Noise in the Brain

Statistical and Dynamical Perspectives

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NATIONAL SCIENCE FOUNDATION

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Brain Dynamics and Statistics: Simulation versus Data

Statistical & Dynamical Perspectives Complement Each Other

$$I = C_M \frac{dV}{dt} + \bar{g}_K n^4 (V - V_K) + \bar{g}_{Na} m^3 h (V - V_{Na}) + \bar{g}_l (V - V_l),$$
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Hodgkin & Huxley 1952d

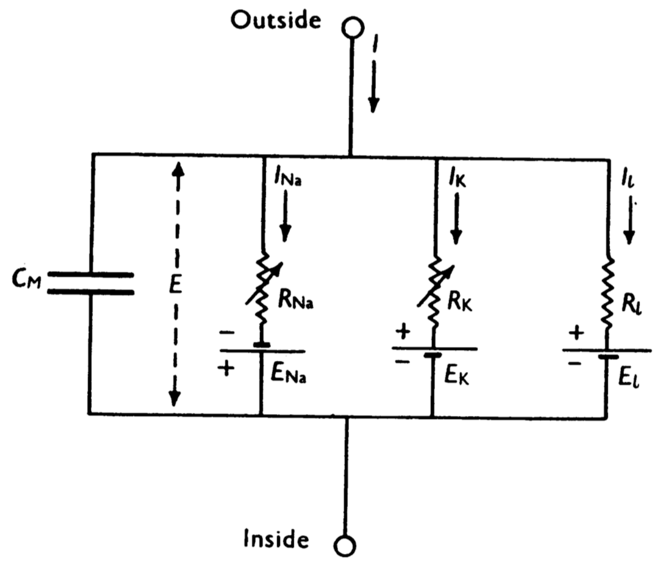
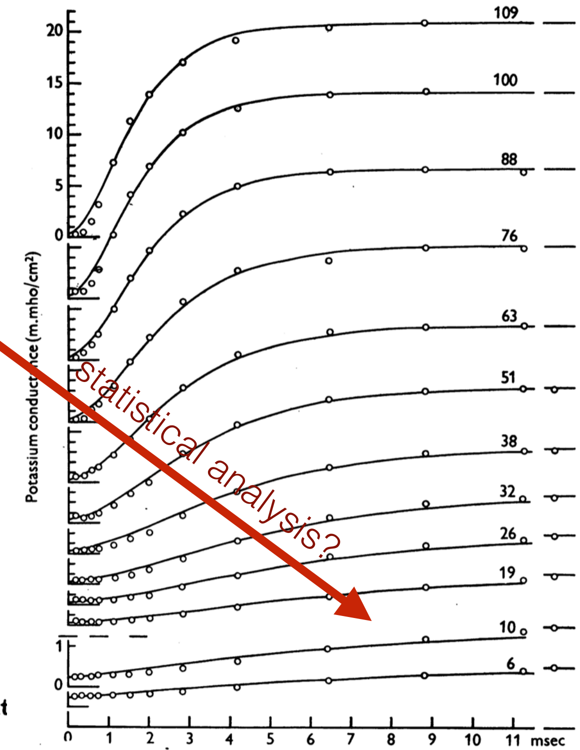


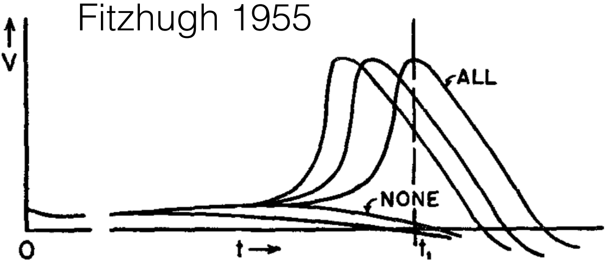
Fig. 1. Electrical circuit representing membrane. $R_{Na} = 1/g_{Na}$; $R_K = 1/g_K$; $R_l = 1/\bar{g}_l$. R_K vary with time and membrane potential; the other components are constant

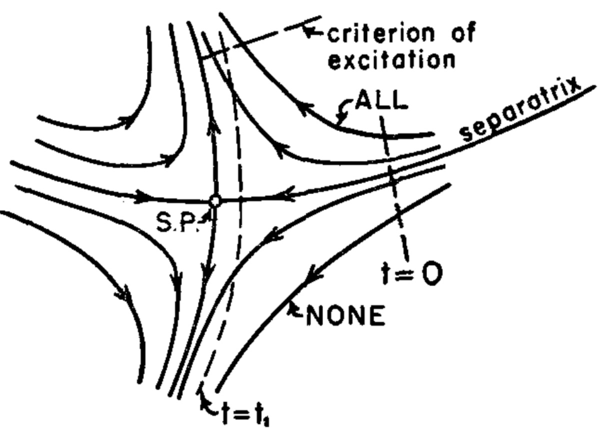


dynamical systems

statistical analysis?

Fitzhugh 1955





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The available observables are equally important:
Spike times or voltage fluctuations?
fMRI or calcium imaging?
Single or multiunit recordings?

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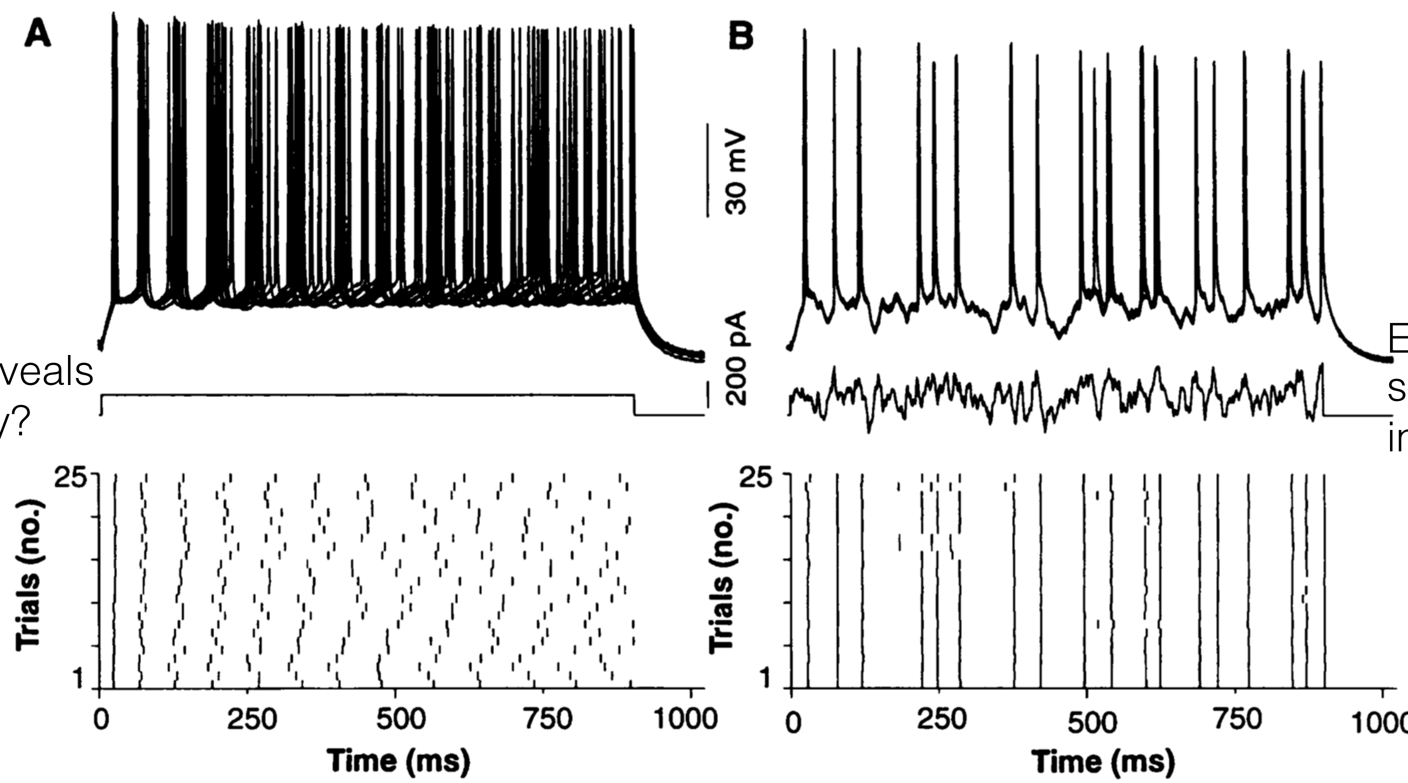
Constant input reveals intrinsic variability?



Extrinsic variability suppresses intrinsic fluctuations?

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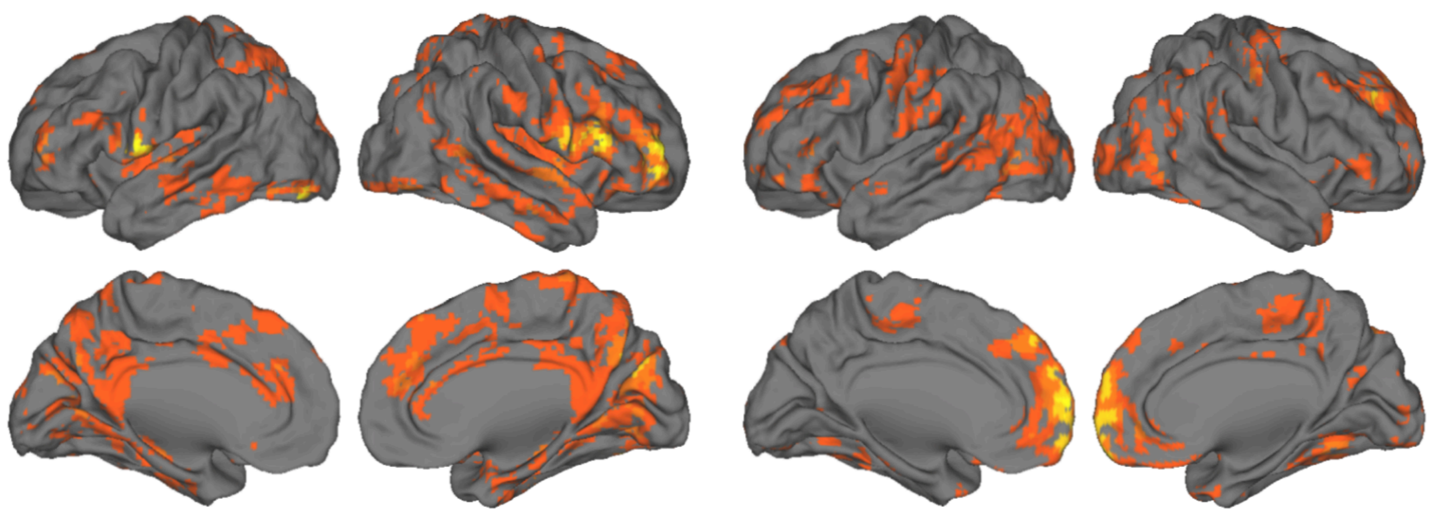
fMRI: default mode network (spontaneous activity) versus task positive network.
Intrinsic or extrinsically generated variability?



fMRI data courtesy of Tony Jack (CWRU)
analysis courtesy of Roberto Galan (CWRU)

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Phenomenological models: neuron as an input-output device.

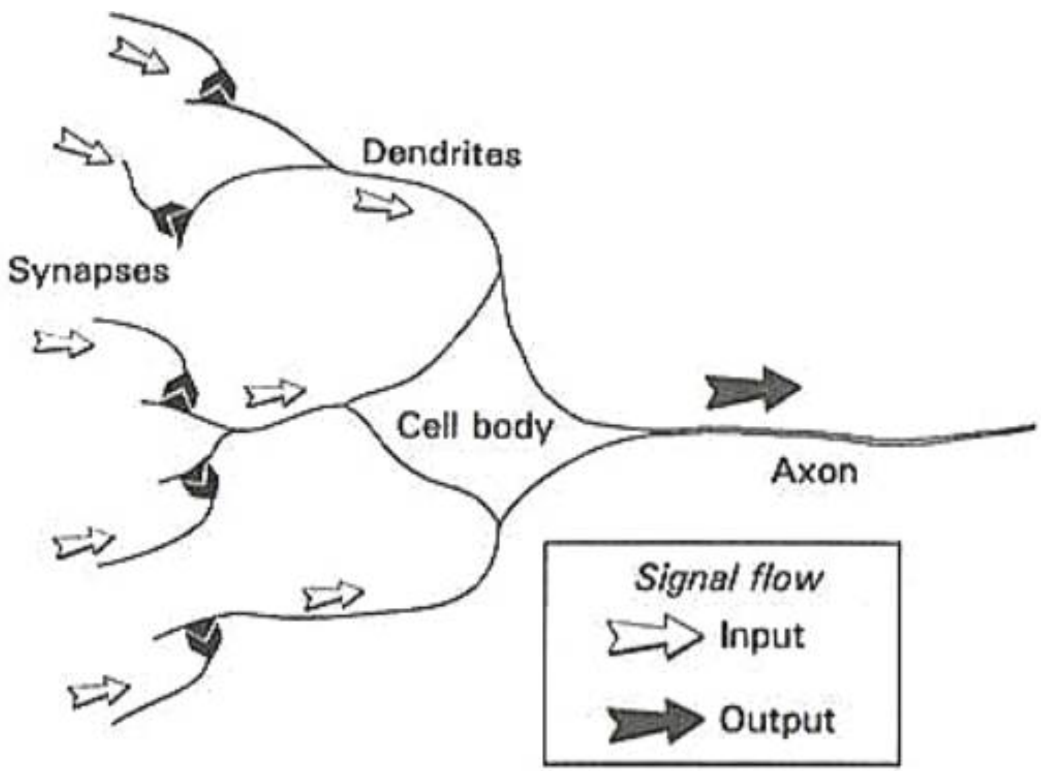

Image from http://www.aishack.in/tutorials/biological-neurons/

Locus of variability is the input ensemble.

Paninski, Liam. "Maximum likelihood estimation of cascade point-process neural encoding models." Network: Computation in Neural Systems (2004)

Brette, Romain, and Wulfram Gerstner. "Adaptive exponential integrate-and-fire model as an effective description of neuronal activity." J. Neurophys. (2005)

Wark, Barry, Adrienne Fairhall, and Fred Rieke. "Timescales of inference in visual adaptation." Neuron (2009).

Kobayashi, Ryota, Yasuhiro Tsubo, and Shigeru Shinomoto. "Made-to-order spiking neuron model equipped with a multi-timescale adaptive threshold." Frontiers in computational neuroscience (2009).

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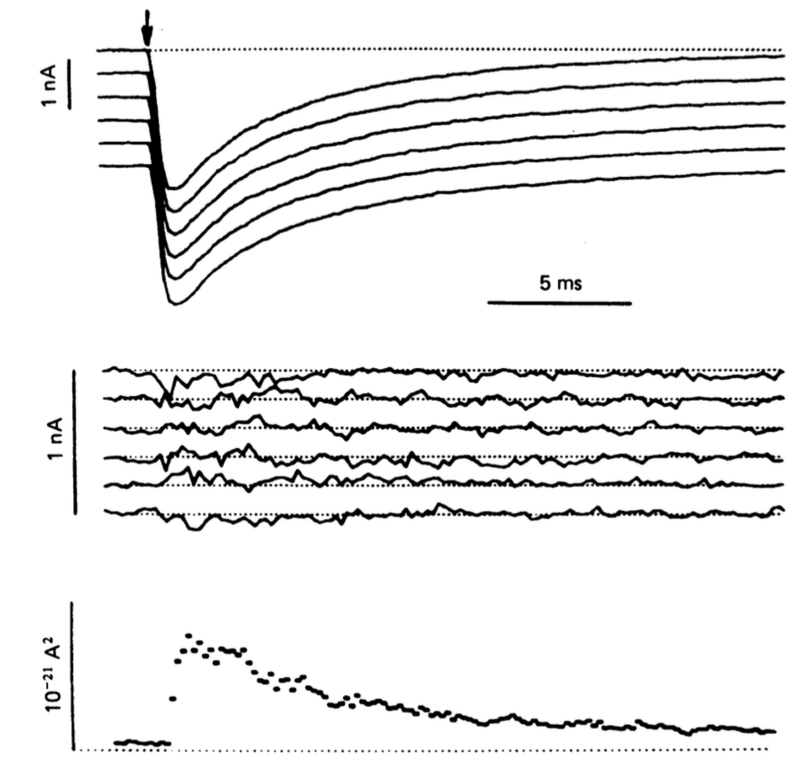
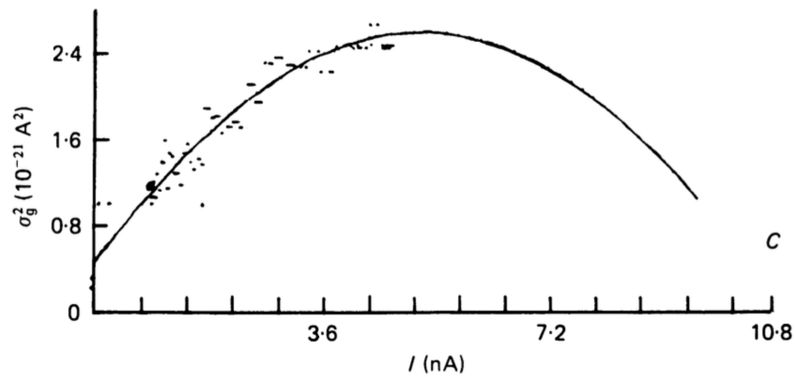
Sigworth's nonstationary variance analysis.

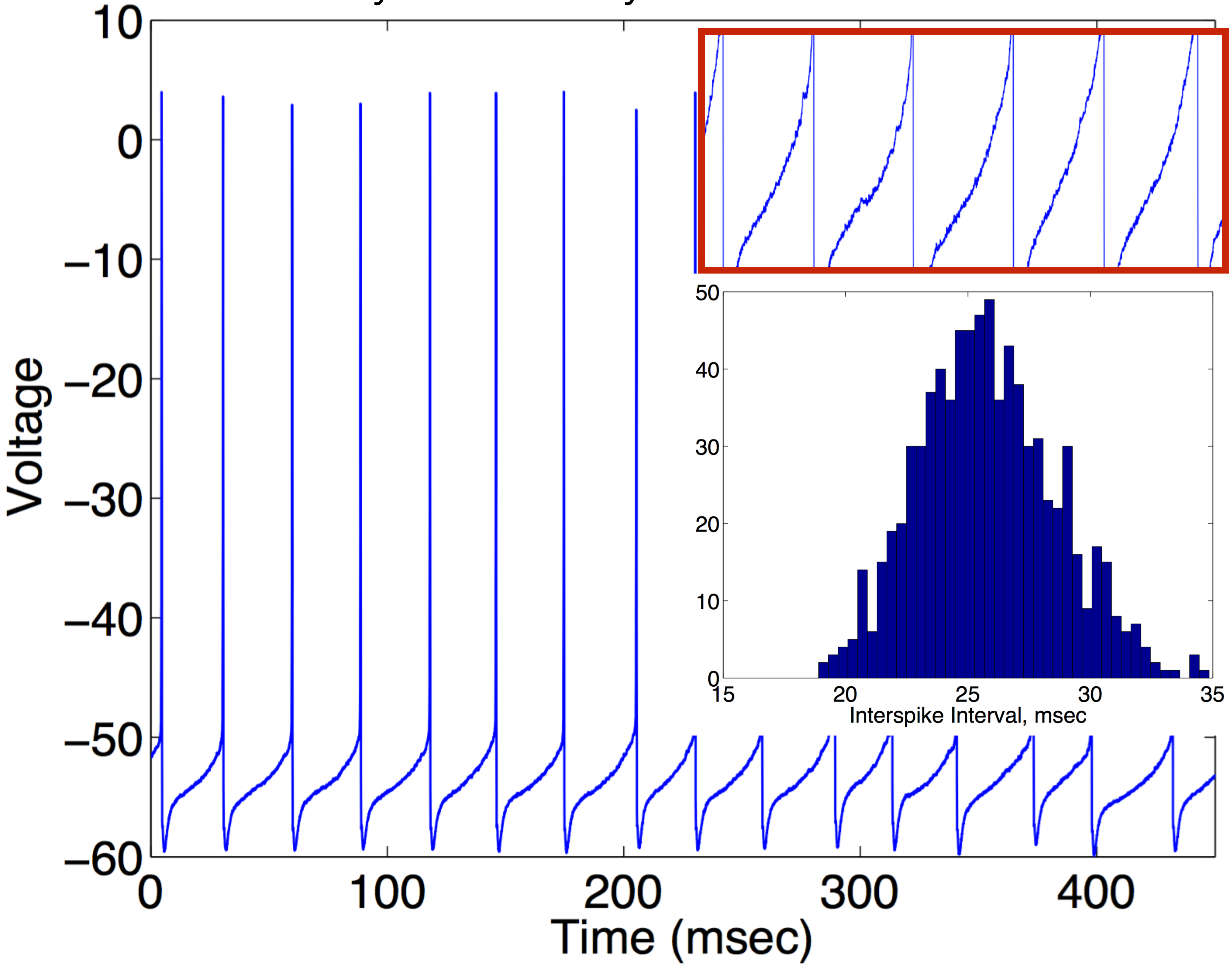


Sigworth (1980) J.Physiol.



