Neuronal Dynamics: Computational Neuroscience

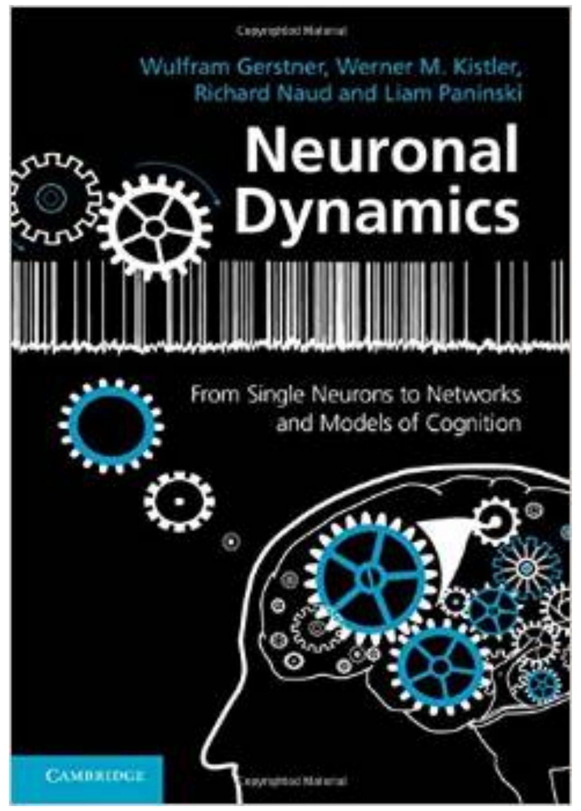
EPFL

Week 2 – Biophysical modeling:
The Hodgkin-Huxley model

Wulfram Gerstner

EPFL, Lausanne, Switzerland

Reading for week 2:
NEURONAL DYNAMICS
- Ch. 2



Cambridge Univ. Press

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

Lecture 2 of video series:
https://lcnwww.epfl.ch/gerstner/NeuronalDynamics-MOOCall.html

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!

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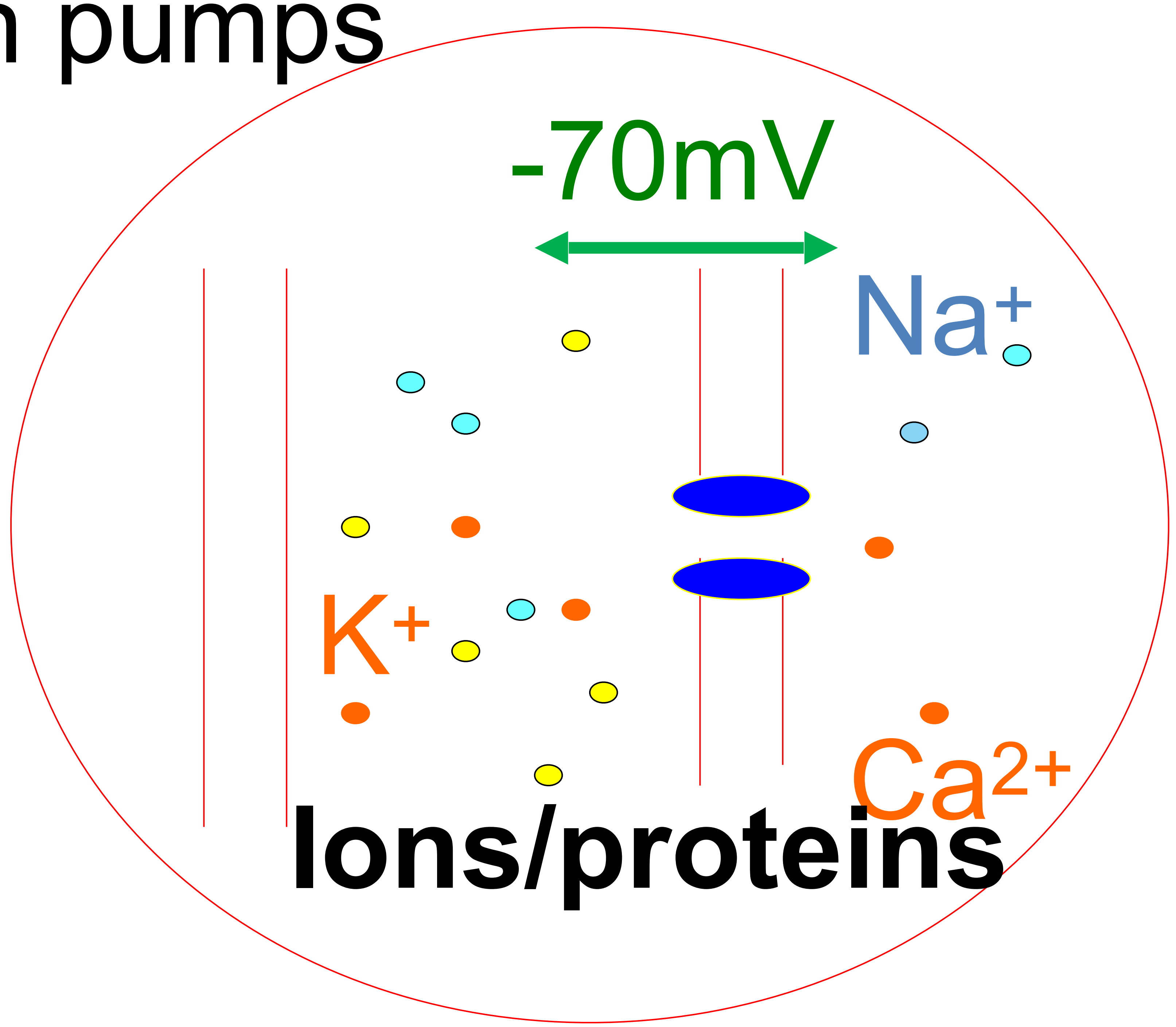
Neuronal Dynamics – week 2: Biophysics of neurons

Cell surrounded by membrane

Membrane contains

- ion channels
- ion pumps



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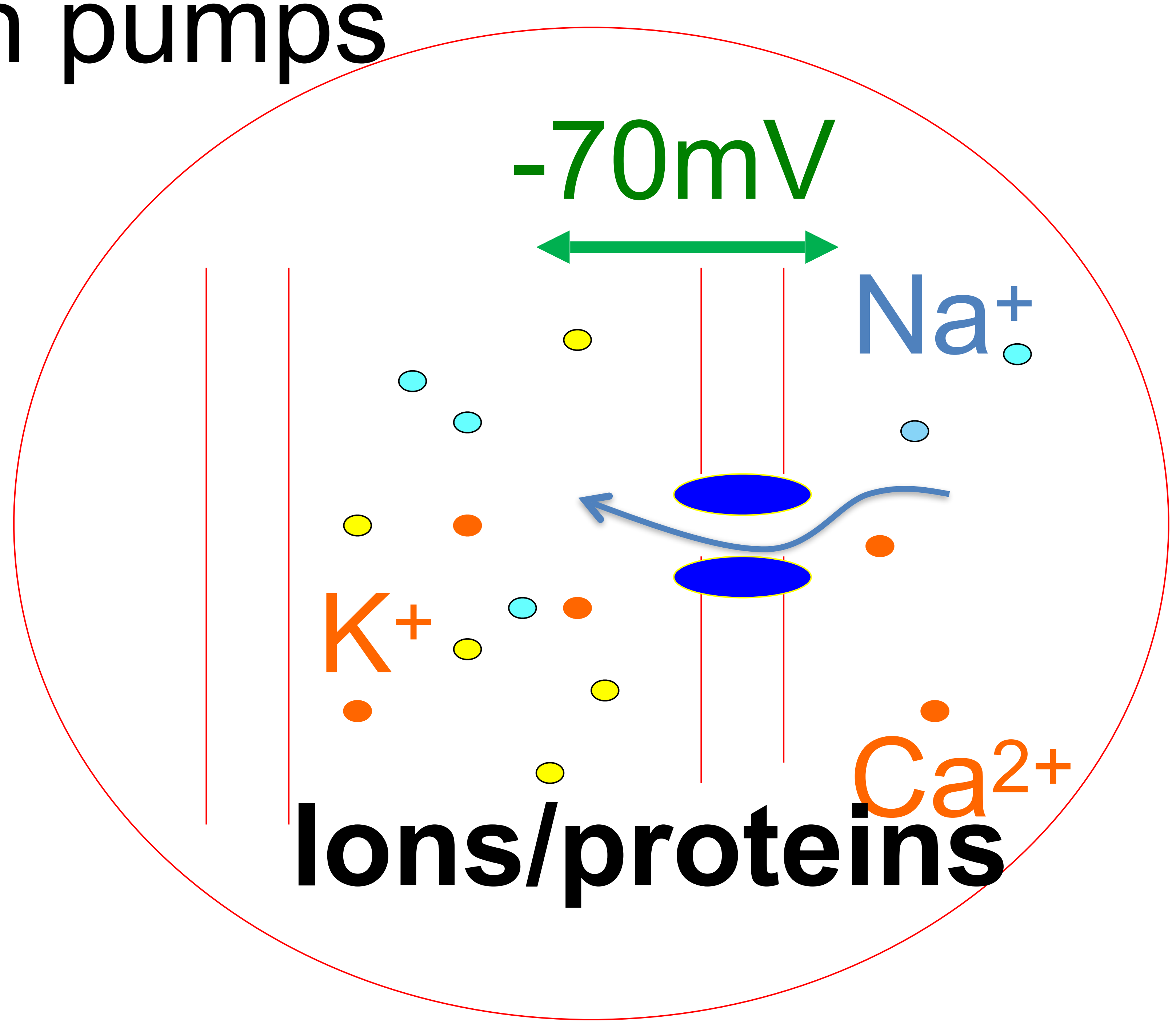

Neuronal Dynamics – week 2: Biophysics of neurons

Cell surrounded by membrane

Membrane contains

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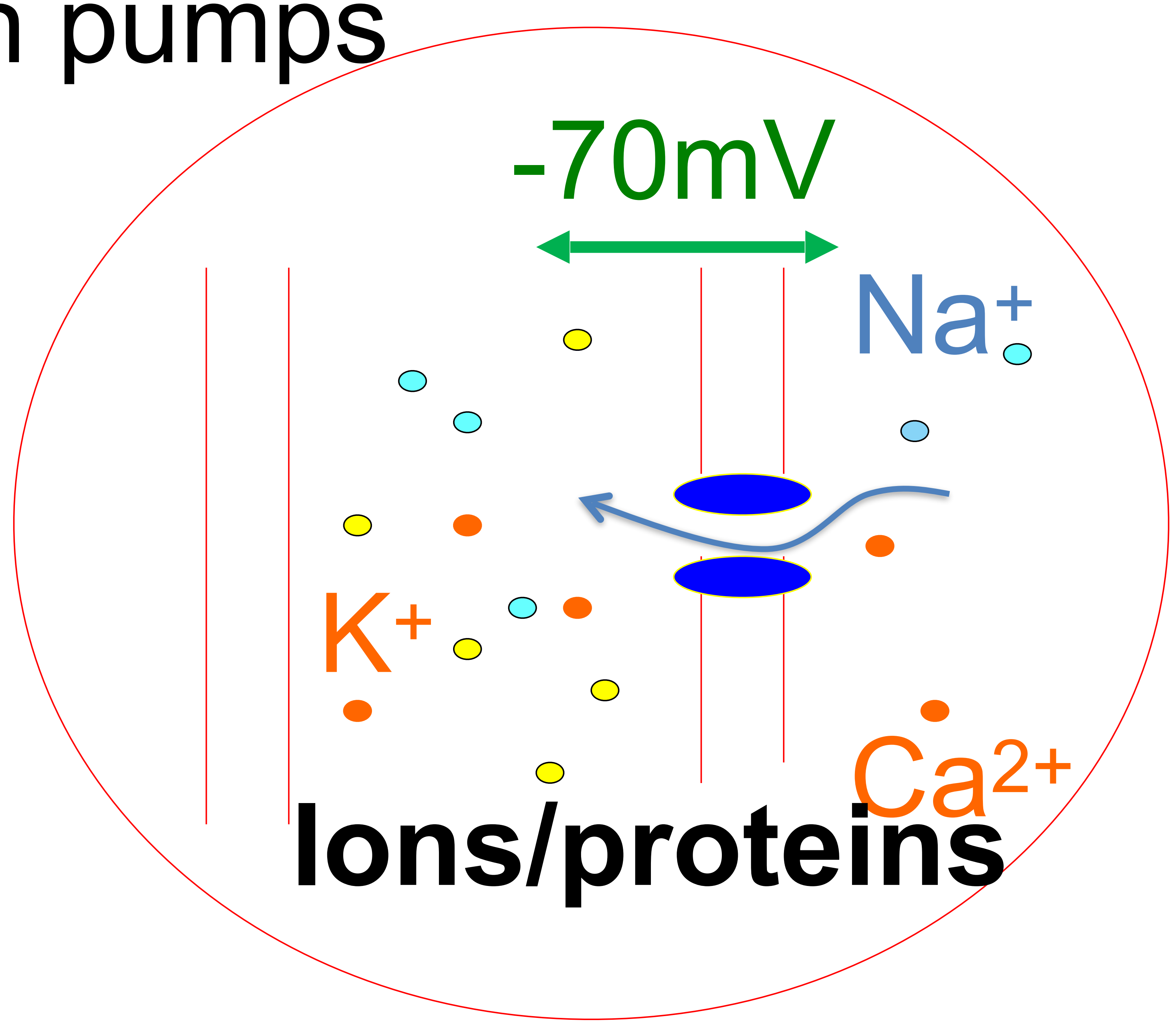
1. Resting potential -70mV
   → how does it arise?



Neuronal Dynamics – week 2: Biophysics of neurons

Cell surrounded by membrane

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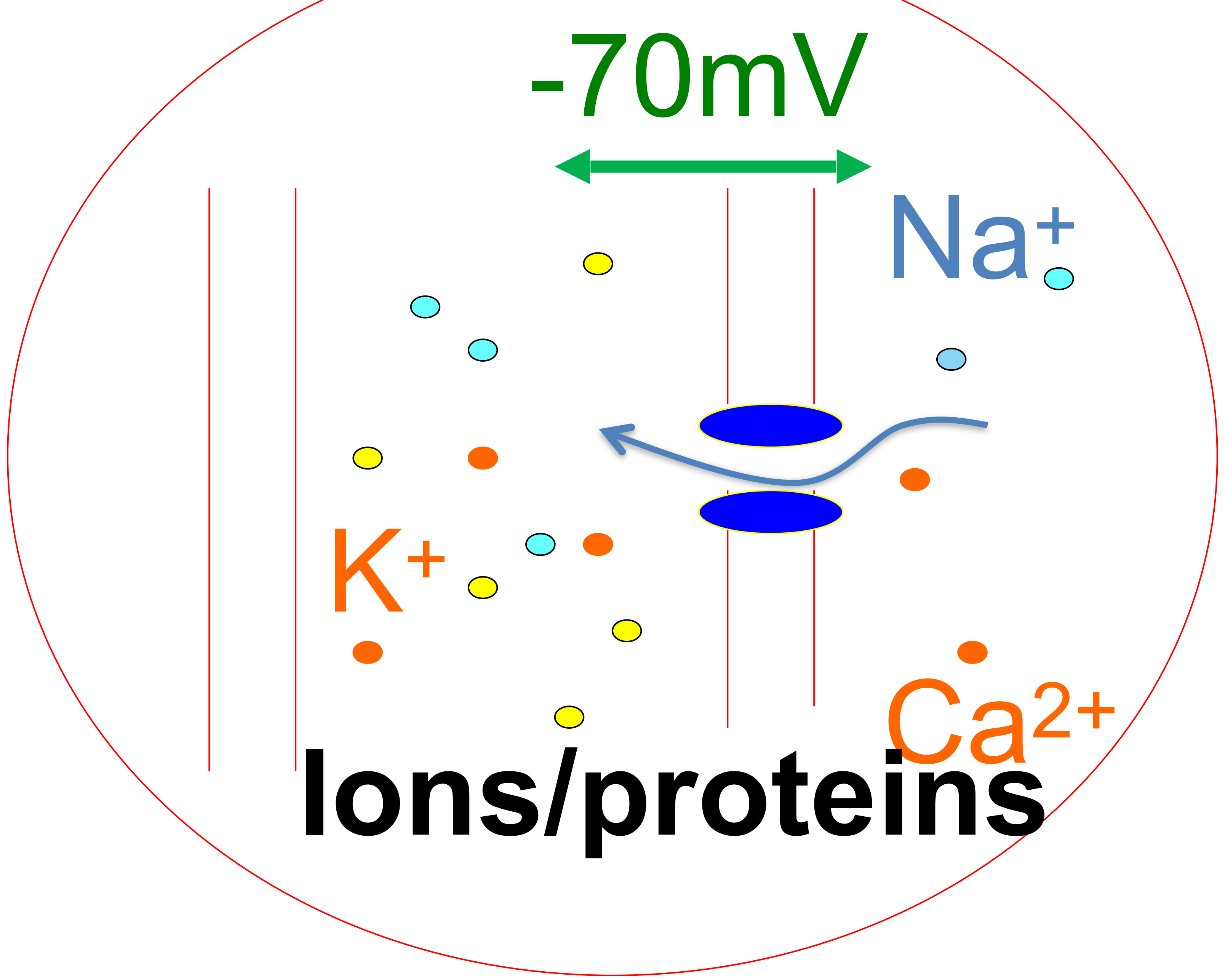

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2. Ions flow through channel
   → in which direction

