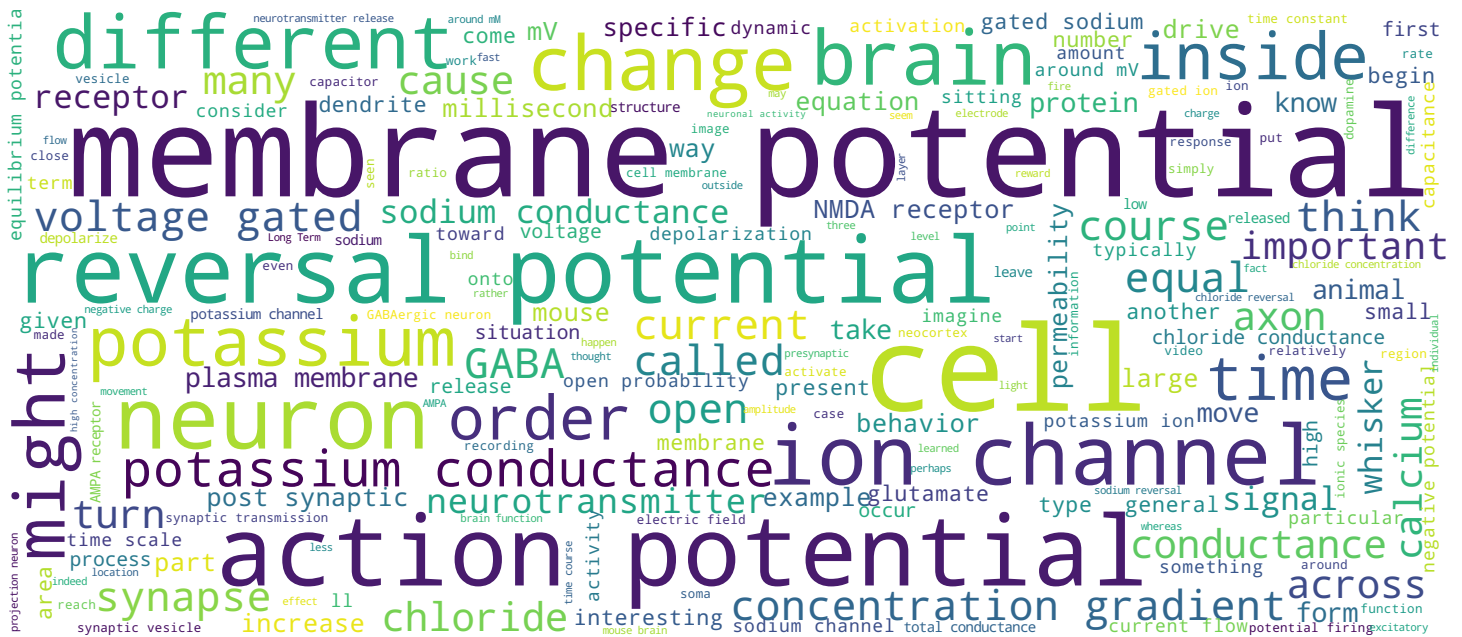
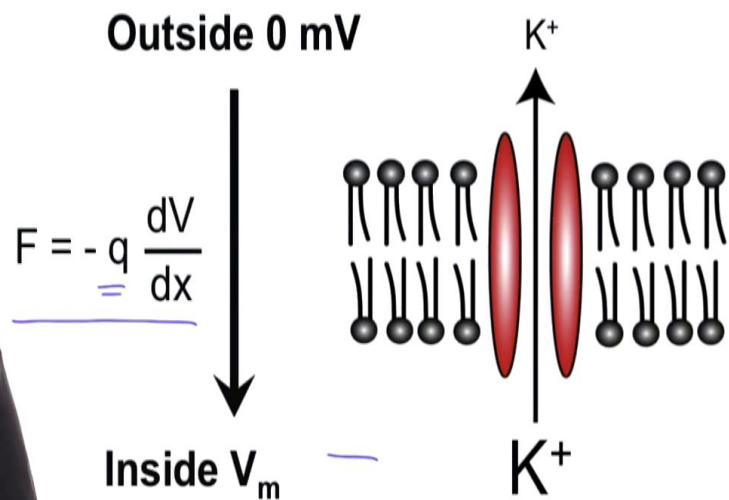


## Cellular Mechanisms of Brain Function

Prof. Carl Petersen



# Electrochemical diffusion



Cellular Mechanisms of Brain Function

In the last lessons we learned that the phospholipid bilayer of the cell membrane electrically acts as a capacitor, and that transmembrane ion channel proteins act as conductances for specific ions. In this lesson, we'll see how the biophysical properties of electrochemical diffusion determine the membrane potential. Let us begin by considering a piece of membrane with a potassium-selective ion channel in it. There are two main forces that act upon the potassium ions. As we've already discussed, there's an electrical potential across the cell membrane, the membrane potential. That membrane potential causes an attraction or a repulsion for ions of a given charge. If we have a negative potential on the inside then potassium ions will be attracted inside, down the electric-field gradient. In general, there's a force applied to any charged ion that depends upon the spatial gradient of the electric field. So one major determinant of ionic movement across ion channels is the electric field. The other major push that moves ions from one side of a membrane to another is concentration.

