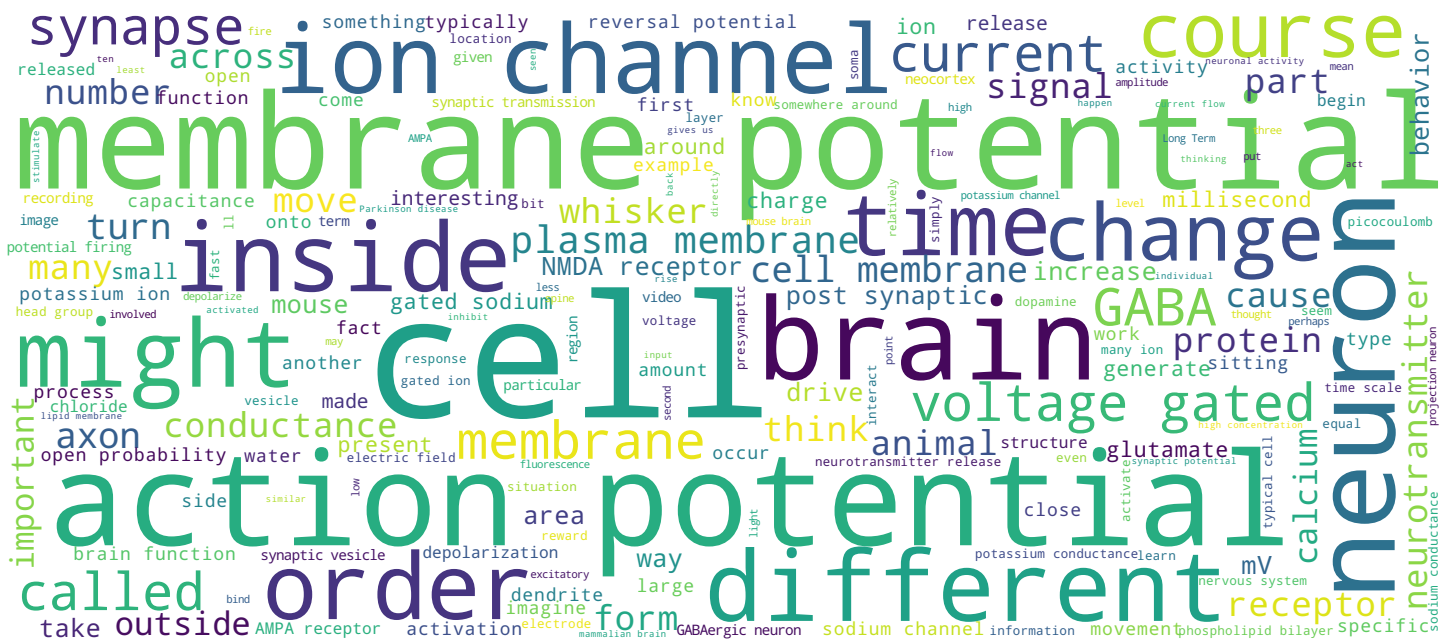


Cellular Mechanisms of Brain Function

Prof. Carl Petersen



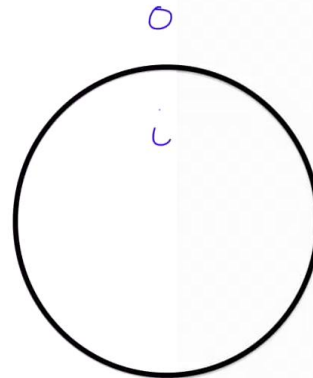
EPFL



The brain is made of cells



Cell



Cellular Mechanisms of Brain Function

The overall goal of this course is to obtain a causal and mechanistic understanding of brain function. We will be taking a bottom-up approach, and so the first thing we need to do is to look at the components: what makes the brain. Like every other organ of the body, the brain is made of cells. There are many types of brain cells, and each performs its own function. In order to get a causal understanding of the brain we therefore must study cellular mechanisms. The cell is a fundamental unit of organization of the brain. A key defining feature of a cell is the so-called cell membrane. It separates the inside of a cell from the outside of a cell. When the cell membrane evolved, some three billion years ago, presumably its primary advantage was to offer a stable intracellular environment for biochemical reactions to take place that wouldn't be affected by changes in the extracellular milieu. As we will learn, the brain has evolved to take exquisite advantage of the electrical properties of the cell membrane, and has turned this into a dedicated computational device working on transmembrane currents changing the electrical field across the plasma membrane.

