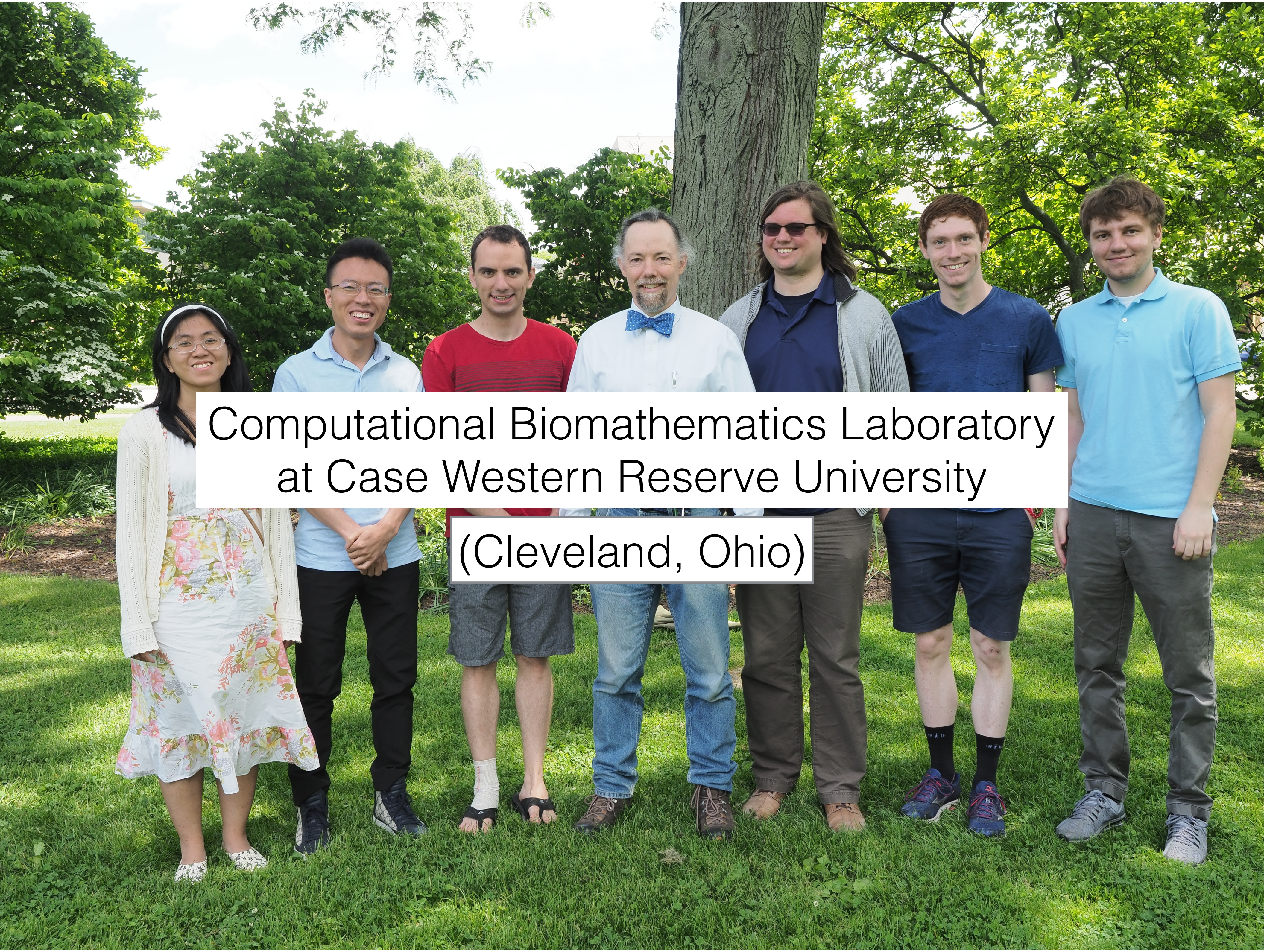
On the channel capacity of channel rhodopsin (and other biological signal transduction pathways)

Peter Thomas
Case Western Reserve University
Joint work with Andrew Eckford, York University

Don’t forget to press the record button.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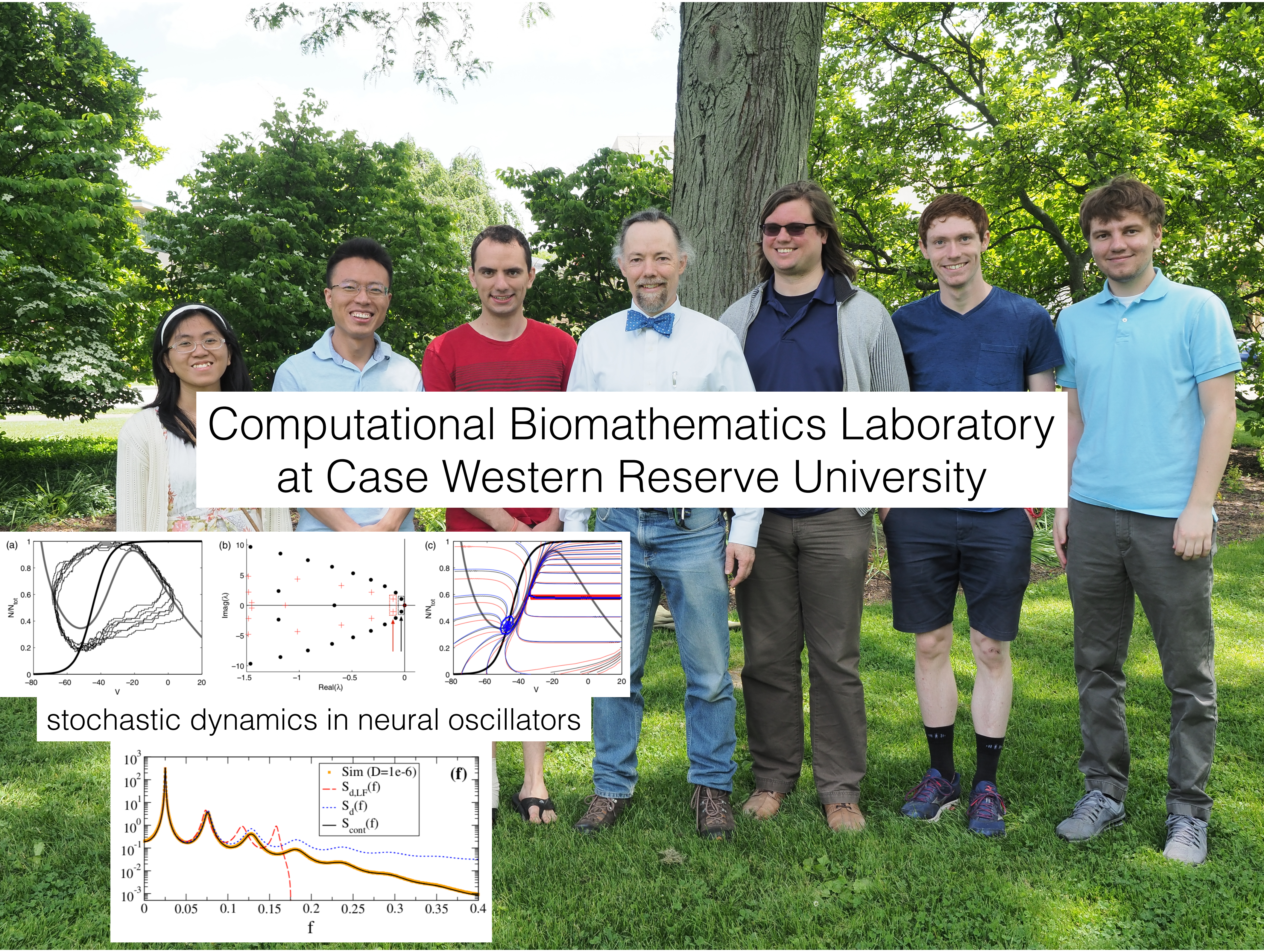
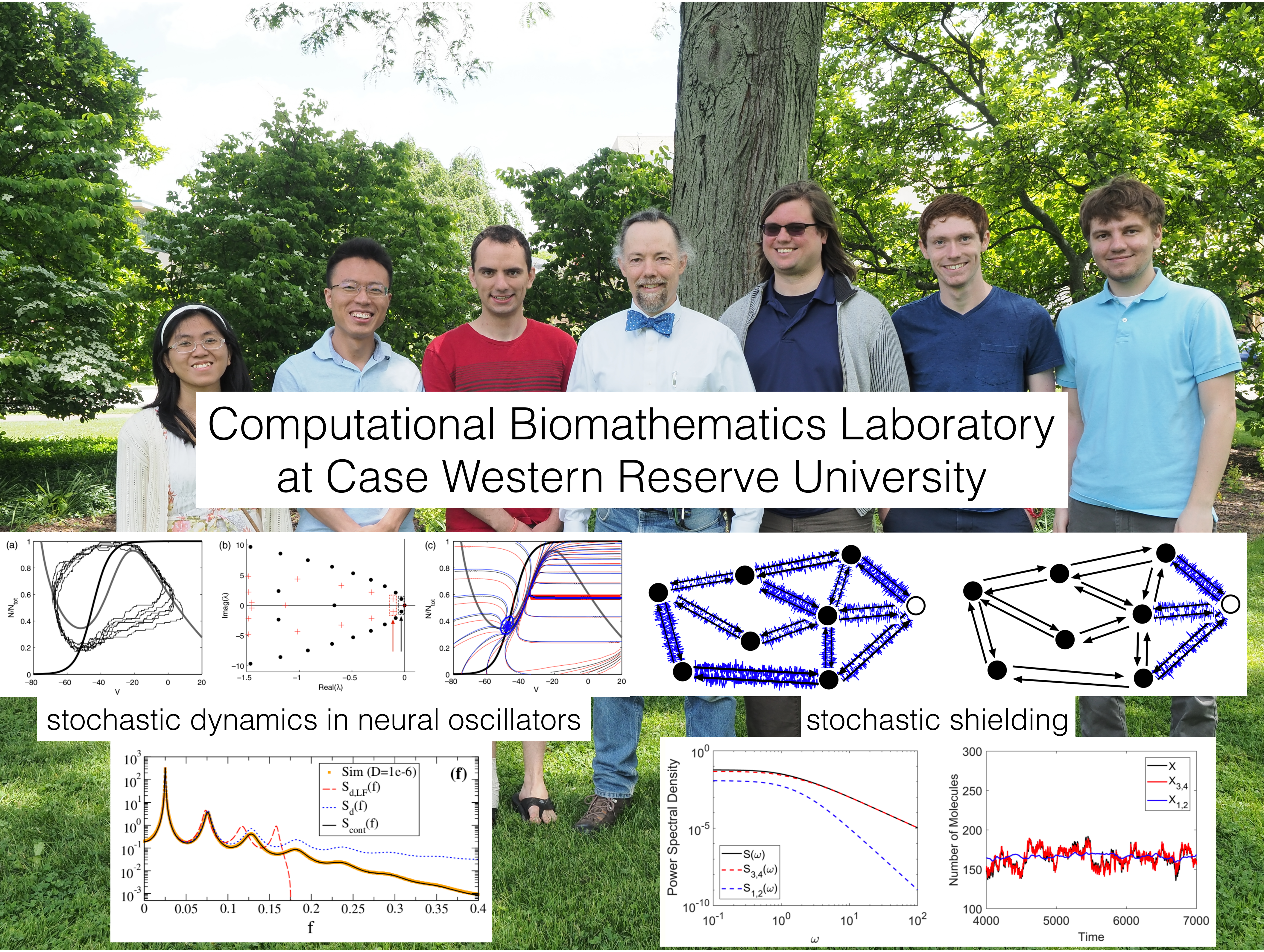

Computational Biomathematics Laboratory
at Case Western Reserve University
(a)
N/Ntot
V
(b)
Imag(λ)
Real(λ)
(c)
N/Ntot
V
stochastic dynamics in neural oscillators
Sim (D=1e-6)
Sd,LF(f)
Sd(f)
Scont(f)
(f)
f



Computational Biomathematics Laboratory
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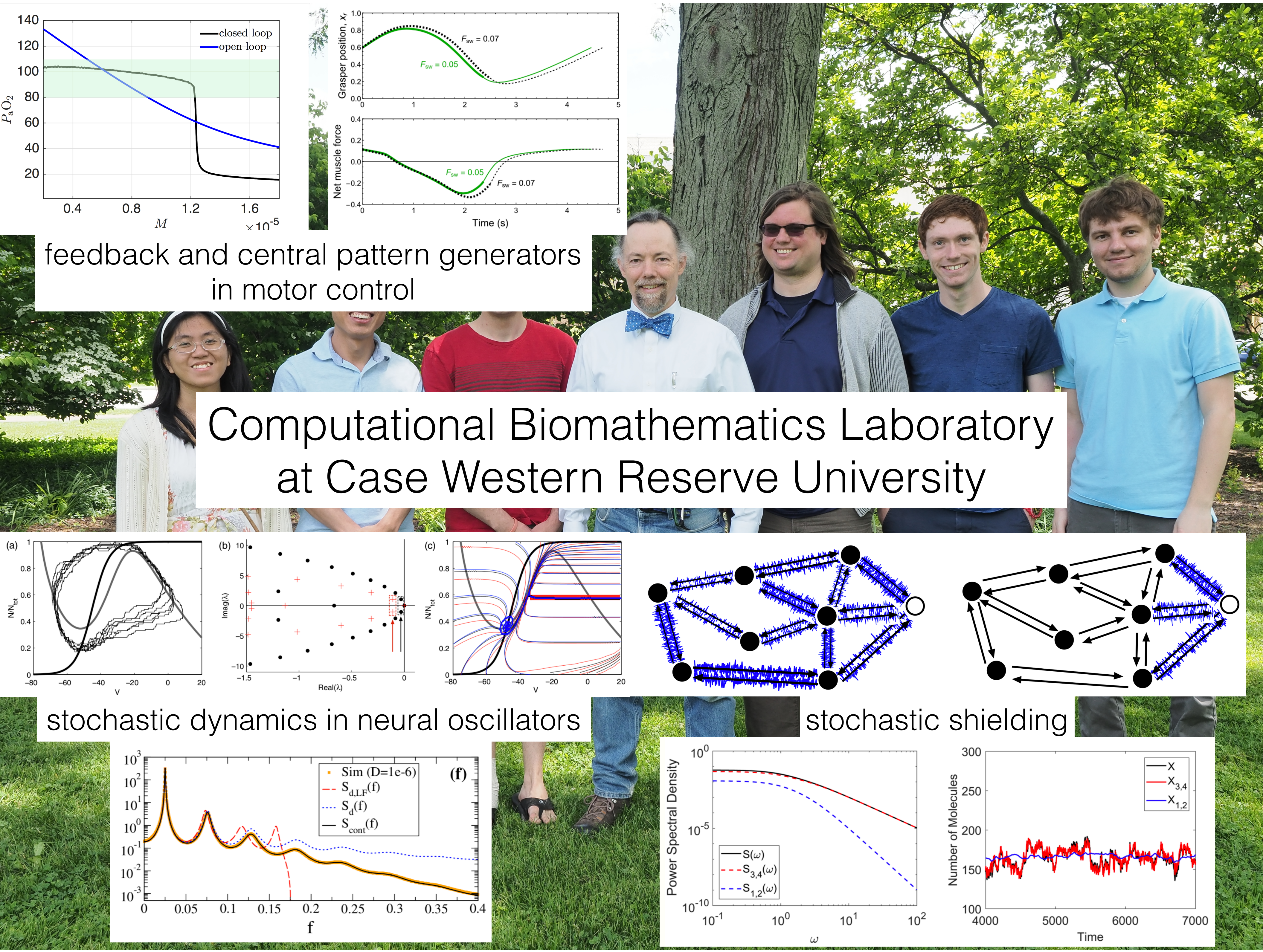
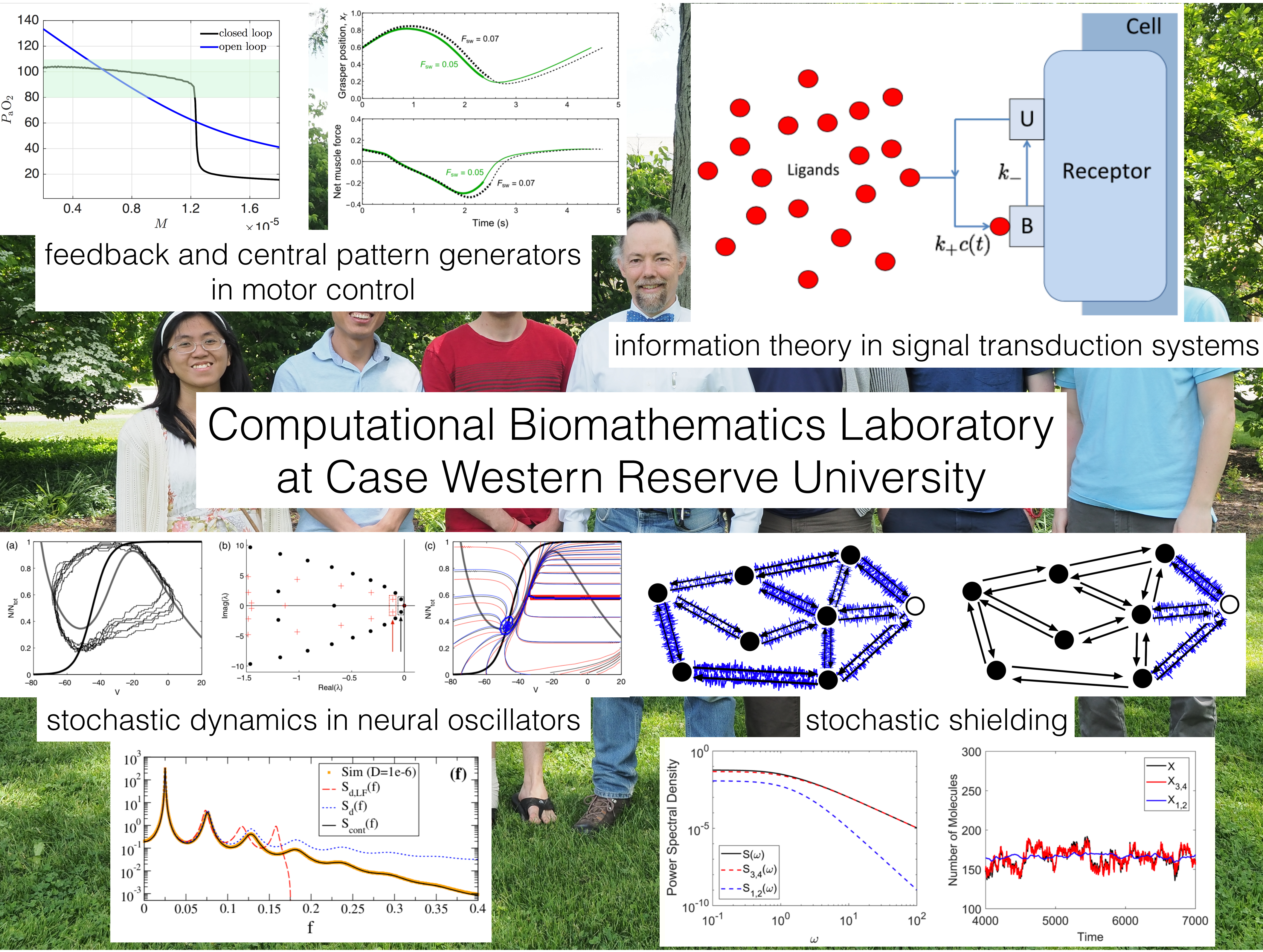
stochastic dynamics in neural oscillators
stochastic shielding
(a)
(b)
(c)
N/N_tot
V
Imag(λ)
Real(λ)
Sim (D=1e-6)
S_d,LF(f)
S_d(f)
S_cont(f)
(f)
f
Power Spectral Density
ω
S(ω)
S_3,4(ω)
S_1,2(ω)
Number of Molecules
Time
X
X_3,4
X_1,2



