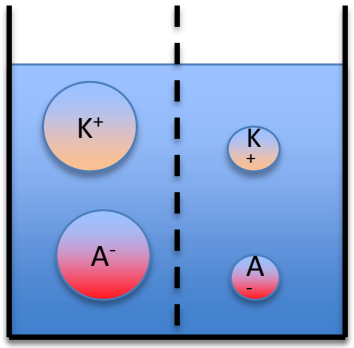
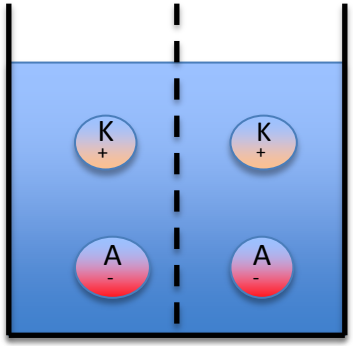
Biophysical neuronal models

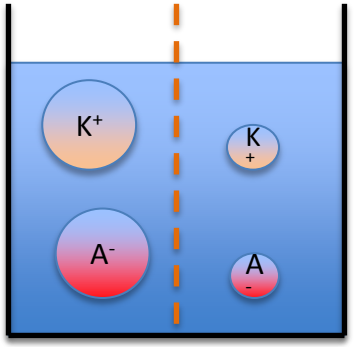
Lecture 2

Electrodiffusion of ions across the cell membrane

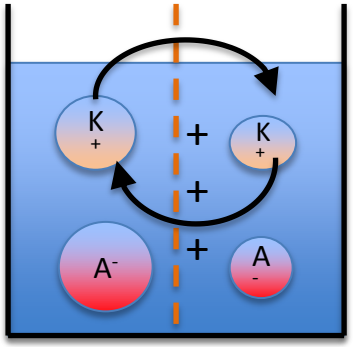


From high to low concentration





(Dynamical) equilibrium potential between the concentration and potential gradients



Nernst equation

For some membrane-permeable ion X, the equilibrium potential is

$$E_X = \frac{RT}{z_X F} \ln \frac{[X]_{out}}{[X]_{in}}$$

See e.g. Steratt et al. for derivation

R: Gas constant of 8.314 J/mol/K
T: Temperature in Kelvins
F: Faradays constant of 9.648 x 10^4 C/mol (charge per mol)
z_X : ions signed valency (e.g. =2 for Ca^{2+} and =-1 for Cl^- , =+1 for K^+)

$[K^+]_{out} \approx 20\ mM$

$[K^+]_{in} \approx 400\ mM$

What's E_K?

Note: 1 mole (mol) = 6.023 x 10^{23}

The Goldman-Hodgkin-Katz equations

What if the membrane potential is permeable to other ions?

E.g. for a membrane permeable to Na^+, K^+, and Cl^-, its resting membrane potential is

$$V_{rest} = E_m = \frac{RT}{F} \ln \frac{P_K[K^+]_{out} + P_{Na}[Na^+]_{out} + P_{Cl}[Cl^-]_{out}}{P_K[K^+]_{in} + P_{Na}[Na^+]_{in} + P_{Cl}[Cl^-]_{in}}$$

where P_X is the (relative) permeability (in units of cm/s) of ion X.

These are all measurable quantities.

For derivations, see Johnston and Wu (1995) "Foundations of cellular neurophysiology" book chapter 2.7.2.

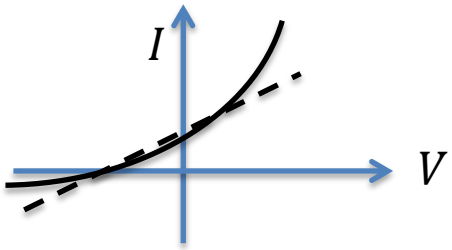
(Quasi-)ohmic approximation of ionic currents

$$\boldsymbol{I_X = g_X(V - E_X)}$$

where g_X is the conductance per unit area (in mS/cm^2), and E_X is the equilibrium potential.

$(V - E_X)$ is called the driving "force".

Linear conductance



We will make use of this approximation rather often.

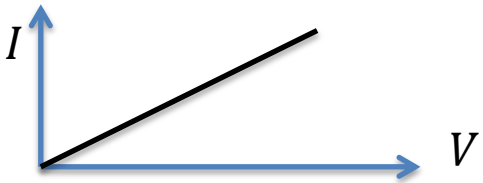
In general, g_X can be a function of V, and nonlinearities can arise.

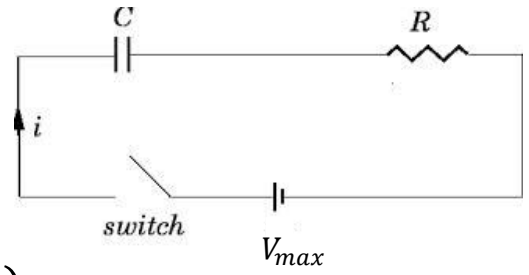
See Sterratt et al. Chapter 2.

Recall (lab): Charging an electrical RC (with constant resistance R and capacitance C) circuit with a battery of voltage V_{max} :

Recall Ohm's law, $\frac{V_{max}}{R} = I$,

$\boldsymbol{I = \frac{dQ}{dt}}$ and $\boldsymbol{Q = C\,V}$





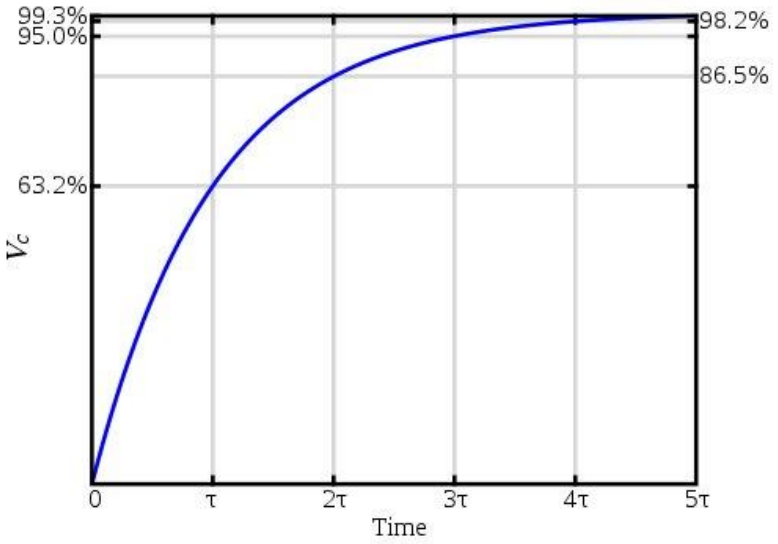
Based on Kirchoff's law: $V_{max} - RI - \frac{Q}{C} = 0$

Rewriting the equation: $\mathrm{I} = \frac{dQ}{dt} = \frac{V_{max}}{R} - \frac{Q}{RC}$

with solution $Q(t) = CV_{max}\left(1 - e^{-\frac{t}{RC}}\right) = Q_{max}\left(1 - e^{-\frac{t}{RC}}\right)$

Or $V(t) = \frac{Q(t)}{C} = V_{max}\left(1 - e^{-\frac{t}{RC}}\right)$

Hence RC acts like a time constant (τ).



