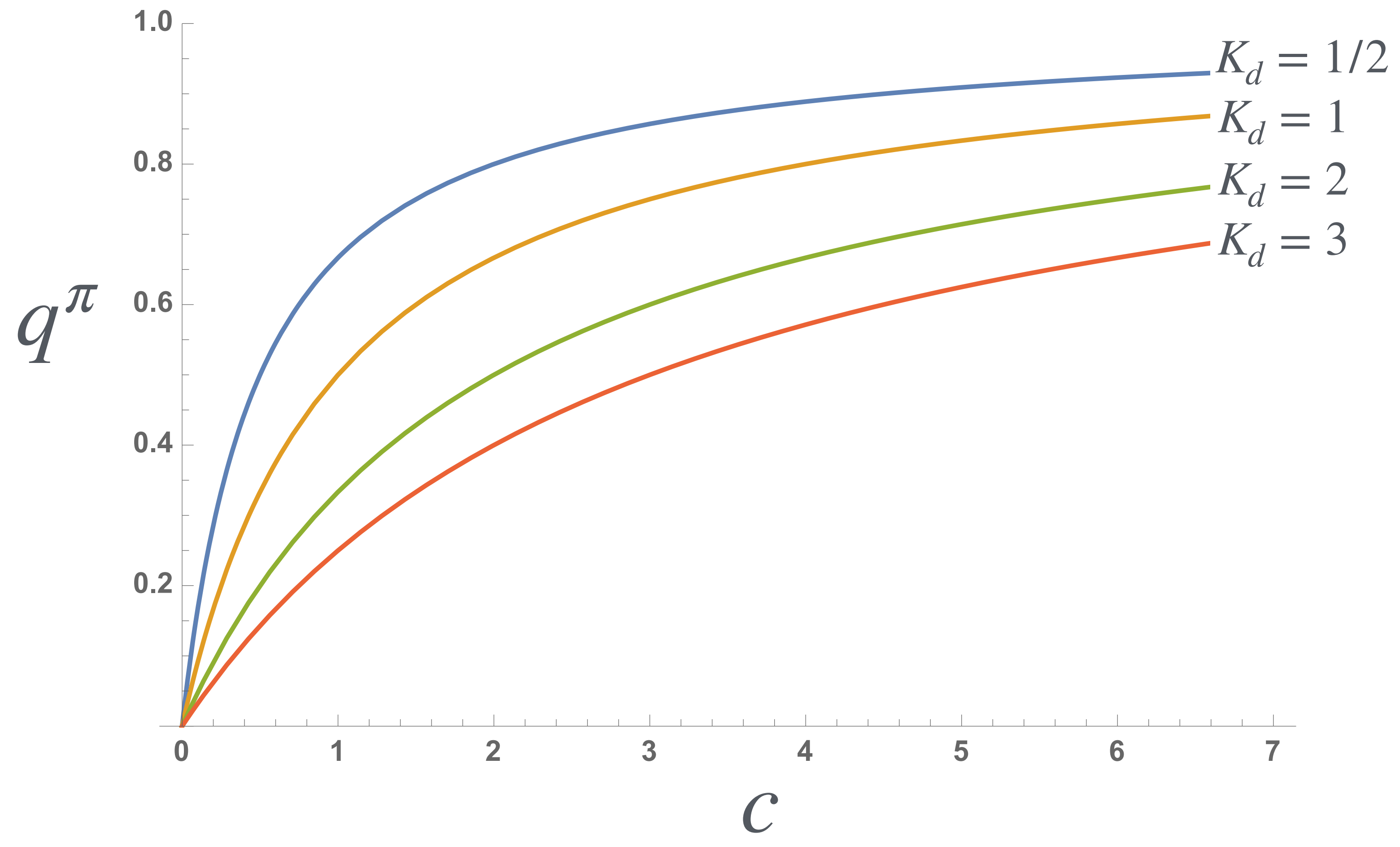

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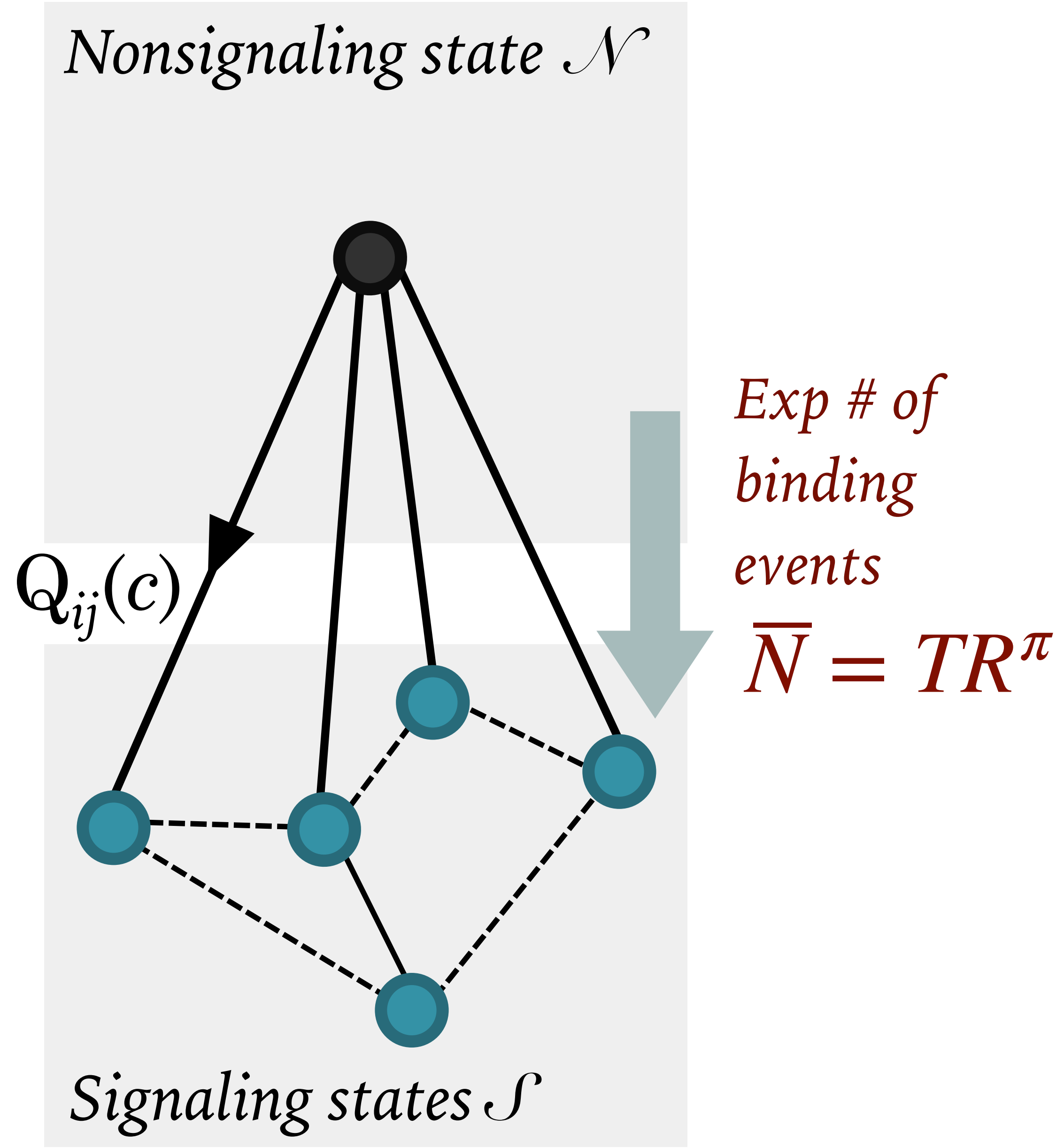
Bound for the Concentration Estimate

