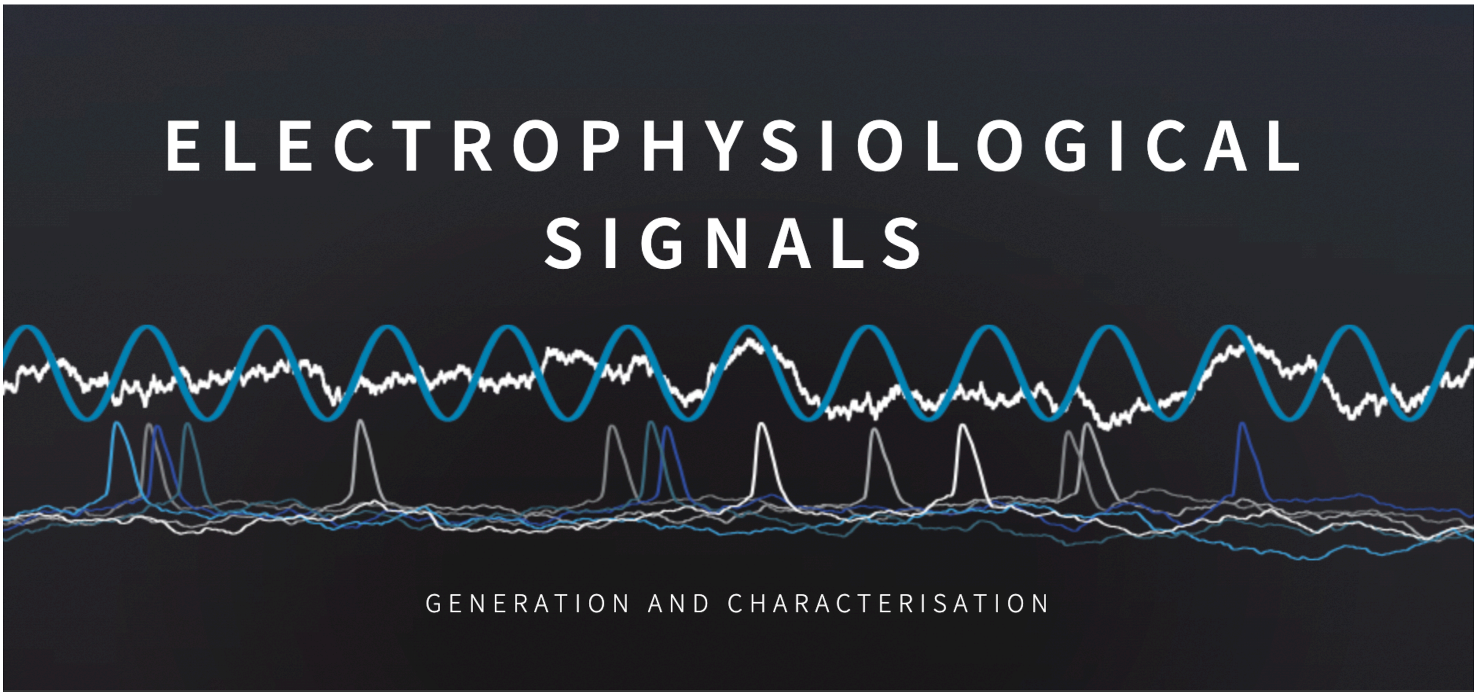


Michele GIUGLIANO

Excitability

ATTENDANCE TRACKING - **code ???**
(for statistical purposes only)

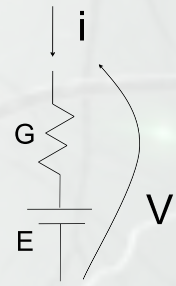
https://www.unimore.it/it/servizi/unimore-app

The ~~resting~~ membrane potential

multiple ion-species, NOT at the equilibrium

Biological membranes have **distinct conductances** (i.e. distinct G_h, h = Na, K, Cl...)

Ions have **distinct reversal potentials** (i.e. distinct E_h, h = Na, K, Cl...)



$$i_h = G_h(V - E_h) \qquad G_h = 1/R_h$$

The **total** ionic current (density) across the membrane?

$$i_{tot} = G_1\ (V - E_1) + G_2\ (V - E_2) + G_3\ (V - E_3) + ... + G_N\ (V - E_N)$$

REMEMBER

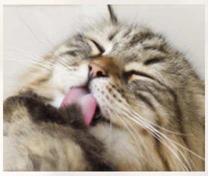
References

supporting your study and understanding

Chapters from

- Sterratt et al. (2011) "*Principles of Computational Modelling…*"
- Abbott LF, Dayan P (2001) "*Theoretical Neuroscience*"
-

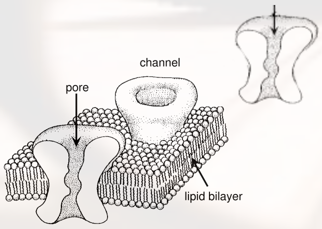
Heterogeneous distributions of (typical) ions, “*inside/outside*” the cell membrane

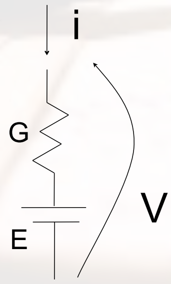


Ion	K^+	Na^+	Cl^-	Ca^{2+}
Concentration inside (mM)				
Concentration outside (mM)				
Equilibrium potential (mV)				

from Sterratt et al., 2011

Equivalent electrical circuit model of ionic permeability

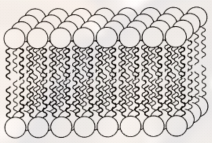


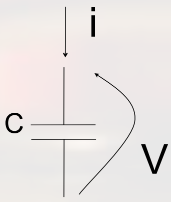


$$i = G\,(V_{in} - E)$$

$$E = \frac{RT}{zF}\, ln\left(\frac{c_{out}}{c_{in}}\right)$$

Equivalent model of capacitive properties



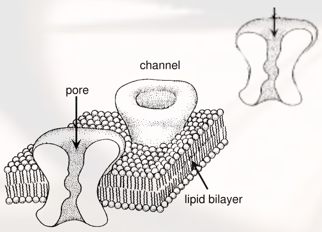


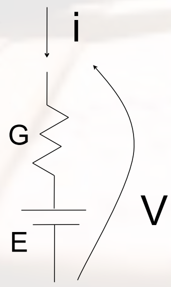
$$i \;=\; C\,\frac{dV}{dt}$$

$$i \;=\; \frac{\Delta Q}{\Delta t}$$

$$C \;=\; \frac{\Delta Q}{\Delta V}$$

Equivalent model of ionic permeability





$$i = G\,(V_{in} - E)$$

$$E = \frac{RT}{zF}\, ln\left(\frac{c_{out}}{c_{in}}\right)$$

Resting membrane potential, multiple ion-species
(i.e. steady-state, NOT thermodynamical equilibrium)

$i_{tot} = 0$ At “rest” (steady-state), the **total current density = 0**

$$i_h = G_h(V - E_h)$$

$$i_{tot} = i_1 + i_2 + i_3 + ... =$$

$$G_1(V - E_1) + G_2(V - E_2) + G_3(V - E_3) + ... = 0$$

$$(G_1 + G_2 + G_3 + ...)V - (G_1E_1 + G_2E_2 + G_3E_3 + ...) = 0$$

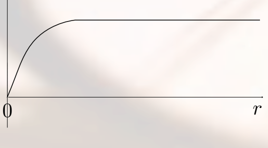
$$V_{rest} = \frac{(G_1E_1 + G_2E_2 + G_3E_3 + ...)}{(G_1 + G_2 + G_3 + ...)}$$

First-order ordinary differential equation, non-homogenous
(with constant “*external input term*”)

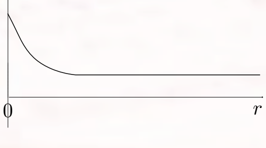
$$\frac{df(x)}{dx} = -af(x) + B$$

Graph of some notable functions

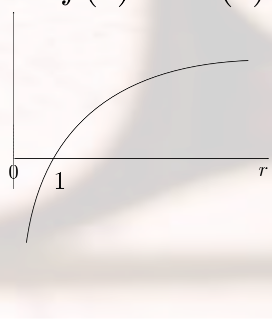
$f(r) = (1 - e^{-\alpha r})$



$f(r) = Ke^{-\alpha r} + B$



$f(r) = ln(r)$



Plan for the day

- Charge balance equation (relaxing the “resting” hypothesis)
- (Lumped parameters) descriptions of cell membranes
  - – full equivalent circuit model of a biological membrane
- (Thevenin’s reduced) circuit model, for non-excitable cells
  - – exercise: response to an external current step
  - – Intuitive explorations from the steady-state
  - – exercise: ions exchanged during an action potential
- Mass Action Law & (deterministic) Kinetic Schemes
- Full Hodgkin-Huxley model

multiple ion-species, distinct concentrations, distinct permeabilities, NOT at the equilibrium,

NOT at the steady-state


A. Lavoisier

“Dans la nature rien ne se crée, rien ne se perd, tout change.”

$$\Delta Q_{tot} = 0$$

Balance of the tot charge change = 0

Balance of the tot net current = 0

$$\Delta Q_d = C \Delta V$$

Displacement

$$i = \frac{\Delta Q}{\Delta t} \qquad \Delta t \qquad \Delta Q_t = (i_1 + i_2 + i_3 + \ldots)\Delta t$$

Transport

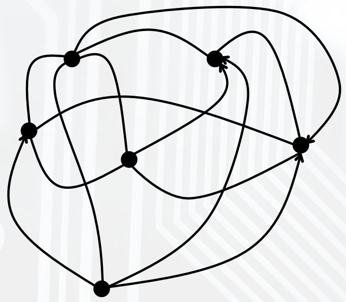
$$C \frac{\Delta V}{\Delta t} = -(i_1 + i_2 + i_3 + \ldots)$$

$$C \frac{d}{dt} V = -(i_1 + i_2 + i_3 + \ldots)$$

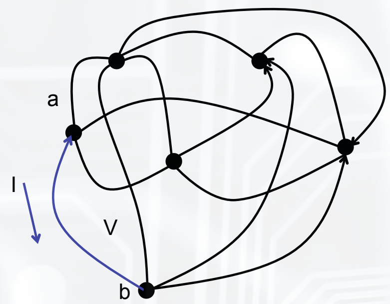
Charge Balance equation

(Linear) Electrical Networks Theory

electric networks = oriented graphs
set of **nodes + links** connecting them



electric network = oriented graph
node + links

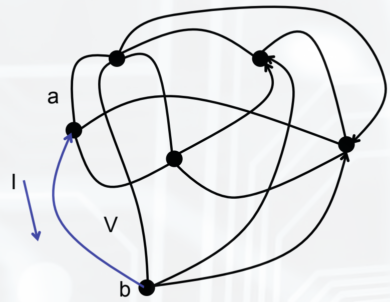


Two quantities ("*voltage*", "*current*") are associated to each link.
Those are the unknowns of the system.

They are "signed" quantities (< 0; > 0) whose sign depends on conventional orientation of the arrows.

We use the "passive" sign convention.

