Week 2 – part 1: Biophysics of neurons

ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

Biological Modeling of Neural Networks

Week 2 – Biophysical modeling:
The Hodgkin-Huxley model

Wulfram Gerstner

EPFL, Lausanne, Switzerland

Week 2 – part 1: Biophysics of neurons

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2.1 **Biophysics of neurons**
- Overview

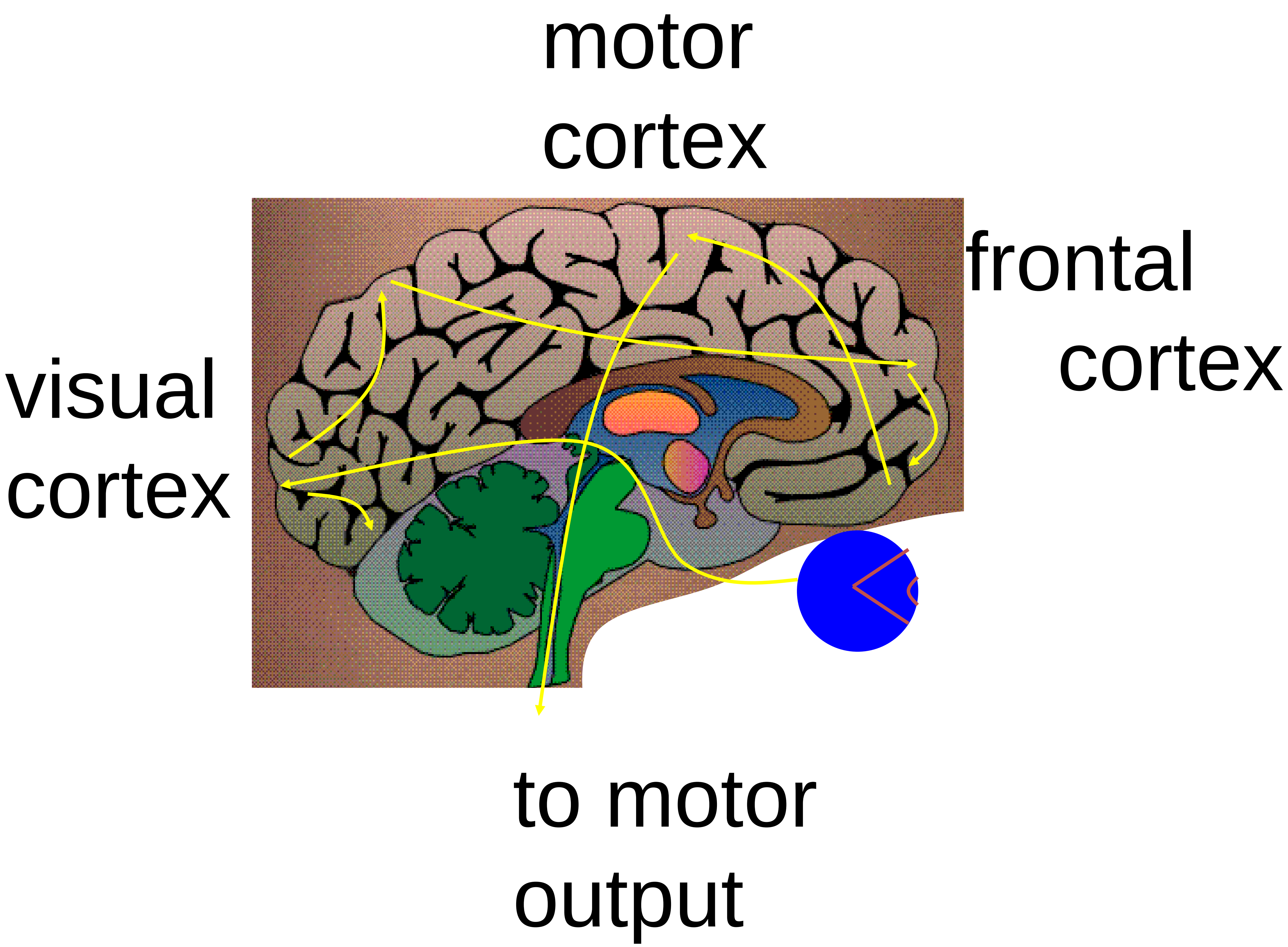
2.2 **Reversal potential**
- Nernst equation

2.3 **Hodgin-Huxley Model**

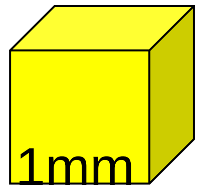
2.4 **Threshold in the Hodgkin-Huxley Model**
- where is the firing threshold?

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

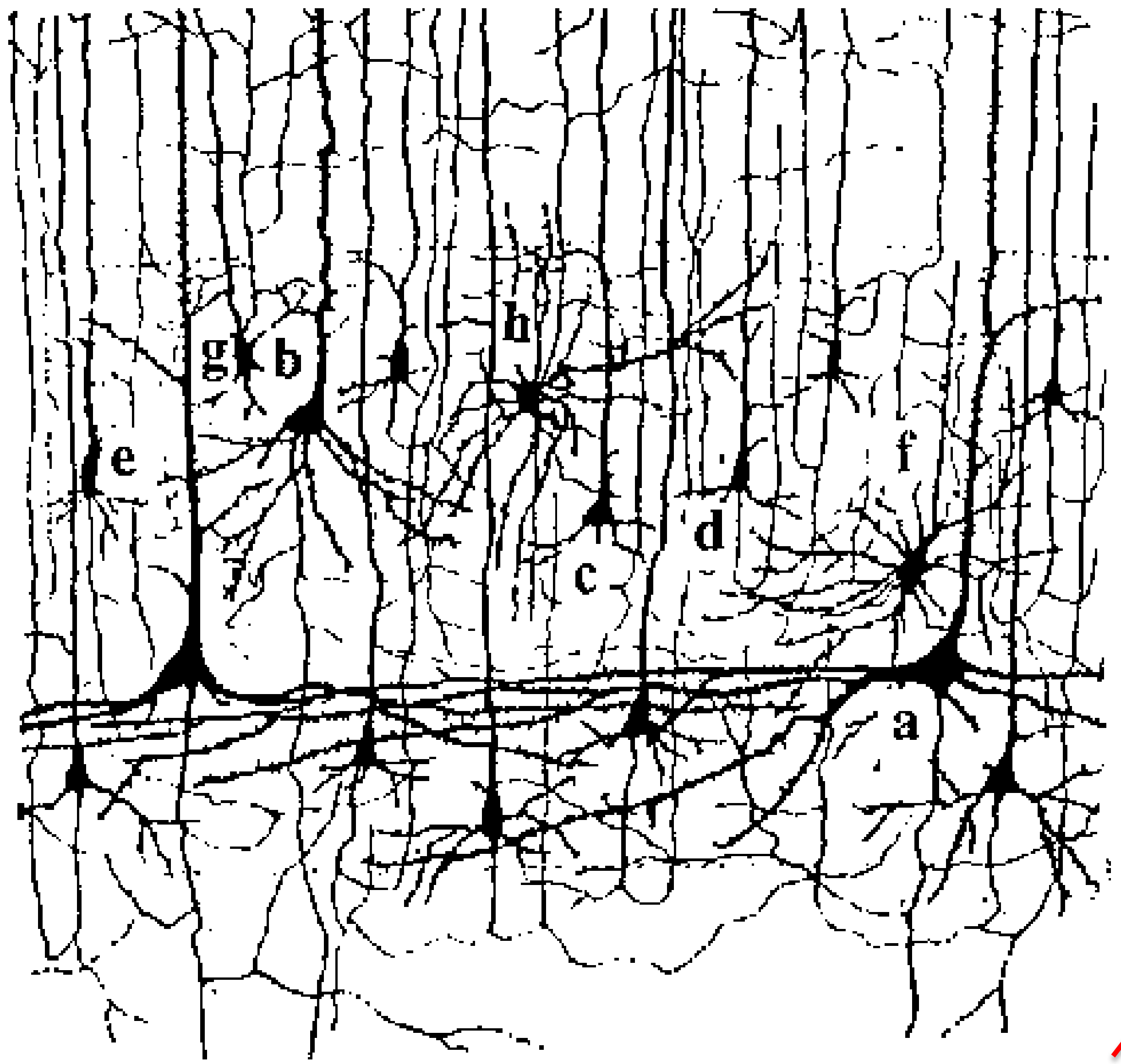
Neuronal Dynamics – 2.1. Introduction



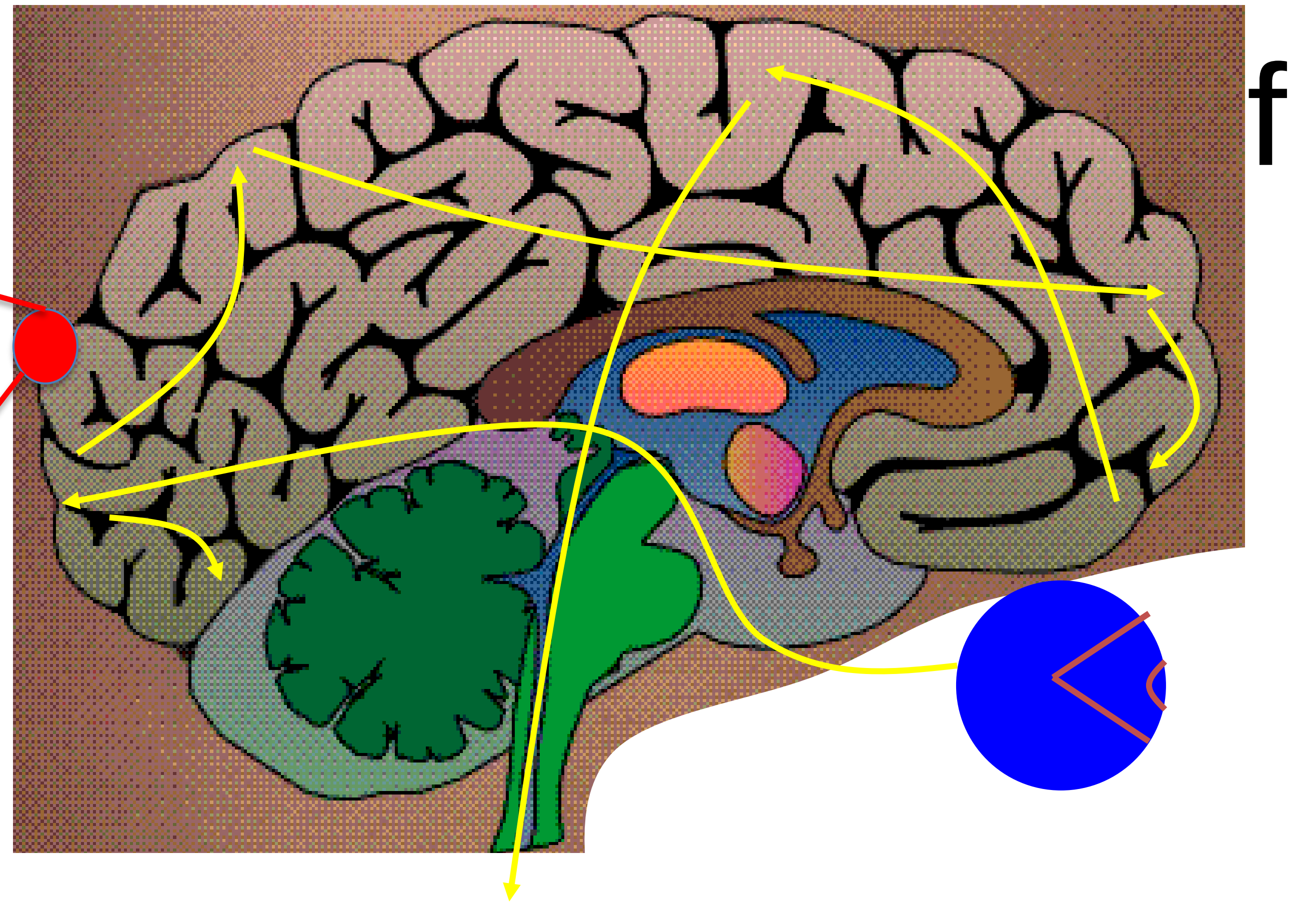
Neuronal Dynamics – 2.1. Introduction



10 000 neurons
3 km wires



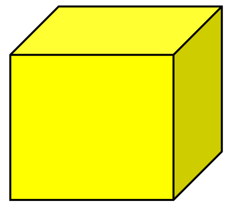
motor
cortex



frontal
cortex

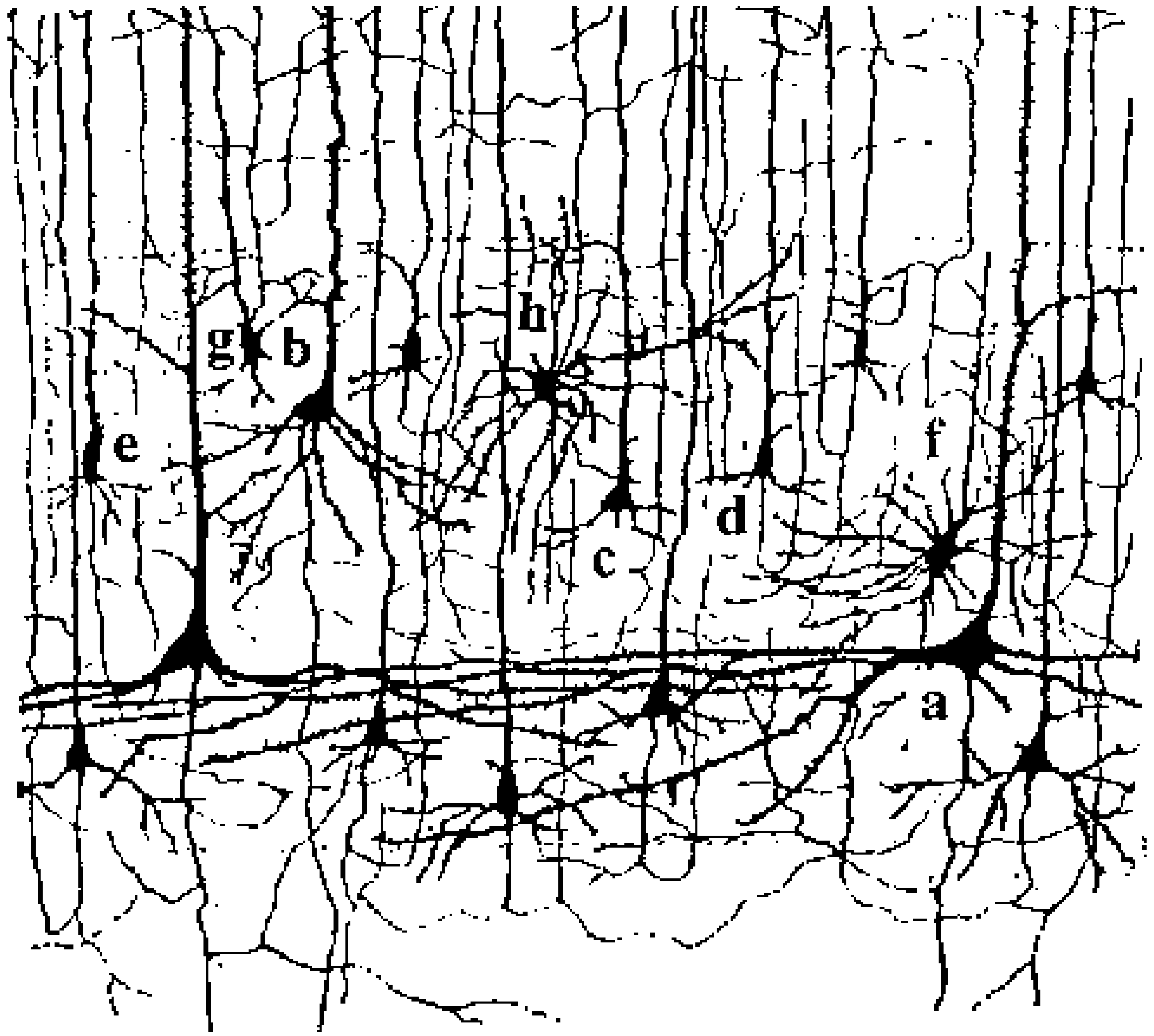
to motor
output

Neuronal Dynamics – 2.1 Introduction



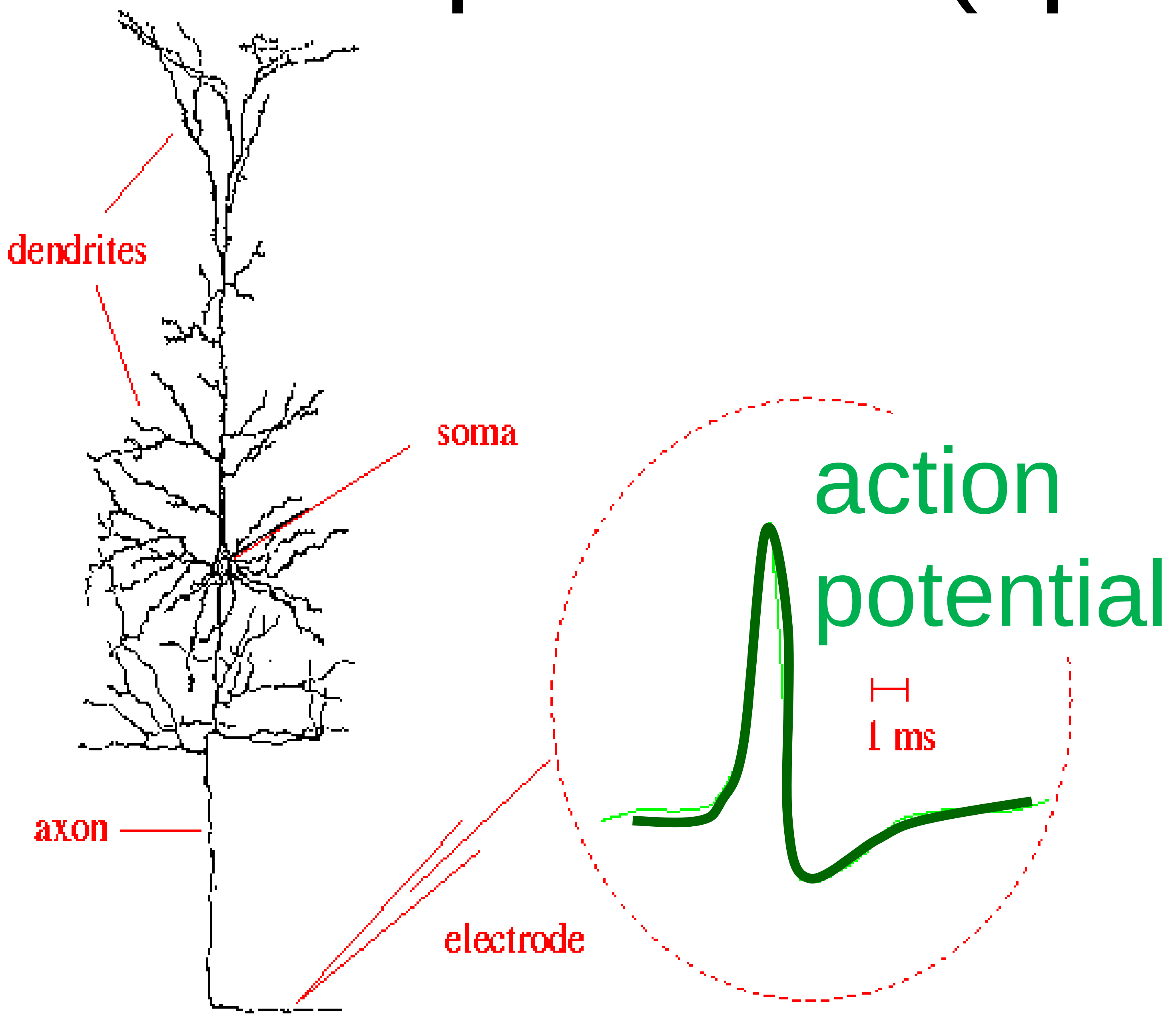
1mm

10 000 neurons
3 km wires



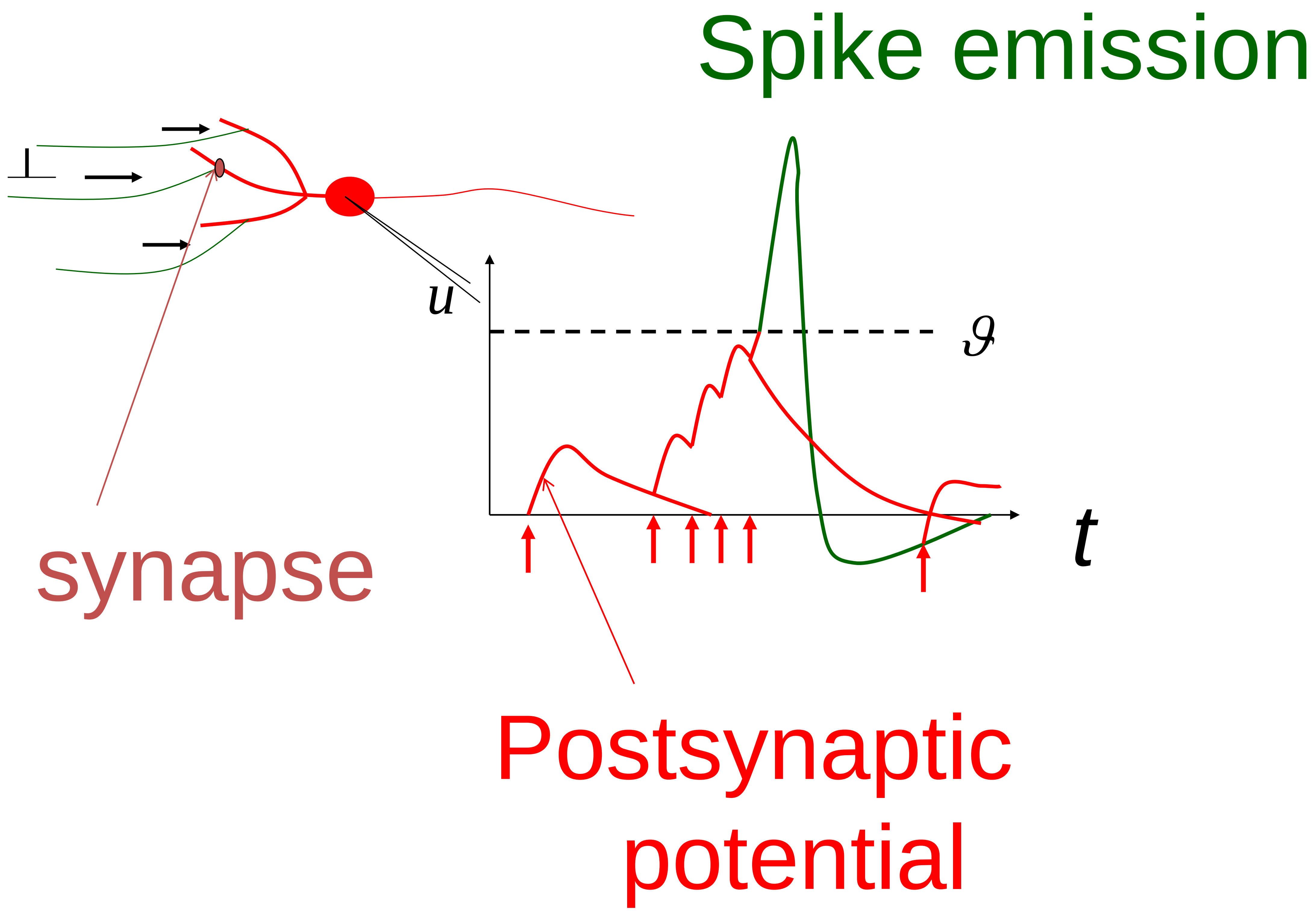
Ramon y Cajal

Signal:
action potential (spike)



How is a spike generated?

Review of week 1: Integrate-and-Fire models



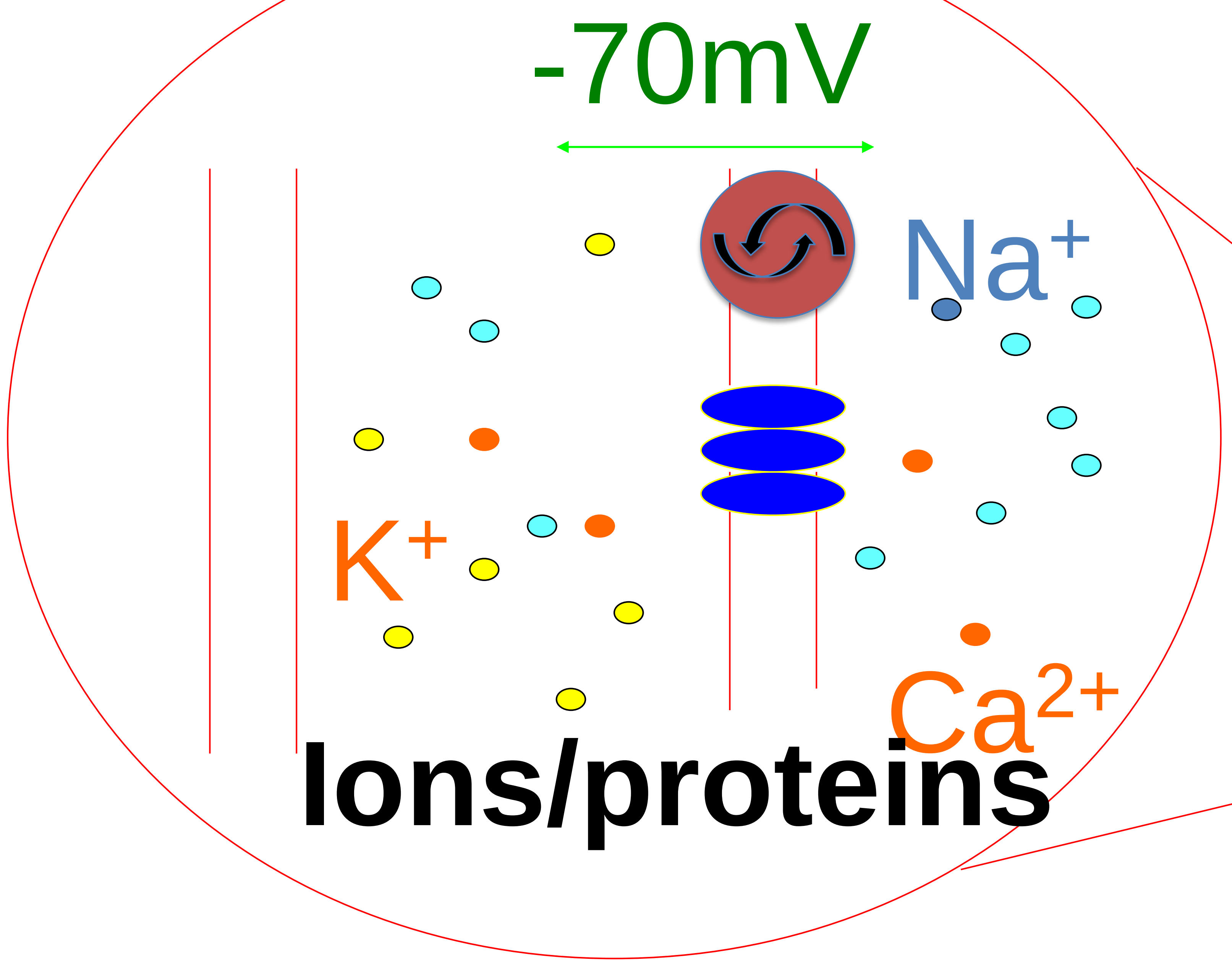
-spikes are events
-triggered at threshold
-spike/reset/refractoriness

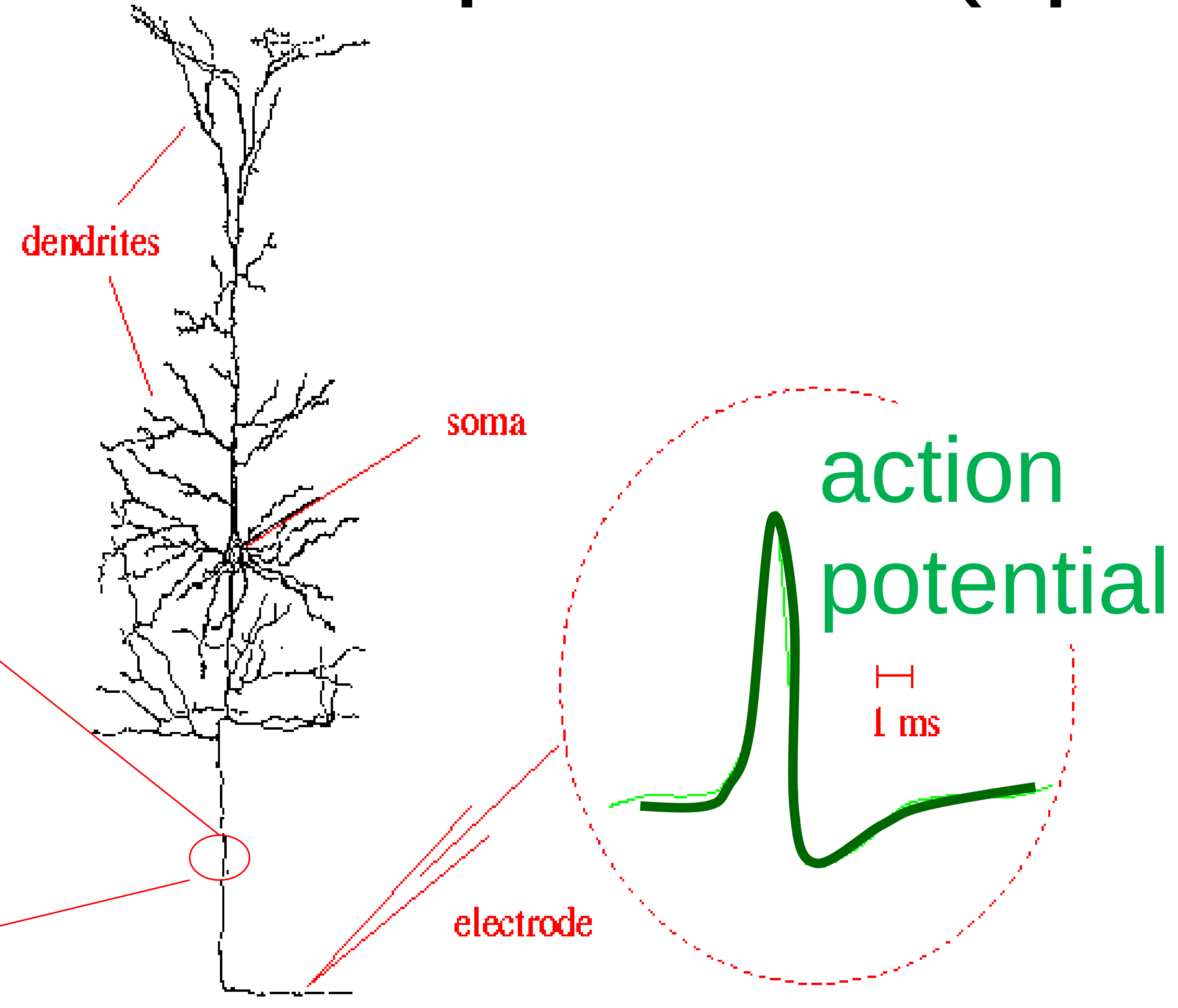
Neuronal Dynamics – week 2: Biophysics of neurons

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
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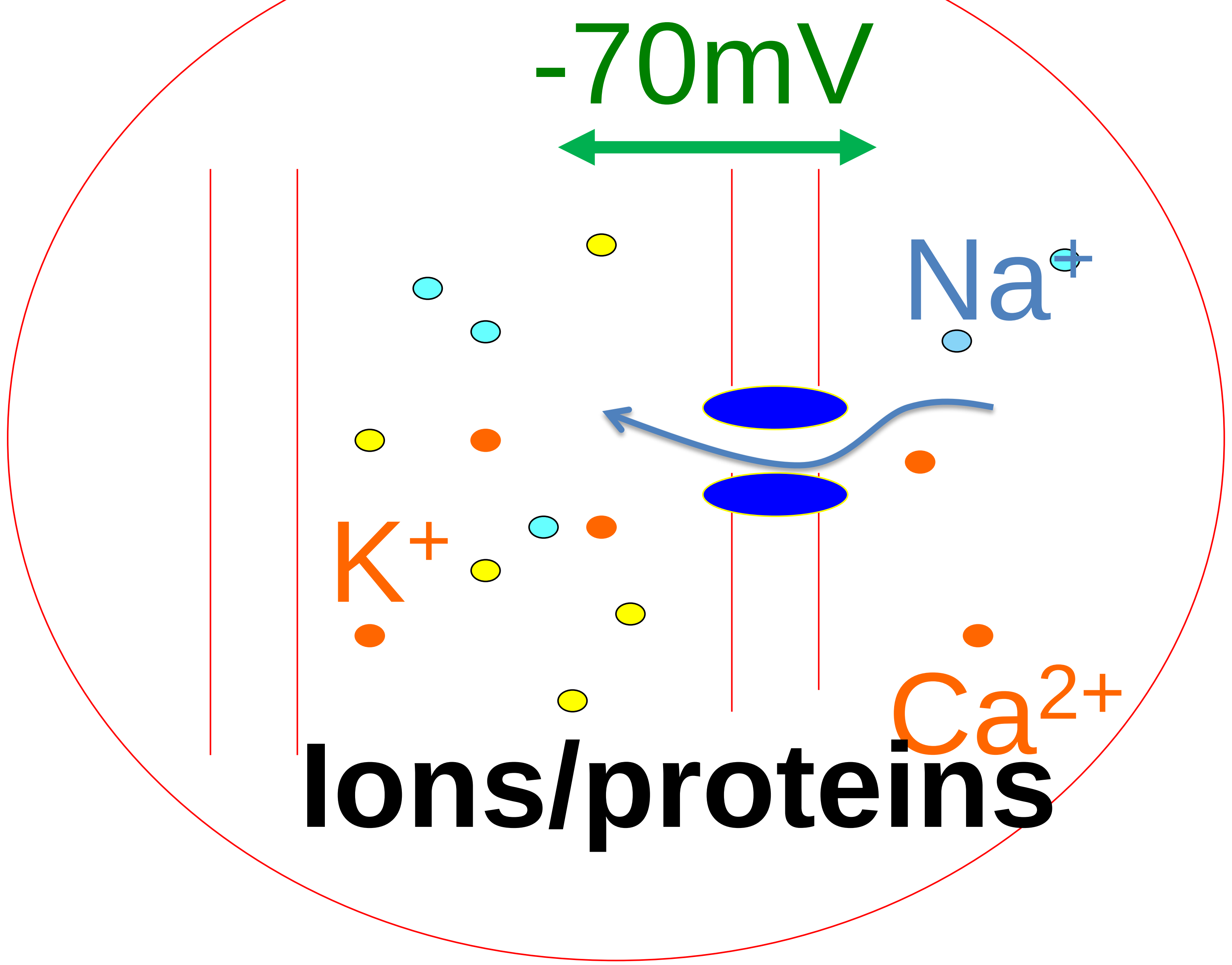


Resting potential -70mV
→ how does it arise?

