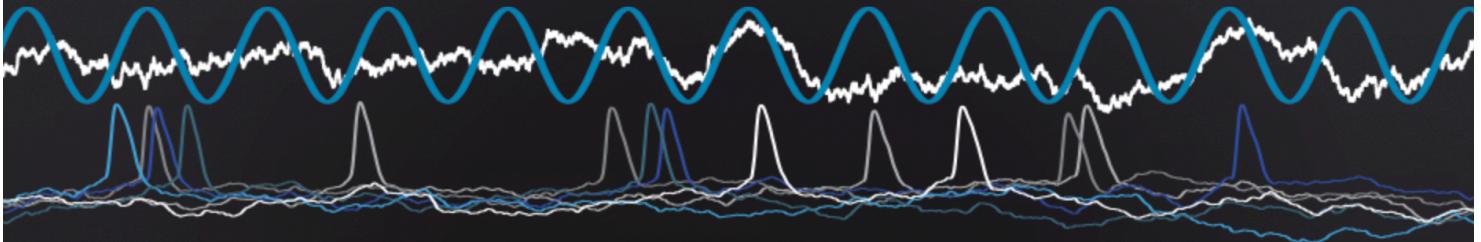


# ELECTROPHYSIOLOGICAL SIGNALS



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"

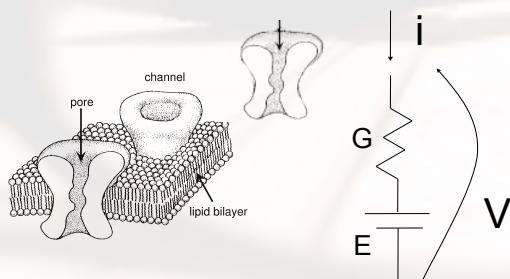
**Heterogeneous distributions of (typical) ions,  
"inside/outside" the cell membrane**



Ion	K <sup>+</sup>	Na <sup>+</sup>	Cl <sup>-</sup>	Ca <sup>2+</sup>
Concentration inside (mM)				
Concentration outside (mM)				
Equilibrium potential (mV)				

from Sterratt et al., 2011

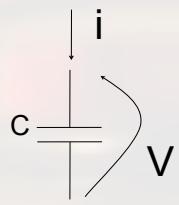
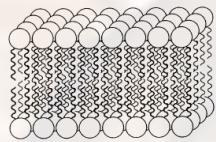
**Equivalent electrical circuit model of ionic permeability**



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

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

## Equivalent model of capacitive properties

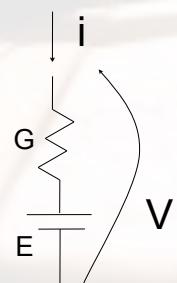
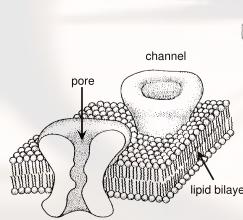


$$i = C \frac{dV}{dt}$$

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

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

## Equivalent model of ionic permeability



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

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

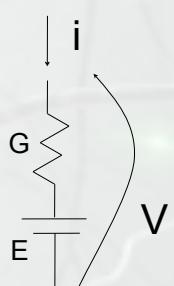
## The resting membrane potential multiple ion-species, NOT at the equilibrium

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**

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

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

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

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

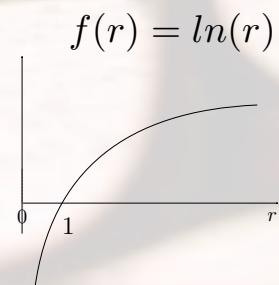
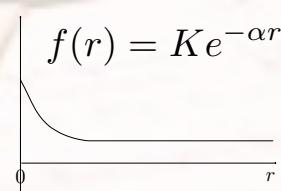
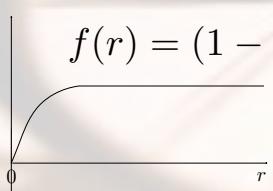
$$V_{rest} = \frac{(G_1E_1 + G_2E_2 + G_3E_3 + \dots)}{(G_1 + G_2 + G_3 + \dots)}$$



**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.”*

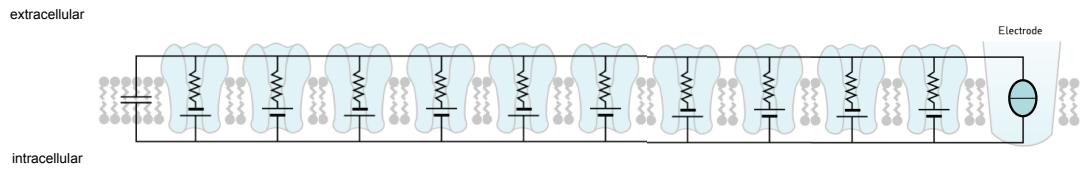
$$\Delta Q_{tot} = 0 \quad \begin{array}{l} \text{Balance of the tot charge change} = 0 \\ \text{Balance of the tot net current} = 0 \end{array}$$

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

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

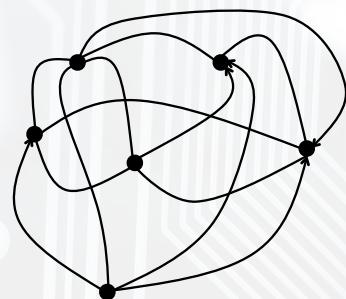
$$C \frac{\Delta V}{\Delta t} = -(i_1 + i_2 + i_3 + \dots) \quad C \frac{d}{dt} V = -(i_1 + i_2 + i_3 + \dots)$$

**Charge Balance equation**

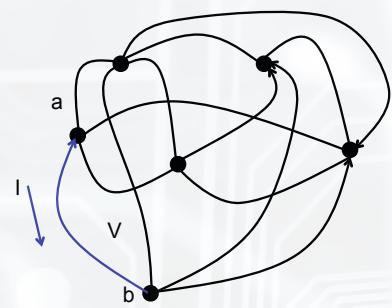


## (Linear) Electrical Networks Theory

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



electric network = oriented graph  
**node + links**

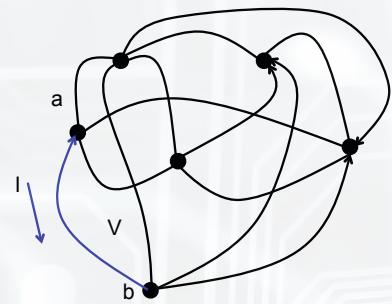


Two quantities (“*voltage*”, “*current*”) are associated to each link.  
 Those are the unknowns of the system.

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

We use the “passive” sign convention.

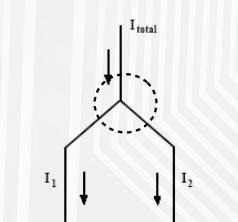
**Kirchoff laws** + components equations  
 $=$   
 enough equations for all the unknowns {V,I}



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

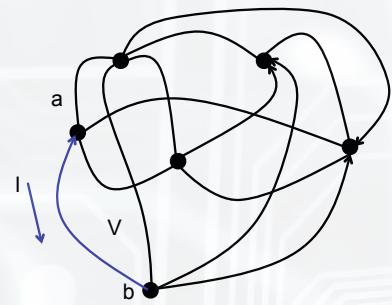
$$\sum_k I_k = 0 \text{ for any junction}$$

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)

$$V_1 - V_2 - V_4 - V_5 = 0$$

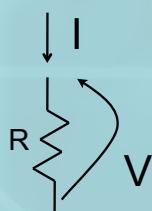
$$V_1 + V_7 - V_5 = 0$$

$$V_6 - V_2 - V_3 = 0$$

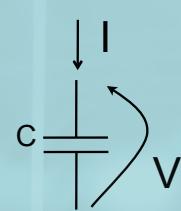
**Kirchoff laws** + components equations  
=  
enough equations for all the unknowns {V,I}



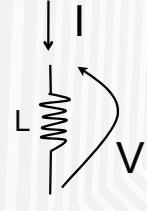
..each component sets a specific functional relationship between the circuit-variables at its nodes..



$$V = R I$$



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

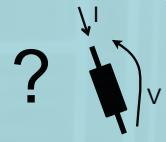


$$L \frac{dI}{dt} = V$$

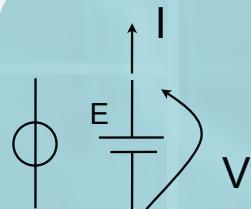
These “**constitutive**” equations rely on the passive sign convention  
(i.e. if you change convention, be consistent and change signs where appropriate)

**Kirchoff laws** + components equations  
=

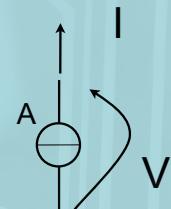
enough equations for all the unknowns {V,I}



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



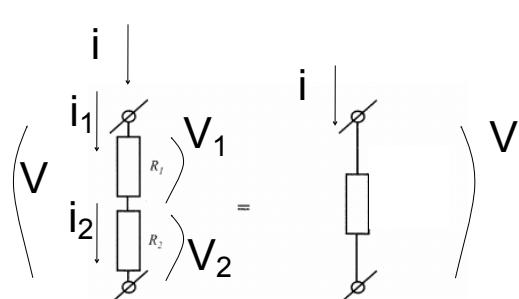
$$V = E$$



$$I = A$$

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



$$i_1 - i_2 = 0$$

$$i - i_1 = 0$$

$$V = V_1 + V_2$$

$$V_1 = R_1 i_1$$

$$V_2 = R_2 i_2$$

$$V = Ri$$

$$i = i_1 + i_2$$

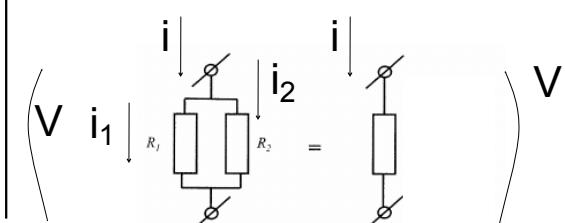
$$V - V_1 = 0$$

$$V_1 - V_2 = 0$$

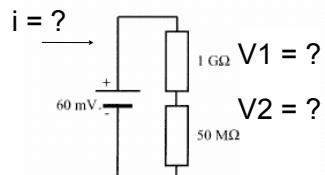
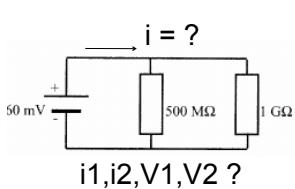
$$V_1 = R_1 i_1$$

$$V_2 = R_2 i_2$$

$$V = Ri$$



## Exercise (for you) & Derivation of known results



$$i = i_1 + i_2$$

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

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

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

$$V_1 = R_1 i$$

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

$$V_2 = R_2 i$$

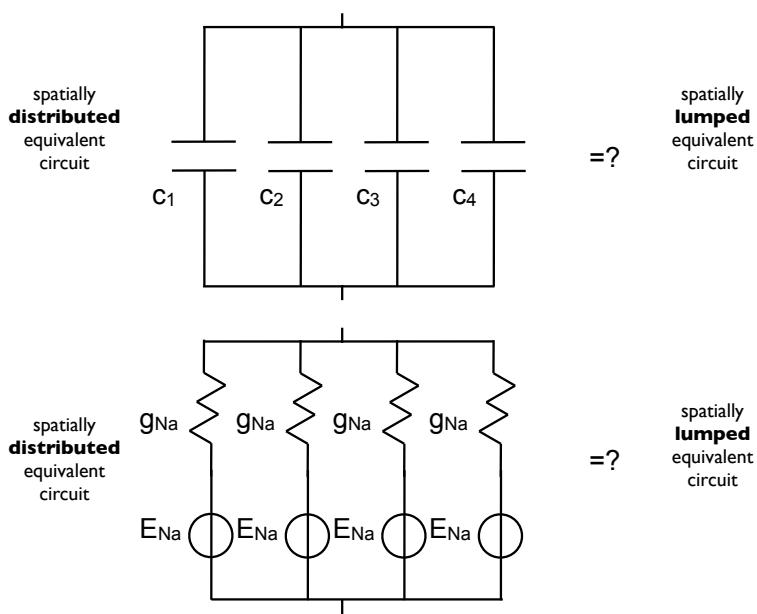
$$V_1 = 57.1 \text{ mV}$$

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

The current “prefers” the path with minimal resistance.

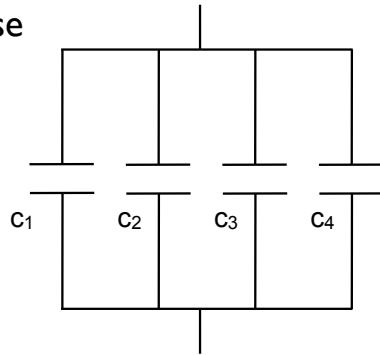
The voltage “divides itself” proportionally to the path resistance.

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

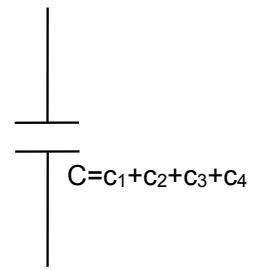


### Exercise

spatially  
**distributed**  
equivalent  
circuit

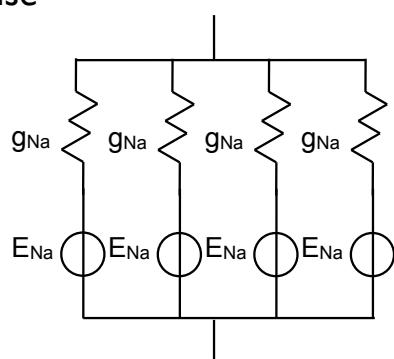


spatially  
**lumped**  
equivalent  
circuit

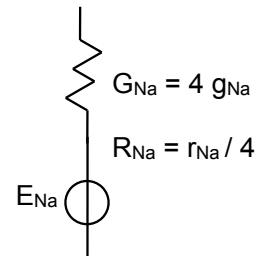


### Exercise

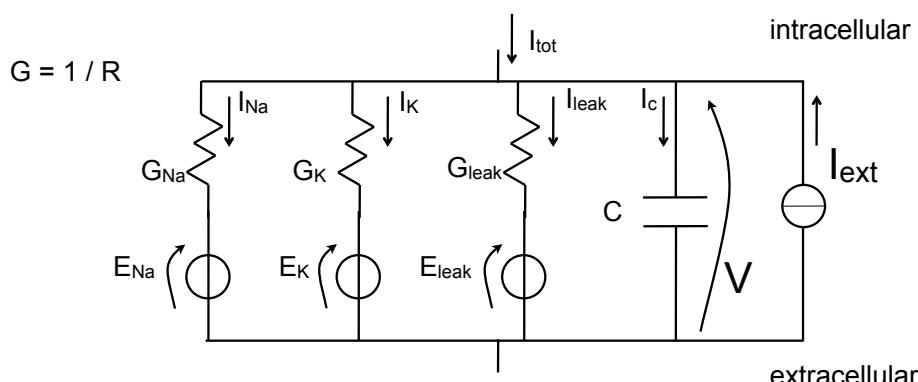
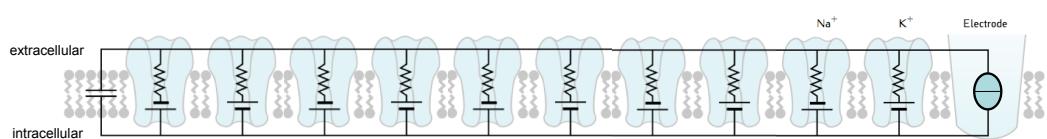
spatially  
**distributed**  
equivalent  
circuit



