Biological Modeling of Neural Networks

Start at 9h15

Location: Room IN-M 200

Biological Modeling of Neural Networks

ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

Week 2 – Biophysical modeling: The Hodgkin-Huxley model

Wulfram Gerstner

EPFL, Lausanne, Switzerland

2.1 Biophysics of neurons
- Overview

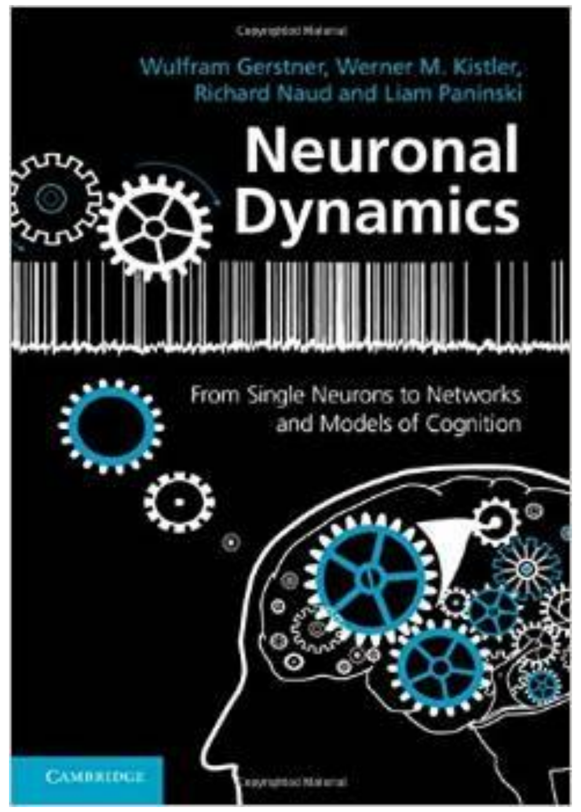
2.2 Reversal potential
- Nernst equation

2.3 Hodgin-Huxley Model

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

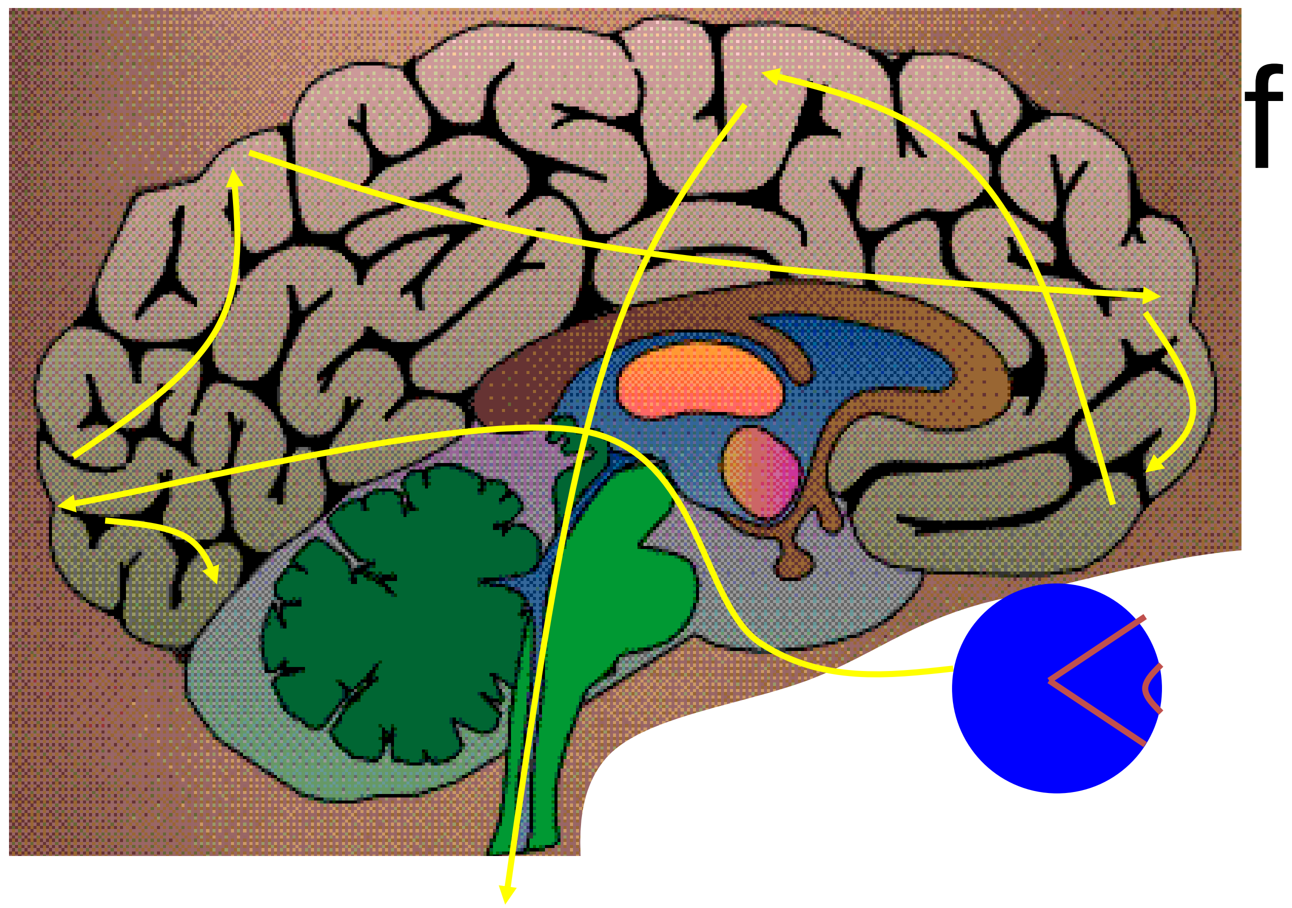
2.5. Detailed biophysical models
- the zoo of ion channels

Reading for week 2:
NEURONAL DYNAMICS
- Ch. 2 (without 2.3.2 - 2.3.5)

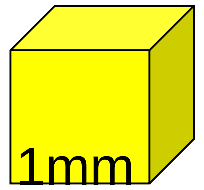


Cambridge Univ. Press

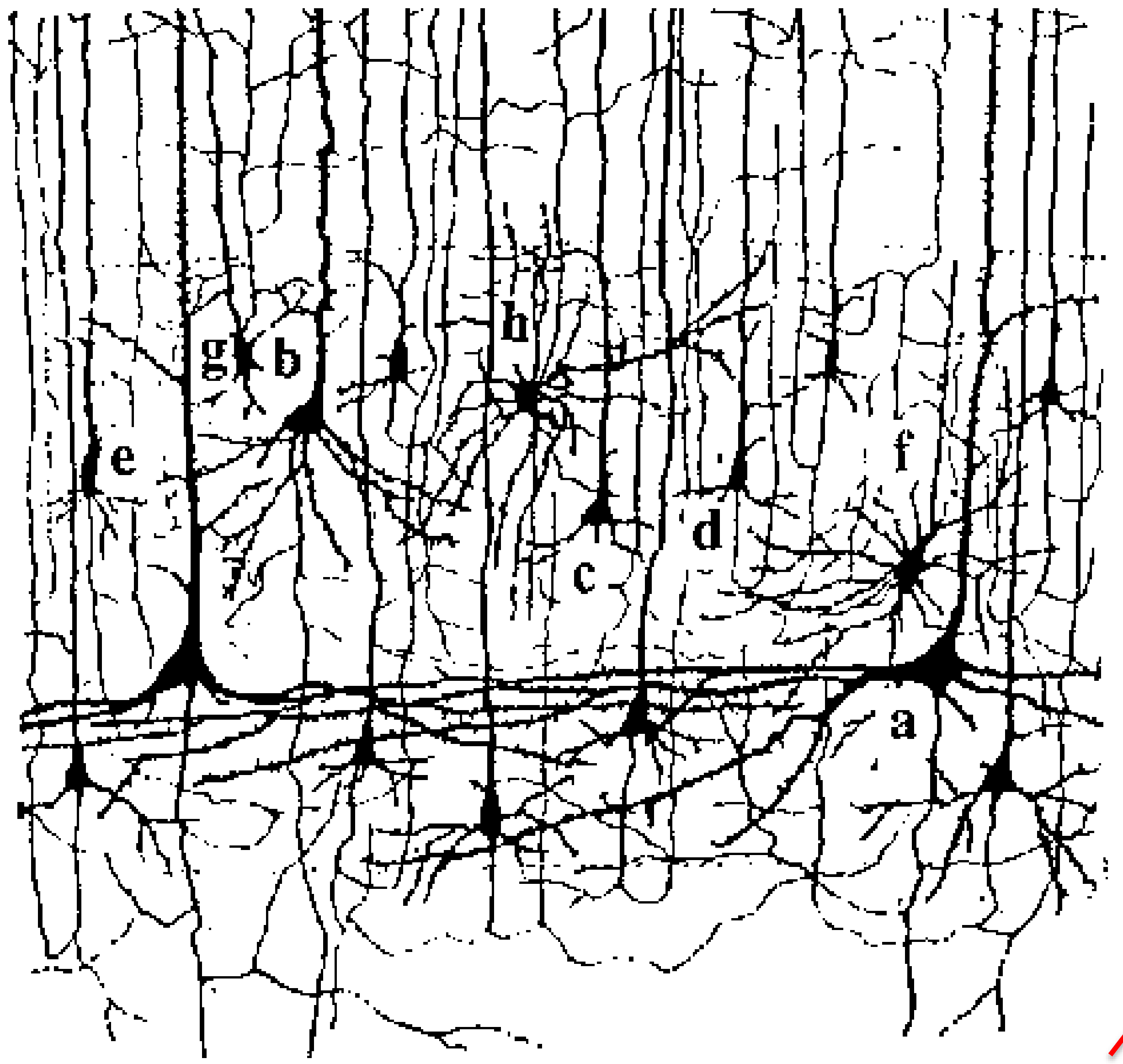
Review of week 1: Neurons and synapses



Review of week 1: Neurons and synapses

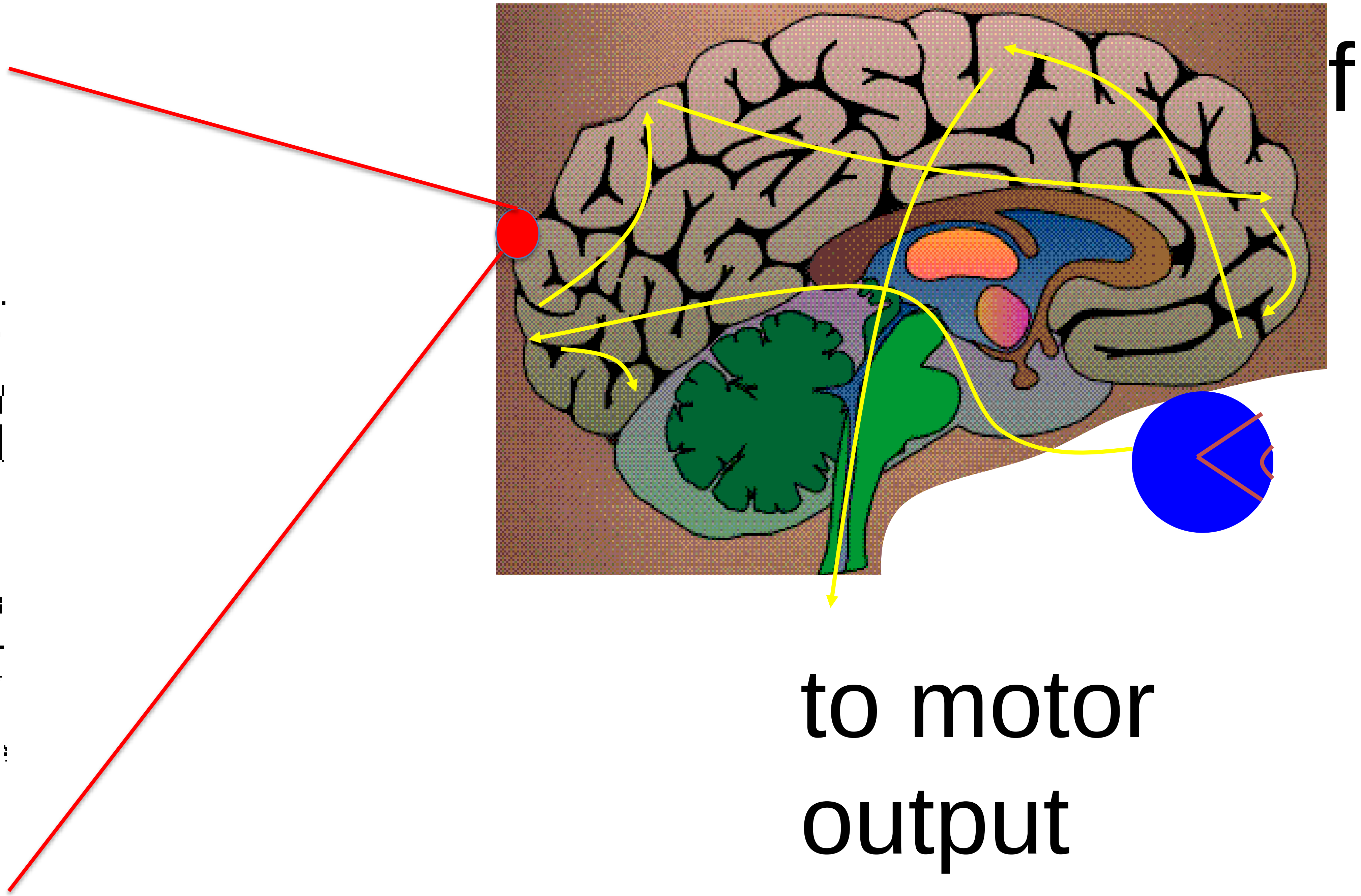


10 000 neurons
3 km of wire



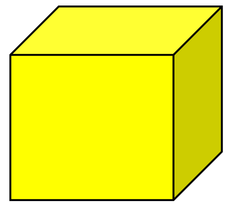
motor cortex

frontal cortex



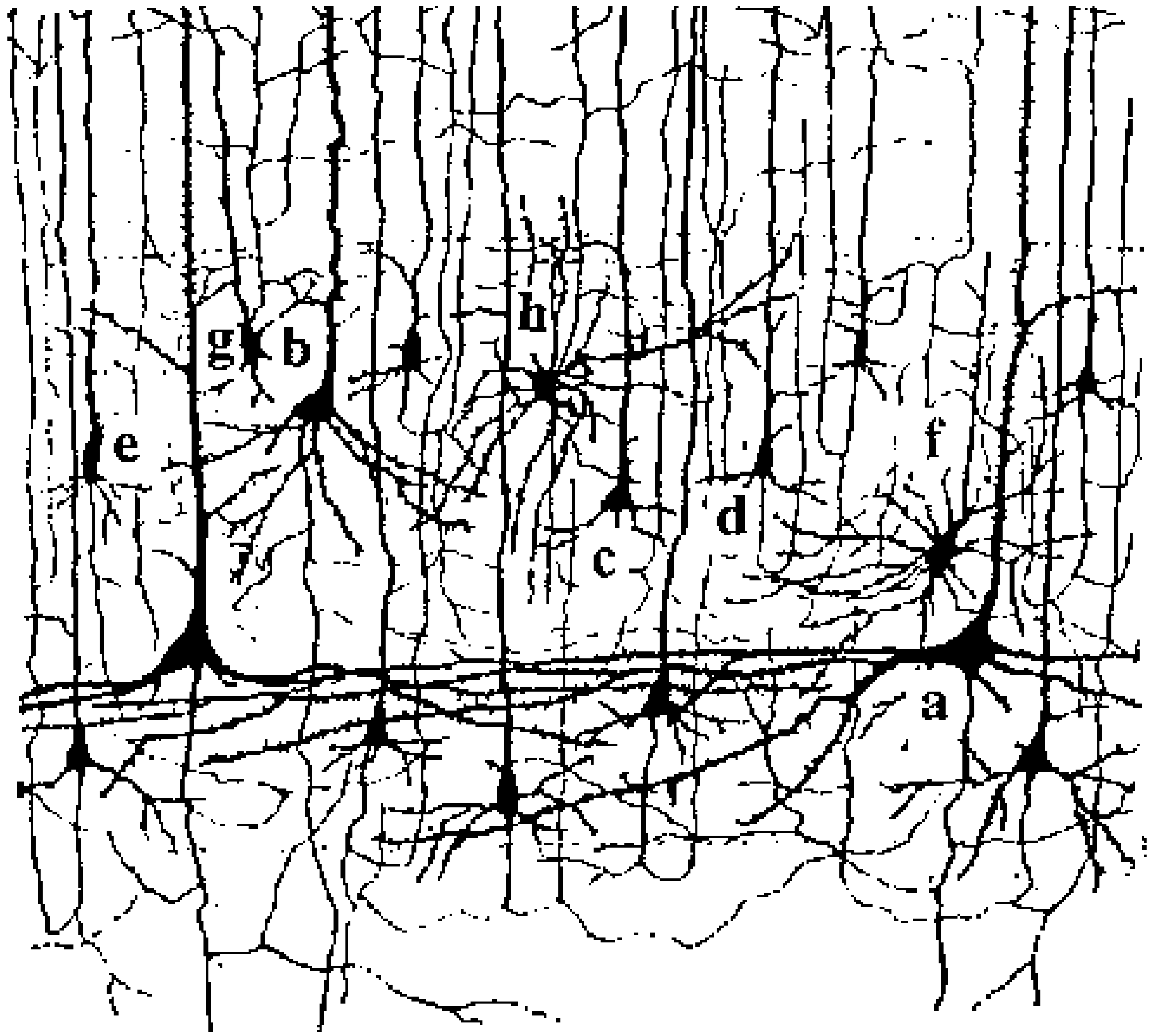
to motor output

Review of week 1: Neurons and synapses



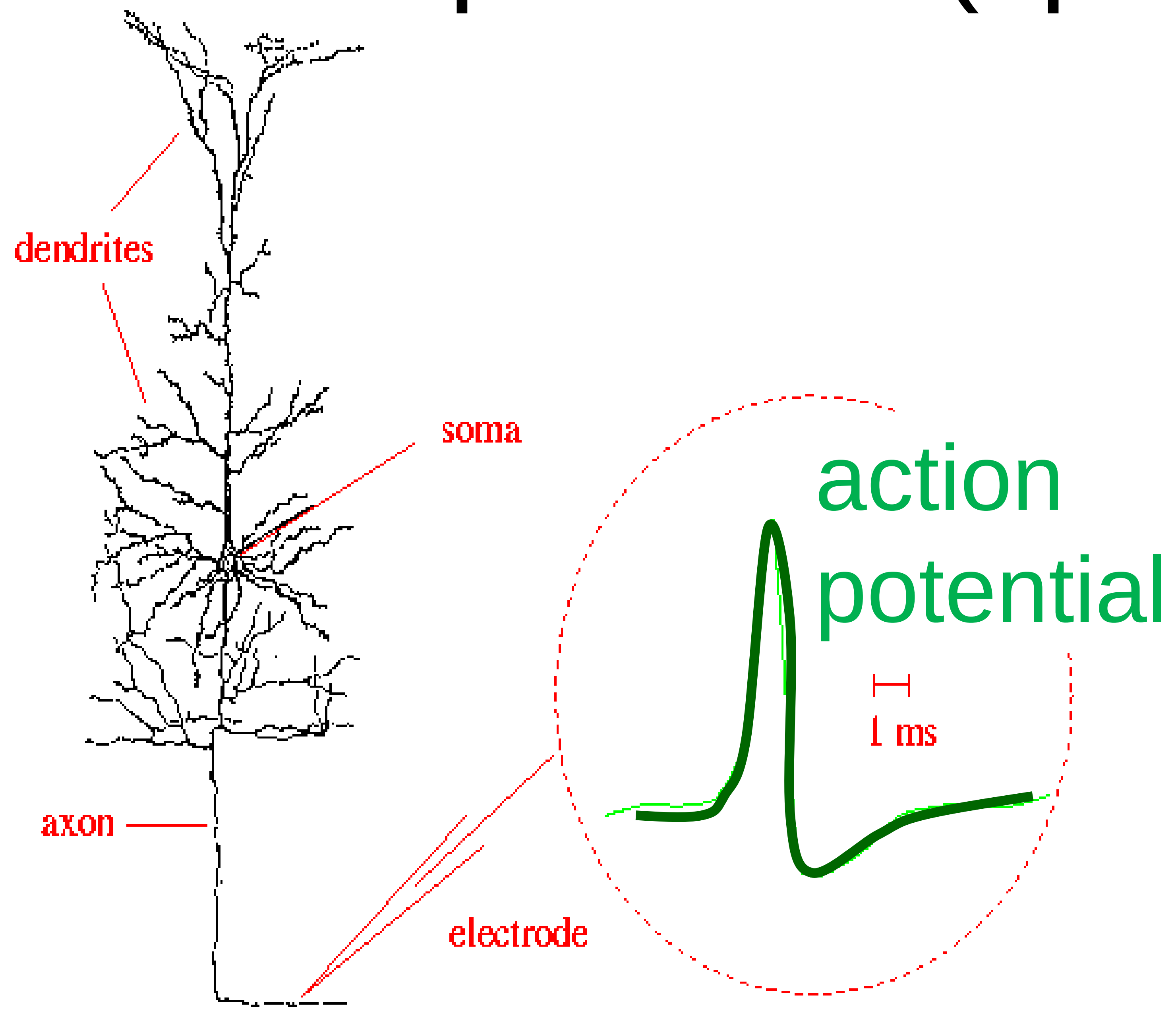
1mm

10 000 neurons
3 km of wire



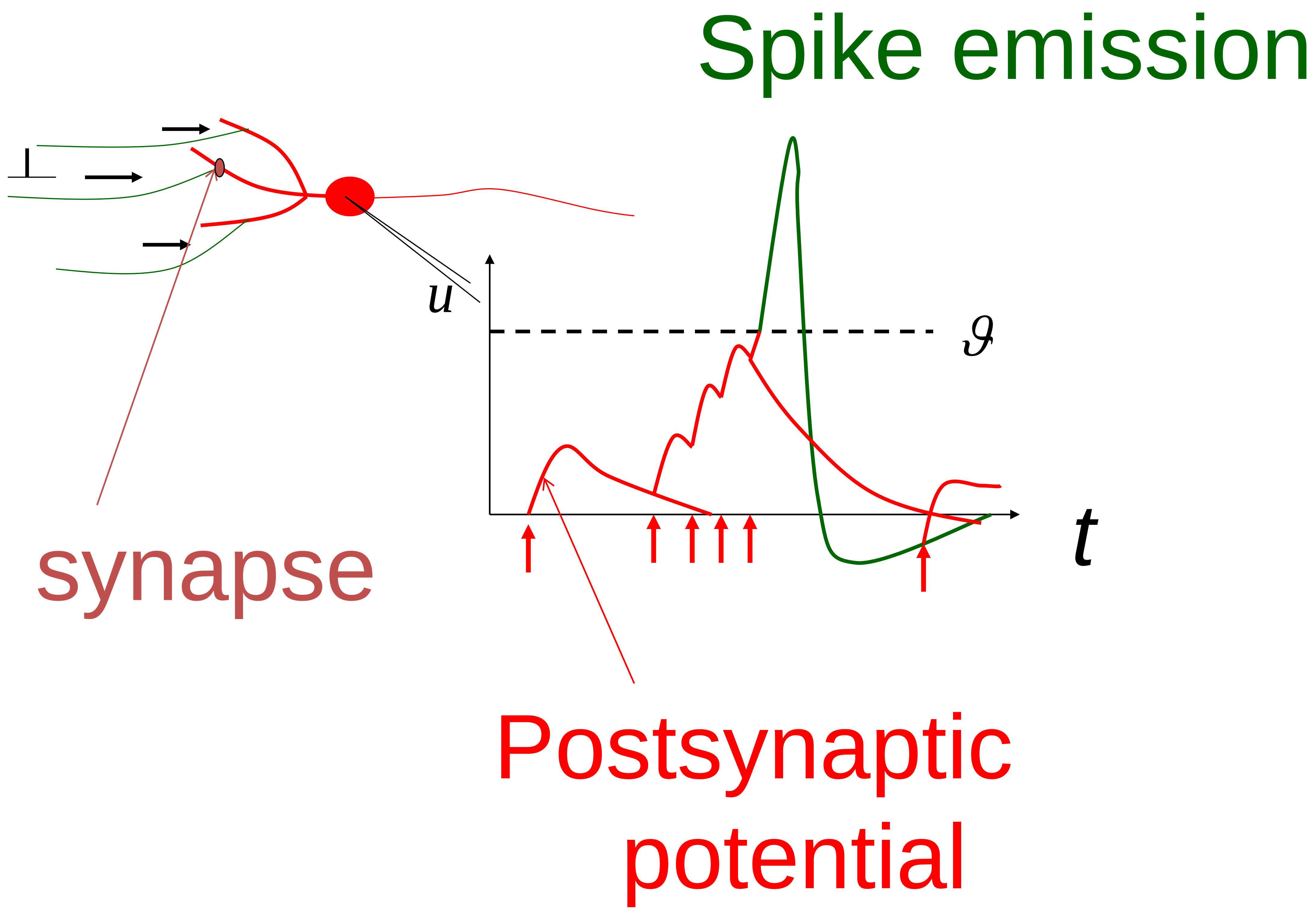
Ramon y Cajal

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

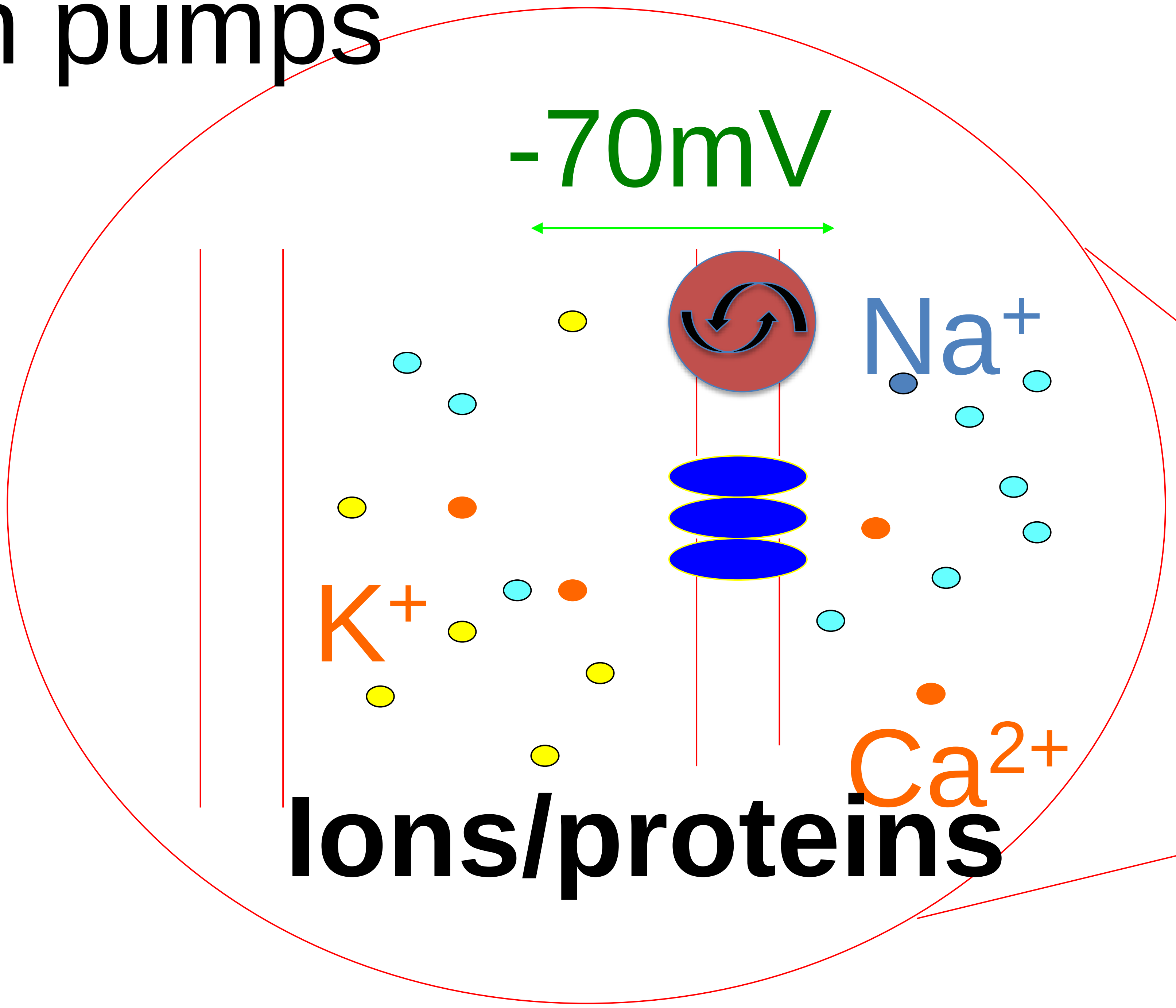
Neuronal Dynamics – week 2: Biophysics of neurons

