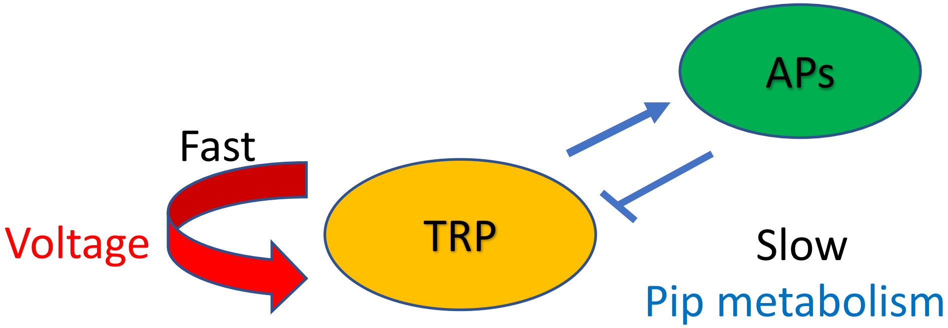
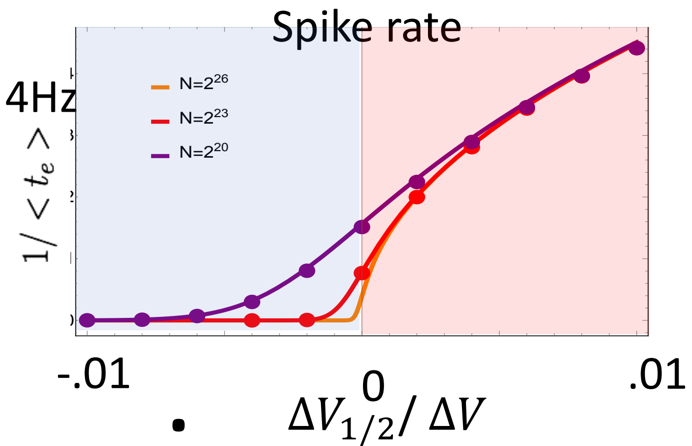




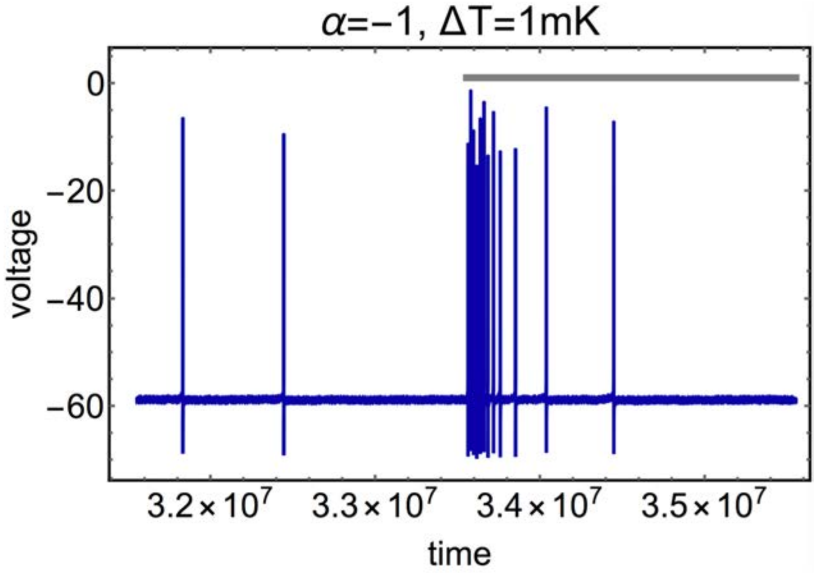
Criticality and Bifurcations in Cellular Sensing

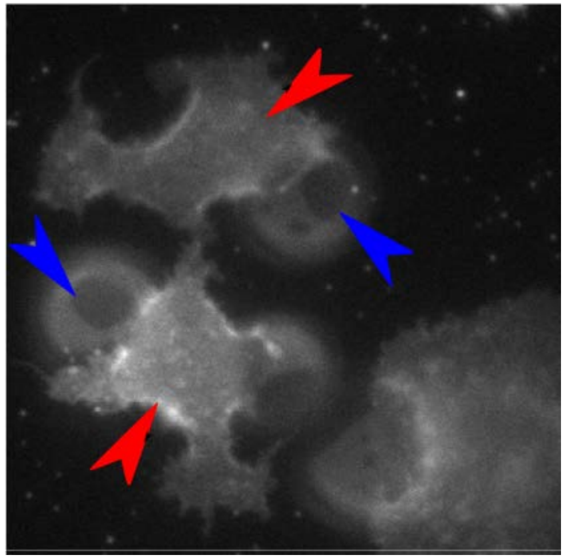
Ben Machta

Physics and Systems Biology,

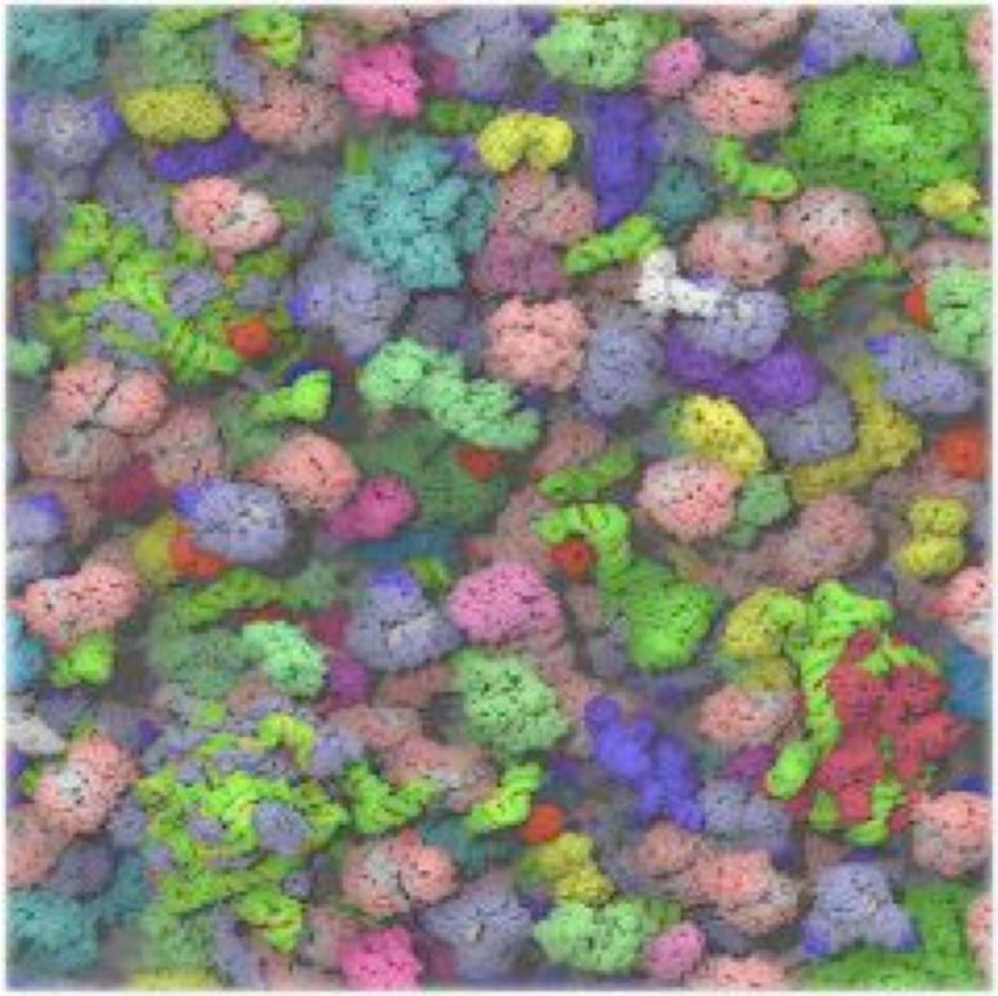
Yale University

Physics Club, April 18

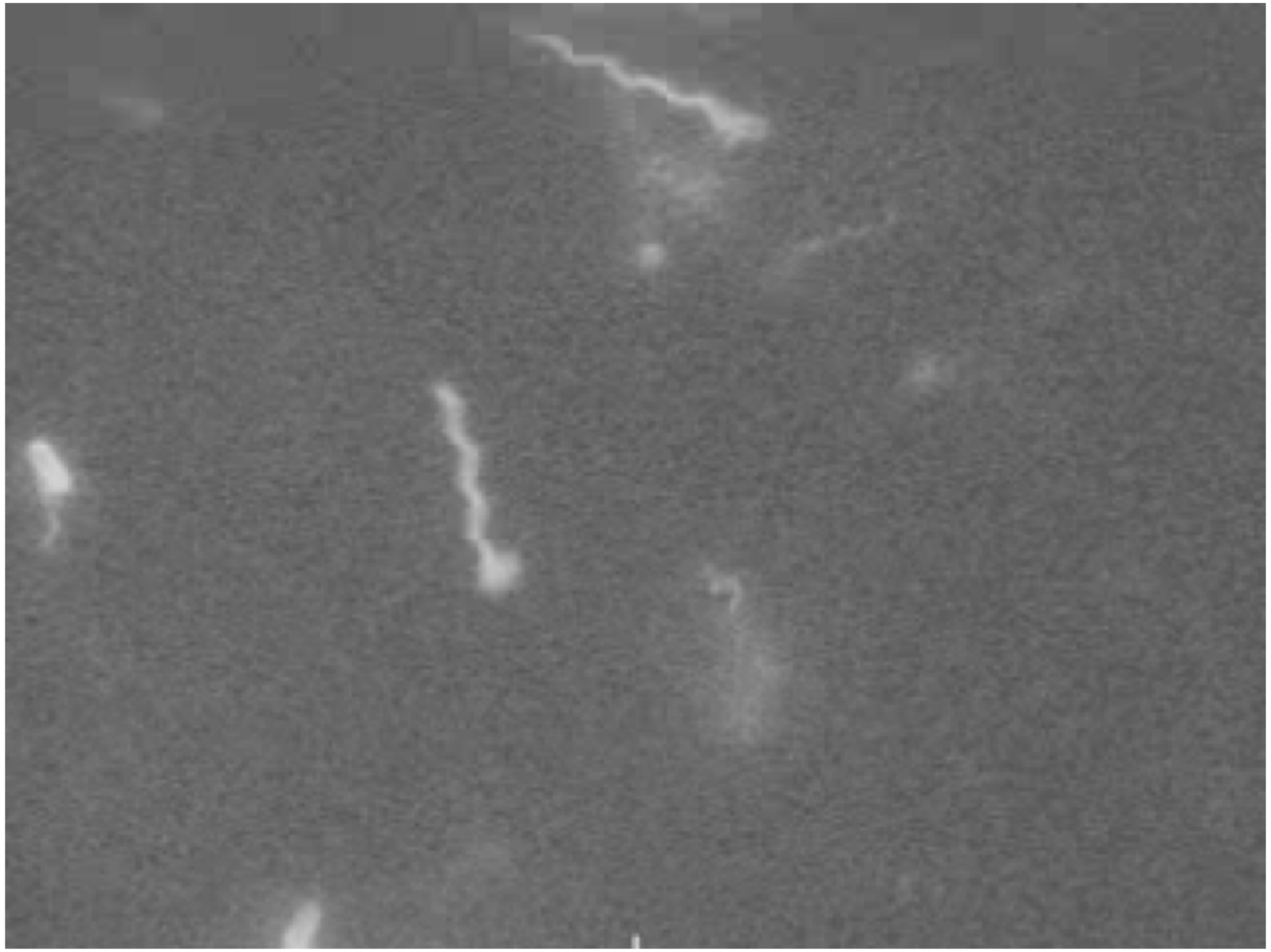




Biology is the ultimate example of emergence

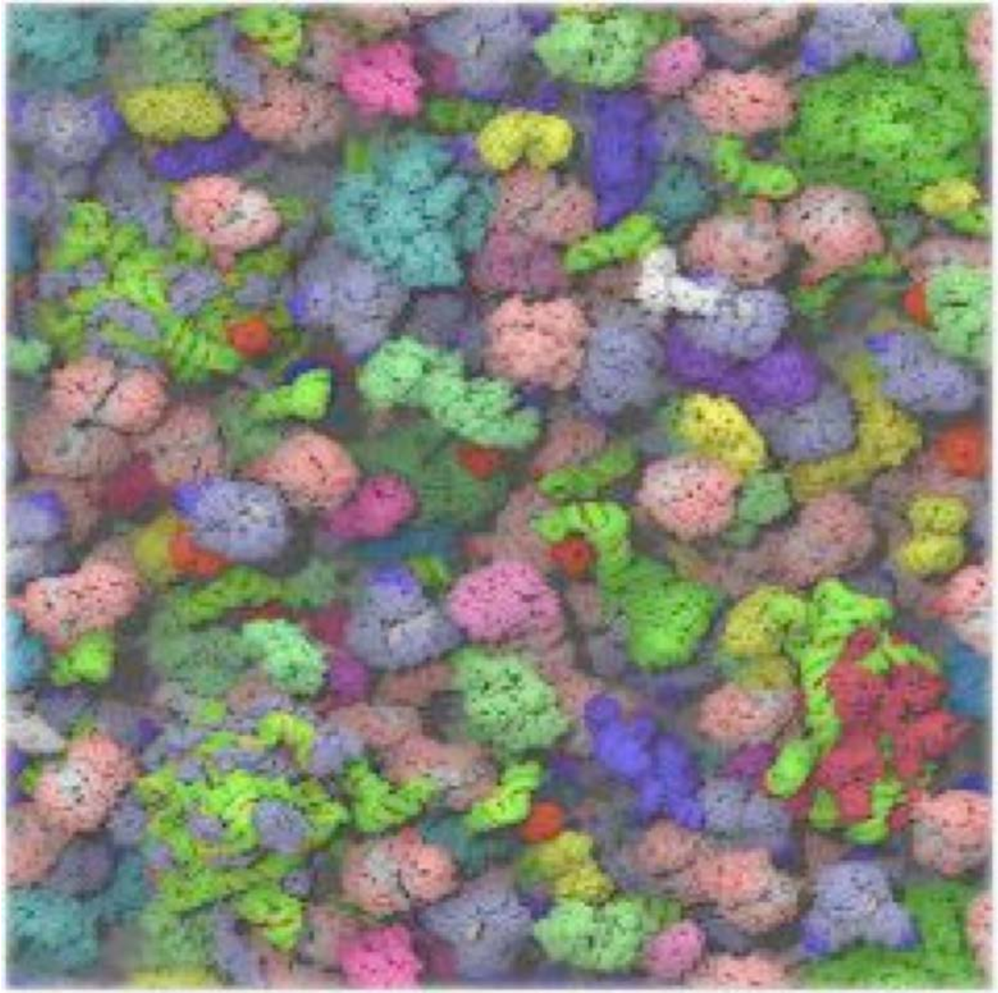


McGuffee SR, Elcock AH (2010)



Berg lab

Biology is the ultimate example of emergence

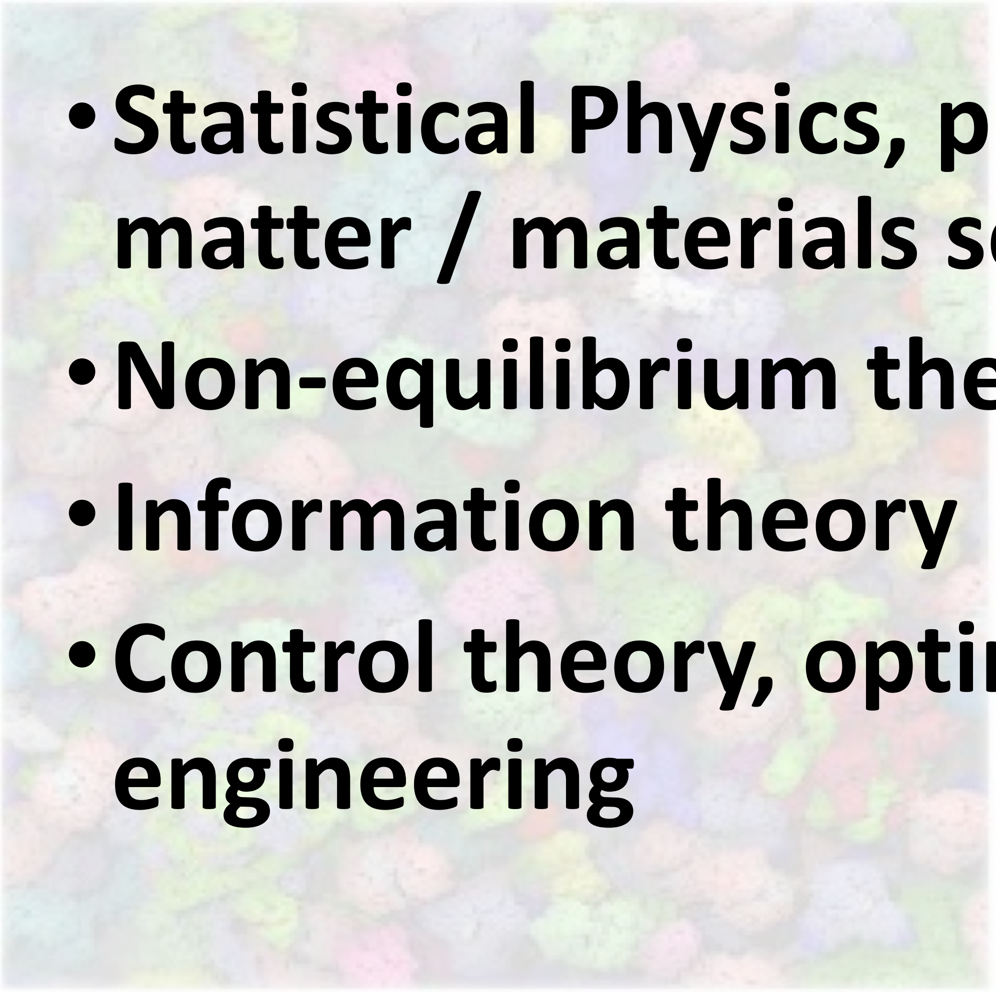


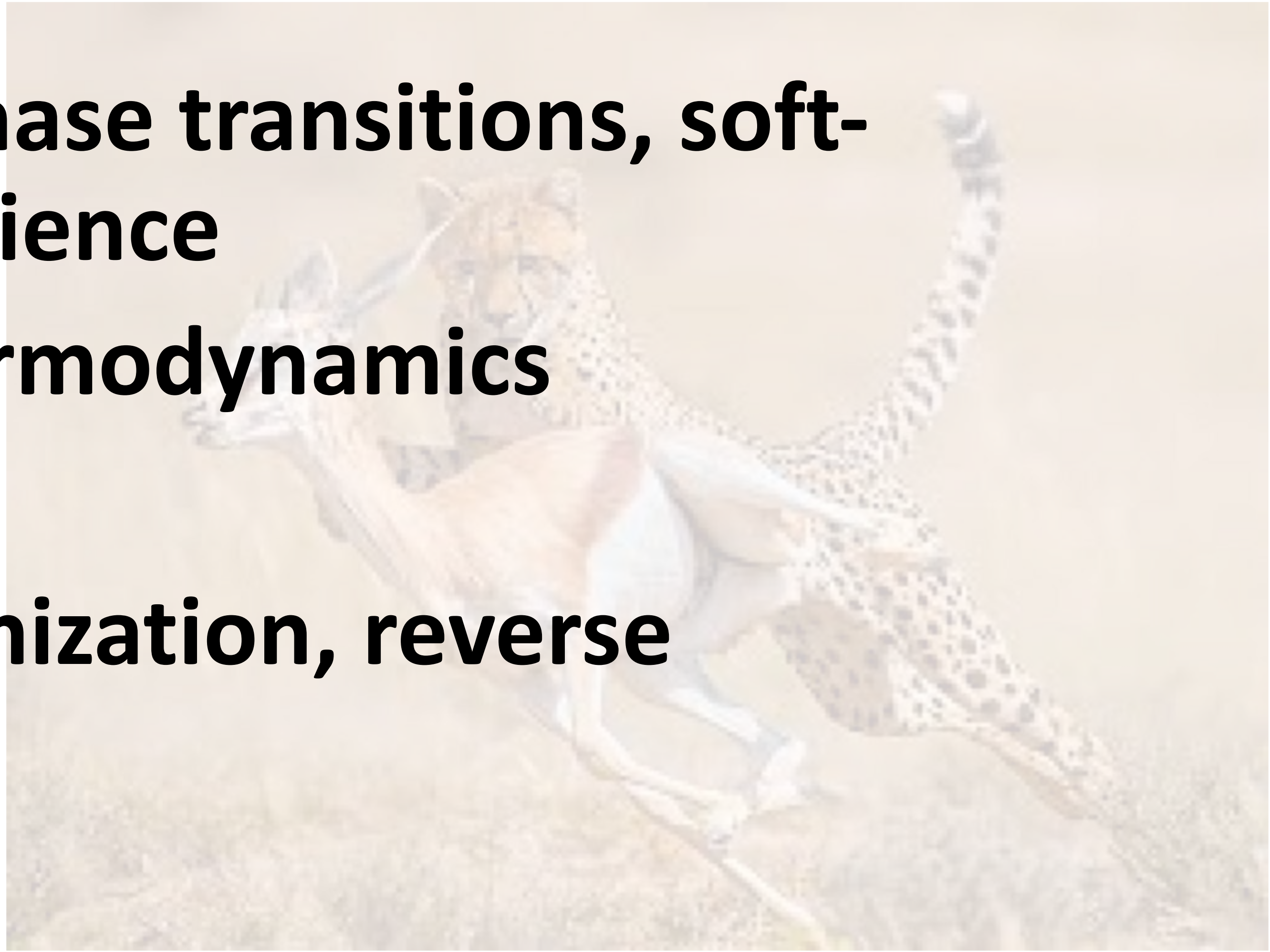
McGuffee SR, Elcock AH (2010)

