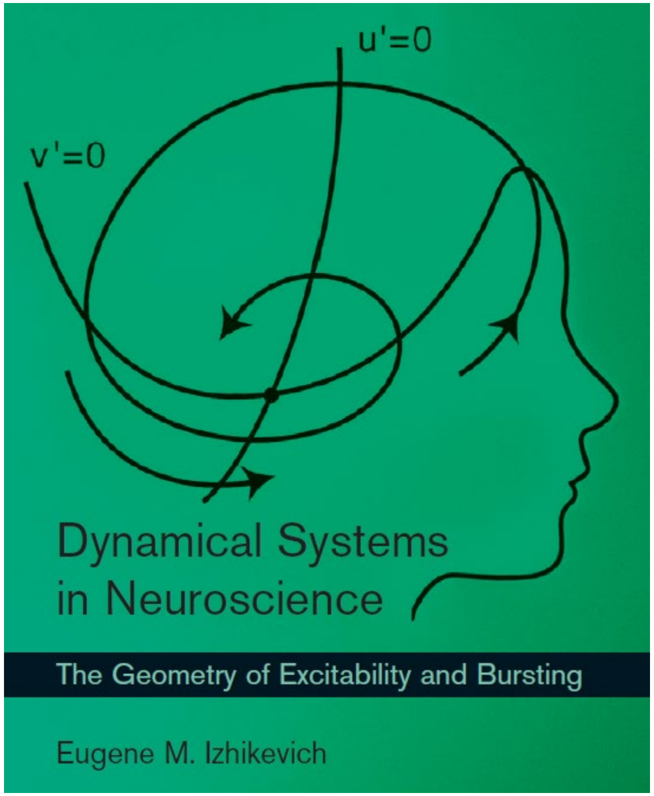
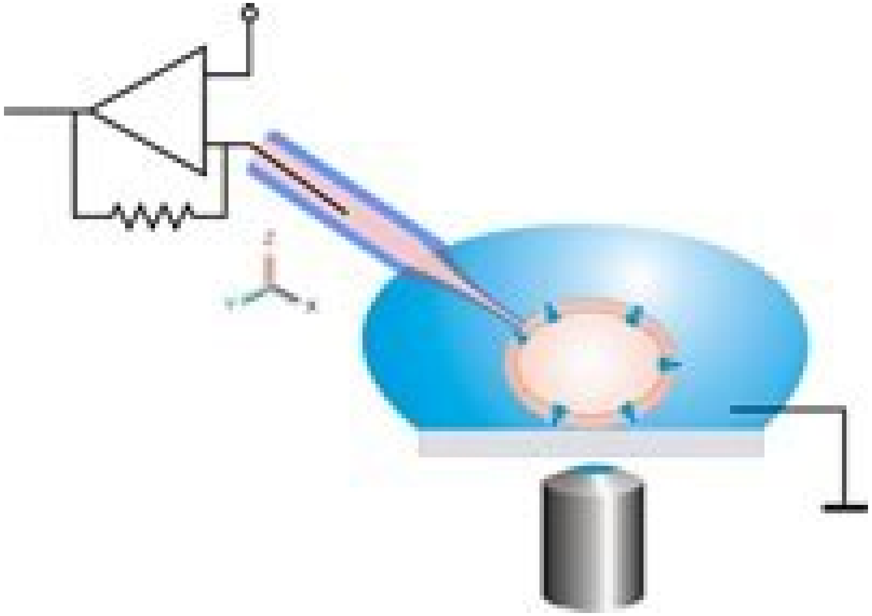
Electrophysiology

Chem 163

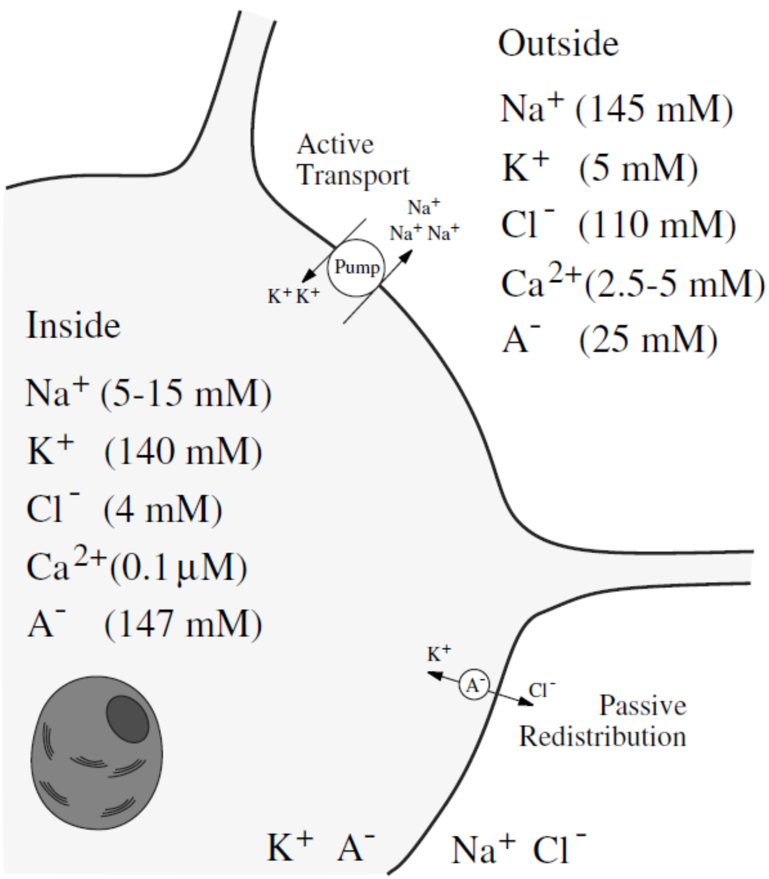
11 Oct. 2022

Today's lecture is from





Ions set the equilibrium potentials



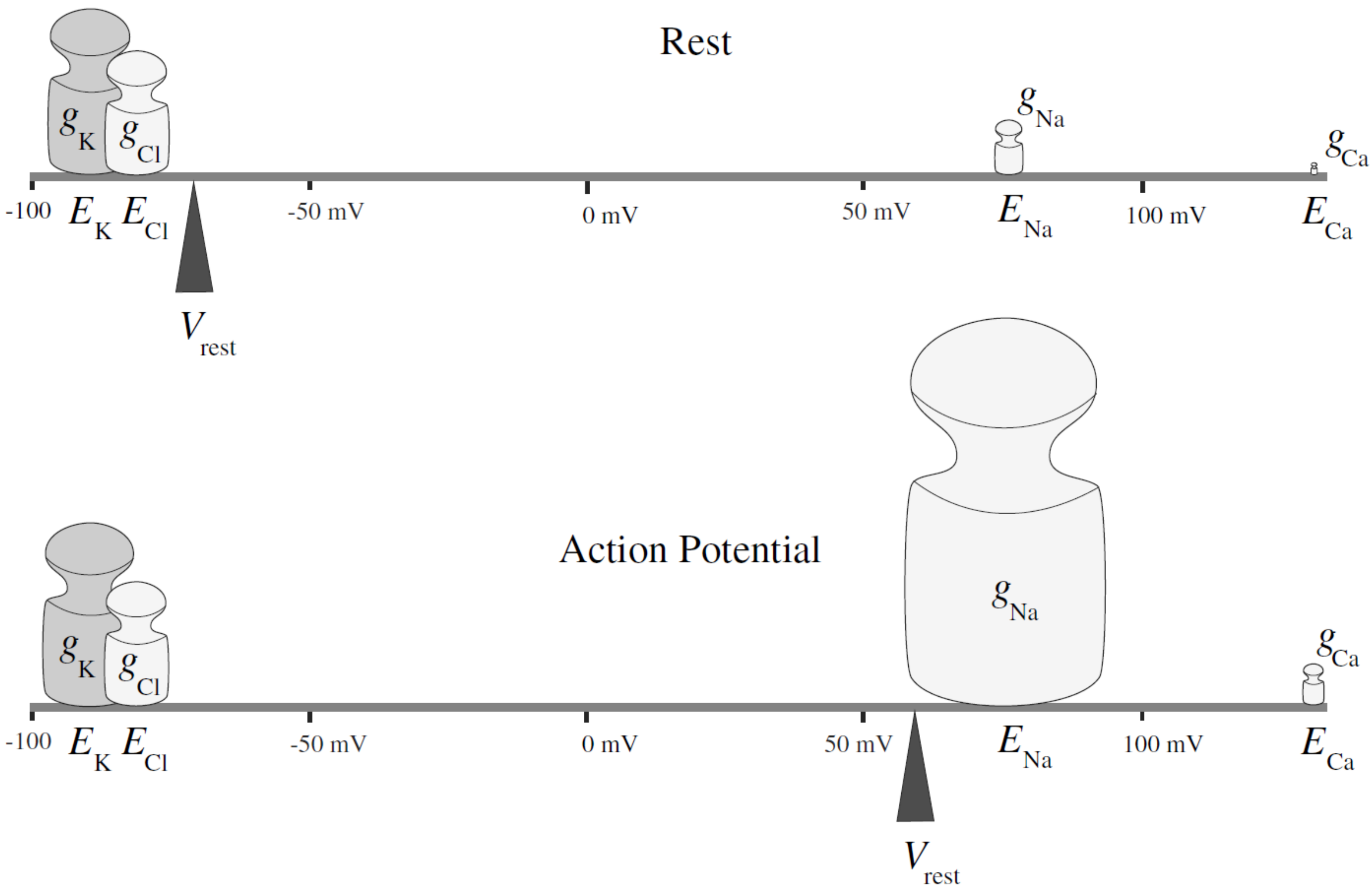
$$E_{\text{ion}} = \frac{RT}{zF} \ln \frac{[\text{Ion}]_{\text{out}}}{[\text{Ion}]_{\text{in}}}$$

$$E_{\text{ion}} \approx 62 \log \frac{[\text{Ion}]_{\text{out}}}{[\text{Ion}]_{\text{in}}} \quad (\text{mV})$$

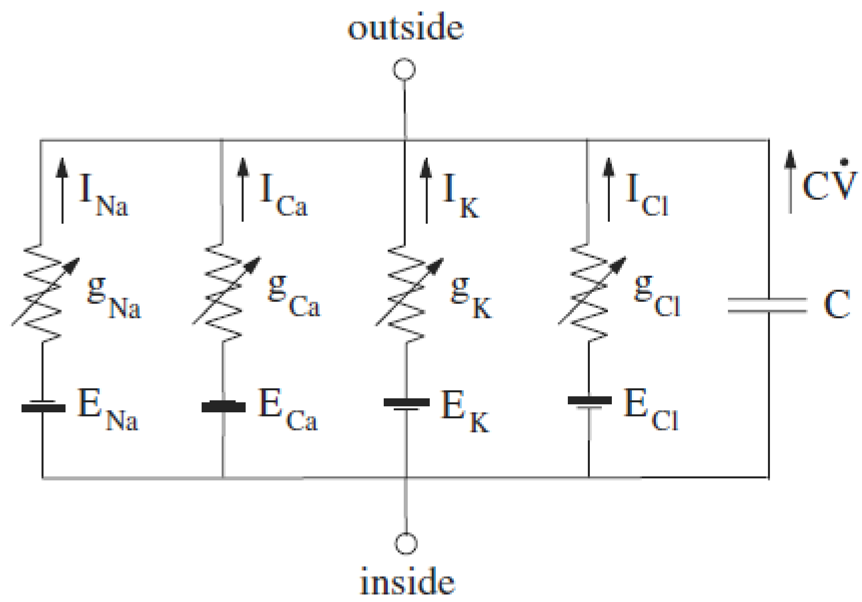
Equilibrium Potentials

Na^+	$62 \log \frac{145}{5}$	=	90 mV
	$62 \log \frac{145}{15}$	=	61 mV
K^+	$62 \log \frac{5}{140}$	=	−90 mV
Cl^-	$-62 \log \frac{110}{4}$	=	−89 mV
Ca^{2+}	$31 \log \frac{2.5}{10^{-4}}$	=	136 mV
	$31 \log \frac{5}{10^{-4}}$	=	146 mV

Zeroth order picture of a spike



Ion channel conductances depend on voltage



$$I_{\mathrm{K}} = g_{\mathrm{K}}\,(V - E_{\mathrm{K}}) \qquad I_{\mathrm{Na}} = g_{\mathrm{Na}}\,(V - E_{\mathrm{Na}})\,, \qquad I_{\mathrm{Ca}} = g_{\mathrm{Ca}}\,(V - E_{\mathrm{Ca}})\,, \qquad I_{\mathrm{Cl}} = g_{\mathrm{Cl}}\,(V - E_{\mathrm{Cl}})$$

$$I = C\dot{V} + I_{\mathrm{Na}} + I_{\mathrm{Ca}} + I_{\mathrm{K}} + I_{\mathrm{Cl}}$$

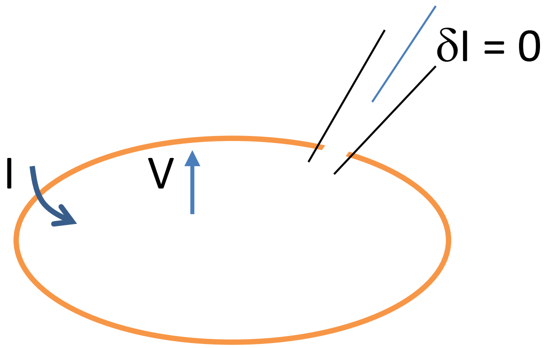
$$C\dot{V} = I - g_{\mathrm{Na}}\,(V - E_{\mathrm{Na}}) - g_{\mathrm{Ca}}\,(V - E_{\mathrm{Ca}}) - g_{\mathrm{K}}\,(V - E_{\mathrm{K}}) - g_{\mathrm{Cl}}\,(V - E_{\mathrm{Cl}})$$

@steady state and I = 0:

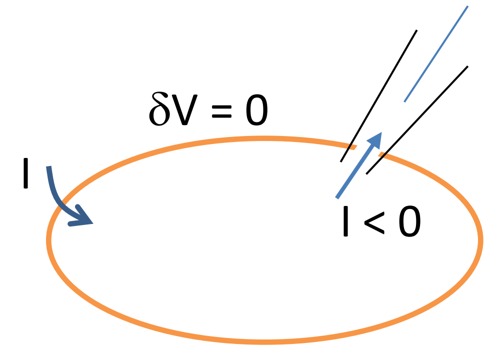
$$\sum_{\substack{i=ion\\channels}} g_i(V - E_i) = 0 \quad \Rightarrow \quad V_{rest} = \frac{\sum_i g_i E_i}{\sum_i g_i}$$