Notes

Summary

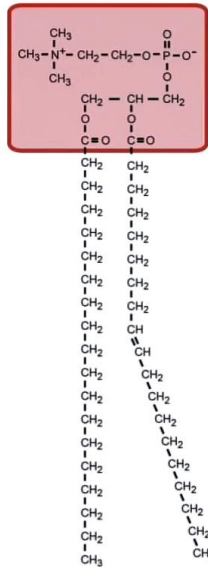


0m 04s

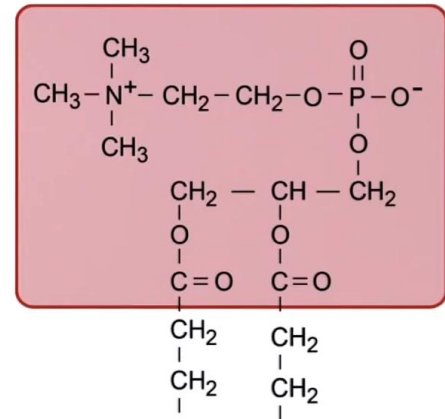
Phospholipids

Phosphate head group
- Polar, Hydrophilic

Hydrocarbon tails
- Non-polar, Lipophilic



Phosphatidylcholine



Cellular Mechanisms of Brain Function

The cell membrane is made of phospholipids, and this is a typical example of a phospholipid. It can be divided into two parts: a phosphate-containing head group, and long hydrocarbon chains. These long hydrocarbon chains are lipophilic, non-polar, and therefore they are hydrophobic, they don't like to interact with water. On the other hand, the phosphate head group that's shown magnified here, that links through the ester bonds to the hydrocarbon tails, is highly polar. It contains a phosphate group with oxygen atoms that carry strong negative charges. These negative charges like to interact with water, and the head group is polar and hydrophilic.

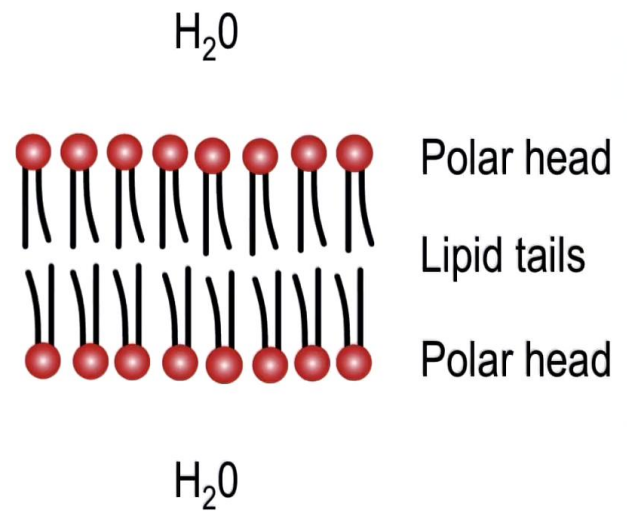
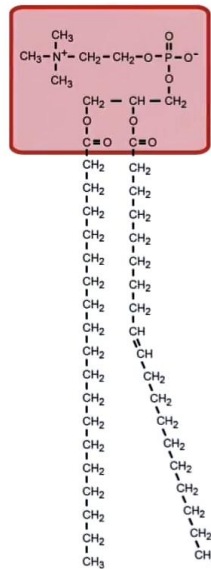
Notes

Summary



1m 42s

Phospholipid bilayers



Cellular Mechanisms of Brain Function

Phospholipids have remarkable properties. In water, they spontaneously form a variety of stable structures, a bit like droplets of oil in water. Of particular interest to us is the fact that phospholipids spontaneously form planar lipid bilayers in water. In a phospholipid bilayer, the polar head groups, containing the phosphate group, interact and are close to the aqueous phase of the solution. The lipid hydrocarbon tails join together the two leaflets of the membrane, and form a lipophilic core surrounded by hydrophilic edges here by the polar head group.

