Techniques in Neurophysiology

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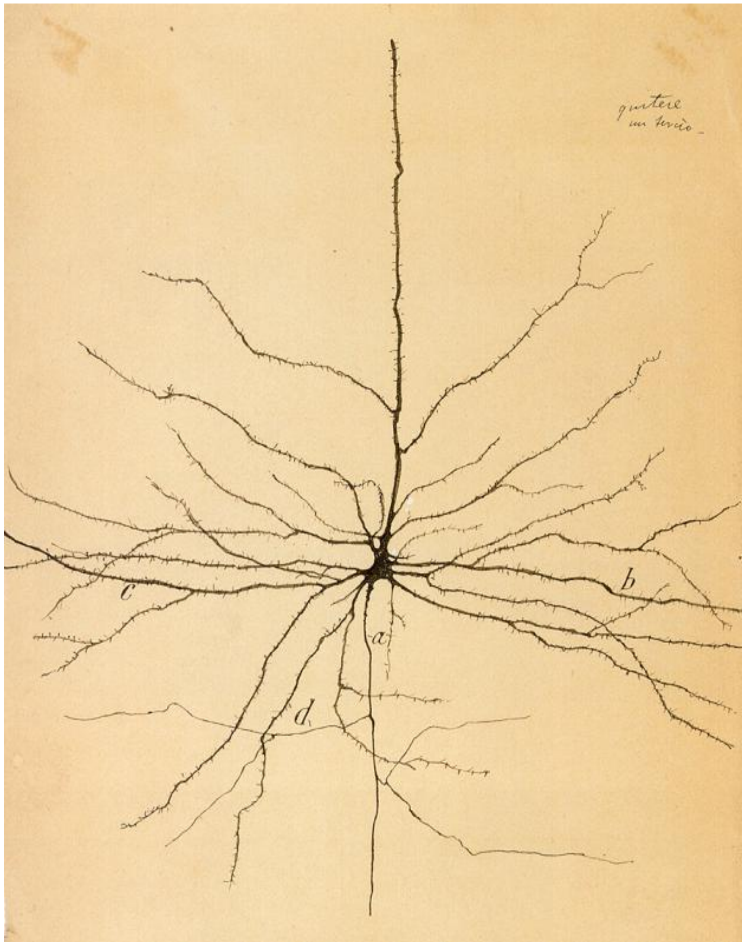
Find a hard problem that interests you

10^{11} neurons
10^{12} glial cells
> 10^{15} connections

http://science.nationalgeographic.com

Basics of neuronal function



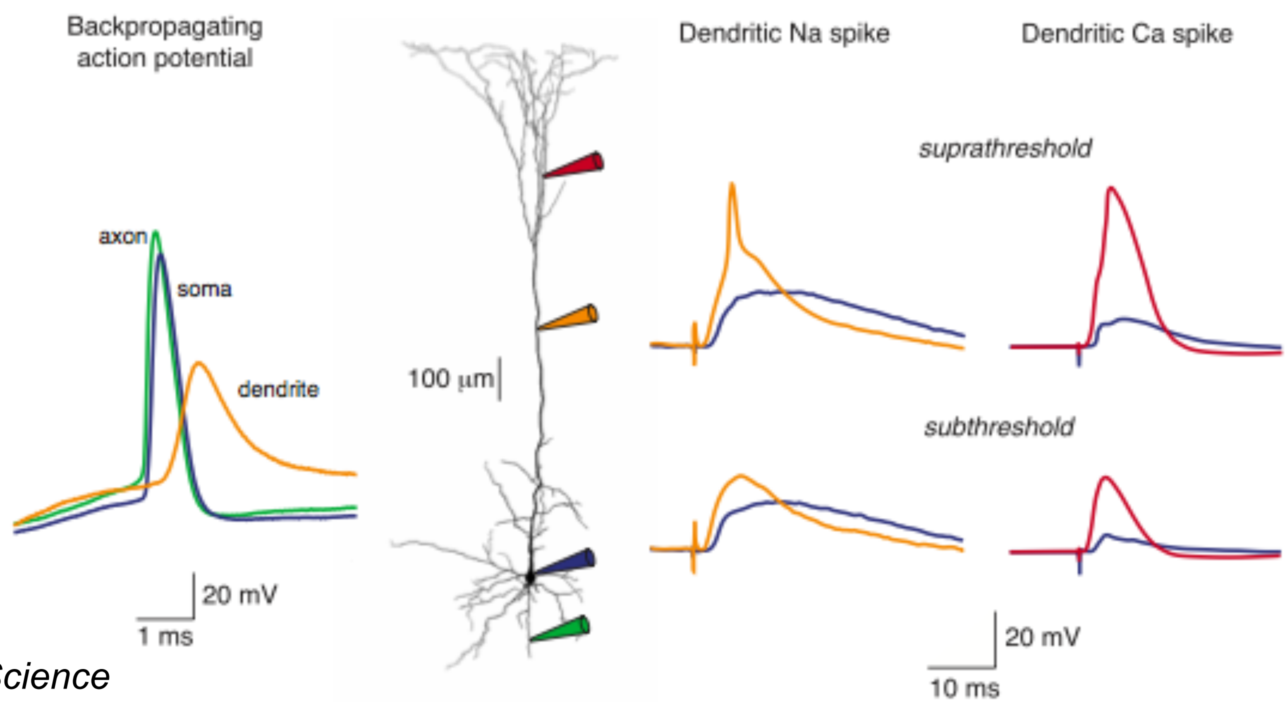
Cajal, 1899

- Cell membrane is lipid-based
- Electrochemical gradients of Na^+, K^+, Ca^{2+}, etc., are maintained at great expense
- Ions pass through discrete "channels" to alter membrane potential V_{in} - V_{out}
- "Dendrites" collect as many as 10^4 inputs
- Neuronal output (soma and axon): digital pulse of amplitude 100 mV, duration 1-5 ms
- To "learn" is to:
  - Alter synaptic strength
  - Alter postsynaptic integration
- Daemons tune the system 24/7

- Dead neurons don't regenerate well
- The brain doesn't like human-made materials
- Our measurement tools are primitive
- Non-stationaries and noise are ubiquitous

State of the art(?)

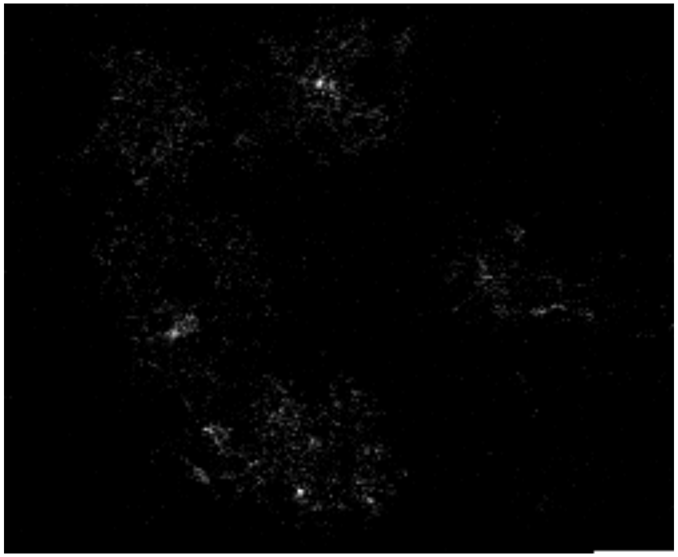
- Measuring membrane potential in one or two spots with good temporal bandwidth
- *Spatial distribution of channel densities is usually unknowable*



Häusser et al. (2000) *Science*

State of the art(?)

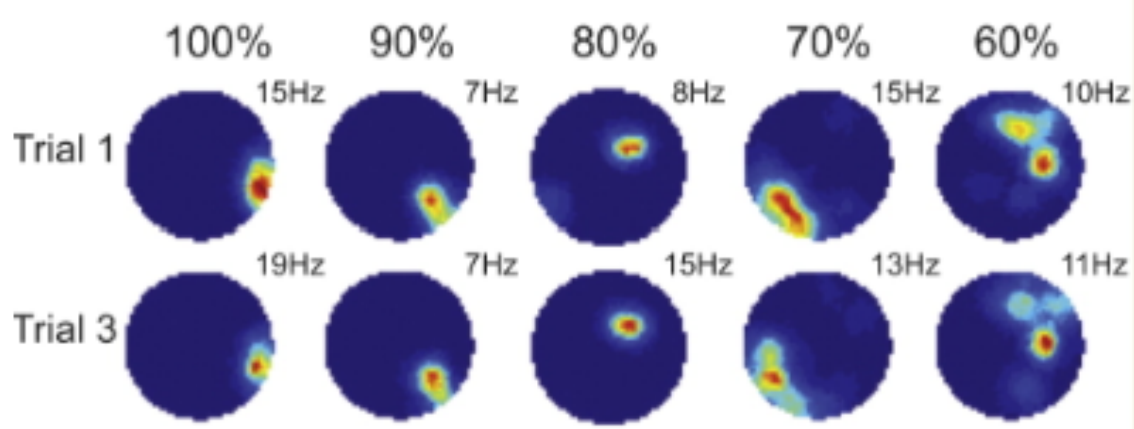
- Measuring qualitative changes in Ca^{2+} with good spatial resolution, but poor and distorted temporal resolution
- *We only have the foggiest idea about intracellular messages; the measurements we have are questionable*



Data collected by Roy Smeal, in collaboration with Mario Capecchi, Petr Tvrdik, and Karen WIlcox

State of the art(?)