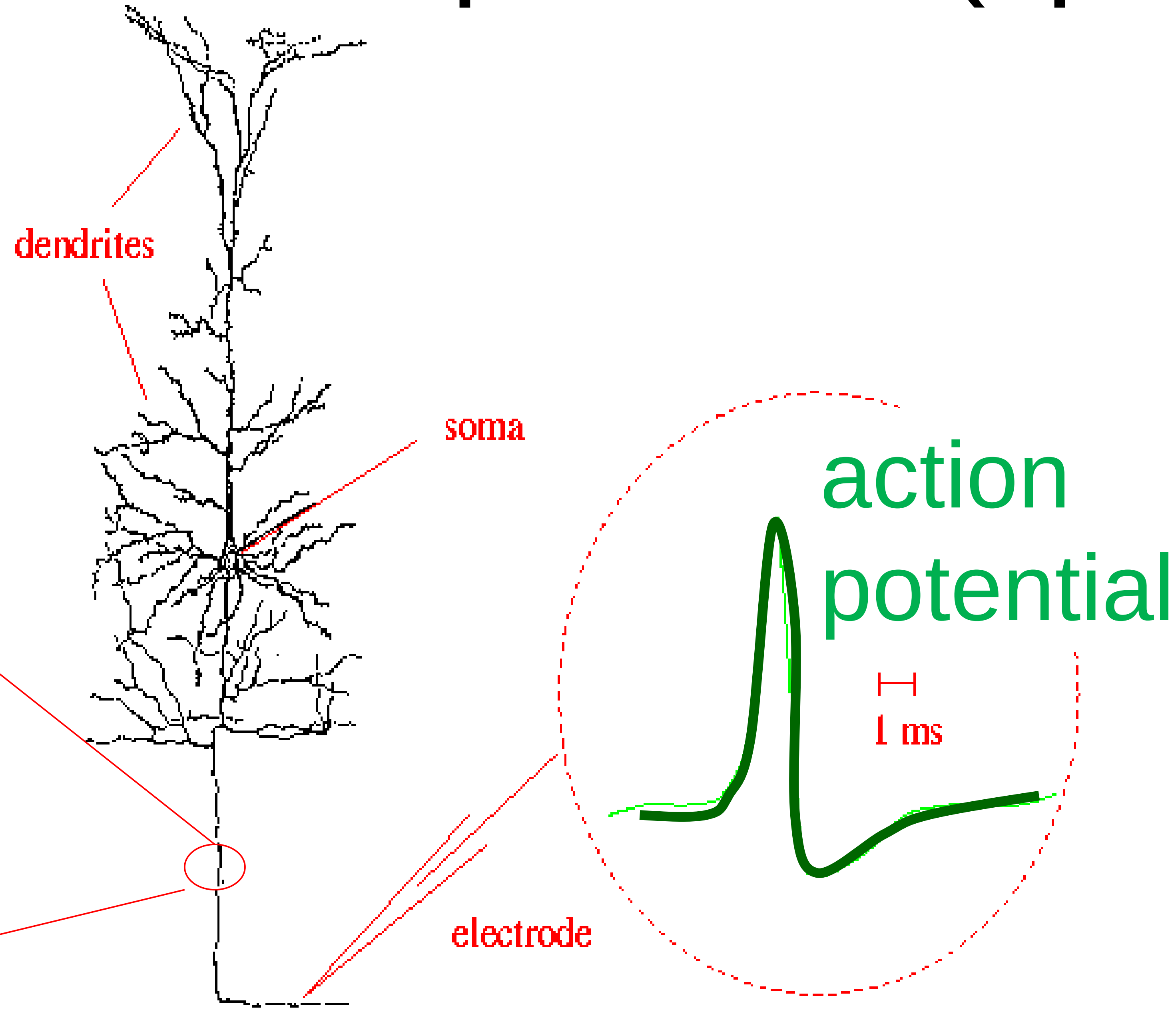
Cell surrounded by membrane

Membrane contains

- ion channels
- ion pumps

Signal:
action potential (spike)





Neuronal Dynamics – week 2: Biophysics of neurons

Cell surrounded by membrane

Membrane contains
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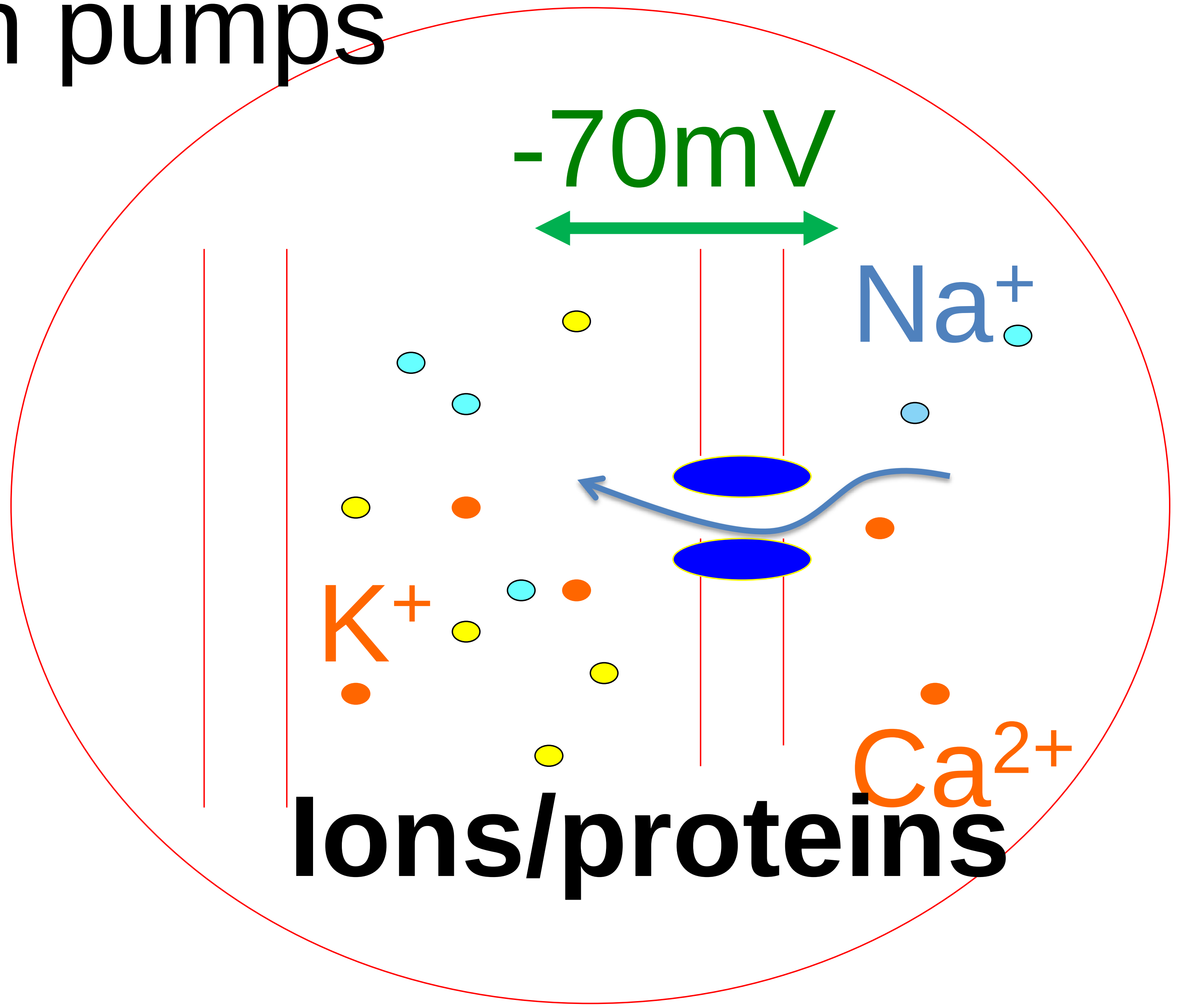

Resting potential -70mV
→ how does it arise?

Ions flow through channel
→ in which direction?

Neuron emits action potentials
→ why?

Resting potential -70mV

→ how does it arise?

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Neuron emits action potentials

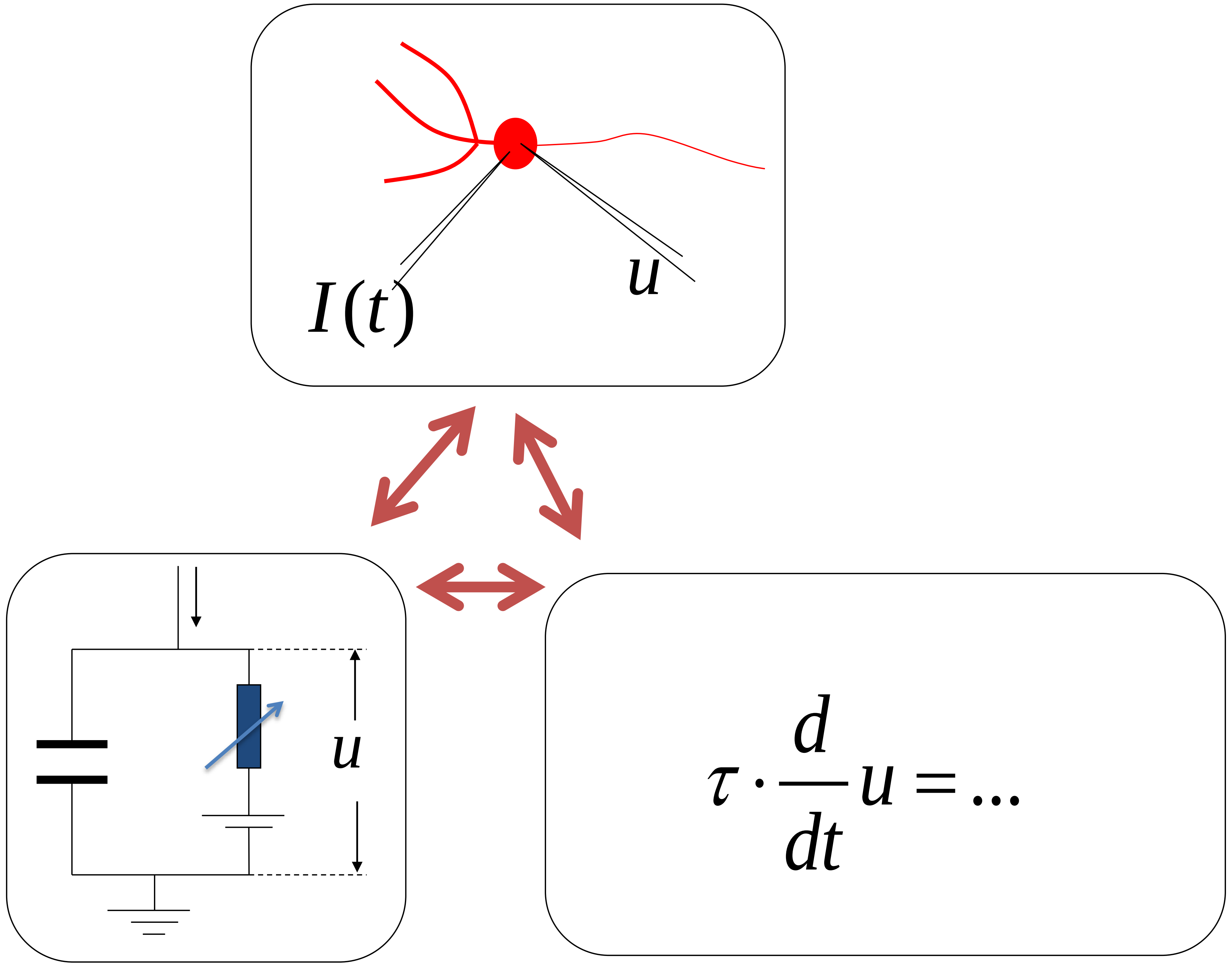
→ why?

→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

Week 2 – 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

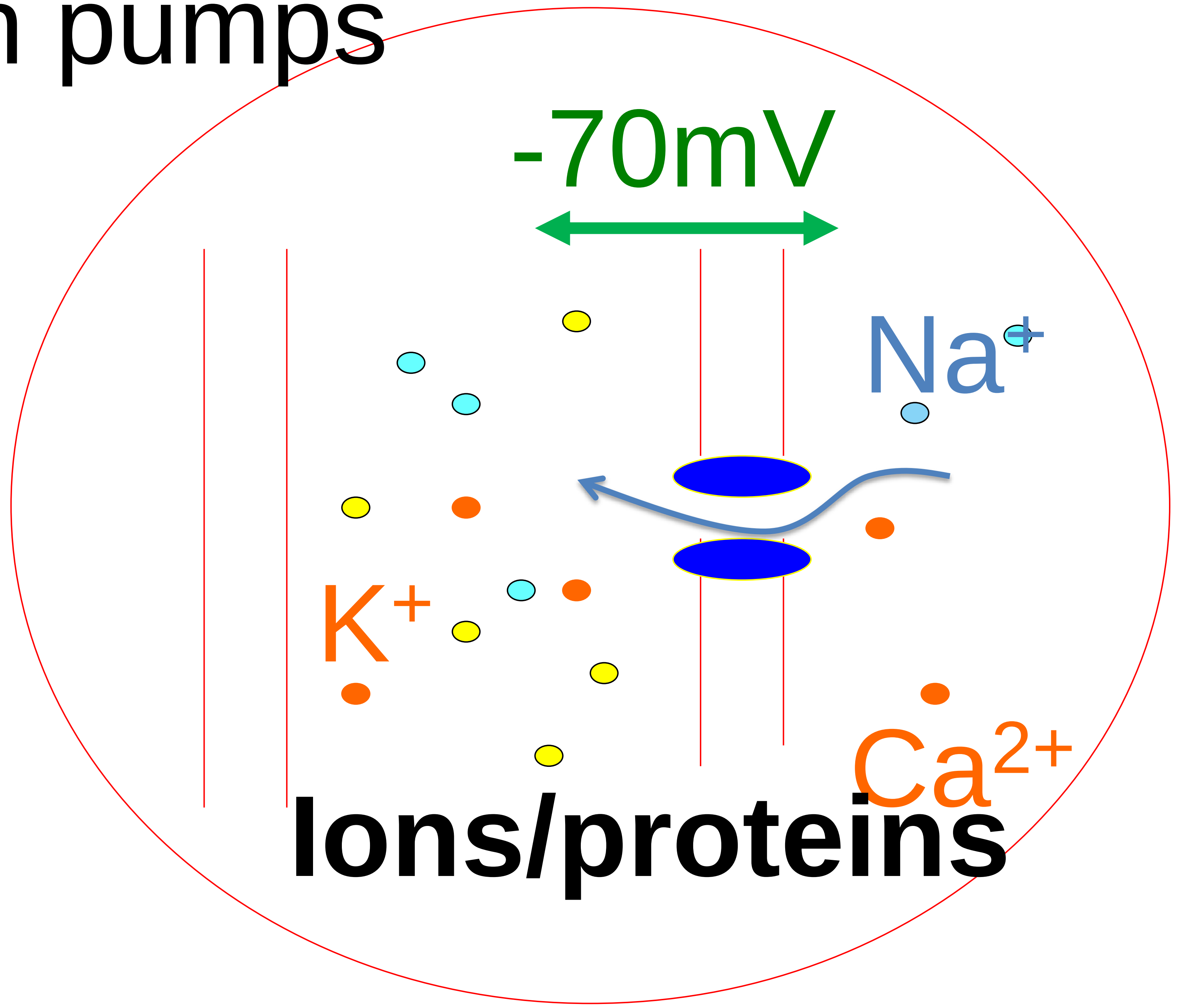
Week 2 – Biophysical modeling: The Hodgkin-Huxley model

Wulfram Gerstner
EPFL, Lausanne, Switzerland

Neuronal Dynamics – 2.2. Resting potential

Cell surrounded by membrane

Membrane contains
- ion channels
- ion pumps



Resting potential -70mV
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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?

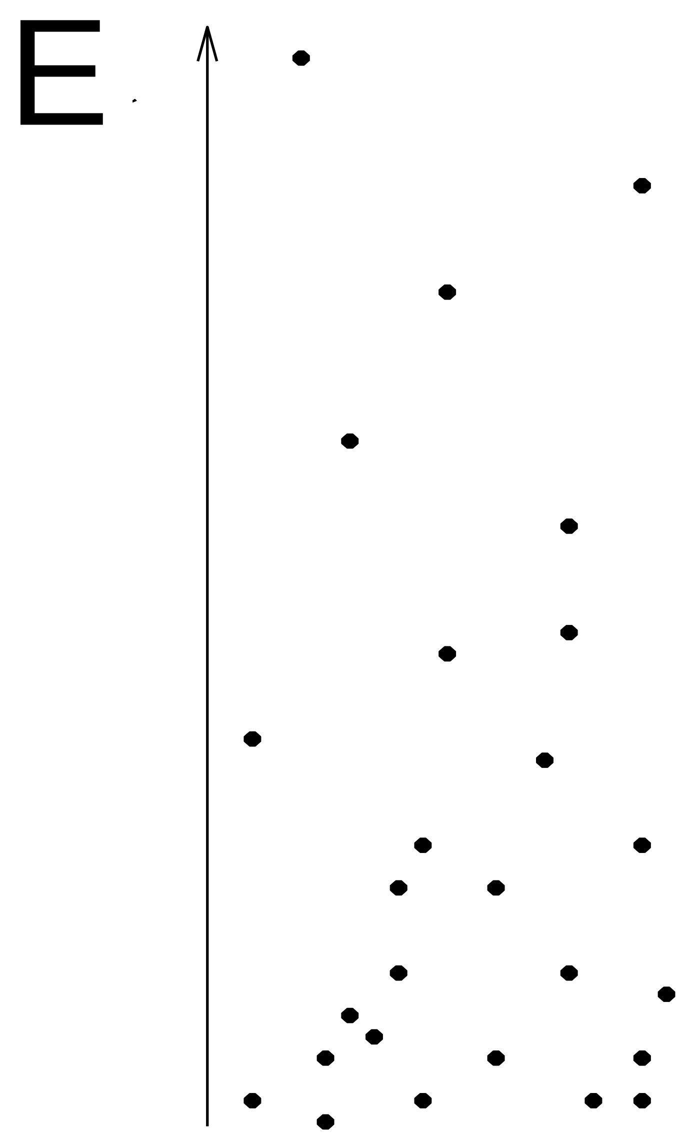
Neuron emits action potentials
→ why?
→Hodgkin-Huxley model

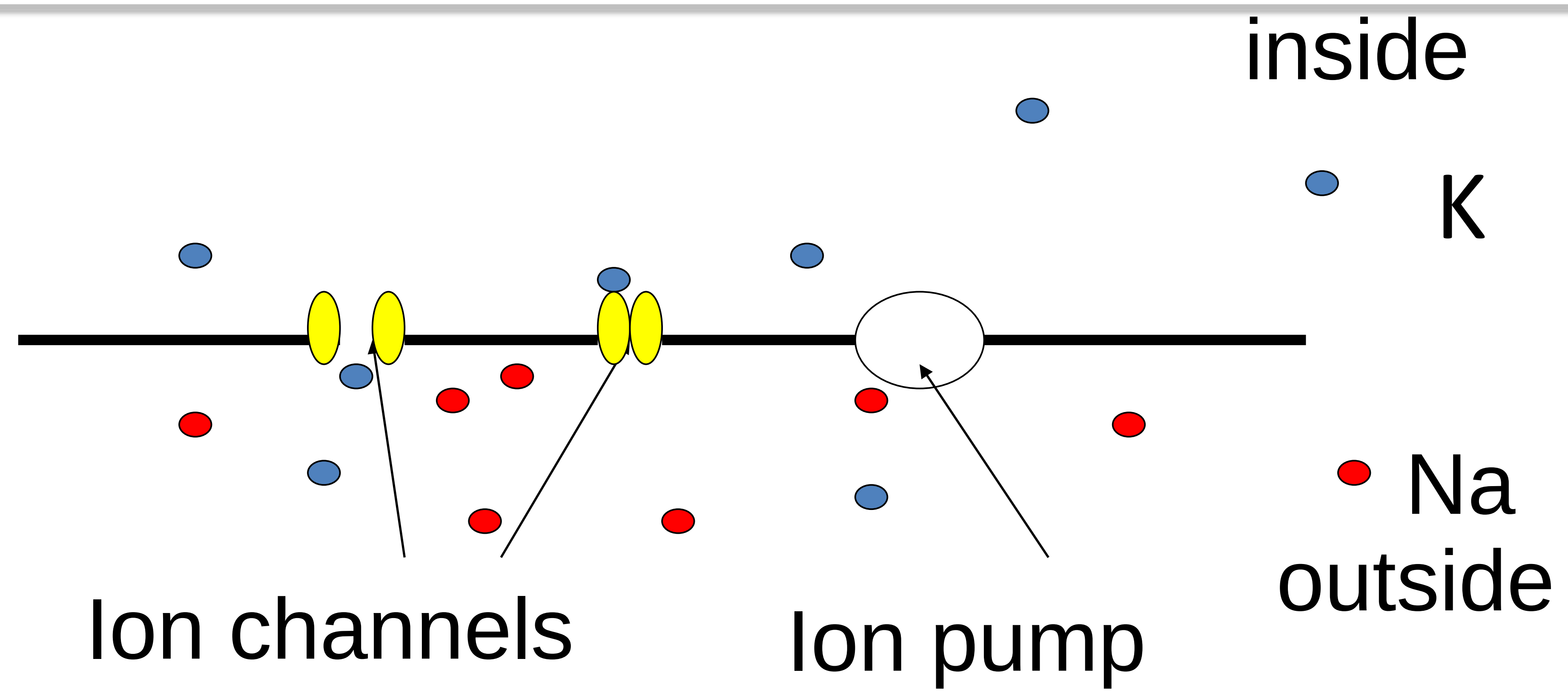
Hodgkin&Huxley (1952)
Nobel Prize 1963

Neuronal Dynamics – 2. 2. Reversal potential

density

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

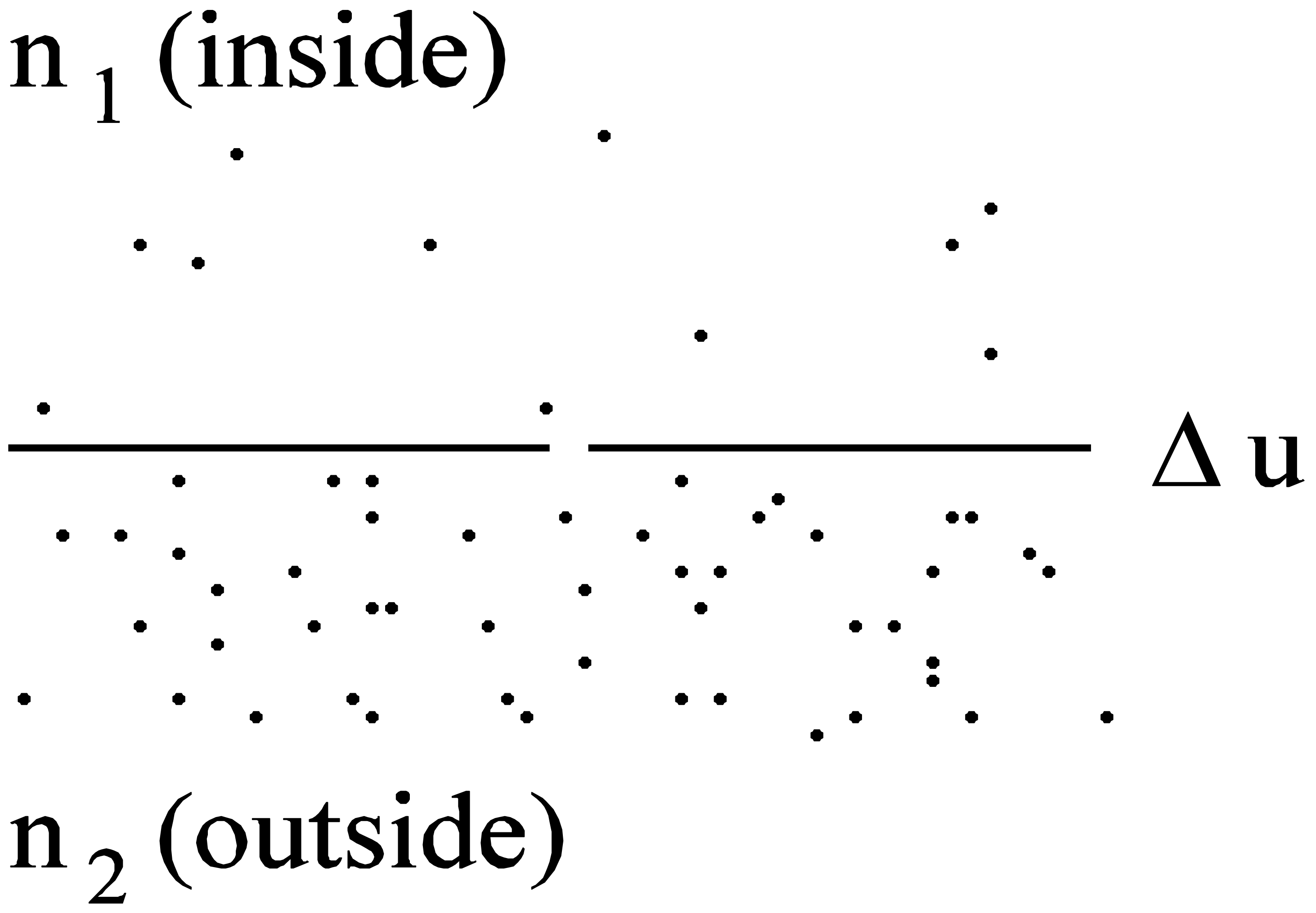




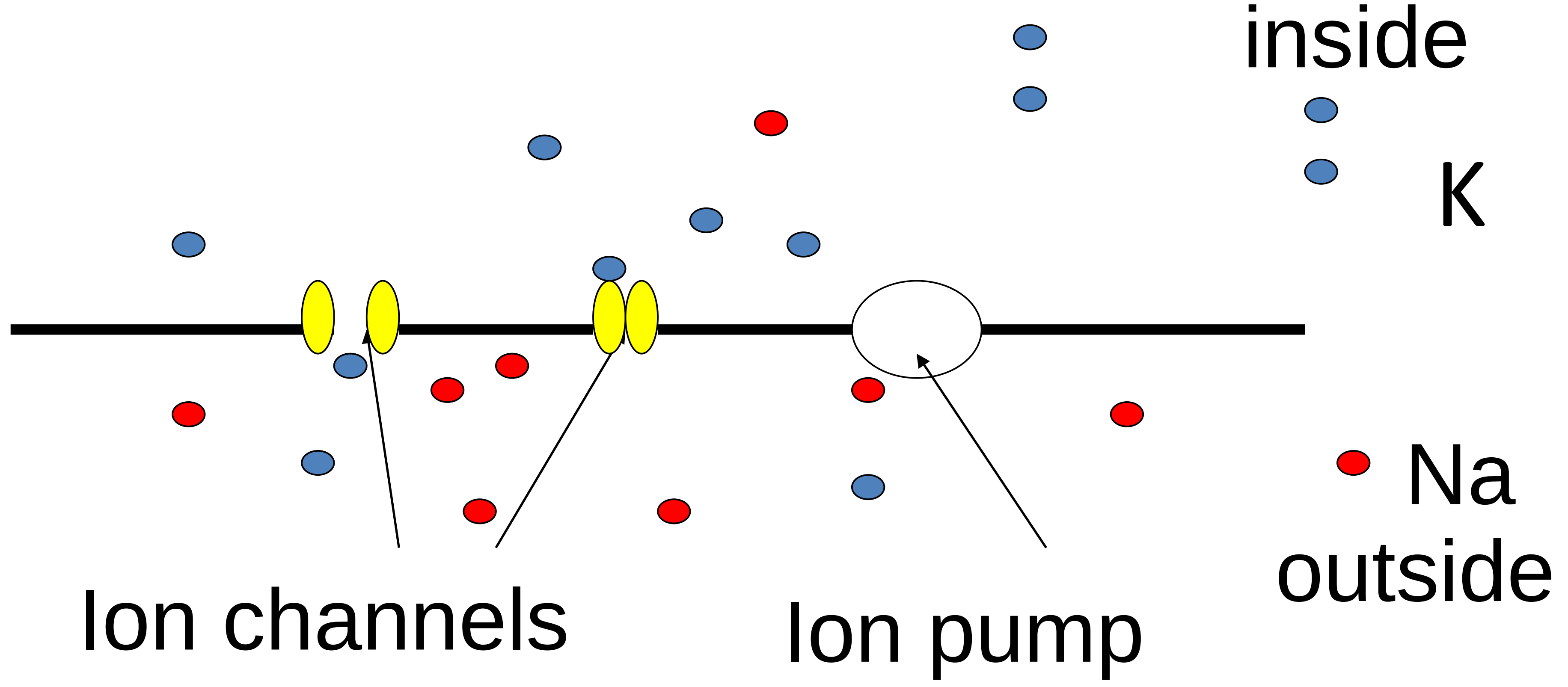
Ion pump ⇔ Concentration difference

Mathetical derivation

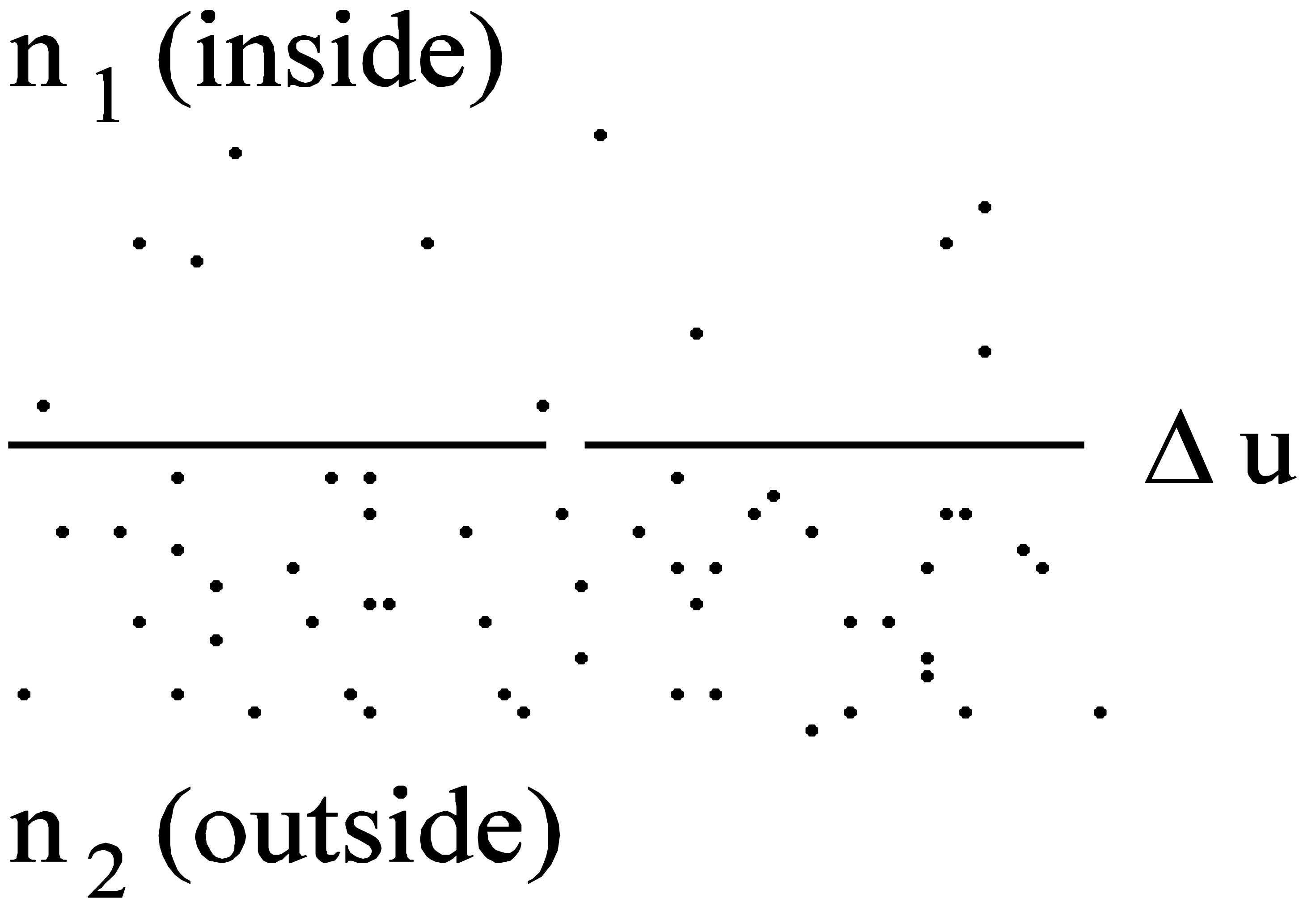
Neuronal Dynamics – 2. 2. Nernst equation