closed loop
open loop
Grasper position, x_r
F_{sw} = 0.07
F_{sw} = 0.05
Net muscle force
Time (s)
feedback and central pattern generators
in motor control
Computational Biomathematics Laboratory
at Case Western Reserve University
stochastic dynamics in neural oscillators
stochastic shielding
Sim (D=1e-6)
(f)
Power Spectral Density
Number of Molecules
Time



feedback and central pattern generators
in motor control
closed loop
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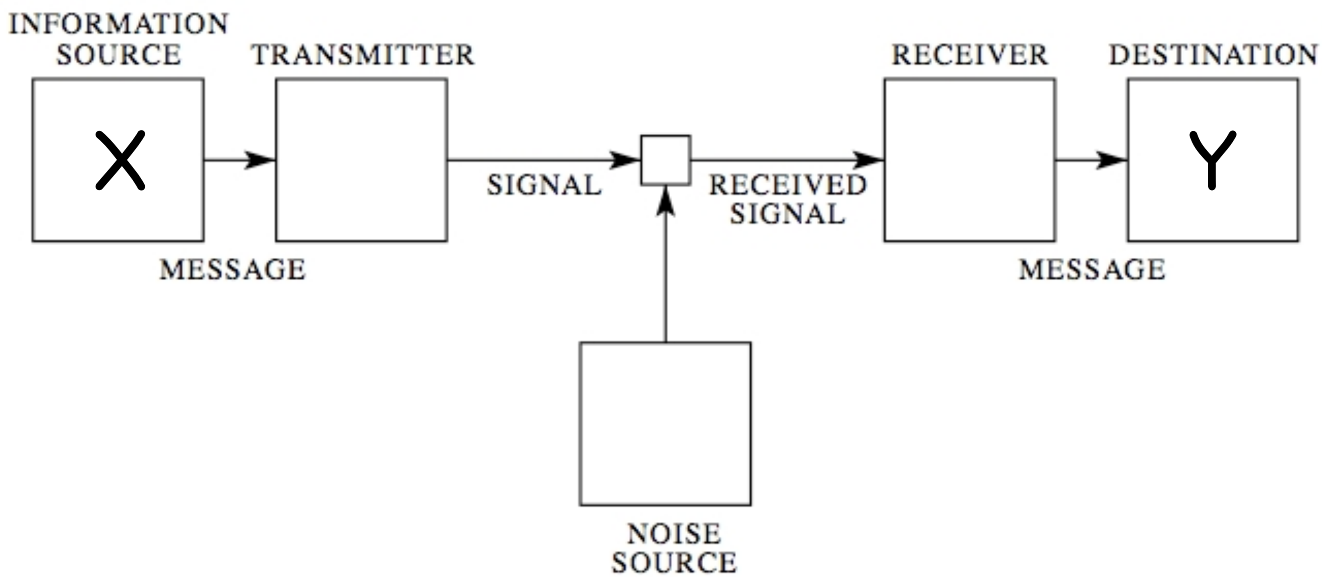
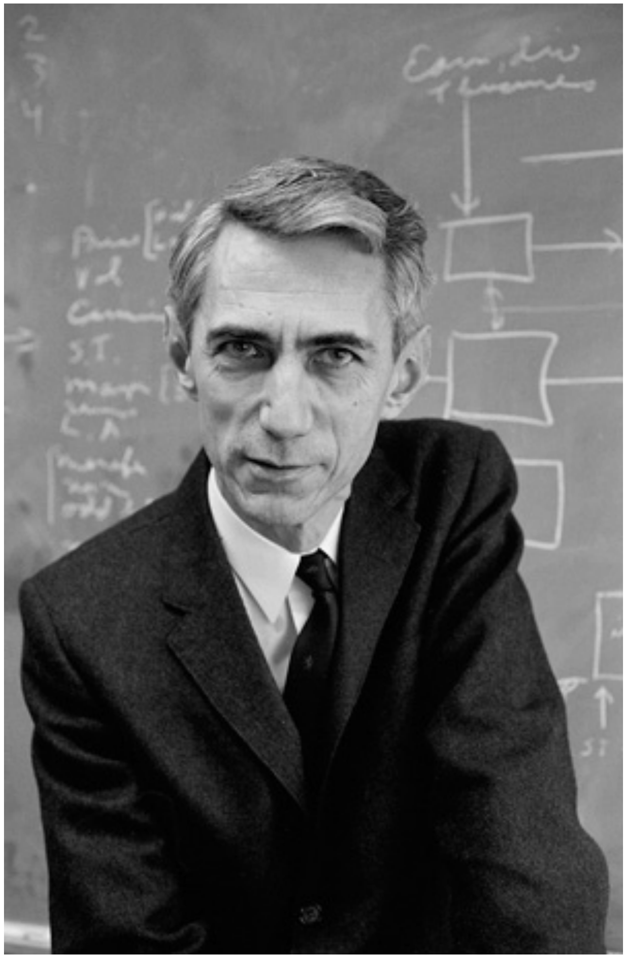
Net muscle force
Time (s)
F_{sw} = 0.07
F_{sw} = 0.05
Cell
Ligands
U
B
Receptor
k_-
$k_+c(t)$
information theory in signal transduction systems
Computational Biomathematics Laboratory
at Case Western Reserve University
stochastic dynamics in neural oscillators
stochastic shielding
Sim (D=1e-6)
$S_{d,LF}(f)$
$S_d(f)$
$S_{cont}(f)$
Power Spectral Density
Number of Molecules
Time

The fundamental question of information theory:
How much information can a communications system communicate?



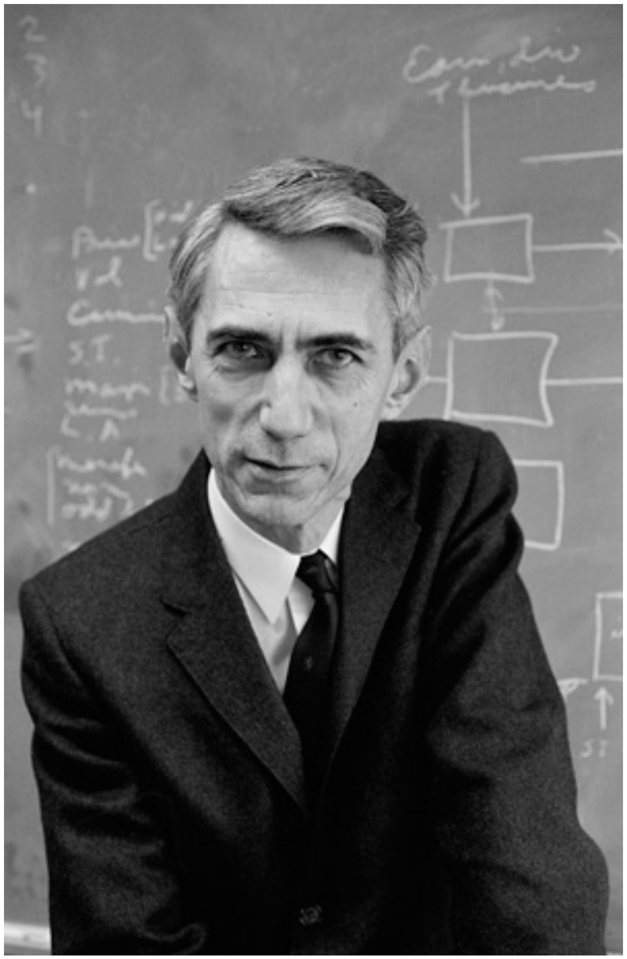
Shannon (1948) A Mathematical Theory of Communication

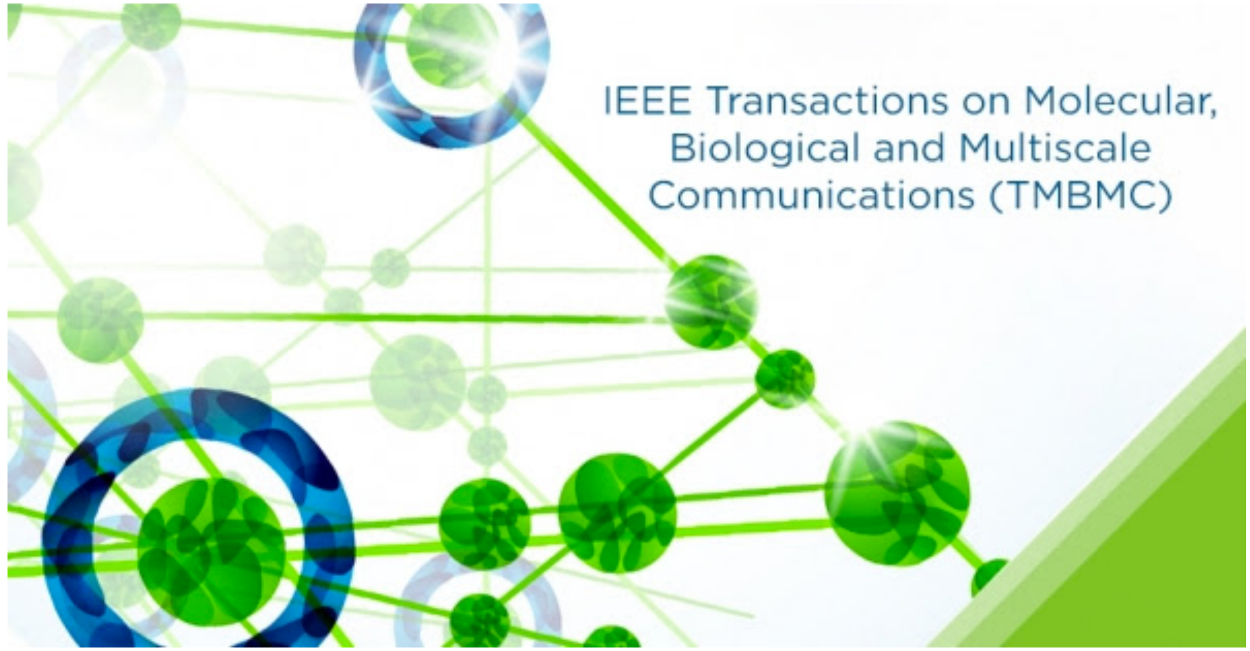
Answer: Channel Capacity = Max(Mutual Information I(X:Y));
Maximize over input ensembles P(X)



Claude Shannon
1916-2001

Alfred Eisenstaedt/The LIFE Picture Collection/Getty Images





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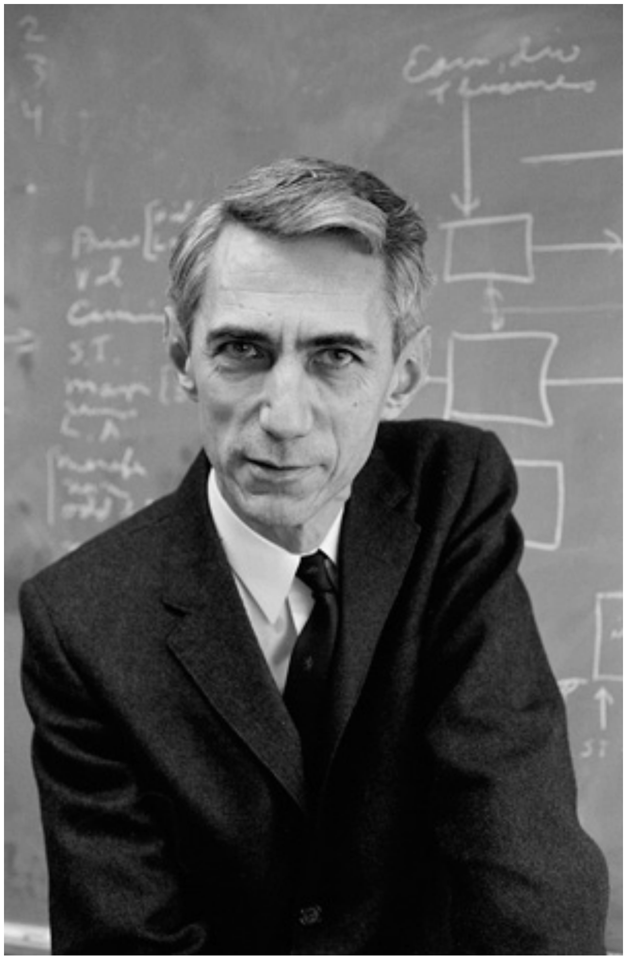

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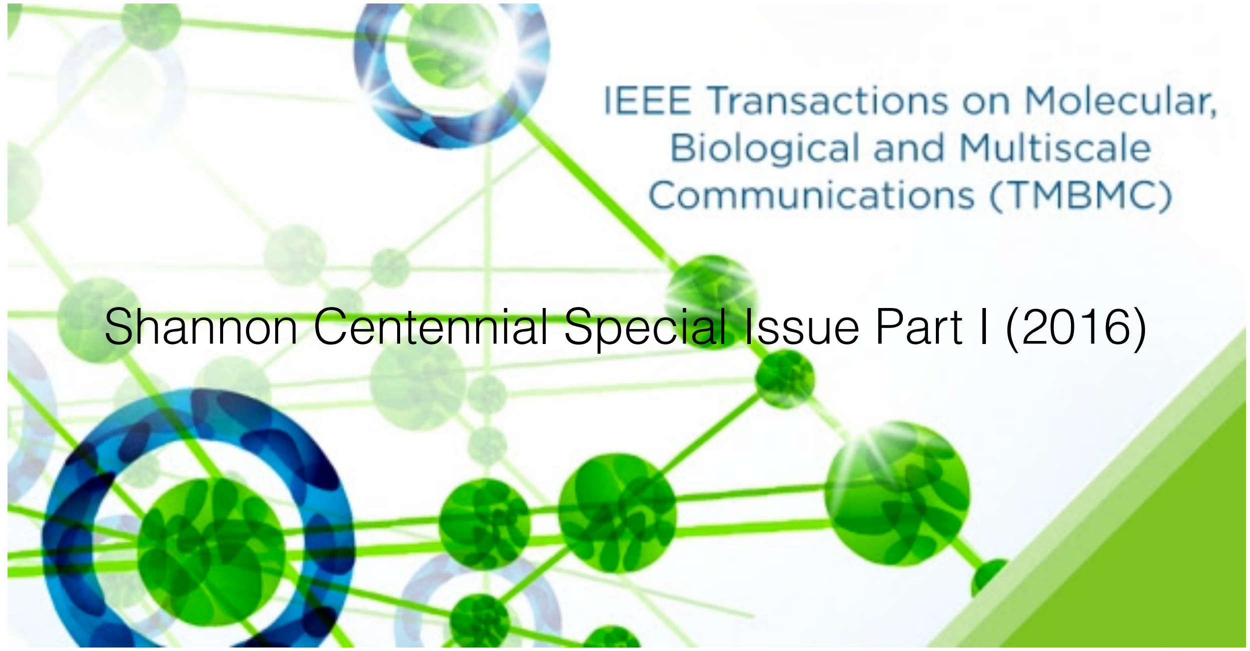
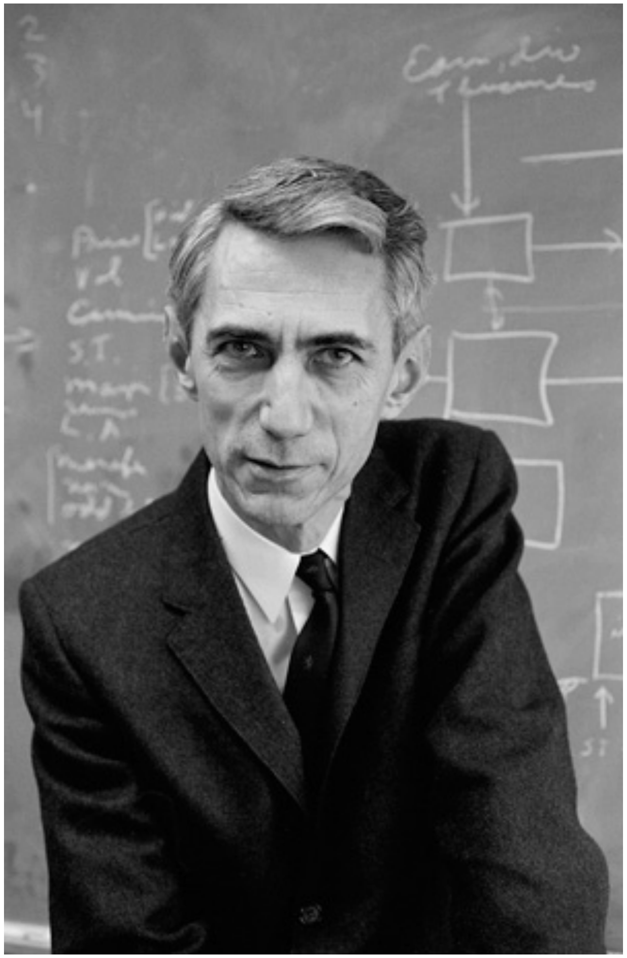


- Mechanisms of information filtering in neural systems (Linder)
- Noise Filtering and Prediction in Biological Signaling Networks (Hathcock, Sheehy, Weisenberger, Ilker, and Hinczewski)
- The Use of Rate Distortion Theory to Evaluate Biological Signaling Pathways (Iglesias)
- Nonlinear Stochastic Dynamics of Complex Systems, III: Noneqilibrium Thermodynamics of Self-Replication Kinetics (Saakian and Qian)
- Inferring Biological Networks by Sparse Identification of Nonlinear Dynamics (Mangan, Brunton, Proctor and Kutz)
- Info-Clustering: A Mathematical Theory for Data Clustering (Chan, Al-Bashabsheh, Kaced, Zhou and Liu)
- Fundamental Bounds for Sequence Reconstruction from Nanopore Sequencers (Magner, Duda, Szpankowski and Grama)
- Inference of Causal Information Flow in Collective Animal Behavior (Lord, Sun, Ouellette and Bollt)



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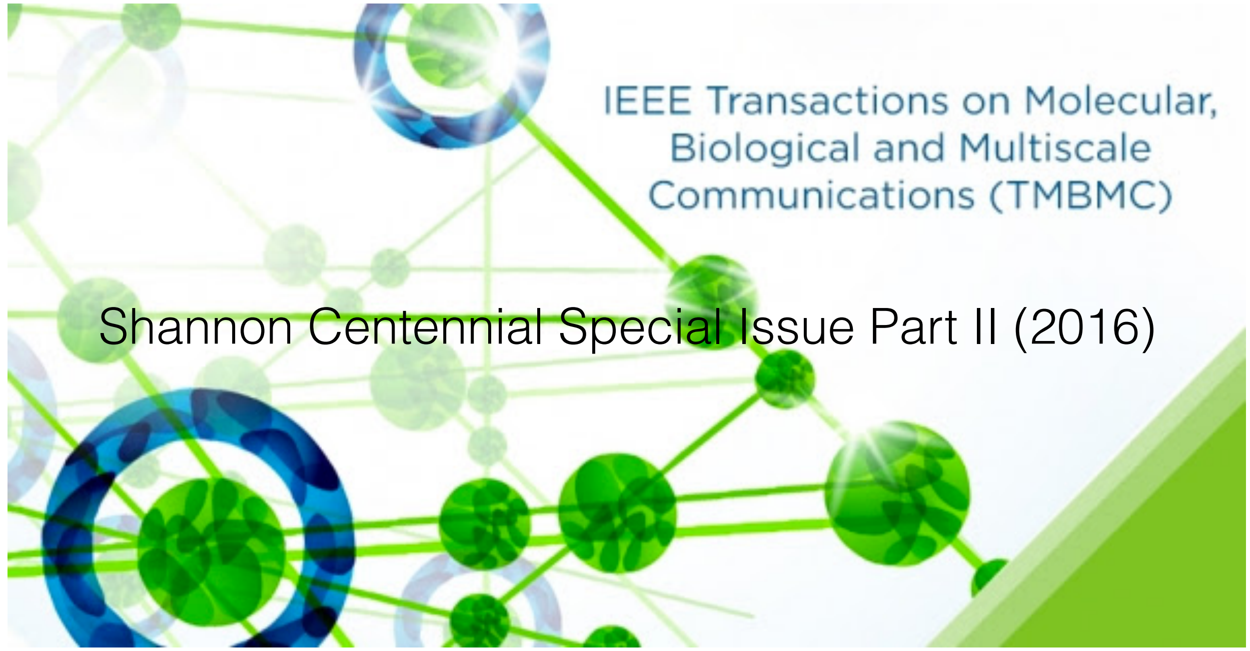

