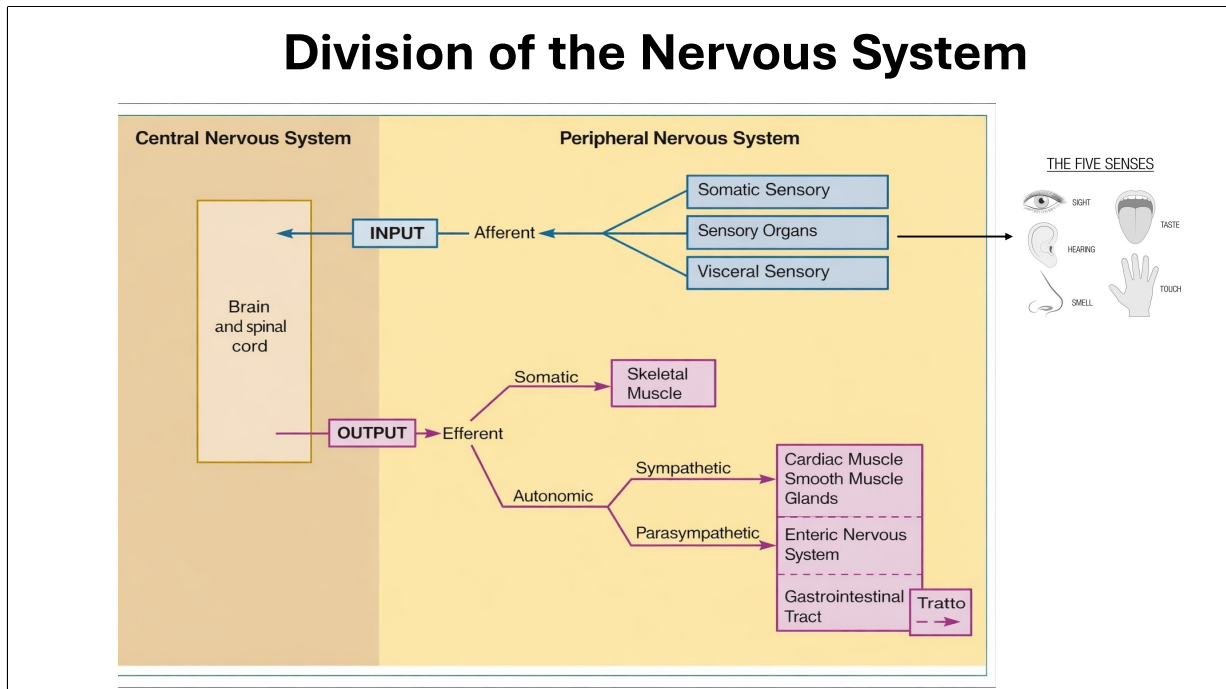


Nervous System

Division of the Nervous System



This image summarizes the functional organization of the nervous system.

Sensory information, called **afferent input**, comes from receptors and travels to the central nervous system, where it is processed.

Then, the central nervous system sends back a response through efferent pathways.

The afferent pathway carries information from sensory receptors, such as the skin, muscles, internal organs, and sense organs.

It includes signals like touch, temperature, pain, body position, and special senses like vision and hearing.

In the central nervous system, this information is integrated and transformed into a response.

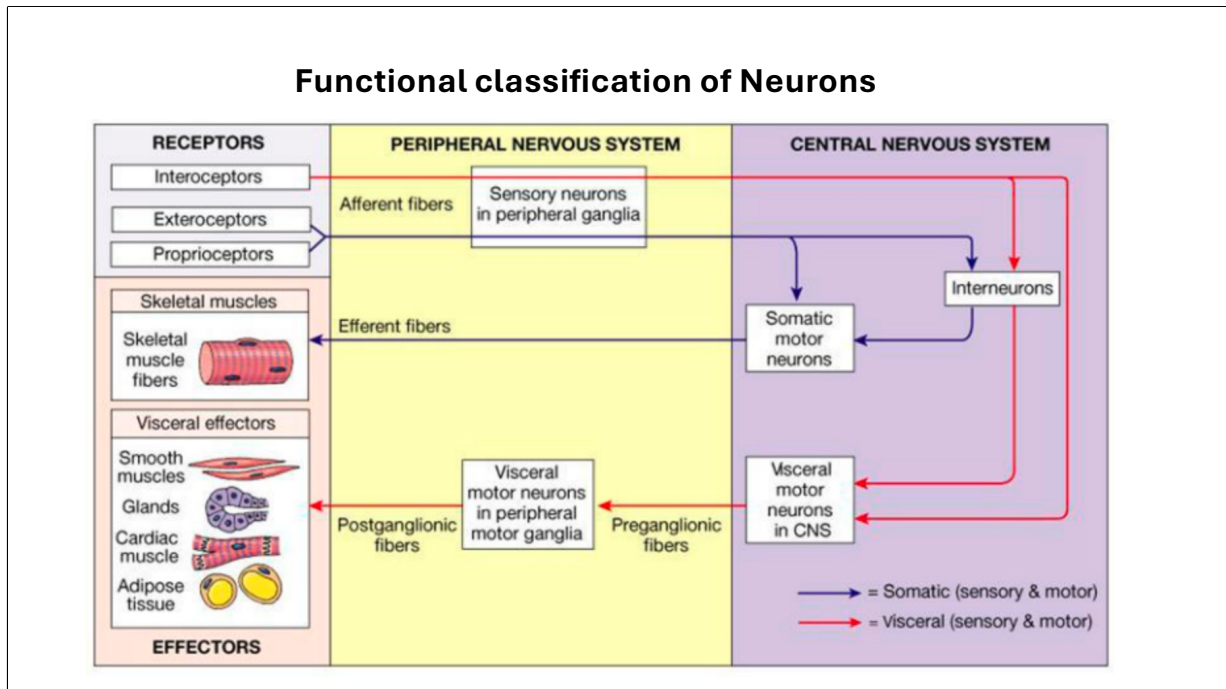
The **efferent pathway** carries motor commands to the effectors.

There are two types of effectors:

Skeletal muscle, controlled by the somatic nervous system (voluntary control)

Smooth muscle, cardiac muscle, and glands, controlled by the autonomic nervous system (involuntary control), which includes the sympathetic and parasympathetic divisions.

Functional classification of Neurons



Let's look in a bit more detail at how neurons are organized in the nervous system and how the peripheral and central nervous systems are connected.

On the left, we see the receptors. Information starts from these receptors and travels through afferent fibers, which are sensory neurons that carry the signal to the central nervous system. In the central nervous system, the information is processed by interneurons. Then a response is generated and travels through efferent fibers, which are motor neurons.

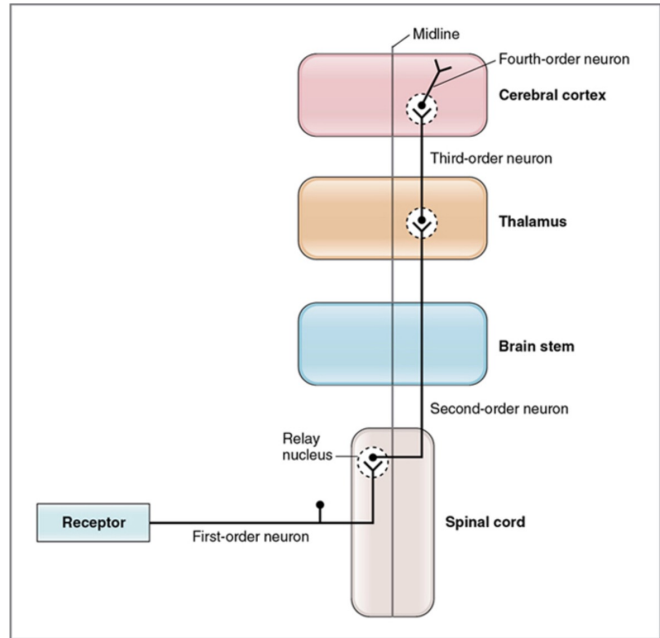
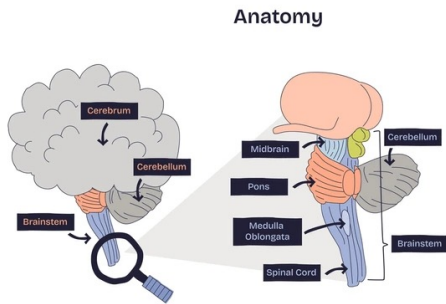
At this point, we can distinguish two pathways:

Somatic pathway (in blue)
controls skeletal muscles
responsible for voluntary movement

Visceral or autonomic pathway (in red)
controls smooth muscle, cardiac muscle, glands, and adipose tissue
regulates involuntary functions

In the autonomic pathway, the signal passes through two neurons:
a preganglionic neuron
a postganglionic neuron.