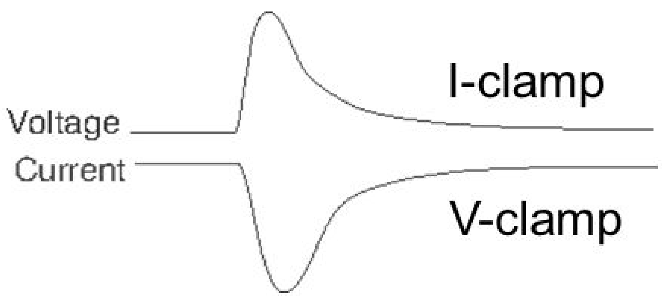
Patch clamp protocols

Current clamp



Voltage clamp





Upward deflections are depolarizing; downward are hyperpolarizing

Downward (negative deflections) are inward currents; upward are outward

A note on units:

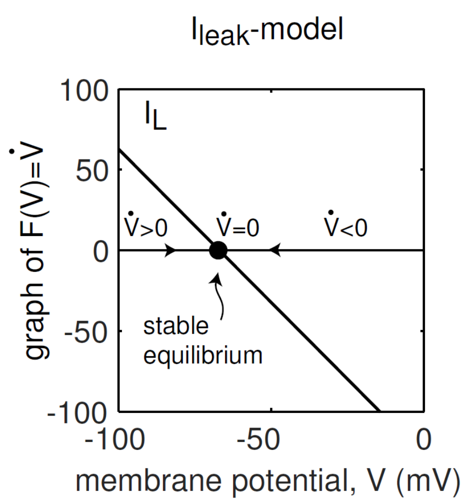
[g] = Siemens (nS, pS) or S/cm^2 or S/uF

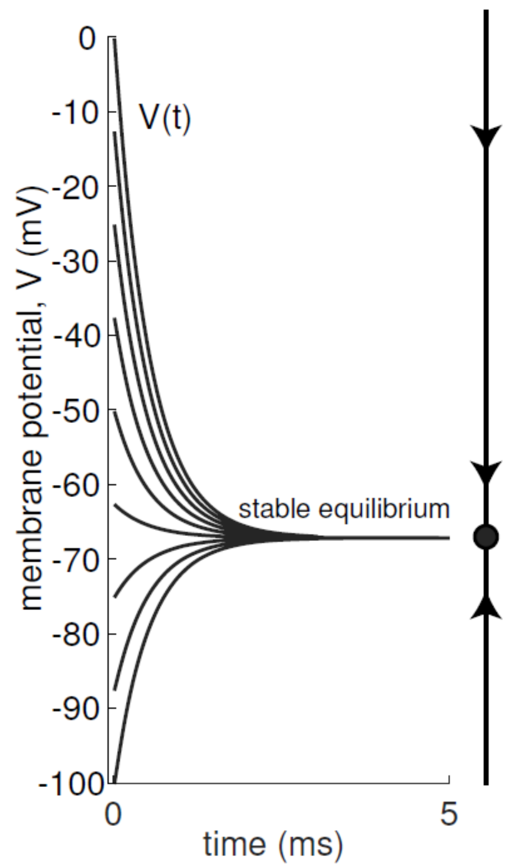
C_m ~ 1 uF/cm^2, always

Leak conductance

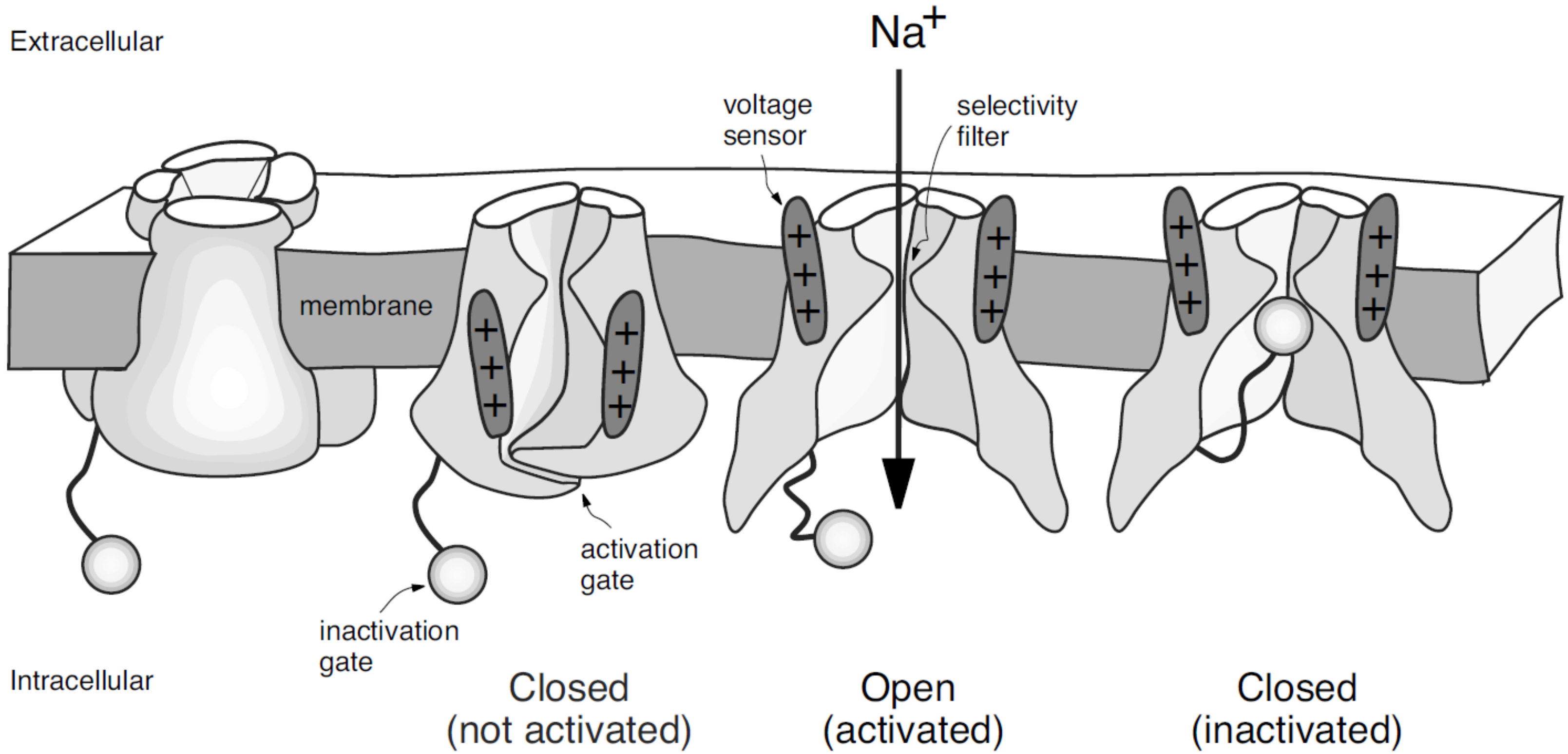
$$C\dot{V} = I - \overbrace{g_{\text{leak}}(V - E_{\text{leak}})}^{\text{Ohmic leakage}}$$

Assume E_L ~ -70 mV





Cartoon of a sodium channel



What is the steady-state activation function of a voltage-gated ion channel?

$$\text{closed} \underset{}{\overset{+V}{\rightleftharpoons}} \text{open}$$

Define m = P(open)

$$\frac{m}{1-m} = K_{eq} e^{\frac{qV}{k_B T}}$$

Assuming +V favors open state

$$m\left(1 + K_{eq} e^{\frac{qV}{k_B T}}\right) = K_{eq} e^{\frac{qV}{k_B T}}$$

$$m = \frac{K_{eq} e^{\frac{qV}{k_B T}}}{\left(1 + K_{eq} e^{\frac{qV}{k_B T}}\right)} \times \frac{K_{eq}^{-1} e^{-\frac{qV}{k_B T}}}{K_{eq}^{-1} e^{-\frac{qV}{k_B T}}}$$

$$m = \frac{1}{\left(1 + K_{eq}^{-1} e^{-\frac{qV}{k_B T}}\right)}$$

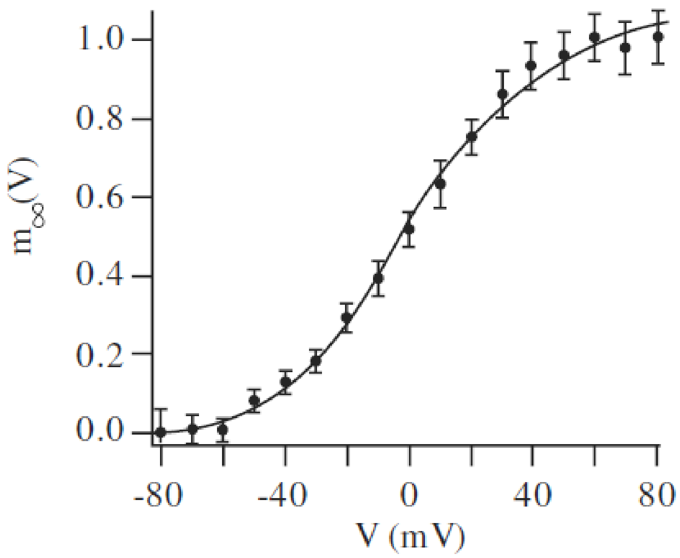
Define: $K_{eq}^{-1} = e^{\frac{qV_{1/2}}{k_B T}}$ $\quad k = \frac{k_B T}{q}$

$$m = \frac{1}{\left(1 + e^{(V_{1/2} - V)/k}\right)}$$

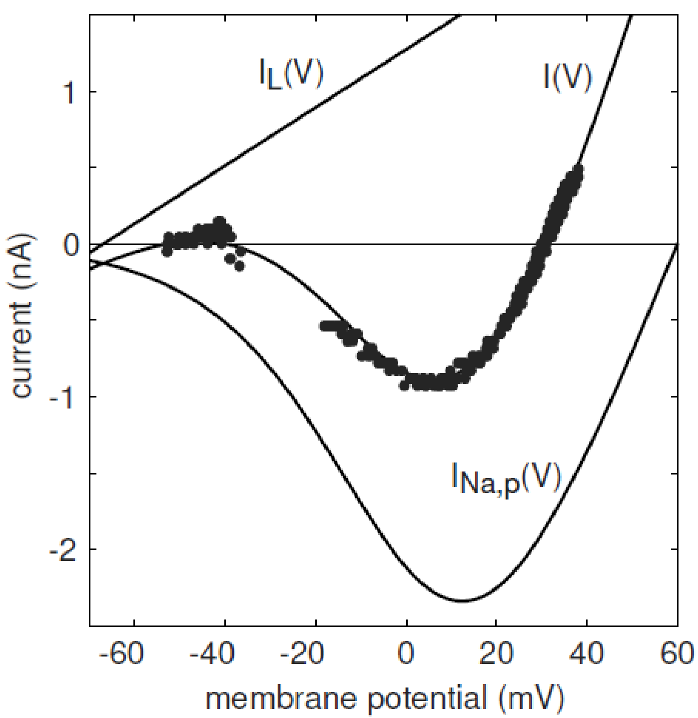
Simple single-channel model

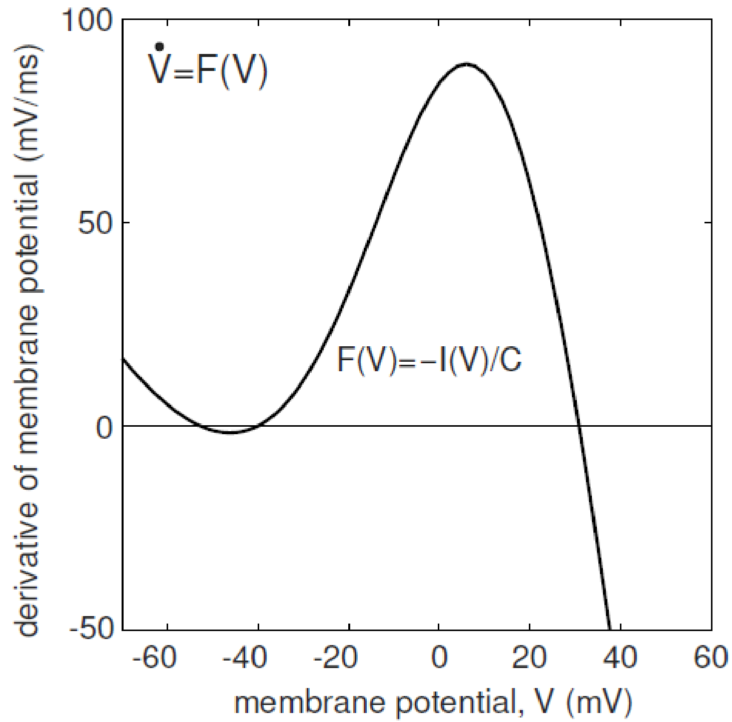
$$C\,\dot{V} = I - g_{\mathrm{L}}(V - E_{\mathrm{L}}) - \overbrace{g_{\mathrm{Na}}\, m_{\infty}(V)\,(V - E_{\mathrm{Na}})}^{\text{instantaneous } I_{\mathrm{Na,p}}}$$

