

Pisa, 5-8 September 2016

An introduction
to the
mathematical modeling
in
human physiology
and
medicine

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Scheme of work

- **Lessons 1 and 2** - An introduction to the mathematical modeling of the **biological neuron**
- **Lesson 3** - An introduction to the mathematical modeling of **sleep**
- **Lesson 4** - An introduction to the mathematical modeling of **insulin secretion**
- All the lessons refer to human physiology (non-pathological conditions)
- The attitude adopted is to derive the models by retracing the concepts and the reasoning of the researchers

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Lesson 1

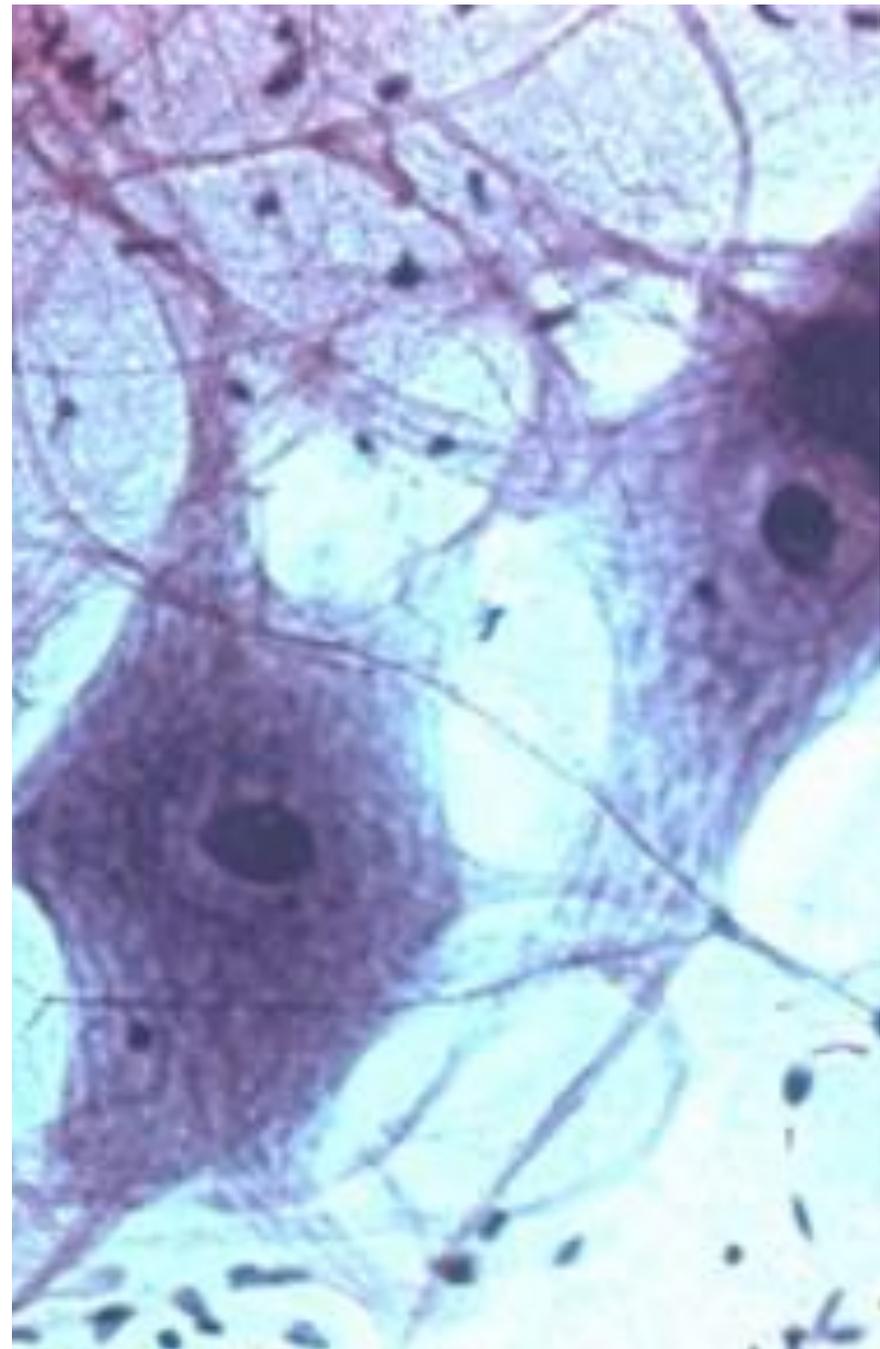
An introduction
to the
mathematical modeling of
the
biological neuron
Part 1:
derivation of
Hodgkin-Huxley equations

What we will study today

- The neuron
- The neuron's membrane
- The resting membrane potential
- The action potential
- The ionic channels
- The derivation of Hodgkin-Huxley equations describing the dynamics of the action potential and ionic channels

The neuron

The neuron, or nerve cell, is the basic working unit of the brain, a specialized cell designed to transmit information to other neurons, muscles, or gland cells

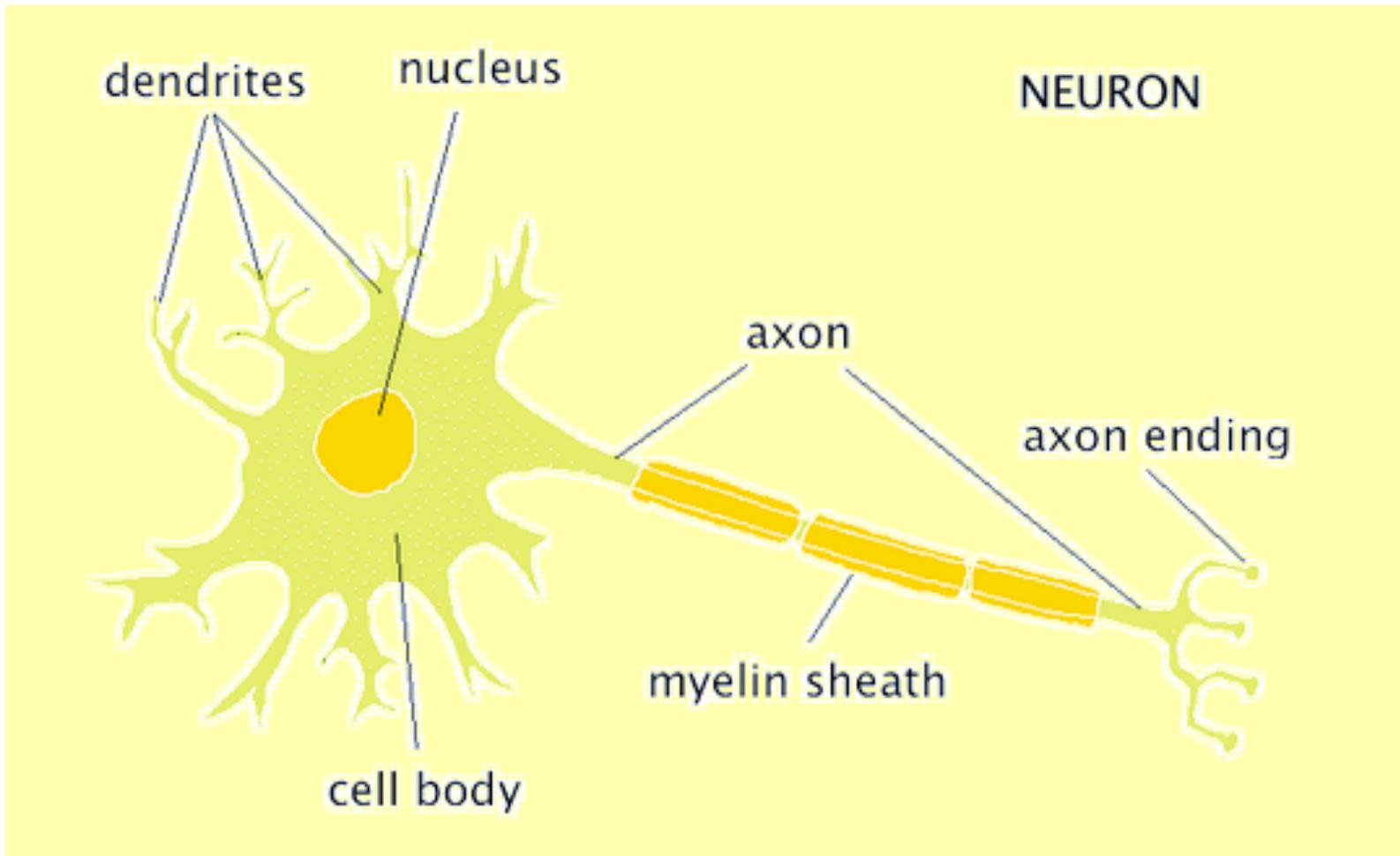


The mammalian brain contains between 100 million and 100 billion neurons, depending on the species

In humans, a neuron typically drives 10^3 to 10^4 connections (equivalent by some estimates to a computer with a 1 trillion bit per second processor)

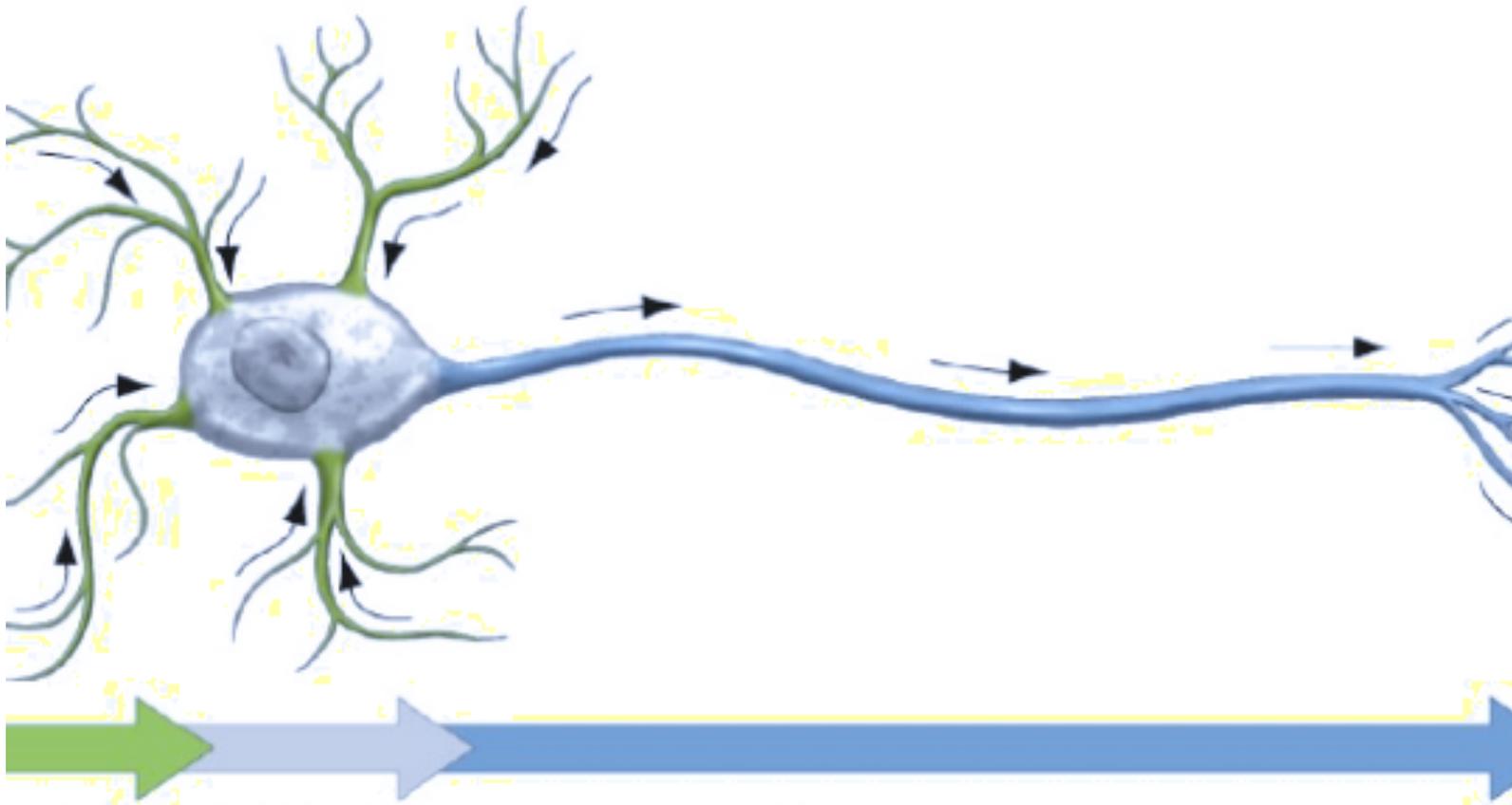
Estimates of the brain's memory capacity vary wildly from 1 to 1000 terabytes (for comparison, the 19 million volumes in the US Library of Congress represents about 10 terabytes of data)





3 main structures can be identified in a typical neuron:

- dendrites or dendritic tree
- cell body or soma
- axon



Dendrites collect signals

Axon passes signals to dendrites of another neuron

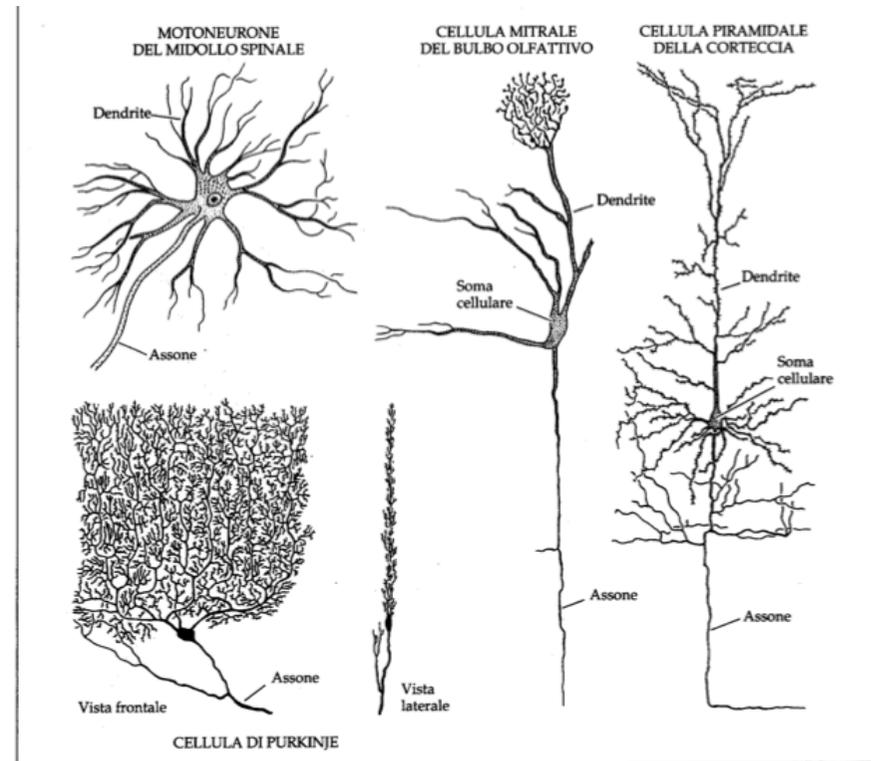
Cell body contains nucleus and organelles

Neurons come in many different shapes and sizes

Some of the smallest neurons have **cell bodies** that are only **4 microns** wide

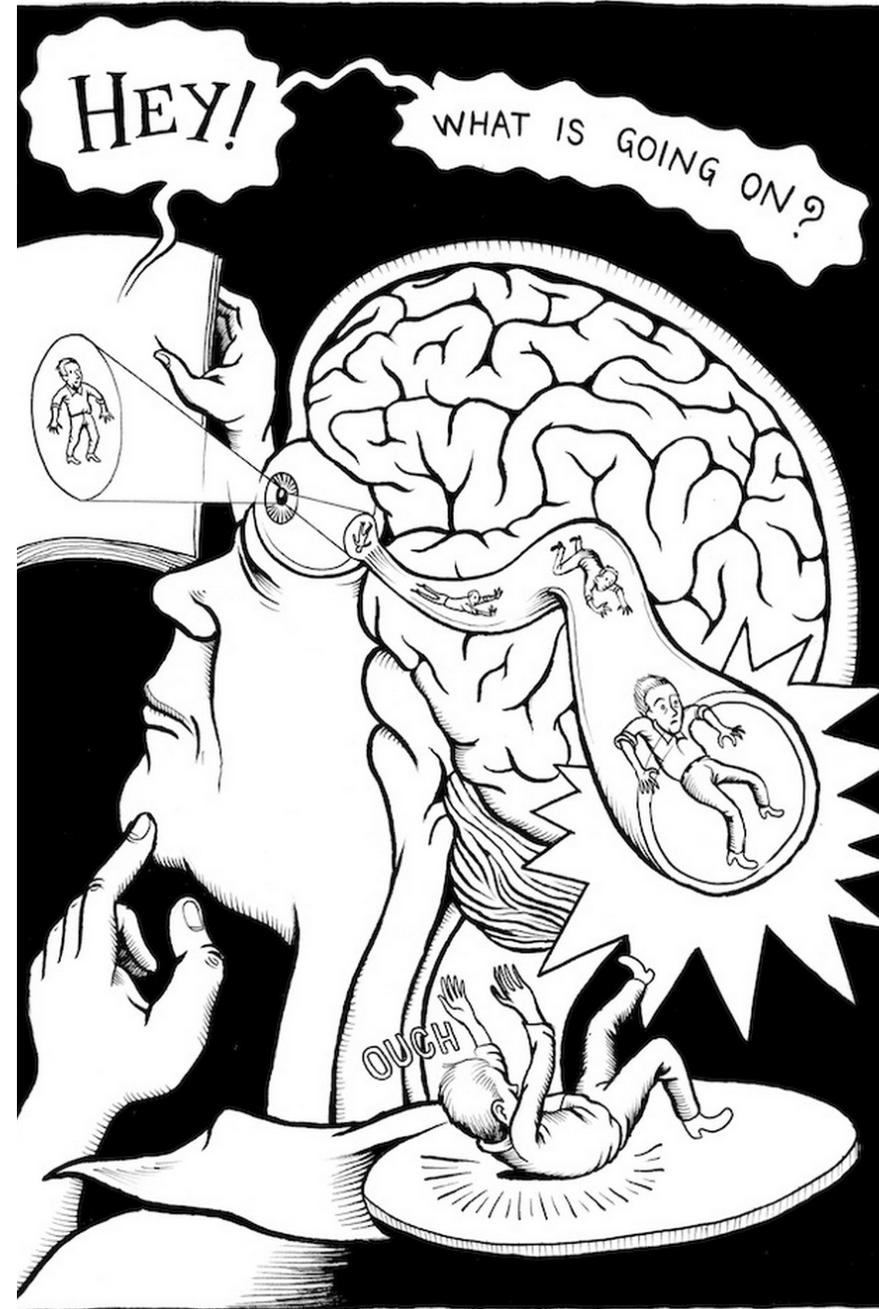
Some of the biggest neurons have cell bodies that are **100 microns** wide

Axon has a length varying **from a fraction of a millimeter to a meter**, in human body



How do neurons communicate?

Communication is achieved at **synapses** by through electrochemical complex mechanisms



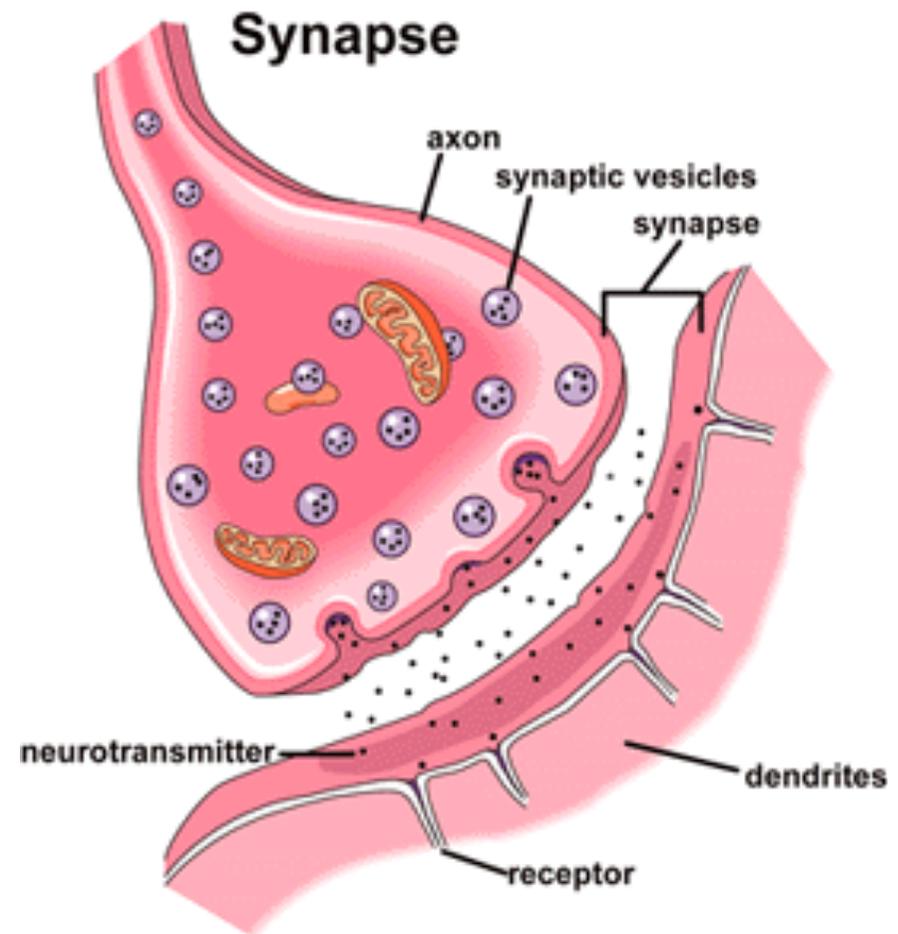
The synapse is the site of transmission of nerve impulses between two neurons or between a neuron and a gland or muscle cell

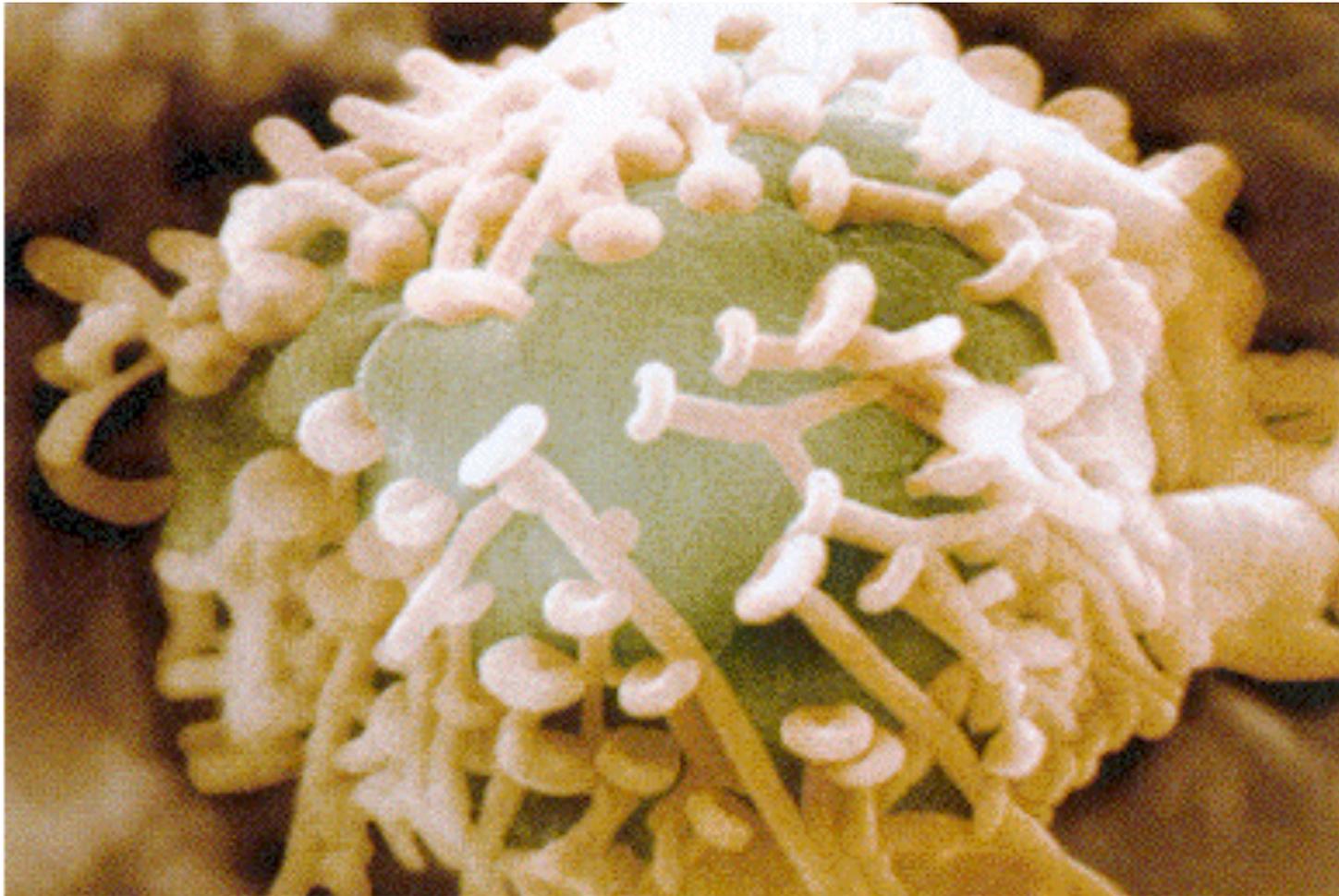
(neuromuscular junction)

There are 2 types of synapses:

- electrical synapses
- **chemical synapses**

(in humans, are more common)





At the very end of the axon is the **axon ending**, which goes by a variety of names such as the **synaptic bouton** or **knob**

It is there that the signal that has travelled the length of the axon is converted into a message that travels to the next neuron

Between the axon ending and the dendrites of the next neuron there is a very tiny gap called the synaptic gap or cleft, which we will briefly discuss

