Workshop Series Summer 2023

CAMBAM

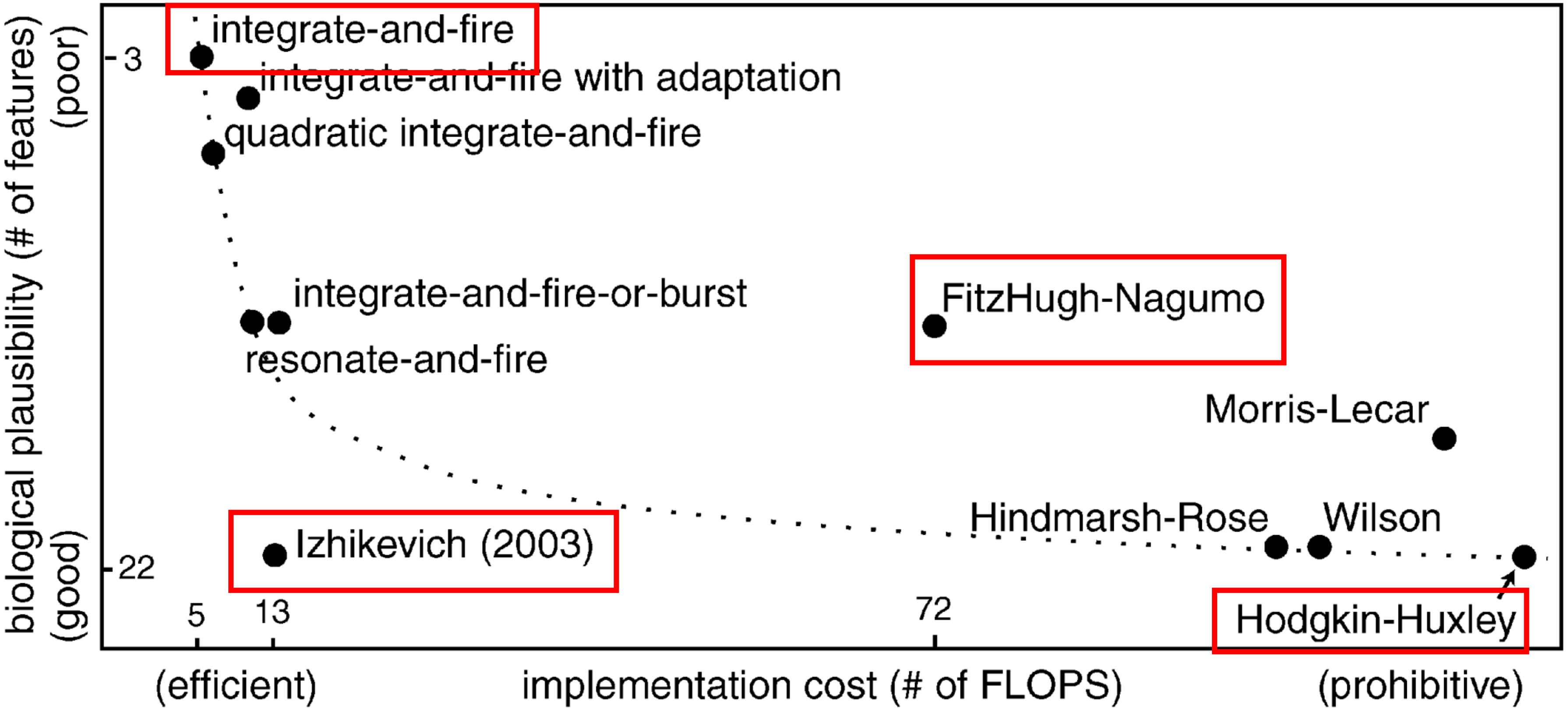
Centre for Applied Mathematics
in Bioscience and Medicine

June 16th, 2023

Exploring Single Neuron Excitability with Mathematical and Computational Models

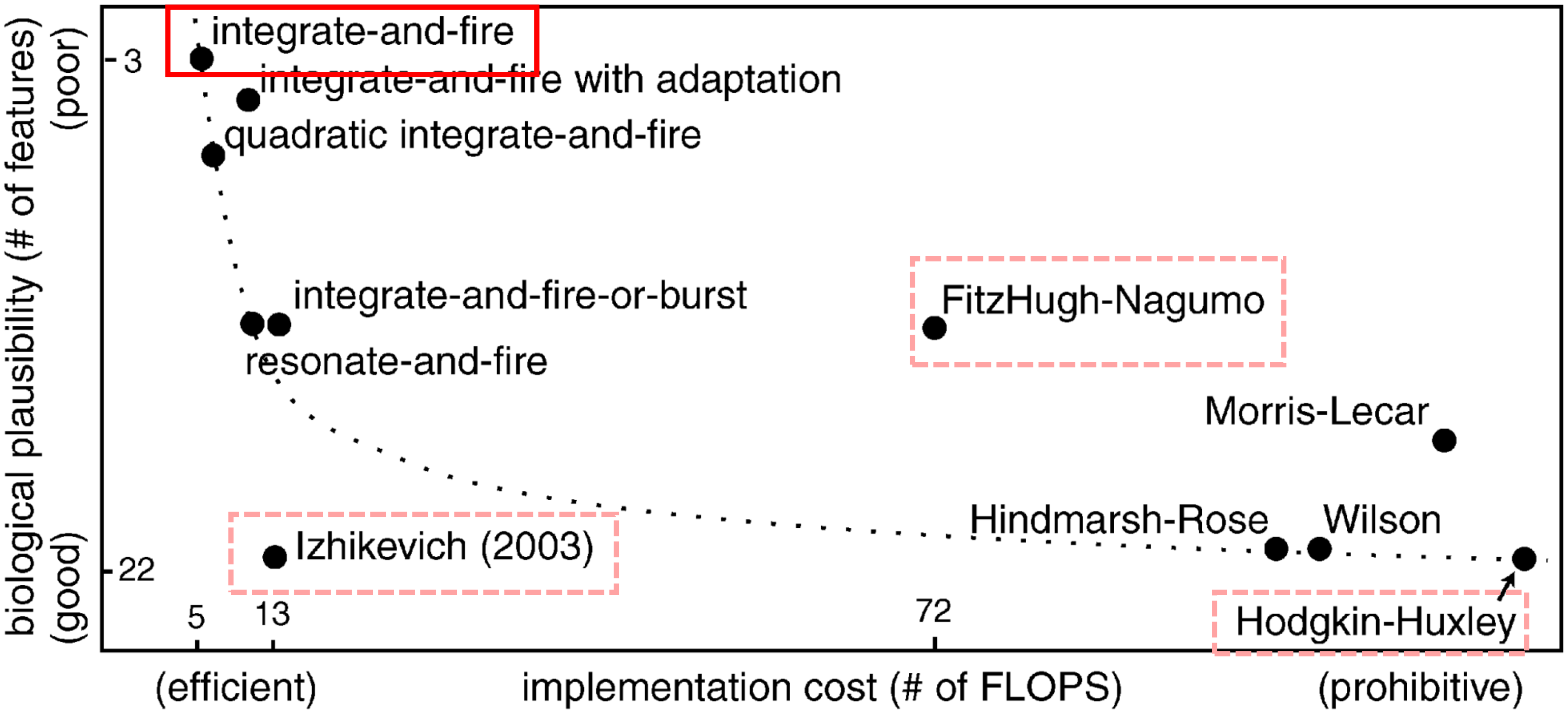
By Niklas Brake and Nils Koch

Models of neuronal excitability: integrate-and-fire



Izhikevich, *IEEE Transactions on Neural Networks* 2004

Models of neuronal excitability: integrate-and-fire



Izhikevich, *IEEE Transactions on Neural Networks* 2004

Models of neuronal excitability: integrate-and-fire

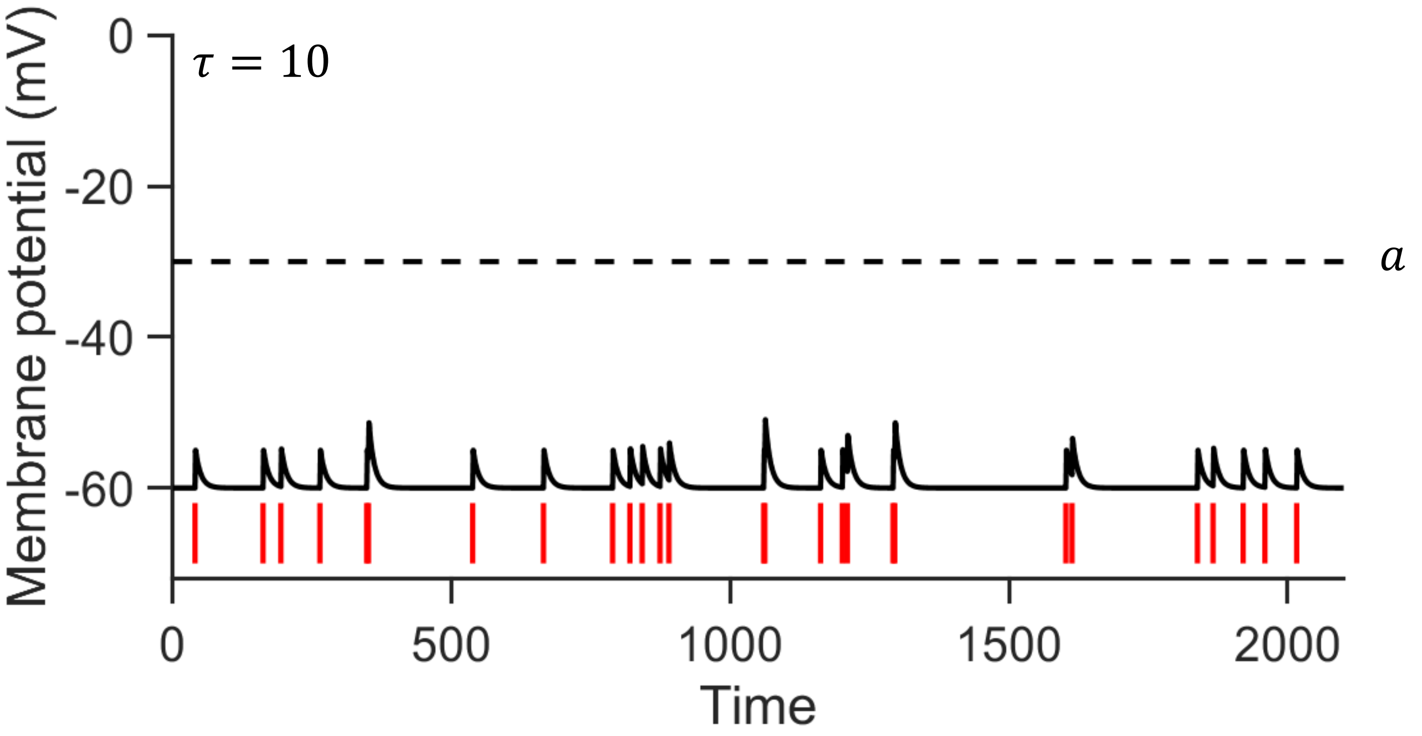
$$\frac{dV(t)}{dt} = \frac{V_0 - V(t)}{\tau} + I(t)$$

If $V(t) > a$**, then**

$\{$

$$V(t) \leftarrow V_0$$

$\}$



Models of neuronal excitability: integrate-and-fire

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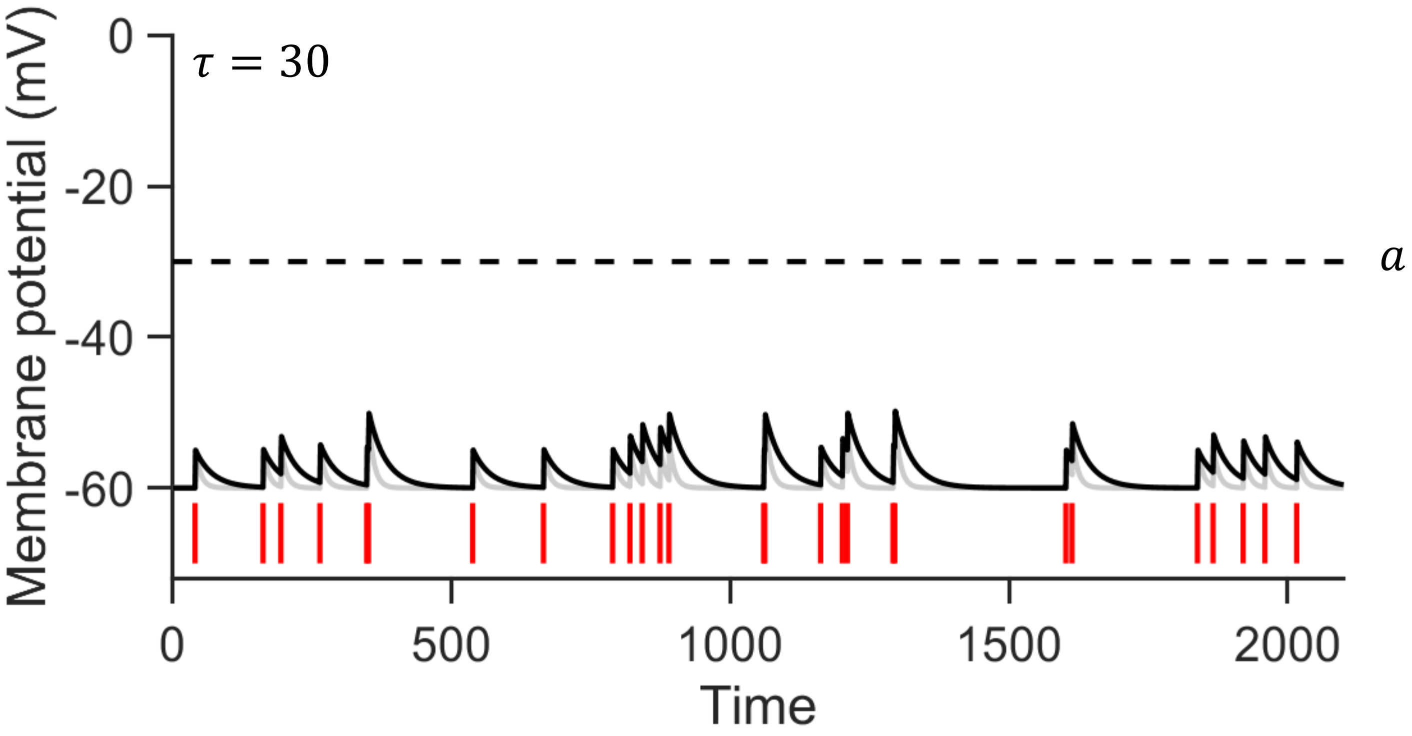

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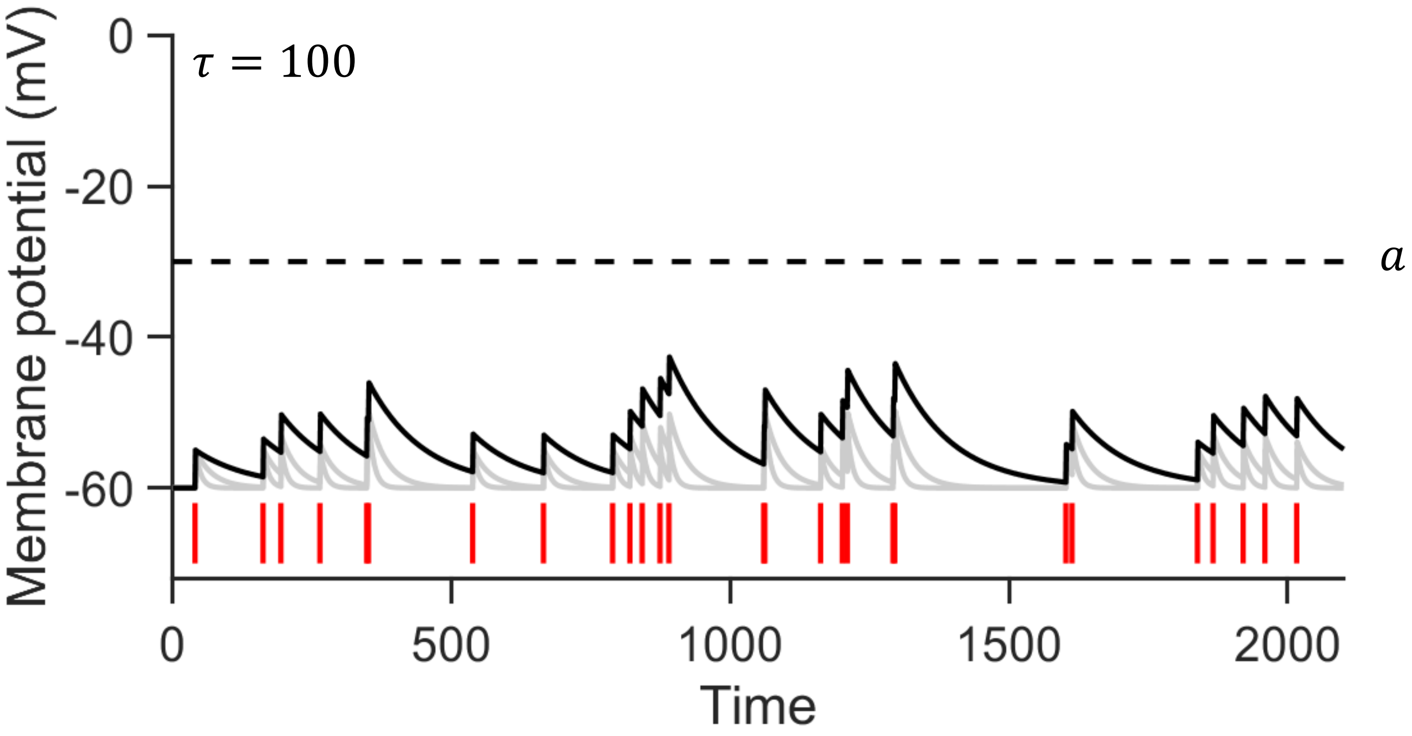