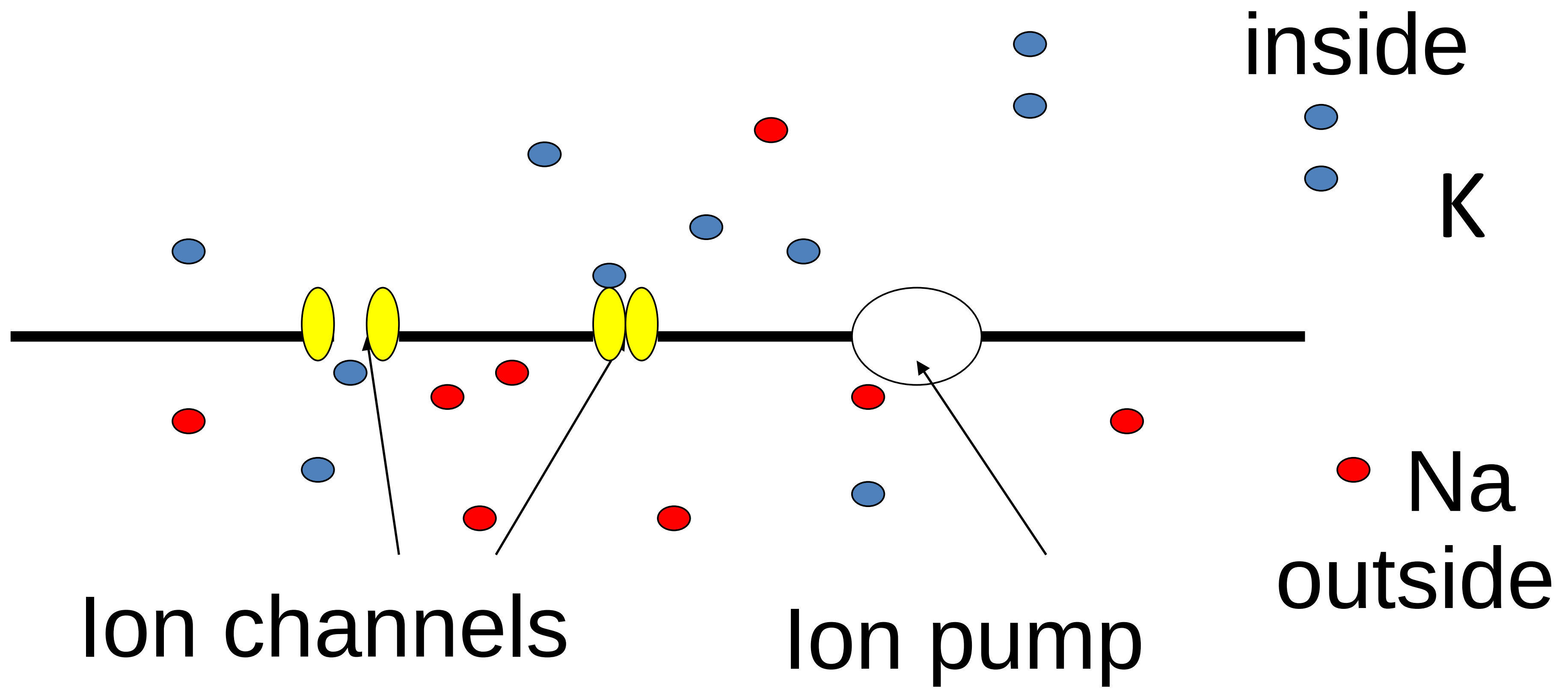


$$n \propto e^{-\frac{E}{kT}}$$



Neuronal Dynamics – 2. 2. Nernst equation



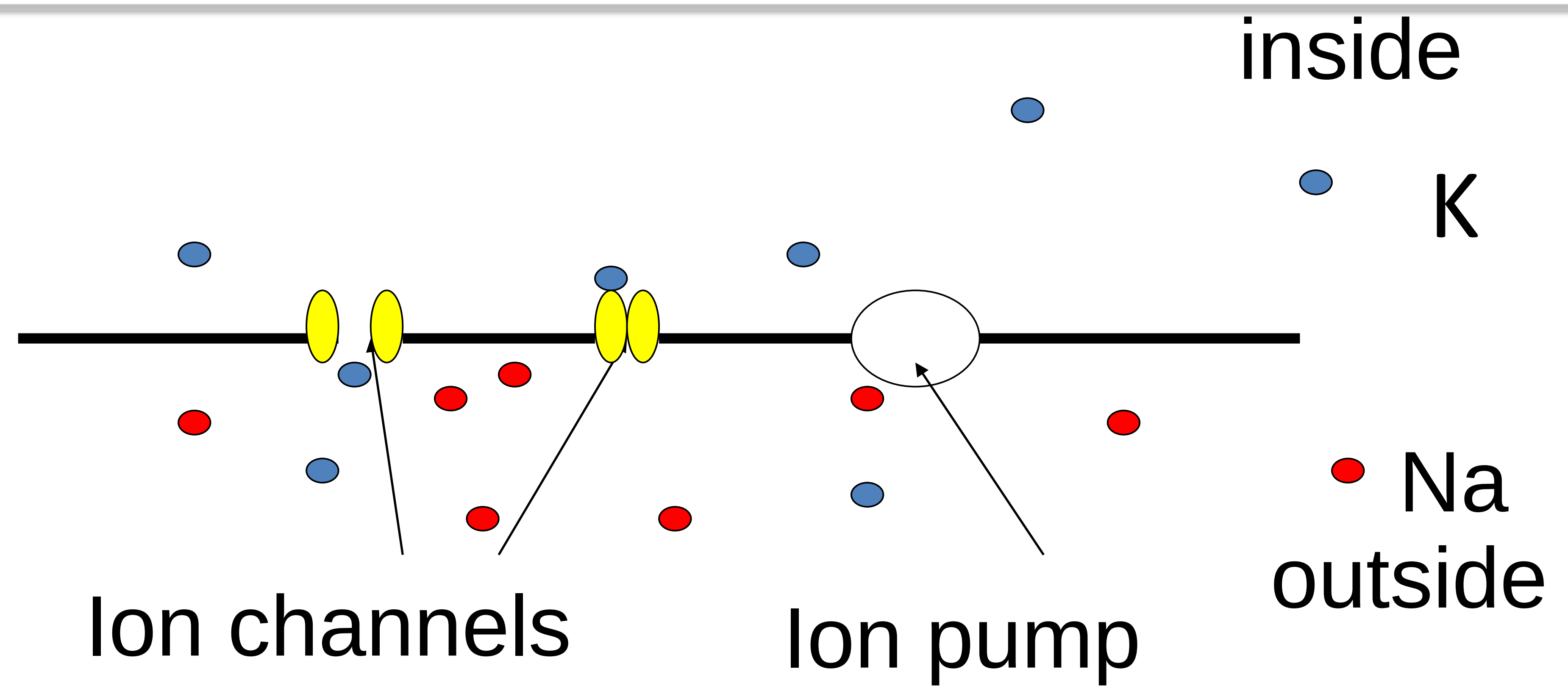


$$\Delta u = u_1 - u_2 = \frac{-kT}{q} \ln \frac{n(u_1)}{n(u_2)}$$

Reversal potential

Concentration difference ⇔ voltage difference

Neuronal Dynamics – 2. 2. Reversal potential



Ion pump → Concentration difference

Concentration difference ⇔ voltage difference

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

Reversal potential

Nernst equation

Week 2 – part 3 : Hodgkin-Huxley Model

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Neuronal Dynamics:
Computational Neuroscience of Single Neurons

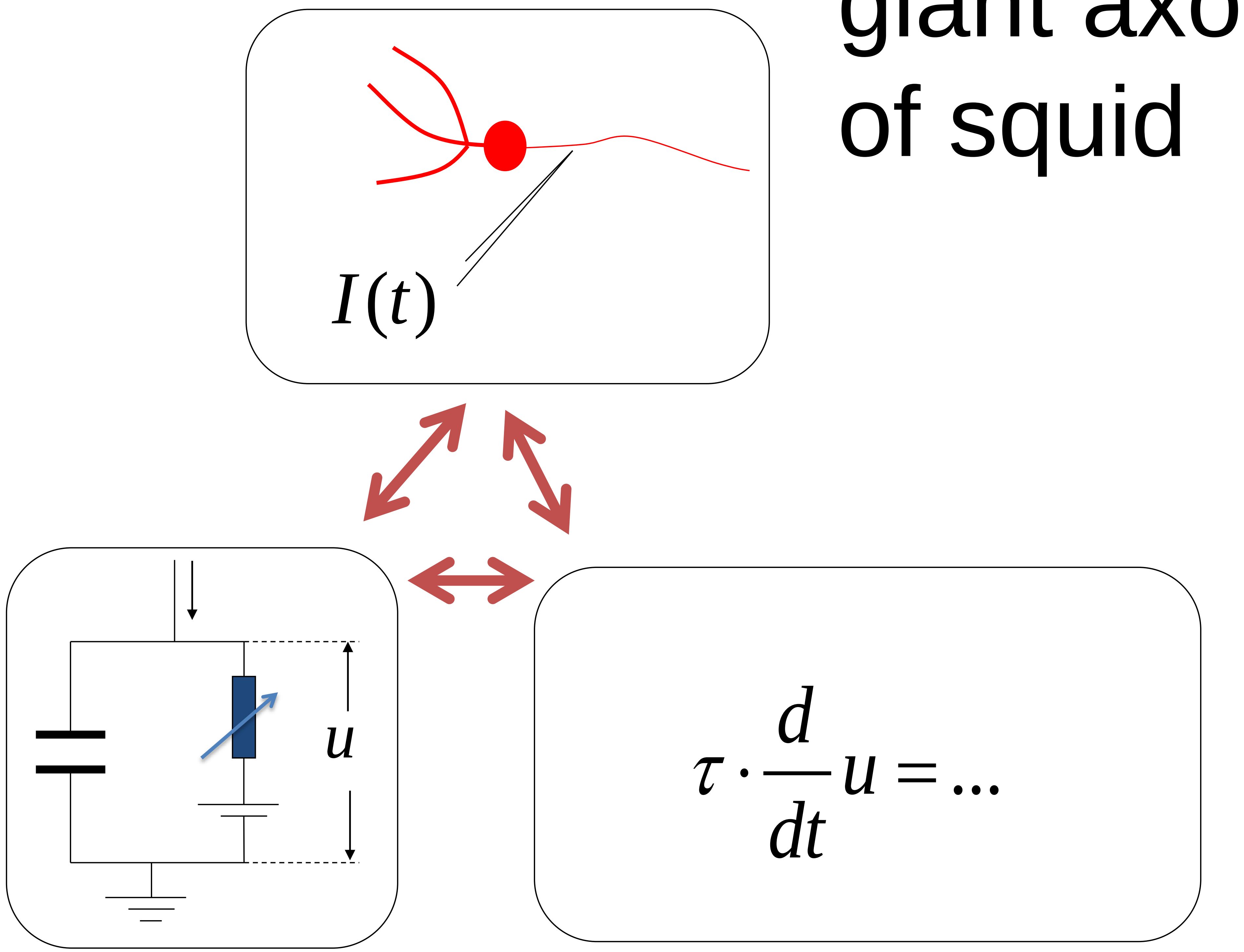
Week 2 – Biophysical modeling:
The Hodgkin-Huxley model

Wulfram Gerstner

EPFL, Lausanne, Switzerland

Neuronal Dynamics – 2. 3. Hodgkin-Huxley Model

giant axon of squid



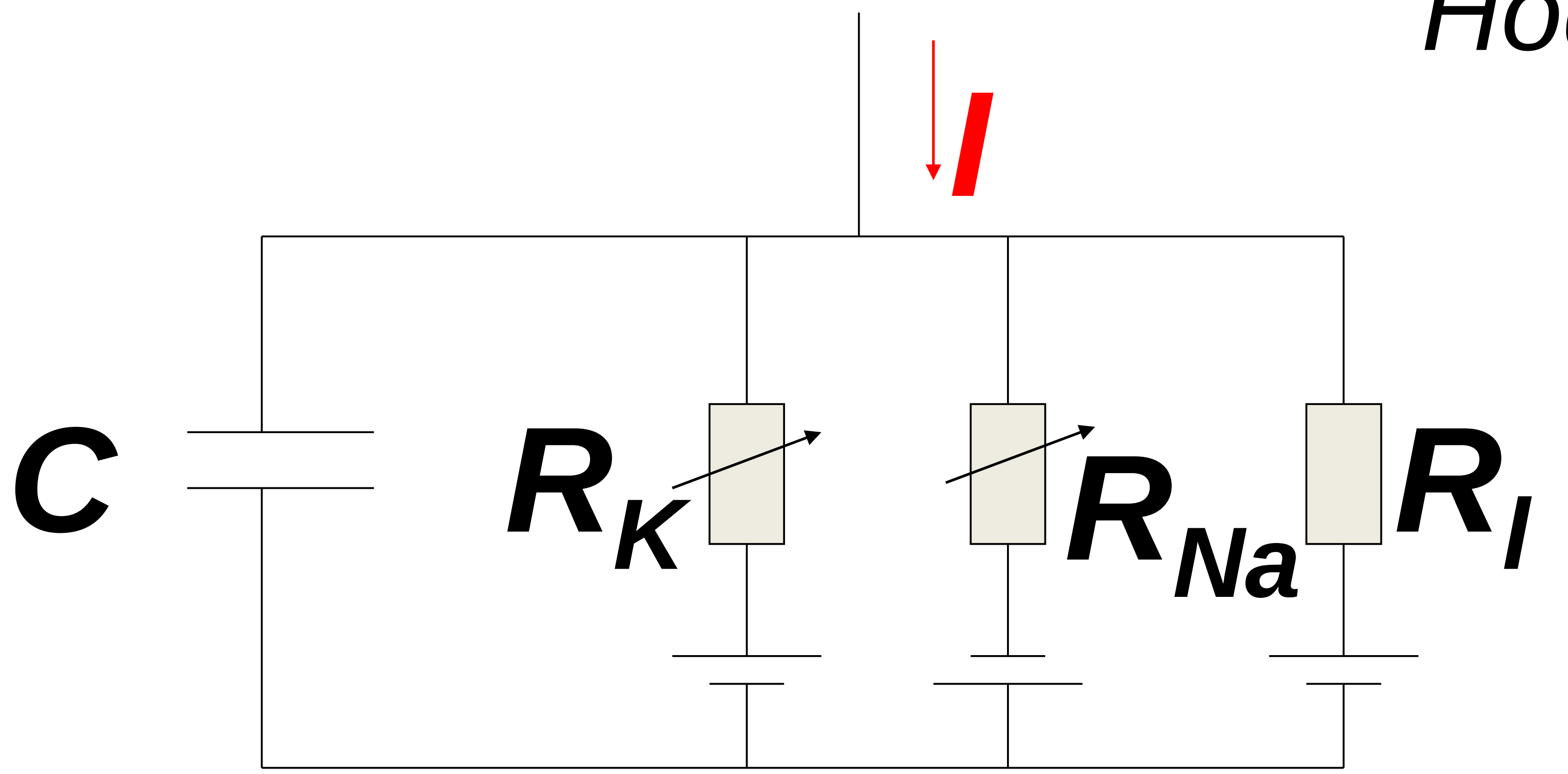
→Hodgkin-Huxley model

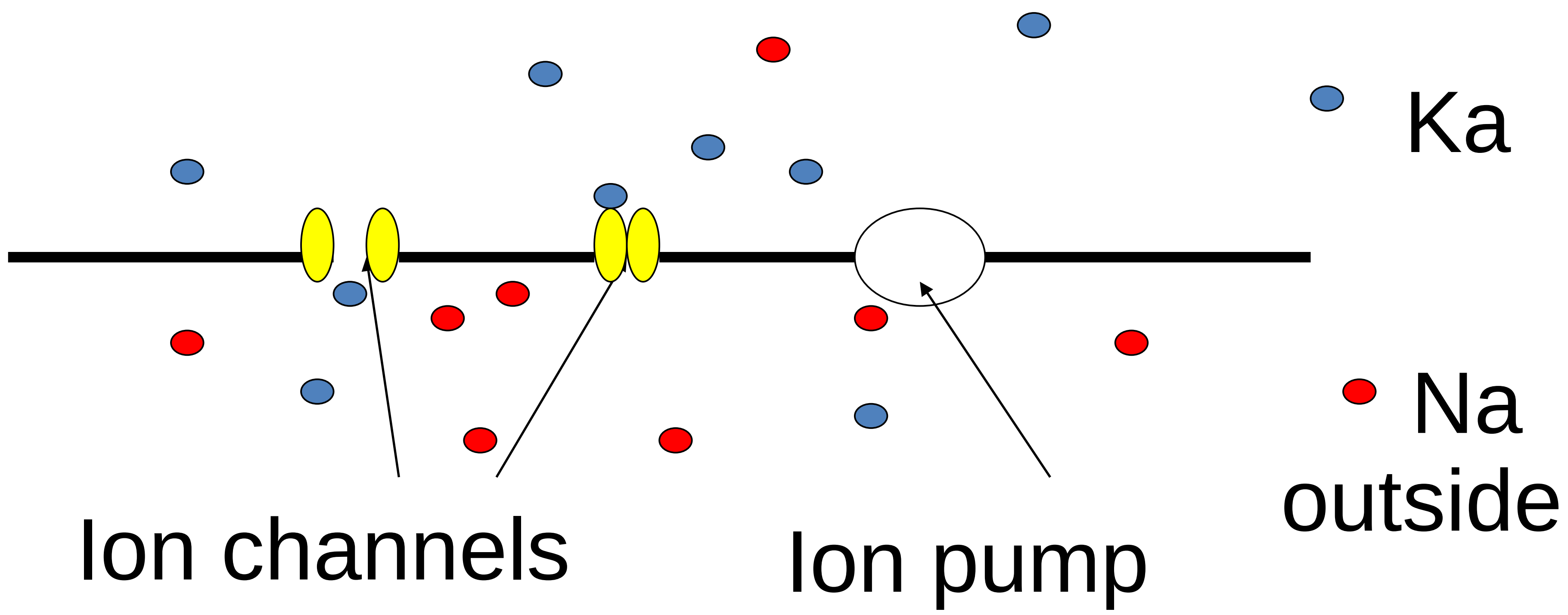
Hodgkin&Huxley (1952)

Nobel Prize 1963

Neuronal Dynamics – 2.3. Hodgkin-Huxley Model

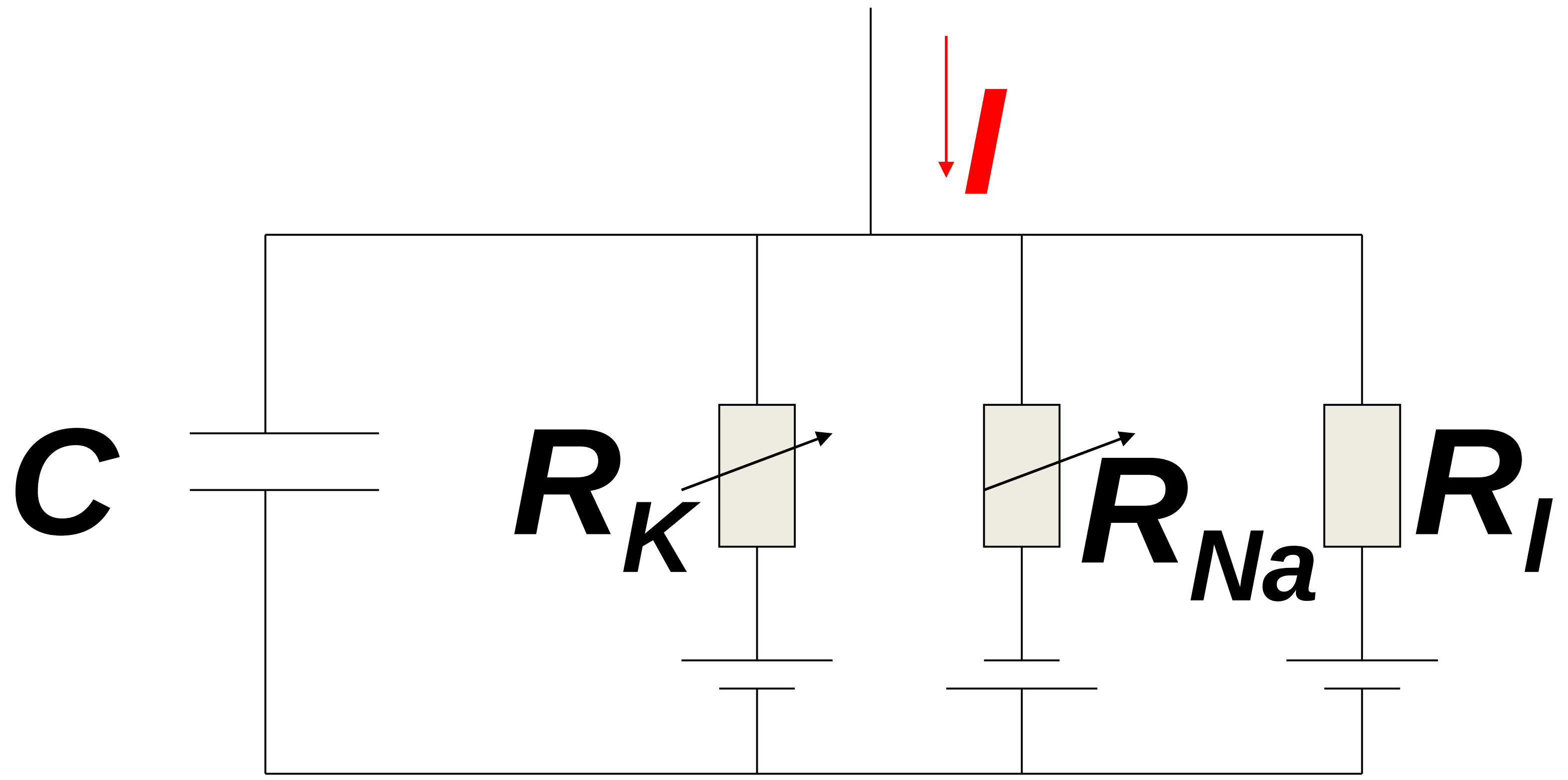
Hodgkin and Huxley, 1952





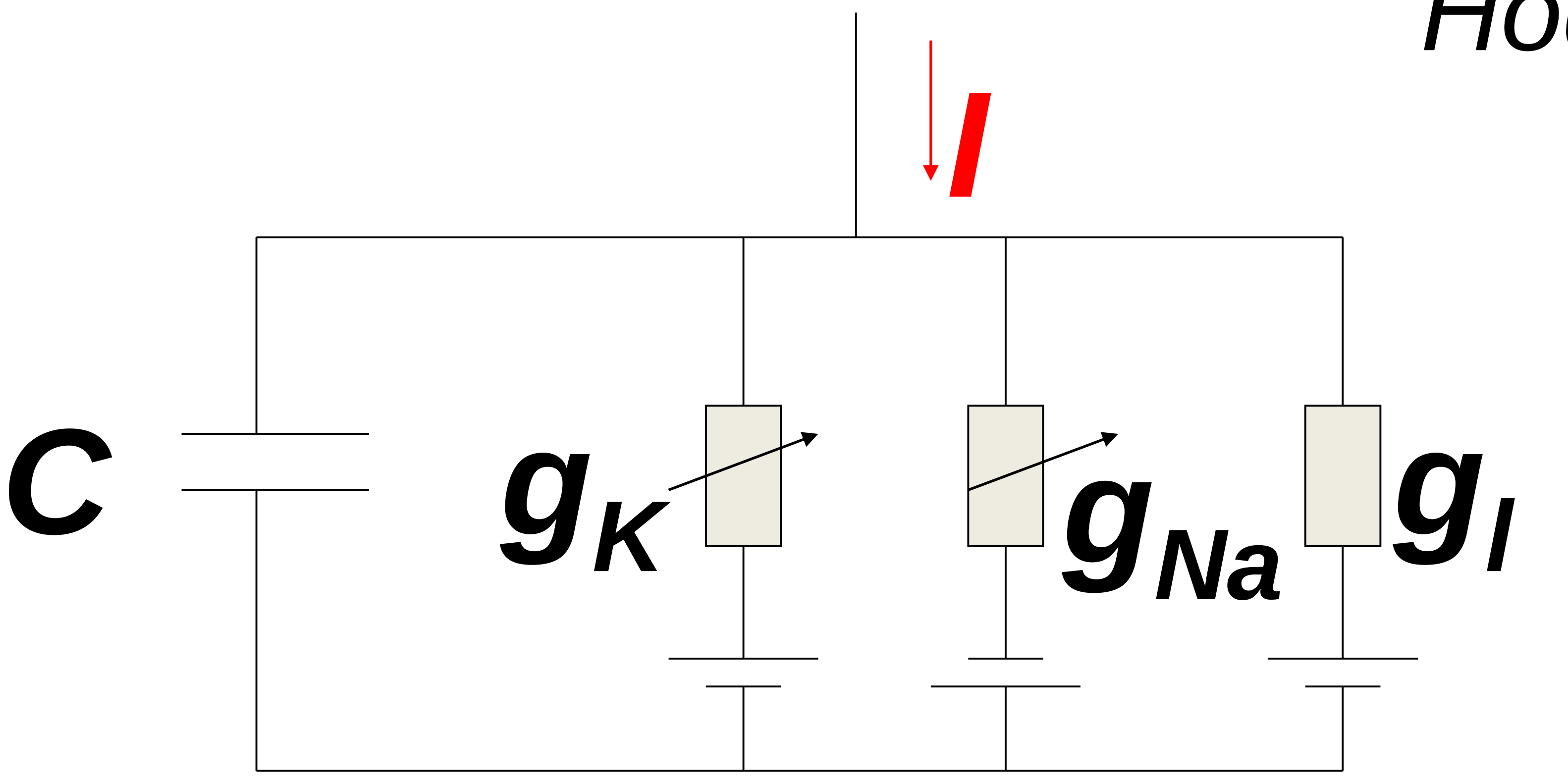
Mathematical derivation

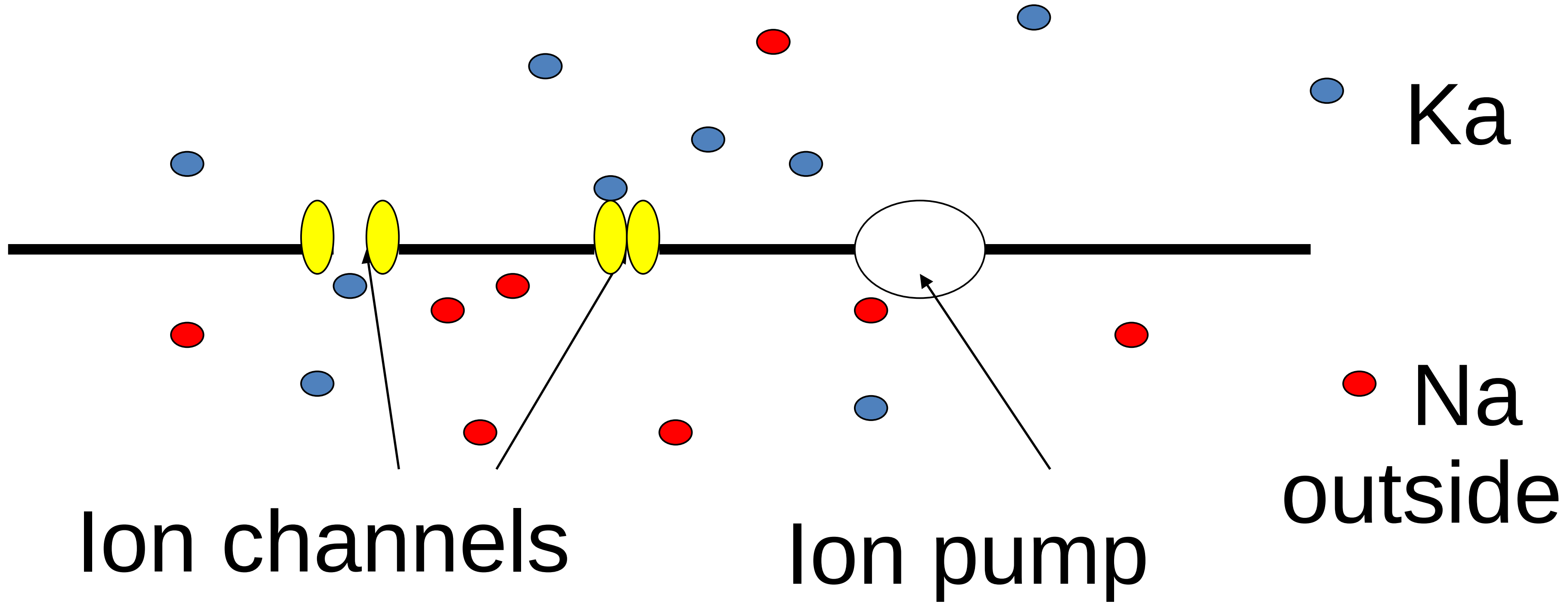
Neuronal Dynamics – 2.3. Hodgkin-Huxley Model



