

# Modélisation des circuits neuronaux

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<http://cns.iaf.cnrs-gif.fr>

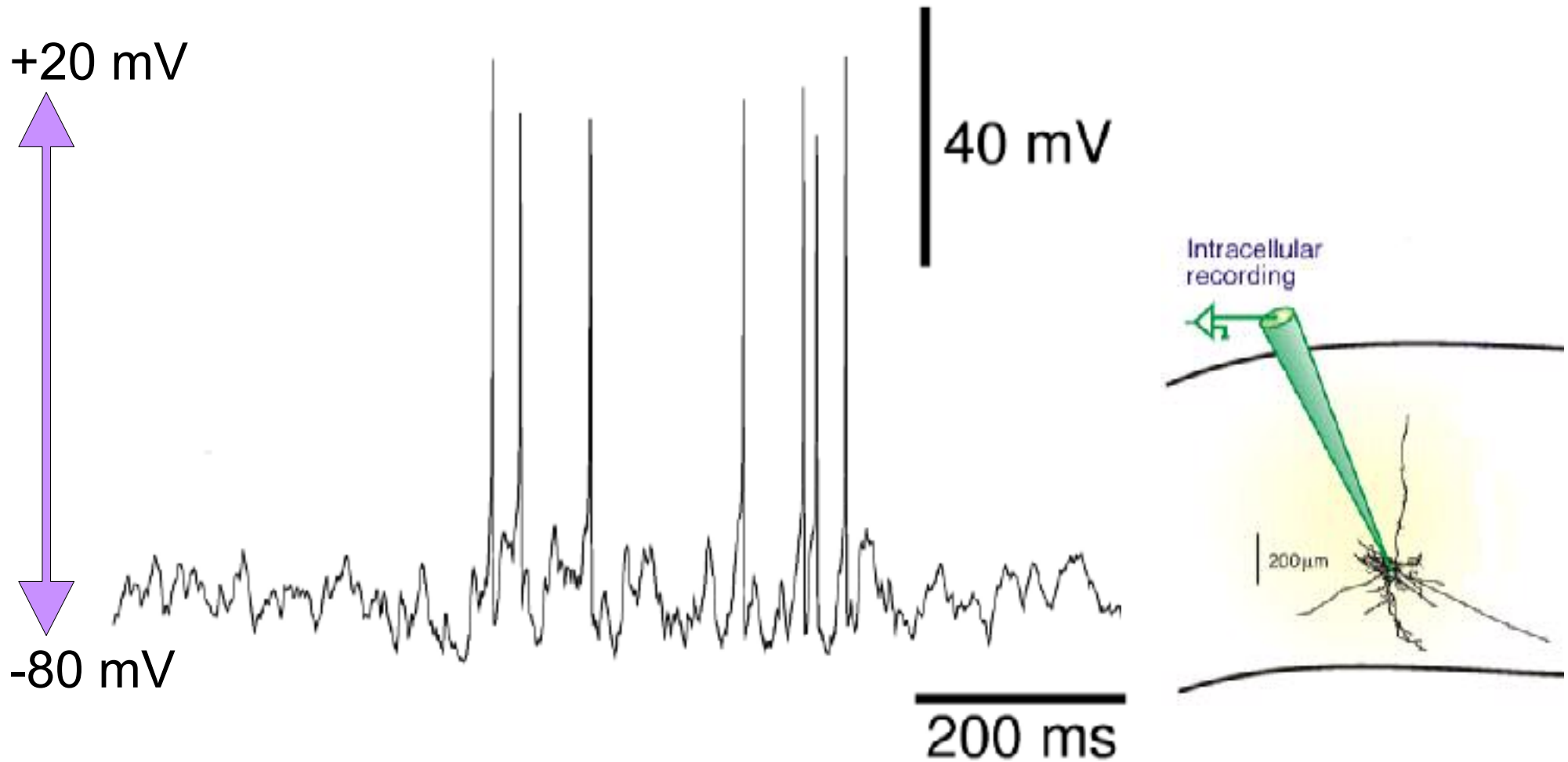


- 1875: découverte de l'EEG par Caton
- 1930: "Circus Movement Theory" (Rothberger, 1931; Bishop, 1936)
- 1940: démonstration que l'EEG provient de potentiels post-synaptiques (Renshaw et al., 1940)
- 1938: première théorie de la genèse de l'EEG basée sur la synchronisation des neurones (Bremer, 1938, 1949); première évocation du concept de *propriétés intrinsèques* des neurones
- 1951: première étude intracellulaire (motoneurones; Brock et al., 1951)

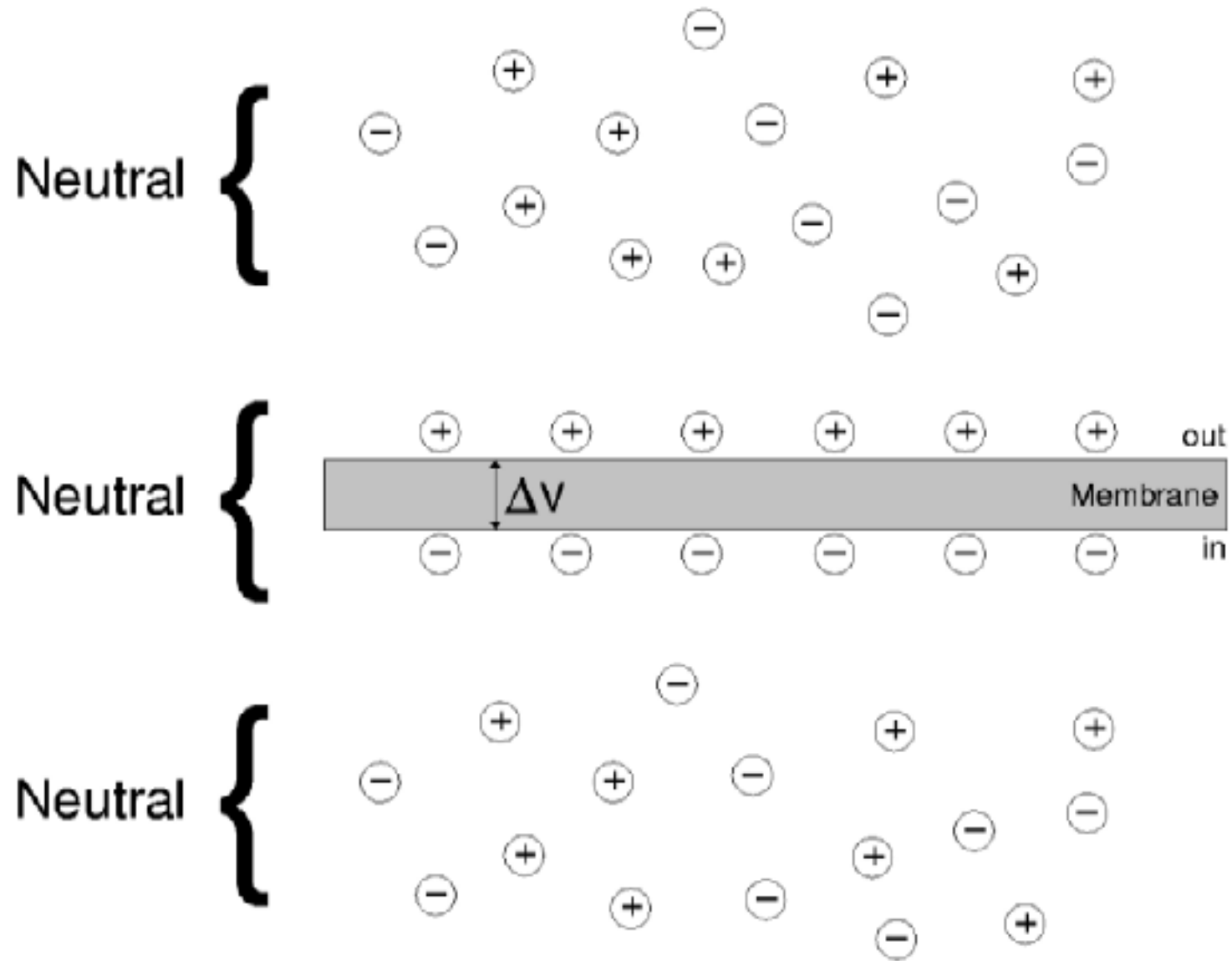
- 1951: naissance du concept d'*integrate-and-fire* (Eccles, 1951);  
conception "connectionniste" du système nerveux central
- 1952: Hodgkin & Huxley expliquent les bases biophysiques des potentiels d'action (axone du calmar);  
naissance des concepts de *conductance* et de *courants ioniques*
- 1970: premiers travaux démontrant l'importance des propriétés intrinsèques des neurones chez les invertébrés (Connor & Stevens, 1971; Kandel, 1976)
- 1980: démonstration du rôle des propriétés intrinsèques dans le système nerveux central (cfr. revue de Llinás, 1988).

1. Modélisation des propriétés passives de la membrane: Circuit électrique équivalent
2. Modélisation des propriétés actives de la membrane I: Formalisme de Hodgkin-Huxley
3. Modélisation des propriétés actives de la membrane II: Propriétés neuronales intrinseques
4. Modélisation des interactions synaptiques
5. Applications: Oscillations dans les circuits de neurones du thalamus

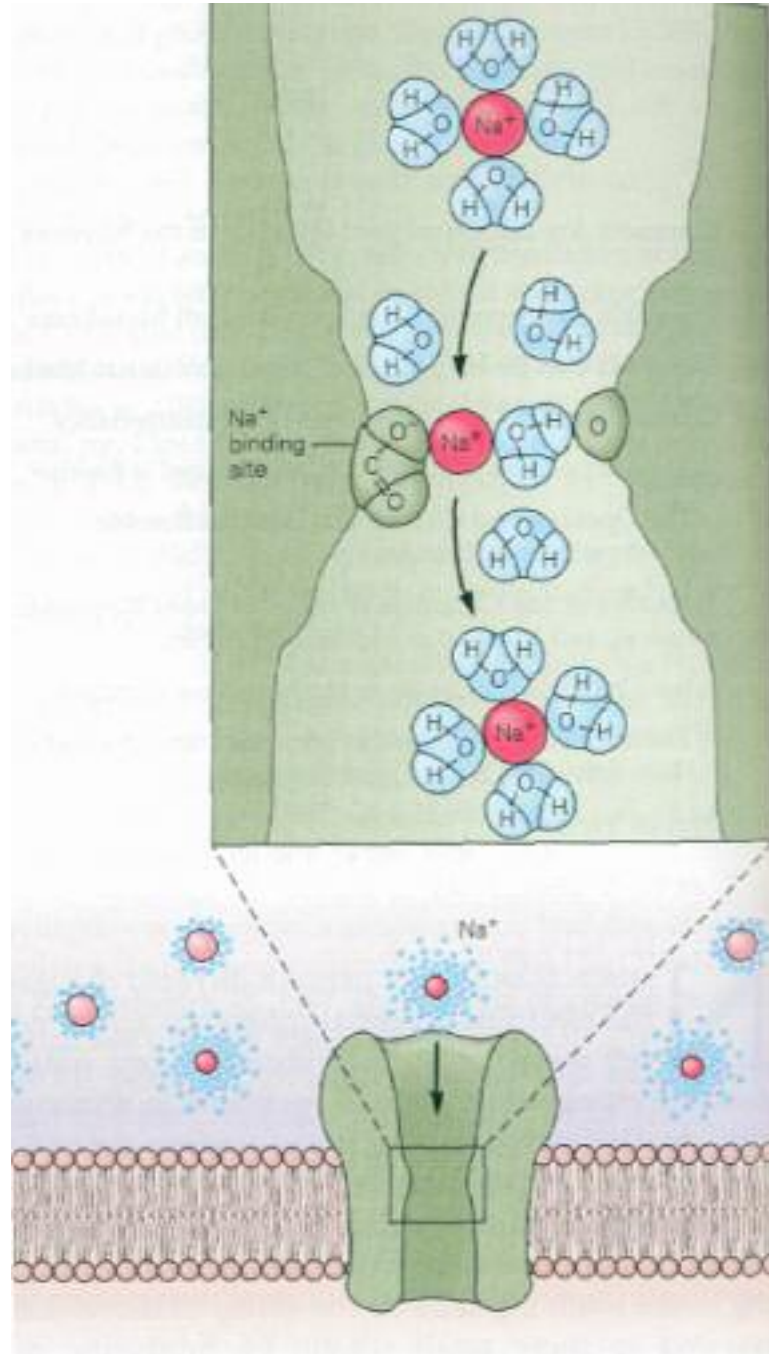
# Potentiel de Membrane



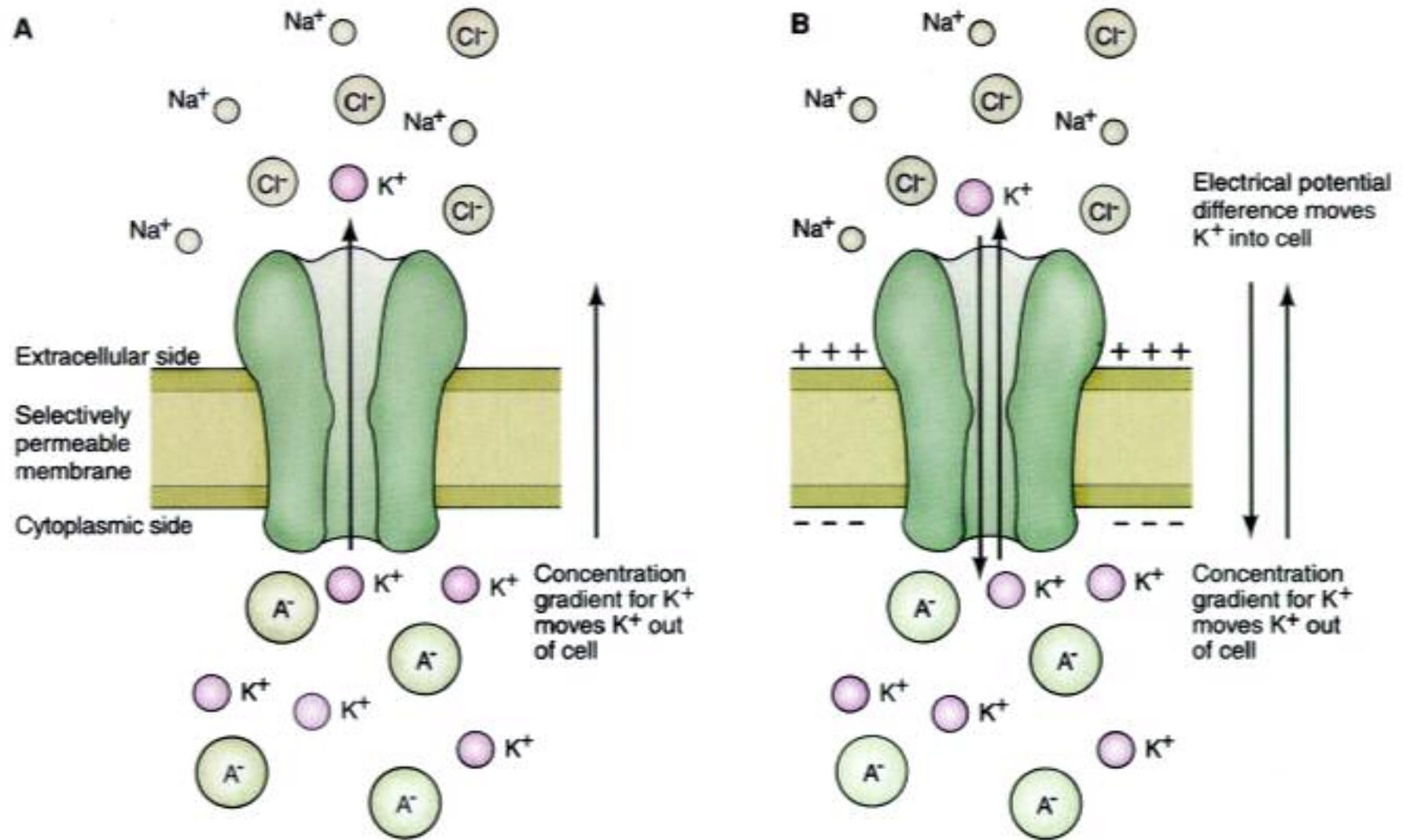
# Distribution de charges



Principe biophysique:  
La sélectivité ionique



# Potentiel de Membrane





Équation de Nernst:

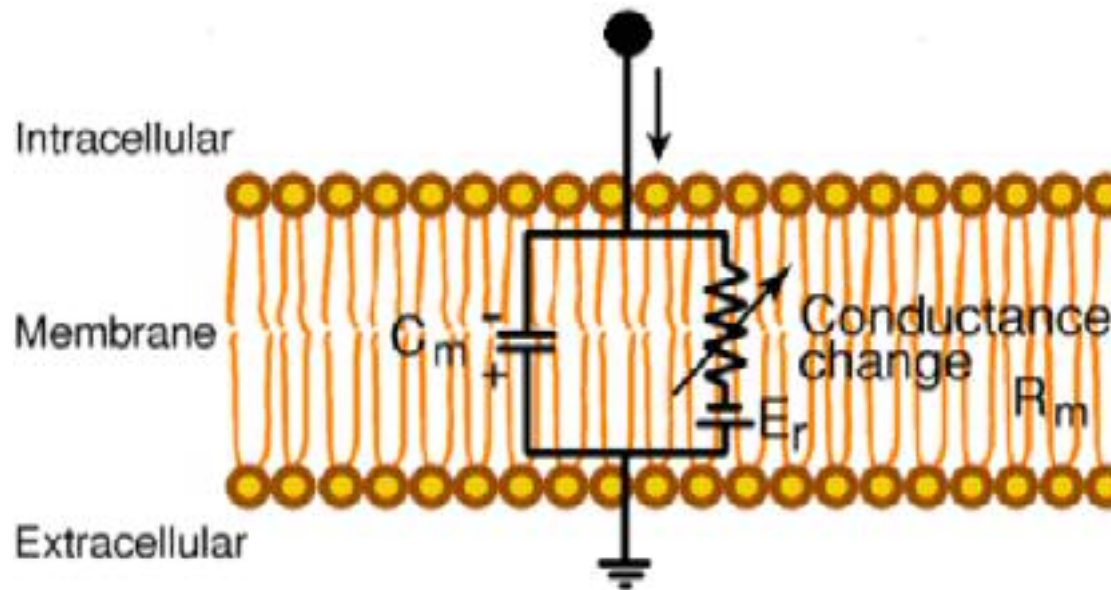
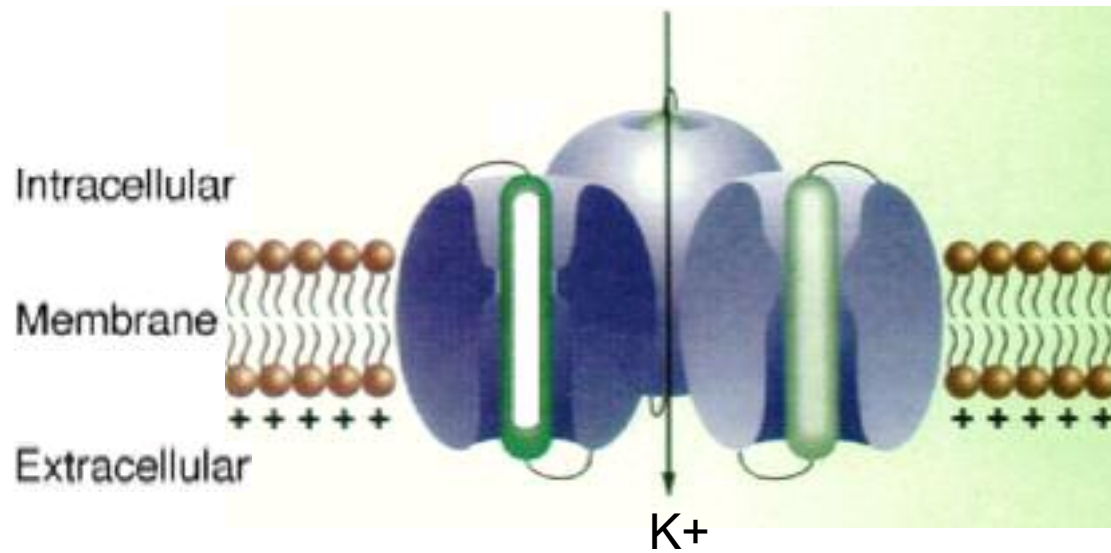
$$E_K = \frac{RT}{F} \log \frac{[K]_o}{[K]_i}$$

où:

$[K]_o$  = concentration extracellulaire en  $K^+$

$[K]_i$  = concentration intracellulaire en  $K^+$

# The neuronal membrane acts as a RC circuit



Loi d'Ohm:

$$I_K = g_K (V - E_K)$$

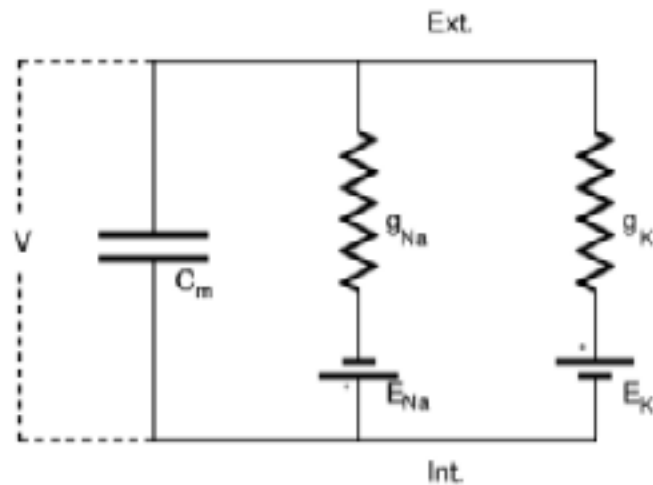
où:

$I_{ion}$  = *courant ionique* (potassium)

$g_K$  = *conductance* du courant  $K^+$

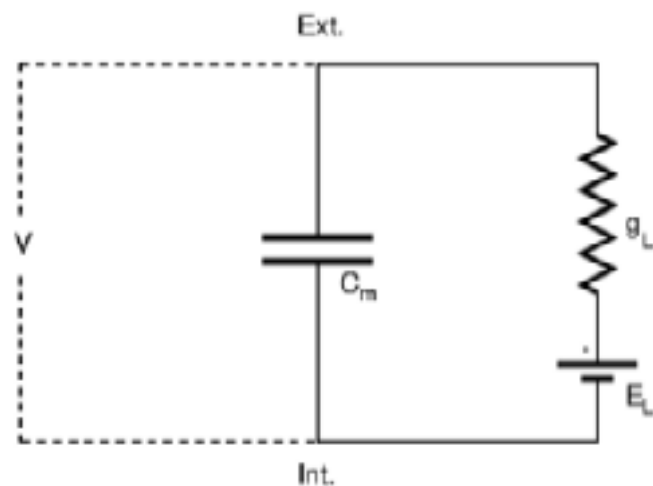
$E_K$  = *potentiel d'équilibre* ou *potentiel d'inversion* du  $K^+$

