

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

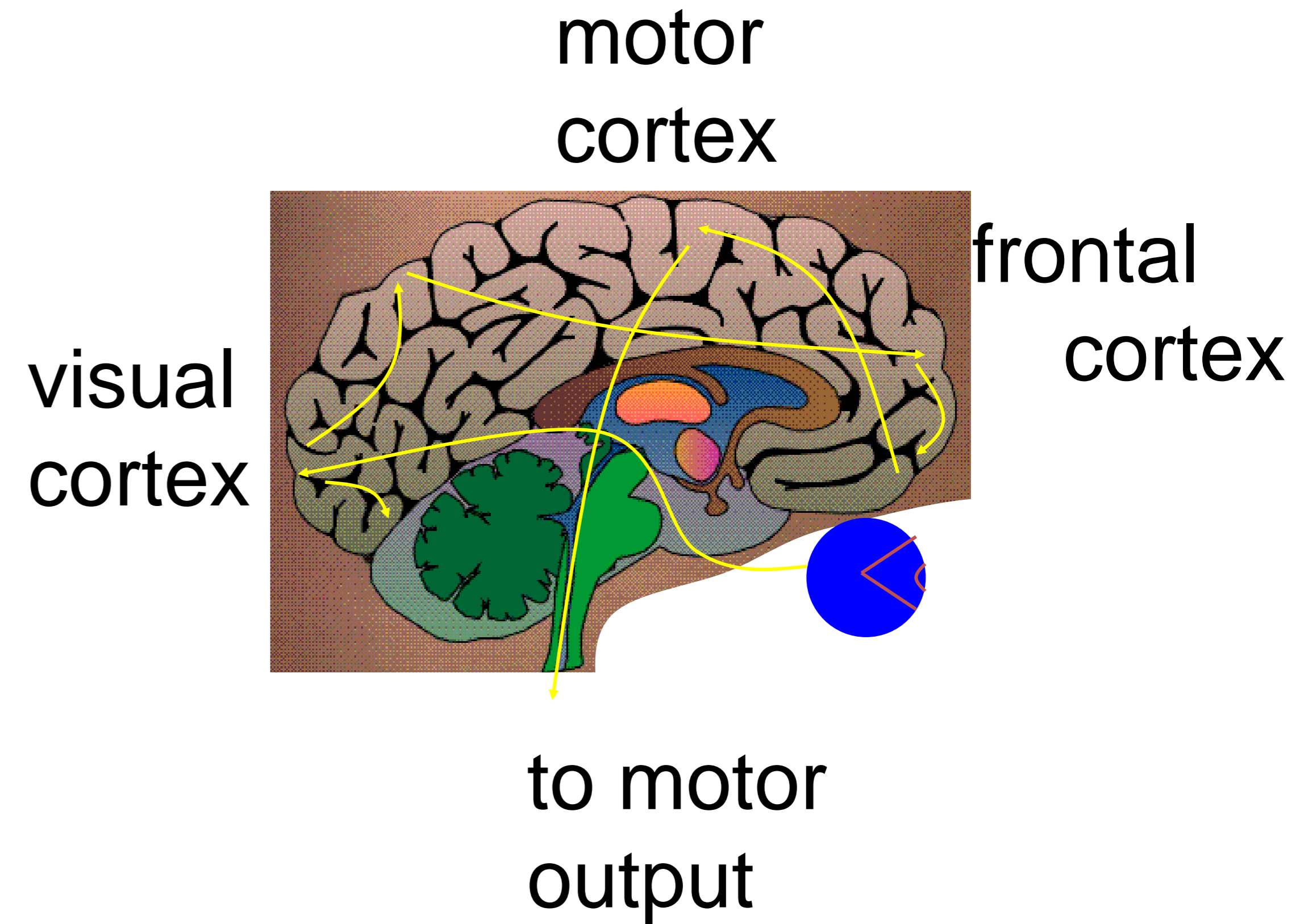
2.4 Threshold in the Hodgkin-Huxley Model

- where is the firing threshold?

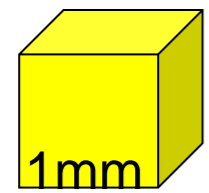
2.5. Detailed biophysical models

- the zoo of ion channels

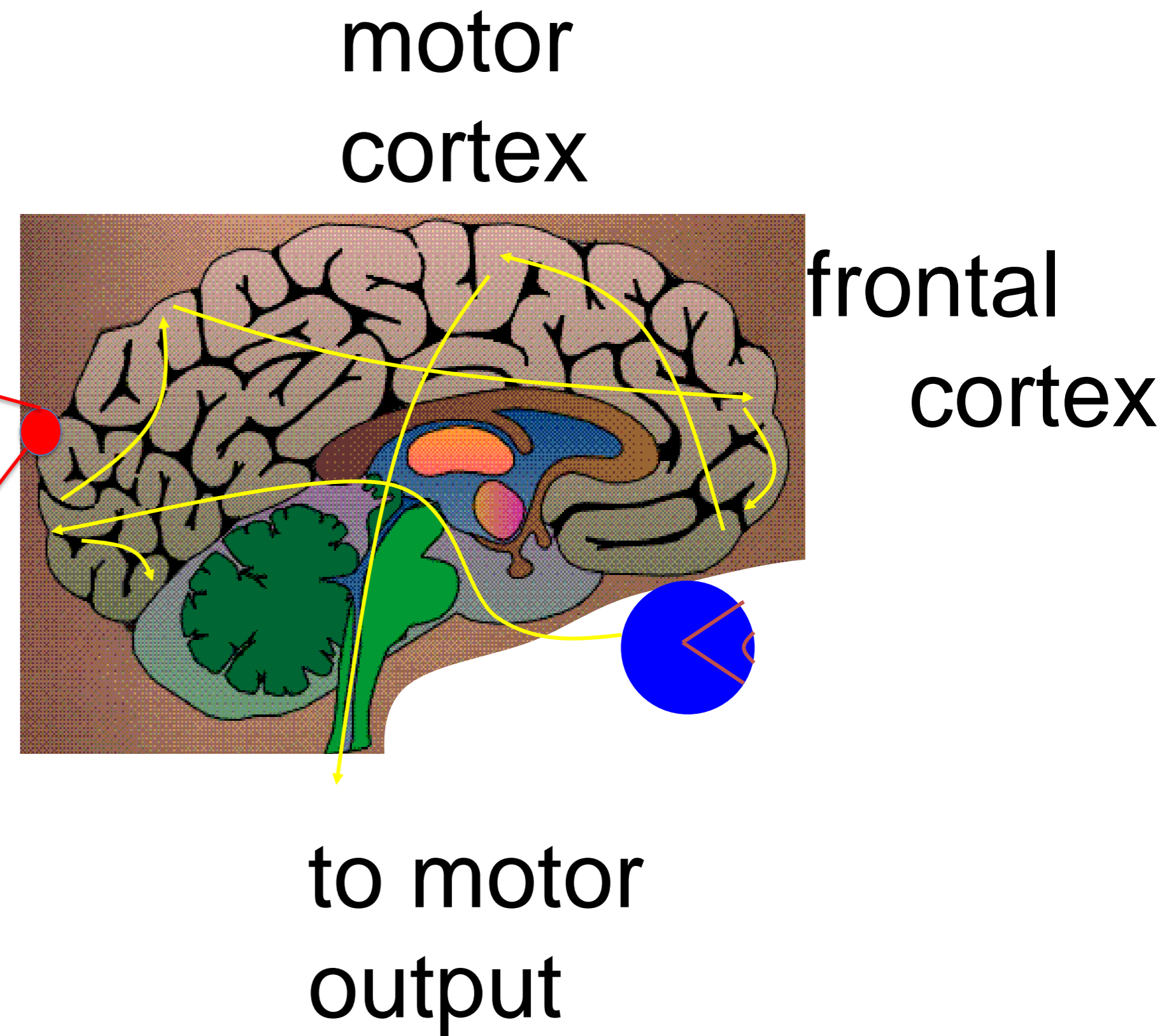
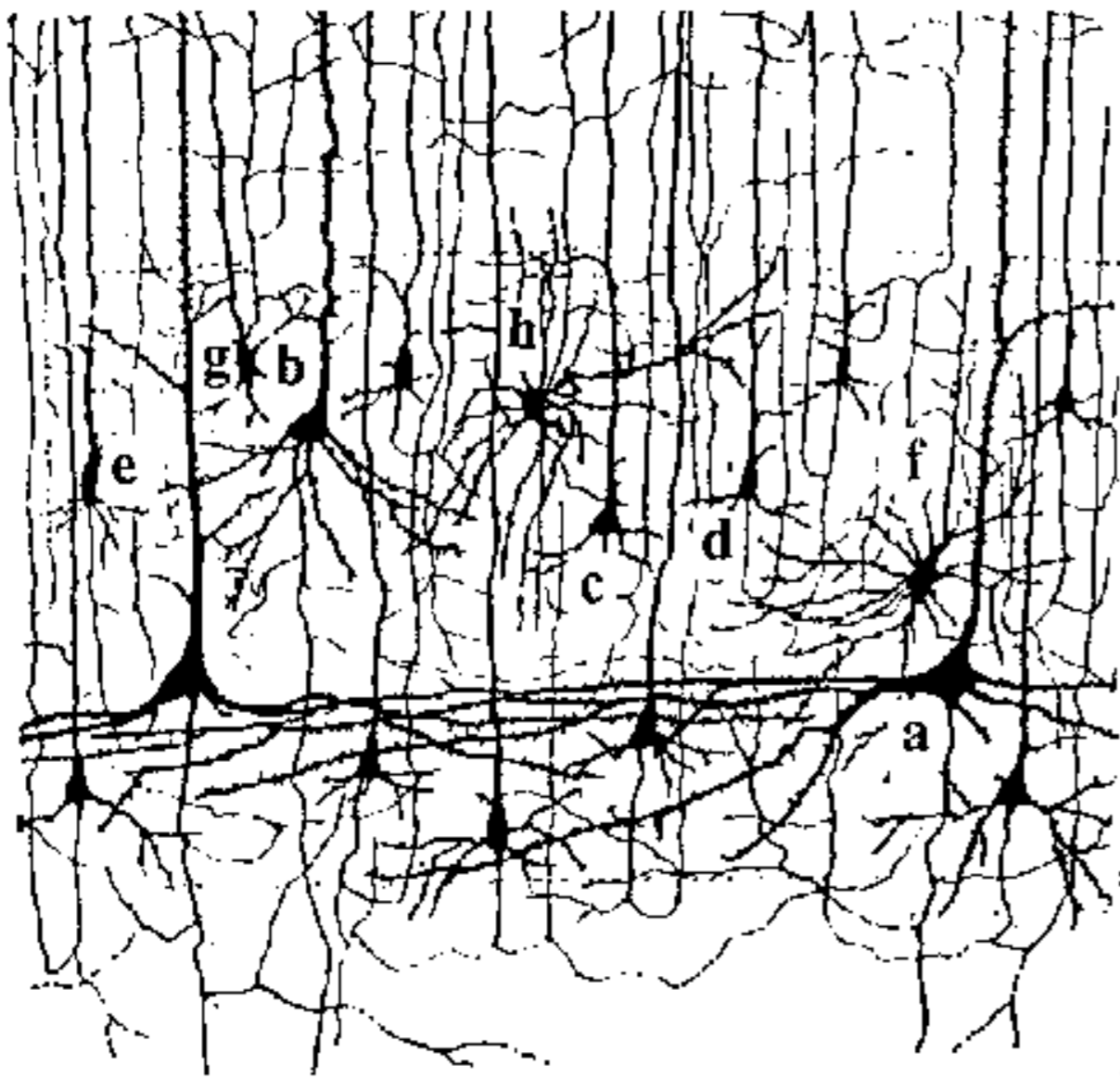
Neuronal Dynamics – 2.1. Introduction



Neuronal Dynamics – 2.1. Introduction

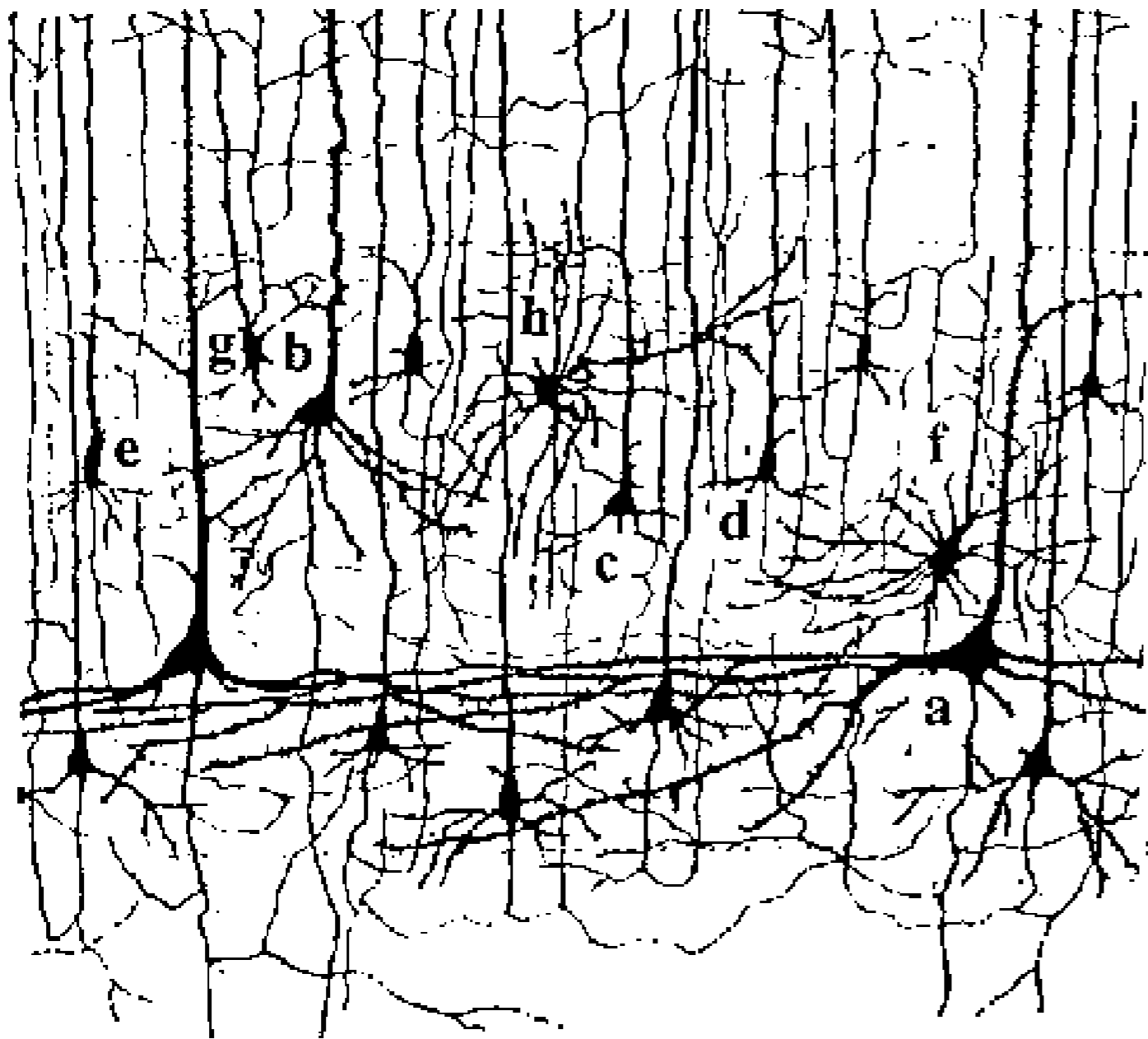


10 000 neurons
3 km wires



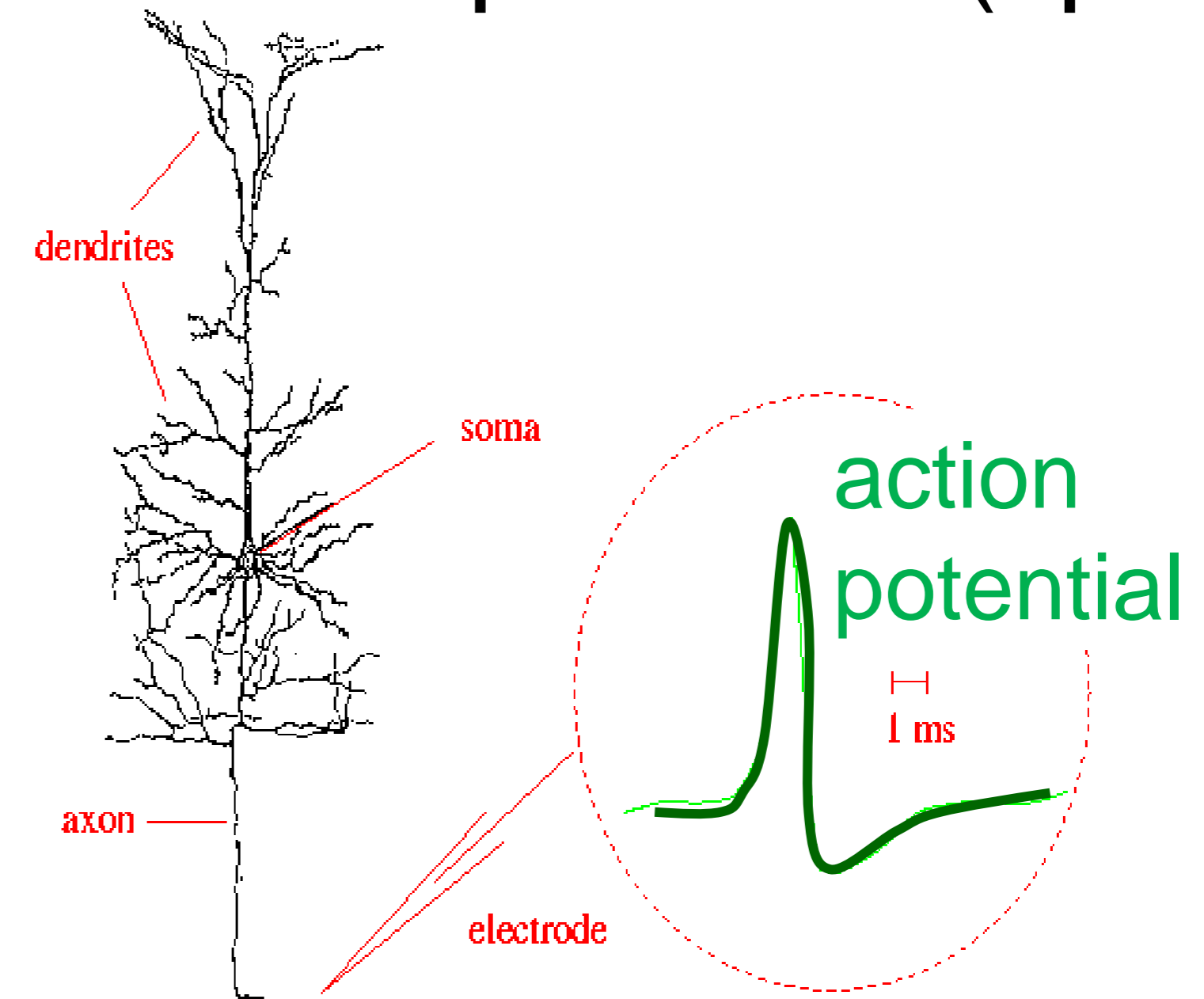
Neuronal Dynamics – 2.1 Introduction

 10 000 neurons
1mm 3 km wires



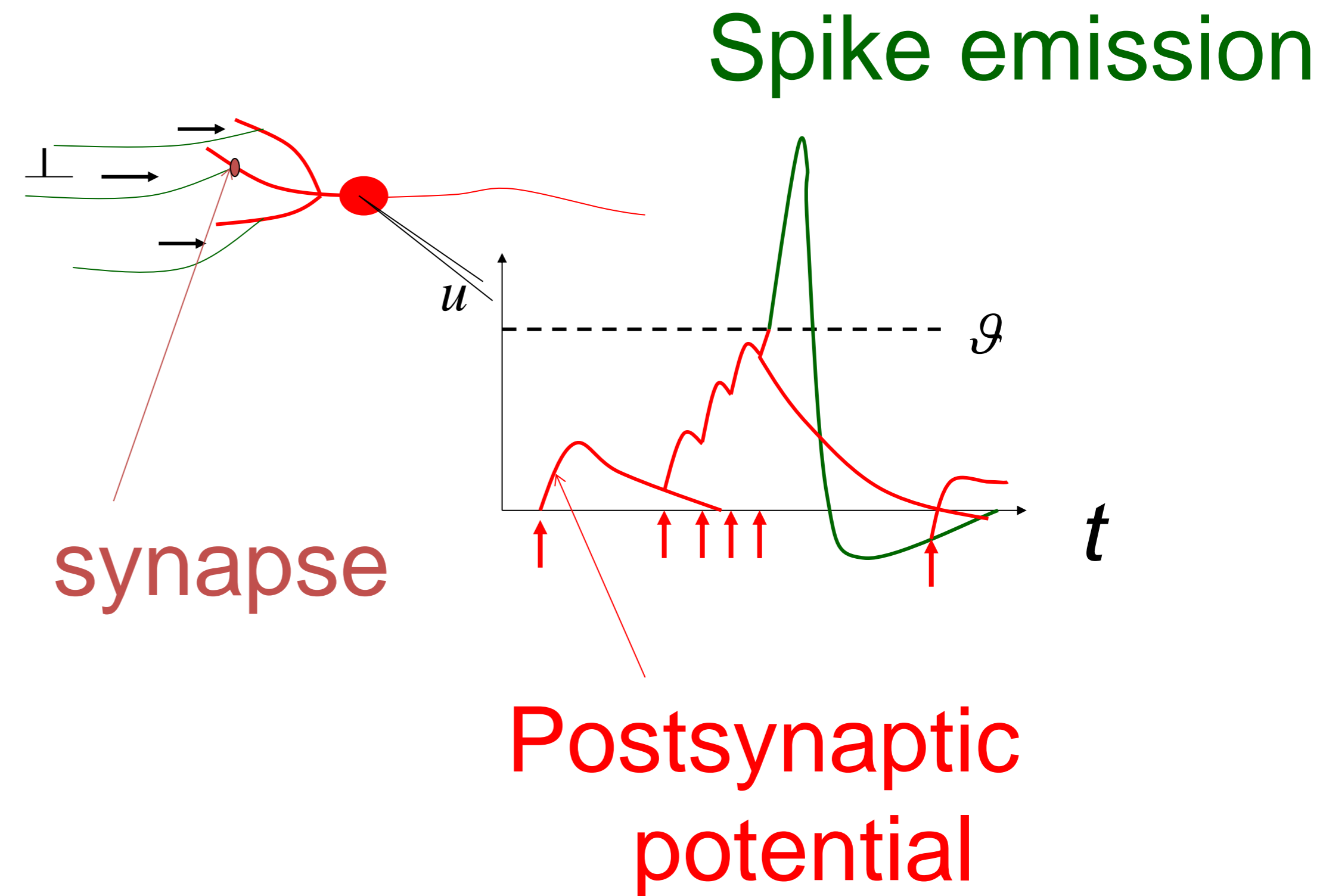
Ramon y Cajal

Signal:
action potential (spike)



How is a spike generated?

Review of week 1: Integrate-and-Fire models



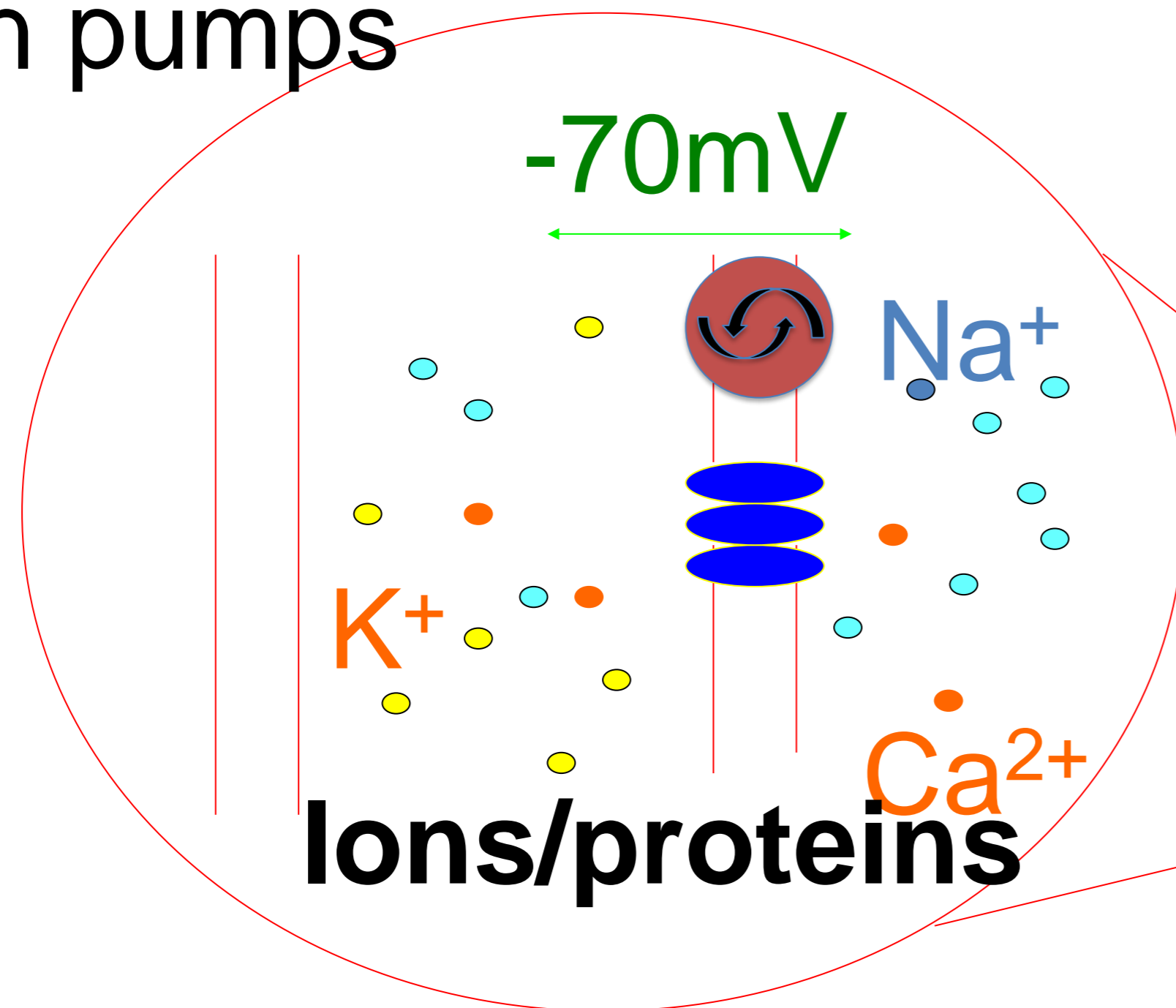
- spikes are events
- triggered at threshold
- spike/reset/refractoriness

Neuronal Dynamics – week 2: Biophysics of neurons

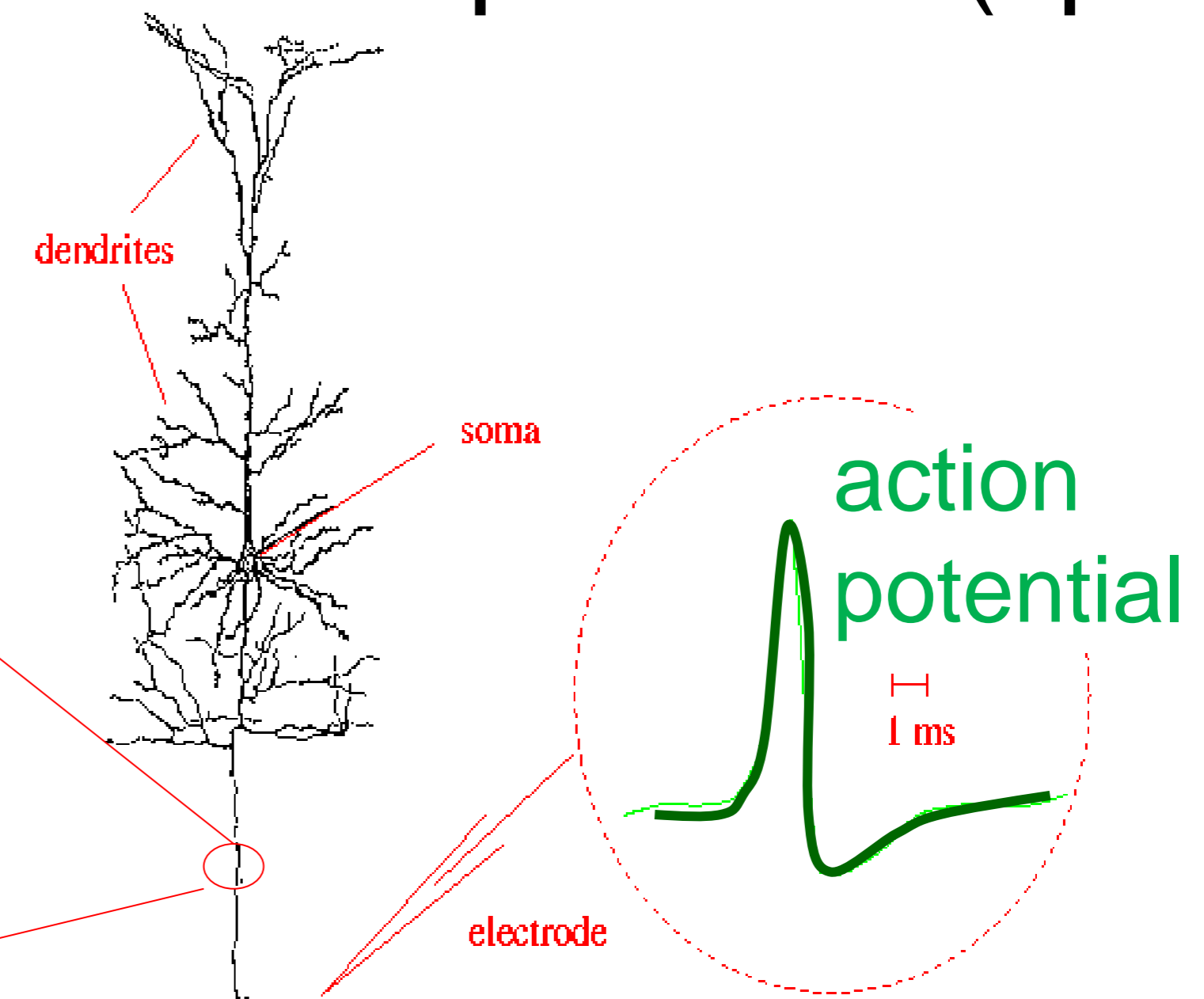
Cell surrounded by membrane

Membrane contains

- ion channels
- ion pumps



Signal:
action potential (spike)

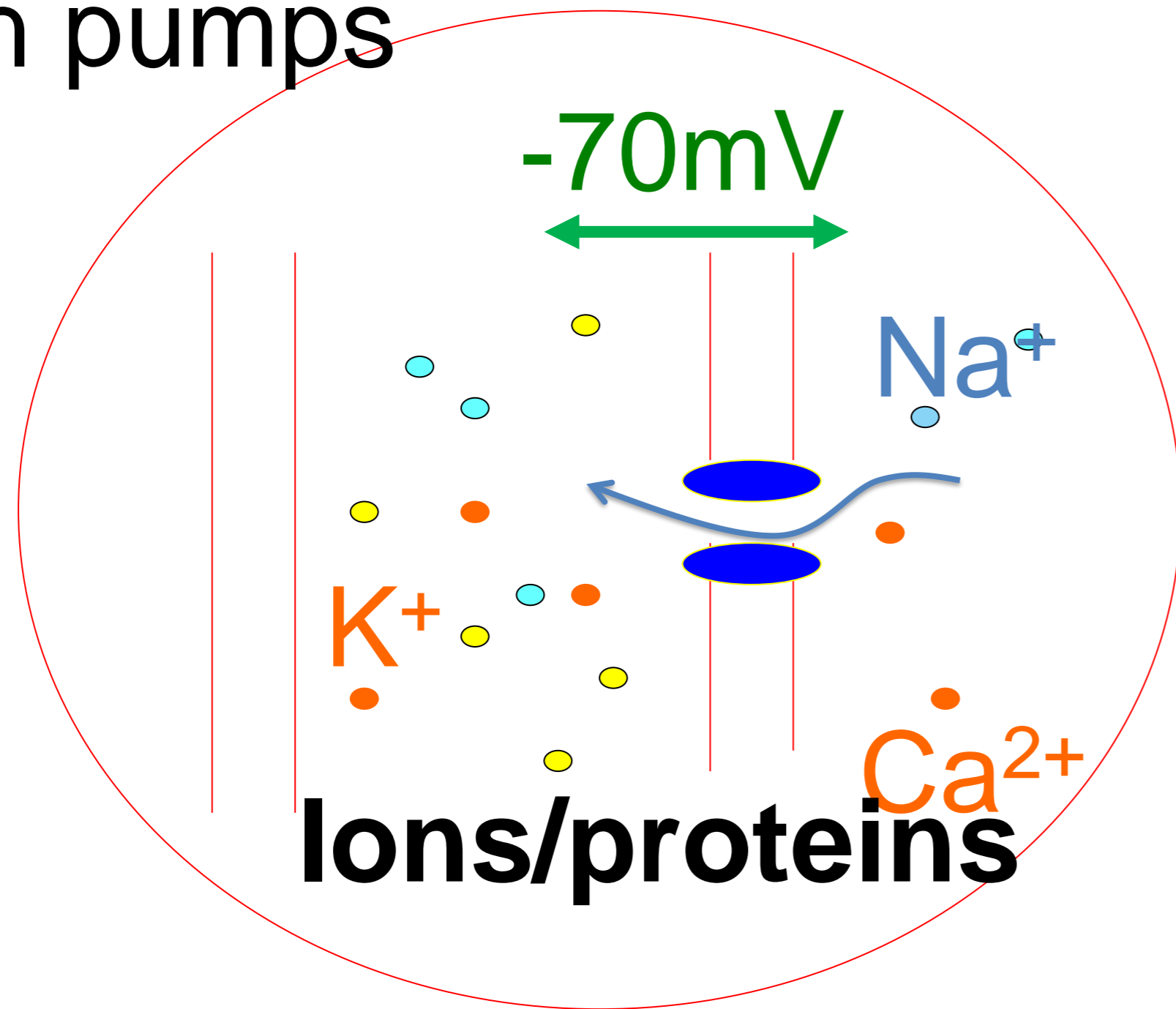


Neuronal Dynamics – week 2: **Biophysics of neurons**

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

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Neuron emits action potentials

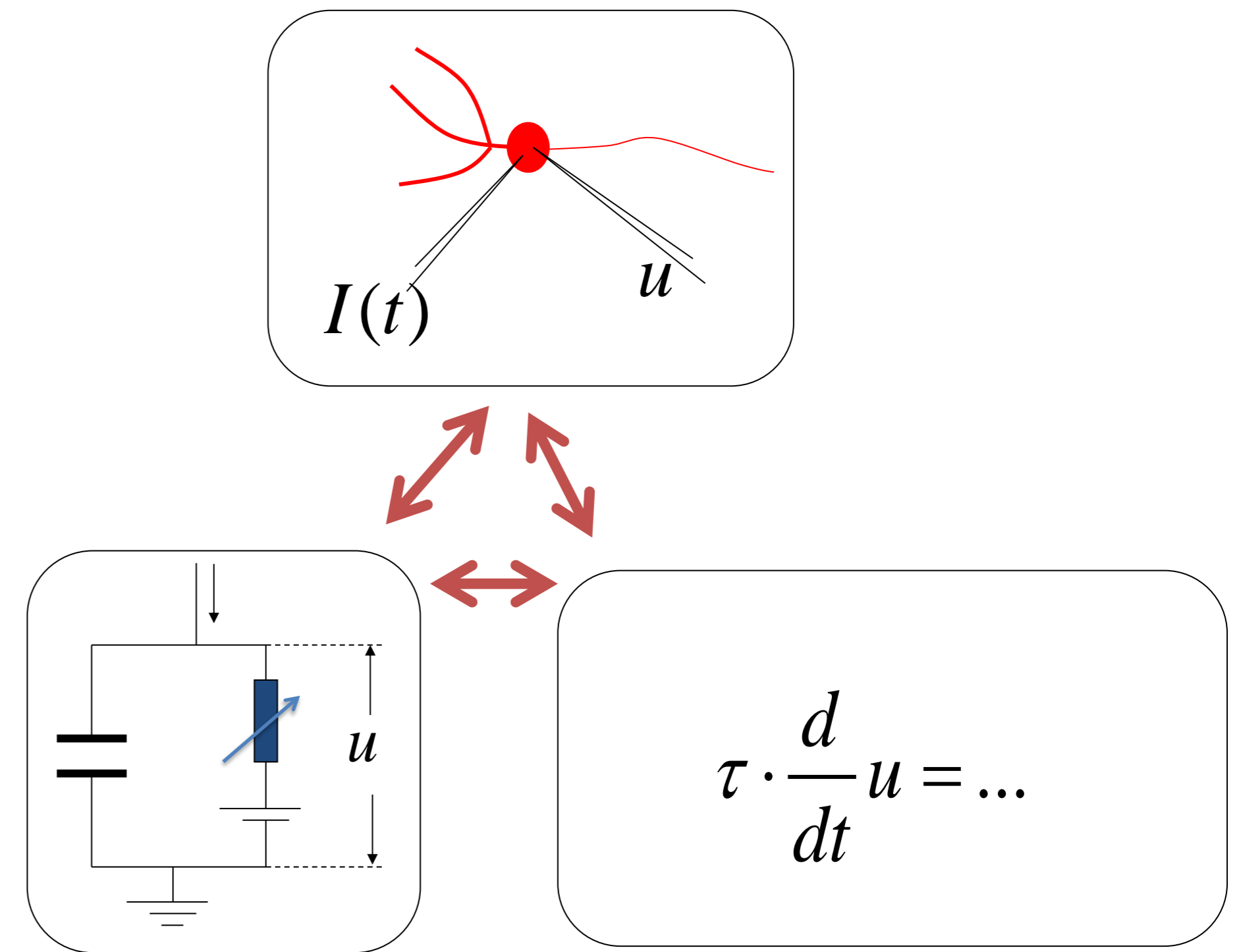
→ why?