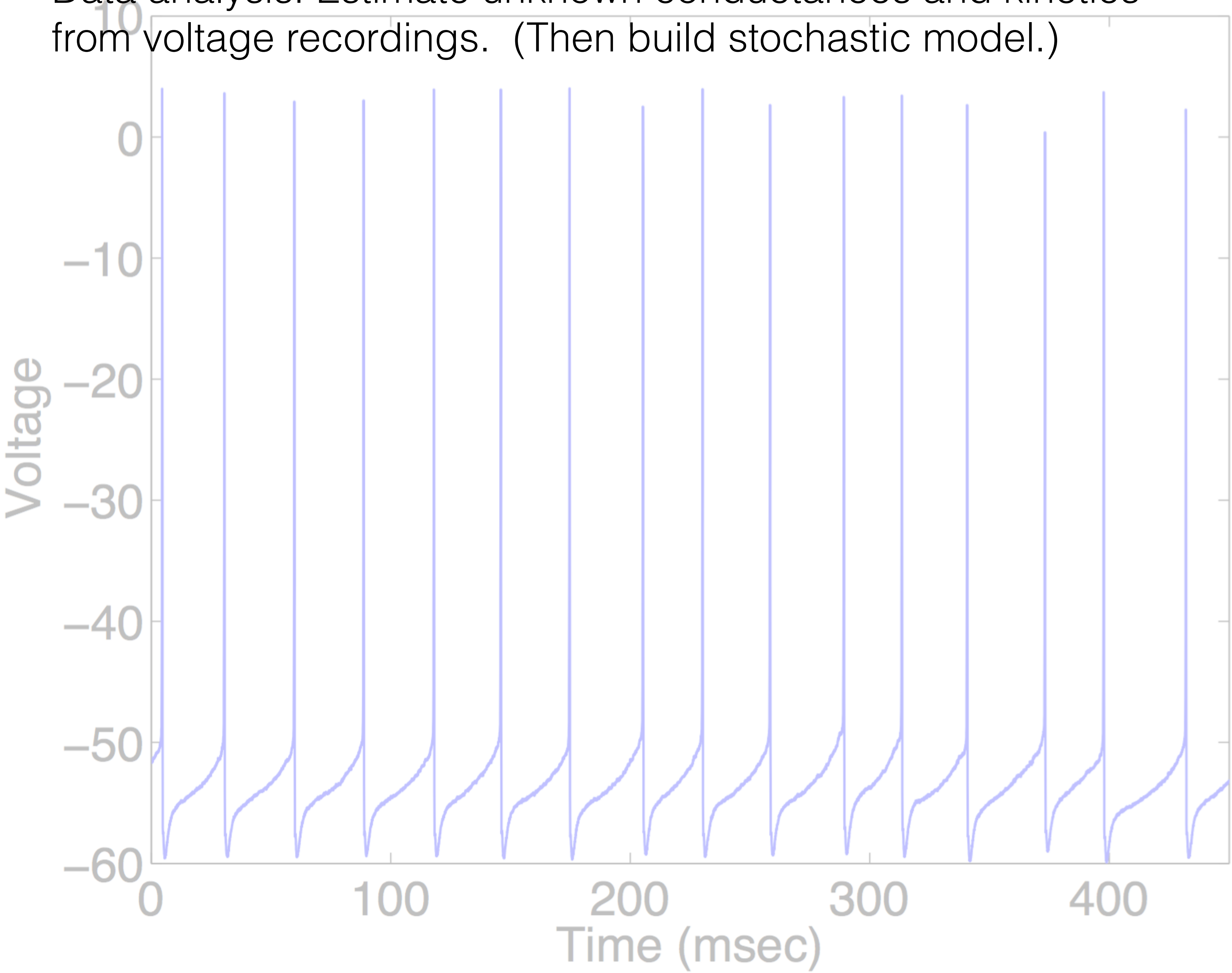
Open probability $p(t)$ obeys a linear DE.
Number of open channels $N(t) \sim \mathrm{Binom}(N_{\mathrm{tot}}, p(t))$.
Current $I(t) = N(t) g^0 (V - E_{\mathrm{ion}})$.
$E[I(t)] = x = N_{\mathrm{tot}} p(t) g^0 (V - E_{\mathrm{ion}})$.
$\sigma_I^2(t) = y = N_{\mathrm{tot}} p(t)(1 - p(t))(g^0(V - E_{\mathrm{ion}}))^2$.
Estimate peak of parabola $y = y_* - (x - x_*)^2$.
Solve for channel number $N_{\mathrm{tot}} = \frac{x_*}{2y_*}$.

ISI variability reflects dynamics w/ intrinsic noise



Purkinje cell spontaneous activity recorded in slice, courtesy D. Friel. ISI coefficient of variation approx 10%.

Data analysis: Estimate unknown conductances and kinetics from voltage recordings. (Then build stochastic model.)



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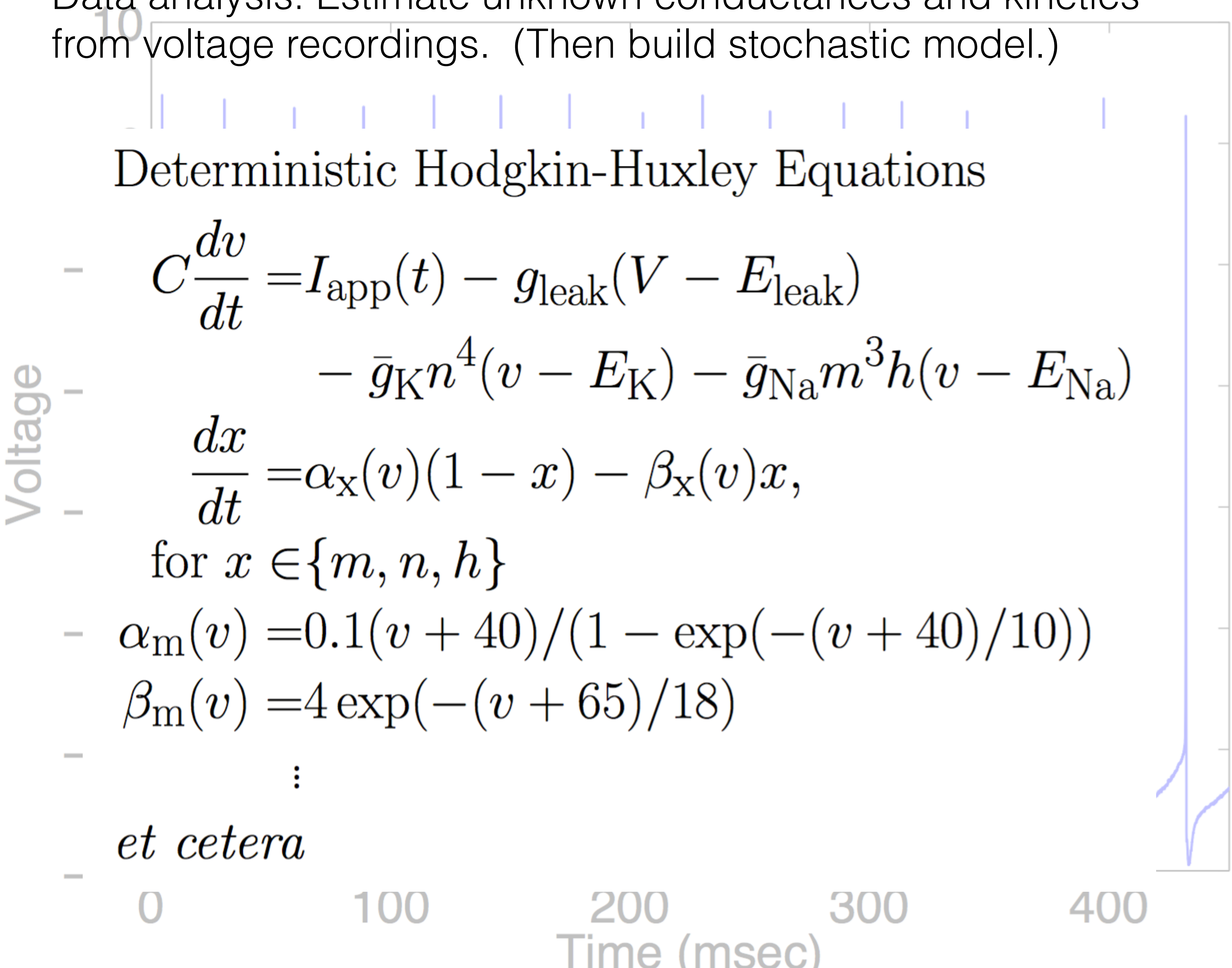

Deterministic Hodgkin-Huxley Equations

$$C\frac{dv}{dt} = I_{\mathrm{app}}(t) - g_{\mathrm{leak}}(V - E_{\mathrm{leak}}) - \bar{g}_{\mathrm{K}}n^4(v - E_{\mathrm{K}}) - \bar{g}_{\mathrm{Na}}m^3h(v - E_{\mathrm{Na}})$$

$$\frac{dx}{dt} = \alpha_{\mathrm{x}}(v)(1-x) - \beta_{\mathrm{x}}(v)x,$$

$$\text{for } x \in \{m, n, h\}$$

$$\alpha_{\mathrm{m}}(v) = 0.1(v+40)/(1-\exp(-(v+40)/10))$$

$$\beta_{\mathrm{m}}(v) = 4\exp(-(v+65)/18)$$

$$\vdots$$

et cetera

Data analysis: Estimate unknown conductances and kinetics from voltage recordings. (Then build stochastic model.)

The model structure — e.g. gating variable network topology — may not be identifiable.

Meng, Liang, Mark A. Kramer, and Uri T. Eden. "A sequential Monte Carlo approach to estimate biophysical neural models from spikes." Journal of neural engineering 8.6 (2011): 065006.

Milescu, Lorin S., Gustav Akk, and Frederick Sachs. "Maximum likelihood estimation of ion channel kinetics from macroscopic currents." Biophysical journal 88.4 (2005): 2494-2515.

Fink, Martin, and Denis Noble. "Markov models for ion channels: versatility versus identifiability and speed." Philosophical Transactions of the Royal Society of London A: Mathematical, Physical and Engineering Sciences 367.1896 (2009): 2161-2179.

Given the structure of the model, not all parameters are identifiable.

Walch, Olivia J., and Marisa C. Eisenberg. "Parameter identifiability and identifiable combinations in generalized Hodgkin–Huxley models." Neurocomputing 199 (2016): 137-143.

Bahr, Tyler, and Mark Transtrum. "Parameter Identifiability in the Hodgkin-Huxley Model of a Single Neuron." Bulletin of the American Physical Society 60 (2015).

Csercsik, Dávid, Katalin M. Hangos, and Gábor Szederkényi. "Identifiability analysis and parameter estimation of a single Hodgkin–Huxley type voltage dependent ion channel under voltage step measurement conditions." Neurocomputing 77.1 (2012): 178-188.

Parameter Estimation Approaches for Conductance Based Models

* Sequential Monte Carlo or particle filtering methods (Meng et al 2011; Meng et al 2014; Huys and Paninski 2009)

* “Data assimilation” through virtual coupling of data and model (Abarbanel et al 2009; Abarbanel 2013)

* Combined statistical and geometric methods for periodic orbits with timescale separation, i.e. bursting activity (Tien and Guckenheimer 2008).

* State space / current based parameter estimation (Lepora et al 2012, Vavoulis et al 2012)

* Kalman filter, extended Kalman filter, unscented Kalman filter; as applied to parameter estimation for ion channel / conductance based models. (cf monograph: Law, Kody, Andrew Stuart, and Konstantinos Zygalakis. Data Assimilation. Springer International Publishing, 2015. 1-23. Voss et al 2004 Chaos. & monograph Data Assimilation (2016) by Asch, Bocquet, Nodet.).

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Hodgkin & Huxley 1952d

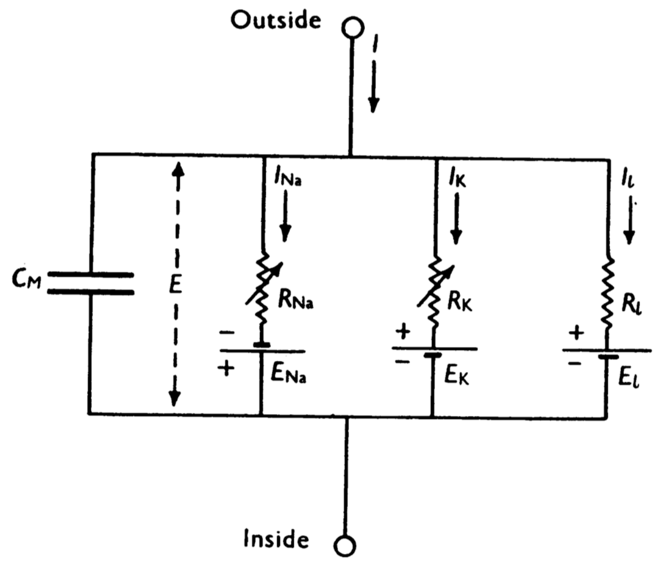
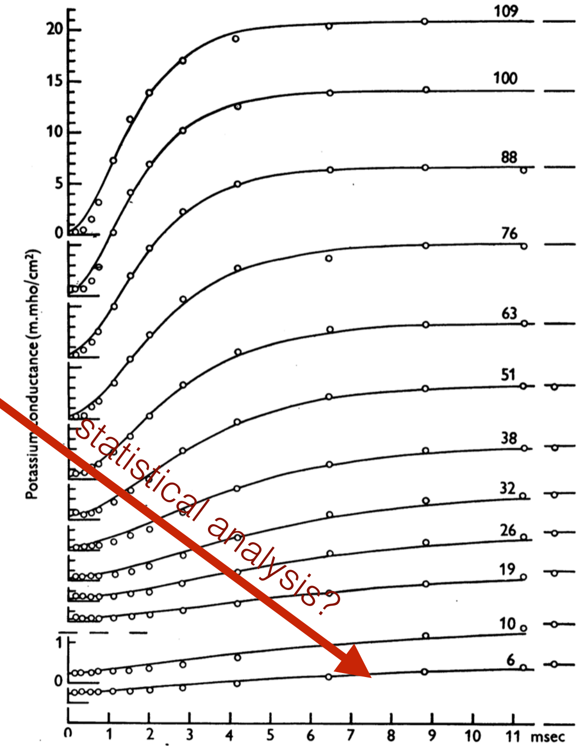


Fig. 1. Electrical circuit representing membrane. $R_{Na} = 1/g_{Na}$; $R_K = 1/g_K$; $R_l = 1/\bar{g}_l$. R_K vary with time and membrane potential; the other components are constant.



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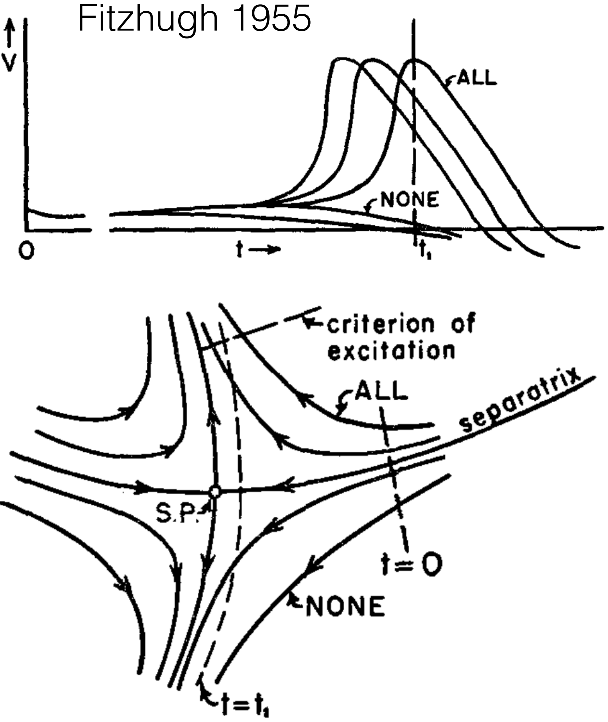
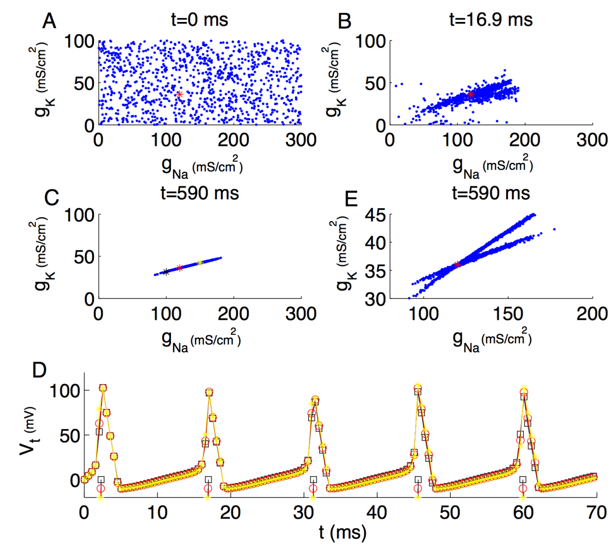


"Data Assimiliation"



Meng et al 2011 J. Neural Eng.