A



$$C_m \frac{dV}{dt} = -g_{Na} (V - E_{Na}) - g_K (V - E_K)$$

B

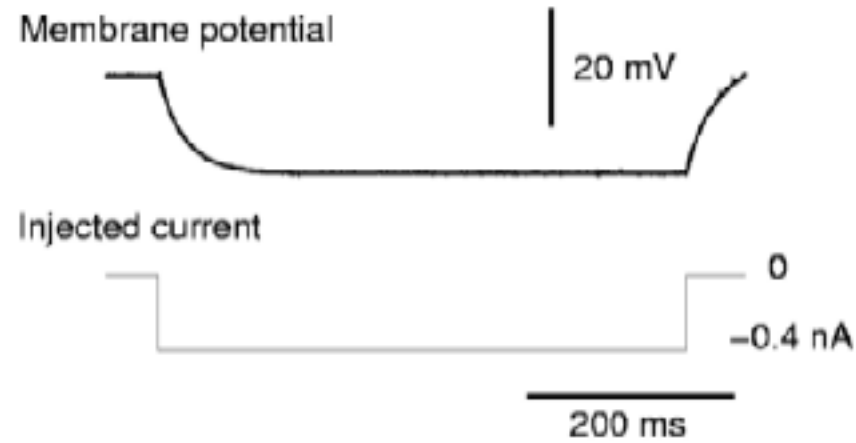


$$C_m \frac{dV}{dt} = -g_L (V - E_L)$$

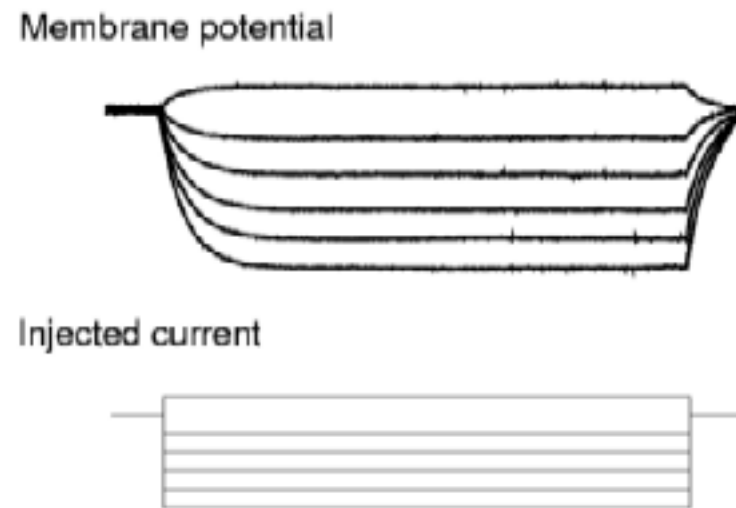
$$g_L = g_{Na} + g_K$$

$$E_L = \frac{g_{Na} E_{Na} + g_K E_K}{g_{Na} + g_K}$$

A

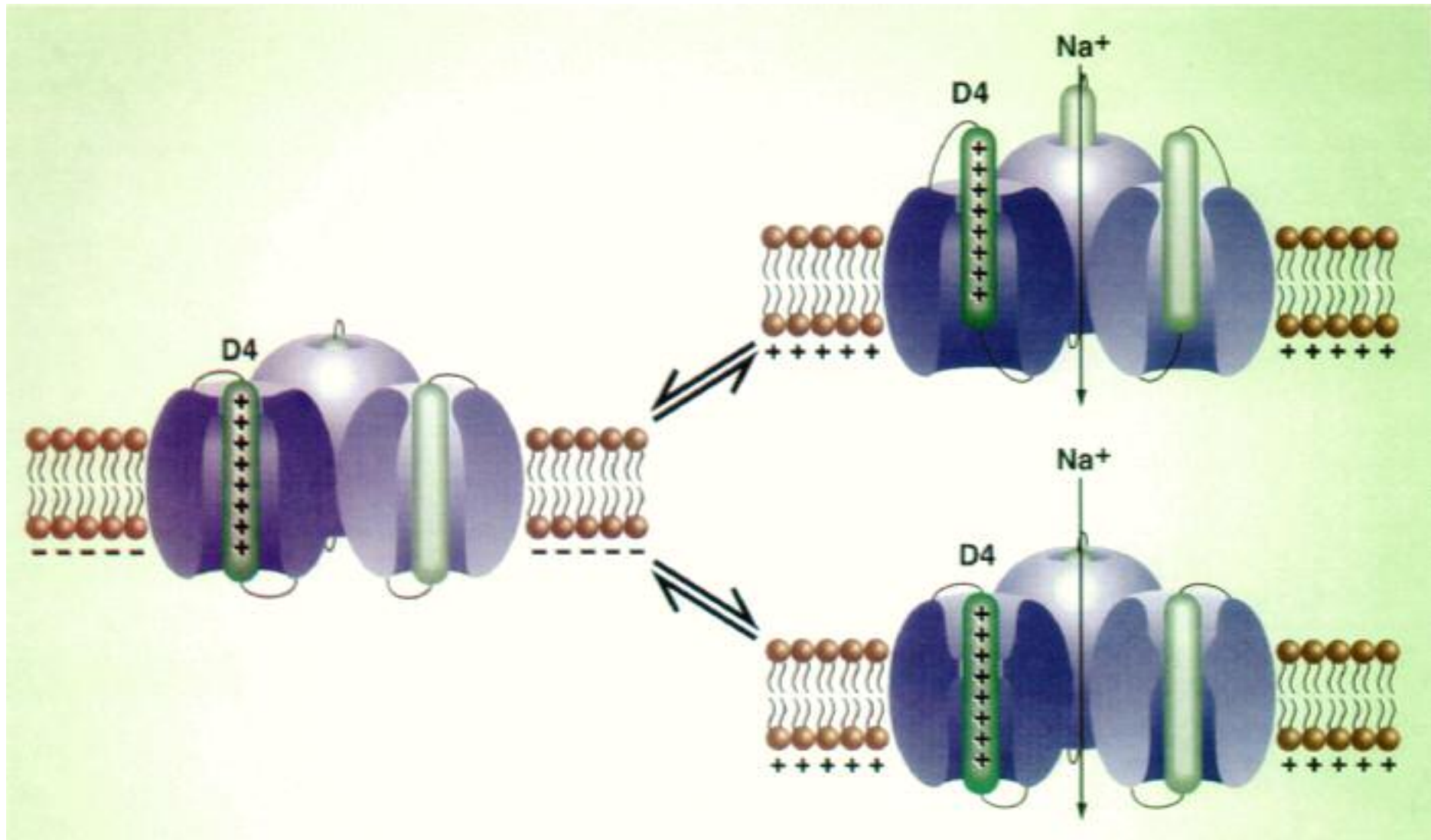


B

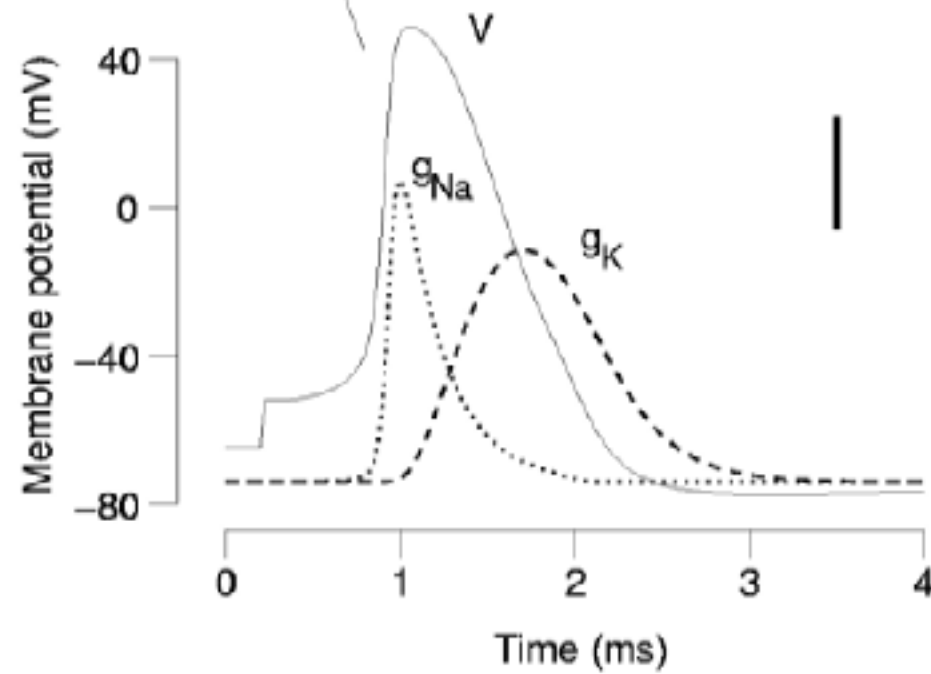
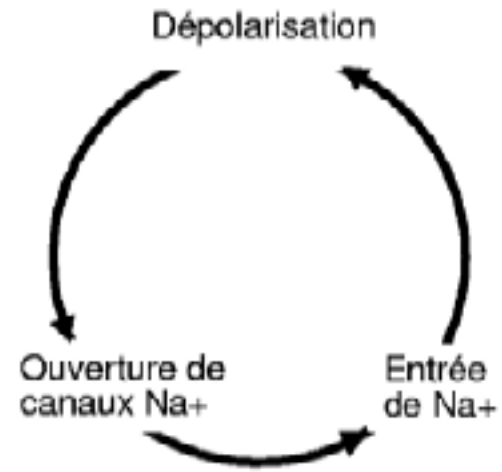


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# Voltage dependence

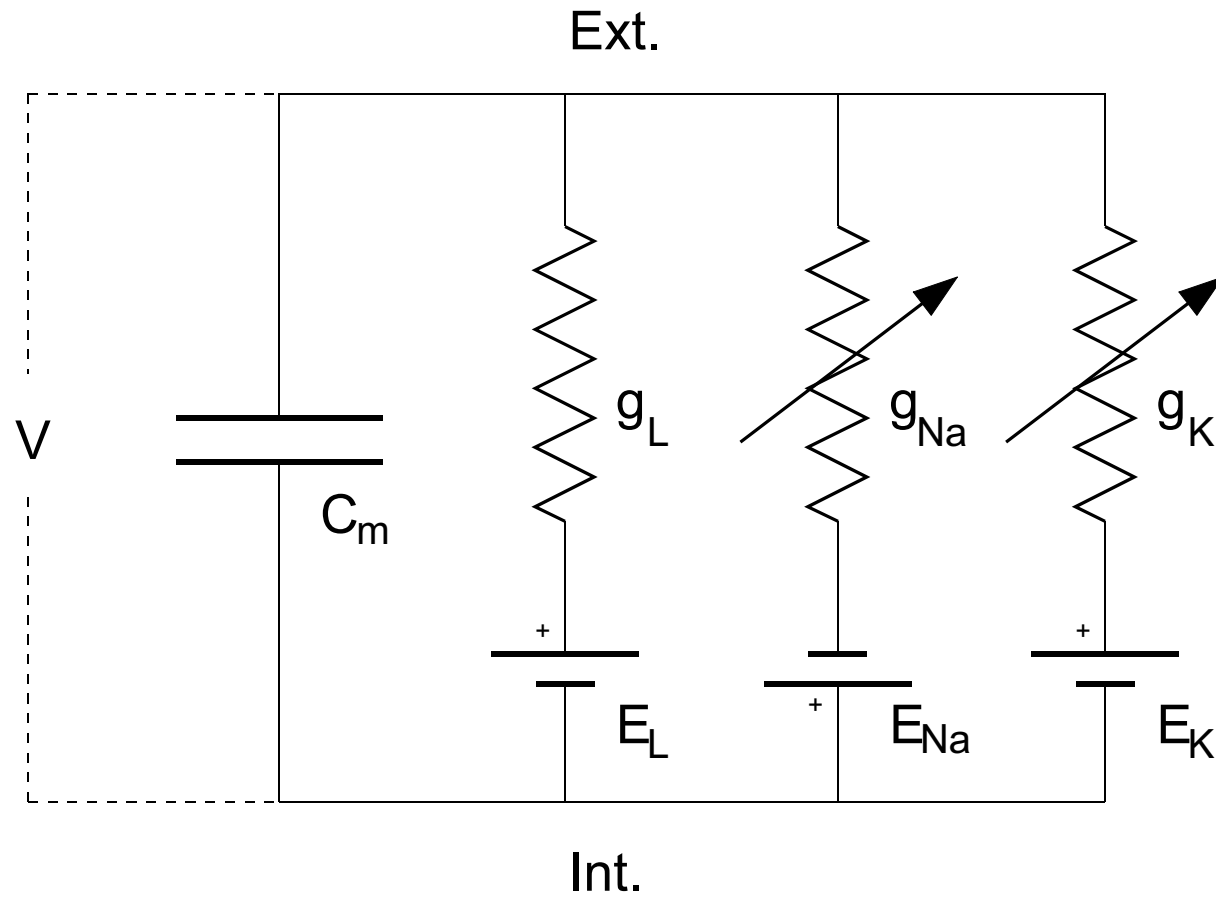


# The Hodgkin-Huxley model

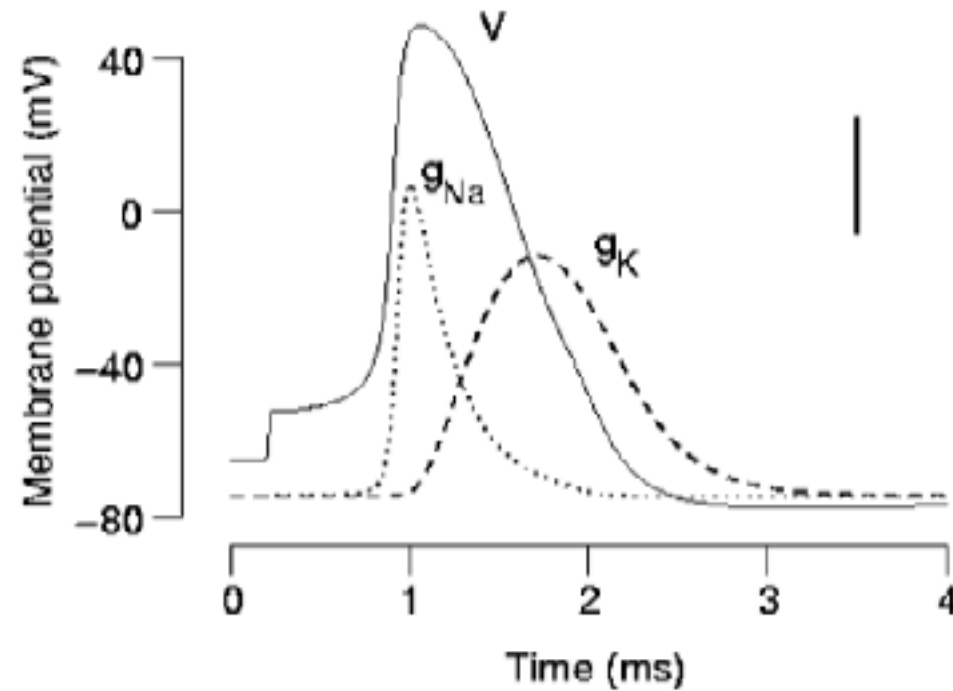




# Equivalent electrical circuit of the membrane



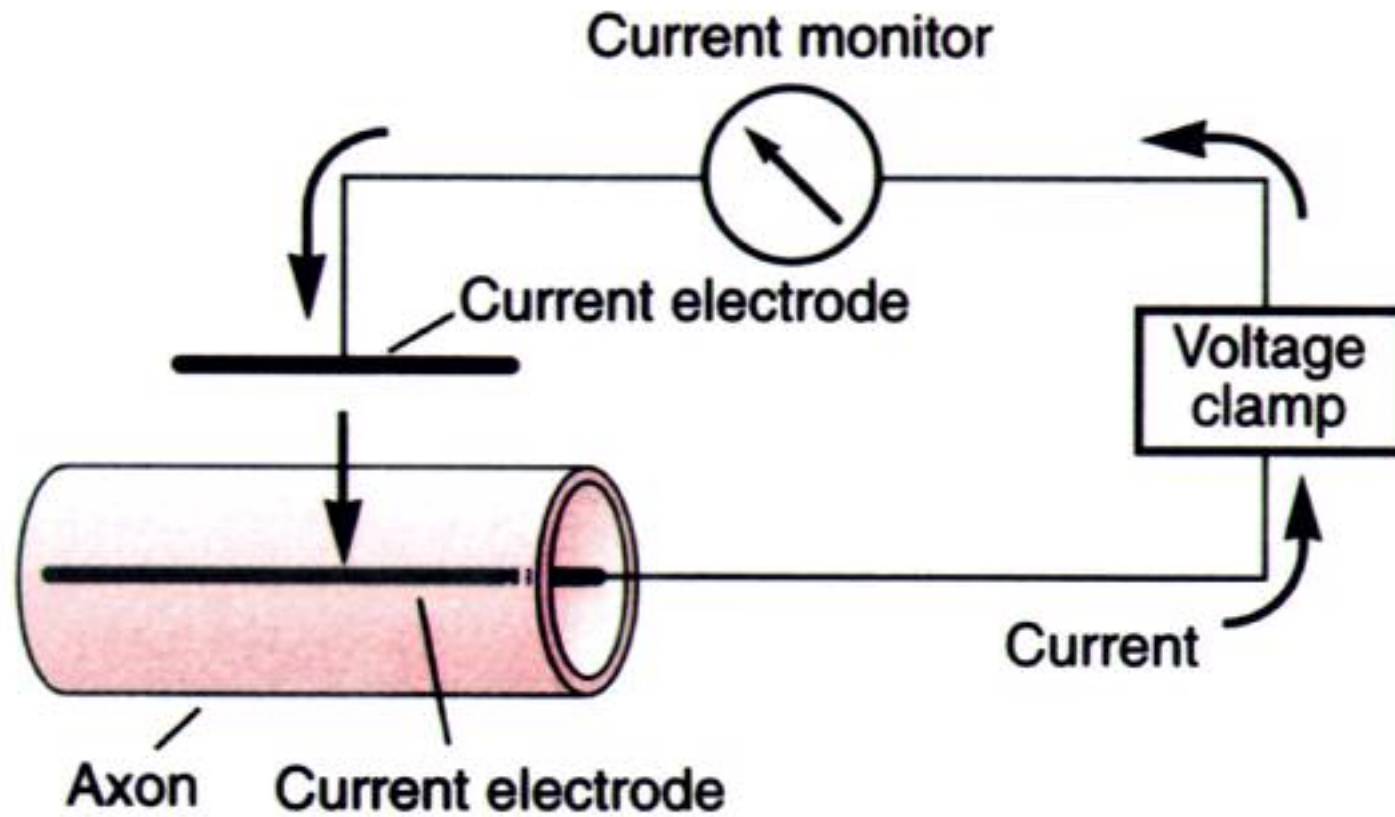
# The Hodgkin-Huxley model



$$C_m \frac{dV}{dt} = -g_L (V - E_L) - g_{Na}(V) (V - E_{Na}) - g_K(V) (V - E_K)$$

From: Hodgkin & Huxley  
J. Physiol., 1952

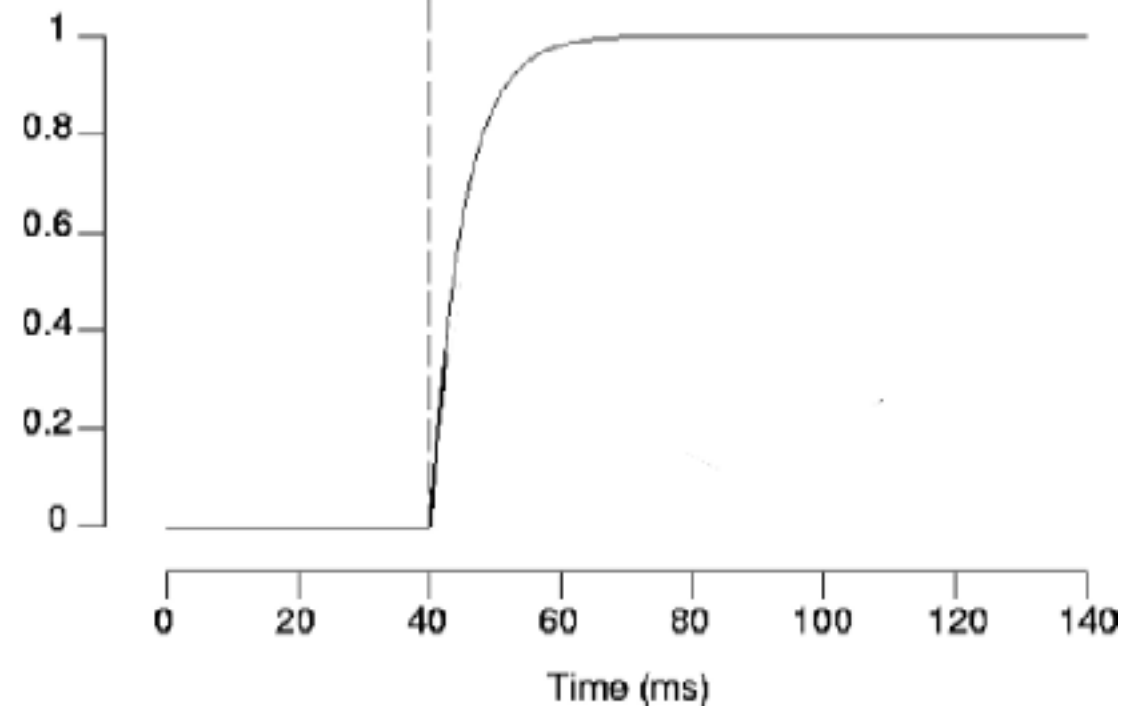
# Voltage-clamp



Voltage:

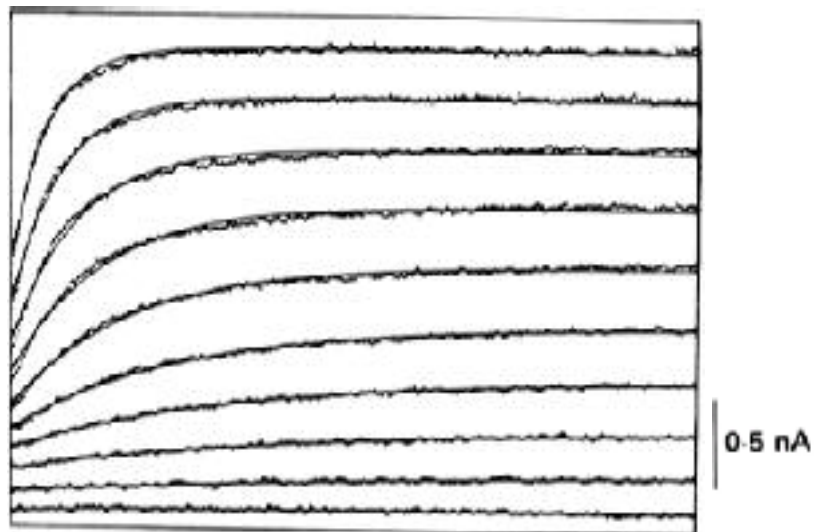
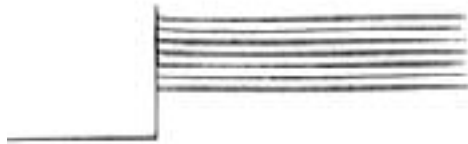


Current:



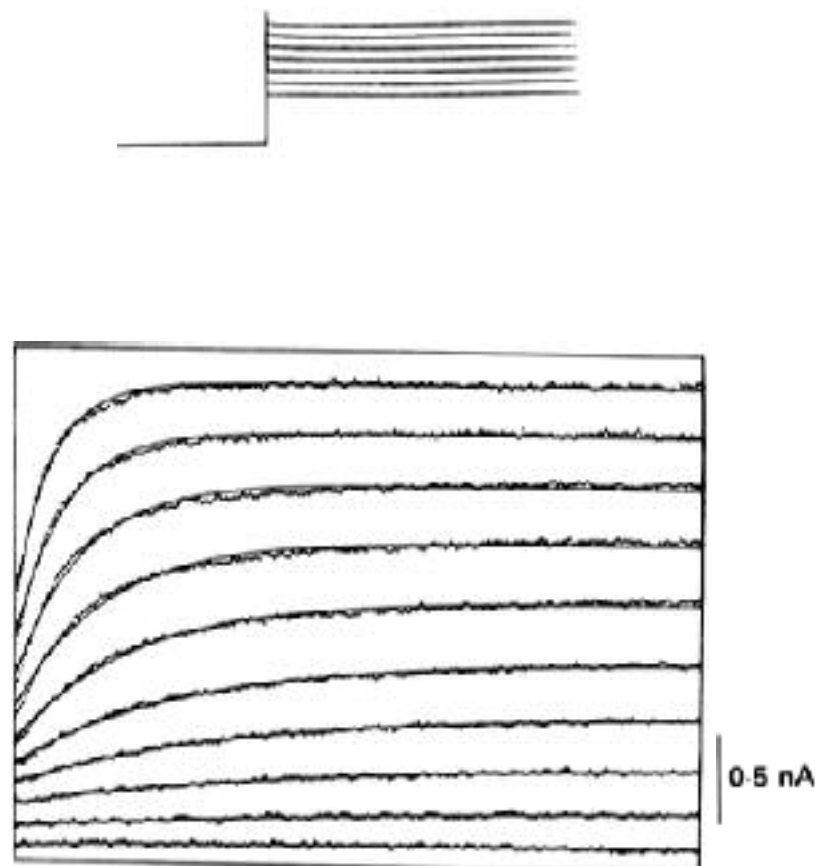
# Voltage-clamp characterization of ionic currents

## 1. Voltage-clamp protocol

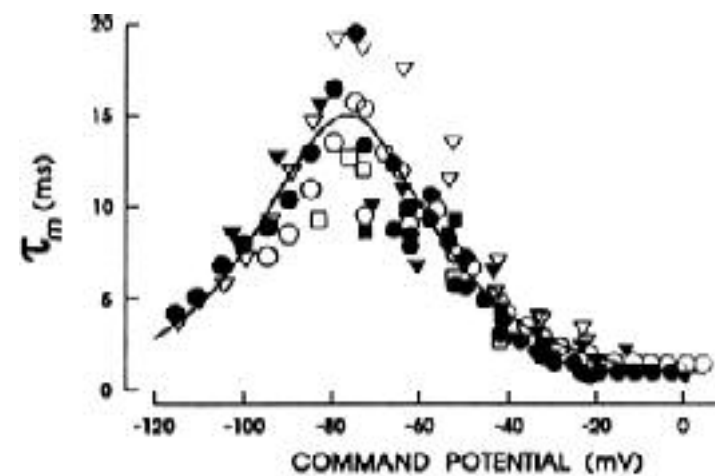
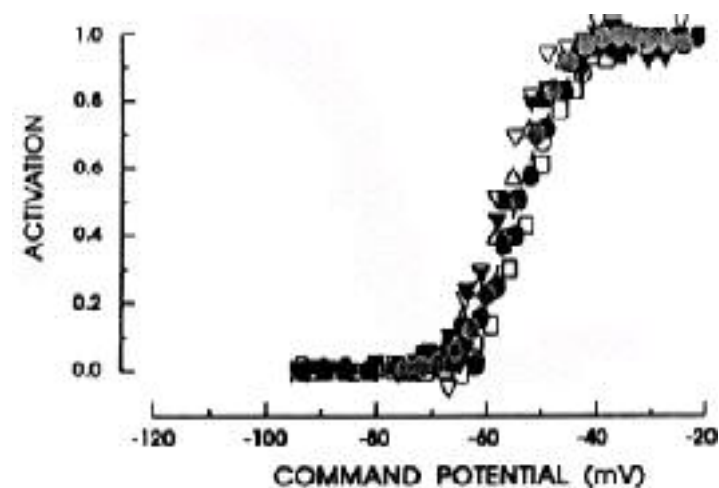


