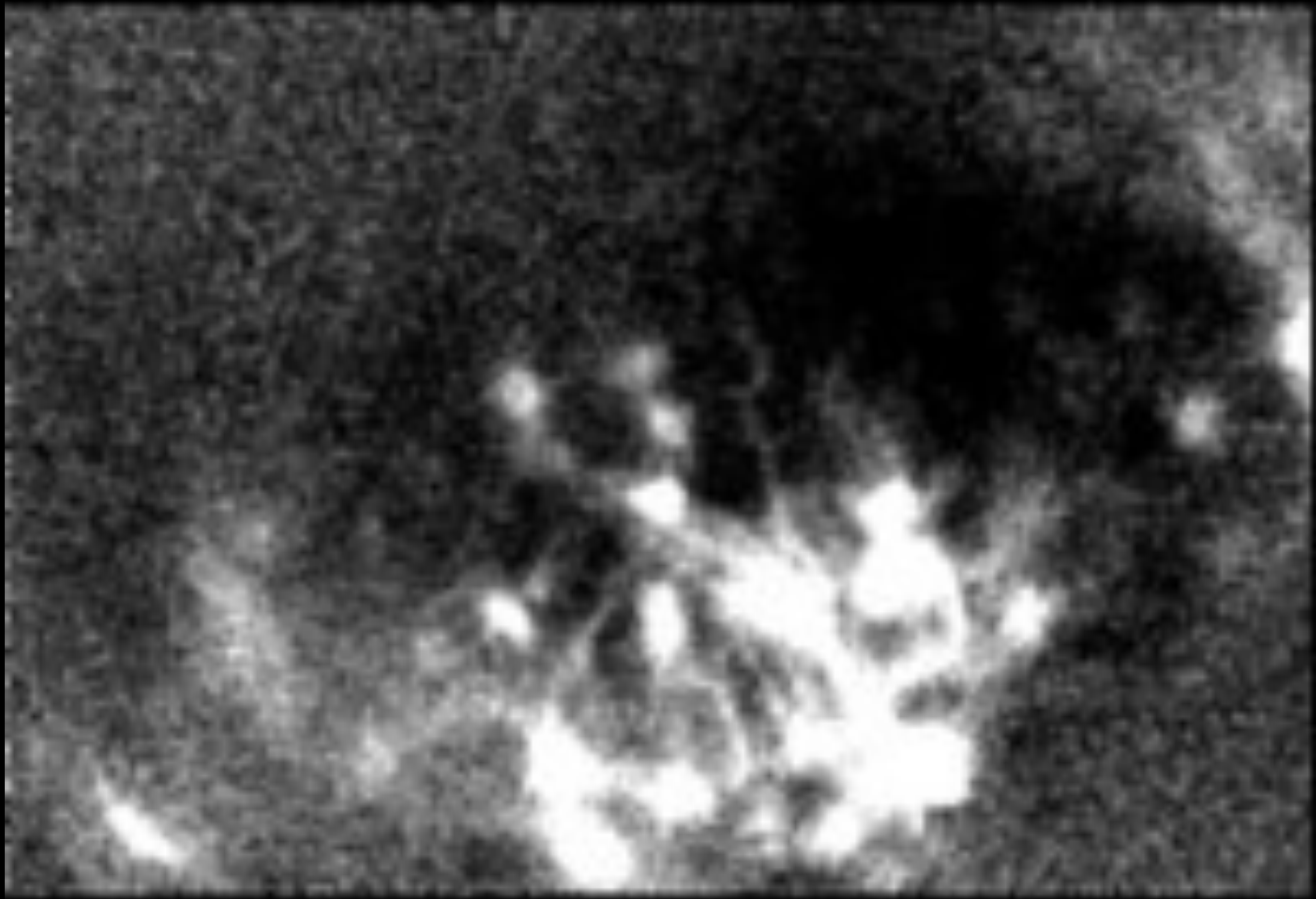
Q355/Q590
Today: Neurophysiology



Stuber lab, UNC - https://www.youtube.com/watch?v=j7aOwjGLOq0

What is happening in that video?

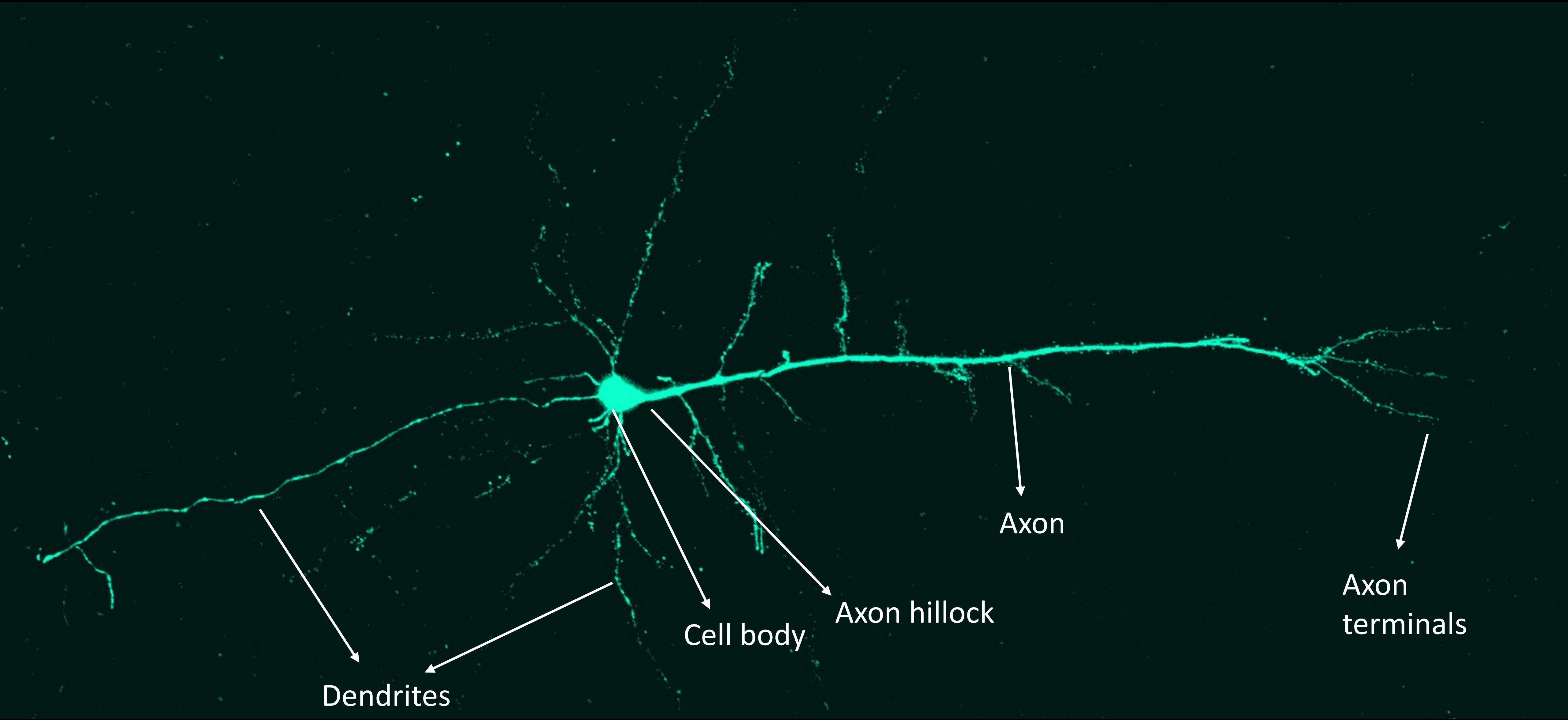
- Neurons are firing
- Neurons are communicating with each other

But, how?