Sensory System



Sensory systems collect information from the environment through specialized receptors located in the body's periphery. These receptors convert physical or chemical stimuli into electrical signals through a process called **sensory transduction**, which involves changes in the membrane potential (receptor potential).

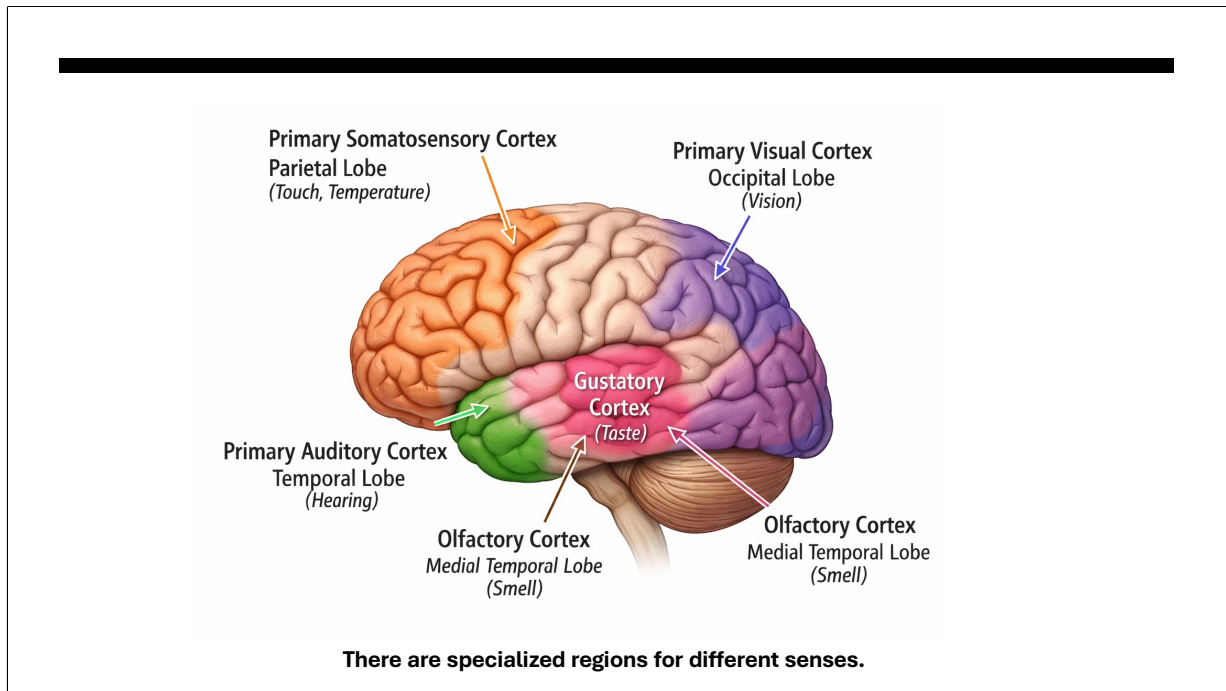
The information is then transmitted to the central nervous system through a chain of afferent neurons organized in a hierarchical order:

First-order neurons: receive input from the receptors

Second-order neurons: located in the spinal cord or brainstem

Third-order neurons: located in the thalamus

Fourth-order neurons: located in the sensory cortex



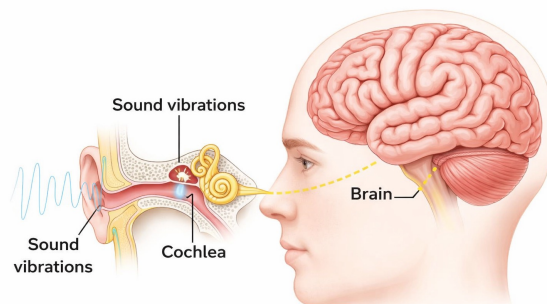
Along this pathway, the information is modified, integrated, and filtered through synapses and interneurons.

Final processing occurs in the cortical sensory areas, where the stimulus is consciously perceived.

Sensory Receptors

Structures specialized to respond to stimuli activating an electrical signal in a sensory neuron:

- Activation of sensory receptors results in depolarizations that trigger impulses to the CNS
- The realization of these stimuli, sensation and perception, occur in the brain



For example, the cochlea in the ear responds to **sound vibrations** and sends signals to the brain through a **cranial nerve**. The brain processes these signals, allowing us to hear.

A sensory receptor is a structure that responds to a specific stimulus and activates an electrical signal (action potential) in a sensory neuron.

For example, the cochlea in the ear responds to sound vibrations and sends signals to the brain through a cranial nerve. The brain processes these signals, allowing us to hear.

Sensory receptors are specialized to detect stimuli. When activated, they generate signals that travel to the central nervous system.

The final processing of these signals (sensation and perception) occurs in the brain.

Classification of Receptors

Three criteria used to describe receptors:

1. receptor distribution
2. modality of stimulus
3. stimulus origin

Receptors can be classified according to different features

DISTRIBUTION

General sense receptors are distributed throughout the skin and organs:

Somatic receptors – skin, muscles, tendons

Visceral receptors – internal organs

Special sense receptors are housed within complex organs in the head:

taste, smell, hearing, balance, vision

MODALITY OF STIMULUS

Mechanoreceptors – respond to touch, pressure, vibration, stretch, and itch

Thermoreceptors – sensitive to changes in temperature

Photoreceptors – respond to light energy (e.g., retina)

Chemoreceptors – respond to chemicals (e.g., smell, taste, changes in blood chemistry)

Nociceptors – sensitive to pain-causing stimuli

STIMULUS ORIGIN

Exteroceptors

WHAT THEY DO

Detect stimuli coming from the external environment.

WHERE THEY ARE

Body surface
Also in mucous membranes that open to the outside of the body (e.g. nasal cavity, oral cavity, vagina, anal canal)

THEY SENSE THE EXTERNAL WORLD

Interoceptors (Visceroceptors)

WHAT THEY DO

Detect stimuli in internal organs (viscera).

WHERE THEY ARE

In internal organs

THEY MONITOR INTERNAL ORGANS

Proprioceptors

WHAT THEY DO

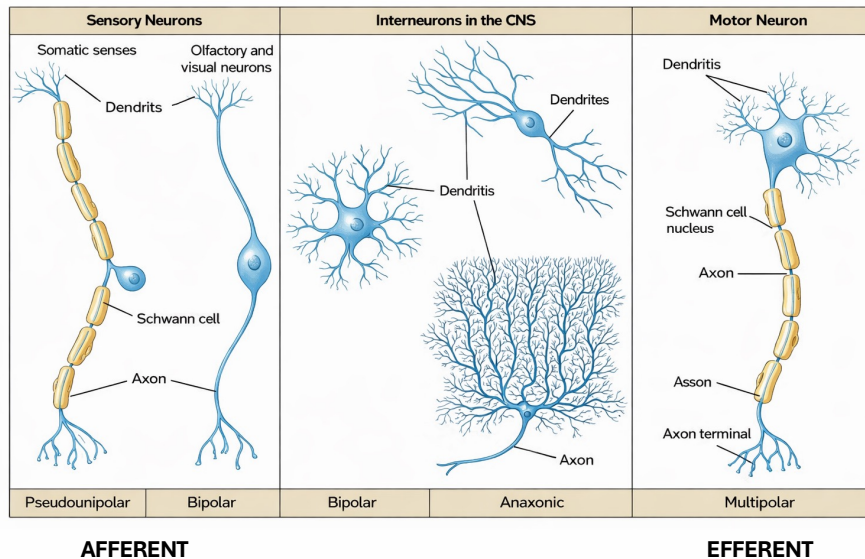
Perceive position and movement

WHERE THEY ARE

Located in muscles, tendons, and joints

THEY TELL THE NERVOUS SYSTEM BODY POSITION

Anatomical and Functional Classification of Neurons



Sensory information travels in the nervous system through specialized cells, called as neurons.

Three main types of neurons can be recognized:

Sensory neurons (afferent)

Interneurons (in the central nervous system)

Motor (efferent) neurons

These three types represent the pathway of nervous information.

1. Sensory neurons (afferent)

On the left side, we see sensory neurons.

They carry information from sensory receptors to the central nervous system (spinal cord or brain).

There are two main types:

Pseudounipolar neurons: typical of touch, pain, and temperature

They have one process that splits into two branches

One branch receives information, the other sends it to the CNS

Bipolar neurons: found in special senses like smell and vision

They have one dendrite and one axon

In both cases, their function is the same:

to send sensory information to the CNS

2. Interneurons (central nervous system)

In the center, we see interneurons.