Neuronal Dynamics – 2.3. Hodgkin-Huxley Model

Hodgkin and Huxley, 1952



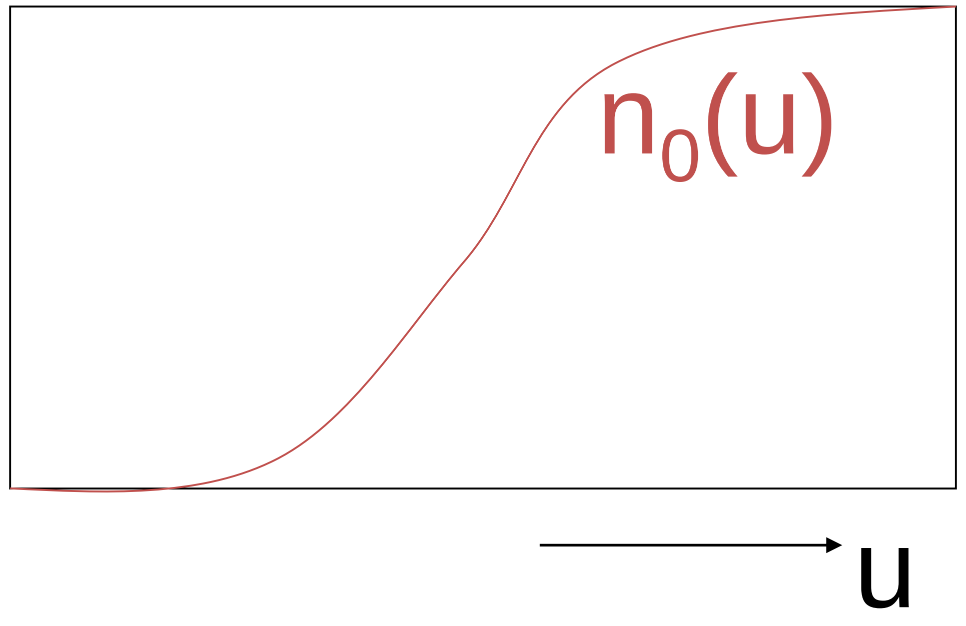


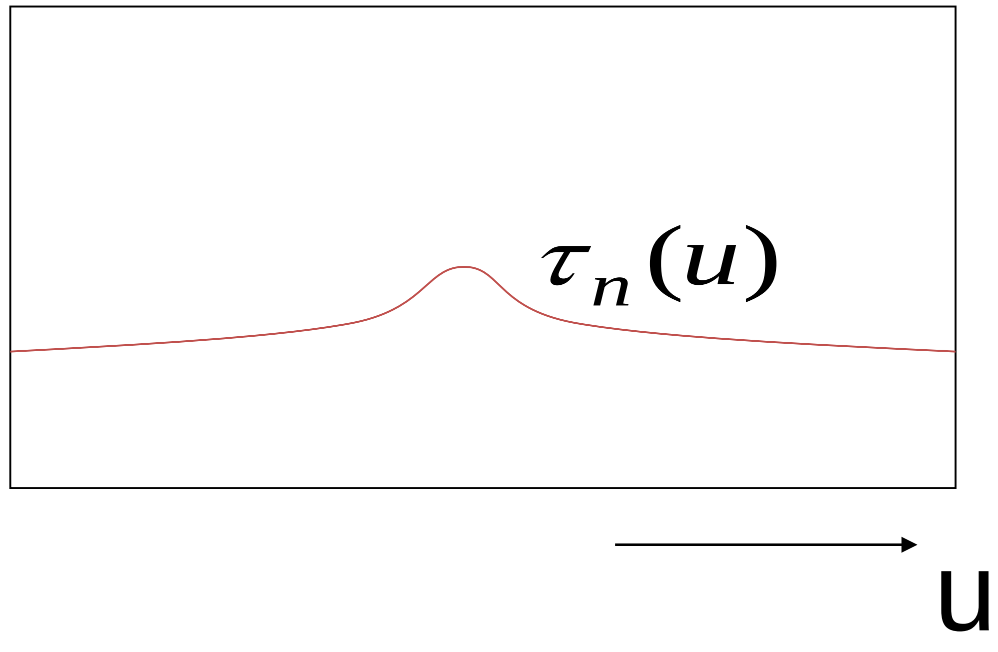
stimulus

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

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

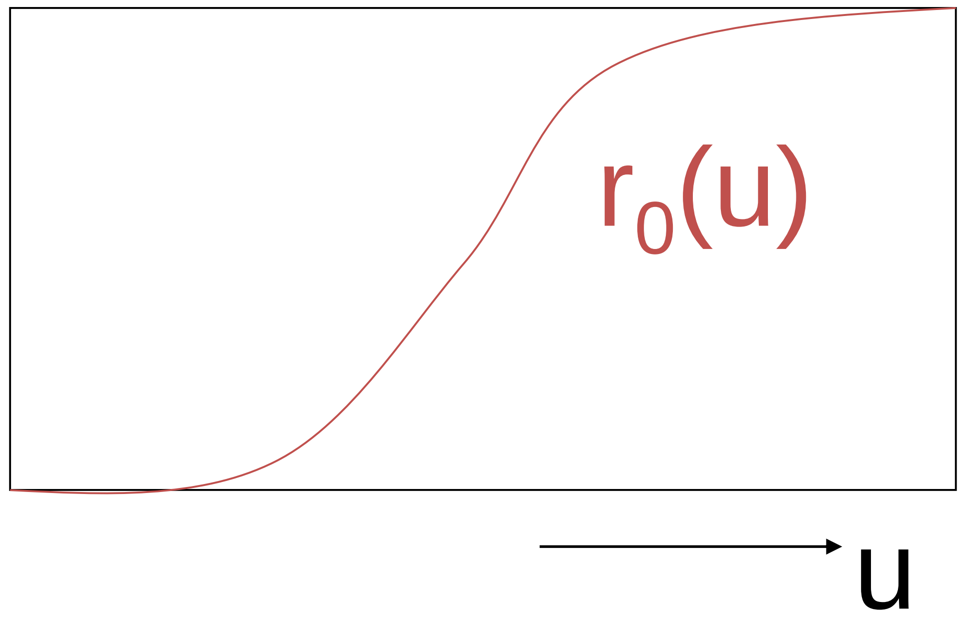
$$\frac{dm}{dt} = -\frac{m-m_0(u)}{\tau_m(u)}$$

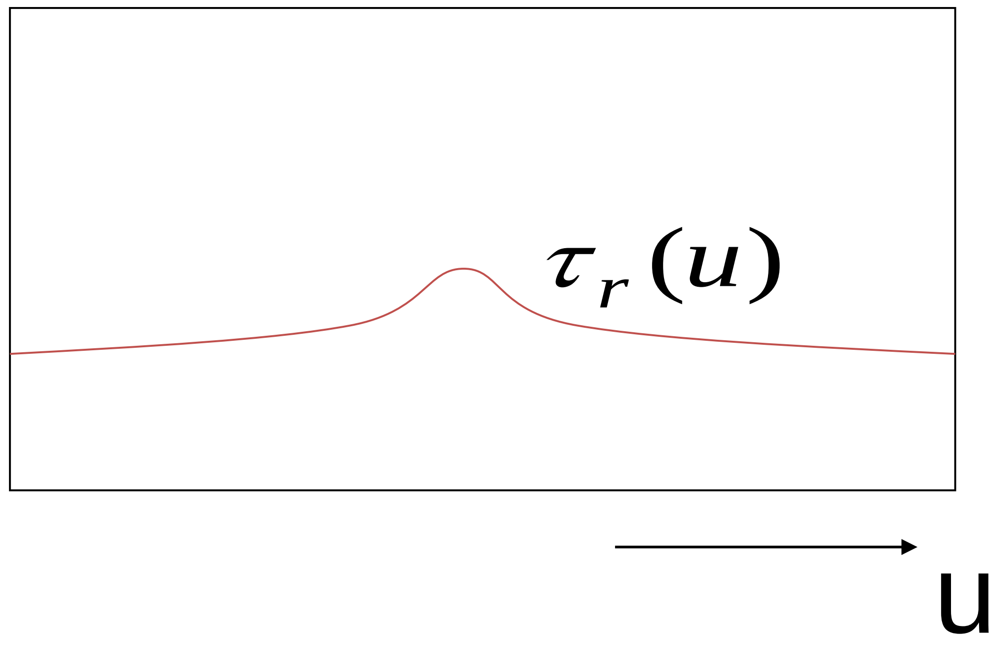




Neuronal Dynamics – 2.3. Ion channel

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





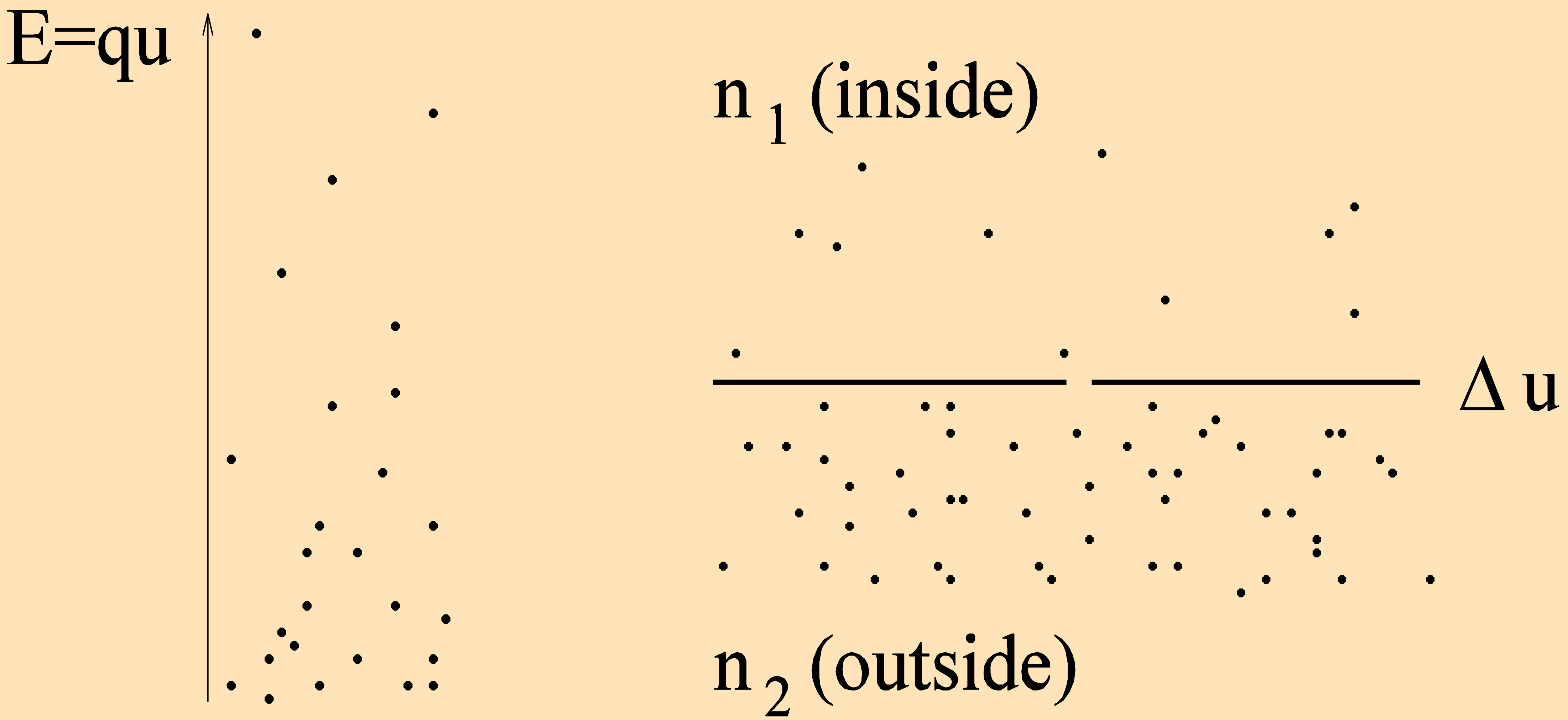
$$I_{ion} = -g_{ion} r^{n_1} s^{n_2} (u - E_{ion})$$

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

Exercise 1.1 Reversal potential of ion channels

Reversal potential

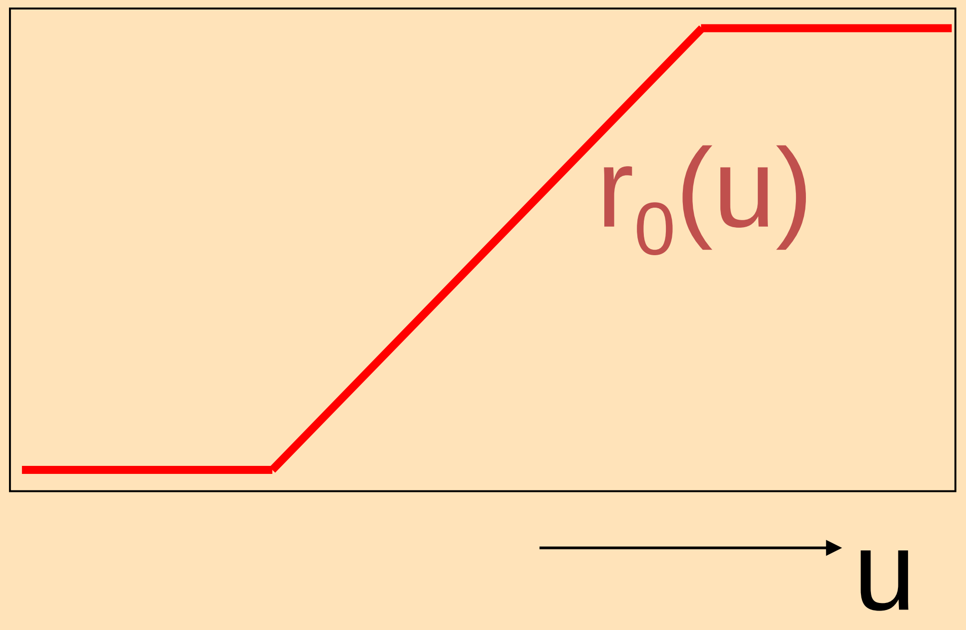
$$\Delta u = u_1 - u_2 = -\frac{kT}{q}\ln\frac{n(u_1)}{n(u_2)}$$

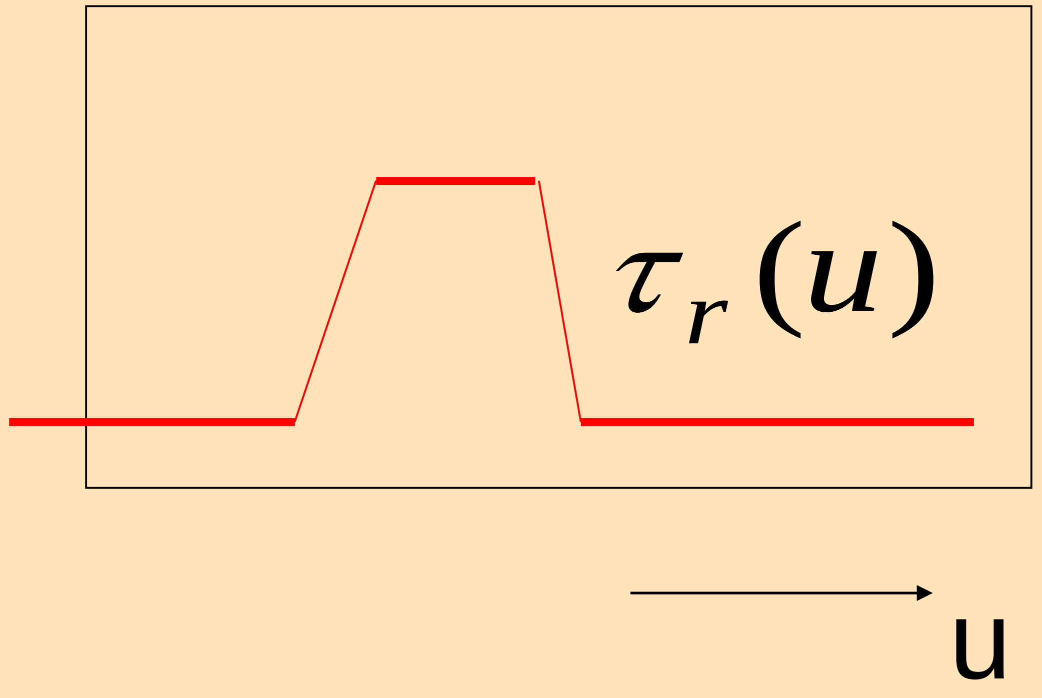


Calculate the reversal potential for Sodium
Postassium
Calcium
given the concentrations

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

Exercise 2 and 1.2 NOW!! - Ion channel





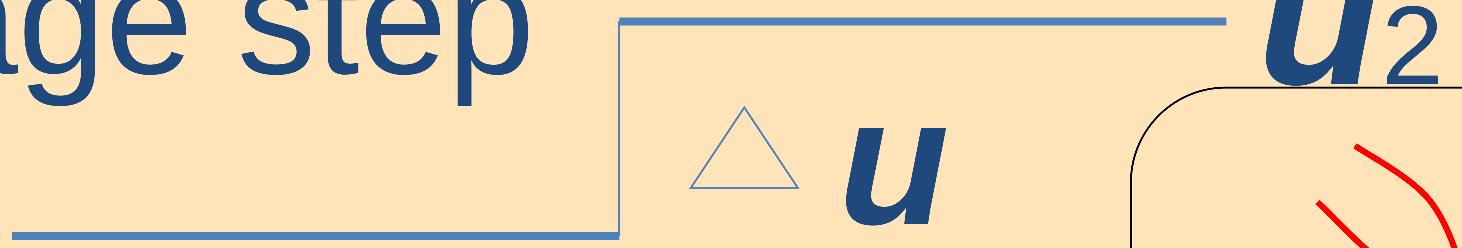
$$C\frac{du}{dt} = -g_{ion} r^{n_1} s^{n_2} (u - E_{ion}) + I(t)$$

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

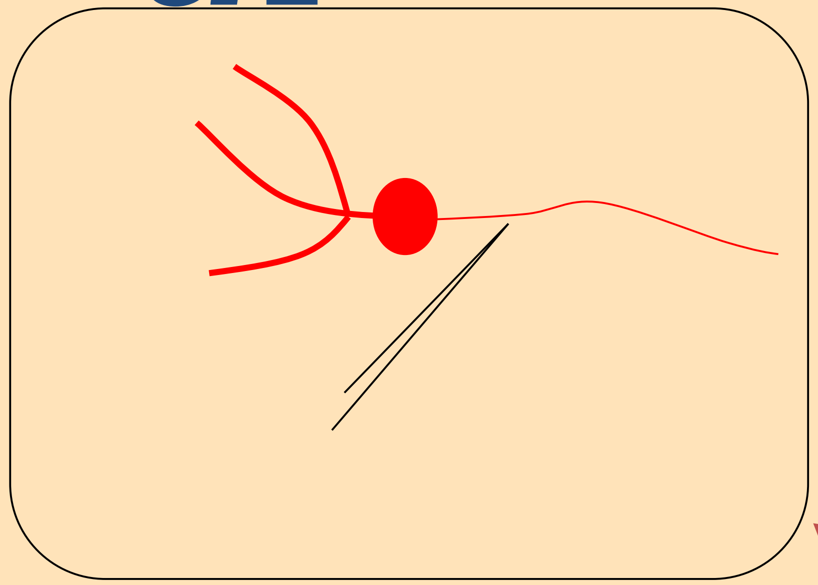
Exercises 1+2 NOW!
If finished, start Exercise 3.
Next lecture At 11:15

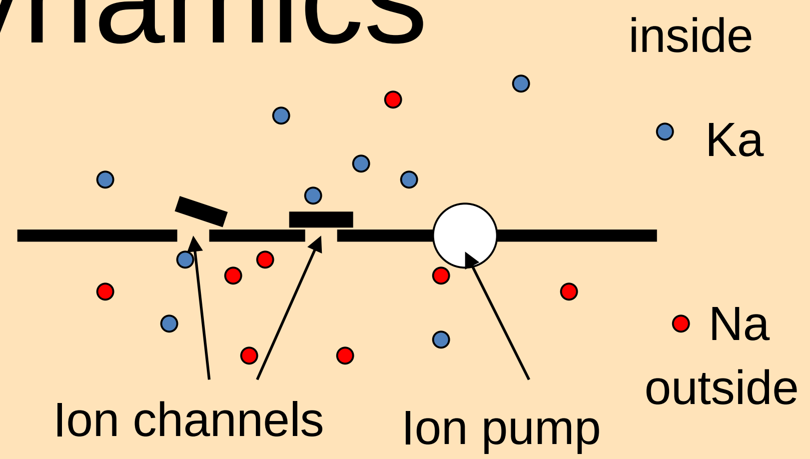
Exercise 3.1-3.3 – Hodgkin-Huxley – ion channel dynamics

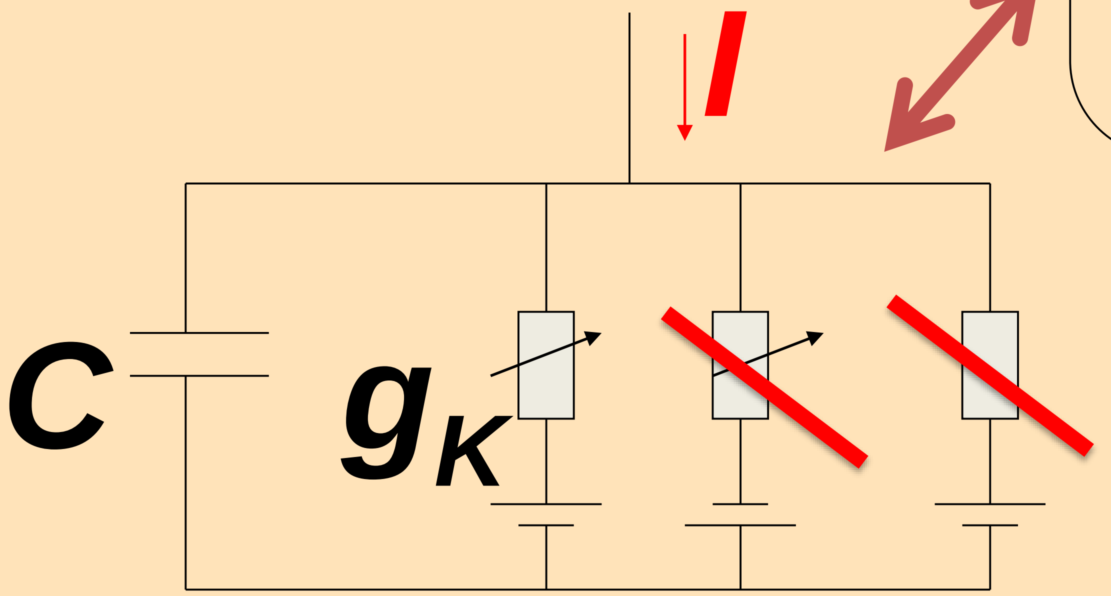
voltage step



Determine ion channel dynamics



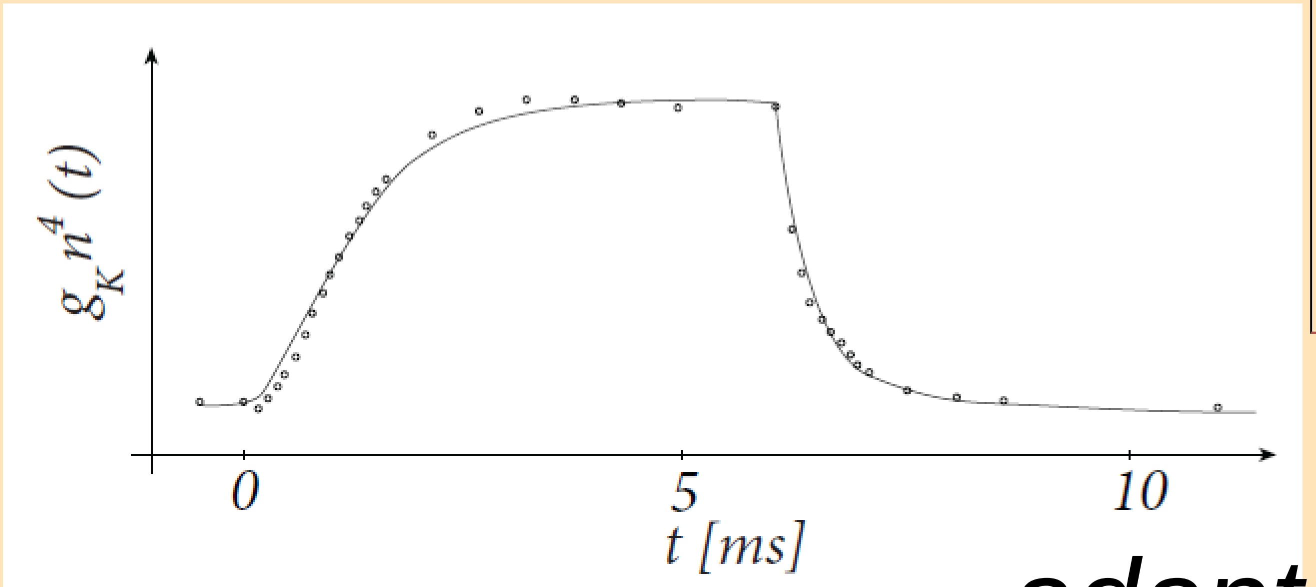


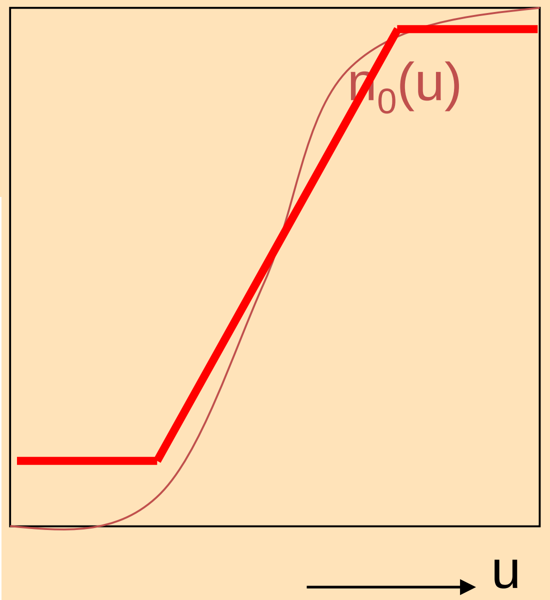


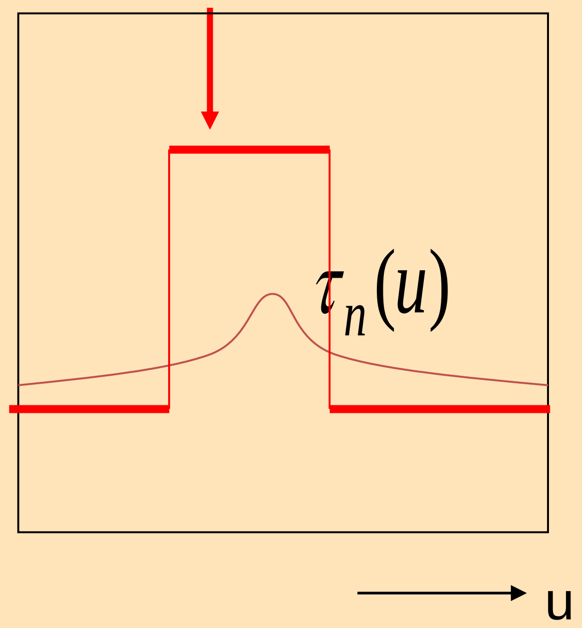
$$C\frac{du}{dt} = -g_K n^4 (u - E_K) + I(t)$$

stimulus

apply voltage step







Start Exercise 3 at 11:33
Next Lecture at:
11.52

adapted from Hodgkin&Huxley 1952

Exercises 1 -3.3 NOW! NEXT lecture at 11:15

Exercise 1: Nernst equation

Using the Nernst equation,

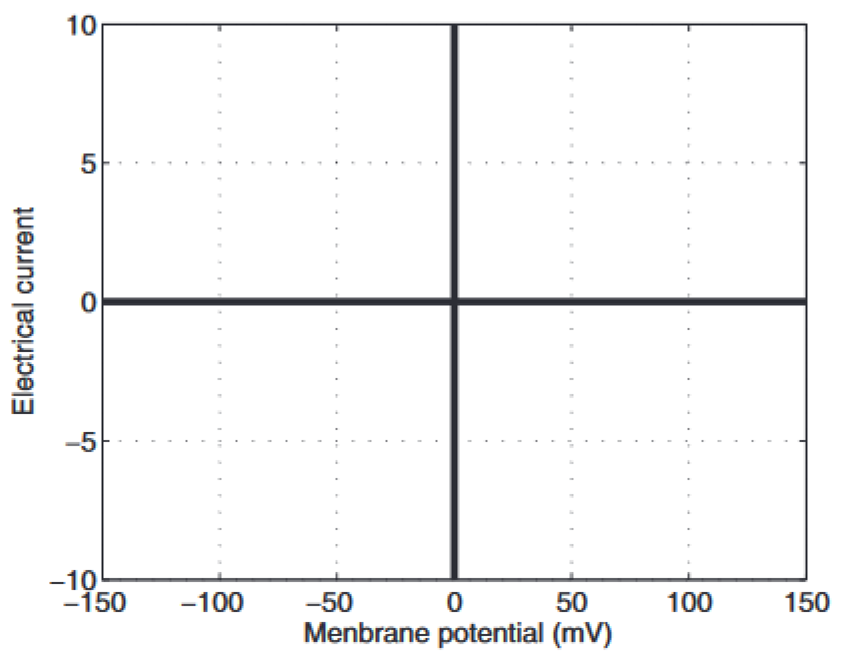
$$E_{\text{rev}} = -\frac{kT}{ze} \ln \left(\frac{C_{\text{int}}}{C_{\text{ext}}} \right) , \qquad (1)$$

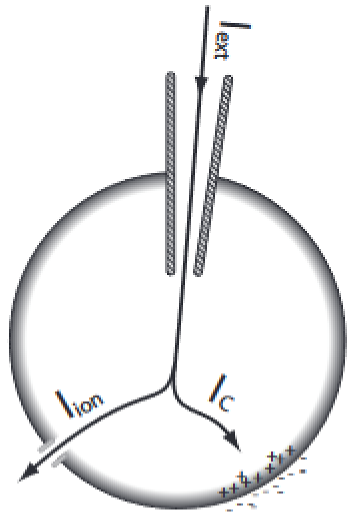
where $k \simeq 1.38 \cdot 10^{-23}$J/K is the Boltzmann constant, T is the absolute temperature, e is the elementary charge $e \simeq 1.60 \cdot 10^{-19}$ Coulomb, and z is the valence of the ion species.