➤ Using this Jacobian, we can convert the variance of density q to the variance of the signal c estimate

$$c\frac{dq^\pi}{dc} = q^\pi(1-q^\pi) \qquad \frac{\mathrm{var}(\hat{c})}{c^2} = \left[c\frac{dq^\pi}{dc}\right]^{-2}\mathrm{var}(q) \qquad \mathrm{var}(q) \geq \frac{8\left[q^\pi(1-q^\pi)\right]^2}{T\left[\Sigma^\pi + 4R^\pi\right]}.$$

→ bound on the signal estimation in terms of the **total entropy production** and the **number of binding events**



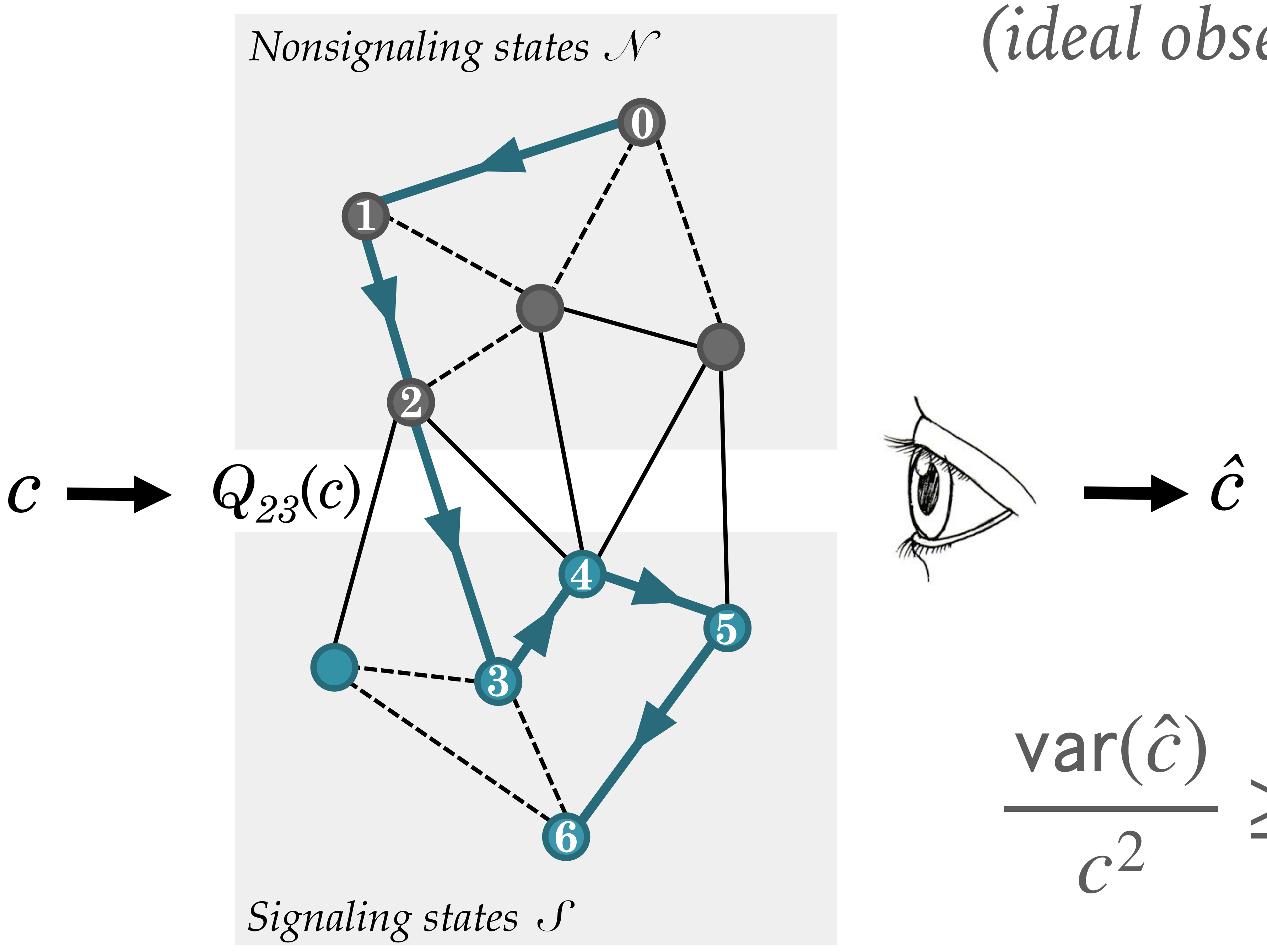
$$\boxed{\frac{\mathrm{var}(\hat{c})}{c^2} \geq \frac{8}{T\Sigma^\pi + 4\overline{N}}}$$

agrees with Berg-Purcell $\epsilon_{\hat{c}}^2 \geq \frac{2}{\overline{N}}$ when $\Sigma^\pi = 0$ (detailed balance)

Recap

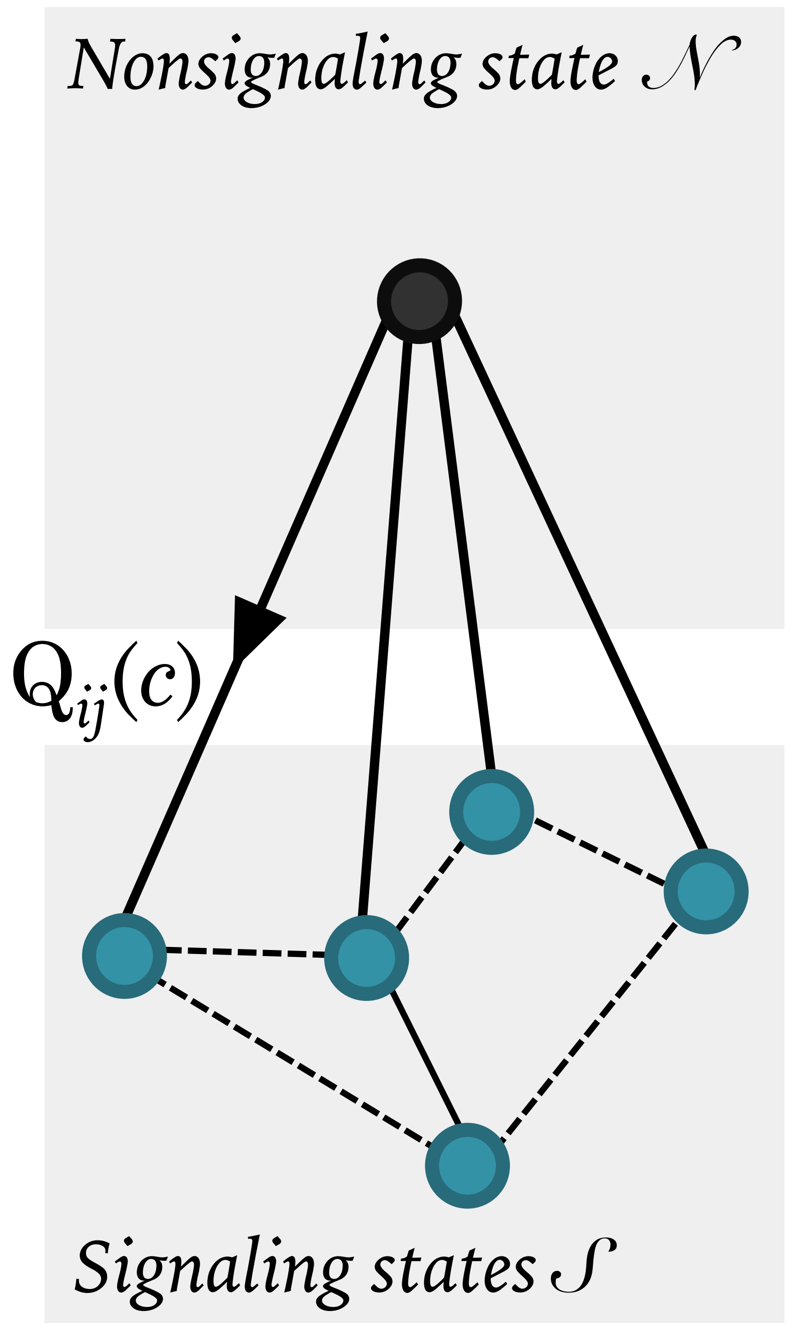
- We derived two theoretical bounds on the uncertainty of a sensor modeled as a continuous-time Markov process, **in different limits** of what is **observable** about the process

