THE RESTING MEMBRANE POTENTIAL
• Our goal is to understand
• (1) how the membrane potential is established, and
• (2) how the membrane potential is maintained.
• **Introduction**
• All cells have a potential difference across their plasma membrane.
• That is, the potential or chemical charge inside of the cell is different to that of the solution outside of the cell.
• This potential difference is referred to as the membrane potential.
• In most cells **the resting membrane potential is negative** (i.e., inside of the cell is negative with respect the outside, which serves as the reference).
The resting membrane potential of a cell is the electrochemical state of a cell (neuron) at rest, i.e. the membrane permeability at rest.

It is the transmembrane potential of the resting cell—at which there is no net movement of a particular ion across the cell membrane.

It is the potential that would be maintained if there were no action potentials, synaptic potentials, or other active changes in the membrane potential.

The resting membrane potential refers to a situation in which the cell is at rest and no perturbations have been done to change the potential.

We will examine all of these ideas in this discussion.
What is the value of the normal resting membrane potential?

- The value of the membrane potential varies from cell to cell; depending on the cell type and ranges from about -20 mV to -100 mV.

- For example, in a typical neuron, its value is -70 mV, in a typical skeletal muscle cell, its value is -90 mV, and in most other mammalian cells, the membrane potential is around -50 mV (-0.05 V).

- In most cells the resting potential has a negative value, which by convention means that there is excess negative charge inside compared to outside.

- In other words, the resting potential has the inside of the neuron 70mV more negative than the extracellular space (V stands for voltage, which is a measure of potential or the difference in electric charge between two places).
Changes in the resting membrane potential difference is the basis of electrical signalling in cells.

In **non-excitable cells**, such as epithelial cells and adipose cells (and others), the resting membrane potential does not change appreciably over time.

In **excitable cells** (such as neurons, muscle cells, some endocrine cells, and some other cells in the body), however, upon stimulation of the cell, **the membrane potential can change dramatically for short periods of time (milliseconds)**.

Therefore, in excitable cells the membrane potential is **not always at the resting membrane potential**.

When we discuss the action potential and synapse later, we will see that deviations from the resting membrane potential in excitable cells are extremely important to the physiological function of these cells.
• All cell membranes produce electrical signals by ion movements, but transmembrane potential is particularly important to neurons, because rapid changes in the membrane potential of neurons bring about the nervous impulse, which is the basis of neuronal signaling.

• In muscle cells, changes in the membrane potential bring about contraction.

• In endocrine cells, changes in the membrane potential bring about release of hormones.

• Details of this will be given in the Physiology section of the NEUROSCIENCE SECTION IN BLOCK 3.
• **Importance of resting potential**
  
  • The cell’s ability to fire an action potential is due to the cell’s ability to maintain the cellular resting potential at approximately –70 mV (-0.07 volt).

  • The basic signaling properties of neurons are determined by changes in the resting potential.

  • **This is the basis of cell to cell communication** (Chemical synapses and the rest.)
How are resting potentials determined/created?

Electricity (i.e., the flow of current) requires 2 things:

1) **Charged particles** -- neurons use **ions** (charged particle)
2) **Separation of charge** -- created by neural membrane
• It is important to keep in mind that the potential difference occurs at the level of the cell membrane.

• This is because biological membranes can act to allow separation of electrical charge, by separating solutions in two compartments by the very short-distance, non-conducting, hydrophobic core of the membrane (=3 nm).

• Charge separation across the membrane leads to an electric field across the membrane.

• This electric field gives rise to the measured membrane potential.
• RECALL that.....
• The inside of the cell is called the **intracellular space**. The outside of the cell is called the **extracellular space**.

The cell membrane is made of two layers of fat (called **lipid bilayer**) and particles cannot pass through this lipid bilayer. *(Figure 3.3).*

However, **ion transport** proteins in the membrane form channels for particles *(Figure 3.6 & 3.7).*

These channels can open and close which allow particles to enter and leave the cell.
• Neurons (and other cells) make use of several ions to create electric currents.

• **Sodium** has a positive charge (Na+)  
  **Chloride** has a negative charge (Cl-)  
  **Potassium** has a positive charge (K +)  
  **Proteins** in cell have a negative charge (A-)

• The resting membrane potential is created by the concentrations of the ions in the fluids on both sides of the cell membrane and the ion transport proteins that are in the cell membrane.

• How the concentrations of ions and the membrane transport proteins influence the value of the resting potential is outlined in the discussion that follows.
For determination of membrane potentials, the two most important types of membrane ion transport proteins are ion channels and ion pumps.

Ion channel proteins create paths across cell membranes through which ions can pass.

