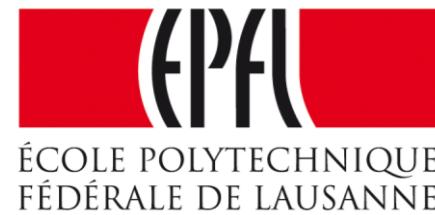


# Week 2 – part 1: Biophysics of neurons



## Neuronal Dynamics: Computational Neuroscience of Single Neurons

### Week 2 – Biophysical modeling: The Hodgkin-Huxley model

Wulfram Gerstner

EPFL, Lausanne, Switzerland

#### 2.1 Biophysics of neurons

- Overview

#### 2.2 Reversal potential

- Nernst equation

#### 2.3 Hodgkin-Huxley Model

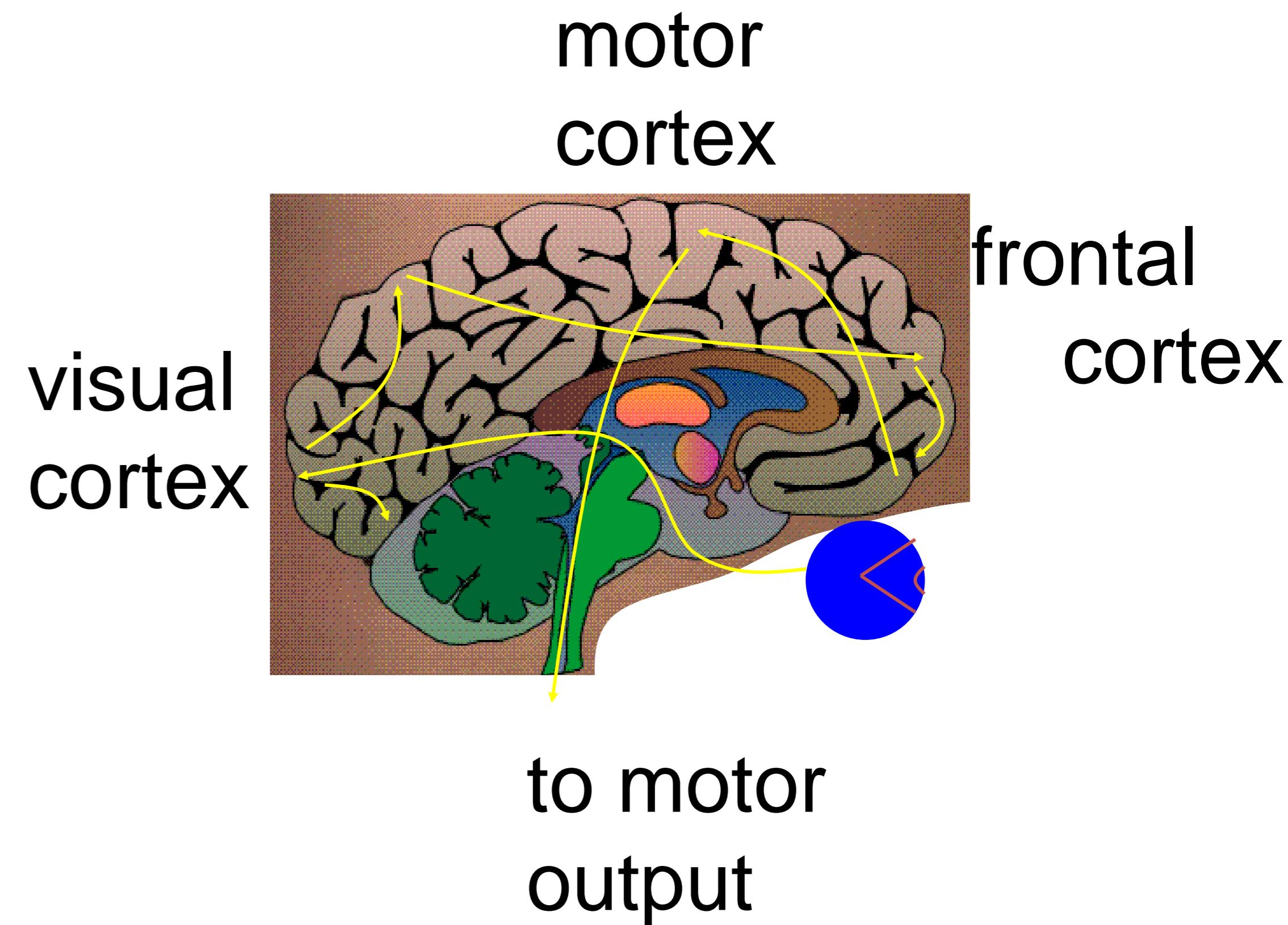
#### 2.4 Threshold in the Hodgkin-Huxley Model

- where is the firing threshold?

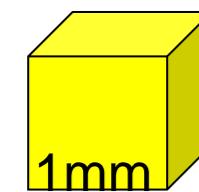
#### 2.5. Detailed biophysical models

- the zoo of ion channels

# Neuronal Dynamics – 2.1. Introduction

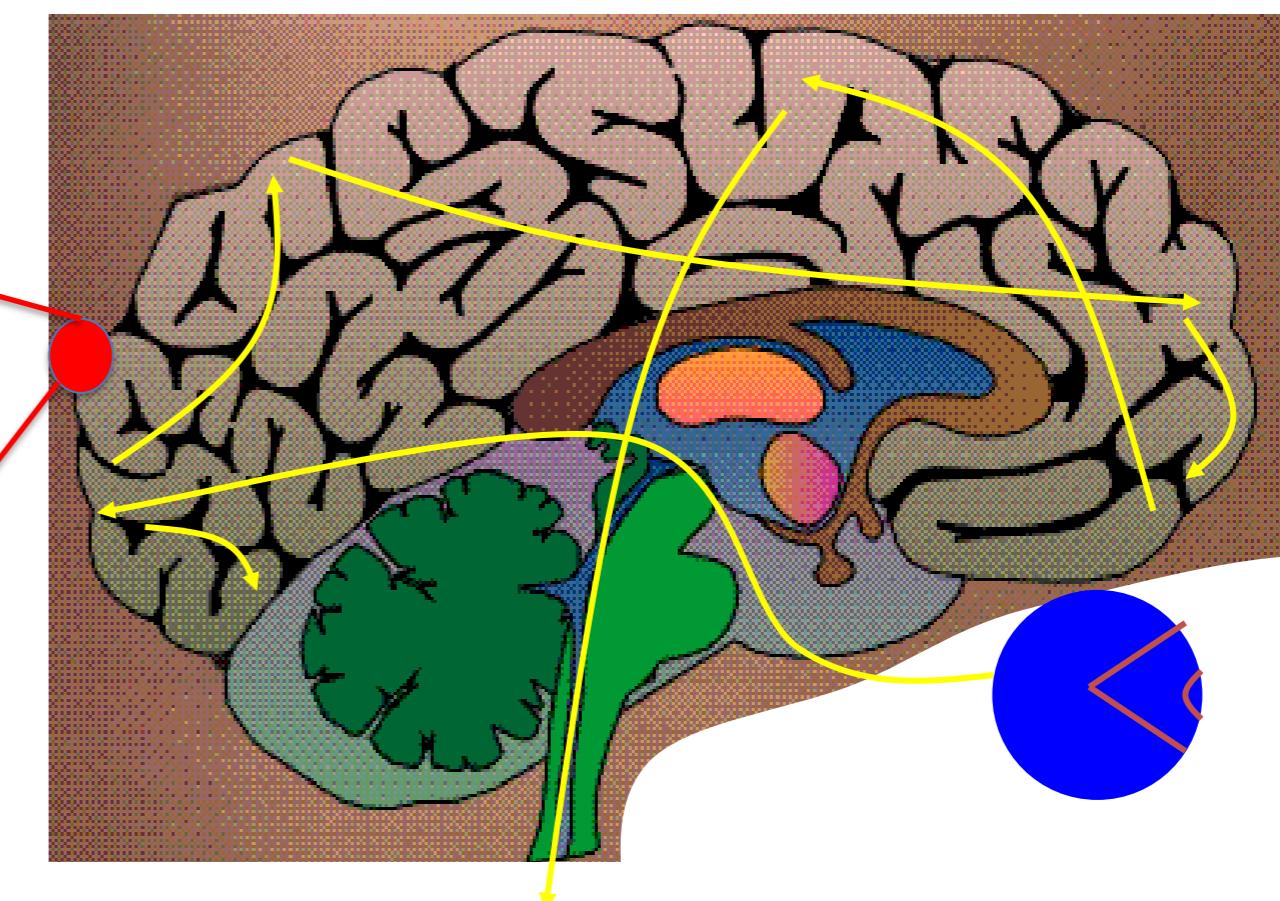
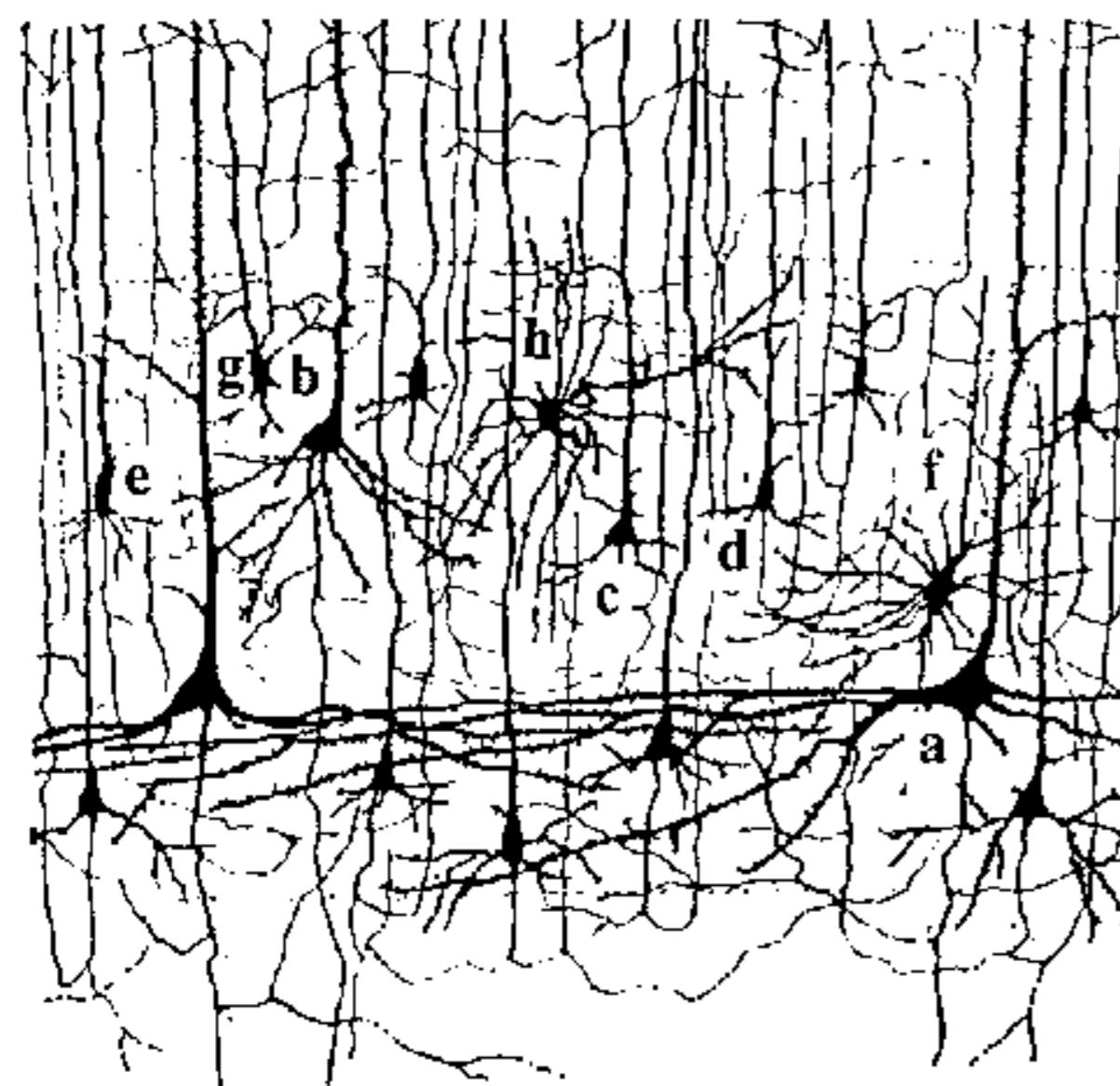


# Neuronal Dynamics – 2.1. Introduction



10 000 neurons

3 km wires

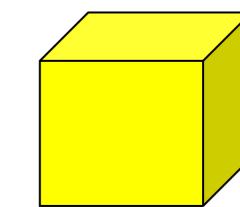


motor  
cortex

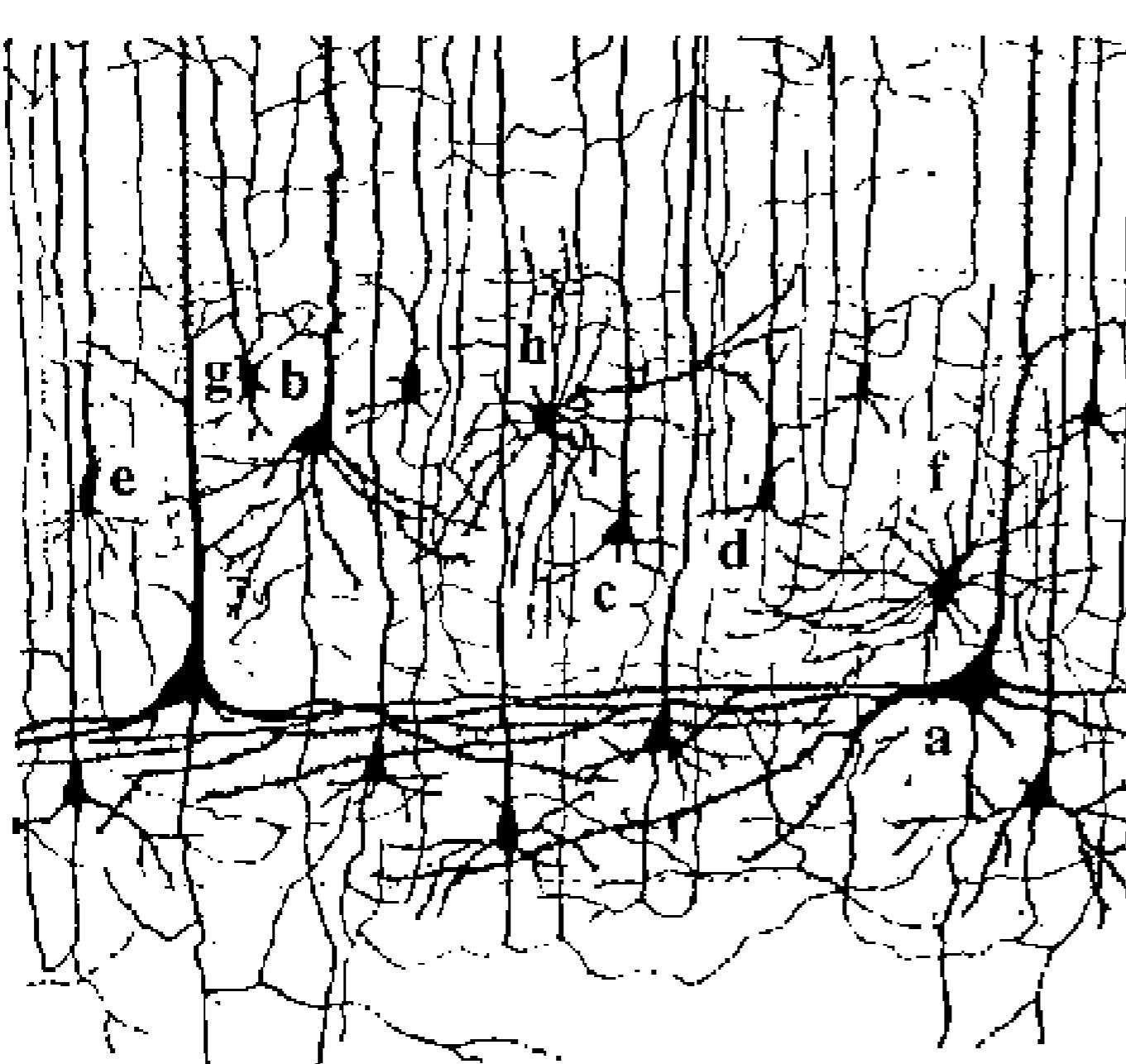
frontal  
cortex

to motor  
output

# Neuronal Dynamics – 2.1 Introduction

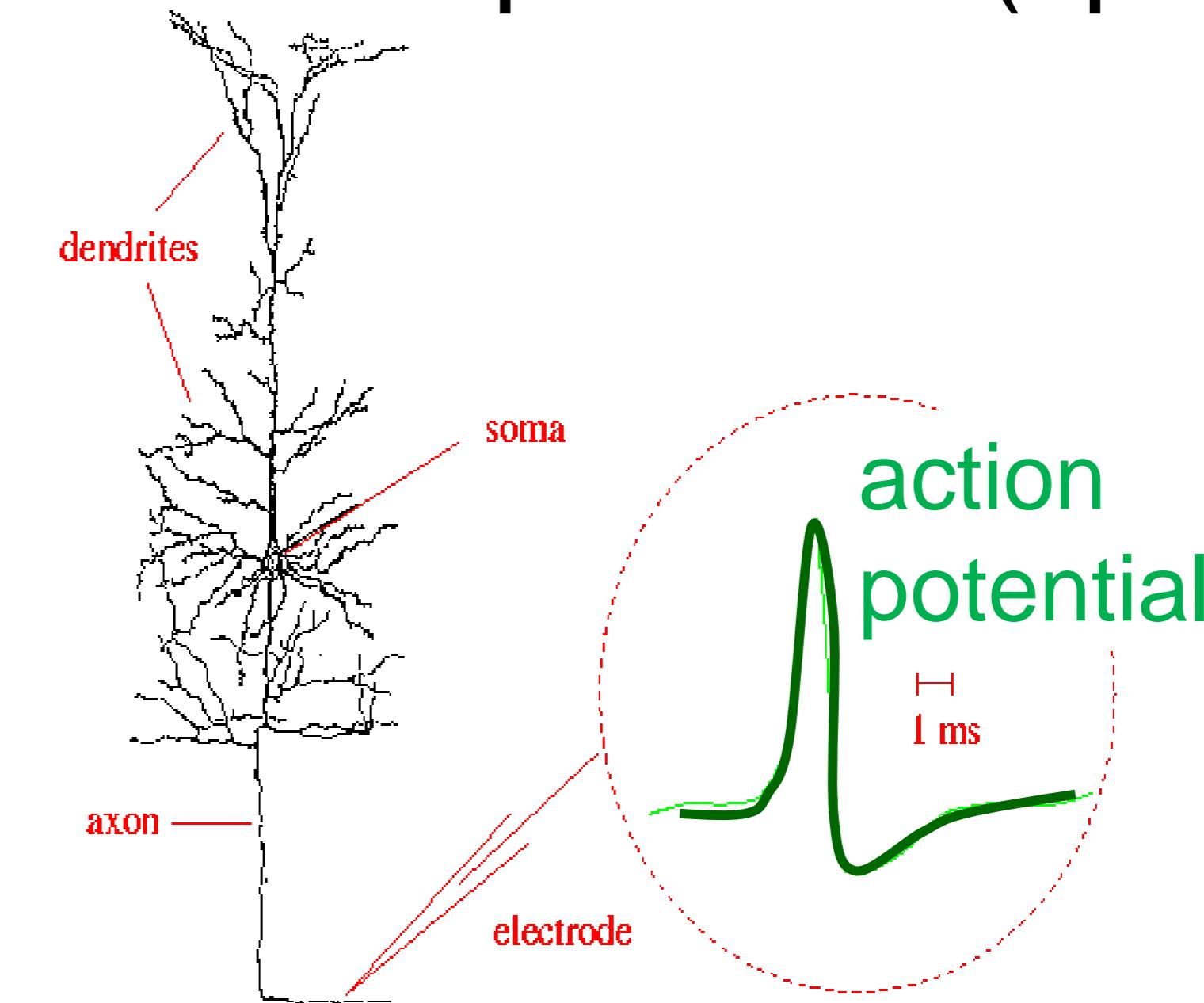


10 000 neurons  
1mm



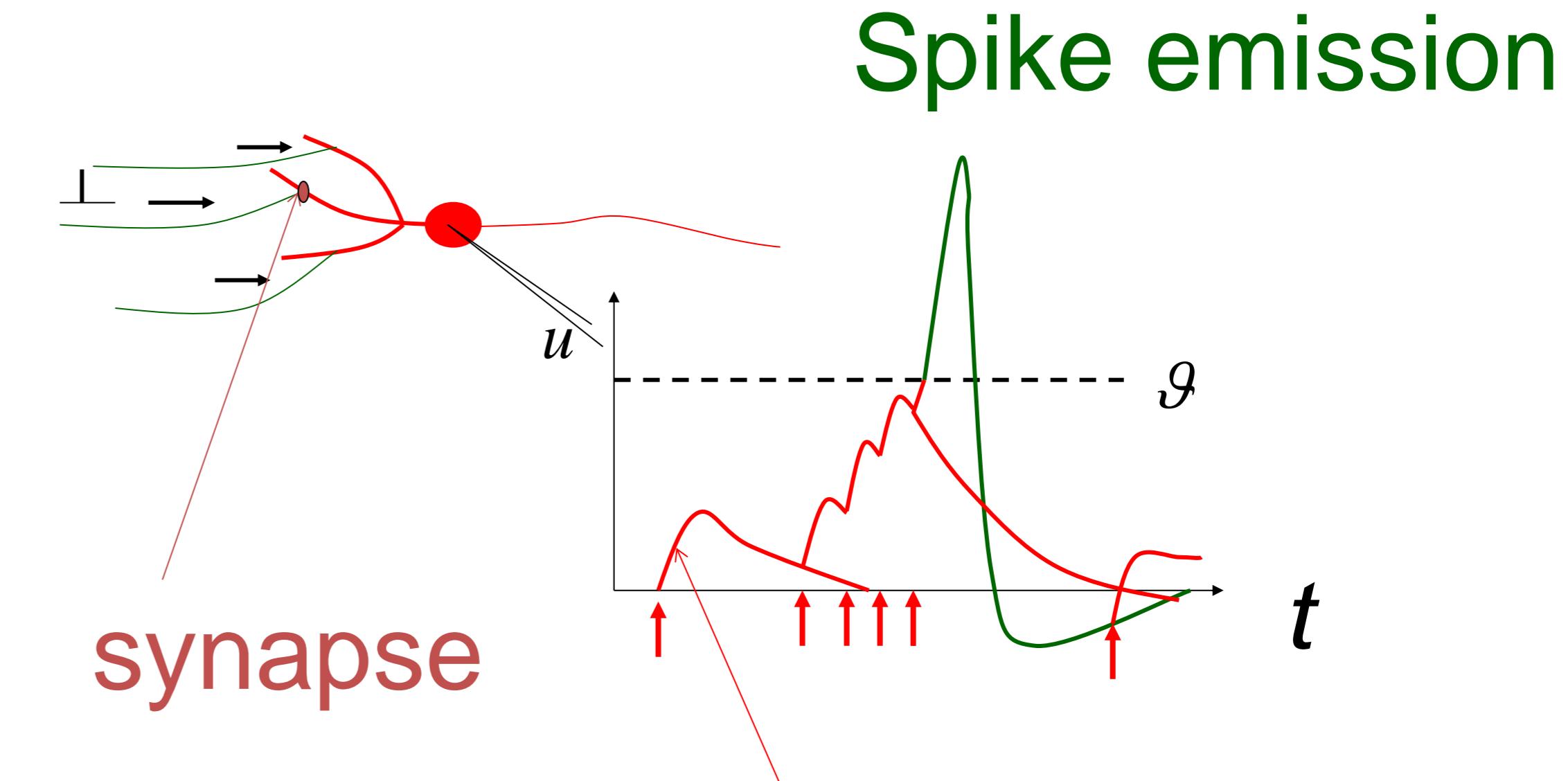
*Ramon y Cajal*

Signal:  
action potential (spike)



How is a spike generated?

# Review of week 1: Integrate-and-Fire models



Postsynaptic potential

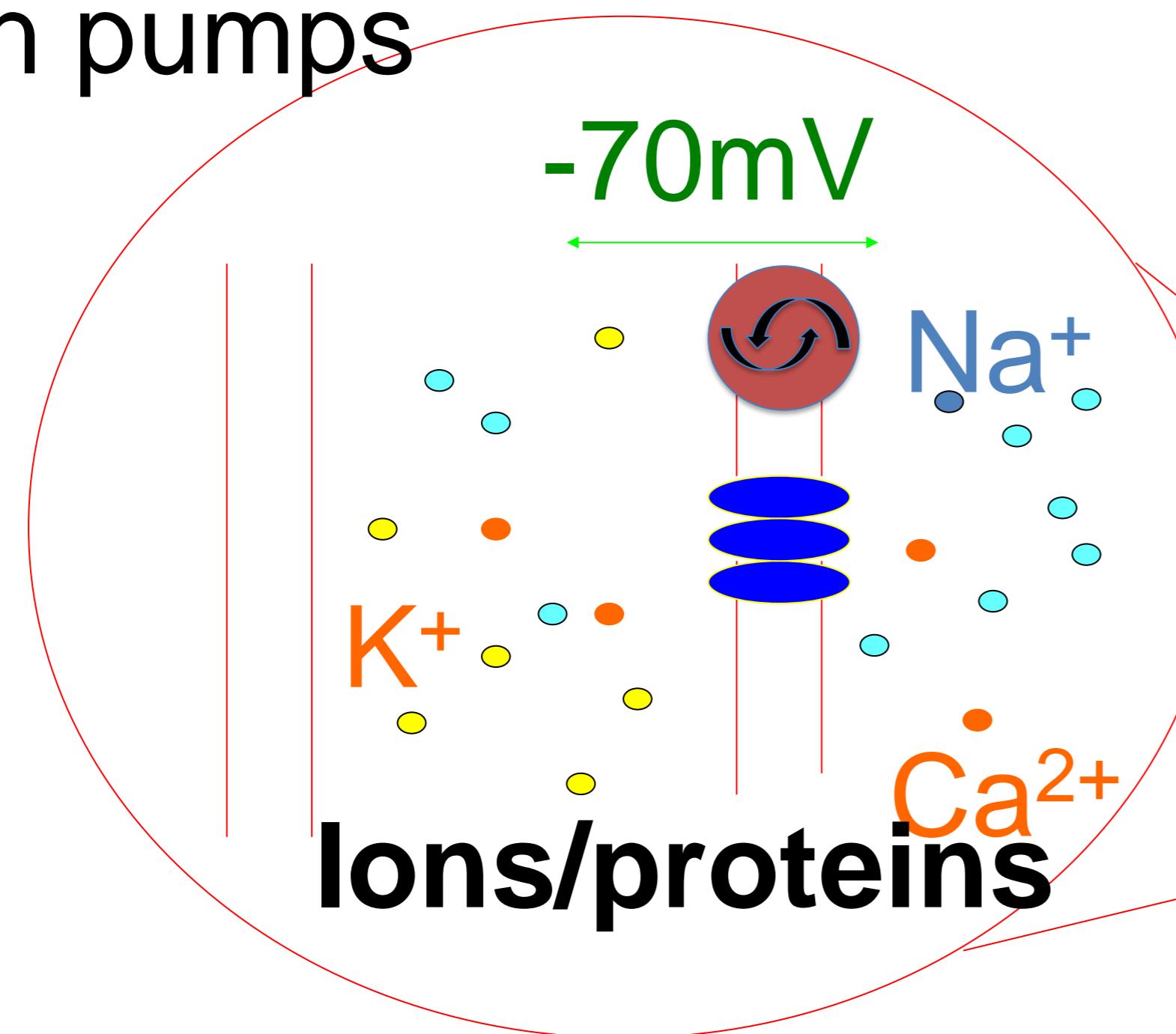
- spikes are events
- triggered at threshold
- spike/reset/refractoriness

# Neuronal Dynamics – week 2: Biophysics of neurons

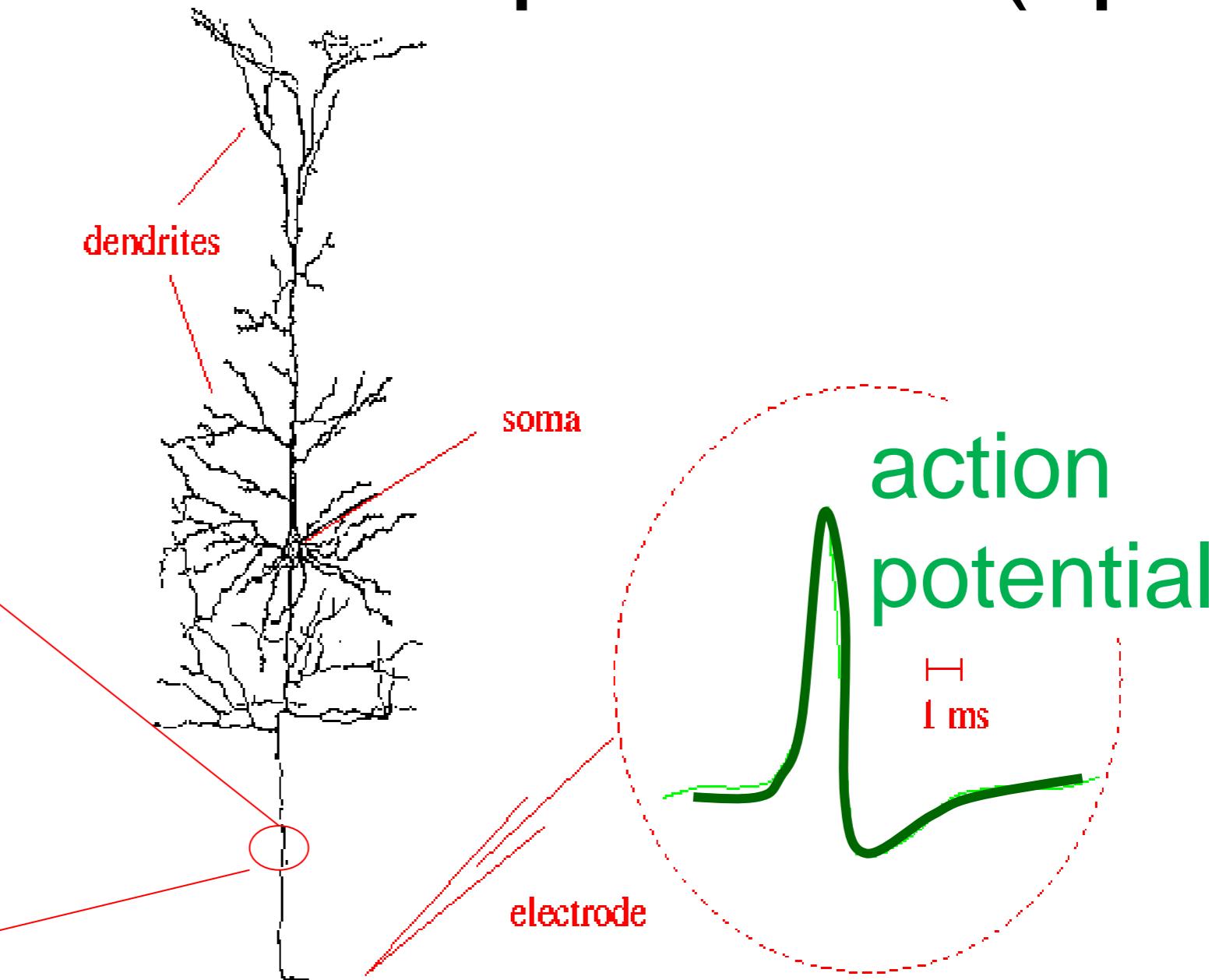
Cell surrounded by membrane

Membrane contains

- ion channels
- ion pumps



Signal:  
action potential (spike)

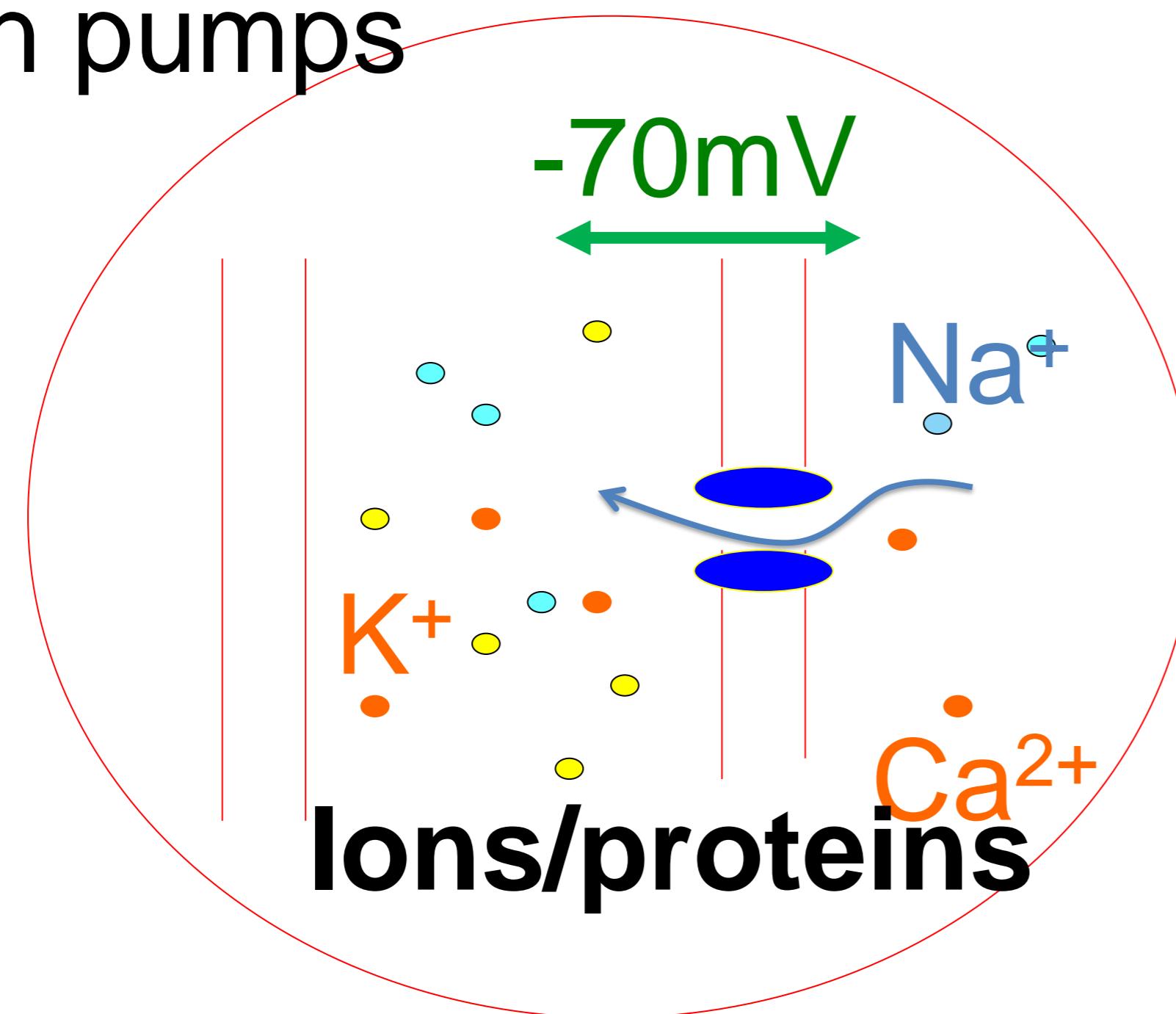


# Neuronal Dynamics – week 2: Biophysics of neurons

Cell surrounded by membrane

Membrane contains

- ion channels
- ion pumps



Resting potential  $-70mV$   
→ how does it arise?

Ions flow through channel  
→ in which direction?

Neuron emits action potentials  
→ why?

# Neuronal Dynamics – 2.1. Biophysics of neurons

Resting potential -70mV  
→ how does it arise?

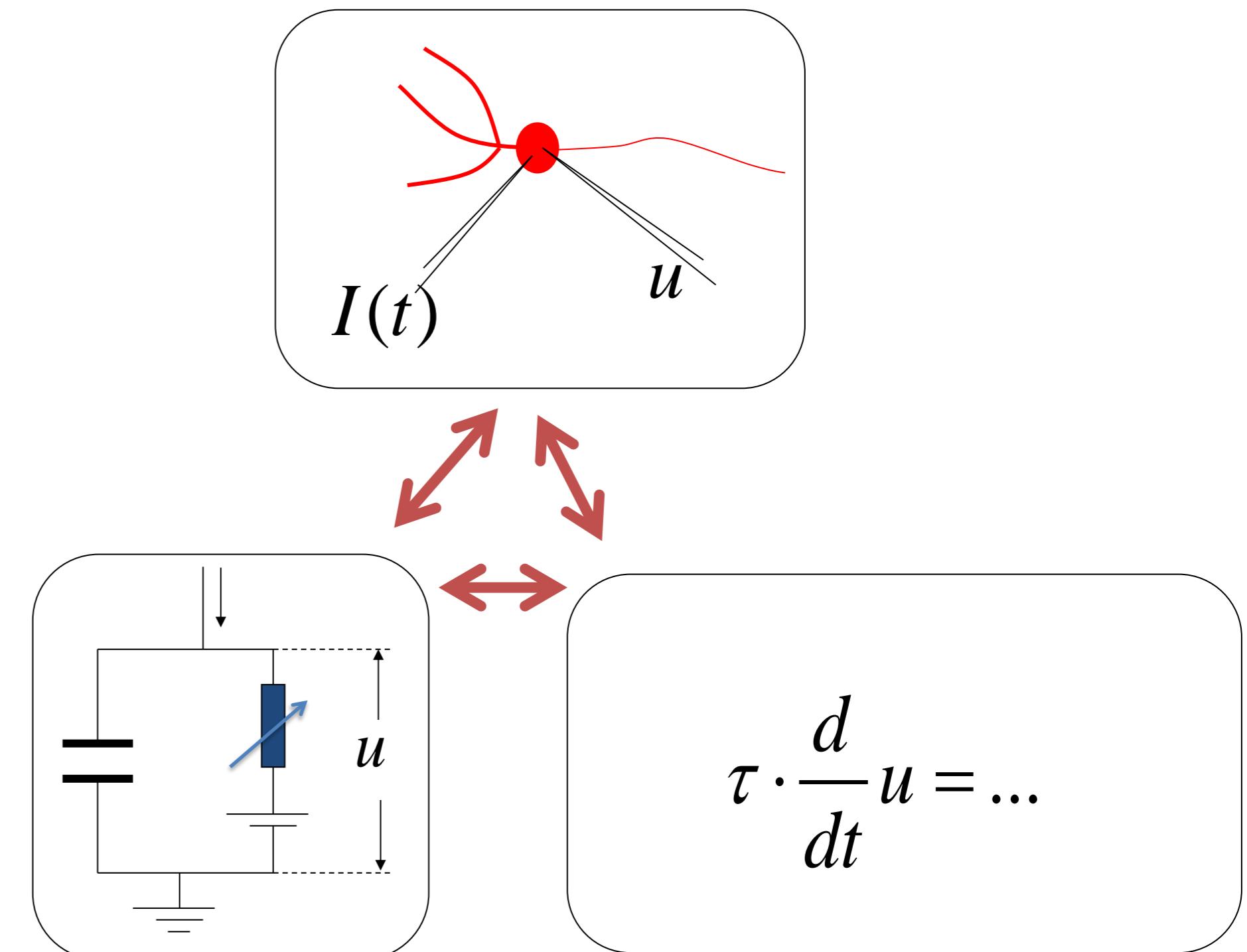
Ions flow through channel  
→ in which direction?