$$m_{\infty}(V) = 1/(1 + \exp\{(V_{1/2} - V)/k\})$$

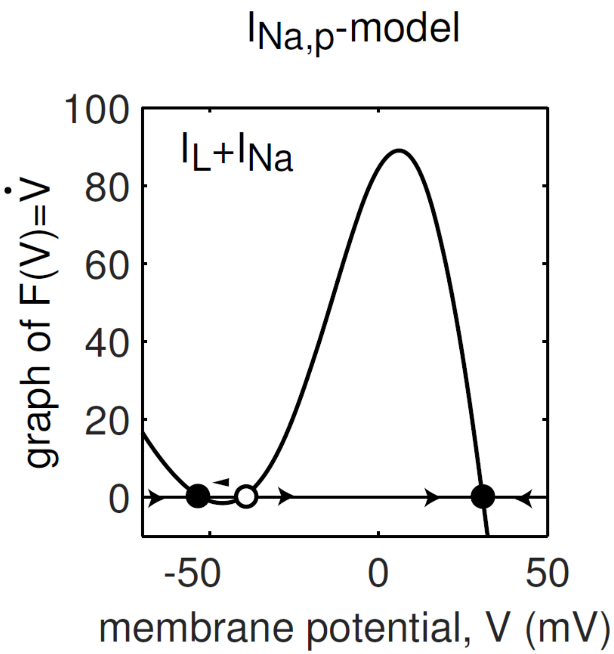


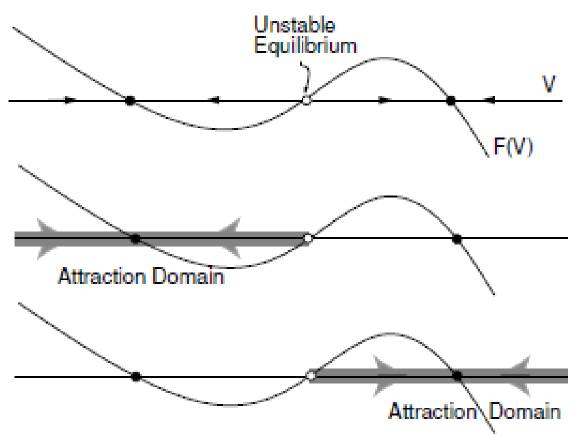
Phase diagram of simple model

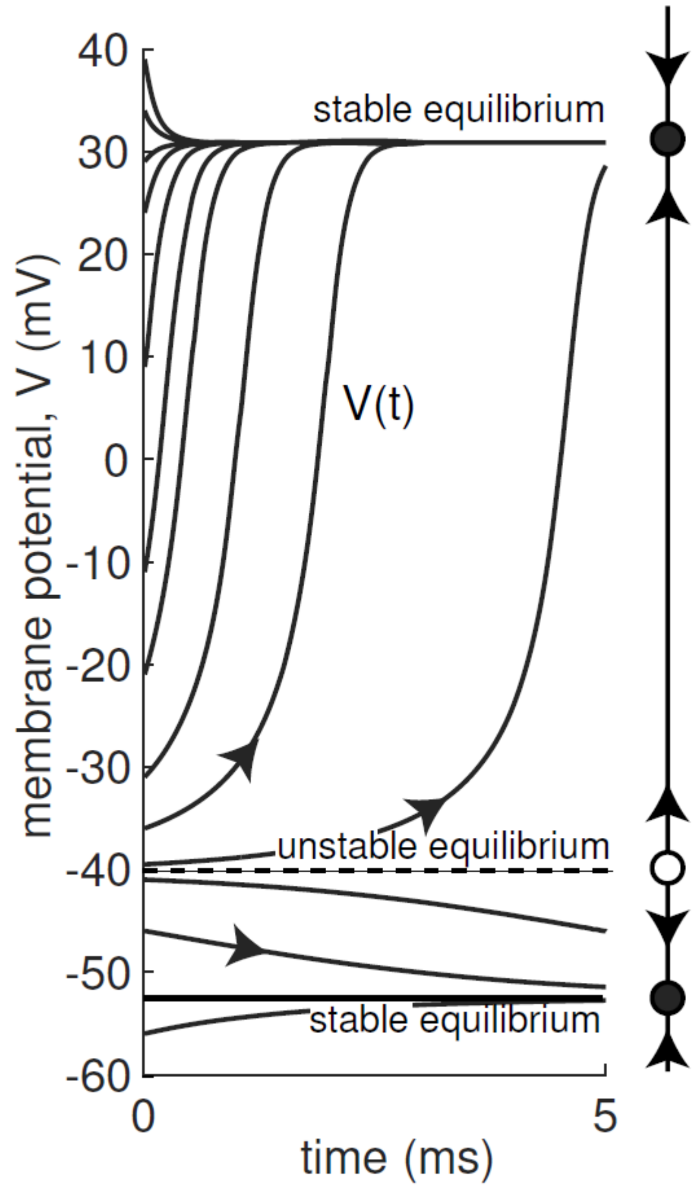




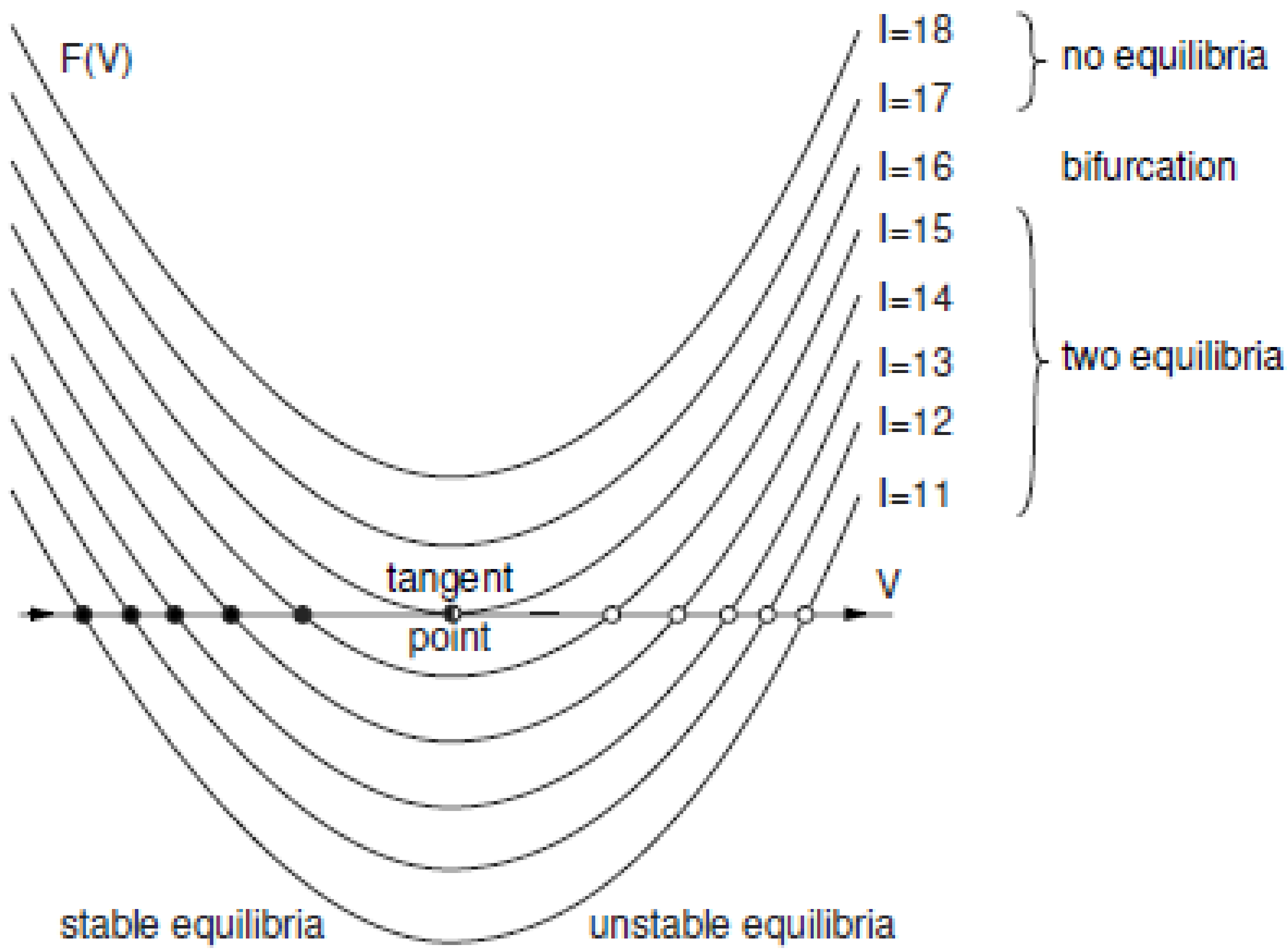
Persistent sodium current model shows bistability