→ 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

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2.3 Hodgkin-Huxley Model

2.4 Threshold in the Hodgkin-Huxley Model

- where is the firing threshold?

2.5. Detailed biophysical models

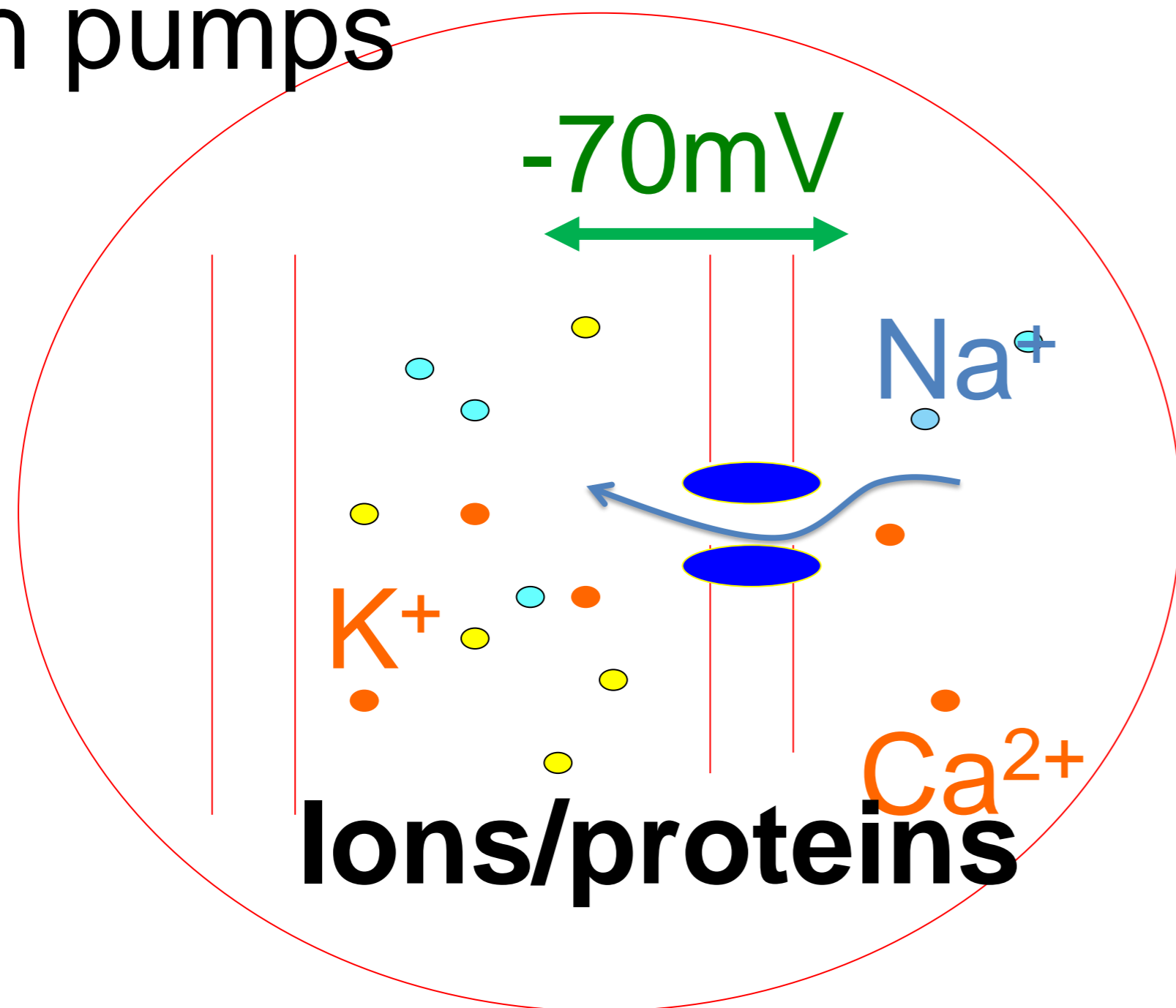
- the zoo of ion channels

Neuronal Dynamics – 2.2. Resting potential

Cell surrounded by membrane

Membrane contains

- ion channels
- ion pumps



Resting potential $-70mV$

→ 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

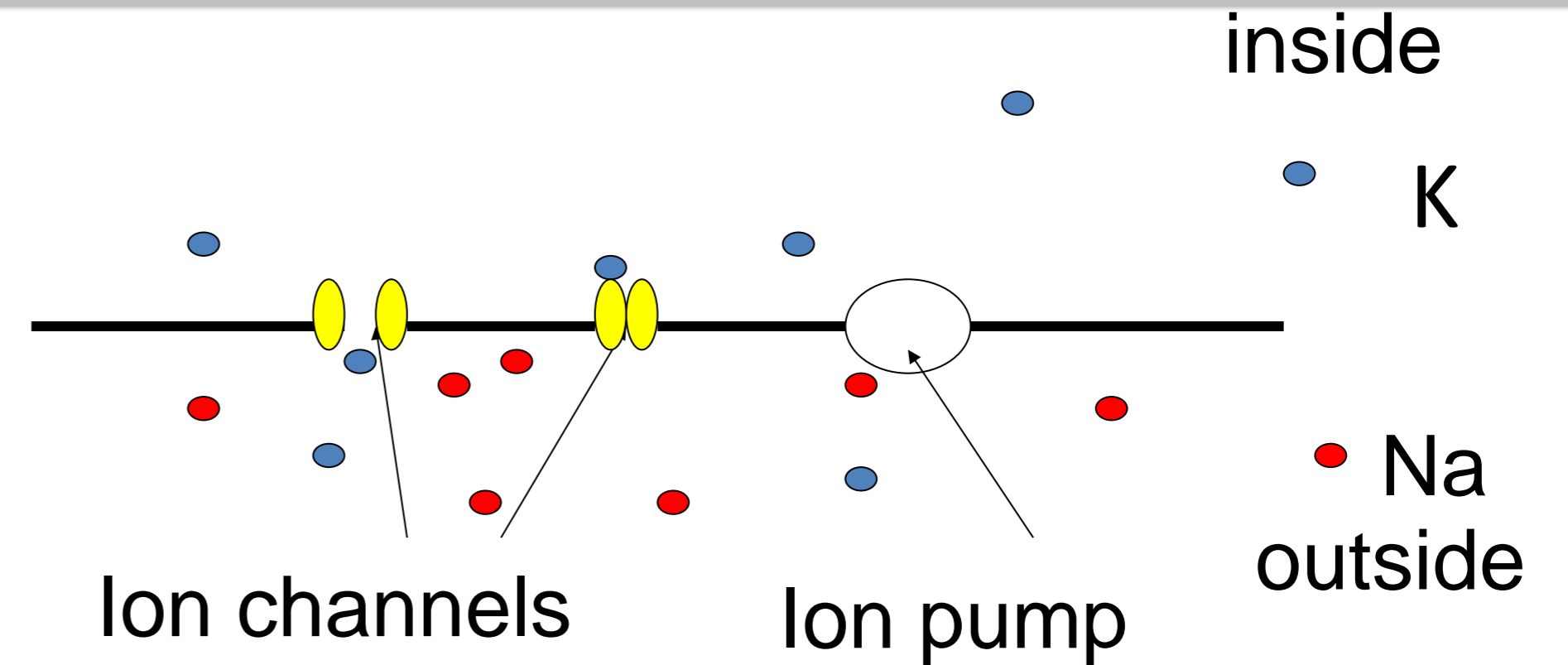
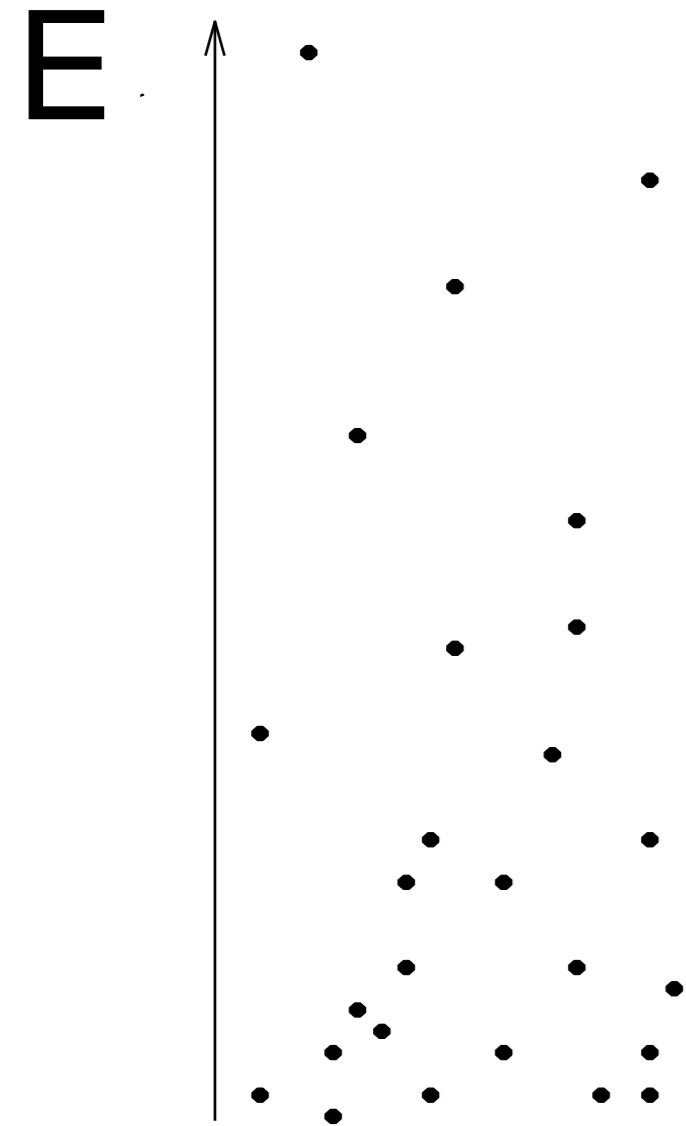
Hodgkin & Huxley (1952)

Nobel Prize 1963

Neuronal Dynamics – 2.2. Reversal potential

density

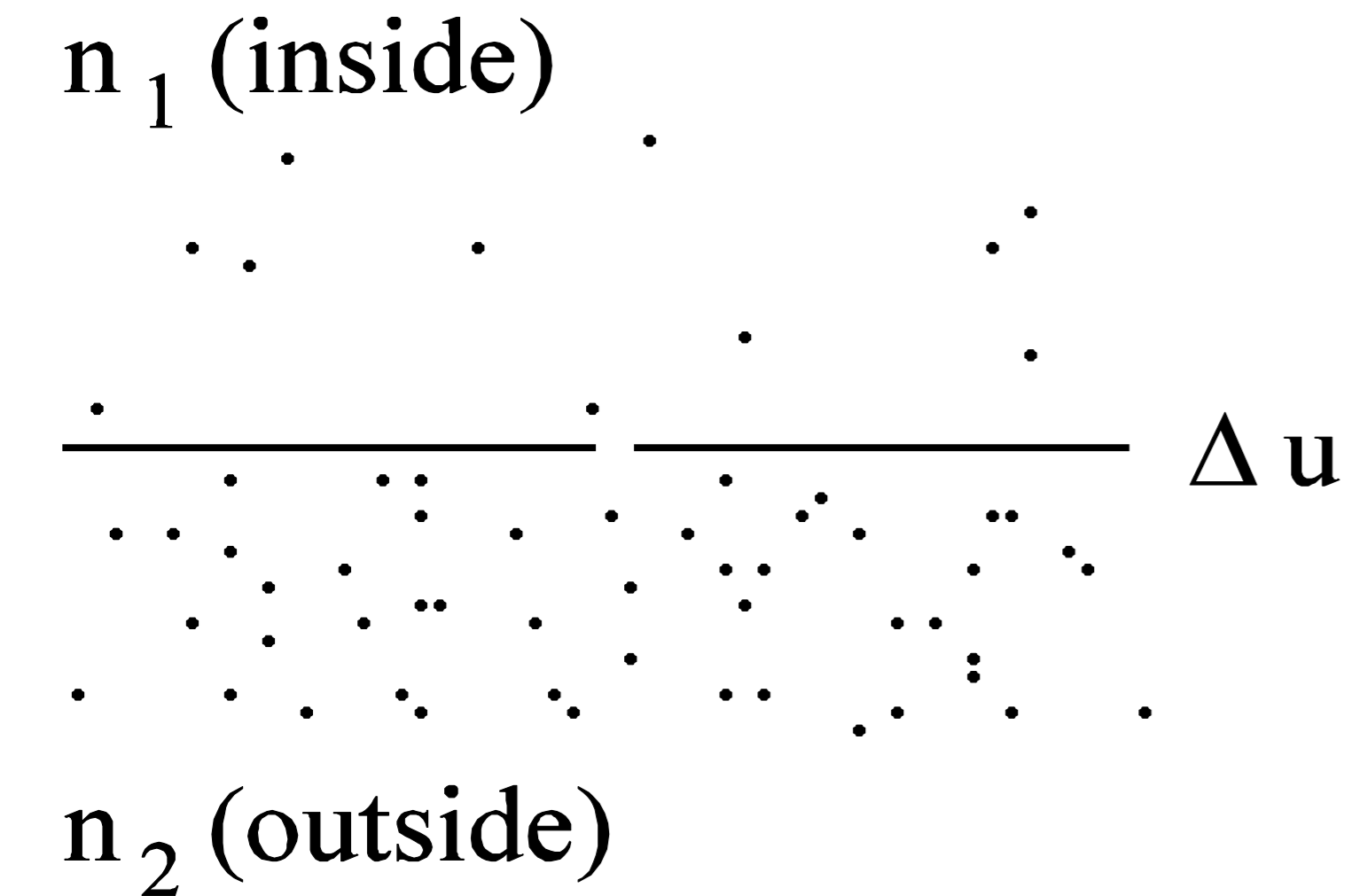
$$n \propto e^{-\frac{E}{kT}}$$



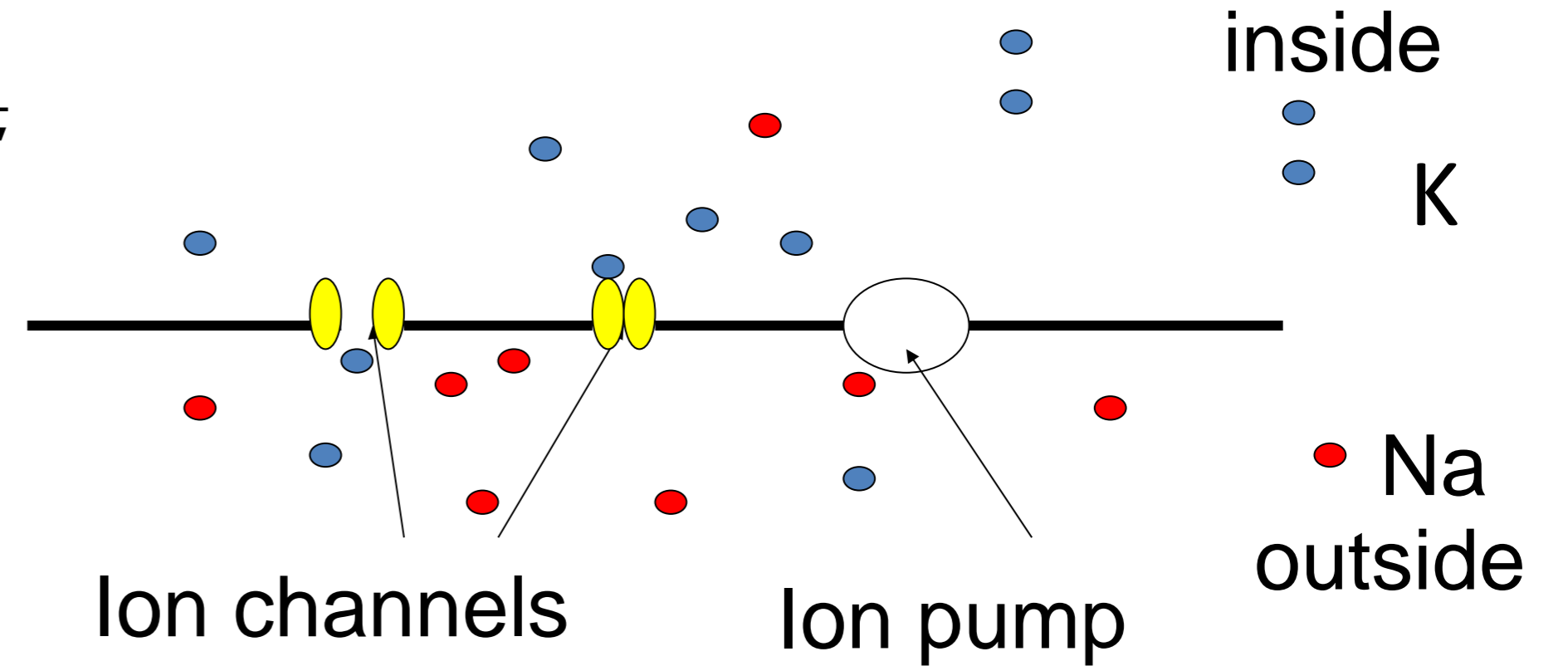
Ion pump \Leftrightarrow Concentration difference

Mathetical derivation

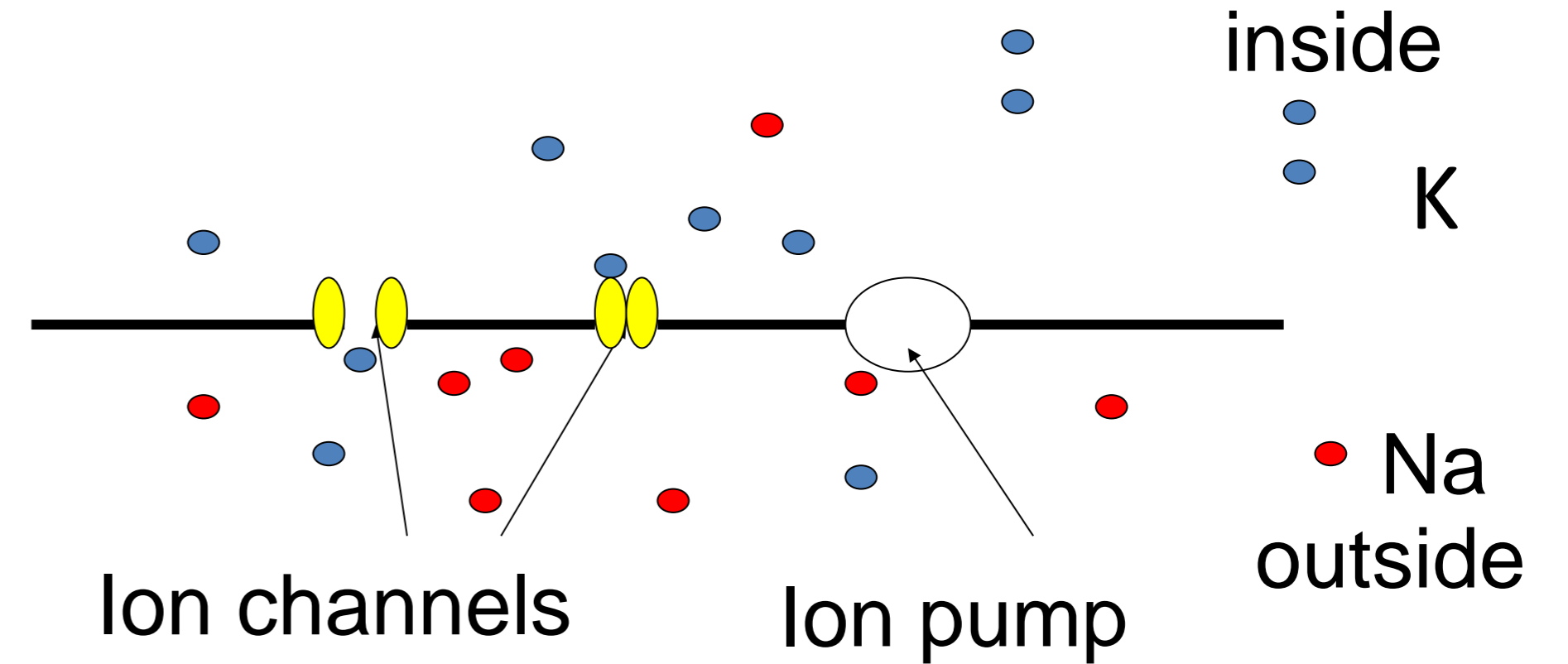
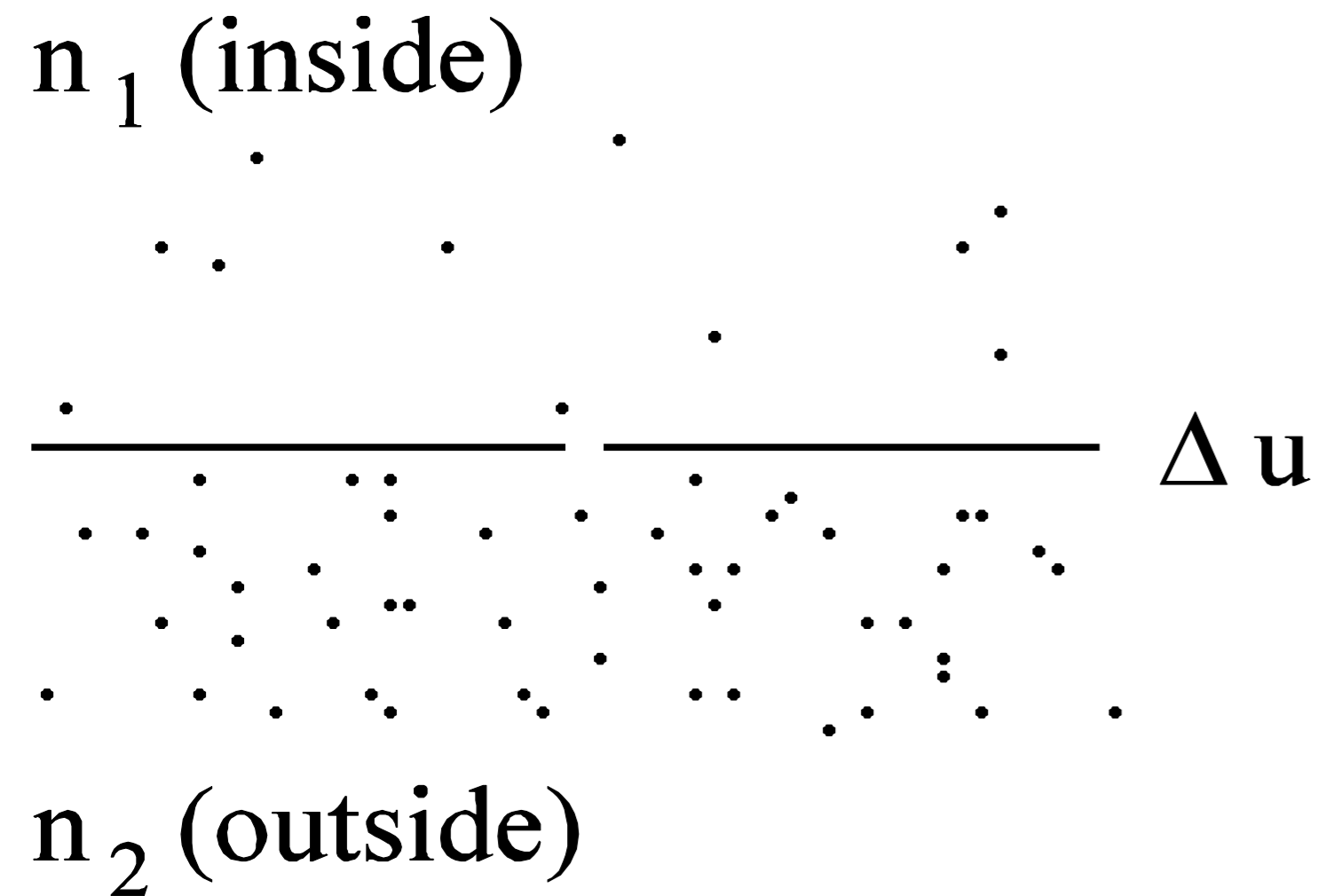
Neuronal Dynamics – 2.2. Nernst equation



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



Neuronal Dynamics – 2.2. Nernst equation

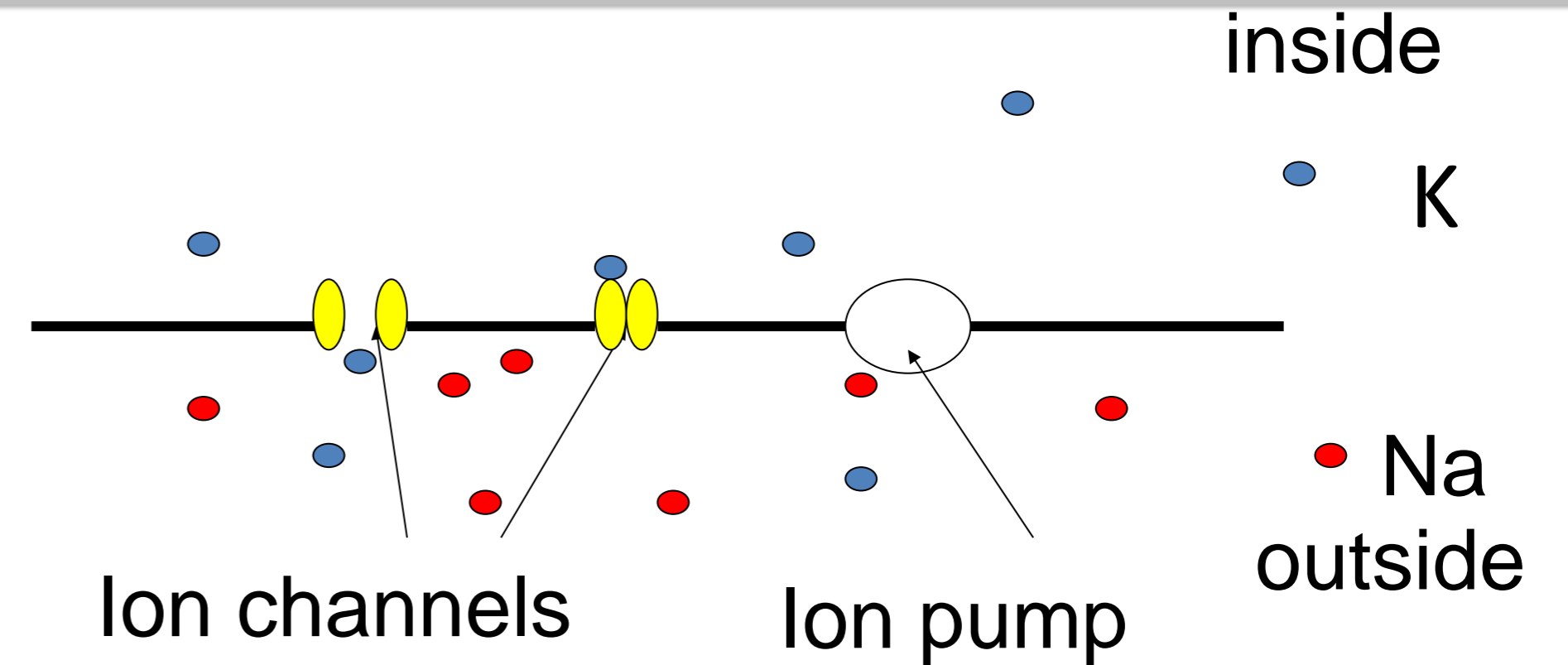


$$\Delta u = u_1 - u_2 = \frac{-kT}{q} \ln \frac{n(u_1)}{n(u_2)}$$

Reversal potential

Concentration difference \Leftrightarrow voltage difference

Neuronal Dynamics – 2.2. Reversal potential



Ion pump → Concentration difference

Concentration difference ⇔ voltage difference

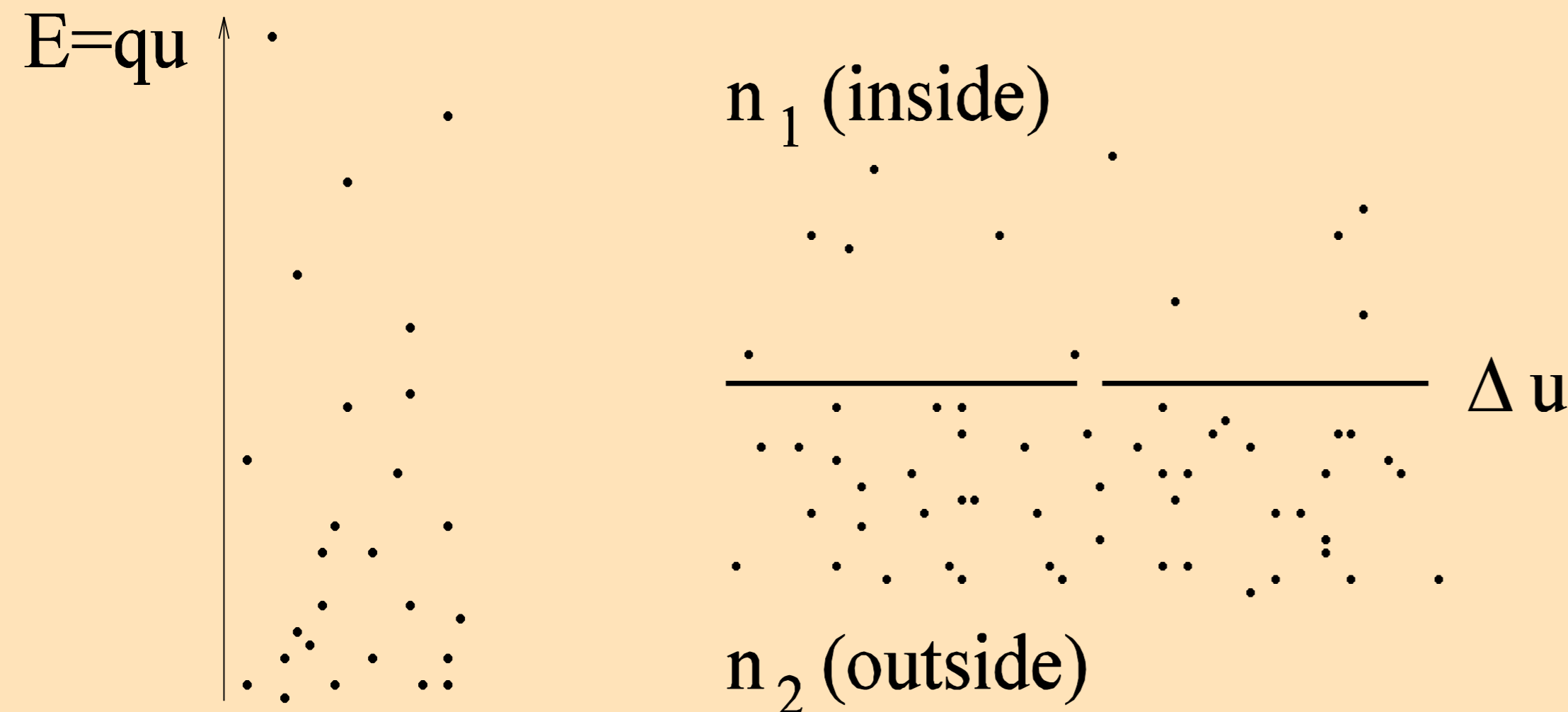
Reversal potential

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

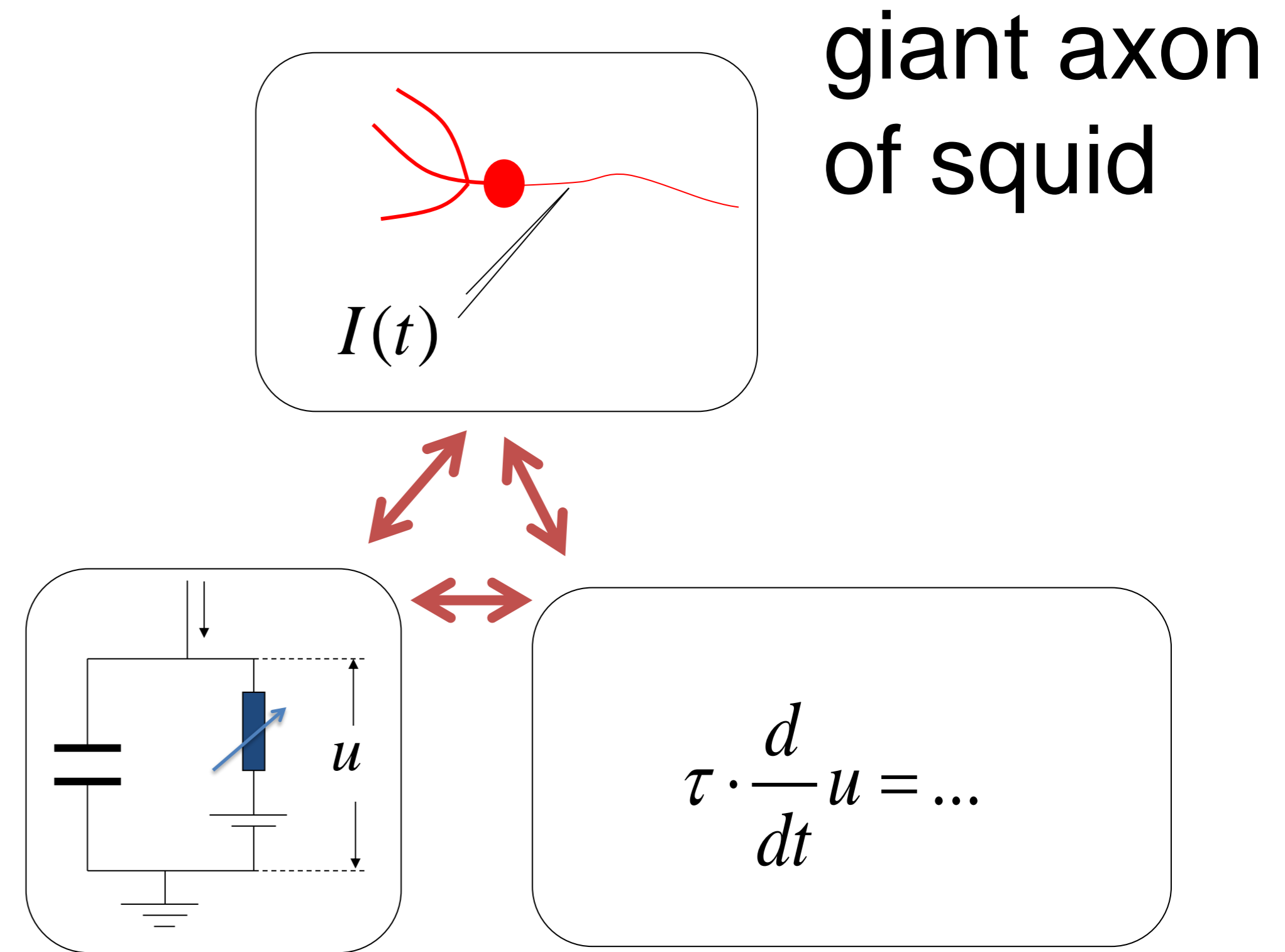
Week 2 – Biophysical modeling: The Hodgkin-Huxley model