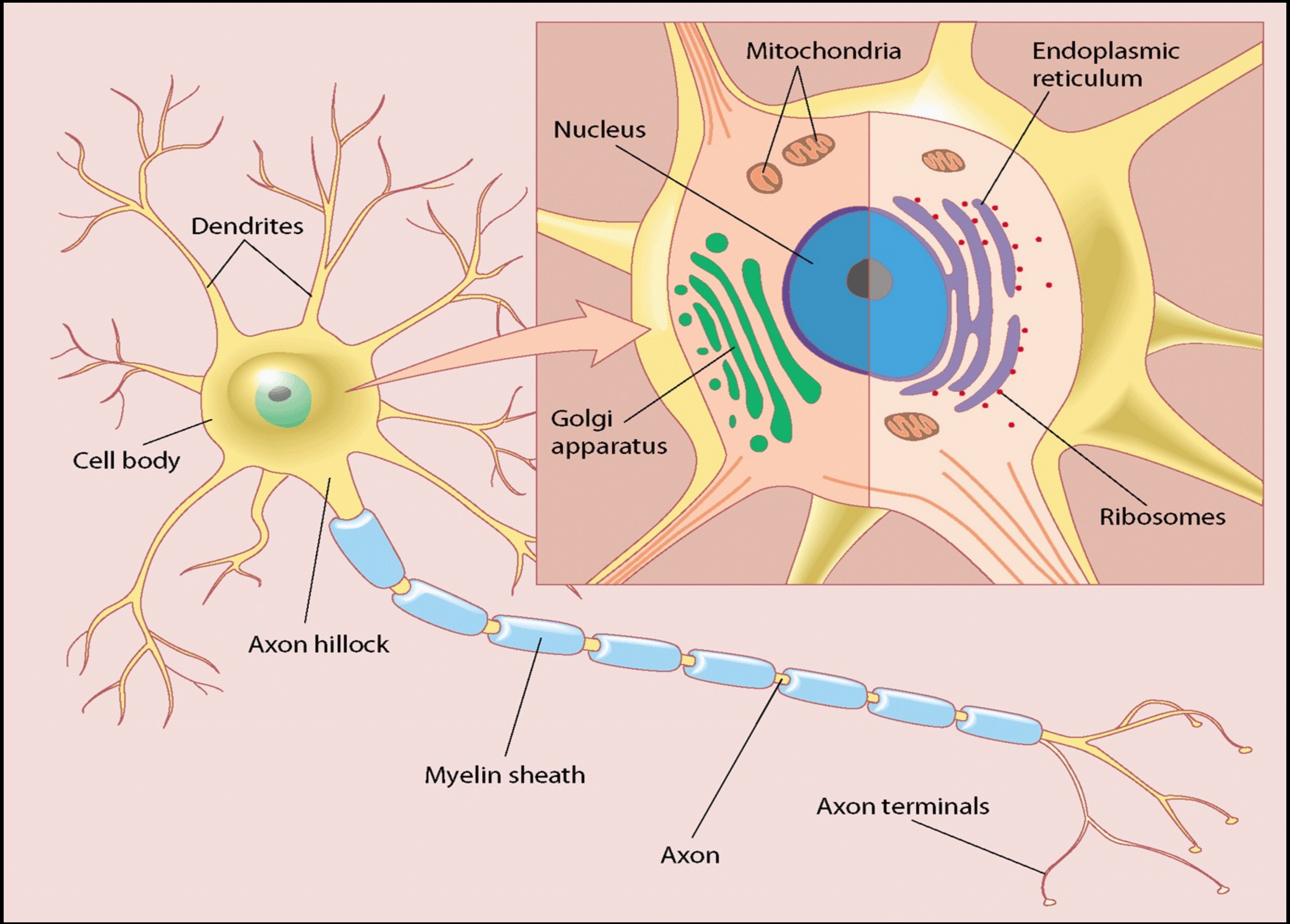
Overview of Lecture

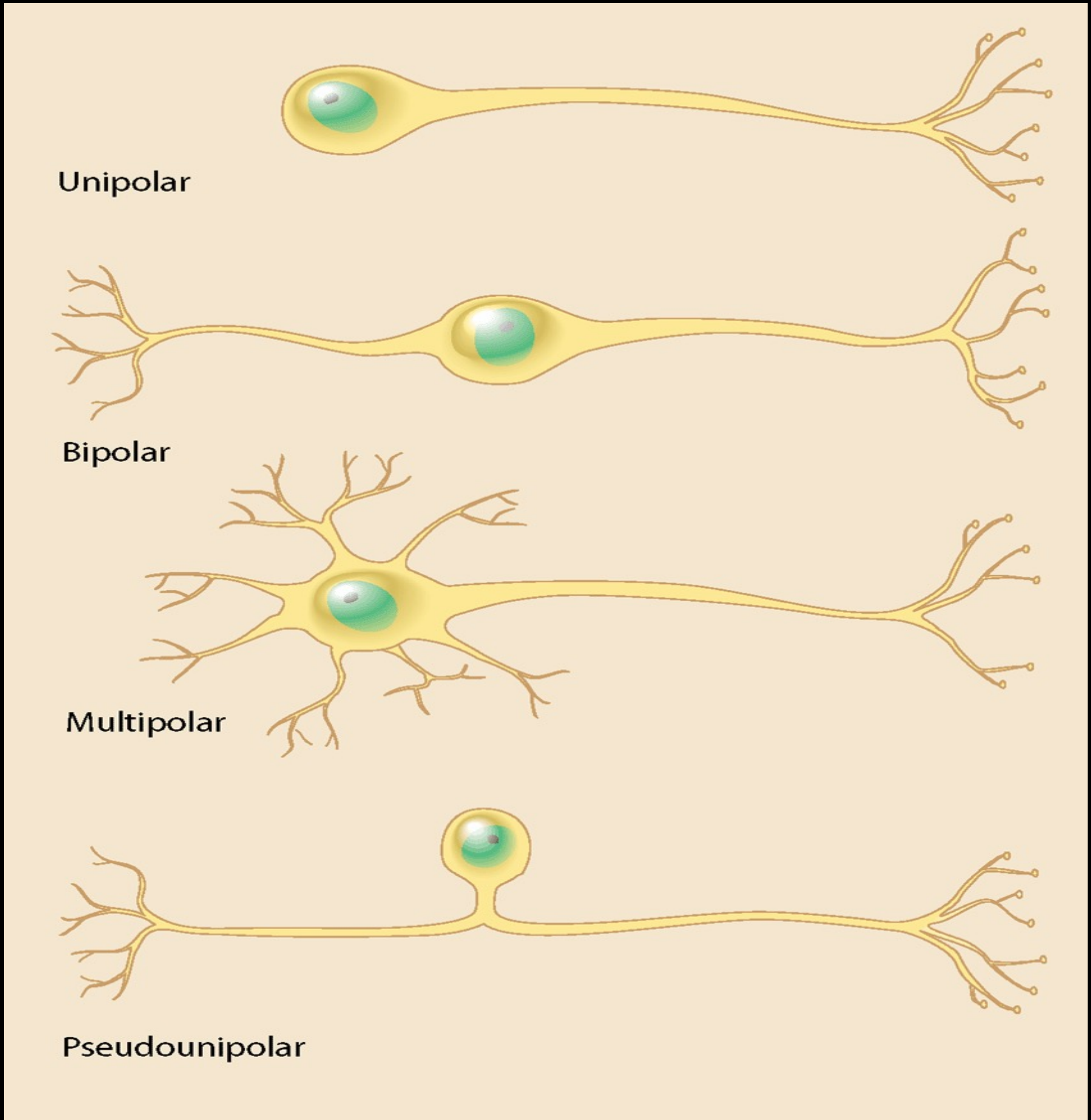
- Neurophysiology of neurons – action potentials
- Hodgkin-Huxley model of action potential generation
- Neurophysiology – transmitter release
- Neurophysiology – learning

What does a single neuron look like?



Stuber lab, UNC - http://www.stuberlab.org/gallery

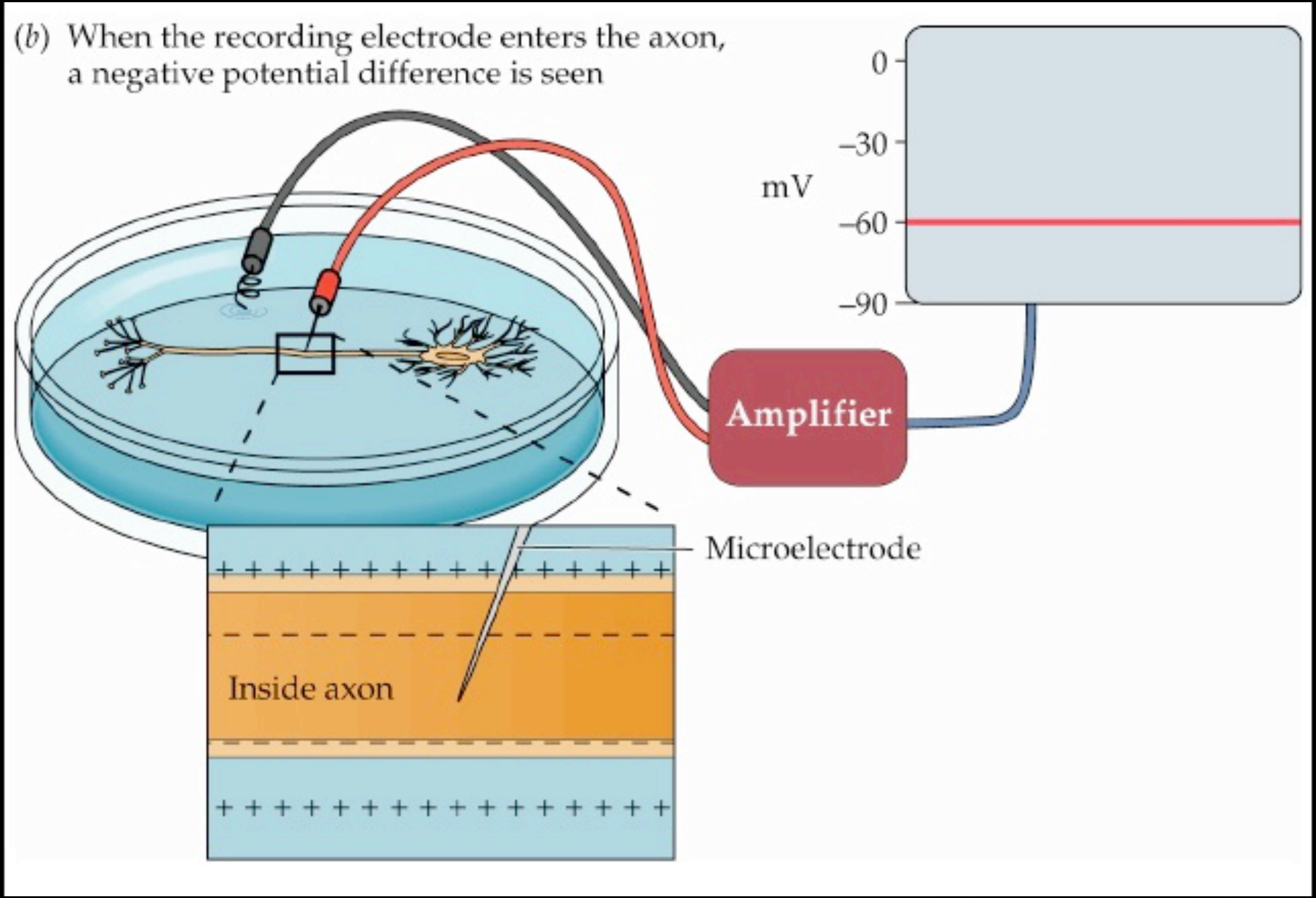

Dendrites
Cell body
Axon hillock
Myelin sheath
Axon
Axon terminals
Mitochondria
Endoplasmic reticulum
Nucleus
Golgi apparatus
Ribosomes



Adapted from Kandel, E.R. Schwartz, J.H., and Jessell, T.M. (Eds.), Principles of Neural Science, 3rd edition. Norwalk, Connecticut: Appleton & Lange, 1991.

How do neurons talk? How is action potential generated?

But first, neuronal membrane potential -



The potential of inside of the resting neuron wrt the outside is negative.