Ions flow through channel
→ in which direction?

Neuron emits action potentials
→ why?

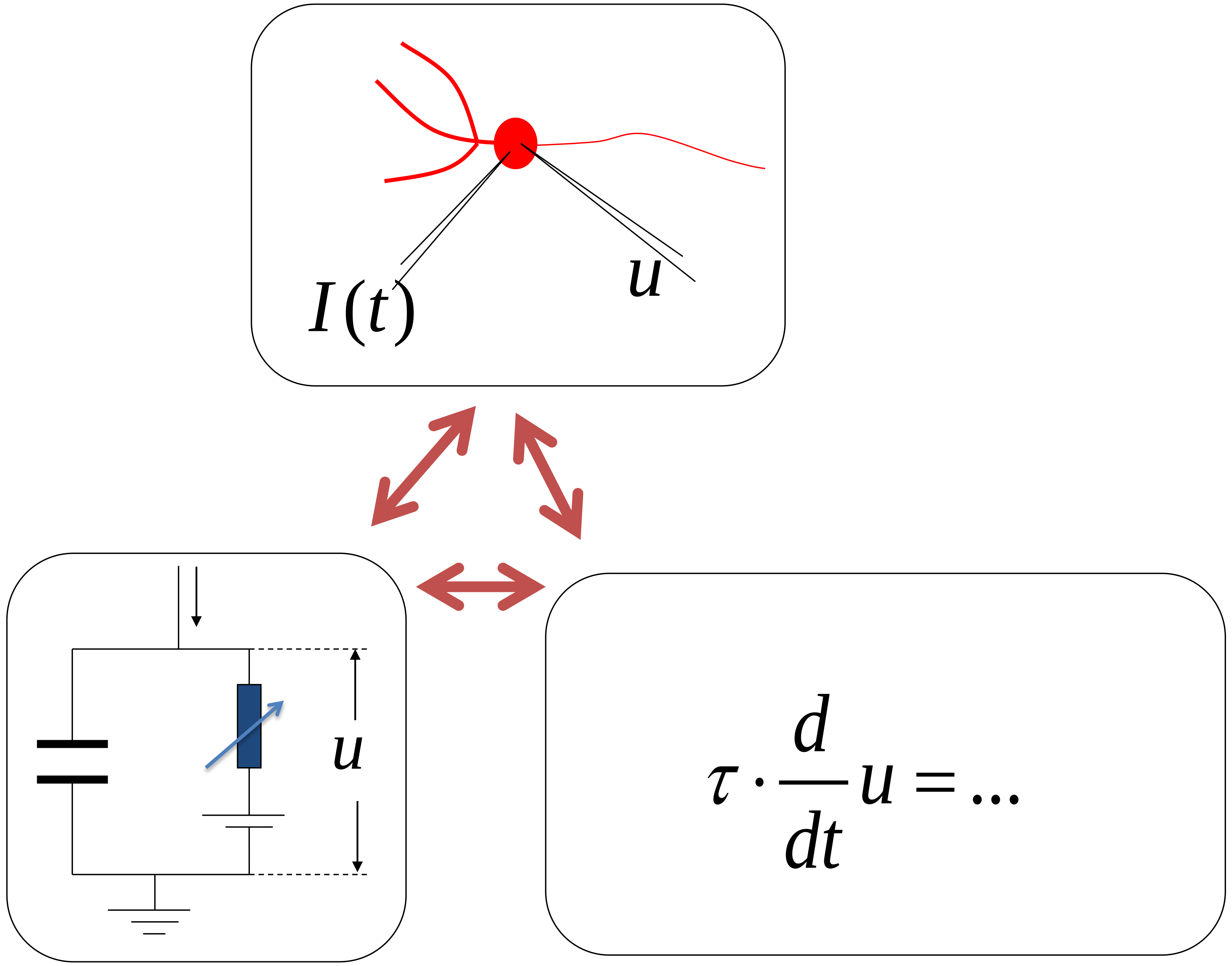
Resting potential -70mV
→ how does it arise?

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 – Quiz

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
- [ ] Neurons are not cells

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

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Biological Modeling of Neural Networks

Week 2 – Biophysical modeling: The Hodgkin-Huxley model

Wulfram Gerstner
EPFL, Lausanne, Switzerland

√ 2.1 **Biophysics of neurons**
- Overview

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- where is the firing threshold?

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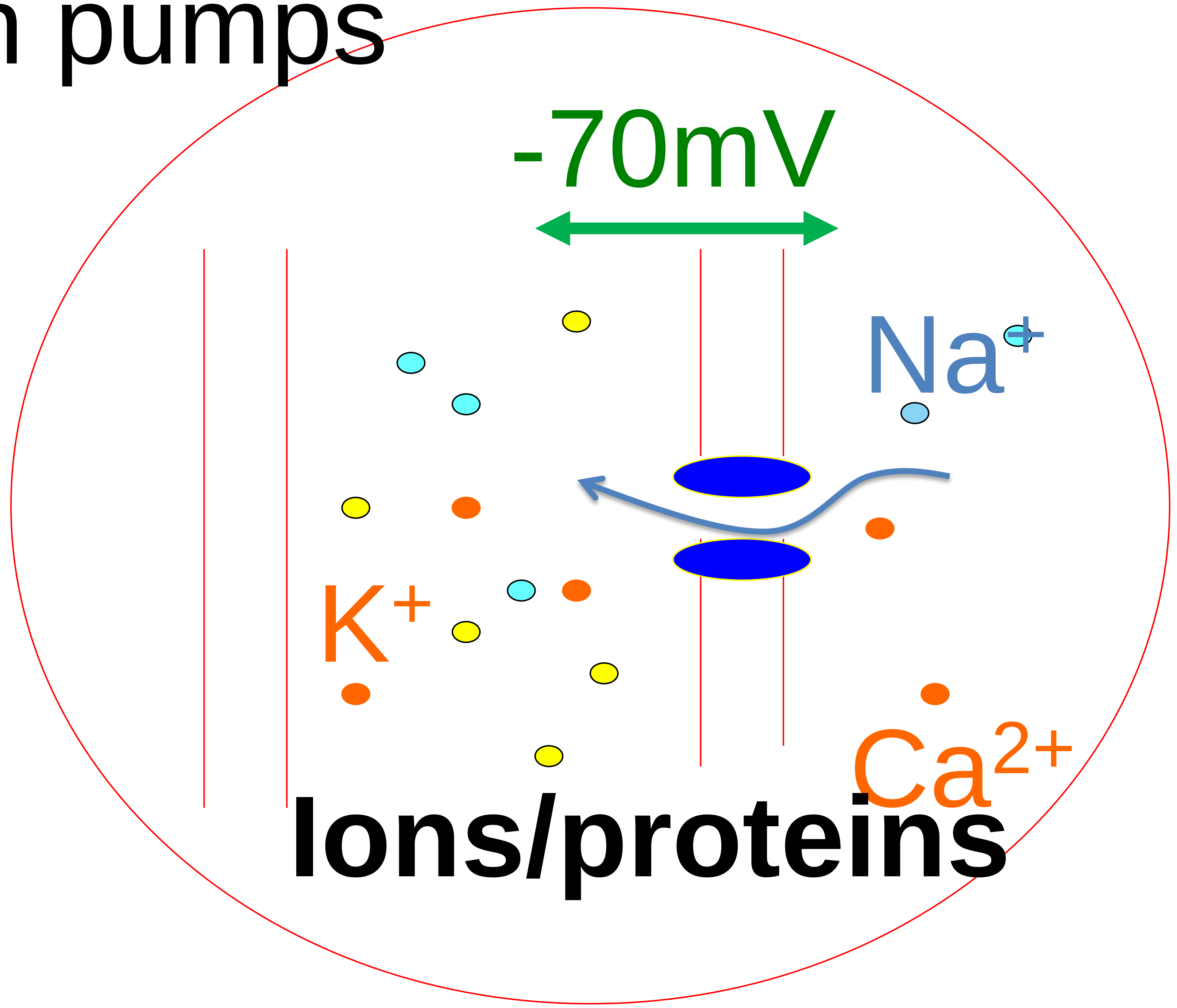
- the zoo of ion channels

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

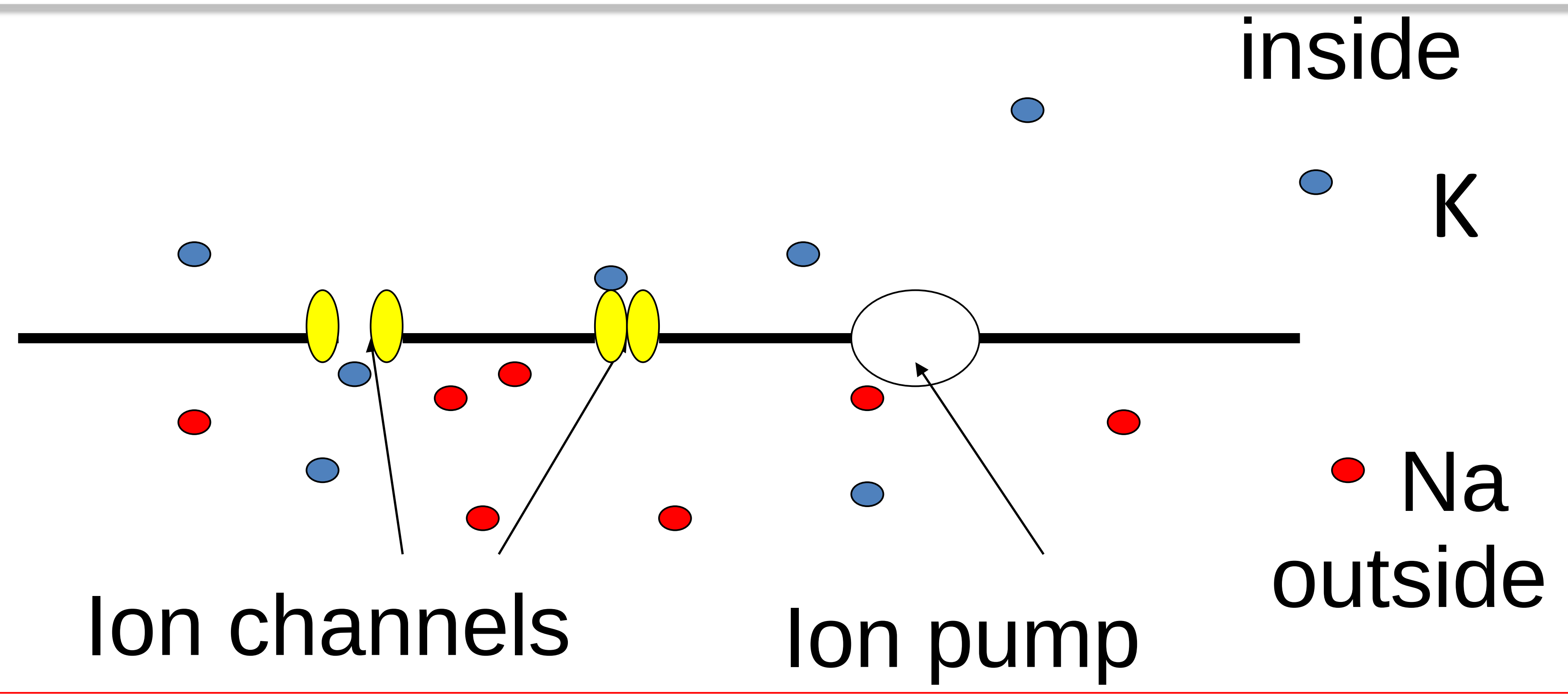
→ why?

→Hodgkin-Huxley model

Hodgkin&Huxley (1952)

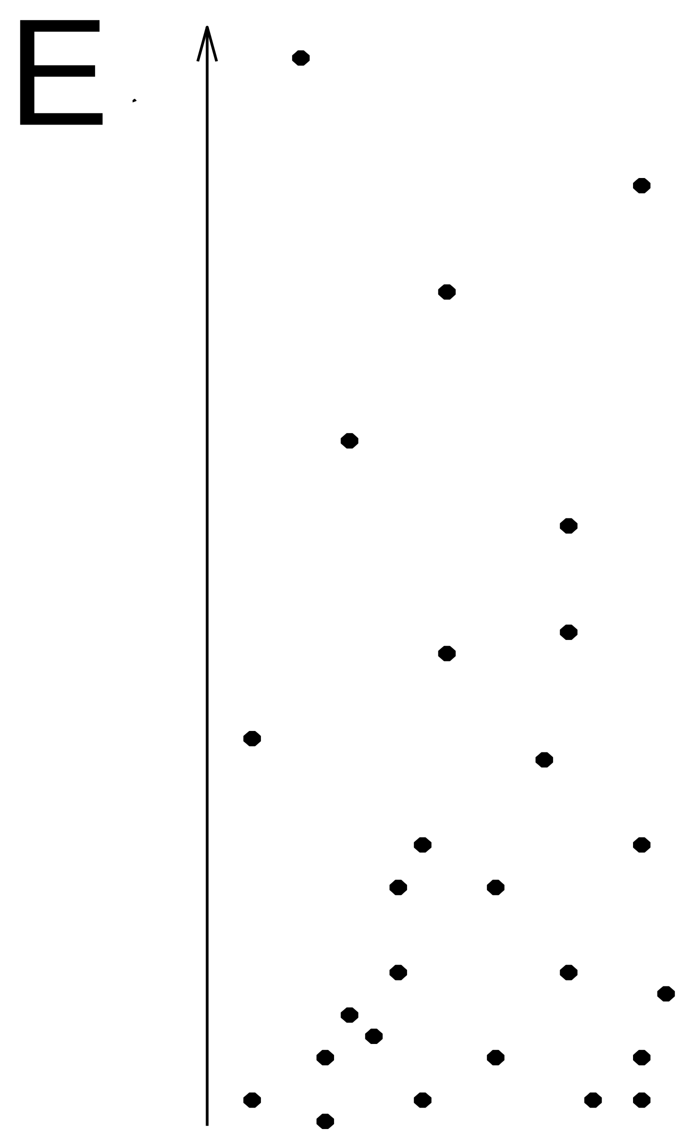
Nobel Prize 1963

Neuronal Dynamics – 2. 2. Reversal potential



density

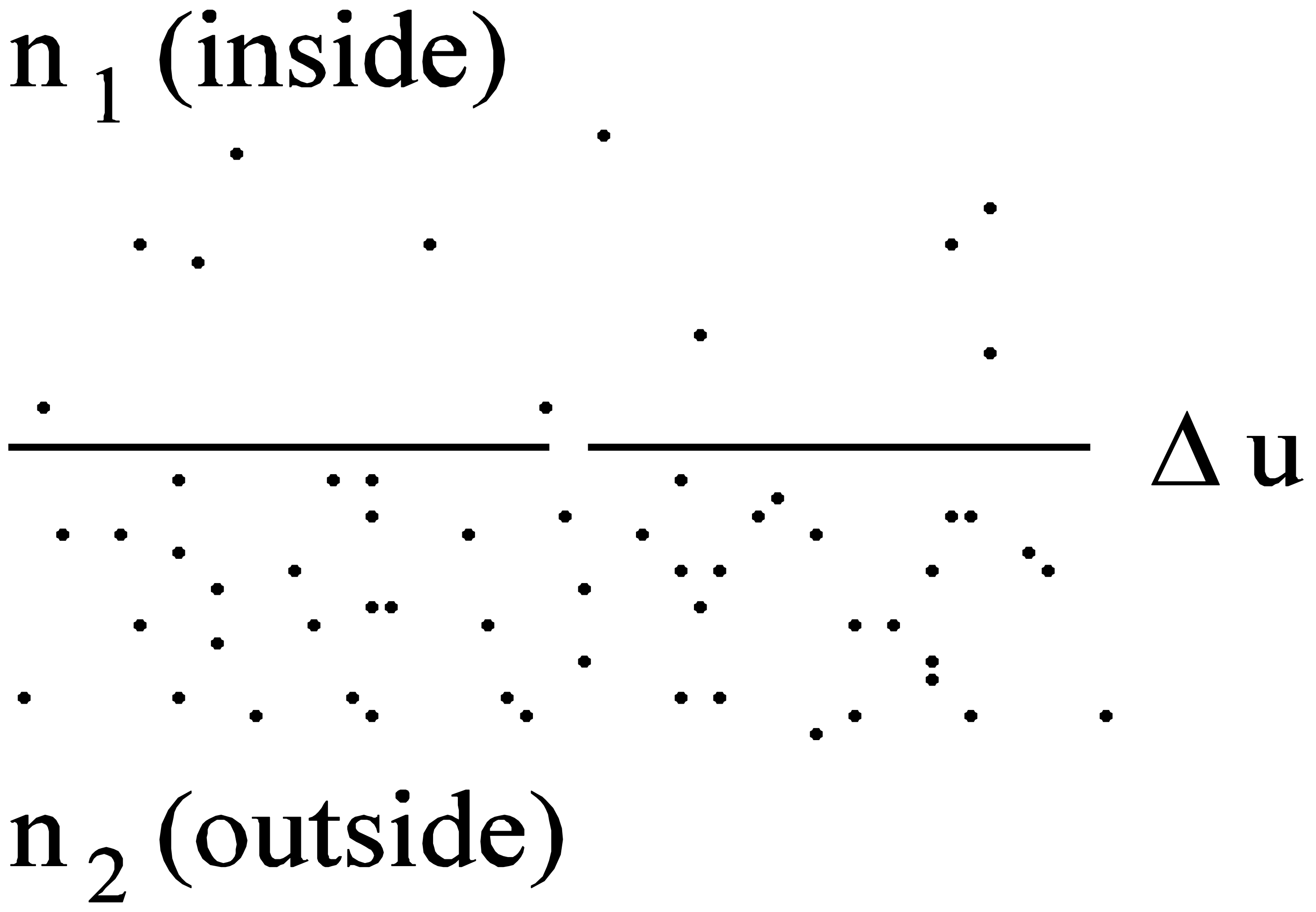
$$n \propto e^{-\frac{E}{kT}}$$



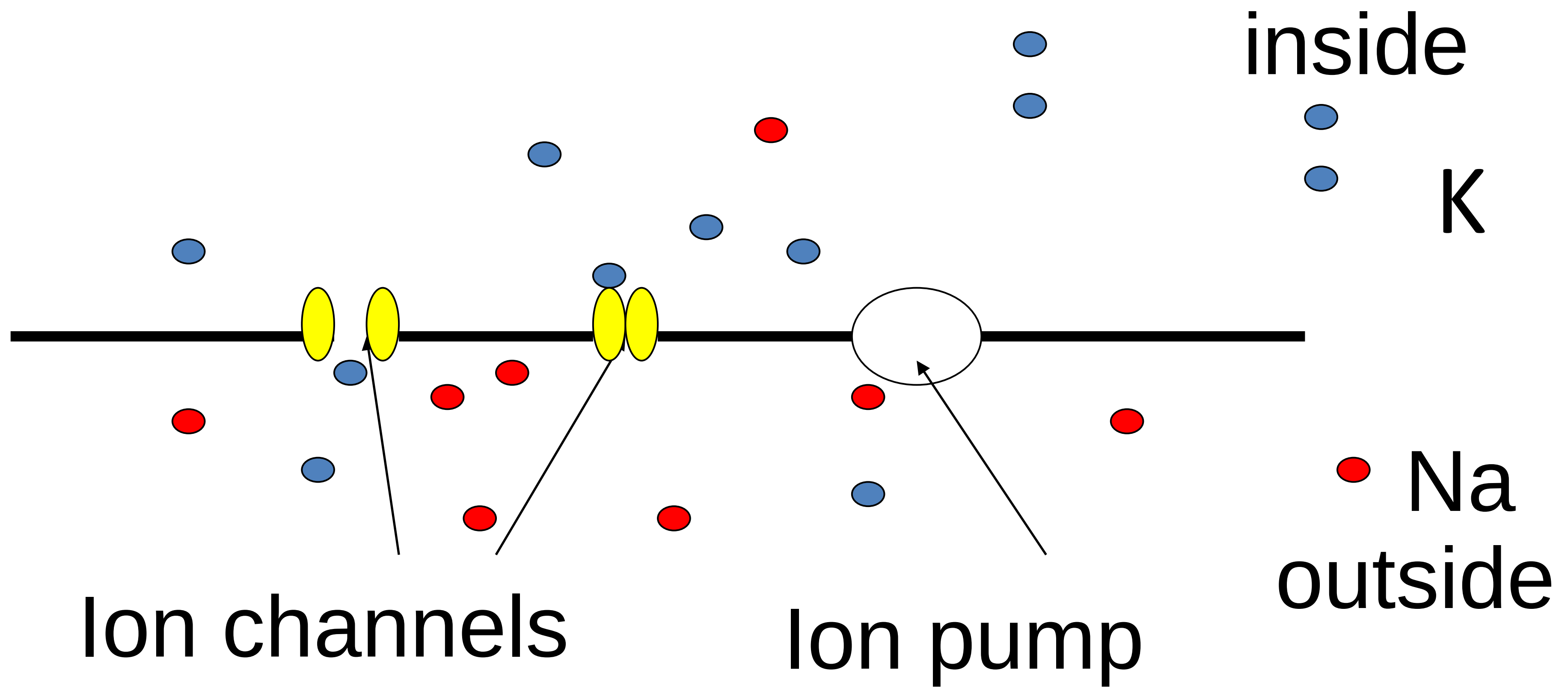
Ion pump ⇔ Concentration difference

Mathetical derivation

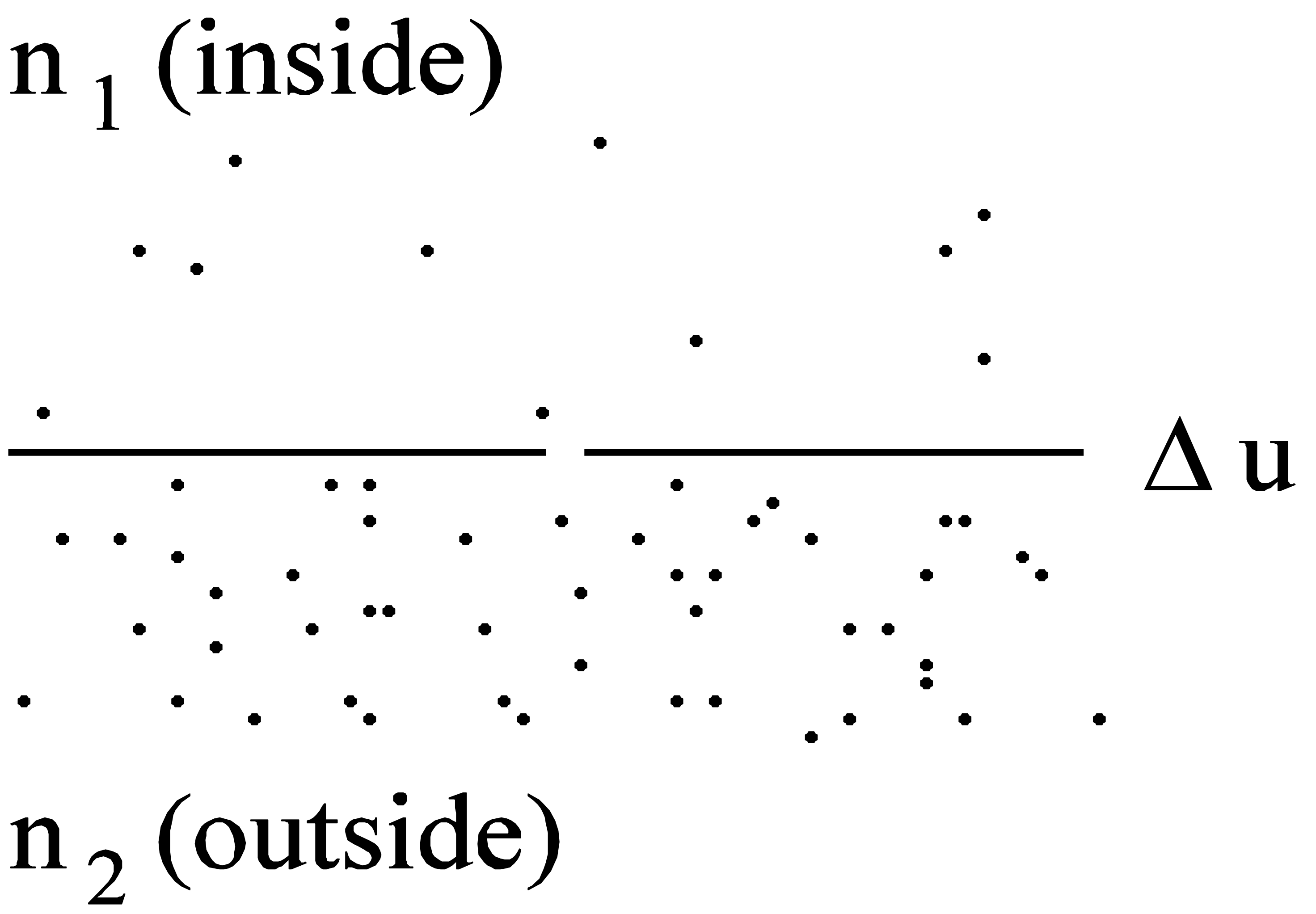
Neuronal Dynamics – 2. 2. Nernst equation

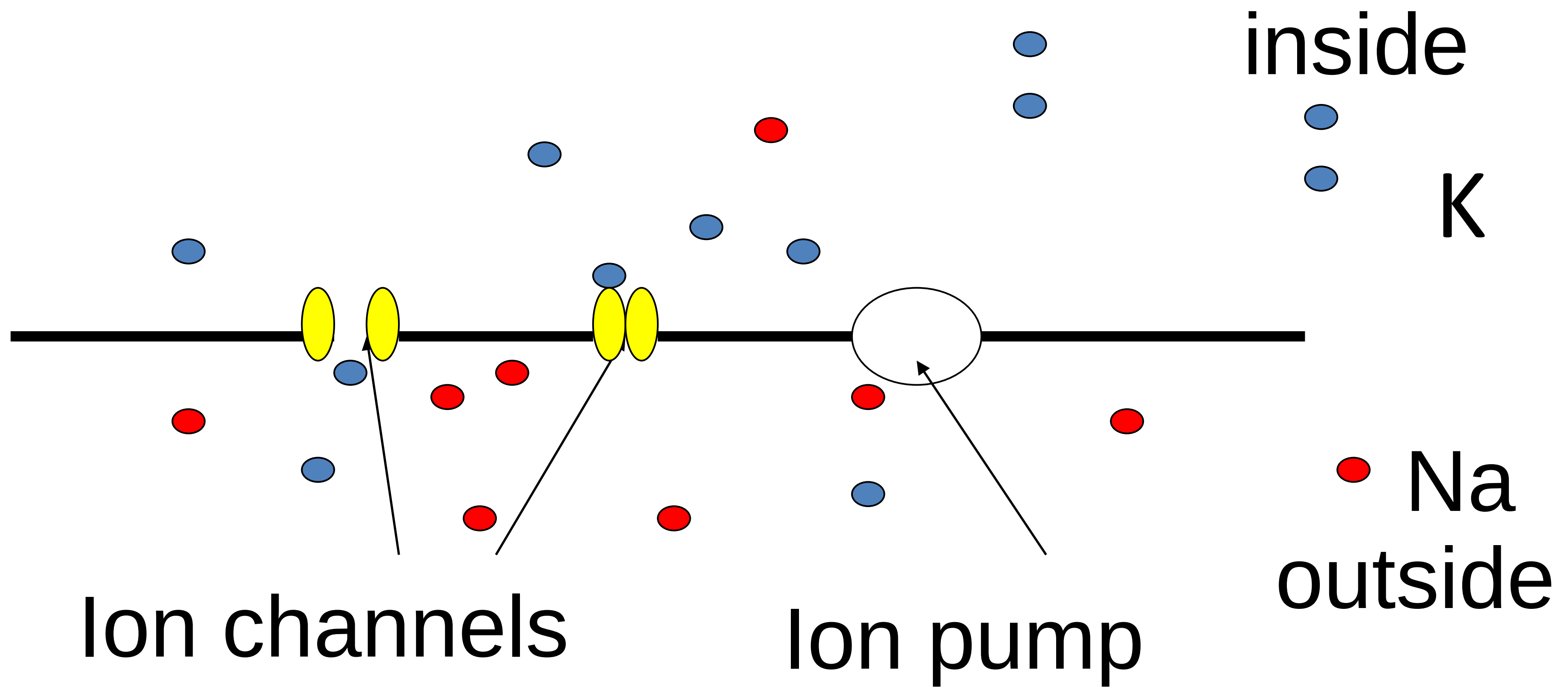


$$n \propto e^{-\frac{E}{kT}}$$



Neuronal Dynamics – 2. 2. Nernst equation



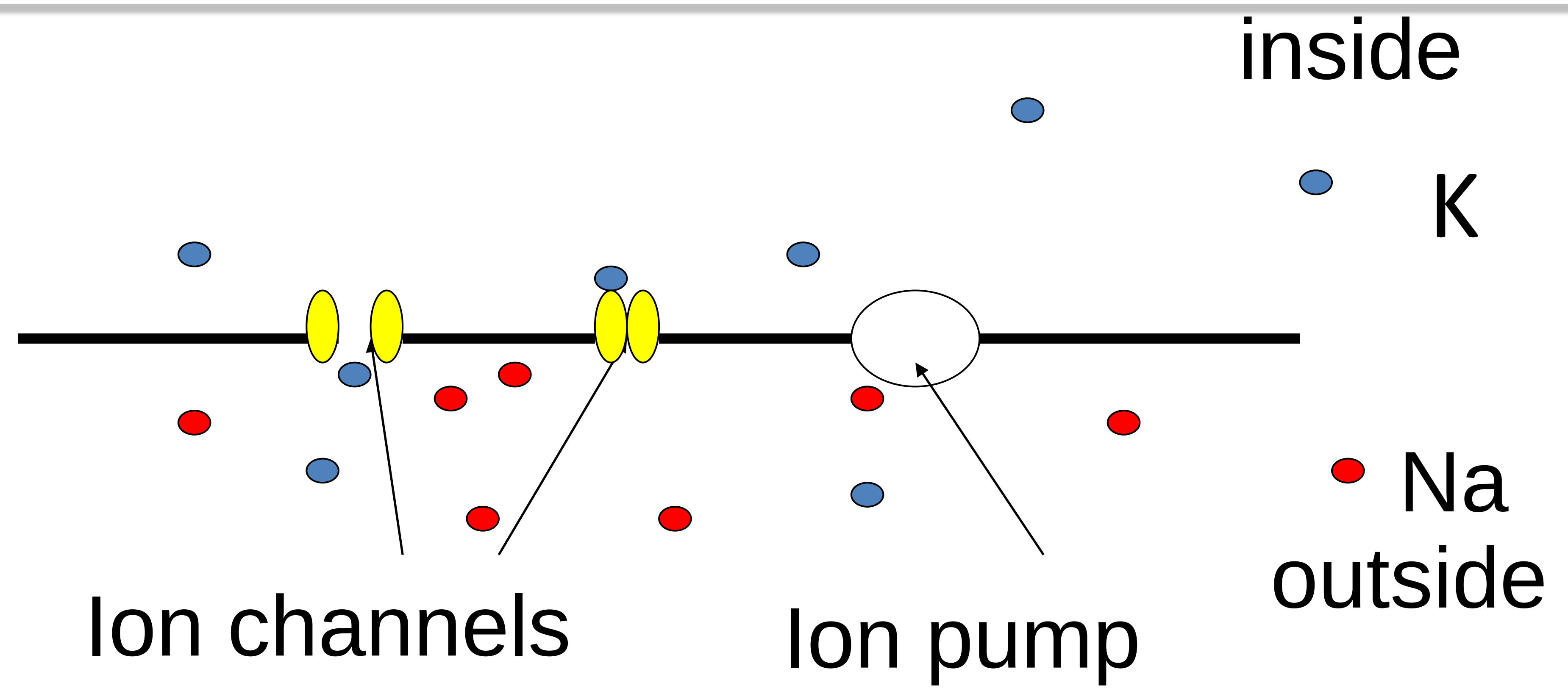


$$\Delta u = u_1 - u_2 = \frac{-kT}{q} \ln \frac{n(u_1)}{n(u_2)}$$

Reversal potential

Concentration difference ⇔ voltage difference

Neuronal Dynamics – 2. 2. Reversal potential



Ion pump → Concentration difference

Concentration difference ⇔ voltage difference

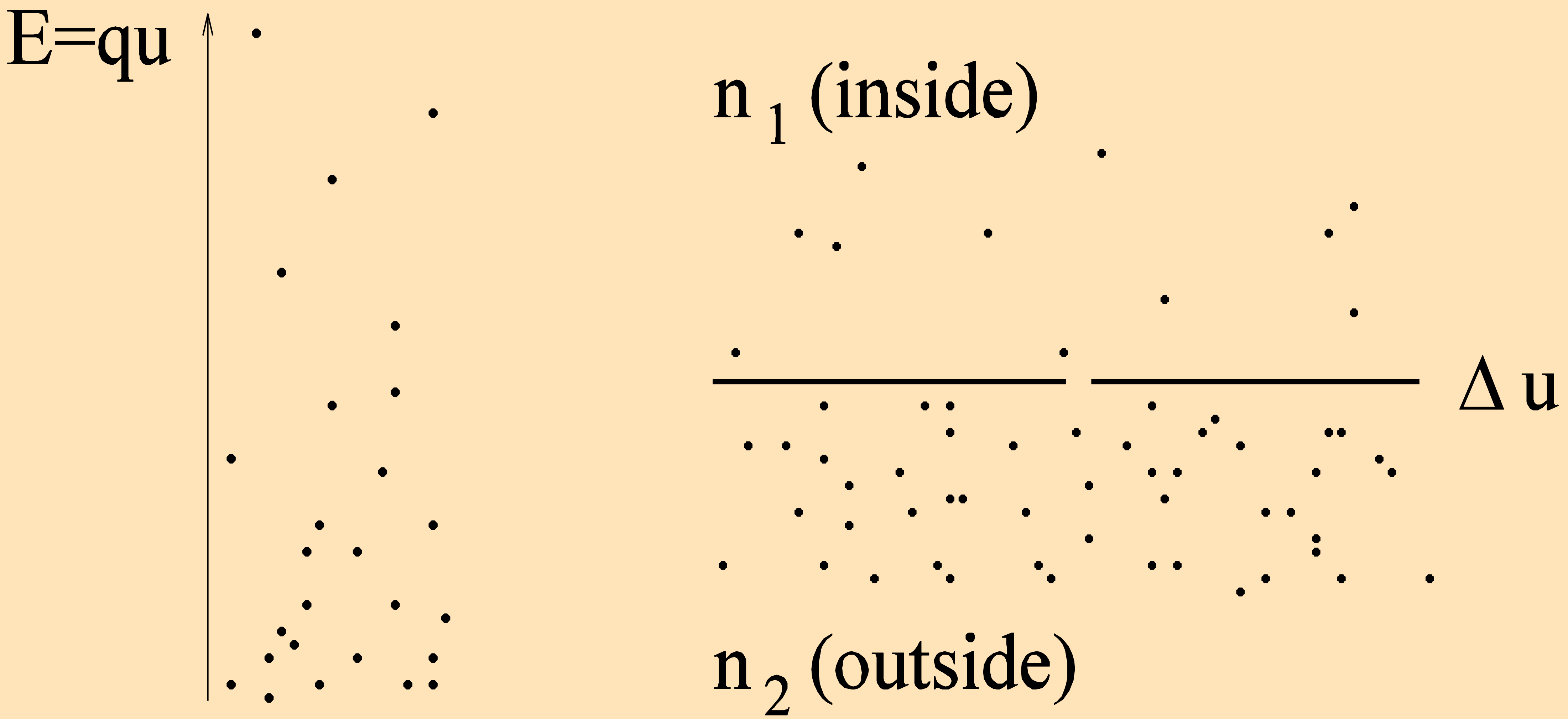
Reversal potential

Nernst equation

Exercise 1.1– 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
Postassium
Calcium
given the concentrations