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



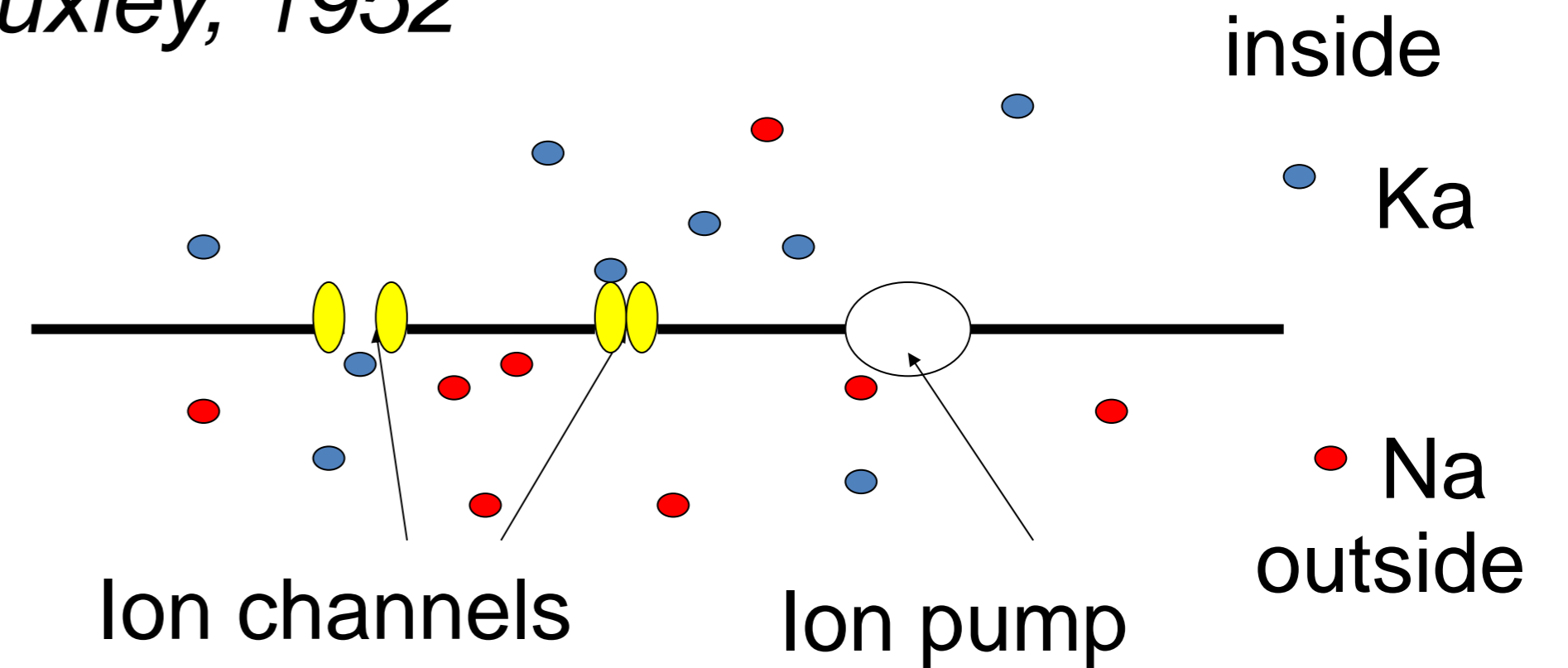
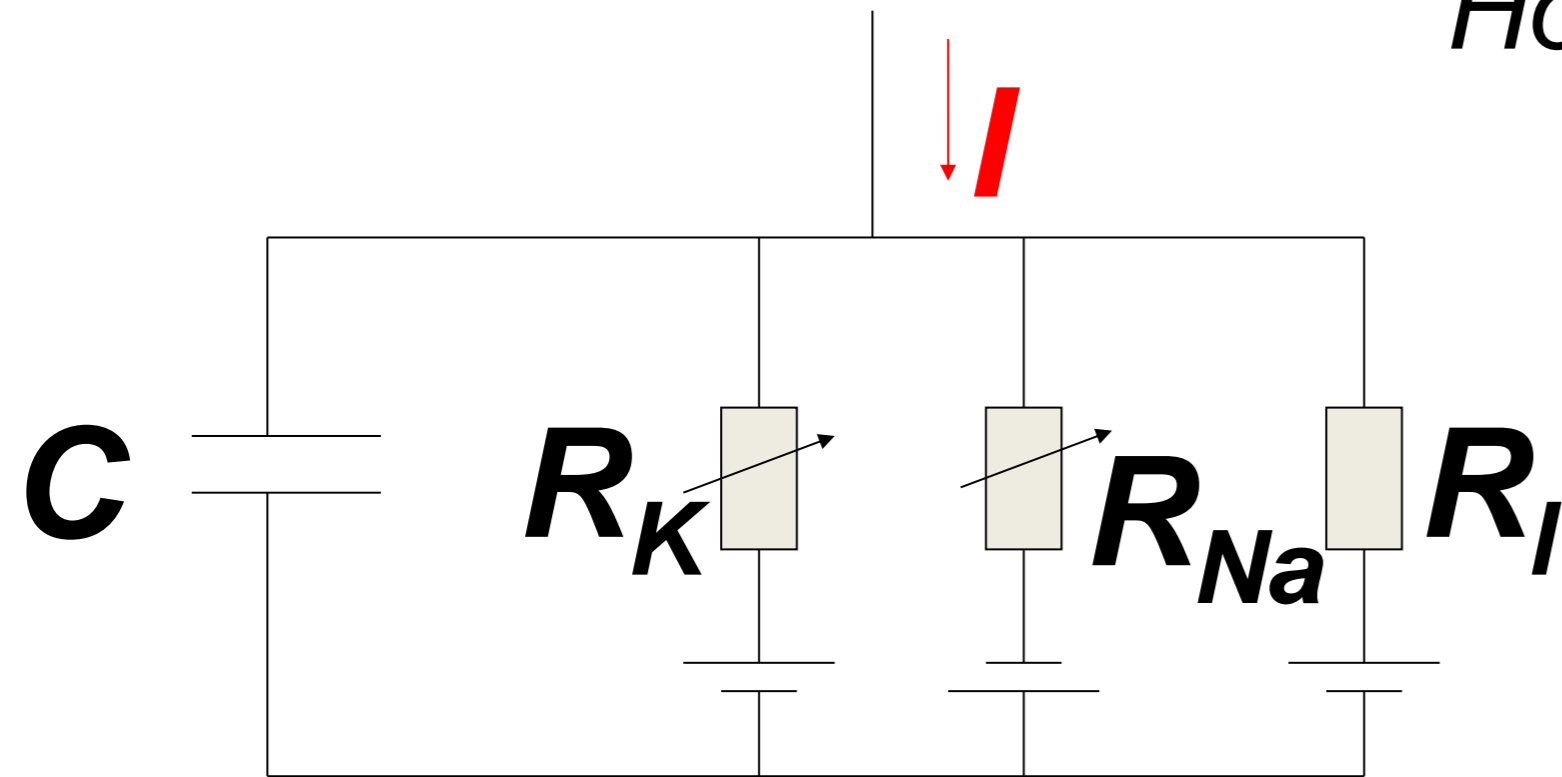
→ Hodgkin-Huxley model

Hodgkin&Huxley (1952)

Nobel Prize 1963

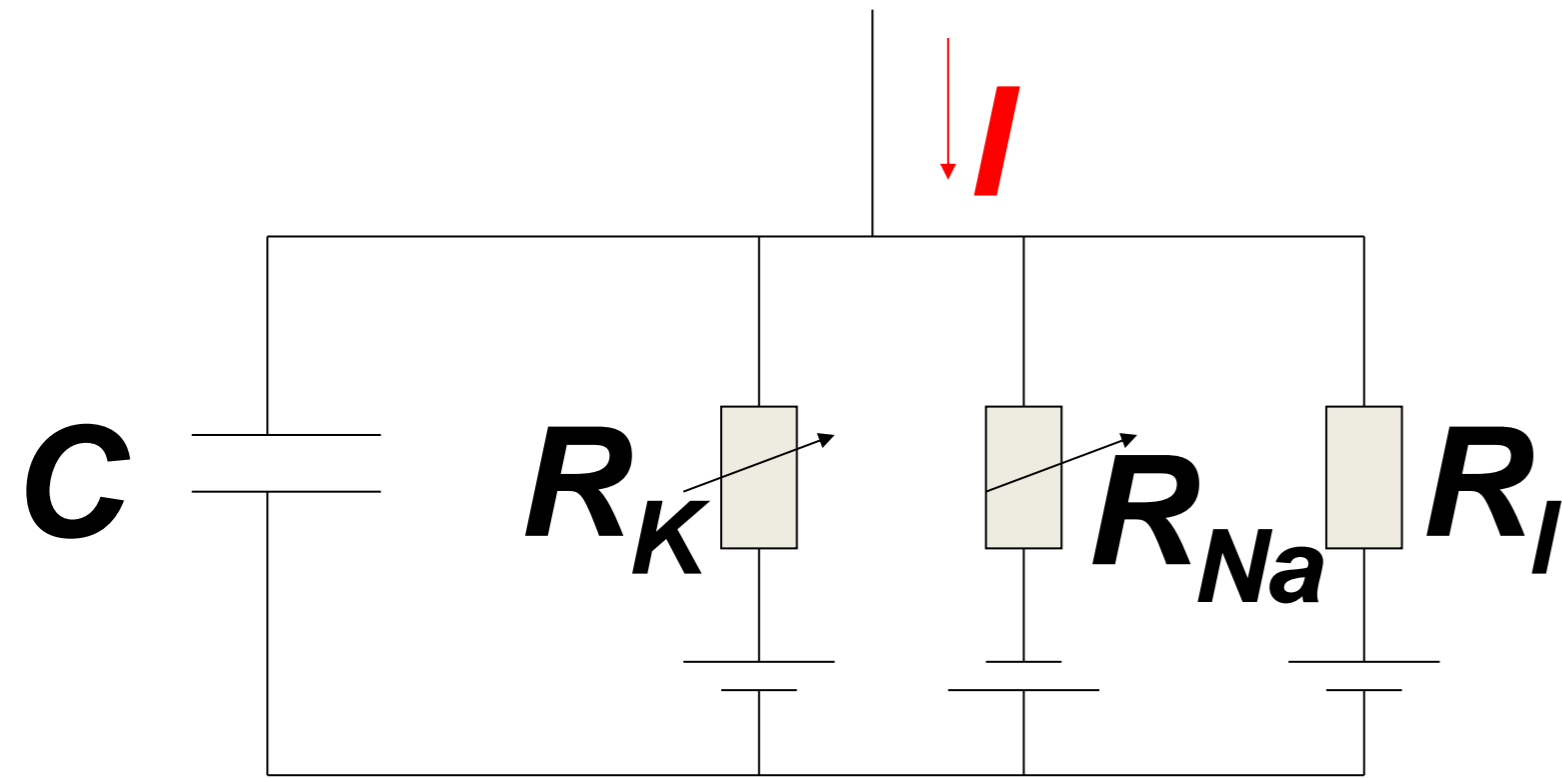
Neuronal Dynamics – 2.3. Hodgkin-Huxley Model

Hodgkin and Huxley, 1952



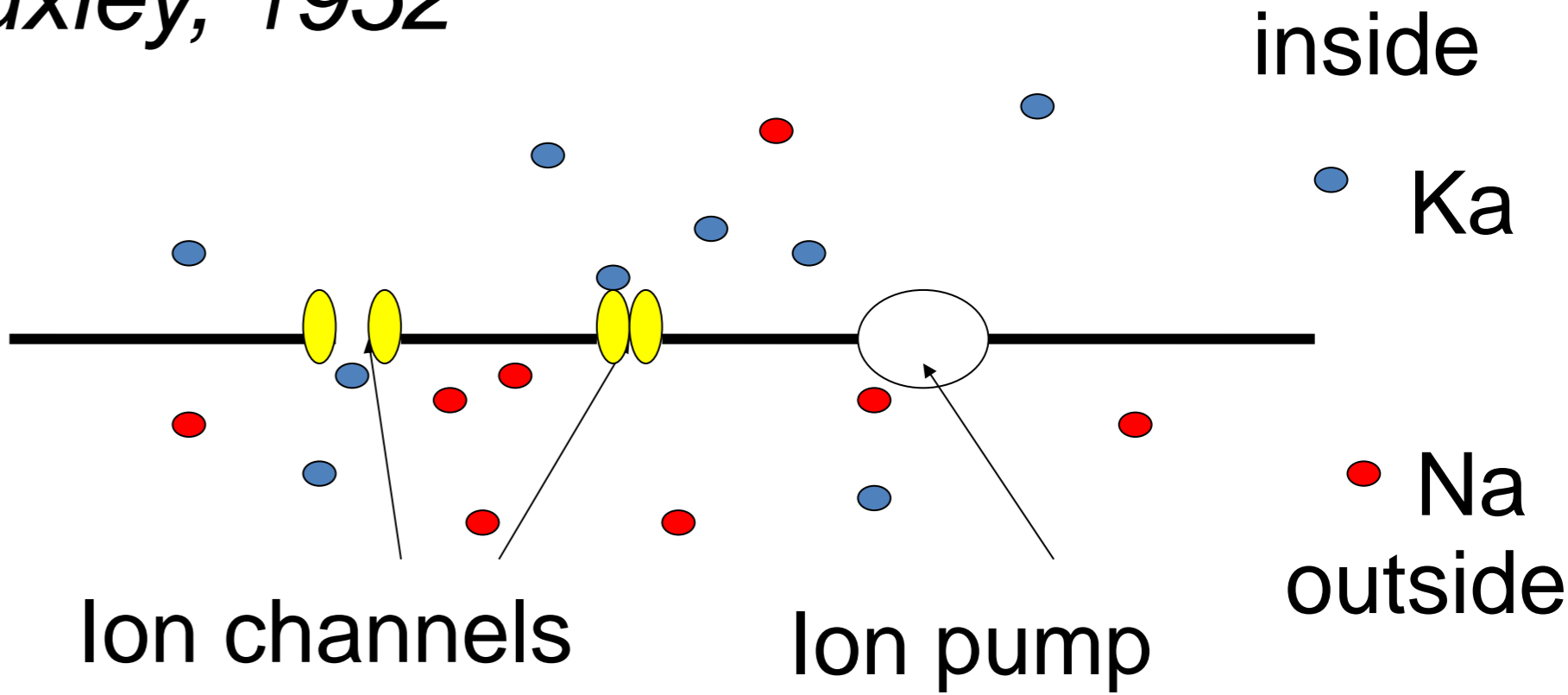
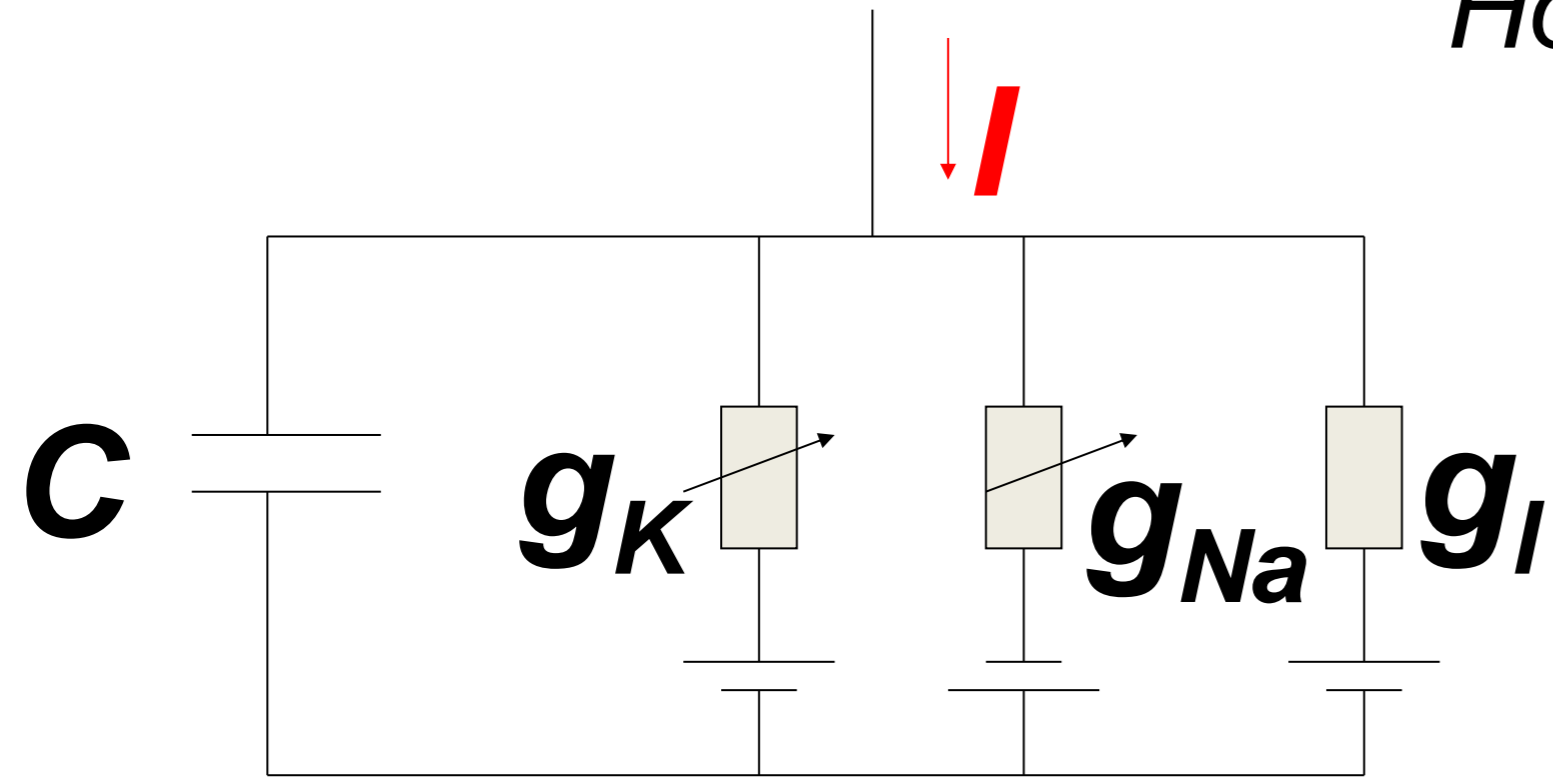
*Mathematical
derivation*

Neuronal Dynamics – 2.3. Hodgkin-Huxley Model



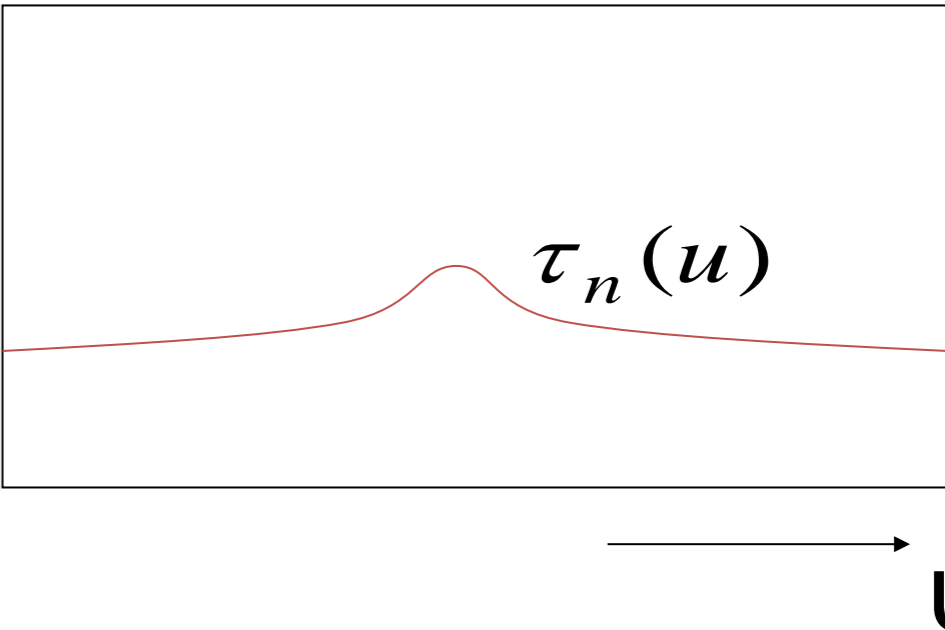
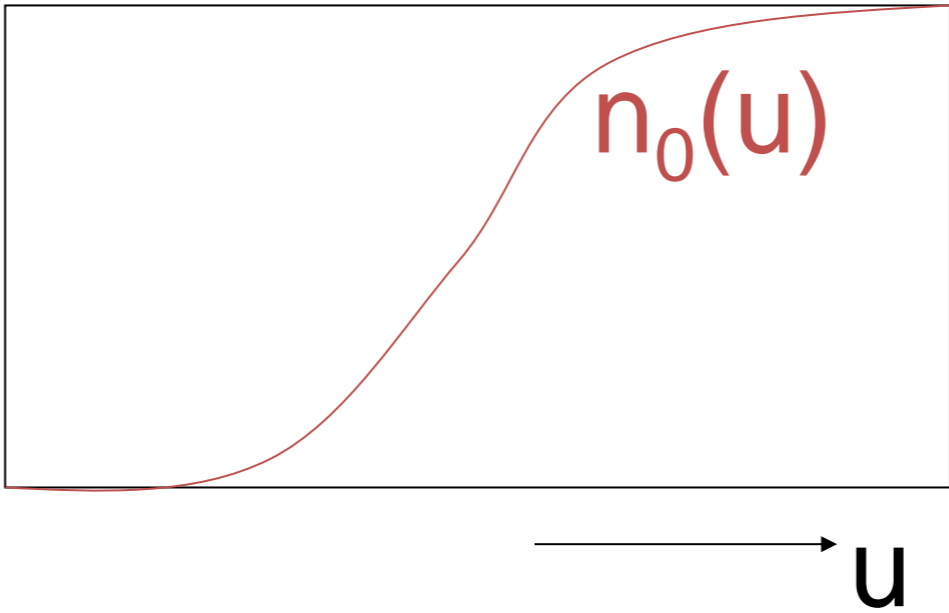
Neuronal Dynamics – 2.3. Hodgkin-Huxley Model

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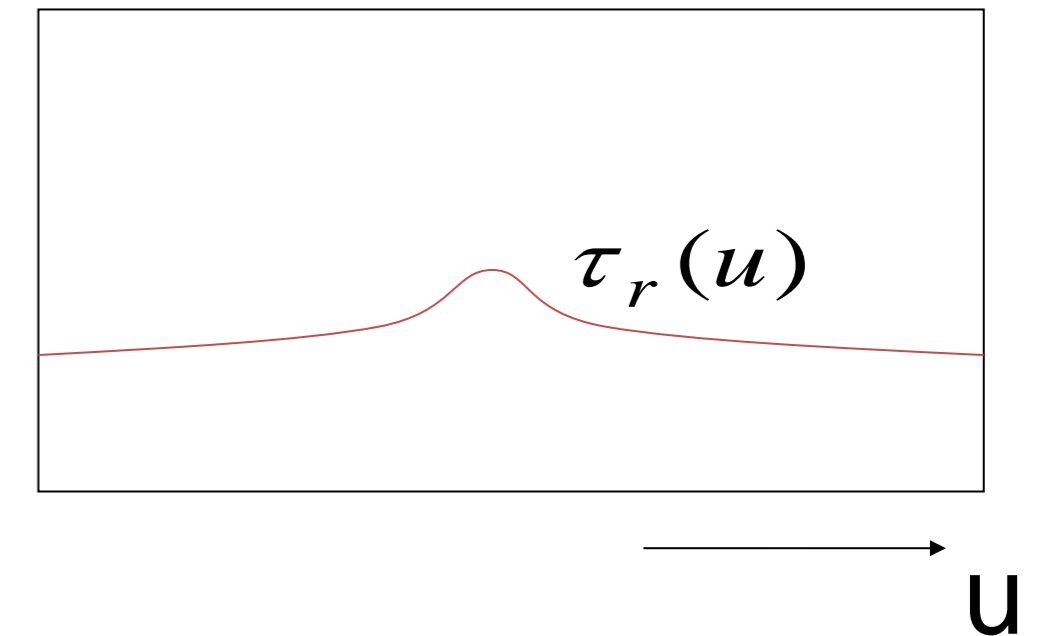
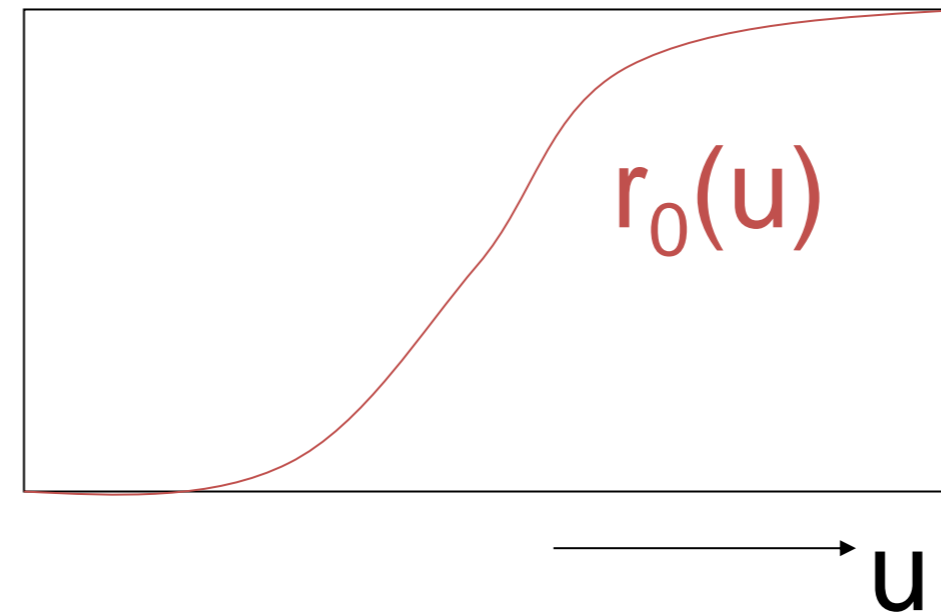
$$C \frac{du}{dt} = \underbrace{-g_{Na} m^3 h (u - E_{Na})}_{I_{Na}} - \underbrace{g_K n^4 (u - E_K)}_{I_K} - \underbrace{g_l (u - E_l)}_{I_{leak}} + \underbrace{I(t)}_{\text{stimulus}}$$

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



Neuronal Dynamics – 2.3. Ion channel

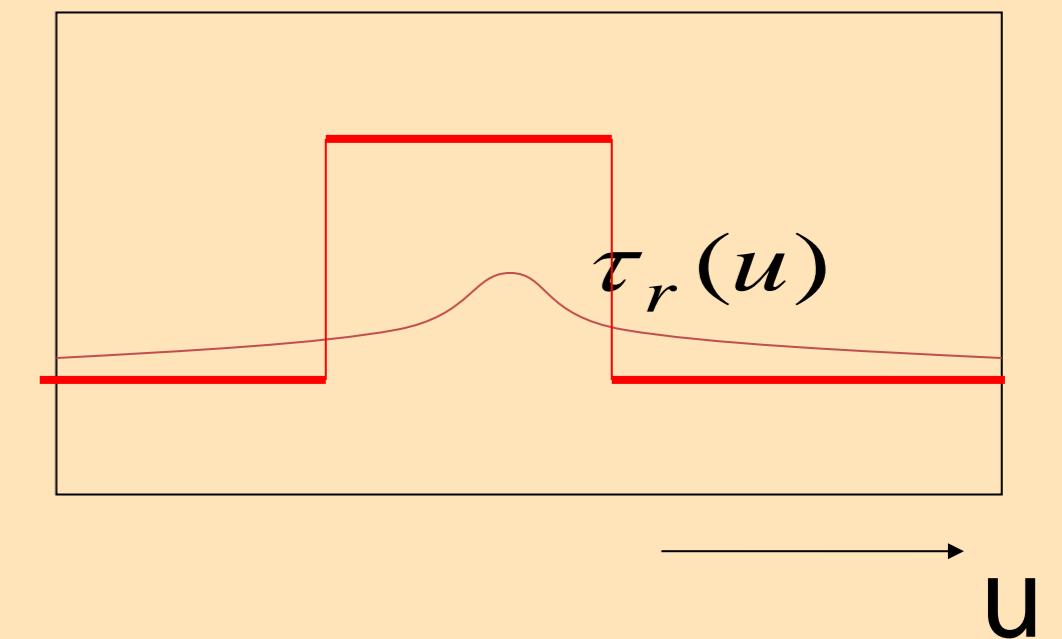
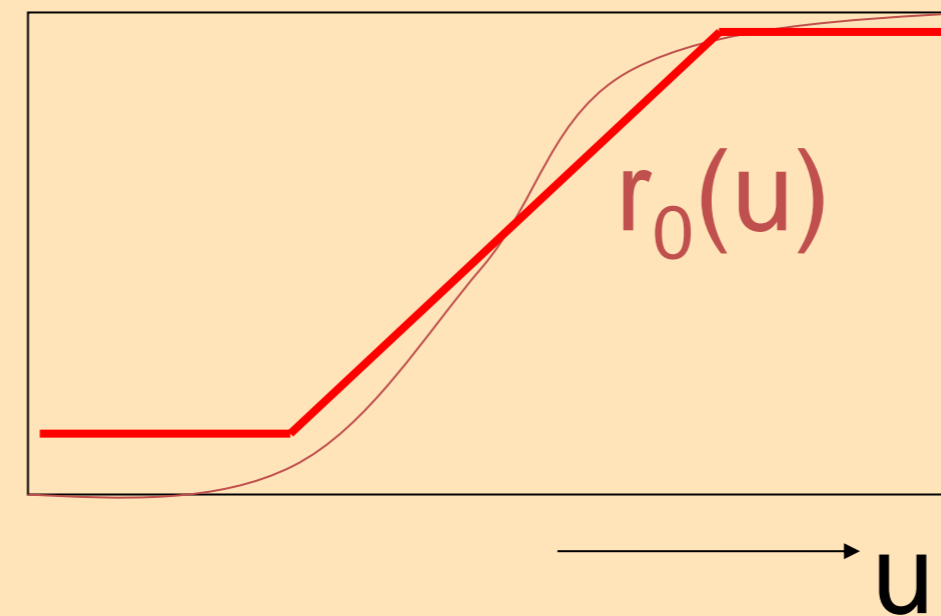
$$C \frac{du}{dt} = - \sum_k I_{ion,k} + I(t)$$



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

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

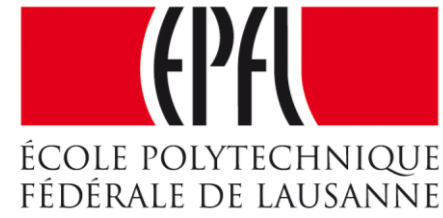
Neuronal Dynamics – Exercise 2.3. Ion channel



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

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

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

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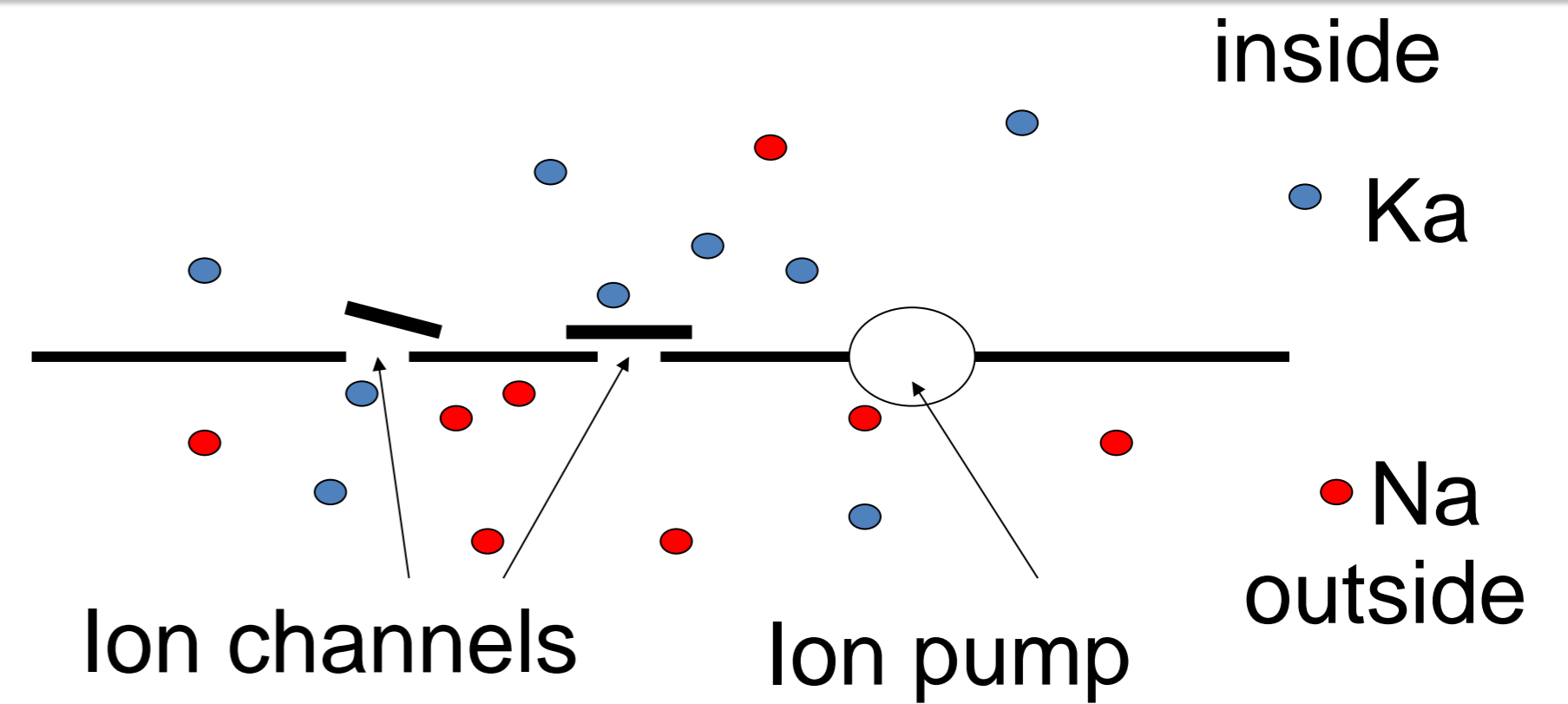
2.4 Threshold in the Hodgkin-Huxley Model

- where is the firing threshold?