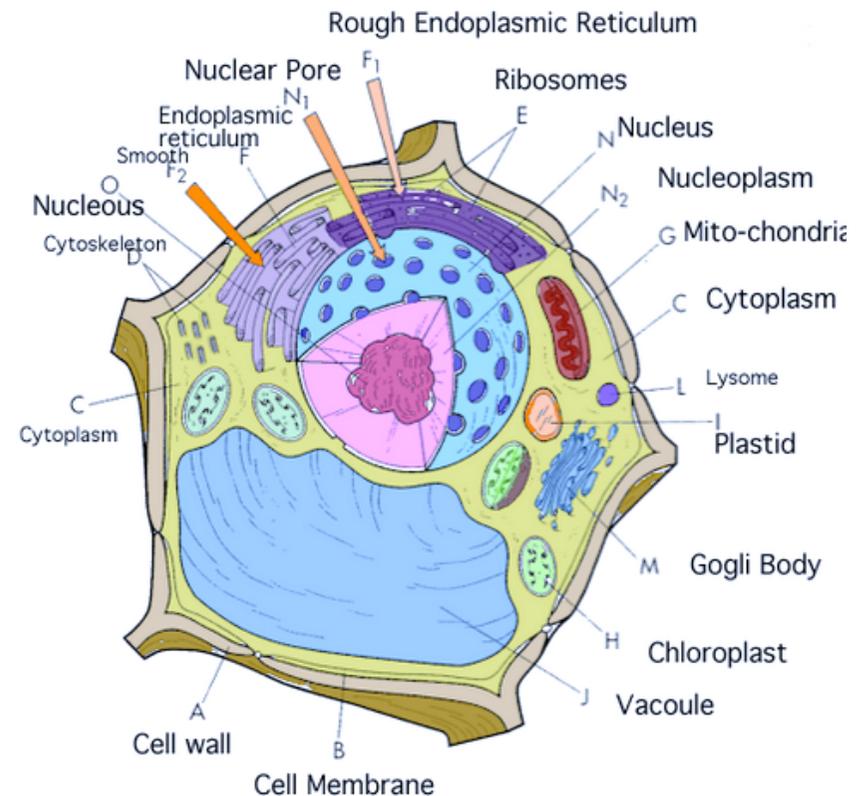
The neuron is a cell

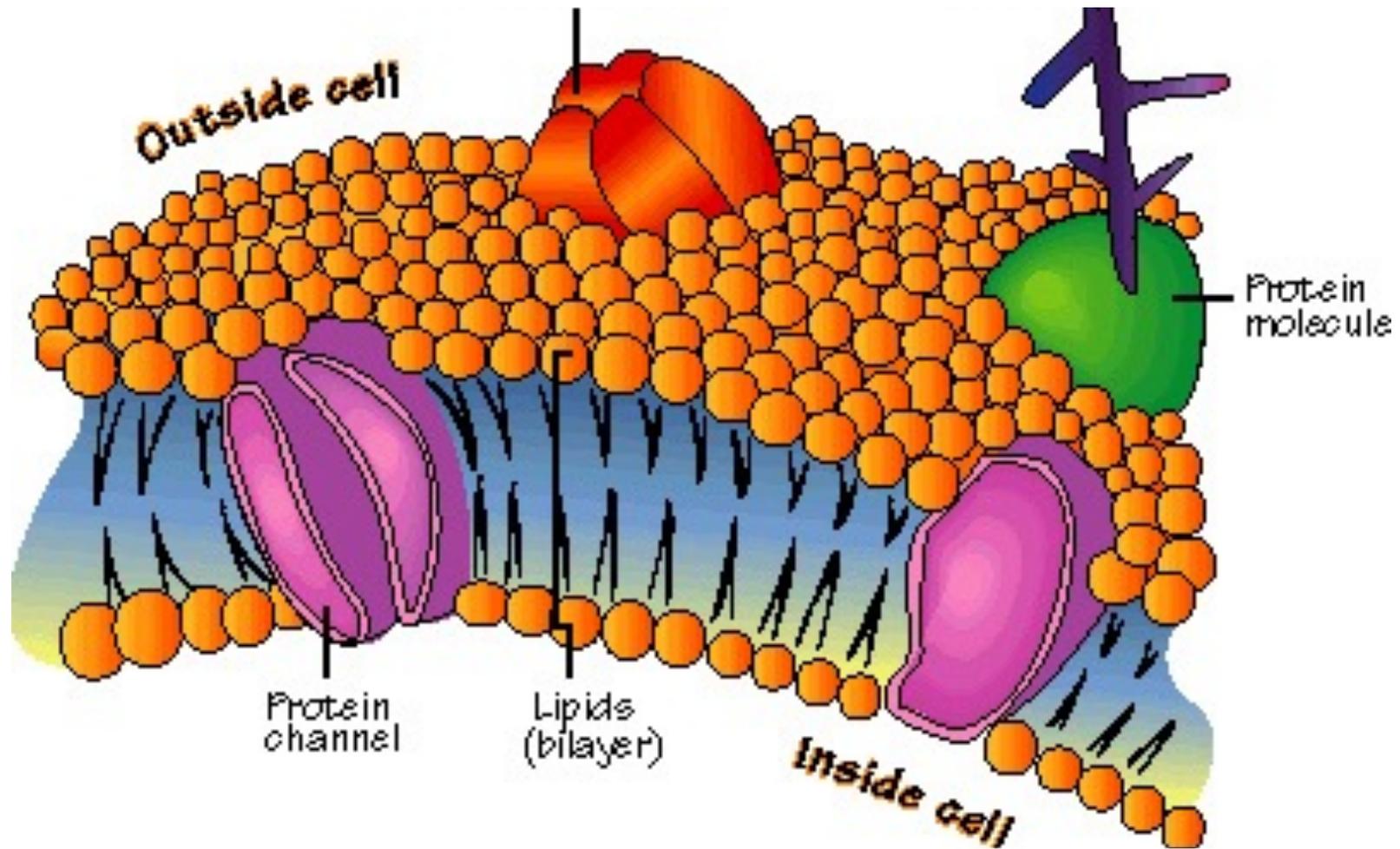
We can observe:

- a membrane
- a nucleus (internal to the soma)
- a cytoplasm
- chromosomes
- lysosomes
- mitochondria...

but

unlike other cells, neurons never divide, and neither do they die off to be replaced by new ones



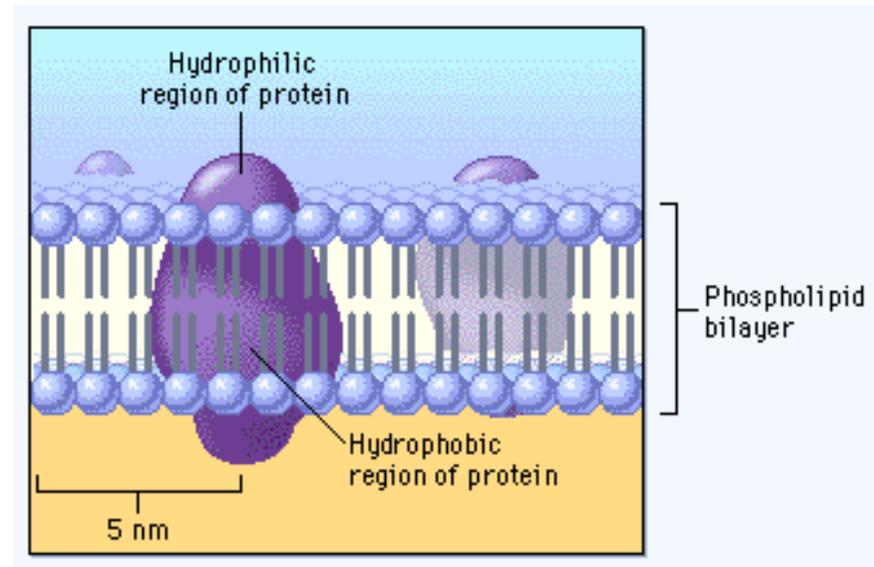


The neuron's membrane

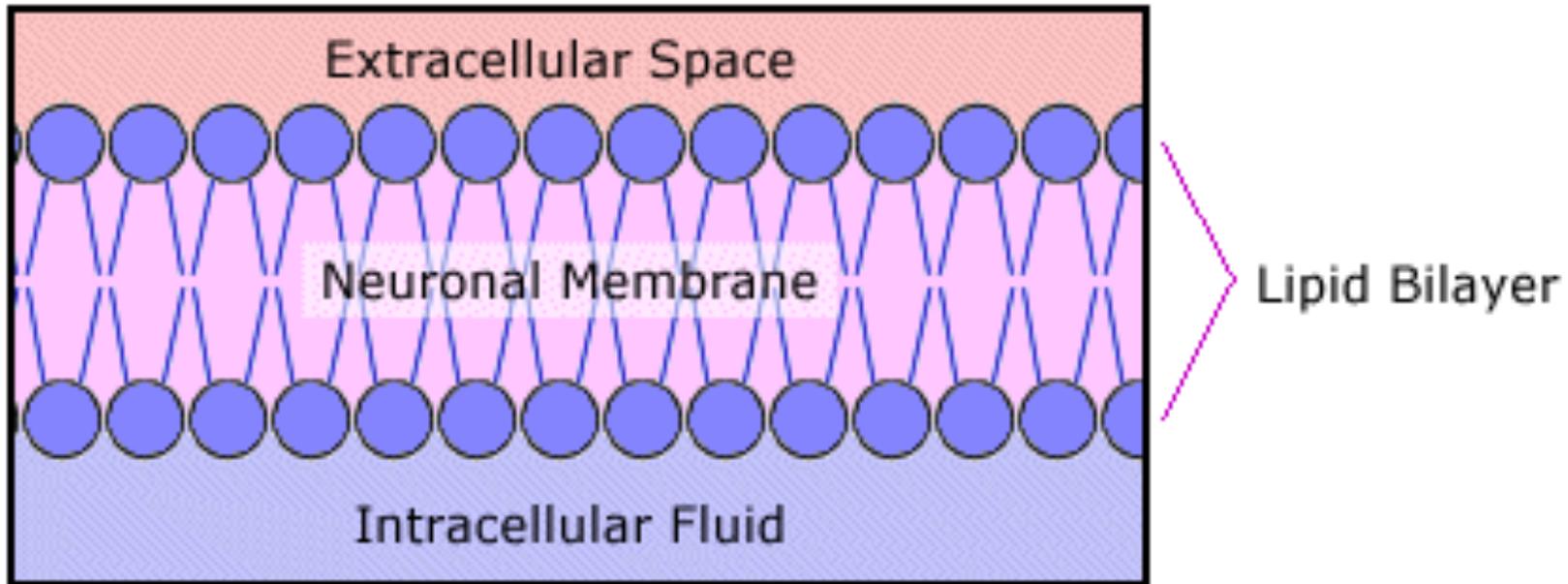
The membrane structure

The membrane (5 nanometer thickness) consists of a phospholipid bilayer combined with a variety of proteins in a fluid arrangement

The surfaces of neuronal membranes are hydrophilic (water-loving) while the interiors are hydrophobic



Selective permeability of the membrane



The membrane serves as a barrier to enclose the cytoplasm inside the neuron, and to exclude certain substances that float in the extracellular space

It is responsible for many important functions of the brain

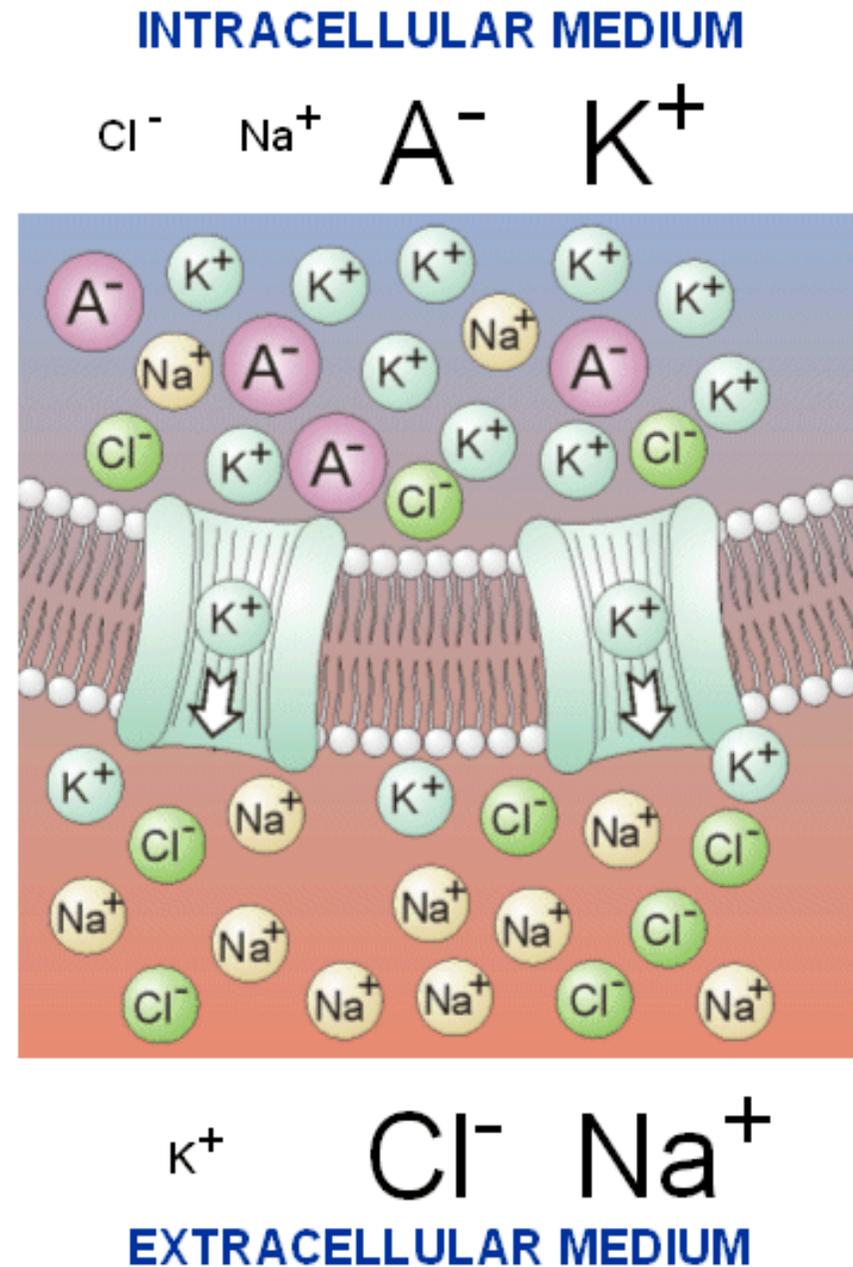
Some ions cross the membrane freely, some cross with assistance, and others do not cross at all