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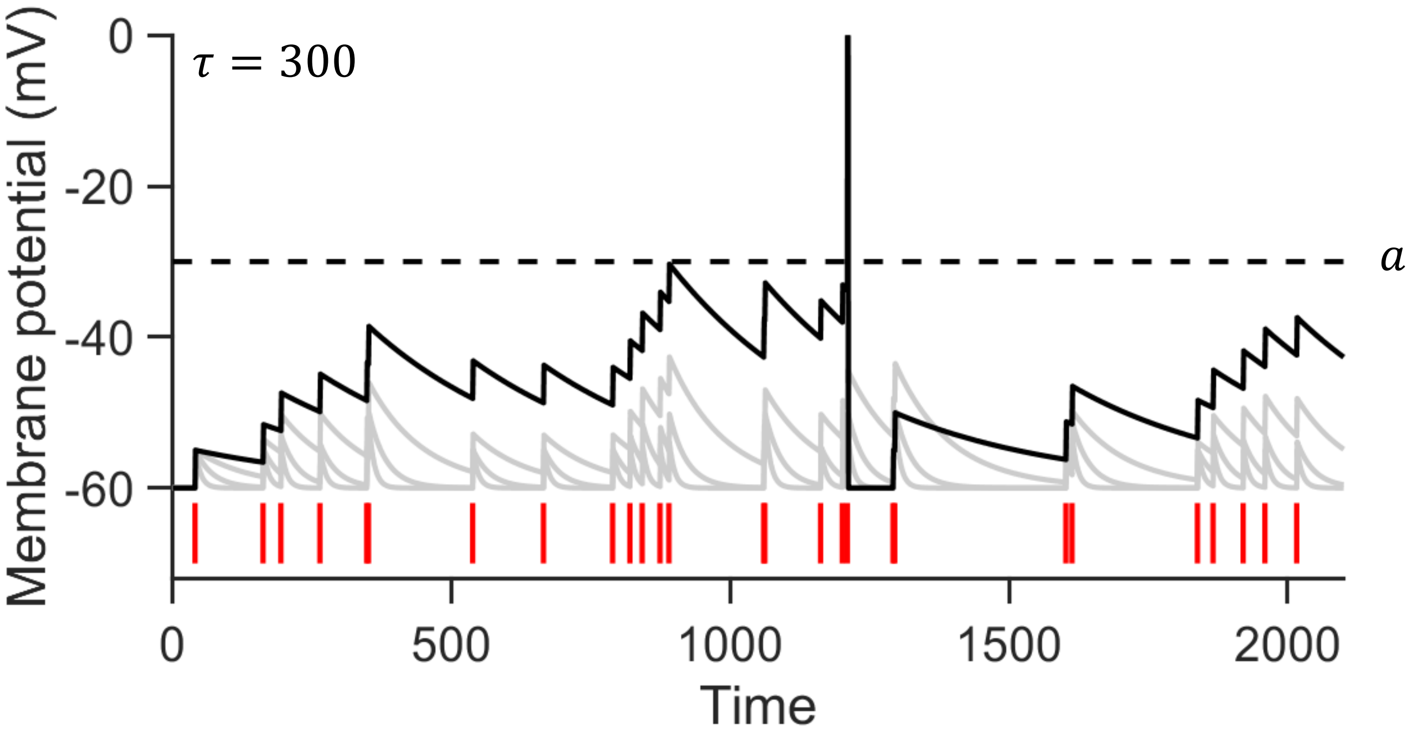

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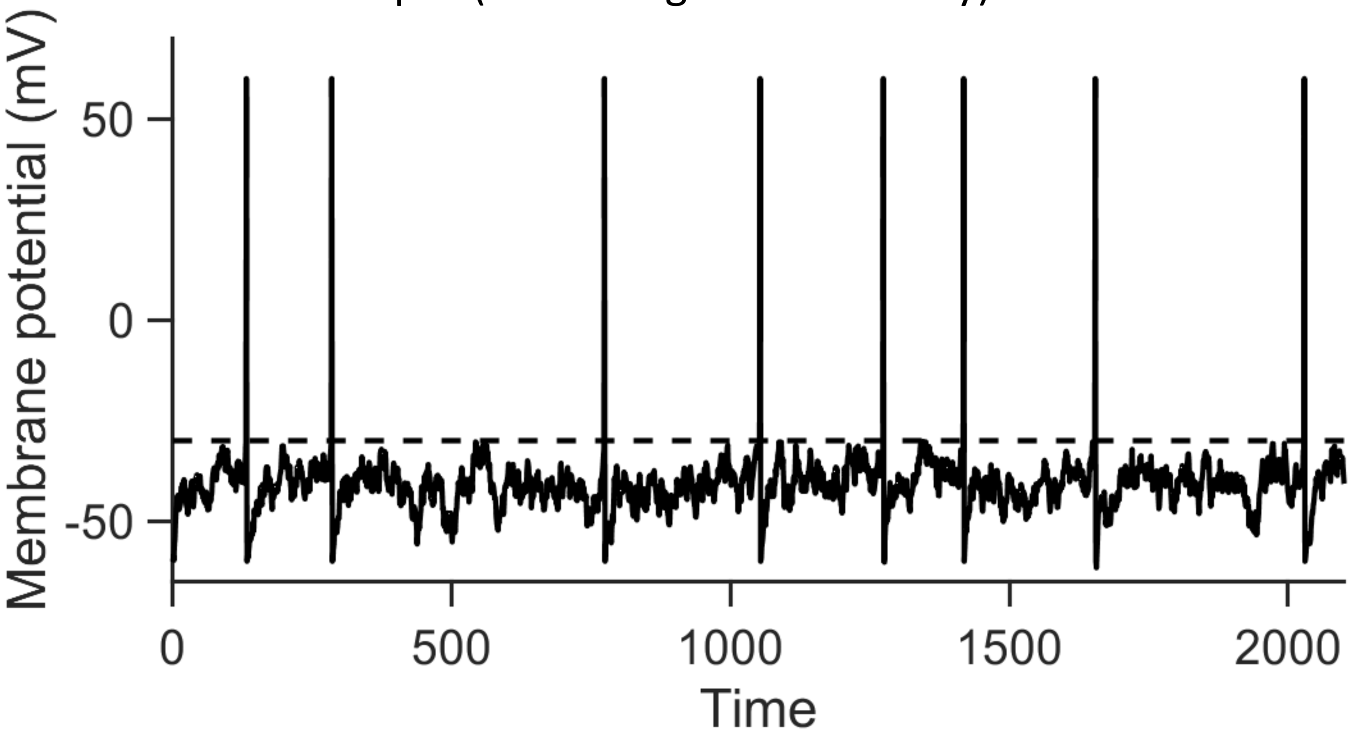
Gaussian input (simulating in vivo activity)



Models of neuronal excitability

Benefits of integrate-and-fire models

- Captures the fundamental computation of neurons
- Computationally cheap

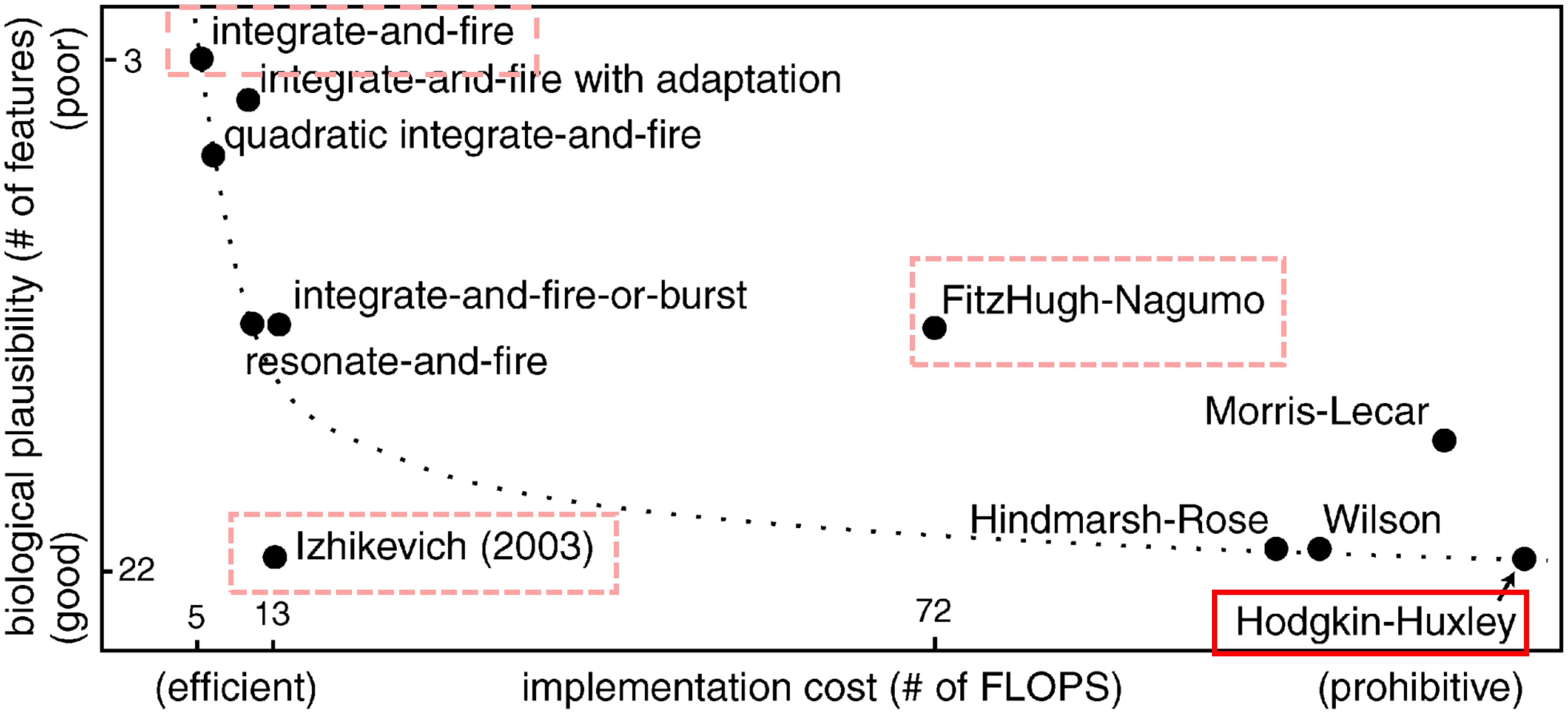
Drawbacks

- Spiking dynamics are oversimplified
- Not biophysically meaningful

Uses

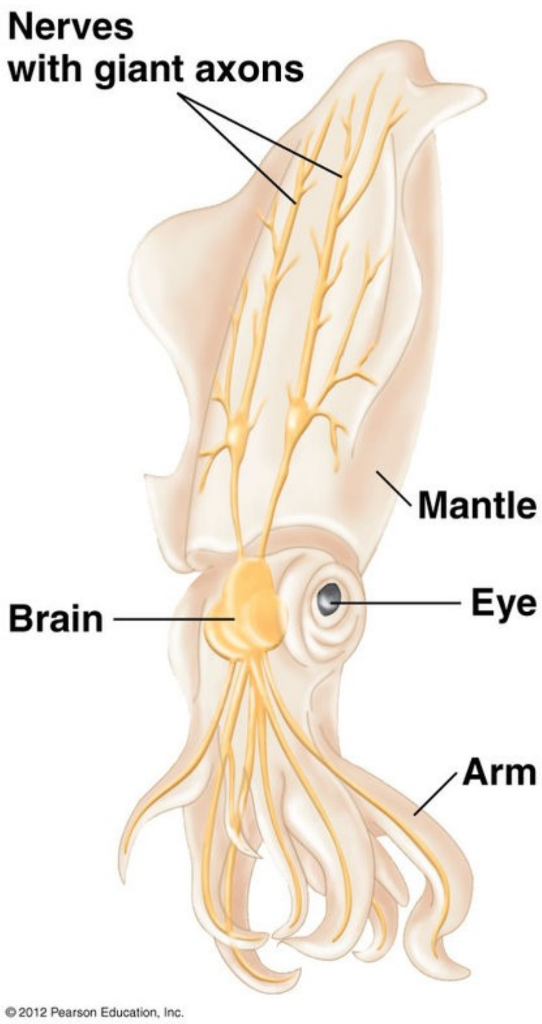
- Analytical results in mathematical neuroscience
- May be useful in large network simulations (especially when using related models, i.e. I-F with adaptation, quadratic I-F, etc.)

Models of neuronal excitability

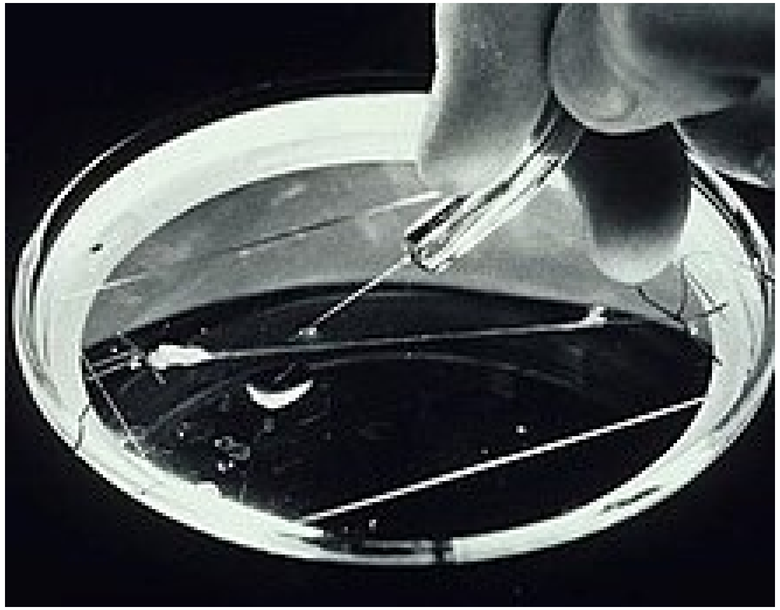


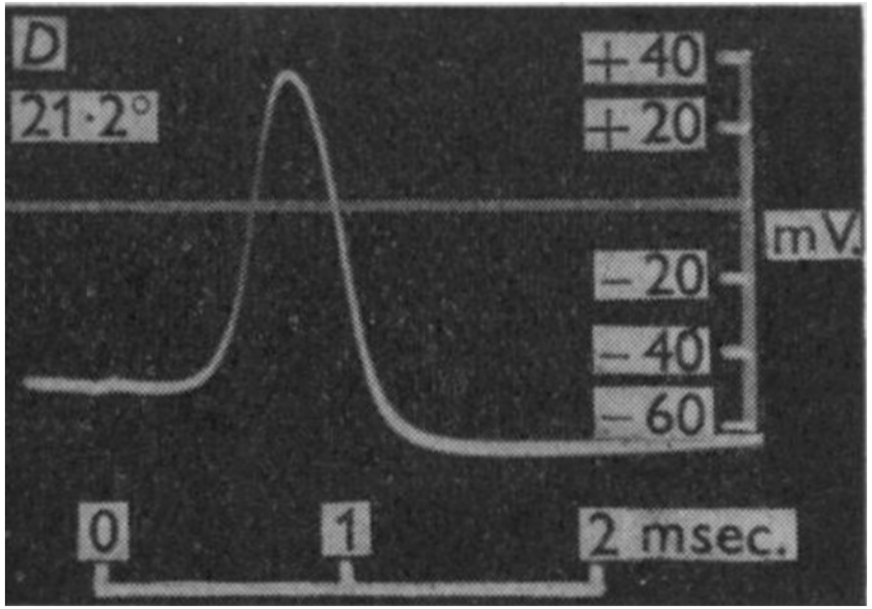
Izhikevich, *IEEE Transactions on Neural Networks* 2004

Models of neuronal excitability: Hodgkin-Huxley



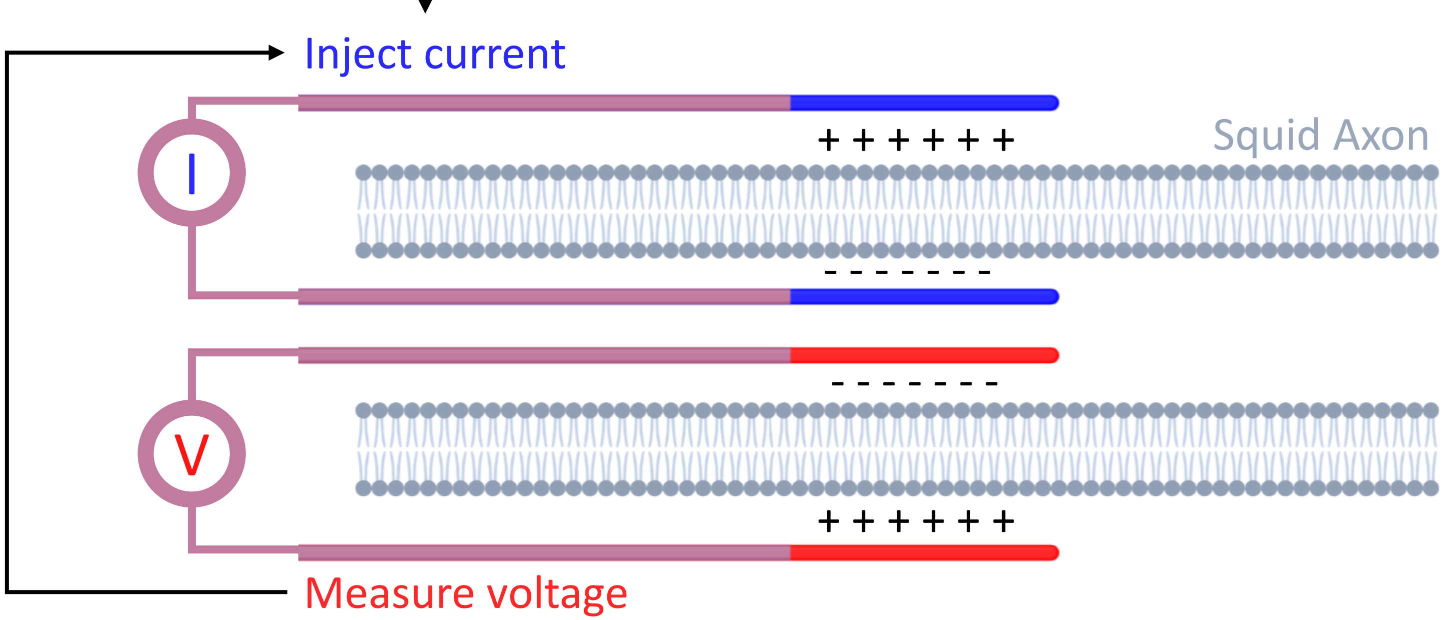
Alan Hodgkin and Andrew Huxley
Nobel Prize in Physiology (1963)