spatially  
**lumped**  
equivalent  
circuit



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



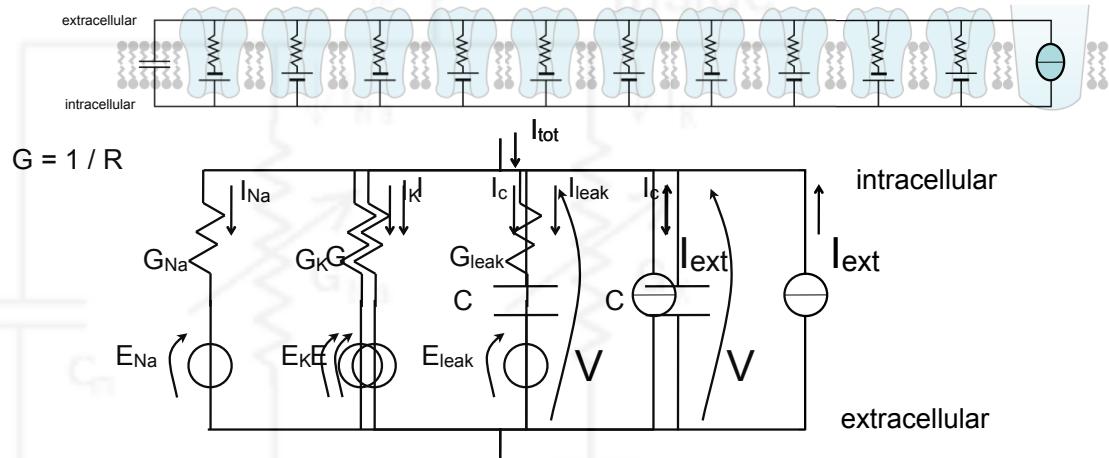
$$I = G(V - E)$$

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

$$I = A$$

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

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



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

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

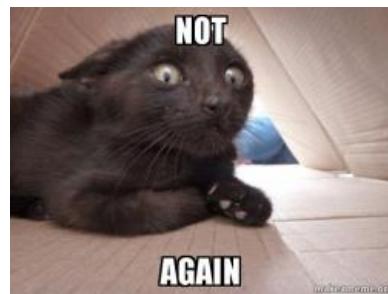
**Consequence of the Thevenin's theorem  
in Electrical Circuit Theory**



$$t \quad V(t)$$

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

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



$$G E + I_{ext}$$

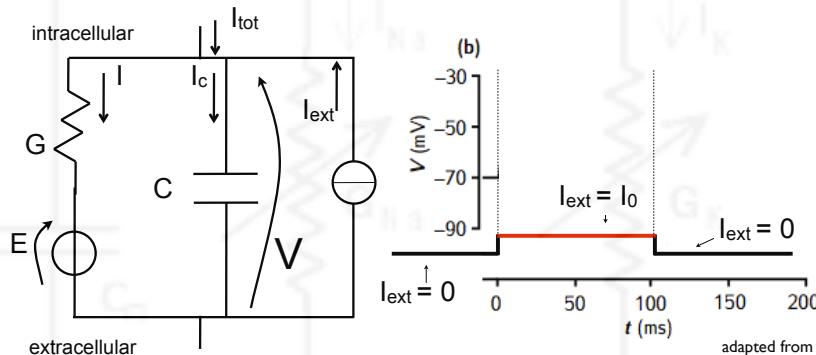
$$x \quad f(x)$$

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

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

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

$$G = 1 / R$$



adapted from Sterratt et al., 2011

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

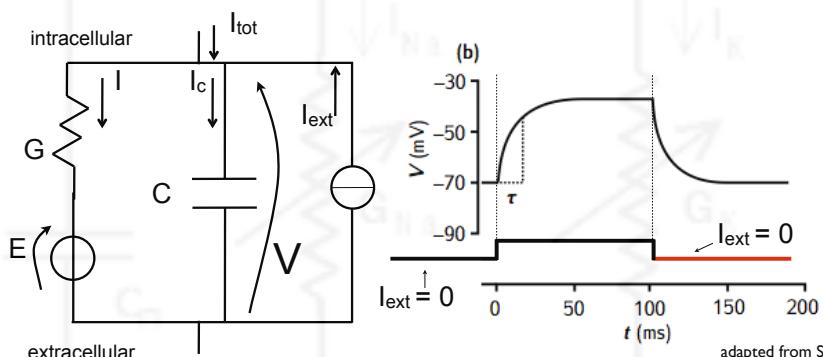
$$V(t) = K e^{-G/C t} + E + I_0/G$$

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



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

$$G = 1 / R$$



adapted from Sterratt et al., 2011

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

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

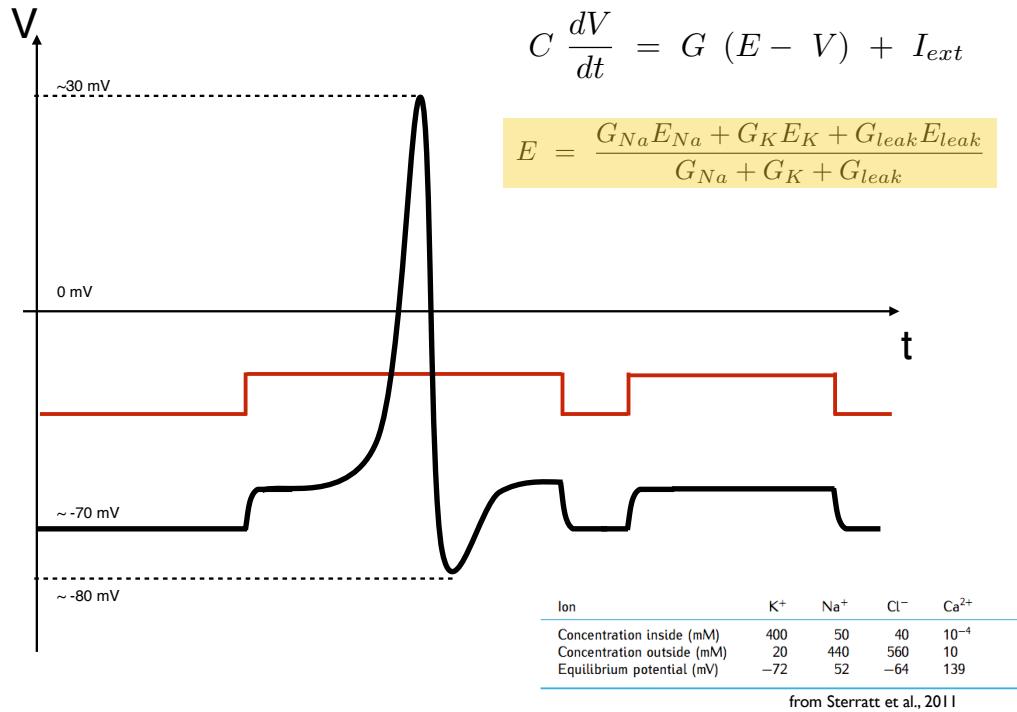
$$t > 100$$

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

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



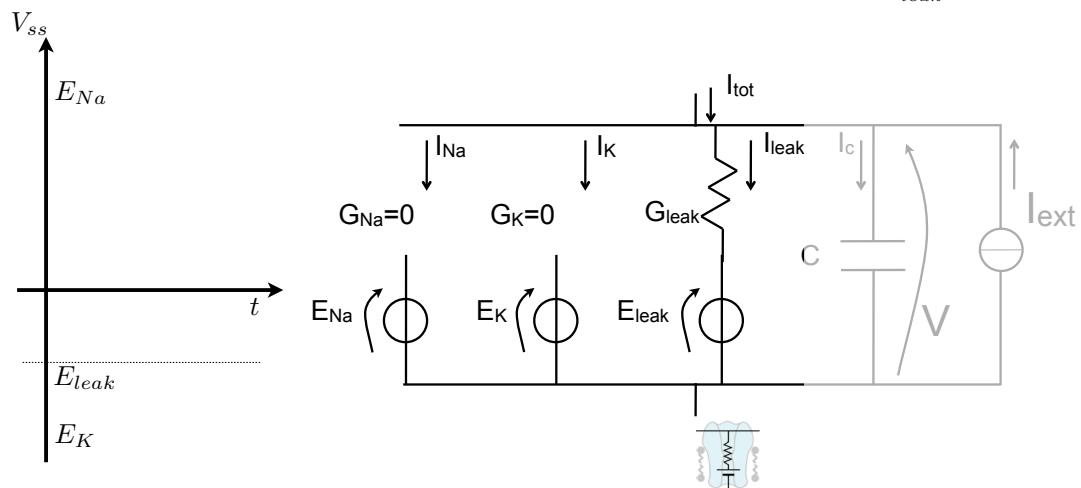
## “Nobel prize” intuitions on the Action Potential (AP)



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

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

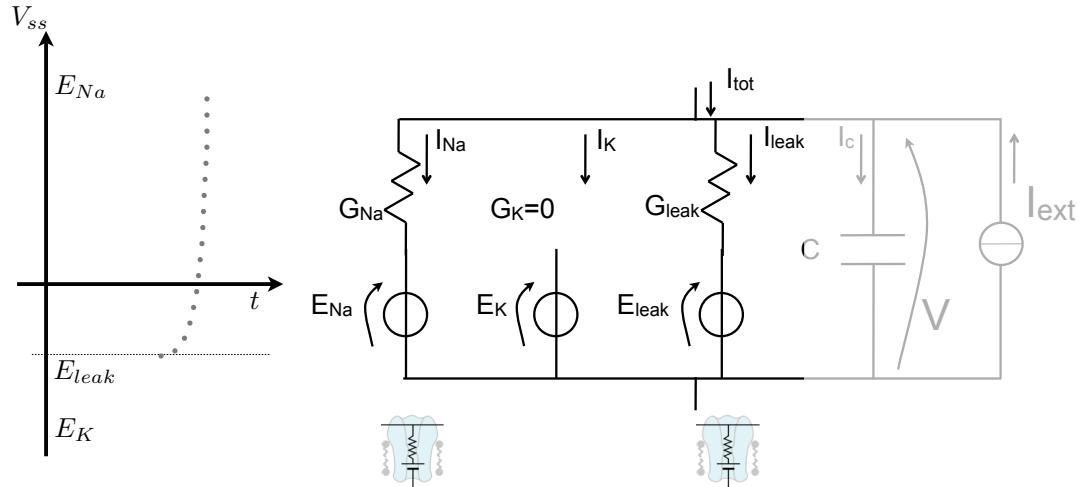
$$\lim_{t \rightarrow +\infty} V(t) = E + \frac{I_{ext}}{G} \quad E = \frac{G_{leak}E_{leak}}{G_{leak}}$$



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

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

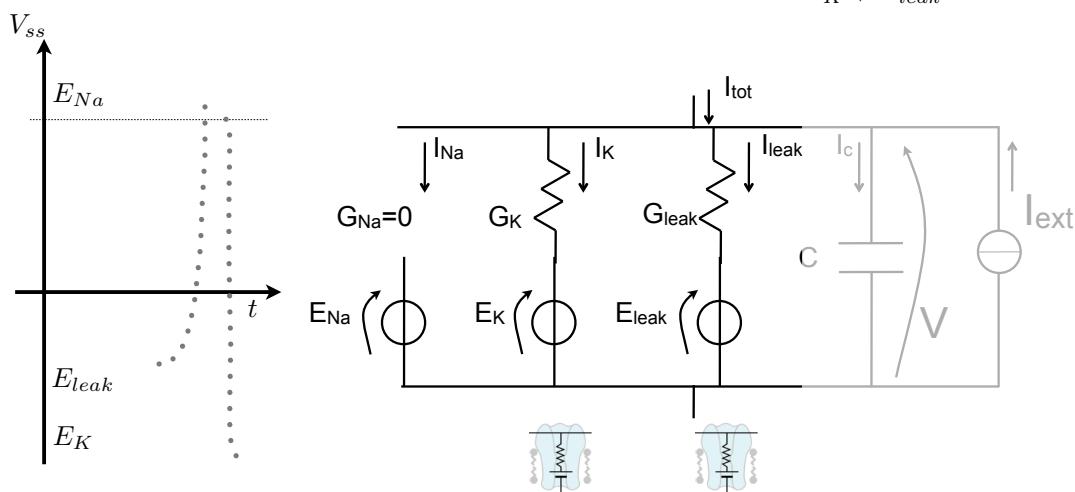
$$\lim_{t \rightarrow +\infty} V(t) = E + \frac{I_{ext}}{G} \quad E = \frac{G_{Na}E_{Na} + G_{leak}E_{leak}}{G_{Na} + G_{leak}}$$



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

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

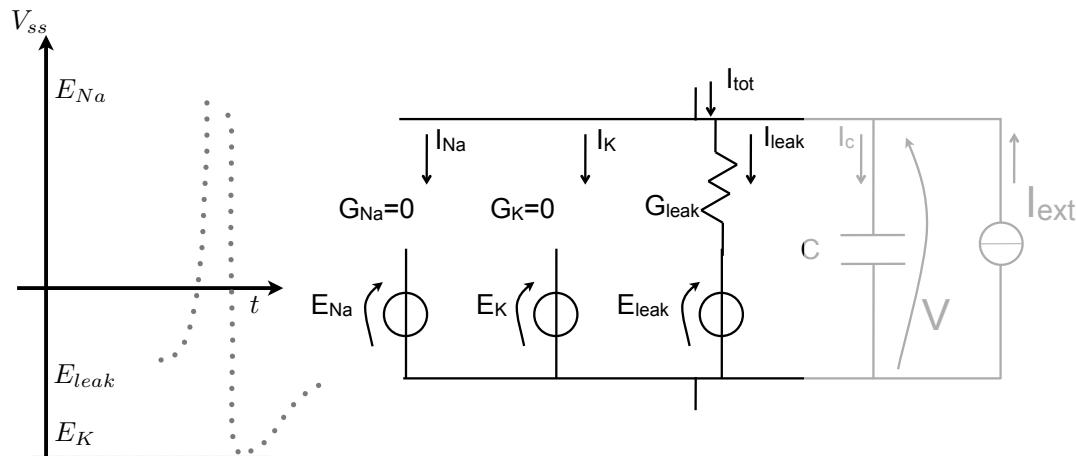
$$\lim_{t \rightarrow +\infty} V(t) = E + \frac{I_{ext}}{G} \quad E = \frac{G_K E_K + G_{leak} E_{leak}}{G_K + G_{leak}}$$



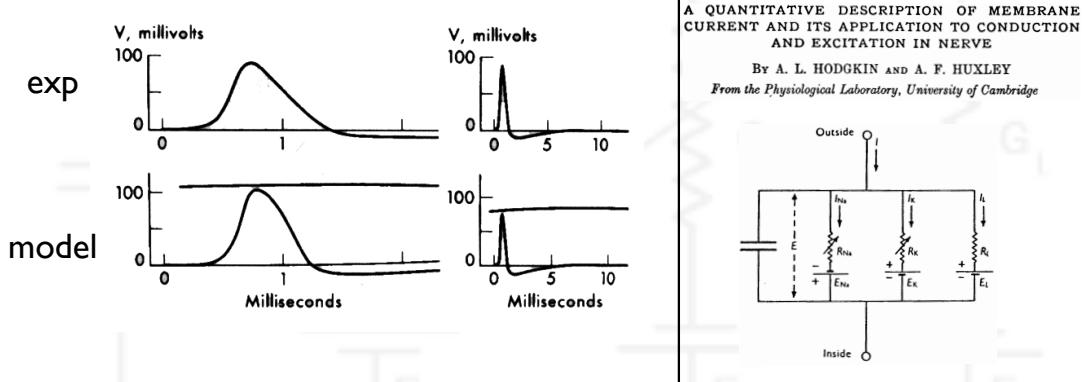
“Nobel prize”-like intuitions: predictions from a (steady-state) selective changes in membrane ionic permeabilities

