Introduction to Cognitive Neuroscience

The Neuronal Membrane at Rest

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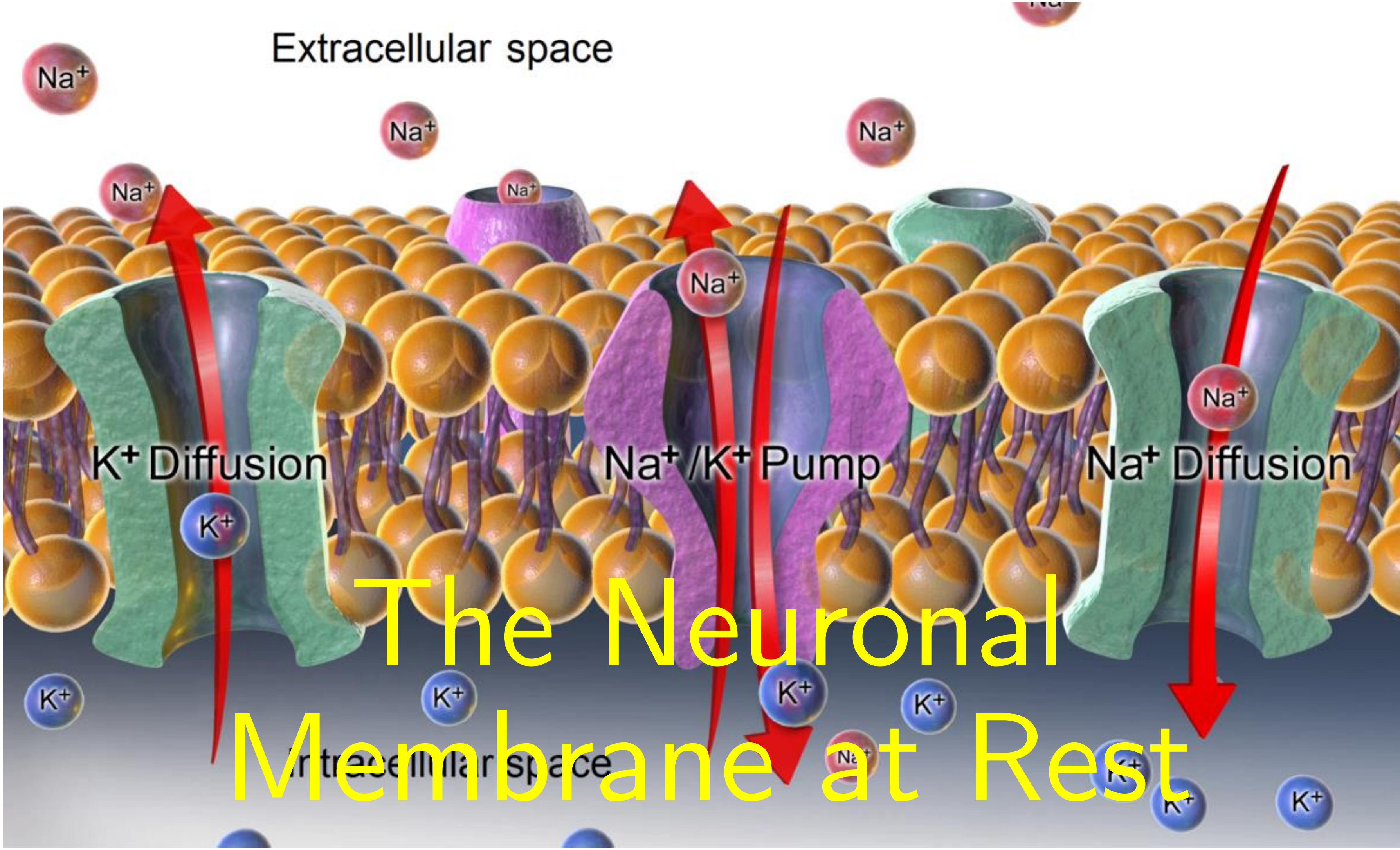
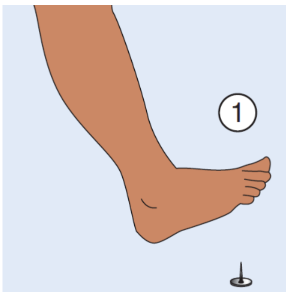
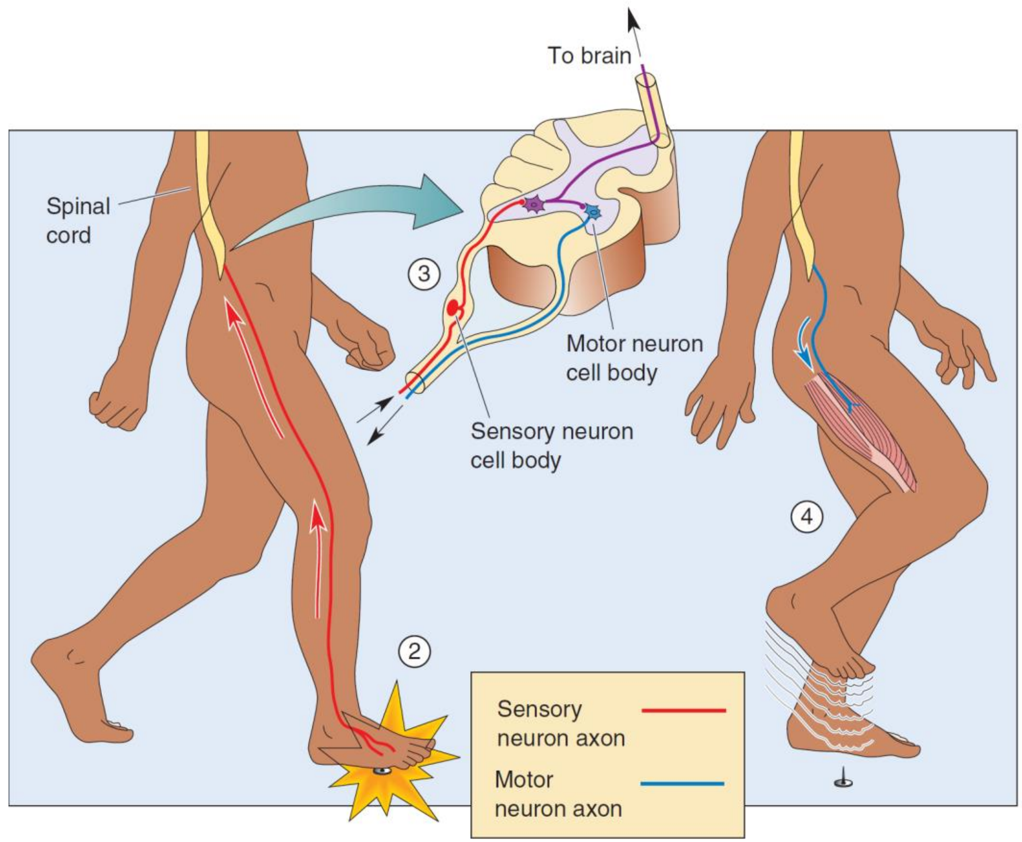
The Neuronal Membrane at Rest



A simple reflex

Steps on a thumbtack





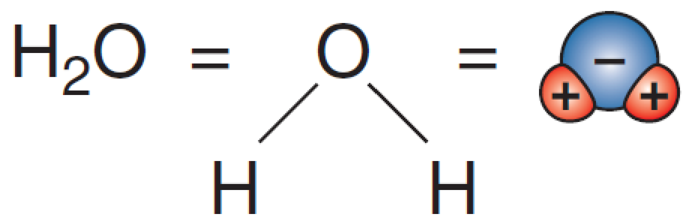
- This simple phenomena, requires the nervous system to ***collect***, ***distribute***, **and** ***integrate*** information
- A **goal of cellular neurophysiology** is to understand the **biological mechanisms** that underlie functions like reflex

Introduction

- The **analogy** of **telephone wires** for **signaling**
  - **Ion** versus **free electrons**
  - **Copper** versus **cytosol** (cytosol as leaky garden hose in rest state)
- Axonal membrane enables to conduct **a special type of signal**, the **nerve impulse**, or **action potential**
  - **Signaling** was done by action potentials that **do not diminish over distance**
- **Excitable membrane** enables cells to **generate** and **conduct** action potentials
- **Excitable membrane at rest**: when it is **not generating** action potential
  - At the **cytosol** along the inside surface of the membrane has a **negative electrical charge compared to the outside**
  - The action **potential** is simply **a brief reversal of this condition**
- Understanding the **resting potential** is the foundation for understanding the rest of **neuronal physiology**

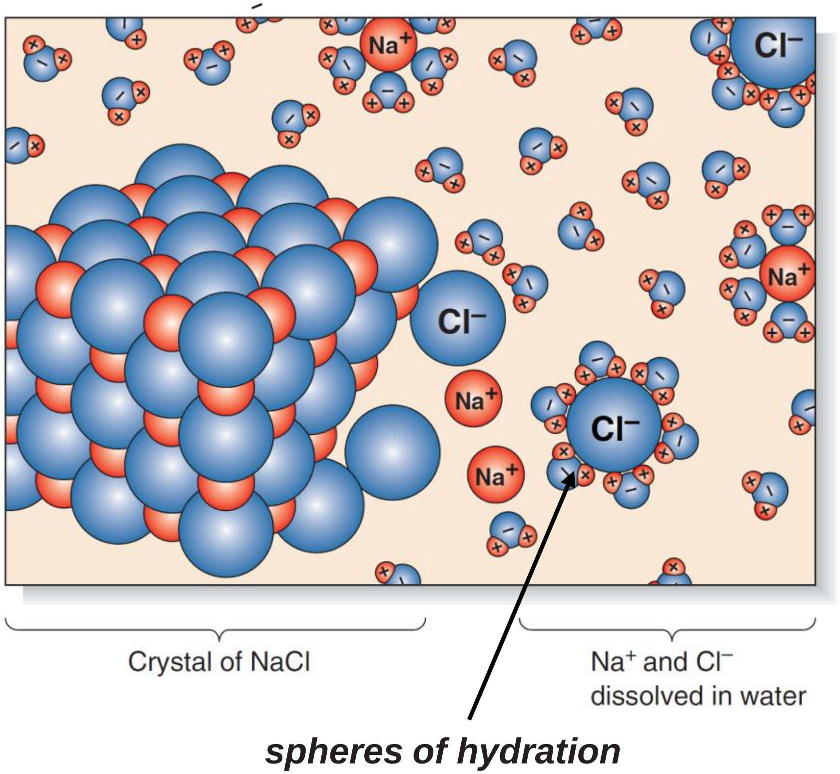
Water

- Water is the main **ingredient** of the fluids inside, **intracellular** or cytosol, and the outside, **extracellular**, that bathes the neuron
- The most important **property** of the water molecule (H_2O) is its **uneven distribution of electrical charge** (**polarity** of the water)
- *Polar covalent bonds*
- Electrical polarity makes water an effective **solvent** of other **charged or polar molecules**



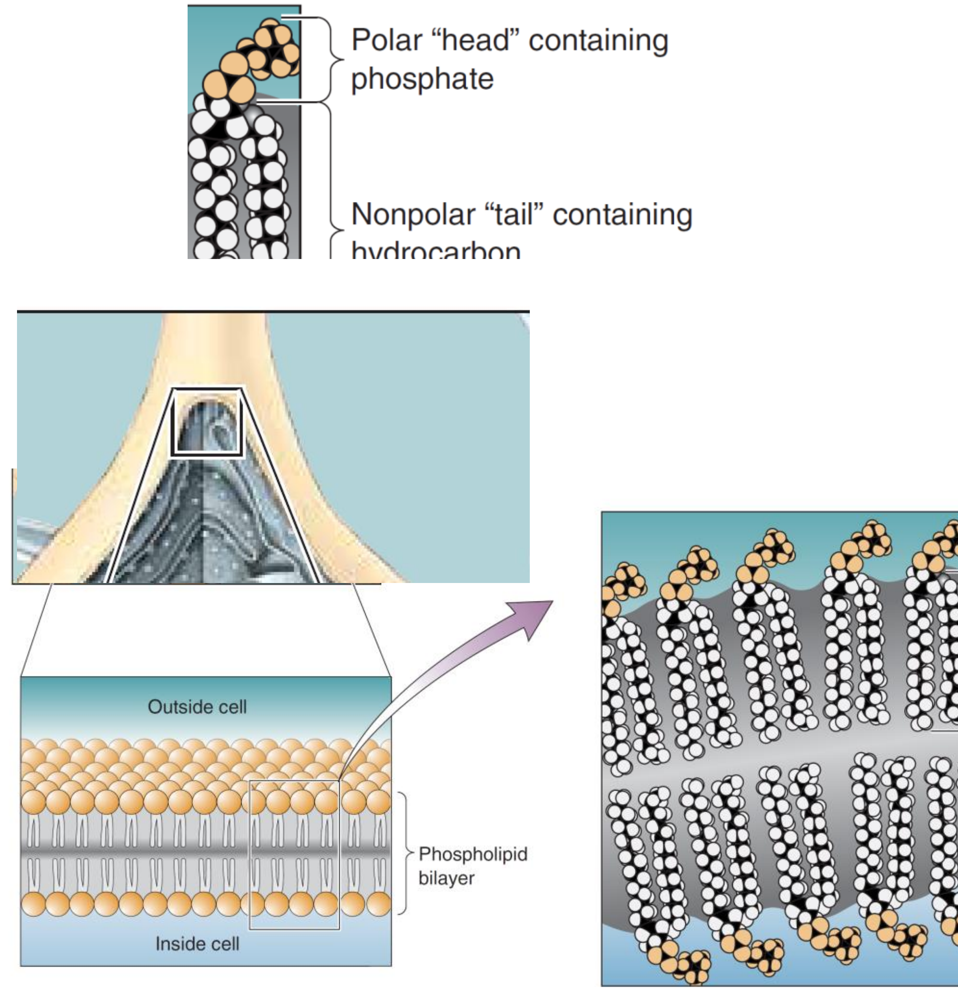
Ions

- Atoms or molecules that have **a net electrical charge** are known as **ions** (versus **molecule**)
- *Ionic bond*
- Water molecules have a **stronger attraction for** the electrically charged sodium and chloride ions **than the ions** do for one another
- Important ion for neurobiology:
  - **monovalent** cations **Na^+**(sodium) and **K^+** (potassium), the **divalent** cation **Ca^{2+}** (calcium), and the monovalent anion **Cl^-** (chloride)