# Voltage-clamp characterization of ionic currents

## 1. Voltage-clamp protocol



## 2. Voltage dependence of steady-state activation and time constant



# Origin of voltage-dependence

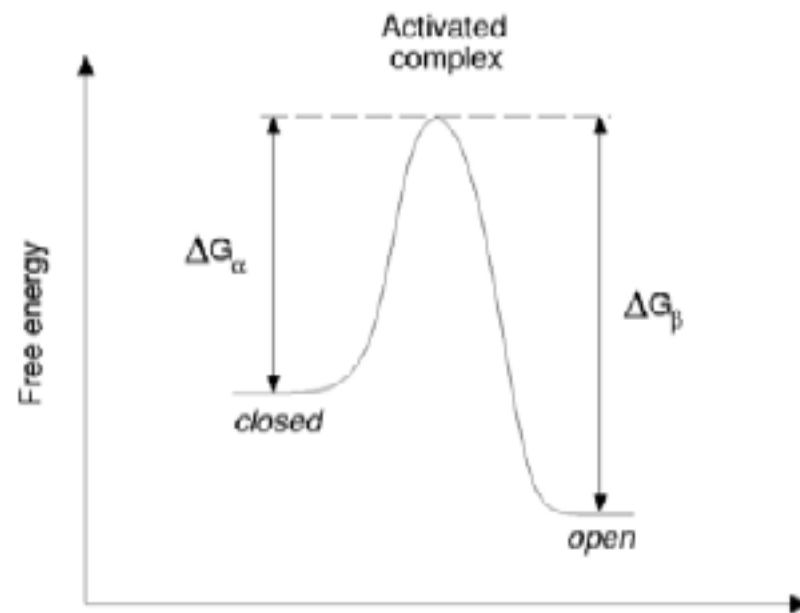
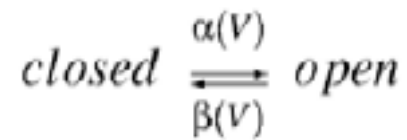


Closed



Open

# Origin of voltage-dependence



$\Delta G_\alpha$  : free energy barrier for the transition *closed*  $\rightarrow$  *open*

$\Delta G_\beta$  : free energy barrier for the transition *open*  $\rightarrow$  *closed*

$$\alpha(V) = v \exp \left[ -\frac{\Delta G_\alpha(V)}{kT} \right]$$

$$\beta(V) = v \exp \left[ -\frac{\Delta G_\beta(V)}{kT} \right]$$



## Voltage-dependence of rate constants

Low field limit:

$$\Delta G(V) = \Delta G_0 - \frac{V}{d} M_k - \frac{V^2}{2d^2} B_k + \dots$$

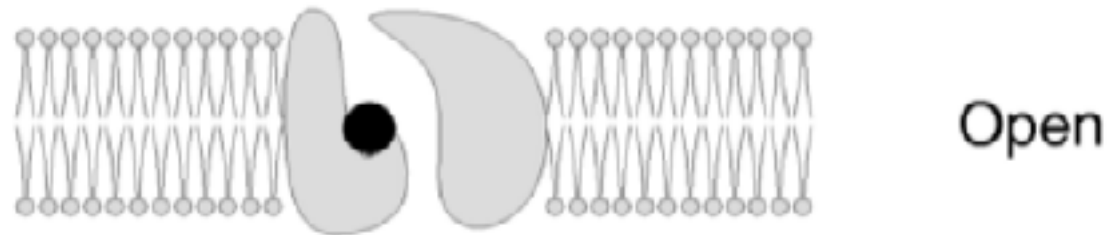
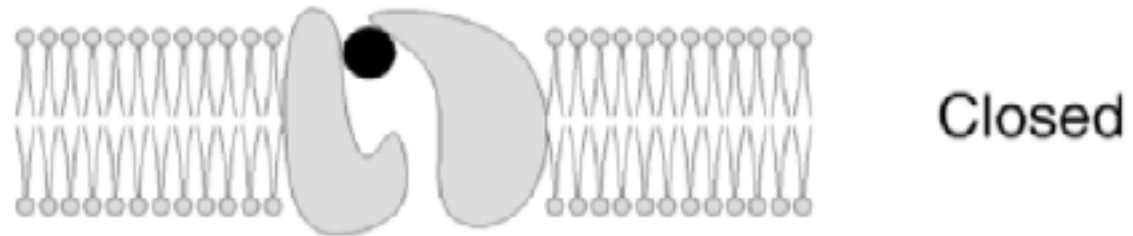
$M_k$  : dipole moment

$B_k$  : distortion polarizability

At first order: *simple exponential*:

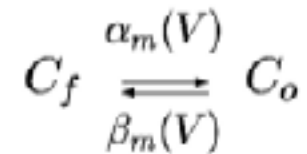
$$\alpha(V) = \exp \left[ -\frac{(a + bV)}{kT} \right]$$

# Origin of voltage-dependence



$$\Delta G \sim zFV$$

Modèle cinétique le plus simple:



où

$C_f$ : canal fermé

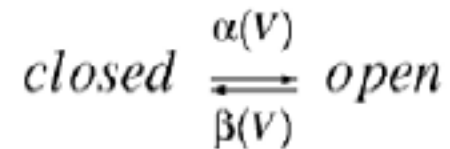
$C_o$ : canal ouvert

Si  $m$  est défini comme la fraction de canaux en configuration ouverte

$$m = \frac{[C_o]}{[C_f] + [C_o]},$$

on obtient:

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



If  $m$  is defined as the fraction of gates in the open state:

$$m = \frac{[\text{open}]}{[\text{open}] + [\text{closed}]},$$

the evolution of the system is given by the kinetic equation:

$$\begin{aligned} \frac{dm}{dt} &= \alpha(V) (1 - m) - \beta(V) m \\ &= \frac{1}{\tau_m} (m_\infty - m) \end{aligned}$$

- *Time constant:*  $\tau_m(V) = 1 / [\alpha(V) + \beta(V)]$
- *Steady-state activation:*  $m_\infty(V) = \alpha(V) / [\alpha(V) + \beta(V)]$

If  $\alpha(V)$  and  $\beta(V)$  are  
first-order exponentials:

$$m_\infty(V) = \frac{1}{1 + \exp\left[-\frac{(V - V_m)}{k_m}\right]}$$

$$g_{Na}(V) = \bar{g}_{Na} m$$

$$g_K(V) = \bar{g}_K n$$

Is this model sufficient to  
generate action potentials ?

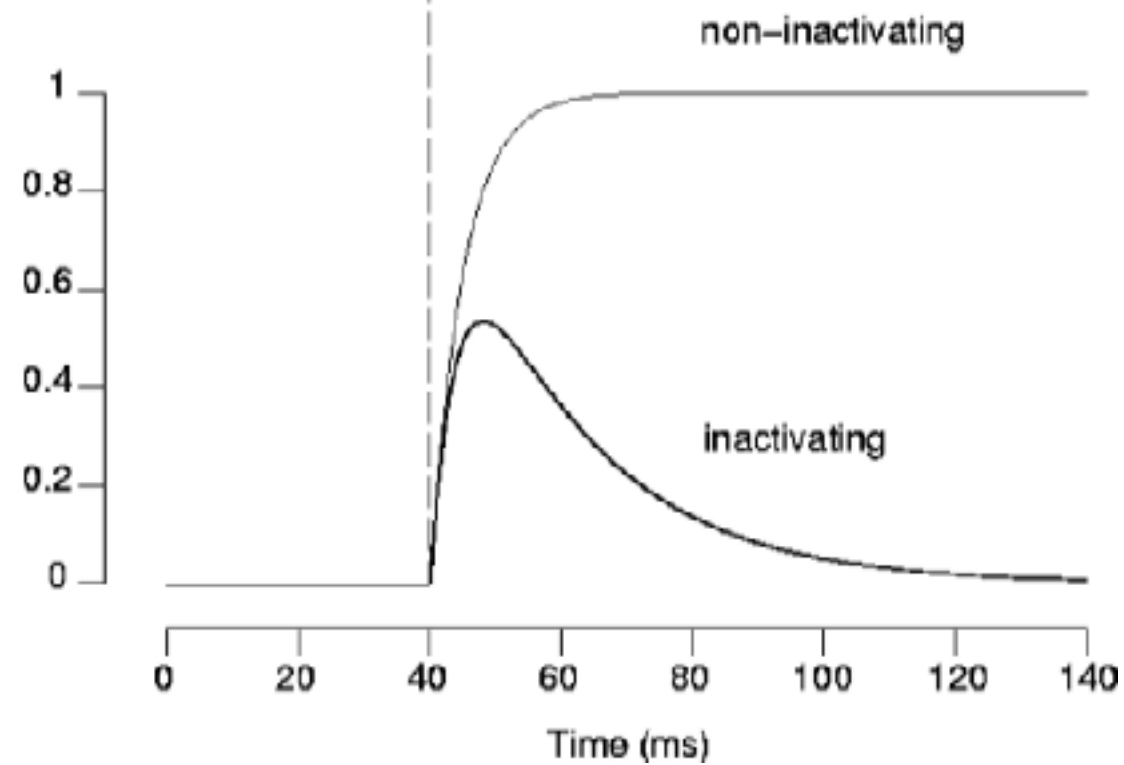
$$g_{Na}(V) = \bar{g}_{Na} m$$

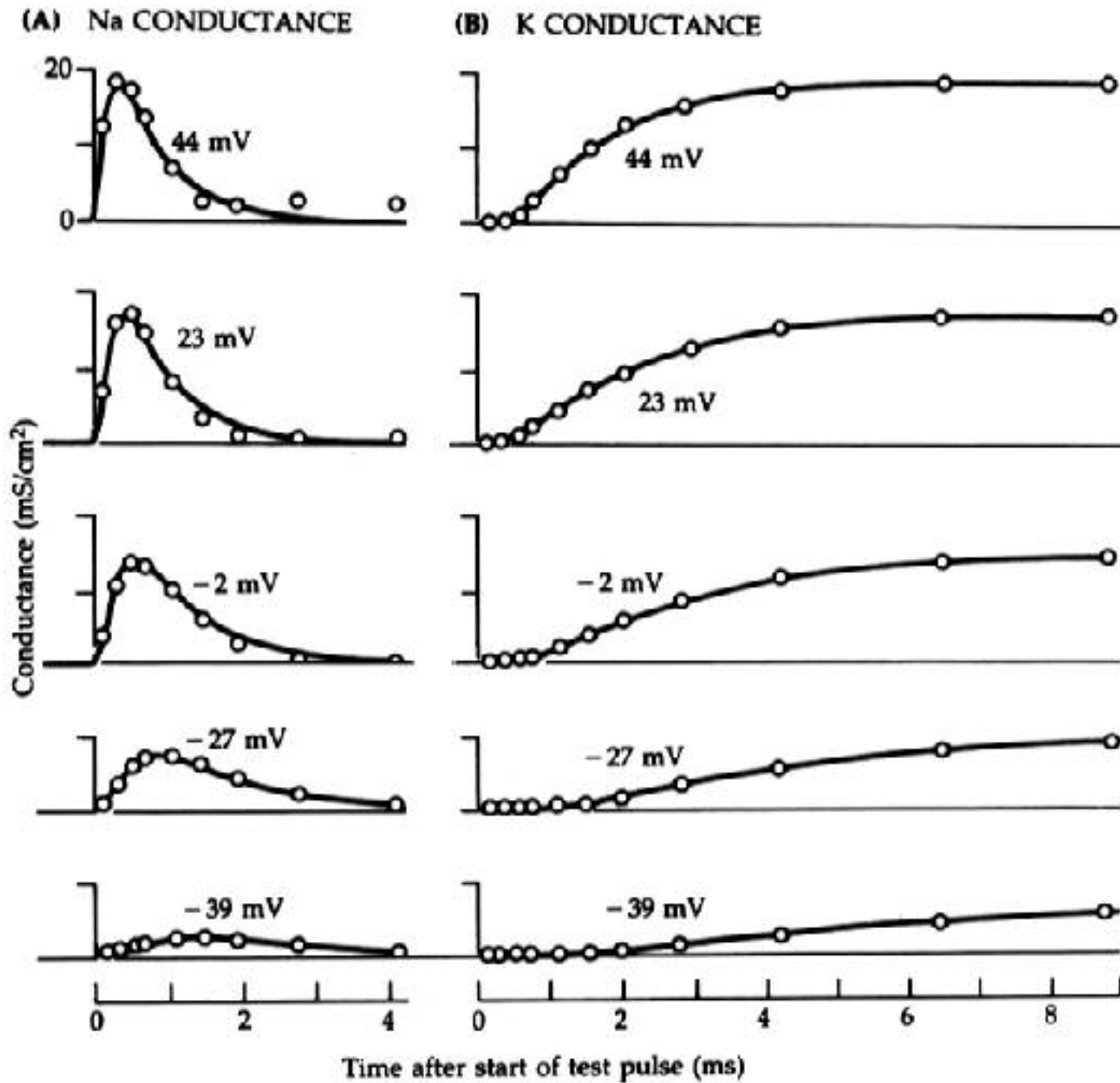
$$g_K(V) = \bar{g}_K n$$

Voltage:



Current:



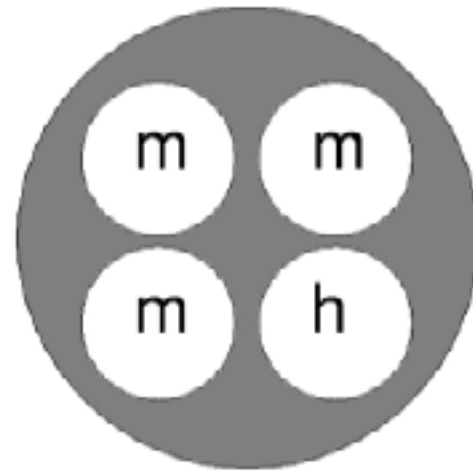




# The Hodgkin-Huxley model

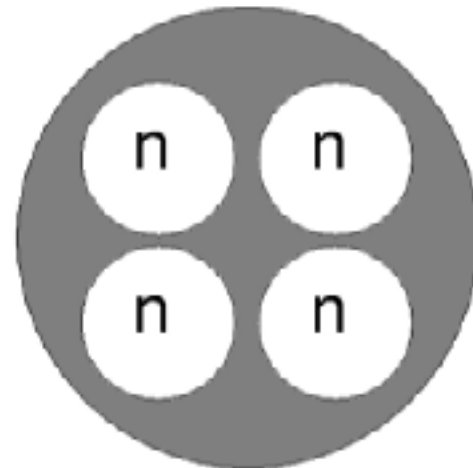
Open probability

Sodium channel



$$m^3 h$$

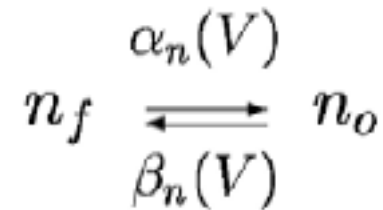
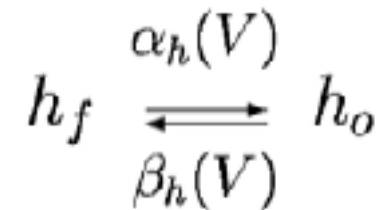
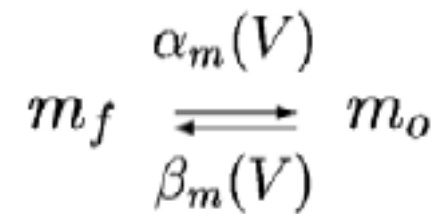
Potassium channel



$$n^4$$

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

$$g_K(V) = \bar{g}_K n^4$$



## The Hodgkin-Huxley model:

$$C_m \frac{dV}{dt} = -g_L (V - E_L) - g_{Na}(V) (V - E_{Na}) - g_K(V) (V - E_K)$$

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

$$g_K(V) = \bar{g}_K n^4(V)$$

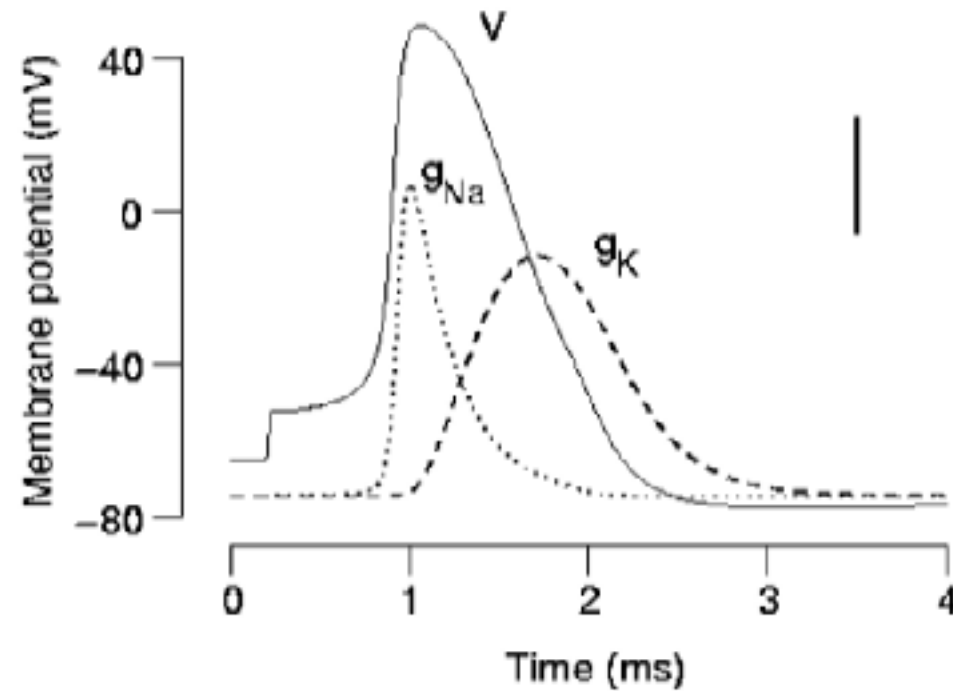
State variables:

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

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

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

# The Hodgkin-Huxley model



$$C_m \frac{dV}{dt} = -g_L (V - E_L) - g_{Na}(V) (V - E_{Na}) - g_K(V) (V - E_K)$$

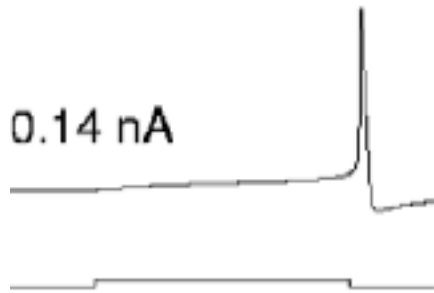
From: Hodgkin & Huxley  
J. Physiol., 1952