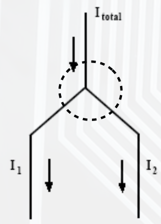
Kirchoff laws + components equations
=
enough equations for all the unknowns {V,I}



junction = point (or any closed surface) where two or more links converge

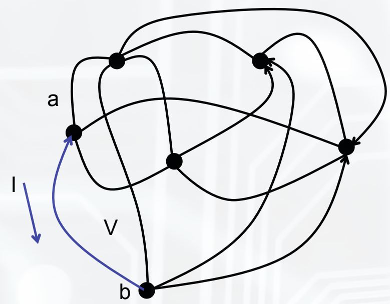
$$\sum_k I_k = 0 \quad \text{for any junction}$$

This is an algebraic sum!!!
(conservation of charge)



$$I_{total} = I_1 + I_2$$

Kirchoff laws + components equations
=
enough equations for all the unknowns {V,I}

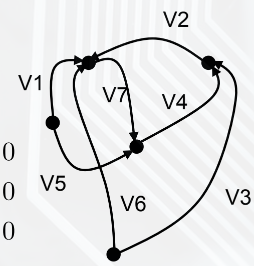


loop = closed path, where initial and final node are the same

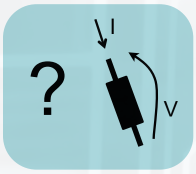
$$\sum_h V_h = 0 \quad \text{for any loop}$$

This is an algebraic sum!!!
(*conservativity* of the electric field)

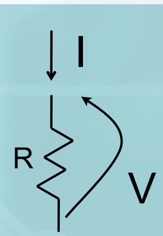
$$V_1 - V_2 - V_4 - V_5 = 0$$
$$V_1 + V_7 - V_5 = 0$$
$$V_6 - V_2 - V_3 = 0$$



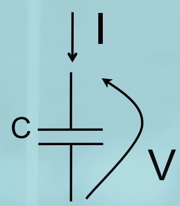
Kirchoff laws + components equations
=
enough equations for all the unknowns {V,I}



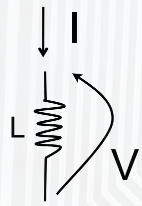
..each component sets a specific functional relationship between the circuit-variables at its nodes..



$$V = R\,I$$



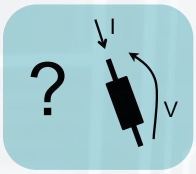
$$C\,\frac{dV}{dt} = I$$



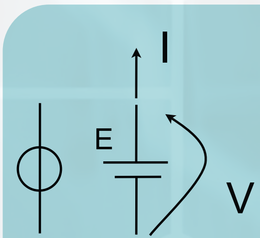
$$L\,\frac{dI}{dt} = V$$

These "*constitutive*" equations rely on the passive sign convention
(i.e. if you change convention, be consistent and change signs where appropriate)

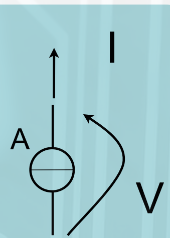
Kirchoff laws + components equations
=
enough equations for all the unknowns {V,I}



..each component sets a specific functional relationship between the circuit-variables at its nodes..



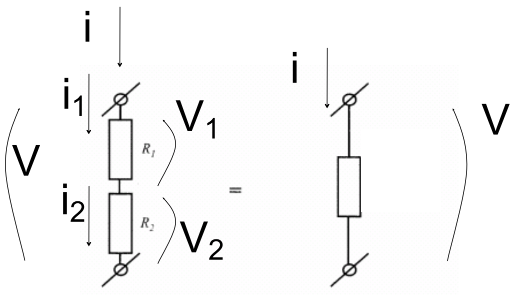
$$V = E$$



$$I = A$$

These "*constitutive*" equations rely on the passive sign convention
(i.e. if you change convention, be consistent and change signs where appropriate)

Exercise (for you) & Derivation of known results

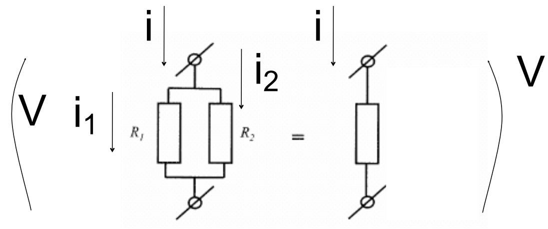


$$i_1 - i_2 = 0$$
$$i - i_1 = 0$$
$$V = V_1 + V_2$$

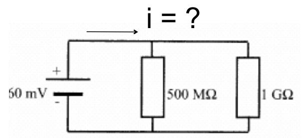
$$V_1 = R_1 i_1 \qquad V = Ri$$
$$V_2 = R_2 i_2$$

$$i = i_1 + i_2$$
$$V - V_1 = 0$$
$$V_1 - V_2 = 0$$

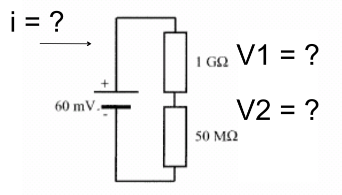
$$V_1 = R_1 i_1 \qquad V = Ri$$
$$V_2 = R_2 i_2$$



Exercise (for you) & Derivation of known results



i1,i2,V1,V2 ?



$$i = i_1 + i_2$$

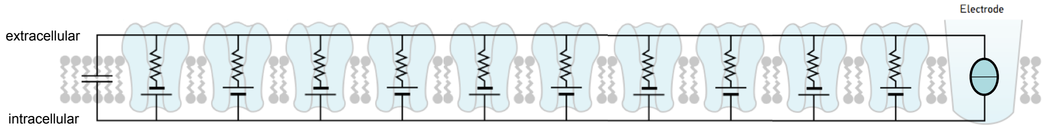
$$i_1 = 50\ mV/500\ M\Omega$$
$$i_2 = 50\ mV/1\ G\Omega$$

$$60\ mV = (R_1 + R_2)i \qquad i = 57.1\ pA$$

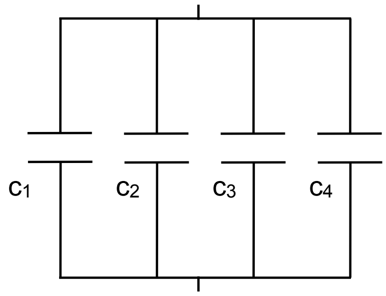
$$V_1 = R_1 i \qquad V_1 = 57.1\ mV$$
$$V_2 = R_2 i \qquad V_2 = 2.9\ mV$$

The current "*prefers*" the path with minimal resistance.
The voltage "*divides itself*" proportionally to the path resistance.

Electrical circuit models, equivalent to a (neuronal) membrane patch



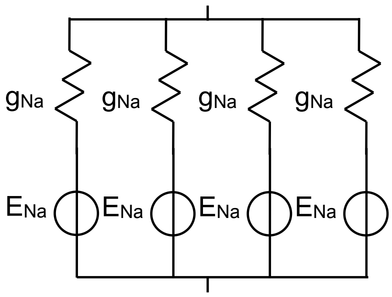
spatially **distributed** equivalent circuit



=?

spatially **lumped** equivalent circuit

spatially **distributed** equivalent circuit

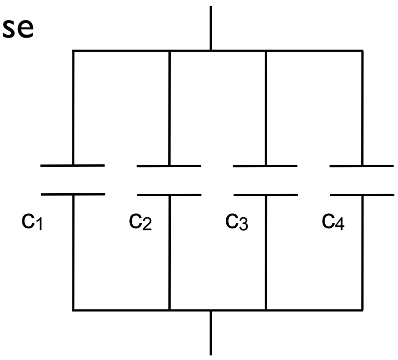


=?

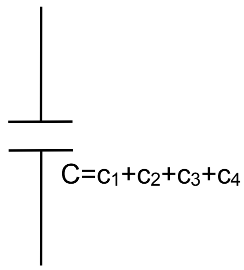
spatially **lumped** equivalent circuit

Exercise

spatially **distributed** equivalent circuit

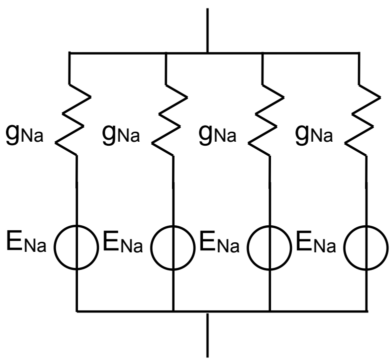


spatially **lumped** equivalent circuit

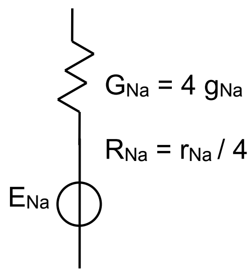


Exercise

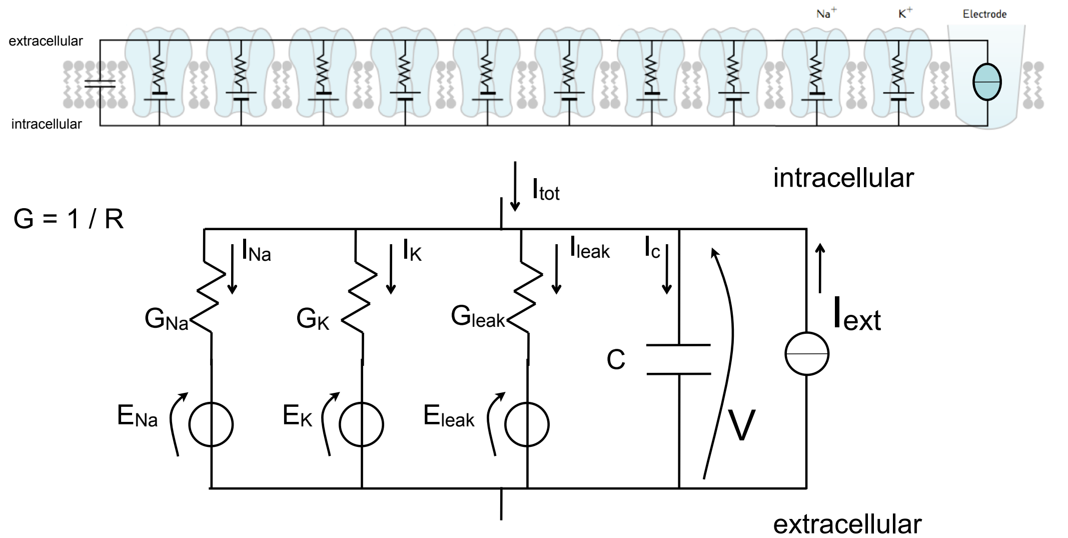
spatially **distributed** equivalent circuit



spatially **lumped** equivalent circuit



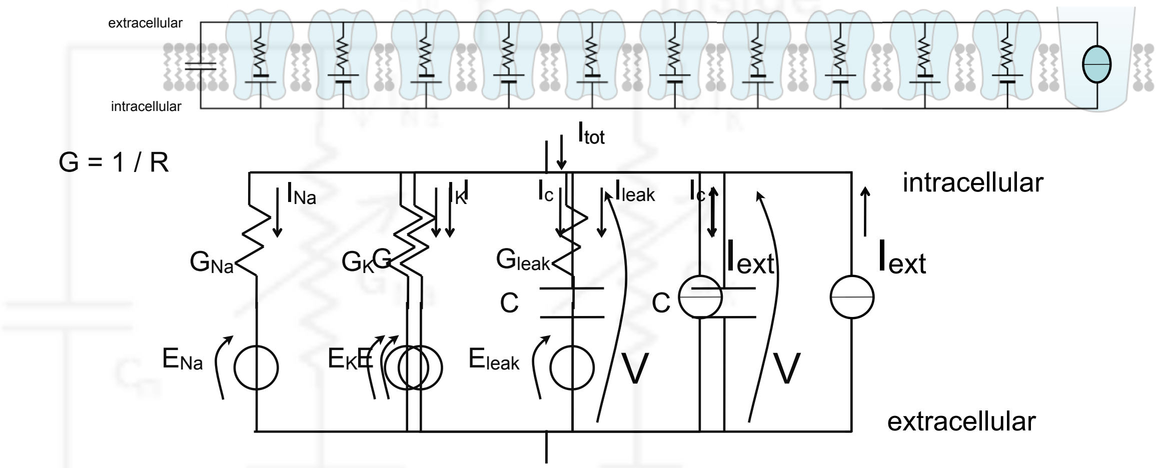
Electrical circuit models, equivalent to a (neuronal) membrane patch



$$I = G\,(V - E) \qquad C\,\frac{dV}{dt} = I \qquad I = A$$

$$E = \frac{RT}{zF}\, ln\left(\frac{c_{out}}{c_{in}}\right)$$

Full and reduced circuit models, equivalent to a cell membrane patch



$$C\,\frac{dV}{dt} = G_{Na}\,(E_{Na} - V) + G_K\,(E_K - V) + G_{leak}\,(E_{leak} - V) + I_{ext}$$

$$C\frac{dV}{dt} = -(G_{Na} + G_K + G_{leak})\,V + G_{Na}E_{Na} + G_K E_K + G_{leak}E_{leak} + I_{ext}$$

