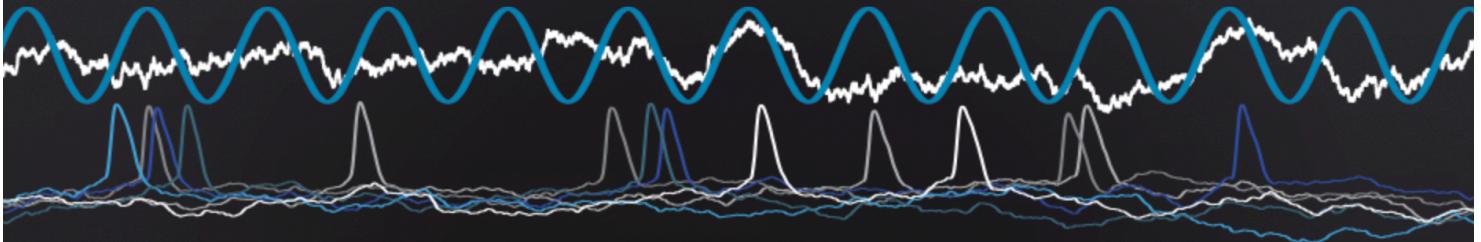


ELECTROPHYSIOLOGICAL SIGNALS



GENERATION AND CHARACTERISATION

Michele GIUGLIANO
Excitability

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

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

References

supporting your study and understanding

Chapters from

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

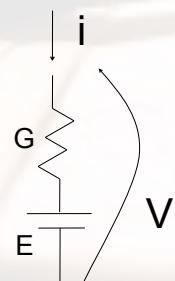
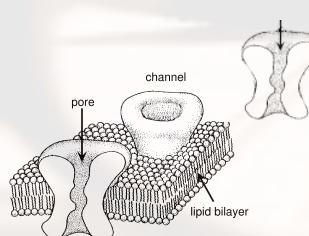
**Heterogeneous distributions of (typical) ions,
"inside/outside" the cell membrane**



Ion	K ⁺	Na ⁺	Cl ⁻	Ca ²⁺
Concentration inside (mM)				
Concentration outside (mM)				
Equilibrium potential (mV)				

from Sterratt et al., 2011

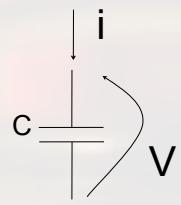
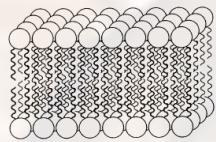
Equivalent electrical circuit model of ionic permeability



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

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

Equivalent model of capacitive properties

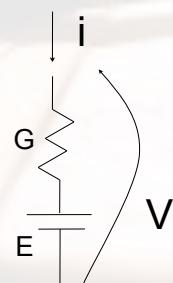
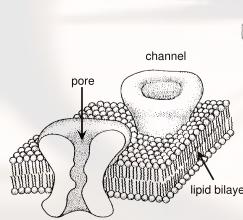


$$i = C \frac{dV}{dt}$$

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

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

Equivalent model of ionic permeability



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

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

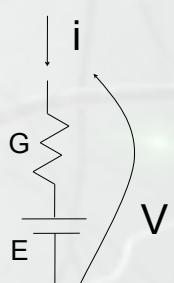
The resting membrane potential multiple ion-species, NOT at the equilibrium

Biological membranes have **distinct conductances** (i.e. distinct G_h , $h = \text{Na, K, Cl...}$)

Ions have **distinct reversal potentials** (i.e. distinct E_h , $h = \text{Na, K, Cl...}$)

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

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



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





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**

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

$$i_{tot} = i_1 + i_2 + i_3 + \dots =$$

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

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

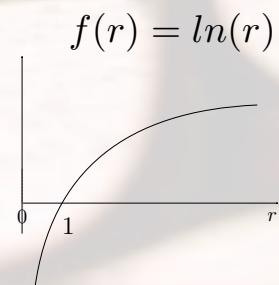
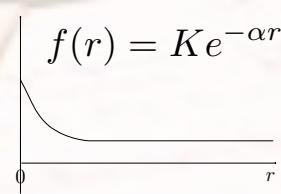
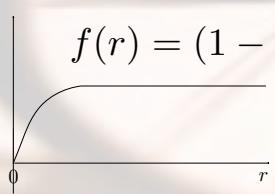
$$V_{rest} = \frac{(G_1E_1 + G_2E_2 + G_3E_3 + \dots)}{(G_1 + G_2 + G_3 + \dots)}$$



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

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

Graph of some notable functions



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-excitatory 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.”*

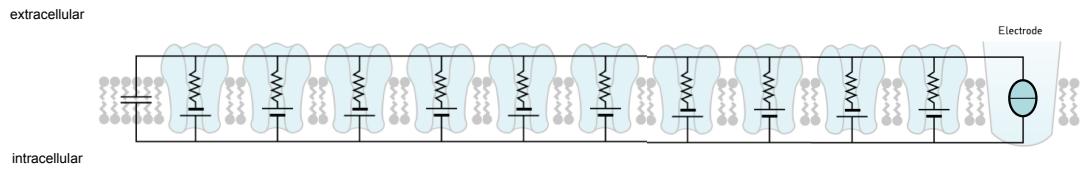
$$\Delta Q_{tot} = 0 \quad \begin{array}{l} \text{Balance of the tot charge change} = 0 \\ \text{Balance of the tot net current} = 0 \end{array}$$

$$\Delta Q_d = C \Delta V \quad \text{Displacement}$$

$$i = \frac{\Delta Q}{\Delta t} \quad \odot \Delta t \quad \Delta Q_t = (i_1 + i_2 + i_3 + \dots) \Delta t \quad \text{Transport}$$

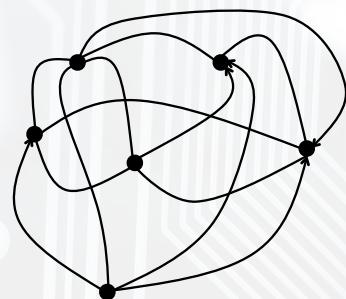
$$C \frac{\Delta V}{\Delta t} = -(i_1 + i_2 + i_3 + \dots) \quad C \frac{d}{dt} V = -(i_1 + i_2 + i_3 + \dots)$$

Charge Balance equation

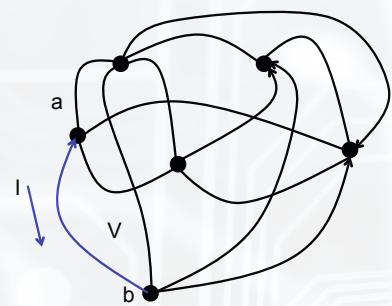


(Linear) Electrical Networks Theory

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



electric network = oriented graph
node + links

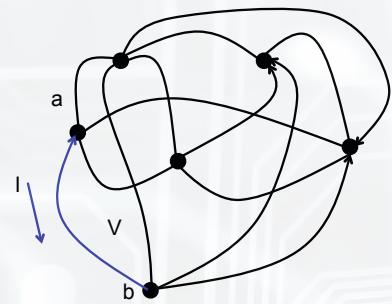


Two quantities (“*voltage*”, “*current*”) are associated to each link.
 Those are the unknowns of the system.

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

We use the “passive” sign convention.

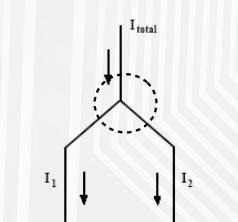
Kirchoff laws + components equations
 $=$
 enough equations for all the unknowns {V,I}



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

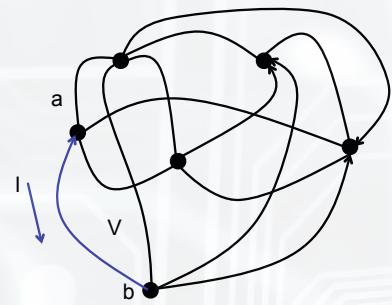
$$\sum_k I_k = 0 \text{ for any junction}$$

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



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

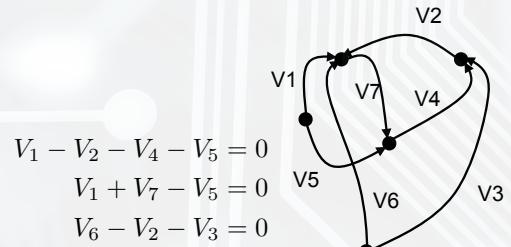
Kirchoff laws + components equations
=
enough equations for all the unknowns {V,I}



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

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

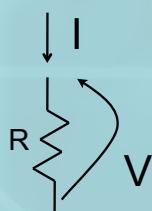
This is an algebraic sum!!!
(conservativity of the electric field)



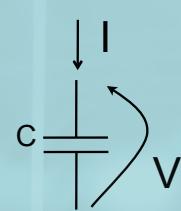
Kirchoff laws + components equations
=
enough equations for all the unknowns {V,I}



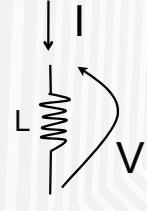
..each component sets a specific functional relationship between the circuit-variables at its nodes..



$$V = R I$$



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

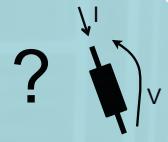


$$L \frac{dI}{dt} = V$$

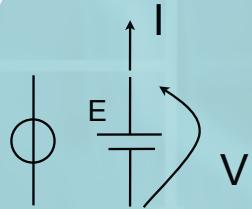
These “**constitutive**” equations rely on the passive sign convention
(i.e. if you change convention, be consistent and change signs where appropriate)

Kirchoff laws + components equations
=

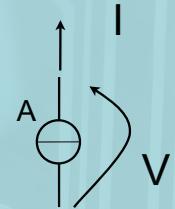
enough equations for all the unknowns {V,I}



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



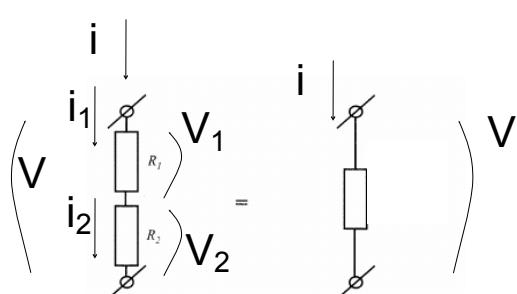
$$V = E$$



$$I = A$$

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



$$i_1 - i_2 = 0$$

$$i - i_1 = 0$$

$$V = V_1 + V_2$$

$$V_1 = R_1 i_1$$

$$V_2 = R_2 i_2$$

$$V = Ri$$

$$i = i_1 + i_2$$

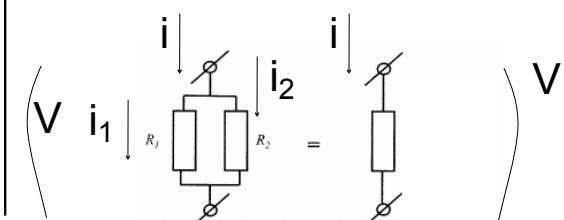
$$V - V_1 = 0$$

$$V_1 - V_2 = 0$$

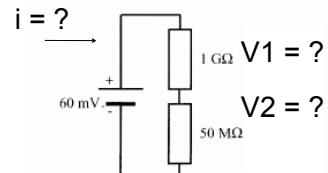
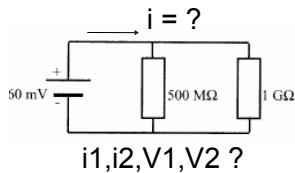
$$V_1 = R_1 i_1$$

$$V_2 = R_2 i_2$$

$$V = Ri$$



Exercise (for you) & Derivation of known results



$$i = i_1 + i_2$$

$$60 \text{ mV} = (R_1 + R_2)i$$

$$i = 57.1 \text{ pA}$$

$$i_1 = 50 \text{ mV}/500 \text{ M}\Omega$$

$$V_1 = R_1 i$$

$$i_2 = 50 \text{ mV}/1 \text{ G}\Omega$$

$$V_2 = R_2 i$$

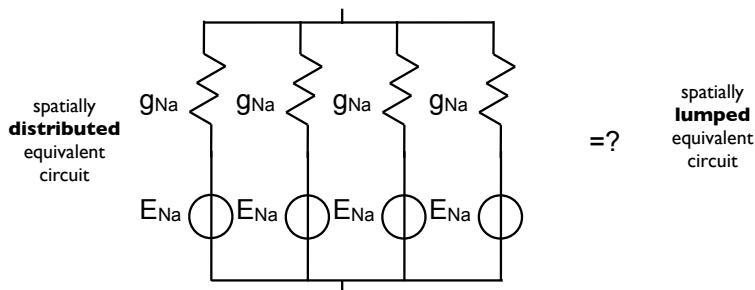
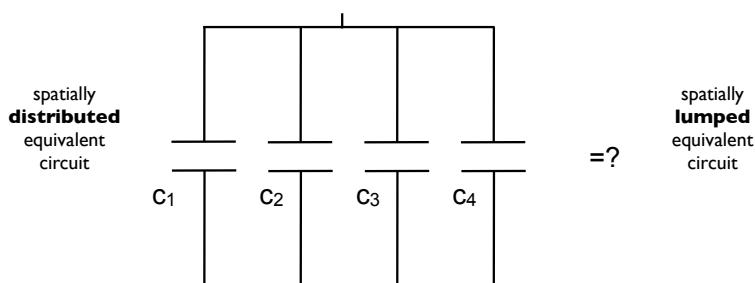
$$V_1 = 57.1 \text{ mV}$$

$$V_2 = 2.9 \text{ mV}$$

The current “prefers” the path with minimal resistance.

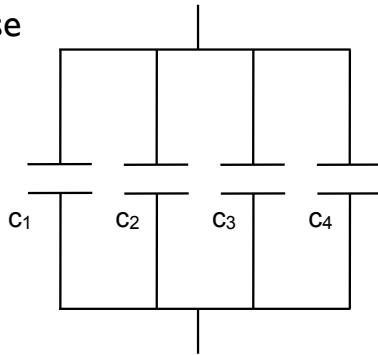
The voltage “divides itself” proportionally to the path resistance.