Ions and membrane

The membrane separates 2 compartments containing solutions of ions (positively or negatively electrically charged particles)

Ions in a medium have a concentration

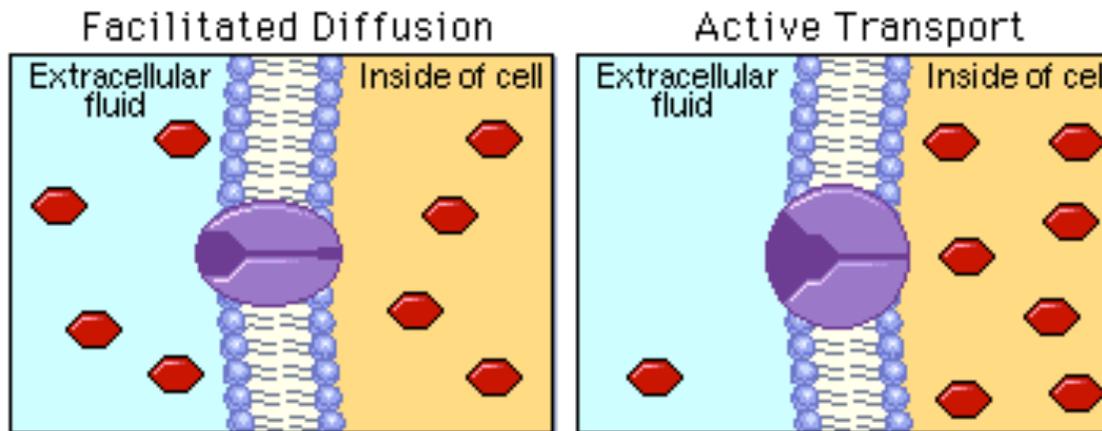
The neuron's membrane is partially permeable to Na^+ , and almost completely permeable to K^+ and Cl^-



Electrical gradient

- Ions of like charges repel (positive with positive or negative with negative)
- Ions of opposite charges attract (positive with negative or negative with positive)
- The electrical gradient is the tension between 2 ions as they “want” to come together or move apart
- In its resting state, an electrical gradient is maintained across the neuron’s membrane

Chemical gradient



A chemical gradient is created when a high concentration of ions is separated from an area of low concentration

Fick's 1st Law

Fick's law relates the diffusive flux to the concentration under the assumption of steady state

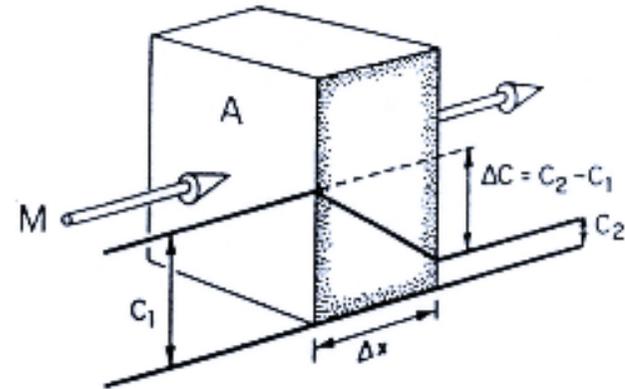
It postulates that the flux goes from regions of high concentration to regions of low concentration, with a magnitude that is proportional to the concentration gradient (spatial derivative)

In the neuron's membrane:

$$M' = - D A C'$$

M' is the velocity of diffusion of the substance M , A the area, D the diffusion coefficient or diffusivity; $C' = \Delta C / \Delta x$, where Δx is the membrane thickness and ΔC represents the difference between the 2 concentrations

The sign minus indicates that the direction of the diffusion is opposite to the gradient



How do molecules cross the membrane?

Some membrane proteins enable ions to pass through the membrane by passive or active transport

In facilitated transport, hydrophilic molecules bind to a "carrier" protein; this is a form of **passive transport** or **passive diffusion** (no energy)

In **active transport** or **active diffusion**, hydrophilic molecules also bind to a "carrier" protein, but **energy is utilized** to transport the molecules against their concentration gradient (pumps)



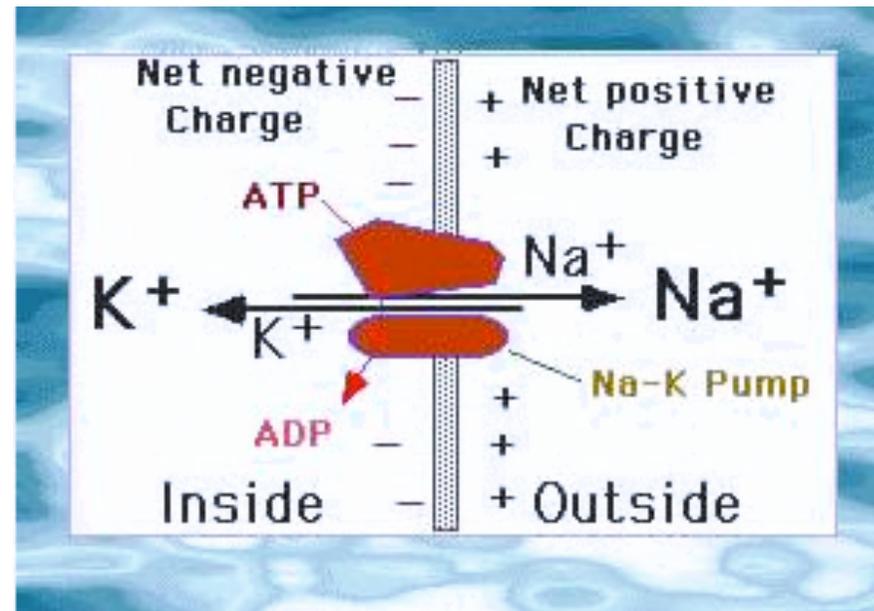
Sodium-Potassium pump

2 ions are responsible: Na^+ and K^+

An unequal distribution of these ions occurs on the 2 sides of a nerve cell membrane because “carrier” proteins actively transport these 2 ions: sodium from the inside to the outside and potassium from the outside to the inside

As a result of this active transport mechanism, there is a higher concentration of sodium on the outside than the inside and a higher concentration of potassium on the inside

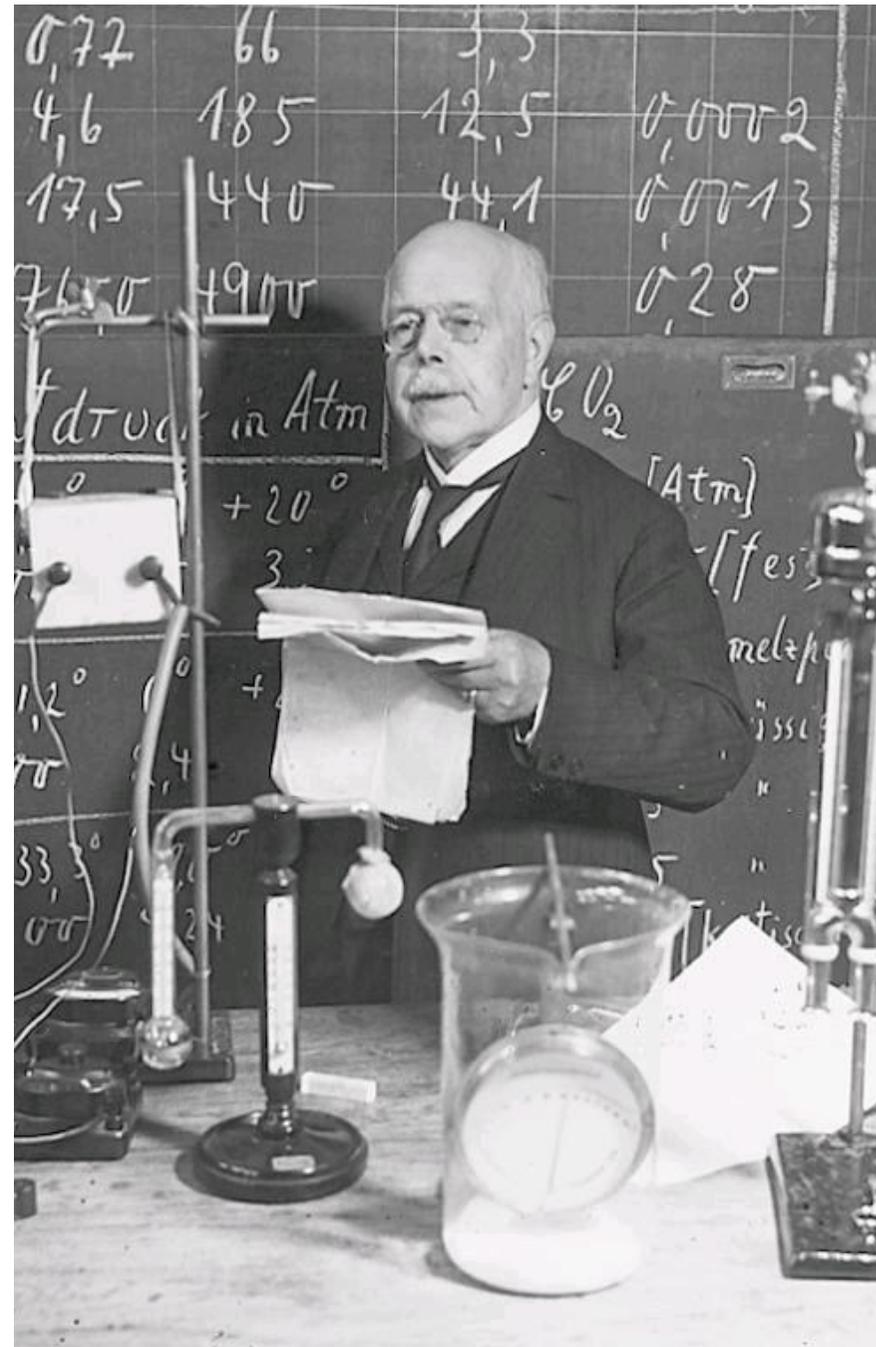
This pump uses energy produced by ATP (adenosine triphosphate) to move 3 sodium ions out of the neuron for every 2 potassium ions it puts in



The Nernst equation (1889)

The Nernst equation is fundamental for understanding the mechanisms generating the membrane potential

This equation gives a formula that associates the numerical values of the **chemical gradient** to the **electrical gradient** that balances it (electrochemical equilibrium)



The Nernst equation

- The general form of the Nernst equation is:

$$E_x = RT / zF * \ln ([x]_e / [x]_i)$$

where E_x (mV) is the equilibrium potential for the x ion, R = gas constant (8314 joule/°K mol), T = absolute temperature in °K, z = ion charge (Na: +1; K: +1, Ca: +2, Cl: -1), F = Faraday constant (96500 Coulomb/mol), \ln = natural logarithm, $[x]_e$ and $[x]_i$ the external and internal concentration of the x ion, respectively

The Nernst equation in biology

- In humans, $T = 310 \text{ °K} = 37\text{°C}$
- $\ln = \log * 2,303$; so:
- $E_x = RT / zF * \ln ([x]_e / [x]_i) =$
 $= RT / zF * 2,303 \log ([x]_e / [x]_i) =$
 $= (8314 \text{ J/°K mol} * 310 \text{ °K}) / (z * 96500 \text{ C/mol}) * 2,303 \log([x]_e/[x]_i)$
 $= 0,0615 \text{ V} / z * \log([x]_e/[x]_i) =$
 $= 61,5 \text{ mV} / z * \log([x]_e/[x]_i)$

Assumptions

- The equation can be solved for 1 ion at a time
- The membrane must be permeable to that ion
- The ion must be at (electrochemical) equilibrium
- If we want to solve for a negative ion (like chloride), we use the absolute value of the valence (+ 1 rather than - 1), but invert the intracellular and extracellular equations (so intracellular is now in the numerator of the equation)
- Because we only solve for one ion at a time, the "E" in the equation will have a subscript denoting what ion you solved for; therefore, we will talk about the Nernst potential for sodium, etc...