Neuron emits action potentials  
→ why?

→ Hodgkin-Huxley model

*Hodgkin & Huxley (1952)*  
*Nobel Prize 1963*

# Neuronal Dynamics – 2.1. Biophysics of neurons



→Hodgkin-Huxley model

*Hodgkin&Huxley (1952)*  
*Nobel Prize 1963*

# Neuronal Dynamics – Exercises 2.1

In a natural situation, the electrical potential inside a neuron is

- the same as outside
- is different by 50-100 microvolt
- is different by 50-100 millivolt

Neurons and cells

- Neurons are special cells because they are surrounded by a membrane
- Neurons are just like other cells surrounded by a membrane
- All cells have a cell membrane

Ion channels are

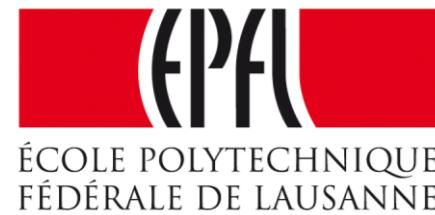
- located in the cell membrane
- special proteins
- can switch from open to closed

If a channel is open, ions can

- flow from the surround into the cell
- flow from inside the cell into the surrounding liquid

*Multiple answers possible!*

# Week 2 – part 2: Reversal potential and Nernst equation



## Neuronal Dynamics: Computational Neuroscience of Single Neurons

### Week 2 – Biophysical modeling: The Hodgkin-Huxley model

Wulfram Gerstner

EPFL, Lausanne, Switzerland



#### 2.1 Biophysics of neurons

- Overview

#### 2.2 Reversal potential

- Nernst equation

#### 2.3 Hodgkin-Huxley Model

#### 2.4 Threshold in the Hodgkin-Huxley Model

- where is the firing threshold?

#### 2.5. Detailed biophysical models

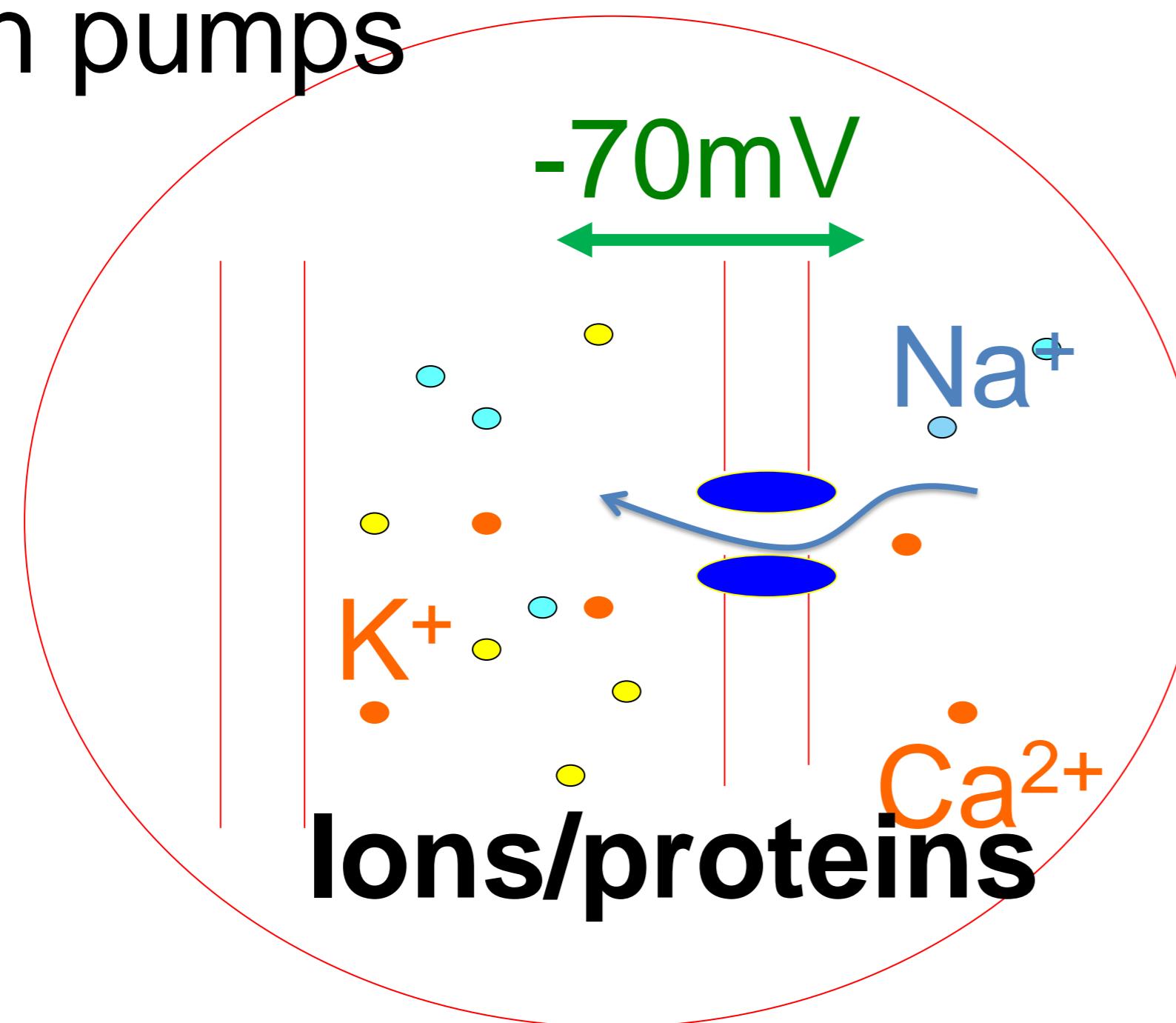
- the zoo of ion channels

# Neuronal Dynamics – 2.2. Resting potential

Cell surrounded by membrane

Membrane contains

- ion channels
- ion pumps



Resting potential  $-70\text{mV}$   
→ how does it arise?

Ions flow through channel  
→ in which direction?

Neuron emits action potentials  
→ why?

# Neuronal Dynamics – 2.2. Resting potential

Resting potential -70mV  
→ how does it arise?

Ions flow through channel  
→ in which direction?

Neuron emits action potentials  
→ why?

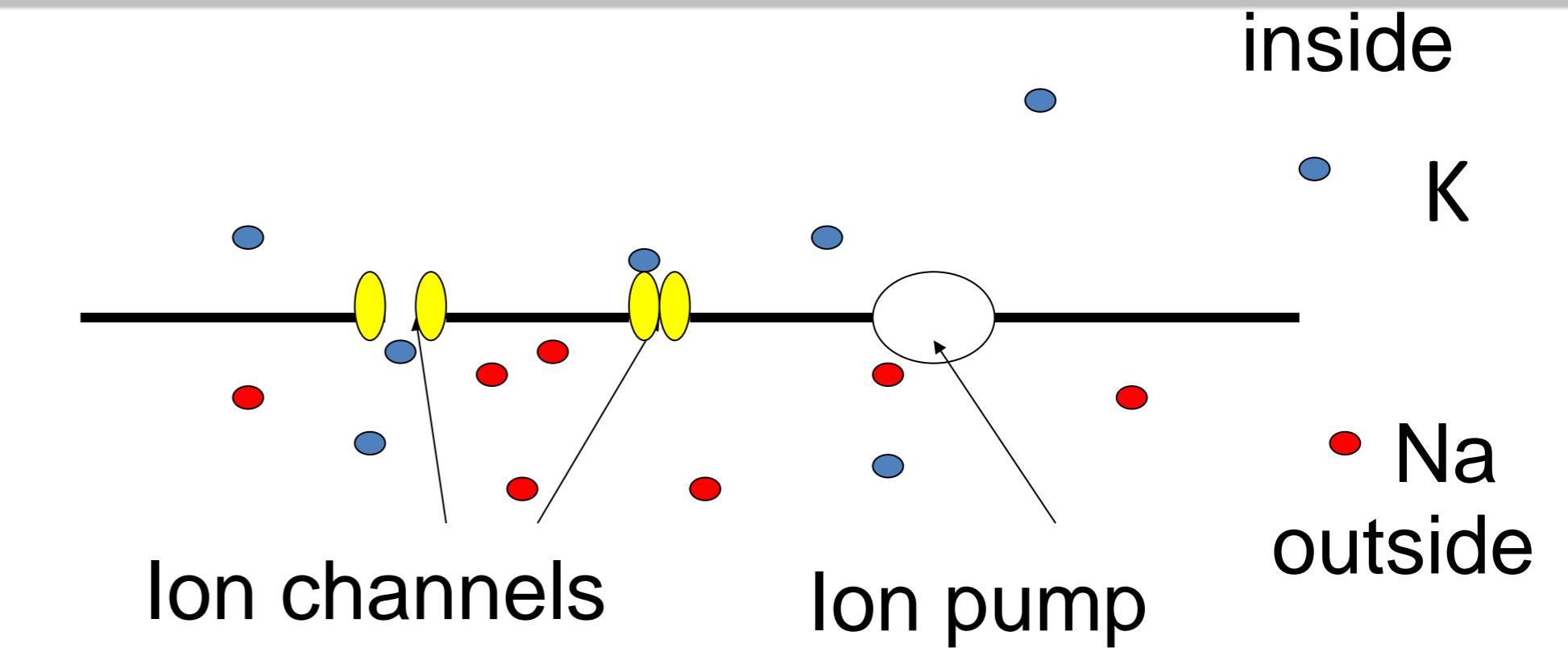
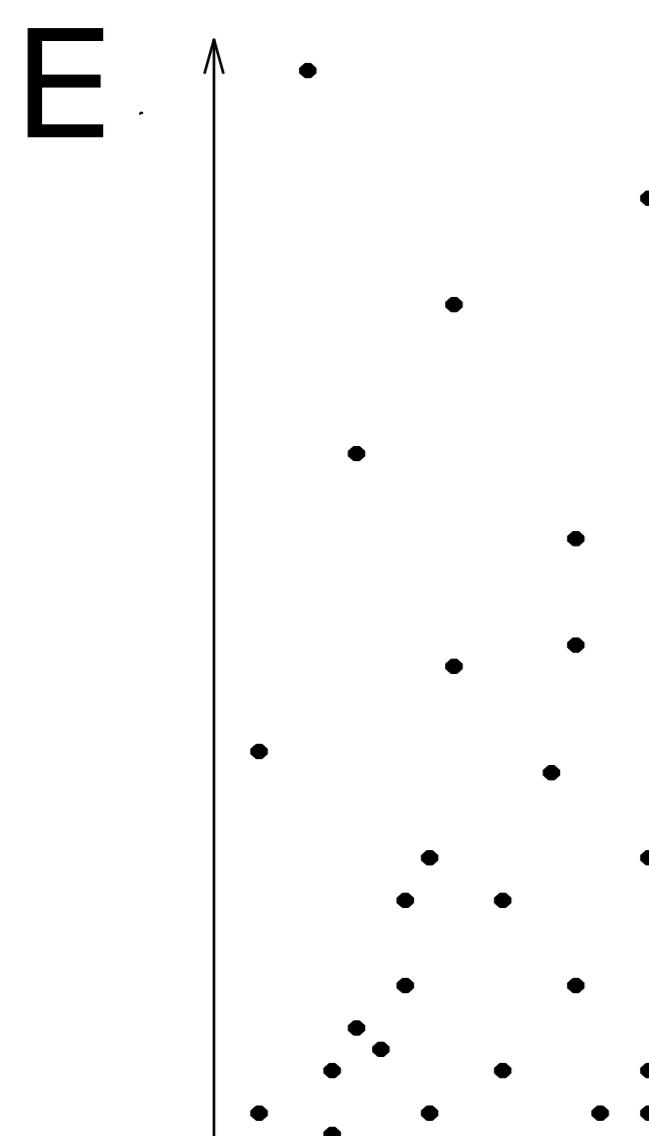
→ Hodgkin-Huxley model

*Hodgkin & Huxley (1952)*  
*Nobel Prize 1963*

# Neuronal Dynamics – 2.2. Reversal potential

density

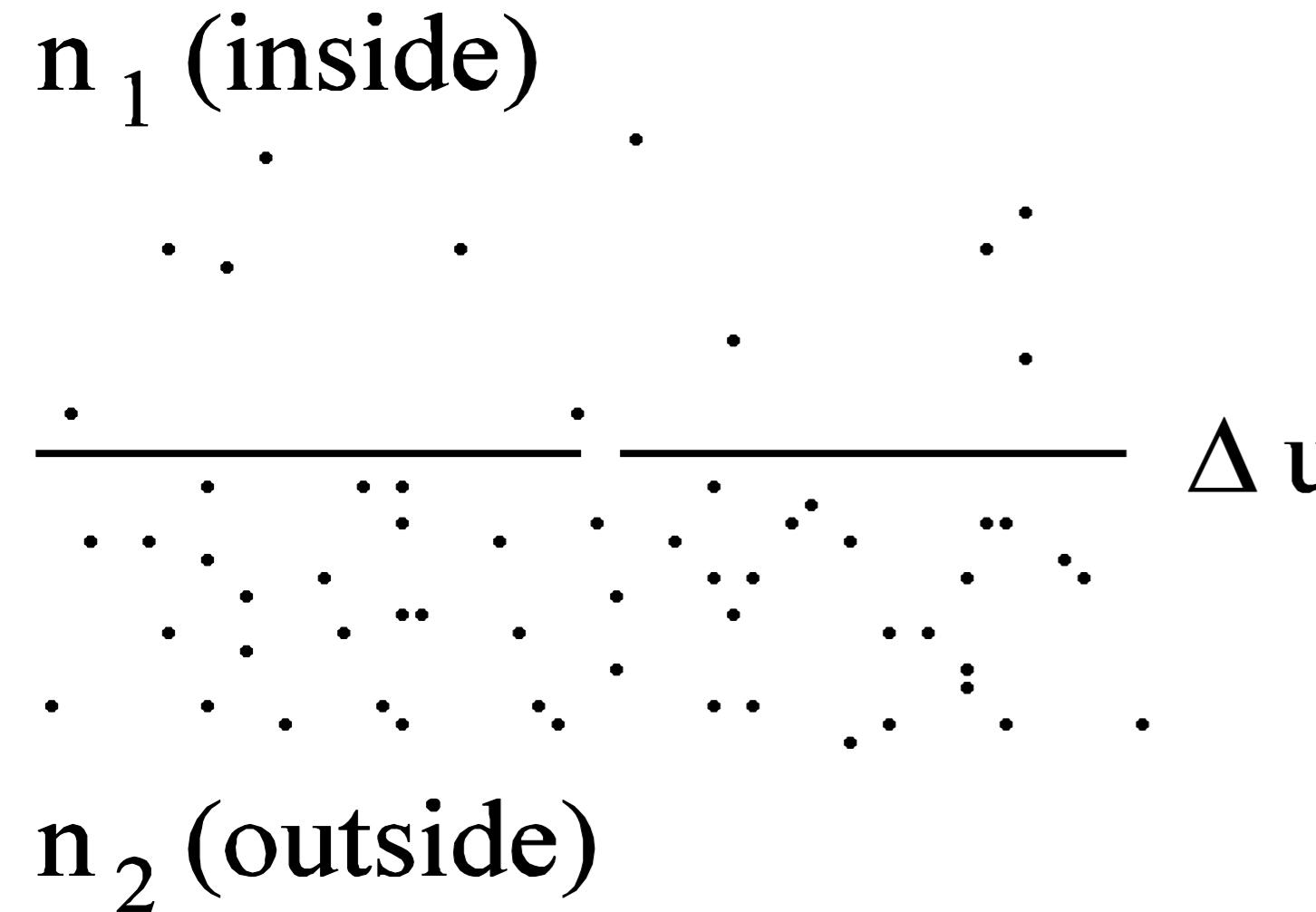
$$n \propto e^{-\frac{E}{kT}}$$



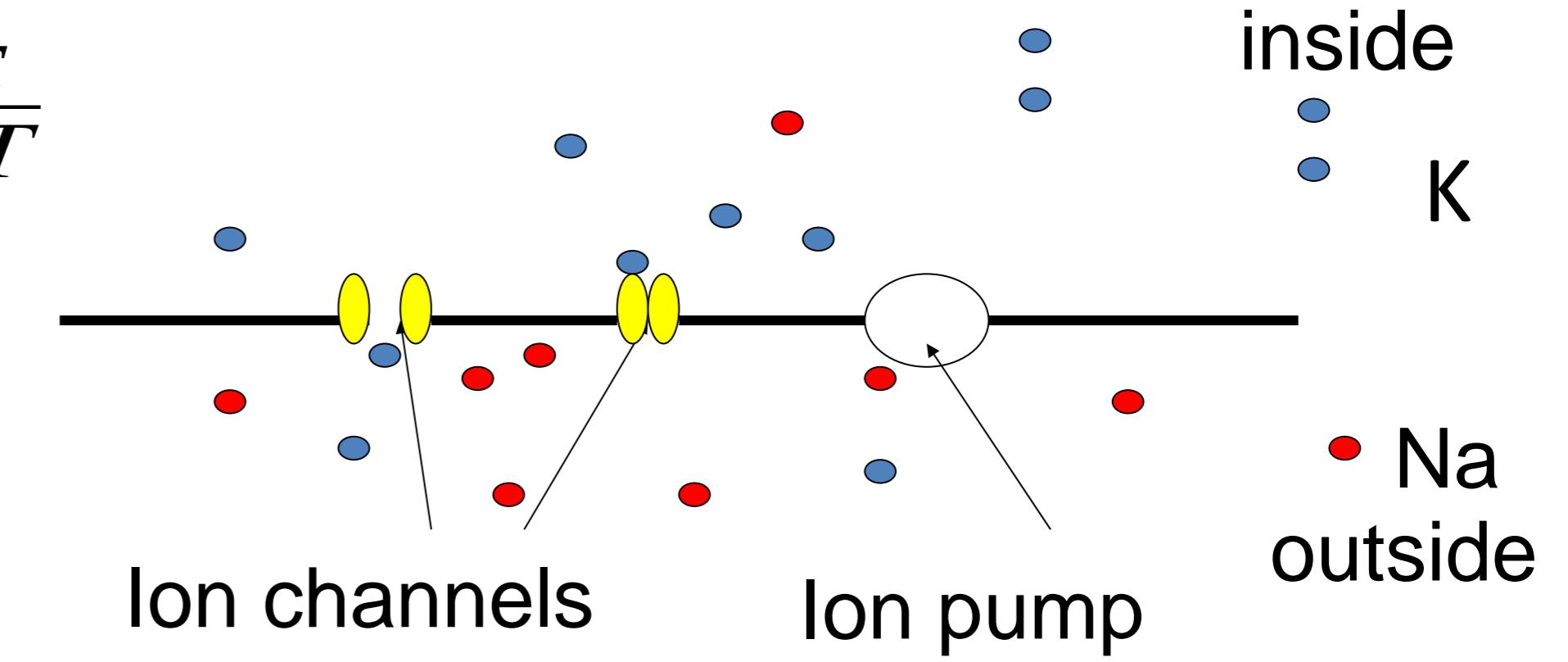
Ion pump  $\leftrightarrow$  Concentration difference

*Mathetical derivation*

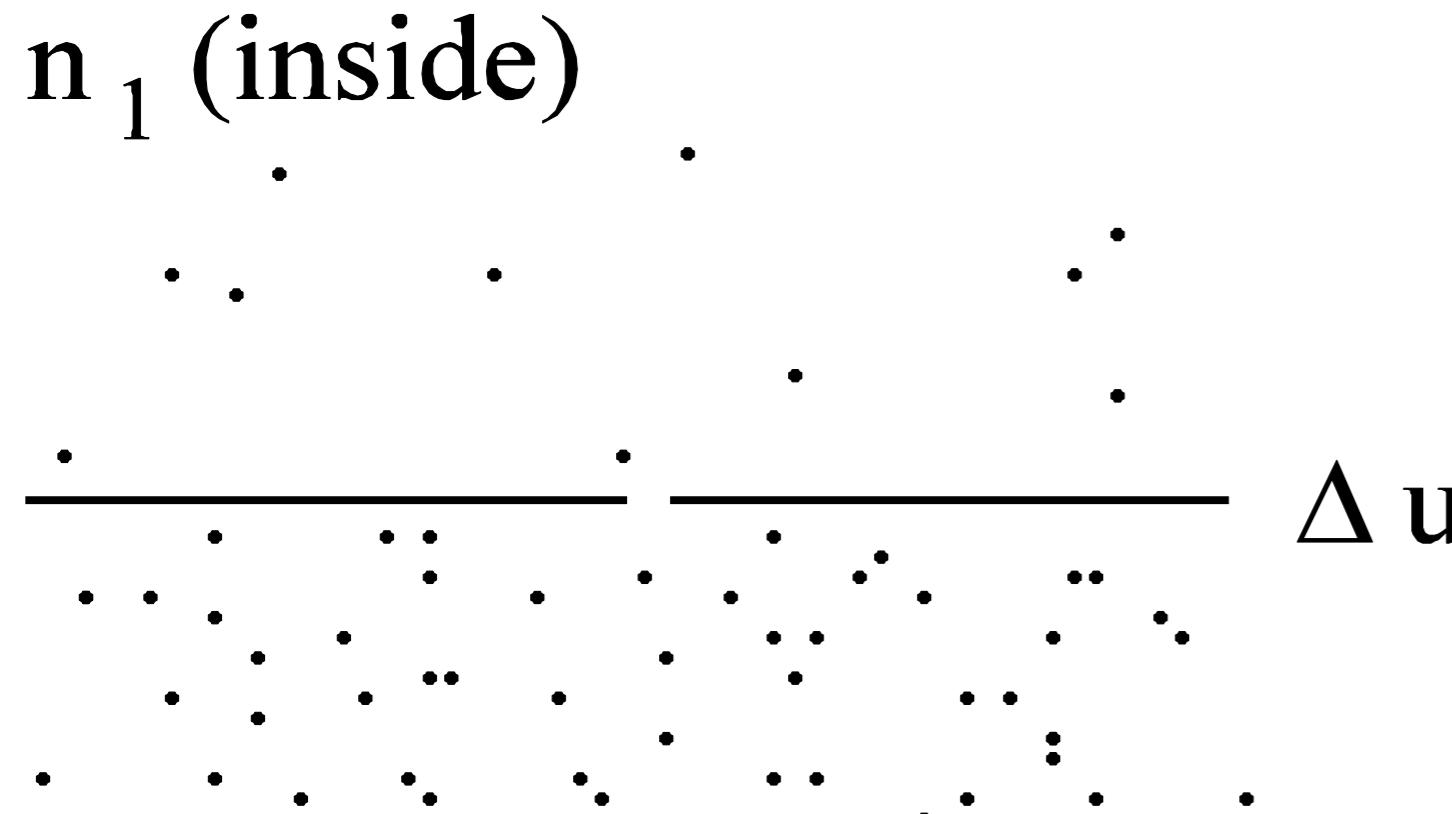
# Neuronal Dynamics – 2.2. Nernst equation



$$n \propto e^{-\frac{E}{kT}}$$



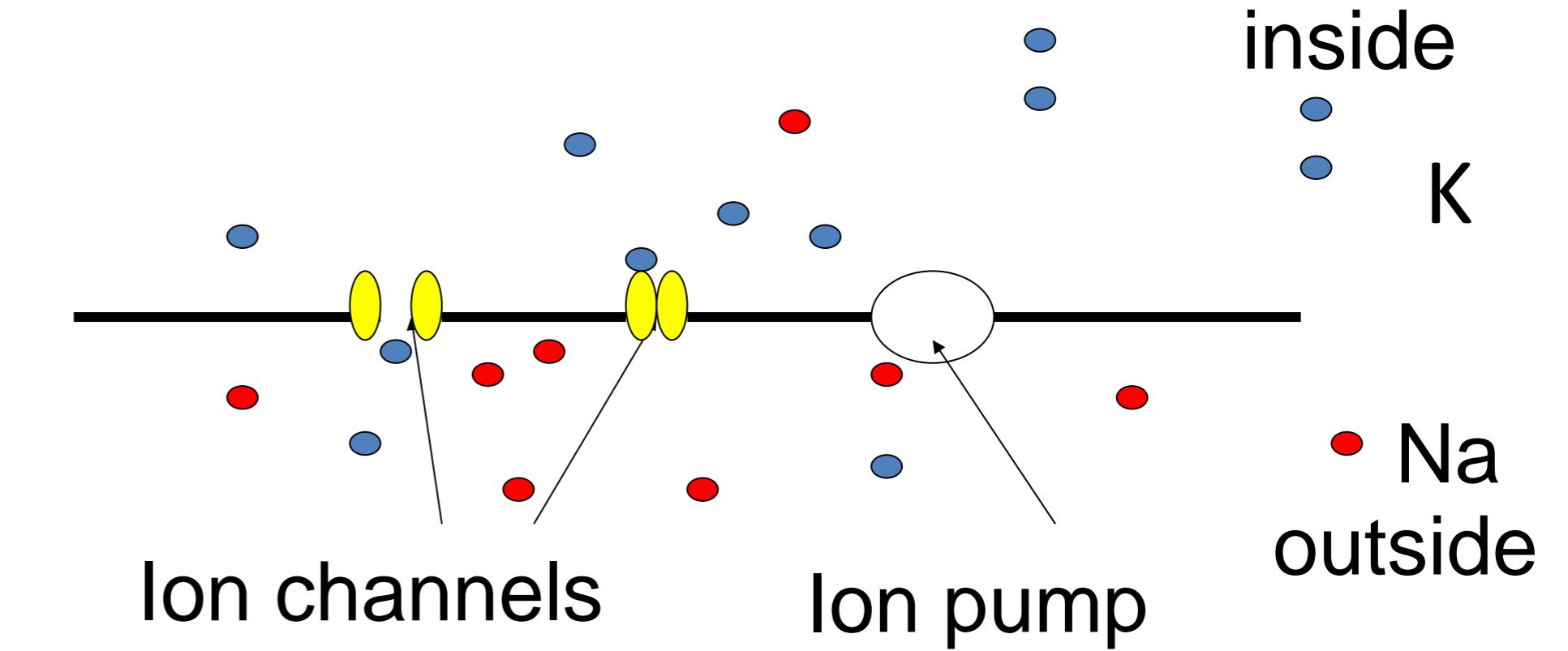
# Neuronal Dynamics – 2.2. Nernst equation



$n_1$  (inside)

$n_2$  (outside)

$\Delta u$



Ion channels

Ion pump

inside

K

Na

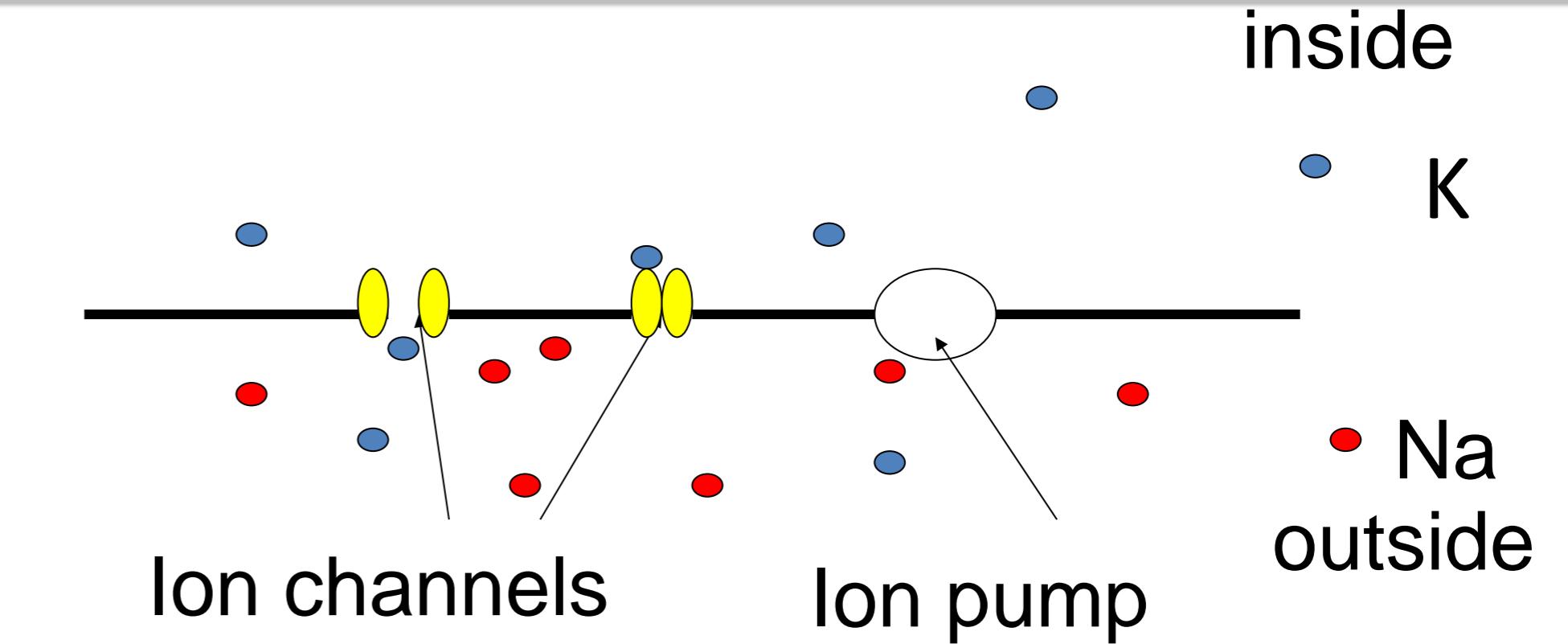
outside

$$\Delta u = u_1 - u_2 = \frac{-kT}{q} \ln \frac{n(u_1)}{n(u_2)}$$

Reversal potential

Concentration difference  $\Leftrightarrow$  voltage difference

# Neuronal Dynamics – 2.2. Reversal potential



**Ion pump → Concentration difference**

Concentration difference  $\leftrightarrow$  voltage difference

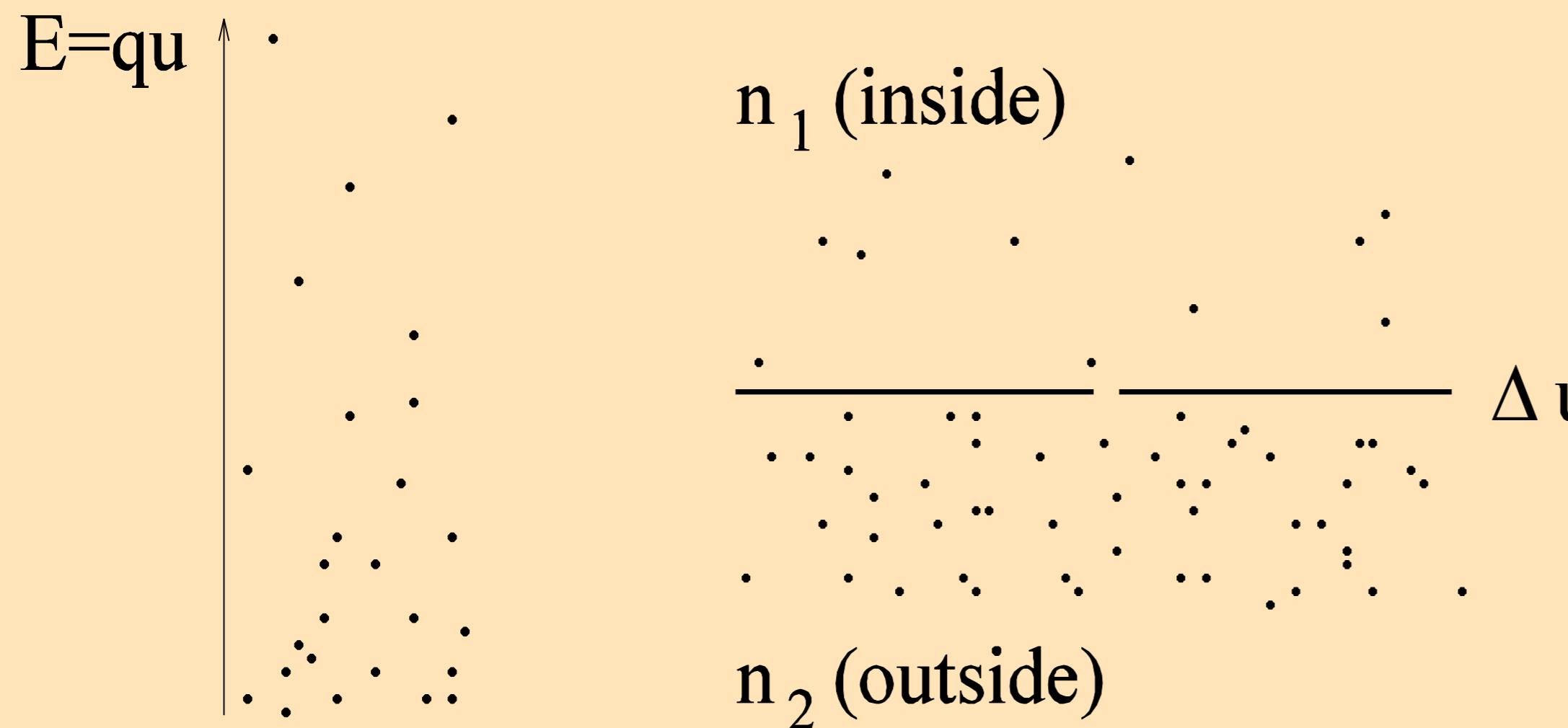
Reversal potential

Nernst equation

## Exercise – 2. 2. Reversal potential of ion channels

### Reversal potential

$$\Delta u = u_1 - u_2 = -\frac{kT}{q} \ln \frac{n(u_1)}{n(u_2)}$$



Calculate the reversal potential  
for Sodium  
Potassium  
Calcium  
given the concentrations

What happens if you change  
the temperature  $T$  from 37  
to 18.5 degree?

# Week 2 – part 3 : Hodgkin-Huxley Model



## Neuronal Dynamics: Computational Neuroscience of Single Neurons

### Week 2 – Biophysical modeling: The Hodgkin-Huxley model

Wulfram Gerstner

EPFL, Lausanne, Switzerland

#### 2.1 Biophysics of neurons

- Overview

#### 2.2 Reversal potential

- Nernst equation

#### 2.3 Hodgkin-Huxley Model

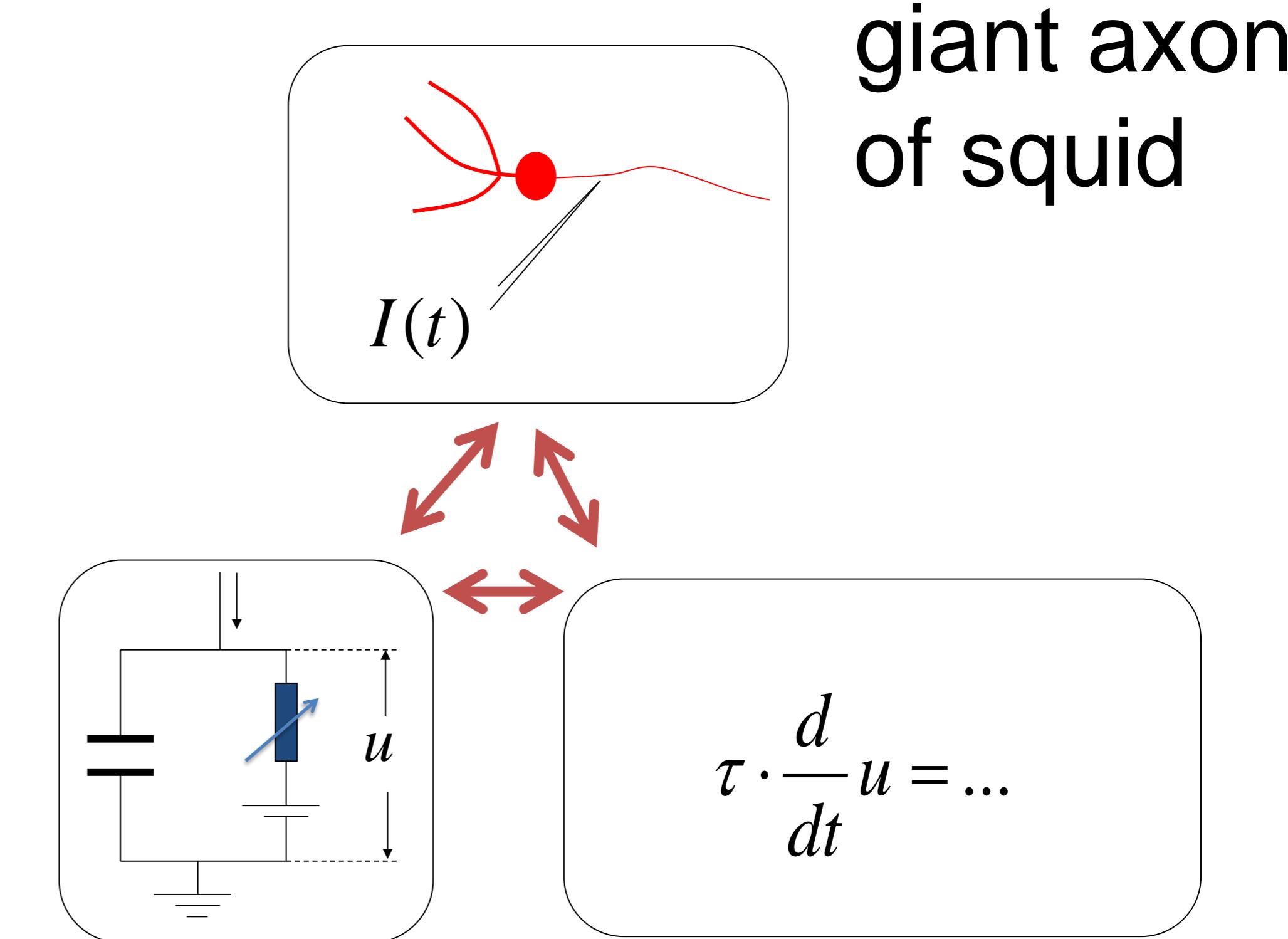
#### 2.4 Threshold in the Hodgkin-Huxley Model

- where is the firing threshold?