Shannon Centennial Special Issue Part II (2016)

- Information Theory of Molecular Communication: Directions and Challenges (Gohari, Mirmohseni, and Nasiri-Kenari)
- On Palimpsests in Neural Memory: An Information Theory Viewpoint (Varshney, Kusuma, and Goyal)
- Neural Computation from First Principles: Using the Maximum Entropy Method to Obtain an Optimal Bits-Per-Joule Neuron (Berger, Levy and Sungkar)
- Mutual Information and Parameter Estimation in the Generalized Inverse Gaussian Diffusion Model of Cortical Neurons (Sungkar, Berger, and Levy)
- Identifying Multisensory Dendritic Stimulus Processors (Lazar and Zhou)
- Fundamental Limits of Genome Assembly under an Adversarial Erasure Model (Shomorony, Courtade, and Tse)
- Inscribed Matter Communication: Part I (Rose and Mian)
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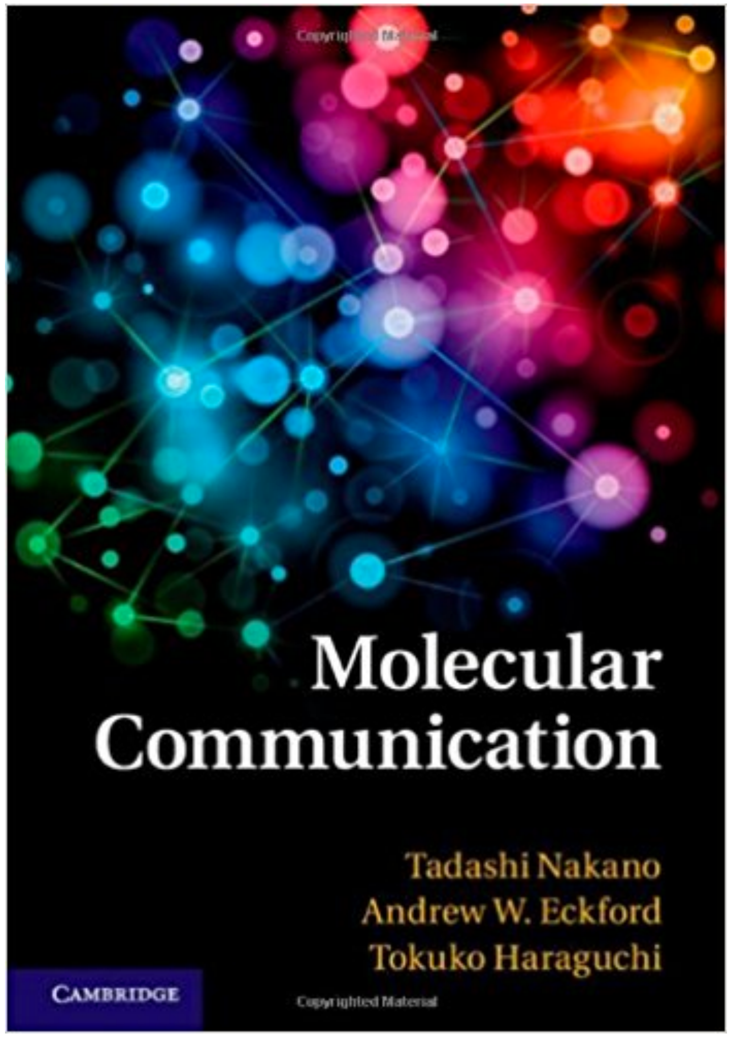
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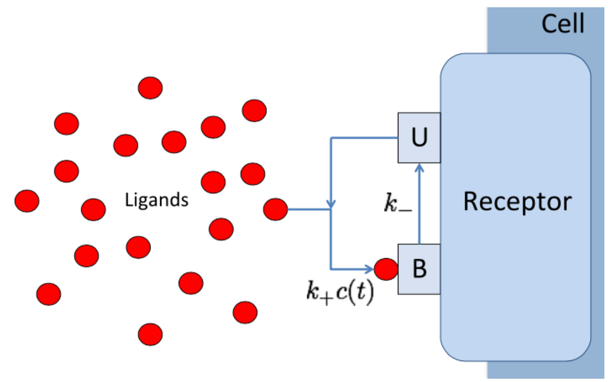
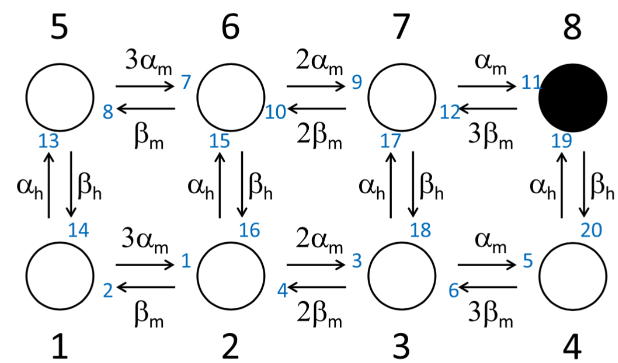
(2013)

Signal Transduction:
Transforming Extracellular Signals into Intracellular Responses

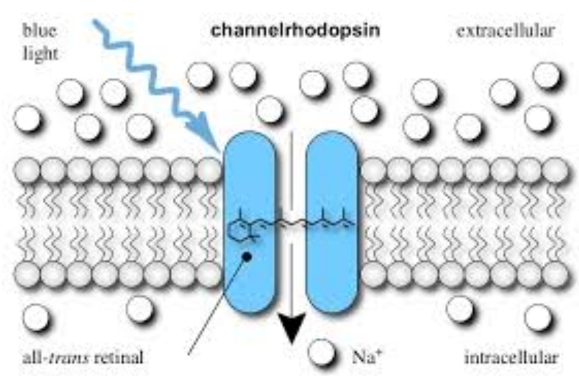
* Ligand-receptor systems
  * cyclic AMP receptor
  * acetylcholine receptor
  * calcium signaling (calmodulin)



* Voltage-gated ion channels
  * Hodgkin-Huxley sodium channel
  * gap junction mediated sync.



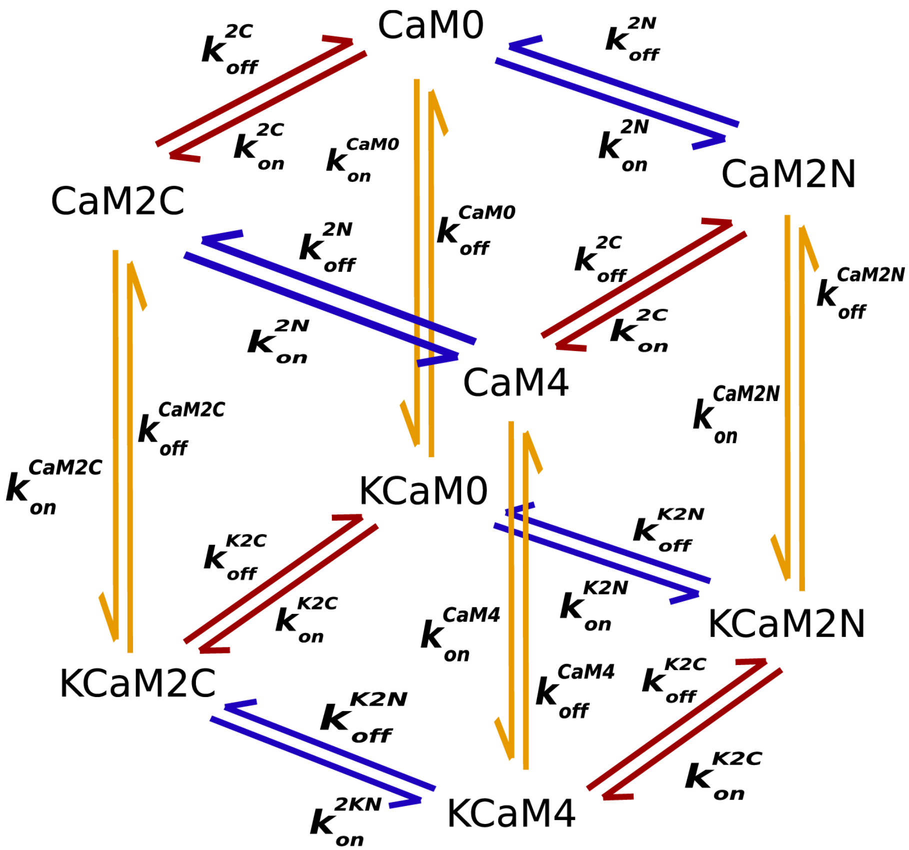
* Light-gated ion channels
  * channelrhodopsin
  * light-driven cAMP synthesis



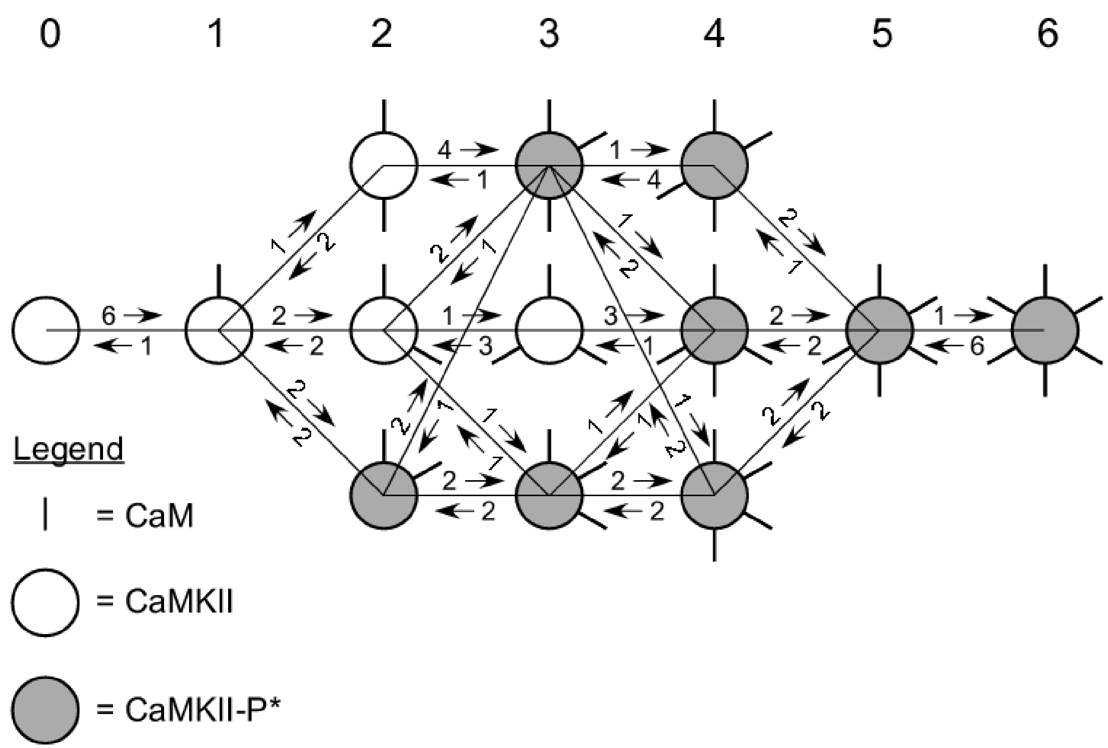
Information Capacity of a Signal Transduction Channel

Transitions between receptor states {1,…,j,…,S} driven by signal concentration X(t).

$$\frac{dp_k}{dt} = \sum_{j=1}^{n} p_j(t) q_{jk}(X(t))$$



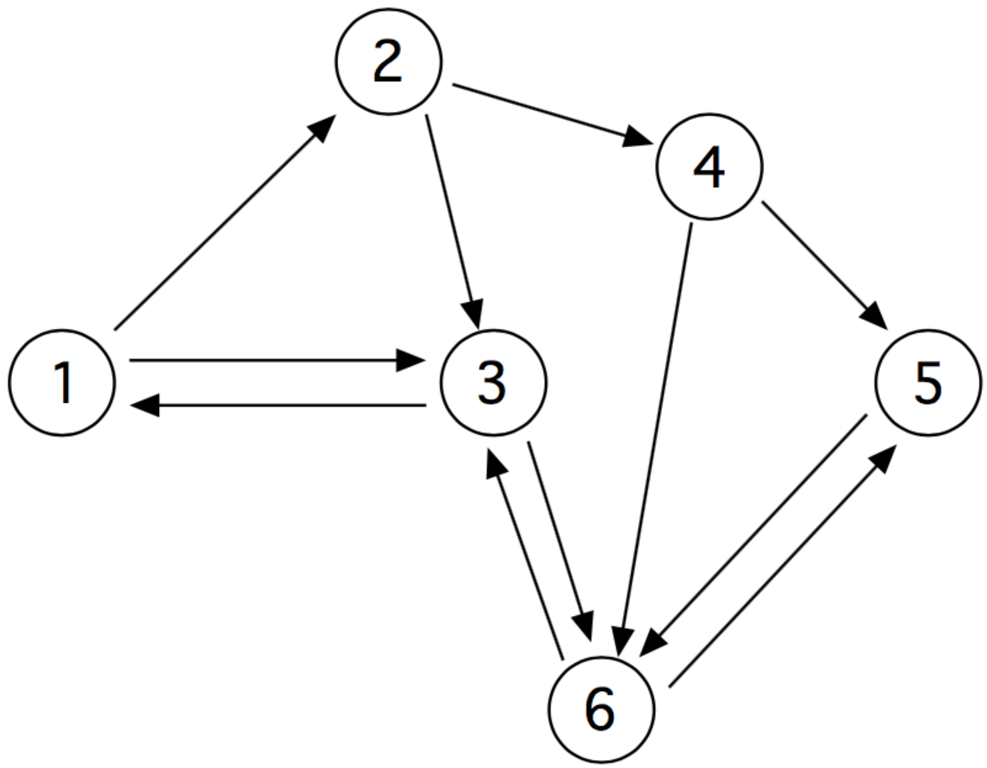
Calcium-Calmodulin Binding Graph



Calmodulin/CaMKII state graph

Graphical representation of signal transduction

- We represent an individual receptor's state as a node in a directed graph $\mathcal{G} = (\mathcal{V}, \mathcal{E}) = (\{\text{vertices}\}, \{\text{edges}\})$.
- Edge $i \to j$ represents a transition from state i to state j.
- If the per capita transition rate α_{ij} depends on the input signal $S(t)$, the state i is *sensitive*.



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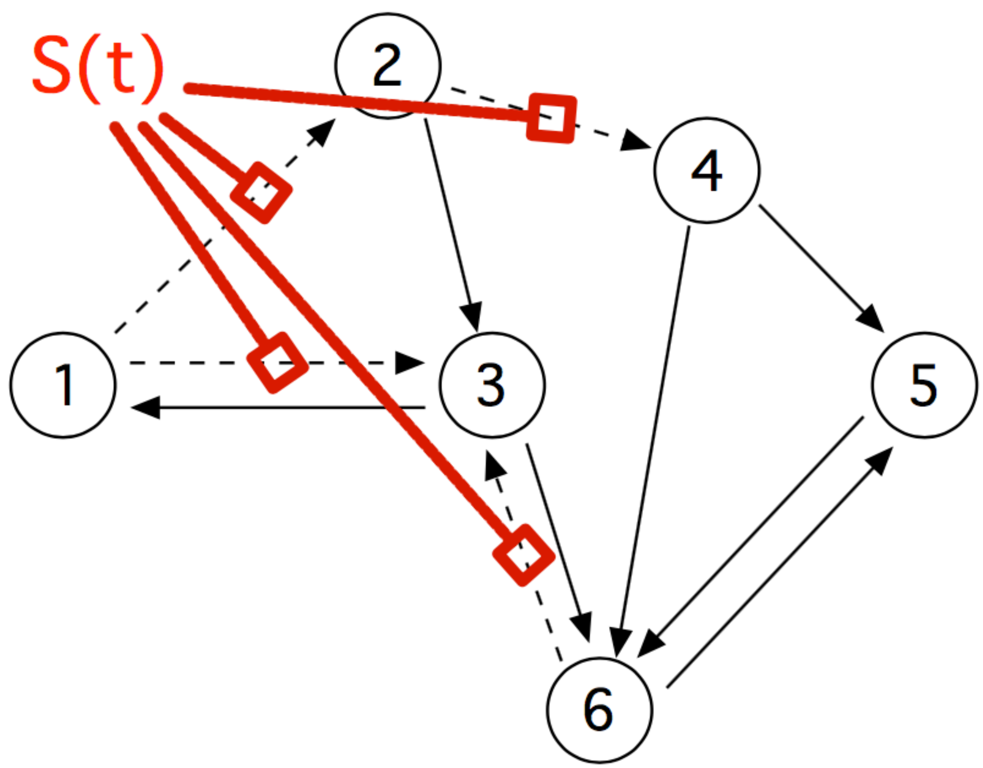

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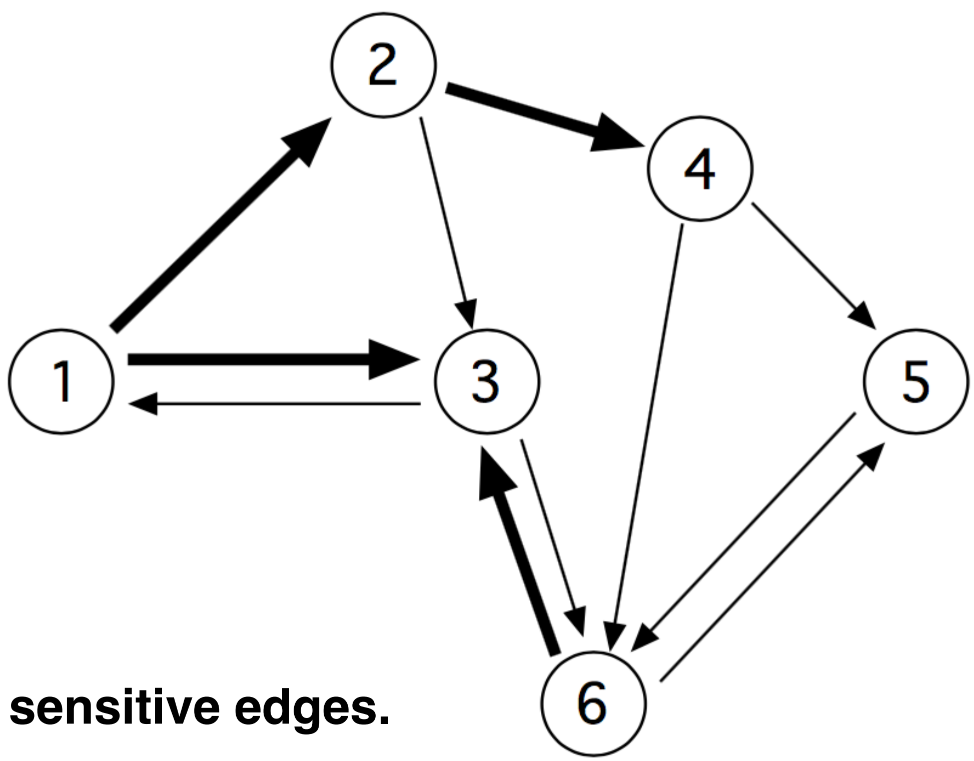
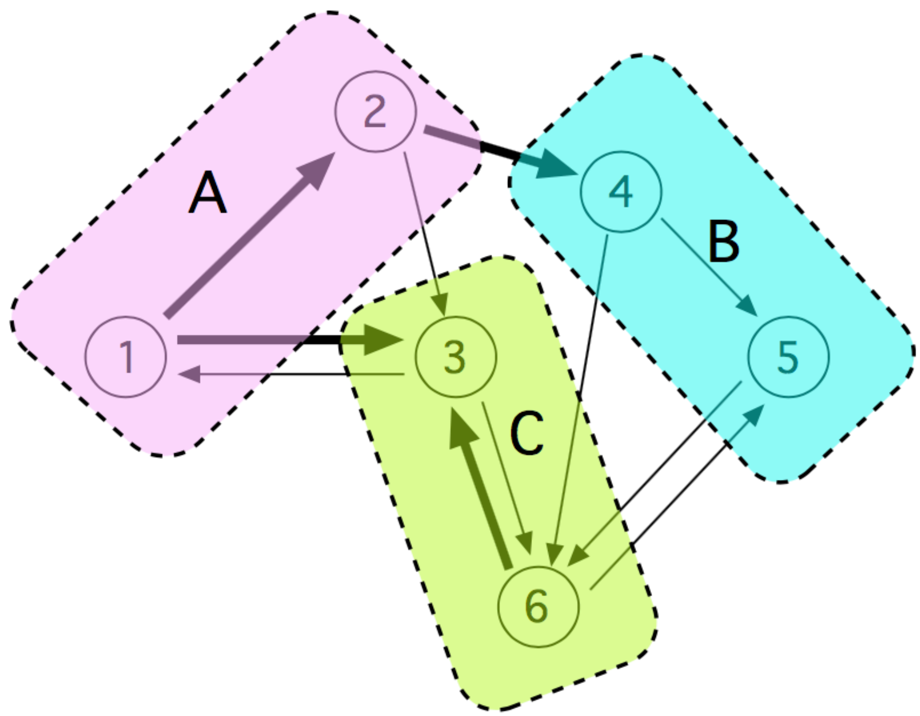


Bold arrows denote sensitive edges.