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

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

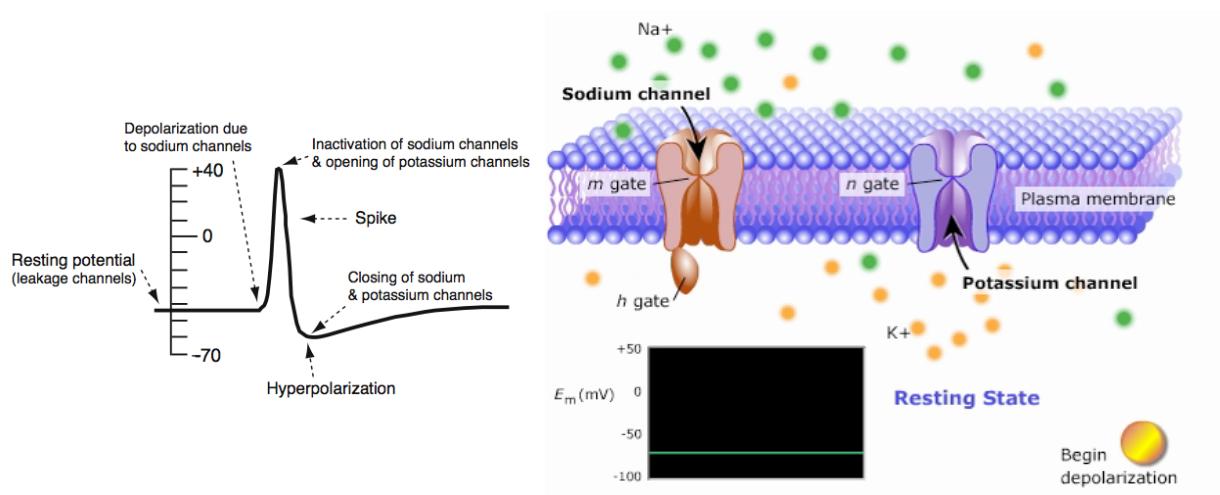


### The Hodgkin-Huxley model of AP

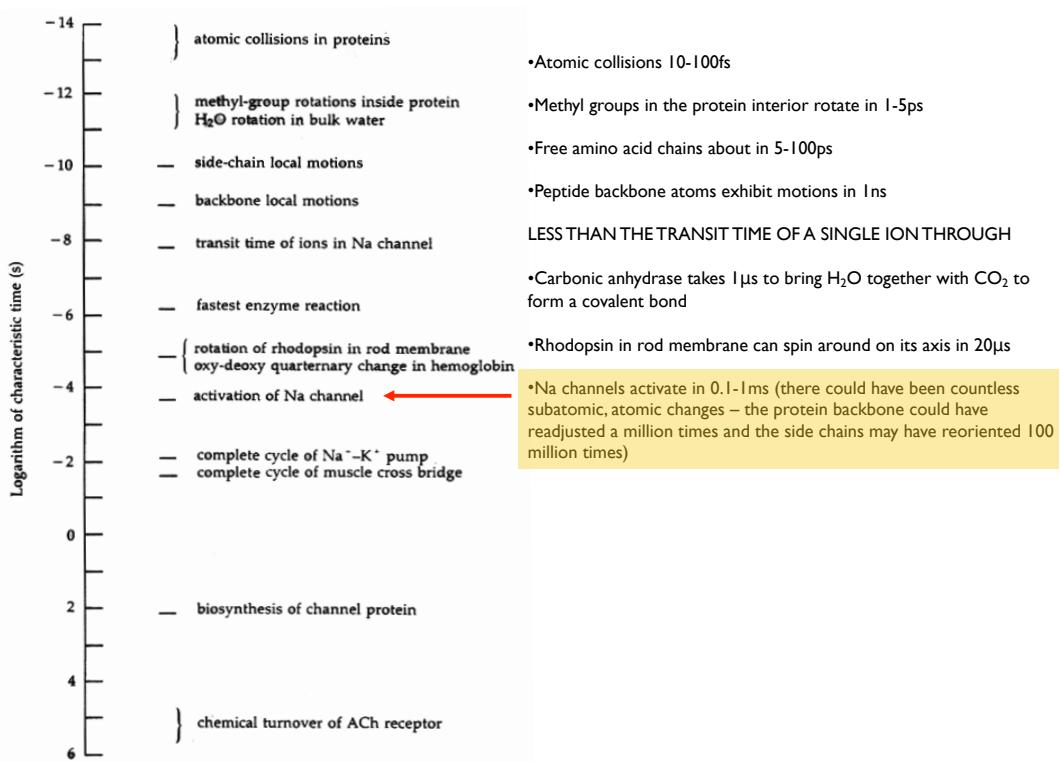


- Bernstein, 1902; Proposed an increase of membrane permeability to ions during excitation...
- Cole & Curtis, 1938; Recorded permeability changes...
- Hodgkin & Huxley, 1952; evidence for several ionic pathways each with its own kinetics...

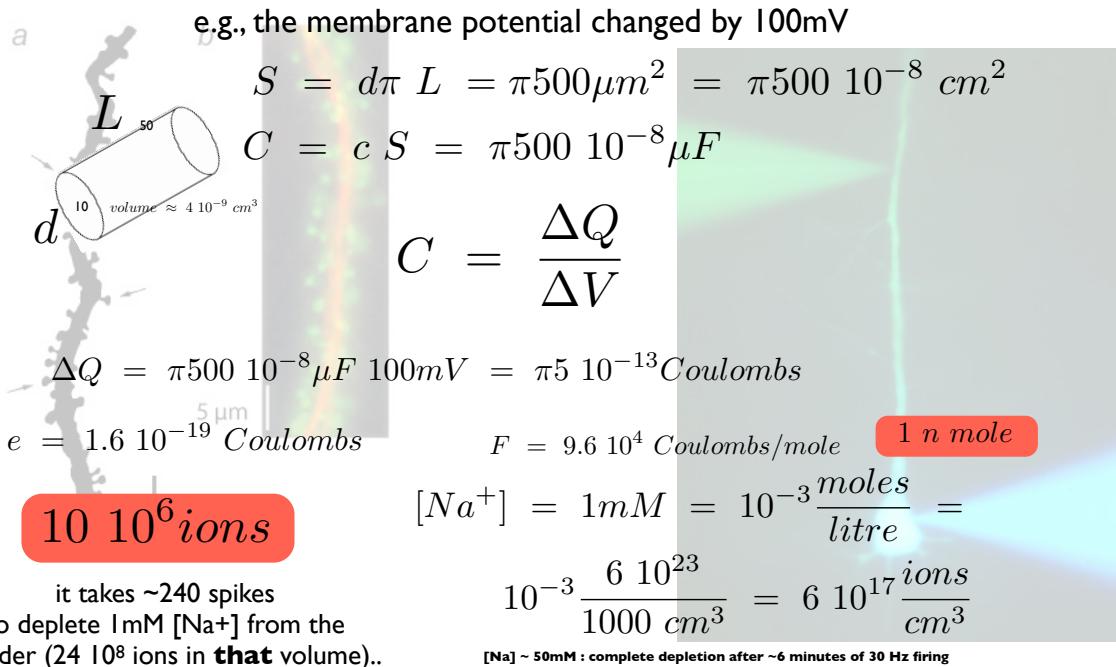
## The AP generation: selective changes in ionic permeabilities



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



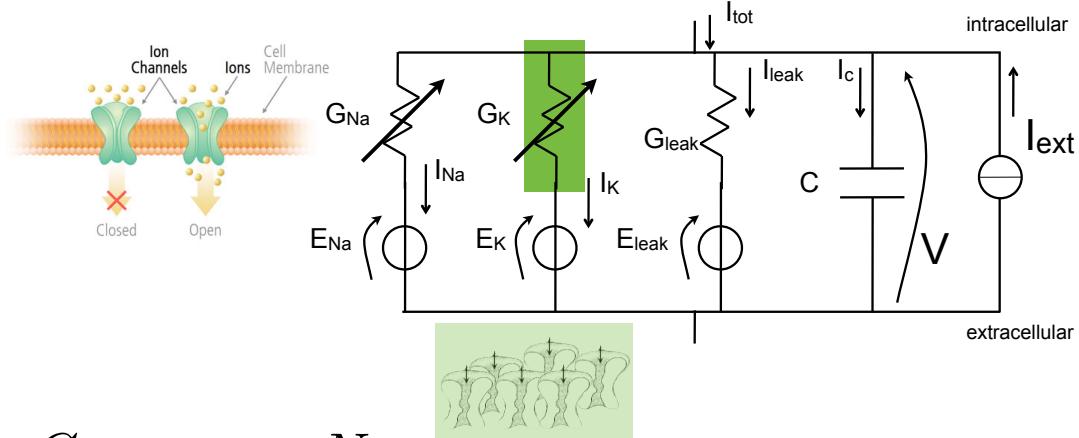
Exercise: how many ions exchanged during an AP? **negligible**



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...;

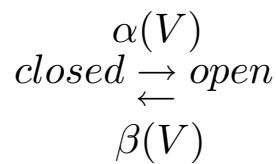


HH described (mesoscopic) membrane permeability by (phenomenological) kinetic schemes

### 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'.



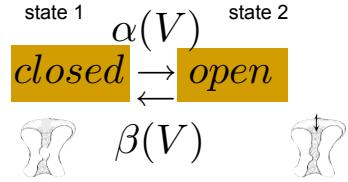
$\alpha(V)$  and  $\beta(V)$  are voltage-dependent rate coefficients

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



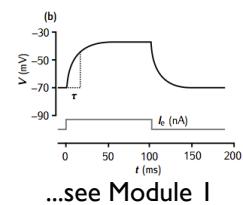
$$\frac{dn}{dt} = -\beta n + \alpha (1 - n)$$

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

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

**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 )

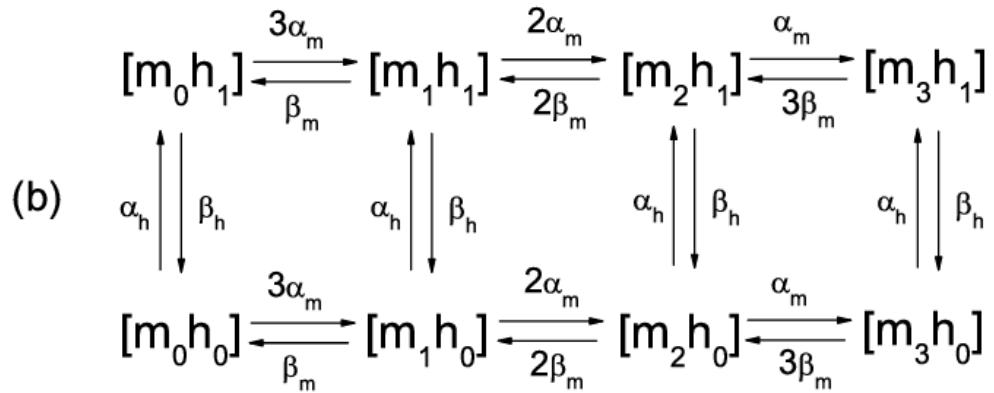
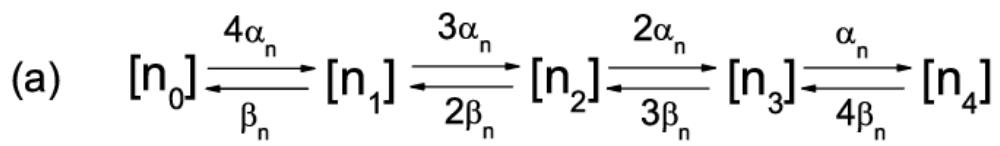
$$x(t) = x(t_0) h(t) + \int_{-\infty}^{+\infty} h(t - \xi) x_\infty(\xi) d\xi \quad h(t) = e^{-\frac{t-t_0}{\tau}} \Theta(t - t_0)$$

intuitive understanding: time-invariant input

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

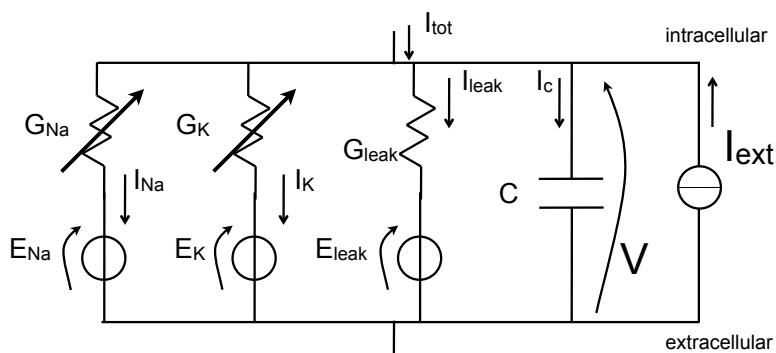
...approximately...