Questions for Physics of Living Systems:

- **How does comprehensible function emerge from many noisy molecular machines?**
- **What are the functions of Living Systems and what constraints limit them?**
- **How do living systems gather and process information distributed among many noisy components?**

Tools for Physics of Living Systems:

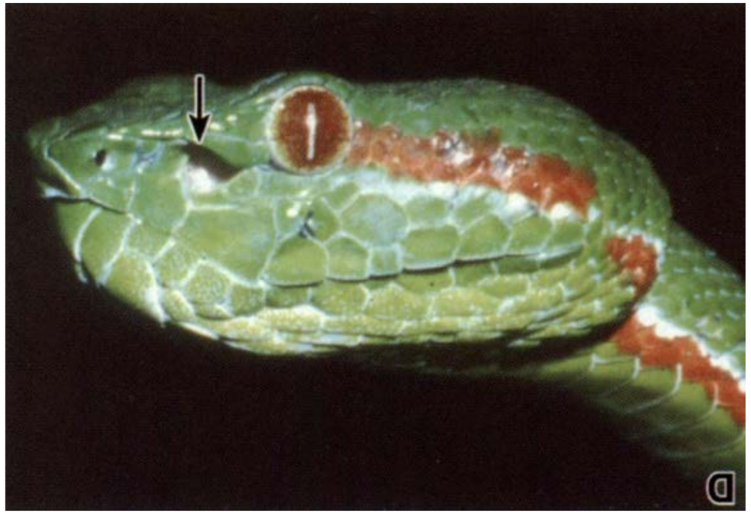




- **Statistical Physics, phase transitions, soft-matter / materials science**
- **Non-equilibrium thermodynamics**
- **Information theory**
- **Control theory, optimization, reverse engineering**

In this talk

- **Overview of recent directions in my group**
- **Main: extreme thermal sensitivity in the pit organ**
  - **Physiology/ecology of pit organ, neurons, TRP family ion channels**
  - **Frame sensing problem pit organ must solve**
  - **Proposed mechanism – dynamical bifurcation in electrical activity**
- **Further Directions / Conclusions**



Acknowledgements

- Group members
  - Michael Abbott
  - Sam Bryant
  - **Isabella Graf**
  - Pranav Kantroo
  - Asheesh Momi
  - Mason Rouches
  - Julian Rubinfien
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  - Derek Sherry
  - Anjiabei Wang
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  - **Sarah Veatch (U Mich)**
  - Thierry Emonet
  - Henry Mattingly
  - Keita Kamino
  - Michael Murrell
  - Erdem Karatekin
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  - Laura Newburgh
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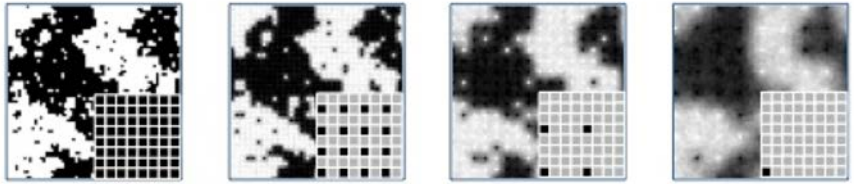
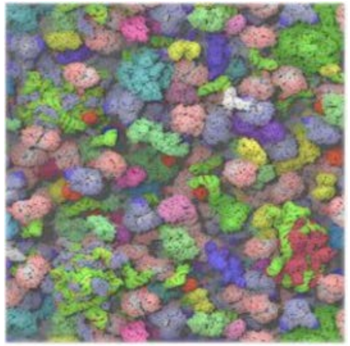
Isabella Graf

Emergent simplicity in complex models





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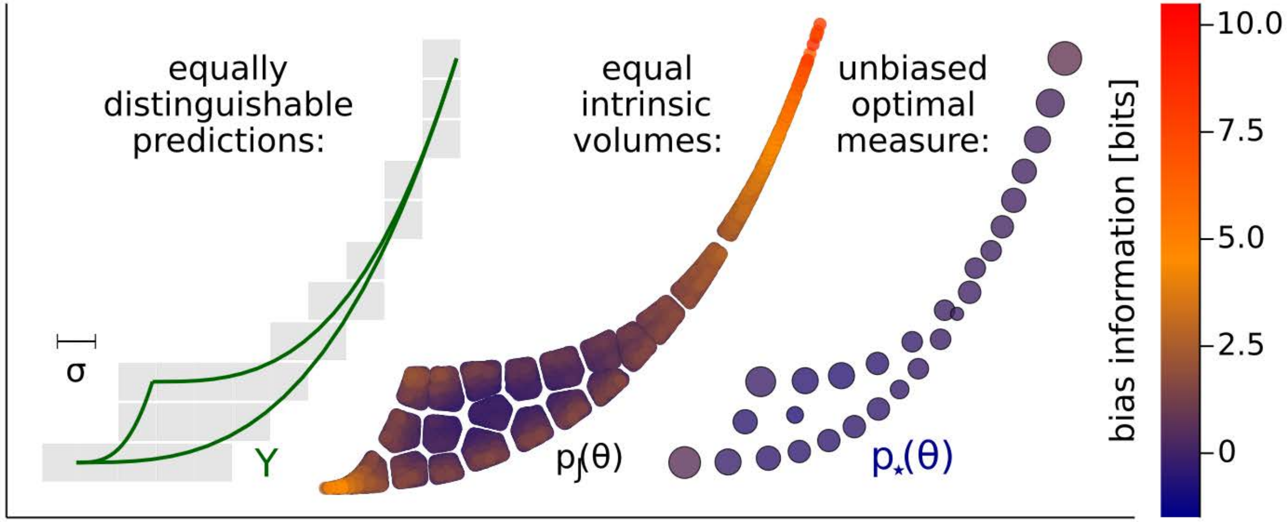
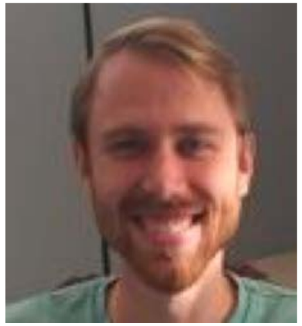


Michael Abbott



Henry Mattingly

BBM, Chachra, Transtrum, Sethna. **Parameter Space Compression Underlies Emergent Theories and Predictive Models.** *Science (2013)*

Mattingly, Transtrum, Abbott and BBM**, Maximizing the information learned from finite data selects a simple model.** PNAS, 2018

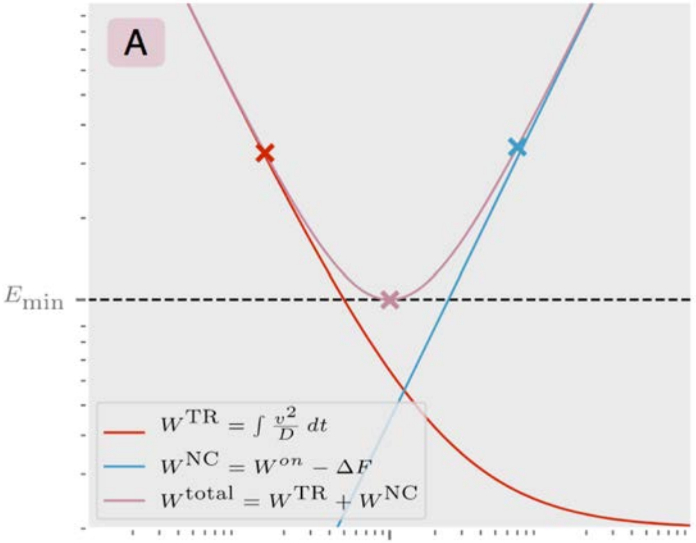
Abbott, BBM, **A scaling law from discrete to continuous solutions of channel capacity problems in the low-noise limit,** J Stat Phys 2019

Energetic bounds

Moving a thermodynamic system requires sub-extensive energy

$$S \geq 2\mathcal{L}(\boldsymbol{\lambda}_i, \boldsymbol{\lambda}_f) + \frac{\tilde{\mathcal{L}}^2(\boldsymbol{\lambda}_i, \boldsymbol{\lambda}_f)}{\Delta t}$$

Sam Bryant

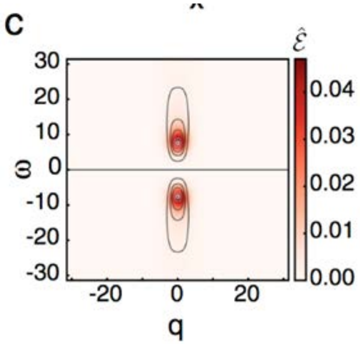


Bryant and BBM**, Energy Dissipation Bounds for Autonomous thermodynamic Cycles.** PNAS, 2020

Time asymmetric data implies entropy production

$$\dot{s} = \int \frac{d\omega}{2\pi} \frac{d^d\mathbf{q}}{(2\pi)^d} \mathcal{E}(\mathbf{q}, \omega);$$

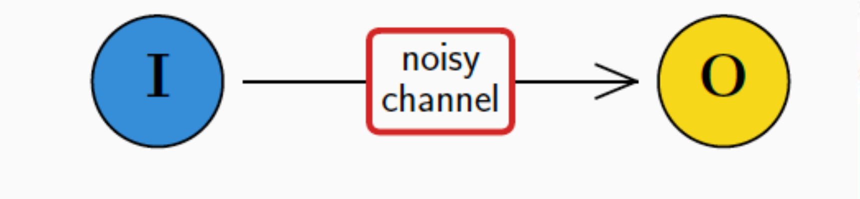
$$\mathcal{E}(\mathbf{q}, \omega) = \frac{1}{2}\left[C^{-1}(\mathbf{q}, -\omega) - C^{-1}(\mathbf{q}, \omega)\right]_{ij} C^{ji}(\mathbf{q}, \omega).$$



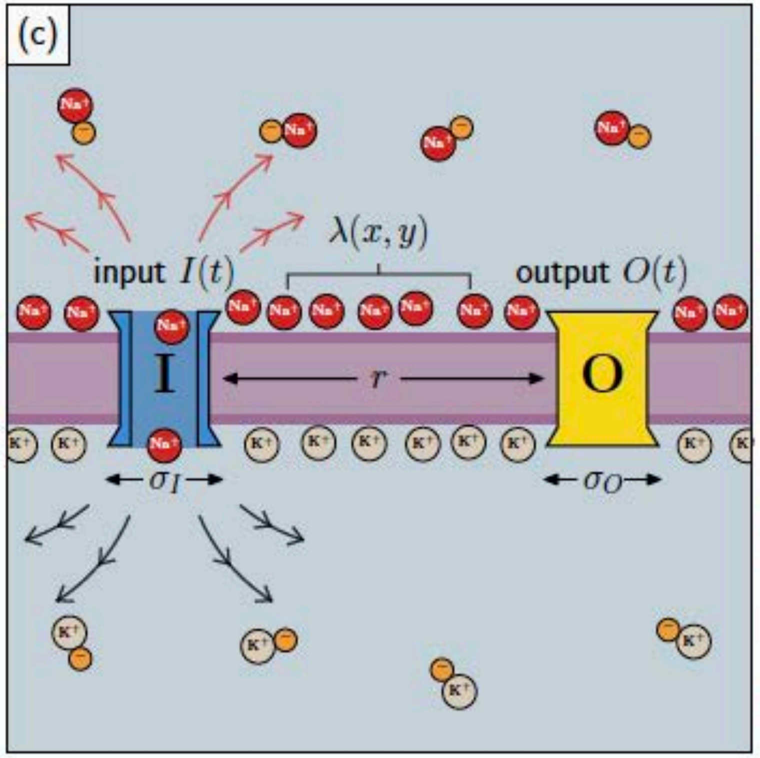
Danny Seara　　Michael Murrell

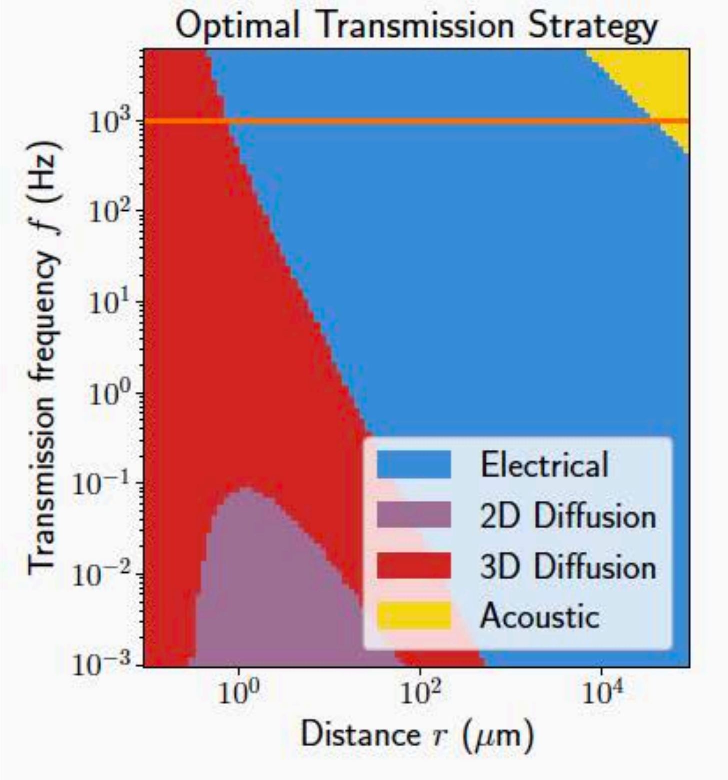
Seara, BBM, Murrell **Energy Dissipation Irriversibility in Dynamical Phases and Trtansitions.** Nat Comm, 2020

Energetic costs of sending information

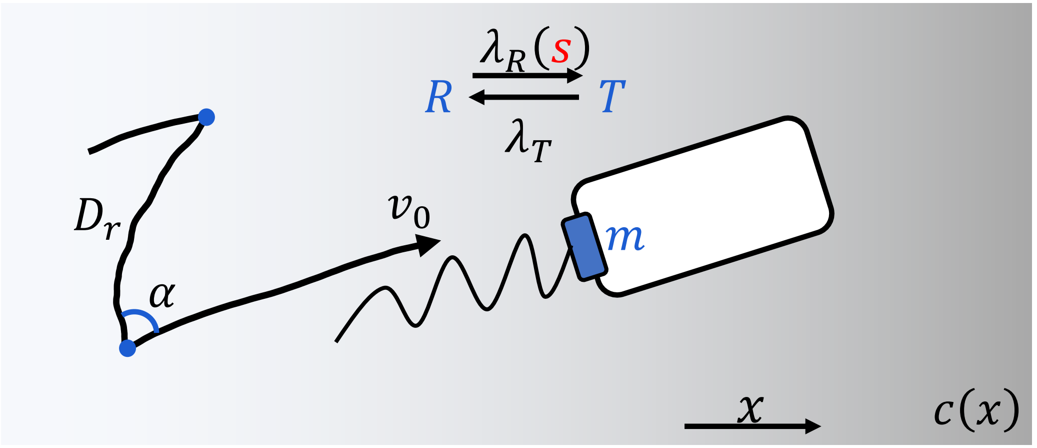


Sam Bryant

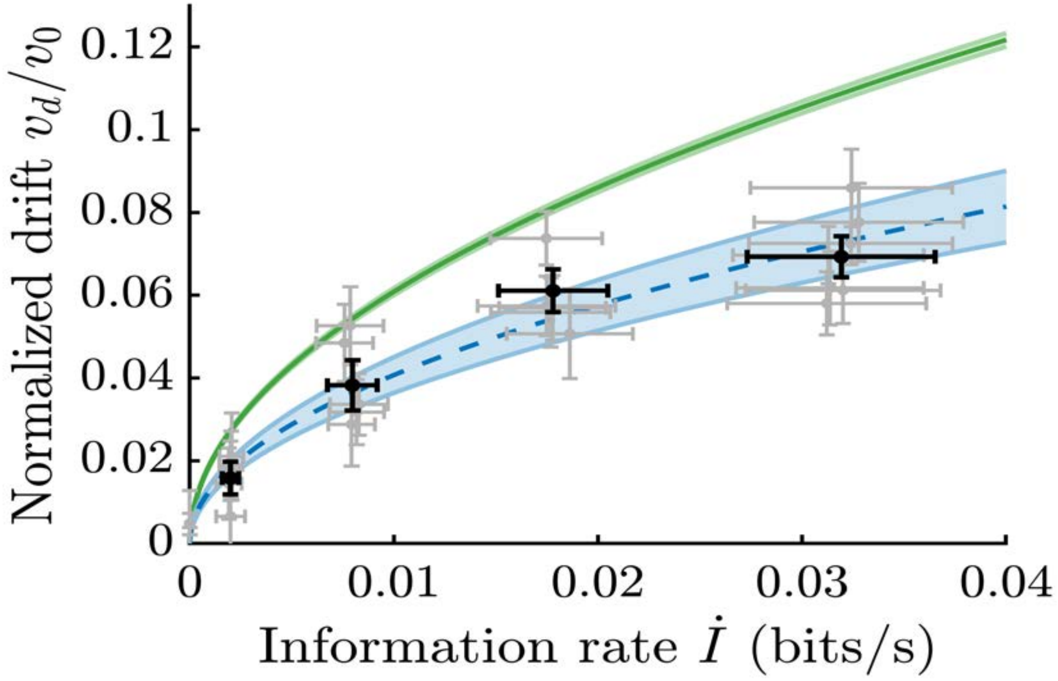




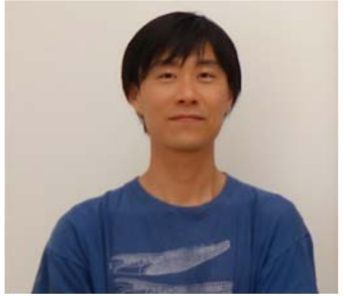
E. coli Chemotaxis is information limited



Performance $\leq$ f(Information rate)



Henry Mattingly



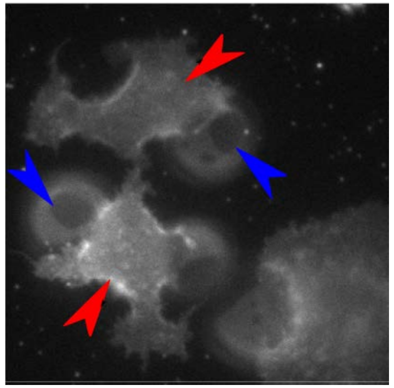
Keita Kamino

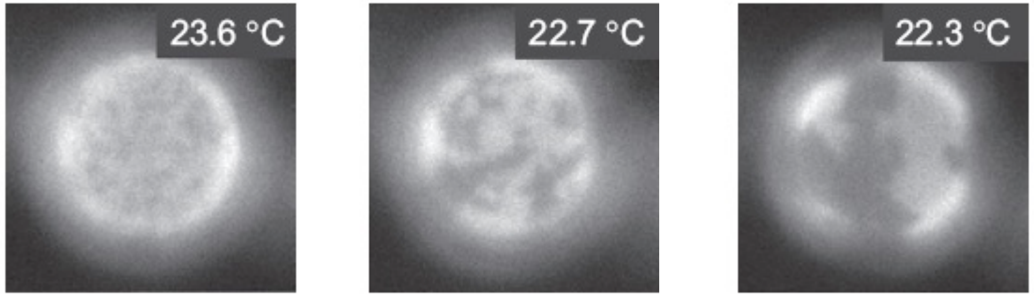
Thierry Emonet

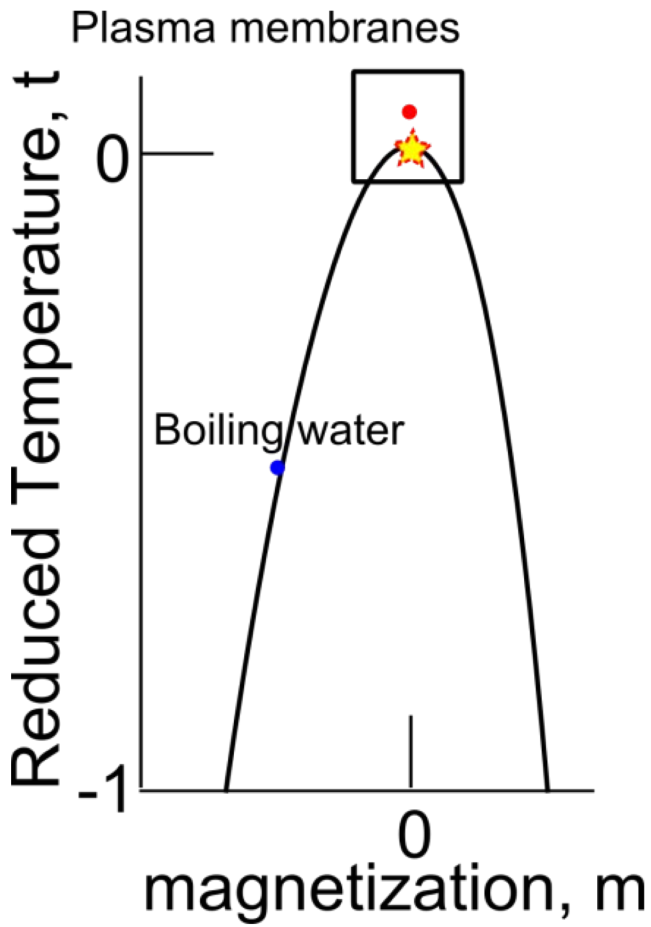
H. Mattingly, K. Kamino, BBM, T. Emonet. ***E. Coli* Chemotaxis is Information limited.** Nat Phys. (2021)

Membrane criticality

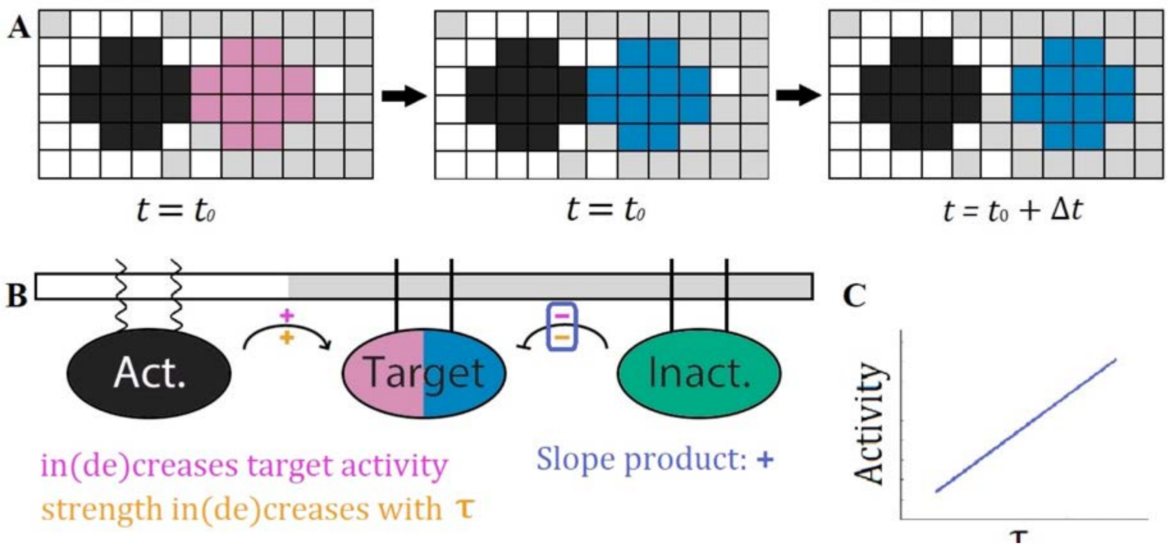
- Vesicles isolated from cells are complex 2D liquids
- Tuned near to an Ising critical point
- What does this critical point mean for function?
- How are these critical points tuned?