They are located only in the central nervous system.

Their function is to process and integrate information.

They:

receive signals from sensory neurons

process the information
send it to motor neurons

They have:

many dendrites
many connections
different shapes

Their role is:

to integrate and process information

3. Motor neurons (efferent)

On the right side, we see motor neurons.

They carry information from the CNS to effectors:

muscles
glands

They have:

many dendrites
one long axon
terminals that contact the effector

Their role is:

to produce a response

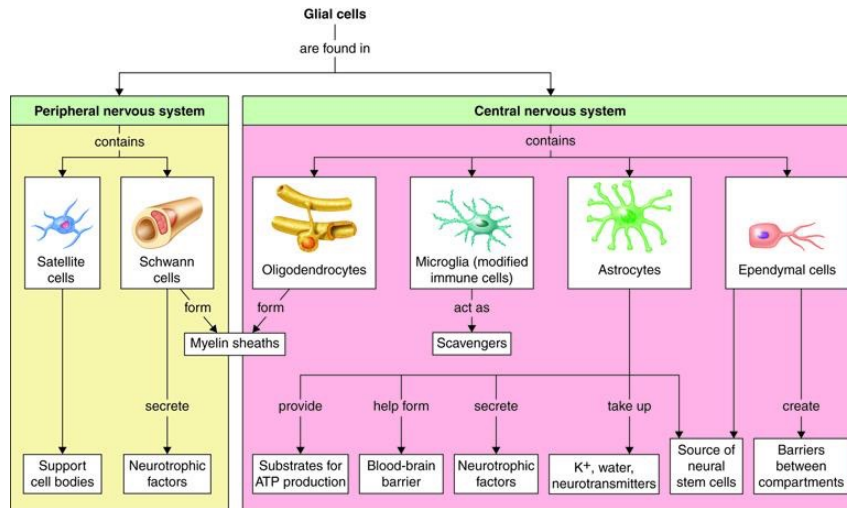
Conclusion

The pathway of information is:

receptor → sensory neuron → interneurons → motor neuron → response

This is the basic scheme of how the nervous system works.

Glial cells: Structure and Function



So far, we have talked about neurons, which are the cells that transmit the nervous signal. However, nervous tissue is not composed only of neurons, but also of another very important cell type: glial cells.

Glial cells do not directly transmit electrical signals, but they perform support, protection, and regulatory functions for neuronal activity.

We can classify glial cells based on their location in the central nervous system or the peripheral nervous system.

In the **central nervous system**, we find:

Oligodendrocytes, which form myelin around axons

Microglia, which have immune and defense functions

Astrocytes, which provide structural and metabolic support to neurons

Ependymal cells, involved in the production and circulation of cerebrospinal fluid

In the **peripheral nervous system**, we find:

Schwann cells, which form myelin in peripheral nerves

Satellite cells, which support neuronal cell bodies in ganglia

It is important to remember that, although glial cells do not generate action potentials, they are essential for the proper functioning of neurons.

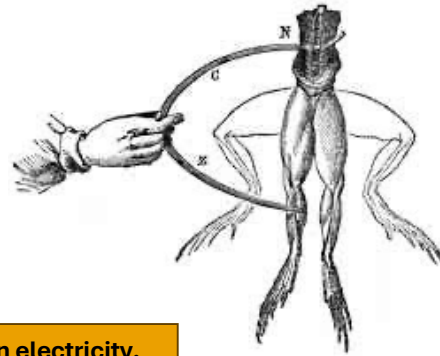
In summary, neurons transmit information, while glial cells support and regulate neuronal activity.

The Frog Battery: Galvani Experiment

18th century

Galvani observed that:

touching a frog's nerves with two different metals
caused the muscle to contract



He concluded that living tissues generate their own electricity.

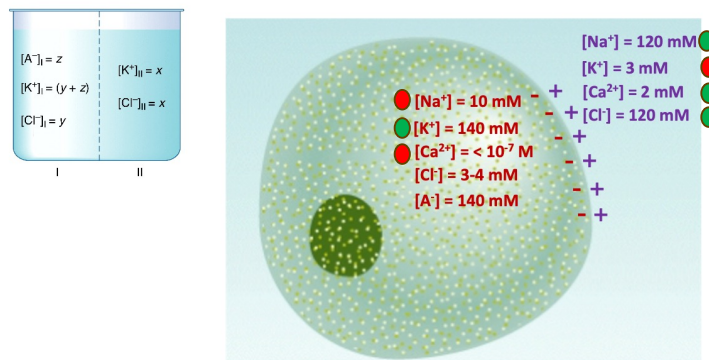
Who was to suggest that electrical signals could be a means of communication?

Luigi **Galvani**. He was an Italian physician, physicist, biologist and philosopher who studied animal electricity. Using a frog, he discovered that the muscles of dead frogs' legs twitched when struck by an electrical spark.

Today we know that neurons transmit information through electrical signals.

These electrical signals depend on the difference in potential across the cell membrane.

Electrical Activity Depends on Membrane Potential



All electrical phenomena in excitable cells depend on the potential difference across the plasma membrane. This difference exists because ion concentrations are different inside and outside the cell.

Inside the cell

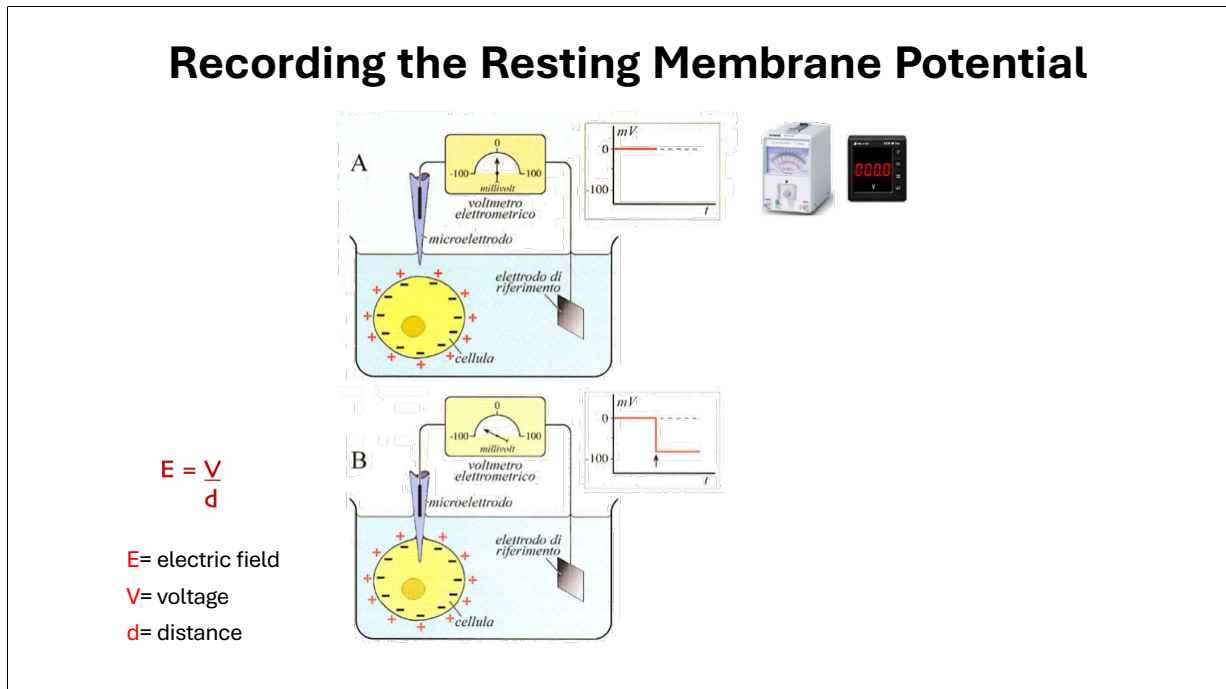
High potassium (K^+)
 Low sodium (Na^+)
 Very low calcium (Ca^{2+})
 Negative intracellular anions

Outside the cell

High sodium (Na^+)
 High chloride (Cl^-)
 Low potassium (K^+)
 More calcium (Ca^{2+}) than inside

This unequal distribution of charges creates an electrical separation between the inside and outside of the membrane. As a result, the cell membrane behaves like a small battery.

Recording the Resting Membrane Potential



This figure shows how membrane potential is measured.

If both electrodes are placed in the extracellular fluid, the voltmeter reads zero because there is no potential difference (A).

When a microelectrode is inserted inside the cell and the reference electrode remains outside, the voltmeter records a potential difference (B).