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



## The generation of Action Potentials (Hodgkin & Huxley)

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



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

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

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

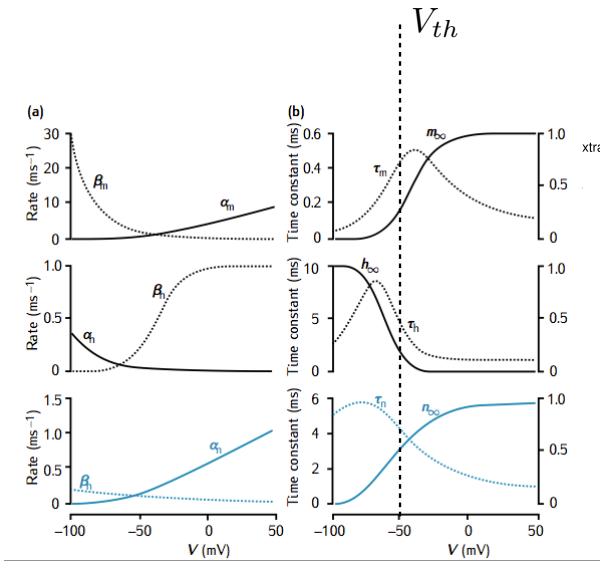


## The Hodgkin-Huxley model of AP generation

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

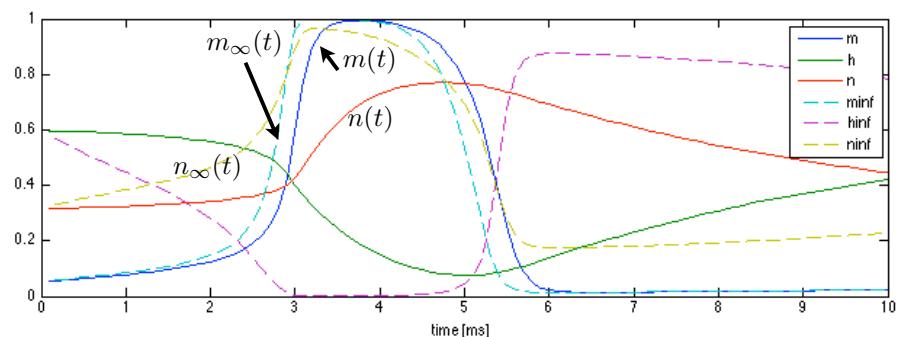
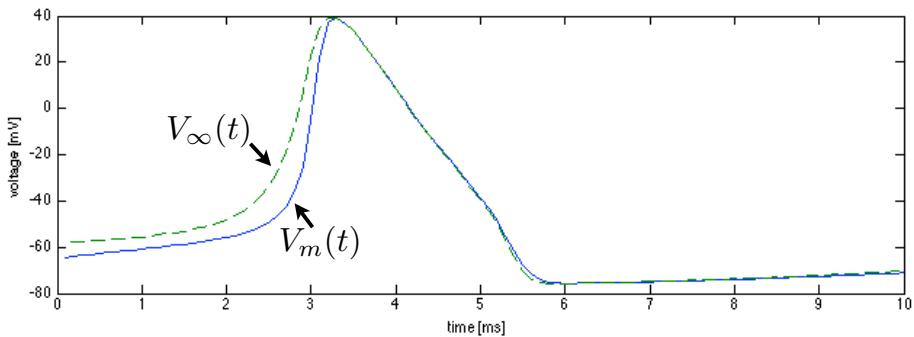
$$h_\infty = \frac{\alpha_h}{\alpha_h + \beta_h}$$

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



from Sterratt et al., 2011

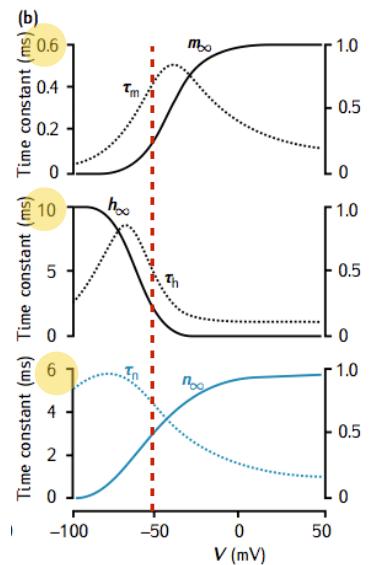
## The Hodgkin-Huxley model of AP generation





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 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

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

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

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

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

$$E_{Na} = 50 mV$$

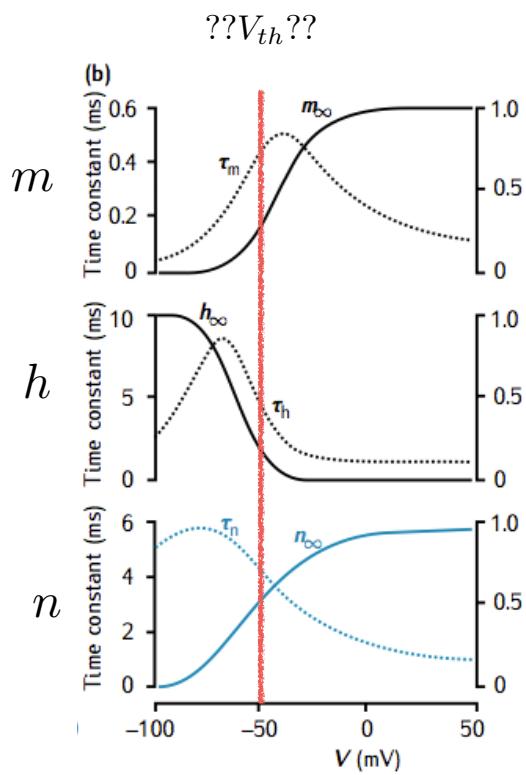
$$E_K = -77 mV$$

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

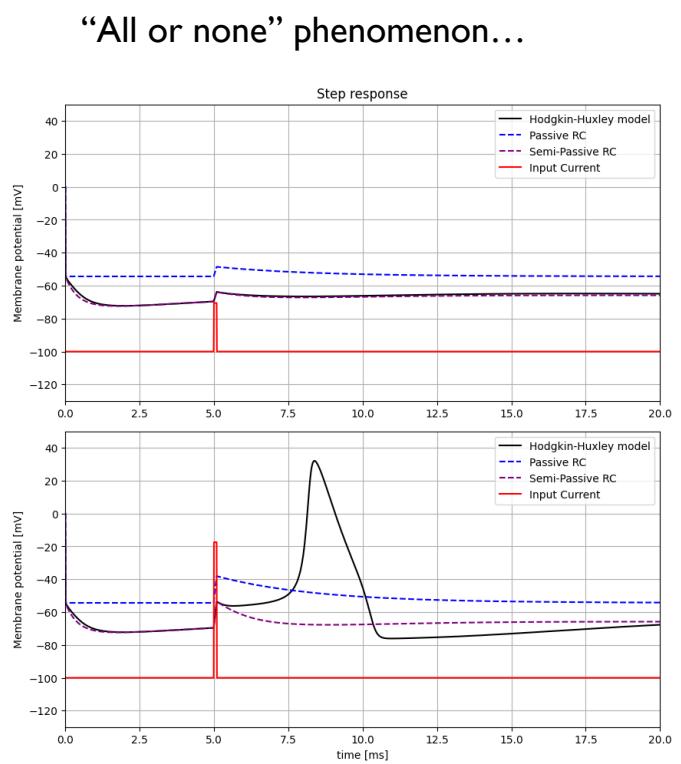
### Functions of V:

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

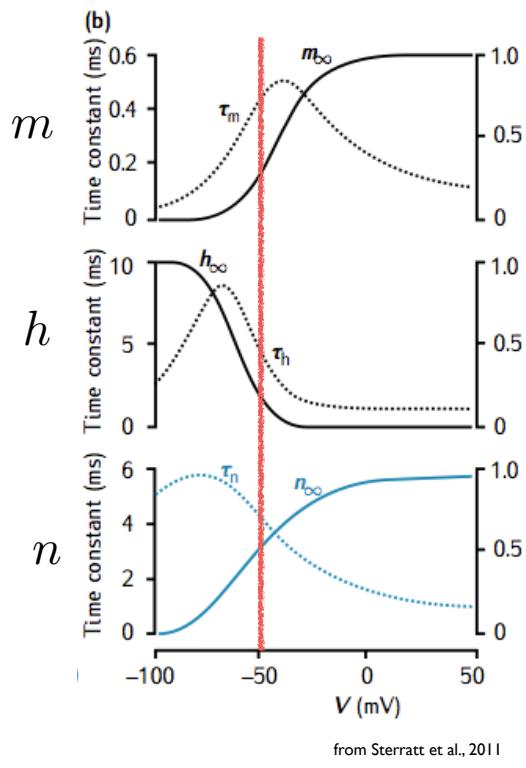
- Existence of a threshold?
- Temporal Integration
- AP generation and velocity of activation of individual gates
- “*F-I curve*” and its approximation as *first-passage time*
- Relative and Absolute refractoriness
- Alteration in extracellular potassium
- Simulating pharmacology



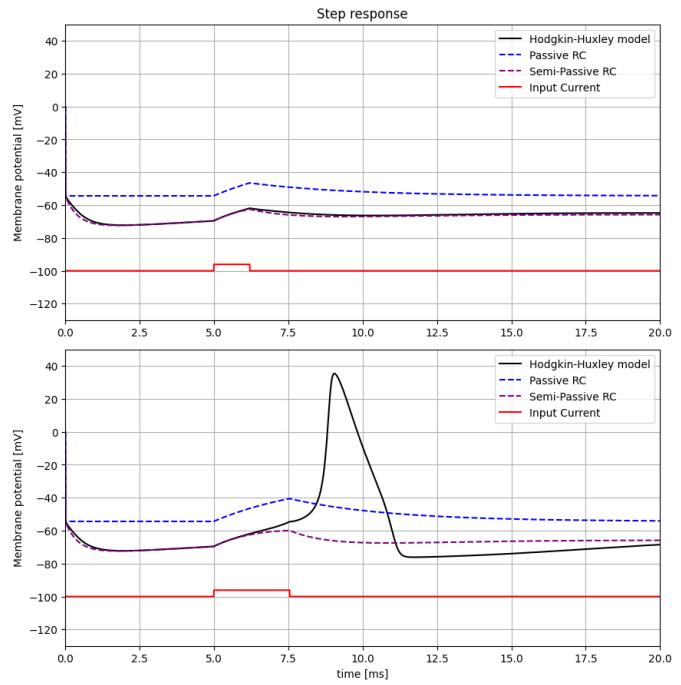
from Sterratt et al., 2011



?? $V_{th}$ ??

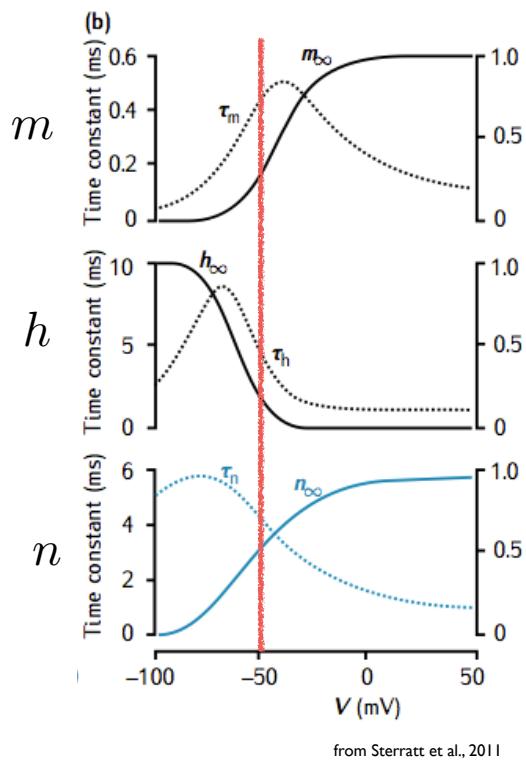


However... same amplitude, different duration

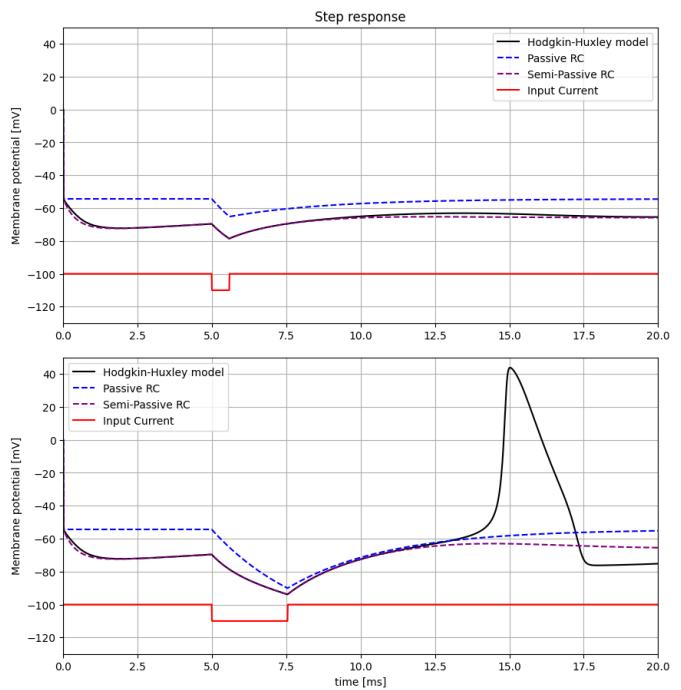


Search for rheobase and chronaxie (on Wikipedia)...

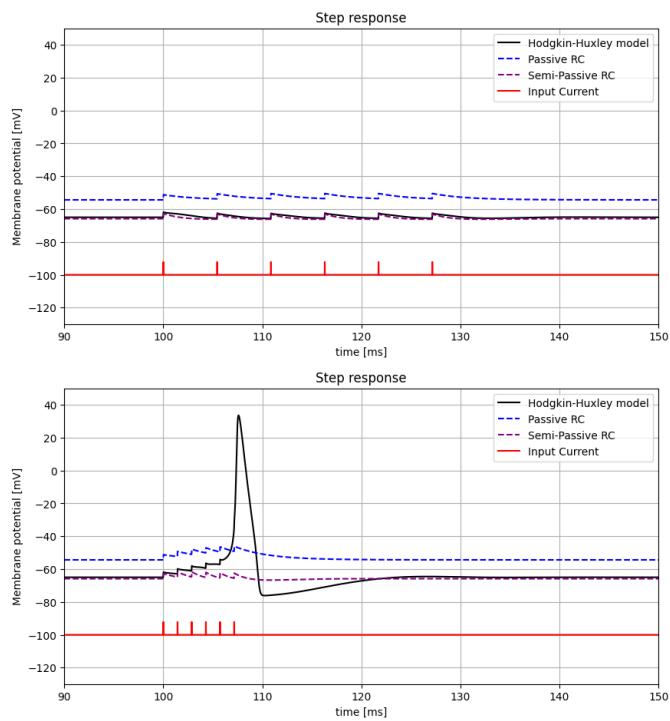
?? $V_{th}$ ??



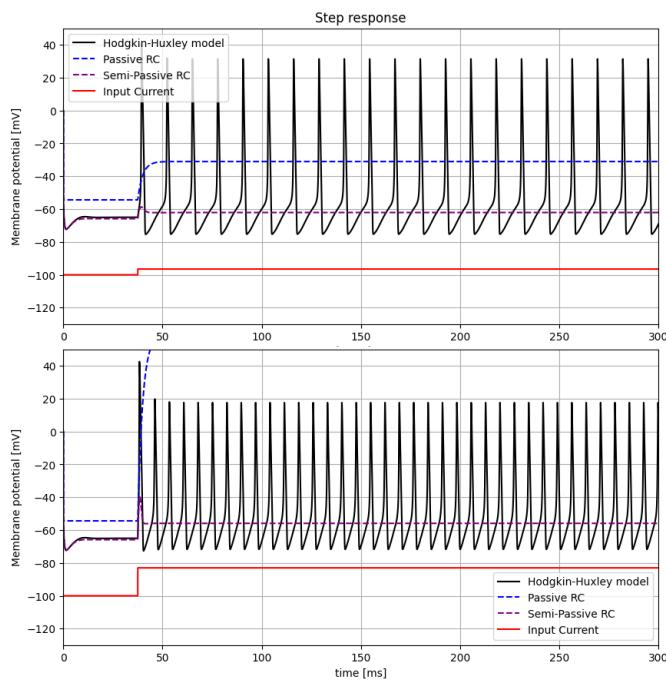
However... hyperpolarizing pulse...



...rebound firing...



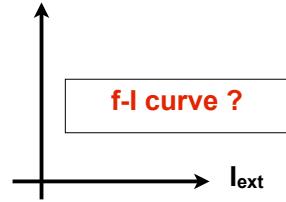
Increasing the amplitude of the injected (DC) current elicits sustained and regular oscillations with increasing frequency



$N_{AP}$  in  $T$  sec

$T$  sec

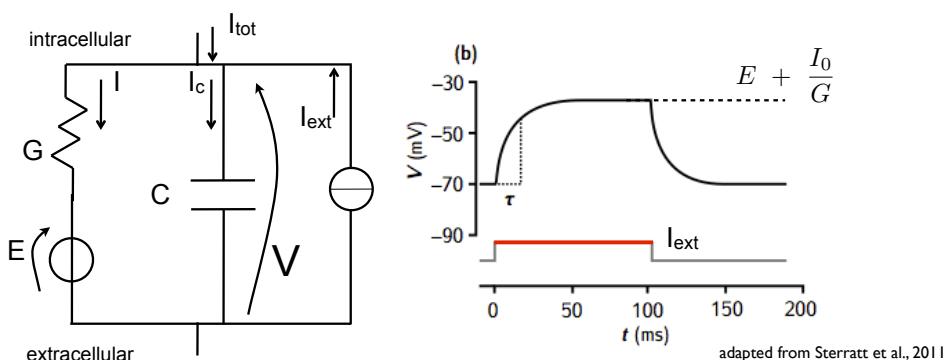
f-I curve ?