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

Next Lecture 9:45

Week 2 – part 3 : Hodgkin-Huxley Model

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Neuronal Dynamics:
Computational Neuroscience of Single Neurons

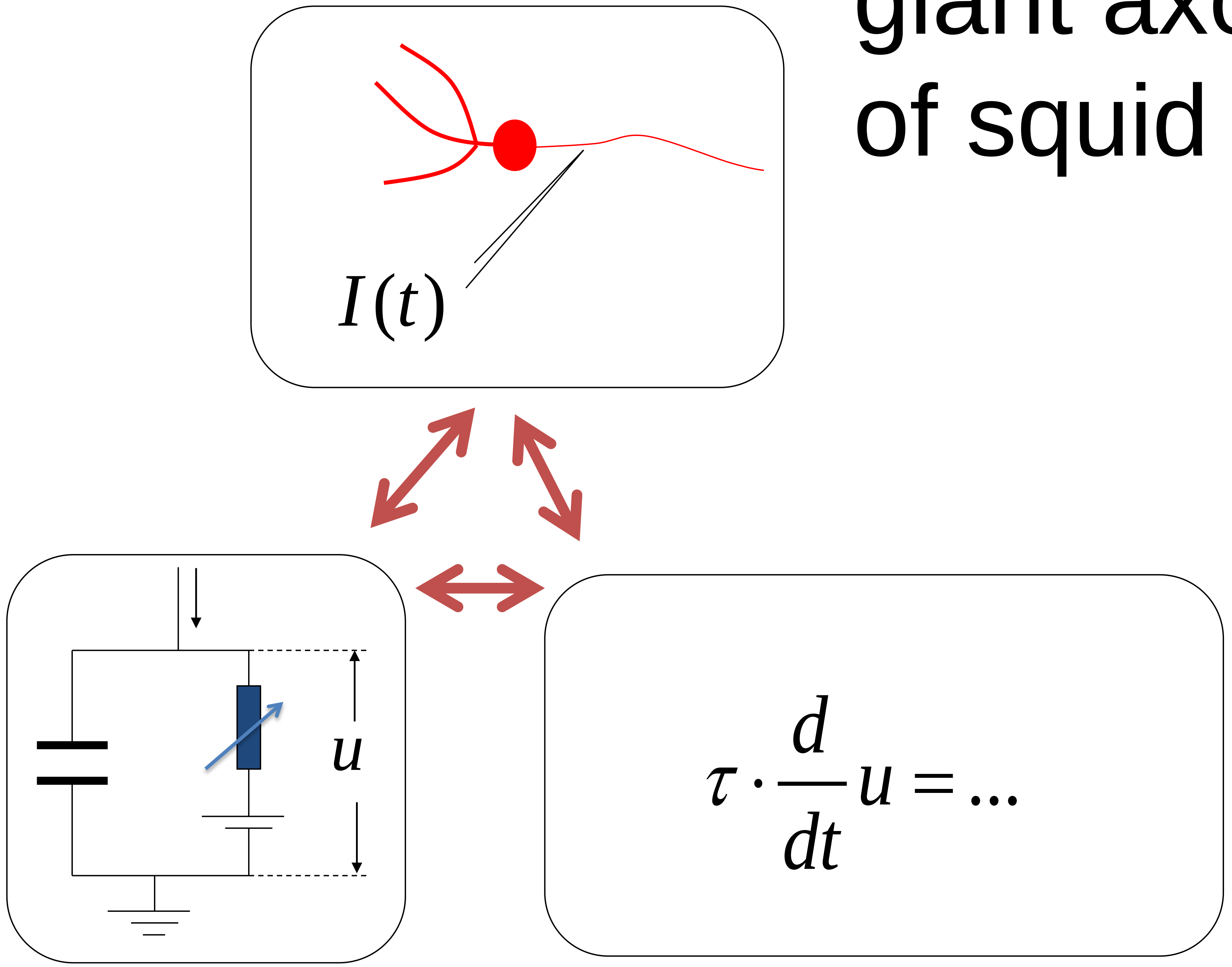
Week 2 – Biophysical modeling:
The Hodgkin-Huxley model

Wulfram Gerstner

EPFL, Lausanne, Switzerland

Neuronal Dynamics – 2. 3. Hodgkin-Huxley Model

giant axon of squid



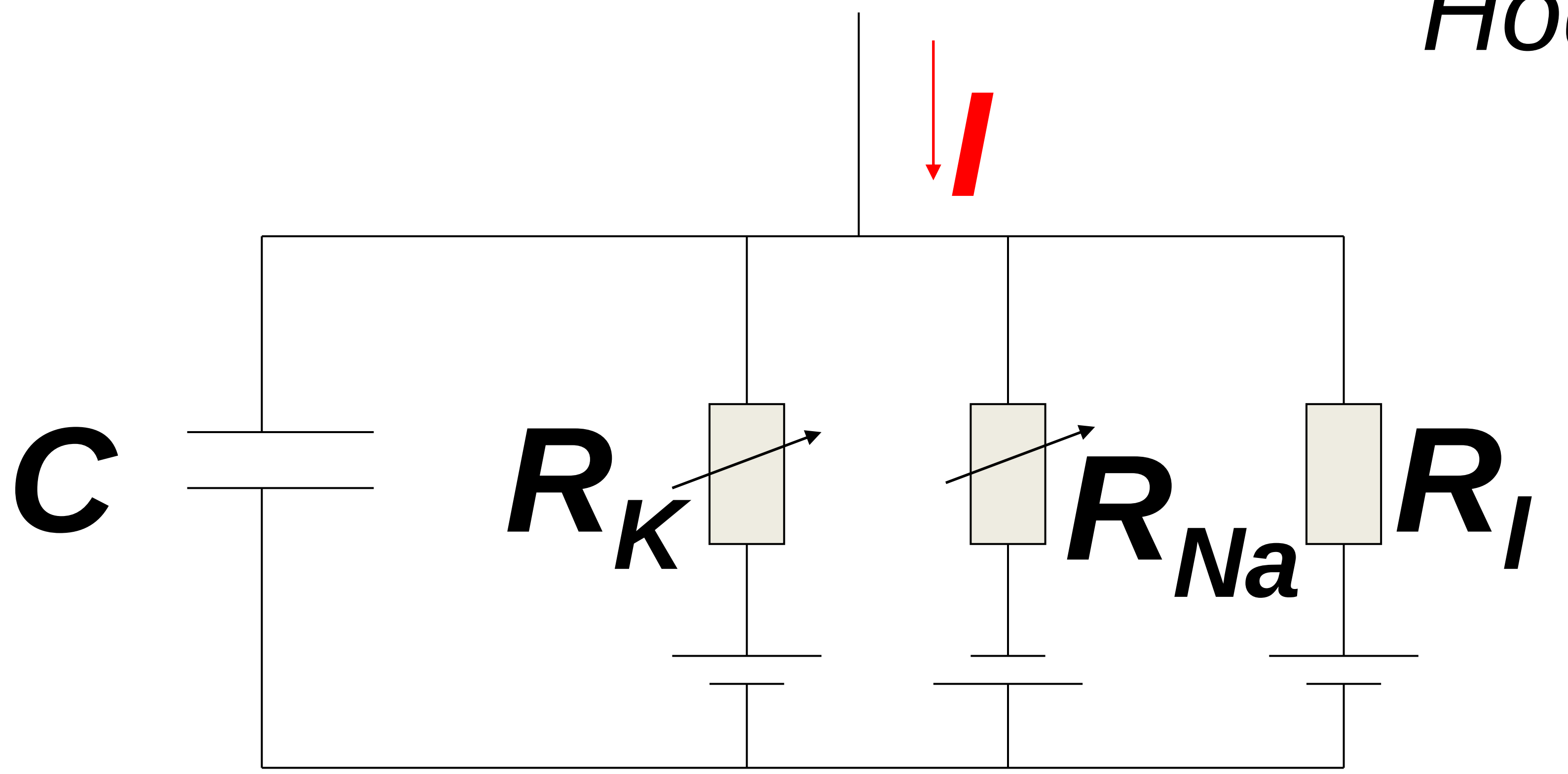
→Hodgkin-Huxley model

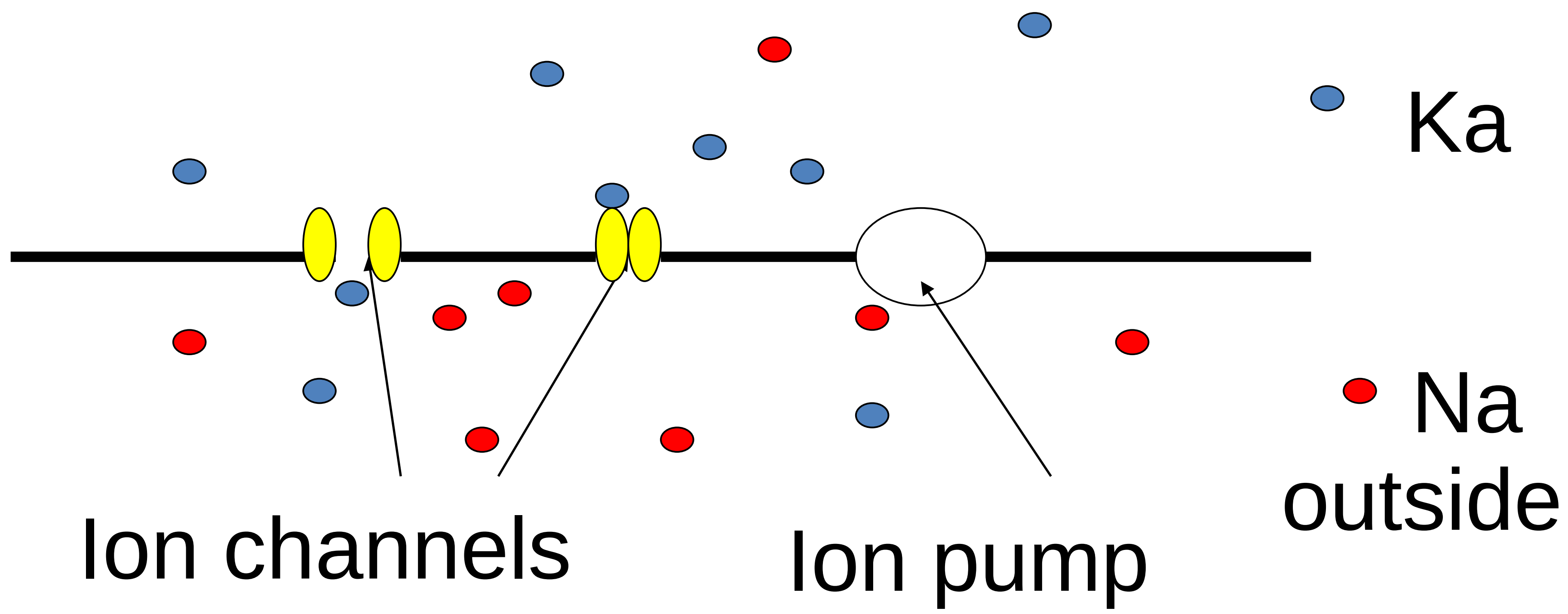
Hodgkin&Huxley (1952)

Nobel Prize 1963

Neuronal Dynamics – 2.3. Hodgkin-Huxley Model

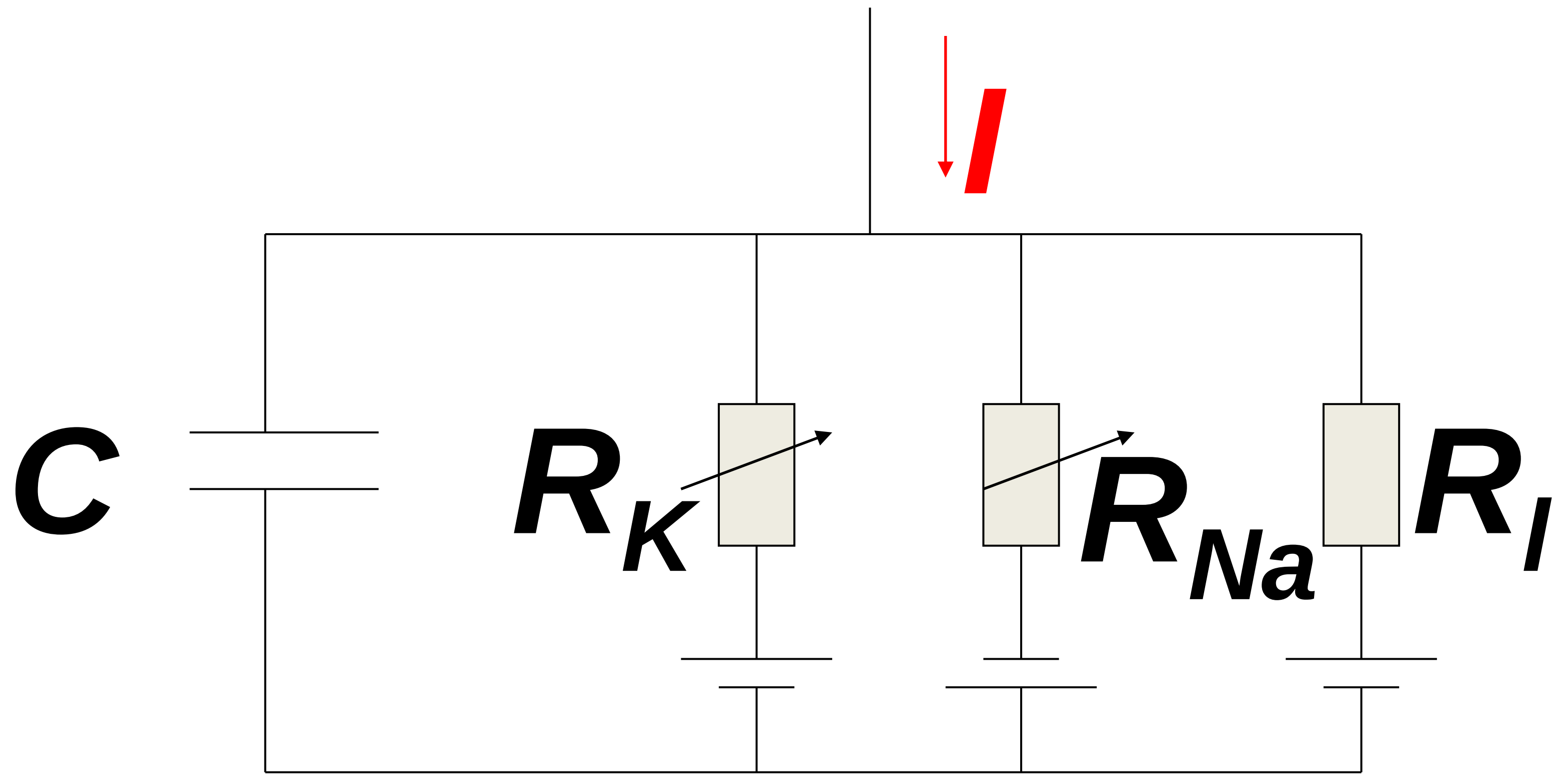
Hodgkin and Huxley, 1952





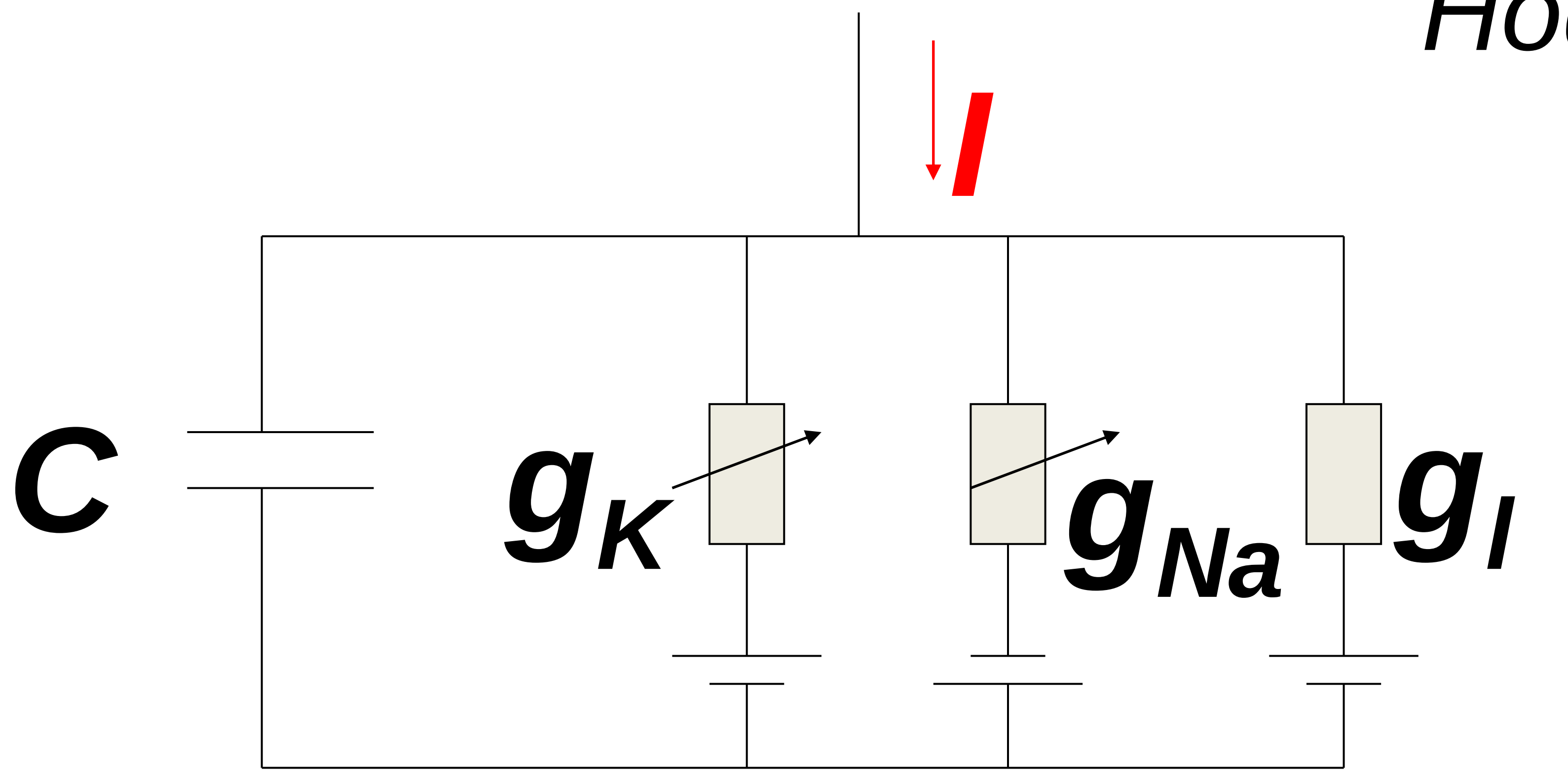
Mathematical derivation

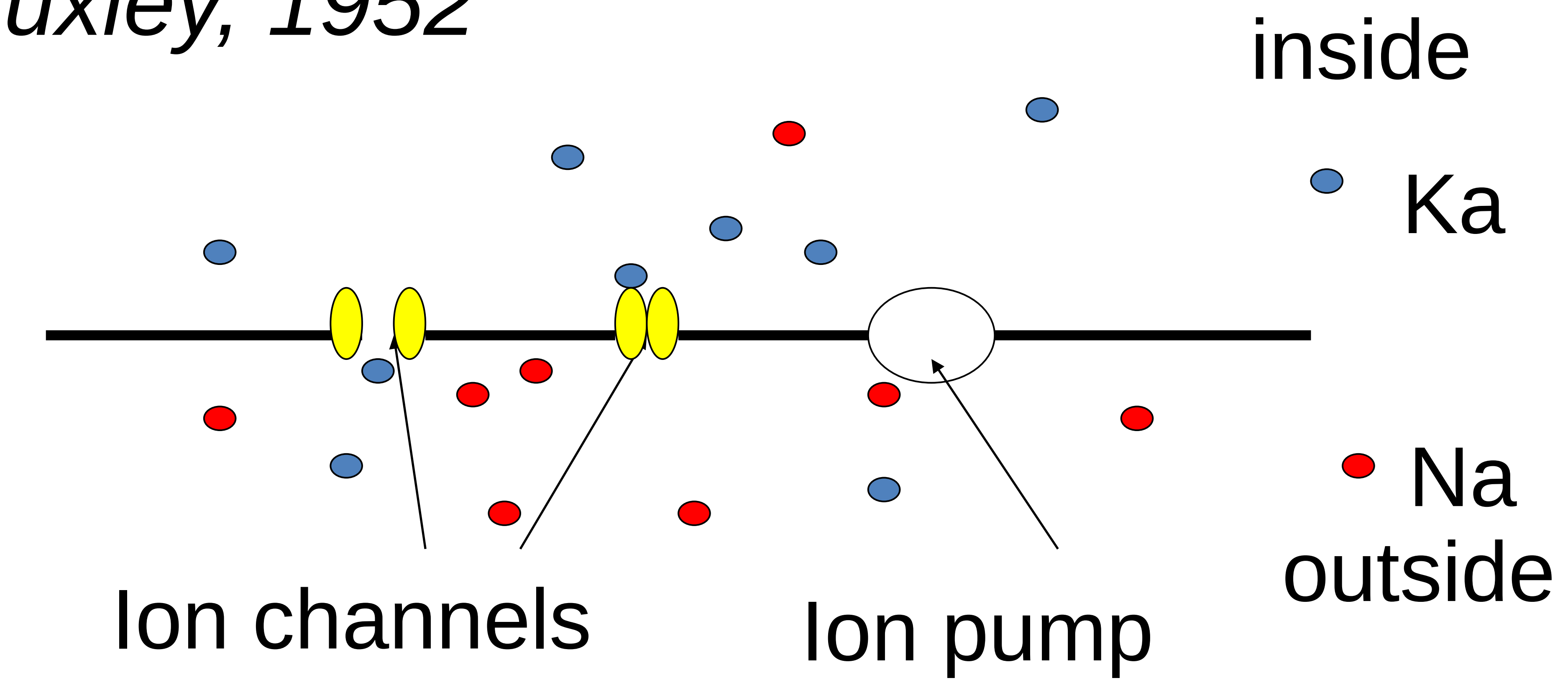
Neuronal Dynamics – 2.3. Hodgkin-Huxley Model



Neuronal Dynamics – 2.3. Hodgkin-Huxley Model

Hodgkin and Huxley, 1952

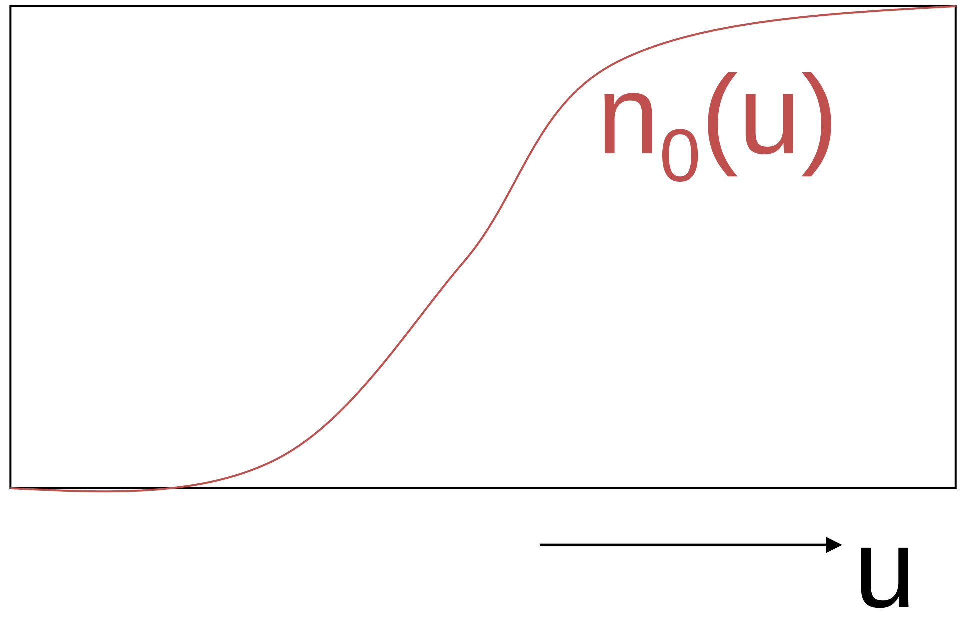


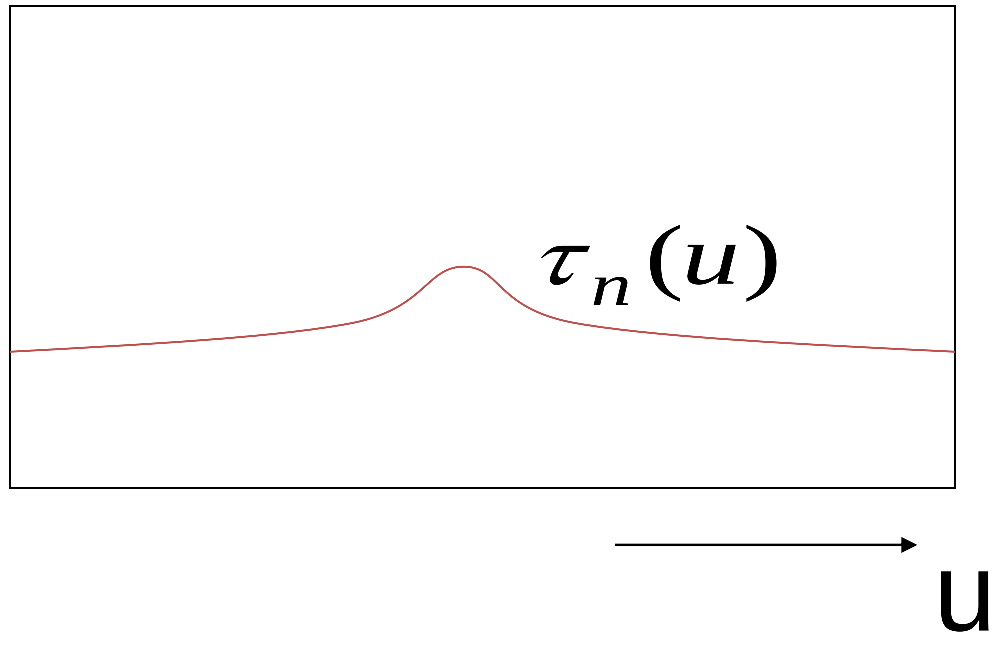


stimulus

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

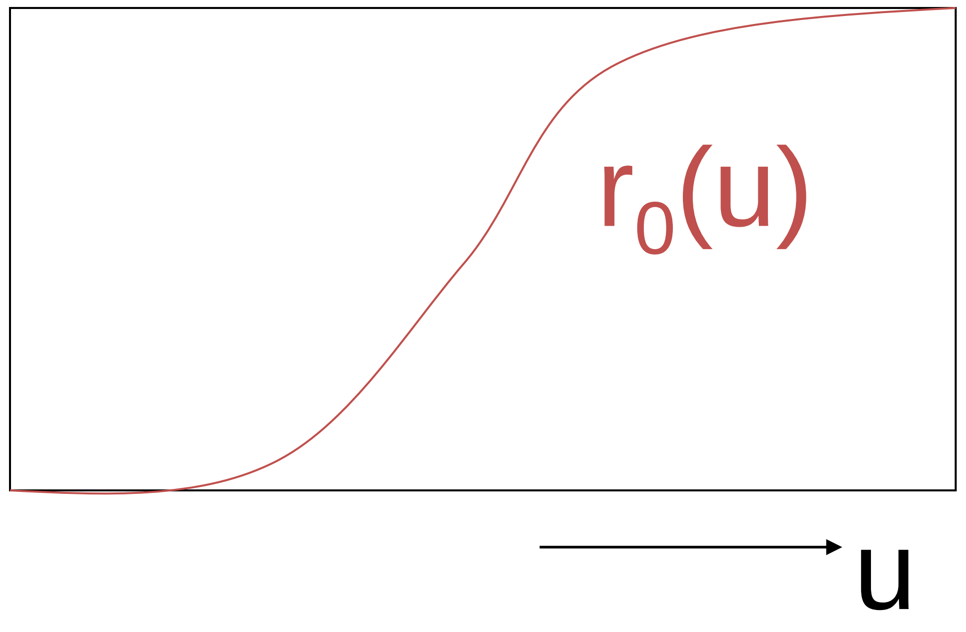
$$\frac{dm}{dt} = -\frac{m - m_0(u)}{\tau_m(u)} \qquad \frac{dh}{dt} = -\frac{h - h_0(u)}{\tau_h(u)}$$

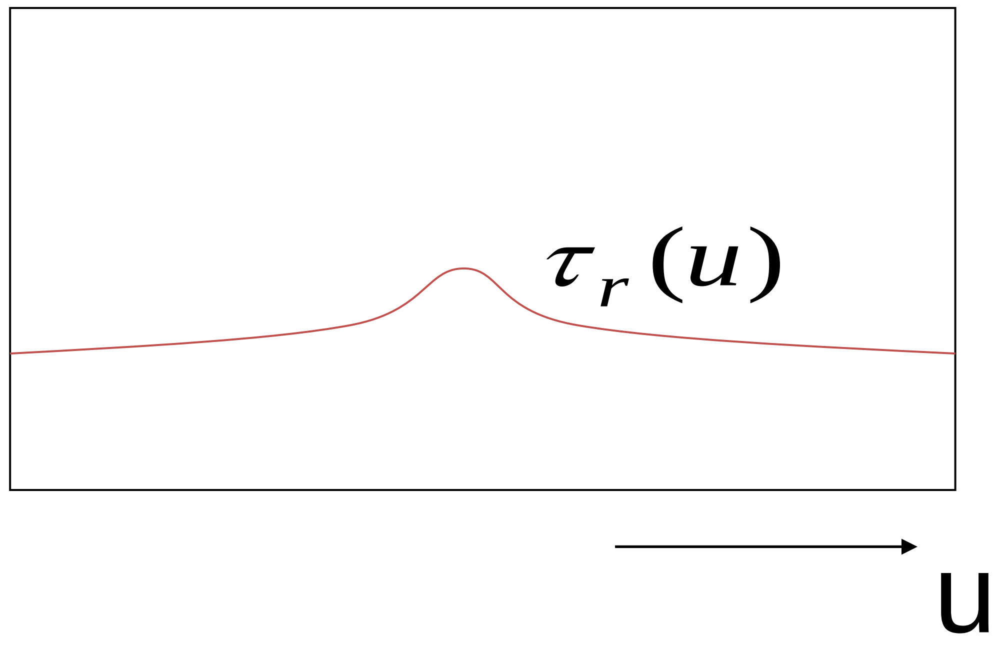




Neuronal Dynamics – 2.3. Ion channel

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



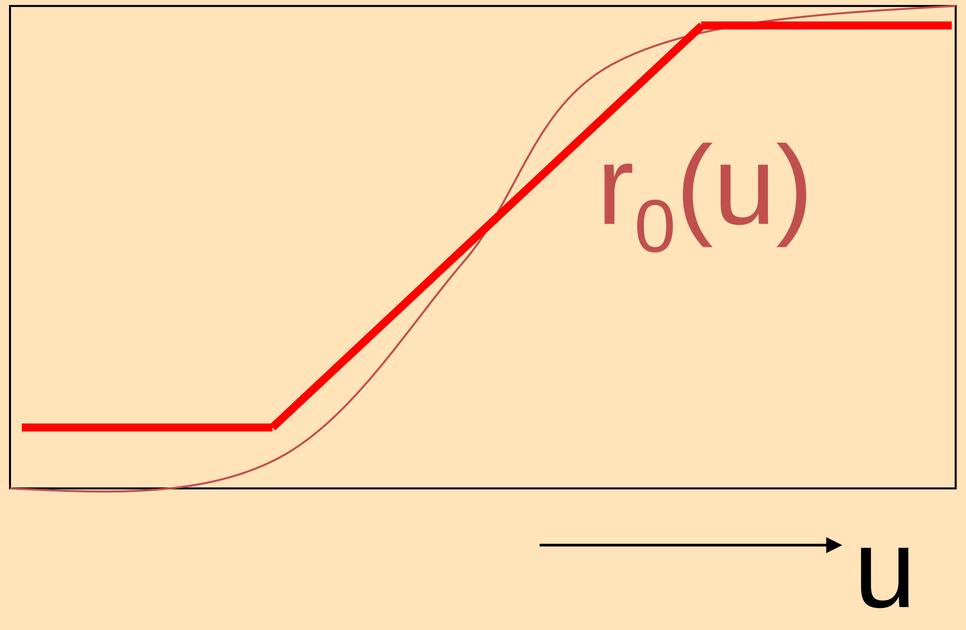


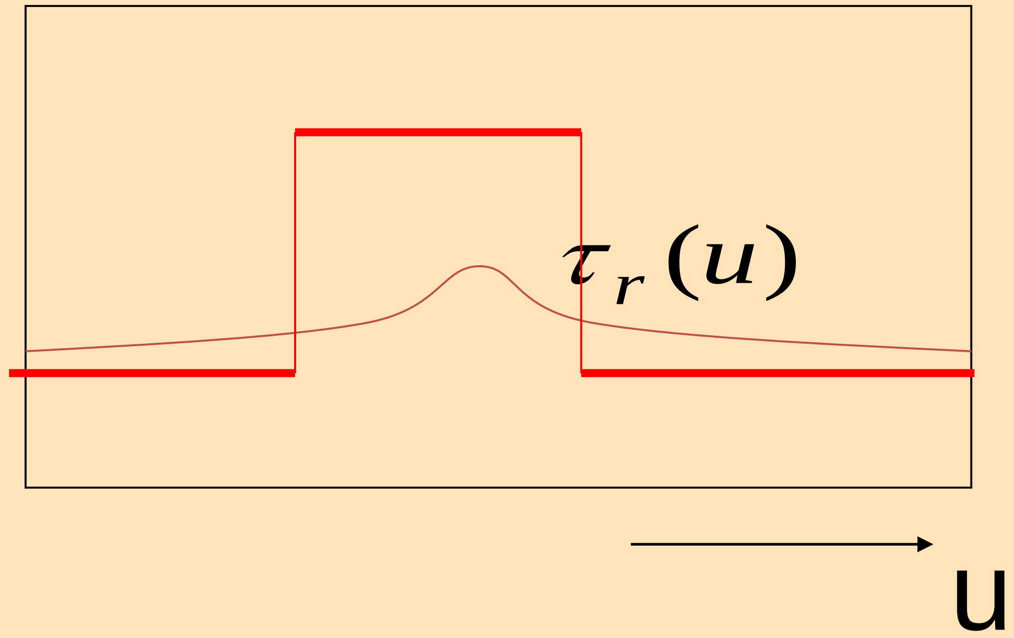
$$I_{ion} = -g_{ion} r^{n_1} s^{n_2}$$

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

Exercise 2 and 1.2 NOW!! - Ion channel

Next lecture at:
10H40





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

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

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

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Biological Modeling of Neural Networks