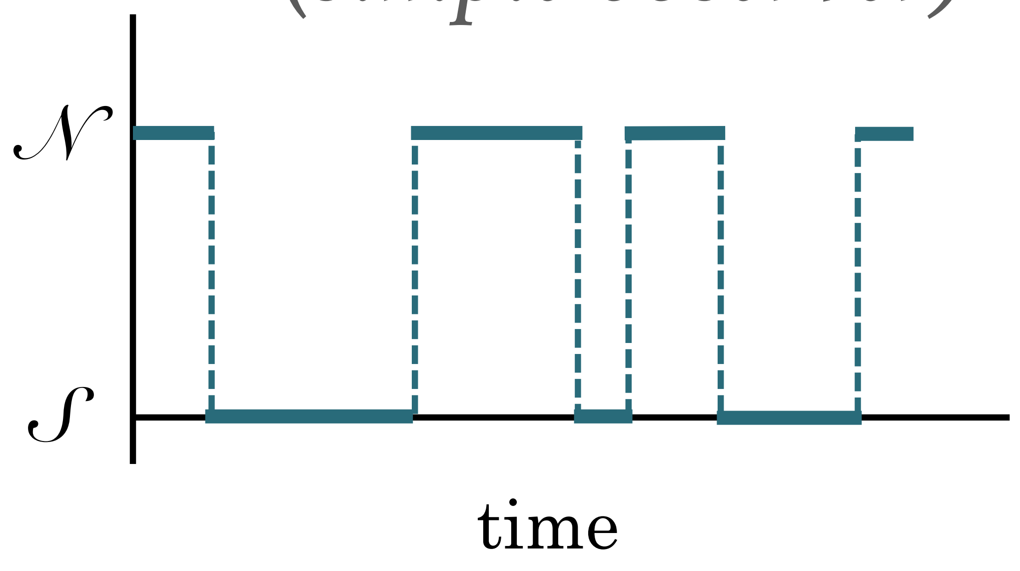
Cramèr-Rao bound
(ideal observer)



$$\frac{\mathrm{var}(\hat{c})}{c^2} \geq \frac{1}{\overline{N}}$$

Coarse-grained bound
(simple observer)





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

Other Helpful Results

- We can find an exact expression for the coarse-grained observer uncertainty by solving the contraction $I(p, j) \to I(q)$ to leading order in $(q - q^\pi)$

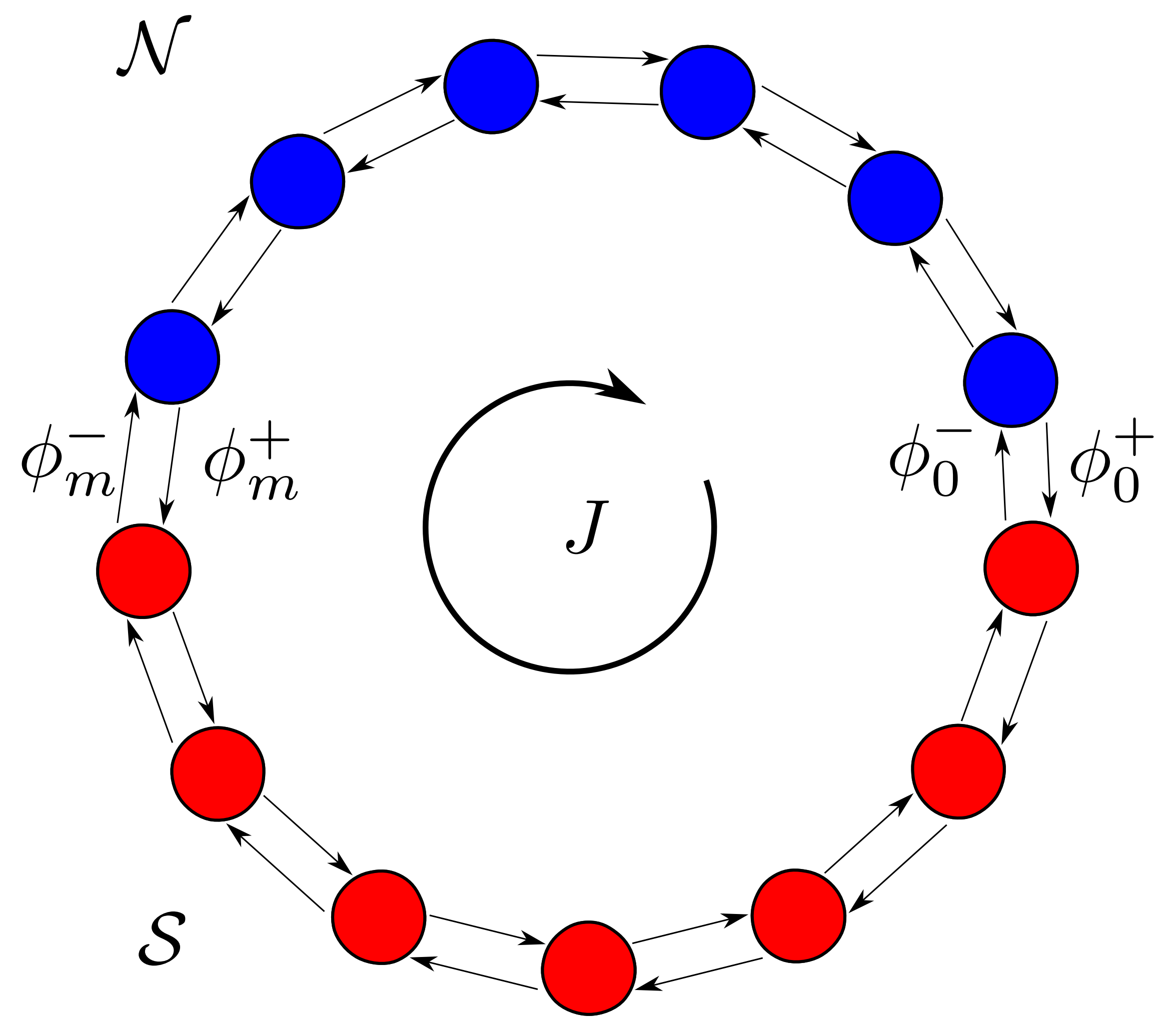
For any $\mathcal{N}$ or $\mathcal{S}$ states:

$$\epsilon_{\hat{c}}^2 = \frac{\text{var}(\hat{c})}{c^2} = \frac{2}{\overline{N}} \frac{R^\pi\left[\sum_{ijk} \pi_i^{\mathcal{N}} \pi_j^{\mathcal{S}} \pi_k^{\mathcal{S}} (\overline{T}_{ik} - \overline{T}_{jk})\right]}{\left[\sum_{ijk} \phi_{ij}^{\mathcal{N}\mathcal{S}} \pi_k^{\mathcal{S}} (\overline{T}_{ik} - \overline{T}_{jk})\right]^2}$$

Use to find optimal networks

Subhaneil Lahiri
Staff Scientist, Ganguli Lab

- Can apply this result to uniform ring networks to find an analytic expression for uncertainty as a function of energy dissipation through one cycle (see S.I.)

