Plasma membranes are peppered with a variety of membrane proteins that create specific ion channels. Some of those are passive or leakage channels that are always open. Others are active or gated channels that open or close in response to a specific signal. Each channel is very selective as to the type of ion it allows to pass.

Ions will diffuse through ion channels according to the thermodynamic principles following their electro-chemical gradients. Thus flowing from a high concentration area to a low concentration area and positive charges being attracted by negative charges.

This flow of charge creates an electrical current and the voltage changes across the membrane according to the law of Ohm. (Voltage = current x resistance).

Communication by neurons depends on the intrinsic impermeability of plasma membranes, the presence of specific ion channels and the existence of electro-chemical gradients.

The Ion Equilibrium Potential

From basic cell physiology, we know that in all cells the internal ion composition differs from the outside. More specifically, the inside has a higher [K⁺], a lower [Na⁺], a lower [Cl⁻] and a much higher protein and phosphate content than the outside interstitial fluid.

Let's consider an impermeable membrane with a higher [K⁺] on one side (inside) than the other. Since charges are always balanced in order to preserve electrical neutrality, we will also find a number of negative charges on both sides to balance with the positive charges of potassium.

If this membrane was complete impermeable, one would not observe a voltage difference since this requires a charge difference between the two sides. Cell membranes are however selectively permeable to K⁺ ions, having 50 to 100 times more K⁺ leakage channels then Na⁺ leakage channels. For the sake of simplicity, let us assume at this point that this impermeable membrane suddenly is given ONLY K⁺ ion leakage channels.

What will occur now if we consider the above mentioned conditions?
• K⁺ ions will diffuse down their concentration gradient from inside to outside (= chemical force)
• For each K⁺ ion leaving, an extra positive charge is added to the outside an extra positive charge is missing on the inside (thus a negative charge builds up on the inside)
• This creates an electrical charge difference = a voltage gradient
• The more K⁺ leave, the greater the charge difference or voltage gradient
• The negative charge build up on the inside will pull K⁺ ions inwards (= electrical force) and prevent the outflow of K⁺ ions
• The greater the voltage gradient becomes, the greater the pull inwards becomes.

The figure shows the initial condition on the left: K⁺ diffuses out of the cell according to the concentration gradient (black arrow = chemical force). This creates a voltage gradient, and a new force comes into play, dragging K⁺ ions back inside (colored arrow = electrical force).

When the charge difference build-up across the membrane pulls as many K⁺ ions back inside as K⁺ ions leave by diffusion, we will have reached an equilibrium. This reflects the fact that the outward chemical force equals the inward electrical force. The voltage difference established at this equilibrium is called the K⁺ equilibrium potential (EP).

An equilibrium potential (EP) is thus the voltage across a membrane where diffusion in one direction is balanced by electrical movement of that ion in the other direction. Thus at equilibrium, there will be no NET movement of that ion. An EP is specific for each ion and is determined by the concentration difference of that specific ion on opposite sides of a membrane and requires the presence of specific channels for that ion.

The Nernst Equation and Equilibrium Potential

The Equilibrium potential can be calculated for each ion and is reflected by the Nernst equation

\[ E_x = - \left\{ \frac{60}{z} \right\} \cdot \log \left\{ \frac{X_{\text{in}}}{X_{\text{out}}} \right\} \]

where
• \( E_x \) = Equilibrium potential in mV (milli-volts) for ion X
• \( z \) = charge and sign value of the ion
• \( X_{\text{in}} \) and \( X_{\text{out}} \) are the intracellular and extracellular concentration of the ion (in mM)
The following table gives some concentrations (in mM) and the calculated EP (in mV) for the ions in question. Make sure you do the calculations yourself and end up with the same results!