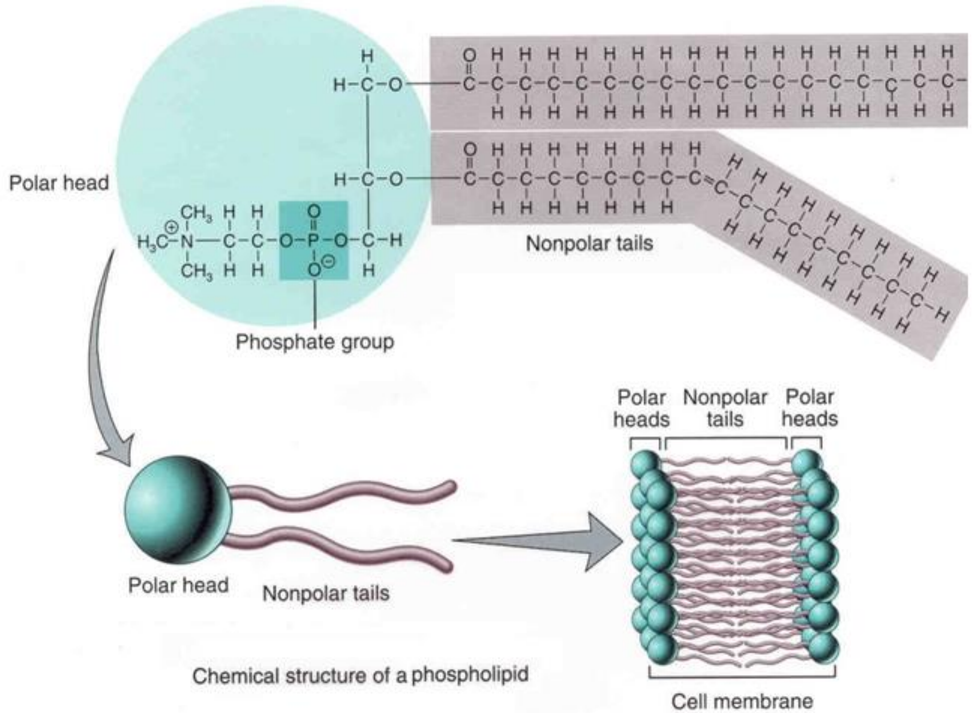


The Phospholipid Membrane

- **Water-loving** or *hydrophilic* (polar bond) **versus water-fearing** or *hydrophobic* (*nonpolar covalent bond*)
- *Lipid*
  - **Water-insoluble** biological molecules
- *Phospholipid*
  - **Building** blocks of cell membranes
  - It has a **polar "head"** (containing **phosphate** that is **hydrophilic**, and a **nonpolar "tail"** (containing hydrocarbon) that is **hydrophobic**.
- **Phospholipid bilayer**



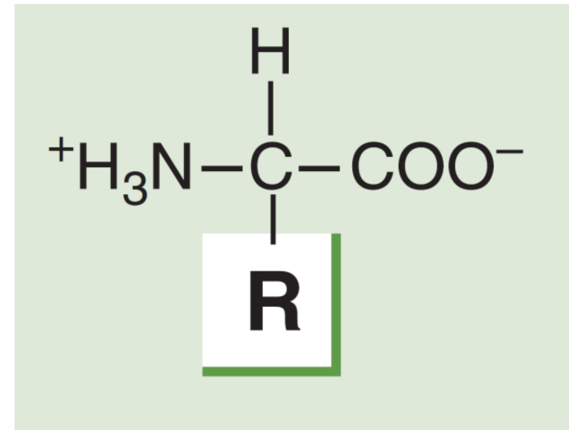
The phospholipid bilayer

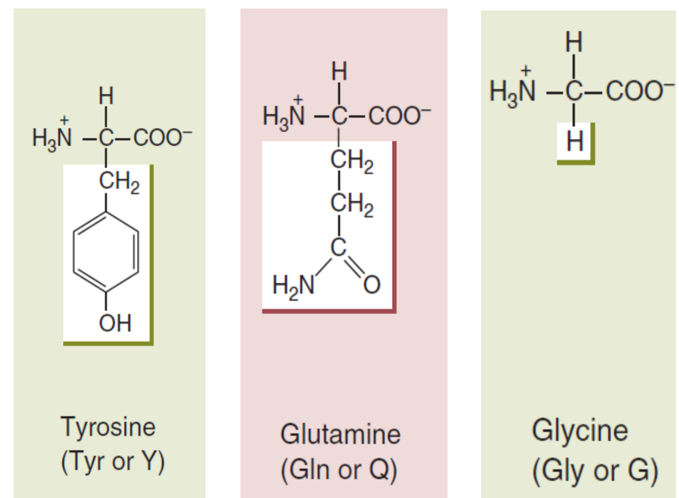


https://www.creative-proteomics.com/images/Phospholipids-Analysis-Service.png

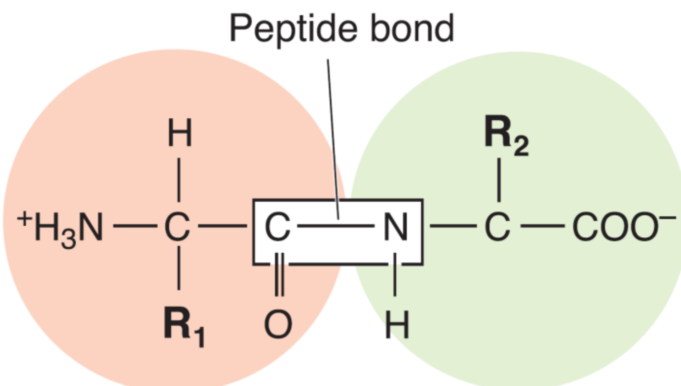
Protein

- **Protein Structure:**
  - It assembled from various combinations of **20 different** amino acids.
- Amino acid:
  - They have in **common** a central alpha carbon, an **amino group** (NH_3^+), a **carboxyl group** (COO^-), and a variable group called the ***R group***
  - Amino acids differ from one another based on a **variable R group**.
- R group determine the **chemical relationships** in which each amino acid can participate
  - e. g. **hydrophobic** or **hydrophilic** R groups



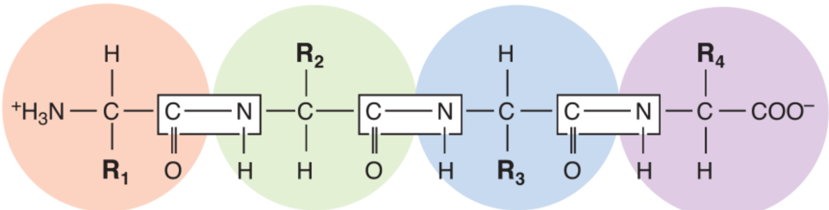


The peptide bond



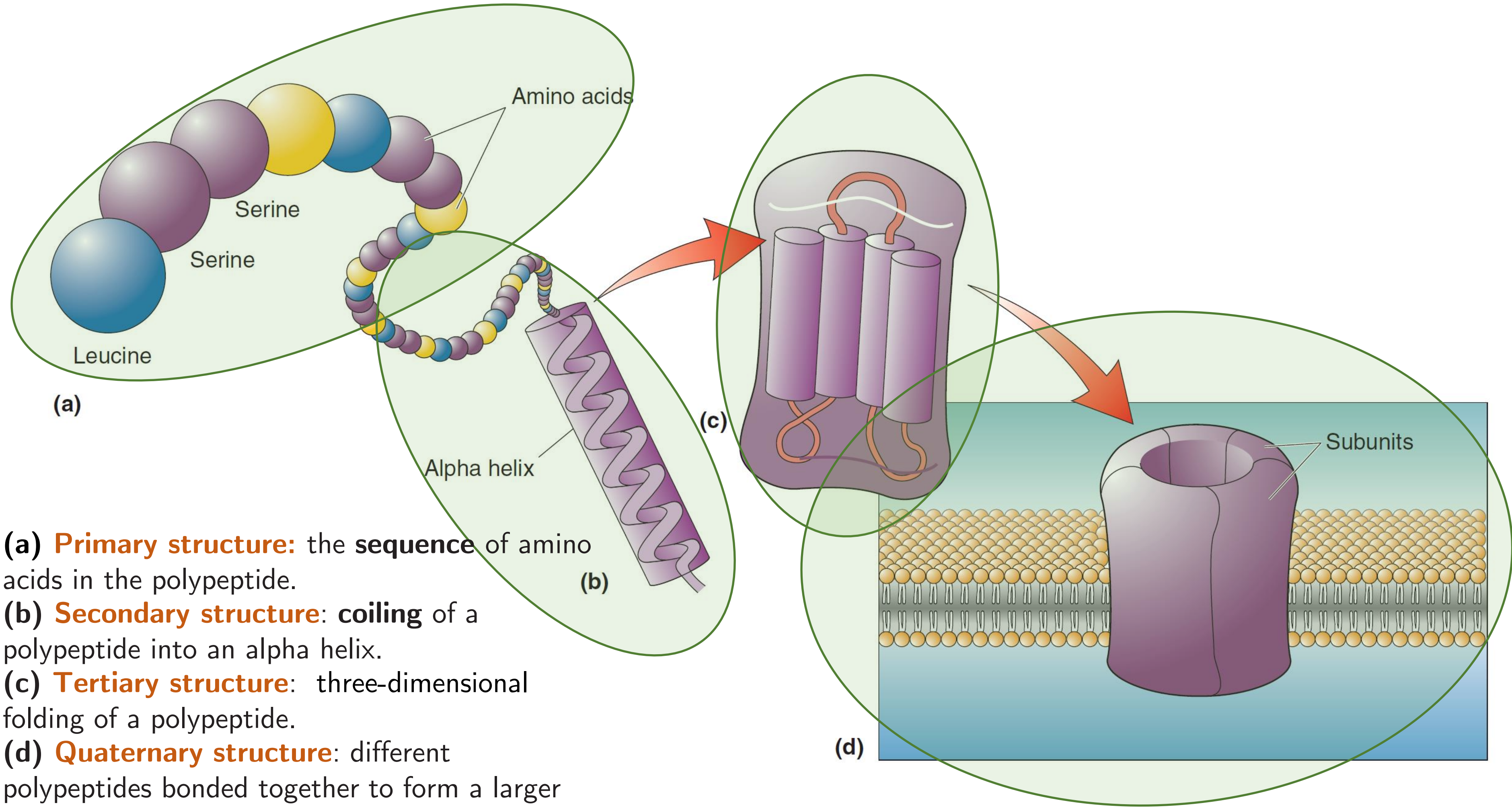
Peptide bonds attach amino acids together. The bond forms between the **carboxyl** group of one amino acid and the **amino group** of another.

The polypeptide



A polypeptide is a **single chain of amino acids**

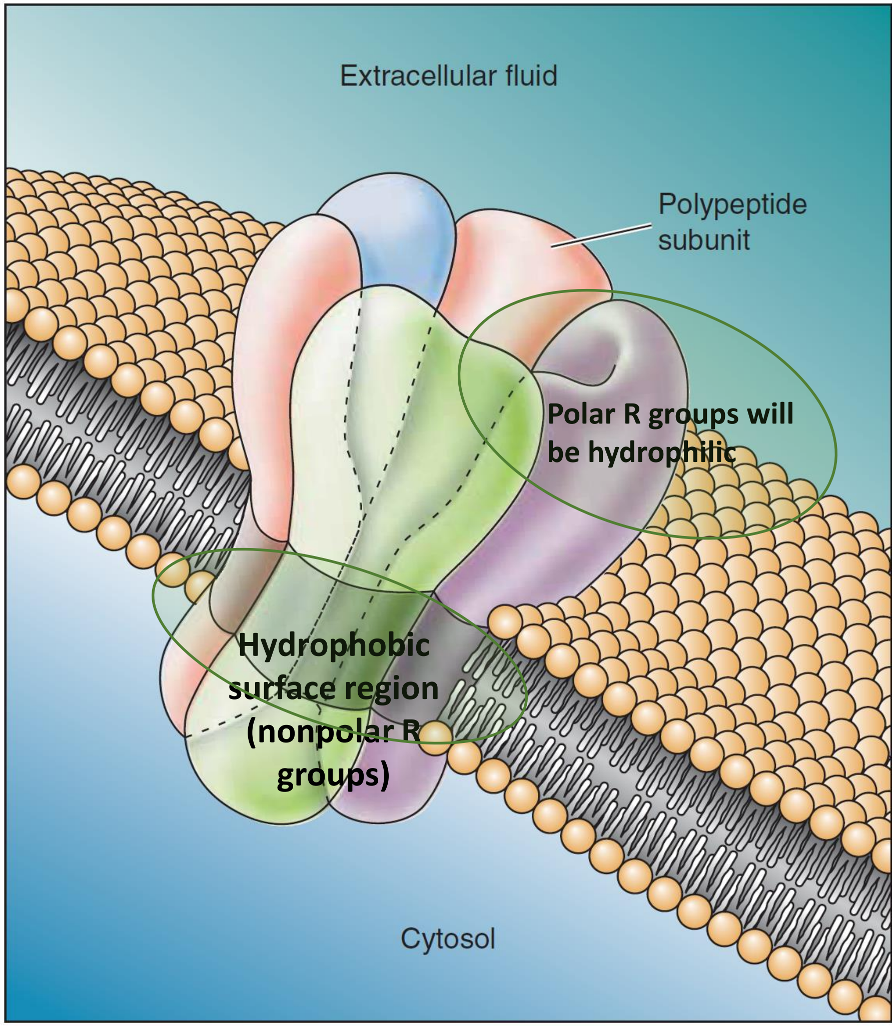
Four levels of protein structure



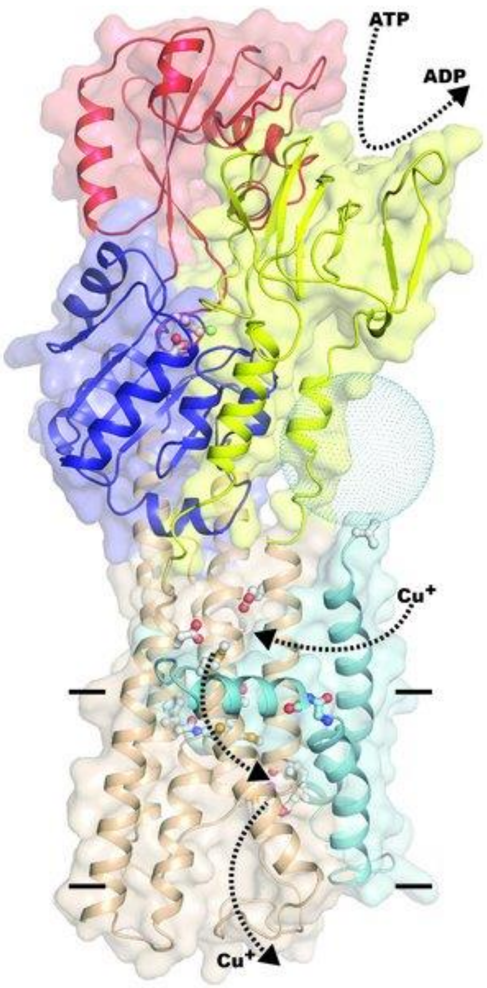
(a) **Primary structure:** the **sequence** of amino acids in the polypeptide.
(b) **Secondary structure**: **coiling** of a polypeptide into an alpha helix.
(c) **Tertiary structure**: three-dimensional folding of a polypeptide.
(d) **Quaternary structure**: different polypeptides bonded together to form a larger protein