# demo

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

$$G = 1 / R$$



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

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

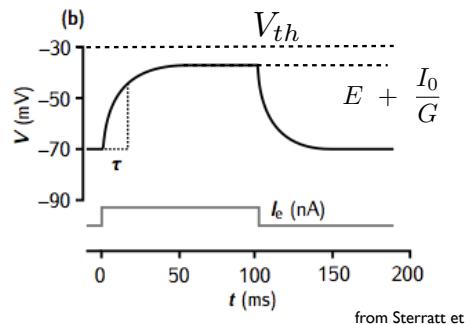
$$V(0) = E \quad V(t) = E + I_0/G \left(1 - e^{-G/C t}\right)$$

$$G = 1 / R$$

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

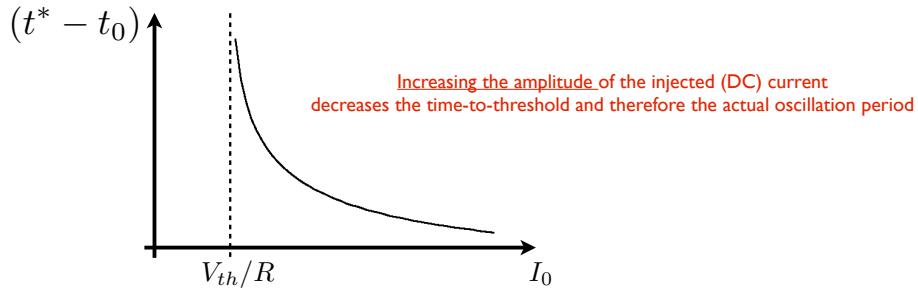
$$V(t^*) = V_{th}$$

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

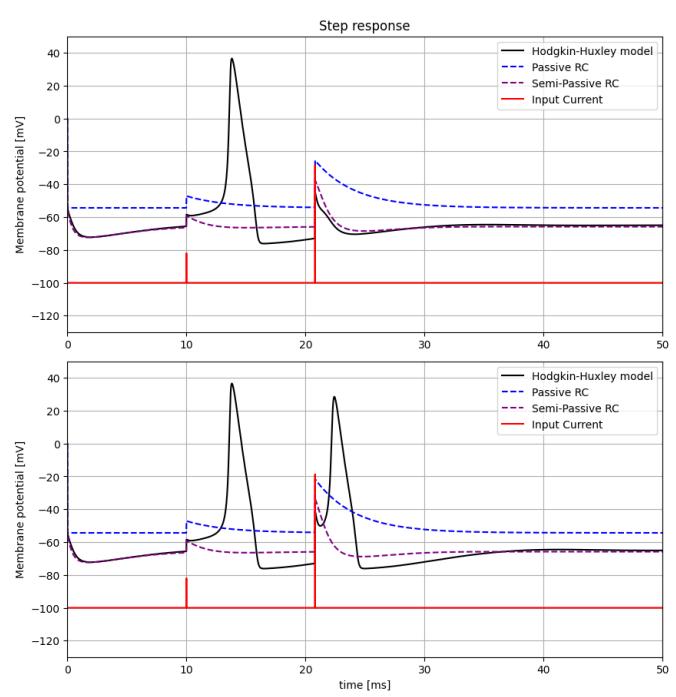
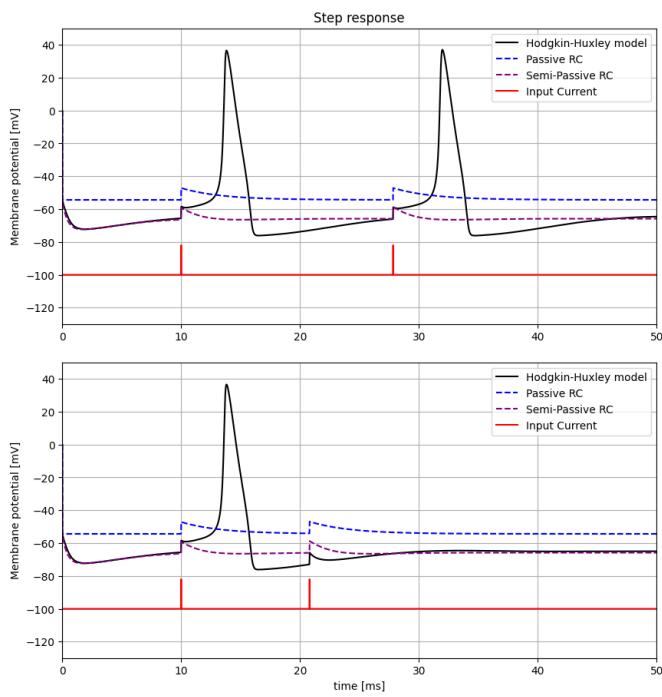


from Sterratt et al., 2011

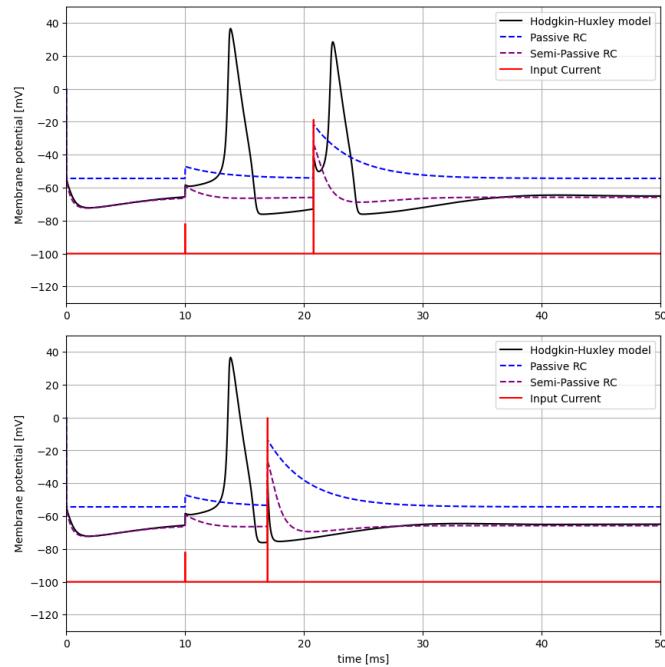
$$t^* = R C \log \left( \frac{R I_0}{(E + R I_0) - V_{th}} \right)$$



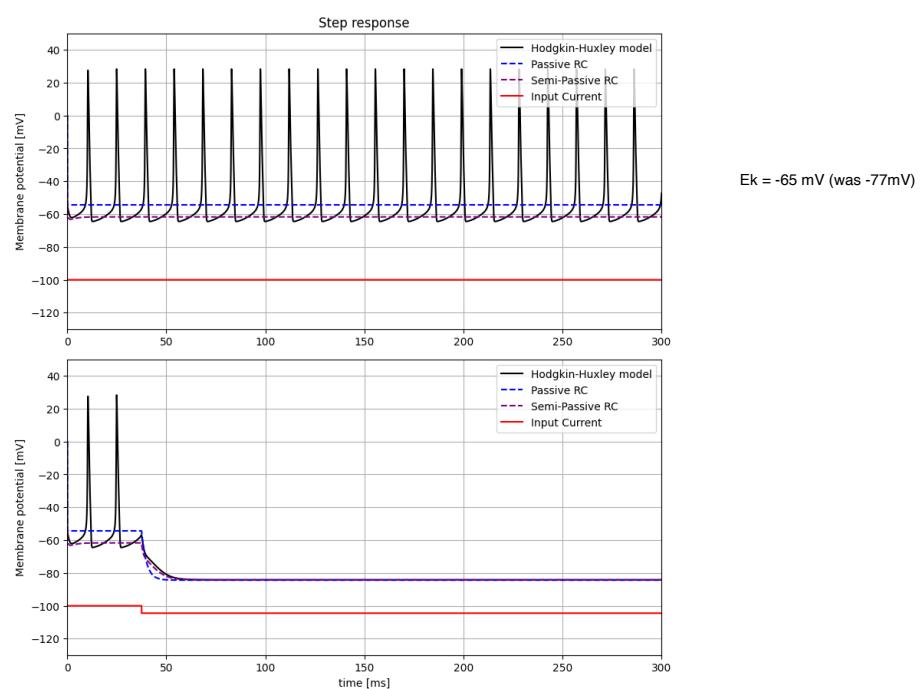
## Absolute and relative refractory period: why?



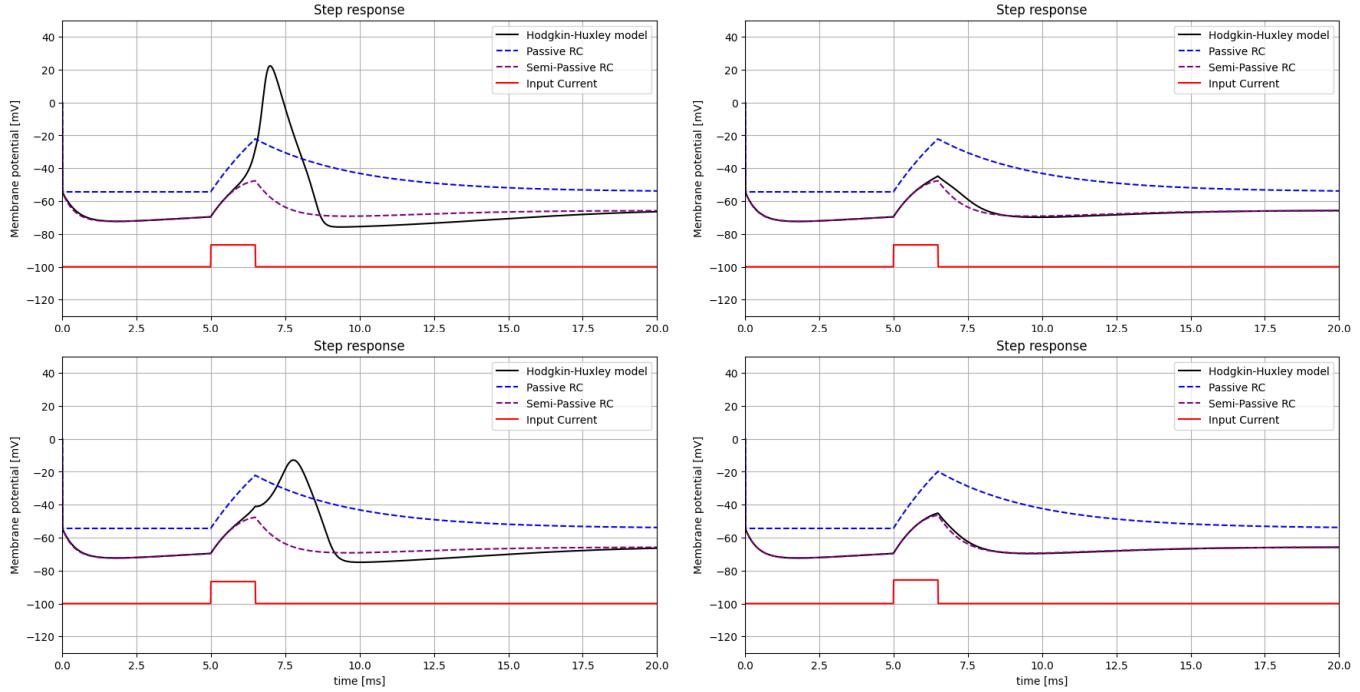
## Absolute and relative refractory period: why?



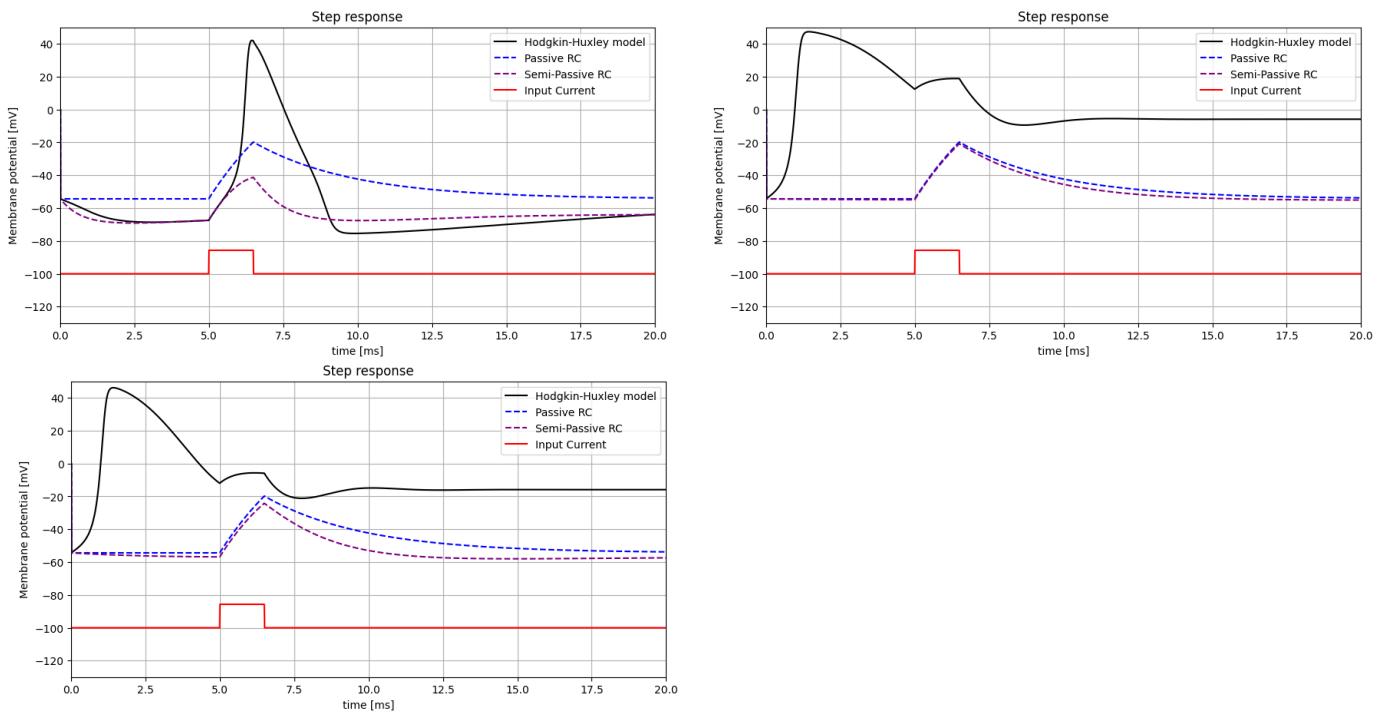
## Increasing the extracellular concentration of K-ions: why?