# Threshold and repetitive firing

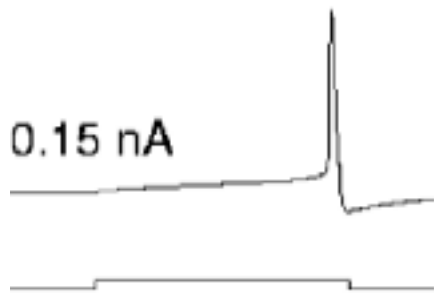
0.13 nA



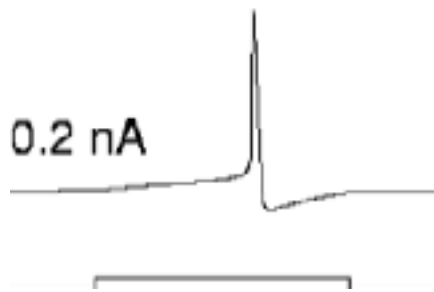
0.14 nA



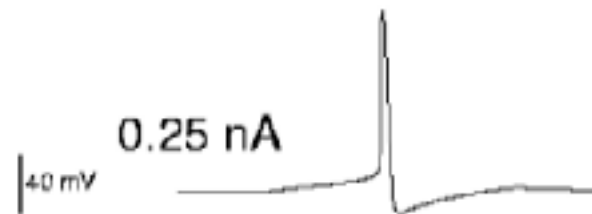
0.15 nA



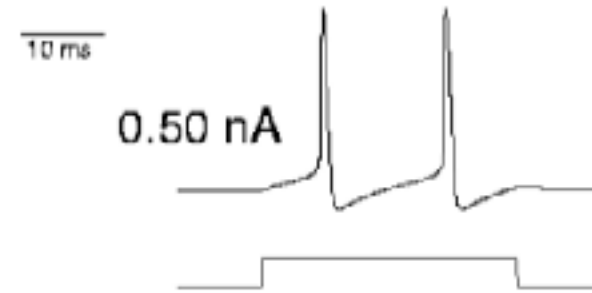
0.2 nA



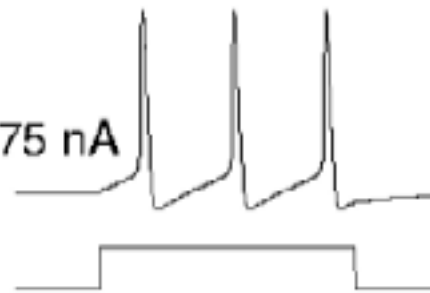
0.25 nA



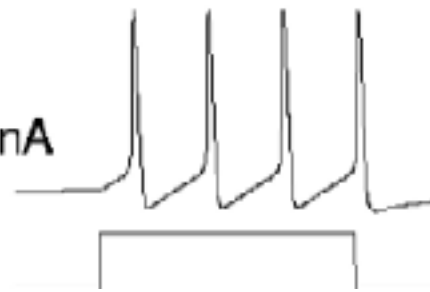
0.50 nA



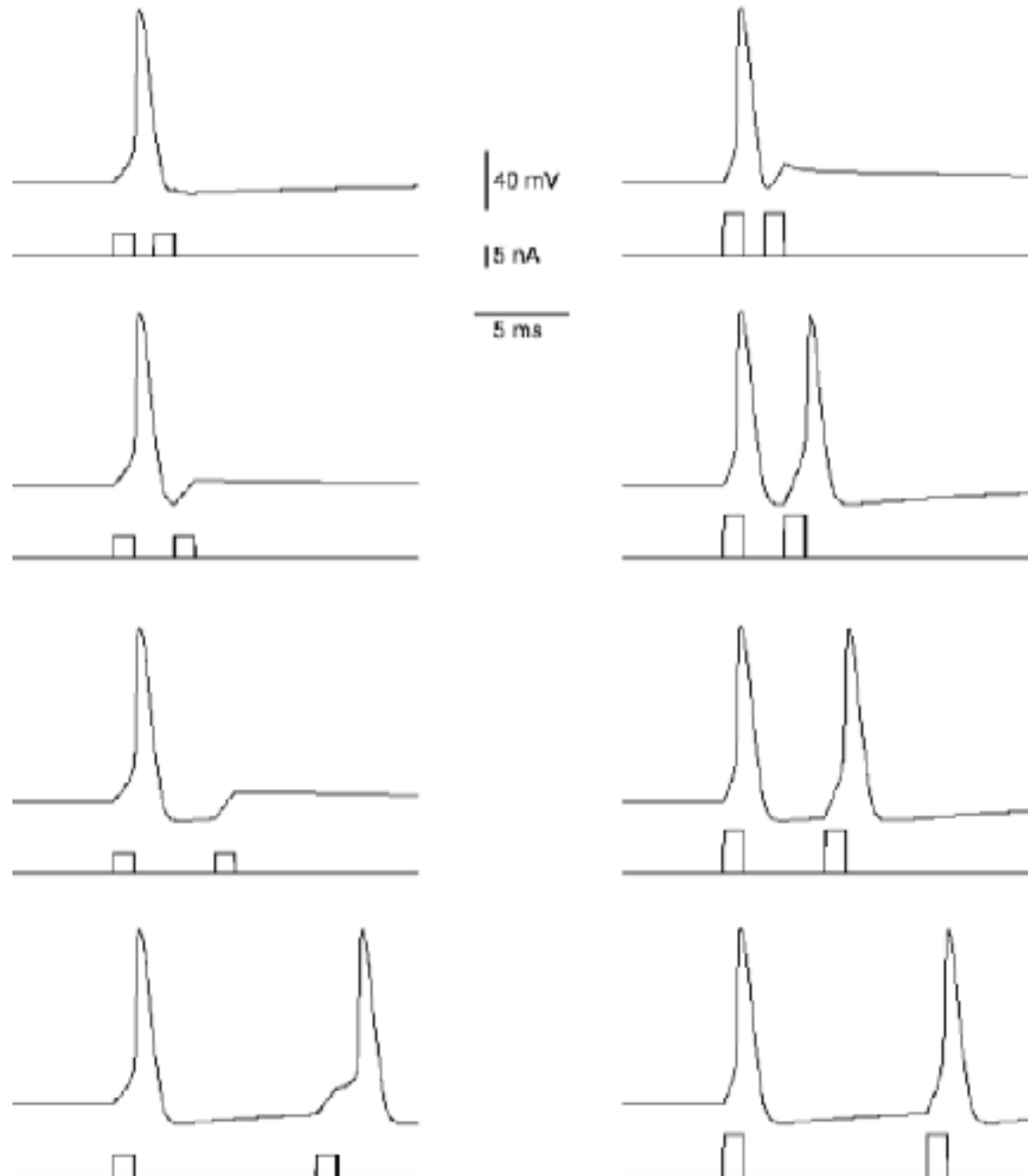
0.75 nA



1 nA

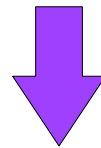


# Refractory period

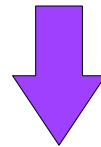


## Voltage-clamp experiments

- *Time constant:*  $\tau_m(V)$
- *Steady-state activation:*  $m_\infty(V)$



Hodgkin-Huxley model



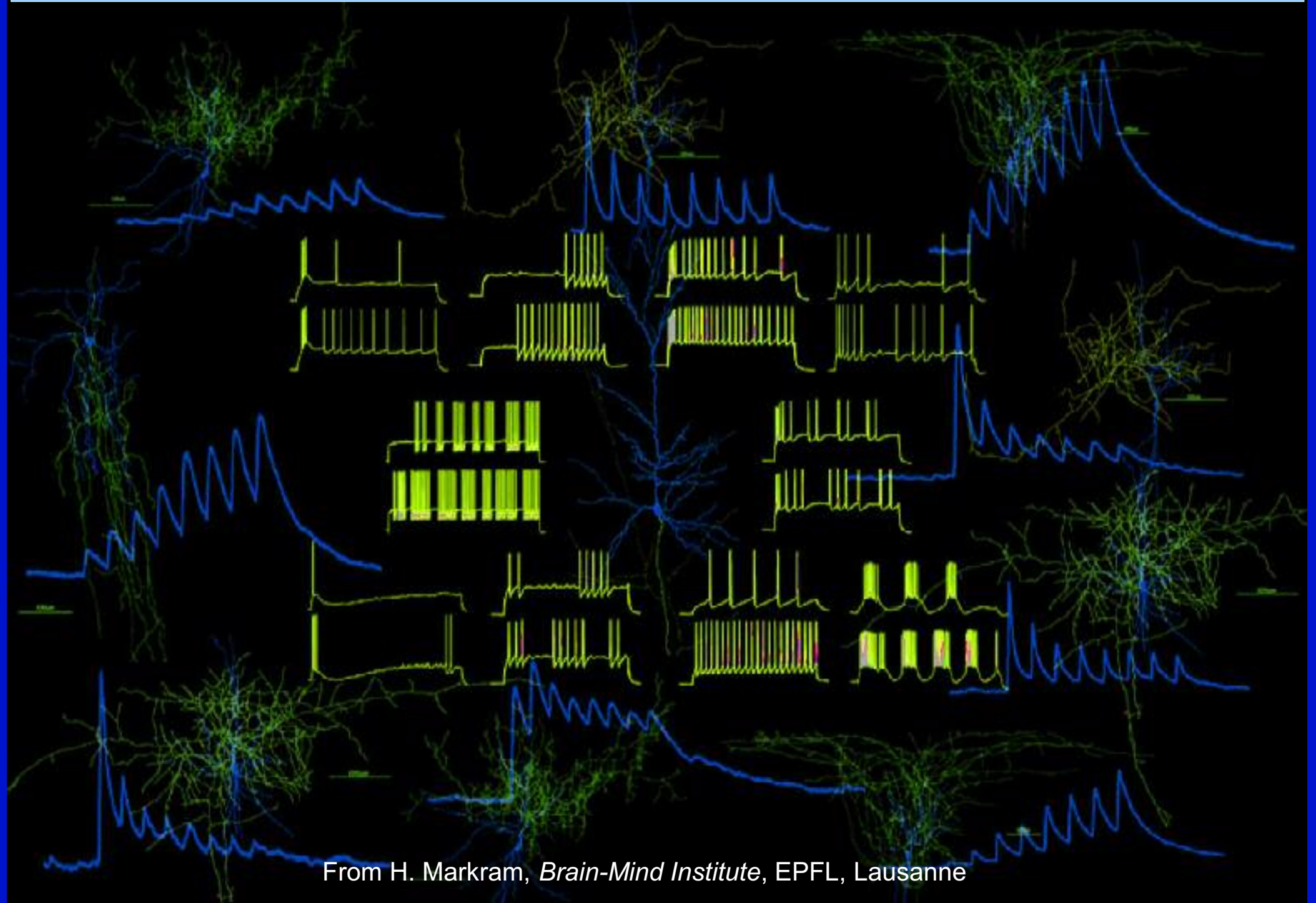
Numerical simulation



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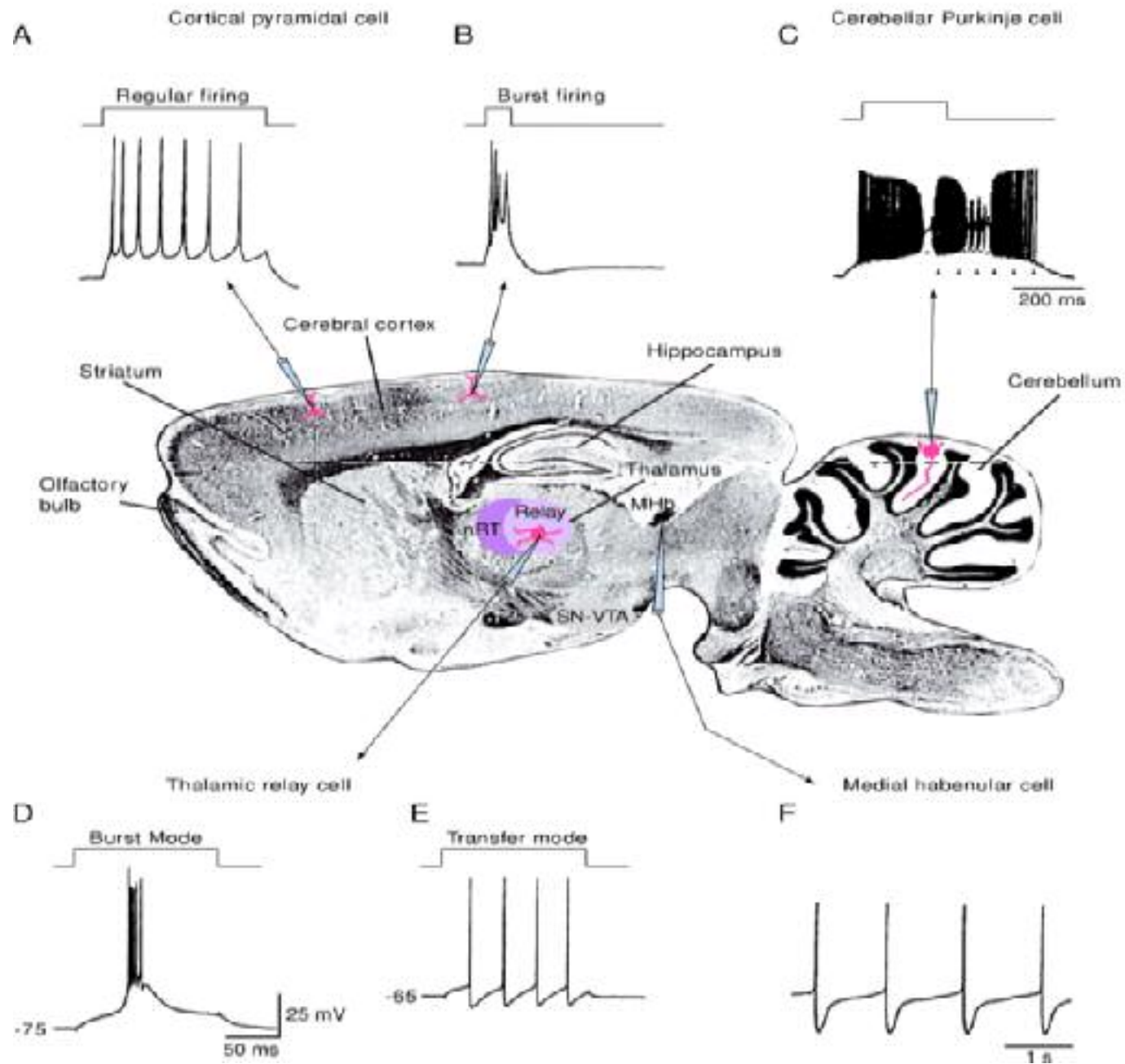


# Intrinsic neuronal properties



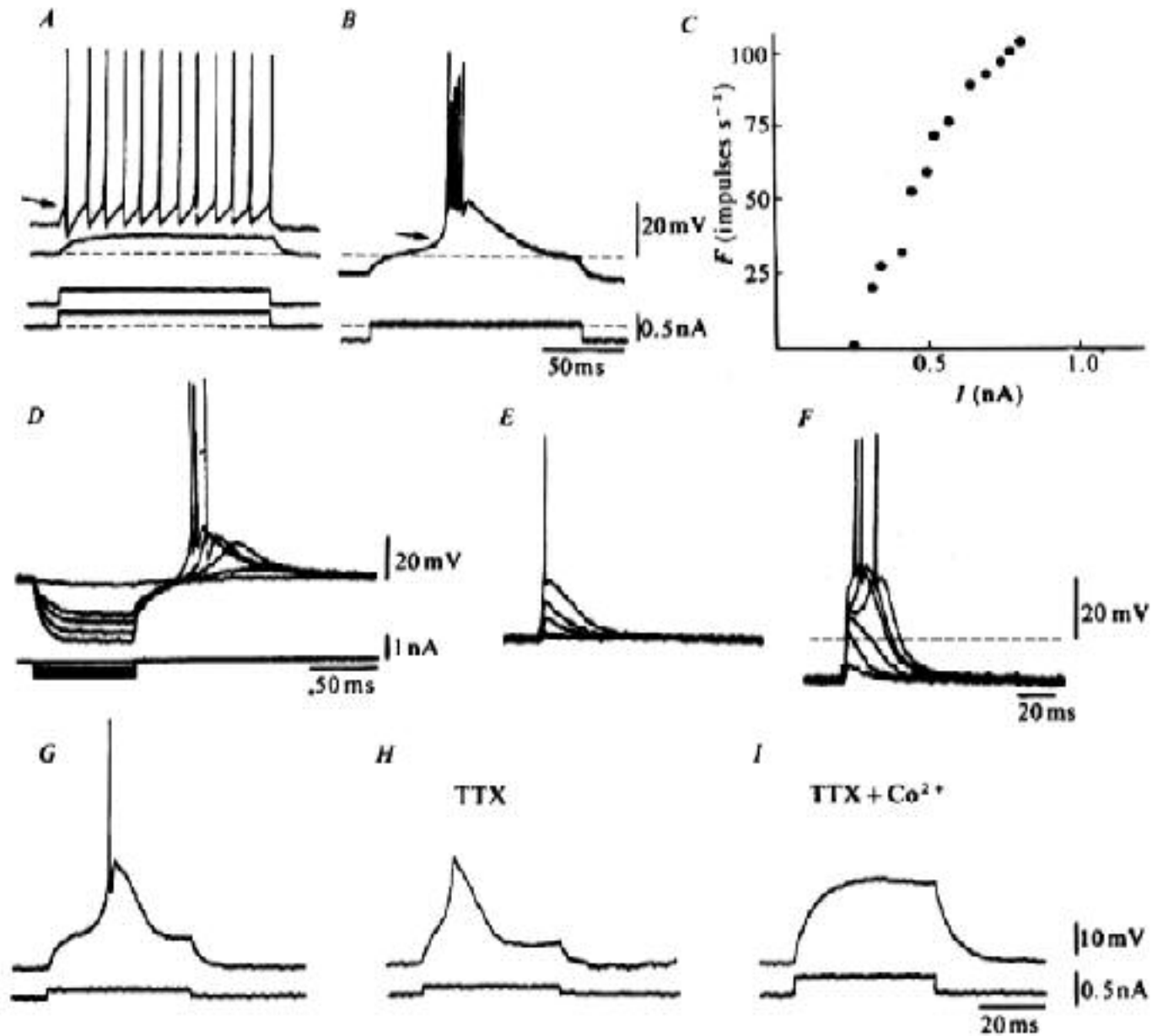
From H. Markram, *Brain-Mind Institute*, EPFL, Lausanne

# Intrinsic neuronal properties

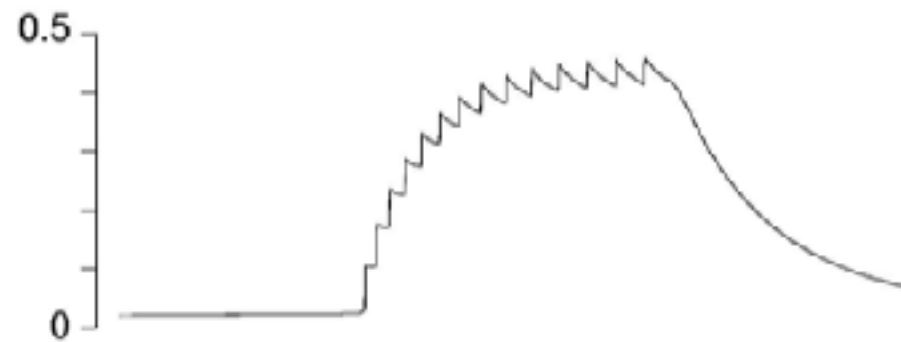
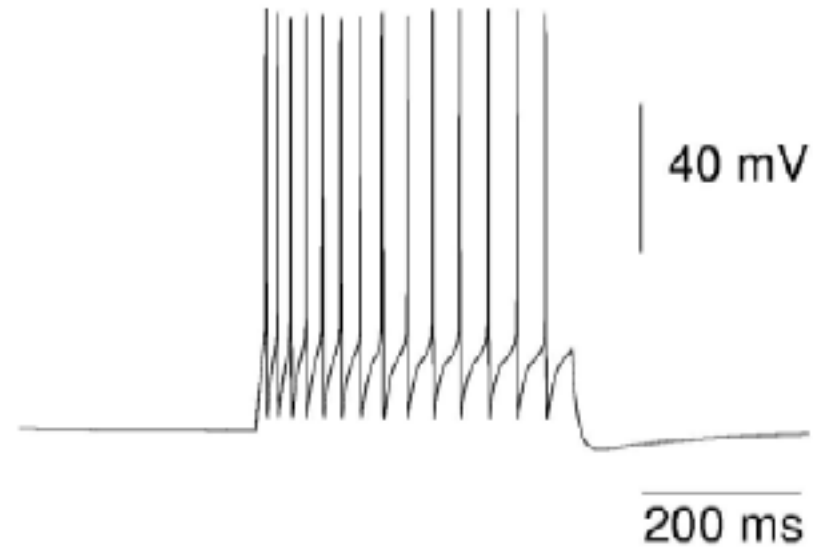
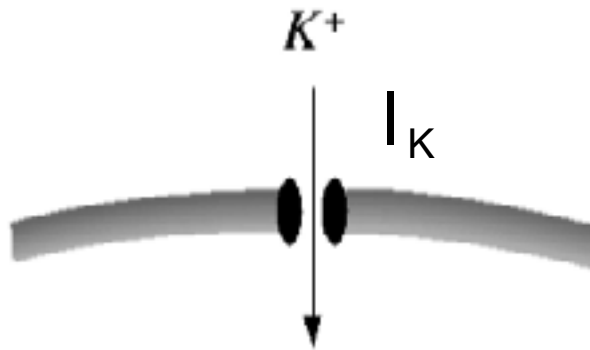


In: *Fundamental Neuroscience* (Academic Press, 1999), Chap.6

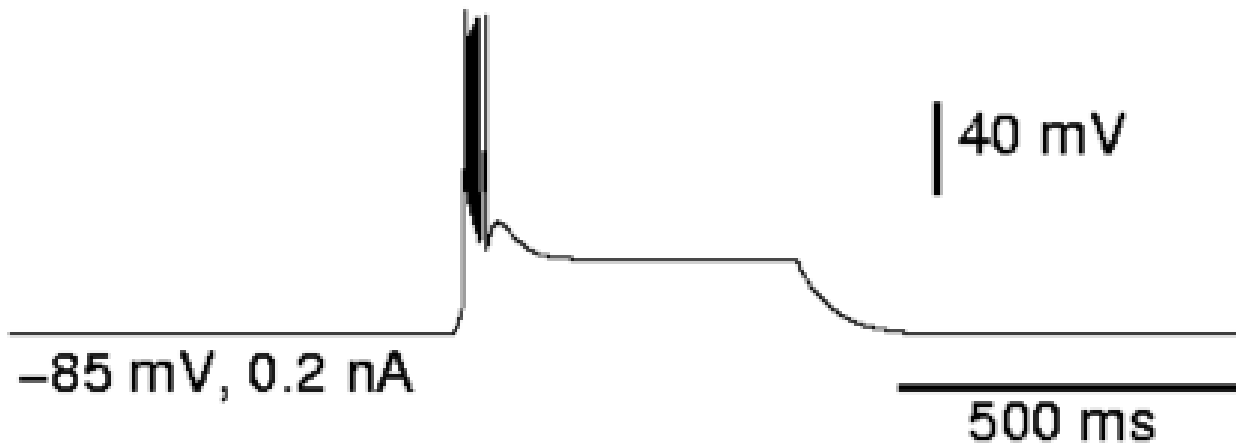
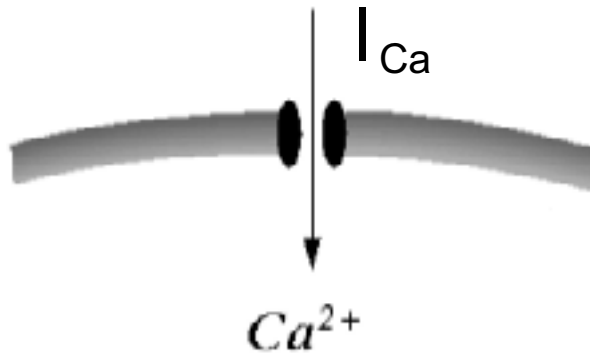
# Intrinsic properties of thalamic neurons



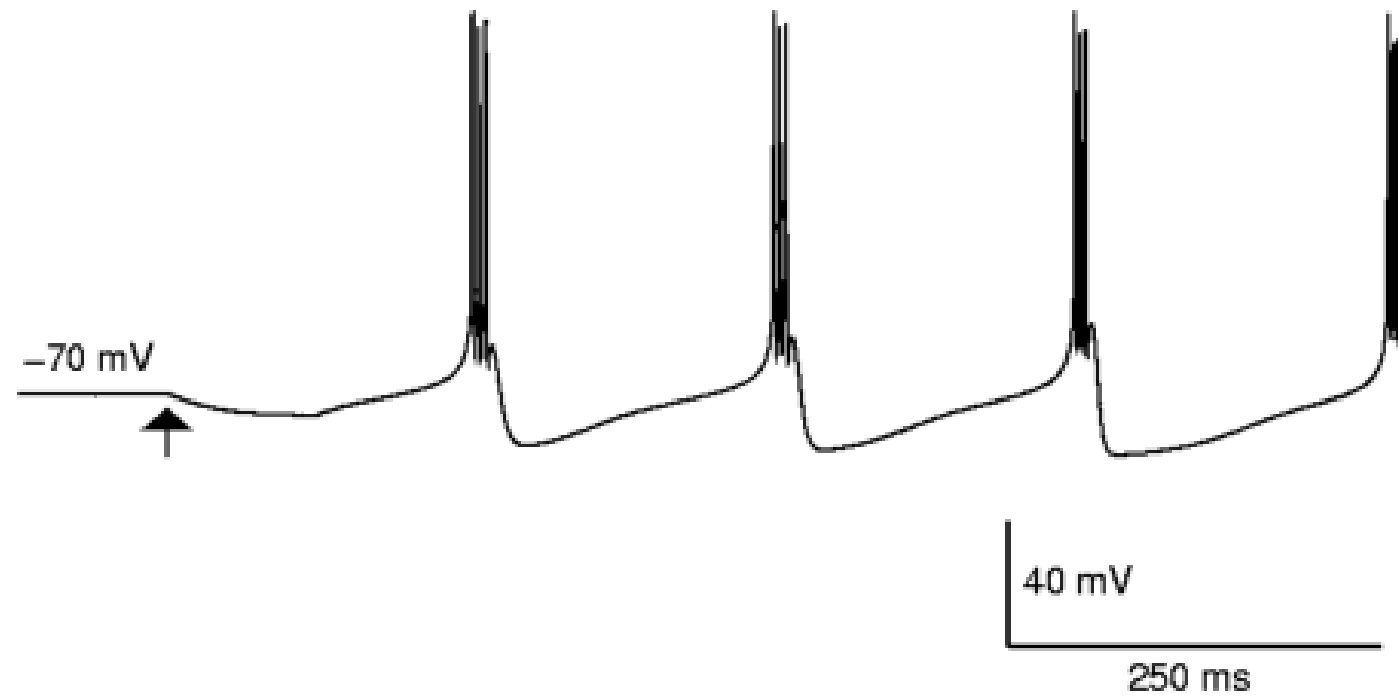
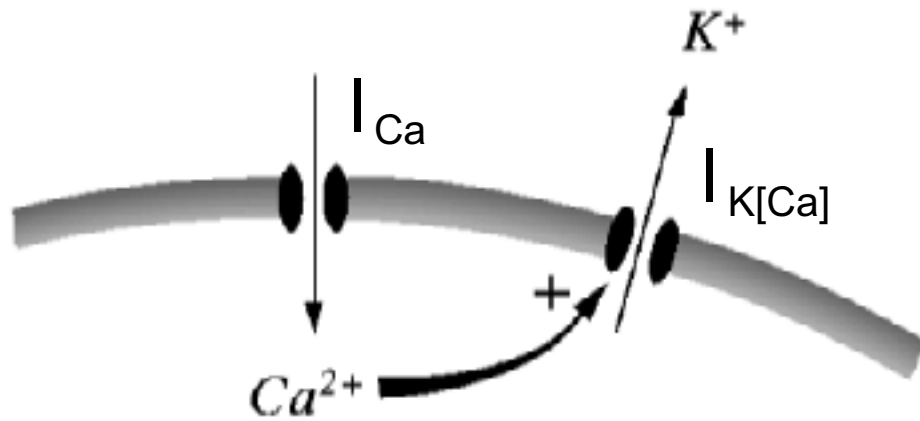
# Hodgkin-Huxley model of adaptation



# Hodgkin-Huxley model of bursting



# Repetitive bursting from $I_{Ca}$ - $I_{K[Ca]}$ interaction



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# Different types of ion channels

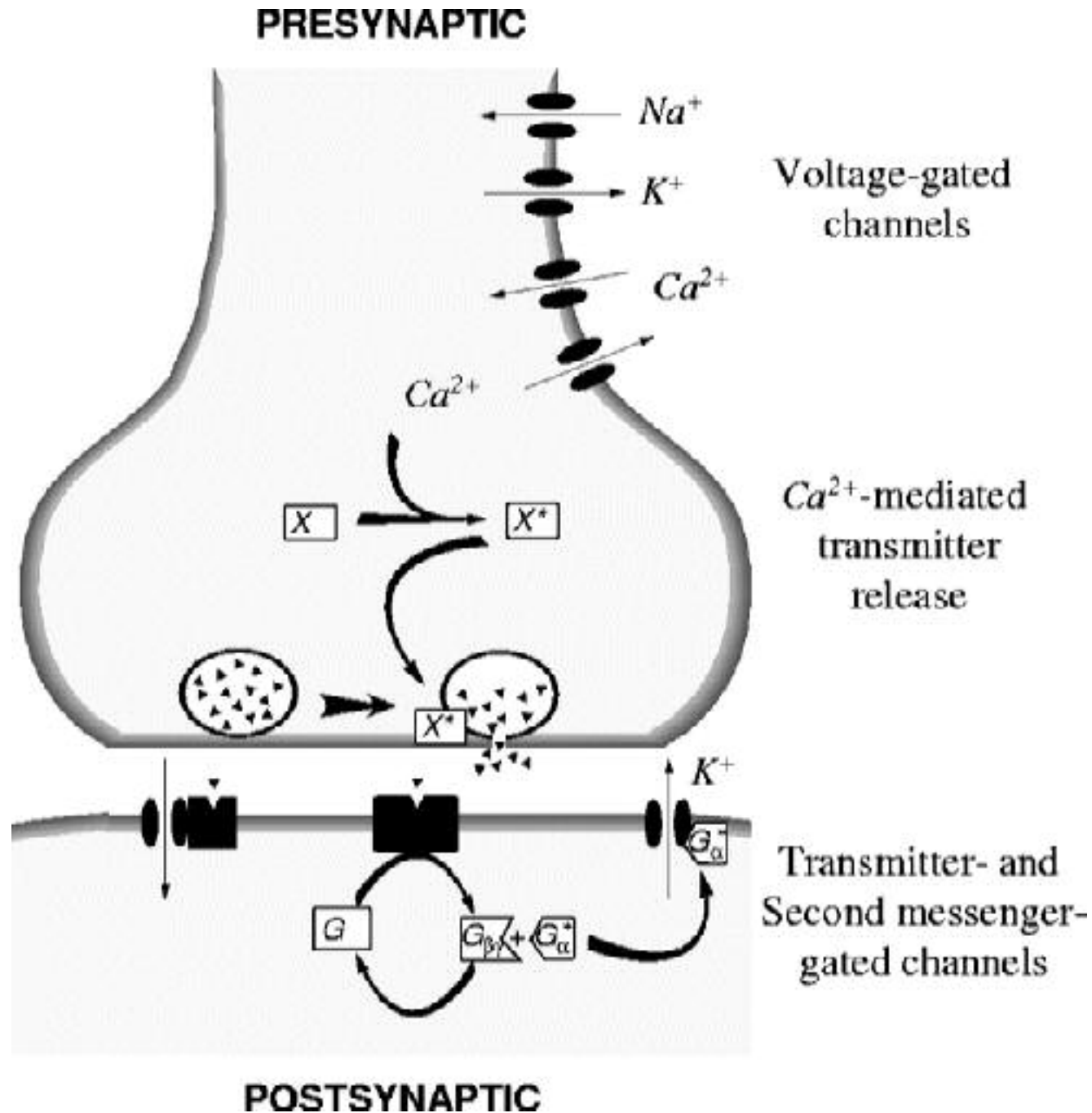
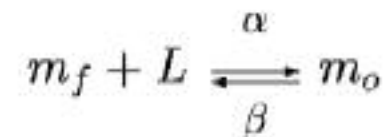




Schéma cinétique:



$$\frac{dm}{dt} = \alpha [L] (1 - m) - \beta m$$

$m$  : fraction de canaux ouverts

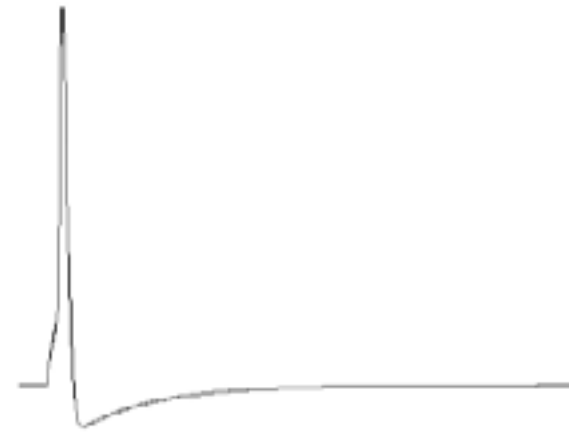
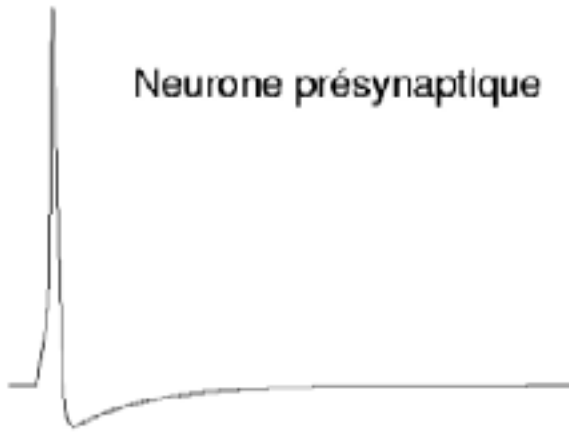
$L$  : "ligand" → Calcium, neurotransmetteur, messenger secondaire, ...