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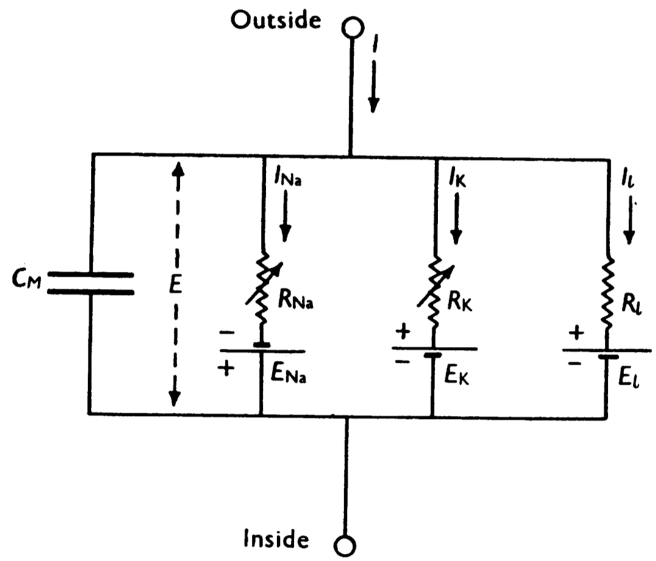

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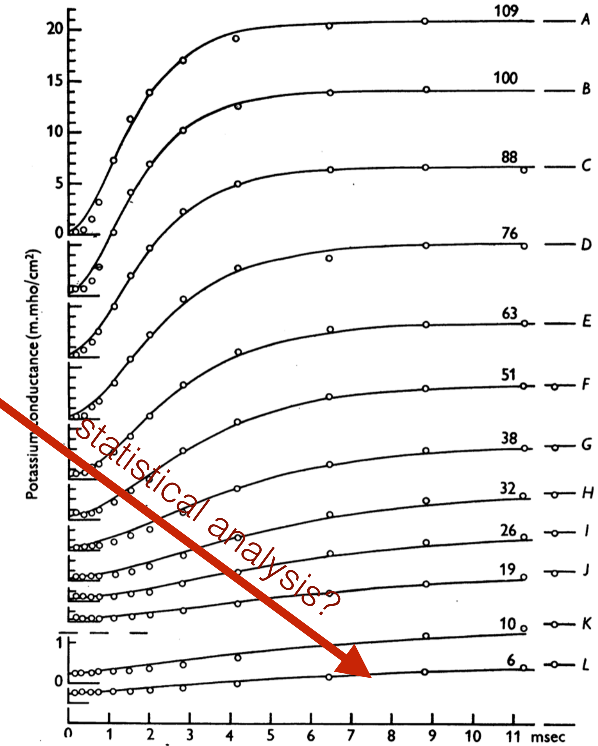

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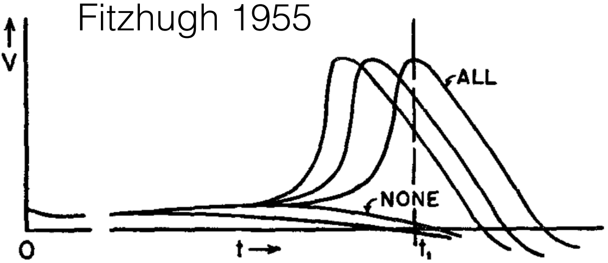
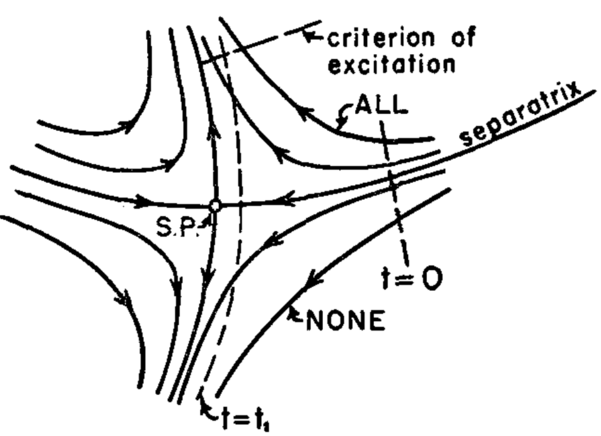




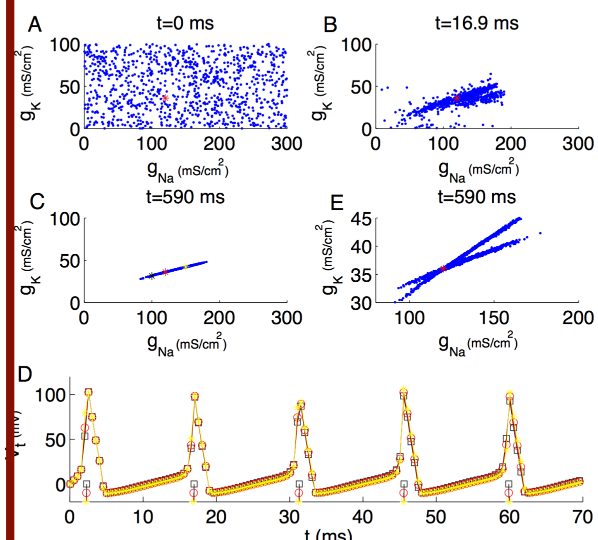
<u>Remainder of the talk</u>

I. Stochastic oscillations

II. Stochastic shielding

III. Closed-loop motor control

"Data Assimiliation"



Meng et al 2011 J. Neural Eng.

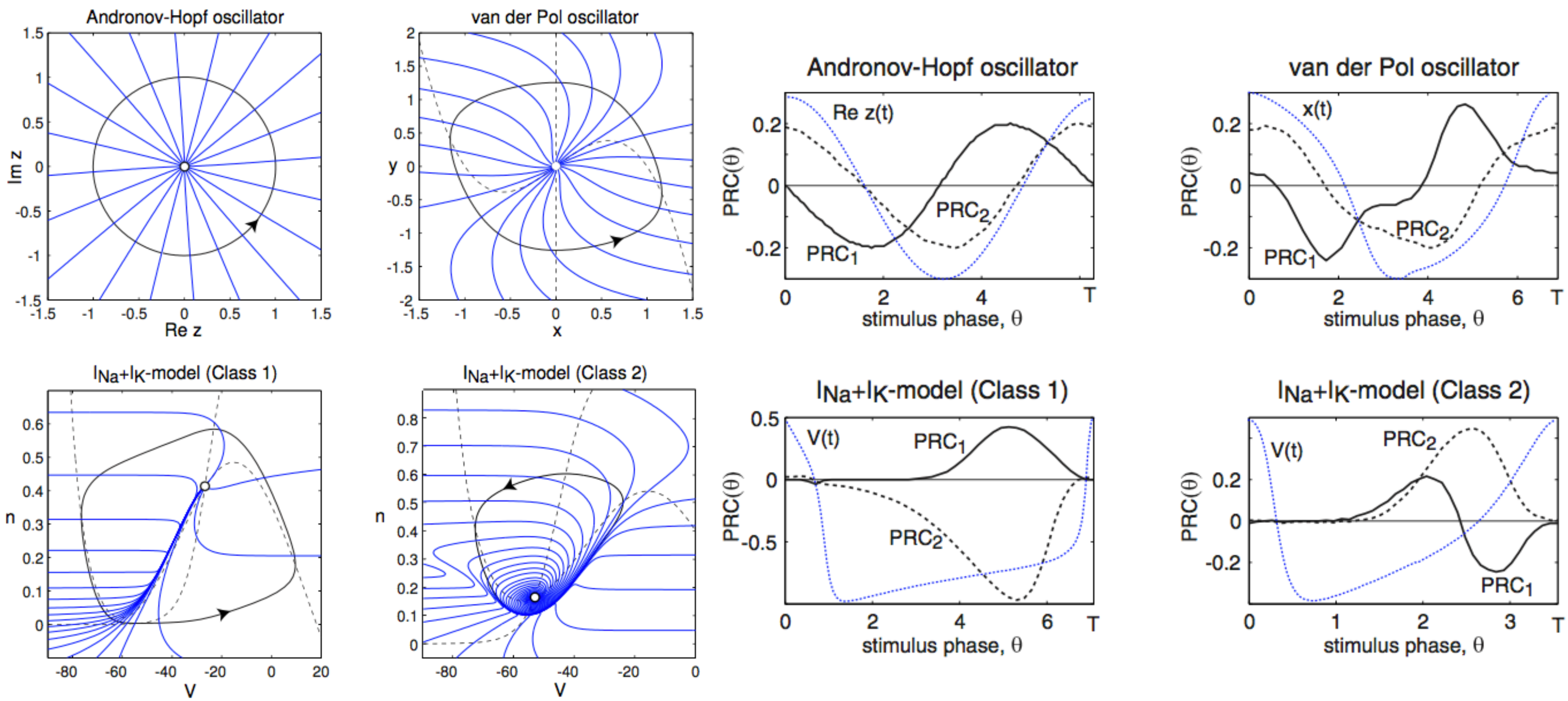
I. On the Problem of Quantifying “Phase Resetting” in Stochastic Neural Oscillators.

A. Inconsistencies in phase resetting analysis.

B. Spectral definition of oscillator “phase”.

C. Statistical definition of oscillator “phase”.

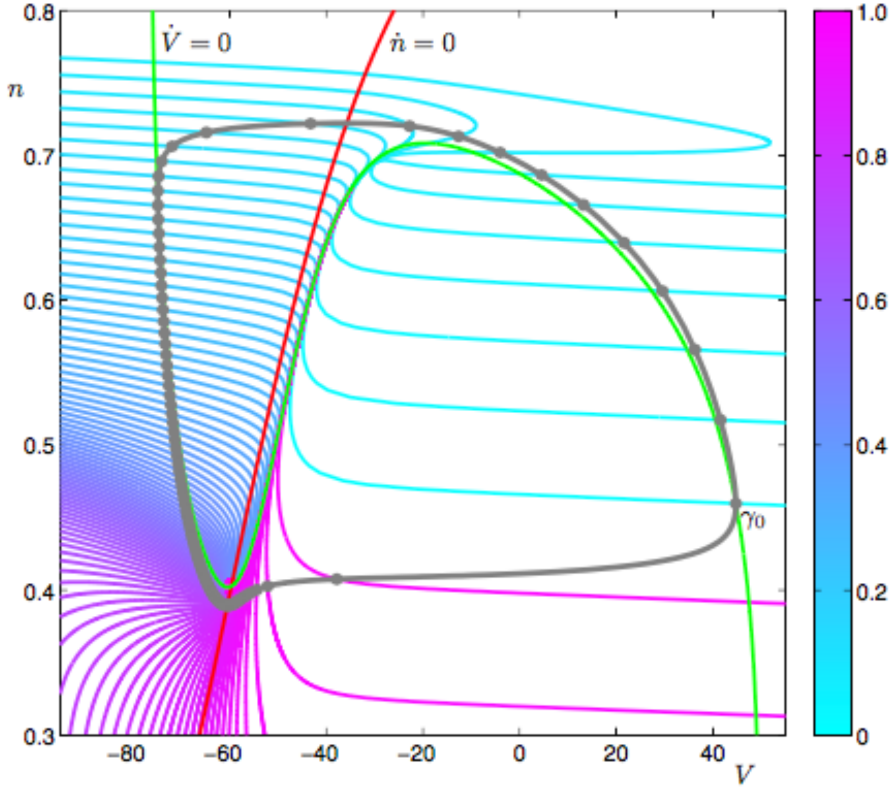
Limit Cycles, Isochrons, and Phase Response Curves



Izhikevich, Dynamical Systems in Neuroscience (2007)

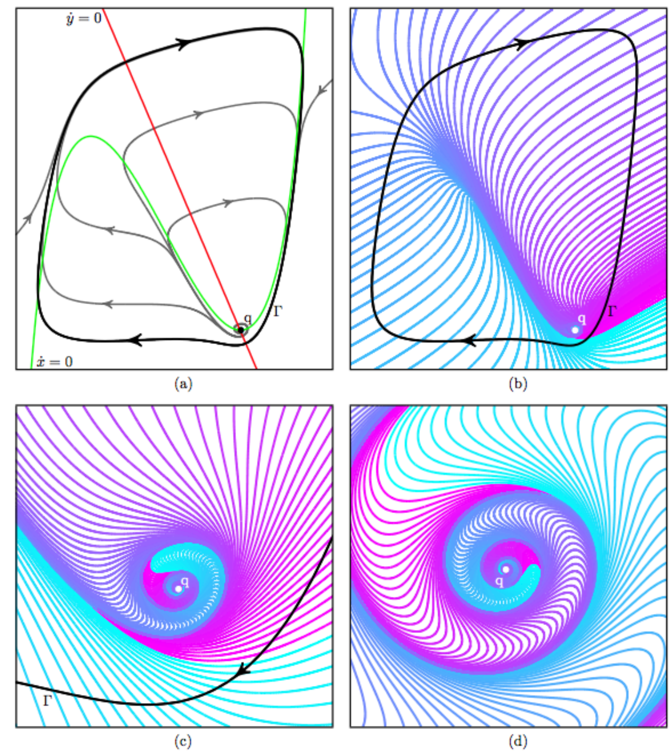
- Oscillations are ubiquitous in neural systems.
- The “asymptotic phase” identifies points converging to a common trajectory.
- Phase response curves measure the shift in timing due to a stimulus.
- PRCs allow analysis of synchronization & entrainment.
- Experimental PRCs are measured via perturbation experiments.

Reduced (planar) Hodgkin-Huxley model:
nullclines, limit cycle, isochrons



Osinga & Moehlis, 2014 SIAM Dyn. Sys

Fitzhugh-Nagumo model (cf van der Pol oscillator):
closeup of isochrons near slow manifold, equilibr. pt.

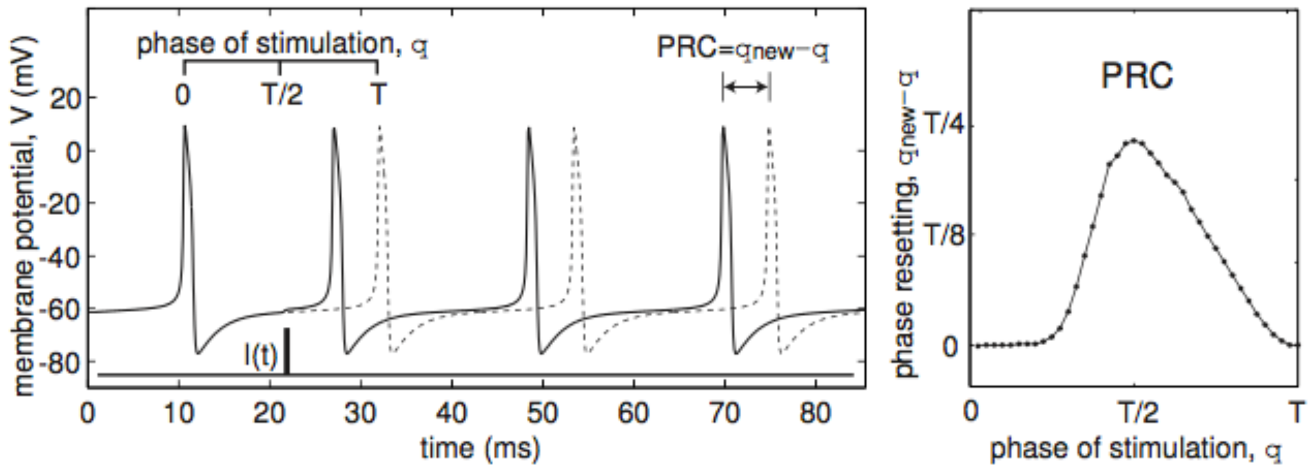


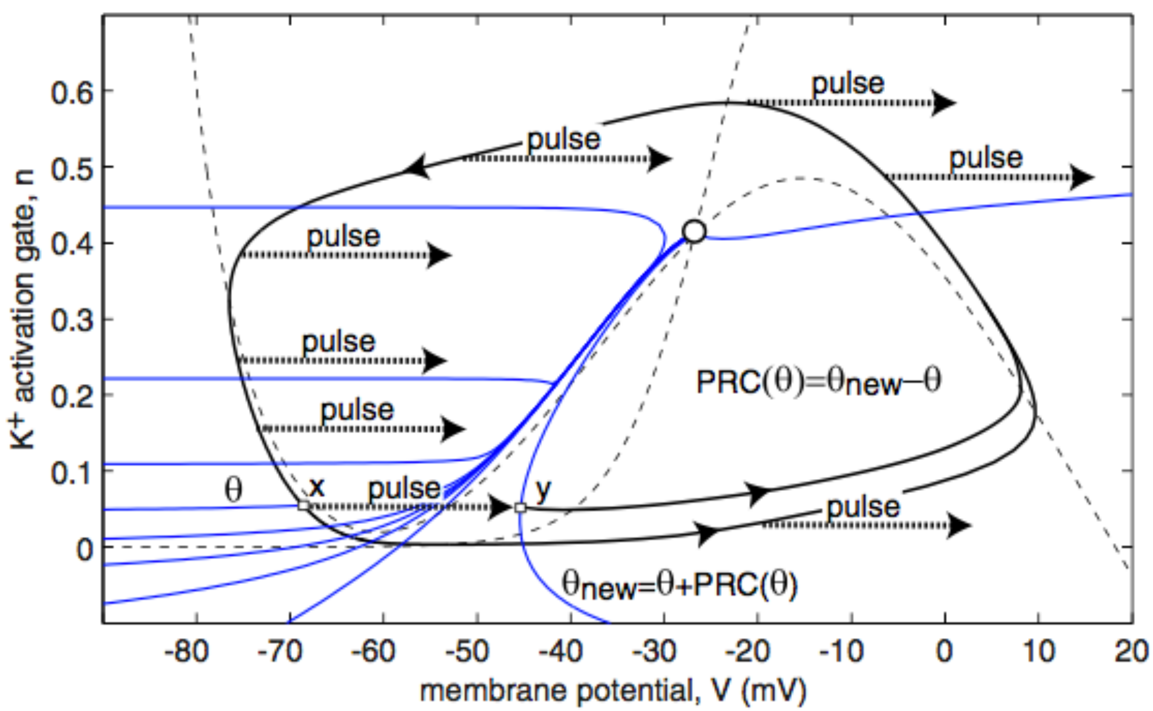
Langfield et al, 2014 Chaos

For a smooth, deterministic dynamical systems with a hyperbolic limit cycle, the isochrons and infinitesimal phase response curves are well understood.

The classical picture can break down in several ways:
1. Limit cycle oscillator with nonsmooth dynamics (Park et al, submitted)
2. Near-heteroclinic oscillators (Shaw, Park, Chiel, Thomas, 2012 SIADS)
3. Stochastic “limit cycle” oscillator (Thomas & Lindner 2014 PRL)

Limit Cycles, Isochrons, and Phase Response Curves





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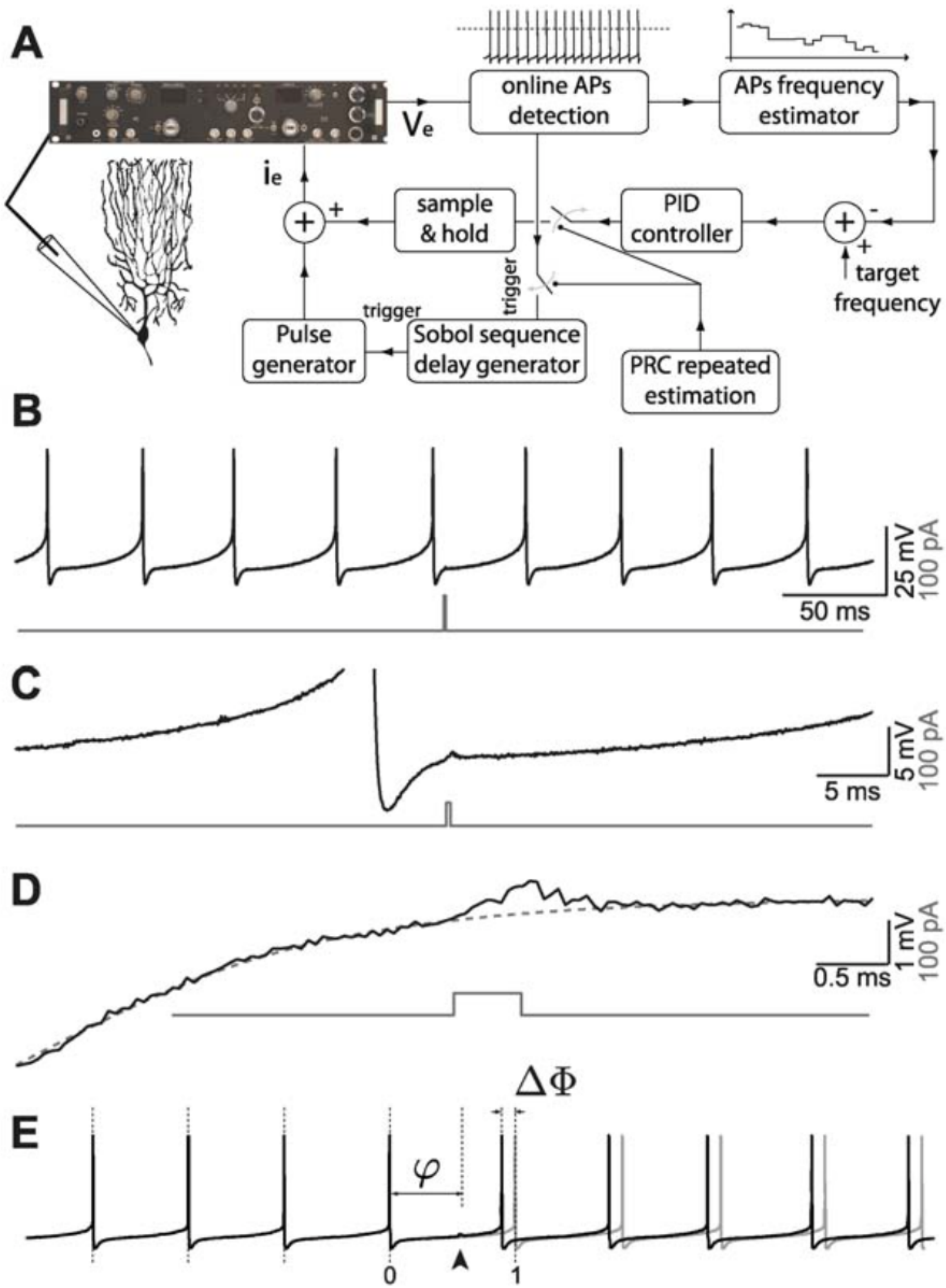


Phase Response Curves

Cuoto et al measured the phase response curve of Purkinje cells and showed the PRC changes shape as a function of firing rate, suggesting a shift in computational properties in different dynamical regimes.