#### 2.5. Detailed biophysical models

- the zoo of ion channels

# Neuronal Dynamics – 2. 3. Hodgkin-Huxley Model

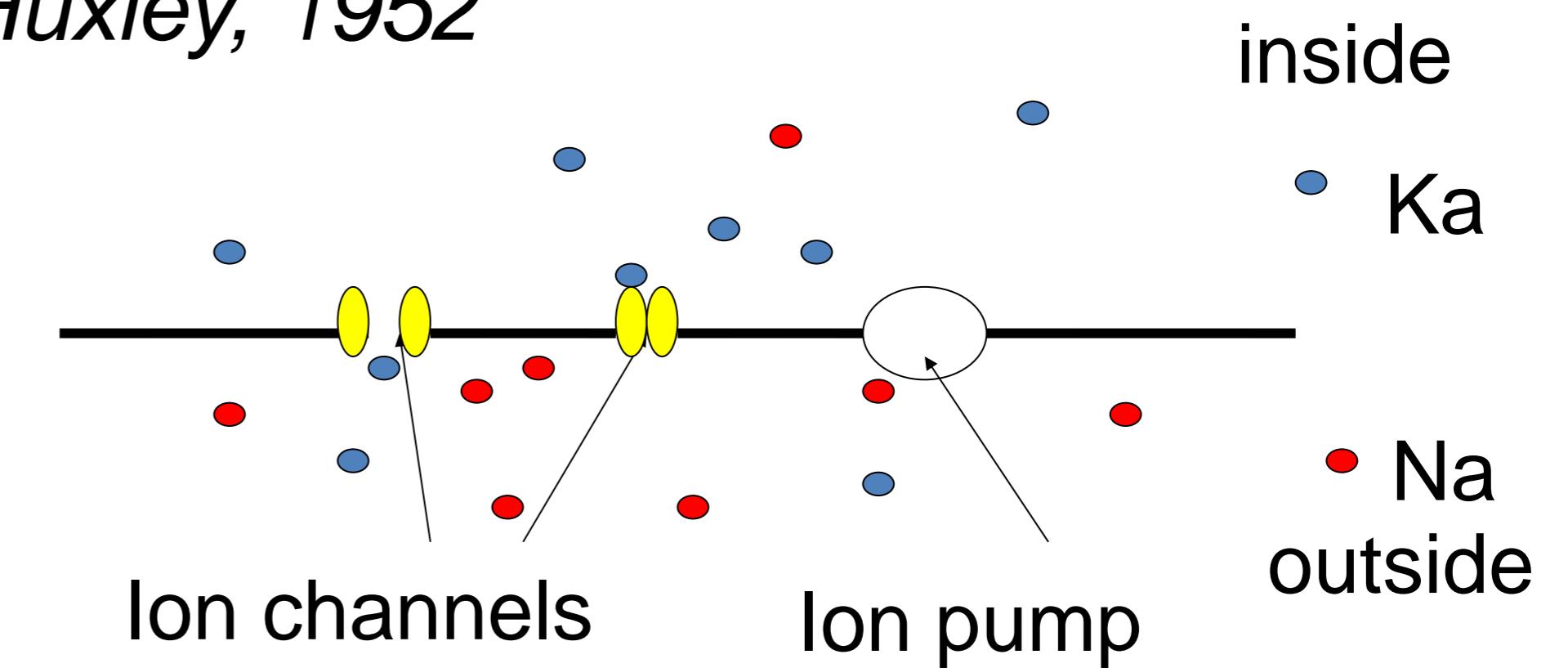
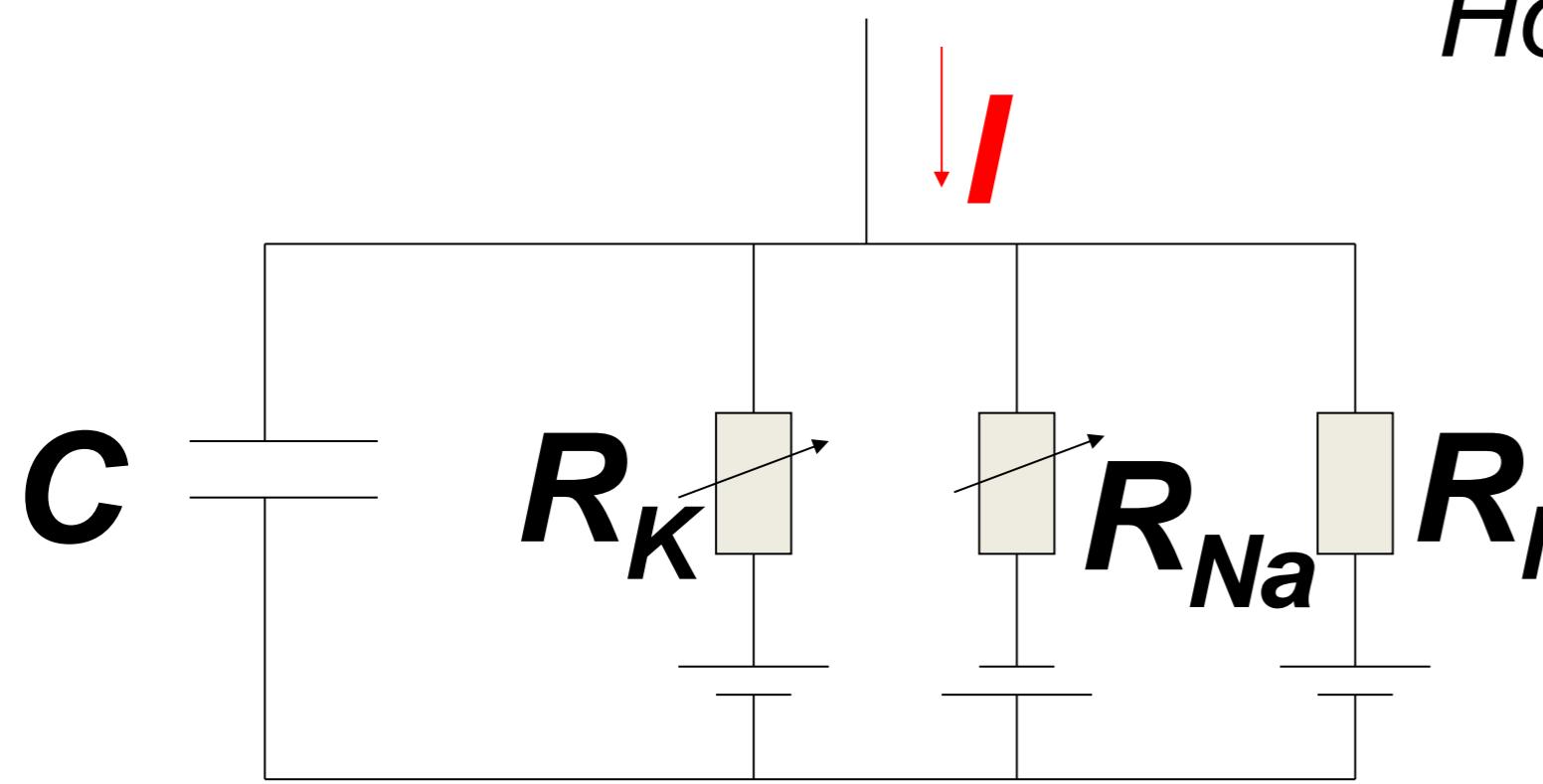


→Hodgkin-Huxley model

*Hodgkin&Huxley (1952)*  
*Nobel Prize 1963*

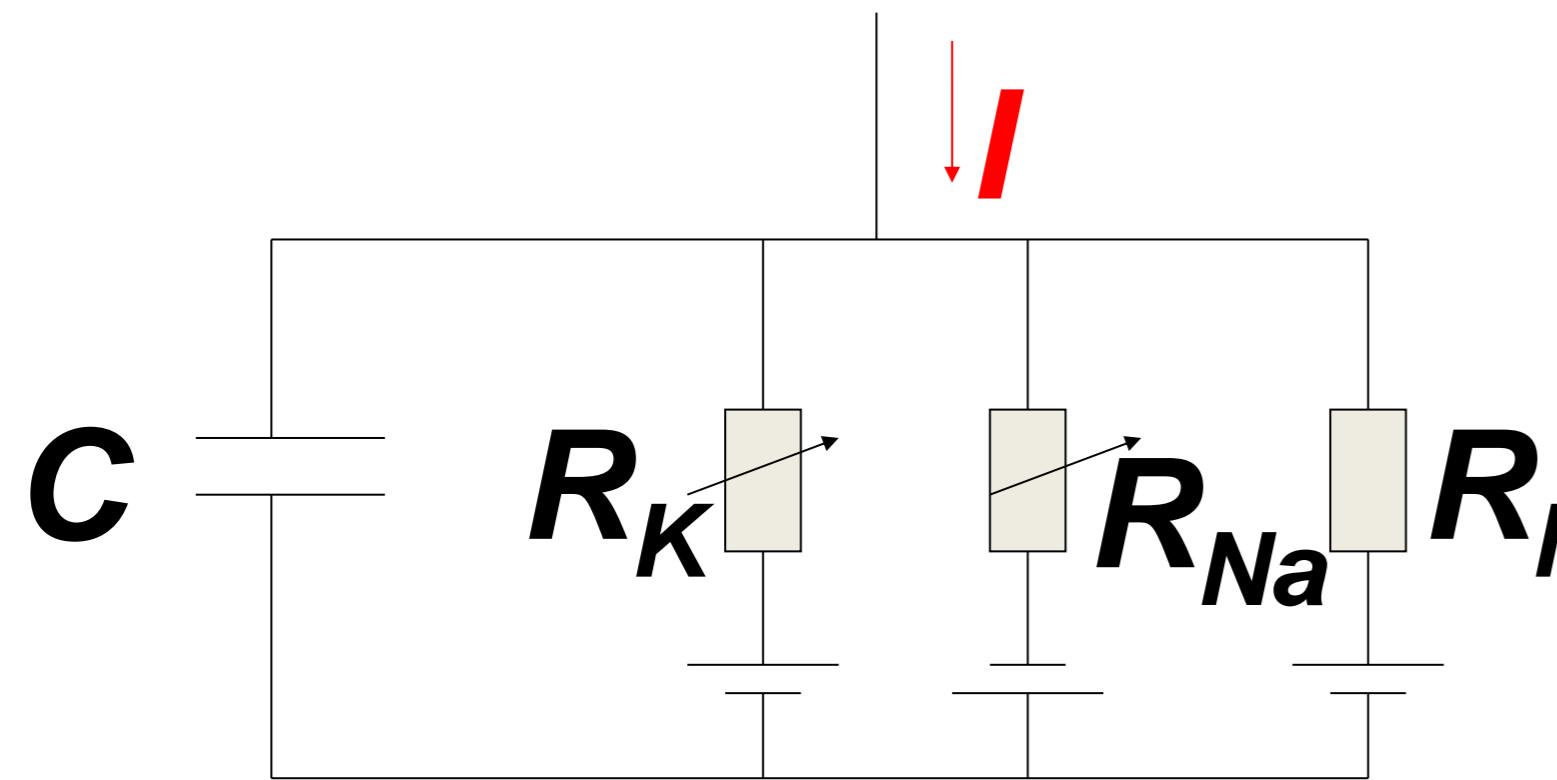
# Neuronal Dynamics – 2.3. Hodgkin-Huxley Model

*Hodgkin and Huxley, 1952*



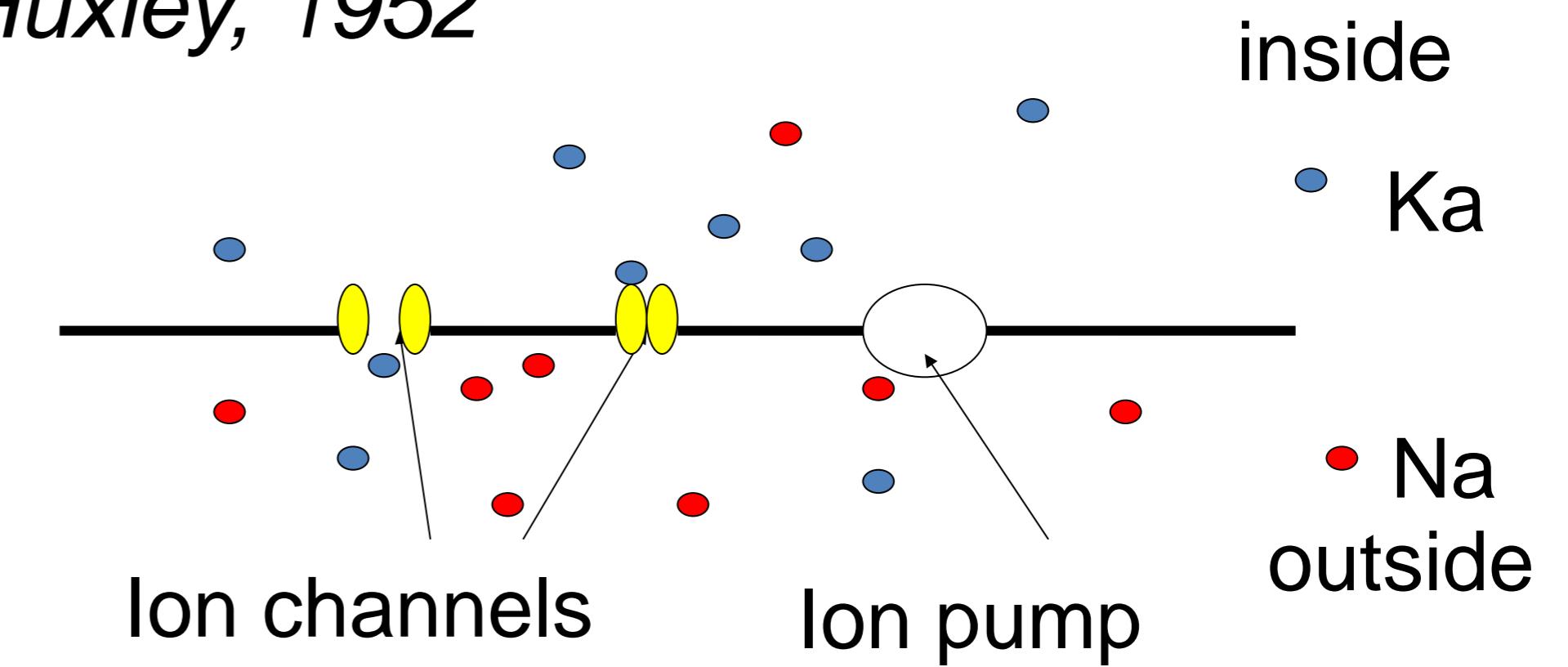
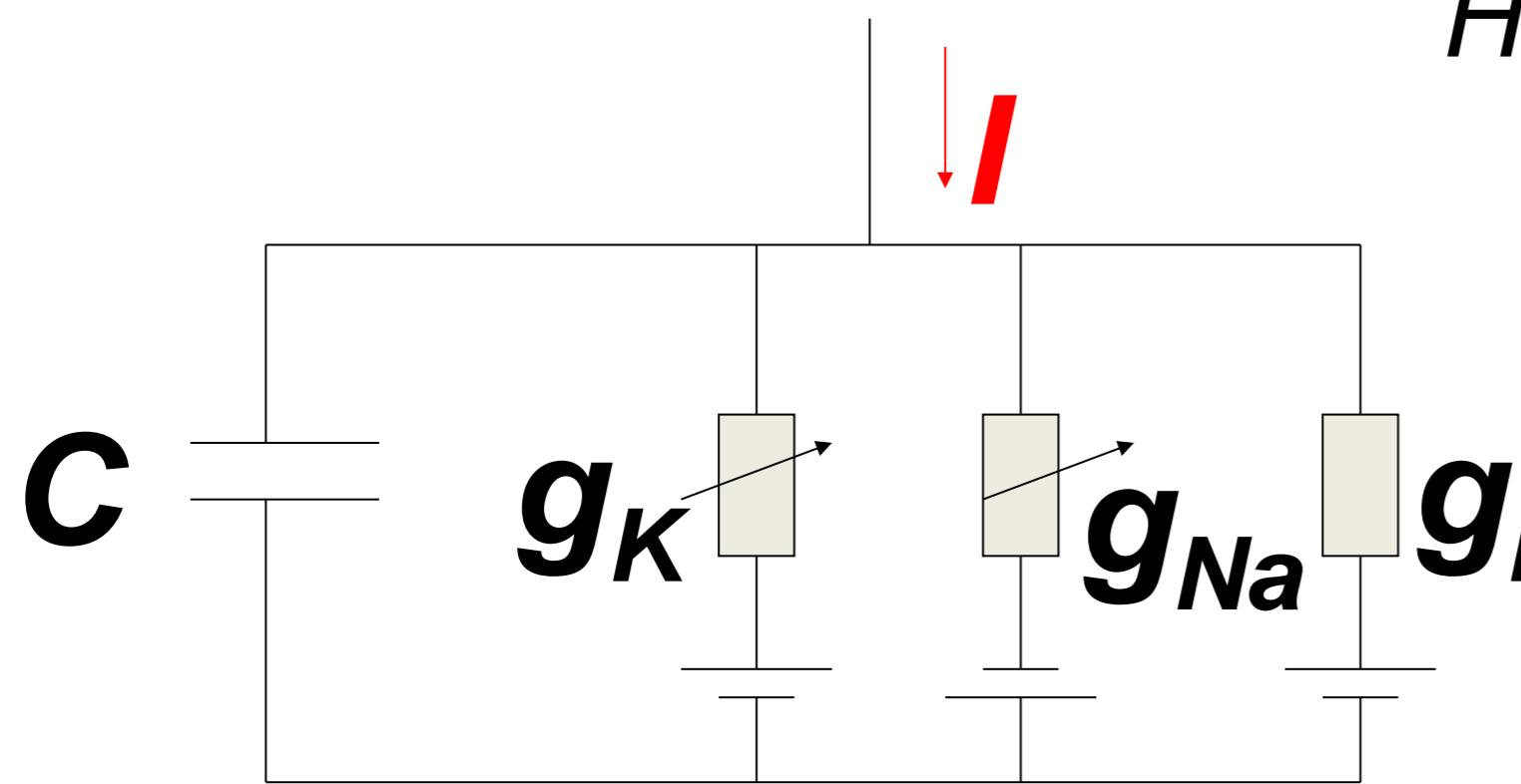
*Mathematical  
derivation*

# Neuronal Dynamics – 2.3. Hodgkin-Huxley Model



# Neuronal Dynamics – 2.3. Hodgkin-Huxley Model

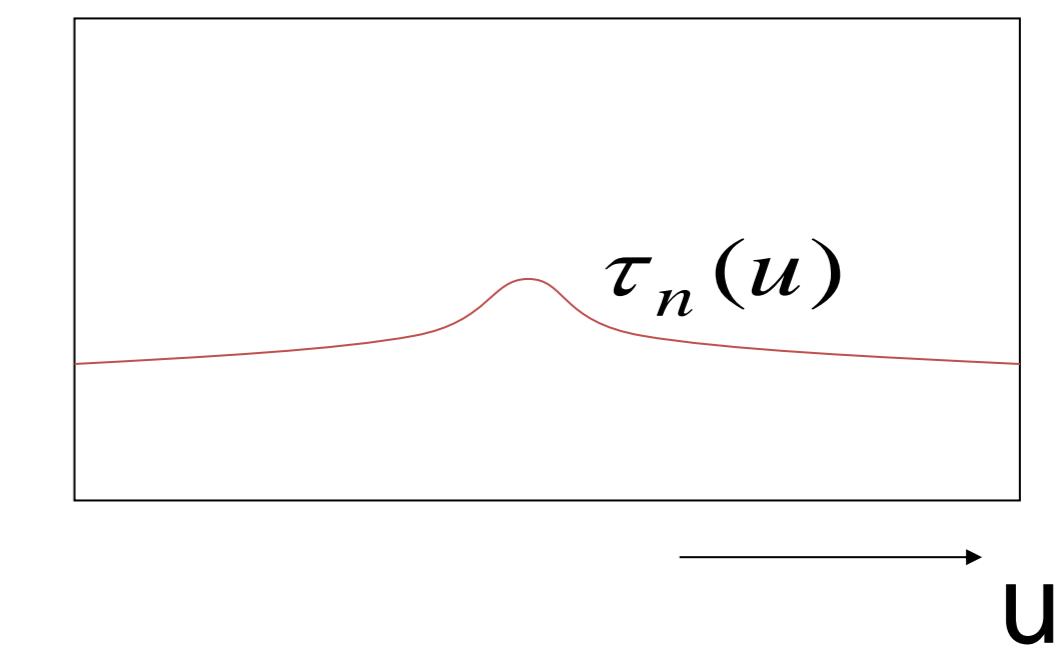
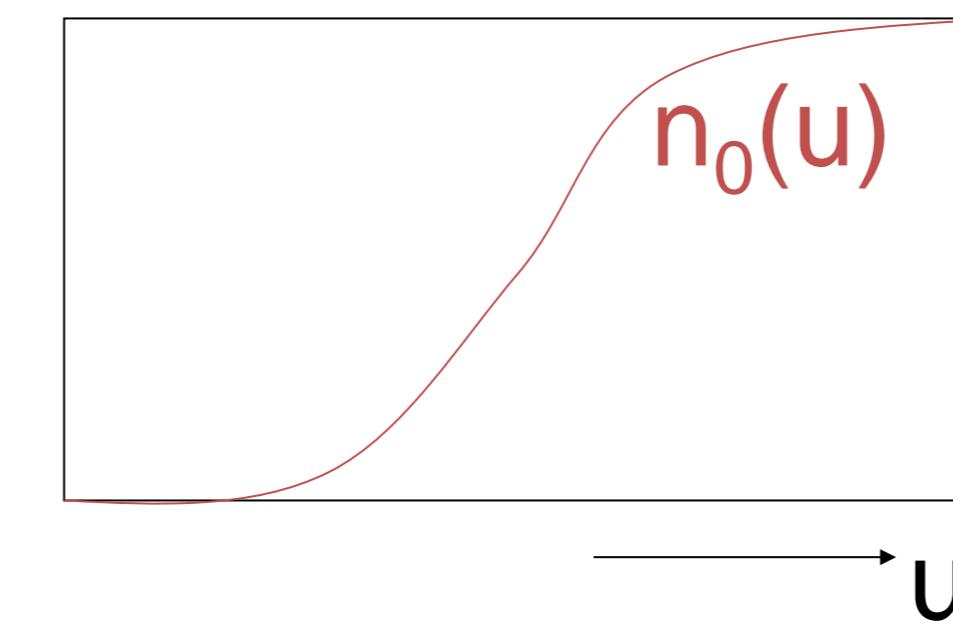
*Hodgkin and Huxley, 1952*



$$C \frac{du}{dt} = -g_{Na}m^3h(u - E_{Na}) - g_Kn^4(u - E_K) - g_l(u - E_l) + I(t)$$

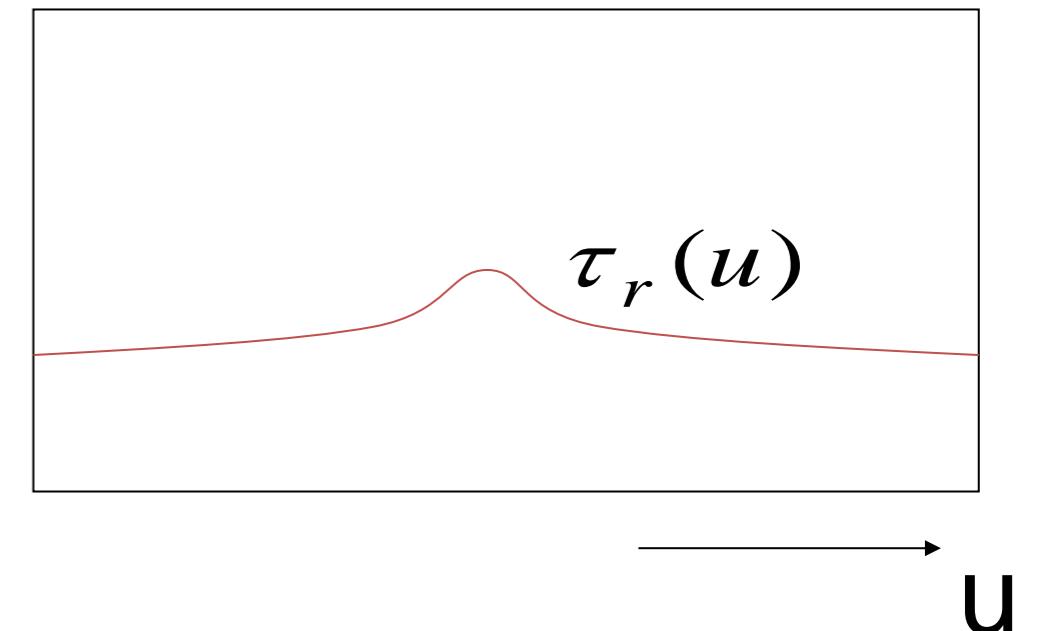
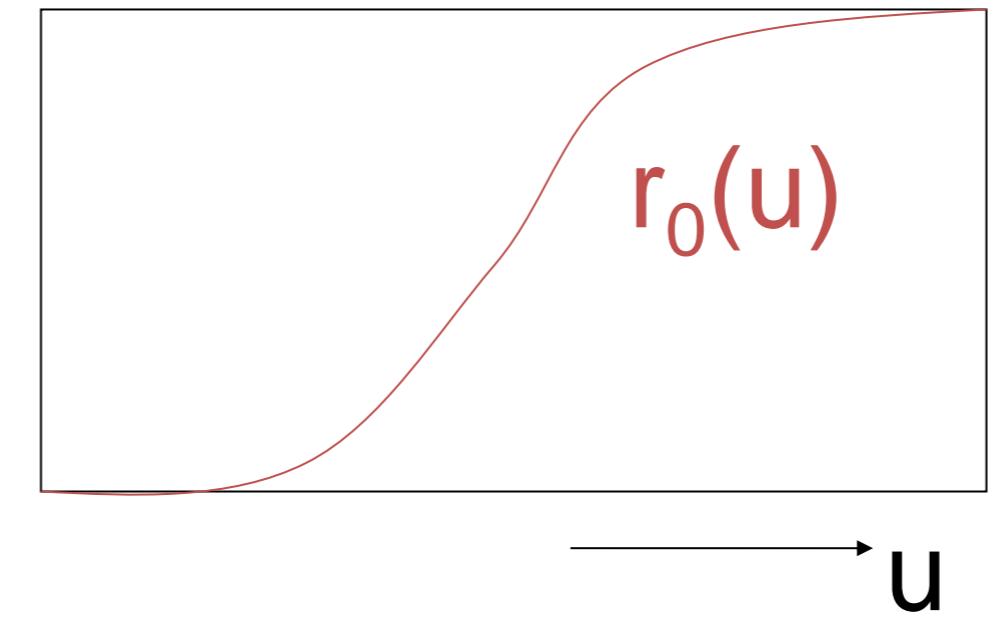
Diagram illustrating the Hodgkin-Huxley equation. The equation is  $C \frac{du}{dt} = -g_{Na}m^3h(u - E_{Na}) - g_Kn^4(u - E_K) - g_l(u - E_l) + I(t)$ . Red brackets above the terms  $I_{Na}$ ,  $I_K$ , and  $I_{leak}$  indicate the contributions of the sodium, potassium, and leak currents, respectively. A red arrow labeled "stimulus" points to the term  $I(t)$ .

$$\frac{dm}{dt} = \frac{h m - h m \bar{m}(u) \bar{m}(u)}{\tau_m \tau_h(u) \bar{m}(u)}$$



# Neuronal Dynamics – 2.3. Ion channel

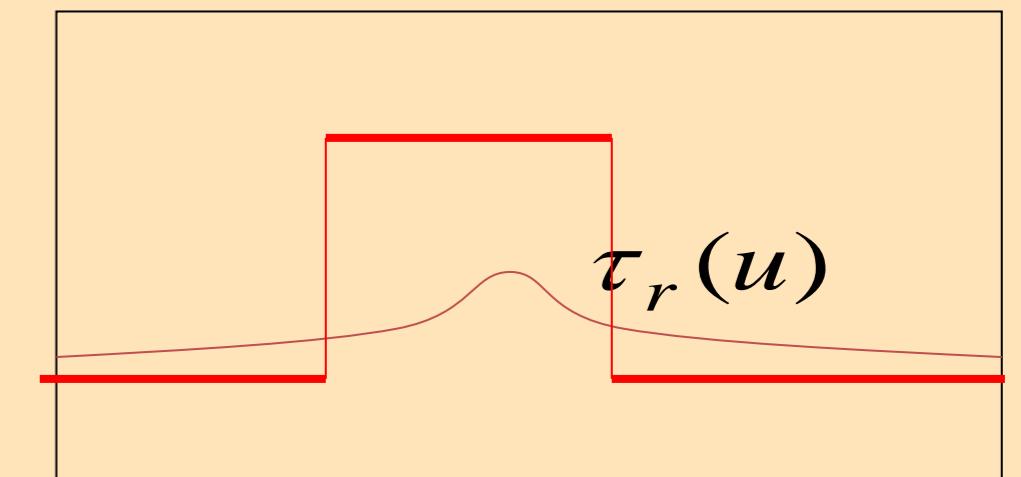
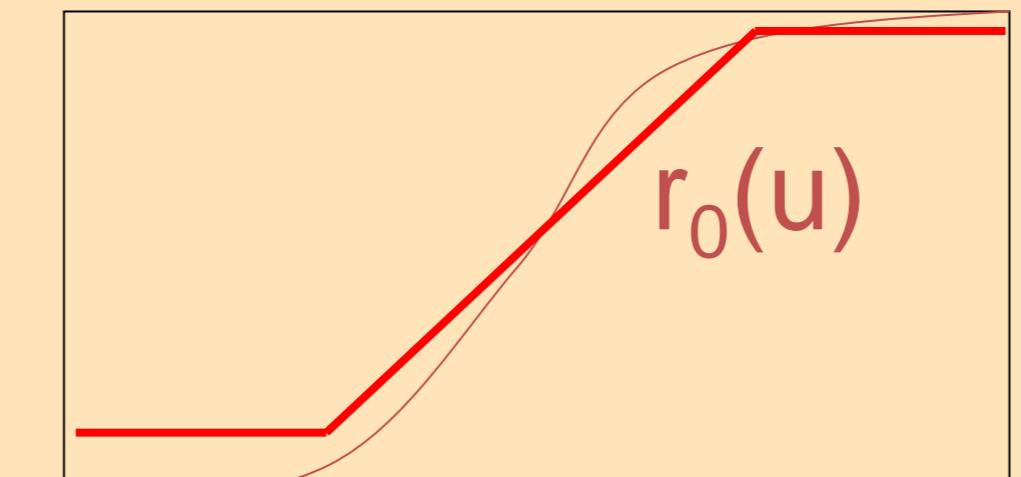
$$C \frac{du}{dt} = - \sum_k I_{ion,k} + I(t)$$



$$I_{ion} = -g_{ion} r^{n_1} s^{n_2}$$

$$\frac{dr}{dt} = -\frac{r - r_0(u)}{\tau_r(u)} \quad \frac{ds}{dt} = -\frac{s - s_0(u)}{\tau_r(u)}$$

# Neuronal Dynamics – Exercise 2.3. Ion channel



$$C \frac{du}{dt} = -g_{ion} r^{n_1} s^{n_2} (u - E_{Na}) + I(t)$$

$$\frac{dr}{dt} = -\frac{r - r_0(u)}{\tau_r(u)}$$

# Week 2 – part 4: Threshold in the Hodgkin-Huxley Model



## Neuronal Dynamics: Computational Neuroscience of Single Neurons

### Week 2 – Biophysical modeling: The Hodgkin-Huxley model

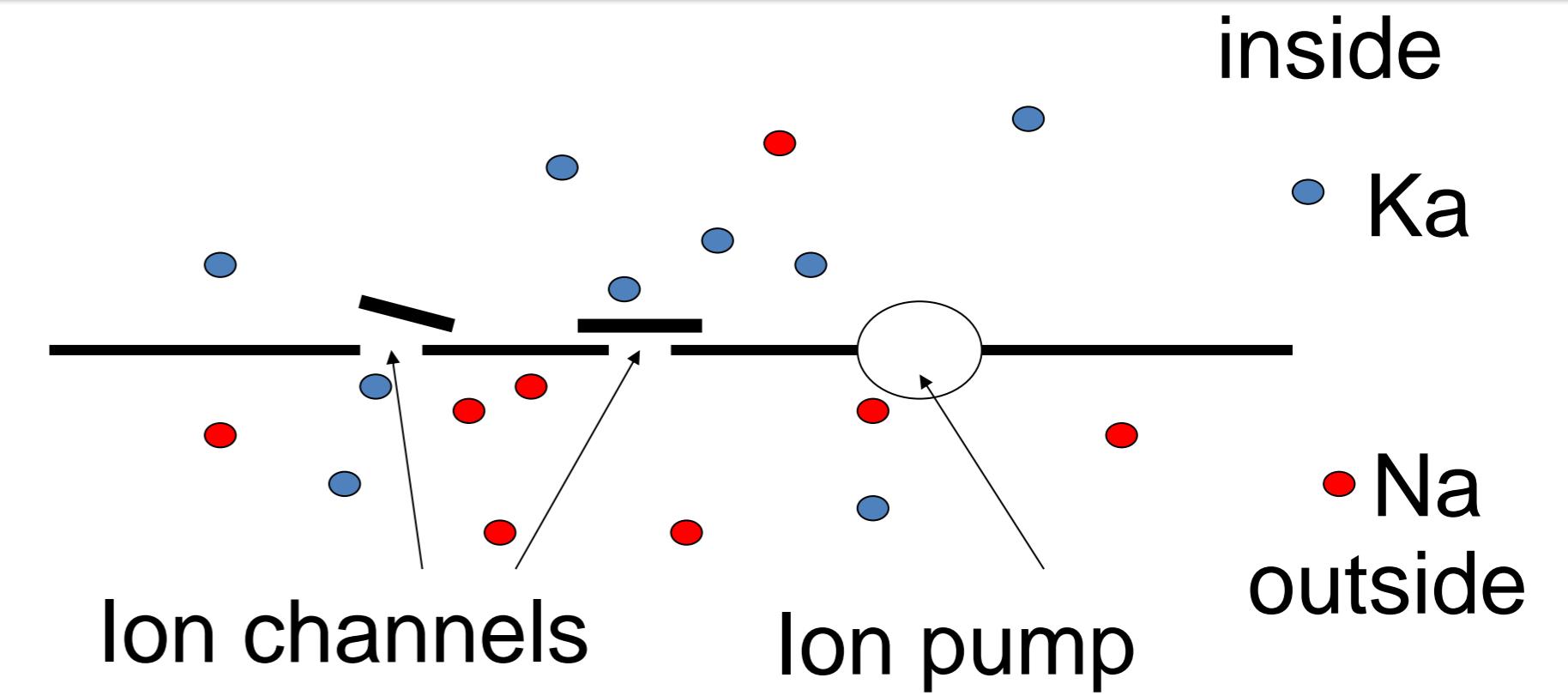
Wulfram Gerstner

EPFL, Lausanne, Switzerland

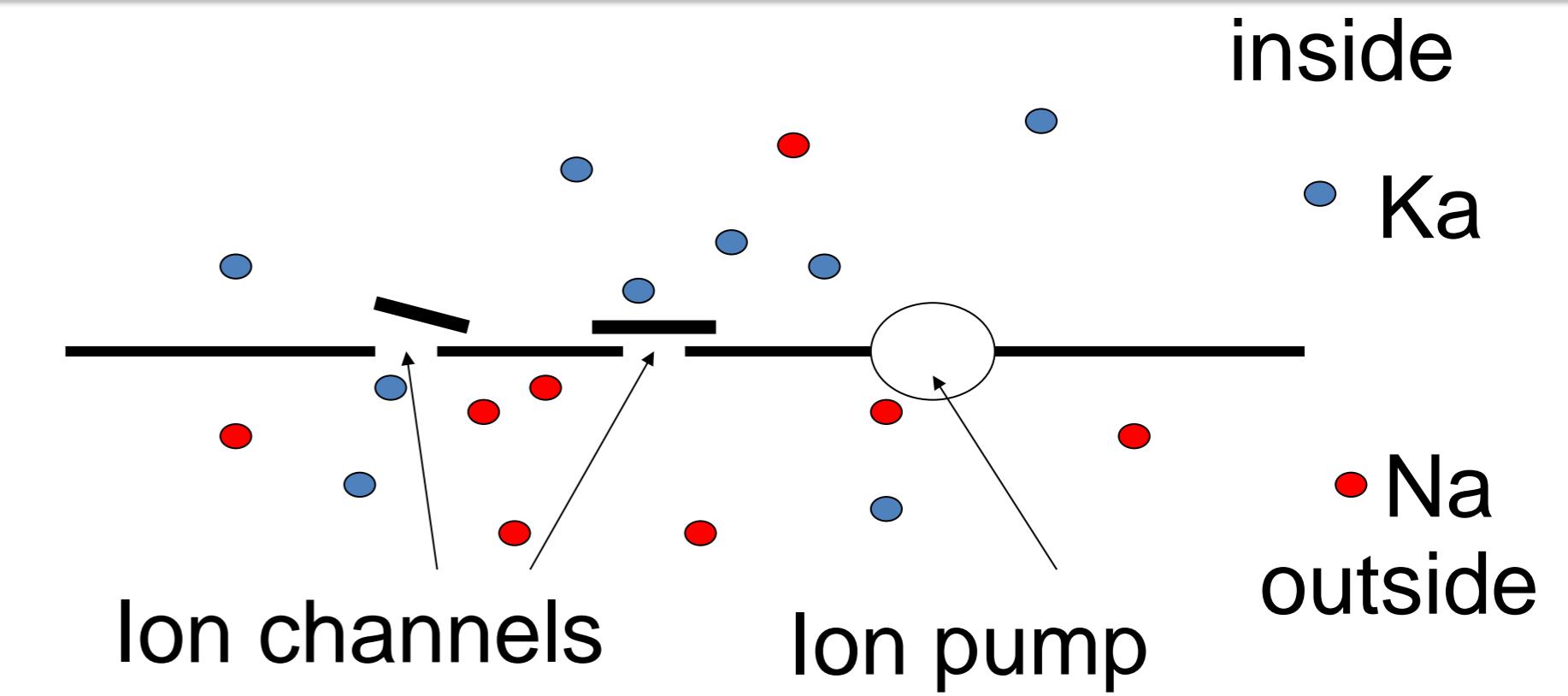
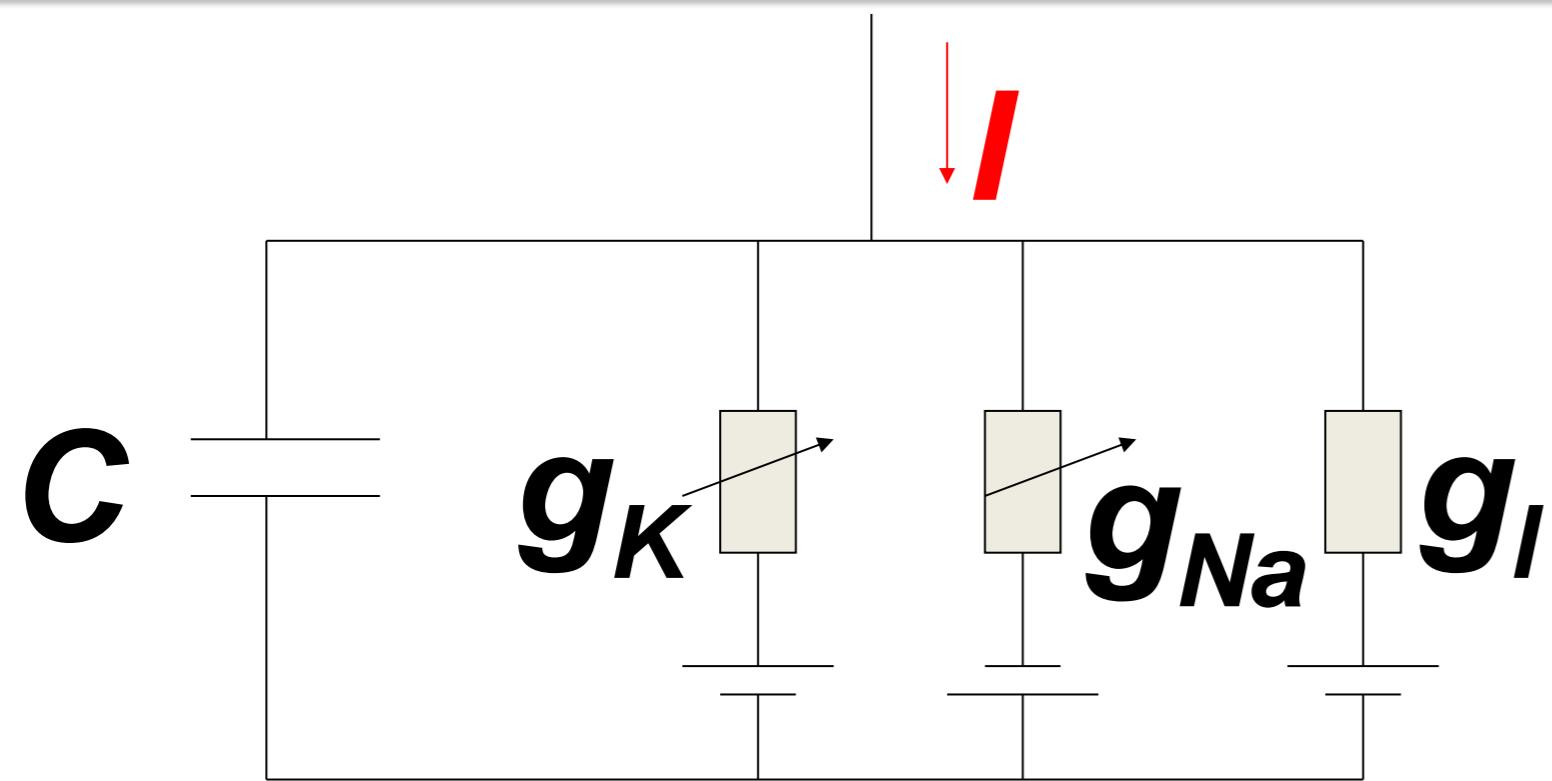
- ✓ 2.1 Biophysics of neurons
  - Overview
- ✓ 2.2 Reversal potential
  - Nernst equation
- ✓ 2.3 Hodgkin-Huxley Model
- ✓ 2.4 Threshold in the Hodgkin-Huxley Model
  - where is the firing threshold?

