MSc in Artificial Intelligence and Robotics
MSc in Control Engineering
A.Y. 2019/20

Neuroengineering

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Teaching material

Books:

- R. Hari and A. Puce, *MEG-EEG primer*, Oxford Press, 2017, ISBN: 9780190497774
- J. Wolpaw and E Wolpaw (eds.), *Brain-Computer Interfaces*, Oxford University Press, 2012. ISBN 9780195388855 / 9780199921485
- **L.F. Dayan and D. Abbott, *Theoretical Neuroscience. Computational and Mathematical Modeling of Neural Systems,* the MIT Press, 2005. ISBN: 9780262041997 / 9780262541855**

Handouts:

- Course notes and scientific articles distributed by the teachers

Course resources:

- Course mailing list
- Class communications and discussion in the Piazza class
- Google Drive shared folder

Questions, clarifications, support with the course

- During lessons breaks
- Through Piazza
- By email
- By remote/in person meetings (according to the measurements for containing the COVID-19 outbreak)→ by appointment

Exams

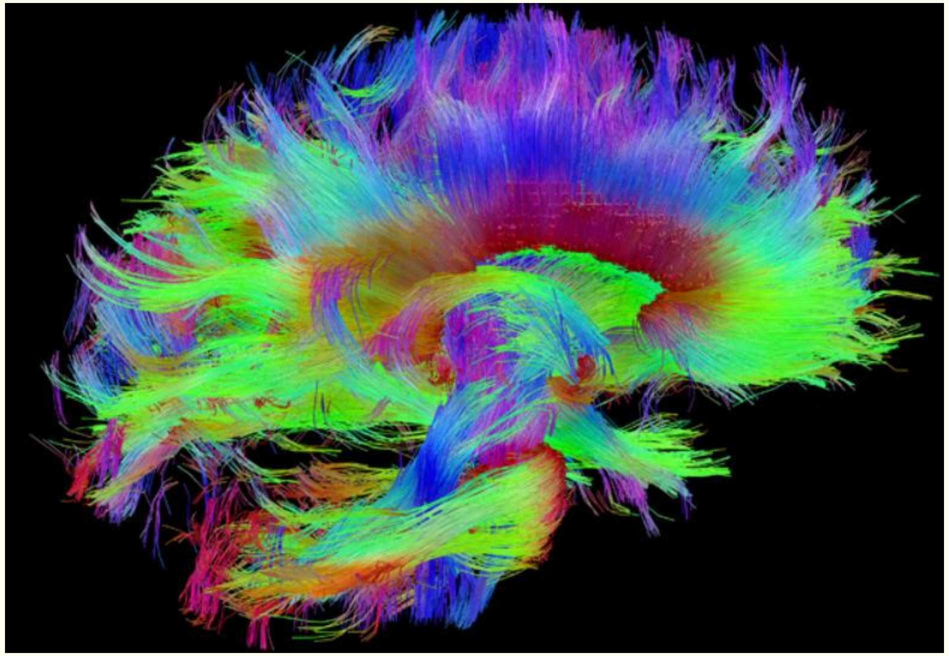
- See introductive lesson by prof. Cincotti for general information
- Open answer and multiple choice questions
- Examples of written tests will be provided throughout the course for self-evaluation

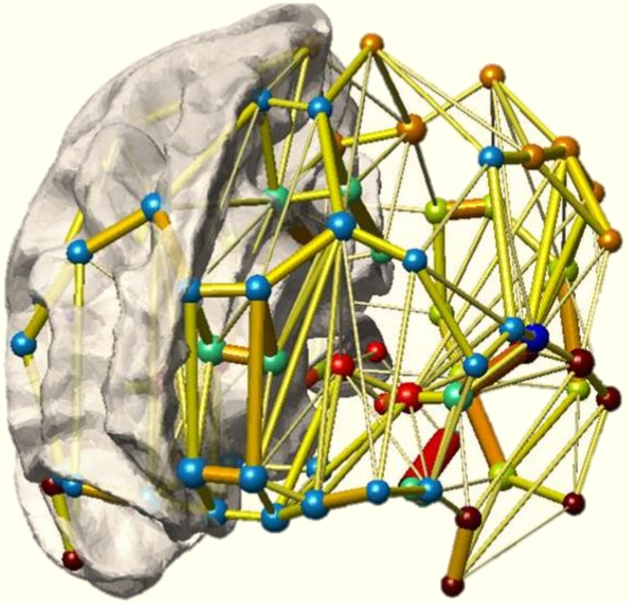
INTRODUCTION

The brain is an extremely complicated learning system. The brain has the purpose to collect info from the nevironment in the form of phisical info. Our brain processes info by the sensors and this process is extremely complicated and fast (millisecond). We continuously take decision which are translate into actions.

Why a Neuroengineering course?

The human brain is a complex learning system able to continuously process an enormous information flow and to translate it into actions with a time scale of milliseconds.





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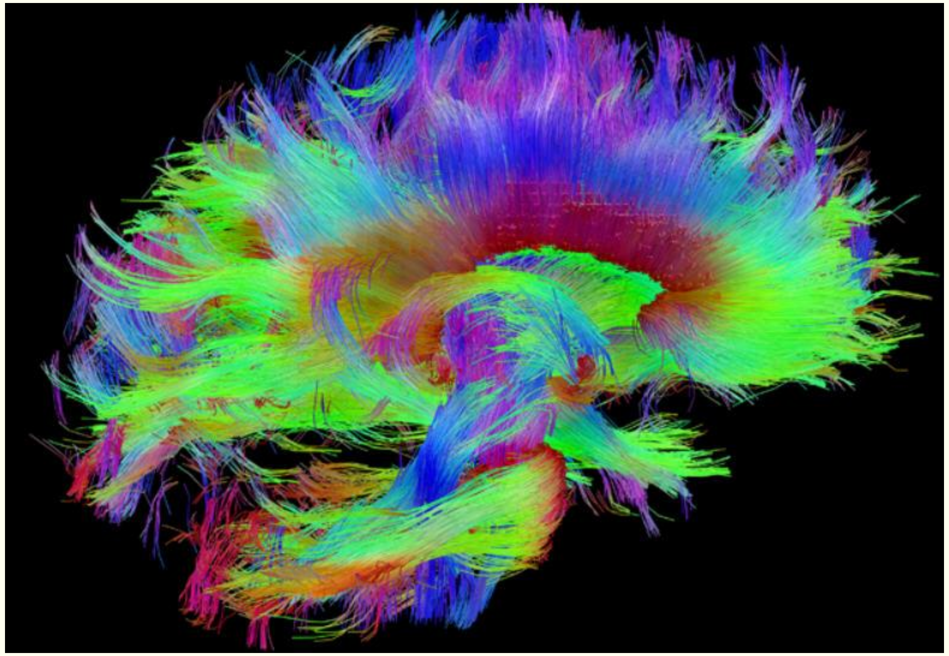
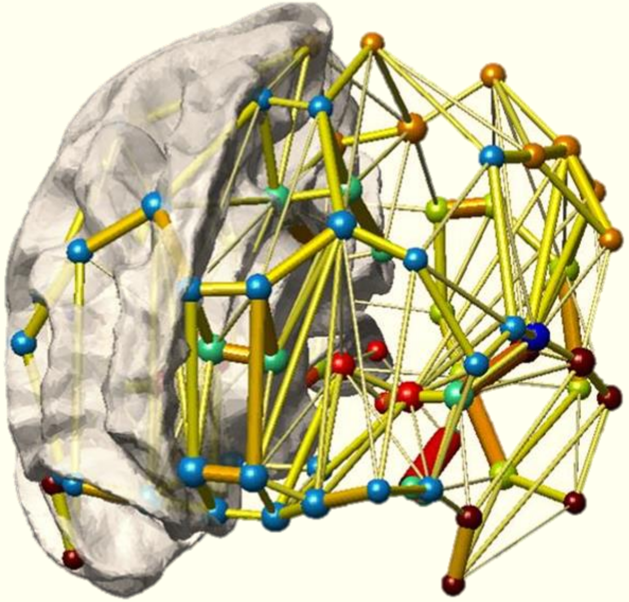


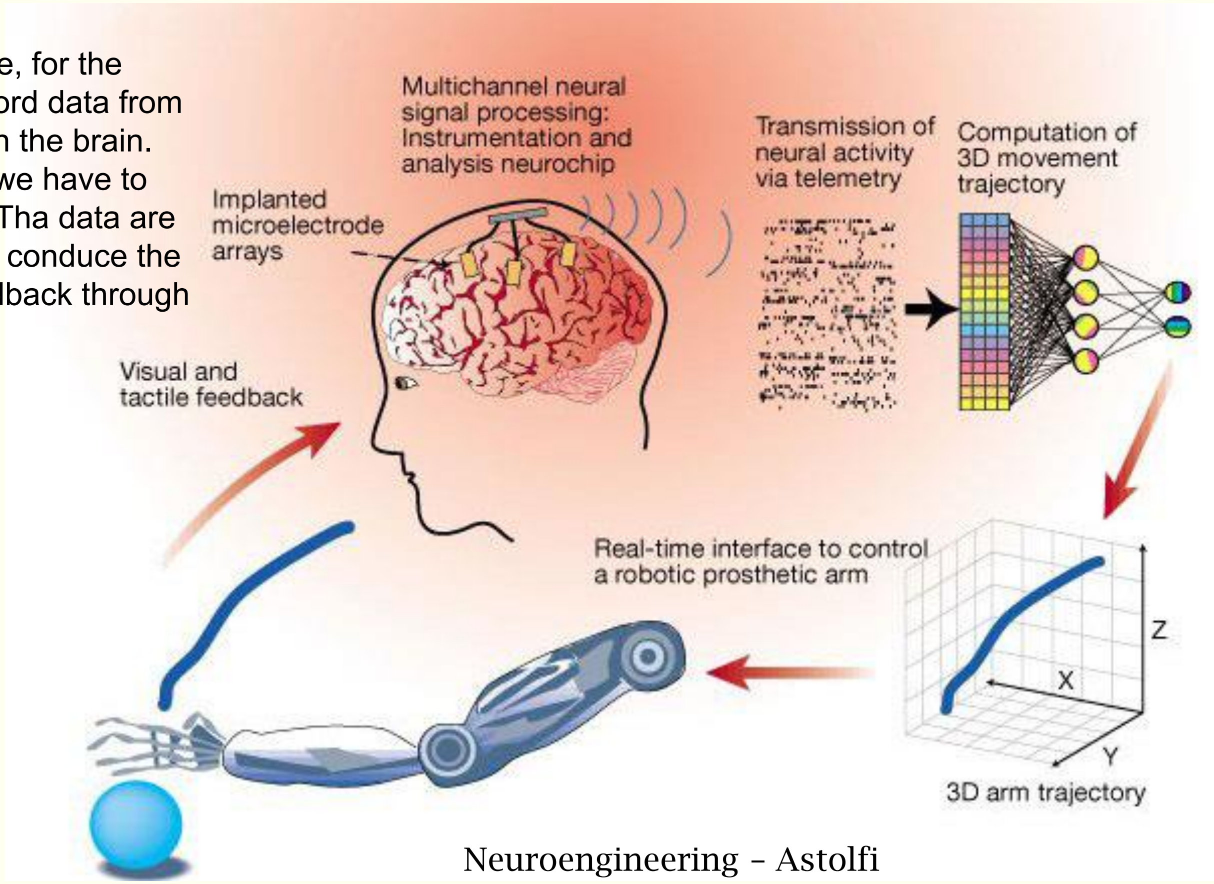
Laboratory of Neuro Imaging at UCLA and Martinos Center for Biomedical Imaging at MGH, Consortium of the Human Connectome Project



Why a Neuroengineering course?

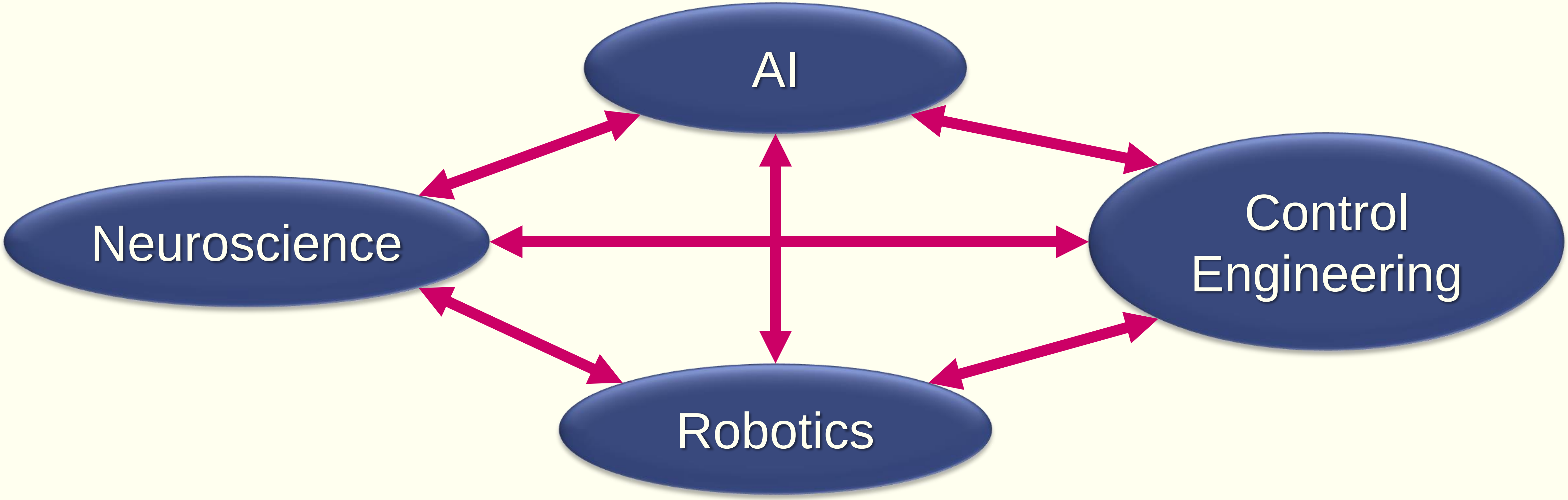
As such, it has inspired many engineering solutions that are currently transforming the way we address problems at all levels and in all domains (including Neuroscience!)

This is an ex. of the brain computer interface, for the control of robotic arm. In this scene, we record data from the brain invasively by putting electrodes in the brain. Data are sended to the computer and then we have to decode this data, using classification (ML). Tha data are translated and converted into a trajectory to conduce the arm. Finally there is a visual and tactile feedback through sensors.



Why a Neuroengineering course?

Neuroengineering, Artificial Intelligence, Robotics and Control Engineering are intertwined: Neuroscience can inspire new engineering approaches and Engineering can provide solutions to many open problems in Neuroscience



Learning objectives of the II module

At the end of the course, you will be able to:

1. Describe the basics of the neural cells structure and organization at different scales
2. Explain their role and functioning, illustrate how neurons exchange information through the propagation of electrical signals
3. Interpret the principal signals correlated to the brain activity and their neurophysiological origin
4. Explain the meaning of the neural encoding and decoding, describe the main techniques used to model these functions and their application
5. Compare different definitions of neural/brain networks and select the most appropriate for the specific application
6. Choose the tools to compute and interpret brain networks, judge the appropriateness of a procedure
7. Provide examples of applications to clinical and physiological problems and devise possible innovative scenarios

Contents of the II module

1. Structure of the neural cell, neuronal groups, brain regions and brain systems
2. Physiology of the neuron: generation, integration and propagation of neural electrical signals
3. Mechanisms of generation of neural electrical and metabolic correlates
4. Neural encoding and decoding
5. Natural neural networks, basic definitions of network neuroscience (synchronicity, causality, influence)
6. Model-free (data driven) vs model-based (biologically inspired) models of the brain as a complex system at different scales
7. Examples of application to clinical and physiological problems

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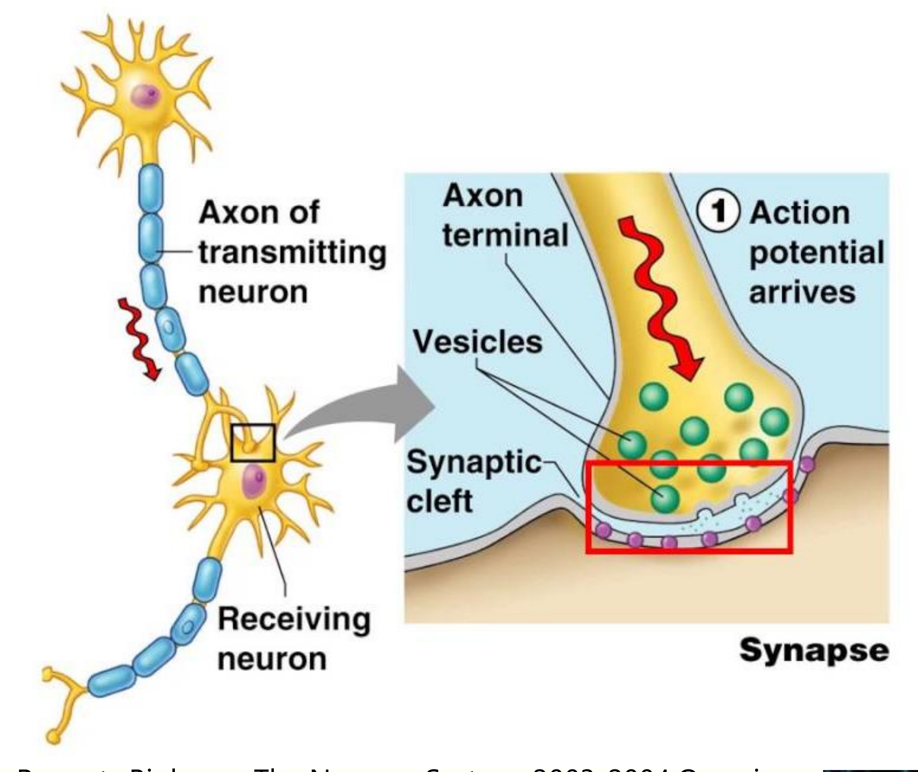
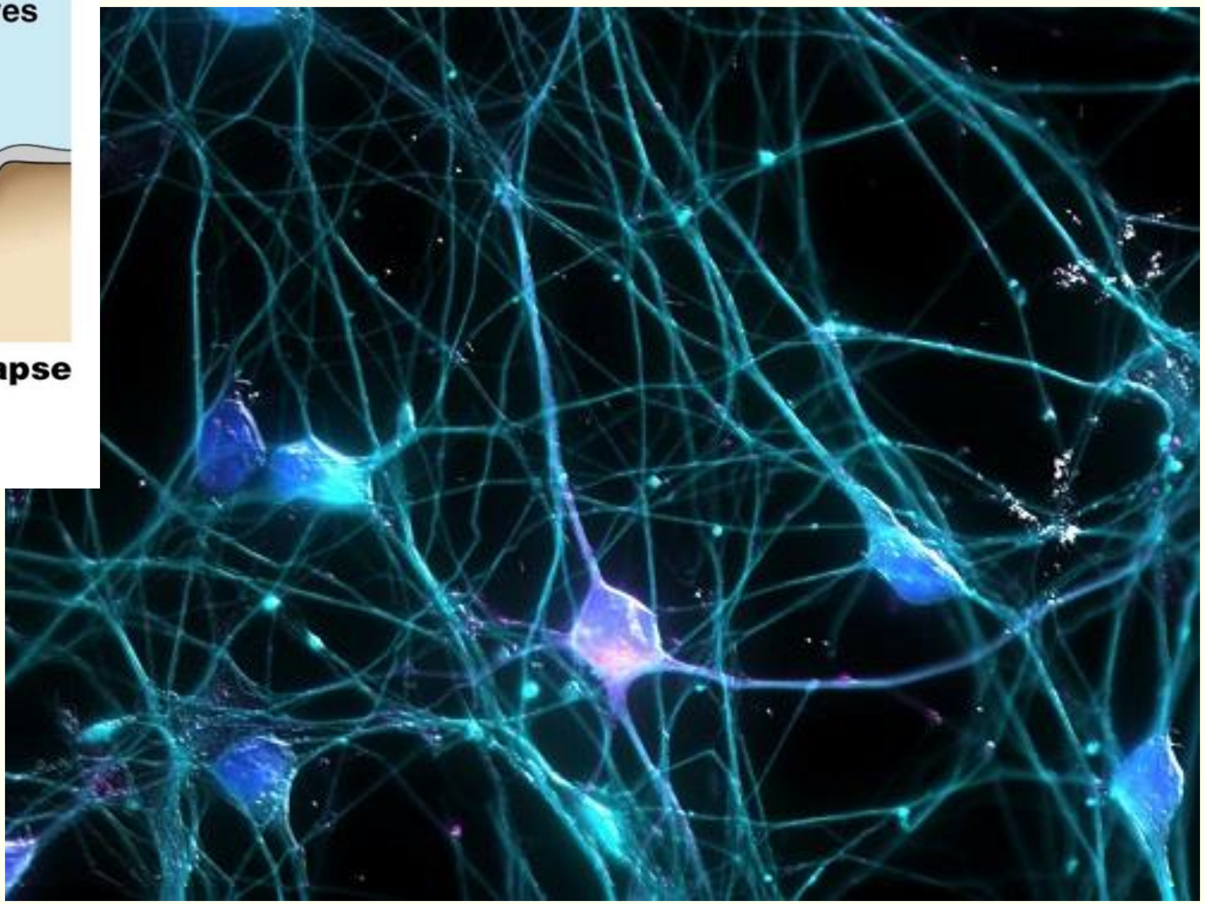
Principles of neuronal structure, functioning and communication