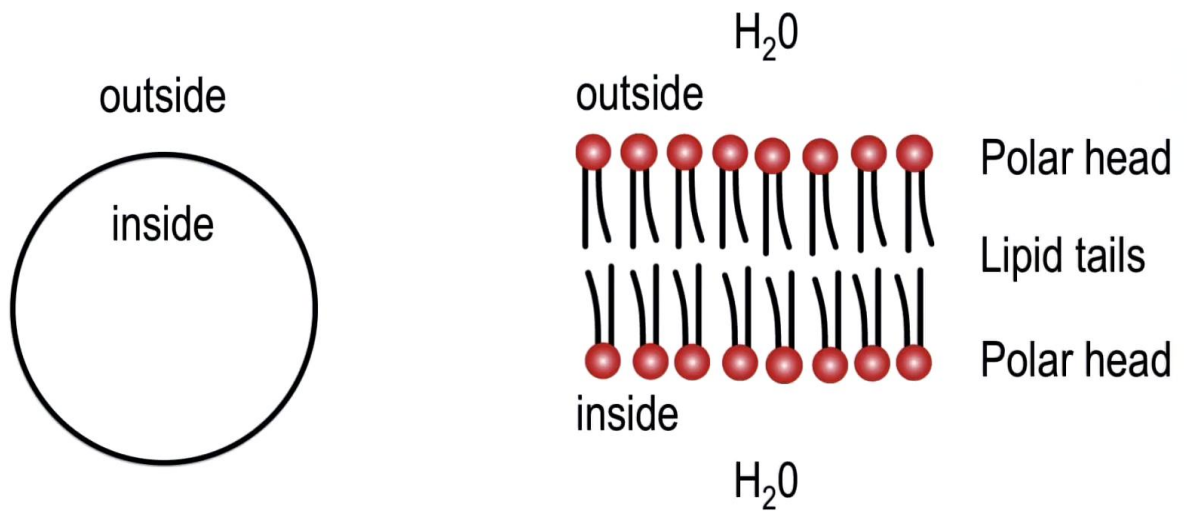
Notes

Summary



2m 44s

The cell membrane is a phospholipid bilayer



Cellular Mechanisms of Brain Function

The phospholipid bilayer then forms the membrane of the cell, separating the inside and the outside. Importantly, as we look at these static images, it's useful to think that actually, in the living cell, these are jiggling around and diffusing at high rates in the two-dimensional structure of the membrane.

Notes

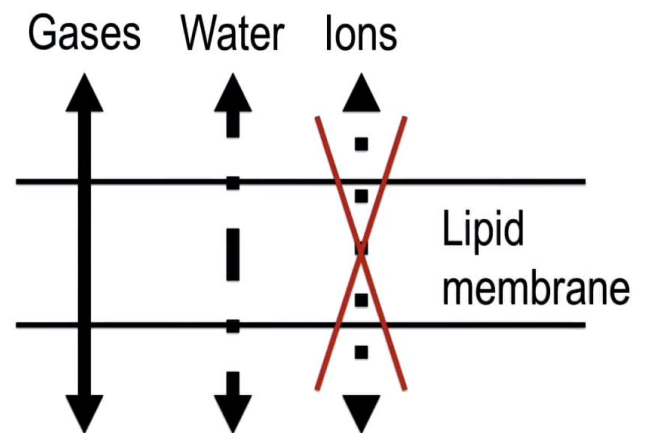
Summary



Membrane permeability

The lipid cell membrane is:

- highly permeable to gases and small uncharged molecules
- limited permeability to water
- impermeable to ions and charged molecules



Cellular Mechanisms of Brain Function

The most important feature of the phospholipid bilayer is that it is only permeable to lipophilic substances such as gases, lipids, and small non-polar molecules. The cell membrane has very limited permeability to water and, most importantly, the cell membrane is impermeable to ions, that is charged atoms, and other charged molecules. Ions are of enormous importance in all biology, but nowhere more so, than in the context of brain function. Ions are charged, and it this charge of the ions that forms the basis of electrical signaling in the nervous system.