Membrane ion channel

- **Channel proteins**:
  - Suspended proteins in a phospholipid bilayer, with its **hydrophobic** portion inside the membrane and its **hydrophilic** ends exposed to the watery environments either side
- **Ion channels:**
  - **Membrane-spanning proteins** that assemble to form a **pore**.
  - Ion channels properties specified by the **diameter of the pore** and the **nature of the R groups lining it**
- **Ion selectivity**:
  - **Selectively permeable** to one ion
- **Gating**:
  - **Opened and closed** by changes in the local **microenvironment** of the membrane



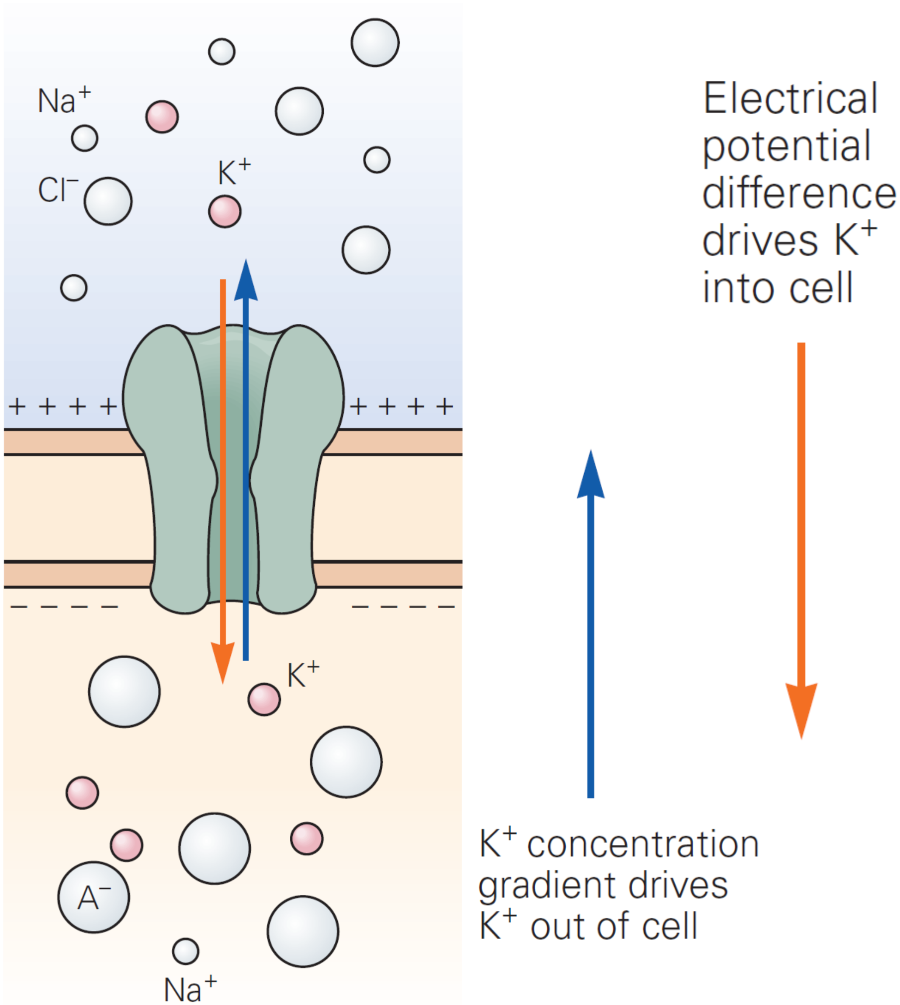
Ion pumps



The **enzymes** that use the energy (released by the breakdown of ATP) to transport certain ions across the **membrane**.

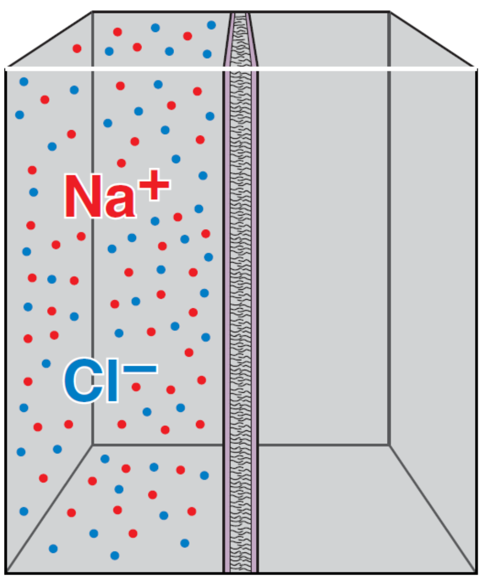
The movement of ions

- Ionic movements through channels are influenced by two factors:
  - **Diffusion**
  - **Electricity**



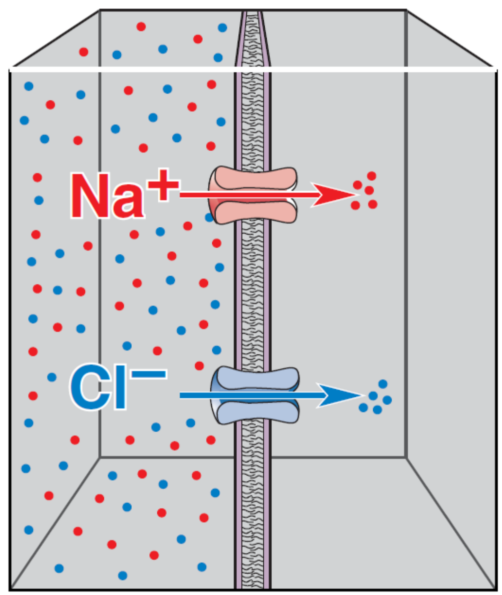
Diffusion

NaCl has been dissolved on the left side of an **impermeable**

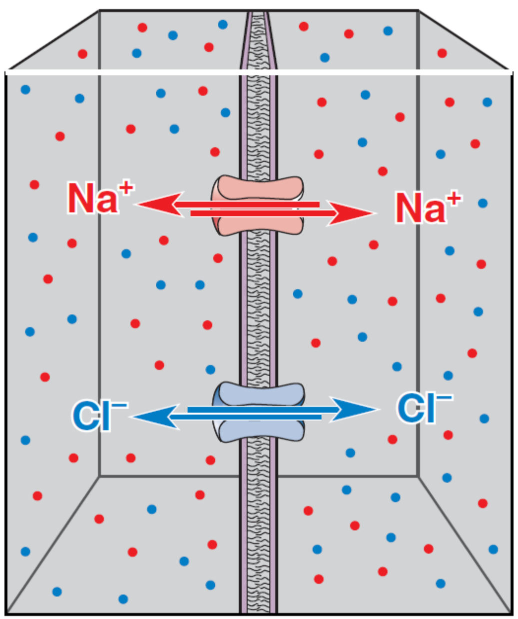


Channels are inserted:

- A **large concentration gradient** across the membrane,
- A **net** movement of ions from **high concentration to the region of low concentration**



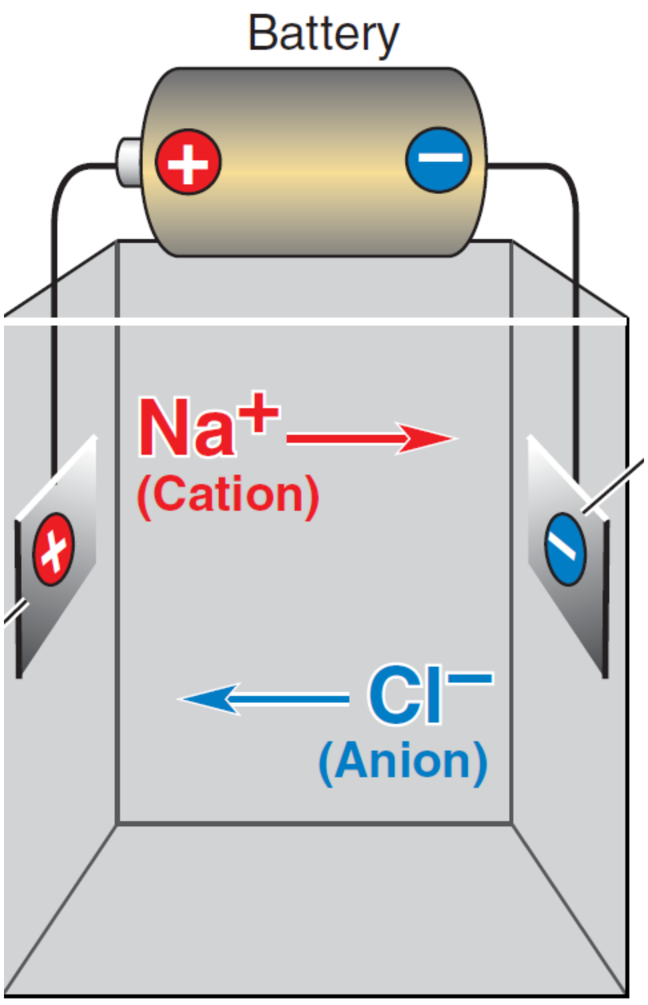
Net movement ceases when they are **equally distributed** on both sides



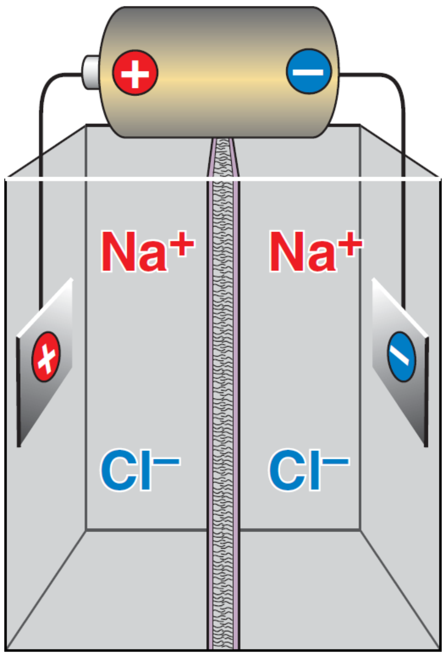
Difference in concentration is called a **concentration gradient**.