Ionic gradients across the membrane lead to neuronal resting membrane potential

Na+: IN < OUT

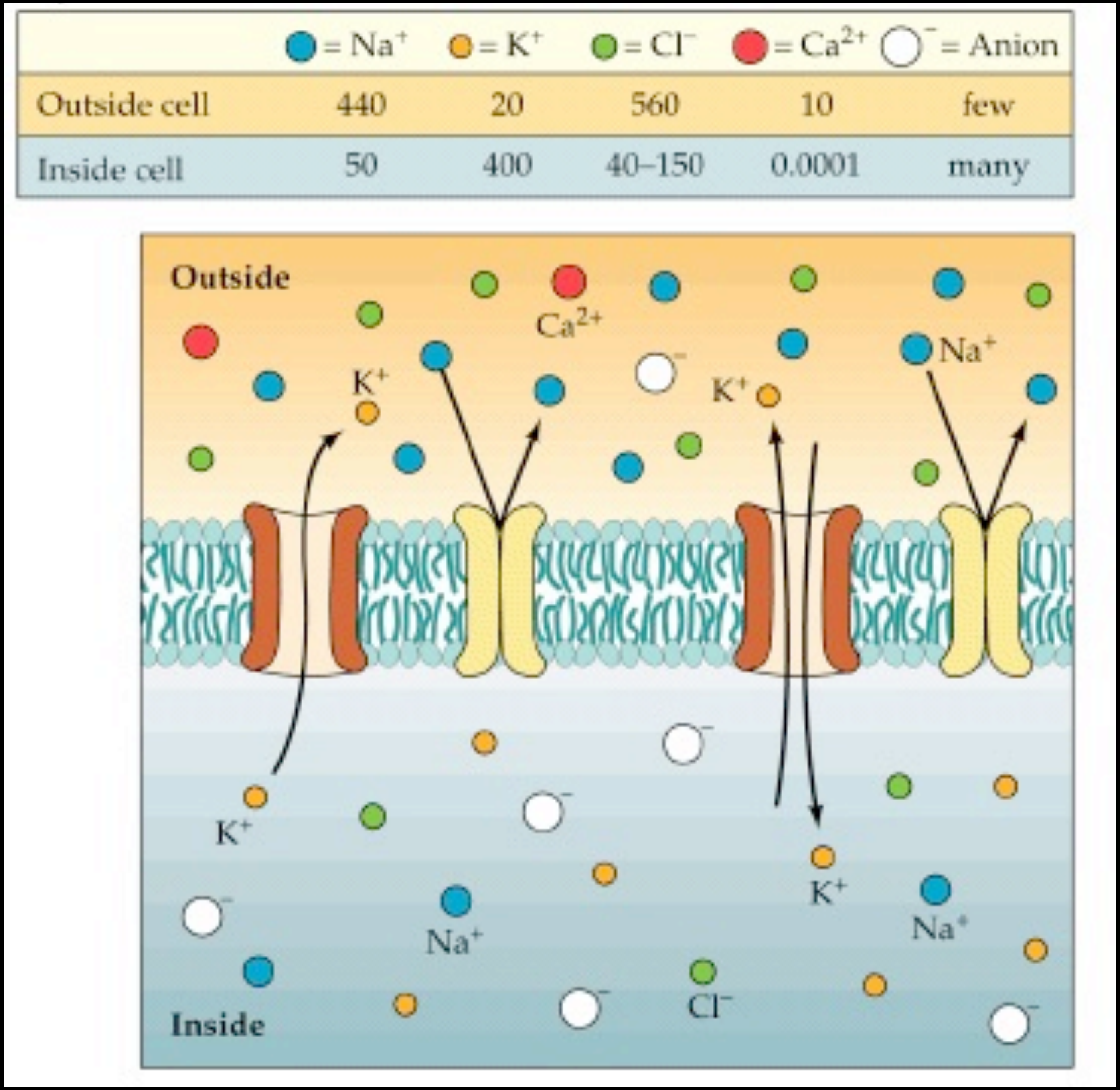
More salty outside!

Cl-: IN < OUT

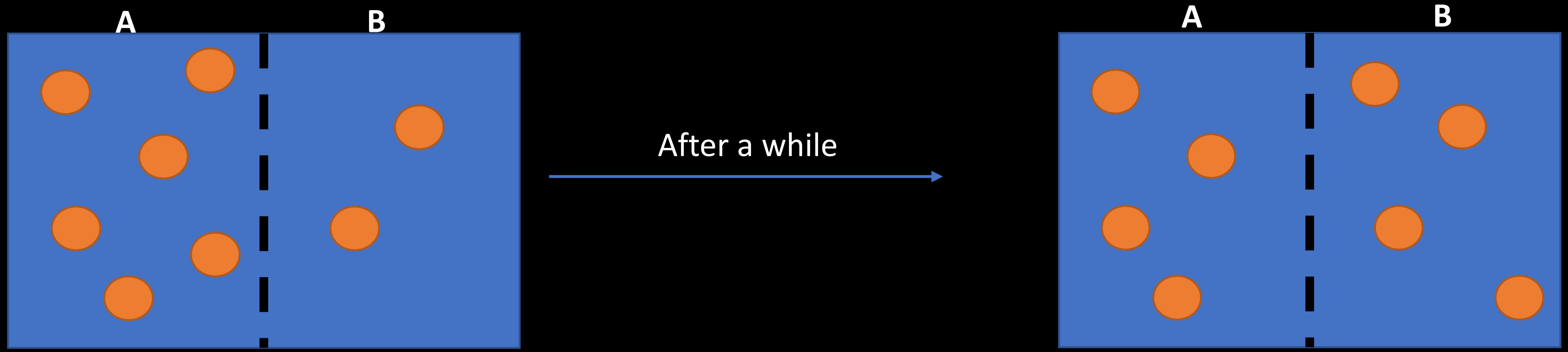
Ca2+: IN < OUT

K+: IN > OUT

A-: IN > OUT



	Na^+	K^+	Cl^-	Ca^{2+}	Anion
Outside cell	440	20	560	10	few
Inside cell	50	400	40–150	0.0001	many

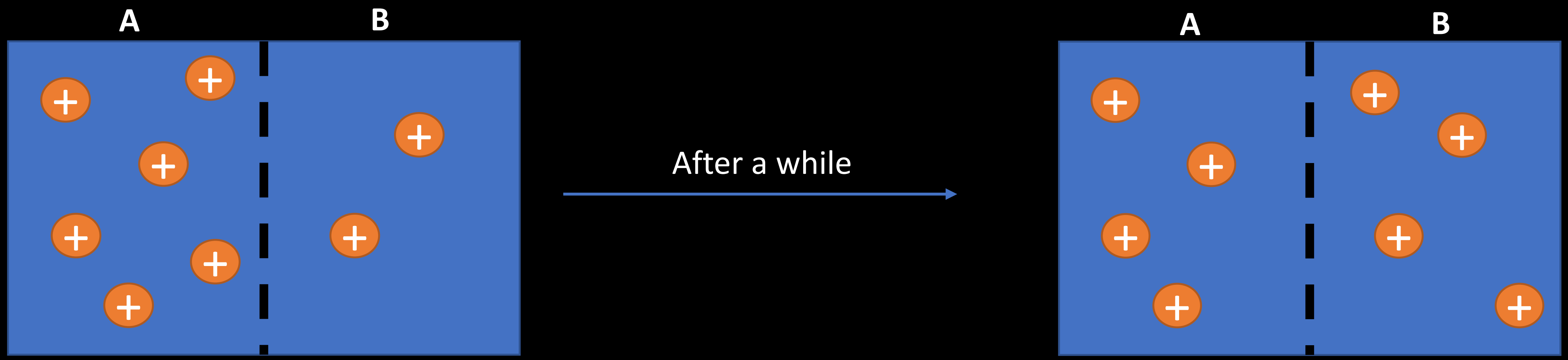


$\mu : A > B, \quad V : A = B$

$Electrochemical\ gradient: \Delta\mu + \Delta V =\ Nonzero$

$\mu : A = B, \quad V : A = B$

$Electrochemical\ gradient: \Delta\mu + \Delta V = 0$

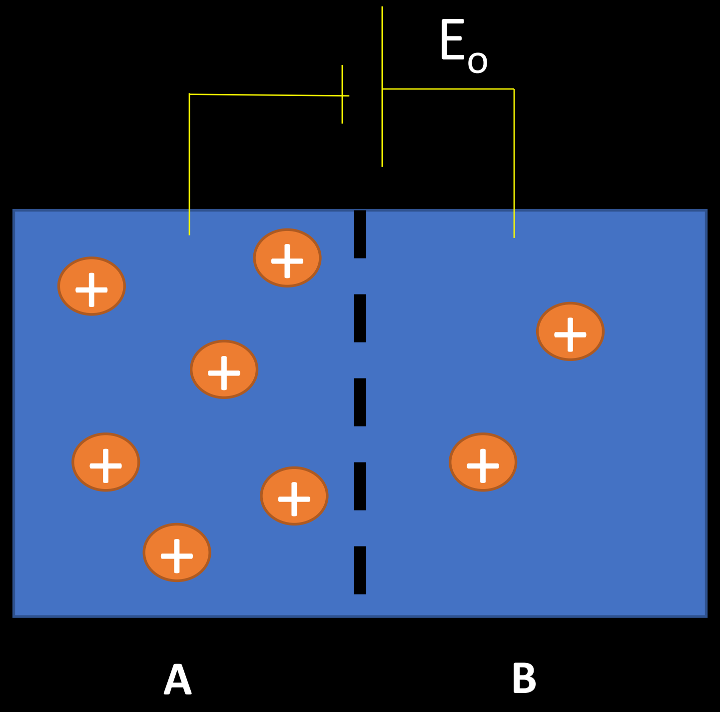


$\mu : A > B, \quad V : A > B$

$Electrochemical\ gradient: \Delta\mu + \Delta V =\ Nonzero$

$\mu : A = B, \quad V : A = B$

$Electrochemical\ gradient: \Delta\mu + \Delta V = 0 + 0 = 0$



The ion gradient between A and B will stay as it is if,

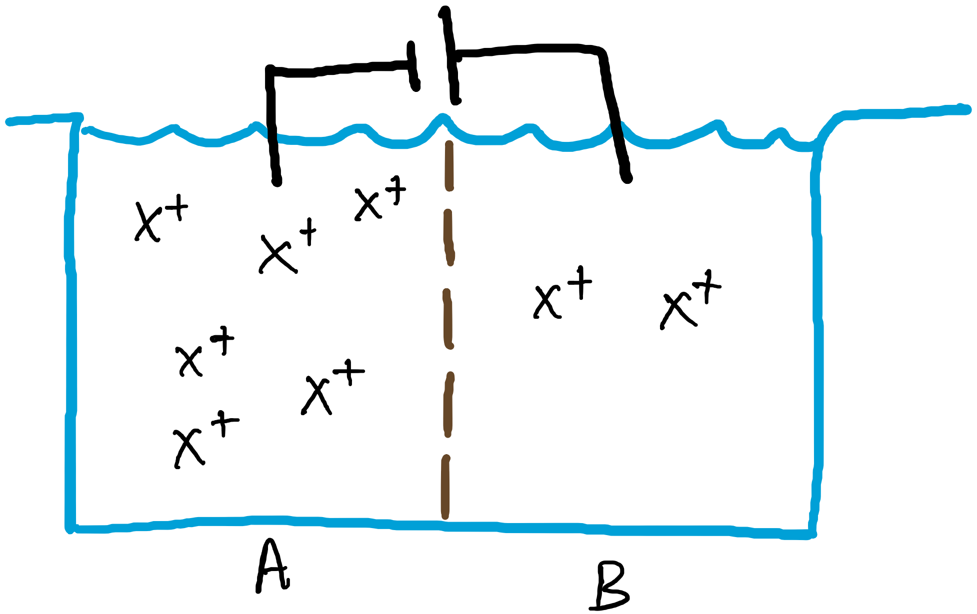
the electrochemical gradient between A and B can somehow be made = 0

In other words, the net electrical potential difference balances the net chemical potential difference between A and B; in several other words, the electrical force on ions cancels out the 'diffusion force'.