Neuronal Dynamics – week 2: Biophysics of neurons

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- ion channels
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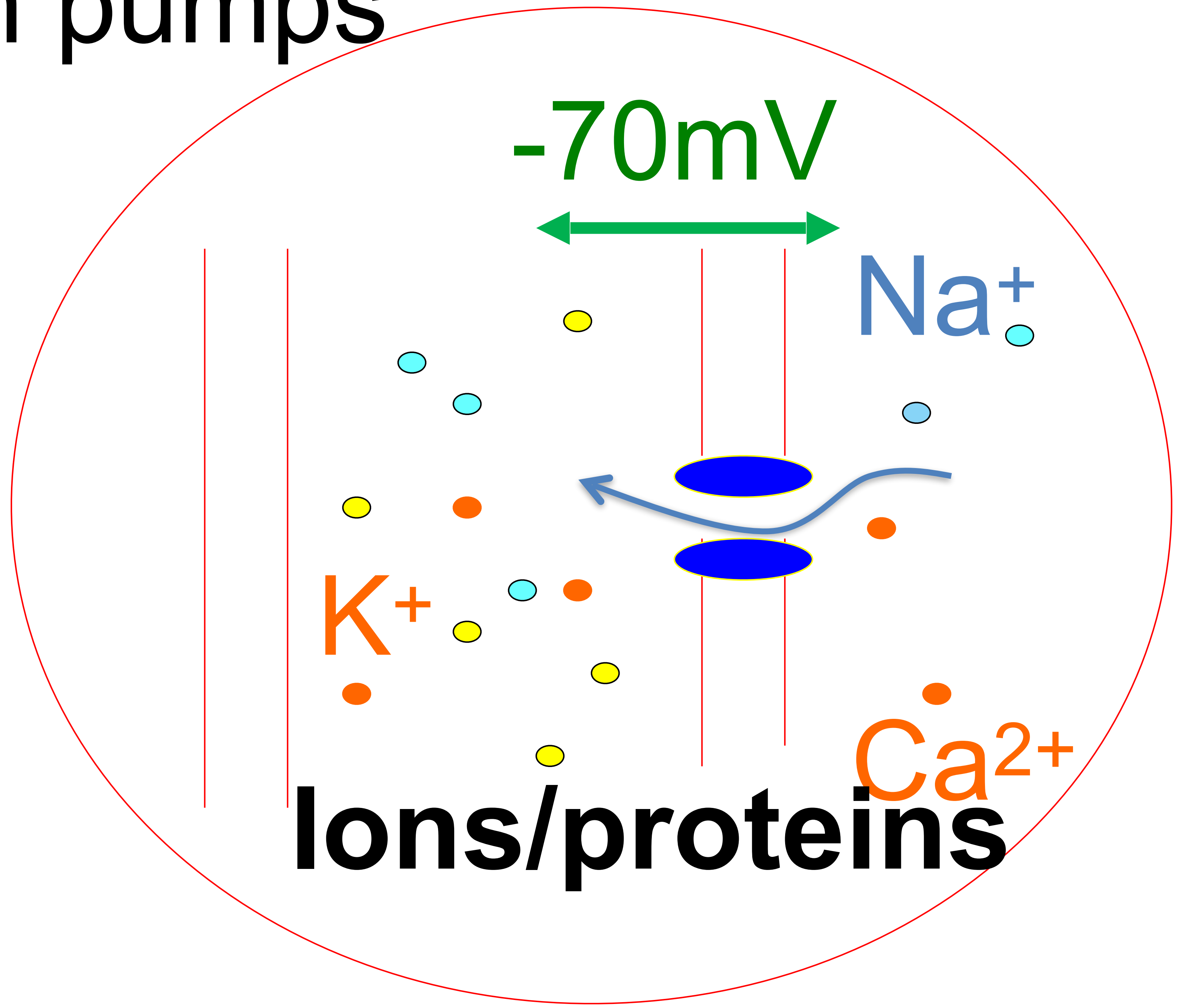


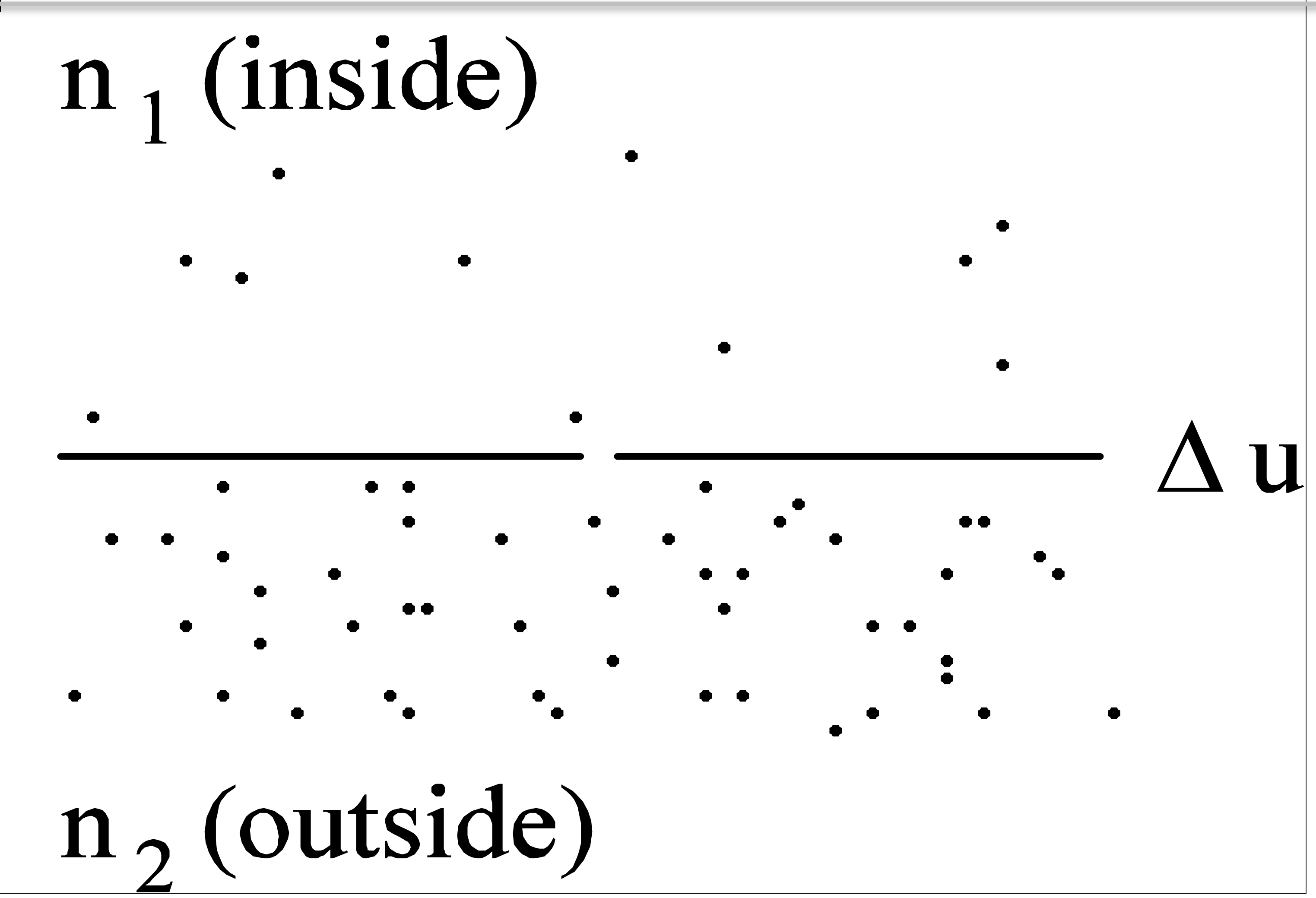
1. Resting potential -70mV
   → how does it arise?

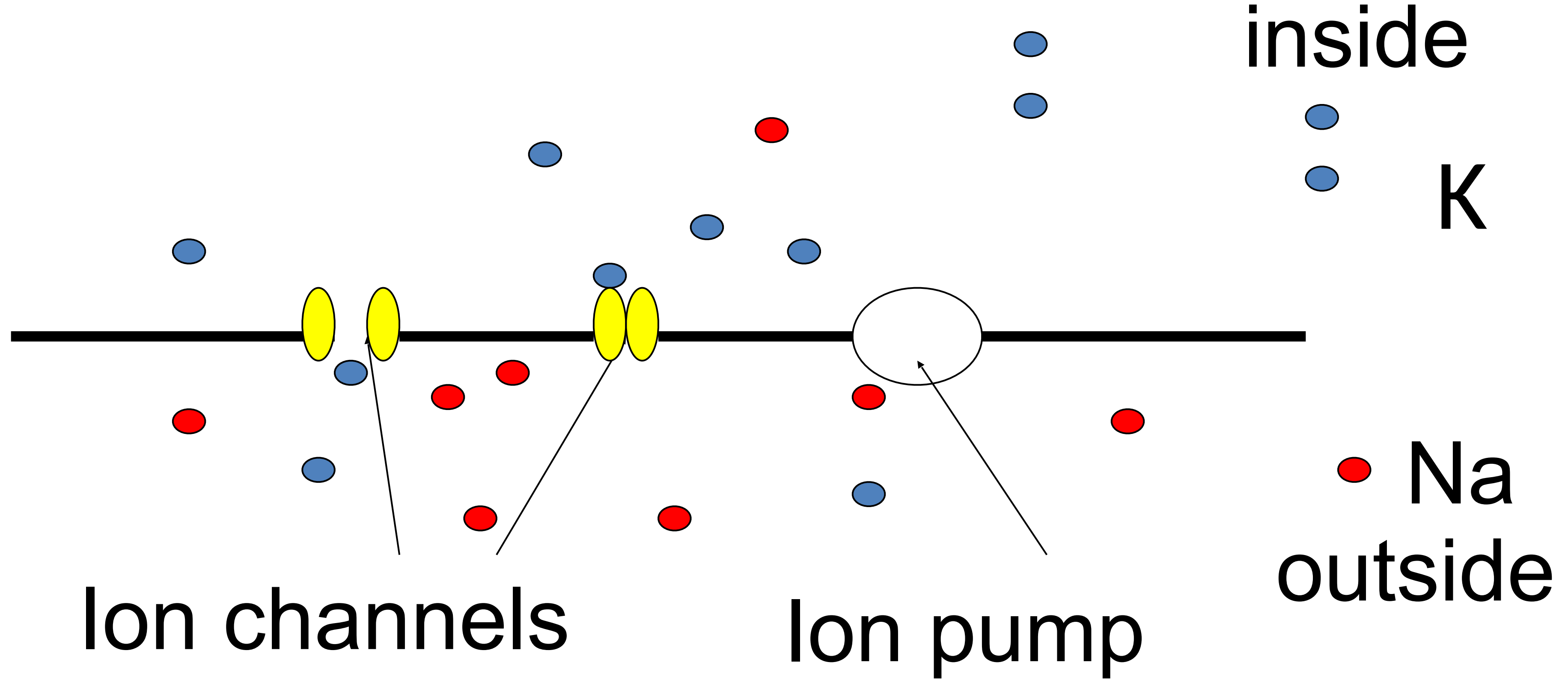
2. Ions flow through channel
   → in which direction

3. Neuron emits action potentials
   → why?

Summary of Section 2.1.

- In the normal state (physiological condition, without intervention of an experimentalist), there is a potential difference between the inside of the cell and the outside.
- The potential difference is in the range -70mV < u < -50mV. The minus sign means that inside the cell is negative compared to the fluid outside the cell.
- The cell membrane contains ion channels and ion pumps
- Ion pumps maintain a concentration difference between inside and outside.
- Ions can pass through ion channels in the membrane if these channels are open.

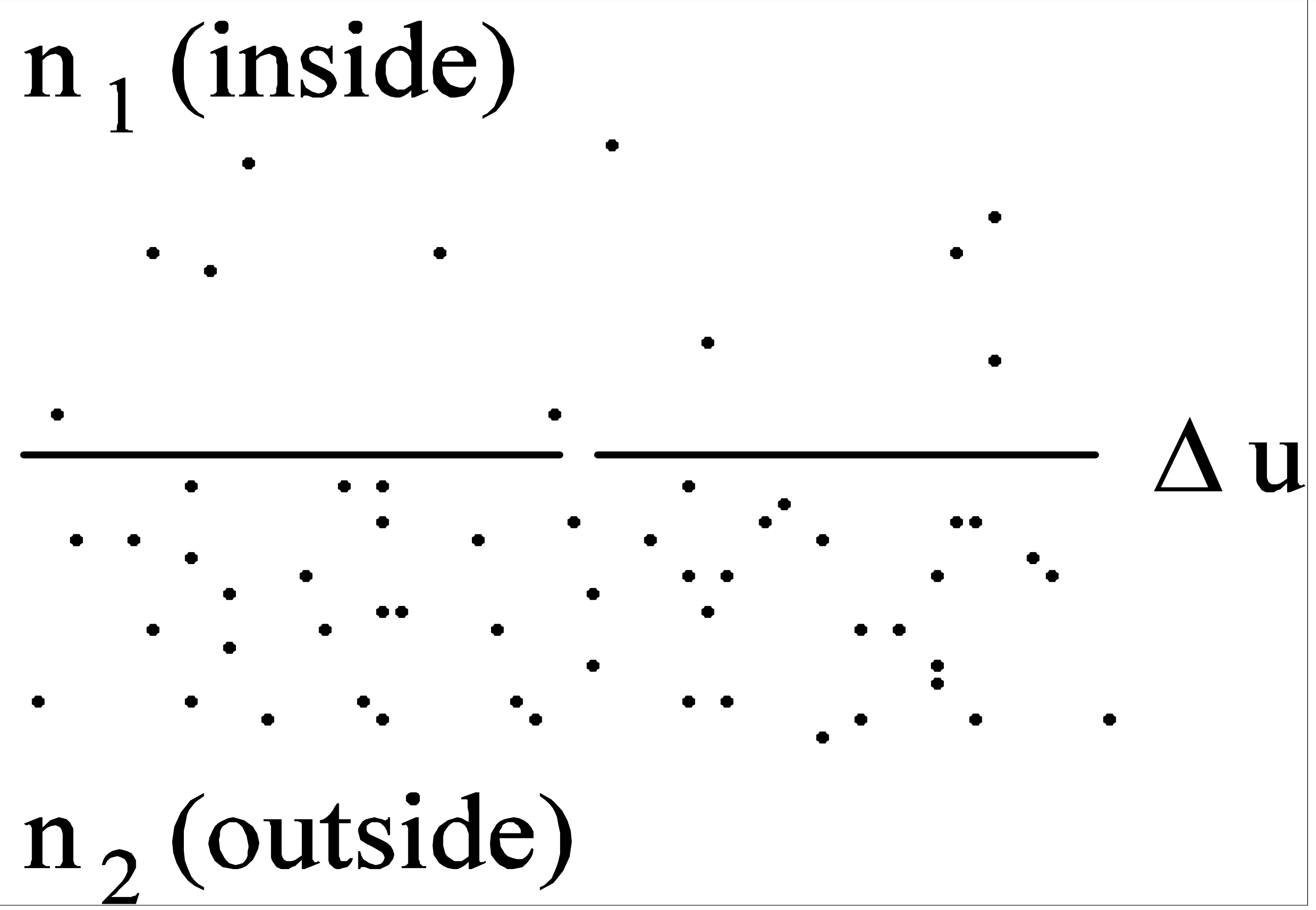


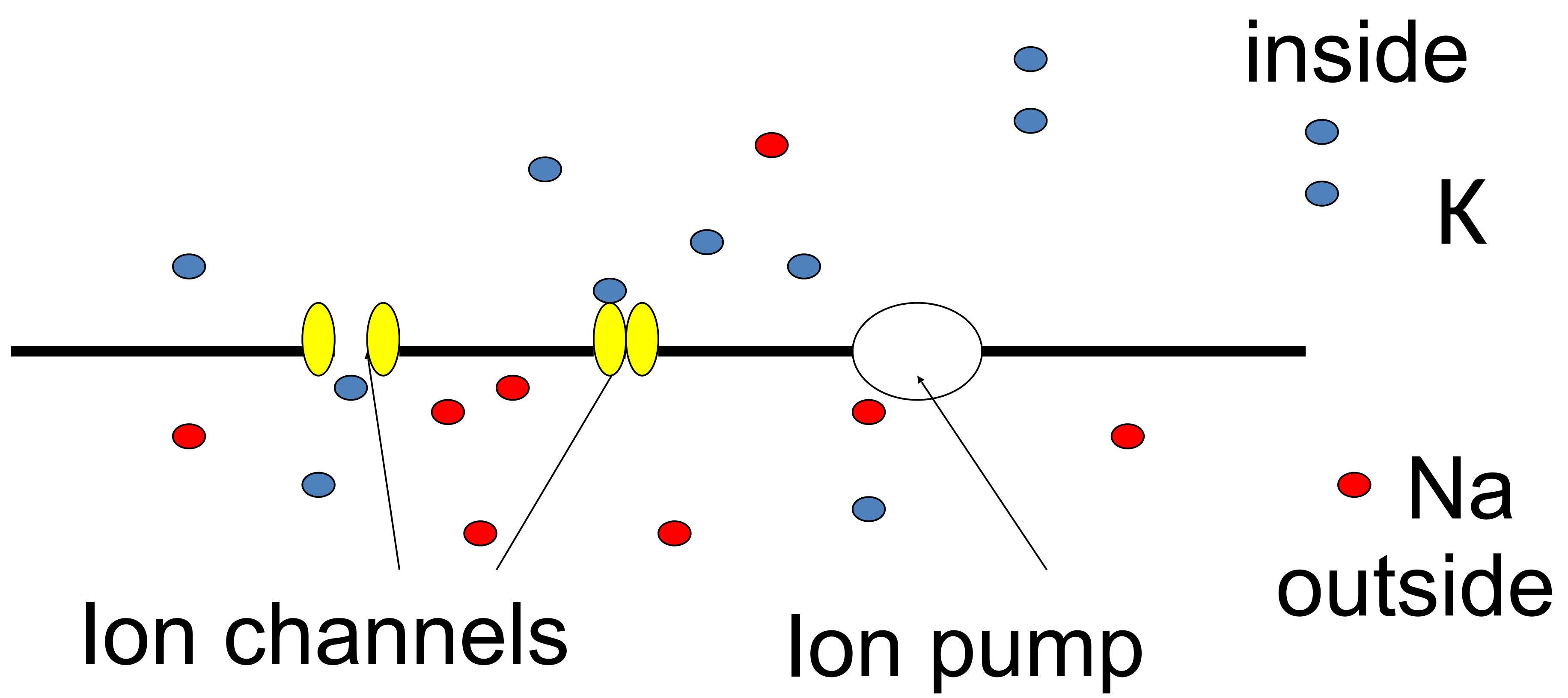


$$\Delta u = u_1 - u_2 = \frac{-kT}{q} \ln \frac{n(u_1)}{n(u_2)}$$

Reversal potential

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

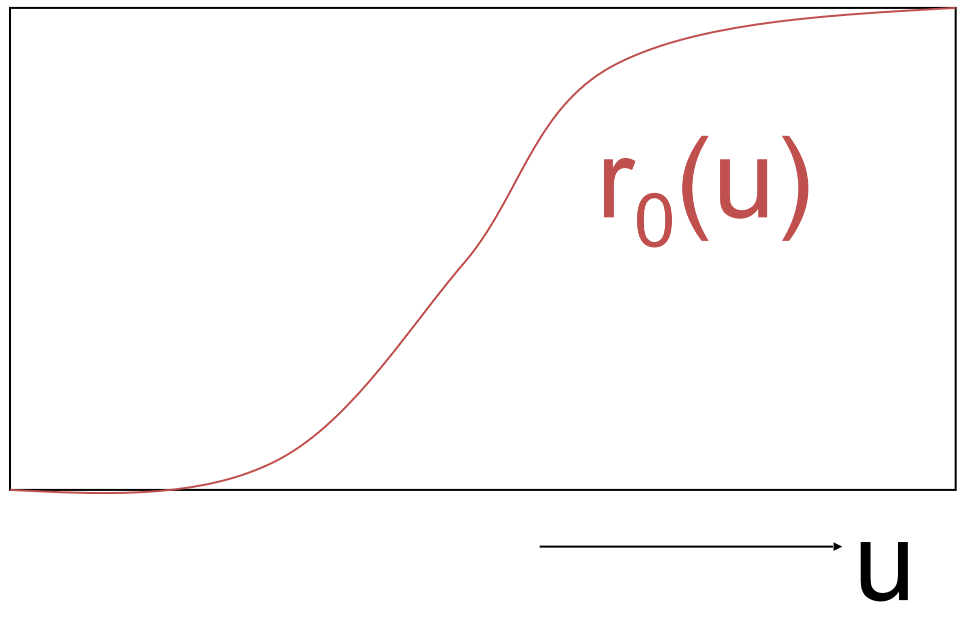
Summary of Section 2.2.