Electricity

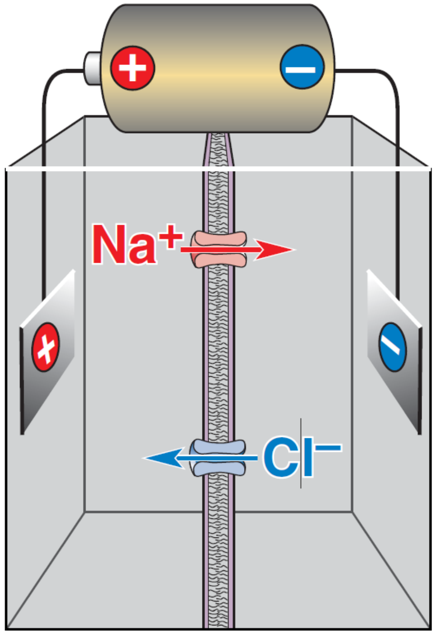
- **Ions** are electrically charged **particles**
- Opposite charges **attract** and like charges **repel**
- Two **main factors** for current passing:
  - **Electrical potential**
    - **Voltage**: difference in charge between the anode and the cathode
  - **Electrical conductance**
    - **Siemens**: **depends** on the number of particles available to carry electrical charge



Electrical current flow across a membrane



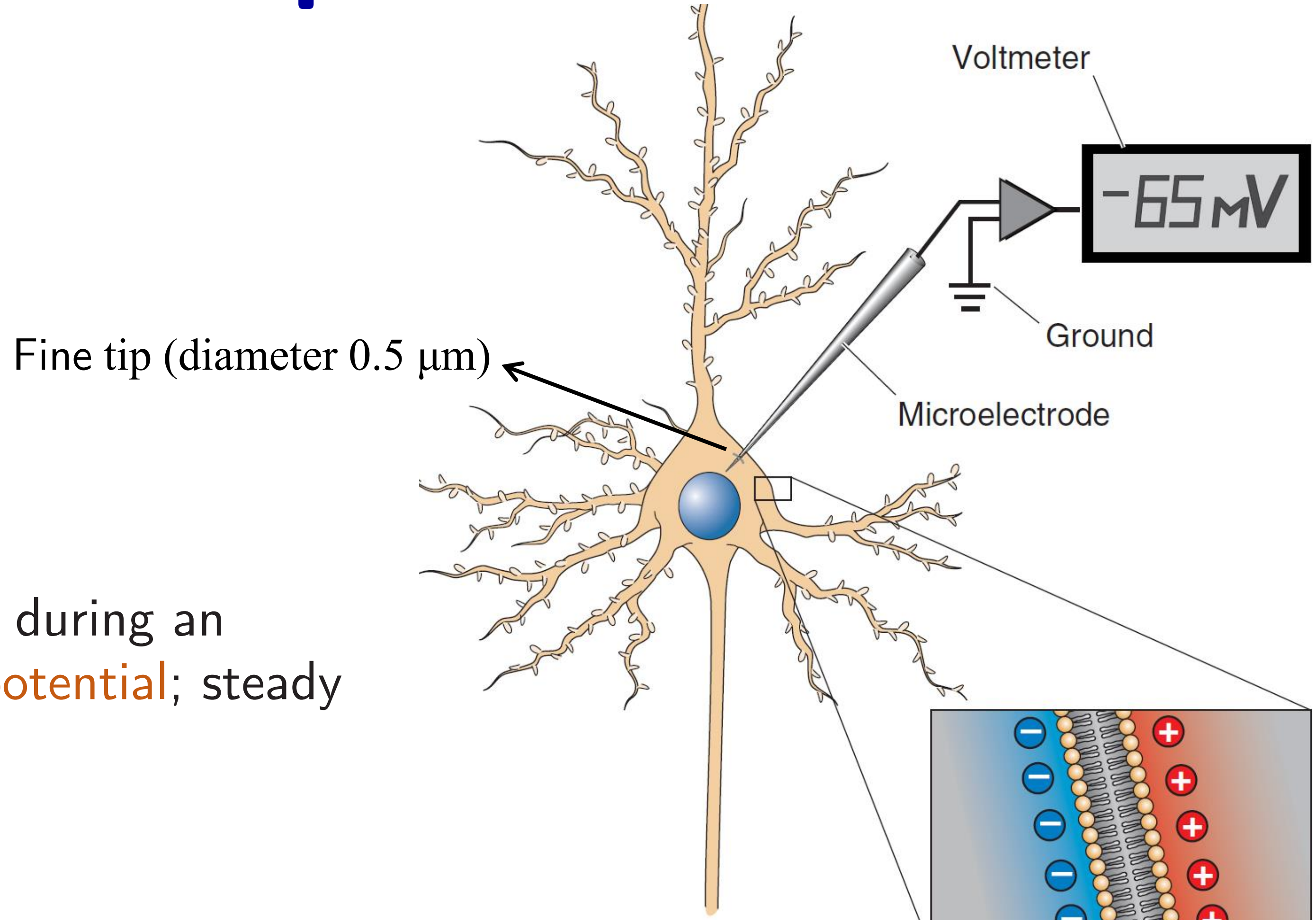
The **electrical potential difference** across the membrane can be thought of as a **battery** whose charge is maintained by the work of the **ion pumps**.



No electrical current because there are **no channels** so the **conductance** of the membrane is zero (g=0)

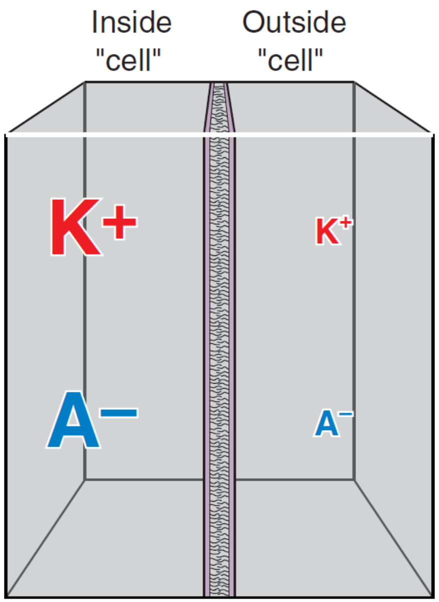
Inserting channels in the membrane allows ions to cross and **electrical current flows**

Measuring the resting membrane potential

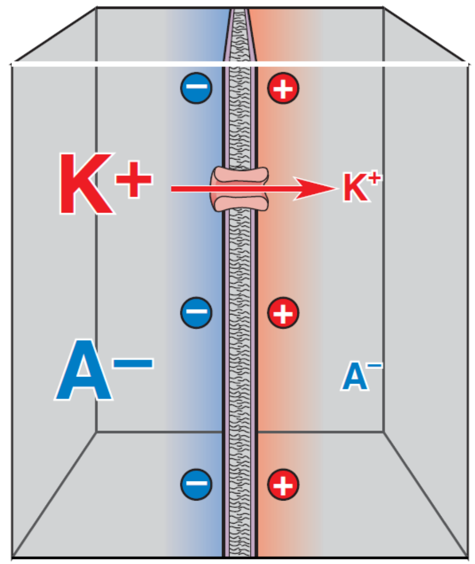


It is not during an action potential; steady state

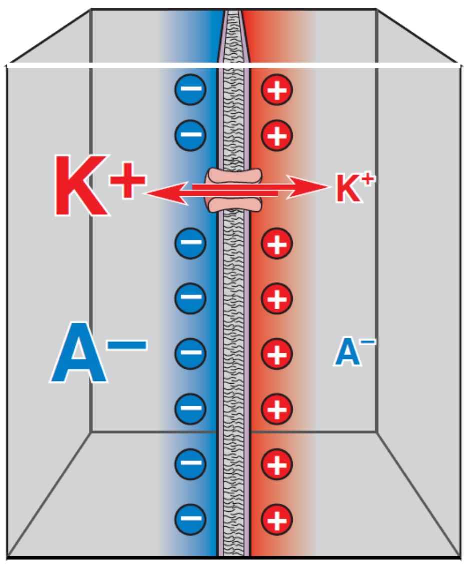
Equilibrium Potentials



- An **impermeable membrane** separates
- **Relative concentrations** of **potassium** (K) and an impermeable **anion** (A) are represented by the **sizes**



- **Inserting a channel** that is **selectively permeable** to K
- It **initially** results in a net movement of K down their **concentration gradient**



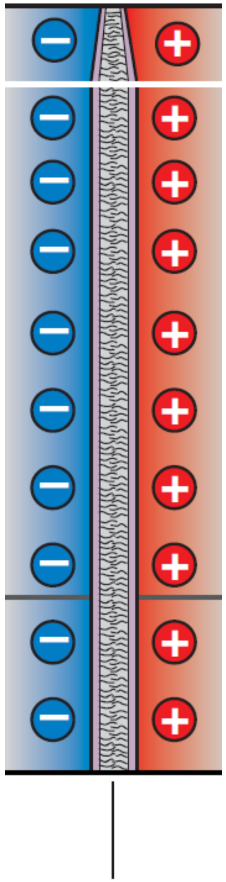
- **Net accumulation** of positive charge on the outside and **negative charge** on the inside **retards** the movement of positively charged
- There is no **net movement** of ions across the membrane (**Equilibrium**)
- The **equilibrium potential**: **-80 mV**

Equilibrium potentials properties

- Large changes in membrane potential are caused by **minuscule changes in ionic concentrations**. (for k^+ 0.00001 mM)
- The net difference in electrical charge **occurs at the inside and outside surfaces** of the membrane.
  - Membrane is thin 5 nm and it is store electrical charge, a property called **capacitance**
- **Ionic driving force**:
  - Ions are driven across the membrane at a rate proportional to the **difference** between the **membrane potential and the equilibrium potential**

$$(V_m - E_{ion})$$

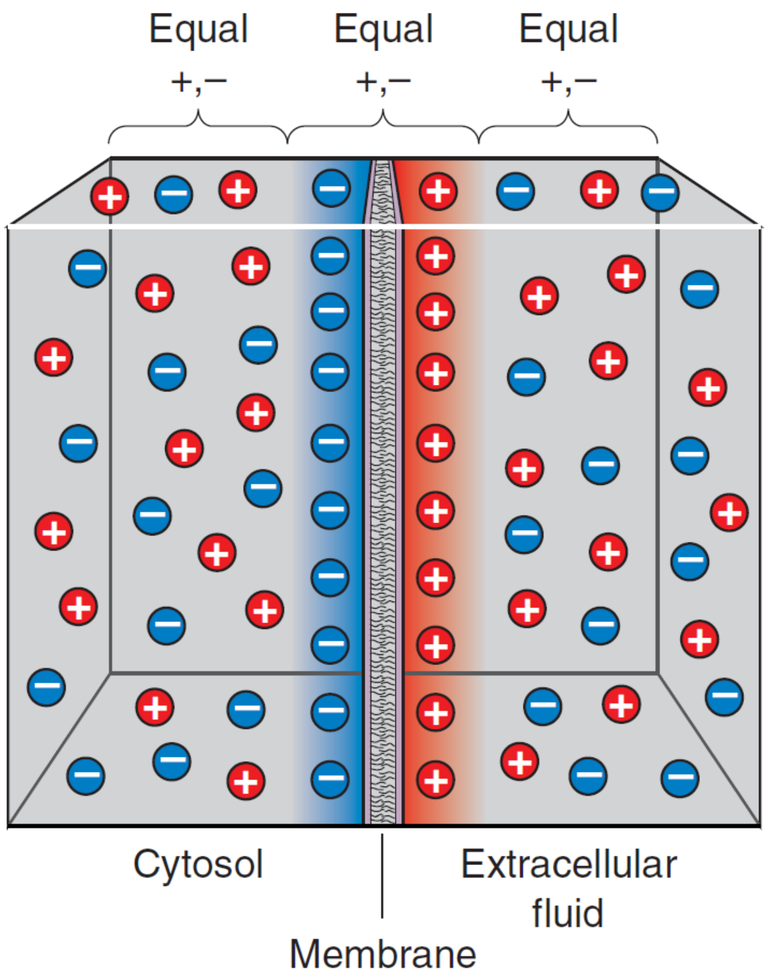
- **If the concentration difference** across the membrane is **known** for an ion, an equilibrium potential can be calculated for that ion.



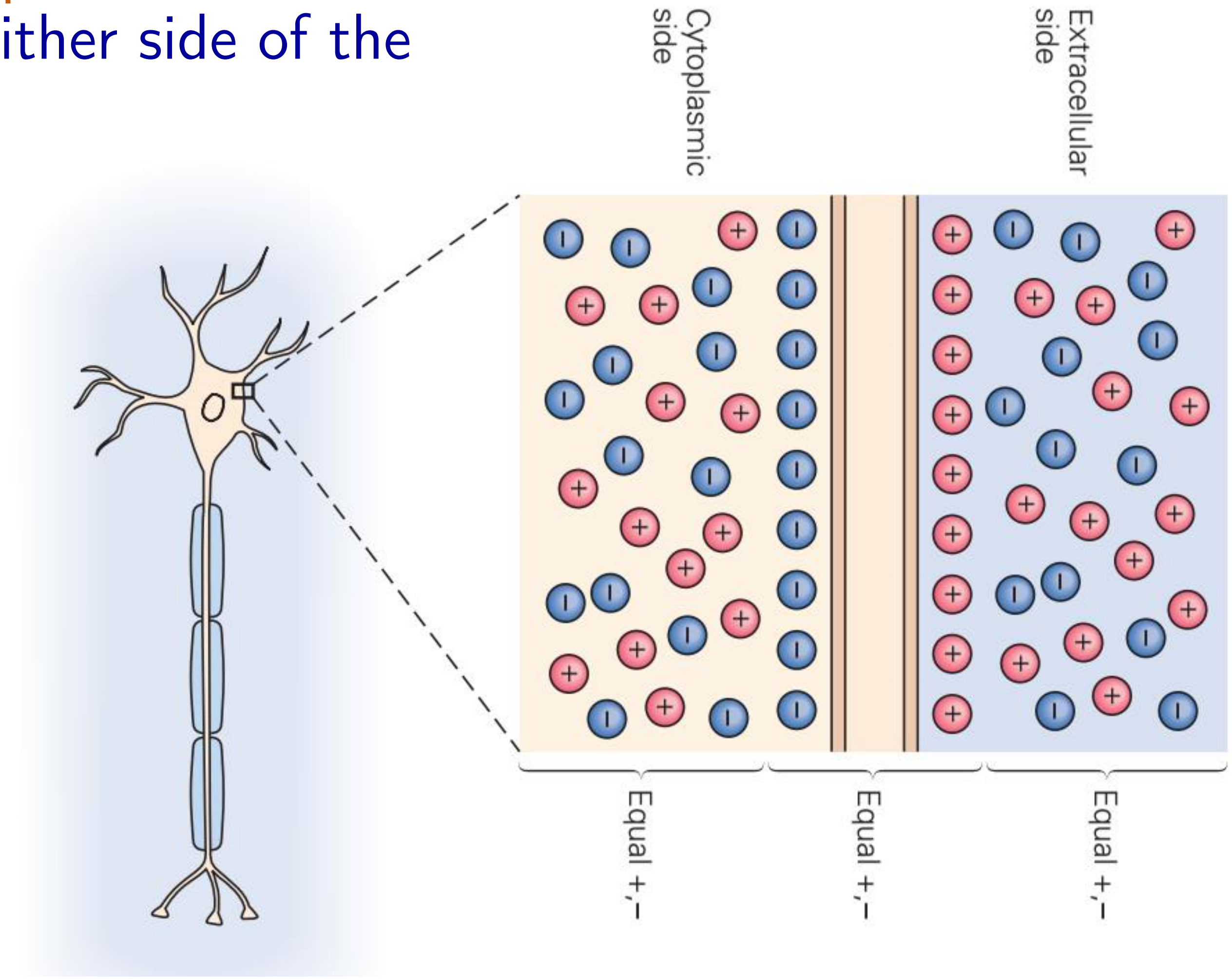
The distribution of electrical charge across the membrane.