Graphical representation of signal transduction

- The observable state of the receptor may be more coarse grained than the underlying state graph, e.g. observables $A = \mathrm{Ind}(\{1, 2\})$, $B = \mathrm{Ind}(\{4, 5\})$, $C = \mathrm{Ind}(\{3, 6\})$.
- If the transition $i \to j$ changes the coarse-grained state, then edge $i \to j$ is *observable*.
- We distinguish the mutual information and capacity for the *fully observed* versus the *partially observed* receptor.

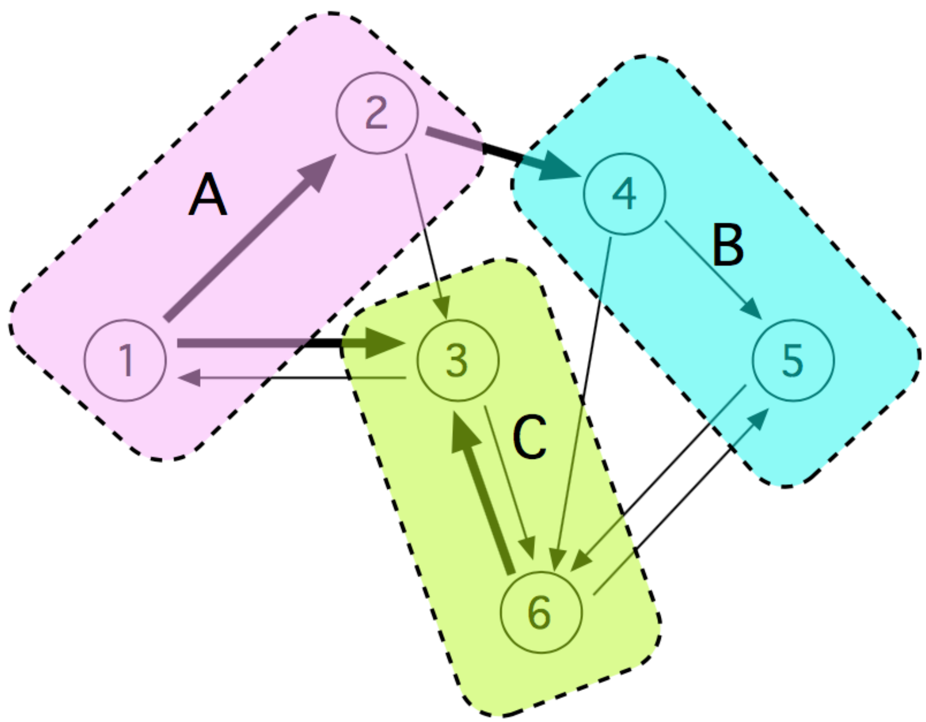


Continuous-time channel model

- Input: $X(t) : [0, \infty) \to [x_{\min}, x_{\max}]$ with $0 \le x_{\min} \le x_{\max}$.
- Channel State: $Y(t) \in \{1, \ldots, K\}$. $p_i(t) = \Pr(Y(t) = i)$.

$$\frac{dp_j}{dt} = \sum_{i=1}^{K} p_i \alpha_{ij}(X(t)), \text{ with } \alpha_{jj} = -\sum_{k \neq j} \alpha_{jk}.$$

- Observable Output: $Z(t) = C \cdot Y(t)$ for an $M \times K$ matrix C.

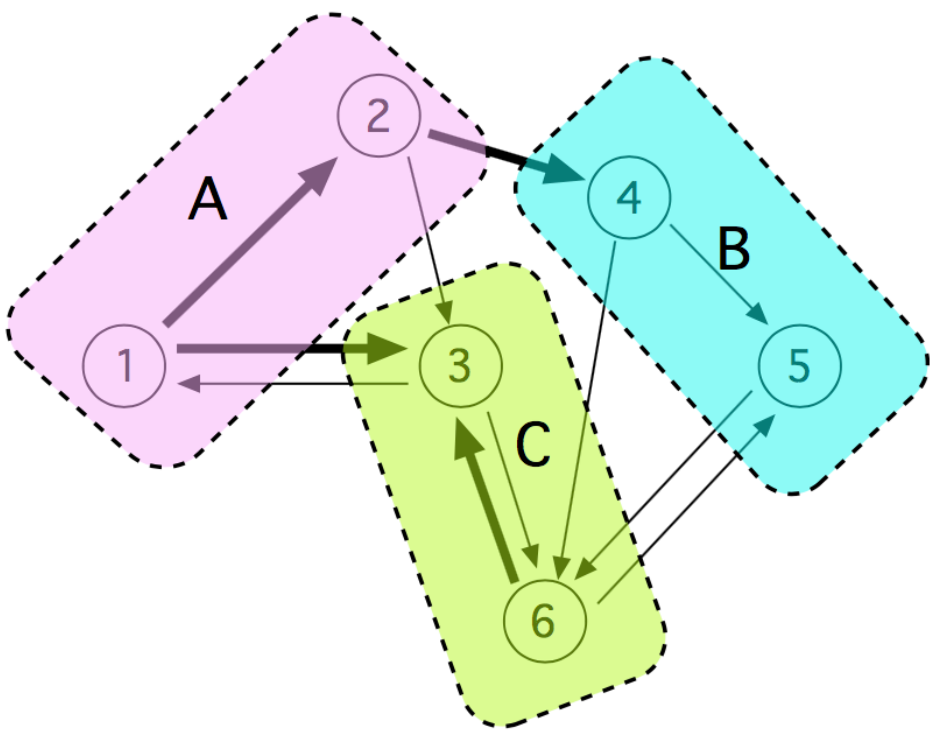


Discrete-time channel model ($0 < \Delta t \ll 1$)

- Input: $X(t) : \{0, \Delta t, 2\Delta t, \ldots\} \to [x_{\min}, x_{\max}]$.
- Channel State: $Y(t) \in \{1, \ldots, K\}$. $p_i(t) = \Pr(Y(t) = i)$.

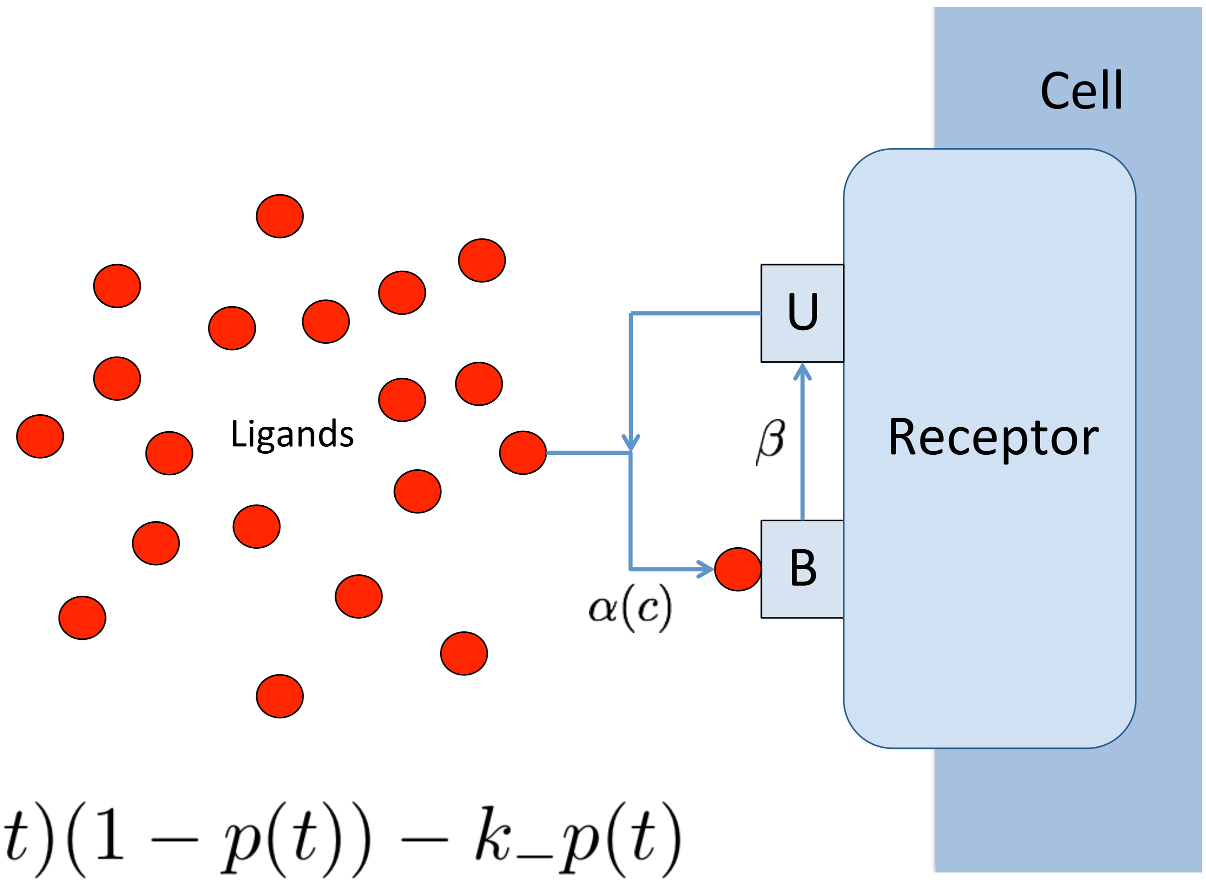
$$p_j(t + \Delta t) = p_j(t)(1 - \alpha_{jj}\Delta t) + \sum_{i \neq j} p_i(t)\alpha_{ij}(X(t)).$$

- Observable Output: $Z(t) = C \cdot Y(t)$ for an $M \times K$ matrix C.



Example 1: the BIND channel (a single binary receptor)

Receptor has only two states (Bound/Unbound).



$$\frac{dp}{dt} = k_+ c(t)(1 - p(t)) - k_- p(t)$$

p: probability receptor is bound.

k_+: binding rate constant.

k_-: unbinding rate constant.

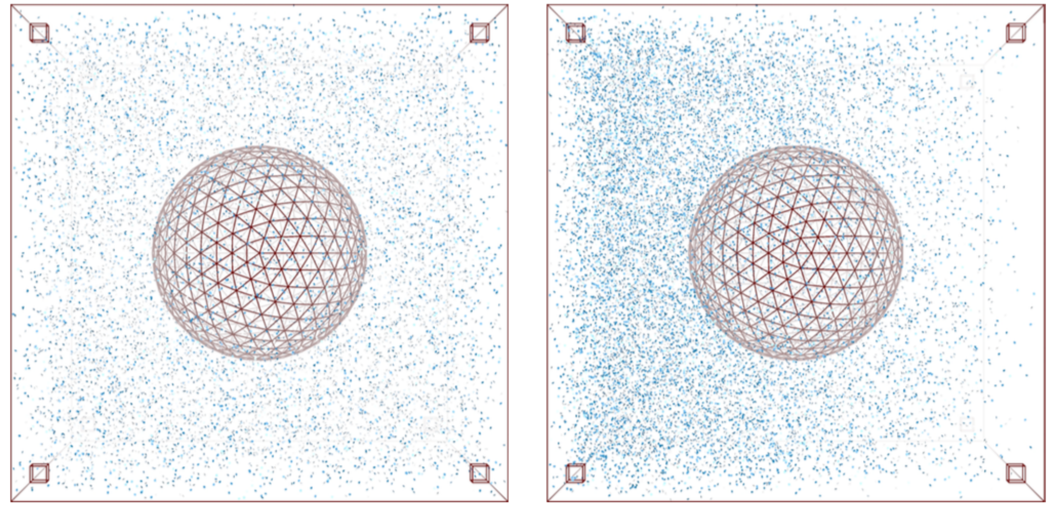
$$\alpha_L = k_+ c_{min} \Delta t$$

$$\alpha_H = k_+ c_{max} \Delta t$$

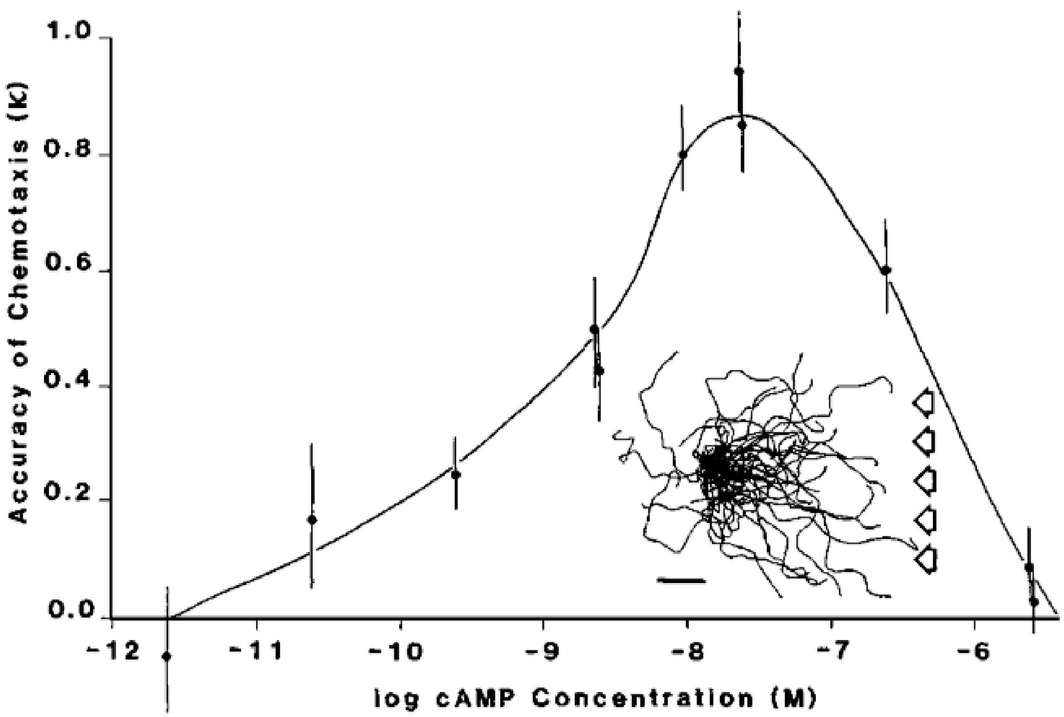
$$\beta = k_- \Delta t$$

Information Theory and Directed Cell Migration (Chemotaxis)

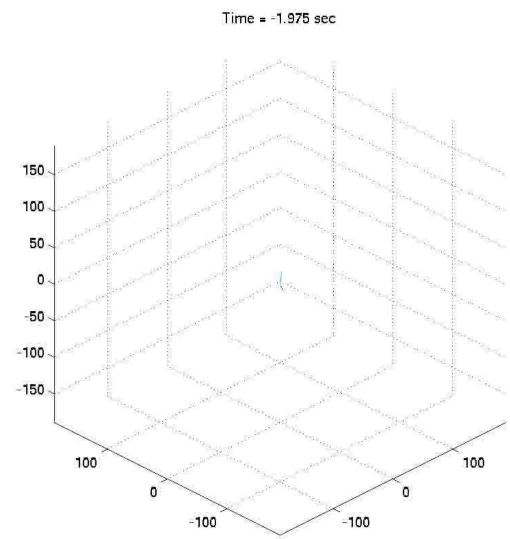
Dictyostelium discoideum amoeba detecting cAMP gradients. G. Gerisch.



Gradient sensing *via* cAMP receptors
Kimmel, Salter & Thomas 2006 NIPS



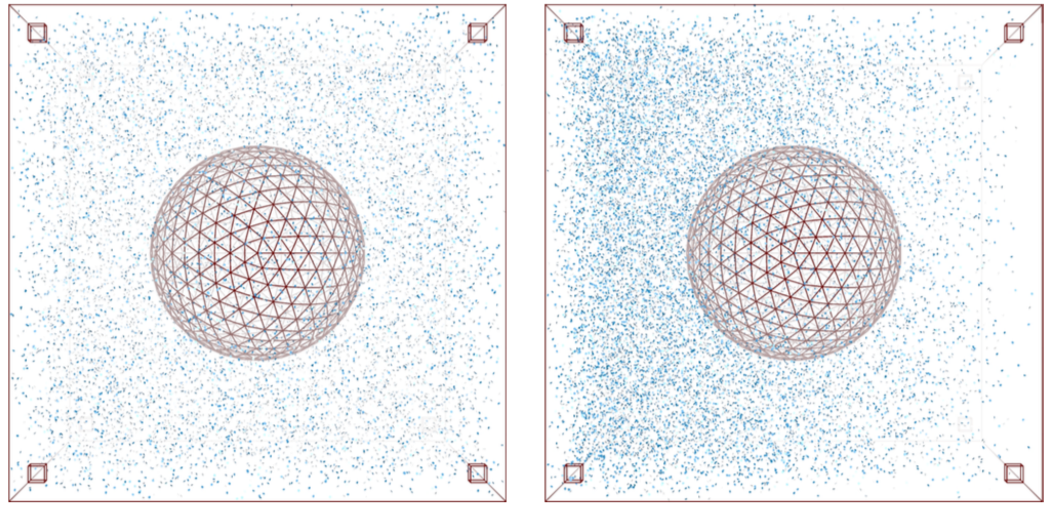
Cell tracks provide individual unit responses.
Fischer et al., J. Cell Biology, 1989



Ensemble of directional estimates:
shallow gradient

Information Theory and Directed Cell Migration (Chemotaxis)

Dictyostelium discoideum amoeba detecting cAMP gradients. G. Gerisch.