- ✓ 2.5. Detailed biophysical models
  - the zoo of ion channels

# Neuronal Dynamics – 2.4. Threshold in HH model



# Neuronal Dynamics – 2.4. Threshold in HH model

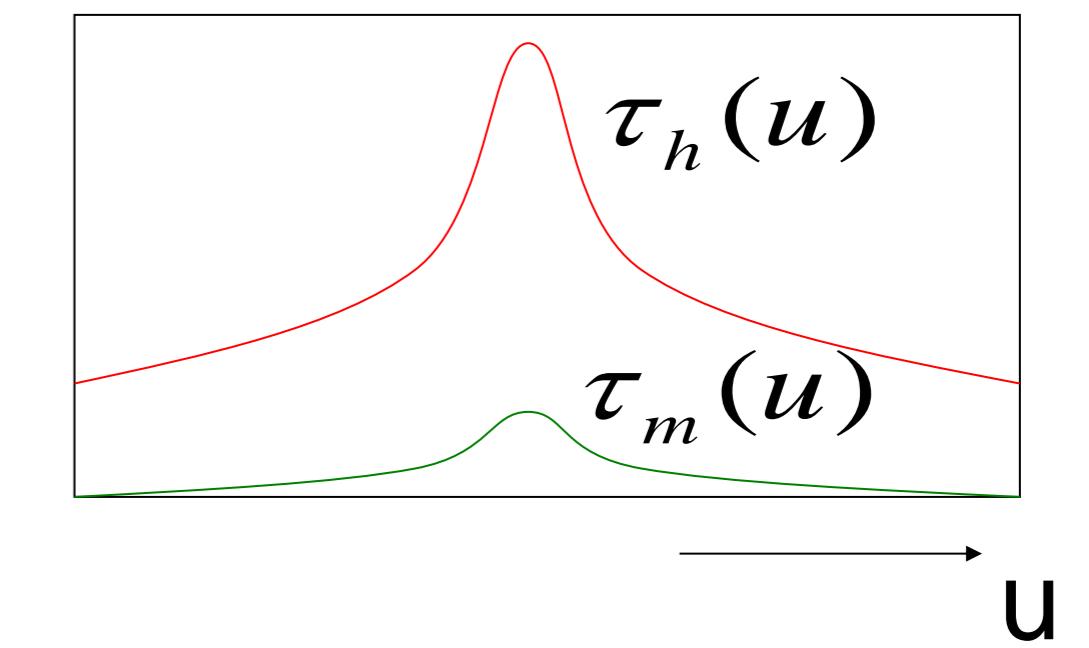
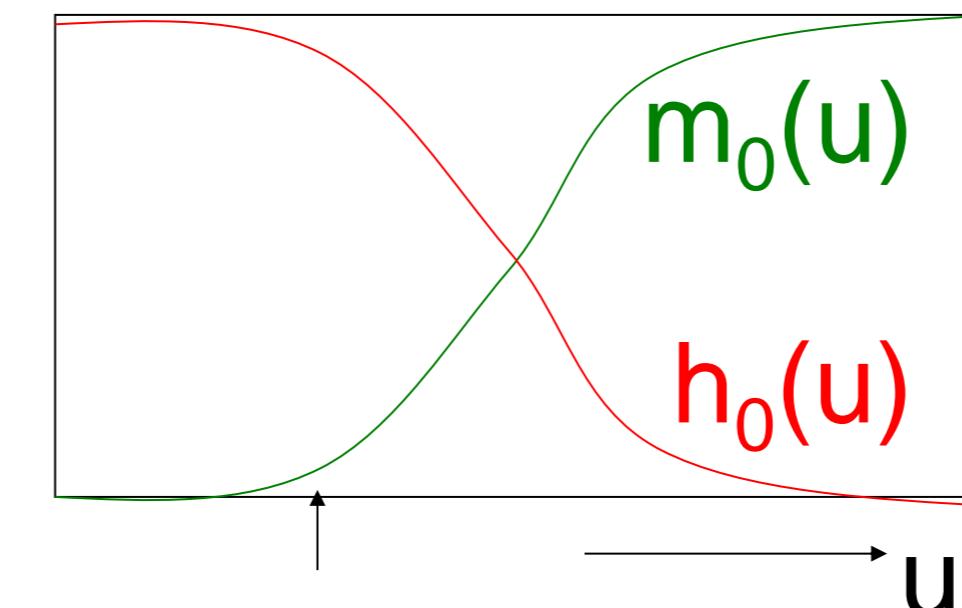


$$C \frac{du}{dt} = -g_{Na} m^3 h (u - E_{Na}) - g_K I_K - g_I I(t) + I$$

$$\frac{dm}{dt} = \frac{m - m_0(u)}{\tau_m(u)}$$

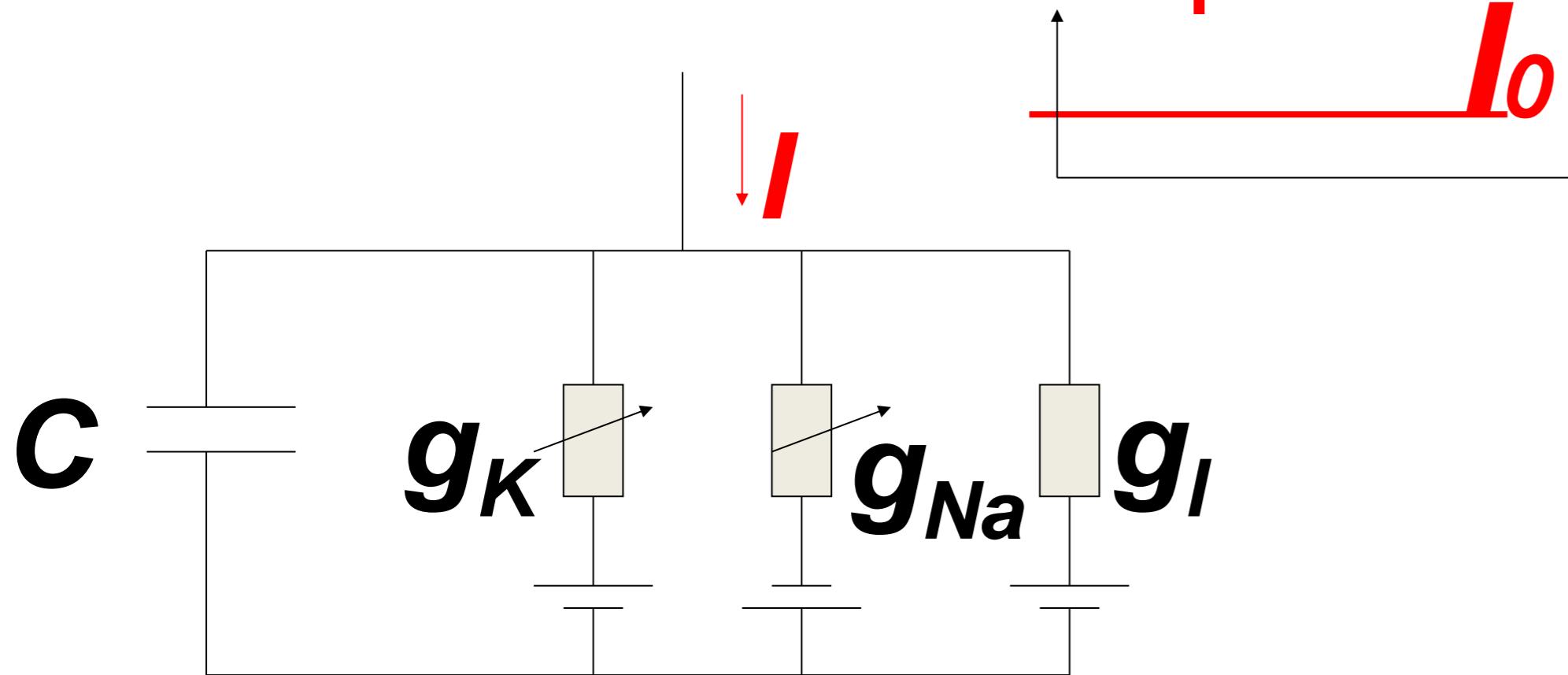
$$\frac{dh}{dt} = -\frac{h - h_0(u)}{\tau_h(u)}$$

**Where is the threshold for firing?**

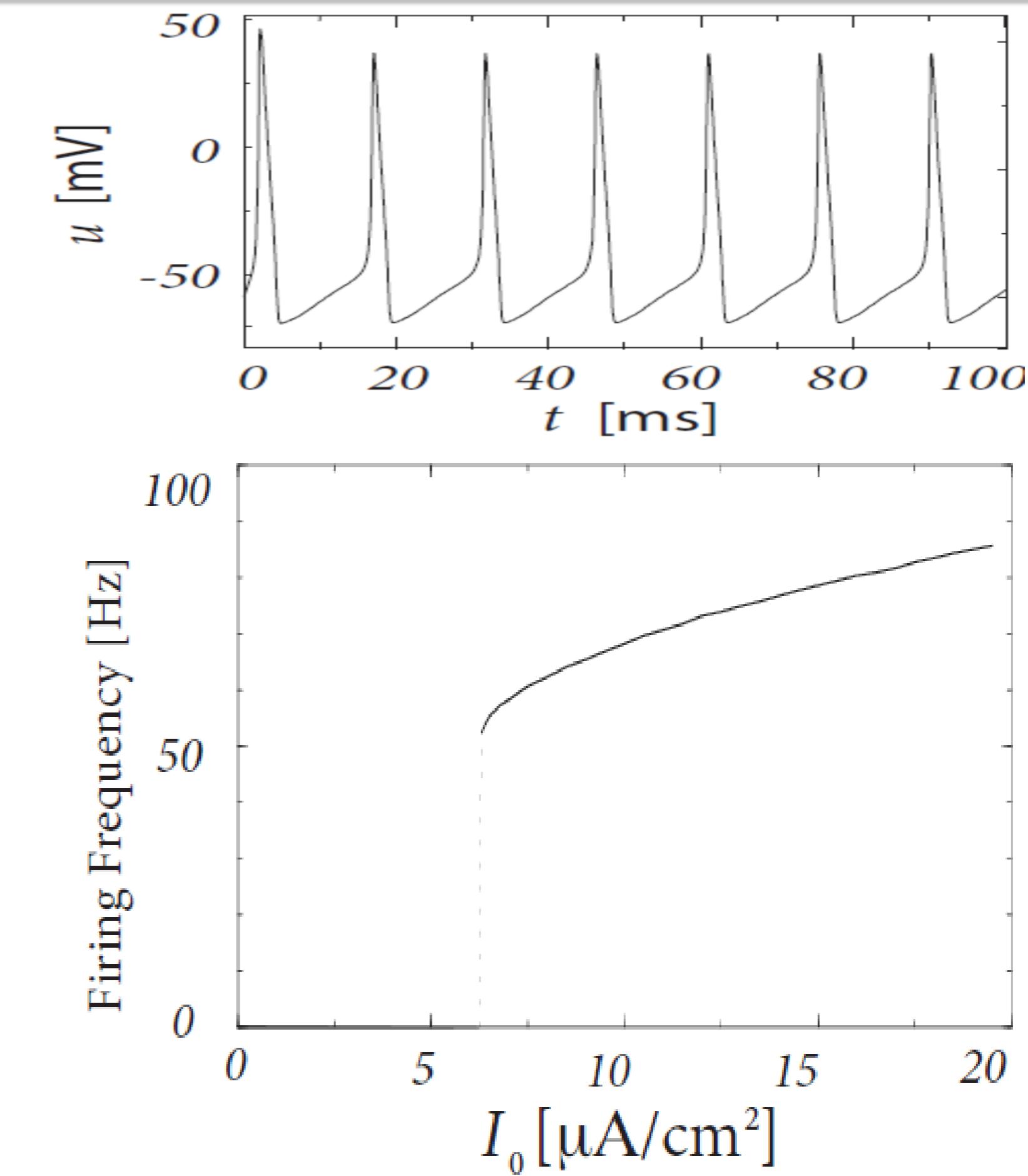


# Neuronal Dynamics – 2.4. Threshold in HH model

Constant current input

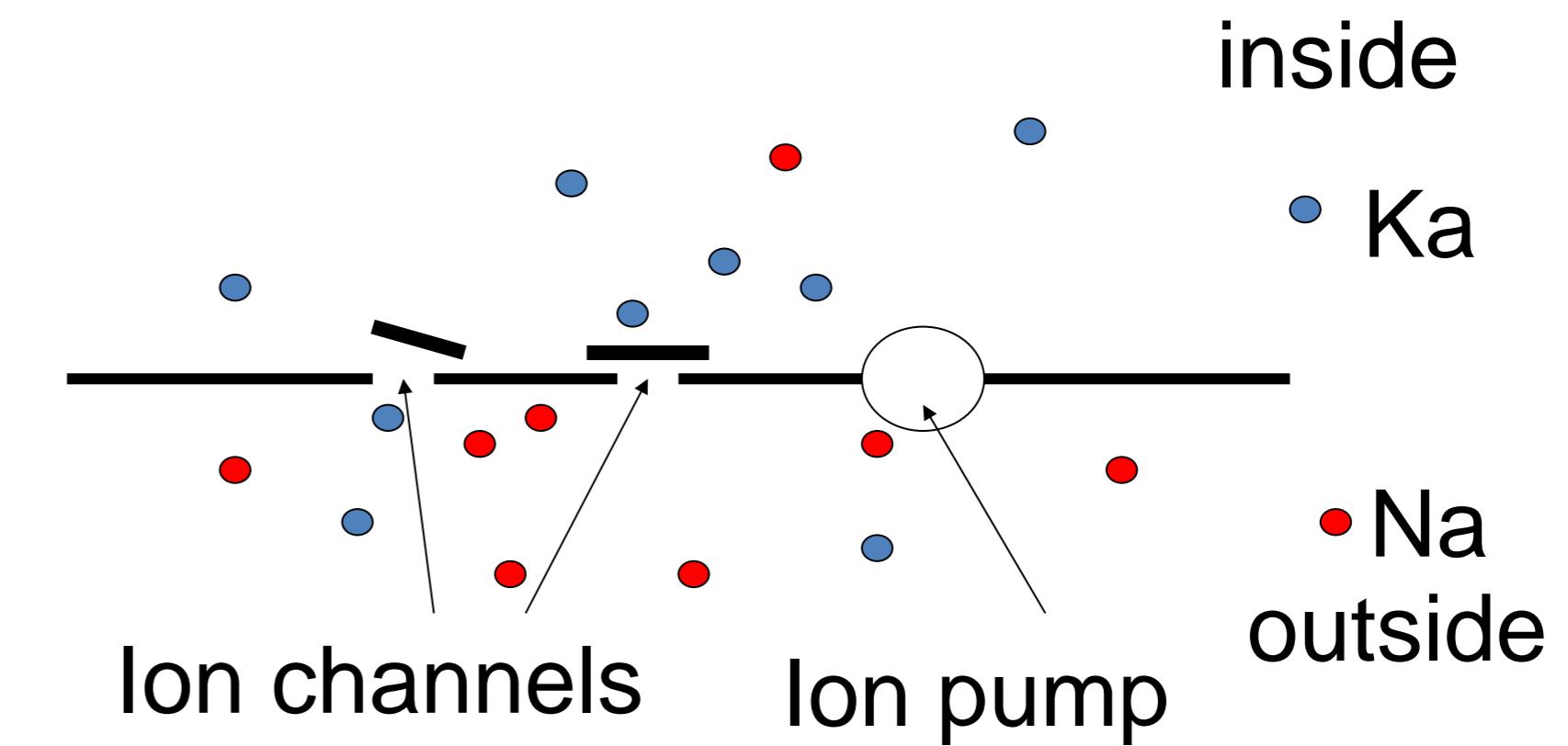
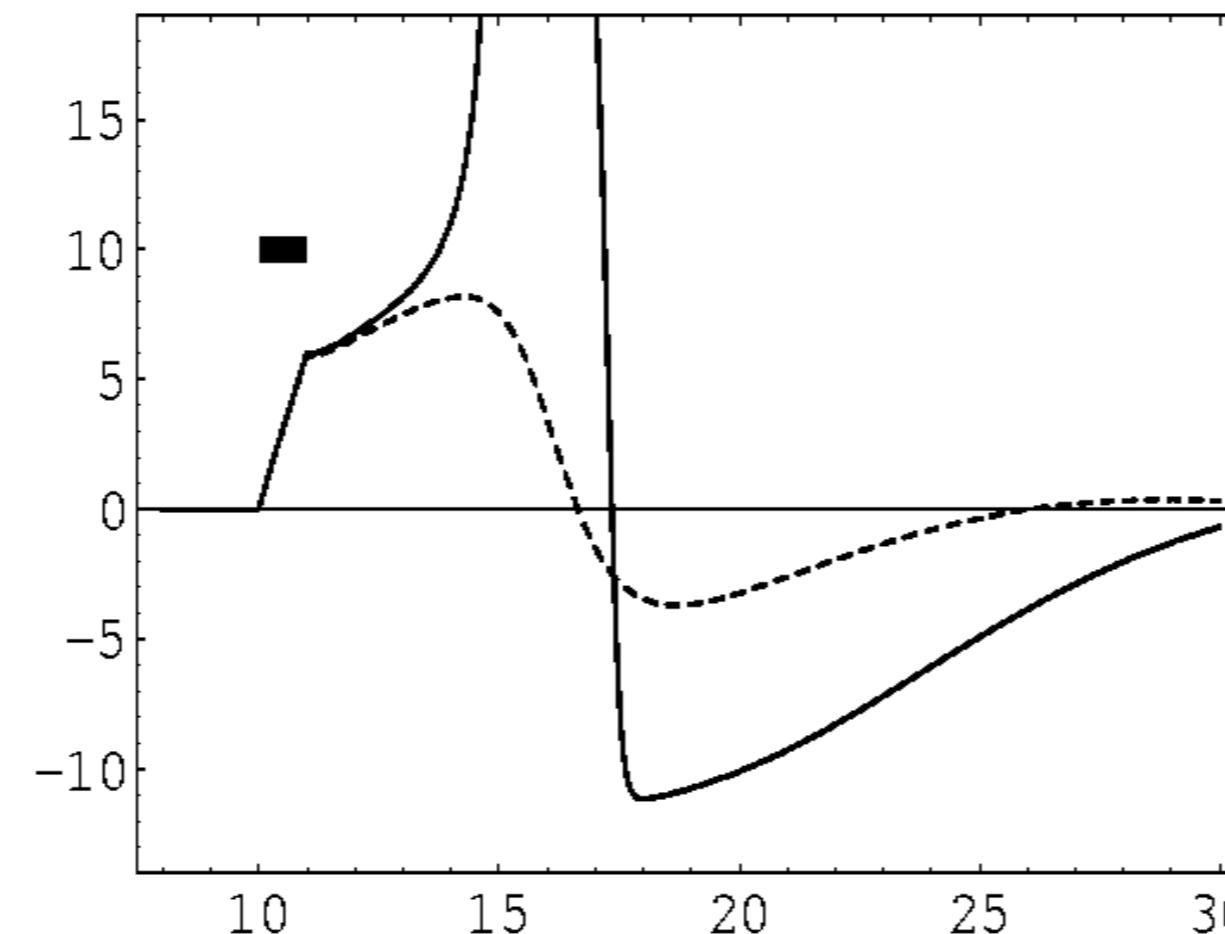
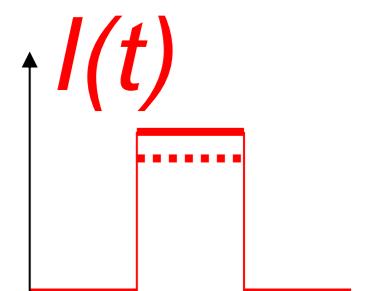


Threshold?  
for repetitive firing  
(*current* threshold)



# Neuronal Dynamics – 2.4. Threshold in HH model

pulse input



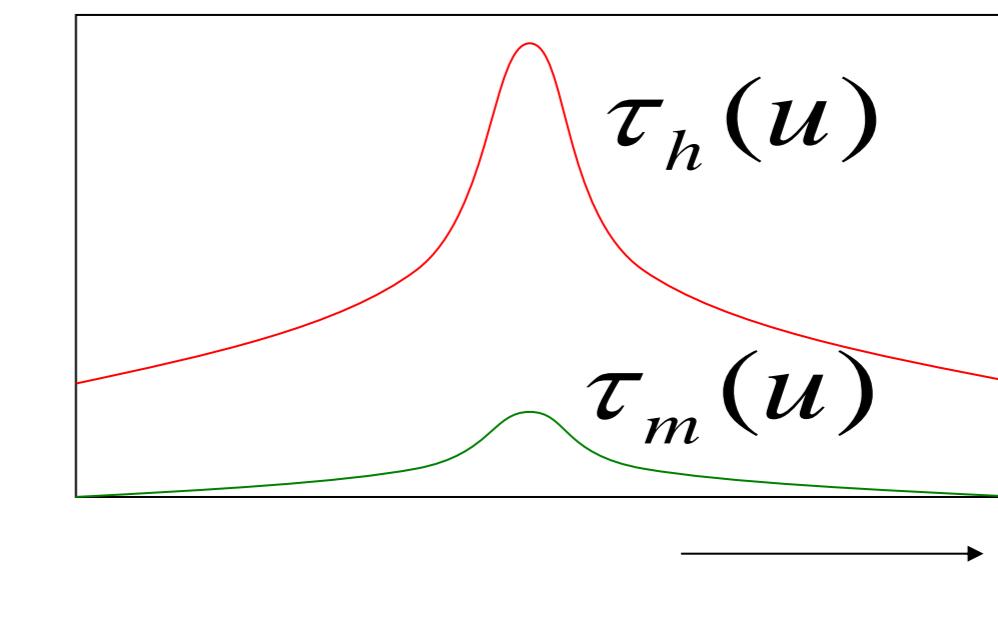
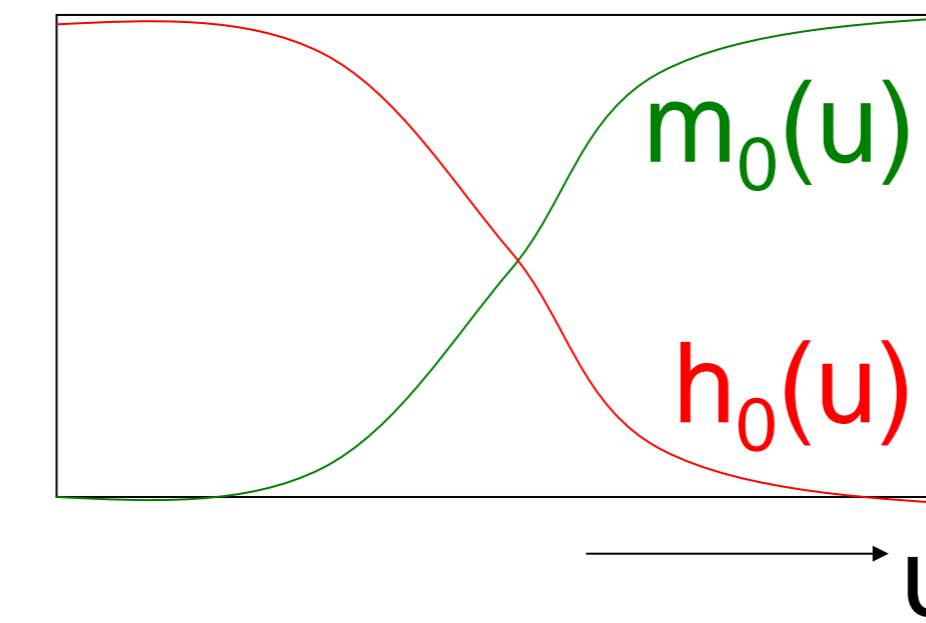
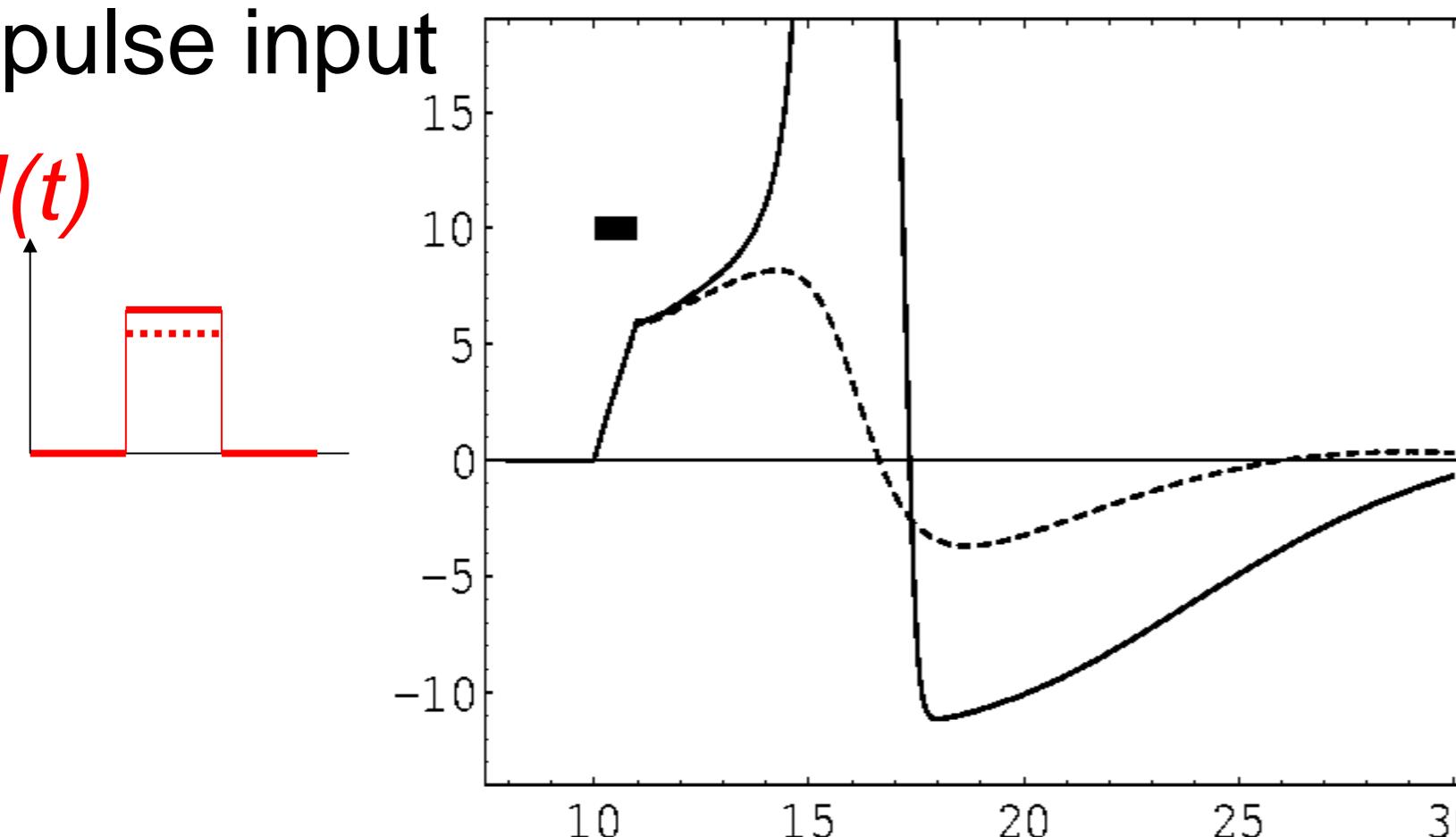
Threshold?

- AP if amplitude 7.0 units
- No AP if amplitude 6.9 units
  - (pulse with 1ms duration)
  - (and pulse with 0.5 ms duration?)