(Couto, J., et al. "On the Firing Rate Dependency of the Phase Response Curve of Rat Purkinje Neurons." *PLoS Comput Biol* 11.3 (2015): e1004112.)

Phase response is measured as the shift in timing of the next spike, T_{k+1}, relative to the average interspike interval <T>, as a function of the phase $(t-T_k)/\langle T \rangle$ at which a small stimulus is applied.

Since some intervals are longer than the mean interval, a stimulus can be applied outside the range [0,1]

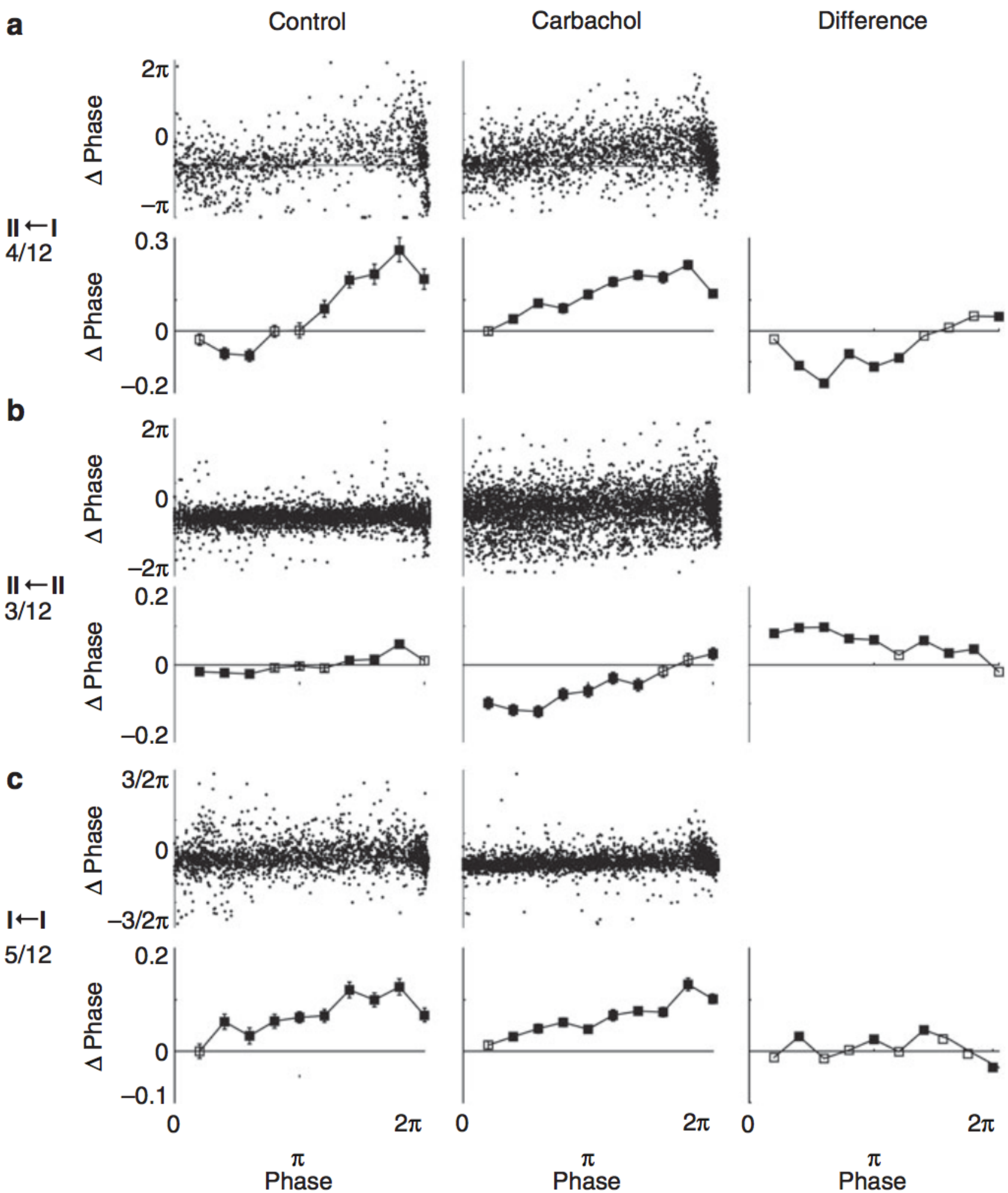


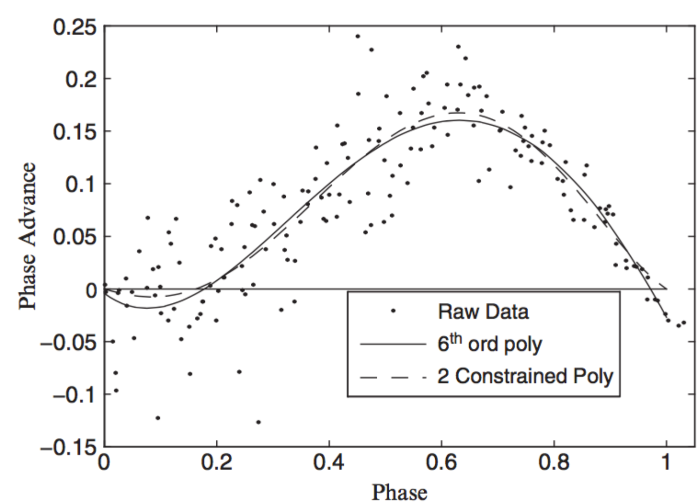
Fig. 12.3 Averages of all cells showing a transition from a type II to a type I PRC (**a**) or remaining with a type II (**b**) or type I PRC (**c**). Figure conventions as in Fig. 12.2. Figure modified from Stiefel et al. 2008

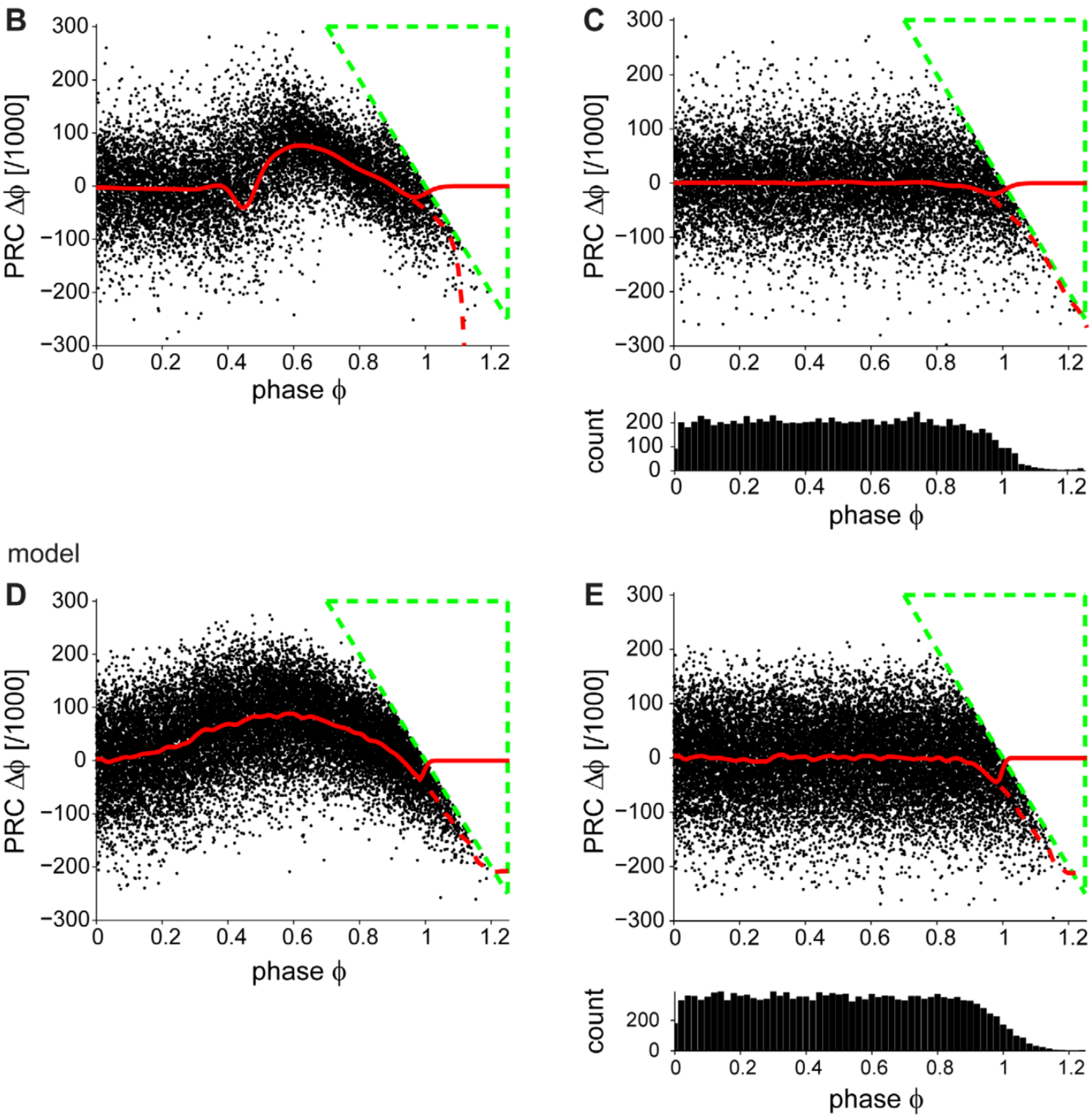
Trial-to-trial phase response is highly variable

Stiefel, Klaus M., Boris S. Gutkin, and Terrence J. Sejnowski. "Cholinergic neuromodulation changes phase response curve shape and type in cortical pyramidal neurons." *PloS one* 3.12 (2008): e3947-e3947.

Ermentrout, G. B., Beverlin II, B., Troyer, T., & Netoff, T. I. (2011). The variance of phase-resetting curves. *Journal of computational neuroscience*, *31*(2), 185-197.

Netoff, Theoden, Michael A. Schwemmer, and Timothy J. Lewis. "Experimentally estimating phase response curves of neurons: theoretical and practical issues." Phase response curves in neuroscience. Springer New York, 2012. 95-129.



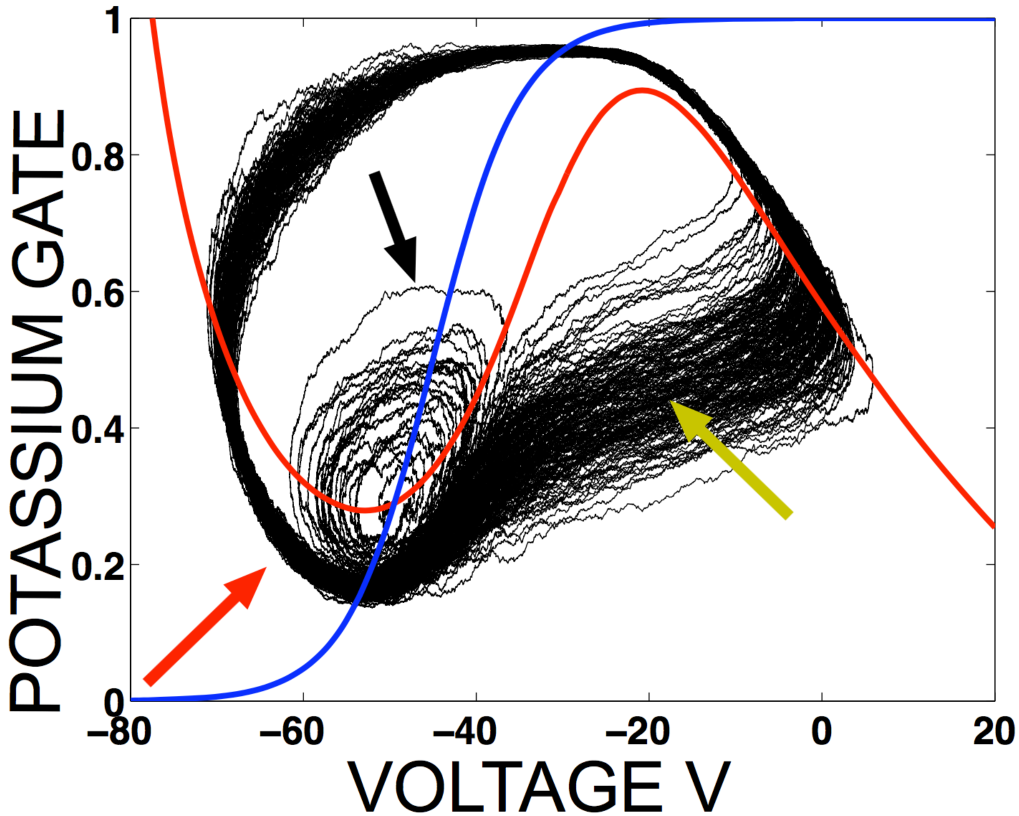


The definition of "phase" for deterministic oscillators is inconsistent when applied to stochastic oscillators.

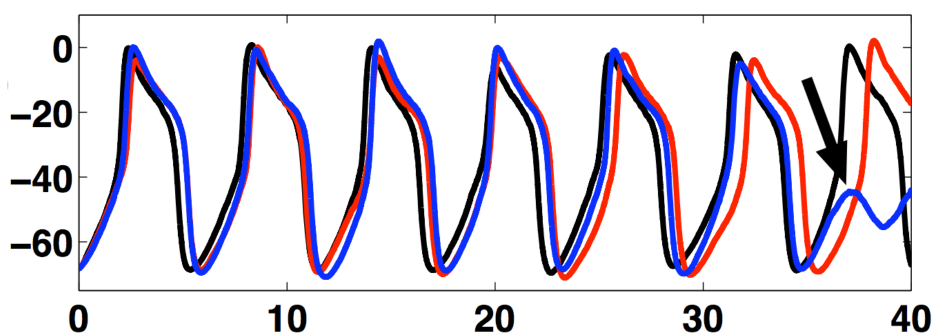
Figure from Phoka et al. "A new approach for determining phase response curves reveals that Purkinje cells can act as perfect integrators." *PLoS Comput Biol* 6.4 (2010): e1000768-e1000768.

Asymptotic phase is not well defined for stochastic oscillators.

* All initial conditions converge (as t -> infinity) to the same stationary density
* Isochrons may not be defined in the vanishing noise limit (e.g. heteroclinic systems)



I_{NaP+K} model with channel noise.



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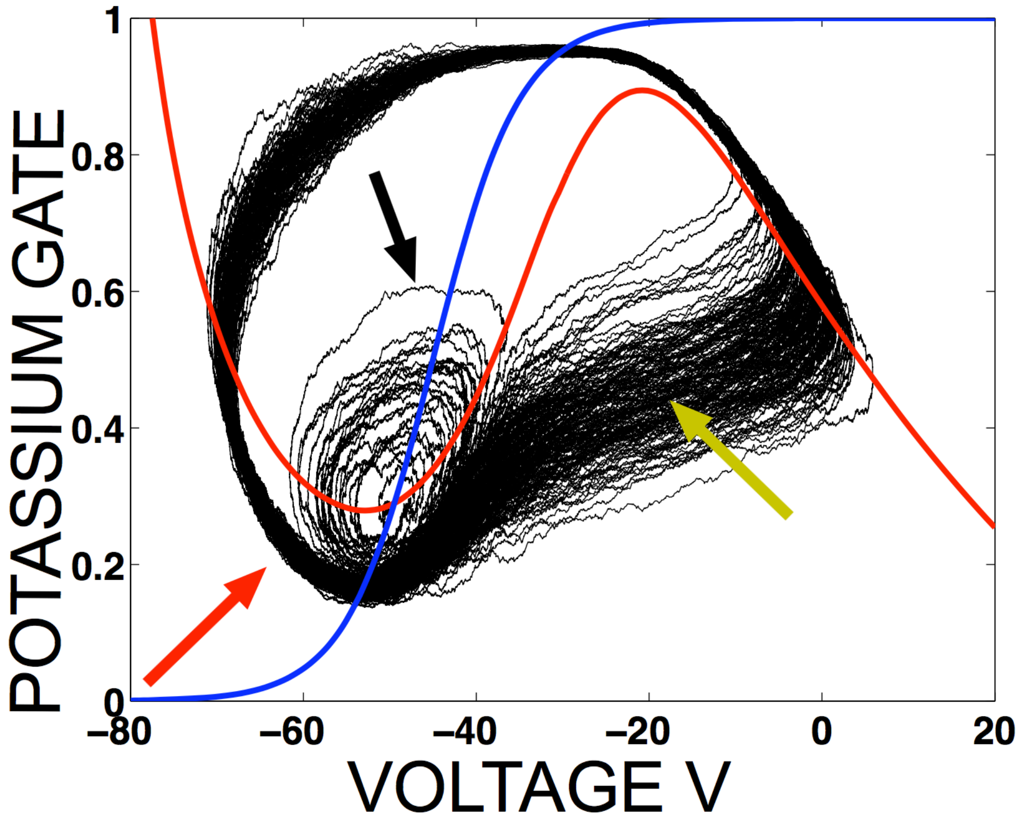

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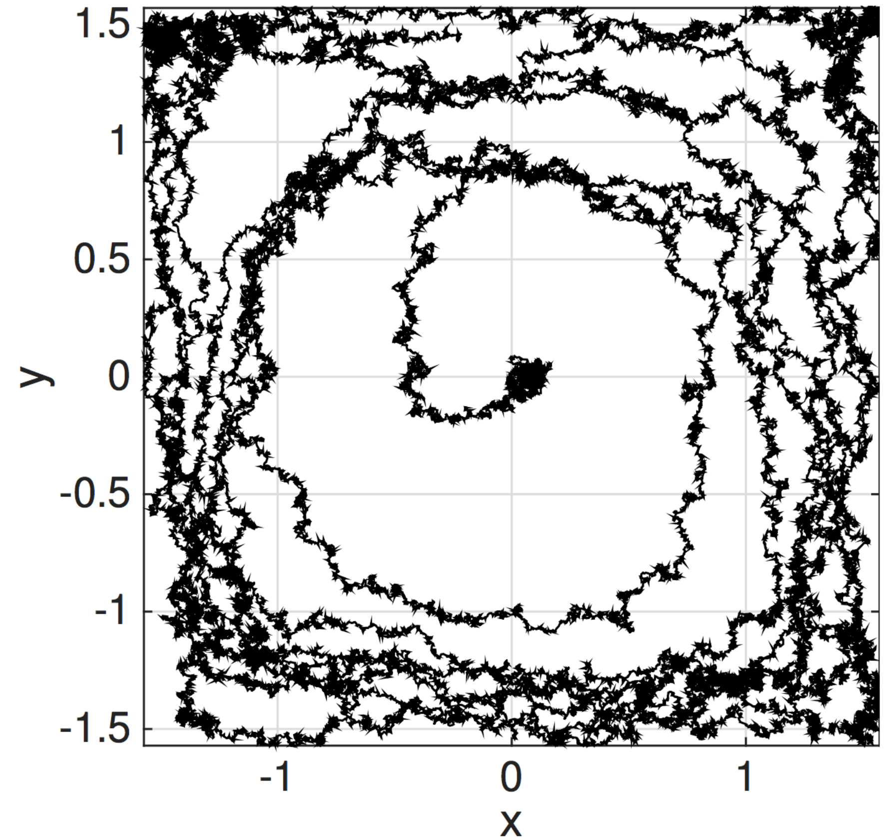
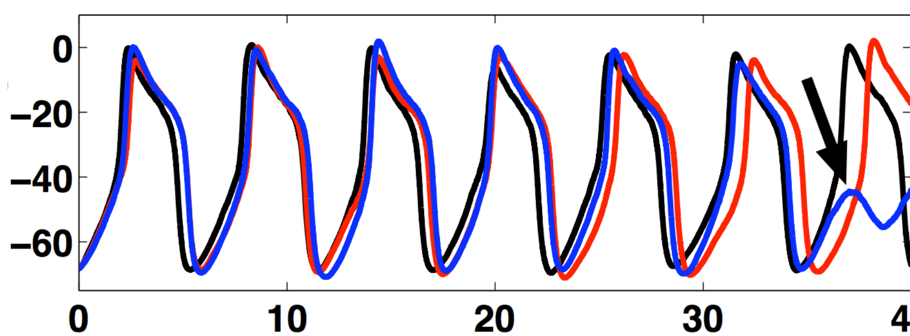


Noise-dependent heteroclinic oscillator.



$$\dot{y}_1 = \cos(y_1)\sin(y_2) + \alpha\sin(2y_1) + \sqrt{2D}\xi_1(t)$$

$$\dot{y}_2 = -\sin(y_1)\cos(y_2) + \alpha\sin(2y_2) + \sqrt{2D}\xi_2(t)$$

What is the “phase” of a stochastic oscillator?