Conventions used in both experiments and models

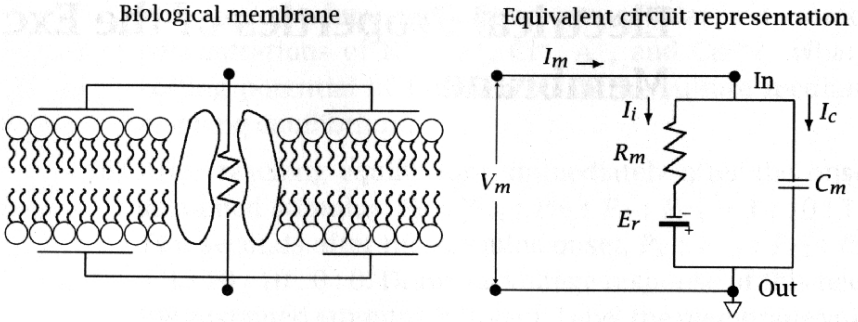
Membrane potential, V = V(intracellular)– V(extracellular)

Positive current: positive charges flowing out of the cell membrane

Neuroelectronics: Basic ohmic properties of a (passive) neuron or glial cell (astrocyte) $\mathrm{I} = \frac{V}{R}$

In general, $CV = Q$, such that for constant capacitance C, $C\frac{dV}{dt} = \frac{dQ}{dt} = I_{total}(V,t)$

Ohmic model



For some applied current (per unit area), I_m , injected into the cell, the dynamical change for the (trans)membrane potential, V_m :

$$\boldsymbol{C_m \frac{dV_m}{dt} = -\frac{V_m - E_r}{R_m} + I_m} \quad \text{or} \quad \frac{dV_m}{dt} = -\frac{V_m - V_{ss}}{\tau_m}$$

where
C_m: membrane capacitance, per unit area (~ 1 μF/cm^2),
R_m: Resistance of the cell membrane (varies across different cell types)
V_m: (trans)membrane potential (from ~ -100 mV to as high as ~ 50 mV at the peak of an action potential)

Without any action potential (spike) generating mechanism,

$$V(t) = V_{ss} - (V_{ss} - V(0))\left(1 - e^{-\frac{t}{\tau_m}}\right)$$

What are V_{ss} and τ_m?

Note: Neuronal membrane resistance may not necessarily be "passive" i.e. membrane resistance being voltage-dependent (Stuart and Sakmann, 1994).

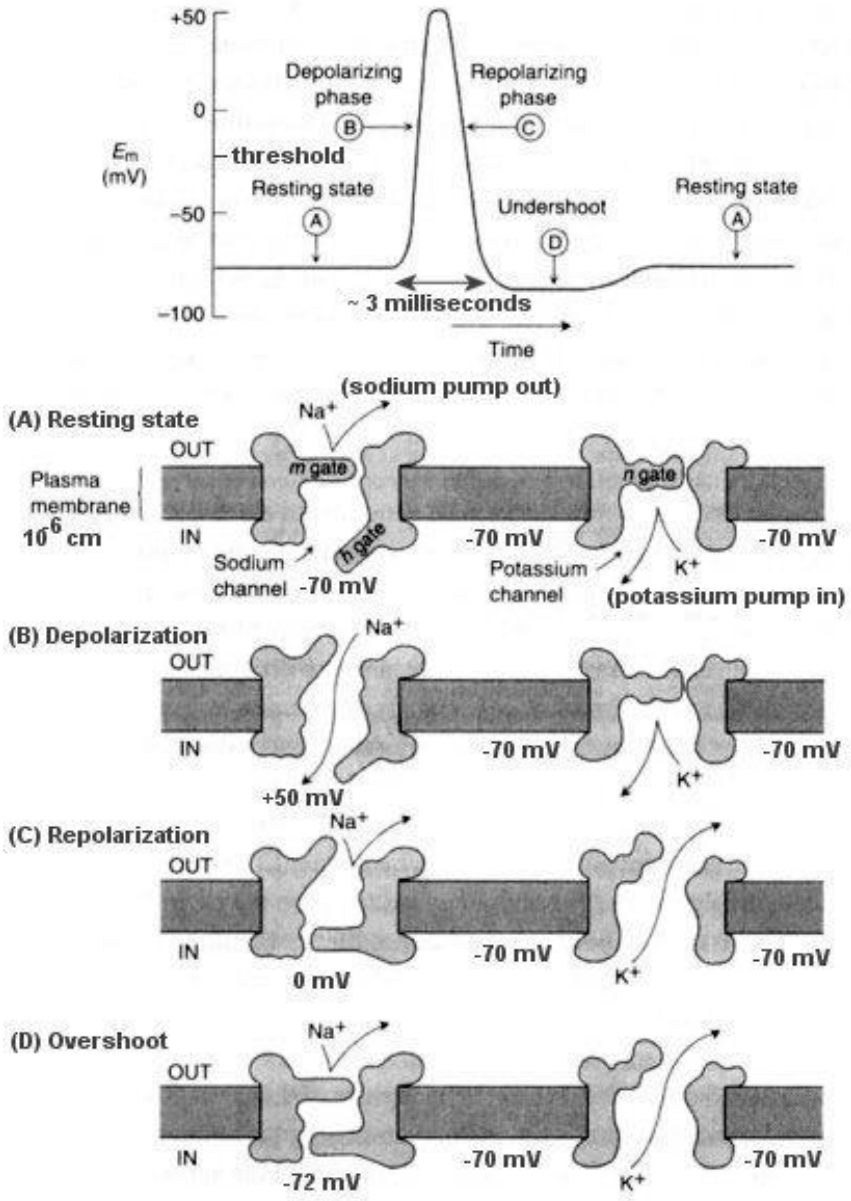
In general, the current (per unit area) I_m can include the below and their combinations (summation):

1. Applied current from external stimulus, which could generally vary over time.

2. Intrinsic currents going into and out of a neuron (e.g. ions such as Na^+, K^+, Ca^{2+}), which can be dependent on V_m ;

3. Synaptic currents with other neurons, which can be dependent on V (certain types of synapses).

Recall basic mechanism of action potential generation



$$C\frac{dV}{dt} = I_{total}$$

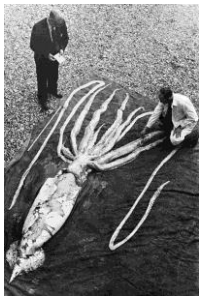
$$I_{total} = -I_{leak} - I_{Na} - I_K + I_{input}$$

This phenomenon requires <u>fast</u> activation of Na^+ ion channels, and <u>slow (delayed rectifier)</u> K^+ ion channels

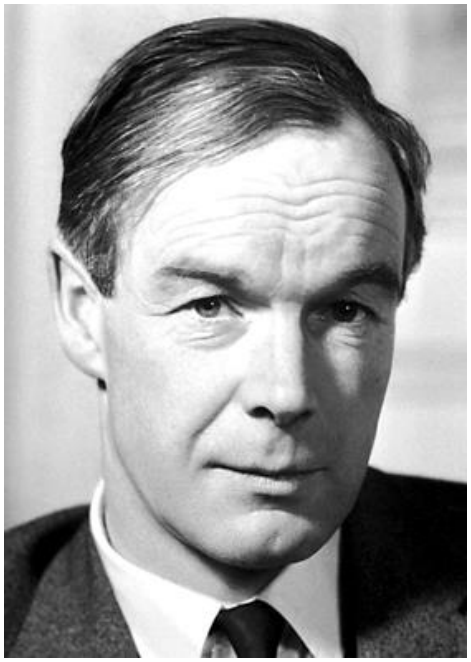
Hodgkin-Huxley Model (1952)

Using motor neuron of a squid giant axon

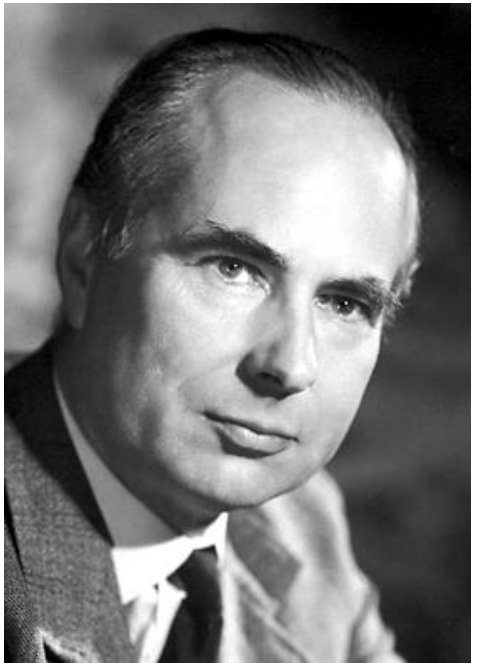
- Birth of Computational Neuroscience?