They have selectivity for certain ions, thus, there are potassium, chloride-, and sodium-selective ion channels.

Different cells and even different parts of one cell (dendrites, cell bodies, nodes of Ranvier) have different amounts of various ion transport proteins.

Typically, the amount of certain potassium channels is most important for control of the resting potential (as we will see).

Some ion pumps such as the Na+/K+ATPase are electrogenic, that is, they produce charge imbalance across the cell membrane and can also contribute to the membrane potential.
Ion Channels are...

- a class of integral proteins that span the cell membrane
- permit transient current flow and thereby facilitate depolarization, or hyperpolarization of the cell membrane.
- Ion channels in the plasma membrane of neurons and muscles contributes to their excitability.
- When open, ions move down their concentration gradients
Transmembrane (membrane) potentials are established primarily by three factors which act on ions:

1) the concentration of ions on the inside and outside of the cell, and their asymmetric distribution across the membrane to form a concentration gradient (Na+, K+) (Figure 3.8)

2) the selective permeability of the cell membrane to those ions (i.e., ion conductance or electrical force (Figure 3.9)) through specific ion channels (K+ channels and Na+ channels); and

3) by the activity of electrogenic pumps (e.g., Na+/K+-ATPase and Ca++ transport pumps). These are special proteins in the membrane that maintain the ion concentrations across the membrane by moving ions.

These parameters maintain a charge difference across the membrane (i.e. resting potential of -70 mV in nerve cells).
Given that the membrane is permeable only to certain ions (e.g., K+), these forces create what is called a resting potential.

Potential means a separation of charge. In this case the separation is across the membrane. Resting means that no current is flowing across the membrane.

These simple principles create the resting potential:

1) **Concentration gradient moves ions from high to low concentration**
2) **Electrical force moves ions with same charge away from each other and ions with opposite charge towards each other.**
3) **Na+/K+ pump moves Na+ to the extracellular space. It can't get back in because the membrane is impermeable to Na+.**
4) **The membrane is permeable to K+ (i.e., it flows either way)**
5) **Large negatively charged proteins (A-) are stuck inside the neuron**
• Na+ and K+ are driven intracellularly to A- by the electrical force.

• The concentration gradient pushes Na+ intracellularly and K+ extracellularly.

• The Na+/K+ pump moves Na+ extracellularly

• Because of this, the extracellular space has lots of Na+ and ends up relatively positive compared to the intracellular space where there are lots of A-.
• Every neuron has a separation of electrical charge across its cell membrane.
• The membrane potential results from a separation of positive and negative charges across the cell membrane.
There is an excess of **positive charges outside and negative charges inside the membrane**. This gives rise to an **electrical potential difference**, which **ranges from about 60 to 70 mV**. This potential difference is maintained because the **lipid bilayer acts as a barrier to the diffusion of ions**.
Resting Potential
• Changes in resting potential occur when ions move in or out of the neuron.
• For example: Moving K+ out of the neuron will cause the cell to be more negative inside. When a neuron becomes more negative inside (or more polarized) it is said to be hyperpolarized.
• In contrast, moving Na+ into the neuron will cause the cell to be less negative inside. When a neuron becomes less polarized it is said to be depolarized.
The charge separation across the membrane, and therefore the resting membrane potential, is disturbed whenever there is a net flux of ions into or out of the cell.

- A reduction of the charge separation is called *depolarization*;

- An increase in charge separation is called *hyperpolarization*
• Normally, the concentration gradient and electrical force are both trying to push Na+ in……but since the membrane is impermeable to Na+ it can't get in.

• However, if Na+ channels in the membrane open, then Na+ will rush in.

• This is called an **Action Potential** (other names include impulse, fire, spike). Action potentials are how electrical messages are transmitted within a neuron.
During an action potential, the cell membrane becomes more permeable to Na+, which increases sodium entry into the cell through sodium channels.

At the peak of the action potential in a cardiac cell (e.g., ventricular myocyte), the membrane potential is approximately +20 mV. Therefore, while the resting potential is far removed from the $E_{qNa}$, the peak of the action potential approaches $E_{qNa}$.

Similar to Na+, there is a large Ca++ concentration difference across the cell membrane. Therefore, Ca++ diffuses into the cell through calcium channels.

The above discussion shows how changes in the concentration of individual ions across the membrane can alter the membrane potential.
Let us try to further understand how the generation and existence of the resting membrane potential across the plasma membrane of cells with its slight excess of negative charge on the inside of the cell. To do this, we must grasp the following four facts.

1. There is a difference in the concentration of potassium ($K^+$) between the inside of the cell and the outside of the cell.