Notes

Summary



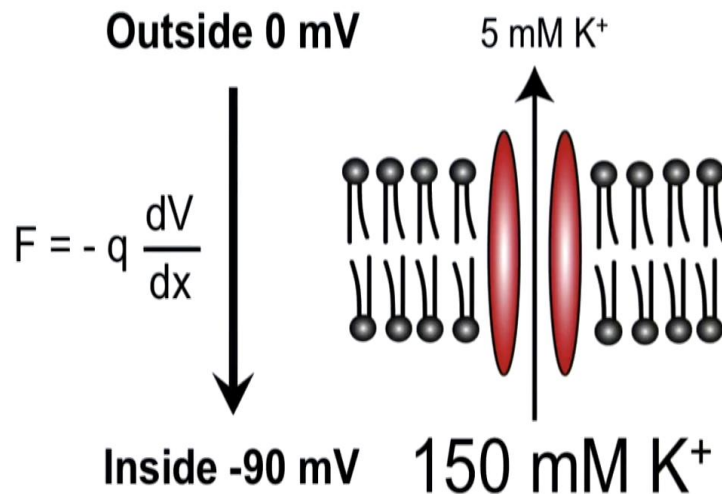
0m 04s

# Nernst equilibrium potential

$$E_{K^+} = \frac{RT}{zF} \ln \frac{[K^+]_o}{[K^+]_i}$$

$$E_{K^+} = 61.5 \log_{10} \frac{5}{150}$$

$$E_{K^+} = \sim -90 \text{ mV}$$



Cellular Mechanisms of Brain Function

If there's a concentration gradient so that, for example, potassium might be high inside a cell compared to the outside of a cell, then naturally there's a gradient for potassium to flow down the concentration gradient. The electrical and the concentration gradients are the two main forces that drive electrochemical diffusion across the plasma membrane. The two forces: the concentration gradient and the electrical gradient, can oppose each other, and can precisely bounce each other out so that at one specific membrane potential it might prevent the overall net flux of ionic flow induced by concentration gradients. For example, for the case of potassium, which is very high inside a cell, there's a natural tendency for potassium to want to leave a cell down its concentration gradient of about 150 mM inside to about 5 mM potassium outside a cell. If we make the inside of a cell more negative, then that will then try to attract positive ions inside the cell. If we make the membrane potential very negative, for example -90 mV, it's so negative that that precisely counters the flow of ions induced by the concentration gradient.