(Sir) John Carew Eccles



Alan Lloyd Hodgkin



(Sir) Andrew F. Huxley

http://www.nobelprize.org/nobel_prizes/medicine/laureates/1963/

http://www.youtube.com/watch?v=omXS1bjYLMI
http://www.youtube.com/watch?v=k48jXzFGMc8

A link to their series of seminal papers http://jp.physoc.org/site/misc/news/news_items.xhtml

Why are we studying this?

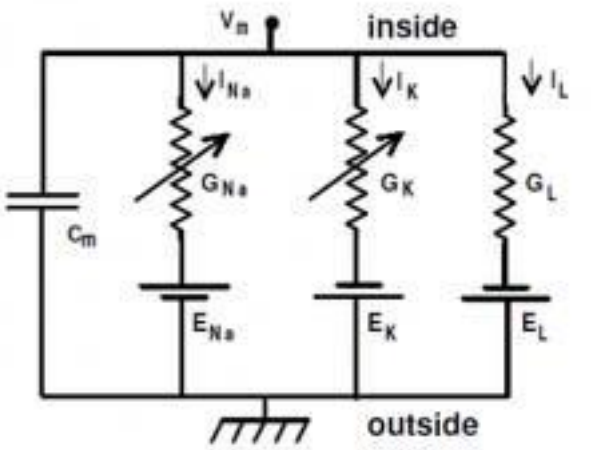
1. One of the best neuroscience work, combining both experiments and modelling to understand fundamental signal processing and transmission in the nervous system.

2. The experimental (e.g. voltage clamp, with some advancements) and modelling approaches are still used today.

3. The HH model forms the basis of modern biophysical neuronal models.

Hodgkin-Huxley Model (1952)

Hodgkin-Huxley equations



$$C_m \frac{dV}{dt} = -g_L (V - V_L) - \bar{g}_{Na} m^3 h (V - V_{Na}) - \bar{g}_K n^4 (V - V_K)$$

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

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

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

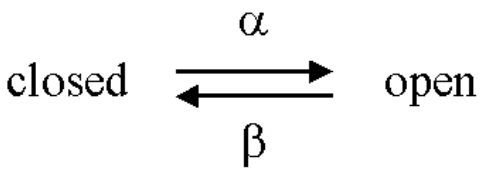
Hodgkin, A., and Huxley, A. (1952): A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol.* **117**:500–544

See Sterratt et al. book chapter 3.

Ionic channel dynamics

Channel variables

Gating variables, c



$$\frac{dc}{dt} = \alpha(V)(1-c) - \beta(V)c$$

Rate coefficients

$$\frac{dc}{dt} = \frac{c_\infty(V) - c}{\tau_c(V)}$$

$$c_\infty(V) = \frac{\alpha(V)}{\alpha(V)+\beta(V)}$$

Limiting values (i.e. steady states)

$$\tau_c(V) = \frac{1}{\alpha(V)+\beta(V)}$$

Time constants

Summary of the Hodgkin-Huxley model

Under space clamp conditions i.e. no axial currents,

$$C_m \frac{dV}{dt} = -g_L(V - E_L) - g_{Na} m^3 h\,(V - E_{Na}) - g_K n^4 (V - E_K)$$

Sodium activation and inactivation gating variables:

$$\frac{dm}{dt} = \alpha_m(1 - m) - \beta_m m \qquad \frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h$$

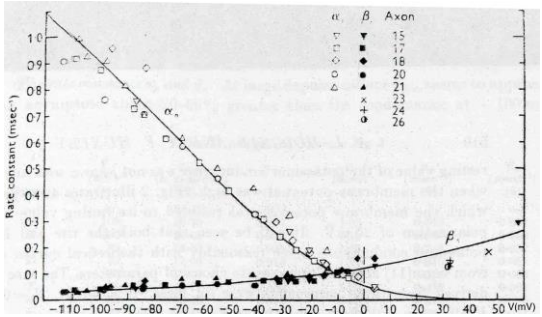
$$\alpha_m = 0.1\,\frac{V+40}{1-\exp(-\frac{V+40}{10})} \qquad \alpha_h = 0.07\exp(-\frac{V+65}{20})$$

$$\beta_m = 4\exp(-V + 65)\,/18) \qquad \beta_h = \frac{1}{\exp\left(-\frac{V+35}{10}\right)+1}$$

Potassium activation gating variables:

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

$$\alpha_n = 0.01\,\frac{V+55}{1-\exp(-\frac{V+55}{10})} \qquad \beta_n = 0.125\exp\left(-\frac{V+65}{80}\right)$$