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

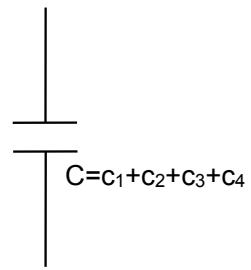


Exercise

spatially
distributed
equivalent
circuit

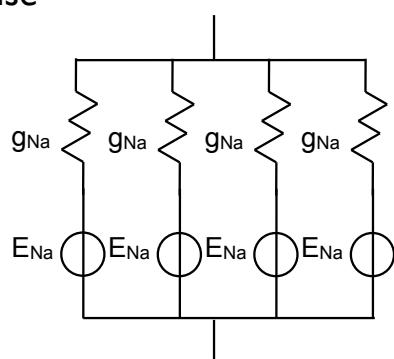


spatially
lumped
equivalent
circuit

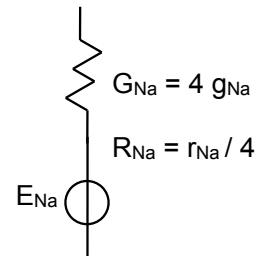


Exercise

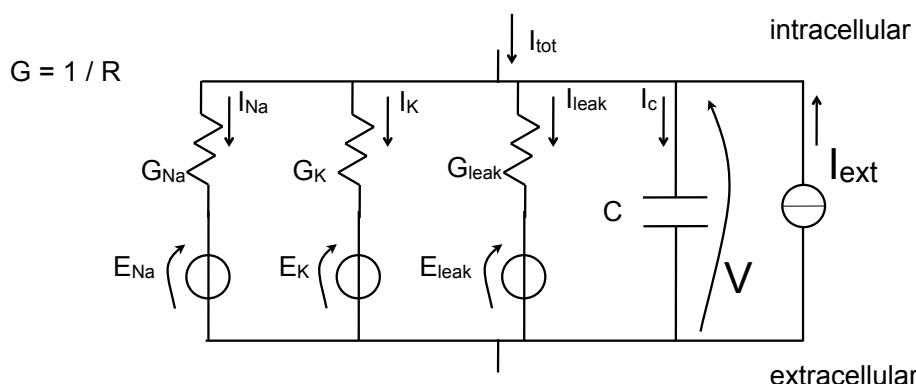
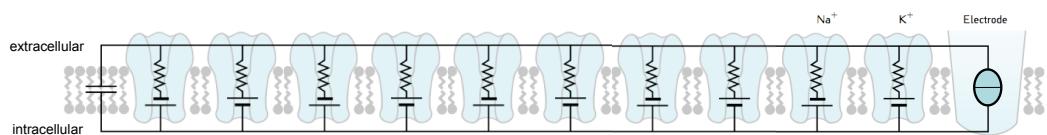
spatially
distributed
equivalent
circuit



spatially
lumped
equivalent
circuit



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



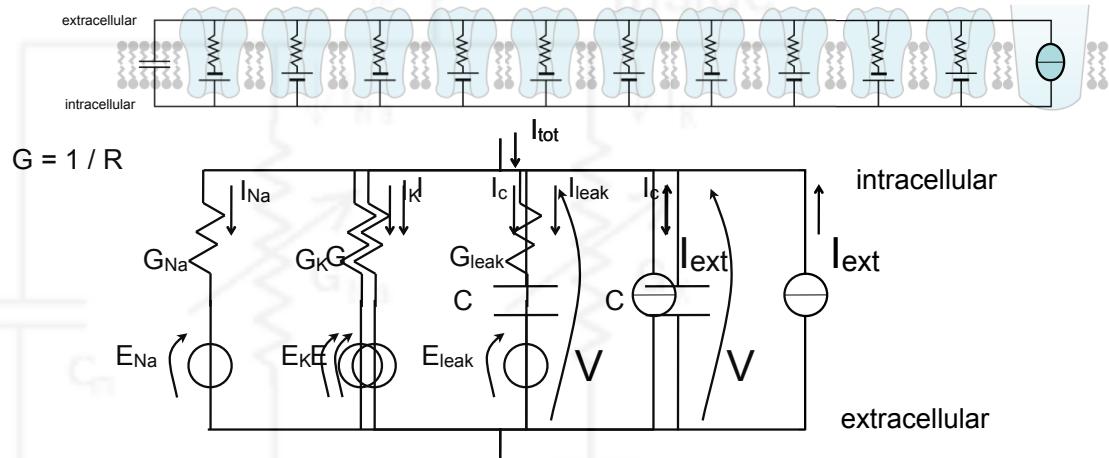
$$I = G(V - E)$$

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

$$I = A$$

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

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



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

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

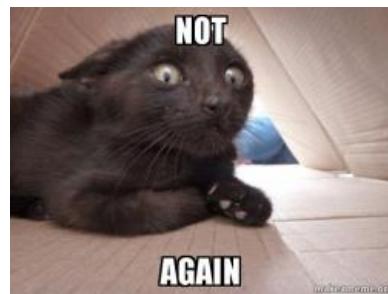
**Consequence of the Thevenin's theorem
in Electrical Circuit Theory**



$$t \quad V(t)$$

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

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



$$G E + I_{ext}$$

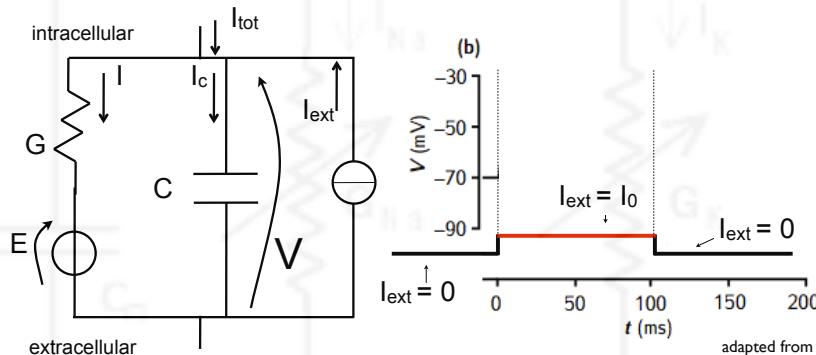
$$x \quad f(x)$$

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

$$\begin{matrix} a \\ b \end{matrix}$$

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

$$G = 1 / R$$



adapted from Sterratt et al., 2011

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

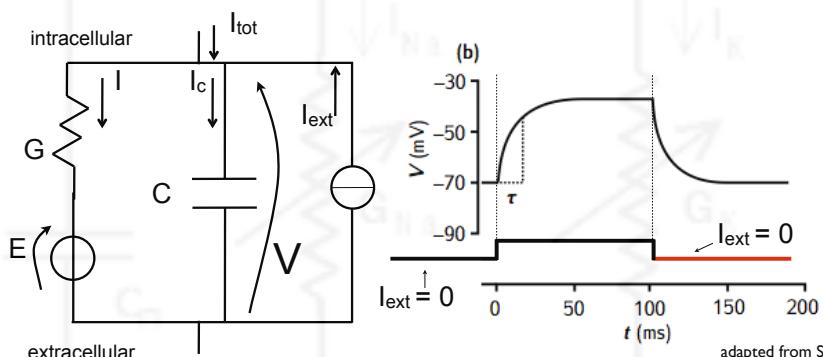
$$V(t) = K e^{-G/C t} + E + I_0/G$$

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



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

$$G = 1 / R$$



adapted from Sterratt et al., 2011

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

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

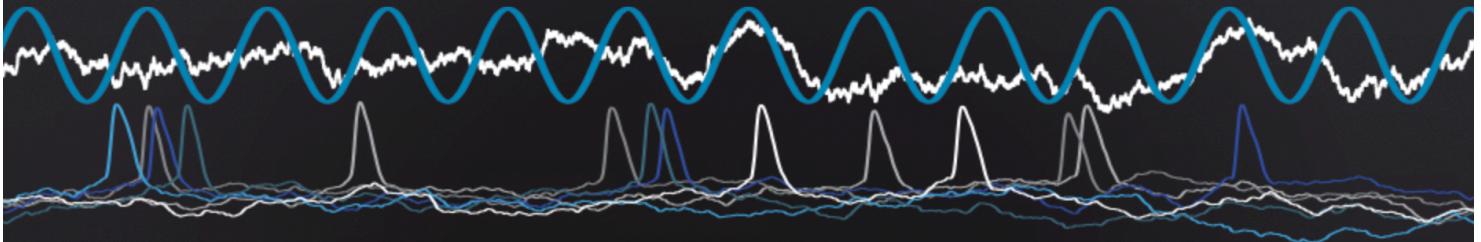
$$t > 100$$

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

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



ELECTROPHYSIOLOGICAL SIGNALS



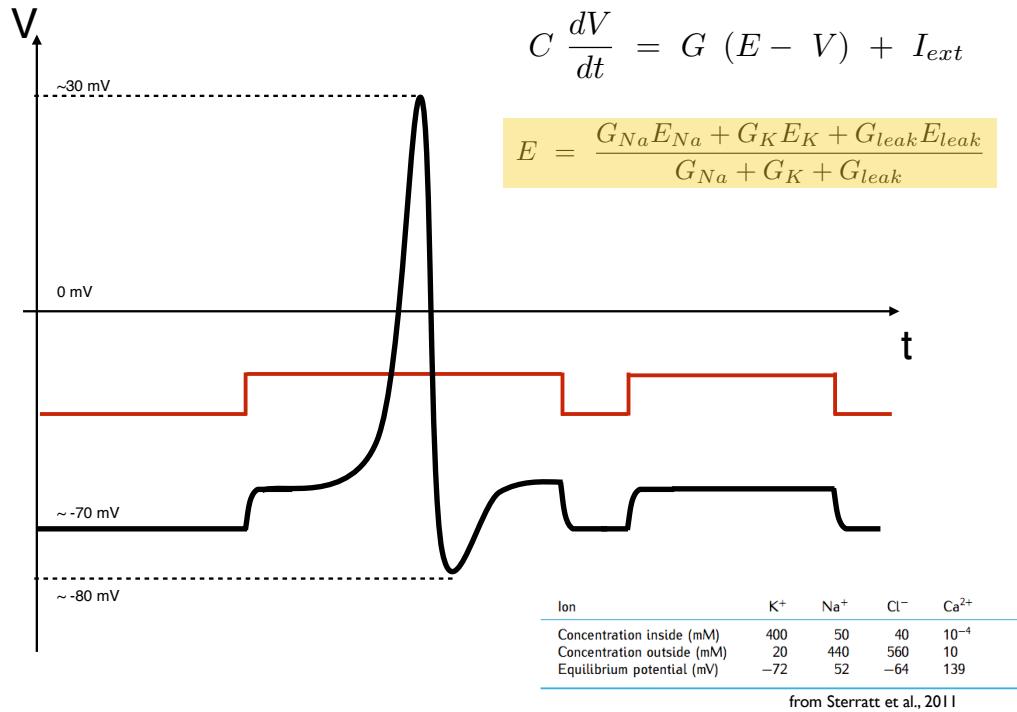
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Excitability

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(for statistical purposes only)

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

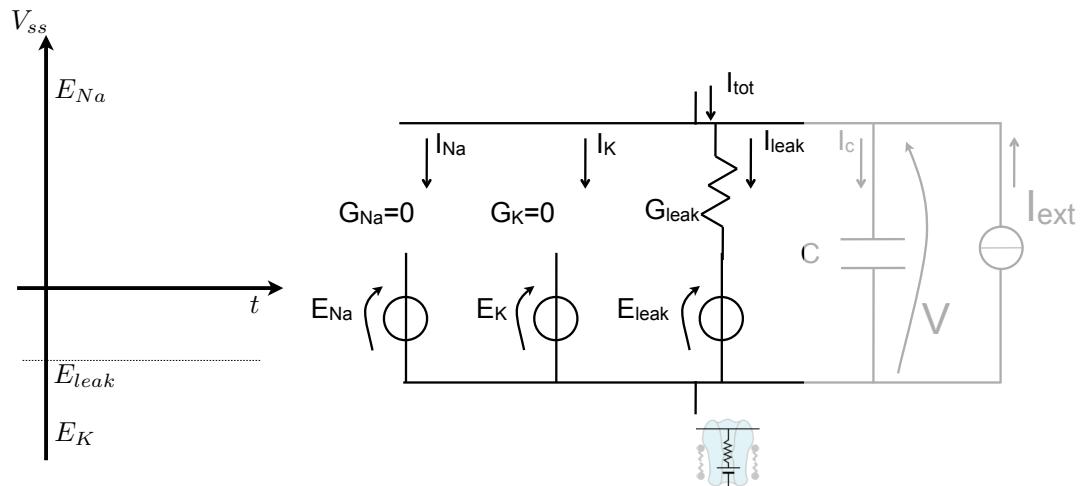
“Nobel prize” intuitions on the Action Potential (AP)



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

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

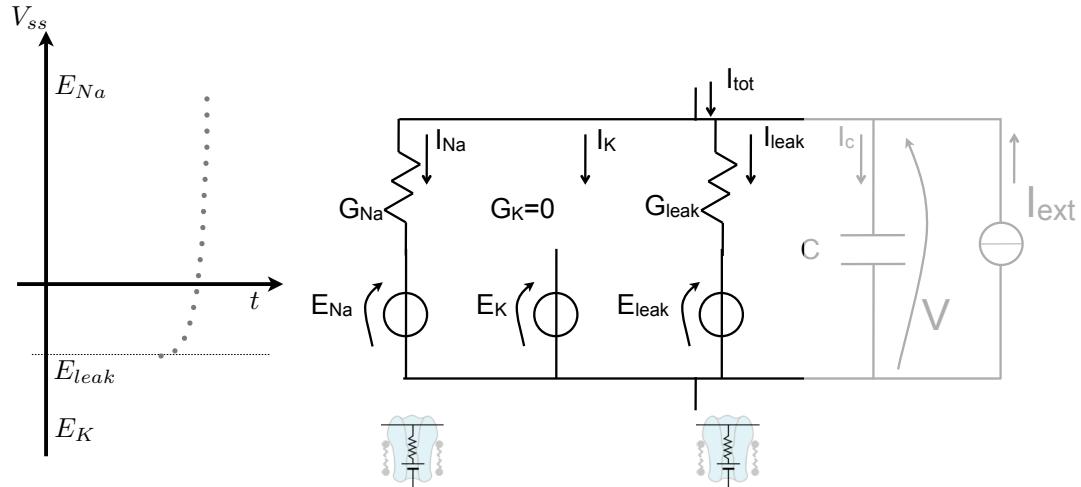
$$\lim_{t \rightarrow +\infty} V(t) = E + \frac{I_{ext}}{G} \quad E = \frac{G_{leak}E_{leak}}{G_{leak}}$$



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

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

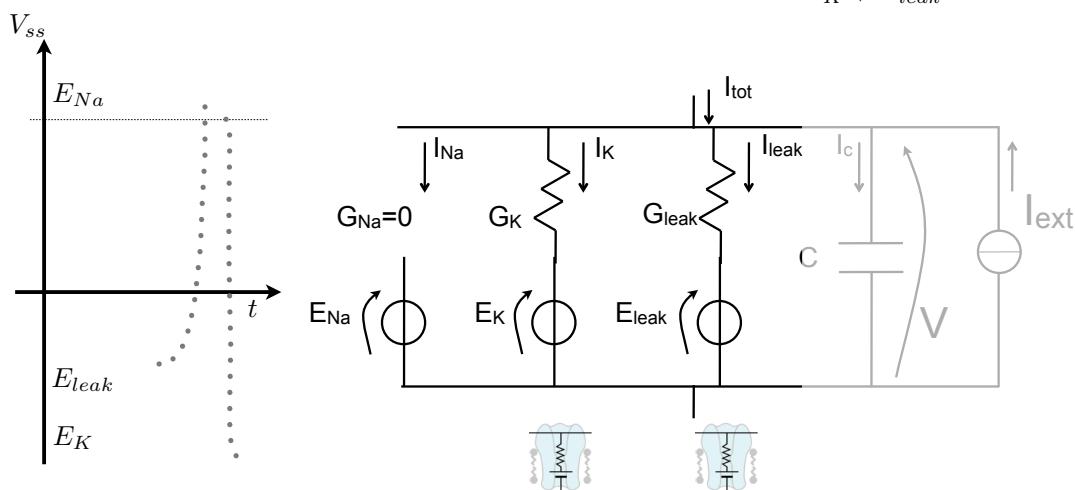
$$\lim_{t \rightarrow +\infty} V(t) = E + \frac{I_{ext}}{G} \quad E = \frac{G_{Na}E_{Na} + G_{leak}E_{leak}}{G_{Na} + G_{leak}}$$



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

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

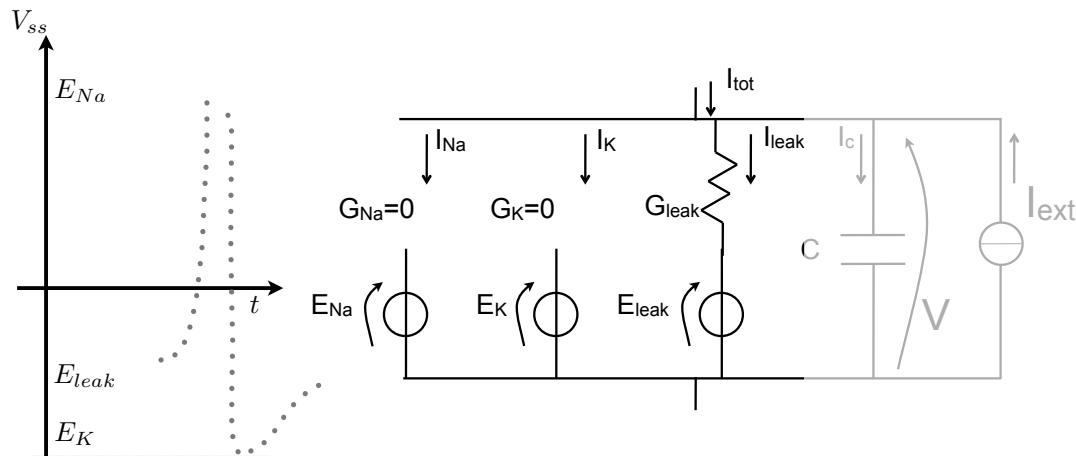
$$\lim_{t \rightarrow +\infty} V(t) = E + \frac{I_{ext}}{G} \quad E = \frac{G_K E_K + G_{leak} E_{leak}}{G_K + G_{leak}}$$