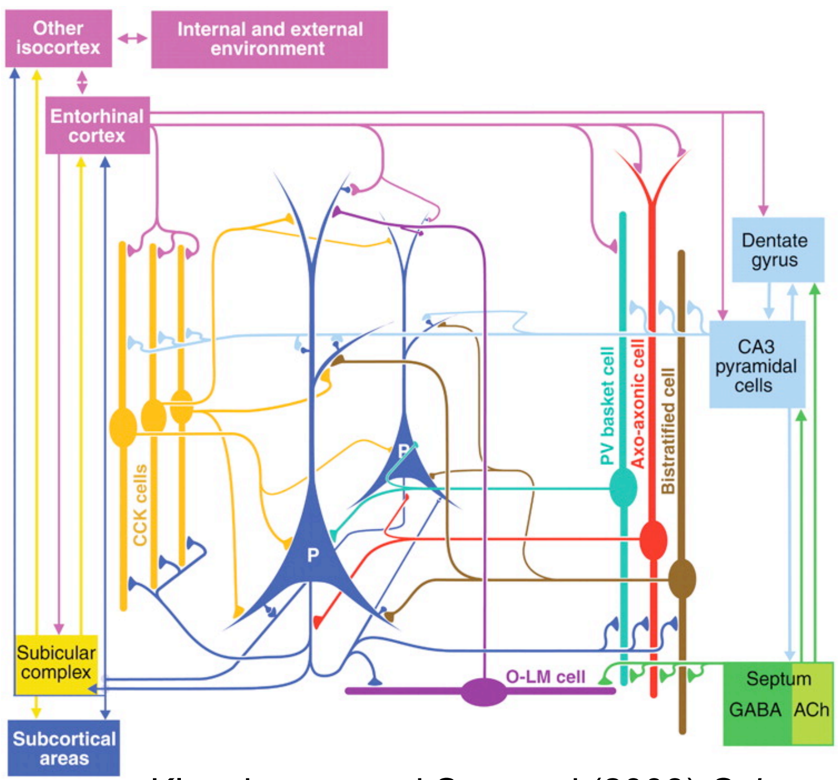
- Measuring spike trains in 1-100 cells simultaneously, and making educated guesses of the cell types
- *Very difficult to parse cell types; measurements biased toward large cells located in dense populations*

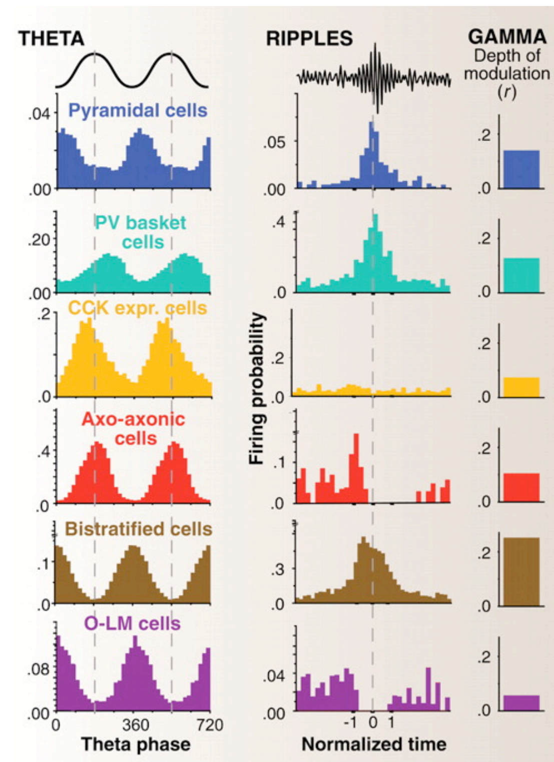


Henriksen et al. (2010) *Neuron*

State of the art(?)

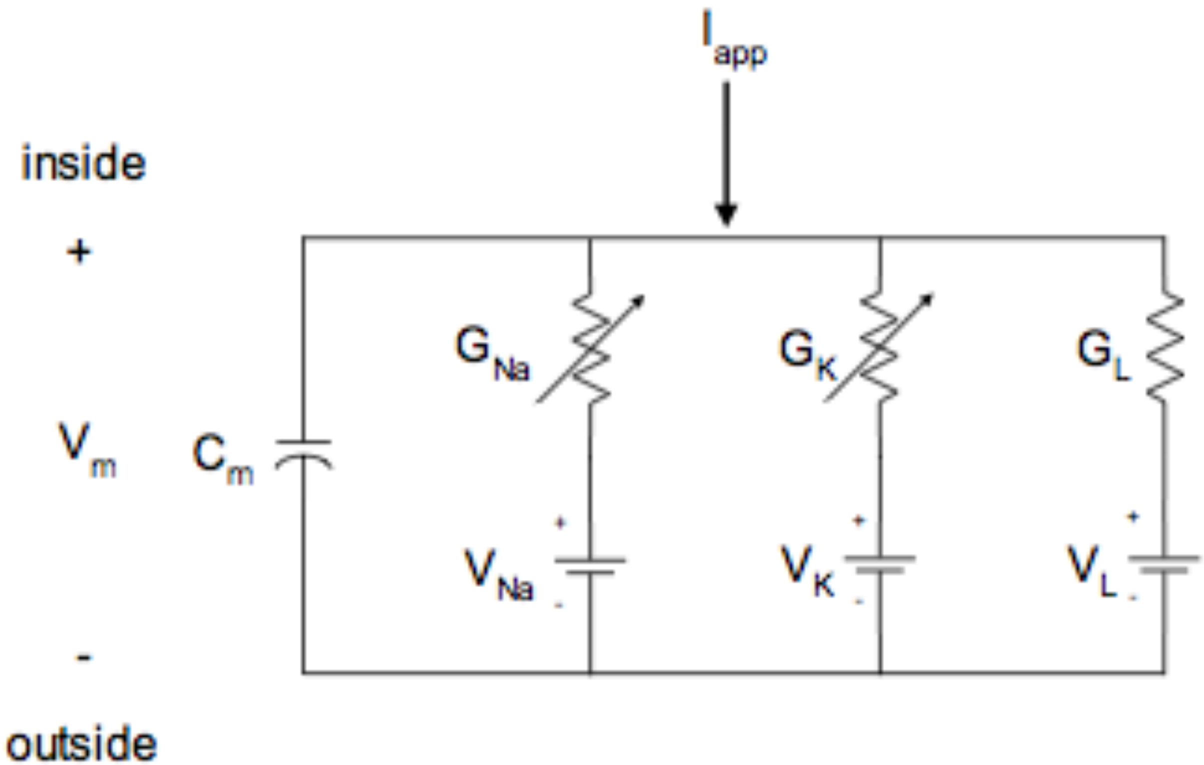
- Intracellular or juxtacellular recording and staining of cells in anesthetized animals
- *Heroic; yields low; anesthesia usually required*





Klausberger and Somogyi (2008) *Science*

The Hodgkin-Huxley model



The Hodgkin-Huxley model

$$C_{\mathrm{m}} \frac{dV_m}{dt} = -[G_{\mathrm{Na}}(V_m - V_{\mathrm{Na}})$$

$$+G_{\mathrm{K}}(V_m - V_{\mathrm{K}}) + G_L(V_m - V_{\mathrm{L}})] + I_{\mathrm{app}}$$

$$G_{\mathrm{Na}} = \bar{G}_{\mathrm{Na}} m^3 h \qquad G_{\mathrm{K}} = \bar{G}_{\mathrm{K}} n^4$$