- **Membrane** stores electrical charge, a property called ***capacitance***

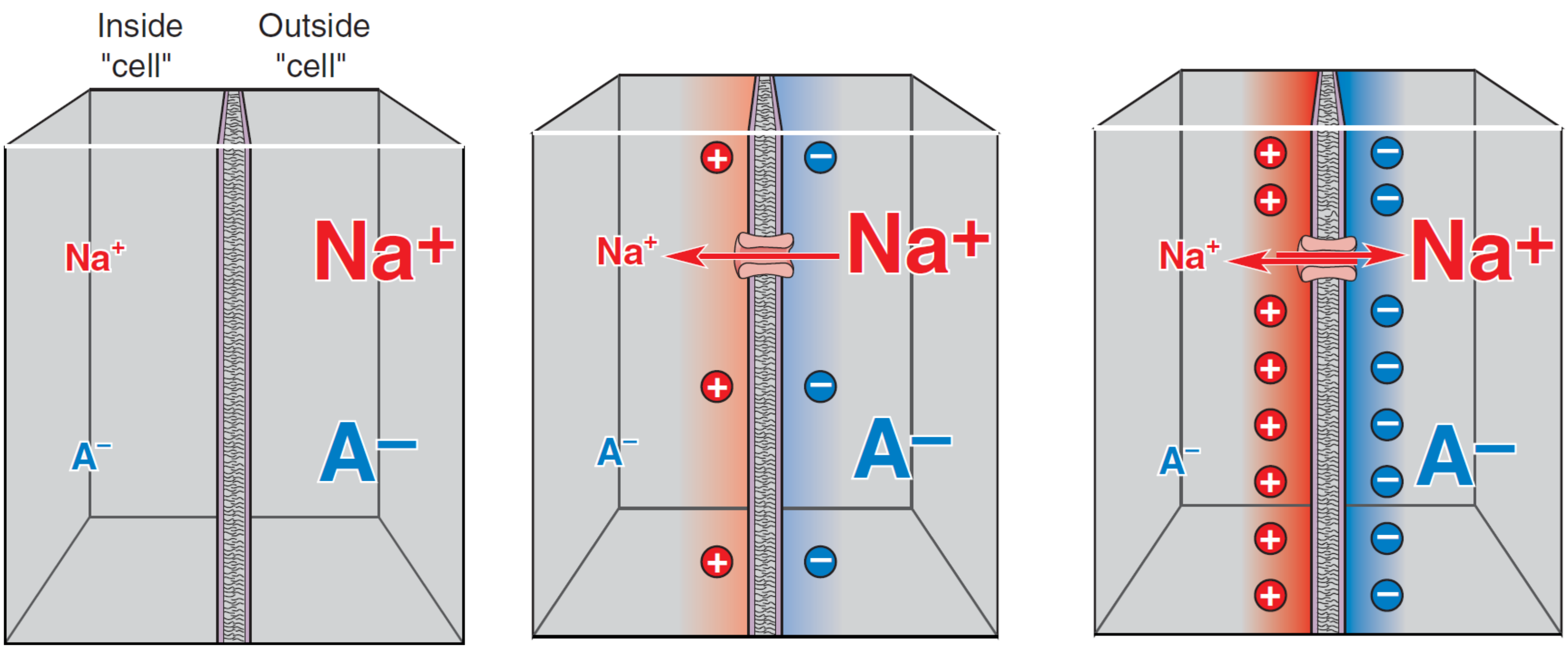
- The **bulk of the cytosol** and **extracellular** fluid is electrically **neutral**



The cell membrane potential results from the separation of net positive and net negative charges on either side of the membrane



Another example of establishing equilibrium in a selectively permeable membrane.



In this case, the inside of the cell is **positively** charged with respect to the outside

Equilibrium potential for each ion; **the Nernst Equation**

$$E_{ion} = 2.303 \frac{RT}{zF} \log \frac{[ion]_o}{[ion]_i}$$

where

E_{ion} = ionic equilibrium potential
R = gas constant
T = absolute temperature
z = charge of the ion
F = Faraday's constant
$\log$ = base 10 logarithm
$[ion]_o$ = ionic concentration outside the cell
$[ion]_i$ = ionic concentration inside the cell

$$E_K = 61.54 \text{ mV} \log \frac{[K^+]_o}{[K^+]_i}$$

$$E_{Na} = 61.54 \text{ mV} \log \frac{[Na^+]_o}{[Na^+]_i}$$

$$E_{Cl} = -61.54 \text{ mV} \log \frac{[Cl^-]_o}{[Cl^-]_i}$$

$$E_{Ca} = 30.77 \text{ mV} \log \frac{[Ca^{2+}]_o}{[Ca^{2+}]_i}$$

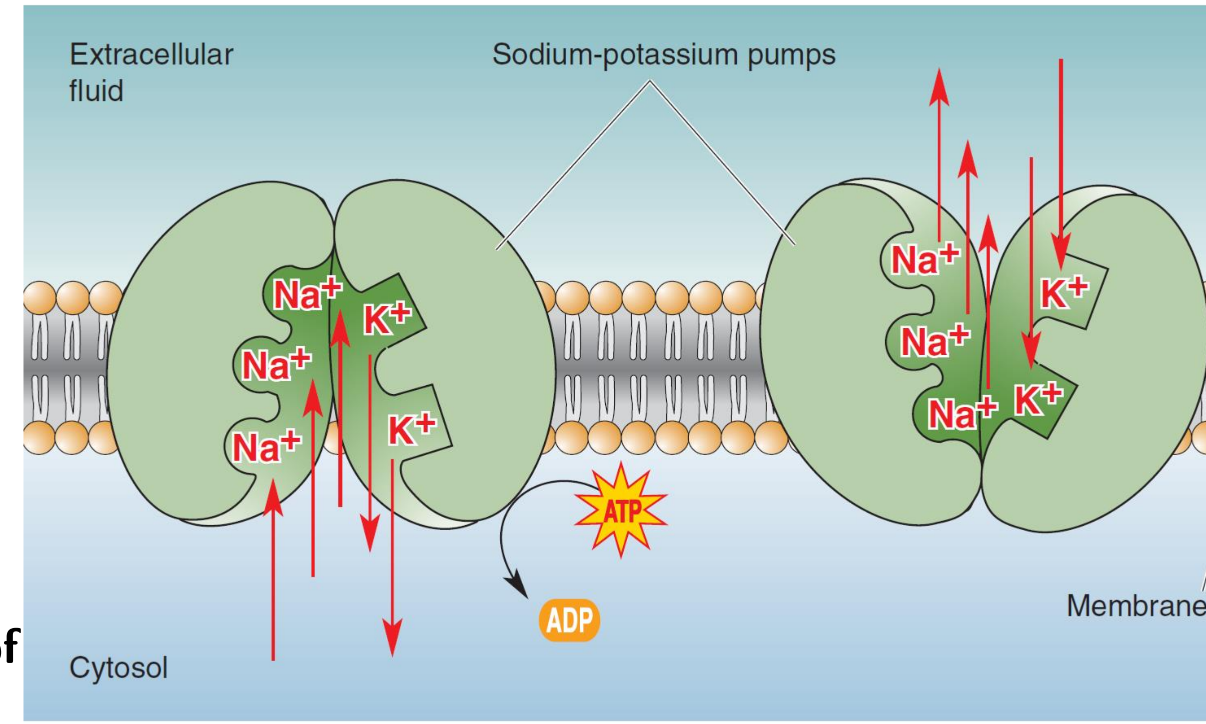
The Distribution of Ions Across the Membrane

- Neuronal membrane potential depends on the ionic **concentrations** on **either side** of the membrane
- K+ is more concentrated on the inside, and Na and Ca^2 are more concentrated on the outside.
- **Ionic concentration gradients** are established by the actions of **ion pumps** in the neuronal membrane

Ion	Concentration outside (in mM)	Concentration inside (in mM)	Ratio Out : In	E_{ion} (at 37°C)
K^+	5	100	1 : 20	−80 mV
Na^+	150	15	10 : 1	62 mV
Ca^{2+}	2	0.0002	10,000 : 1	123 mV
Cl^-	150	13	11.5 : 1	−65 mV

The sodium-potassium pump

- It is **an enzyme** that breaks down ATP in the presence of internal Na
- It works against the concentration **gradients** at the expense of energy
- Without ion pumps, the **resting membrane potential would not exist**
- Sodium-potassium pump expends as much as **70% of the** total amount of ATP utilized by the brain



Goldman equation; relative ion permeabilities of the membrane at rest

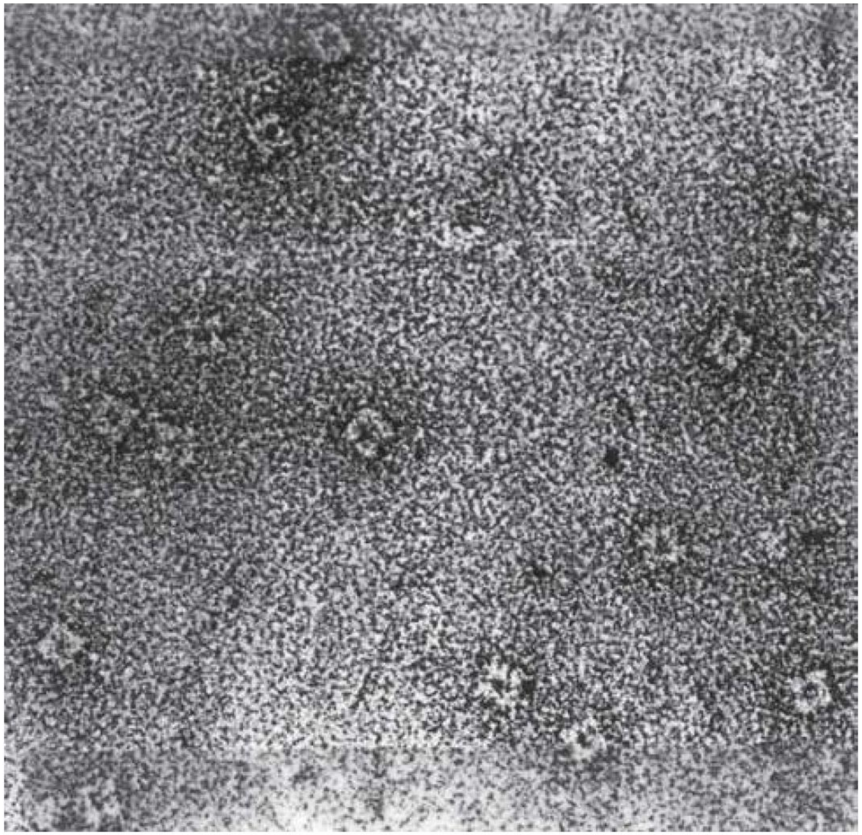
- **Resting membrane potential** can be calculated using the **Goldman equation**
- It take into consideration the **relative permeability of the membrane** to different **ions**.
- Permeability to K is **fortyfold greater than it is to Na**
  - Resting membrane is similar to E_k

Relative permeability

$$V_m = 61.54 \text{ mV} \log \frac{P_K [K^+]_o + P_{Na} [Na^+]_o}{P_K [K^+]_i + P_{Na} [Na^+]_i}$$

$$\begin{aligned} V_m &= 61.54 \text{ mV} \log \frac{40\,(5) + 1\,(150)}{40\,(100) + 1\,(15)} \\ &= 61.54 \text{ mV} \log \frac{350}{4015} \\ &= -65 \text{ mV} \end{aligned}$$

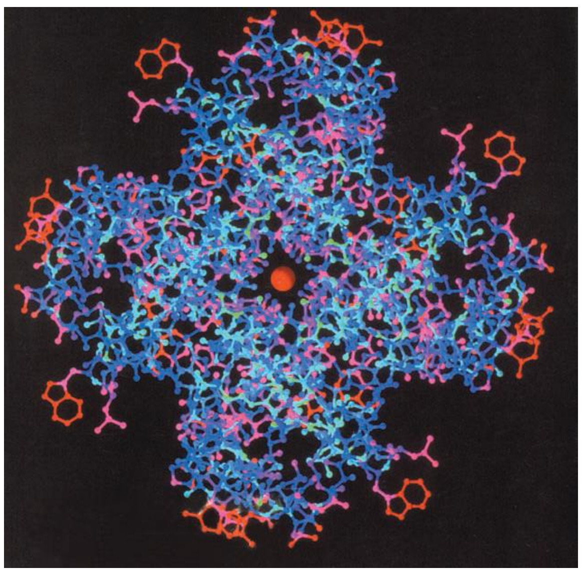
The wide world of potassium channels



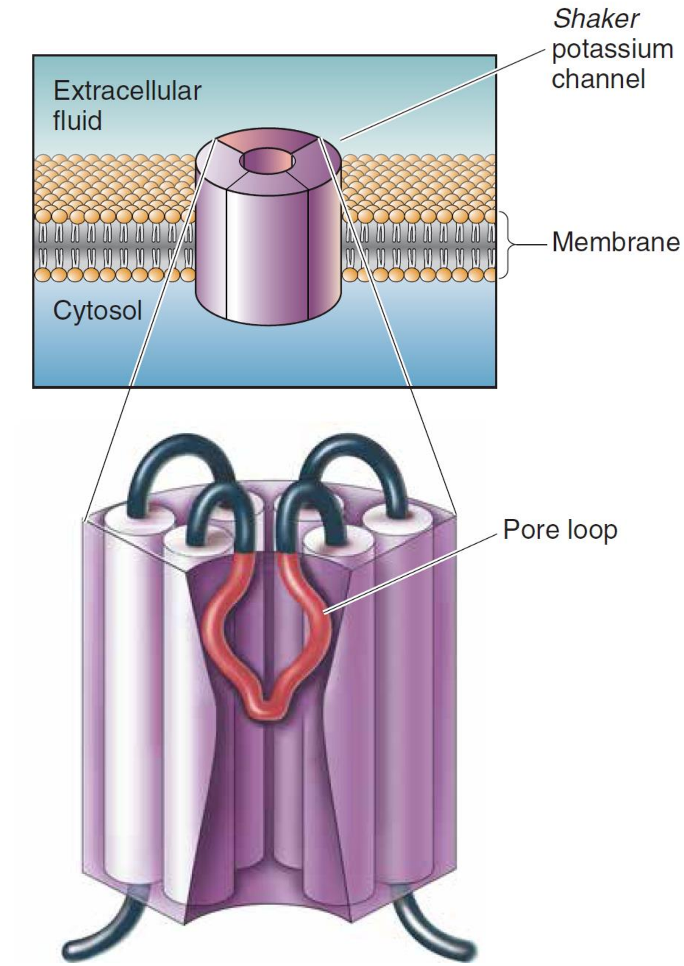
Potassium channels in the cell membrane of the fruit *fly Drosophila*