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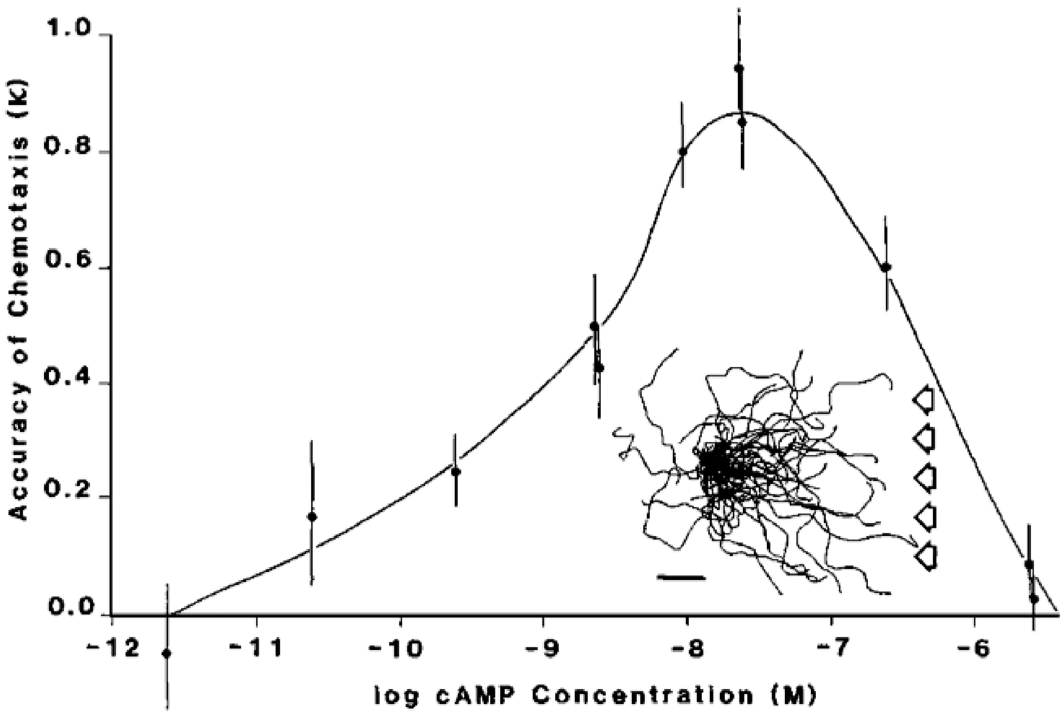

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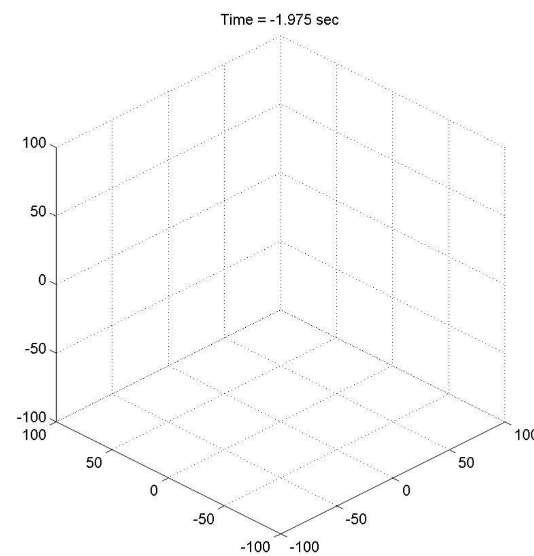
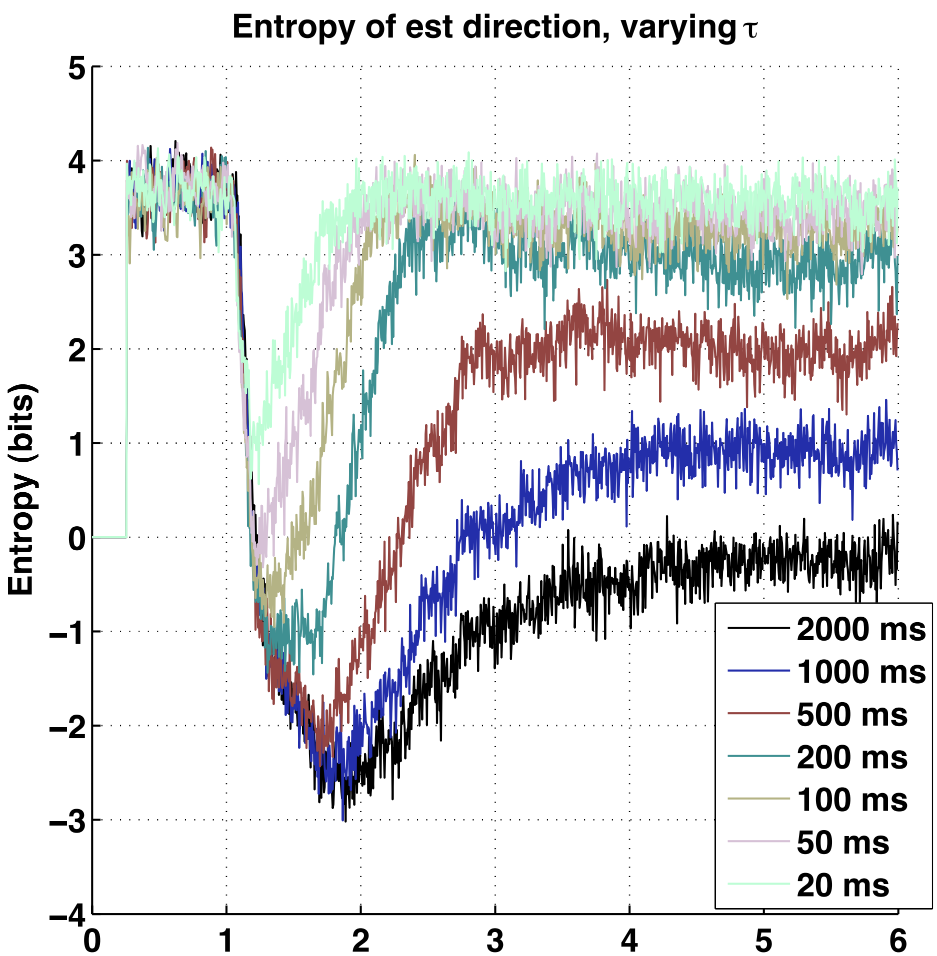


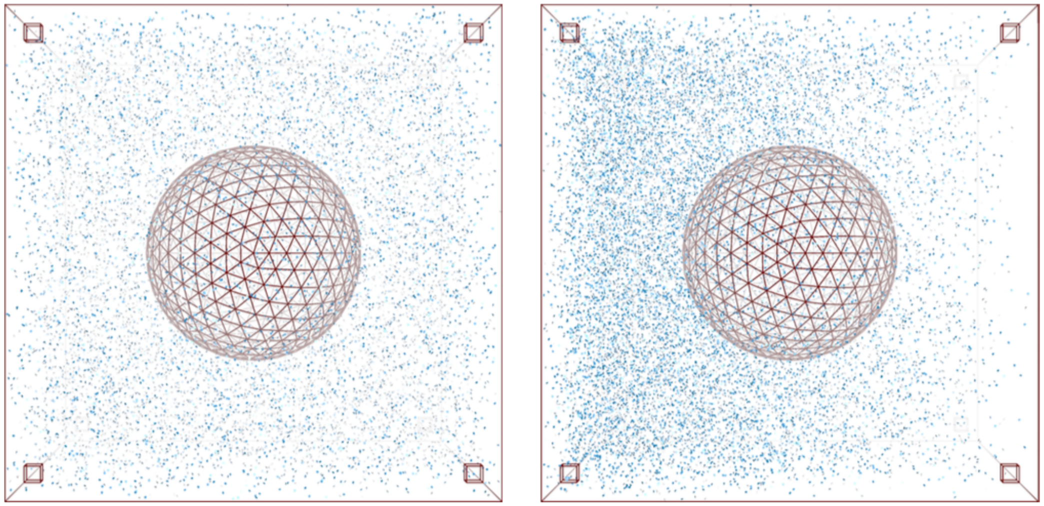
Ensemble of directional estimates: steep gradient

Information Theory and Directed Cell Migration (Chemotaxis)



Mutual information peaks then recedes for saturating gradient signal (200 nM mean concentration; Keq=25nM).

Tau = filtering time scale for estimate.



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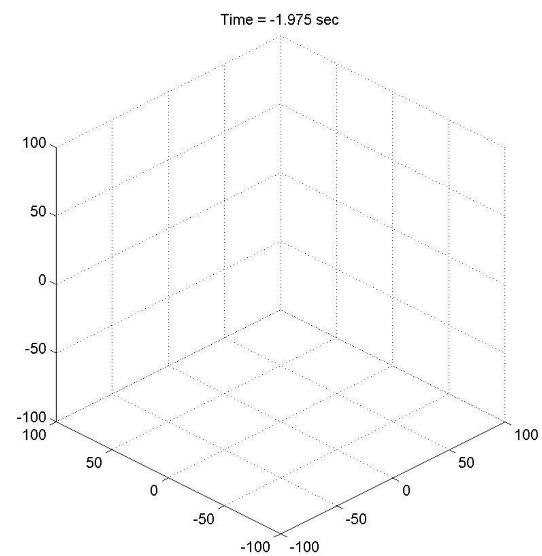
Kimmel, Salter & Thomas 2006 NIPS



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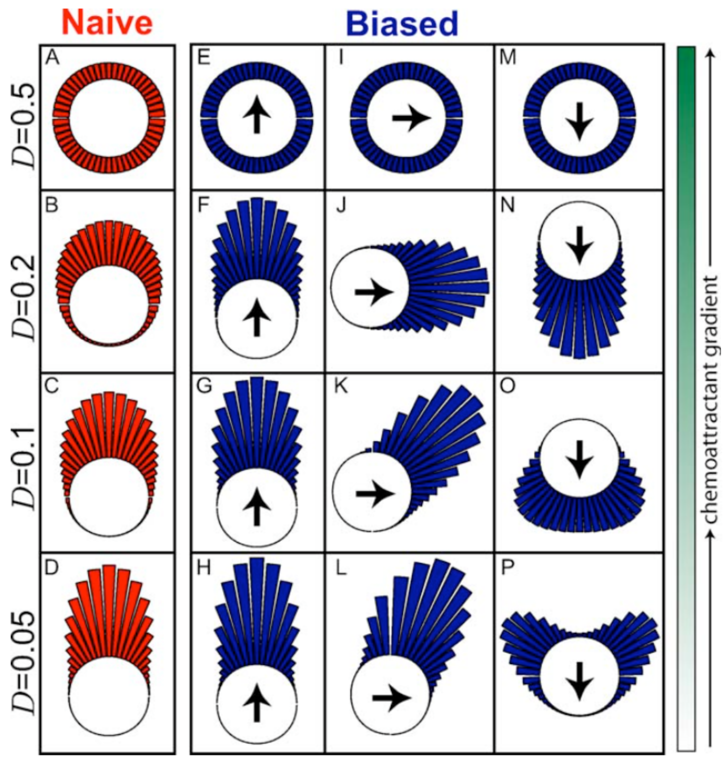
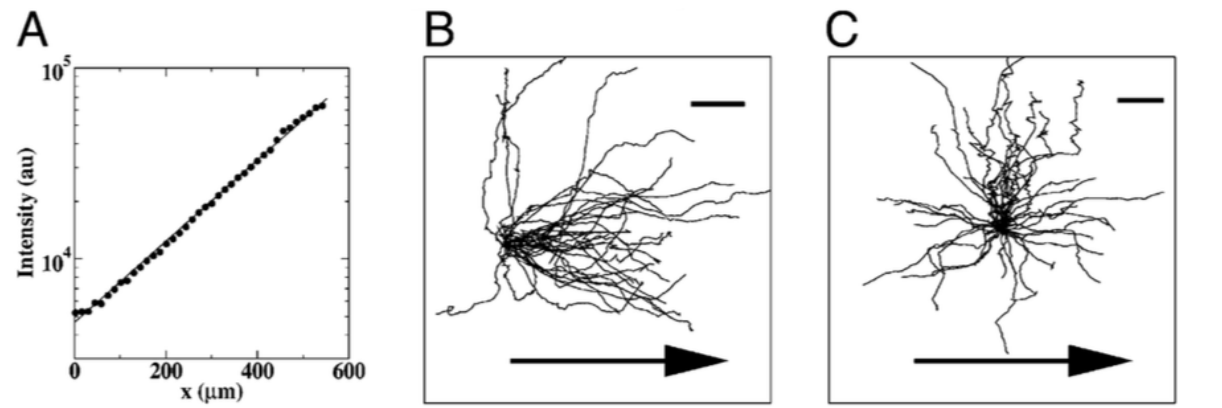


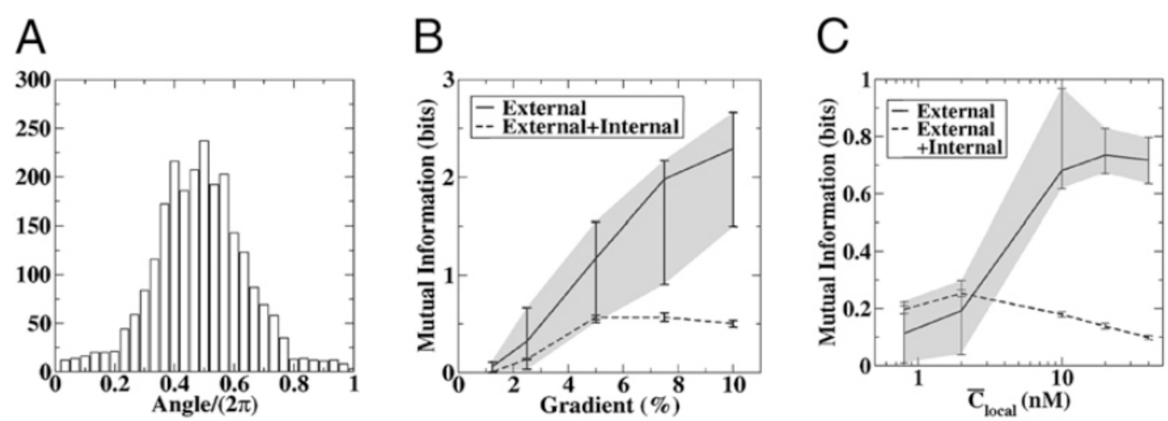
Optimal Gradient Sensing Response
Andrews & Iglesias 2007 PLoS CB



Cell tracks in a microfluidic device (exponential gradient)

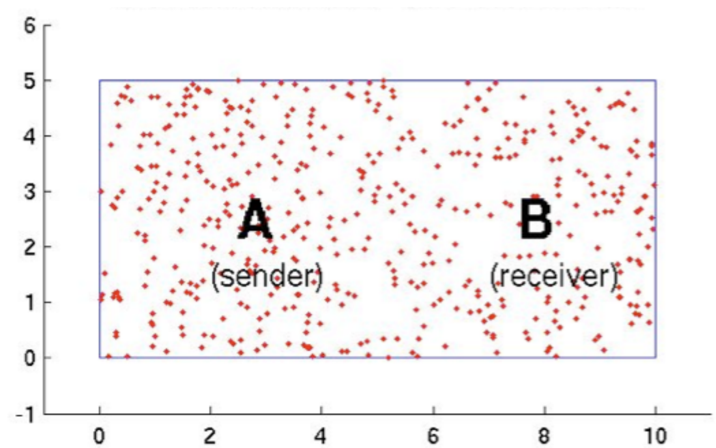
(Fuller et al 2010 PNAS)

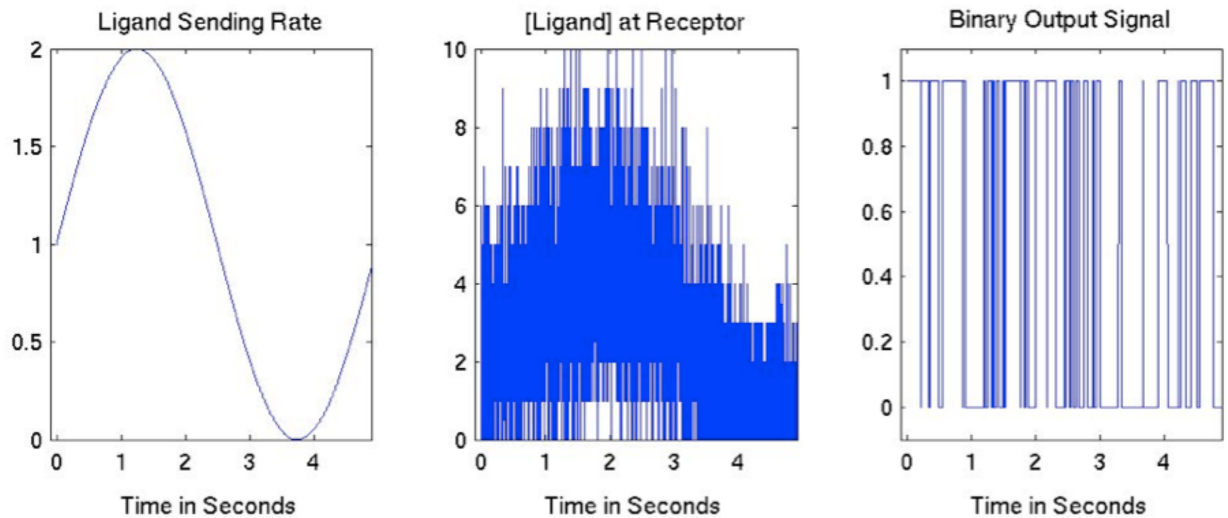
Mutual Information of chemotactic response;
resolution of internal versus external noise sources.



Information Capacity of a Signal Transduction Channel

1. Secretion of signaling molecule
2. Diffusion from sender to receiver
3. Ligand binding to receptor protein





Thomas et al 2003 NIPS

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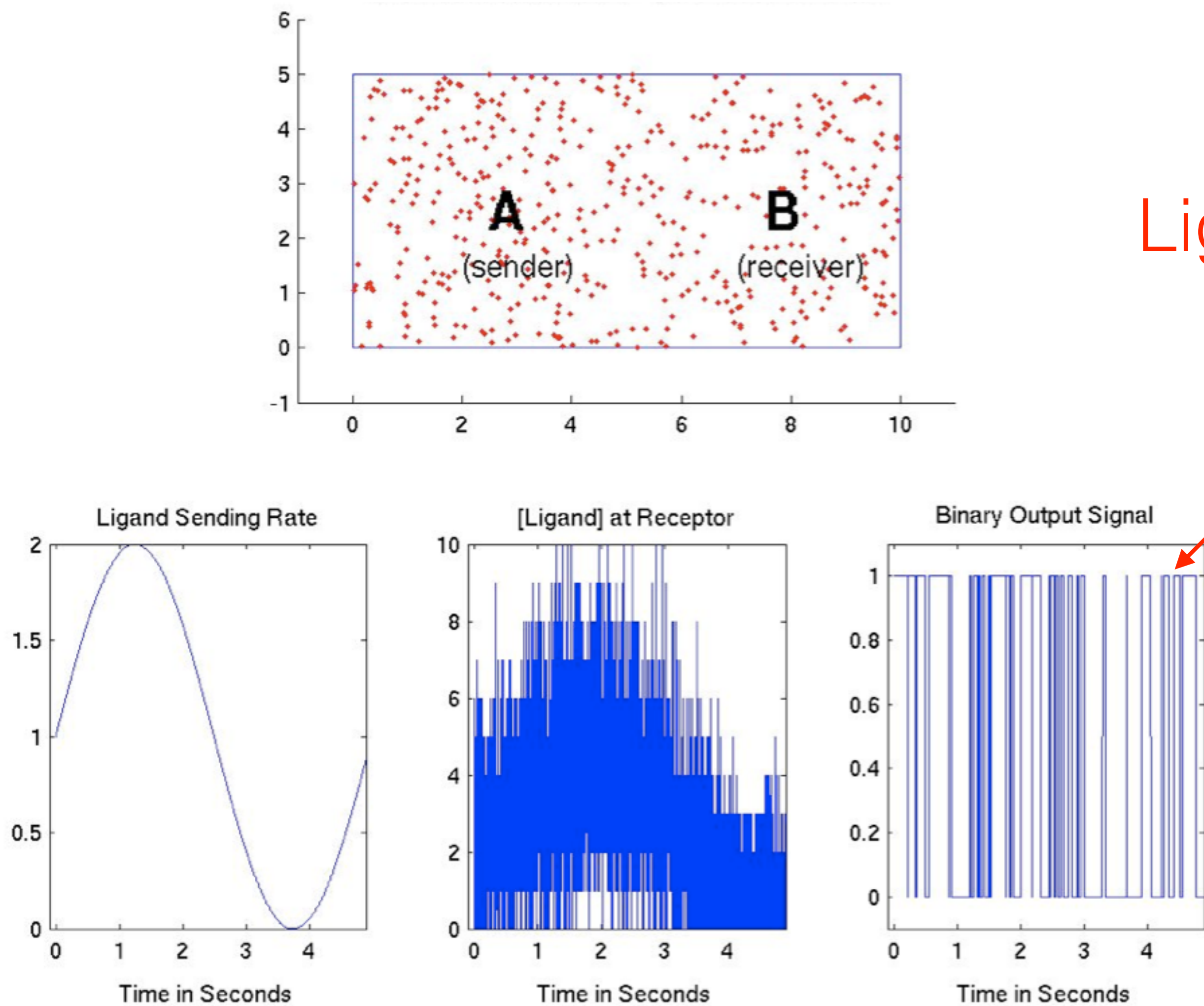
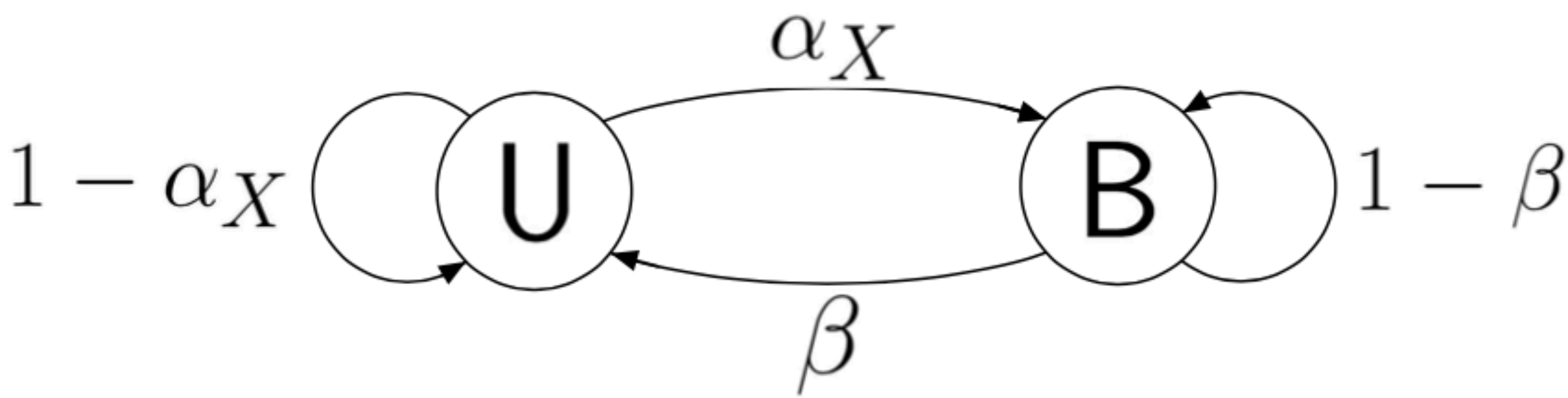


Ligand-receptor binding

Thomas et al 2003 NIPS

Example 1: the BIND channel (a single binary receptor)

Receptor has only two states (Bound/Unbound).