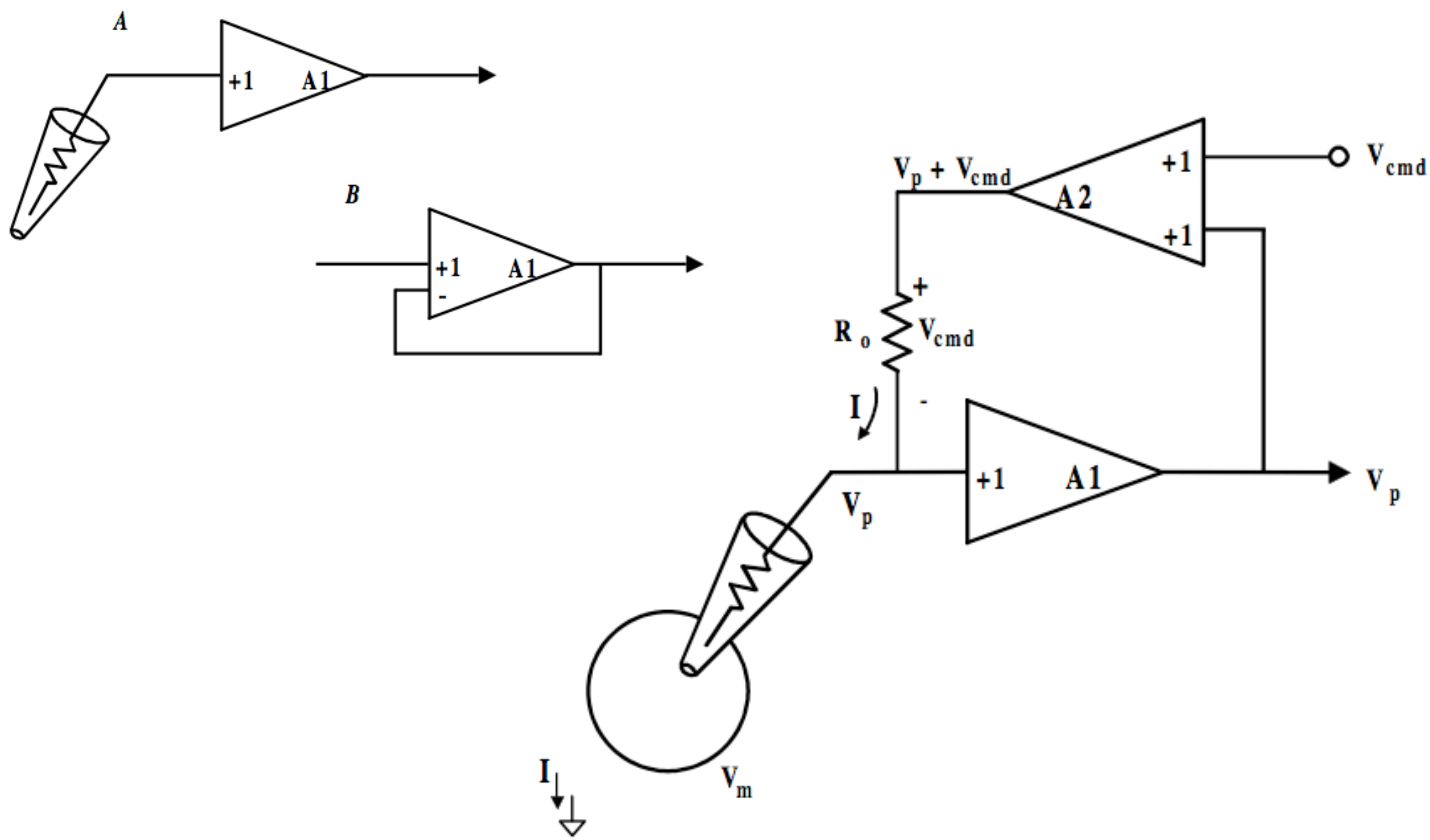
$$\frac{dm}{dt} = \frac{m_\infty(V_m) - m}{\tau_m(V_m)} \qquad \frac{dh}{dt} = \frac{h_\infty(V_m) - h}{\tau_h(V_m)}$$

$$\frac{dn}{dt} = \frac{n_\infty(V_m) - n}{\tau_n(V_m)}$$

Intracellular measurement techniques

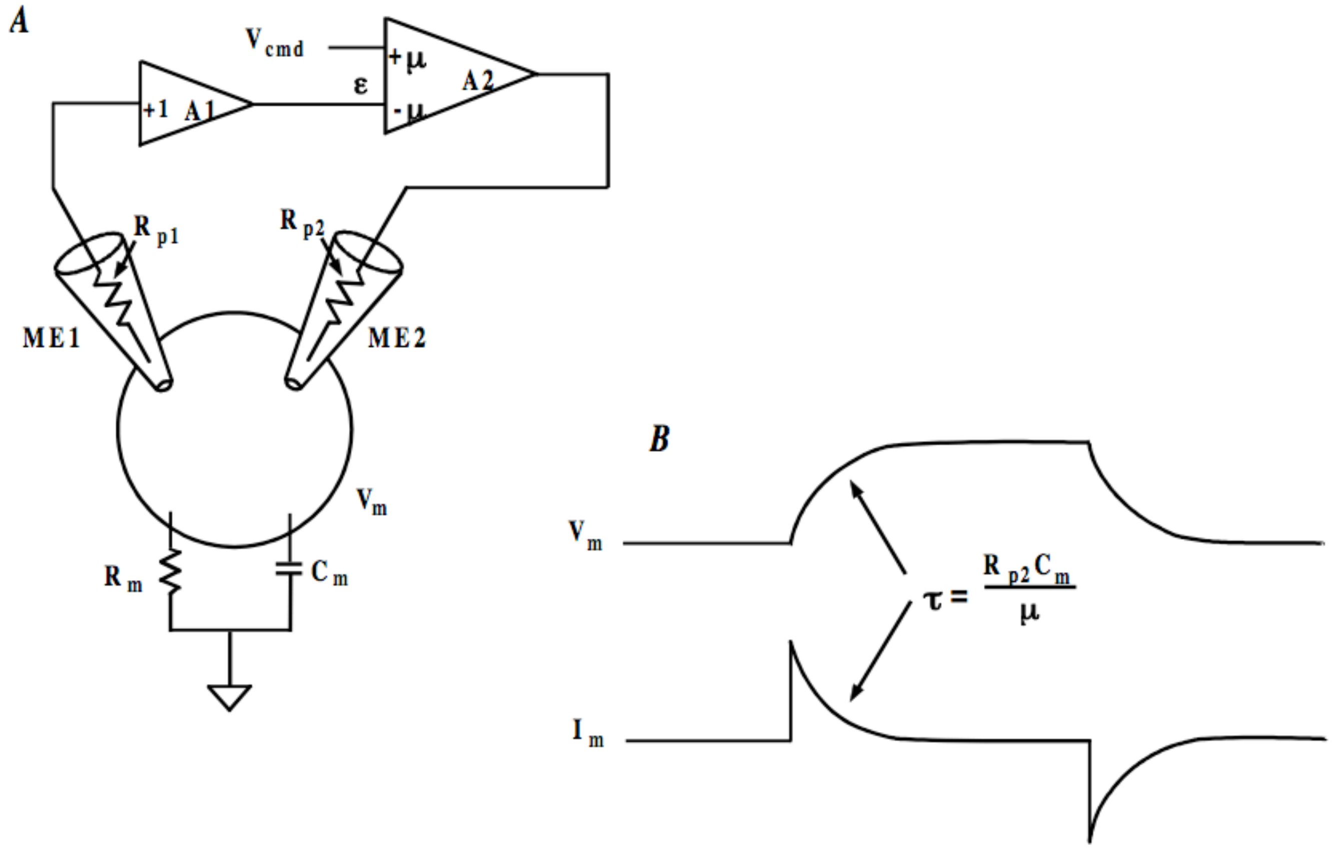
- Current clamp – control current "injected" into cell, measure V_m
- Voltage clamp – control V_m, measure amount of current required to do so
- "Dynamic" clamp – measure V_m, inject current that can represent voltage-gated channels or postsynaptic effects of virtual neurons

Current clamp



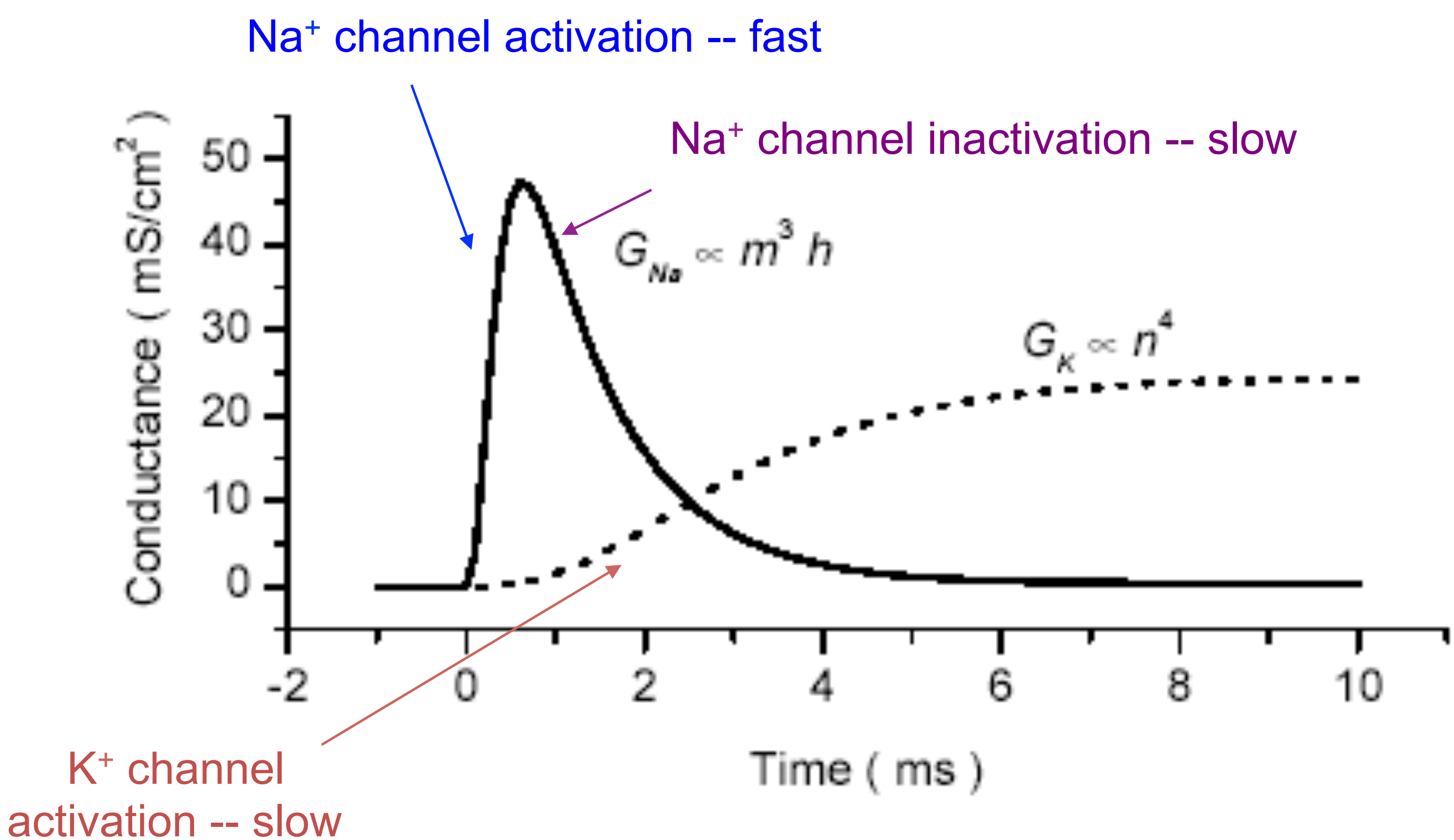
The Axon Guide (1993)