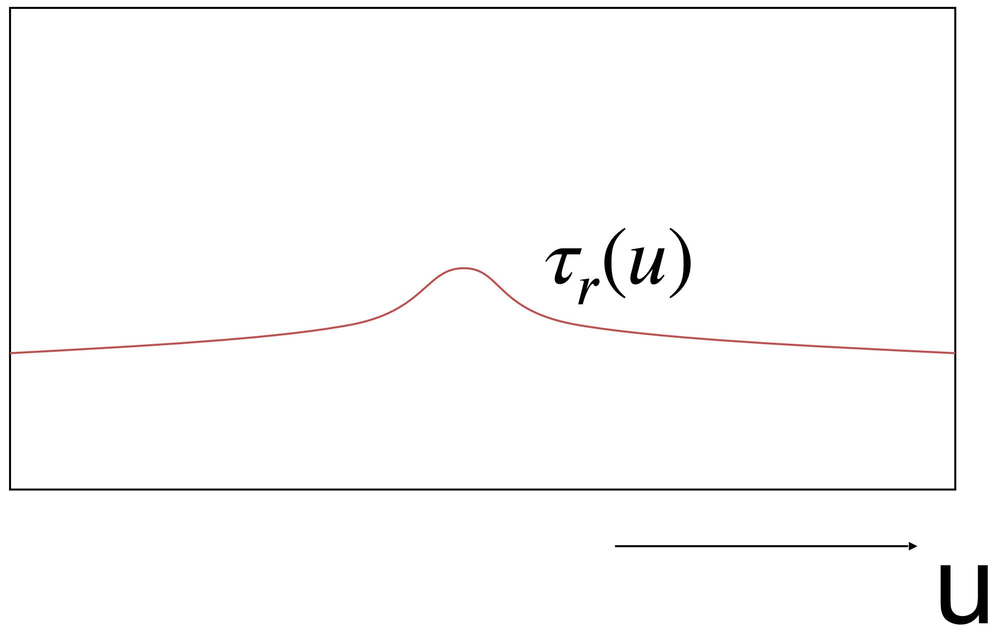
- In the normal resting state (physiological condition, without intervention of an experimentalist), there is a potential difference between the inside of the cell and the outside.
- The measured potential difference reflects a multi-ion equilibrium
- Each ion type has its own equilibrium potential which reflects the equilibrium between temperature-induced diffusion and electrical forces induced by the concentration difference.
- The concentration difference is maintained by ion pumps.
- The Nernst-equation for the voltage difference is related to the Boltzmann distribution.

Neuronal Dynamics – 2.3. Ion channel

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

The variable r
- is called?
- controls?





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

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

Neuronal Dynamics – 2.3. Ion channel

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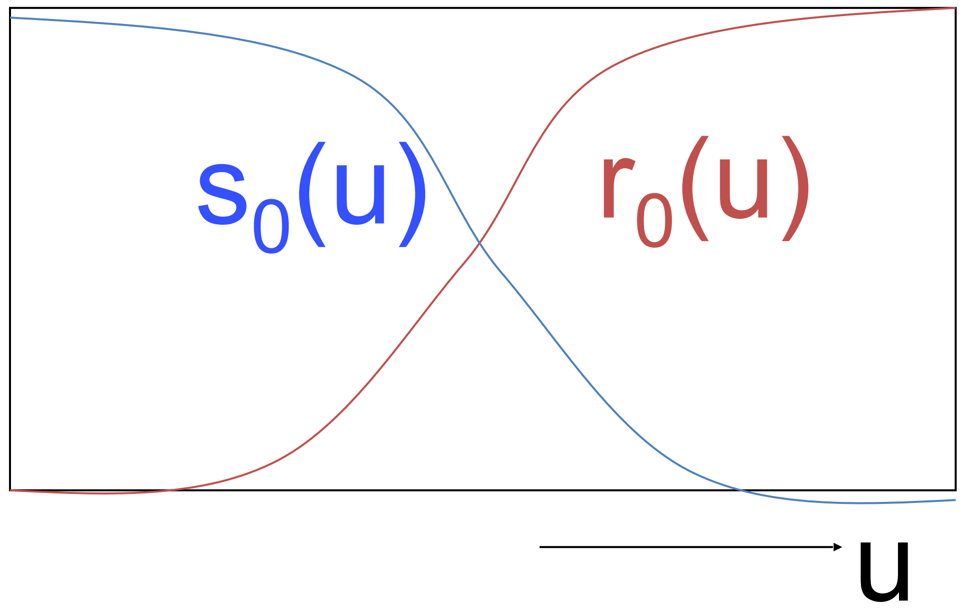

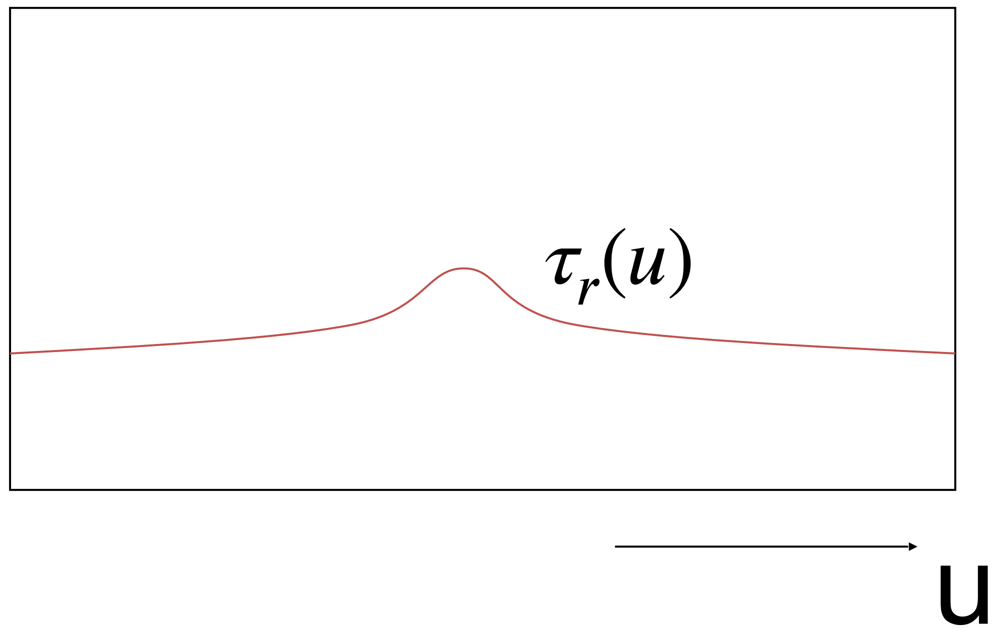

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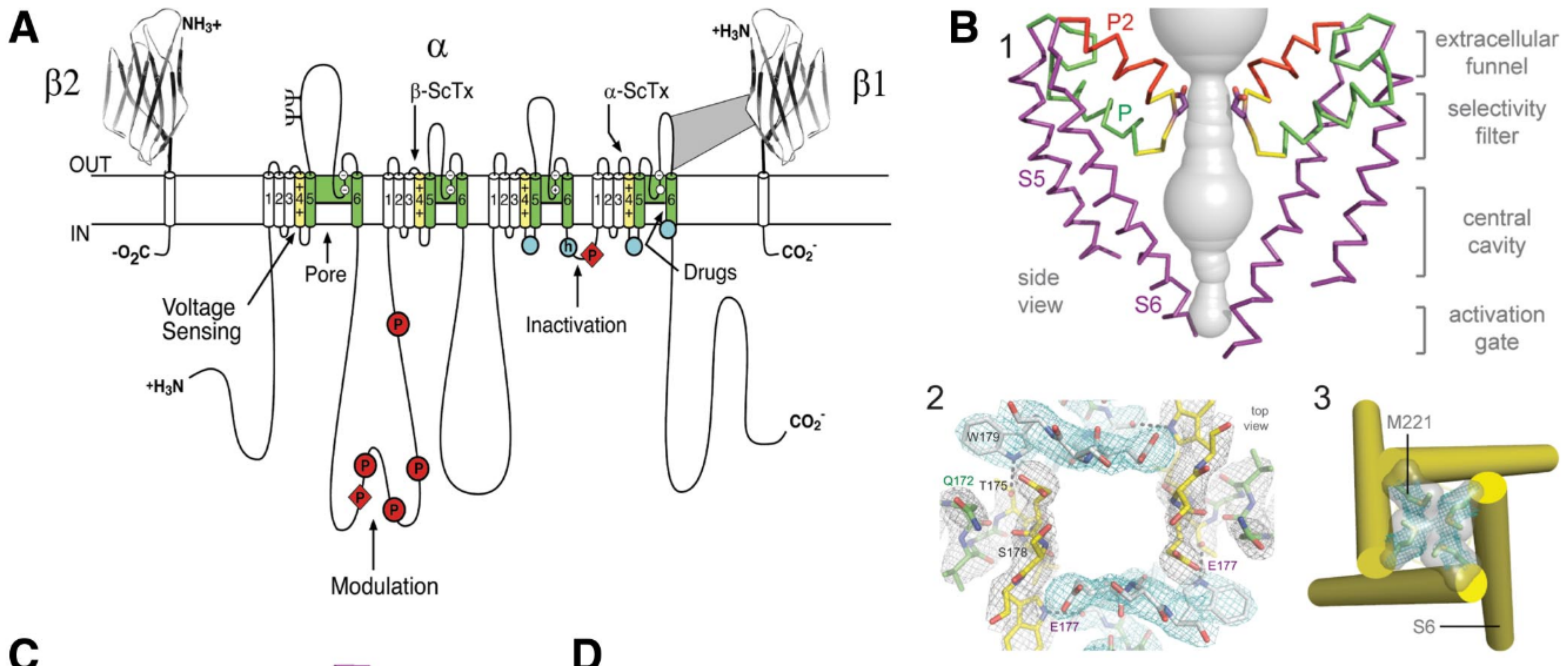
I did not understand why for Na channel,
we need 2 constants m and h,
what do they refer to physically.

I did not understand why there is a power of 4 for n, 3 for m and 1 for h.



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Symposium

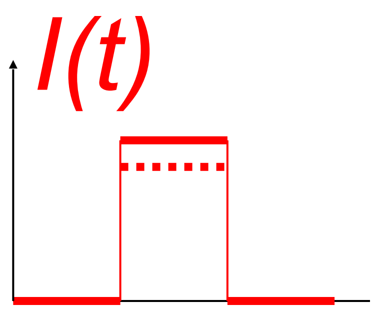
The Hodgkin-Huxley Heritage: From Channels to Circuits

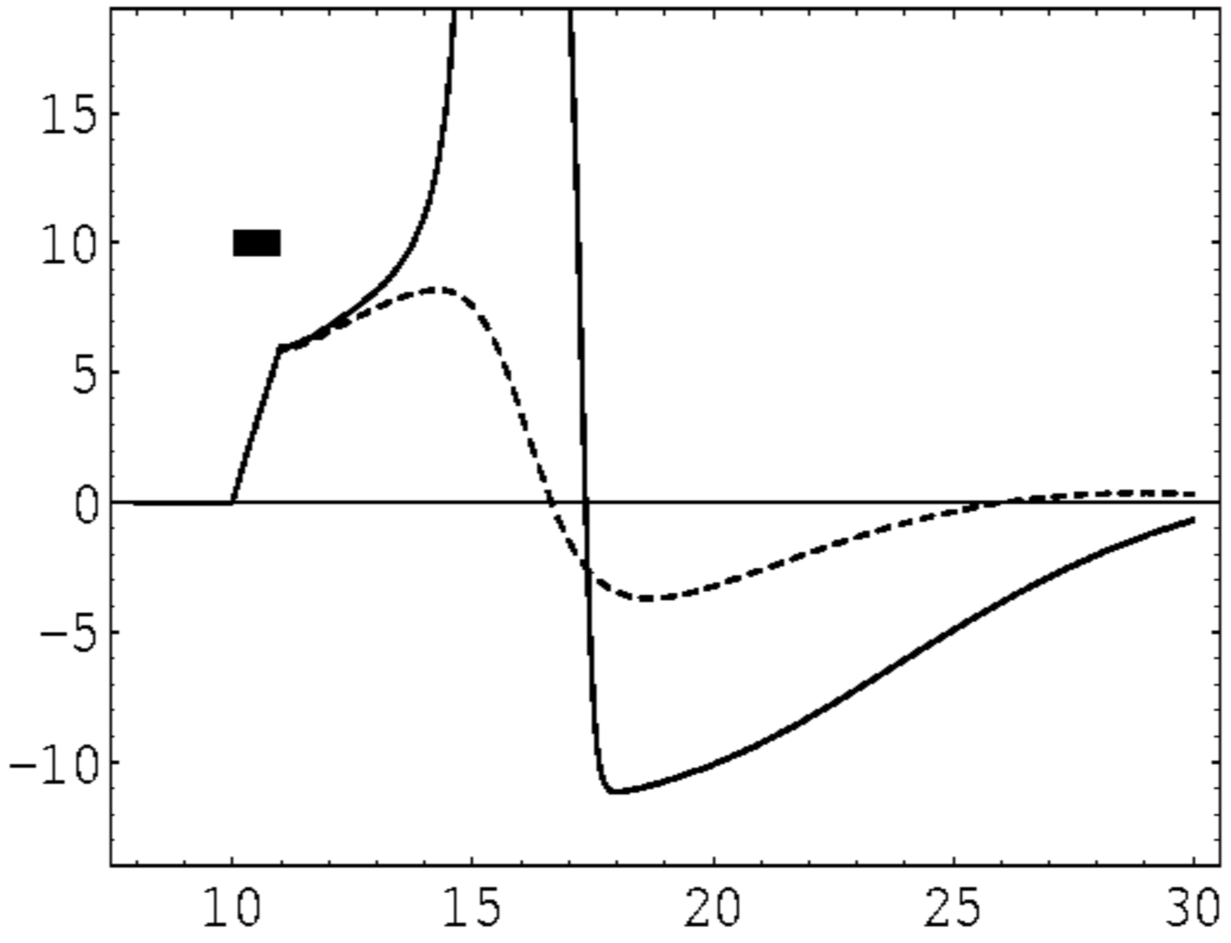
William A. Catterall,[1] Indira M. Raman,[2] Hugh P. C. Robinson,[3] Terrence J. Sejnowski,[4,5] and Ole Paulsen[3]

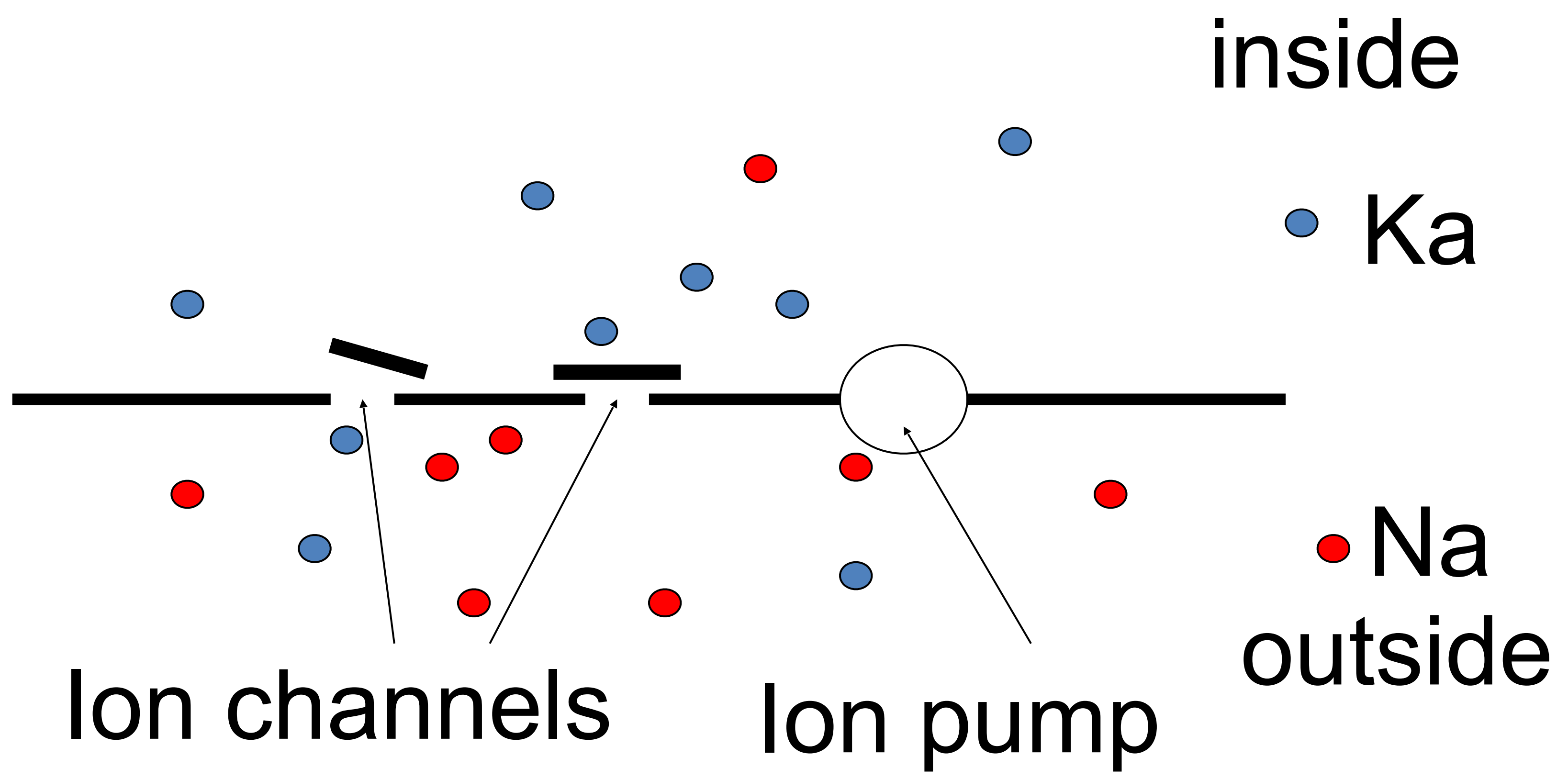
Summary of Section 2.3.