Week 2 – Biophysical modeling: The Hodgkin-Huxley model

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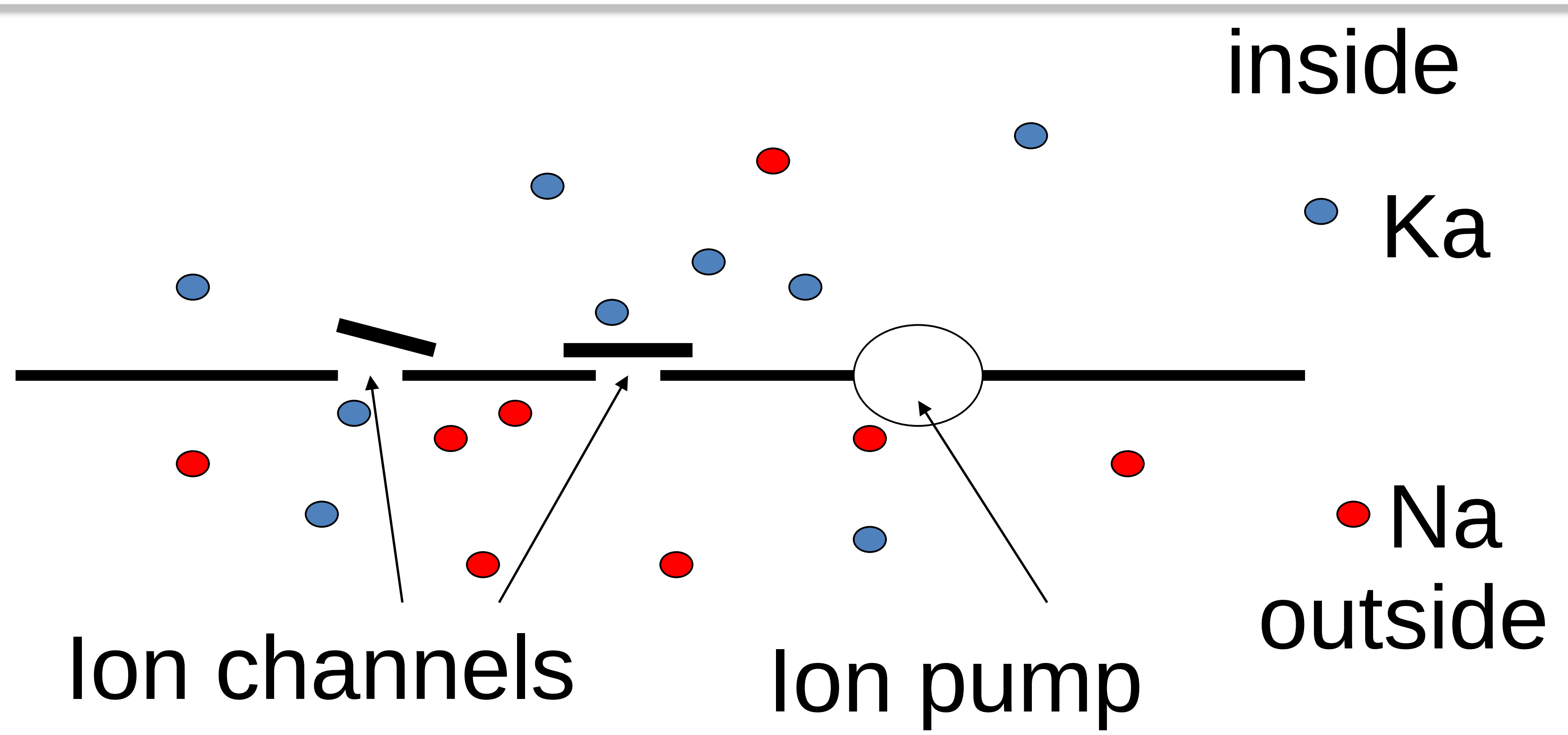
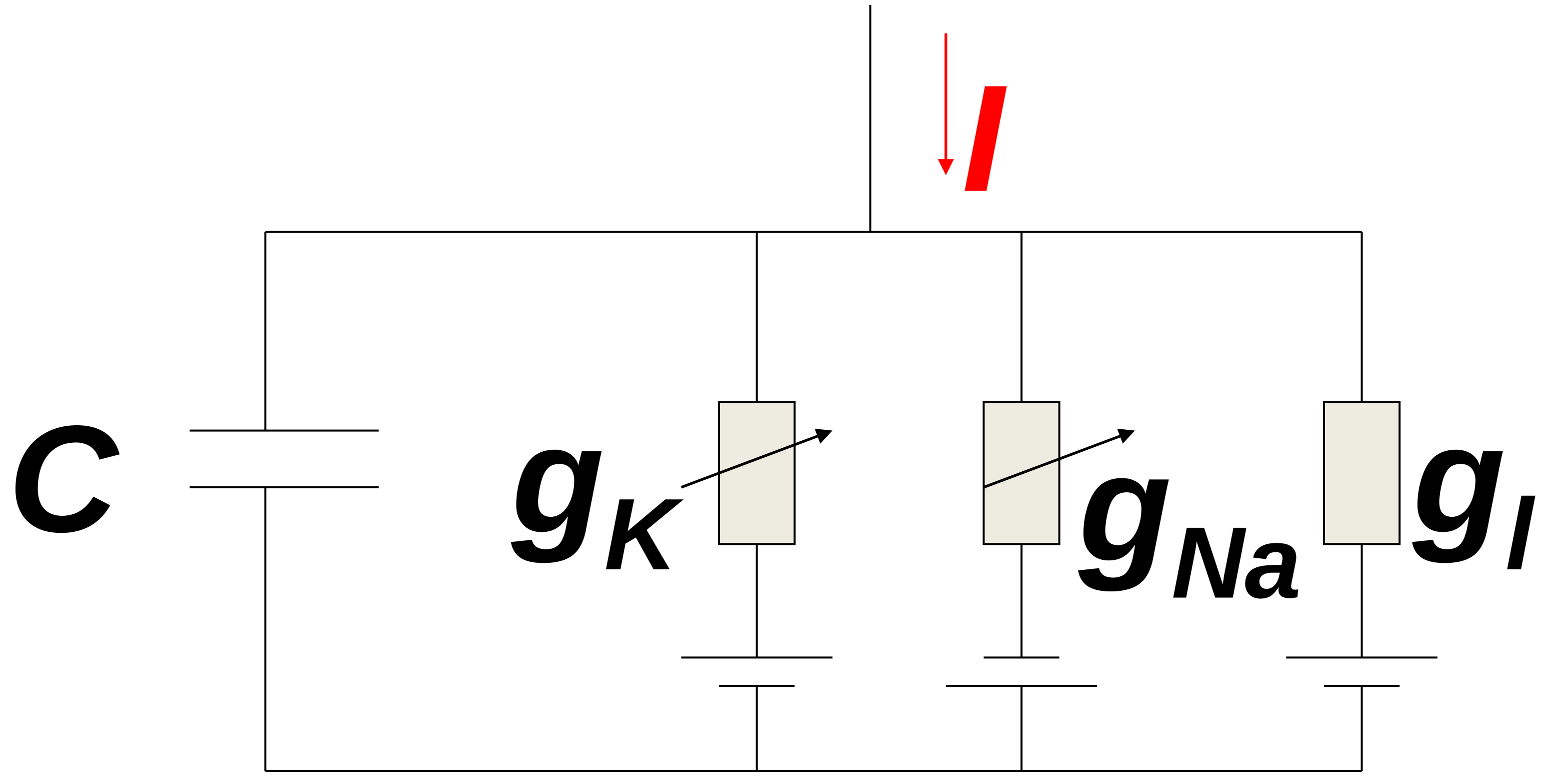
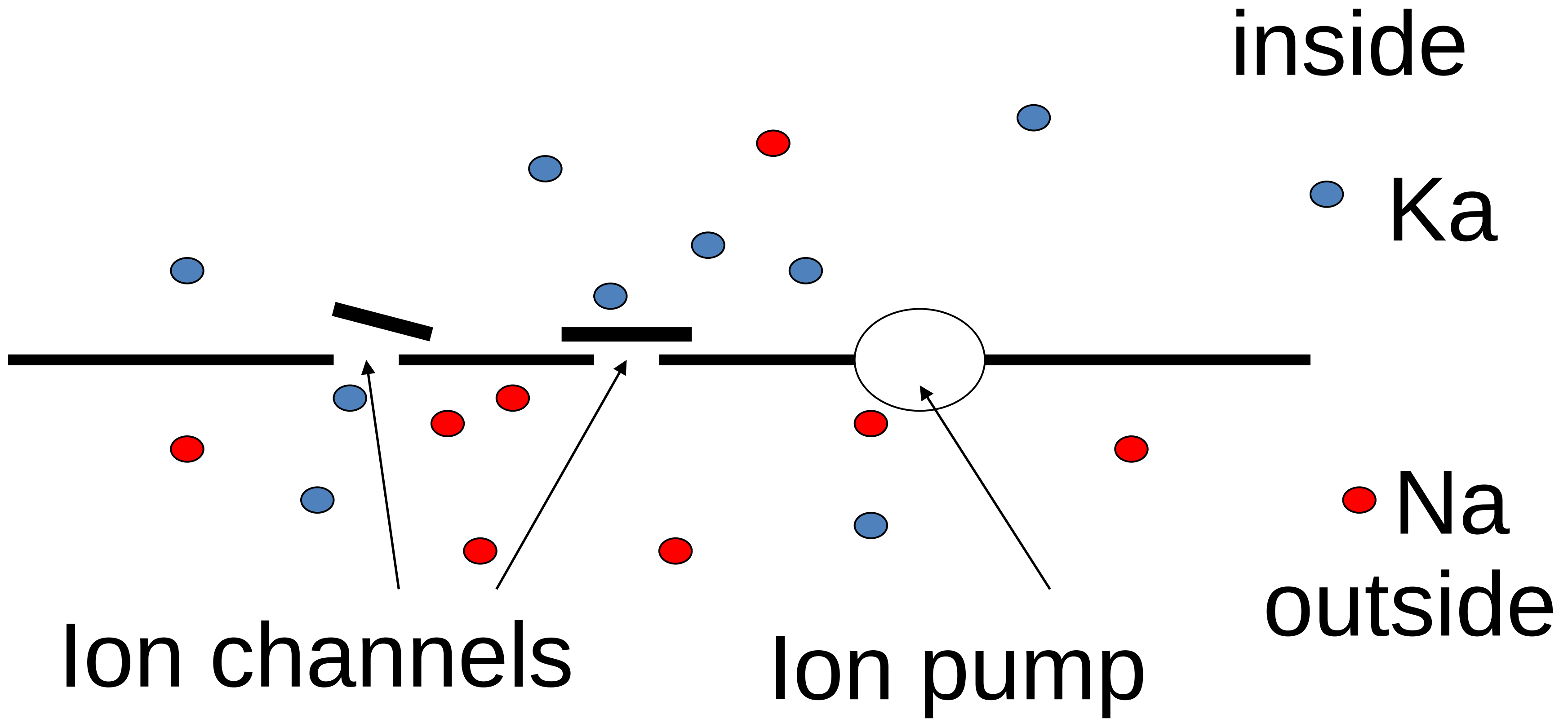
Neuronal Dynamics – 2.4. Threshold in HH model



Neuronal Dynamics – 2.4. Threshold in HH model



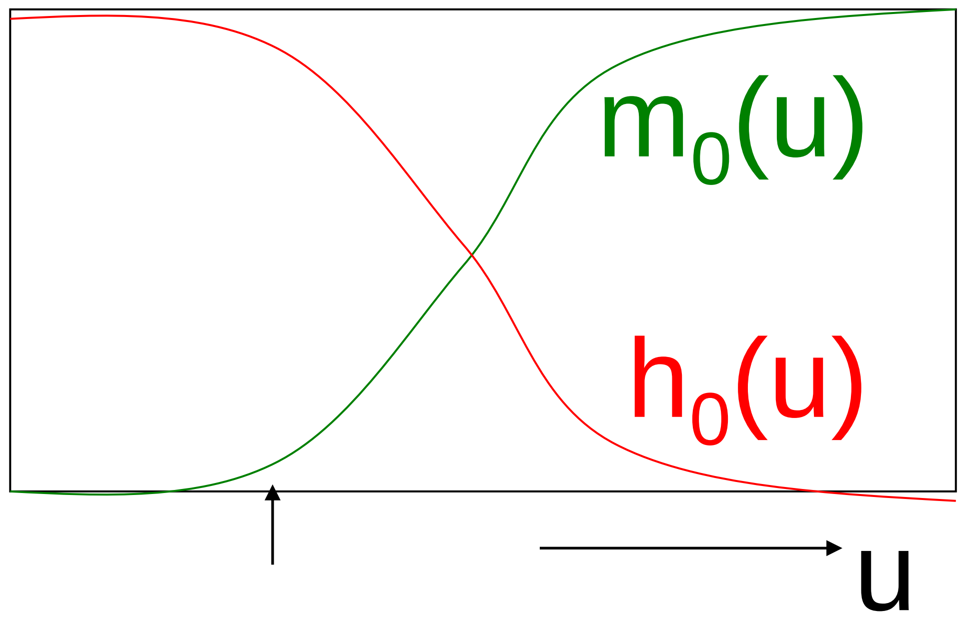


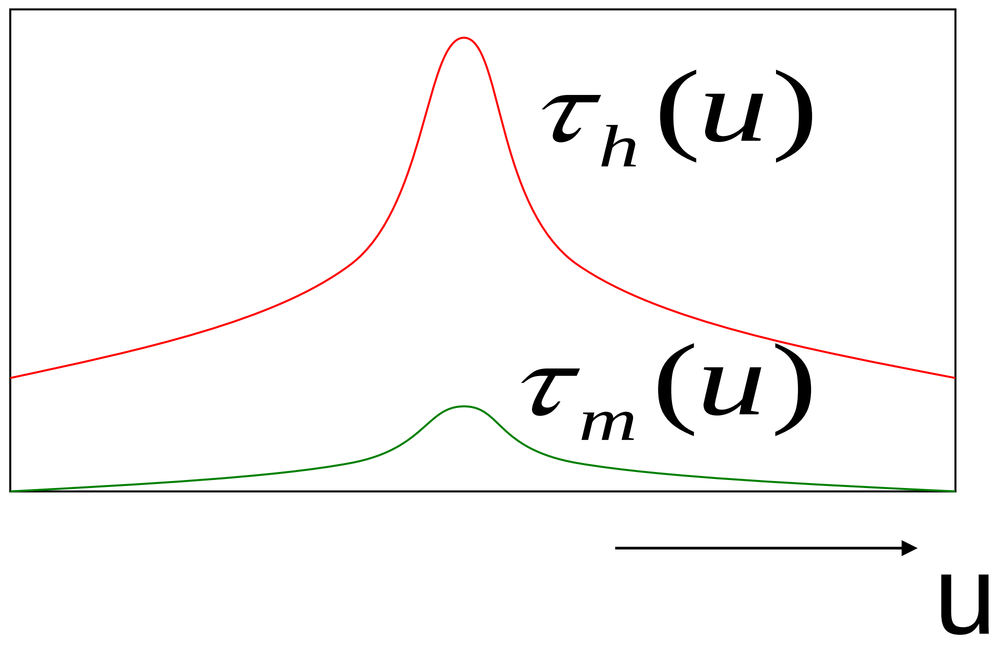
$$C\frac{du}{dt} = \overbrace{-g_{Na} m^3 h(u-E_{Na})}^{I_{Na}} \overbrace{- g \ldots}^{I_K} \ldots g_l(u-E_l) + I(t)$$

Where is the threshold for firing?

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

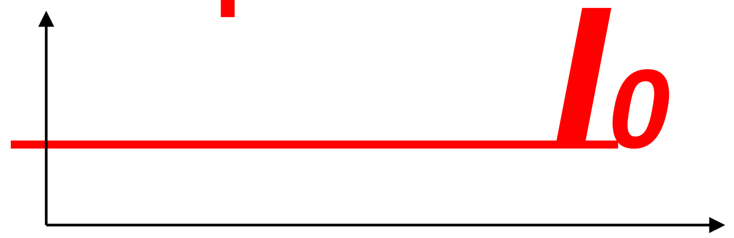
$$\frac{dh}{dt} = -\frac{h - h_0(u)}{\tau_h(u)}$$

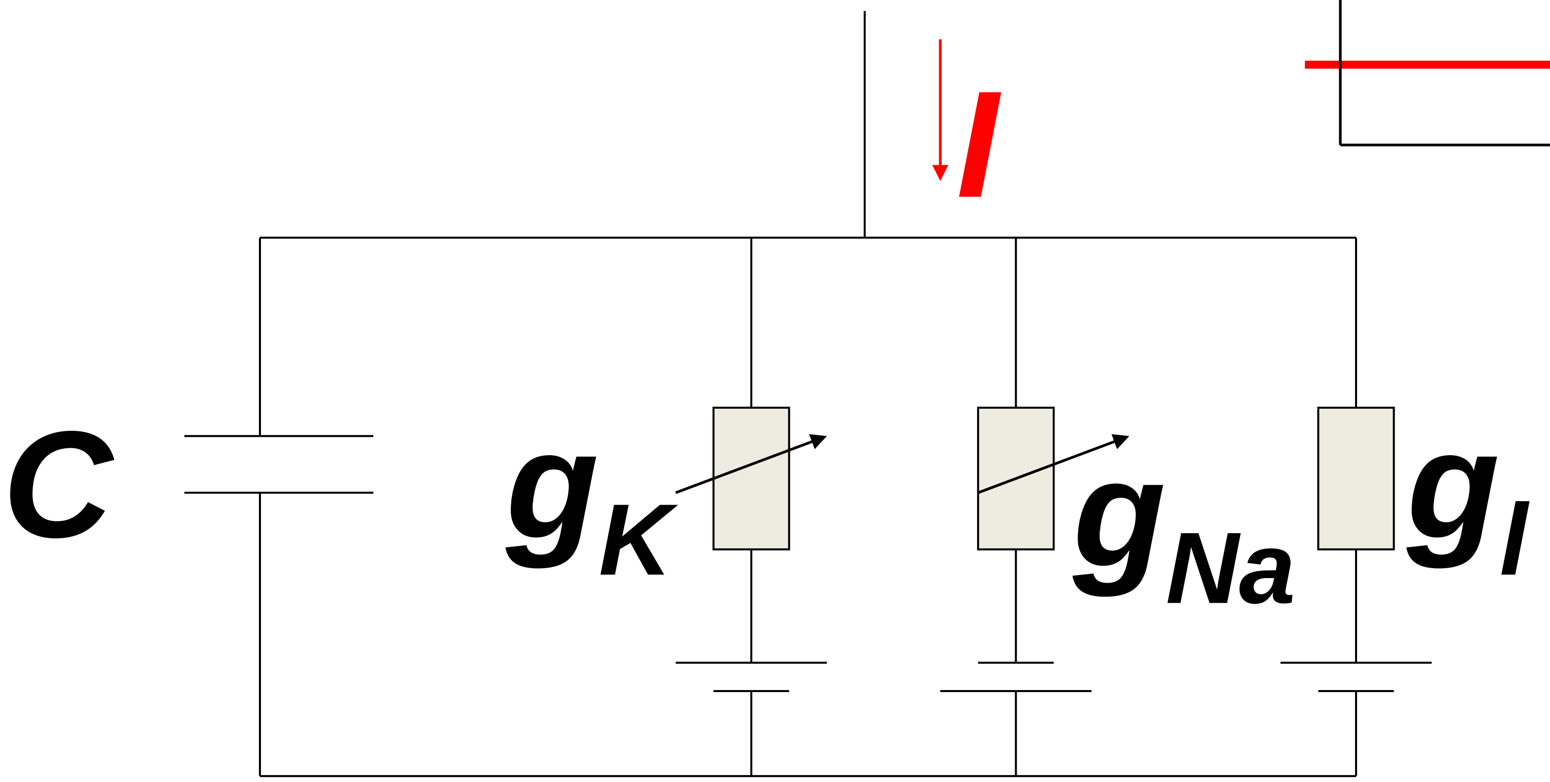


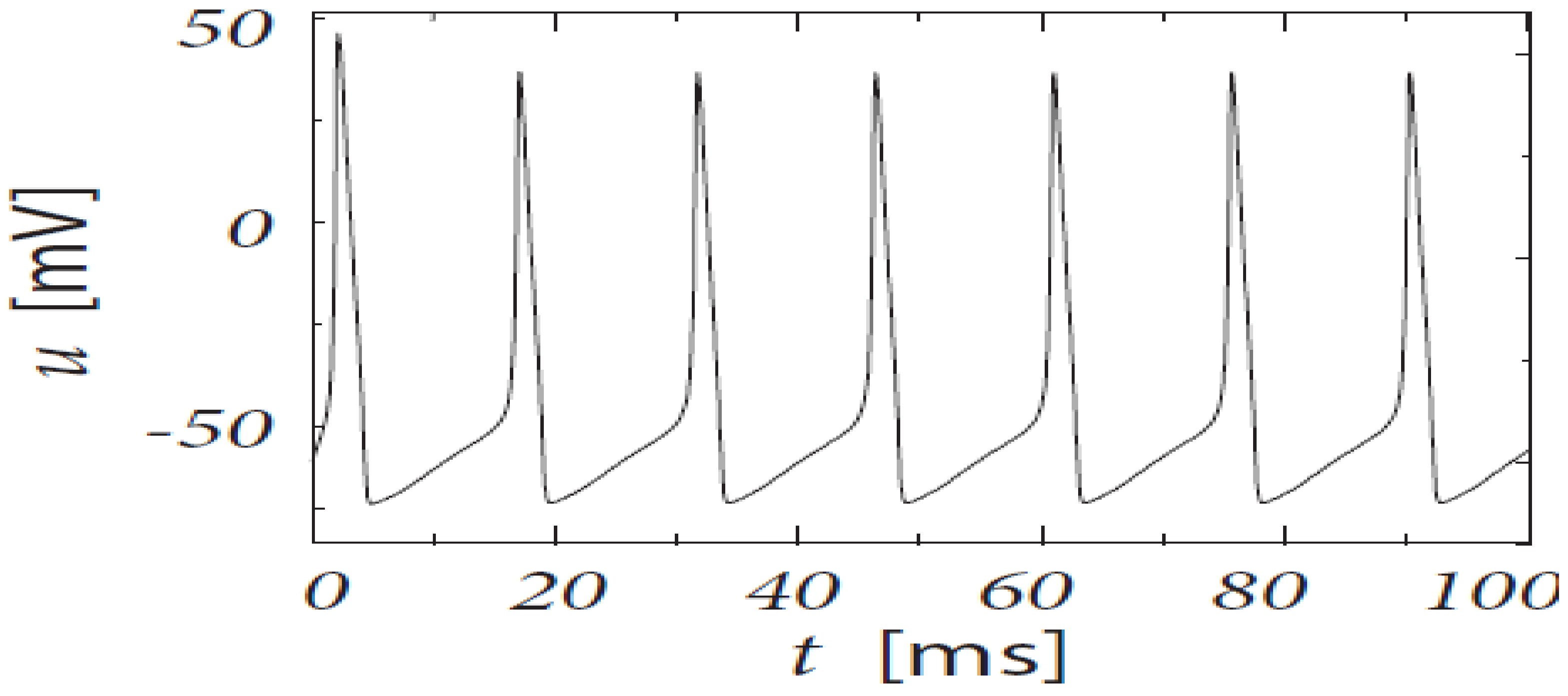


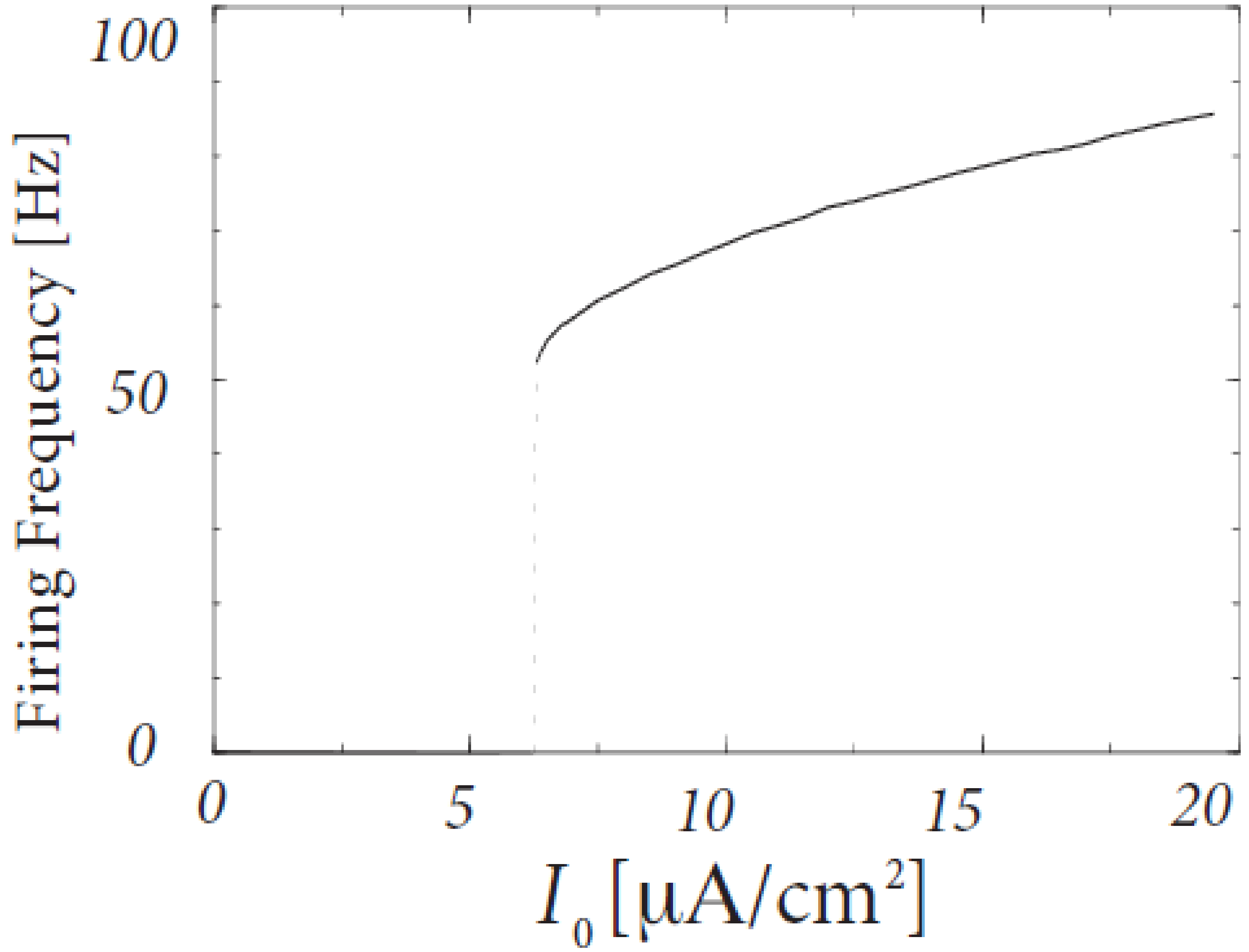
Neuronal Dynamics – 2.4. Threshold in HH model

Constant current input









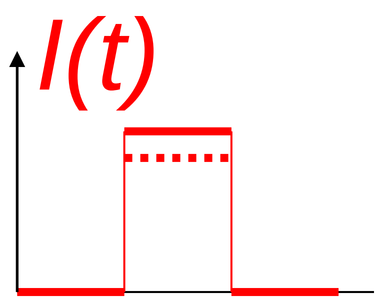
Threshold?

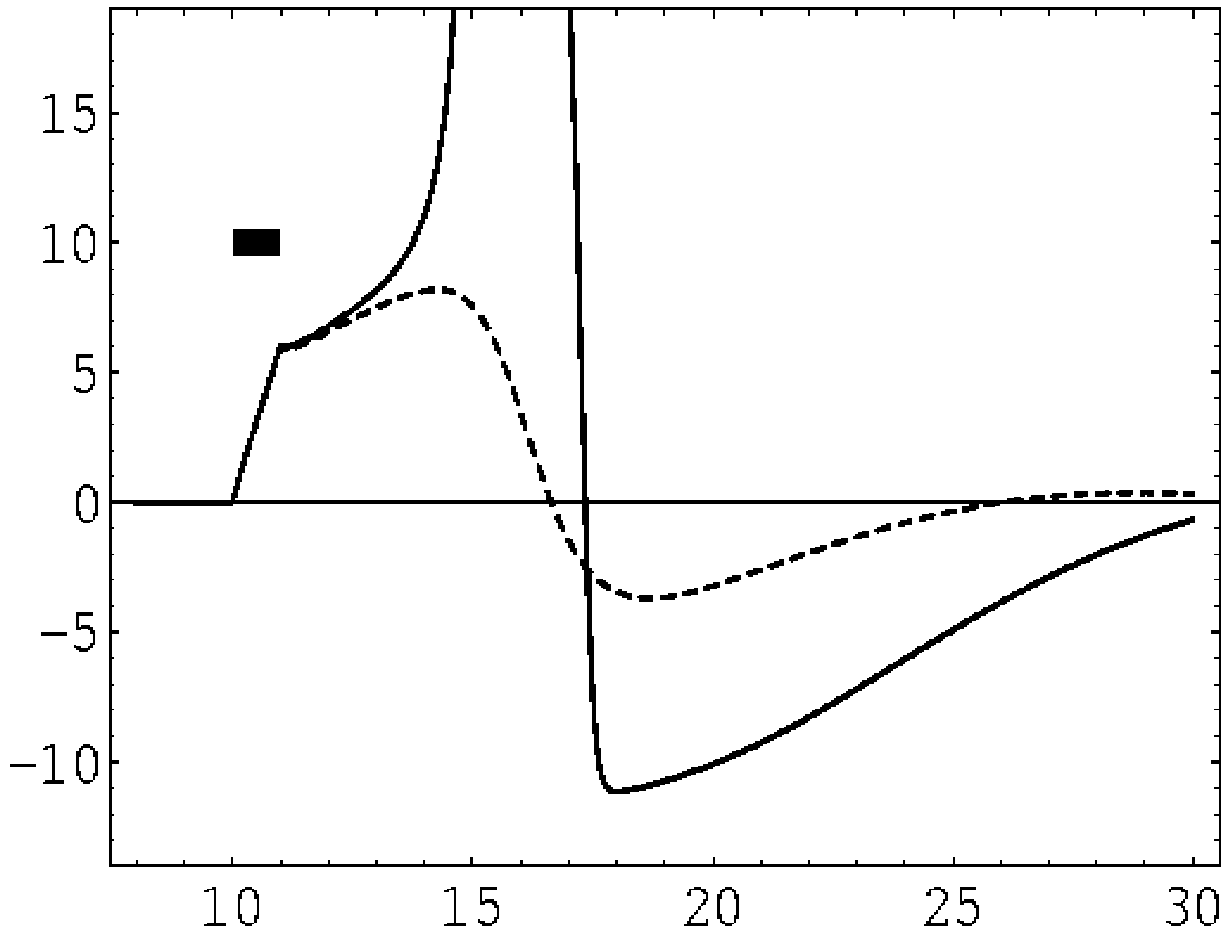
for repetitive firing

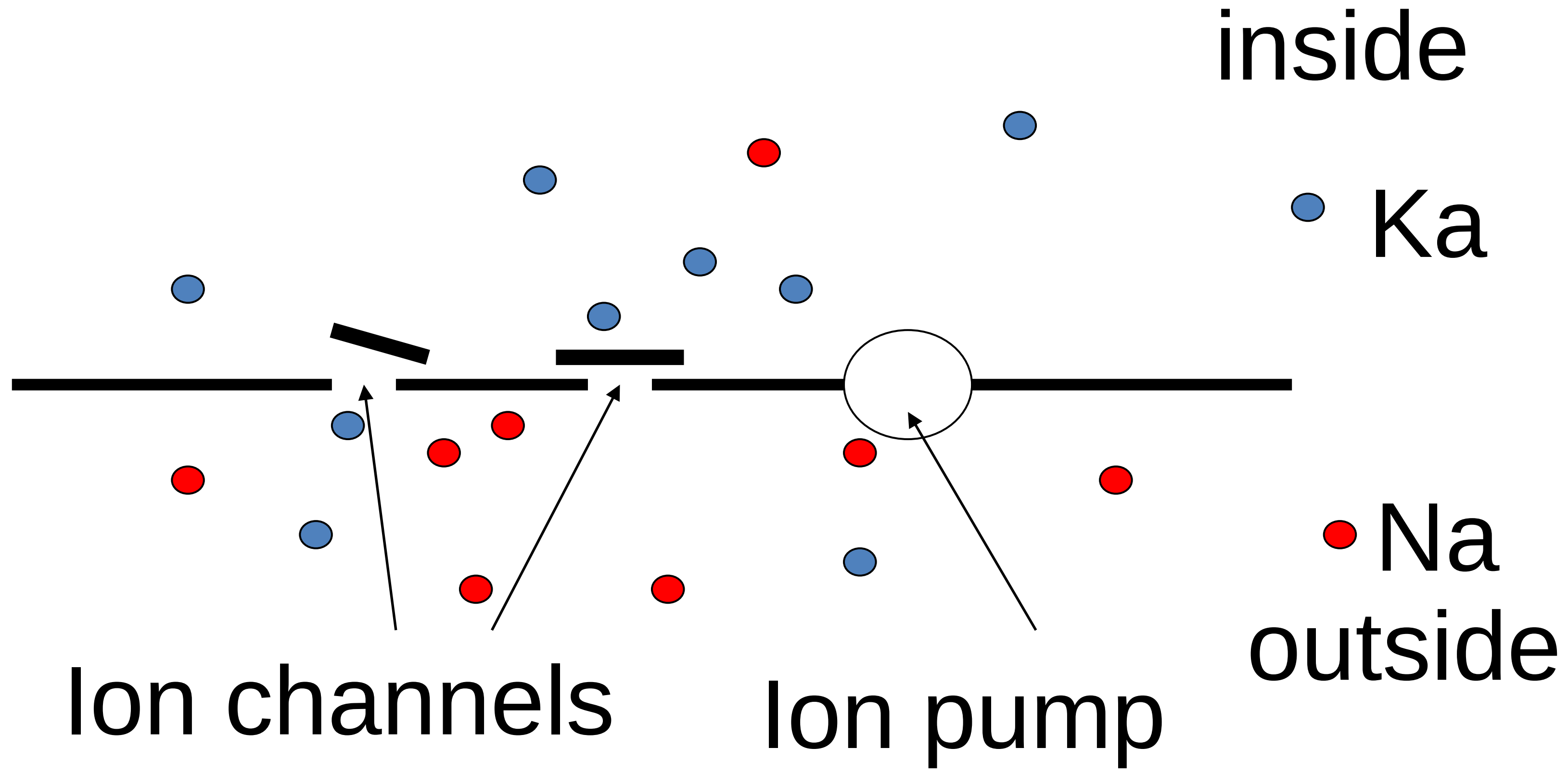
(***current*** threshold)

Neuronal Dynamics – 2.4. Threshold in HH model

pulse input







Threshold?