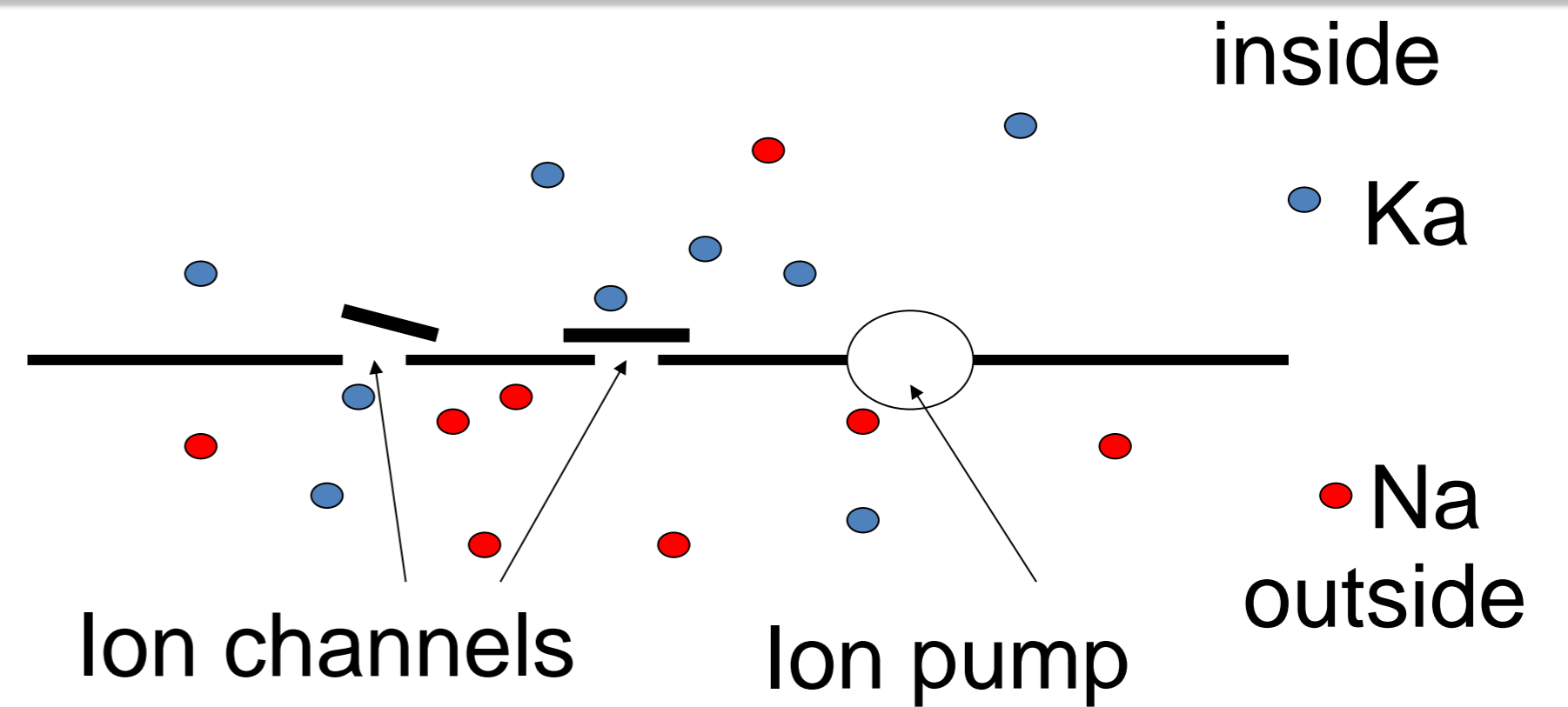
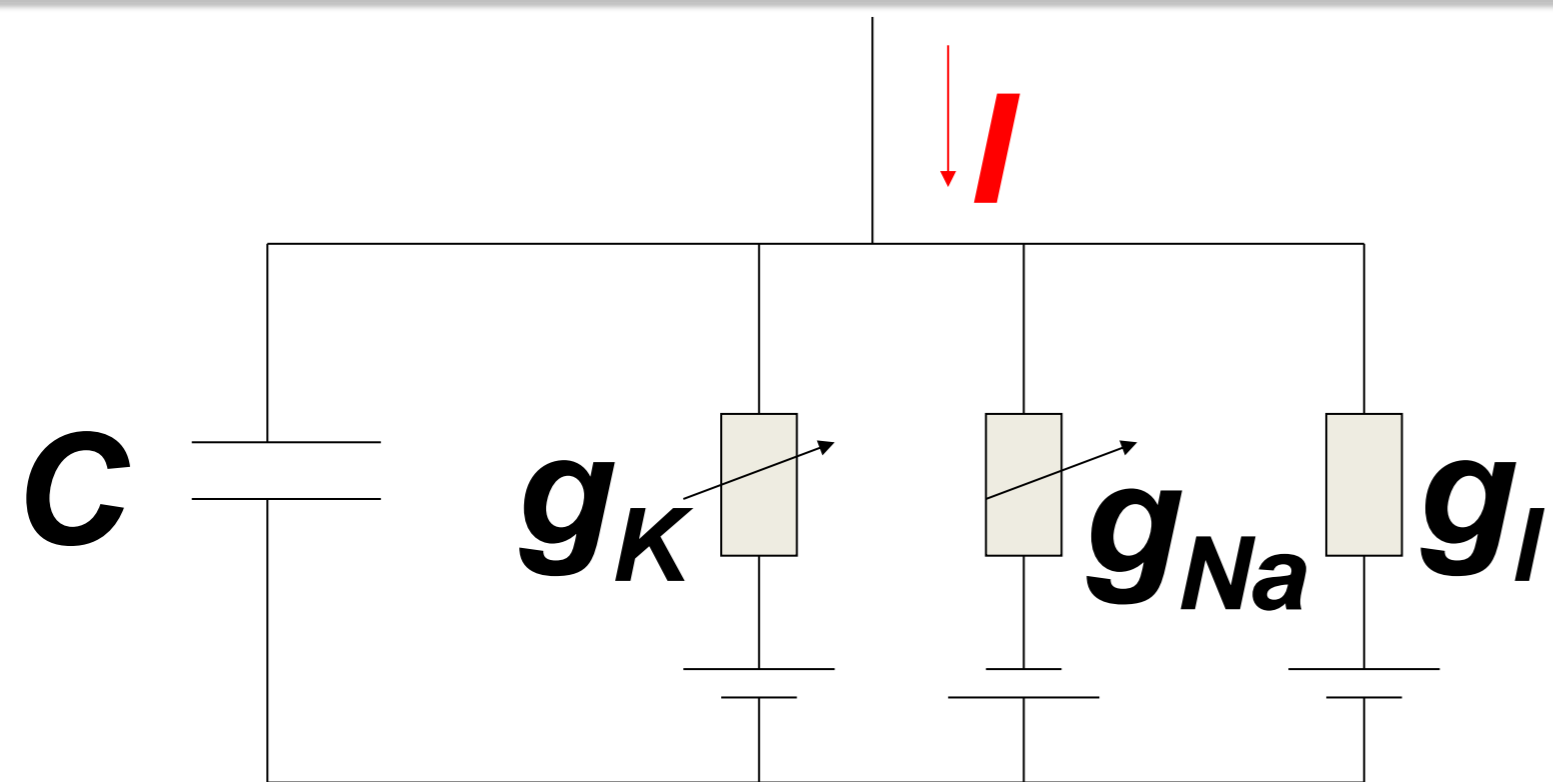
2.5. Detailed biophysical models

- the zoo of ion channels

Neuronal Dynamics – 2.4. Threshold in HH model



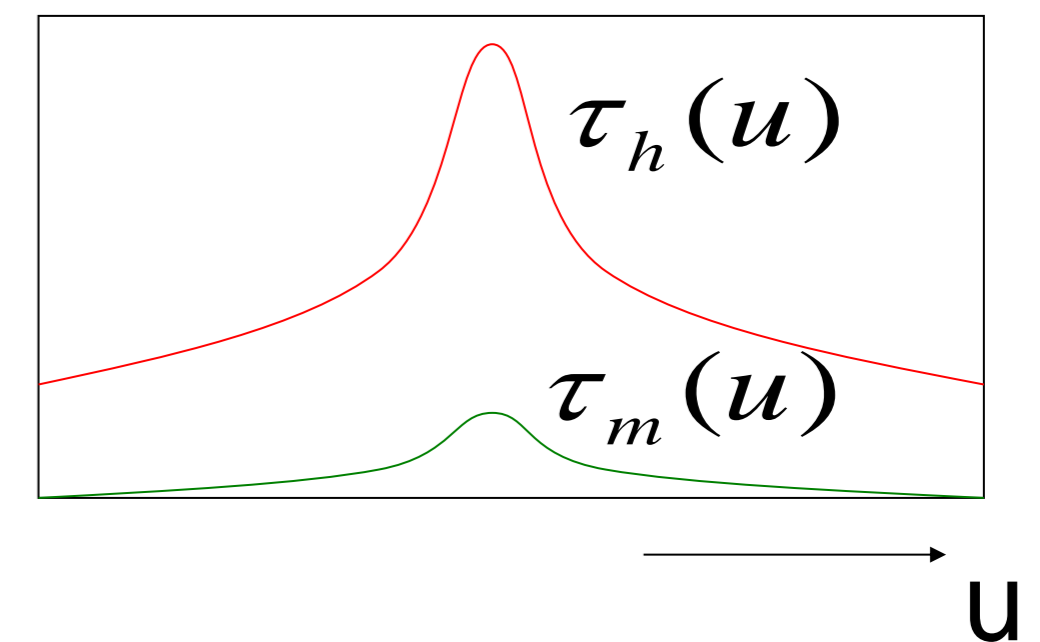
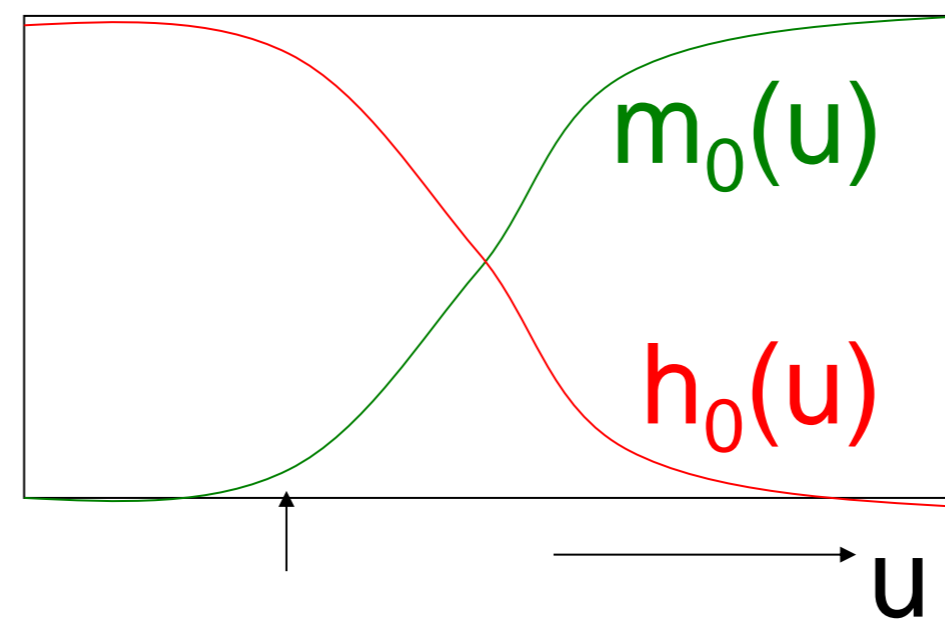
Neuronal Dynamics – 2.4. Threshold in HH model



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

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

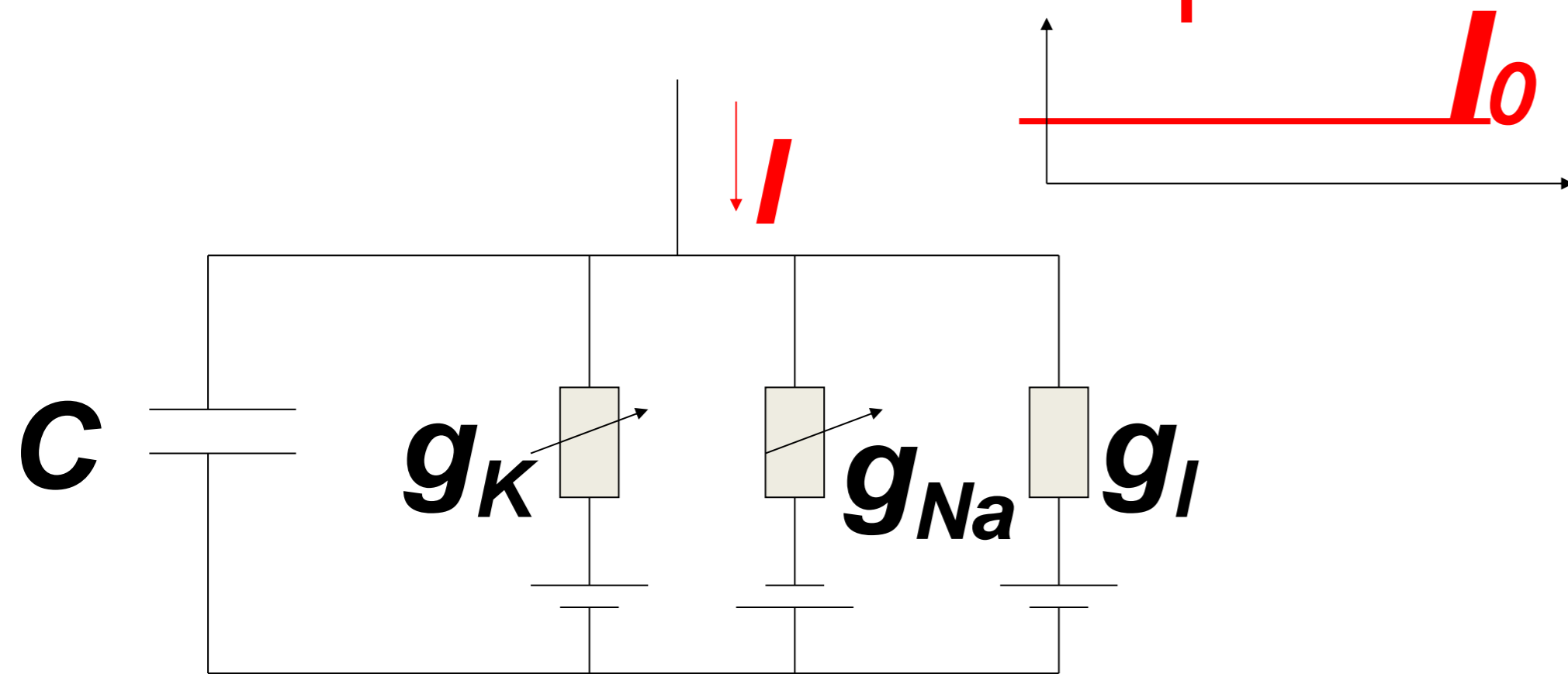
$$\frac{dh}{dt} = \frac{h_{\infty} - h}{\tau_h(u)}$$



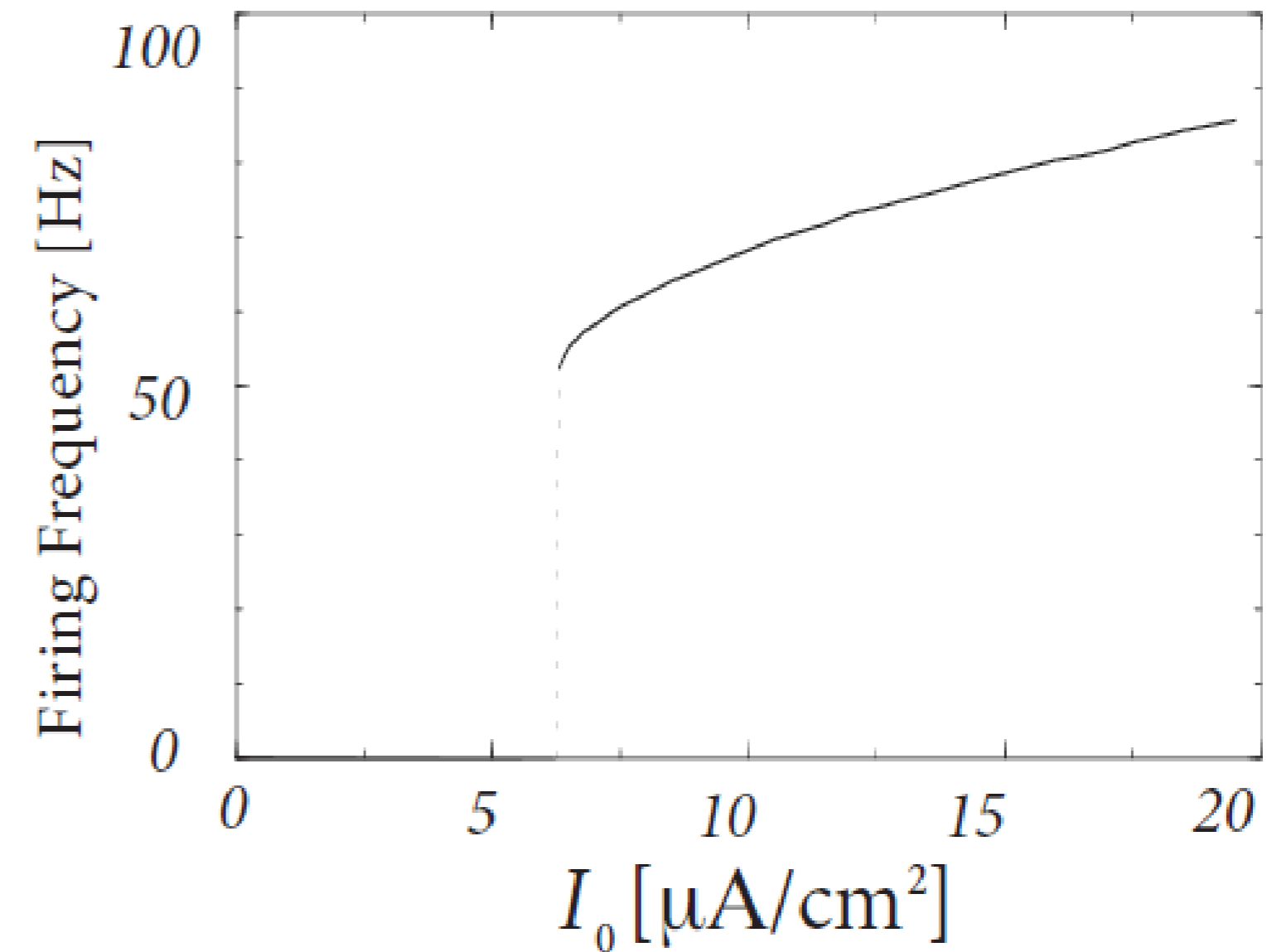
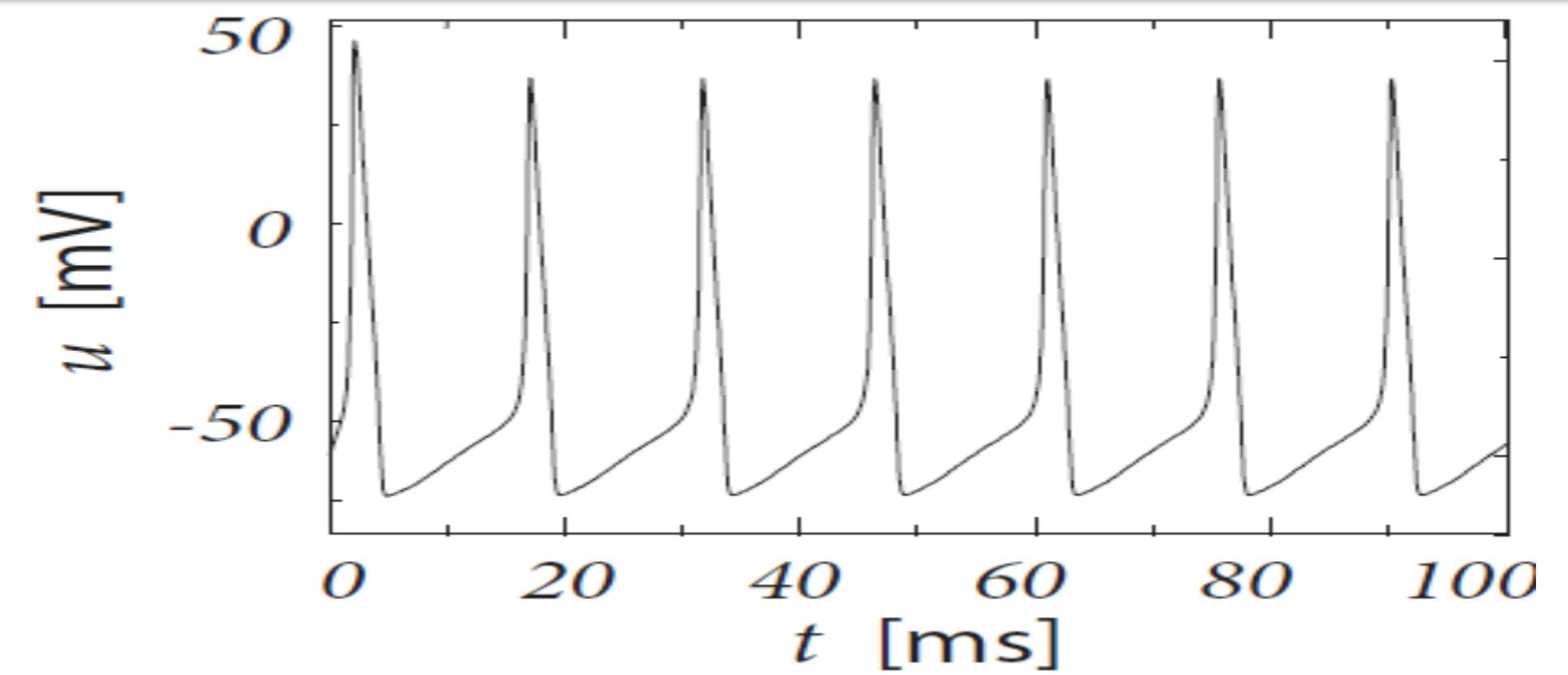
Where is the threshold for firing?

Neuronal Dynamics – 2.4. Threshold in HH model

Constant current input

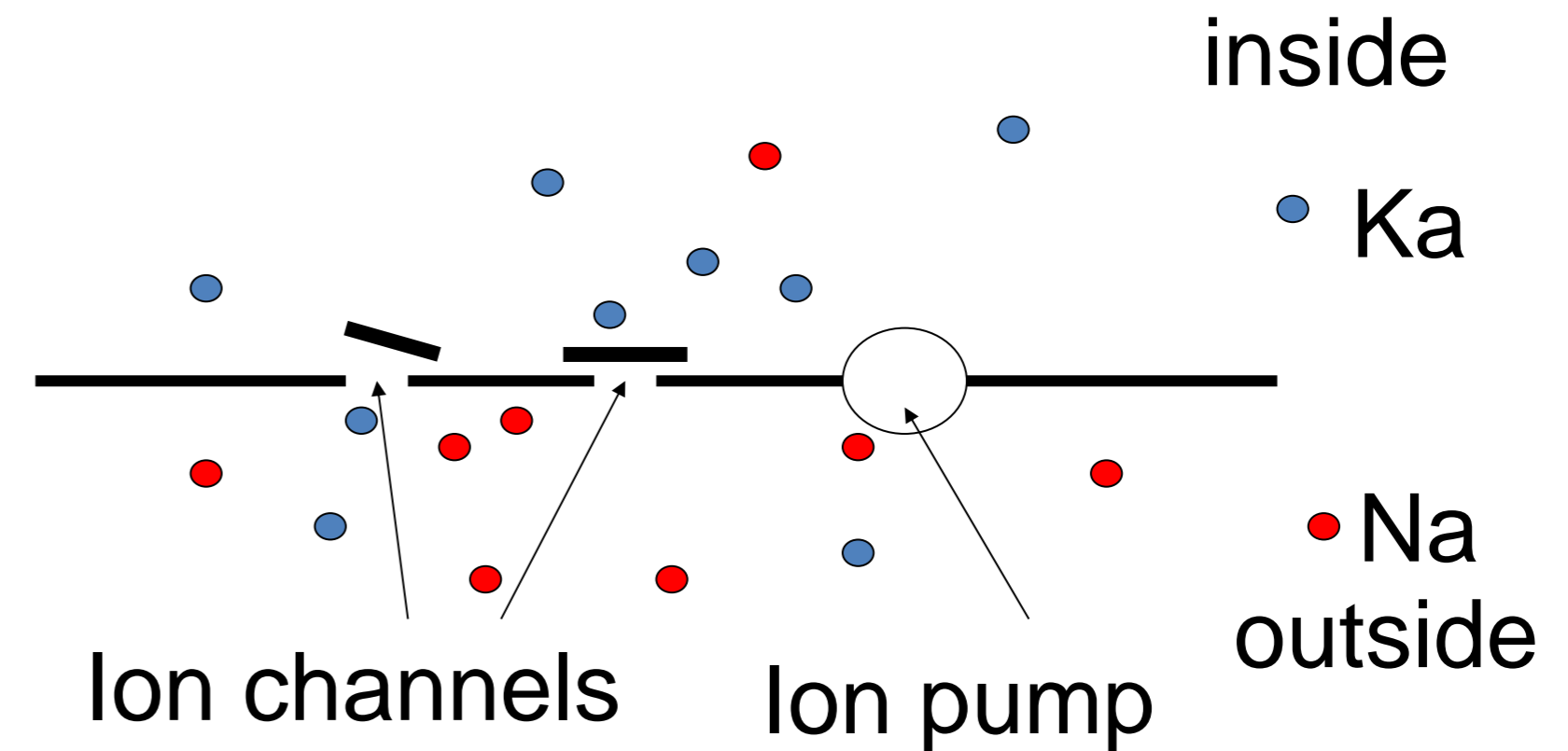
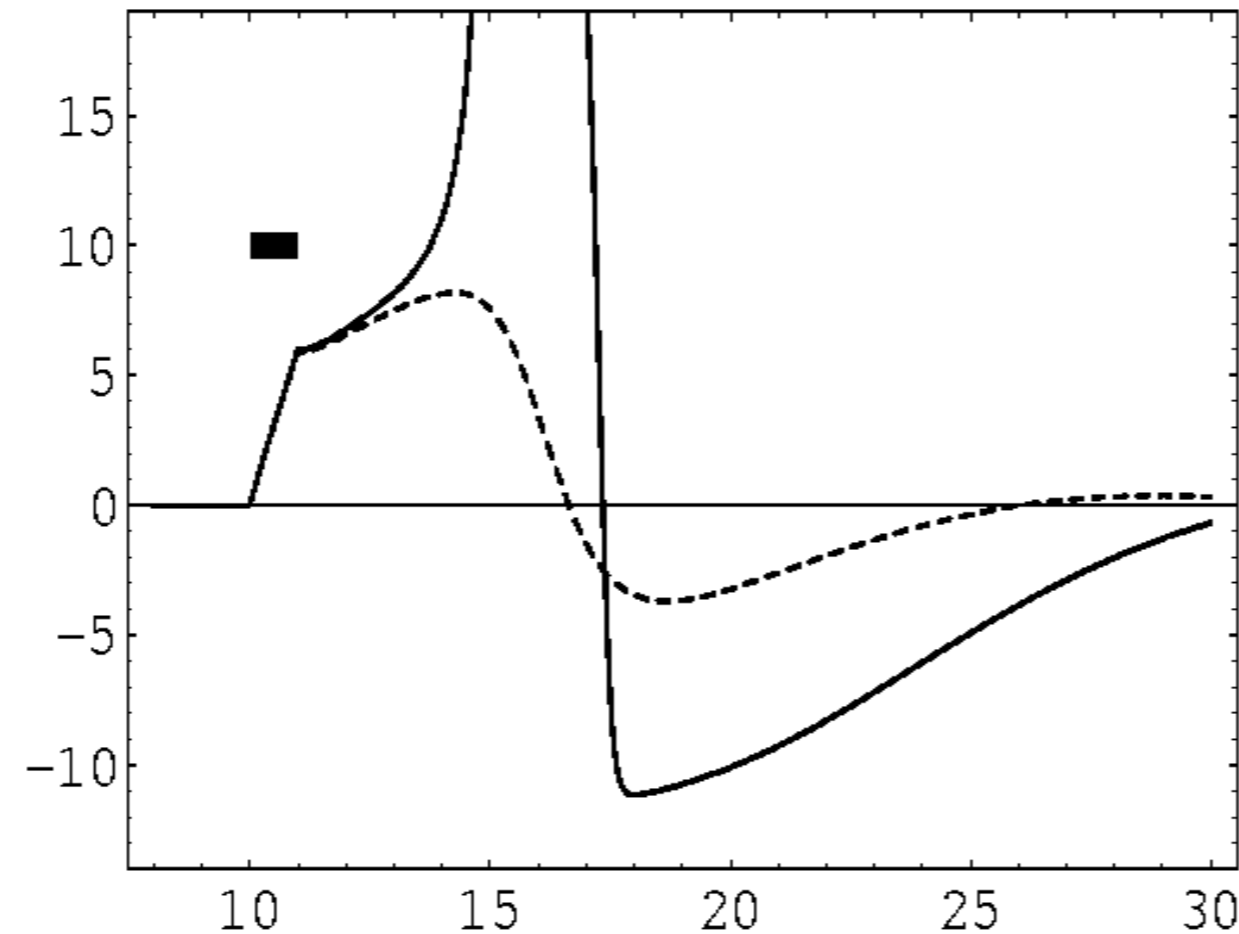
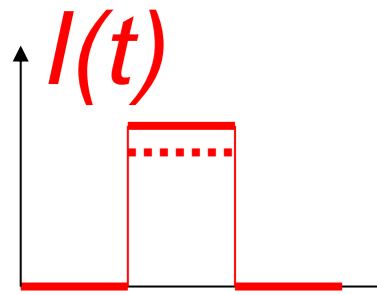


Threshold?
for repetitive firing
(**current** threshold)



Neuronal Dynamics – 2.4. Threshold in HH model

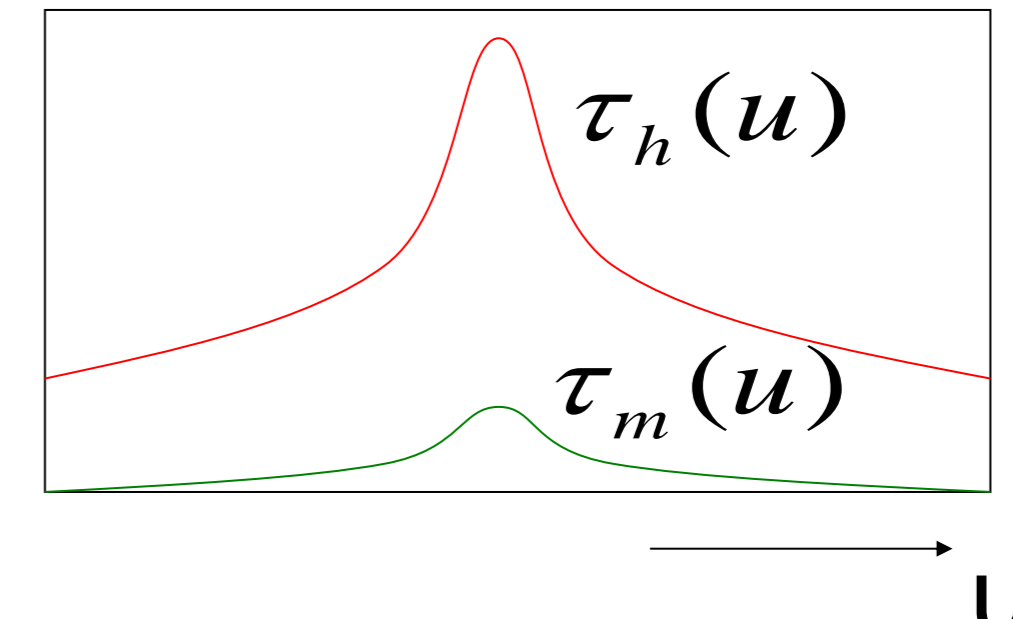
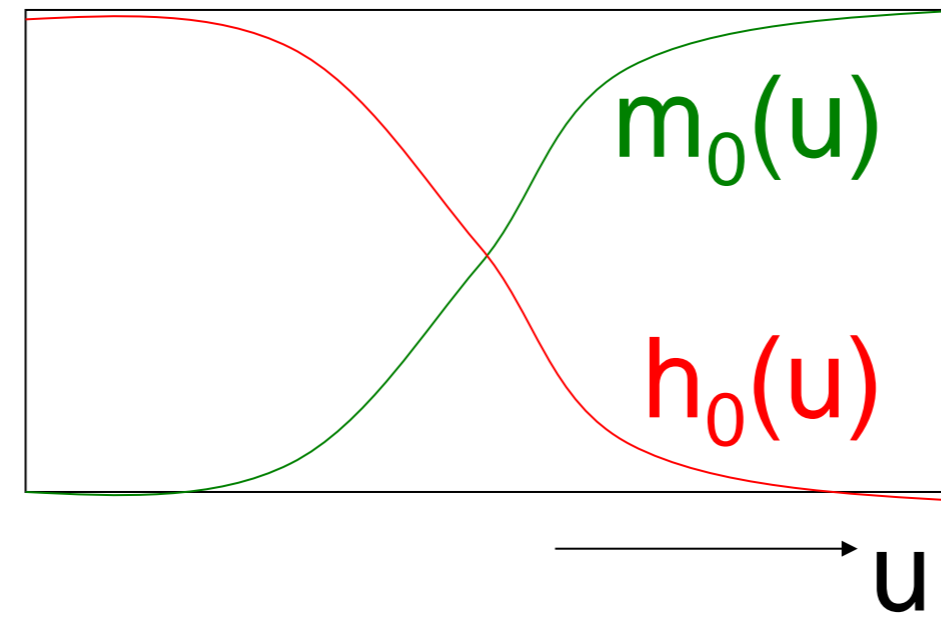
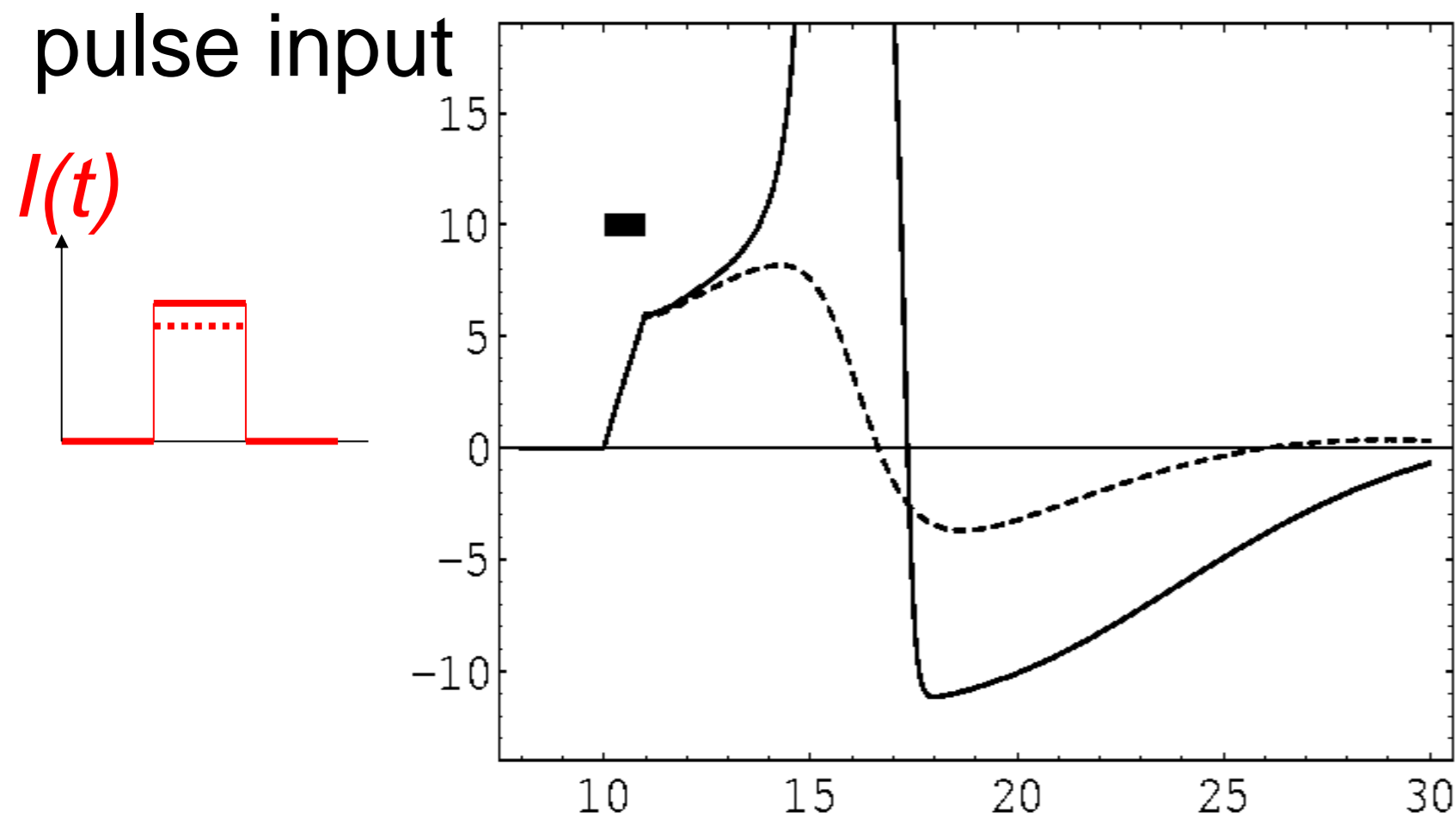
pulse input