Examples

$$E_x = 61,5 \text{ mV} / z * \log([x]_e/[x]_i)$$

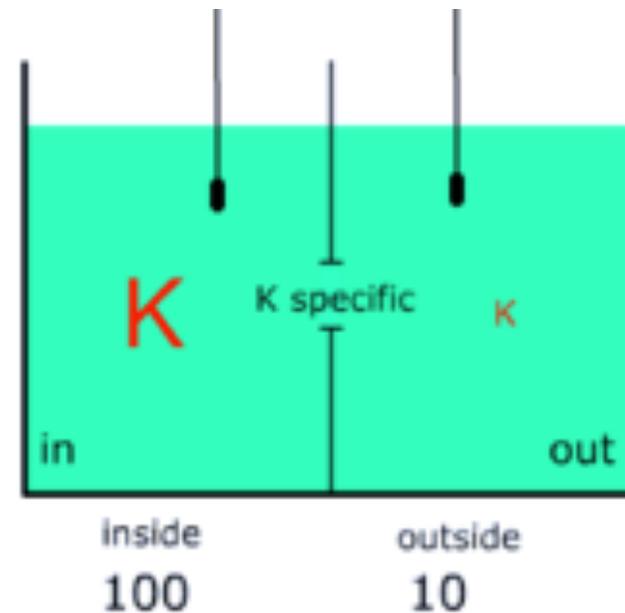
The K concentration ratio is 10:100 and K is monovalent

$$E_K = - 61,5 / 1 \log (0,1) = + 61,5 \text{ mV}$$

If you reverse the direction of the concentration gradient, then the absolute value is the same, but its polarity reversed:

$$E_K = - 61,5 / 1 \log(10) = - 61,5 \text{ mV}$$

Notice that it is the ratio that counts and not the absolute values of the concentrations

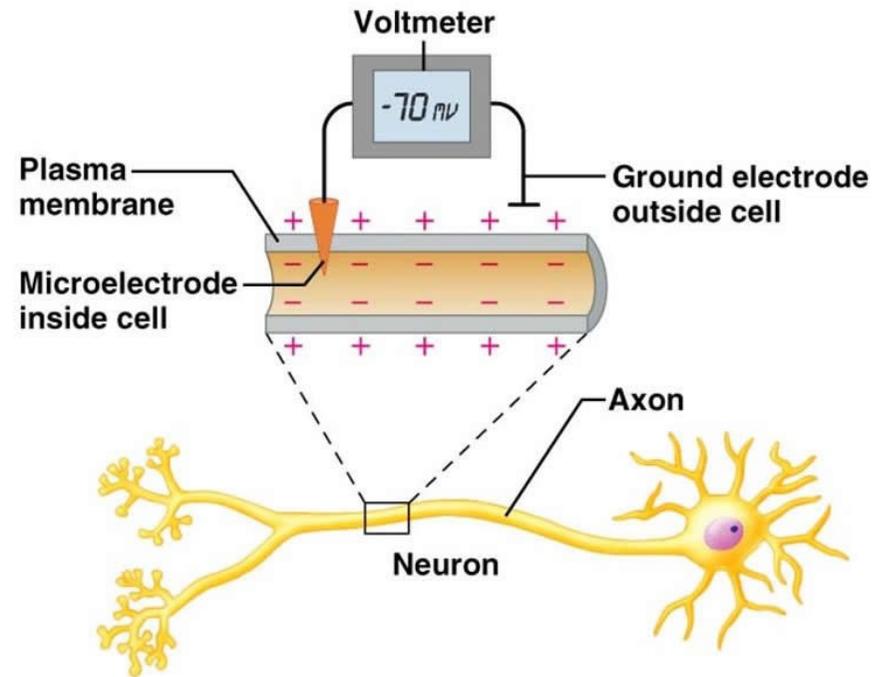


And if do you consider multiple ions?

The equation of Nernst represents a simplification of the resting membrane potential

At rest, the Na⁺/K⁺ pump is activated, K⁺ ions can cross the membrane, while Na⁺ ions can not

The neuron's membrane potential coincides with a dynamical equilibrium between potassium and sodium (the equation of Goldman - Hodgkin)



Resting membrane potential

Before stimulation, a neuron has a negative electric polarization, that is, its interior has a negative charge compared with the extracellular fluid

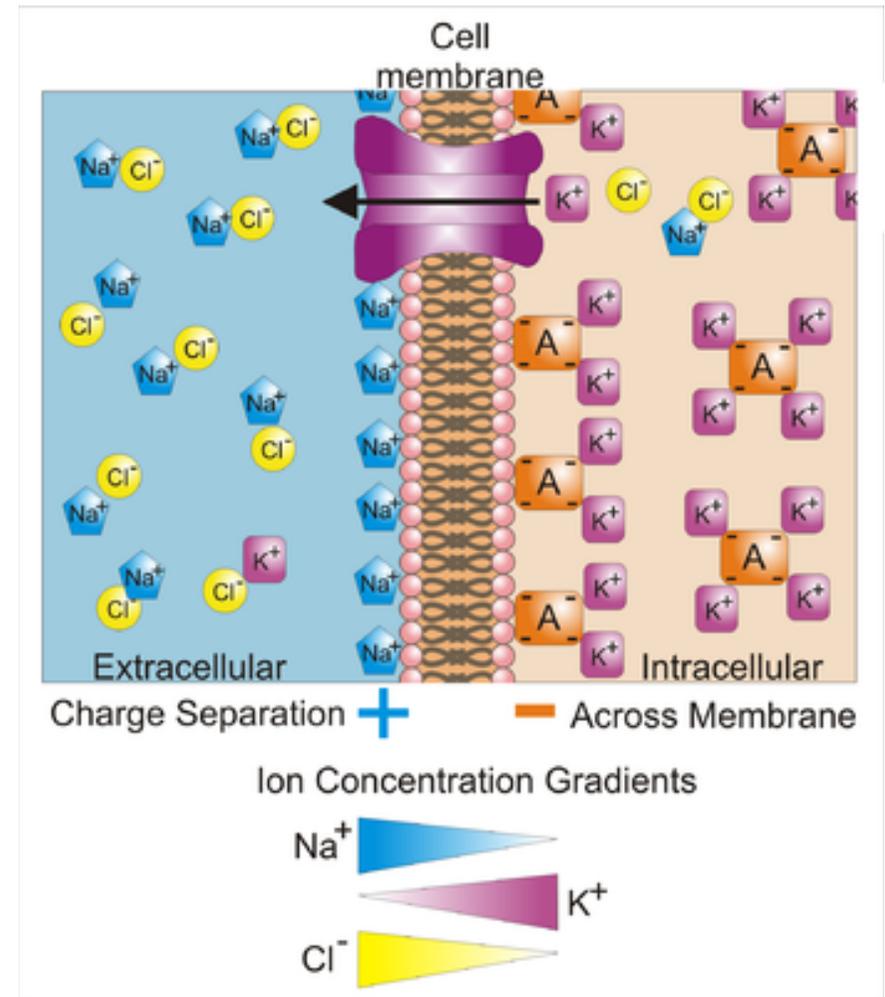
This polarized state is created by a high concentration of positively charged Na^+ ions and a high concentration of negatively charged Cl^- ions outside the neuron, as well as a lower concentration of positively charged K^+ ions inside

The resting potential V usually measures about -70 mV , the minus sign indicating a negative charge inside

V does not coincide with the Nernst potential of Na^+ or K^+

In particular, V is more negative (roughly -10 mV) than V_k

In rest conditions, internal and external concentrations of K^+ and Na^+ ions are constants because of the Na^+/K^+ pump

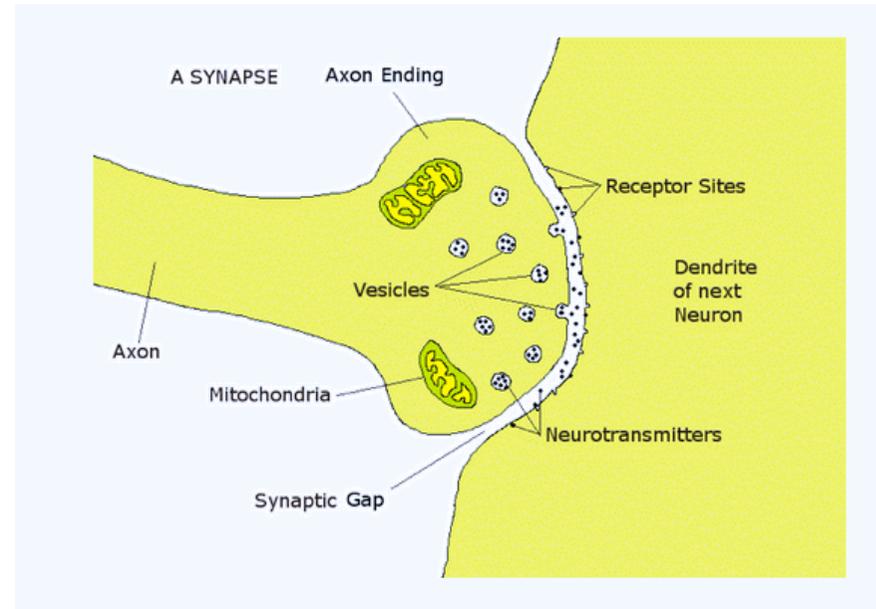


The chemical synapse

The part of the synapse that belongs to the initiating neuron is called the **presynaptic membrane**.

The part of the synapse that belongs to the receiving neuron is called the **postsynaptic membrane**

The space between the two membranes is called the **synaptic cleft** (approximately 20 nm wide)

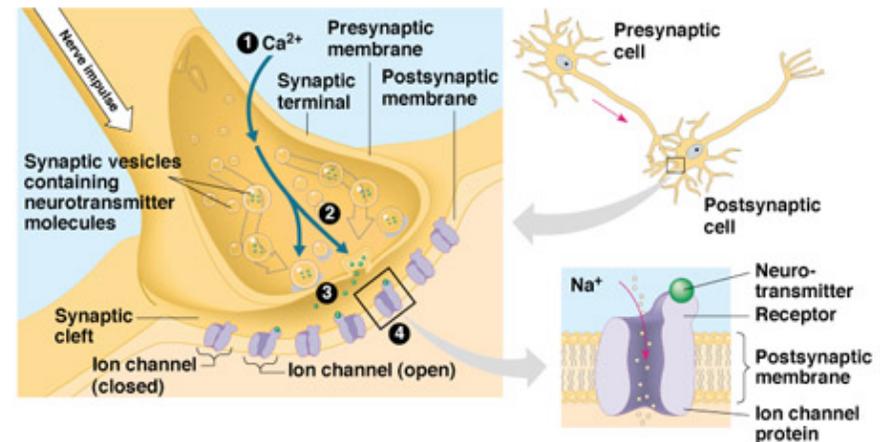


The chemical synapse

In the presynaptic membrane there are numerous synaptic vesicles, containing neurotransmitters (chemical substances which ultimately cause postsynaptic changes in the receiving neuron)

The 2 most common neurotransmitters in the brain are the amino acids glutamate and GABA

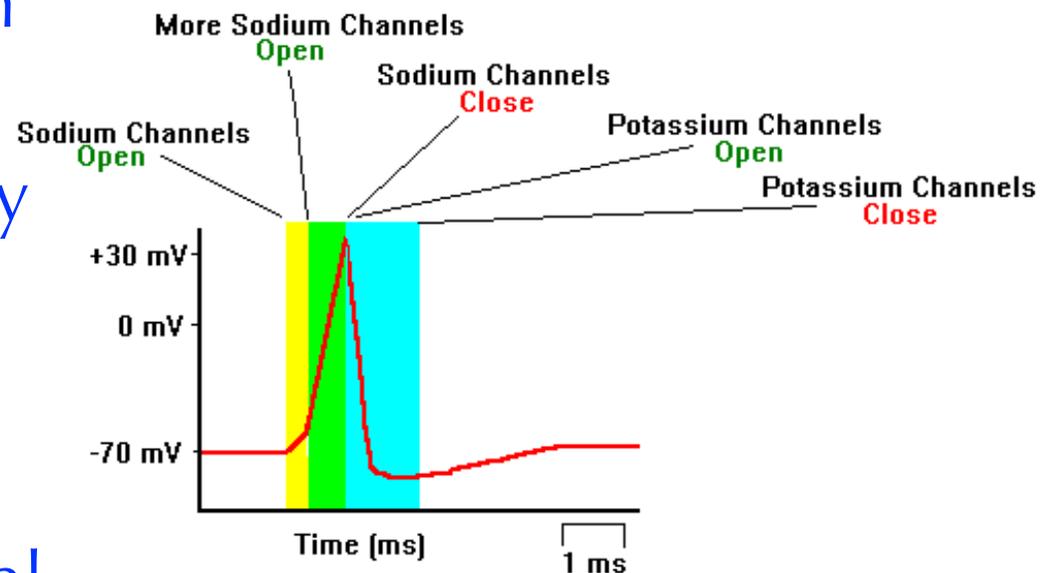
The postsynaptic membrane contains hundreds of **receptor sites** or **ion channels** (or protein channels) that bind to neurotransmitters



The action potential

The action potential (or spike or neuron fire) is a short-lasting event (1 - 2 msec) in which the membrane potential of a neuron rapidly rises and falls, following a consistent trajectory