Regents Biology - The Nervous System: 2003-2004 Overview

UCI Research



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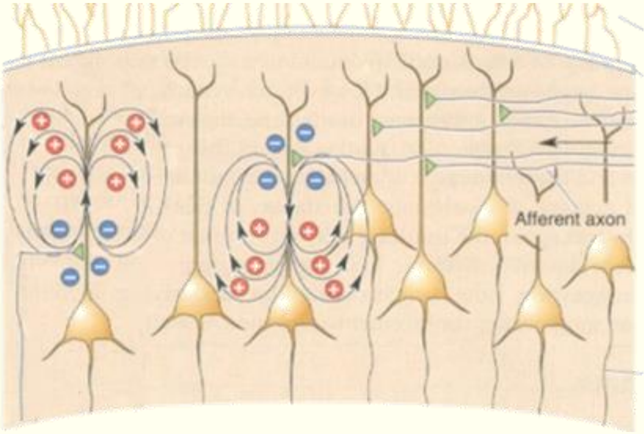
Generation of neural correlates

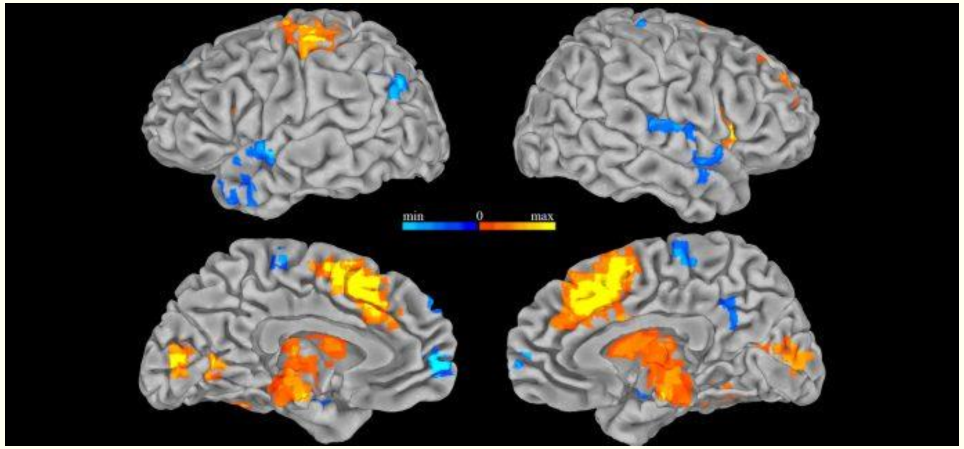
- Electrical correlates

  Non invasively

We will see how neurons generate elechtrical signals
whish propagate through the tissues of the head.



- Metabolic correlates



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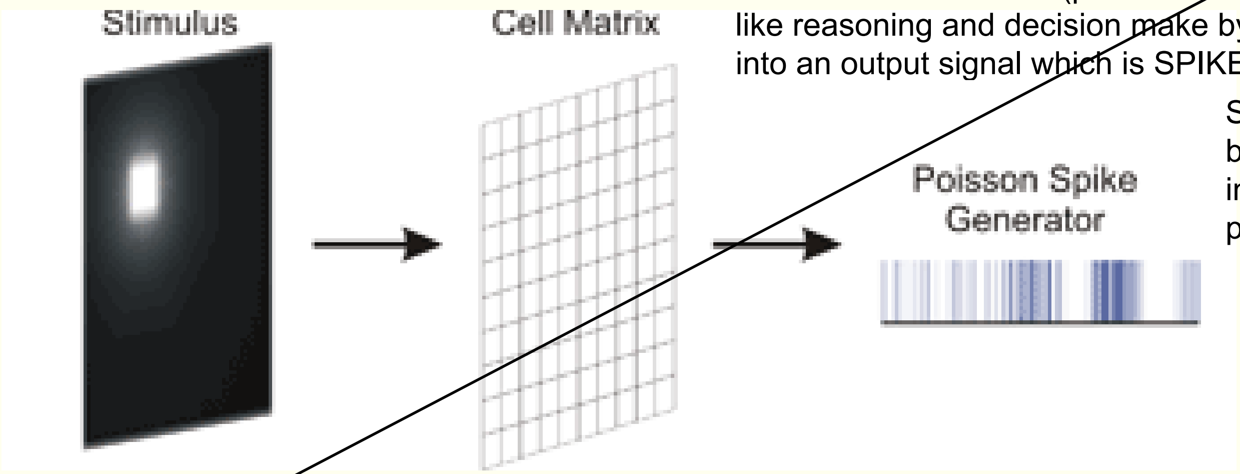
Two main procedures that the brain performs in order to translate info from the external world into decision.

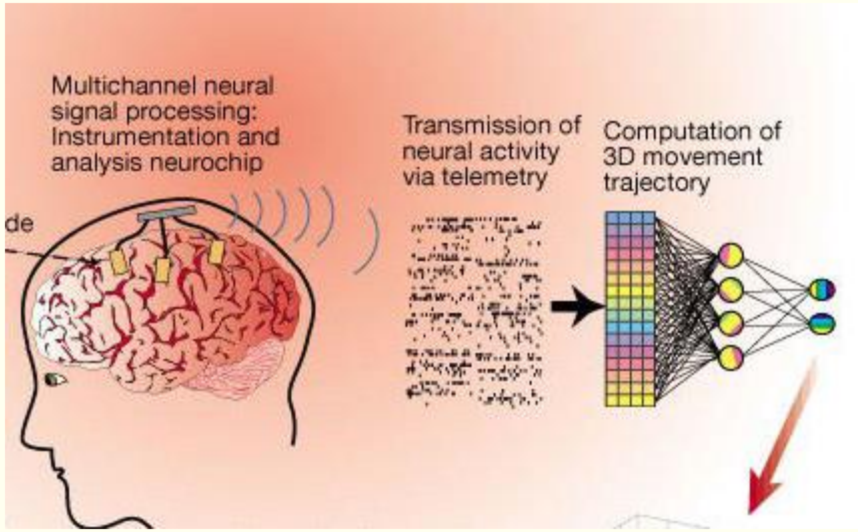
Basics of neural encoding and decoding

Procedure by which a neuron or a group of neurons collect info from the exernal world (phisical stimulation) and from the internal like reasoning and decision make by the subject and traduce it into an output signal which is SPIKE TRAIN.



So the neural endcoding is how we can model the behaviour of neuron when the input is a phisical or internal stimulation and the output is a binary signal produced by the neuron itself.

It's the reverse procedure. In the neural decoding we start from the output of the neuron and to use what we know about the encoding procedure to understand what is the stimulus that produce our output. (To understand which are the intentions of the subject)



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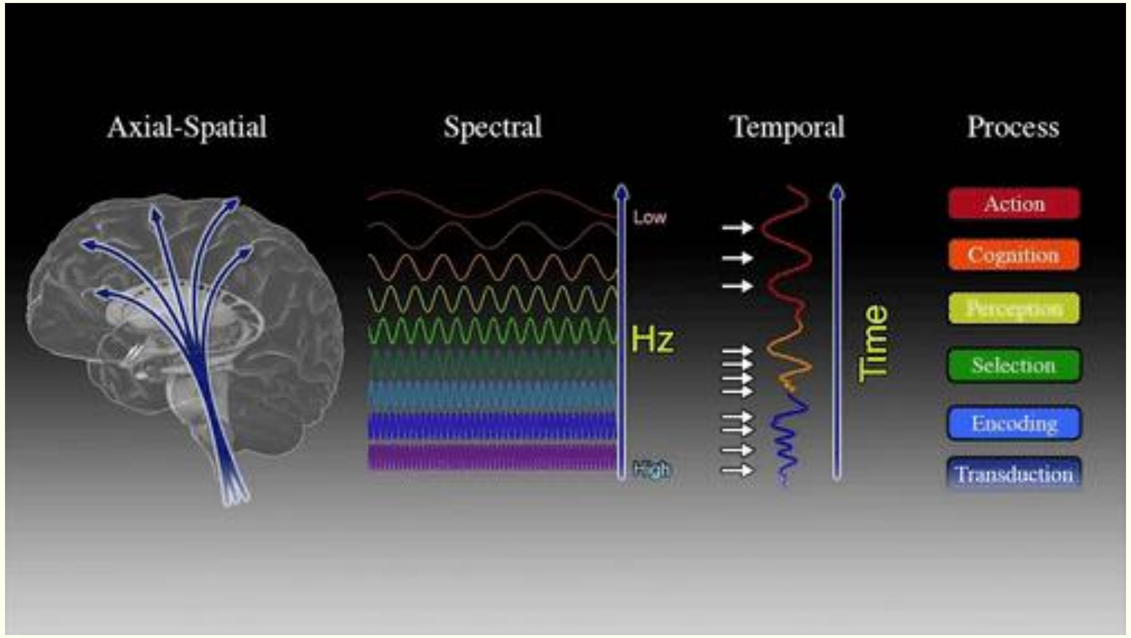
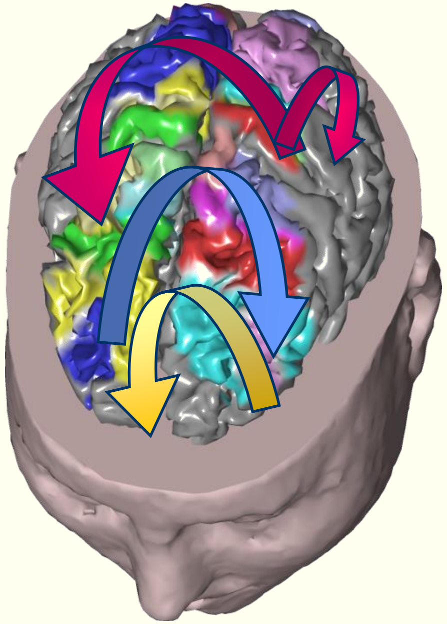
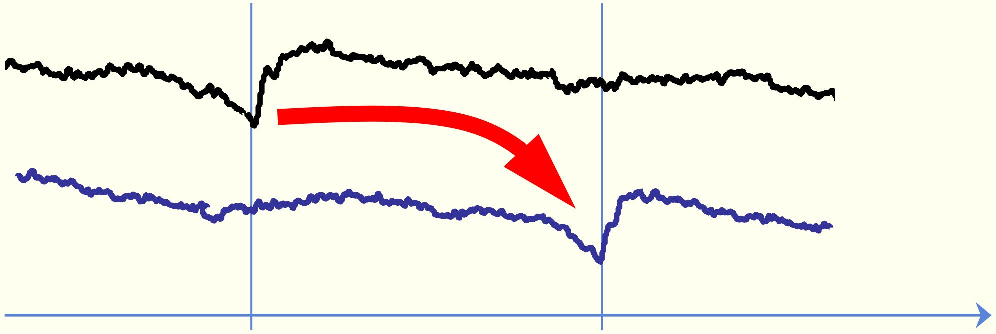
Synchronicity, causality, influence







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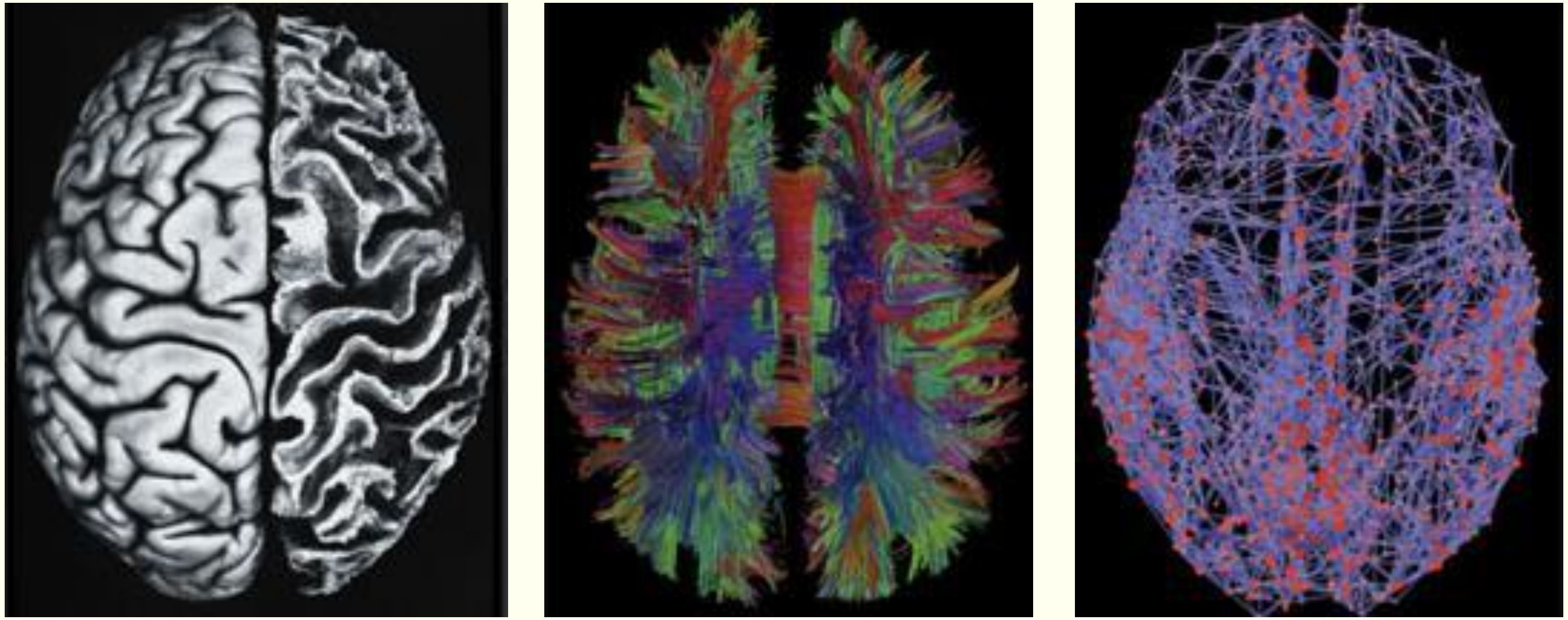
Principles of the brain organization, natural neural networks, different levels of organization



Adapted from: Sporns, Olaf, and Patric Hagmann. 2008. *The Human Connectome*.

Neural populations (functionally specialized regions) are physically connected (anatomical connectivity) and interact within and among themselves (brain networks)

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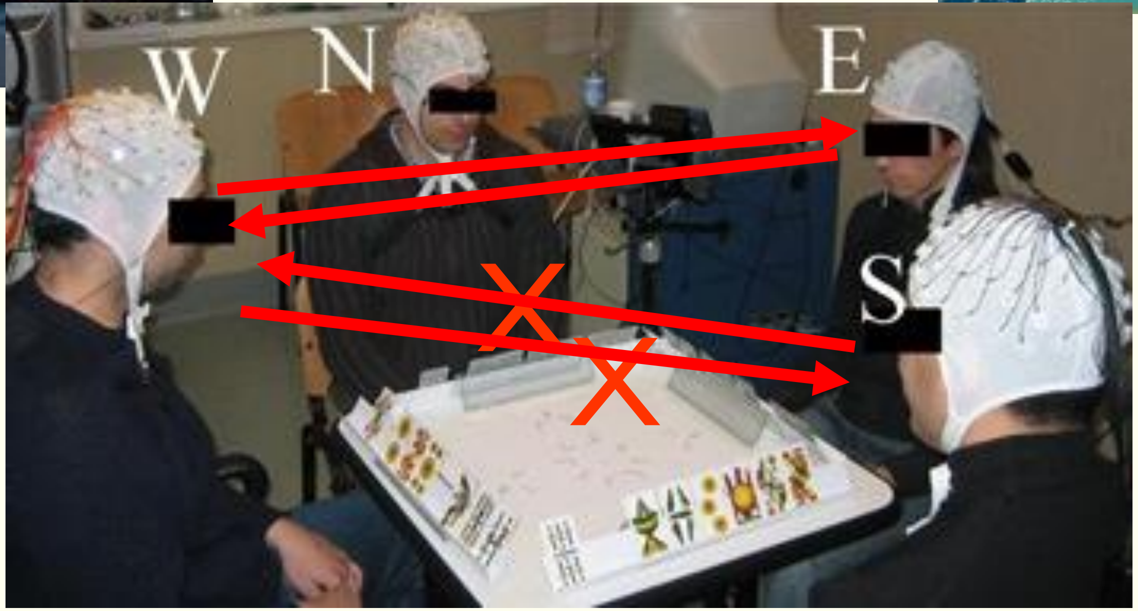
Applications