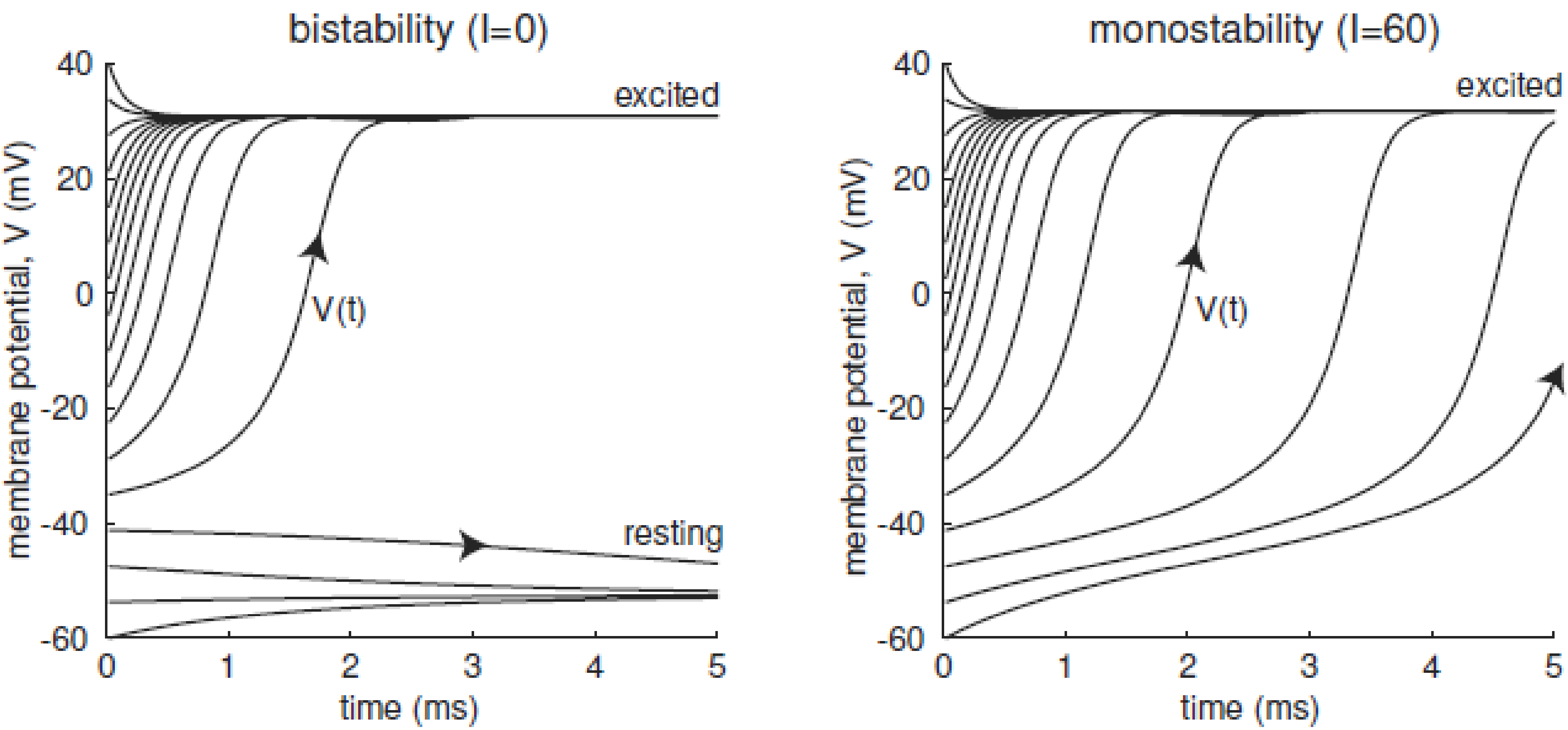




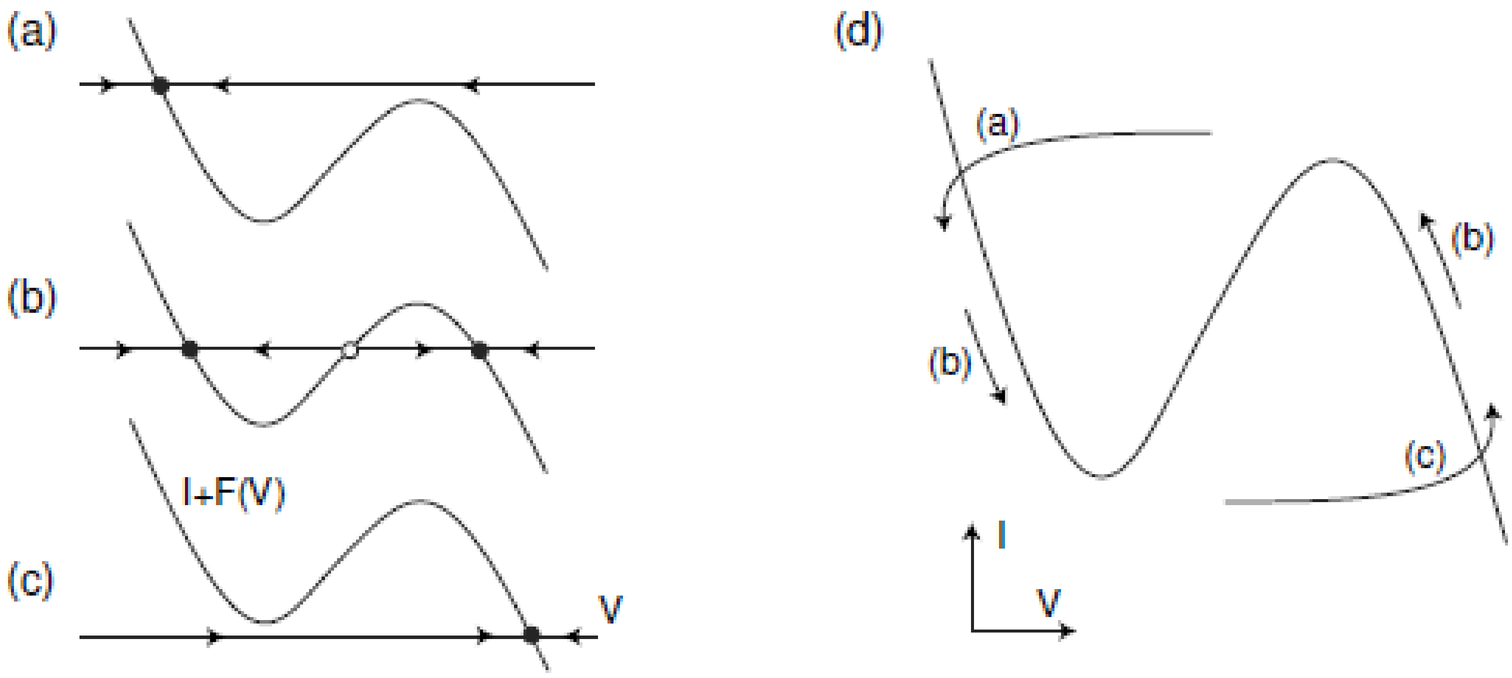
Saddle node bifurcation



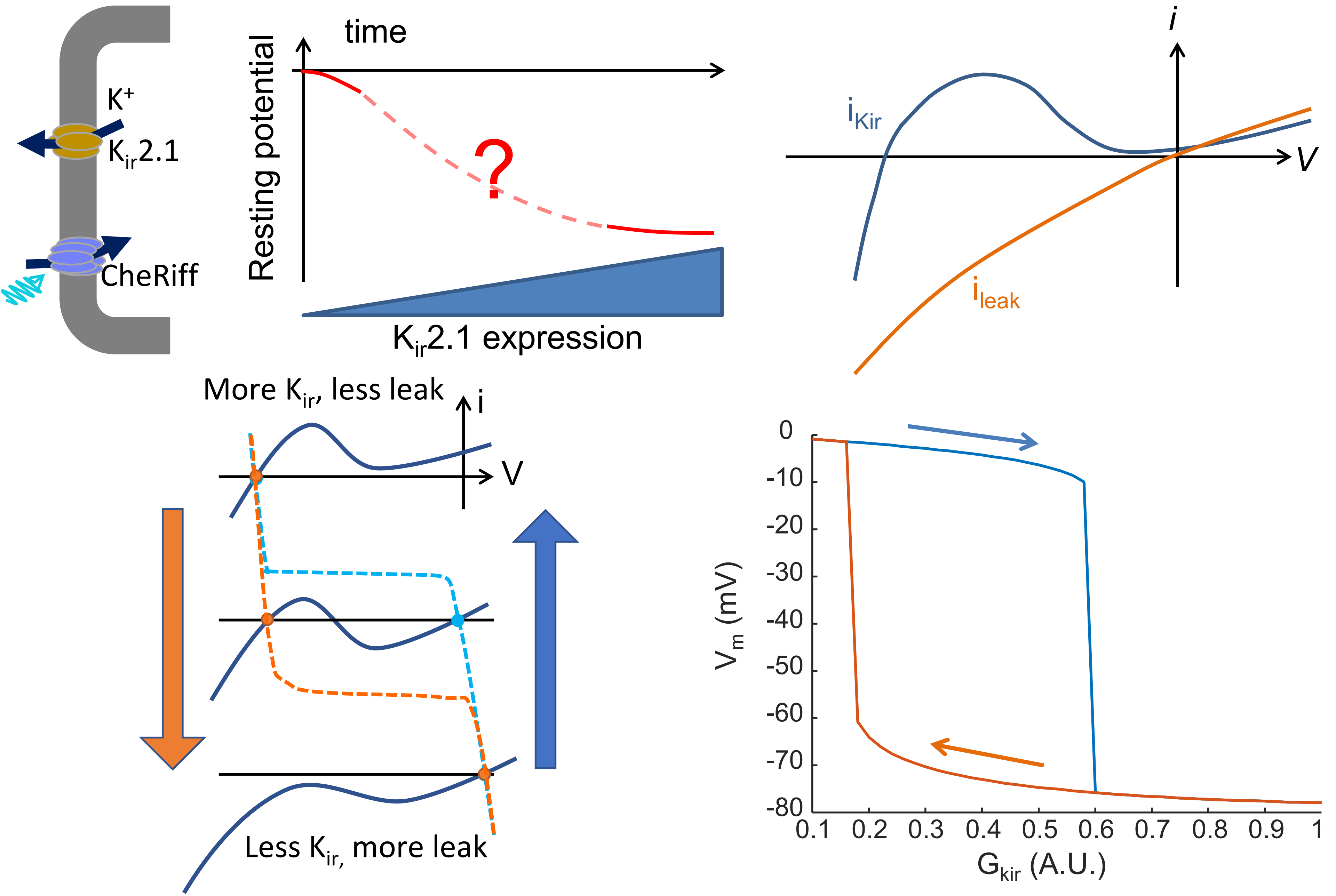
Basins of attraction



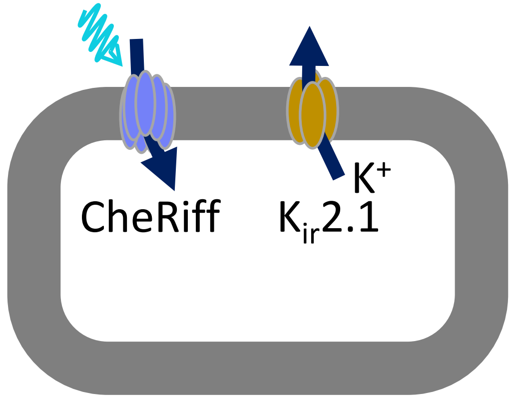
Hysteresis

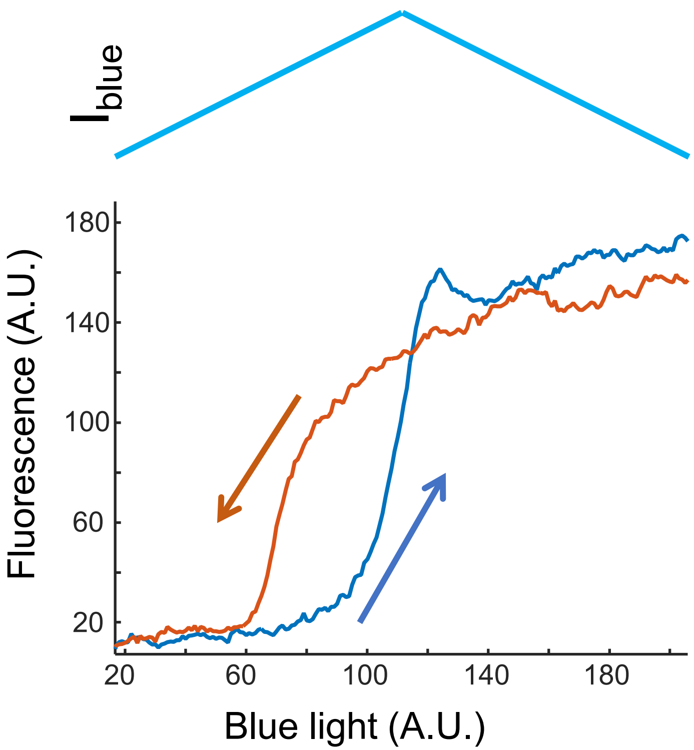


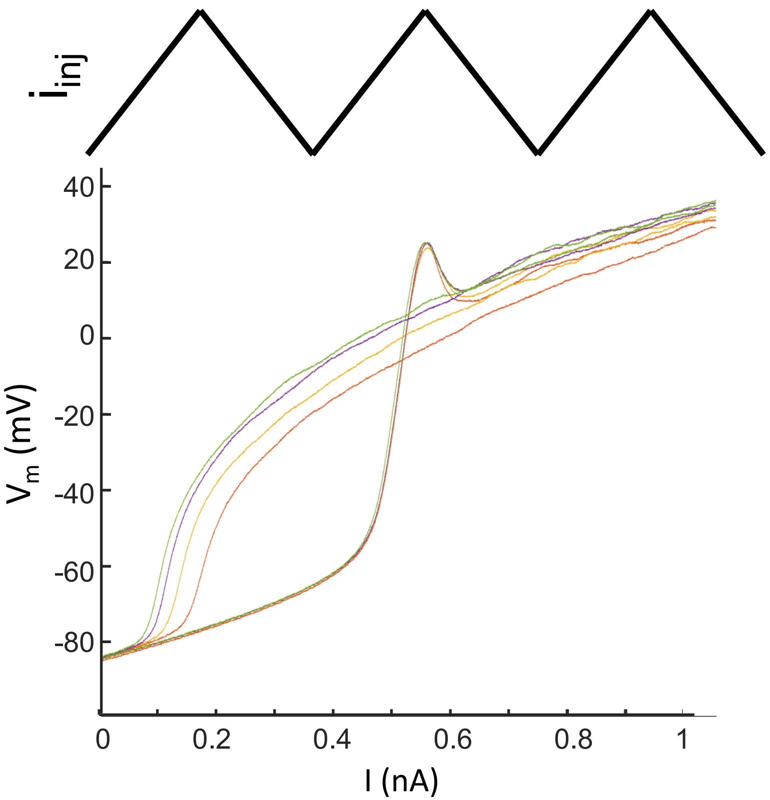
How does a tissue polarize?



Bistability in HEK cells expressing $K_{ir}2.1$

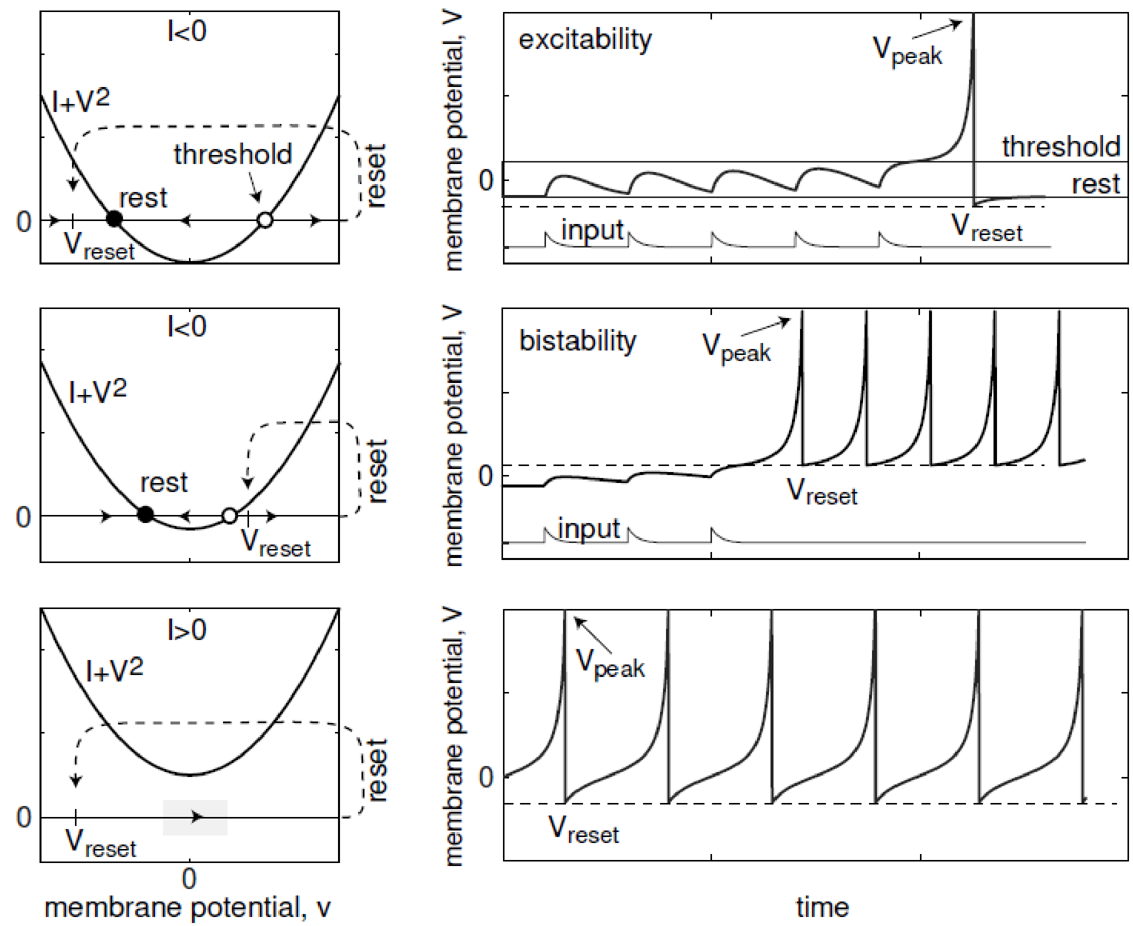






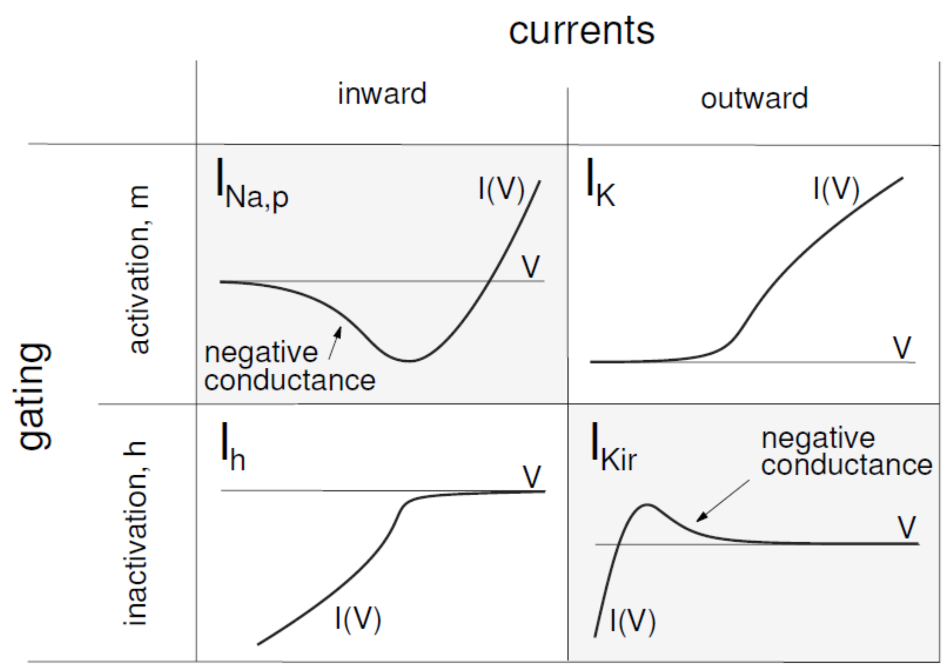
Quadratic integrate and fire neuron

$$\dot{V} = I + V^2 , \qquad \text{if } V \geq V_{\text{peak}}, \quad \text{then } V \leftarrow V_{\text{reset}}$$



Classes of voltage-dependent behavior

Gating	Current: inward	Current: outward
activation	$I_{Na,p}$	I_K
inactivation	I_h	I_{Kir}