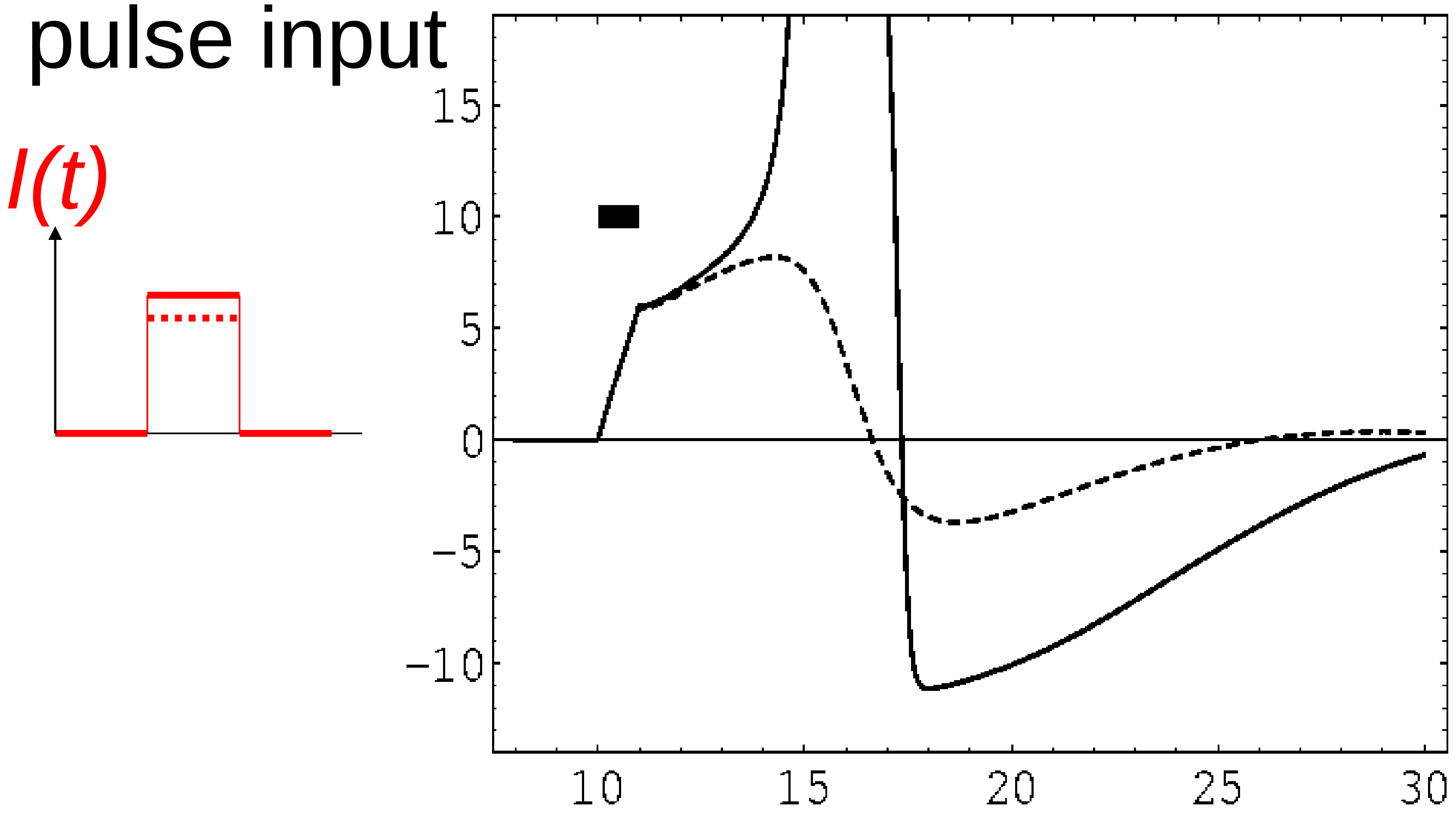
- AP if amplitude 7.0 units
- No AP if amplitude 6.9 units

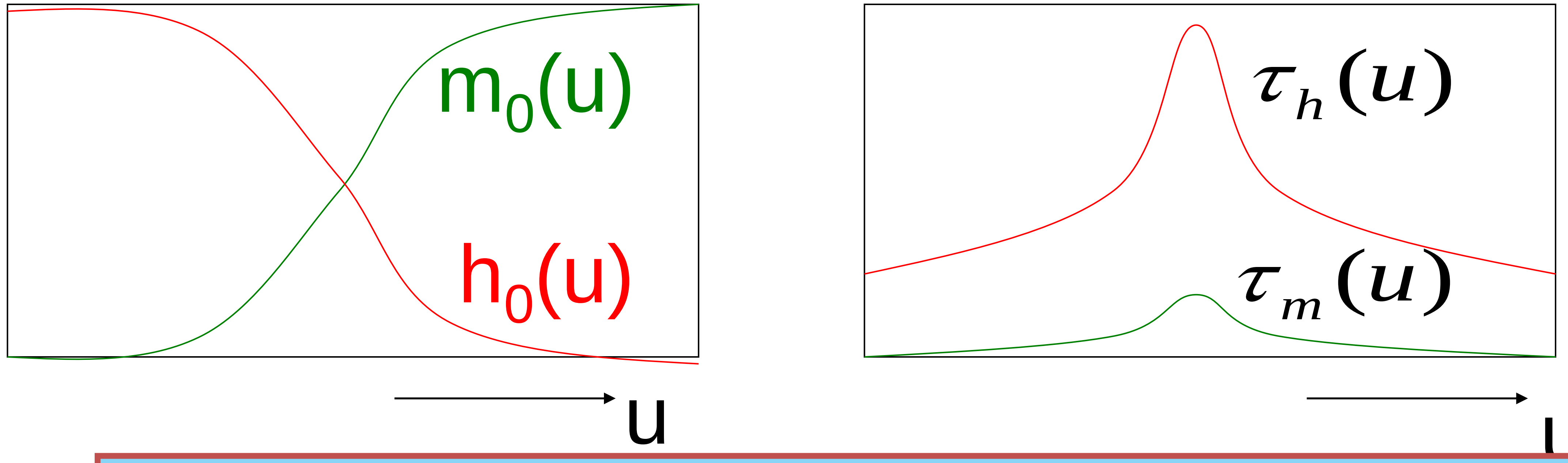
(pulse with 1ms duration)

(and pulse with 0.5 ms duration?)

Neuronal Dynamics – 2.4. Threshold in HH model

pulse input





Mathematical explanation

I_{Na} I_K I_{leak} Stim.

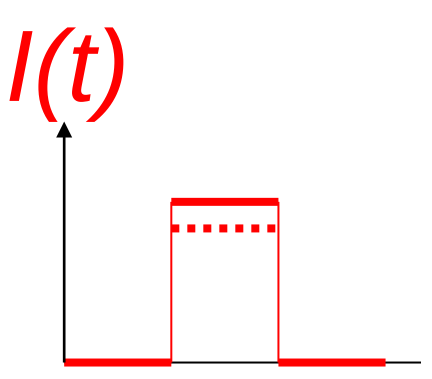
$$C\frac{du}{dt} = -g_{Na}m^3h(u-E_{Na}) - g_K n^4(u-E_K) - g_l(u-E_l) + I(t)$$

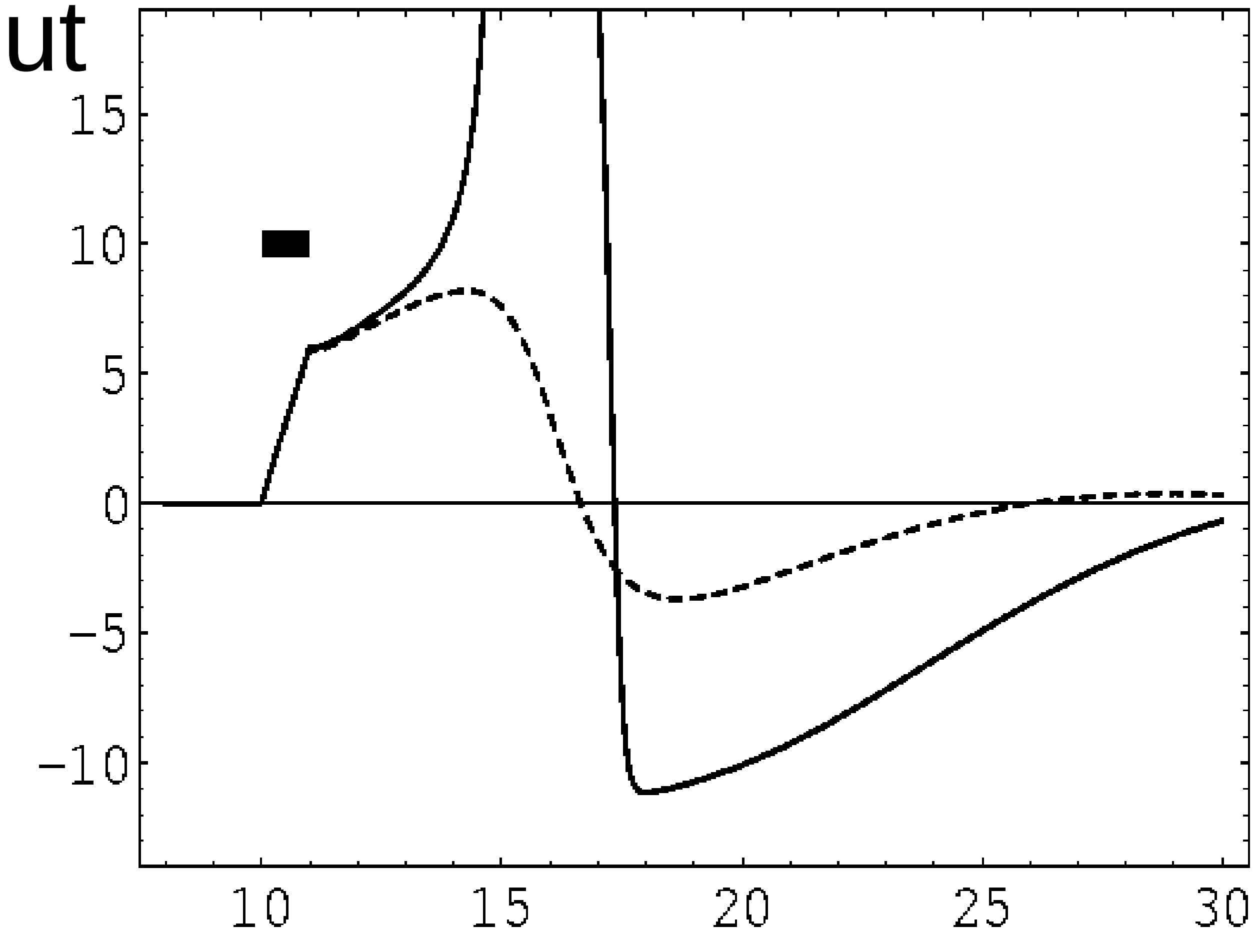
$$\frac{dm}{dt} = -\frac{m-m_0(u)}{\tau_m(u)}$$

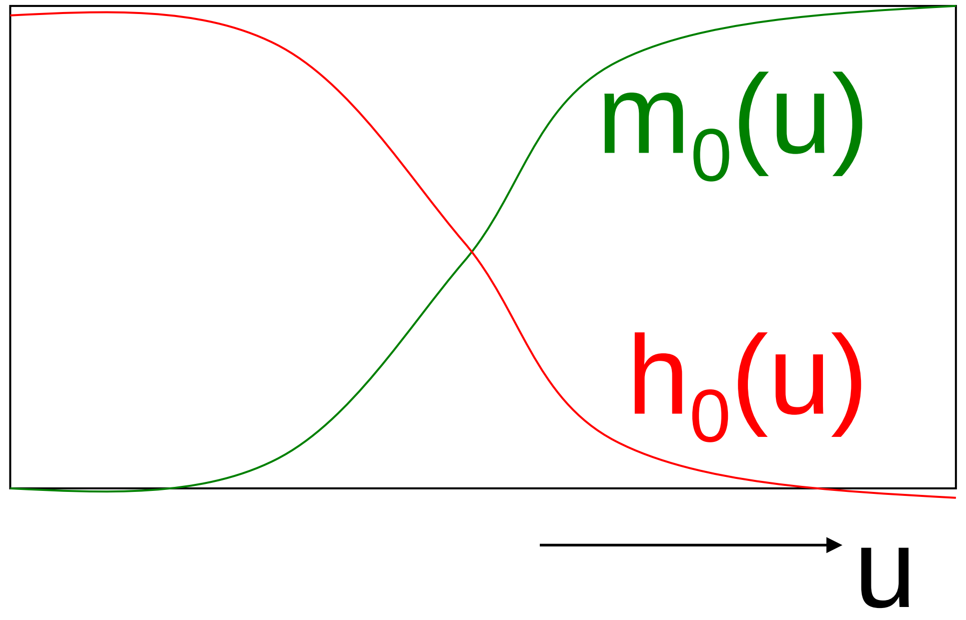
$$\frac{dh}{dt} = -\frac{h-h_0(u)}{\tau_h(u)}$$

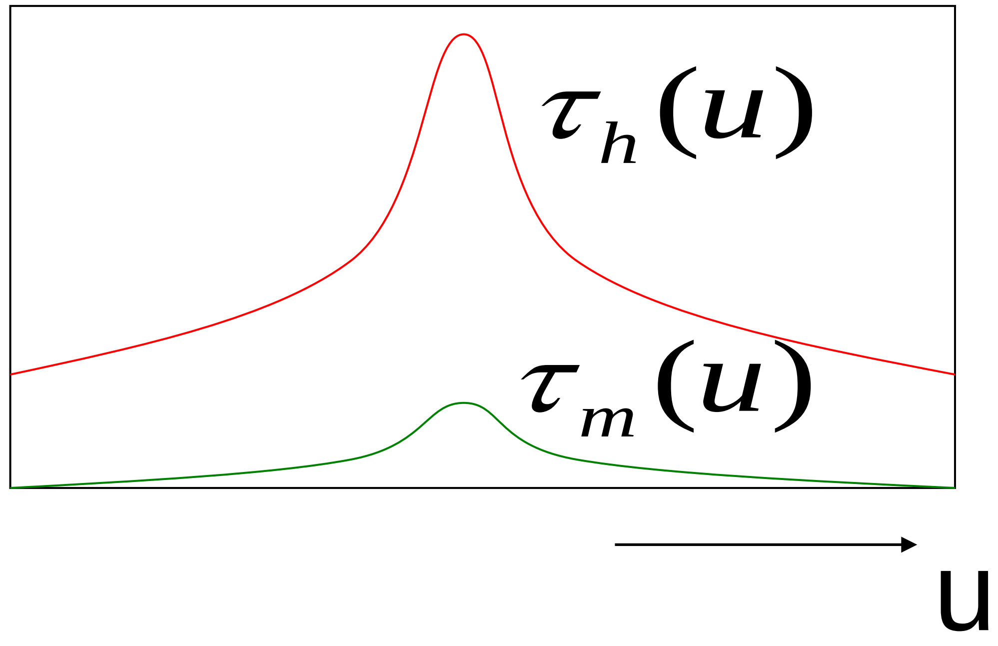
Neuronal Dynamics – 2.4. Threshold in HH model

pulse input









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

Stim. → $I(t)$

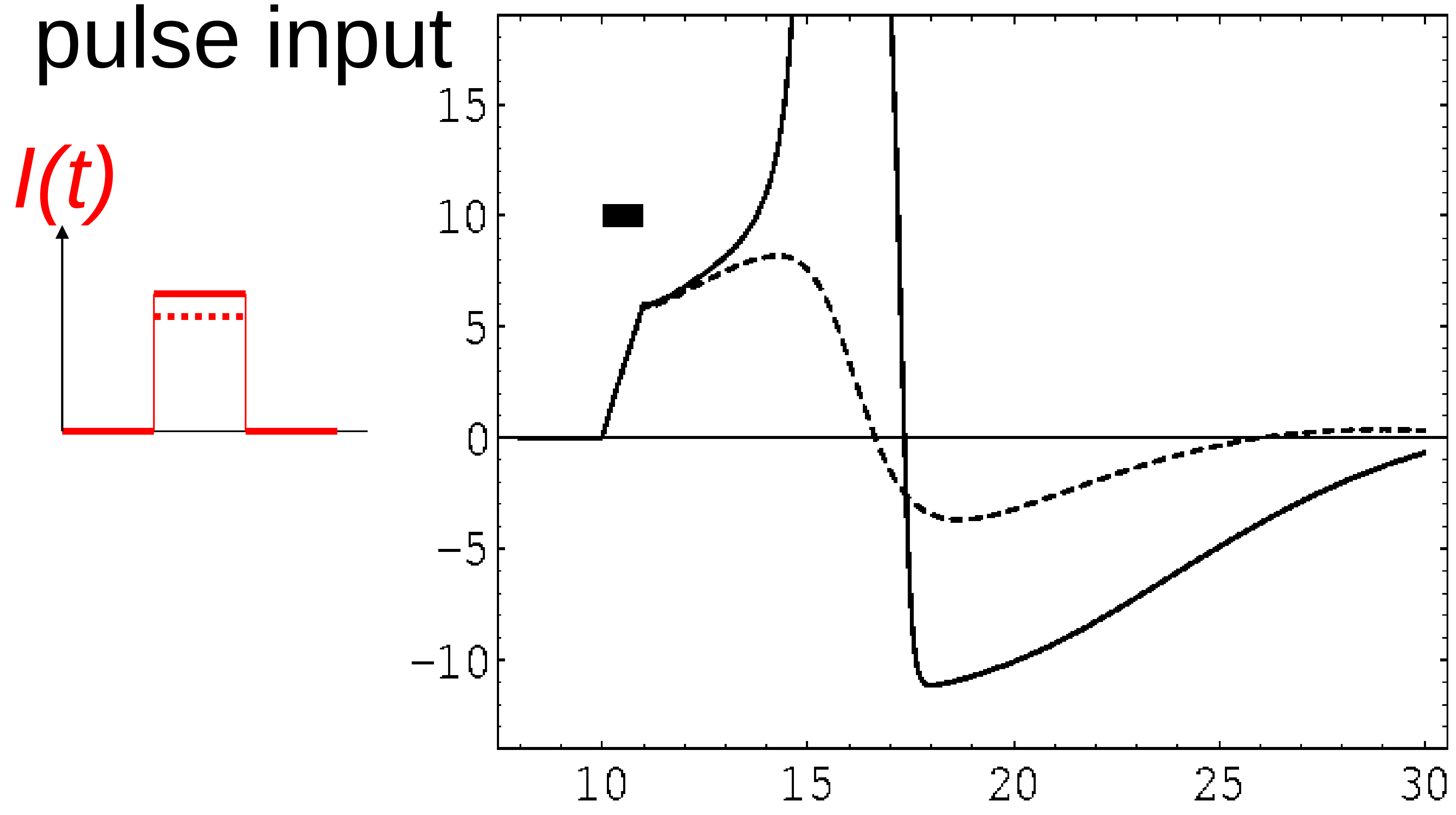
$$\frac{dm}{dt} = -\frac{m-m_0(u)}{\tau_m(u)}$$

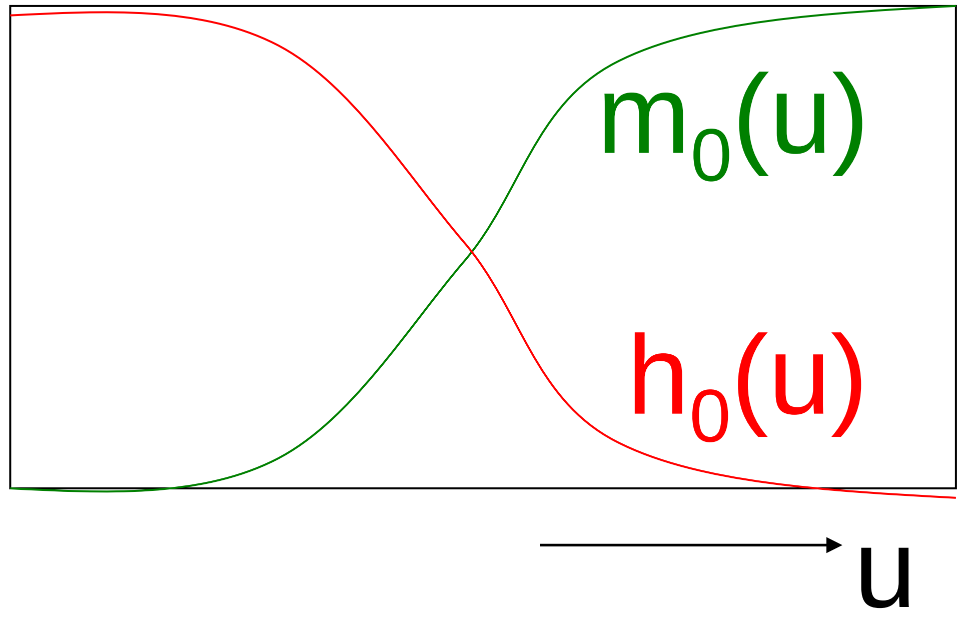
$$\frac{dh}{dt} = -\frac{h-h_0(u)}{\tau_h(u)}$$

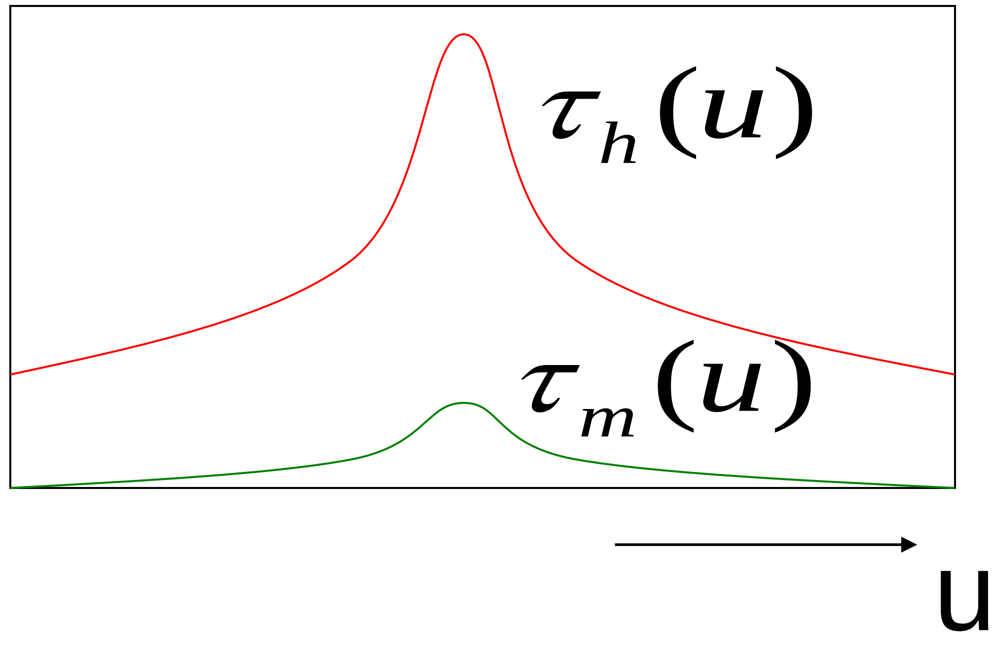
Where is the threshold?
Blackboard!

Neuronal Dynamics – 2.4. Threshold in HH model

pulse input







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

What about *n*?

Where is the threshold?

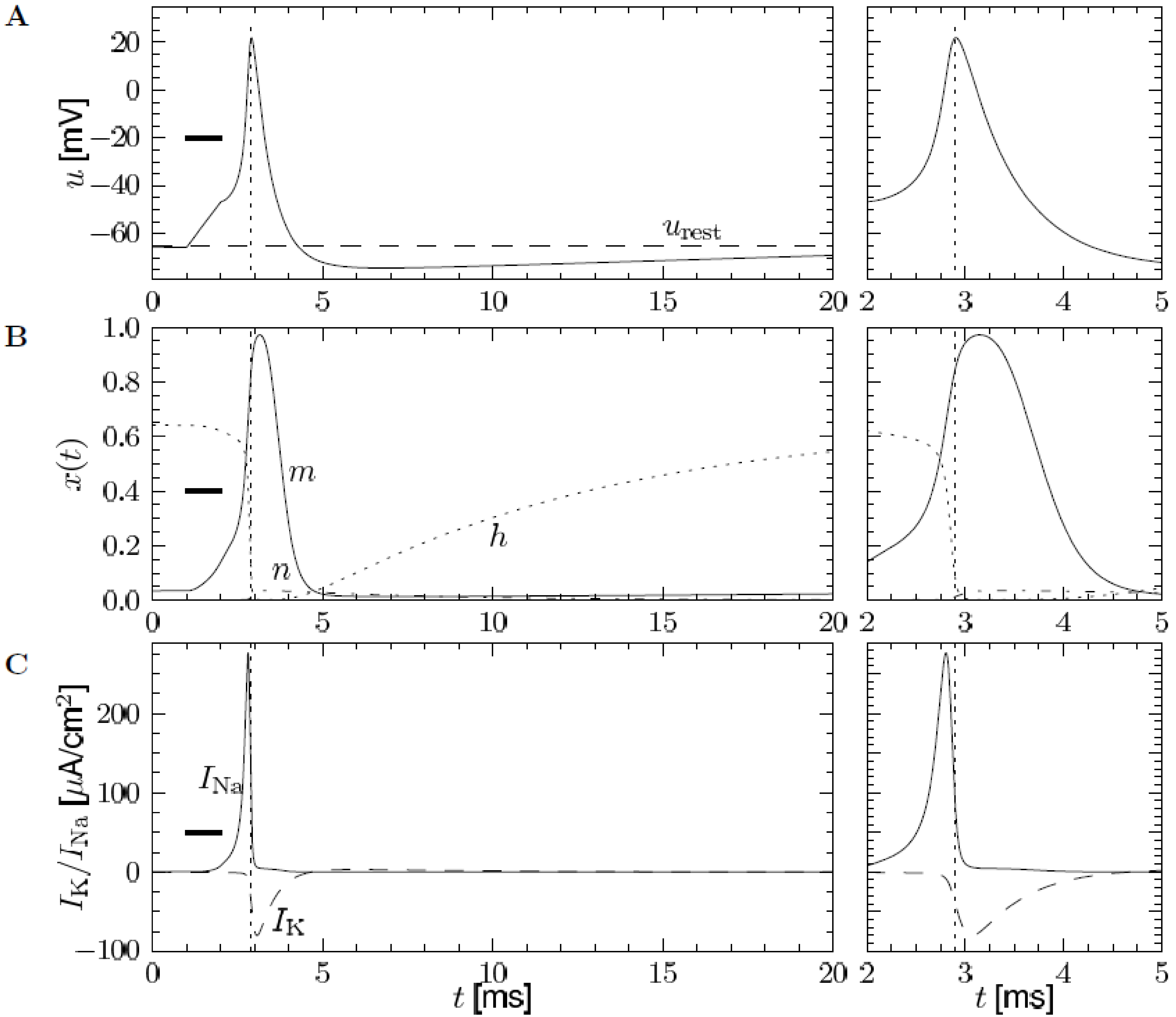
$$C\frac{du}{dt} = \overbrace{-g_{Na}m^3h(u-E_{Na})}^{I_{Na}} \overbrace{-g_K n^4(u-E_K)}^{I_K} \overbrace{-g_l(u-E_l)}^{I_{leak}} + \overbrace{I(t)}^{\text{Stim.}}$$

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

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

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

Neuronal Dynamics – 2.4. Threshold in HH model



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

First conclusion:

There is no strict threshold:

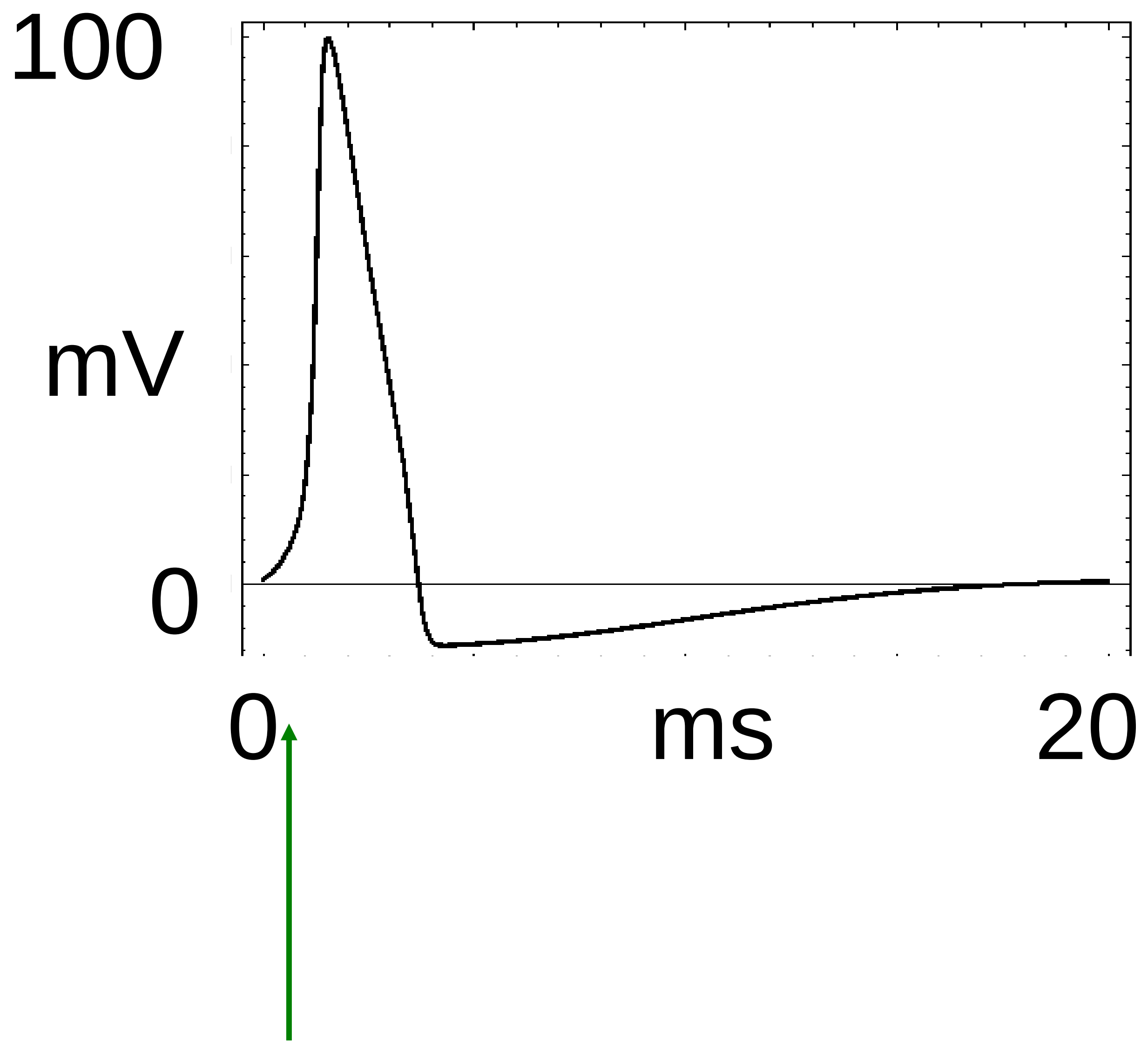
Coupled differential equations

'Effective' threshold
in simulations?