THE NEURAL CELL

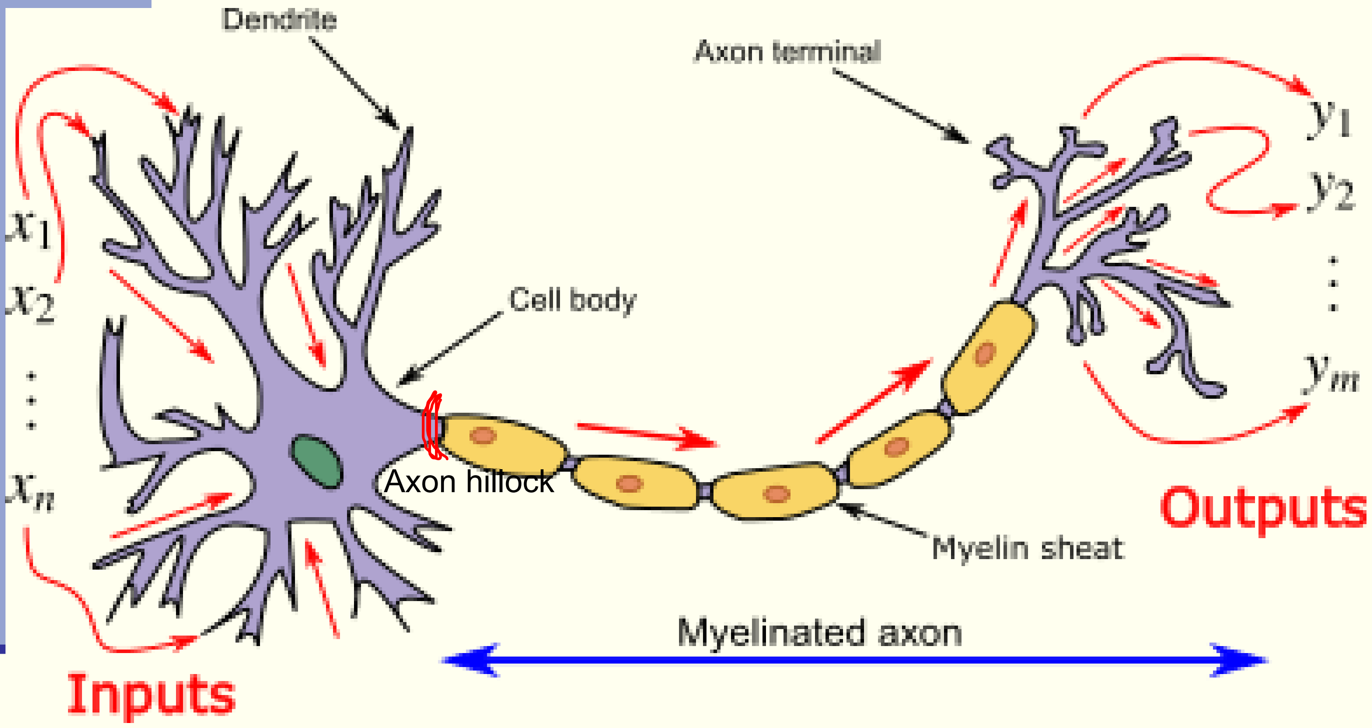
Learning objectives of the lesson

1. List the 3 main functions of the neural cell (neuron)
2. Describe the specialized structure allowing the neuron to carry out its functions and the nature of membrane potentials
3. Explain the role of the main ion families in the electrical behavior of the neuronal membrane
4. Understand how the information is collected by the cell post-synaptic membrane and tell the difference between excitatory and inhibitory synapses
5. Explain how the analog, multiple information collected by the neuron is translate into a binary decision (output)
6. Illustrate the nature of the neuronal cell output signal

It's a cell with a soma and a nucleus in the citoplasm. It has specific functions and structure. The first function is to collect info. It receive this info from many sources (this info arrive continuously, it's a dynamic process). The function goes with the structure (dendrites). The dendrites collect info. The second function is the processing of info. The processing is based on mathematical operation which is integration. Integration means a summation in time and space.

The neuron

Tha axon is unique because the info which arrives to cell are multiple but the input is single.

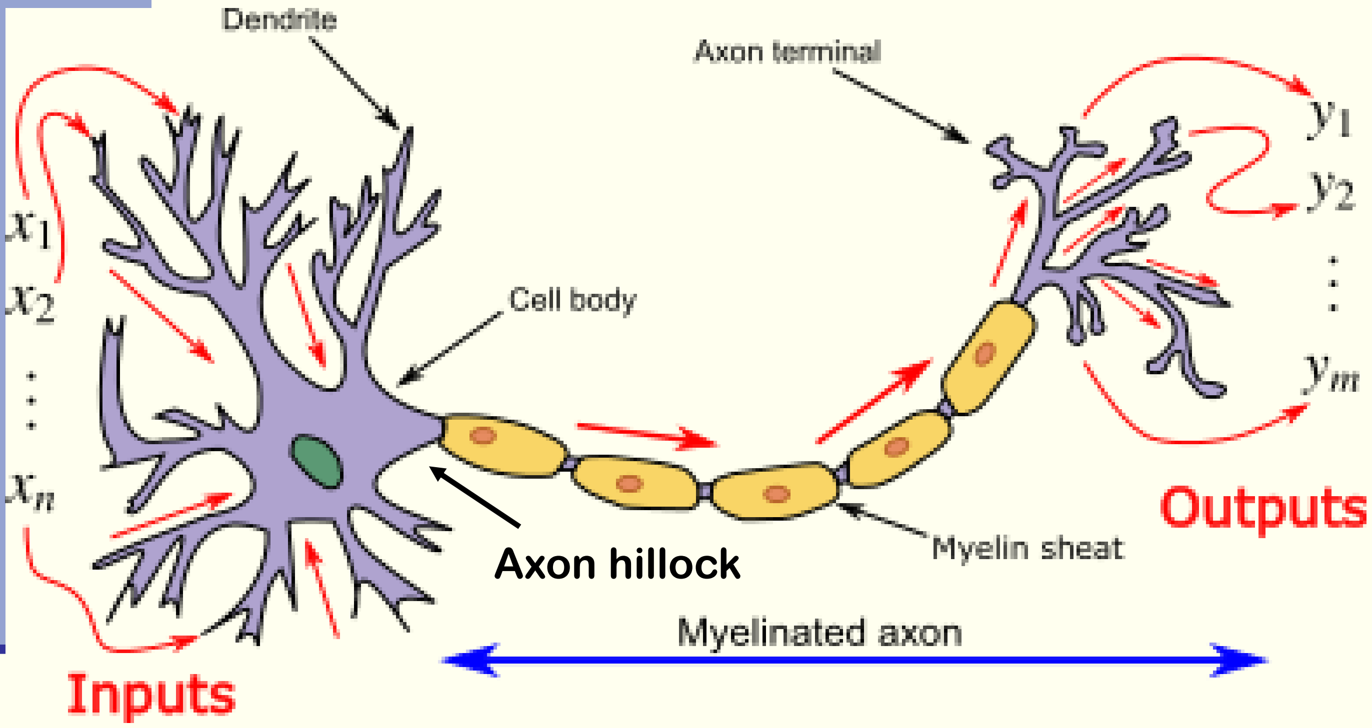


Basics of neuron structure and functions:

1. Collection of information from multiple sources (other neural cells/receptors)
2. Integration (in time and space) of incoming information to provide a binary decision through dendrites and some.
3. Generation and propagation of a bit of information up to target cells (other neural cells, muscle cells)

BINARY DECISION: result of integration. This is a binary so it will be 1 or 0. It's 0 if the decision of the cell is not to produce a signal to be sent to other cells. It's 1 if the decision of the cell is to produce this binary signal which is the output of the cell. The input is more complicated because isn't binary. This is a continuously produced result.

The neuron



"Anatomy and Physiology" by the US National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program, modified by Prof. Loc Vu-Quoc

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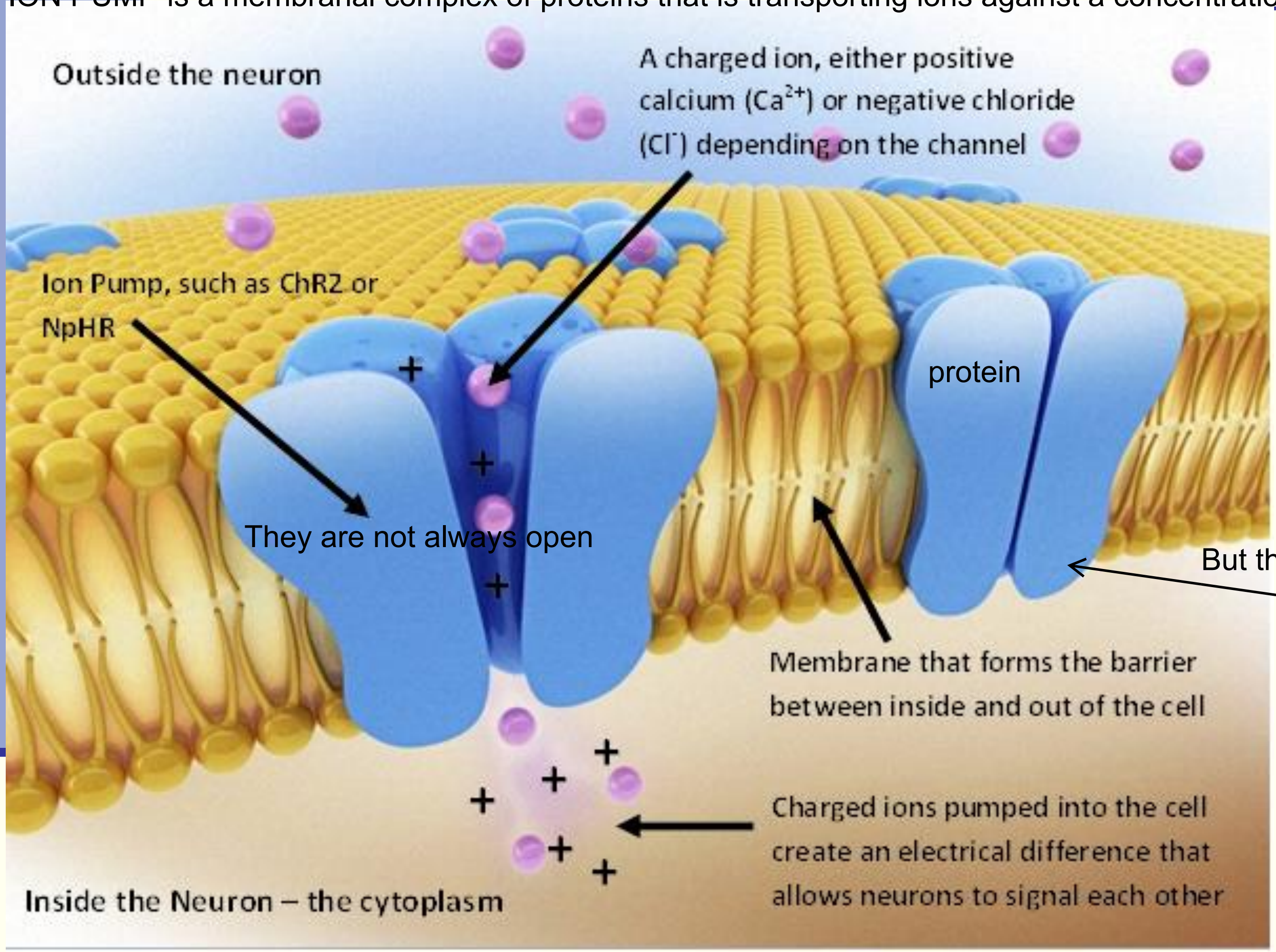
The yellow elements are phospholipids. they are made by phosphoric head (in contact with water) and a lipidic tail (idrophobic). In the internal there is the cytoplasm, and externaly there is a water solution. Very few substances can cross the layer

The neuronal membrane

ION CHANNEL is a protein that acts as a pore in a cell membrane and permits the selective passage of ions
ION PUMP is a membranal complex of proteins that is transporting ions against a concentration gradient using the energy of ATP



- It's the main morphologically specialized structure of the neuron
- Selectively permeable to ions (electrically charged atoms or molecules)

The ion are elechtrical, and the elechtrical charge do not cross the double layer.

- Main ion families: Na^+, K^+, Cl^-, Ca^{++}

But there isn't impossible for these to cross the membrane

- Ion channels and ion pumps allow ions to move into and out of the cell by opening and closing in response to voltage changes and to both internal and external signals.

If you are curious about membrane transport mechanisms: https://youtu.be/J5pWH1r3pgU (not part of the course program)

It's the mean in which the neuron performs its functions. It's based on 2 elechtrical signals related to the membrane. They are the MEMBRANE CURRENT and MEMBRANE POTENTIAL which is a conseguence of the first.

Membrane potential

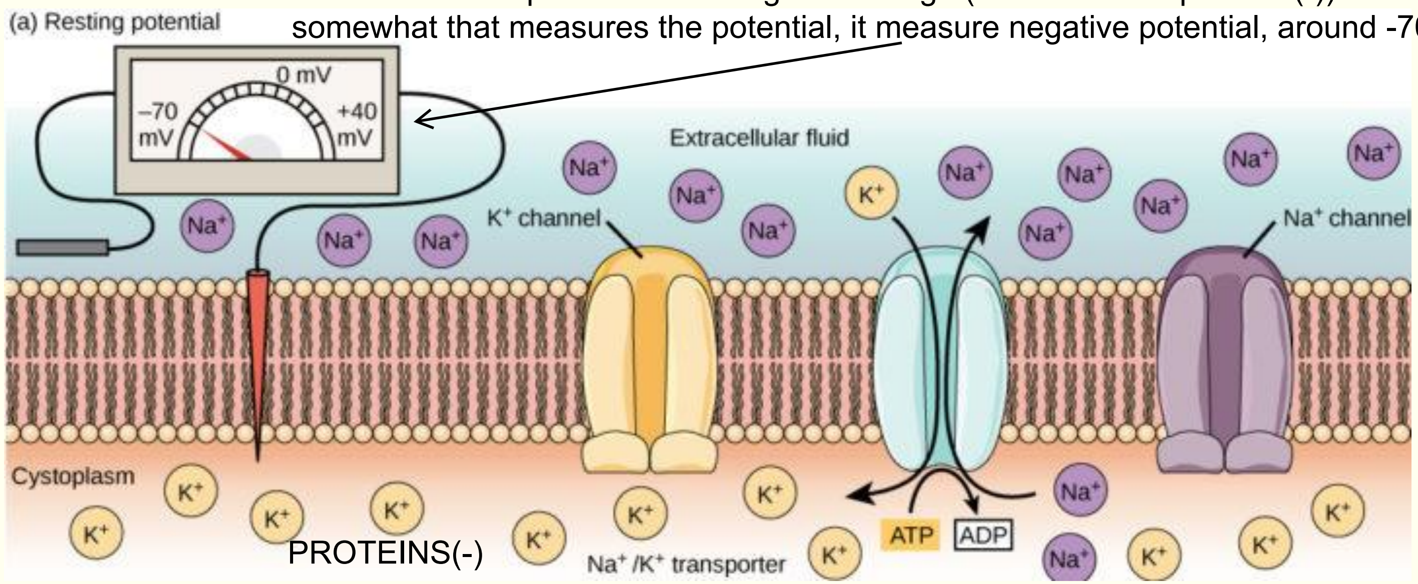
Membrane current: the membrane is elechtrical charged, when charges are in movement we have an elechtric current. In certain circumstances ions are free to move across the membrane. When they do this the ions cross the membrane, it means that current crosses the membrane. The current direction follows the sign of the ions.
When info don't arrive, in the membrane we have an equilibrium in all the transport mechanisms (channel, pumps, ions movements) through the membrane, so we are in stable condition but the concentration of ions in and out the cell isn't the same.

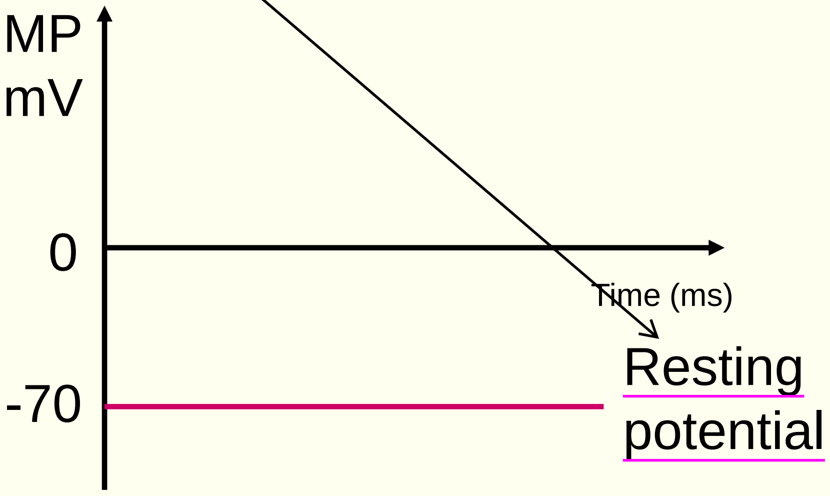
- It's the difference in electrical potential between the interior of a neuron and the surrounding extracellular fluid
- It is due to the different ion concentrations on the two ends of the membrane

One of the role of proteins is to mantain the resting potential (for ex. the ion pumps: it uses energy in the form of ATP, and it uses energy. They keep the resting potential or go back to this).

- At rest (unperturbed membrane) it's around -70 mV
- The cell membrane is said to be polarized

Inside there is a prevalence of negative charge (there are also proteins(-)) while externaly there is a prevalence of positive charges. If we put somewhat that measures the potential, it measure negative potential, around -70 milliVolt.