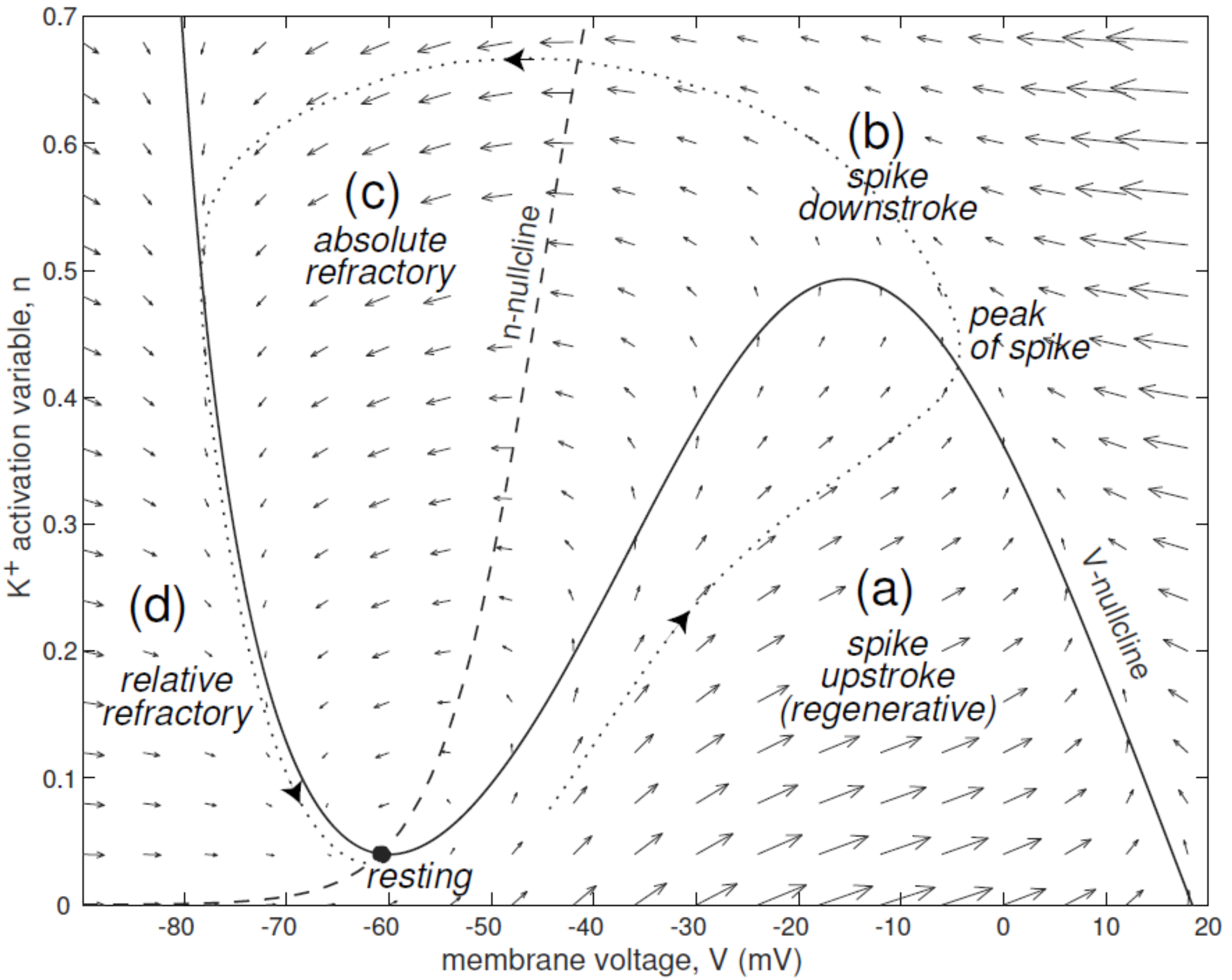


This cartoon only models ion channel ‘steady-state’ behavior. Over very short time channel activation kinetics are important. Over very long times channel inactivation and recovery kinetics are important.

(More) realistic neuron model

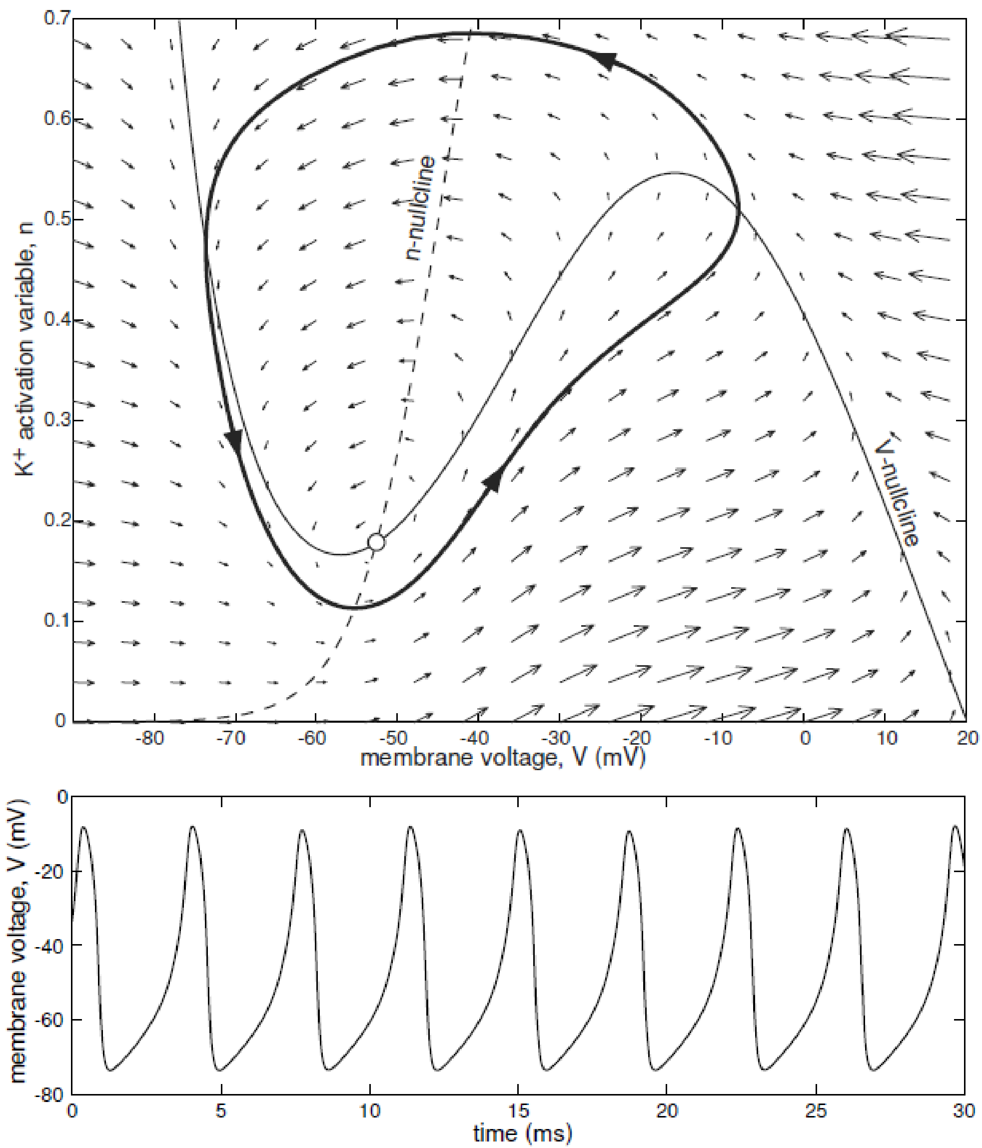
$$C\dot{V} = I - \overbrace{g_L(V - E_L)}^{\text{leak } I_L} - \overbrace{g_{Na}\, m_\infty(V)\,(V - E_{Na})}^{\text{instantaneous } I_{Na,p}} - \overbrace{g_K\, n\,(V - E_K)}^{I_K},$$

$$\dot{n} = (n_\infty(V) - n)/\tau(V),$$



Activates at positive voltages

Stable limit cycle



Analyzing stability around 2-D fixed points

Arbitrary 2-D vector-field

$$\begin{aligned}\dot{x} &= f(x,y)\\ \dot{y} &= g(x,y)\end{aligned}$$

$$\begin{aligned}f(x,y) &= a(x-x_0)+b(y-y_0)+\text{higher-order terms},\\ g(x,y) &= c(x-x_0)+d(y-y_0)+\text{higher-order terms},\end{aligned}$$

$$a=\frac{\partial f}{\partial x}(x_0,y_0), \qquad b=\frac{\partial f}{\partial y}(x_0,y_0),$$

$$c=\frac{\partial g}{\partial x}(x_0,y_0), \qquad d=\frac{\partial g}{\partial y}(x_0,y_0)$$

Linearized dynamics around a fixed point

Let:

$$u = x - x_0$$

$$w = y - y_0$$

The dynamics then become:

$$\begin{pmatrix} \dot{u} \\ \dot{w} \end{pmatrix} = \begin{pmatrix} a & b \\ c & d \end{pmatrix} \begin{pmatrix} u \\ w \end{pmatrix}$$

Let:

$$L = \begin{pmatrix} a & b \\ c & d \end{pmatrix}$$

So:

$$\dot{\boldsymbol{U}} = \boldsymbol{L}\boldsymbol{U}$$

The solution is:

$$\boldsymbol{U}(\boldsymbol{t}) = \boldsymbol{e}^{\boldsymbol{L}\boldsymbol{t}}\boldsymbol{U}(\boldsymbol{0})$$

Define:

$$\tau = \mathrm{tr}\ L = a + d$$

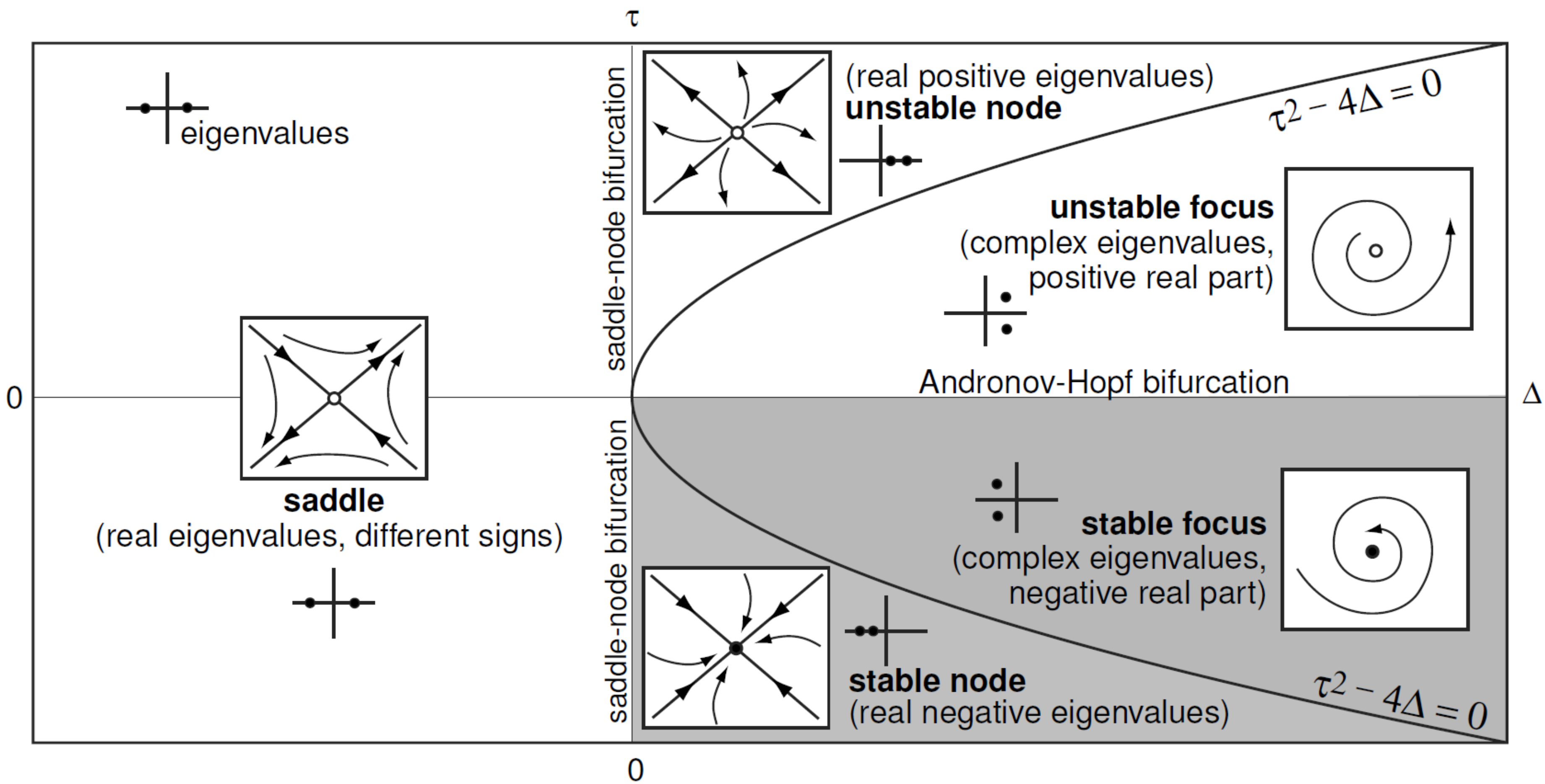
$$\Delta = \det L = ad - bc$$

The qualitative dynamics depend on the eigenvalues of **L**:

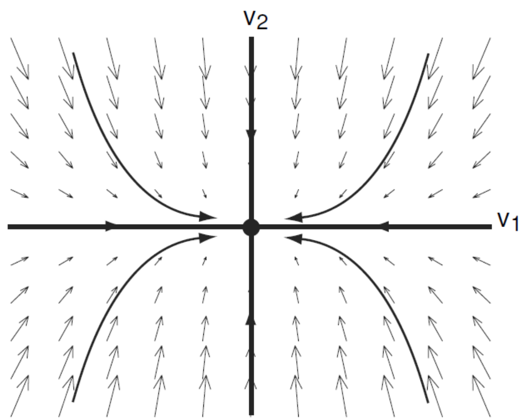
$$\lambda_1 = \frac{\tau + \sqrt{\tau^2 - 4\Delta}}{2}$$

$$\lambda_2 = \frac{\tau - \sqrt{\tau^2 - 4\Delta}}{2}$$

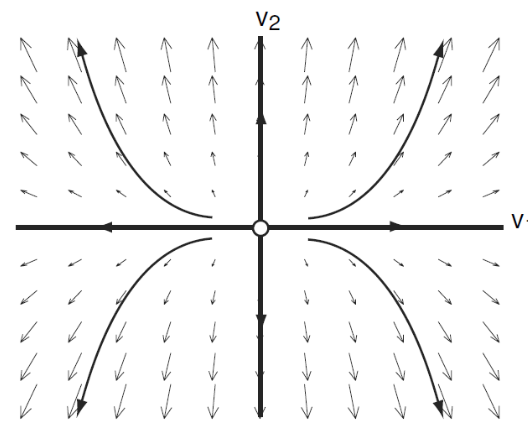
Classification of equilibria



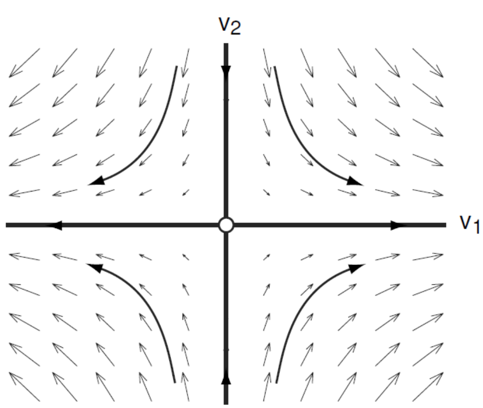
Types of fixed points



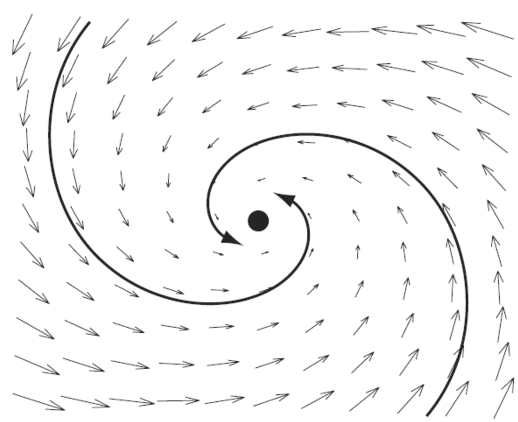
stable node



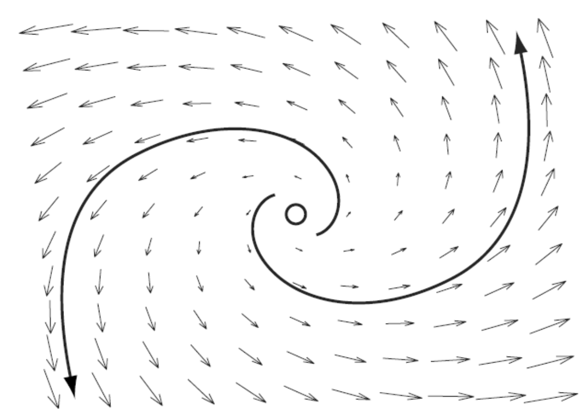
unstable node



saddle

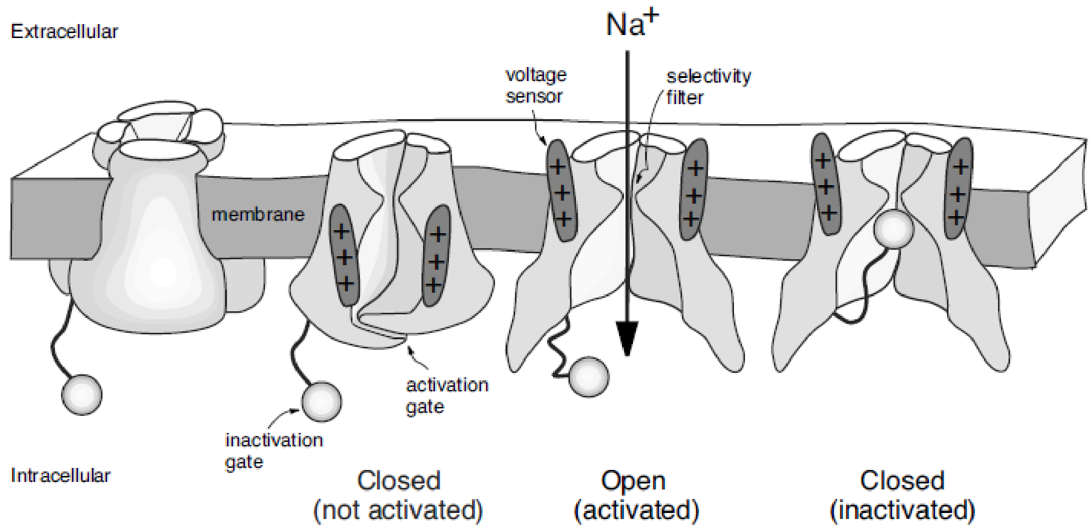


stable focus



unstable focus

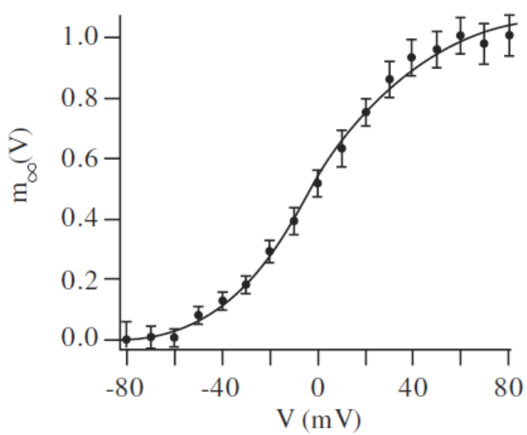
Include Na_V channel inactivation



$$I = \bar{g}\, p\, (V - E)$$

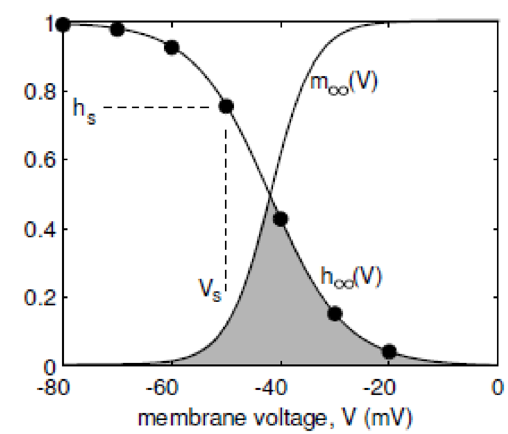
$$p = m^a\, h^b$$

Na_V Activation



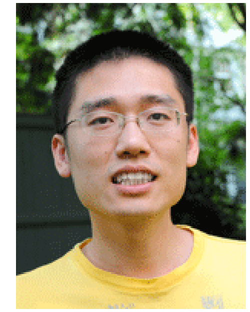
$$\dot{m} = (m_\infty(V) - m)/\tau(V)$$

Na_V Inactivation



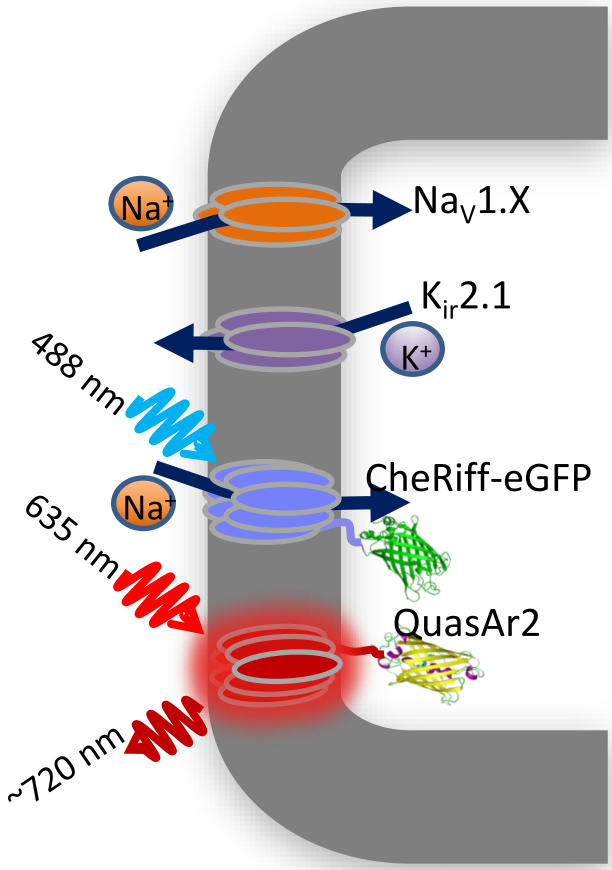
$$\dot{h} = (h_\infty(V) - h)/\tau(V)$$

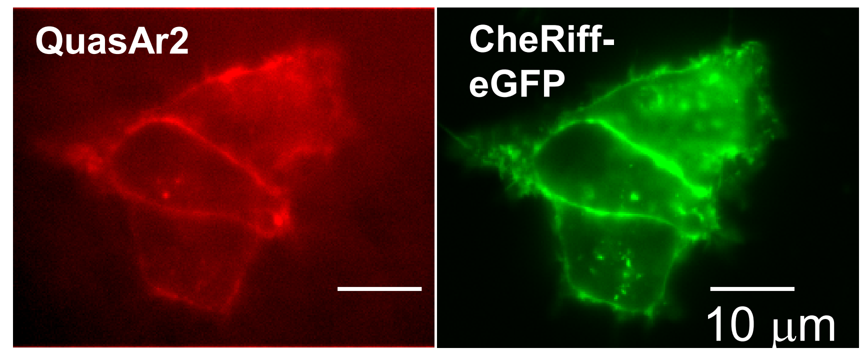
Optical electrophysiology in engineered cells

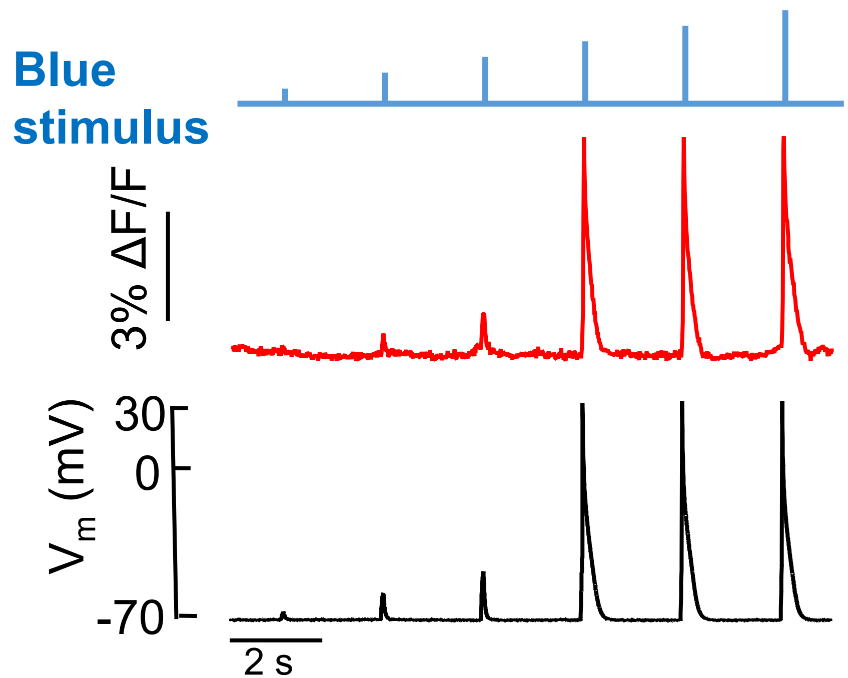


Hongkang Zhang

Kit Werley







Na_V 1.3, 1.5, 1.7, 1.9

eLife, 10.7554/eLife.15202, (2016)

Ion channel dynamics described by two-state gates

Recall for a two-state system:

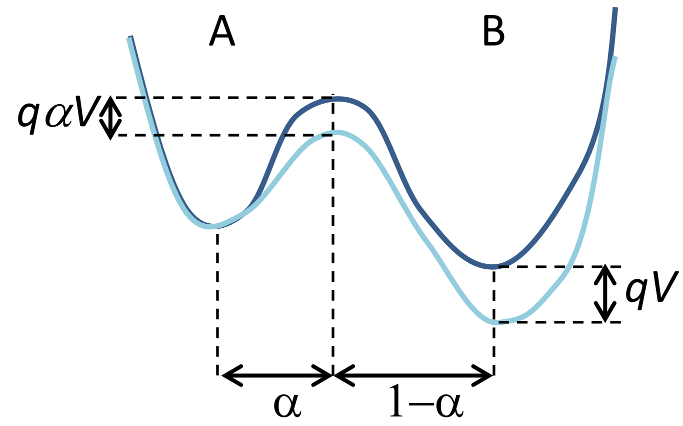
$$A \underset{k_b}{\overset{k_f}{\rightleftharpoons}} B$$

Equilibrium probability of being in state B

$$P_B = \frac{k_f}{k_f + k_b}$$

Relaxation time constant

$$\tau = \frac{1}{k_f + k_b}$$



k_f and k_b depend on voltage:

$$k_f = k_f^0 e^{\frac{\alpha q (V - V_{1/2})}{k_B T}} \qquad k_b = k_b^0 e^{-\frac{(1-\alpha) q (V - V_{1/2})}{k_B T}}$$

HH Equations

$$C\dot{V} = I - \overbrace{\bar{g}_K n^4 (V - E_K)}^{I_K} - \overbrace{\bar{g}_{Na} m^3 h (V - E_{Na})}^{I_{Na}} - \overbrace{g_L (V - E_L)}^{I_L}$$

$$\begin{aligned} \dot{n} &= (n_\infty(V) - n)/\tau_n(V) , \\ \dot{m} &= (m_\infty(V) - m)/\tau_m(V) , \\ \dot{h} &= (h_\infty(V) - h)/\tau_h(V) , \end{aligned}$$