# Neuronal Dynamics – 2.4. Threshold in HH model

pulse input

$I(t)$



*Mathematical explanation*

$$C \frac{du}{dt} = -g_{Na} m^3 h (u - E_{Na}) - g_K n^4 (u - E_K) - g_l (u - E_l) + I(t)$$

$$\frac{dm}{dt} = -\frac{m - m_0(u)}{\tau_m(u)}$$

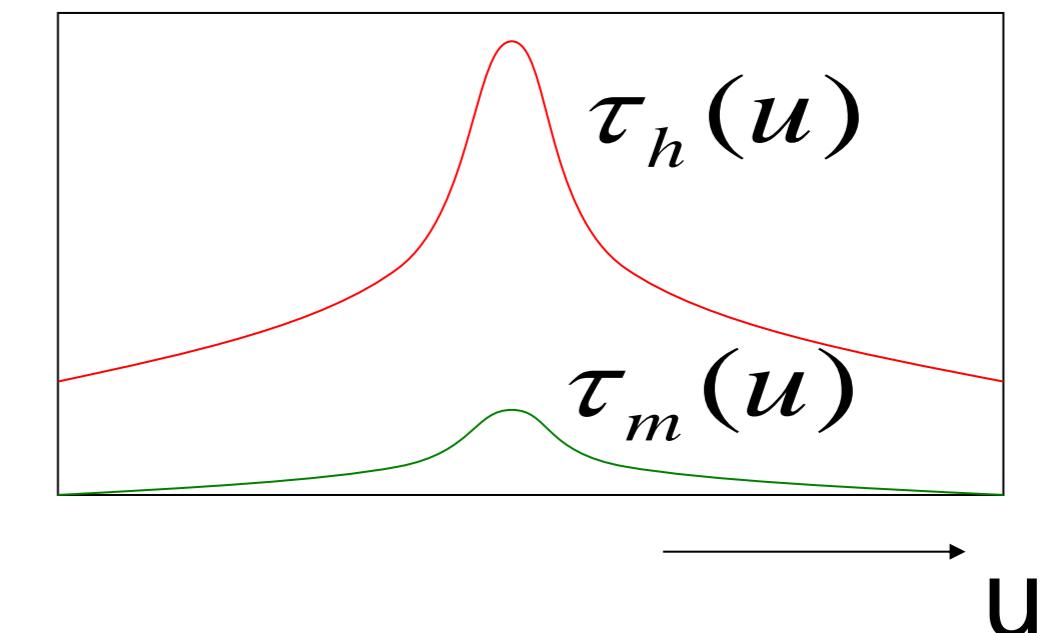
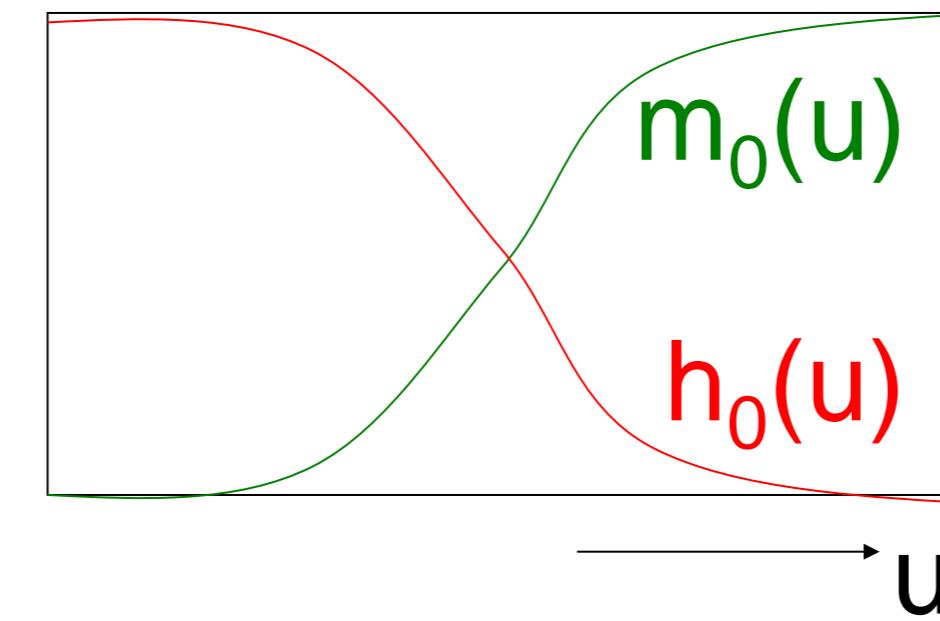
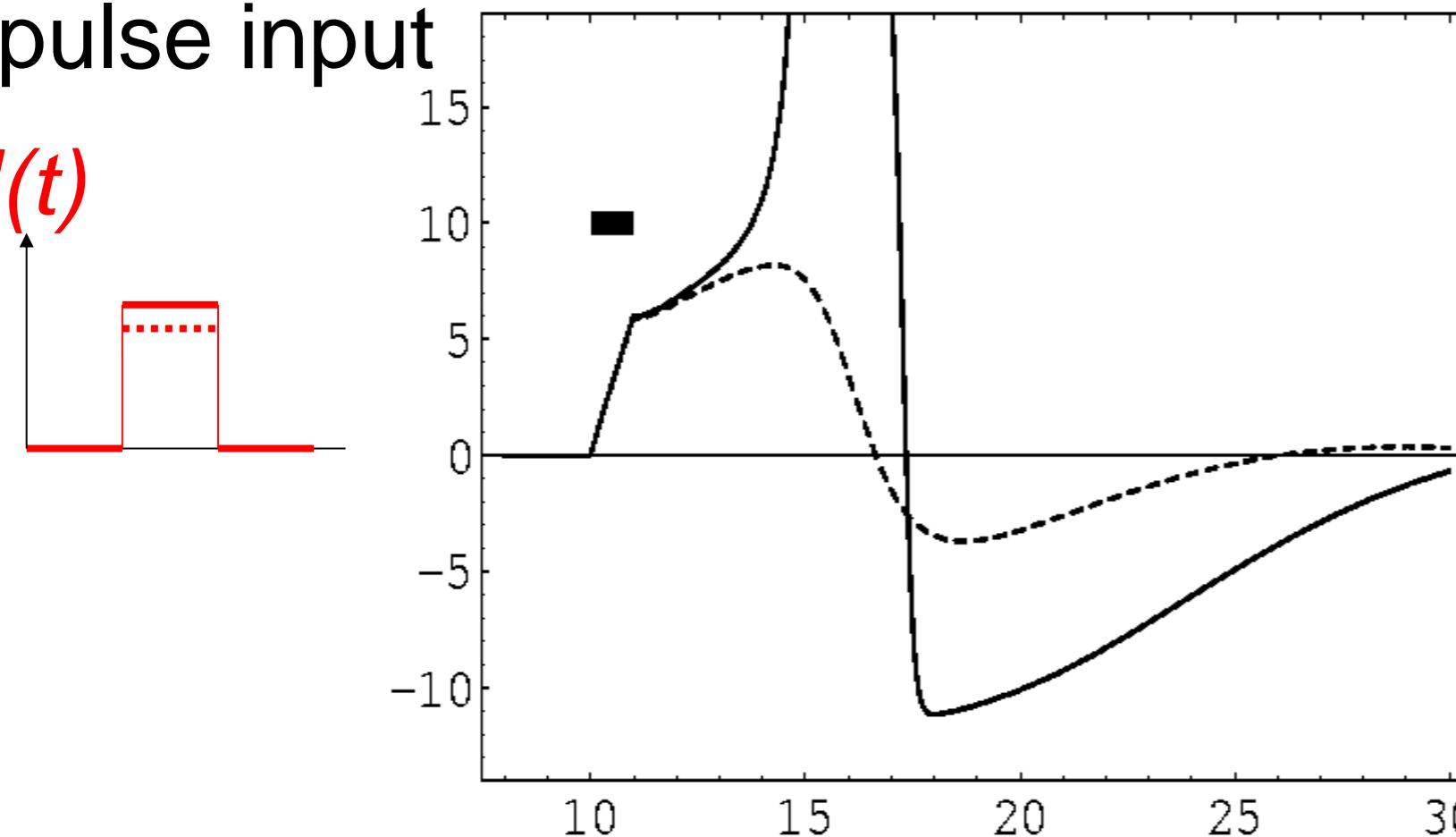
$$\frac{dh}{dt} = -\frac{h - h_0(u)}{\tau_h(u)}$$

Stim.  
↓

# Neuronal Dynamics – 2.4. Threshold in HH model

pulse input

$I(t)$



Stim. ↓

$$C \frac{du}{dt} = -g_{Na} m^3 h (u - E_{Na}) - I_K - I_{leak} + I(t)$$

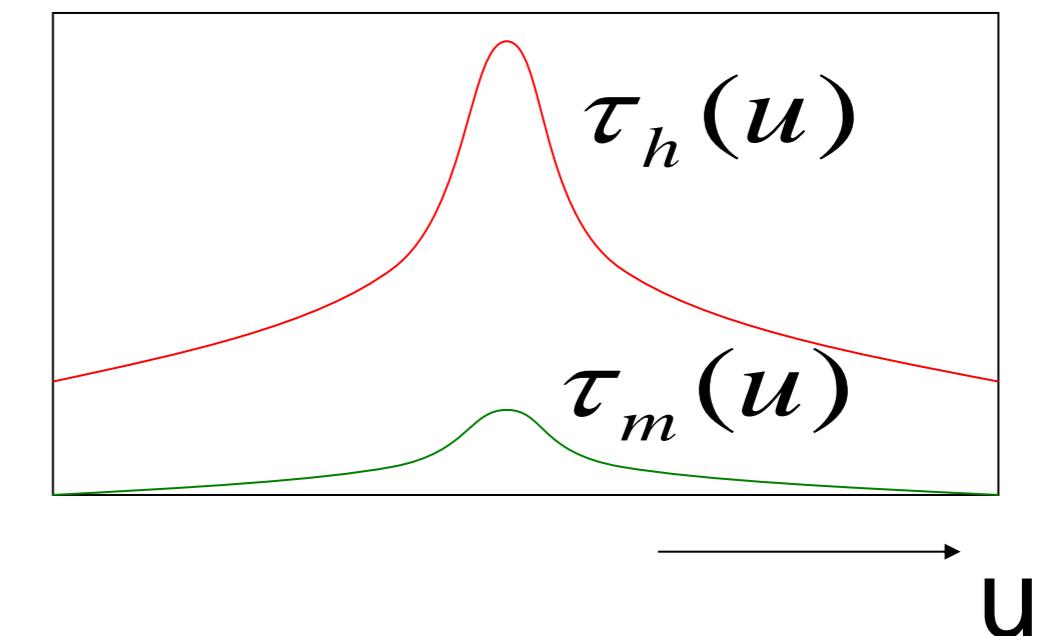
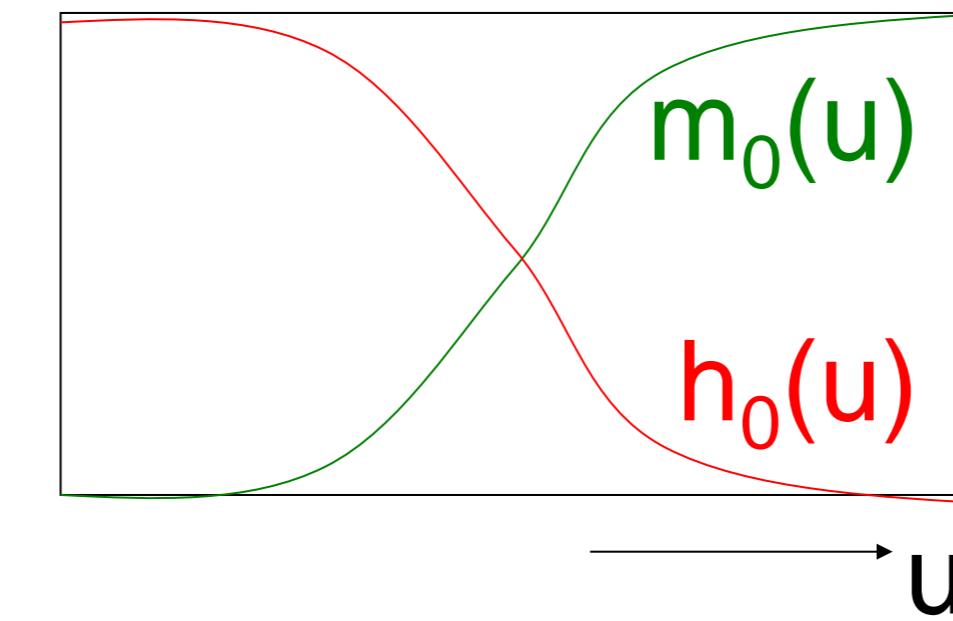
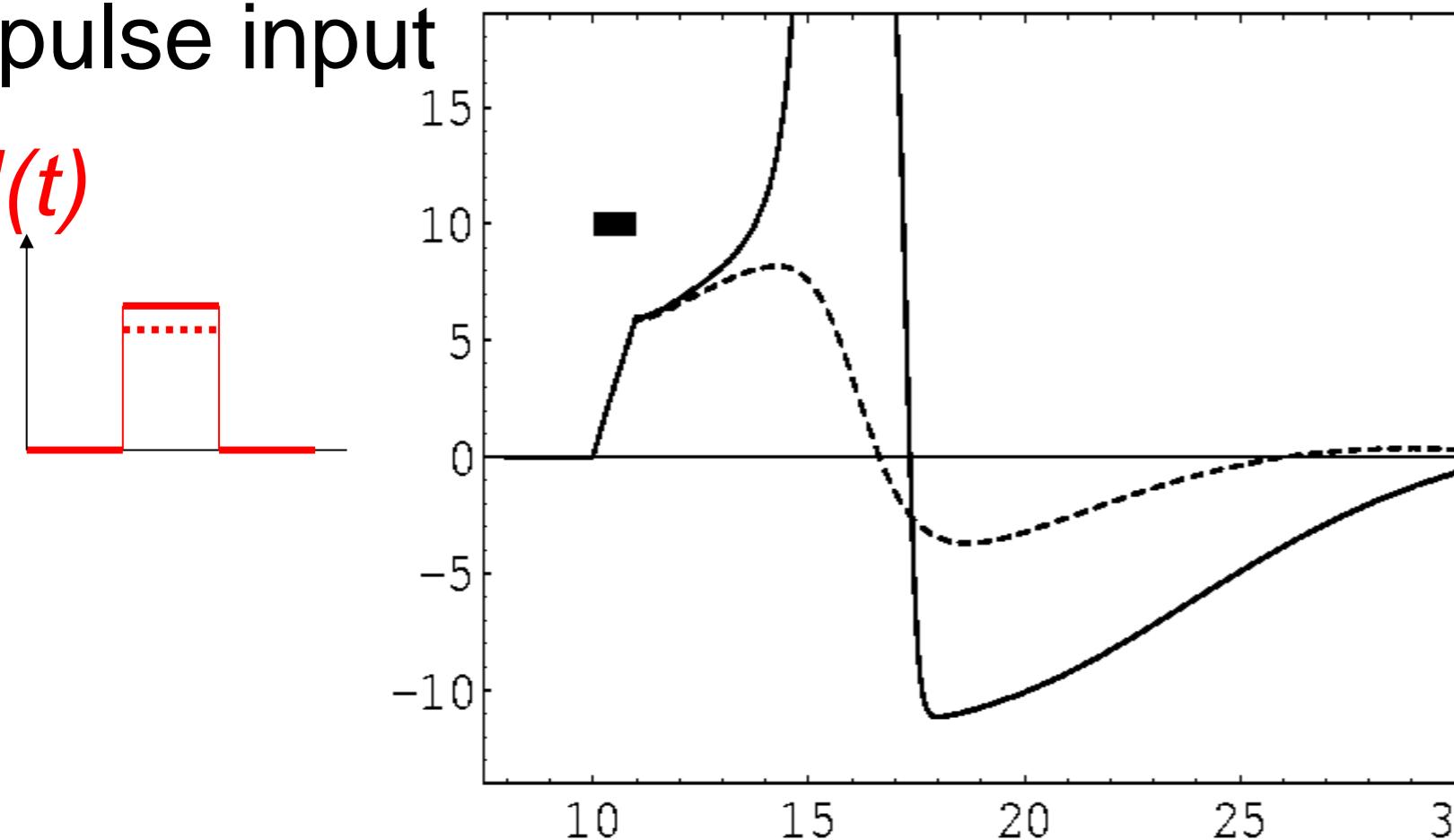
$$\frac{dm}{dt} = -\frac{m - m_0(u)}{\tau_m(u)}$$

$$\frac{dh}{dt} = -\frac{h - h_0(u)}{\tau_h(u)}$$

# Neuronal Dynamics – 2.4. Threshold in HH model

pulse input

$I(t)$



Why start the explanation with  $m$  and not  $h$ ?

What about  $n$ ?

Where is the threshold?

$$C \frac{du}{dt} = -g_{Na} m^3 h (u - E_{Na}) - g_K n^4 (u - E_K) - g_l (u - E_l) + I(t)$$

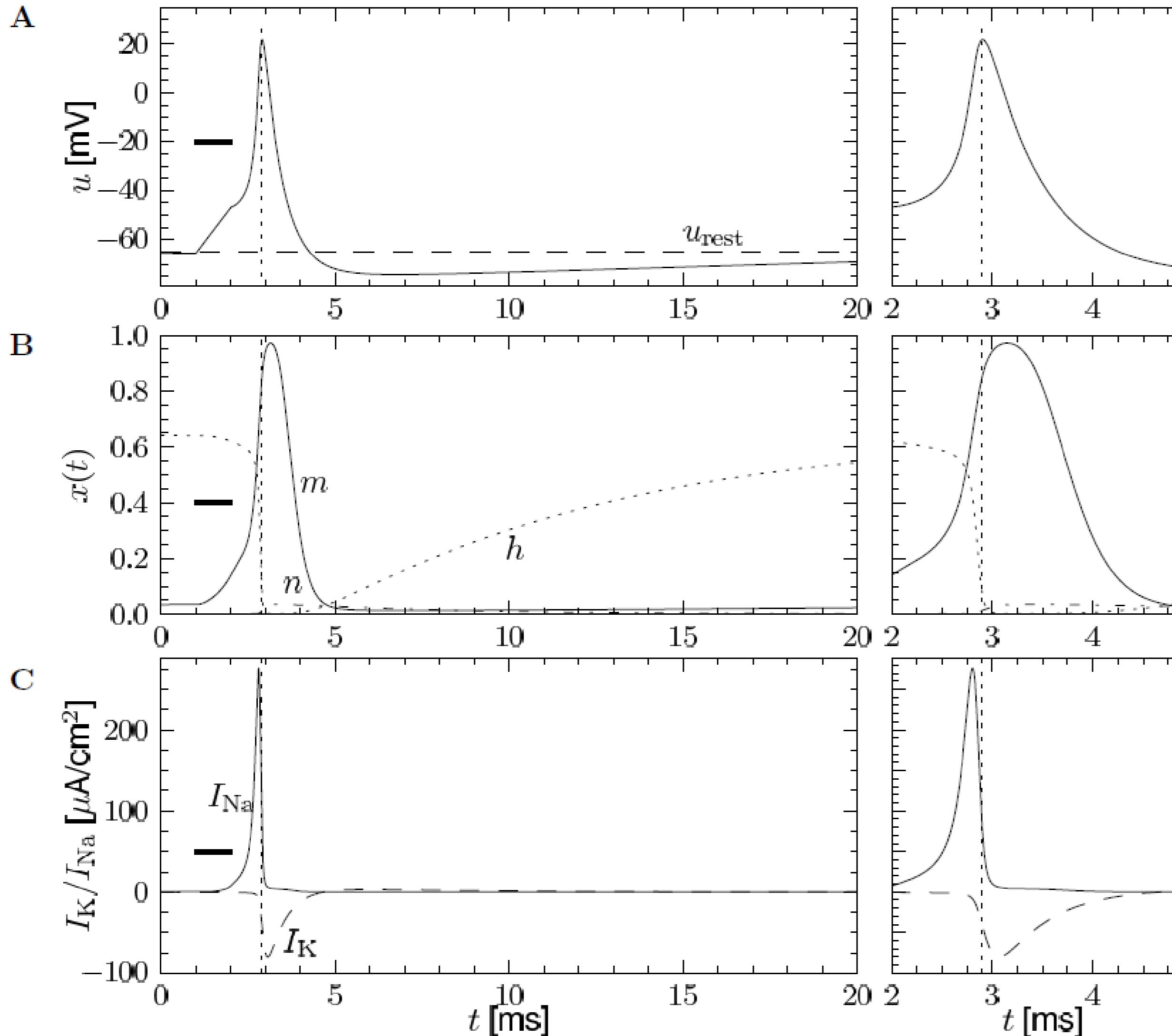
$$\frac{dm}{dt} = -\frac{m - m_0(u)}{\tau_m(u)}$$

$$\frac{dh}{dt} = -\frac{h - h_0(u)}{\tau_h(u)}$$

$$\frac{dn}{dt} = -\frac{n - n_0(u)}{\tau_n(u)}$$

Stim.

# Neuronal Dynamics – 2.4. Threshold in HH model



$$C \frac{du}{dt} = -g_{\text{Na}} m^3 h (u - E_{\text{Na}}) - g_K n^4 (u - E_K) - g_l (u - E_l) + I(t)$$

# Neuronal Dynamics – 2.4. Threshold in HH model

There is no strict threshold:

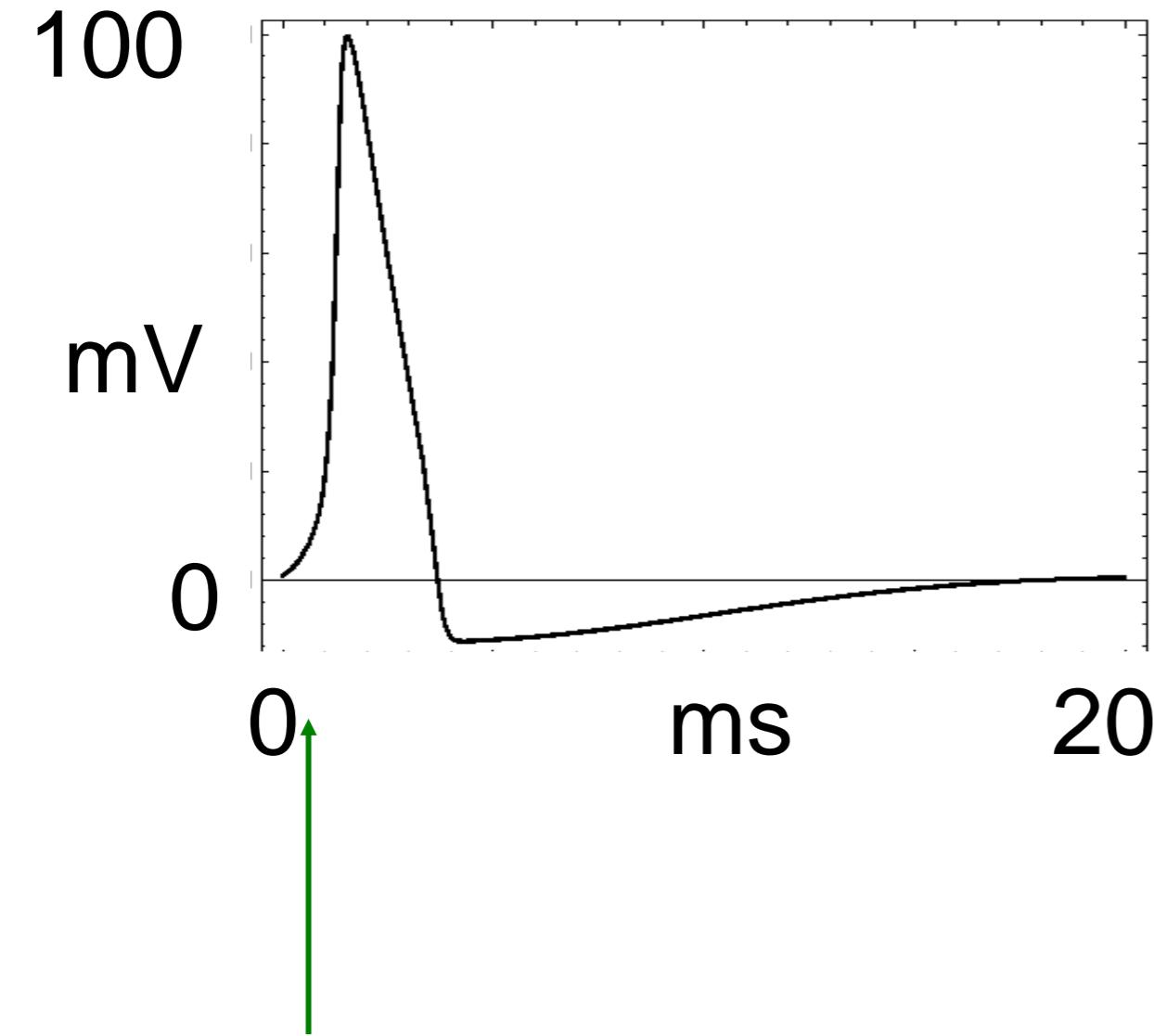
Coupled differential equations

*‘Effective’ threshold  
in simulations?*

# Neuronal Dynamics – 2.4. Refractoriness in HH model

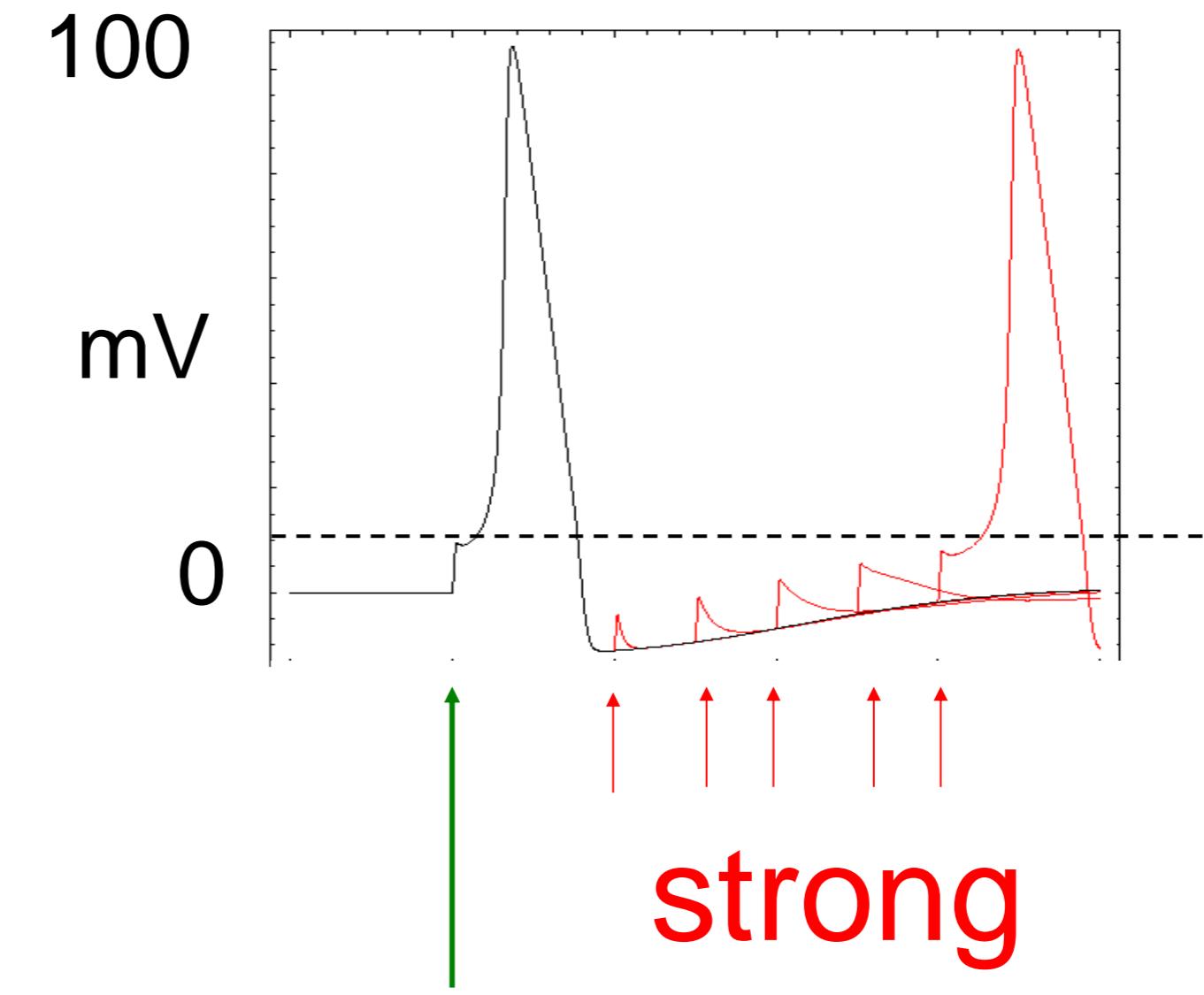
Where is the firing threshold?

Action potential



Strong  
stimulus

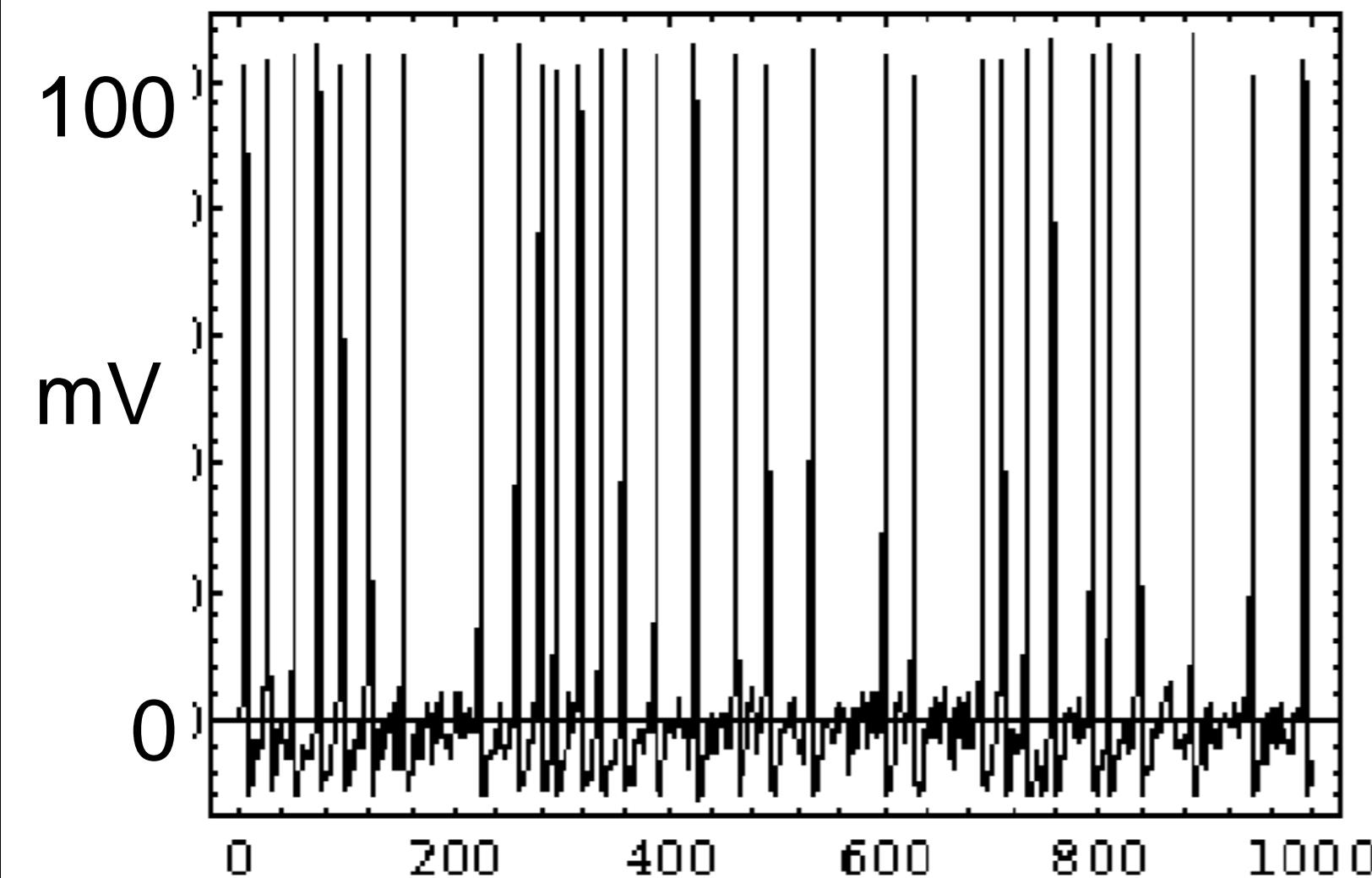
refractoriness



Strong  
stimuli  
strong  
stimulus

**Refractoriness!** Harder to elicit a second spike

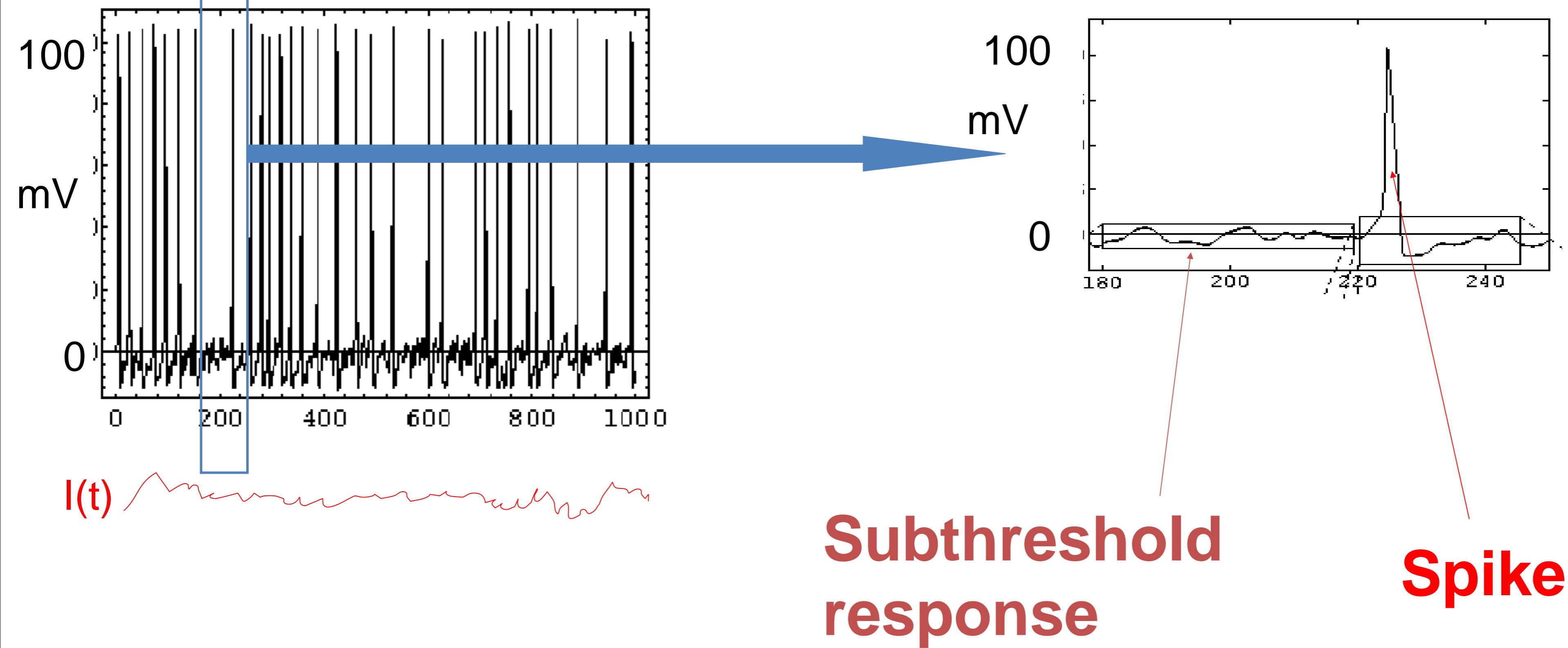
# Neuronal Dynamics – 2.4. Simulations of the HH model



Stimulation with  
time-dependent  
input current

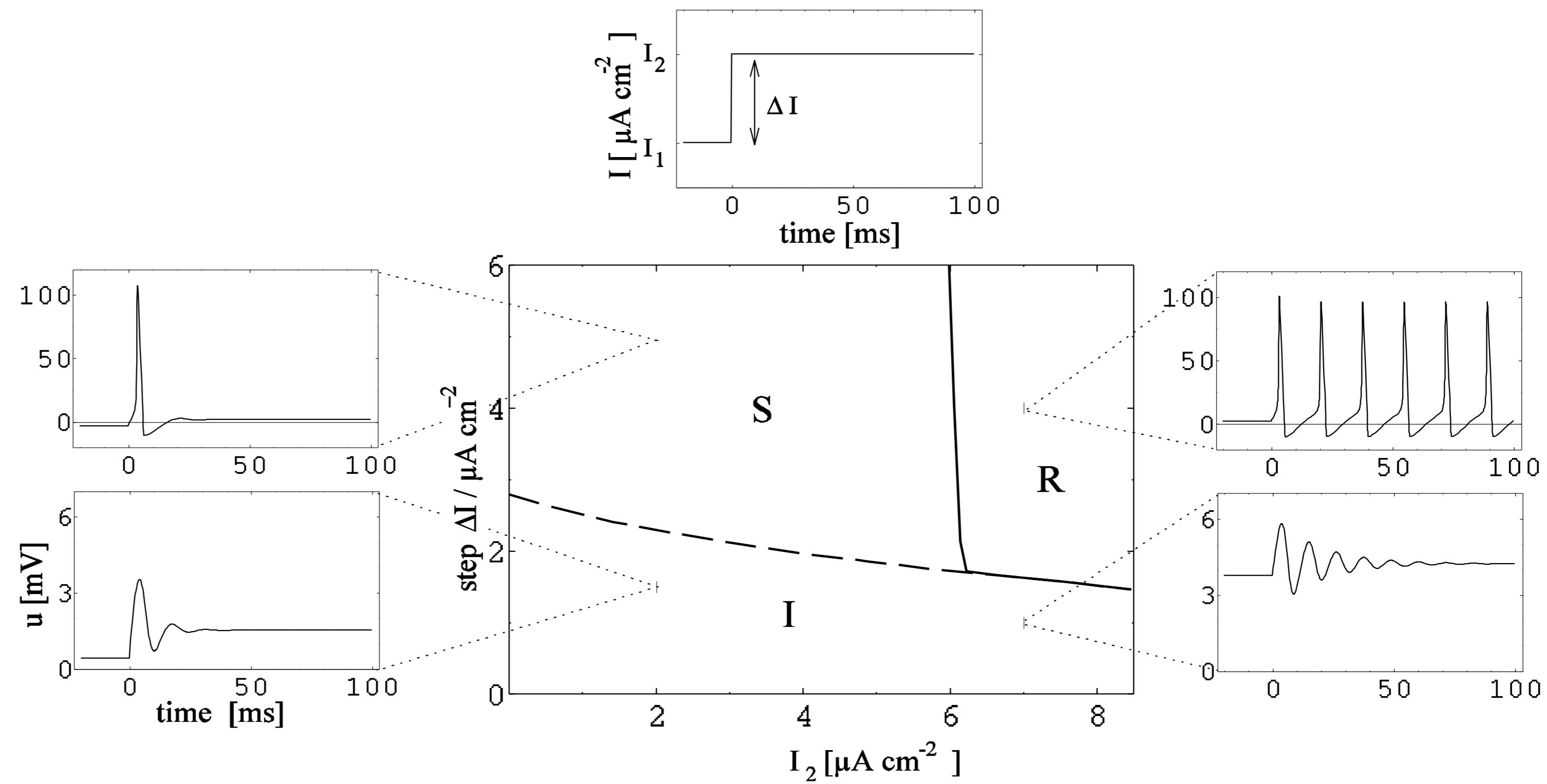


# Neuronal Dynamics – 2.4. Simulations of the HH model



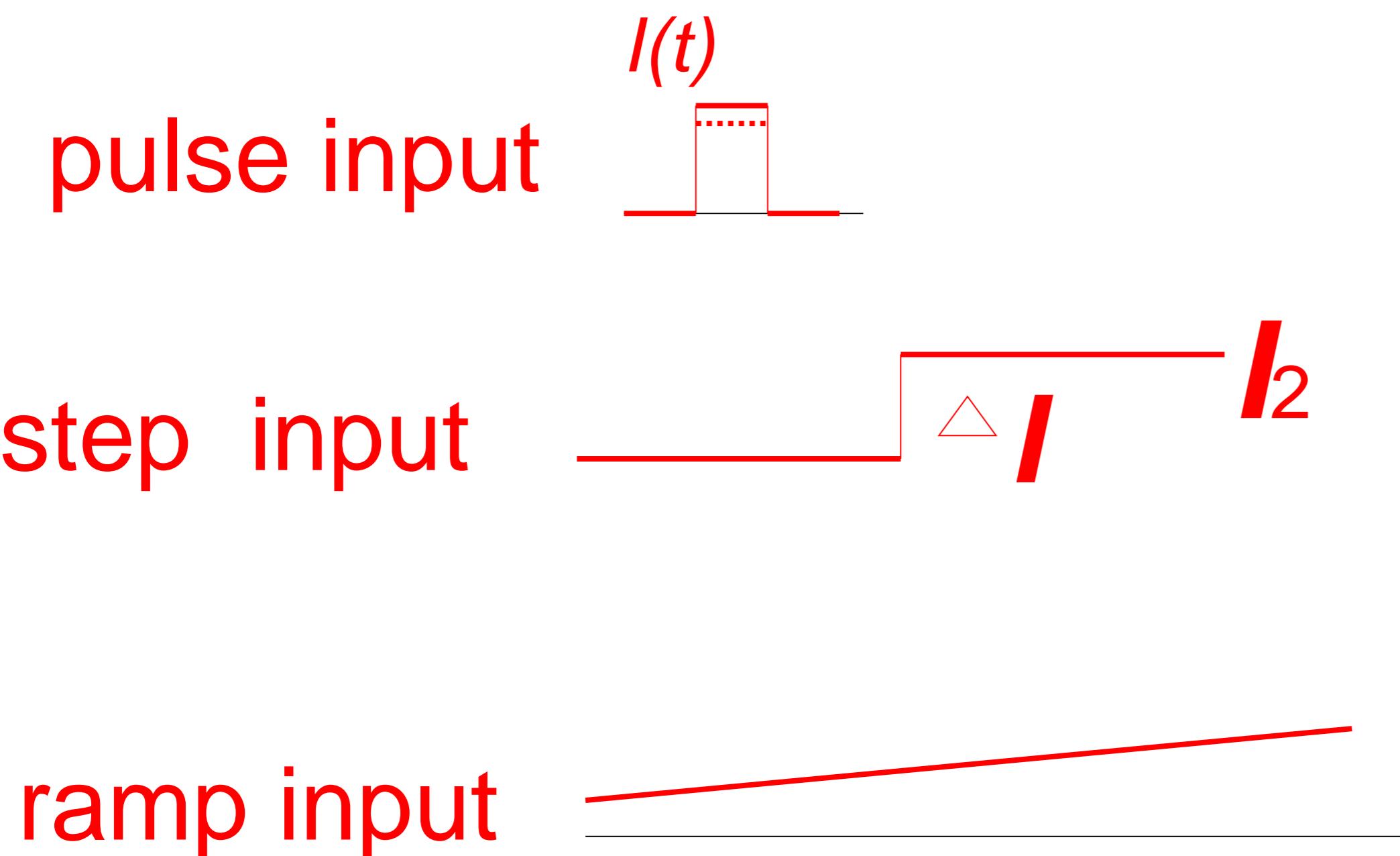
# Neuronal Dynamics – 2.4. Threshold in HH model