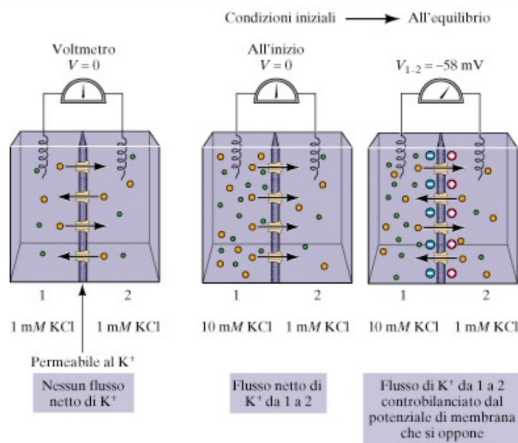
This means that the inside of the cell is electrically different from the outside.

In particular, the inside of the cell is negative compared to the outside.

In many excitable cells, this value is about -70 millivolts and is called the resting potential.

So, **membrane potential is simply the electrical difference between the inside and the outside of the cell.**

Electrochemical Basis of the Membrane Potential



The **chemical gradient** drives ions to diffuse from areas of higher concentration to areas of lower concentration.

The **electrical gradient** depends on charge differences and attracts or repels ions.

Electrochemical equilibrium = EQUILIBRIUM POTENTIAL
Is reached when chemical and electrical are equal and opposite

The transmembrane potential difference is an electrochemical potential.

This means it depends on two forces:

chemical gradient
electrical gradient

The **chemical gradient** pushes ions to move from areas of high concentration to low concentration.

The **electrical gradient** depends on charge differences and attracts or repels ions.

When the membrane is permeable to an ion (for example potassium), the ion moves according to its concentration gradient.

However, as ions move, a separation of charges is created, generating an opposite electrical force.

Electrochemical equilibrium is reached when:

the chemical and electrical forces are equal and opposite.

At this point, there is no net movement of the ion.

This value is called the **equilibrium potential** for that ion.

Each ion has its own equilibrium potential

The Nernst Equation

The Nernst equation establishes a quantitative relationship between the electrical potential difference and the concentration ratio of a single ion across the plasma membrane.

$$E_x = \frac{RT}{zF} \ln \frac{[X]_e}{[X]_i}$$

E_x: equilibrium potential for ion X

R: gas constant (8.314 Joule/mol × K)

T: absolute temperature (Kelvin)

F: Faraday constant (96,485 coulomb/mol)

z: valence of the ion

[X]_e and [X]_i: ion concentrations on the two sides of the membrane

At a temperature of 311.15 K (38 °C), and converting ln to log (ln = 2.302 log).

The membrane potential is determined by multiple ionic species
Goldman-Hodgkin-Katz Equation

$$V_m = \frac{RT}{F} \ln \left(\frac{P_K [K^+]_e + P_{Na} [Na^+]_e + P_{Cl} [Cl^-]_i}{P_K [K^+]_i + P_{Na} [Na^+]_i + P_{Cl} [Cl^-]_e} \right)$$

P = membrane permeability

[]_e = extracellular concentration

[]_i = intracellular concentration

P K⁺, P Na⁺, P Cl⁻: permeability of potassium, sodium and Chlorum

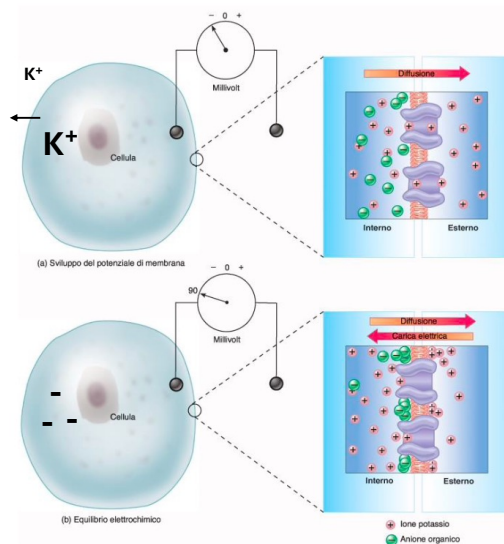
R-T-F: Gas, Temperature and Faraday constants

So far, we have seen that each ion has its own equilibrium potential, calculated using the Nernst equation.

However, the real membrane is permeable to multiple ions at the same time.

The **Goldman-Hodgkin-Katz equation** allows us to calculate the membrane potential by considering multiple ions and their permeability.

How Does the Membrane Potential Arise?



Let's see how the membrane potential is generated.

Inside the cell there is a lot of potassium, while outside there is less.

For this reason, potassium tends to move out of the cell following its concentration gradient.

The resting membrane is very permeable to potassium, so potassium can leave the cell.

When potassium leaves, it leaves behind negative charges inside the cell, because intracellular anions cannot exit.

As a result, the inside of the cell becomes more negative.

This negative charge attracts potassium back into the cell.

Now we have two opposite forces:

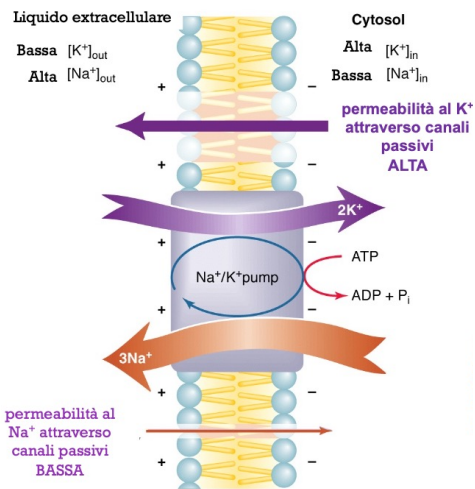
the chemical gradient pushes potassium out

the electrical force pulls it back in

When these two forces balance each other, potassium stops moving.

At this point, the membrane potential is established.

Maintenance of the Membrane Potential: The Na⁺/K⁺ Pump



This pump uses energy and transports:
3 sodium ions out of the cell
2 potassium ions into the cell

to keep the inside negative

Mainwhile K exits passively, Na enters.
The pump continuously counteracts these movements.
It moves:
sodium out
potassium in.

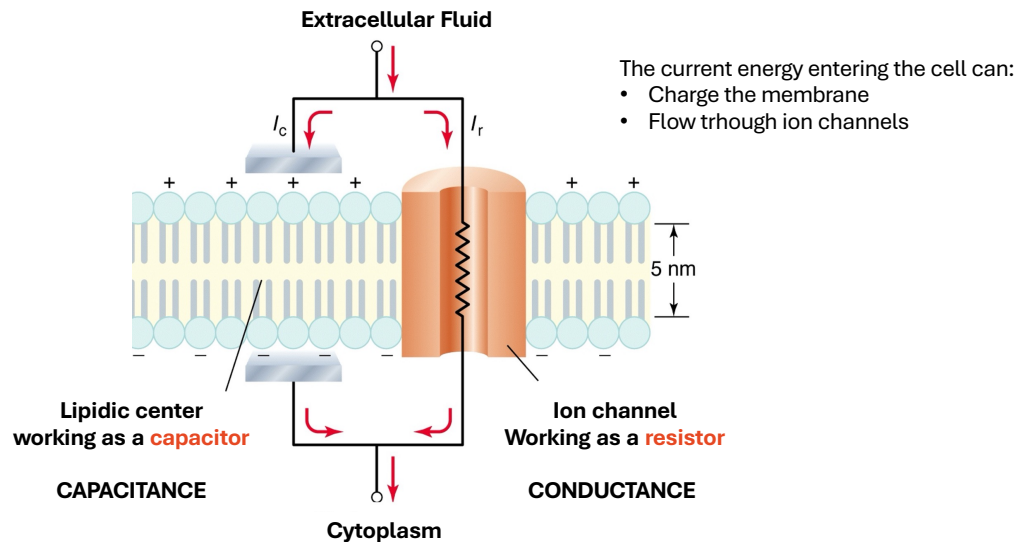
The membrane potential must be maintained stable over time.
This is possible thanks to the sodium-potassium pump.
This pump uses energy and transports:
3 sodium ions (Na⁺) out of the cell
2 potassium ions (K⁺) into the cell
So, more positive charges leave the cell than enter.
This helps keep the inside of the cell negative.

At the same time:
potassium tends to leave passively
a small amount of sodium enters
The pump continuously corrects these movements:
it moves sodium out
it brings potassium back in

In this way, it maintains a stable resting potential.

How does the membrane potential change when a stimulus arrives?

Equivalent Membrane Circuit



To understand how a sensory signal — such as light, sound, or pressure — is converted into nervous activity, we must first understand how the cell membrane behaves electrically.

All sensory receptors and neurons communicate through changes in membrane potential.

So the question is:

how does the membrane potential change when a stimulus arrives?