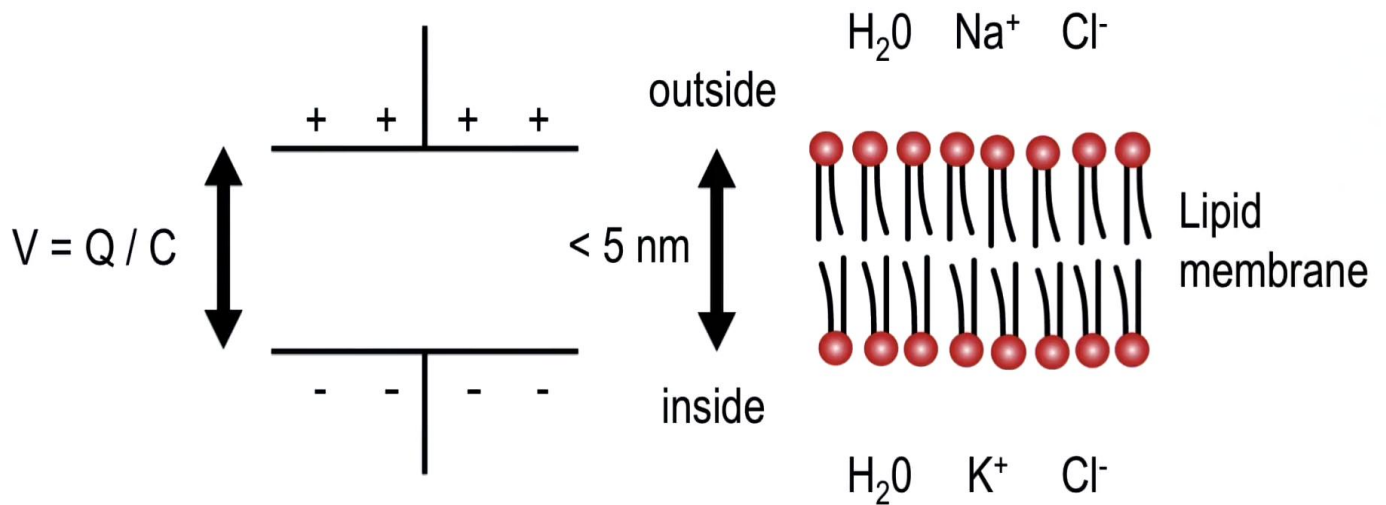
Notes

Summary



4m 09s

Membrane capacitance



V, voltage; Q, charge; C, capacitance

Cellular Mechanisms of Brain Function

That the cell membrane is impermeable to ions means that there can be different concentrations of ions on the two sides of the cell membrane. In a typical cell there is a high concentration of positively-charged potassium ions on the inside of a cell, and on the outside of a cell the extracellular solution contains high concentrations of positively-charged sodium ions and high concentrations of negatively-charged chloride ions. So the extracellular solution is made out of salt, just like the salt that we use in the kitchen. The plasma membrane is very thin. It's about five nanometers in thickness. And this very small distance allows the charged ions on one side of the membrane to interact, through electrostatic fields, with the charged membranes on the other side of the plasma membrane. The fact that the ions can't move across the membrane, but that they can interact through electrostatic forces, means that the lipid membrane is a capacitor, it's a dielectric, and there is electric fields that are strong across the lipid membrane. If ions are moved from one side of the membrane to another side of the membrane, they generate an electric field.