<table>
<thead>
<tr>
<th>Ion</th>
<th align="right">X_{in}</th>
<th align="right">X_{out}</th>
<th>EP</th>
</tr>
</thead>
<tbody>
<tr>
<td>K^+</td>
<td align="right">150</td>
<td align="right">5.5</td>
<td>-86.1</td>
</tr>
<tr>
<td>Na^+</td>
<td align="right">15</td>
<td align="right">150</td>
<td>60.0</td>
</tr>
<tr>
<td>Cl^-</td>
<td align="right">9.0</td>
<td align="right">125</td>
<td>-68.5</td>
</tr>
</tbody>
</table>

The amount of ions needed to create a membrane potential of -86 mV is extremely small compared to the bulk of ions present. It is calculated that only 1 charge difference across a membrane for every 200,000 charges present is sufficient to create a potential difference of 100 mV. Thus movement of these ions will not significantly change the concentrations gradient in the short run.

**The Resting Membrane Potential**

The actual voltage potential that one measures when a micro-electrode is inserted into a neuron is called The resting membrane potential (RMP). It follows thus that, if a RMP across a membrane is equal to the EP for a specific ion, then that ion will experience no NET movement back and forth across the membrane.

However, if the RMP is NOT equal to the EP for a specific ion, net movement will occur in order to re-establish the EP conditions. If you look at the table above, you should be able to deduce that, if the RMP is equal to -86.1 mV, then there will be no net movement of K+ across the membrane but the other two ions will show net movement. On the other hand, if the RMP equals -69.5 mV, then Chloride will have no net movement but potassium and sodium will move across the membrane.

This table shows what will happen to the forces acting upon K+ ions when the RMP deviates from the EP. In this case, assume the EP for K+ to be -86 mV. Since ion movements will not change the concentration gradient, the chemical force will always remain the same magnitude and direction. By changing the RMP (which happens quite often as we will see later), the size and direction of the electrical force will be influenced dramatically.

<table>
<thead>
<tr>
<th>RMP</th>
<th align="right">C.F.</th>
<th>E.F</th>
<th>N.F</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mV</td>
<td align="right">out</td>
<td>&lt;</td>
<td>in</td>
<td>in</td>
</tr>
<tr>
<td>-86.1 mV</td>
<td align="right">out</td>
<td>=</td>
<td>in</td>
<td>zero</td>
</tr>
<tr>
<td>-50.0 mV</td>
<td align="right">out</td>
<td>&gt;</td>
<td>in</td>
<td>out</td>
</tr>
<tr>
<td>0 mV</td>
<td align="right">out</td>
<td>&gt;</td>
<td>zero</td>
<td>out</td>
</tr>
<tr>
<td>10.0 mV</td>
<td align="right">out</td>
<td></td>
<td>out</td>
<td>out</td>
</tr>
<tr>
<td>30.0 mV</td>
<td align="right">out</td>
<td></td>
<td>out</td>
<td>out</td>
</tr>
</tbody>
</table>
To analyze this table
- at -86 mV, both forces are equal but opposite, thus no net movement
- at 0 mV, there is no electrical force; the only one left is the chemical force and it points outwards
- at -120 mV, more negative charge exists on the inside of the cell. Thus while the chemical force has not changed, the electrical force pulling K⁺ back ion has increased. The net effect is thus a force drawing K⁺ in.

These are basically the only two items to check. If you look at the table, K⁺ moves out when the RMP is more negative than the EP, and moves in the cell when it becomes less negative than the EP.

Do this now for Na⁺ and you should come to the conclusion that if the RMP is less than the EP for Na⁺, that sodium will move into the cell.

**Relationship between RMP and EP.**

If our hypothetical membrane only had K⁺ ion leakage channels, the RMP would equal the EP for K⁺. What is observed is that the RMP is not equal to the EP for potassium but is close to -70 mV. The fact that this differs from the K⁺ EP is due to the presence of some Na⁺ leakage channels, allowing the flow of positive charge (Na⁺) into the cell according to the chemical and electrical gradient and thus reducing the negativity of the membrane potential (because sodium entry brings in positive charges).

The RMP is thus a net effect of all ion flow distribution across a membrane. Considering the resistance of each channel and logical assumptions about the specificity of ions that can flow through the leakage channels, the following observation should always be kept in mind.