To answer this, we use a simple model: the **equivalent circuit of the membrane**.

The membrane behaves like two elements:

a **capacitor** (lipids)

a **resistor** (ion channels)

This is important because it shows that the current entering the cell can:

charge the membrane

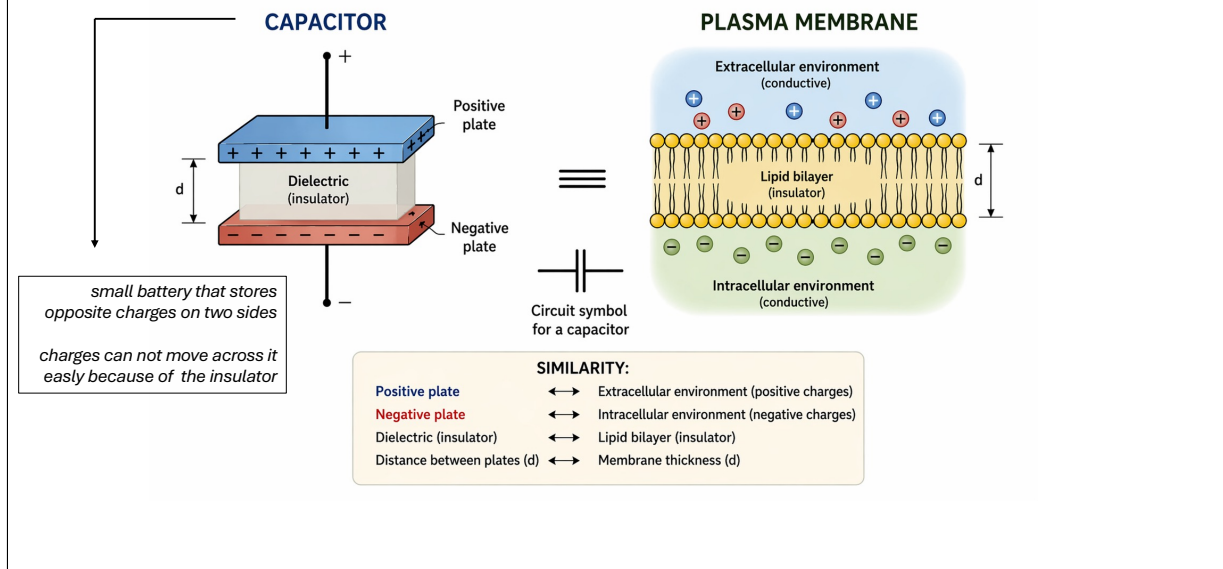
flow through ion channels

This determines how the membrane potential changes.

This is exactly what happens when a sensory receptor is activated:

stimulus → channels open → current enters → membrane potential changes

The membrane acts as a capacitor



The membrane separates positive and negative charges. This means it can be described as a **biological capacitor**.

This is because it is made of a lipid bilayer, which is an insulator, placed between two conductive solutions:
intracellular fluid
extracellular fluid

In this situation, electric charges cannot easily cross the membrane, so they accumulate on the two sides.

As a result, there is a separation of charges:

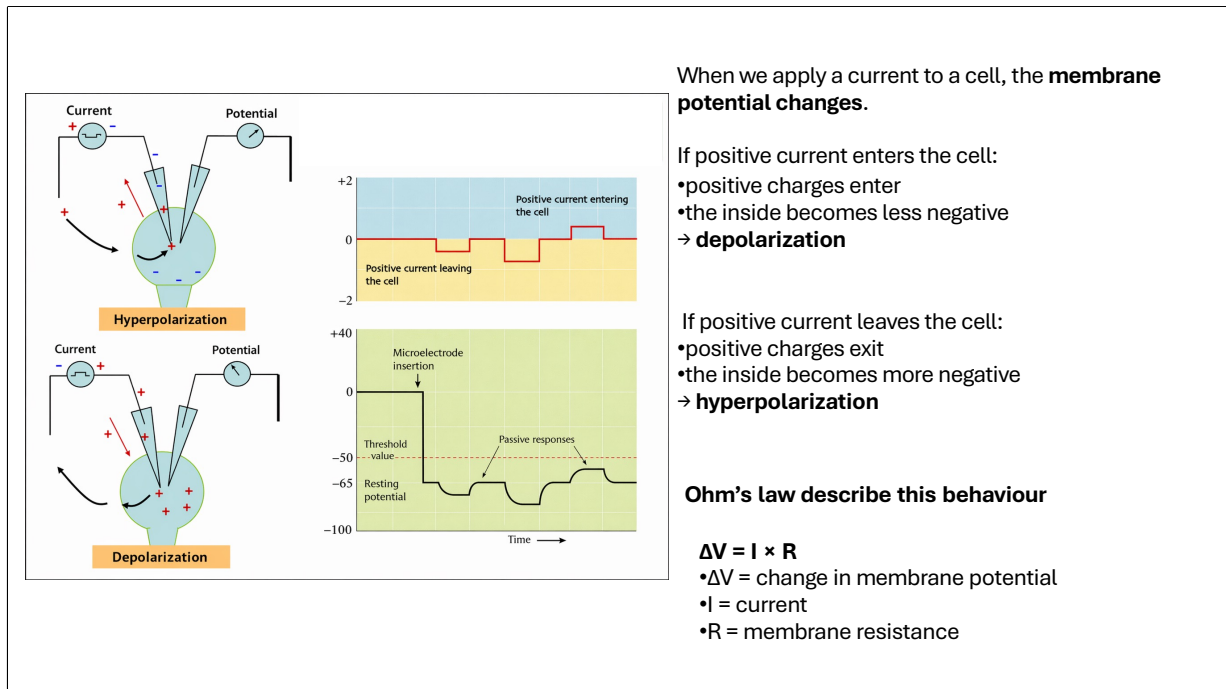
positive charges on one side
negative charges on the other

This separation occurs only near the membrane, while the rest of the fluids remains electrically neutral.

This is exactly how a **capacitor** works: it stores opposite charges on two sides separated by an insulator.

For this reason, the membrane behaves like a capacitor:

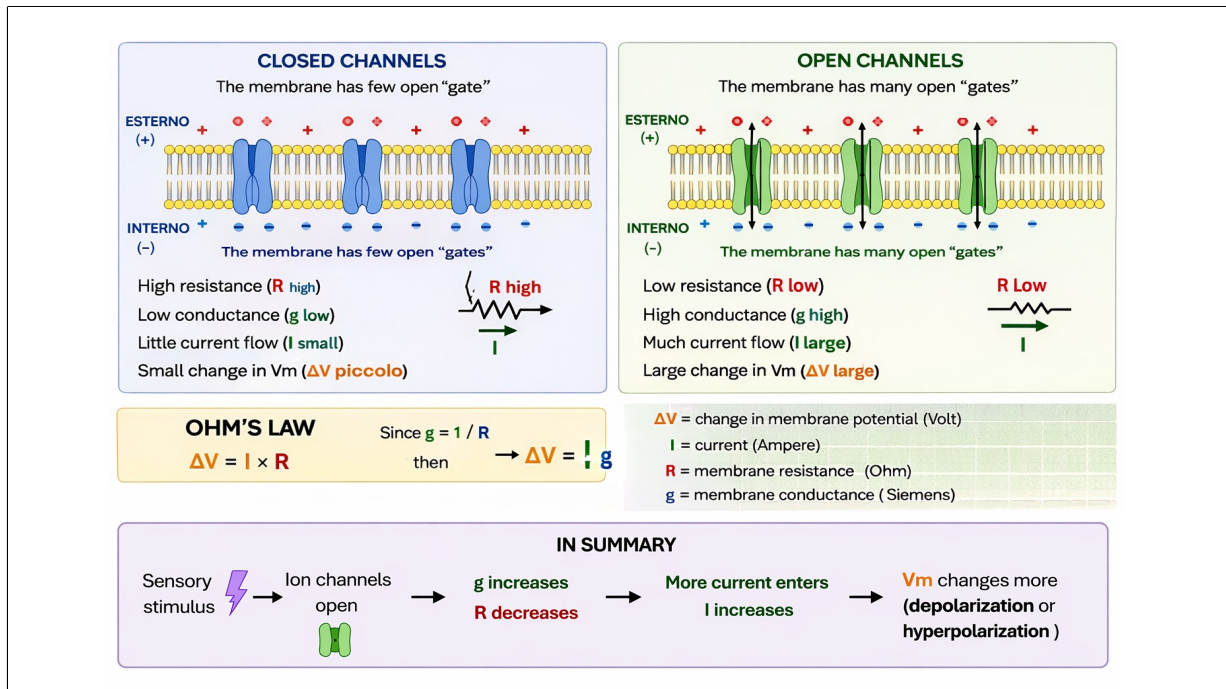
it stores charges and generates a membrane potential.