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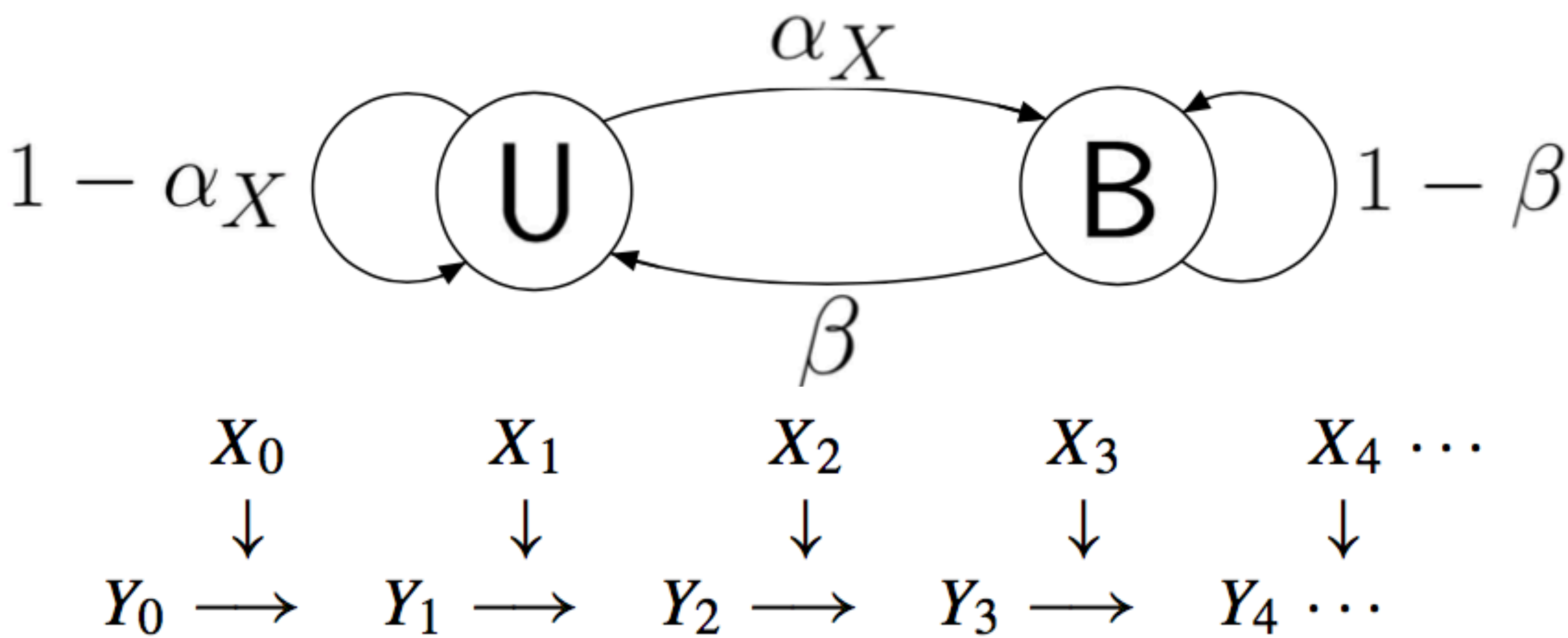

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Example 1: the BIND channel (a single binary receptor)

Applying a general theorem due to Chen and Berger to the two-state discrete time Markov channel, we can show that

1. Capacity C of the discrete channel model is

$$C = \max_{p_{\mathsf{H}}} \frac{\mathscr{H}(p_{\mathsf{L}}\alpha_{\mathsf{L}} + p_{\mathsf{H}}\alpha_{\mathsf{H}}) - p_{\mathsf{L}}\mathscr{H}(\alpha_{\mathsf{L}}) - p_{\mathsf{H}}\mathscr{H}(\alpha_{\mathsf{H}})}{1 + (p_{\mathsf{L}}\alpha_{\mathsf{L}} + p_{\mathsf{H}}\alpha_{\mathsf{H}})/\beta},$$

where $p_{\mathsf{L}} = 1 - p_{\mathsf{H}}$ and $\mathscr{H}(p) = p \log \frac{1}{p} + (1-p) \log \frac{1}{1-p}$.

2. The capacity cannot be increased by feedback.
3. The capacity can be realized by an IID input source.

Eckford & Thomas, 2013 International Symposium on Information Theory (ISIT)
Thomas & Eckford, 2016 IEEE Transactions on Information Theory

Example 1: the BIND channel (a single binary receptor)

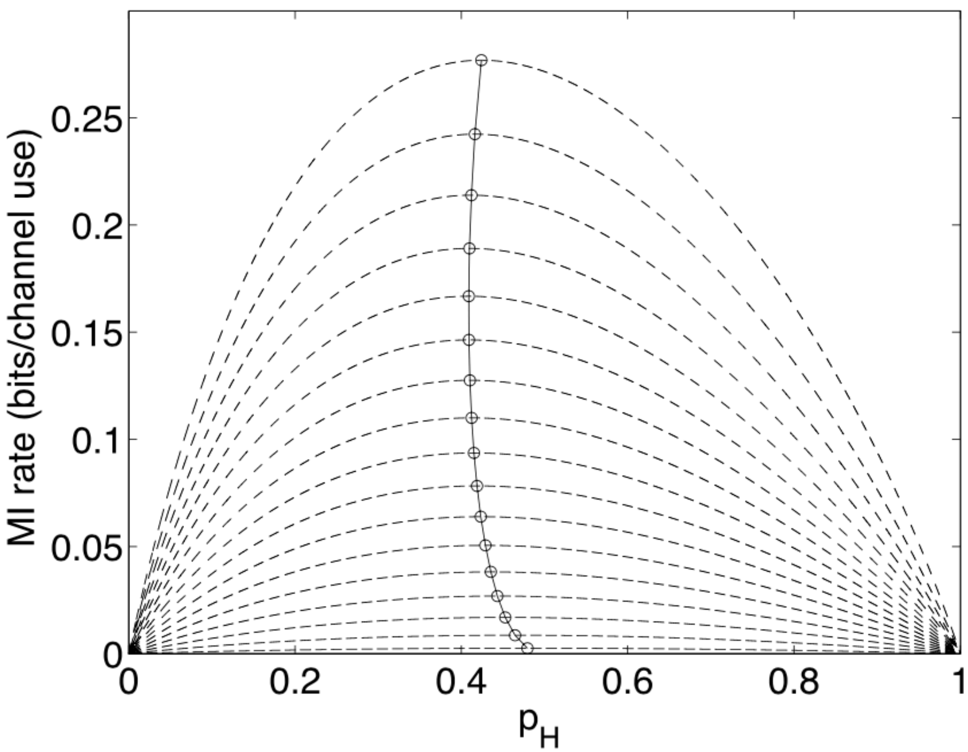


Fig. 3. Information maximizing values of p_H, with $\alpha_L = 0.1$ and $\beta = 0.9$. Each dashed curve corresponds to a particular value of α_H: from the bottom, $\alpha_H = 0.15$; each higher curve increases α_H by 0.05, up to $\alpha_H = 0.95$ in the topmost curve. The maxima are circled and connected with a solid line.

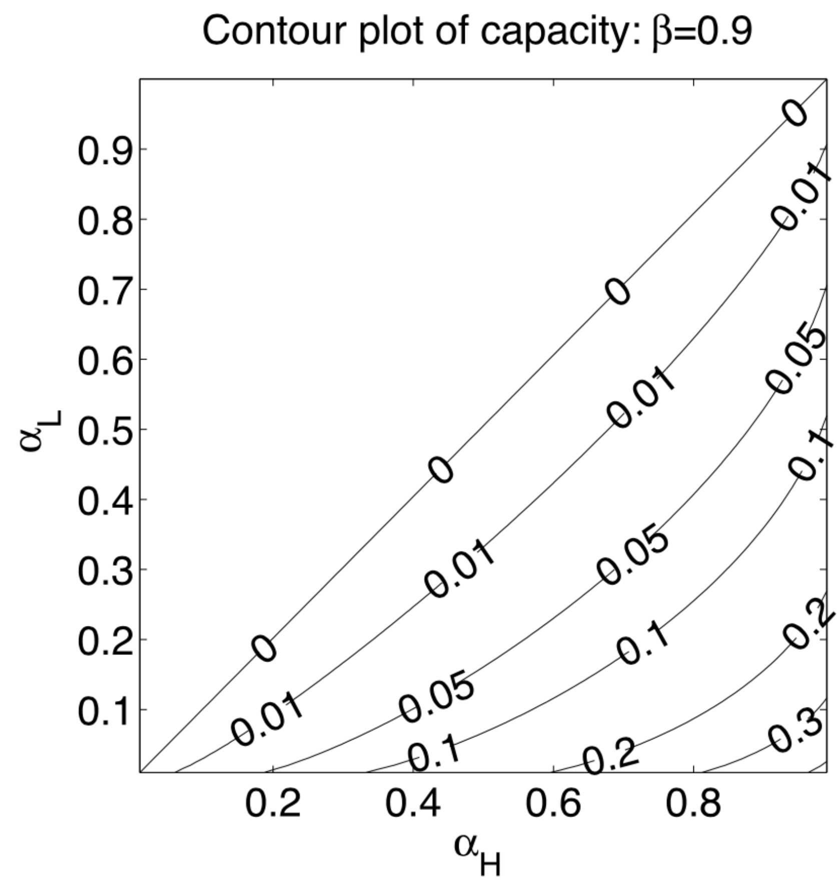


Fig. 4. Contour plot of capacity with respect to α_L and α_H, fixing $\beta = 0.9$. Note that $\alpha_L > \alpha_H$ in the upper left triangle, so capacity here is undefined.

Thomas & Eckford 2016 IEEE Transactions on Information Theory

Example 1: the BIND channel (a single binary receptor)

The mutual information decomposes:

$$I(X:Y) = \langle \mathbf{1}_{Y=\mathsf{U}} \rangle \left(\mathscr{H}\left(\langle \alpha \rangle\right) - \langle \mathscr{H}(\alpha) \rangle \right)$$

As $\Delta t \to 0$ we obtain a continuous time mutual information rate

$$\mathcal{I}(x) = -\left(\frac{\beta}{\beta + \bar{\alpha}}\right) \left(\bar{\alpha} \log(\bar{\alpha}) - (x \alpha_{\mathsf{H}} \log \alpha_{\mathsf{H}} + (1-x)\alpha_{\mathsf{L}} \log \alpha_{\mathsf{L}})\right)$$

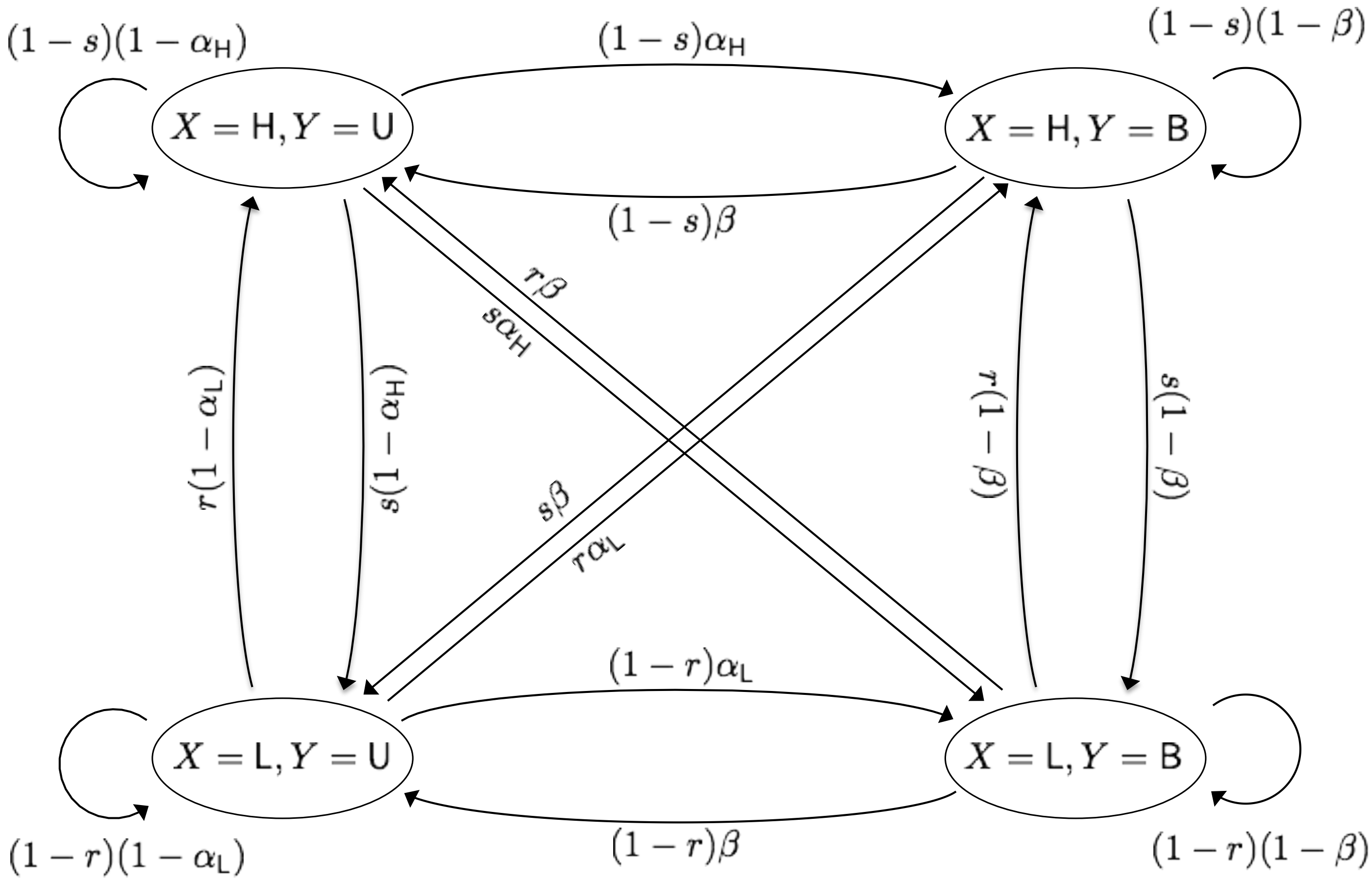
of the same form.
Here x is fraction of time input concentration signal is "high".
In the limit of rapid unbinding ($\beta \to \infty$) we recover Kabanov's capacity for the Poisson channel:

$$C_{\text{Kab}}(m, \lambda) = \frac{1}{e}(\lambda + m)\left(1 + \frac{m}{\lambda}\right)^{\lambda/m} - \lambda\left(1 + \frac{\lambda}{m}\right) \log\left(1 + \frac{m}{\lambda}\right)$$

where $\lambda = \alpha_{\mathsf{L}}$ and $m = \alpha_{\mathsf{H}} - \alpha_{\mathsf{L}}$.

Example 1: the BIND channel (a single binary receptor)

Special Case: Markov Inputs



Transition probabilities

$X : \mathsf{L} \to \mathsf{H}$ with prob. r.

$X : \mathsf{H} \to \mathsf{L}$ with prob. s.

$Y : \mathsf{U} \to \mathsf{B}$ with prob. $\alpha_{\mathsf{L}/\mathsf{H}}(X)$.

$Y : \mathsf{B} \to \mathsf{U}$ with prob. β.