Membrane potential

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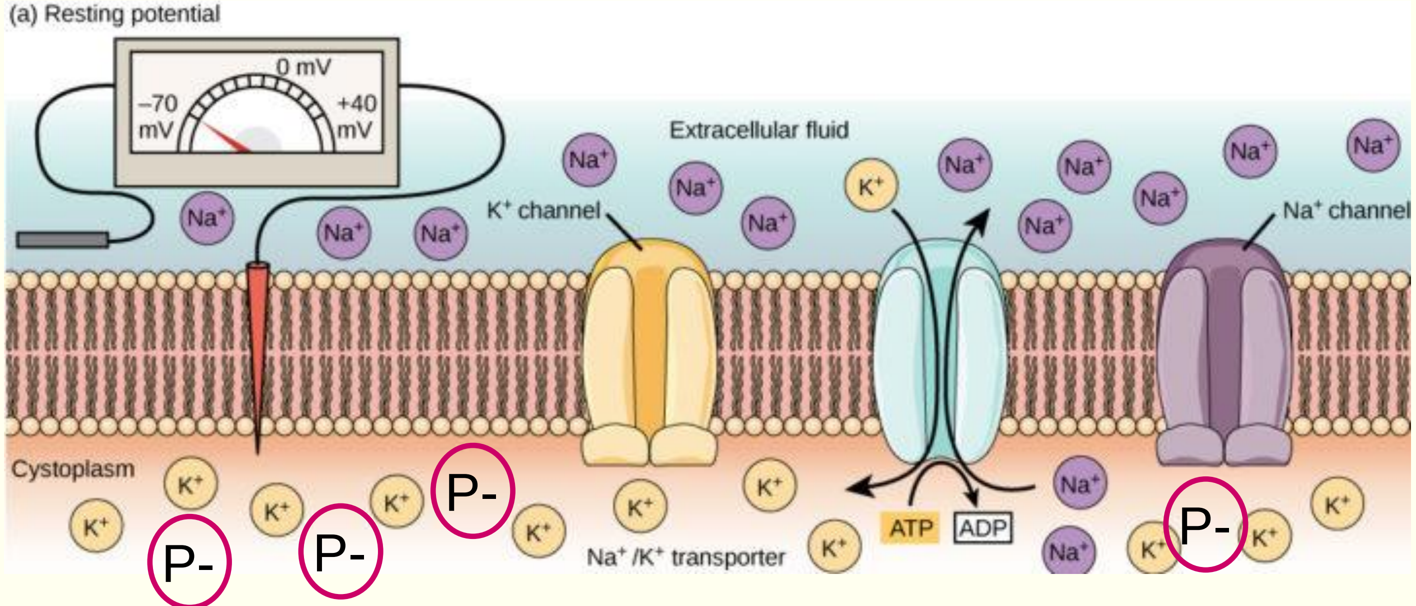
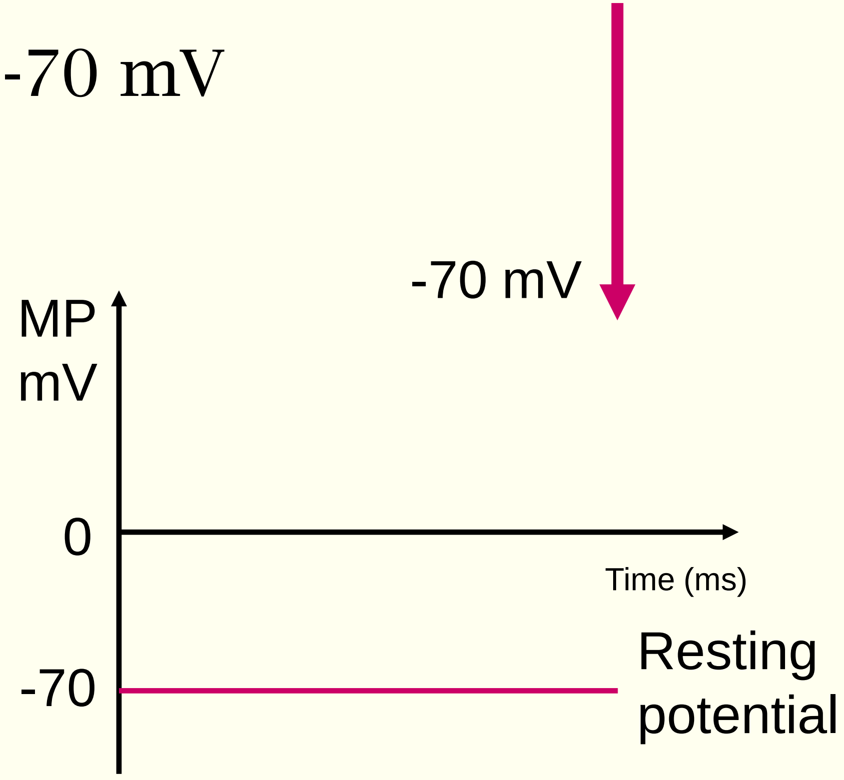
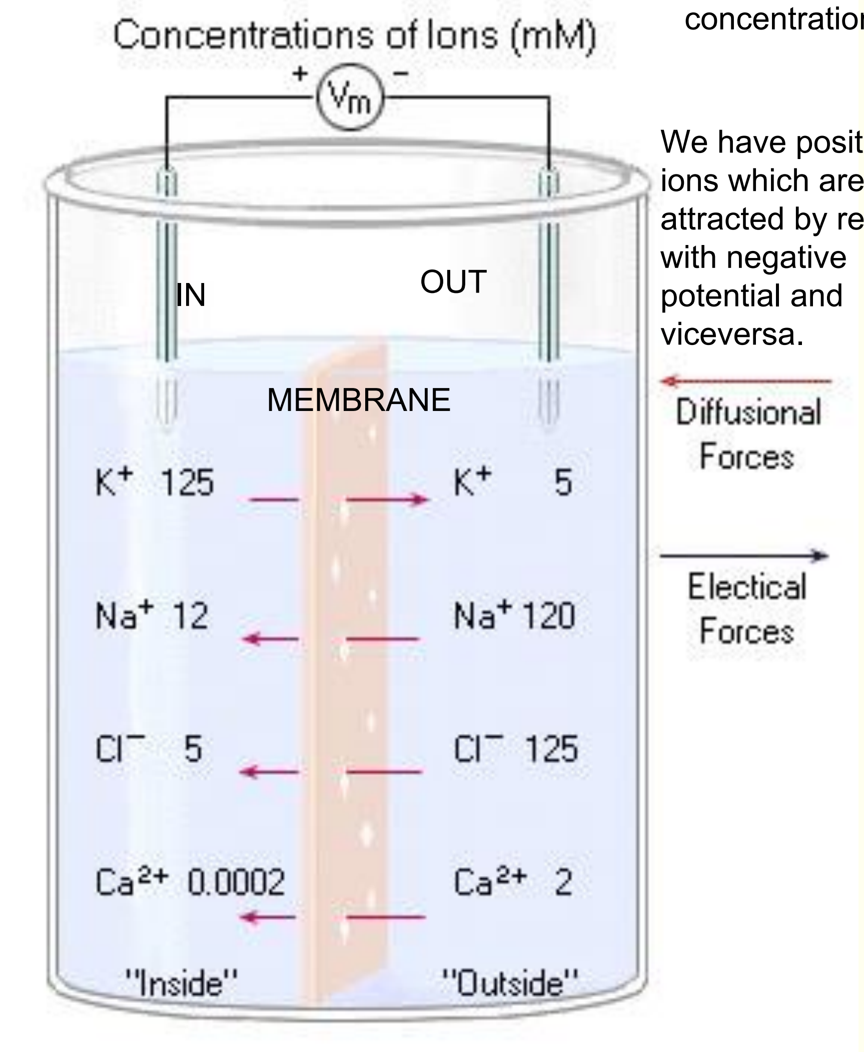




The difference between concentrations of ions is necessary.

Membrane potential at rest and electrochemical equilibrium

If I have 2 solutions and a membrane between them and different concentration in an out the membrane of a substance, I have a force that flows from the higher concetration to the lower. This is the DIFFUSIONAL FORCE. the aim of this force is to reduce this difference and to reach the same concentration (For ex. the sugar is mix completely with water).

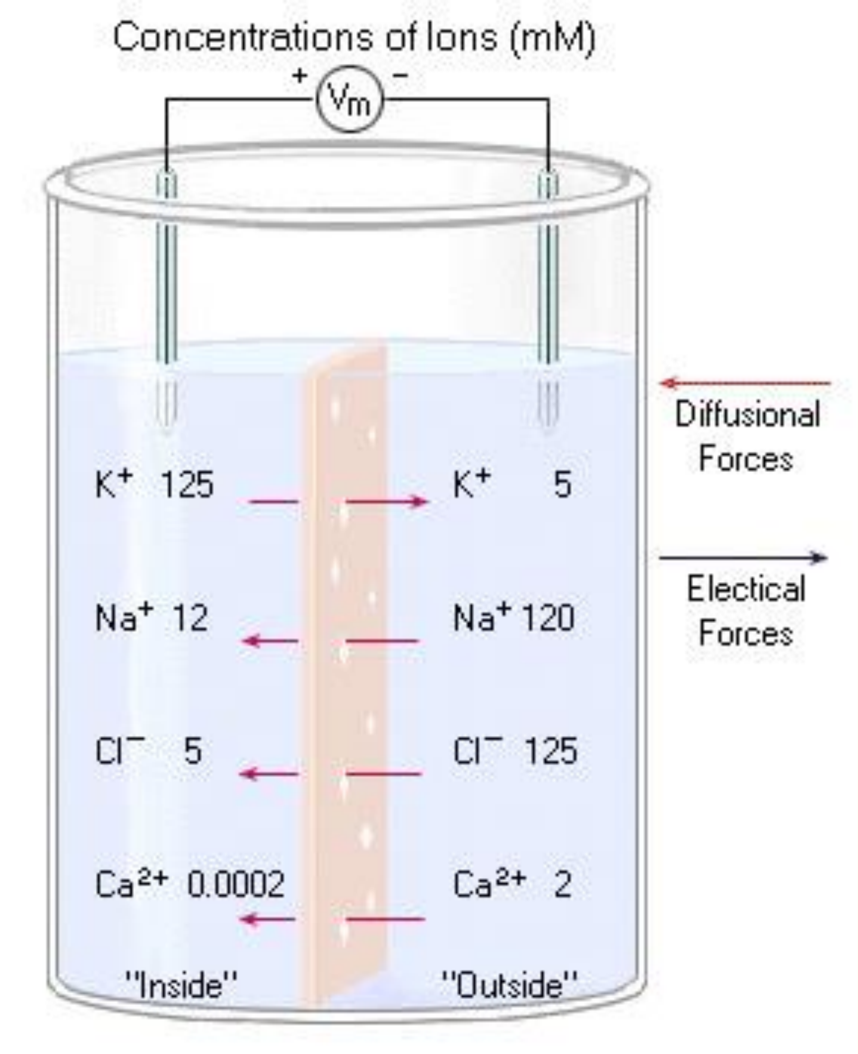


We have positive ions which are attracted by region with negative potential and viceversa.

- Diffusional forces: due to the chemical gradient (different concentrations of ions in the intra- and extra-cellular fluids)
- Electrical forces: positive ions are attracted toward the region with a negative potential, and vice versa (electrical gradient)
- The sum and balance of diffusional and electrical forces leads to an **equilibrium**
- The equilibrium is given by the Nernst equation:

$$\Delta\mu = \boxed{RT \ln \frac{[X]_A}{[X]_B}} + \boxed{zF(E_A - E_B)}$$

Membrane potential at rest and electrochemical equilibrium



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There is a third force acting on the ions which is not due to there charge or concentration but is provided by the membrane and this is provided by specifical channels which are ions pumps. When an ion channel is open, the ions move through the cell acoording to diffusional and elechtrical forces. If you have a passive channel the ions move through the membrane according to electrochemical gradient

Causes of the membrane potential at rest

If we want to move ions against the elechtrochemical gradient it is possible but it requires energy, so isn't a passive mechanism but is active. The energy is in the form of ATP.

Rest potential

The sodium potassium pump works in cycle continuously throughout the life of the cell. At each cycle it uses a molechol of ATP(energy coin) and collects 2 potassium ions from the outside of the cell and realizes 3 sodium ions to outside of the cell.

=

1. Diffusional forces

The ion pumps move the sodium from the lower concentration to the higher concentration. In the ion channel is the opposite, for this reason the pumps require energy(ATP). The same happens for the potassium

+

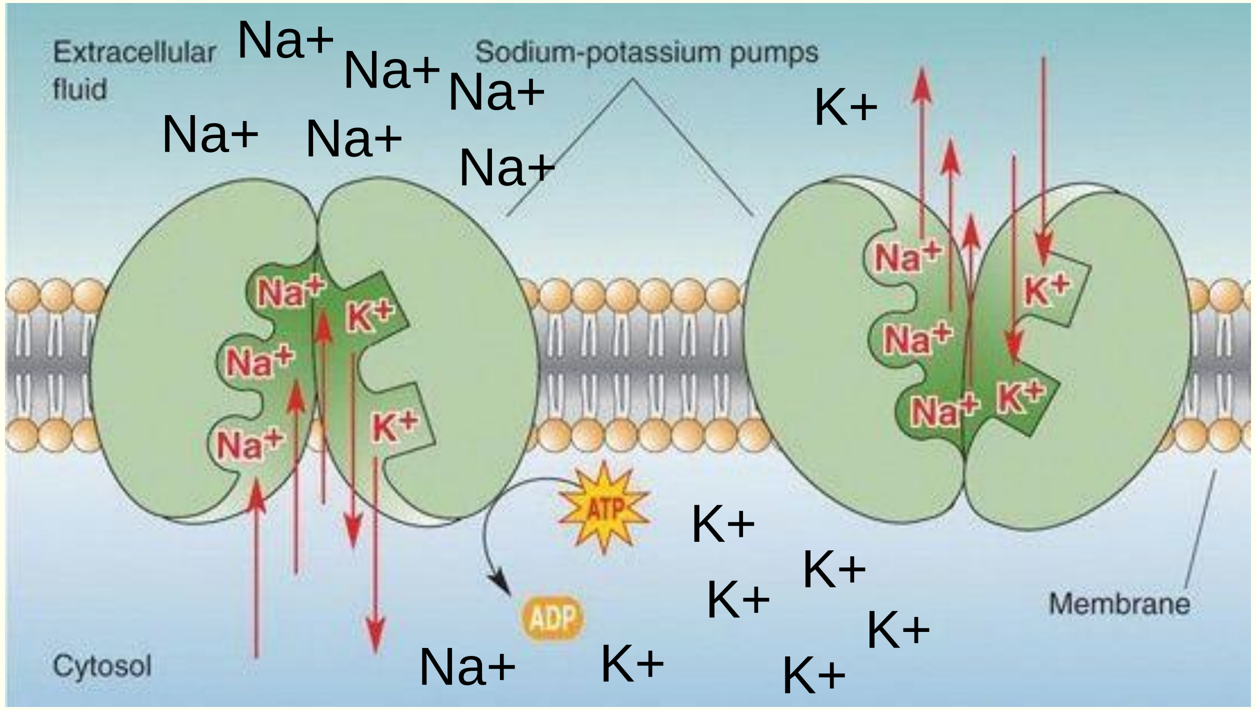
2. Electrical forces

Na+ flows from in(lower concentration) to out (higher concentration) the cell
K+ flows from out(lower concentration) to in (higher concentration) the cell

+

3. Ion pumps

Ion pumps: they move ions **against** their electrochemical gradient by **active** (energy consuming) **transport**
The most important one is the **sodium-potassium pump** :

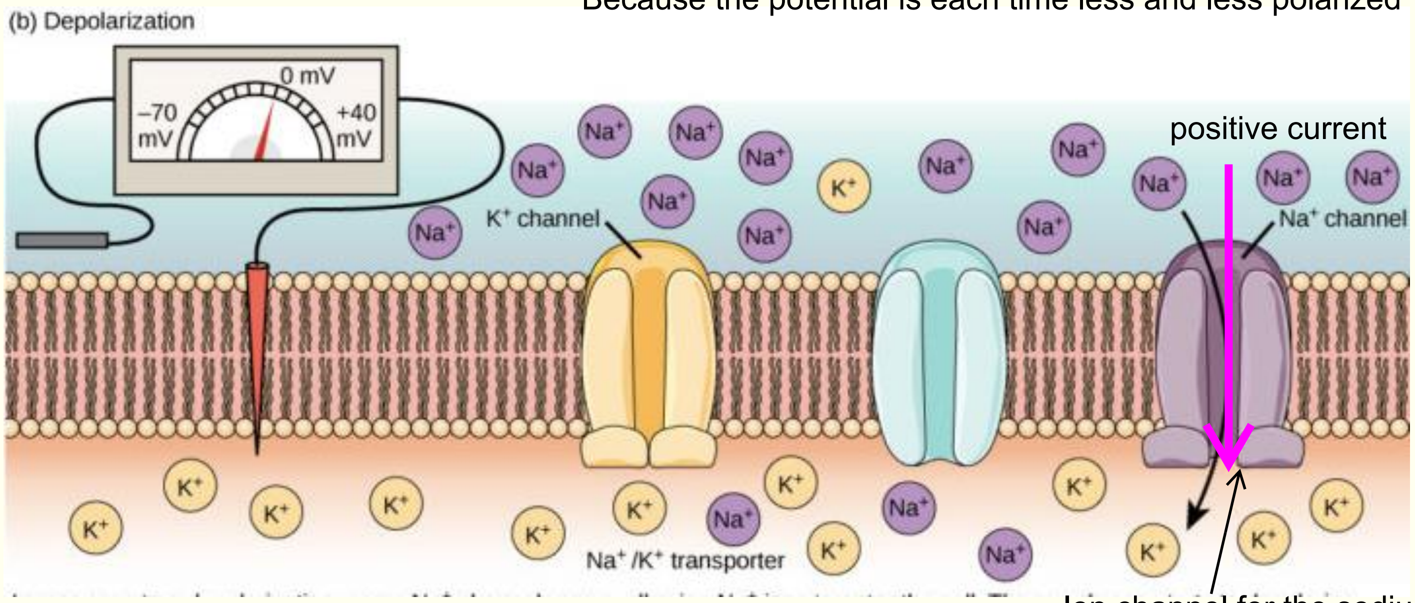


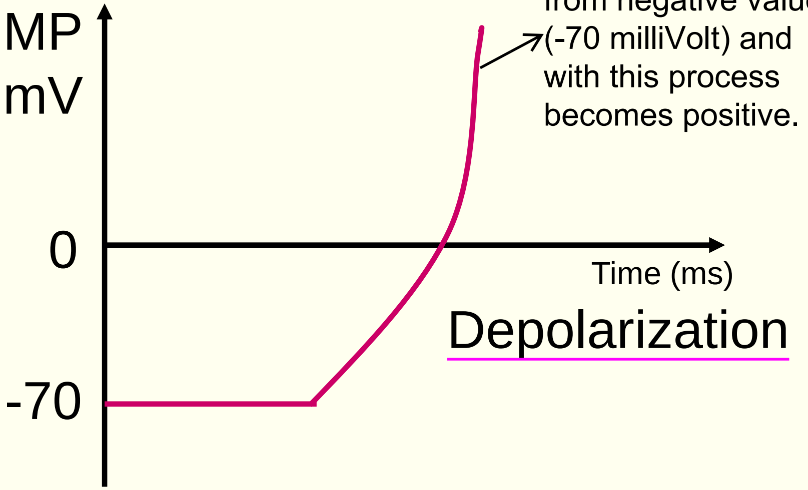
Membrane depolarization

The sodium has more concentration out of the cell with respect to the in. When the gate is open and sodium can cross the membrane, positive charges move to the region with higher concentration to the region with lower concentration. At rest, the current through the membrane is zero and membrane potential is constant. The positive current moves the ions to the positive region into a region that has more negative charge. The membrane potential becomes less negative, because positive charges are in the negative zone.

- Current in the form of **positively charged ions** flowing **into** the cell (or **negatively charged ions** flowing **out of** the cell) makes the membrane potential **less negative** or even **positive** → membrane **depolarization**

Because the potential is each time less and less polarized





The potential start from negative value (-70 milliVolt) and with this process becomes positive.