- Ions can pass through channels in the membrane.
- The Hodgkin-Huxley equations describe two ion channels (a sodium channel and a potassium channel) each as a non-linear, time-dependent resistor and fixed battery potential.
- The battery potential is caused by the concentration difference
- The nonlinearity of the resistor is caused by opening and closing of ion channels.
- The dynamics of opening and closing is described by gating variables m,h, and n
- The variable m is called an activation variable because it increases with voltage (→ a large positive voltage step 'activates' the channel)
- The variable h is called an inactivation variable because it decreases with voltage (→ a large positive voltage step 'inactivates' the channel)
- Partial or full activation or inactivation becomes effective only after a delay.

pulse input

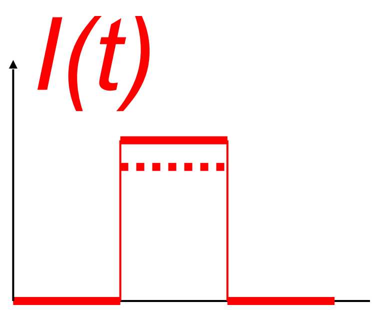

I(t)

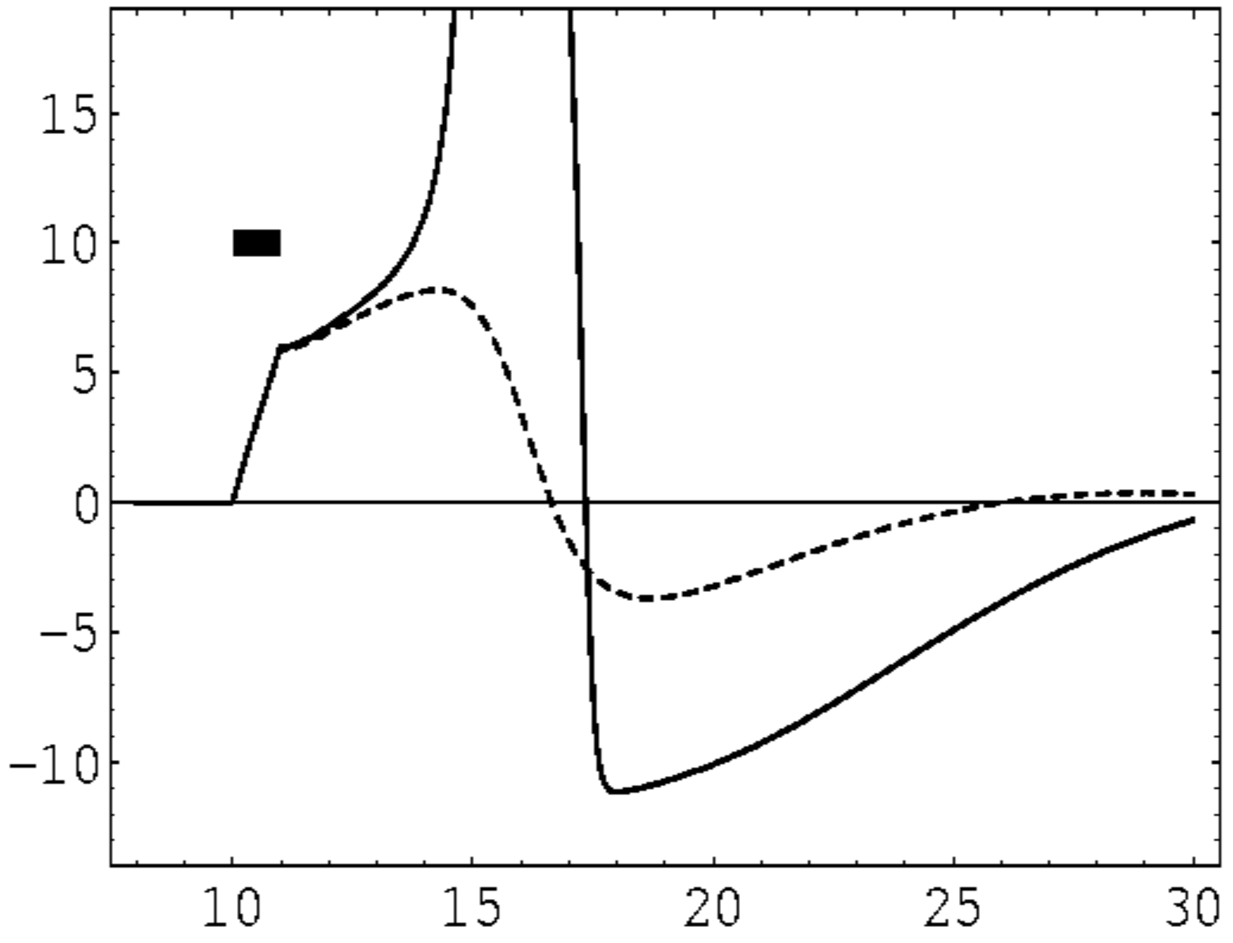

15
10
5
0
−5
−10
10
15
20
25
30

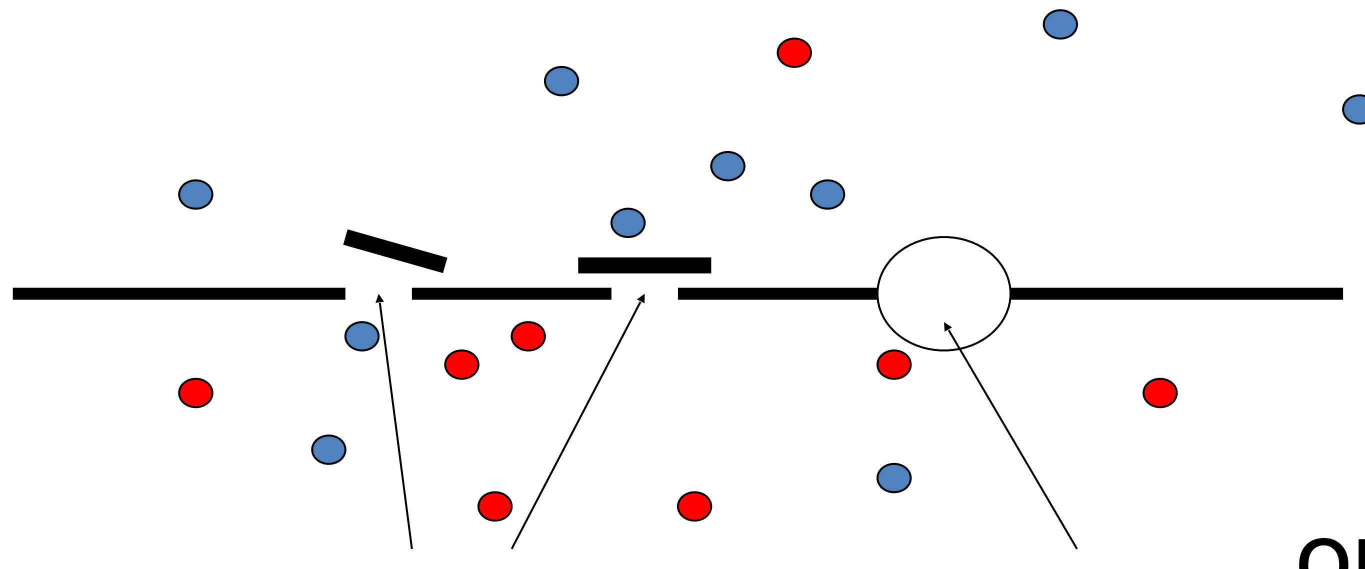

inside
Ka
Na
outside
Ion channels
Ion pump

Neuronal Dynamics – 2.4. Threshold in HH model

pulse input







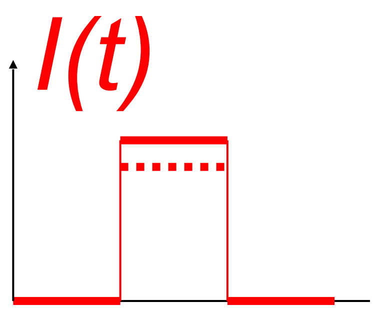
Threshold?

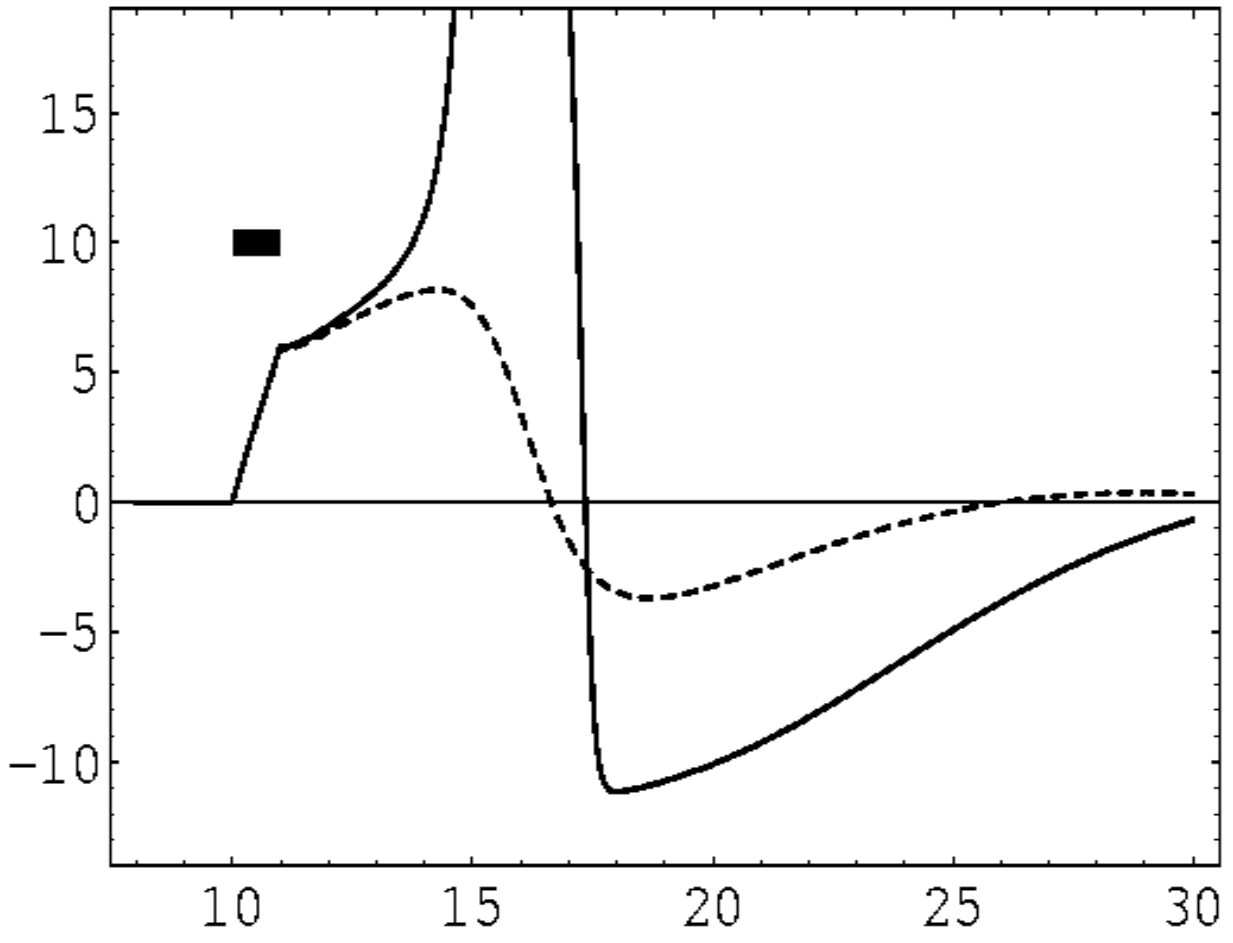
- AP if amplitude 7.0 units
- No AP if amplitude 6.9 units

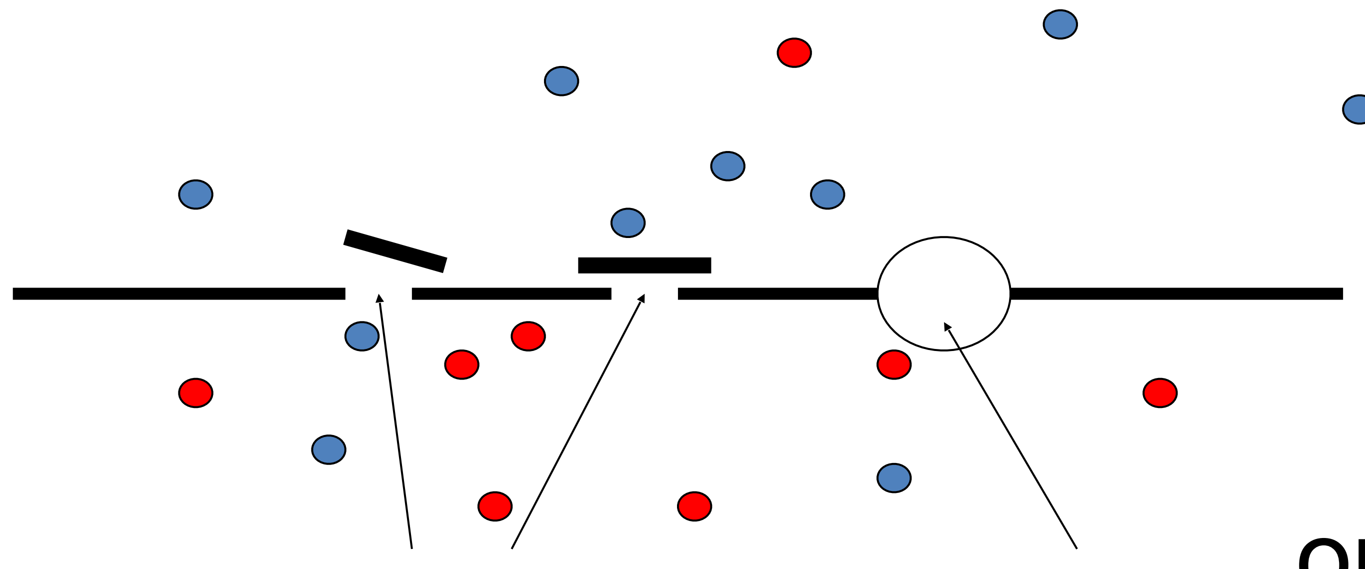
(pulse with 1ms duration)

Neuronal Dynamics – 2.4. Threshold in HH model

pulse input







Threshold?

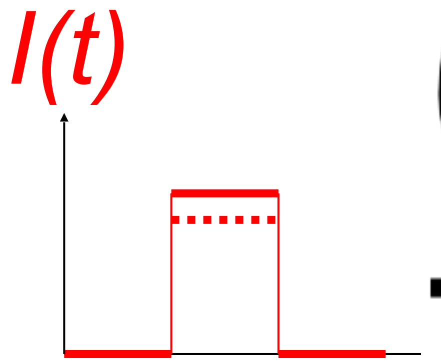
- AP if amplitude 7.0 units
- No AP if amplitude 6.9 units

(pulse with 1ms duration)

(and pulse with 0.5 ms duration?)

Neuronal Dynamics – 2.4. Threshold in HH model

pulse input



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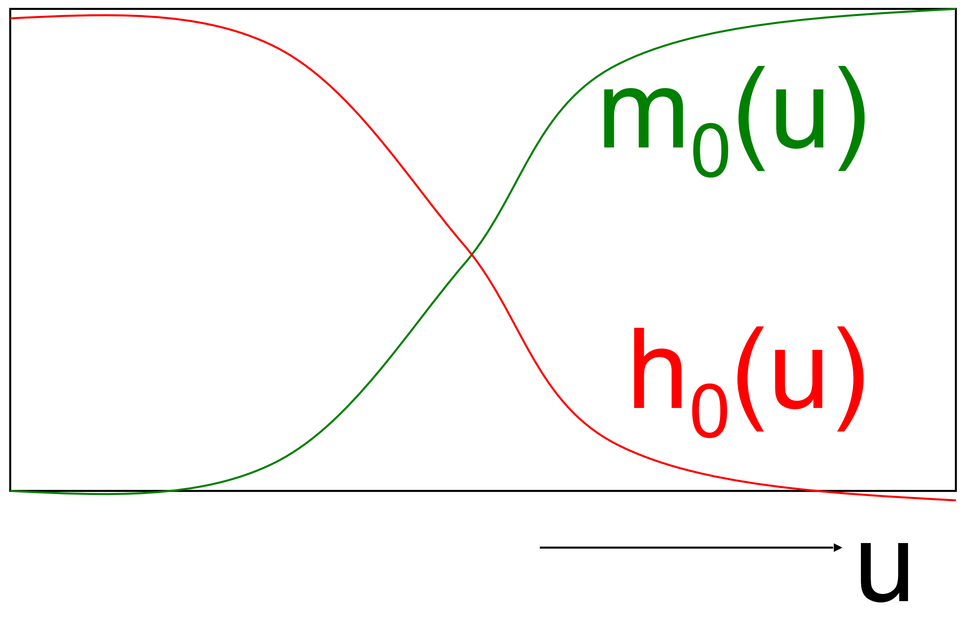

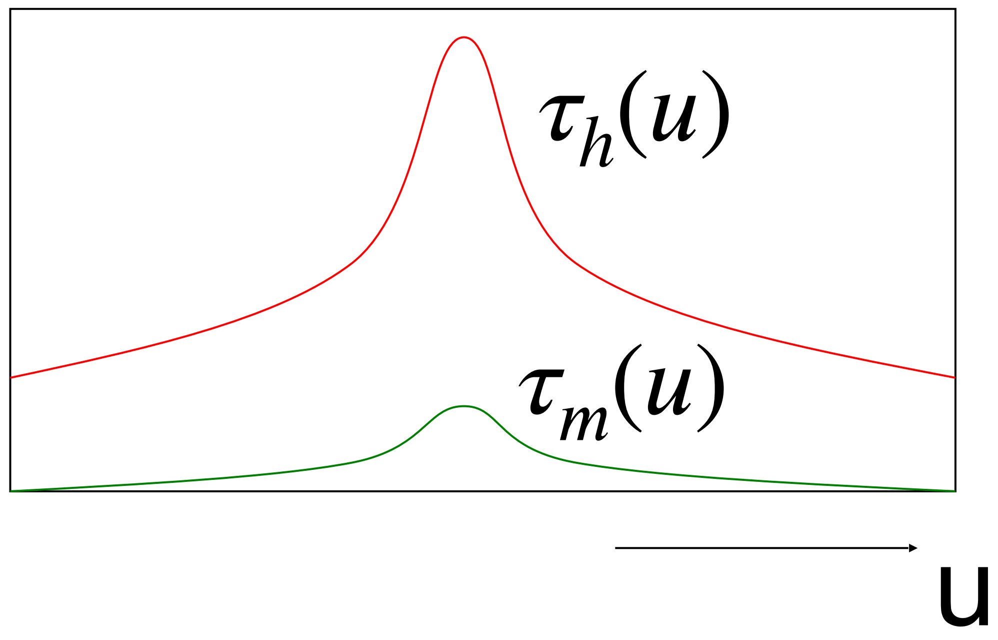

I_{Na} I_K I_{leak} Stim.

