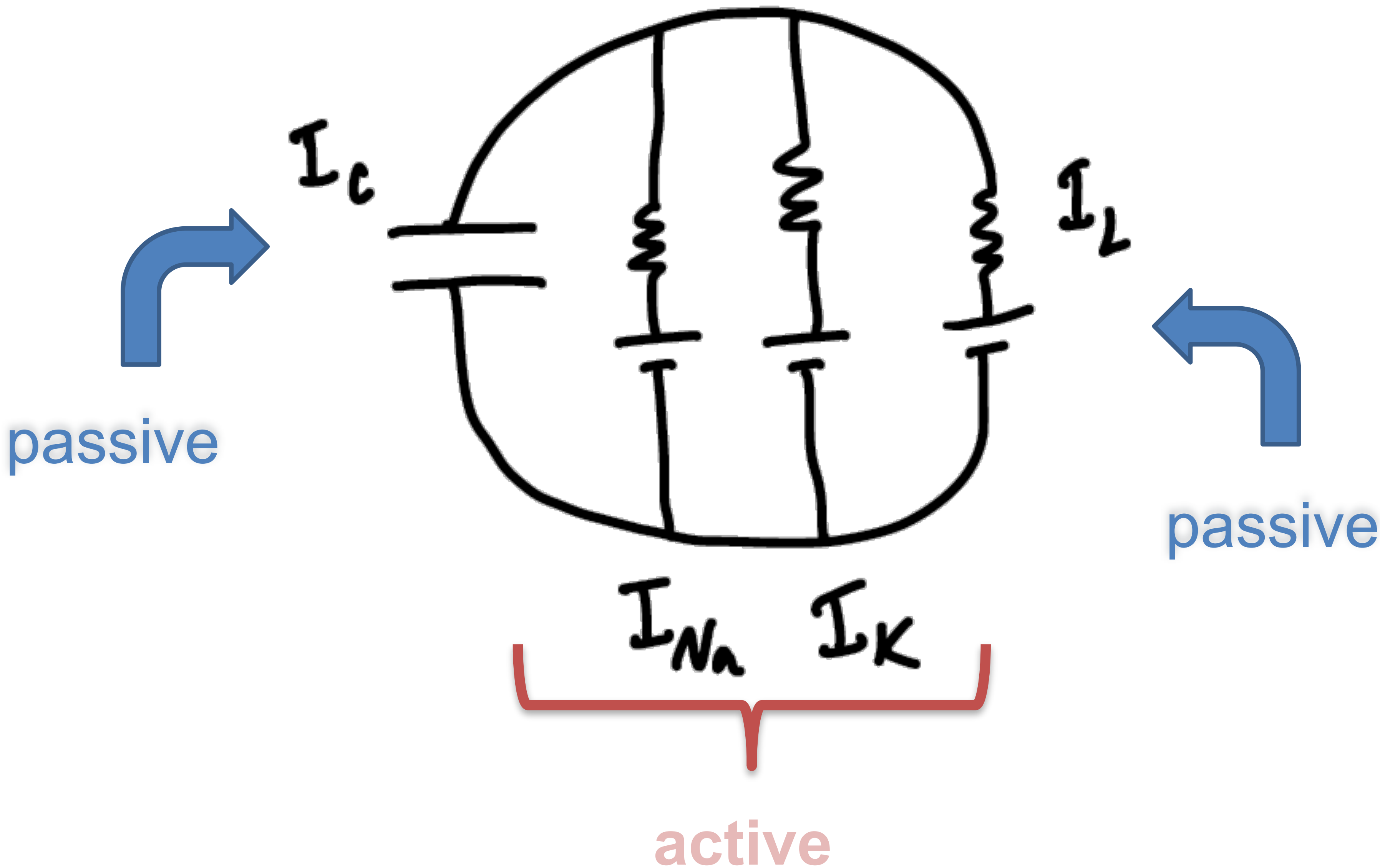
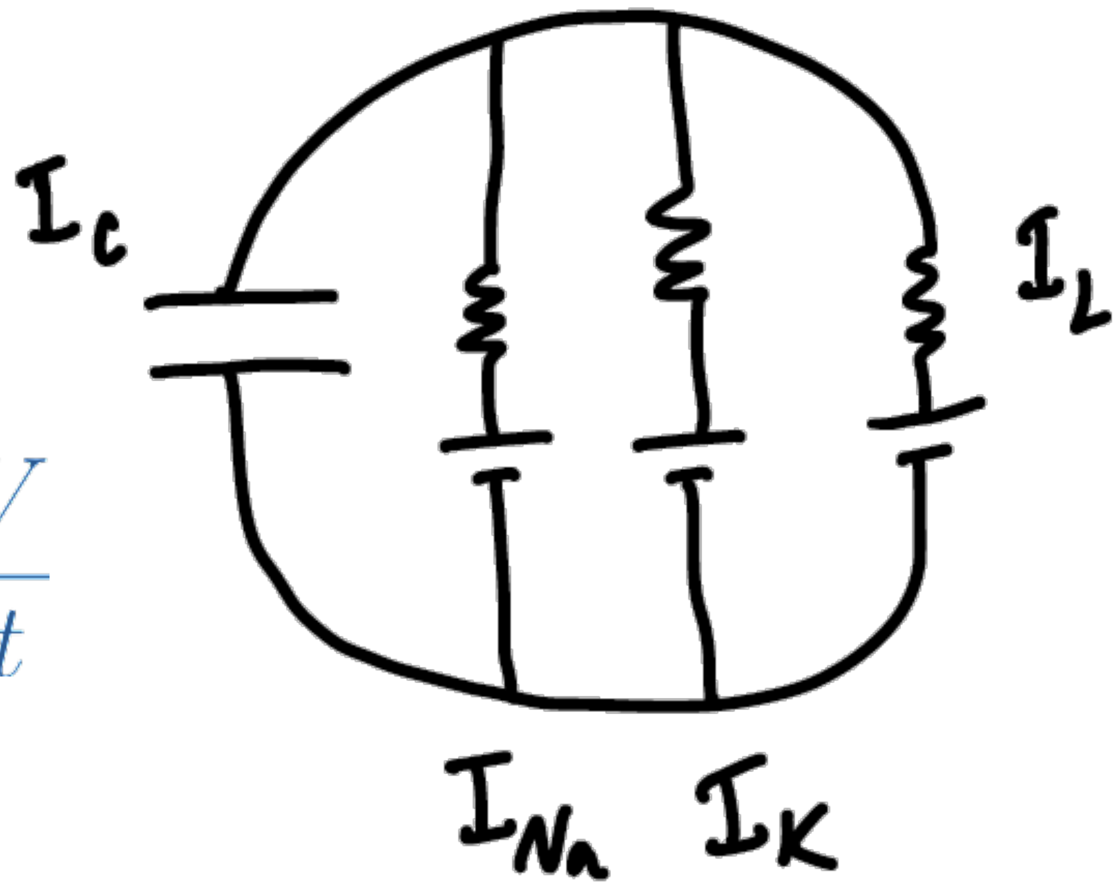
Thank you! Many slides by Drs. Gabrielle Guiterrez and Adrienne Fairhall