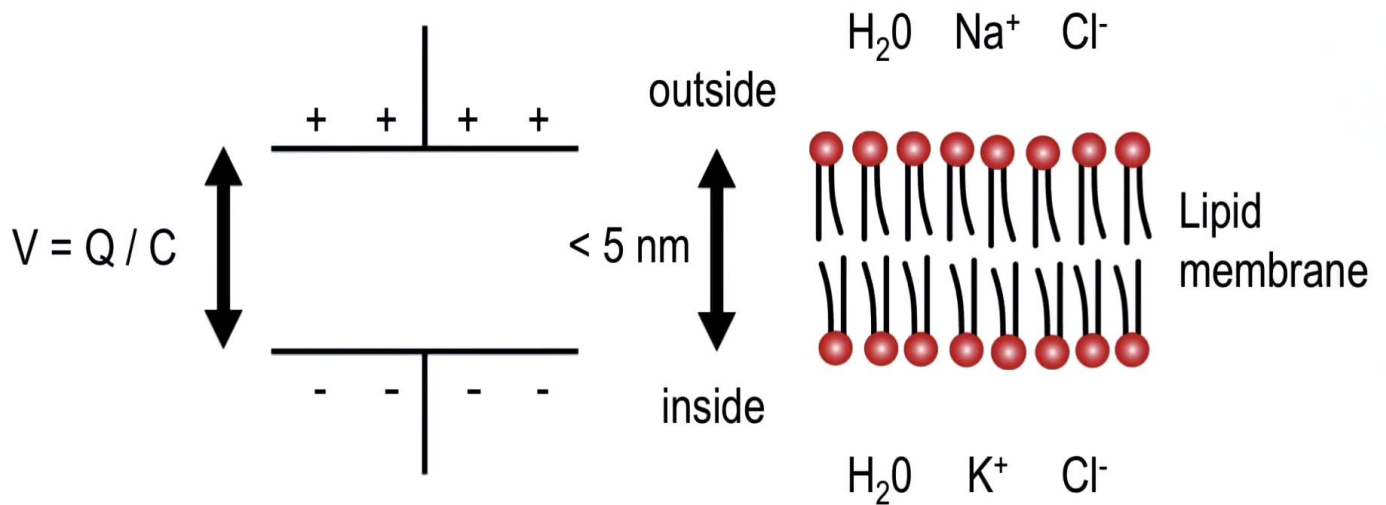
Notes

Summary



4m 58s

Membrane capacitance



V, voltage; Q, charge; C, capacitance

Cellular Mechanisms of Brain Function

And the potential difference, across the plasma membrane, is called the membrane potential. Membrane potential is of fundamental importance to neuroscience. That the lipid membrane can be considered electrically as a capacitor means that we can also apply some of the simple equations of physics to uncover the membrane biophysics. From physics we know that the potential of a capacitor is equal to the charge of that capacitor divided by the capacitance. And so by placing different amounts of charge on the two sides of the plasma membrane we can generate membrane potentials, and the amount of the membrane potential will depend upon the charge and the capacitance of the lipid membrane.

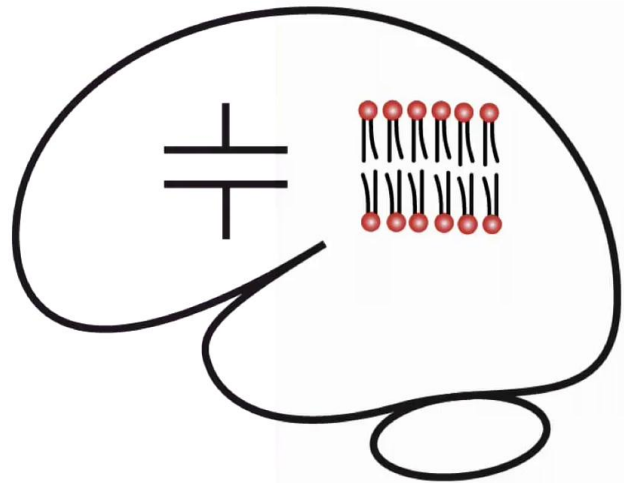
Notes

Summary



6m 33s

The cell membrane is a capacitor



Cellular Mechanisms of Brain Function

In this first lesson we've learned that the cell membrane is made of a phospholipid bilayer that's impermeable to ions, and is of about five nanometer thickness, allowing the cell membrane to act as an electrical capacitor. Charges separated on the different sides of the plasma membrane generate electric fields, a membrane potential, and this membrane potential is of fundamental importance, forming the basis of electrical cycling in the nervous system. Now I'd like to be a bit more specific, and get to some numbers, just some ballpark numbers from back of the envelope calculations so that you can see approximately how many ions, how much charge is involved in generating membrane potentials and electrical signals in biological cells.

Notes

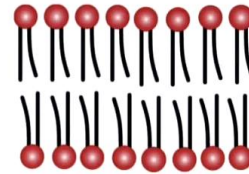
Summary



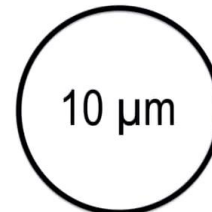
7m 31s

Some numbers - typical cell capacitance

Lipid membranes have a specific capacitance of $\sim 1 \mu\text{F} / \text{cm}^2$.



The capacitance of a typical cell is $\sim 10 \text{ pF} = 10 \times 10^{-12} \text{ F}$.



Cellular Mechanisms of Brain Function

The cell membrane has a specific capacitance that is a capacitance per unit area of around one microfarad per centimeter square. The area of a cell, of a small circular cell, with a radius of around 10 micrometers means that the capacitance of a typical cell is somewhere around 10 picofarad, a number useful to bear in mind when you're thinking about how the membrane biophysics of cells works.

Notes

Summary

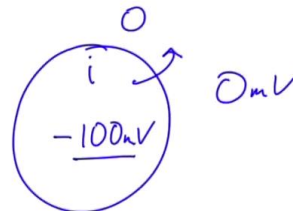


8m 29s

Some numbers - charge

- How much positive charge would need to move from the inside to the outside of a cell in order to give a membrane potential of -100 mV?

$$Q = C \cdot V$$



Hand-drawn diagram of a cell with a membrane potential of -100 mV and a capacitance of 10 pF.

$$\begin{aligned} Q &= C \times V \\ &= 10 \times 10^{-12} \times 0.1 \\ &= 10^{-12} \text{ C} \\ &= \underline{\underline{1 \text{ pC}}} \end{aligned}$$

Cellular Mechanisms of Brain Function

Knowing the capacitance of a cell, we can now calculate how much positive charge would need to move from the inside of a cell to the outside of a cell in order to generate a membrane potential of -100 mV. The outside of a cell, by convention, is always fixed to be at 0 mV. So we take our standard equation: charge is equal to the capacitance times the voltage. We agreed that the capacitance of a typical cell was somewhere around 10×10^{-12} farad, and the voltage is 0.1 volts. This gives us a charge of 10^{-12} coulomb, and that is one picocoulomb. So one picocoulomb of charge needs to move from the inside to the outside in order to generate a membrane potential of -100 mV.