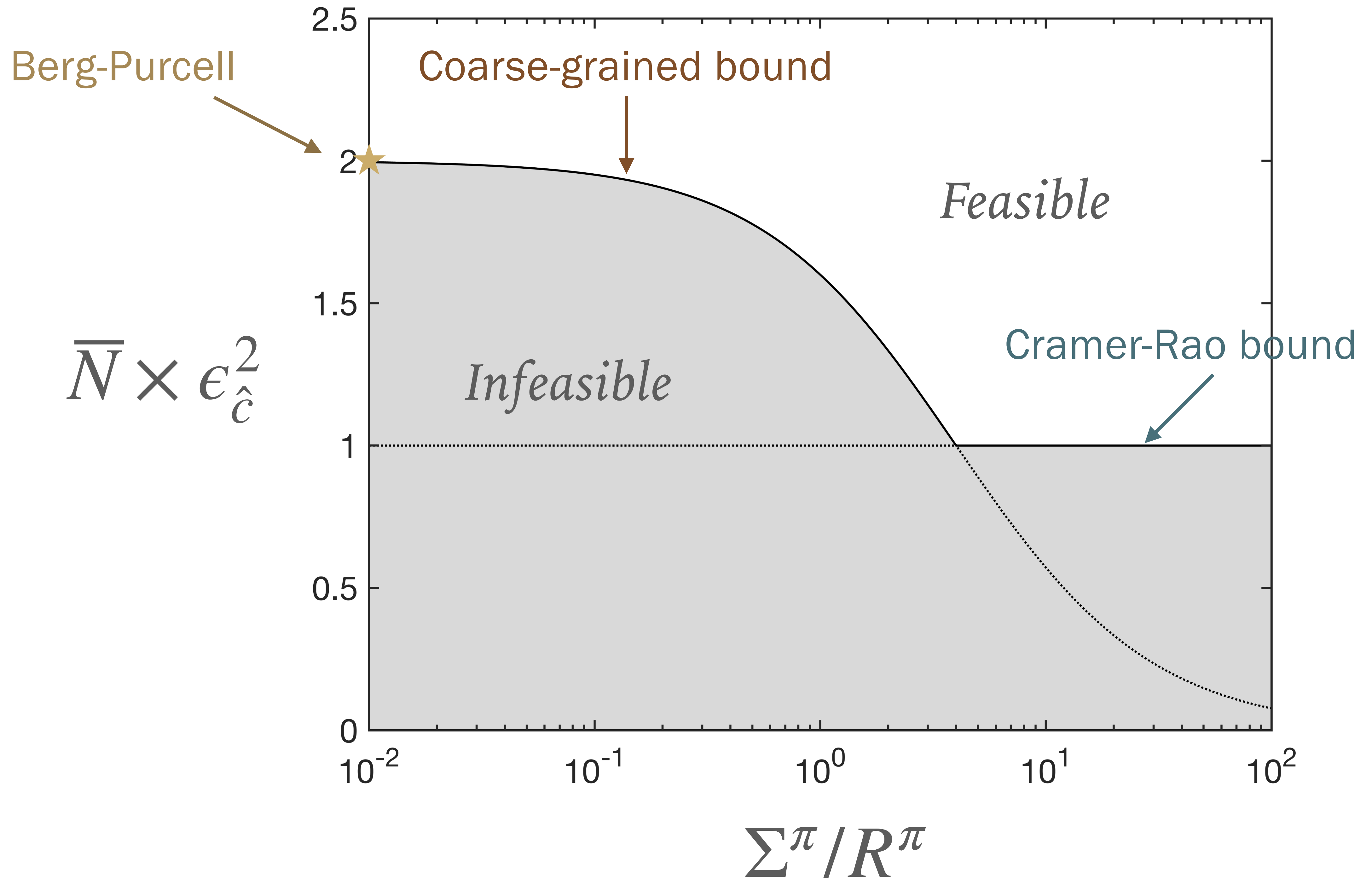


- Compare bounds with numerical studies of continuous time Markov processes
  - Direct simulation
  - Optimization

$$\overline{N} = R^{\pi} T$$

Cramer-Rao bound
"ideal observer" $\Longrightarrow \overline{N} \times \epsilon_{\hat{c}}^{2} \geq 1$

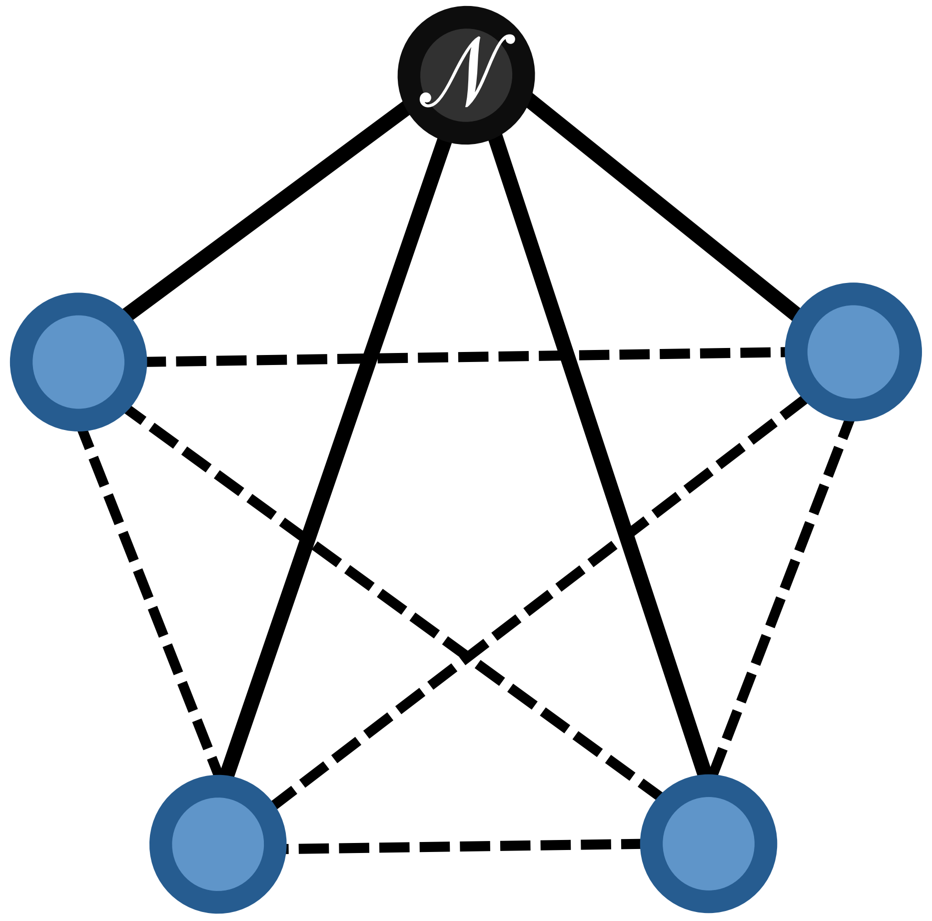
Coarse-grained bound
"simple observer" $\Longrightarrow \overline{N} \times \epsilon_{\hat{c}}^{2} \geq \dfrac{8}{\Sigma^{\pi}/R^{\pi} + 4}$