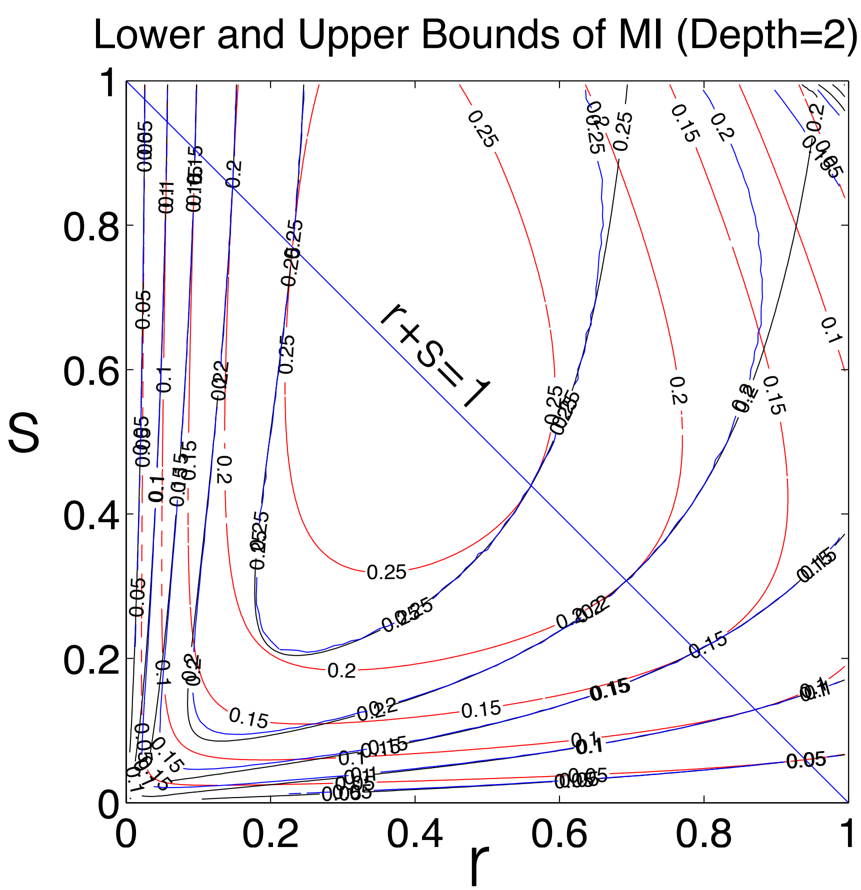
Example 1: the BIND channel (a single binary receptor)

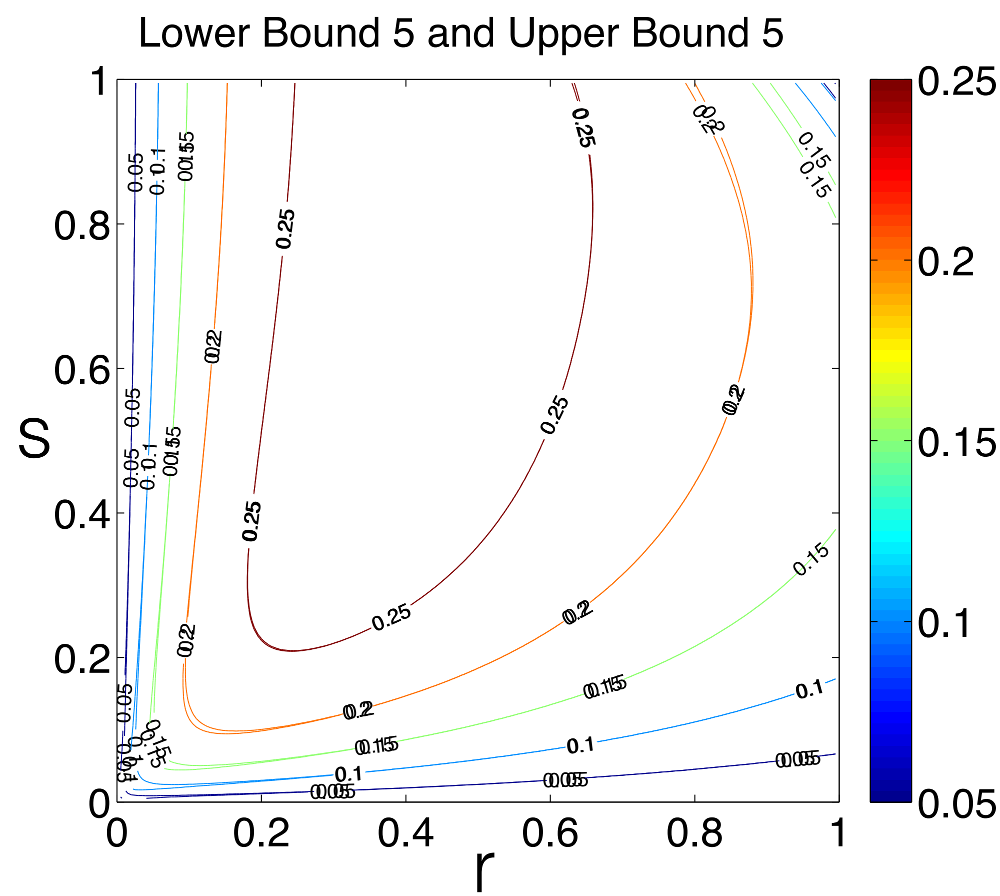
Joint process is Markov on four states: $X \in \{\mathsf{L}, \mathsf{H}\}, Y \in \{\mathsf{U}, \mathsf{B}\}$.

$$\mathcal{I}(X:Y) = \mathcal{H}(X,Y) - \mathcal{H}(X) - \mathcal{H}(Y)$$

Entropy rates $\mathcal{H}(X,Y)$ and $\mathcal{H}(X)$ are known in closed form.
Approximate $\mathcal{H}(Y) = \lim_{n\to\infty} H(Y_n|Y_{n-1},\ldots,Y_0)$ with

$$H(Y_n|Y_{n-1},\ldots,Y_0,X_0) \le \mathcal{H}(Y) \le H(Y_n|Y_{n-1},\ldots,Y_0)$$





Multiple Independent Receptors

* One BIND receptor.

$$U \underset{\tau\beta}{\overset{\tau\alpha_{H/L}}{\rightleftharpoons}} B$$

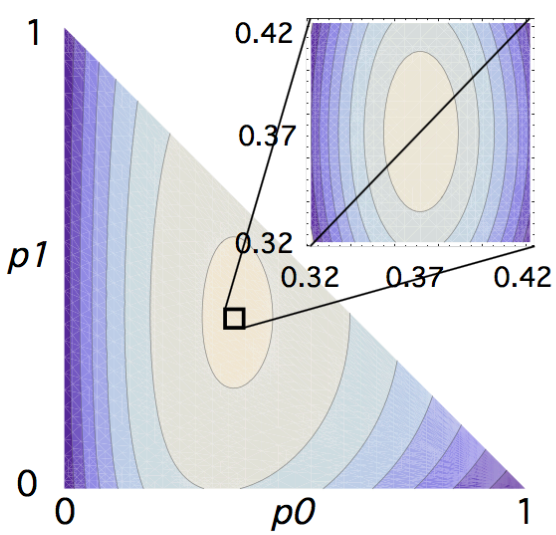
* Two independent BIND receptors

$$0 \underset{\tau\beta}{\overset{2\tau\alpha_{H/L}}{\rightleftharpoons}} 1 \underset{2\tau\beta}{\overset{\tau\alpha_{H/L}}{\rightleftharpoons}} 2$$

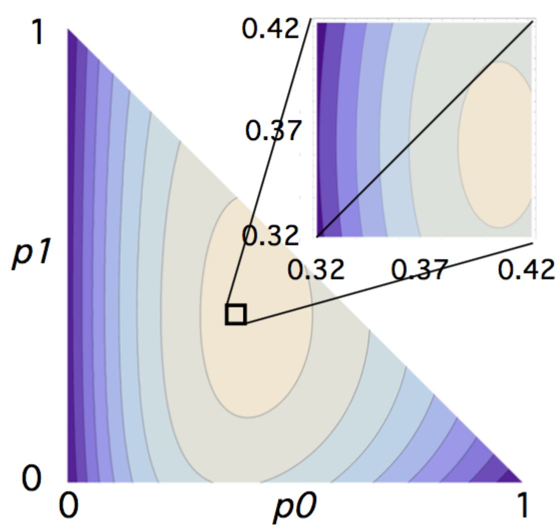
* n independent BIND receptors

$$0 \underset{\tau\beta}{\overset{n\tau\alpha_{H/L}}{\rightleftharpoons}} 1 \underset{2\tau\beta}{\overset{(n-1)\tau\alpha_{H/L}}{\rightleftharpoons}} 2 \cdots k \underset{(k+1)\tau\beta}{\overset{(n-k)\tau\alpha_{H/L}}{\rightleftharpoons}} k+1 \cdots n-1 \underset{n\tau\beta}{\overset{\tau\alpha_{H/L}}{\rightleftharpoons}} n$$

two independent receptors



two non-independent receptors

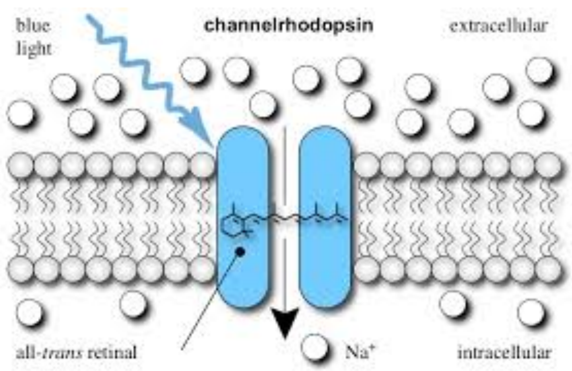


Capacity for n independent receptors is n times the single-receptor capacity.

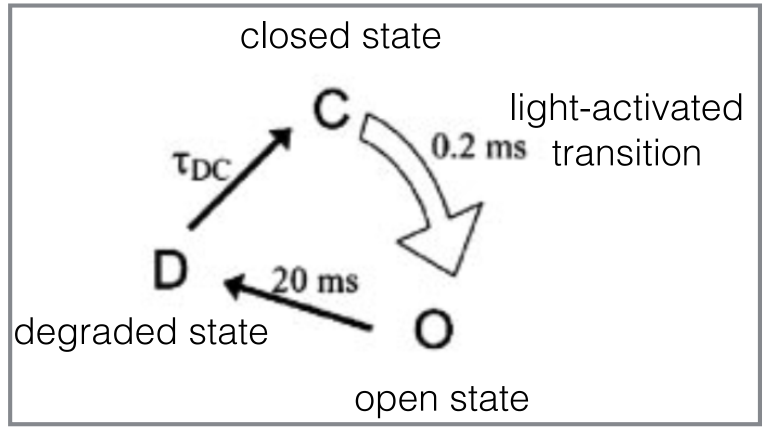
Thomas and Eckford 2016 ISIT

Example 2: Channelrhodopsin

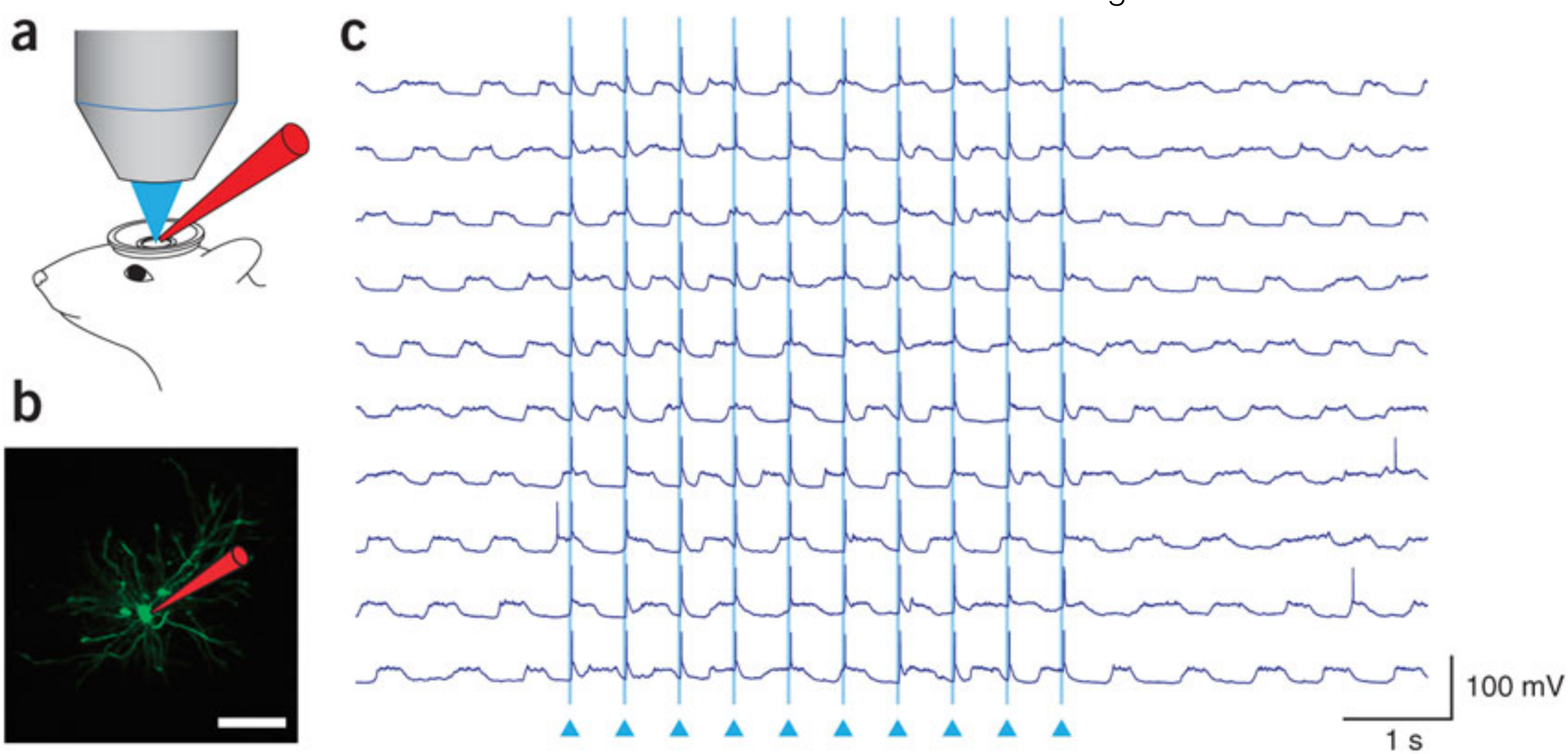
(Eckford & Thomas, under review)



openoptogenetics.org



Nagel et al 2003 PNAS

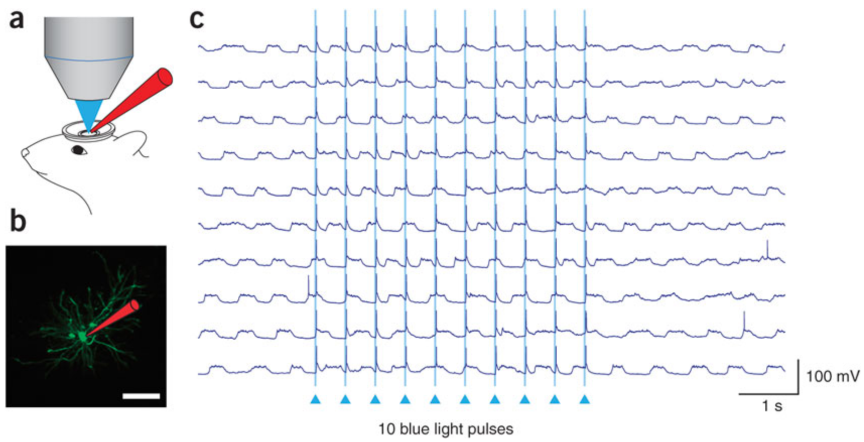


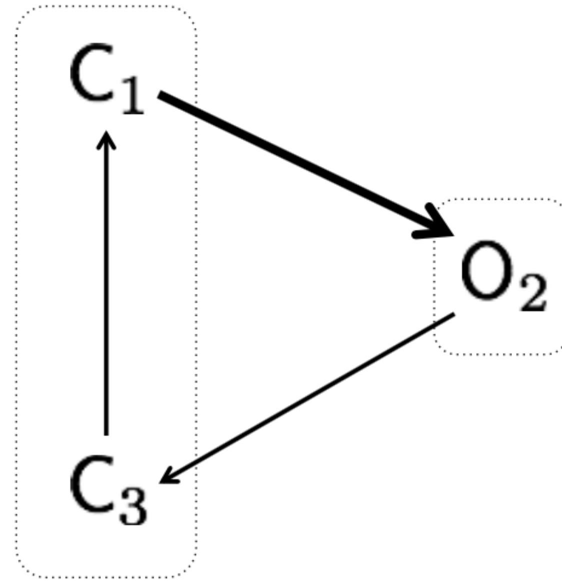
Judkewitz et al 2009 Nat. Protocols

10 blue light pulses

Example 2: Channelrhodopsin

(Eckford & Thomas, under review)





$$Q = \begin{bmatrix} R_1 & q_{12}x(t) & 0 \\ 0 & R_2 & q_{23} \\ q_{31} & 0 & R_3 \end{bmatrix}$$

Parameter	from [2]	Units
$q_{12}x(t)$	$(5 \times 10^3)x(t)$	s^{-1}
q_{23}	50	s^{-1}
q_{31}	17	s^{-1}

Input: Light intensity
Channel States: 2 closed, 1 open.
One sensitive state; one observable transition.

Channelrhodopsin under IID inputs

(Eckford & Thomas, under review)

- If the input sequence is IID, the channel state $\{Y(k\Delta t)\}_{k\geq 0}$ forms a Markov chain[1] with stationary distribution π_y.
- The mutual information between input X & channel state Y is

$$\mathcal{I}(X;Y) =$$
$$\sum_{(y_{i-1},y_i)\in\mathcal{S}} \pi_{y_{i-1}} \left(\sum_{x_i\in\mathcal{X}} p(x_i)\phi\Big(p(y_i \mid x_i, y_{i-1})\Big) - \phi\left(\sum_{x_i\in\mathcal{X}} p(x_i)p(y_i \mid x_i, y_{i-1})\right)\right).$$

Here $\mathcal{S}$ is the set of sensitive transitions and $\phi(p) = p \log p$.

- For channelrhodopsin we find

$$\begin{aligned}
&\mathcal{I}(X;Y)\\
&= \pi_{C_1}\Big(\mathscr{H}(p_L\Delta t q_{12}x_L + p_H\Delta t q_{12}x_H) - p_L\mathscr{H}(\Delta t q_{12}x_L) - p_H\mathscr{H}(\Delta t q_{12}x_H)\Big)\\
&= \frac{\mathscr{H}(p_L\Delta t q_{12}x_L + p_H\Delta t q_{12}x_H) - p_L\mathscr{H}(\Delta t q_{12}x_L) - p_H\mathscr{H}(\Delta t q_{12}x_H)}{1 + E[x](q_{12}/q_{23} + q_{12}/q_{31})},
\end{aligned}$$

where $E[x] = p_L x_L + p_H x_H$ is the average input intensity.

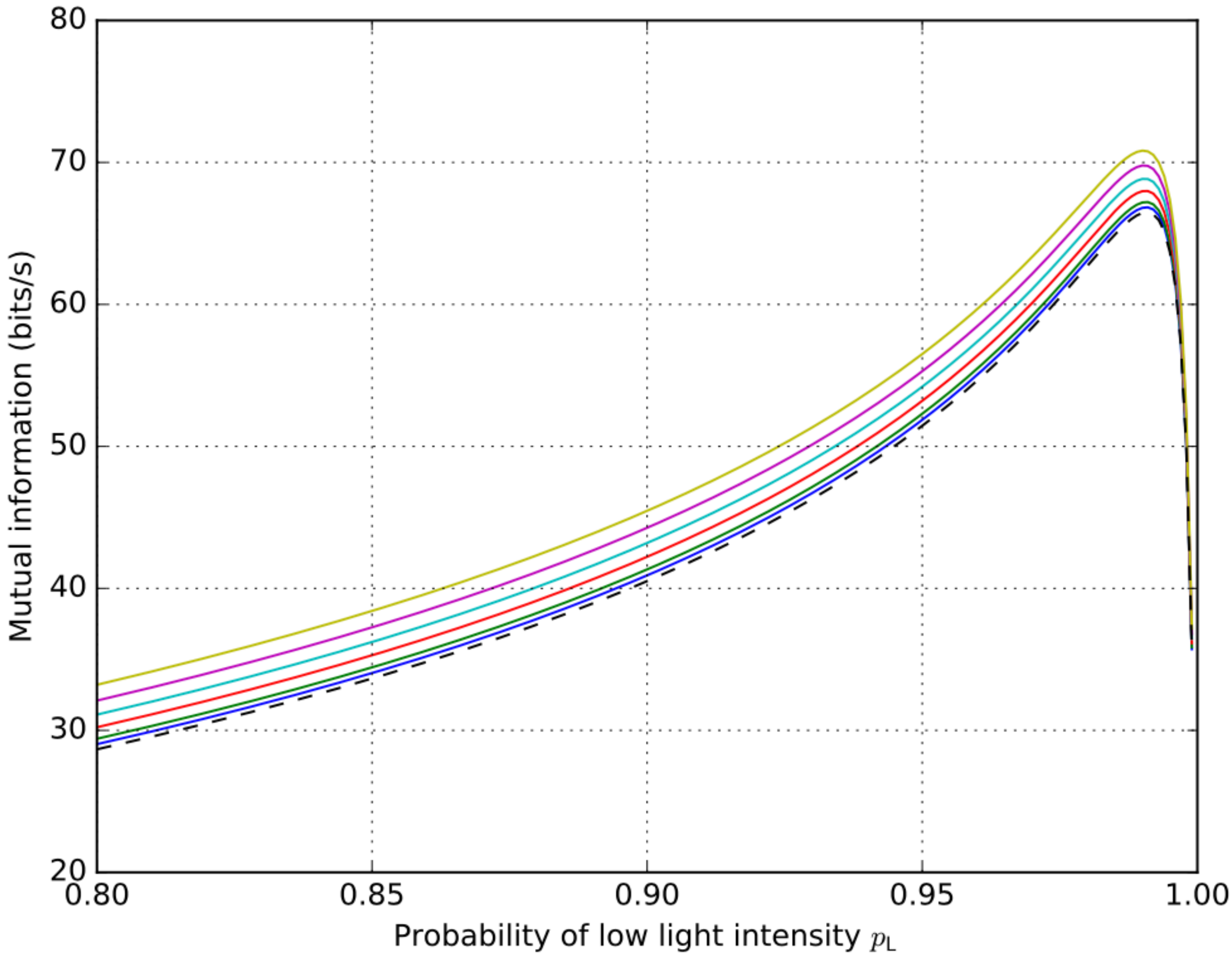
---

[1] Y is time-homogeneous, irreducible, aperiodic, and positive recurrent.