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

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Neuronal Dynamics – 2.4. Threshold in HH model

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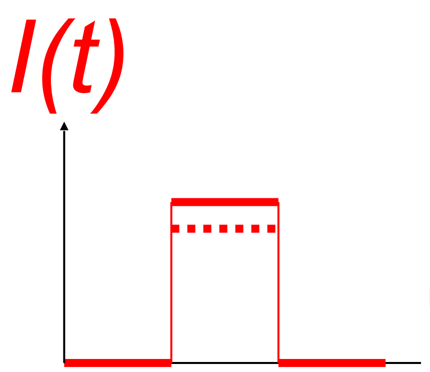

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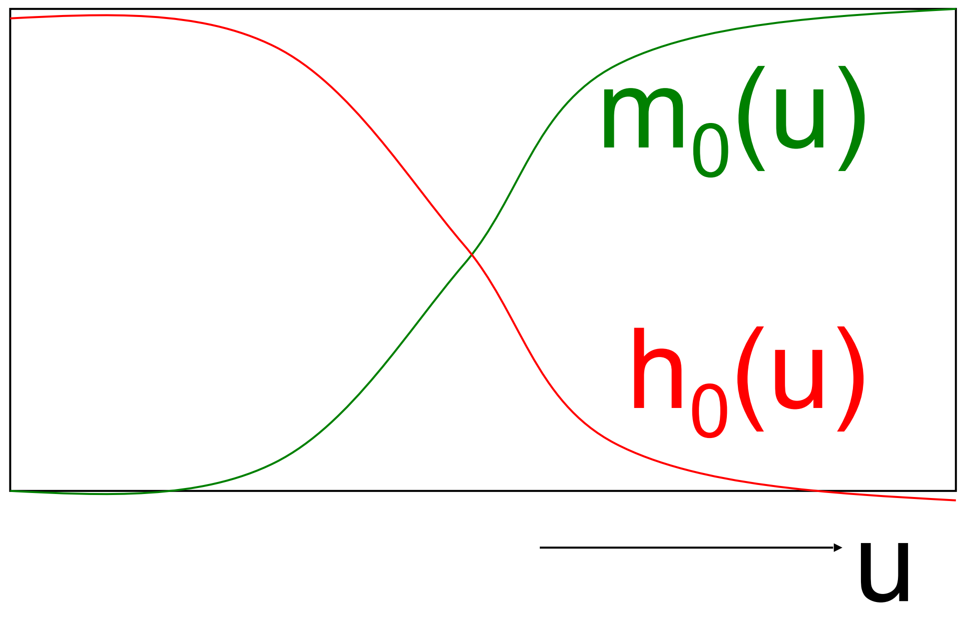

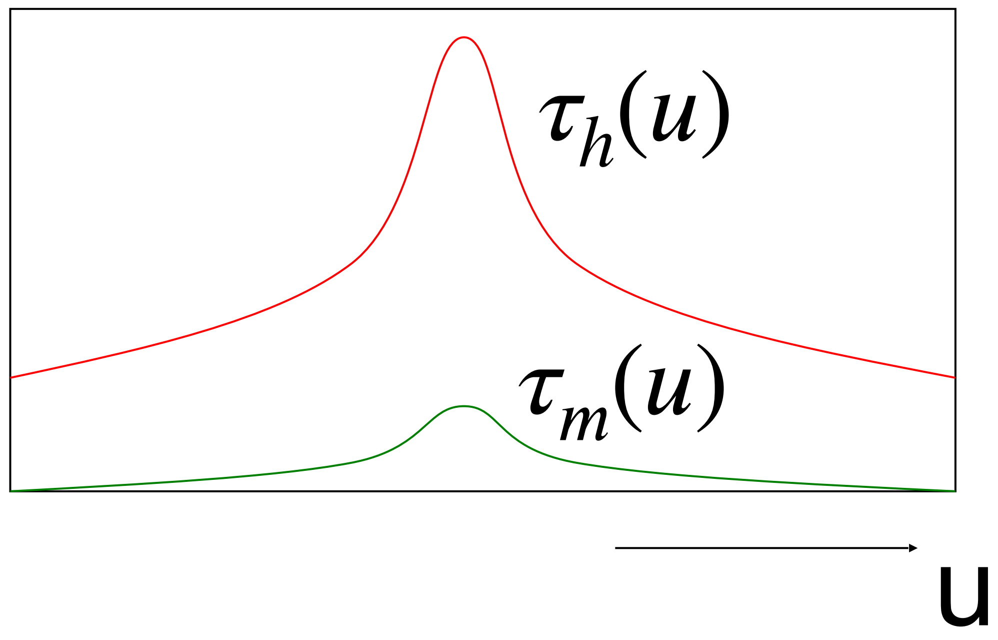

What instability triggers the AP?

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

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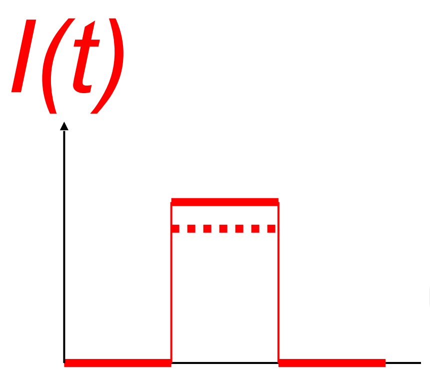
Neuronal Dynamics – 2.4. Threshold in HH model

pulse input



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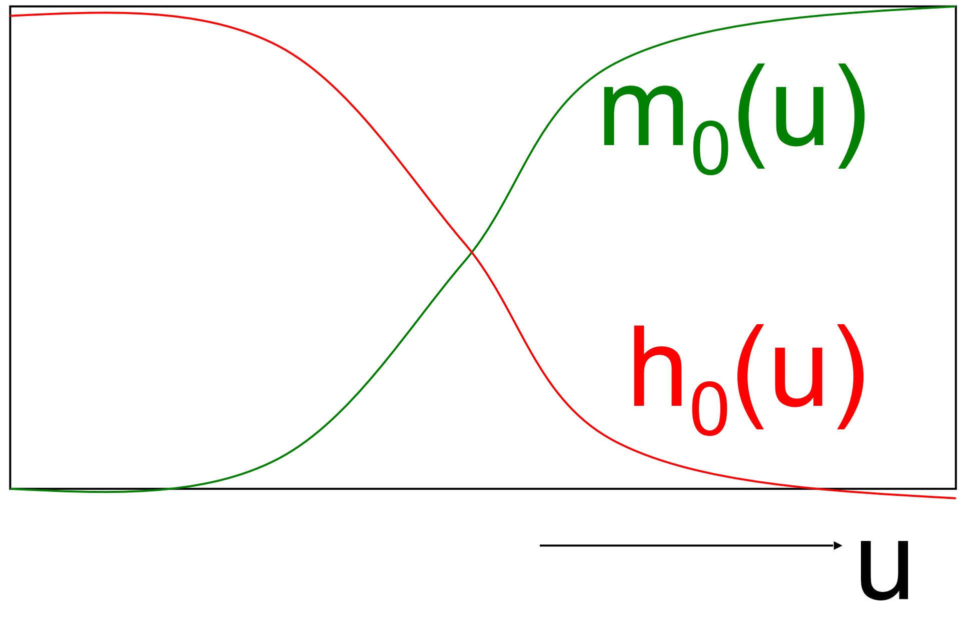

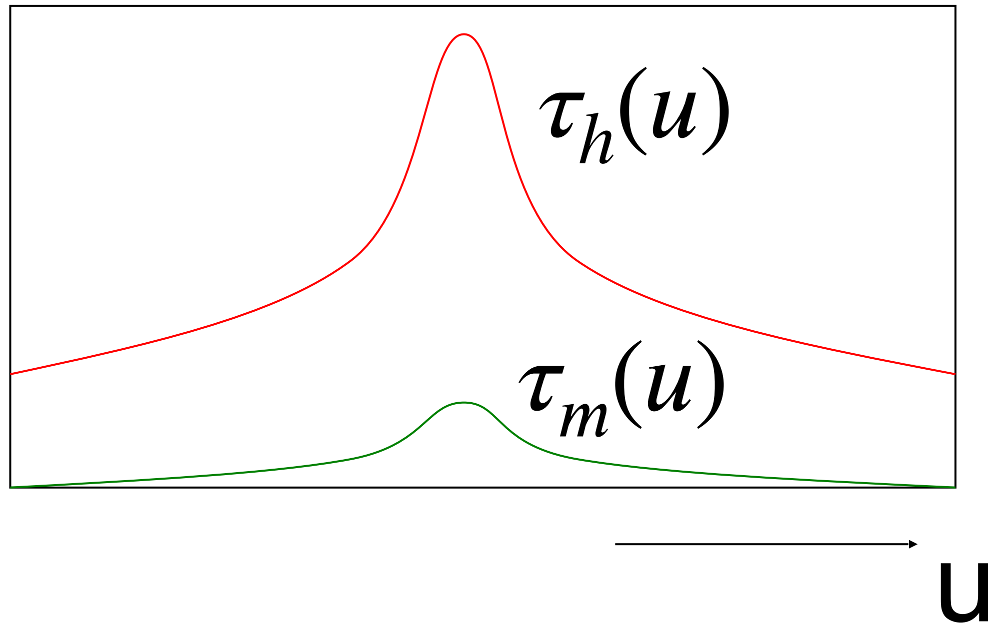

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Why start the explanation with *m* and not *h*?

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Neuronal Dynamics – 2.4. Threshold in HH model

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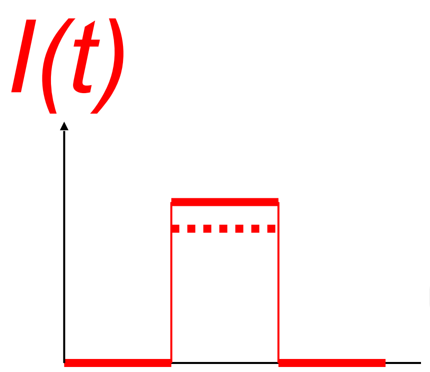

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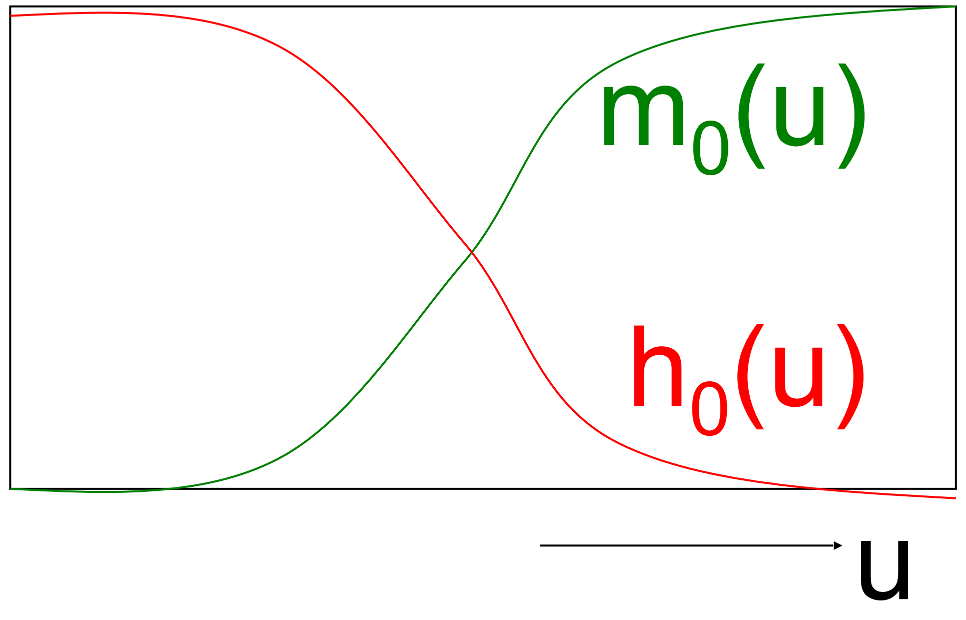

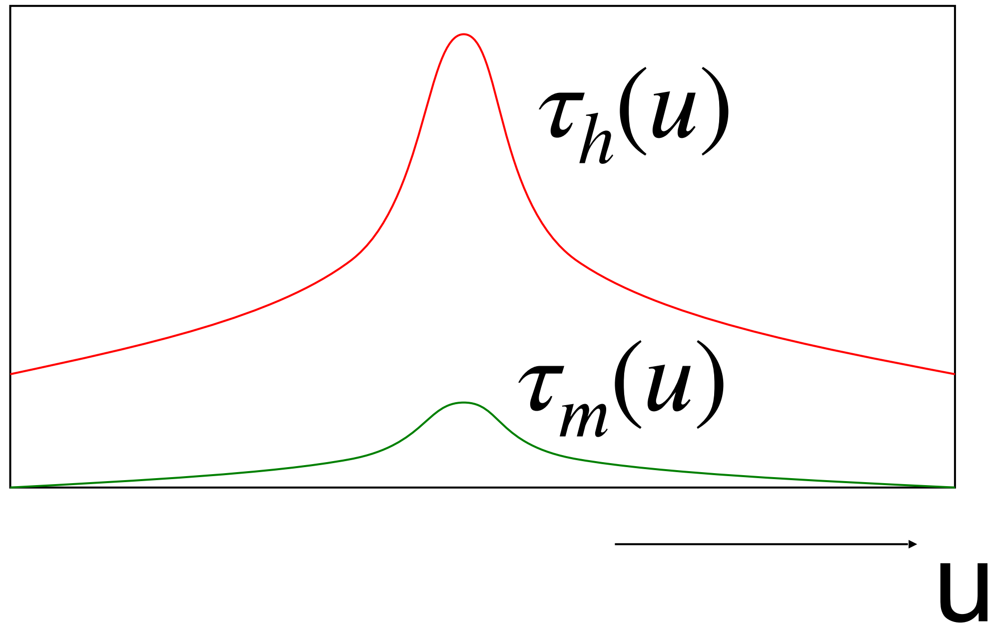

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What about τ_n ?

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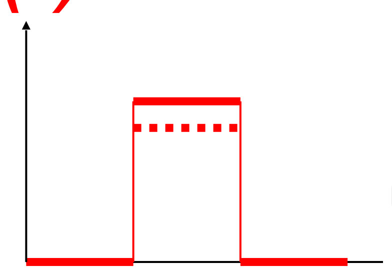
Neuronal Dynamics – 2.4. Threshold in HH model

pulse input



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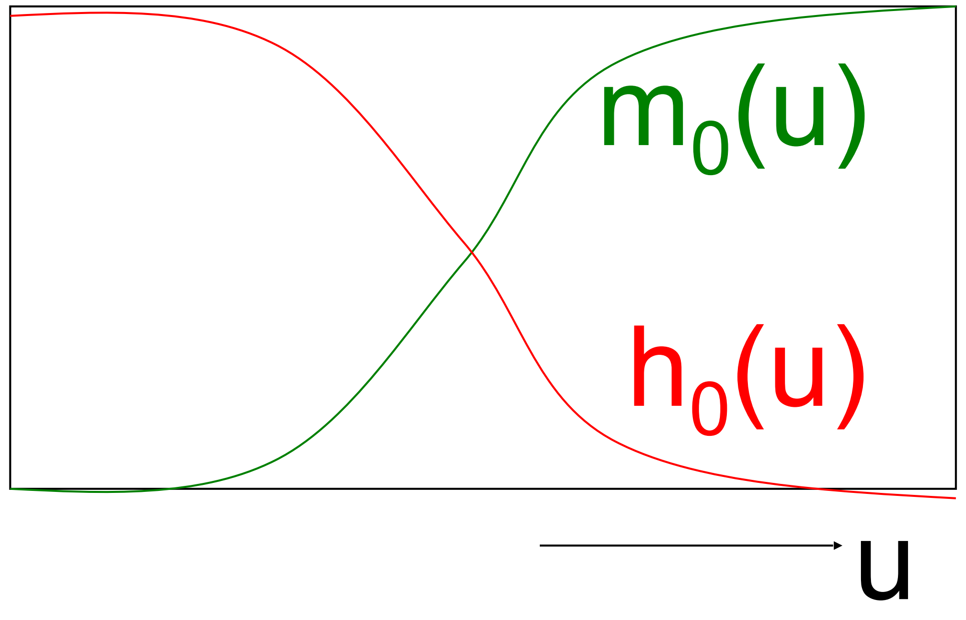

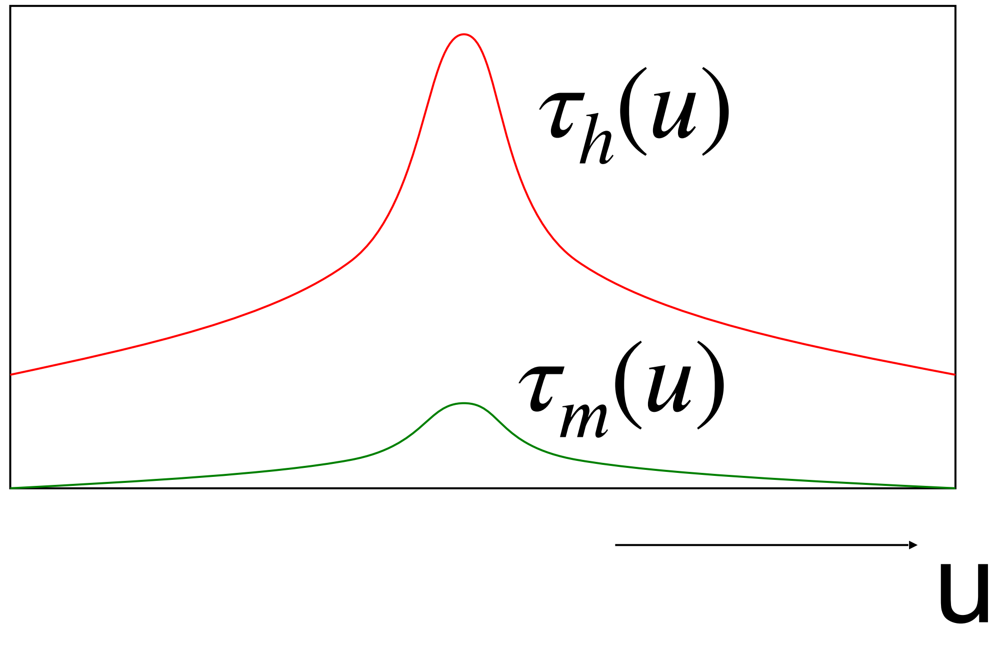

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Why start the explanation with *m* and not *h*?