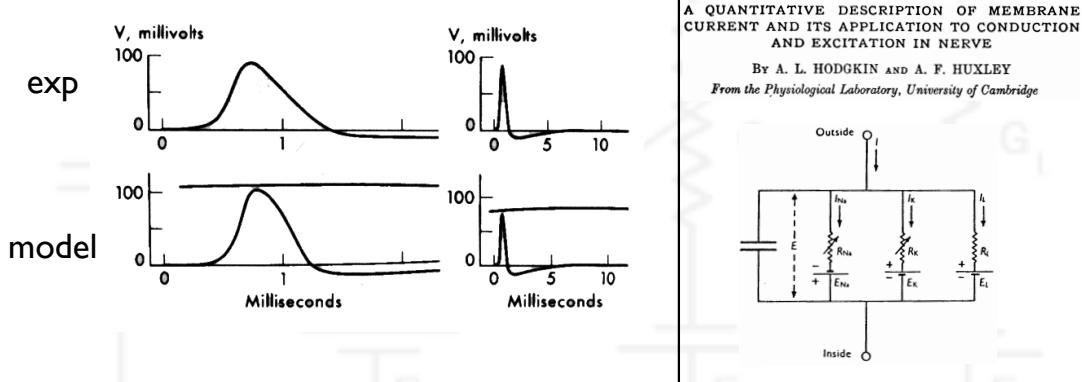
“Nobel prize”-like intuitions: predictions from a (steady-state) selective changes in membrane ionic permeabilities

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

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

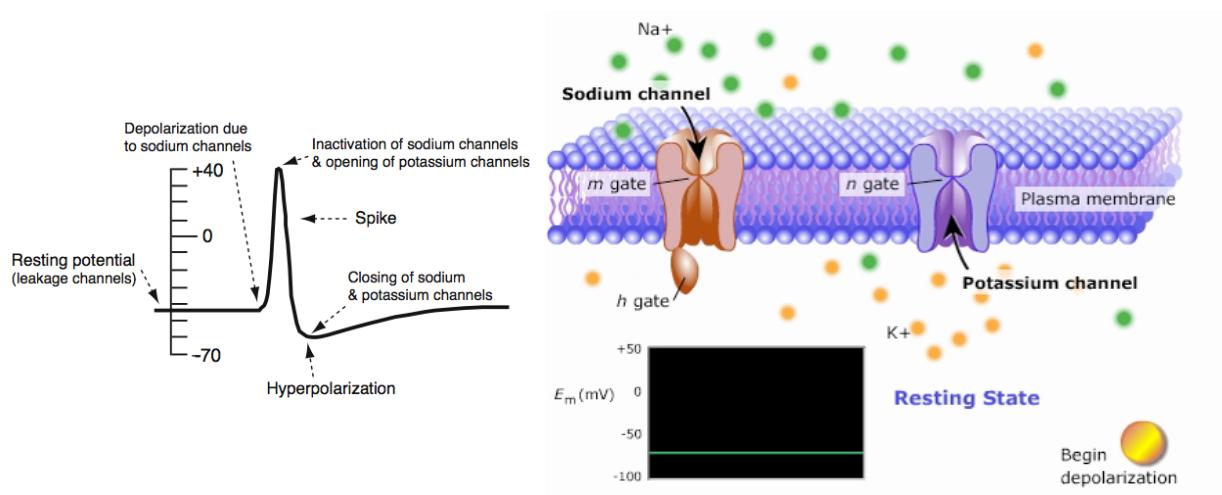


The Hodgkin-Huxley model of AP

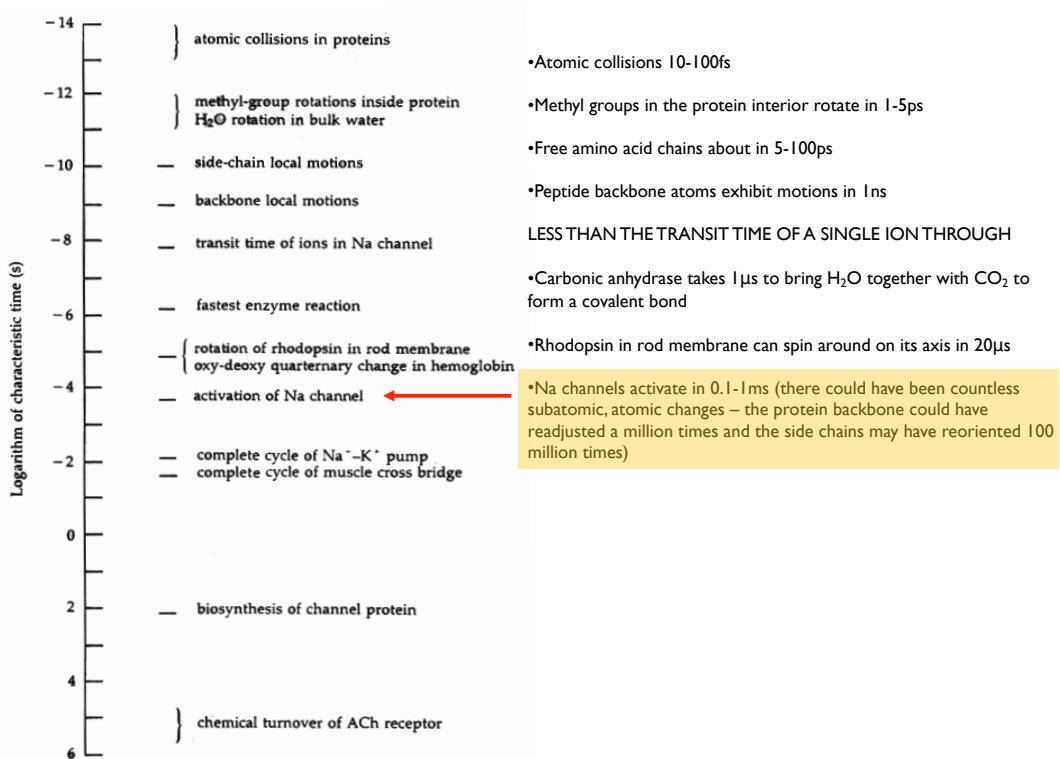


- Bernstein, 1902; Proposed an increase of membrane permeability to ions during excitation...
- Cole & Curtis, 1938; Recorded permeability changes...
- Hodgkin & Huxley, 1952; evidence for several ionic pathways each with its own kinetics...

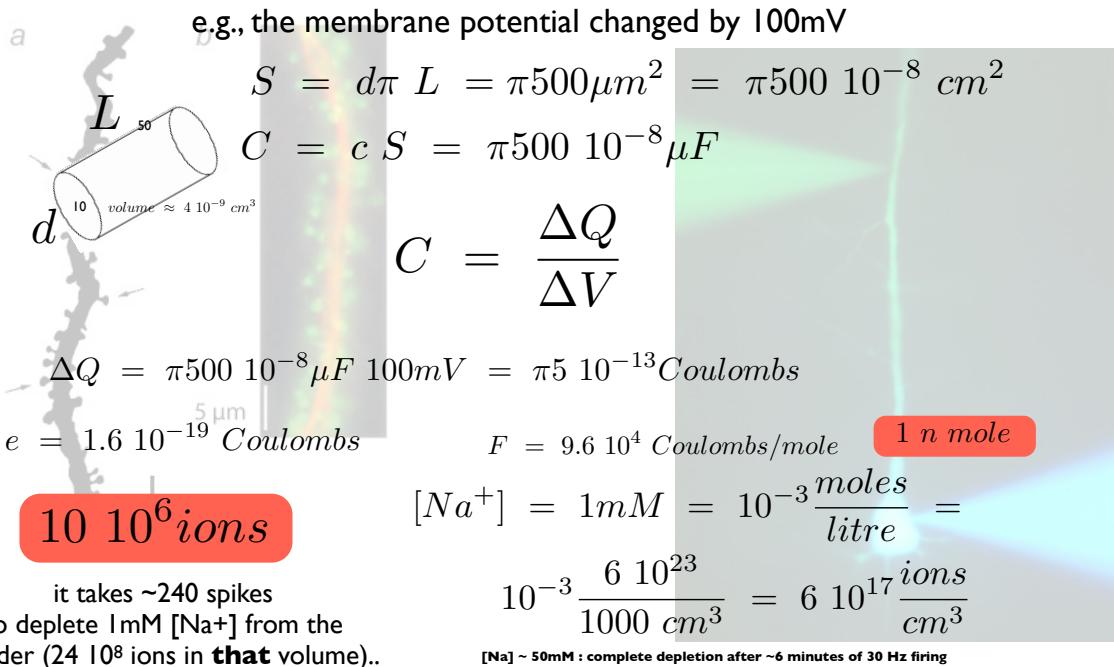
The AP generation: selective changes in ionic permeabilities



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



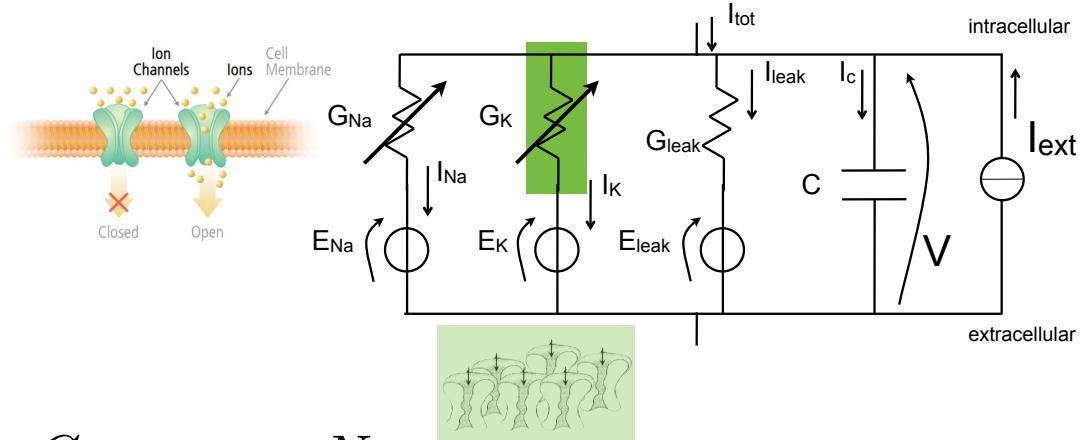
Exercise: how many ions exchanged during an AP? **negligible**



Digression on **(mesoscopic) (chemical) reactions**
(i.e., alias kinetic schemes): population descriptions!



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



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

$[n] = ??$
Fraction of channels in the 'open' state...;
or Density of channels in the 'open' state...;

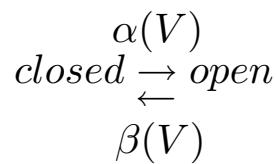


HH described (mesoscopic) membrane permeability by (phenomenological) kinetic schemes

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'.



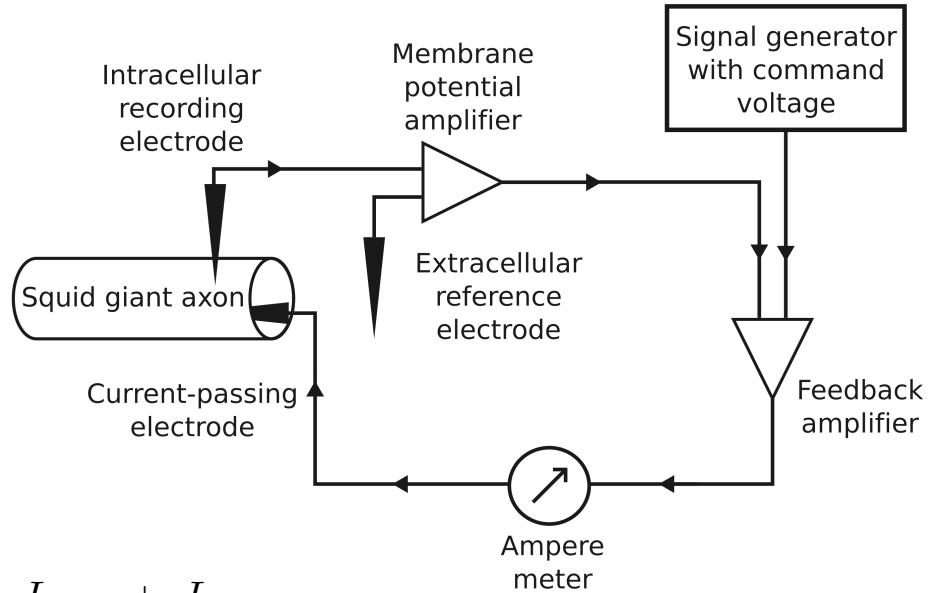
$\alpha(V)$ and $\beta(V)$ are voltage-dependent rate coefficients

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.



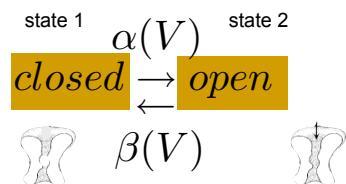
HH described (mesoscopic) membrane permeability
by (phenomenological) kinetic schemes



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



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



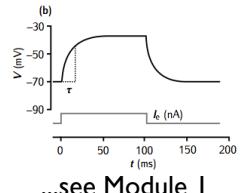
$$\frac{dn}{dt} = -\beta n + \alpha (1 - n)$$

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

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

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)

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

intuitive understanding: time-invariant input

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

...approximately...

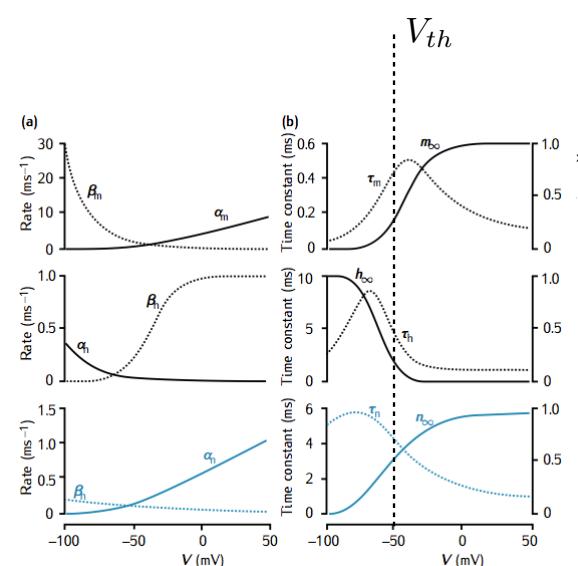
if x_∞ varies in time, x follows it,
unless it varies too quickly, then it lags behind...