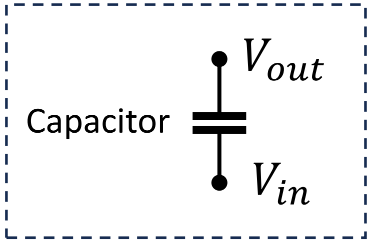


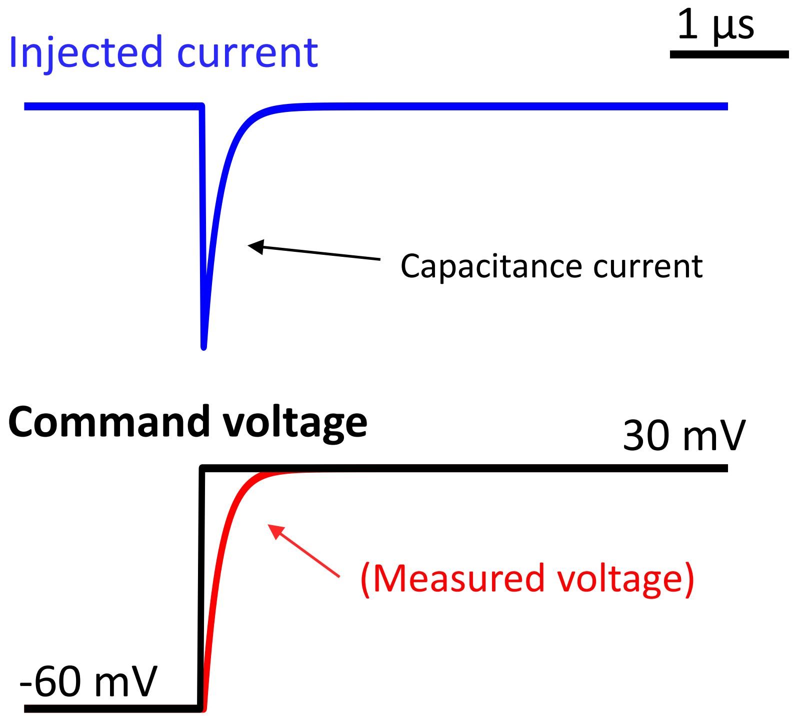
Hodgkin and Katz, *J. Physiol.* 1949

Models of neuronal excitability: Hodgkin-Huxley



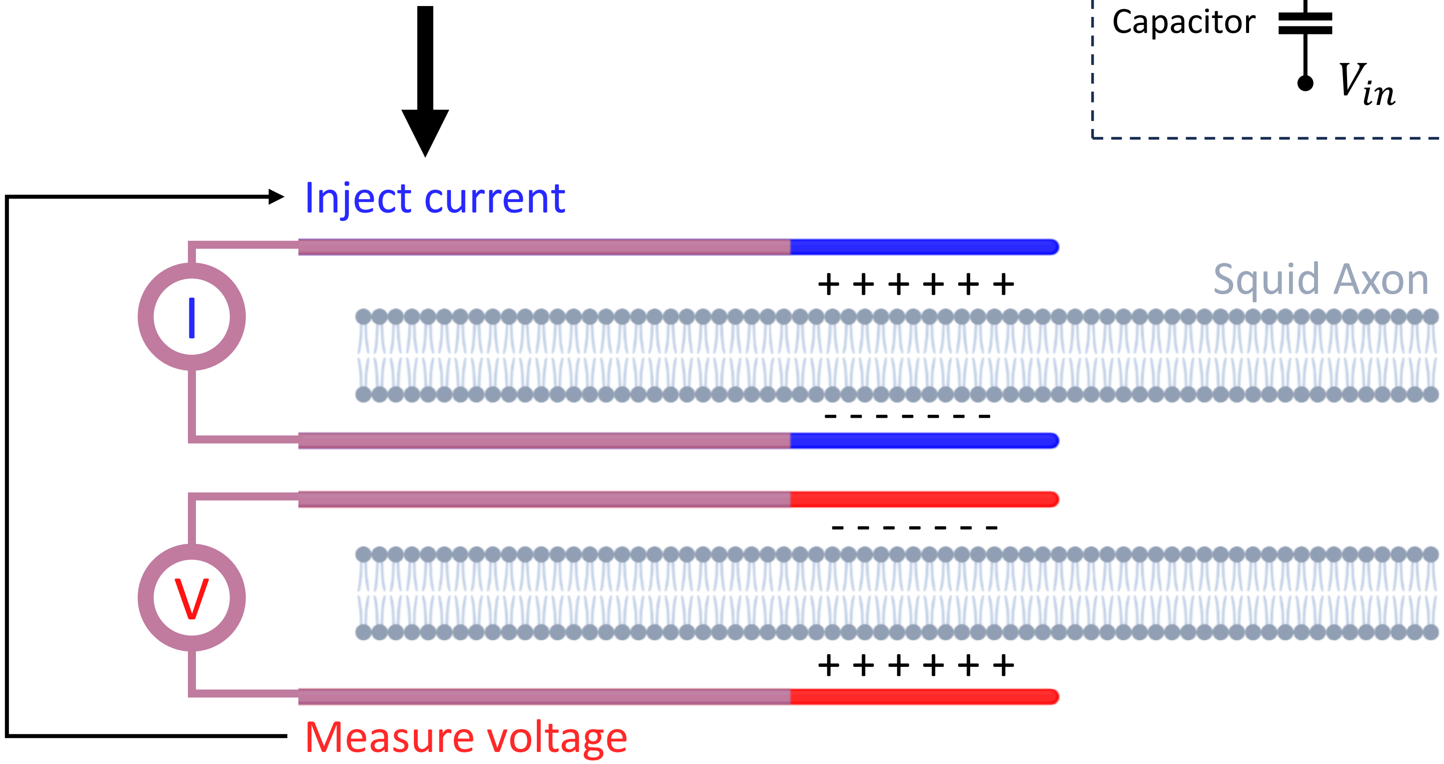
Adapt current injection
using feedback loop





Models of neuronal excitability: Hodgkin-Huxley

Command voltage



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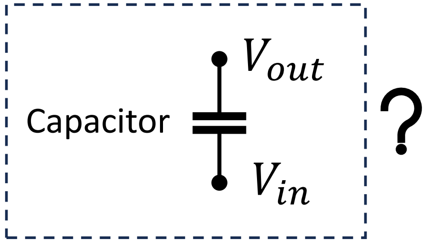
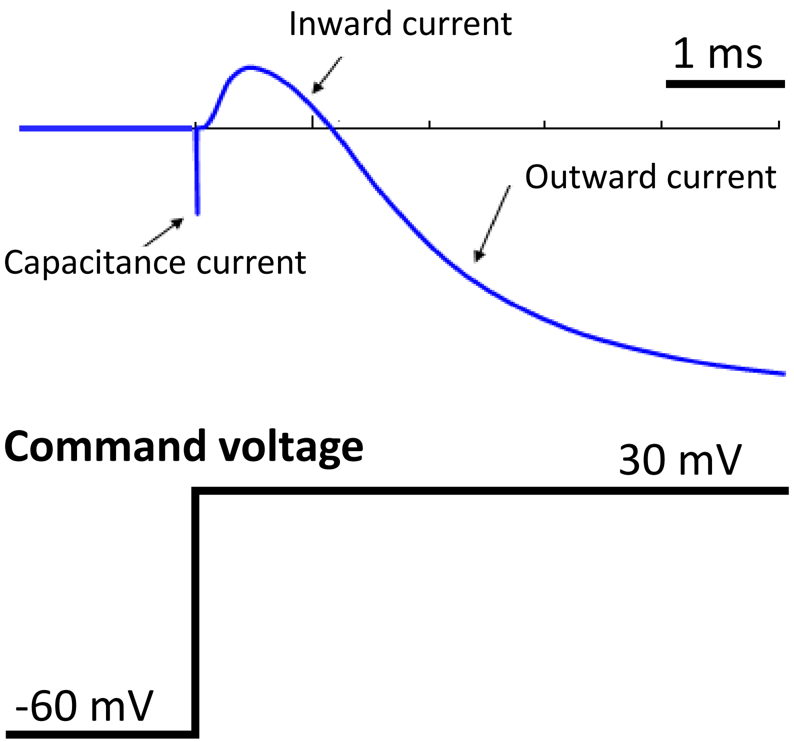
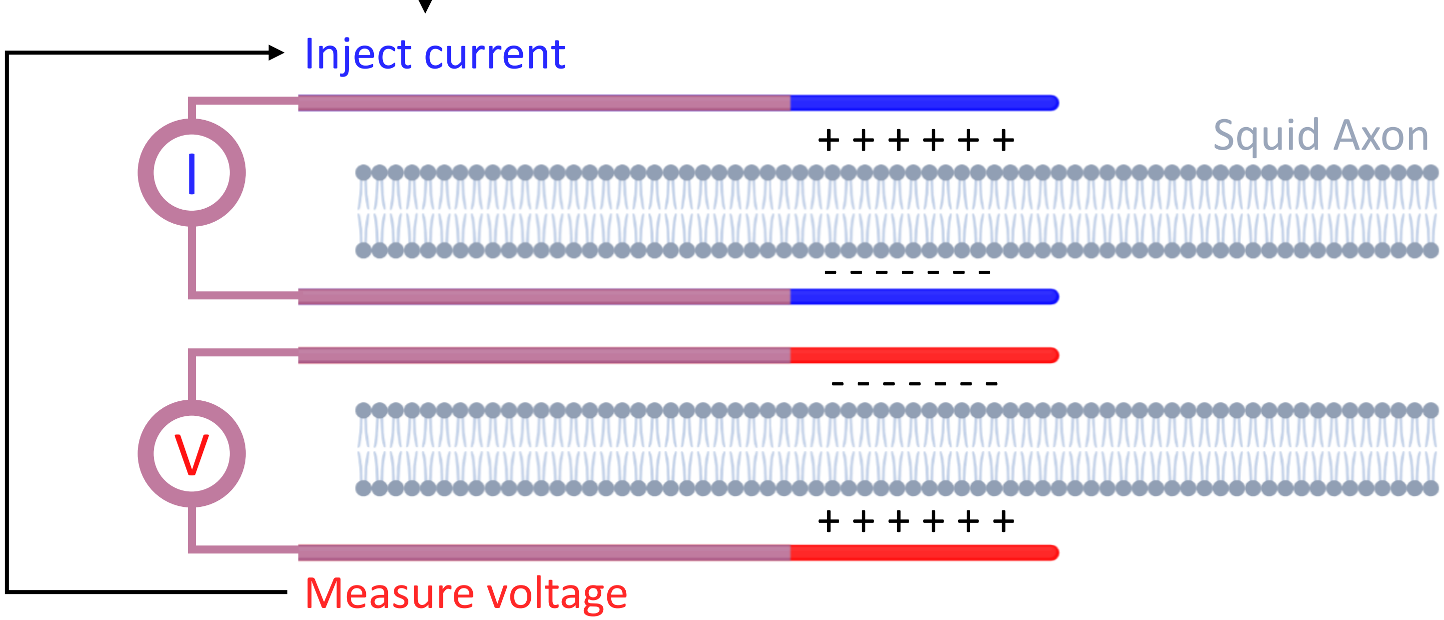




Models of neuronal excitability: Hodgkin-Huxley



Adapt current injection
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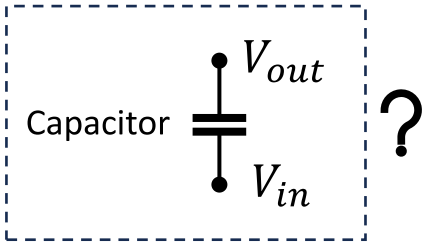
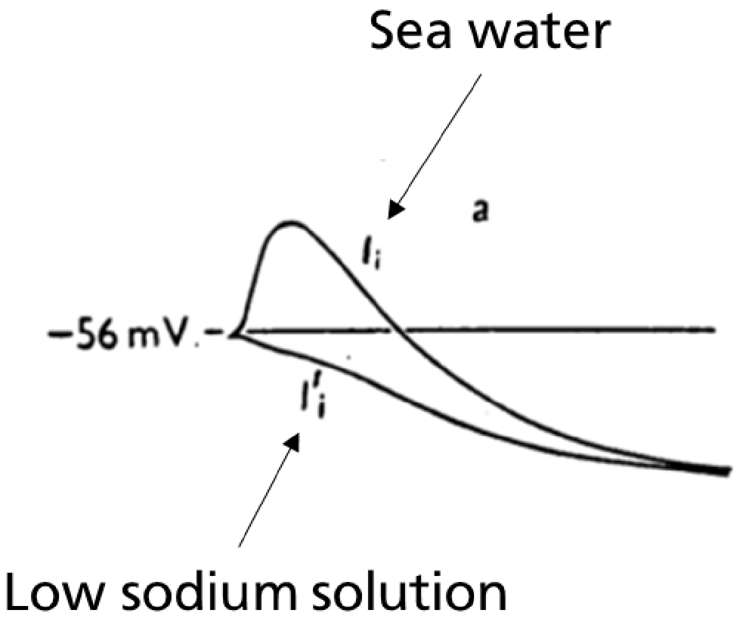
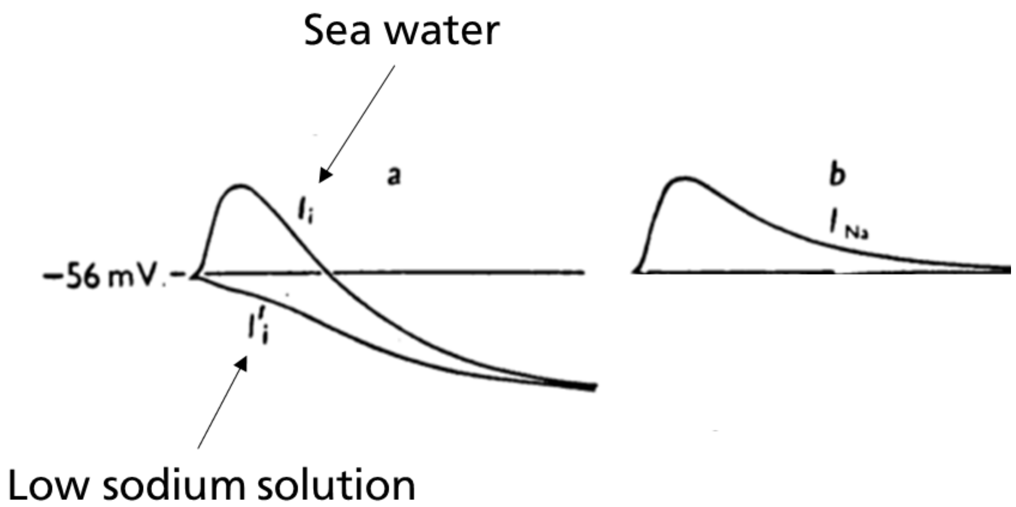
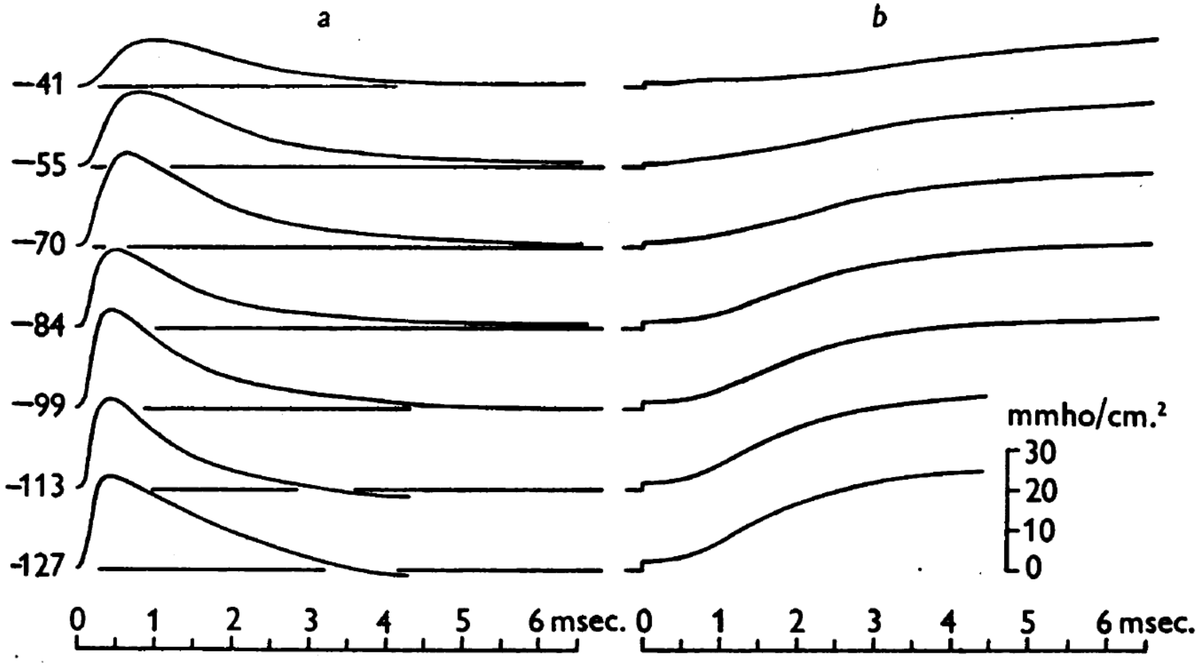