It is an explosion of electrical activity that is created by a current



The all-or-none principle

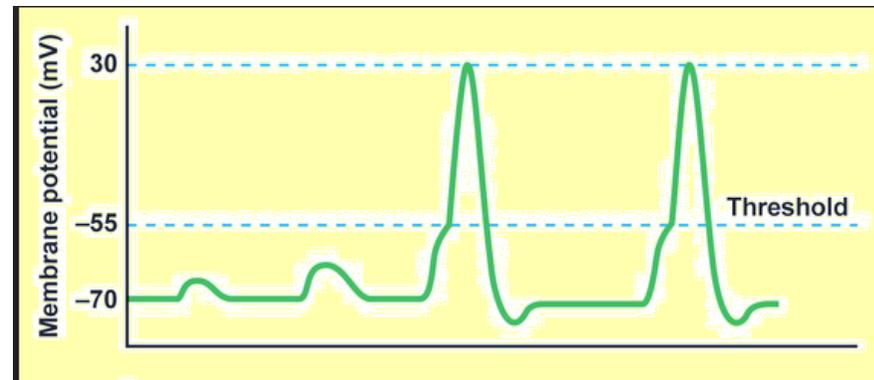
When the membrane potential reaches about

- 55 mV (threshold), the neuron will fire an action potential

If the neuron does not reach this critical threshold level, then no action potential will fire

When the threshold level is reached the size and the shape of the action potential are always the same

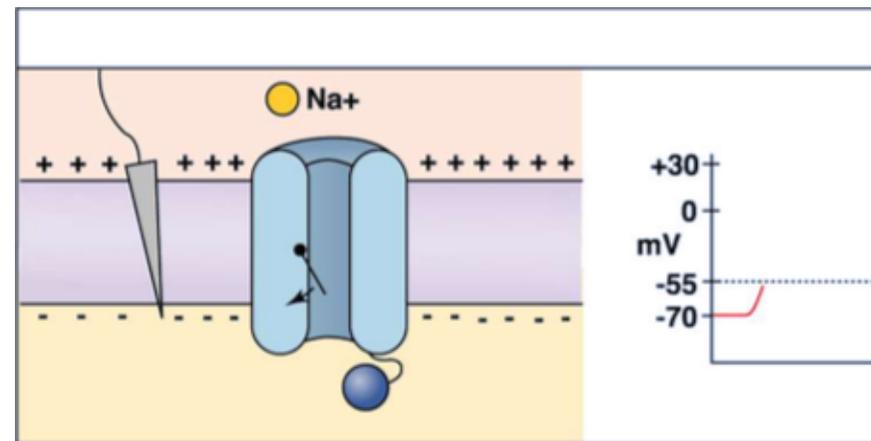
The neuron either does not reach the threshold or a full action potential is fired



The action potential: opening of the Na⁺ channel

At resting potential, the activation gates of Na⁺ are closed while the inactivation gate is open

During the membrane **depolarization** between -70 mV to -55 mV (threshold value), the activation gates open and the membrane is permeable to Na⁺

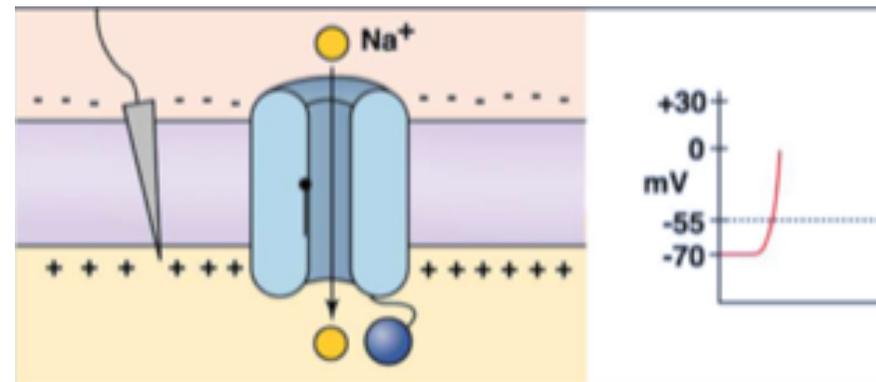


The action potential: depolarization

When the Na^+ channel is open, Na^+ ions enter into the neuron

Furthermore, K^+ ions begin to leave the neuron

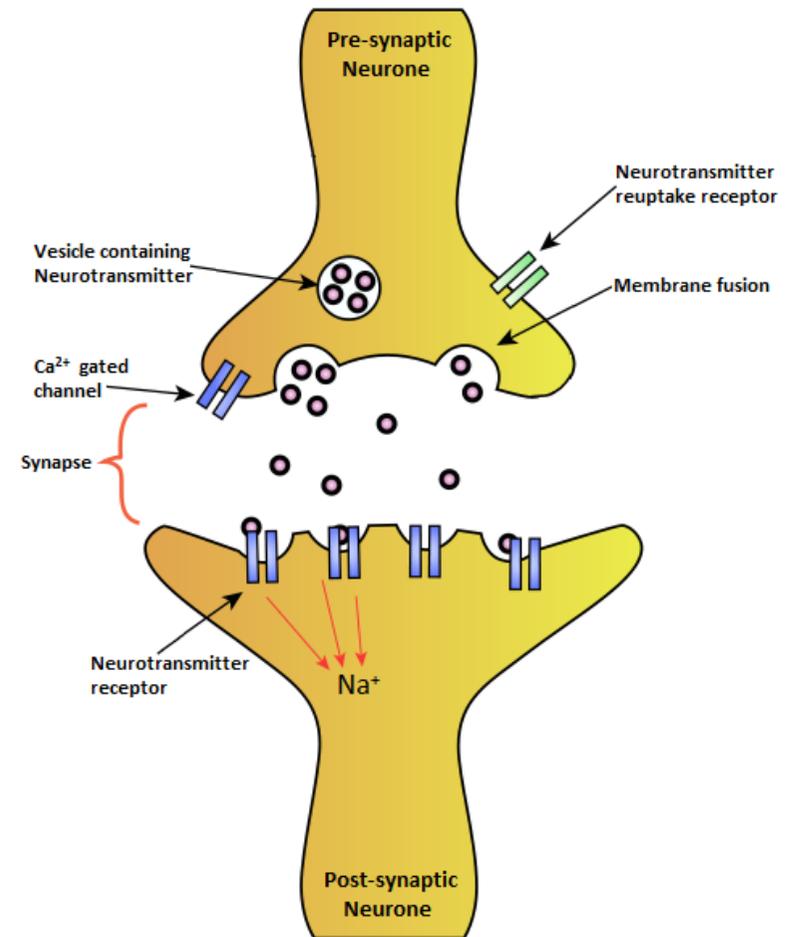
The action potential rapidly increases



The action potential: neurotransmitters and receptors

The depolarization produces the opening of the Ca^{++} channel

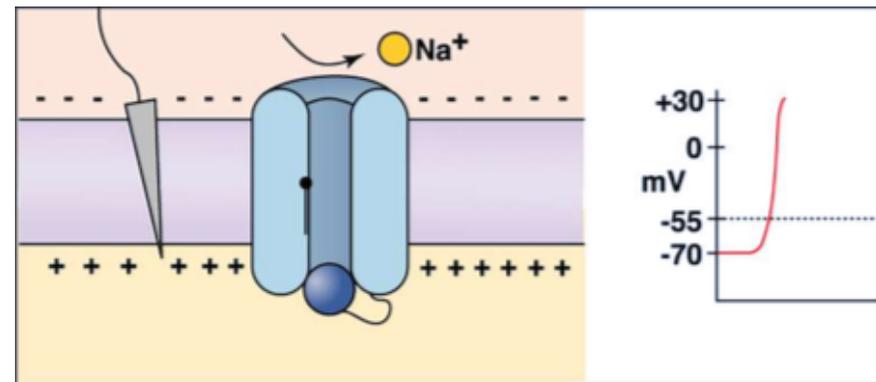
The increase of the calcium ions in the presynaptic neuron induced the release on neurotransmitters by the vesicles



The action potential: inactivation of Na⁺ channels

When the activation gate is closed, Na⁺ can not enter into the neuron

By depolarization increasing, the activation gate is closed and the membrane is not permeable to Na⁺ ions

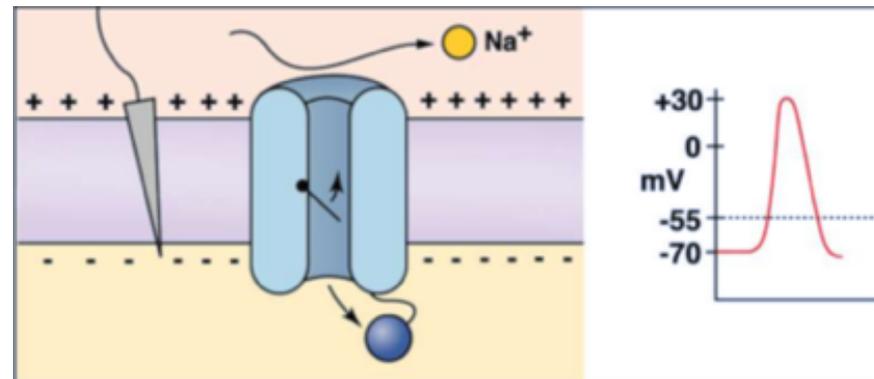


The action potential: repolarization

During the **repolarization**, due to the exit of K^+ ions, the Na^+ inactivation gate opens and the activation gates close

First, the membrane potential becomes more negative than the rest -approximately -90mV - (**hyperpolarization**, about 1 msec)

Then, the initial configuration (roughly -70mV) is reached by the Na^+/K^+ pump



The model of the action potential of Hodgkin-Huxley (1952)

- How HH derived the model equations
- What to hope from a mathematical model in medicine

500

J. Physiol. (1952) 117, 500-544

A QUANTITATIVE DESCRIPTION OF MEMBRANE CURRENT AND ITS APPLICATION TO CONDUCTION AND EXCITATION IN NERVE

BY A. L. HODGKIN AND A. F. HUXLEY

From the Physiological Laboratory, University of Cambridge

(Received 10 March 1952)

This article concludes a series of papers concerned with the flow of electric current through the surface membrane of a giant nerve fibre (Hodgkin, Huxley & Katz, 1952; Hodgkin & Huxley, 1952 *a-c*). Its general object is to discuss the results of the preceding papers (Part I), to put them into mathematical form (Part II) and to show that they will account for conduction and excitation in quantitative terms (Part III).

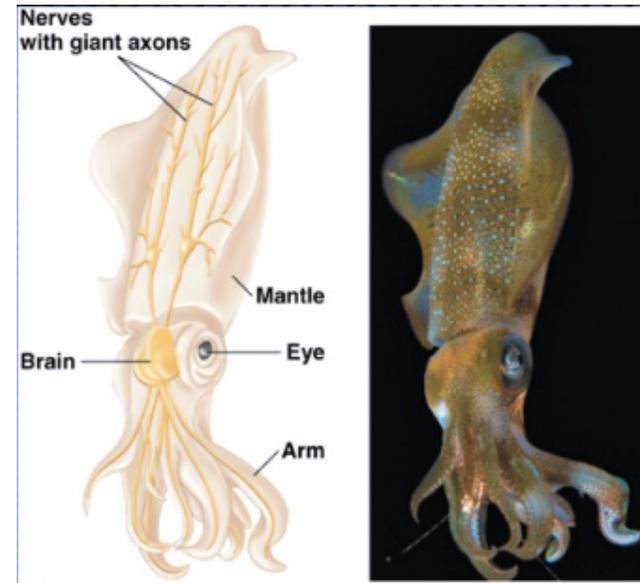
PART I. DISCUSSION OF EXPERIMENTAL RESULTS

The results described in the preceding papers suggest that the electrical behaviour of the membrane may be represented by the network shown in Fig. 1. Current can be carried through the membrane either by charging the membrane capacity or by movement of ions through the resistances in parallel with the capacity. The ionic current is divided into components carried by sodium and potassium ions (I_{Na} and I_K), and a small 'leakage current' (I_l) made up by chloride and other ions. Each component of the ionic current is determined by a driving force which may conveniently be measured as an electrical potential difference and a permeability coefficient which has the dimensions of a conductance. Thus the sodium current (I_{Na}) is equal to the sodium conductance (g_{Na}) multiplied by the difference between the membrane potential (E) and the equilibrium potential for the sodium ion (E_{Na}). Similar equations apply to I_K and I_l and are collected on p. 505.