The Hodgkin-Huxley model of AP generation

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

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

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



from Sterratt et al., 2011

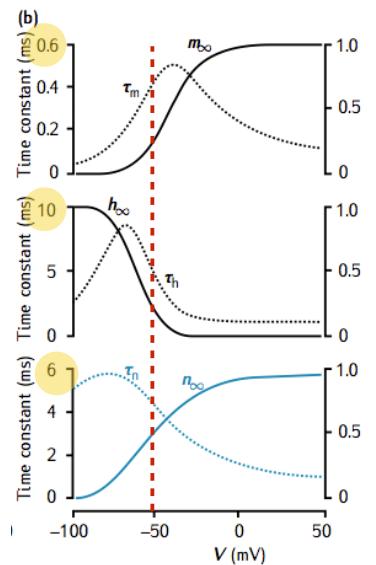




state 1 $\alpha(V)$ state 2
closed $\xrightarrow{\hspace{1cm}}$ **open**

$\beta(V)$

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



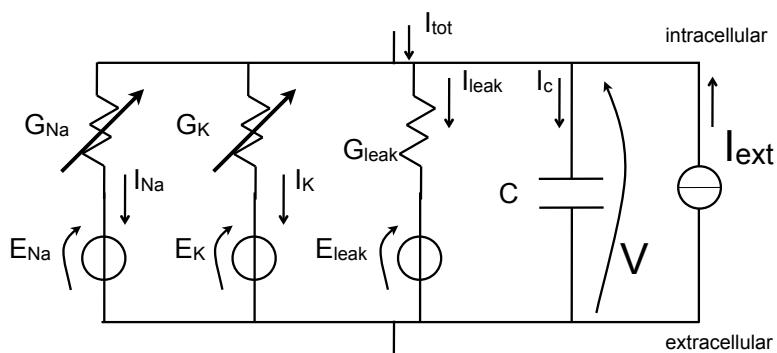
$$\tau_m(V) \frac{dm}{dt} = -m + m_\infty(V)$$

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

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

The generation of Action Potentials (Hodgkin & Huxley)

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



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

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

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



ATTENDANCE TRACKING - **code ???**

(for statistical purposes only)

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

The Hodgkin-Huxley model of AP generation

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

$$\tau_m(V) \frac{dm}{dt} = -m + m_\infty(V) \quad \tau_x = \frac{1}{\alpha_x(V) + \beta_x(V)}$$

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

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

Parameters

$$C = 1 \mu F/cm^2$$

$$\bar{g}_{Na} = 120 mS/cm^2$$

$$\bar{g}_K = 36 mS/cm^2$$

$$\bar{g}_{leak} = 0.3 mS/cm^2$$

$$E_{Na} = 50 mV$$

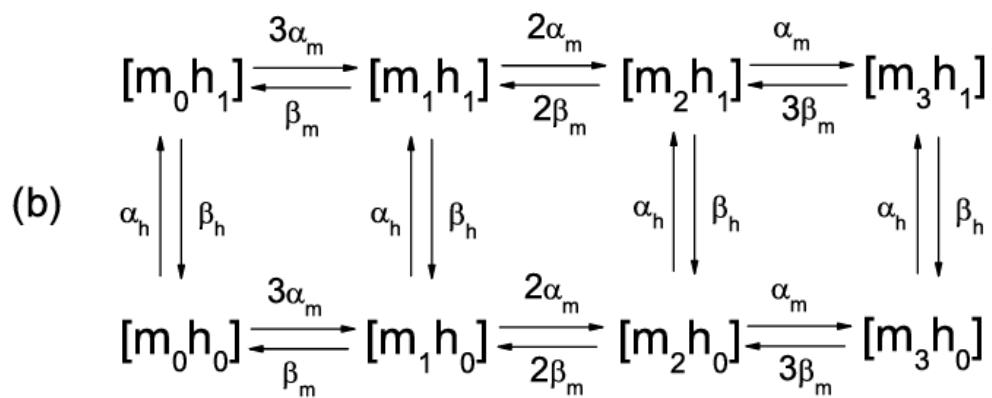
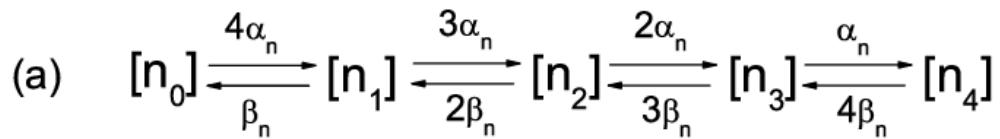
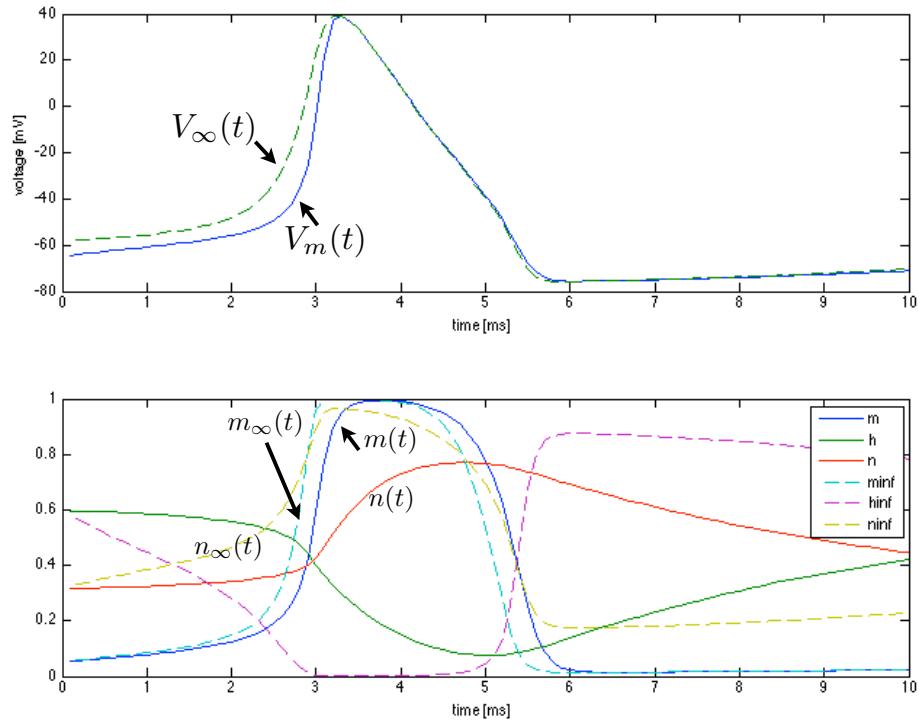
$$E_K = -77 mV$$

$$E_{leak} = -54.387 mV$$

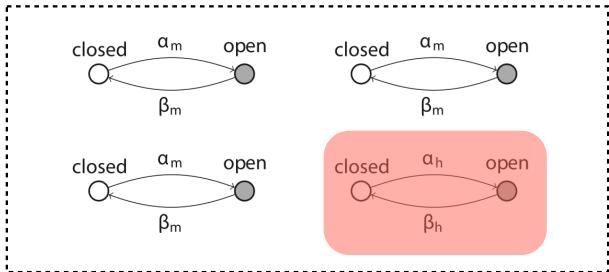
Functions of V:

$\beta_m = 4 e^{-(V+65)/18}$	$\beta_n = 0.125 e^{-(V+65)/80}$
$\alpha_m = 0.1 \frac{V+40}{1 - e^{-(V+40)/10}}$	$\alpha_n = 0.01 \frac{V+55}{1 - e^{-(V+55)/10}}$
<hr/>	
$\beta_h = \frac{1}{1 + e^{-(V+35)/10}}$	
$\alpha_h = 0.07 e^{-(V+65)/20}$	

The Hodgkin-Huxley model of AP generation



Reduction to independent “sub-units”

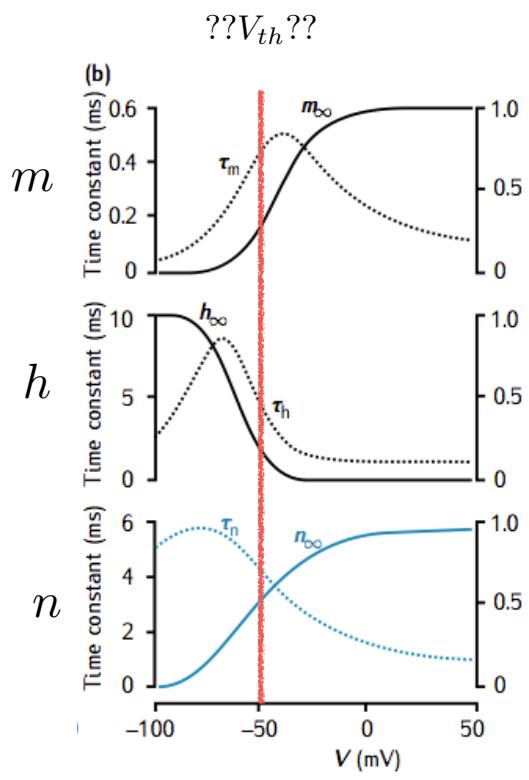


e.g. for Na^+ channels

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

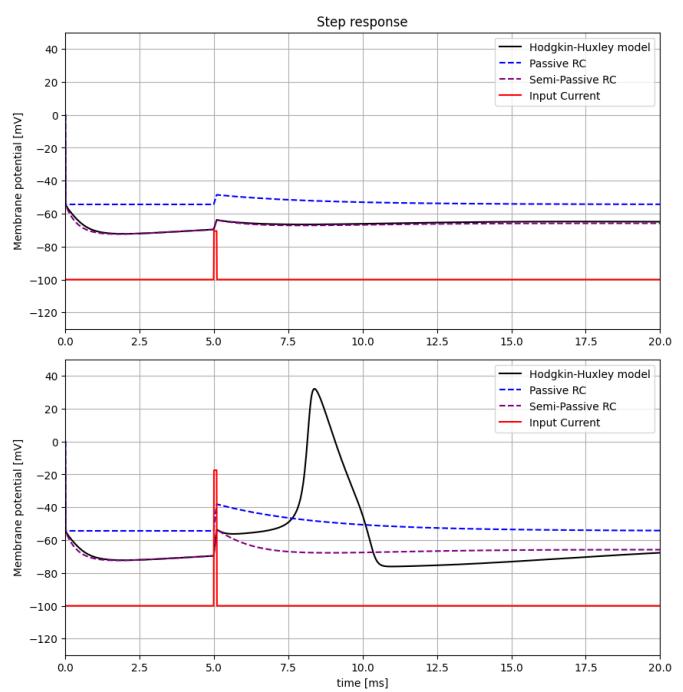
- Existence of a threshold?
- Temporal Integration
- AP generation and velocity of activation of individual gates
- “F-I curve” and its approximation as *first-passage time*
- Relative and Absolute refractoriness
- Alteration in extracellular potassium
- Simulating pharmacology

demo

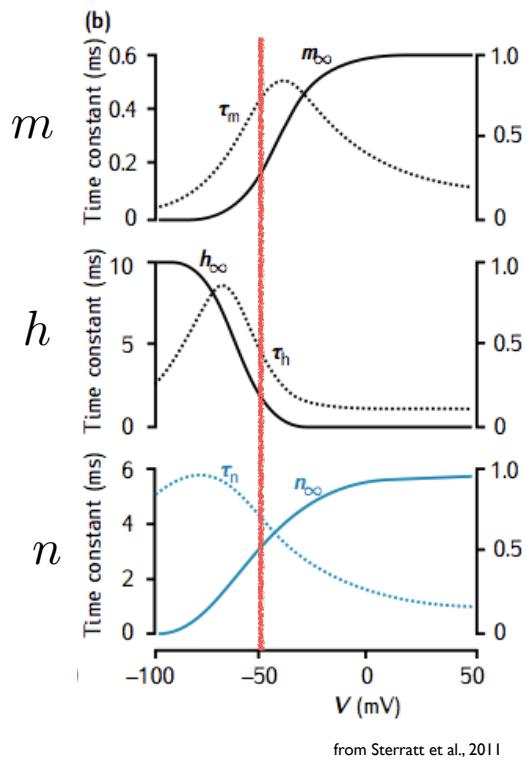


from Sterratt et al., 2011

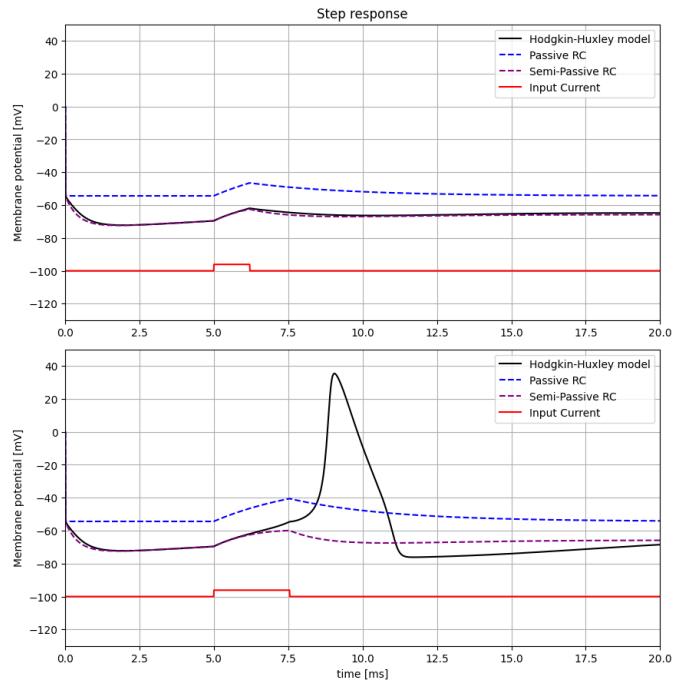
“All or none” phenomenon...



?? V_{th} ??

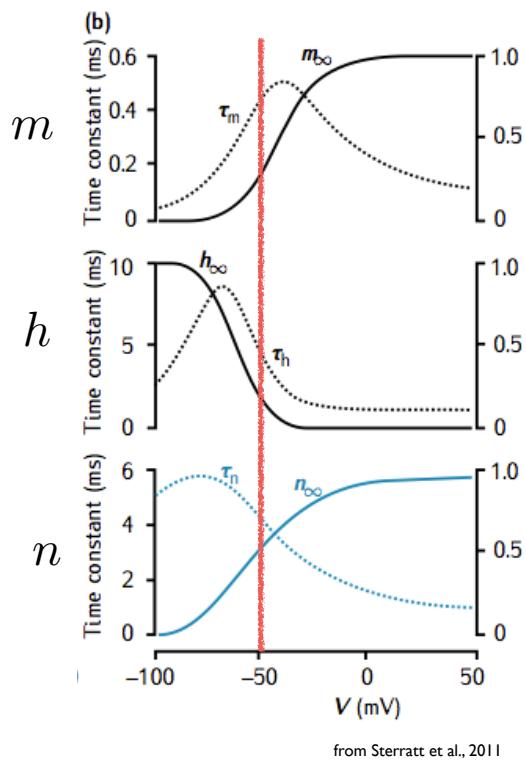


However... same amplitude, different duration

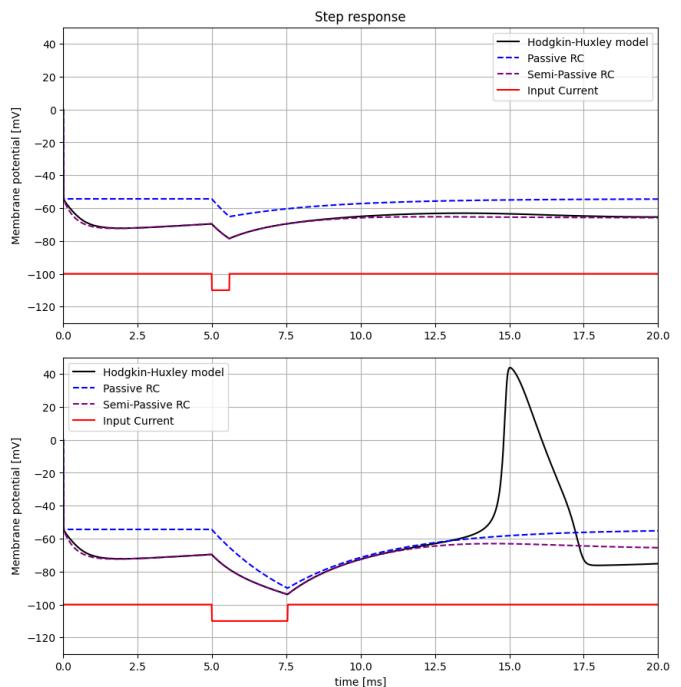


Search for rheobase and chronaxie (on Wikipedia)...

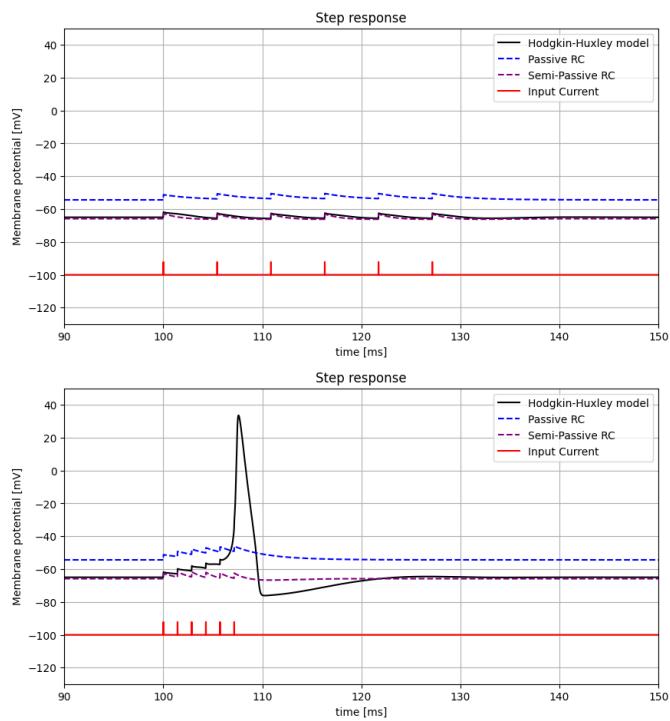
?? V_{th} ??