Net $\triangle V$ = $\triangle \mu$

This happens when, $E = \frac{RT}{zF} \ln \frac{Ca}{Cb}$ → Nernst Equation

(here, E is electric potential of compartment B wrt A; Ca is concentration of ions in A, and Cb is concentration of ions in B)



$$V = V_B - V_A$$

A: C_A, V_A B: C_B, V_A

1 mole X^+ $\longrightarrow$

- Flows against electrical pot. (Energy required $= zFV$)
- Flows down chemical potential (Gibbs free energy released $= RT \ln\left(\frac{C_A}{C_B}\right)$)

No ions flow between A & B, when

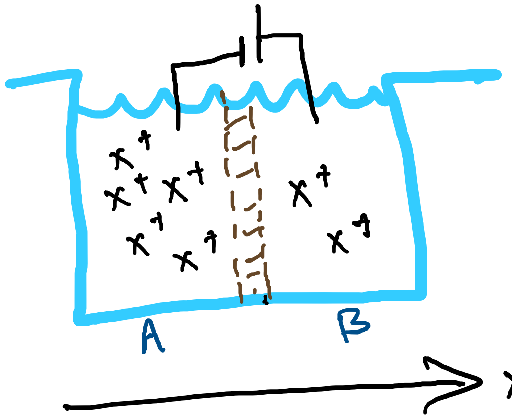
$$zFV = RT \ln\left(\frac{C_A}{C_B}\right)$$

$$V = \frac{RT}{zF} \ln\left(\frac{C_A}{C_B}\right) \Rightarrow \text{Nernst equation}$$

Another approach,

ion flux due to electrical potential difference = ion flux due to concentration gradient

$$\mu z c \frac{\partial V}{\partial x} = D \frac{\partial C}{\partial x}$$

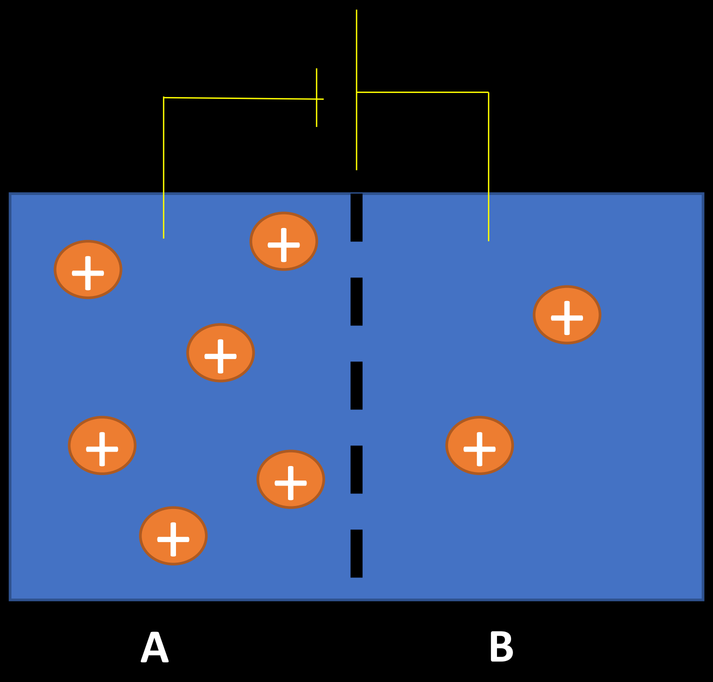


Integrate ∂V from 0 to V & ∂c from c_a to c_b.

$\Downarrow$

Gives Nernst equation

(Use, $D = \frac{\mu RT}{F}$)



E is called the Nernst potential of ion C → Potential required to maintain the ionic gradient at concentrations (Ca, Cb)

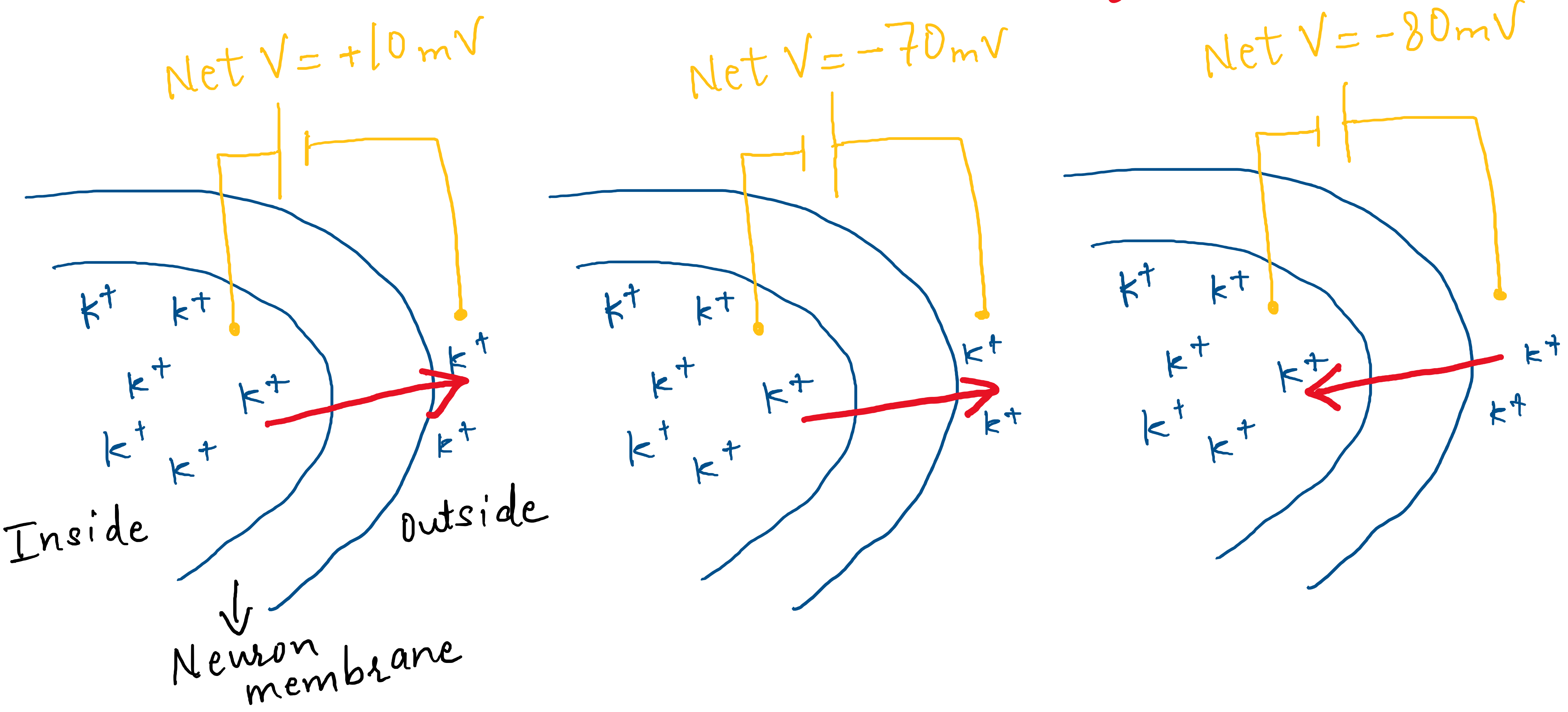
Nernst potentials for Na, and K ions across the membrane:

E_{Na} ~ +60 mV

E_K ~ -75 mV

Note: When we talk about neuronal membrane potentials, the convention is to refer to the potential inside wrt the outside of the cell.

Consider K^+ ions ($E_K = -75\,mV$): What will be the direction of K^+ ion flow in following scenarios?



Goldman-Hodgkin-Katz equation

In case of multiple ions (which is the case around neuronal membrane), the required voltage that needs to be maintained to keep them at their ionic gradients is given by Goldman-Hodgkin-Katz equation –

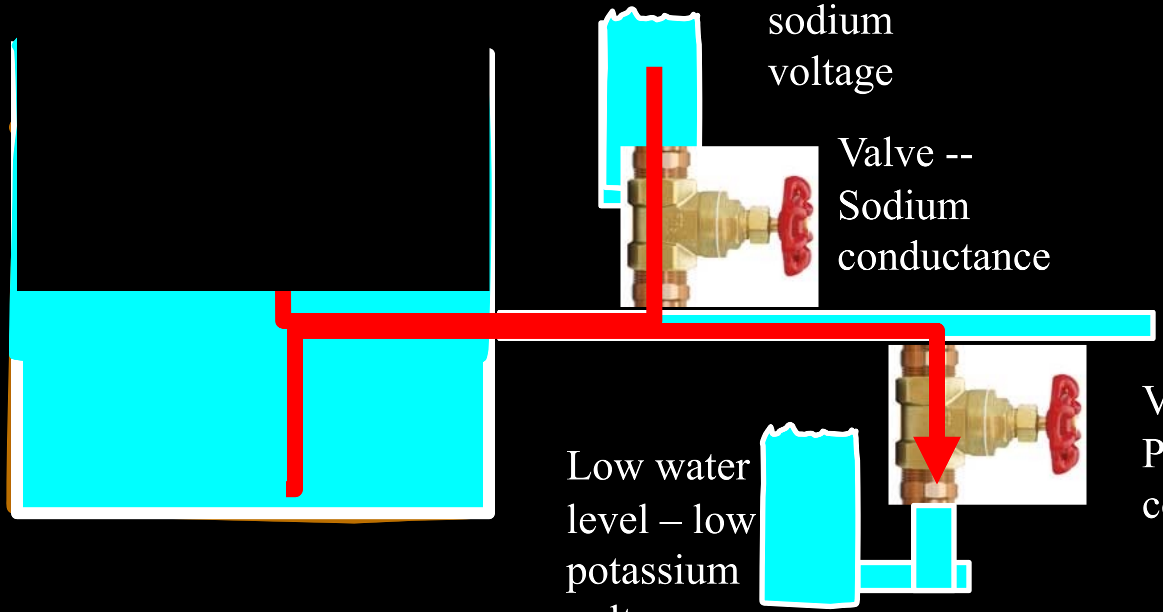
$$V_M = \frac{RT}{F} \ln \frac{P_K[K^+]_{out} + P_{Na}[Na^+]_{out} + P_{Cl}[Cl^-]_{in}}{P_K[K^+]_{in} + P_{Na}[Na^+]_{in} + P_{Cl}[Cl^-]_{out}},$$

= roughly, -70 mV

Here, $[X]_{out}$ - concentration of ion X outside the cell
$[X]_{in}$ - concentration of the ion X inside the cell
P_x – Permeability of the ion X through the membrane
R – Ideal gas constant
T – Temperature
F – Faraday's constant

Note: This equation is for mono-valent ions. For divalent ions, a '2' would appear in denominator; For a mix of mono and divalent ions → write the flux balance equation shown a couple slides back for multiple ions taken together, assume V to be constant across the length of the membrane→ this will give a quadratic equation in x where, x = e-FV/RT, solve for x.