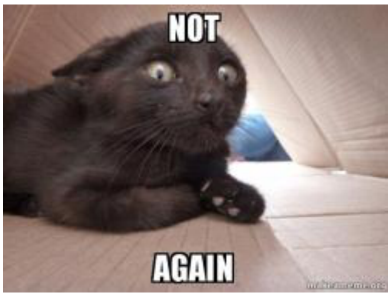
$$C\,\frac{dV}{dt} = G\,(E - V) + I_{ext}$$

Consequence of the *Thevenin's theorem* in Electrical Circuit Theory

$$C\,\frac{dV}{dt} = G\,(E - V) + I_{ext}$$

t $\quad V(t)$

$$\frac{G}{C}$$



$G\,E + I_{ext}$

a

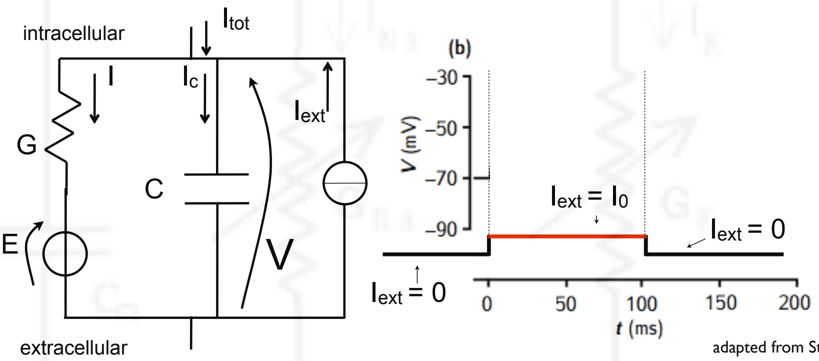
x $\quad f(x)$

$$\frac{df}{dx} = -ax + b$$

b

Exercise: response to a current (constant-amplitude) step

G = 1 / R



adapted from Sterratt et al., 2011

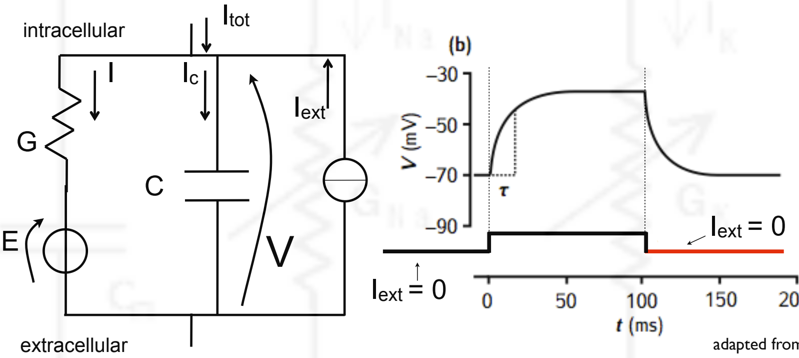
$$C\,\frac{dV}{dt} = G\,(E - V) + I_{ext} \qquad V(0) = E$$

$$V(t) = K\,e^{-G/C\;t} + E + I_0/G$$

$$V(t) = E + I_0/G\,\left(1 - e^{-G/C\;t}\right) \quad t \in [0\,;\,100]$$

Electrical circuit models, equivalent to a (neuronal) membrane patch

G = 1 / R



adapted from Sterratt et al., 2011

$$C \frac{dV}{dt} = G\ (E - V) + 0$$

$$V(t) = H\ e^{-G/C(t - 100ms)} + E \qquad t > 100$$

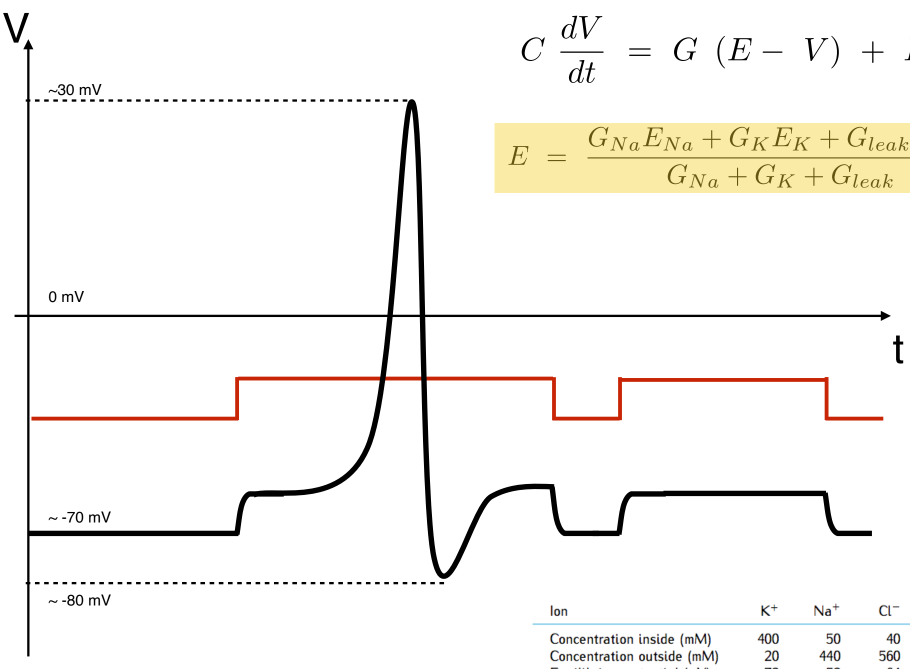
$$V(100) = E + I_0/G\ \left(1 - e^{-G/C\ 100ms}\right)$$

$$V(t) = I_0/G\ \left(1 - e^{-G/C\ 100ms}\right)\ e^{-G/C(t-100ms)} + E$$

"*Nobel prize*" intuitions on the Action Potential (AP)

$$C \frac{dV}{dt} = G\ (E - V) + I_{ext}$$

$$E = \frac{G_{Na}E_{Na} + G_K E_K + G_{leak}E_{leak}}{G_{Na} + G_K + G_{leak}}$$



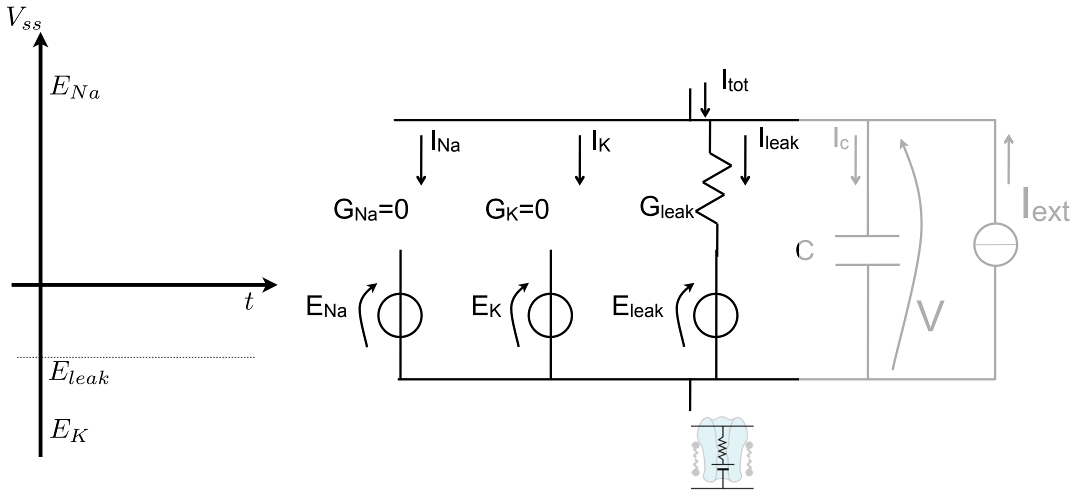
Ion	K^+	Na^+	Cl^-	Ca^{2+}
Concentration inside (mM)	400	50	40	10^{-4}
Concentration outside (mM)	20	440	560	10
Equilibrium potential (mV)	−72	52	−64	139

from Sterratt et al., 2011

“*Nobel prize*”intuitions: predictions from a (steady-state) selective changes in membrane ionic permeabilities

$$C \frac{dV}{dt} = G\ (E - V) + I_{ext}$$

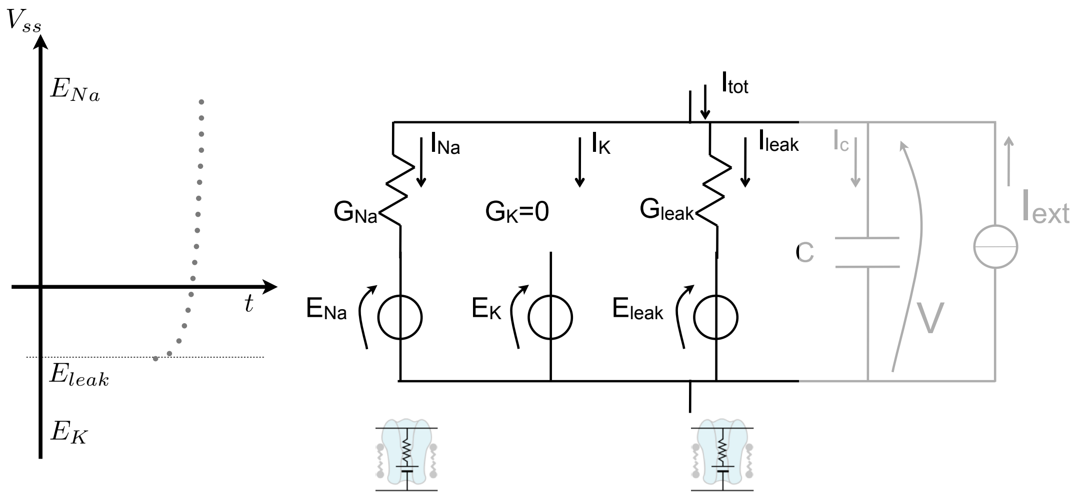
$$lim_{t \to +\infty}\ V(t) = E + \frac{I_{ext}}{G} \qquad E = \frac{G_{leak}E_{leak}}{G_{leak}}$$