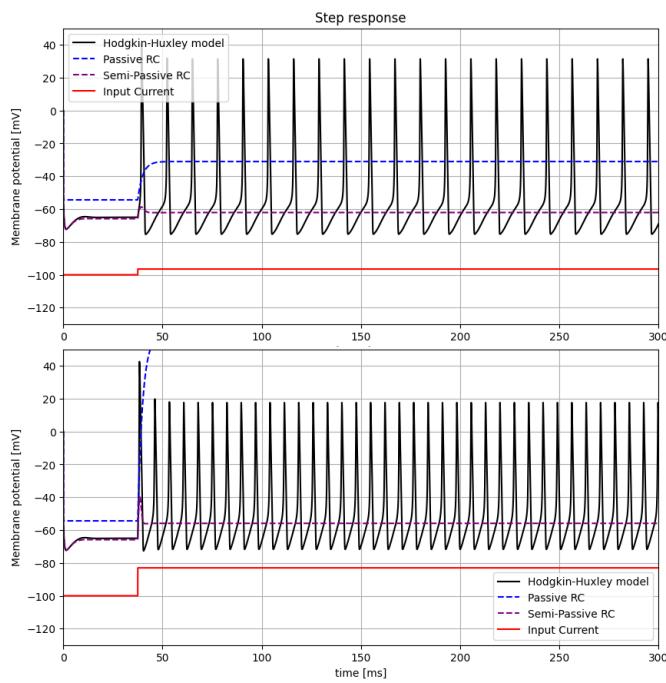
However... hyperpolarizing pulse...



...rebound firing...



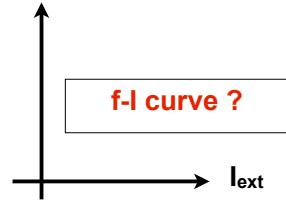
Increasing the amplitude of the injected (DC) current elicits sustained and regular oscillations with increasing frequency



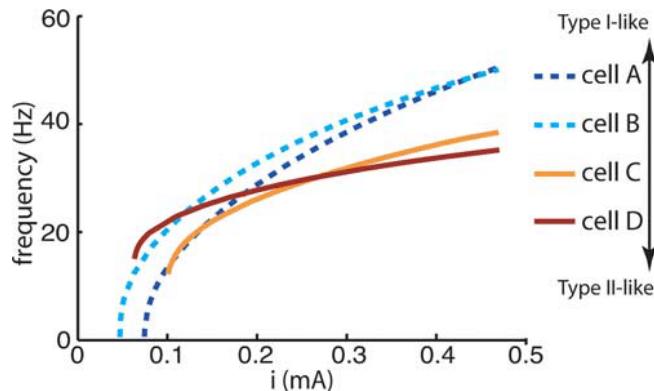
N_{AP} in T sec

T sec

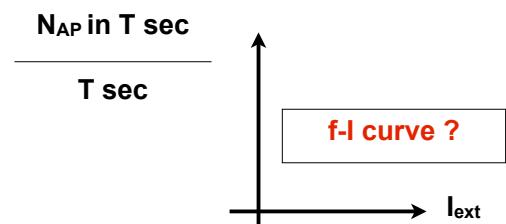
f-I curve ?



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

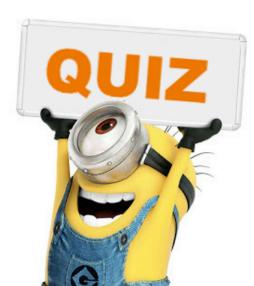


Bogaard *et al.* (2009). J. Neurosci. 29. 1677-87



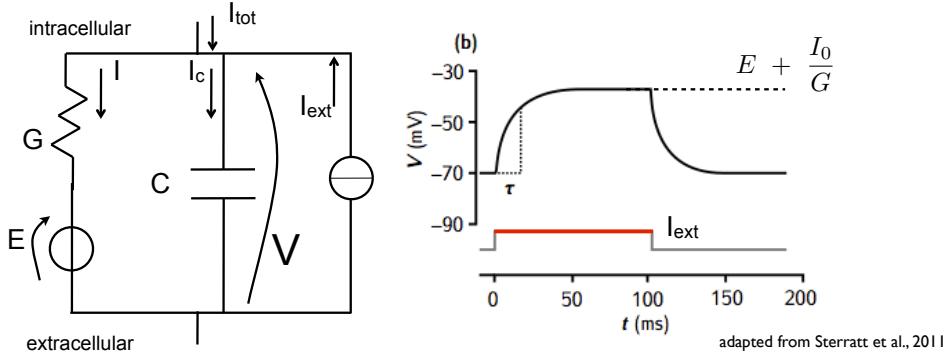
Intuition on “why F-I is increasing”

- “Frequency” => periodic/repeating regime
- “Frequency” and “Period” of a periodic regime?
- In a passive membrane (RC circuit) ?
- In an active membrane (e.g., HH) ?



Increasing the amplitude of the injected (DC) current elicits sustained and regular oscillations with increasing frequency
intuitive explanation

$$G = 1 / R$$



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

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

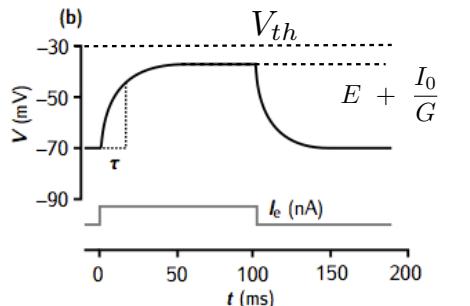
$$V(0) = E \quad V(t) = E + I_0/G \left(1 - e^{-G/C t} \right)$$

$$G = 1 / R$$

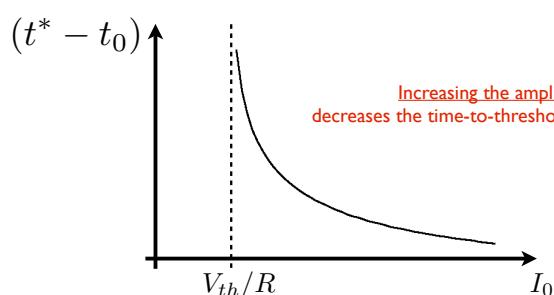
$$V(t) = E + I_0/G \left(1 - e^{-G/C t} \right)$$

$$V(t^*) = V_{th}$$

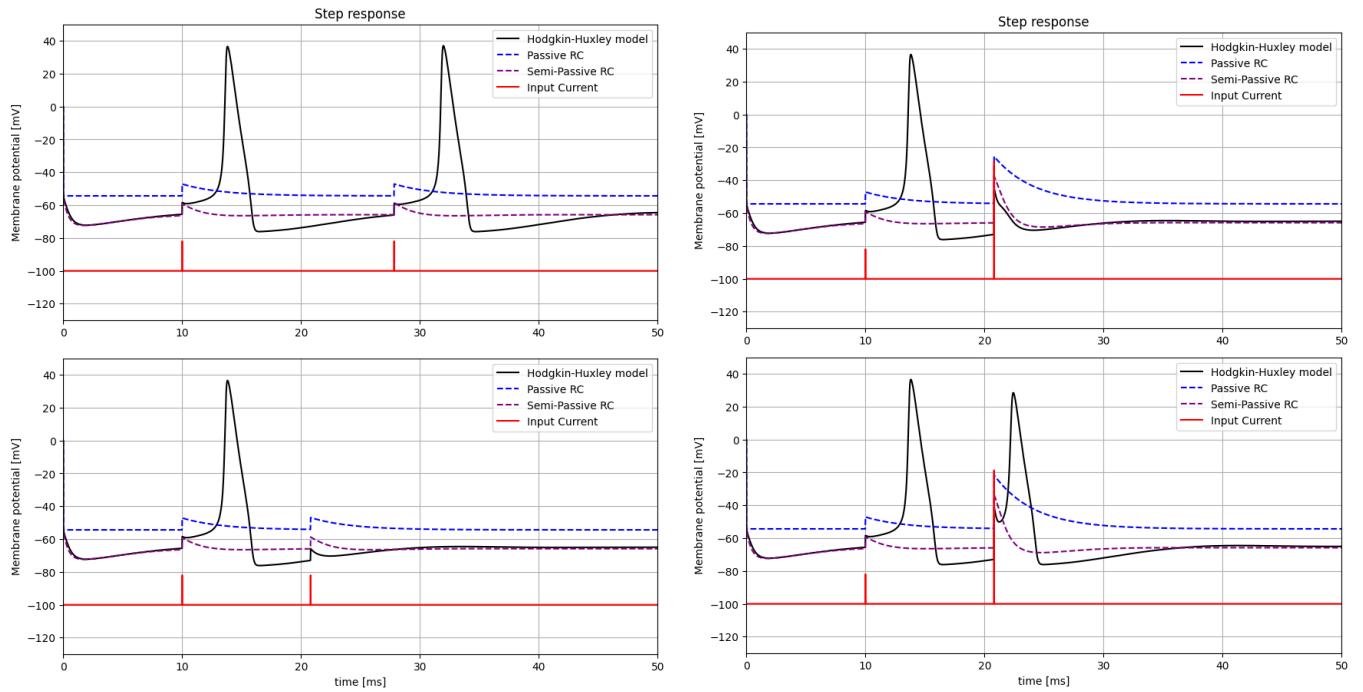
$$\frac{t^*}{R C} = \log \left(\frac{R I_0}{(E + R I_0) - V_{th}} \right)$$



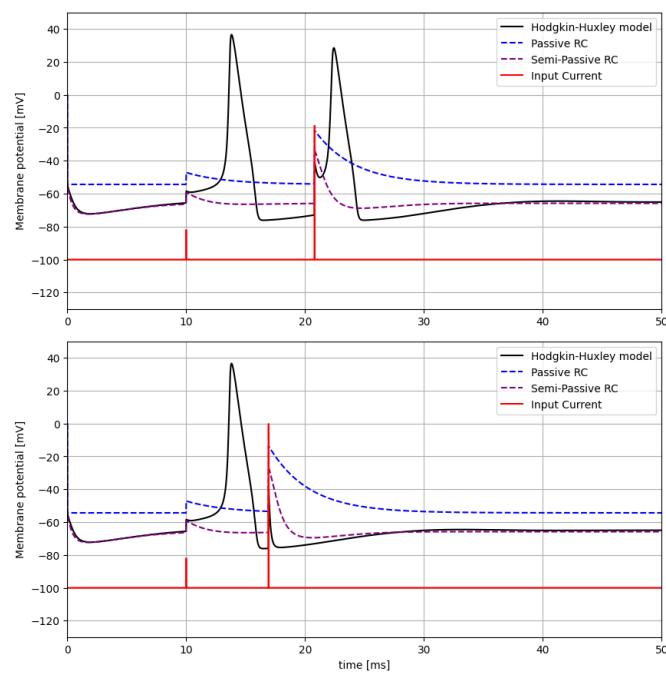
$$t^* = R C \log \left(\frac{R I_0}{(E + R I_0) - V_{th}} \right)$$



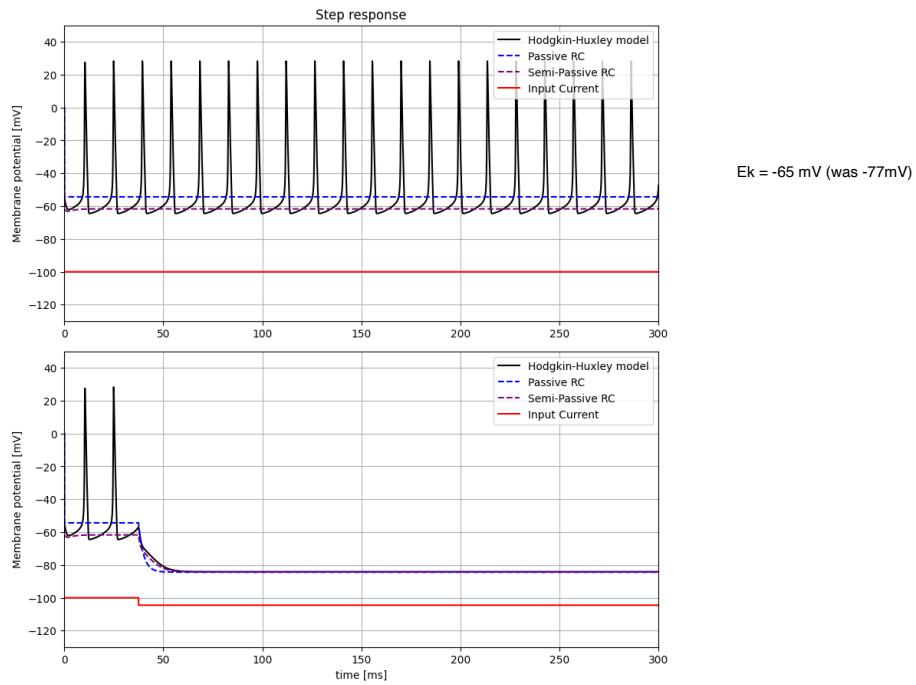
Absolute and relative refractory period: why?



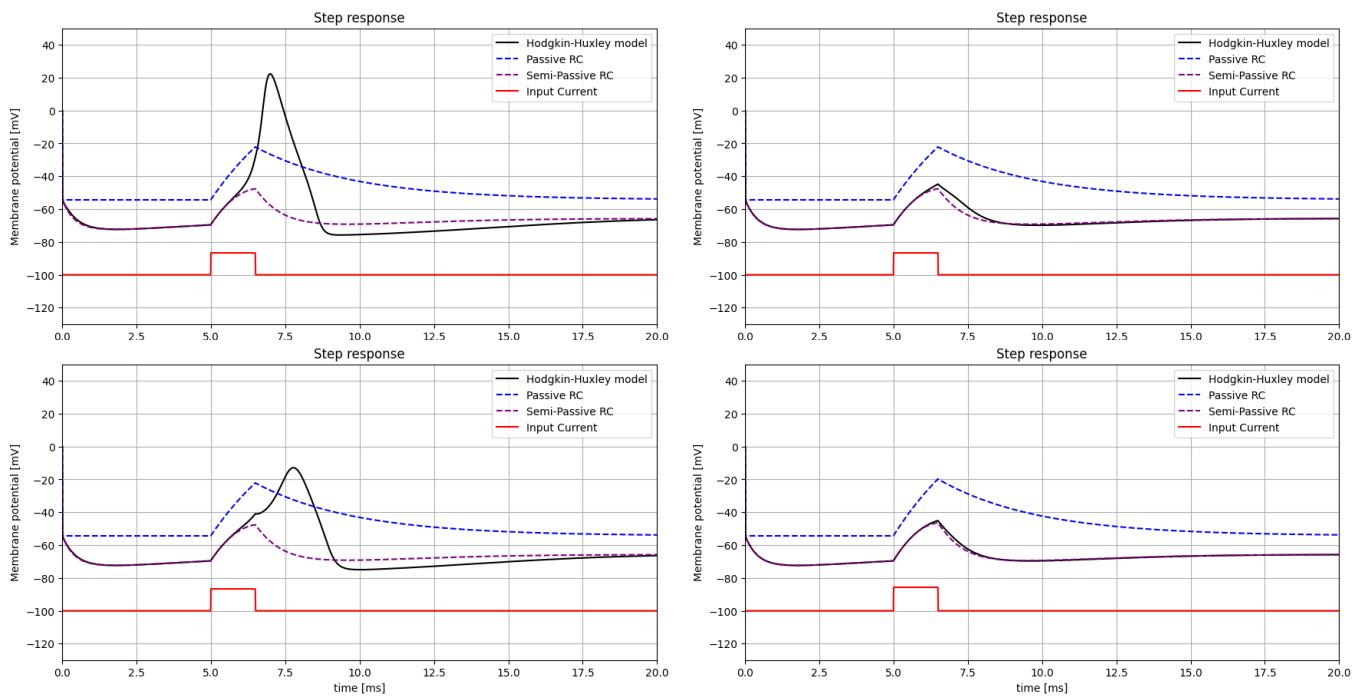
Absolute and relative refractory period: why?