What about τ_n ?

What limits the maximum the of AP?

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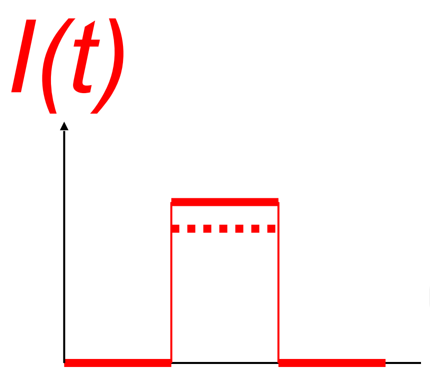
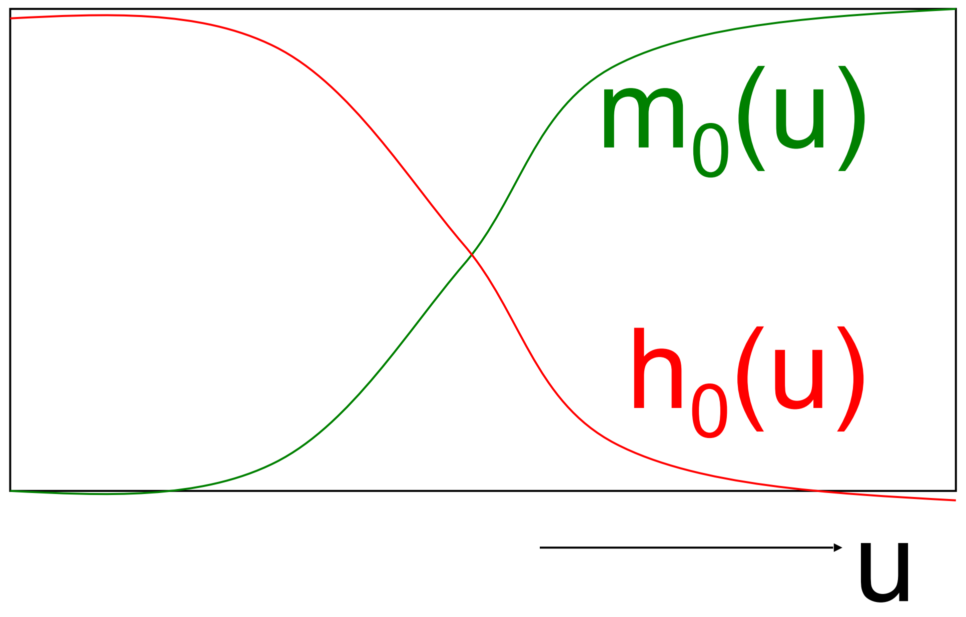
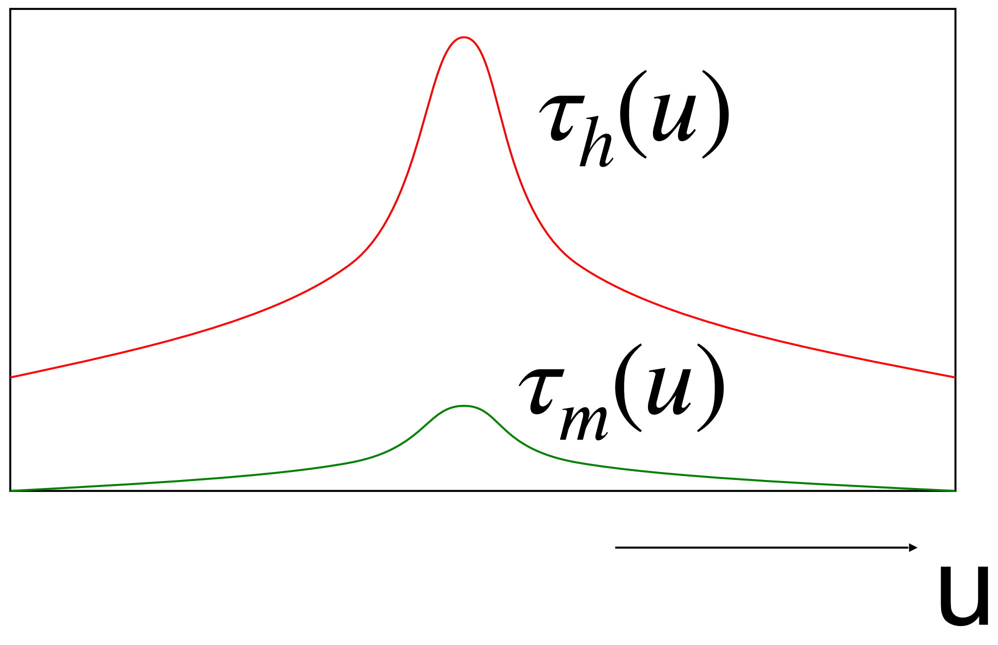
Neuronal Dynamics – 2.4. Threshold in HH model

pulse input



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





What instability triggers the AP?

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

What about τ_n ?

What limits the maximum the of AP?

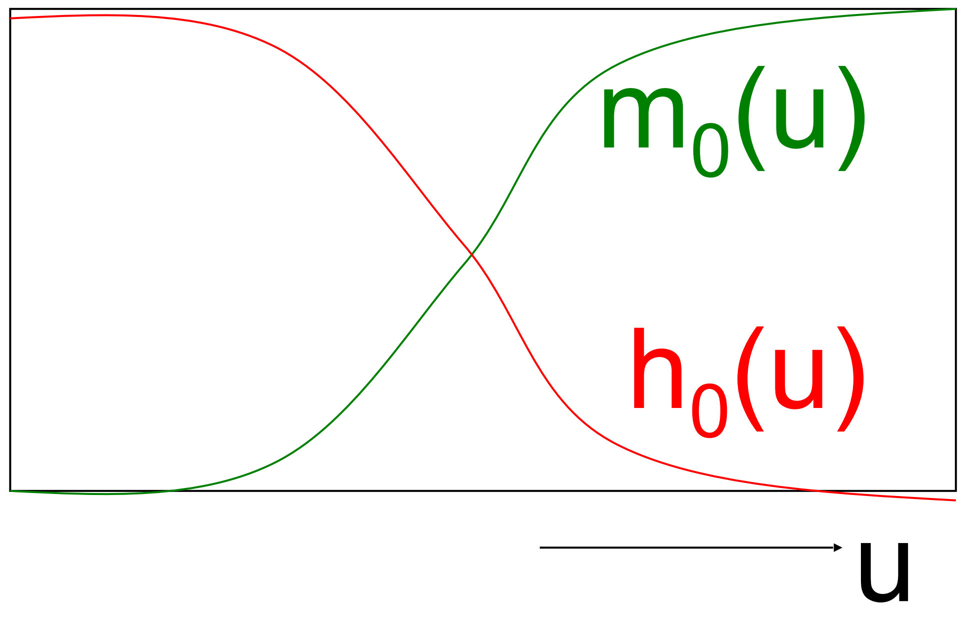
Where is the threshold of AP firing?

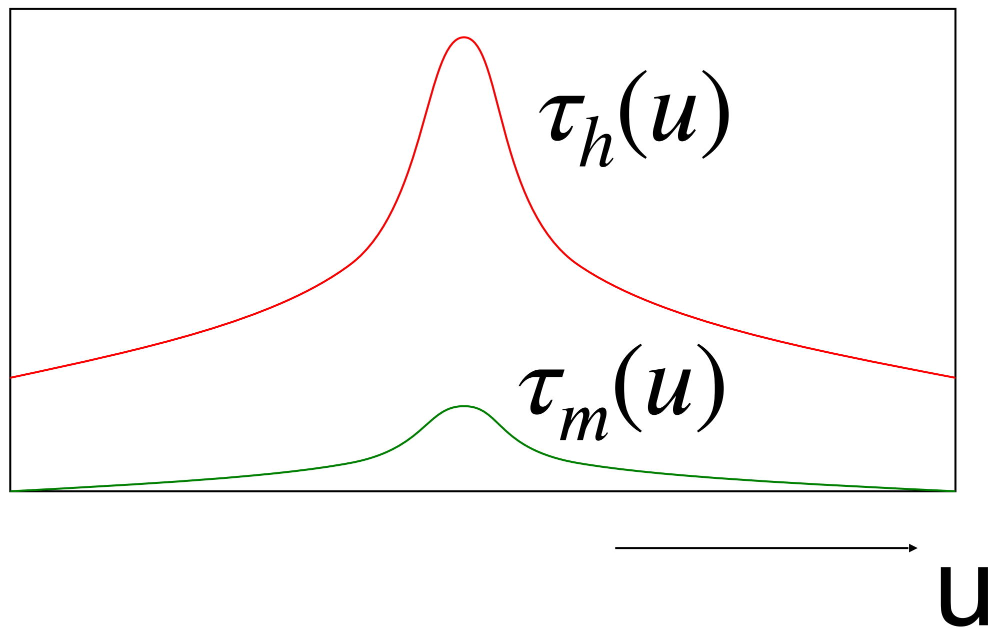
$$C\frac{du}{dt} = -\underbrace{g_{Na}m^3h(u - E_{Na})}_{I_{Na}} - \underbrace{g_K n^4(u - E_K)}_{I_K} - \underbrace{g_l(u - E_l)}_{I_{leak}} + \underbrace{I(t)}_{\text{Stim.}}$$

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

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

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





I_{Na} I_K I_{leak}

I do not see how the 4 equations model the refractory period.

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

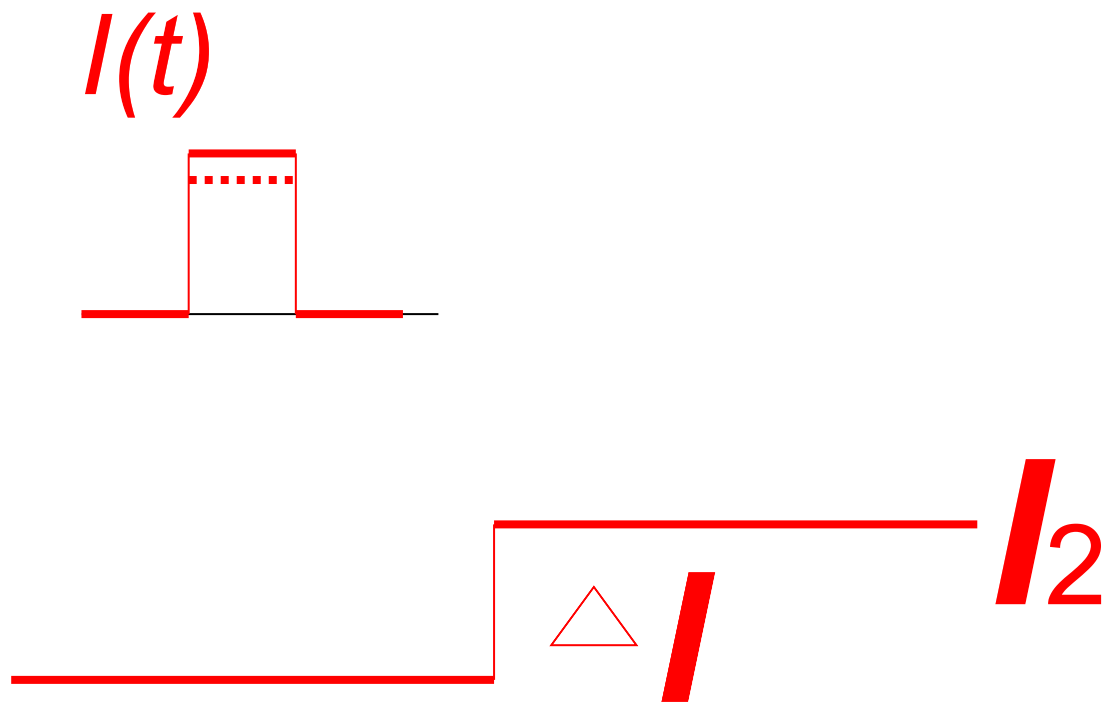
$$\frac{dh}{dt} = -\frac{h - h_0(u)}{\tau_h(u)}$$

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

Will we find the same threshold for these stimulations?

pulse input

step input

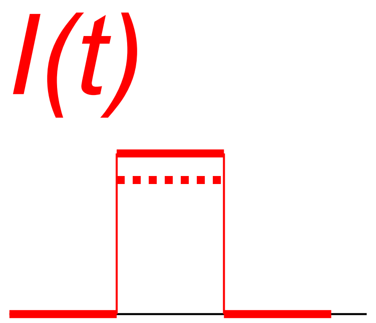


$$C\frac{du}{dt} = -g_{Na}m^3h(u - E_{Na}) - \ldots$$

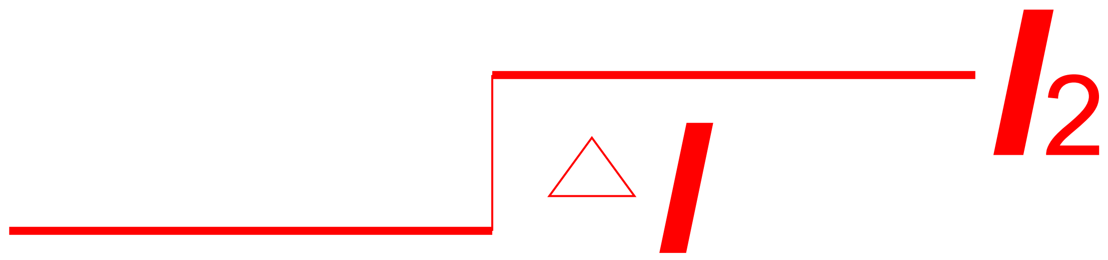
Neuronal Dynamics – 2.4. Threshold in HH model

Will we find the same threshold for these stimulations?

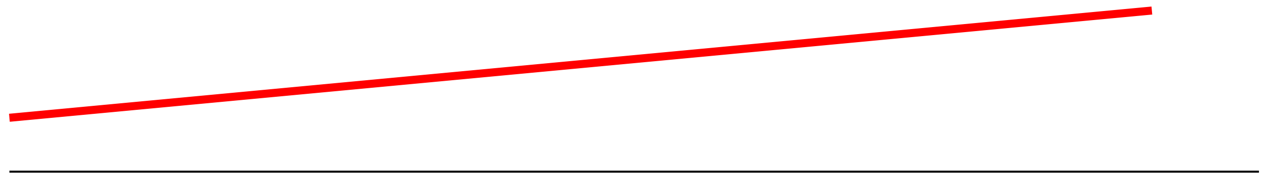
pulse input



step input



ramp input



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

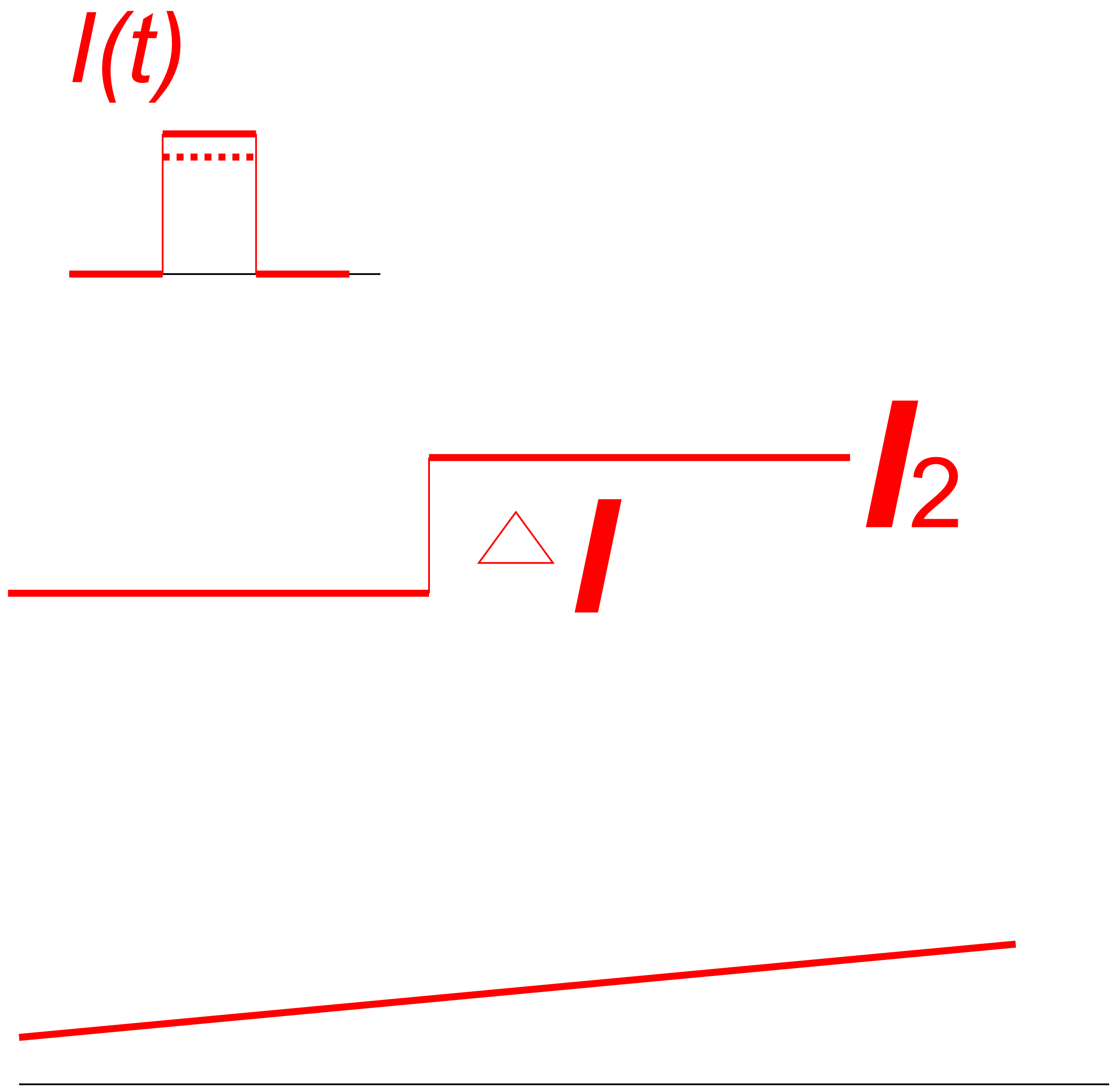
Neuronal Dynamics – 2.4. Threshold in HH model

Will we find the same threshold for these stimulations?