PRL **110,** 204102 (2013) PHYSICAL REVIEW LETTERS week ending 17 MAY 2013

Phase Description of Stochastic Oscillations

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Department of Physics and Astronomy, Potsdam University, 14476 Potsdam, Germany
(Received 29 January 2013; published 13 May 2013)

PRL **113,** 254101 (2014) PHYSICAL REVIEW LETTERS week ending 19 DECEMBER 2014

Asymptotic Phase for Stochastic Oscillators

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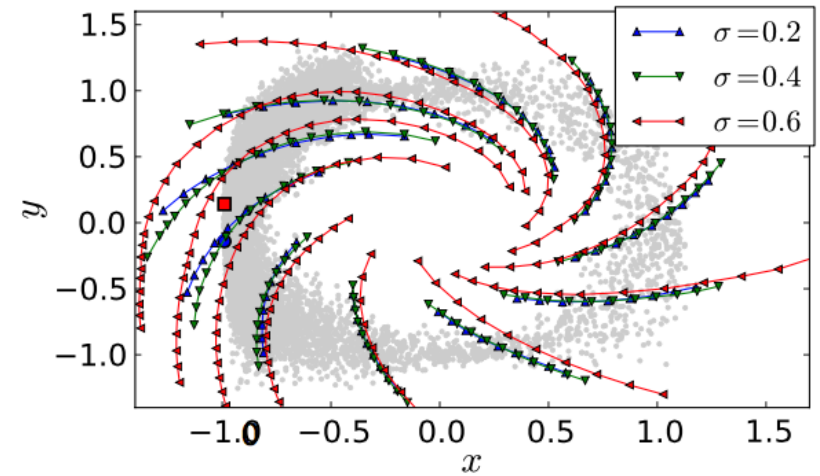
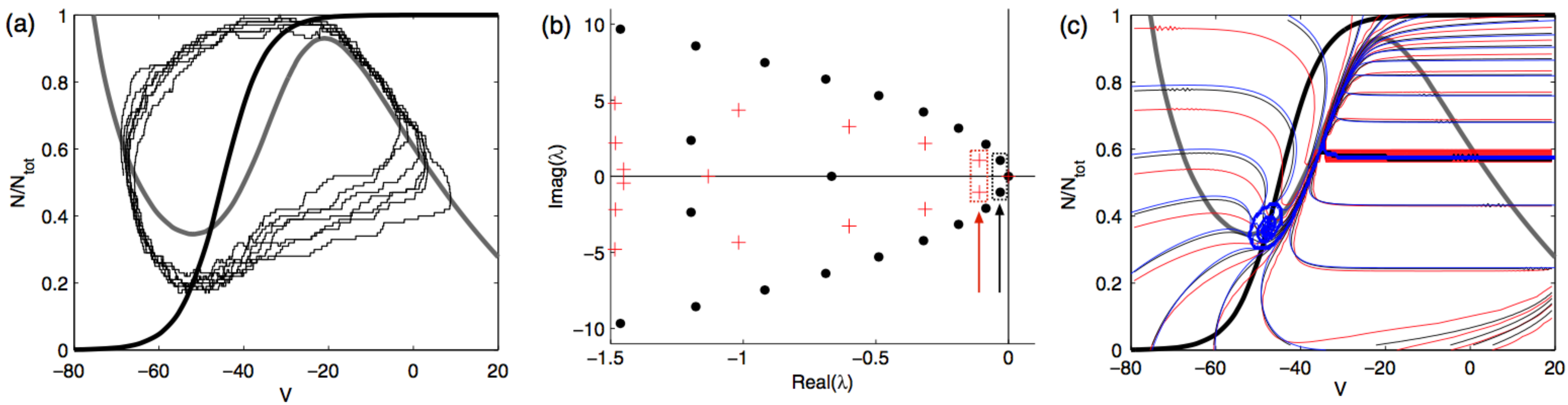


“Phase” based on mean first passage times
versus
“Phase” based on eigenfunctions of the generator



Open question: Can the right definition of “phase” clarify the analysis of phase resetting for stochastic oscillators?

Spectral Asymptotic Phase

SDE: $dX = A(X)\,dt + \mathcal{B}(X)\,dW$ (Itô interpretation)

Define $B = \mathcal{B}\mathcal{B}^\intercal$. For $t > s$, density is:

$$\rho(y,t\,|\,x,s) = \frac{1}{dy}\Pr\{X(t) \in [y, y+dy)\,|\,X(s) = x\}$$

$$\frac{\partial}{\partial t}\rho(y,t\,|\,x,s) = \mathcal{L}_y[\rho]$$ (forward operator)

$$= -\sum_i \frac{\partial}{\partial y_i}\left(A_i(y)\rho(y,t\,|\,x,s)\right)\frac{1}{2}\sum_i\sum_j \frac{\partial^2}{\partial y_i \partial y_j}\left(B_{ij}(y)\rho(y,t\,|\,x,s)\right)$$

$$-\frac{\partial}{\partial s}\rho(y,t\,|\,x,s) = \mathcal{L}_x^\dagger[\rho]$$ (backward operator)

$$= \sum_i A_i(x)\frac{\partial}{\partial x_i}\rho(y,t\,|\,x,s) + \frac{1}{2}\sum_i\sum_j B_{ij}(x)\frac{\partial^2}{\partial x_i \partial x_j}\rho(y,t\,|\,x,s)$$

Spectral Asymptotic Phase

$$\mathcal{L}[P_\lambda] = \lambda P_\lambda \text{ (forward eigenfunctions, discrete spectrum)}$$

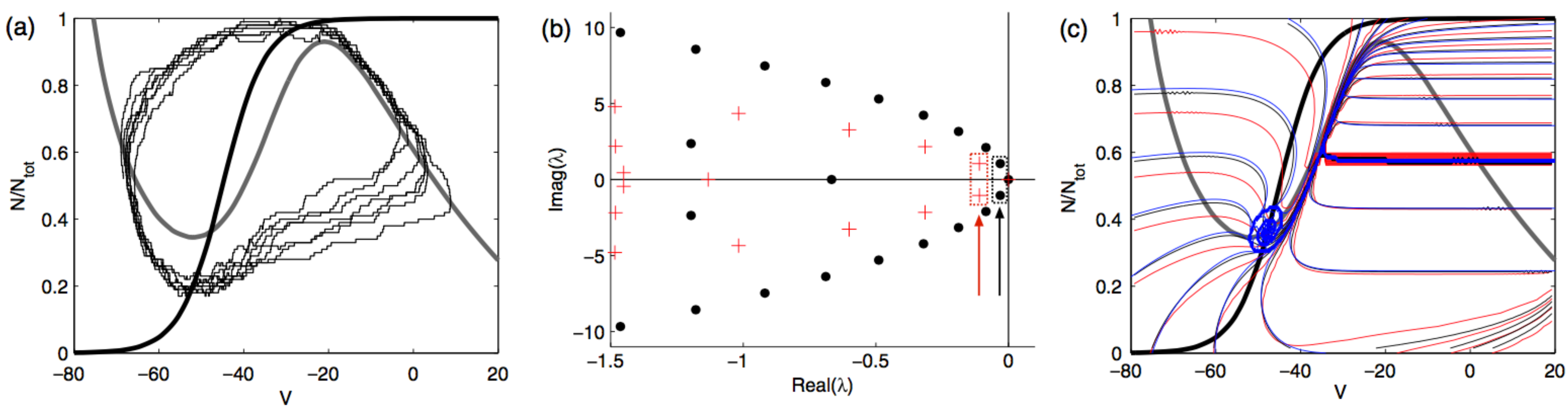
$$\mathcal{L}^\dagger[Q^*_\lambda] = \lambda Q^*_\lambda \text{ (backward eigenfunctions, discrete spectrum)}$$

$$\int Q^*_\lambda(x) P_{\lambda'}(x)\,dx = \delta(\lambda' - \lambda) \text{ (complete biorthogonal system)}$$

$$\lambda_1 = \mu + i\omega \text{ (slowest decaying eigenvalue is complex)}$$

$$P_{\lambda_1}(y) = v(y)e^{i\phi(y)} \text{ (forward magnitude, phase)}$$

$$Q_{\lambda_1}(x) = u(x)e^{-i\psi(x)} \text{ (backward magnitude, phase).}$$

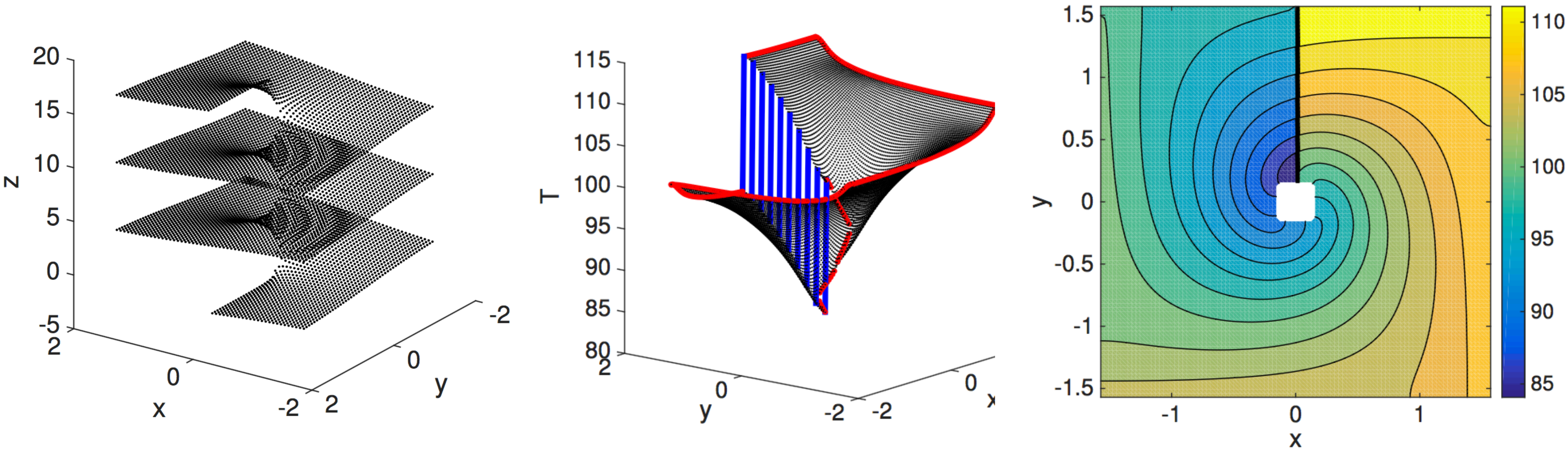


Average Isophase (Mean First Passage Times)

Mean first passage time $T(x)$ from x to an absorbing boundary $\mathcal{S}_{\text{abs}}$

$$\mathcal{L}_x^\dagger[T(x)] = -1, \quad T(x) = 0, x \in \mathcal{S}_{\text{abs}}, \quad n \cdot \nabla T(x) = 0, x \in \mathcal{S}_{\text{refl}}$$

To establish the correct boundary conditions, we unwrap the oscillator.



Alexander Cao, 2017 MS thesis (CWRU), joint with B. Lindner

Equivalently, we impose $T(x^+) = T(x^-) + \overline{T}$ along a radial section.

In general, average isophase differs from spectral phase. Which gives a better approach to synchrony, entrainment, and "phase response curves" remains an open question.

II. Stochastic Shielding

Identifying the most salient source of noise in a partially observed Markov model.

Joint work with Deena Schmidt (University of Nevada) & Roberto Galan (CWRU)

PRL **109,** 118101 (2012) PHYSICAL REVIEW LETTERS week ending 14 SEPTEMBER 2012

Stochastic-Shielding Approximation of Markov Chains and its Application to Efficiently Simulate Random Ion-Channel Gating

Nicolaus T. Schmandt and Roberto F. Galán*

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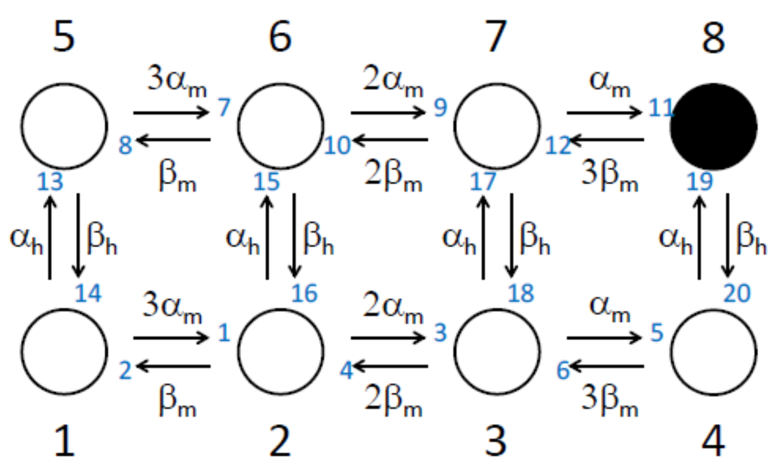
(Received 16 February 2012; published 11 September 2012)

Markov chains provide realistic models of numerous stochastic processes in nature. We demonstrate that in any Markov chain, the change in occupation number in state *A* is correlated to the change in occupation number in state *B* if and only if *A* and *B* are directly connected. This implies that if we are only interested in state *A*, fluctuations in *B* may be replaced with their mean if state *B* is not directly connected to *A*, which shortens computing time considerably. We show the accuracy and efficacy of our approximation theoretically and in simulations of stochastic ion-channel gating in neurons.



Hodgkin-Huxley sodium channel model:
8 vertices (only vertex 8 is "observable")
20 directed edges (independent Poisson processes)
SS: discard fluctuations in all but 4 Poissons
Fluctuations in transitions along edges 11, 12, 19, 20 should contribute most to the variance of vertex 8.

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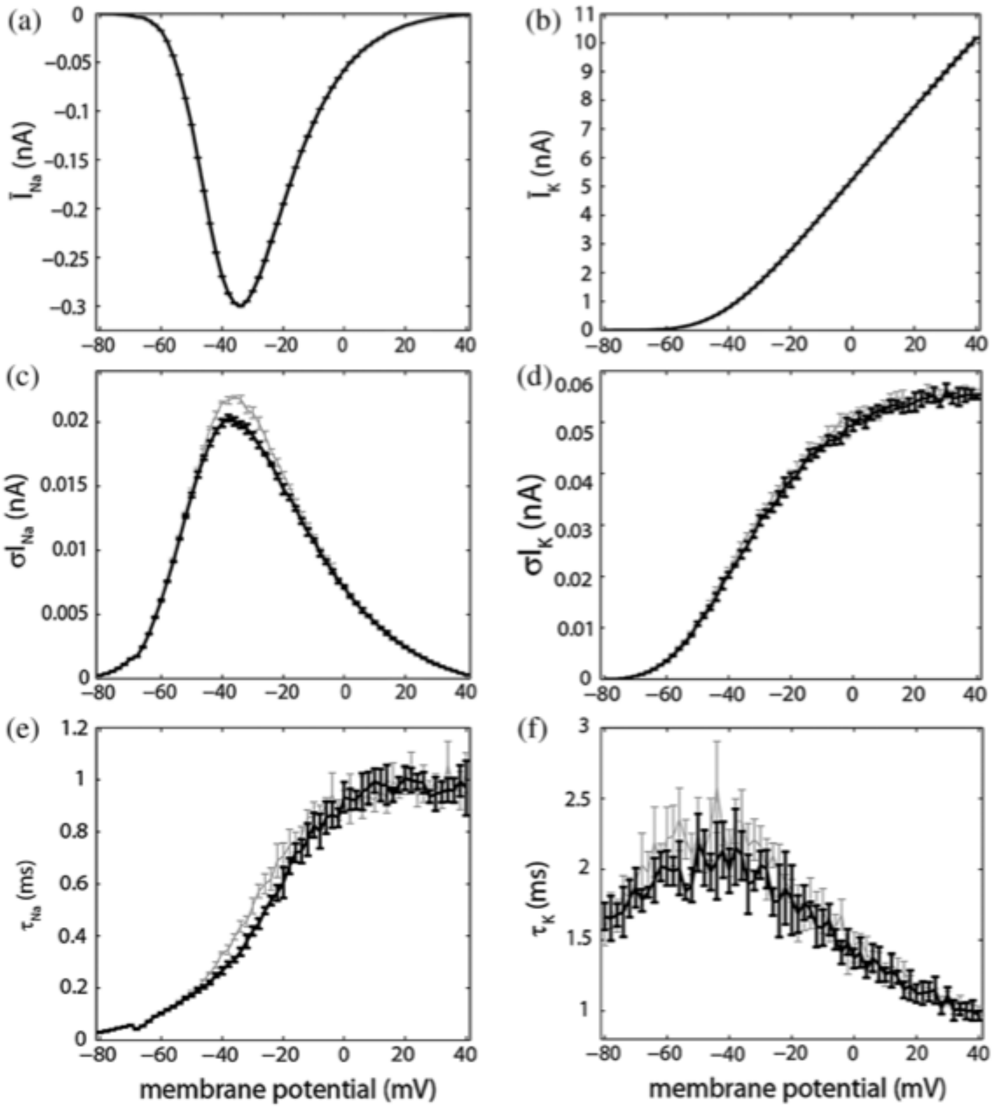
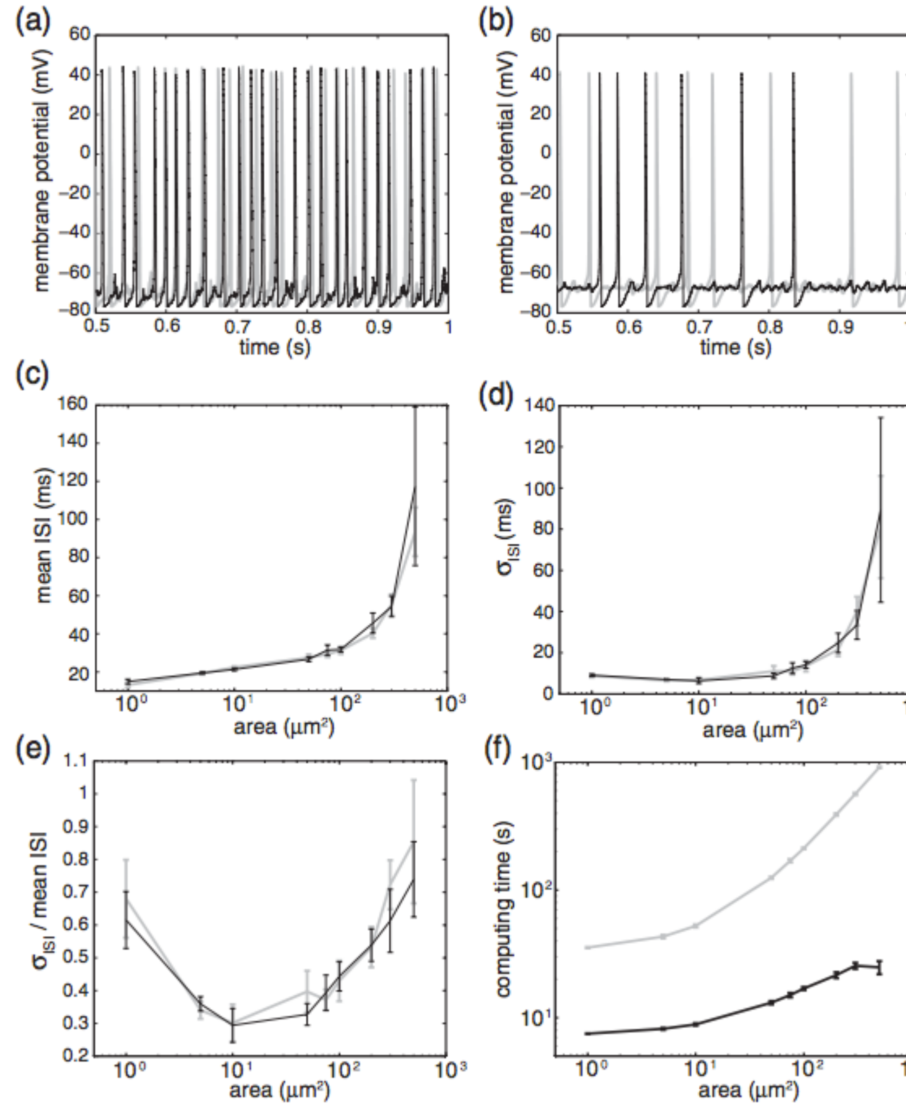