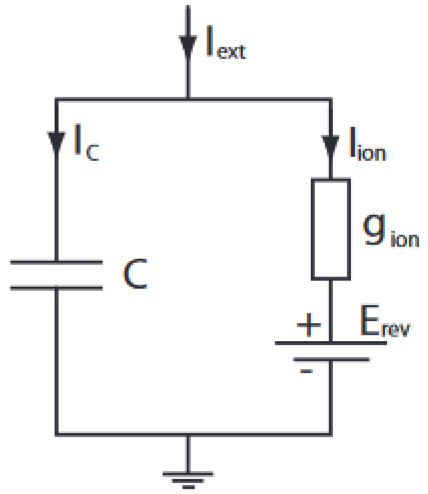
1.1 Calculate the reversal potential for Na^+, K^+ and Ca^{2+} assuming a temperature of 37 °C and the following concentrations:

ion	C_{int}	C_{ext}	E_{rev}
K^+	140	5	
Na^+	10	145	
Ca^{2+}	10^{-4}	1.5	

1.2 An experimentalist studies an ion channel by applying constant voltage while measuring the injected current. Sketch the current-voltage relationship for the three ion species in the graph below, assuming $I_{\text{ion}} = g(u - E_{\text{rev}})$, $g_{\text{Na}} = 120$nS, $g_{\text{K}} = 36$nS, $g_{\text{Ca}} = 0.3$nS.







1.3 How can one read off the reversal potential and the conductance from the graph? Assuming a resting potential of −65 mV, which type of ion generates an inward/outward current?

Exercise 2: Model of an ion channel

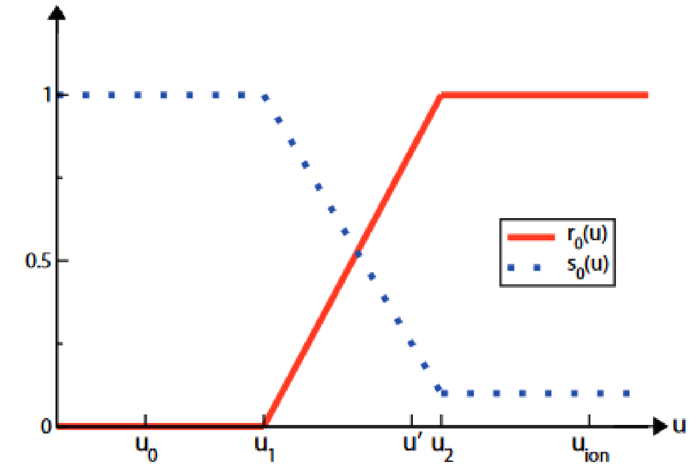
Consider the following model for an ion channel: the electrical current I_{ion} through the channel is given by

$$I_{ion} = g_{\text{ion}} r^{n_1} s^{n_2} (u - u_{\text{ion}})$$

where u is the membrane potential of the neuron, g_{ion} and u_{ion} are two constants, and $n_1 = 2$, $n_2 = 1$. The quantities r and s obey the equations

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

$$\frac{ds}{dt} = -\frac{s - s_0(u)}{\tau_s(u)}$$



with r_0, s_0, τ_r and τ_s as shown in Fig.1.

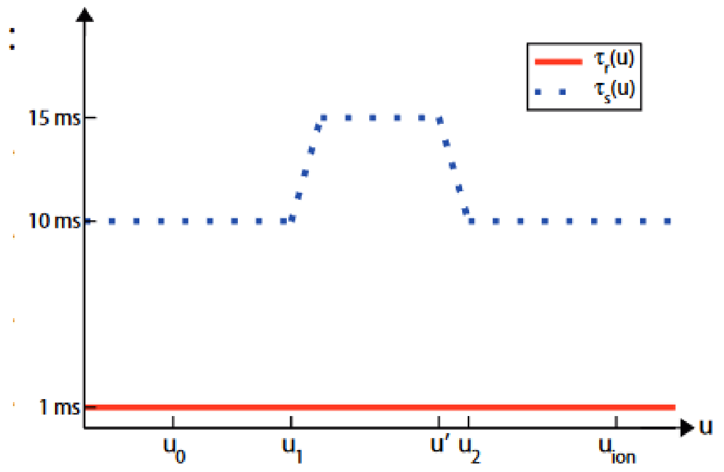
2.1 What is the *biological* interpretation of the following parameters :

r : ....

s : ....

g_{ion} : ....

u_{ion} : ....



2.2 How does the channel react (in terms of partial or full opening/closing) to a step change in membrane potential? Suppose that for $t < 0$, the membrane potential is clamped at a value u_0, and that at $t = 0$ it instantaneously jumps to a value $u' = u_2(1 - \varepsilon)$ with $\varepsilon \ll 1$ (see figure 1 for the values of u_0, u', u_2 and u_{ion}) where it is maintained for all $t \geq 0$.

- For $t < 0$, the channels is .... because ....
- At $t = 1$ ms, the channel is .... because ....
- At $t = 3$ ms, the channel is .... because ....
- At $t = 20$ ms, the channel is .... because ....
- At $t = 100$ ms, the channel is .... because ....

Exercises 1 -3.3 NOW! NEXT lecture at 11:15

Exercise 3: Dynamics of conductances

In the Hodgkin-Huxley model, the potassium current obeys the equation:

$$I_K = \bar{g}_K n(t)^4 \left(u(t) - E_K\right)$$

where $\bar{g}_K$ is the maximal conductance, E_K the potassium reversal potential, and $n(t)^4$ is the proportion of channels that are open at time t. The quantity n obeys a first-order dynamics

$$\frac{dn}{dt} = \frac{n_\infty(u) - n}{\tau_n(u)},$$

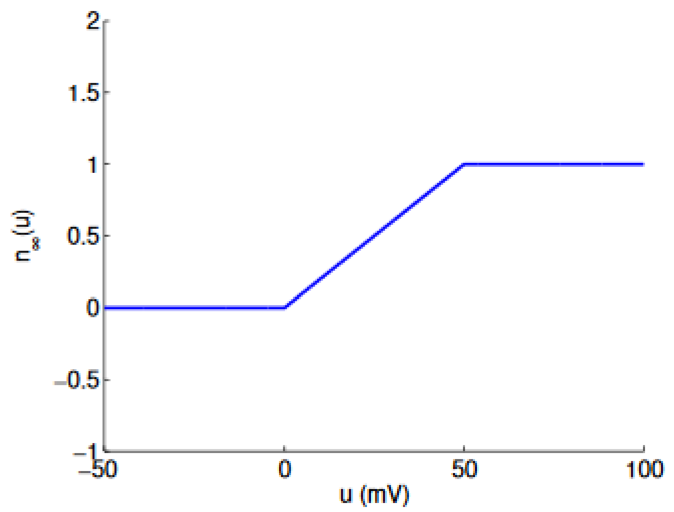
with voltage-dependent time constant τ_n and equilibrium value n_∞.

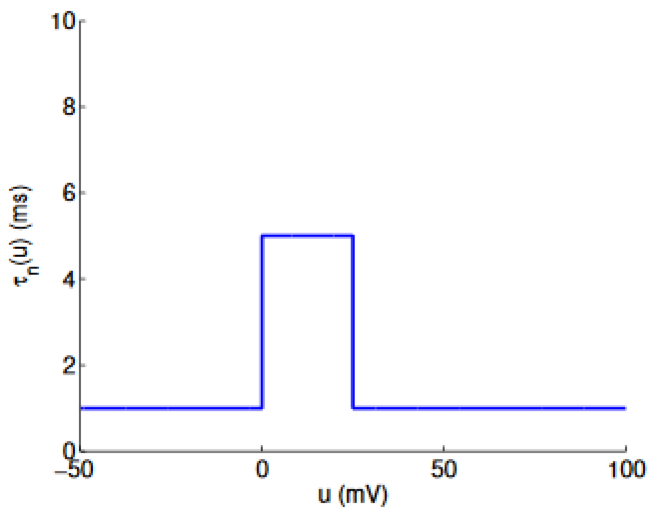
In order to determine τ_n and n_∞, Hodgkin and Huxley pharmacologically blocked the sodium current and measured the response of the potassium current to voltage jumps of various amplitudes. The goal of this exercise is to understand this key experiment by studying a simplified version of the Hodgkin-Huxley model. Suppose τ_n and n_∞ have the following form:

$$\tau_n(u) = \begin{cases} 1 \text{ ms} & \text{if} \quad u \leq 0 \; mV \\ 5 \text{ ms} & \text{if} \quad 0 < u \leq 25 \; mV \\ 1 \text{ ms} & \text{if} \quad u > 25 \; mV \end{cases}$$

3.1 Calculate the response of $n(t)$ to a voltage jump:

$$u(t) = \begin{cases} 0 & \text{for} \quad t < 0 \\ u_0 & \text{for} \quad t \geq 0 \end{cases}$$





3.2 Sketch the evolution of $n(t)$ for $u_0 = 10,\ 20,$ and $40\ mV$.

3.3 For $u_0 = 40$ mV, sketch the behaviour of $n(t)$, $n^2(t)$ and $n^4(t)$ assuming $t \ll \tau_n$. What is the difference between $n(t)$ and $n^4(t)$?

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

ÉCOLE POLYTECHNIQUE
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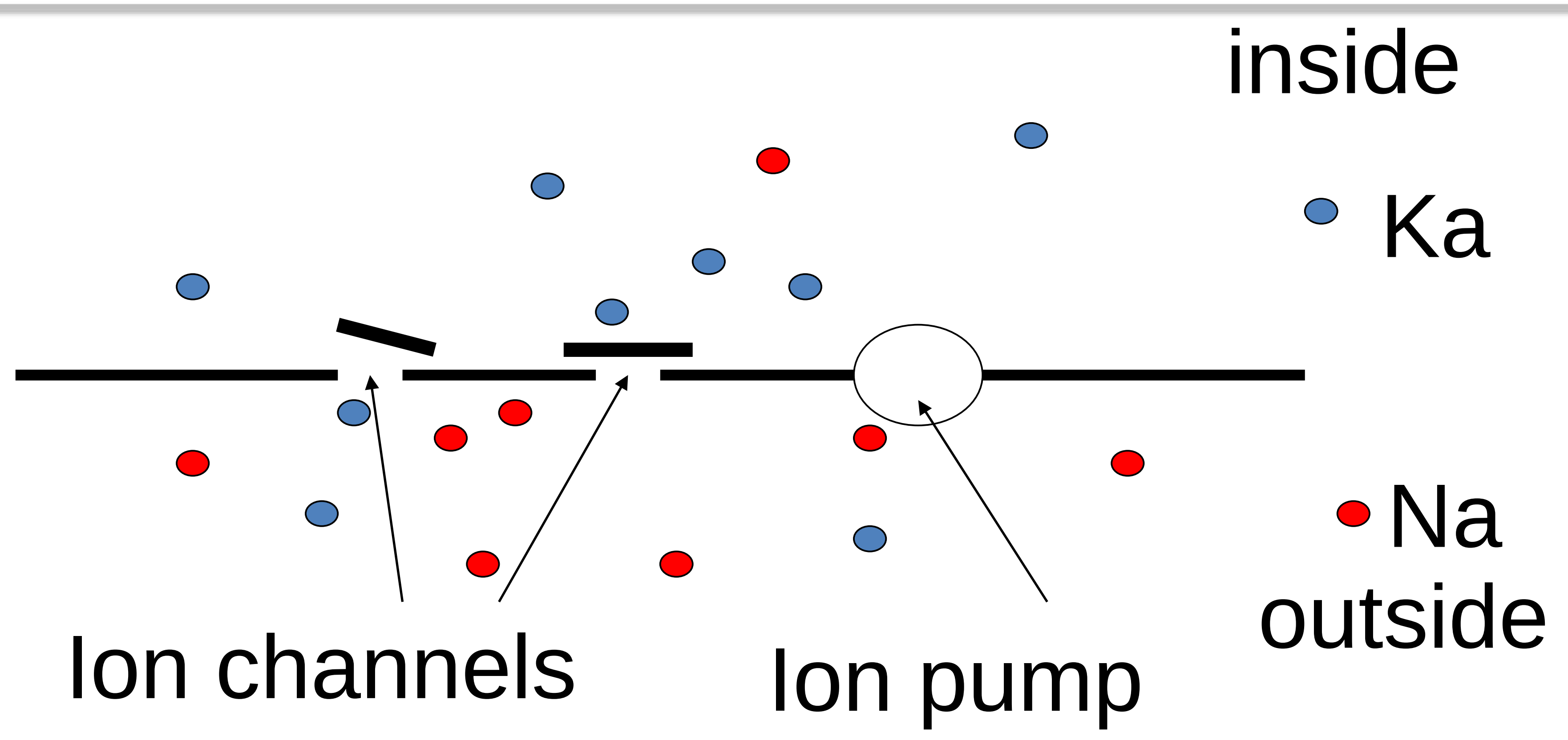
Biological Modeling of Neural Networks

Week 2 – Biophysical modeling: The Hodgkin-Huxley model

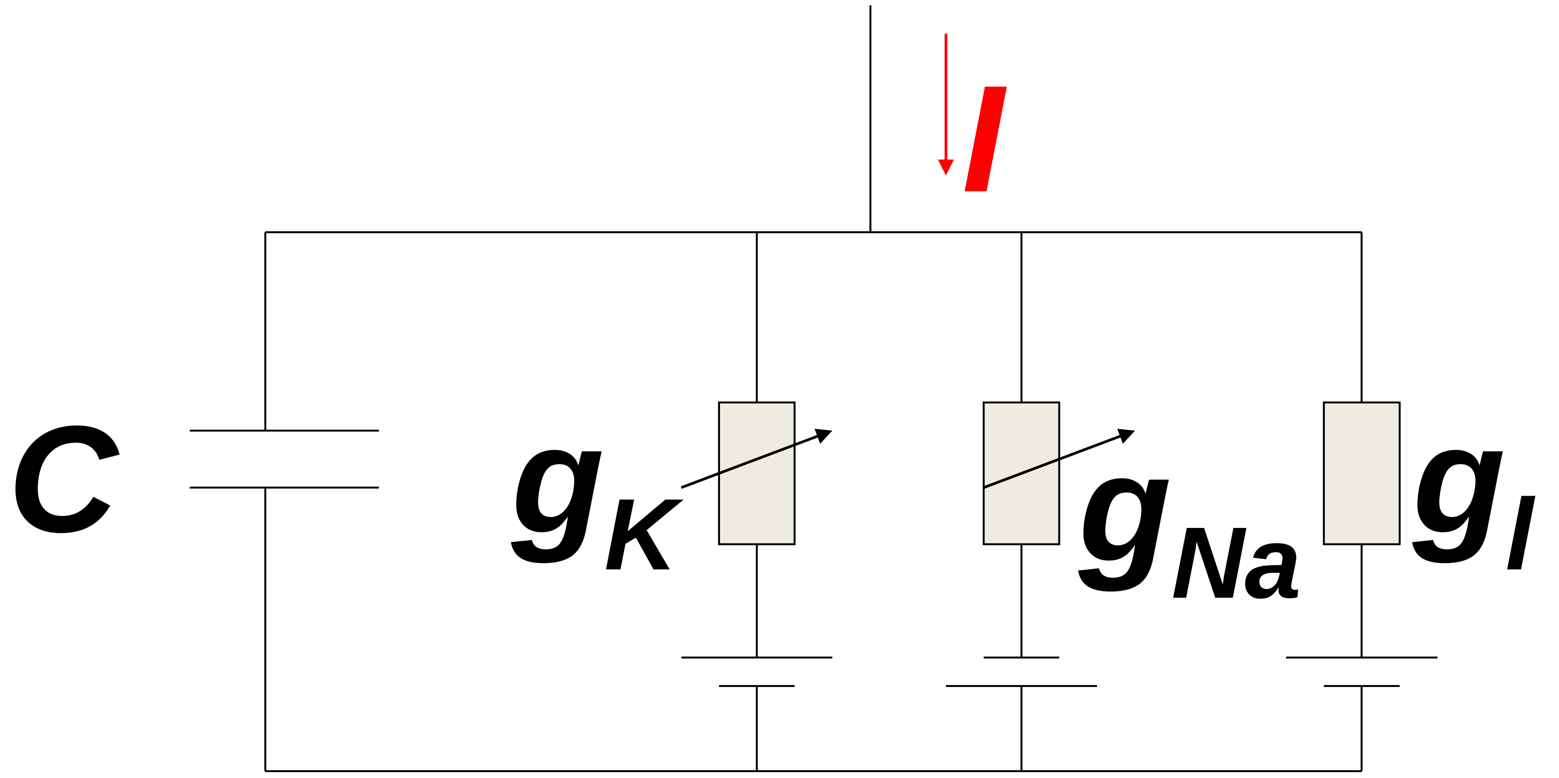
Wulfram Gerstner

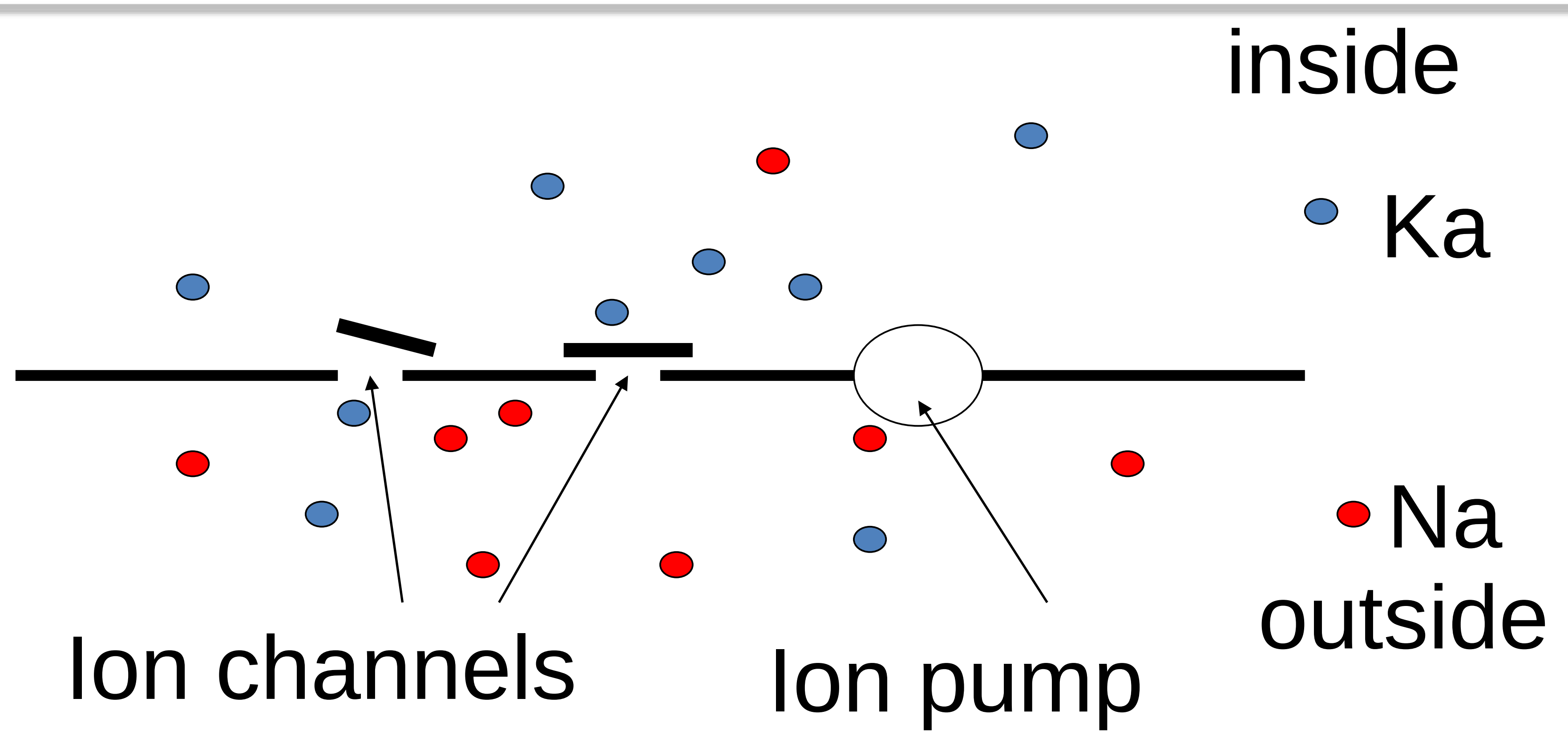
EPFL, Lausanne, Switzerland

Neuronal Dynamics – 2.4. Threshold in HH model



Neuronal Dynamics – 2.4. Threshold in HH model





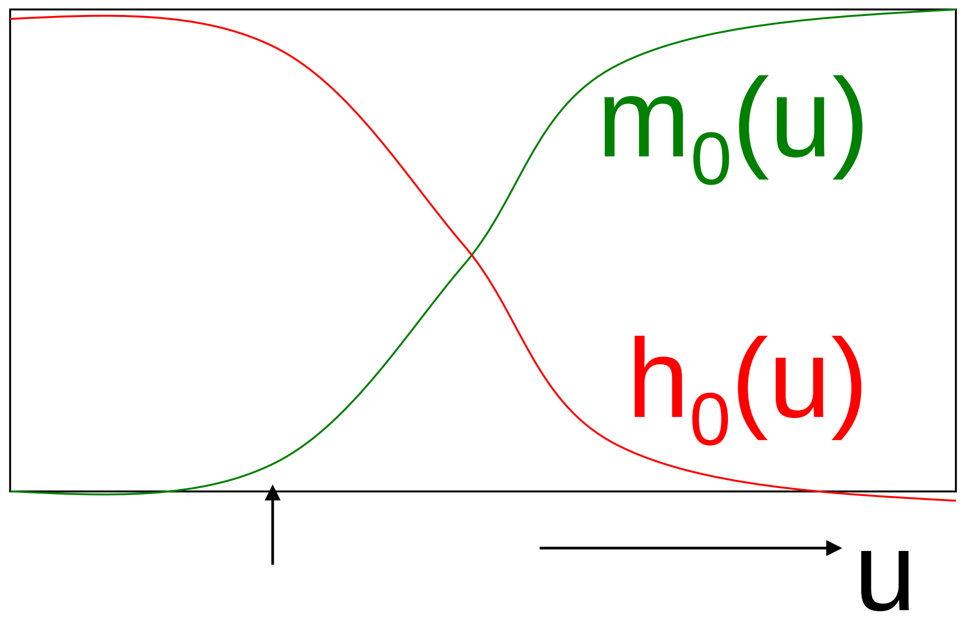
I_{Na} I_K I_l

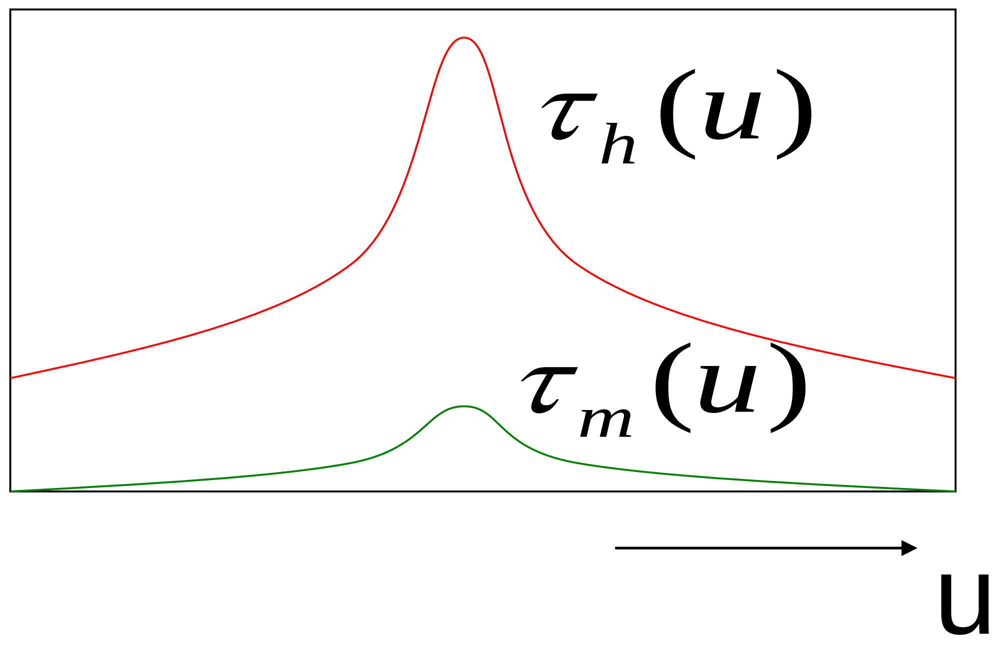
$$C\frac{du}{dt} = -g_{Na}m^3h(u-E_{Na}) - g \dots g_l(u-E_l) + I(t)$$

Where is the threshold for firing?

$$\frac{dm}{dt} = -\frac{m \dots}{\dots_m(u)}$$

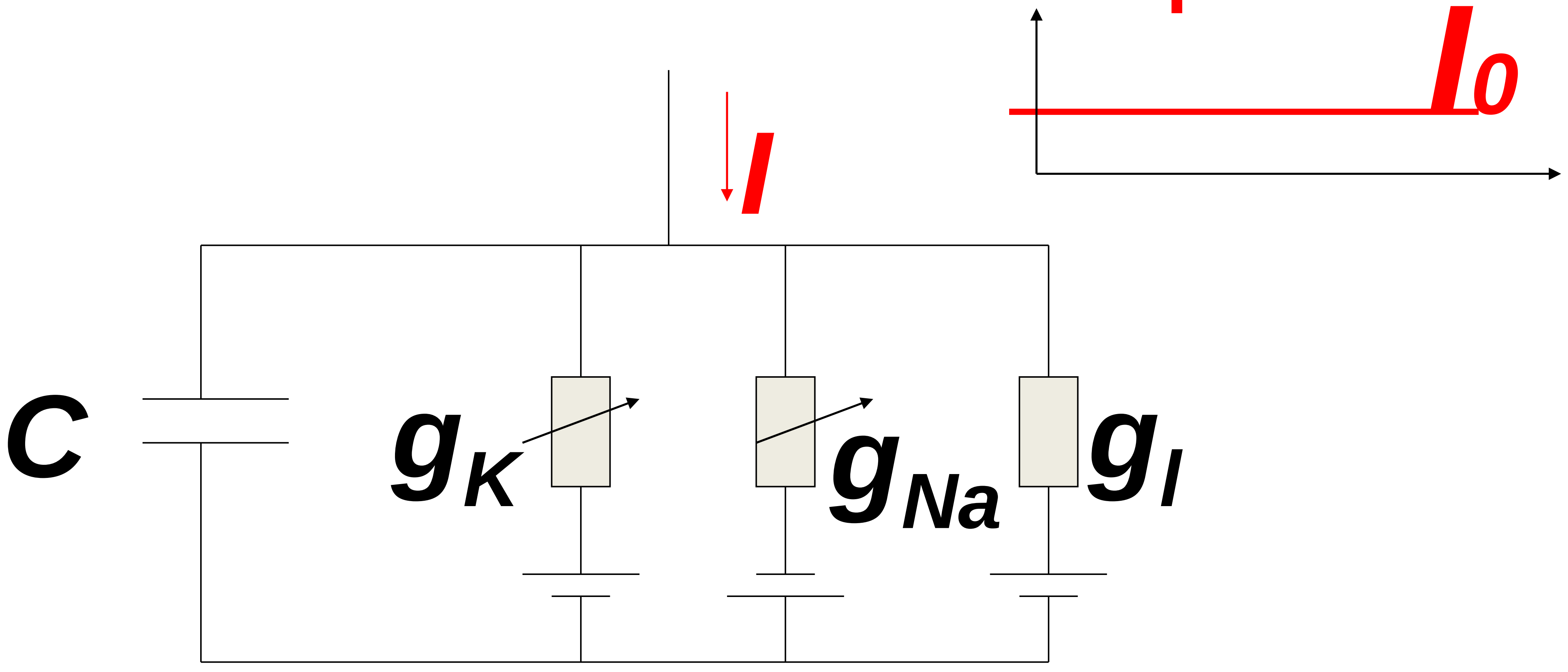
$$\frac{dh}{dt} = -\frac{h-h_0(u)}{\tau_h(u)}$$