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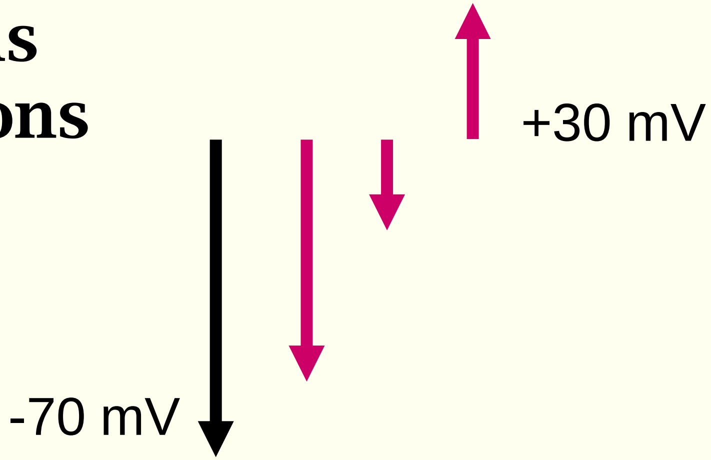
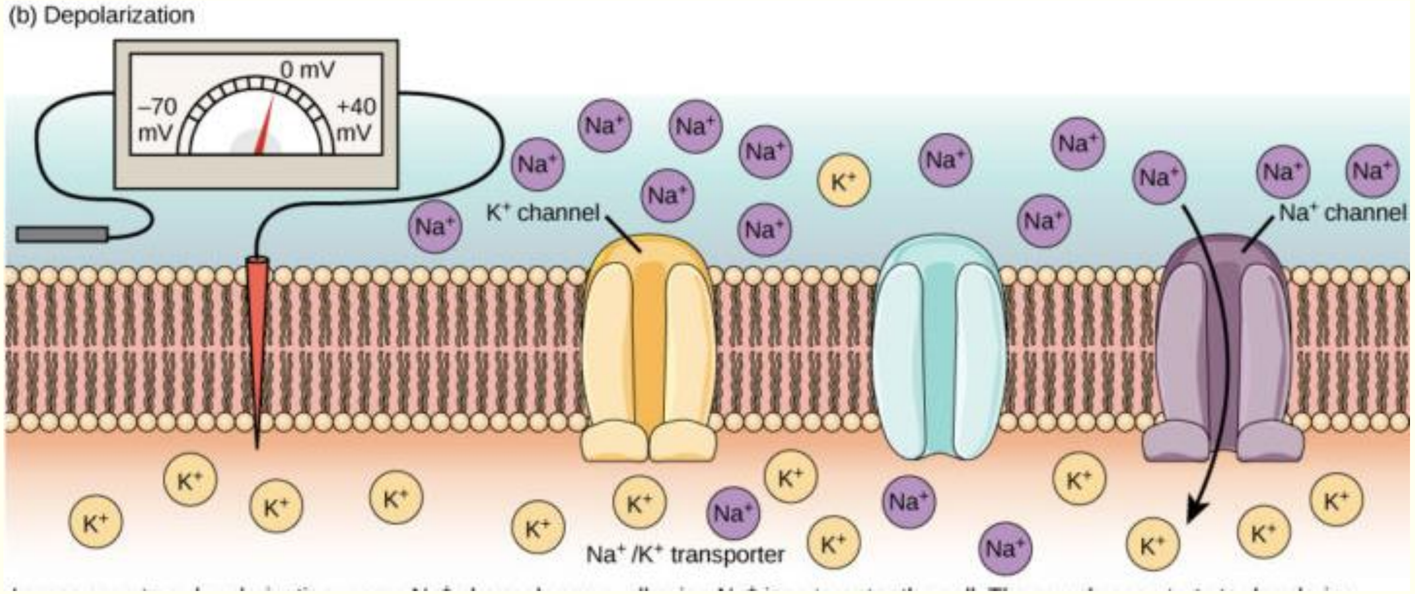
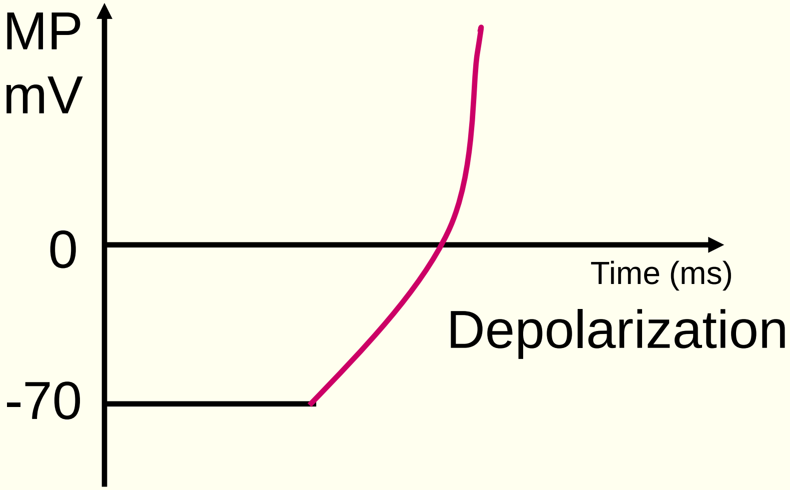




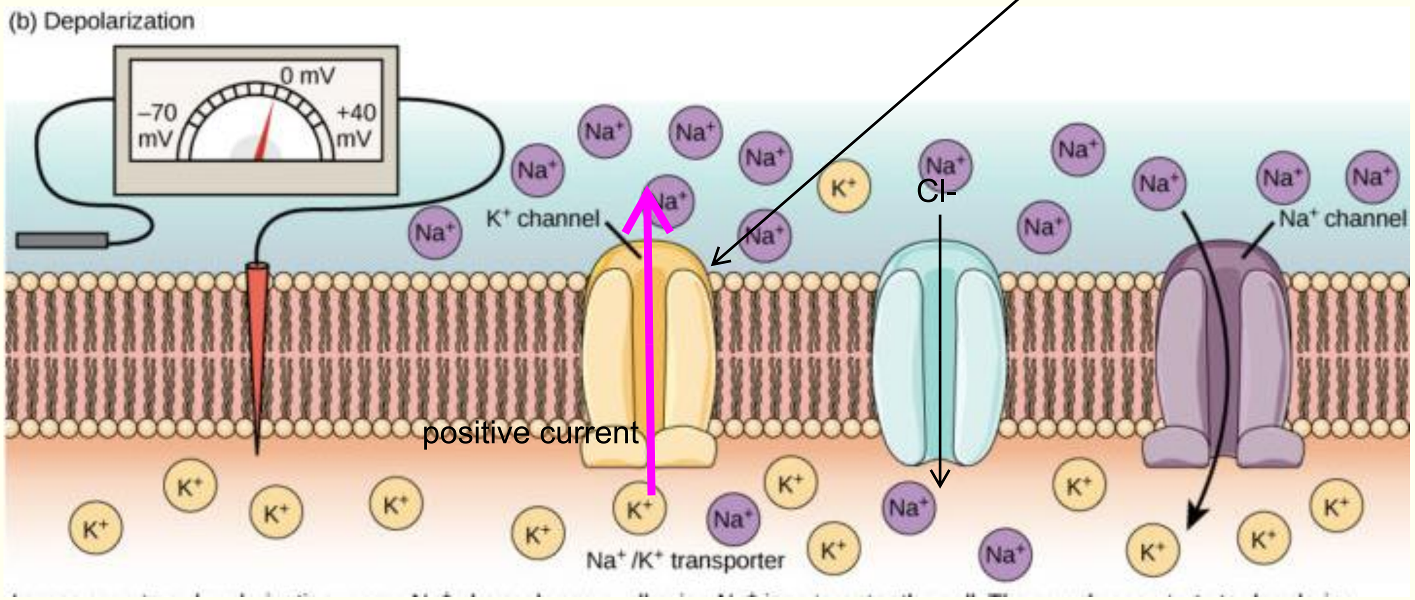


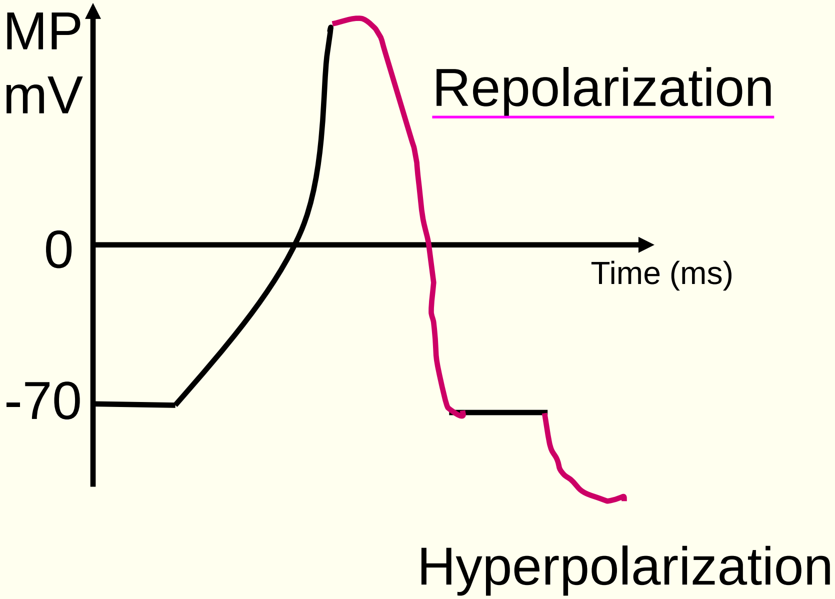
Membrane hyperpolarization

A different case is that of potassium. It has more concentration in the cell with respect to the out. When the gate is open the current move the gharges from the internal to the external, so the potential becomes more negative, because we are removing positive charges.

- Current in the form of **positively charged ions** flowing **out of** the cell (or **negatively charged ions** flowing **into** the cell) makes the membrane potential **more negative** → membrane **hyperpolarization/repolarization**

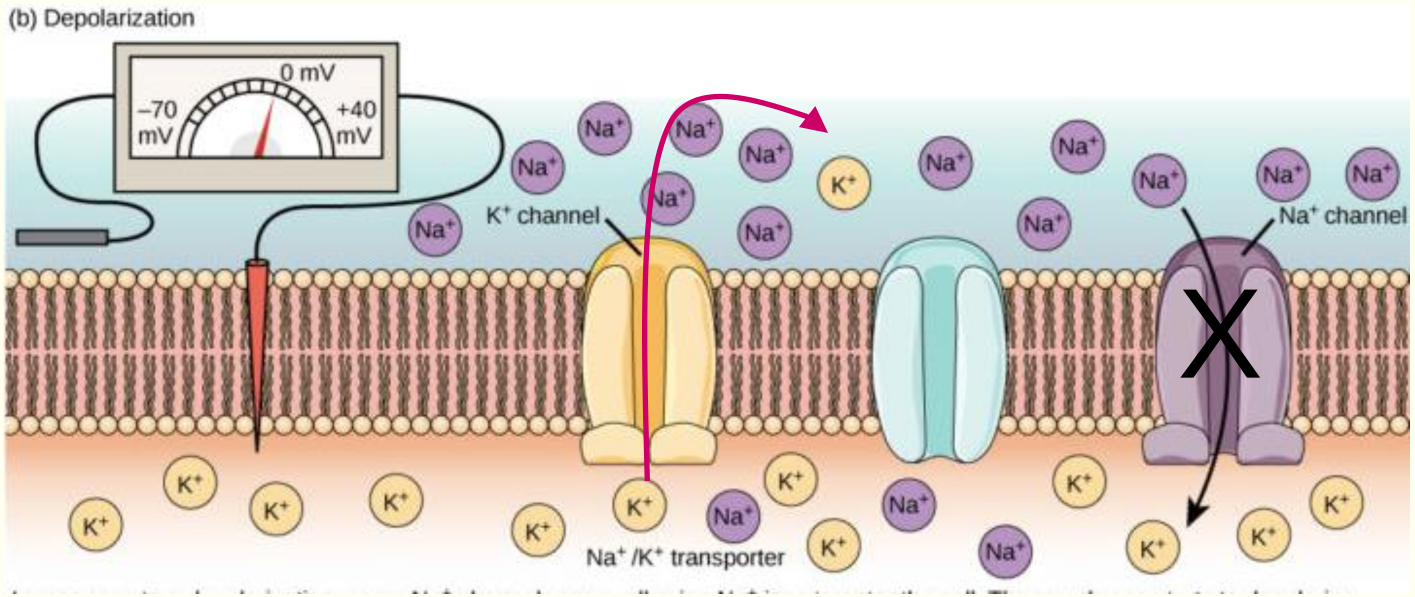
When we have chlorine Cl-, that is a negative ion, when the current moves this fron the external of the cell to the internal, what happens is exactly the same. The negative charges enter the cell and the membrane potential becomes more negative

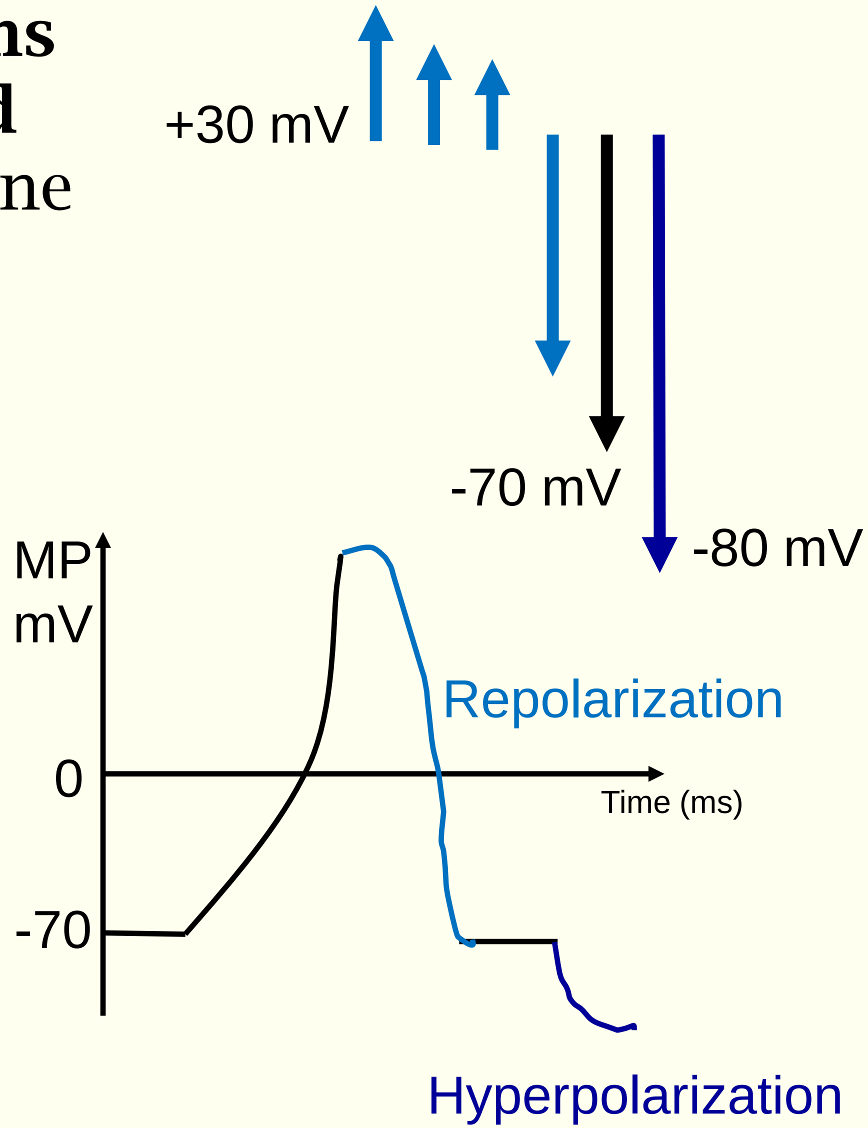




Membrane hyperpolarization

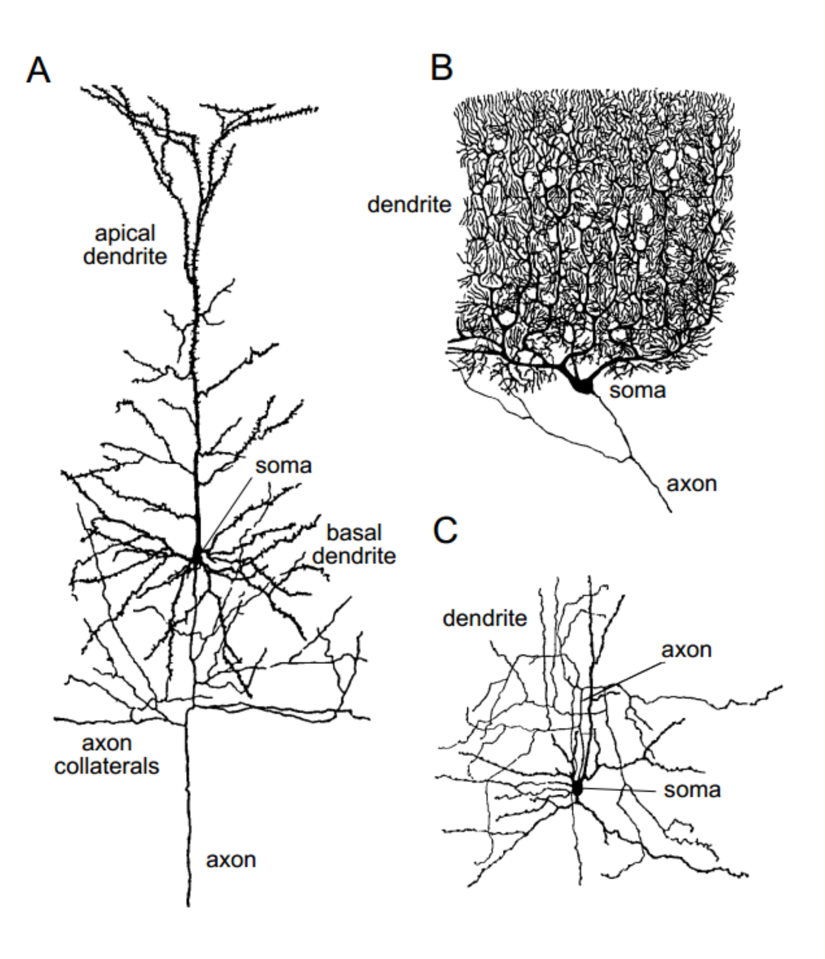
- Current in the form of **positively charged ions** flowing **out of** the cell (or **negatively charged ions** flowing **into** the cell) makes the membrane potential **more negative** → membrane **hyperpolarization/repolarization**





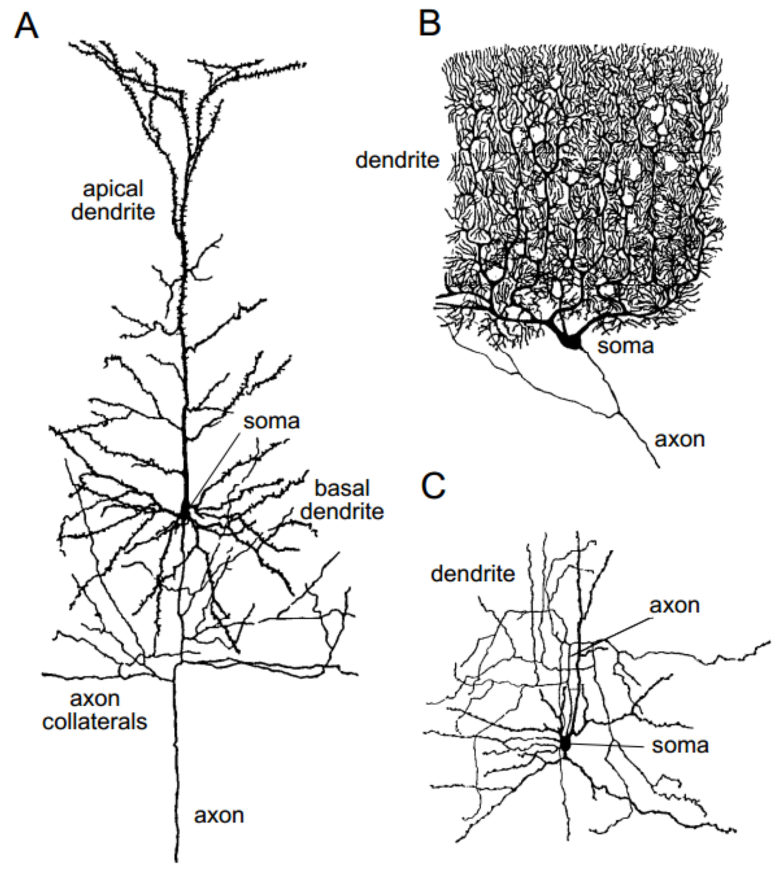
The first function, as we said, is the collection of info. It is performed in the dendridic tree.