Neuronal Dynamics – 2.4. Refractoriness in HH model

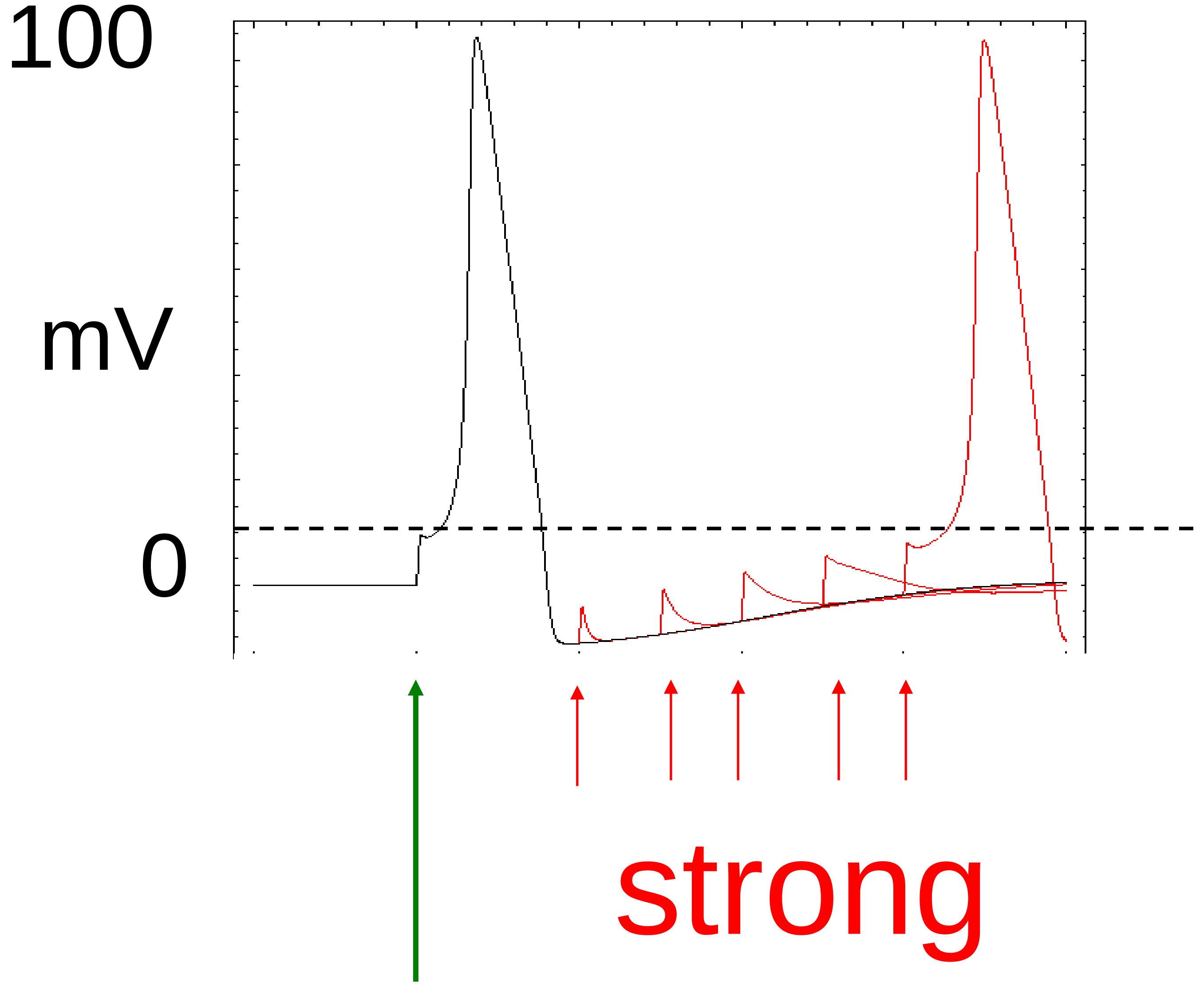
Where is the firing threshold?

Action potential



Strong stimulus

refractoriness

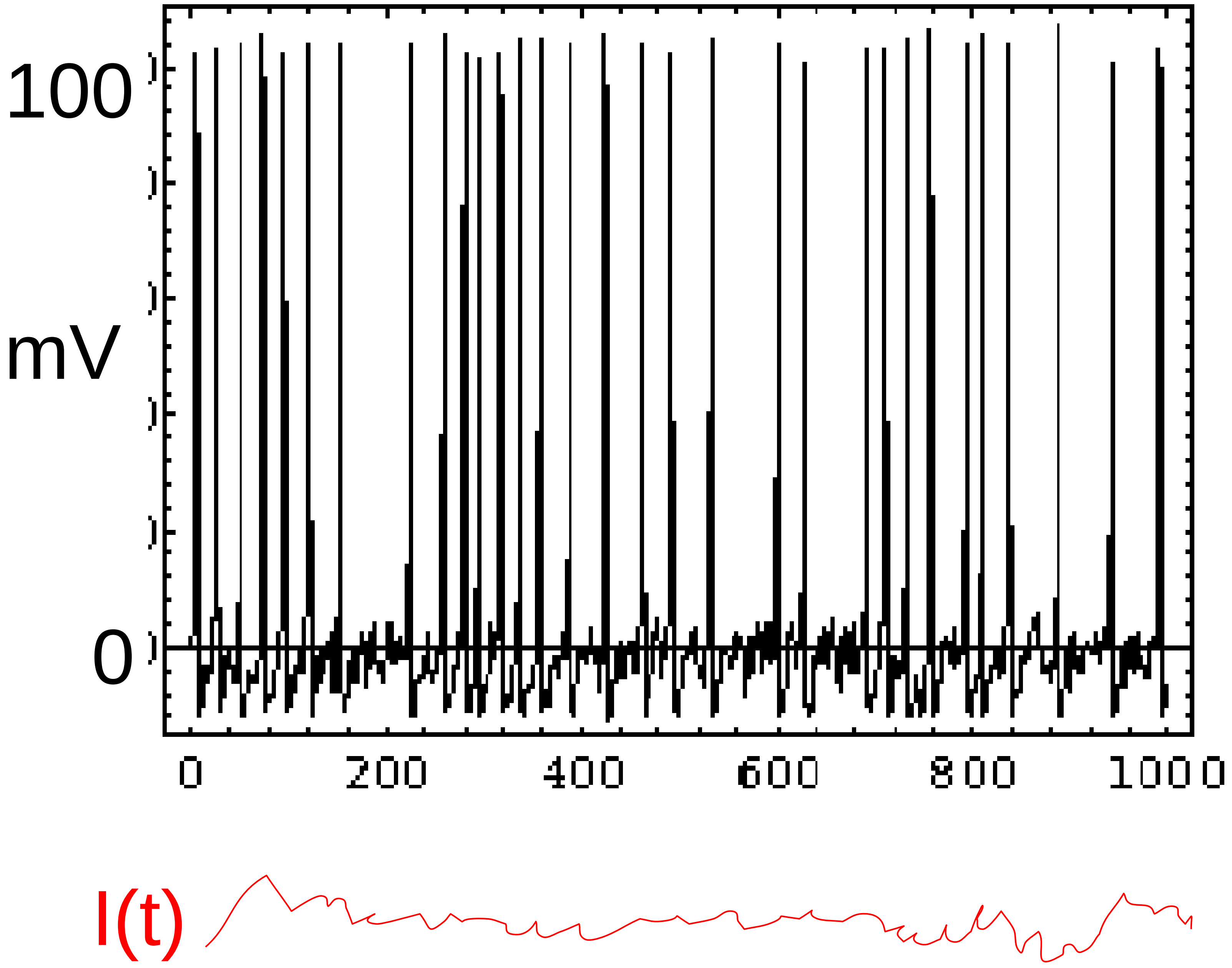


strong stimuli

Strong stimulus

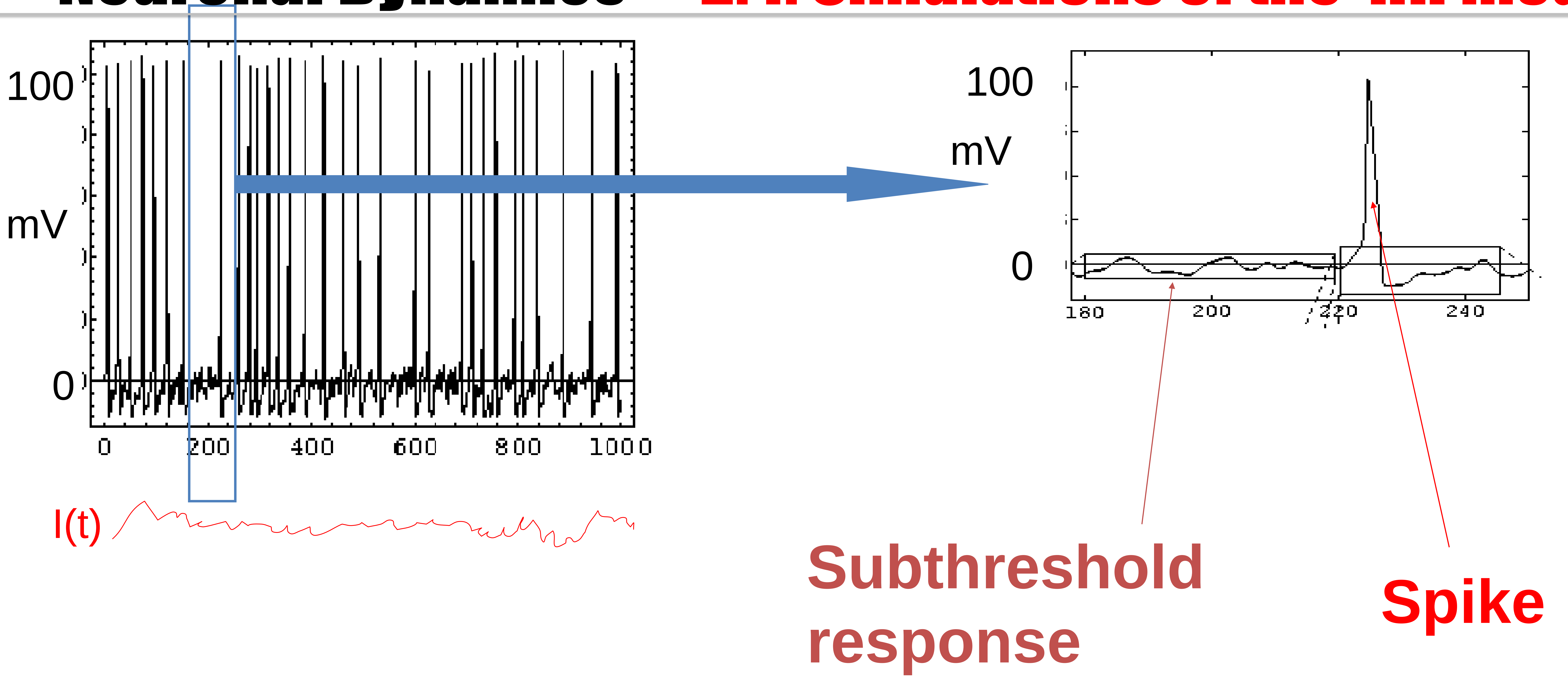
Refractoriness! Harder to elicit a second spike

Neuronal Dynamics – 2.4. Simulations of the HH model



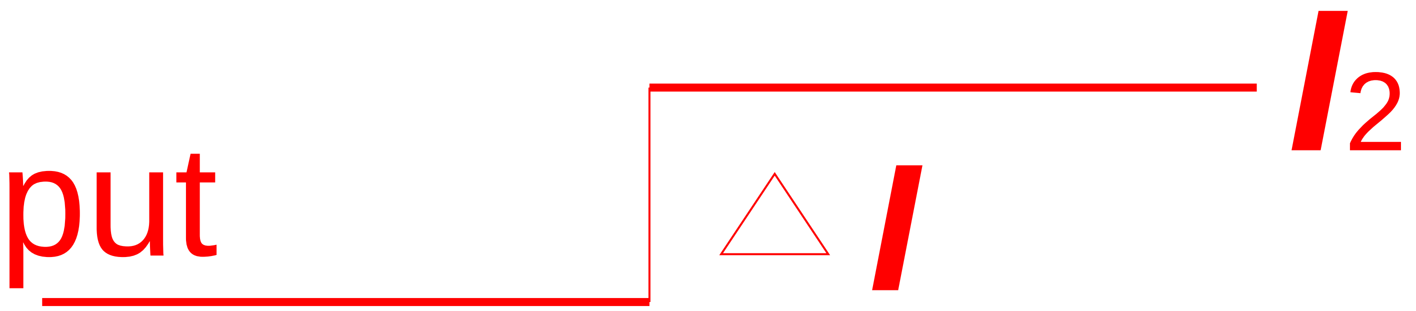
Stimulation with time-dependent input current

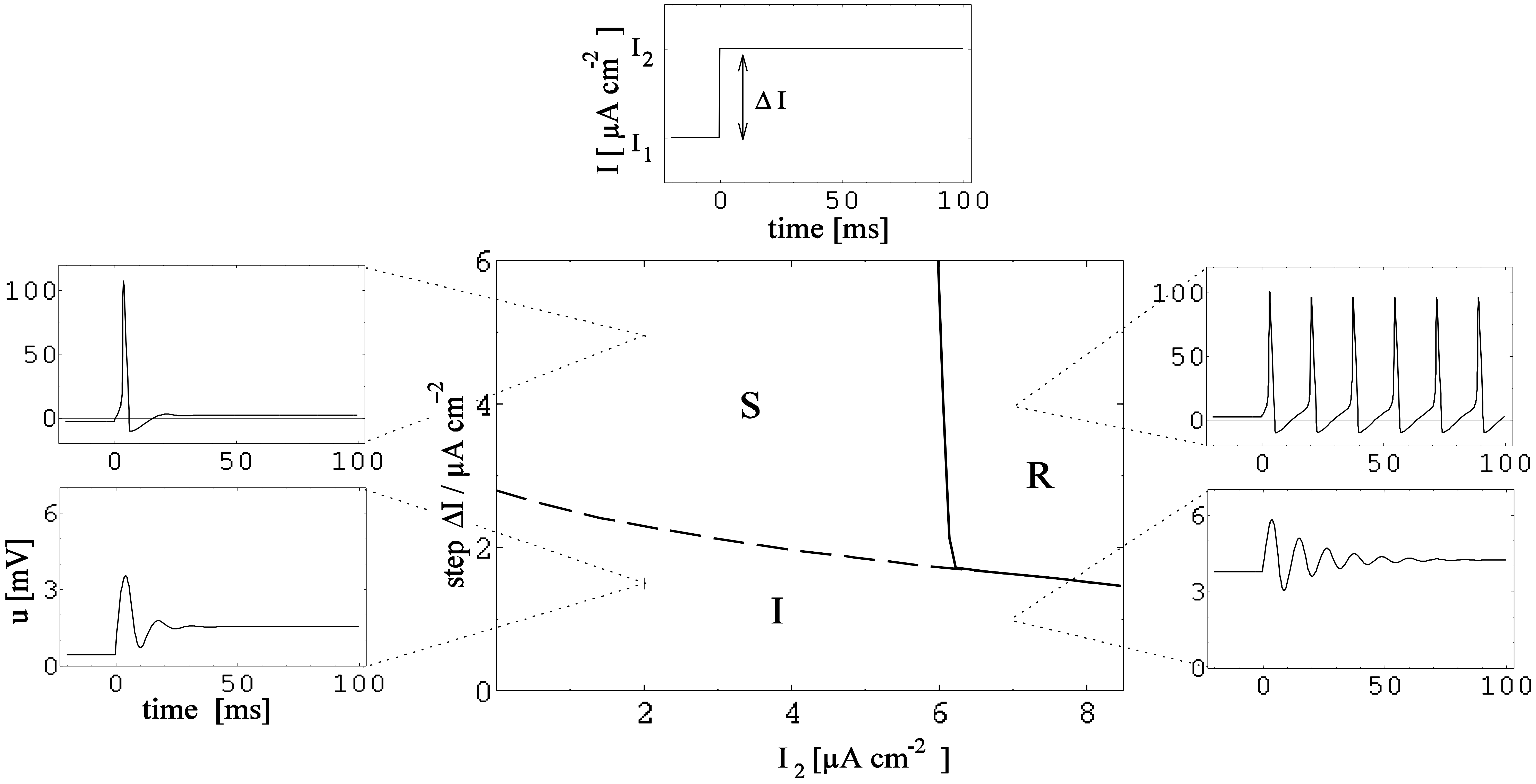
Neuronal Dynamics – 2.4. Simulations of the HH model



Neuronal Dynamics – 2.4. Threshold in HH model

Step current input



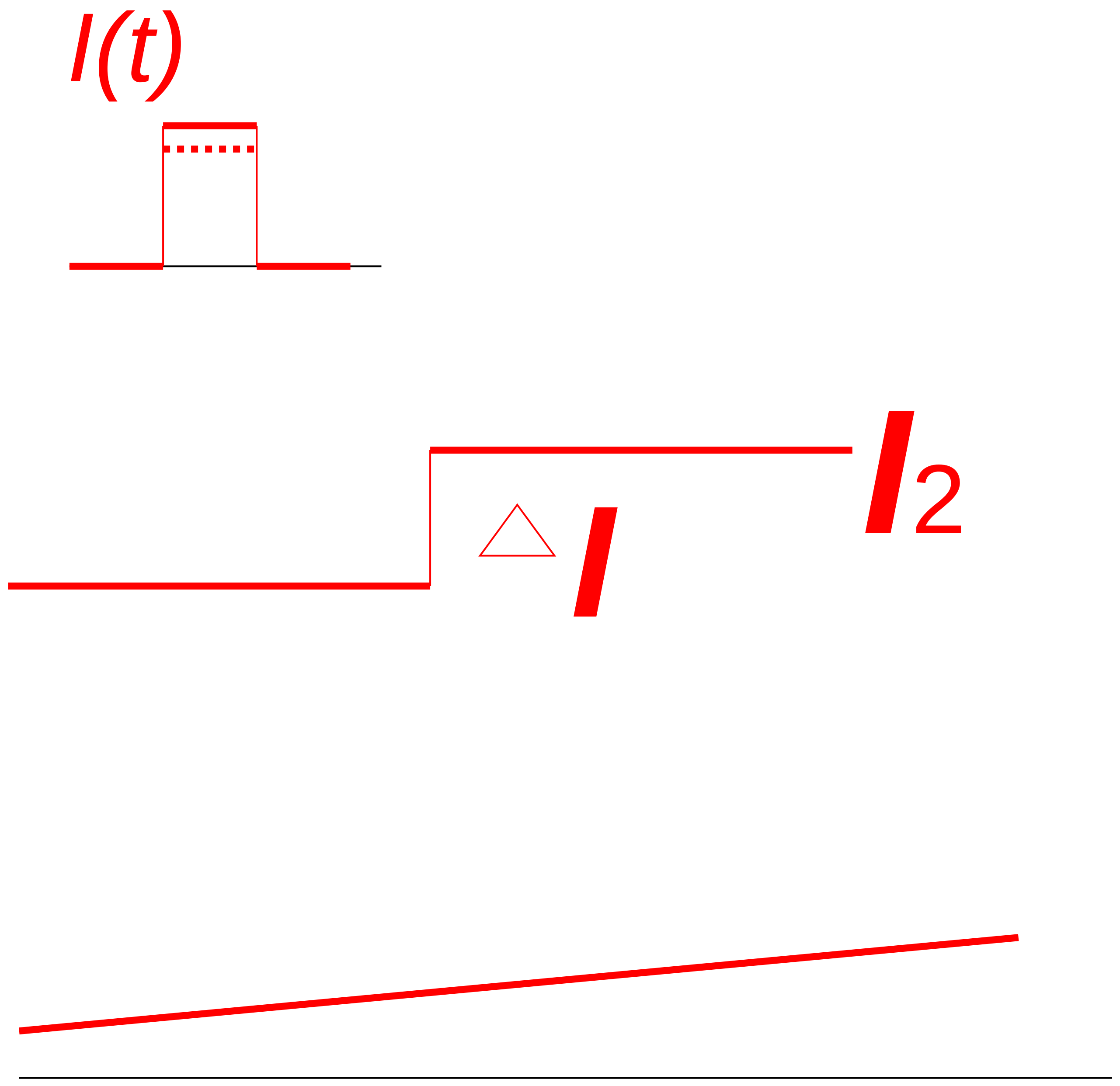


Where is the firing threshold?

pulse input

step input

ramp input



There is no threshold
- no current threshold
- no voltage threshold

'effective' threshold
- depends on typical input

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

Neuronal Dynamics – 2.4. Type I and Type II

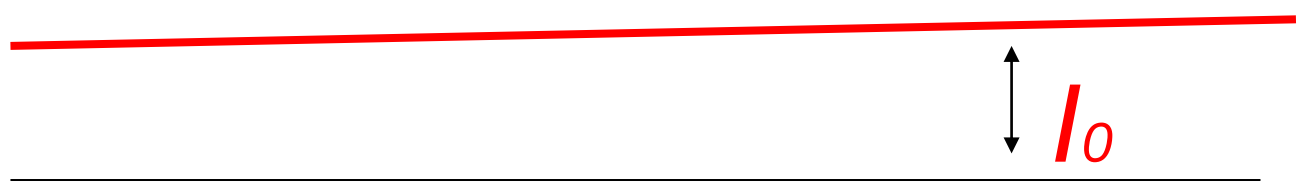
Hodgkin-Huxley model with other parameters (e.g. for cortical pyramidal Neuron)

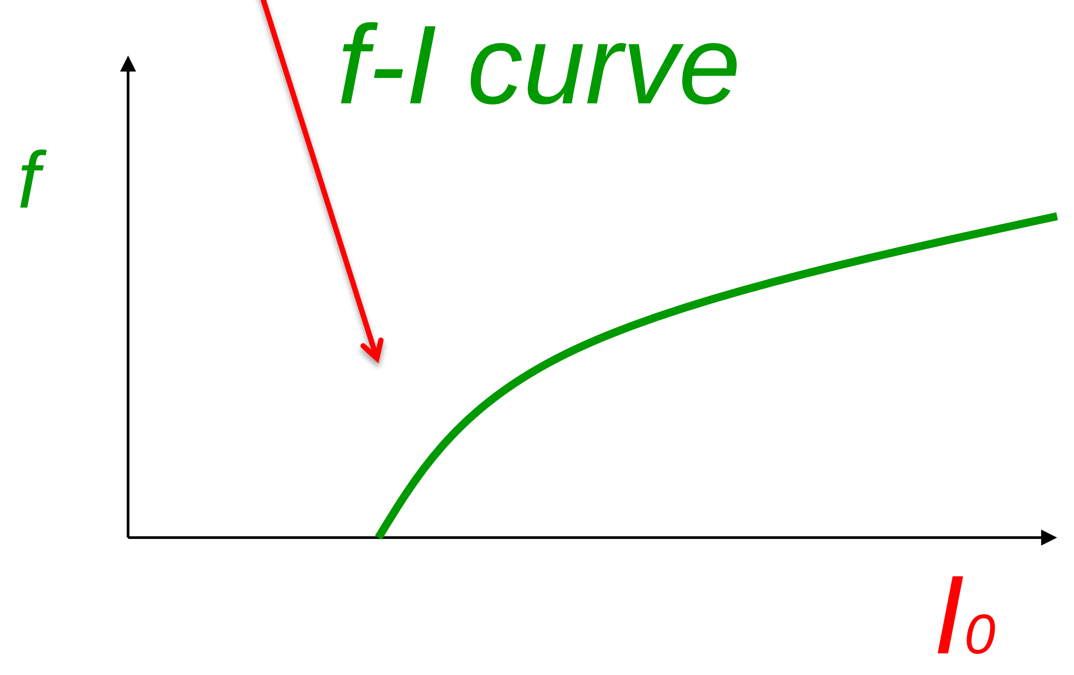
Hodgkin-Huxley model with standard parameters (giant axon of squid)

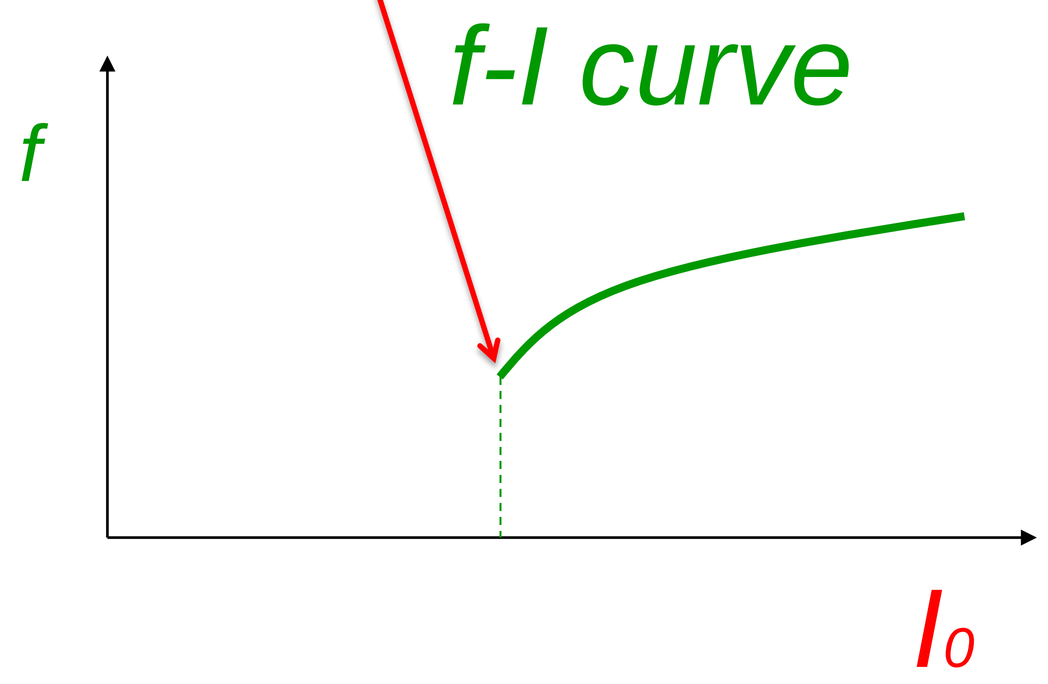
Response at firing threshold?

Type I	type II

ramp input/
constant input







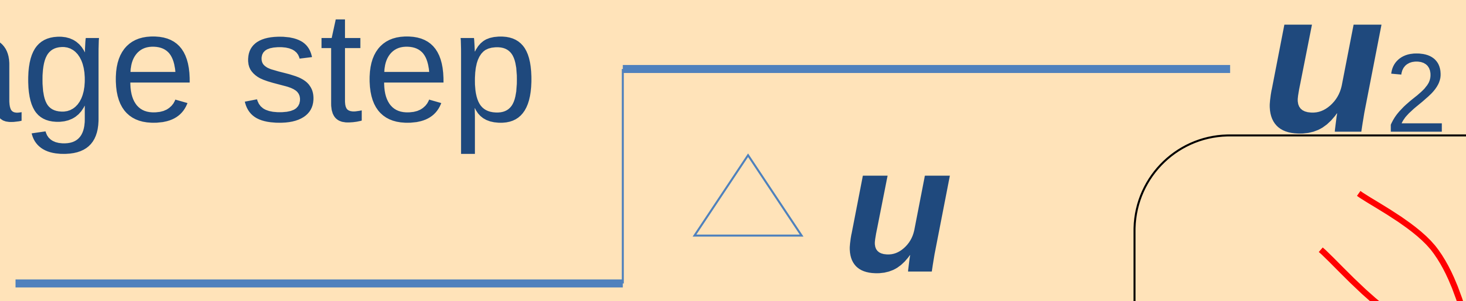
Neuronal Dynamics – 2.4. Hodgkin-Huxley model

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

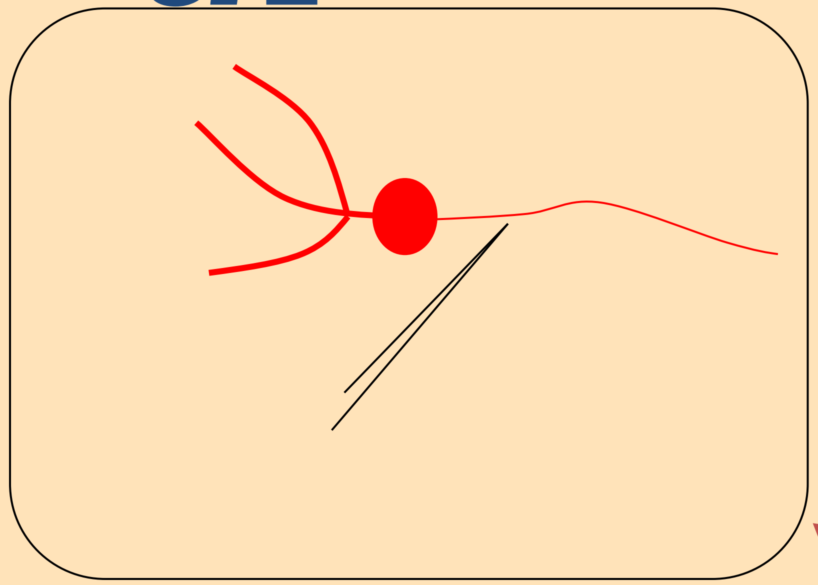
Giant axon of the squid
→ cortical neurons
-Change of parameters
-More ion channels
-Same framework

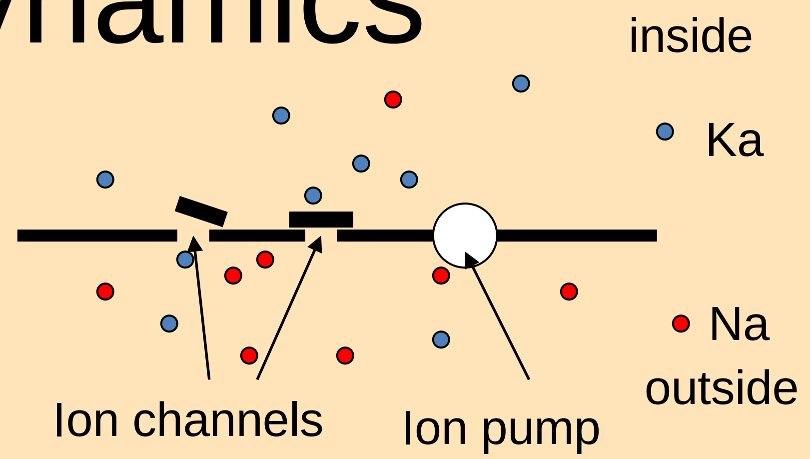
Exercise 3.1-3.3 – Hodgkin-Huxley – ion channel dynamics