Step current input



# Neuronal Dynamics – 2.4. Threshold in HH model

## Where is the firing threshold?



**There is no threshold**

- no current threshold
- no voltage threshold

‘effective’ threshold

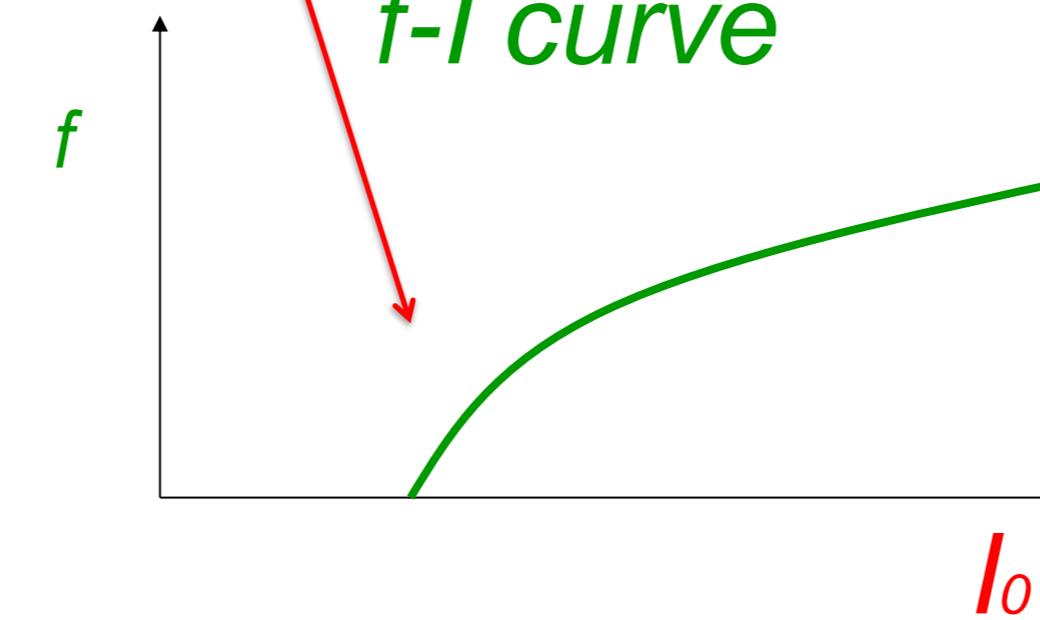
- depends on typical input

$$C \frac{du}{dt} = -g_{Na}m^3h(u - E_{Na}) - \dots$$

# Neuronal Dynamics – 2.4. Type I and Type II

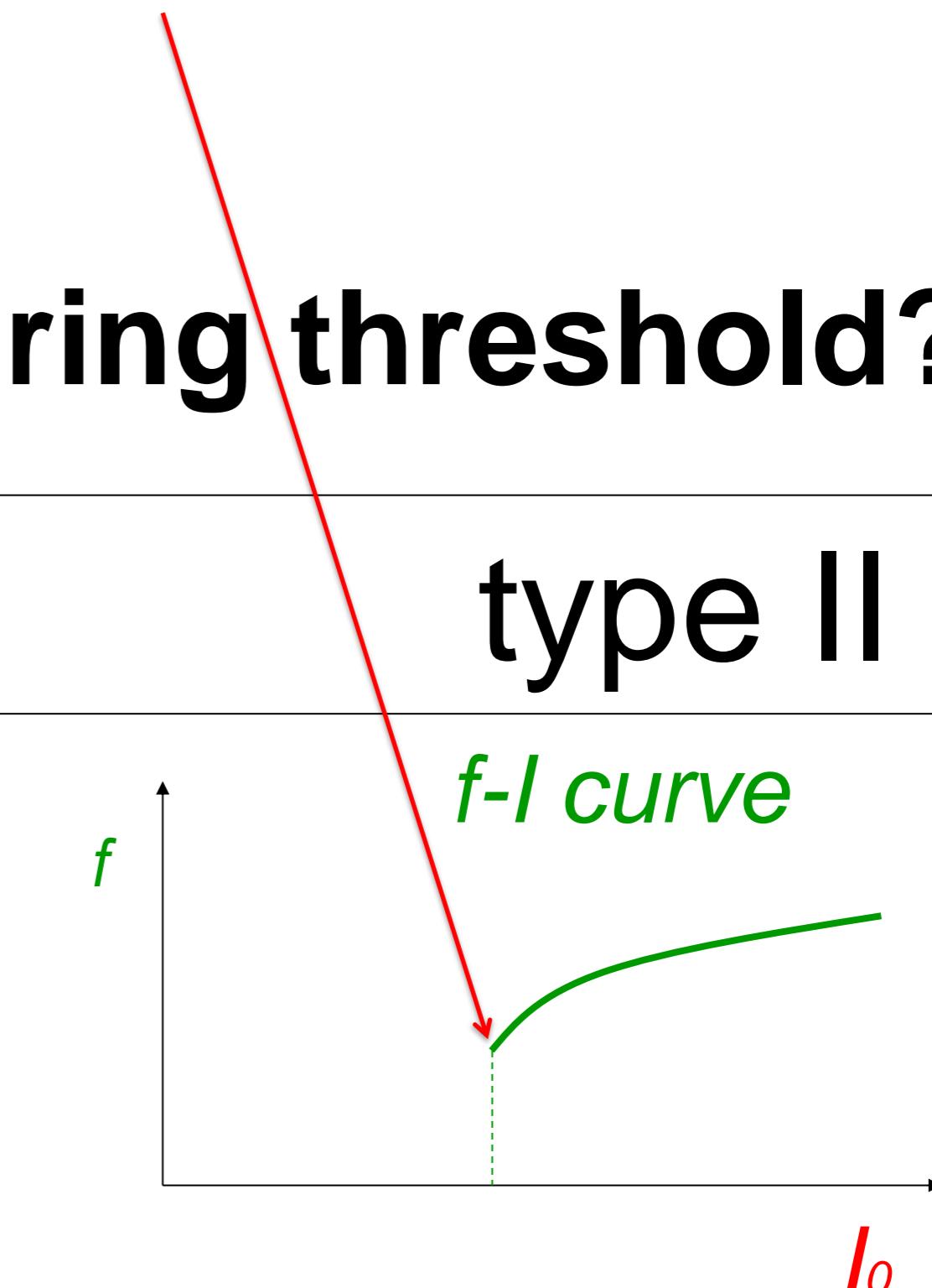
Hodgkin-Huxley model  
with other parameters  
(e.g. for cortical pyramidal  
Neuron )

ramp input/  
constant input



Type I

Hodgkin-Huxley model  
with standard parameters  
(giant axon of squid)



type II

Response at firing threshold?

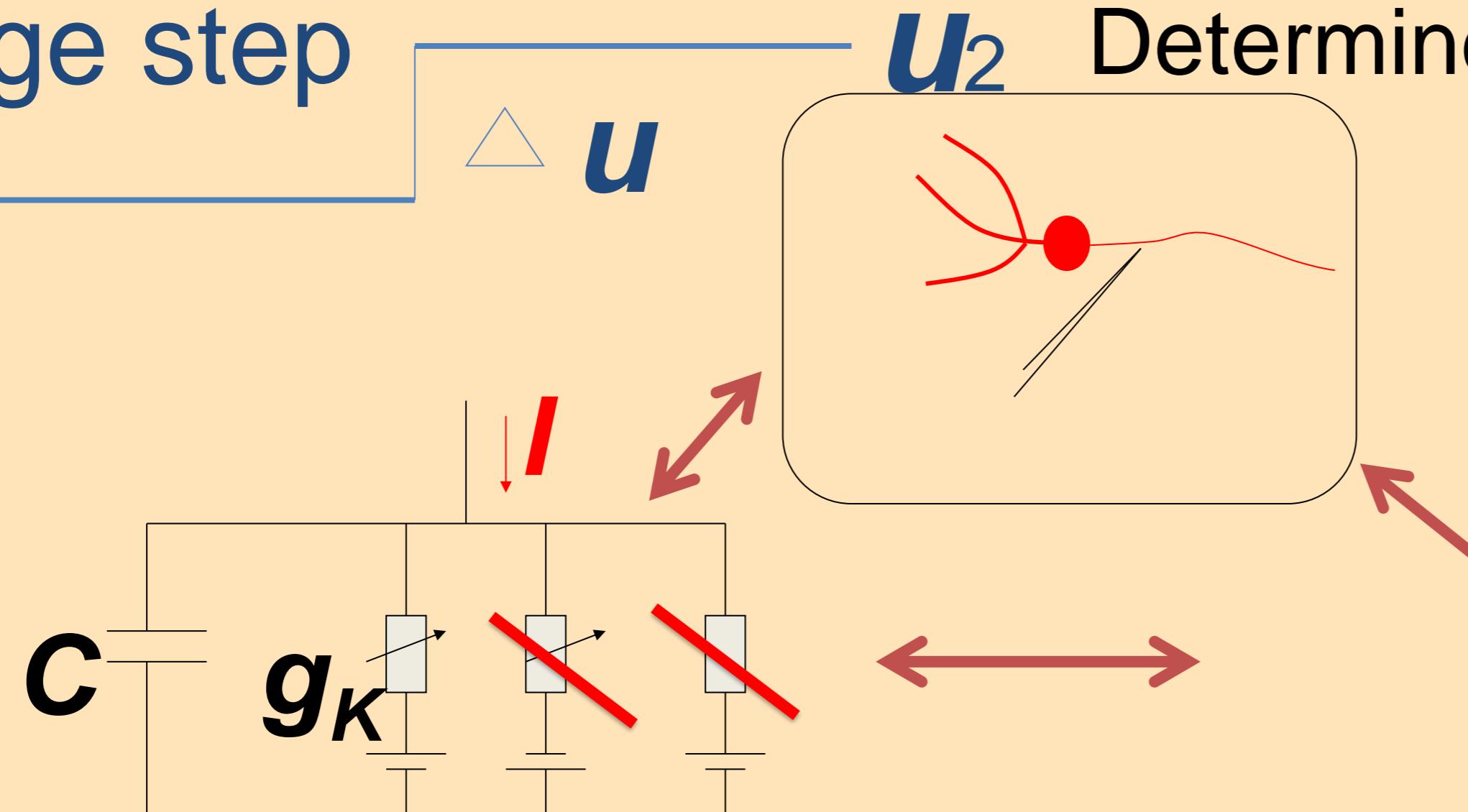
# Neuronal Dynamics – 2.4. Hodgkin-Huxley model

- 4 differential equations
- no explicit threshold
- effective threshold depends on stimulus
- BUT: voltage threshold good approximation

- Giant axon of the squid  
→ cortical neurons
- Change of parameters
- More ion channels
- Same framework

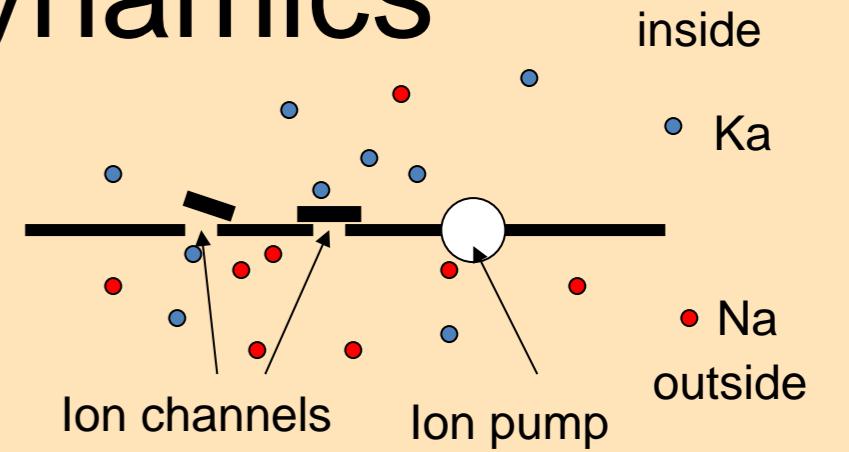
# Exercise – 2.4. Hodgkin-Huxley model – ion channel

voltage step

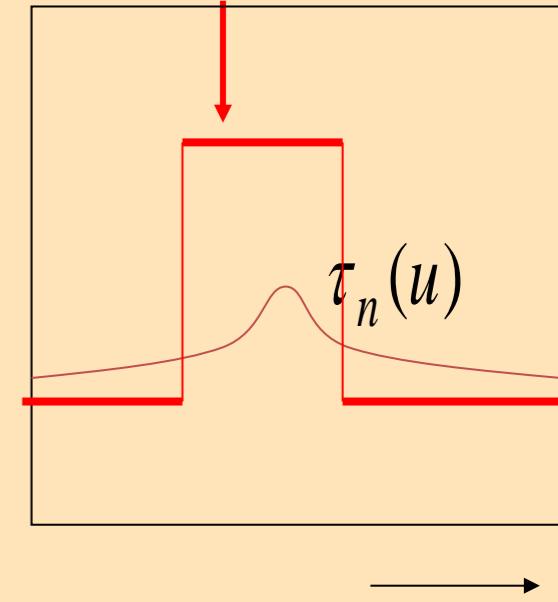
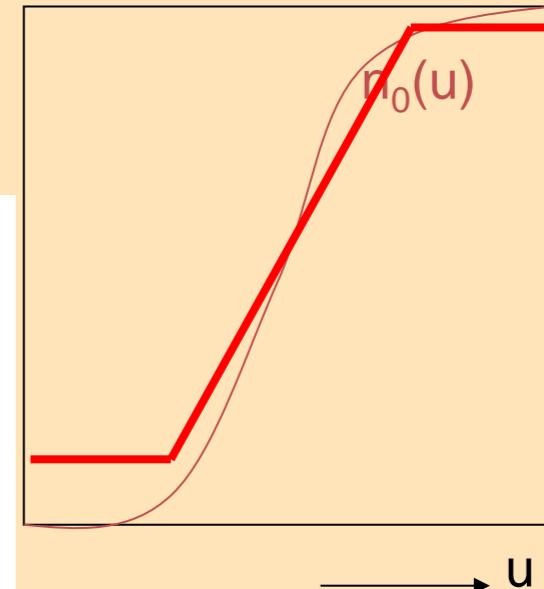
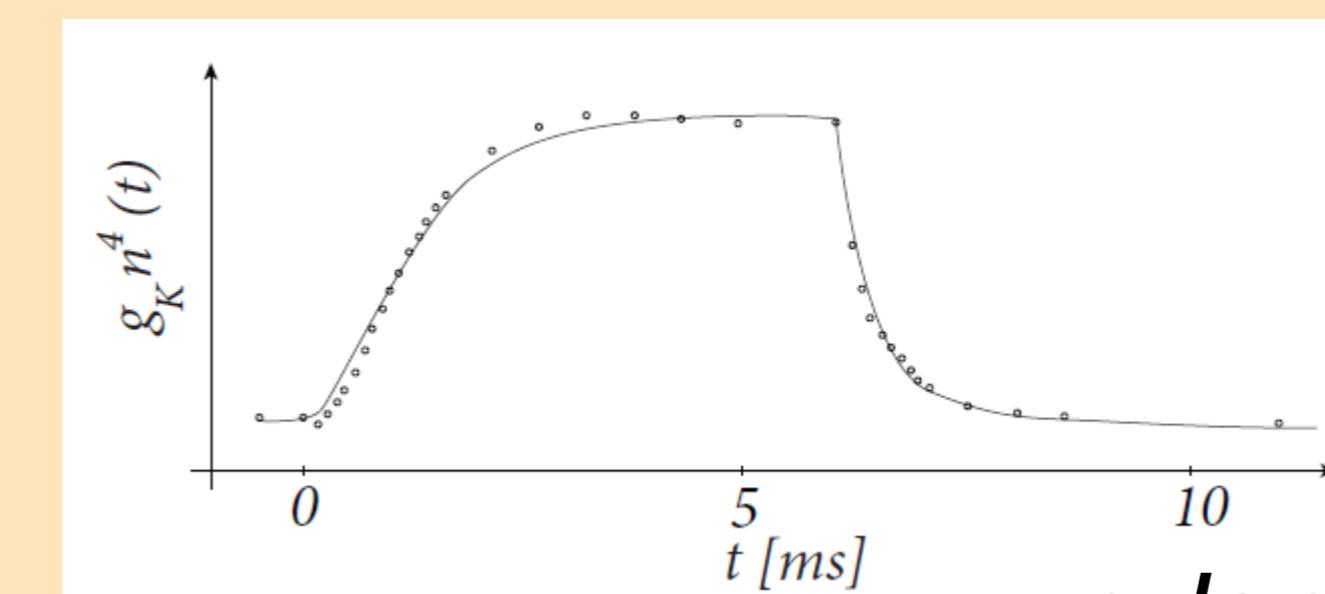


$$C \frac{du}{dt} = -g_K n^4 (u - E_K) + I(t)$$

stimulus



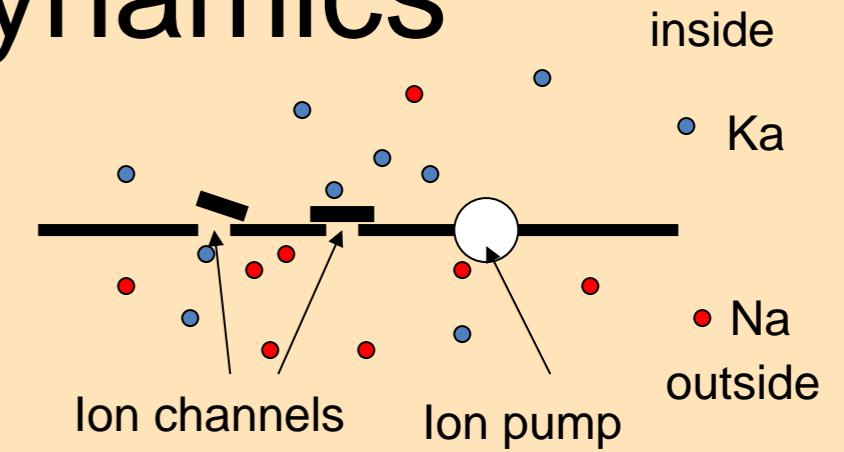
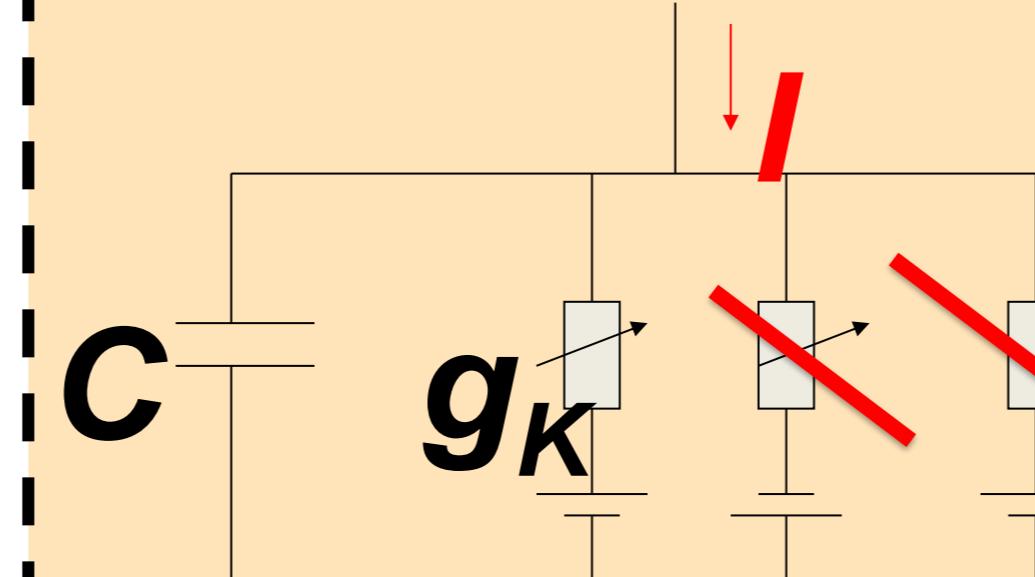
apply voltage step



adapted from  
Hodgkin&Huxley 1952

# Exercise – 2.4. Hodgkin-Huxley model – ion channel

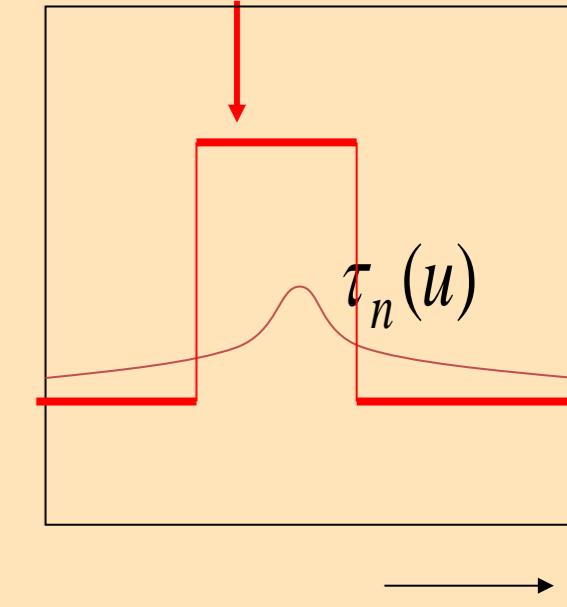
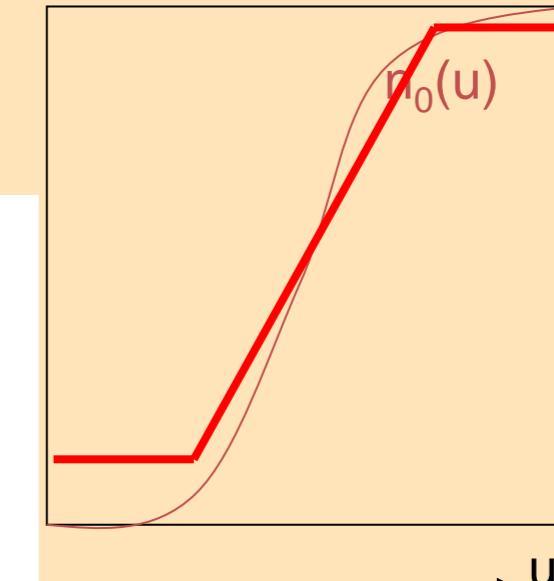
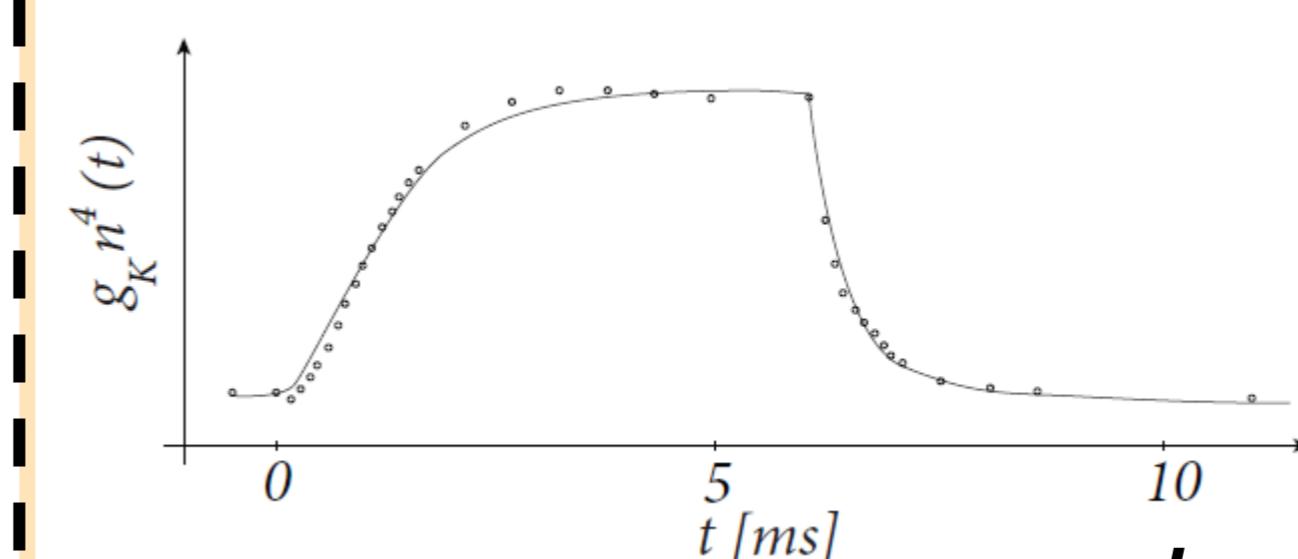
Determine ion channel dynamics



$$C \frac{du}{dt} = -g_K n^4 (u - E_K) + I(t)$$

stimulus

apply voltage step



adapted from  
Hodgkin&Huxley 1952

# Week 2 – part 5: Detailed Biophysical Models



## Neuronal Dynamics: Computational Neuroscience of Single Neurons

### Week 2 – Biophysical modeling: The Hodgkin-Huxley model

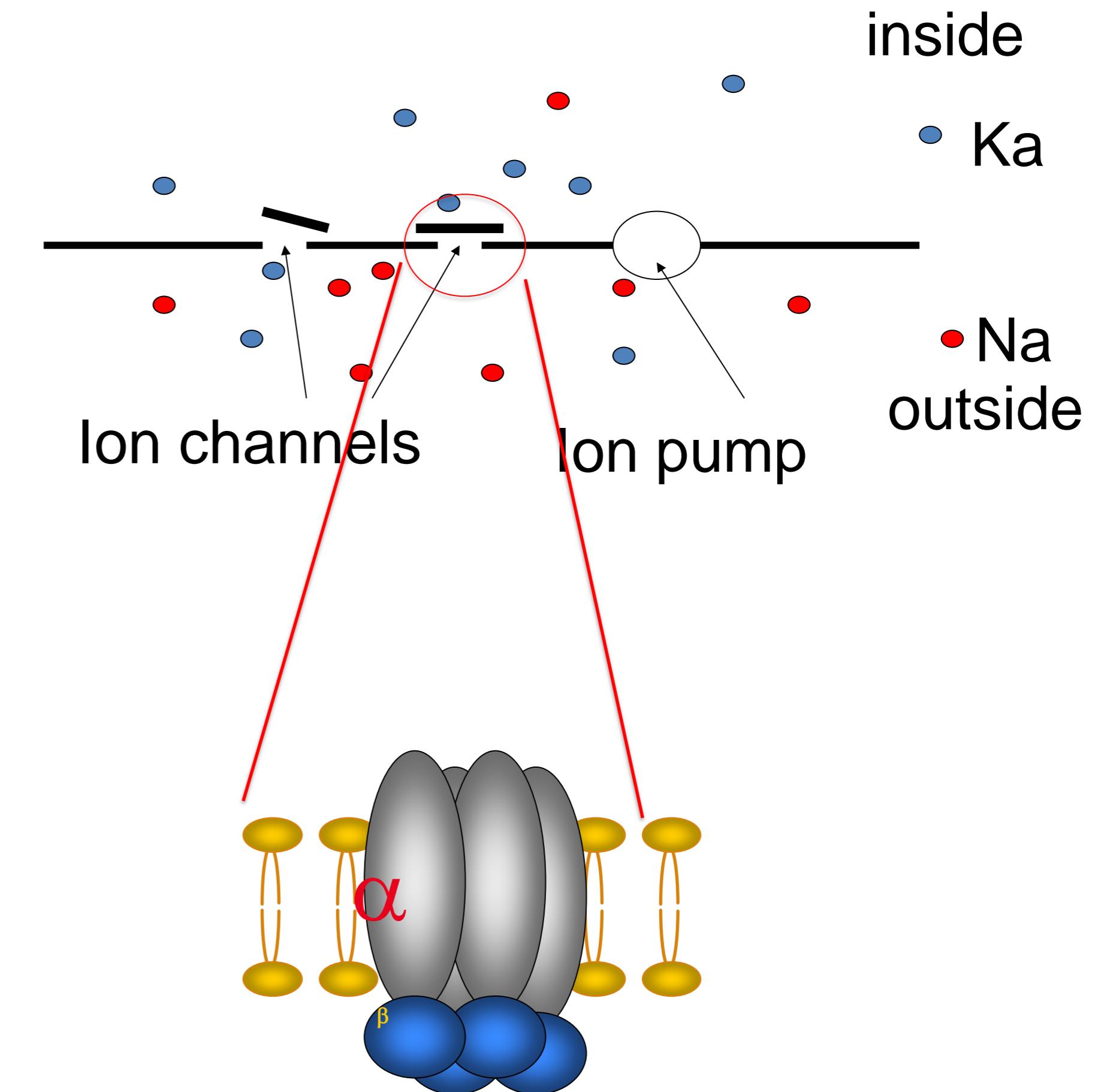
Wulfram Gerstner

EPFL, Lausanne, Switzerland

- ✓ 2.1 Biophysics of neurons
  - Overview
- ✓ 2.2 Reversal potential
  - Nernst equation
- ✓ 2.3 Hodgkin-Huxley Model
- ✓ 2.4 Threshold in the Hodgkin-Huxley Model
  - where is the firing threshold?

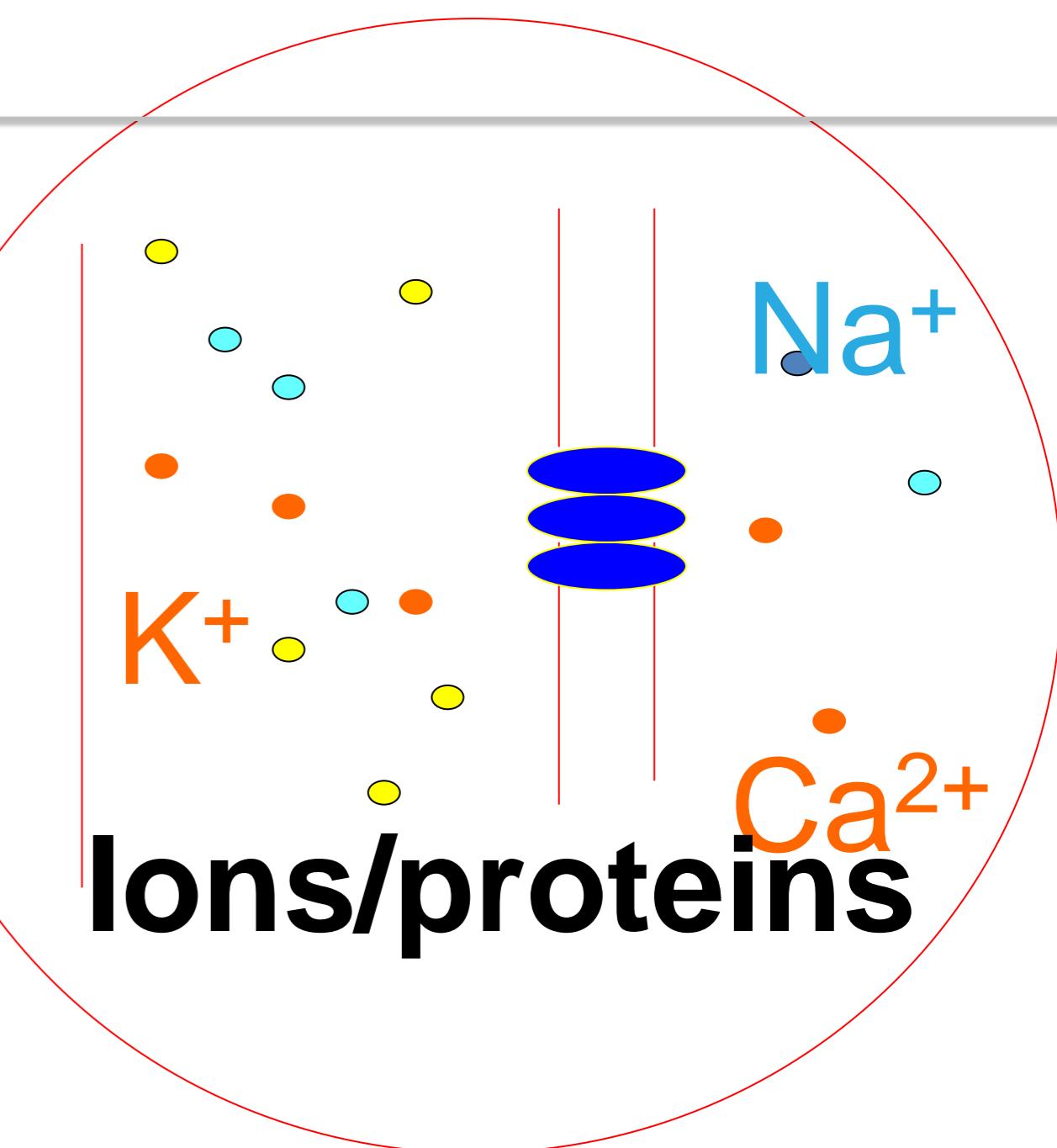
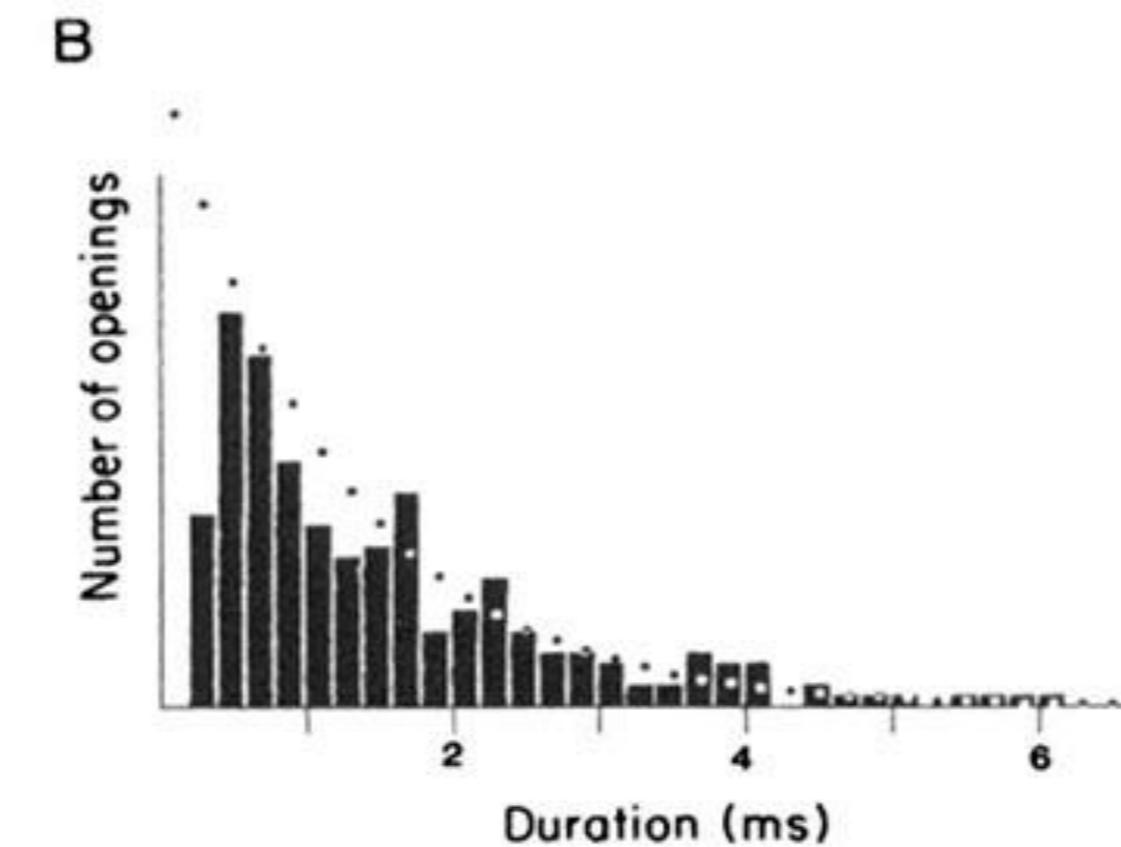
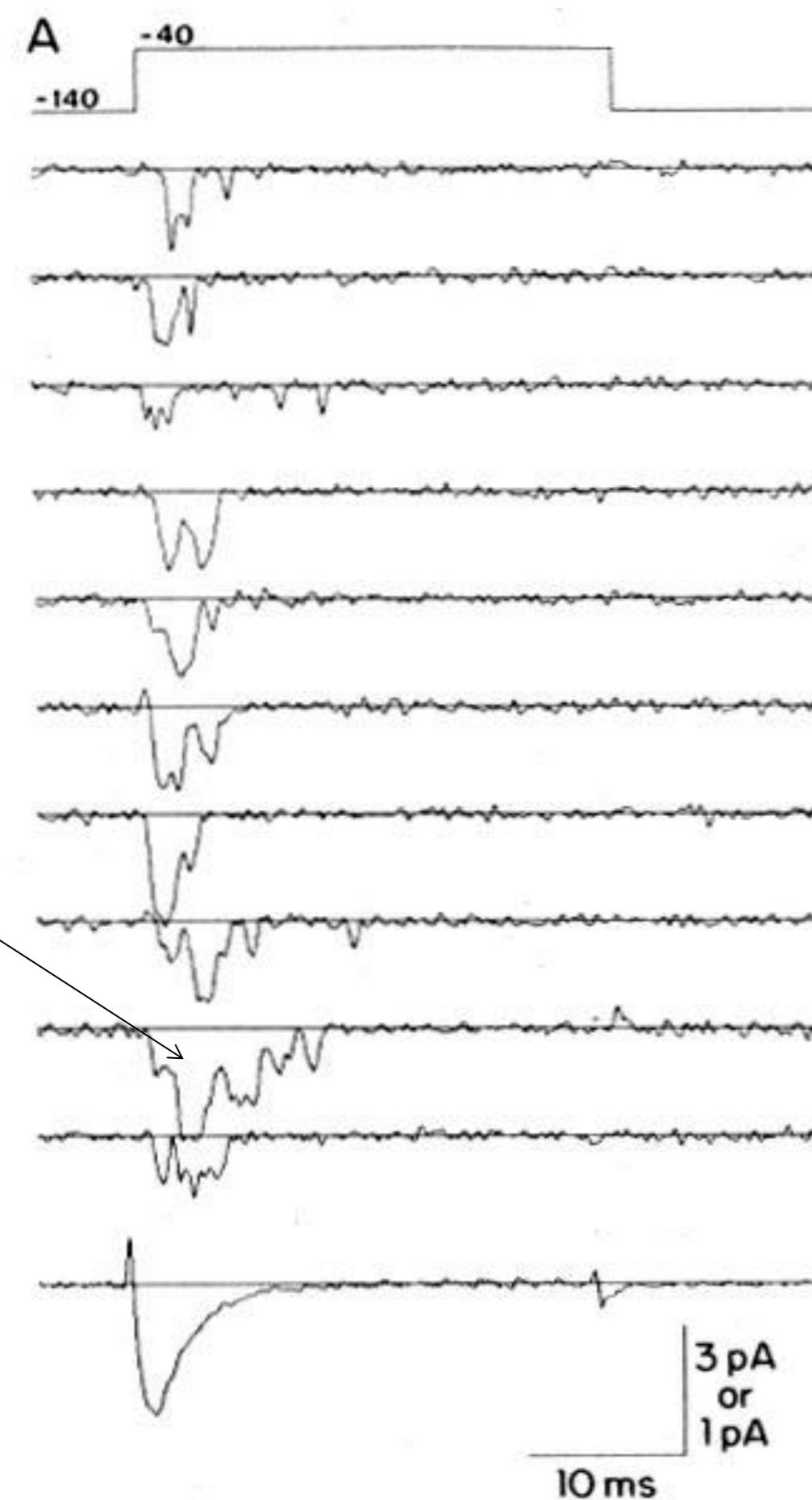
- 2.5. Detailed biophysical models
  - the zoo of ion channels