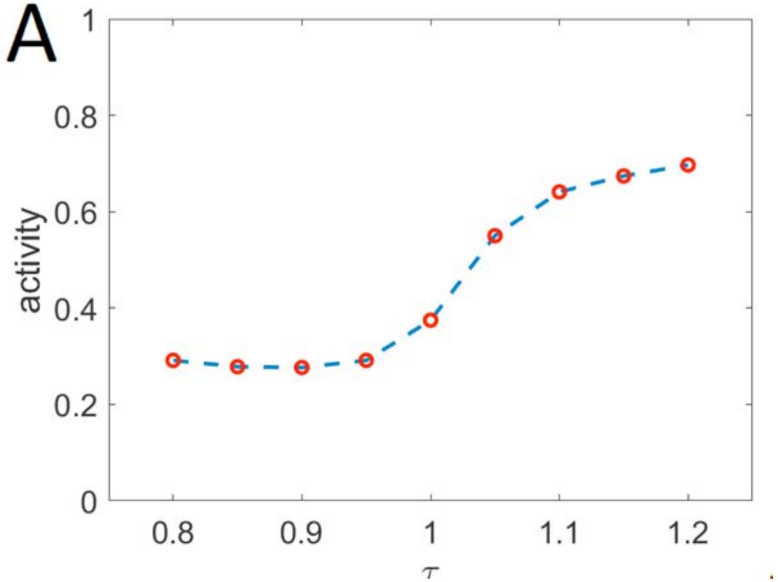




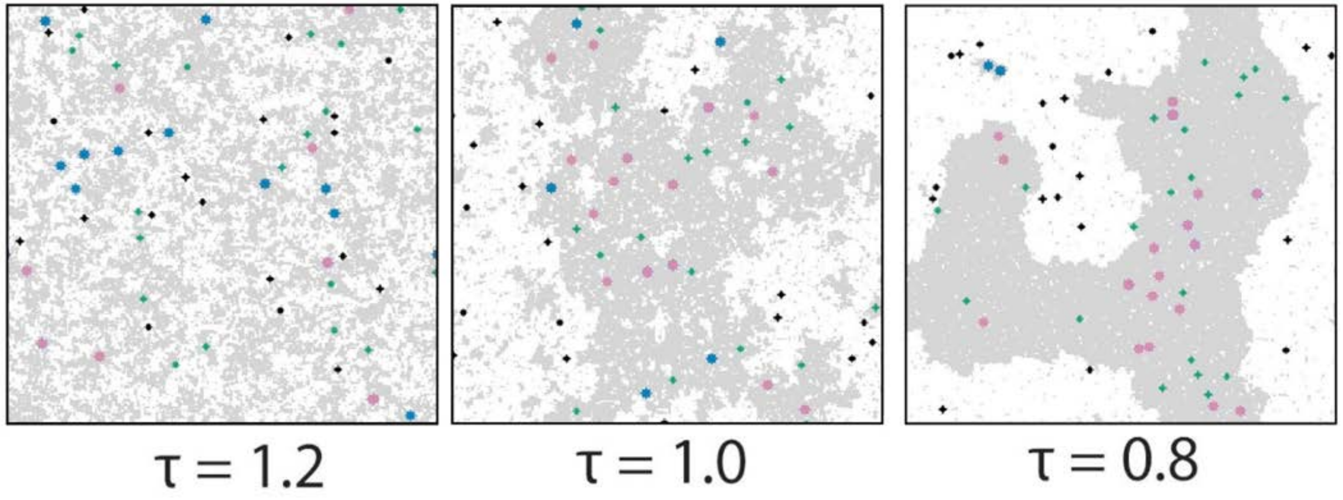


Membrane criticality sensitively modulates protein interactions



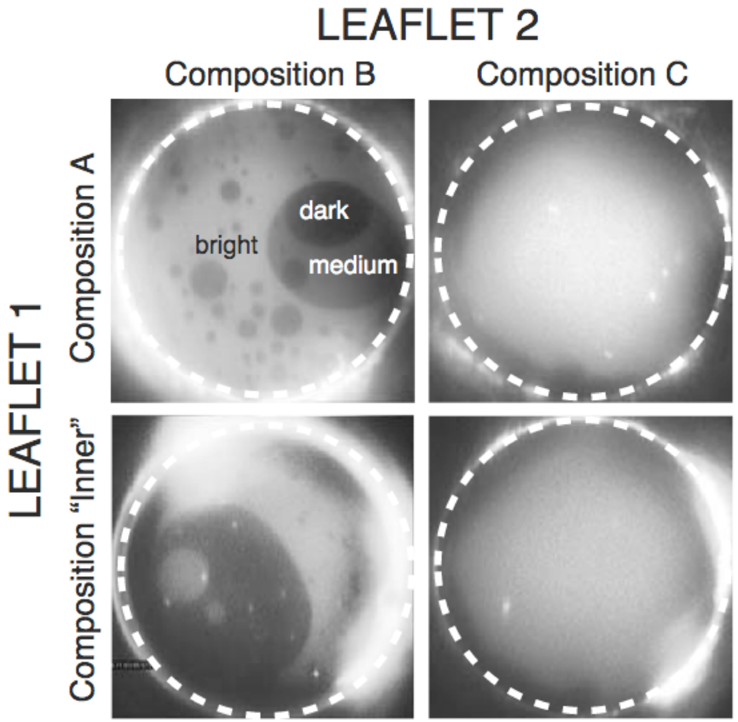


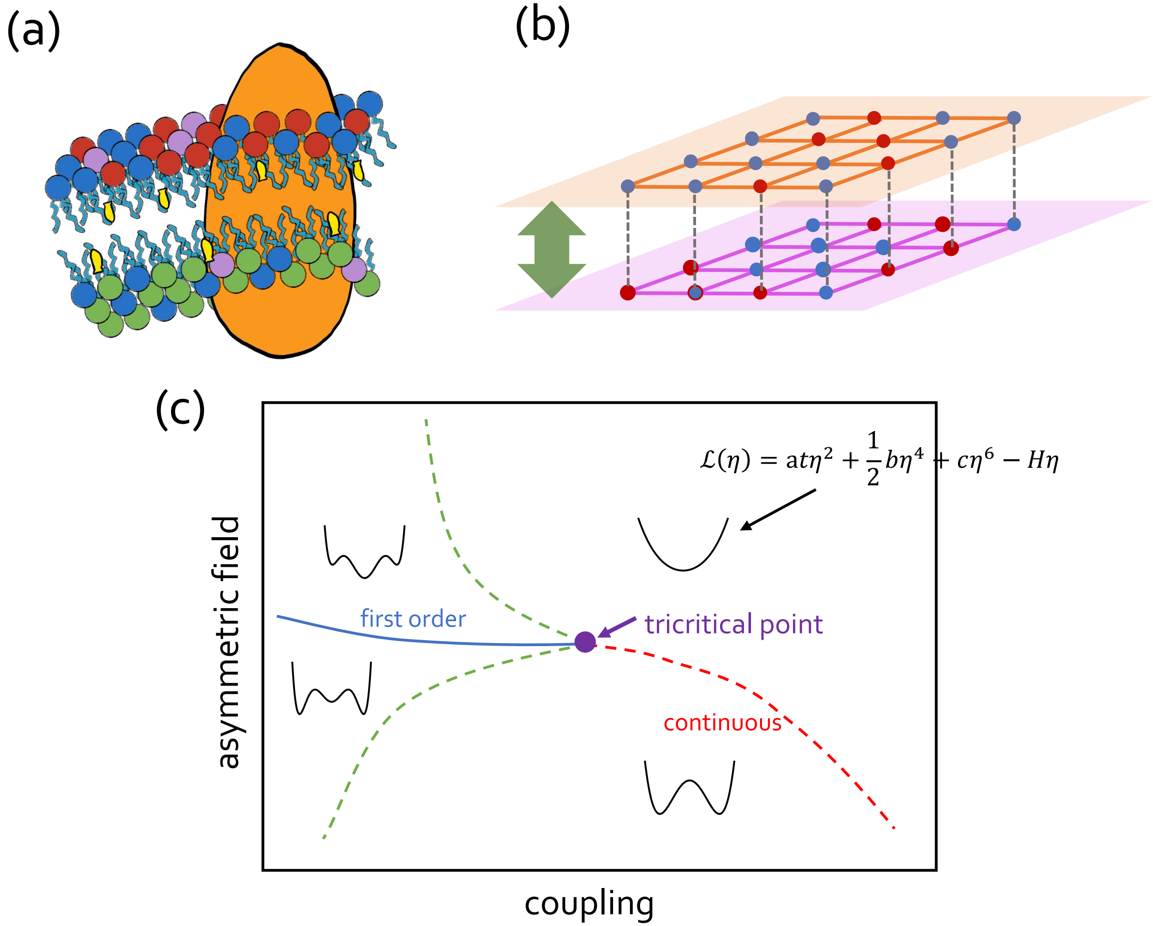
Taylor Schaffner



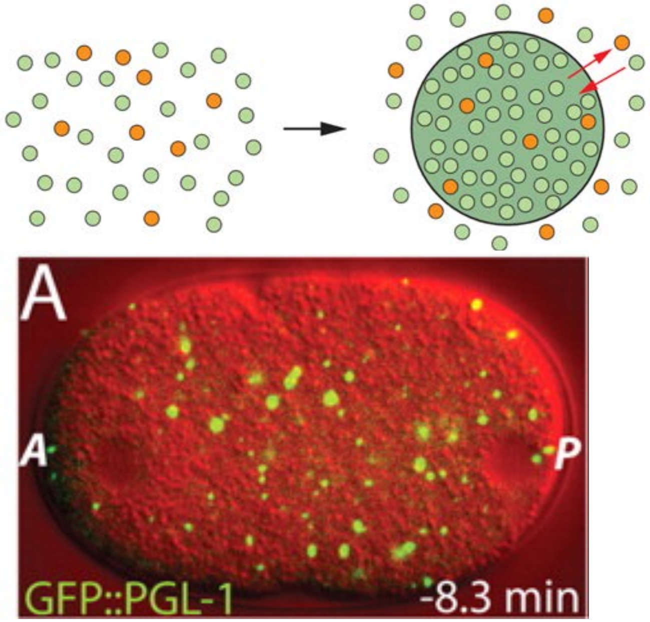
Tri-critical points in asymmetric membranes

Anjiabei Wang



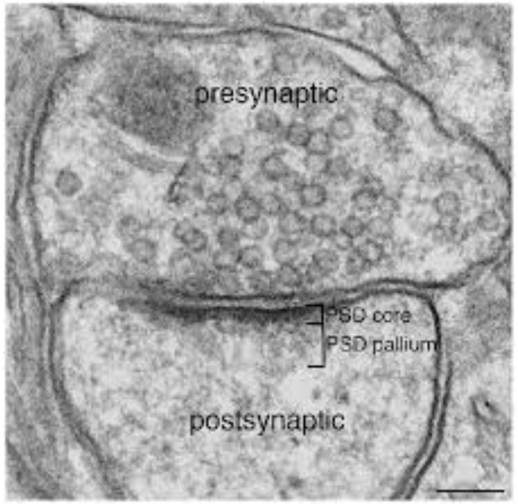


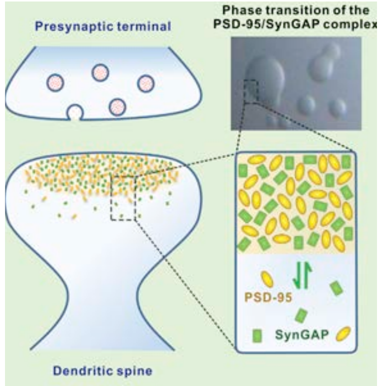
Prewetting proteins to critical membranes



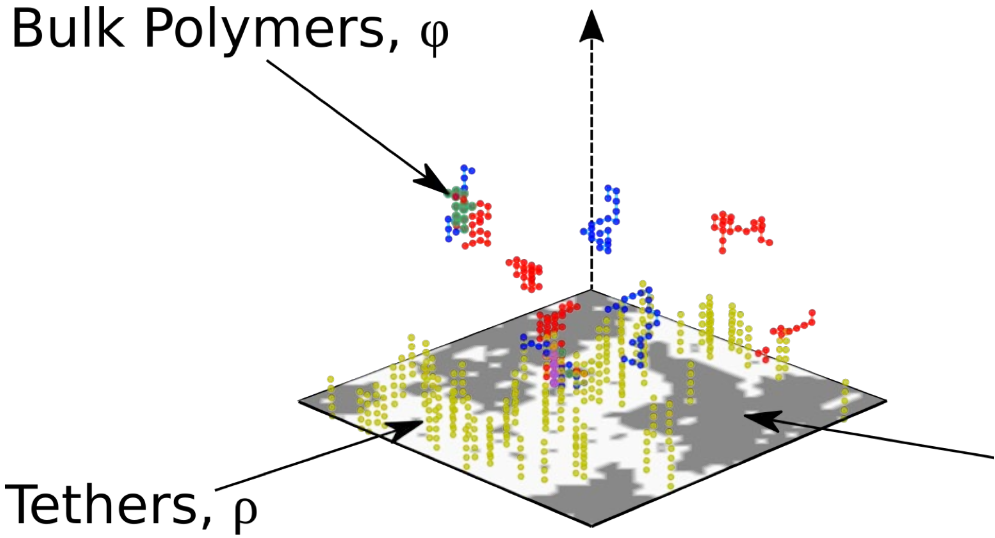
Brangwynne et al. *Science* (2009)

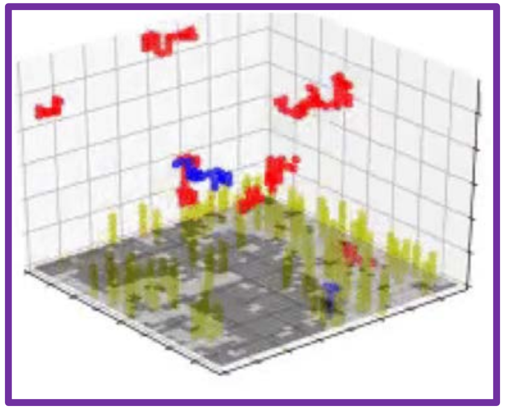
Mason Rouches





Zeng et al, Cell 2016

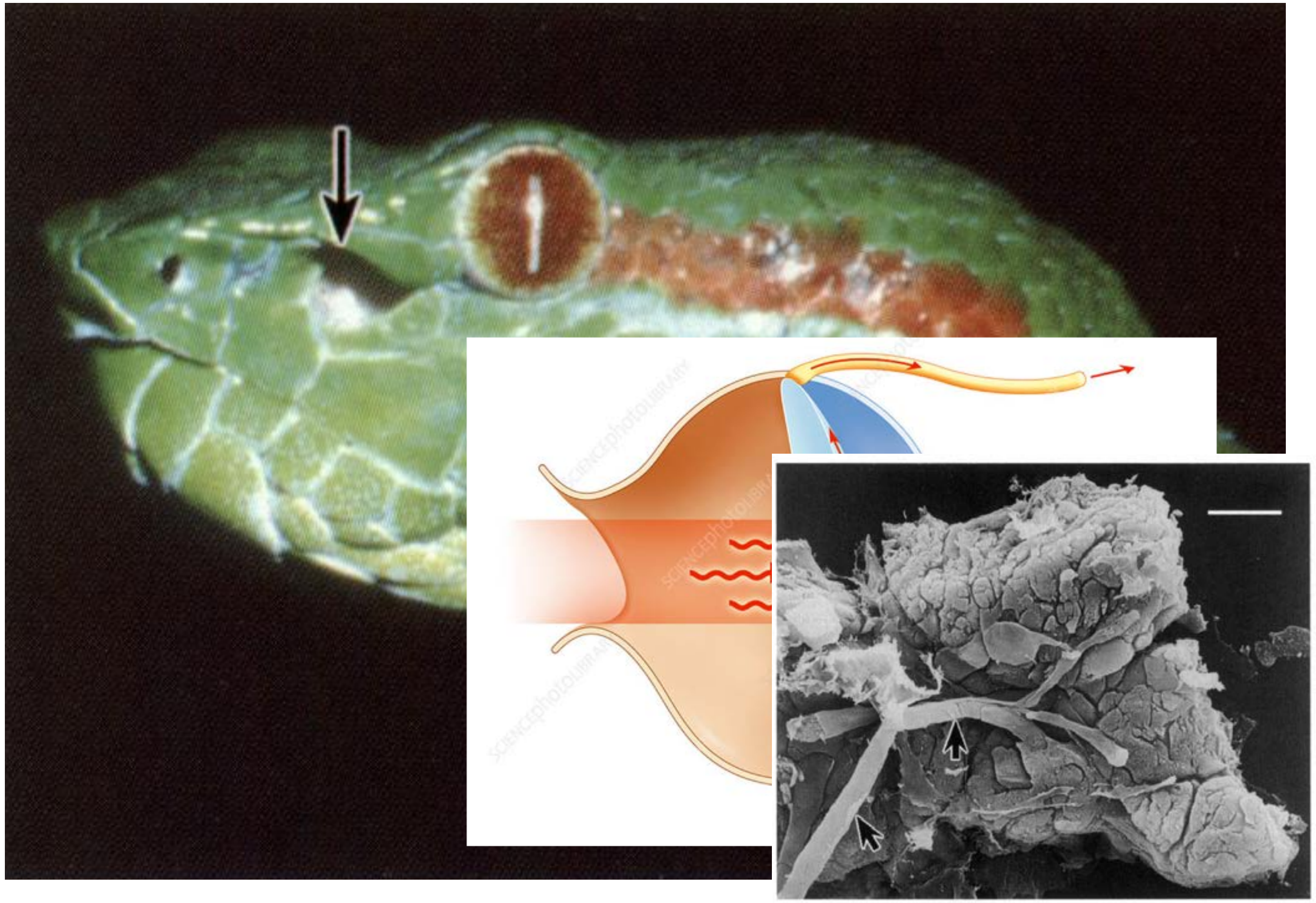




Mason Rouches, Sarah L. Veatch, BBM. **Surface Densities are pre-wetting to a nearly critical membrane,** *PNAS.* 2021

Pit organs are infrared imagers

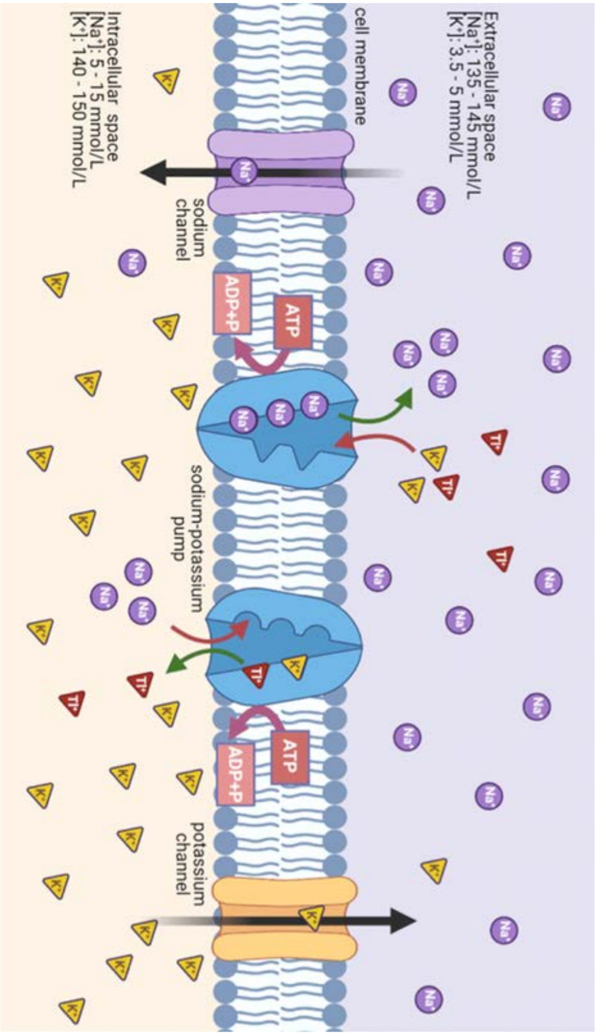
- Pit Vipers have pit organs.
- Pits are thermal imaging organs
  - For hunting small mammals
  - pit opening a pinhole camera
  - Heat absorbed on thin membrane
  - ~10k myelinated nerve fibers with 10um sensory endings
  - low resolution thermal image