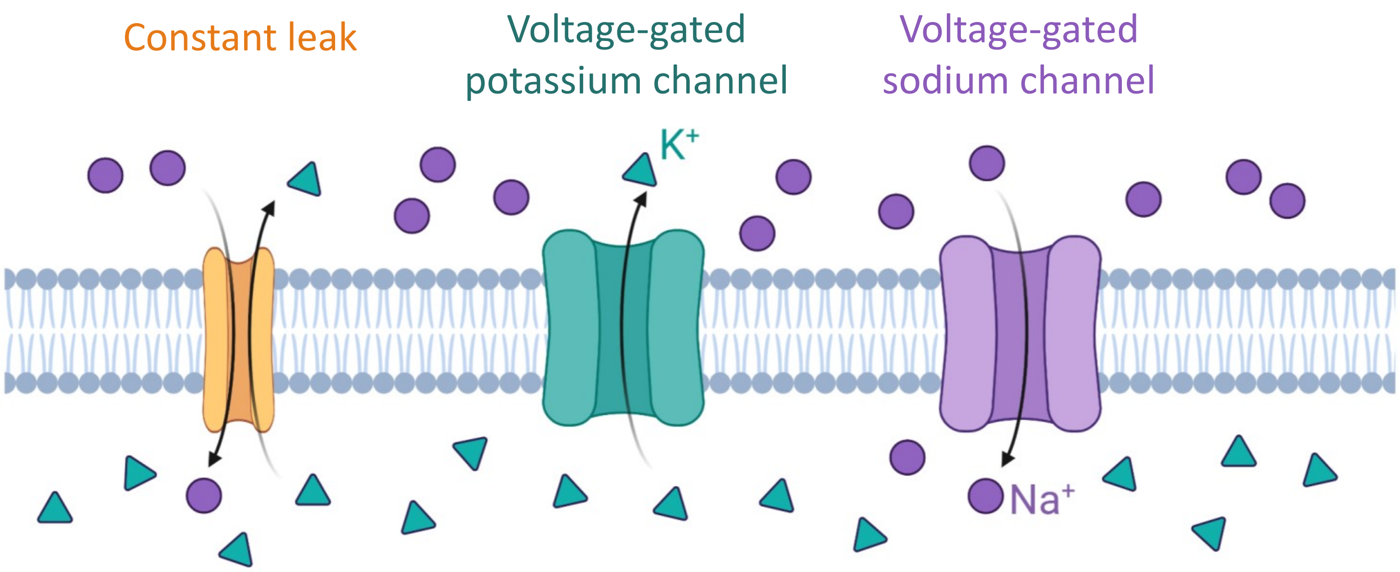
Hodgkin and Huxley, *J. Physiol.* 1952a

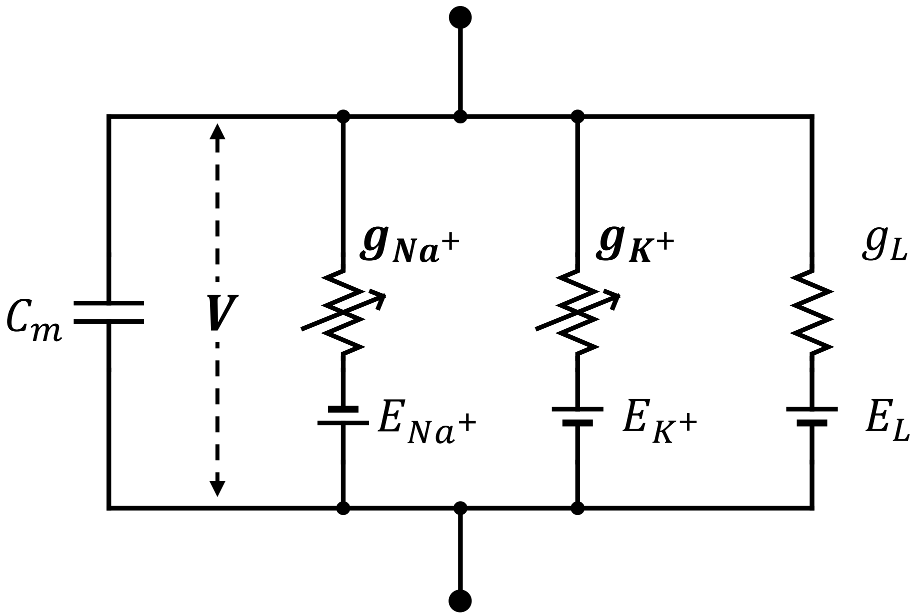
Models of neuronal excitability: Hodgkin-Huxley





Models of neuronal excitability: Hodgkin-Huxley



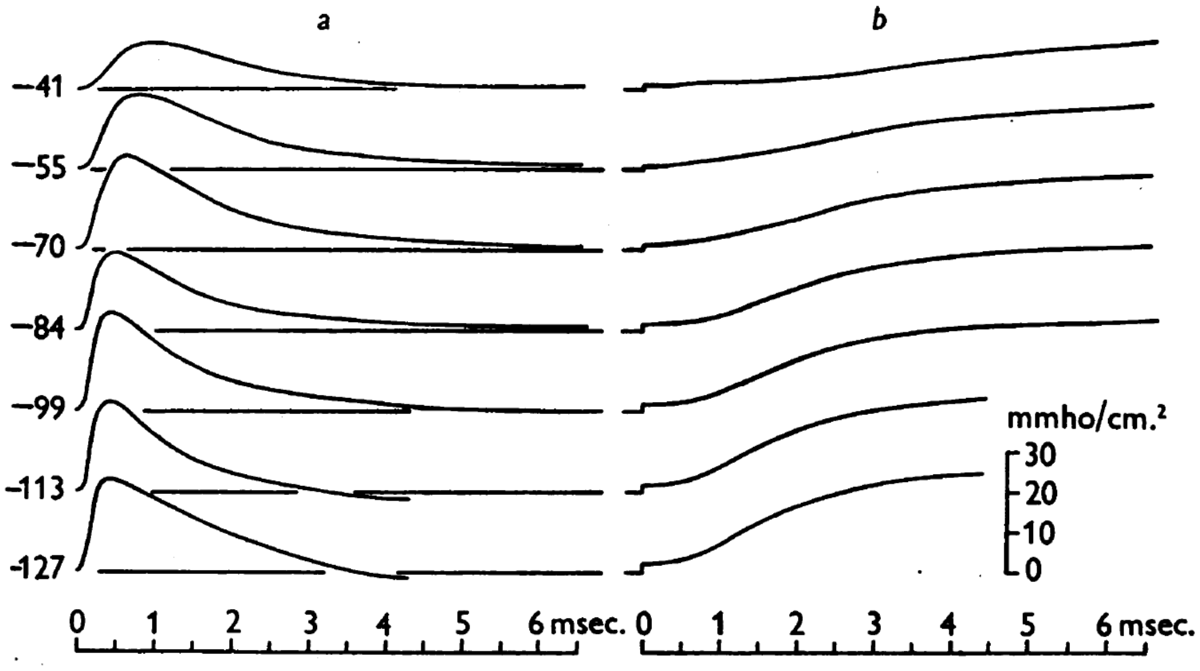


$$C_m \frac{d\boldsymbol{V}}{dt} = I_{app} - g_L \cdot (V - E_L) - g_K(V) \cdot (V - E_K) - g_{Na}(V) \cdot (V - E_{Na})$$

Models of neuronal excitability: Hodgkin-Huxley

Current carried by sodium ions

Current carried by potassium ions



$$I_{Na}(V) = \bar{g}_{Na} m^3(V) h(V)(\mathrm{V} - \mathrm{E_{Na}})$$

$\bar{g}_{Na} = 120\ \mathrm{mS/cm^2}$ $E_{Na} = 115\ \mathrm{mV}$

$$\frac{dm}{dt} = \frac{0.1(25 - V)}{\exp\left(\frac{25 - V}{10}\right) - 1}(1 - m) - 4\exp\left(-\frac{V}{18}\right) m$$

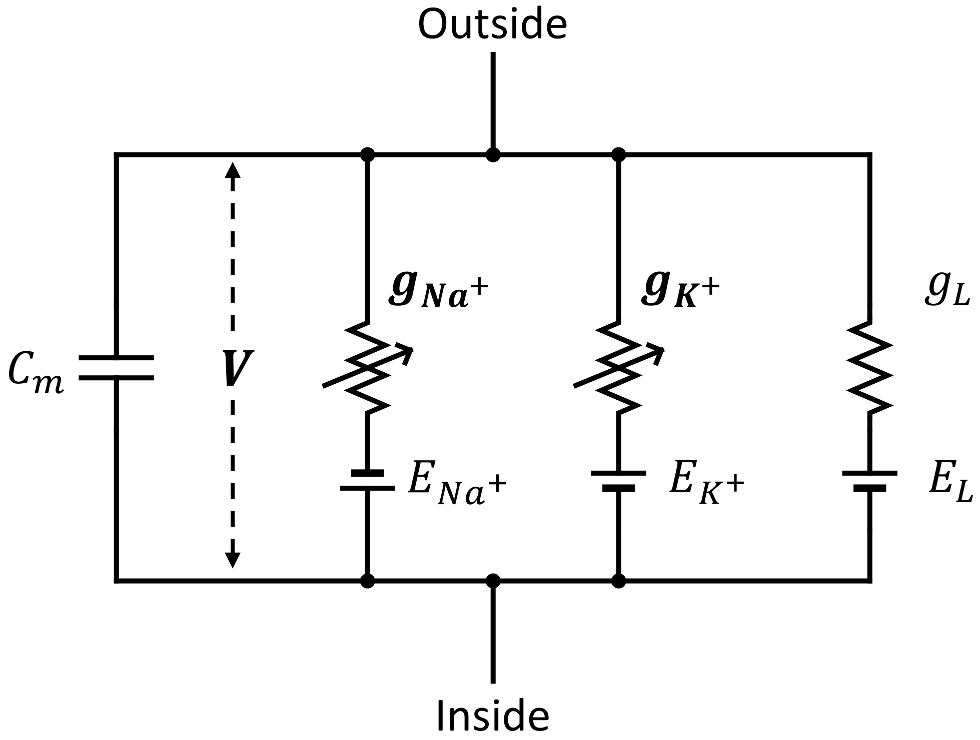
$$\frac{dh}{dt} = 0.07\exp\left(-\frac{V}{20}\right)(1 - h) - \frac{1}{\exp\left(\frac{30 - V}{10}\right) + 1} h$$

$$I_K(V) = \bar{g}_K n^4(V)(\mathrm{V} - \mathrm{E_K})$$

$\bar{g}_K = 36\ \mathrm{mS/cm^2}$ $E_K = -12\ \mathrm{mV}$

$$\frac{dn}{dt} = \frac{0.01(10 - V)}{\exp\left(\frac{10 - V}{10}\right) - 1}(1 - n) - 0.125\exp\left(-\frac{V}{80}\right) n$$

Models of neuronal excitability: Hodgkin-Huxley



Differential equations

$$C_m \frac{d\boldsymbol{V}}{dt} = I_{app} - \bar{g}_{Na}\boldsymbol{m}^3\boldsymbol{h}(\boldsymbol{V} - E_{Na}) - \bar{g}_K\boldsymbol{n}^4(\boldsymbol{V} - E_k) - g_L(\boldsymbol{V} - E_L)$$

$$\frac{d\boldsymbol{m}}{dt} = \frac{0.1(25 - \boldsymbol{V})}{\exp\left(\frac{25 - \boldsymbol{V}}{10}\right) - 1}(1 - \boldsymbol{m}) - 4\exp\left(-\frac{\boldsymbol{V}}{18}\right)\boldsymbol{m}$$

$$\frac{d\boldsymbol{h}}{dt} = 0.07\exp\left(-\frac{\boldsymbol{V}}{20}\right)(1 - \boldsymbol{h}) - \frac{1}{\exp\left(\frac{30 - \boldsymbol{V}}{10}\right) + 1}\boldsymbol{h}$$

$$\frac{d\boldsymbol{n}}{dt} = \frac{0.01(10 - \boldsymbol{V})}{\exp\left(\frac{10 - \boldsymbol{V}}{10}\right) - 1}(1 - \boldsymbol{n}) - 0.125\exp\left(-\frac{\boldsymbol{V}}{80}\right)\boldsymbol{n}$$

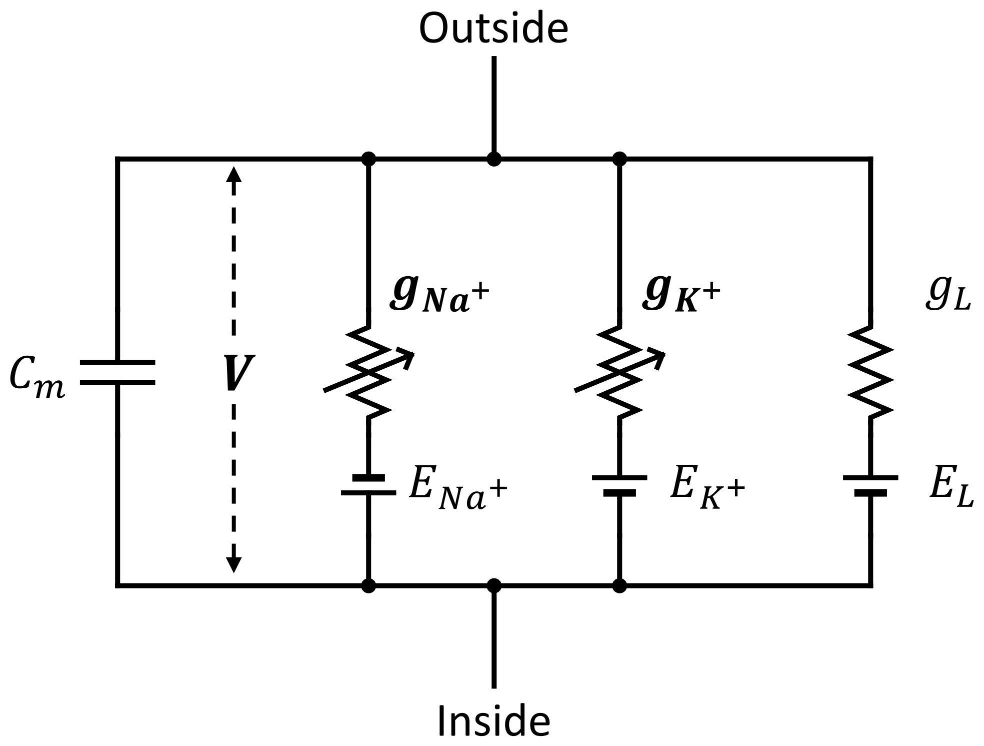
Parameter values

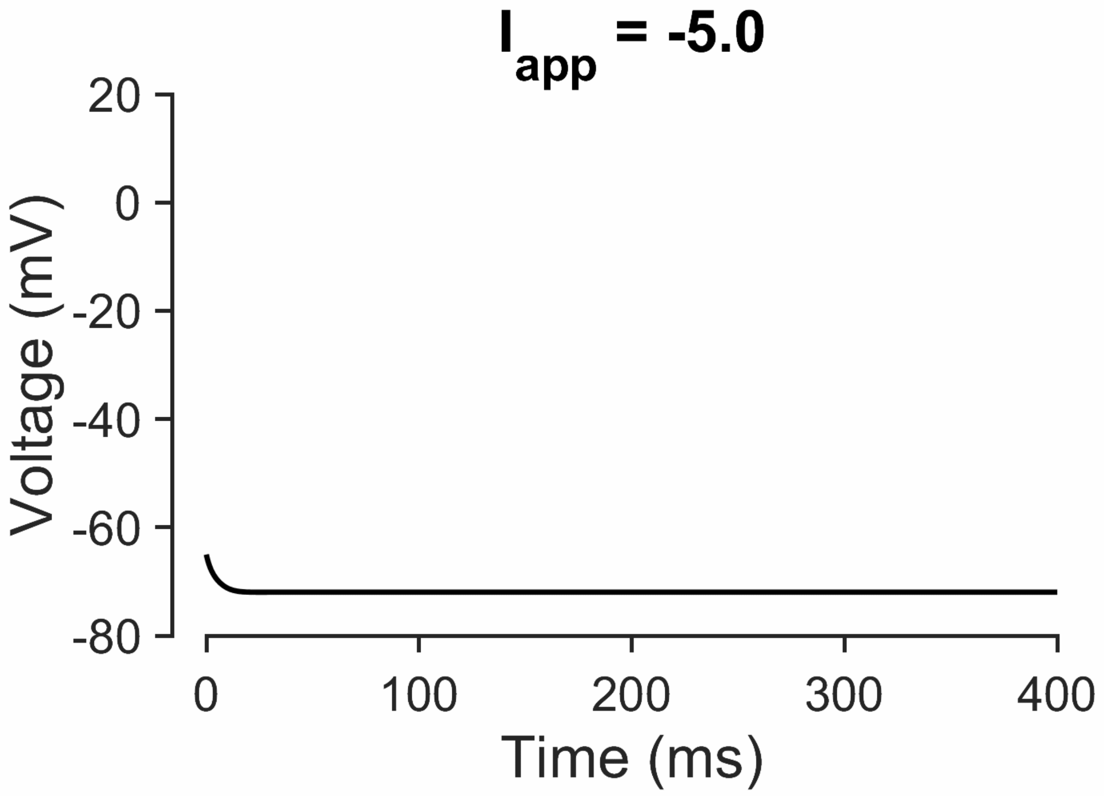
$g_L = 0.3\ \mathrm{mS/cm^2}$ | $E_L = 10\ \mathrm{mV}$