# Neuronal Dynamics – 2.5 Biophysical models



# Neuronal Dynamics – 2.5 Ion channels

Steps:  
Different number  
of channels



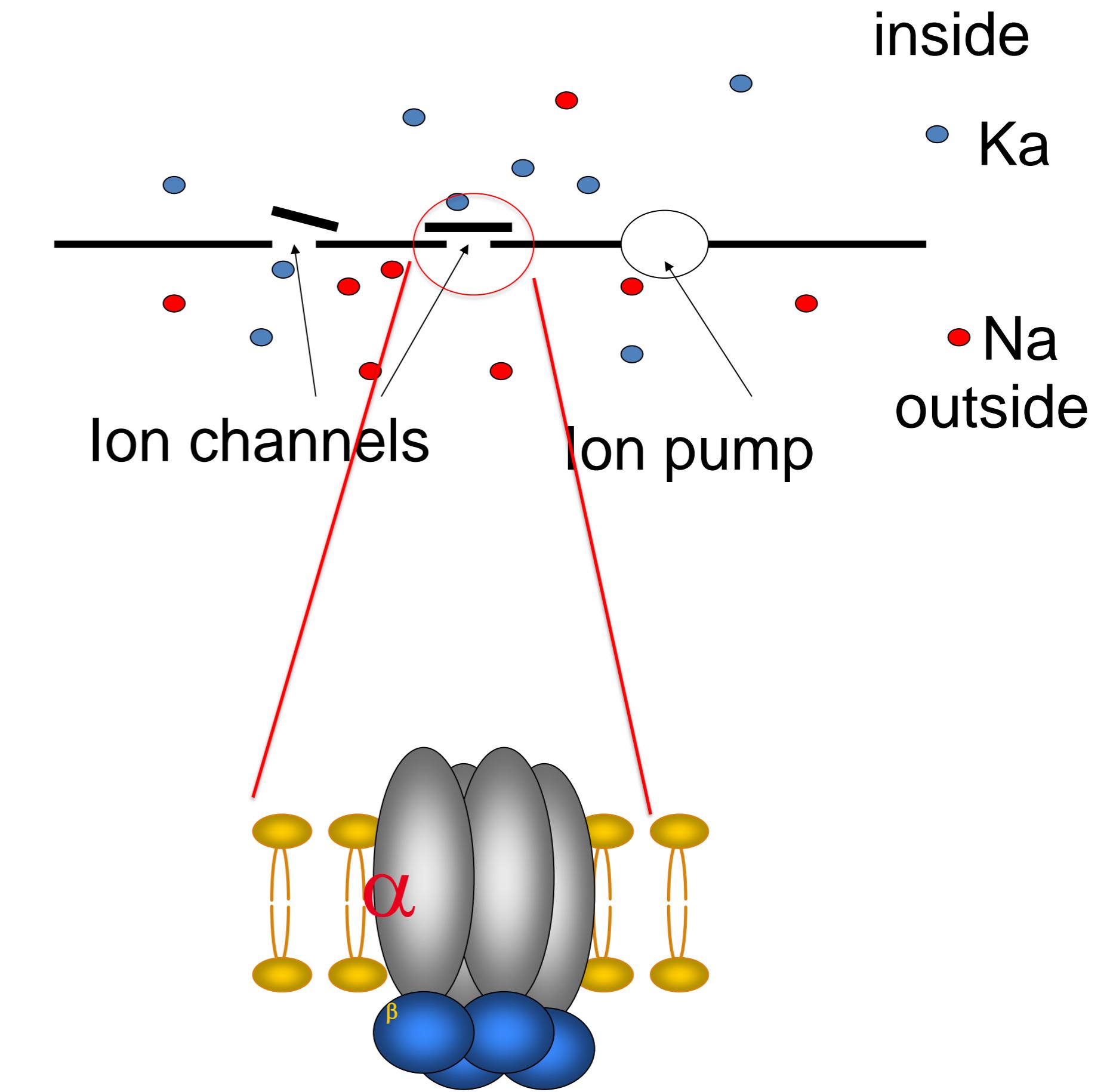
Na<sup>+</sup> channel from rat heart (*Patlak and Ortiz 1985*)  
A traces from a patch containing several channels.  
Bottom: average gives current time course.  
B. Opening times of single channel events

# Neuronal Dynamics – 2.5 Biophysical models

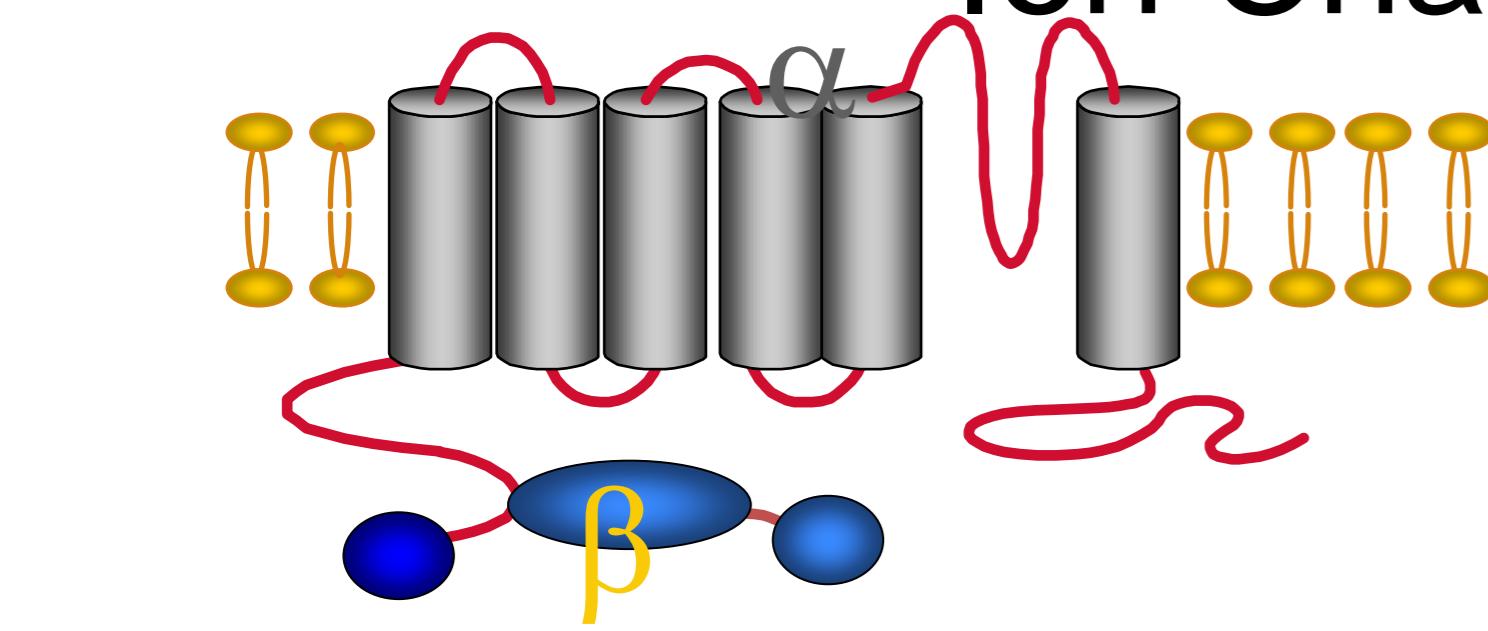
*There are about 200 identified ion channels*

<http://channelpedia.epfl.ch/>

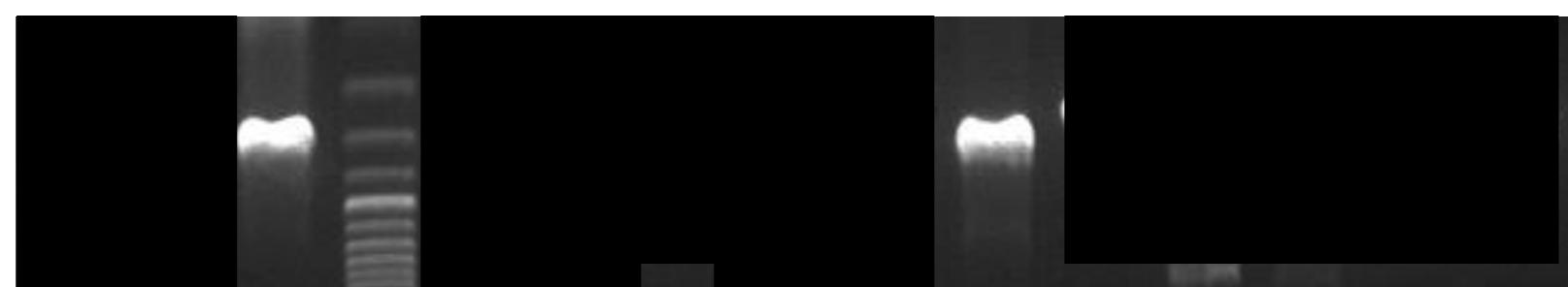
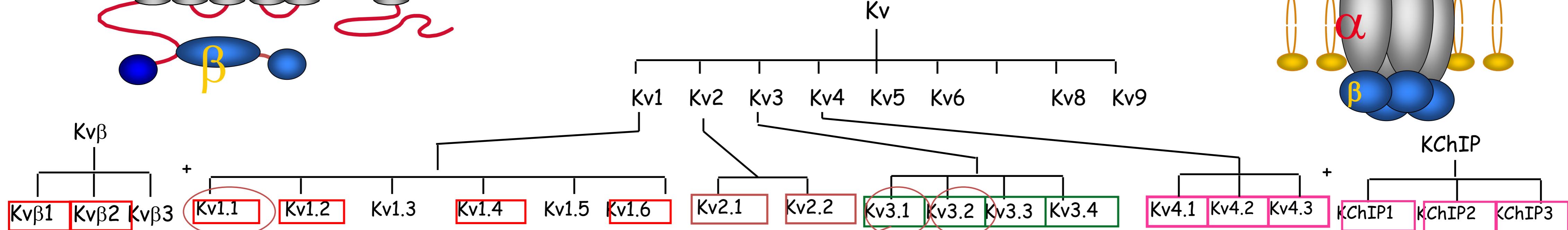
How can we know which ones are present in a given neuron?



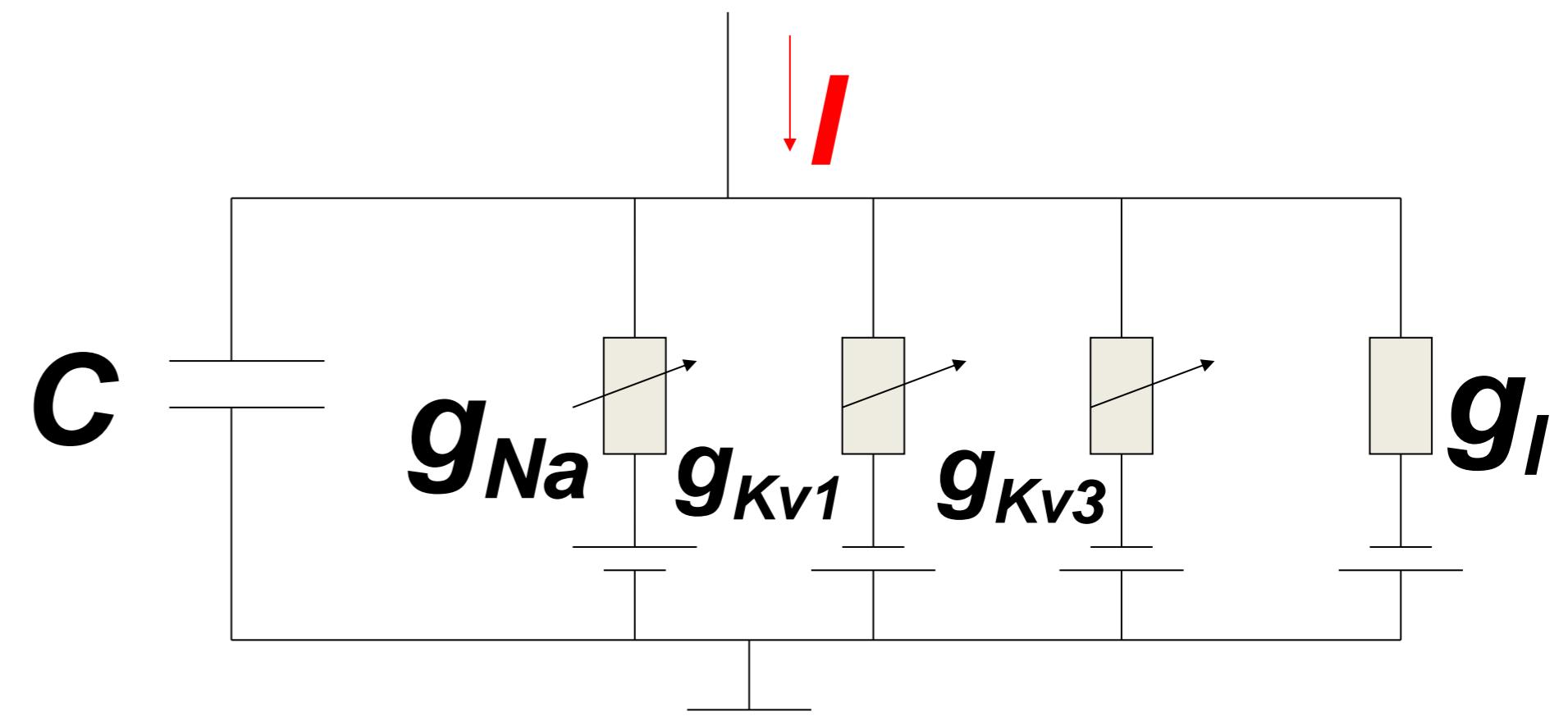
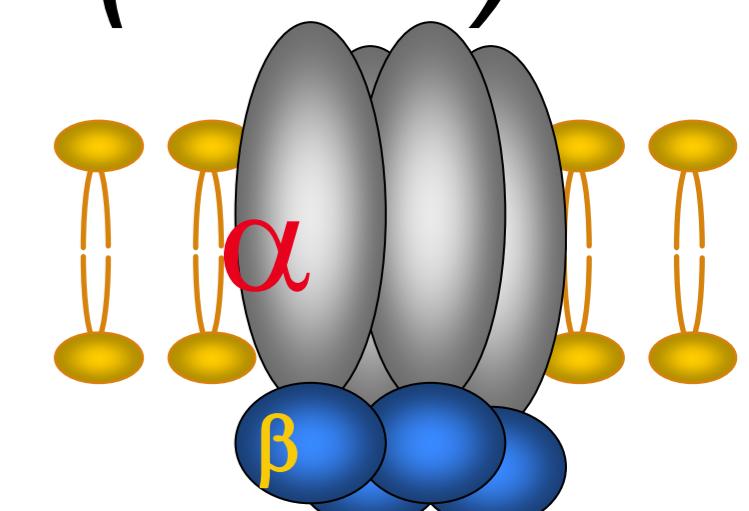
# Ion Channels investigated in the study of Toledo-Rodriguez, ..., Markram (2004)



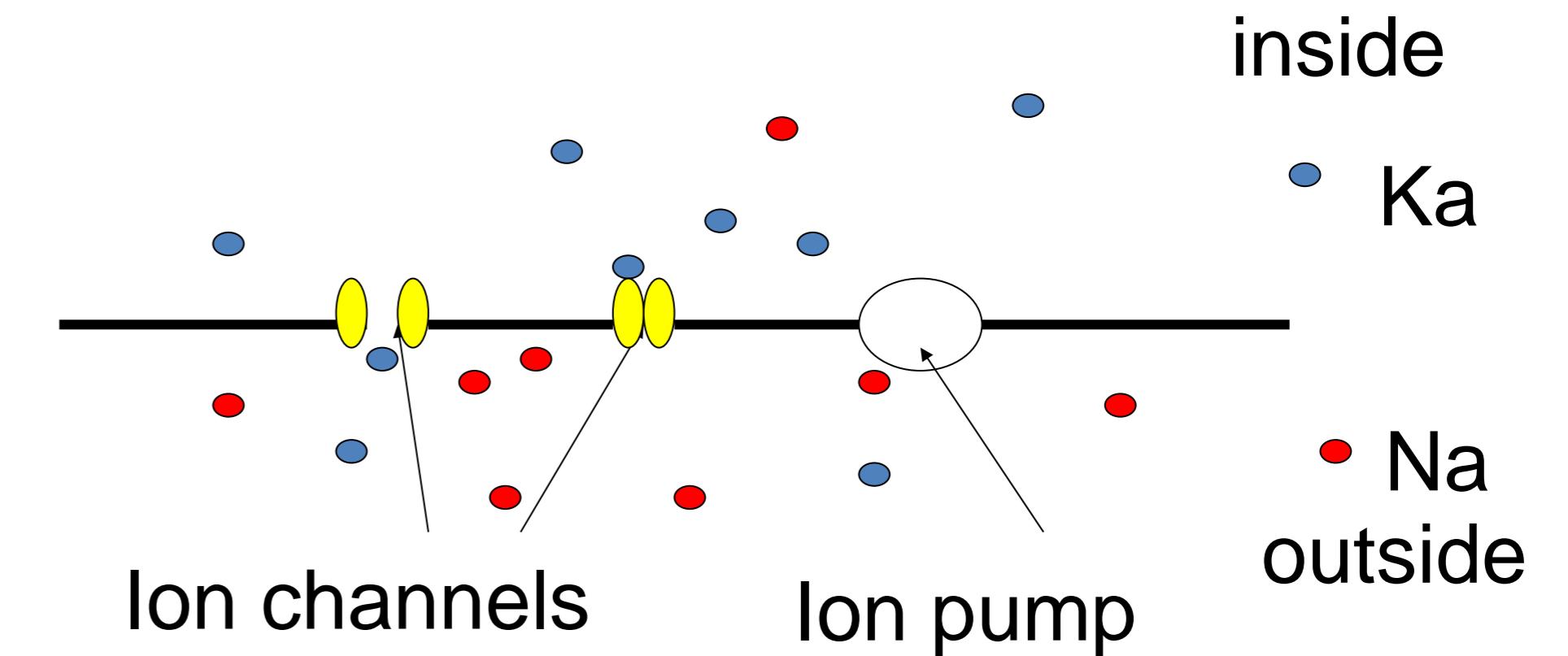
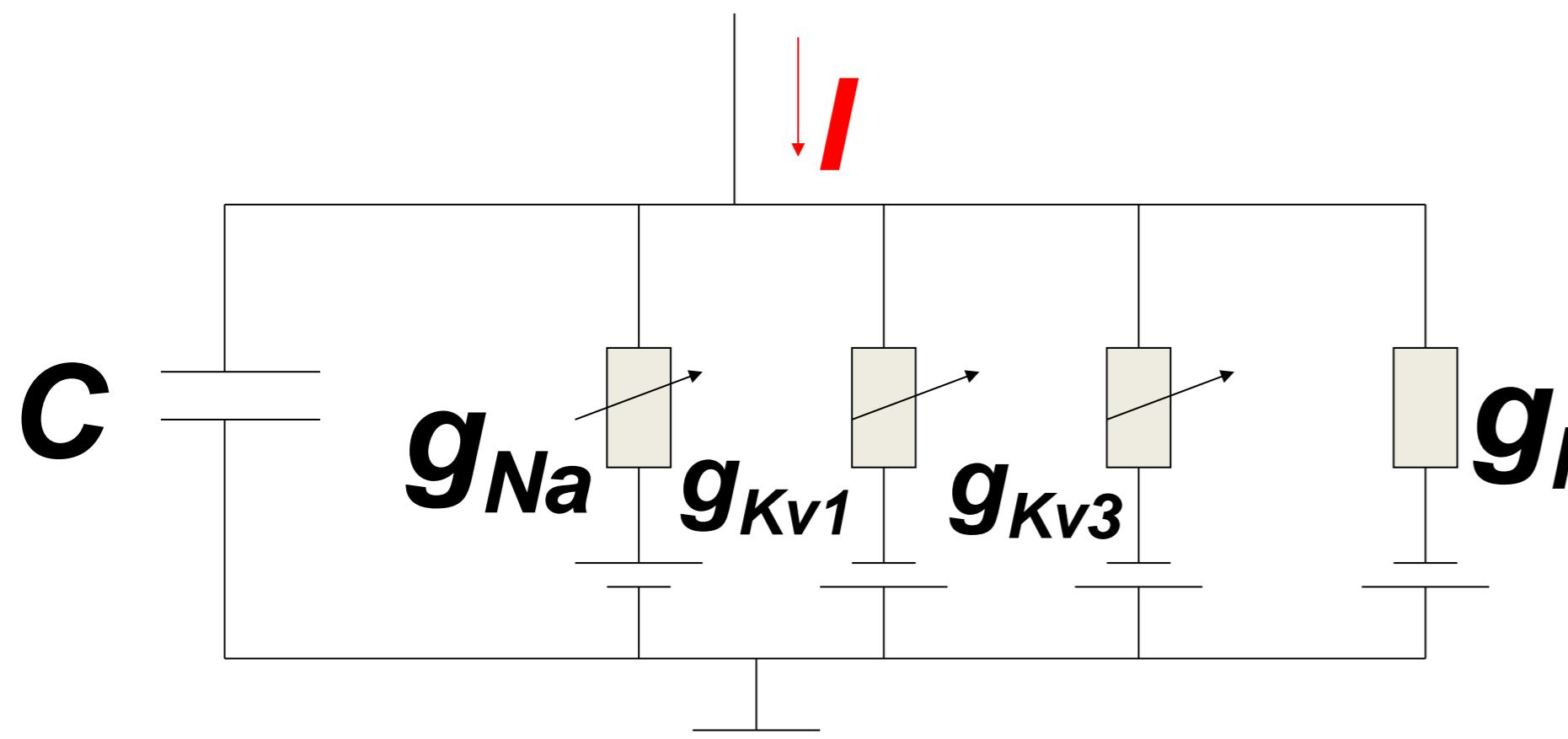
## Voltage Activated K<sup>+</sup> Channels



schematic mRNA  
Expression profile



# Model of a hypothetical neuron



$$C \frac{du}{dt} = -g_{Na} m^3 h (u - E_{Na}) - g_{Kv1} n_{Kv1}^4 (u - E_K) - g_{Kv3} n_{Kv3}^2 (u - E_K) - g_l (u - E_l) + I(t)$$

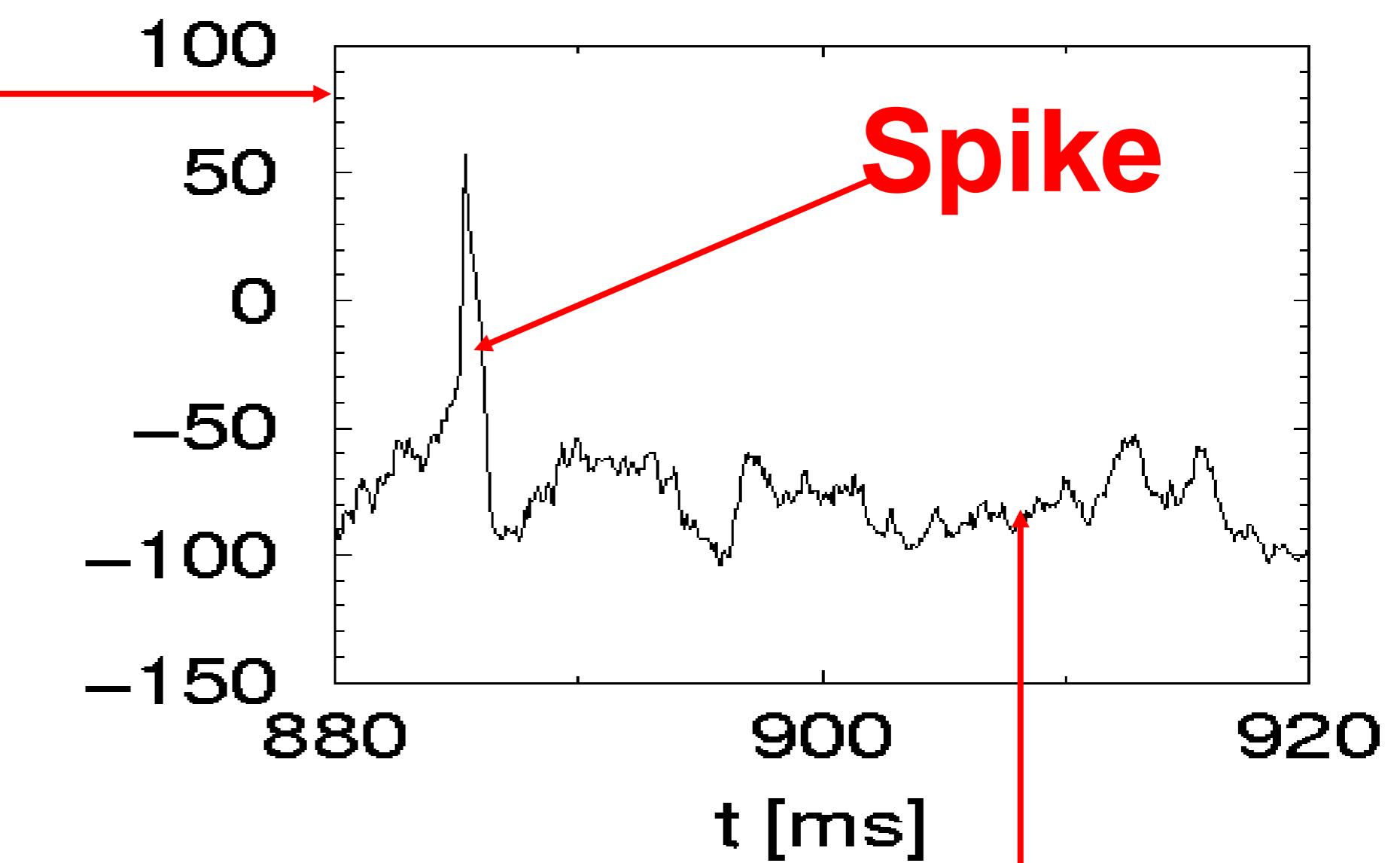
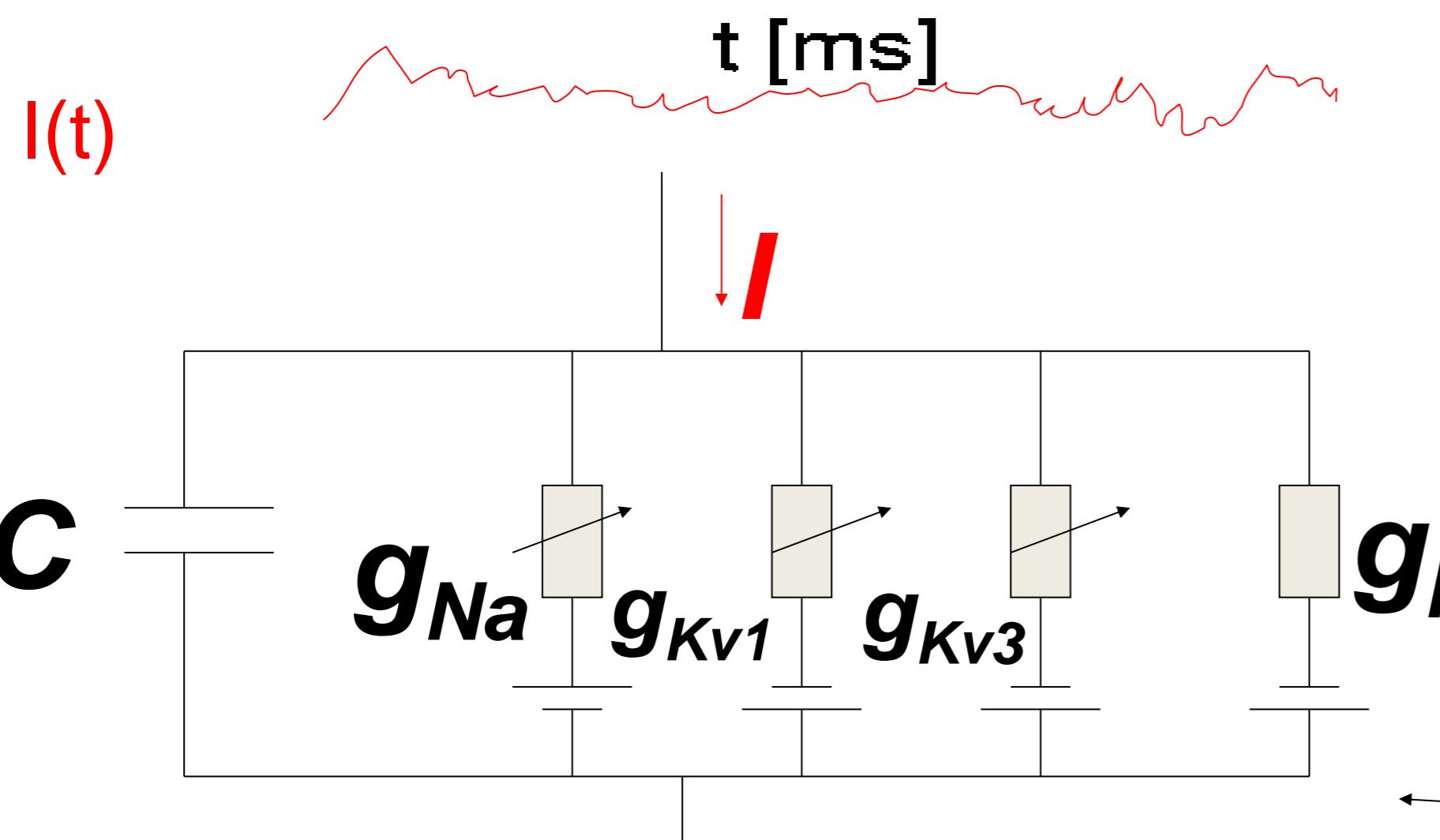
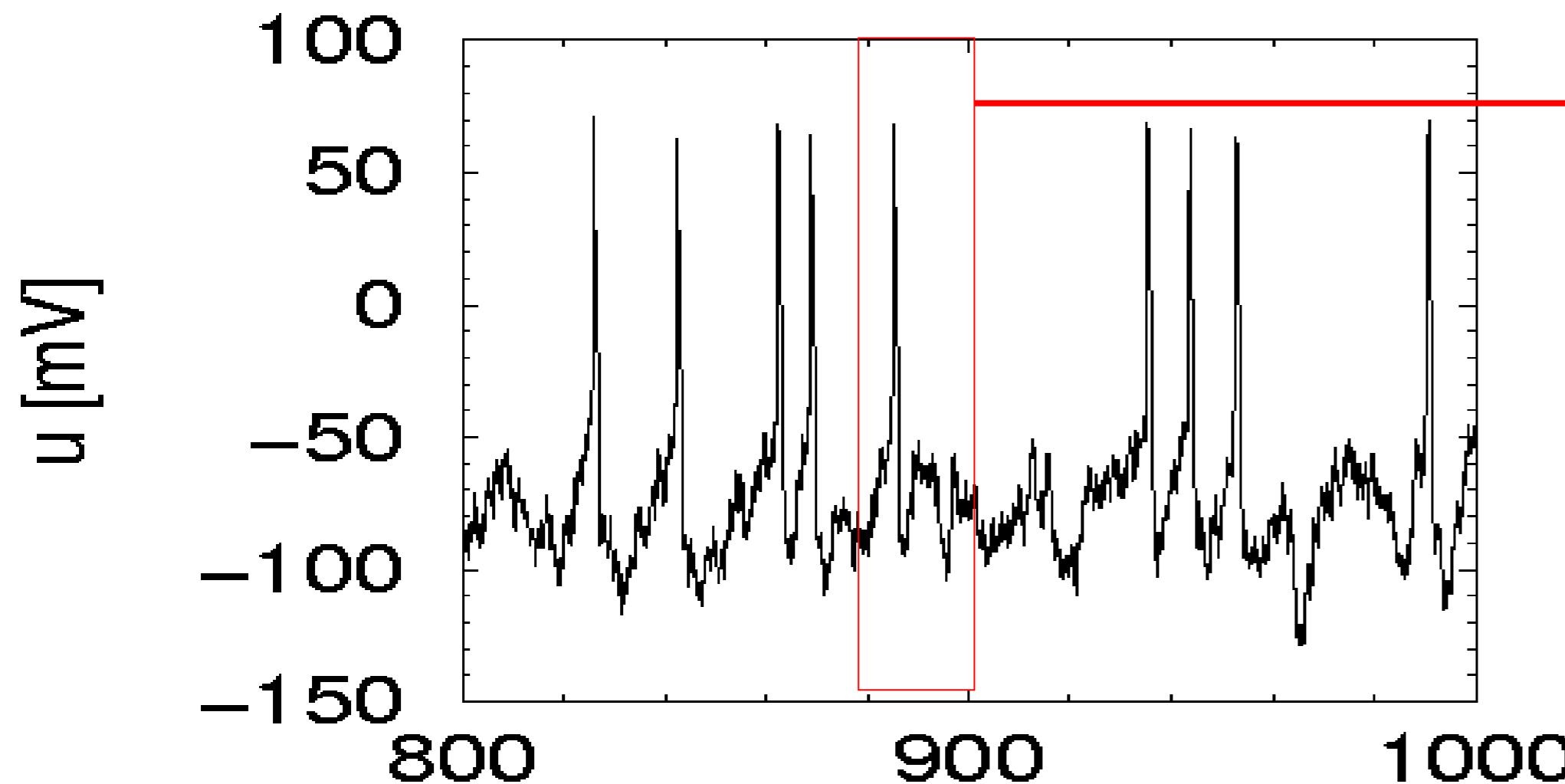
How many parameters per channel?