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



Mathematical explanation

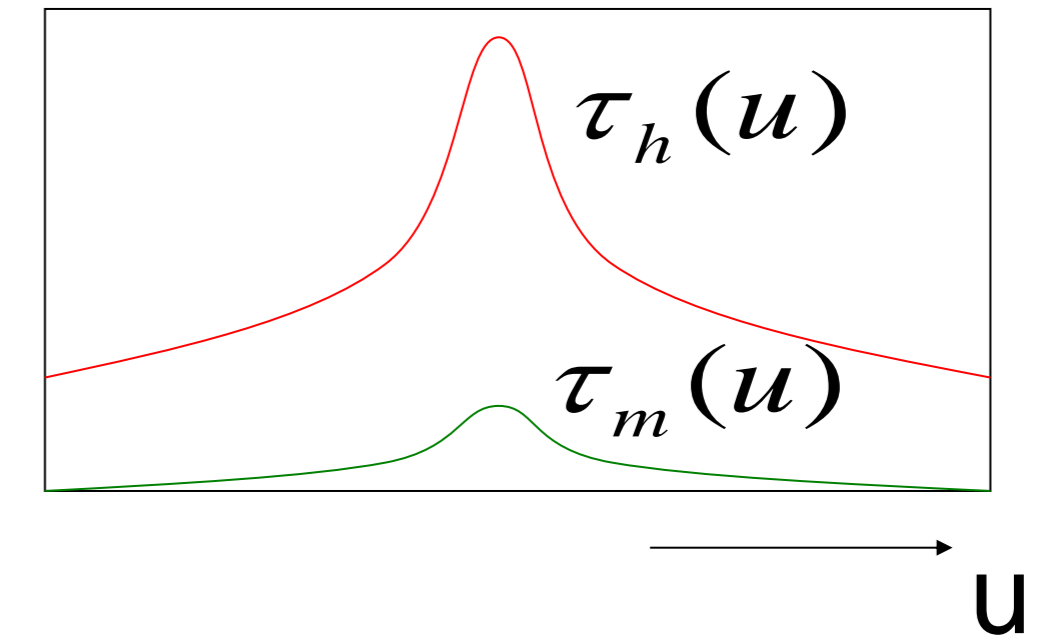
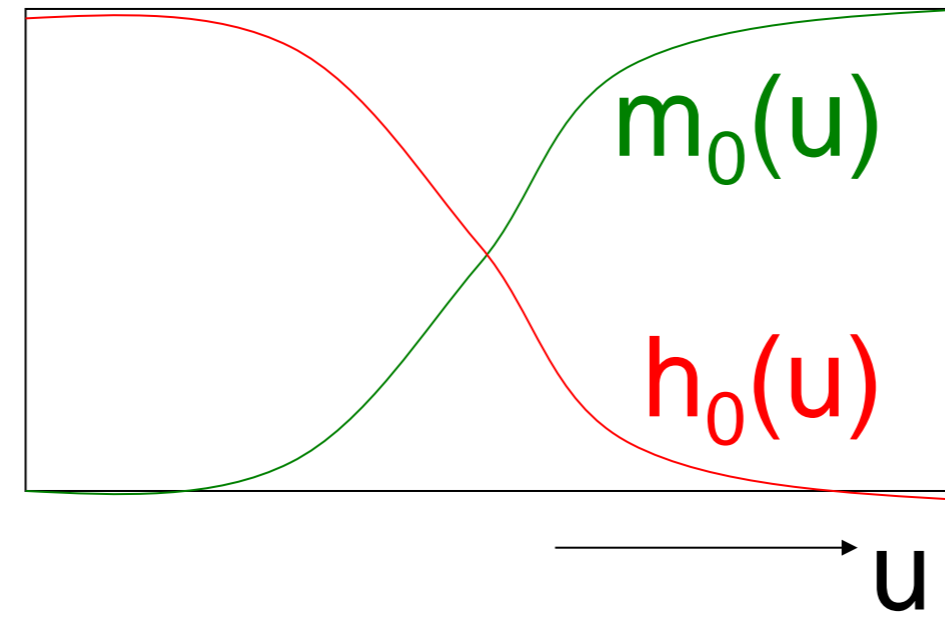
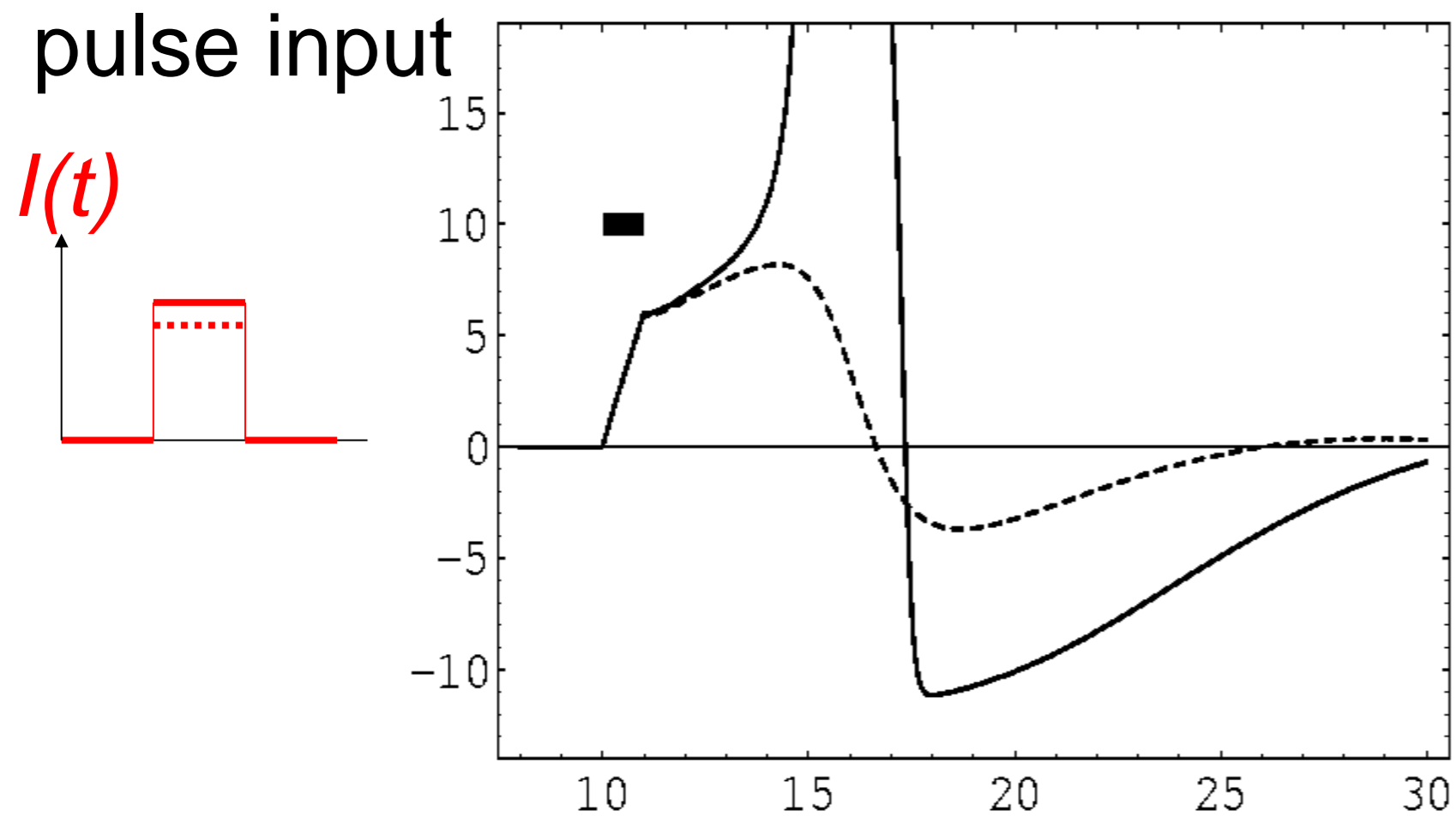
$$C \frac{du}{dt} = - \overbrace{g_{Na} m^3 h}^{I_{Na}} (u - E_{Na}) - \overbrace{g_K n^4}^{I_K} (u - E_K) - \overbrace{g_l}^{I_{leak}} (u - E_l) + I(t)$$

Stim. ↓

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

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

Neuronal Dynamics – 2.4. Threshold in HH model

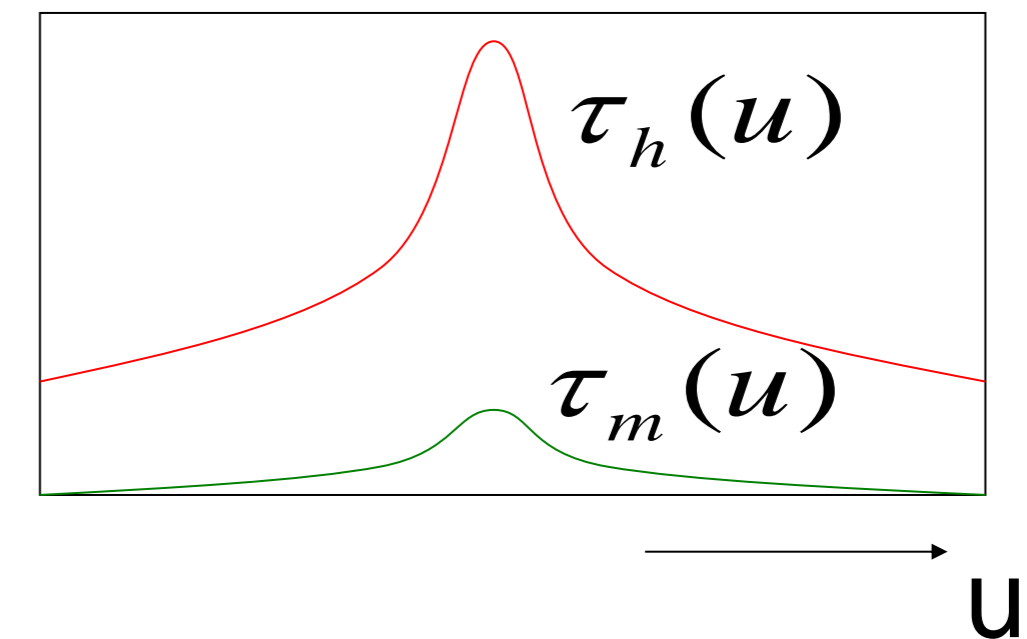
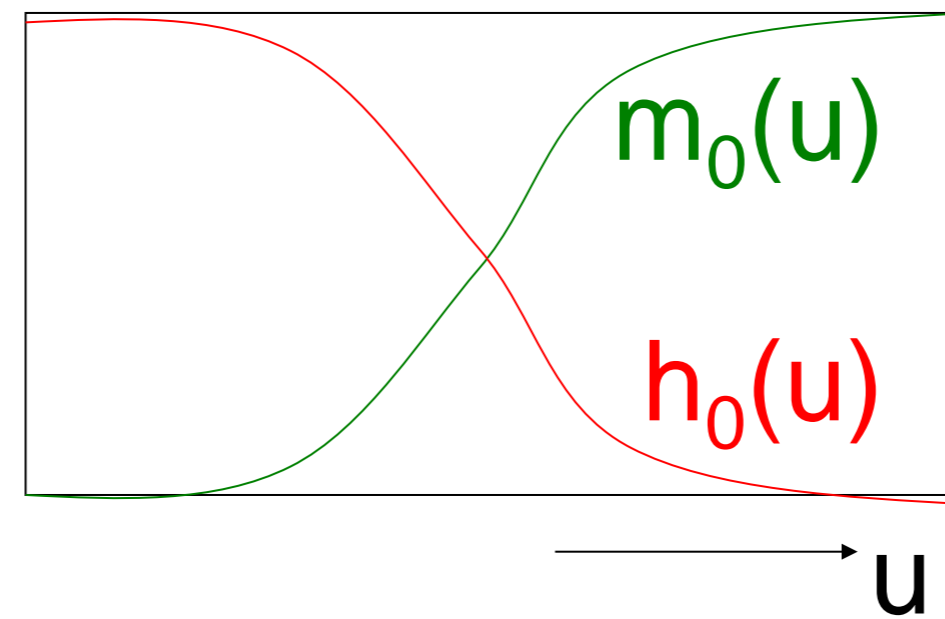
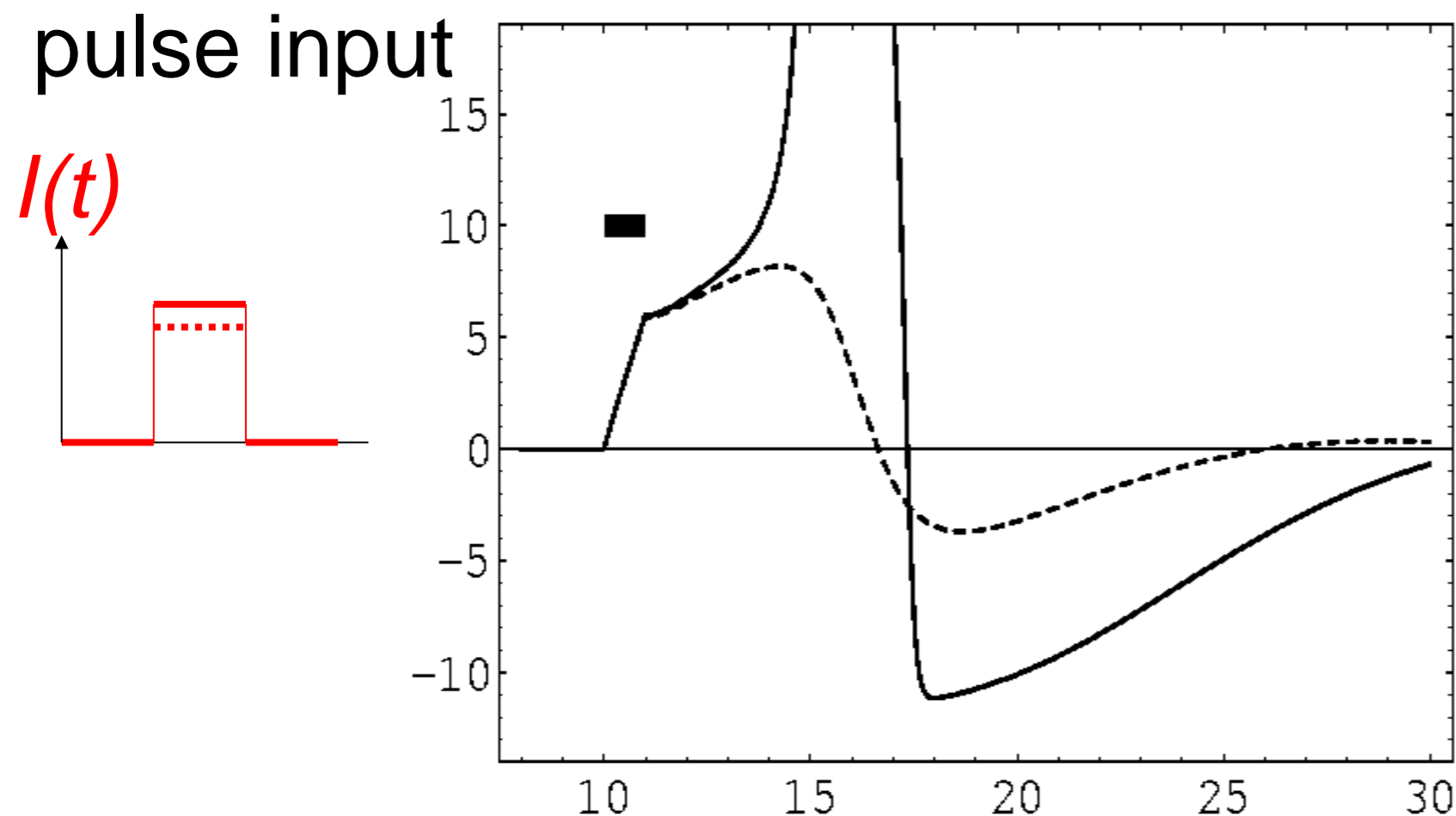


$$C \frac{du}{dt} = - \overbrace{g_{Na} m^3 h}^{I_{Na}} (u - E_{Na}) - I_K - I_{leak} + \overset{\text{Stim.}}{\downarrow} I(t)$$

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

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

Neuronal Dynamics – 2.4. Threshold in HH model



Why start the explanation with m and not h ?

What about n ?

Where is the threshold?

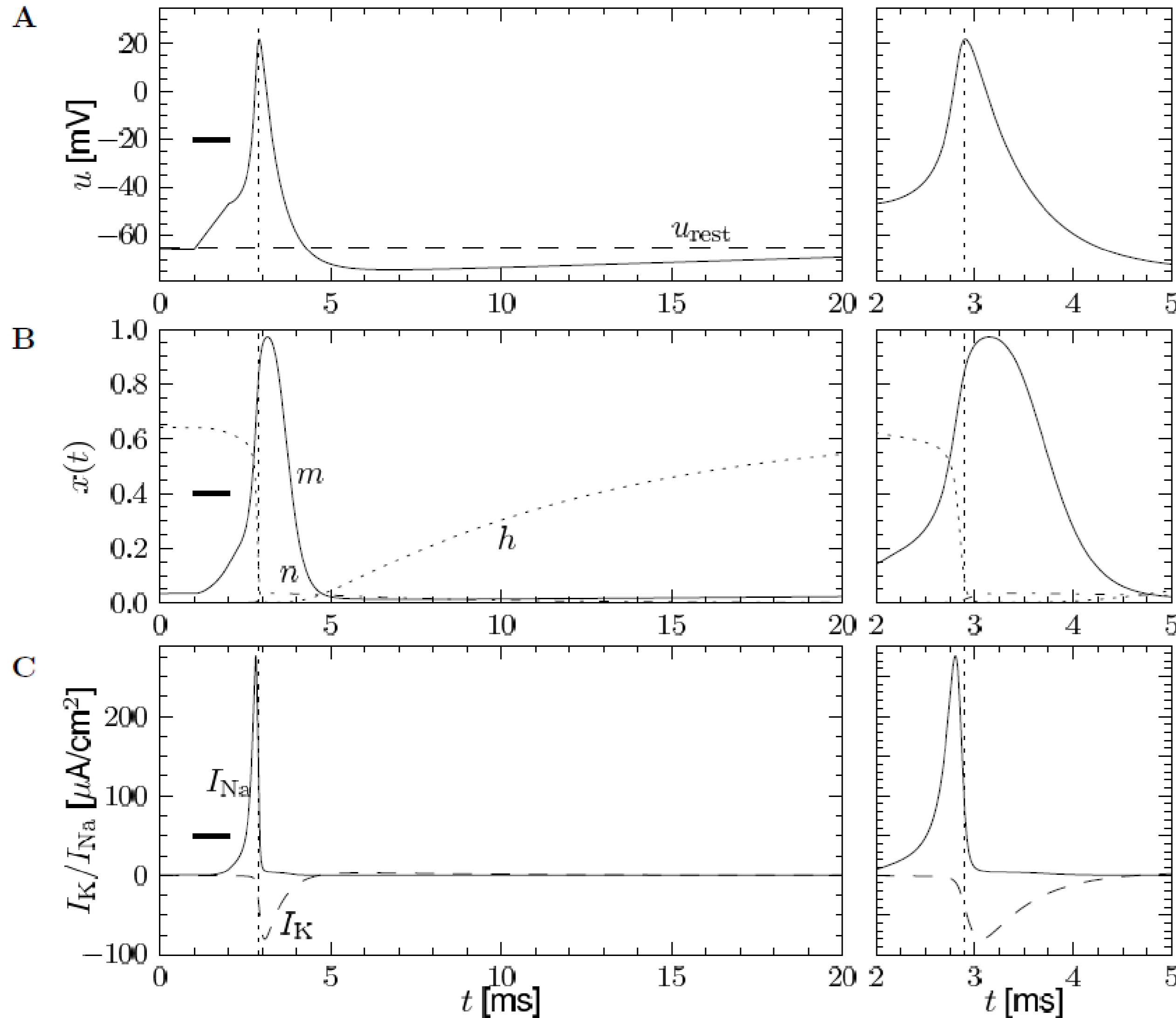
$$C \frac{du}{dt} = \underbrace{-g_{Na} m^3 h (u - E_{Na})}_{I_{Na}} - \underbrace{g_K n^4 (u - E_K)}_{I_K} - \underbrace{g_l (u - E_l)}_{I_{leak}} + I(t) \quad \text{Stim.} \downarrow$$

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

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

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

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:

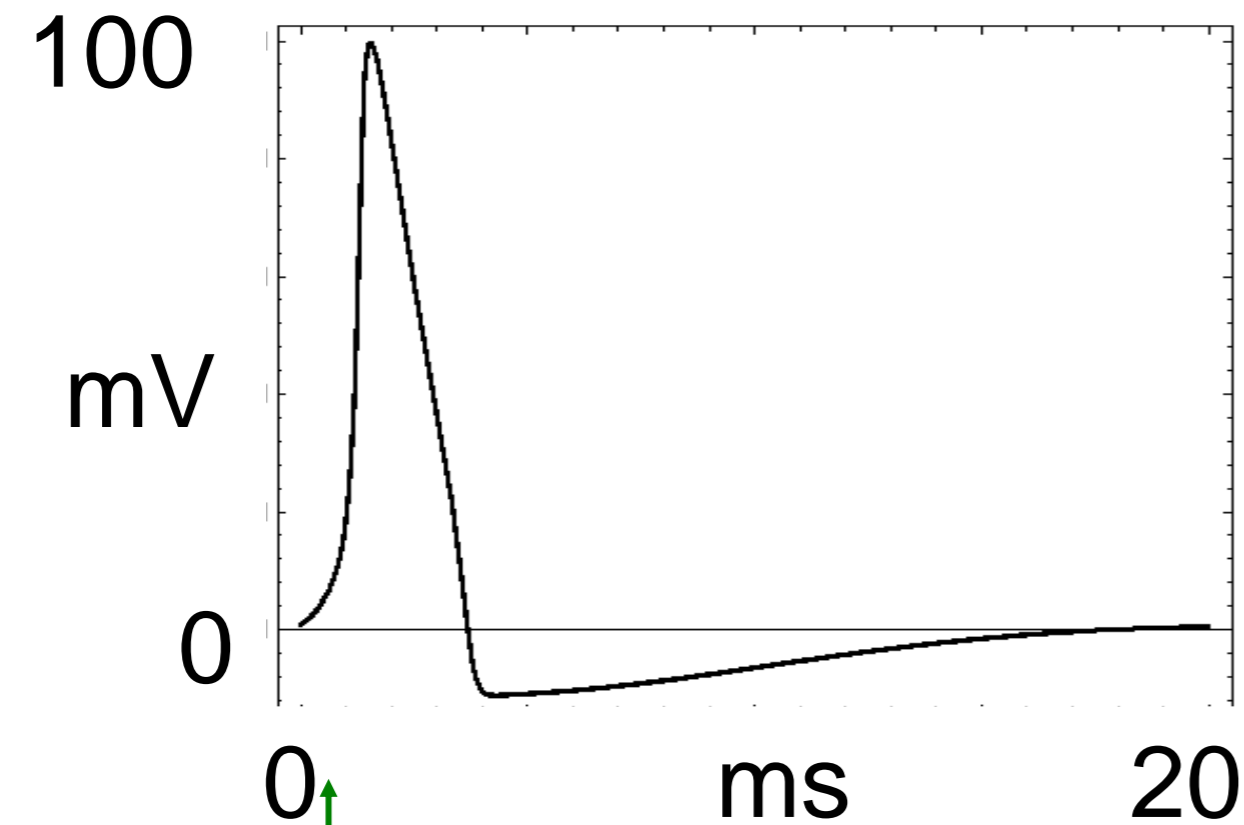
Coupled differential equations

‘Effective’ threshold
in simulations?

Neuronal Dynamics – 2.4. Refractoriness in HH model

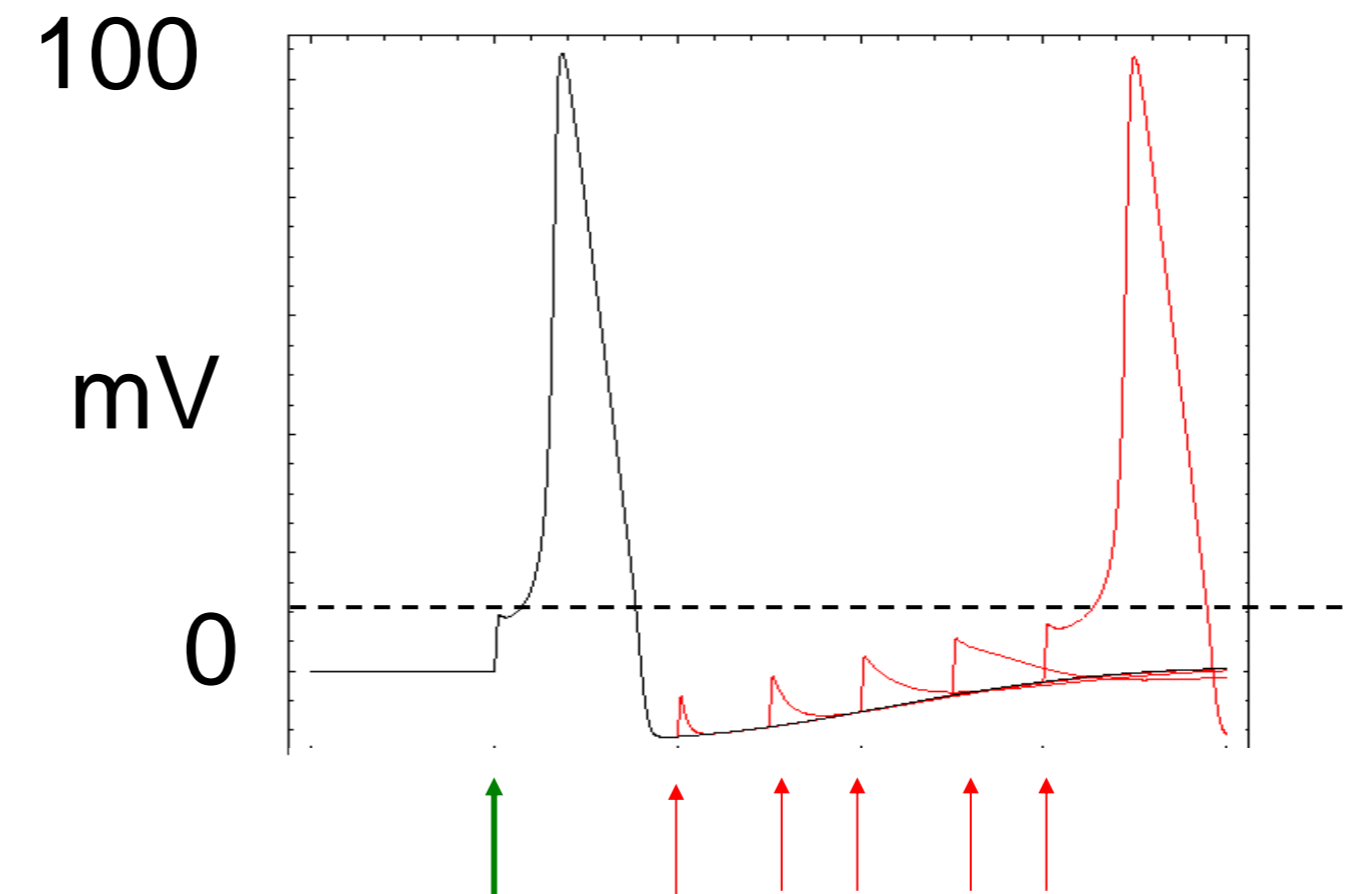
Where is the firing threshold?

Action potential



Strong stimulus

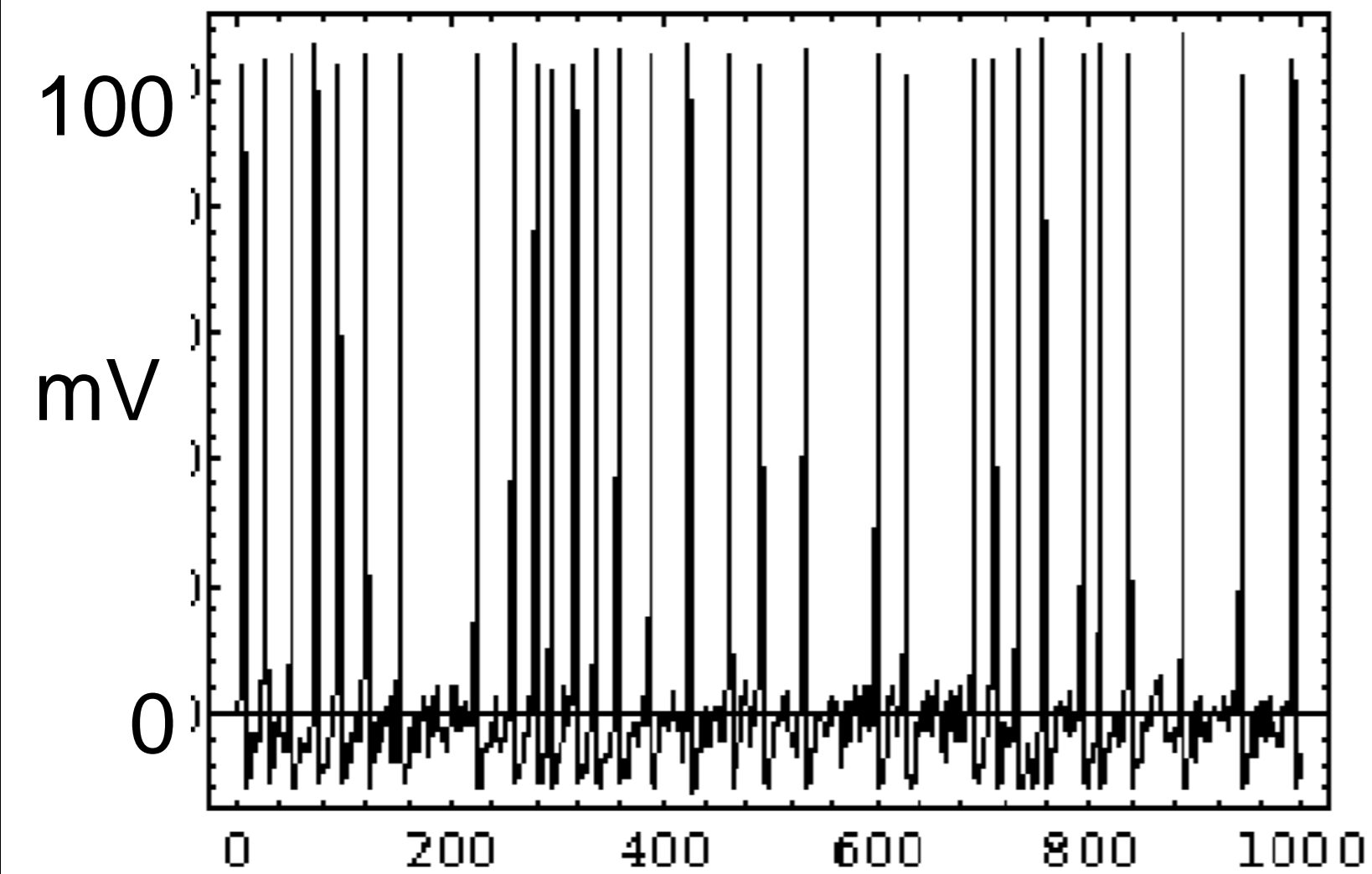
refractoriness




Strong stimuli

Refractoriness! Harder to elicit a second spike

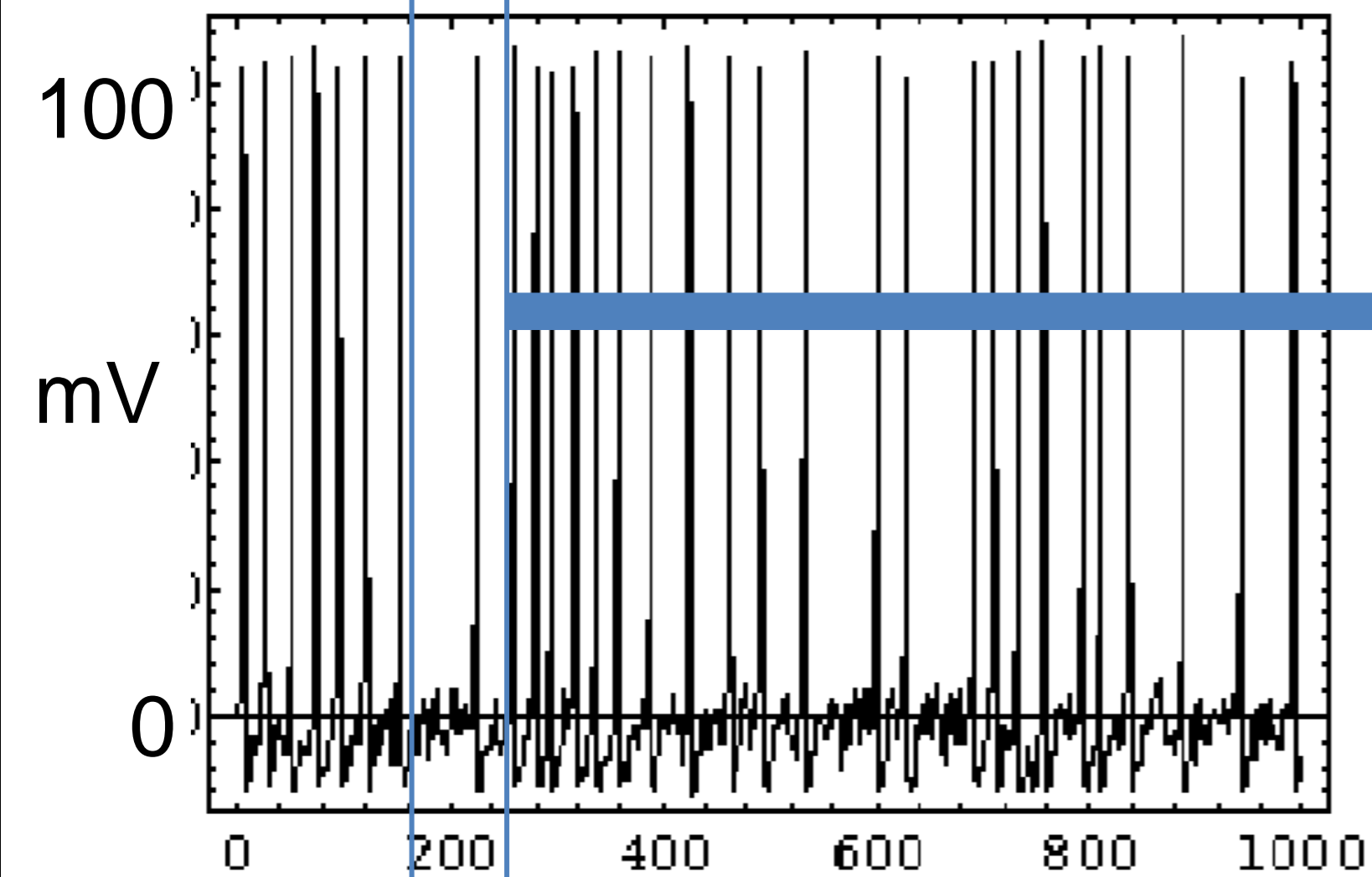
Neuronal Dynamics – 2.4. Simulations of the HH model



$I(t)$ 

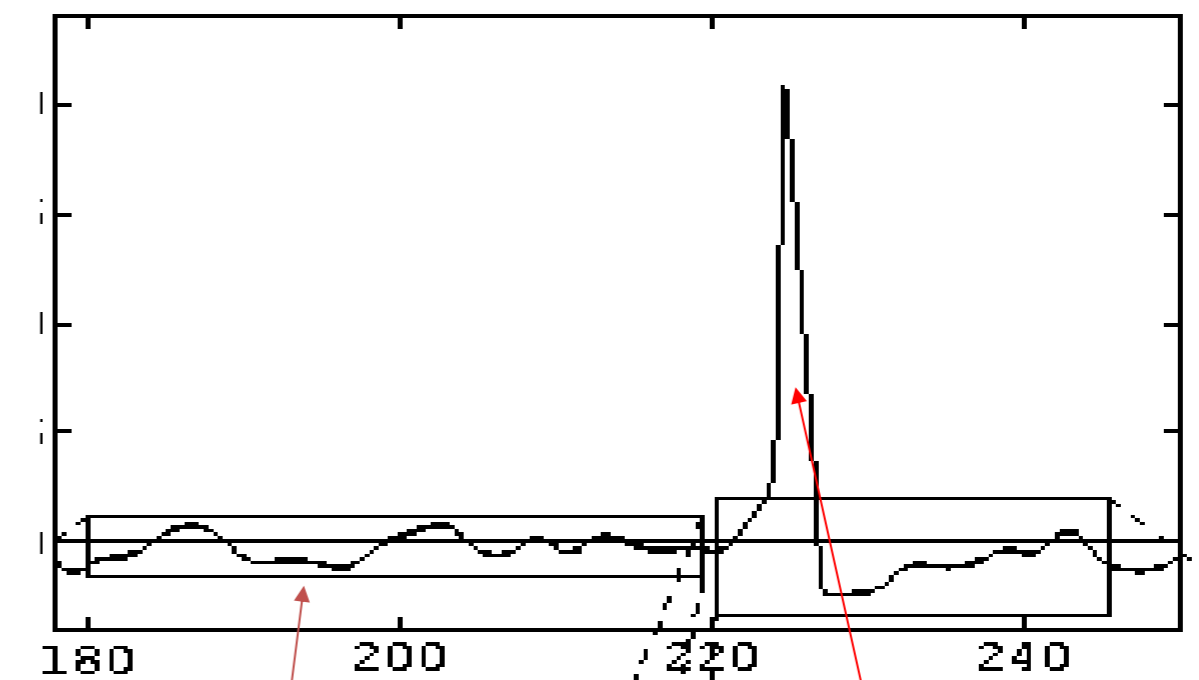
Stimulation with
time-dependent
input current