2. The membrane is highly permeable to potassium. This means that potassium can get through the membrane with ease.

3. The majority of the negative charges (anions, $A^-$) inside the cell are proteins so that for every potassium inside the cell there is a negative charge on a protein (not totally true, but nearly true).

4. The proteins cannot get out. The membrane is not permeable to proteins because they are too big.
• 1. There is a difference in the concentration of potassium (K+) between the inside of the cell and the outside of the cell.

• For most animal cells potassium ions (K+) are the most important for the resting potential.

• Due to the active transport of potassium ions, there is a potassium concentration gradient such that the concentration of potassium inside the cell is a lot higher (about 150 mM) than the potassium concentration outside (about 5 mM) the cell.
• Most cells have potassium-selective leakage (non-gated) ion channels that remain open all the time, and contribute to the resting potential.

• By being open continually there is net movement of positively-charged potassium ions through these potassium channels by random molecular motion (diffusion) with a resulting accumulation of excess positive charge outside of the cell.

• Since nerve cells have more K+ than Na+ leakage channels, the membrane permeability to K+ is higher.

• As a result, K+ leaks out of cell and its inside becomes more negative. K+ is then pumped back in to the cell.

• This continues until enough excess positive charge accumulates outside the cell to form a membrane potential which can balance the difference in concentration of potassium between inside and outside the cell.
"Balance" means that the electrical force that acts to move the ions tends to increase until it is equal in magnitude but opposite in direction to the tendency for net movement of potassium due to diffusion.

This balance point is an "equilibrium potential".

Potassium equilibrium potentials of about 70 millivolts (inside negative) are common in neurons.

For typical animal cells, the most important equilibrium potential is the potassium equilibrium potential.

This is because for the resting membrane, the membrane is most permeable to potassium ions and not other ions.

This is due to the presence of potassium leakage channels that are open at the resting membrane potential, as we just mentioned.

At rest, cell membranes are more permeable to K+ ions than other ionic species because of facilitated diffusion through K+ channel proteins which form K+ specific pores in the membrane.
2. The membrane is highly permeable to potassium. This means that potassium can get through the membrane with ease.

3. The majority of the negative charges (anions, $A^-$) inside the cell are proteins so that for every potassium inside the cell there is a negative charge on a protein (not totally true, but nearly true). So the negative charge on the proteins inside the cell nearly electrically balances the positive charge on the potassium.

4. The proteins cannot get out. The membrane is not permeable to proteins because they are too big.

We mentioned that the lipid bilayer is not permeable to large molecules (proteins are large molecules). So proteins cannot get out of cells.
• **REMEMBER:**

• The extracellular and intracellular K+ concentrations in a ‘typical’ cell are 4.5 mM and 160 mM, respectively; therefore, K+ tends to move outwards down its concentration gradient.

• Since large protein anions inside the cell are unable to follow K+ out of the cell, a negative potential develops on the intracellular face of the plasma membrane. This growing potential difference then opposes the further efflux of K+ ions.

• An equilibrium is reached when the diffusional and electrical forces are balanced and there is no net movement of K+ ions.

• At equilibrium, the potential across the membrane is termed the potassium equilibrium potential (E_K) (Fig. 8.1). Equilibrium potentials can be calculated using the Nernst equation (Table 8.1).
<table>
<thead>
<tr>
<th>Ion</th>
<th>External Concentration (mM)</th>
<th>Internal Concentration (mM)</th>
<th>Equilibrium potential (37°C) (mM)</th>
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<tbody>
<tr>
<td>K⁺</td>
<td>4.5</td>
<td>160</td>
<td>-95</td>
</tr>
<tr>
<td>Na⁺</td>
<td>145</td>
<td>10</td>
<td>+71</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>1</td>
<td>0.0001</td>
<td>+122</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>114</td>
<td>3</td>
<td>-96</td>
</tr>
</tbody>
</table>

Table 8.1 Calculation of equilibrium potentials. Given the extracellular and intracellular concentrations, the equilibrium potentials for the major membrane permeant ion in a ‘typical’ cell can be calculated from the Nernst Equation:

\[ E_{\text{ion}} = \frac{RT}{zF} \ln \left( \frac{[\text{ion]}_{\text{out}}}{[\text{ion]}_{\text{in}}} \right) \]

where \( R \) = the gas constant, \( T \) = the absolute temperature, \( F \) = Faraday’s number and \( z \) = valency (+1 for K⁺, −1 for Cl⁻ etc.); \([\text{ion}]_{\text{out}} \) and \([\text{ion}]_{\text{in}} \) are the extracellular and intracellular concentrations of the ion.