$\bar{g}_{Na} = 120\ \mathrm{mS/cm^2}$ | $E_{Na} = 115\ \mathrm{mV}$ | $C_m = 1\ \mathrm{\mu F/cm^2}$

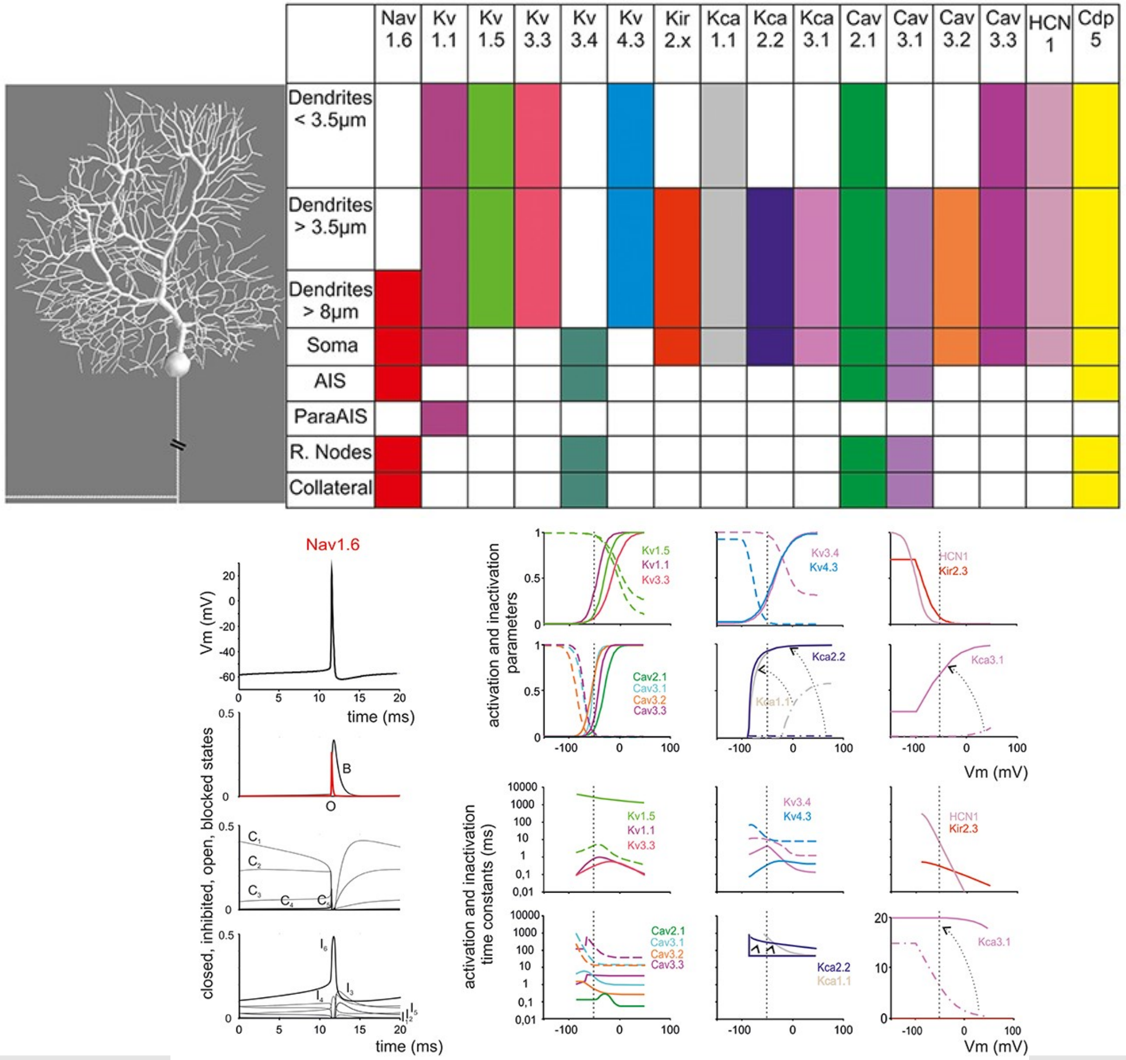
$\bar{g}_K = 36\ \mathrm{mS/cm^2}$ | $E_K = -12\ \mathrm{mV}$

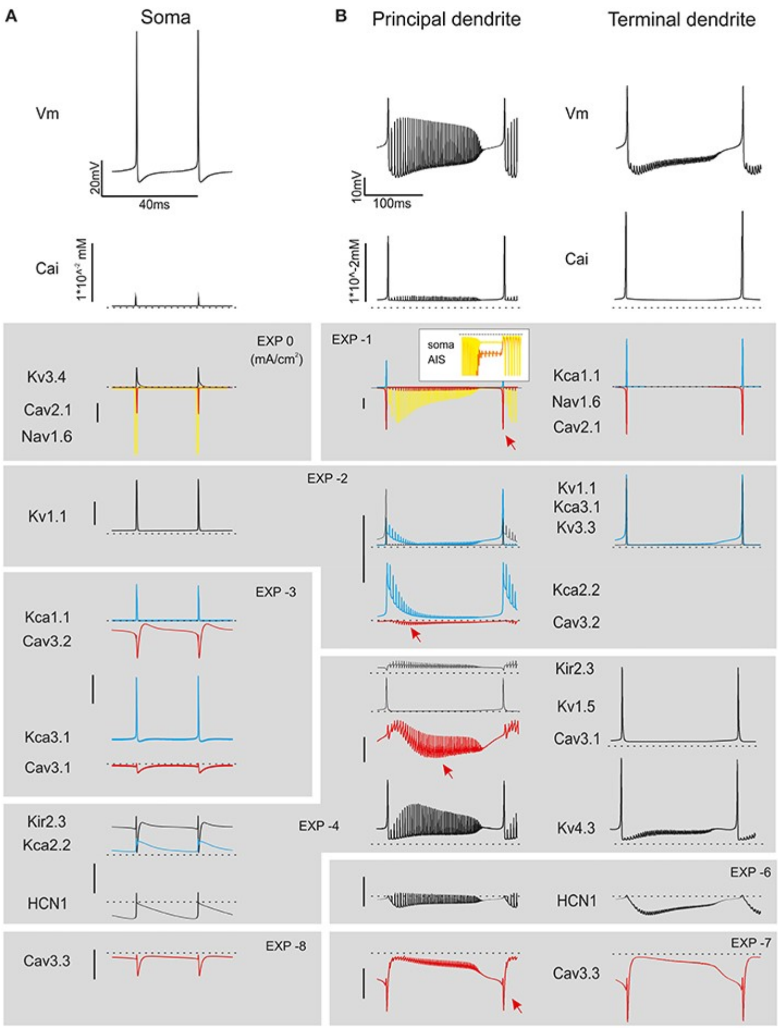
Models of neuronal excitability: Hodgkin-Huxley





Models of neuronal excitability: Hodgkin-Huxley





Masoli et al., *Front. Cell. Neurosci.* 2015

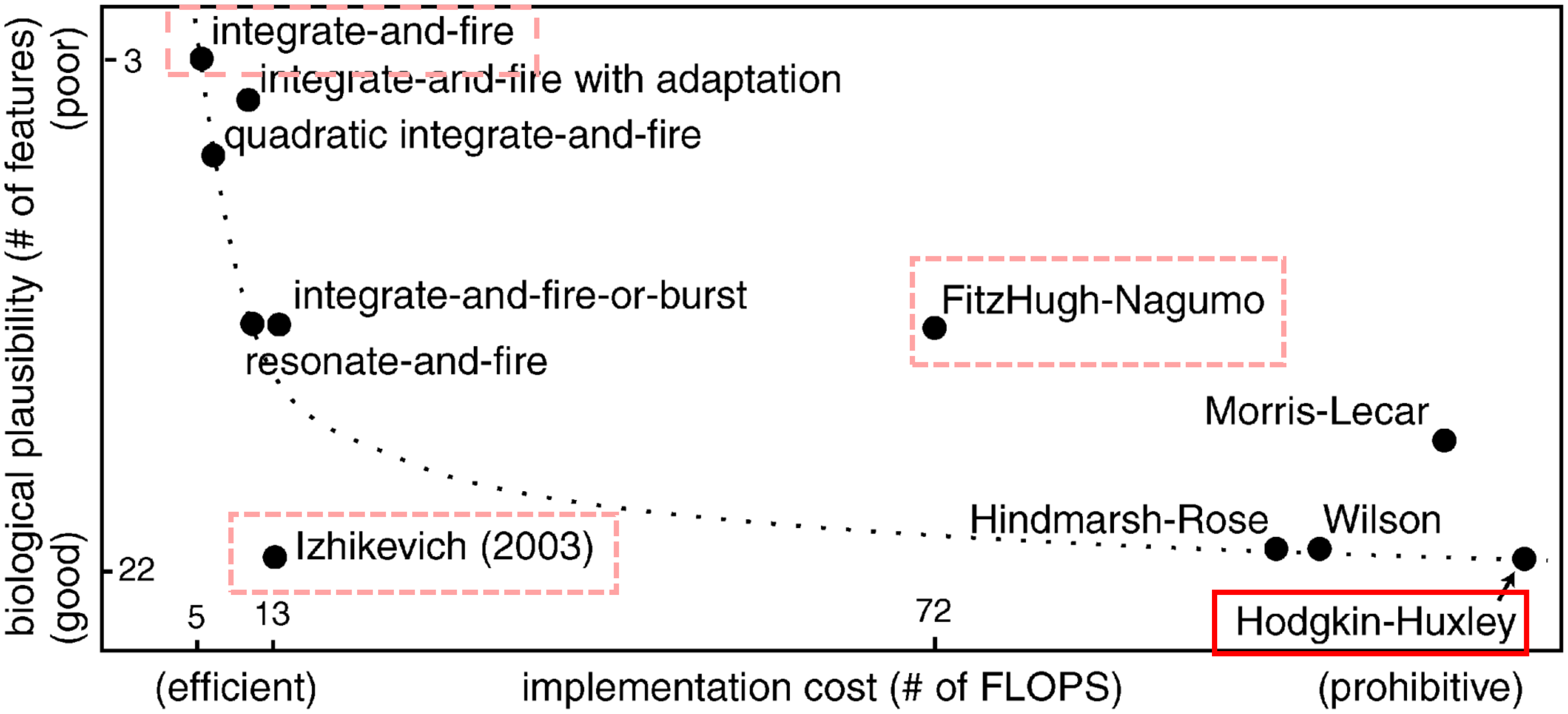
Models of neuronal excitability

Benefits of Hodgkin-Huxley models
- Biophysically interpretable
- Capable of all types of neuronal excitability

Drawbacks
- Computationally expensive
- Very often under constrained, i.e. too many parameters

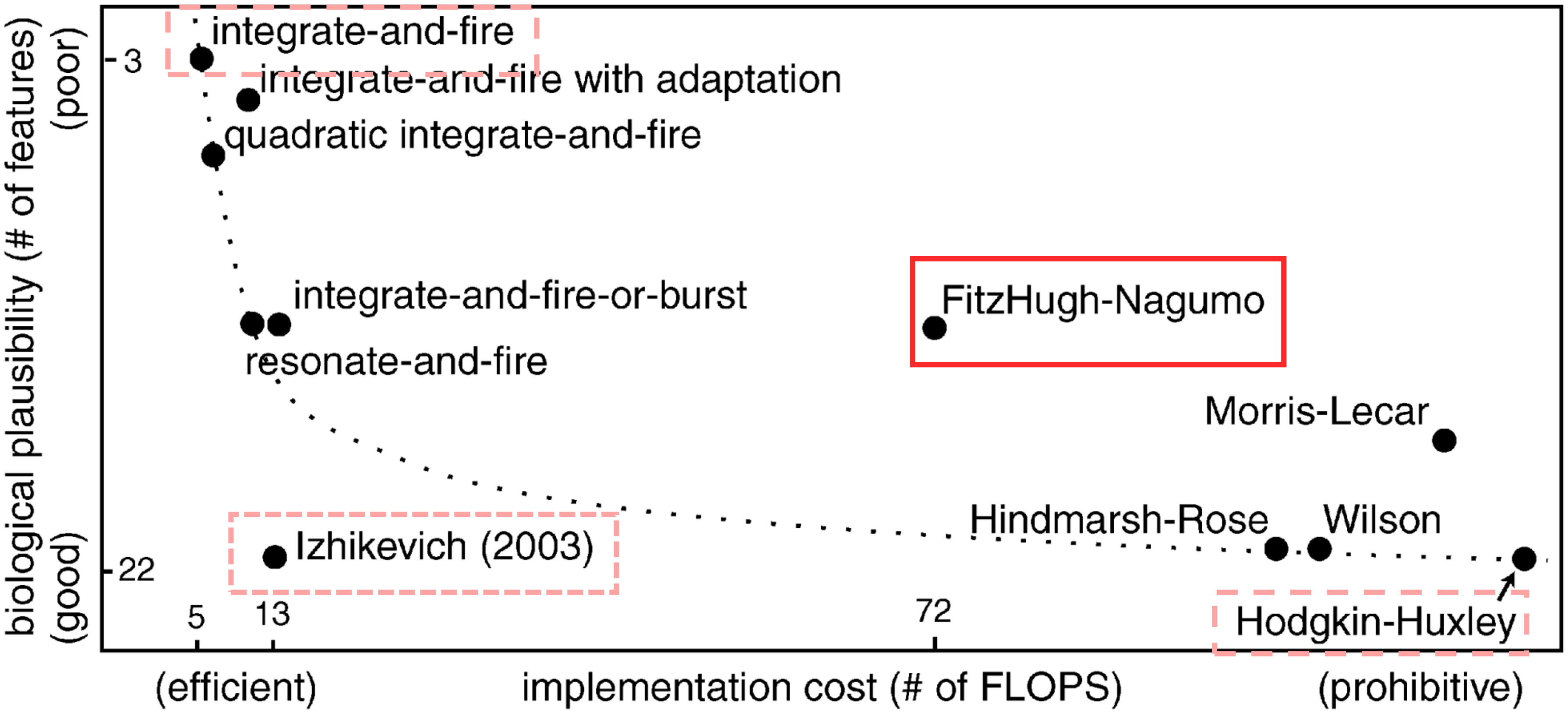
Uses
- Investigate molecular basis of excitability properties
- Explaining pharmacological/genetic effects on neuronal firing

Models of neuronal excitability



Izhikevich, *IEEE Transactions on Neural Networks* 2004

Models of neuronal excitability



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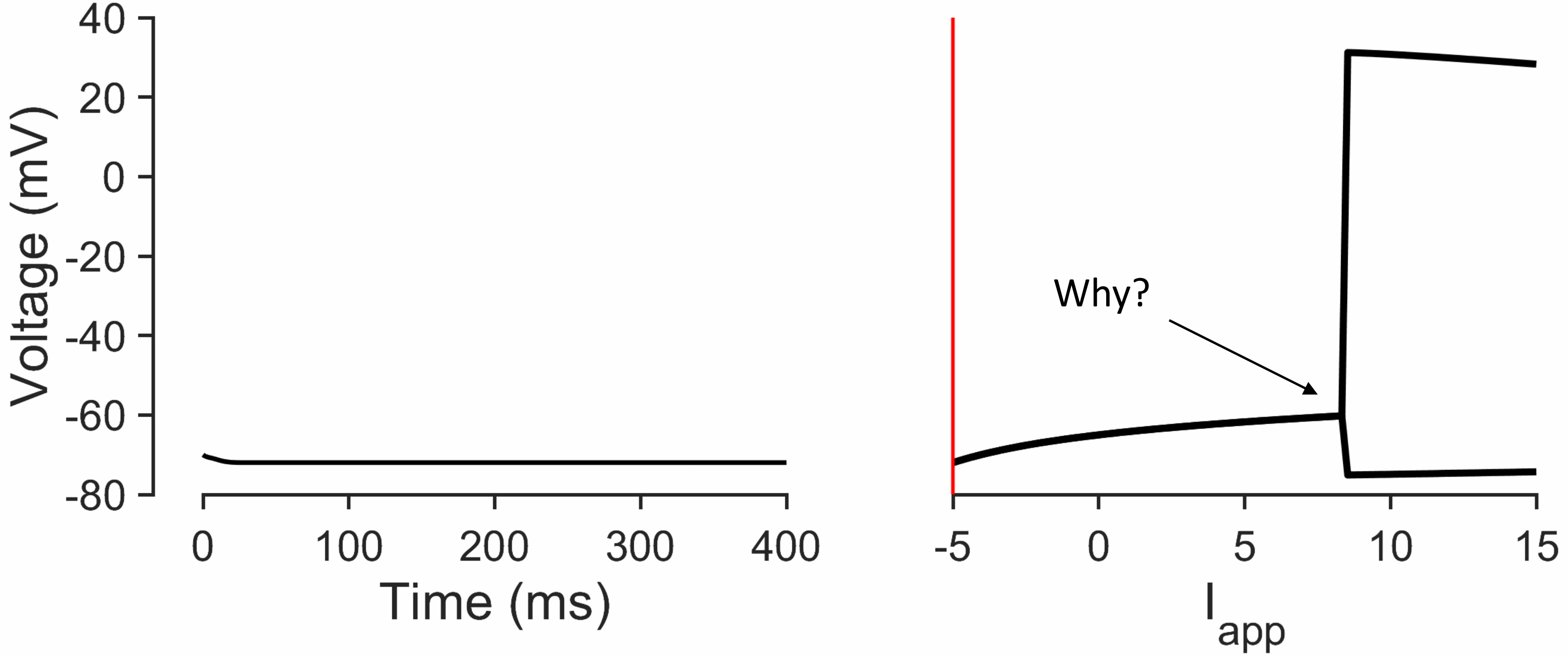
Models of neuronal excitability: Fitzhugh-Nagumo

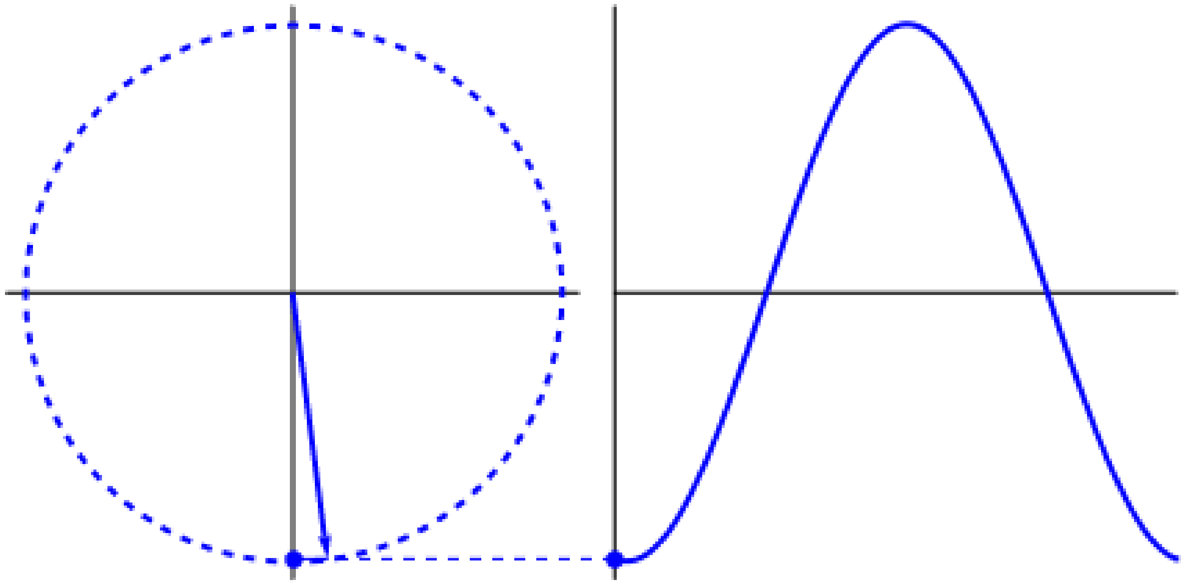
1. Can we simplify the Hodgkin-Huxley model?
2. What is the mathematics underlying its behaviour?
3. What do we mean by excitability?