Water tank analogy

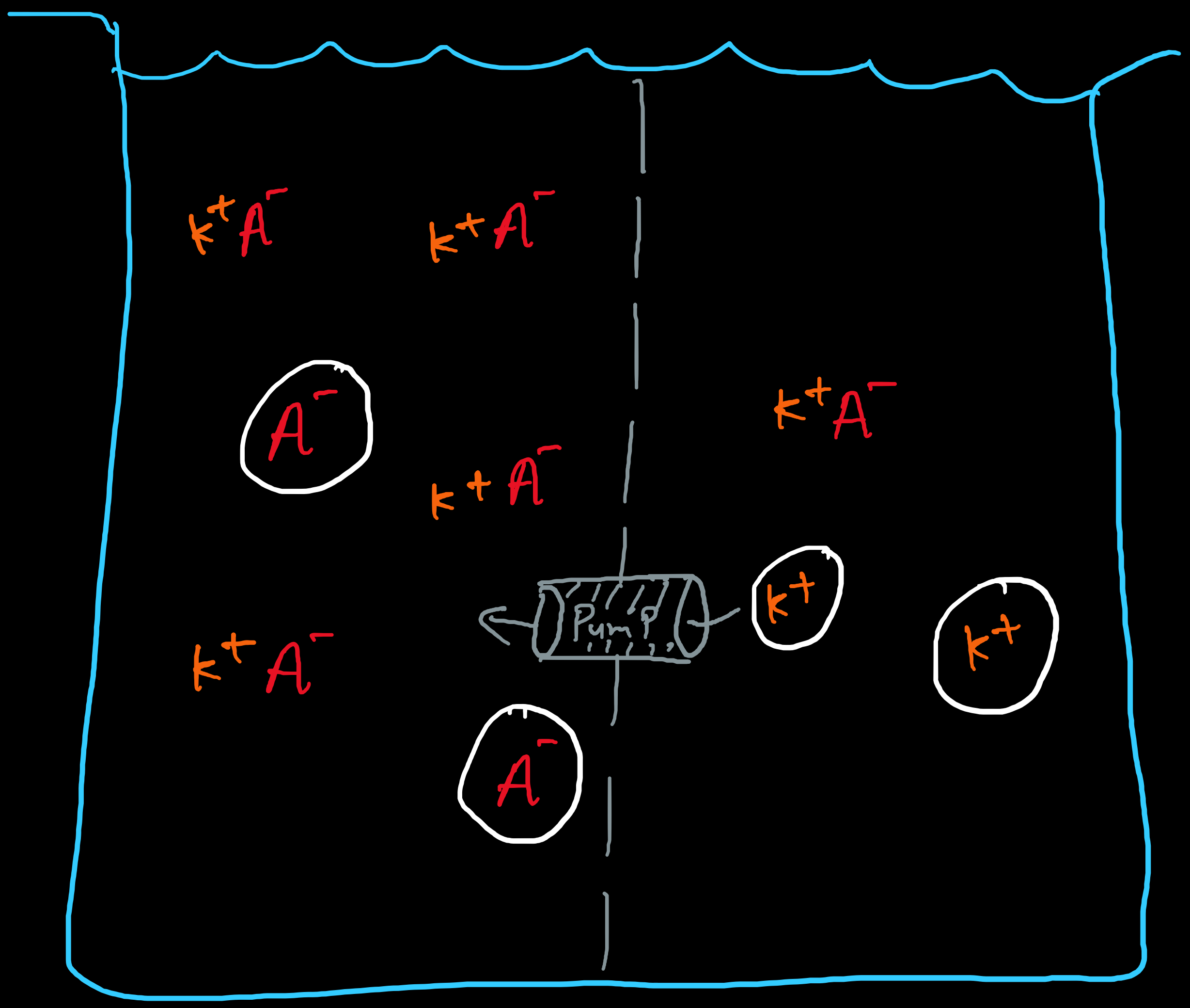


Sodium valve open → Water level rises (by analogy, membrane voltage rises)

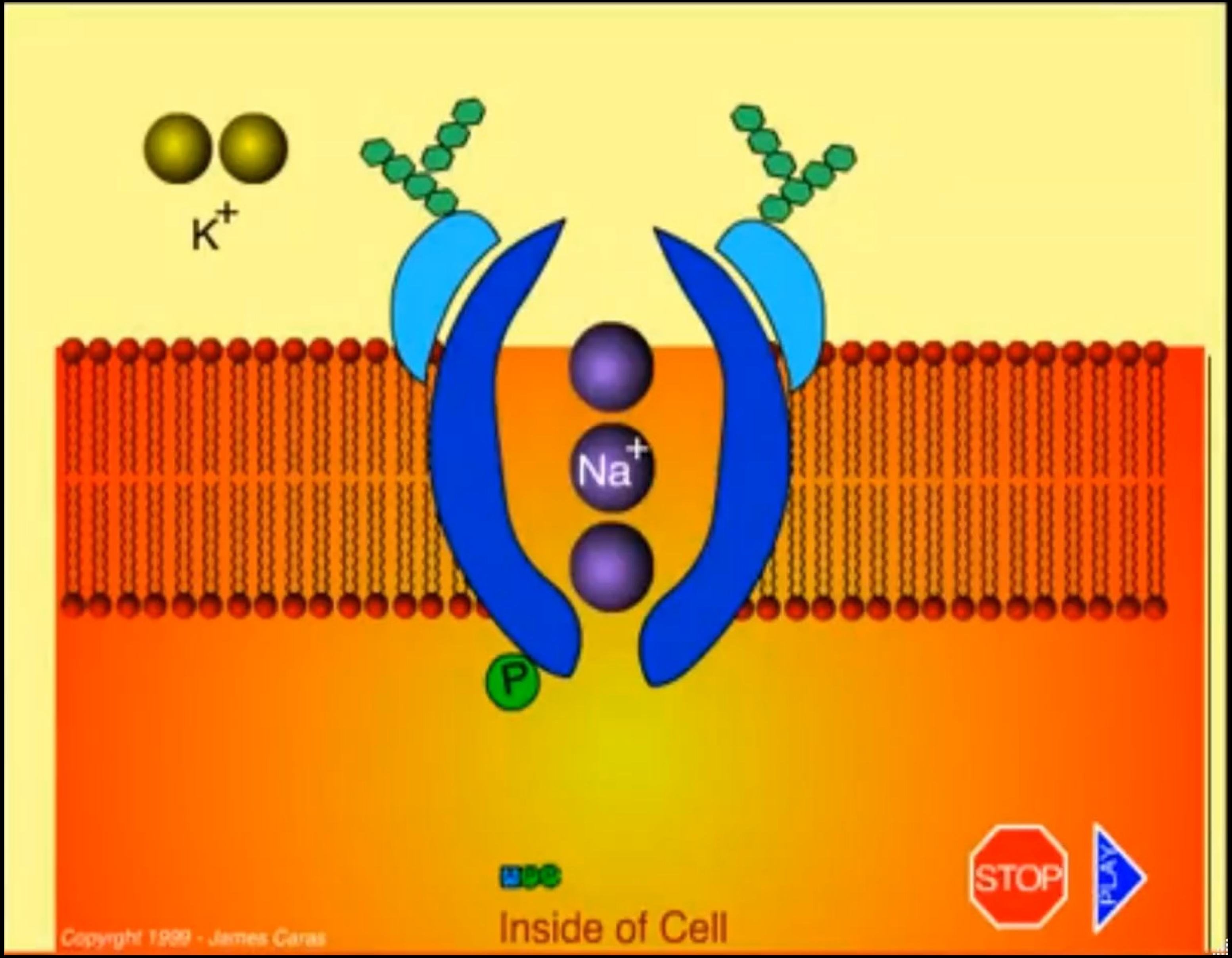
Potassium valve open → Water level falls (by analogy, membrane voltage falls)

How is the required V_M maintained across neuron membrane?

- Organic anions, A-, to which the membrane is impermeable
- Electrogenic pumps that actively transfer ions against their ionic gradients



Importance of Na-K pump



At, resting potential V_M = -70 mV

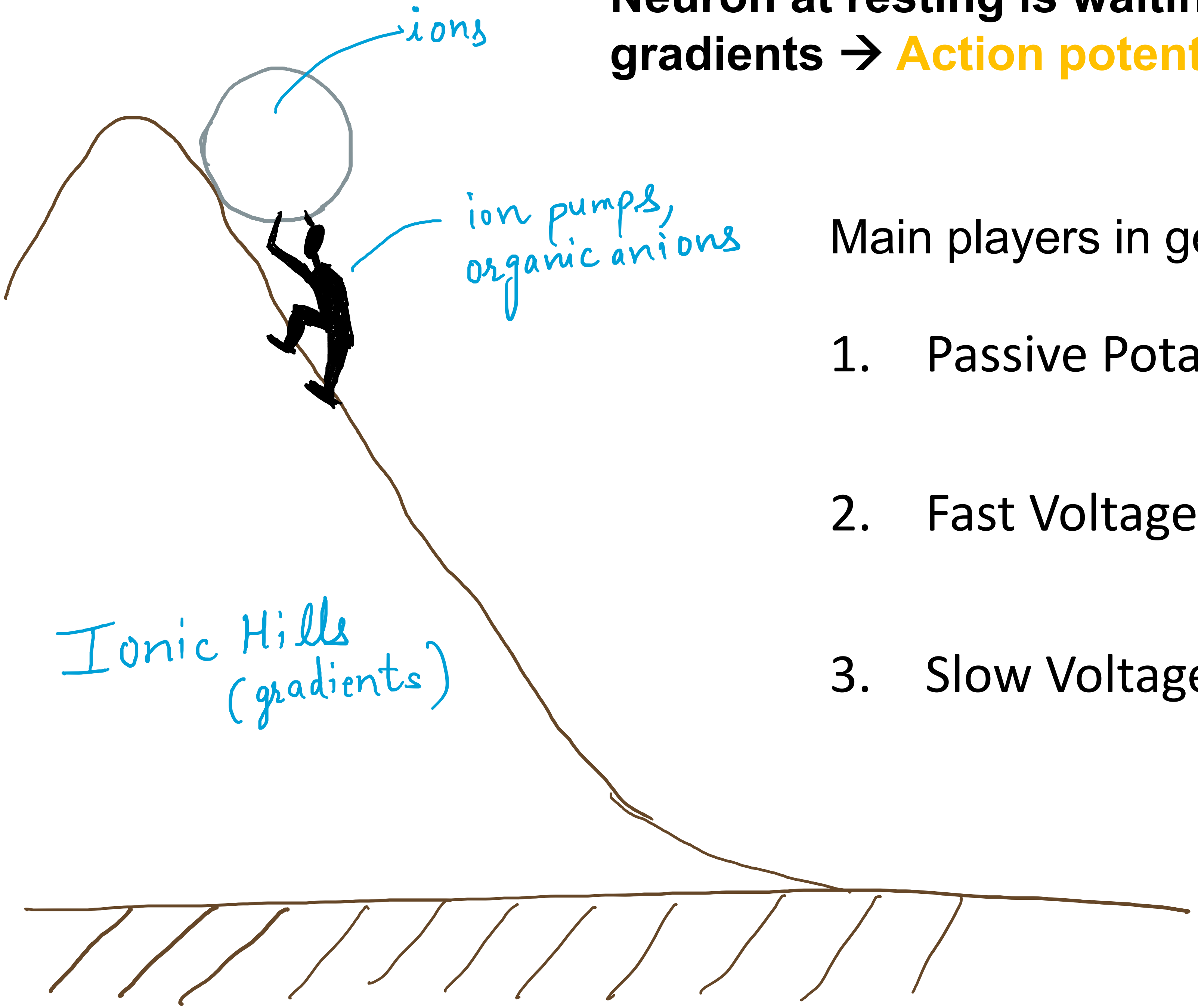
$I = I_{Na} + I_K + I_{cl} + I_{leak} = 0$