pulse input

step input

ramp input



There is no threshold

- no current threshold
- no voltage threshold

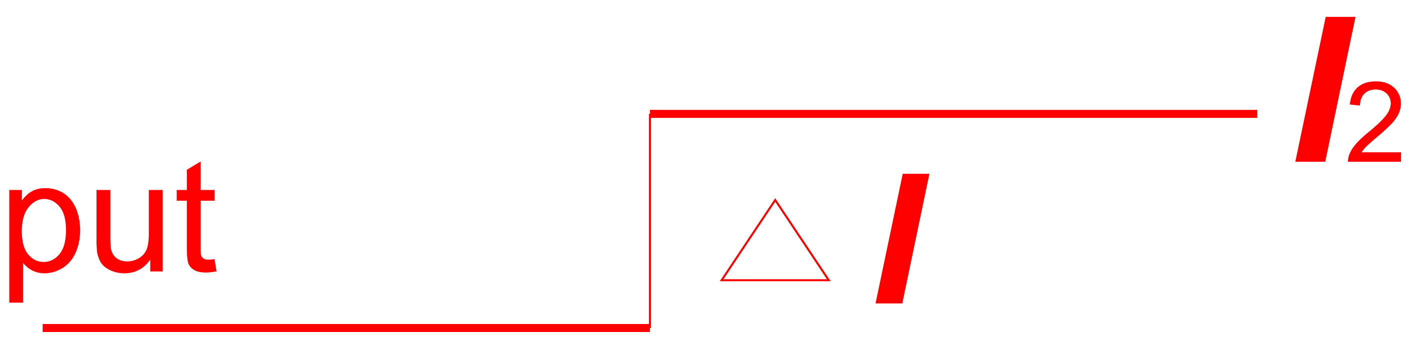
'effective' threshold

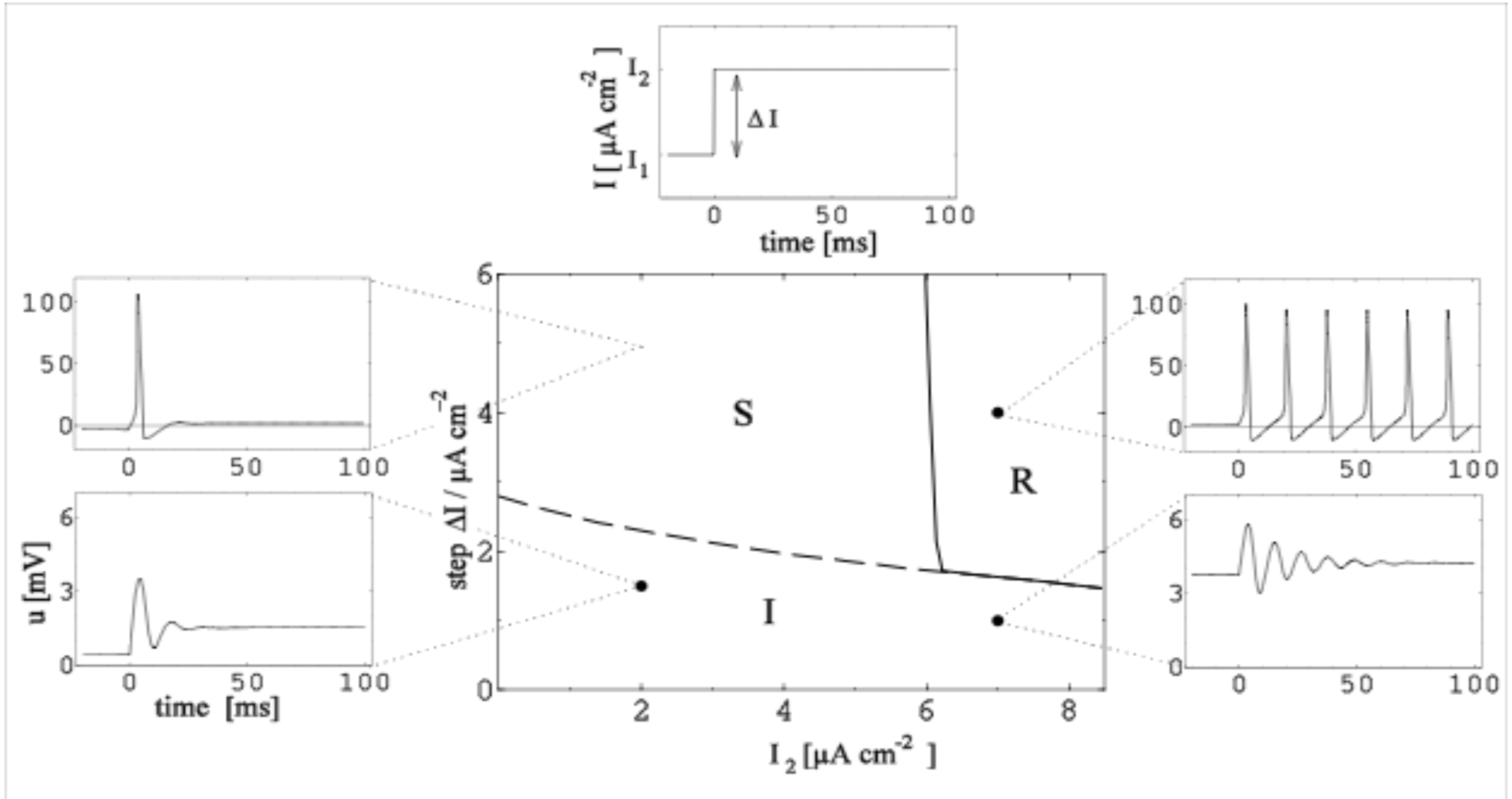
- depends on typical input

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

Neuronal Dynamics – 2.4. Threshold in HH model

Step current input





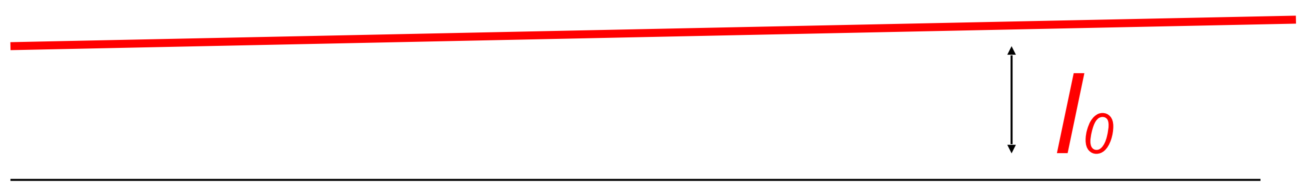
Neuronal Dynamics – 2.4. Type I and Type II

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

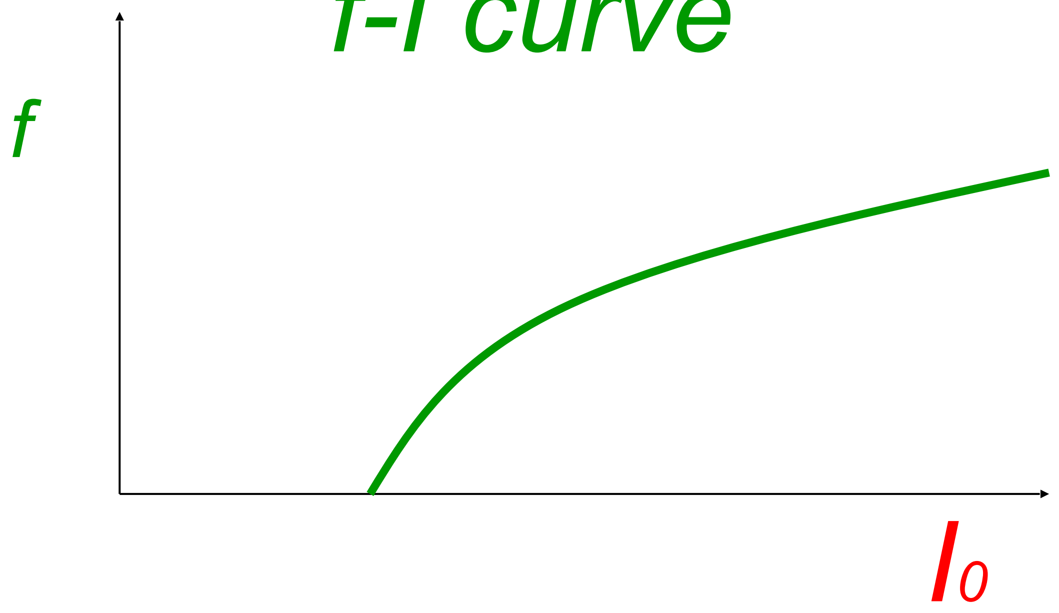
Response at firing threshold?

Type I	type II

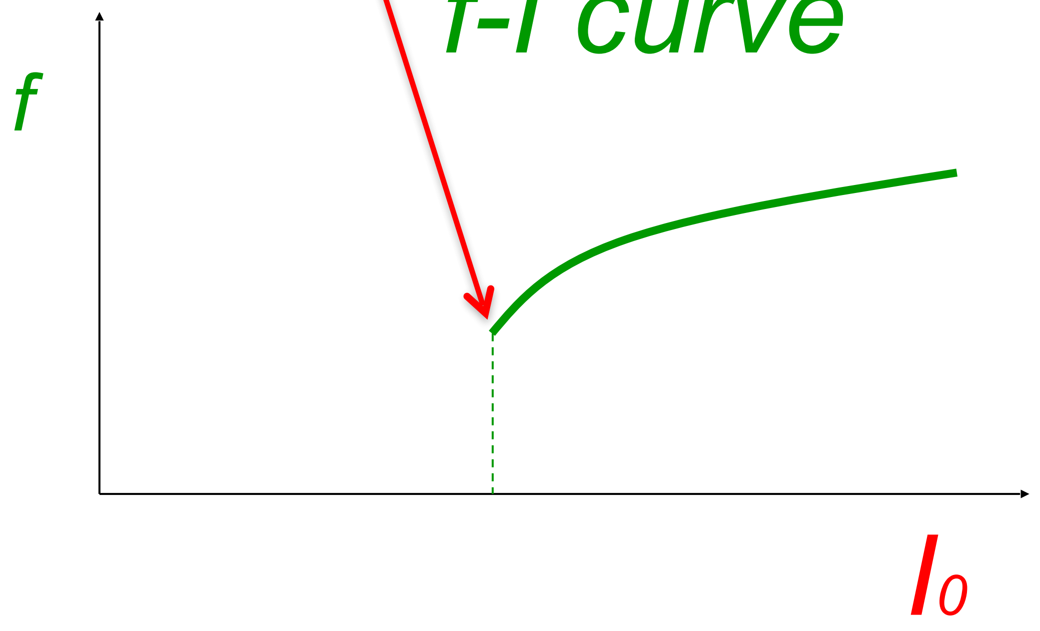
ramp input/
constant input



f-I curve



f-I curve



Neuronal Dynamics – 2.4. Type I and Type II

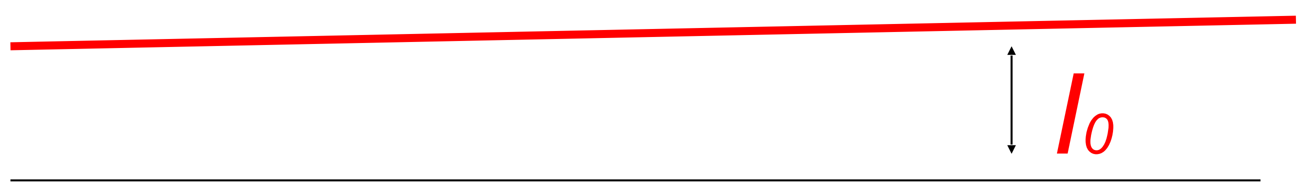
Hodgkin-Huxley model
with other parameters
(e.g. for cortical pyramidal
Neuron)

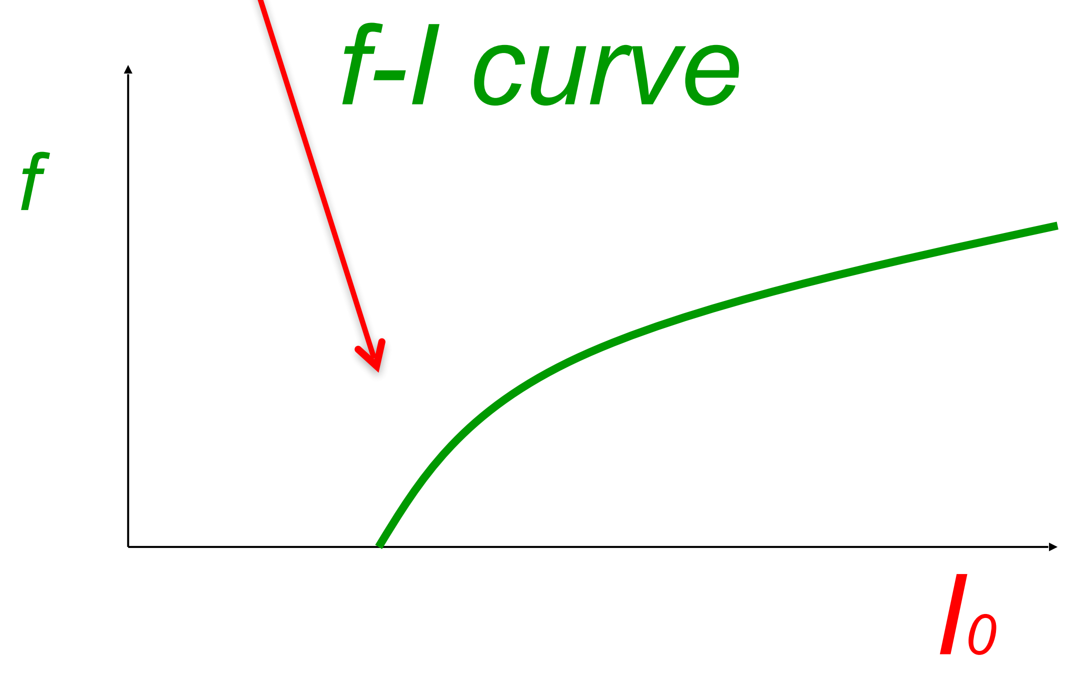
Hodgkin-Huxley model
with standard parameters
(giant axon of squid)

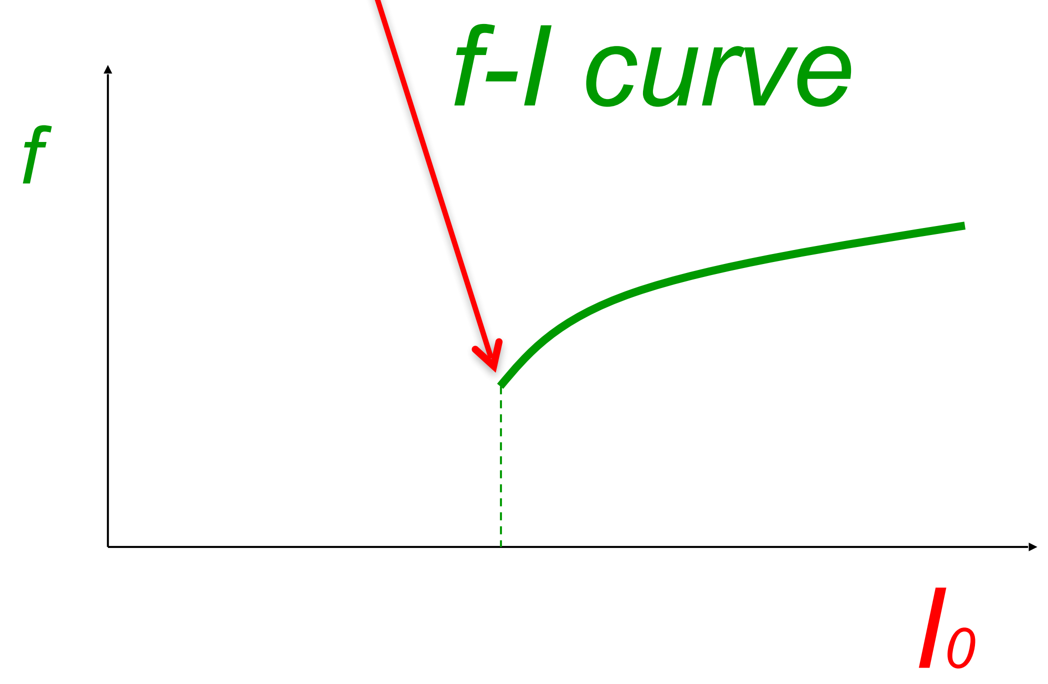
Response at firing threshold?