Our experiments suggest that g_{Na} and g_K are functions of time and membrane potential, but that E_{Na} , E_K , E_l , C_M and \bar{g}_l may be taken as constant. The influence of membrane potential on permeability can be summarized by stating: first, that depolarization causes a transient increase in sodium conductance and a slower but maintained increase in potassium conductance; secondly, that these changes are graded and that they can be reversed by repolarizing the membrane. In order to decide whether these effects are sufficient to account for complicated phenomena such as the action potential and refractory period, it is necessary to obtain expressions relating

The squid giant axon

- Hodgkin and Huxley (HH) proposed a **model of the dynamics of the action potential and the 3 ionic currents** underlying the initiation and propagation of the action potential, **in the squid giant axon (not the giant squid axon!)**, based on a system of 4 differential equations
- They received the 1963 Nobel Prize in Physiology and Medicine
- It is a very simple system, and the axon has a large diameter (up to 1 mm), allowing to insert the electrodes into the axon

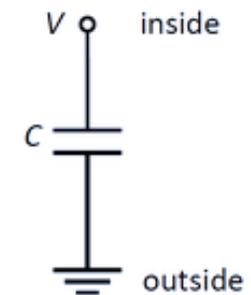
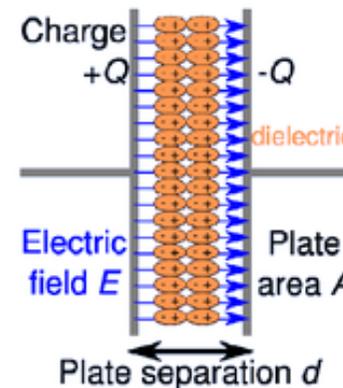


Resistors

- HH model the neuron's membrane as a physical circuit with a resistor R and a capacitor C
- The current I that flows through the resistor is given by the Ohm's Law: $I = V/R = gV$ where V is the voltage drop across the resistance R and the conductance $g = 1/R$
- When there are more open ion channels, more currents can flow through these channels to the extracellular medium
- With this property each ion channel acts as a small resistor and the number of ion channels increased can be represented by more number of resistors that are in parallel

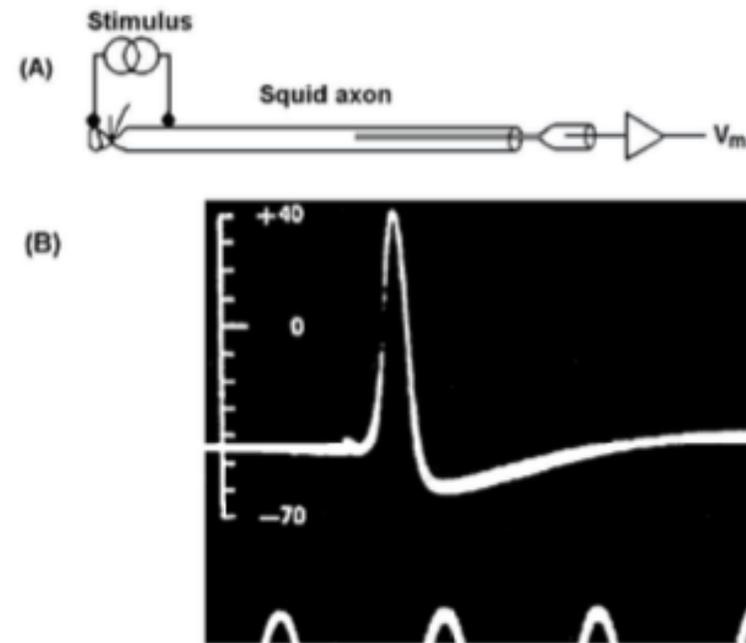
Capacitors

- In a neuron, the conducting plates are the intracellular and extracellular solutions, separated by the phospholipid bilayer (non-conducting) membrane
- If an impulse arrives, the current: $I = C \, dV / dt$, where C is the capacitance and V the voltage



Experimental observations

- The experiments, at the squid giant axon, revealed that the membrane potential not only goes toward zero but overshoots and reverses sign
- The question of how the (different) permeability changes of the K^+ and Na^+ ions were dynamically linked to the action potential were not clear

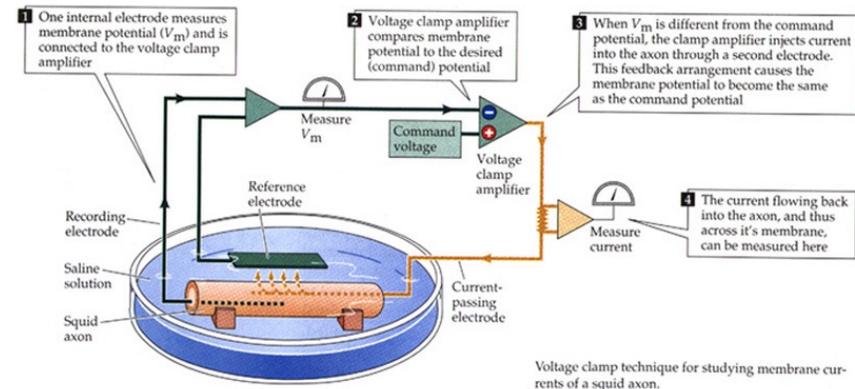


The voltage clamp

Why? The membrane potential depends on conductances that depends on the potential, so HH maintained a constant potential, and augmented it with discrete quantities

The membrane is “clamped” to a fixed potential and currents that need to maintain this potential level are recorded

The axon was immersed in sea water, so V_m represented the difference between the inside of the axon and the water
HH inserted 2 silver electrodes in the axon, one measuring V_m and the other transmitting a current able to maintain V_m constant



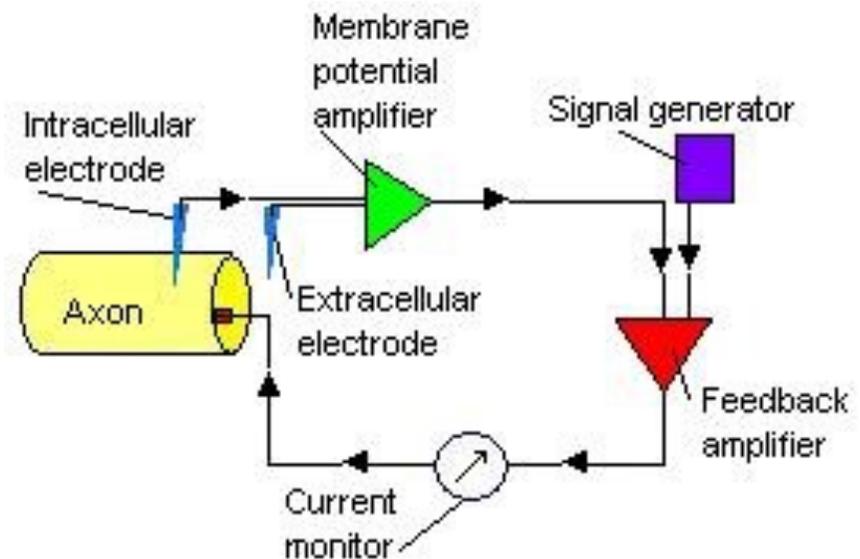
Advantages of the voltage clamp

It is possible to measure the temporal dependence of conductance with a constant V_m

By introducing the electrodes in the axon, there is a space-clamp, i.e. V_m is constant along its entire length

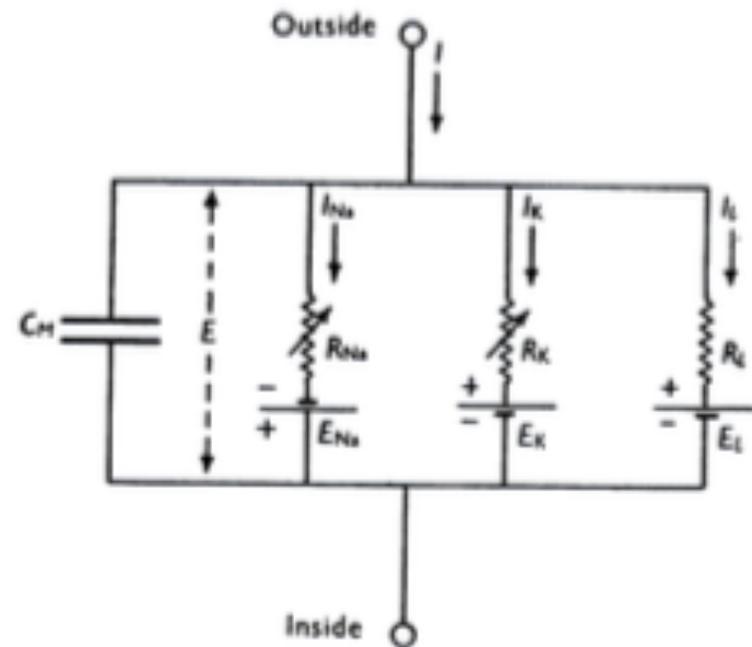
By observing the experimental data recorded with the voltage clamp, HH hypothesized that in the first phase of the action potential the most important ions were the Na^+ ions and in the second one the K^+ ions

HH separated I_{Na} and I_{K} contribution, using “blockants” like choline



The model scheme

In order to represent the simultaneous presence of multiple ions, HH proposed an electrical circuit for a patch of axon membrane with a capacity and ionic currents from the flow of Na^+ and K^+ as well as a leak current (Cl^-)



from Hodgkin & Huxley,
J. Physiol. (1952)

Total membrane current

- Kirchoff's law: the total current flowing across the cell membrane is the sum of the capacitive current (due to conductor) and the ionic currents (due to resistors)

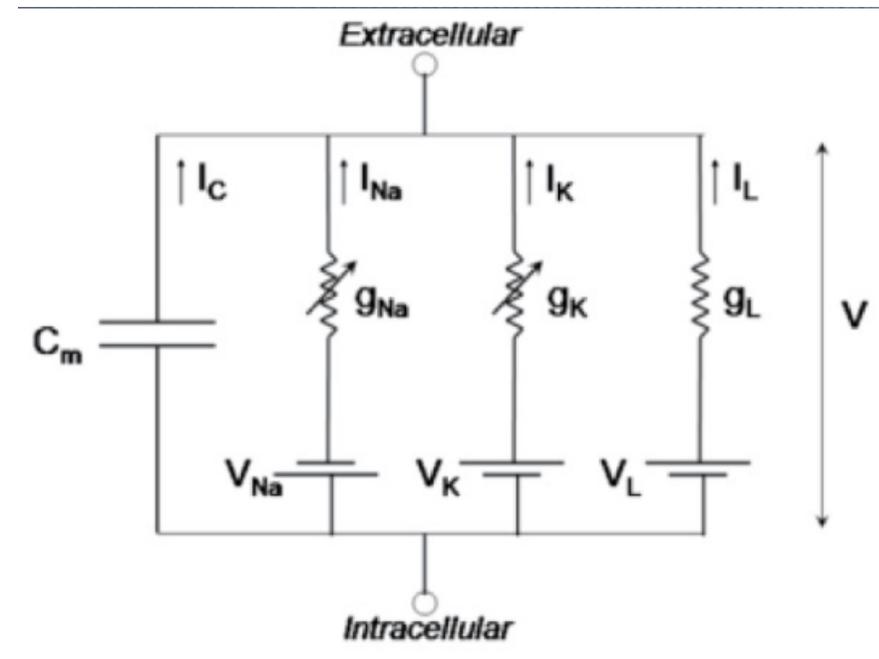
- HH applied to the axon a current I

- I can be divided into a capacity current, $C_M dV/dt$, and an ionic current where I_i

$$I = C_M \frac{dV}{dt} + I_i$$

- V is the displacement of the membrane potential from its resting value, C_M is the membrane capacity per unit area (assumed constant), and t the time

- Notice that the equation takes no account of dielectric loss in the membrane and of the Na_+/K_+ pump



The ionic current

In turn, the ionic current is splitted into components carried by sodium ions (I_{Na}), potassium ions (I_K), and other ions, mainly chloride (leakage current I_L):

$$I_i = I_{Na} + I_K + I_L$$

The individual ionic currents

- $I_i = I_{Na} + I_K + I_L$, and for the Ohm's Law:

$$I_{ion} = \underbrace{G_{Na}(V_m, t)(V_m - E_{Na})}_{I_{Na}} + \underbrace{G_K(V_m, t)(V_m - E_K)}_{I_K} + \underbrace{G_L(V_m - E_L)}_{I_L}$$

- where E_x are the Nernst equilibrium potential for the x ion and V_m the membrane potentials
- From experimental data, HH understood that the conductances (inverse of resistances) of sodium and potassium depended on the membrane potential V_m (the chloride conductance is independent on the potential)

Conductances in cell membranes varied with time and potential, but how?