1 - Dendridic tree



- Collects information from other neural cells/receptors through synaptic connections
- 1/100 thousands inputs for each cell
- Summation effects (in time and space)

1 - Dendridic tree



Dayan and Abbott, Fig. 1.1

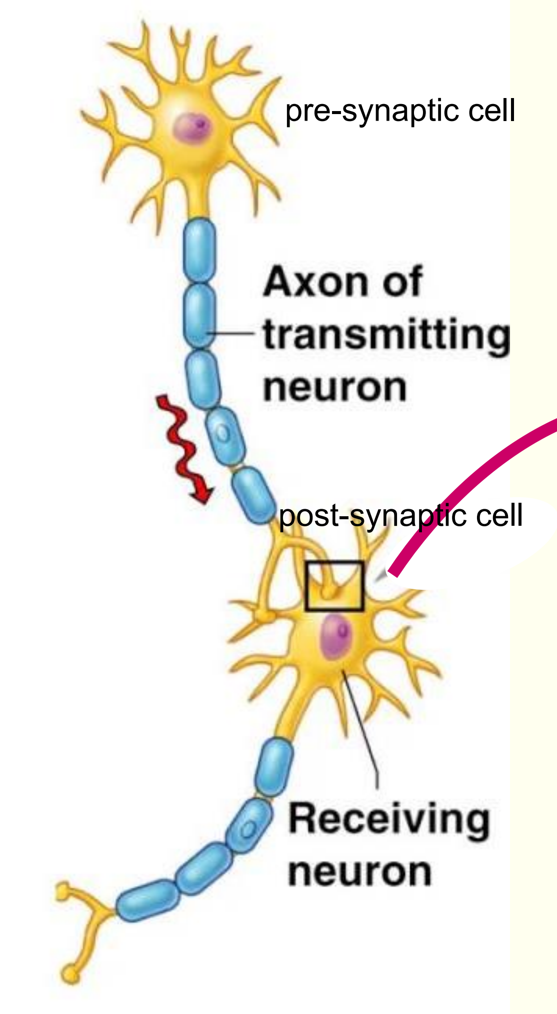
- Collects information from other neural cells/receptors through synaptic connections
- 1/100 thousands inputs for each cell
- Summation effects (in time and space)

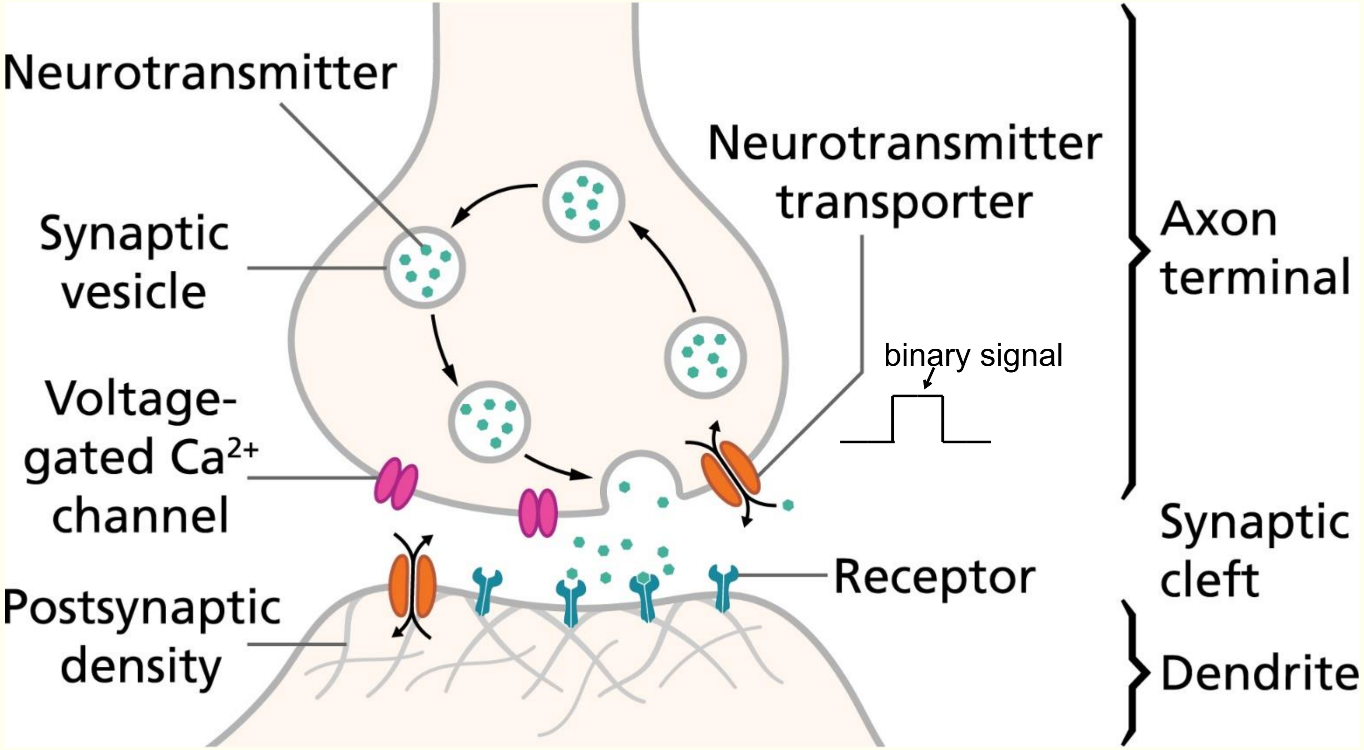
How binary output signal is traduced into non binary input signal? This happens by means of synapses. They are the parts where synapses communicate and are connected.

1- Synapses

The PRE cell is the neuron which is sending the binary output and the POST is the neuron which is receiving this with output of many other cells. What happens in the synapses? Here there is a translation of the elechtrical signal into a chemical signal, and then again into an elechtrical signal.

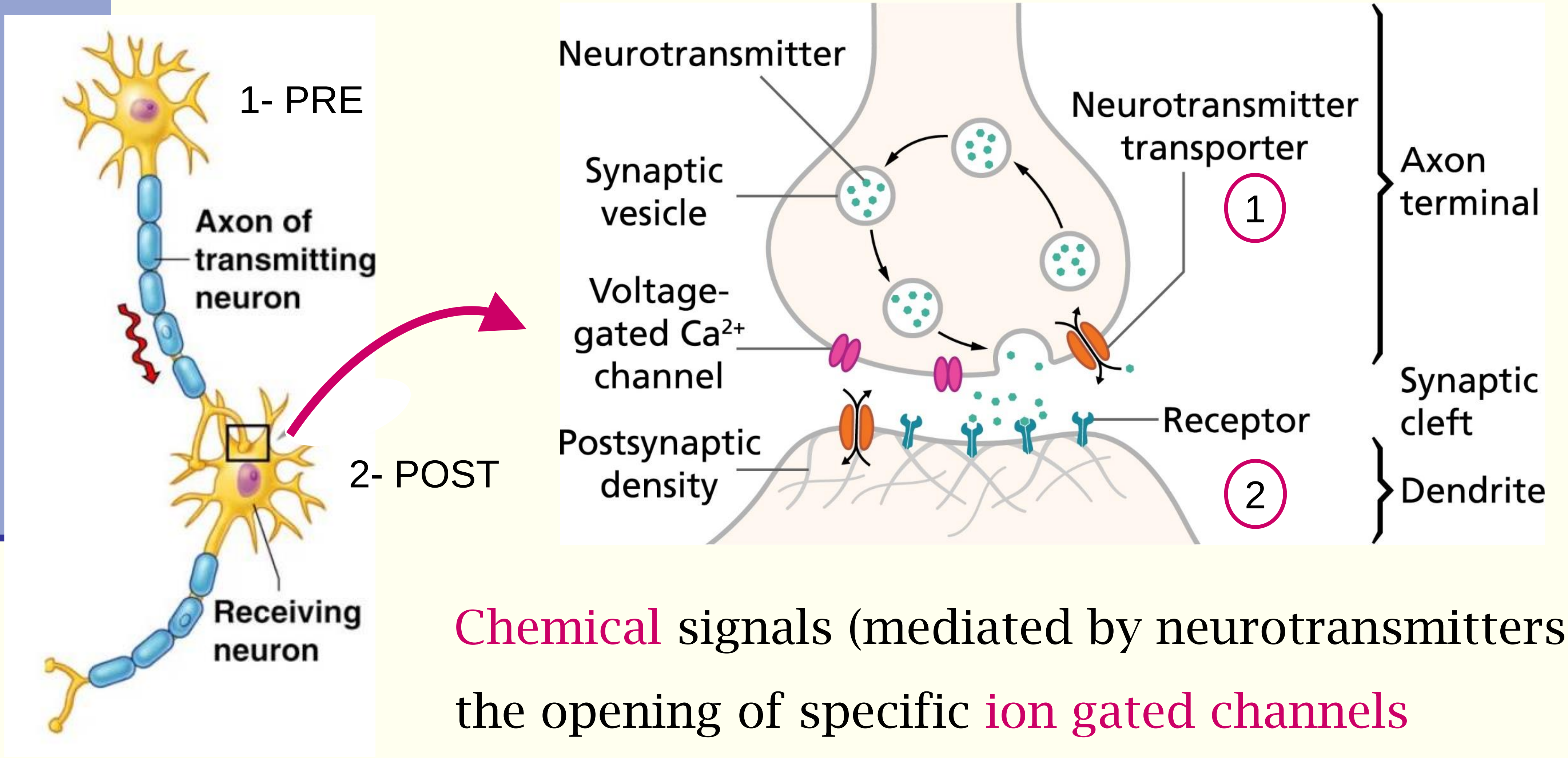
When the binary signal arrives here, each time the signal is equal to 1 (if it is zero nothing happens) the pre-synaptic neuron realize a chemical transmitter which is called neurotransmitter (it is like the key to open the gate). When the gate is open an ion current cross it.





Chemical signals (mediated by neurotransmitters) cause the opening of specific ion gate channels

1- Synapses

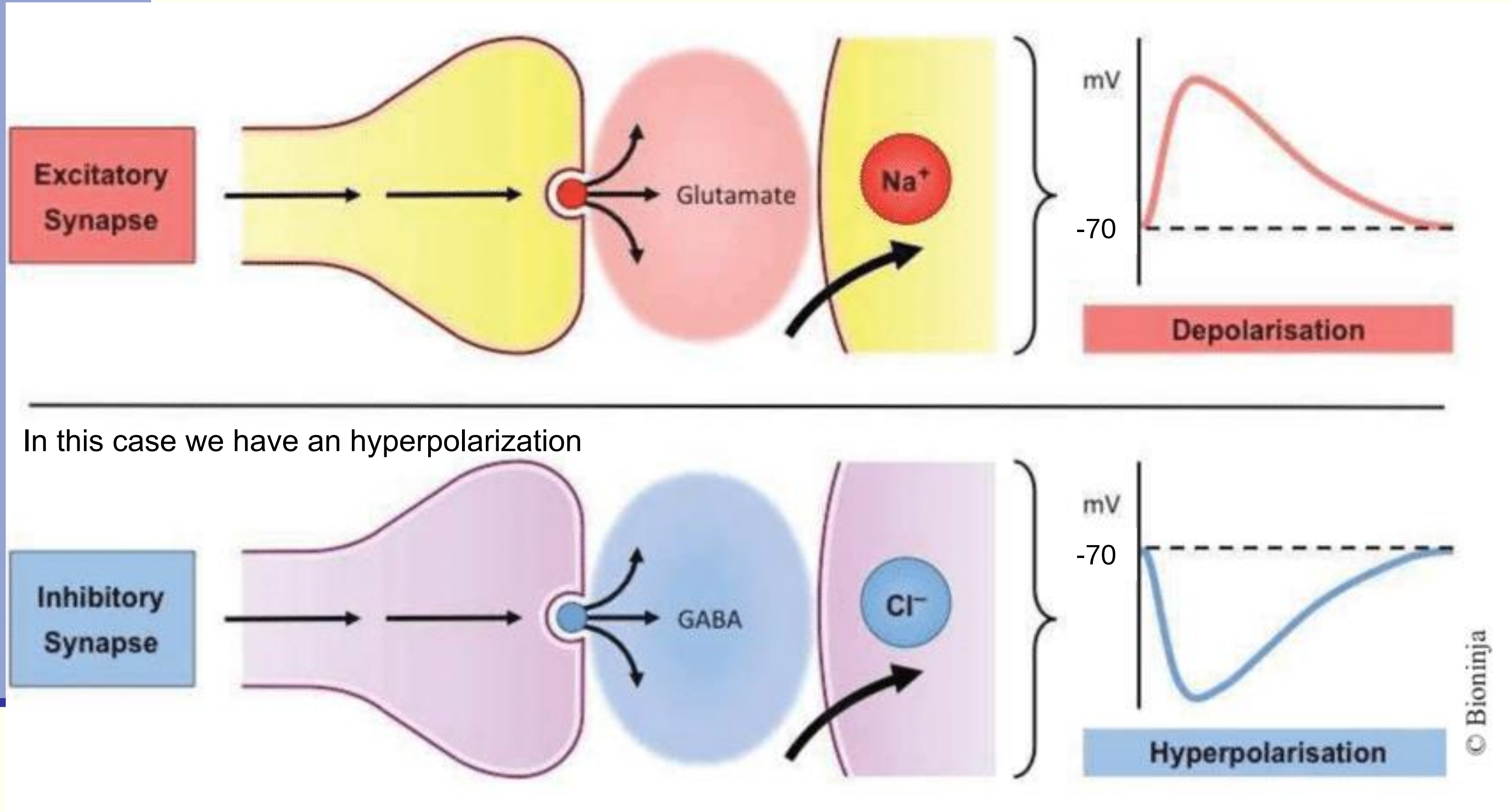


Chemical signals (mediated by neurotransmitters) cause the opening of specific ion gated channels

The gates are open for few milliseconds and then they close. The synapses cannot be both excitatory and inhibitory.

1 - Excitatory and inhibitory synapses

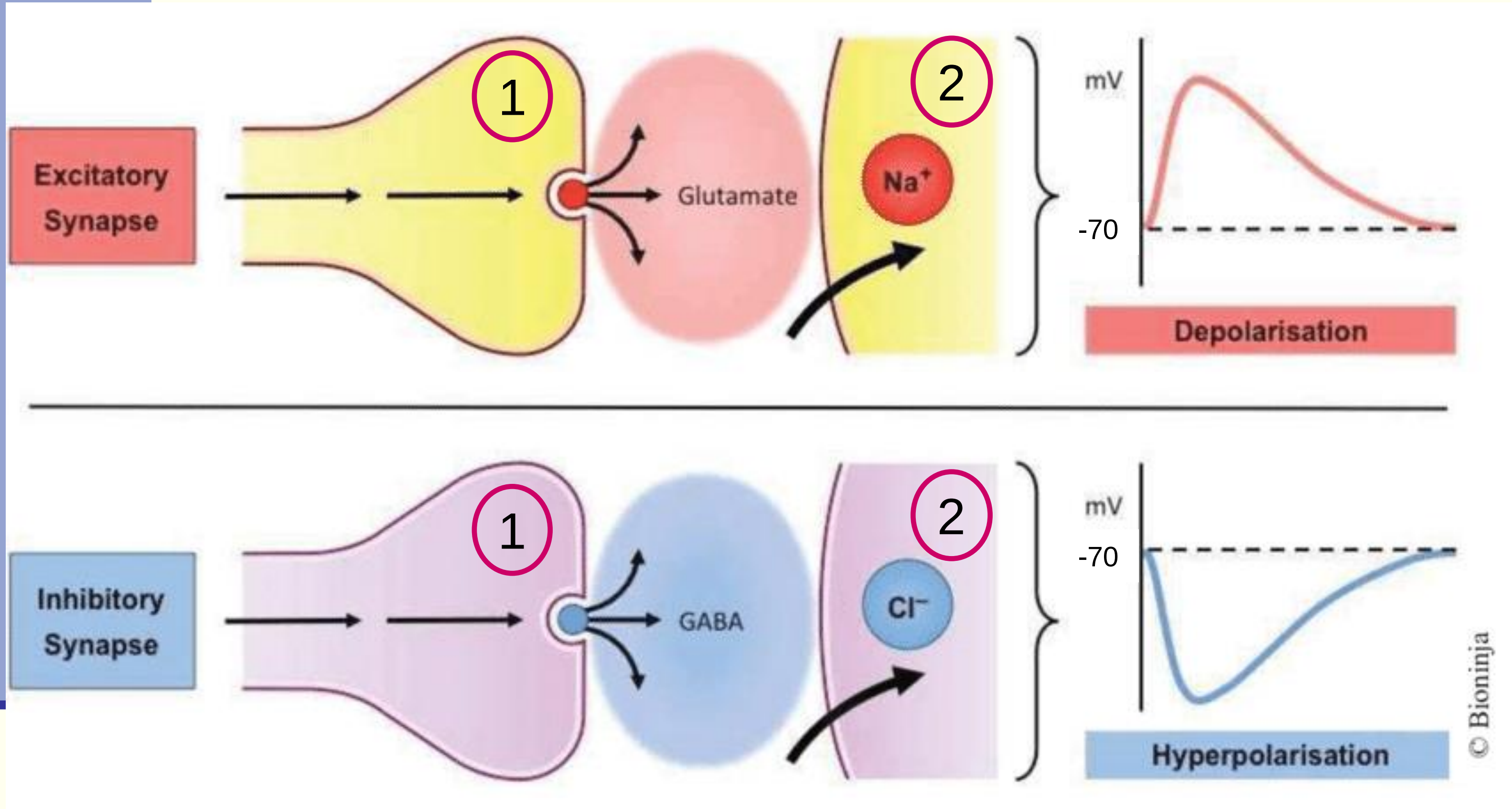
If the gate is a sodium gate, we will have a sodium current. Happens a depolarization



- Excitatory Post-Synaptic Potential (EPSP) → depolarisation
- Inhibitory Post-Synaptic Potential (IPSP) → hyperpolarization

Excitatory and inhibitory to what? To the neuron response!

1 - Excitatory and inhibitory synapses



- Excitatory Post-Synaptic Potential (EPSP) → depolarization
- Inhibitory Post-Synaptic Potential (IPSP) → hyperpolarization

When a potassium channel or a cl channel is open we have a different current flowing through the membrane, because we have a negative current flowing inside the cell if it's a Cl channel or flowing outside if it's a K channel. In both cases we have an increases of the negativitty inside the channel(HYPERPOLARIZATION).