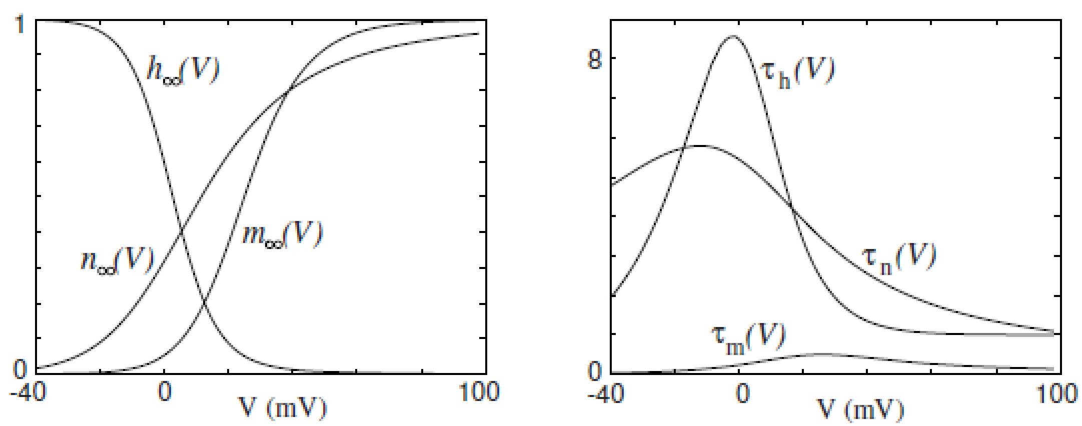
$$\begin{aligned} n_\infty &= \alpha_n/(\alpha_n + \beta_n) , & \tau_n &= 1/(\alpha_n + \beta_n) , \\ m_\infty &= \alpha_m/(\alpha_m + \beta_m) , & \tau_m &= 1/(\alpha_m + \beta_m) , \\ h_\infty &= \alpha_h/(\alpha_h + \beta_h) , & \tau_h &= 1/(\alpha_h + \beta_h) \end{aligned}$$

$$\alpha_p(V_m) = p_\infty(V_m)/\tau_p$$

$$\beta_p(V_m) = (1 - p_\infty(V_m))/\tau_p .$$

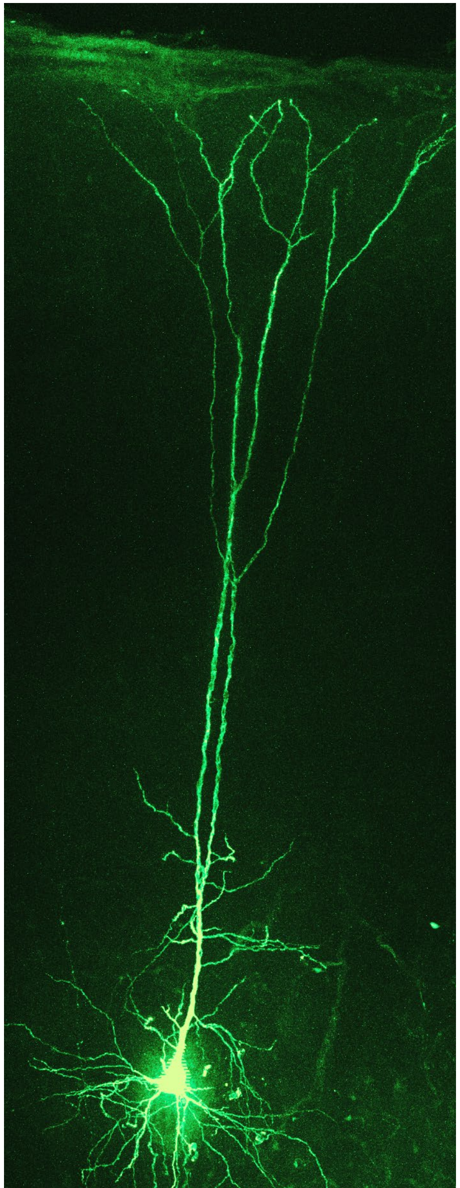
$$\alpha_n(V_m) = \frac{0.01(10-V_m)}{\exp\left(\frac{10-V_m}{10}\right)-1} \qquad \alpha_m(V_m) = \frac{0.1(25-V_m)}{\exp\left(\frac{25-V_m}{10}\right)-1} \qquad \alpha_h(V_m) = 0.07\exp\left(\frac{-V_m}{20}\right)$$

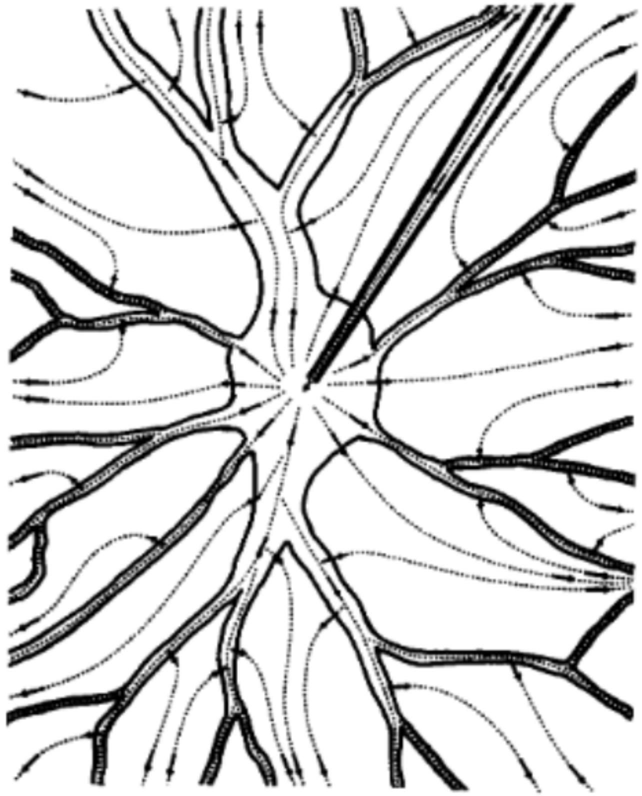
$$\beta_n(V_m) = 0.125\exp\left(\frac{-V_m}{80}\right) \qquad \beta_m(V_m) = 4\exp\left(\frac{-V_m}{18}\right) \qquad \beta_h(V_m) = \frac{1}{\exp\left(\frac{30-V_m}{10}\right)+1}$$



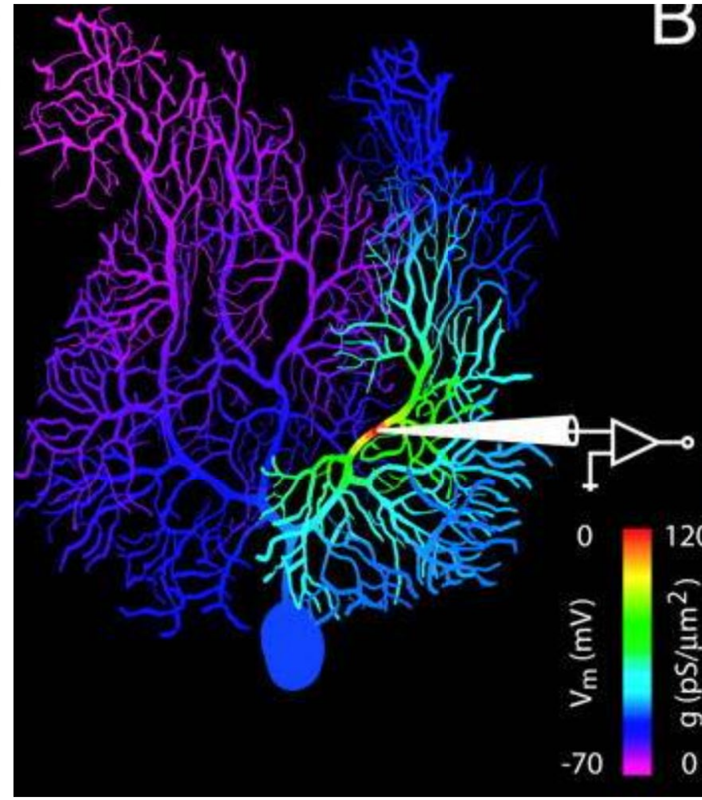
$$\bar{g}_K = 36 \text{ mS/cm}^2 , \qquad \bar{g}_{Na} = 120 \text{ mS/cm}^2 , \qquad g_L = 0.3 \text{ mS/cm}^2$$

Spatial structure of membrane voltage



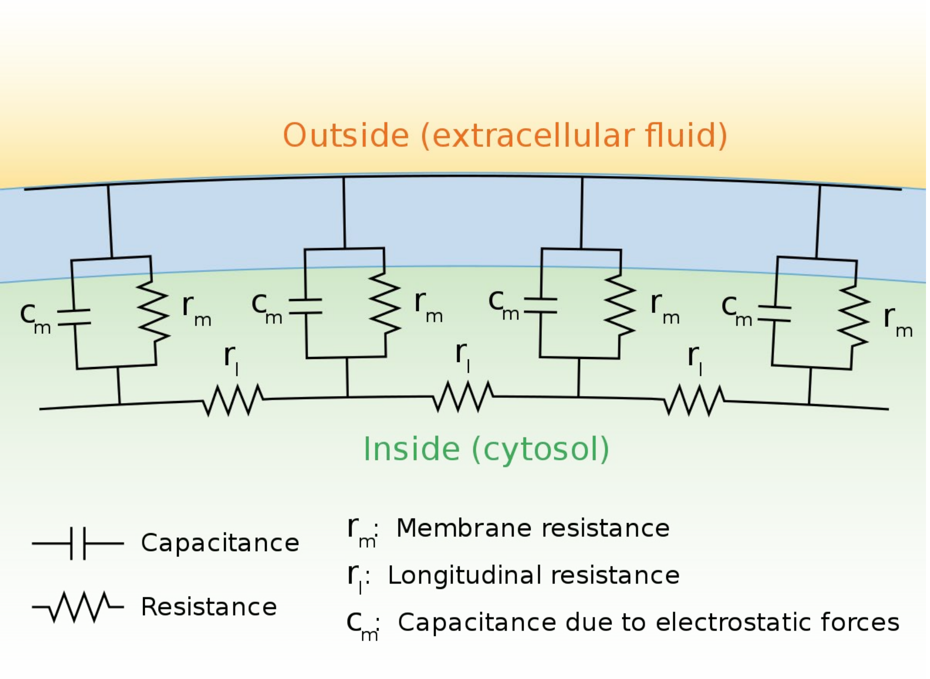


Rall, Wilfrid. "Branching dendritic trees and motoneuron membrane resistivity." *Experimental neurology* 1.5 (1959): 491-527.



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1302937/

Cable equation for a membrane tube



Material properties:

$$r_m = \frac{R_m}{2\pi a} \qquad c_m = C_m 2\pi a \qquad r_l = \frac{\rho_l}{\pi a^2}$$

Constitutive relations:

$$\frac{\partial V}{\partial x} = -i_l r_l \qquad i_c = c_m \frac{\partial V}{\partial t} \qquad i_r = \frac{V}{r_m}$$

Conservation of charge

$$\frac{\partial i_l}{\partial x} = -i_m = -\left(\frac{V}{r_m} + c_m \frac{\partial V}{\partial t}\right)$$

Cable equation

$$\frac{1}{r_l}\frac{\partial^2 V}{\partial x^2} = c_m \frac{\partial V}{\partial t} + \frac{V}{r_m}$$

Dimensionless

$$\lambda^2 \frac{\partial^2 V}{\partial x^2} = \tau \frac{\partial V}{\partial t} + V$$

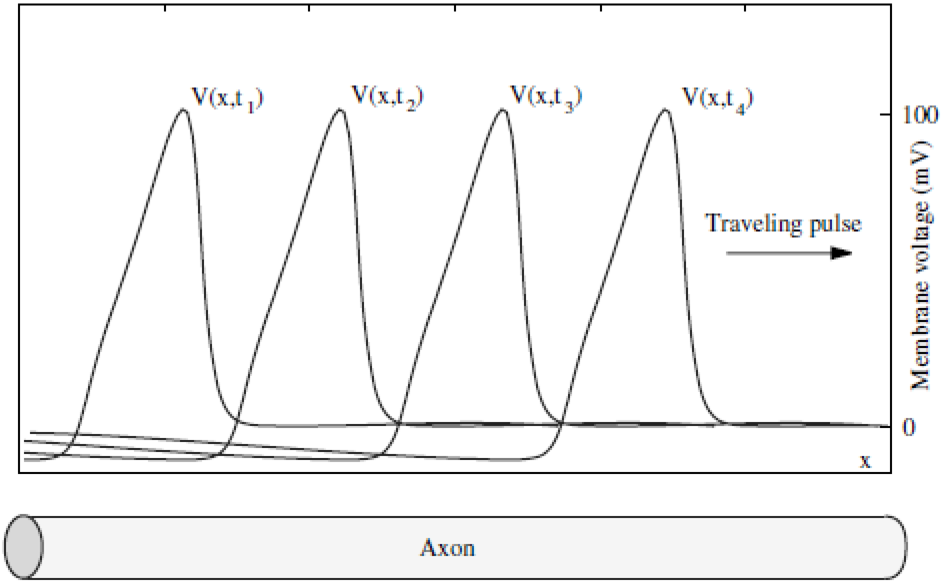
$$\tau = c_m r_m$$

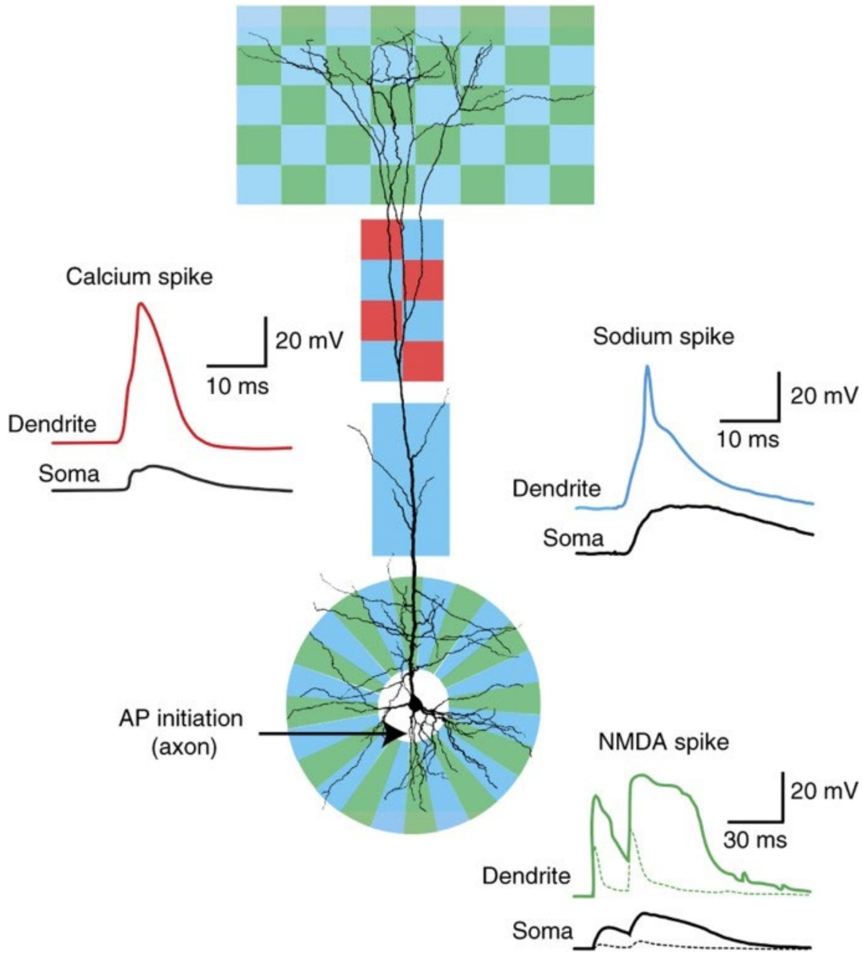
$$\lambda^2 = r_m / r_l$$

$$\lambda = \sqrt{\frac{R_m}{\rho_l}\frac{a}{2}}$$

Propagation of APs

$$C\,V_t = \frac{a}{2R} V_{xx} + I - I_{\mathrm{K}} - I_{\mathrm{Na}} - I_{\mathrm{L}}$$