The *Shaker potassium* channel has four subunits arranged like staves of a barrel to form a pore

Critical part of the filter that makes the channel selectively permeable to K ions



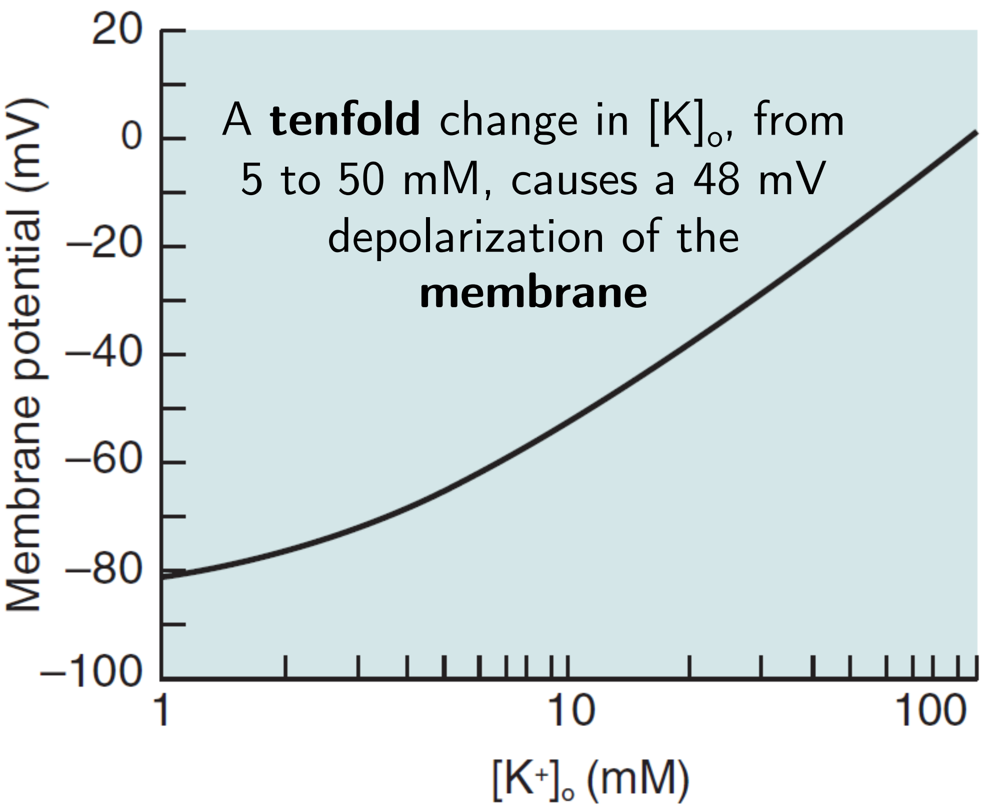
A view of the potassium channel pore



- Chris Miller and his student Roderick MacKinnon observed that **scorpion** toxin **blocks** potasssium channels

- They found the **physical basis** of ion selectivity and earned the 2003 **Nobel Prize in Chemistry**

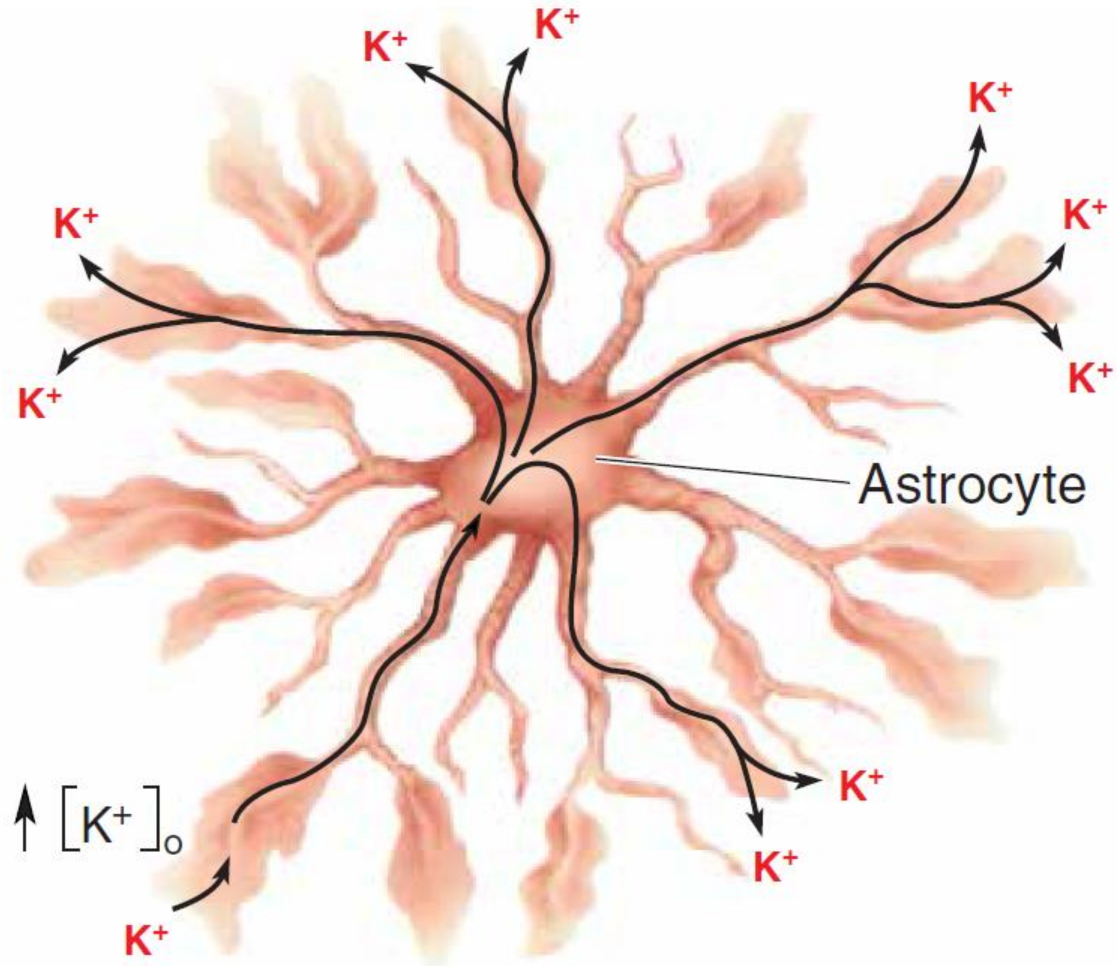
The importance of regulating the external potassium concentration



- **Evolution** of mechanisms that tightly regulate extracellular potassium concentrations:
    - **Blood brain barrier**
    - Glia, particularly astrocytes
- Elevations of K have serious consequences on body physiology as well (**Death by Lethal Injection)**

Potassium spatial buffering by astrocytes

- The extensive **network of astrocytic processes** helps **dissipate** the K over a large area
- Astrocytes **have membrane potassium pumps** that concentrate K in their cytosol, and they also have **potassium channels**

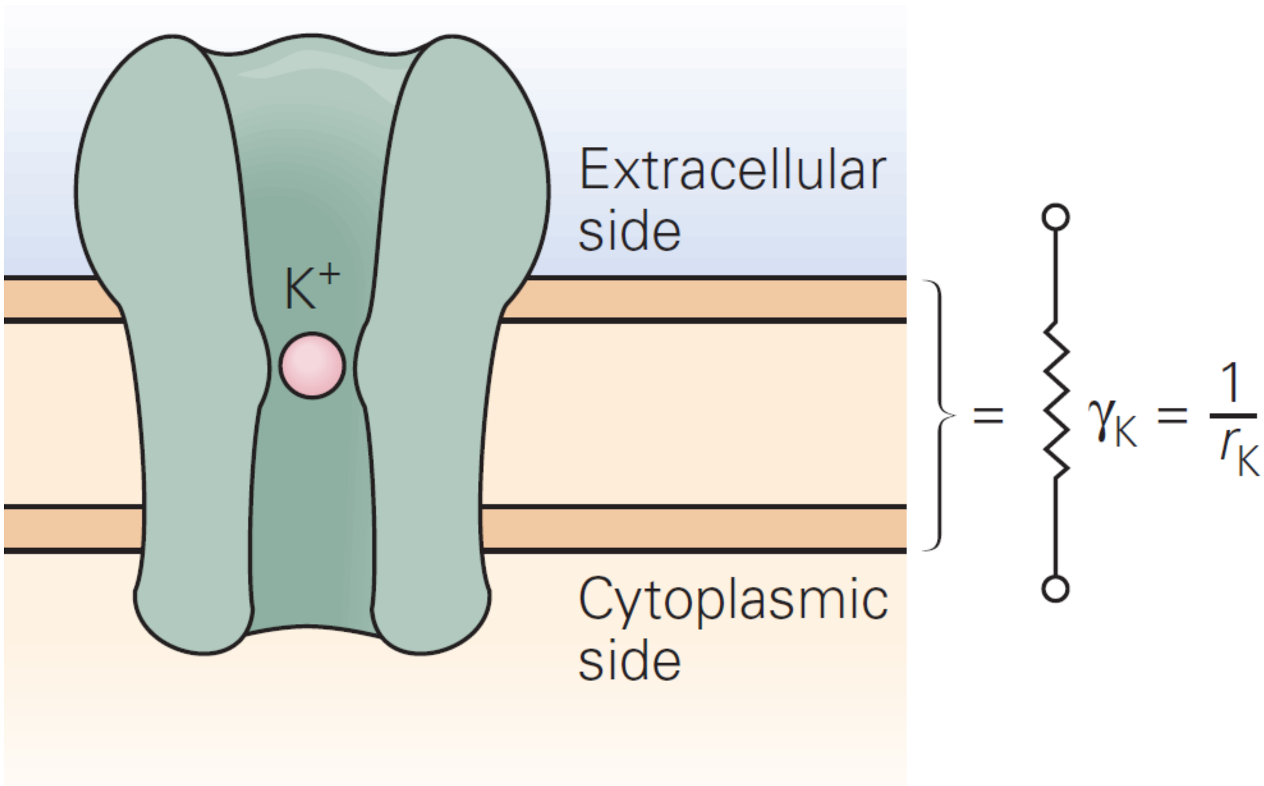


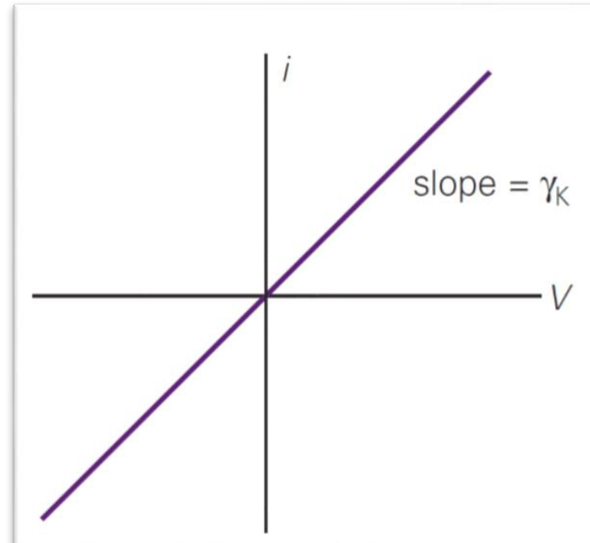
The functional properties of the neuron can be represented as an electrical equivalent circuit

Lipid bilayer

- Electrical *capacitance* $V = Q/C,$
- Q is the net excess positive or negative **charge** and C is the **capacitance**.
- Typical value of **membrane capacitance:**~ **1 μF per cm^2**
- Cell diameter = 50 μm, and a resting potential of −60 mV needs 29×10^6 ions (1/200,000 of all ions)