“*Nobel prize*”-like intuitions: predictions from a (steady-state) selective changes in membrane ionic permeabilities

$$C \frac{dV}{dt} = G\ (E - V) + I_{ext}$$

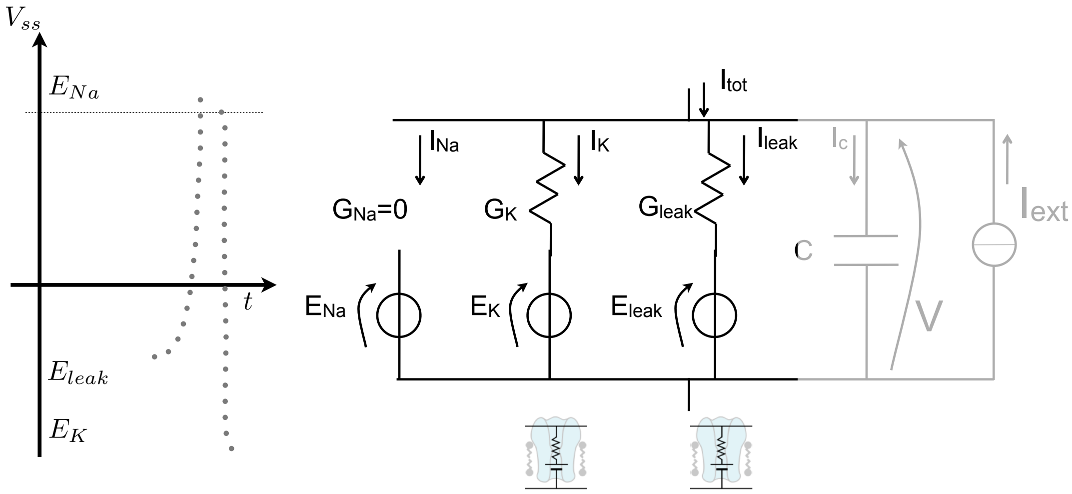
$$lim_{t \to +\infty}\ V(t) = E + \frac{I_{ext}}{G} \qquad E = \frac{G_{Na}E_{Na} + G_{leak}E_{leak}}{G_{Na} + G_{leak}}$$



“*Nobel prize*”-like intuitions: predictions from a (steady-state) selective changes in membrane ionic permeabilities

$$C\,\frac{dV}{dt} = G\,(E - V) + I_{ext}$$

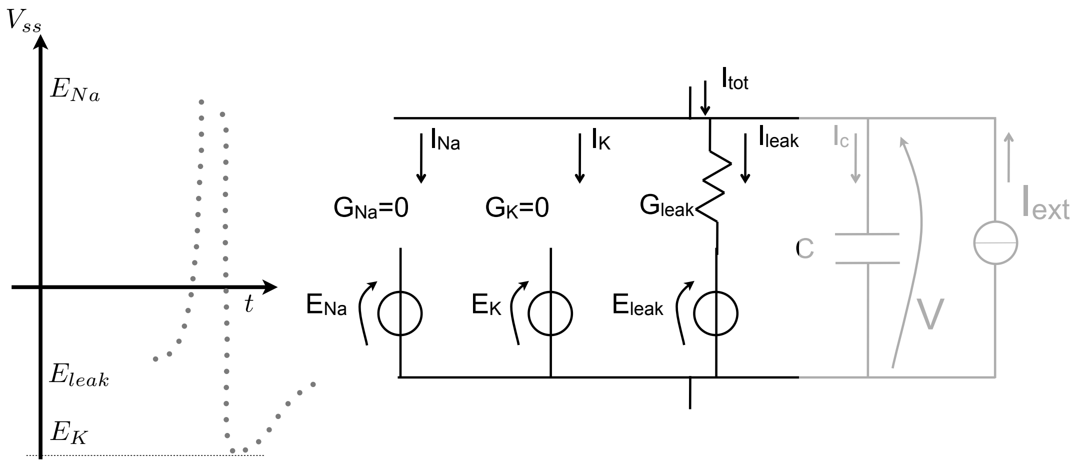
$$lim_{t\to+\infty}\,V(t) = E + \frac{I_{ext}}{G} \qquad E = \frac{G_K E_K + G_{leak} E_{leak}}{G_K + G_{leak}}$$



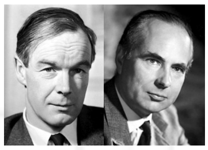
“*Nobel prize*”-like intuitions: predictions from a (steady-state) selective changes in membrane ionic permeabilities

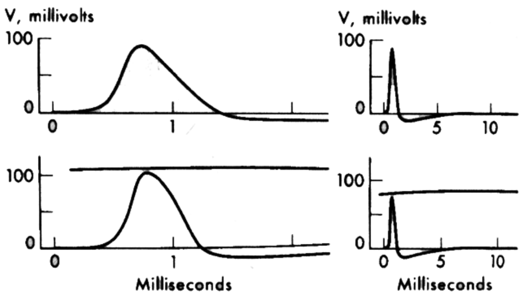
$$C\,\frac{dV}{dt} = G\,(E - V) + I_{ext}$$

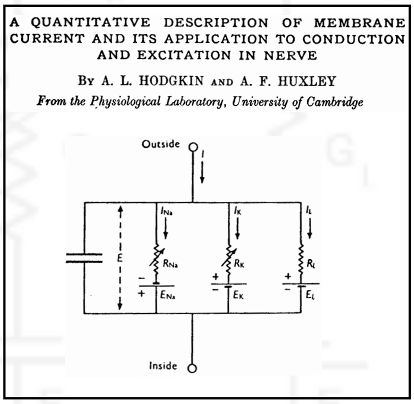
$$lim_{t\to+\infty}\,V(t) = E + \frac{I_{ext}}{G} \qquad E = \frac{G_{leak} E_{leak}}{G_{leak}}$$



The Hodgkin-Huxley model of AP





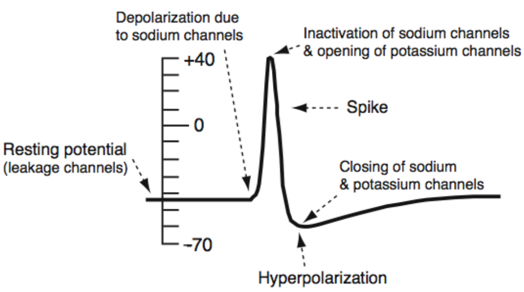

A QUANTITATIVE DESCRIPTION OF MEMBRANE CURRENT AND ITS APPLICATION TO CONDUCTION AND EXCITATION IN NERVE

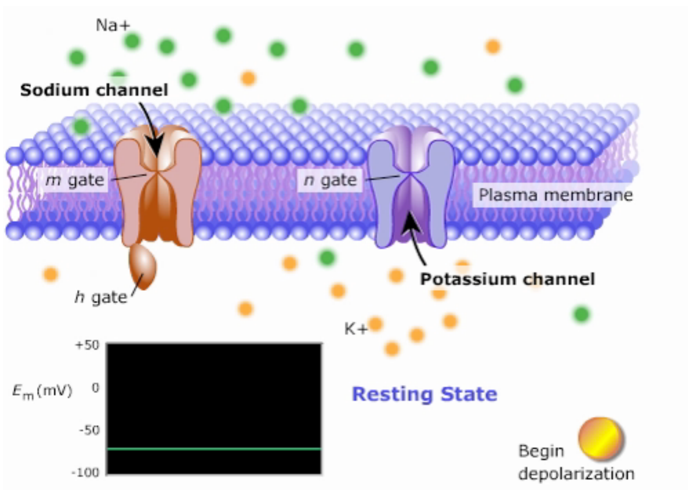
By A. L. HODGKIN AND A. F. HUXLEY

From the Physiological Laboratory, University of Cambridge

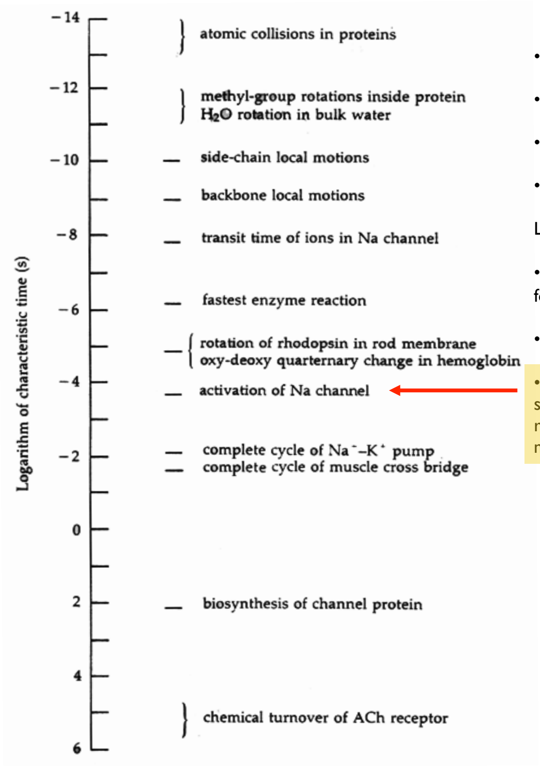
•Bernstein, 1902; Proposed an increase of membrane permeability to ions during excitation...
•Cole & Curtis, 1938; Recorded permeability changes...
•Hodgkin & Huxley, 1952; evidence for several ionic pathways each with its own kinetics...

The AP generation: selective changes in ionic permeabilities





http://www.blackwellpublishing.com/matthews/channel.html



•Atomic collisions 10-100fs

•Methyl groups in the protein interior rotate in 1-5ps

•Free amino acid chains about in 5-100ps

•Peptide backbone atoms exhibit motions in 1ns

LESS THAN THE TRANSIT TIME OF A SINGLE ION THROUGH

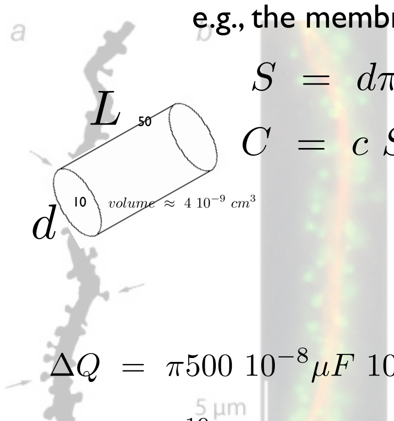
•Carbonic anhydrase takes 1µs to bring H_2O together with CO_2 to form a covalent bond

•Rhodopsin in rod membrane can spin around on its axis in 20µs

•Na channels activate in 0.1-1ms (there could have been countless subatomic, atomic changes – the protein backbone could have readjusted a million times and the side chains may have reoriented 100 million times)

Exercise: how many ions exchanged during an AP? **negligible**

e.g., the membrane potential changed by 100mV



$$S = d\pi\ L = \pi 500 \mu m^2 = \pi 500\ 10^{-8}\ cm^2$$

$$C = c\ S = \pi 500\ 10^{-8} \mu F$$

$$C = \frac{\Delta Q}{\Delta V}$$

$$\Delta Q = \pi 500\ 10^{-8} \mu F\ 100 mV = \pi 5\ 10^{-13} Coulombs$$

$$e = 1.6\ 10^{-19}\ Coulombs$$

$$F = 9.6\ 10^4\ Coulombs/mole$$

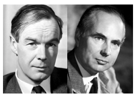
$1\ n\ mole$

$10\ 10^6 ions$

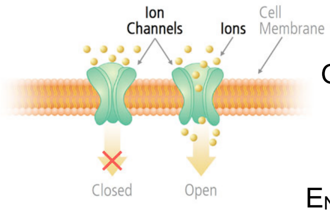
$$[Na^+] = 1mM = 10^{-3} \frac{moles}{litre} = 10^{-3} \frac{6\ 10^{23}}{1000\ cm^3} = 6\ 10^{17} \frac{ions}{cm^3}$$

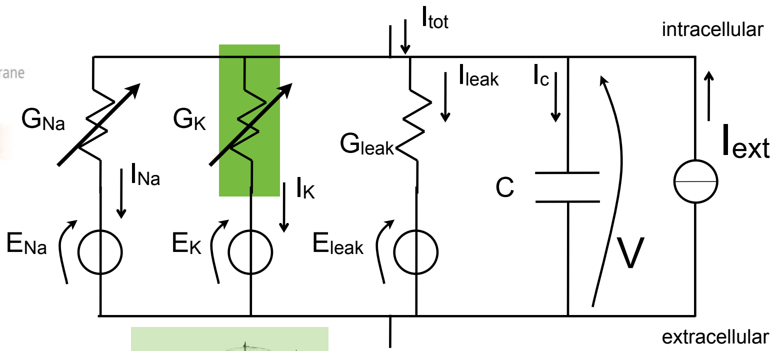
it takes ~240 spikes to deplete 1mM [Na+] from the cylinder (24 10^8 ions in **that** volume)..