This means that the change in membrane potential depends on the **current entering the cell** and the **membrane resistance**.

If positive current **enters** the cell:
 $I > 0 \rightarrow \Delta V$ increases \rightarrow **depolarization**

If positive current **leaves** the cell:
 $I < 0 \rightarrow \Delta V$ decreases \rightarrow **hyperpolarization**



Membrane resistance depends on ion channels.

When channels are closed, resistance is high and little current flows.

When channels open, resistance decreases and current increases.

Since conductance is the inverse of resistance:

$g = 1 / R$

Ohm's law can also be written as:

$\Delta V = I / g$

Therefore:

High conductance → more current flows → membrane potential changes more easily

Low conductance → less current flows → membrane potential changes less

In sensory receptors, the stimulus acts through this mechanism:

it opens ion channels, increases conductance, allows current to enter, and changes the membrane potential, producing depolarization or hyperpolarization.

Example

Imagine the membrane as a wall with doors (ion channels):

Closed channels

few doors open

difficult to pass

high resistance (high R)

little current flows

small change in membrane potential

Open channels

many doors open

easy to pass

low resistance (low R)

high conductance (high g)

a lot of current flows

large change in membrane potential

Typical biological stimuli

DEPOLARIZATION

Membrane potential becomes less negative

- 1 Voltage-gated sodium (Na^+) channels open.
- 2 Sodium ions (Na^+) flow into the cell.
- 3 Positive charge enters the cell, making the inside less negative.

Outside of cell

Inside of cell

Membrane potential

0 mV
-70 mV +30 mV

The membrane potential moves toward 0 mV (less negative).
Example: during an action potential or excitatory neurotransmitter activity

HYPERPOLARIZATION

Membrane potential becomes more negative

- 1 Voltage-gated potassium (K^+) channels open or chloride (Cl^-) channels open.
- 2 Potassium ions (K^+) flow out of the cell or chloride ions (Cl^-) flow into the cell.
- 3 Positive charge leaves the cell or negative charge enters, making the inside more negative.

Outside of cell

Inside of cell

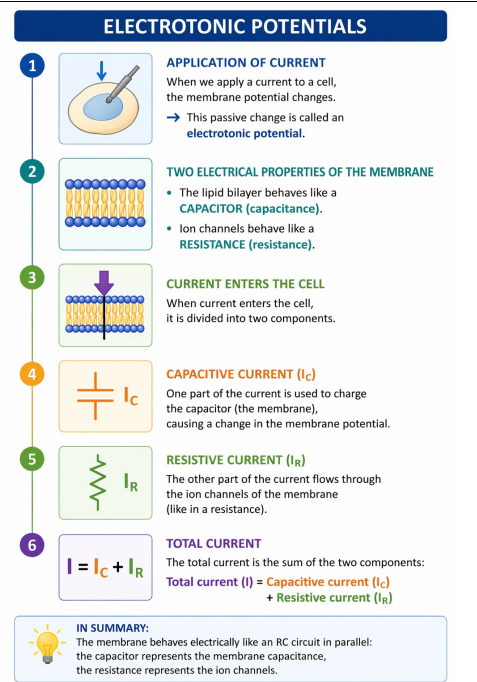
Membrane potential

0 mV
-70 mV +30 mV

The membrane potential moves away from 0 mV (more negative).
Example: during inhibitory neurotransmitter activity (e.g., GABA)

Why hyperpolarization and depolarization are not instantaneous?

Membrane Passive Reply
(The Electrotonic potential)



We have seen that when we apply a current to a cell, the membrane potential changes. This passive change is called an electrotonic potential.

The change is not instantaneous because the membrane has two electrical properties:

the lipid bilayer behaves like a **capacitor**

ion channels behave like a **resistance**

Therefore, when current enters the cell, it is divided into two components:

one part charges the membrane → **capacitive current**

one part flows through ion channels → **resistive current**

So, the total current is the sum of these two components:

total current = capacitive current + resistive current

Because the membrane must first charge, the potential does not change immediately but increases gradually over time.

For this reason, the potential follows an **exponential time course**.

The speed of this change depends on the **time constant**:

$$\tau = R_m \times C_m$$

This depends on:

R_m → membrane resistance (ion channels)

C_m → membrane capacitance (lipid bilayer)

Physical meaning

Large τ → membrane charges slowly → slow response

Small τ → membrane charges quickly → fast response

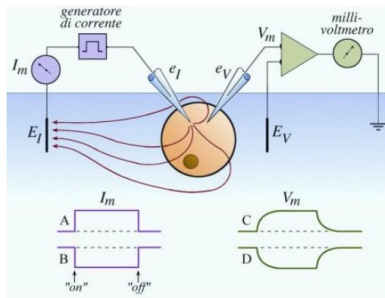
In other words, when we apply a step of current:

first, the current charges the membrane

then, the current flows through ion channels

For this reason, the membrane potential does not change instantly, but increases progressively until it reaches its final value.

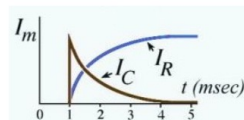
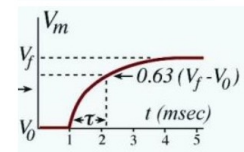
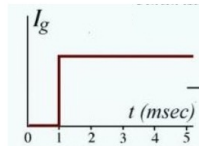
The law behind the Electrotonic potential



Because the membrane must first charge, the potential does not change immediately

It increases gradually over time

For this reason, the potential follows an **exponential time course**.



RC equation:

$$I = C \frac{dV}{dt} + \frac{V}{R}$$

The potential follows an exponential trend:

$$V_m(t) = V_f(1 - e^{-t/\tau})$$

where

$$\tau = R_m C_m$$

→ Membrane capacitance
→ Membrane resistance

τ High- slow reply
 τ Low- quick reply

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first, the current charges the membrane

then, the current flows through ion channels

For this reason, the membrane potential does not change instantly, but increases progressively until it reaches its final value.

Electrotonic Potential Features

Local

The change in membrane potential remains close to the point where the stimulus is applied.
It is not regenerated along the membrane.

This means that the signal is confined to the region where the current enters

Graded

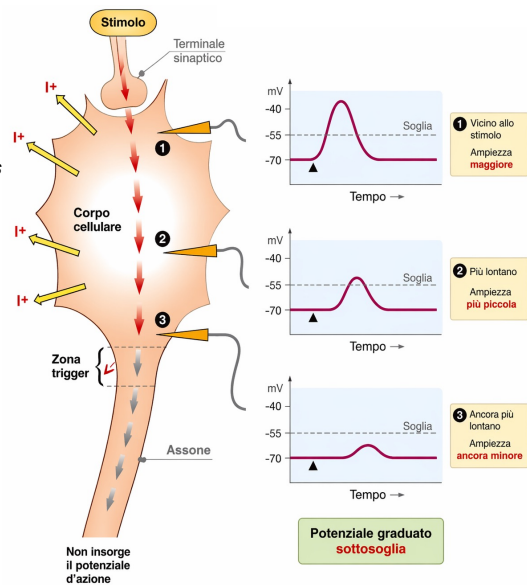
The amplitude of the potential depends on the strength of the stimulus.
Small stimulus → small depolarization
Large stimulus → large depolarization

Therefore, it is not all-or-none, but proportional to the stimulus.

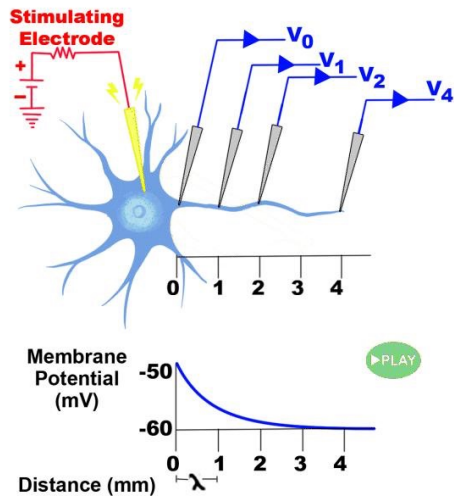
Decreases with distance

The signal decreases as it spreads along the membrane.
This happens because:
part of the current flows through ion channels
part of the current is lost along the membrane

As a result, the potential becomes progressively smaller.