# How to model synaptic interactions ?

Excitation

Inhibition

Neurone présynaptique



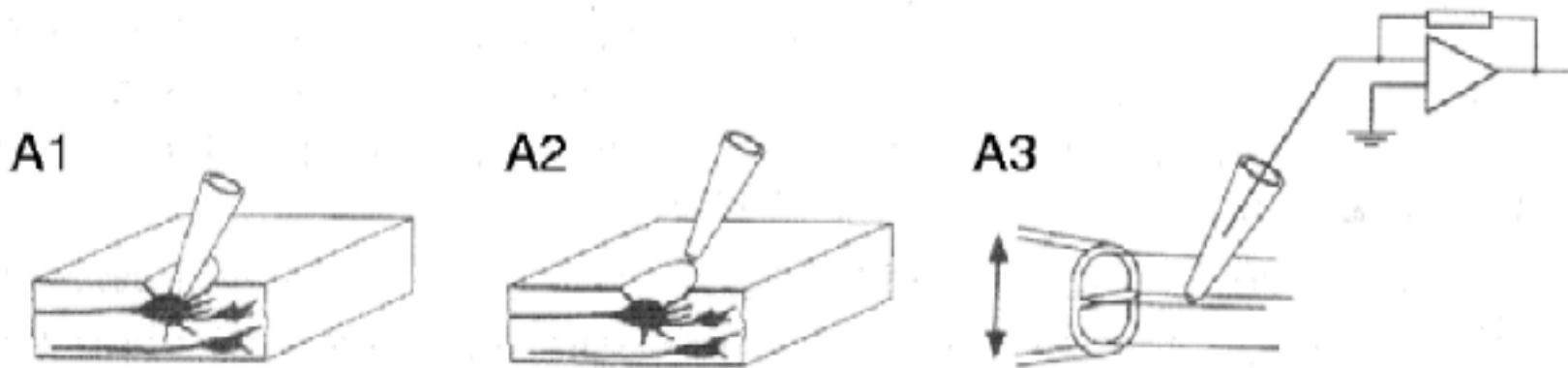
Neurone postsynaptique

EPSP

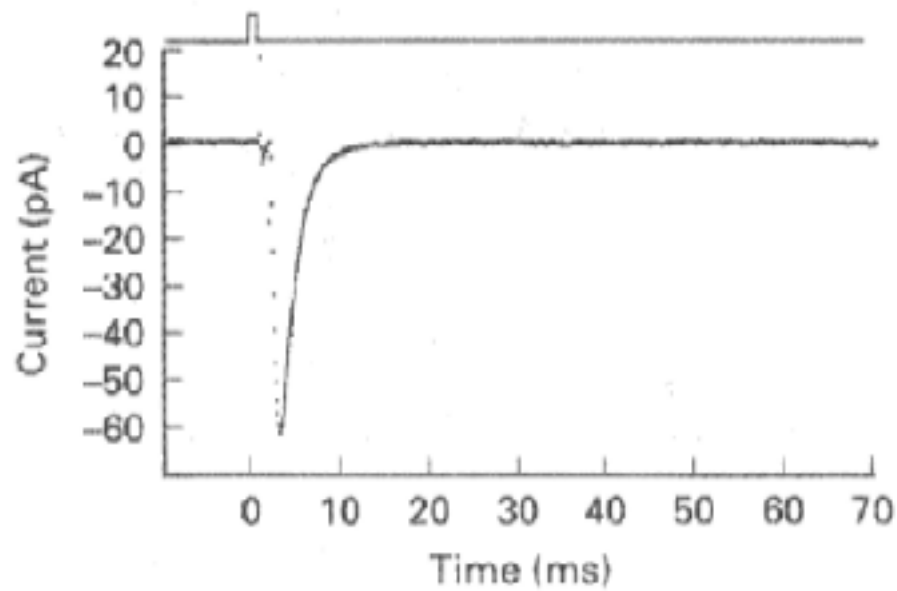


IPSP

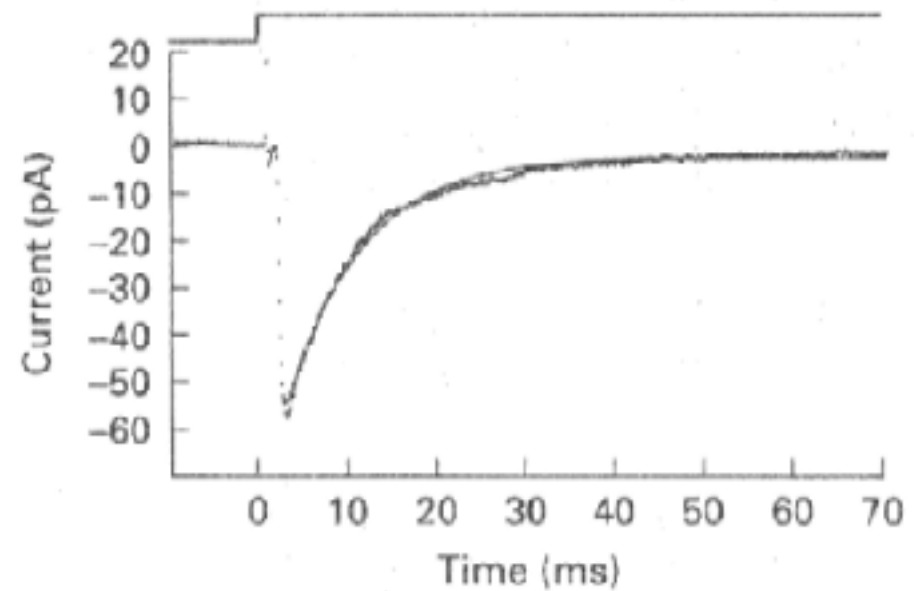




B1



B2

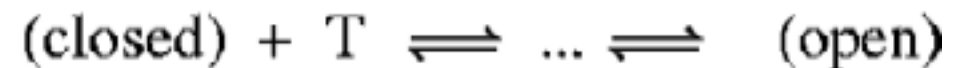


# Pulse-based model of synaptic currents

1. transmitter (T) is produced as a pulse

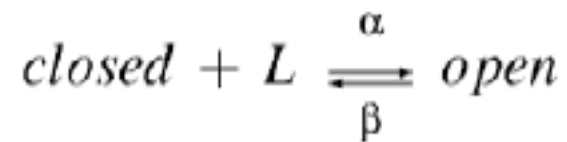


2. T binds to receptors



3. Postsynaptic current is evaluated from the fraction of open receptors

$$I_{\text{syn}} = g_{\text{syn}} [r] (V - E_{\text{syn}})$$



$$\begin{aligned} \frac{dm}{dt} &= \alpha [L] (1 - m) - \beta m \\ &= \frac{1}{\tau_m} (m_\infty - m) \end{aligned}$$

$m$  : fraction of gate in the open state

$\tau_m = 1 / (\alpha[L] + \beta)$  : time constant

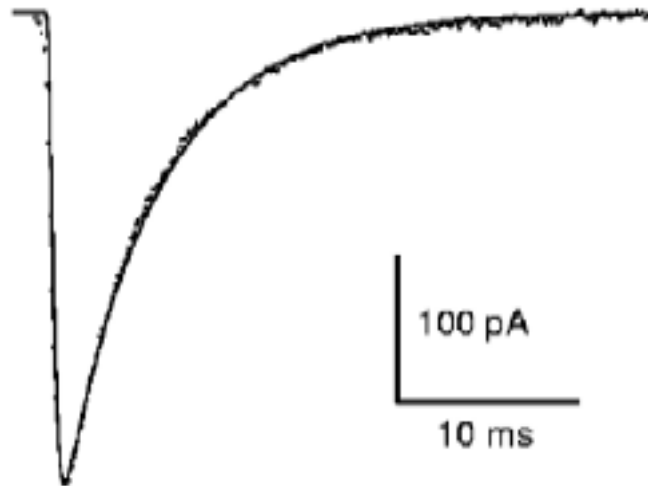
$m_\infty = \alpha[L] / (\alpha[L] + \beta)$  : steady-state activation

If expressed as a function of  $C = \log([L])$  :

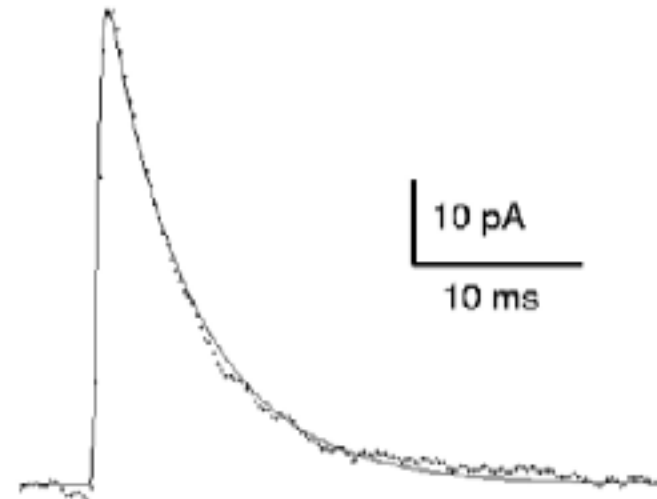
$$m_\infty = \frac{1}{1 + \exp\left[-\frac{(C - C_m)}{k_m}\right]}$$

# Models of synaptic currents

Glutamate AMPA receptors

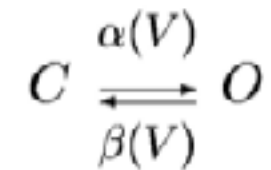


GABA(A) receptors

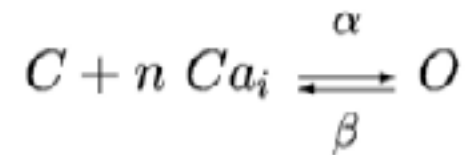


# Different types of ion channels

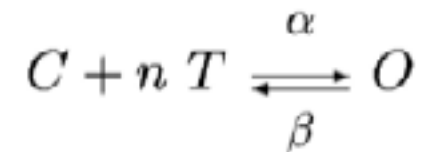
Voltage-dependent gating  
(Hodgkin-Huxley)



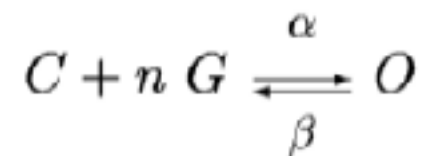
Calcium-dependent gating



Transmitter gating



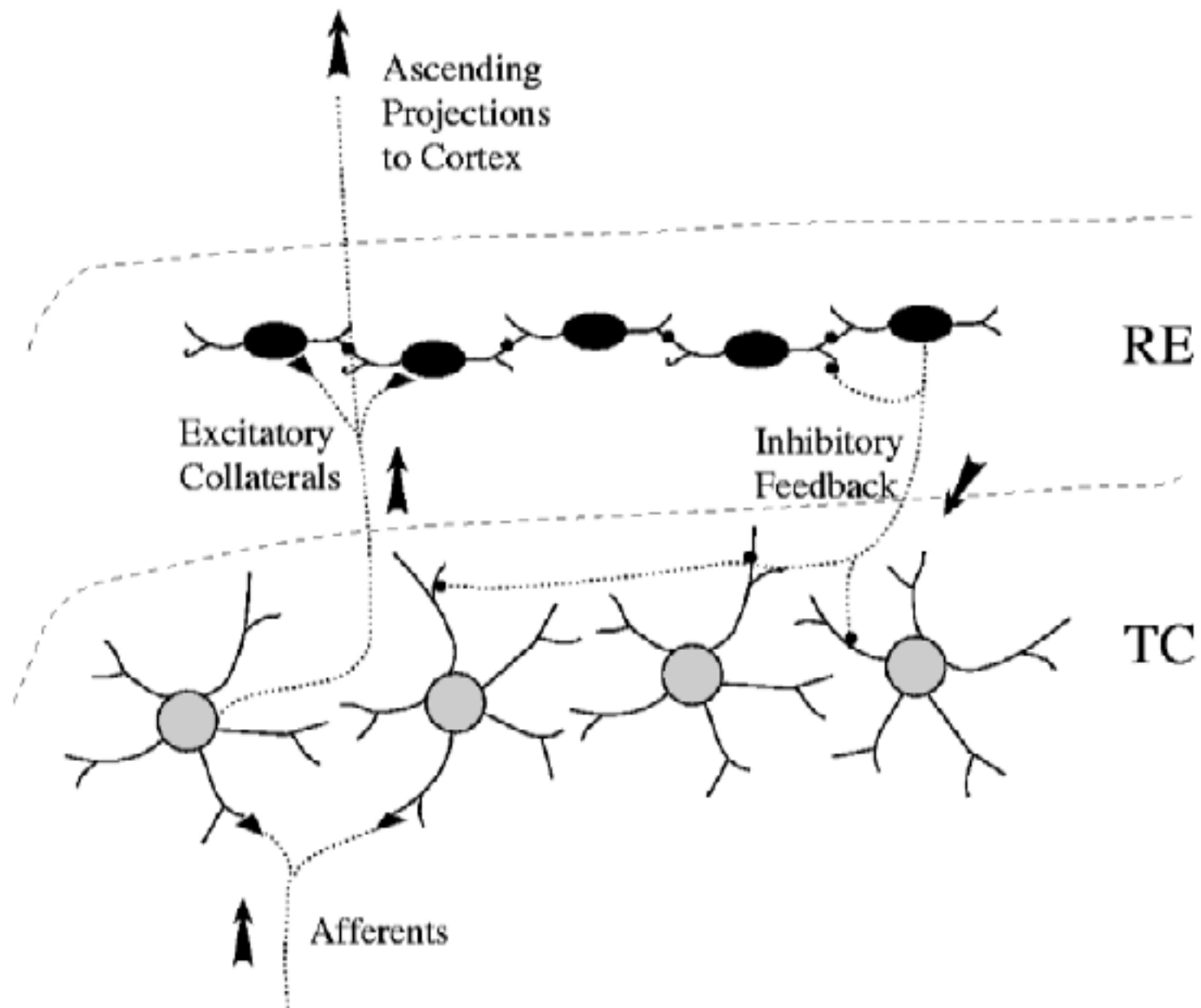
Second-messenger gating



1. Modélisation des propriétés passives de la membrane: Circuit électrique équivalent
2. Modélisation des propriétés actives de la membrane I: Formalisme de Hodgkin-Huxley
3. Modélisation des propriétés actives de la membrane II: Propriétés neuronales intrinseques
4. Modélisation des interactions synaptiques
5. Applications: Oscillations dans les circuits de neurones du thalamus



# Connectivity of thalamic cell types



# Intrinsic properties of thalamic neurons

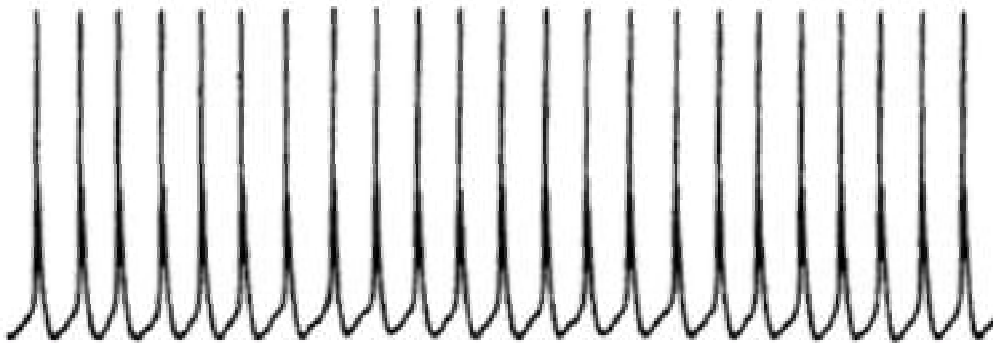
Control



Cs<sup>+</sup>, 2 mM (5 min)



Cs<sup>+</sup>, 2 mM (10 min)



Cs<sup>+</sup>, 2 mM (17 min)

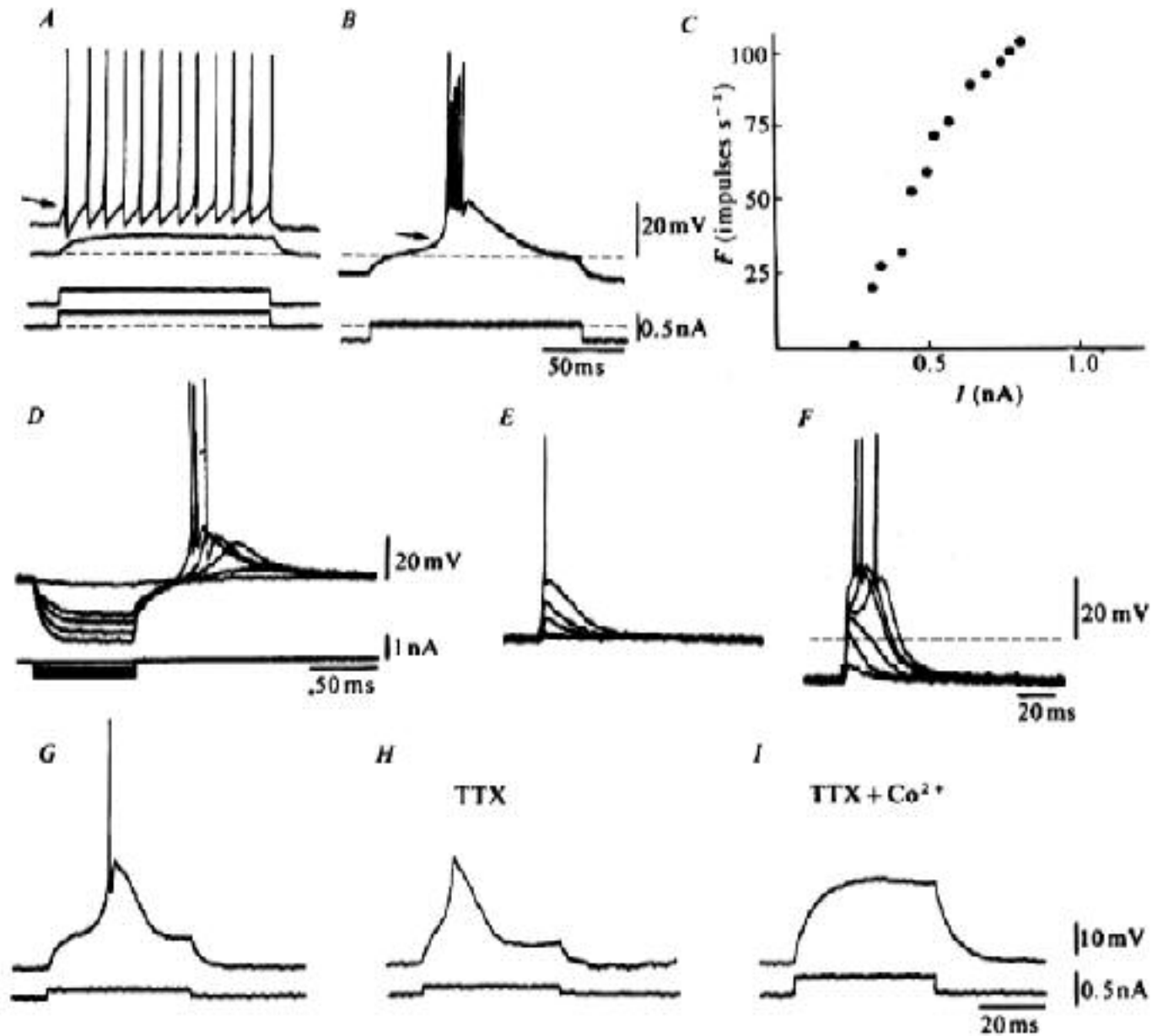


15 mV

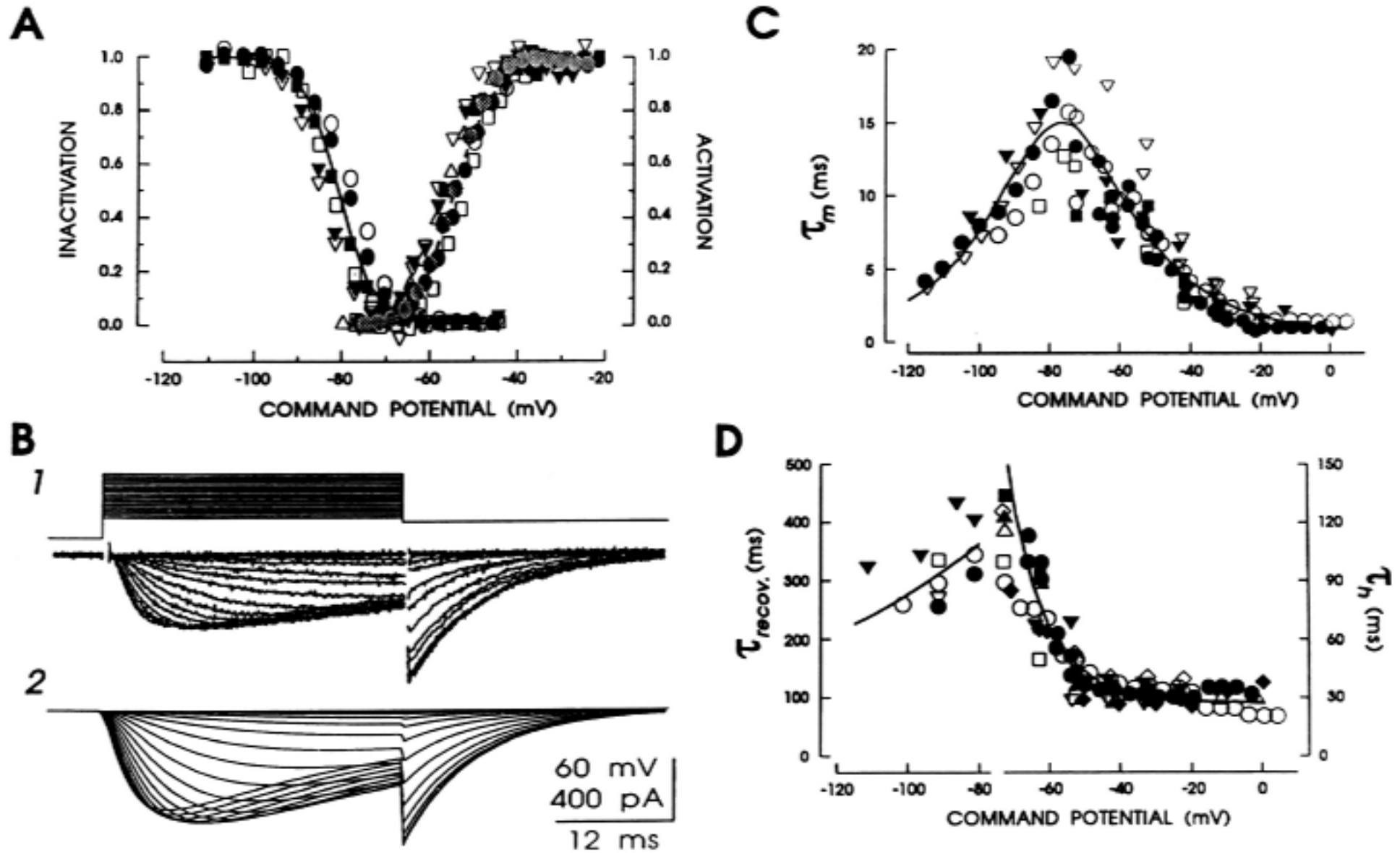
3 s

Soltesz et al.,  
J Physiol, 1991

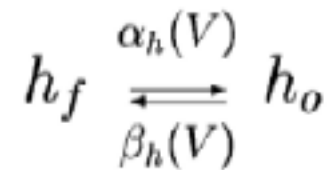
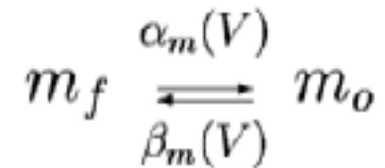
# Intrinsic properties of thalamic neurons