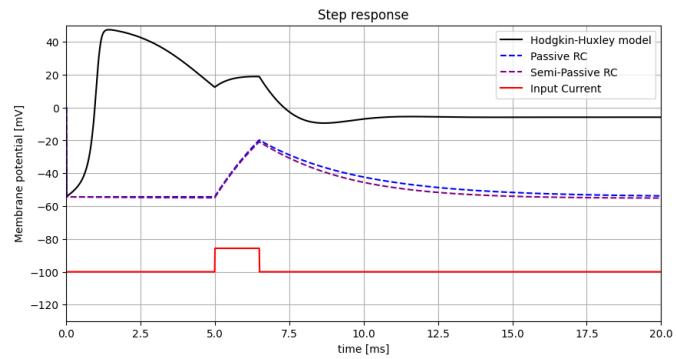
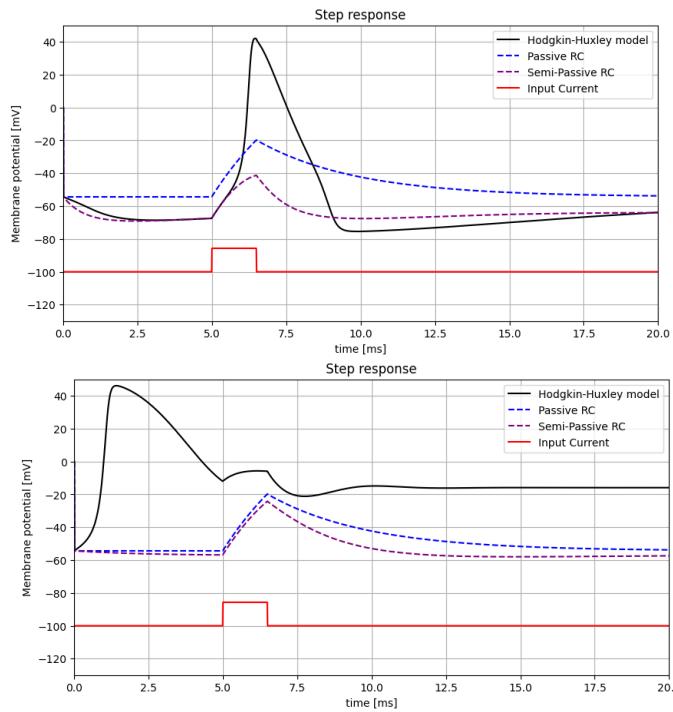
Increasing the extracellular concentration of K-ions: why?



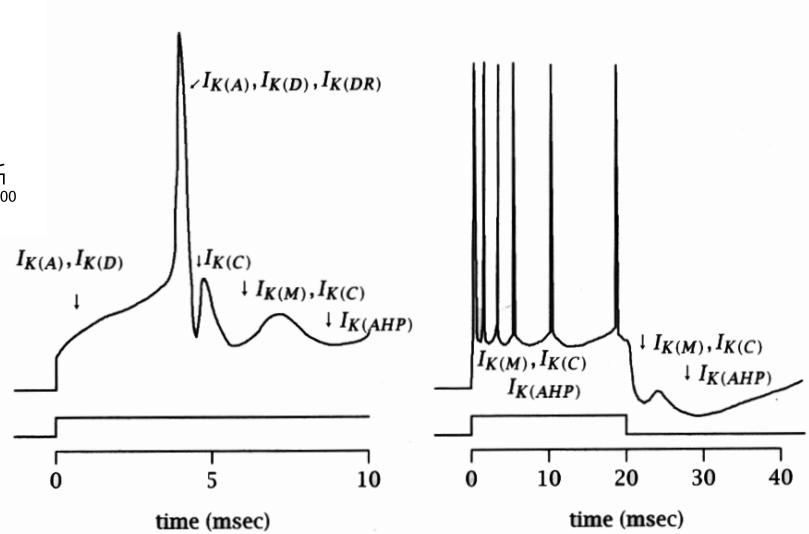
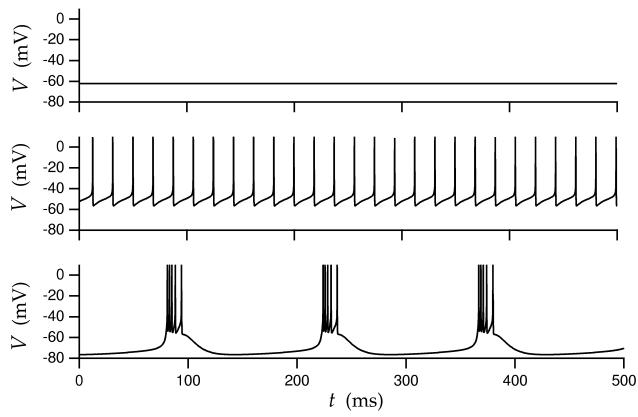
Simulating pharmacology and toxins: which one? why?

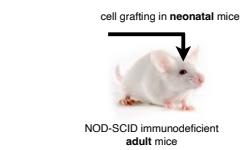


Simulating pharmacology and toxins: which? why?



The ‘zoo’ of ion channels....

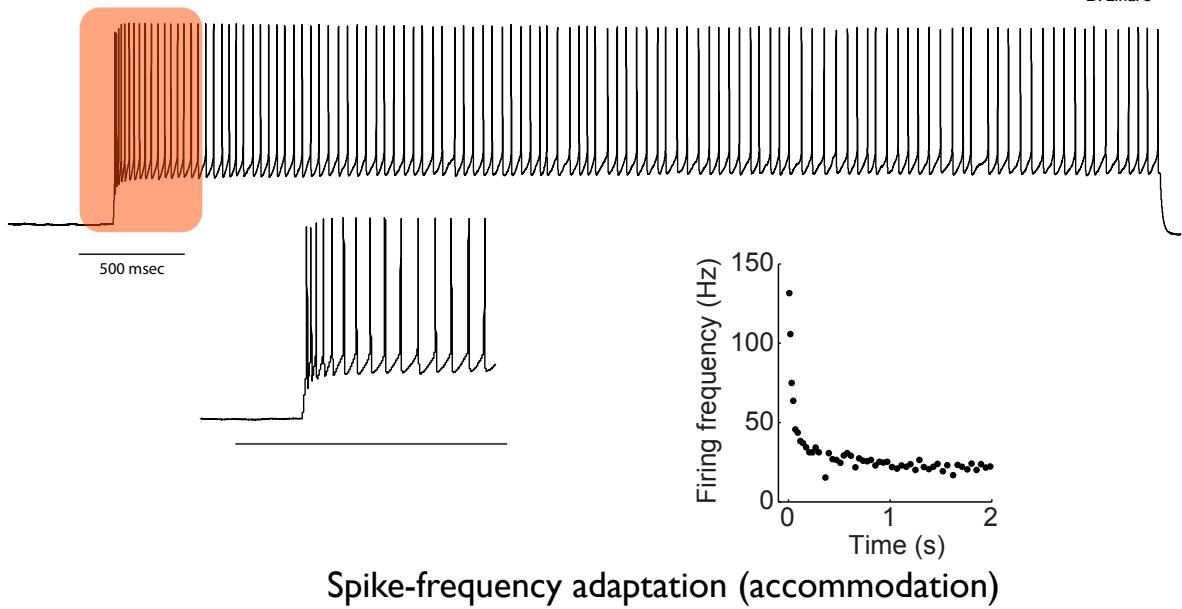




Additional Potassium-currents:
e.g., Ca- or Na-dependent K-currents



D. Linaro

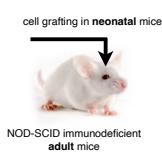


Spike-frequency adaptation (accommodation)

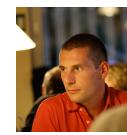
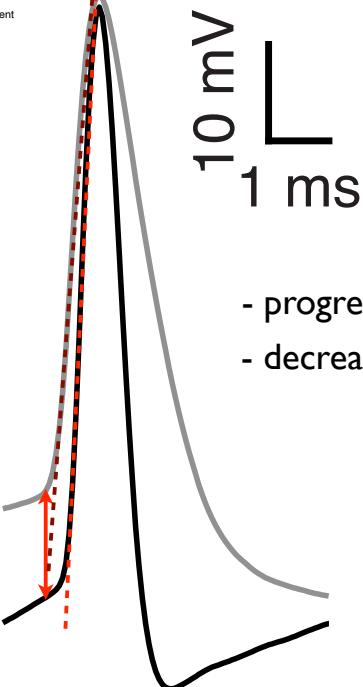
Spike-frequency adaptation

- What does act as “break” for excitability?
- Inter-spike-intervals decreasing over time? Why?





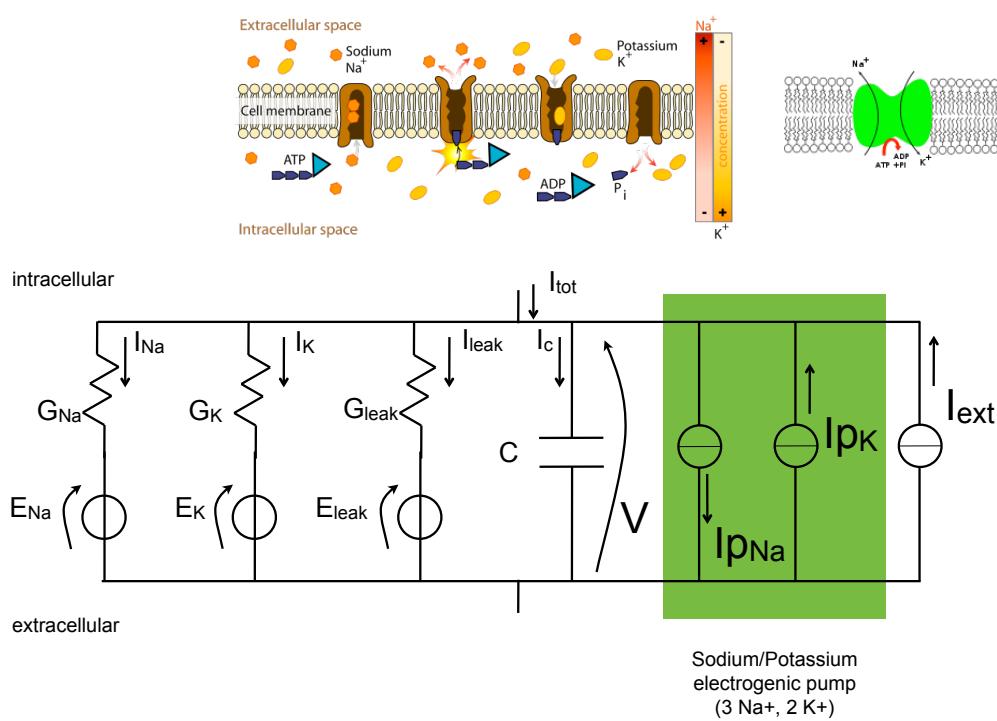
(Cumulative) sodium-channels inactivation



D. Linaro

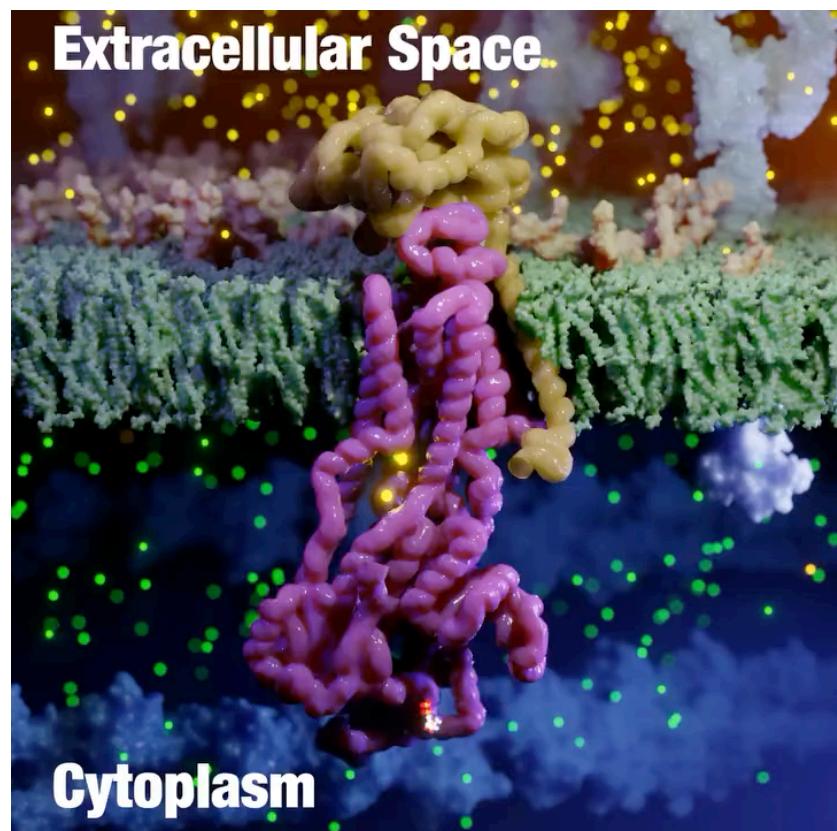
- progressive depolarisation: why?
- decrease in “slope” (or upstroke velocity) of APs: why?