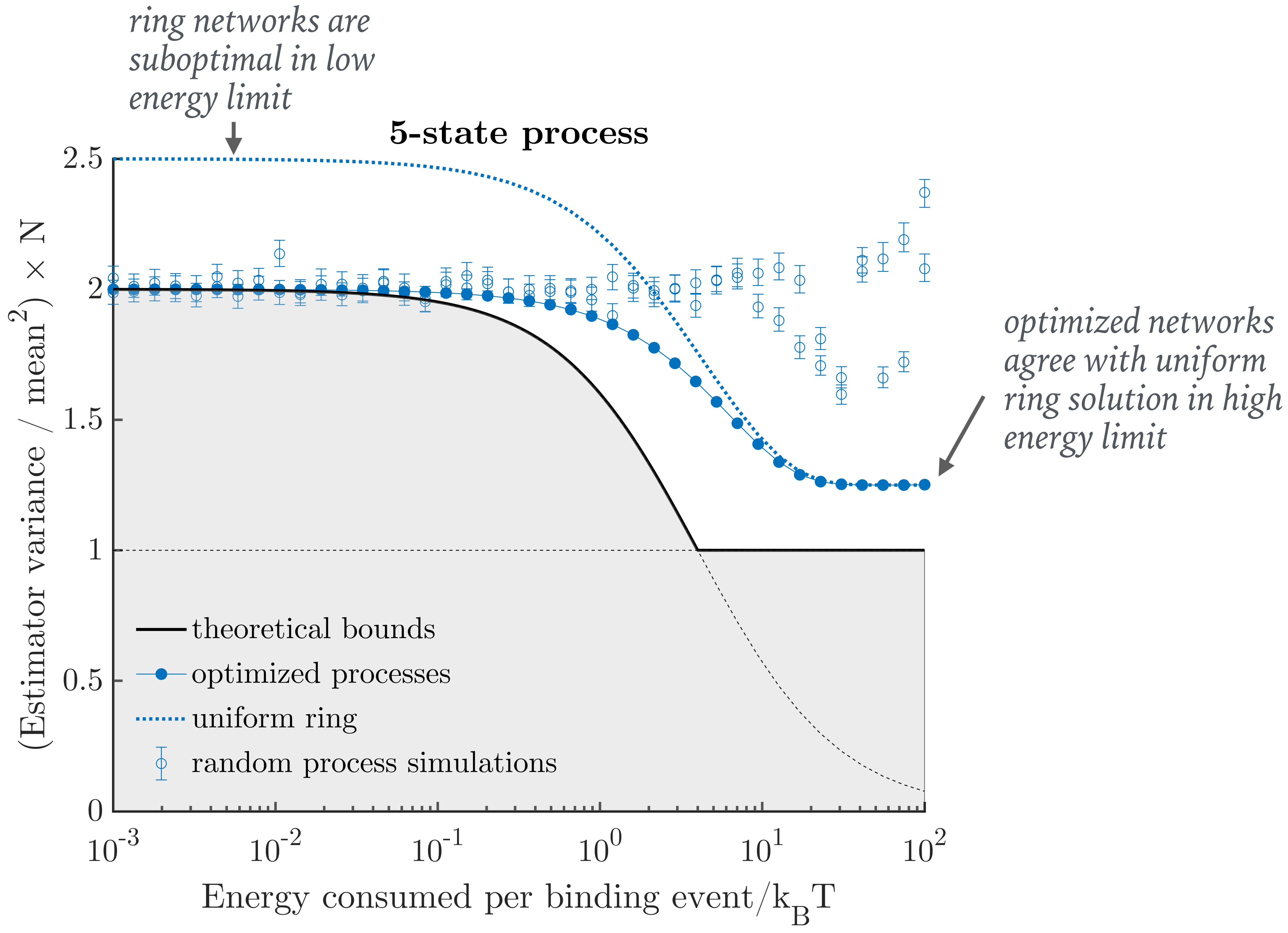


'Energy consumed per binding event'

Numerical Studies Verify Bounds

We can optimize the exact expression for ϵ_c^2 (in terms of first passage times) by varying transition rates