Stochastic Shielding: Gaussian SDE (3-state chain)

Graph Laplacian $L = \begin{pmatrix} -\alpha_{12} & \alpha_{21} & 0 \\ \alpha_{12} & -(\alpha_{21}+\alpha_{23}) & \alpha_{32} \\ 0 & \alpha_{23} & -\alpha_{32} \end{pmatrix}$

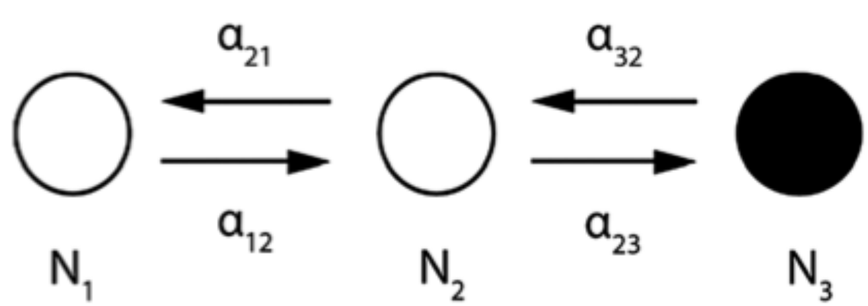
$$dX = LX\,dt + \begin{pmatrix} -\sqrt{X_1\alpha_{12}} & \sqrt{X_2\alpha_{21}} & 0 & 0 \\ \sqrt{X_1\alpha_{12}} & -\sqrt{X_2\alpha_{21}} & -\sqrt{X_2\alpha_{23}} & \sqrt{X_3\alpha_{32}} \\ 0 & 0 & \sqrt{X_2\alpha_{23}} & -\sqrt{X_3\alpha_{32}} \end{pmatrix} dW$$

Stochastic shielding approximation for observable $M = [0,0,1]^\intercal$

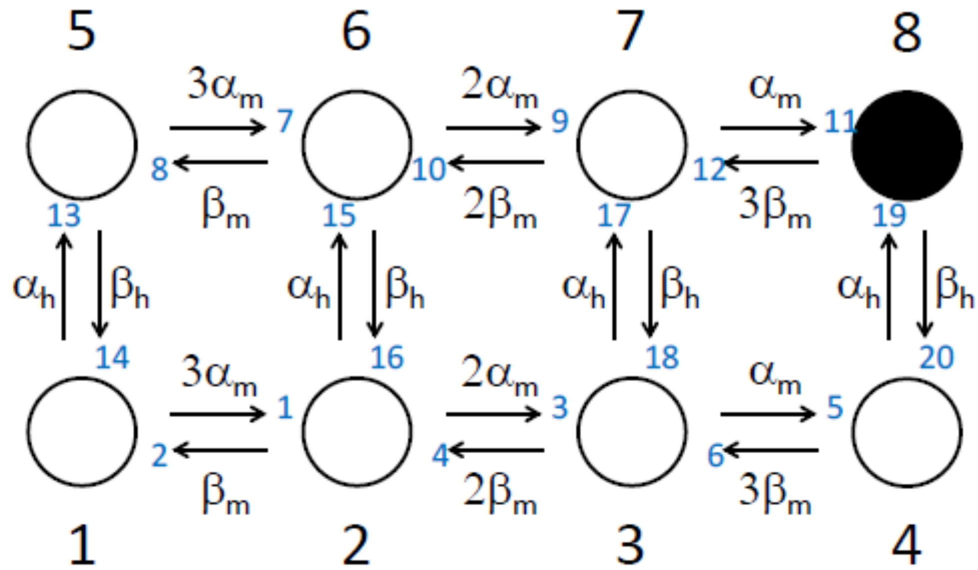
$$d\tilde{X} = L\tilde{X}\,dt + \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & -\sqrt{\tilde{X}_2\alpha_{23}} & \sqrt{\tilde{X}_3\alpha_{32}} \\ 0 & 0 & \sqrt{\tilde{X}_2\alpha_{23}} & -\sqrt{\tilde{X}_3\alpha_{32}} \end{pmatrix} dW$$

Error $R_{12} = J_{12} \sum_{\lambda_i \neq 0} \sum_{\lambda_j \neq 0} \left(\frac{-1}{\lambda_i + \lambda_j} \right) (M^\intercal v_i)(w_i^\intercal \zeta_{12})(\zeta_{12}^\intercal w_j)(v_j^\intercal M)$

Stationary Variance $E\left[(M^\intercal X)^2\right] = R_{12} + R_{23}$



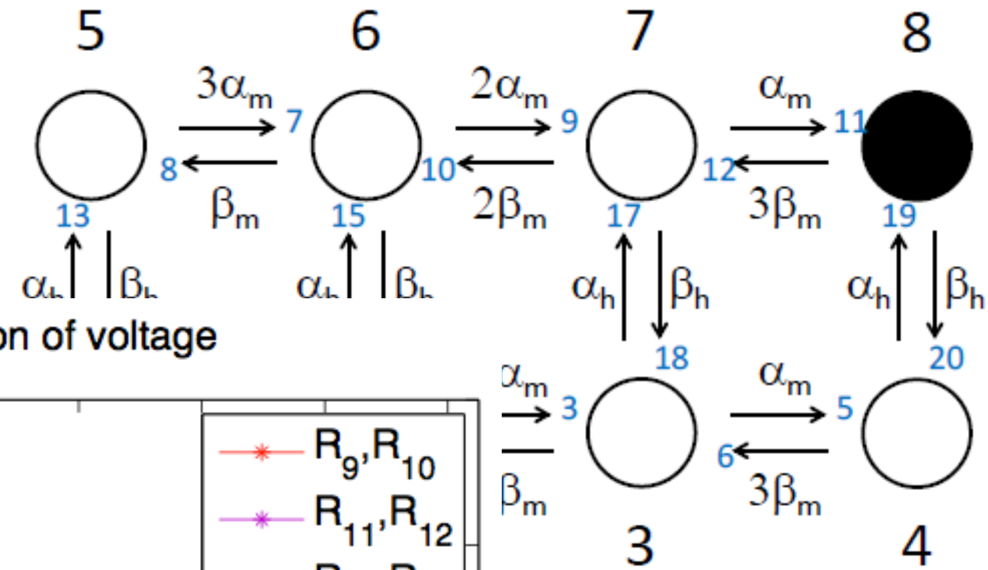
Hodgkin-Huxley Sodium Channel:

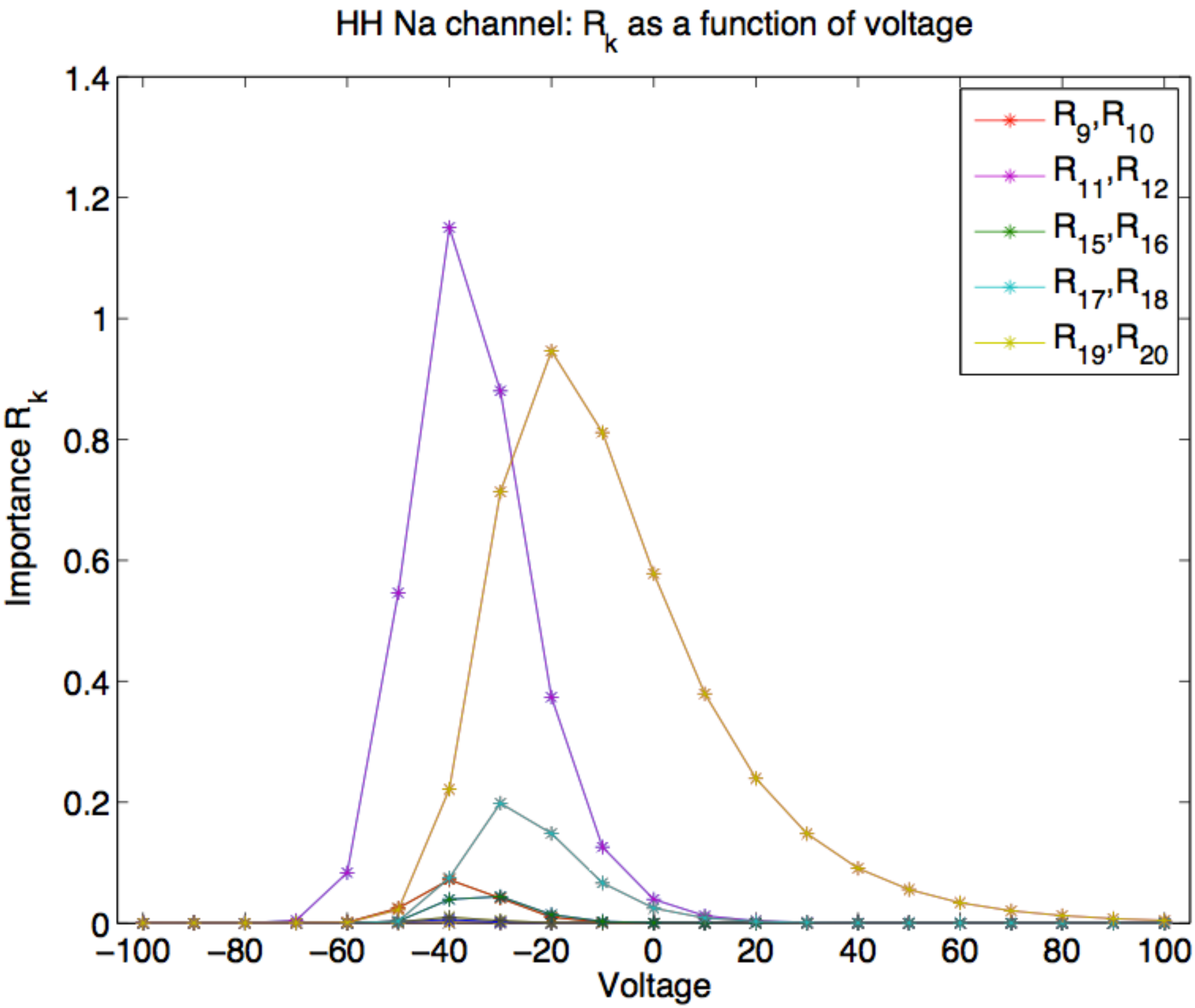


$$L = \begin{pmatrix} -D_{11}(V) & \beta_m(V) & 0 & 0 & \beta_h(V) & 0 & 0 & 0 \\ 3\alpha_m(V) & -D_{22}(V) & 2\beta_m(V) & 0 & 0 & \beta_h(V) & 0 & 0 \\ 0 & 2\alpha_m(V) & -D_{33}(V) & 3\beta_m(V) & 0 & 0 & \beta_h(V) & 0 \\ 0 & 0 & \alpha_m(V) & -D_{44}(V) & 0 & 0 & 0 & \beta_h(V) \\ \alpha_h(V) & 0 & 0 & 0 & -D_{55}(V) & \beta_m(V) & 0 & 0 \\ 0 & \alpha_h(V) & 0 & 0 & 3\alpha_m(V) & -D_{66}(V) & 2\beta_m(V) & 0 \\ 0 & 0 & \alpha_h(V) & 0 & 0 & 2\alpha_m(V) & -D_{77}(V) & 3\beta_m(V) \\ 0 & 0 & 0 & \alpha_h(V) & 0 & 0 & \alpha_m(V) & -D_{88}(V) \end{pmatrix}$$

$$B = \left(\sqrt{r_1(V)\bar{N}_{i(1)}(V)}\zeta_1, \ldots, \sqrt{r_k(V)\bar{N}_{i(k)}(V)}\zeta_k, \ldots, \sqrt{r_m(V)\bar{N}_{i(m)}(V)}\zeta_m \right)$$

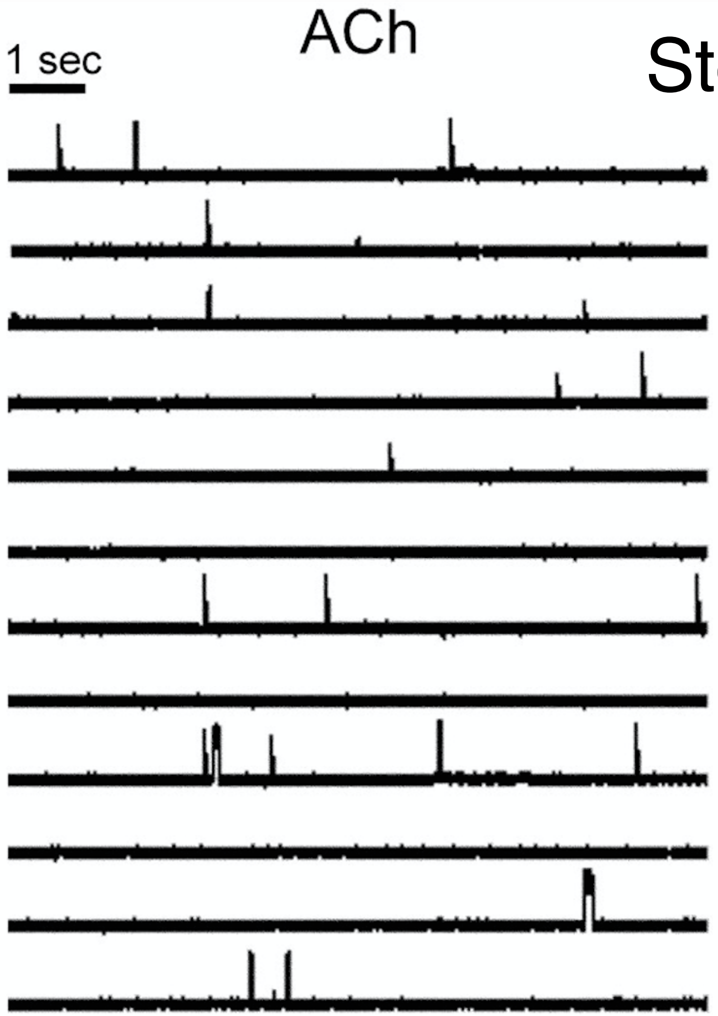
Hodgkin-Huxley Sodium Channel:

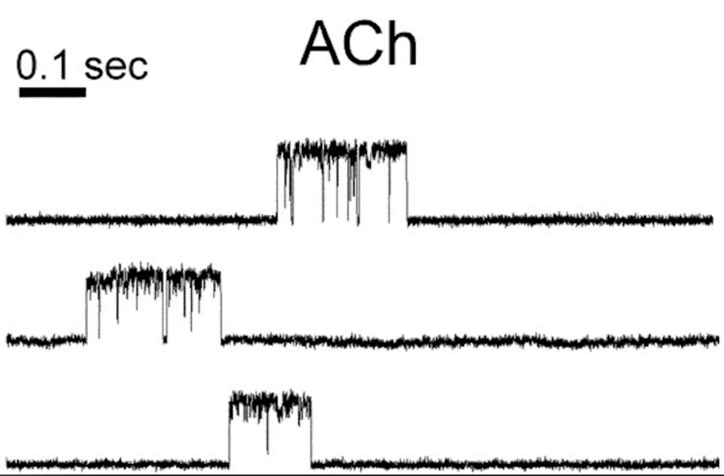


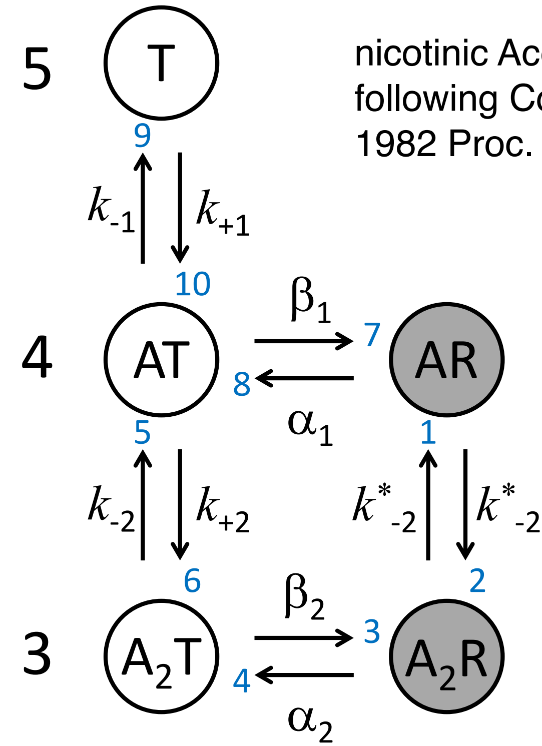


D. Schmidt & P. Thomas, J. Math. Neurosci 2014.

Stochastic Shielding for Bursty Systems



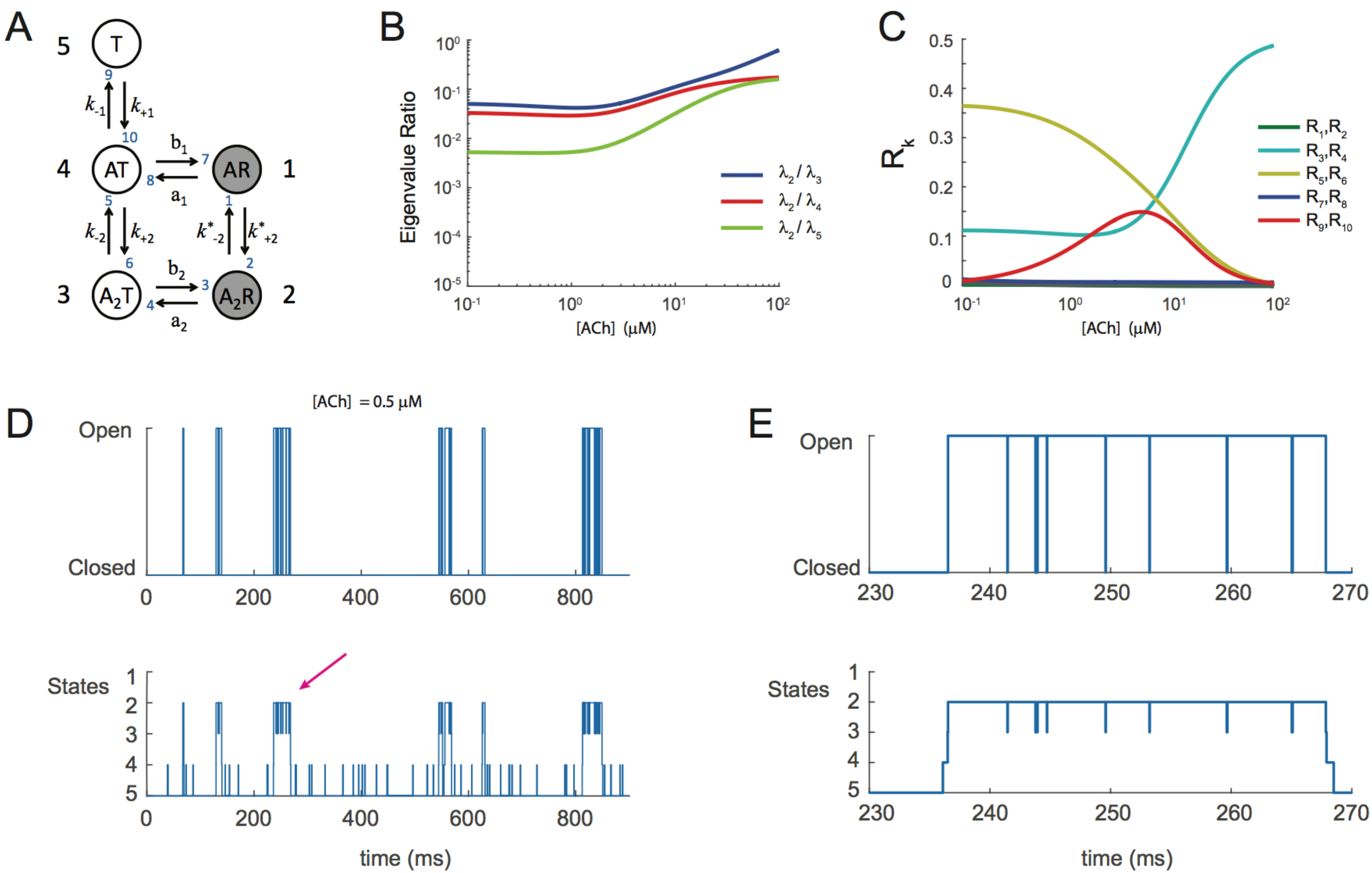




nicotinic Acetylcholine receptor, following Colquhoun & Hawkes 1982 Proc. Roy. Soc.