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

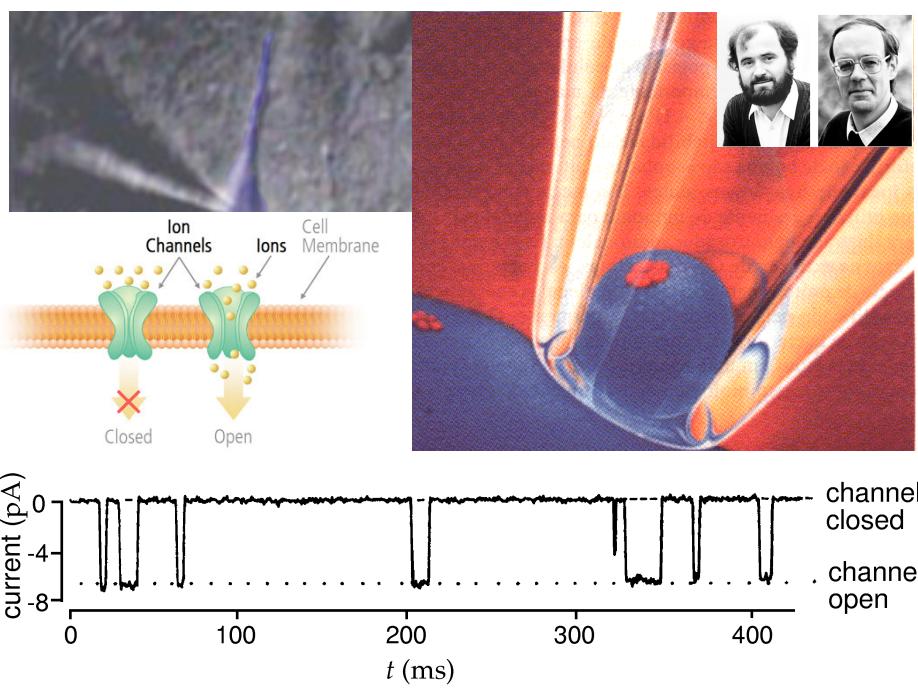




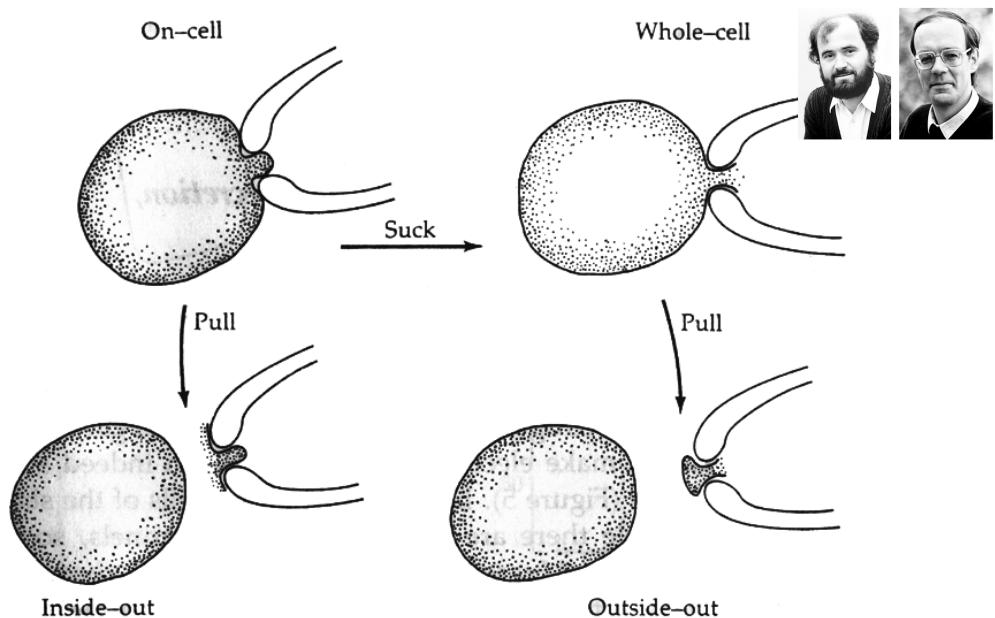
<https://www.ribosome.studio/>



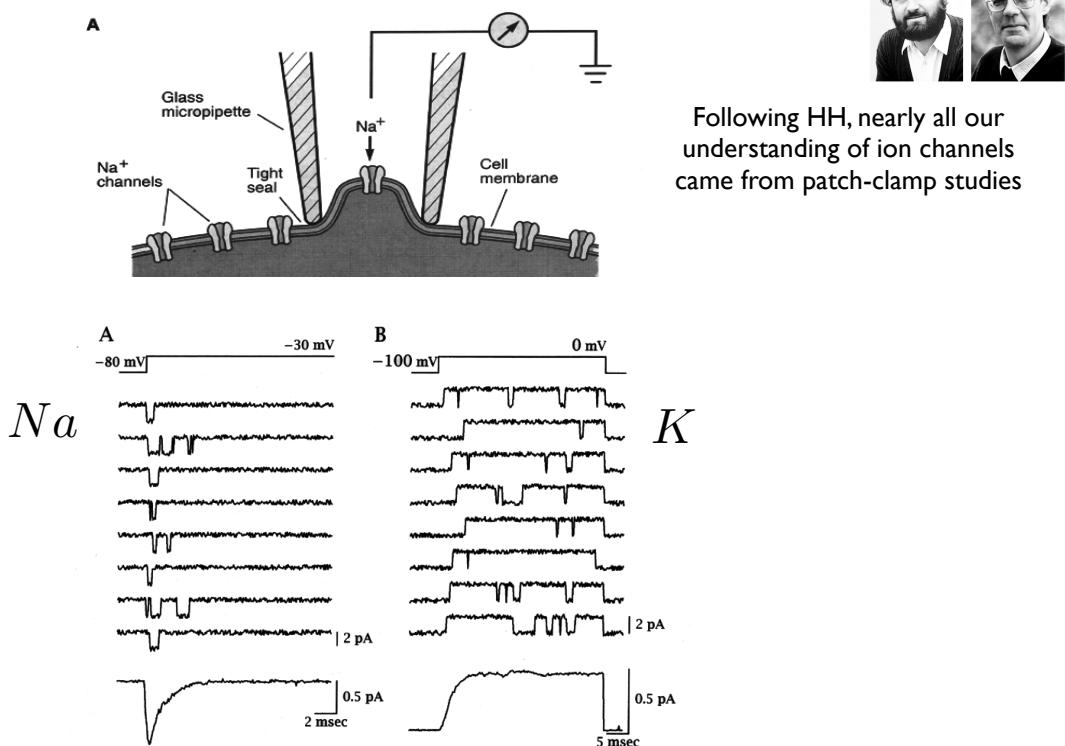
(Microscopically) membrane permeability: patch-clamp electrophysiology
discrete, **not** distributed property; stochastic, **not** deterministic phenomena



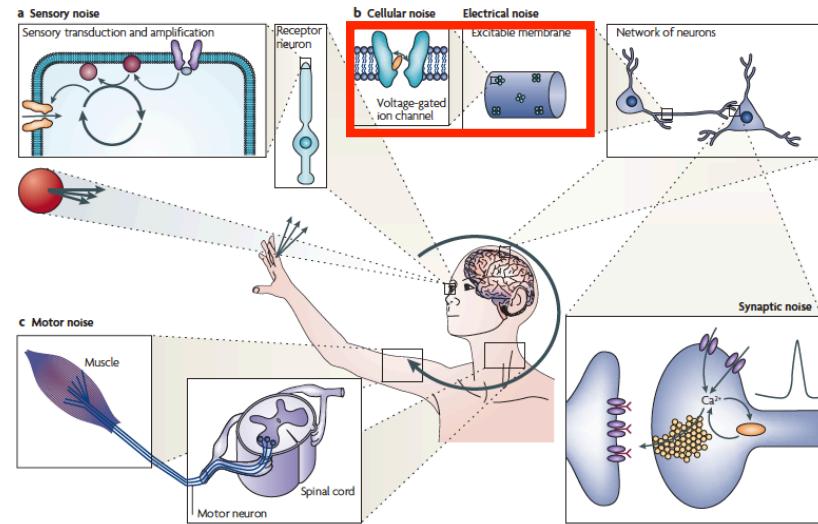
(Microscopically) membrane permeability: patch-clamp electrophysiology
 discrete, **not** distributed property; stochastic, **not** deterministic phenomena



Patch-Clamp Reveals Single Ion Channels

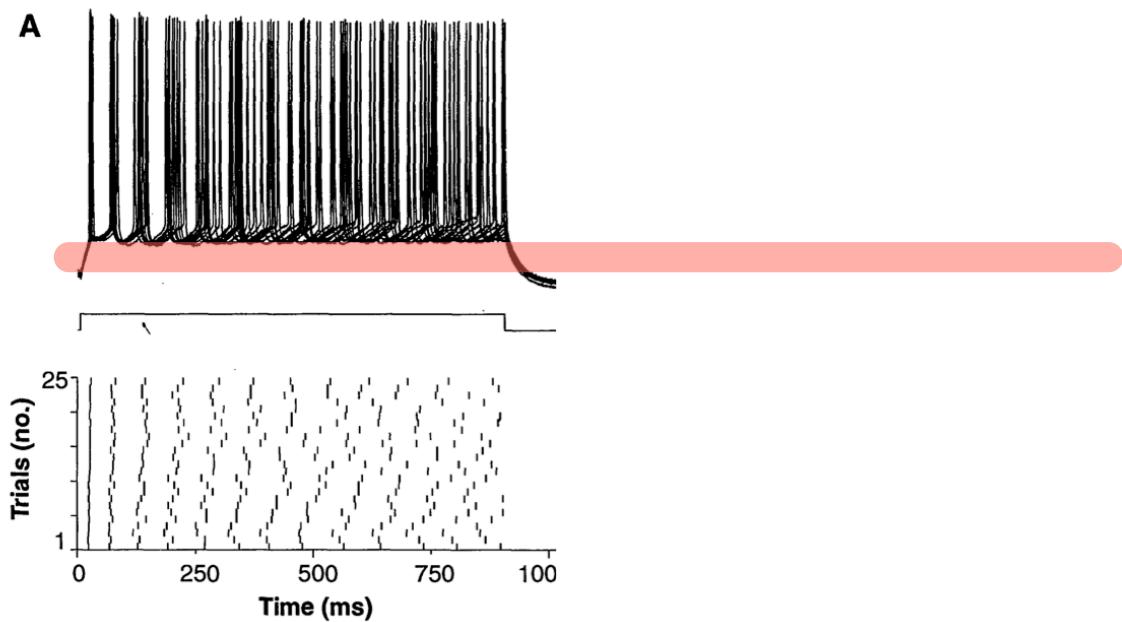


Impact of “Noise” in cellular and network-level electrophysiology



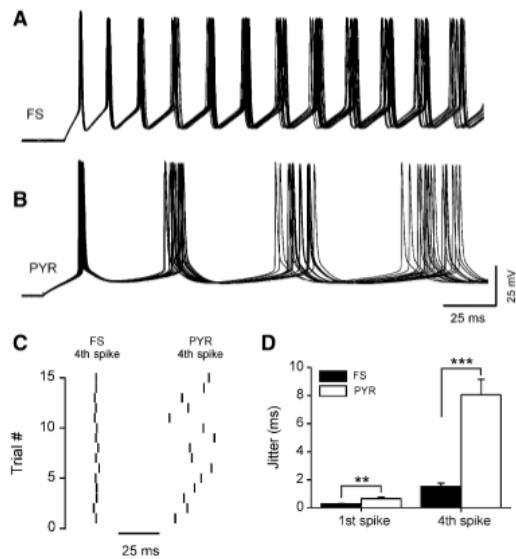
adapted from Faisal et al., 2008

Intrinsic noise sources affect spike-timing precision in (pyramidal) cortical neurons: how?



Mainen & Sejnowski, 1995

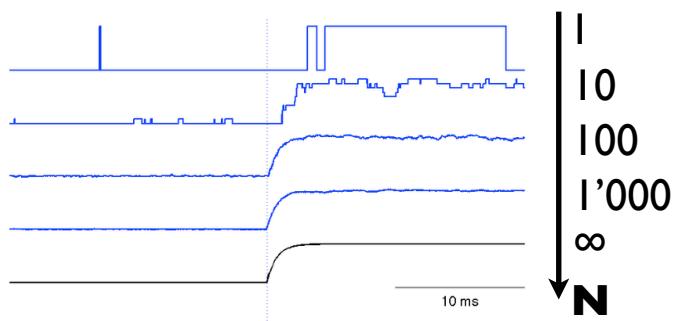
Fast-spiking (FS) interneurons are more precise than pyramidal neurons: why?



Bacci & Huguenard, 2006

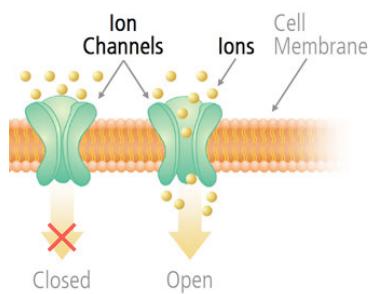
Single ion-channels undergo stochastic transitions among conformational states

Channel flickering is a noise source

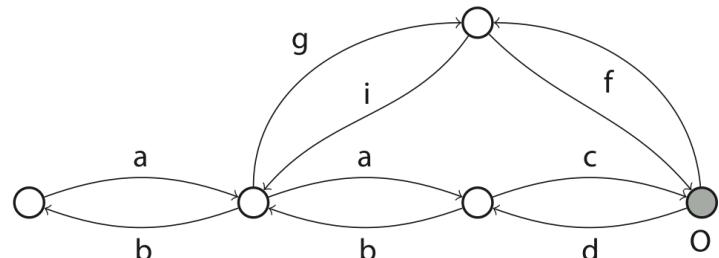


- **Markovian formulation** (i.e. microscopic, exact)
- **Langevin formulation** (i.e. effective, approximate)

Markovian formulation

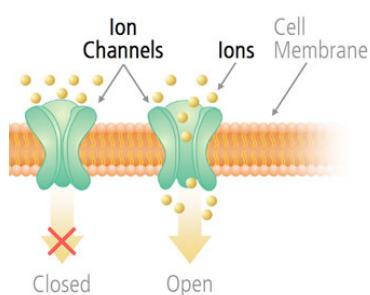


$$s_i = \begin{cases} 1, & p_o \\ 0, & 1-p_o \end{cases}$$



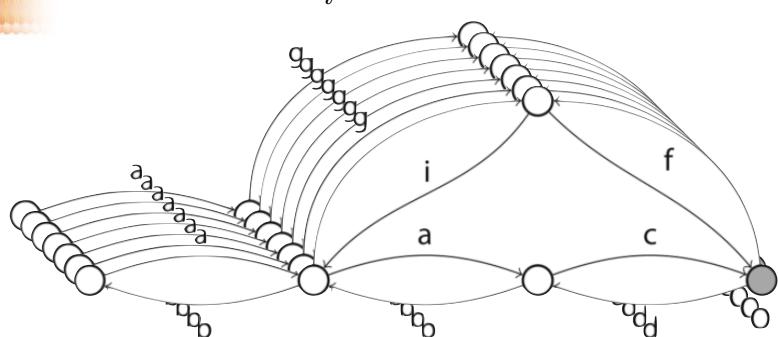
adapted from Vandenberg & Bezanilla, 1991

Markovian formulation



$$I = \bar{g} n(t) (V - E)$$

$$n(t) = \frac{1}{N} \sum_i s_i \quad s_i = \begin{cases} 1, & p_o \\ 0, & 1-p_o \end{cases}$$



adapted from Vandenberg & Bezanilla, 1991

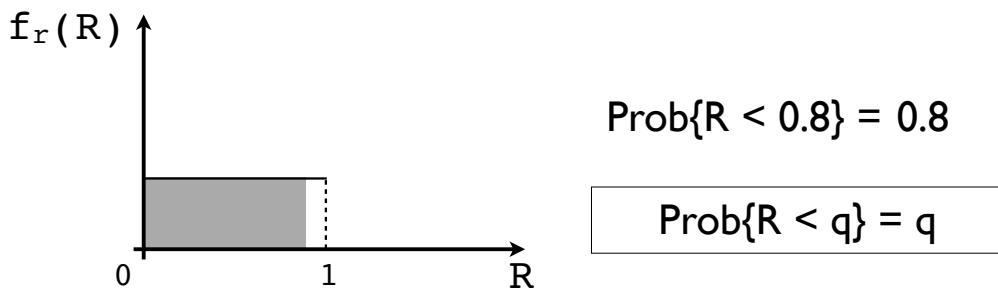
How do I “generate” a random event???

(a *random* transition)

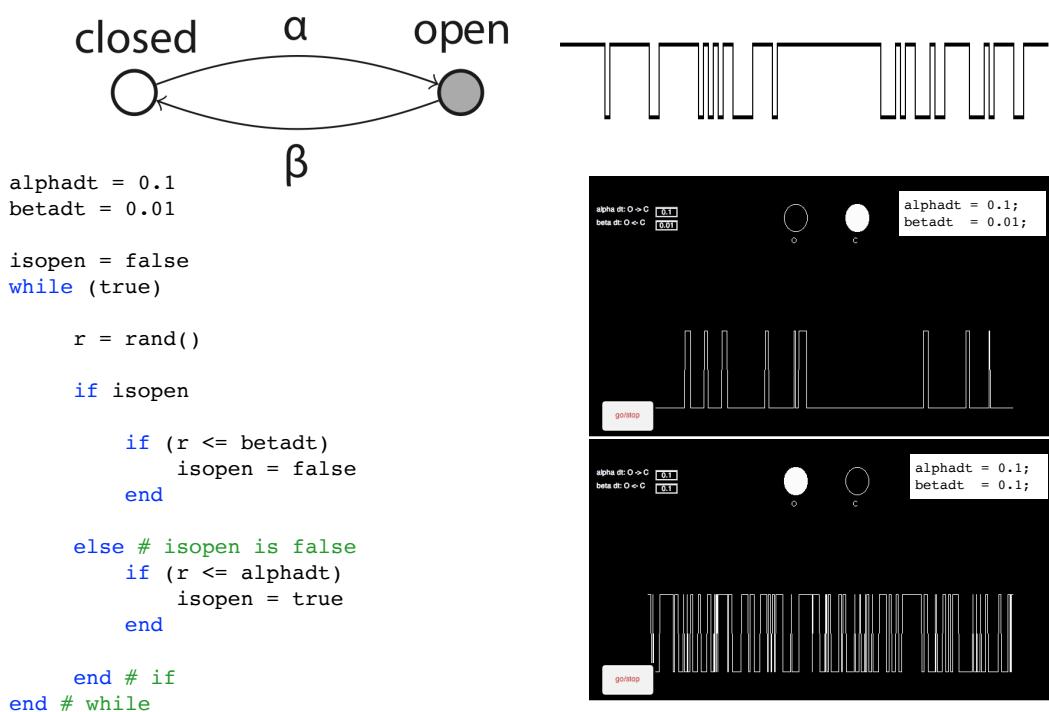
$$Pr\{A \rightarrow B \text{ in } (t ; t + \Delta t] / \text{state } A \text{ at } t\} = k_1 \Delta t + O(\Delta t)$$

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

Let “r” be a pseudo-random number, uniform in [0 ; 1]
 $r = \text{rand}()$



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



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



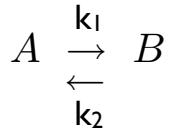
$$P(A, t) = Pr\{in state A at time t\}$$

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

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

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

Probability theory: conditional probabilities definition



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

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

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

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

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

$$\begin{aligned} x &= 1, \quad \text{if state is } A & P(A, t) \\ x &= 0, \quad \text{if state is } B \end{aligned}$$

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

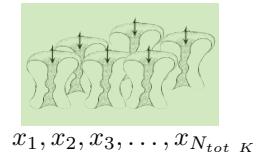
$$\frac{d\bar{x}}{dt} = -(k_1 + k_2) \bar{x} + k_2 \quad \text{Ensemble-average = det. description}$$

$$\begin{aligned} Var\{x(t)\} &= E\{(x(t) - \bar{x}(t))^2\} = E\{(x(t)^2\} - \bar{x}(t)^2 = \\ &= \end{aligned}$$

$$Var\{x(t)\} = P(A, t) (1 - P(A, t)) \quad \text{Fluctuations, flickering, not captured by the det. description}$$

$$\begin{aligned} G_K &= \gamma_K N_{open \ K} \\ &= N_{tot \ K} \gamma_K \frac{N_{open \ K}}{N_{tot \ K}} \end{aligned}$$