Single K^+ channel in the absence of a concentration gradient

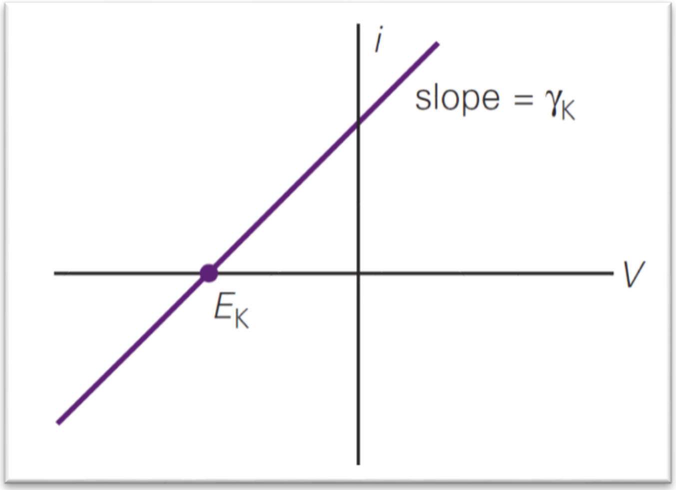




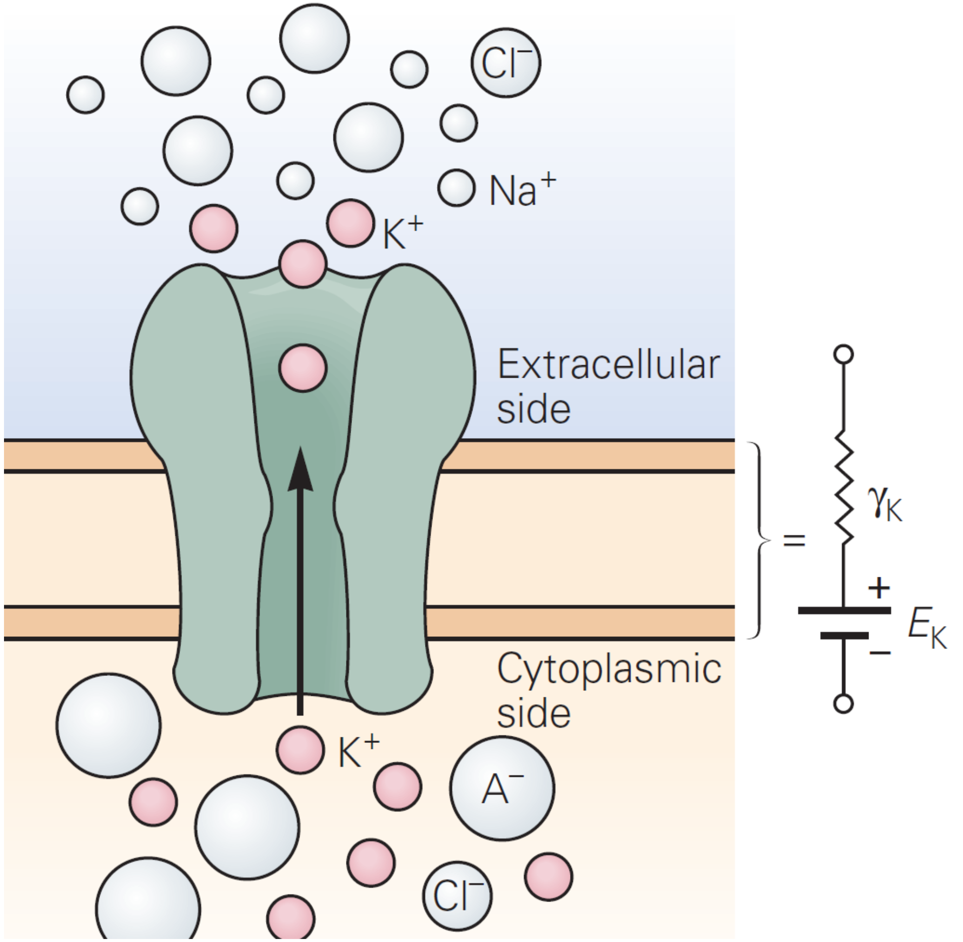
The **relationship of current** (i) and voltage (V) for a single **K_+ channel** in the absence of a concentration gradient

Chemical and electrical forces contribute to current through an ion channel

A concentration gradient for K^+ gives rise to an **electromotive** force, which has a value equal to E_K, the **Nernst potential for K^+**



The **potential** at which the **current is zero** is equal to **Nernst potential**

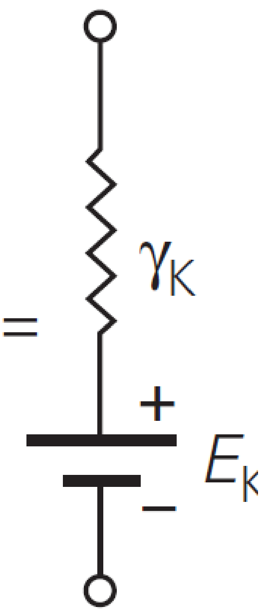


The sum of the currents caused by the electrical and chemical driving forces

Ionic current through a membrane is determined not only by the **voltage across the membrane** but also by the ionic **concentration gradients**

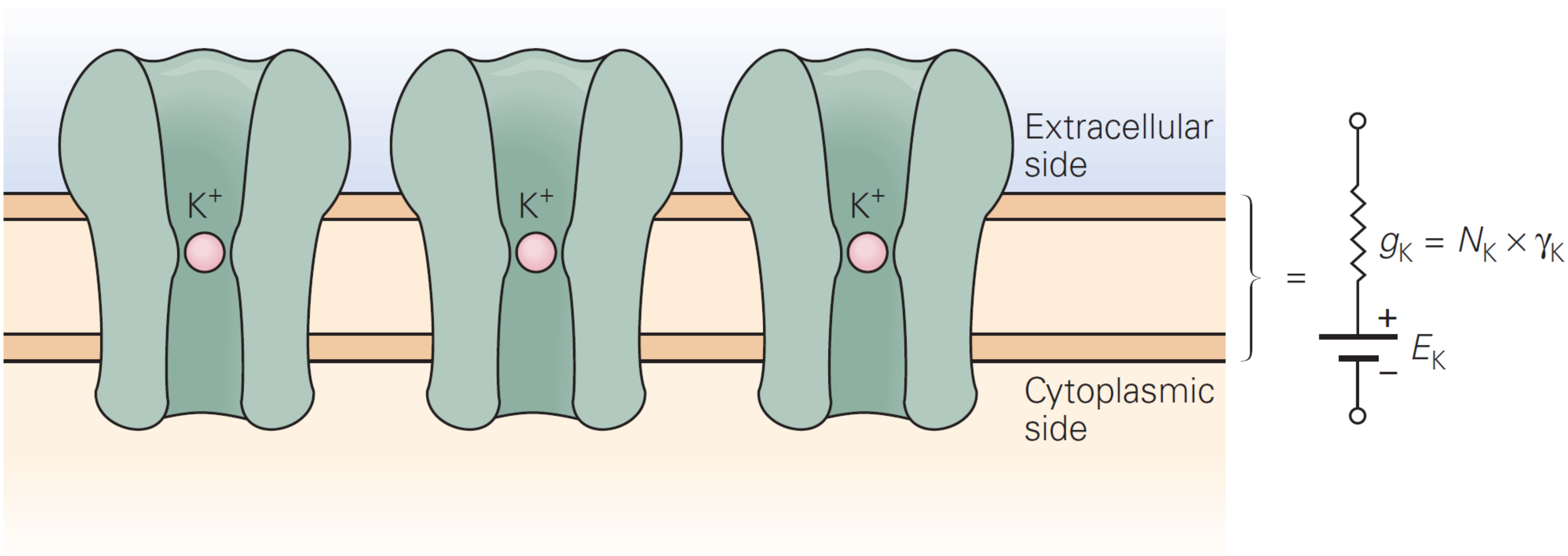
$$i_K = (\gamma_K \times V_m) - (\gamma_K \times E_K) = \gamma_K \times (V_m - E_K).$$

Electrochemical driving force.

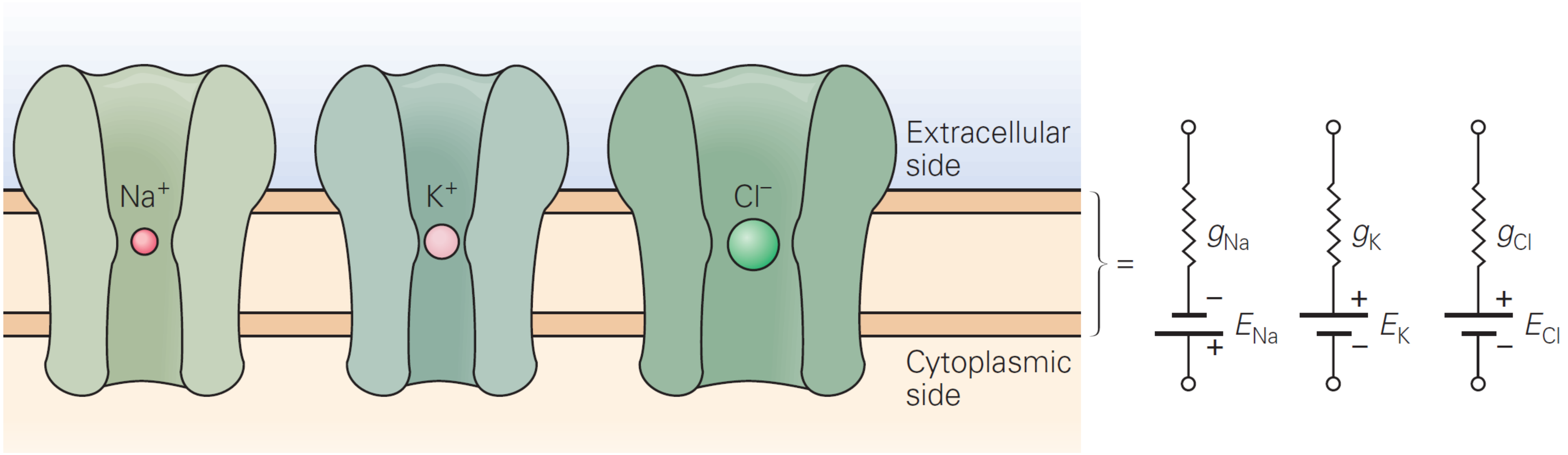
= 

All the resting K^+

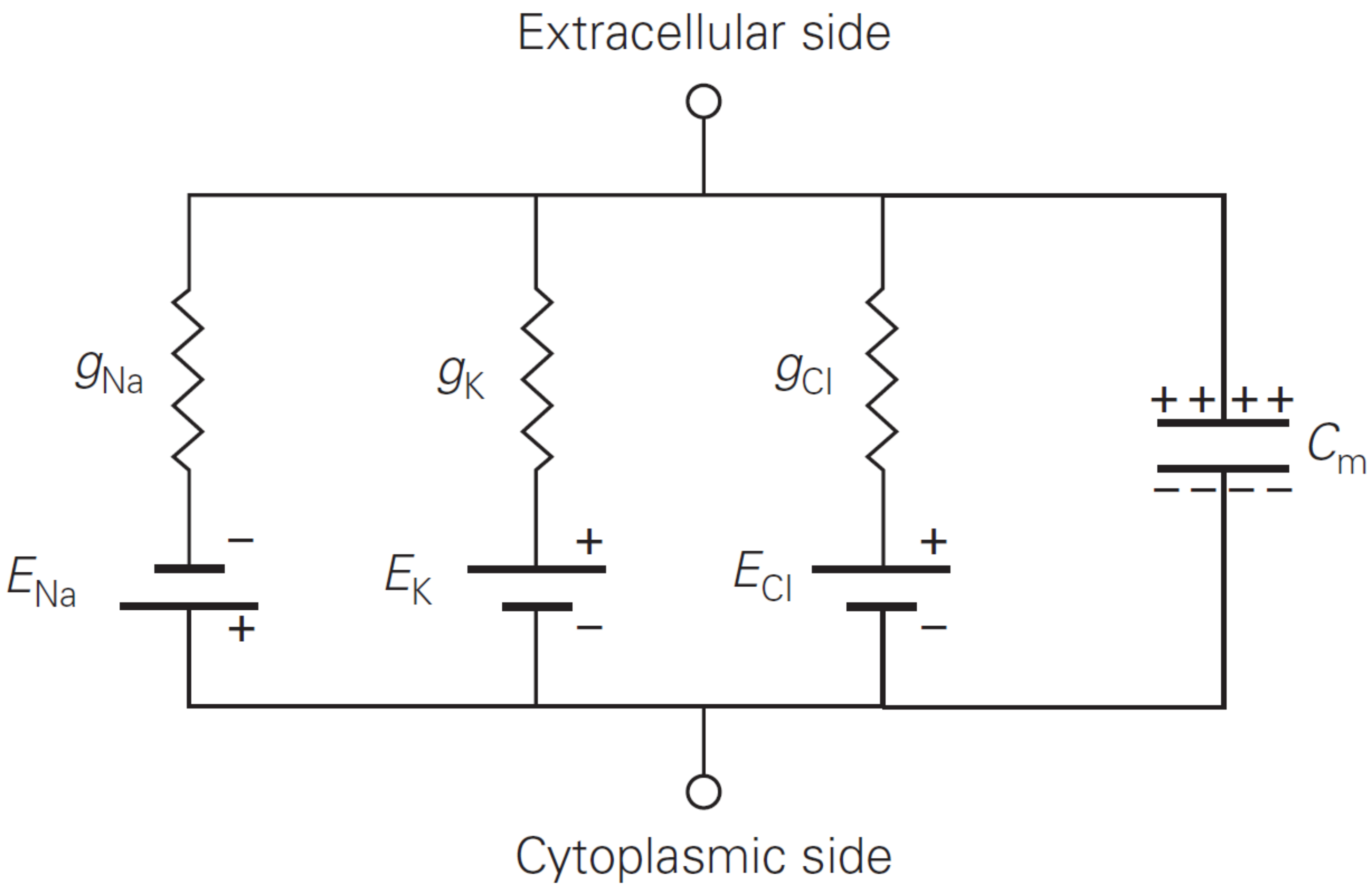
All the resting K+ channels in a nerve cell membrane can **be lumped into** a single **equivalent circuit** comprised of a battery in series with a conductor.