Fig. 8.2 The resting membrane potential is determined by the contribution of the relative permeabilities of several permeant ions.
Fig. 8.1 Development of the resting membrane potential. In this example K⁺ is the sole membrane permeant ion and the resting membrane potential ($E_k$) is attained when the cells come to electrochemical equilibrium with the medium.
• The Nernst equation is used to estimate the equilibrium potential for an ion.

• If we consider a cell in which K+ is the only ion across the membrane other than the large negatively charged proteins inside of the cell.

• We know that because the cell has K+ through which K+ can move in and out of the cell, that K+ diffuses down its chemical gradient because its concentration is much higher inside the cell than outside.

• We know too that as K+ diffuses out of the cell, it leaves behind negatively charge proteins, which creates a separation of charge and therefore a potential difference across the membrane.

• It is possible, experimentally, to prevent the K+ from diffusing out of the cell.
This could be achieved by applying a negative charge to the inside of the cell that prevents K+, a positively charge ion, from leaving the cell.

The membrane potential that would be necessary to oppose the movement of K+ down its concentration gradient is termed the **equilibrium potential for K+** (EK; **Nernst potential**). The Nernst potential for K+ is:

\[
EK = -61 \log \left( \frac{[K^+]_i}{[K^+]_o} \right) = -96 \text{ mV} \quad \text{(where } [K^+]_i = 150 \text{ mM and } [K^+]_o = 4 \text{ mM)}
\]

The EK is the potential difference across the membrane required to maintain the normal K+ concentration gradient across the membrane.

In other words, EK represents the electrical potential necessary to keep K+ from diffusing down its chemical gradient and out of the cell.

If the outside K+ concentration were increased from 4 to 10 mM, then the chemical gradient for diffusion out of the cell would be reduced, and therefore the membrane potential required to maintain electrochemical equilibrium (EK) would be less negative according to the Nernst relationship.
• The resting potential for a ventricular myocyte is about -90 mV, which is near the equilibrium potential for K+.

• Since the equilibrium potential for K+ is -96 mV and the resting membrane potential is -90 mV, there is a net driving force of 6 mV acting on the K+ to cause it to diffuse out of the cell.

• Therefore, because the resting cell has a finite permeability to K+ and there is a small net outward driving force acting upon K+, there is a slow outward leak of K+ from the cell.
• NOTE that…..Although the passage of K+ ions through K+ channels predominates in the resting cell, the resting membrane potential never reaches $E_K$.

• This is because the plasma membrane is not totally impermeable to other ions and the passage of these ions through selective ion channels contributes to the overall membrane potential (Fig. 8.2).

• Note too that….. Only very few ions need to move across the plasma membrane to establish a membrane potential.
• **Sodium and calcium ions.**

• Because the Na+ concentration is higher outside the cell, this ion diffuses down its chemical gradient into the cell.

• To prevent this inward flux of Na+, there would need to be a large positive charge inside the cell (relative to the outside) in order to balance out the chemical diffusion forces.

• This potential is called the **equilibrium potential for Na+** (ENa) and is calculated by:

\[
ENa = -61 \log \left( \frac{[Na^+]_i}{[Na^+]_o} \right) = +50 \text{ mV} \]

(\text{where } [Na^+]_i = 20 \text{ mM} \text{ and } [Na^+]_o = 145 \text{ mM})
The positive ENa means that in order to balance the inward directed chemical gradient for Na+, the cell interior would need to be +50 mV to prevent Na+ from diffusing into the cell.

At a resting membrane potential of -90 mV, there is a very large electrical and chemical driving force (-140 mV) acting upon external Na+ to cause these ions to diffuse into the cell.

At rest, however, the permeability of the membrane to Na+ is very low so that only a small amount Na+ leaks into the cell.
Why is the cell slightly negative on the inside compared to the outside?
• Well, we can think about it this way.

• Potassium wants to diffuse out of the cell. There is a higher potassium concentration inside the cell than outside so there is a chemical gradient that favors the movement of potassium out of the cell.

• Since there are potassium channels in the membrane, the membrane is permeable to potassium. Therefore, potassium can easily leave the cell. However, as potassium leaves the cell, the charge-balancing proteins cannot follow because the membrane is not permeable to proteins.

• Thus, movement of K out of the cell leads to the net transfer of positive charge out of the cell and, consequently, leads to the accumulation of some negative charge inside the cell. The charge separation across the membrane is then responsible for the generation of the resting membrane potential.
• It may now be asked why do not all of the intracellular potassium ions leak out of the cell?

• The negative charge that has built up holds them in. After the first few potassium ions leave, the inside of the cell becomes negative.