Notes

Summary



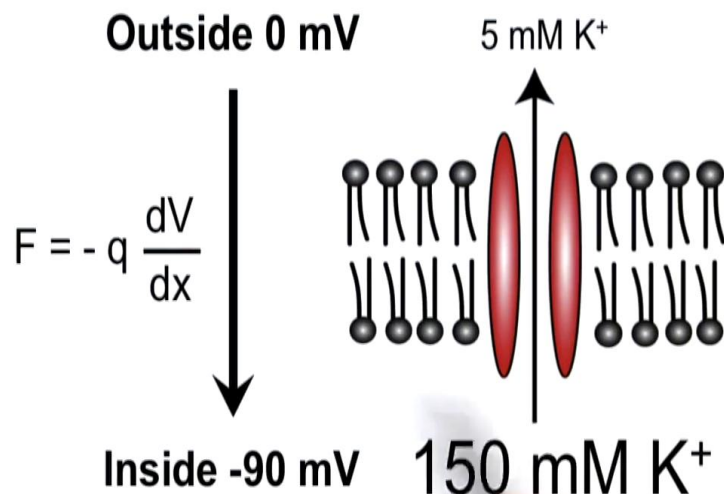
1m 41s

# Nernst equilibrium potential

$$E_{K^+} = \frac{RT}{zF} \ln \frac{[K^+]_o}{[K^+]_i}$$

$$E_{K^+} = 61.5 \log_{10} \frac{5}{150}$$

$$E_{K^+} = \sim -90 \text{ mV}$$



Cellular Mechanisms of Brain Function

The reversal potential is the potential at which there's no net flux of ions, and that can be calculated exactly from biophysical considerations. The Nernst equation, here described for potassium ions, precisely describes the relationship of the potential at which an ion, given the intracellular and extracellular concentrations are in precise match, so that there's an equilibrium, and no net flux of ions across the potassium-selective conductance. The Nernst equation describes that the reversal potential is given by the gas constant, Avogadro's gas constant, the temperature in kelvins, divided by the Faraday constant, and Z is the charge on the ion. For potassium, that's +1, for chloride, it's -1, and for calcium, it's +2, so that's the charge associated with the ionic species. RT over zF multiplies the logarithm of the ratio of the outside to the inside ionic concentration. At 37 degrees Celsius, so that's at physiological temperatures, RT over zF for a monovalent, positively-charged ion, and converting this to a base 10 logarithm, gives us a 61.5 times base 10 logarithm of the ratio of the outside to the inside potassium concentrations, here we've set as 5 mM potassium; outside, 150 mM of potassium.

Notes

Summary

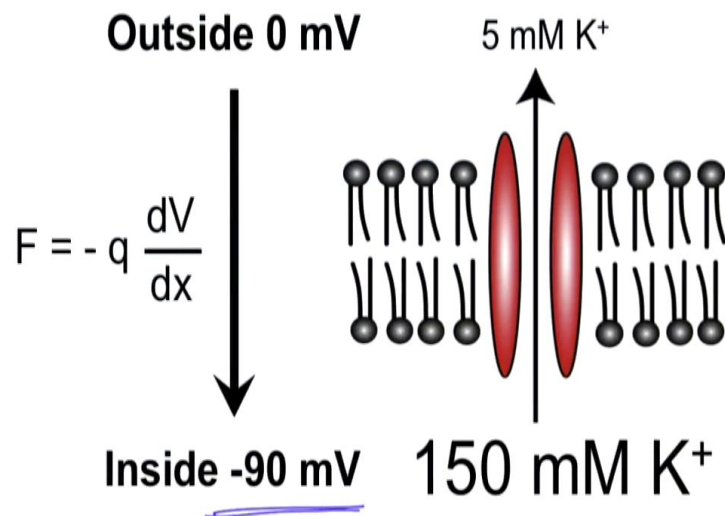


# Nernst equilibrium potential

$$E_{K^+} = \frac{RT}{zF} \ln \frac{[K^+]_o}{[K^+]_i}$$

$$E_{K^+} = 61.5 \log_{10} \frac{5}{150}$$

$$E_{K^+} = \sim -90 \text{ mV}$$



Cellular Mechanisms of Brain Function

Inside, if we do the math, we find out that that comes out with a reversal potential of -90 mV. That's the membrane potential that's needed to counter the concentration gradient that tries to drive potassium out. We counter that by having a negative potential on the inside that tries to attract the potassium channels in, and at this potential, with these concentrations, it's precisely balanced, it's at equilibrium, at the Nernst equilibrium potential.

Notes

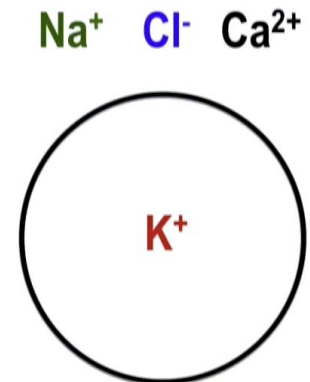
Summary



5m 12s

# Ion concentrations

Ion	Intracellular	Extracellular
$K^+$	150 mM	4 mM
$Na^+$	12 mM	145 mM
$Cl^-$	5 mM	120 mM
$Ca^{2+}$	100 nM	1 mM



Cellular Mechanisms of Brain Function

Although potassium is the most important ion in determining membrane potential, it is certainly not the only one. And so we need to find out what the relevant biological concentrations are of ions on the intracellular and extracellular side. And in general, these are approximate values, but are entirely indicative. The potassium ions are high intracellularly at about 150 mM, and extracellularly low at about 4 mM. Sodium ions are low inside cells, around 12 mM, and extracellularly they're high, at somewhere around 140 mM. Chloride concentration is also low inside cells, around 4 or 5 mM, and extracellularly is high at around 120 mM. Calcium ions are low inside cells, at about 100 nM, and much higher outside, around 1-2 mM outside cells. These concentrations, inside and outside, can then be plugged into the Nernst equilibrium potential to define the reversal potentials of these different ionic species.