Channelrhodopsin under IID inputs

(Eckford & Thomas, under review)

As $\Delta t \to 0$ the mutual information rate $I(X;Y)$ converges.



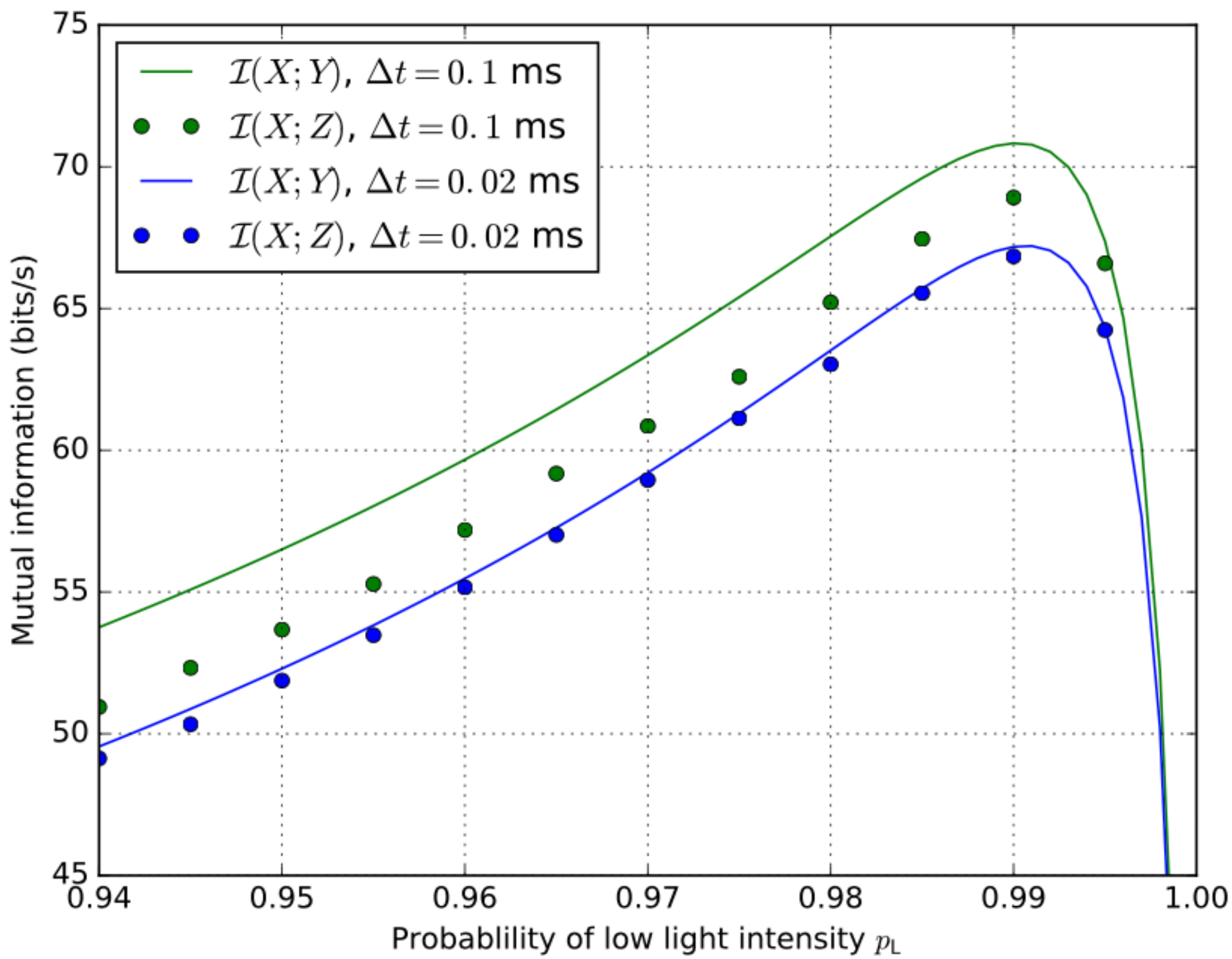
Channelrhodopsin under IID inputs

(Eckford & Thomas, under review)

For the *partially observed* channel, $I(X;Z) \leq I(X;Y)$.

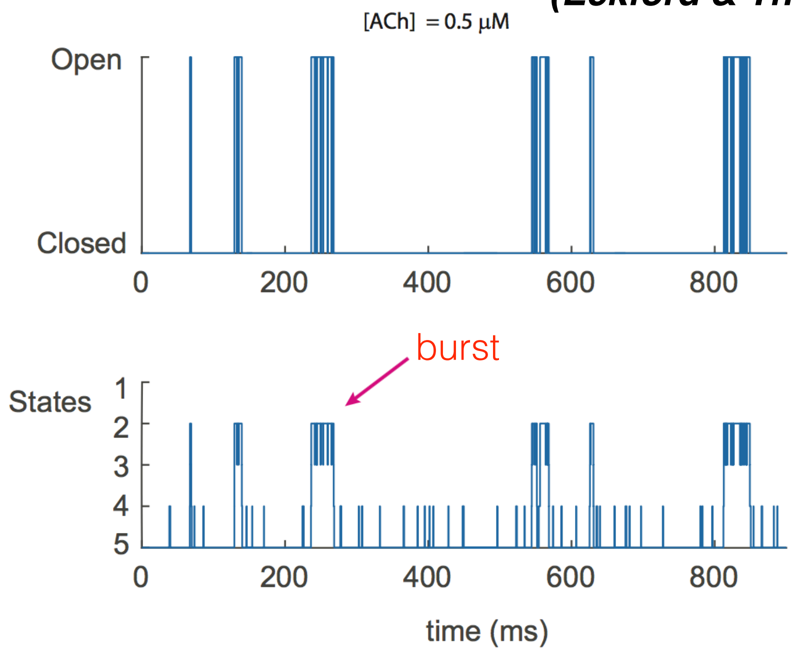
For channelrhodopsin, all sensitive transitions are observable.

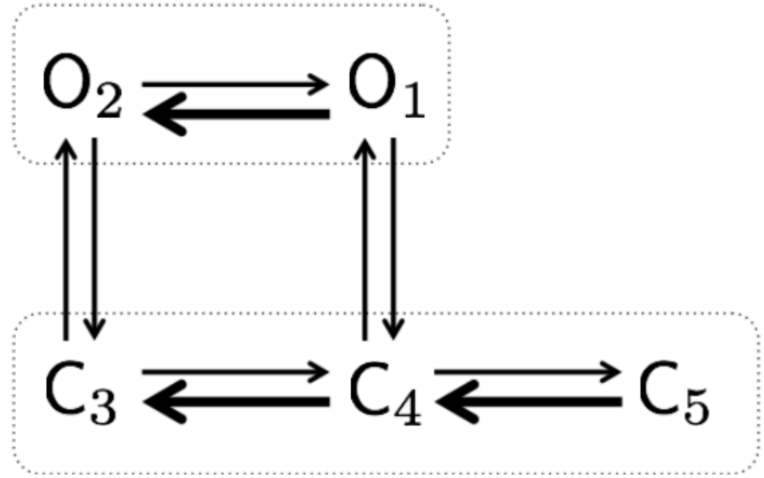
Monte Carlo estimates suggest that as $\Delta t \to 0$, we have $I(X;Z) \to I(X;Y)$.



Example 3: Acetylcholine receptor

(Eckford & Thomas, under review)



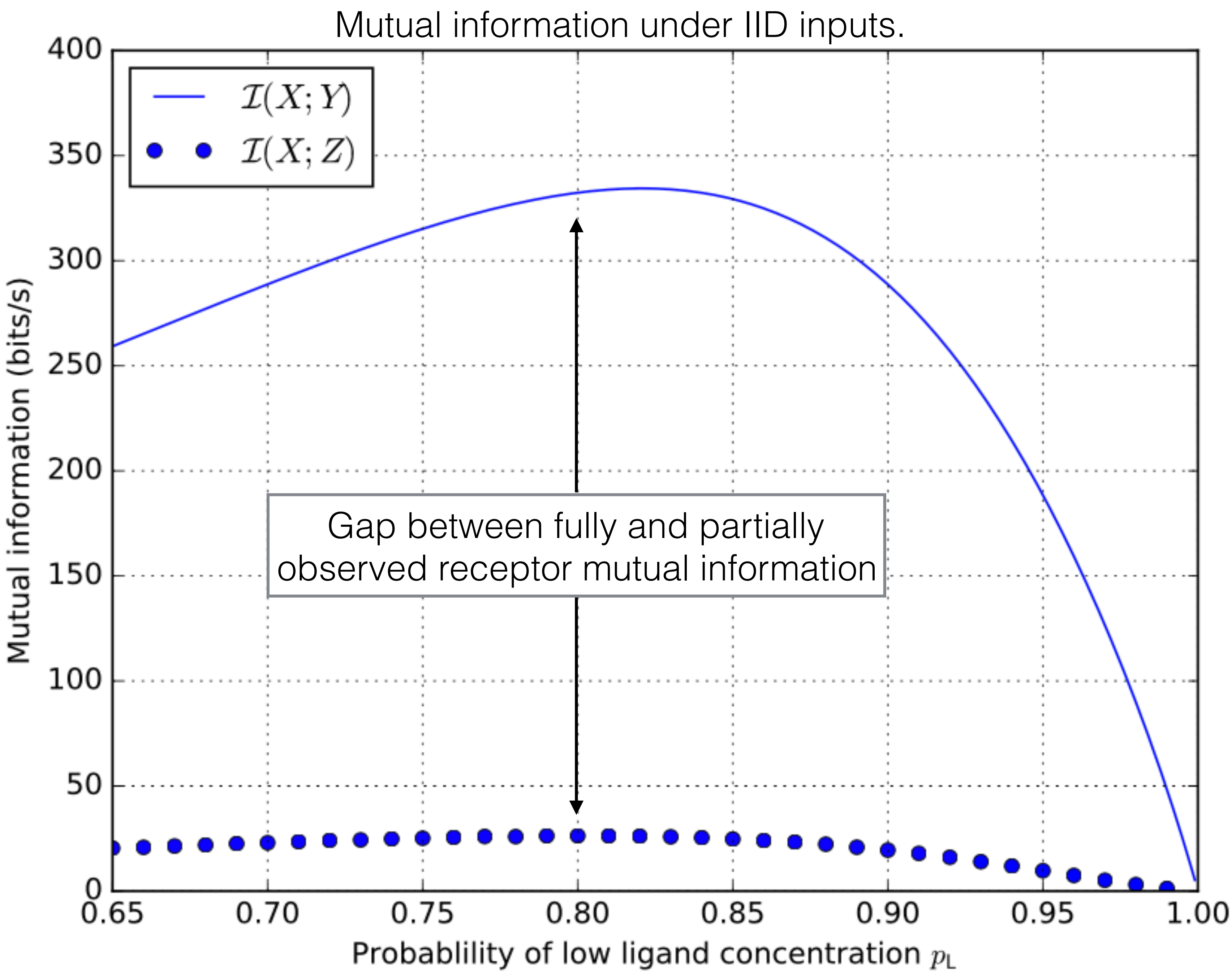


$$Q = \begin{bmatrix} R_1 & q_{12}x(t) & 0 & q_{14} & 0 \\ q_{21} & R_2 & q_{23} & 0 & 0 \\ 0 & q_{32} & R_3 & q_{34} & 0 \\ q_{41} & 0 & q_{43}x(t) & R_4 & q_{45} \\ 0 & 0 & 0 & q_{54}x(t) & R_5 \end{bmatrix}$$

Parameter	Name in [3]	Value/range	Units
$q_{12}x(t)$	$k_{+2}x$	$(5 \times 10^8)x(t)$	s^{-1}
q_{14}	α_1	3×10^3	s^{-1}
q_{21}	$2k^*_{-2}$	0.66	s^{-1}
q_{23}	α_2	5×10^2	s^{-1}
q_{32}	β_2	1.5×10^4	s^{-1}
q_{34}	$2k_{-2}$	4×10^3	s^{-1}
q_{41}	β_1	15	s^{-1}
$q_{43}x(t)$	$k_{+2}x$	$(5 \times 10^8)x(t)$	s^{-1}
q_{45}	k_{-1}	2×10^3	s^{-1}
$q_{54}x(t)$	$2k_{+1}x$	$(1 \times 10^8)x(t)$	s^{-1}

Input: Acetylcholine [ACh] concentration
Channel States: 3 closed, 2 open
Three sensitive states; 4 observable transitions.

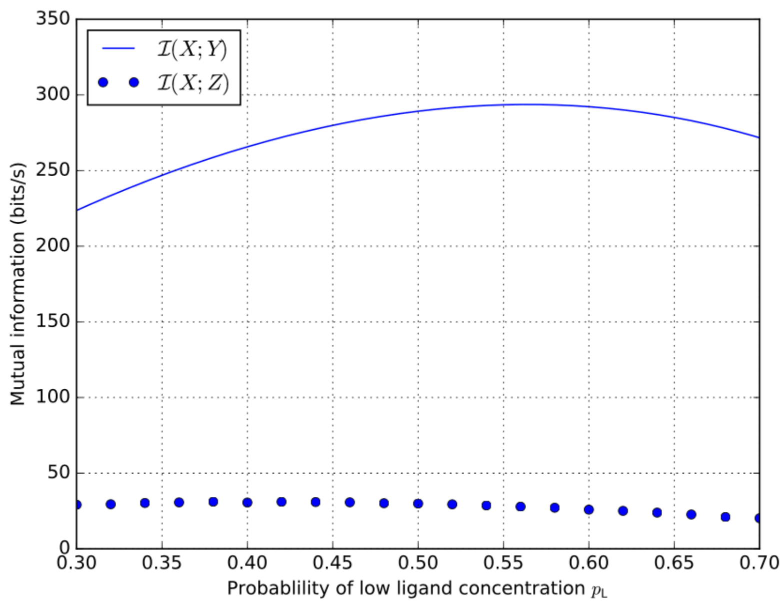
Example 3: Acetylcholine receptor

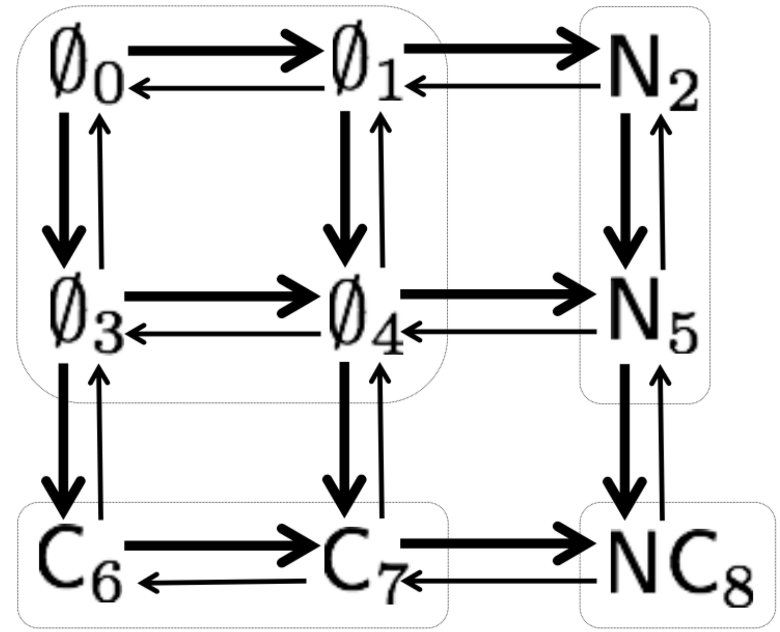


(Eckford & Thomas, under review)

Example 4: Calmodulin (a Calcium binding protein)

(Eckford & Thomas, under review)





$$\begin{bmatrix}
R_0 & q_{01}x(t) & 0 & q_{03}x(t) & 0 & 0 & 0 & 0 & 0 \\
q_{10} & R_1 & q_{12}x(t) & 0 & q_{14}x(t) & 0 & 0 & 0 & 0 \\
0 & q_{21} & R_2 & 0 & 0 & q_{25}x(t) & 0 & 0 & 0 \\
q_{30} & 0 & 0 & R_3 & q_{34}x(t) & 0 & q_{36}x(t) & 0 & 0 \\
0 & q_{41} & 0 & q_{43} & R_4 & q_{45}x(t) & 0 & q_{47}x(t) & 0 \\
0 & 0 & q_{52} & 0 & q_{54} & R_5 & 0 & 0 & q_{58}x(t) \\
0 & 0 & 0 & q_{63} & 0 & 0 & R_6 & q_{67}x(t) & 0 \\
0 & 0 & 0 & 0 & q_{74} & 0 & q_{76} & R_7 & q_{78}x(t) \\
0 & 0 & 0 & 0 & 0 & q_{85} & 0 & q_{87} & R_8
\end{bmatrix}$$

Parameter	Name in [4]	Value/range	Units
$q_{01}x(t)$, $q_{34}x(t)$, $q_{67}x(t)$	$k_{\mathrm{on(T),N}}$	$(7.7 \times 10^8)x(t)$	s^{-1}
q_{10}, q_{43}, q_{76}	$k_{\mathrm{off(T),N}}$	1.6×10^5	s^{-1}
$q_{12}x(t)$, $q_{45}x(t)$, $q_{78}x(t)$	$k_{\mathrm{on(R),N}}$	$(3.2 \times 10^{10})x(t)$	s^{-1}
q_{21}, q_{54}, q_{87}	$k_{\mathrm{off(R),N}}$	2.2×10^4	s^{-1}
$q_{03}x(t)$, $q_{14}x(t)$, $q_{25}x(t)$	$k_{\mathrm{on(T),C}}$	$(8.4 \times 10^7)x(t)$	s^{-1}
q_{30}, q_{41}, q_{52}	$k_{\mathrm{off(T),C}}$	2.6×10^3	s^{-1}
$q_{36}x(t)$, $q_{47}x(t)$, $q_{58}x(t)$	$k_{\mathrm{on(R),C}}$	$(2.5 \times 10^7)x(t)$	s^{-1}
q_{63}, q_{74}, q_{85}	$k_{\mathrm{off(R),C}}$	6.5	s^{-1}

Input: Calcium [Ca2+] concentration
Channel States: 9 states of 4 types
8 sensitive states
6 of 12 sensitive transitions are also observable.

Conclusions

- Bio to Engineering: Intensity-driven signal transduction systems provide a broad class of biologically motivated communications channel models.
- Engineering to Bio: Fully and partially observed channel models under IID inputs are amenable to capacity analysis.
- The mutual information gap between fully and partially observed channels depends on the observability of those edges which are sensitive to the input.

Ongoing work

- Capacity of general N-state intensity-driven receptor.
- Gap between partially & fully observed receptors: theory?
- Net capacity of ligand secretion, diffusion, binding channel.
- Energetics: metabolic burden; information cost *vs* fitness.

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