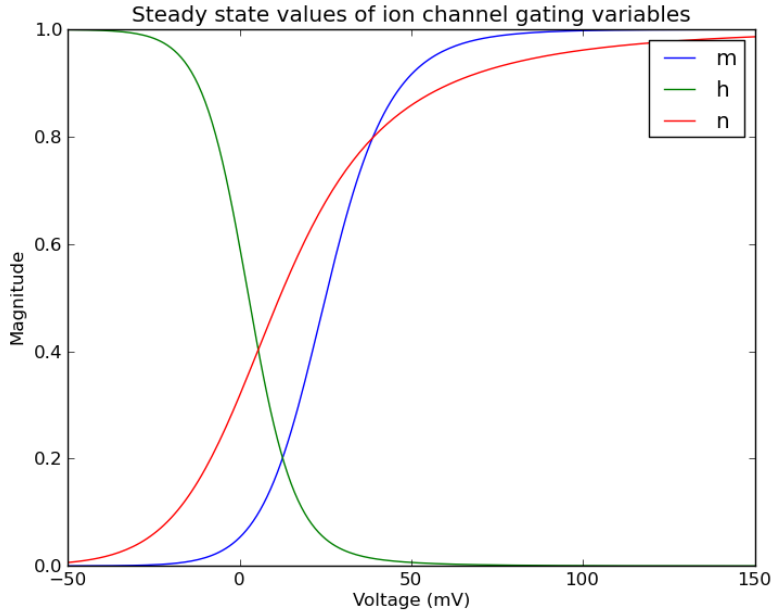


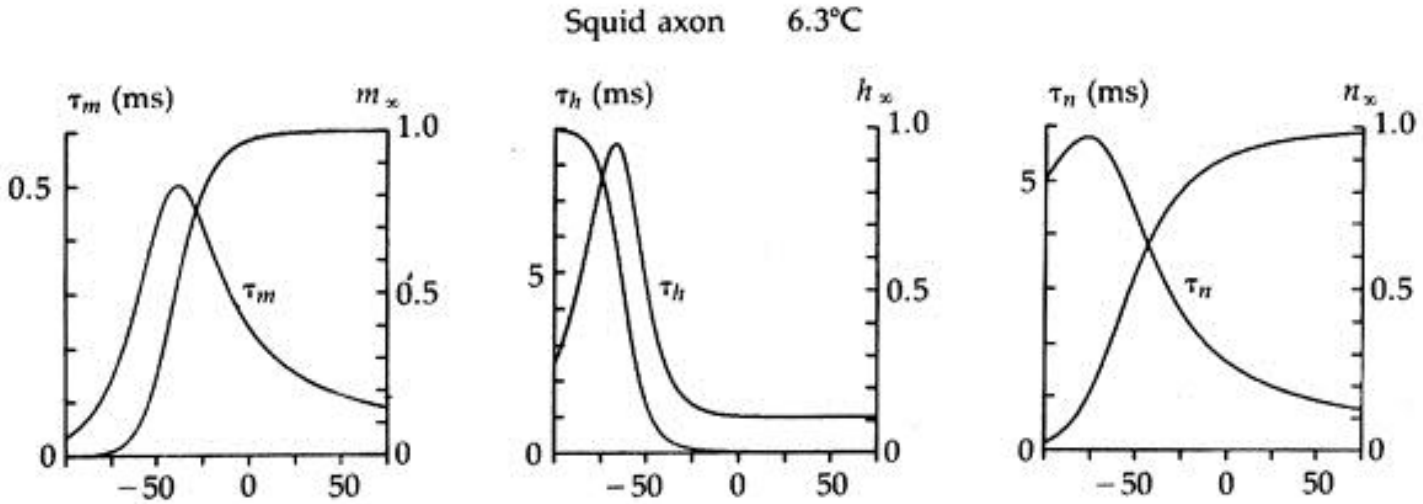
Parameters from Hodgkin-Huxley (1952):

$C_m = 1.0\ \mu F/cm^2$,

$E_{Na} = \mathbf{50}\ mV$, $E_K = -77\ mV$, $E_L = -54.4\ mV$

$g_{Na} = \mathbf{120}\ mS/cm^2$, $g_K = 36\ mS/cm^2$, $g_L = 0.3\ mS/cm^2$


Steady state values of ion channel gating variables
Magnitude
Voltage (mV)
m
h
n
1.0
0.8
0.6
0.4
0.2
0.0
−50
0
50
100
150

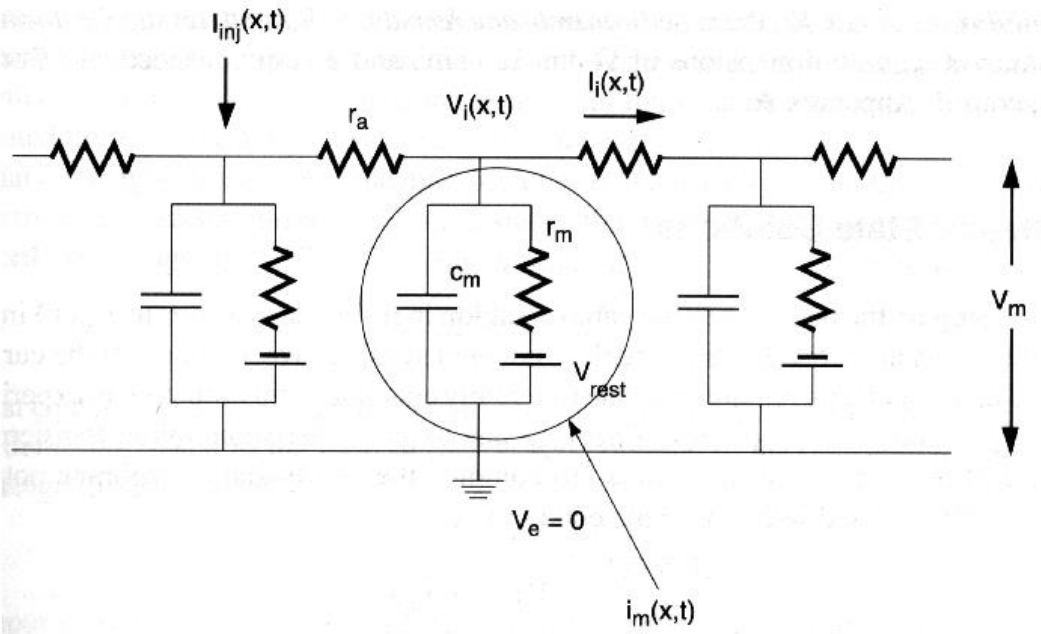

Squid axon 6.3°C
τ_m (ms)
m_∞
τ_h (ms)
h_∞
τ_n (ms)
n_∞
τ_m
τ_h
τ_n
0.5
1.0
5
−50
0
50

Some HH model assumptions

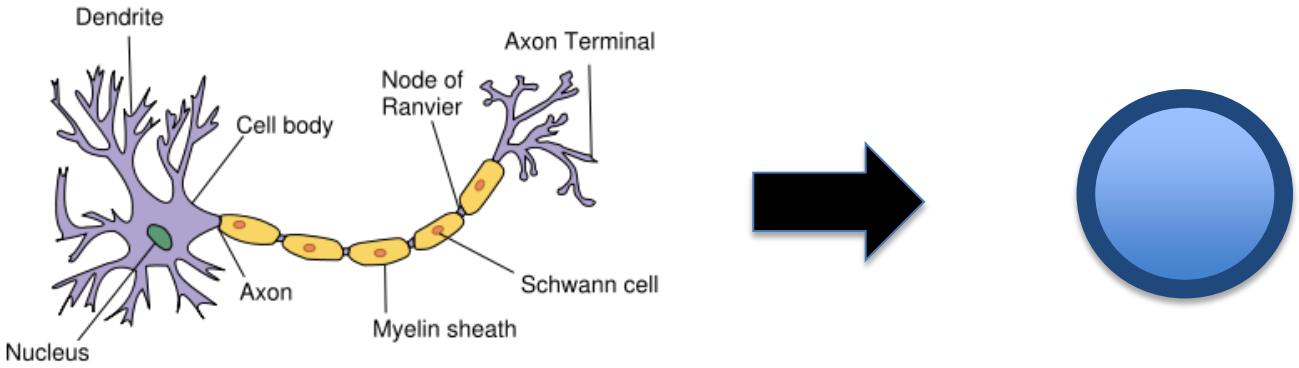
- Each channel is permeable to only 1 type of ion
- Each current type does not depend on the concentrations of other ionic types (see GHK).
- Obey Ohm's law – linear I-V characteristic.
- Independence of gating particles

Sterratt et al. chapter 3.5.1.