• At this time two opposing forces act on K⁺ ions. One force tends to make potassium ion leave the cell, and that force is the difference in potassium concentration (chemical gradient).

• The other force results from the accumulated negative charge inside of the cell that tends to prevent K⁺ from leaving the cell (electrical gradient). K⁺ is a positively charged ion and the inside of the cell is now negative.
• We know that opposite charges attract so the accumulated negative charge acts to prevent the movement of the rest of the potassium ions out of the cell.

• Therefore, a point is reached at which $K^+$ ions are said to be in **equilibrium**. That is at equilibrium, there is no net movement of $K^+$ into or out of the cell.

• Therefore, at equilibrium, there are two forces that act in opposition to each other, and they tend to balance each other; one is the chemical gradient and the other is the electrical gradient.

• The two put together define the **electrochemical gradient** for $K^+$ ion.
• So far we have seen that………..
• 1-The resting membrane potential exists across the plasma membrane of all cells.
• 2-It is established and maintained mostly by K+ leak channels and to a lesser extent by the Na+ -K+ pump, which actively transports three Na+ ions out of the cell in exchange for two K+ ions.
• 3- It requires asymmetric ionic distribution across the membrane (i.e., a concentration gradient of ions (Na+, K+) and selective permeability through ion channels (K+ channels and Na+ channels).
• The later is secured because the K+ concentration is 20-fold higher inside neurons than outside, whereas the Na+ concentration is 10-fold higher outside than inside.
• 4- Because the plasma membrane is more permeable to \( K^+ \) than to other ions, \( K^+ \) ions tend to leak out until the accumulated positive charge outside the cell inhibits further \( K^+ \) movement.

• 5- The resting potential exists when there is no net movement of \( K^+ \) ions (i.e., when outward diffusion of \( K^+ \) ions is just balanced by the external positive charge acting against further diffusion).

• 6- In this state of equilibrium, the inside of the cell is negatively charged relative to the outside; this potential difference (voltage) across the membrane is the resting membrane potential.

• 7- Energy-requiring pumps in the plasma membrane help maintain the resting potential, keeping the cell (neuron) ready to receive and transmit signals.

• 8- The best known pump is \( Na^+/K^+ -ATPase \), which exchanges internal \( Na^+ \) for escaped \( K^+ \) when ATP is available.
• How is a membrane potential maintained?
Maintenance of the Resting Membrane Potential
In order to have a complete understanding of the membrane potential, we need to know the role played by sodium (Na\(^+\)) ions as well.

As we all know, the plasma membrane also contains a small number of Na\(^+\) channels. The concentration of sodium outside of the cell is much higher (150 mM) than the concentration of sodium inside of the cell (10 mM).

Therefore, there is a strong driving force for the movement of Na\(^+\) ions into the cell.

Two forces act on Na\(^+\) ions that favor their movement into the cell; one is the Na\(^+\) concentration gradient, and the other is the negative membrane potential.

Consequently, there is a very slow leak of sodium into the cell.
Resting Membrane Potential

• But what about sodium?
• Electrostatic and Chemical forces act together on Na ions to drive them into the cell

Na is more concentrated outside than inside and therefore tends to flow into the cell down its concentration gradient.

Na is driven into the cell by the electrical potential difference across the membrane.
• Every time a Na\(^+\) ion leaks into the cell, a K\(^+\) ion leaves the cell (this is so that electrical balance is maintained). If this were to continue with no compensation by the cell, in time, this would tend to dissipate the K\(^+\) concentration gradient, so that the K\(^+\) concentration will be equal inside and outside of the cell.

• If the K\(^+\) concentration gradient is eliminated, the membrane potential will also be eliminated, because the generation of the membrane potential depends on the K\(^+\) concentration gradient.

• Thus, the cell has to do something to counteract the inescapable leak of sodium into the cell, and efflux of potassium out of the cell.

• The cell's defense against this is the Na\(^+\)/K\(^+\) ATPase (also referred to as the sodium potassium exchange pump, or simply the sodium pump).
This membrane transport protein pumps sodium out of the cells and at the same time pumps potassium into the cell in the ratio $3 \text{Na}^+ : 2\text{K}^+$ for every ATP hydrolyzed).

It must be there in order to keep the potassium concentration higher inside of the cell, and also to keep the sodium concentration lower in the cytoplasm.

It is important to realize that the $\text{Na}^+/\text{K}^+/\text{ATPase}$ is not directly responsible for the generation of the resting membrane potential.
• However, the Na\(^+\)/K\(^+\)/ATPase is responsible for the *maintenance* of the membrane potential by maintaining the normal intracellular K\(^+\) (150 mM) and Na\(^+\) (10 mM) concentrations.