https://www.nature.com/articles/nn.4157#ref-CR7

Neuron

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Article

Single cortical neurons
deep artificial neural networks

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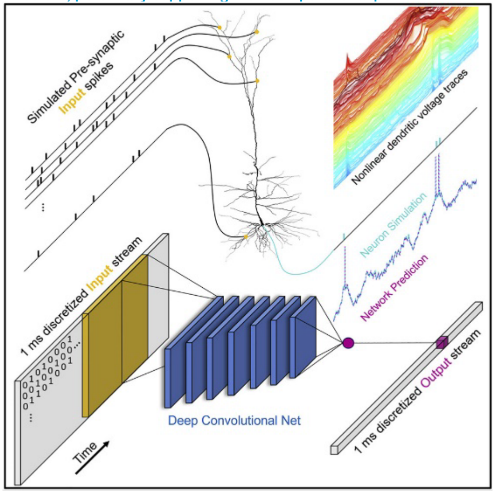
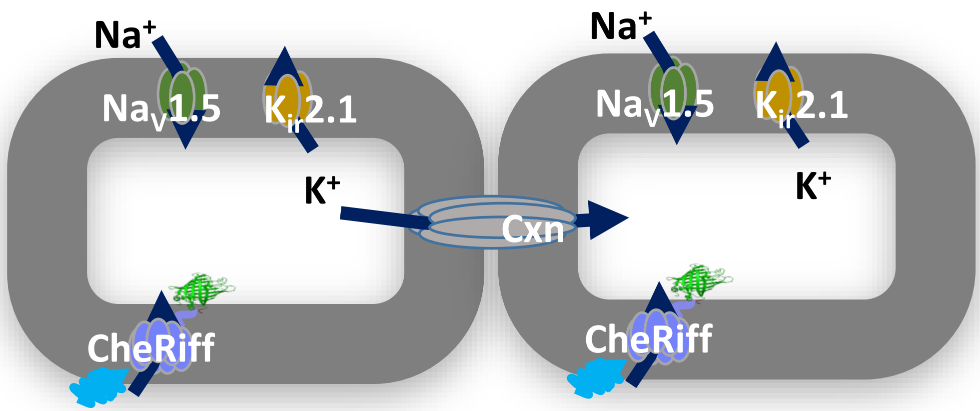
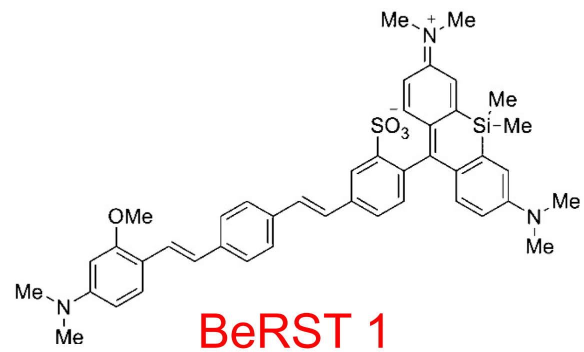
ng recent advances in machine learning, we introduce a systematic approach to characterize ns' input/output (I/O) mapping complexity. Deep neural networks (DNNs) were trained to faithfully ate the I/O function of various biophysical models of cortical neurons at millisecond (spiking) resolu- A temporally convolutional DNN with five to eight layers was required to capture the I/O mapping of a tic model of a layer 5 cortical pyramidal cell (L5PC). This DNN generalized well when presented with s widely outside the training distribution. When NMDA receptors were removed, a much simpler rk (fully connected neural network with one hidden layer) was sufficient to fit the model. Analysis DNNs' weight matrices revealed that synaptic integration in dendritic branches could be conceptu- as pattern matching from a set of spatiotemporal templates. This study provides a unified character- n of the computational complexity of single neurons and suggests that cortical networks therefore a unique architecture, potentially supporting their computational power.



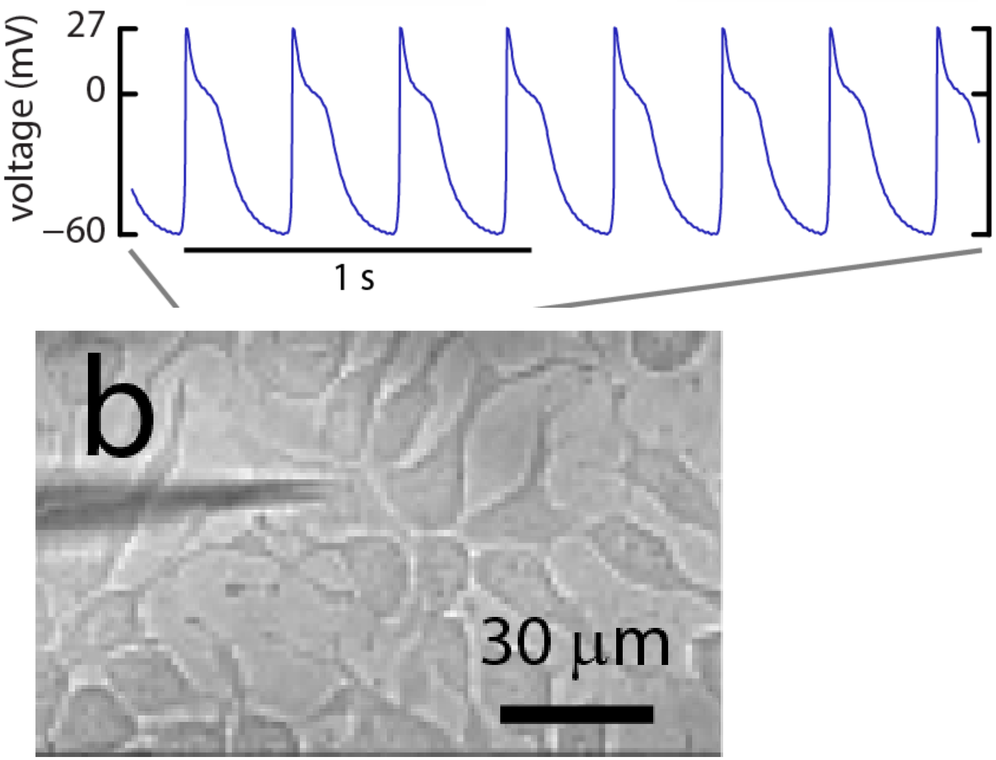
https://www.quantamagazine.org/how-computationally-complex-is-a-single-neuron-20210902/

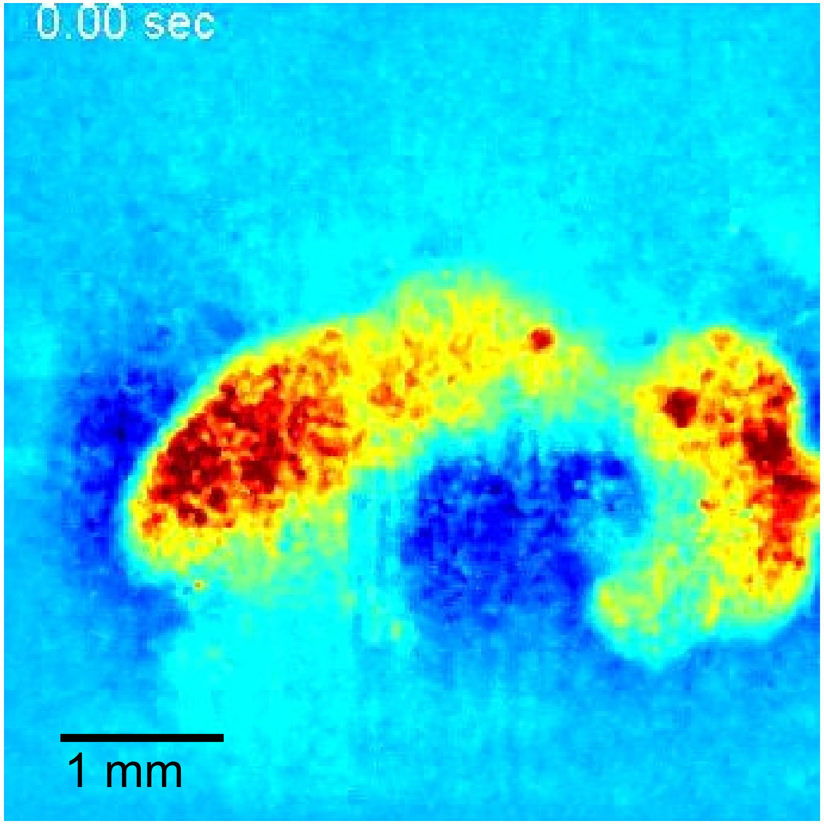
Spiking HEK cells as an excitable medium





BeRST 1





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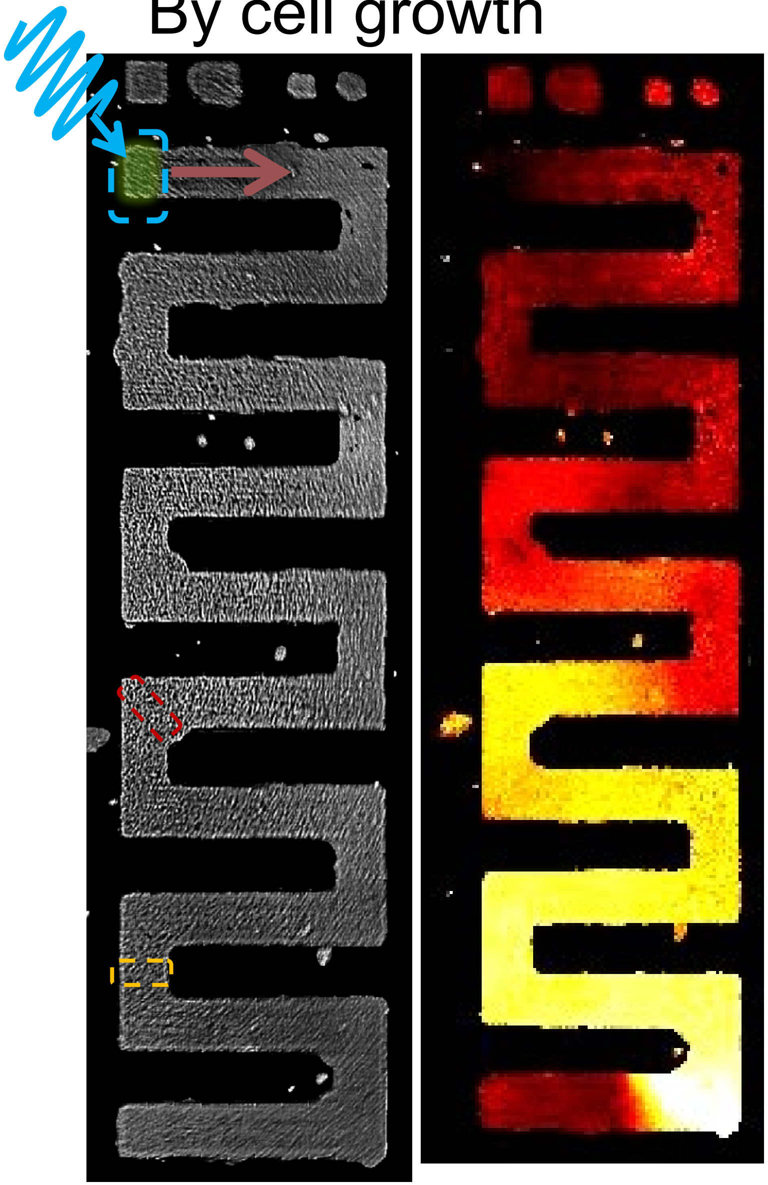
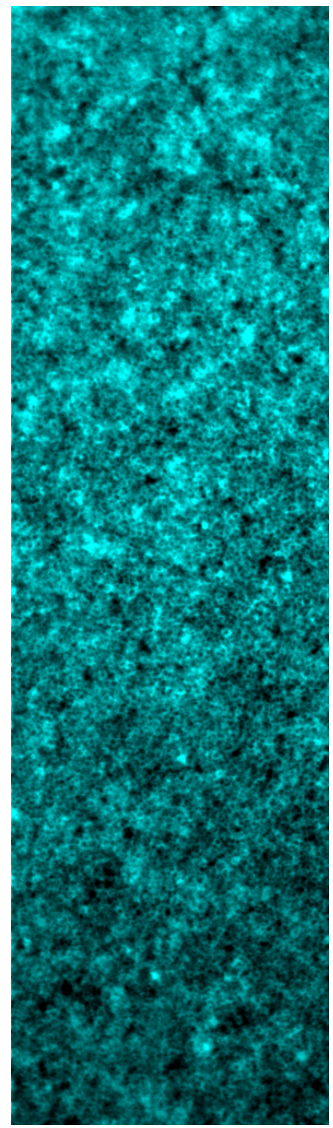
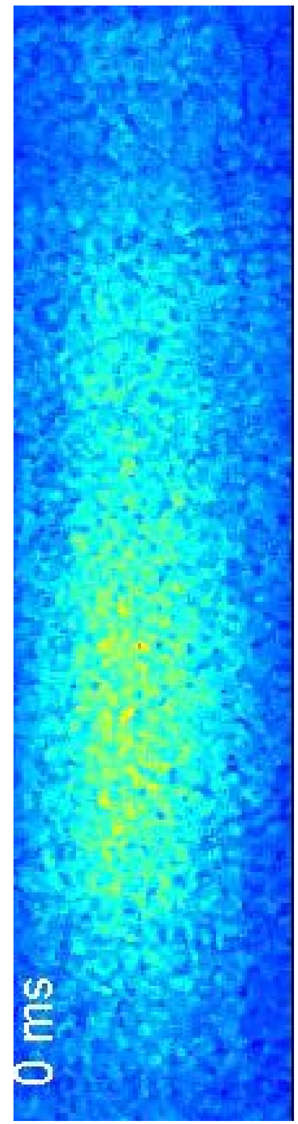
Electrical waves can be patterned…

By cell growth



Or by light





Harry McNamara

Phys. Rev., X **6**, 031001 (2016)