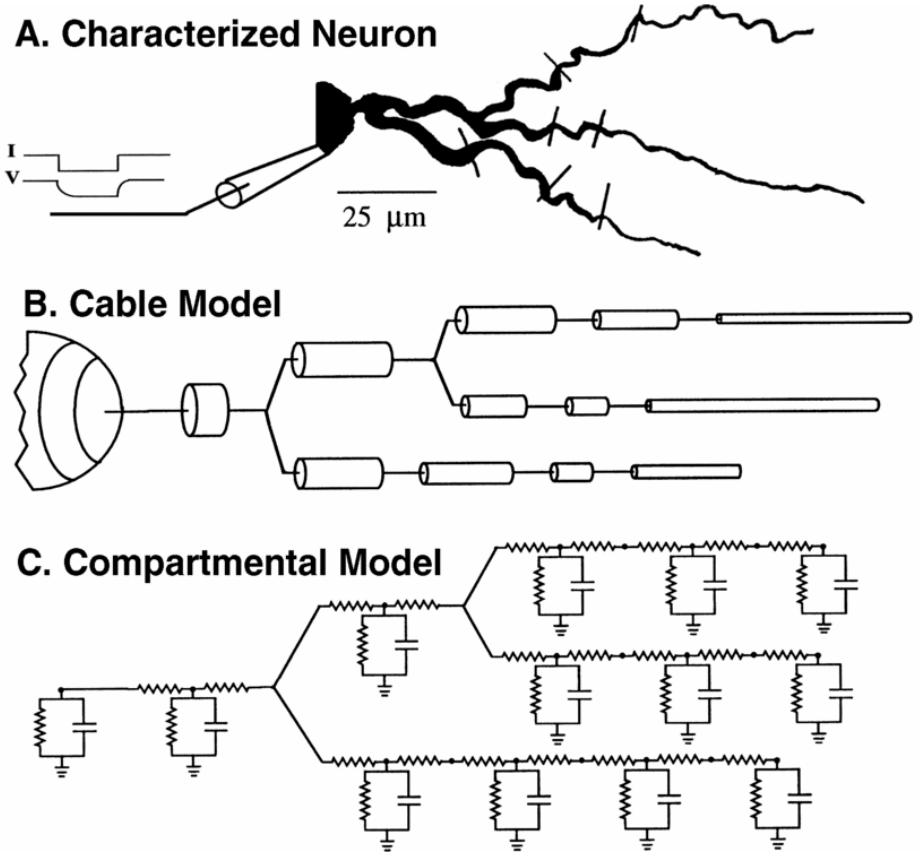
In reality, the membrane is not isopotential, so V_m has spatial as well as temporal structure.



Consider only “single-compartmental” (point) neuronal model (otherwise check out “Cable Theory for Dendritic Neurons”, e.g. Wilfried Rall). Assume iso-potential.

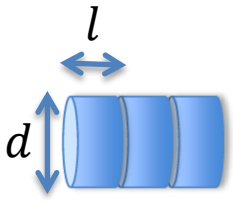


Incorporating neuronal morphology and dendritic computation (Cable theory and multi-compartmental models)



$$C_m \frac{\partial V}{\partial t} = -\sum_k I_{i,k}(x) + \frac{d}{4\,R_a}\frac{\partial^2 y}{\partial x^2} + \frac{I_e(x)}{\pi d}$$

Solve the partial differential equation (PDE)!



Discrete approximation (for j^{th} compartment):

$$C_m \frac{dV_j}{dt} = -\sum_k I_{i,k,j}(x) + \frac{d}{4\,R_a}\frac{V_{j+1}-V_j}{l^2} + \frac{d}{4\,R_a}\frac{V_{j-1}-V_j}{l^2} + \frac{I_e(x)}{\pi d l}$$

Sterratt et al. Chapters 2.8, 2.9 and 4; Koch and Segev Chapters 2 and 3.

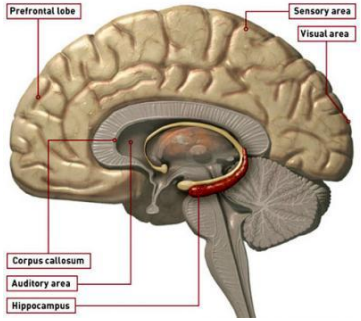
Conductance-based models: Additional ionic currents

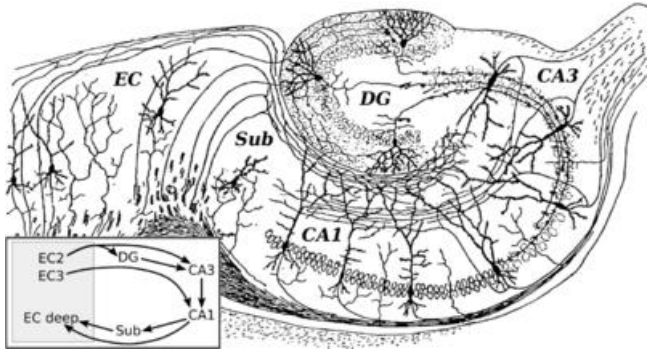
The Hodgkin-Huxley (type) model belongs to the wider class of conductance-based neuronal models where the conductances are explicitly modelled. There are many different types of conductances and its associated currents found in experiments (e.g. various potassium- or calcium-related channels), which may modulate the way a neuron spikes.

Sterratt et al. Chapter 6; De Schutter Chapter 5; Izhikevich Chapters 2 and 5

E.g. A two-compartmental model of the hippocampal (CA1) pyramidal neuron

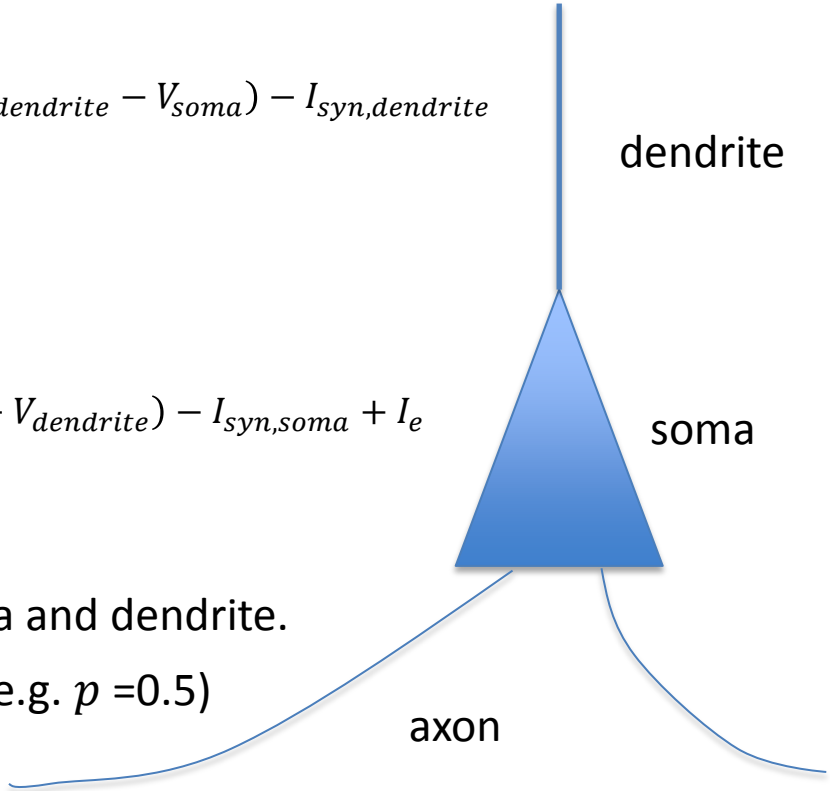
(Warman et al. 1994; Pinksky and Rinzle 1994; Wang 1998; Csicsvari et al., 1999; Zou et al., 2011; Zou et al., 2012)





$$C_m \frac{dV_{dendrite}}{dt} = -I_L - I_{Ca} - I_{AHP} - I_A - I_{CT} - I_h - \frac{g_c}{1-p}(V_{dendrite} - V_{soma}) - I_{syn,dendrite}$$

$$C_m \frac{dV_{soma}}{dt} = -I_L - I_{Na} - I_K - I_{Ca} - I_A - I_{CT} - I_h - \frac{g_c}{p}(V_{soma} - V_{dendrite}) - I_{syn,soma} + I_e$$



g_c is the coupling conductance between soma and dendrite.

p is the soma area divided by the total area (e.g. p =0.5)

A-type potassium conductance (I_A)