The actual observed membrane potential of a cell will drift towards the Equilibrium Potential of that ion with the most abundant open channels present. The fact that our cells contain almost 50 times more K⁺ leakage channels than Na⁺ leakage channels results in a RMP of -70 mV, which is close to the EP for K⁺.

**Question:** What is the net flow for Cl⁻ ions at the RMP of -70 mV?

**Question:** If everything else remained the same, what would be a good guess for the RMP if our cells had mostly Na⁺ leakage channels with only a few K⁺ channels?
With the RMP being \(-70\, \text{mV}\), K\(^+\) will never be at equilibrium and continue to flow outwards and Na\(^+\) will continue to flow inwards. Over the long run, this would collapse the concentration gradients and the membrane potential would vanish. This is prevented by the presence of the ATP driven Na-K pump, ejecting 3 Na\(^+\) ions from the cell while simultaneously pumping 2 K\(^+\) ions back in. It thus re-distributes K\(^+\) and Na\(^+\) and maintains their concentration differences but also slightly contributes to the Membrane Potential itself as it leaves an extra negative charge behind each time.

Poisoning (blocking) the Na-K pump would thus result in cessation of electrical activity. Any component that blocks the operation of the Na-K pump, direct or indirect, will automatically have an effect on the resting membrane potential. For example, excess Digitalis (a drug from an orchid) blocks the pump directly while cyanide, which blocks the respiratory chain in the mitochondria, has an indirect effect as it reduces the ATP produced by the mitochondria.

---

**How about a Little Medical Story**

Digitalis is an example of a cardio-active or cardiotonic drug, in other words a steroid which has the ability to exert a specific and powerful action on the cardiac muscle in animals, and has been used in the treatment of heart conditions ever since its discovery in 1775.

The discovery of digitalis is accredited to the Scottish doctor William Withering, and makes for quite an interesting historical story. While working as a physician in Staffordshire in the 16th Century, his girlfriend got him interested in plants and botany—so much so, that in 1776 he published a huge treatise, whose title begins 'A botanical arrangement of all the vegetables growing in Great Britain,...' and goes on for a further 24 lines! By the age of 46 he'd become the richest doctor outside of London, and bought Edgbaston Hall in Birmingham, which is now Edgbaston Golf Club. Another of his claims to fame is that he owned the first water closet (indoor bathroom) in Birmingham!

In 1775, one of his patients came to him with a very bad heart condition and since Withering had no effective treatment for him, thought he was going to die. The patient, being an independent type, went instead to a local gypsy, took a secret herbal remedy—and promptly got much better!

When Withering heard about this, he became quite excited and searched for the gypsy throughout the by-ways of Shropshire. Eventually he found her, and demanded to know what was in the secret remedy. After much bargaining, the gypsy finally told her secret. The herbal remedy was made from a whole concoction of things, but the active ingredient was the **purple foxglove**, digitalis purpurea. The potency of digitalis extract had been known since the dark ages, when it had been used as a poison for the mediaeval 'trial by ordeal', and also used as an external application to promote the healing of wounds.

So, Withering tried out various formulations of digitalis plant extracts on 163 patients, and found that if he used the dried, powdered leaf, he got amazingly successful results. He introduced its use officially in 1785.
Even today, drugs based on digitalis extract, such as *Digitoxin* and *Digoxin*, are some of the best known treatments to control the heart rate. It works by increasing the intensity of the heart muscle contractions but diminishing the rate, and doses as low as 0.3mg daily are all that is needed. The exact mechanism is not really known, but the consensus is that it inhibits the Na/K pump. Since digitalis purpurea contains a mixture of several cardiac glucosides and also several saponins in amounts and proportions which vary with locality and with season, digitalis preparations vary considerably in potency and quality. Because of this, and the fact that the therapeutic dose is so small, it is very easy to exceed the safe dosage. Indeed, Withering recommended that the drug be diluted and administered repeatedly in small doses until a therapeutic effect became evident. This procedure was very effective in experienced hands, but was also very time-consuming. Nowadays, therefore, preparations from digitalis leaves are made using modern re-crystallization methods and are carefully standardized by bio-assay.