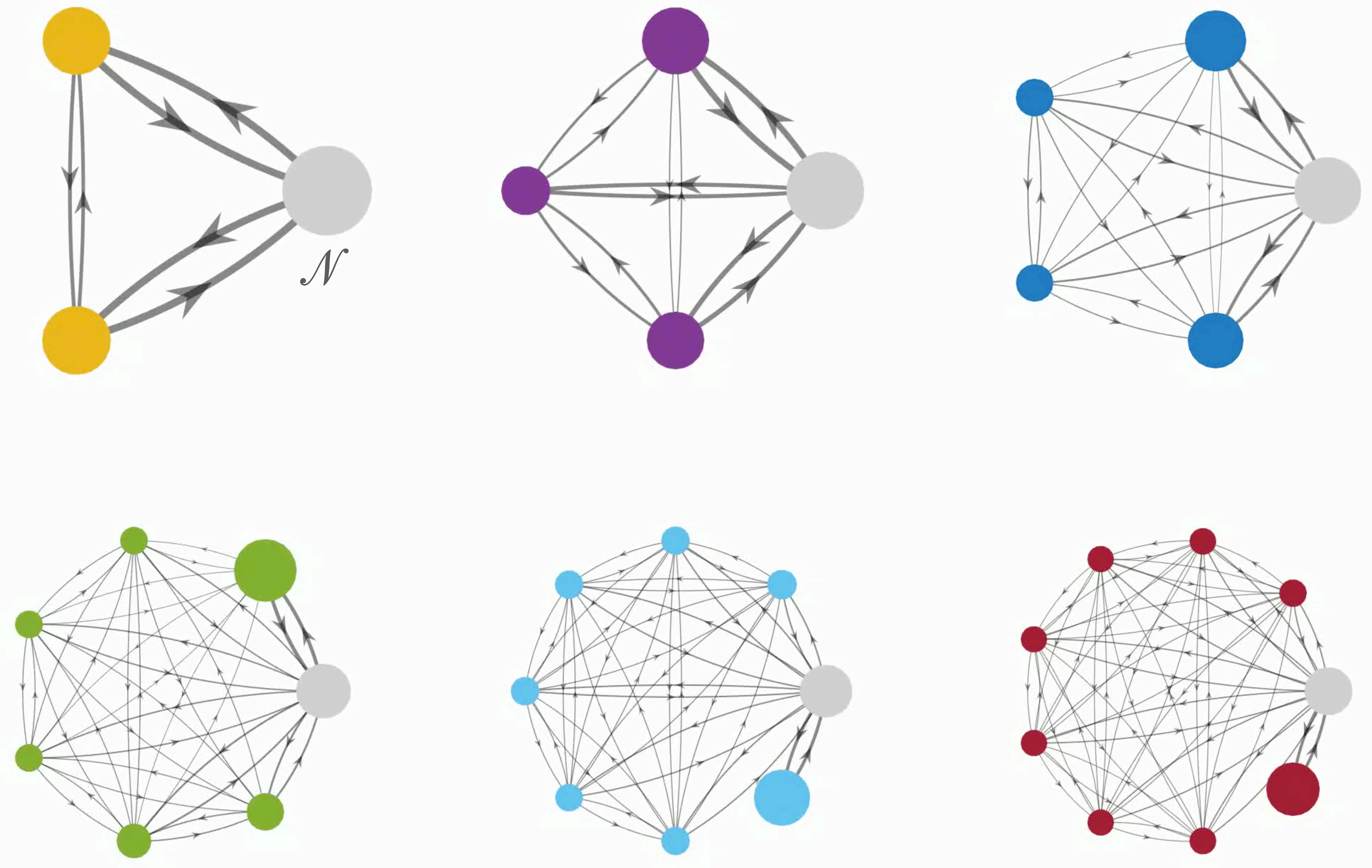


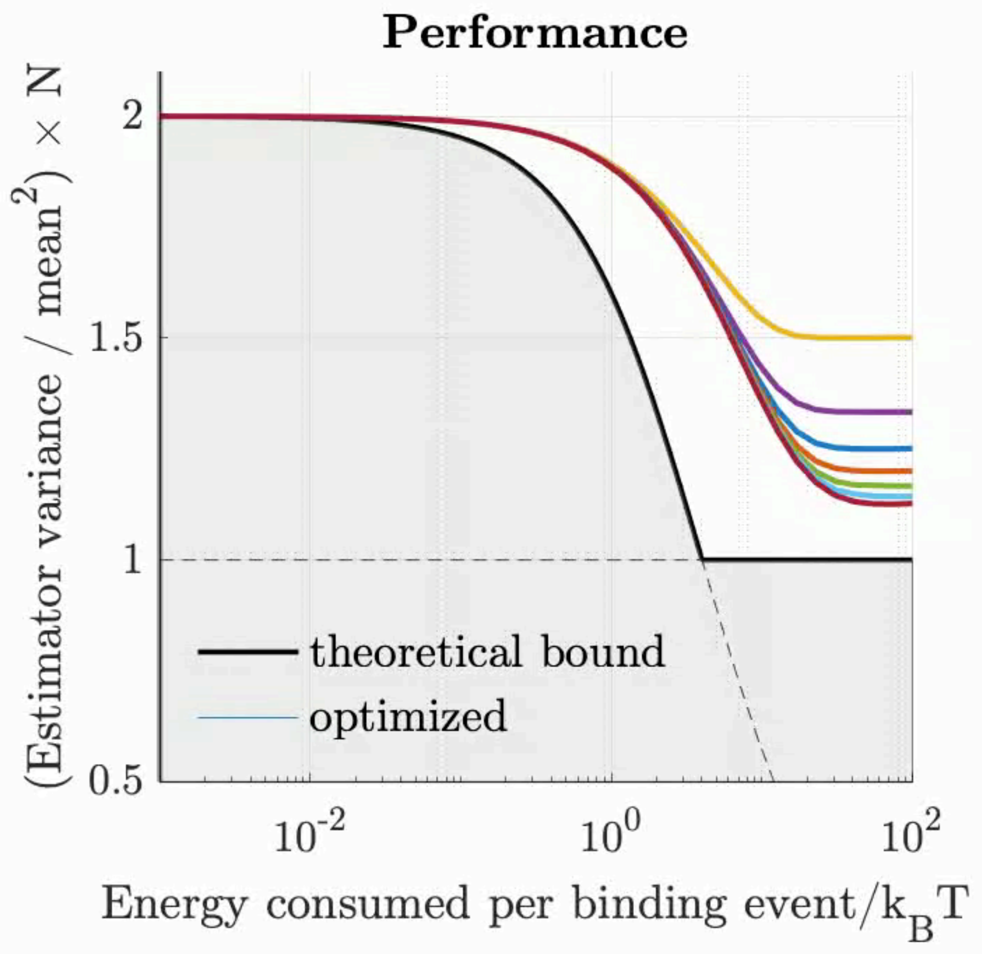
Optimized Networks as a Function of Energy/Binding

Increasing 'energy budget'