• In fact you can poison the sodium potassium exchange pump with a chemical called *ouabain* and the cell will continue to have a resting potential for hours.

• However, *in the absence of Na\(^+\)/K ATPase activity, the constant leak of K\(^+\) out of the cell will lead to a reduction of the intracellular K\(^+\) concentration*. ............which would lead to a reduction in the membrane potential, such that the membrane potential will slowly go from -70 to 0 (at this point, the cell is dead!).

• Thus, the activity of the Na\(^+\)/K\(^+\) ATPase is necessary for the maintenance of the membrane potential.
• Sodium–potassium ATPase (exchange pump):
  – are powered by ATP
  – are active forces across the membrane
  – carries 3 Na$^+$ out and 2 K$^+$ in
  – balances passive forces of diffusion
  – maintains resting potential (—70 mV)
• At this point, it may be wondered what maintains the extracellular concentrations of K\(^+\) and Na.
• Two organ-systems are responsible for maintaining the low extracellular K\(^+\) concentration and the high extracellular Na\(^+\) concentration.
• The kidneys (urinary system) working in conjunction with the endocrine system are responsible for extracellular K\(^+\) and Na homeostasis.
In summary, the membrane potential exists because there is a higher concentration of potassium inside the cell, and the potassium can leave through potassium channels, and the negatively charged proteins cannot.

- **This produces an electrical potential across the membrane called the resting membrane potential.**

- The sodium pump is important for creating the potassium concentration gradient, but it is only indirectly responsible for the membrane potential by maintaining the normal intracellular K and Na\(^+\) concentrations.

- Since the sodium pump is actually moving charged particles, it was originally hypothesized that the pump directly created the membrane potential, but the experiment with ouabain proved that the membrane potential would continue to exist, even if the pump stopped working. This was a very important experiment for understanding the real basis of the membrane potential.
**REVIEW**

- Neurons and some other excitable cells in mammals send messages **electrochemically**.
- This means that chemicals cause an electrical signal.
- Chemicals in the body are "electrically-charged" -- when they have an electrical charge, they are called "ions."
- The **important ions in the nervous system** are sodium and potassium (both have 1 positive charge, +), calcium (has 2 positive charges, ++) and chloride (has a negative charge, -).
- There are also some negatively charged protein **molecules**.
- It is also important to remember that **nerve cells are surrounded by a membrane** that allows some ions to pass through and blocks the passage of other ions.
- This type of membrane is called **semi-permeable**.
• When a neuron is not sending a signal, it is "at rest."
• When a neuron is at rest, the inside of the neuron is negative relative to the outside.
• Although the concentrations of the different ions attempt to balance out on both sides of the membrane, they cannot because the cell membrane allows only some ions to pass through channels (ion channels).
• **At rest, potassium ions (K\(^+\)) can cross through the membrane easily, but chloride ions (Cl\(^-\)) and sodium ions (Na\(^+\)) have a more difficult time crossing.**
• The negatively charged protein molecules (A\(^-\)) inside the neuron cannot cross the membrane.
• In addition to these selective ion channels, there is the Na\(^+\)/K\(^+\) ATPase exchange pump that uses energy to move three sodium ions out of the neuron for every two potassium ions it puts in.
Finally, when all these forces balance out, and the difference in the voltage between the inside and outside of the neuron is measured, you have the resting potential.

The resting membrane potential of a neuron is about -70 mV (mV=millivolt) - this means that the inside of the neuron is 70 mV less than the outside.

At rest, there are relatively more sodium ions outside the neuron and more potassium ions inside that neuron.
• As there are more $K^+$ channels than $Na^+$ channels, there are more outgoing $K^+$ ions than incoming $Na^+$ ions.

• As a result, an electrical potential difference is created across the membrane.

• The outside is about 70 mV higher than the inside.

• If the potential of extracellular space is used as the reference, the membrane potential is negative 70 mV.

• The neuron with this resting potential difference is said to be polarized.
• Remember !!