Goris, Journal of Herpetology, 2010

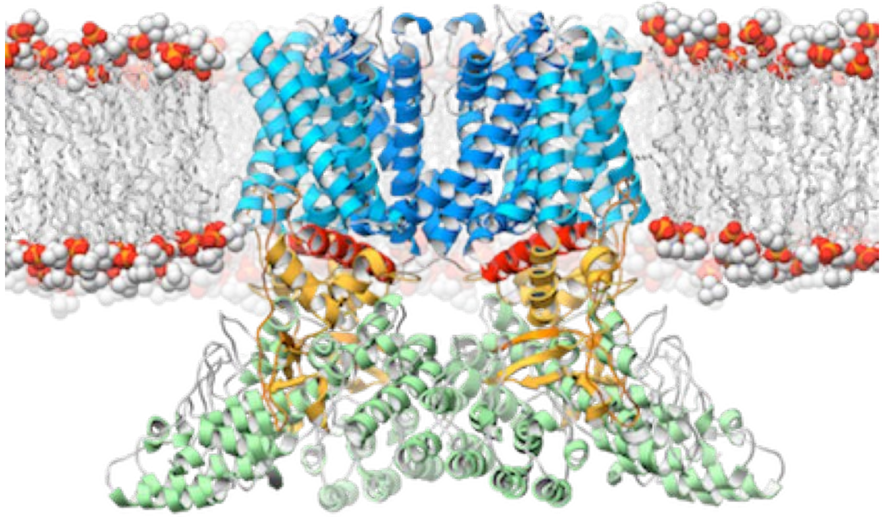
Neurons have active electrical dynamics

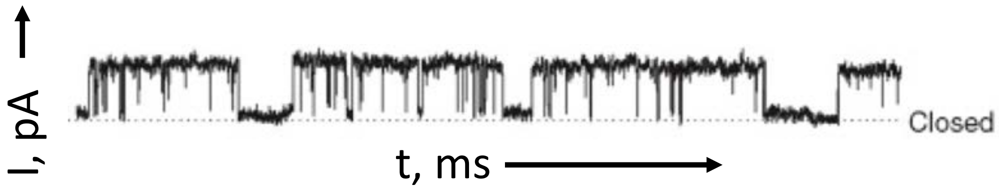
- Neuronal membrane a capacitor
- Chemical pumps maintain voltage chemical gradients
  - Na^+,Ca^{2+} are high extracellularly
  - K^+ is high intracellularly
  - 'resting' voltage of around -70mV
- Membrane is excitable
  - Na^+ current will depolarize
  - K^+ will hyperpolarize the cell

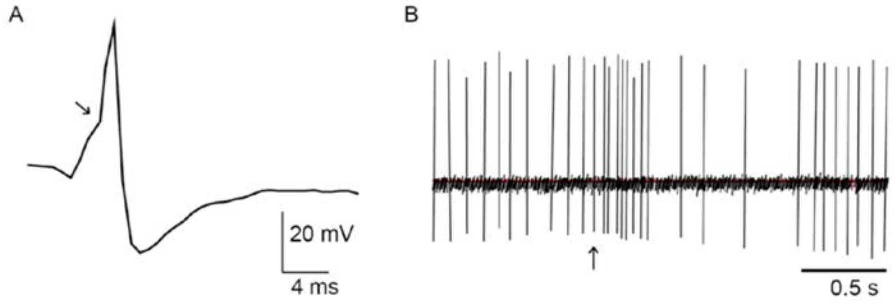


Ion channel proteins mediate currents

- Ion channels mediate currents
  - Specificity to particular ions
  - Respond to chemical signals, voltage
- Open and close stochastically
  - Currents ~pA
  - Correlation time ~5ms
- Voltage sensitivity leads to dramatic fast dynamics
  - Collective action potentials trigger cells to signal

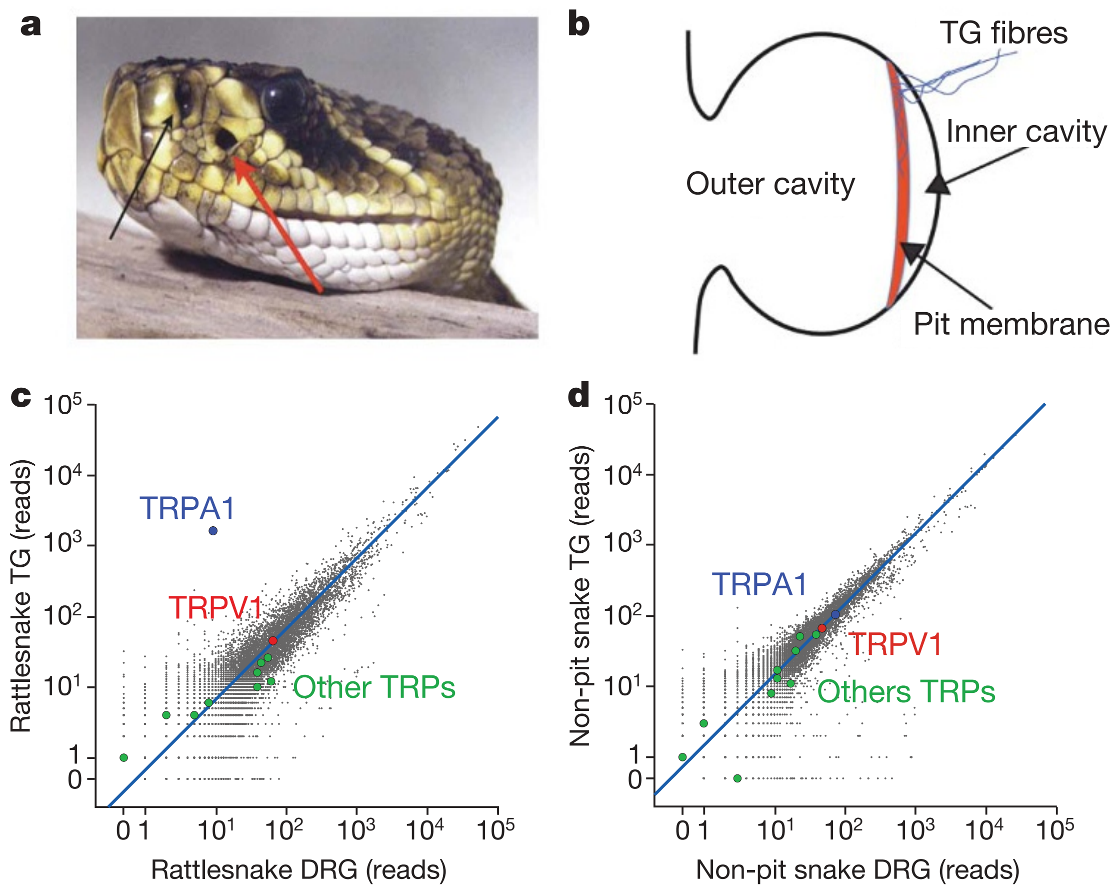






Molecular sensors are thermo-TRP channels

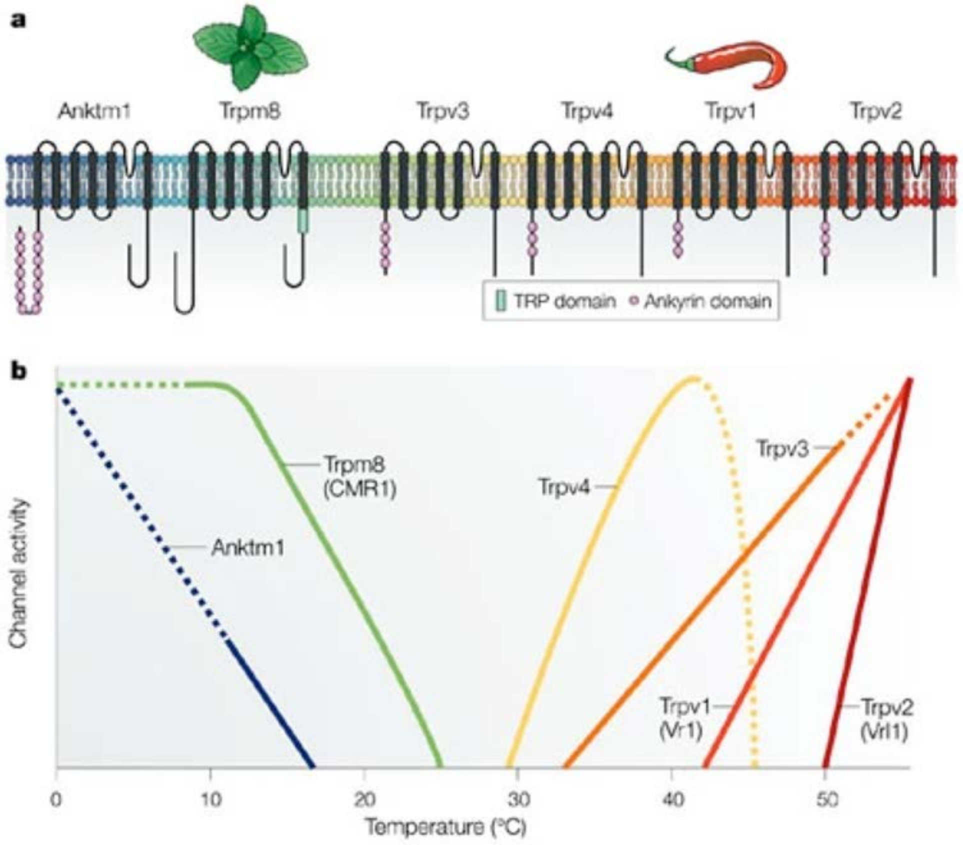
- Neurons that innervate the pit organ are dense with TRPA1, a thermo-TRP channel (2010)
  - TRP family of ion channels are often thermally sensitive
- True infrared detection - not photochemical like vision



Gracheva et al, Nature, 2010

What are thermo-TRP channels?

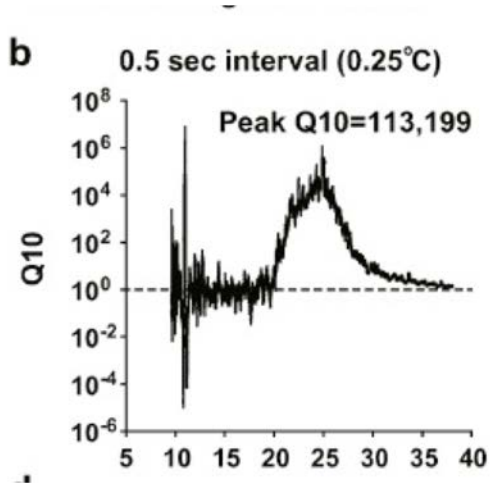
- TRP channels are most thermally sensitive single molecules in biology
  - Nobel prize in physiology in 2021
  - Q10 values in the range of 10-100
  - TRPV1 opens over a few K heat
  - TRPM8 similar for cold
  - All TRPs are cation channels mediating + current
- Sensitive to voltage, calcium, pip lipids, …
- Mechanism of thermal sensitivity debated (not here)



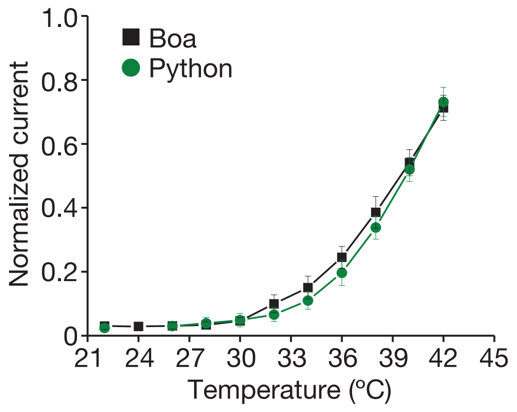
Patapoutian et al, Nat. Rev. Neuroscience, 2003

TRPA1 in pit-vipers is especially sensitive

- TRPA1 is a cold sensor in mammals
- TRPA1 in snakes is a hot sensor
  - Rattlesnake TRPA1 Maximal Q10 of $5*10^4$
  - Corresponds to 3x increase in activity for 1K change in temperature
  - 3-5x more sensitive than TRPV1
- Here, assume sigmoidal activation with width 1K



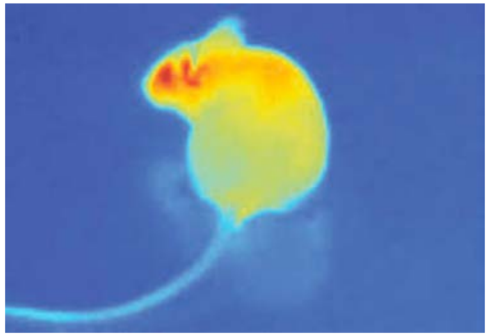
Kang, BBA Biomembranes, 2016



Gracheva,… Julius et al, Nature, 2010

Behavioral response requires a very sensitive detector

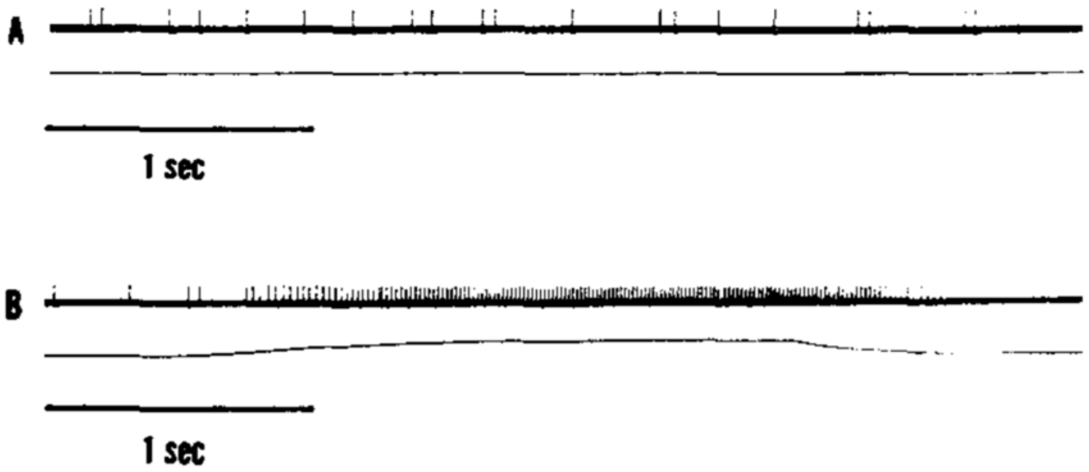
- Pit organ can detect a small mammal at 1m distance
  - Back of the envelope calculation suggests ~1mK sensitivity required
- Careful experiments suggest a single neuron has robust neural response to heating of 1mK



Gracheva

Spontaneous action potentials

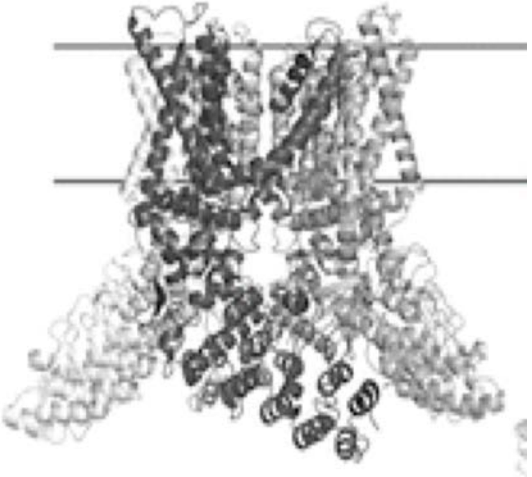
With warm object in field of view:

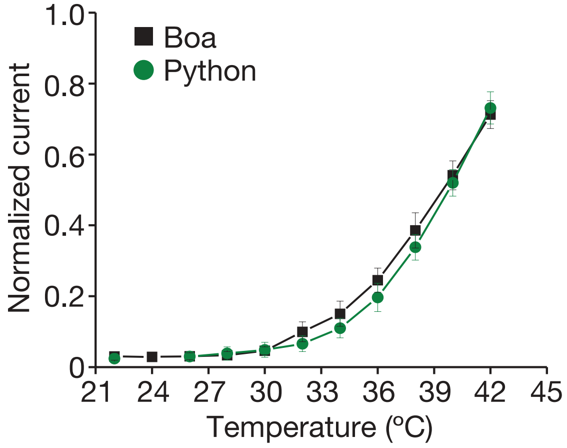


Goris, R. C., & Nomoto, M. (1967). *Comparative Biochemistry And Physiology, 23*(3).

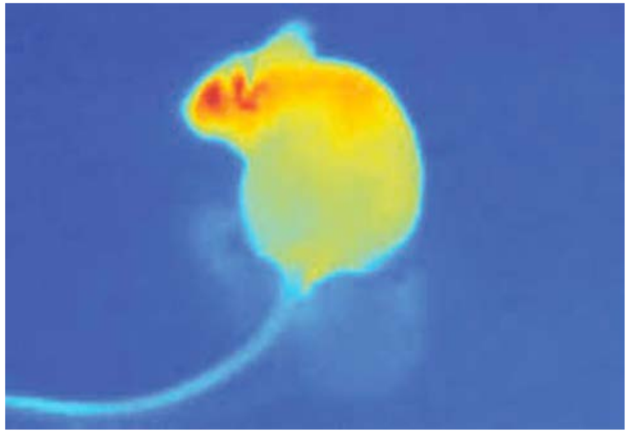
A mismatch

- Individual channels sense ~1K





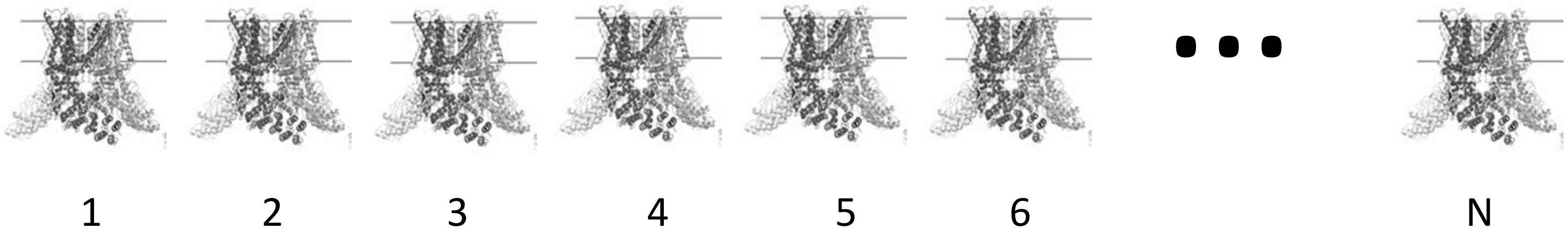
- The pit organ must be ~1000x more sensitive.



- Cell senses ΔT that changes the likelihood of opening by < .1%

Information is in principle contained in many channels…

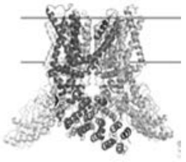
- A single channel can detect the temperature with accuracy $\sigma_{T,1} \sim 1K$



- N (independent) channels would give an estimate with error equal to
  - $\sigma^2_{T,N} = \sigma^2_{T,1}/\mathrm{N}$,
  - $\sigma_{T,N} = \frac{1\mathrm{K}}{\sqrt{N}}$
  - $\sim\mathrm{N} = 10^6$ channels required to accurately measure $\Delta T \sim 1\mathrm{mK}$

Information could also be read out from a single channel read out for finite time

- A single channel event can record with accuracy $\sigma_{T,1} \sim 1K$



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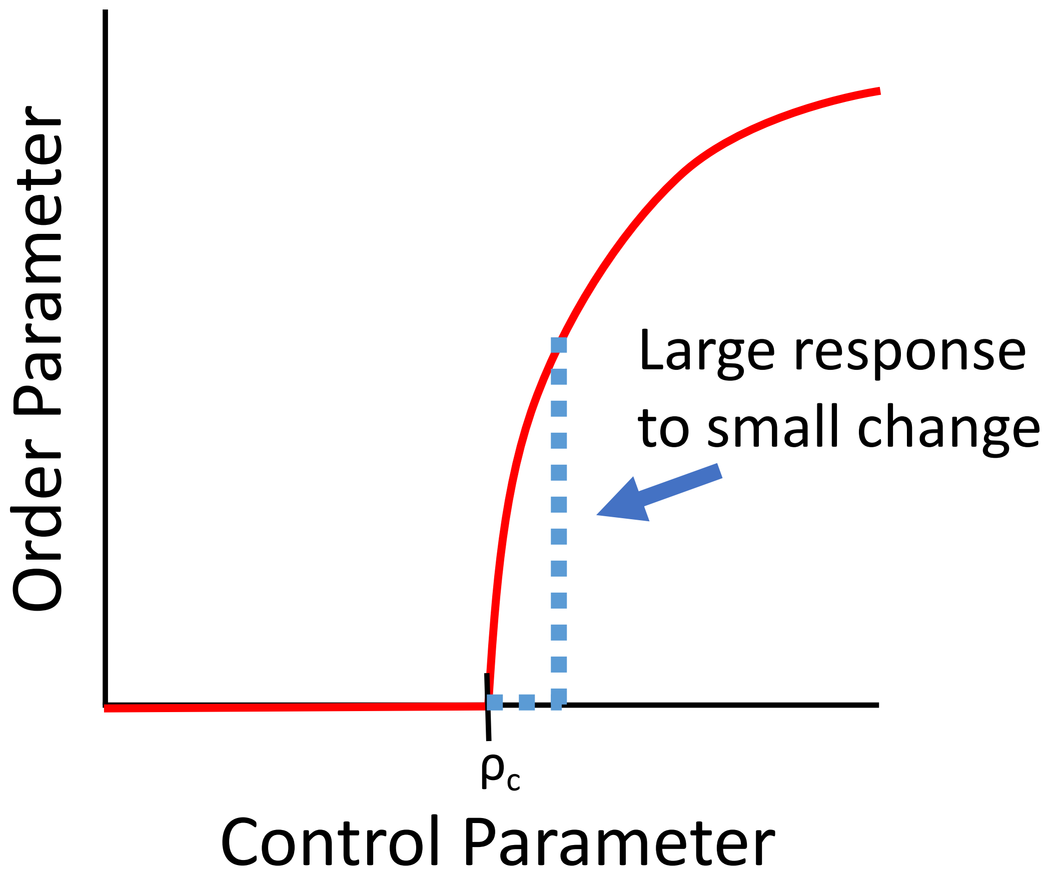
- Observing for a time $\tau > \tau_o$ yields $\frac{\tau}{\tau_o}$ ind. measurements
  - $\sigma^2_{T,1}(\tau) = \frac{\tau_o}{\tau}\sigma^2_{T,1}$

Number of receptors and int. time bounds accuracy of a temperature measurement

- Perfectly observing for time τ with N receptors yields an error estimate of
  - $\sigma_{T,N}^2(\tau) = \frac{\tau_{open}}{N\tau}\sigma_{T,1}^2$, $\sigma_{T,N}(\tau) = \sqrt{\frac{\tau_{open}}{N\tau}}\sigma_{T,1}$
  - 'Rate of information' G ($1/K^2s$), G<G_b: $G_b = \frac{d}{d\tau}\frac{1}{\sigma_{T,N}^2} = \frac{\mathrm{N}}{\sigma_{T,1}^2\tau_{open}}$
- Note: this absolute bound is not discouraging: in 100ms neuron would need just $N=10^5$ channels.
- Still, by what mechanism could this be read out?
  - Spike timing must contain information from ~10^6 channels
  - How is this information integrated and amplified into a collective response?