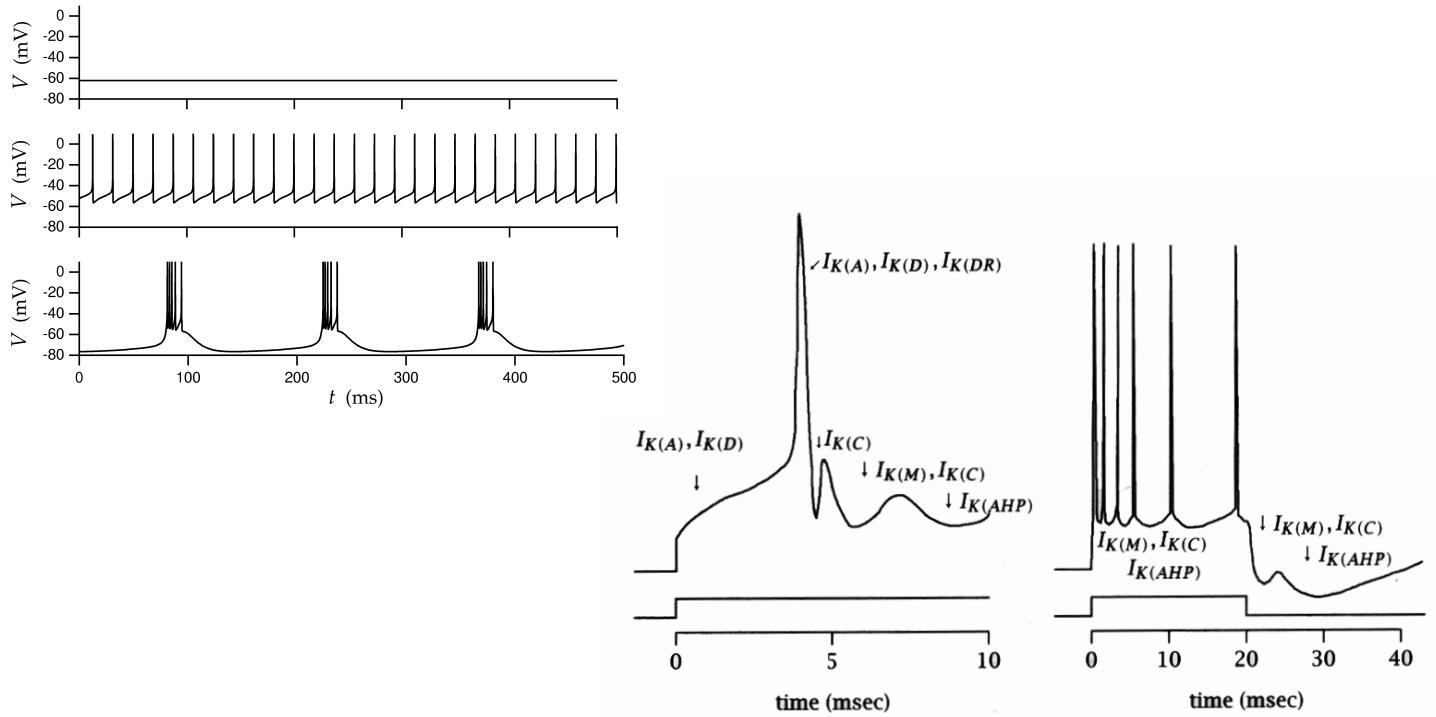
## Simulating pharmacology and toxins: which one? why?



## Simulating pharmacology and toxins: which? why?



## The ‘zoo’ of ion channels....



cell grafting in neonatal mice

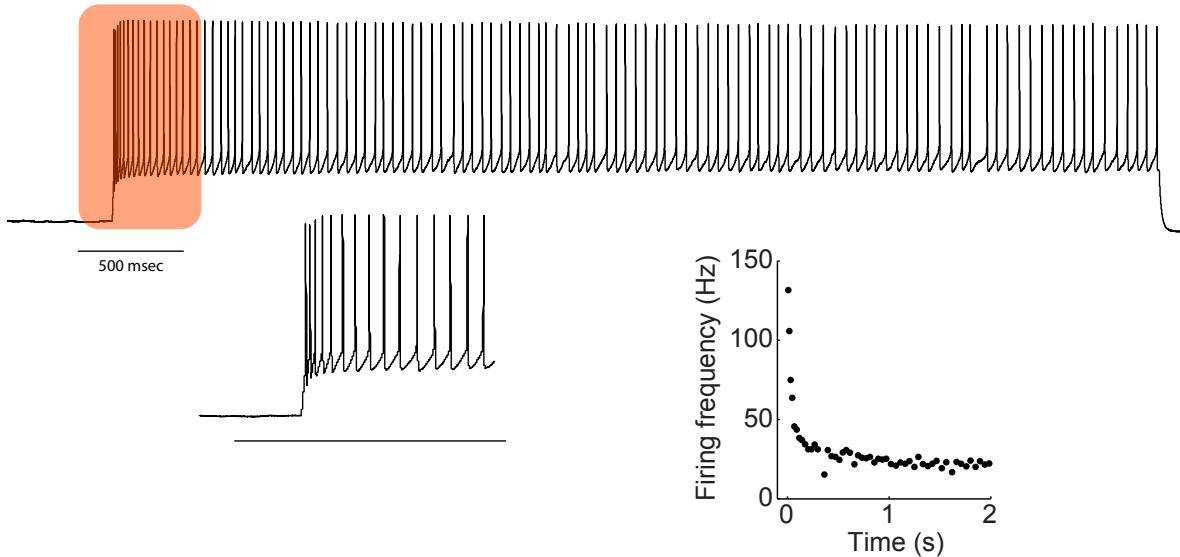


NOD-SCID immunodeficient adult mice

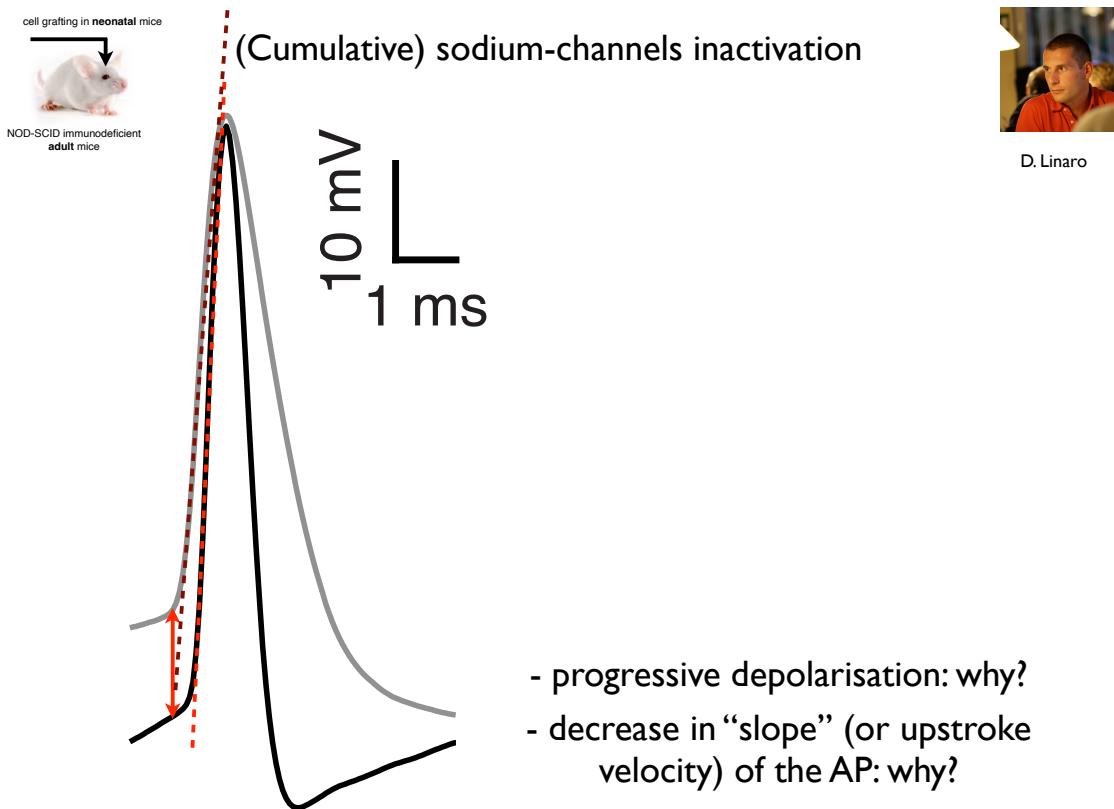
Additional Potassium-currents:  
e.g., Ca- or Na-dependent K-currents



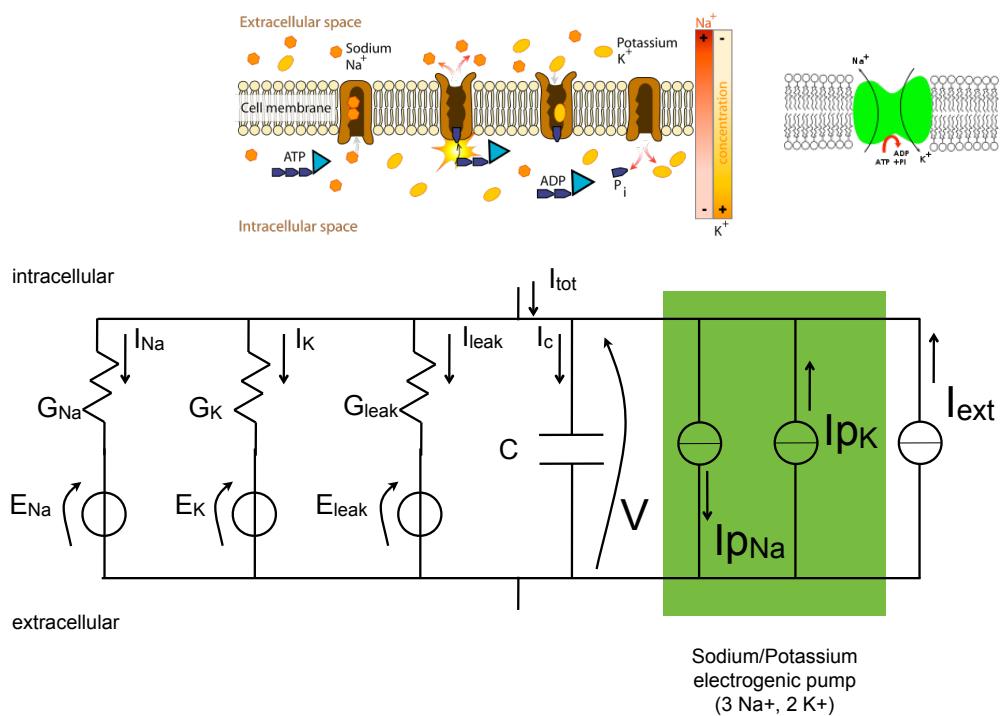
D. Linaro



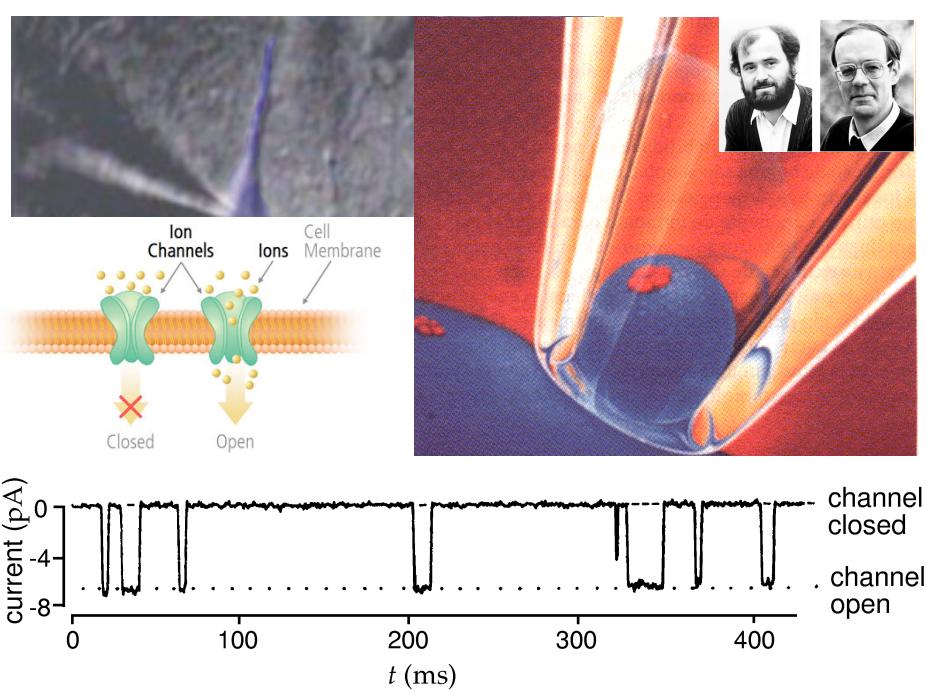
Spike-frequency adaptation (accommodation)



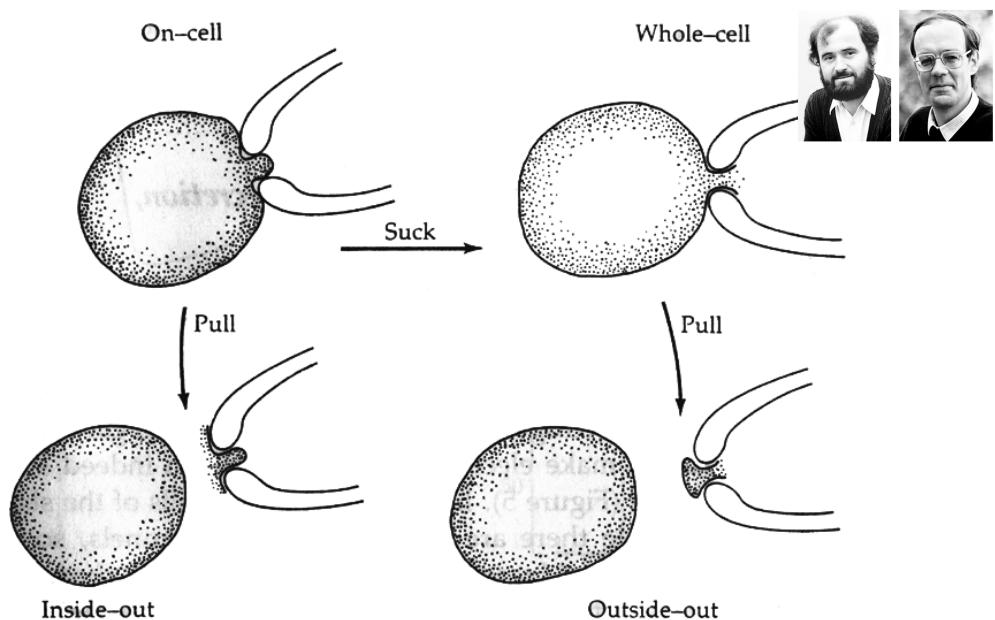
### Including the effects of electrogenic ion pumps: $\text{Na}^+/\text{K}^+$ -ATPase