Notes

Summary



5m 47s

# Equilibrium potentials

Ion	Intracellular	Extracellular	$E_{ion}$
$K^+$	150 mM	4 mM	-97 mV
$Na^+$	12 mM	145 mM	+67 mV
$Cl^-$	5 mM	120 mM	-85 mV
$Ca^{2+}$	100 nM	1 mM	+123 mV

Cellular Mechanisms of Brain Function

As before, we see that the reversal potential for potassium ions is very negative. The sodium ions have positive reversal potentials, and the reason is that the relative concentrations of sodium and potassium are opposite to each other. Potassium concentrations are high inside the cell, and so potassium wants to leave the cell. In order to counter that concentration gradient of potassium wanting to leave the cell, we can apply a negative potential to try and attract those positive ions back to reach an equilibrium situation where potassium has no net flux through potassium-selective ion channels. For sodium, the situation's different. We have a high extracellular concentration of sodium. Sodium wants to flow inside a cell, and in order to prevent that flux we would have to have a positive potential inside a cell that would then repel the positively-charged sodium ions, and so we have a positive reversal potential for sodium. For chloride we have a similar situation as with sodium, in that it's high extracellularly, and low intracellularly, so chloride, through its diffusion down the concentration gradient, wants to enter a cell, and bring negative charges inside a cell, and in order to prevent that, we would then have to have a negative potential that would then repel the negatively-charged chloride ions from entering the cell.

Notes

Summary



7/m 08s



# Equilibrium potentials

Ion	Intracellular	Extracellular	$E_{ion}$
$K^+$	150 mM	4 mM	-97 mV
$Na^+$	12 mM	145 mM	+67 mV
$Cl^-$	5 mM	120 mM	-85 mV
$Ca^{2+}$	100 nM	1 mM	+123 mV

Cellular Mechanisms of Brain Function

And, finally, calcium has an enormous concentration gradient, 10,000 times more calcium outside a cell than inside, and that then naturally means that whenever a calcium conductance opens, calcium flows inside the cell, and you need to go to very positive potentials in order to reverse the effect of a calcium conductance.

Notes

Summary



8m 41s



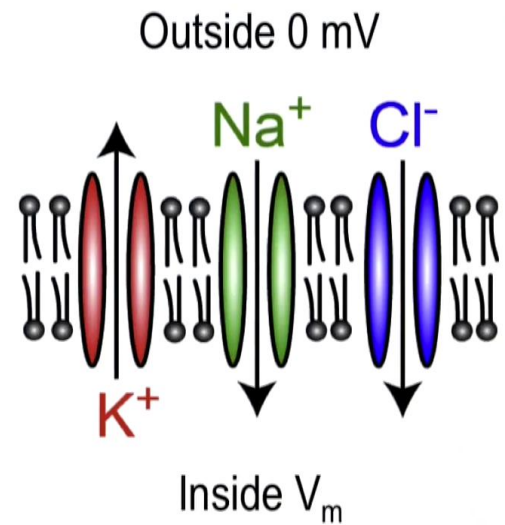
# Goldman-Hodgkin-Katz (GHK) equation

$$V_m = \frac{RT}{F} \ln \frac{P_{K^+}[K^+]_o + P_{Na^+}[Na^+]_o + P_{Cl^-}[Cl^-]_i}{P_{K^+}[K^+]_i + P_{Na^+}[Na^+]_i + P_{Cl^-}[Cl^-]_o}$$

$$P_{K^+} : P_{Na^+} : P_{Cl^-} = 1 : 0.04 : 0.45$$

$$V_m = 61.5 \log_{10} \frac{4 + 5.8 + 2.25}{150 + 0.48 + 54}$$

$$V_m = -76 \text{ mV}$$



Cellular Mechanisms of Brain Function

In general, a cell has permeability to many different types of ions. And so there are permeabilities to potassium, sodium and chloride that are all mixed on the plasma membrane of a single cell. And indeed, an individual ion channel, although primarily selective for, say, potassium, would also have some degree of permeability for other ions, and so even a single ion channel opening doesn't have a reversal potential that's exactly that of an individual ionic species, but rather it would be a mixed permeability of several different ions. In order to calculate the equilibrium potentials when there are permeabilities to several different ions, one can use the Goldman-Hodgkin-Katz equation, which is a modified version of the Nernst potential. And it states that the equilibrium potential is equal to  $RT$  over  $F$  again times a natural logarithm of the permeability to potassium times the extracellular potassium concentration, plus the permeability to sodium times the extracellular sodium concentration, plus the permeability to chloride times the intracellular chloride concentration divided by the permeability to potassium times the intracellular concentration of potassium plus the permeability to sodium times the intracellular sodium concentration plus the permeability to chloride times the extracellular chloride concentration.