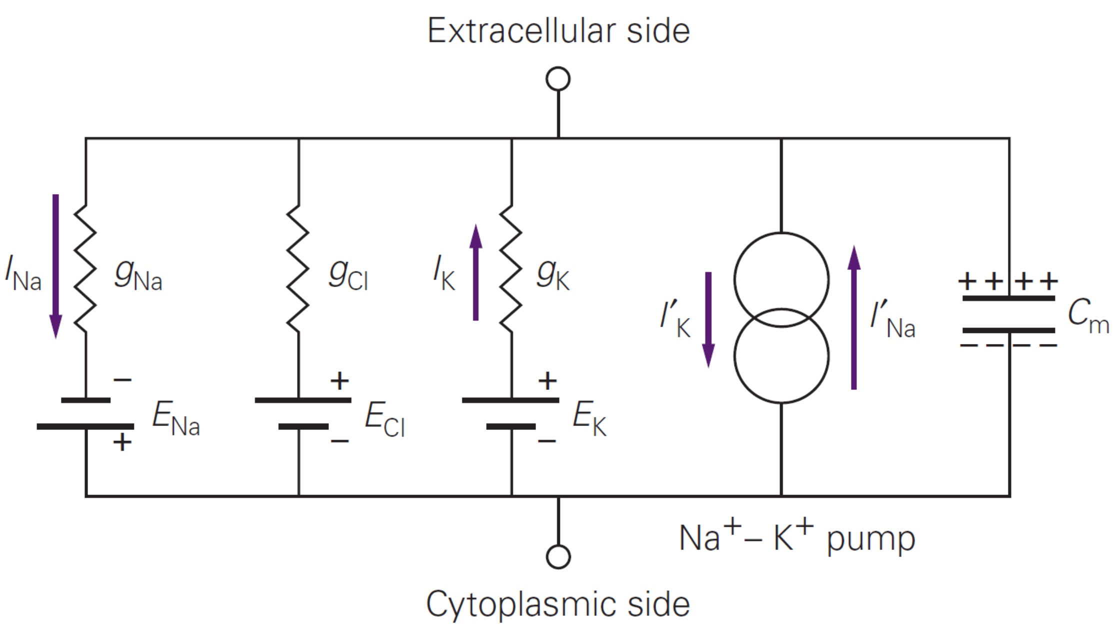
The populations of Na+, K+, and Cl− ion channels



An equivalent circuit of the neuronal membrane



An equivalent circuit of passive and active current in a neuron



Transports **three Na+** ions out for every two K+ ions it transports into the cell.

The active Na+ flux is 50% greater than the active K+ flux

Using the equivalent circuit model to calculate resting membrane potential

$$V_m = E_{Na} + I_{Na}/g_{Na}.$$

$$V_m = E_K + I_K/g_K.$$

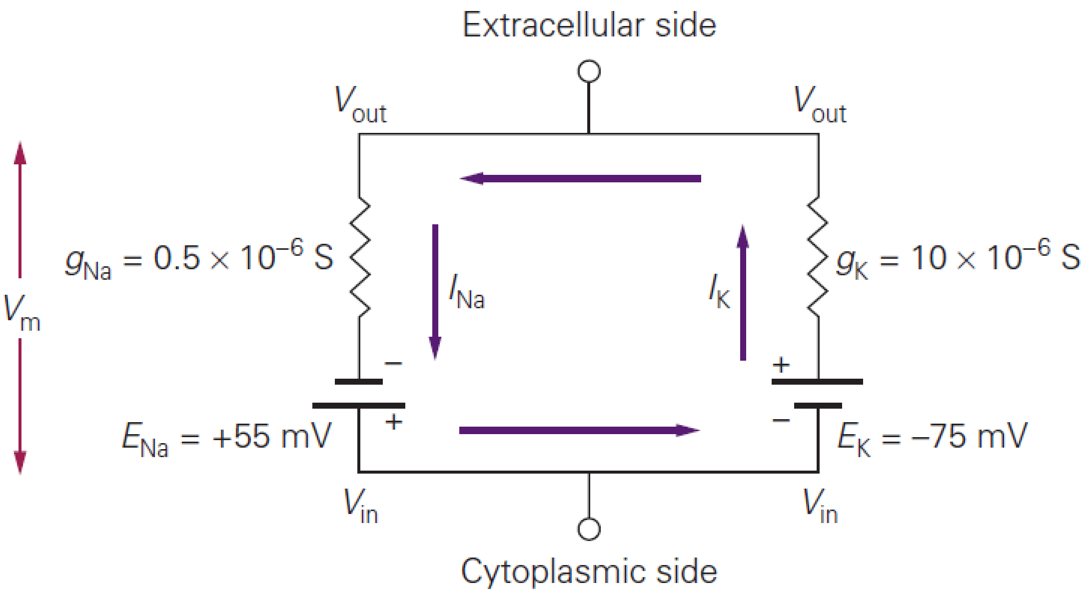
$$I_{Na} = g_{Na} \times (V_m - E_{Na})$$

$$I_K = g_K \times (V_m - E_K).$$

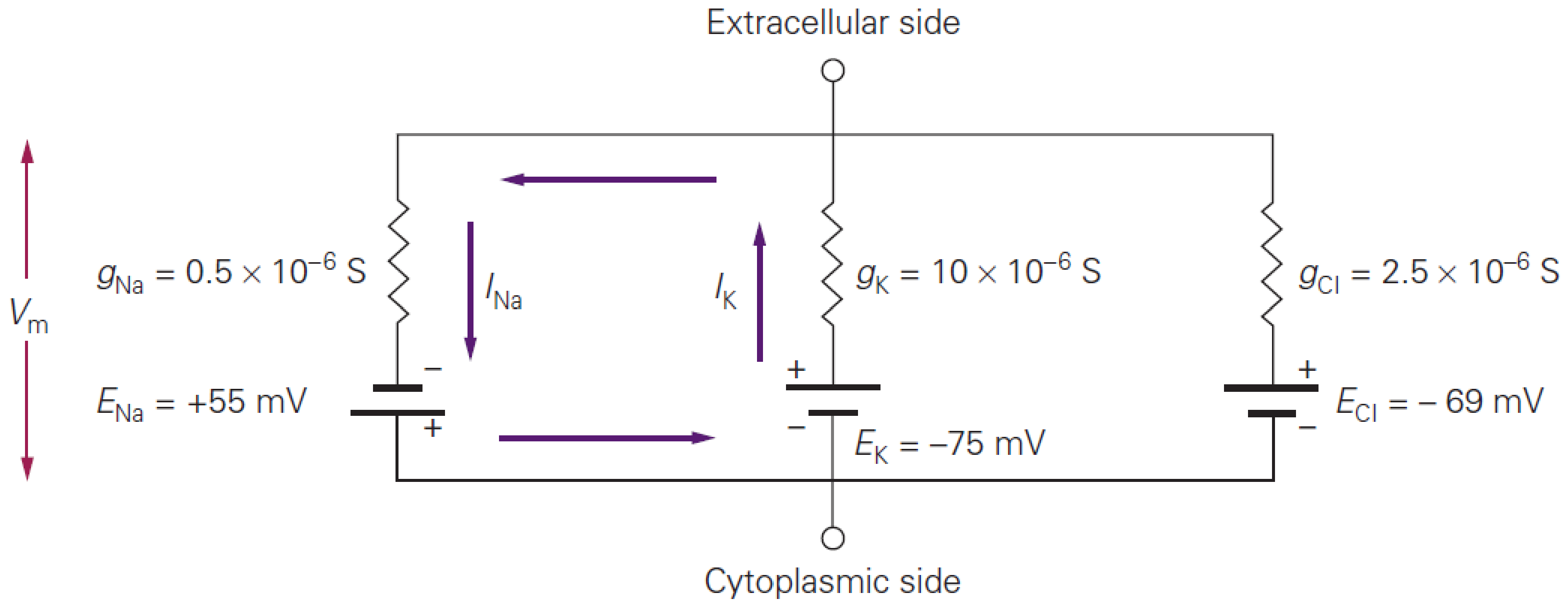
$$-I_{Na} = I_K$$

$$V_m \times (g_{Na} + g_K) = (E_{Na} \times g_{Na}) + (E_K \times g_K).$$

$$V_m = \frac{(E_{Na} \times g_{Na}) + (E_K \times g_K)}{g_{Na} + g_K}$$



Considering Cl



$$V_m = \frac{(E_{Na} \times g_{Na}) + (E_K \times g_K) + (E_{Cl} \times g_{Cl})}{g_{Na} + g_K + g_{Cl}}.$$

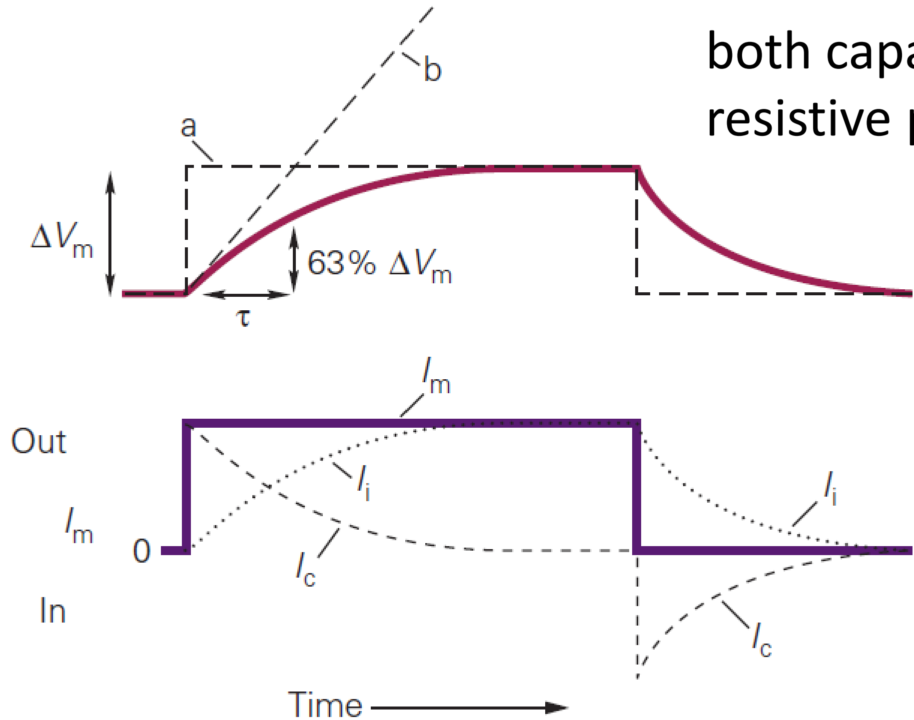
The rate of change in the membrane potential is slowed by the membrane capacitance.

$$\Delta V = \Delta Q/C.$$

$$\Delta V = I_c \cdot \Delta t/C.$$

$$\Delta V_m(t) = I_m R_m (1 - e^{-t/\tau}),$$

tau is important for temporal summation; *membrane time constant;* range from 20 to 50 ms



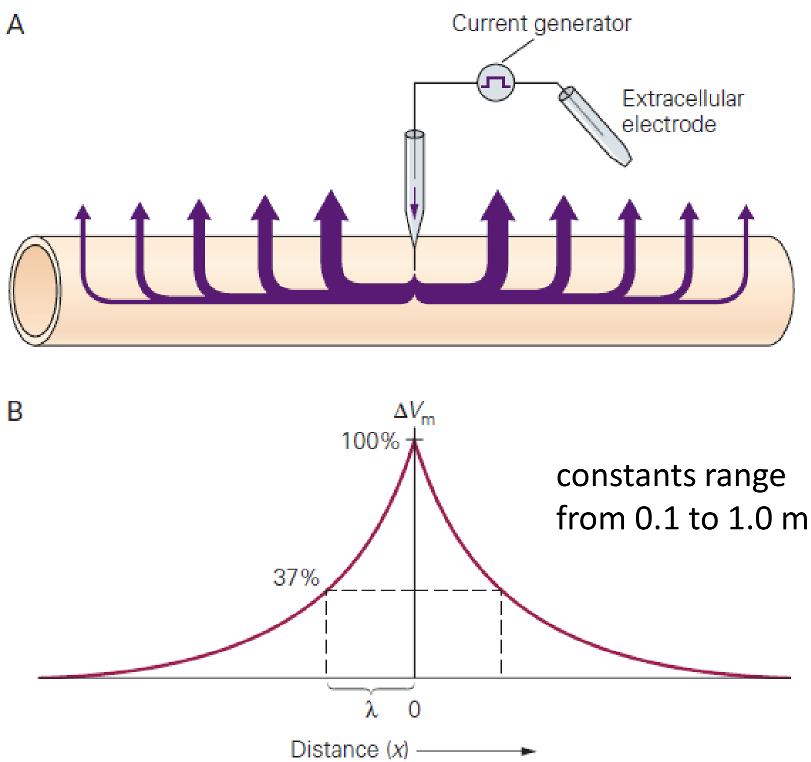
both capacitive (b) and resistive properties (a)

Membrane and axoplasmic resistance affect the eficiency of signal conduction

Subthreshold voltage signal traveling along extended structures such as dendrites, axons, and muscle fibers decreases in amplitude with distance from the site of initiation

$$\lambda = \sqrt{(r_m / r_a)}.$$

$$\Delta V(x) = \Delta V_0 e^{-x/\lambda},$$

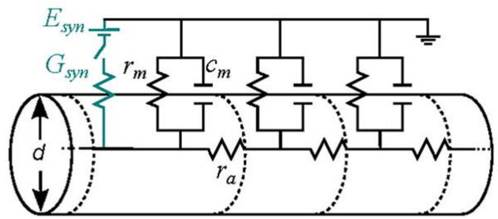


constants range from 0.1 to 1.0 mm.

Membrane and axial resistance as: better the **insulation** of the membrane (that is, the greater *r*m) and the better the **conducting properties** of the inner core (the lower *r*a), the greater the length constant of the dendrite

Axon diameter affect the velocity

B



where $r_m = R_m \pi d$ and $r_a = \frac{4R_i}{\pi d^2}$

$$\lambda^2 \frac{\partial^2 V_m}{\partial x^2} = \tau_m \frac{\partial V_m}{\partial t} + V_m \quad \textbf{(2)}$$

with $\begin{cases} \tau_m = r_m c_m \\ \lambda \approx \sqrt{\frac{r_m}{r_a}} \end{cases}$

For an infinite cable:

$$\begin{cases} \lambda_{DC} = \sqrt{\frac{r_m}{r_a}} \\ \lambda_{AC} = \lambda_{DC} \sqrt{\frac{2}{1+\sqrt{1+(2\pi f \tau_m)^2}}} \\ \lambda_{AC} \approx \sqrt{\frac{1}{\pi f r_a c_m}} \quad \text{if } f > 100\text{Hz} \end{cases}$$

Input resistance for an infinite cable:

$$R_{inf} = \frac{\sqrt{r_m r_a}}{2} \quad \textbf{(3)}$$