Notes

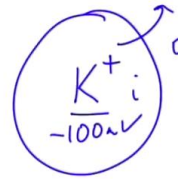
Summary



9m 06s

Some numbers – number of ions

- How many K^+ ions are in 1 pC ?



1pC

$$e = 1.6 \times 10^{-19} \text{ C}$$

$$\frac{10^{-12}}{1.6 \times 10^{-19}} = 6 \times 10^6$$

6 million K^+

$e = 1.6 \times 10^{-19} \text{ C}$
Elementary charge

Cellular Mechanisms of Brain Function

How many ions does that correspond to? So one picocoulomb of charge needs to move from the inside to the outside in order to generate a membrane potential of -100 mV. Now the inside of a cell contains a lot of potassium ions. And so let's wonder how many potassium ions it would take in order to move one picocoulomb. In order to make that calculation we need to look at the charge on each individual potassium ion. The potassium ions are monovalent, they carry a single charge, and that charge is then given by e , the elementary charge: 1.6×10^{-19} coulomb. And so in order to see how many ions is in one picocoulomb, we take 10^{-12} coulomb, and we divide it by 1.6×10^{-19} , and that gives us a number of 6×10^6 . So six million potassium ions need to move from the inside of a cell to the outside of a cell in order to generate -100 mV membrane potential in a small typical cell.

Notes

Summary



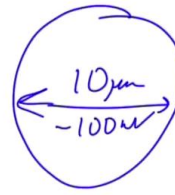
10m 18s

Some numbers – total number of ions in a cell

- Is 6 million ions a lot?
- How many ions are in a cell?
- Total number of ions in a cell =
Concentration x Volume x N_A

$$N_A = 6 \times 10^{23} \text{ mol}^{-1}$$

Avogadro constant



1 pl

$$[K^+]_i = 150 \text{ mM}$$

$$K^+ \text{ mol} = 0.15 \times 10^{-12} \text{ mol}$$

$$=$$

$$K^+_{\text{ion}} = 0.15 \times 10^{-12} \times 6 \times 10^{23}$$

$$= \underline{\underline{10^{11} \text{ ion } K^+}}$$

Cellular Mechanisms of Brain Function

Is six million ions a lot? Are there even six million ions inside a cell? Well let's find out. How many ions are there inside a cell? A cell has a diameter of around 10 micrometers. The volume is then around one picoliter, and in order to work out how many mole of potassium there are inside this we then need to know the potassium concentration and the intracellular potassium concentration of a typical nerve cell is sitting at around 150 millimolar. So the number of moles of potassium inside a typical cell is then 0.15×10^{-12} , and that is then the number of mole in a given cell. In order to find out how many ions that is, we'll then need to multiply this number by Avogadro's number. And so the total number of ions, then, is equal to the above number, $0.15 \times 10^{-12} \times$ Avogadro's number, 6×10^{23} , and that gives us a final number of 10^{11} ions of potassium inside an individual cell. So we found that we needed to move six million ions to generate the -100 mV membrane potential, but inside a cell we have 10^{11} ions, 100 thousand times more than are needed to generate the electric field.

Notes

Summary



11m 51s

Electrical signals in cells



- Only a small fraction of the total number of intracellular ions need to redistribute to generate biologically relevant membrane potentials.
- The membrane potential can change dramatically without substantially changing ionic concentrations.

Cellular Mechanisms of Brain Function

This back of the envelope calculation has told us a number of useful things. Most importantly, we find that only a small fraction of the total number of ions inside a cell need to move across some plasma membrane in order to generate biologically- relevant membrane potentials. This means that electrical cycling can be extremely efficient. You can generate large changes in membrane potential without changing the intracellular concentrations. As we will see in the next lessons, the nervous system has evolved specific mechanisms to move ions across the plasma membrane and rapidly change membrane potential, and this forms the underlying signals that drive brain function and neuronal computations.

Notes

Summary



13m 52s