~ *flux (average transitions per time)*

~ *density*

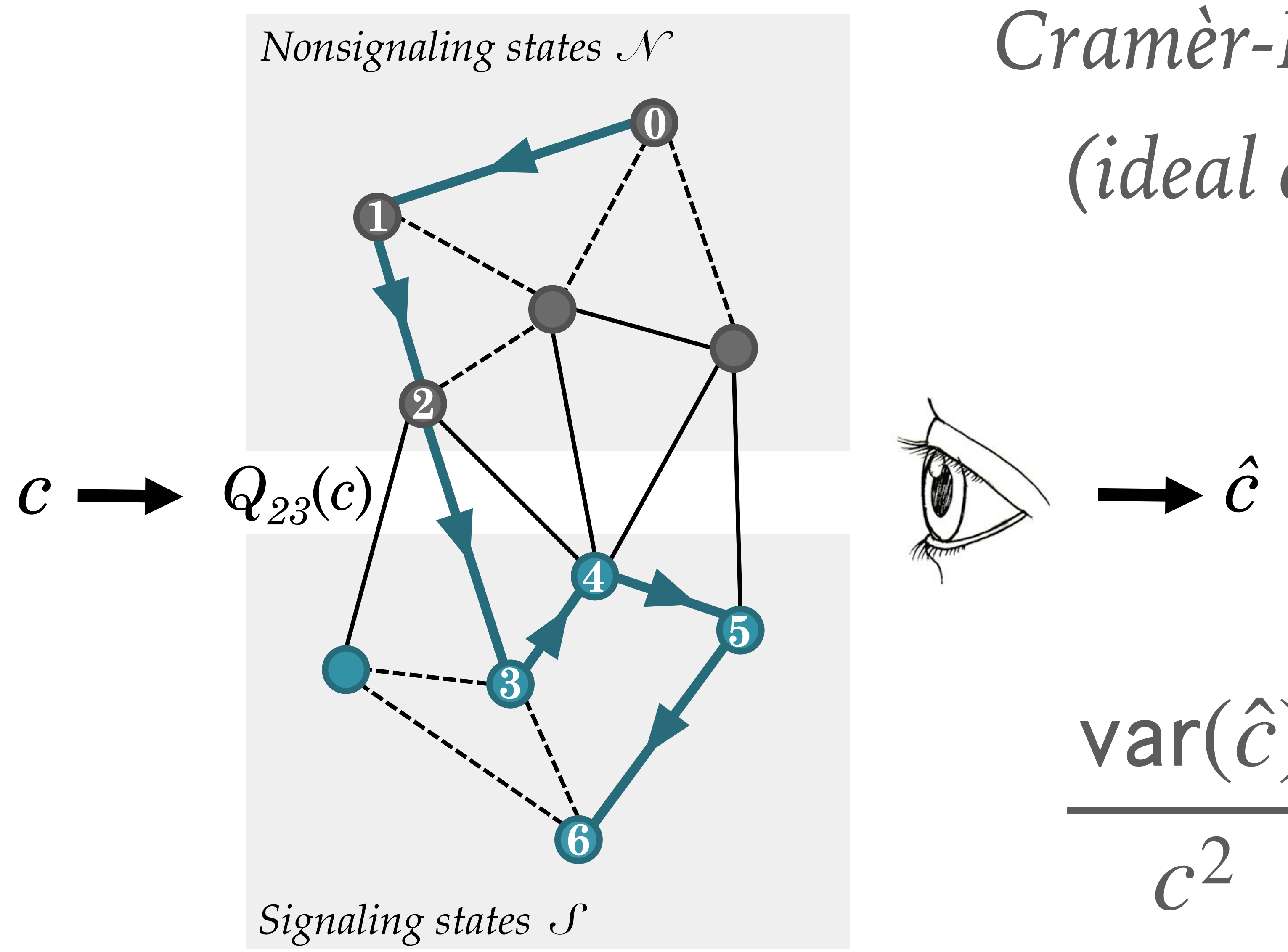




https://github.com/ganguli-lab/Energy_Accuracy_Tradeoff_Cellular_Sensing

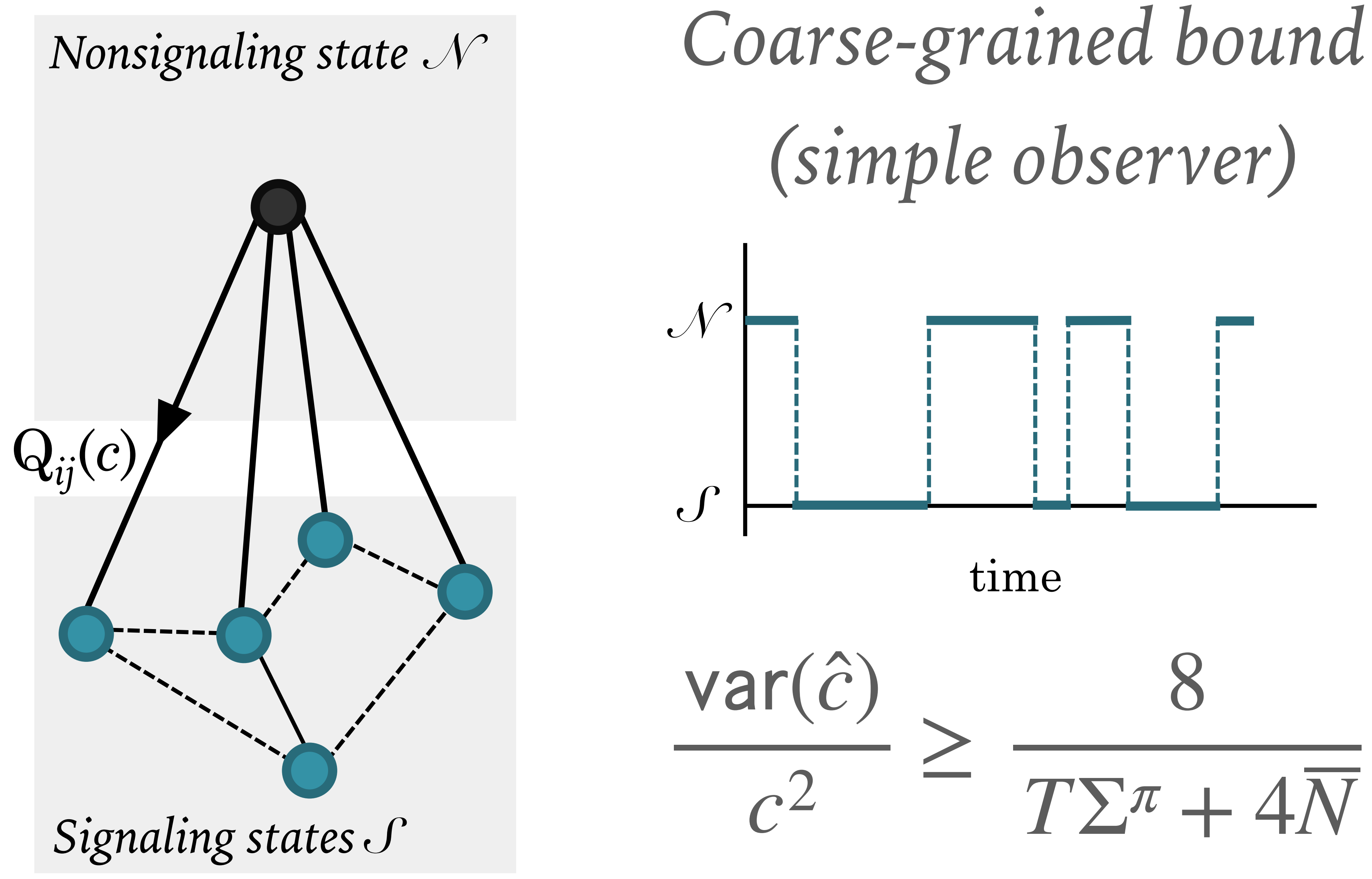
Summary

- We derived 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



Cramèr-Rao bound
(ideal observer)

$$\frac{\mathrm{var}(\hat{c})}{c^2} \geq \frac{1}{\overline{N}}$$



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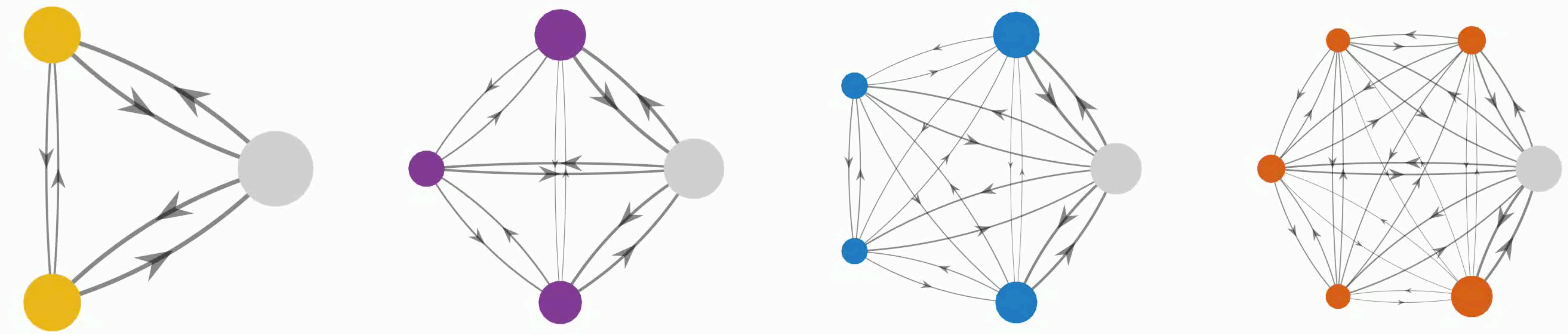
Numerical optimization



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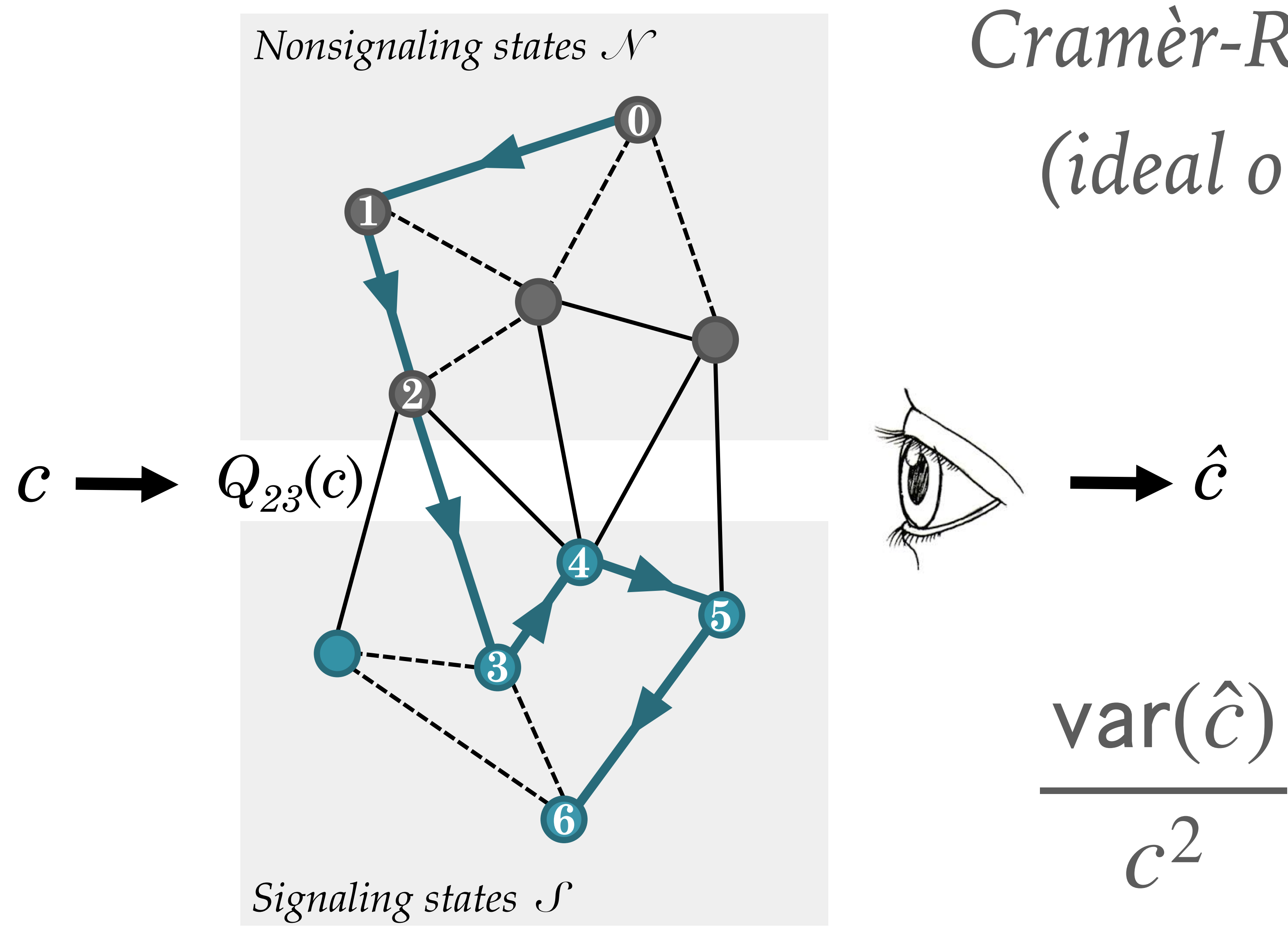