$$\frac{dm}{dt} = \frac{h n m_0 (m_0)_0 (u)}{\tau_h (u) (u)}$$

$$\frac{dn_3}{dt} = -\frac{n_1 - n_{0,3}(u)}{\tau_{n,3}(u)}$$

*Erisir et al, 1999*  
*Hodgkin and Huxley, 1952*

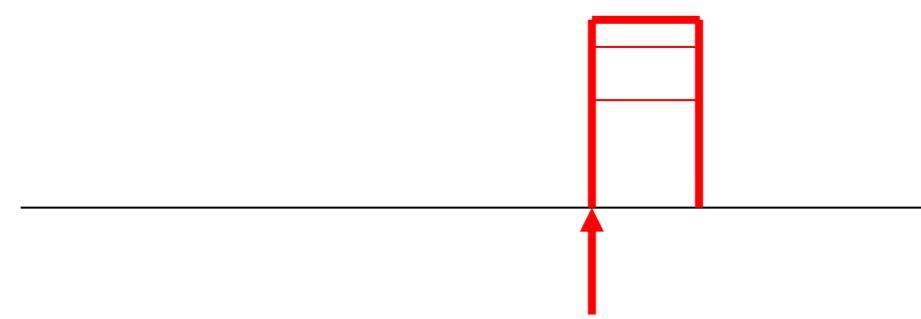
# Model of a hypothetical neuron



Detailed model, based  
on ion channels

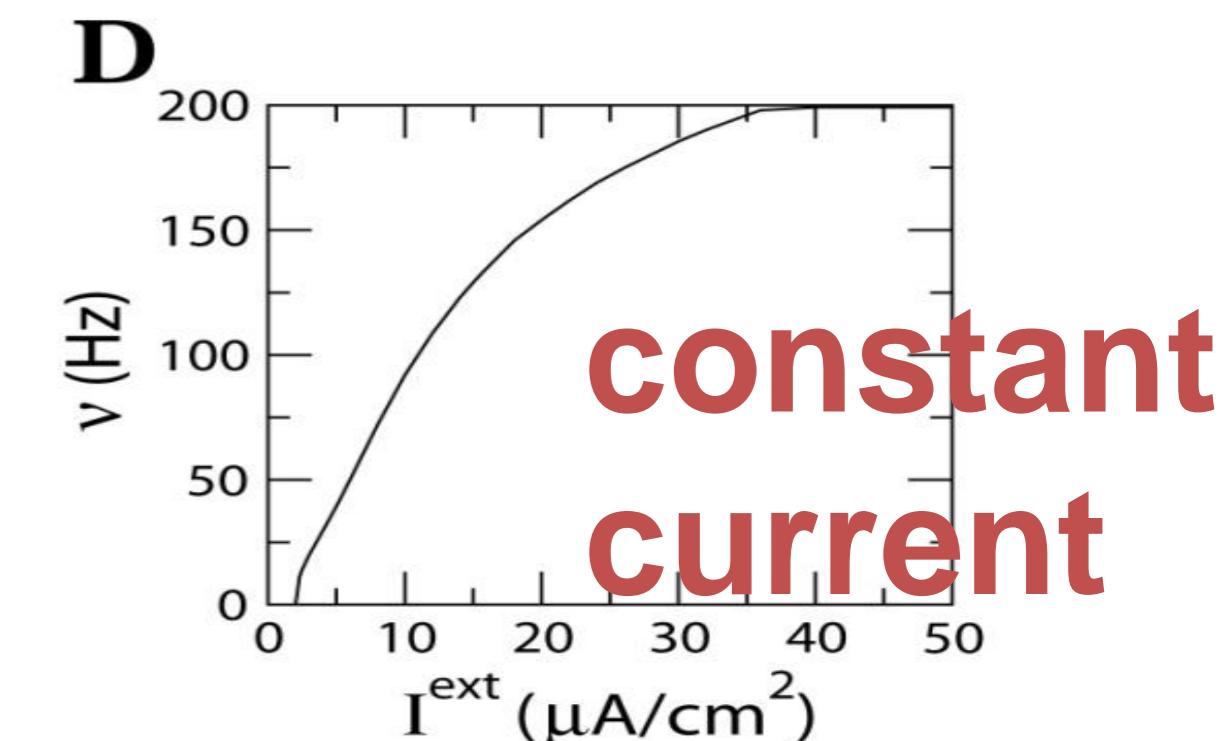
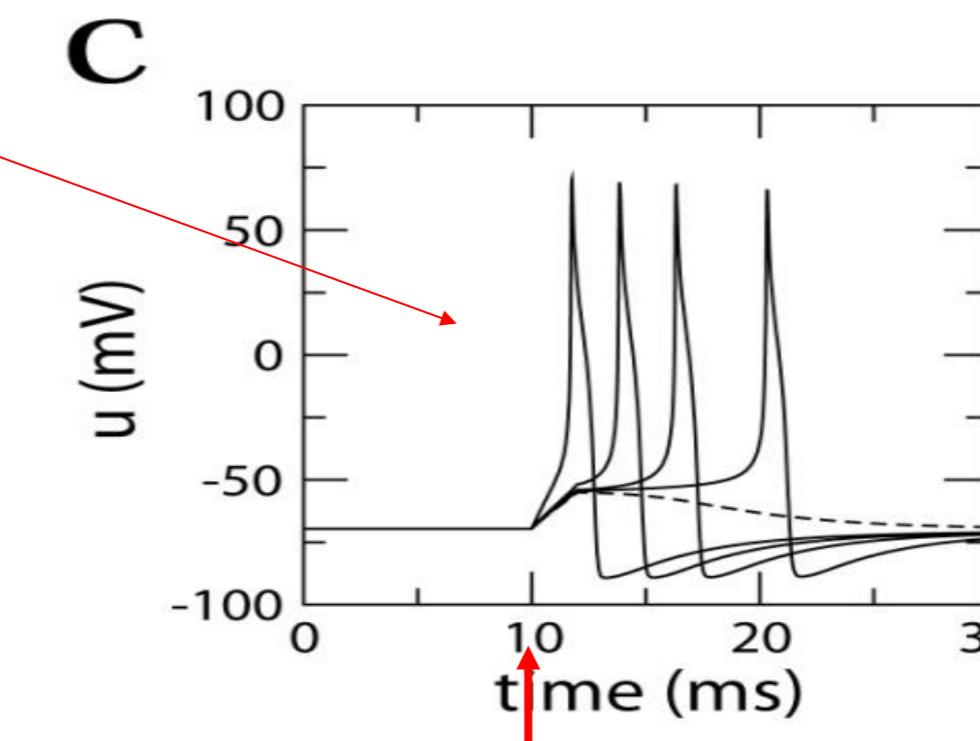
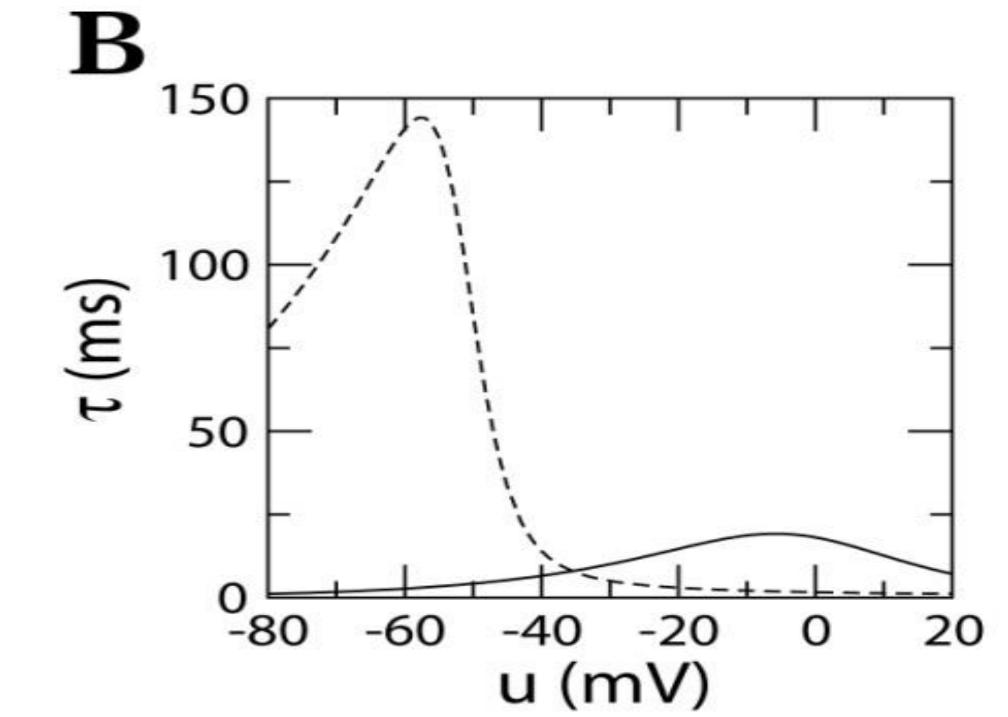
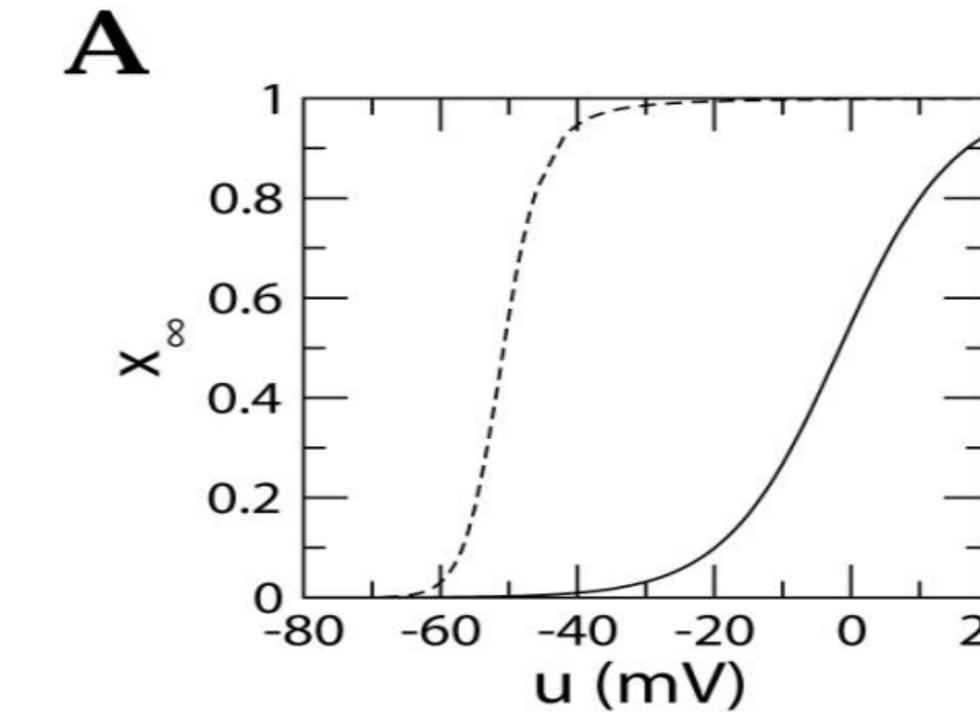
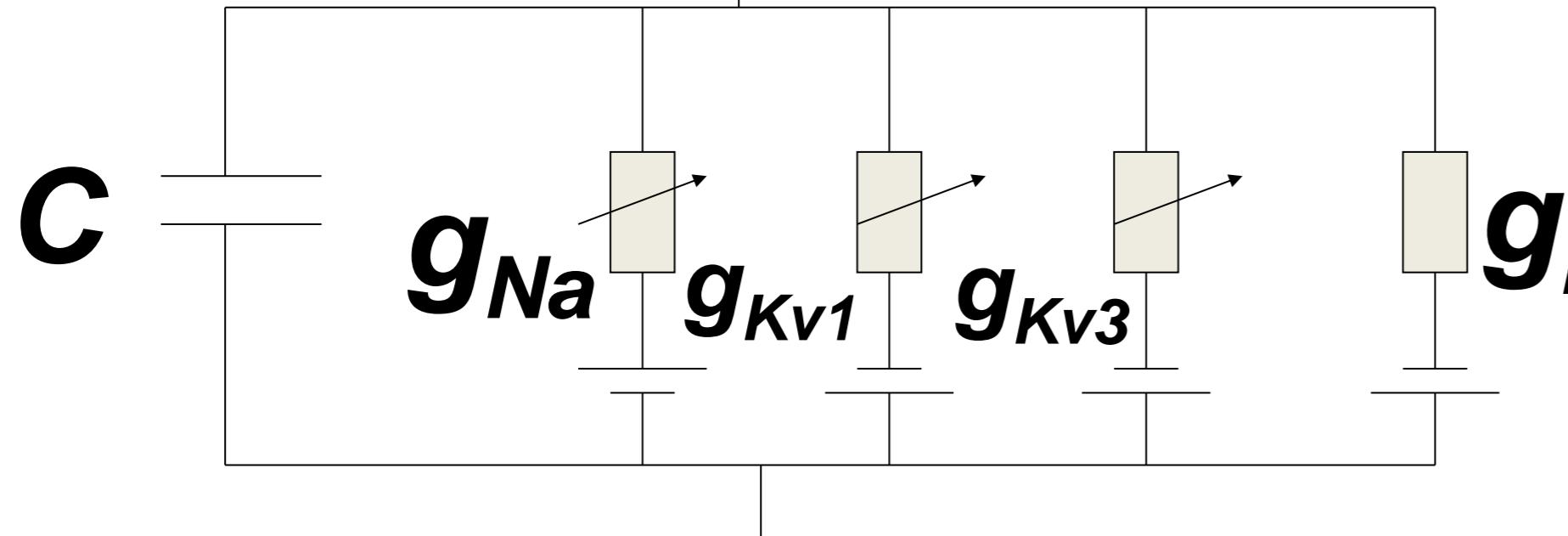
# Model of a hypothetical neuron (type I)

Current pulse



Biophysical model, based  
on ion channels

$I$

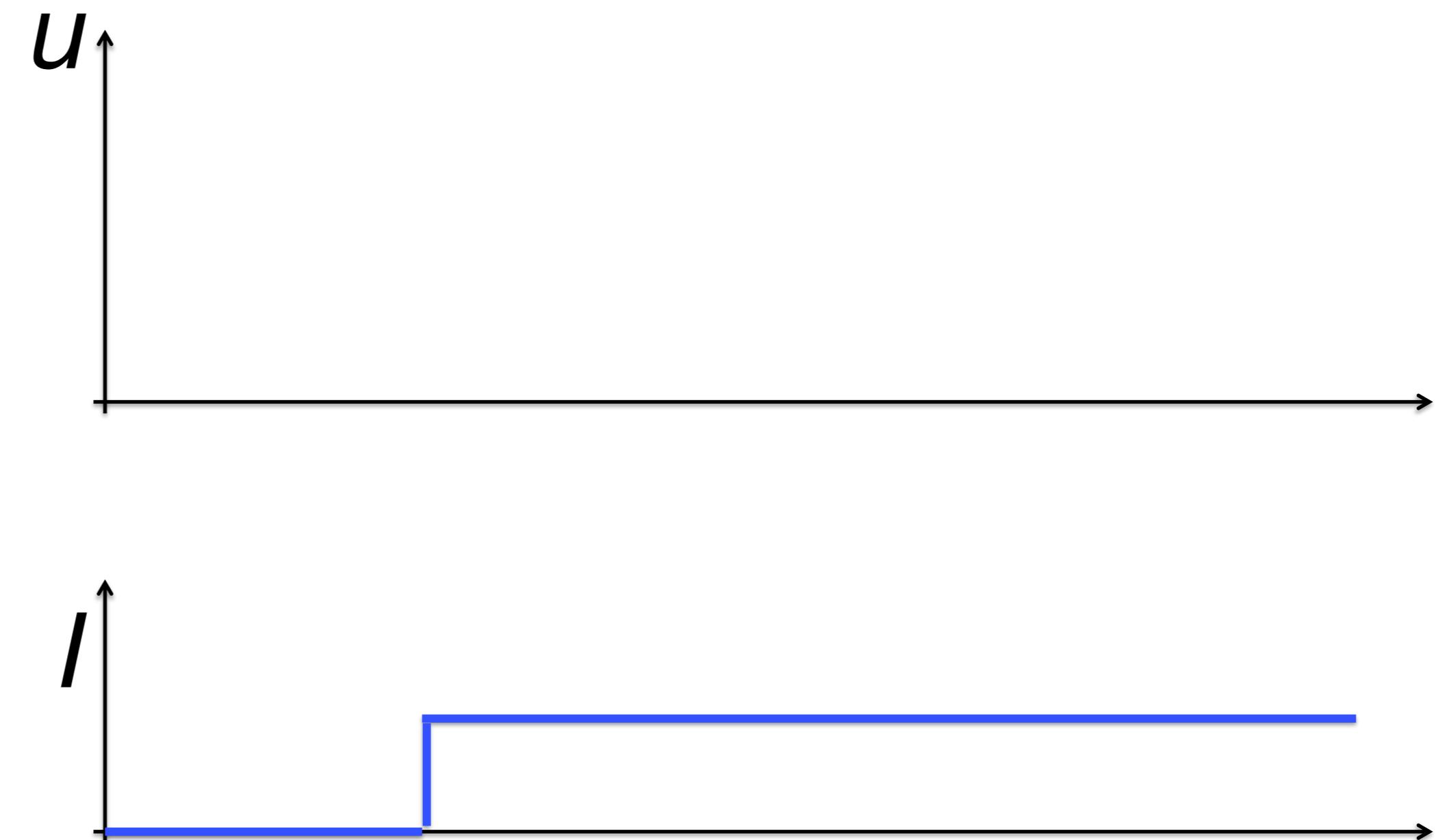


- Delayed AP initiation
- Smooth  $f$ - $I$  curve

type I neuron

# Neuronal Dynamics – 2.5 Adaptation

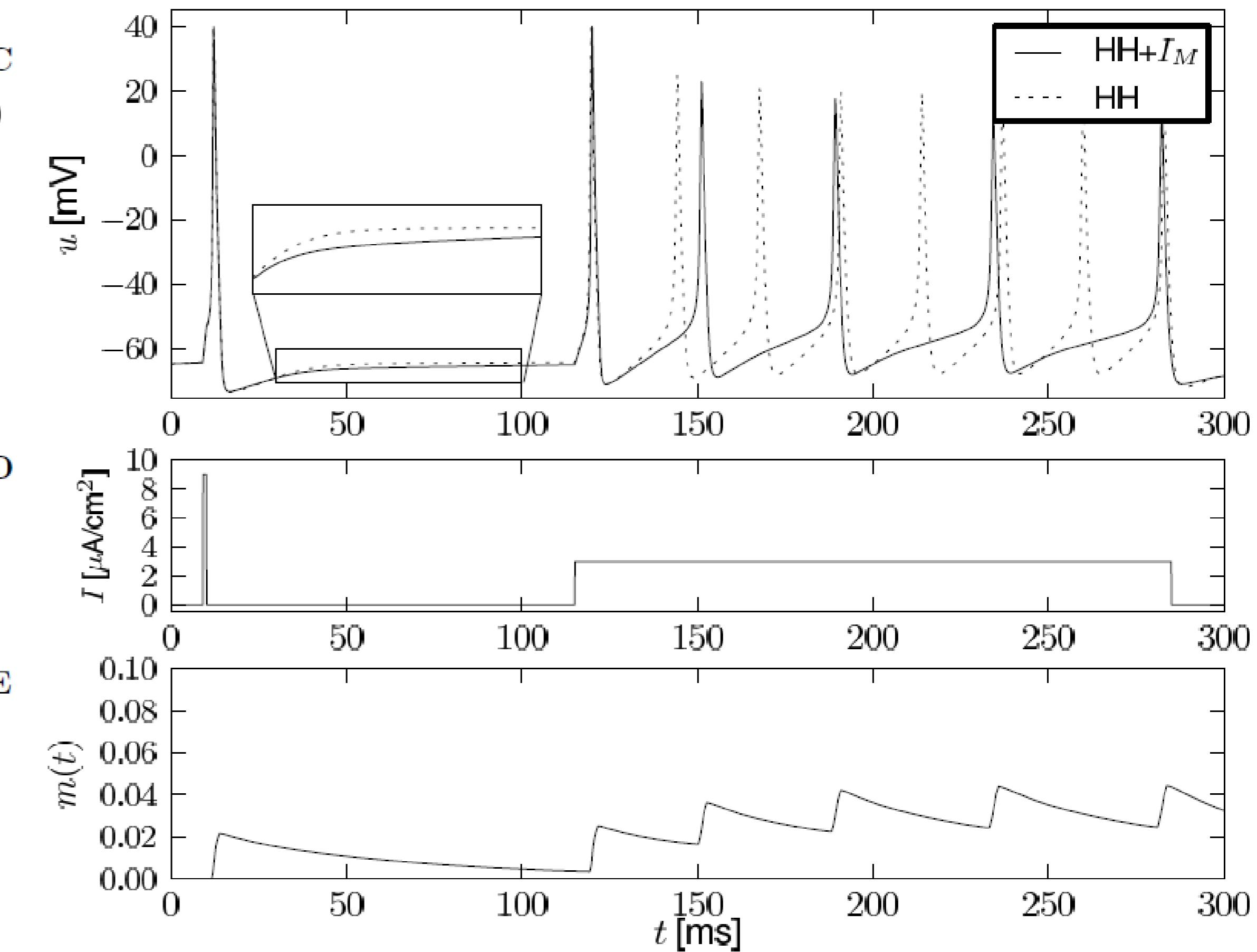
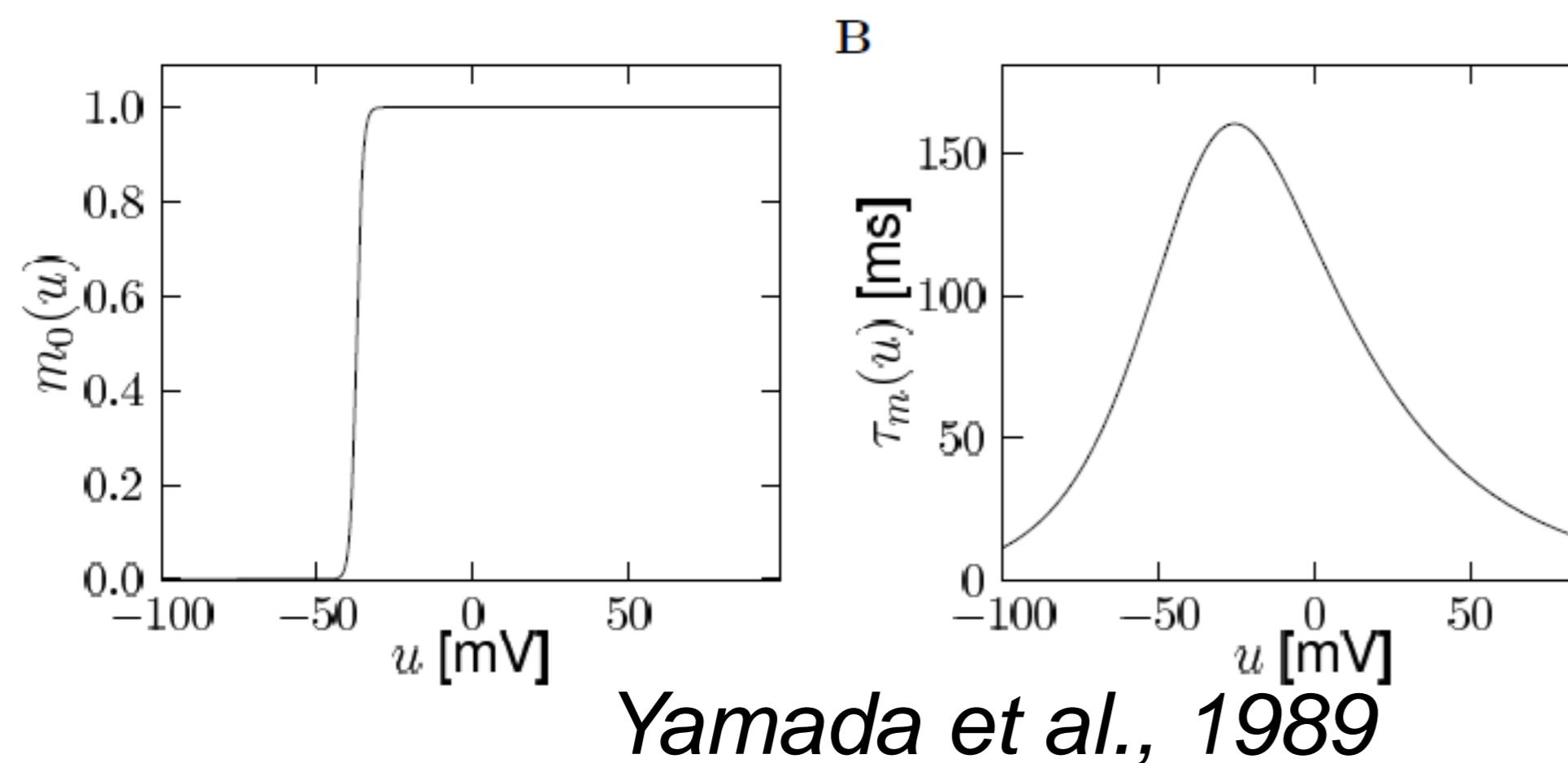
Functional roles of channels?  
- Example: adaptation



# Neuronal Dynamics – 2.5 Adaptation: $I_M$ -current

M current:  $I_M = g_M m (u - E_K)$

- Potassium current
- Kv7 subunits
- slow time constant

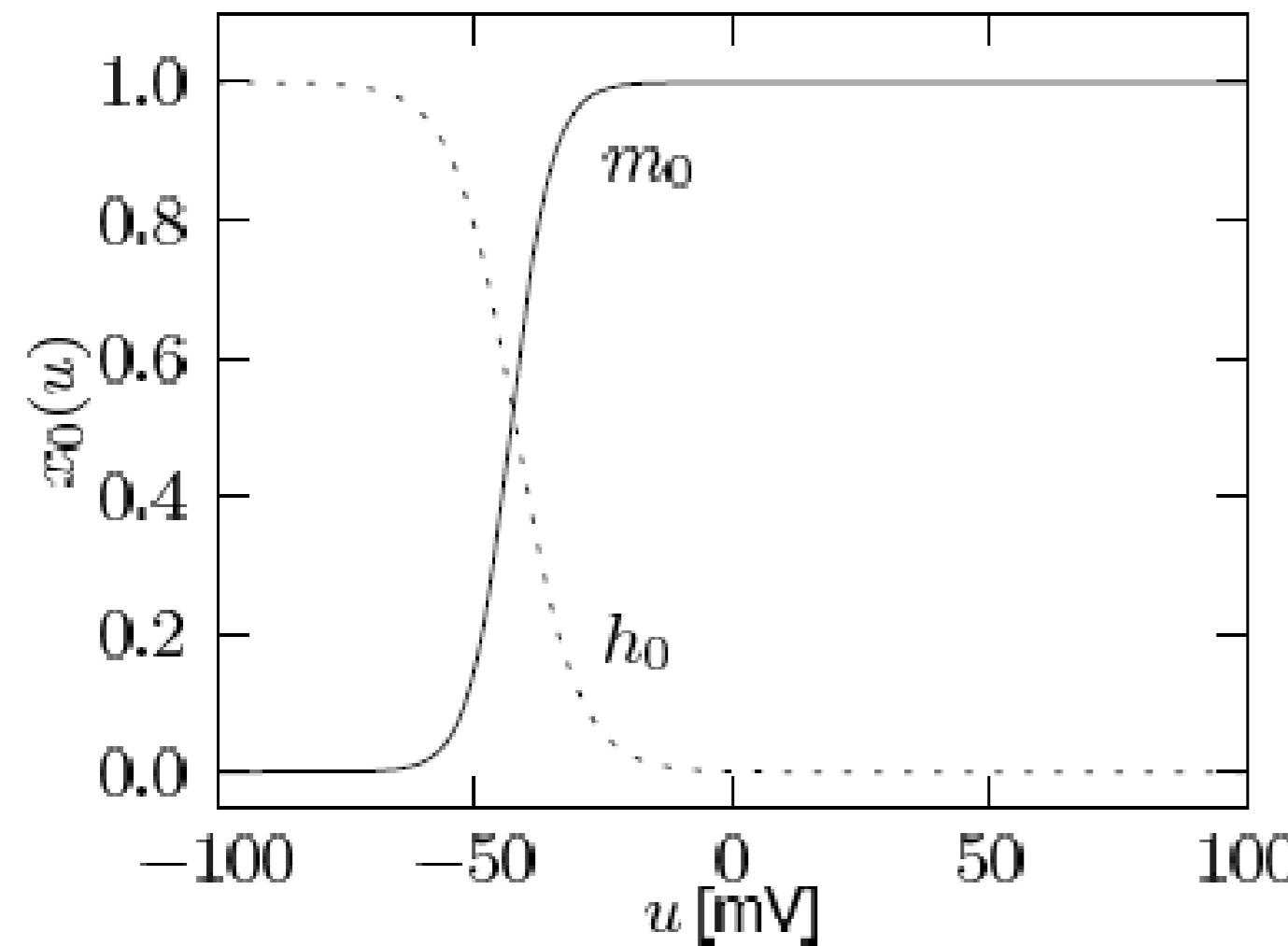


$I_M$  current is one of many potential sources of adaptation

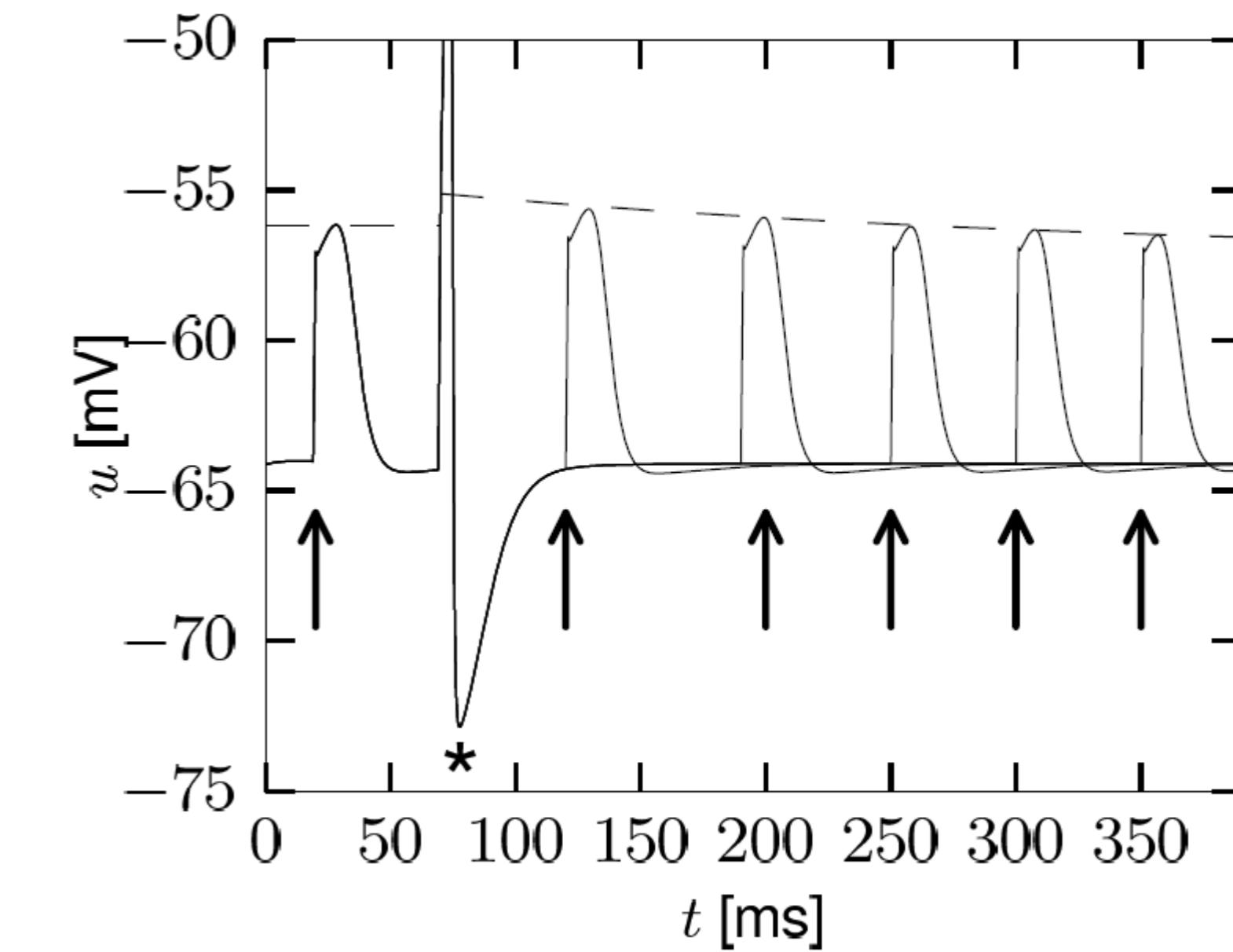
# Neuronal Dynamics – 2.5 Adaptation – $I_{NaP}$ current

current:  $I_{NaP} = g_{NaP}m h (u - E_{Na})$

- persistent sodium current
- fast activation time constant
- slow inactivation ( $\sim 1s$ )



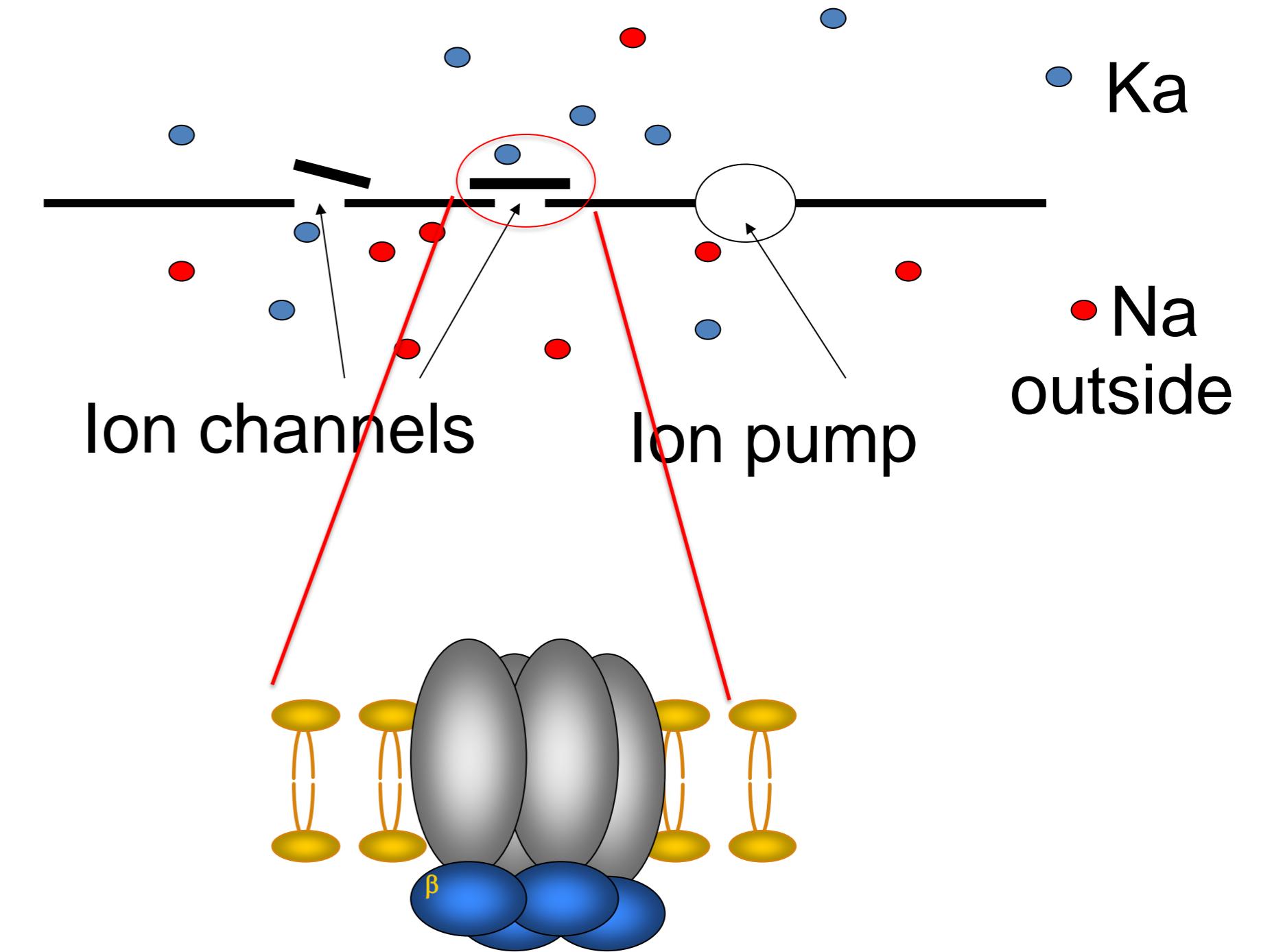
Aracri et al., 2006



$I_{NaP}$  current

- increases firing threshold
- source of adaptation

# Neuronal Dynamics – 2.5 Biophysical models



Hodgkin-Huxley model  
provides flexible framework

*Hodgkin&Huxley (1952)*  
*Nobel Prize 1963*

## Exercise – 2.5. Hodgkin-Huxley model – gating dynamics

A) Often the gating dynamics is formulated as

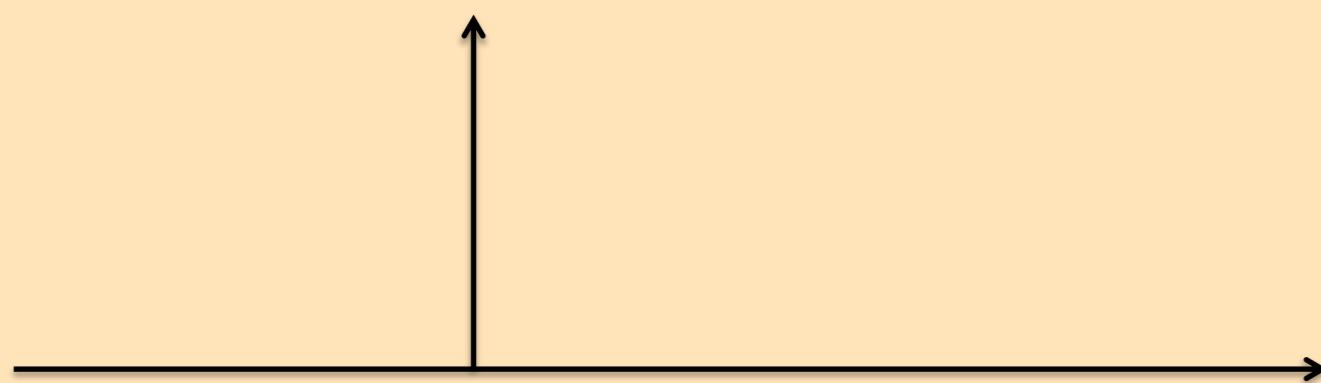
$$\frac{dm}{dt} = \alpha_m(u)(1-m) - \beta_m(u)m$$

$$\frac{dm}{dt} = -\frac{m - m_0(u)}{\tau_m(u)}$$

Calculate  $m_0(u)$  and  $\tau_m(u)$

B) Assume a form  $\alpha_m(u) = \beta_m(u) = \frac{1}{1 - \exp[-(u + a)/b]}$

How are  $a$  and  $b$  related to  $\gamma$  and  $\theta$  in the equations



$$\frac{dm}{dt} = -\frac{m - m_0(u)}{\tau_m(u)}$$

$$m_0(u) = 0.5\{1 + \tanh[\gamma(u - \theta)]\}$$

C) What is the time constant  $\tau_m(u)$  ?

# Neuronal Dynamics – References and Suggested Reading

- Hodgkin, A. L. and Huxley, A. F. (1952). *A quantitative description of membrane current and its application to conduction and excitation in nerve*. J Physiol, 117(4):500-544.
- Ranjan, R., et al. (2011). *Channelpedia: an integrative and interactive database for ion channels*. Front Neuroinform, 5:36.
- Toledo-Rodriguez, M., Blumenfeld, B., Wu, C., Luo, J., Attali, B., Goodman, P., and Markram, H. (2004). *Correlation maps allow neuronal electrical properties to be predicted from single-cell gene expression profiles in rat neocortex*. Cerebral Cortex, 14:1310-1327.
- Yamada, W. M., Koch, C., and Adams, P. R. (1989). *Multiple channels and calcium dynamics*. In Koch, C. and Segev, I., editors, *Methods in neuronal modeling*, MIT Press.
- Aracri, P., et al. (2006). *Layer-specific properties of the persistent sodium current in sensorimotor cortex*. Journal of Neurophysiol., 95(6):3460-3468.

**Reading:** W. Gerstner, W.M. Kistler, R. Naud and L. Paninski,

*Neuronal Dynamics: from single neurons to networks and*

*models of cognition*. Chapter 2: *The Hodgkin-Huxley Model*, Cambridge Univ. Press, 2014

OR W. Gerstner and W. M. Kistler, Spiking Neuron Models, Chapter 2, Cambridge, 2002