Connor and Stevens 1971; Connor et al. 1997

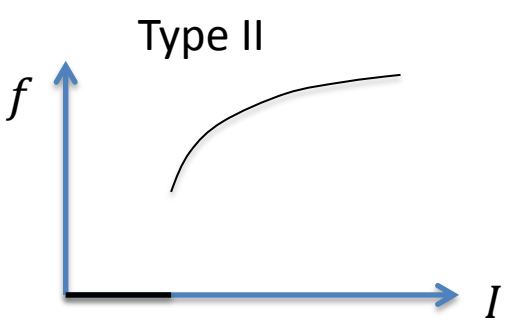
$$I_A = g_A a^3 b (V - E_K)$$

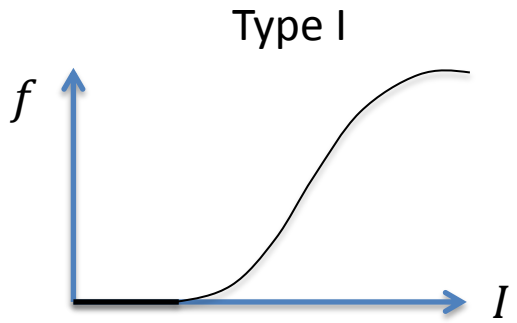
$$\alpha_a = -0.05(V + 20) / \left\{ \exp\left[-\frac{V + 20}{15} \right] - 1 \right\}$$

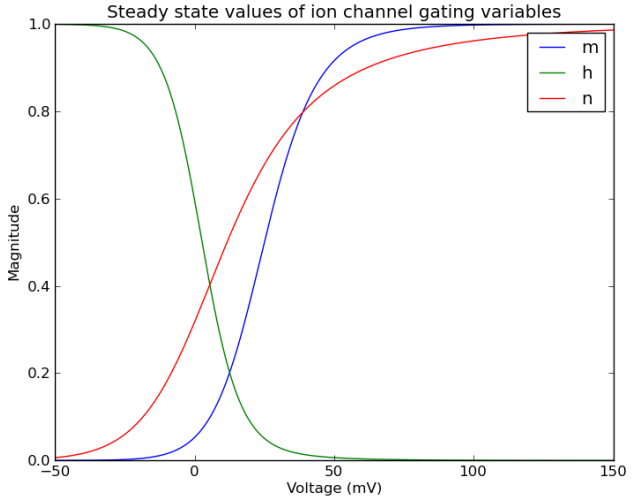
$$\beta_a = \frac{0.1(V + 10)}{\left\{ \exp\left[\frac{V + 10}{8} \right] - 1 \right\}}$$

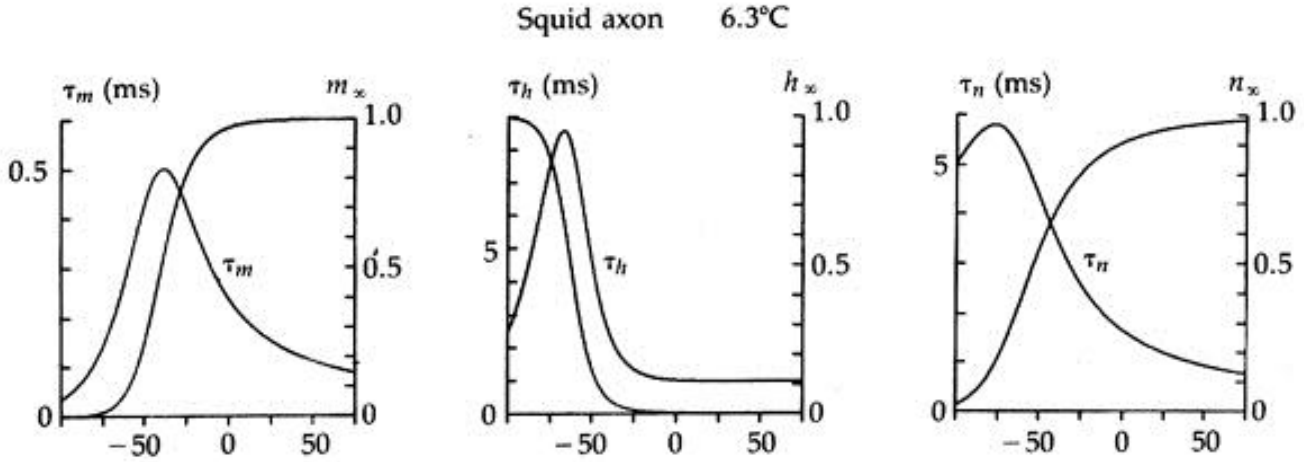
$$\alpha_b = \frac{0.00015}{\exp\left[\frac{V + 18}{15} \right]}$$

$$\beta_b = 0.06 / \left\{ \exp\left[-\frac{V + 73}{12} \right] + 1 \right\}$$









Notice that (Rinzel 1985):

- $\tau_m \ll \tau_h \approx \tau_n$ **(can assume *m* has relatively instantaneous dynamics)**
- $h_\infty \approx 1 - n_\infty$ **(replace *h* with *1-n*)**

$$C_m \frac{dV}{dt} = -g_L(V - E_L) - g_{Na} m^3 h\,(V - E_{Na}) - g_K n^4 (V - E_K)$$

$$\frac{dn}{dt} = \frac{1}{\tau_n(V)}(-n + G(V))$$

$$\tau_n(V) = 1 + 5\exp\left(-(V + 60)^2/55^2\right)$$

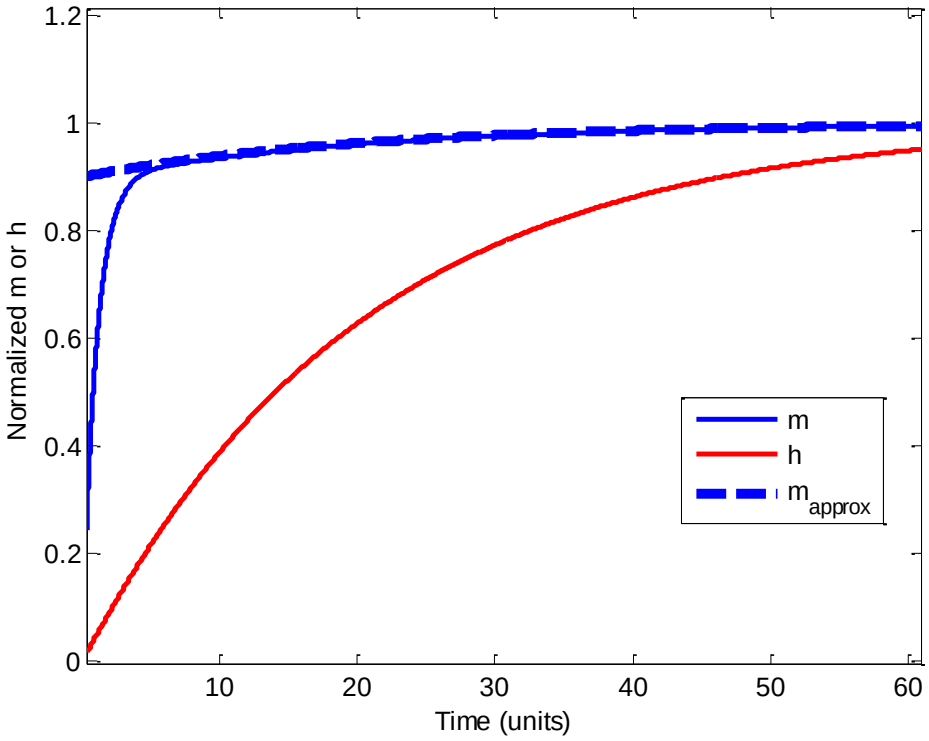
Wilson book chapter 9

Hence reduced from 4 to 2 dynamical (differential) equations, but still essentially capturing the main features of the HH model

How can we approximate a fast variable by having it to reach steady state?