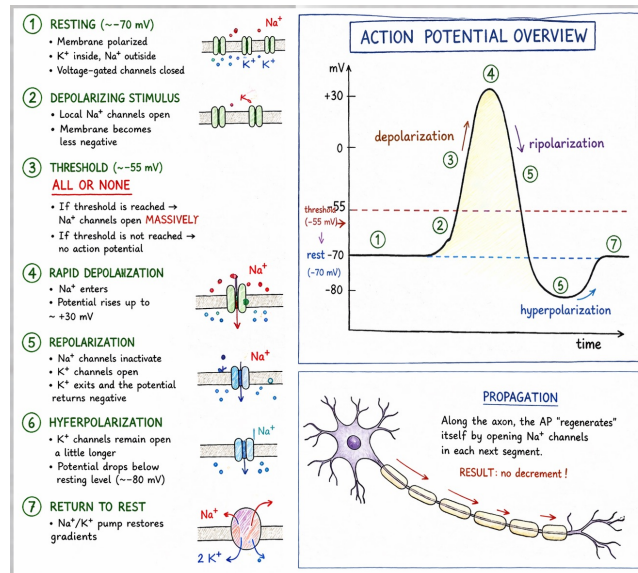
We have seen that when current enters the cell, the membrane charges and the potential changes gradually over time. This passive change in membrane potential is called an electrotonic potential. Now, let's look at its main characteristics.
see slide



- Electrotonic potential cannot travel long distances.

To transmit a signal along the neuron, a different mechanism is needed

Action Potential: How it is generated and propagated



The action potential, an active signal that can travel without decreasing.

The action potential is an active electrical signal that propagates along the neuron without fading, unlike the electrotonic potential, which is passive and decreases with distance.

The process starts from the resting potential, about -70 mV.

When a depolarizing stimulus arrives, the membrane becomes less negative.

If depolarization reaches the threshold (about -55 mV), voltage-gated sodium channels open.

Sodium enters the cell, causing a rapid depolarization up to about $+30$ mV.

Then, sodium channels inactivate and potassium channels open.

Potassium leaves the cell, leading to repolarization.

Because potassium channels stay open longer, a brief hyperpolarization occurs.

Finally, the membrane returns to the resting potential thanks to channel closure and the sodium–potassium pump.

Action Potential: Features

- ★ **ALL-OR-NONE**
either exceeds the threshold
or it does not happen
- ★ **CONSTANT AMPLITUDE**
about 100 mV, does not depend
on the stimulus
- ★ **PROPAGATION WITHOUT DECREMENT**
does not fade along the axon
- ★ **UNIDIRECTIONAL**
goes only forward (refractory period)
- ★ **REFRACTORY PERIOD**
 - **ABSOLUTE**: cannot generate another AP
 - **RELATIVE**: requires a stronger stimulus
- ★ **CODES IN FREQUENCY**
 - stronger stimuli = more action potentials
(not bigger)

The action potential has some key properties:

it follows the all-or-none law, has a constant amplitude, propagates without decreasing along the axon, is unidirectional due to the refractory period, and the stimulus intensity is coded in the frequency of action potentials.

Focus on some concepts:

All-or-none

If threshold is not reached → nothing happens

If threshold is reached → full action potential

There are no partial responses.

Not graded

The amplitude is always the same

(about **100 mV**)

This is different from the electrotonic potential.

Does not decrease with distance

The signal is regenerated along the axon

so it does not fade

This allows propagation.

Self-regenerating

Each segment of the membrane

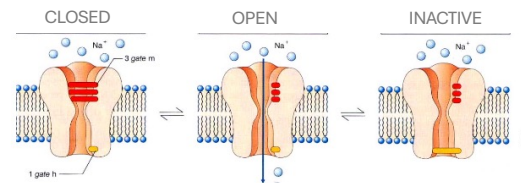
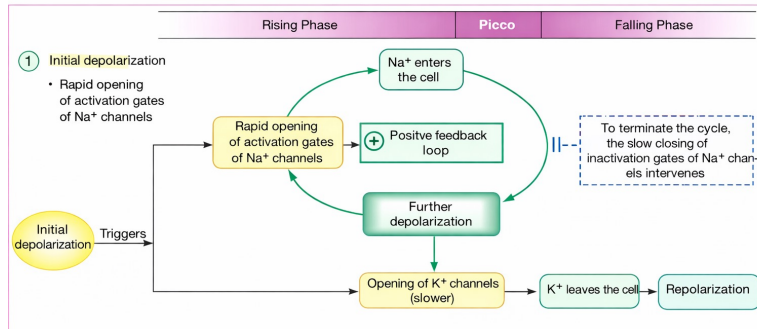
activates the next one

This creates the propagation.

COMPARISON

ELECTROTONIC POTENTIAL	ACTION POTENTIAL
<ul style="list-style-type: none">• PASSIVE• FADES• GRADED• SUMMATION POSSIBLE• BIDIRECTIONAL	<ul style="list-style-type: none">• ACTIVE• DOES NOT FADE• ALL-OR-NONE• NO SUMMATION• UNIDIRECTIONAL

Hodgkin Cycle



So, the stimulus reaches the axon hillock.

If it is strong enough, it reaches a threshold.

At that point, something very fast and automatic happens: a cycle is activated that generates the action potential.

This is the Hodgkin cycle.

Let's look at it step by step:

At the beginning, there is a small depolarization, called an **electrotonic potential**.

If this depolarization is strong enough to reach the threshold, voltage-gated sodium channels open.

Sodium enters the cell and makes the inside more positive.

This causes more sodium channels to open:

this is a positive feedback loop.

At this point, depolarization increases very rapidly:

this is the rising phase of the action potential.

Soon after, sodium channels inactivate (they do not simply close), and potassium channels open.

Potassium leaves the cell, and the potential returns toward negative values:

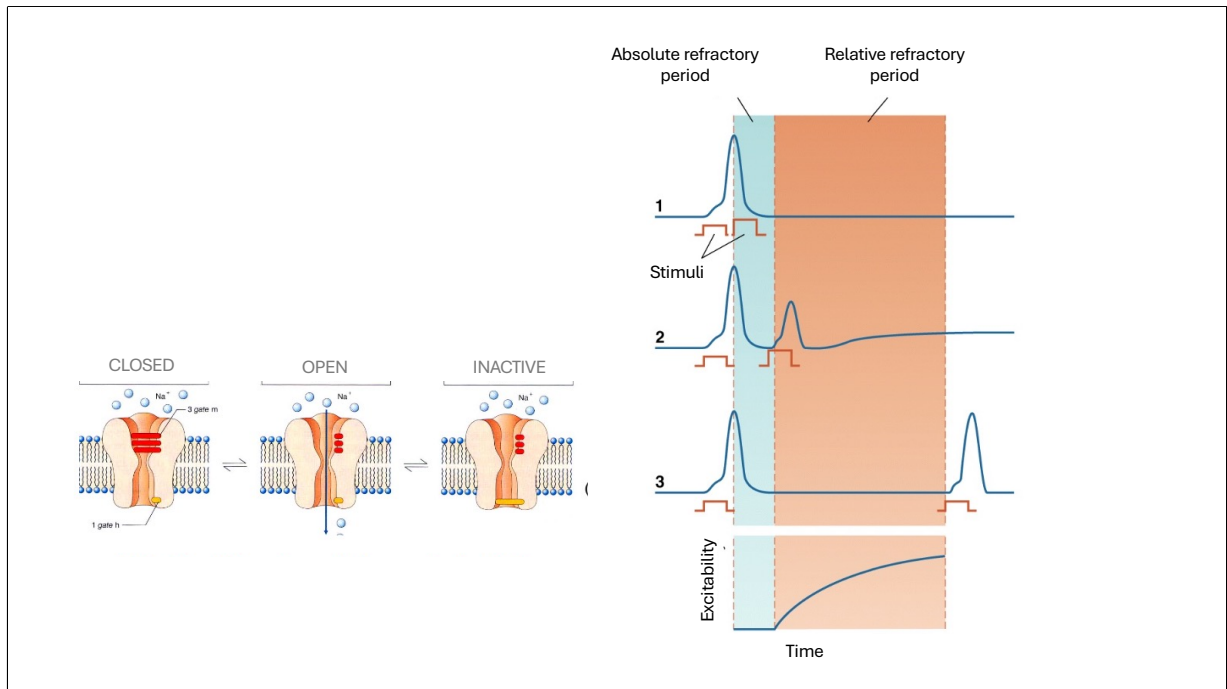
this is **repolarization**.

The Na⁺ channel has two "gates":

Activation gate (red) → opens with depolarization

Inactivation gate (orange) → closes automatically after a short time

So, the sodium channel opens in response to voltage, but then inactivates on its own after a short time, independently of voltage.



As long as sodium channels are inactivated, they cannot be used. The time window during which they are unavailable is called the **absolute refractory period**. During this period, a new action potential cannot be generated. The neuron is completely unexcitable.