But,

$I_K \neq 0$, $I_{leak} \neq 0$

- These individual ion flows would cause the individual ion gradients to change (dissipate)
- Na-K pump prevents that by specifically moving 3 Na+ ions outside the cell for every 2 K+ ions moved inside the cell.

Neuron at resting is waiting to roll down its ionic gradients → Action potential



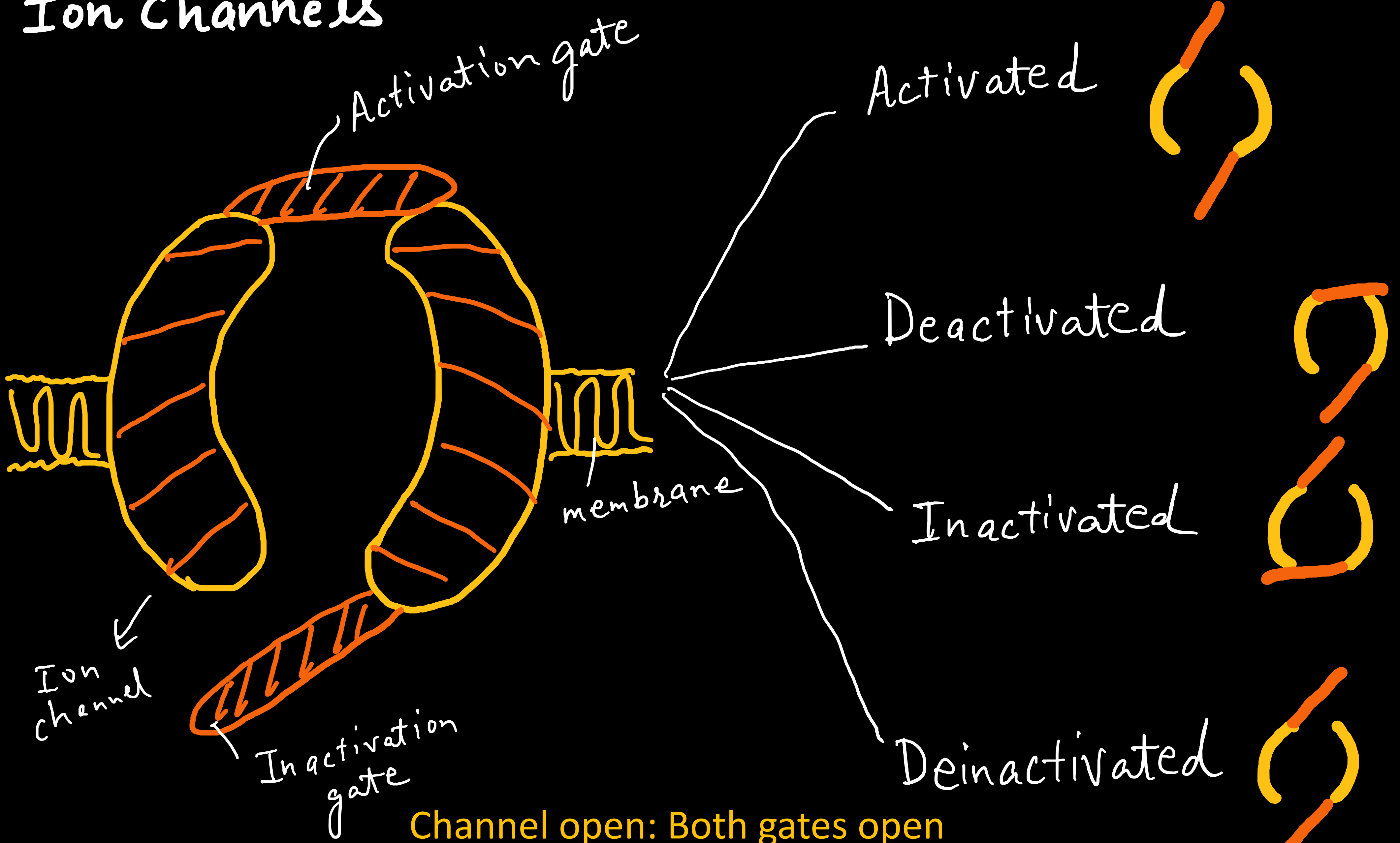
Main players in generating an action potential -

1. Passive Potassium (K) Channels

2. Fast Voltage-gated Sodium (Na) Channels

3. Slow Voltage-gated Potassium Channels

Ion Channels



Channel open: Both gates open

Channel closed: At least one gate closed

Few terms

Both sodium and potassium channels OPEN with increase in voltage,

BUT

Potassium channels are slow

(Also, sodium channels get inactivated (CLOSE) as voltage becomes very high)