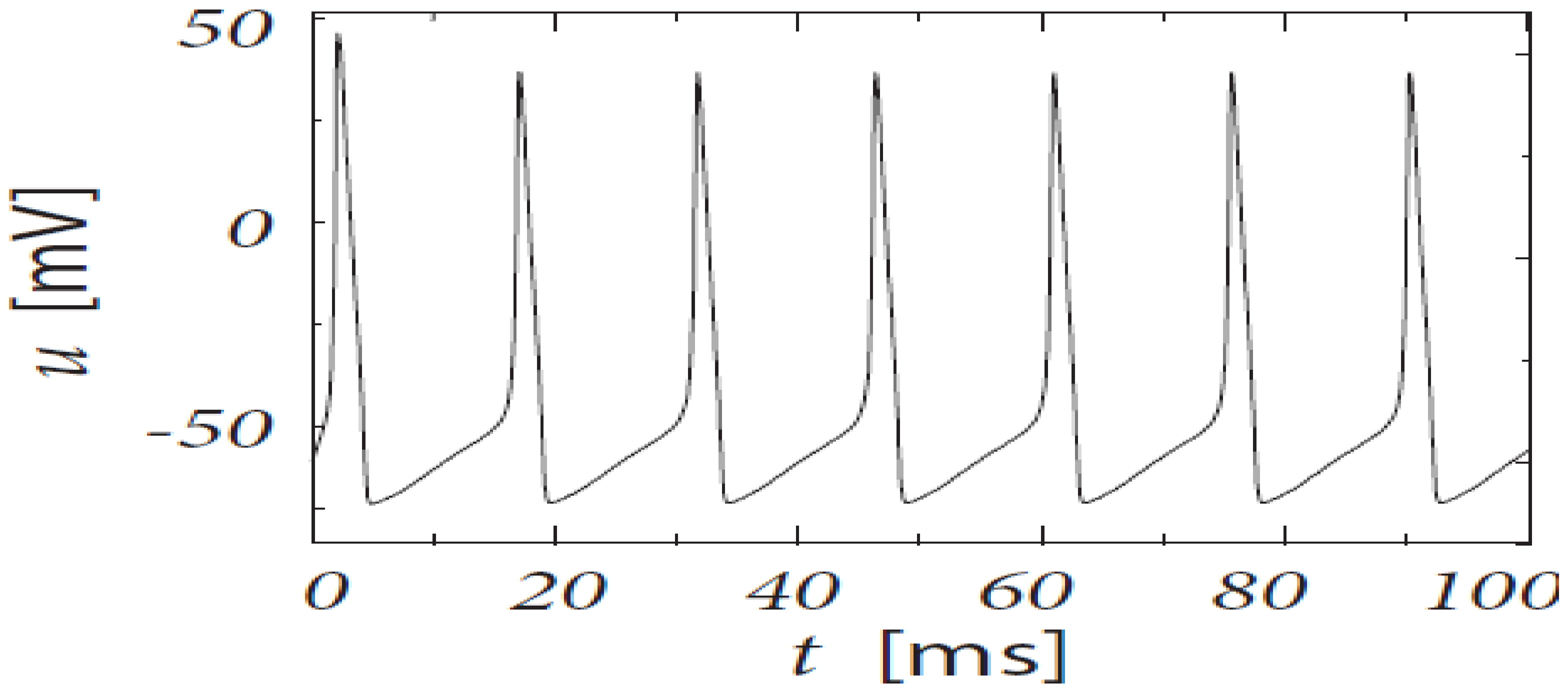


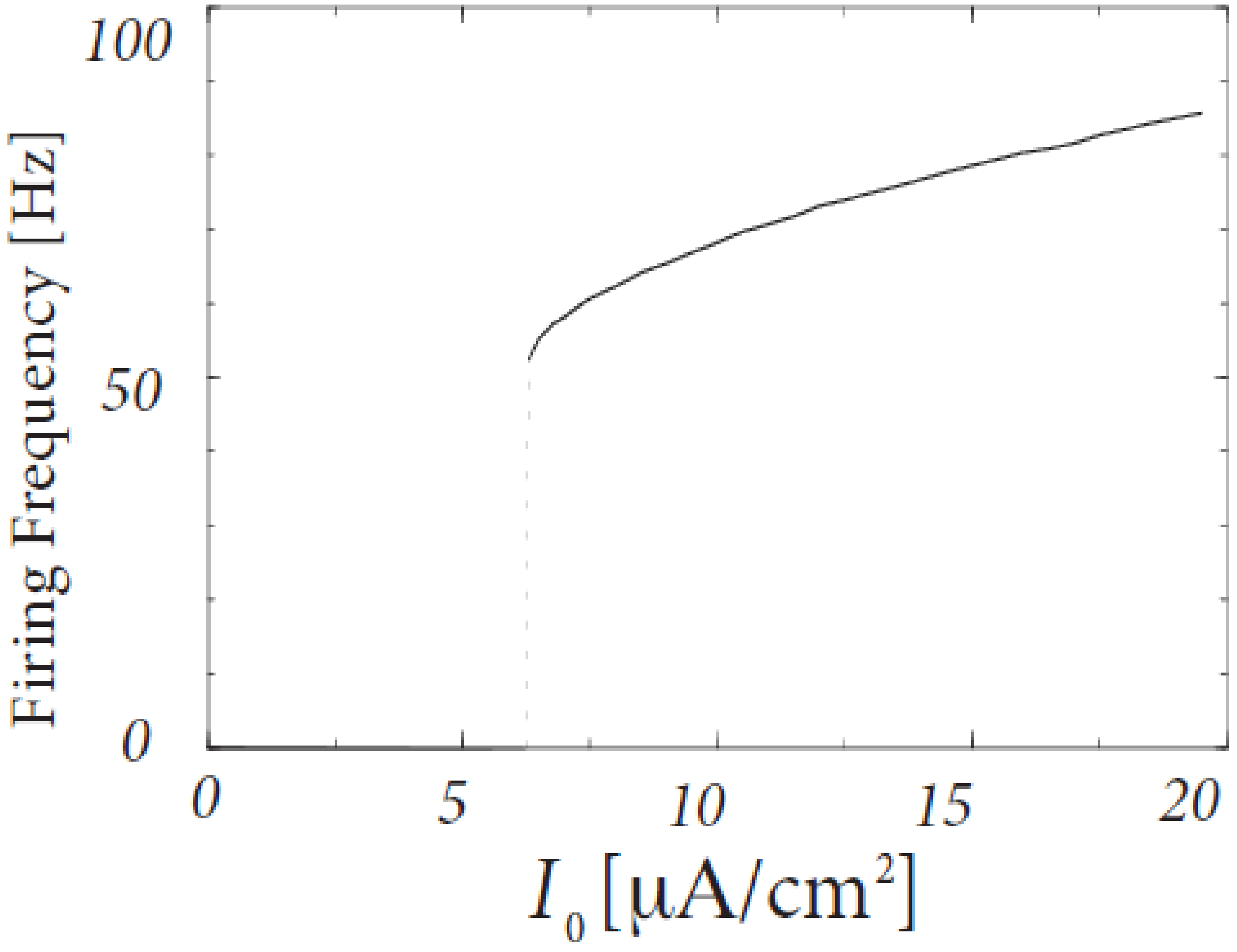


Neuronal Dynamics – 2.4. Threshold in HH model

Constant current input







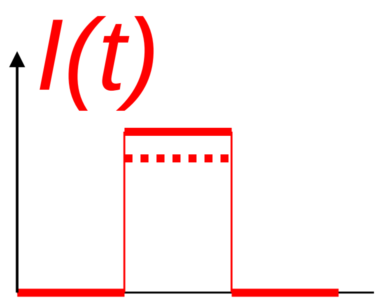
Threshold?

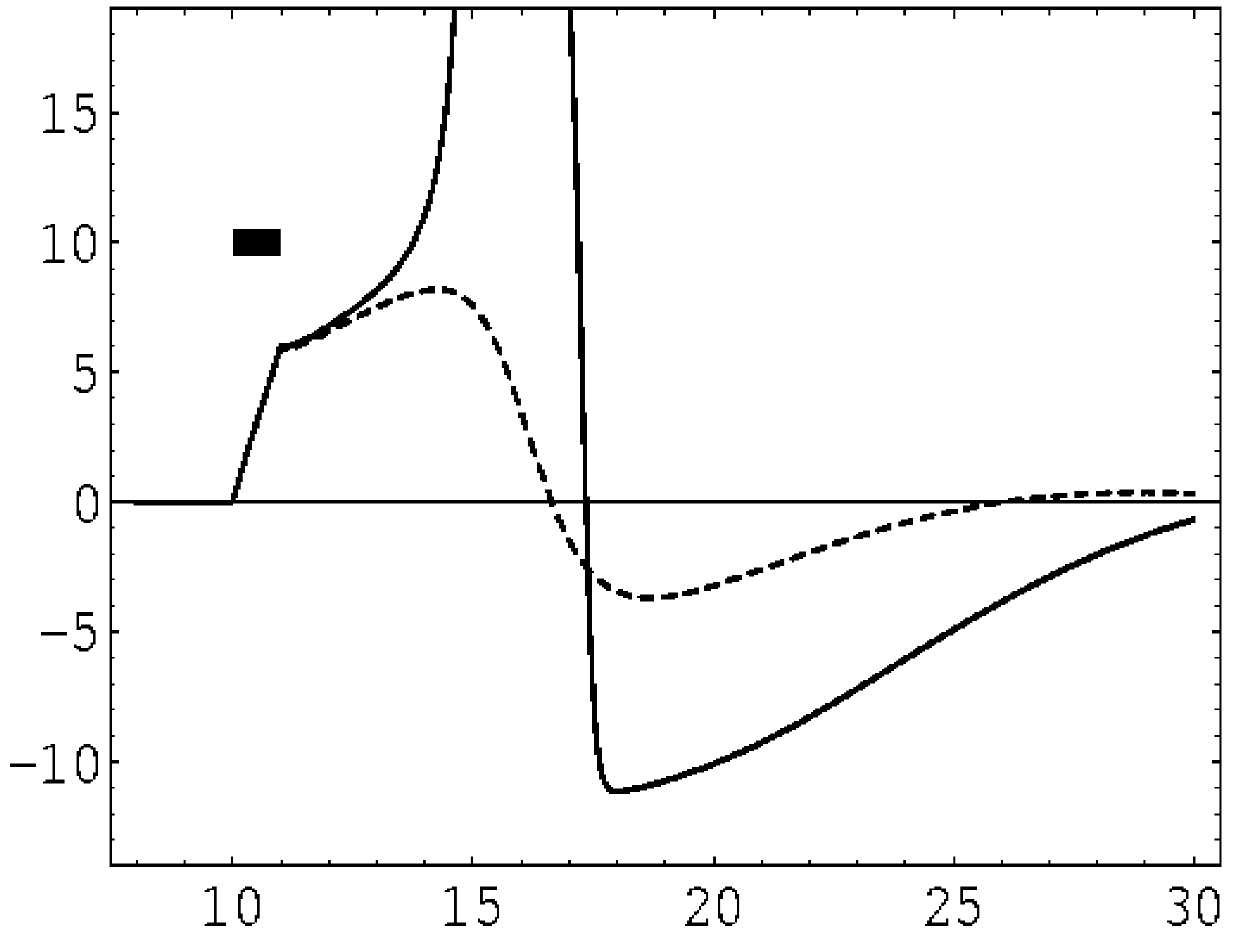
for repetitive firing

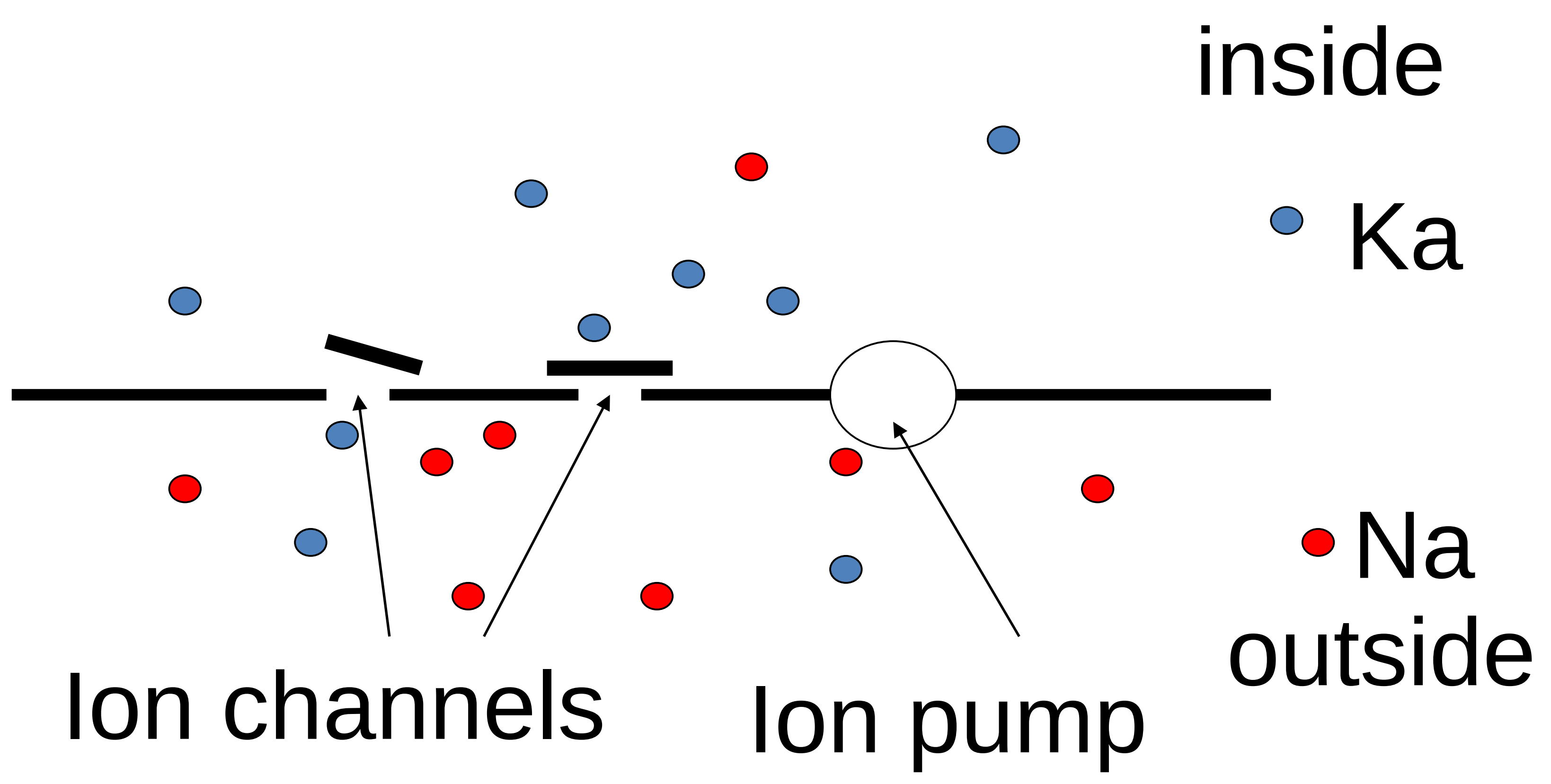
(***current*** threshold)

Neuronal Dynamics – 2.4. Threshold in HH model

pulse input







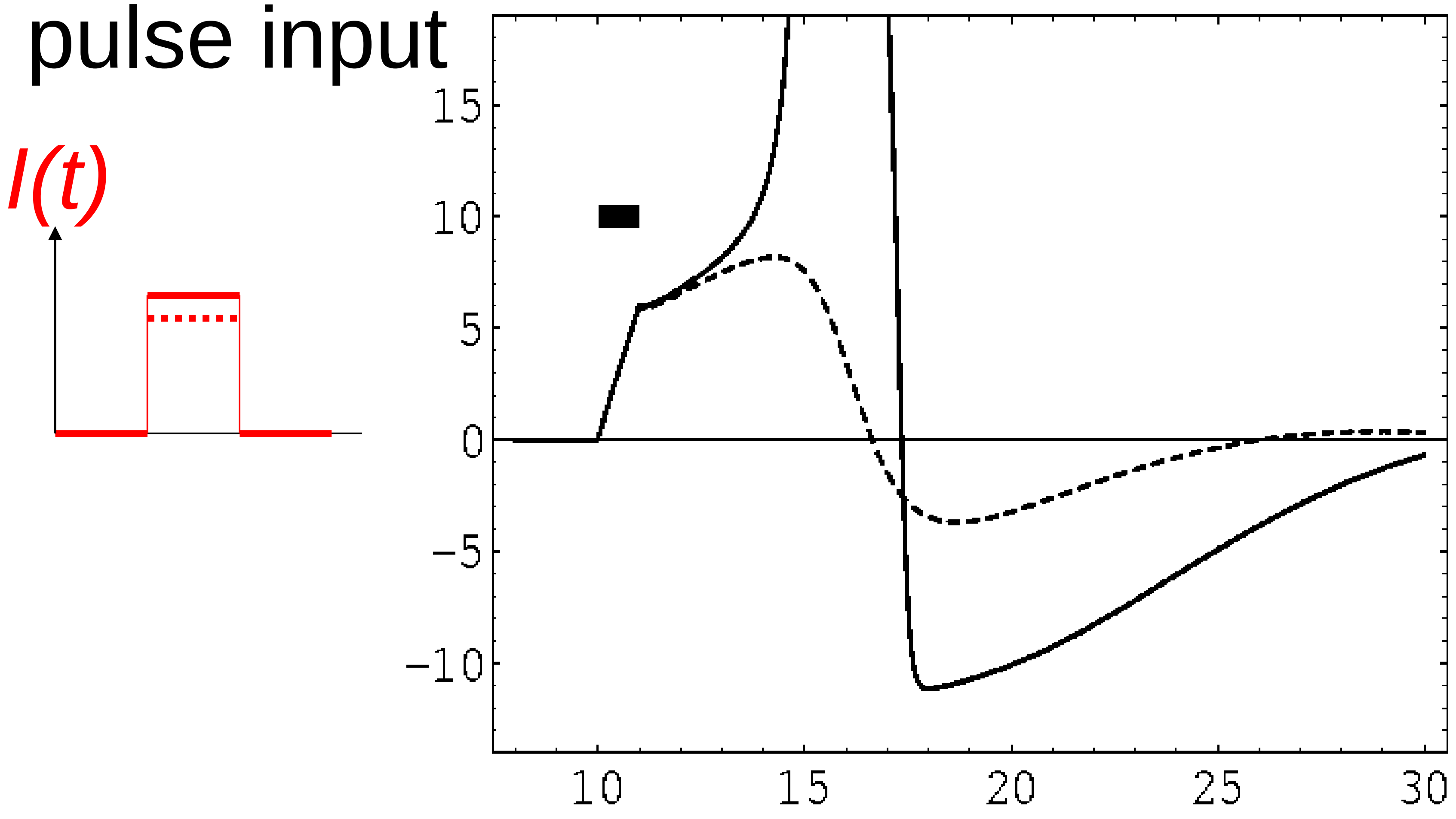
Threshold?

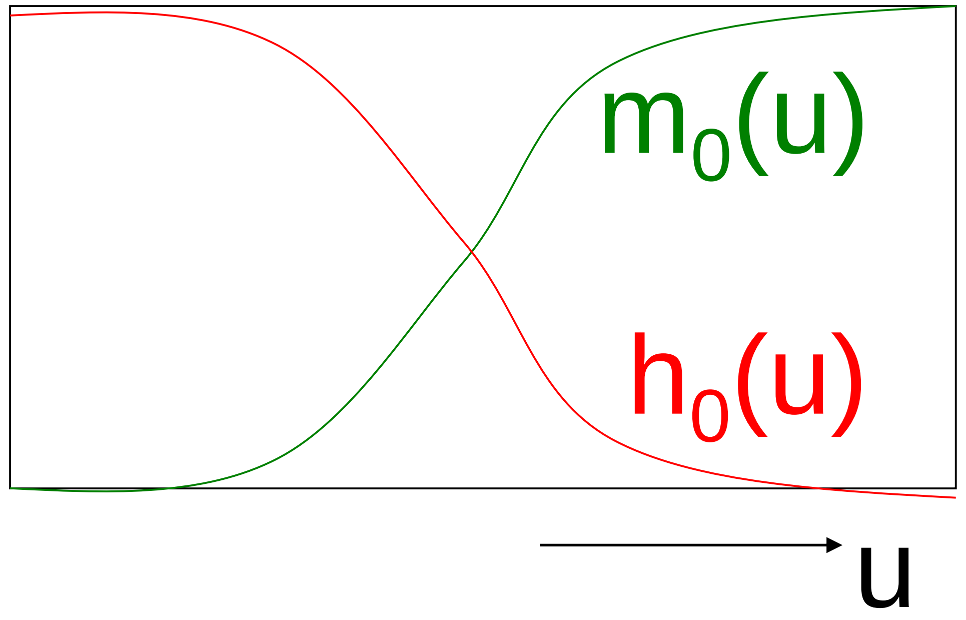
- AP if amplitude 7.0 units
- No AP if amplitude 6.9 units

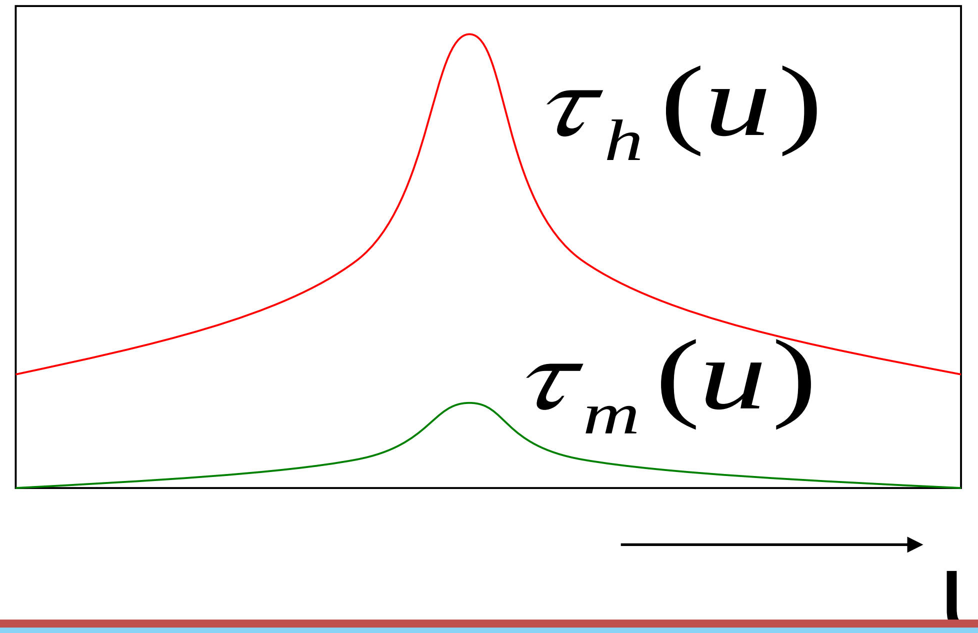
(pulse with 1ms duration)

(and pulse with 0.5 ms duration?)

Neuronal Dynamics – 2.4. Threshold in HH model







Mathematical explanation

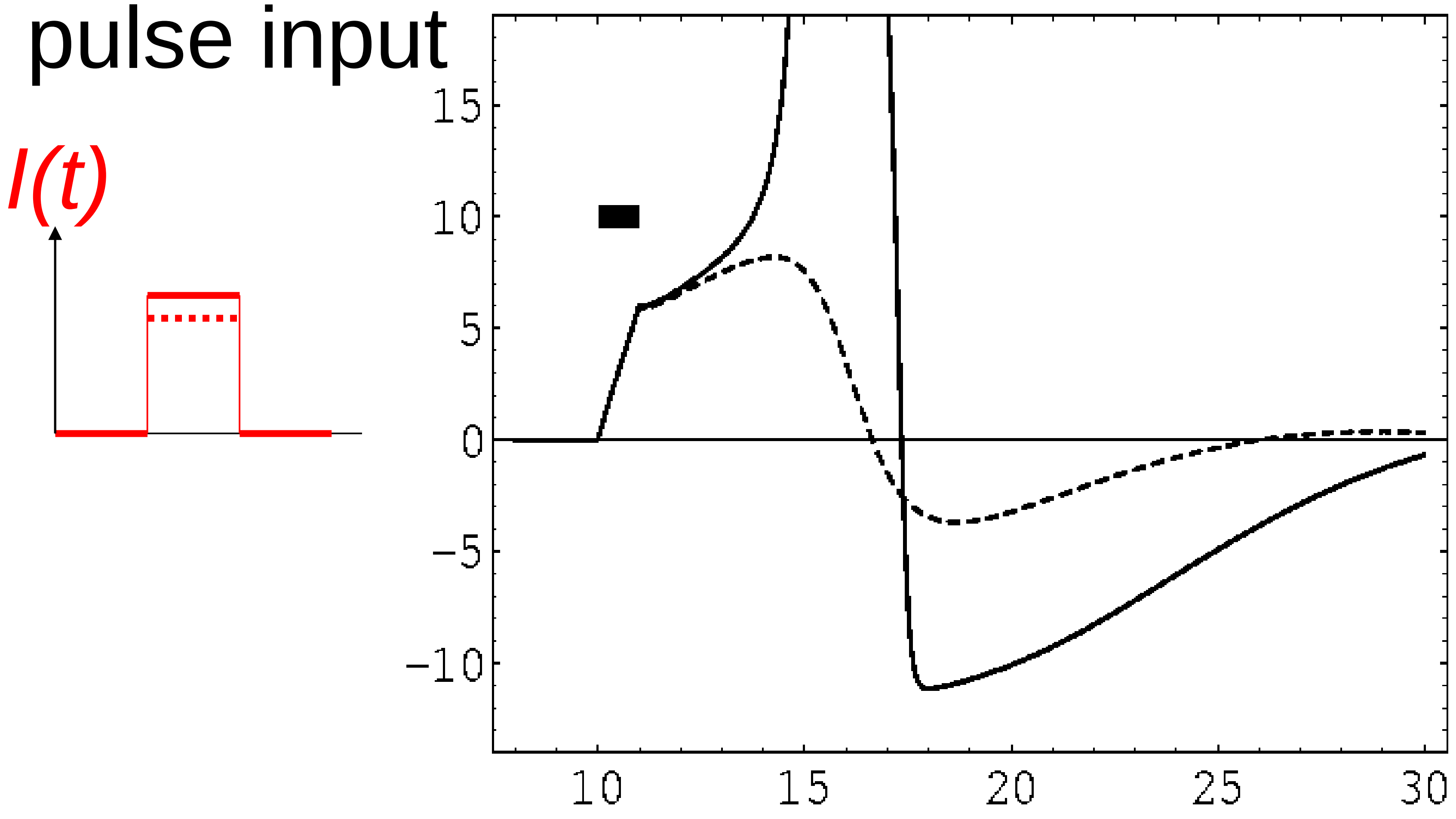
I_{Na} I_K I_{leak} Stim.

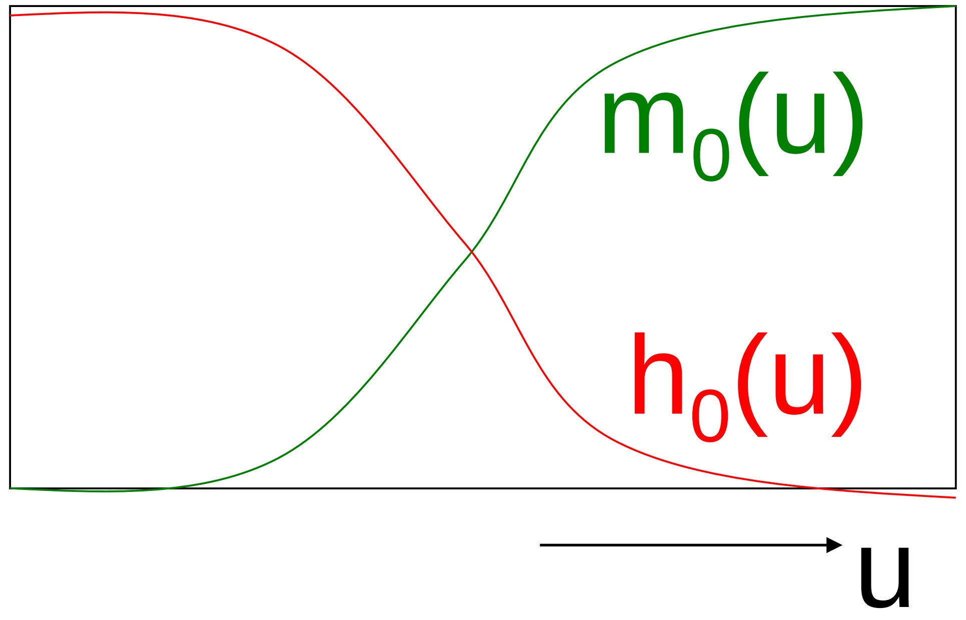
$$C\frac{du}{dt} = -g_{Na}m^3h(u-E_{Na}) - g_K n^4(u-E_K) - g_l(u-E_l) + I(t)$$

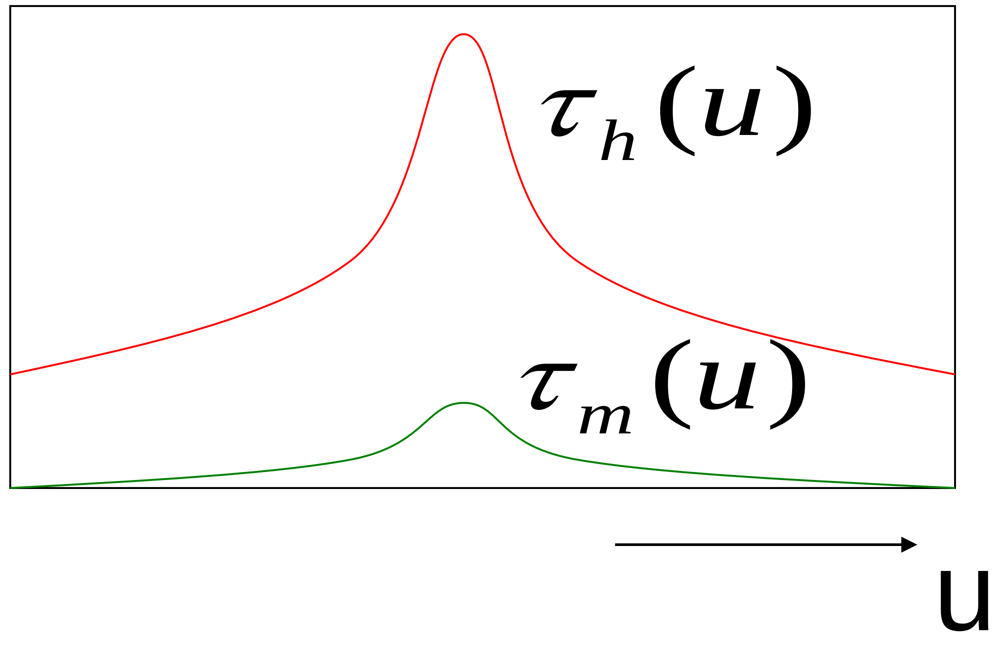
$$\frac{dm}{dt} = -\frac{m-m_0(u)}{\tau_m(u)}$$

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

Neuronal Dynamics – 2.4. Threshold in HH model







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

What about *n*?