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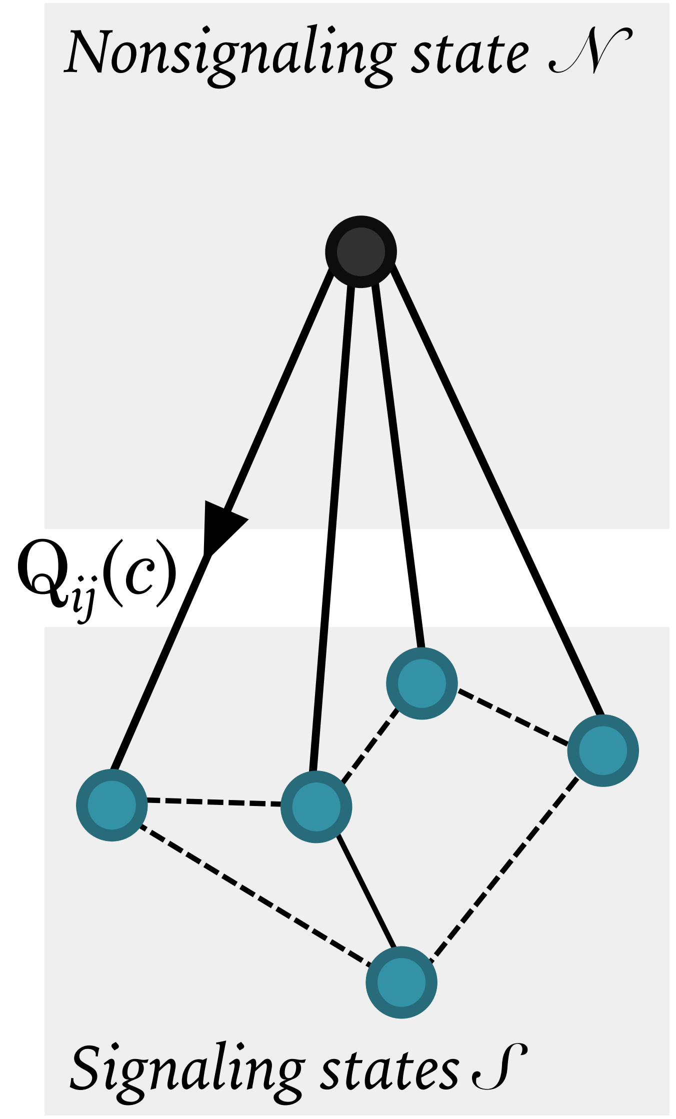
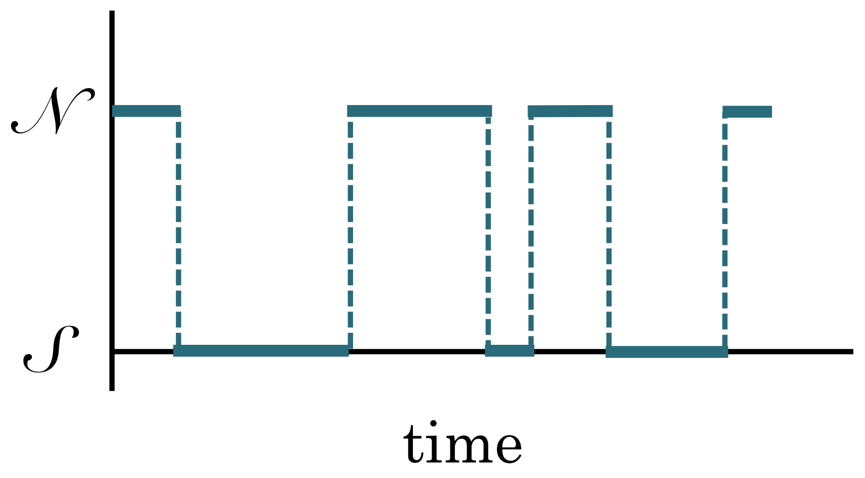
(ideal observer)

$$\frac{\mathrm{var}(\hat{c})}{c^2} \geq \frac{1}{\overline{N}}$$

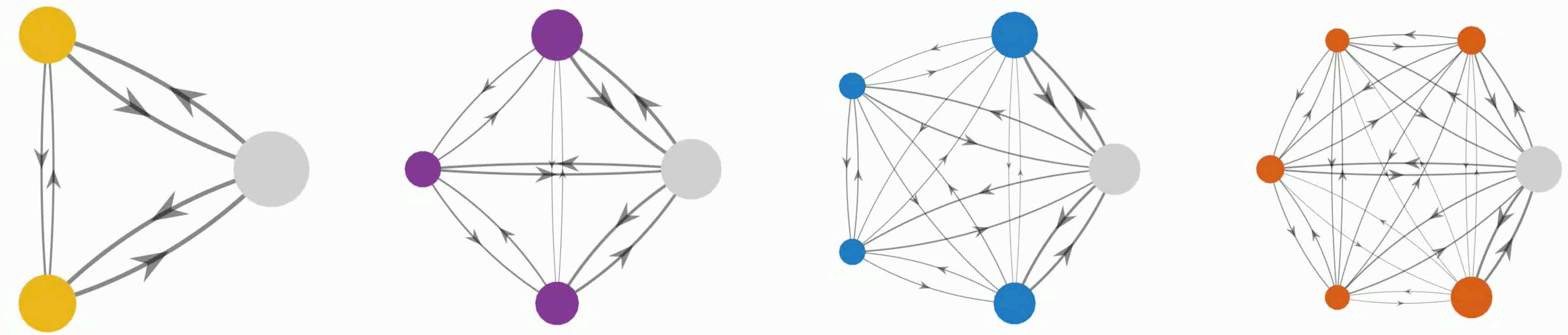


Coarse-grained bound
(simple observer)



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

Numerical optimization



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