Intrinsic neuron currents



Intrinsic neuron currents

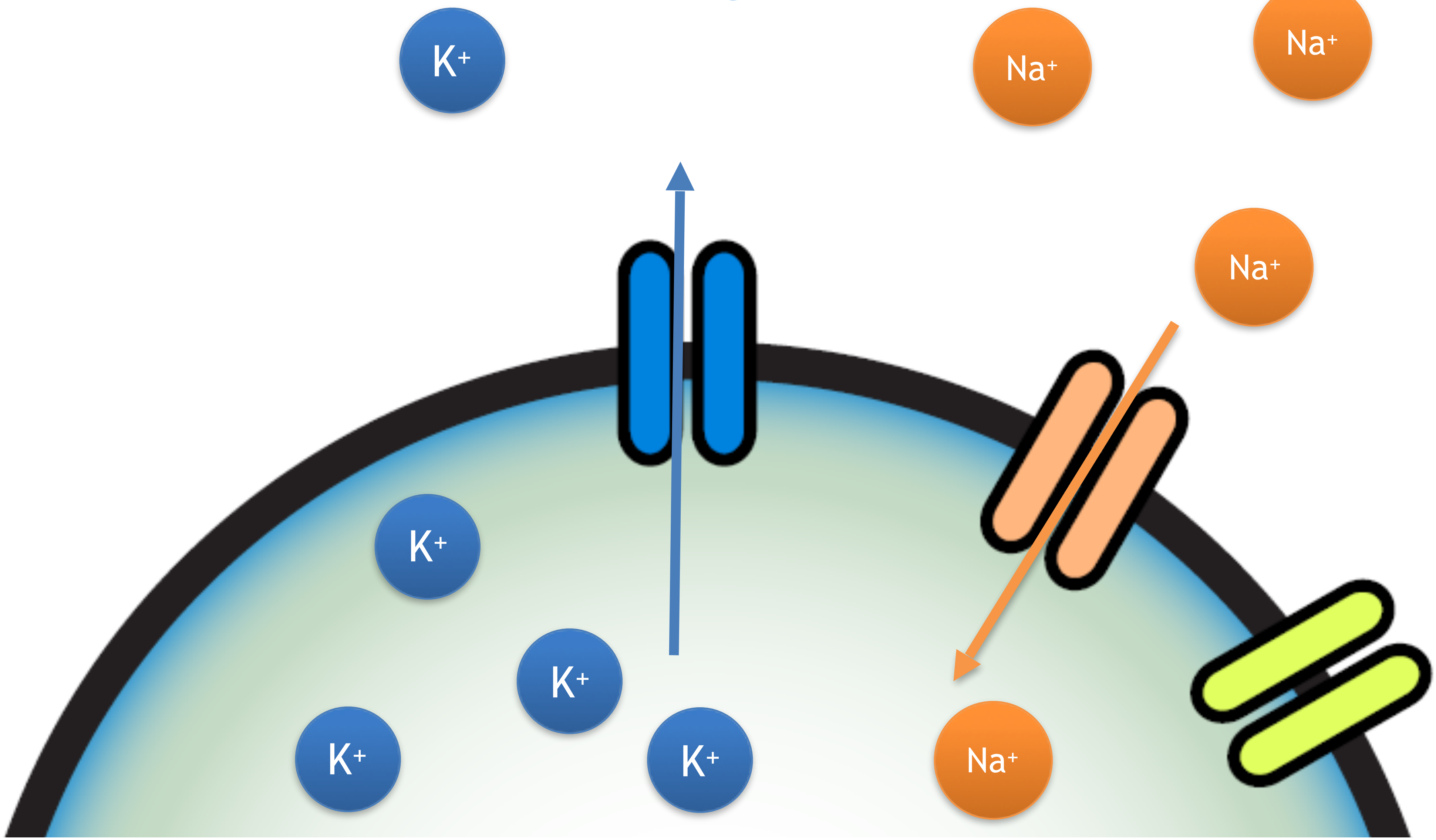


$$I_C = C\frac{dV}{dt}$$

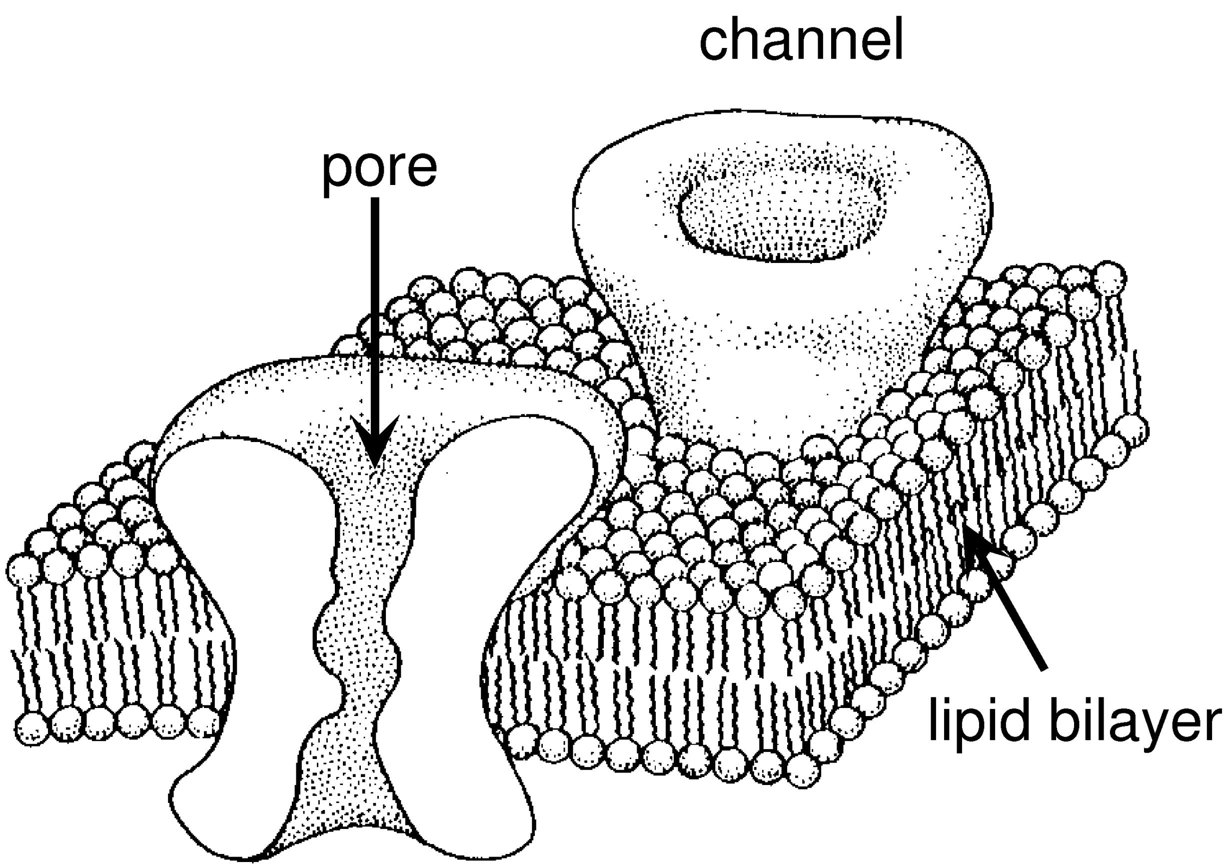
$$i_m = \sum_j g_j(V - E_j)$$

Driving force via E_j; conductance g_j

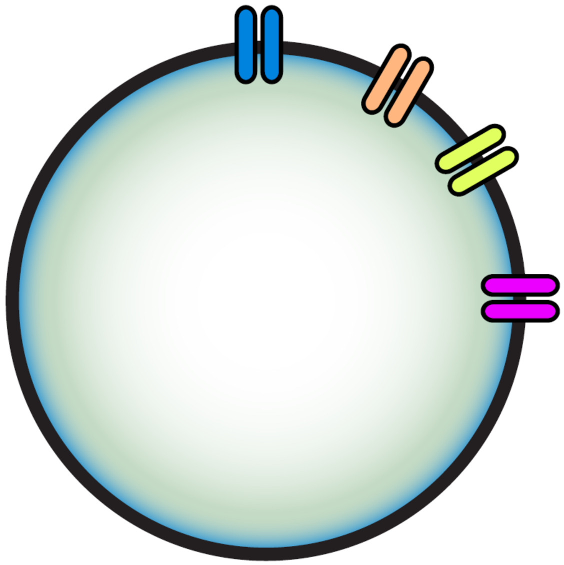
$$i_m = \sum_j g_j(V - E_j)$$



Membrane patch

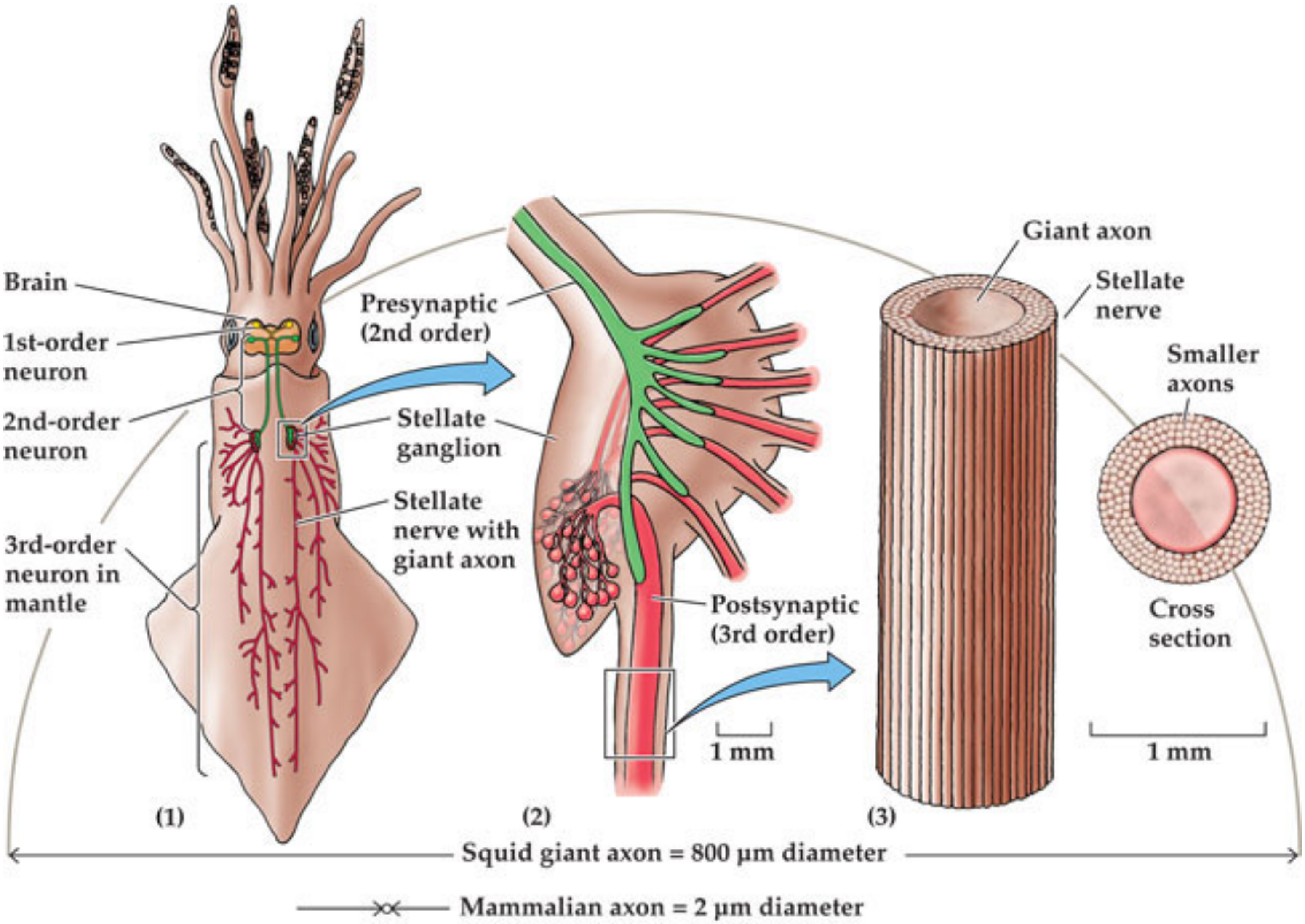


The Hodgkin-Huxley model

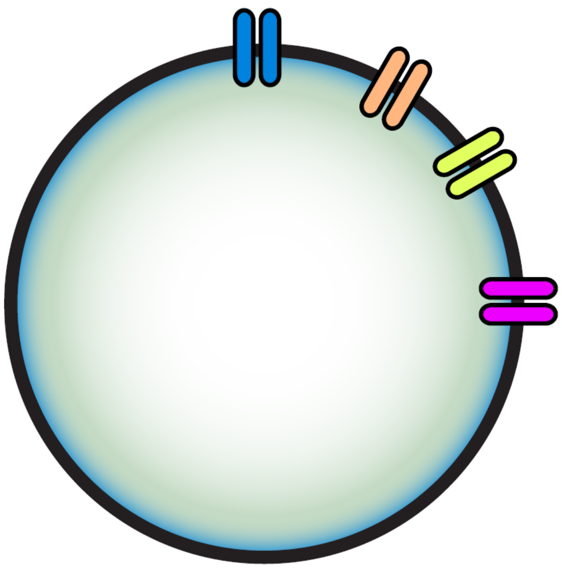


$$C_m \frac{dV}{dt} = -[I_L + I_K + I_{Na}]$$

The Hodgkin-Huxley model



The Hodgkin-Huxley model



$$g_K = \bar{g}_K n^4 \qquad g_{Na} = \bar{g}_{Na} m^3 h$$

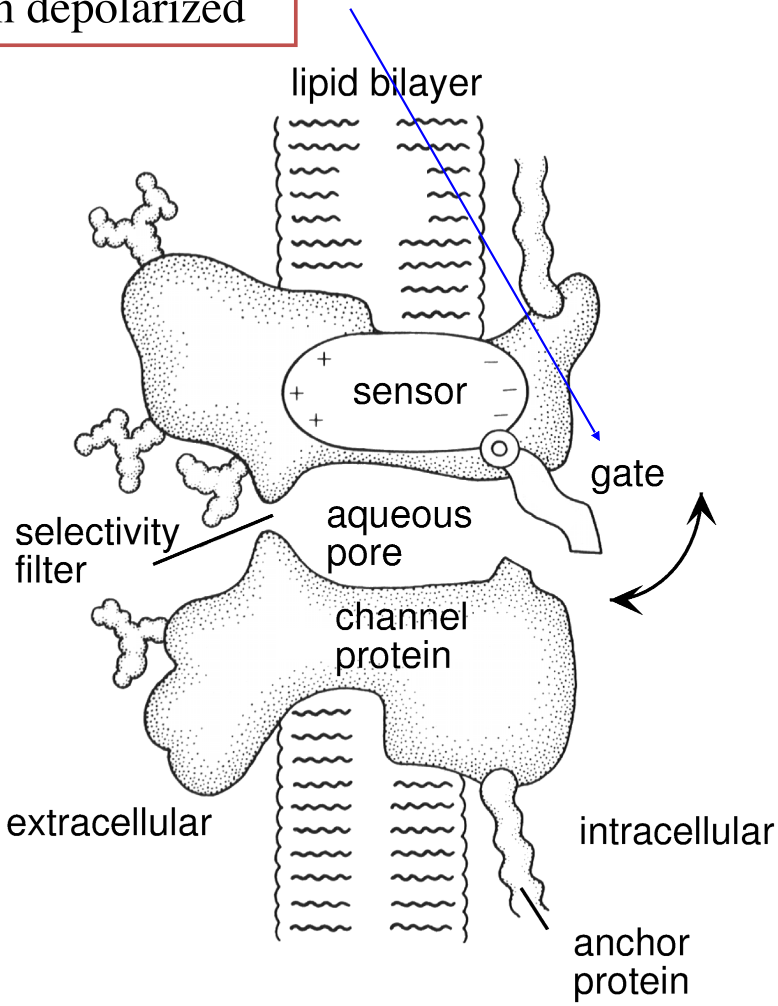
Maximal conductances

$$C\frac{dV}{dt} = -\bar{g}_L(V - E_L) - \bar{g}_K n^4 (V - E_K) - \bar{g}_{Na} m^3 h (V - E_{Na})$$

Gating variables

The ion channel is a cool molecular machine

K channel: open probability increases when depolarized



$P_K \sim n^4$

Persistent conductance

n describes a subunit

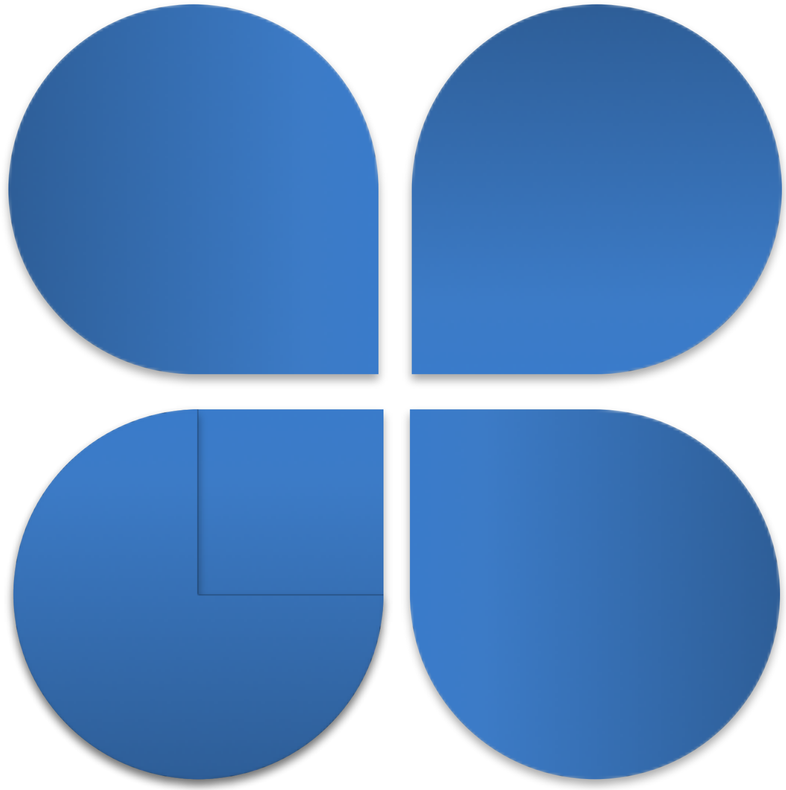
n	is open probability
$1 - n$	is closed probability

Transitions between states occur at voltage dependent rates

$\alpha_n(V)$	C → O
$\beta_n(V)$	O → C

$$\frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n(V)n$$

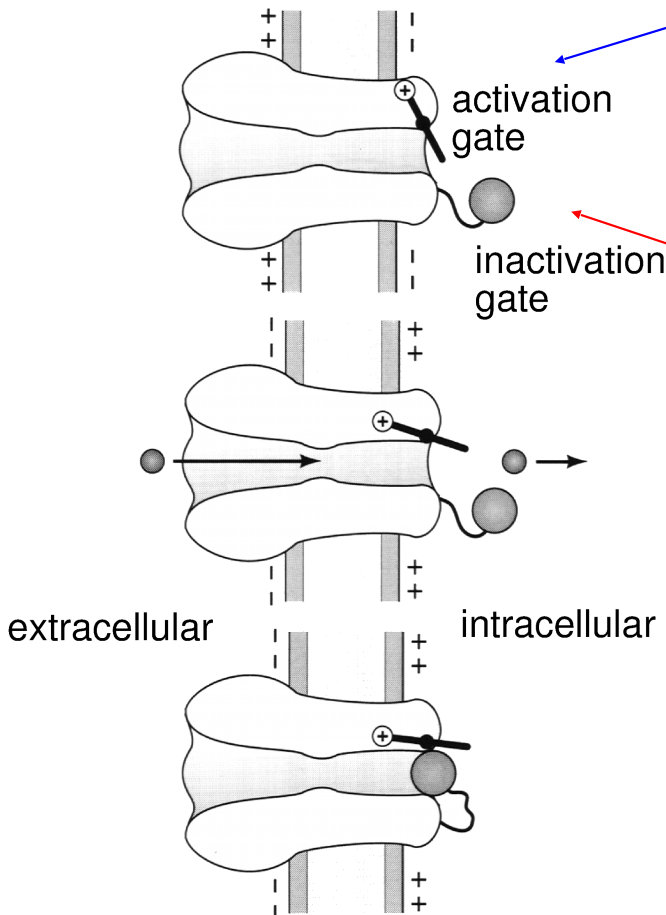
There are 4 “independent” subunits in the K channel



$$proba(\text{ 1 subunit open}) = n$$

$$proba(\text{ all 4 subunits, and hence channel open}) = n^4$$

Transient conductances



Gate acts as in previous case

Additional gate can block channel when open

$P_{Na} \sim m^3h$

m is activation variable
h is inactivation variable

m and *h* have opposite voltage dependences:

depolarization increases *m*, activation
hyperpolarization increases *h*, deinactivation