Where is the threshold?

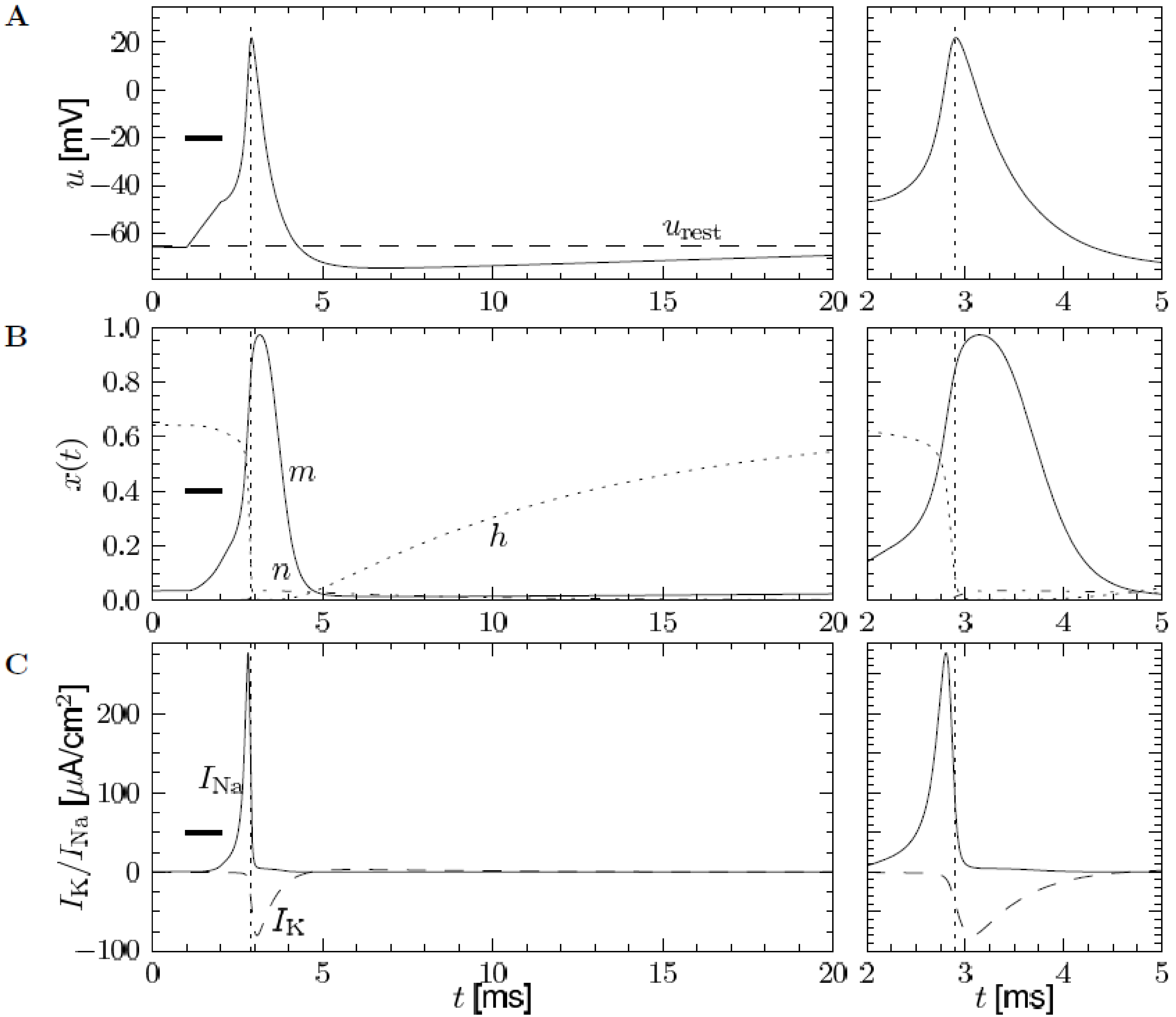
$$C\frac{du}{dt} = \underbrace{-g_{Na}m^3h(u-E_{Na})}_{I_{Na}} \underbrace{-g_K n^4(u-E_K)}_{I_K} \underbrace{-g_l(u-E_l)}_{I_{leak}} + \underbrace{I(t)}_{\text{Stim.}}$$

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

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

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

Neuronal Dynamics – 2.4. Threshold in HH model



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

$$-g_K n^4 (u - E_K)$$

$$-g_l (u - E_l)$$

$$+I(t)$$

First conclusion:

There is no strict threshold:

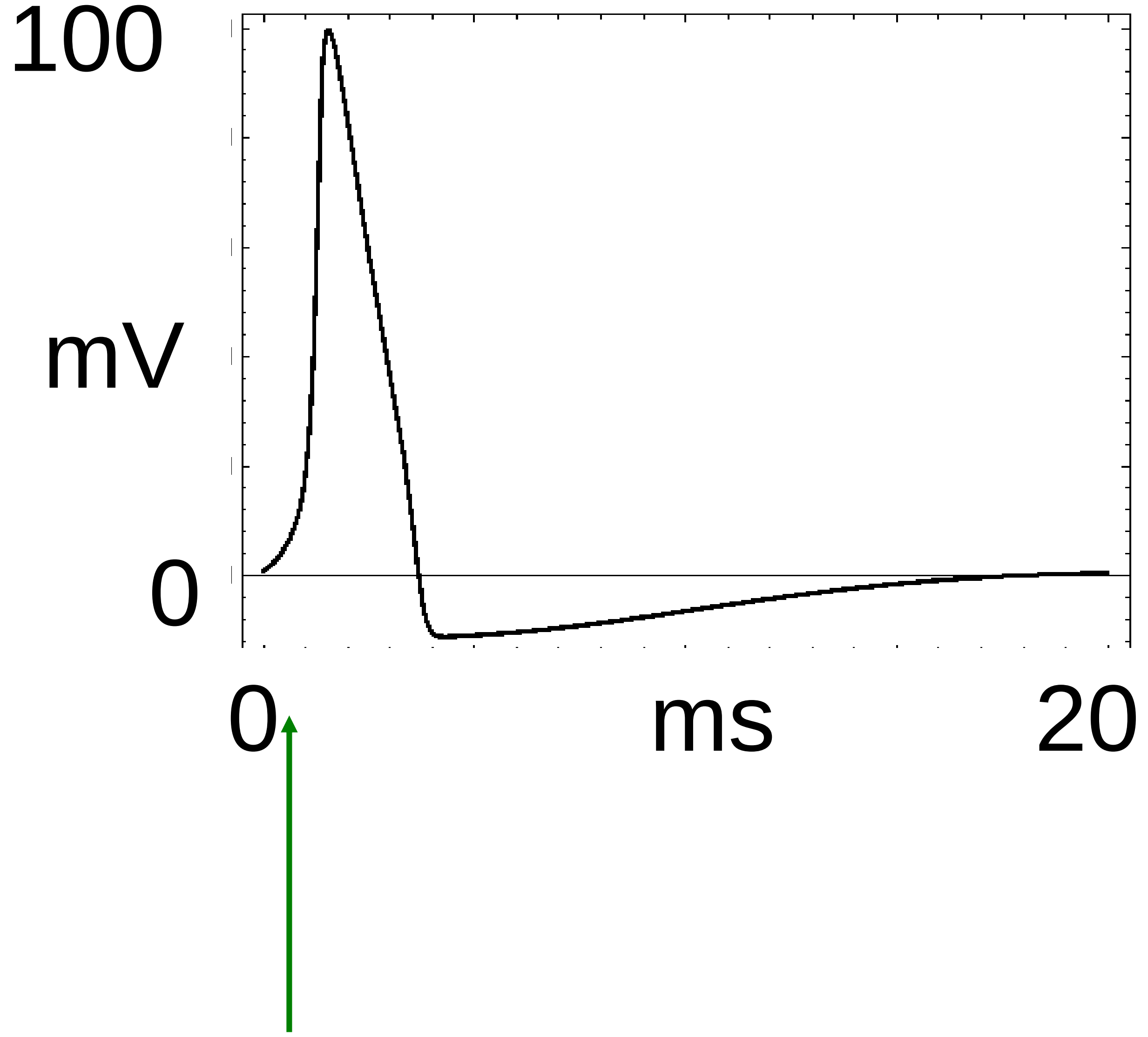
Coupled differential equations

‘Effective’ threshold
in simulations?

Neuronal Dynamics – 2.4. Refractoriness in HH model

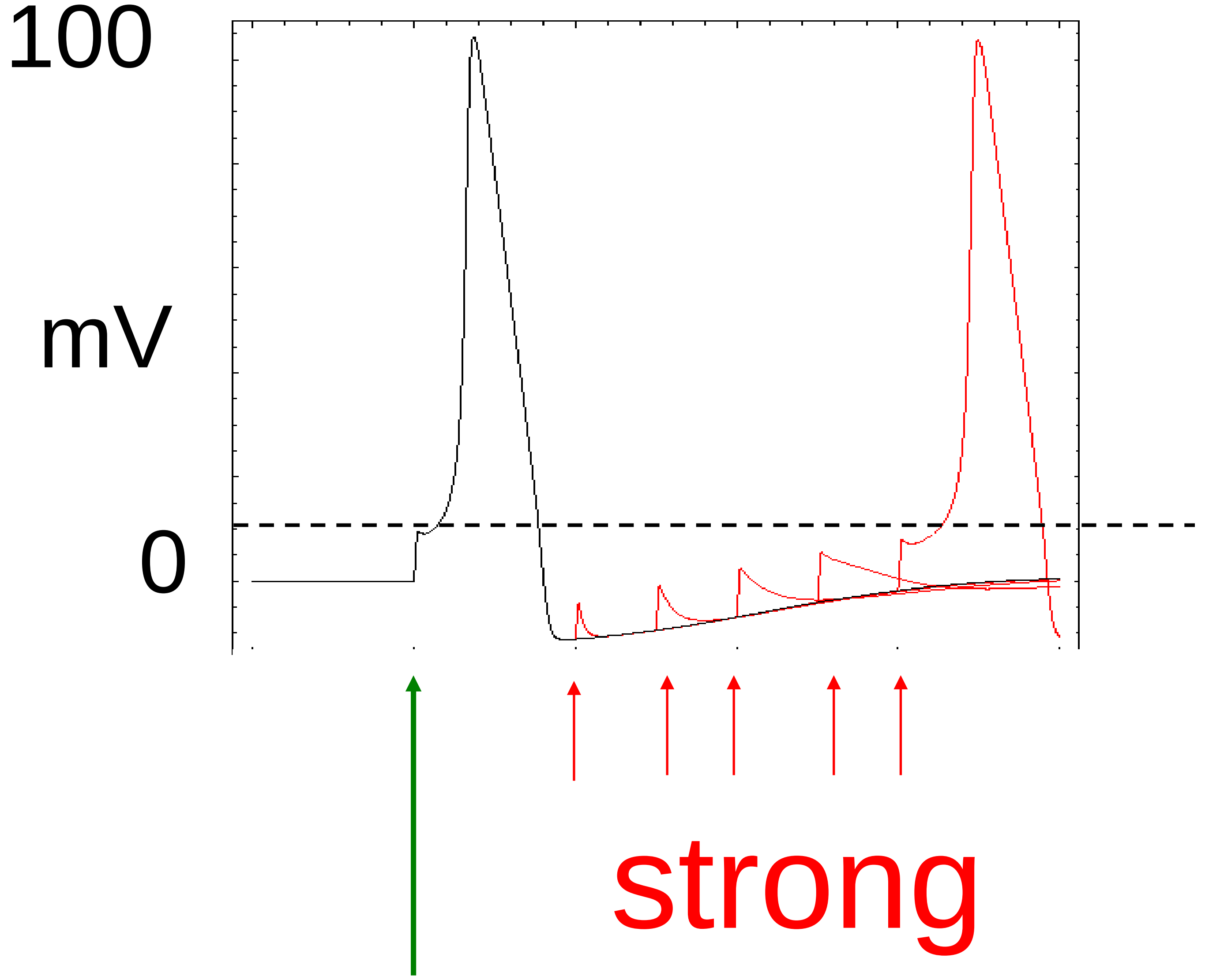
Where is the firing threshold?

Action potential



Strong stimulus

refractoriness

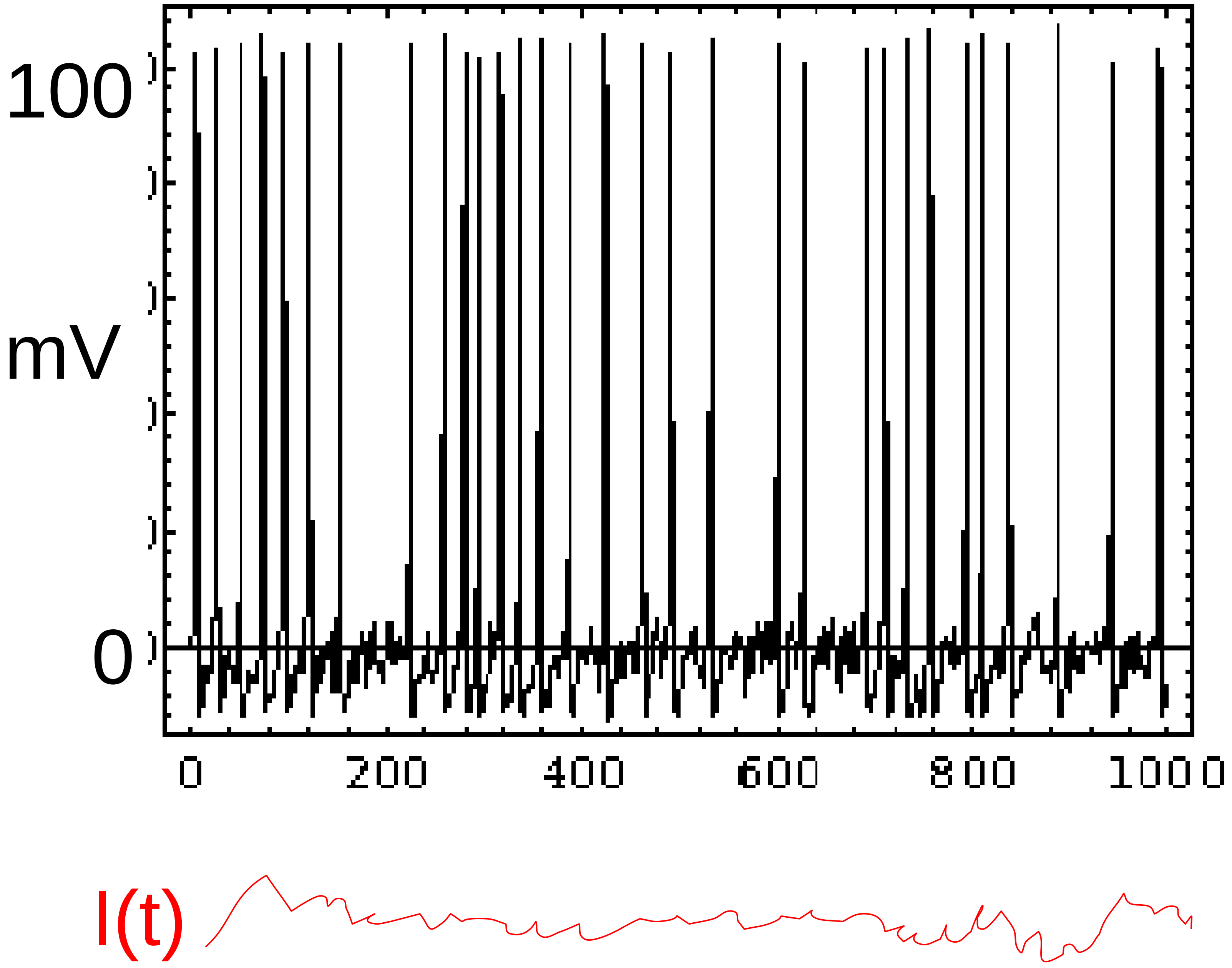


Strong stimulus

strong stimuli

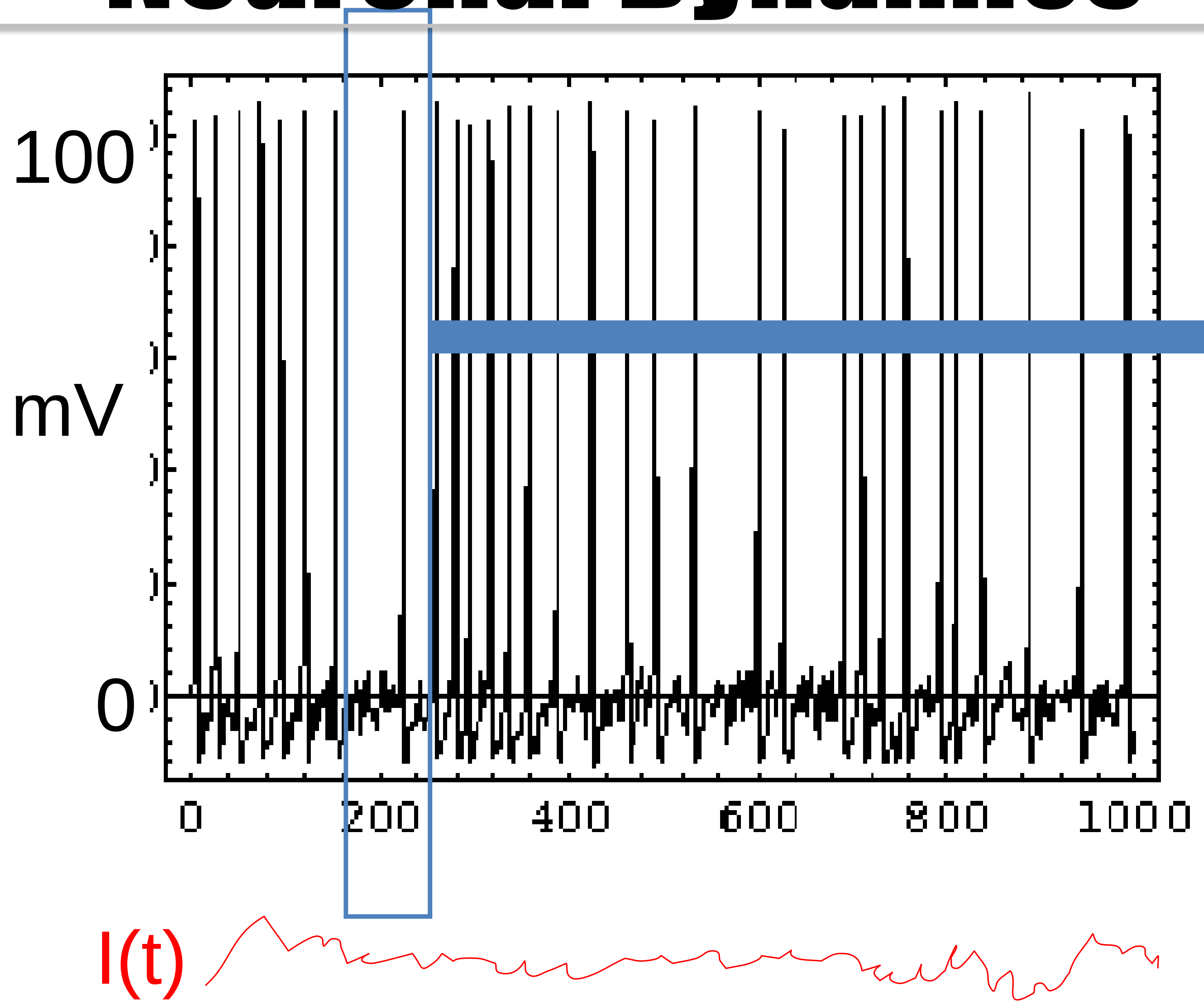
Refractoriness! Harder to elicit a second spike

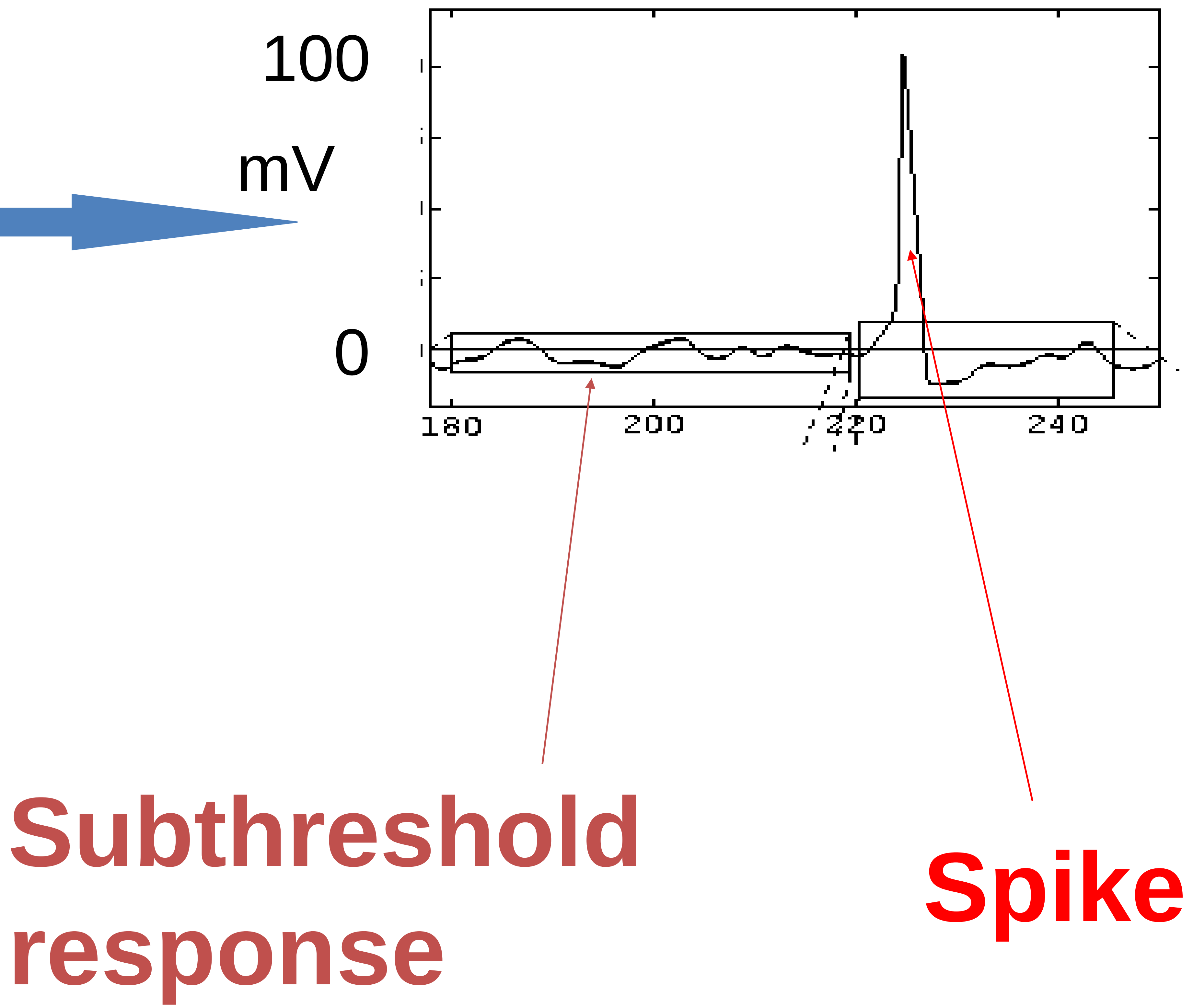
Neuronal Dynamics – 2.4. Simulations of the HH model



Stimulation with time-dependent input current

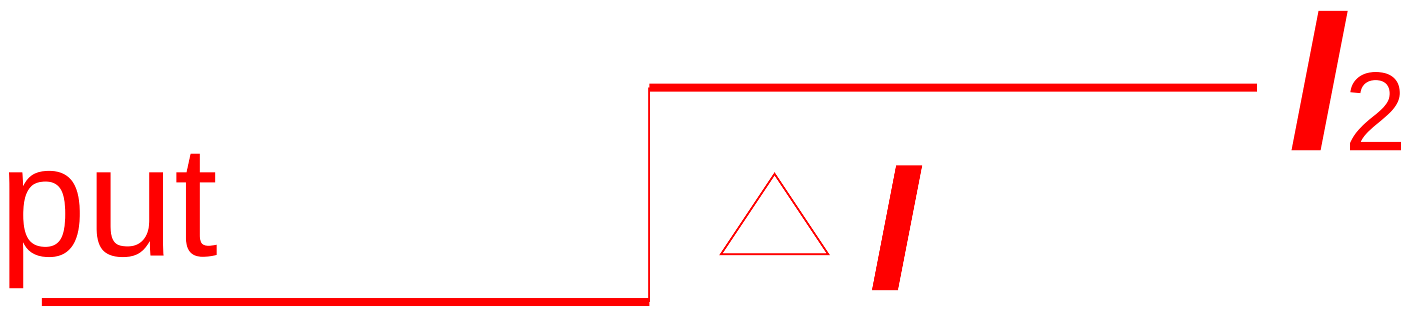
Neuronal Dynamics – 2.4. Simulations of the HH model