Models of neuronal excitability: Fitzhugh-Nagumo



Models of neuronal excitability: Fitzhugh-Nagumo

An oscillation is equivalent to a cycle.



Models of neuronal excitability: Fitzhugh-Nagumo

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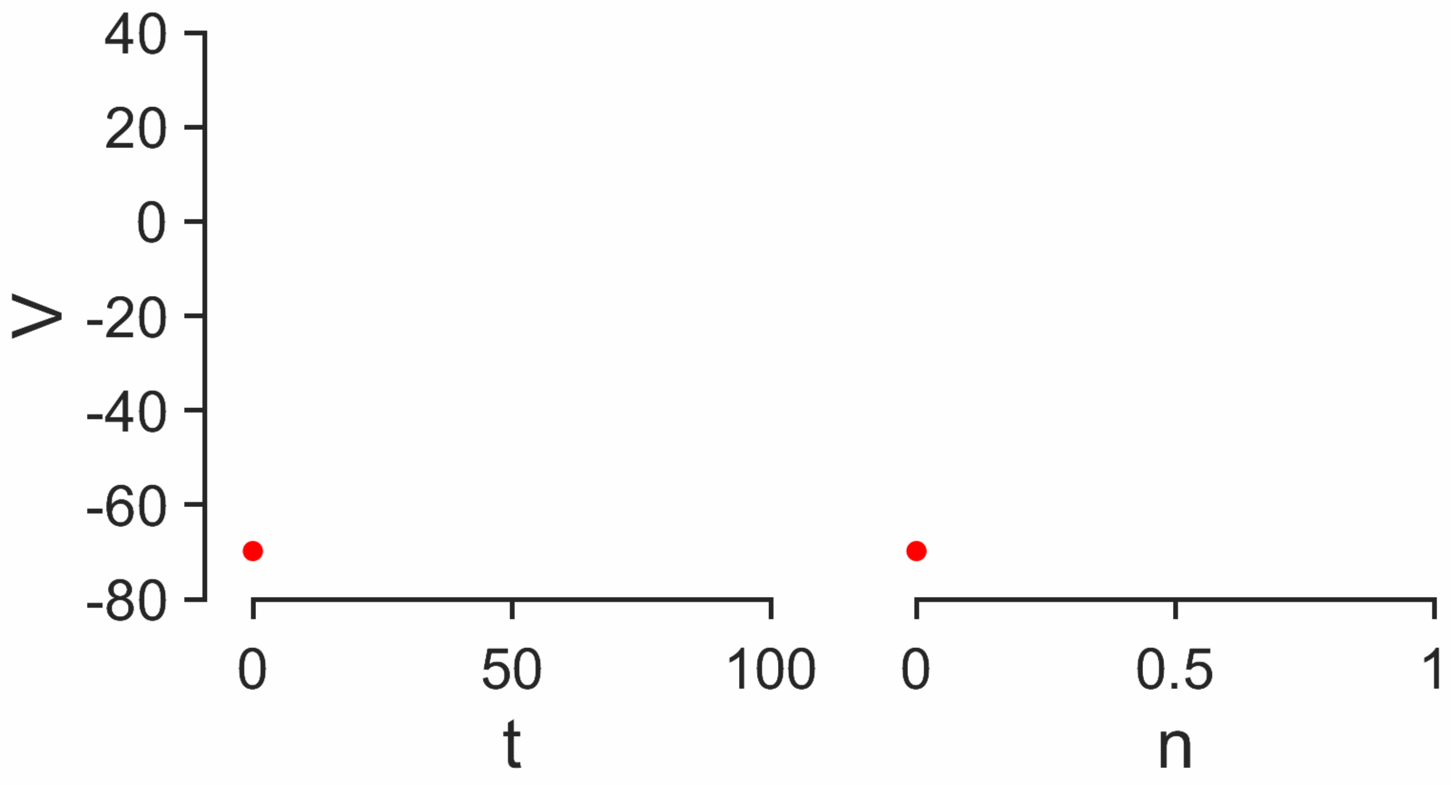
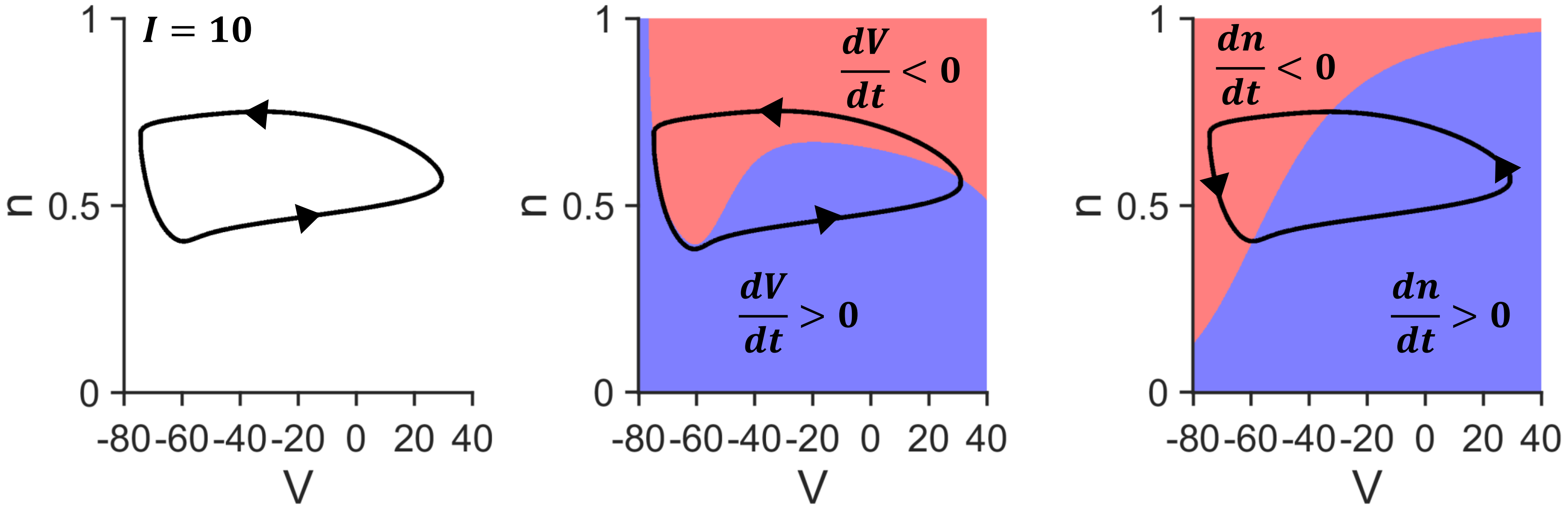
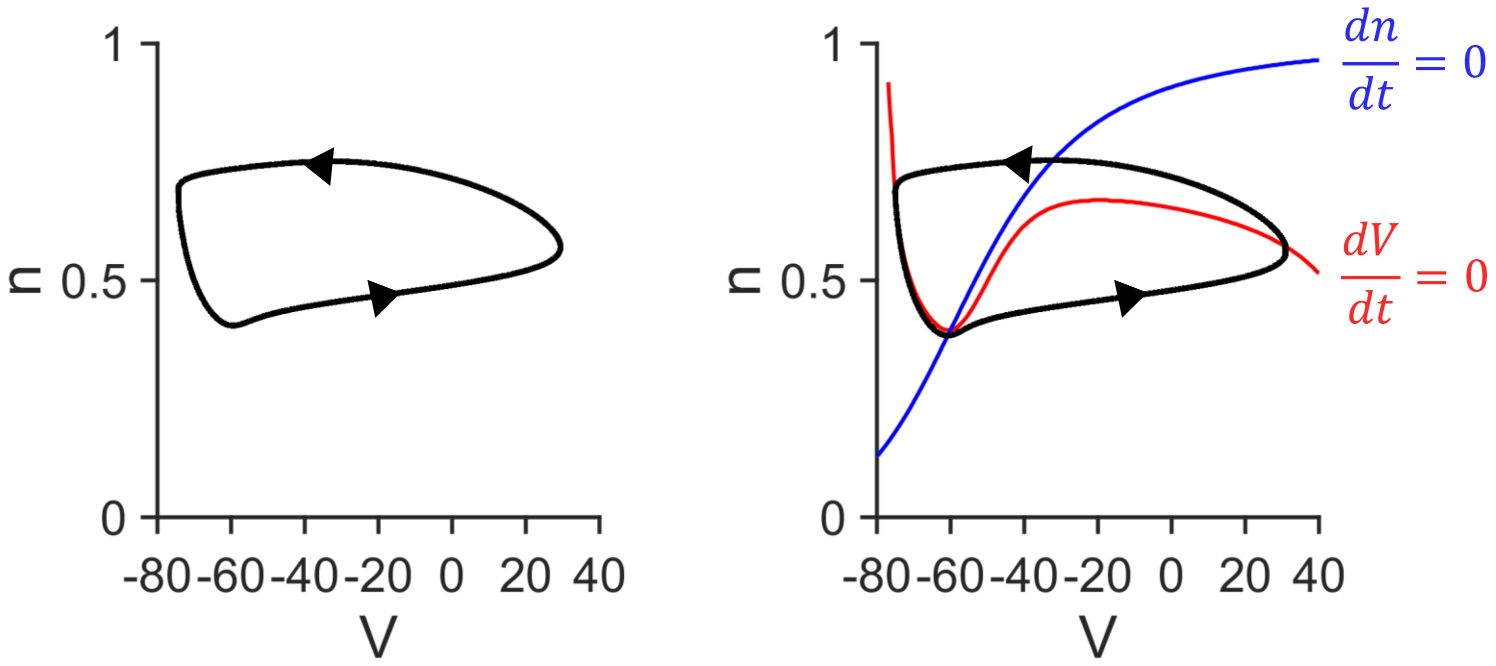


Models of neuronal excitability: Fitzhugh-Nagumo



Models of neuronal excitability: Fitzhugh-Nagumo



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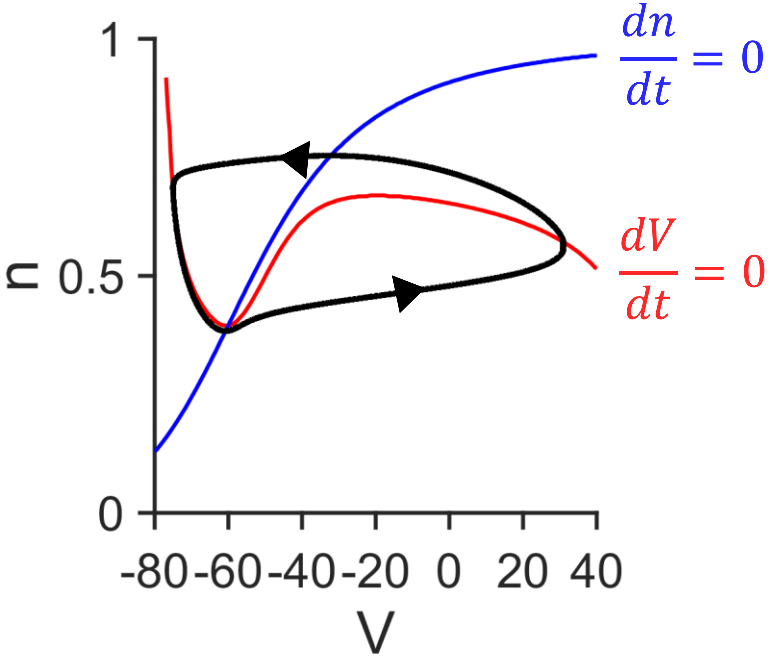
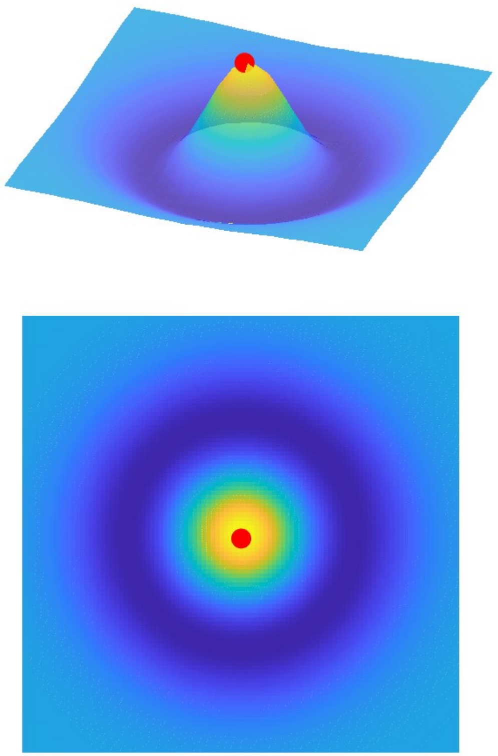
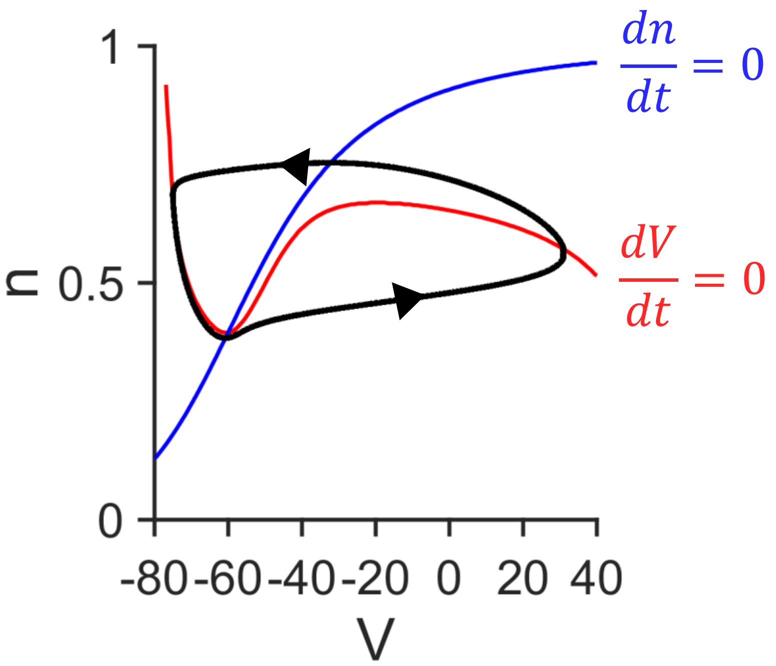
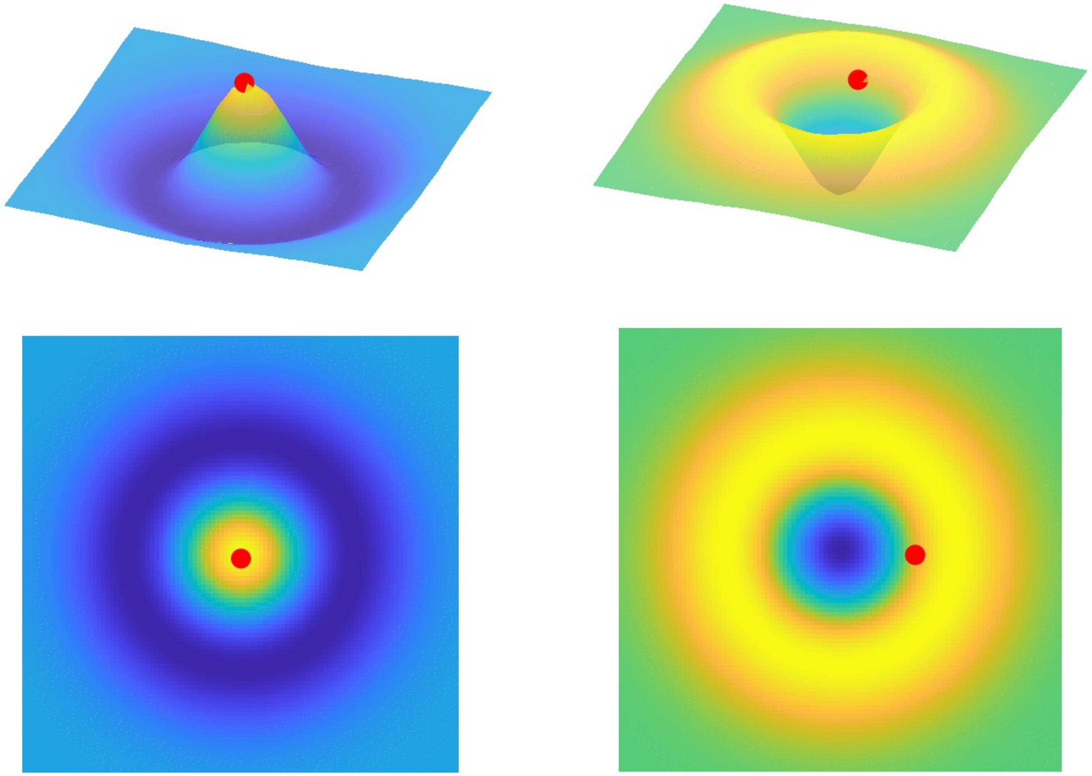