Method of separation of timescales (“adiabatic” approximation)

E.g. A weakly coupled system of a fast variable m and a slow variable h with decay time constants of 1 and 20 time units, respectively.



Reduced 2-D models

Morris-Lecar Model (1981)

Approximation: Assume fast Ca^+ channel dynamics is instantaneous, but slow K^+ dynamics not negligible. Also a leak current. Low dim allows rigorous analysis.

$$C\,dV/dt = -g_{Na}\,M_{ss}(V)(V-V_{Na}) - g_K W(V-V_K) - g_L(V-V_L) + I_{app}$$

$$dW/dt = (W_{ss}(V) - W)/T_W(V)$$

where W is some recovery variable i.e. K^+ in our case, and

$$M_{ss}(V) = (1+\tanh[(V-V_1)/V_2])/2$$
$$W_{ss}(V) = (1+\tanh[(V-V_3)/V_4])/2$$
$$T_W(V) = T_0\,\mathrm{sech}[(V-V_3)/2V_4]$$

Morris, Catherine; Lecar, Harold (July 1981), "Voltage Oscillations in the barnacle giant muscle fiber", *Biophys J.* **35** (1): 193–213

http://www.scholarpedia.org/article/Morris-Lecar_model

Sterratt et al. Chapter 8.1.3. and Appendix B.2.

Phase-plane analysis of 2-D systems

Suppose we have two coupled differential/dynamical equations with dynamical variables V and w,

$$\frac{dV}{dt} = f(V, w)$$
$$\frac{dw}{dt} = g(V, w)$$

Next, suppose there exists an equilibrium point (steady state), (V_0, w_0), then by definition $f(V_0,\ w_0) = 0$ and $g(V_0,\ w_0) = 0$

We can use Taylor expansion about this point/state:

$$f(V_0 + \Delta V, w_0 + \Delta w) \approx f(V_0, w_0) + \frac{\partial f}{\partial V}\Delta V + \frac{\partial f}{\partial w}\Delta w$$

and similarly for $g(V_0 + \Delta V, w_0 + \Delta w)$. Then we can linearise the dynamics near the steady state:

$$\frac{d\Delta V}{dt} \approx \frac{\partial f}{\partial V}\Delta V + \frac{\partial f}{\partial w}\Delta w$$
$$\frac{d\Delta w}{dt} \approx \frac{\partial g}{\partial V}\Delta V + \frac{\partial g}{\partial w}\Delta w$$

Then the general solution is:

$$\Delta V = A\, e^{\lambda_1 t} + B\, e^{\lambda_2 t}$$
$$\Delta w = C\, e^{\lambda_1 t} + D\, e^{\lambda_2 t}$$

where λ_1 and λ_2 are the eigenvalues of the (Jacobian) matrix:

$$\begin{pmatrix} \frac{\partial f}{\partial V} & \frac{\partial f}{\partial w} \\ \frac{\partial g}{\partial V} & \frac{\partial g}{\partial w} \end{pmatrix}$$

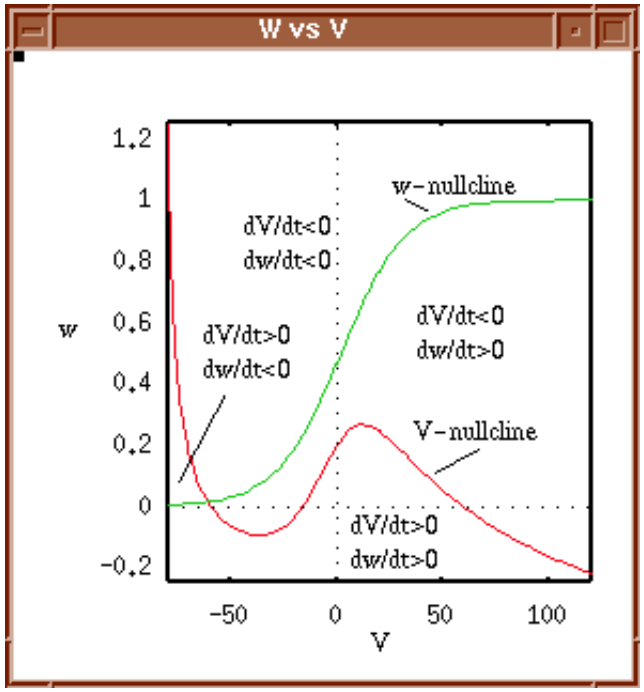
In general, the eigenvalues are complex, i.e. have a real and an imaginary component. The stability of the system about the steady state or equilibrium can be determined from the real parts. In particular, if

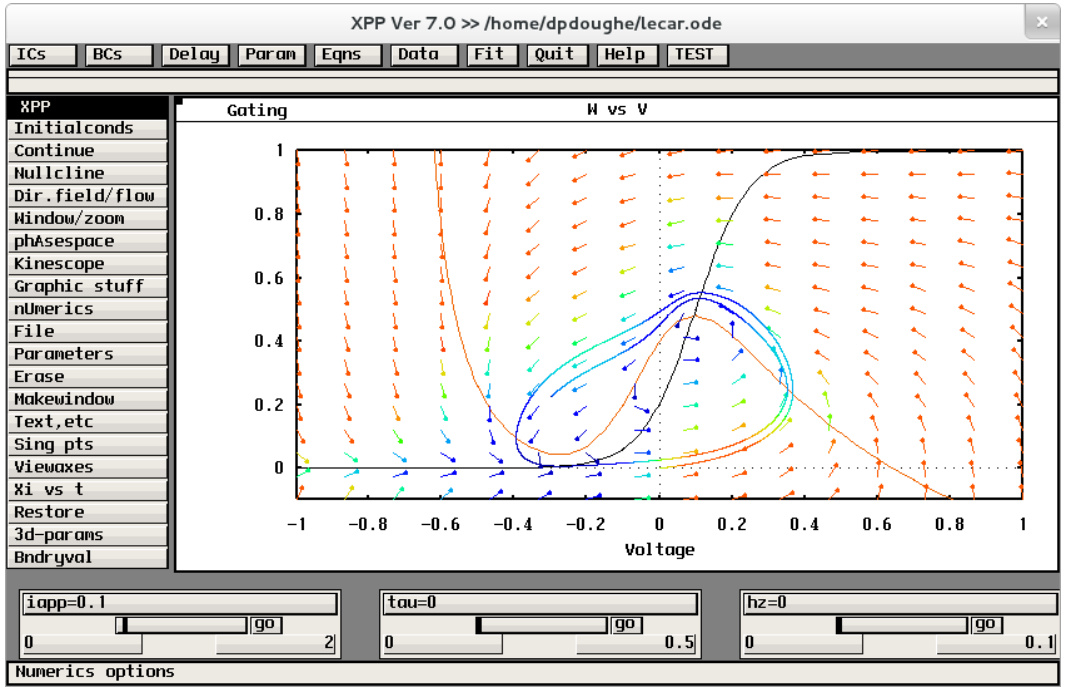
1. Both the real parts are negative, then (asymptotically) stable equilibrium;
2. One real part is positive while the other real part is negative, then unstable or metastable (a saddle node/point);
3. Both real parts are positive, then unstable equilibrium.