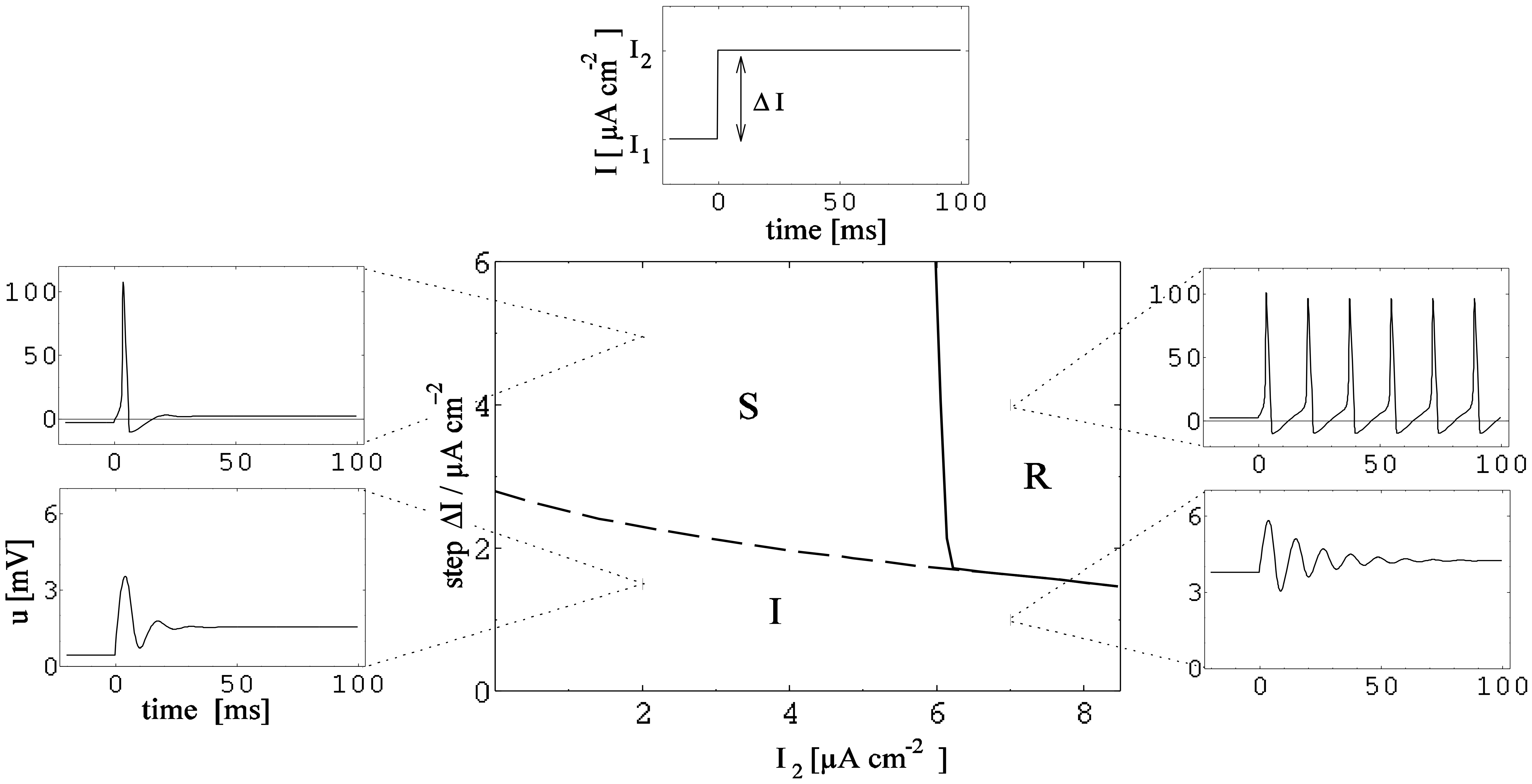




Neuronal Dynamics – 2.4. Threshold in HH model

Step current input



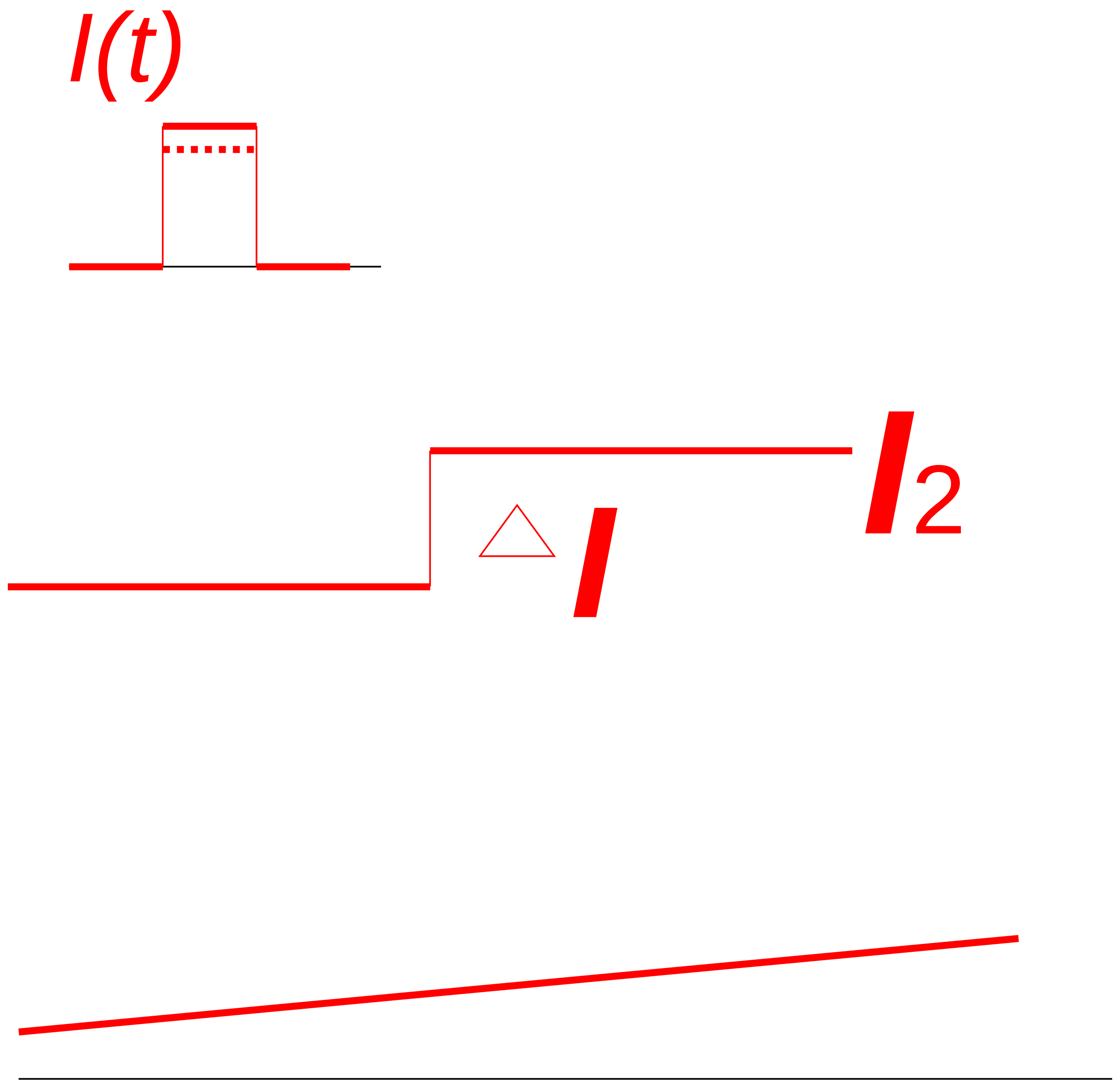


Where is the firing threshold?

pulse input

step input

ramp input



There is no threshold

- no current threshold
- no voltage threshold

'effective' threshold

- depends on typical input

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

Neuronal Dynamics – 2.4. Type I and Type II

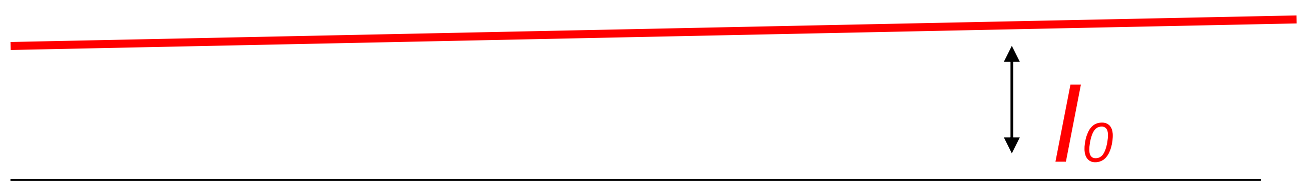
Hodgkin-Huxley model
with other parameters
(e.g. for cortical pyramidal
Neuron)

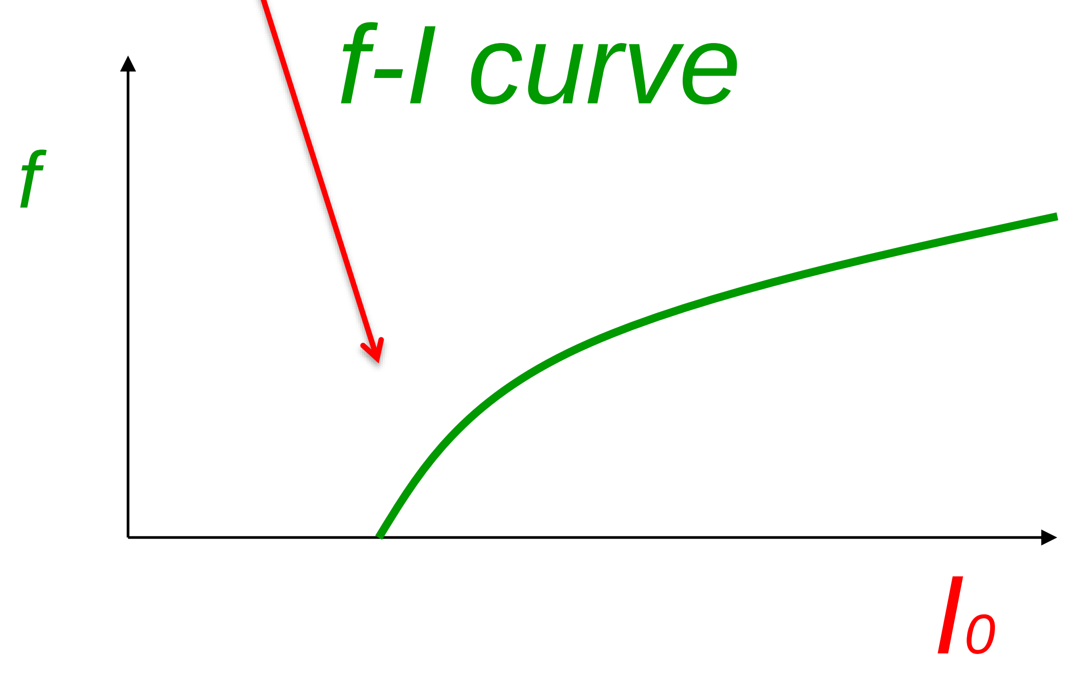
Hodgkin-Huxley model
with standard parameters
(giant axon of squid)

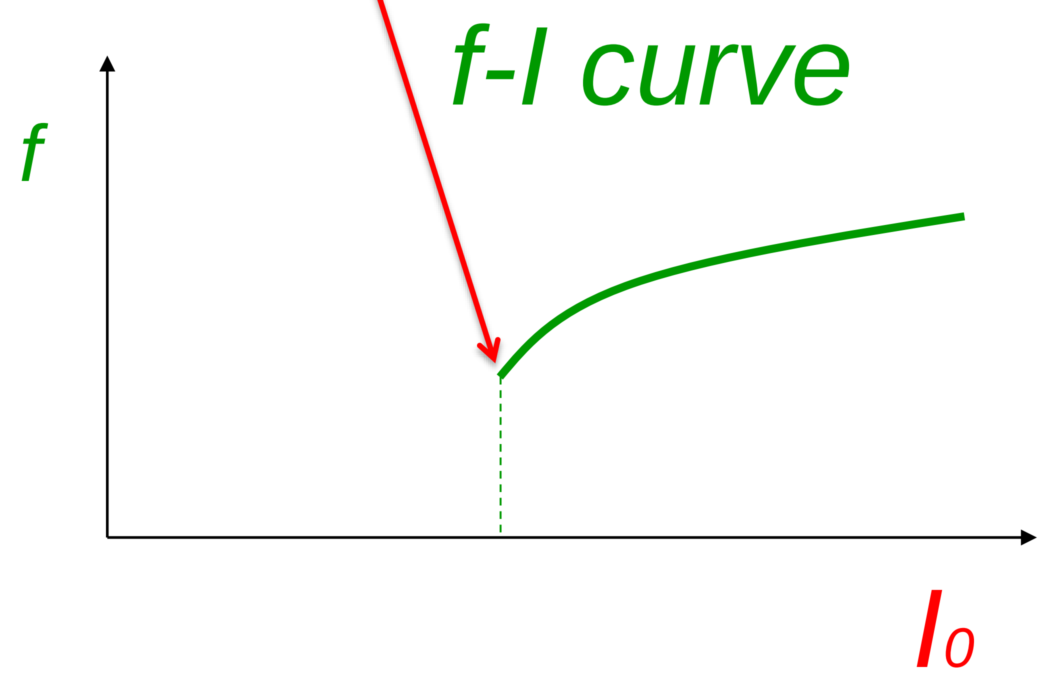
Response at firing threshold?

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

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?

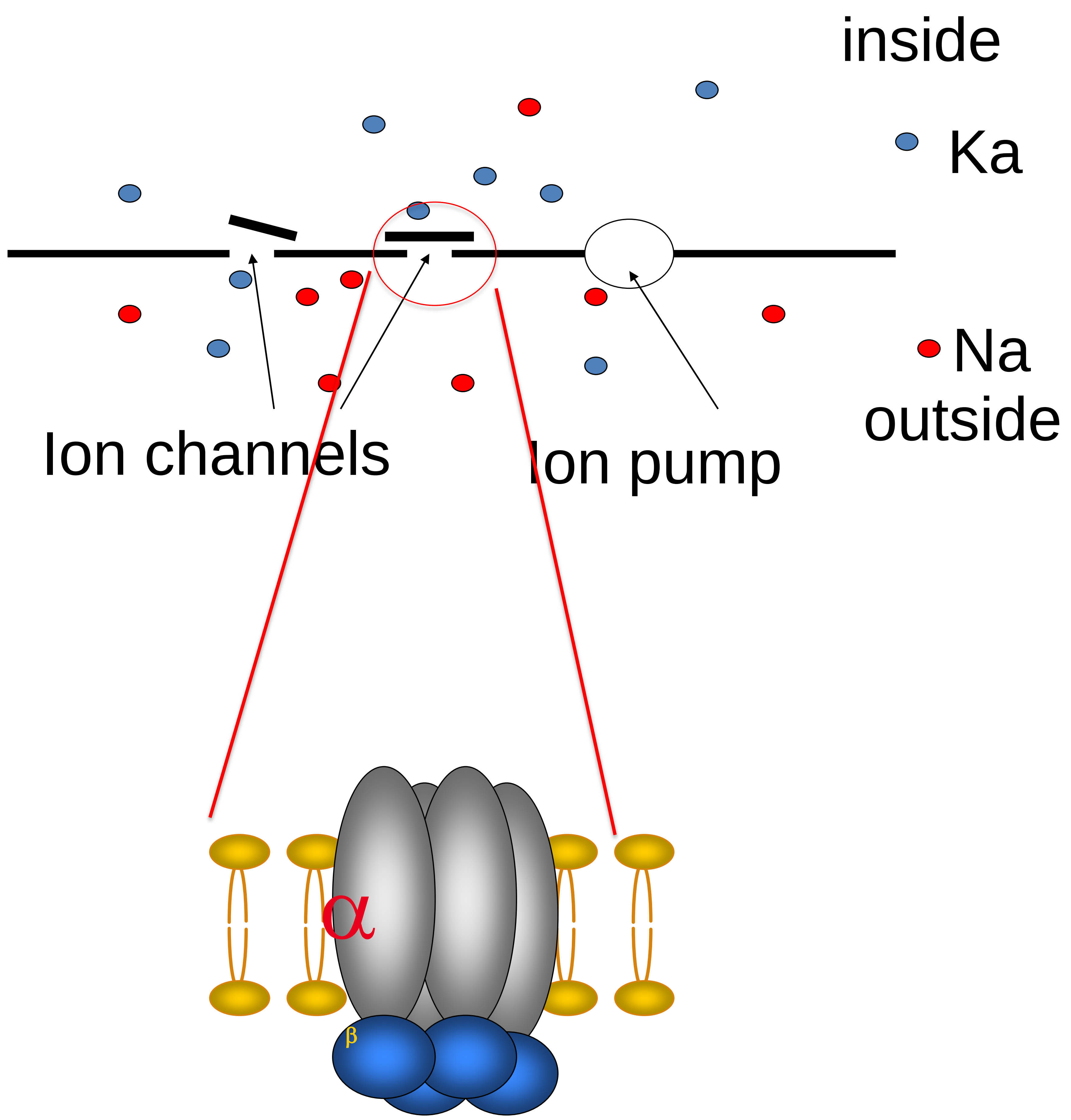
2.5. **Detailed biophysical models**
- the zoo of ion channels

Neuronal Dynamics – 2.5 Biophysical models

There are about 200 identified ion channels

http://channelpedia.epfl.ch/

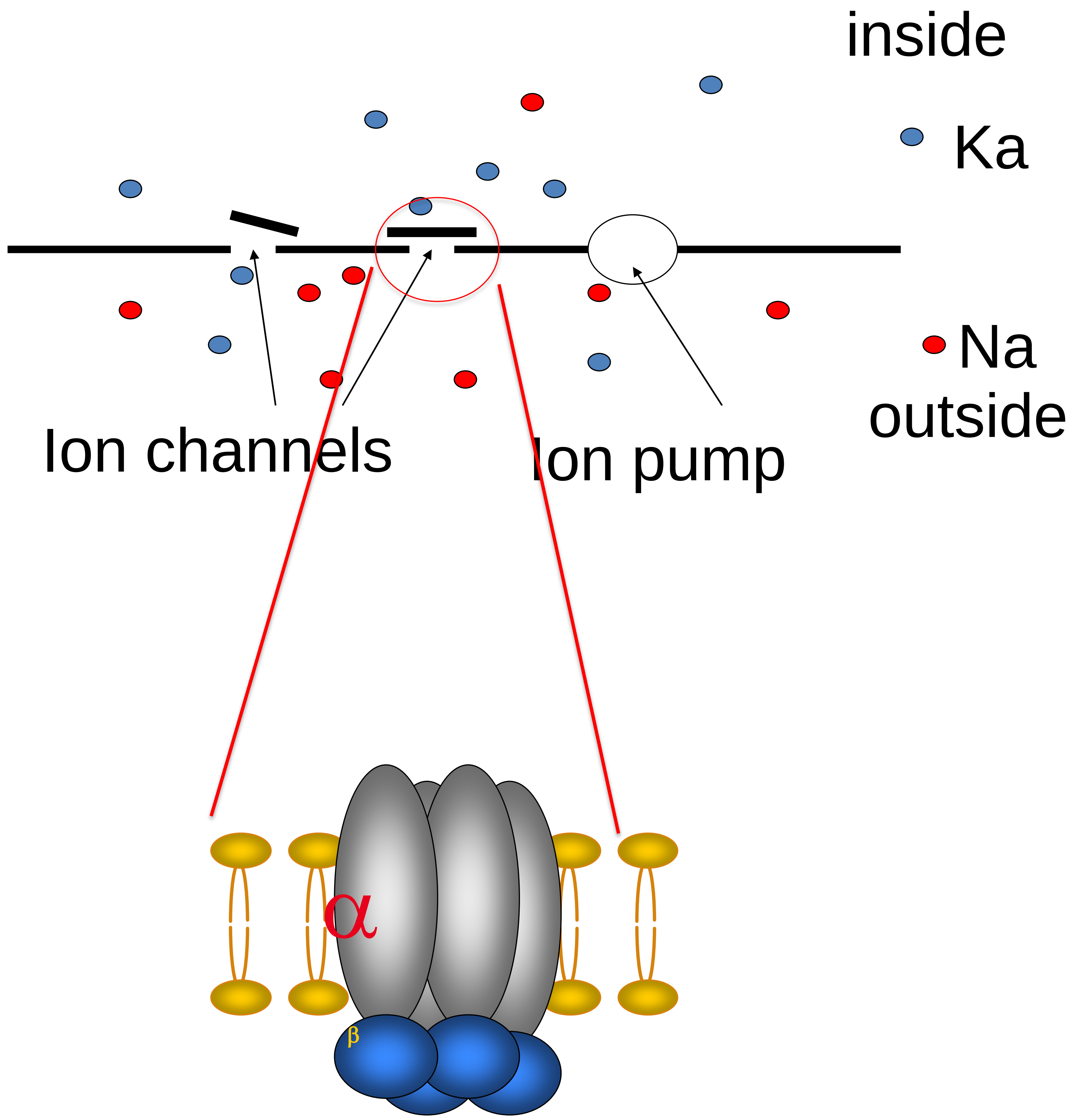
Hodgkin-Huxley model
Provides flexible framework



Neuronal Dynamics – 2.5 Biophysical models

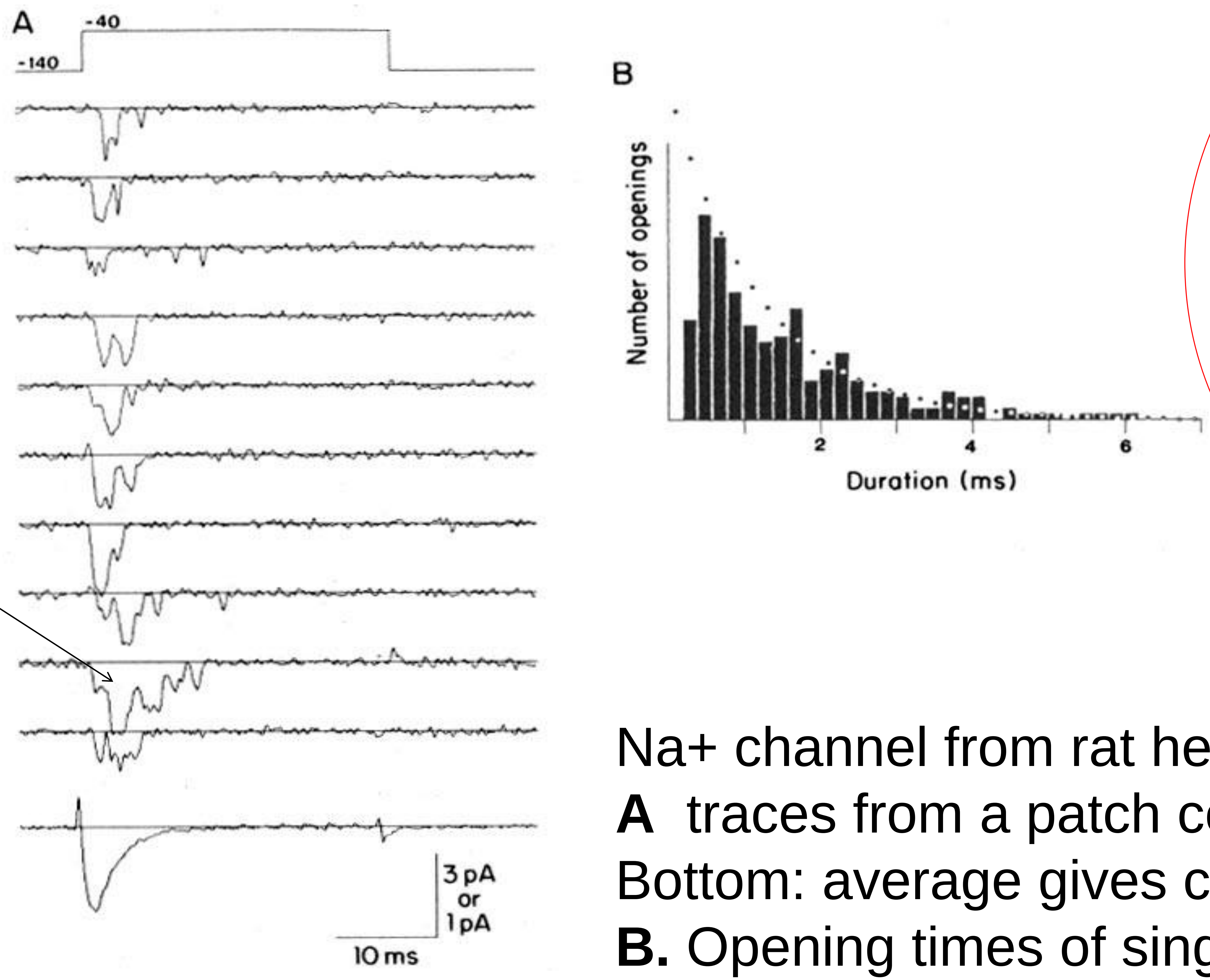
Individual ion channels can be measured.

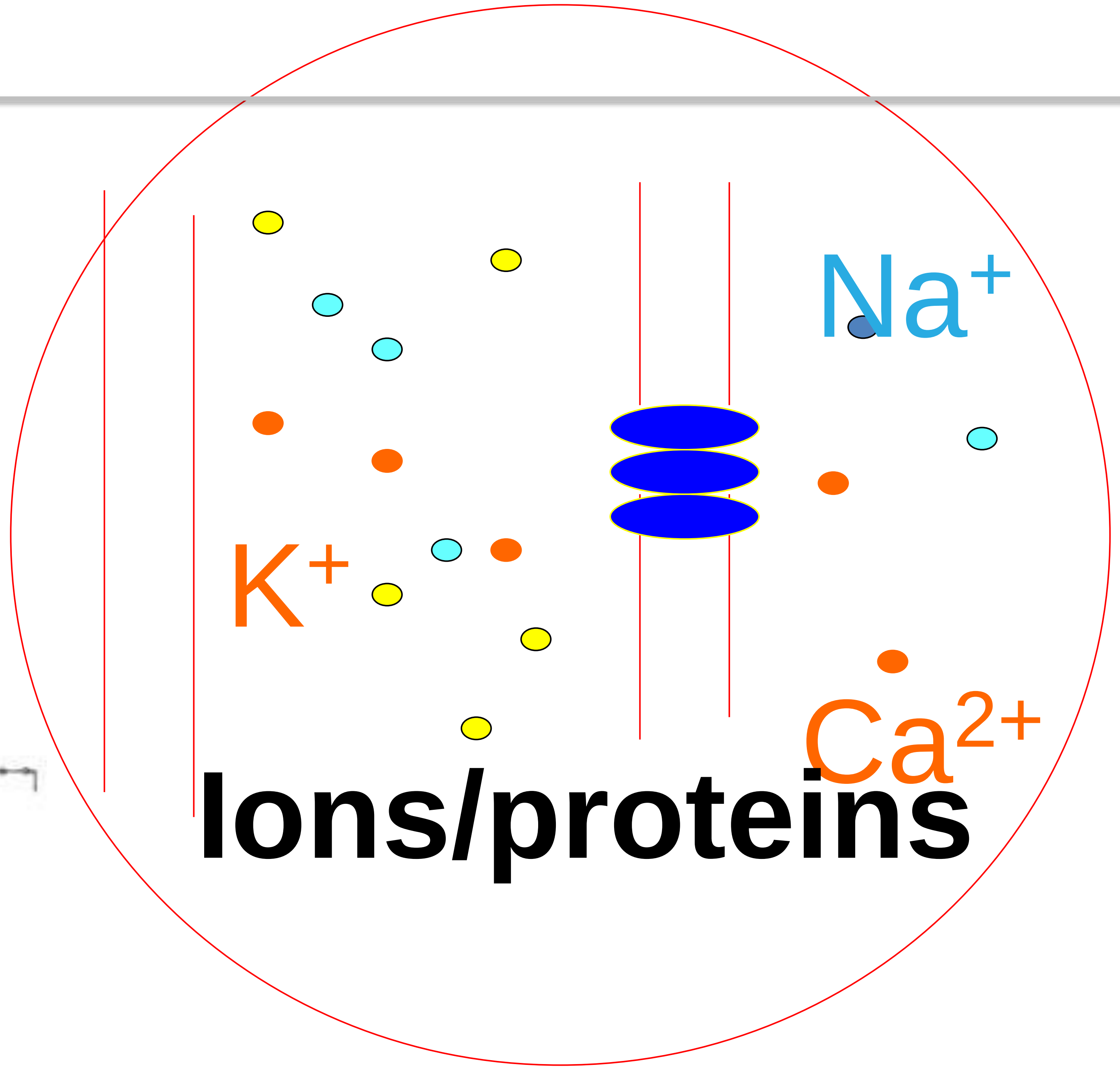
Opening and closing is stochastic



Neuronal Dynamics – 2.5 Ion channels

Steps:
Different number
of channels

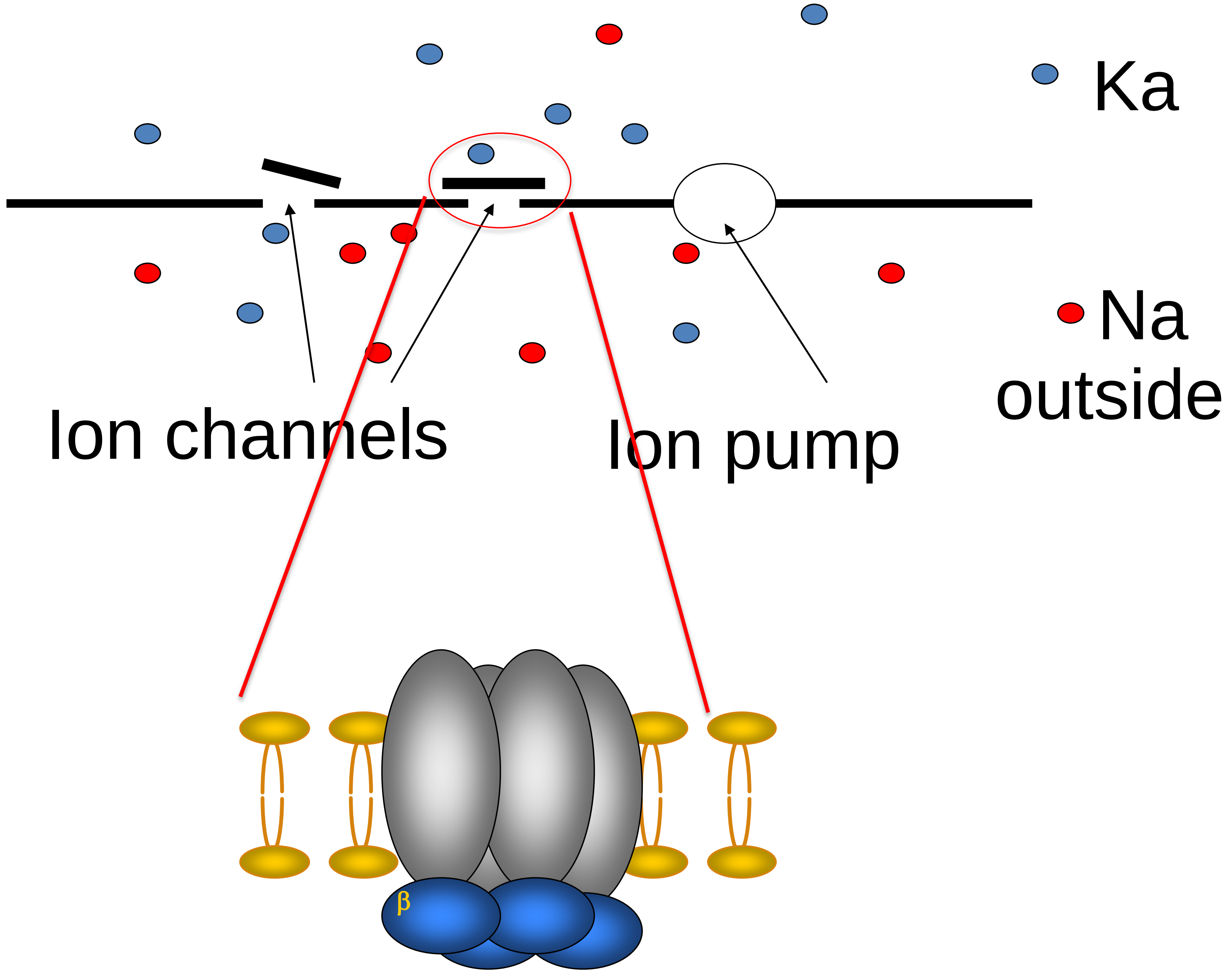




Na+ channel from rat heart *(Patlak and Ortiz 1985)*
A traces from a patch containing several channels.
Bottom: average gives current time course.
B. Opening times of single channel events

Neuronal Dynamics – 2.5 Biophysical models

Hodgkin-Huxley:
-Cambridge lab
-Plymouth lab



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

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 $\tau_m(u)$?

Now Computer Exercises:

Play with Hodgkin-Huxley model

The End

Week 2 – References and Suggested Reading

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

- 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.