Notes

Summary



9m 05s

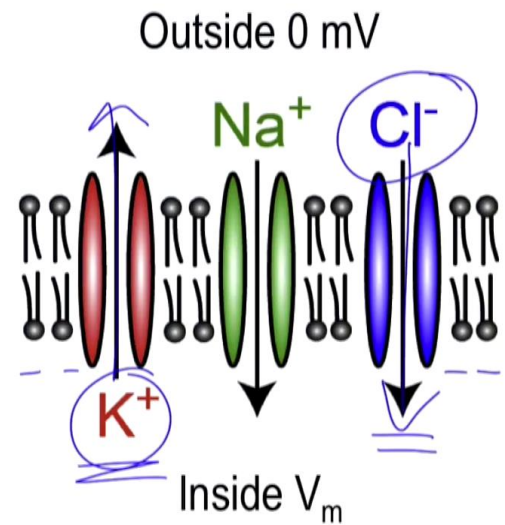
# Goldman-Hodgkin-Katz (GHK) equation

$$V_m = \frac{RT}{F} \ln \frac{P_{K^+}[K^+]_o + P_{Na^+}[Na^+]_o + P_{Cl^-}[Cl^-]_i}{P_{K^+}[K^+]_i + P_{Na^+}[Na^+]_i + P_{Cl^-}[Cl^-]_o}$$

$$P_{K^+} : P_{Na^+} : P_{Cl^-} = 1 : 0.04 : 0.45$$

$$V_m = 61.5 \log_{10} \frac{4 + 5.8 + 2.25}{150 + 0.48 + 54}$$

$$V_m = -76 \text{ mV}$$



Cellular Mechanisms of Brain Function

Note that whereas here we have the extracellular concentration for the positively charged cations of potassium and sodium, here we have the intracellular concentration of chloride, because this is negatively charged. As an example we can consider a cell that has a relative permeability ratio of potassium, to sodium to chloride of 1 to .04 to .45. So this would be a cell that has a high potassium conductance, a much lower sodium conductance, and an intermediate chloride conductance. If we plug the numbers in, and the concentrations from the previous slide, we reach a situation where the equilibrium potential for this particular cell, with a high potassium permeability and a high chloride permeability has a membrane potential of around -76 mV. And so in this case we have a negative membrane potential, and that's because our permeability is dominated by potassium and chloride. Potassium has a high concentration inside a cell, it wants to leave, and so that creates negative charges. Chloride has a high concentration outside cells, and therefore wants to enter, again bringing in negative charges. And so you can see that at resting conditions, at equilibrium, we would expect hyperpolarized, negative membrane potentials, sitting somewhere close to the potassium and chloride reversal potentials, in this case -76 mV.

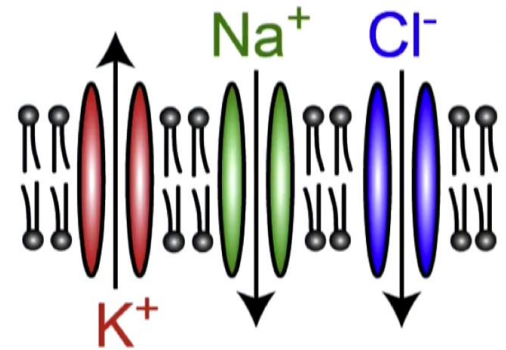
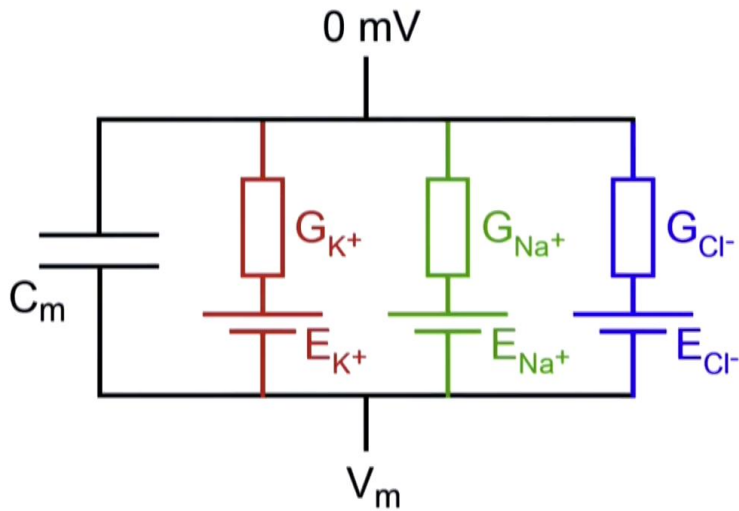
Notes

Summary



10m 46s

# Electrical equivalent of a cell



Cellular Mechanisms of Brain Function

We can now also return to our electrical model of a cell. As before, we have membrane capacitance formed by the lipid bilayers. We have ionic conductances where we now add the reversal potentials for the individual species, so we have a potassium conductance with a reversal potential of potassium, and that's here, this potassium ion channel. We have sodium conductances with the reversal potential of sodium going through the sodium ion channels, and we have chloride conductances, chloride ion channels, again with their own reversal potential.