Depolarization

$Change\ in\ V = +$

$Change\ in\ V = -$

Towards resting

Repolarization

Both sodium and potassium channels CLOSE with increase in voltage,

BUT

Potassium channels are slow

Resting membrane potential = - 70 mV

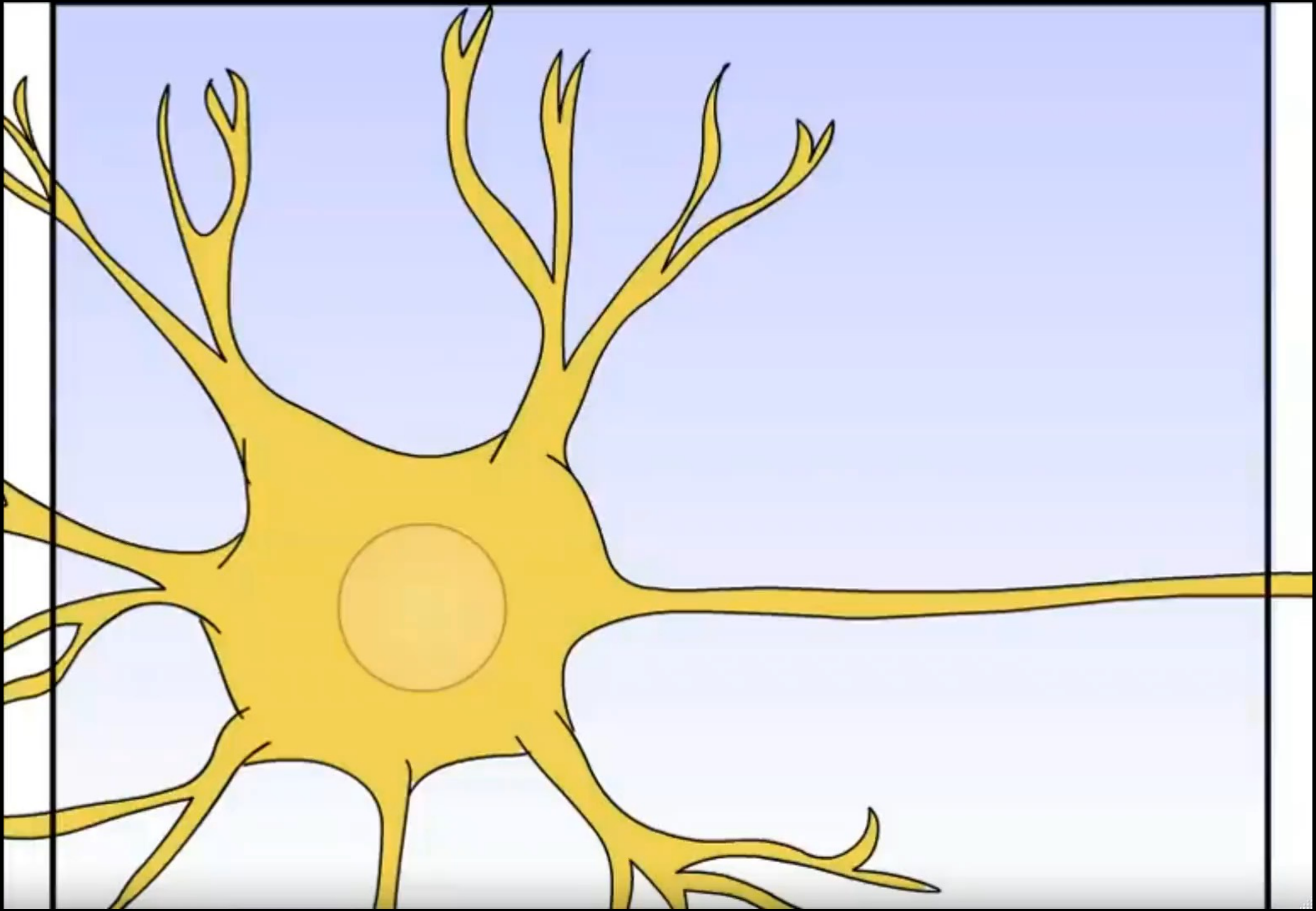
$Change\ in\ V = -$

Away from resting

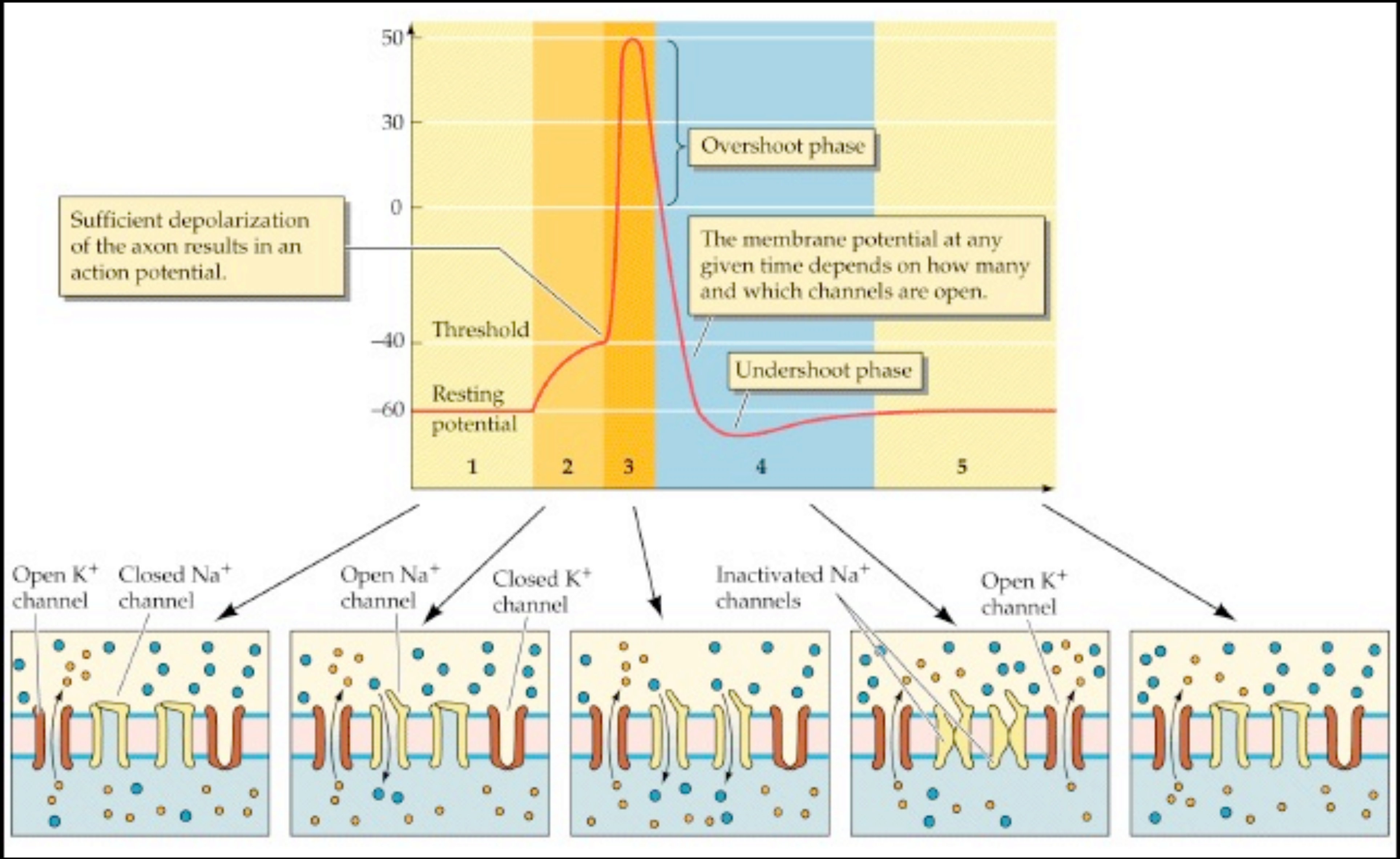
Hyperpolarization

V: Membrane potential ($V_{in} - V_{out}$)

Action potential - animation

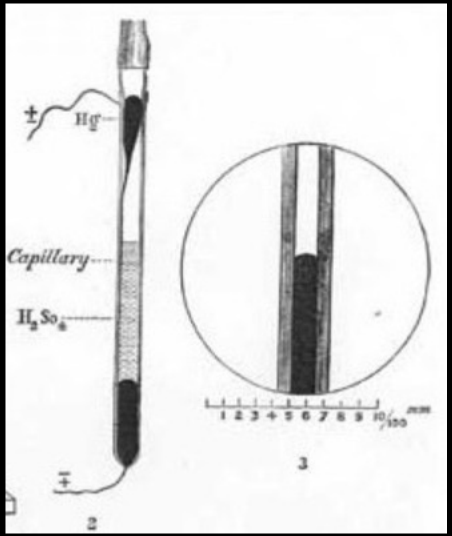


Action Potential



All or none principle

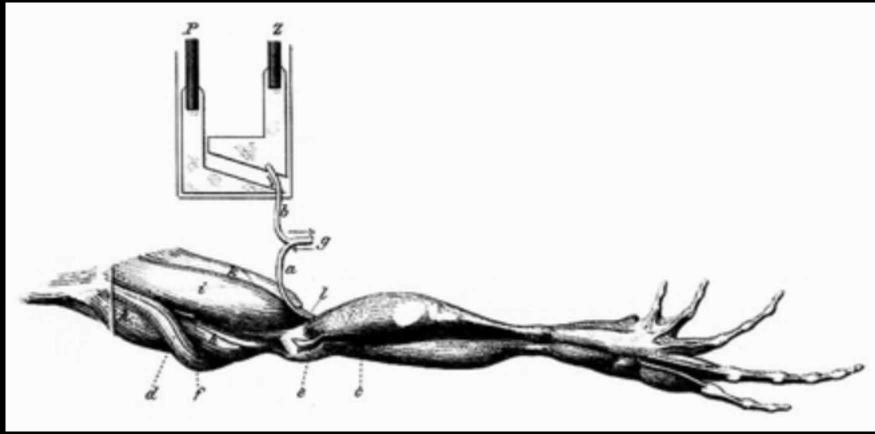
Francis Gotch (1853 – 1913)



Capillary electrometer: Current from nerve impulses was passed through the mercury inside the capillary – this caused mercury to rise – Always rose the same height; Also, a second height deflection could not be produced right after the first one. Discovery of all or none principle and refractory period

For any input that is able to induce an action potential in a neuron, the amplitude and the duration of an action potential always remains the same irrespective of the intensity of the input.

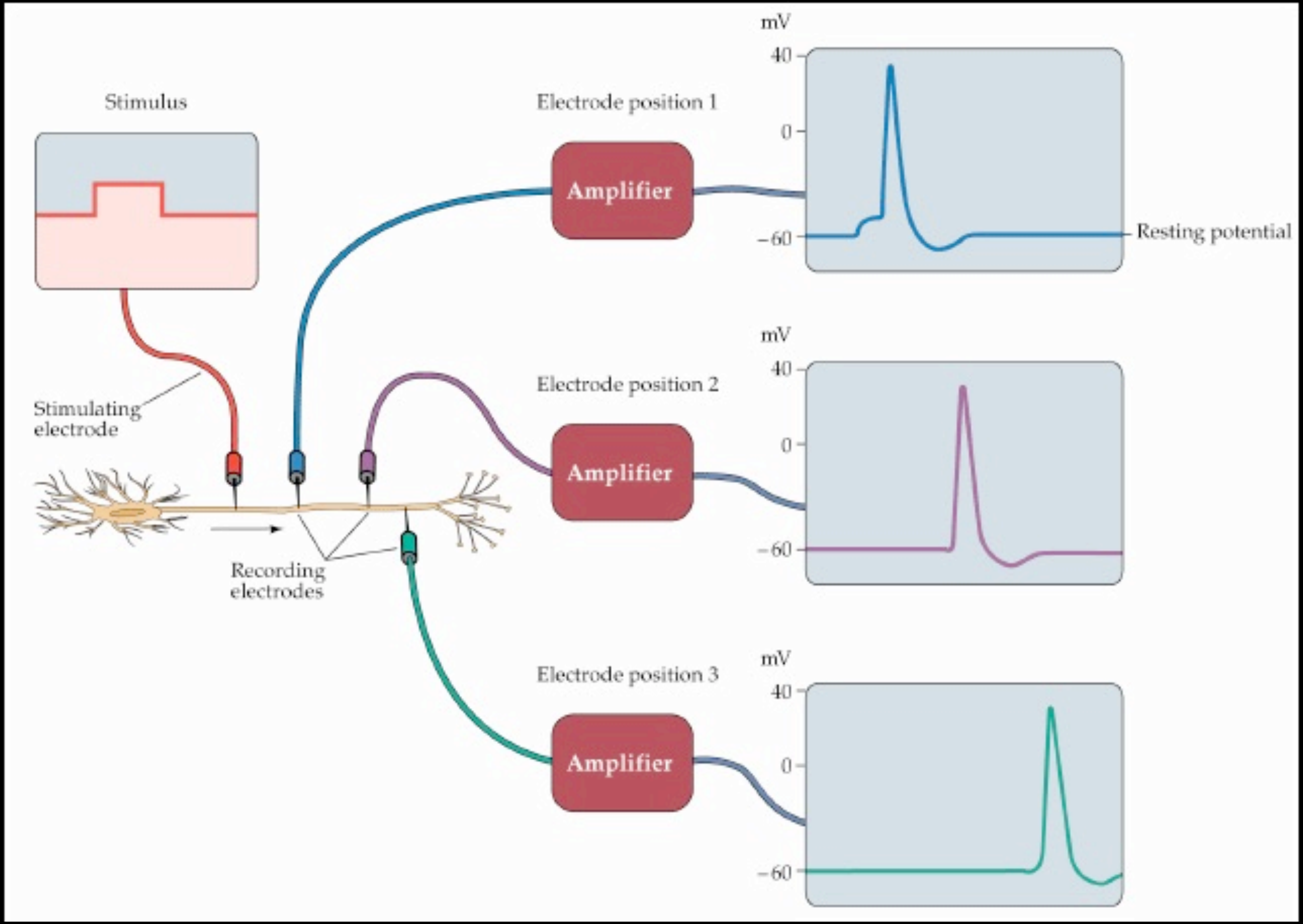
Why is it called ‘action’ potential?