Voltage clamp

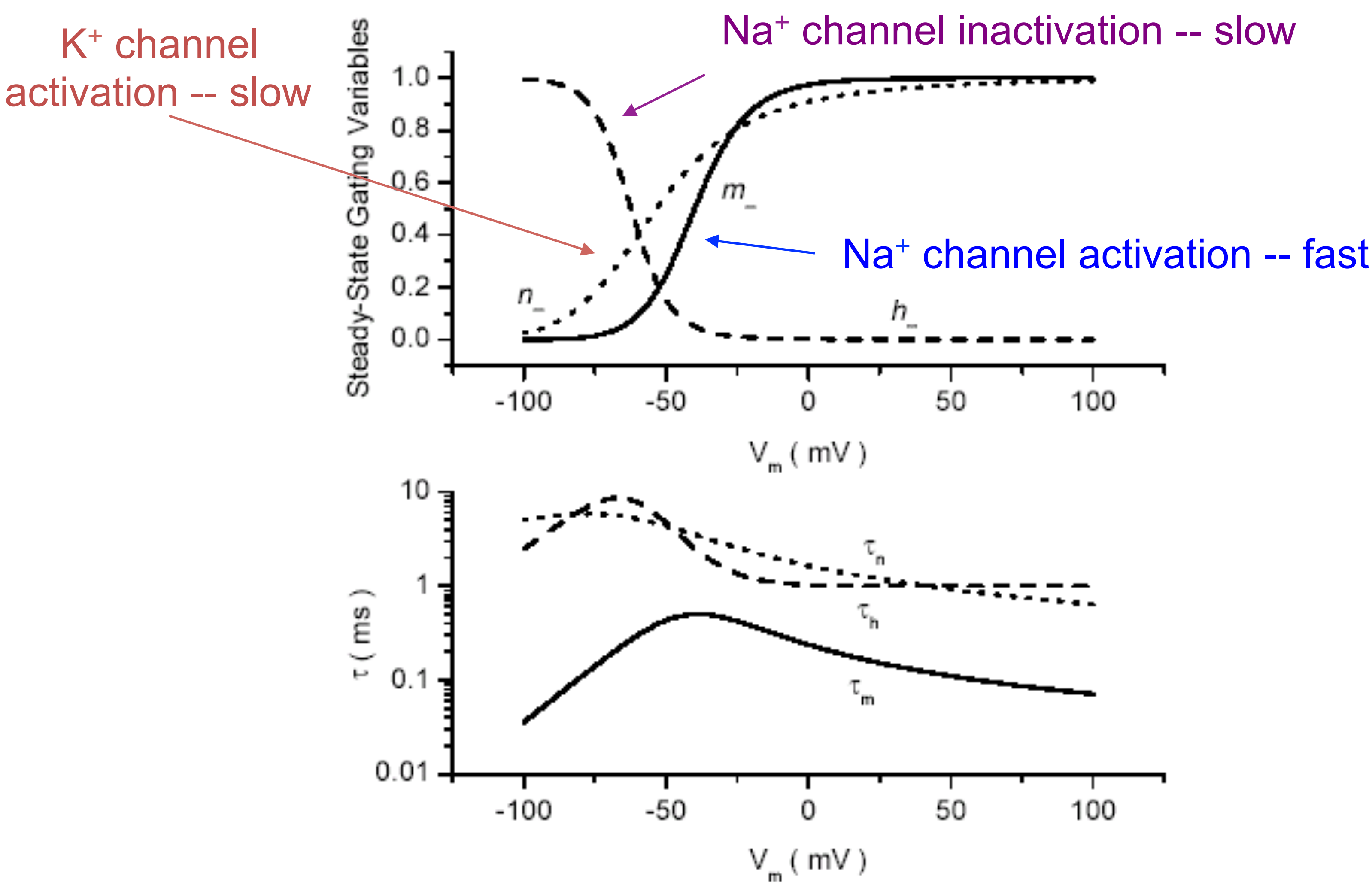


The Axon Guide (1993)

Typical Voltage-Clamp Responses



Parameters for Squid Na^+ and K^+ Channels



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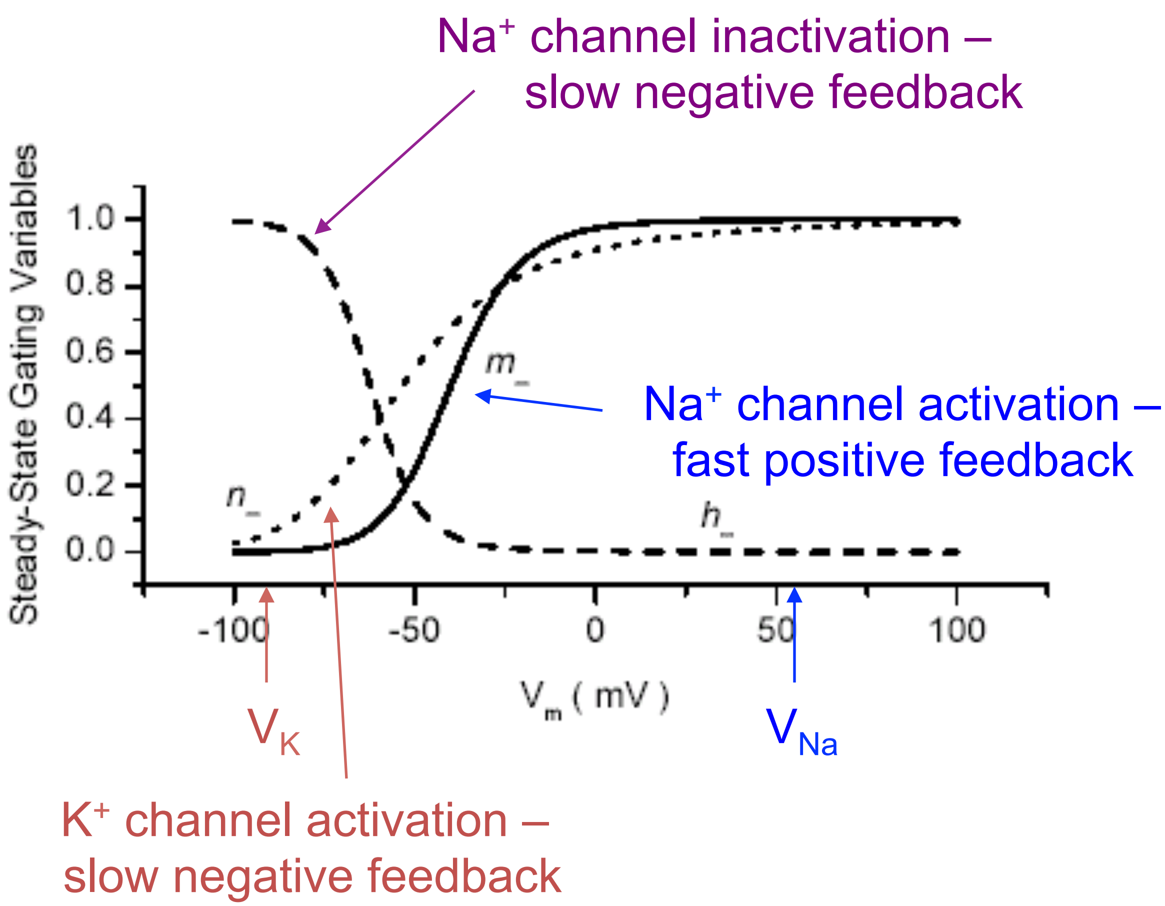
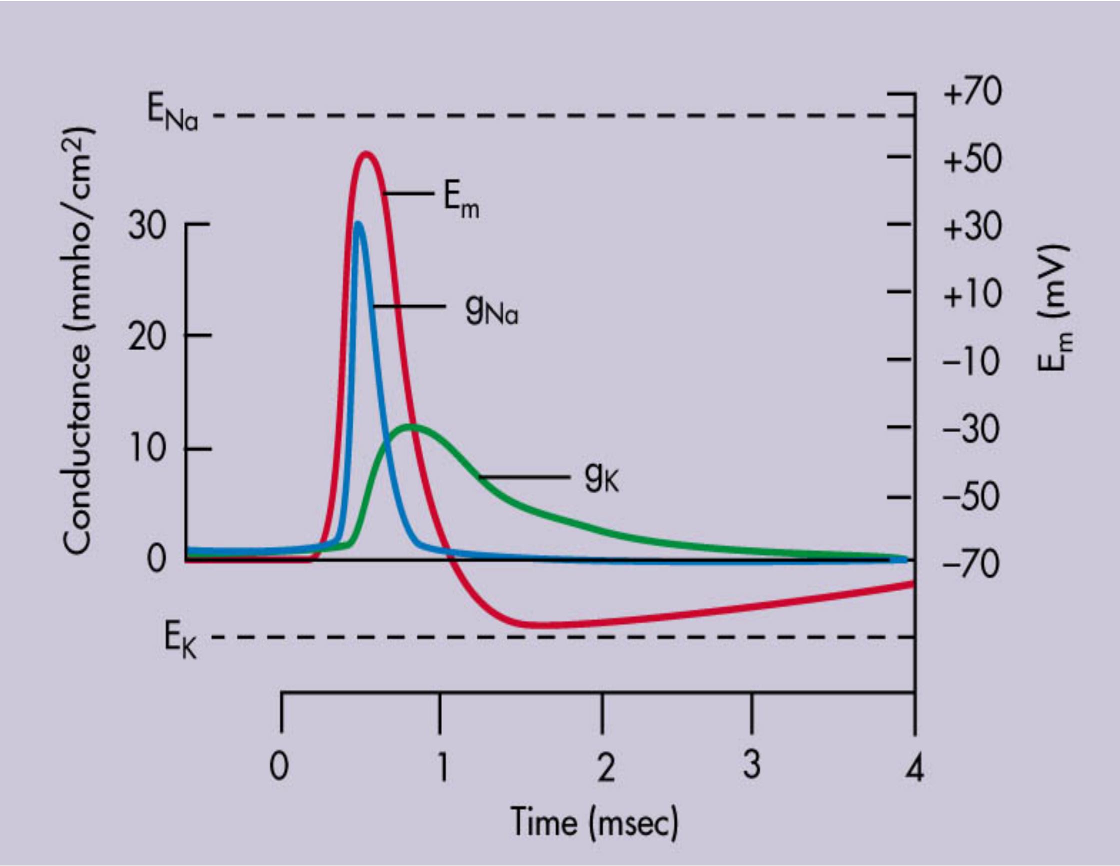