Neuronal Dynamics – 2.4. Simulations of the HH model



$I(t)$

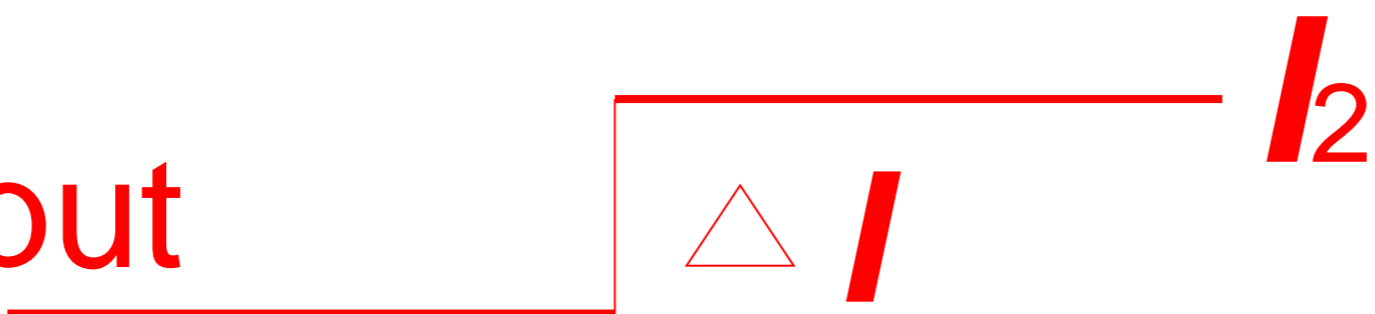
mV

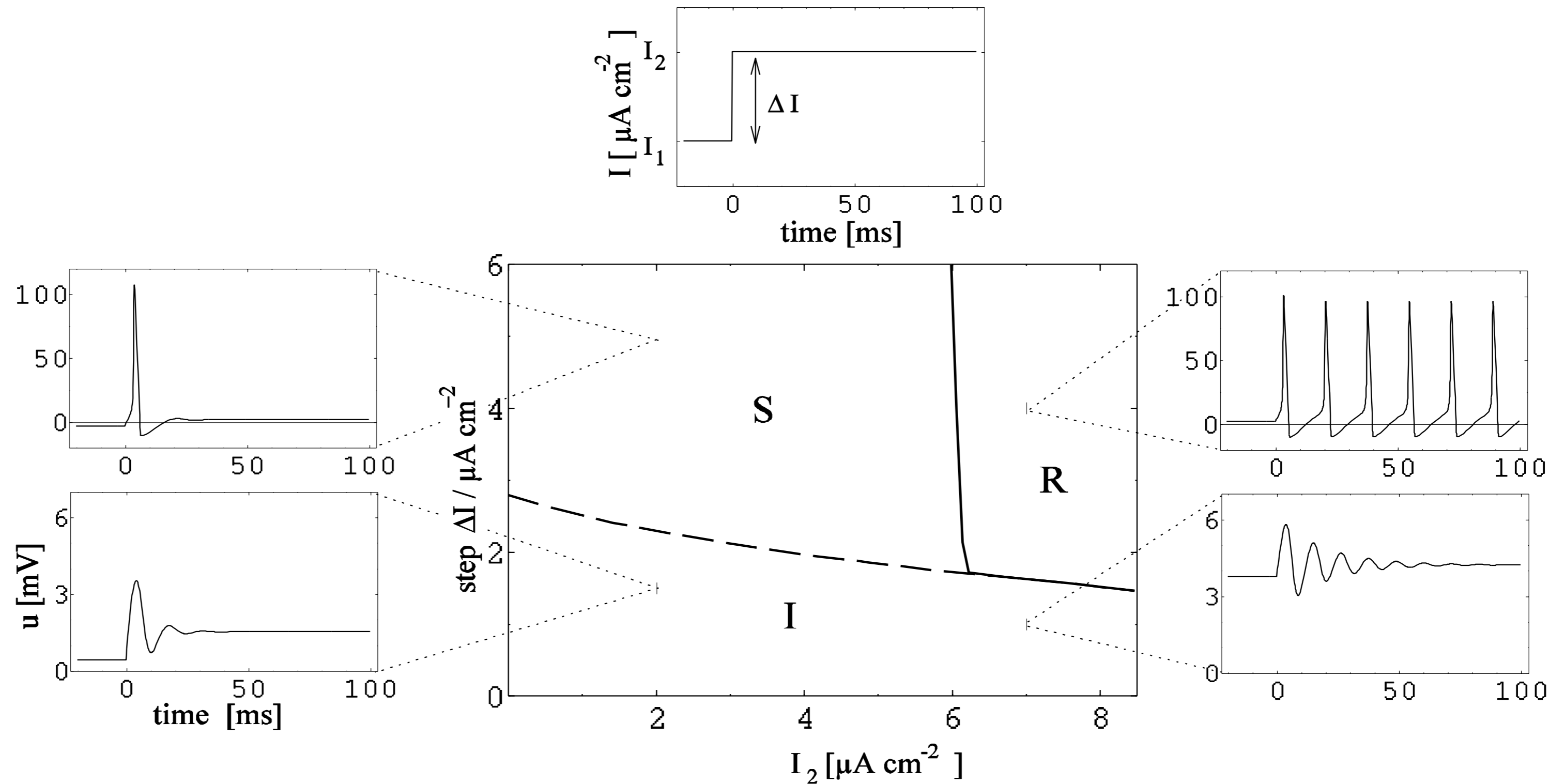


Subthreshold
response

Spike

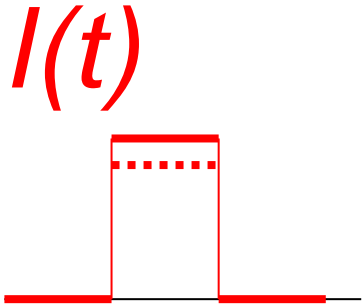
Neuronal Dynamics – 2.4. Threshold in HH model

Step current input 

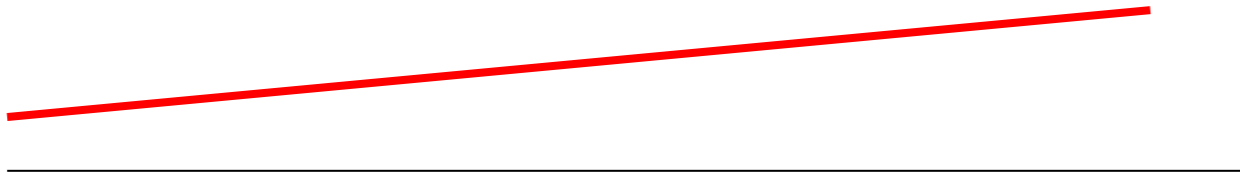


Neuronal Dynamics – 2.4. Threshold in HH model

Where is the firing threshold?

pulse input 

step input 

ramp input 

There is no threshold

- no current threshold
- no voltage threshold

‘effective’ threshold

- depends on typical input

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

Neuronal Dynamics – 2.4. Type I and Type II

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

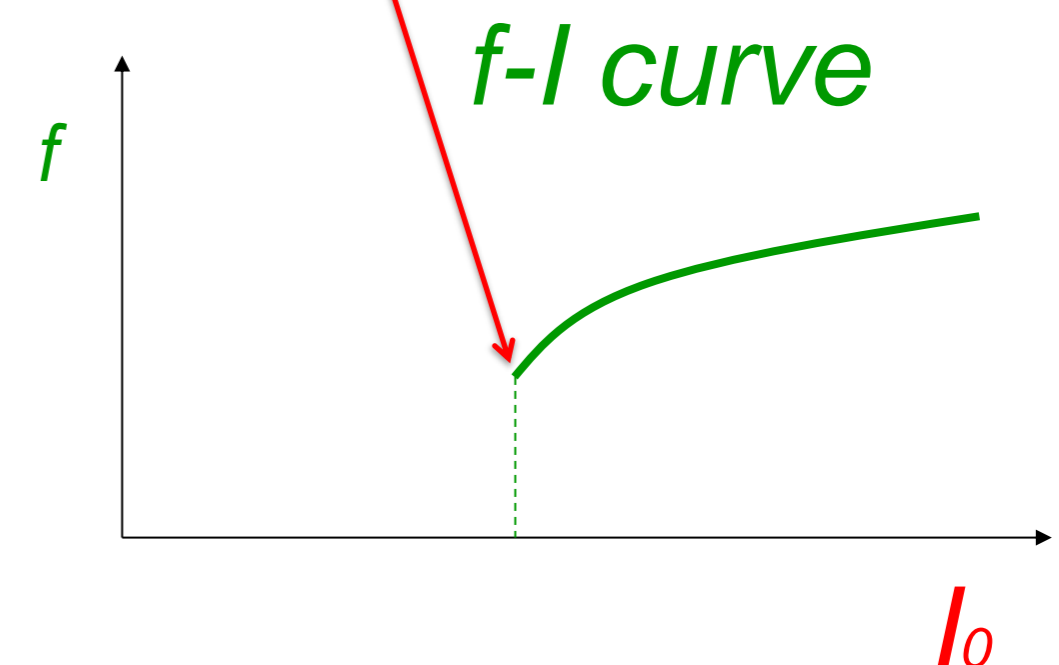
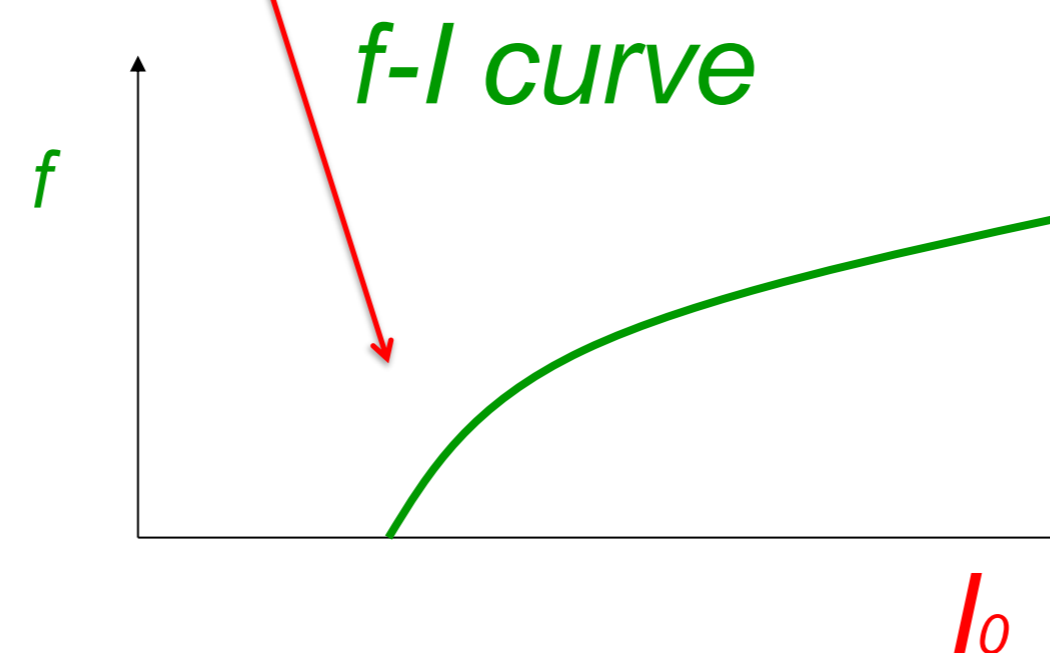
Hodgkin-Huxley model
with standard parameters
(giant axon of squid)

Response at firing threshold?

Type I

type II

ramp input/
constant input



Neuronal Dynamics – 2.4. Hodgkin-Huxley model

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

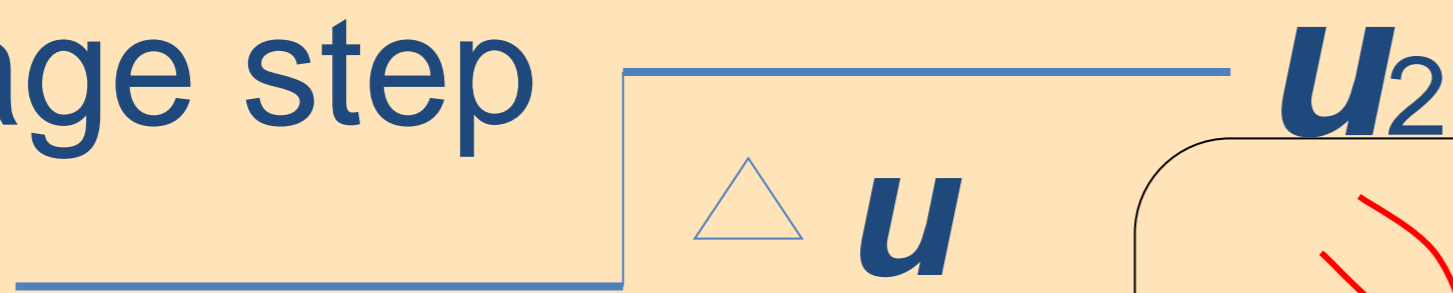
Giant axon of the squid

→ cortical neurons

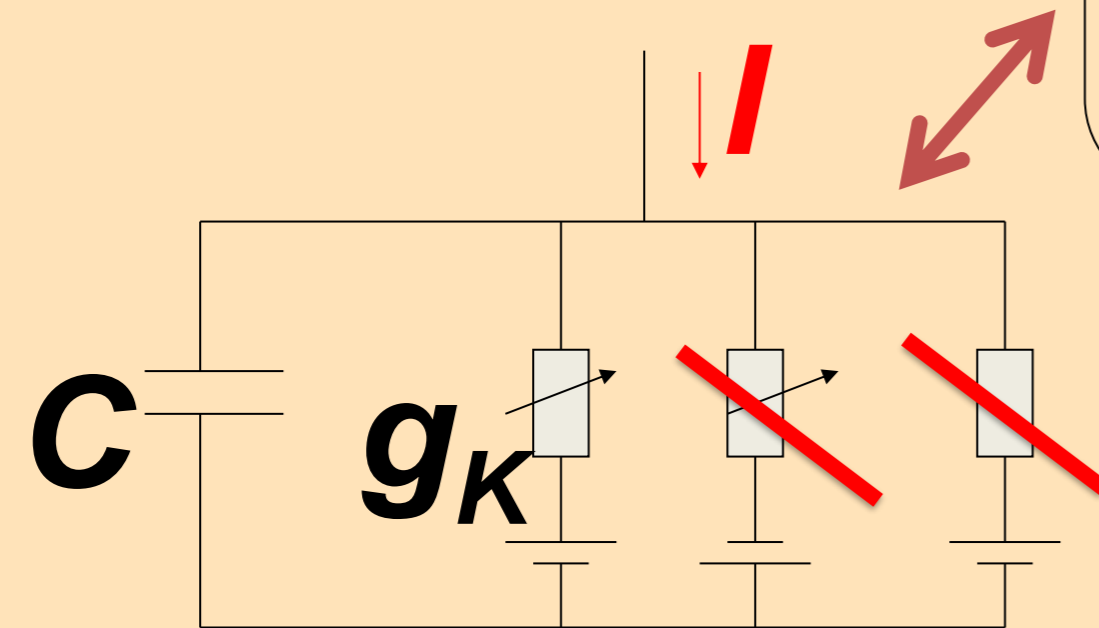
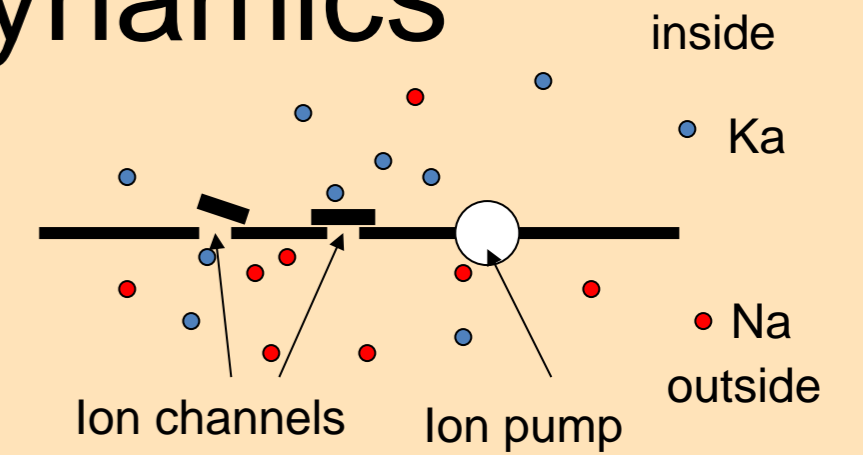
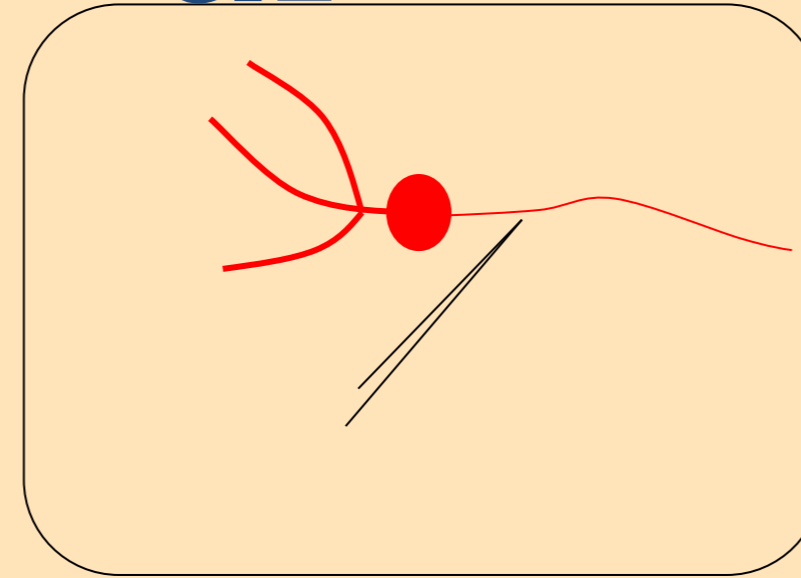
- Change of parameters
- More ion channels
- Same framework

Exercise – 2.4. Hodgkin-Huxley model – ion channel

voltage step



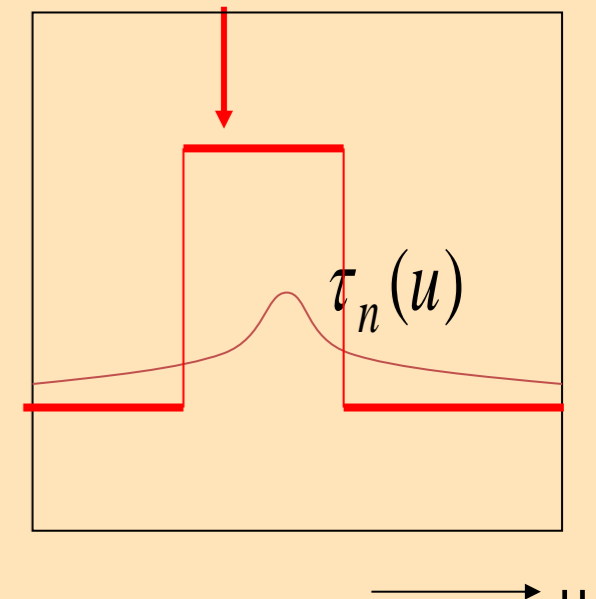
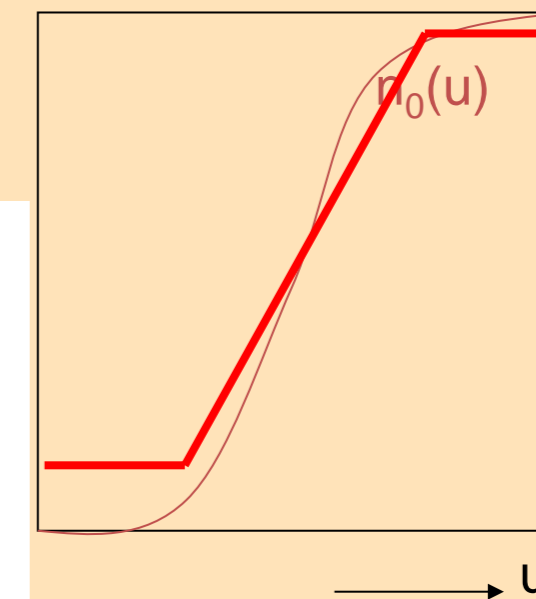
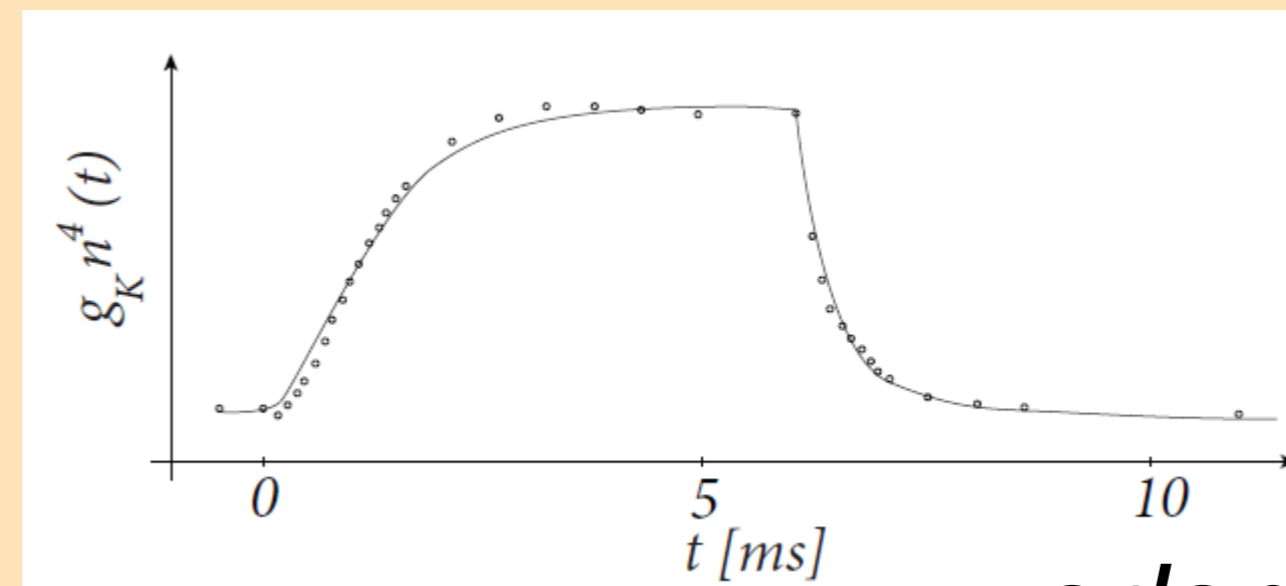
Determine ion channel dynamics



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

stimulus

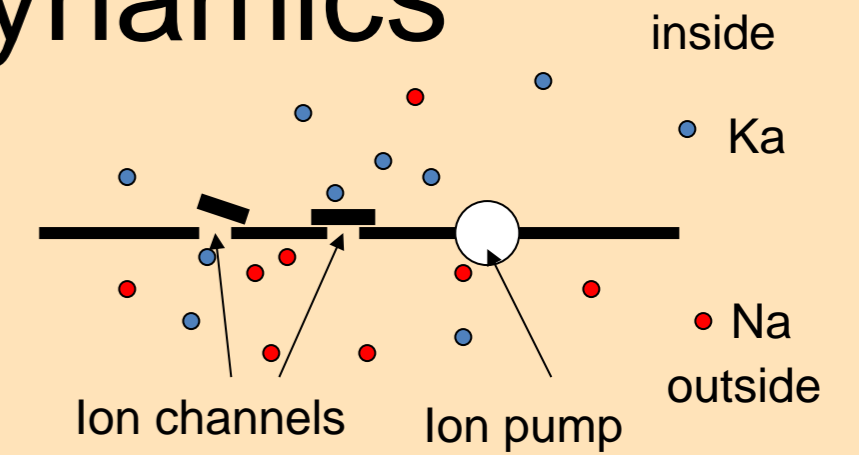
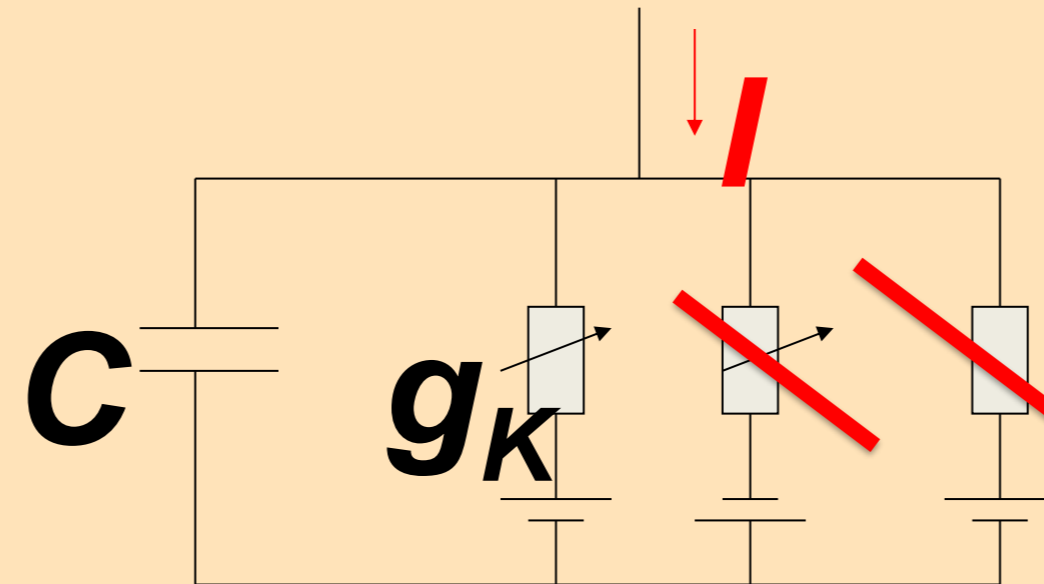
apply voltage step



adapted from
Hodgkin&Huxley 1952

Exercise – 2.4. Hodgkin-Huxley model – ion channel

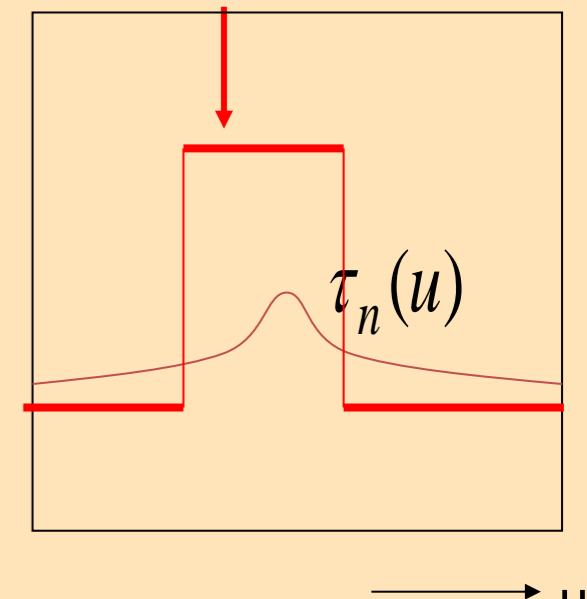
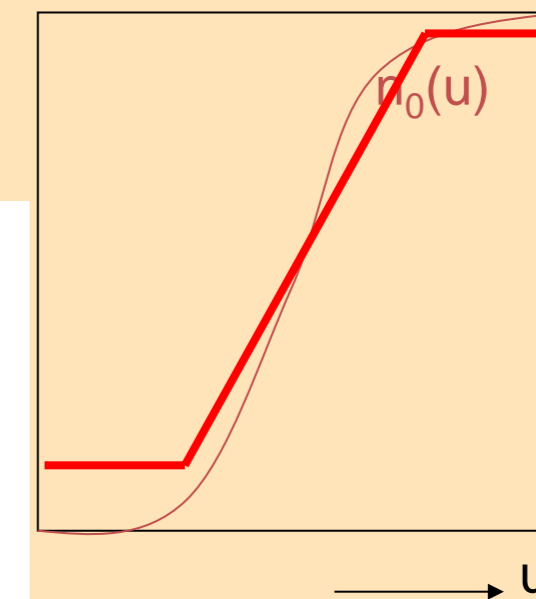
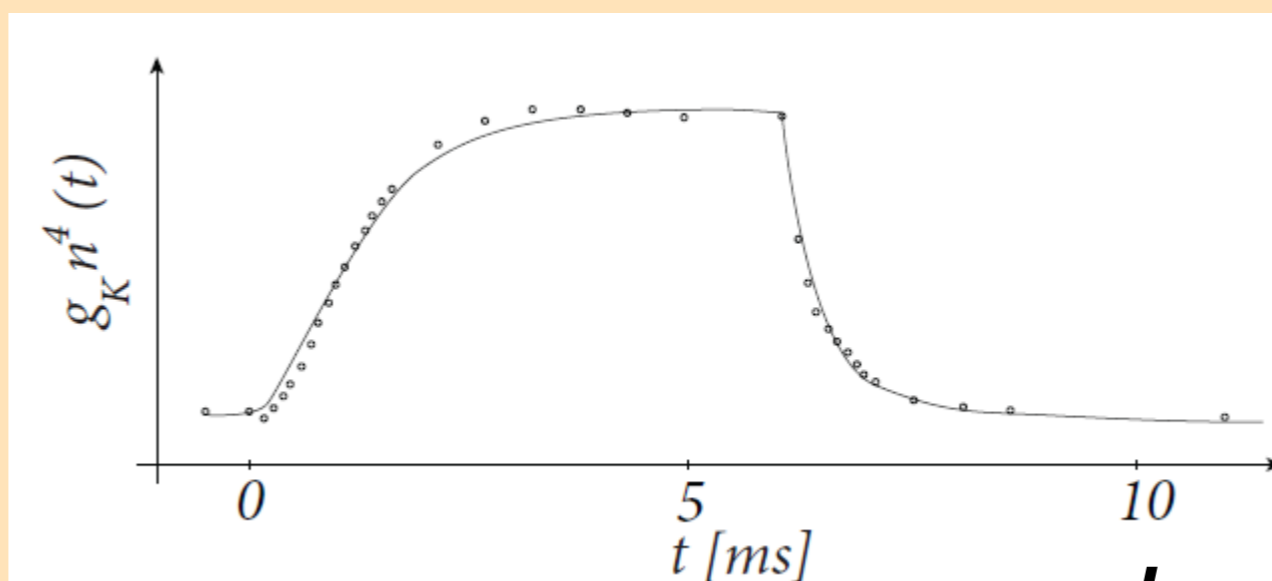
Determine ion channel dynamics



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

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

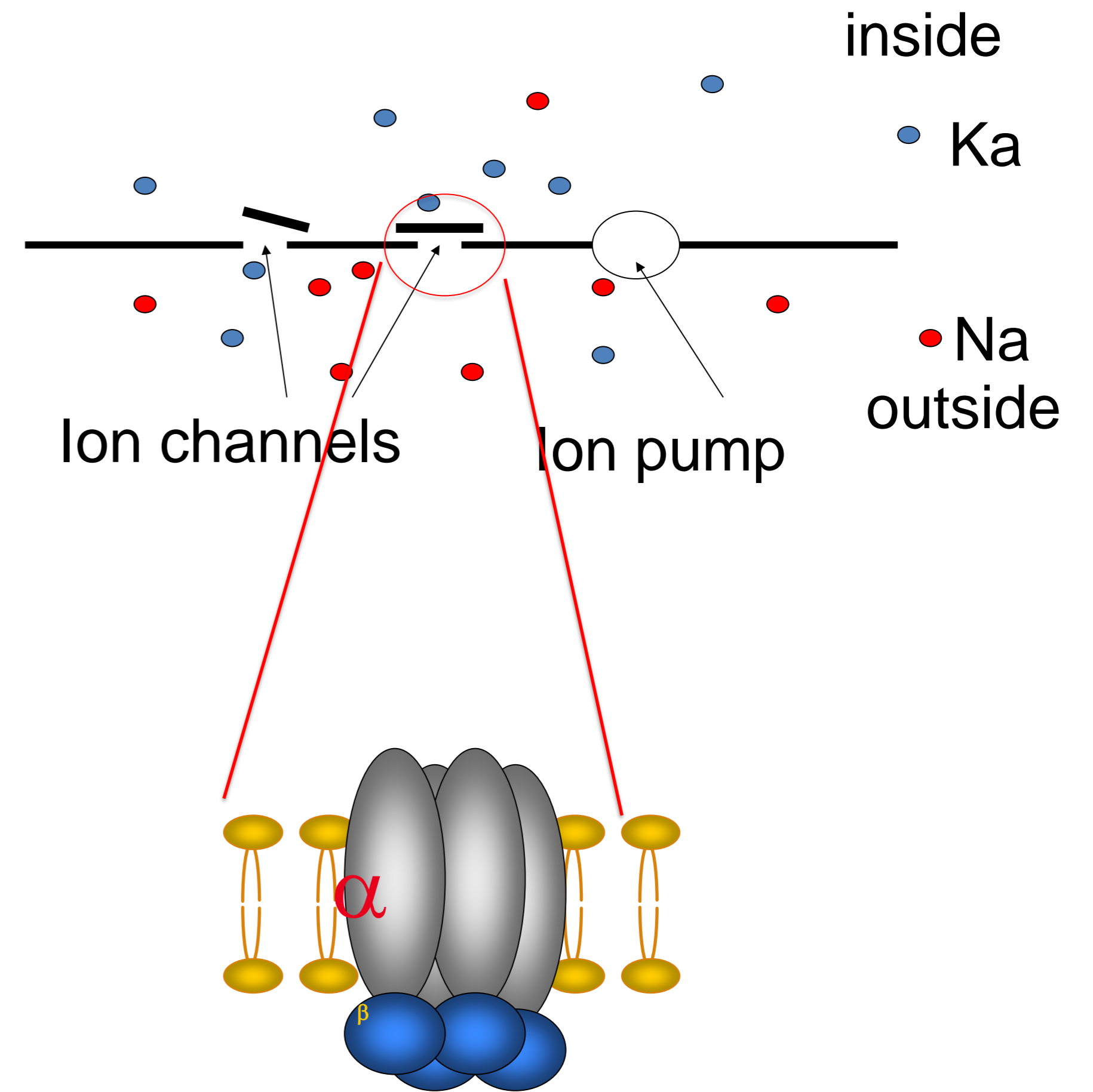
✓ 2.4 Threshold in the Hodgkin-Huxley Model

- where is the firing threshold?