By fitting the data, HH found the following relations, where G_x are the maximum values for the conductances g_x , corresponding to the opening of the gates of the ion channels

$$g_L = G_L$$

$$g_{Na} = G_{Na} m(t)^3 h(t)$$

$$g_K = G_K n(t)^4$$

Conductances

- Conductance g_x is assumed to be generated by ion channels in the axonal membrane patch, each with a number of physical gates that regulate ion flow
- Each gate can be in a permissive or non-permissive state
- HH supposed that a channel is open if all gates are in the permissive state and closed otherwise

K⁺ conductance

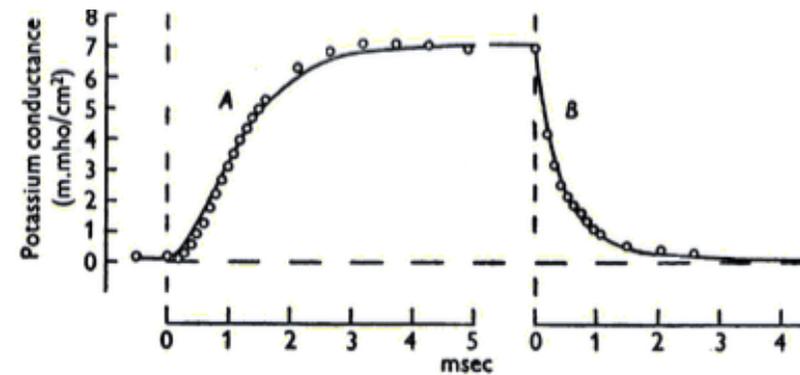
The Figure shows the change in potassium conductance (associated with a depolarization of 25 mV lasting 4-9 sec)

The end of the record (B) can be fitted by a first-order equation but a third- or fourth-order equation is needed to describe the beginning (A)

A useful simplification is achieved by supposing that g_K is proportional to the fourth power of a variable which obeys a first-order equation

n is a dimensionless variable which can vary between 0 and 1

$$g_K = \bar{g}_K n^4,$$
$$\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n,$$



$$g_K = \bar{g}_K n^4,$$

$$\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n,$$

0

n represents the proportion of the K^+ at the inside of the membrane (“ON” position) and $1-n$ represents the proportion that are at the outside (“OFF” position), at time t

In other words, n is the probability that one of the 4 gates is open, and n^4 the probability that all the gates are open (i.e. the K^+ channel is open), at time t

Alpha and beta are functions of the membrane potential, and the dimension is t^{-1}

Alpha determines the rate of transfer of K^+ from outside to inside of the neuron (to the “ON” position), while beta determines the transfer in the opposite direction (to the “OFF” position)

β_n

α_n

$n \rightarrow (1 - n)$ and $(1 - n) \rightarrow n$

Alpha and beta

HH derived experimentally
alpha and beta values, for
different potential membrane
levels

V (mV) (1)	$g_{K\infty}$ (m.mho/cm ²) (2)	n_{∞} (3)	τ_n (msec) (4)	α_n (msec ⁻¹) (5)	β_n (msec ⁻¹) (6)
(-∞)	(24-31)	(1-000)	—	—	—
-109	20-70	0-961	1-05	0-915	0-037
-100	20-00	0-953	1-10	0-866	0-043
-88	18-60	0-935	1-25	0-748	0-052
-76	17-00	0-915	1-50	0-610	0-057
-63	15-30	0-891	1-70	0-524	0-064
-51	13-27	0-859	2-05	0-419	0-069
-38	10-29	0-806	2-60	0-310	0-075
-32	8-62	0-772	3-20	0-241	0-071
-26	6-84	0-728	3-80	0-192	0-072
-19	5-00	0-674	4-50	0-150	0-072
-10	1-47	0-496	5-25	0-095	0-096
-6	0-98	0-448	5-25	0-085	0-105
(0)	(0-24)	(0-315)	—	—	—

Na⁺ conductance

Using the same method, HH empirically derived the relation for the Na⁺ conductance

The relation is more complicated; in fact sodium channel first opens and then closes

First, we might assume that the sodium conductance is determined by a variable which obeys a second-order differential equation

Secondly, we might suppose that it is determined by 2 variables, each of which obeys a first-order equation

The second alternative was chosen since it was simpler to apply to the experimental results, where alpha and beta are functions of the membrane potential:

$$g_{\text{Na}} = m^3 h \bar{g}_{\text{Na}},$$
$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m,$$
$$\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h,$$

Na⁺ conductance

$$g_{\text{Na}} = m^3 h \bar{g}_{\text{Na}},$$
$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m,$$
$$\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h,$$

- Alpha and beta represent the rates of transfer
- There are 4 gates, and each gate can be open or close
- m is the probability that one of 3 gates is open (or the proportion of Na⁺ ions inside), at t time
- h is the probability that the 4th gate is open, at t time
- Na⁺ channel is open is all the 4 gates are open (m³h is the probability that all the gates are open, at t time)

Alpha and beta

HH derived experimentally alpha and beta values, for different potential membrane levels

V (mV)	β_{α} (m.mho/cm ²)	α_{α} (1.00)	τ_{α} (msec)	α_{β} (msec ⁻¹)	β_{β} (msec ⁻¹)	α_{β} (msec)	λ_{α}	α_{β} (msec ⁻¹)	β_{β} (msec ⁻¹)
(-∞)	(42.9)	(1.00)	—	—	—	—	—	—	—
-109	40.3	0.990	0.140	7.0	(0.14)	0.67	(0)	(0)	1.50
-100	42.6	0.997	0.180	6.2	(0.02)	0.67	(0)	(0)	1.50
-88	46.8	1.029	0.200	5.15	(-0.14)	0.67	(0)	(0)	1.50
-76	39.5	0.975	0.189	5.15	0.13	0.84	(0)	(0)	1.19
-63	38.2	0.963	0.252	3.82	0.15	0.84	(0)	(0)	1.19
-51	30.7	0.895	0.318	2.82	0.33	1.06	(0)	(0)	0.94
-38	20.0	0.778	0.382	2.03	0.58	1.27	(0)	(0)	0.79
-32	15.3	0.709	0.520	1.36	0.56	1.33	(0)	(0)	0.75
-26	7.90	0.569	0.600	0.95	0.72	(1.50)	(0.029)	(0.02)	(0.65)
-19	1.44	0.323	0.400	0.81	1.49	(2.30)	(0.069)	(0.03)	(0.40)
-10	0.13	0.145	0.220	0.66	3.9	(5.52)	(0.263)	(0.05)	(0.13)
-6	0.046	0.103	0.200	0.51	4.5	(6.73)	(0.388)	(0.06)	(0.09)
(0)	(0.0033)	(0.042)	—	—	—	—	(0.608)	—	—

Summary of equations and parameters

$$I = C_M \frac{dV}{dt} + \bar{g}_K n^4 (V - V_K) + \bar{g}_{Na} m^3 h (V - V_{Na}) + \bar{g}_l (V - V_l), \quad (26)$$

where

$$\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n, \quad (7)$$

$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m, \quad (15)$$

$$\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h, \quad (16)$$

Measures units:

$$C \text{ } \mu\text{F/cm}^2$$

$$V \text{ mV}$$

$$I \text{ } \mu\text{A/cm}^2$$

$$g \text{ mS/cm}^2$$

Summary of equations and parameters

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and

$$\alpha_n = 0.01 (V + 10) / \left(\exp \frac{V + 10}{10} - 1 \right), \quad (12)$$

$$\beta_n = 0.125 \exp (V/80), \quad (13)$$

$$\alpha_m = 0.1 (V + 25) / \left(\exp \frac{V + 25}{10} - 1 \right), \quad (20)$$

$$\beta_m = 4 \exp (V/18), \quad (21)$$

$$\alpha_h = 0.07 \exp (V/20), \quad (23)$$

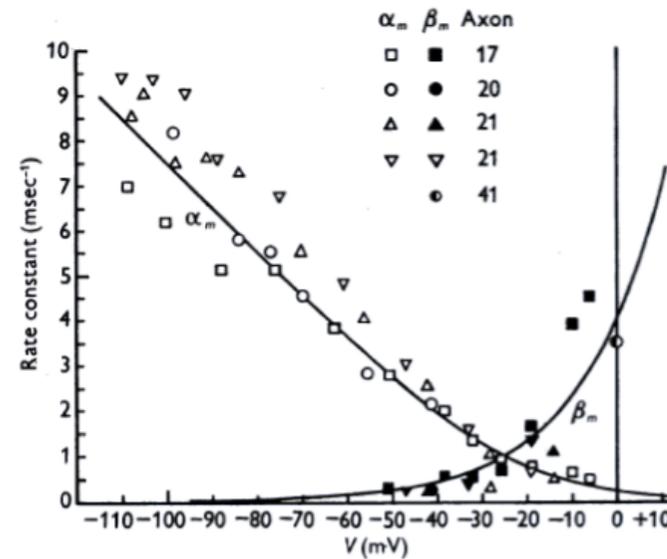
$$\beta_h = 1 / \left(\exp \frac{V + 30}{10} + 1 \right). \quad (24)$$

Alpha and beta depend only on the instantaneous value of the membrane potential V

Their expressions are appropriate to an experimental temperature of 6.3°C

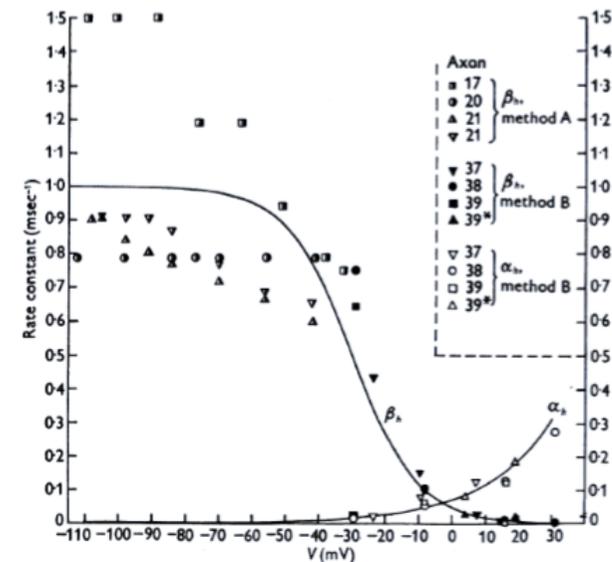
Na+

m is the activation function for the sodium
 h is the inactivation function for the sodium



The picture on the top shows that $\alpha > \beta$ values if V levels are small, so the first effect of the change in potential membrane is the activation of sodium current to the inside of the cell

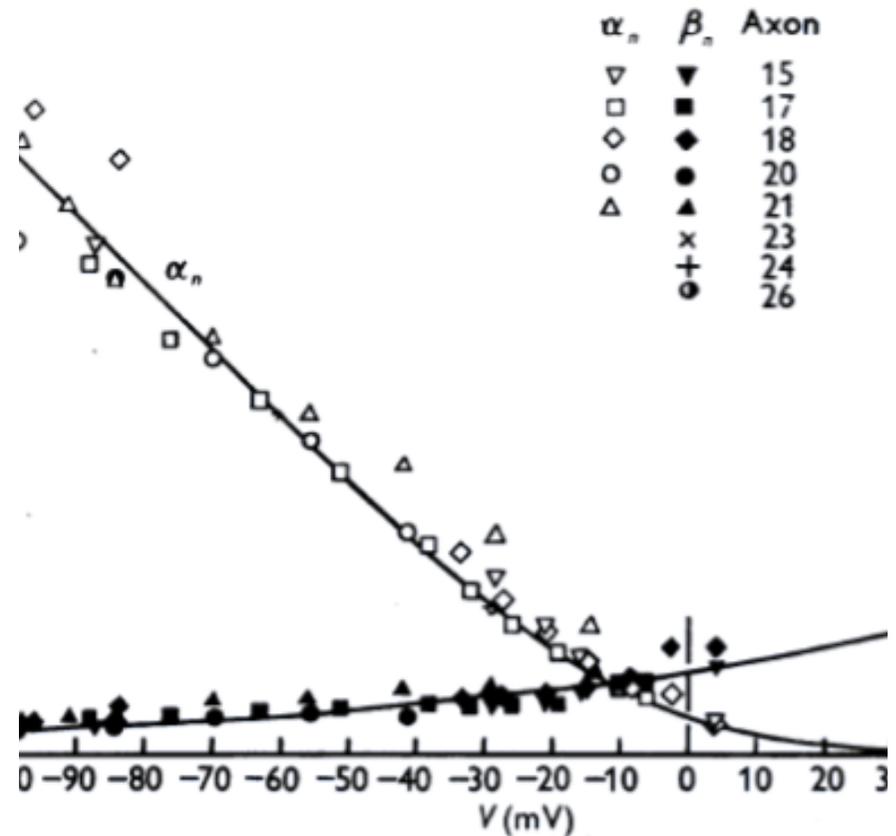
The picture on the bottom reveals that for high levels of V $\alpha > \beta$, so the sodium channel is disactivated



K⁺

We can observe that if the membrane potential is greater than 20 mV beta values are higher than alpha values

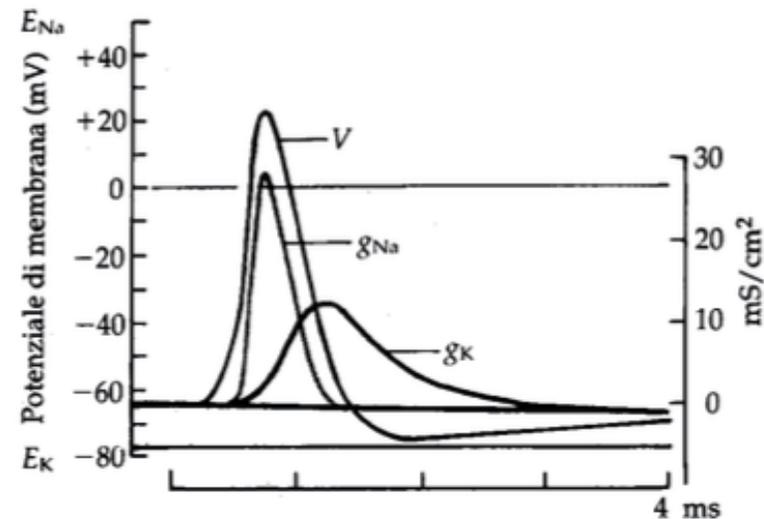
There is a prevalence of K⁺ ions current from the inside of the neuron to the external space, contributing to the repolarization



The Hodgkin-Huxley model

The equations reproduce many characteristics of action potential such as:

- the role, **at different time**, of Na⁺ and K⁺ currents
- the dynamics of the membrane potential in response to an input
- the all-or-none phenomenon



HH found experimentally these values

Ion	$E_x(\text{mV})$	$g_x(\text{mS}/\text{cm}^2)$
Na+	50	120
K+	-77	36
L (Cl-)	-54,4	0,3

The Hodgkin-Huxley model is one of the great success in biomathematics

HH model is used until today

HH equations are not a simple description of the time series of observations but

- the equations parameters have a biological and physical explanation
- there is an hypothesis, to prove or confute

The study reflects a combination of experimental work, theoretical hypothesis, computational data fitting, and model prediction

The enduring contributing of the HH model is in physiological insight it provided, and its power and generality as a modeling method

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