Conductance Changes Underlying the Action Potential



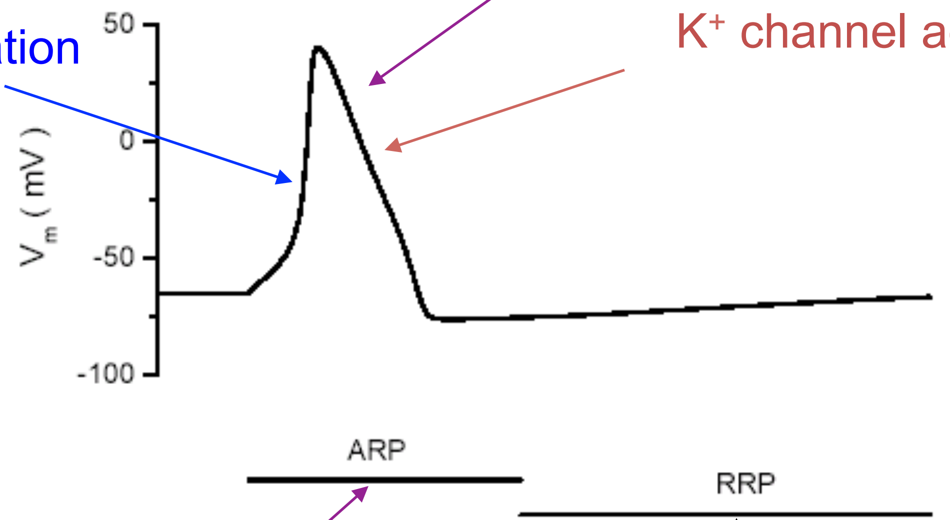
Berne and Levy

The Action Potential Explained

Na+ channel inactivation

Na+ channel activation

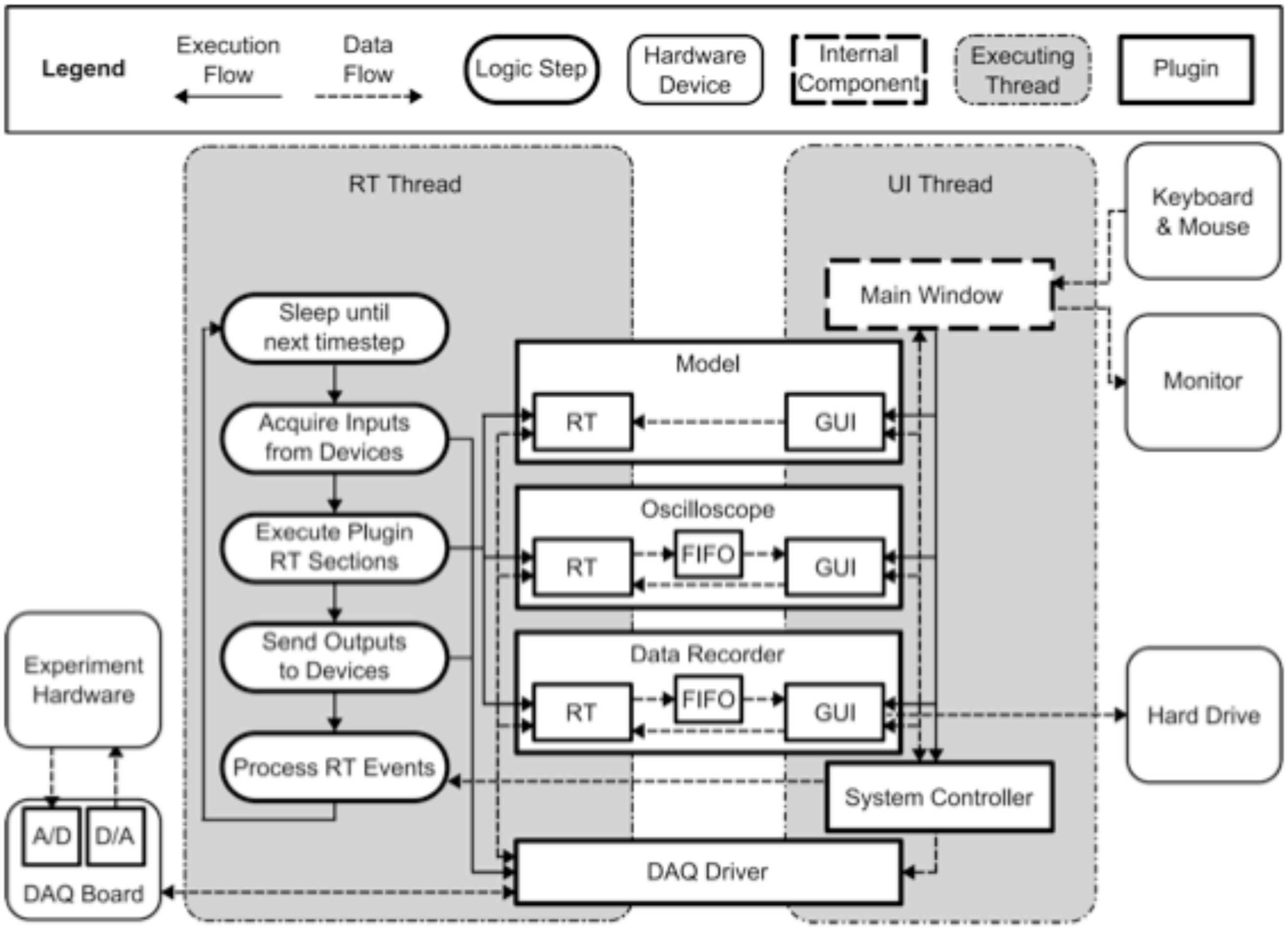
K+ channel activation



Na+ channels are inactivated
Impossible to generate another AP

Na+ channels still recovering from inactivation
K+ channels still recovering from activation
Possible, but more difficult, to generate AP

Dynamic clamp: adding arbitrary conductances to living neurons



Lin et al. *Proc IEEE EMBS* 2010

RTXI: Current applications

- Measuring responses to artificial synaptic inputs to build nonlinear-dynamics-inspired descriptions of cellular I-O properties and network coherhence
  Netoff et al. *J Neurophysiol* 93: 1197-1208, 2005; Netoff et al. *J Comput Neurosci* 18: 287-295, 2005; Pervouchine et al. *Neural Comput* 18:2617-2650, 2006; Fernandez and White *J Neurosci* 28: 3790-3803, 2008; Fernandez and White *J Neurosci* 29: 973-986, 2009; Economo et al. *J Neurosci* 30:2407-2413; Fernandez and White *J Neurosci* 30: 230-241, 2010; Fernandez et al. *J Neurosci* 31: 3880-3993, 2011.