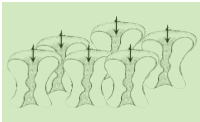
[Na] ~ 50mM : complete depletion after ~6 minutes of 30 Hz firing



HH described (mesoscopic) membrane permeability by (phenomenological) kinetic schemes







$$G_K = \gamma_K \; N_{open\ K}$$

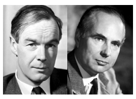
$$= N_{tot\ K}\; \gamma_K \frac{N_{open\ K}}{N_{tot\ K}}$$

$$G_K = \bar{g}_K \; n$$

$$[n] = ??$$

Fraction of channels in the 'open' state...;

or Density of channels in the 'open' state...;



HH described (mesoscopic) membrane permeability by (phenomenological) kinetic schemes

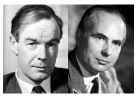
Assumptions of the (phenomenological) *Gating* Model

Populations of channels undergo collectively conformational changes, in response to variations in transmembrane electric field.
This makes the *ion channel population* to effectively "move" or translocate between discrete '*states*'.

$$closed \underset{\beta(V)}{\overset{\alpha(V)}{\rightleftarrows}} open$$

α(V) and β(V) are voltage-dependent rate coefficients

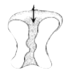
The *reaction* between the open and closed states is first-order: i.e.,
it depends only on the concentration of the "reactants".
Same concept behind the mesoscopical description of chem. reactions
Exponential time course is associated to such a dynamics.



HH described (mesoscopic) membrane permeability by (phenomenological) kinetic schemes

state 1 state 2

$$\mathit{closed} \underset{\beta(V)}{\overset{\alpha(V)}{\rightleftarrows}} \mathit{open}$$

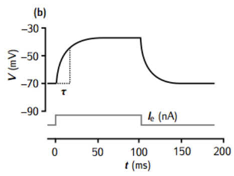
$$\frac{dn}{dt} = -\beta\, n + \alpha\, (1-n)$$

$$\frac{dn}{dt} = -(\alpha+\beta)\, n + \alpha$$

$$\frac{1}{(\alpha+\beta)}\frac{dn}{dt} = -n + \frac{\alpha}{(\alpha+\beta)} \qquad \tau_n \frac{dn}{dt} = -n + n_\infty$$

Non-homogenous ordinary differential equations, with time-varying (particular) inputs

$$\tau \frac{dx}{dt} = x_\infty - x$$



...see Module I

exact analytical solution: convolution integral (i.e., filtering)

$$x(t) = x(t_0)\, h(t) + \int_{-\infty}^{+\infty} h(t-\xi)\, x_\infty(\xi)\, d\xi \qquad h(t) = e^{-\frac{t-t_0}{\tau}}\, \Theta(t-t_0)$$

intuitive understanding: time-invariant input

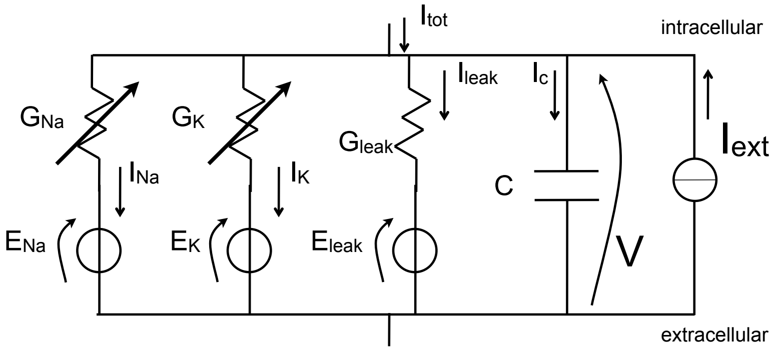
$$x \cong (x_0 - x_\infty)\, e^{-\frac{t-t_0}{\tau}} + x_\infty$$

...approximately...

if x_∞ varies in time, x *follows* it,
unless it varies too quickly, then it lags behind...

The Hodgkin-Huxley model of AP generation

$$C\,\frac{dV}{dt} = I_{Na} + I_K + I_{leak} + I_{ext}$$



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

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

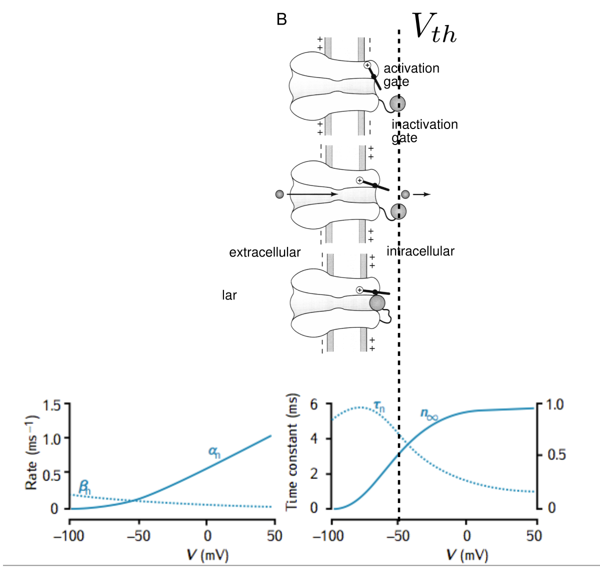
$$I_{leak} = \bar{g}_{leak}(E_{leak} - V)$$

The Hodgkin-Huxley model of AP generation

$$m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m}$$

$$h_\infty = \frac{\alpha_h}{\alpha_h + \beta_h}$$

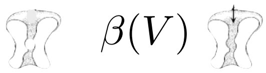
$$n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n}$$



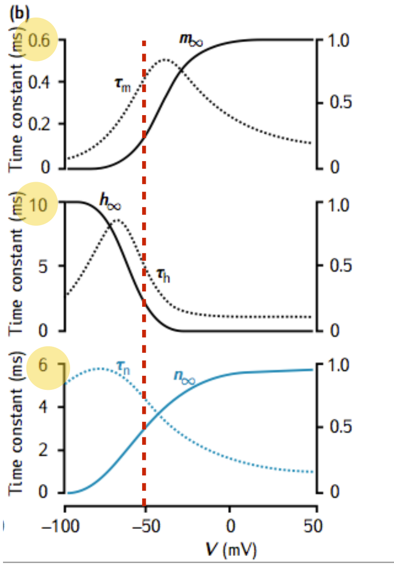
from Sterratt et al., 2011

$$\text{state 1} \qquad \qquad \text{state 2}$$

$$\text{closed} \underset{\beta(V)}{\overset{\alpha(V)}{\rightleftarrows}} \text{open}$$



$$x_\infty = \frac{\alpha_x(V)}{\alpha_x(V)+\beta_x(V)} \qquad \tau_x = \frac{1}{\alpha_x(V)+\beta_x(V)}$$



$$\tau_m(V)\frac{dm}{dt} = -m + m_\infty(V)$$

$$\tau_h(V)\frac{dh}{dt} = -h + h_\infty(V)$$

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

(a) $$[n_0] \underset{\beta_n}{\overset{4\alpha_n}{\rightleftarrows}} [n_1] \underset{2\beta_n}{\overset{3\alpha_n}{\rightleftarrows}} [n_2] \underset{3\beta_n}{\overset{2\alpha_n}{\rightleftarrows}} [n_3] \underset{4\beta_n}{\overset{\alpha_n}{\rightleftarrows}} [n_4]$$

(b) $$\begin{tikzcd}
{[m_0h_1]} \arrow[r, shift left, "3\alpha_m"] \arrow[d, shift left, "\beta_h"] & {[m_1h_1]} \arrow[l, shift left, "\beta_m"] \arrow[r, shift left, "2\alpha_m"] \arrow[d, shift left, "\beta_h"] & {[m_2h_1]} \arrow[l, shift left, "2\beta_m"] \arrow[r, shift left, "\alpha_m"] \arrow[d, shift left, "\beta_h"] & {[m_3h_1]} \arrow[l, shift left, "3\beta_m"] \arrow[d, shift left, "\beta_h"] \\
{[m_0h_0]} \arrow[r, shift left, "3\alpha_m"] \arrow[u, shift left, "\alpha_h"] & {[m_1h_0]} \arrow[l, shift left, "\beta_m"] \arrow[r, shift left, "2\alpha_m"] \arrow[u, shift left, "\alpha_h"] & {[m_2h_0]} \arrow[l, shift left, "2\beta_m"] \arrow[r, shift left, "\alpha_m"] \arrow[u, shift left, "\alpha_h"] & {[m_3h_0]} \arrow[l, shift left, "3\beta_m"] \arrow[u, shift left, "\alpha_h"]
\end{tikzcd}$$

demo

The Hodgkin-Huxley model of AP generation

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

$$\tau_m(V)\frac{dm}{dt} = -m + m_\infty(V)$$

$$\tau_x = \frac{1}{\alpha_x(V) + \beta_x(V)}$$

$$\tau_h(V)\frac{dh}{dt} = -h + h_\infty(V)$$

$$x_\infty = \frac{\alpha_x(V)}{\alpha_x(V) + \beta_x(V)}$$

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

Functions of V:

$$\beta_m = 4\ e^{-(V+65)/18}$$
$$\alpha_m = 0.1\ \frac{V+40}{1\ -\ e^{-(V+40)/10}}$$

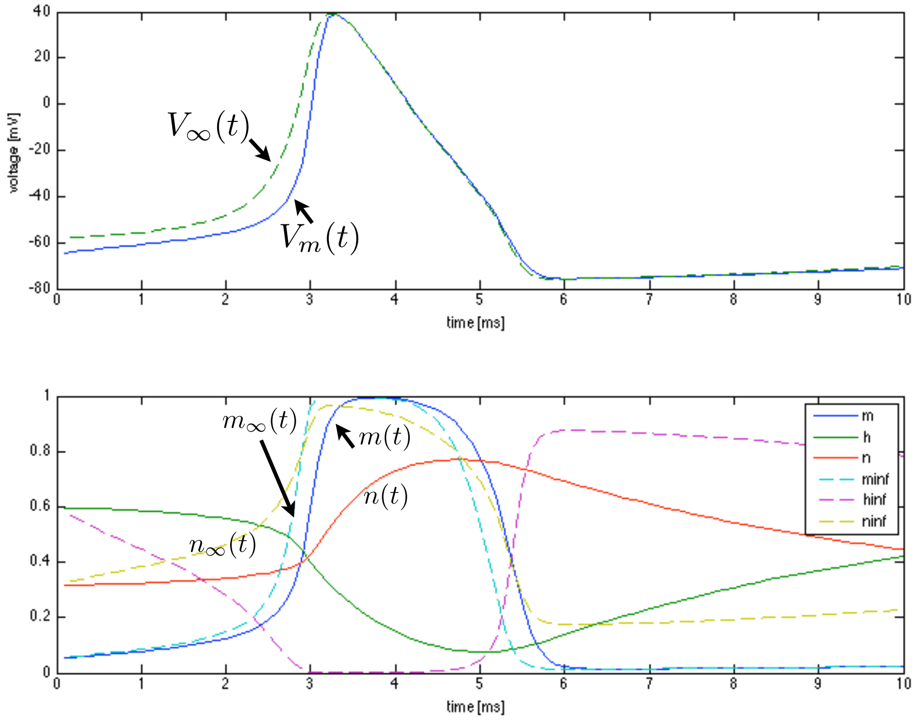
$$\beta_n = 0.125\ e^{-(V+65)/80}$$
$$\alpha_n = 0.01\ \frac{V+55}{1\ -\ e^{-(V+55)/10}}$$

$$\beta_h = \frac{1}{1\ +\ e^{-(V+35)/10}}$$
$$\alpha_h = 0.07\ e^{-(V+65)/20}$$

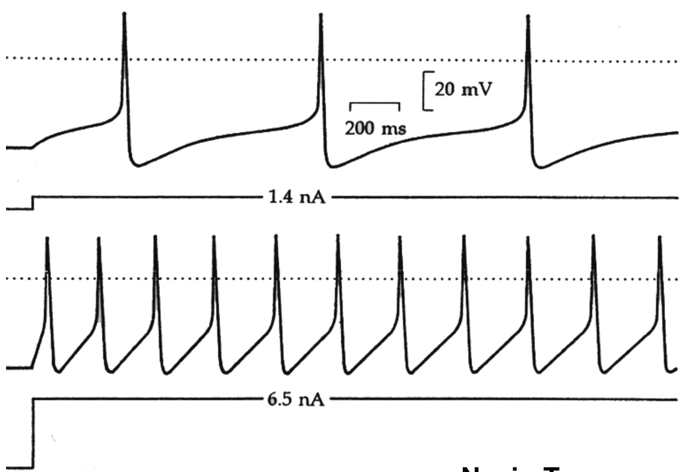
Parameters

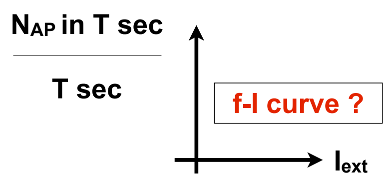
$$C = 1\ \mu F/cm^2$$
$$\bar{g}_{Na} = 120\ mS/cm^2$$
$$\bar{g}_K = 36\ mS/cm^2$$
$$\bar{g}_{leak} = 0.3\ mS/cm^2$$
$$E_{Na} = 50\ mV$$
$$E_K = -77\ mV$$
$$E_{leak} = -54.387\ mV$$