How is collective response so much sharper than individual channels?

- Hypothesis: TRPA1 channels are embedded in a dynamical system tuned close to a bifurcation
- Diverging susceptibility found near bifurcation amplifies the effect a tiny change in temperature makes to single channel properties



How is collective response so much sharper than individual channels?

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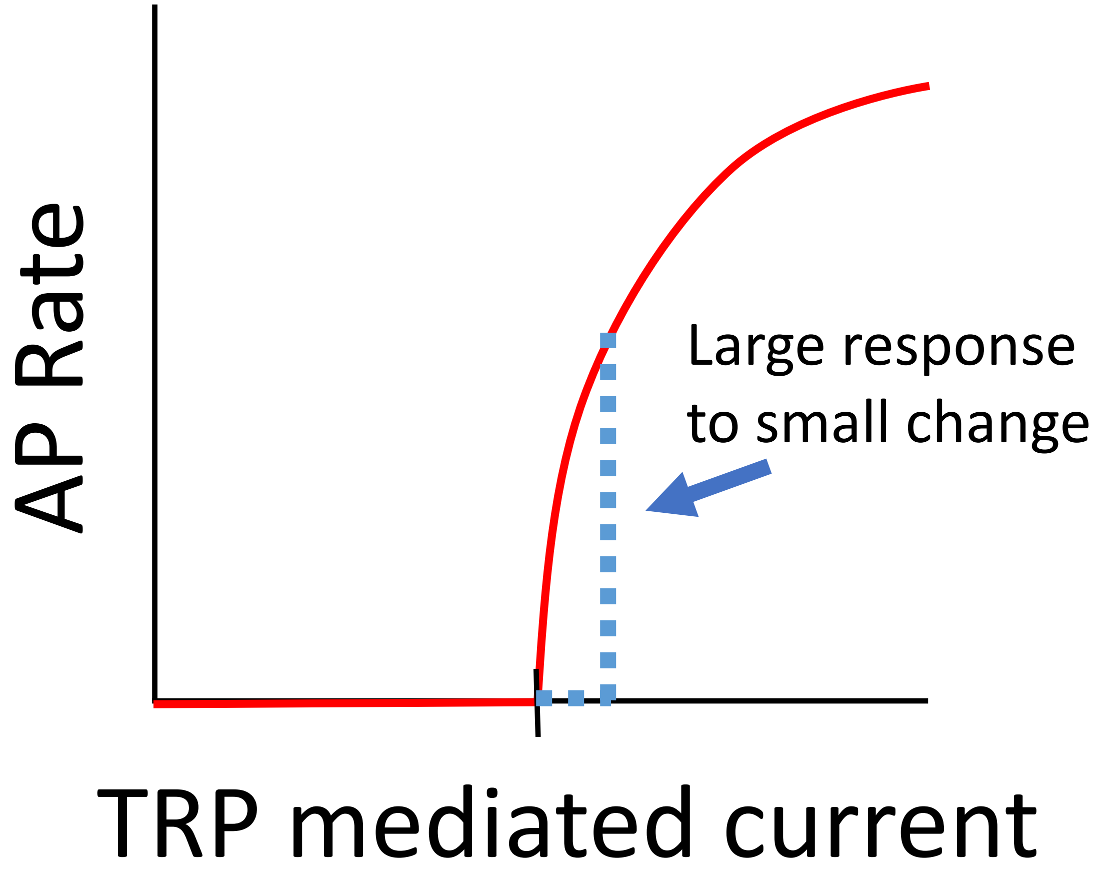
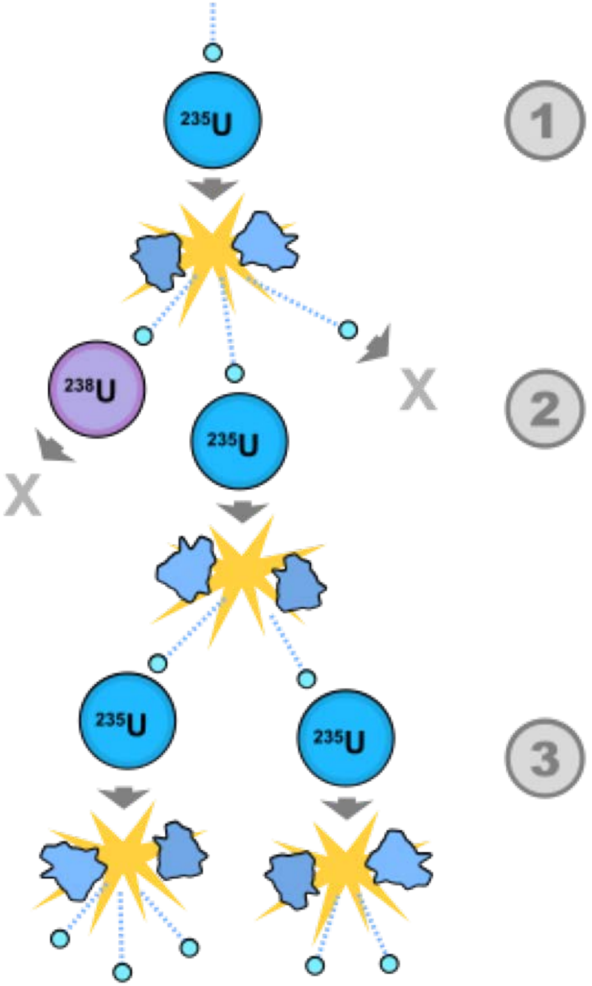


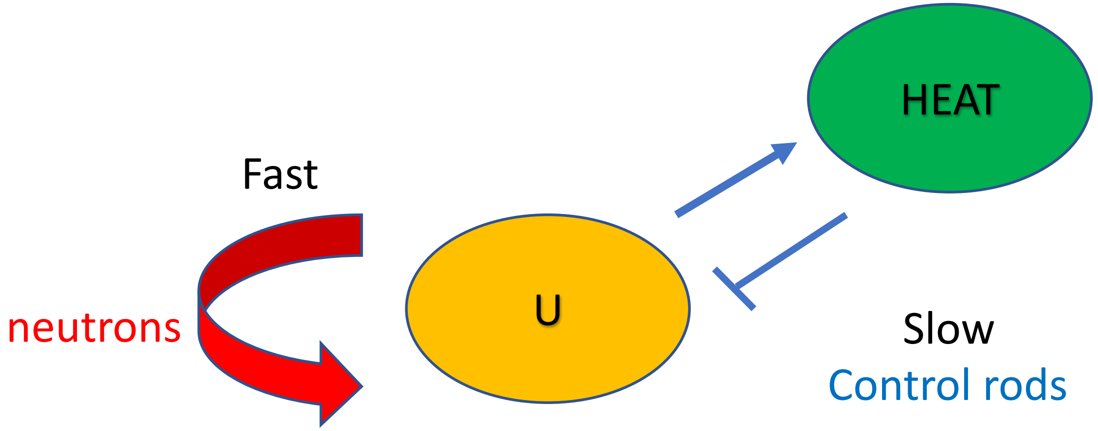
Example: Nuclear criticality in a reactor

- R_0 the reproduction number: # of decays each decay triggers
  - $R_0<1$ and the reactor will fizzle
  - $R_0>1$ and the reactor will meltdown
  - Effective timescale is ms
- An operating Nuclear plant averages an $R_0=1$ with *tiny* fluctuations
  - Control rods (s timescale) adjust the third digit of R_0 with real time feedback
- Could very sensitively detect a change in R_0
- Feedback signal is easy to come by:
  - Small change in R_0 quickly amplified

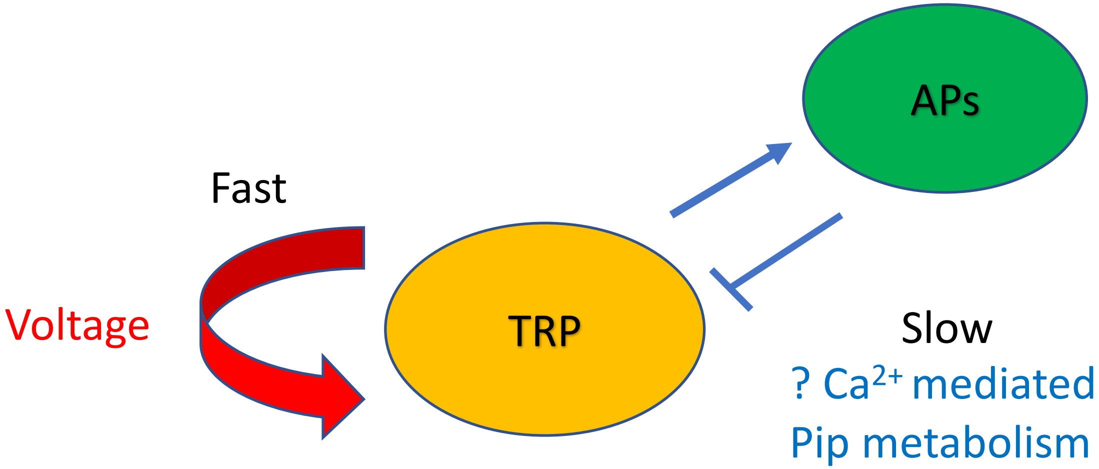


A Qualitative overview of our model

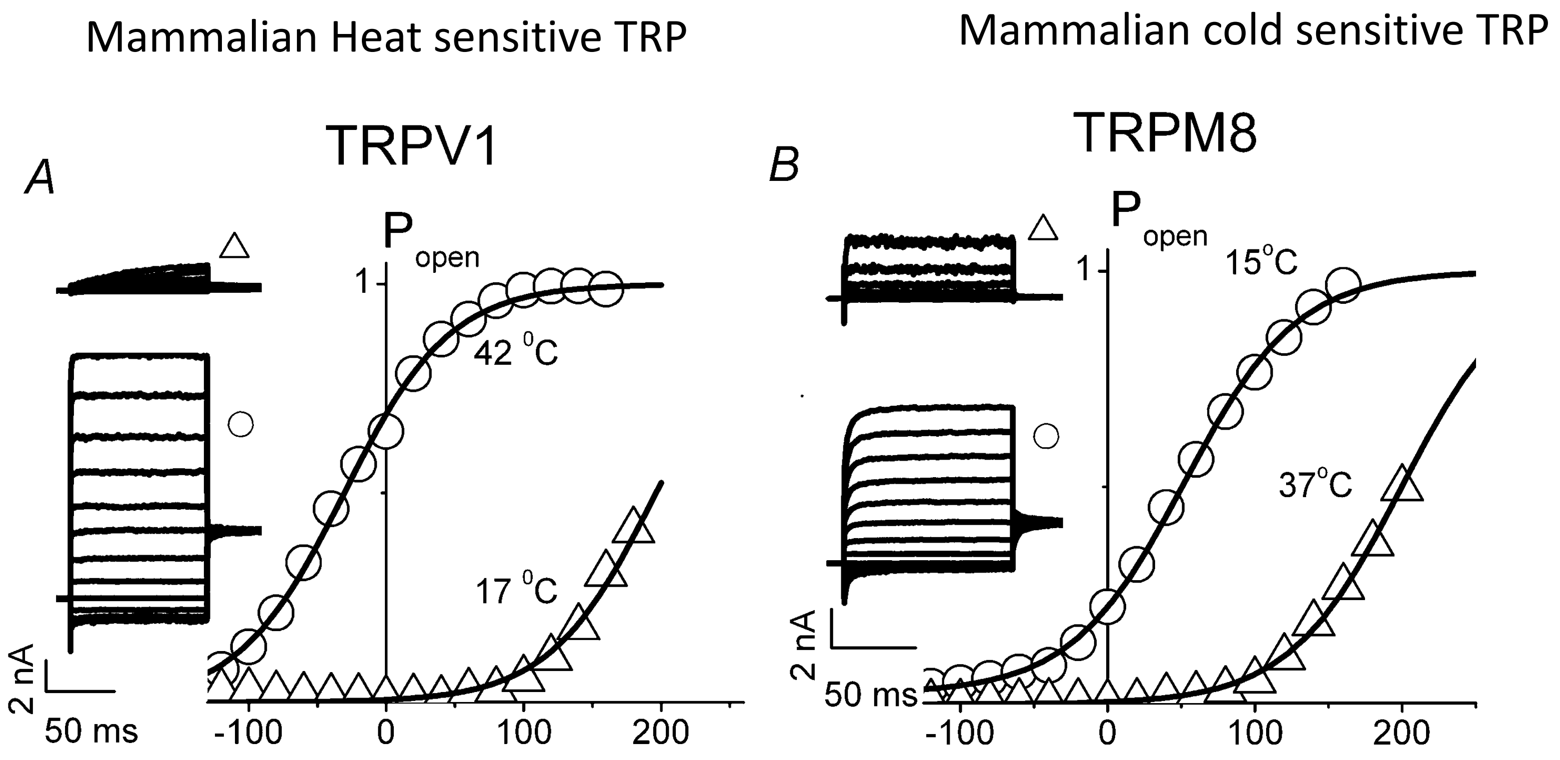
- In nuclear decay, each decay triggers R_0 additional decays



- Model: TRP channels activate other TRP channels



A mechanism for fast positive feedback



- TRPs are voltage gated channels with a Temperature dependent $V_{1/2}$
- TRP channels activate other TRP channels electrically

Nilius et al, J Physiology, 2005

A mode detailed model

$$\frac{dV}{dt} = \frac{(V_{eq} - V)}{\tau_V} + \frac{V_{max}}{\tau_V} P_0 (V - V_{1/2}(T)) + \sqrt{\left(\frac{\tau_0}{N}\right) V_{max} (P_o)(1 - P_0)} \xi(t)$$

Int. elect. dynamics | TRP signal | Single (TRP) channel noise

when voltage reaches a threshold an action potential is fired

Signal is read out by timing of action potentials

TRP signal is sigmoidal in voltage, temperature

$$\frac{dV}{dt} = \frac{(V_{eq} - V)}{\tau_V} + \frac{V_{max}}{\tau_V} P_0(V - V_{1/2}(T)) + \sqrt{\left(\frac{\tau_0}{N}\right) V_{max}(P_o)(1 - P_0)\xi(t)}$$

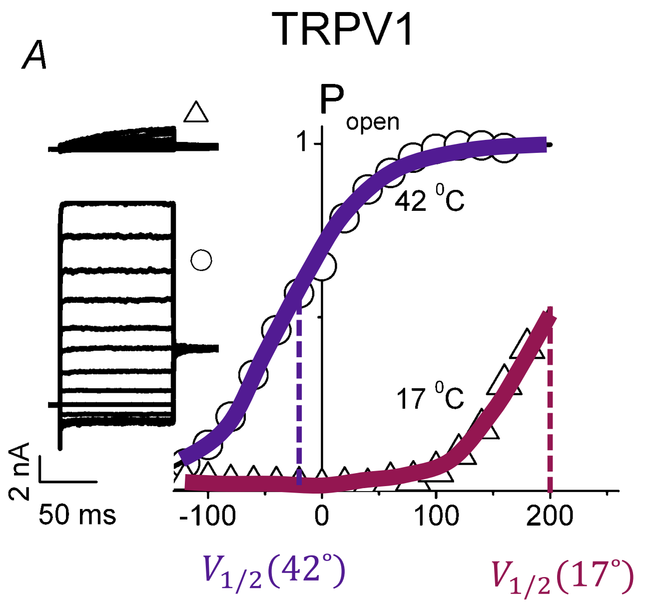
Int. elect. dynamics | TRP signal | Single (TRP) channel noise

$$P_0(V - V_{1/2}) = \frac{1}{1 + \exp(-(V - V_{1/2})/\Delta V)}$$

$\Delta V \sim 30mV$,

$V_{1/2}$ dependent on T, feedback (unspecified)

$V_{max} = \mathrm{Ni}_0 \tau_v / C$ is steady state w/ all open



TRP noise decreases with N/τ_0

$$\frac{dV}{dt} = \frac{(V_{eq} - V)}{\tau_V} + \frac{V_{max}}{\tau_V} P_0(V - V_{1/2}(T)) + \sqrt{\left(\frac{\tau_0}{N}\right) V_{max}(P_o)(1 - P_0)}\xi(t)$$

Int. elect. dynamics | TRP signal | Single (TRP) channel noise

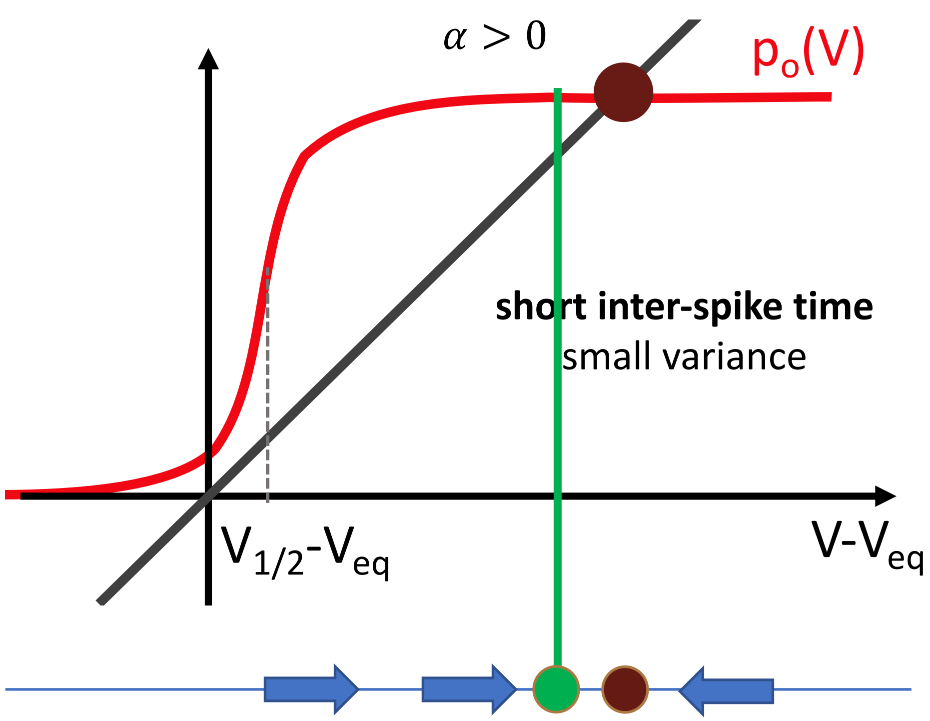
Scale of noise decreases with increasing number of channels

Assumes channels act independently – conditioned on voltage and temperature

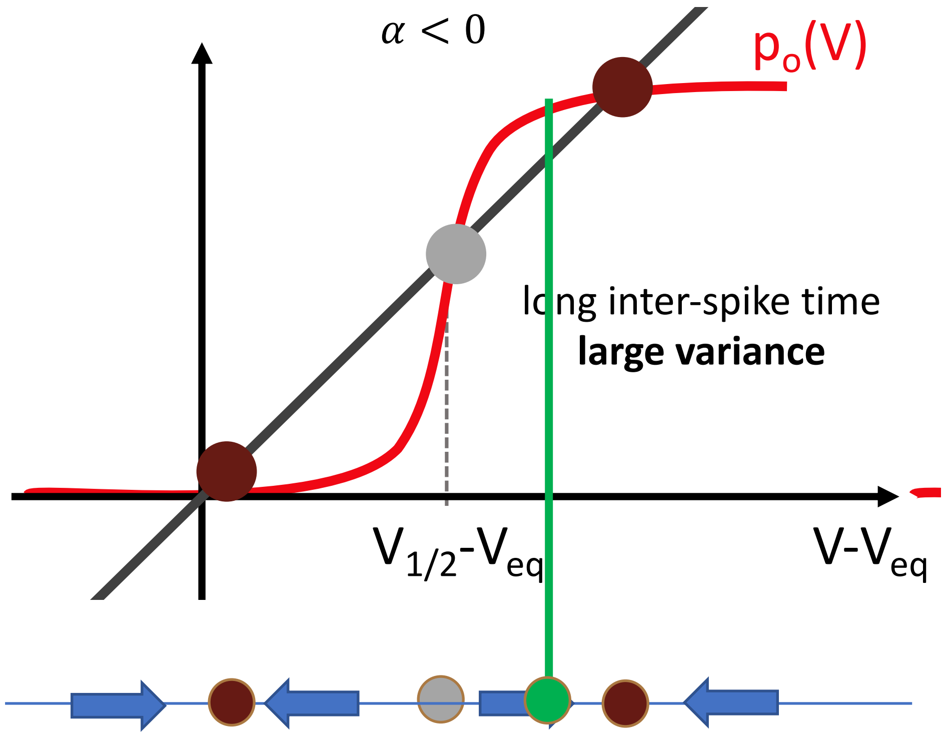
We neglect noise from other sources, most prominently other channels