Dynamics of activation and inactivation

$$\frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n(V)n$$

$$\frac{dm}{dt} = \alpha_m(V)(1-m) - \beta_m(V)m$$

$$\frac{dh}{dt} = \alpha_h(V)(1-h) - \beta_h(V)h$$

We can rewrite:

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

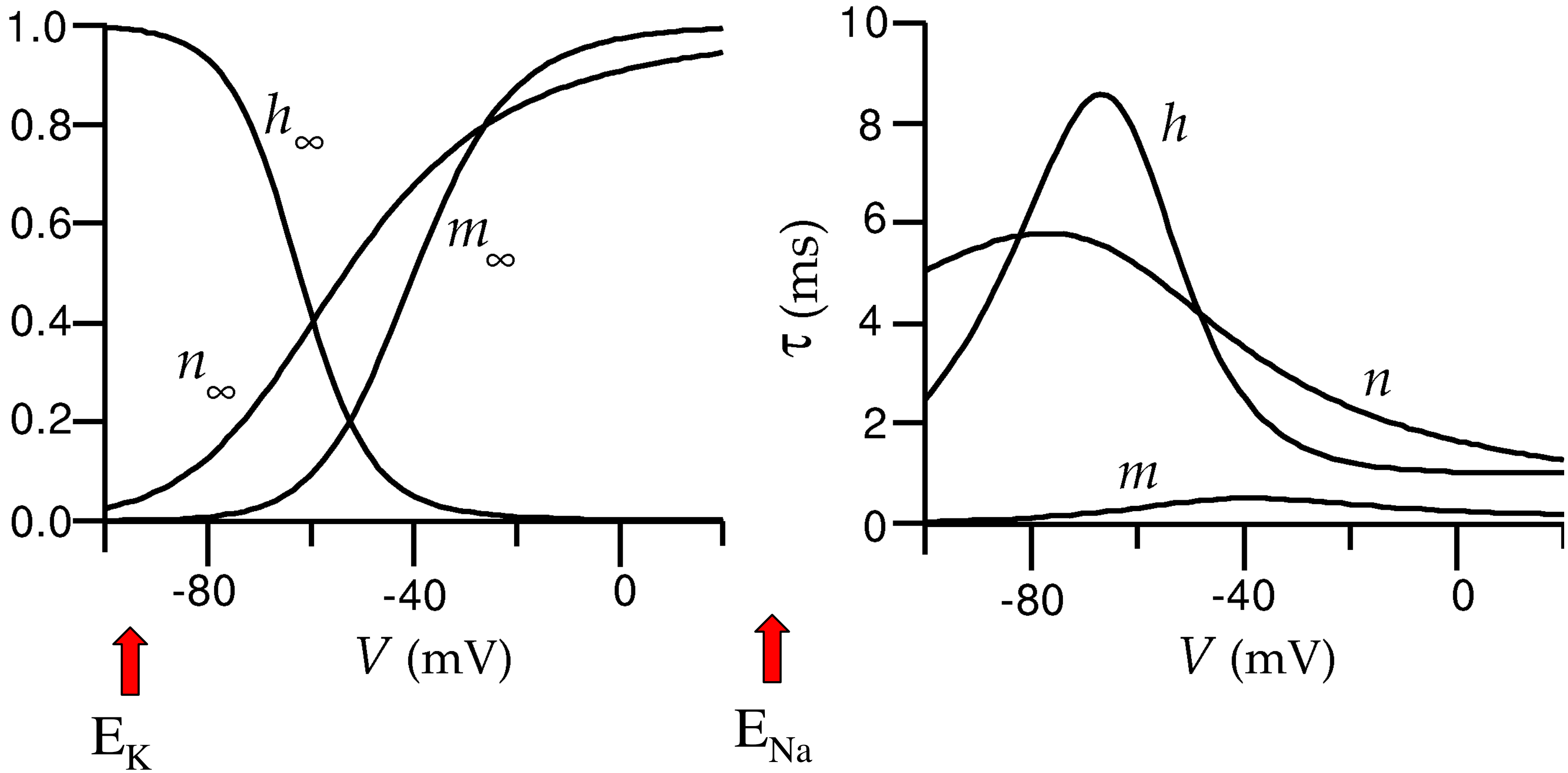
where

$$\tau_n(V) = \frac{1}{\alpha_n(V) + \beta_n(V)}$$

$$n_\infty(V) = \frac{\alpha_n(V)}{\alpha_n(V) + \beta_n(V)}$$

Anatomy of a spike

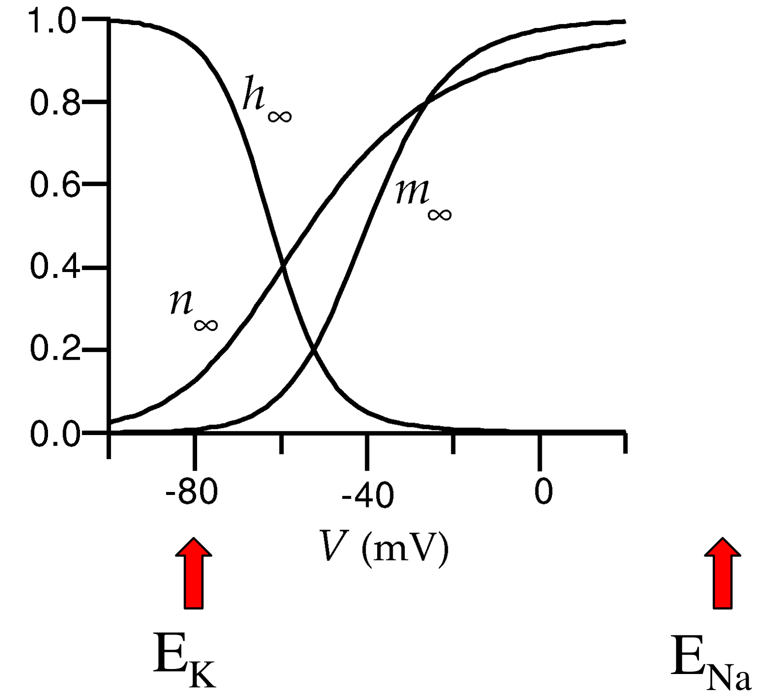
$$C\frac{dV}{dt} = -\bar{g}_L(V - E_L) - \bar{g}_K n^4(V - E_K) - \bar{g}_{Na} m^3 h(V - E_{Na})$$

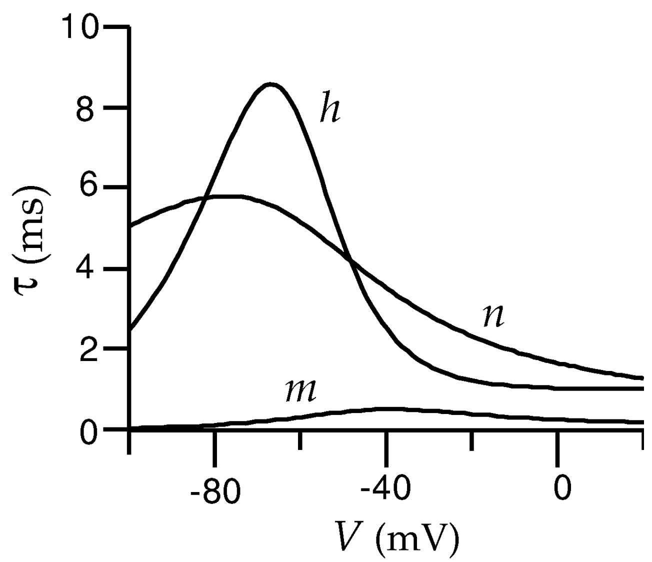


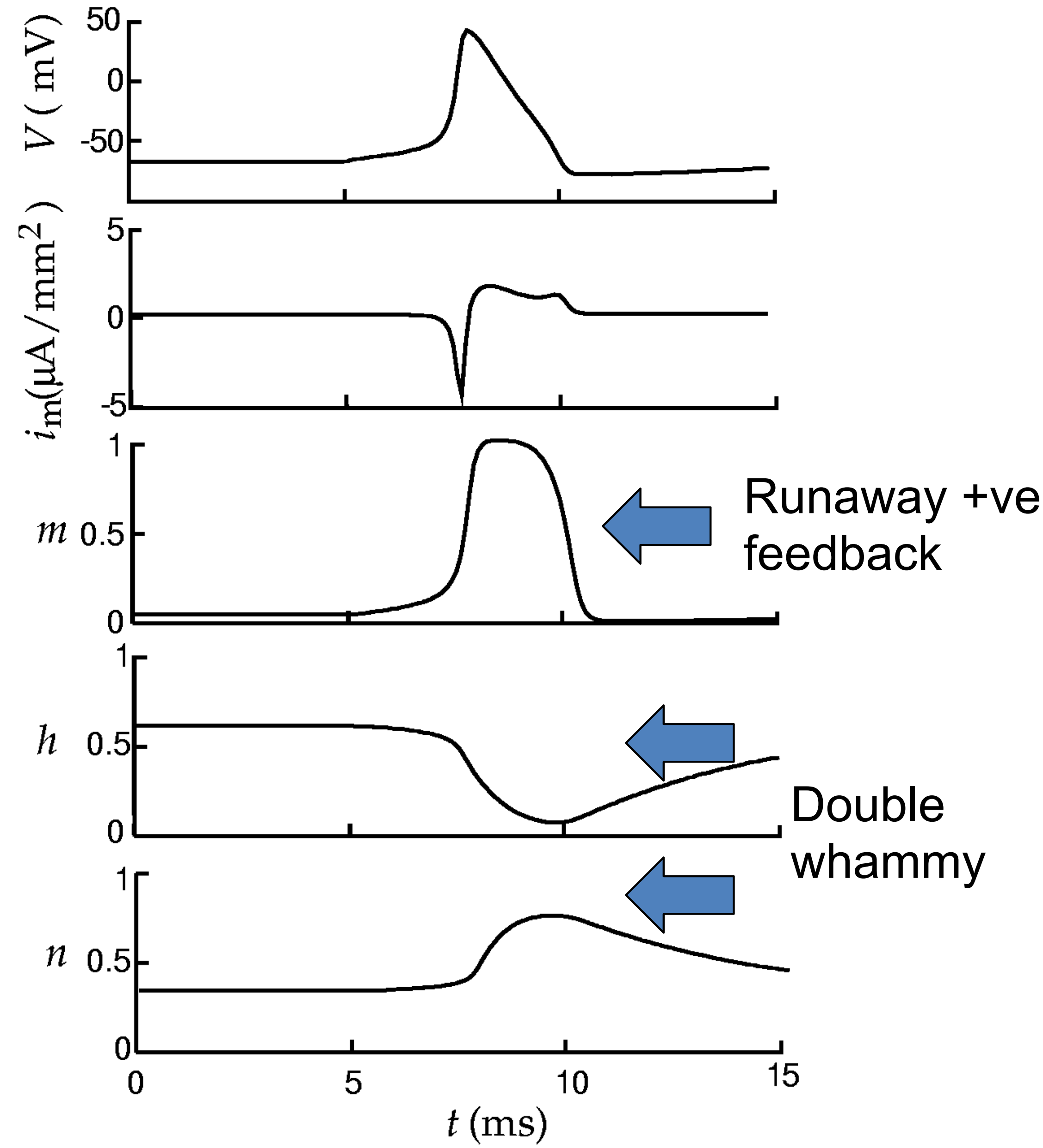
$g_{Na} \sim m^3h$

$g_K \sim n^4$

$$C\frac{dV}{dt} = -\bar{g}_L(V - E_L) - \bar{g}_K n^4(V - E_K) - \bar{g}_{Na}m^3h(V - E_{Na})$$



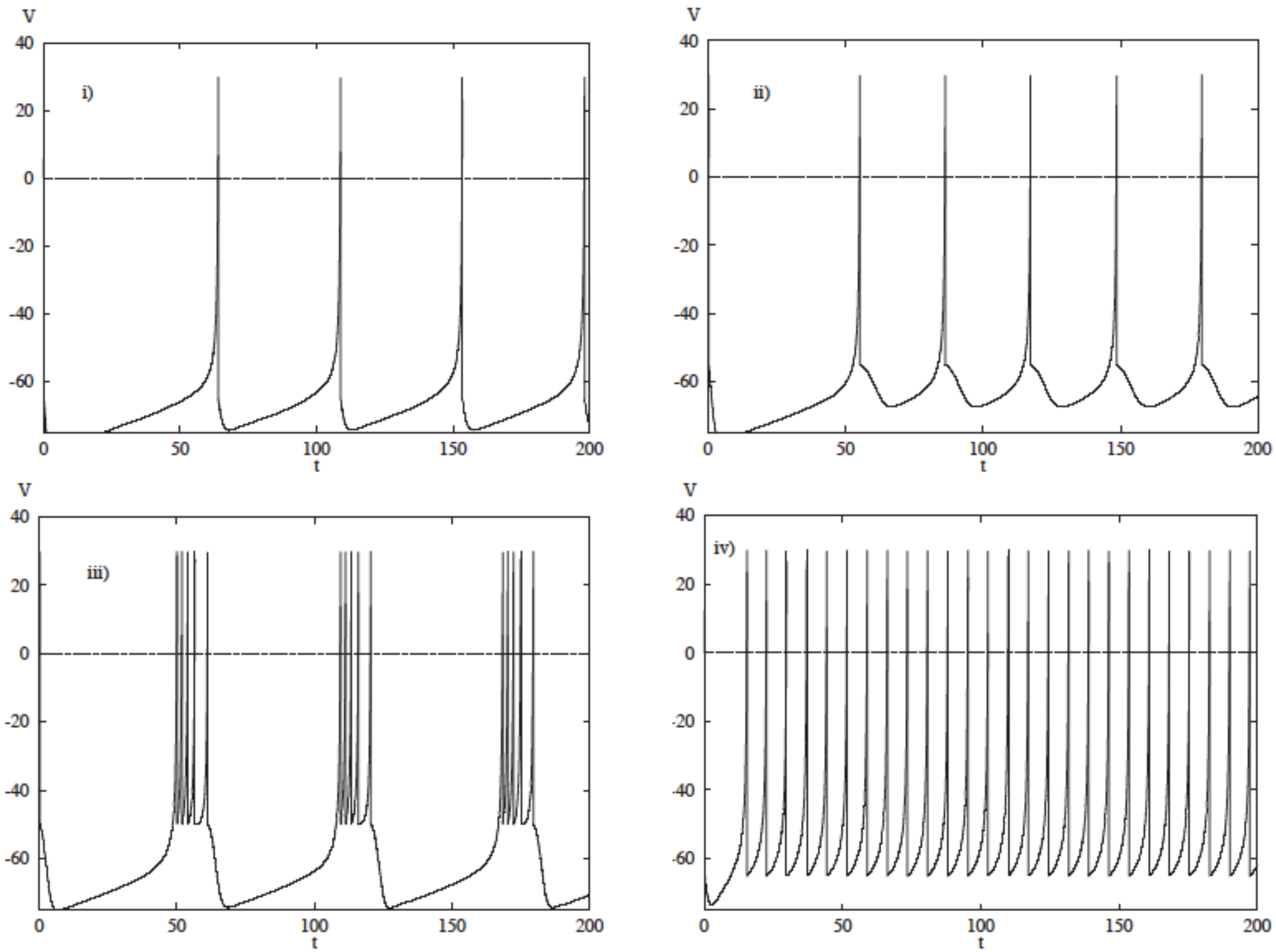




HH code

- Please download HH.m and allied codes from folder on our website
- Run with different choices of input current
- How does this change the kind of spiking that you see?