2.5. Detailed biophysical models

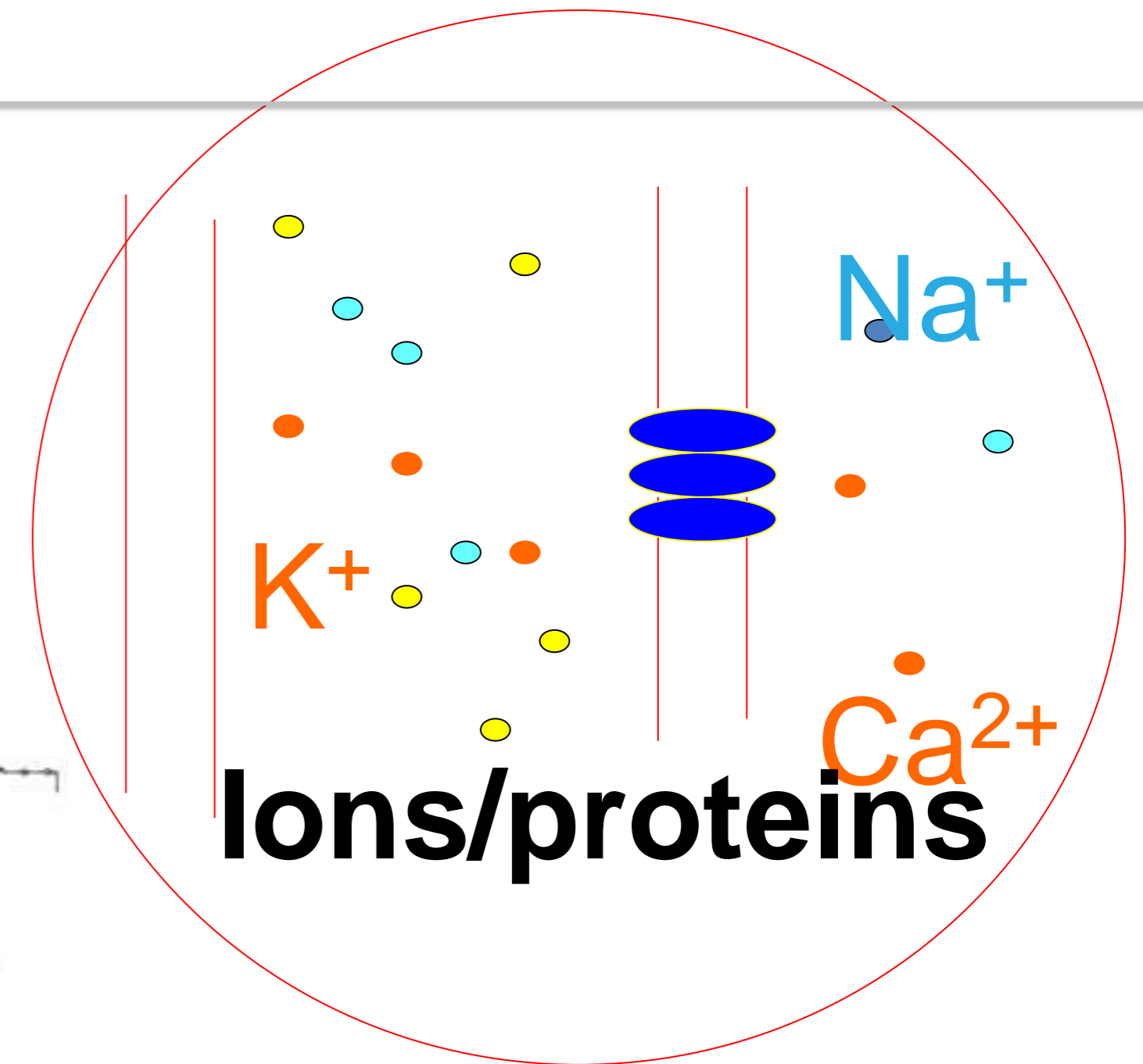
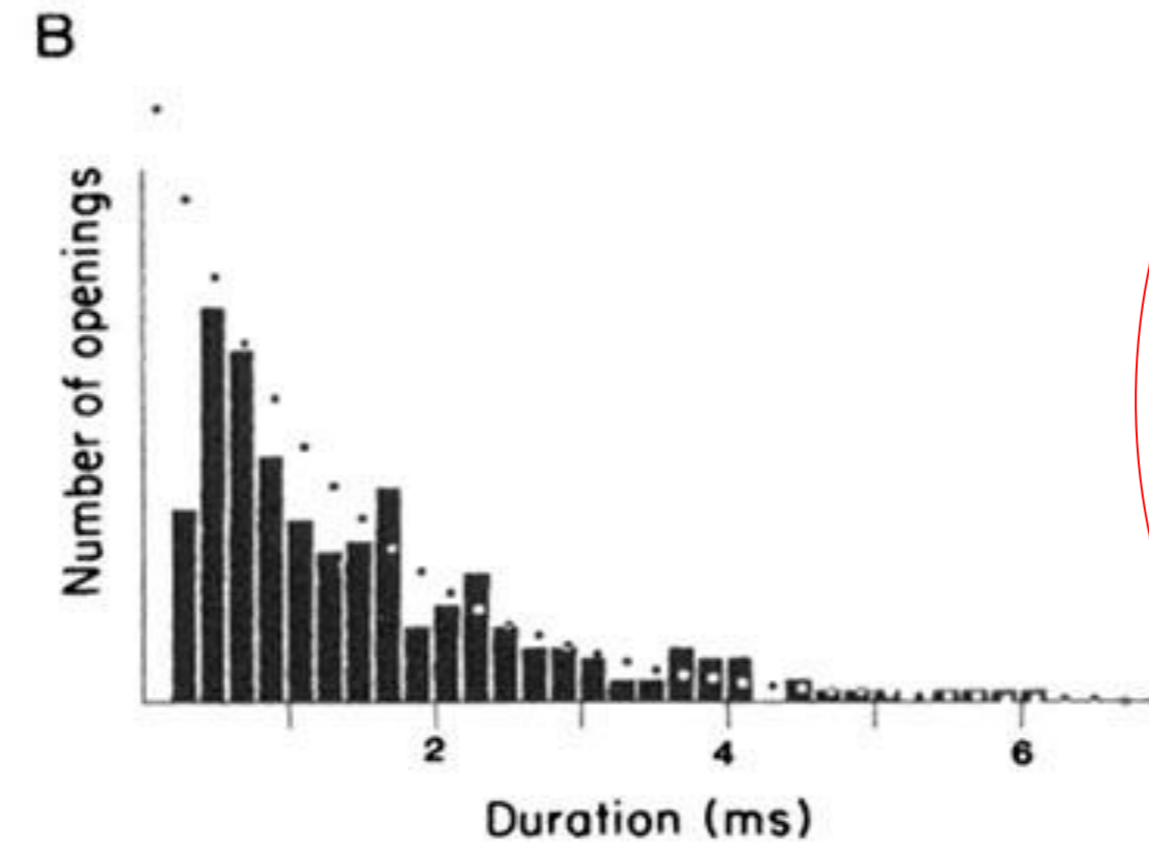
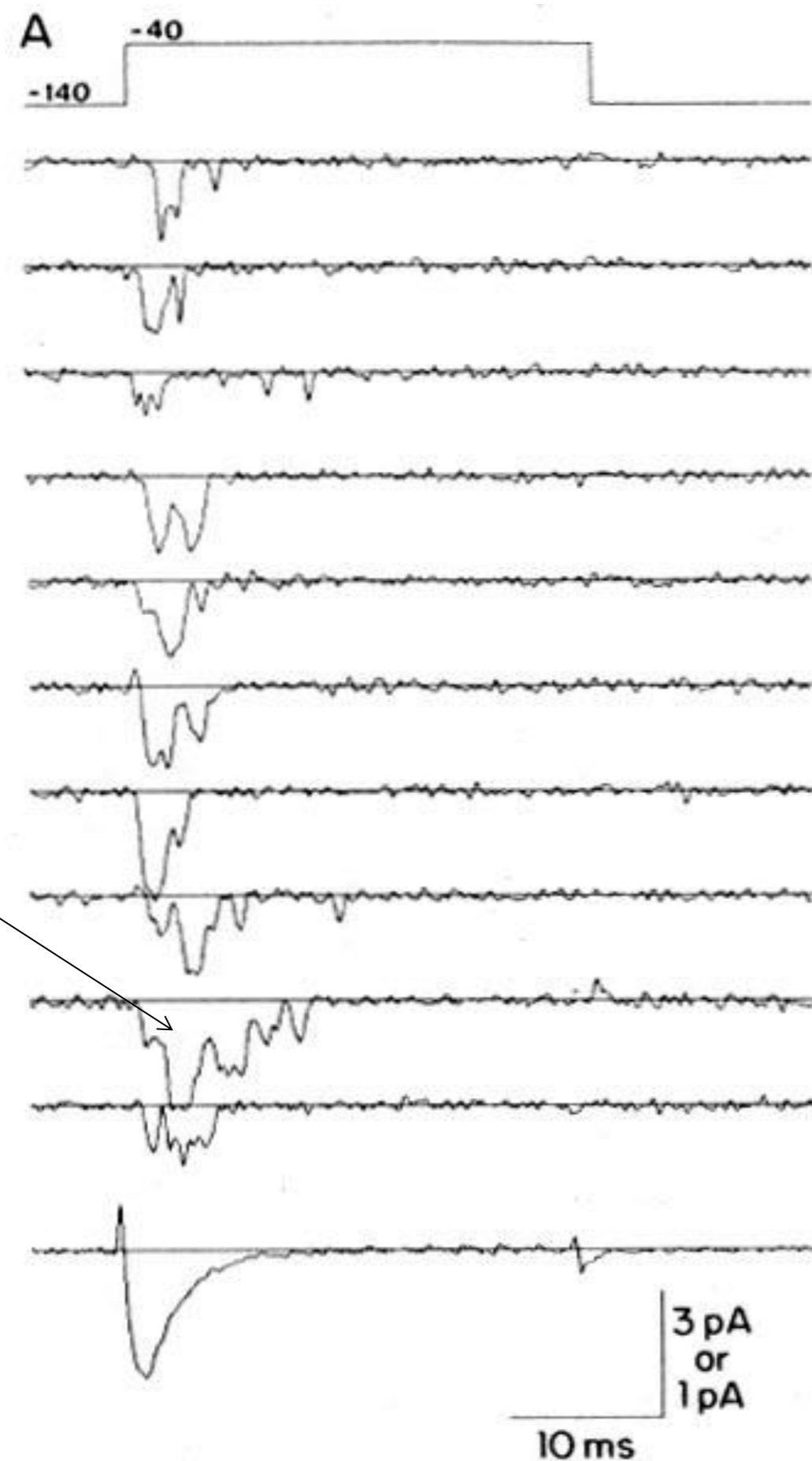
- the zoo of ion channels

Neuronal Dynamics – 2.5 Biophysical models



Neuronal Dynamics – 2.5 Ion channels

Steps:
Different number
of channels



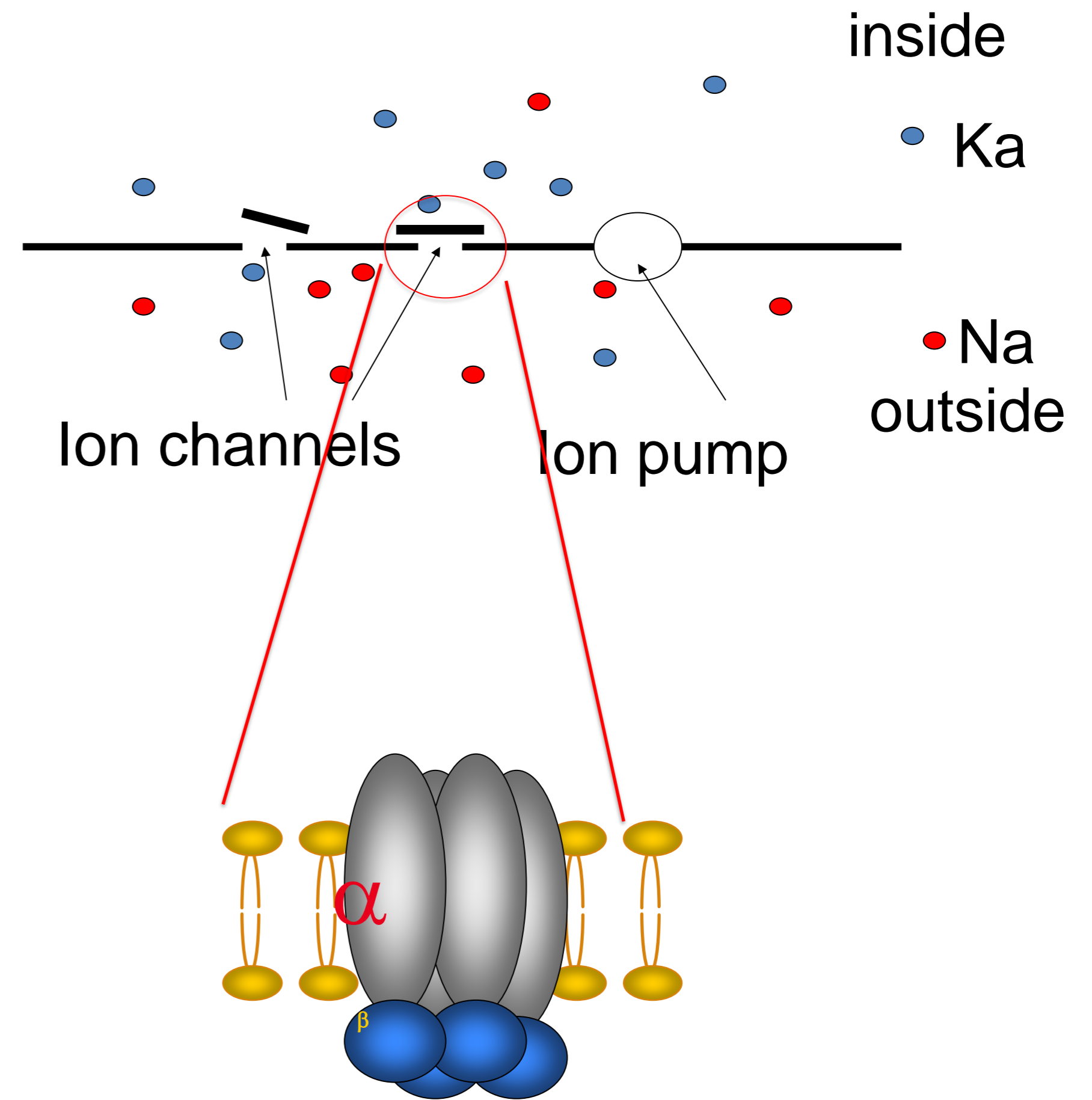
Na⁺ channel from rat heart (*Patlak and Ortiz 1985*)
A traces from a patch containing several channels.
Bottom: average gives current time course.
B. Opening times of single channel events

Neuronal Dynamics – 2.5 Biophysical models

*There are about 200
identified ion channels*

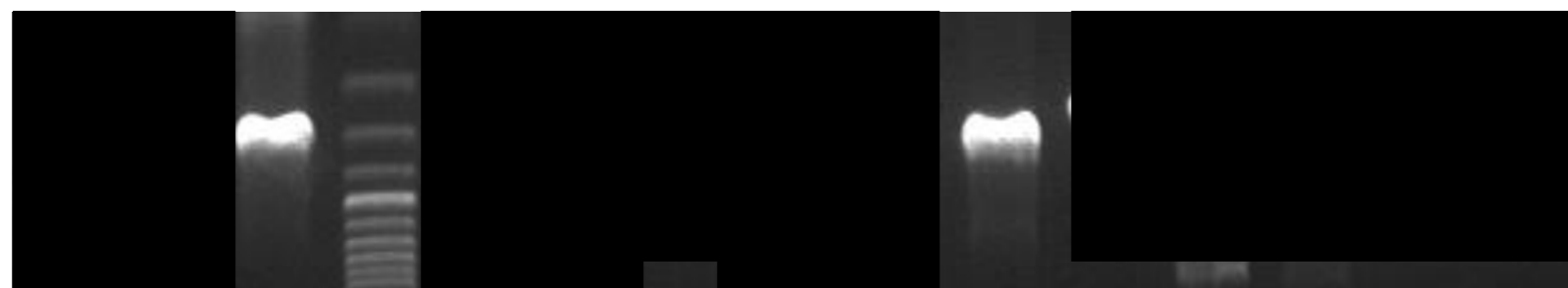
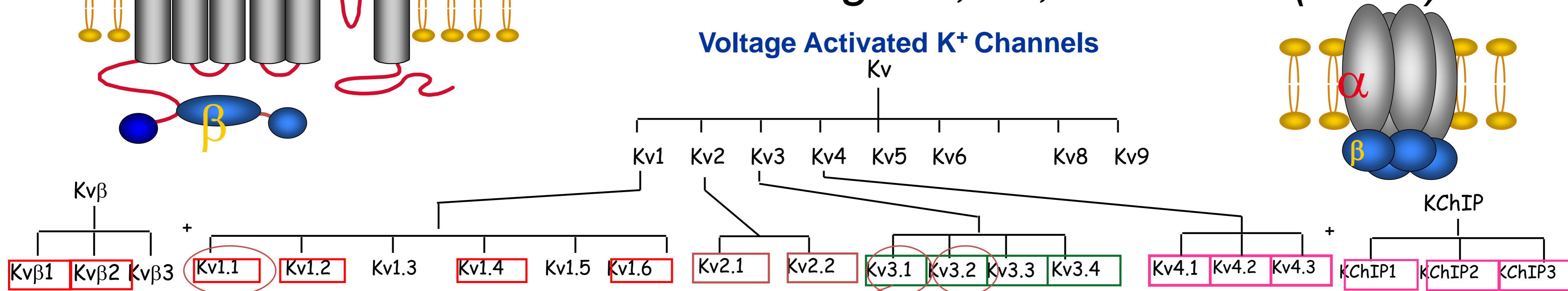
<http://channelpedia.epfl.ch/>

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

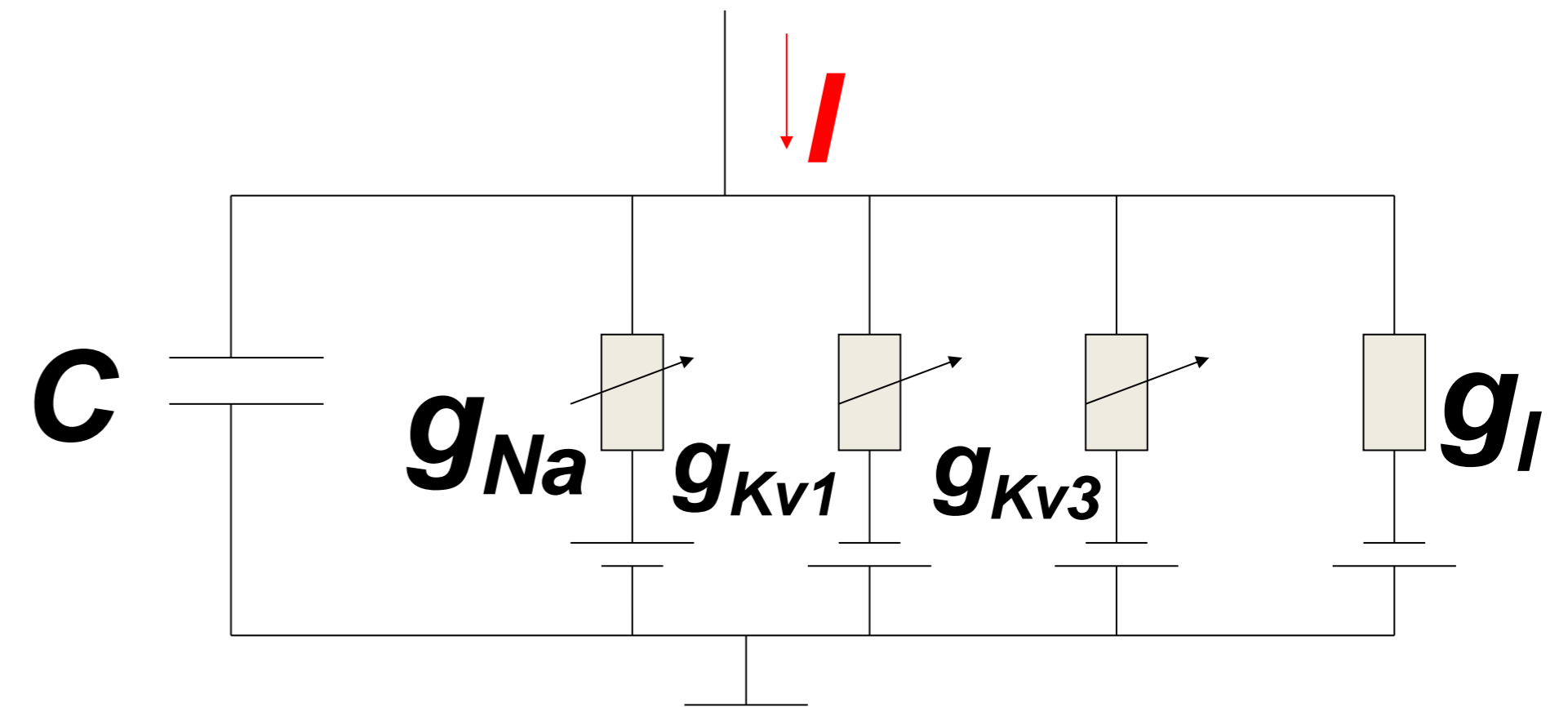


Ion Channels investigated in the study of *Toledo-Rodriguez, ..., Markram (2004)*

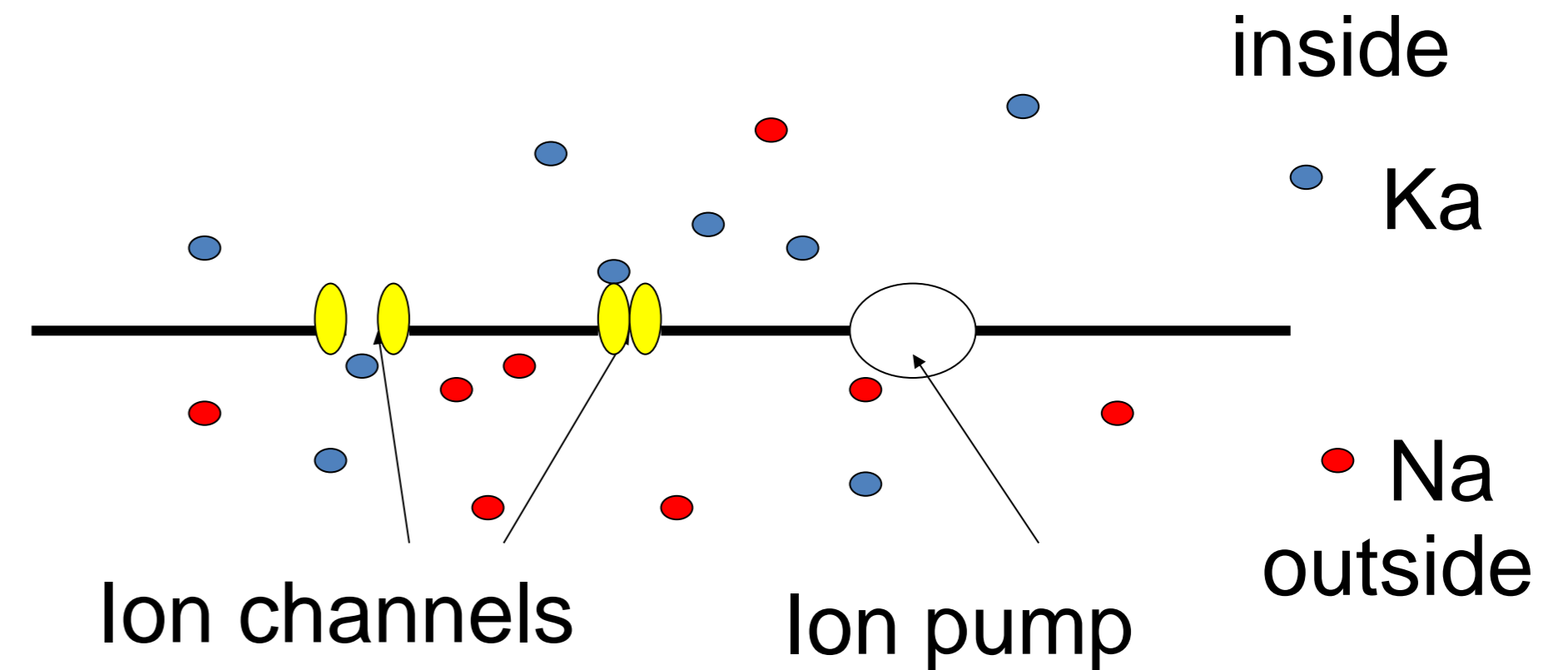
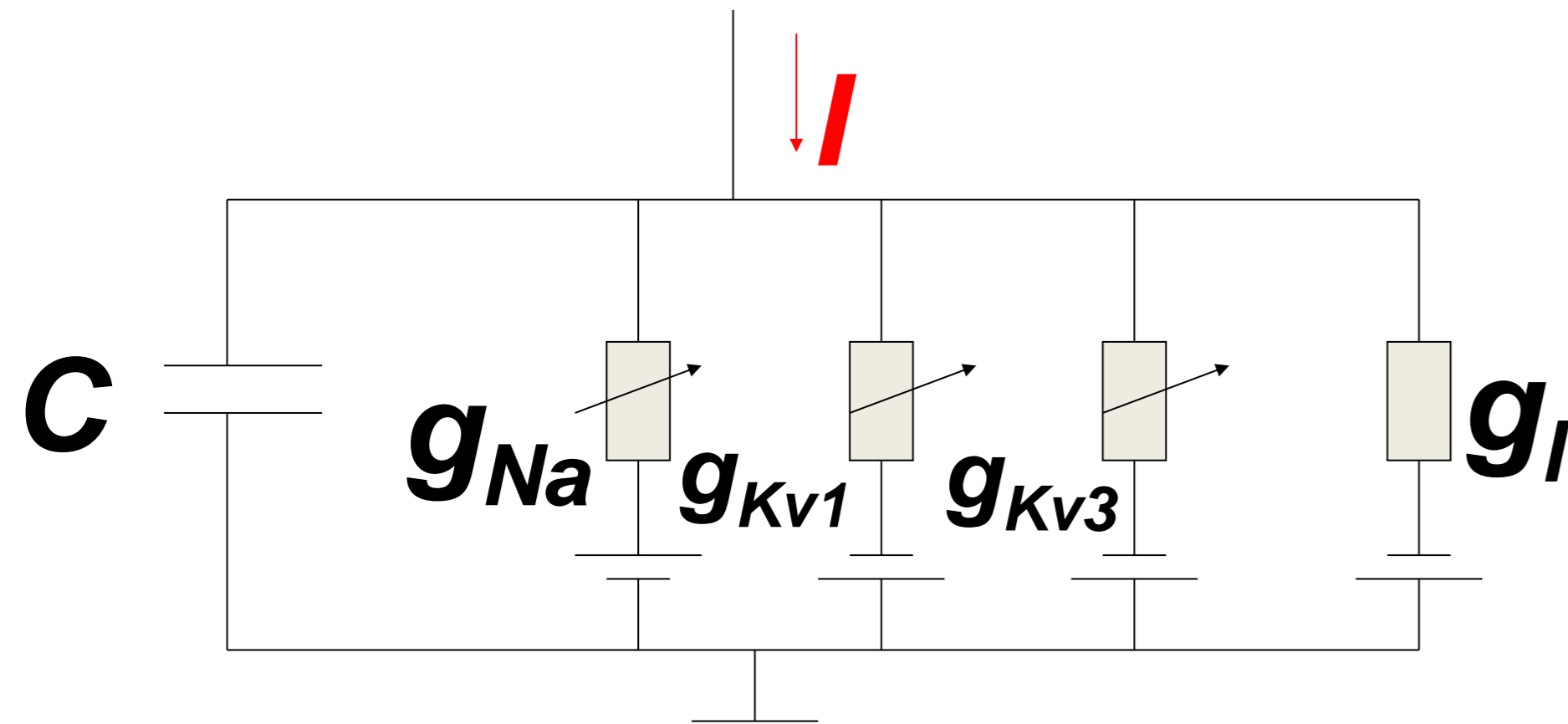
Voltage Activated K⁺ Channels



schematic mRNA
Expression profile



Model of a hypothetical neuron



$$C \frac{du}{dt} = - \underbrace{g_{Na} m^3 h (u - E_{Na})}_{I_{Na}} - \underbrace{g_{Kv1} n_{Kv1}^4 (u - E_K) - g_{Kv3} n_{Kv3}^2 (u - E_K)}_{I_K} - \underbrace{g_l (u - E_l)}_{I_{leak}} + \overset{\text{stimulus}}{I(t)}$$

How many parameters per channel?

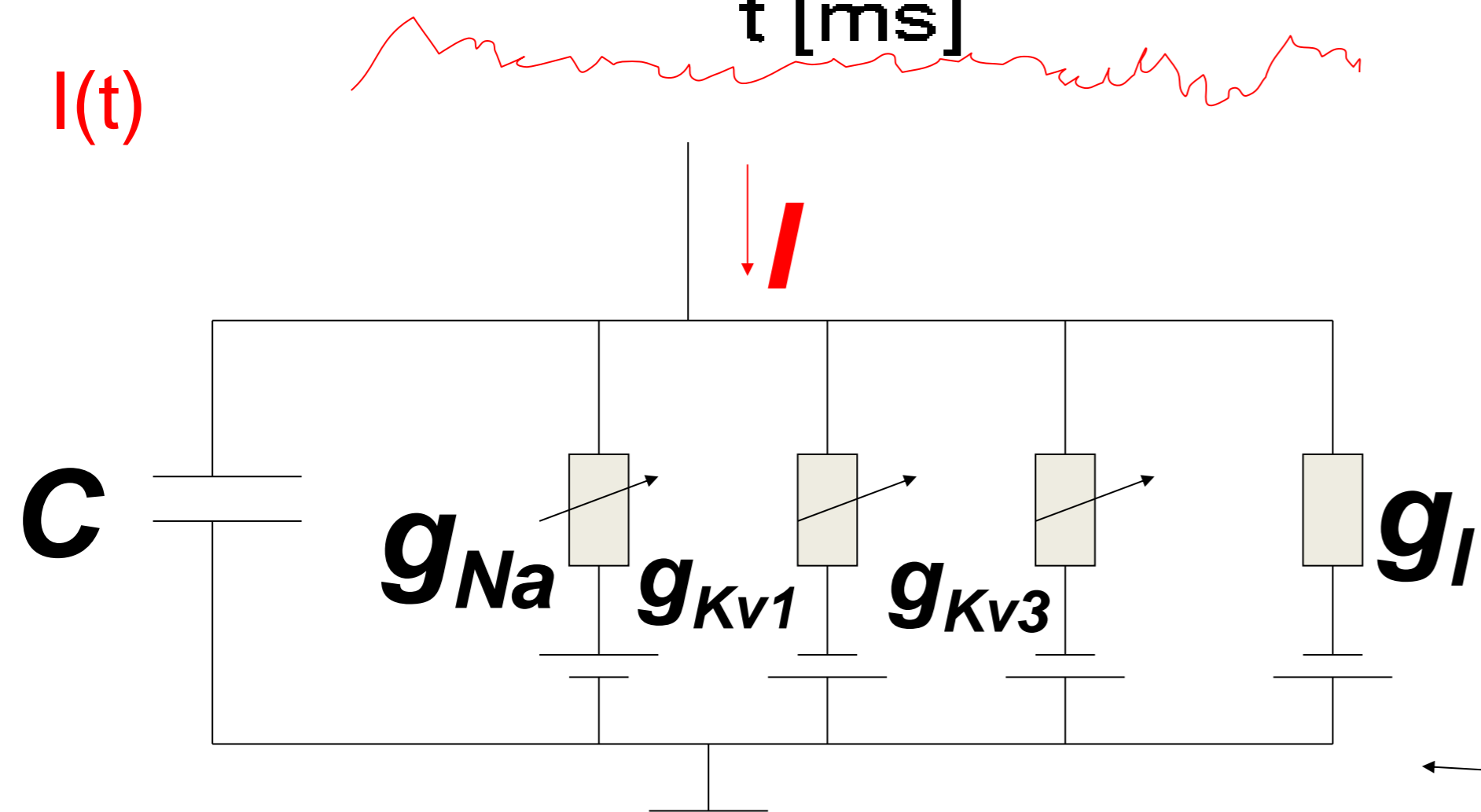
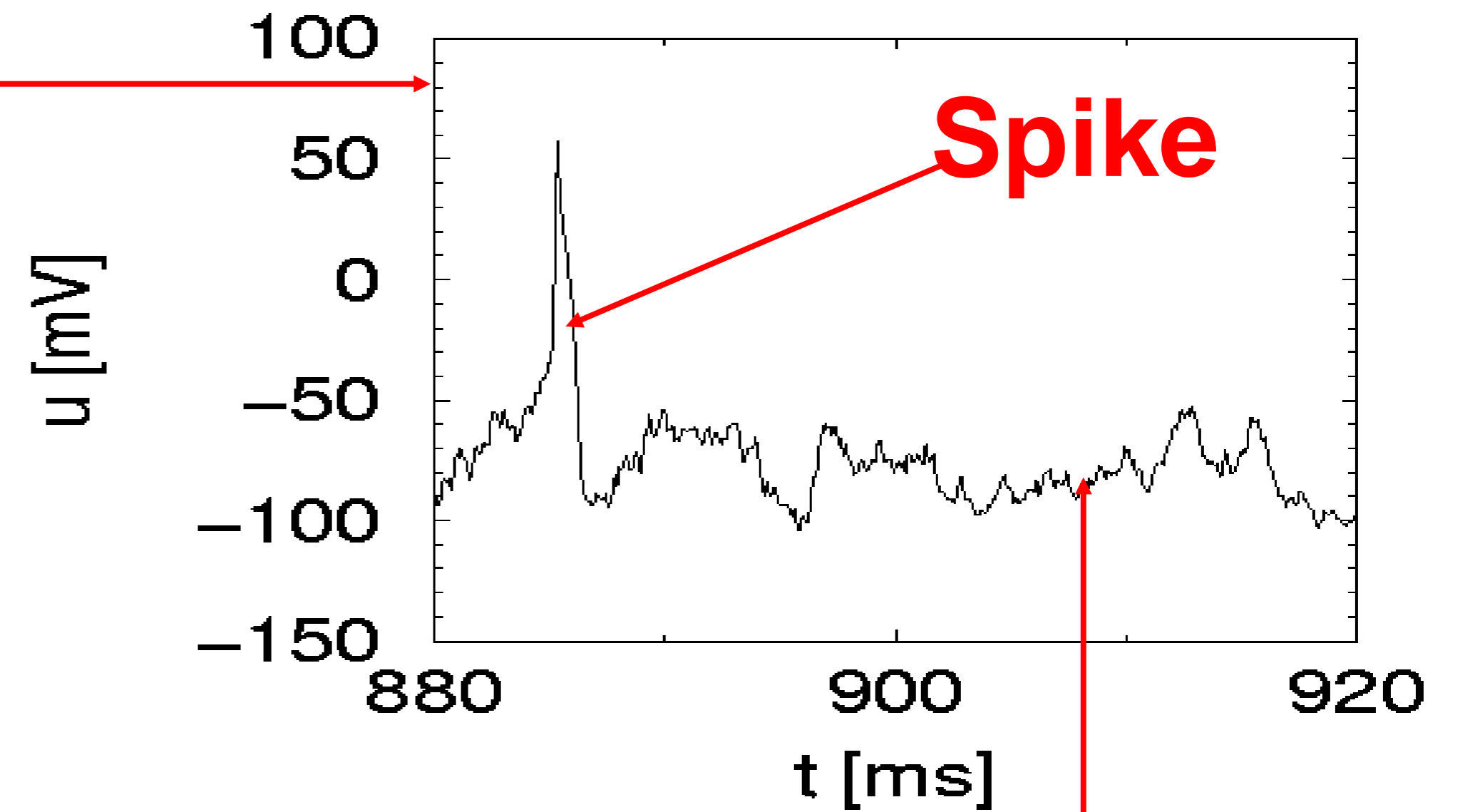
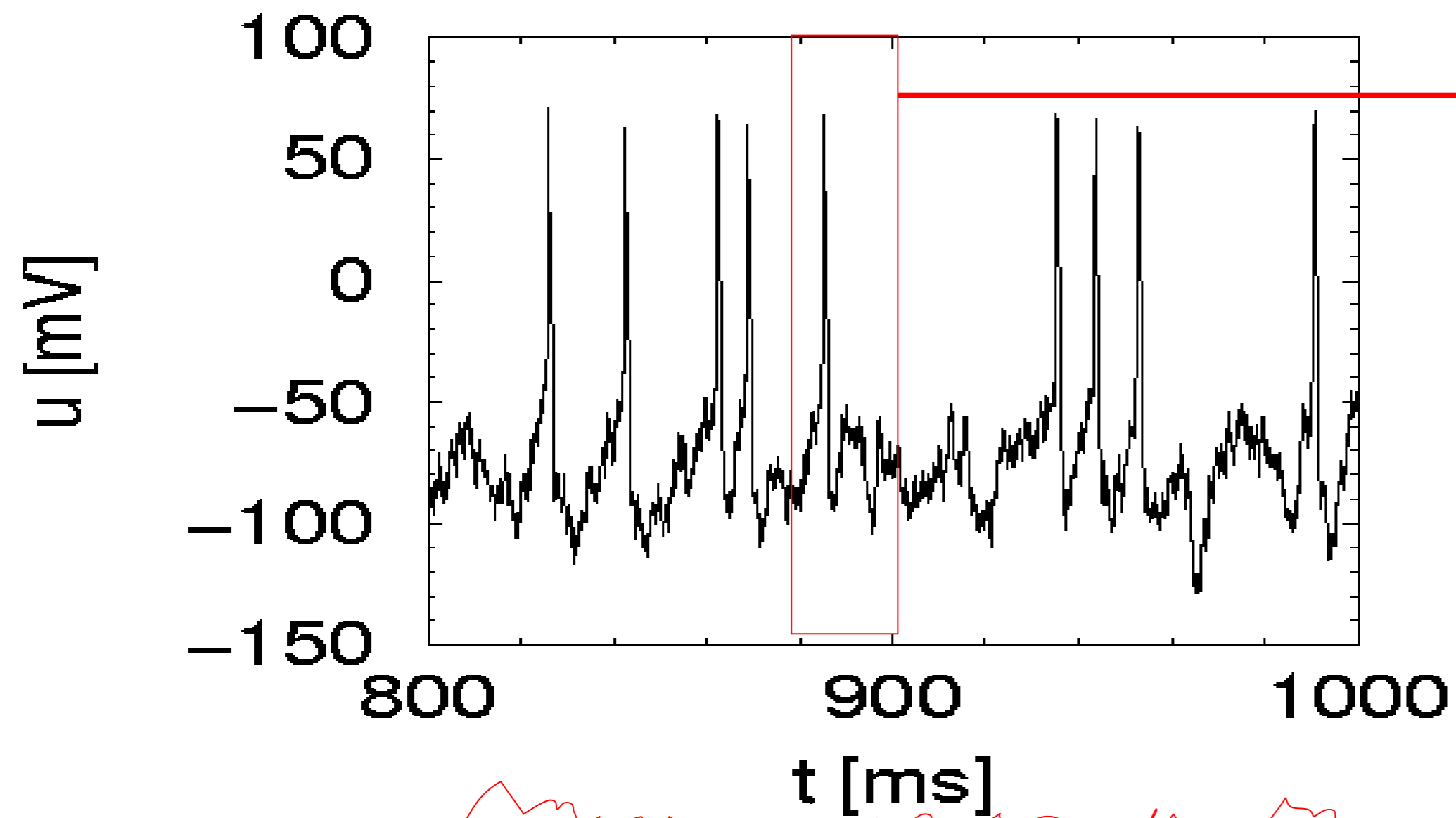
$$\frac{dm}{dt} = \frac{h - m}{\tau_h(u)} - \frac{m - m_0(u)}{\tau_m(u)}$$