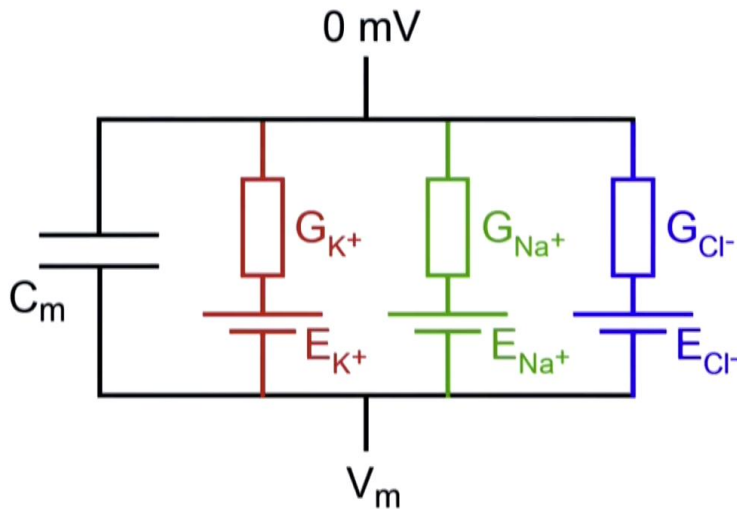
Notes

Summary



12m 38s

# Electrical equivalent of a cell



Ohm's law:

$$V = I R$$

$$I = V G$$

$$R = 1/G$$

Capacitance:

$$Q = C V$$

$$I = C dV/dt$$

$$I = \frac{dQ}{dt}$$

Cellular Mechanisms of Brain Function

Notes

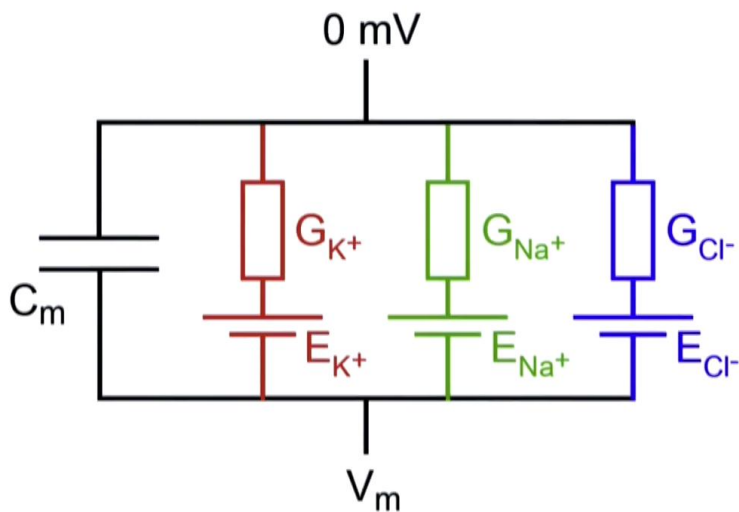
We can use our two simple electrical equations to derive some interesting facts about how the membrane potential behaves. We can use Ohm's law, thinking about the ionic conductances where we have the voltage is equal to the current flow times the resistance, and we know that the resistance is 1 over the conductance, so we can rewrite that, and say that the current flow is equal to the voltage times the conductance. And for the capacitance we know that the charge stored in a capacitor is equal to the capacitance times the voltage. We also know that a current is equal to the rate of change of charge. And so we can differentiate this equation to give us the capacitive current flow, which is equal to the derivative of this. The capacitance times dV by dt.

Summary



13m 23s

# Electrical equivalent of a cell



$$I_m = I_C + I_{K^+} + I_{Na^+} + I_{Cl^-}$$

$$I_C = C_m dV_m/dt$$

$$I_{K^+} = (V_m - E_{K^+}) G_{K^+}$$

$$I_{Na^+} = (V_m - E_{Na^+}) G_{Na^+}$$

$$I_{Cl^-} = (V_m - E_{Cl^-}) G_{Cl^-}$$

Cellular Mechanisms of Brain Function

If we now think about the electrical circuit of the cell we can say that the total transmembrane current,  $I_m$ , can be composed of four different channels. There's the capacitive current,  $I_C$ . We have a potassium current,  $I_K$ . We have a sodium current,  $I_{Na}$ , and we have a chloride current,  $I_{Cl}$ . And that's what we have here, we simply sum up these different conductances. Now we've already said that the capacitive conductance is equal to  $C, dV, dt$ . We can, by inspection, see that the potassium conductance is equal to the difference between the membrane potential and the reversal potential of potassium times the potassium conductance, and so on for sodium and for chloride. At the membrane potential that is equal to the reversal potential, there's no current flux, as expected.