The Hodgkin-Huxley model of AP generation

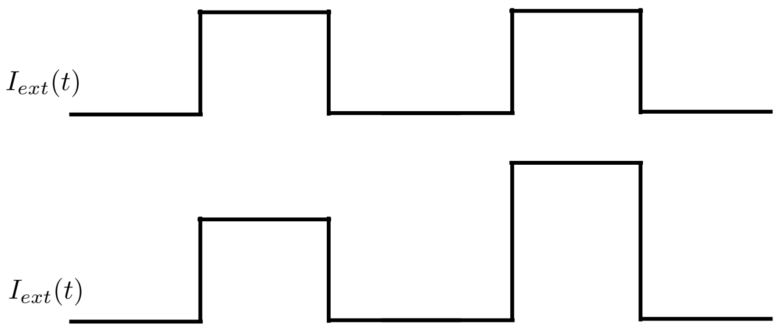


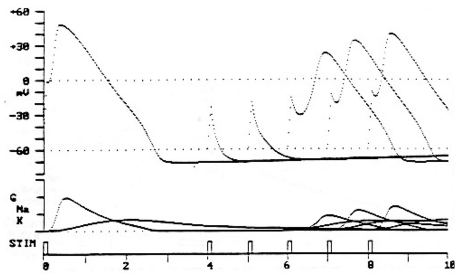
<u>Increasing the amplitude</u> of the injected (DC) current elicits sustained and regular oscillations with <u>increasing frequency</u>





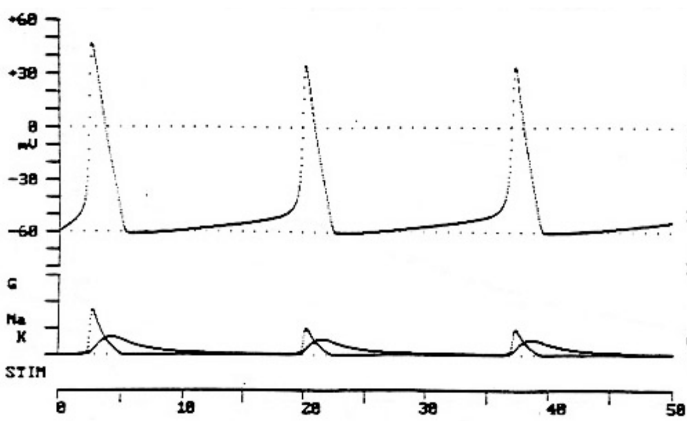
Absolute and relative refractory period: why?





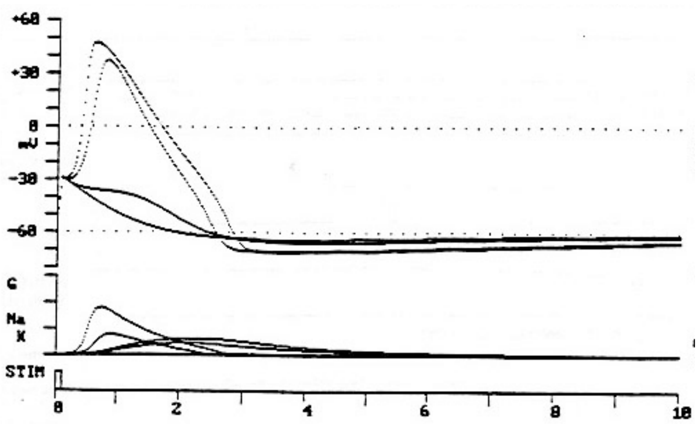
Perumalla and MacKay

Increasing the extracellular concentration of K-ions: why?



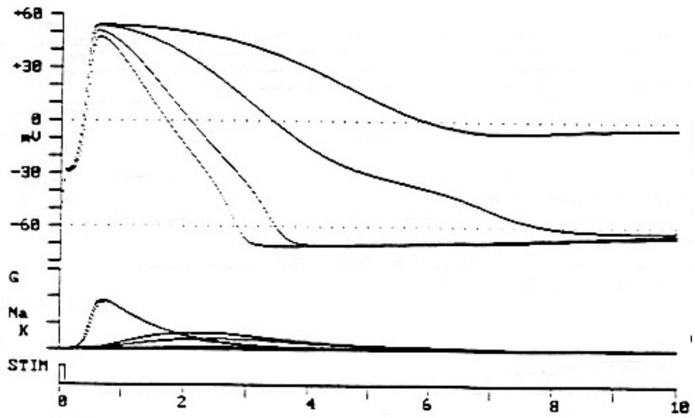
Perumalla and MacKay

Simulating pharmacology and toxins: which one? why?



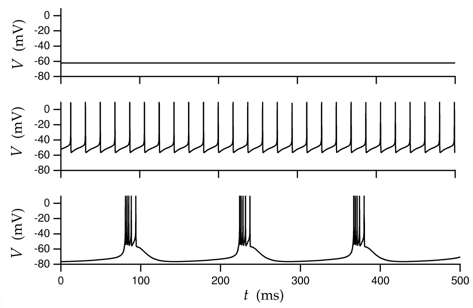
Perumalla and MacKay

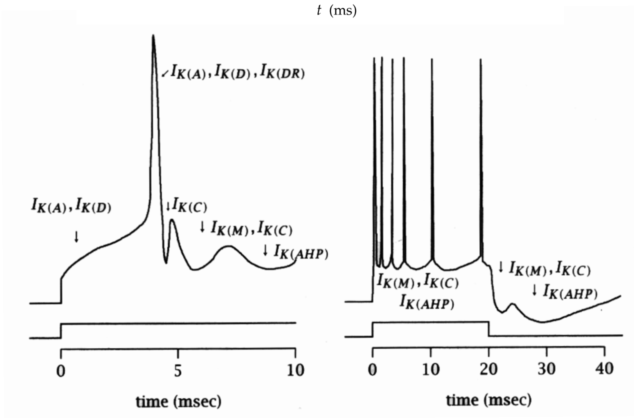
Simulating pharmacology and toxins: which? why?



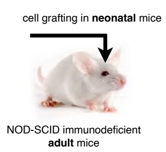
Perumalla and MacKay

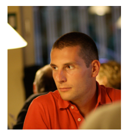
The 'zoo' of ion channels….



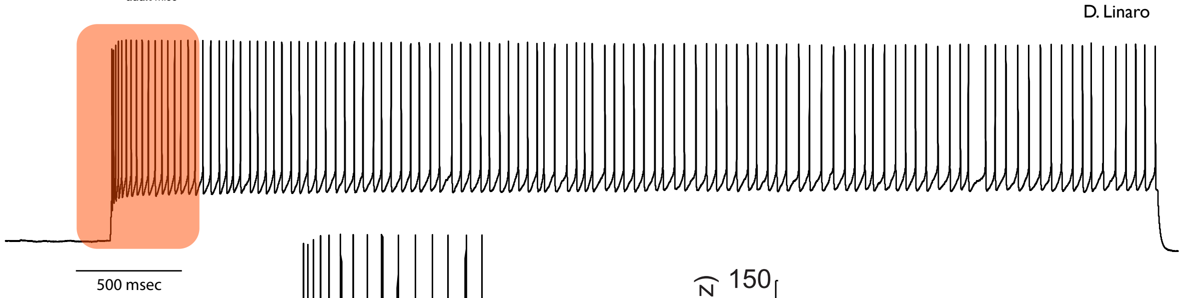


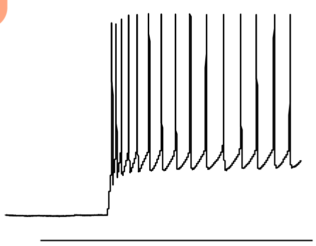
Additional Potassium-currents:
e.g., Ca- or Na-dependent K-currents

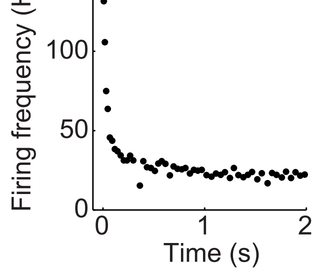




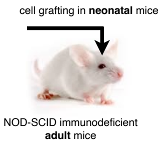
D. Linaro



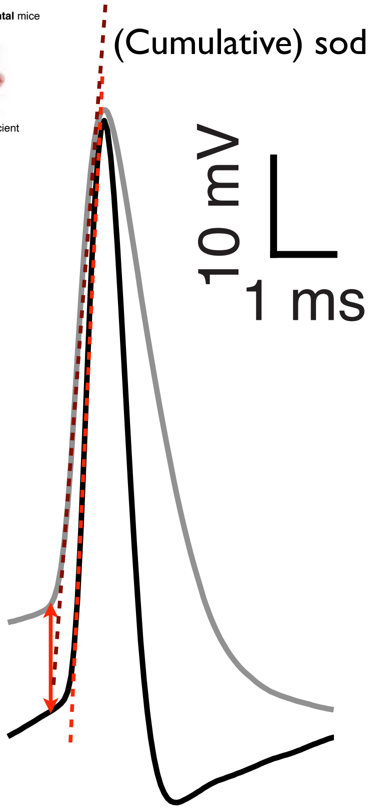


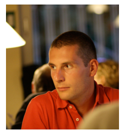


Spike-frequency adaptation (accommodation)



(Cumulative) sodium-channels inactivation

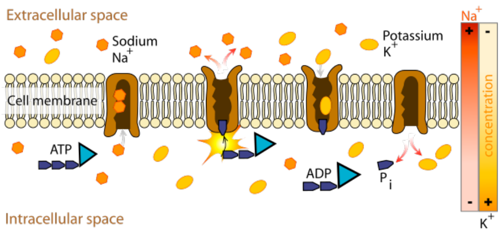


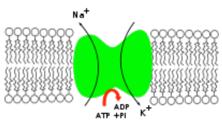


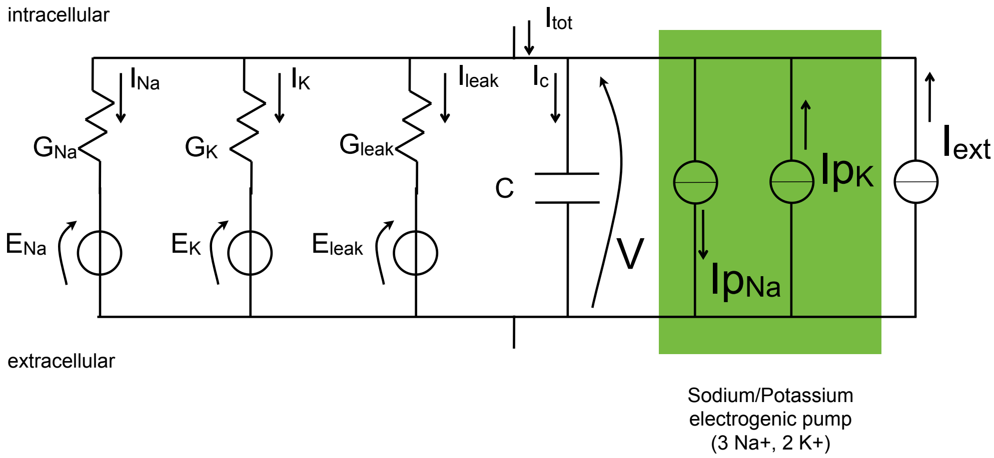
D. Linaro

- progressive depolarisation: why?
- decrease in “slope” (or upstroke velocity) of the AP: why?