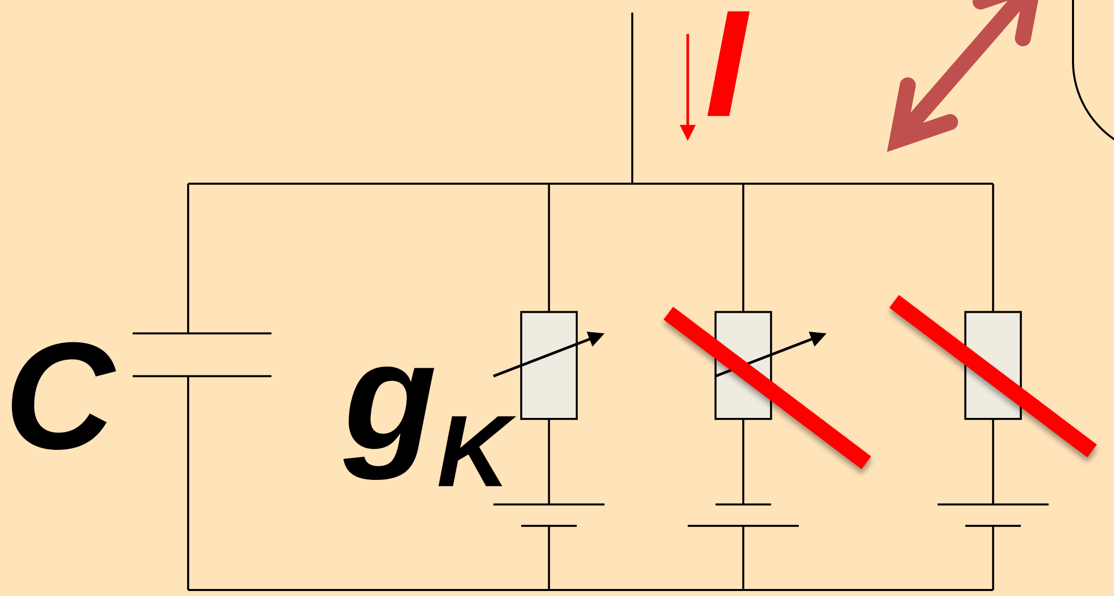
voltage step



Determine ion channel dynamics



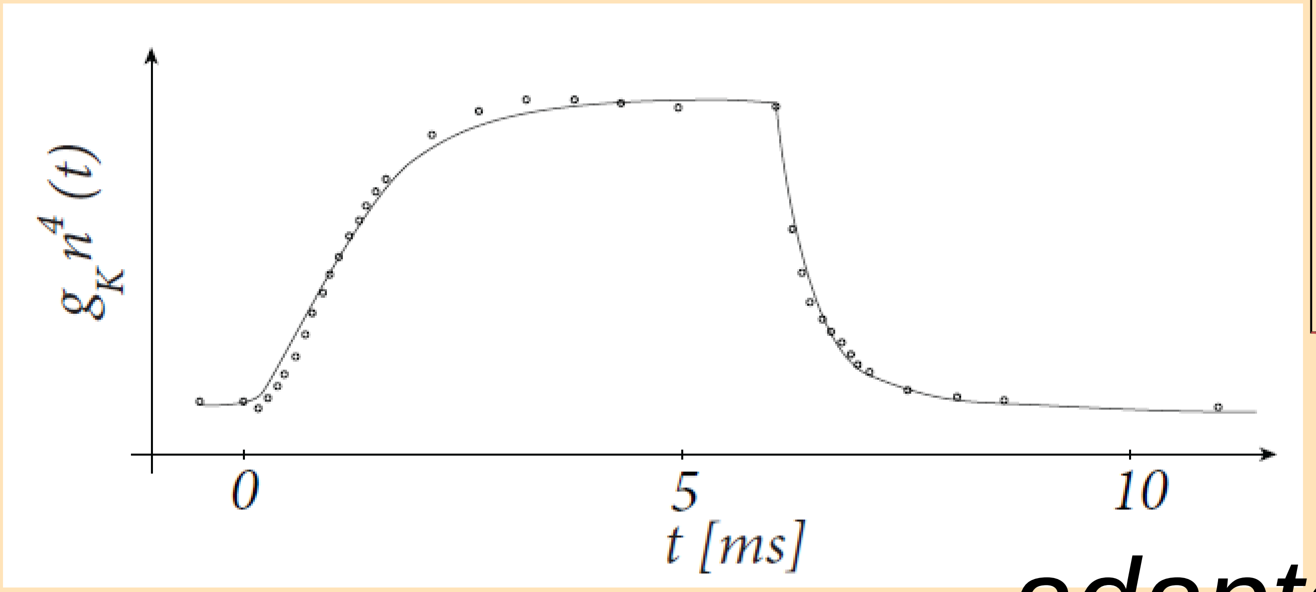


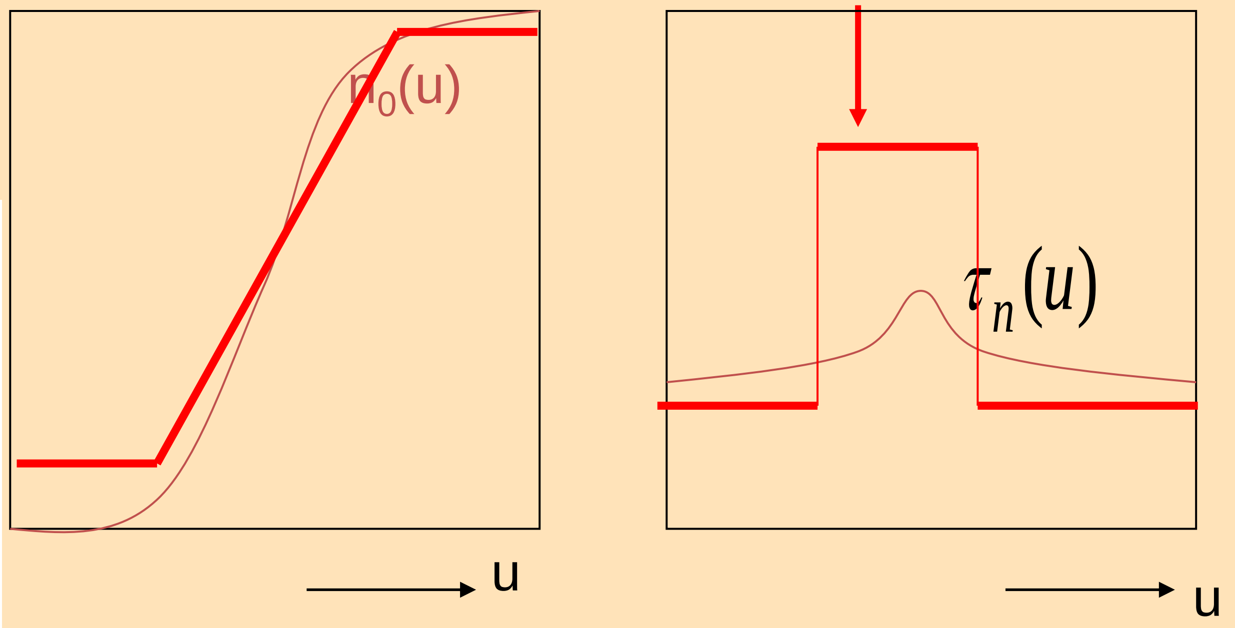


$$C\frac{du}{dt} = -g_K n^4 (u - E_K) + I(t)$$

stimulus

apply voltage step





Next Lecture at: 11.38

adapted from Hodgkin&Huxley 1952

Week 2 – part 5: Detailed Biophysical Models

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

Biological Modeling of Neural Networks

Week 2 – Biophysical modeling: The Hodgkin-Huxley model

Wulfram Gerstner

EPFL, Lausanne, Switzerland

√ 2.1 **Biophysics of neurons**
- Overview

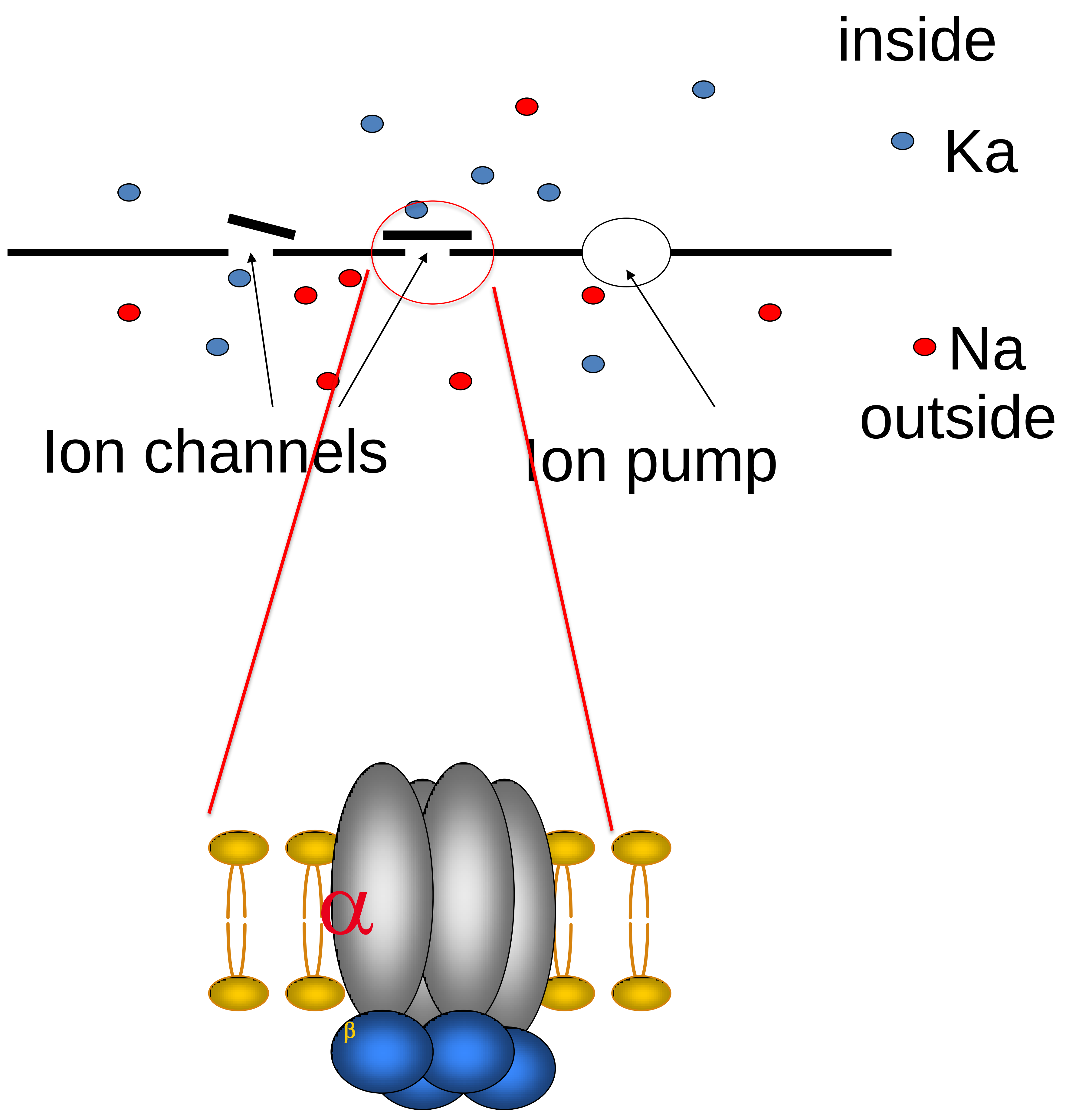
√ 2.2 **Reversal potential**
- Nernst equation

√ 2.3 **Hodgkin-Huxley Model**

√ 2.4 **Threshold in the Hodgkin-Huxley Model**
- where is the firing threshold?

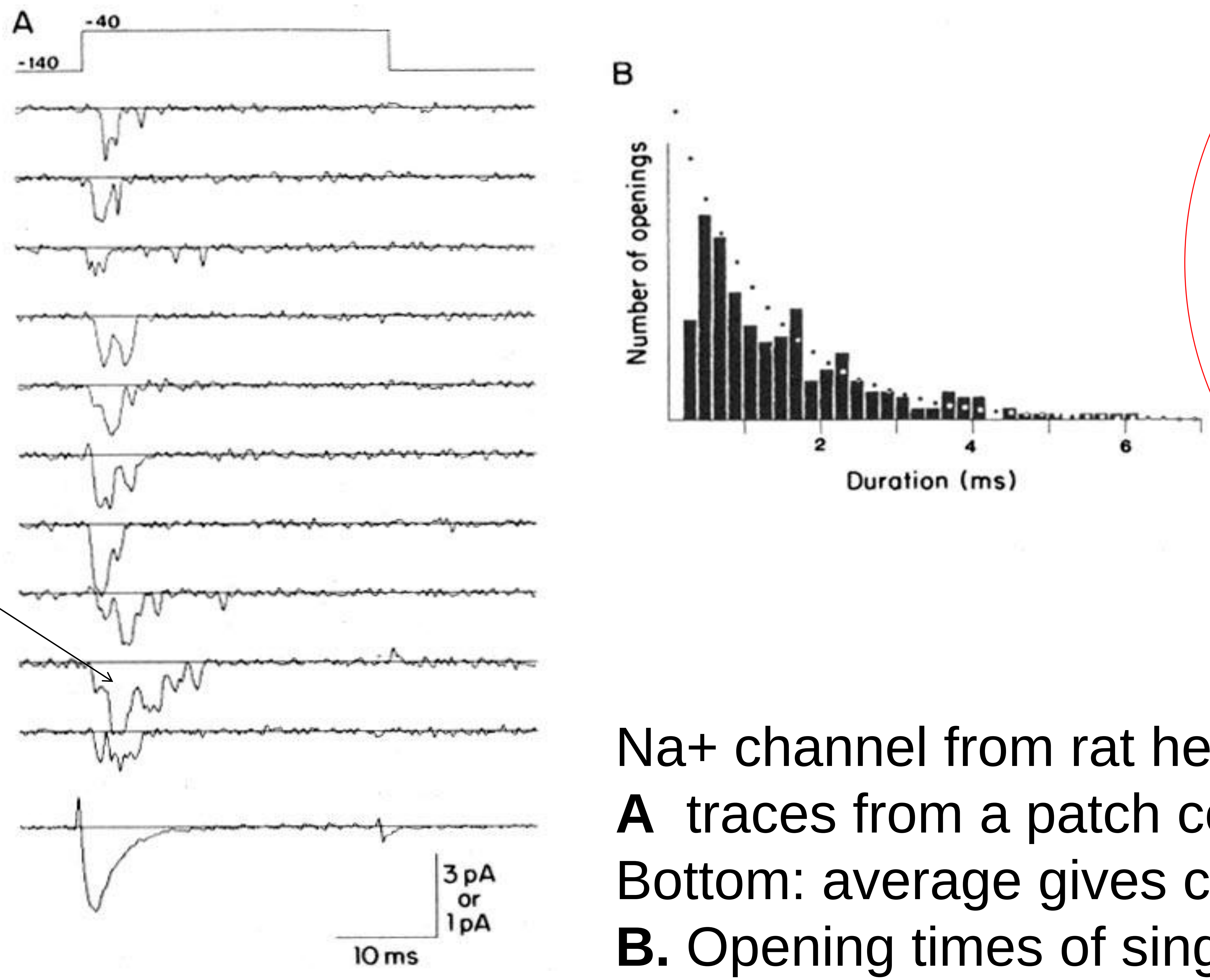
2.5. **Detailed biophysical models**
- the zoo of ion channels

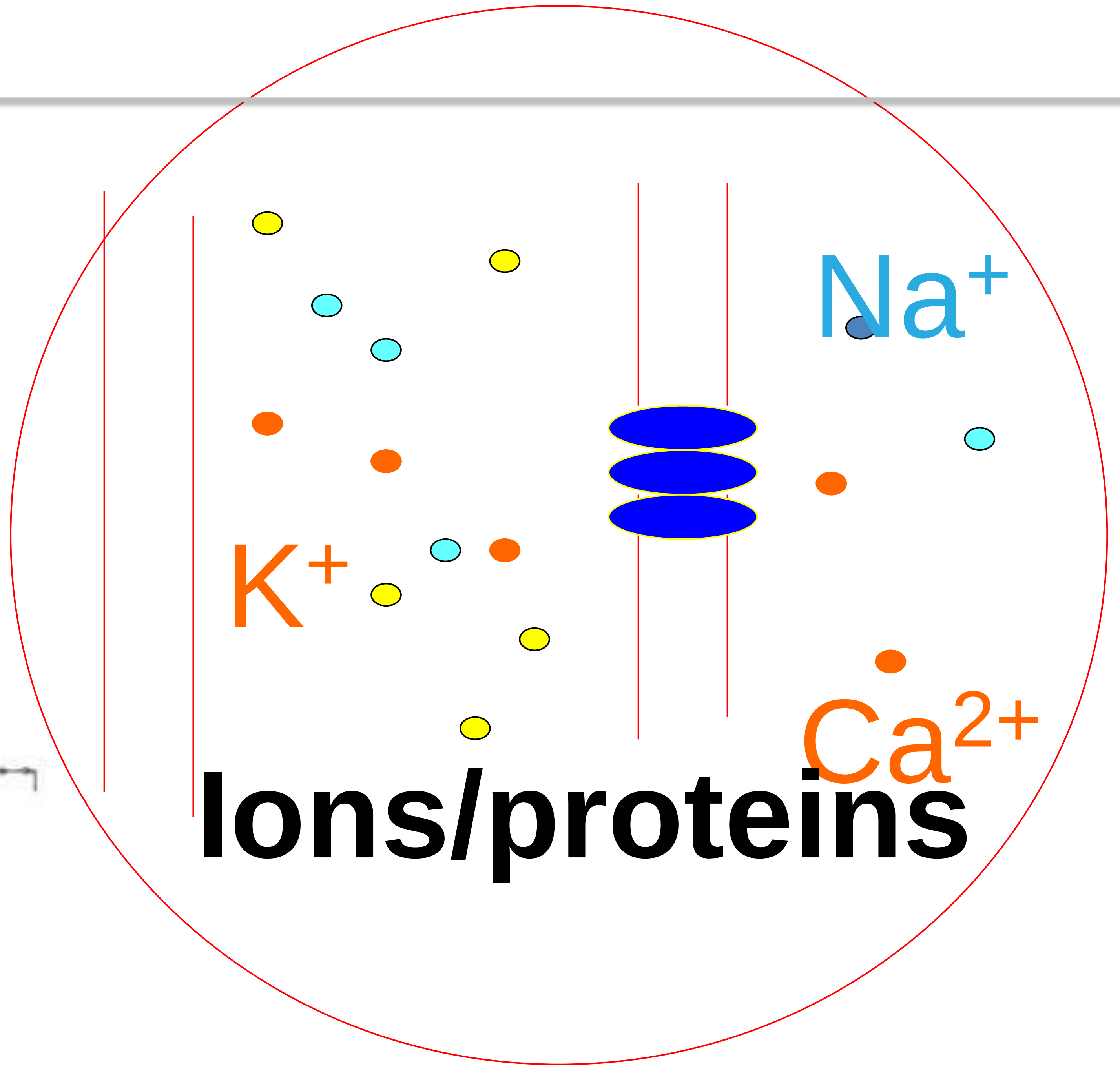
Neuronal Dynamics – 2.5 Biophysical models



Neuronal Dynamics – 2.5 Ion channels

Steps:
Different number
of channels





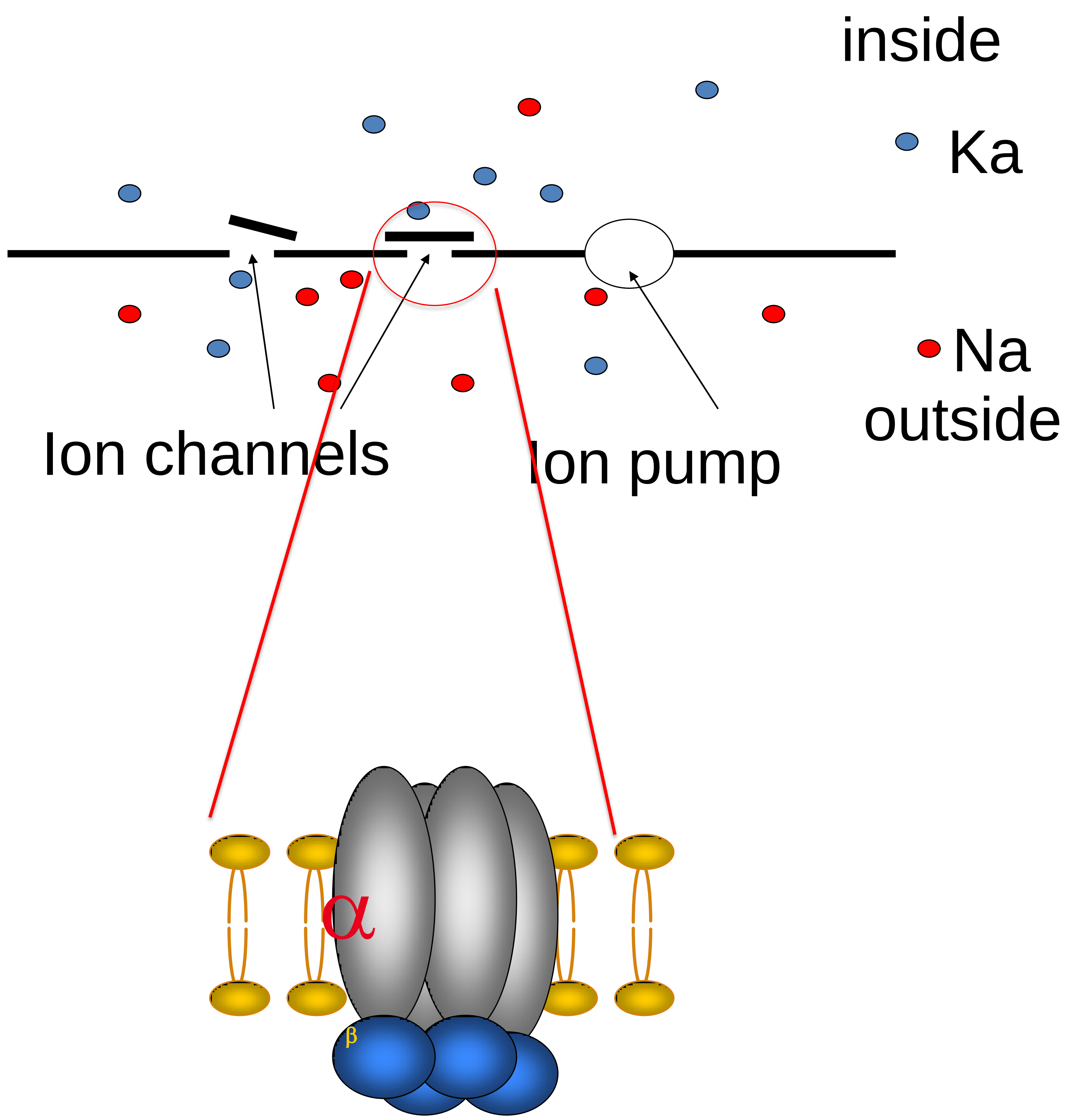
Na+ channel from rat heart *(Patlak and Ortiz 1985)*
A traces from a patch containing several channels.
Bottom: average gives current time course.
B. Opening times of single channel events

Neuronal Dynamics – 2.5 Biophysical models

There are about 200 identified ion channels

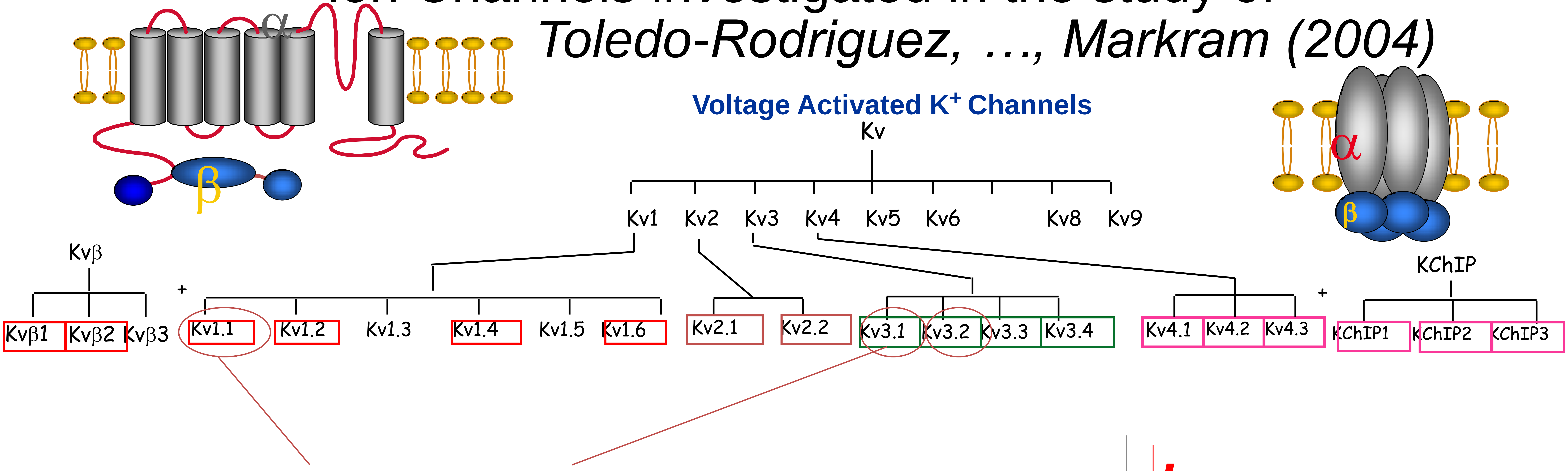
http://channelpedia.epfl.ch/

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

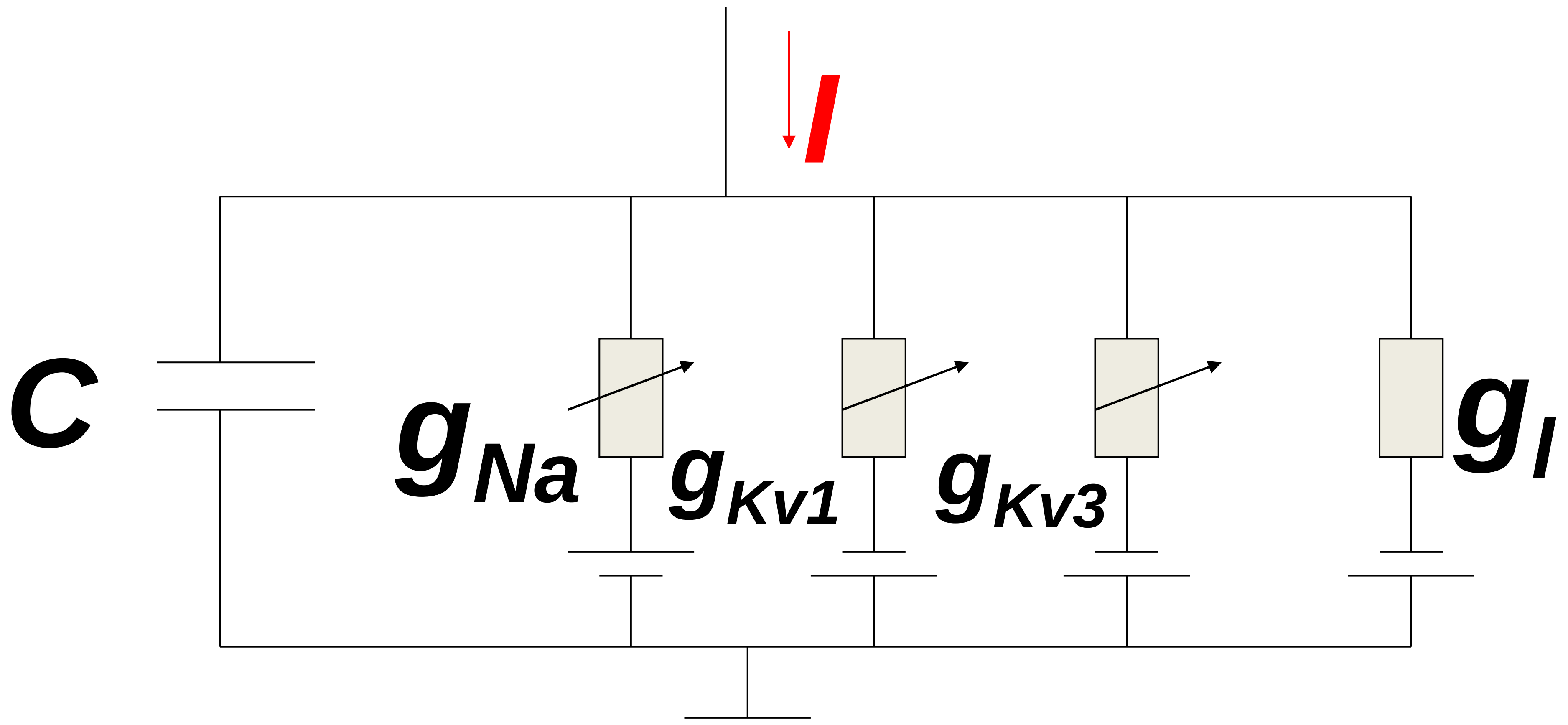


Ion Channels investigated in the study of *Toledo-Rodriguez, …, Markram (2004)*

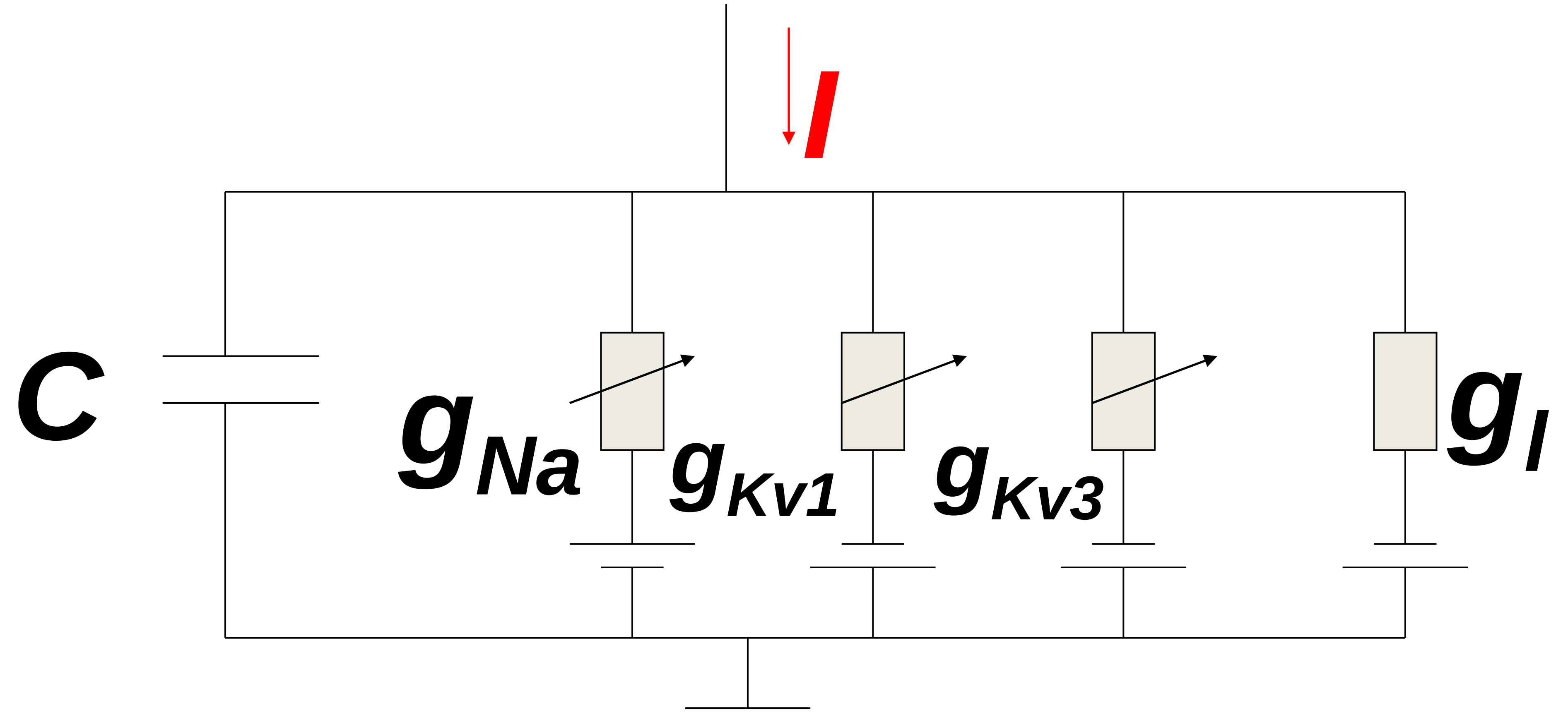
Voltage Activated K^+ Channels

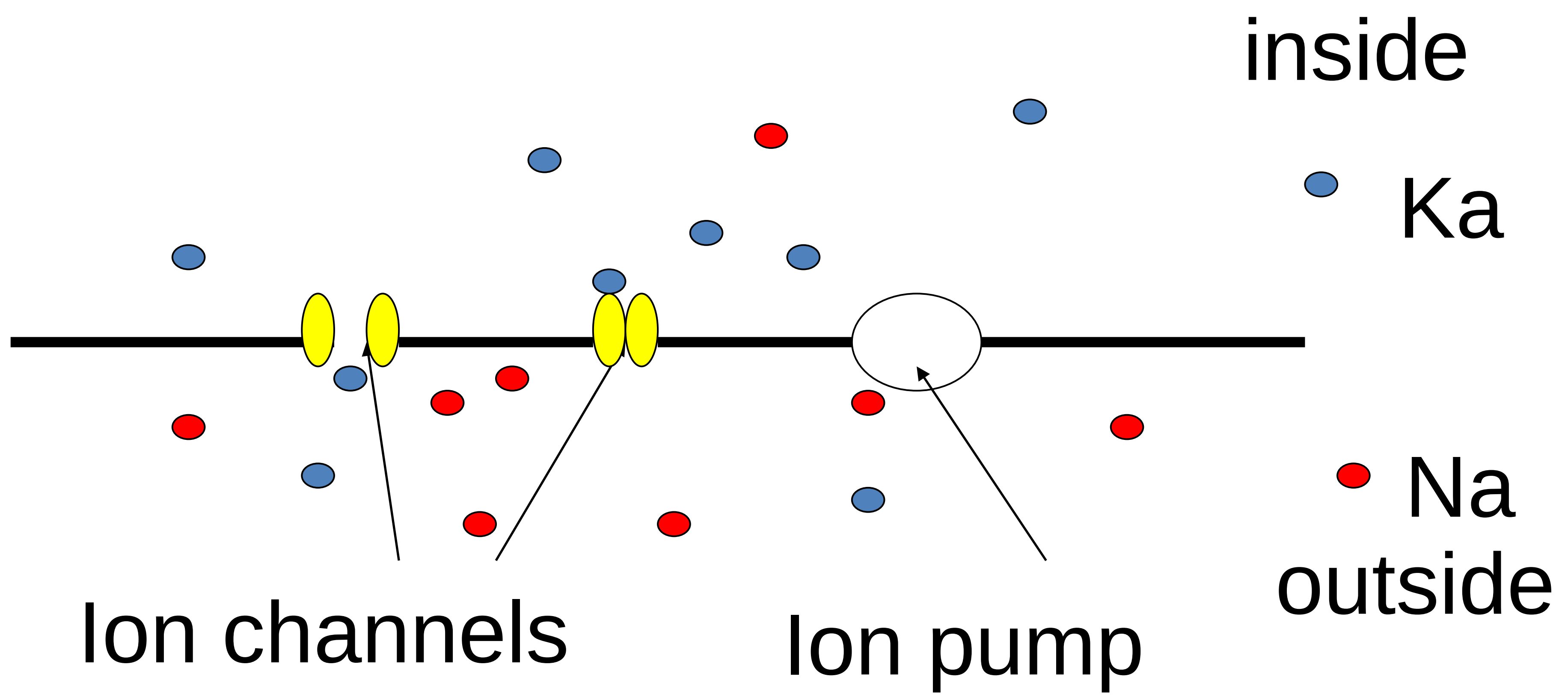


schematic mRNA
Expression profile



Model of a hypothetical neuron





stimulus

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

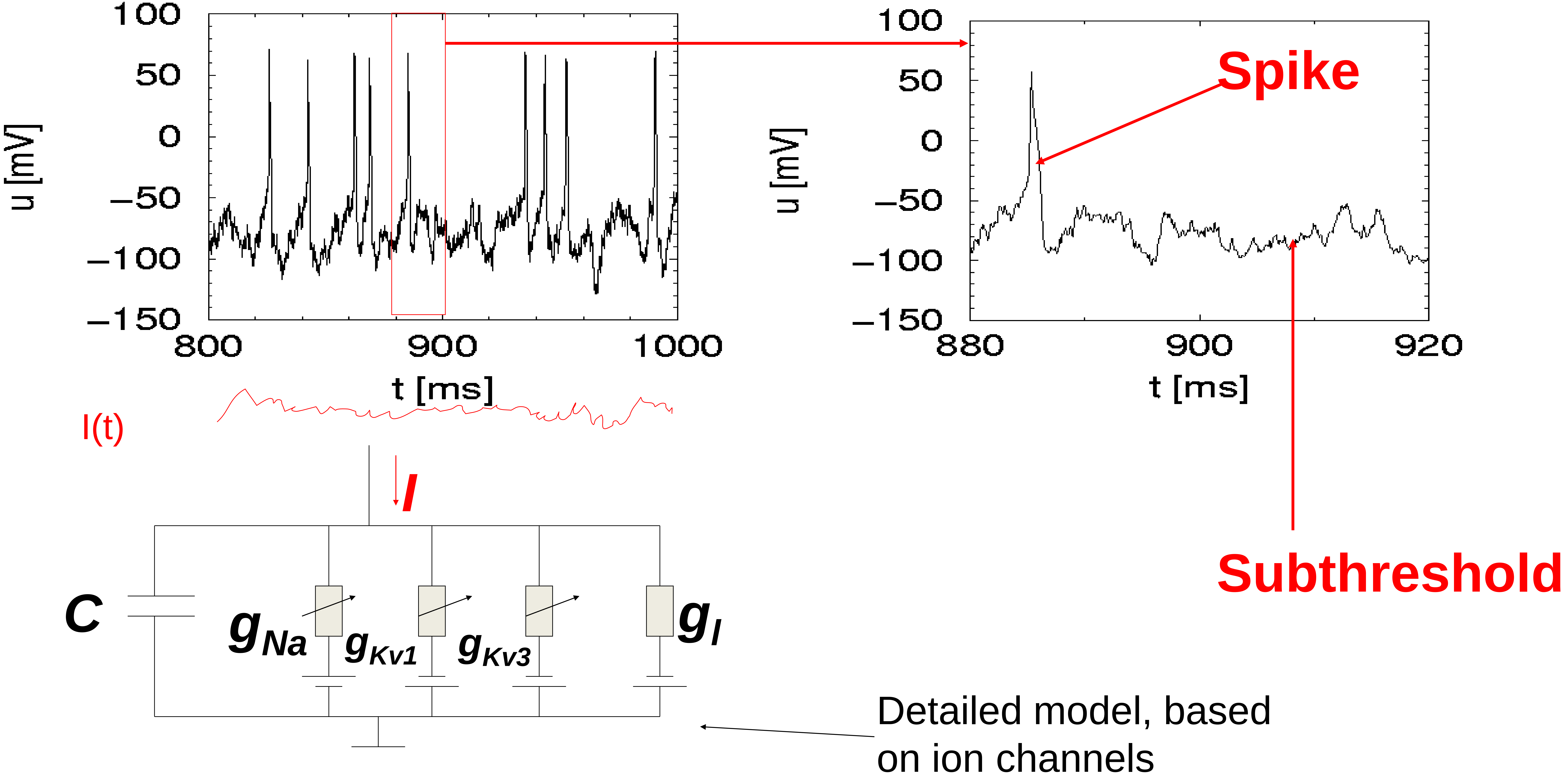
How many parameters per channel?