• that cells contain a high concentration of $K^+$ at rest, and that they have membranes that are essentially permeable to $K^+$

• that membrane electrical potential difference (the resting membrane potential) is generated by diffusion of $K^+$ ions and charge separation

• that typically resting membrane potentials in neurones are -70 mV

• that the membrane potential is due to diffusion of $K^+$ ions
The main points:

• The Na-pump keeps internal Na\(^+\) low and internal K\(^+\) high
• If a membrane is permeable to one type of ion an equilibrium potential develops
• Very few ions move to cause this potential to develop
• The potential is determined by the balance of the concentration gradient driven flux and the electrically driven flux
• Concentration gradients are ‘batteries’ they represent stored or potential energy
Intracellular ionic homeostasis

Equilibrium potentials for a typical nerve cell

Resting potential

Energy required
In a resting cell the electrical potential called the resting potential depends on

1- The relationship between potential and concentration of ions
2- Ionic concentrations
3- Membrane permeabilities
4- Current generating pumps (proteins)
5- The fact that electricity results from the separation of charge.
Summary: Resting Potential

<table>
<thead>
<tr>
<th>SUMMARY TABLE 12-1</th>
<th>THE RESTING POTENTIAL</th>
</tr>
</thead>
</table>

- Because the cell membrane is highly permeable to potassium ions, the resting potential is fairly close to $-90$ mV, the equilibrium potential for $K^+$.  

- Although the electrochemical gradient for sodium ions is very large, the membrane's permeability to these ions is very low. Consequently, $Na^+$ has only a small effect on the normal resting potential, making it just slightly less negative than it would otherwise be.  

- The sodium–potassium exchange pump ejects 3 $Na^+$ ions for every 2 $K^+$ ions that it brings into the cell. It thus serves to stabilize the resting potential when the ratio of $Na^+$ entry to $K^+$ loss through passive channels is $3:2$.  

- At the normal resting potential, these passive and active mechanisms are in balance. The resting potential varies widely with the type of cell. A typical neuron has a resting potential of approximately $-70$ mV.
• Changing the membrane potential
• Changing the permeability of the plasma membrane to a particular ion can cause a change in the membrane potential.
• Opening an ion channel for any ion results in the movement of the membrane potential towards the equilibrium potential for that ion (see Table 8.1).
• Thus, opening K+ or Cl- channels results in an increase in membrane potential with the inside of the cell becoming more negative (Fig. 8.3).
• This is termed hyperpolarization. Conversely, opening Na+ or Ca++ channels results in a decrease in membrane potential with the inside becoming less negative. This is termed depolarization.
• In another lecture: we will see in more detail how cells can change their potential by changing the ionic permeability of the cell membrane
Fig. 8.3 Increasing membrane permeability to a single ionic species can modify the membrane potential $V_m$. 
Let us now relate this information to the function of our bodies and clinical medicine.......just a bit!
NOTE that.................

• In some cells, the membrane potential is always changing (such as cardiac pacemaker cells).

• For such cells there is never any “rest” and the “resting potential” is a theoretical concept only.
Cardiac cells, like all living cells, have different concentrations of ions, particularly Na\(^+\), K\(^+\), Cl\(^-\), and Ca\(^{++}\), across the cell membrane (see figure to right).

There are also impermeable negatively charged proteins within the cell.

In a cardiac cell, the concentration of K\(^+\) is high inside the cell and low outside.

Therefore, there is a chemical gradient for K\(^+\) to diffuse out of the cell.

The opposite situation is found for Na\(^+\) and Ca\(^{++}\) where their chemical gradients favor an inward diffusion.
Increased membrane excitability in hyperkalaemia

- The consequences of hyperkalaemia, where the extracellular concentration of K+ is raised, are a more positive Ek and, hence, a more positive resting membrane potential.

- Cellular electrical activity depends on the ability to depolarize membranes.

- Thus, in the heart in hyperkalaemia, a lesser change in ion conductance is required to depolarise and so excite cardiac membranes.

- The result of this increased excitability is ventricular arrhythmia, which can lead to fibrillation and, if left untreated, can be life threatening.
• ASSIGNMENT.
• Look up the causes of high K+ levels.
• Look up the consequences of high K+ levels with the concomitant use of the cardiac glycoside digitalis.
Resting Membrane Potential

- Na⁺ and Cl⁻ are more concentrated outside the cell
- K⁺ and organic anions (organic acids and proteins) are more concentrated inside.
- The overall effect of this ionic distribution is the resting potential
Resting Membrane Potential

- The same mechanisms operate on potassium...
Resting Membrane Potential

- Chloride ions, concentrated outside the cell tend to move inward down their concentration gradient through nongated chloride channels.

- But the relative excess of negative charge inside the membrane tend to push chloride ions back out of the cell.

- Two forces acting on a given ionic species.
- Chemical forces tend to drive ions down their concentration gradients.
The Sodium-Potassium Pump

- Dissipation of ionic gradients is ultimately prevented by Na-K pumps

extrudes Na from the cell while taking in K
The Sodium-Potassium Pump

The energy necessary for this process is obtained from the hydrolysis of ATP (an energy carrying molecule).