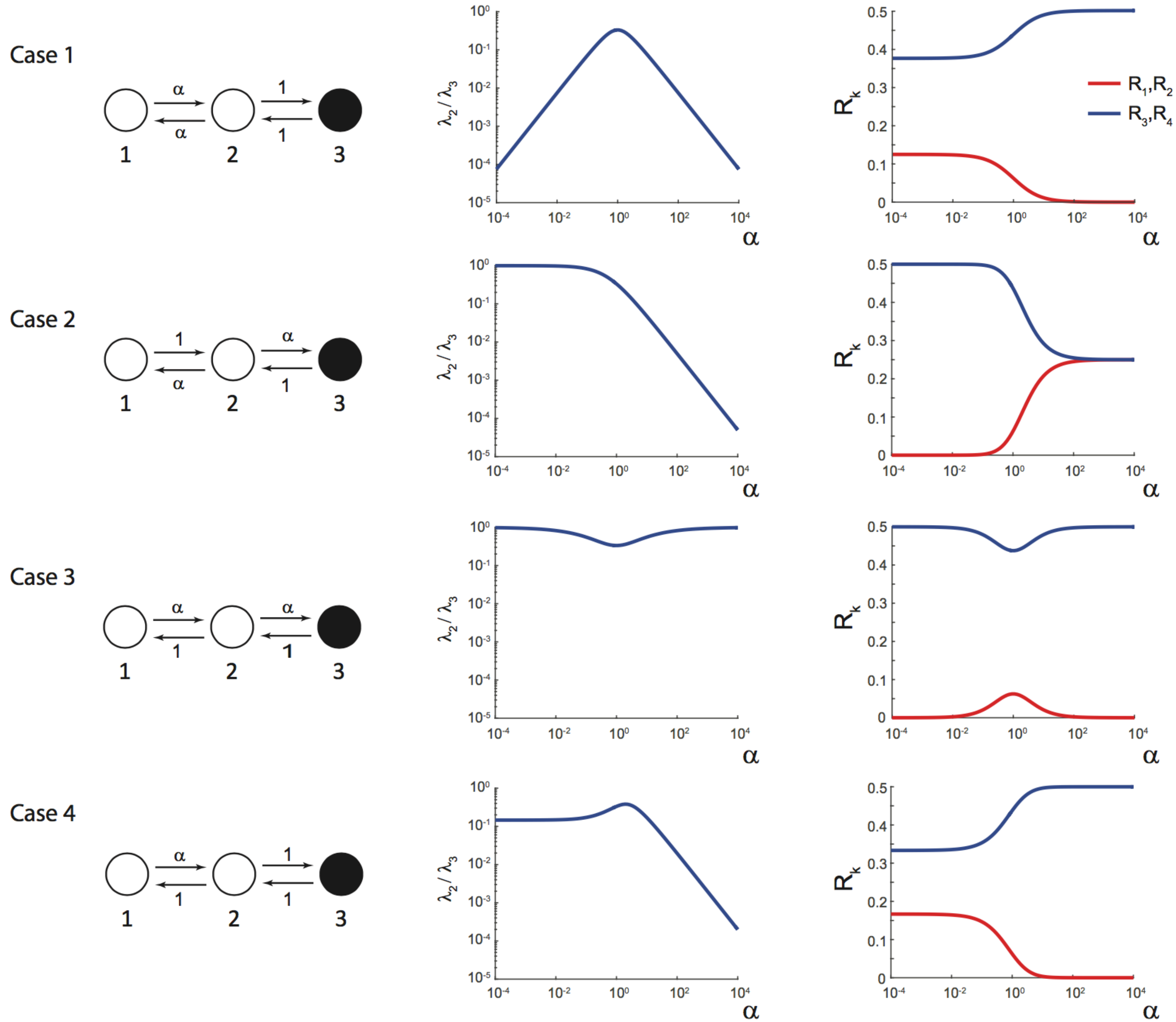
Hsiao, Mihalak, Magleby, Luetje, 2008 J. Neurophys.
Low agonist concentration (0.1 micromol ACh).

Acetylcholine shows a reversal of edge importance



When is edge importance reversed?

* Can introducing fast and slow timescales reverse edge-importance?
* We introduced two rates (1 and alpha) in all 3-state chain motifs.
* Time scale separation: ratio of nonzero eigenvalues is large.



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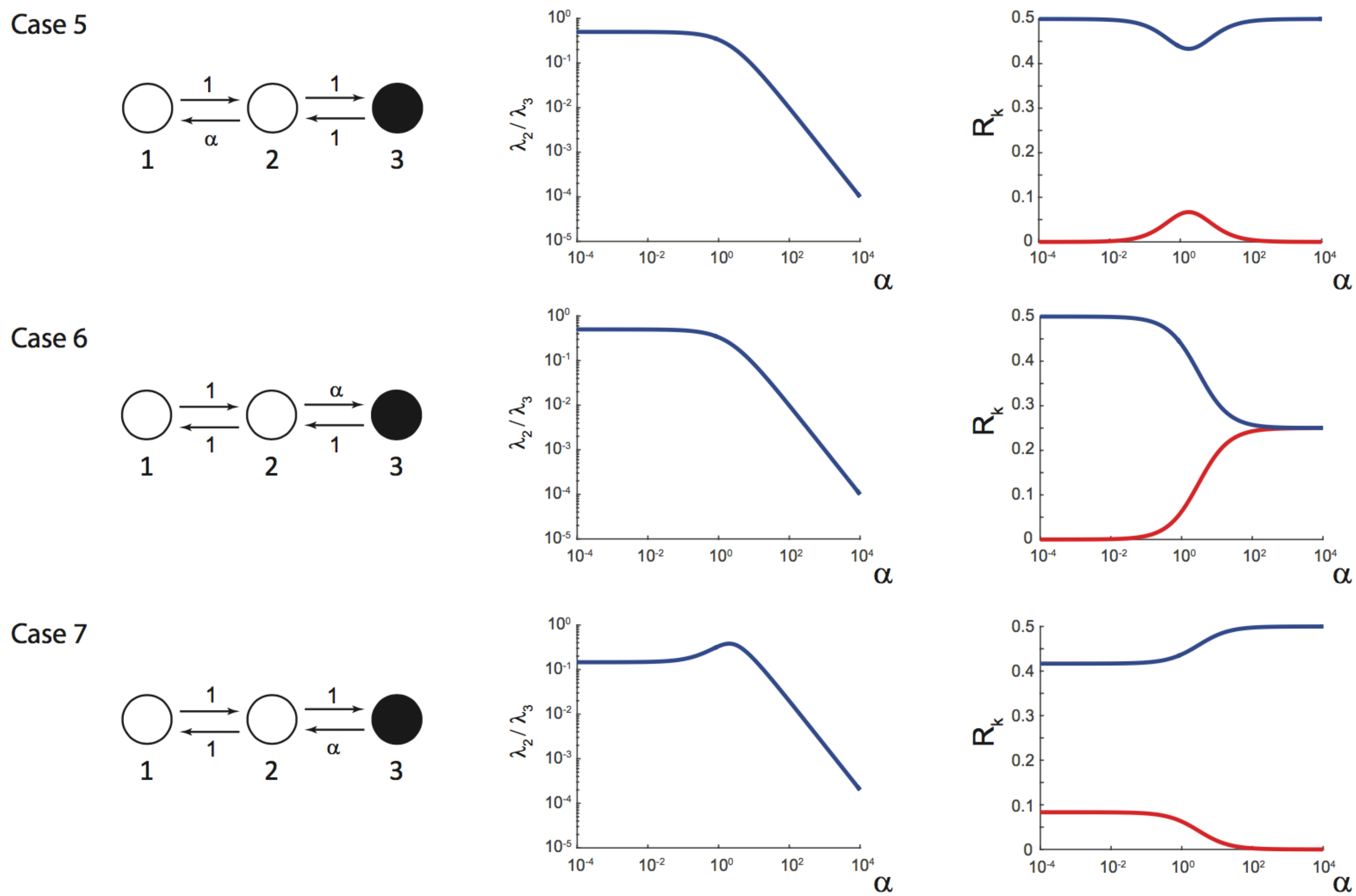


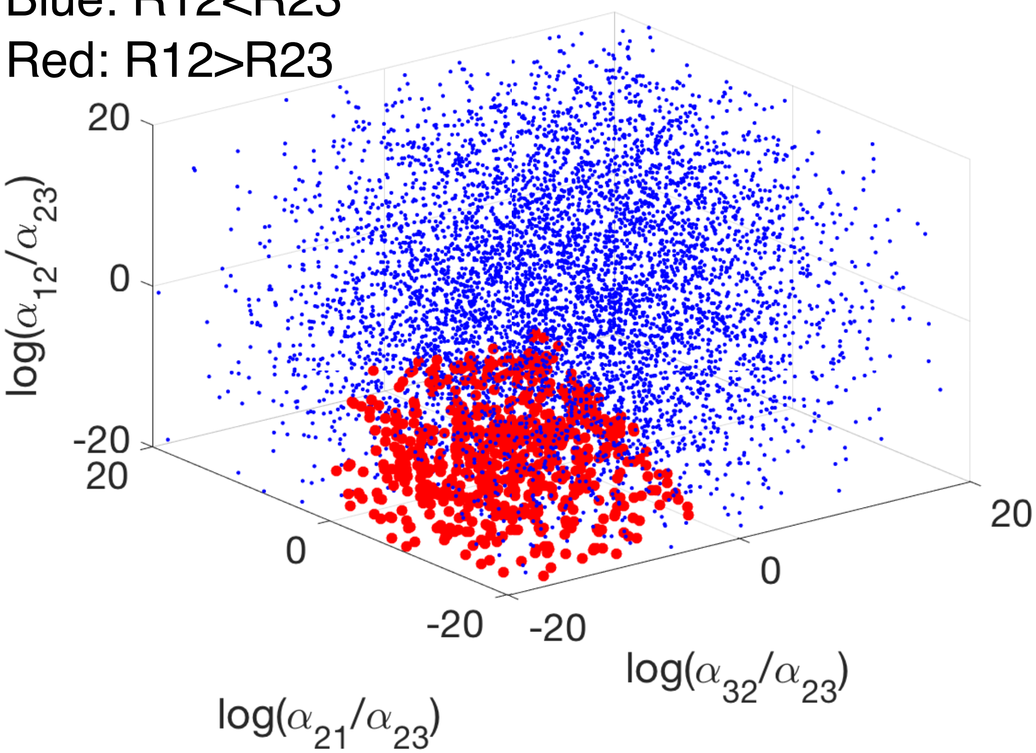
Edge-importance reversal never occurs in any single-parameter 3-state chain cases.

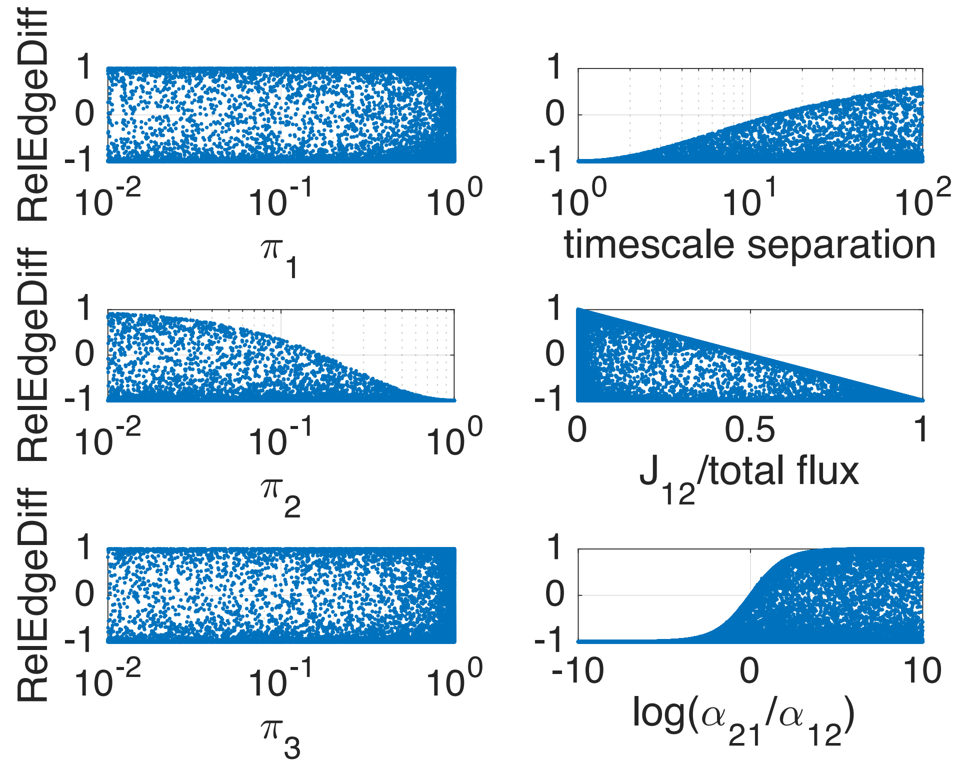
Edge importance is reversed ($R_{1\rightleftharpoons 2} > R_{2\rightleftharpoons 3}$) when we introduce *three* timescales:

- $\alpha_{23} \gg \max(\alpha_{32}, \alpha_{21})$, and
- $\alpha_{12} \ll \alpha_{21}$.

Relative importance of hidden edges $\Delta R = \dfrac{R_{12} - R_{23}}{R_{12} + R_{23}}$

Blue: R12<R23
Red: R12>R23





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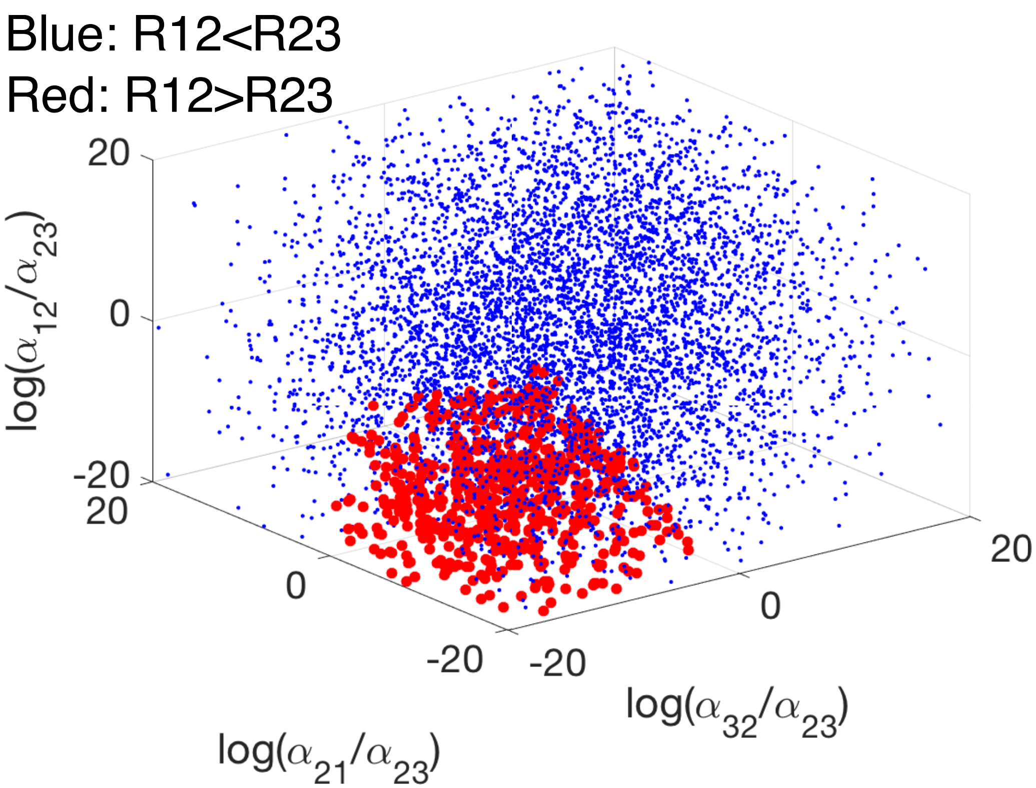
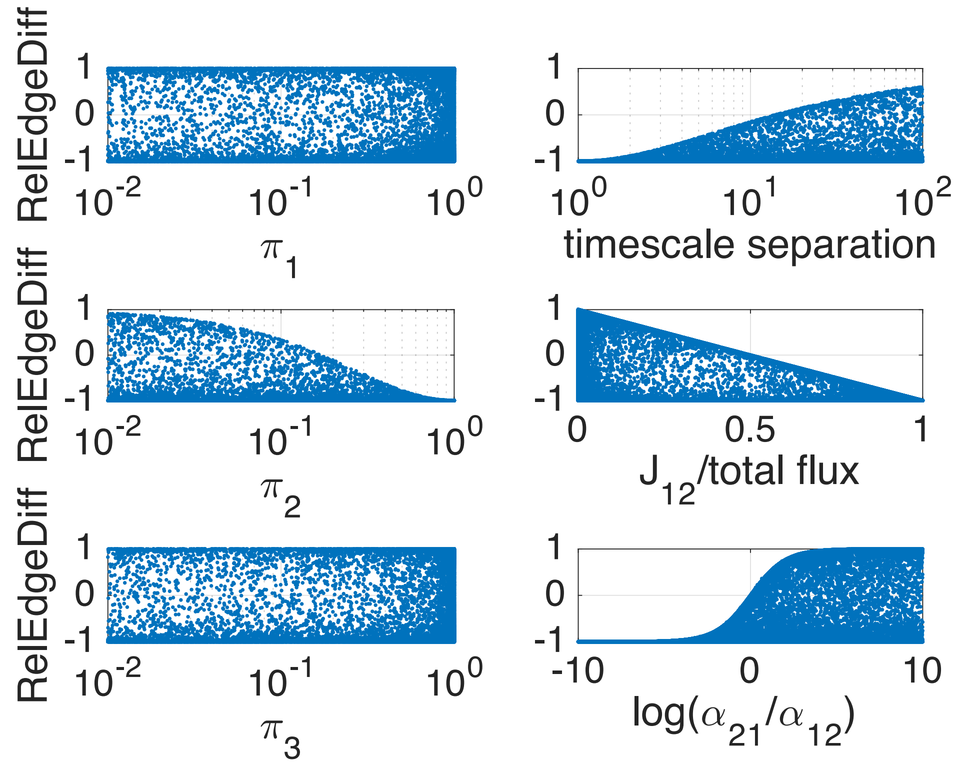


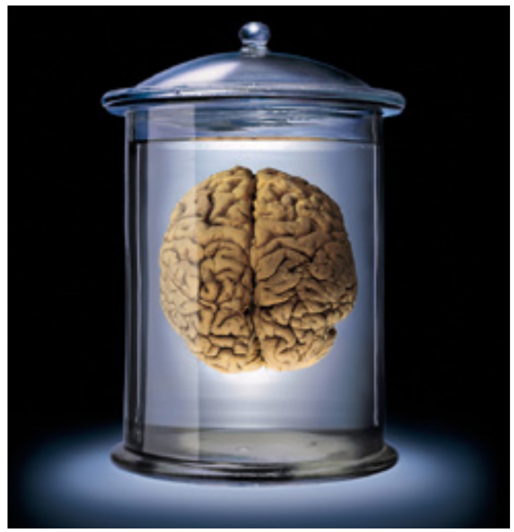


Exact Result:

$$\frac{R_{12}}{R_{12} + R_{23}} = \left(\frac{\alpha_{21}}{\alpha_{12} + \alpha_{21}}\right)\left(\frac{\alpha_{23}}{\alpha_{12} + \alpha_{21} + \alpha_{23} + \alpha_{32}}\right)$$

III: On the danger of studying a disembodied brain

Both experimentally and mathematically, it is easier to study the brain when the body has been removed.