Ion channel types, what are they good for?

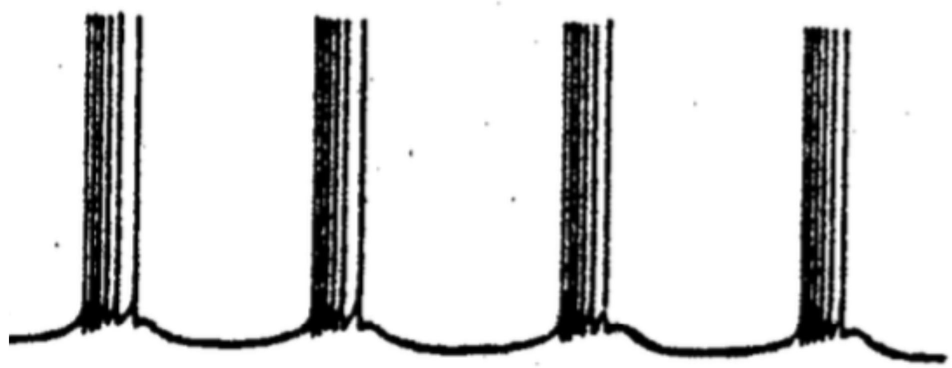


DOI: 10.1016/j.physd.2011.05.012

1. Calcium processing can cause single neurons to autonomously produce rich dynamical behavior (much discovered at UW):

Tritonia “bursting pacemaker” cells, Stephen Smith thesis ‘77

Mechanism: Ca-gated K current (I_K,Ca):



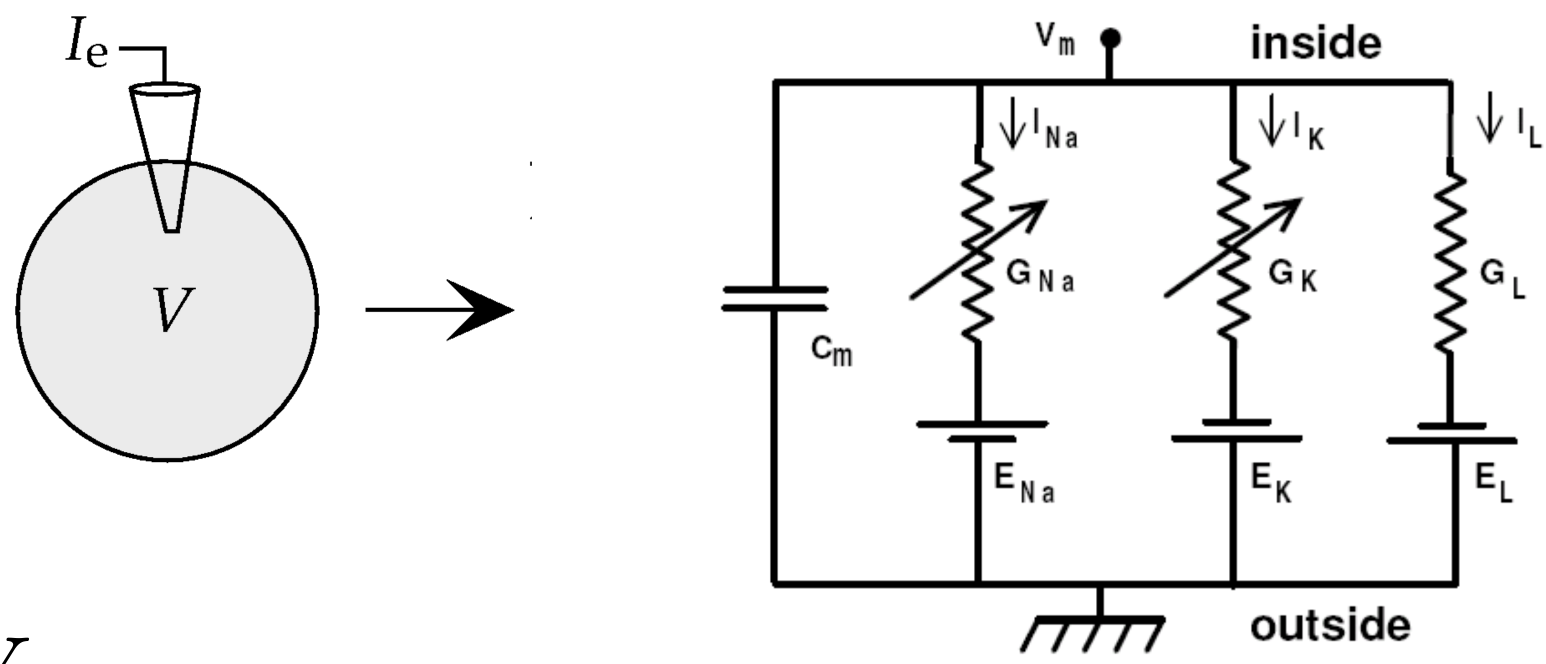
GOAL : MODEL THIS BURSTING PROCESS

When neuron spikes, Ca flows into cell

This opens Ca-gated K channels

… which increases K conductance, switching off a burst

Modeling Ca dynamics:



$$C\frac{dV}{dt} = \sum_j g_j(t)(E_j - V) + I_e(t)$$

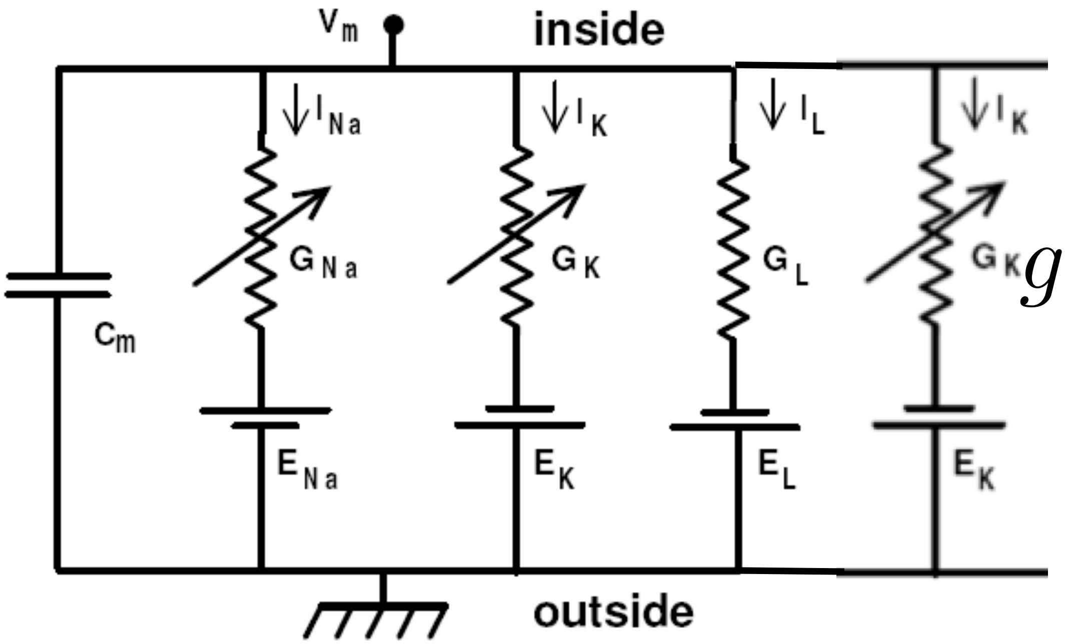
Voltage-gated conductances
("standard" HH:)

$$\frac{dg_j}{dt} = F_j(g_j, V)$$

Calcium-dependent conductances
(Smith, Connor/Stevens, ...)

$$\frac{dg_j}{dt} = F_j(g_j, Ca)$$

Model I_K,Ca as added current in HH equation.

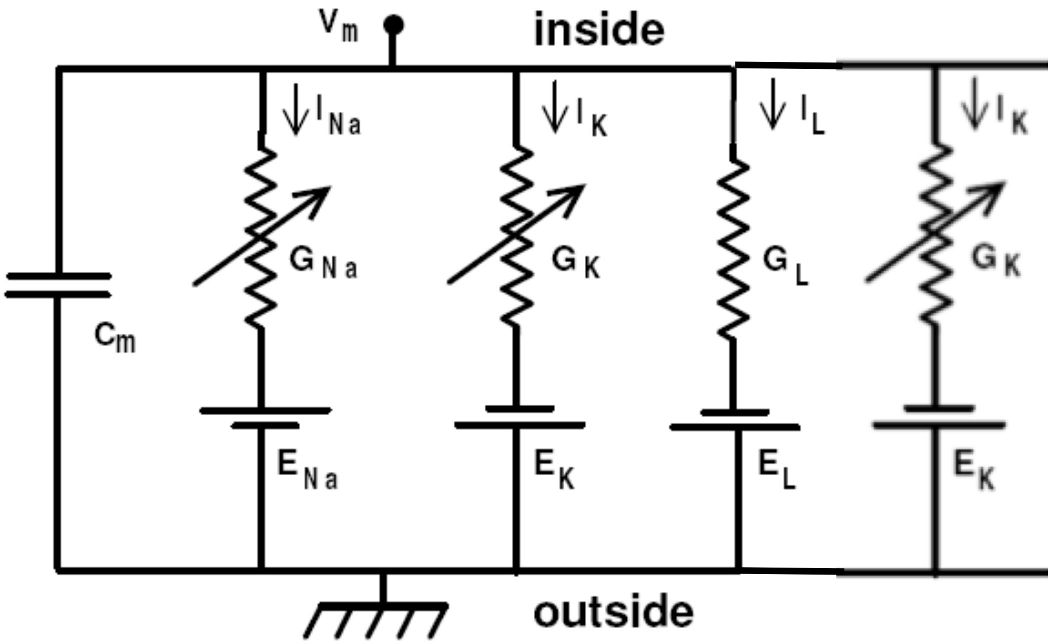


$g_{K,Ca}(t)$

$$C\frac{dV}{dt} = ... + g_{K,Ca}(t)(E_K - V)$$

$$... = \text{standard HH terms}$$

Warmup lab exercise: add constant K conductance



$g_{K,extra}$

$$C\frac{dV}{dt} = ... + g_{K,extra}(E_K - V)$$

$$... = \text{standard HH terms}$$

Warmup Lab exercise.

Start with HH.m code from website.
Set I=16.35; %baseline current well into periodic spiking regime
Adjust initial conditions (typical values with this I)
v_init=-65; %the initial conditions
m_init=.052;
h_init=.596;
n_init=.317;

Add constant conductance gK,extra. Thus, you should be simulating

$$C\frac{dV}{dt} = \ldots + g_{K,extra}(E_K - V)$$

How large does gK,extra need to be to terminate periodic spiking?

Warmup Lab exercise.

Start with HH.m code from website.
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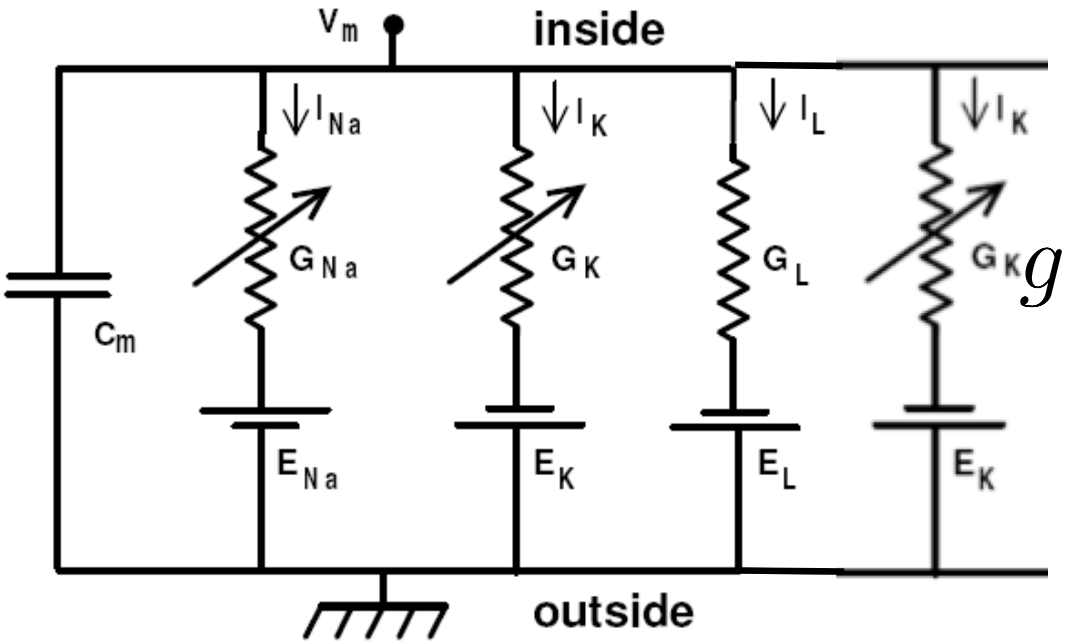
Add constant conductance gK,extra. Thus, you should be simulating

$$C\frac{dV}{dt} = \ldots + g_{K,extra}(E_K - V)$$

How large does gK,extra need to be to terminate periodic spiking?