Qualitative dynamics 1

$$\frac{dV}{dt} = \frac{(V_{eq} - V)}{\tau_V} + \frac{V_{max}}{\tau_V} P_0(V - V_{1/2}(T)) + \sqrt{\left(\frac{\tau_0}{N}\right) V_{max}(P_o)(1 - P_0)\xi(t)}$$



Deterministic regime, spikes are regular



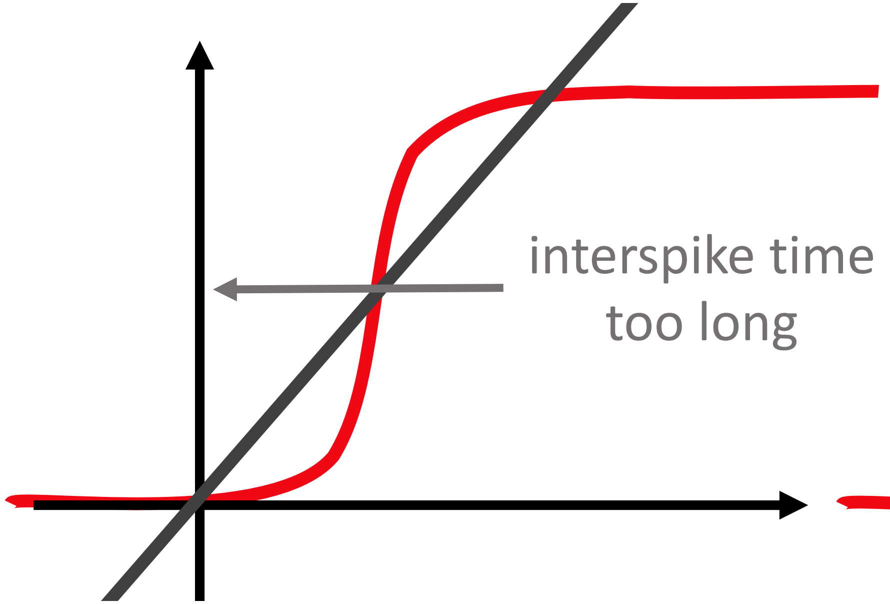
Stochastic regime, spikes are sparse and random

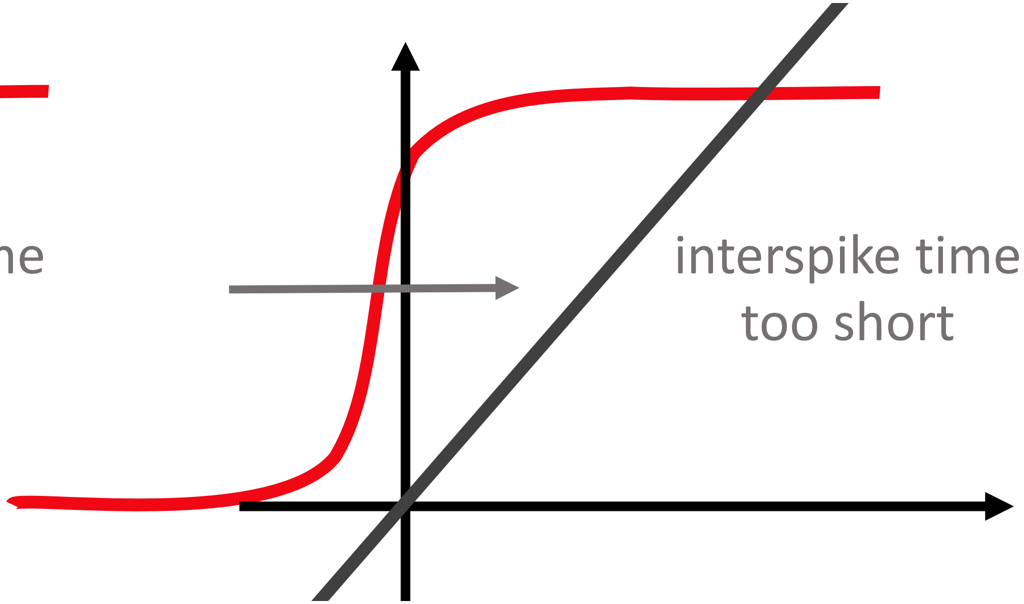
stable fixed point

instable fixed point

Qualitative dynamics 2: feedback

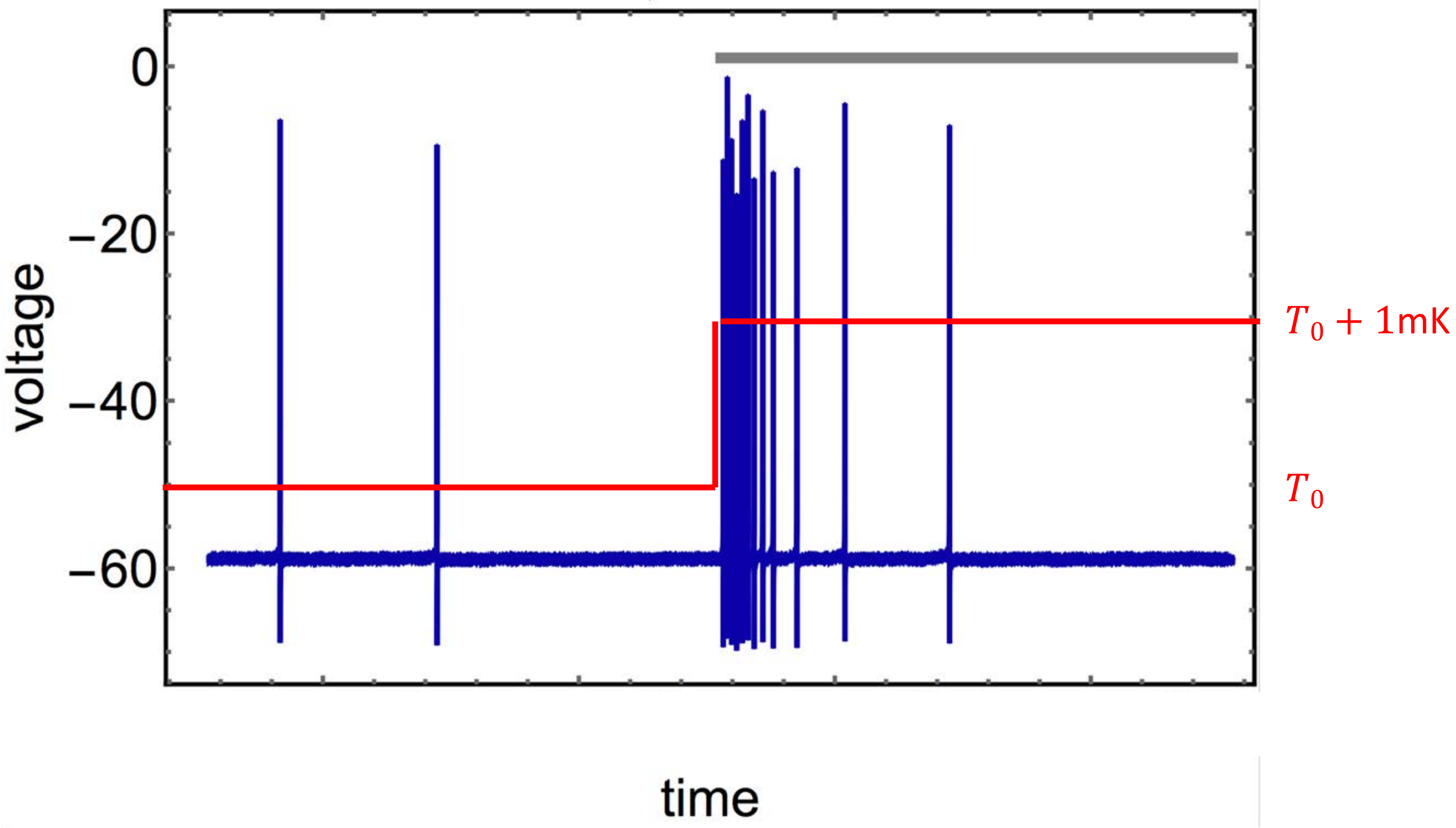
$$\frac{dV}{dt} = \frac{(V_{eq} - V)}{\tau_V} + \frac{V_{max}}{\tau_V} P_0(V - V_{1/2}(T)) + \sqrt{\left(\frac{\tau_0}{N}\right) V_{max}(P_o)(1 - P_0)\xi(t)}$$





Response to a small temperature

- Before change in temperature:
  - Stochastic spikes
  - Tuned near the bifurcation
- Change in T
  - Bifurcation crossed
  - Burst of spikes
  - Slow adaptation

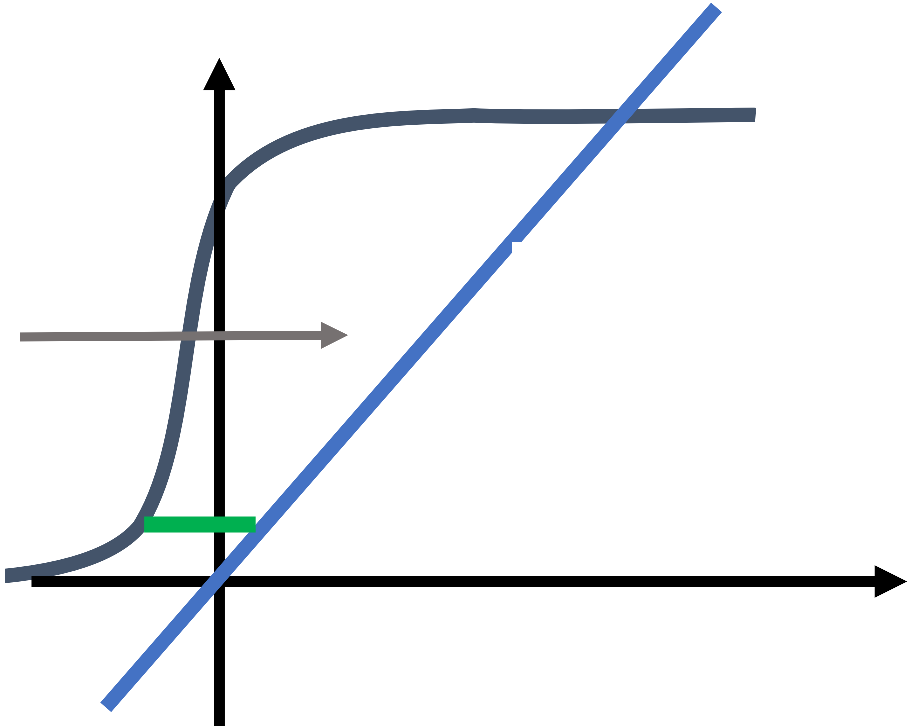


Analyzing the proximity of the bifurcation

$$\frac{dV}{dt} = \frac{(V_{eq} - V)}{\tau_V} + \frac{V_{max}}{\tau_V} P_0(V - V_{1/2}(T)) + \sqrt{\left(\frac{\tau_0}{N}\right) V_{max}(P_o)(1 - P_0)\xi(t)}$$

$$P_0(V - V_{1/2}) = \frac{1}{1 + \exp(-(V - V_{1/2})/\Delta V)}$$

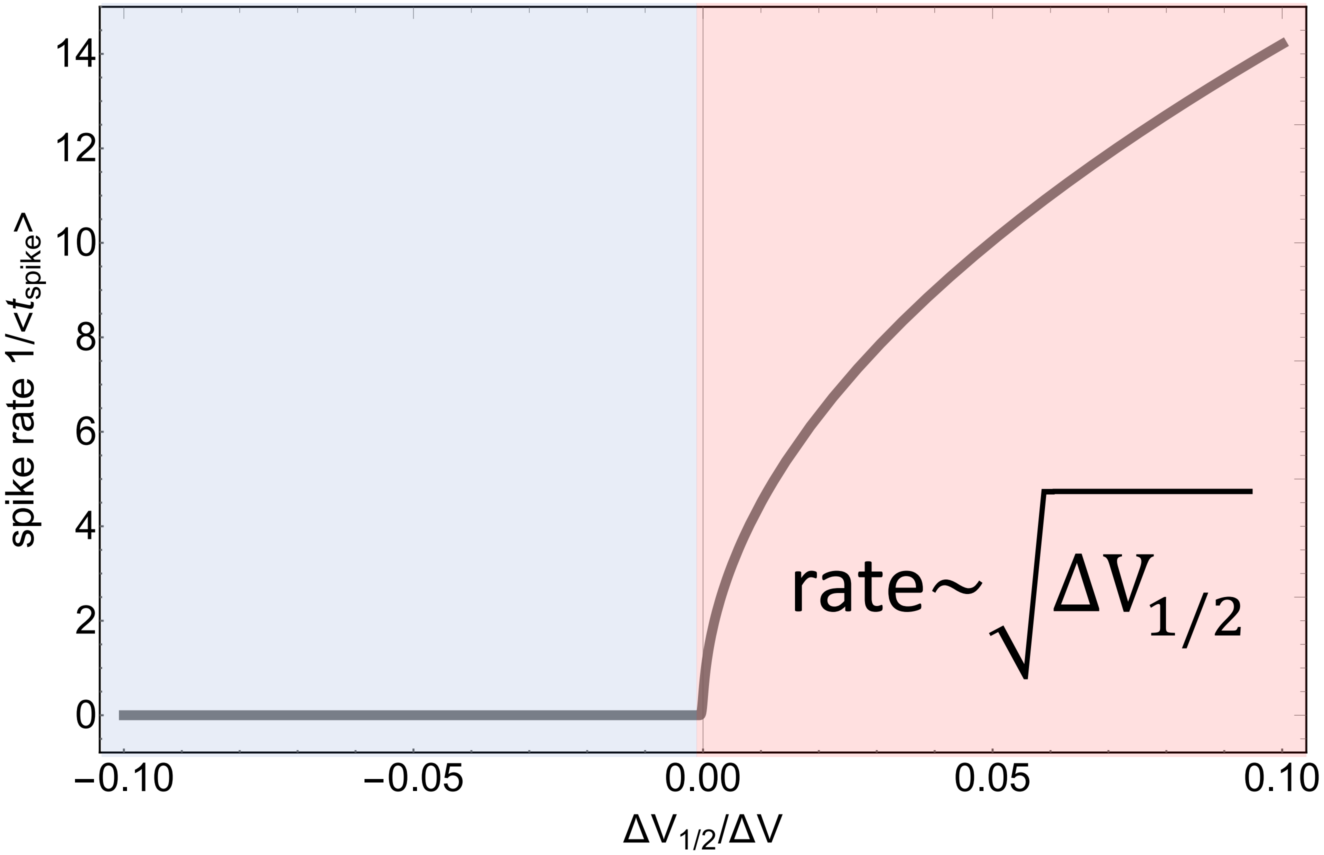
- For every value of $\Delta V / V_{max} \leq \frac{1}{4}$ there is a critical point for $V_{1/2} = V_b$, defining $\Delta V_{1/2} = -V_{1/2} + V_b$ is the distance to the bifurcation



slowing of spike rate near the bifurcation

- Away from bifurcation, spike timescale is near $1/\tau_V$ (~100Hz)
- Below the transition $\Delta V_{1/2}<0$, spikes are sparse
- Near but above the transition, timescale has steep $\Delta V_{1/2}$ dependence
  - Steepness ~ $\Delta V_{1/2}^{-1/2}$

Spike rate vs $\Delta V_{1/2}/\Delta V$



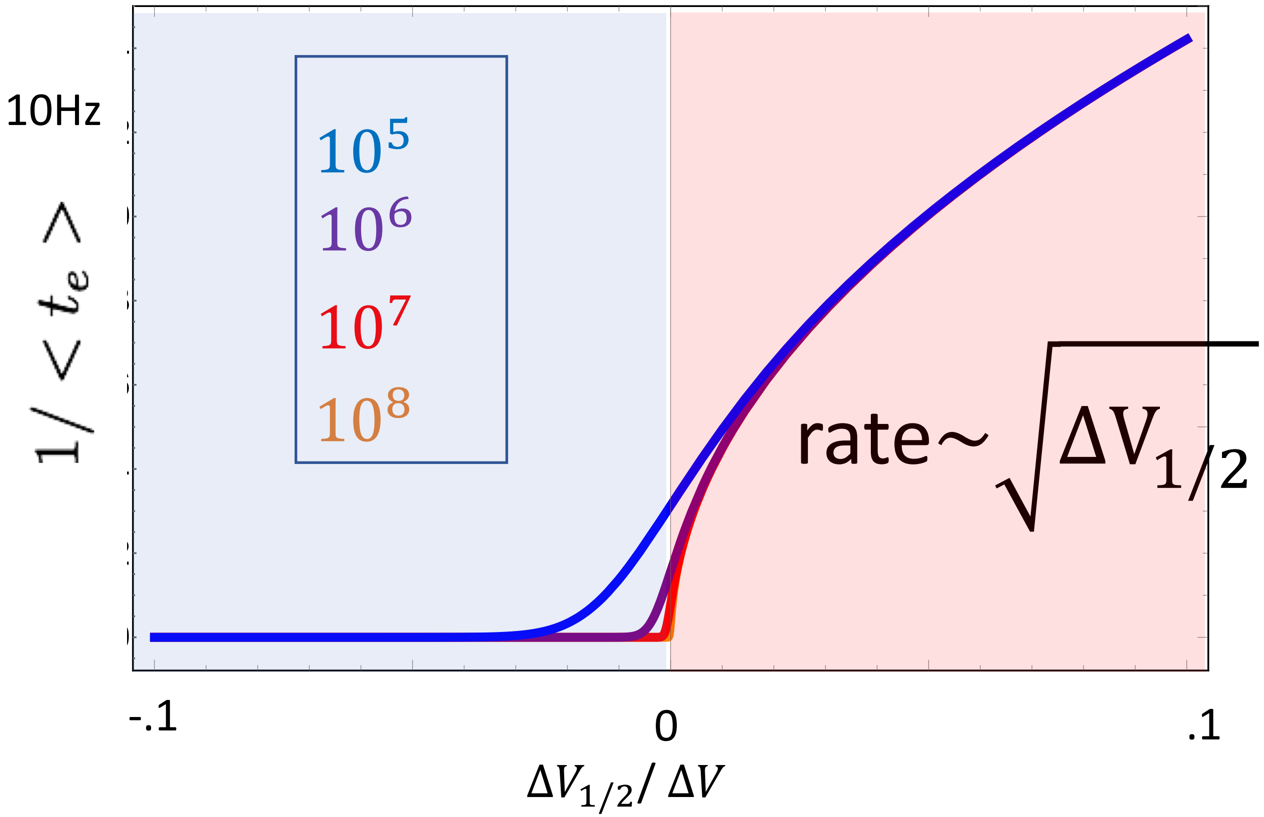
Barrier crossing Results modified from Hatchock and Sethna, Phys. Rev. Research, 2021

Understanding finite N

- Near the bifurcation noise becomes important
  - Scaling: noise dominates when

    $N < \left(\Delta V_{1/2}/\Delta V\right)^{-3/2}$

Spike rate vs $\Delta V_{1/2}$



Barrier crossing Results modified from Hatchock and Sethna, Phys. Rev. Research, 2021

Noise and finite N

- Near the bifurcation noise becomes important

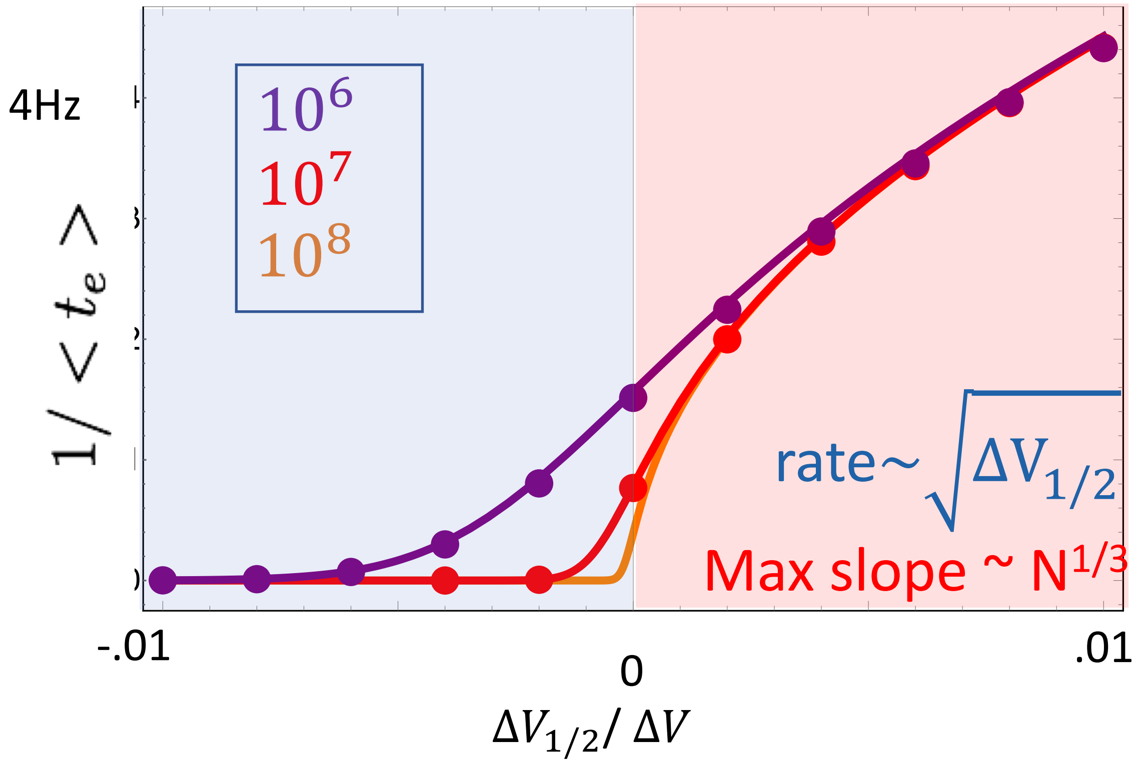
  Scaling: noise dominates when

  $N < \left(\Delta V_{1/2}/\Delta V\right)^{3/2}$

  Max slope scales as $N^{1/3}$

  Amplification: log slope at bifurcation scales as $N^{2/3}$

Spike rate vs $\Delta V_{1/2}$ (10x zoom)