Setting each dynamical equation to be zero gives us a “nullcline” (or “isocline”)

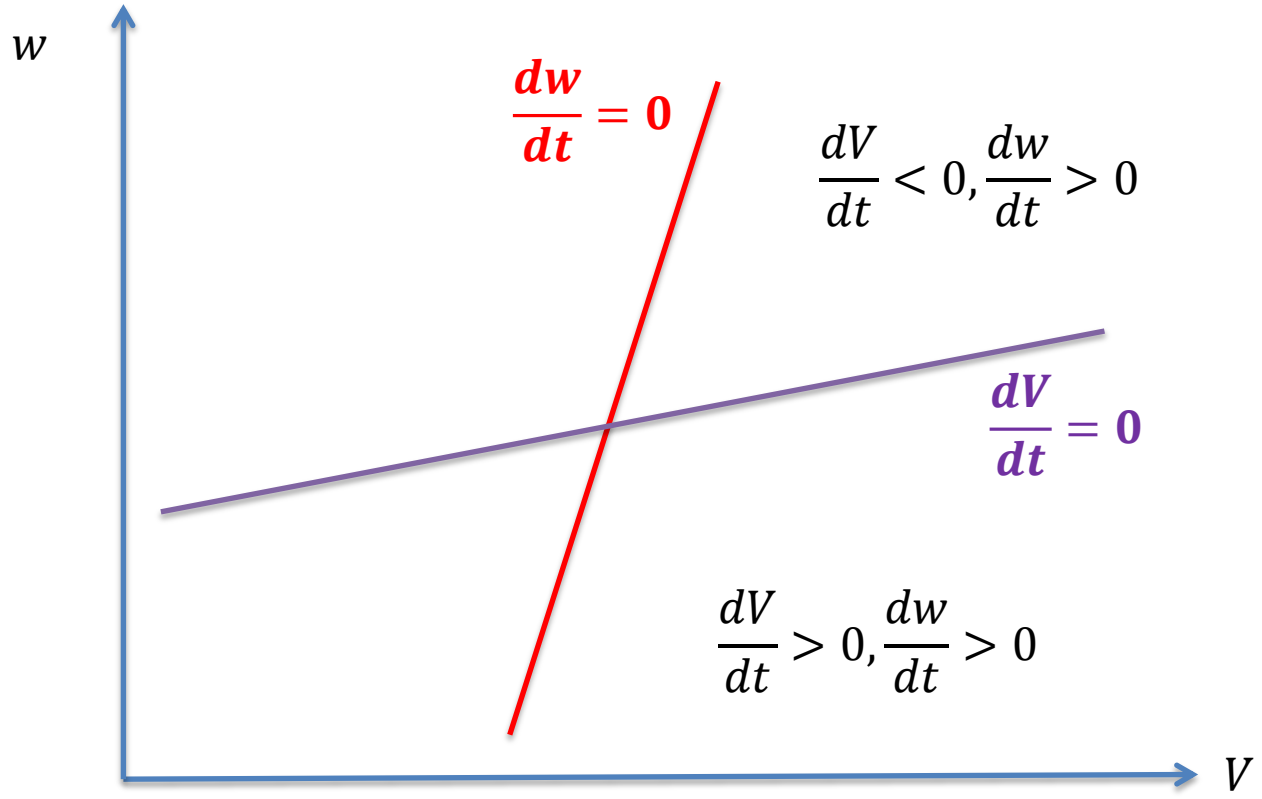
$$\frac{dV}{dt} = 0 = f(V, w)$$

$$\frac{dw}{dt} = 0 = g(V, w)$$





E.g. Guess the vector fields based on these 2 linear nullclines.

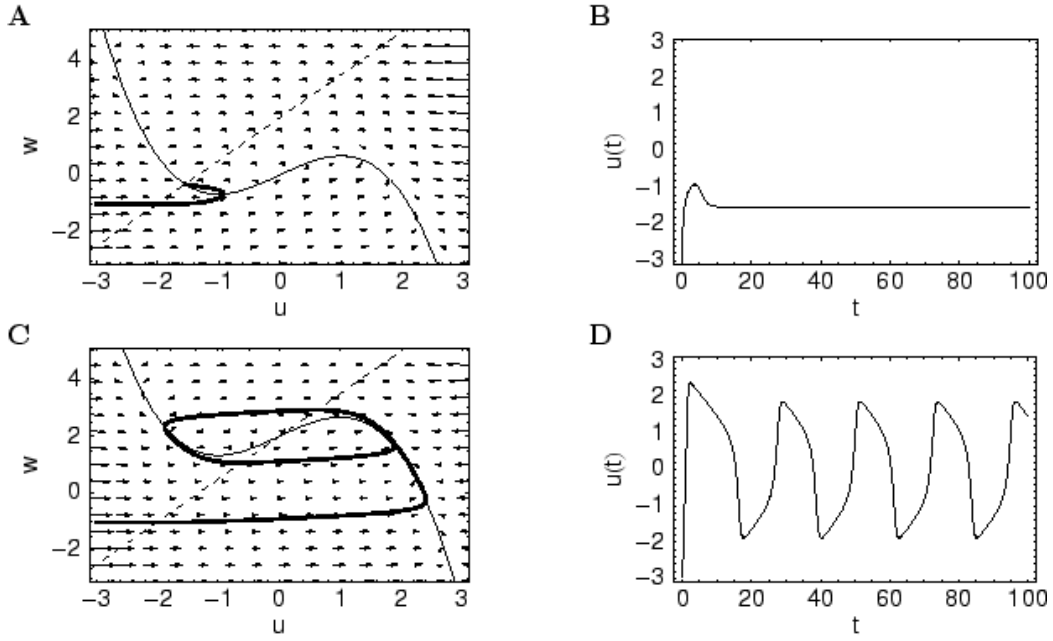


Reduced 2-D models
Fitzugh-Nagumo Model (1981)

A more abstract mathematical version but capturing the qualitative features (of the nullclines)

$$\frac{dV}{dt} = V - \frac{1}{3}V^3 - \mathrm{W} + \mathrm{I}$$

$$\frac{dW}{dt} = 0.08(V + 0.7 - 0.8W)$$



http://www.scholarpedia.org/article/FitzHugh-Nagumo_model

Key points and summary

- Neuronal signal processing consists of a mix of complex chemical and electrical processes.
- We can understand these processes through combination of experiments and modelling.
- A good biophysical model can account for detailed features and provide insights into the mechanisms.
- Reduced biophysical models can replicate essential behaviours of the original model, and allow rigorous or full analysis of its behaviour.
- Phase-plane analysis is a useful (dynamical systems) tool for analysing low level (2-D) models.

Reading, practising and revising

- Dayan and Abbott (2002) *Theoretical Neuroscience*. Chapters 5 and 6.
- Hugh Wilson. *Spikes, Decisions and Actions.* Chapters 3 and 9.
- Steratt et al. *Principles of Computational Modelling in Neuroscience*. Chapters 2, 3, a bit of 4, 8.1, and Appendix B.
- De Schutter *Computational Modeling Methods for Neuroscientists* (MIT, 2009). Chapters 1, 5, and 11, and a bit of 10.
- Koch and Segev. *Methods in Neuronal Modeling.* Chapter 7 and a bit of 2 and 3.
- Izhikevich. *Dynamical Systems in Neuroscience.* Chapters 2, 4 and a bit of 5.
- Koch. *Biophysics of Computation – Information processing in single neurons.* Multiple chapters…
- Johnston and Wu. *Foundations of Cellular Neurophysiology.* Chapters 2, 3 and 6.

- Familiarise with XPPAUT software. Codes: lecar.ode.

- Keep searching, thinking, and discussing with me regarding topics that interest you!

- Next week's lab (on 10th Feb) will be on Simple Neuronal Models. It will be assessed (10% of overall module marks) through individual reports submitted by the end of the lab.