# Voltage-clamp characterization of the T-current



# Hodgkin-Huxley model of the T-current



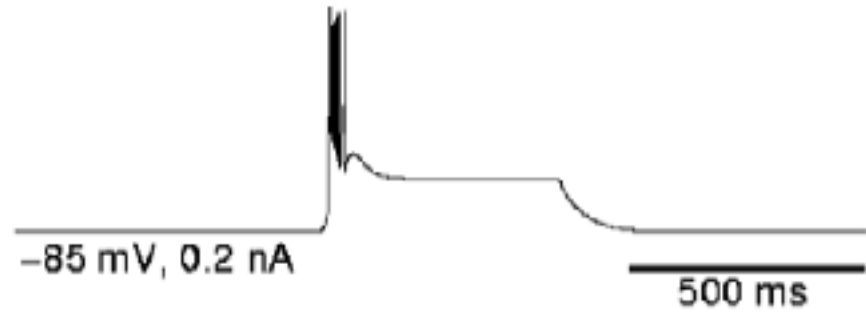
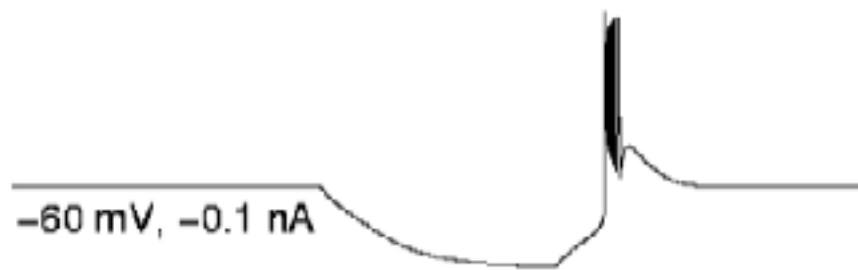
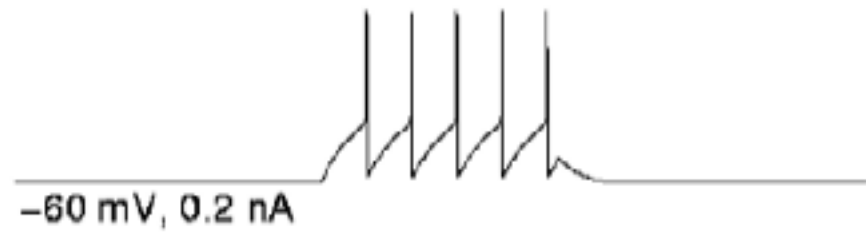
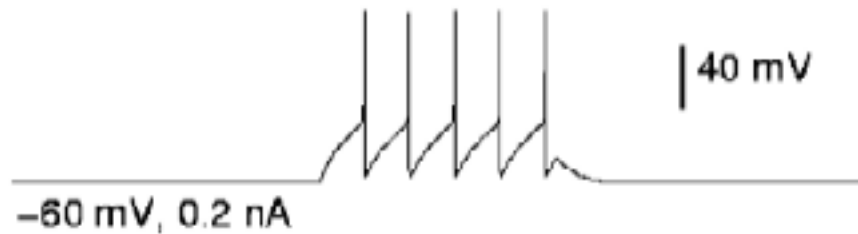
$$g_T(V) = \bar{g}_T m^2(V) h(V)$$

Equations cinétiques:

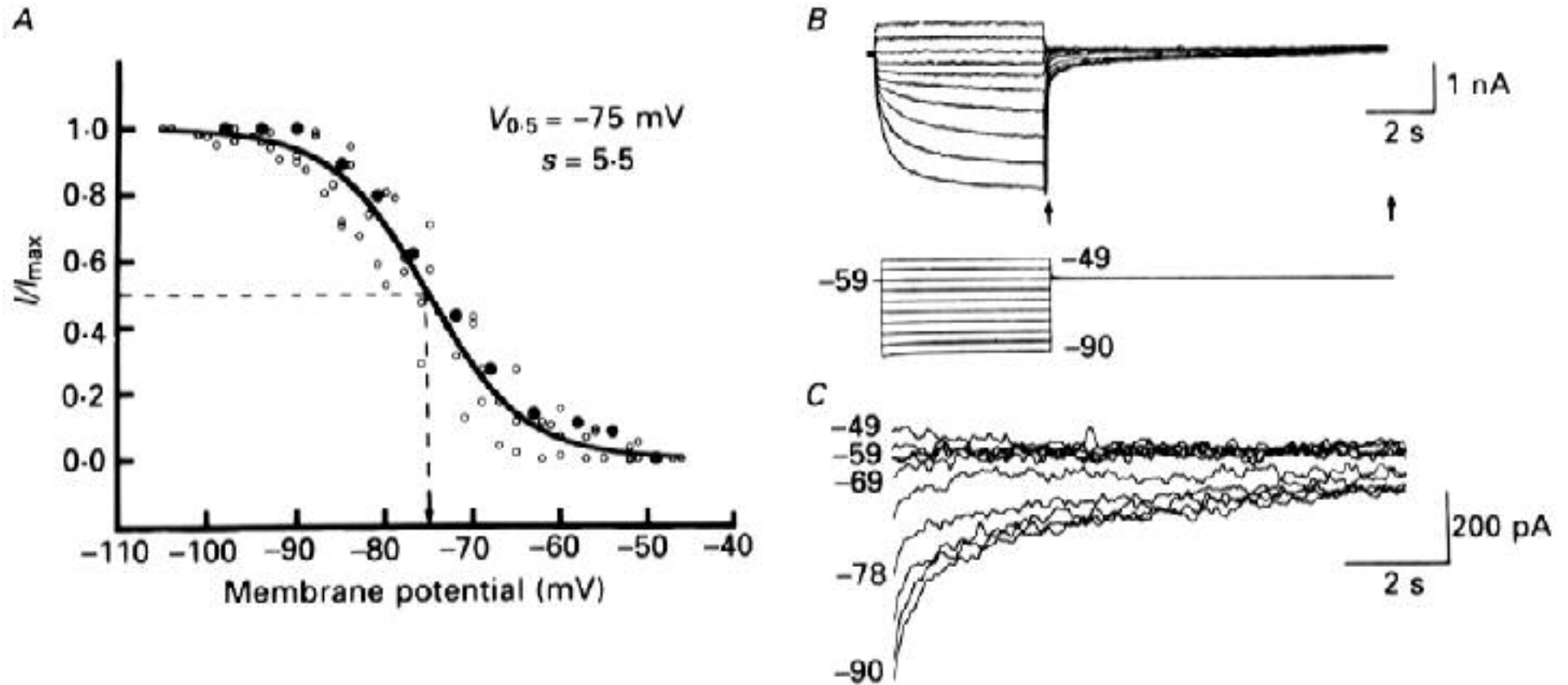
$$\frac{dm}{dt} = \alpha_m(V) (1 - m) - \beta_m(V) m$$

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

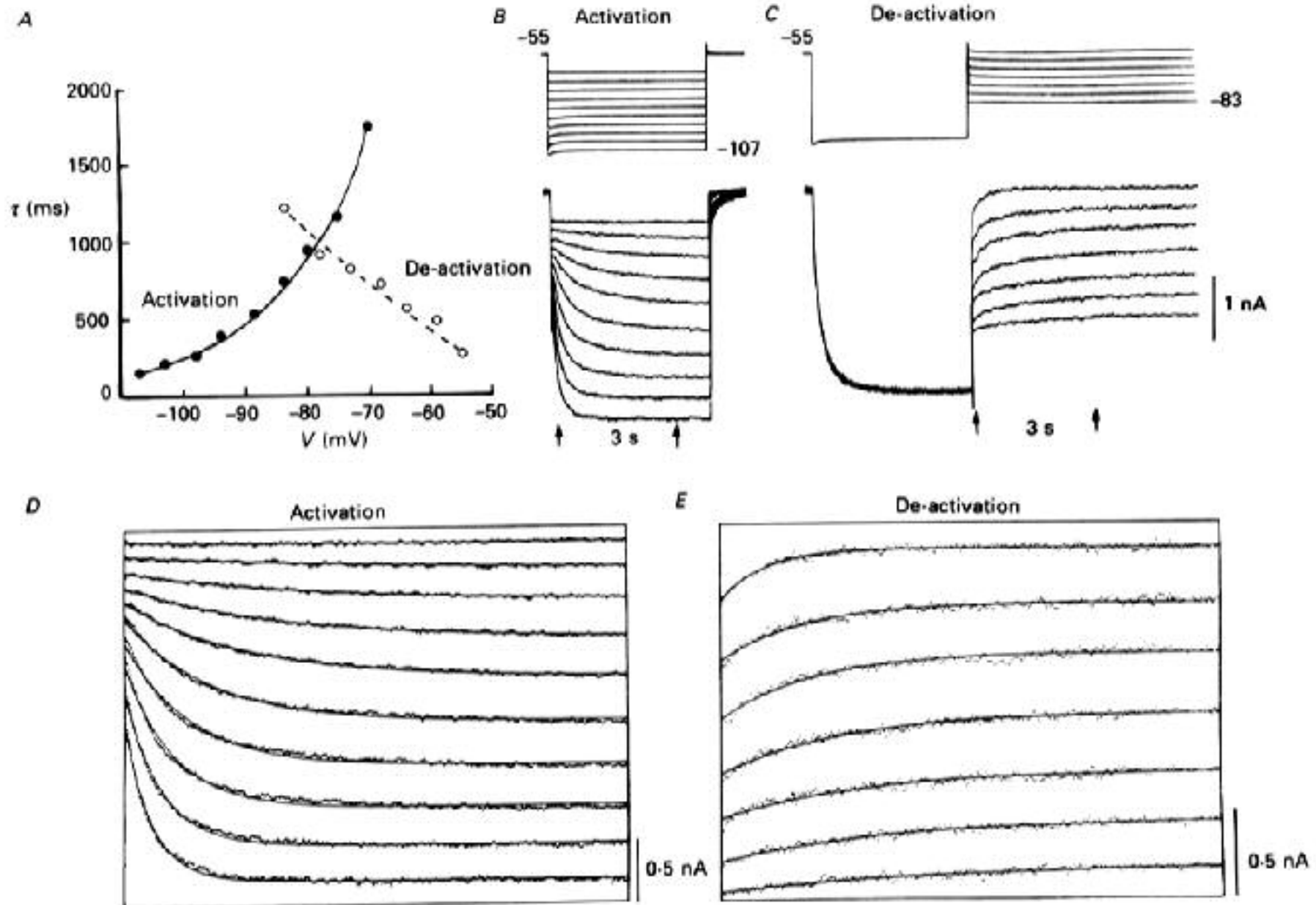
# Hodgkin-Huxley model of the T-current



# Voltage-clamp characterization of the H-current

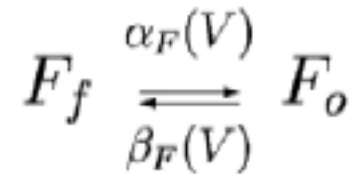
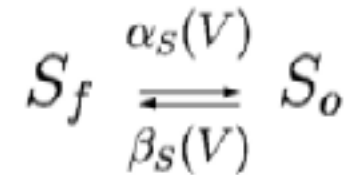


# Voltage-clamp characterization of the H-current





# Hodgkin-Huxley model of the H-current



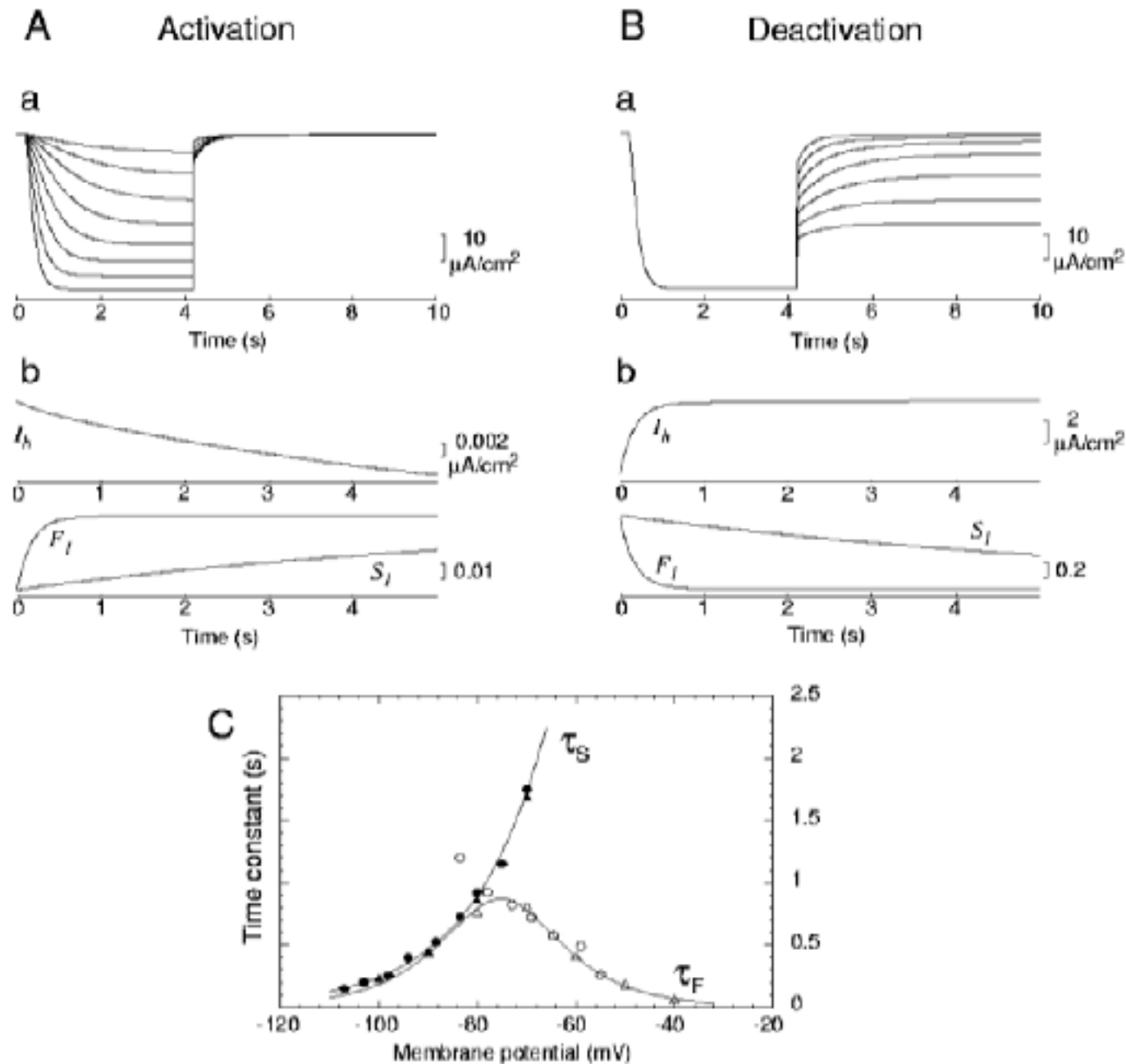
$$g_h(V) = \bar{g}_h S^2(V) F(V)$$

Equations cinétiques:

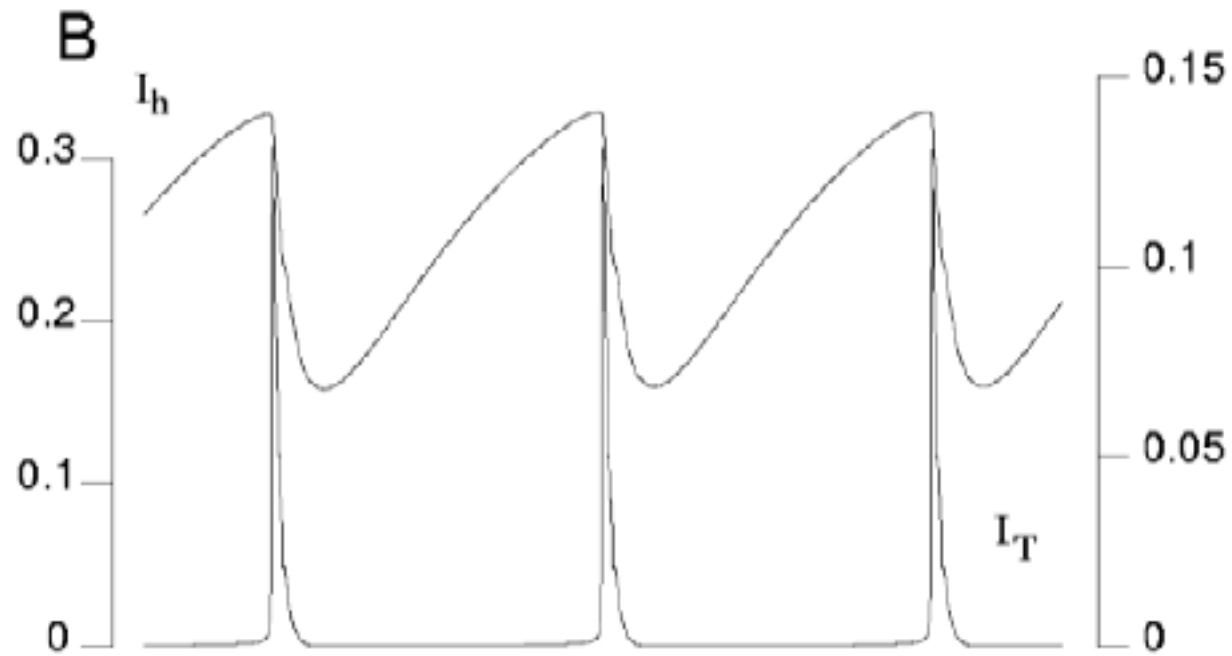
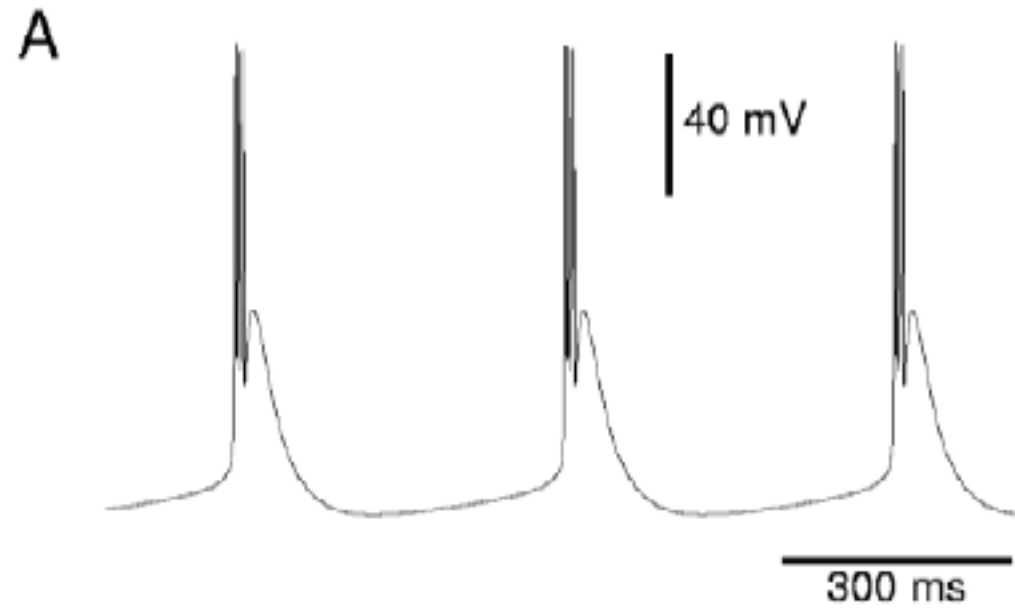
$$\frac{dS}{dt} = \alpha_S(V) (1 - S) - \beta_S(V) S$$

$$\frac{dF}{dt} = \alpha_F(V) (1 - F) - \beta_F(V) F$$

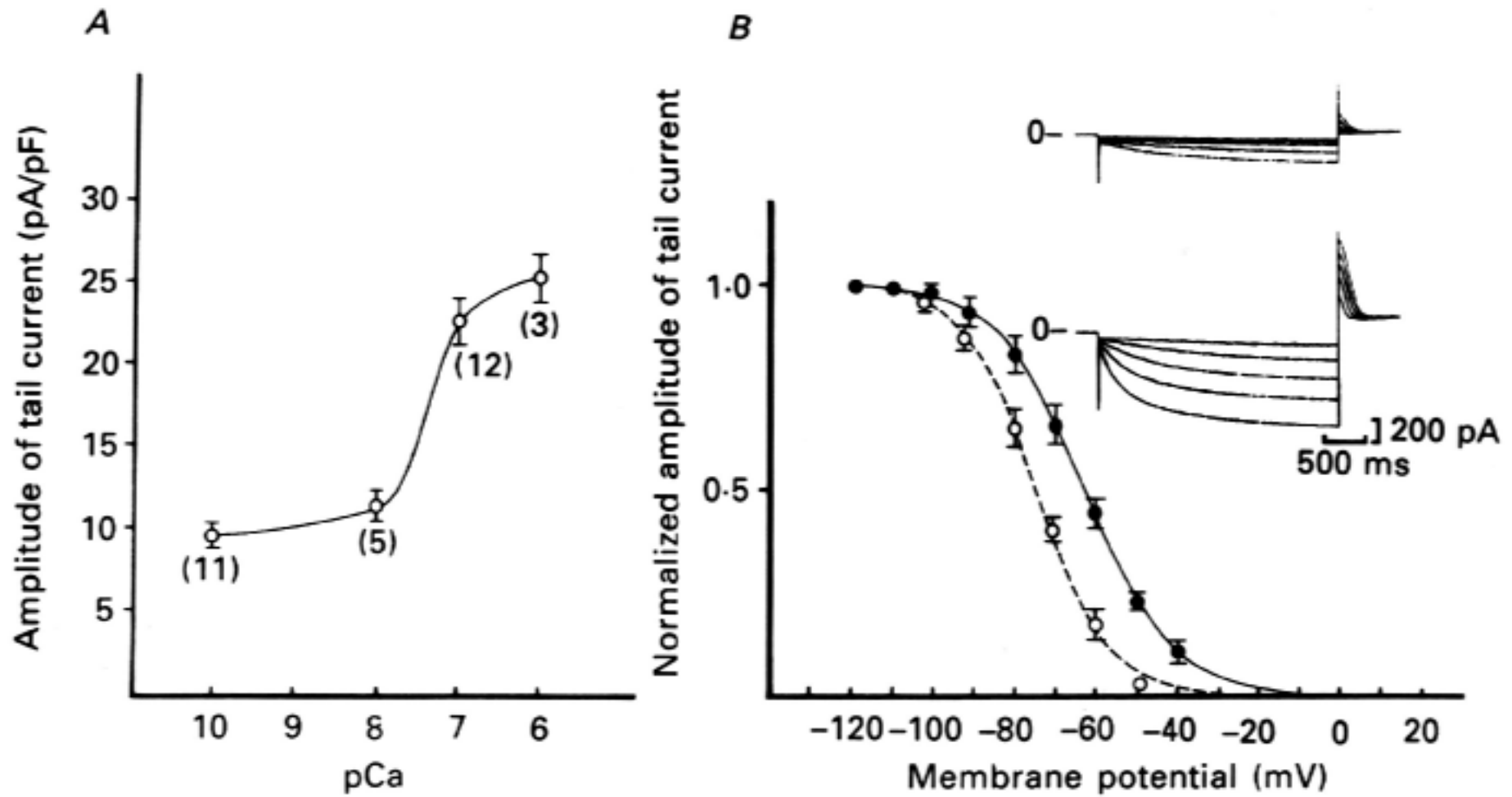
# Hodgkin-Huxley model of the H-current



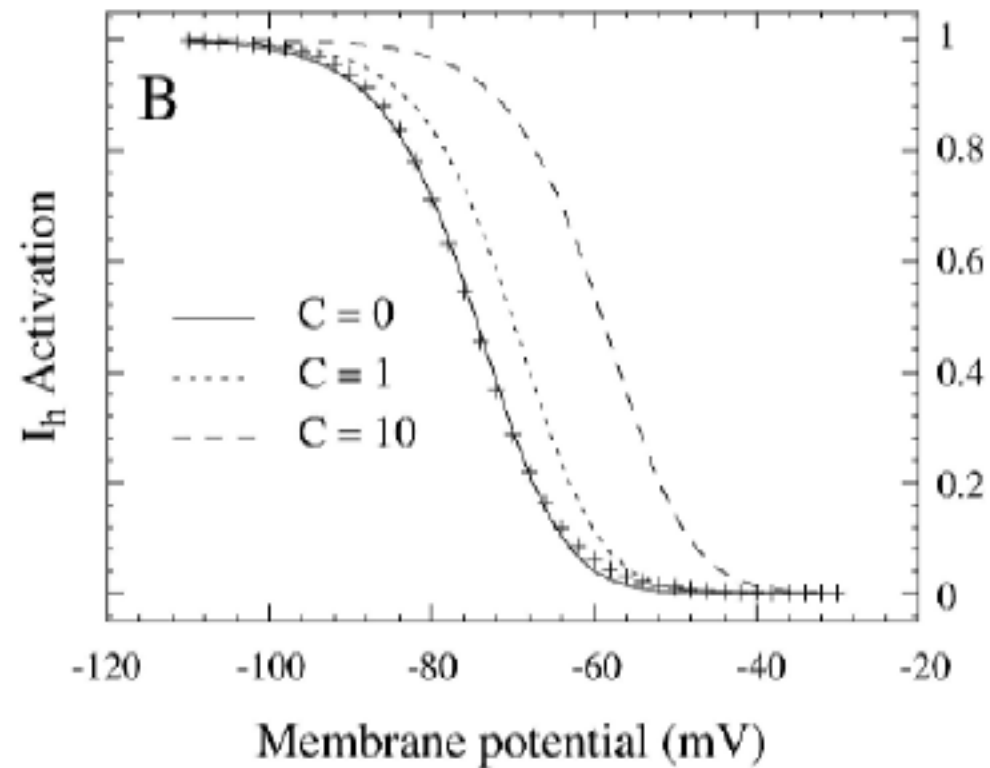
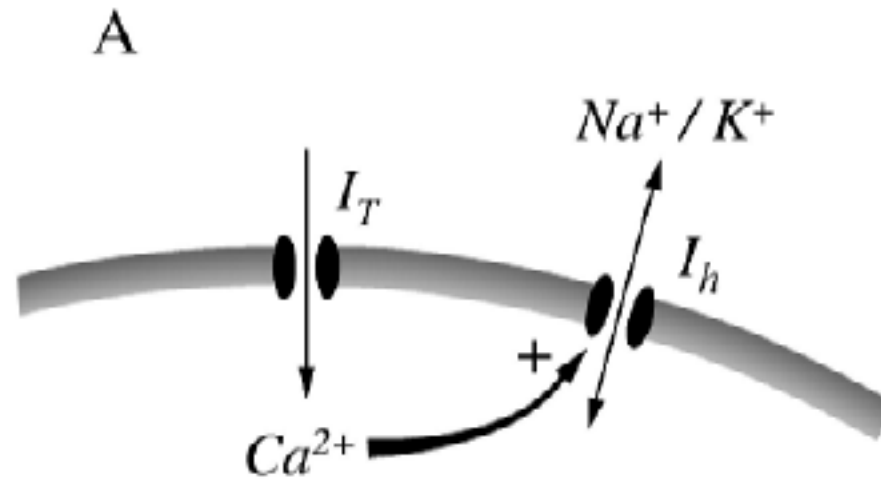
# Oscillations from IT - I<sub>h</sub> interaction