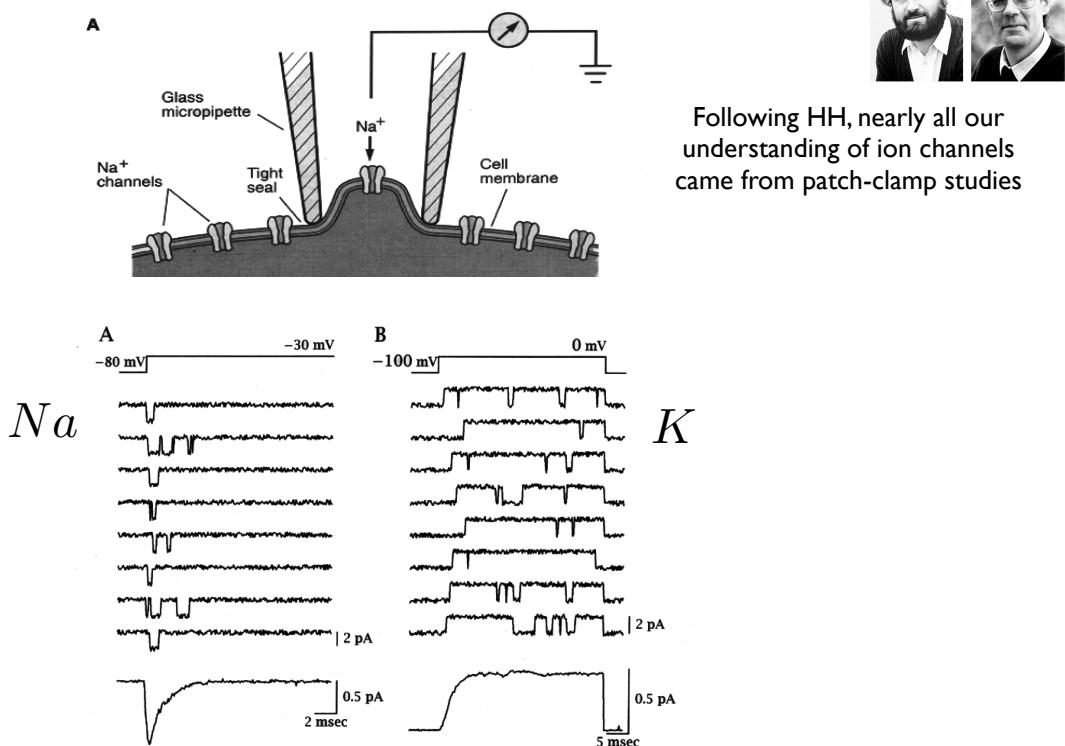
(Microscopically) membrane permeability: patch-clamp electrophysiology  
discrete, **not** distributed property; stochastic, **not** deterministic phenomena



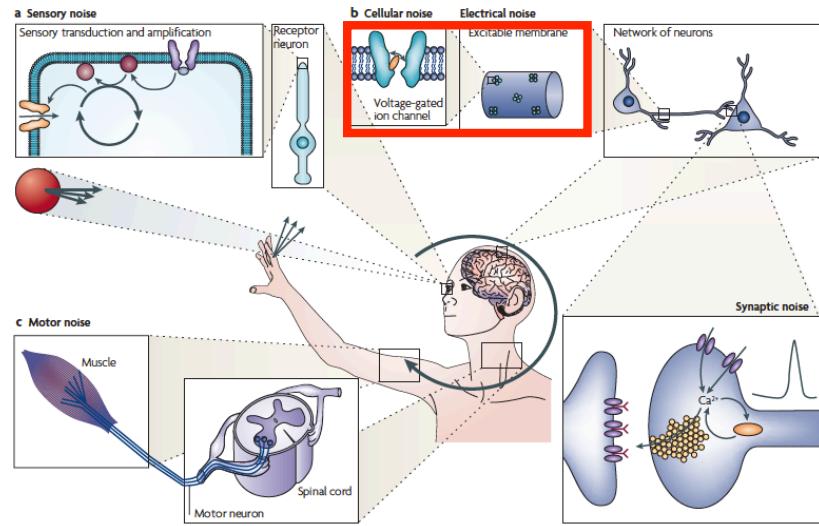
(Microscopically) membrane permeability: patch-clamp electrophysiology  
 discrete, **not** distributed property; stochastic, **not** deterministic phenomena



### Patch-Clamp Reveals Single Ion Channels



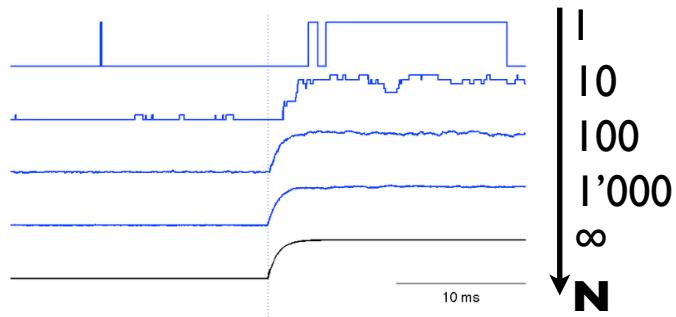
# Impact of “Noise” in cellular and network-level electrophysiology



adapted from Faisal et al., 2008

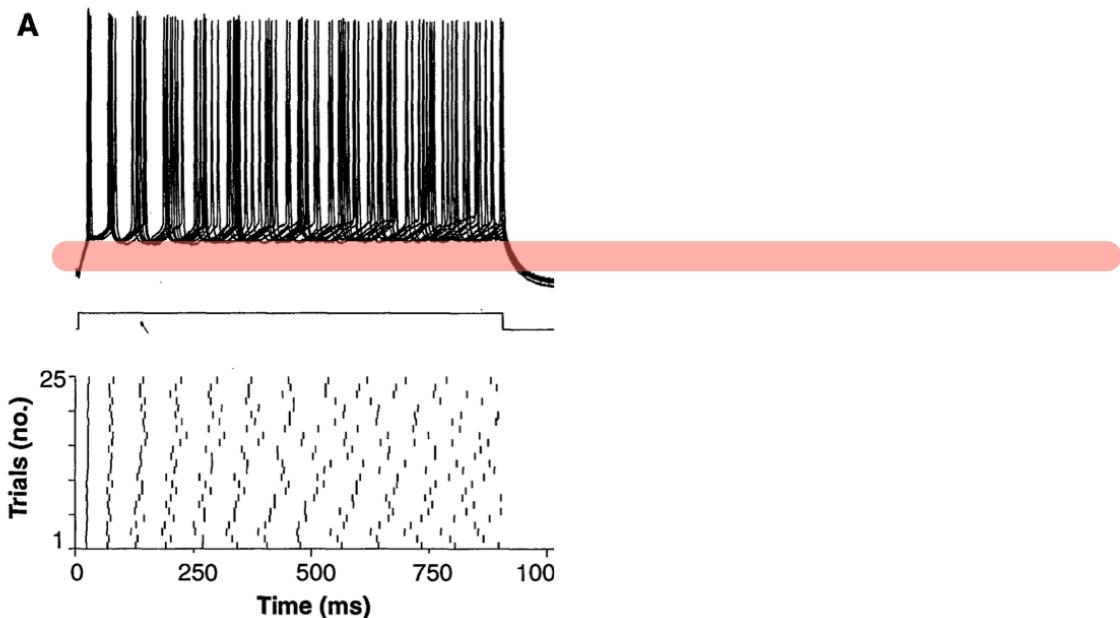
**Single ion-channels undergo stochastic transitions among conformational states**

**Channel flickering is a noise source**

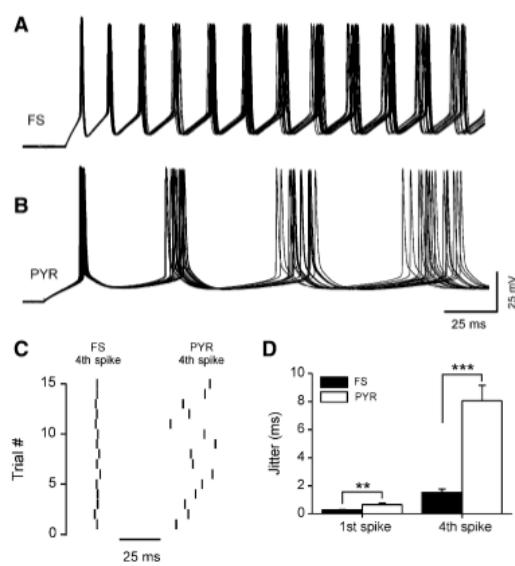


- **Markovian formulation** (i.e. microscopic, exact)
- **Langevin formulation** (i.e. effective, approximate)

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

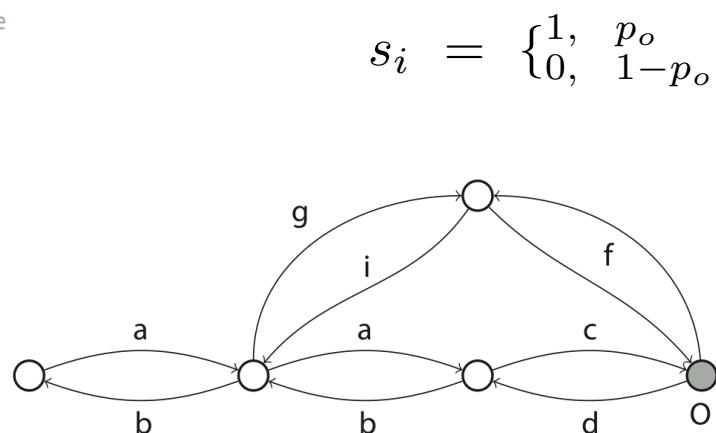
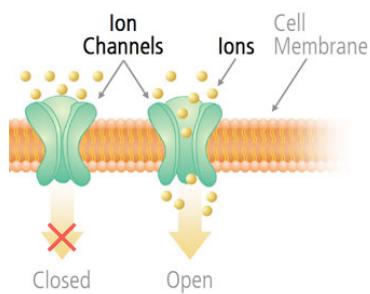


**Fast-spiking (FS) interneurons are more precise than pyramidal neurons: why?**



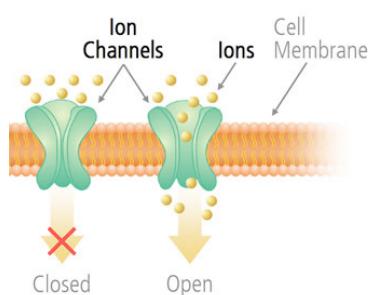
Bacci & Huguenard, 2006

# Markovian formulation



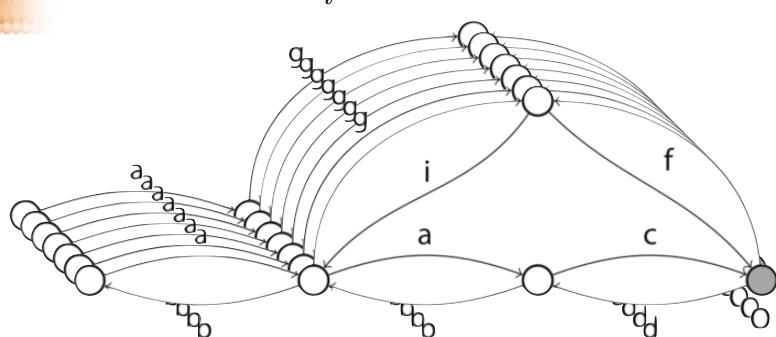
adapted from Vandenberg & Bezanilla, 1991

# 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

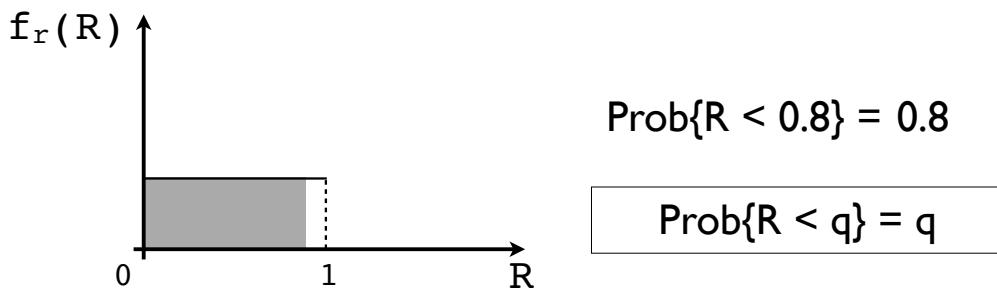
# How do I “generate” a random event???

(a *random* transition)

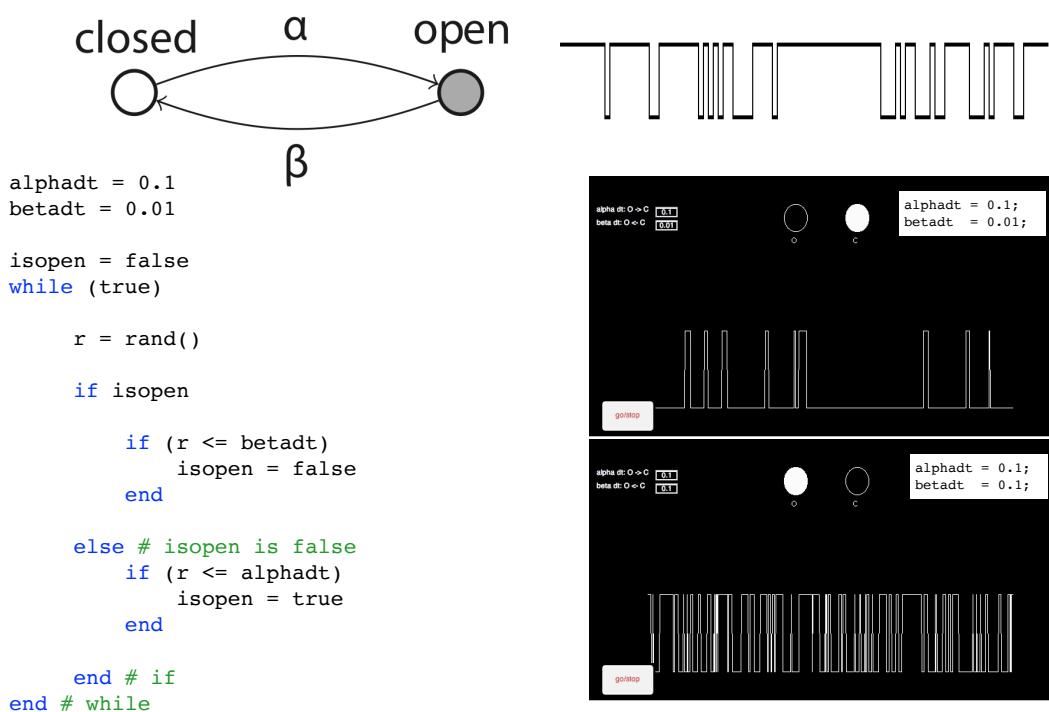
$$Pr\{A \rightarrow B \text{ in } (t ; t + \Delta t] / \text{state } A \text{ at } t\} = k_1 \Delta t + O(\Delta t)$$

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

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

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

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

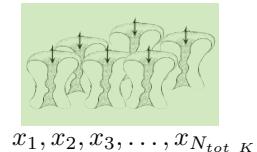
$$\frac{d\bar{x}}{dt} = -(k_1 + k_2) \bar{x} + k_2 \quad \text{Ensemble-average = det. description}$$