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

Erisir et al, 1999

Hodgkin and Huxley, 1952

Model of a hypothetical neuron



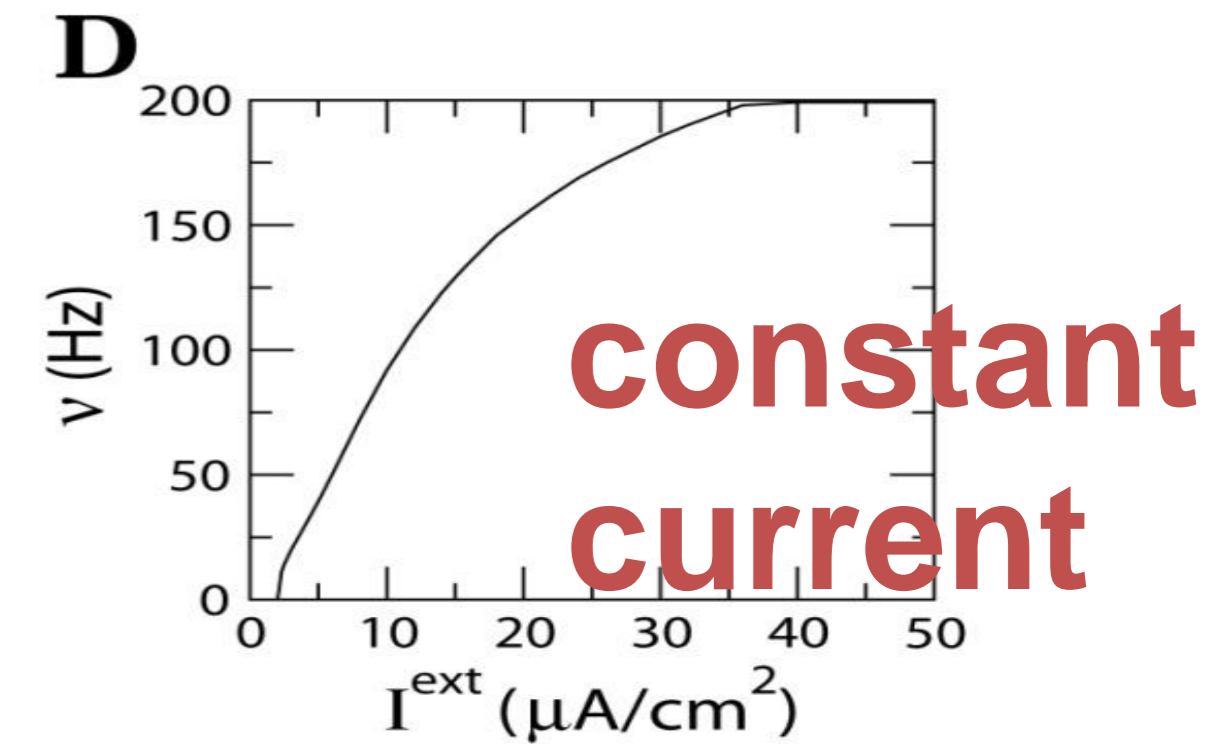
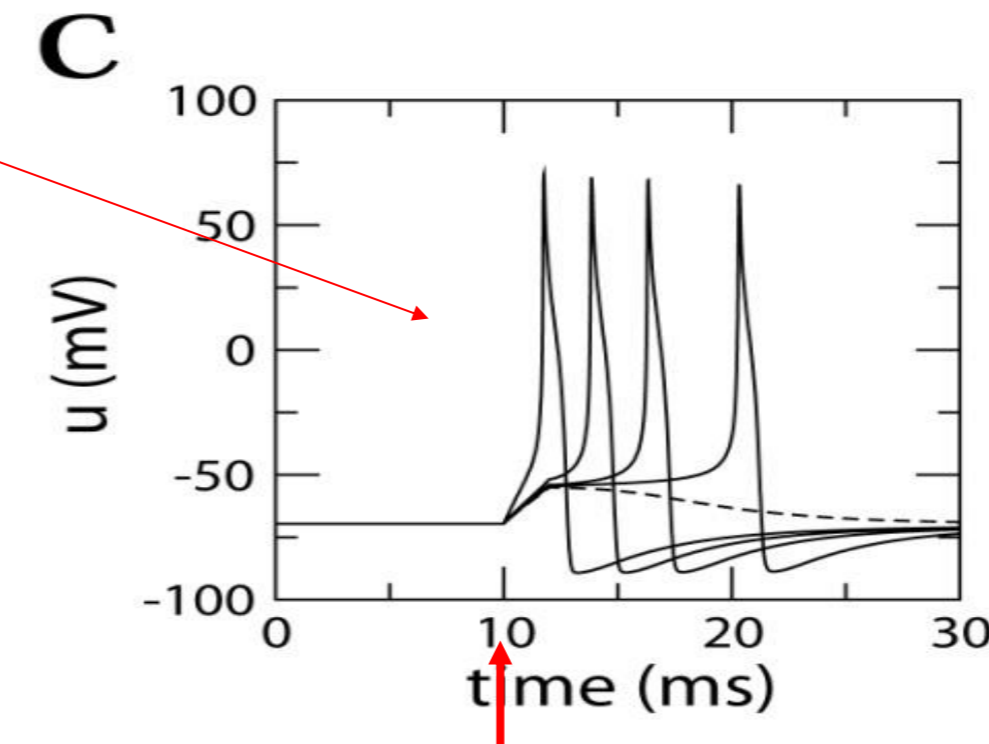
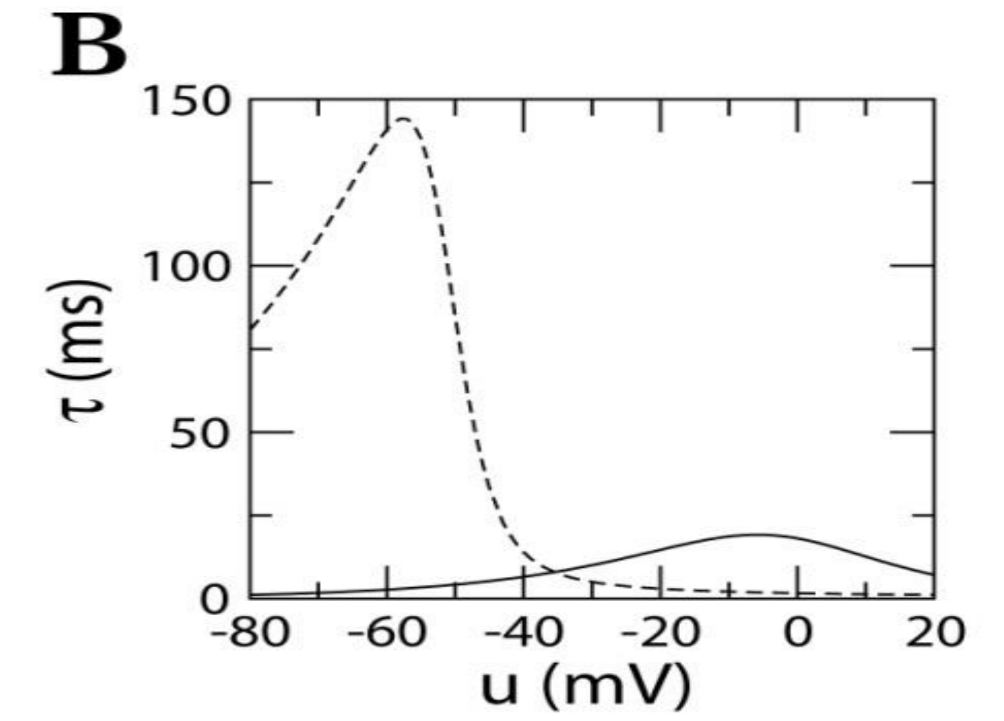
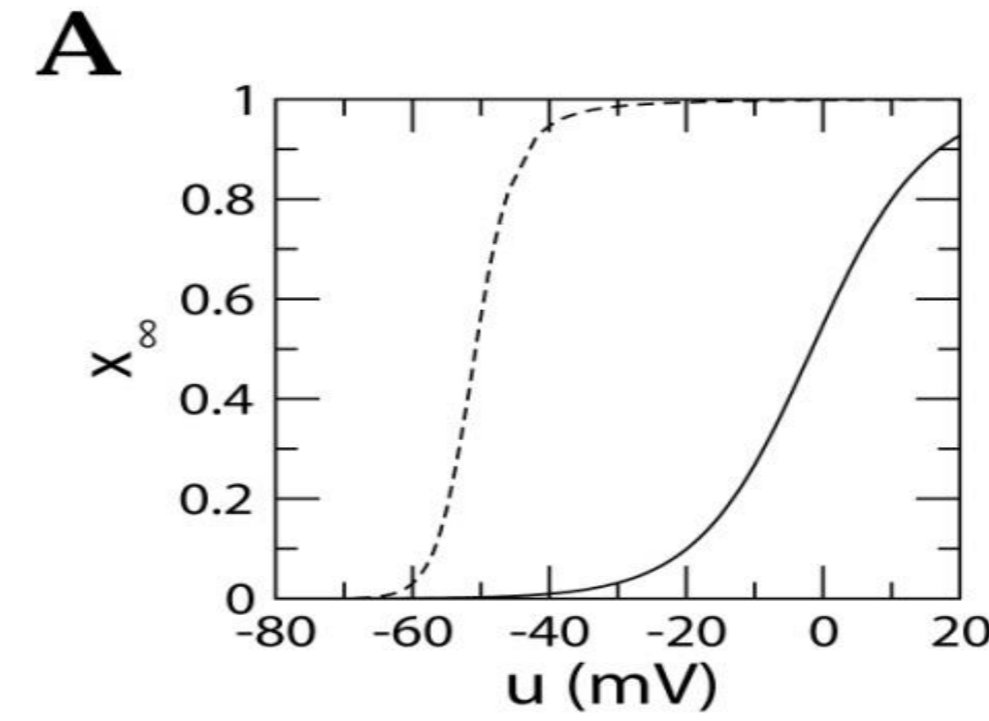
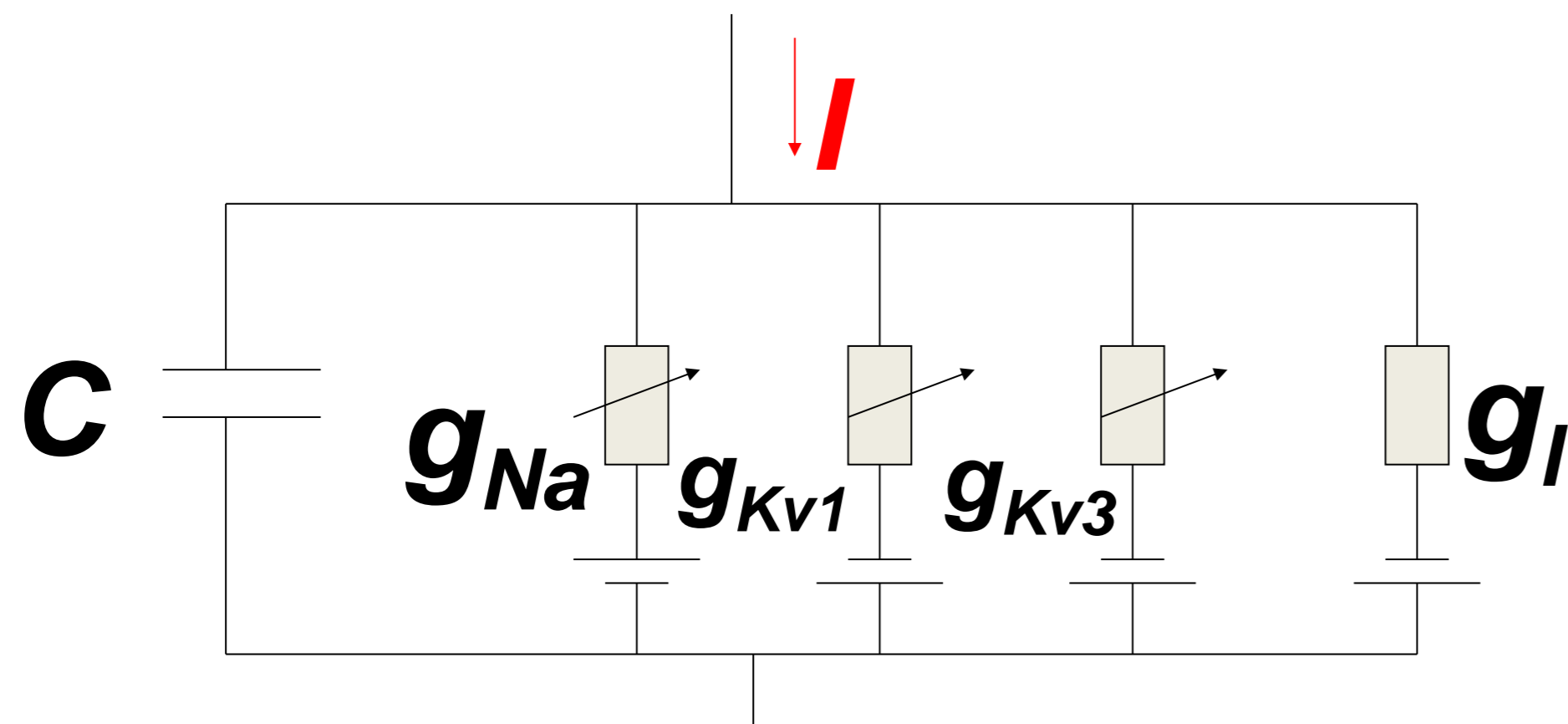
Detailed model, based
on ion channels

Model of a hypothetical neuron (type I)

Current pulse



Biophysical model, based
on ion channels

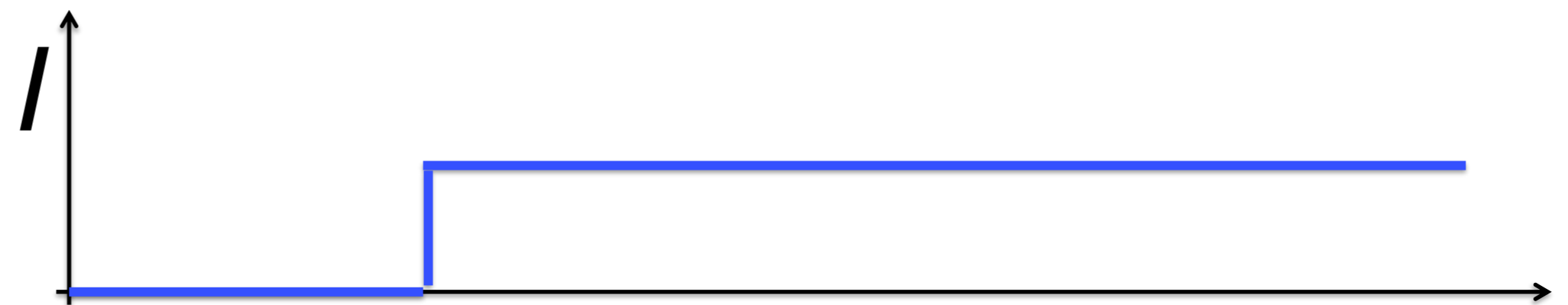


- Delayed AP initiation
 - Smooth f - I curve
- type I neuron**

Neuronal Dynamics – 2.5 Adaptation

Functional roles of channels?

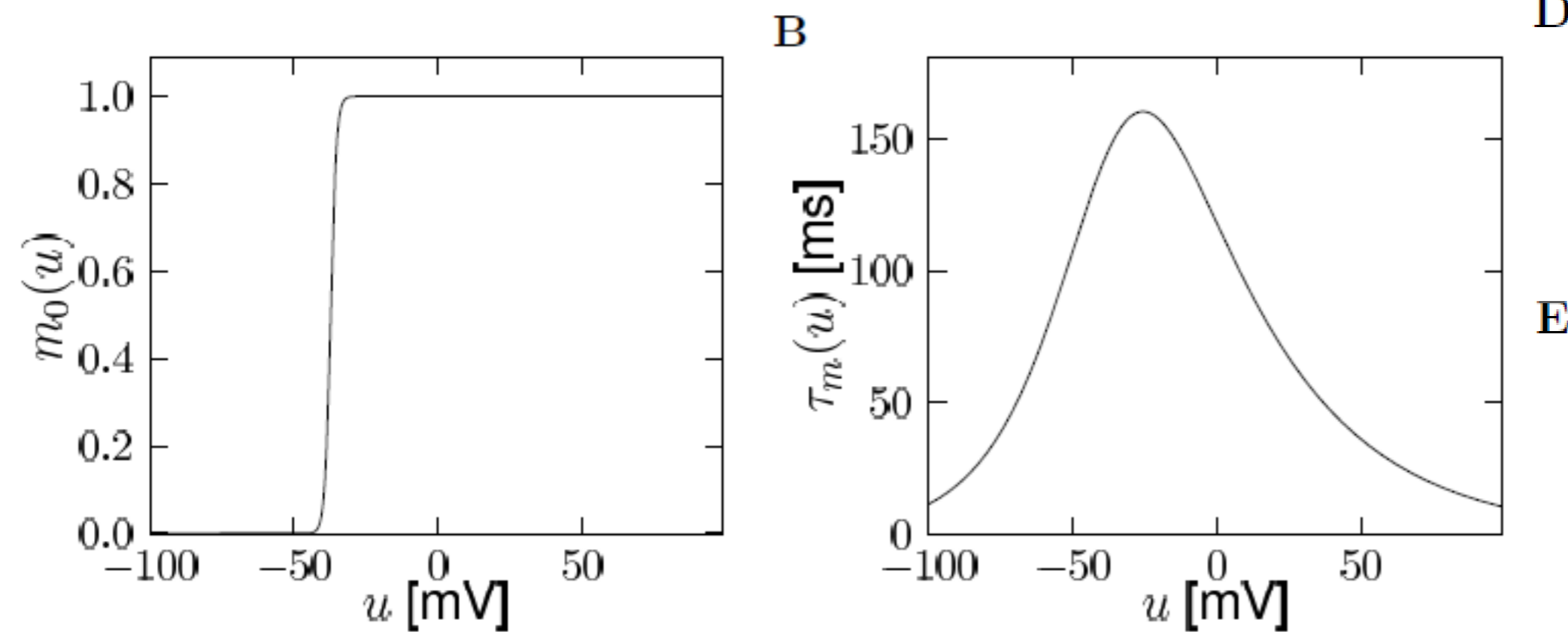
- Example: adaptation



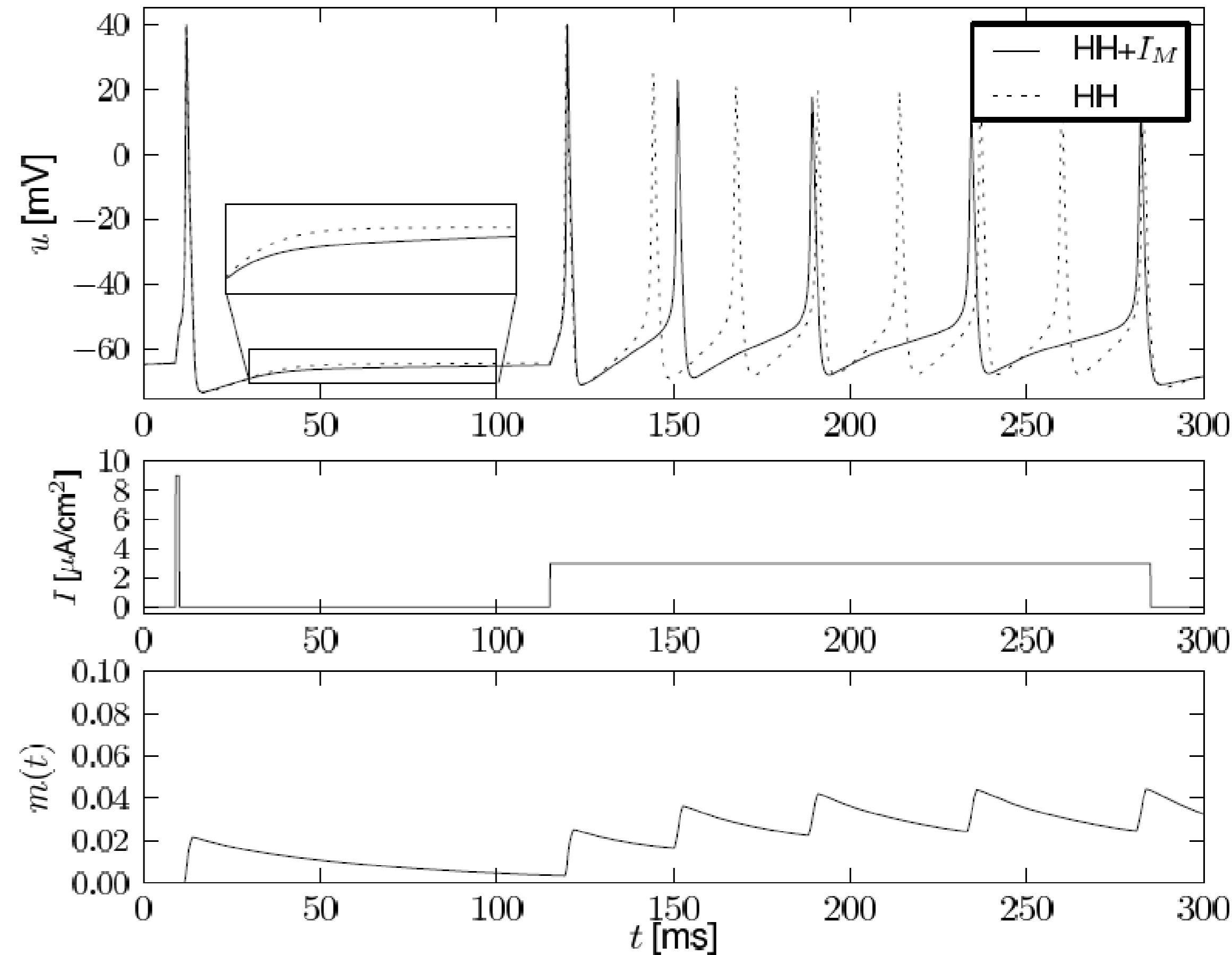
Neuronal Dynamics – 2.5 Adaptation: I_M -current

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

- Potassium current
- Kv7 subunits
- slow time constant



Yamada et al., 1989

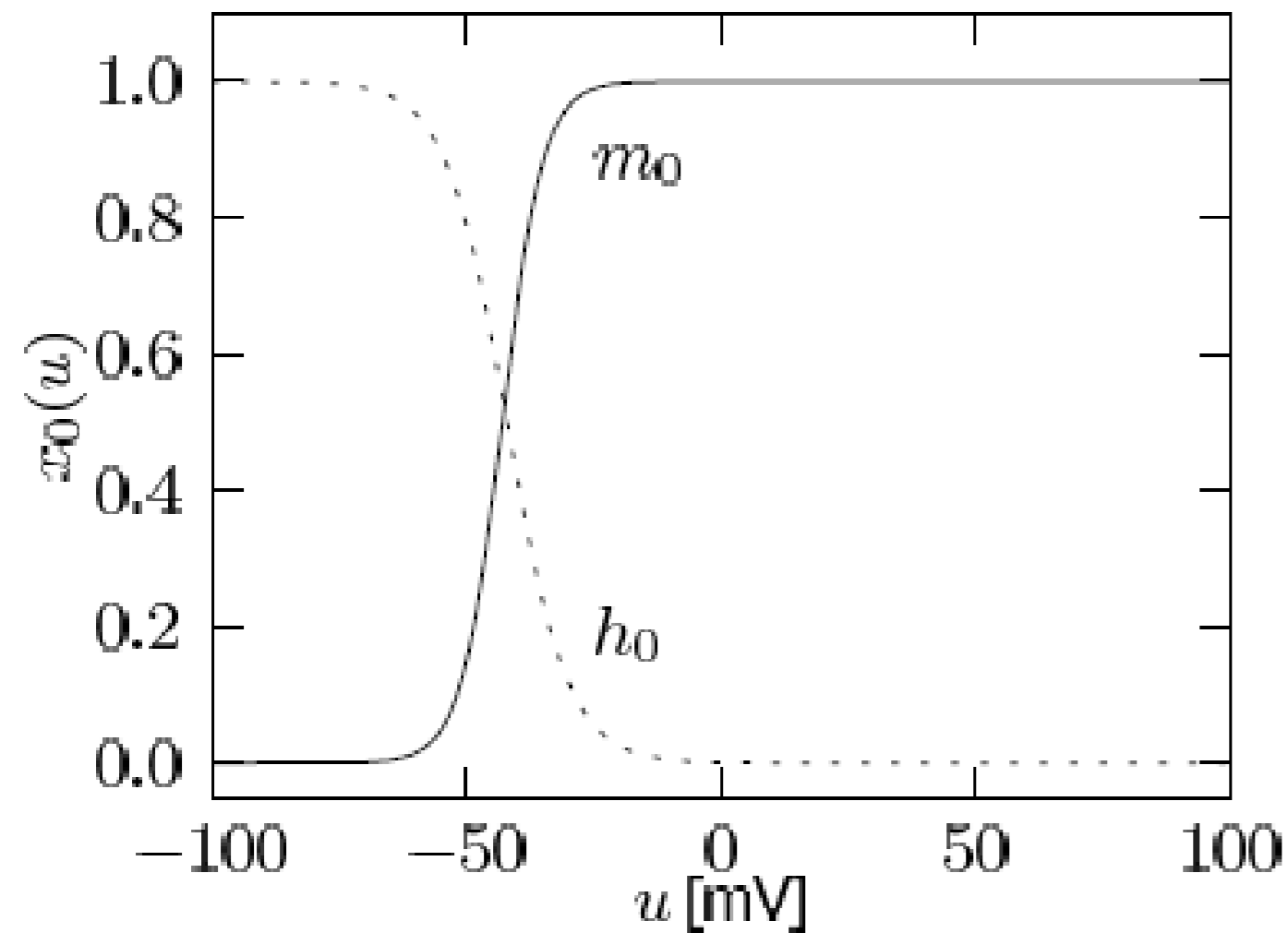


I_M current is one of many potential sources of adaptation

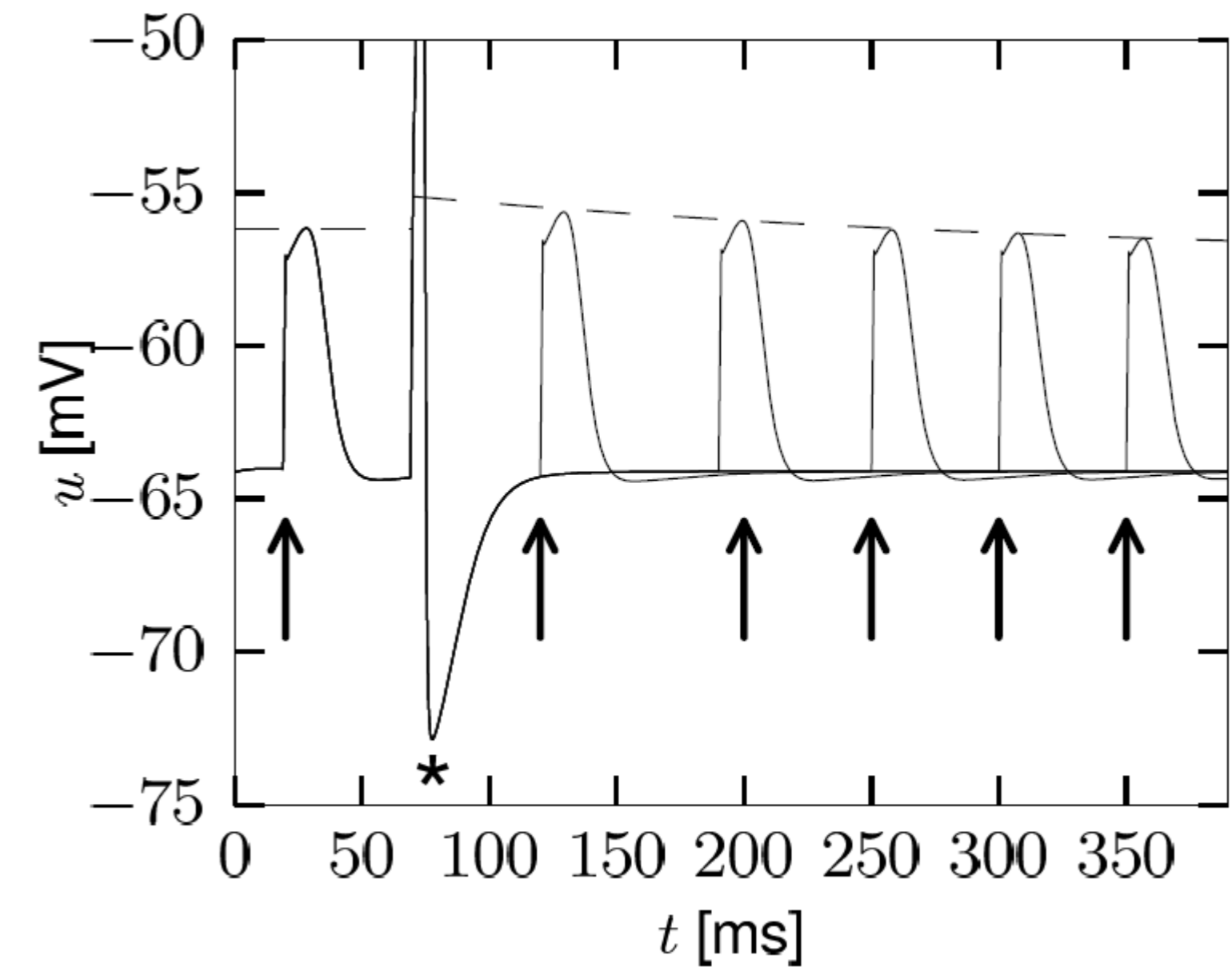
Neuronal Dynamics – 2.5 Adaptation – I_{NaP} current

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

- persistent sodium current
- fast activation time constant
- slow inactivation (~ 1 s)



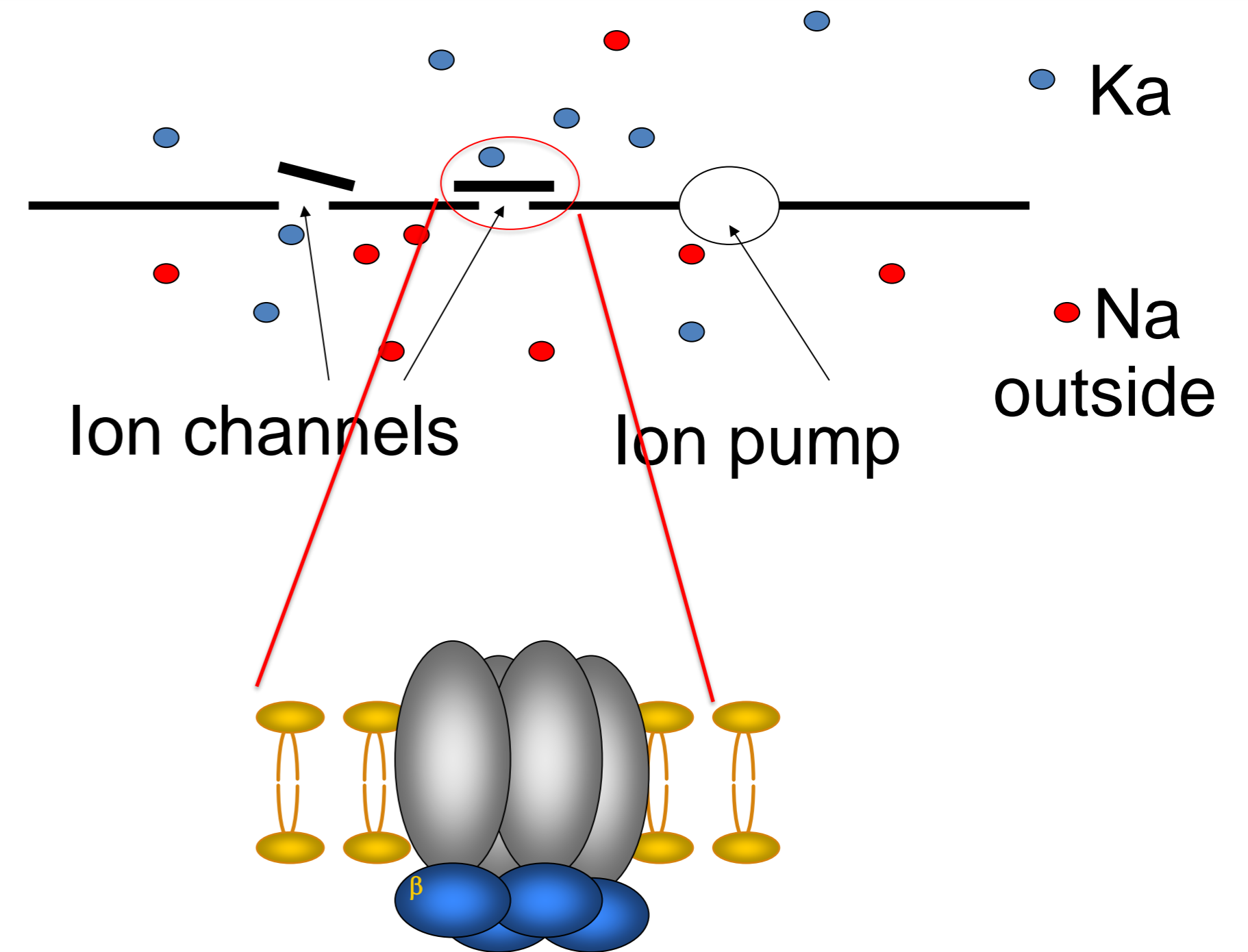
Aracri et al., 2006



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

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

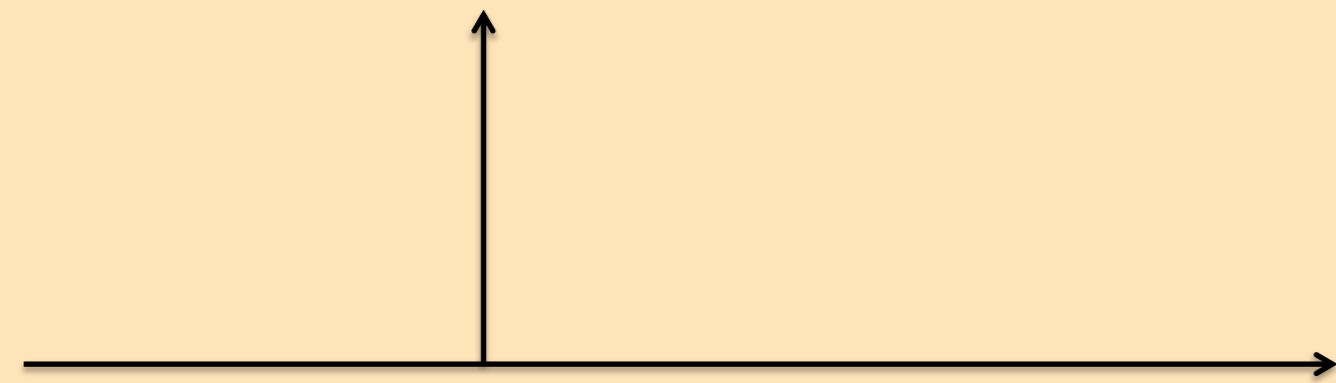
$$\frac{dm}{dt} = -\frac{m - m_0(u)}{\tau_m(u)}$$

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 γ and θ 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