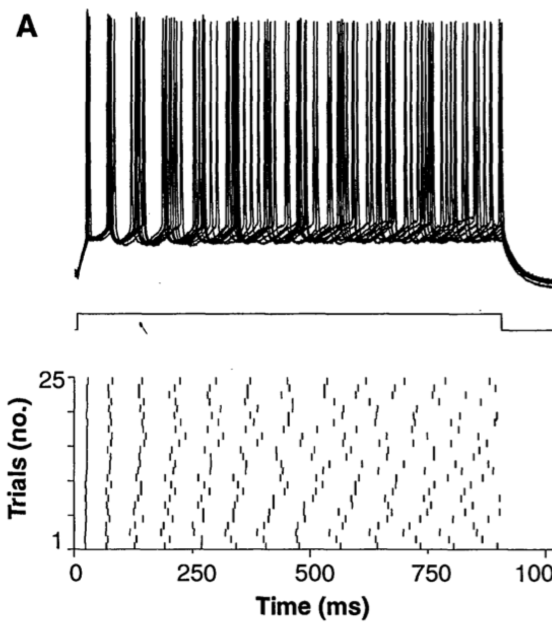
Including the effects of electrogenic ion pumps: Na+/K+-APTase







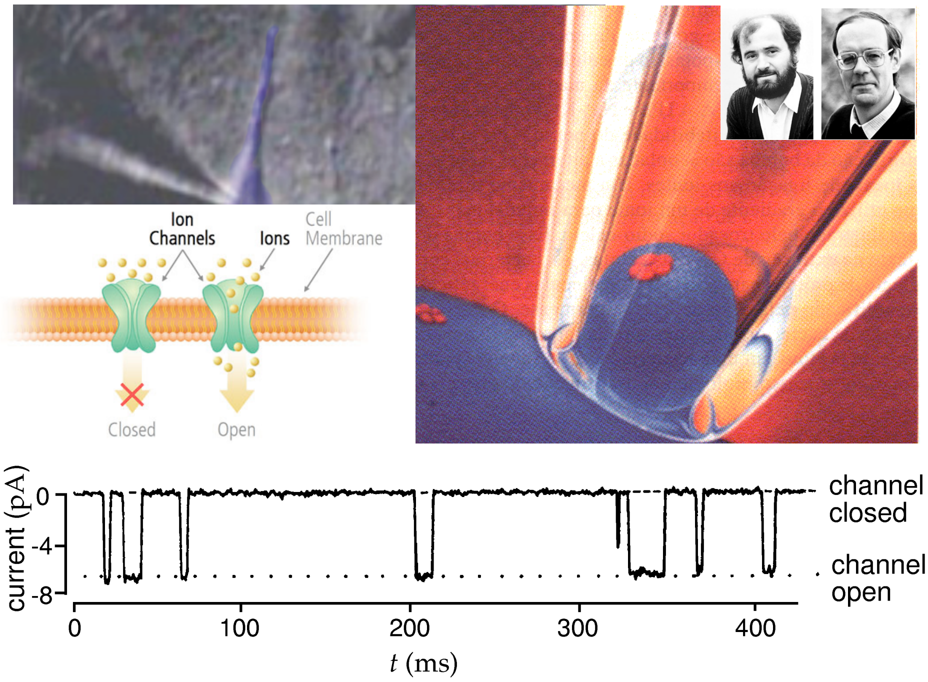
Channels random opening-closing creates jitter, ultimately affecting spike-timing precision in neocortical neurons



Mainen & Sejnowski, 1995

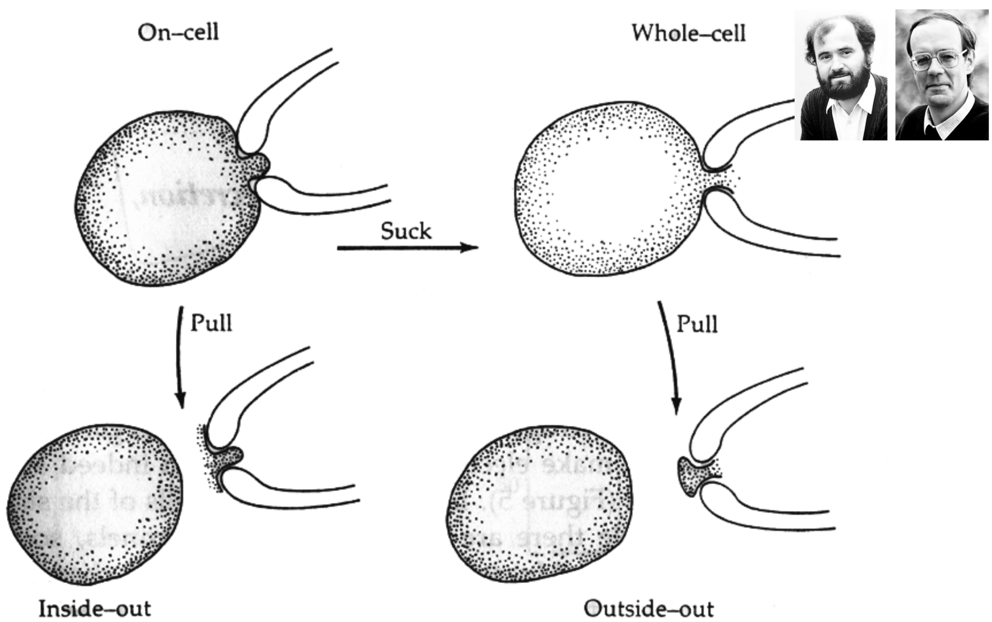
(Microscopically) membrane permeability: patch-clamp electrophysiology

discrete, **not** distributed property; stochastic, **not** deterministic phenomena

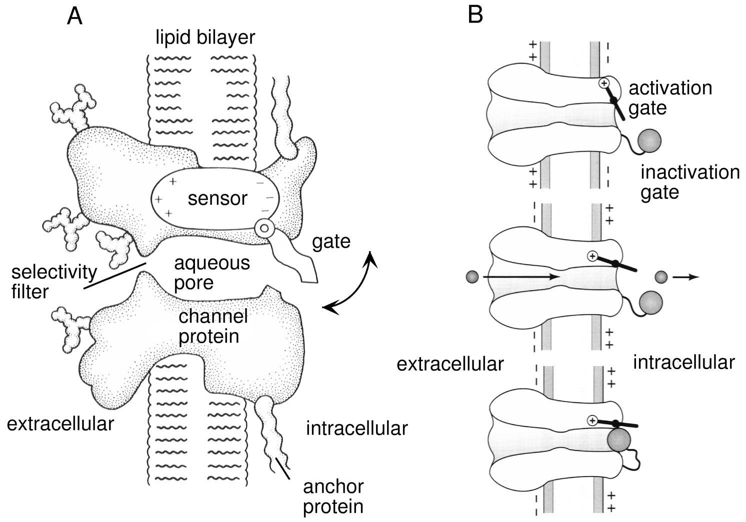


(Microscopically) membrane permeability: patch-clamp electrophysiology

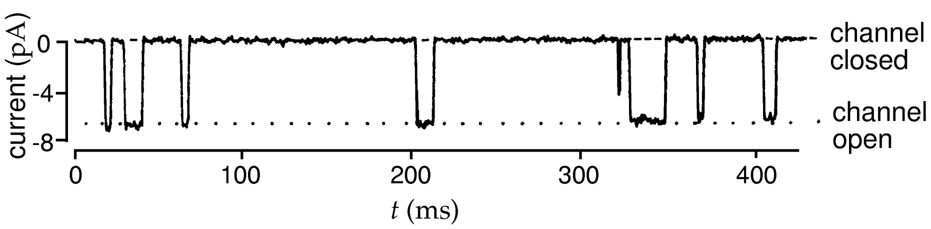
discrete, **not** distributed property; stochastic, **not** deterministic phenomena



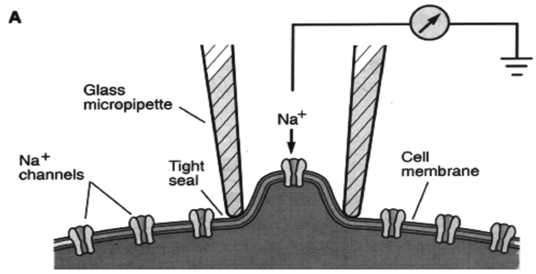
Membrane permeability is discrete, not continuous!



Membrane permeability is discrete and it is stochastic!

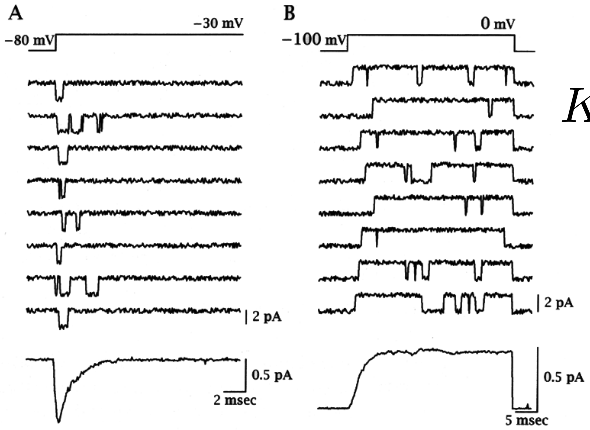


Patch-Clamp Reveals Single Ion Channels



Following HH, nearly all our understanding of ion channels came from patch-clamp studies

Na



K

Capturing "flickering" by a microscopic, i.e., single-channel, description of permeability

$$closed \underset{\beta(V)}{\overset{\alpha(V)}{\rightleftarrows}} open \qquad\qquad A \underset{k_2}{\overset{k_1}{\rightleftarrows}} B$$

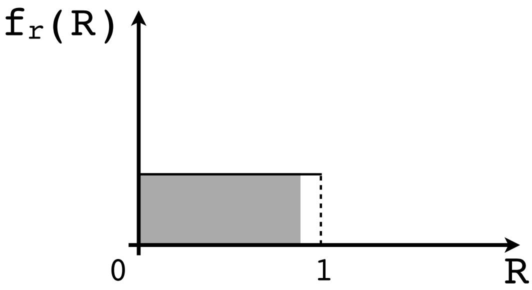
How do I “simulate” a random event???
(a *random* transition)

$$Pr\{A \rightarrow B \; in \; (t \, ; \, t + \Delta t] \; / state \; A \; at \; t\} = k_1 \, \Delta t + O(\Delta t)$$

$$Pr\{B \rightarrow A \; in \; (t \, ; \, t + \Delta t] \; / state \; B \; at \; t\} = k_2 \, \Delta t + O(\Delta t)$$