- Altering the properties of voltage-gated channels *in vitro*
  Dorval and White *J Neurosci* 25: 10025-10028, 2005; Fernandez and White *J Neurosci* 28: 3790-3803, 2008; Fernandez and White *J Neurosci* 29: 973-986, 2009; Economo et al. *J Neurosci* 30:2407-2413; Fernandez and White *J Neurosci* 30: 230-241, 2010; Fernandez et al. *J Neurosci* 31: 3880-3993, 2011

- Virtual acoustic environments for studying the use of dynamic cues in sound localization
  Scarpaci et al. *Proc ICAD* 05, 214-246

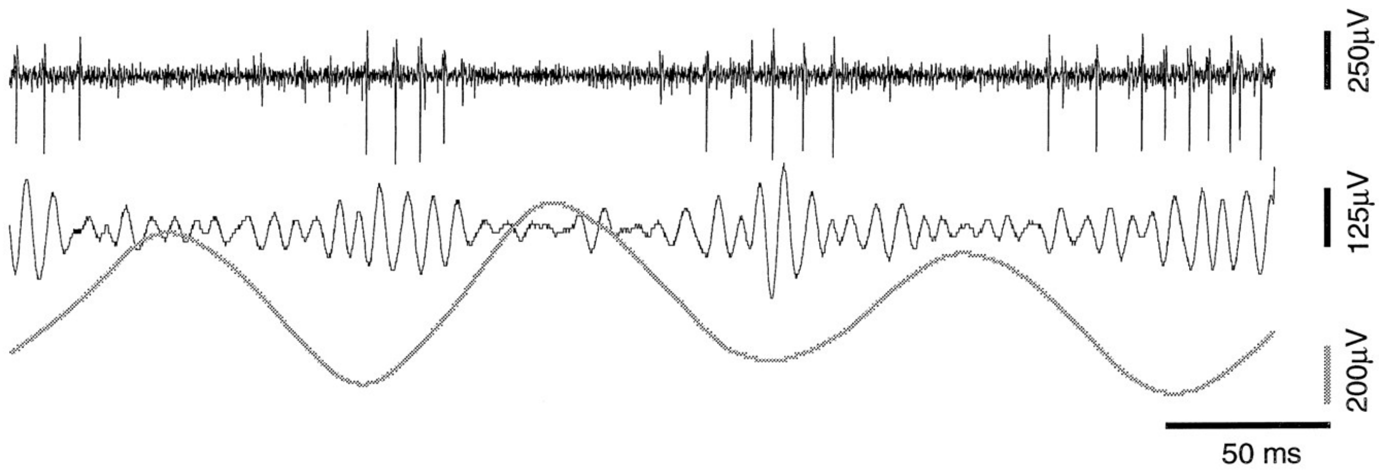
What does it mean to "inject" conductance?

$$I_{virtual}(t) = G_{virtual}(t)\left(V_m(t) - E_{rev,virtual}\right)$$

Typical choices of $G_{virtual}$:

- Poisson-process-driven synaptic waveforms
- Solutions from HH-style gating equations
- Synaptic waveforms driven by spikes in a biological cell

Synchronous rhythmic activity in hippocampus

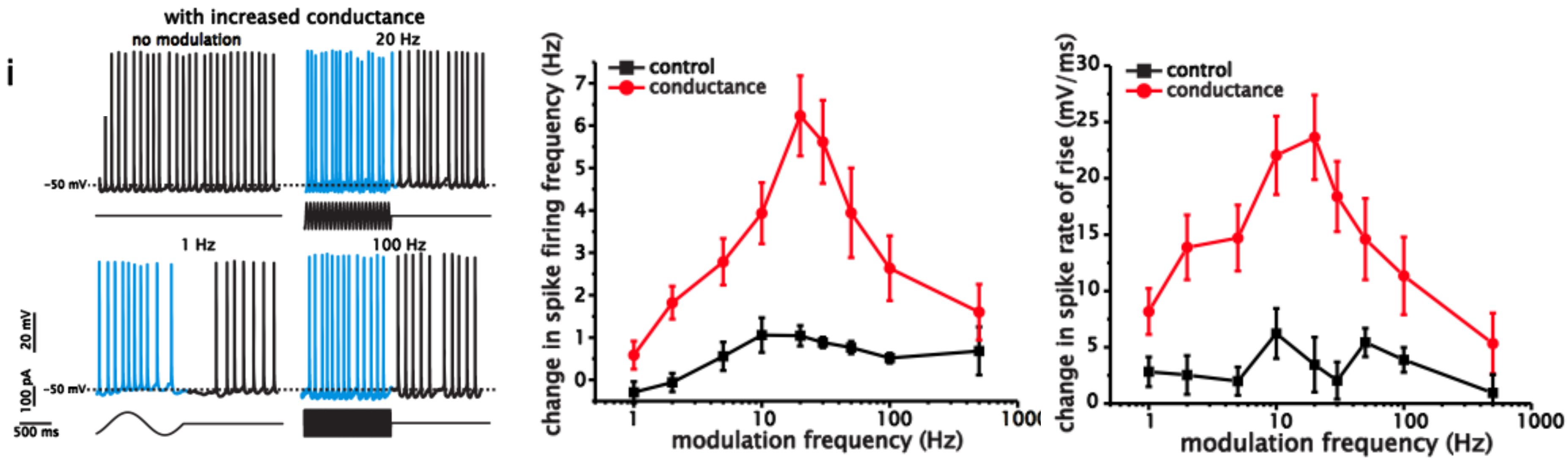


Chrobak and Buzsáki (1998) *J. Neurosci.* 18: 388-398

Is coherent activity important for mnemonic function?

- Synchronous activity appears during learning
- Blocking synchrony blocks memory
- Epochs of correlated pre- and postsynaptic activity change the effective synaptic weight
  e.g. Keck et al. (2008) *J Neurosci* 28: 7359-7369
- Synaptic plasticity depends on timing
  e.g. Zhou et al. (2005) *PNAS USA* 102: 19121-19125
- Bouts of correlated activity affect postsynaptic gain
  e.g. Fernandez*, Broicher* et al. (2011) *J Neurosci* 31:3880-3993

Periodic perturbations "rescue" inactivated Na^+ channels and restore gain in CA1 PCs