- Because the pump moves Na and K against their net electrochemical gradients, energy is required to drive these actively transported fluxes.
- Chloride pumps also actively transport chloride ions toward the outside assure that the extra- to intracellular Cl concentration is greater than what would result from passive diffusion alone.
Resting Membrane Potential

- Electrostatic and Chemical forces act together on Na ions to drive them into the cell.

- This process cannot be allowed to continue unopposed.
- Otherwise, the K pool would be depleted, intracellular Na would increase, and the ionic gradients would gradually run down, reducing the resting membrane potential.
More on action potentials
Transmission of a Nerve Impulse along a Neuron

- **Depolarization** – stimulus causes a change in membrane permeability
- Allows sodium (Na\(^+\)) to enter the neuron
Transmission of a Nerve Impulse along a Neuron

- The exchange of ions creates an *action potential* in the neuron
  - “potential to do work”
  - Sound familiar??

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(a) Resting membrane

(b) Stimulus initiates depolarization

(c) Depolarization and generation of the action potential
The Action Potential

- Once the action potential (nerve impulse) begins, it spreads along the entire neuron
  - “all-or-none” law: sound familiar??
- Potassium ions (K⁺) leave the neuron after Na⁺ enters
The Action Potential

- Exchange of Na\(^+\) and K\(^+\) repolarizes the membrane
- The *sodium-potassium pump* restores ions to their original location
  - Protein pump in the membrane
  - This action requires ATP
Nerve Impulse Propagation

- The impulse continues to move along the neuron
- Impulses travel faster along myelinated fibers
Nerve Impulse Propagation

- Myelinated fibers: ~200 feet/second
- Unmyelinated fibers: ~10 feet/second
Transmission of the Nerve Impulse between Neurons

- Impulses can cross the synapse to another nerve
  - Depolarization activates vesicles in axon terminal
  - Requires Ca$$^{++}$$
  - Neurotransmitter is released
Transmission of the Nerve Impulse between Neurons

- The dendrite of the “next” neuron has receptor sites
- Neurotransmitter attaches to receptors
- If enough molecules of NT attach:
  - A new action potential is generated
  - Sound familiar??
How Neurons Communicate at Synapses

1. Action potential arrives
2. Vesicle fuses with plasma membrane
3. Neurotransmitter is released into synaptic cleft
4. Neurotransmitter binds to receptor on receiving neuron's membrane
5. Ion channel opens
6. Ion channel closes
7. Neurotransmitter broken down and released
• Some BASIC INTERESTING PHYSIOLOGY
Measuring Membrane Potentials.

- An unstimulated cell usually have a **resting potential** of -70mV.

Fig. 48.6a
(a) Distribution of charges
Equal numbers of + and – charges in most of ECF

Equal numbers of + and – charges near plasma membrane

Equal numbers of + and – charges in most of cytosol

(b) Distribution of ions
Chloride ion
Sodium ion
Phosphate ion
Potassium ion
Protein

12.09ab
(a) Hyperpolarizing graded potential

(b) Depolarizing graded potential
1. Resting state:
   All voltage-gated Na⁺ and K⁺ channels are closed.

2. Depolarizing phase:
   Depolarization to threshold opens Na⁺ channel activation gates. Na⁺ inflow further depolarizes the membrane, opening more Na⁺ channel activation gates.

3. Repolarizing phase:
   Na⁺ channel inactivation gates close and K⁺ channels open. Outflow of K⁺ causes repolarization.

4. Repolarization continues:
• The Action Potential: All or Nothing Depolarization.
  – If graded potentials sum to \( \approx -55 \text{mV} \) a **threshold potential** is achieved.
  • This triggers an **action potential**.
    – Axons only.
(a) Spatial summation

(b) Temporal summation
Time
1 msec
Cell body

Na⁺

Trigger zone
Current flow due to opening of Na⁺ channels

5 msec

Na⁺

10 msec

(a) Continuous conduction

(b) Saltatory conduction

Nodes of Ranvier
Current flow due to opening of Na⁺ channels

Leading edge of action potential
(a) Diverging circuit
(b) Converging circuit
(c) Reverberating circuit
(d) Parallel after-discharge circuit
• **Saltatory conduction.**
  
  – In myelinated neurons only unmyelinated regions of the axon depolarize.
  • Thus, the impulse moves faster than in unmyelinated neurons.
• **Summation**: graded potentials (EPSPs and IPSPs) are summed to either depolarize or hyperpolarize a postsynaptic neuron.

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(a) Subthreshold, no summation  
(b) Temporal summation  
(c) Spatial summation  
(d) Spatial summation of EPSP and IPSP