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



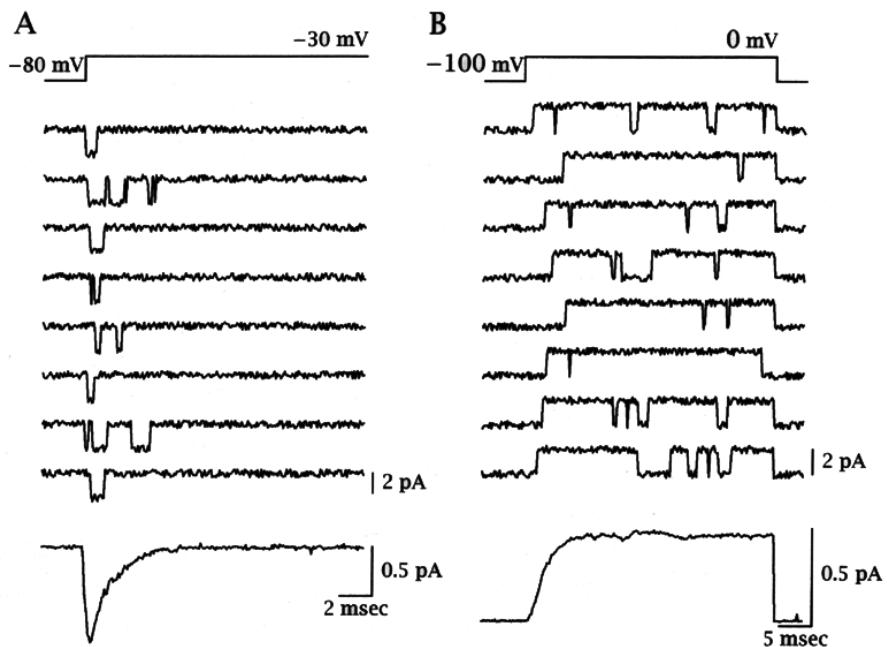
$x_1, x_2, x_3, \dots, x_{N_{tot \ K}}$

$$n = \left(\sum_{i=1}^{N_{tot \ K}} x_i \right) / N_{tot \ K} \quad \text{I describe } x_i \text{ as a random variable!}$$

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

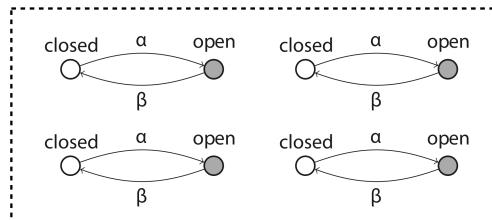
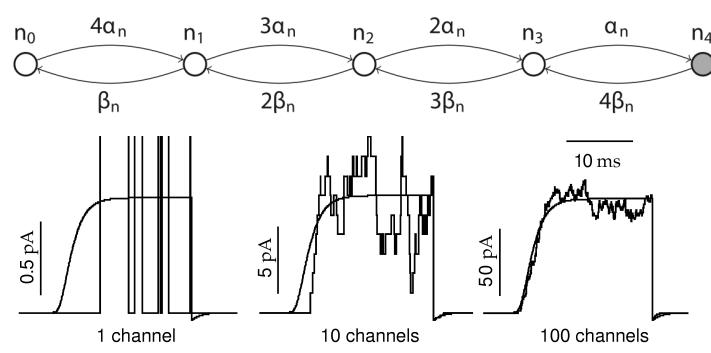
Large number theorem says that “for very large $N_{tot \ K}$, the chances that n takes actual values close to its expected value $E\{n\}$, are very high.
(Kolmogorov’s inequality)

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

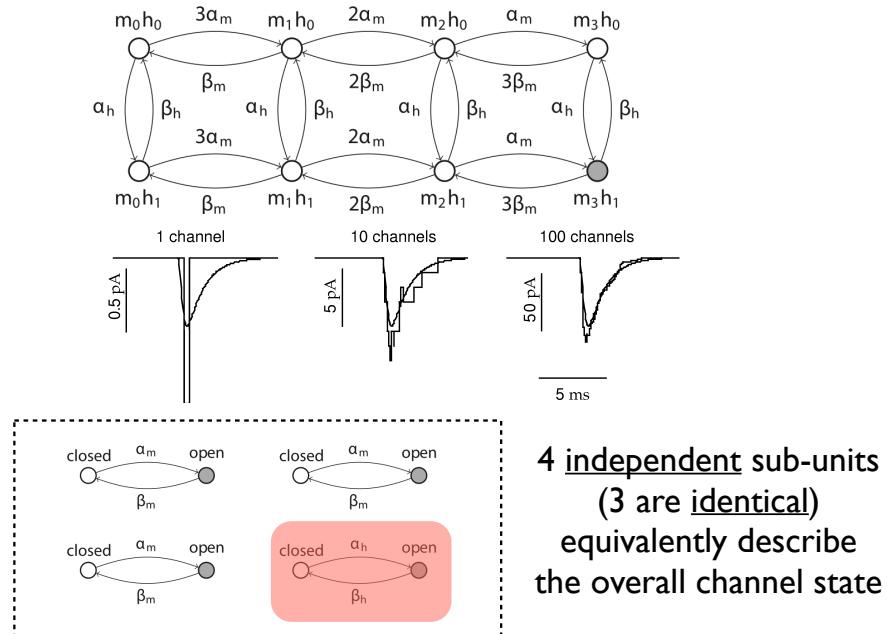
e.g. K^+ , delayed-rectifier channel



4 identical and independent 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 independent sub-units
(3 are identical)
equivalently describe
the overall channel state

Langevin-like formulation

where and how does one “plug” an effective channel-noise term, into the usual (deterministic) conductance-based equations ??!

- I) gaussian current noise (simplest; heuristic; combined effect)
no method available to design the noise intensity, or its dep. on V

$$C \frac{dV}{dt} + \sum_k I_k + I_L + \xi_V(t) = I_{ext}$$

Rowat, 2007

Gerstein & Mandelbrot, 1964; Tuckwell, 1988; Brunel and collaborators

- 2) gaussian subunit-noise (subunits-limited; heuristic; system-size expansion; may not reduce to deterministic case; gaussianity!)

$$\frac{dx}{dt} = \frac{x_\infty - x}{\tau_x} + \xi_x(t)$$

Goldwyn & Shea-Brown, 2010, 2011

Fox *et al.*, *Phys. Rev. E* (1994) and Fox, *Biophys J.* (1997)... and >60 papers

Langevin-like formulation

where and how does one “plug” an effective channel-noise term, into the usual (deterministic) conductance-based equations ??

3) gaussian conductance-noise (rigorous derivation; accurate; general)

$$I = \bar{g} [x^p(t)y^q(t) + \xi(t)] (V - E)$$

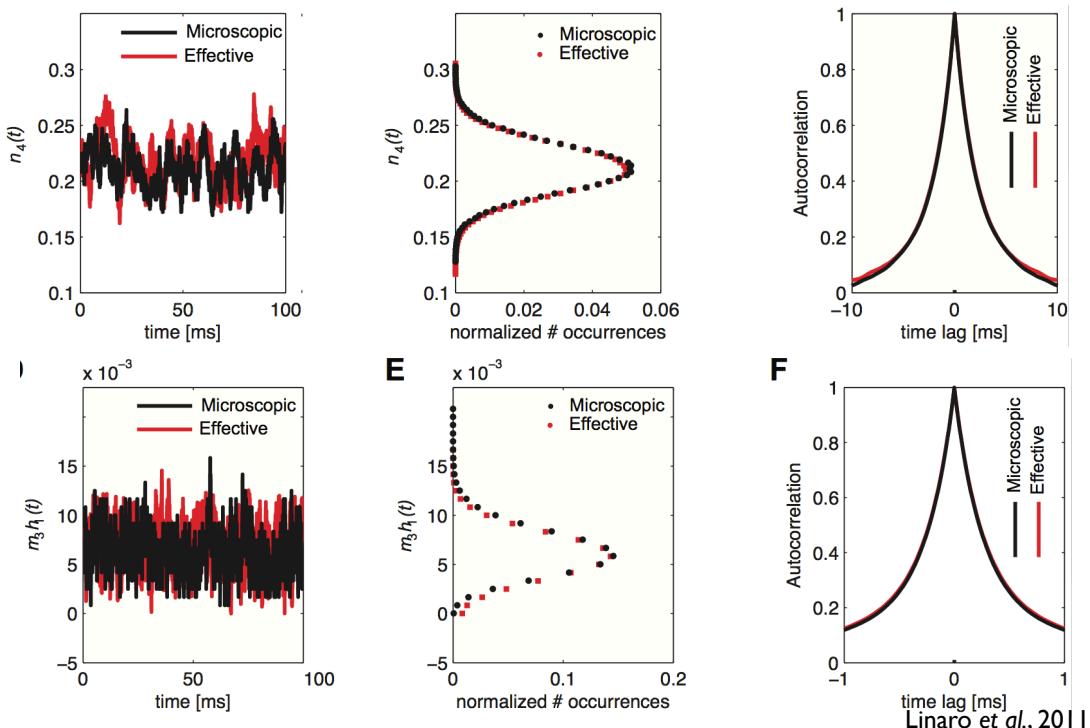
Linaro *et al.*, 2011

Steinmetz *et al.*, 2000

Conti & Wanke, 1975

1. Determine analytically the stochastic properties (mean and co-variance) of the fraction of open channels as emulated by Markov models.
2. Use a continuous (i.e., diffusion) stochastic process to **approximate** the fraction of open channels as a superposition of independent Ornstein Uhlenbeck stochastic processes.

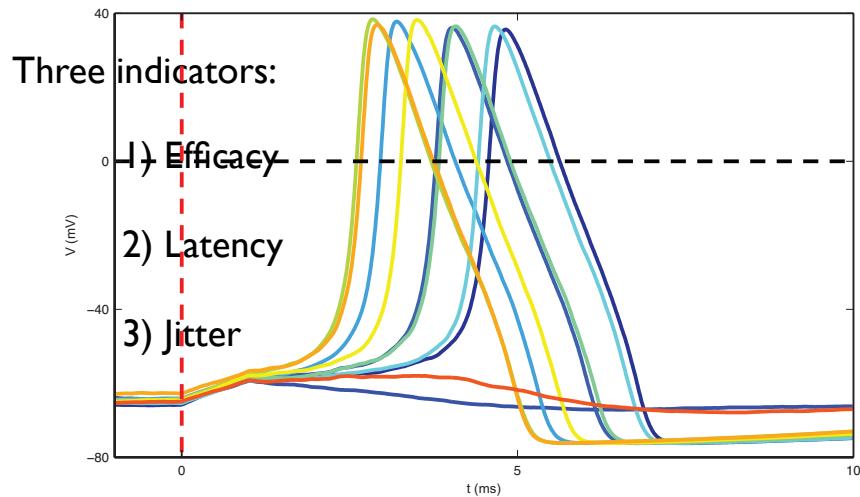
Steady-state properties (voltage-clamp)



Linaro *et al.*, 2011

dynamical PROPERTIES

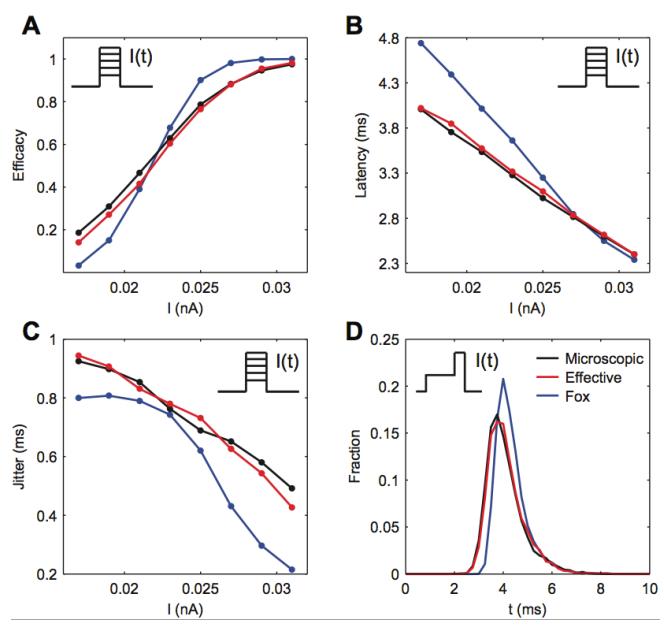
action potentials



Linaro et al., 2011

dynamical PROPERTIES

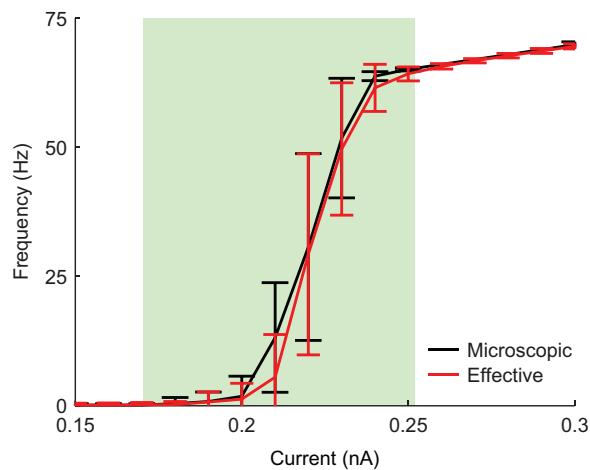
action potentials



Linaro et al., 2011

dynamical PROPERTIES

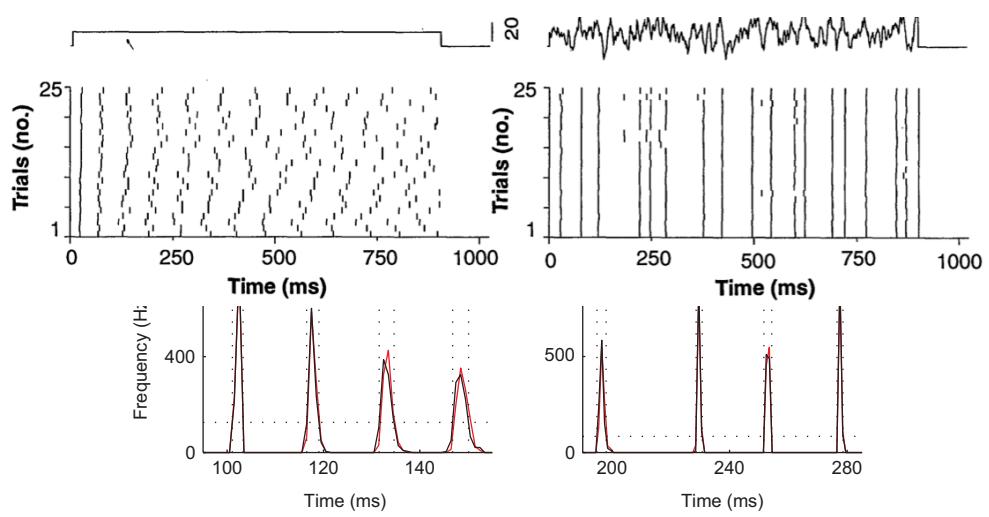
F-I curves



Linaro et al., 2011

dynamical PROPERTIES

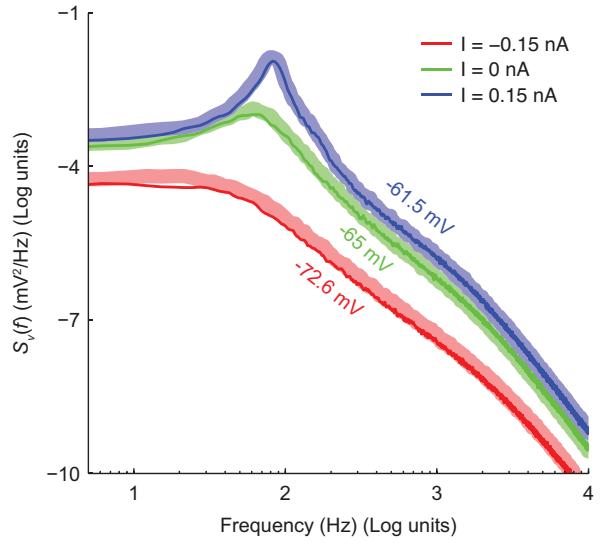
reliability



Linaro et al., 2011

dynamical PROPERTIES

subthreshold voltage fluctuations, power-spectra



Linaro et al., 2011