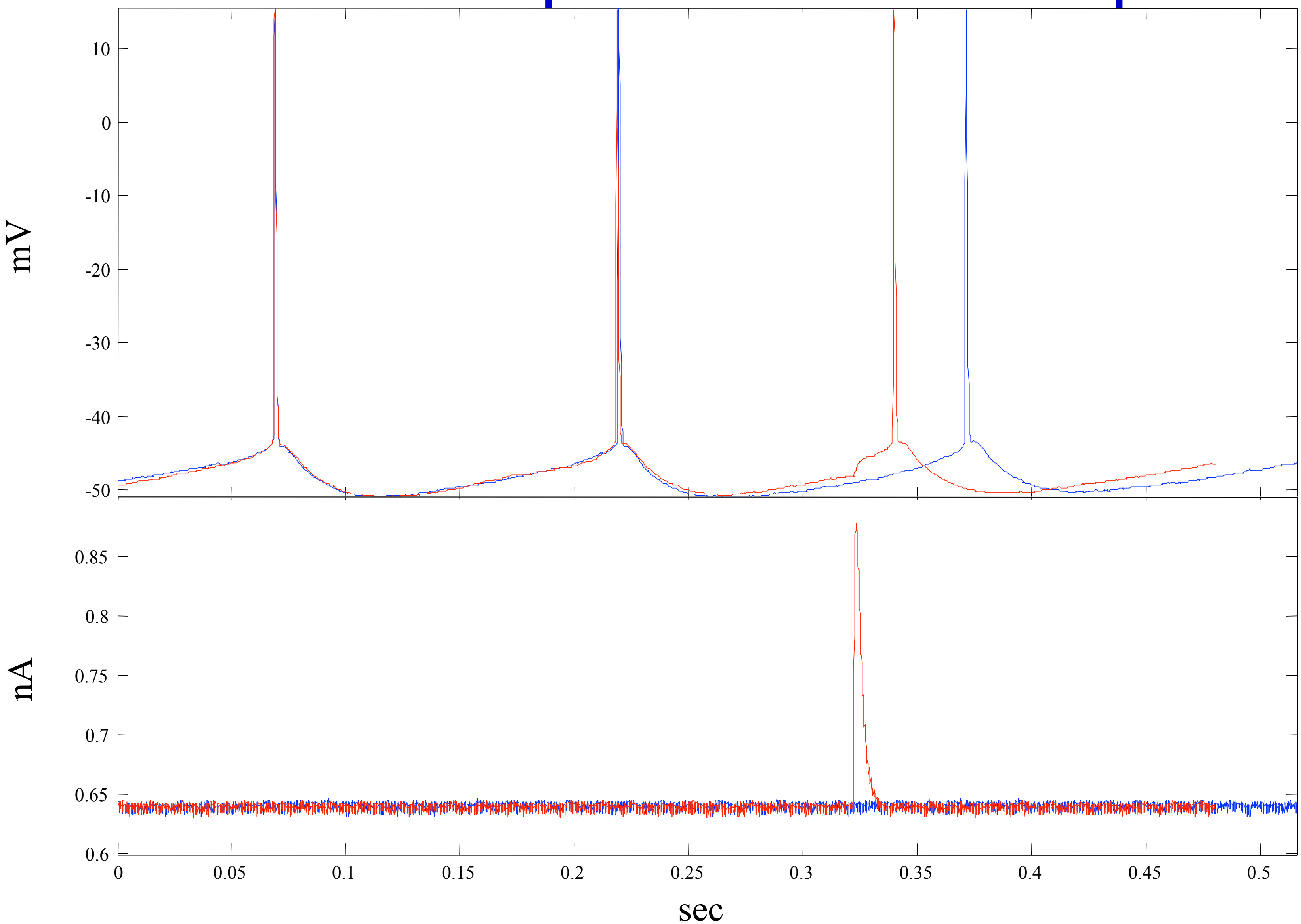


Fernandez*, Broicher* et al. (2011) *J Neurosci*

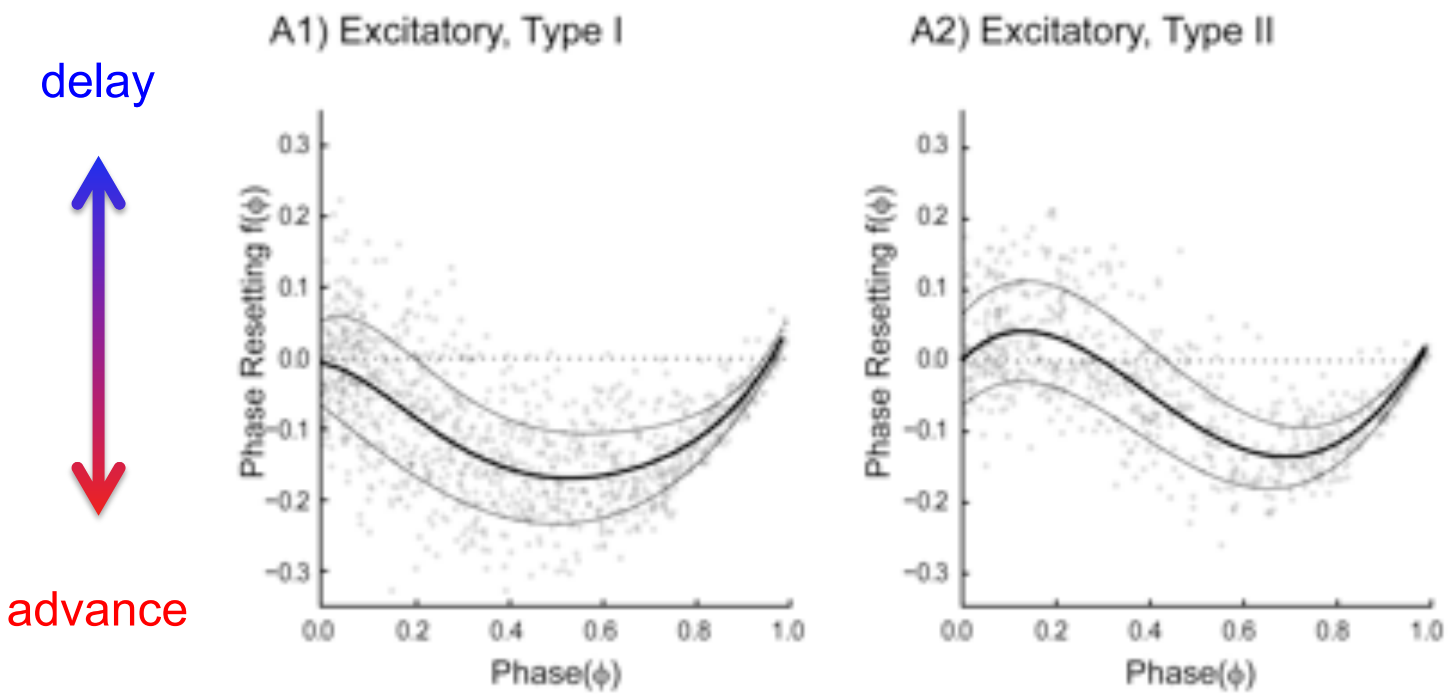
Applications: Phase-response curves

- Cells act like oscillators
- Inputs perturb phase, with short-lived effects: *phase-response curve* describes this effect
- Helpful, but not necessary, if effects can be superimposed