Solution code: HH_increase_constant_gK_terminate_spiking.m

Model I_K,Ca as added current in HH equation.



$g_{K,Ca}(t)$

$$C\frac{dV}{dt} = ... + g_{K,Ca}(t)(E_K - V)$$

$$... = \text{standard HH terms}$$

Blackboard: discussion of how we do this!
Step through HW problem pdf

Quick lab exercise:

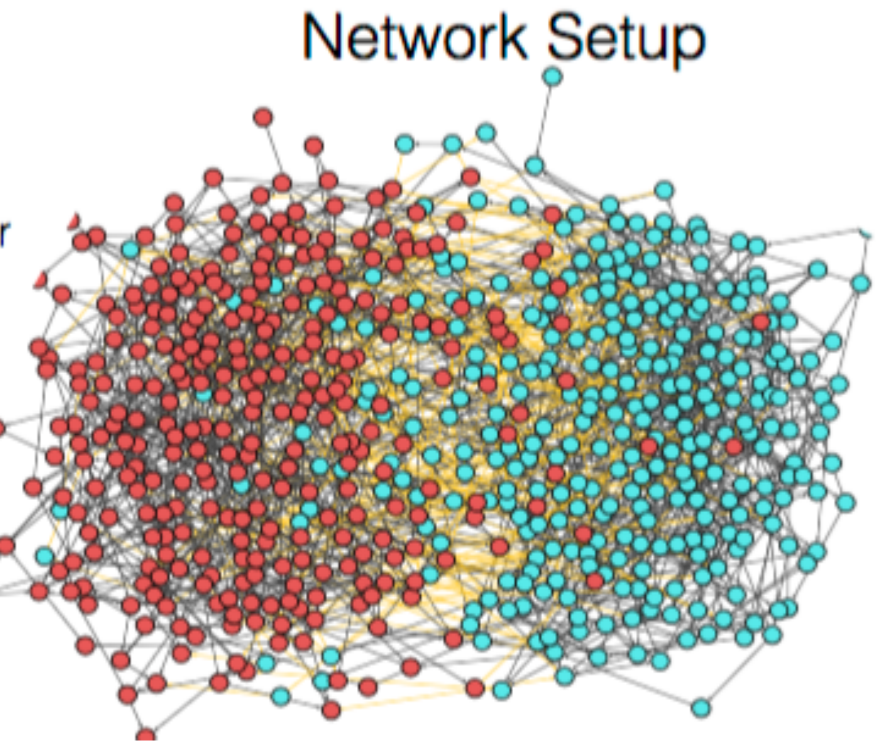
Download HH_burst_via_gK_Ca_conductance.m from our website

Explain to your neighbor, line by line, how the gK_Ca conductance is implemented

See if you can find parameters that implement a burst.

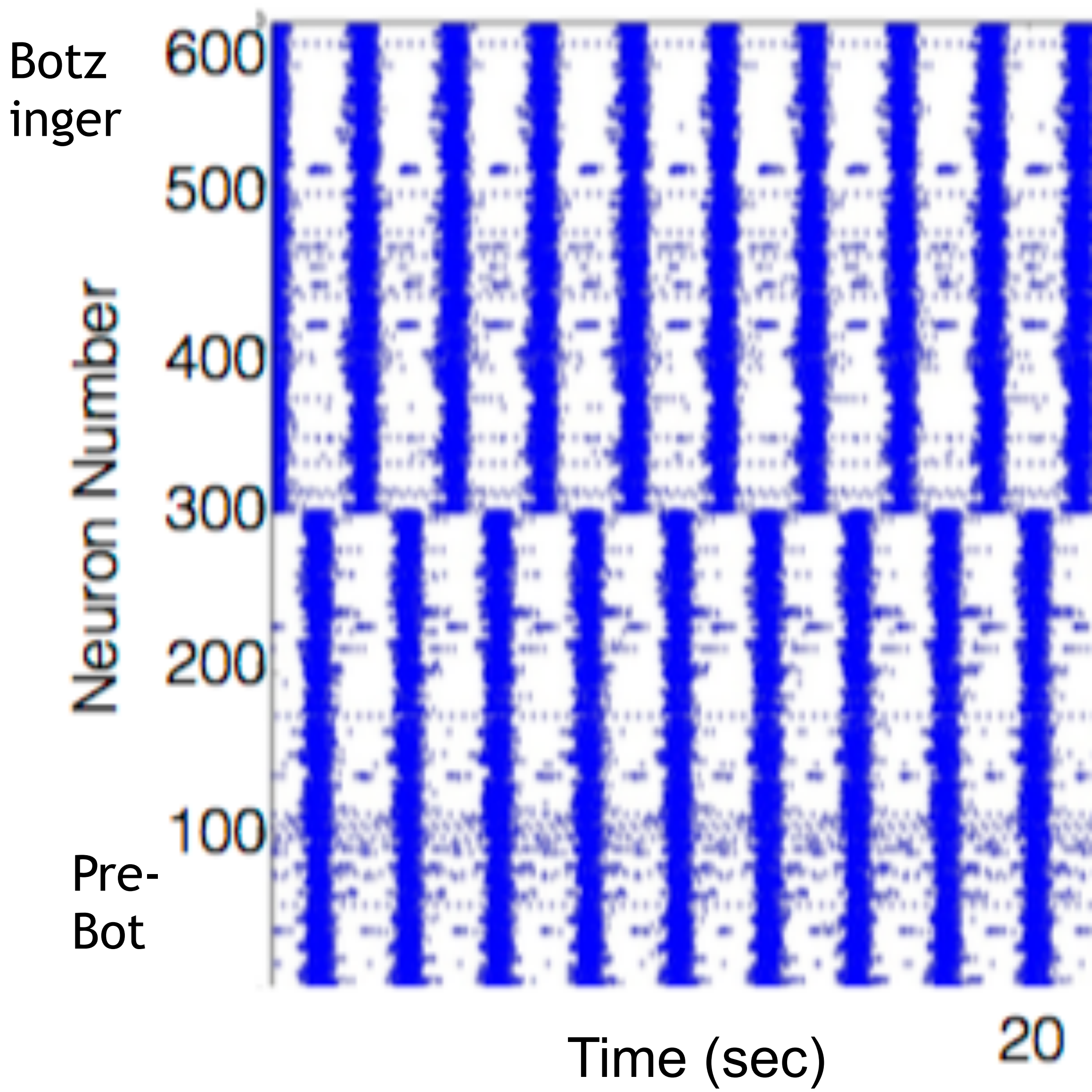
Who cares about bursting?

Bursting rhythms drive breathing:



otzinger complex
xpiration)

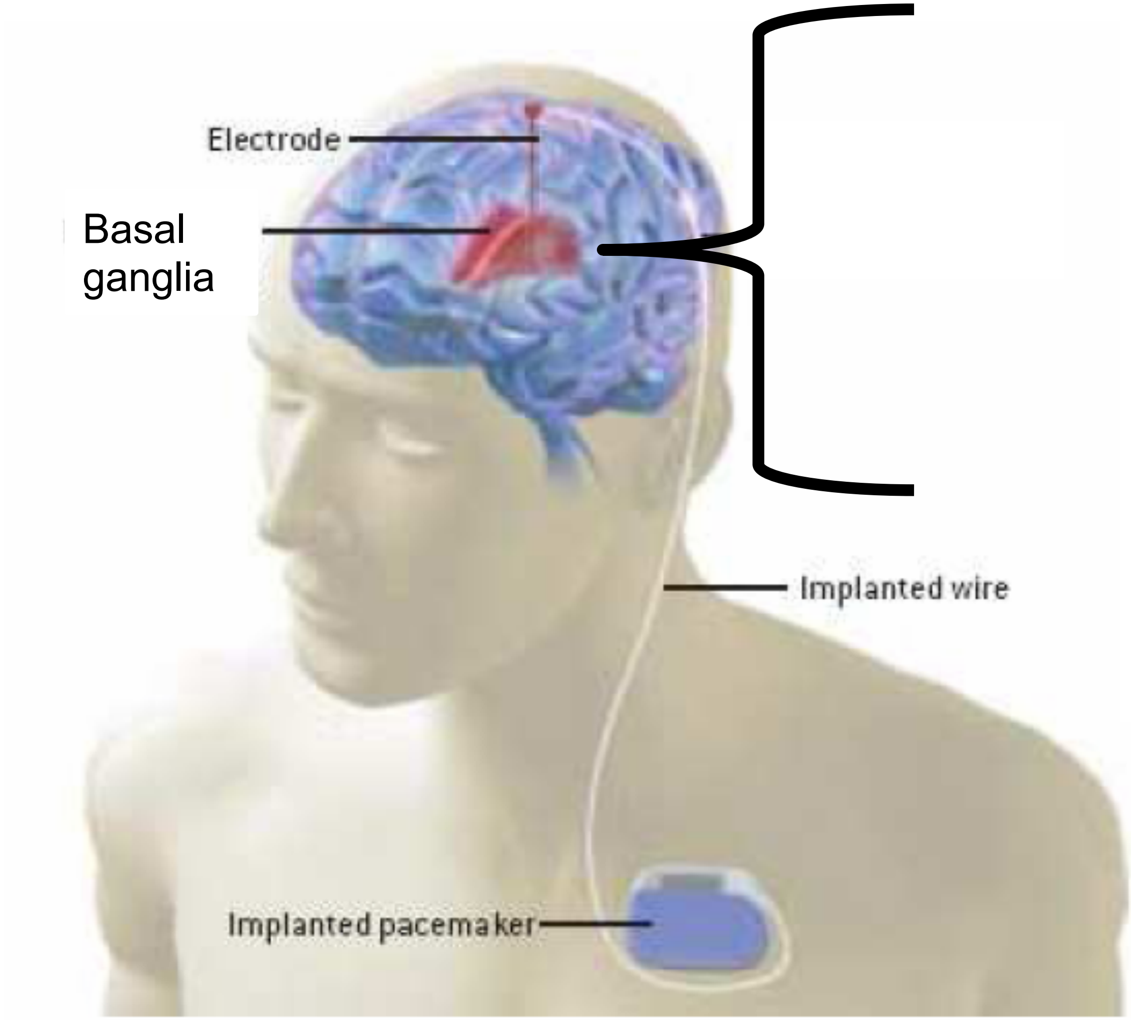
Pre-Botzinger
complex
(inspration)

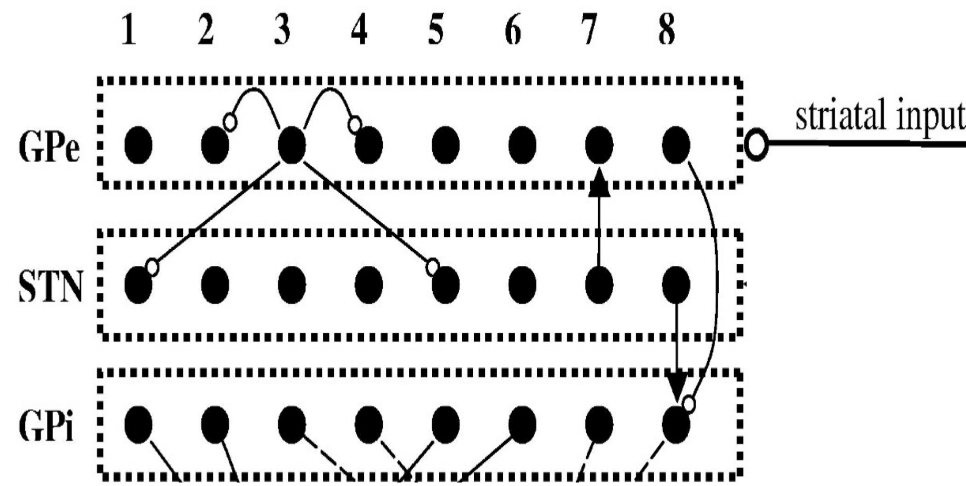


J. Mendoza, UW Hon.Thesis ‘15

Who cares about bursting?