I = 10 (spiking)

Models of neuronal excitability: Fitzhugh-Nagumo





I = 10 (spiking)

I = 0 (quiescence)

Further readings on stability analysis
- Steven Strogatz, *Nonlinear Dynamics And Chaos* (Westview Press 2001)
- Eugene Izhikevich *Dynamical Systems in Neuroscience* (MIT Press 2007)

Models of neuronal excitability: Fitzhugh-Nagumo

FitzHugh-Nagumo approximates the structure underlying action potential cycle in the HH model

Hodgkin-Huxley

$$C_m \frac{d\boldsymbol{V}}{dt} = I_{app} - \bar{g}_{Na}\boldsymbol{m}^3\boldsymbol{h}(\boldsymbol{V} - E_{Na}) - \bar{g}_K\boldsymbol{n}^4(\boldsymbol{V} - E_k) - g_L(\boldsymbol{V} - E_L)$$

$$\frac{d\boldsymbol{n}}{dt} = \frac{0.01(10 - \boldsymbol{V})}{\exp\left(\frac{10 - \boldsymbol{V}}{10}\right) - 1}(1 - \boldsymbol{n}) - 0.125\exp\left(-\frac{\boldsymbol{V}}{80}\right)\boldsymbol{n}$$

$$\frac{d\boldsymbol{h}}{dt} = 0.07\exp\left(-\frac{\boldsymbol{V}}{20}\right)(1 - \boldsymbol{h}) - \frac{1}{\exp\left(\frac{30 - \boldsymbol{V}}{10}\right) + 1}\boldsymbol{h}$$

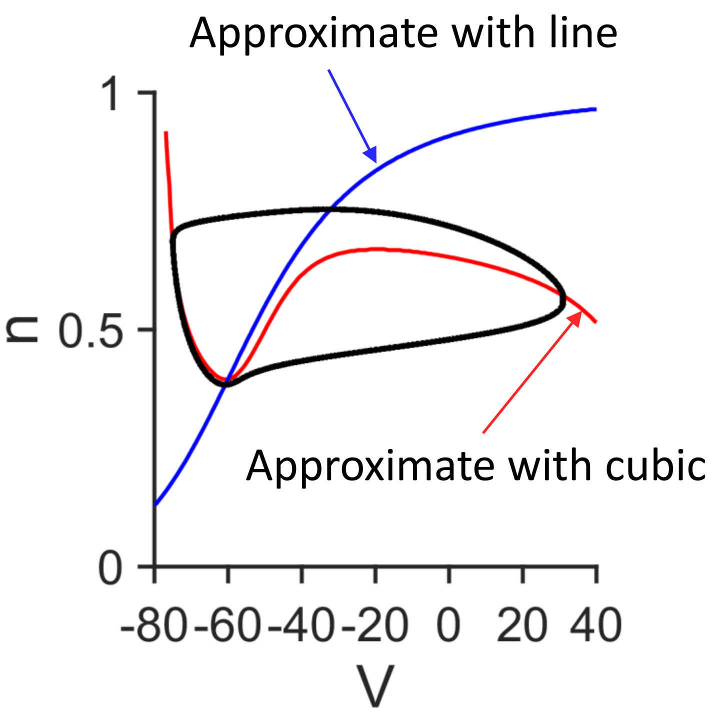
$$\frac{d\boldsymbol{m}}{dt} = \frac{0.1(25 - \boldsymbol{V})}{\exp\left(\frac{25 - \boldsymbol{V}}{10}\right) - 1}(1 - \boldsymbol{m}) - 4\exp\left(-\frac{\boldsymbol{V}}{18}\right)\boldsymbol{m}$$

FitzHugh-Nagumo

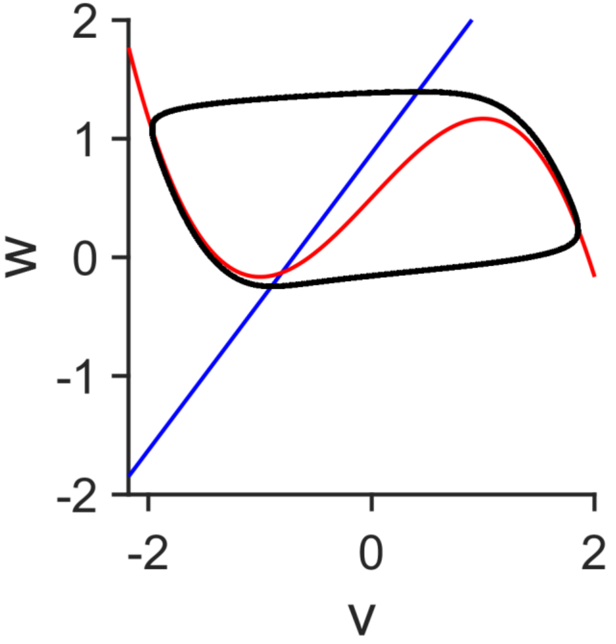
$$\frac{dv}{dt} = v - \frac{v^3}{3} - w + I$$

$$\tau\frac{dw}{dt} = v + a - bw$$

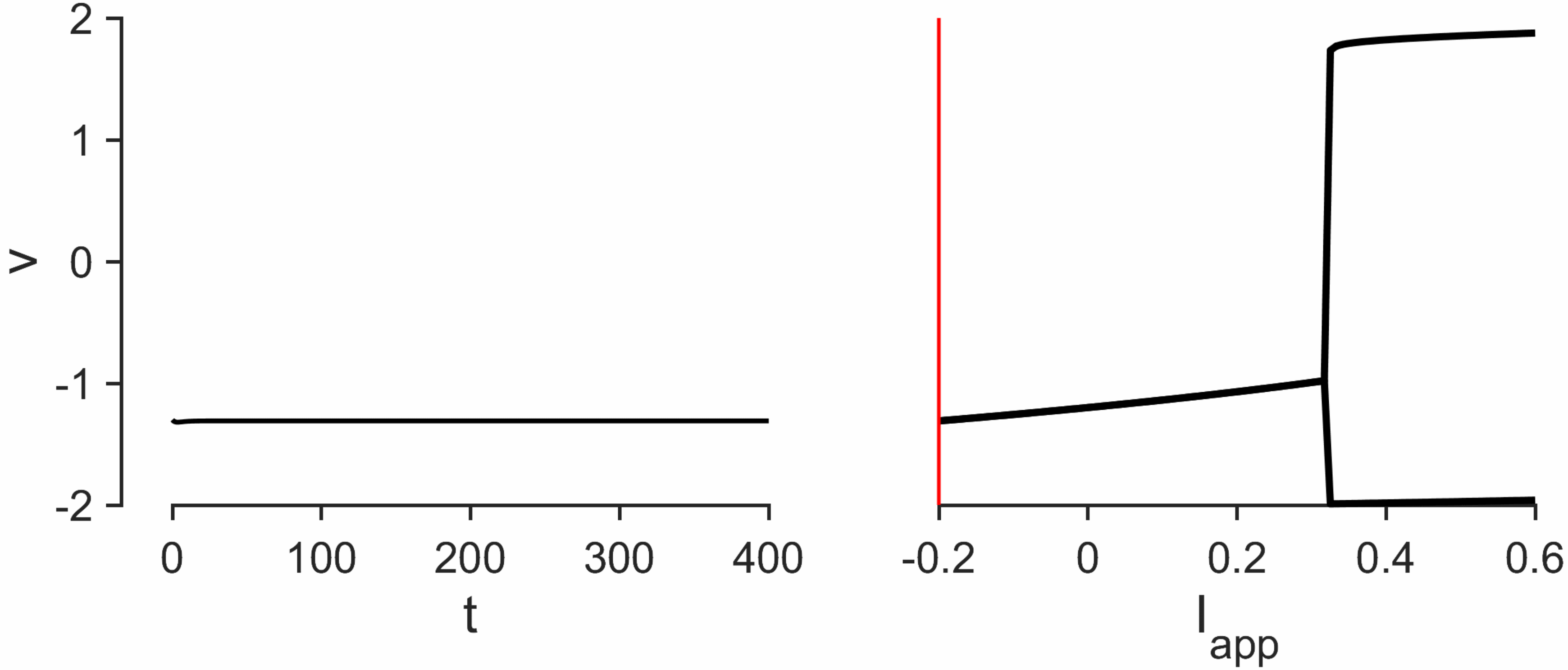
Hodgkin-Huxley



FitzHugh-Nagumo



Models of neuronal excitability: Fitzhugh-Nagumo



Models of neuronal excitability

Benefits of Fitzhugh-Nagumo

- Captures the transition from quiescence to tonic firing
- Simple and fast to simulate

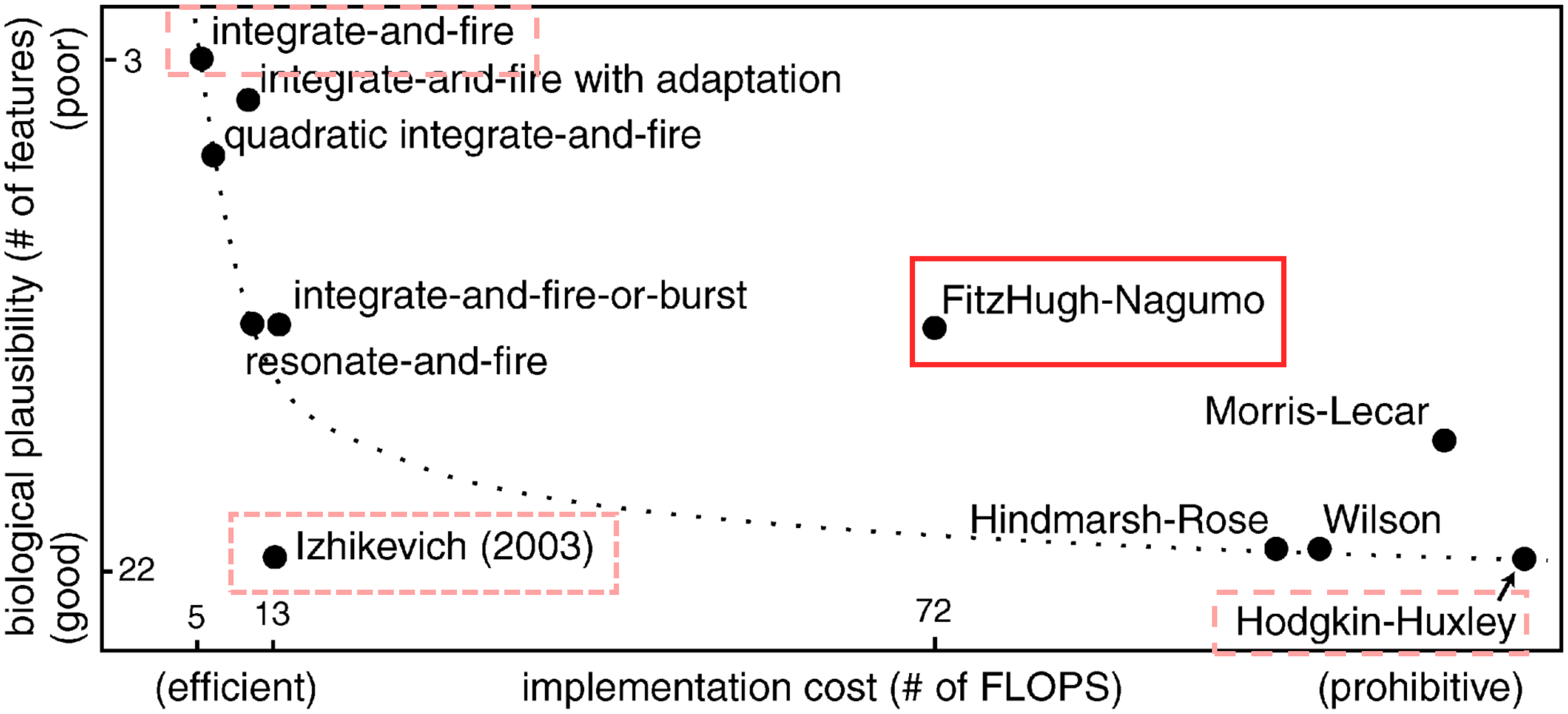
Drawbacks

- No longer biophysically meaningful
- Shape of action potentials not realistic
- Can’t capture other excitability properties of neurons like bursting

Uses

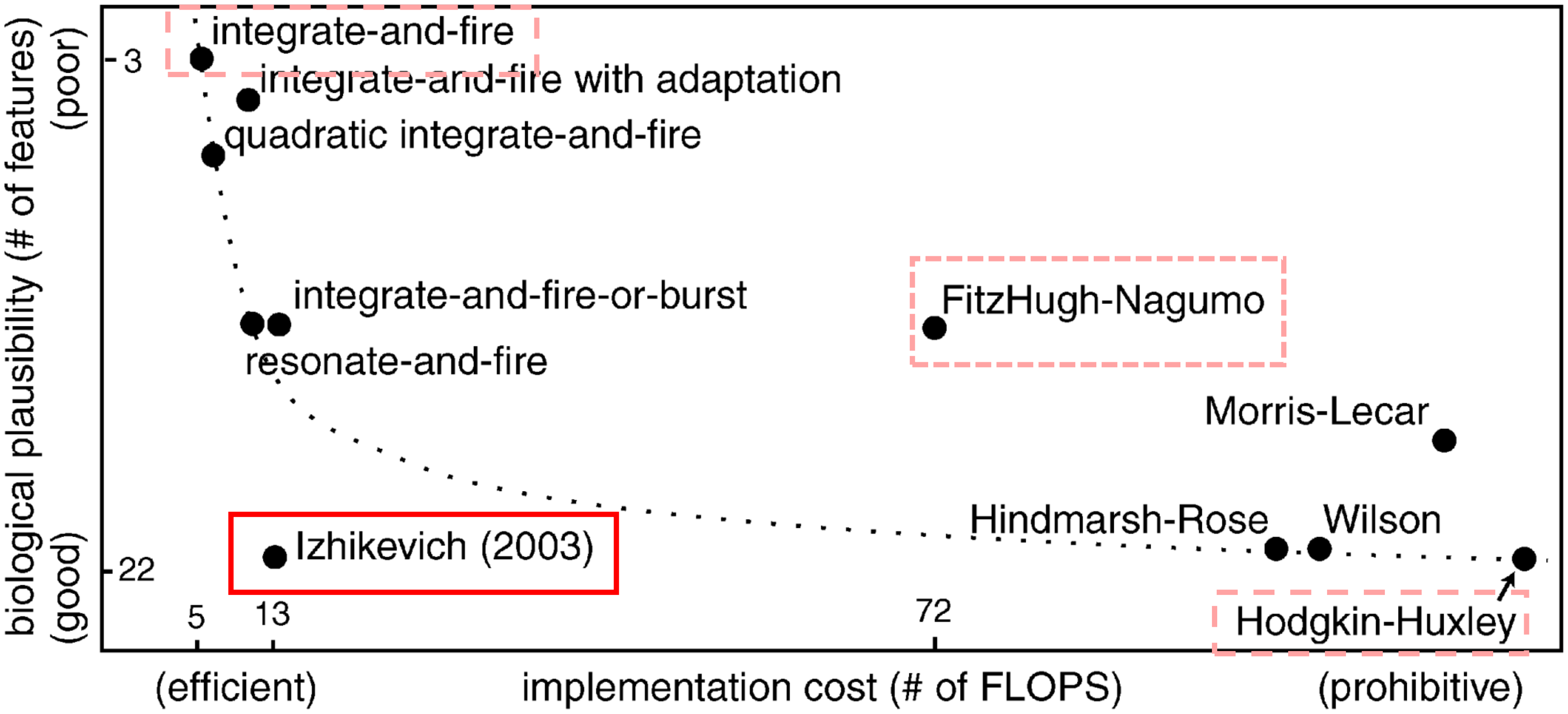
- Explicates the mathematical structure underlying neuronal excitability