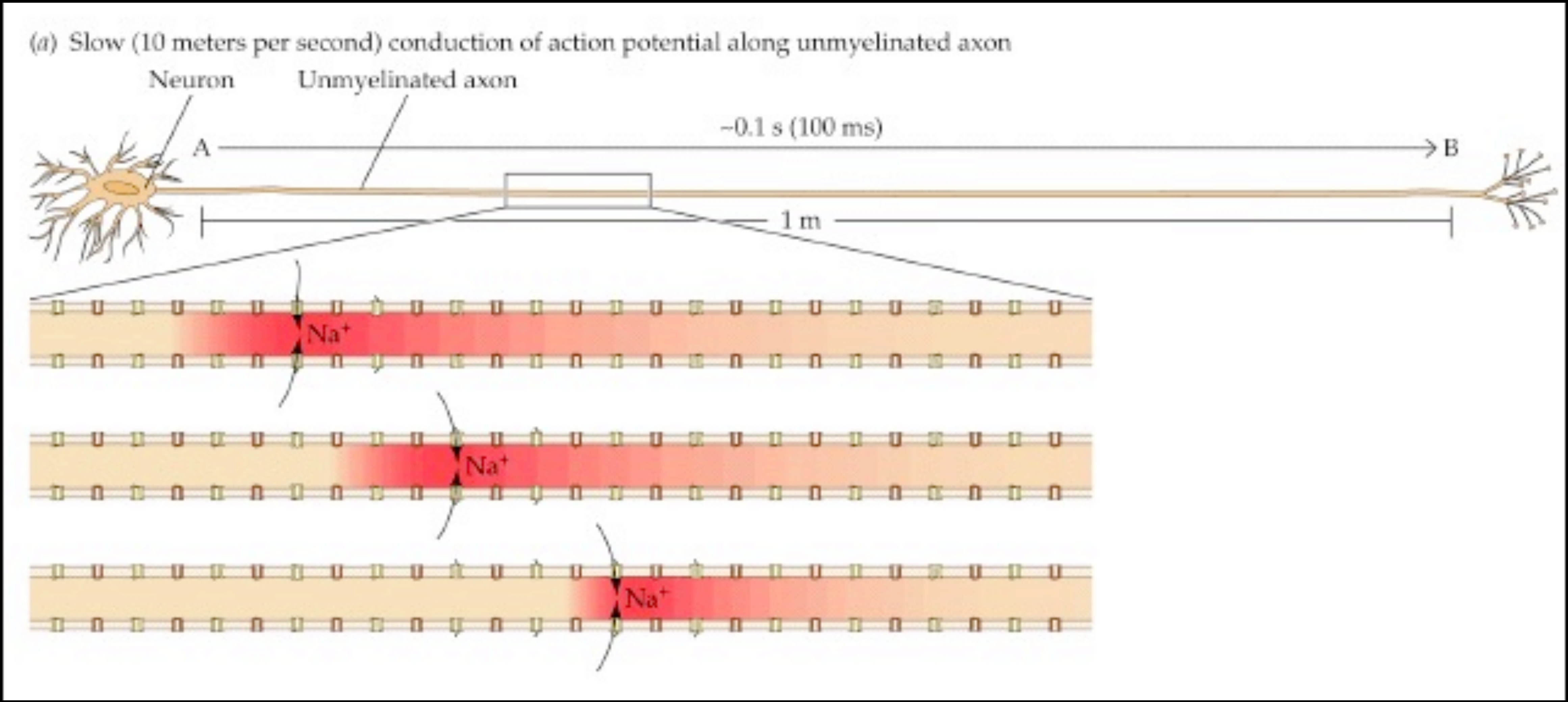


First observation of action potential (1843): Sciatic nerve of a frog - Wave of relative negativity observed to be necessary for muscle contraction (‘Action electricity’)

Emil Du Bois Reymond (1818 – 1896)

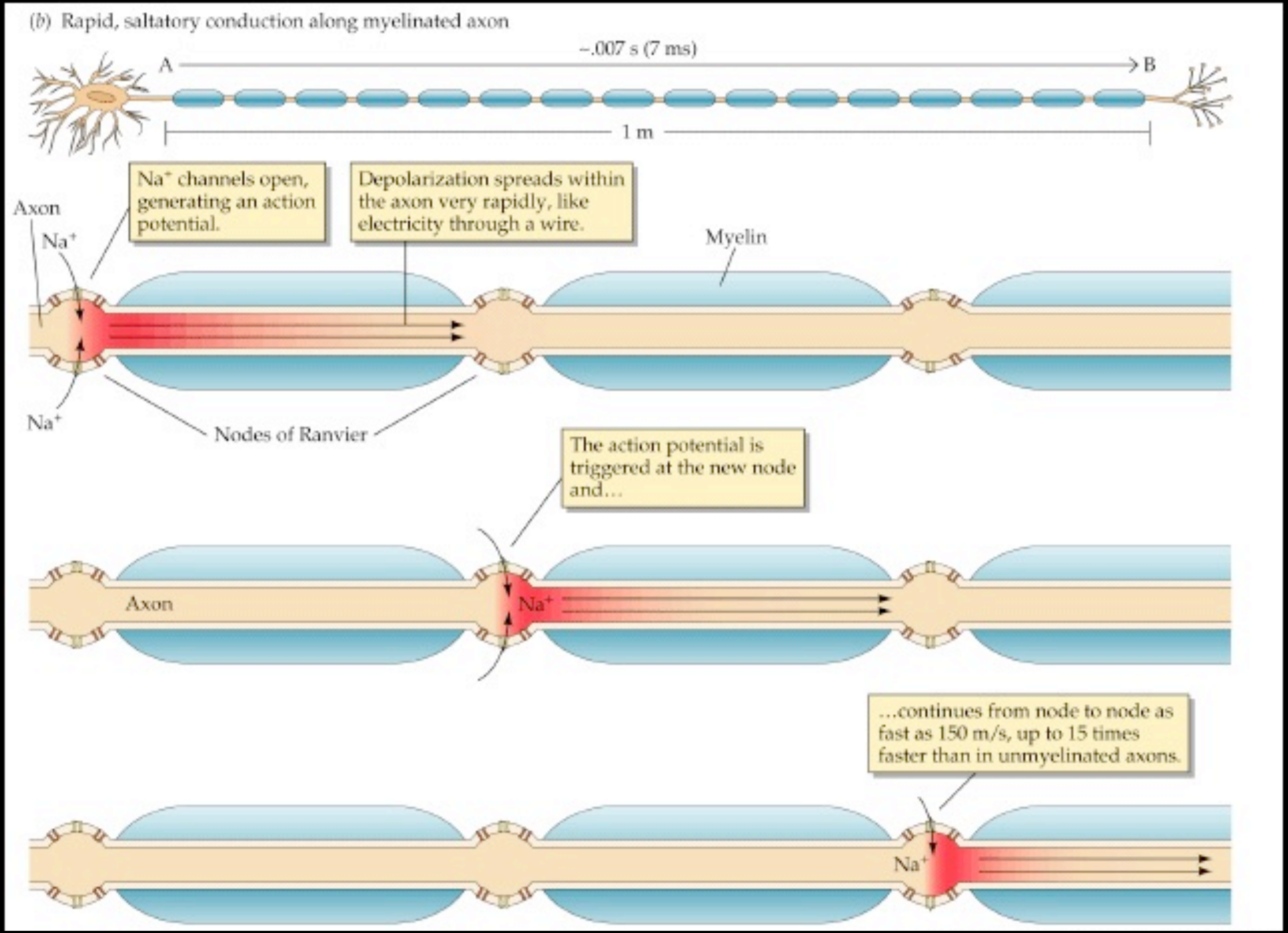
Action Potential Propagation – unmyelinated axon (~ 10 m/sec)

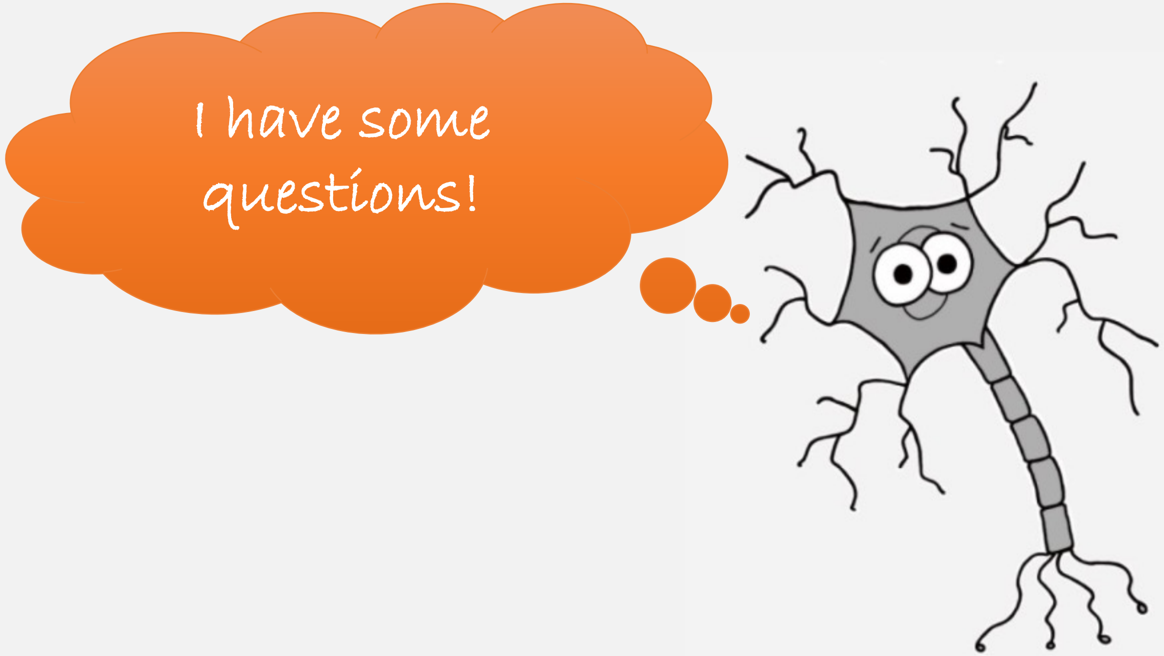



(a) Slow (10 meters per second) conduction of action potential along unmyelinated axon
Neuron
Unmyelinated axon
~0.1 s (100 ms)
A
B
1 m
Na+
Na+
Na+

Action Potential Propagation – Myelinated axon (~ 100 m/sec)

- Nodes of Ranvier
- Saltatory conduction





1. Where is the decision to fire or not made in the neuron?

A. Dendrites B. Axon terminals
B. Nodes of Ranvier D. Axon hillock

2. Which among the following pulls down the resting membrane potential?

A. Na^+ B. K^+

3. Which among the following constitutes the current during the upshoot of the action potential?

A. Na^+ B. K^+

4. Which ion among the following is responsible for repolarization of the action potential?

A. Na^+ B. K^+

5. The period immediately after an action potential during which the neuron cannot fire another action potential is called?

A. Repolarization period B. Revenge of K+ C. Refractory period

6. If myelination improves speed, why can't the whole axon be myelinated?

7. Why doesn't the action potential propagate in both directions?