Phase response relationships

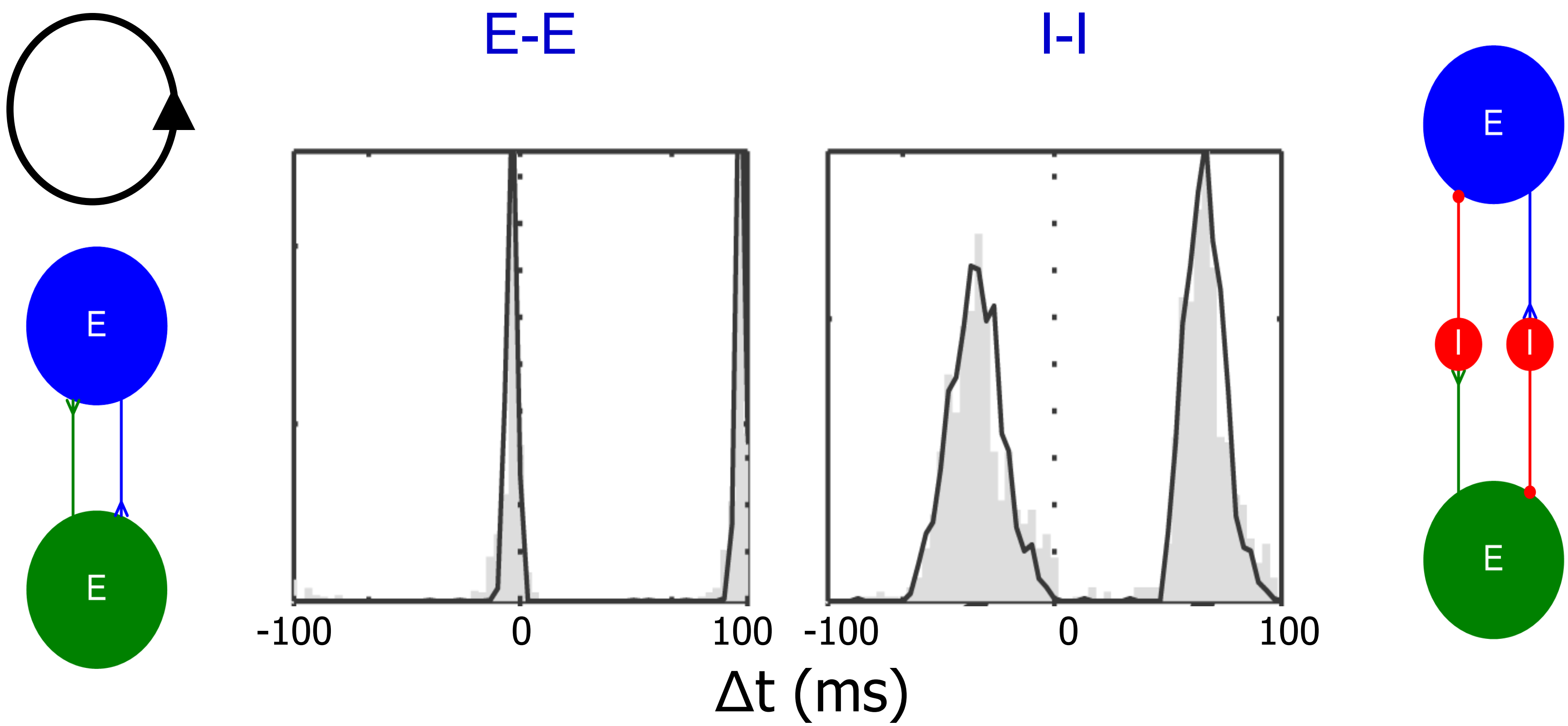


Example PRCs: Entorhinal stellate cells



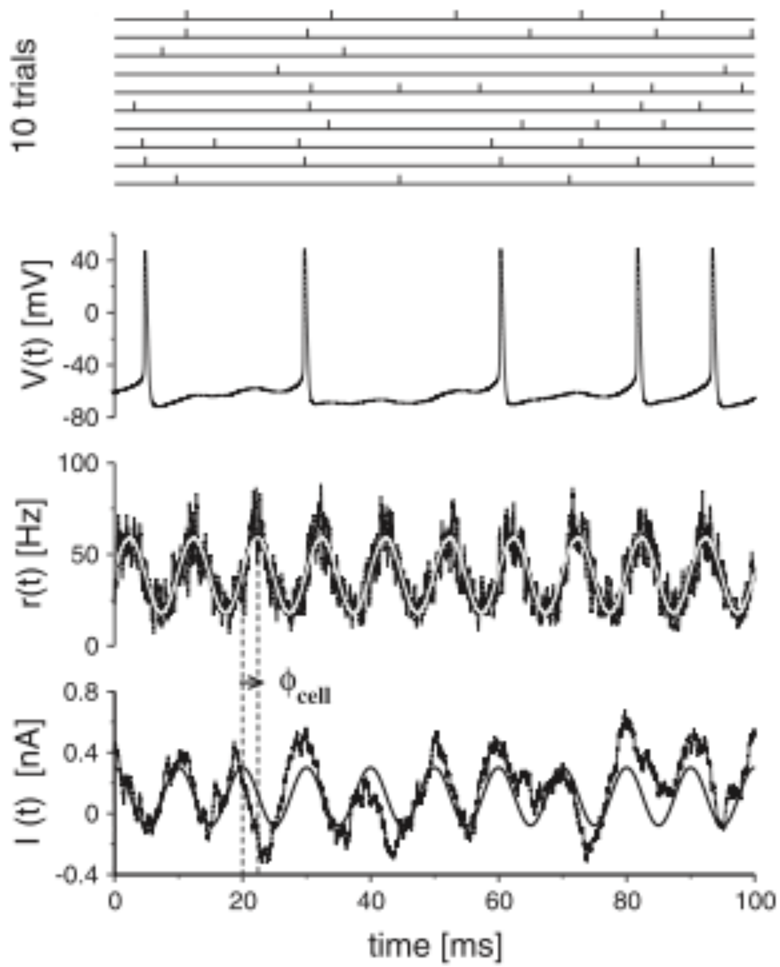
Data collected by Fernando Fernandez,
in collaboration with Carmen Canavier

SCs synchronize via mutual excitation, anti-synchronize via mutual inhibition



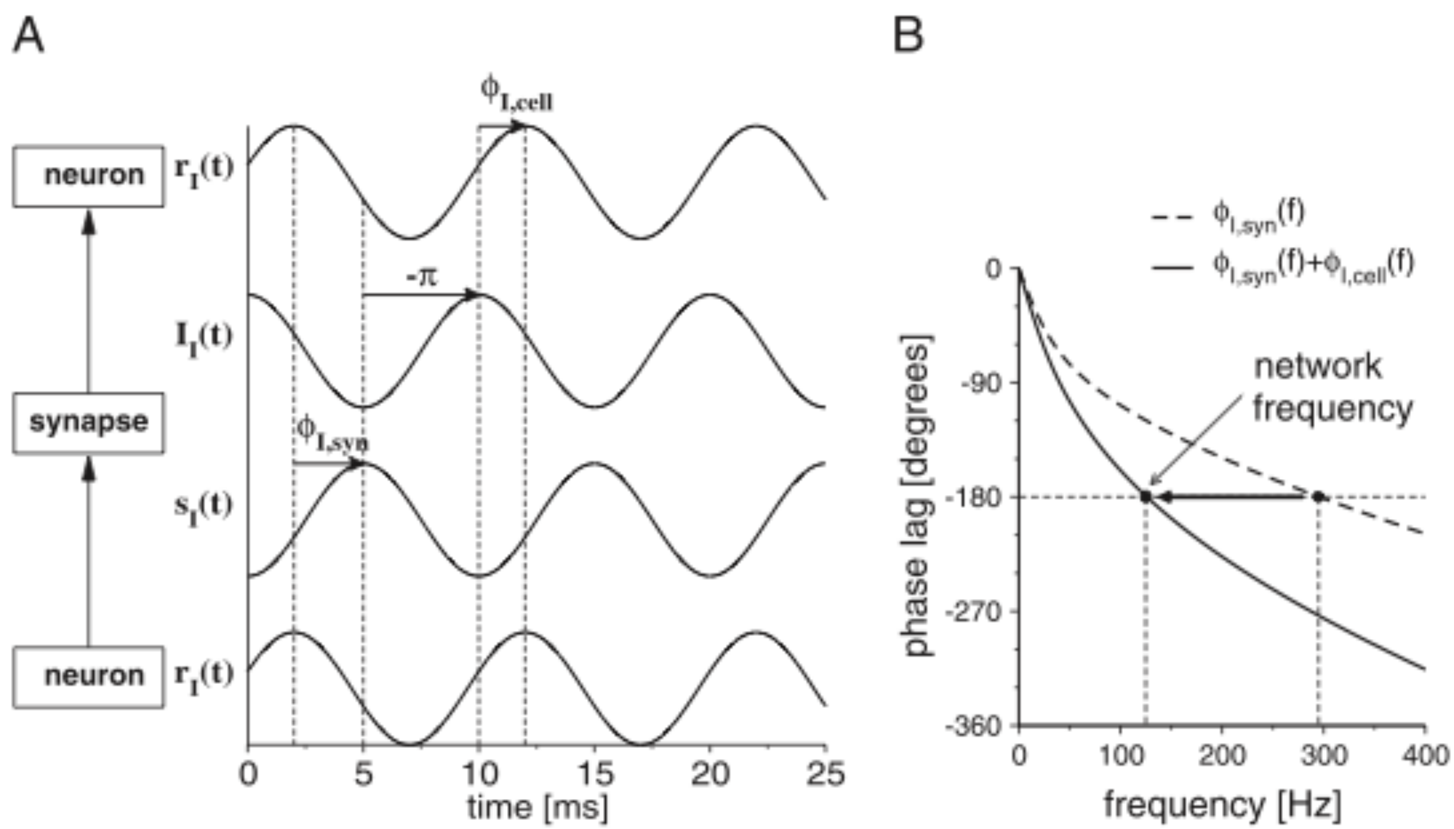
Netoff et al. (2005) *J Neurophysiol* 93: 1197-1208
Netoff et al. (2005) *J Comp Neurosci* 18: 287-295
Pervouchine et al. (2006) *Neural Computation* 18:2617-2650

Synchronization with irregular firing at low rates (1)



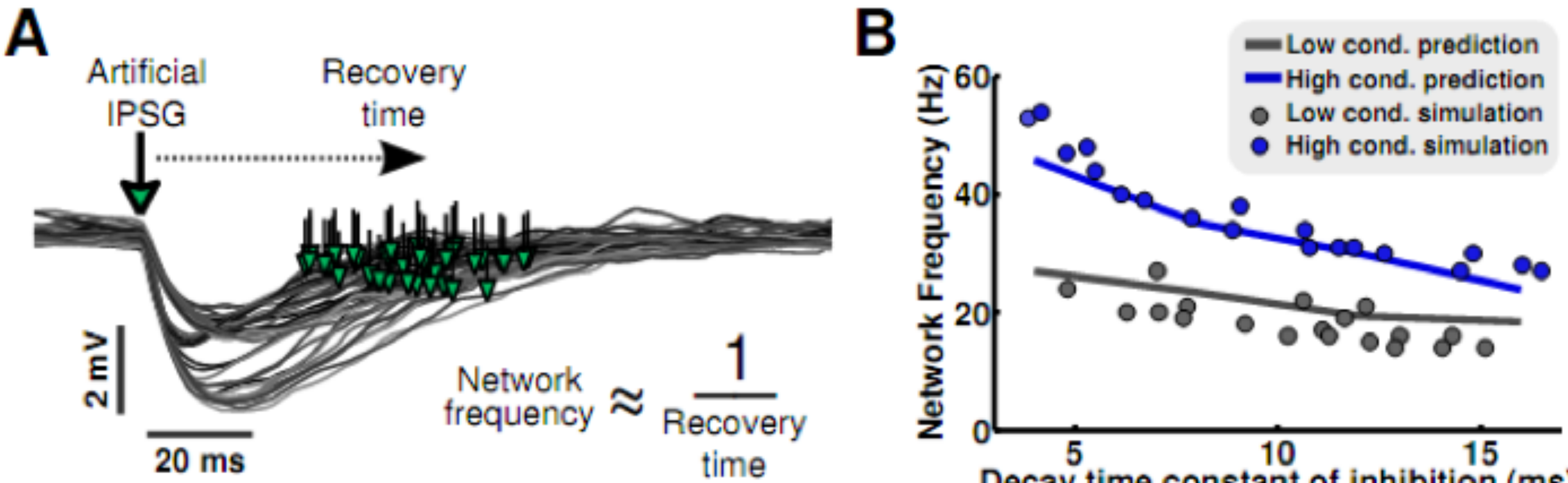
Geisler, Brunel, and Wang (2005) *J Neurophysiol* 94: 4344-4361

Synchronization with irregular firing at low rates (2)



Geisler, Brunel, and Wang (2005) *J Neurophysiol* 94: 4344-4361

Estimating $\phi_{I,cell}$ experimentally



Economo and White, in preparation