This is followed by a period in which some sodium channels become available again, but potassium channels are still open. This causes the membrane to be more negative (hyperpolarized). This phase is called the **relative refractory period**. During this period, generating a new action potential is not impossible, but a stronger stimulus is required to reach the threshold.

This property is fundamental because it allows the action potential to propagate in only one direction along the axon.

Where does the action potential originate?

From the **graded potential**

small local electrical signal, proportional to the stimulus

1 Graded

not all-or-none

✓ stronger stimulus → larger response

2 Local

does not travel far

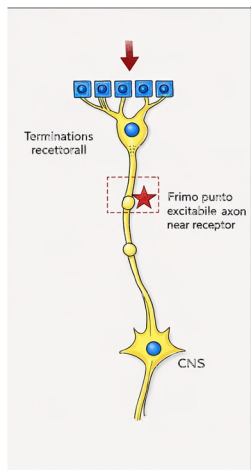
✓ decreases with distance

3 Can generate an action potential

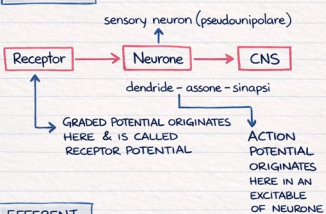
if it reaches threshold

The action potential originates from a graded potential.

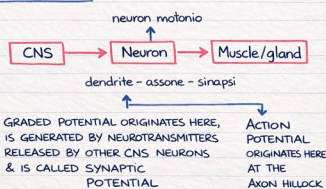
Sensory Neuron



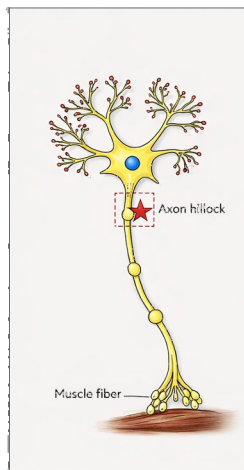
AFFERENT



EFFERENT

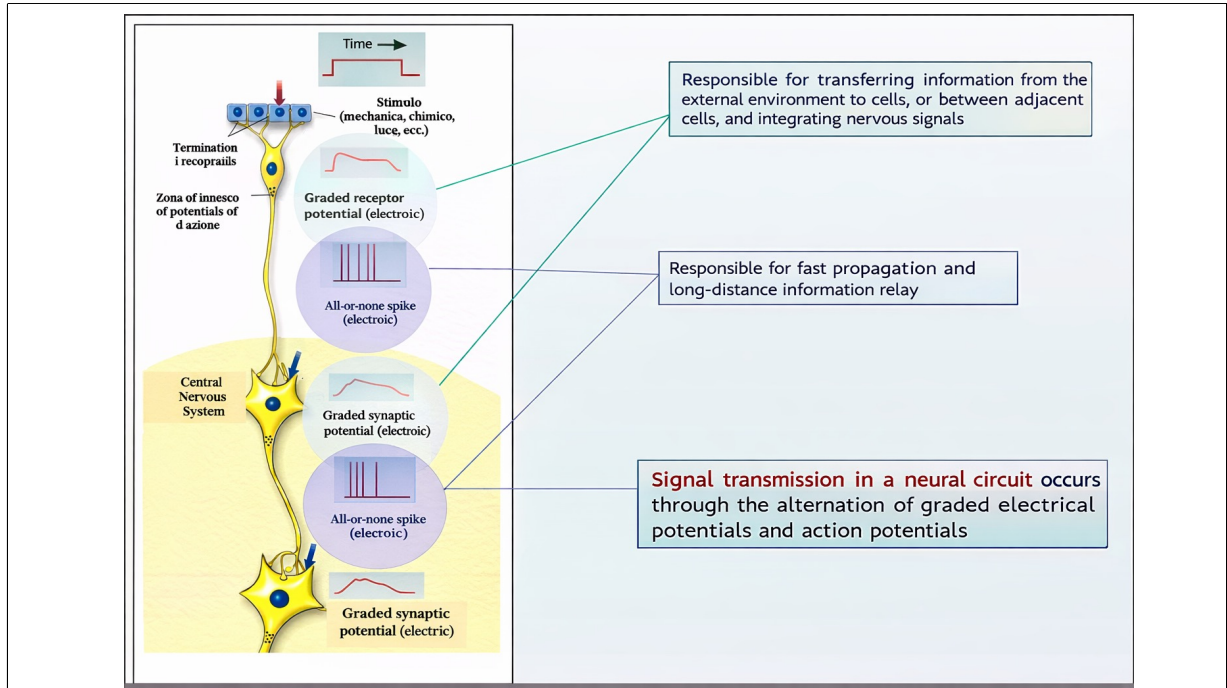


Motor Neuron



COMPARISON

GRADED POTENTIAL		ACTION POTENTIAL
Where originates	Receptors, dendrites, soma	Axon hillock
Type of signal	Local	Propagates along the axon
Amplitude	Variable, proportional to stimulus	Constant, all-or-none
Propagation	Decreases with distance	Does not decrease
Summation	Yes	No
Function	Signal integration	Long-distance transmission
Function	Signal integration	Long-distance transmission



Graded Potential vs. Electrotonic Potential

- The graded potential is the local signal that originates in the membrane
- The electrotonic potential is the passive way in which this signal spreads along the neuron



Graded is the *what*, electrotonic is the *how*

Imagine throwing a stone into water:

the point where the stone hits is the graded potential (the signal originates there)

the waves that spread out are the electrotonic propagation

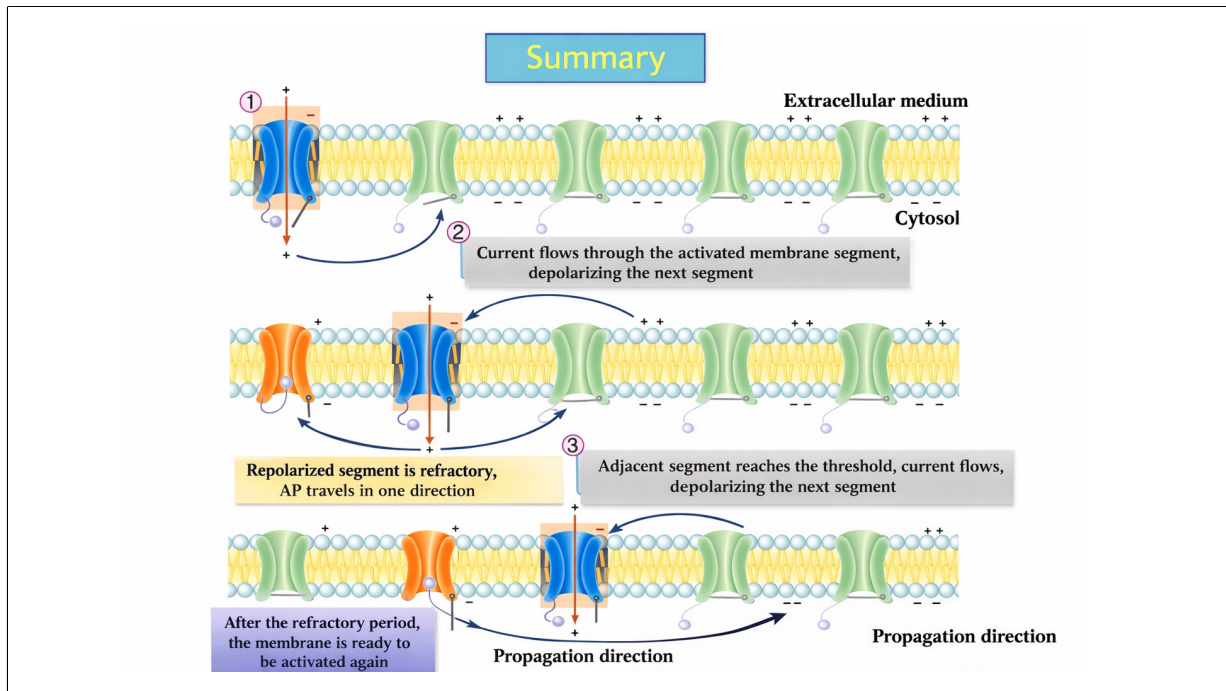
and as they move away, they become weaker

So we can say that:

The action potential always originates from an electrotonic potential

The action potential is a regenerative, all-or-none event

The action potential propagates anterogradely (that is, it moves forward—from the point where it originates toward the synaptic terminals)



The action potential starts in one segment of the membrane, and the incoming current depolarizes the next segment. If this segment reaches the threshold, it becomes activated as well, allowing the signal to propagate along the axon. The segment that has just been activated enters a refractory period, so it cannot be activated again immediately. This prevents the signal from going backward and ensures forward propagation.