Anomalous bursting rhythms drive Parkinsonian Rhythms:





Network model: Terman, Rubin et al., `02, `04

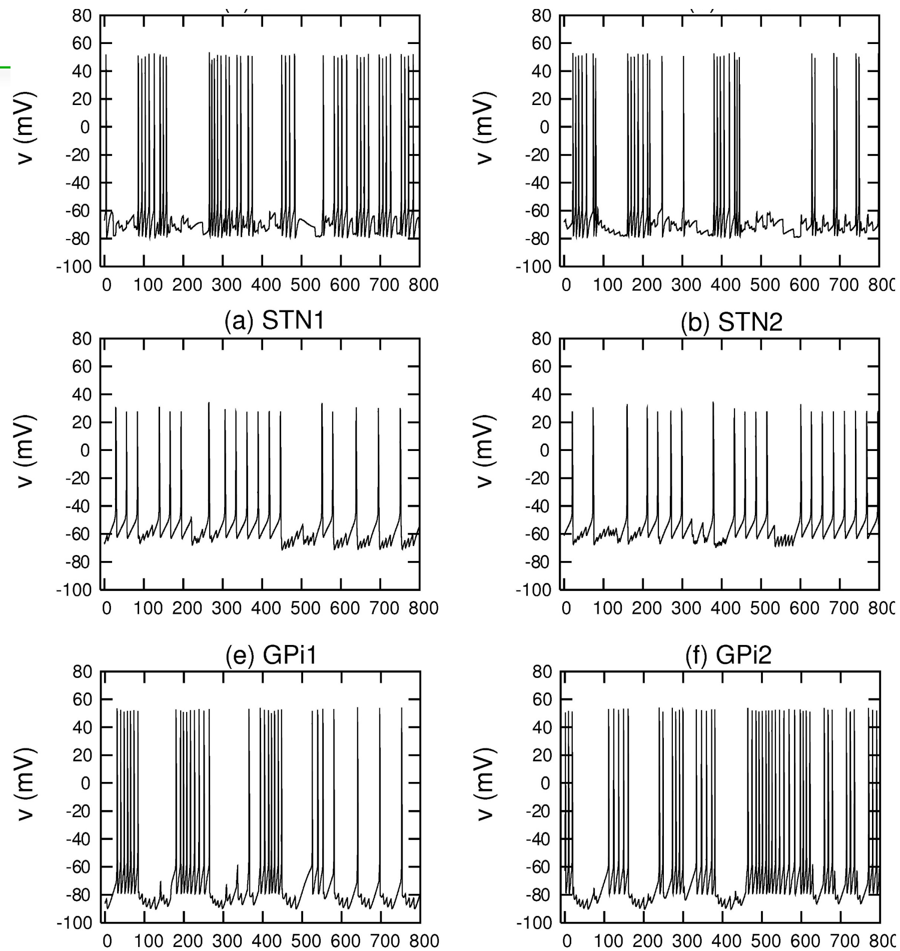
G. Lajoie, UW PhD Thesis '13

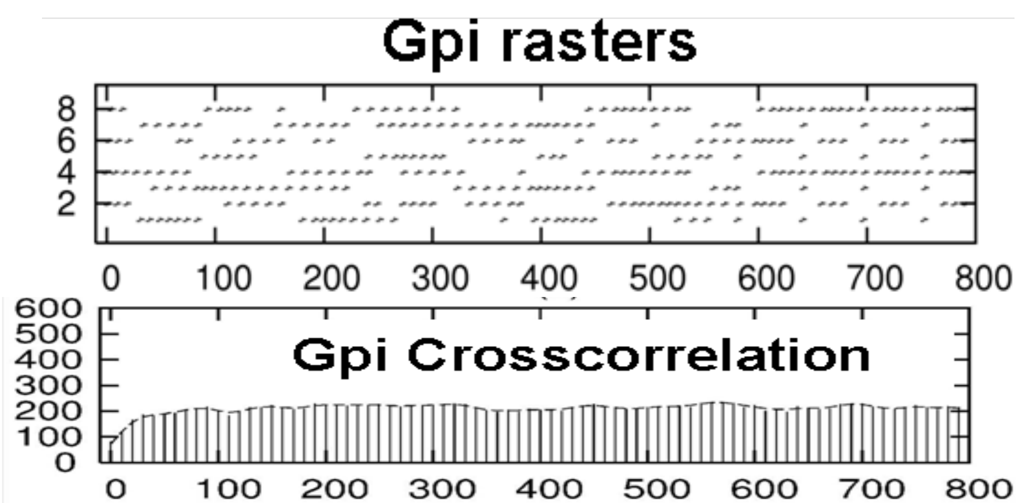
Normal state

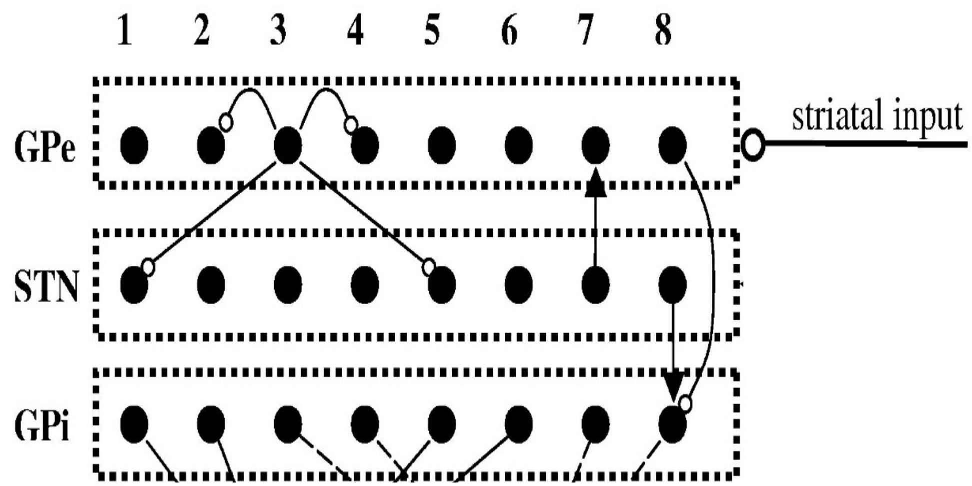
Gpe

STN

Gpi







Network model: Terman, Rubin et al., `02, `04

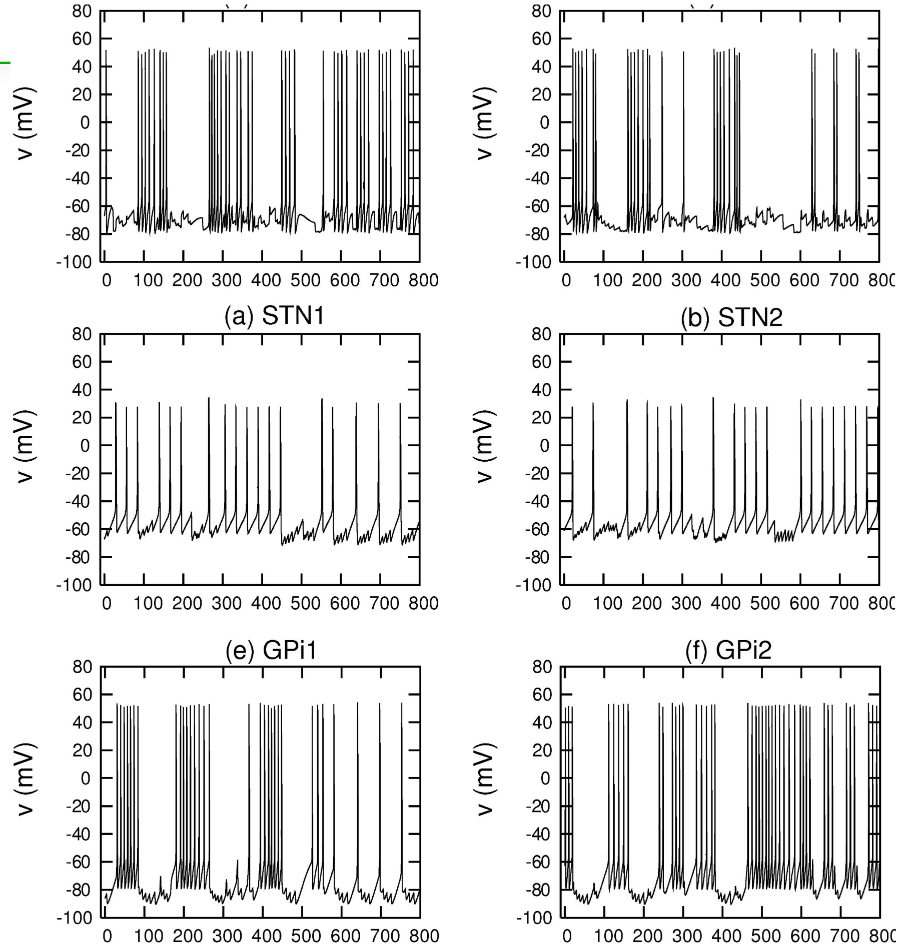
Normal state

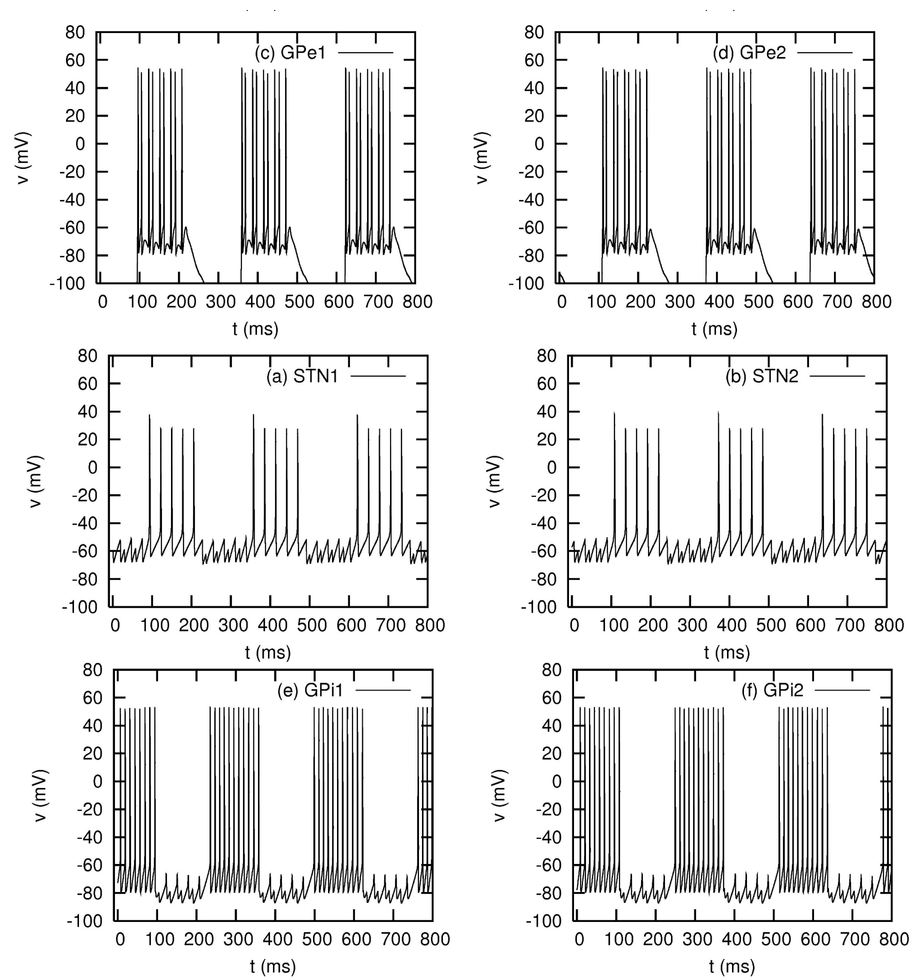
Parkinsonian state

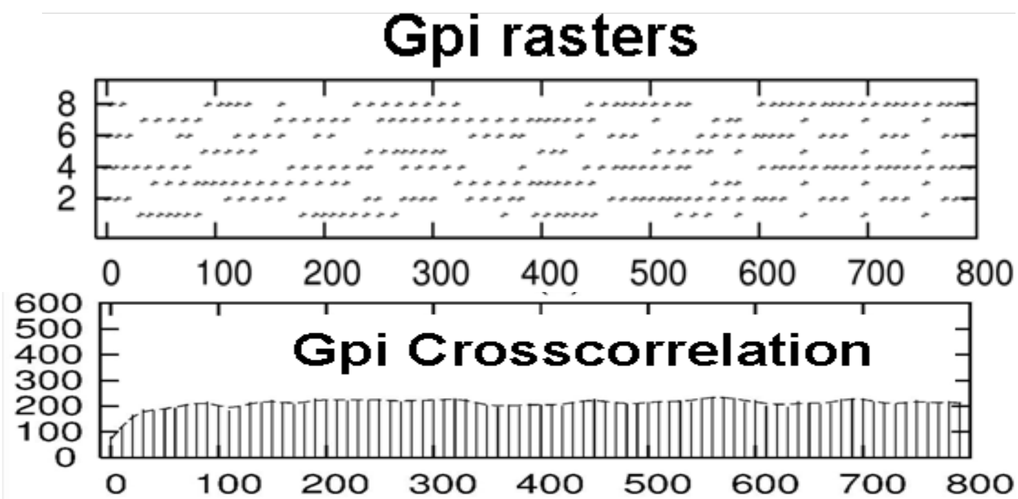
Gpe

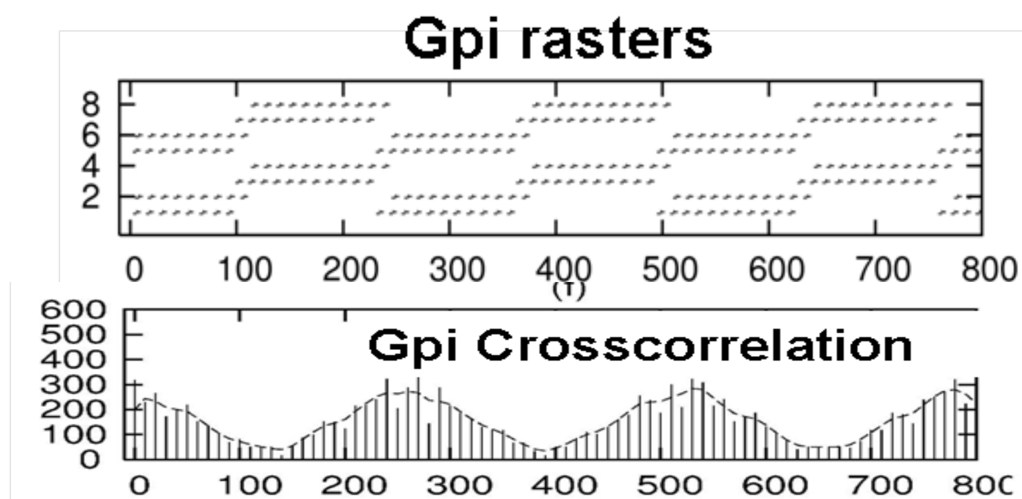
STN

Gpi









HUGE NEURAL DYNAMICS QUESTION:

Our brains have a zoo of ion channels:

g_{Na}, g_K, $g_{K,Ca}$, g_L, and … 100's more!

The conductance of each determines normal vs. pathological dynamics

(i.e., burst or not)

What is the strategy for "programming" a functioning brain?

Option 1: rigidly set all of these parameters.

(Questionable: enough space in genome?)

Consequence: expect similar conductances in different "normal" individuals.