$$\frac{dh}{dt} = -\frac{h-h_0(u)}{\tau_h(u)} \qquad \frac{dm}{dt} = -\frac{m-m_0(u)}{\tau_m(u)} \qquad \frac{dn_1}{dt} = -\frac{n_1-n_{0,1}(u)}{\tau_{n,1}(u)}$$

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

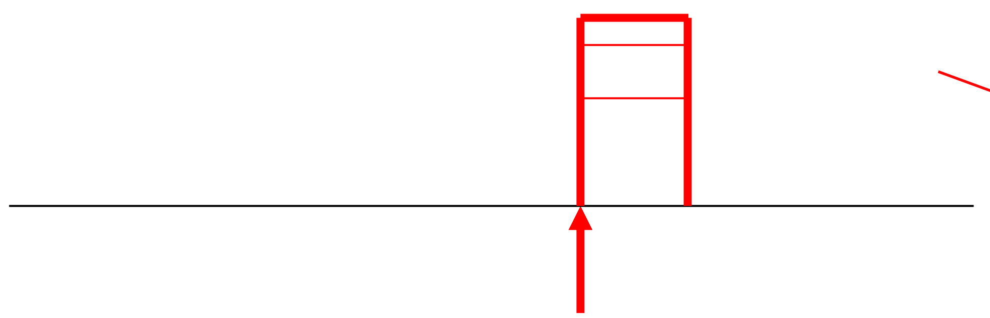
Erisir et al, 1999
Hodgkin and Huxley, 1952

Model of a hypothetical neuron

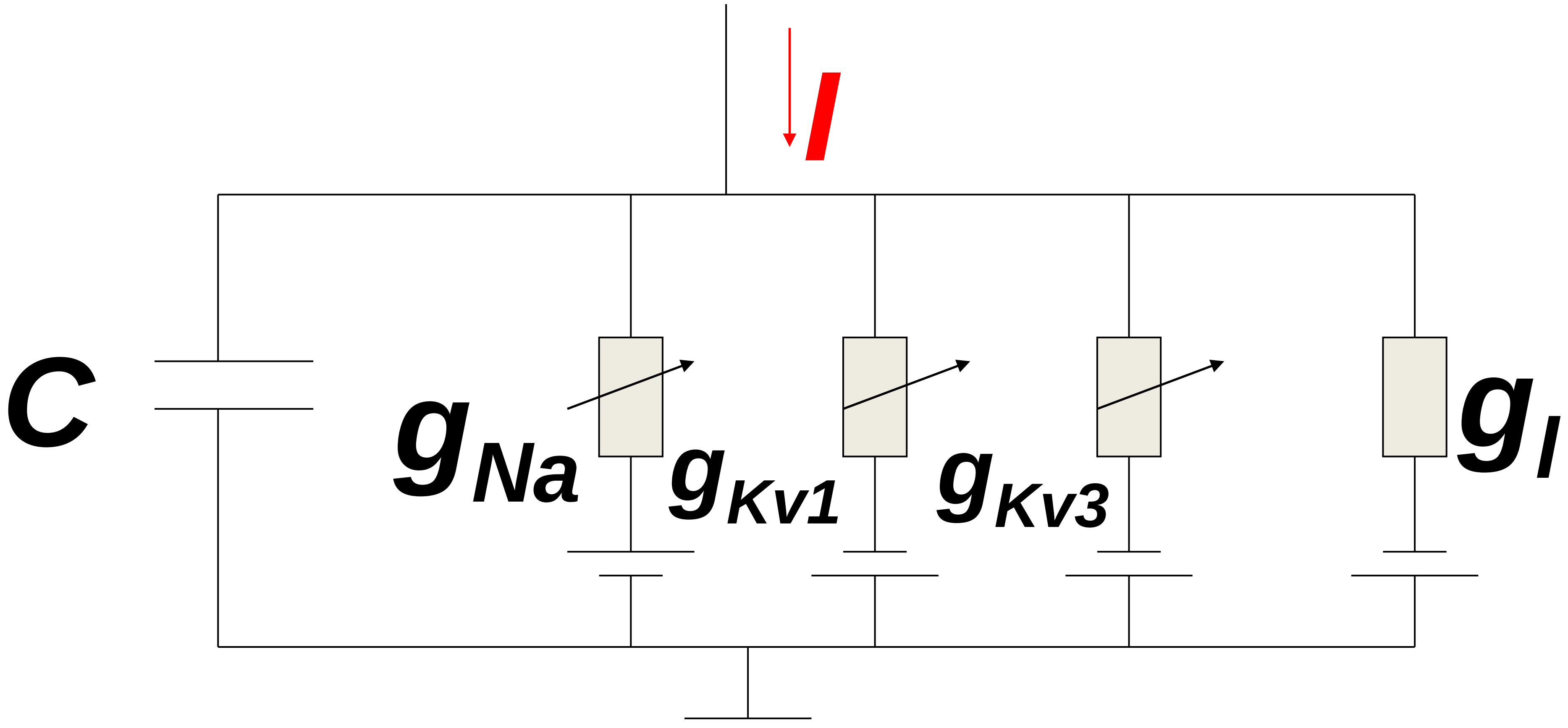


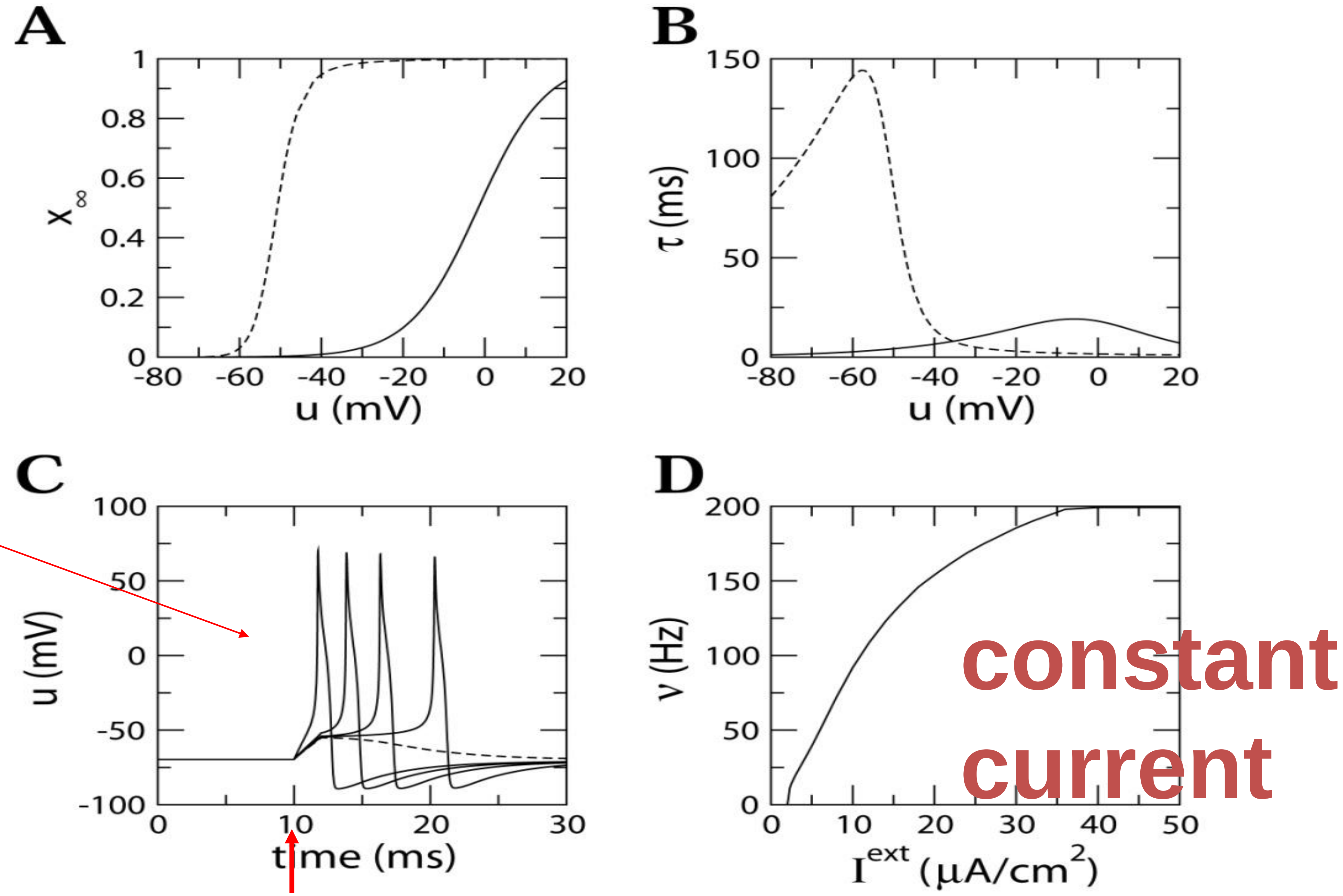
Model of a hypothetical neuron (type I)

Current pulse



Biophysical model, based on ion channels





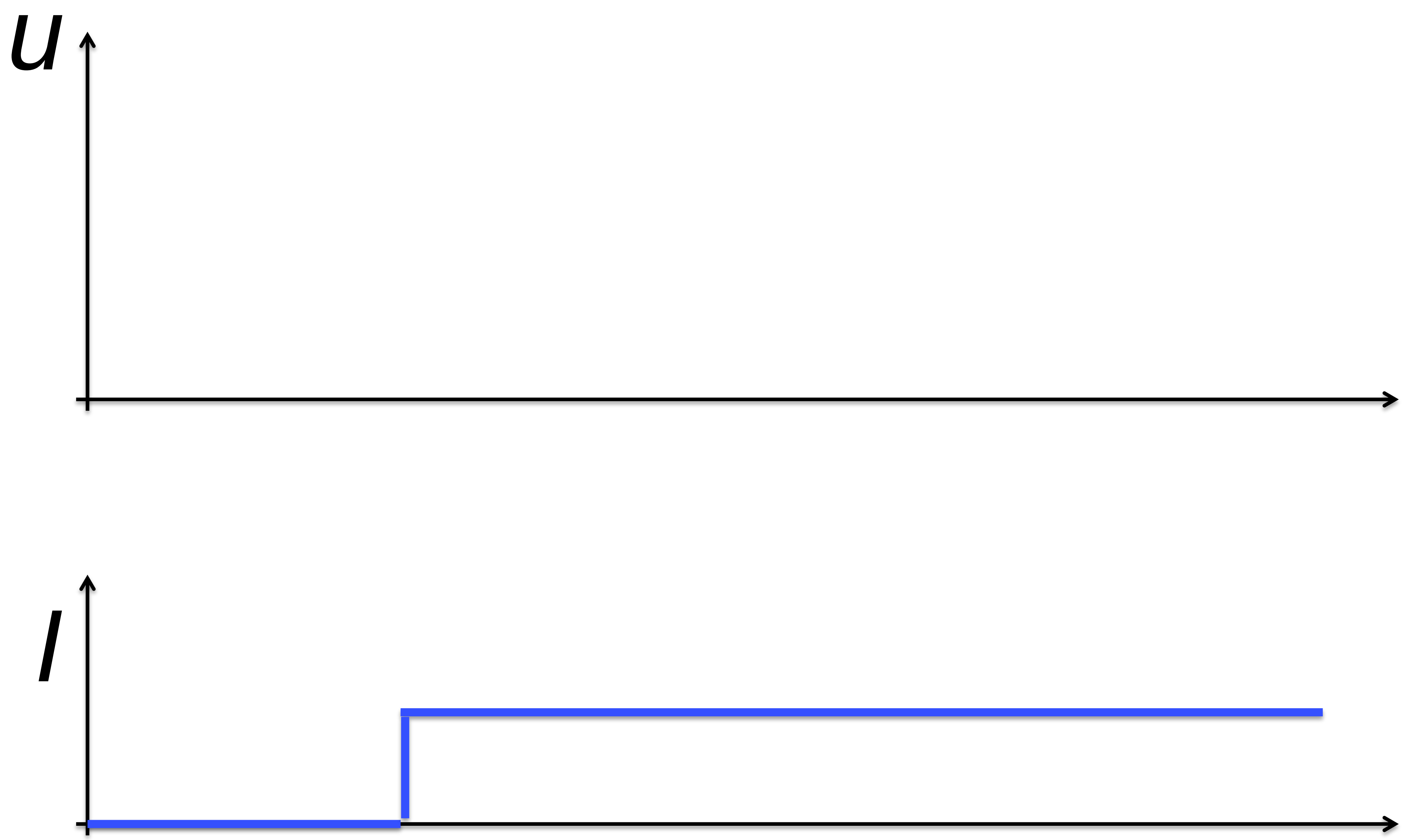
- Delayed AP initiation
- Smooth *f-I* curve

type I neuron

Neuronal Dynamics – 2.5 Adaptation

Functional roles of channels?

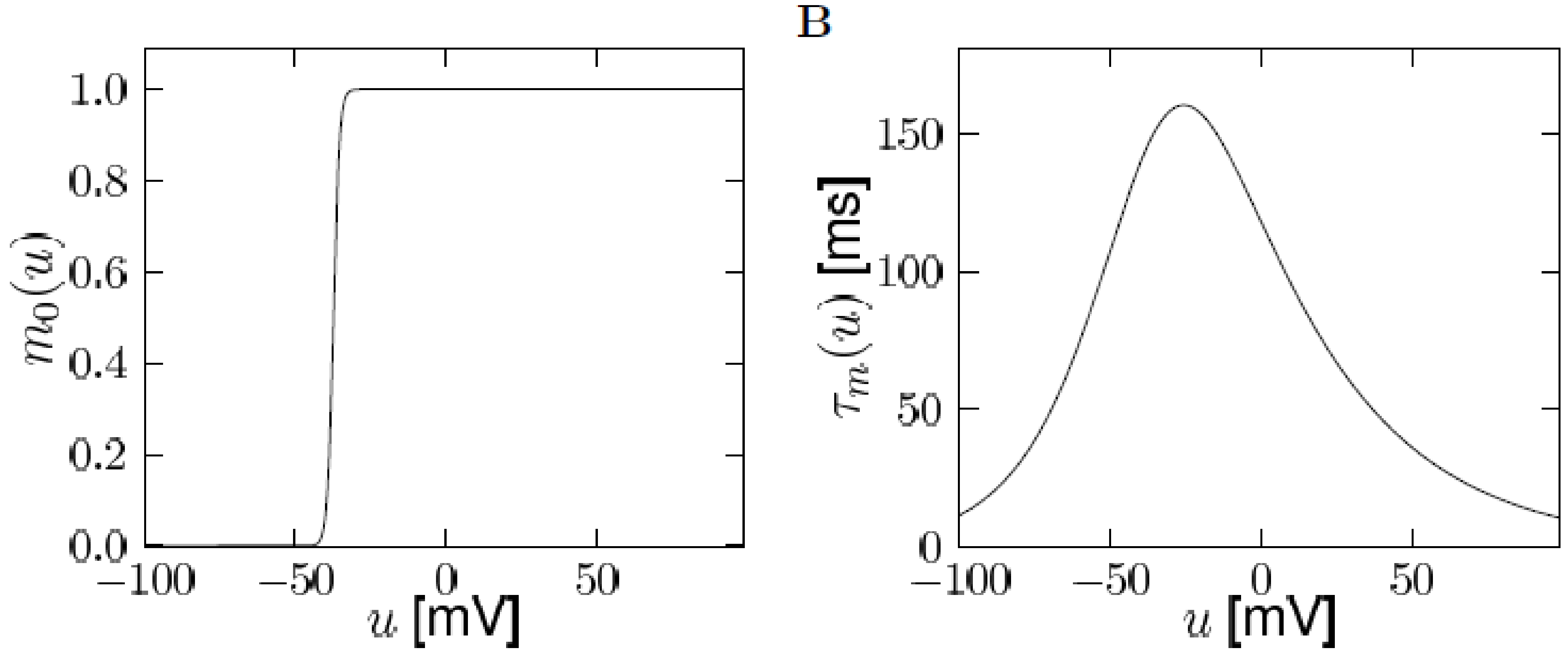
- Example: adaptation

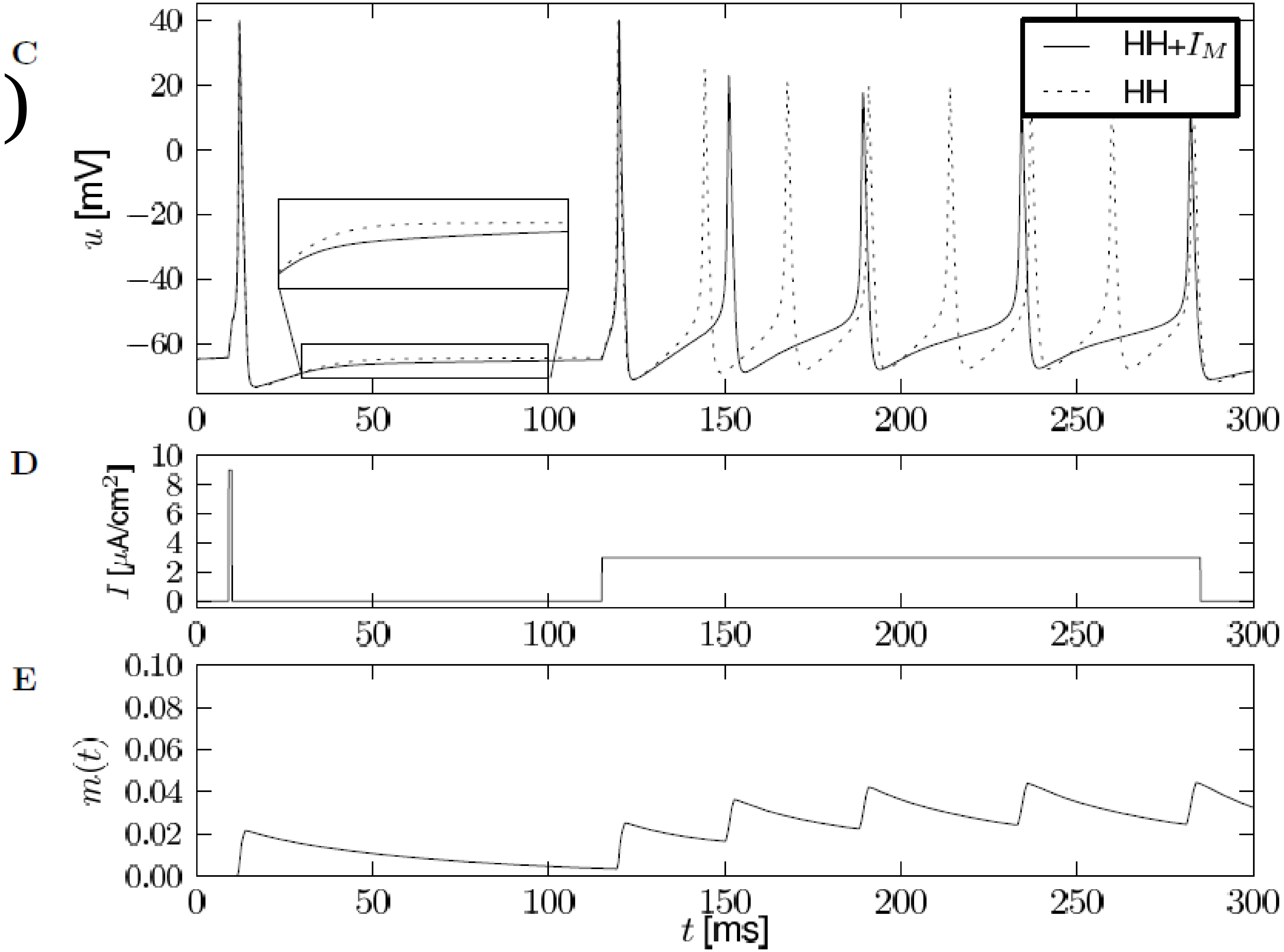


Neuronal Dynamics – 2.5 Adaptation: I_M-current

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

- Potassium current
- Kv7 subunits
- slow time constant





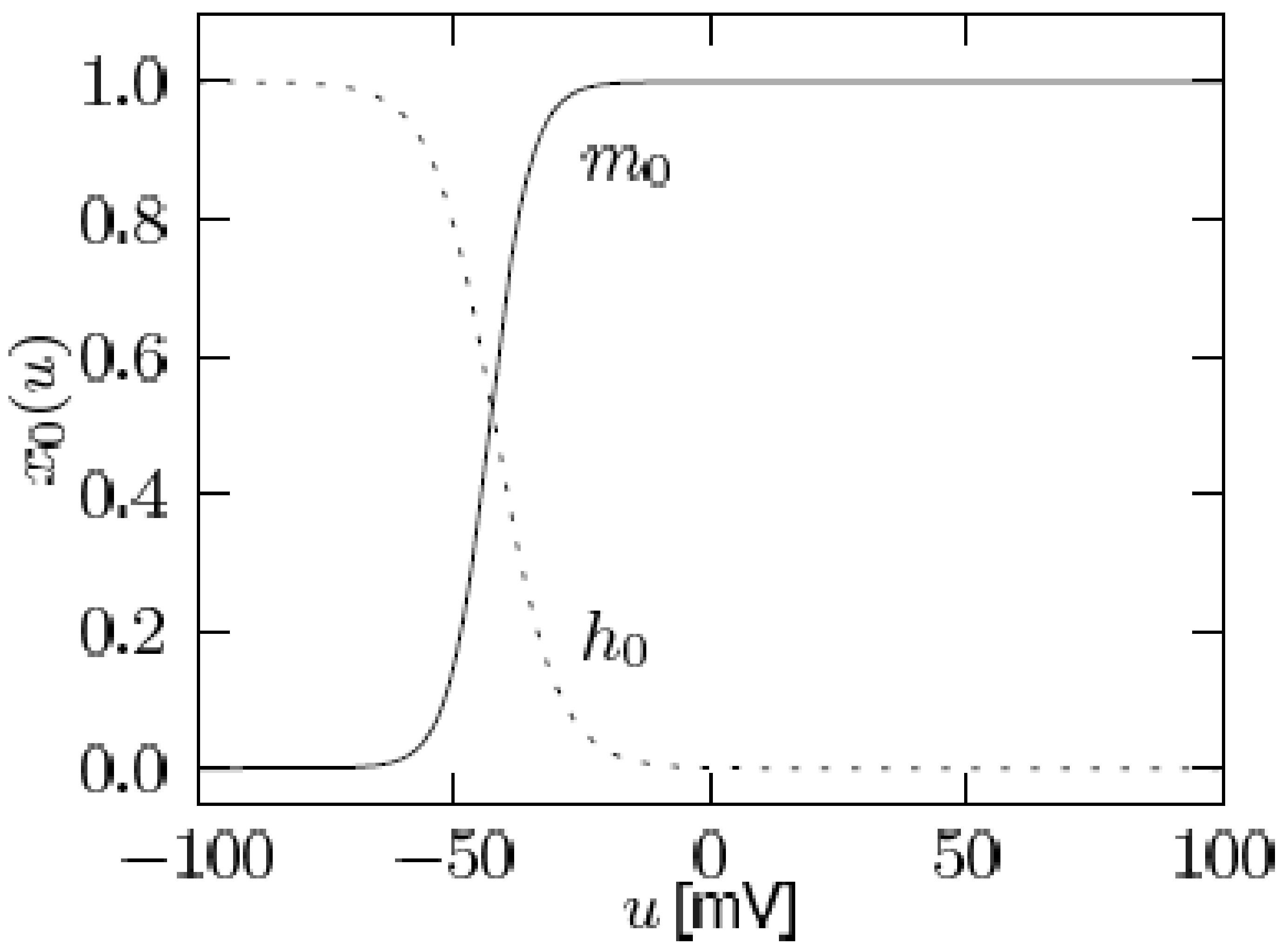
Yamada et al., 1989

I_M current is one of many potential sources of adaptation

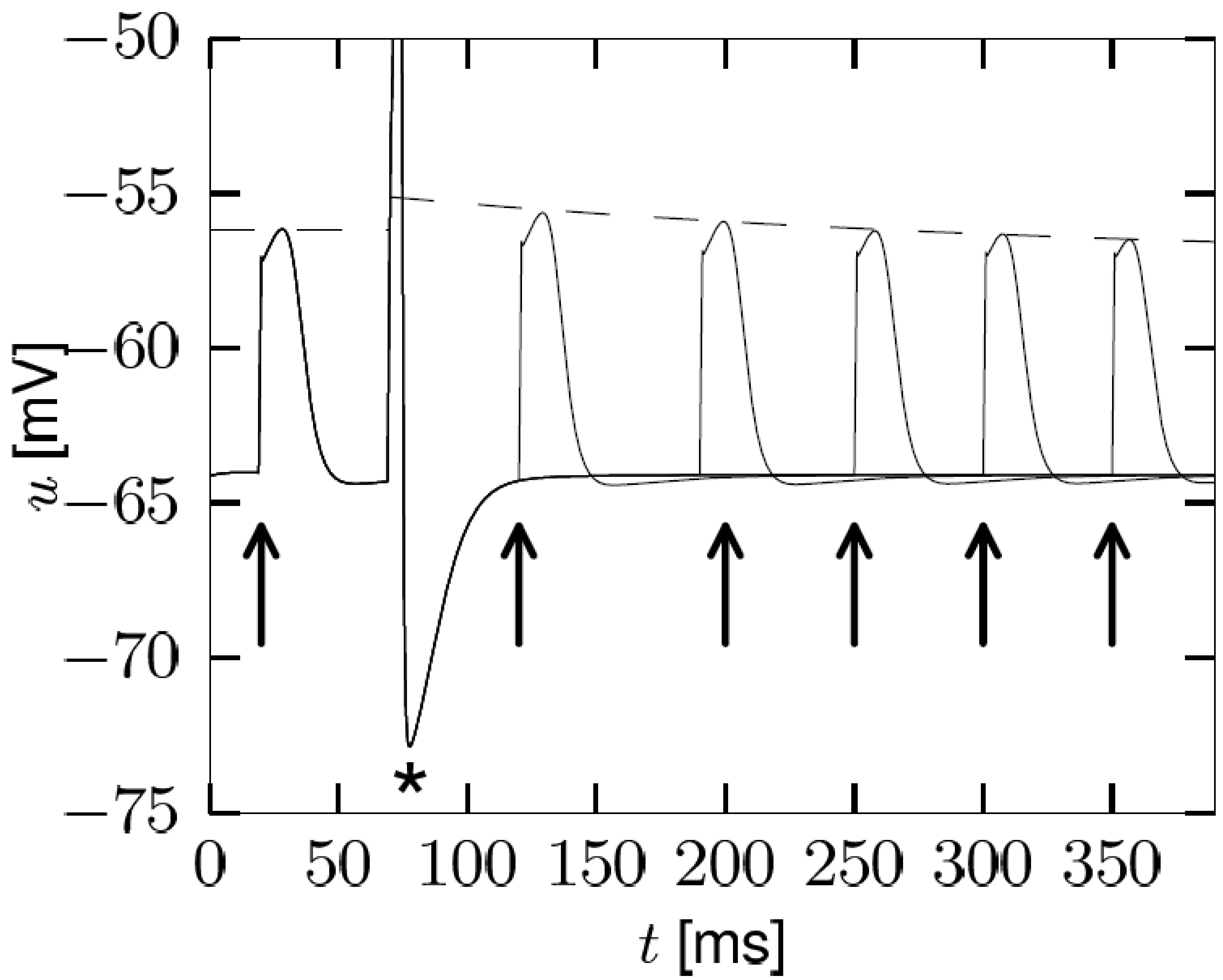
Neuronal Dynamics – 2.5 Adaptation – I_{NaP} current

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

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



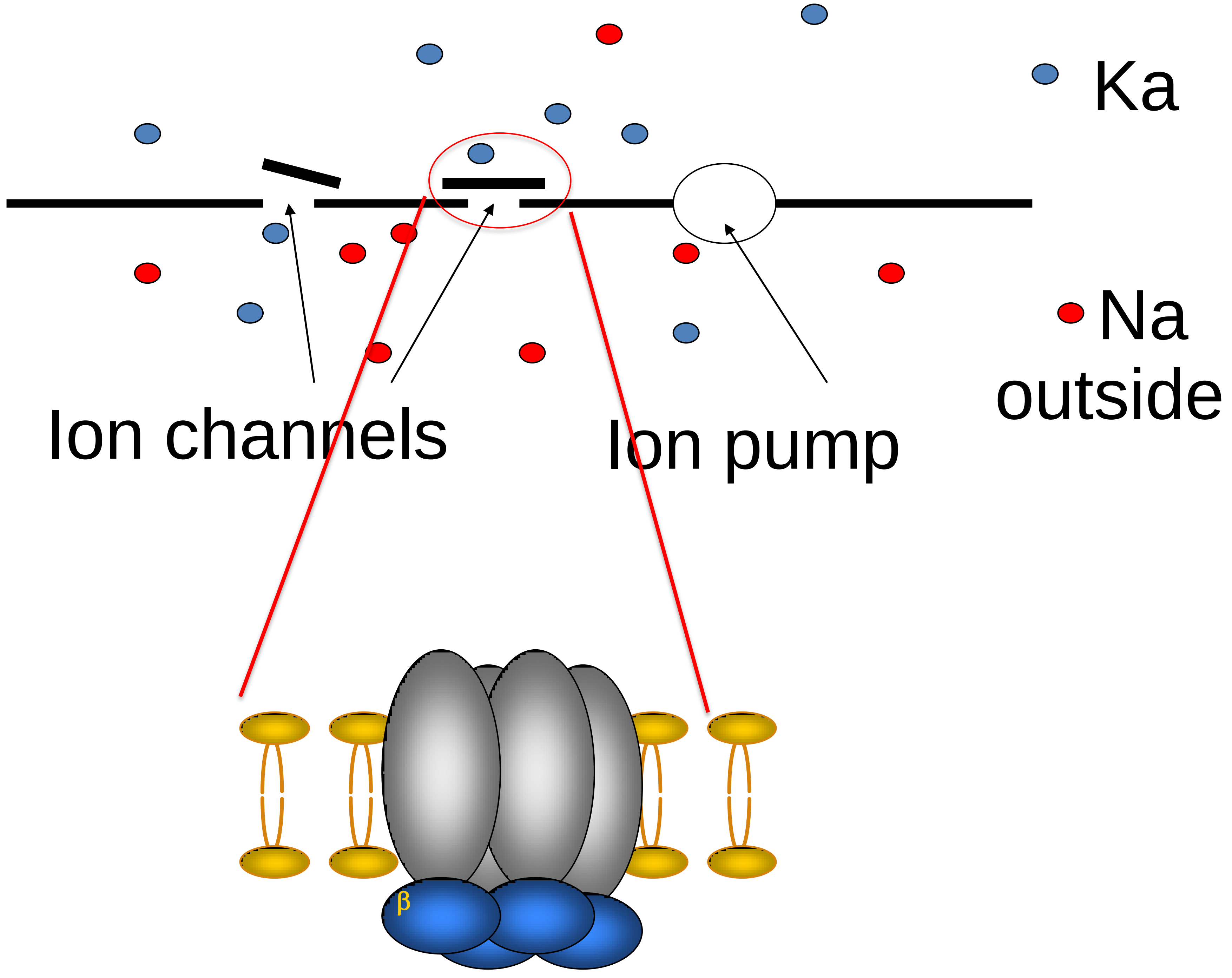
Aracri et al., 2006



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 4 – Hodgkin-Huxley model – gating dynamics

A) Often the gating dynamics is formulated as

$$\frac{dm}{dt} = \alpha_m(u)(1-m) - \beta_m(u)m \qquad \frac{dm}{dt} = -\frac{m - m_0(u)}{\tau_m(u)}$$

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

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

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 $\tau_m(u)$?

Now Computer Exercises:

Play with Hodgkin-Huxley model

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-specic 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