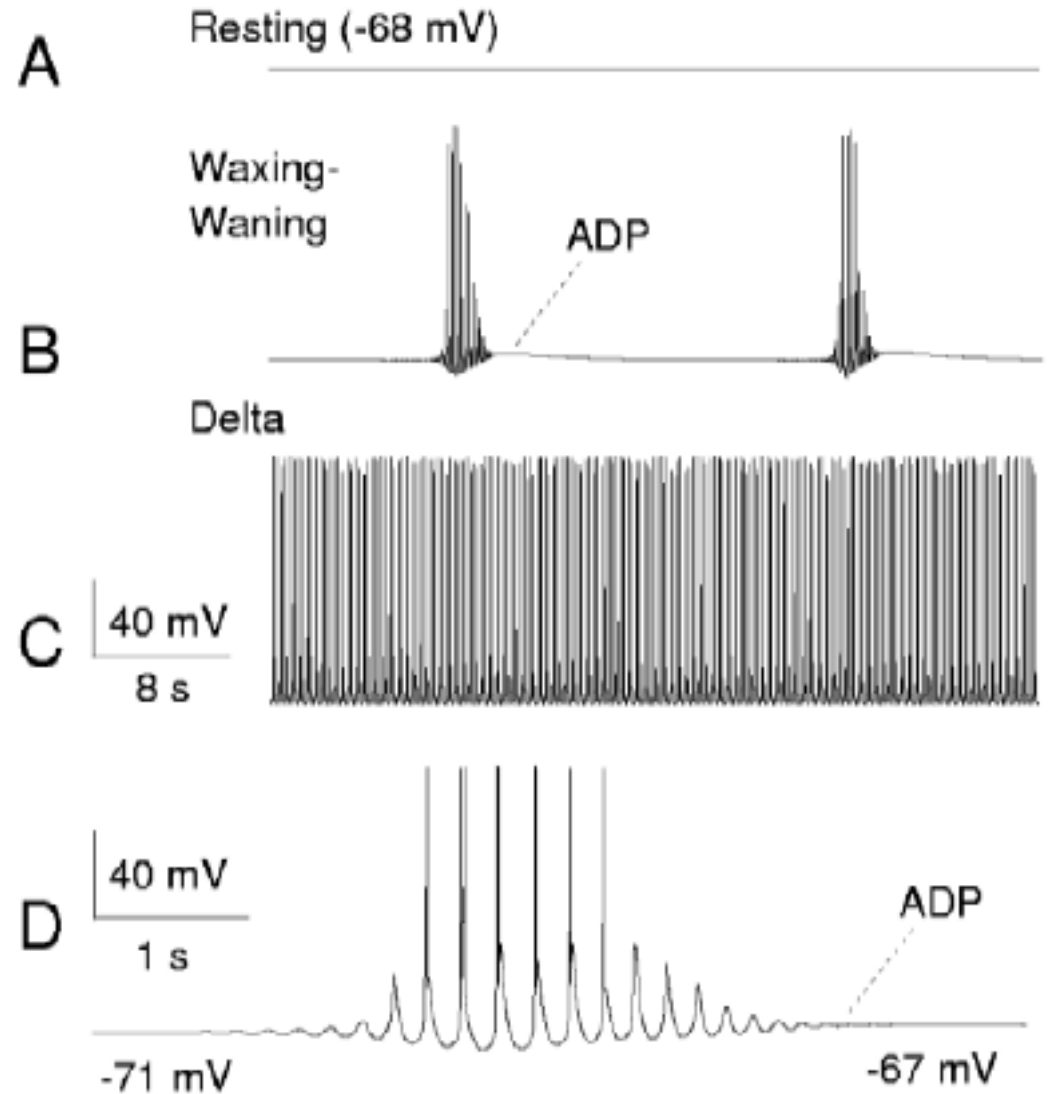
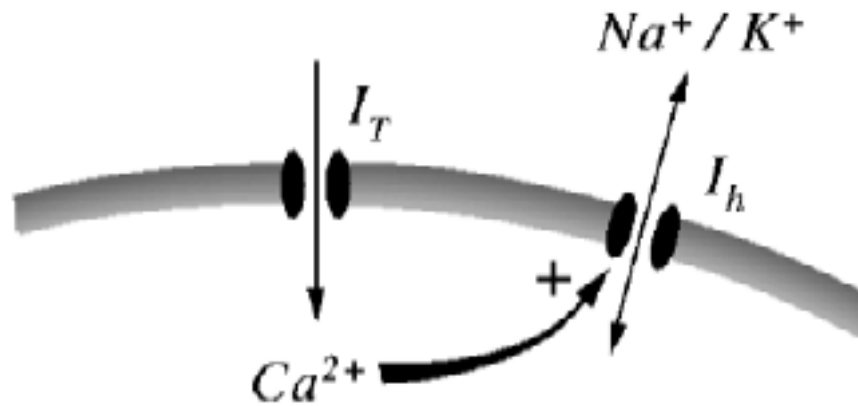
# Calcium regulation of the H-current

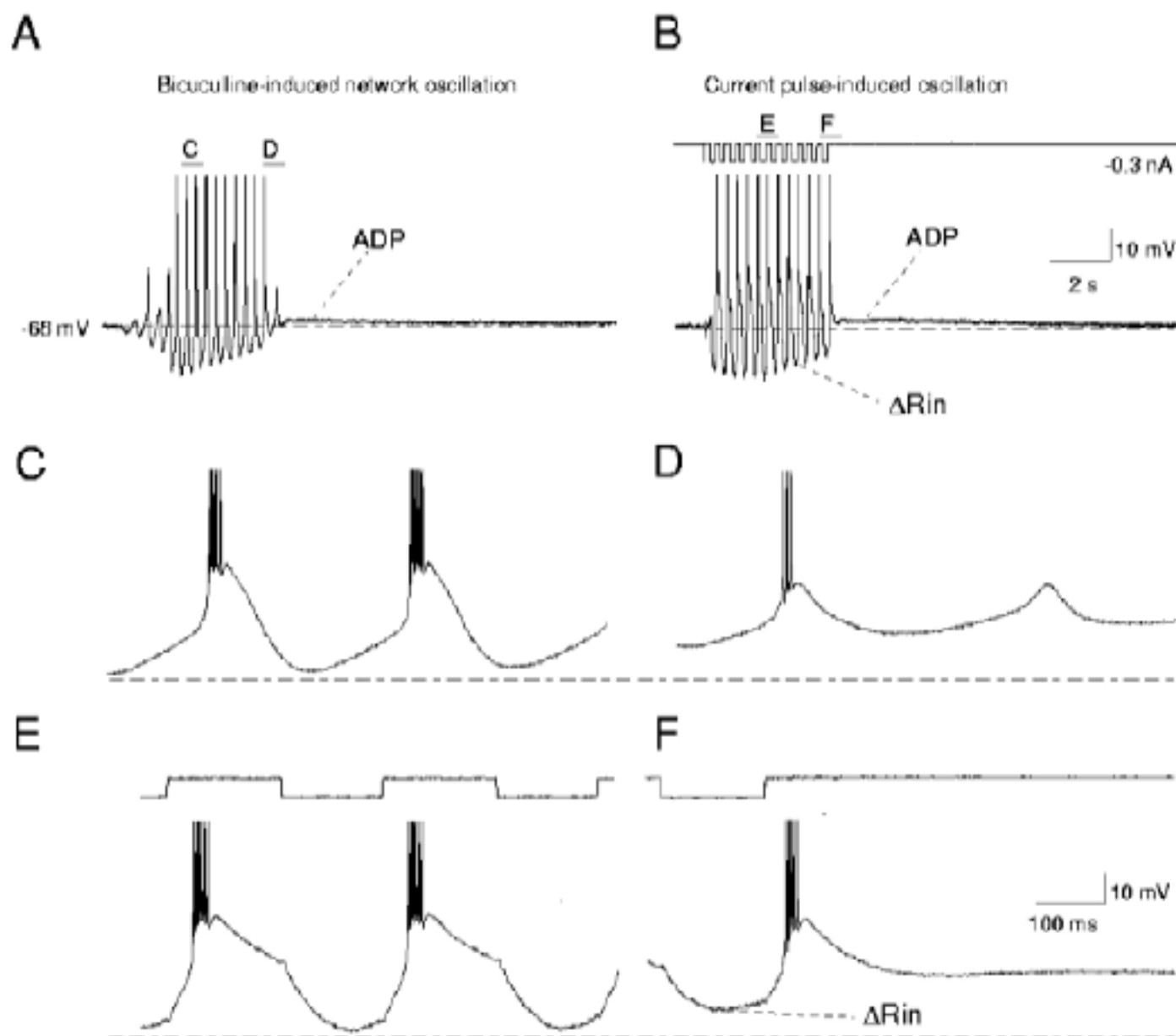


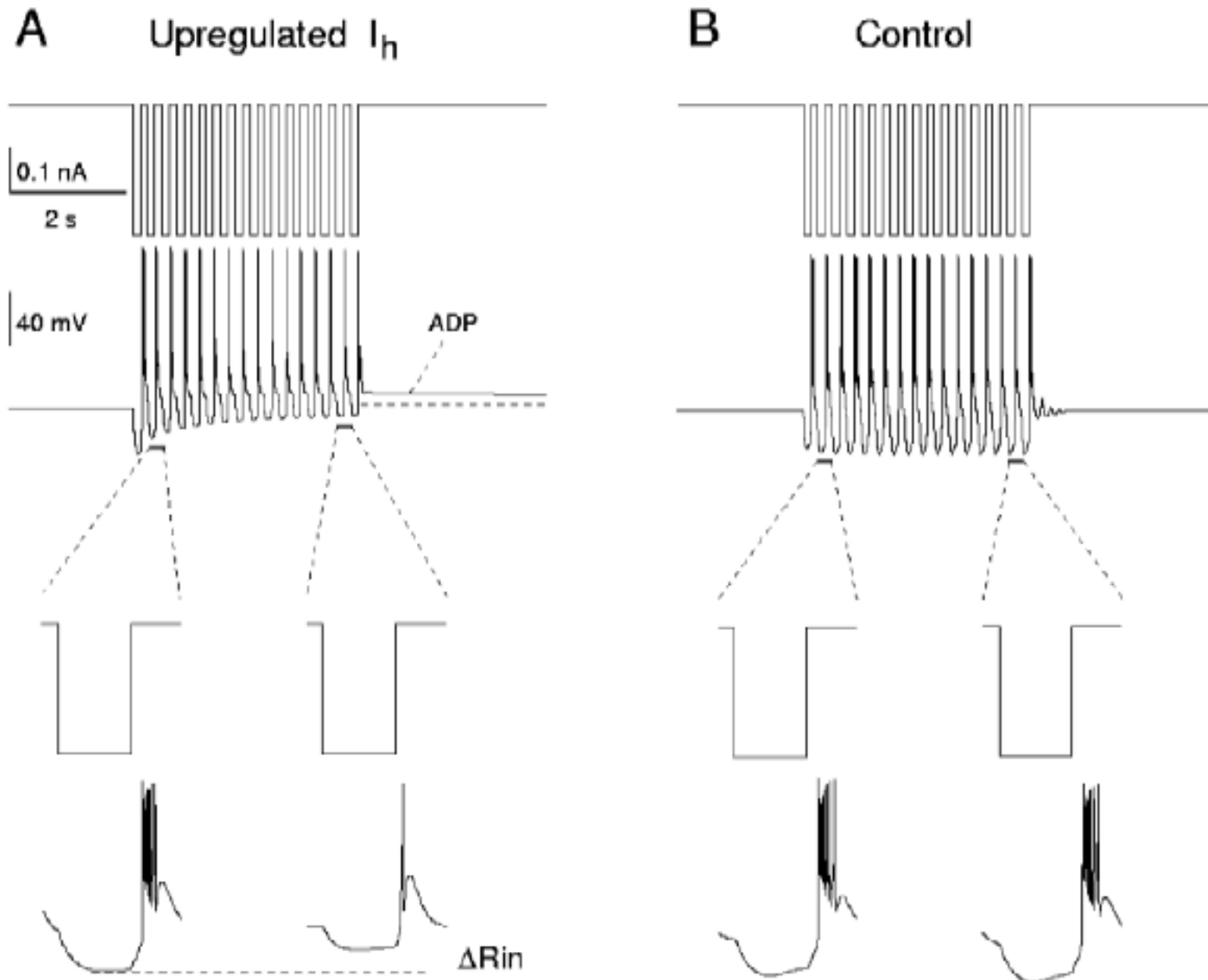
# Calcium regulation of the H-current



# Oscillations from IT - I<sub>h</sub> - Calcium interaction

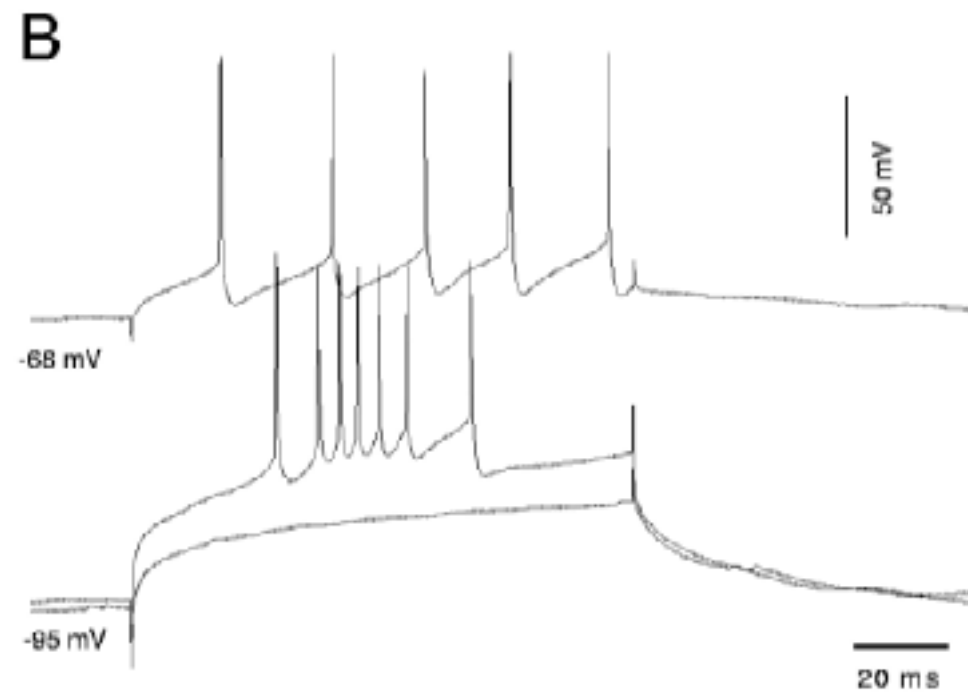
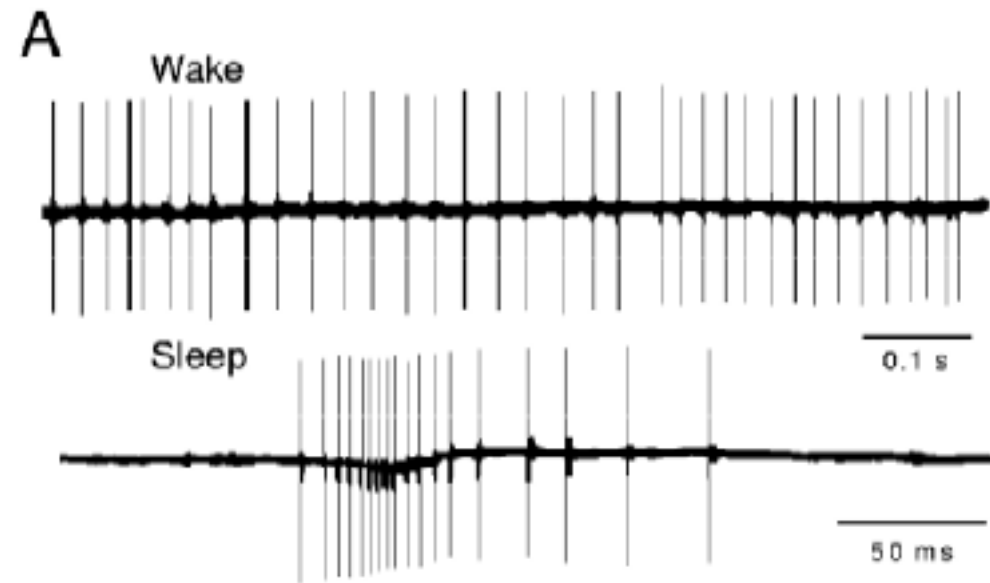




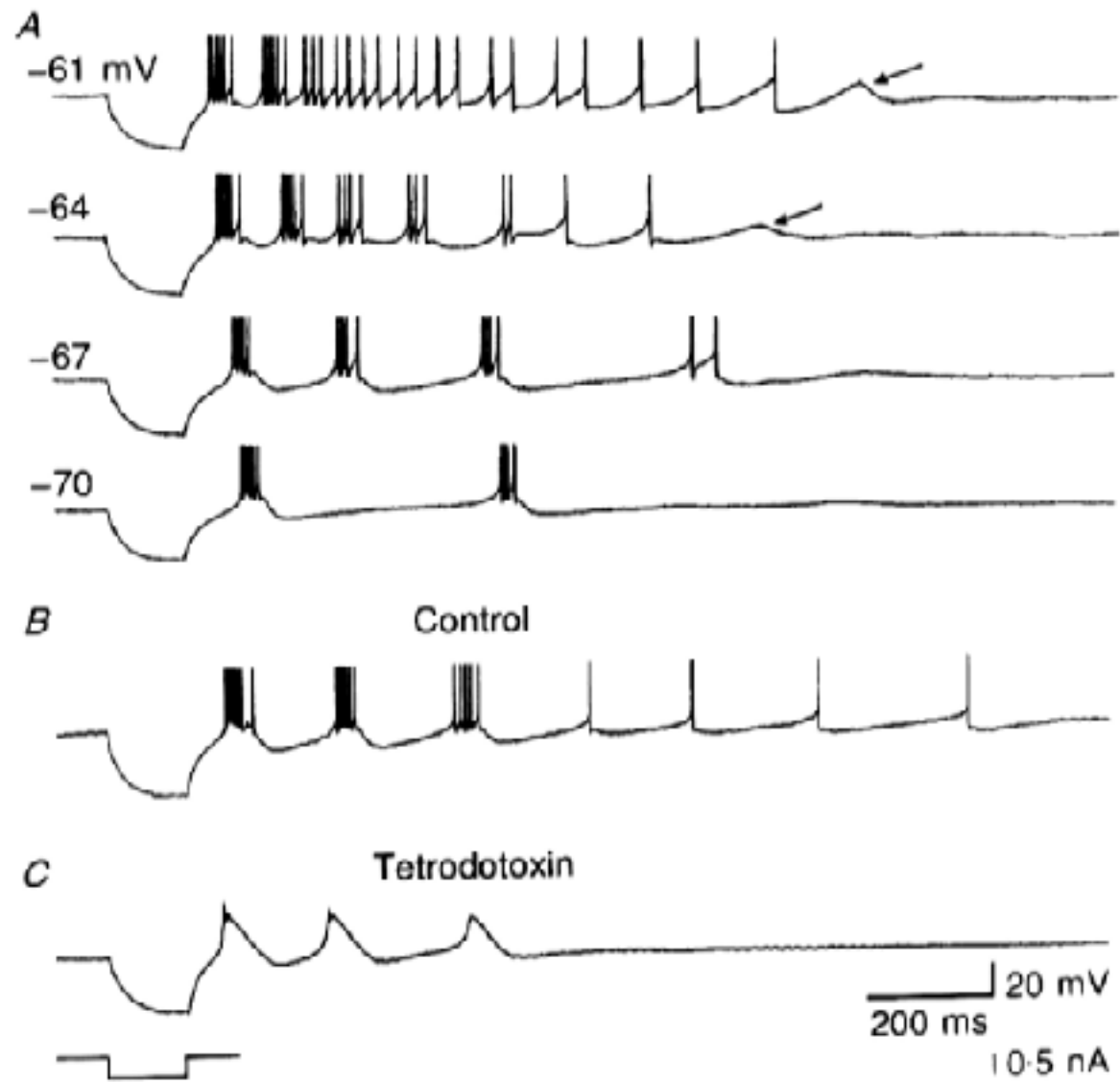




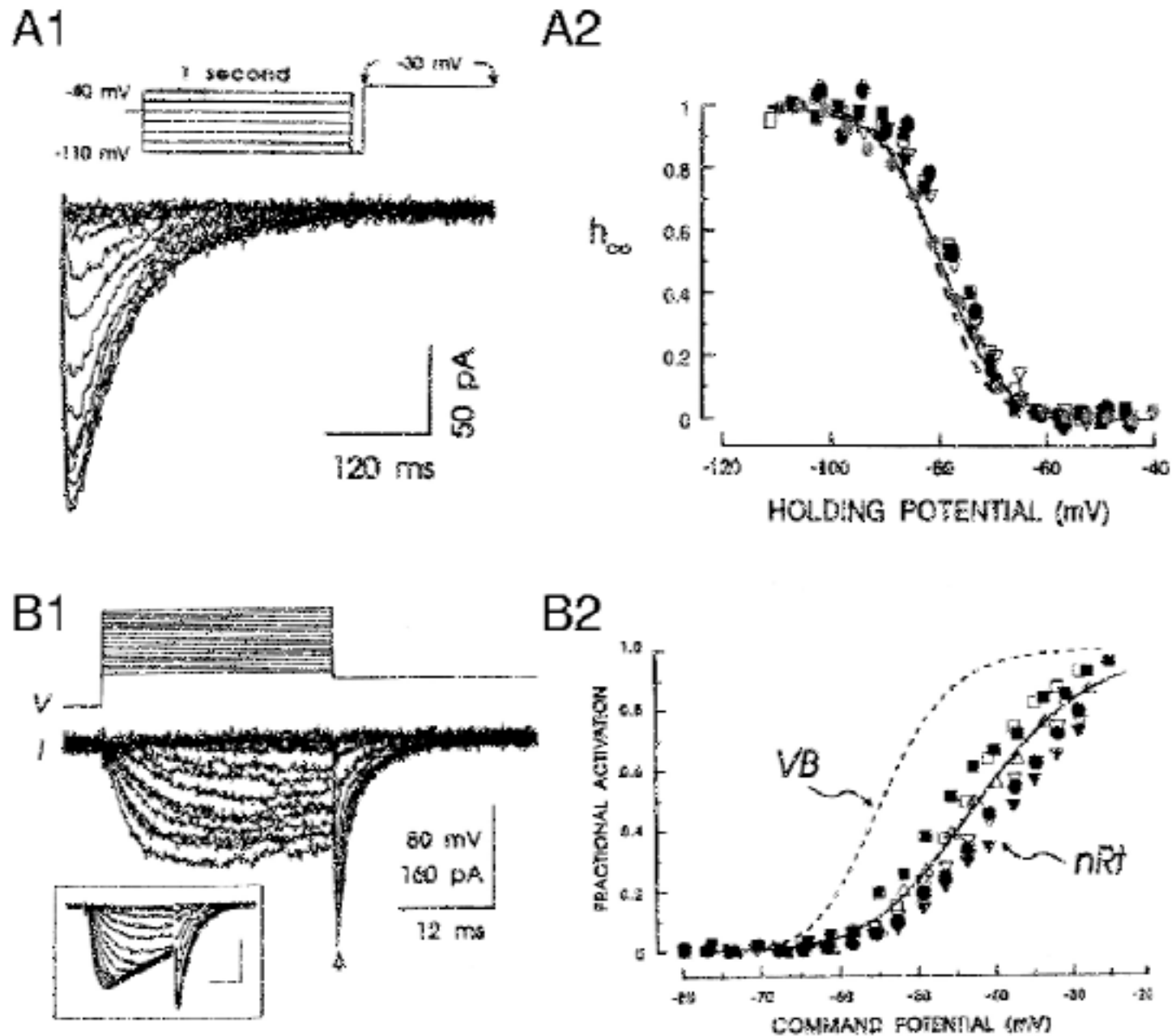
# Thalamic reticular neurons



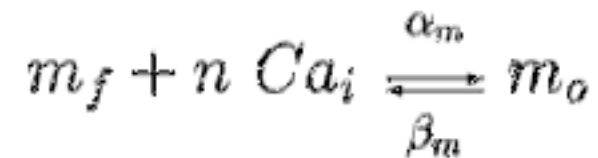
# Repetitive bursting properties



# Characterization of IT in RE cells



# Calcium-dependent potassium currents (K[Ca])

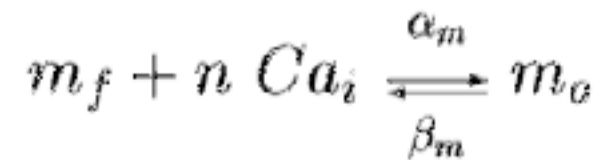


$$g_{K[Ca]}(V) = \bar{g}_{K[Ca]} m^4(V)$$

Equations cinétiques:

$$\frac{dm}{dt} = \alpha_m [\text{Ca}_i]^n (1 - m) - \beta_m m$$

# Calcium-dependent cation currents (CAN)

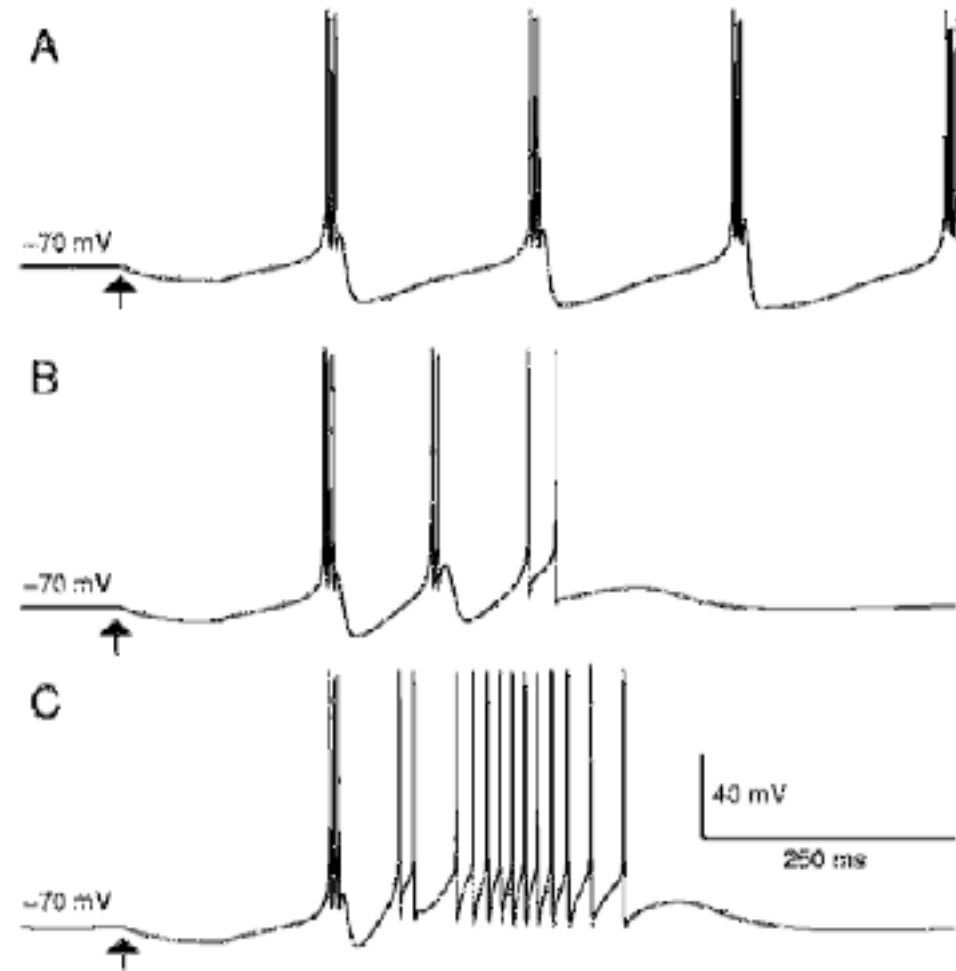
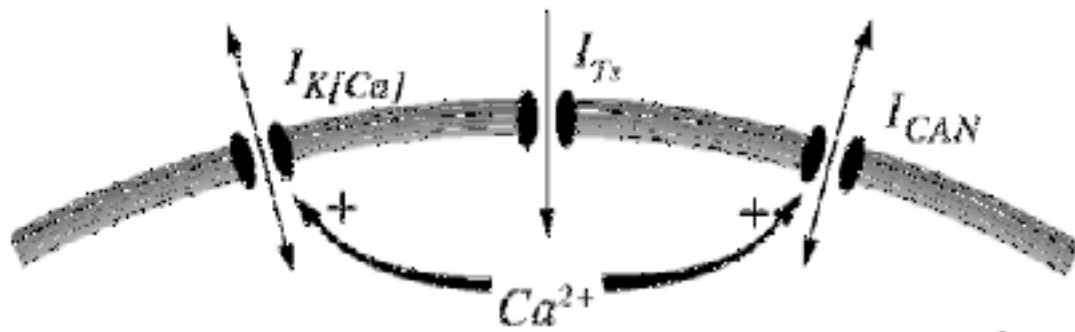


$$g_{CAN}(V) = \bar{g}_{CAN} m^4(V)$$

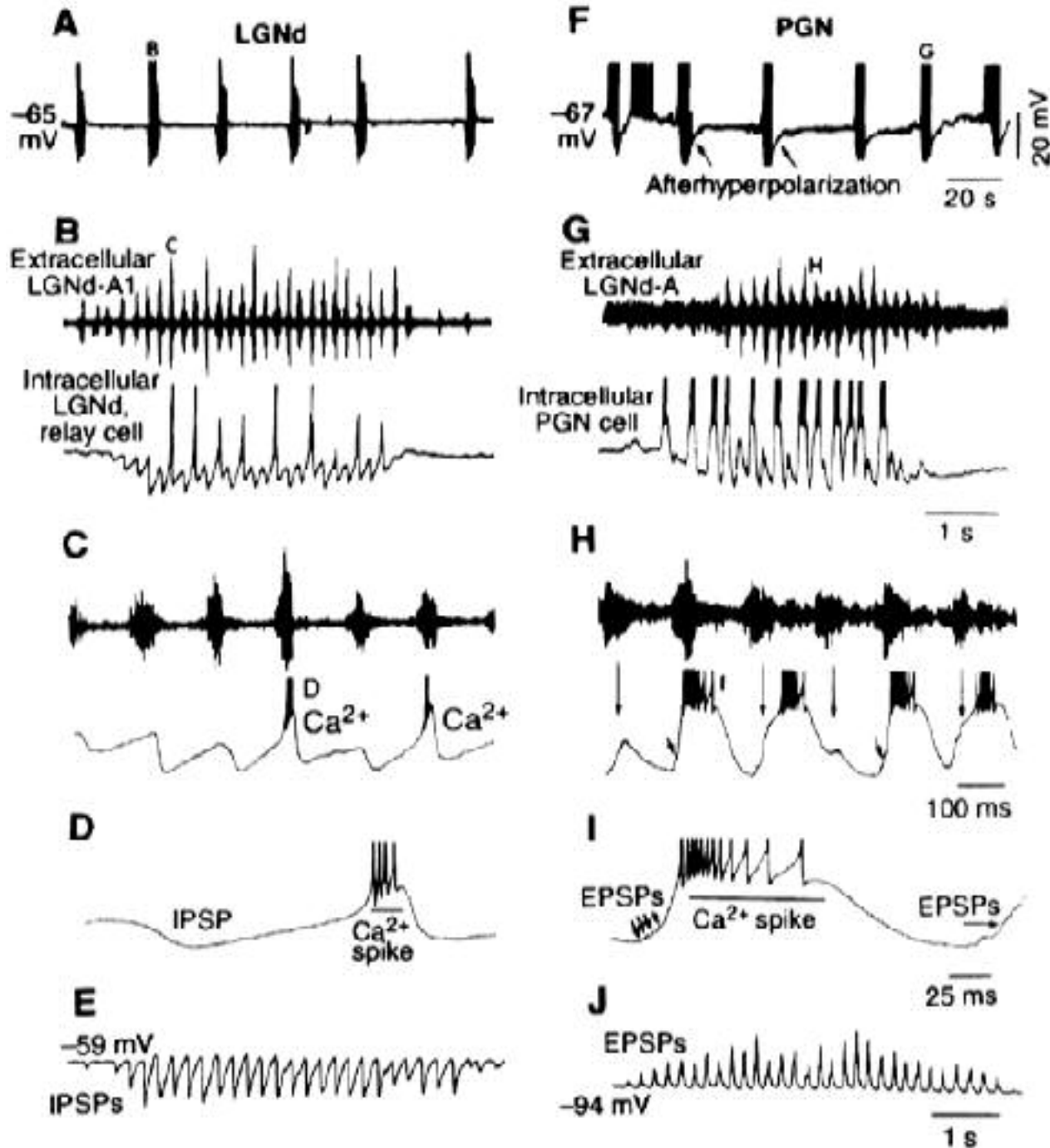
Equations cinétiques:

$$\frac{dm}{dt} = \alpha_m [Ca_i]^n (1 - m) - \beta_m m$$

# Repetitive bursting from IT, IK[Ca], ICAN interaction

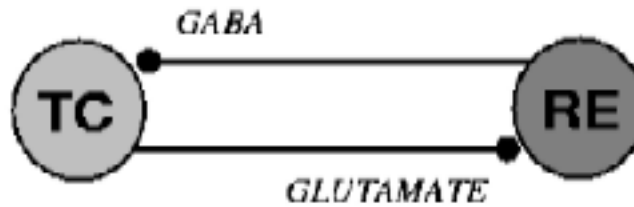


# Thalamic oscillations *in vitro*



# Model of thalamic oscillations

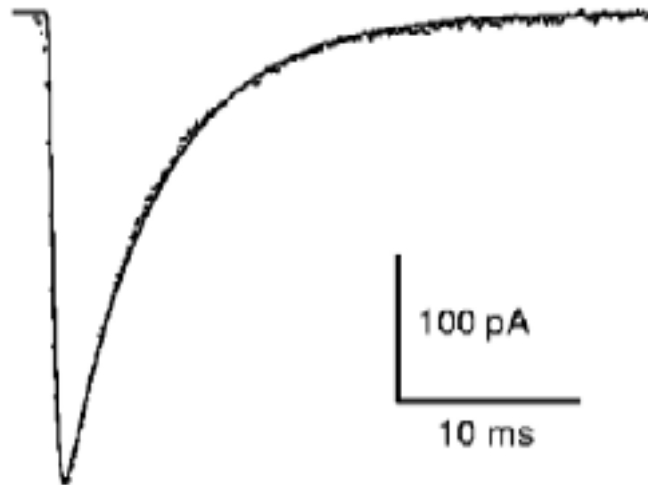
TC cells: IT, I<sub>h</sub>,  
Calcium regulation



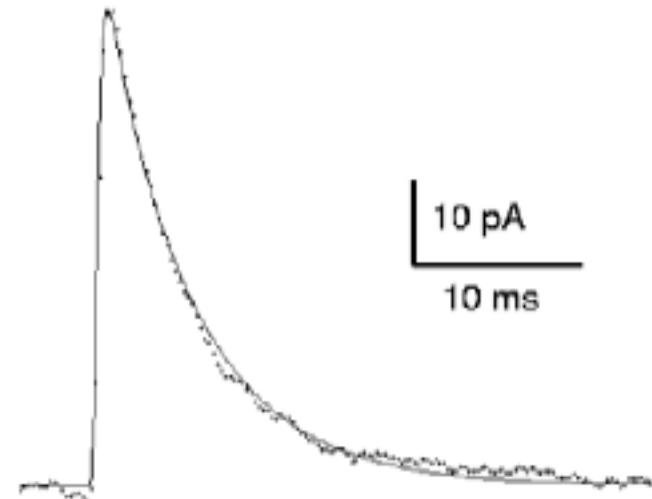
RE cells: IT, I<sub>K</sub>[Ca],  
ICAN, Calcium

Synapses:

Glutamate AMPA receptors

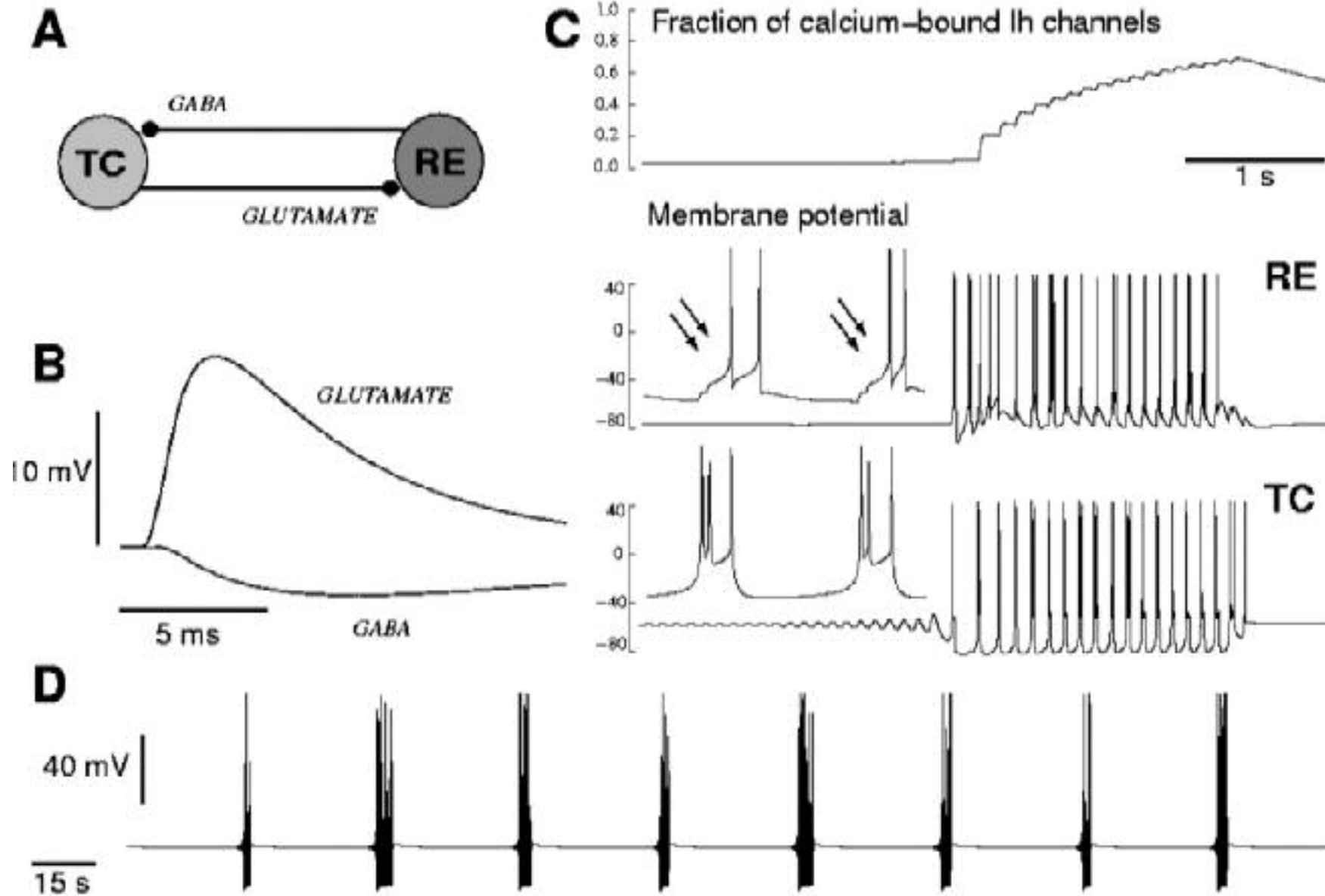


GABA(A) receptors

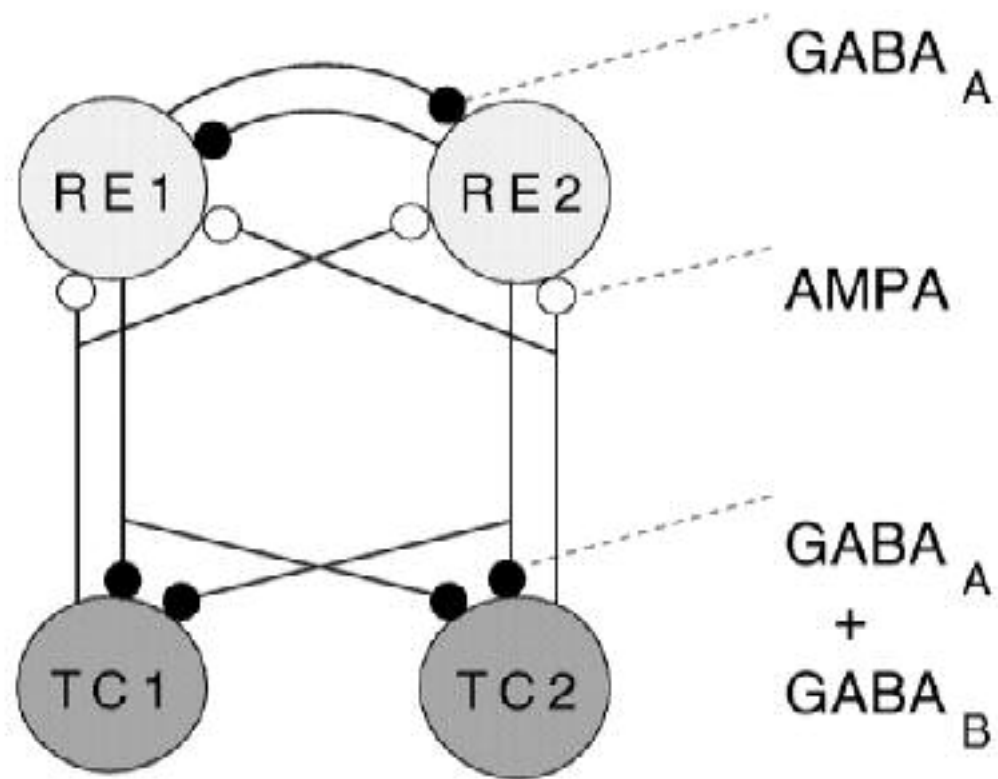




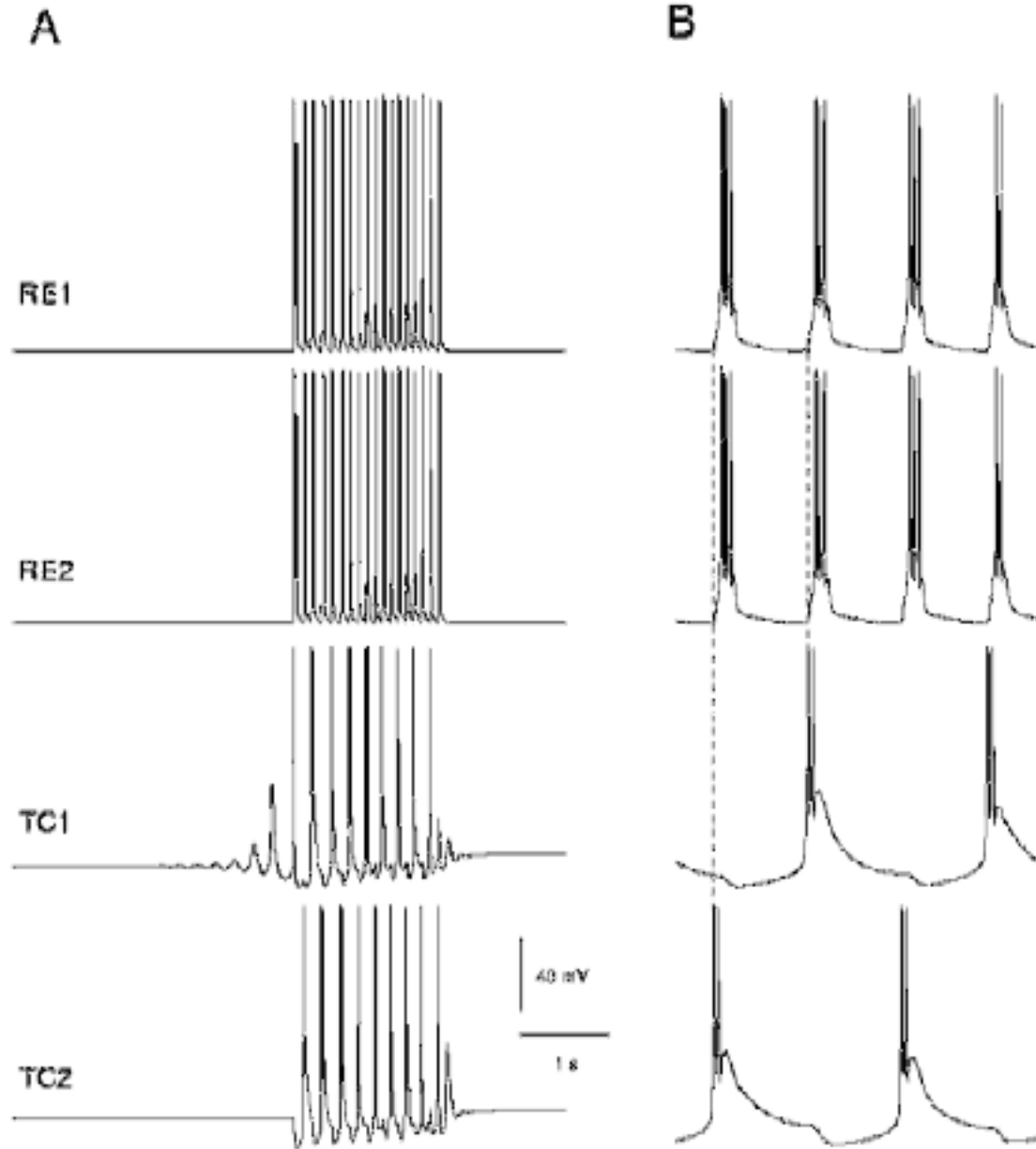
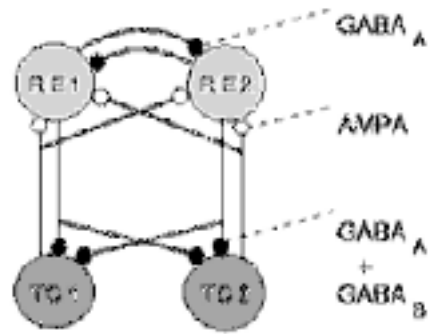
# Model of thalamic oscillations



# Small circuits of thalamic neurons

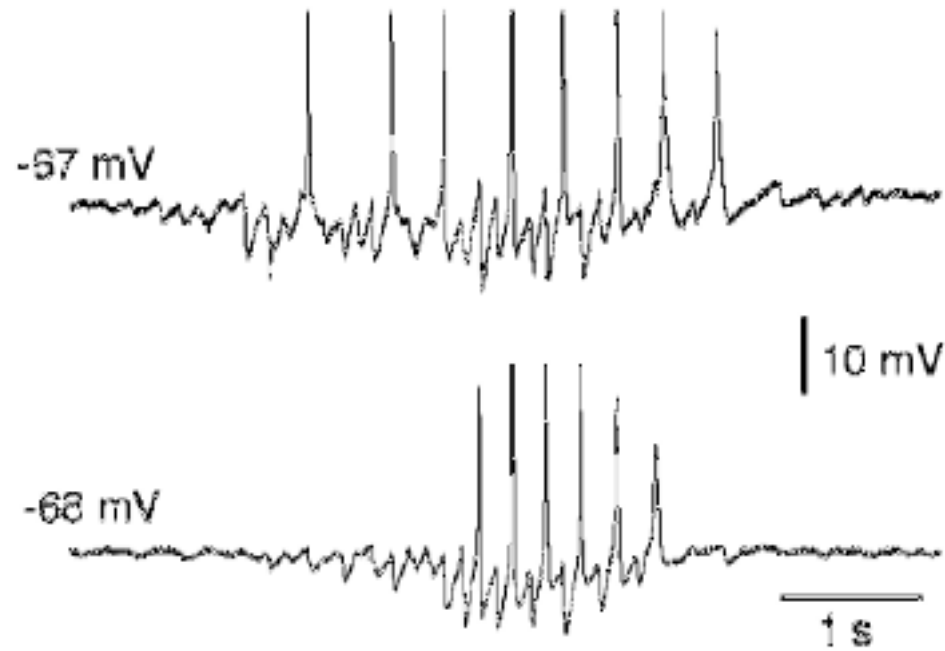


# Small circuits of thalamic neurons

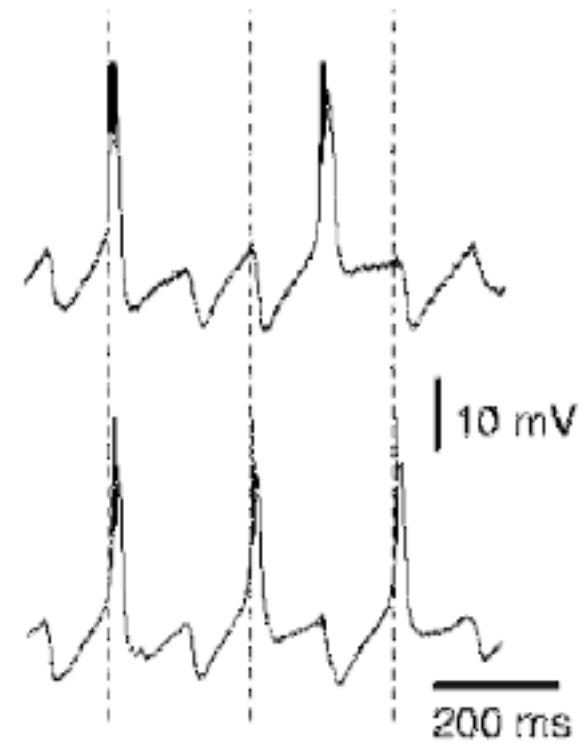


# Small circuits of thalamic neurons

A



B



## Simulation de neurones et synapses en temps réel