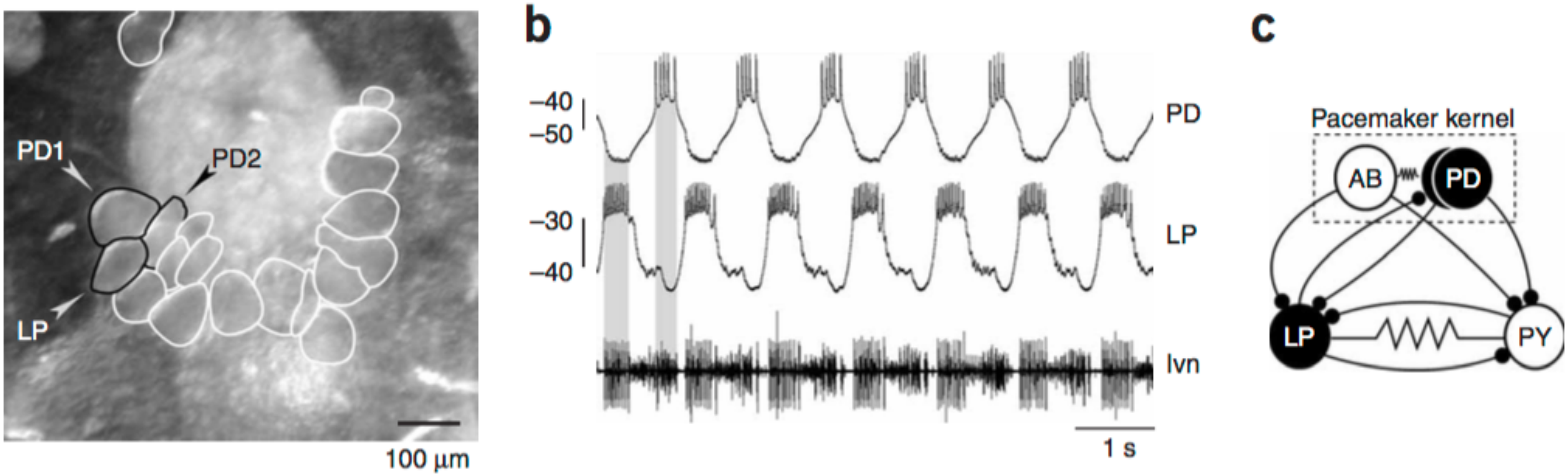
Eve Marder Lab: THAT'S DEFINITELY NOT WHAT HAPPENS!

Variable channel expression in identified single and electrically coupled neurons in different animals

David J Schulz[1,2], Jean-Marc Goaillard[1] & Eve Marder[1]

nature neuroscience

Isolate neurons from different animals with *similarly functioning* pyloric rhythm generation circuits

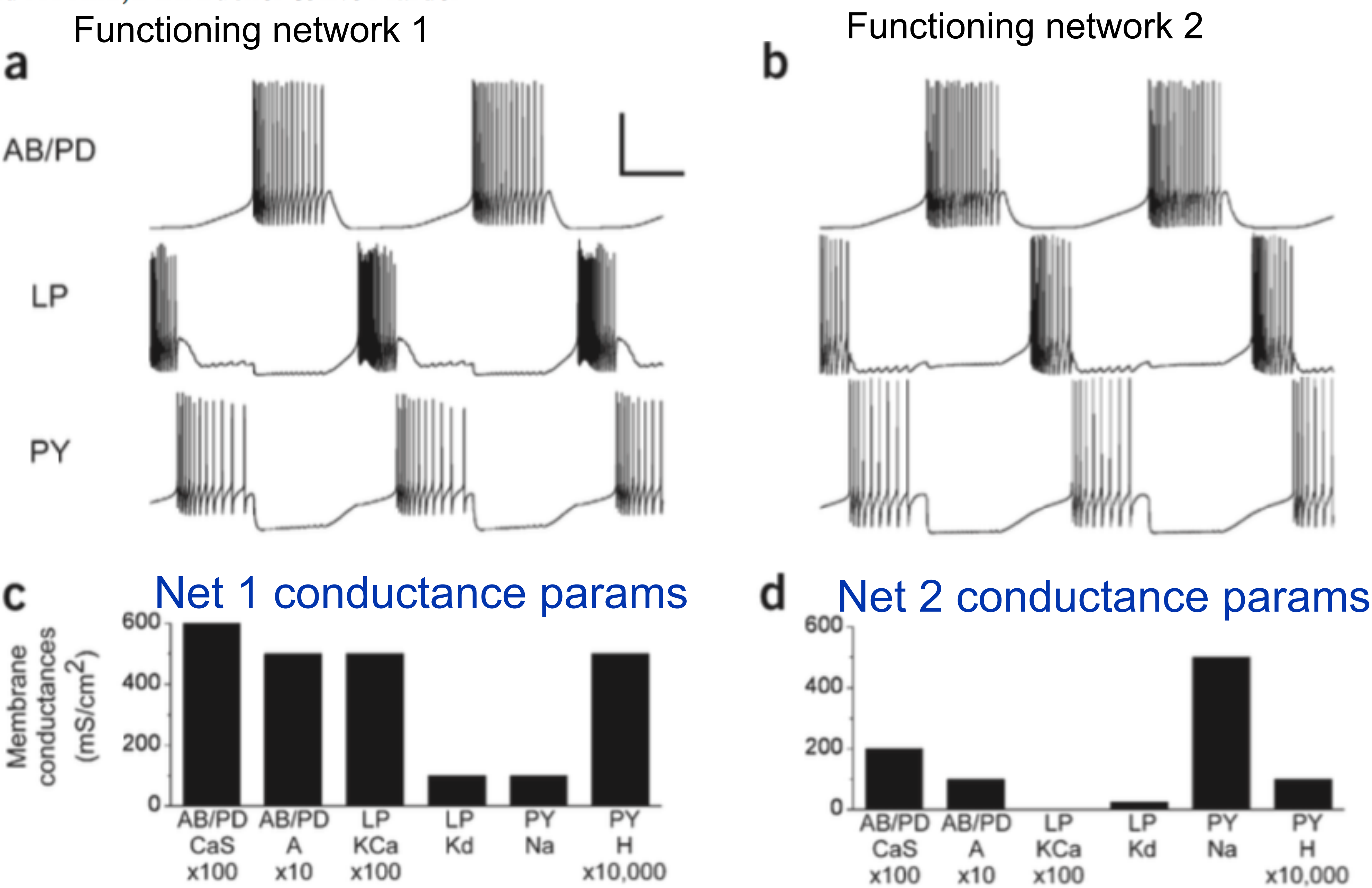


"See: Two-to-four-fold inter-animal variability for 3 K currents and their mRNA expression"

Similar network activity from disparate circuit parameters

Same idea, but use computation to do 20 million experiments (!!!!!)

Astrid A Prinz, Dirk Bucher & Eve Marder



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(i.e., burst or not)

What is the strategy for "programming" a functioning brain?

Option 1: rigidly set all of these parameters.

Consequence: expect similar conductances in different "normal" individuals.

Option 2: brain must have control mechanisms that steer parameters into "functional" regimes. "Homeostasis."

Questions: What are useful "sensors"? (Ca!)

What are useful parameter adjustments?

Homeostasis: dynamical theory

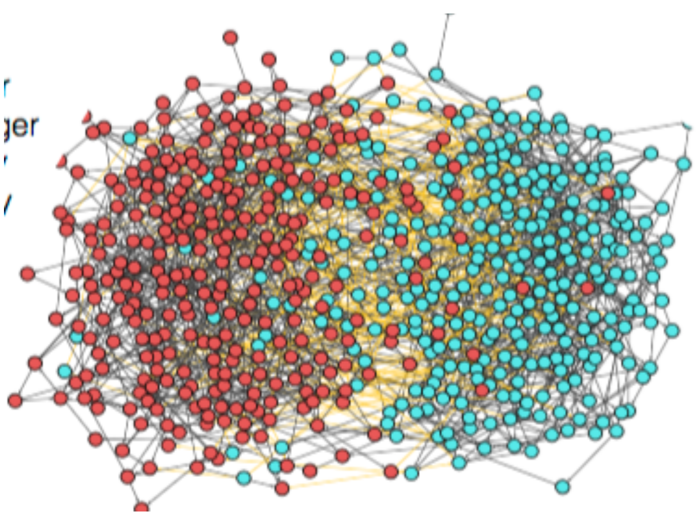
... At level of single neurons:

The Journal of Neuroscience, April 1, 1998, *18*(7):2309–2320

A Model Neuron with Activity-Dependent Conductances Regulated by Multiple Calcium Sensors

Zheng Liu, Jorge Golowasch, Eve Marder, and L. F. Abbott
Volen Center and Department of Biology, Brandeis University, Waltham, Massachusetts 02254

... At level of networks: extremely important, many open Q's



Marder, E. and Prinz, A.A. (2002) Modeling stability in neuron and network function: the role of activity in homeostasis. *BioEssays*, 24:1145-1154

Interlude

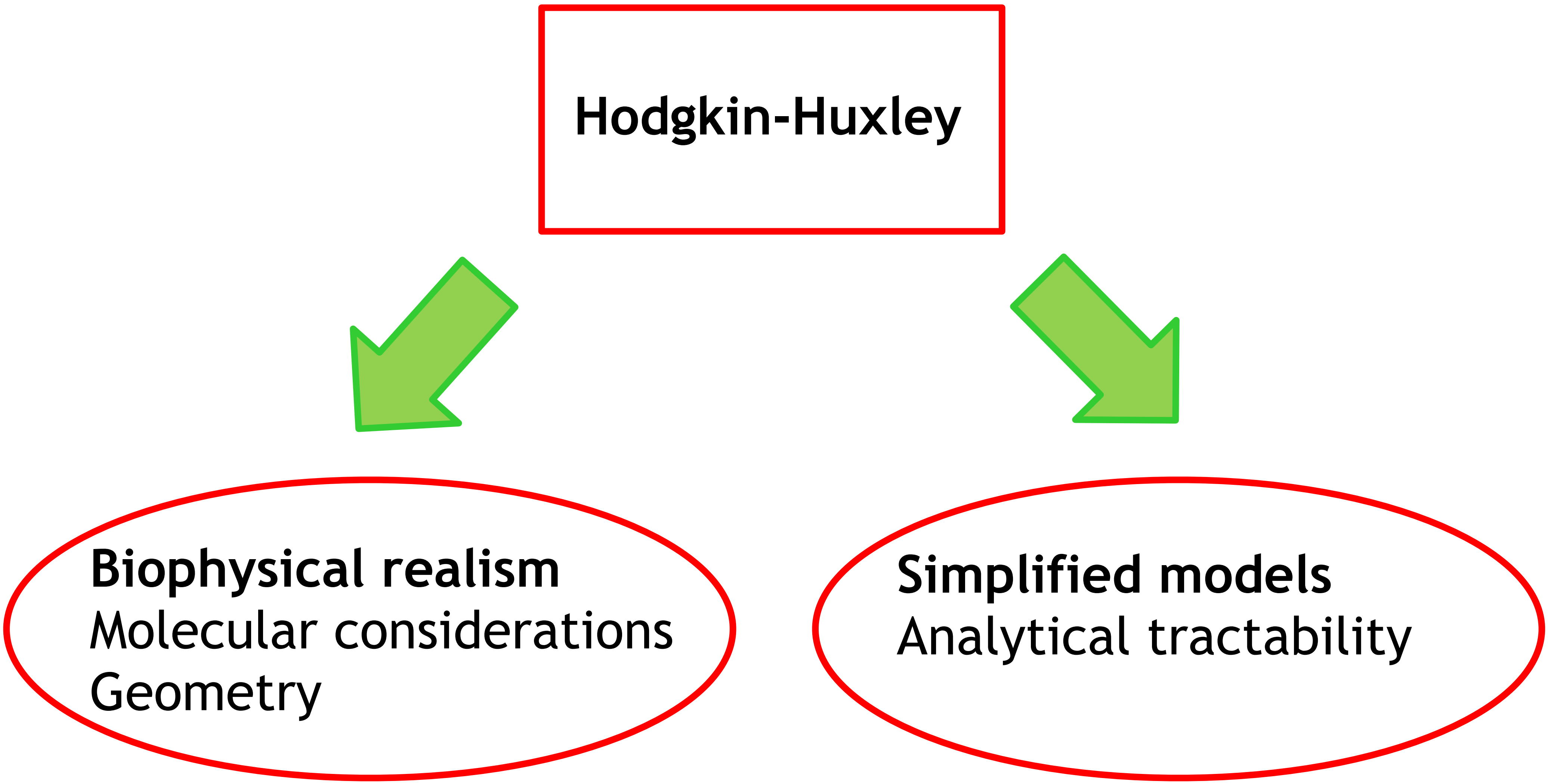
BUILDING A THEORY …

WAY 1: full-scale simulations, clever "data" analysis, insights

WAY 2: simplified spiking models and simplified ion channels, analytical solutions, insights

Certainly need both! Here's a glimpse at WAY 2:

Where to from here?