But things can turn out differently than one expects. For example…

III: On the danger of studying a disembodied brain

Image from the movie *Fiend Without a Face* (Arthur Crabtree, 1958)

III: On the danger of studying a disembodied brain

… for example, the mechanism underlying motor rhythms in an isolated central pattern generator can be distinct from the mechanism of rhythmicity in the intact brain-body system.

III: On the danger of studying a disembodied brain

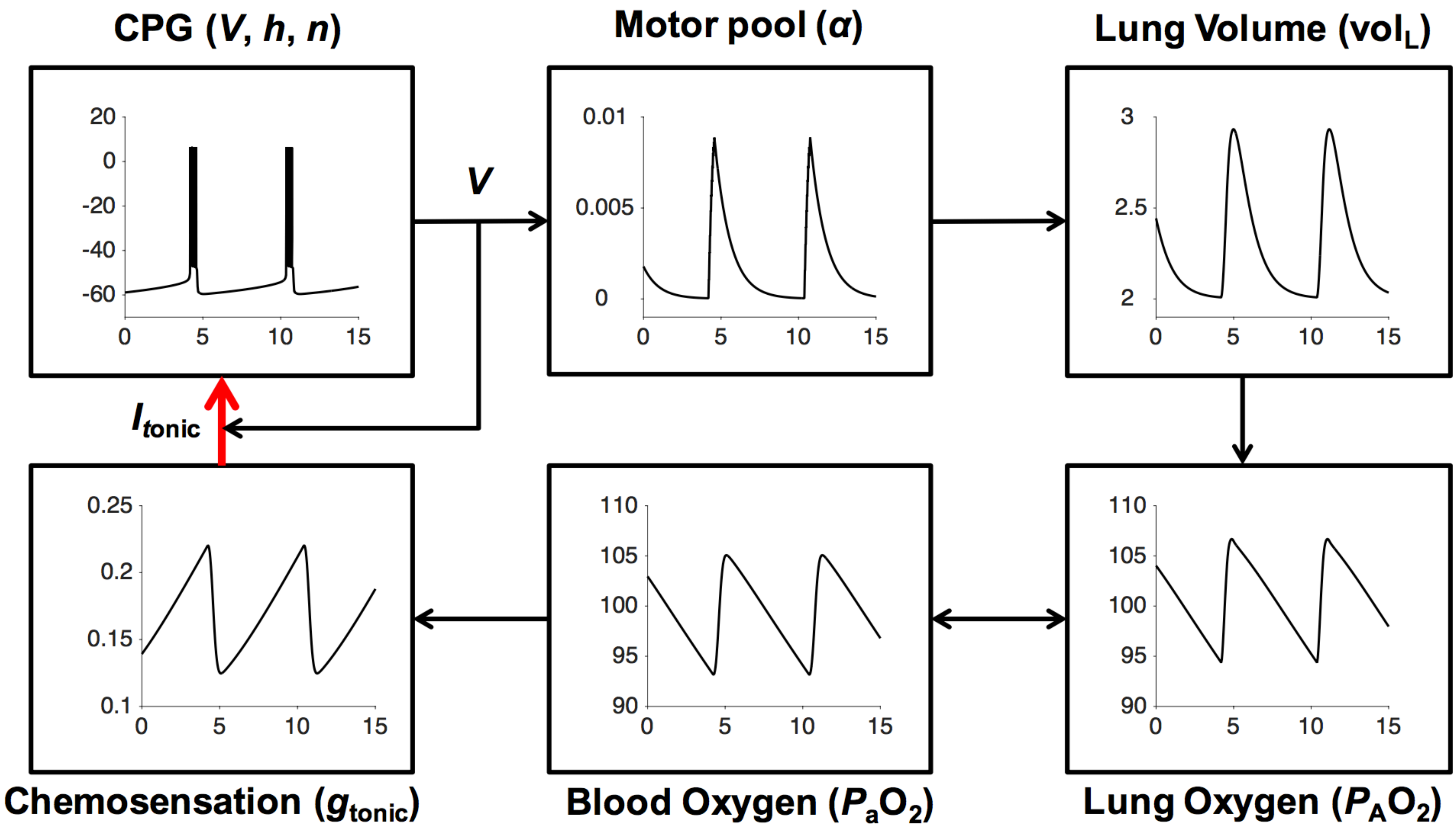
… for example, the mechanism underlying motor rhythms in an isolated central pattern generator can be distinct from the mechanism of rhythmicity in the intact brain-body system.

Eupnea, Tachypnea, and Autoresuscitation in an Open-Loop versus Closed-Loop Respiratory Control Model

* Closed-loop respiratory control model incorporating a central pattern generator (CPG), the Butera-Rinzel-Smith (BRS) model, together with lung mechanics, oxygen handling, and chemosensory components.
* Although both closed-loop and open-loop (isolated) CPG systems support eupnea-like (normal breathing) activity, they do so via distinct mechanisms.

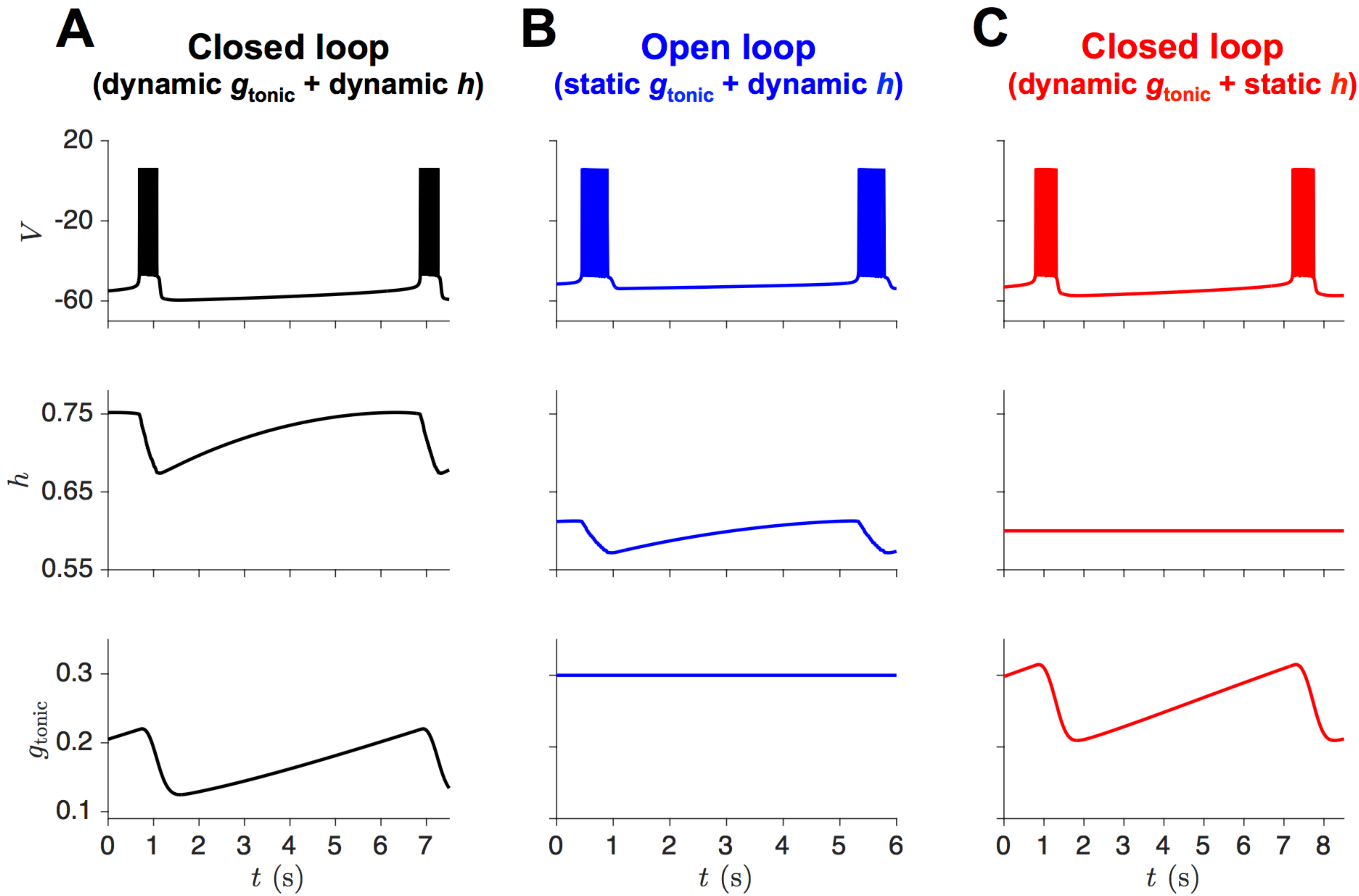
Joint work with Casey Diekman (NJIT) & Chris Wilson (Loma Linda University)

Closed-loop Respiratory Control Model



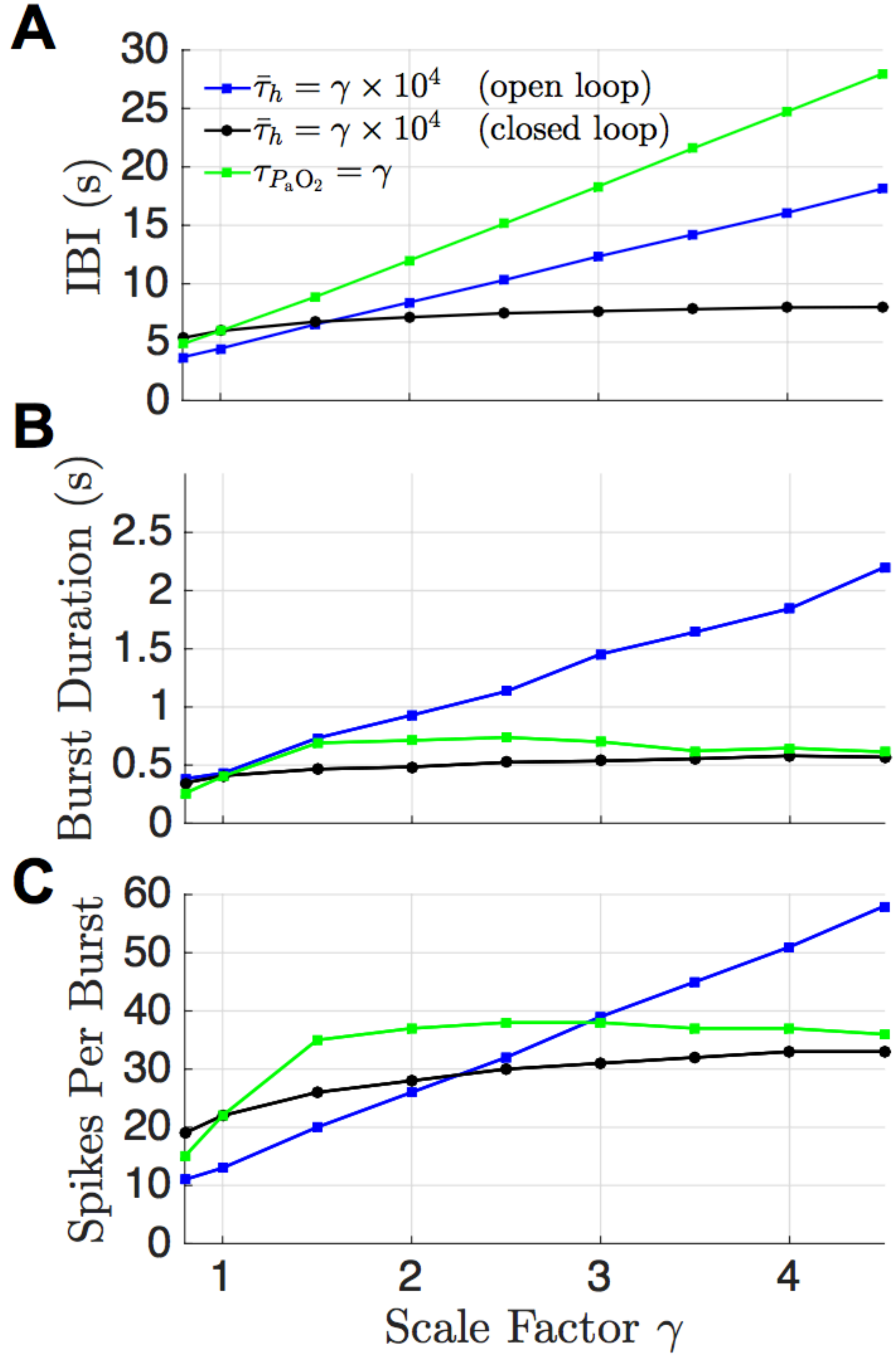
Model components: Central pattern generator (CPG), the Butera-Rinzel-Smith (BRS) model; lung mechanics, gas exchange, oxygen handling, and chemosensory feedback.

Normal (eupneic) breathing occurs in open and closed loop

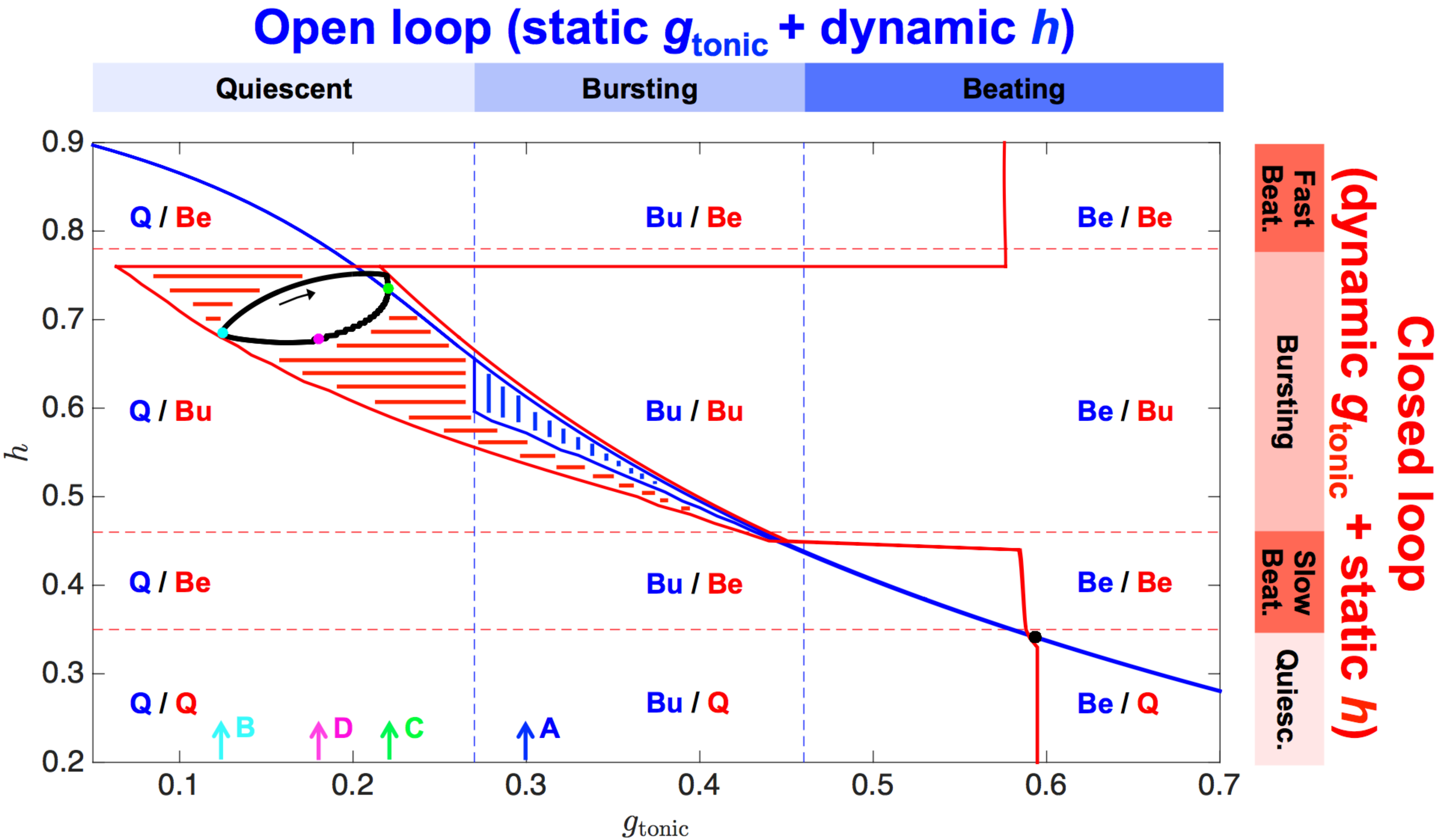


In open loop, persistent-sodium inactivation variable h determines burst timing. In closed loop, bursts continue with h frozen.

Changing the time constant for *h* changes the timing of bursts in open loop (blue traces), but not in closed loop (black traces). Recording and replaying a decelerated sensory feedback signal also changes the interburst interval (green traces), but not within-burst features.



Bursting regimes in closed versus open loop



Eupneic bursting in the full closed-loop model (black trace) remains in a region where the open loop would be quiescent (blue traces), and the closed loop model with *h* fixed would support bursting.

Conclusion: the isolated and intact systems “breathe” via different mechanisms.

Noise in the Brain:
Statistical and Dynamical Perspectives

Conclusions

0. Statistics and dynamical systems offer complementary tools, integrated in "data assimilation" broadly defined.
I. Stochastic oscillators admit more than one generalization of "phase". Which is best for *phase resetting* is unknown.
II. Stochastic shielding provides a powerful framework for accurately approximating Markov processes on graphs.
III. Central circuits studied in isolation can lead to erroneous conclusions about mechanisms in the intact organism.