Models of neuronal excitability



Izhikevich, *IEEE Transactions on Neural Networks* 2004

Models of neuronal excitability



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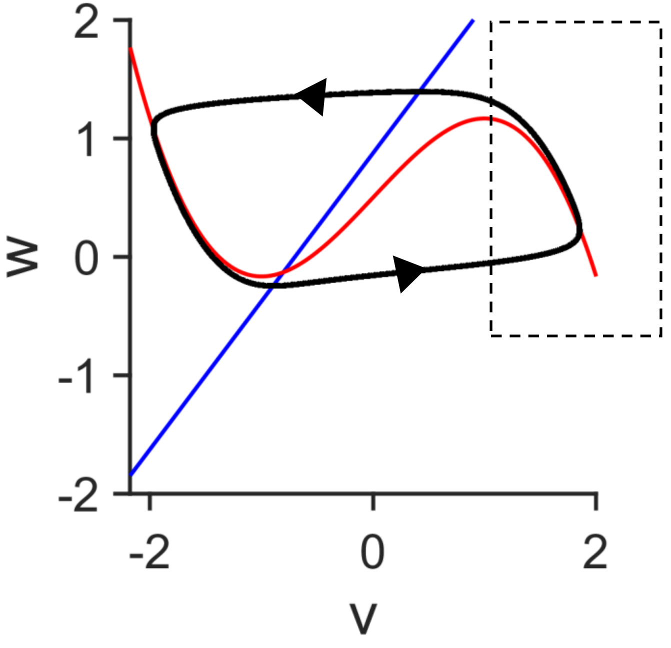
Models of neuronal excitability: Izhikevich

FitzHugh-Nagumo



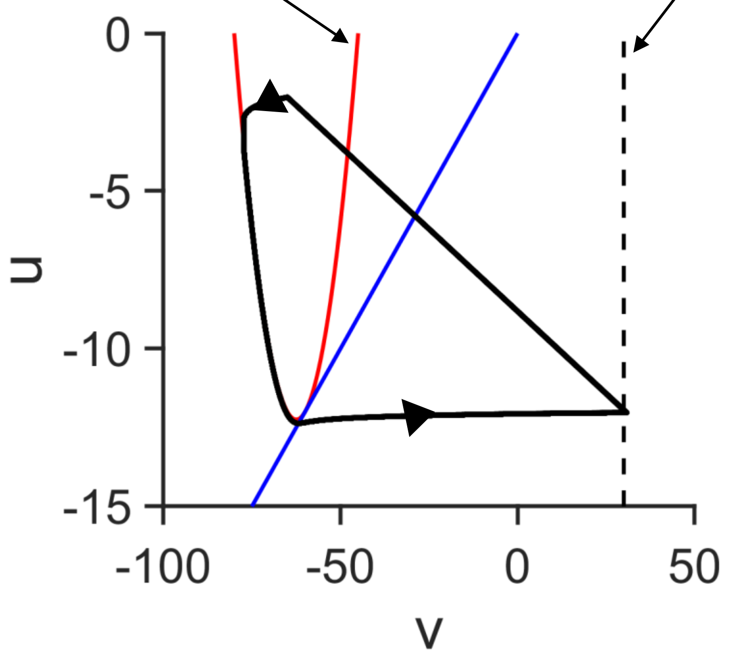
Trajectory makes a U-turn back towards resting membrane potential

Simplify more by replacing U-turn with an "Integrate-and-fire" type threshold and resetting mechanisms

Izhikevich model

Replace cubic with quadratic

Add resetting mechanism

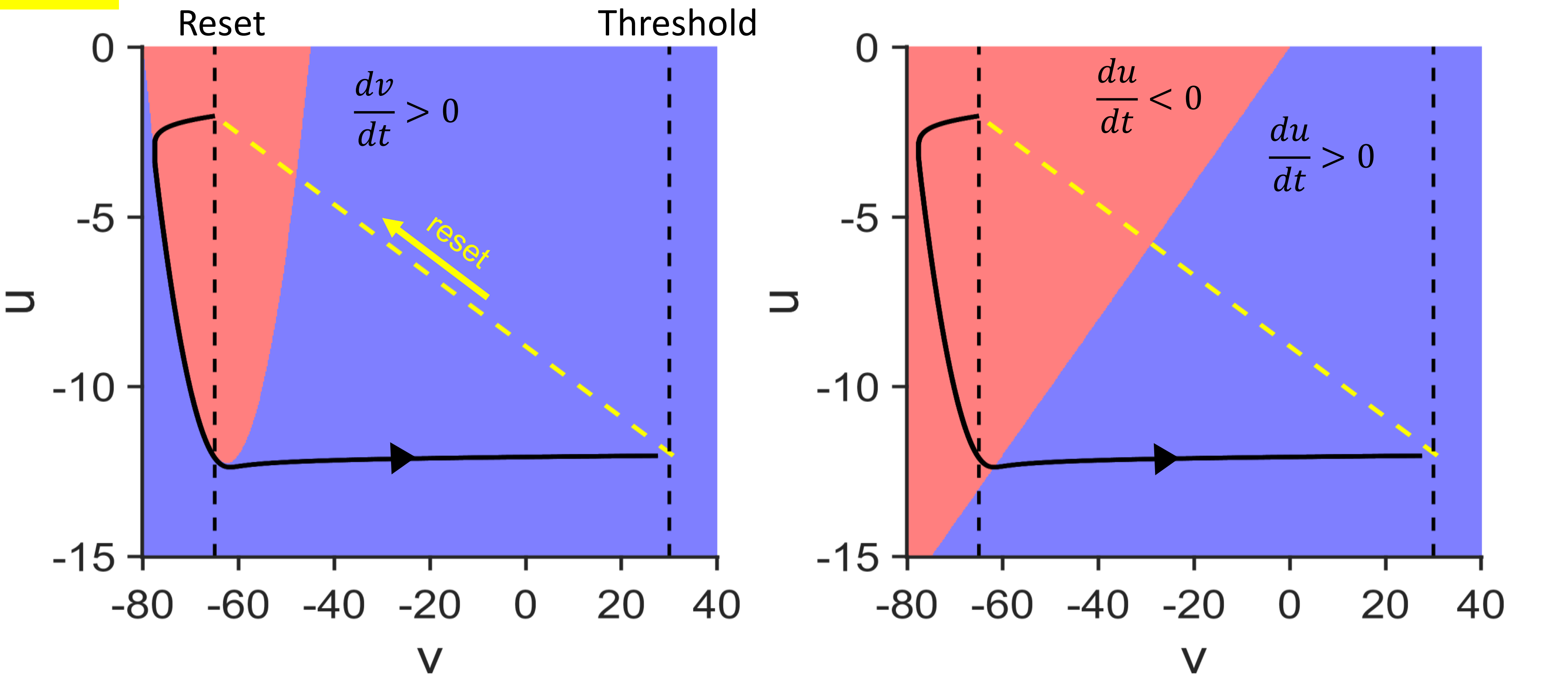


Models of neuronal excitability: Izhikevich

Resetting mechanism:

If $v > 30$, then

$$v \rightarrow c$$
$$u \rightarrow u + d$$



Models of neuronal excitability: Izhikevich

Simplified nondimensional model

$$\mathrm{d}v/\mathrm{dt} = 0.04v^2 + 5v + 140 - u + I$$
$$\mathrm{d}u/\mathrm{dt} = a(bv - u)$$

$$\text{if } v \geq v_{peak}, \text{then}$$
$$v \leftarrow c, u \leftarrow u + d$$

I – input current (unitless)
a – timescale of recovery variable (unitless)
b – sensitivity of recovery variable (unitless)
c – sensitivity of recovery variable (unitless)
d – reset value of recovery variable (unitless)
v_{peak} – peak amplitude triggering reset (unitless)

Models of neuronal excitability: Izhikevich

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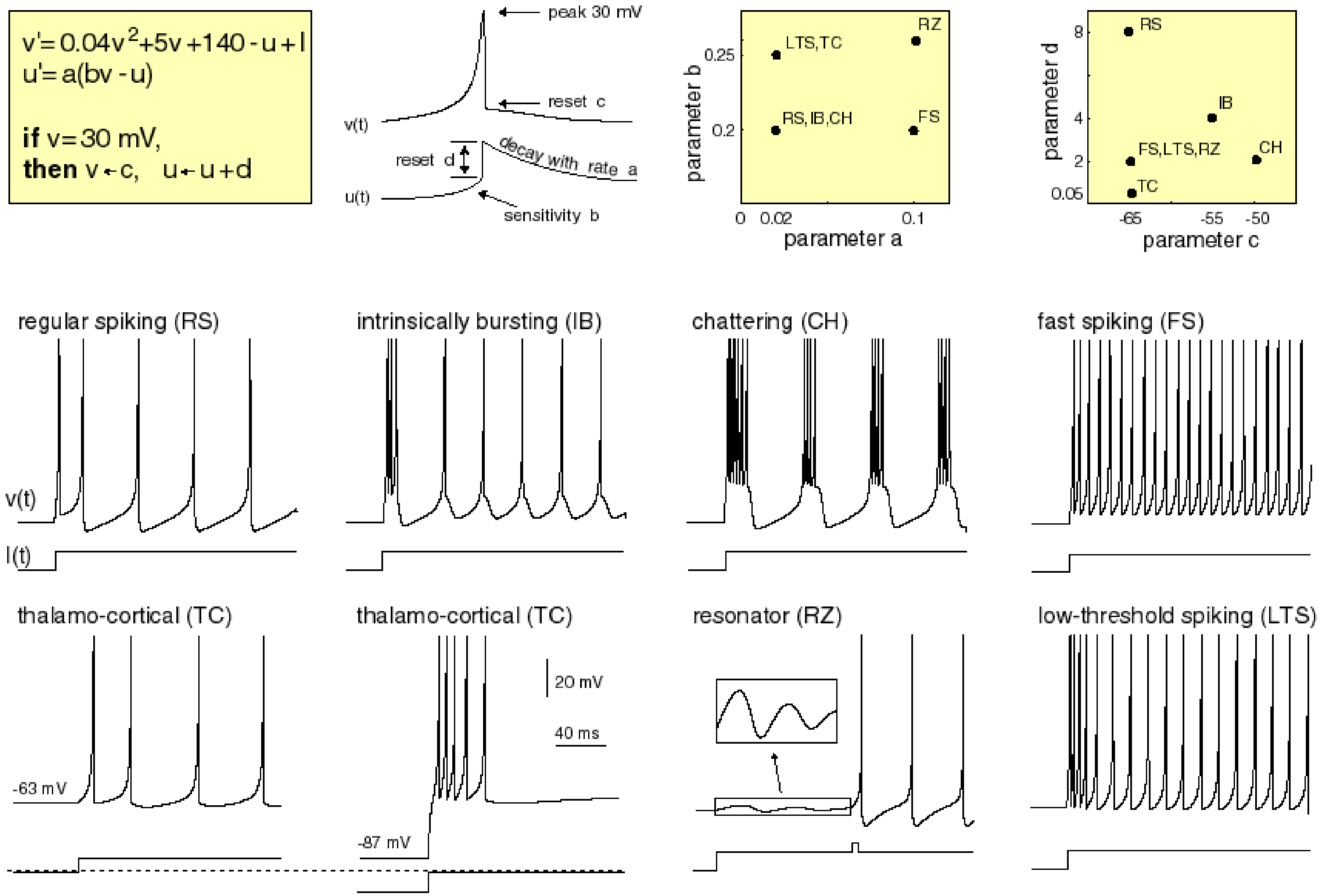


Models of neuronal excitability: Izhikevich

Full Izhikevich model (better for fitting to data)

$$C\ \mathrm{d}v/\mathrm{dt} = k(v - v_r)(v - v_t) - u + I$$
$$\mathrm{d}u/\mathrm{dt} = a(b(v - v_r) - u)$$

if $v \geq v_{peak}$, then
$v \leftarrow c, u \leftarrow u + d$

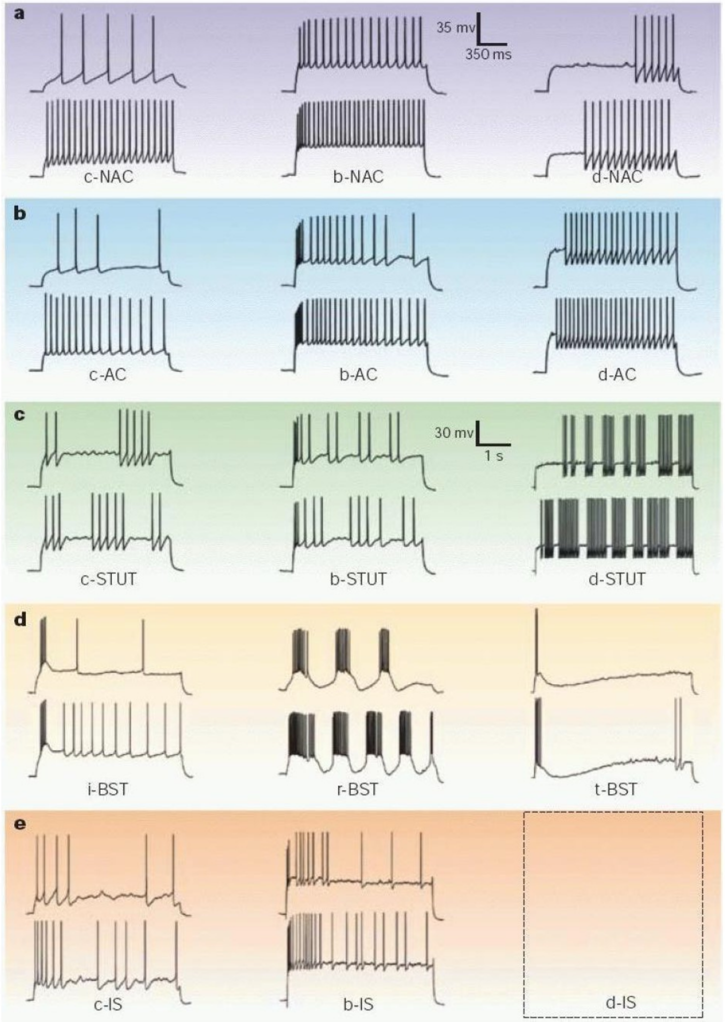
I – injected current in picoamps (pA)
C – membrane capacitance in picofarads (pF)
k – scaling factor (nS)
v_r – resting membrane potential in millivolts (mV)
v_t – instantaneous threshold potential in millivolts (mV)
v_{peak} – peak amplitude triggering reset (mV)
a – timescale of recovery variable in 1/milliseconds (ms^{-1})
b – sensitivity of recovery variable (nS)
c – voltage after resetting (mV)
d – reset value of recovery variable (nS)

Some standard values:
$C = 100$ pF
$k = 1$ nS
$v_r = -60$ mV
$v_t = -40$ mV
$v_{peak} = 30$ mV
Parameters k and b can be estimated from rheobase and input resistance.

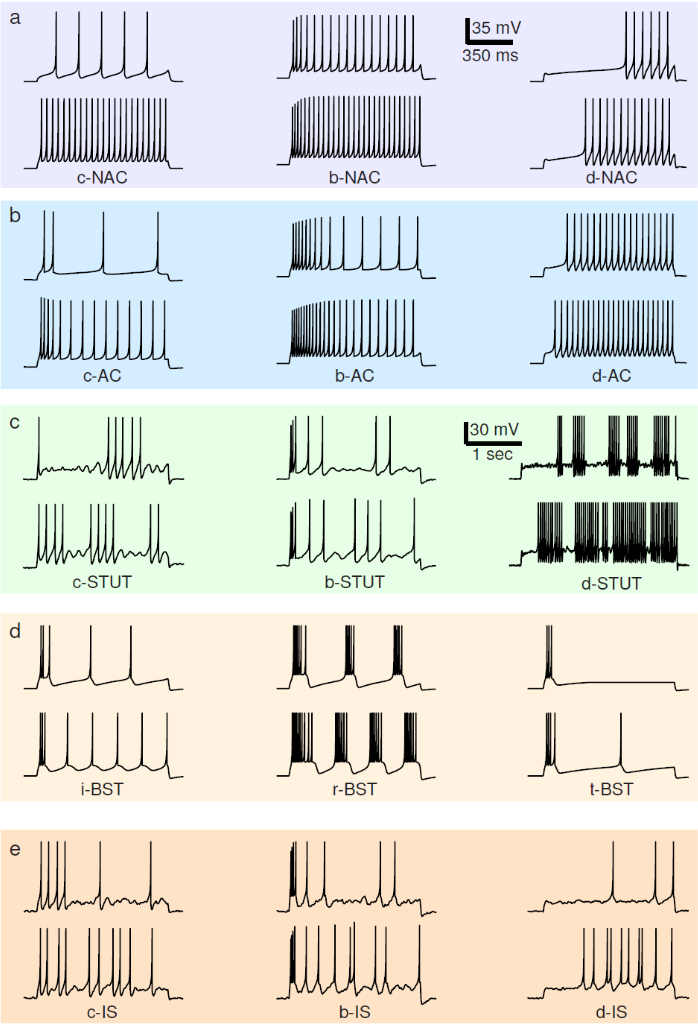
Models of neuronal excitability: Izhikevich

Figs. 8.29 & 8.30; Dynamical Systems in Neuroscience, Izhikevich (2007)

Data



Model



Models of neuronal excitability: Izhikevich

Benefits of Izhikevich models

- Capable of majority of excitability behaviours
- Simple and fast to simulate

Drawbacks

- Does not provide physiological insight into mechanism of firing properties

  "We stress that the simple model is useful only when one wants to simulate largescale networks of spiking neurons. He or she still needs to use the Hodgkin-Huxley-type conductance-based models to study the behavior of one neuron or a small network of neurons." – Izhikevcih (2007) Dynamic Systems in Neuroscience p. 320.

Uses

- Large scale simulations of neural networks with realistic spiking dynamics

Models of neuronal excitability: Conclusion

In this lecture, we have introduced the following models of neuronal excitability:

- Integrate-and-fire
- Hodgkin-Huxley
- Fitzhugh-Nagumo
- Izhikevich

The right model depends on the research question.

- Hodgkin-Huxley: *Good for exploring the effects of ion channels on neuronal excitability*
- Izhikevich: *Good for exploring the effects of neuronal excitability on network dynamics*

Up next: Explaining experimental observations requires finding model parameters that best reproduce the data. This is variously referred to as parameter tuning / optimization / fitting.