The integrate-and-fire neuron

Like a passive membrane:

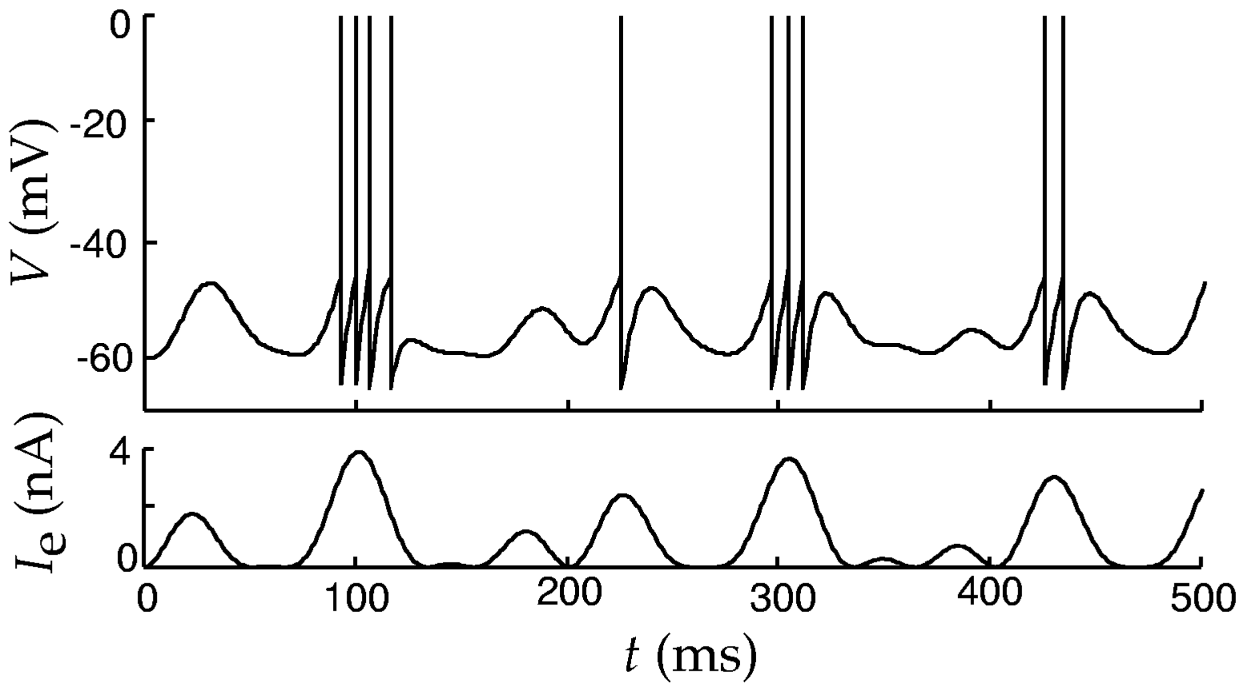
$$C_m \frac{dV}{dt} = -g_L(V - E_i) - I_e$$

but with the additional rule that

when $V \rightarrow V_T$, a spike is fired

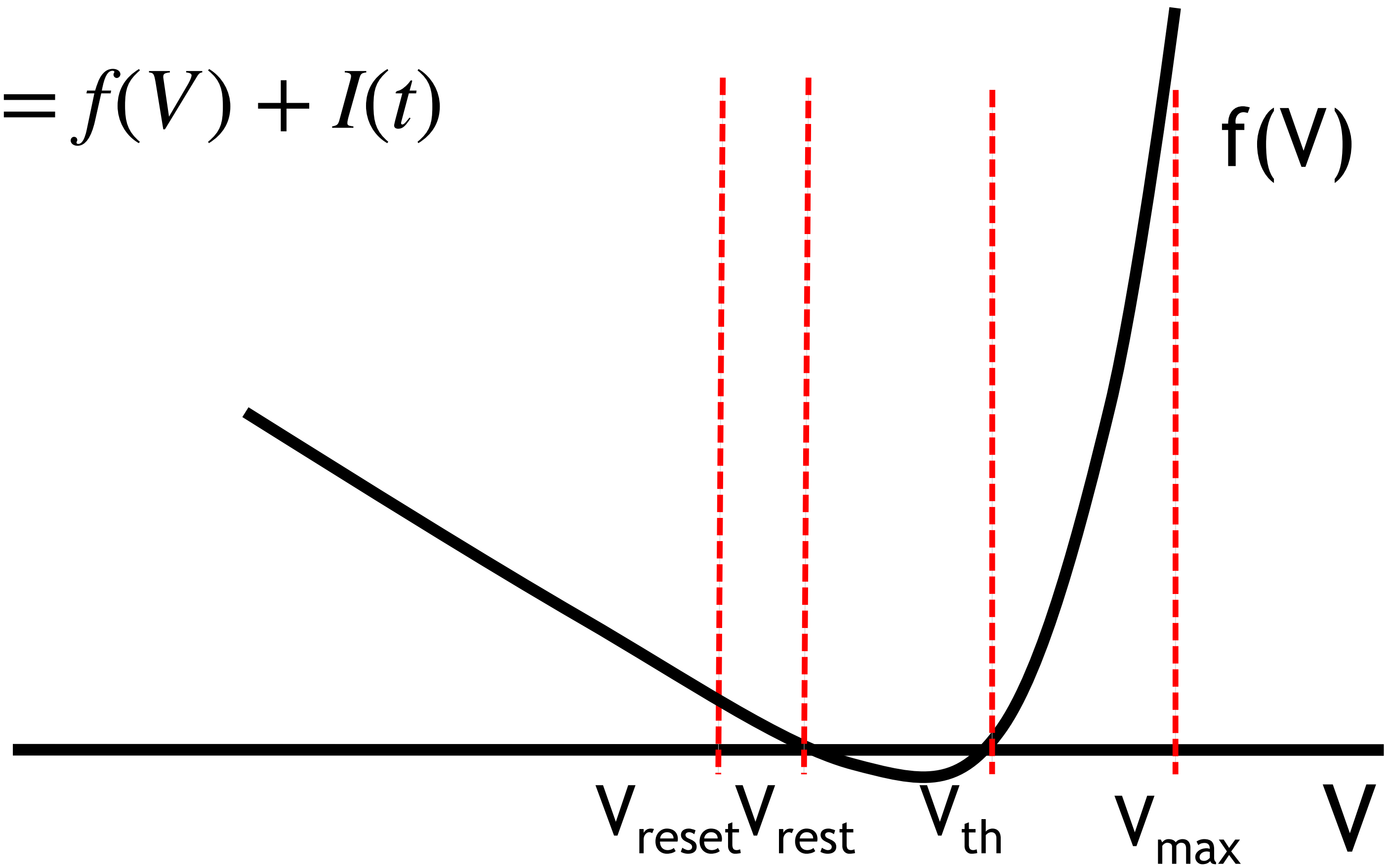
and $V \rightarrow V_{reset}$.

E_L is the resting potential of the "cell".



Exponential integrate-and-fire neuron

$$\frac{dV}{dt} = f(V) + I(t)$$



$$f(V) = -V + \exp([V-V_{th}]/\Delta)$$

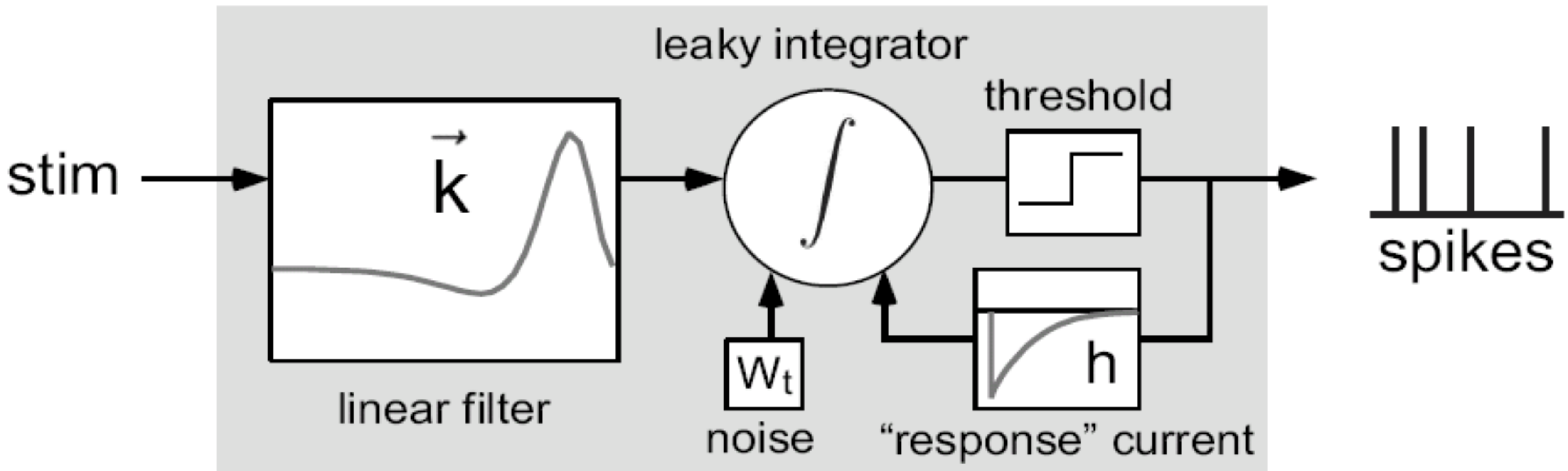
The spike response model

Function f for subthreshold response ← replaces leaky integrator
Function for spikes ← replaces "line"

- determine f from the linearized HH equations
- fit a threshold
- paste in the spike shape and AHP

Gerstner and Kistler

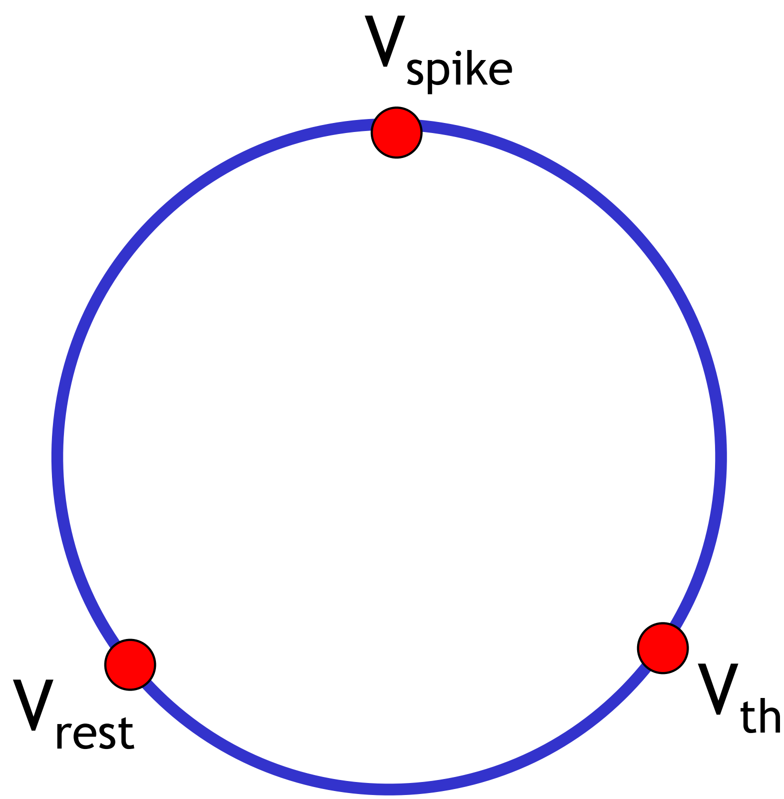
The generalized linear model



• general definitions for k and h
• robust maximum likelihood fitting procedure

Truccolo and Brown, Paninski, Pillow, Simoncelli

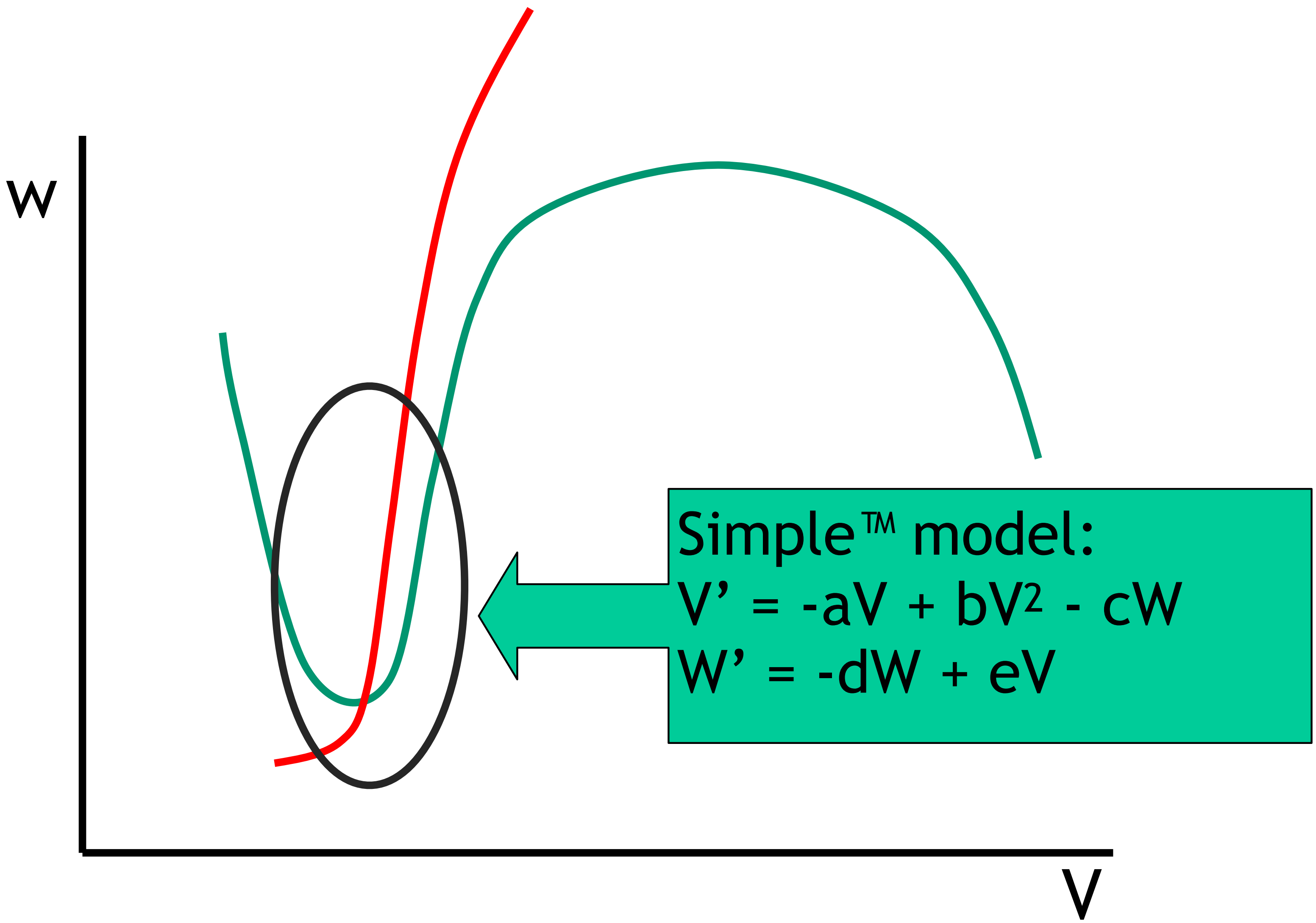
The theta neuron



$$d\theta/dt = 1 - \cos\theta + (1 + \cos\theta)\, I(t)$$

Ermentrout and Kopell

Two-dimensional models



Where to from here?

Hodgkin-Huxley

Biophysical realism
Molecular considerations
Geometry

Simplified models
Analytical tractability

neuron.yale.edu