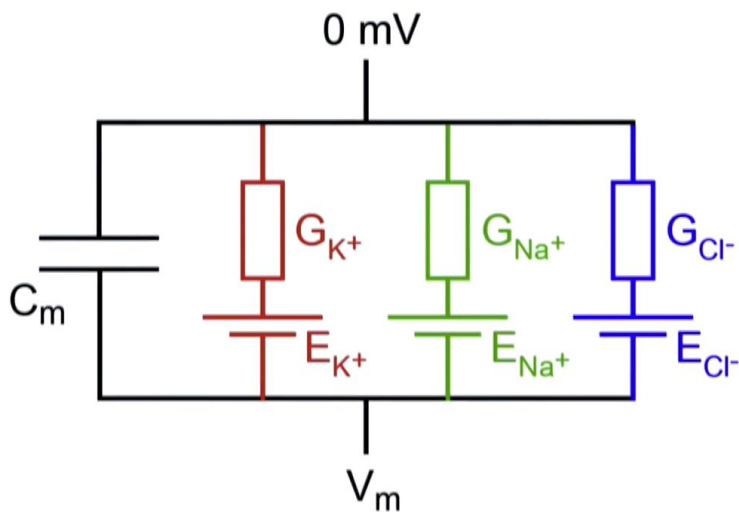
Notes

Summary



14m 23s

# Ion conductances determine $V_m$



Solving for steady state  $V_m$   
( $I_m = 0$  and  $dV_m/dt = 0$ )

$$G_{\text{Total}} = G_K + G_{Na} + G_{Cl}$$

$$V_m = \frac{G_K}{G_{\text{Total}}} E_K + \frac{G_{Na}}{G_{\text{Total}}} E_{Na} + \frac{G_{Cl}}{G_{\text{Total}}} E_{Cl}$$

Cellular Mechanisms of Brain Function

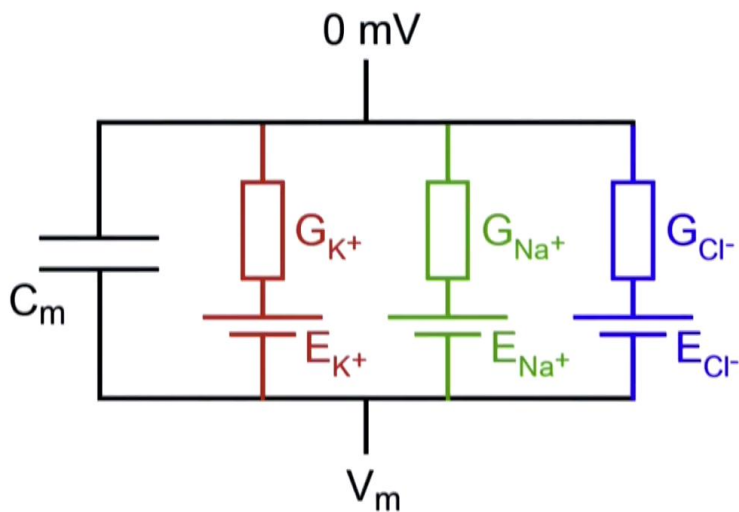
Now, we can put these equations together and solve for membrane potential, and we can do it under one interesting condition, the steady-state equilibrium condition where the total transmembrane current is zero, and by definition, the rate of change of membrane potential is also zero. In order just to simplify the writing of our equations, we can consider the total conductance of the cell as being the sum of the potassium, sodium and chloride conductances. The solution to the equation we presented on the previous slide then has that the membrane potential is equal to the ratio of the potassium conductance, relative to the total conductance times the reversal potential of potassium plus the ratio of the sodium conductance to the total conductance times the reversal potential of sodium plus the ratio of the chloride conductance to the total conductance times the reversal potential of chloride. So in order to change the membrane potential, what we have to do is to change the relative importance of each of these ionic conductances. If we want to have a membrane potential that's quite close to the reversal potential of potassium, then the potassium conductance should dominate the total conductance.

Notes

Summary



# Ion conductances determine $V_m$



Solving for steady state  $V_m$   
( $I_m = 0$  and  $dV_m/dt = 0$ )

$$G_{\text{Total}} = G_K + G_{\text{Na}} + G_{\text{Cl}}$$

$$V_m = \frac{G_K}{G_{\text{Total}}} E_K + \frac{G_{\text{Na}}}{G_{\text{Total}}} E_{\text{Na}} + \frac{G_{\text{Cl}}}{G_{\text{Total}}} E_{\text{Cl}}$$

Cellular Mechanisms of Brain Function

Similarly, if we want to have a membrane potential that begins to approach the reversal potential of sodium, then the sodium conductance should dominate the total conductance of the cell. By inspecting this equation you can see that it's very easy to change the membrane potential of a cell. All you need to do is to change the conductance of different ionic species, and you'll change the membrane potential, forcing it towards these different reversal potentials that are being driven to by the conductances.