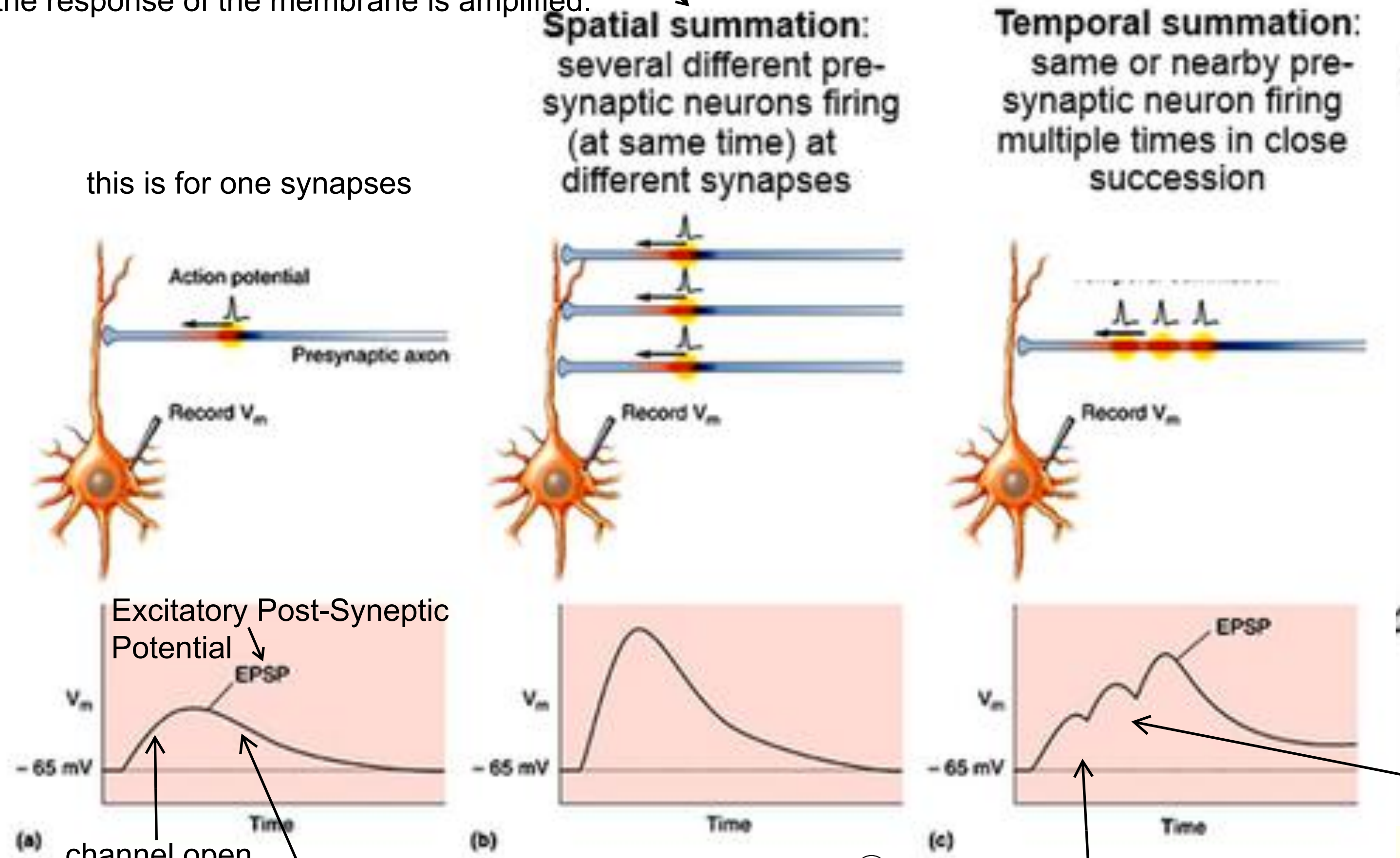
Excitatory and inhibitory to what? To the neuron response!

How are the info integrated and processed by the cell? This is the second function of the cell. The cell makes this through integration that is performed by summation. This summation is also the reason why the binary output signal of the neuron is translated into a continuous input signal to another neuron.

2 - Summation of PSP

we have many synapses with the bits of info arriving each one of them simultaneously. So dfferent synapses close to each other and bit of info arriving on all of them simultaneously. Happens that the response of the membrane is amplified.

this is for one synapses

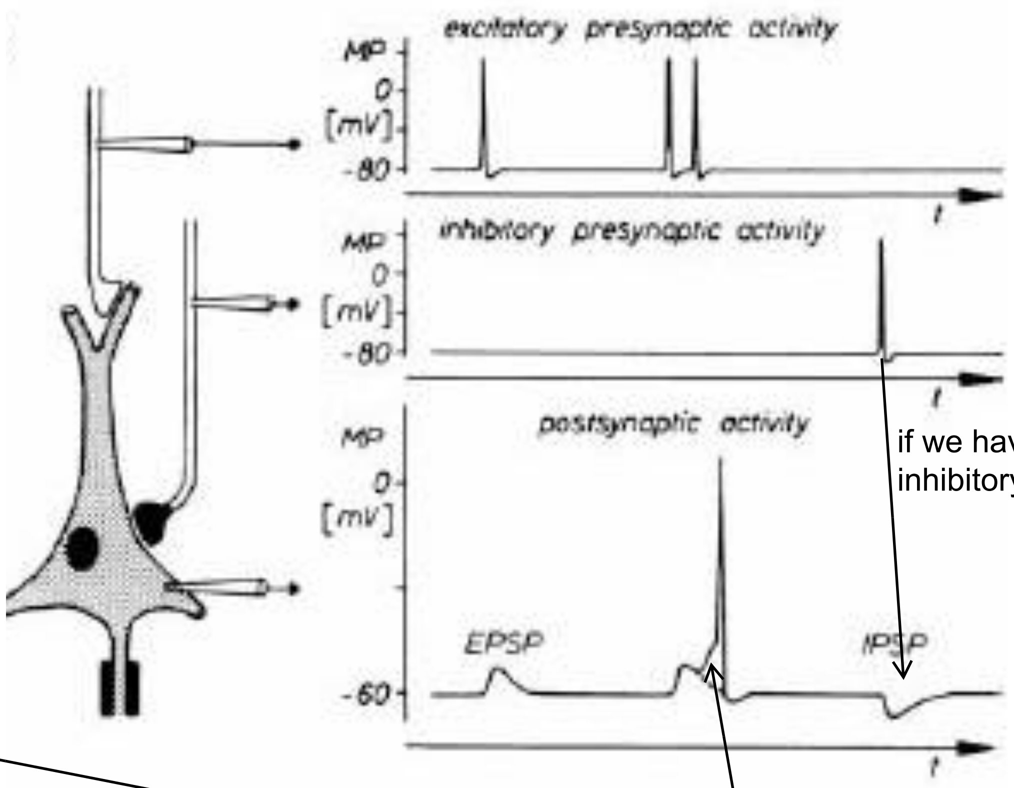


Excitatory Post-Syneptic Potential

channel open

channel close: returns to the initial potential by means of pumps

when we have temporal summation, the result is this summation always with the same sign. We have 3 spikes close in time

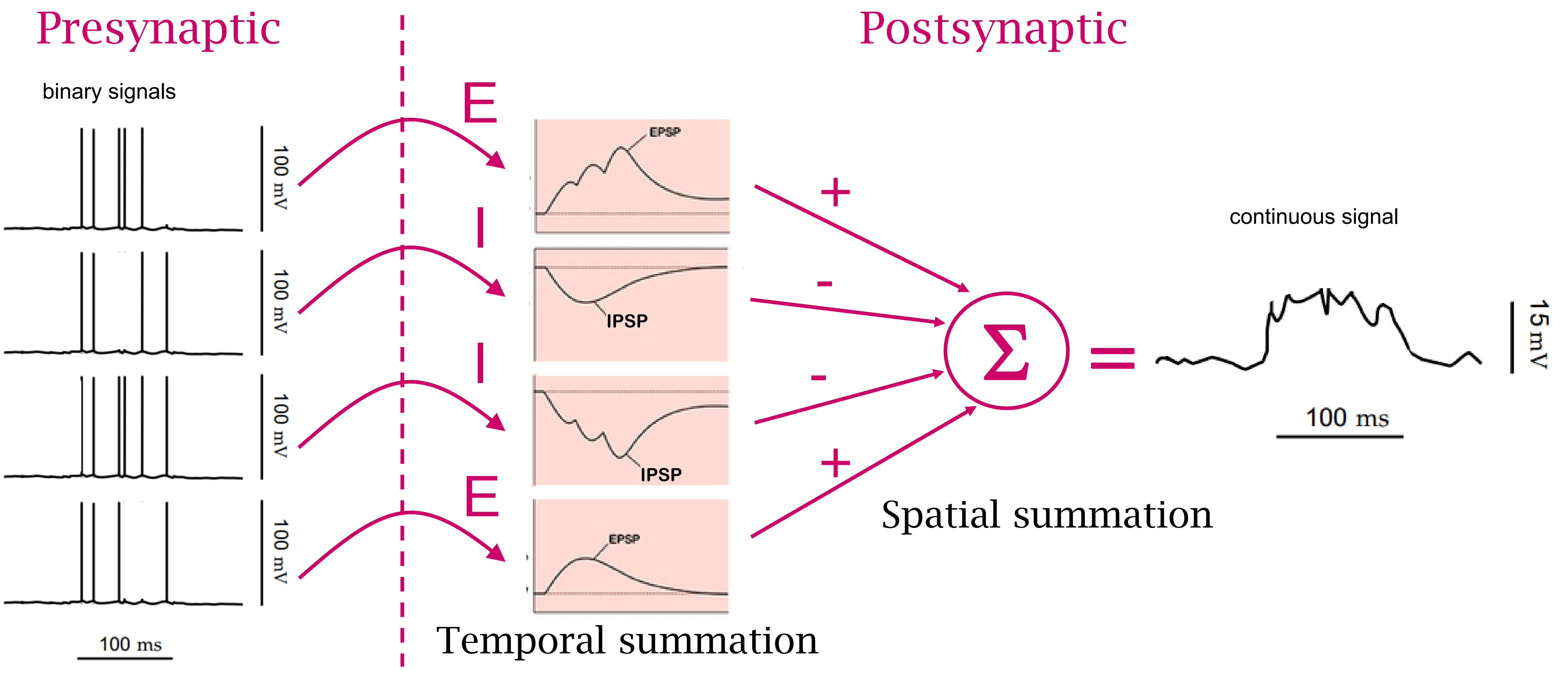


if we have an inhibitory

the second spike arrive when the effect of the first one are still there. The mebrane don't have the time to go back to the resting state and so the effect is the sum

If we have simultaneously spike, one excitatory and one inhibitory, we will have both effect simultaneously and the result is zero. They will compensate each others.

2- From a binary output to a continuous input



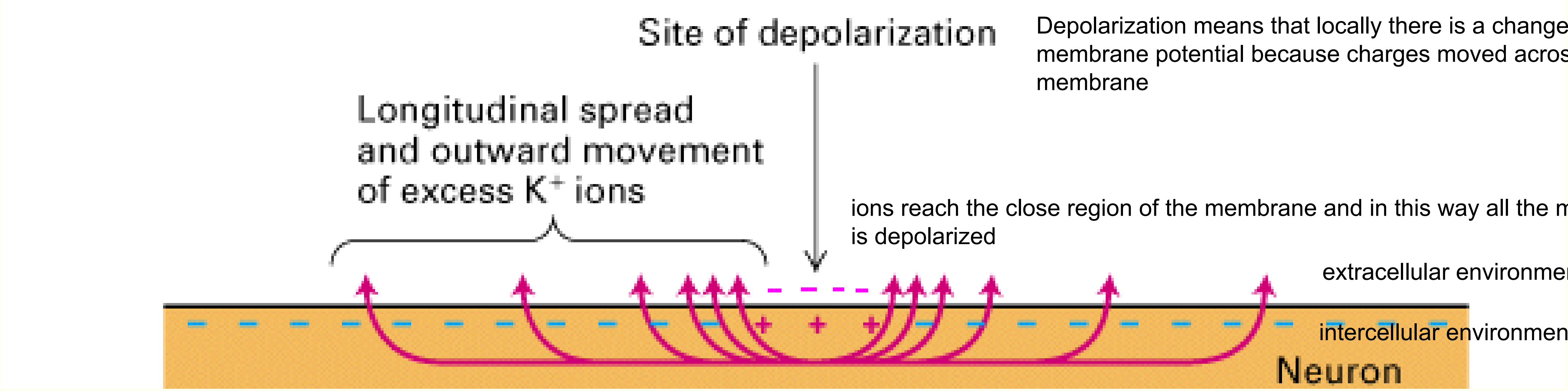
How can, then, integrated info reach a specific part of the membrane which is the axon hilloc?

2- Propagation of the post-synaptic potentials

- A local de/hyperpolarization causes intra- and extra-cellular ion currents
- It is passively propagated to adjacent sections of the membrane

Usually the postsynaptic potentials are propagated by means of a so called passive propagation.

- The perturbation effects decrease with distance



Depolarization means that locally there is a change in the membrane potential because charges moved across the membrane

ions reach the close region of the membrane and in this way all the membrane is depolarized

extracellular environment(fluid)

intercellular environment(fluid)

At the axon hillock we have the signal that is integrated.

2- Integration of the information

- The information processing by the neuron consists of the summation (with sign) of EPSPs and IPSPs
- Spatial + temporal summation produce the membrane de/hyperpolarization
- The result is propagated along the membrane up to the axon hillock
- According to the result, the cell may (or not) fire an action potential

It's one of the most visible charachteristic of the neural cell. The action potential it's variation of the membrane potential which has the power to perform an action. This action is to reach another cell.

3- The action potential

- It's a variation of the membrane potential which appears only in neural, muscular and cardiac cells
- It's an all-or-none process: → process in which we have only 2 possible situations. We have a given threshold and a stimulus
  - If the stimulus does not reach a given threshold, it does not happen
  - If the threshold is reached, it has always the same shape, duration and intensity, irrespectively to the stimulus amplitude

    the action potential
- It's the cell binary «decision» because there is no grey zone, it is only no or yes

To understand the generaton and propagation of the action potential, we need to know the functioning of 2 ions channel.

3- The voltage-gated Na^+ and K^+ channels

We have only 2 condition: open(ions can cross passively according to their elechtochemical gradient) and close(ions can't cross).

Na^+ channel

- Resting potential (-70mV) = closed (ions cannot cross it, it can be open)
- Opening threshold potential (-60 mV) = open, ions can cross
- Inactivation threshold (+30 mV) = inactivated (it cannot be open)
- Closing threshold (-70 mV) = closed (ions cannot cross, it can be open)

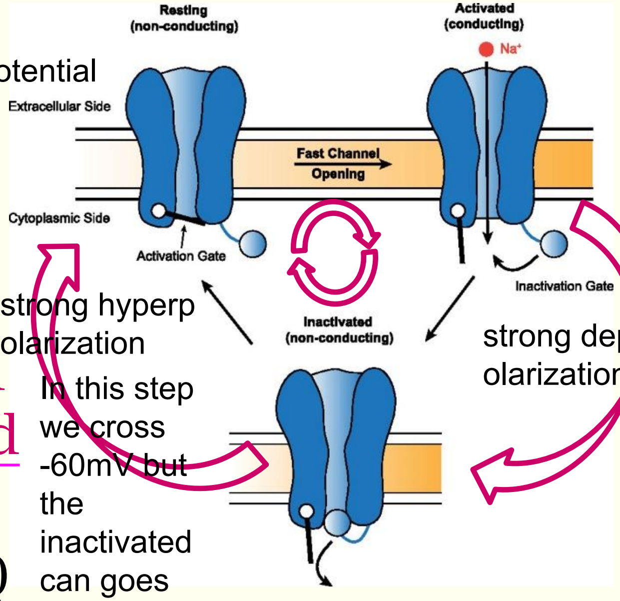
An open channel cannot close so it can be in inactivated condition

changing membrane potential

depolarization

-70 mV

-60 mV



strong hyperpolarization

strong depolarization

In this step we cross -60mV but the inactivated can goes only to close condition

+30 mV

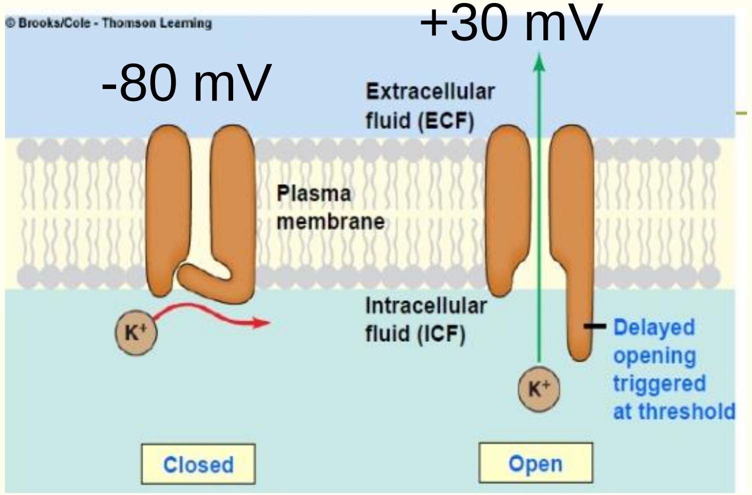
It's more complicated. It can be in 3 possible conditions. These are the closing condition(no ions can cross but it can be open). The second contition is the open(ions can cross). An open channel cannot close but it can move into the inactivated condition(ions don't cross the channel but the channel cannot open while in the close condition it can open)

K^+ channel

- Resting potential (-70mV) = closed (ions cannot cross it, it can be open)
- Opening threshold potential (+30 mV) = open, ions can cross
- Closing threshold (<-70 mV) = closed (ions cannot cross, it can be open)

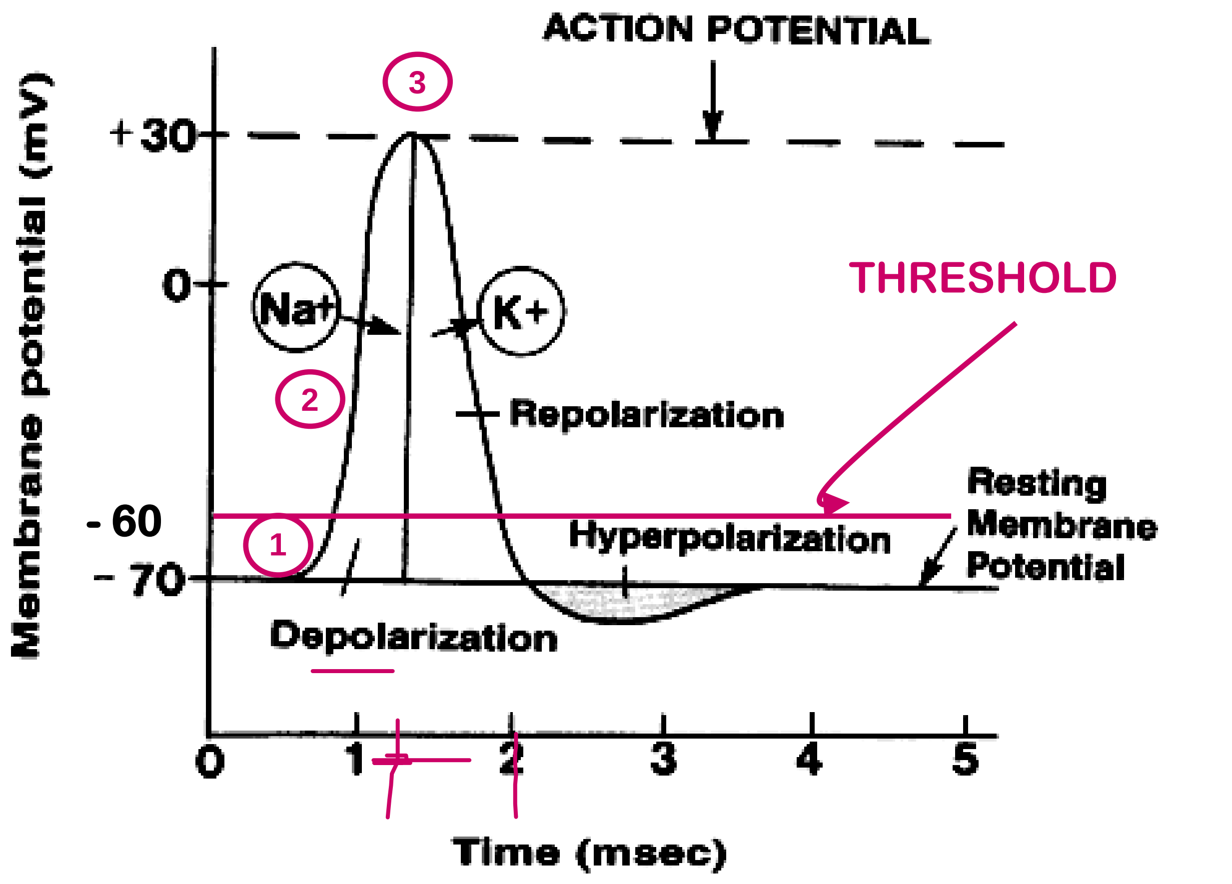
+30 mV

-80 mV



Now we see in which way the action potential is produced, trasmetted and propagated by the cell. We have 6 phases.