Let “r” be a pseudo-random number, uniform in [0 ; 1]

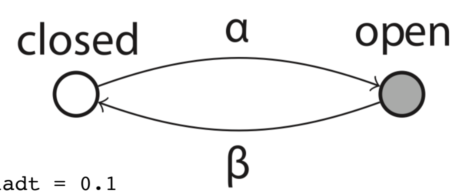
`r = rand()`

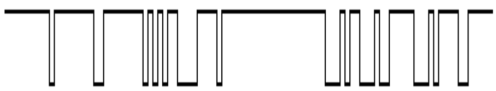


Prob{R < 0.8} = 0.8

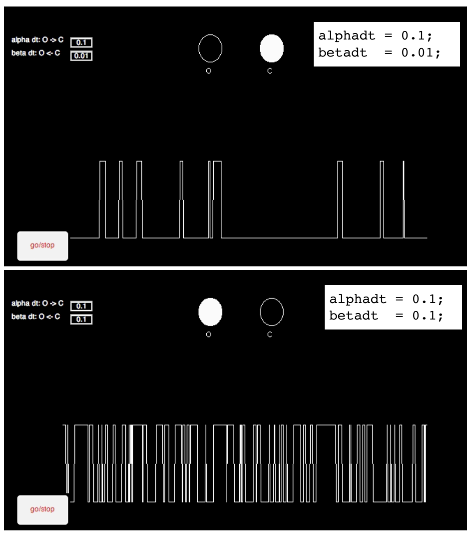
Prob{R < q} = q

Stochastic Markov-schemes can be used to describe (voltage-gated) opening/closing of ion channels





```
alphadt = 0.1
betadt = 0.01

isopen = false
while (true)

    r = rand()

    if isopen

        if (r <= betadt)
            isopen = false
        end

    else # isopen is false
        if (r <= alphadt)
            isopen = true
        end

    end # if
end # while
```



Capturing “flickering” by a microscopic, i.e., single-channel, description of permeability

$$closed \underset{\beta(V)}{\overset{\alpha(V)}{\rightleftarrows}} open \qquad\qquad A \underset{k_2}{\overset{k_1}{\rightleftarrows}} B$$

$$P(A,t) \;=\; Pr\{in\ state\ A\ at\ time\ t\}$$

$$P(A,t) \;+\; P(B,t) \;=\; 1$$

$$\begin{aligned} &Pr\{in\ state\ A\ at\ time\ t+\Delta t\} \;= \\ &Pr\{in\ state\ A\ at\ time\ t+\Delta t \quad \& \quad in\ state\ A\ at\ time\ t\} \;+ \\ &Pr\{in\ state\ A\ at\ time\ t+\Delta t \quad \& \quad in\ state\ B\ at\ time\ t\} \end{aligned}$$

Identical, independent, particles,
each described by the same kinetic scheme

Probability theory: conditional probabilities definition

$$\begin{aligned} &Pr\{in\ state\ A\ at\ time\ t+\Delta t\} \;= \\ &Pr\{in\ state\ A\ at\ time\ t+\Delta t \quad \& \quad in\ state\ A\ at\ time\ t\} \;+ \\ &Pr\{in\ state\ A\ at\ time\ t+\Delta t \quad \& \quad in\ state\ B\ at\ time\ t\} \end{aligned}$$

$$\begin{aligned} &Pr\{in\ state\ A\ at\ time\ t+\Delta t\} \;= \\ &Pr\{in\ state\ A\ at\ time\ t+\Delta t \quad / \quad in\ state\ A\ at\ time\ t\}\ Pr\{in\ state\ A\ at\ time\ t\} + \\ &Pr\{in\ state\ A\ at\ time\ t+\Delta t \quad / \quad in\ state\ B\ at\ time\ t\}\ Pr\{in\ state\ Bat\ time\ t\} \end{aligned}$$

$$P(A,t+\Delta t) \;=\; (1 \;-\; k_1\Delta t)\;\; P(A,t) \;+\; k_2\Delta t\ P(B,t)$$

$$P(A,t+\Delta t) \;=\; (1 \;-\; k_1\Delta t)\;\; P(A,t) \;+\; k_2\Delta t\;\; (1-P(A,t))$$

$$\frac{dP(A,t)}{dt} \;=\text{-}(k_1+k_2)\;\; P(A,t) \;+\; k_2$$

Binary {1,0} random variable *x*, for each channel

$$x = 1, \quad if\ state\ is\ A \qquad P(A,t)$$
$$x = 0, \quad if\ state\ is\ B$$

$$\bar{x}(t) = E\{x(t)\} =$$

$$\frac{d\bar{x}}{dt} = -(k_1 + k_2)\ \bar{x} + k_2$$

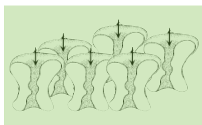
Ensemble-average = det. description

$$Var\{x(t)\} = E\{(x(t) - \bar{x}(t))^2\} = E\{(x(t)^2\} - \bar{x}(t)^2 =$$
$$=$$

$$Var\{x(t)\} = P(A,t)\ (1 - P(A,t))$$

Fluctuations, flickering,
not captured by the det. description

$$G_K = \gamma_K\ N_{open\ K}$$
$$= N_{tot\ K}\ \gamma_K\ \frac{N_{open\ K}}{N_{tot\ K}}$$
$$G_K = \bar{g}_K\ n$$



$x_1, x_2, x_3, \ldots, x_{N_{tot\ K}}$

$$n = \left(\sum_{i=1}^{N_{tot\ K}} x_i \right) / N_{tot\ K}$$

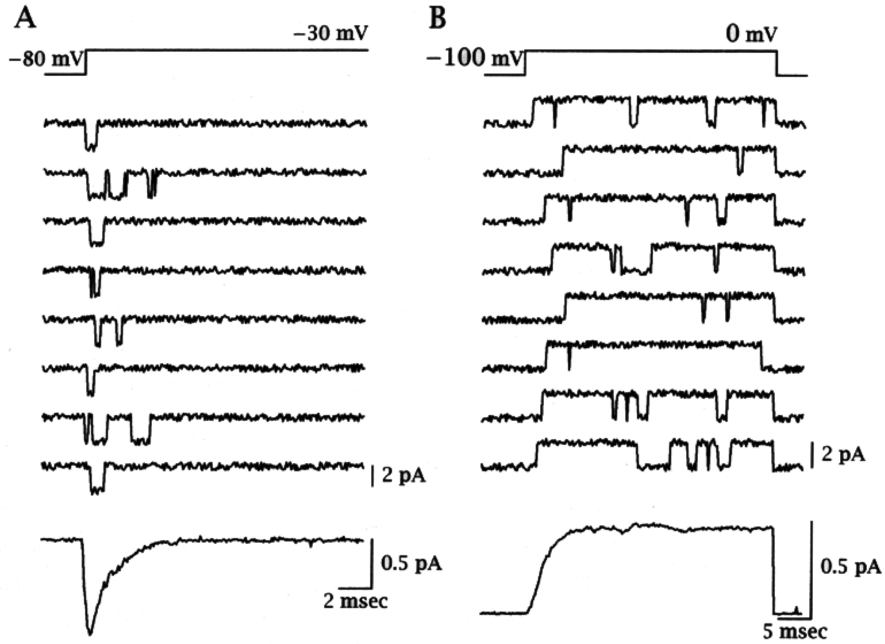
I describe x_i as a random variable!

$$E\{n\} = \bar{x}\ N_{tot\ K} / N_{tot\ K}$$

$$\boxed{Var\{n\} = \frac{\bar{x}\ (1 - \bar{x})}{N_{tot\ K}}}$$

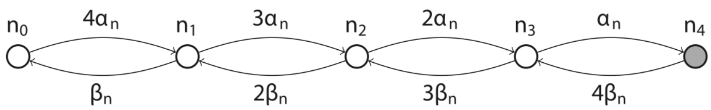
Large number theorem says that "for very large $N_{tot\ K}$, the chances that n takes actual values close to its expected value E{n}, are very high.
(Kolmogorov's inequality)

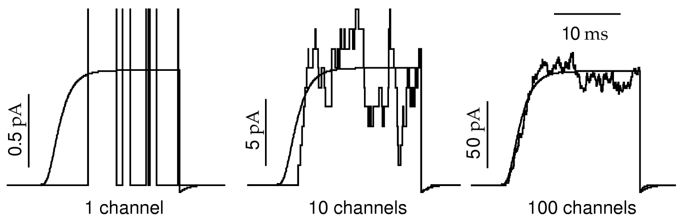
Inactivating (e.g. Na+) and non-inactivating (e.g. K+) ionic channels

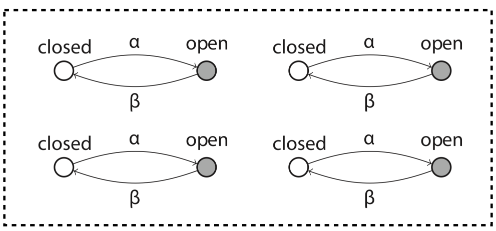


Stochastic Markov-schemes can be used to describe voltage-gated opening/closing of ion channels

e.g. K+, delayed-rectifier channel



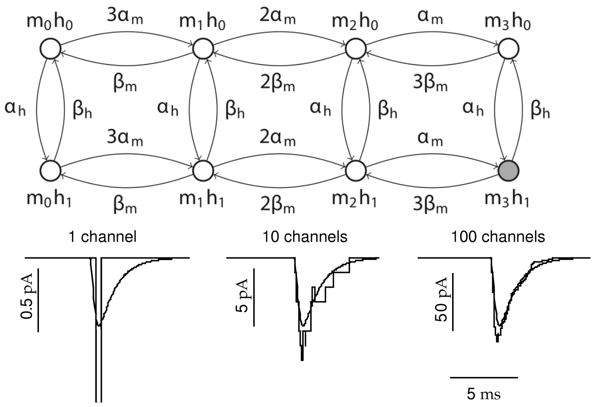


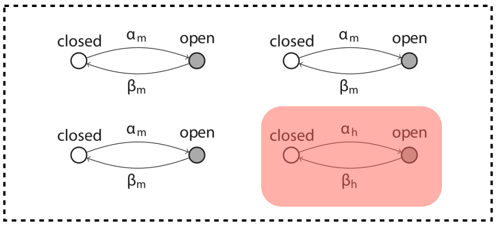


4 <u>identical</u> and <u>independent</u> sub-units equivalently describe the overall channel state

Stochastic Markov-schemes can be used to
describe voltage-gated opening/closing of ion channels

e.g. Na+, fast-inactivating channel

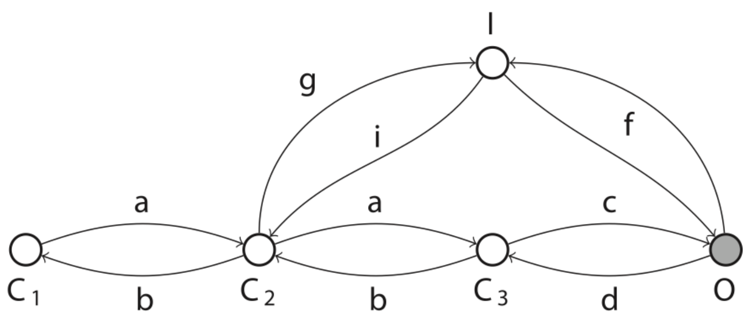




4 <u>independent</u> sub-units
(3 are <u>identical</u>)
equivalently describe
the overall channel state

Stochastic Markov-schemes can be used to
describe (voltage-gated) opening/closing of ion channels

e.g. Na+, fast-inactivating (alternative, non HH-description)



no equivalent individual sub-units description
is possible for this case but the model can be simulated anyway