Type I	type II

ramp input/
constant input







Original HH Model:

-4 differential equations

-no explicit threshold

-effective threshold depends on stimulus

-BUT: voltage threshold good approximation

Neuronal Dynamics – 2.4. Hodgkin-Huxley model

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

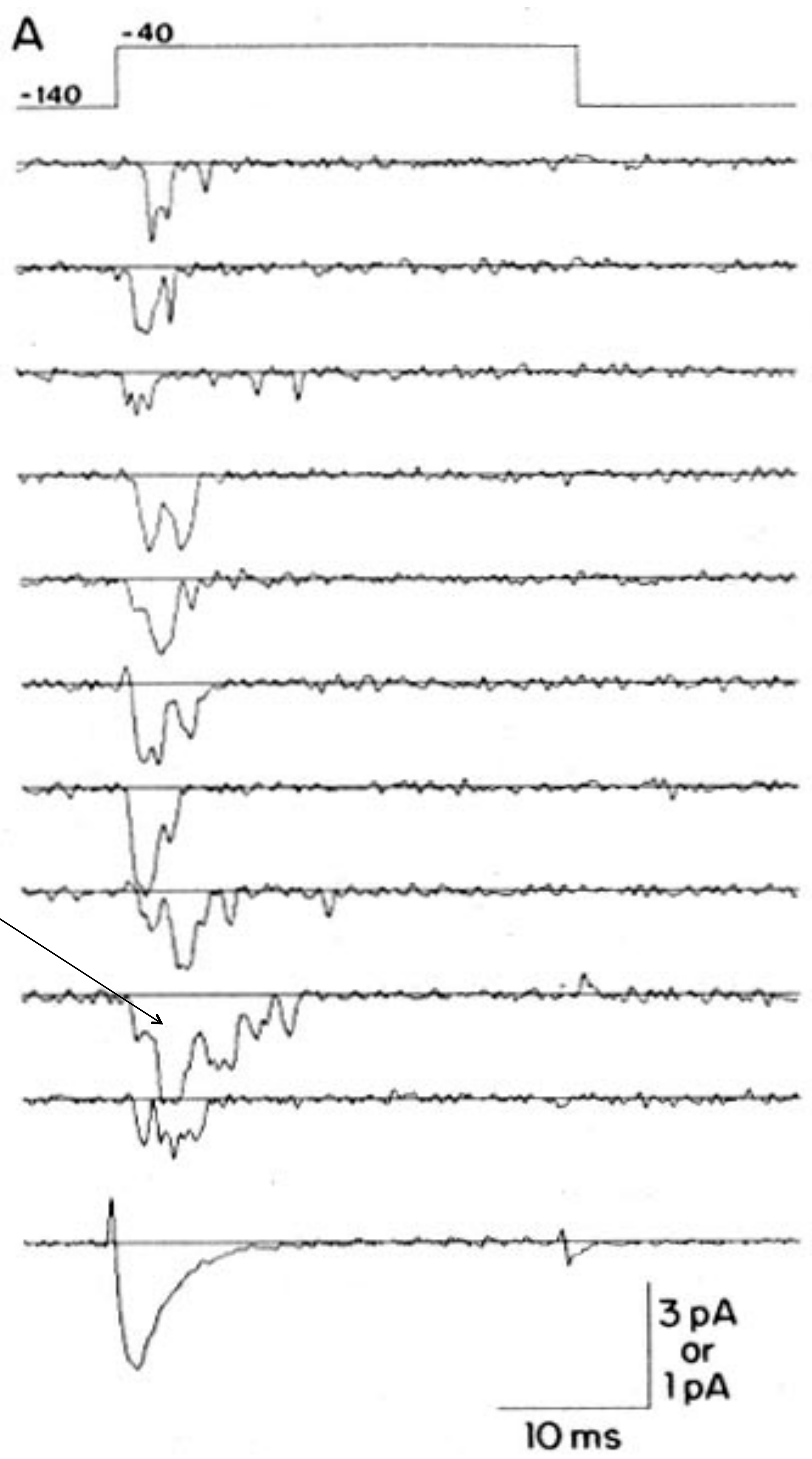
Extended HH Model:
Giant axon of the squid
→ cortical neurons
-Change of parameters
-More ion channels
-Same framework

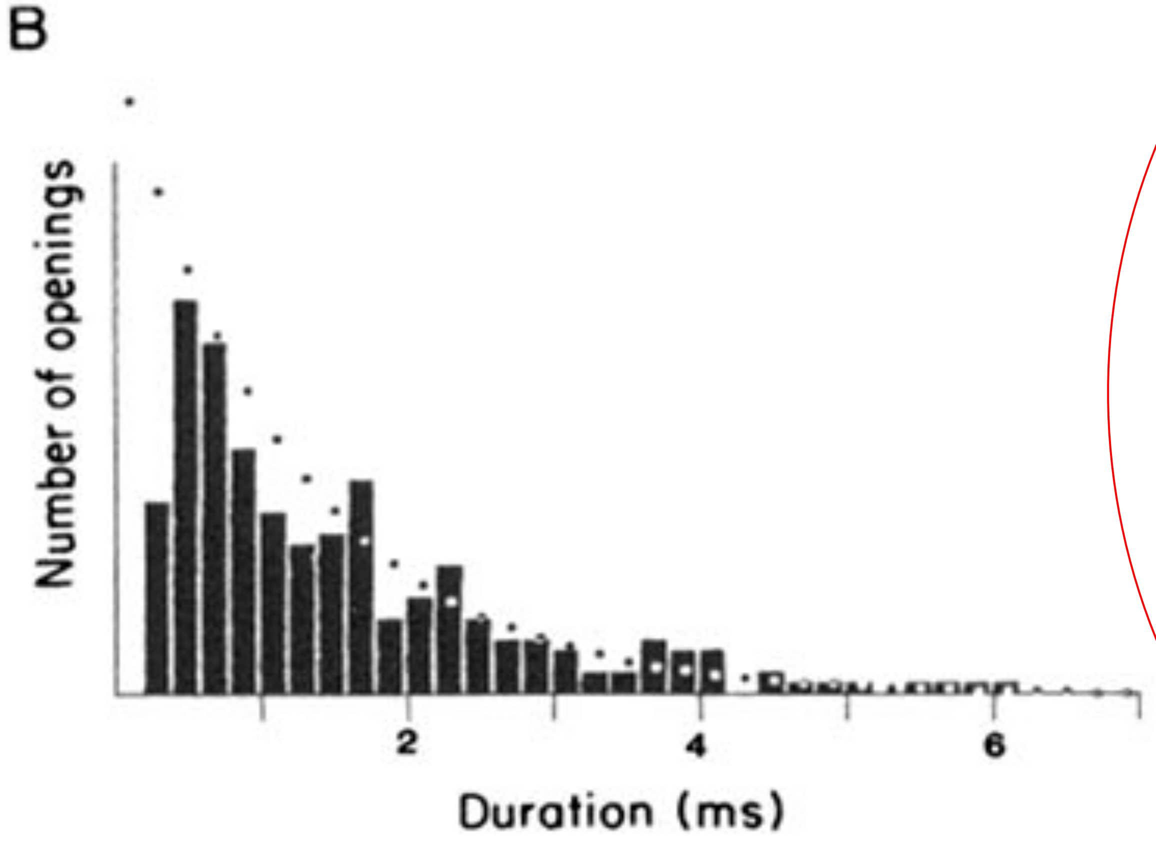
Summary of Section 2.4.

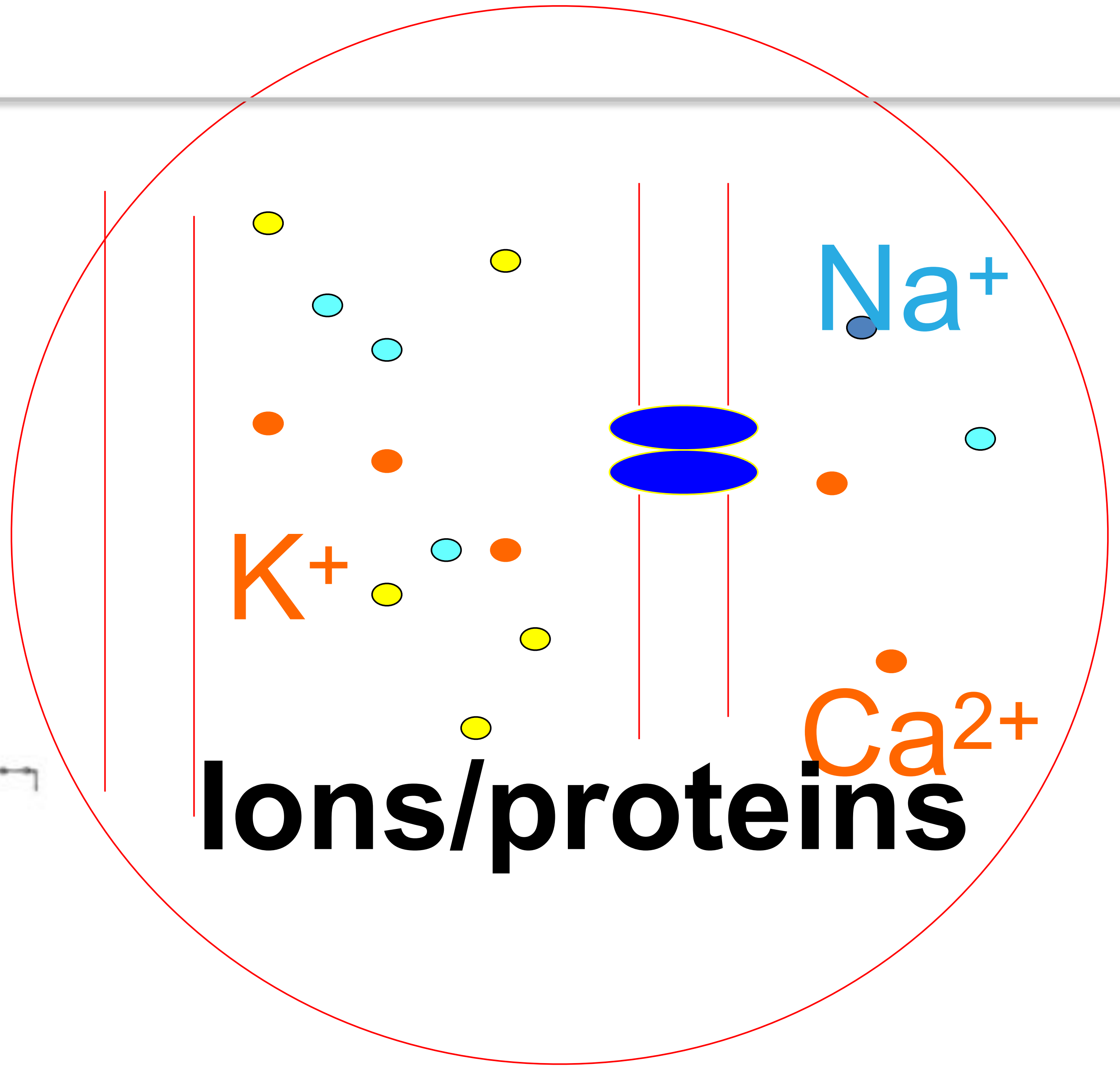
- The dynamics of opening and closing of ion channels is described by gating variables m,h, and n.
- The time ‘constants’ of the differential equations for m,h,n capture the time it takes to switch from the closed state to the open state and vice versa.
- The ‘time constants’ are not constant, but depend on the voltage
- As a consequence of the four-dimensional dynamics, there is no fixed spiking threshold for the Hodgkin-Huxley model
- If we search for a spiking threshold, the result depends on the stimulation paradigm that we choose.
- The f-I curve (for constant input) has a qualitatively different shape for neurons of Type 1 or Type 2.

Neuronal Dynamics – 2.5 Ion channels

Steps:
Different number
of channels



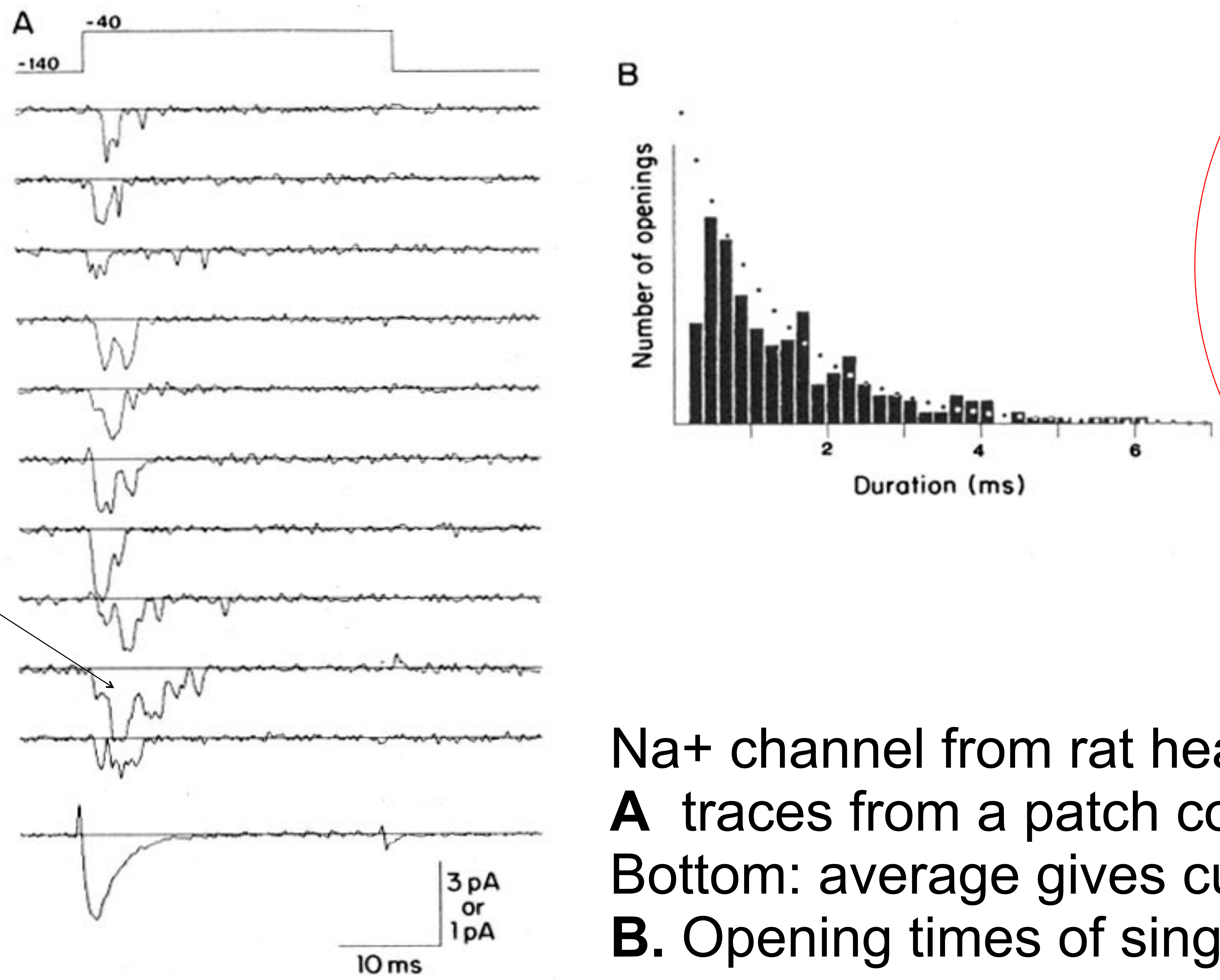


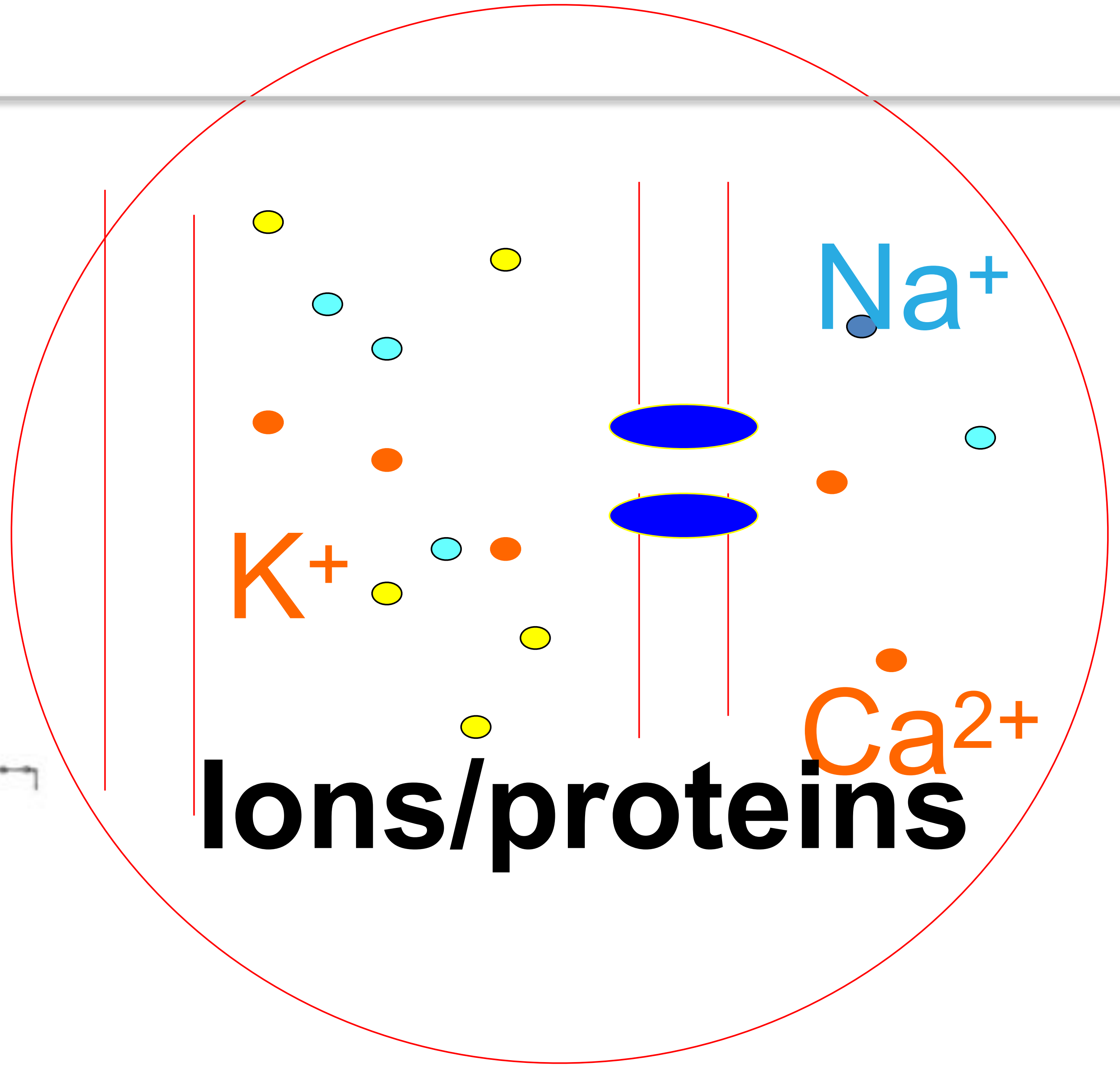


Na+ channel from rat heart *(Patlak and Ortiz 1985)*
A traces from a patch containing several channels.
Bottom: average gives current time course.
B. Opening times of single channel events

Neuronal Dynamics – 2.5 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

Quiz – 2. 5. stochastic ion channels

1) Often the gating dynamics is formulated as

$$\frac{dn}{dt} = \alpha_n(u)(1 - m) - \beta_n(u)m$$

Think of 1000 identical ion channels all held at potential u.

May we interpret $\alpha_m(u)$ *Multiple answers possible!*

[ ] as the probability that a channel transits from close to open?

[ ] as the probability per unit time that a channel transits from closed to open?

[ ] as the rate at which channels transits from closed to open?

[ ] as the probability that a channel is open?

[ ] how would you interpret $n_0(u)$ in a probabilistic setting?

Quiz – 2. 5. stochastic ion channels

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Quiz – 2. 5. stochastic ion channels

1) Often the gating dynamics is formulated as

$$\frac{dn}{dt} = \alpha_n(u)(1-m) - \beta_n(u)m \qquad \frac{dn}{dt} = -\frac{n - n_0(u)}{\tau_n(u)}$$

Think of 1000 identical ion channels all held at potential u.

May we interpret $\alpha_m(u)$ *Multiple answers possible!*

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[ ] how would you interpret $n_0(u)$ in a probabilistic setting?

Summary of Section 2.5.

- The Hodgkin-Huxley model was designed for the giant axon of the squid, but can be generalized to different neuron types.
- While the Hodgkin-Huxley model described only two channel types, more general Hodgkin-Huxley type models can include dozens of different ion channels.
- The dynamics of activation and inactivation of each ion channels is described by two variables that are analogous to m and h in the original model.
- Inactivation variables are irrelevant/absent for some channel types.
- The voltage dependence of time ‘constants’ and ‘activation/inactivation’ curves can be extracted from experiments.
- The Hodgkin-Huxley model has been extremely influential for the development of neuroscience.

Final Remark: Hodgkin-Huxley model and Nobel Prize

Is the Nobel prize for Hodgkin and Huxley (1963) justified?

4 papers published in J. Physiology during 1952, based
on data collected in Plymouth lab during summer 1947,48,49

https://en.wikipedia.org/wiki/Alan_Hodgkin

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.