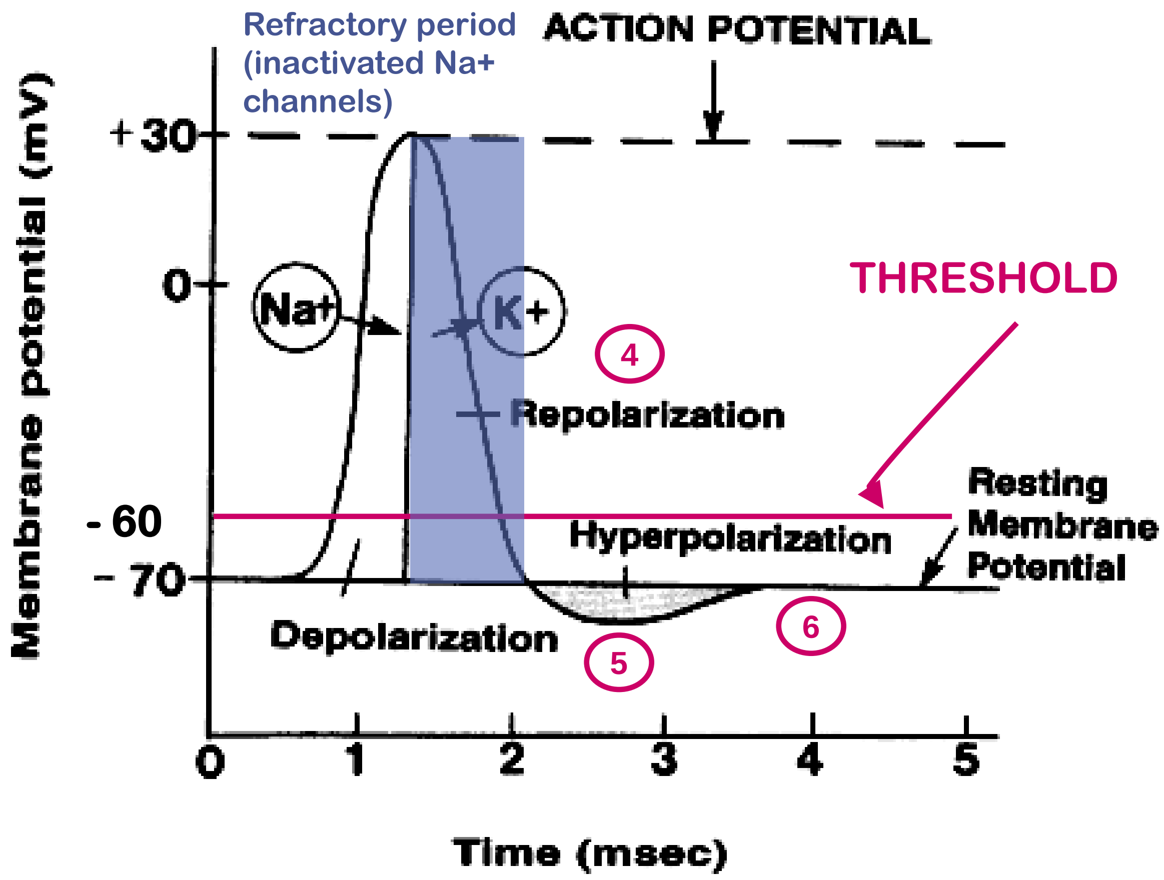
3 - Action potential



to reach the threshold(-60mV)

1. Depolarization to the Na+ opening threshold level (-60 mV) If we have less than 10mV(-60mV, -70mV) we don't reach the threshold and nothing happens, it returns to the resting condition.
2. Fast depolarization, due to the Na+ depolarizing currents (Na+ flows into the cell) in less than 1 ms
3. Closing of the Na+ channels and opening of the K+ channels (+30 mV) At 30mV the 2 channels have different behaviour

3 - Action potential



4. Repolarization, due to the K+ repolarizing currents (K+ flows outside of the cell)
   positive charges are moved outside
5. Undershoot (hyperpolarization) until the K+ channels are closed
6. Return to the resting potential (due to the sodium-potassium pump)

During the inactivation of the Na^{+} channels no further depolarization is possible (refractory period)

It's the time interval during which the sodium channels are inactivated (+30mV, -60mV). Thanks to this, the action propagation of the action potential is unidirectional

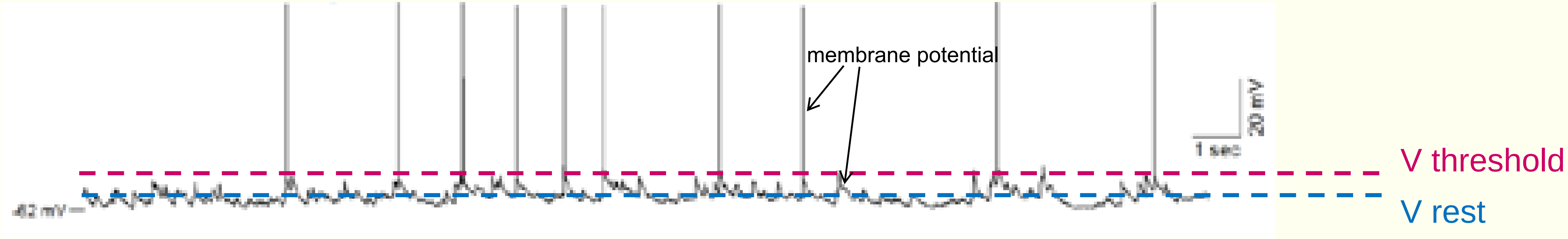
How the action potential is propagated. The procedure according to which we move from a continuous input to a binary output(contrary of previous) is that each time the signal crosses the threshold, the signal is 1, when it is below the threshold is 0.

3 - Action potential

- Same shape, same duration (2 ms), same amplitude (100 mV)
- Very fast, very intense: similar to a spike
- The information is not in its shape, but in the temporal distance between two spikes
- From a continuous input to a binary output (spike train) by a threshold mechanism

the changes are very short

each time the threshold is reached we will have the spike which is then propagated to others cells



- It's propagated to the synaptic bouton (next synapses) action potential is 10 times stronger than the postsynaptic potential

3- Propagation of the action potential – unmyelinated axons

because it performs an action that is to reach another cell (neuron or muscolar cell)

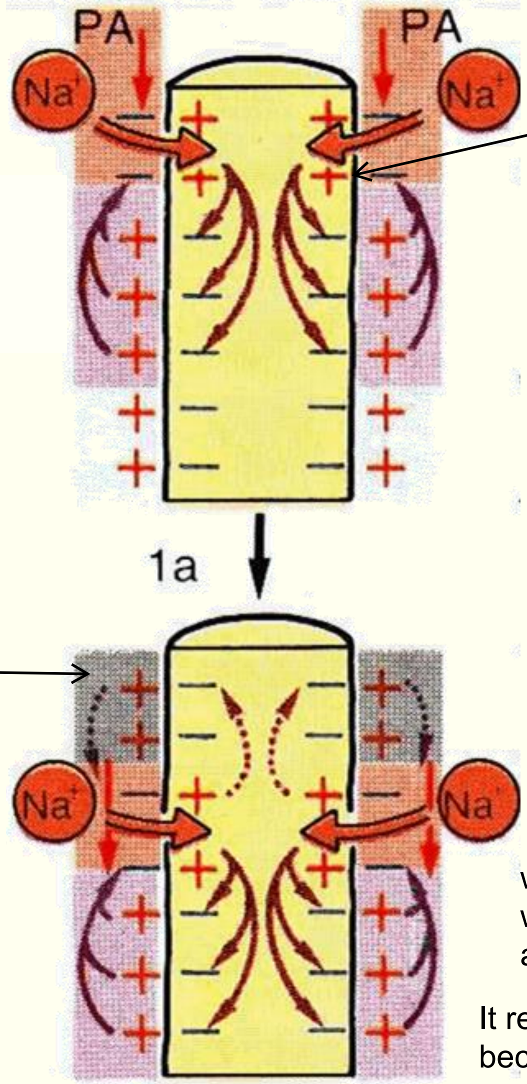
last part of the cell and it has the aim to propagate the action potential at to the final destination that is another synapses.

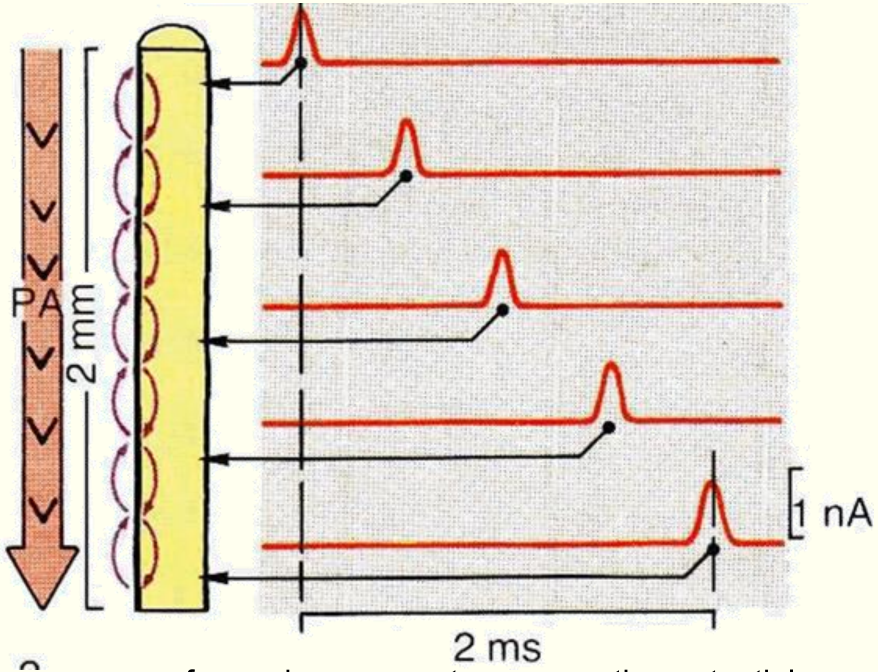
are extroflections of the cell, so they are filled by intracellular fluid and they are surrounded by the membrane. This has a lot of voltage gated ions channel. Unmyelinated axons can produce an action potential in any part of it.

- The action potential is continuously generated at each membrane section
- Unidirectional (from the soma to the synaptic bouton) because of the refractory period
- It is propagated along the fiber up to the synapses

grey zone

local depolarization of the membrane which is 100mV. This means that we have positive charges in the yellow part and increasing of negative charges outside. In this situation there are also extracellular and intracellular currents as result.





when we move forward we generate a new action potential, when we move backward we are not be able to generate action potential.

We will have a continuous generation of the action potential along the axon. Each small portion of the membrane along the axon will generate new action potential(ACTIVE PROPAGATION). Finally the action potential reaches the synapses.

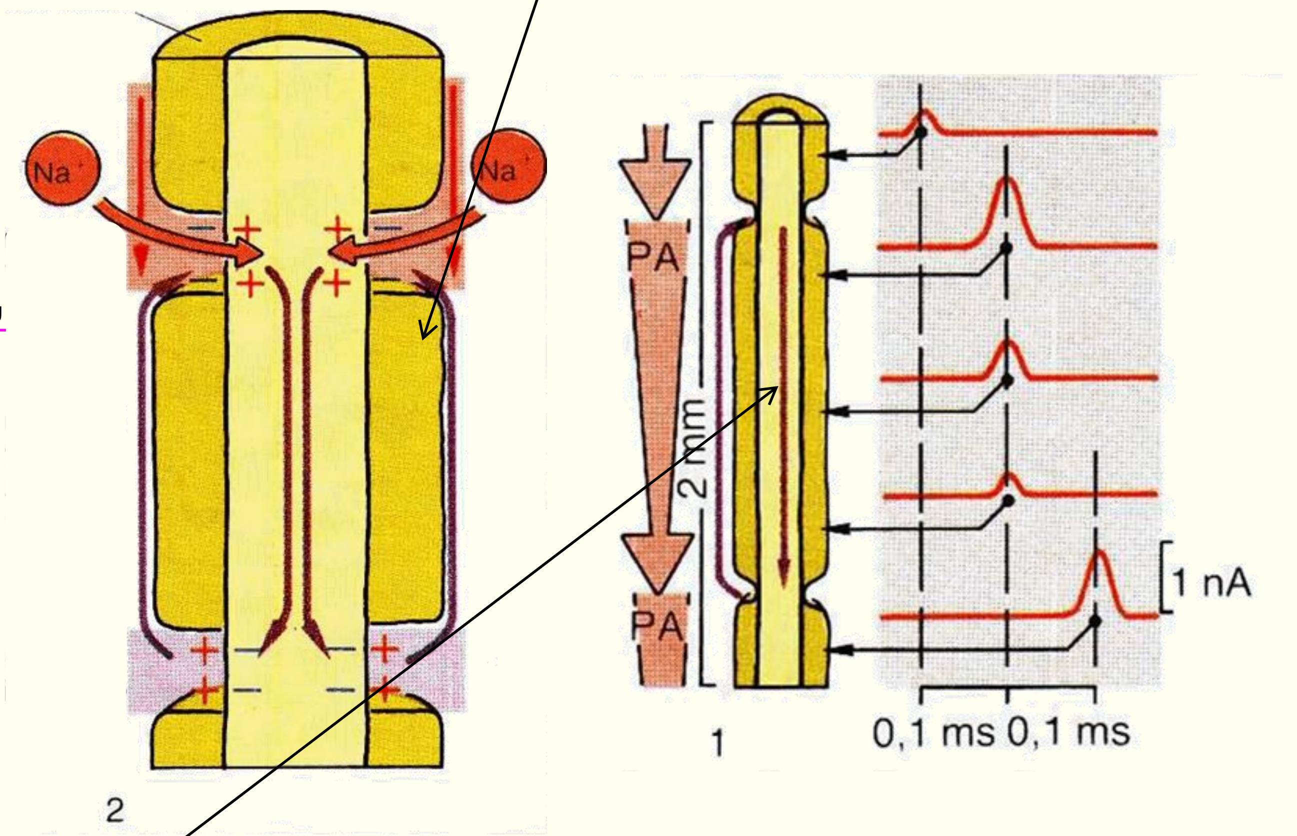
It requires time for each propagation of the action potential, and because the length of the axon creates delay. The myelinated axons exist for this reason.

3- Propagation of the action potential – myelinated axons

here the membrane of the cell for the axon part is isolated from the outside by the sheath which is the myelinated part of the axon(yellow part)

Are leaved some spots called the Runvier nodes. The membrane is exactly as we know(it has voltage gated sodium and potassium channel). In the sheathed parts of the axon no transmembrane currents is allowed, so no ions can cross the membrane.

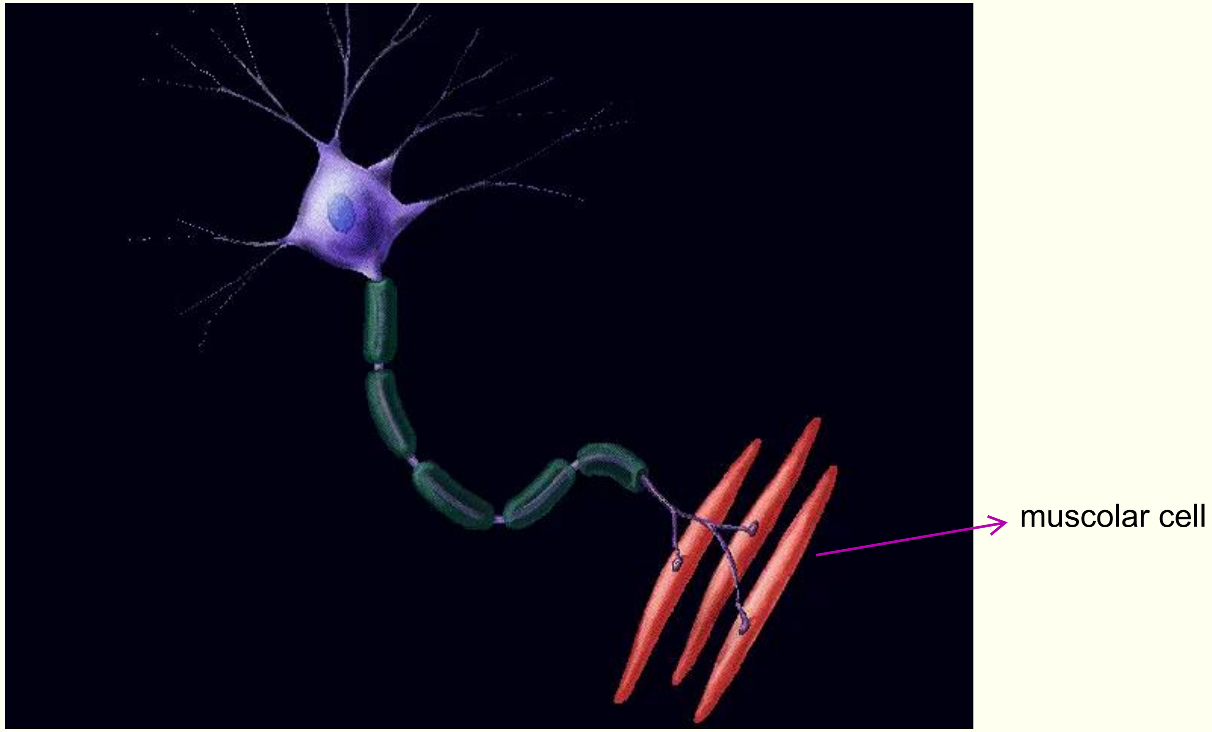
- The action potential is generated only at the Ranvier nodes (interruptions of the myelinated sheath)
- Along the myelinated segments, the propagation is passive
- Alternated passive conduction (where the sheath prevents the membrane currents) and generation of the action potential (at the unmyelinated nodes)
- Much faster than the previous conduction



In myelinated section no action potential can be produced because there isn't interaction between the inside and the outside. Passive propagation is very efficient.

3 - Propagation of the action potential - summary

- Action potentials travel down nerve fibers at high speed and are propagated rapidly over large distances (centimeters)



References

- Dayan & Abbott:
  - Chapter 1, section 1.1
  - Chapter 5, sections 5.2, 5.5, 5.8
  - Chapter 6, sections 6.4
- Hari & Puce:
  - Section I, Chapter 2, pagg.18-23

Self-evaluation test

1. What are the 3 main functions of the neural cell?
2. What are the four main ion families having a role in the neuron functioning?
3. How is the resting membrane potential determined? What value does it assume?
4. How is the membrane potential modified by an excitatory synapse? And by an inhibitory one?
5. What's the difference between temporal and spatial summation? Can they occur simultaneously?
7. Why is a depolarizing post-synaptic potential called "excitatory"?
8. What is the use of an inhibitory PSP?

Self-evaluation test

9. Do we have to measure the amplitude and duration of an action potential each time it occurs to understand the cell behavior?
10. Which parameter of the spike train in output to a neuronal cell is the most informative:
    A. The amplitude of the spikes
    B. The spatial position in which the spikes are generated
    C. The temporal distance between spikes
11. What will the frequency of the spikes influence:
    A. The temporal summation of the PSPs
    B. The spatial summation of the PSPs
    C. The amplitude of the resulting action potential in the post-synaptic cell