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

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

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

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



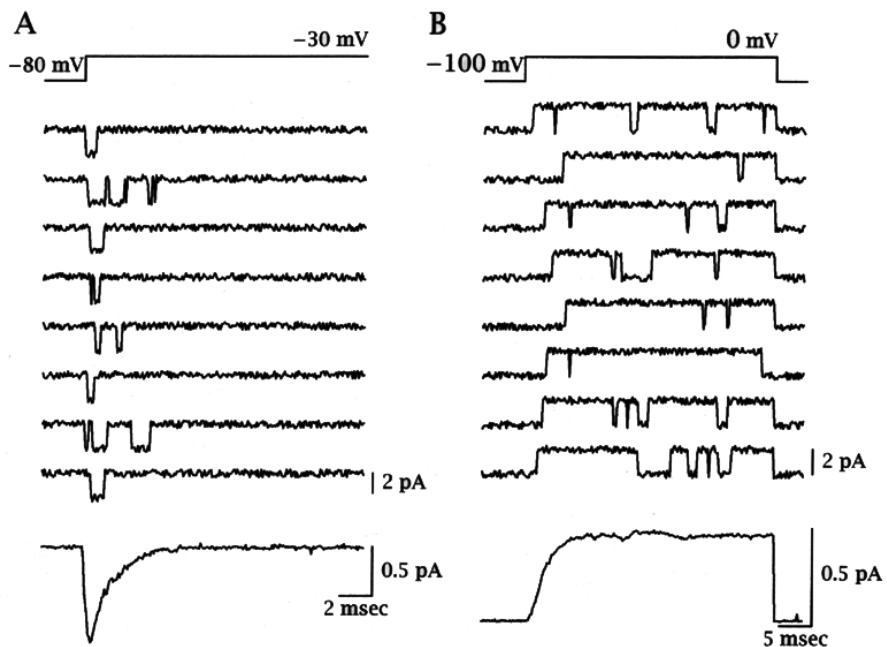
$x_1, x_2, x_3, \dots, x_{N_{tot \ K}}$

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

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

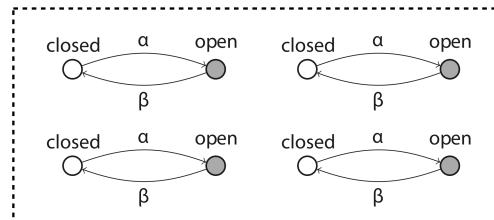
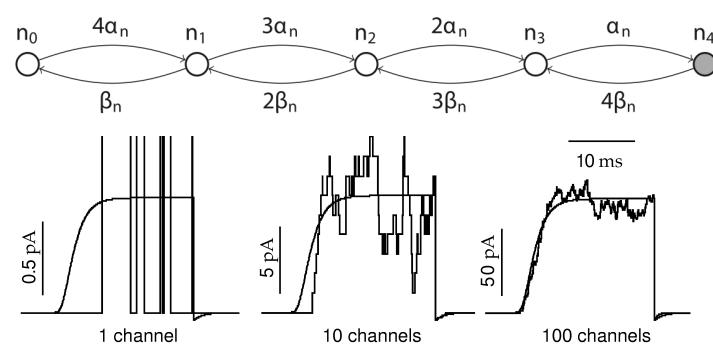
Large number theorem says that “for very large  $N_{tot \ K}$ , the chances that  $n$  takes actual values close to its expected value  $E\{n\}$ , are very high.  
(Kolmogorov’s inequality)

Inactivating (e.g.  $\text{Na}^+$ ) and non-inactivating (e.g.  $\text{K}^+$ ) ionic channels



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

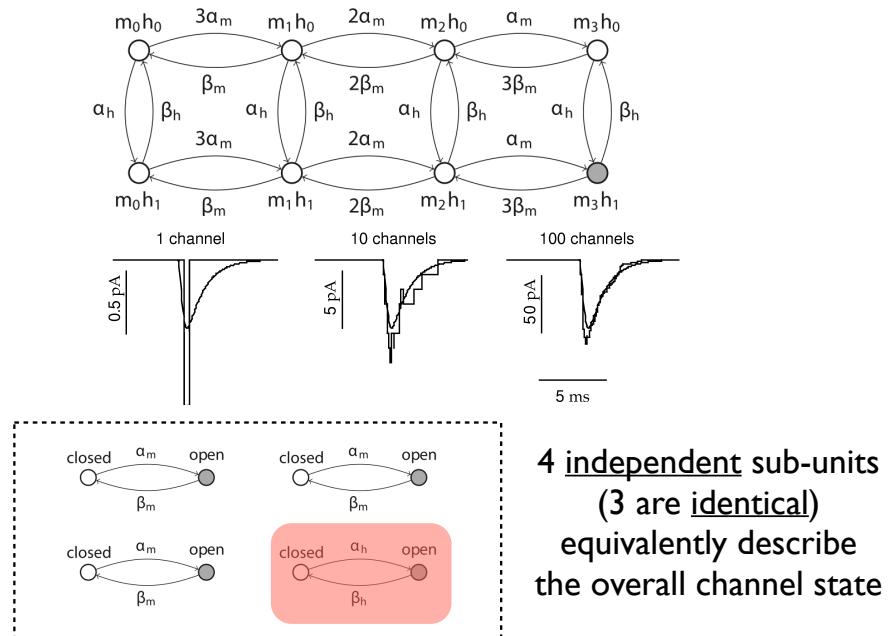
e.g.  $\text{K}^+$ , delayed-rectifier channel



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

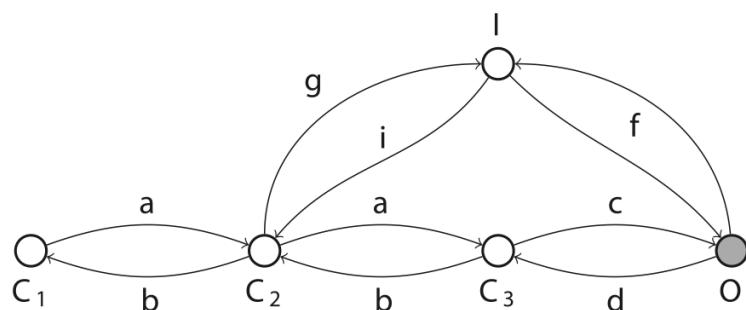
e.g. Na<sup>+</sup>, fast-inactivating channel



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

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

e.g. Na<sup>+</sup>, fast-inactivating (alternative, non HH-description)



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

# Langevin-like formulation

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

- 1) 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)

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

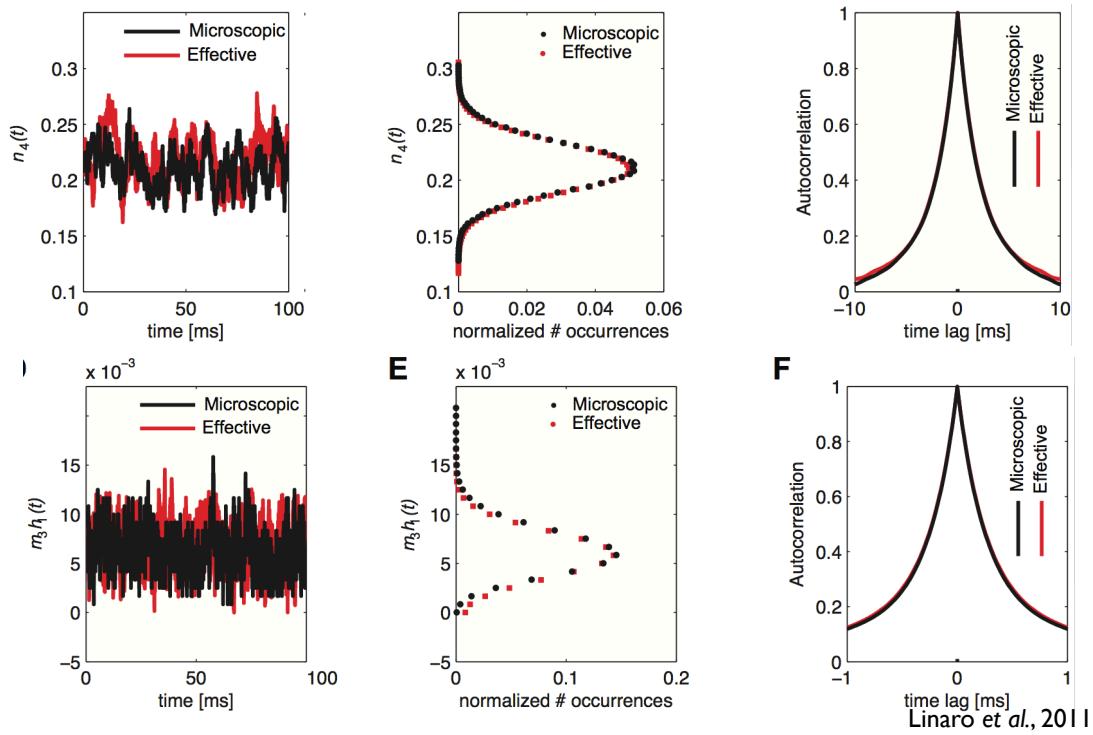
Linaro *et al.*, 2011

Steinmetz *et al.*, 2000

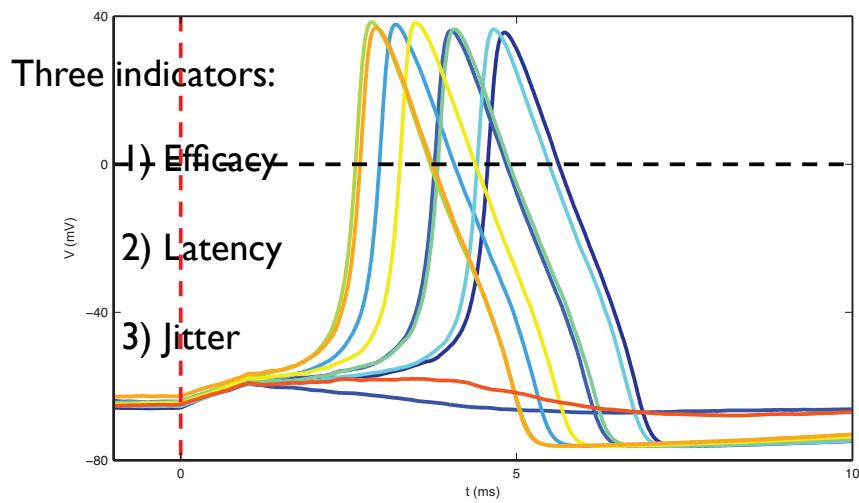
Conti & Wanke, 1975

1. Determine analytically the stochastic properties (mean and covariance) 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)



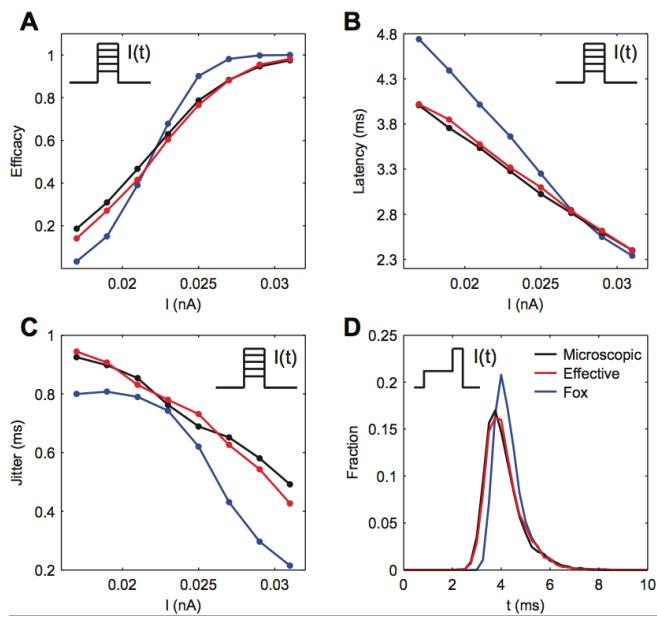
## dynamical PROPERTIES action potentials



Linaro et al., 2011

# dynamical PROPERTIES

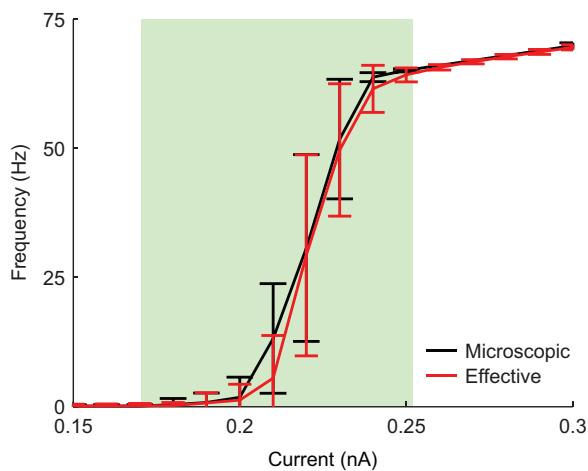
action potentials



Linaro et al., 2011

# dynamical PROPERTIES

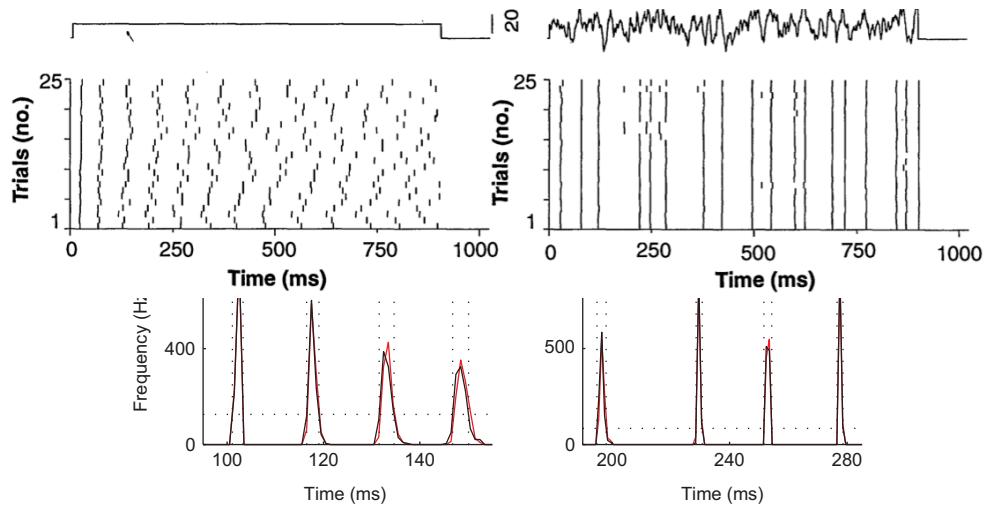
$F$ - $/$  curves



Linaro et al., 2011

# dynamical PROPERTIES

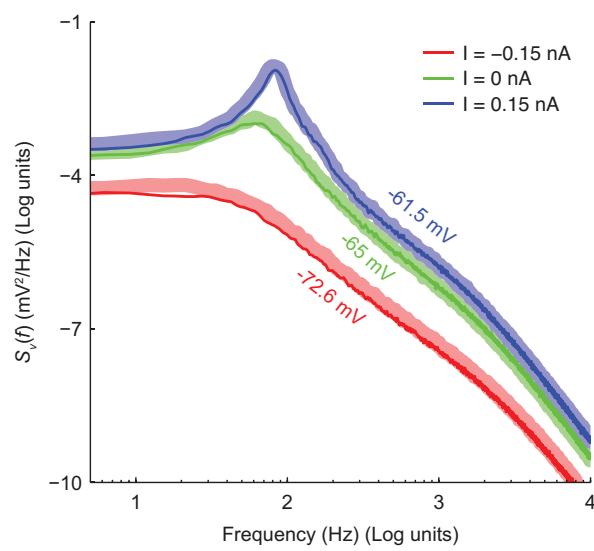
reliability



Linaro et al., 2011

# dynamical PROPERTIES

subthreshold voltage fluctuations, power-spectra



Linaro et al., 2011