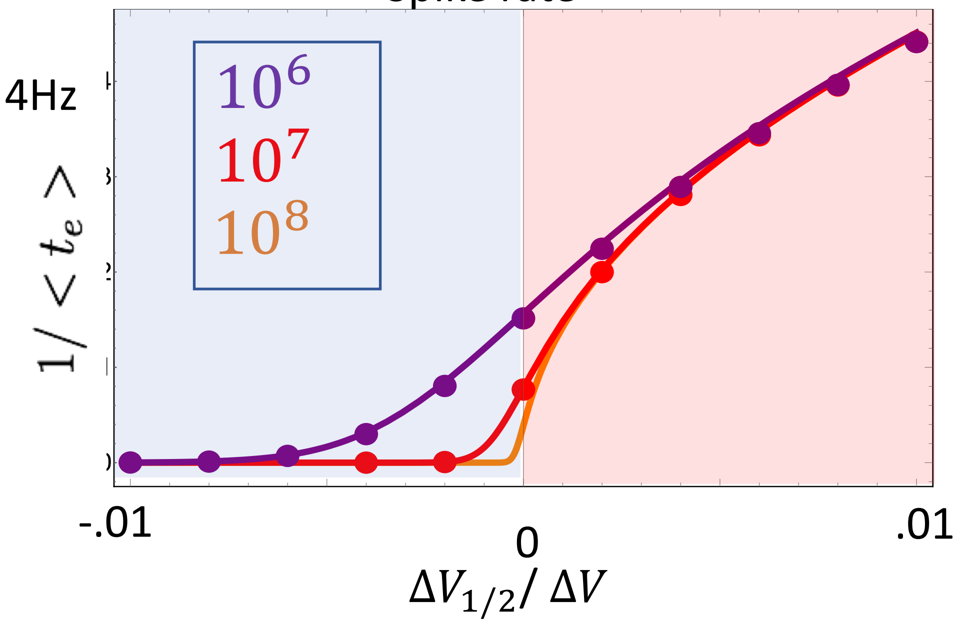


Barrier crossing Results modified from Hatchock and Sethna, Phys. Rev. Research, 2021

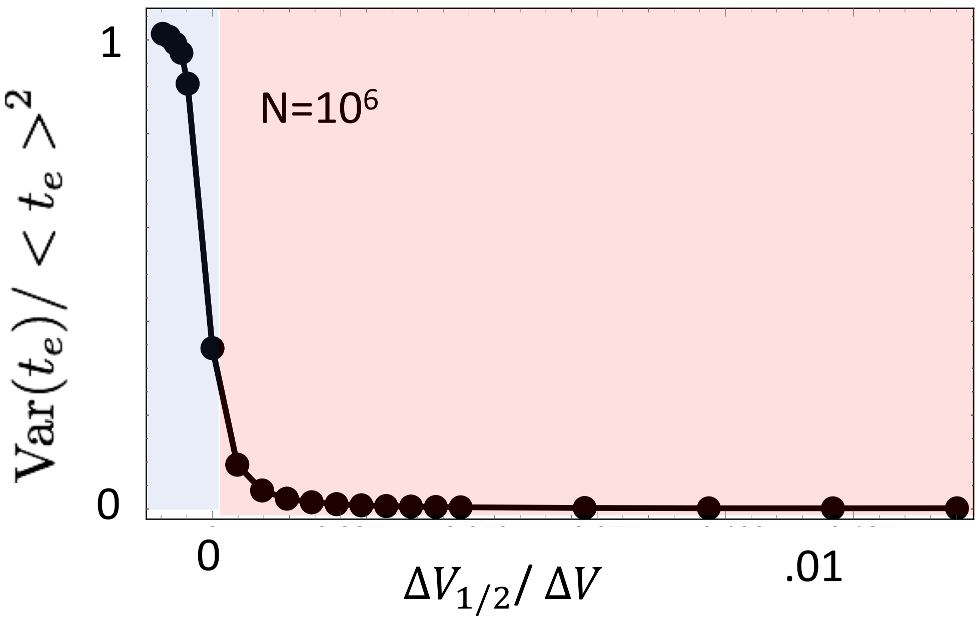
Information rate from spiking?

- By looking at a spike train, how well could you infer temperature?
  - Recall: absolute bound on information rate G_b from single channel noise.
- Here: measure G, rate of information from spike rate
  - Need $<t_e>$ and $Var(t_e)$:

Spike rate



scaled spike variance

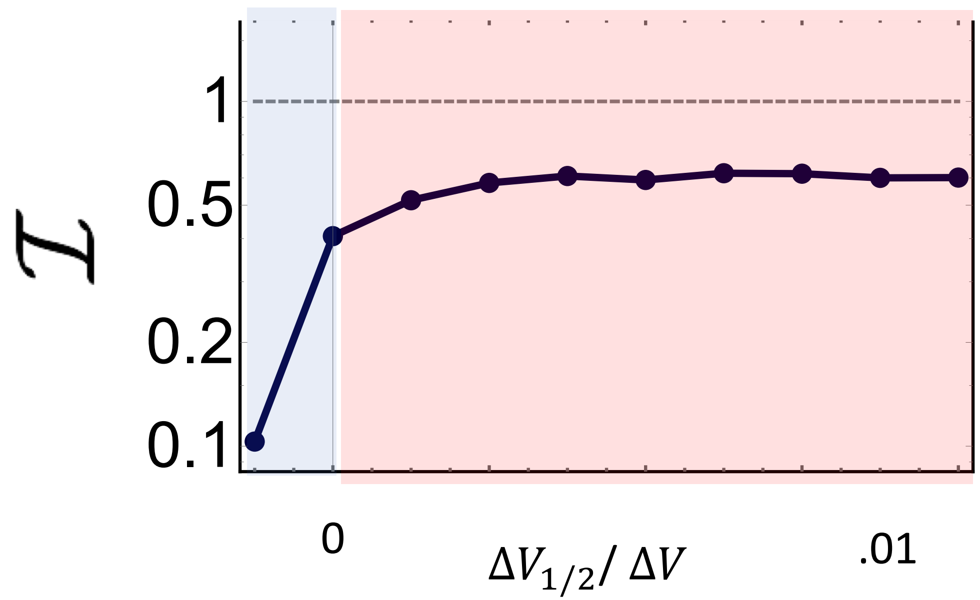


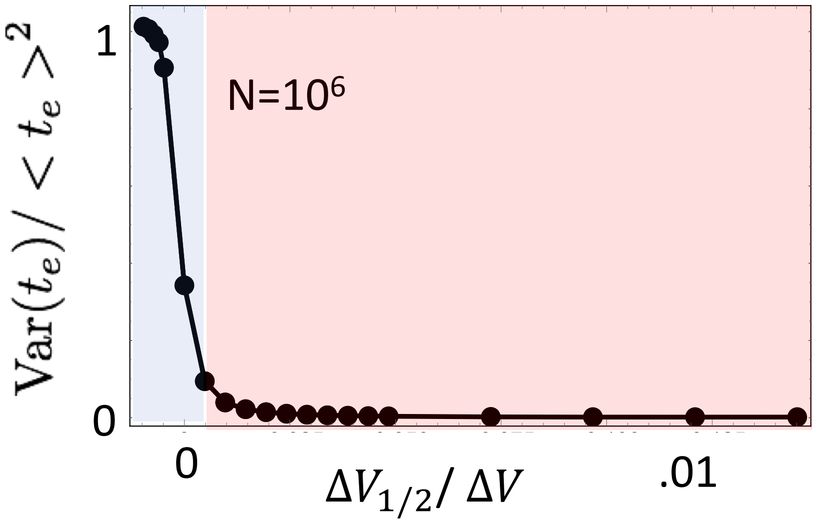
Information is (mostly) preserved in the deterministic regime

- We can define the Information fidelity
  - Fraction of information in single channels contained in spike train

$$\mathcal{I} = G/G_b$$

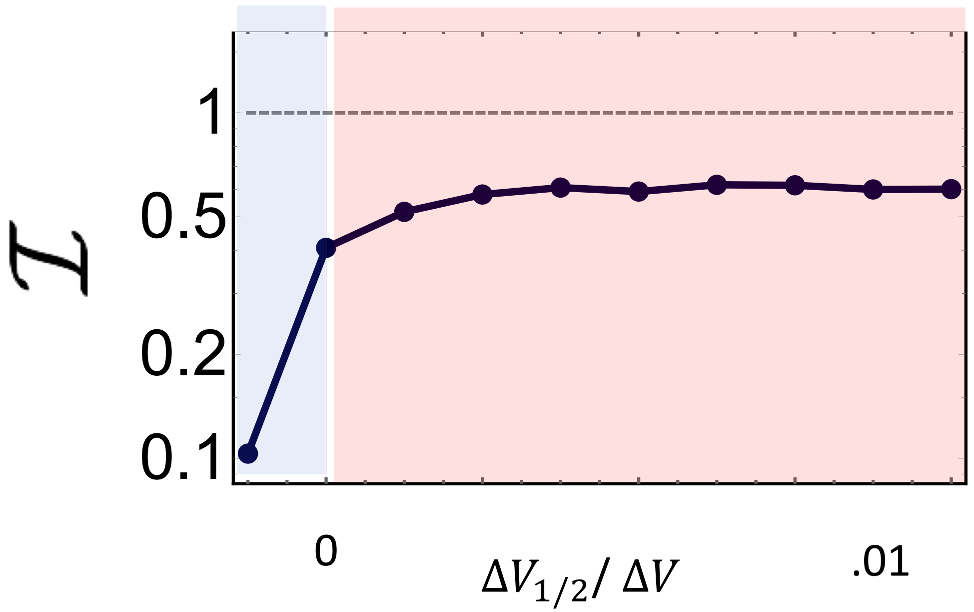
  - Order 1 fraction preserved in deterministic regime!
  - BUT: away from bifurcation information is contained in **tiny** changes in spike timing

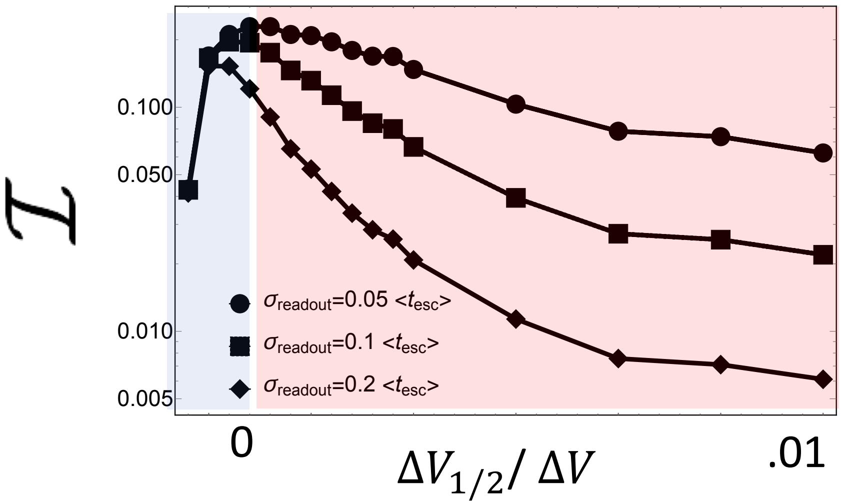




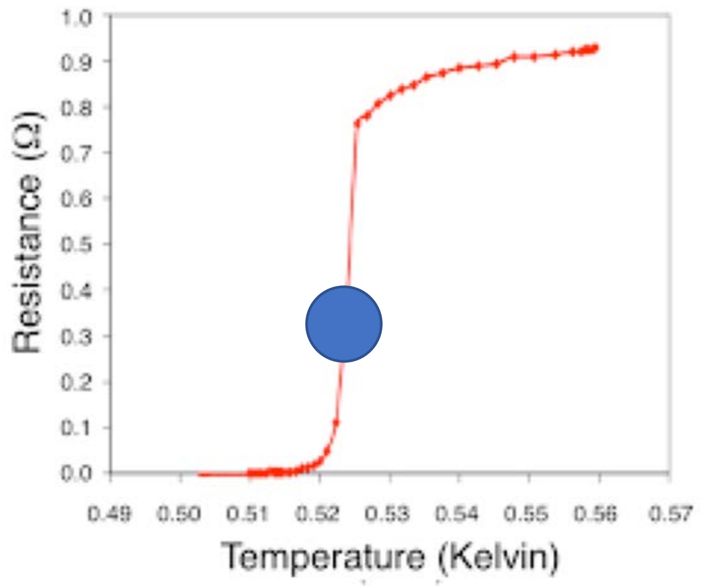
Information is accessible near the bifurcation

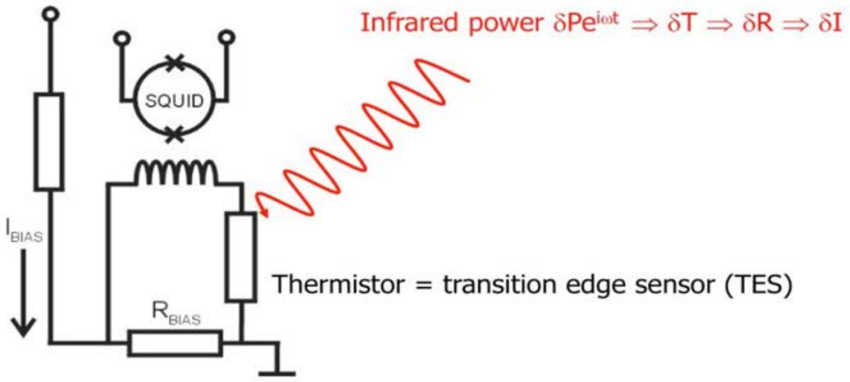
- Away from bifurcation information is contained in tiny and likely unmeasurable changes in spike timing
- We can put this in information theory terms by adding extra stochasticity to the spiking
- Close proximity to the bifurcation is essential for making information accessible





Parallels with cutting edge bolometry





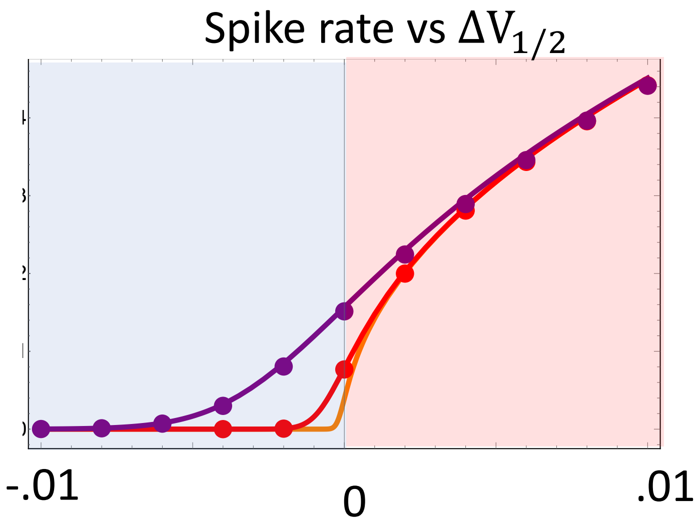
From Zakosarenko et al

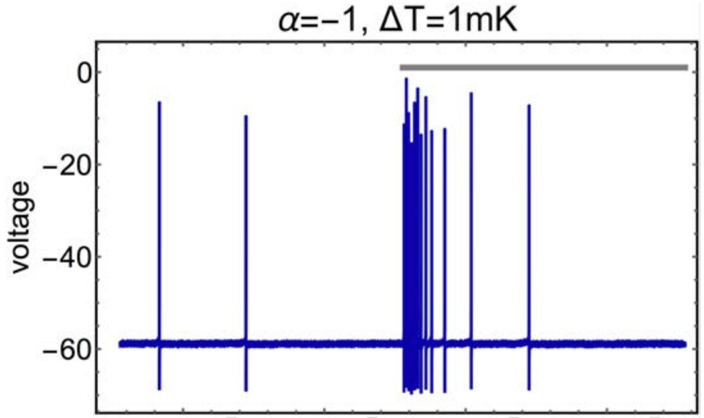
- Transition Edge Sensors are state of the art for detecting heat
- Idea: sensor is superconducting element near its superconducting transition upon which incident radiation is focused
  - Critical point amplifies a weak signal
- Circuit is voltage biased:
  - Temperature too (high) low, current. (de) increases (heating) cooling thermistor
  - Self tunes to (superconducting) critical point
- Current through detector reads out temperature

(Casual chat with Laura Newburgh)

Recap of the pit organ

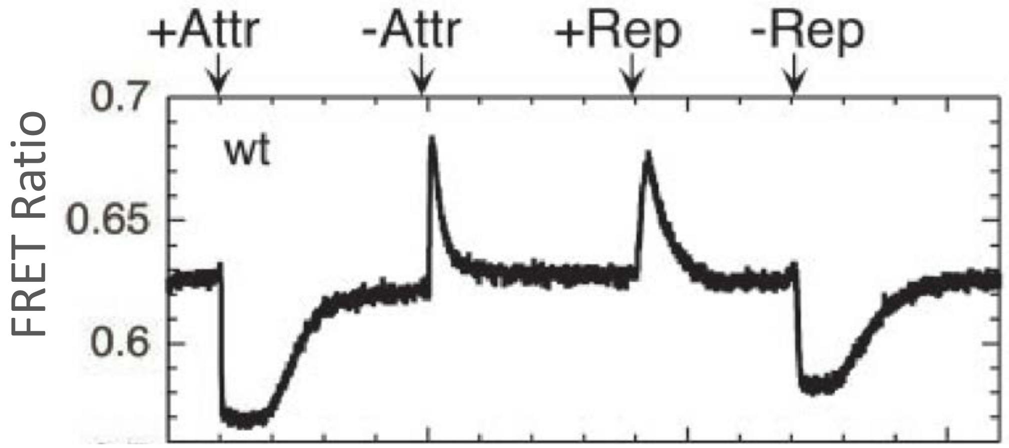
- Critical point / Bifurcation integrates information
- Nature of the bifurcation:
  - TRP ion channels are coupled electrically
  - Saddle Node bifurcation separates quiet from firing
- Functional role
  - Information distributed in many (~10^6) receptors
  - AP rate Amplification near bifurcation
- Tuning
  - Feedback from AP rate onto $V_{1/2}$ naturally tunes to bifurcation
- Further directions
- Other systems?
  - Chemoreception
  - Hearing
- Reverse engineering design principles



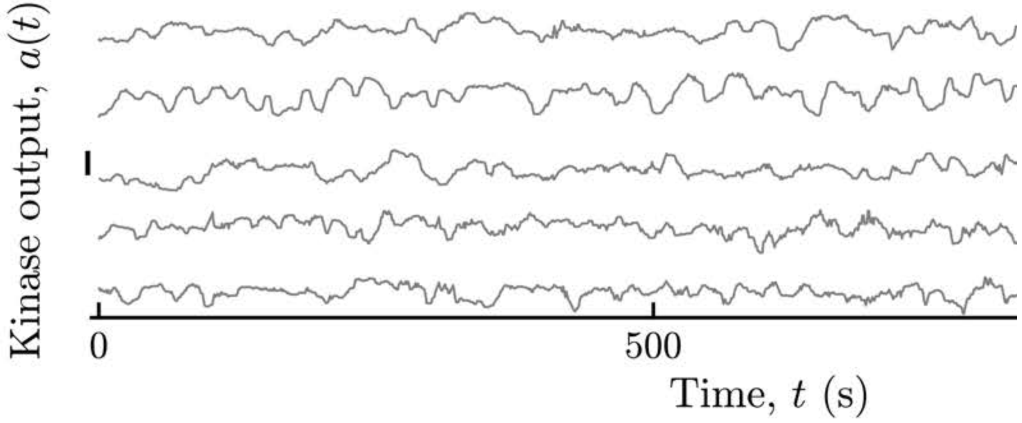


E. Coli chemoreceptor arrays amplify signals from many receptors

- To climb gradients E. coli must sense ~1% changes in concentration
  - Time derivative of concentration behaviorally relevant
  - System must operate over 10^4 changes in background
- Response is strongly amplified
- Response perfectly adapts
- Individual cells are noisy

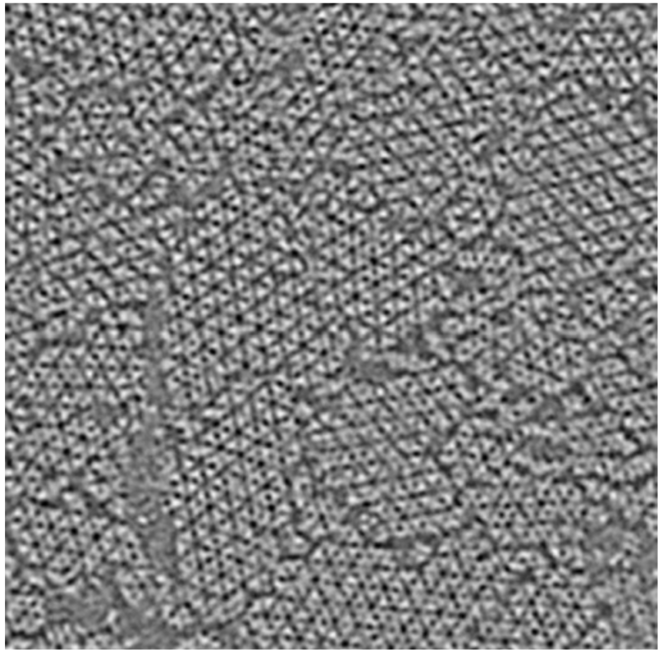


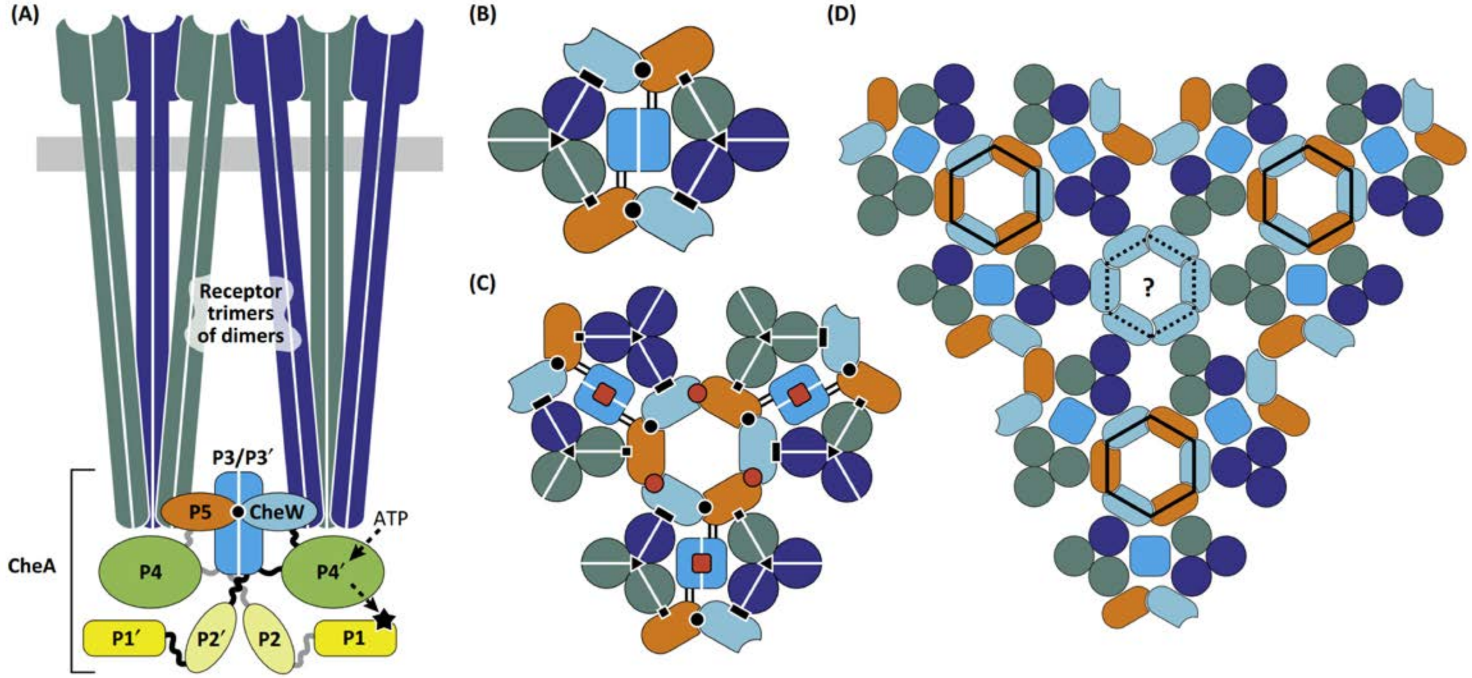
Sourjik and Berg PNAS 2002c



Mattingly et al, Nat Phys 2021

Chemoreceptors are arranged in a lattice with signaling enzymes





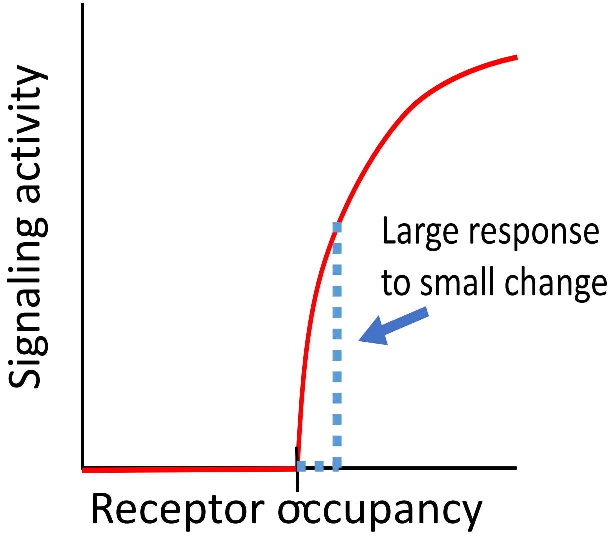
Cassidy et al. *Communications Biology.* 2020

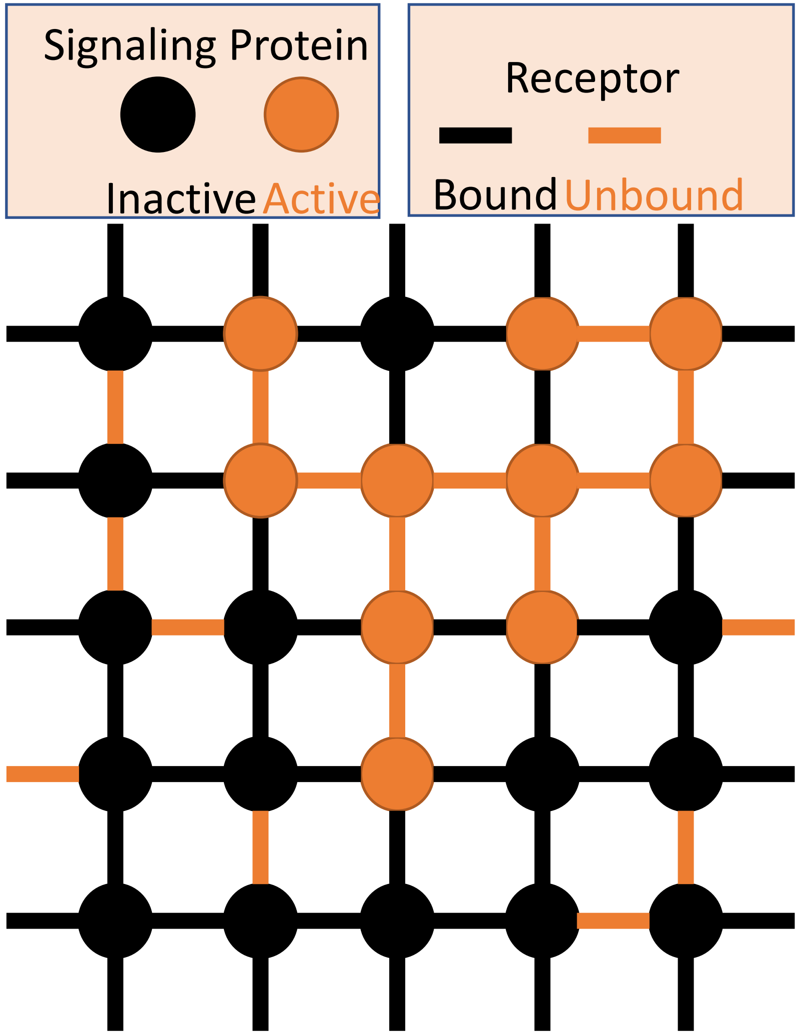
Reinterpreting biochemistry as self-tuning to an active percolation-like critical point

- (in)activity spreads through (un)bound receptors
- Feedback tunes to a bifurcation
  - Large amplification
  - Large noise (critical fluctuations)

Derek Sherry

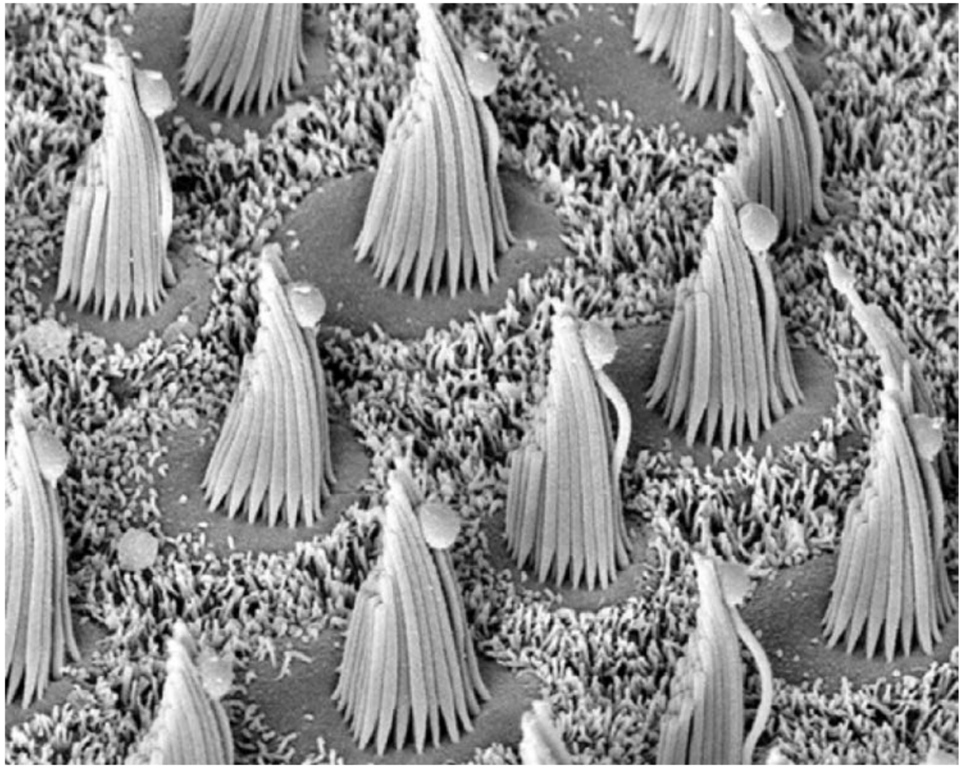
Isabella Graf





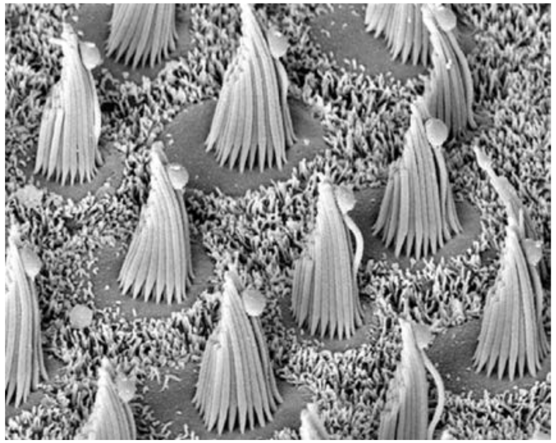
Hair cells are poised near a Hopf bifurcation

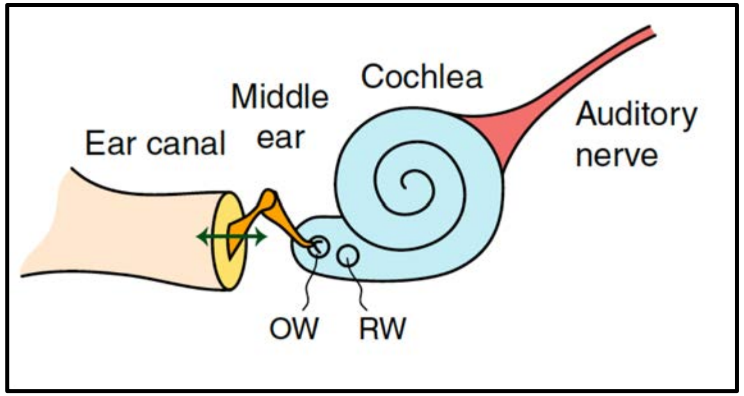
- We can hear over >100dB
  - 10 orders of magnitude in incident power
- Hair cells detect sound
  - 'compressive nonlinearity', hair cell displacement ~1/3 power of pressure amplitude
  - In silence hair cells spontaneously vibrate, emitting auto-acoustic emissions
  - implies active process
- ~2000, Magnasco, Hudspeth and Julicher: Hopf bifurcation
  - Confirmed in experiments with bullfrog hair cells (10Hz)



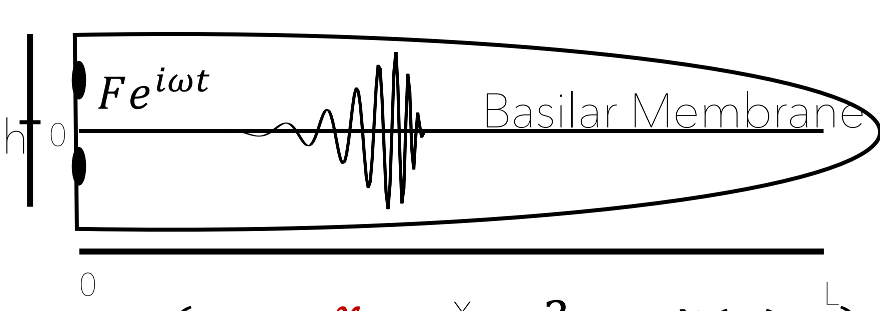
(Reichenbach and Hudspeth, 2014)

Hair cells and basilar membrane that detect sound are poised near a Hopf bifurcation



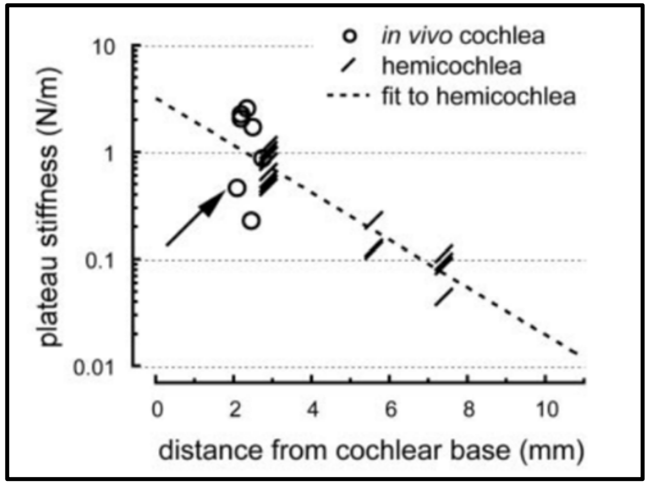


(Reichenbach and Hudspeth, 2014)



- $Z = (K_o e^{-x} - m\omega^2 + i\xi(x)\omega)$

  $= \text{stiffness} - \text{mass} + \text{friction}$



Asheesh Momi

Julian Rubinfien

Isabella Graf

Reverse Engineering I: Are these systems near physical limits?

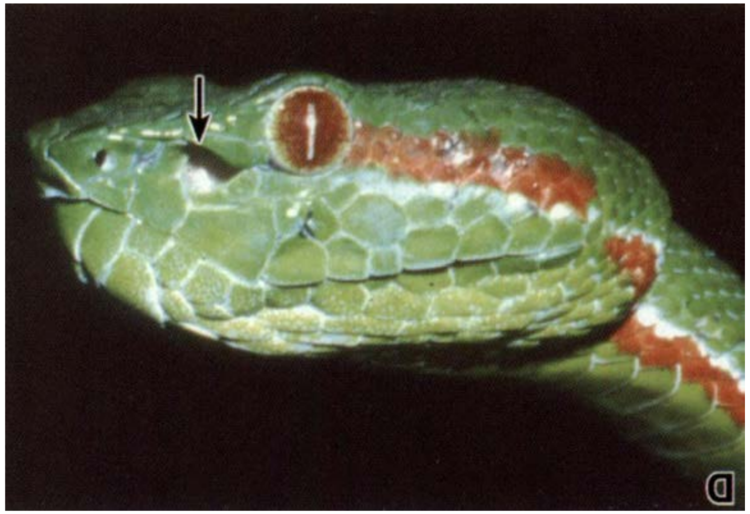
- Chemo-sensing:
  - Accuracy of a concentration measurement bounded by shot noise of single particle diffusion to the cell surface (Berg and Purcell 1977)
  - Behaviorally relevant for *E. coli*: measuring concentration change driven by their own motion.
  - In progress: What Is this bound and how close do E. coli get?
- Pit Organs:
  - Thermal fluctuations in heat bound accuracy of thermal imaging
  - In addition to $G<G_b$ must also have $G<G_p$ with G_p related to the heat capacity and thermal diffusion time of the neurons
  - What is this bound and how close are pit nerves to it?

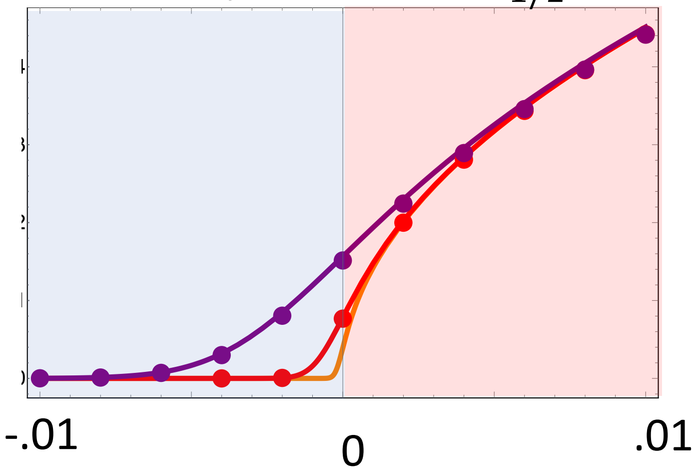
Reverse Engineering II: Do these systems efficiently use energy?

- Chemo-sensing
  - Individual chemoreceptors must communicate with each other
  - Sensory information must be sent to the motor
  - Sensory apparatus burns ~$10^5 K_B T$/s
  - Can we account for this?
- Pit Organs:
  - Single TRP channels must communicate their local information to the ensemble, fighting against thermal noise in the local voltage
  - Every opening of a TRP channel dissipates ~$10^5 k_B T$ of free energy (around $10^{11} K_B T$/s per neuron)
  - Can we understand these numbers?

Conclusions

- Information can be integrated from many receptors through the sensitivity of transitions
- Thermosensation in the pit organ
  - Information from ~10^6 channel events into APs
  - Amplification by proximity to bifurcation
  - Tuning by feedback from AP rate onto TRP $V_{1/2}$
- Other systems likely use bifurcations and critical points for broadly similar functions
- Lots of work for physicists in reverse engineering these systems





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Isabella Graf

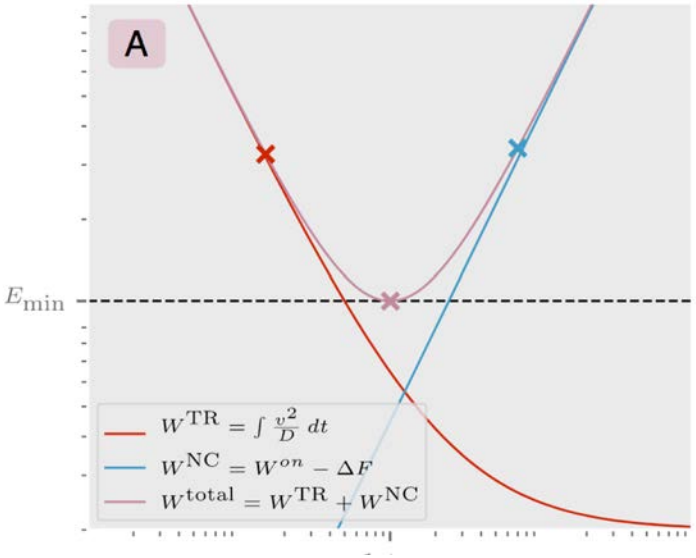

Questions?

Energetic bounds

Moving a thermodynamic system requires sub-extensive energy

$$S \geq 2\mathcal{L}(\boldsymbol{\lambda}_i, \boldsymbol{\lambda}_f) + \frac{\tilde{\mathcal{L}}^2(\boldsymbol{\lambda}_i, \boldsymbol{\lambda}_f)}{\Delta t}$$

Sam Bryant

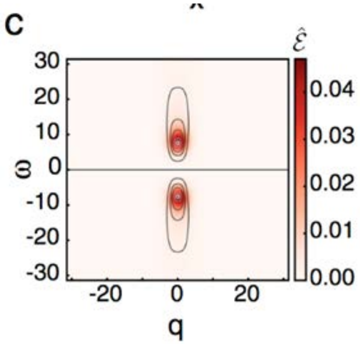


Bryant and BBM**, Energy Dissipation Bounds for Autonomous thermodynamic Cycles.** PNAS, 2020

Time asymmetric data implies entropy production

$$\dot{s} = \int \frac{d\omega}{2\pi} \frac{d^d\mathbf{q}}{(2\pi)^d}\, \mathcal{E}(\mathbf{q}, \omega);$$

$$\mathcal{E}(\mathbf{q}, \omega) = \frac{1}{2}\left[C^{-1}(\mathbf{q}, -\omega) - C^{-1}(\mathbf{q}, \omega)\right]_{ij} C^{ji}(\mathbf{q}, \omega).$$



Danny Seara

Michael Murrell

Seara, BBM, Murrell **Energy Dissipation Irriversibility in Dynamical Phases and Trtansitions.** Nat Comm, 2020