Notes

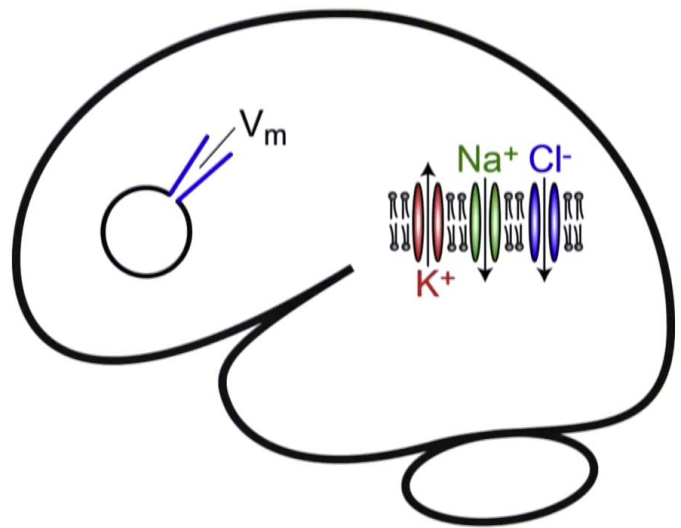
Summary



16m 56s



# Membrane potential - $V_m$



Cellular Mechanisms of Brain Function

So we've now seen that simple biophysical laws determine electrochemical diffusion. Concentration gradients and electrical fields determine the flux of ions across the plasma membrane. We can define reversal potentials given by the Nernst potential, and we can see that it's easy to move the membrane potential from one value to another by simply changing the relative permeability of the plasma membrane to specific ionic species, each of which have their own reversal potential, determined by their concentration gradients. Let's next consider some specific examples, and get towards some numbers and dynamics as to how membrane potential changes when ion channels open.

Notes

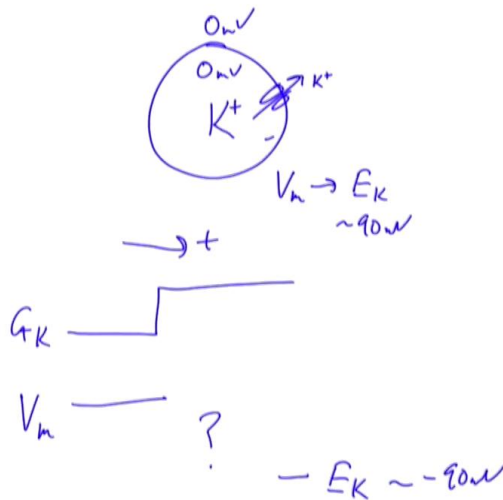
Summary



17m 35s

# Some numbers – $K^+$ conductance and $V_m$

What happens to  $V_m$  if  $K^+$  channels increase their open probability?



Cellular Mechanisms of Brain Function

Let's consider what happens if potassium channels suddenly increase their open probability. Let's imagine we start off with a simple situation where the membrane potential is at 0 mV initially. We have a potassium-rich intracellular, and lower concentration of potassium outside the cell. A potassium conductance suddenly opens, and of course potassium ions want to leave, and go down the concentration gradient, and create a negative potential inside. We've just learned that there's a potential to which the membrane potential will tend to. The membrane potential will go towards the reversal potential for potassium, which is around -19 mV. But let's think about the dynamics of the situation. If we have time running here, we begin and think about the potassium conductance. It starts off low, and at some stage it suddenly jumps up. Membrane potential we say starts at 0 mV, and we know that at equilibrium it's going down to the reversal potential of potassium, at around -19 mV. What are the dynamics? How does the membrane potential reach the equilibrium potential for potassium? Let's return to our electrical equivalent of a cell, where we have a capacitance, and we have a conductance.

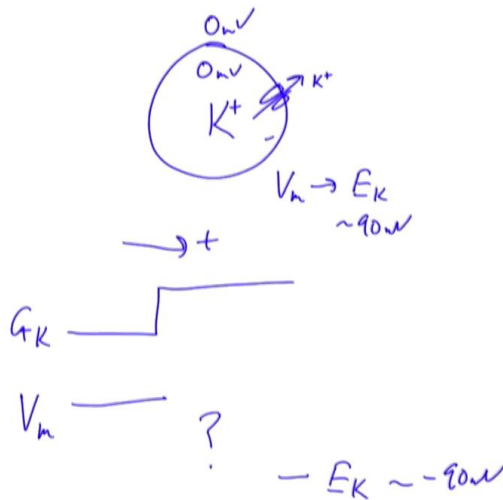
Notes

Summary



# Some numbers – K<sup>+</sup> conductance and V<sub>m</sub>

What happens to V<sub>m</sub> if K<sup>+</sup> channels increase their open probability?



$$Q = CV$$

$$I = \frac{dQ}{dt} = C \frac{dV}{dt}$$

$$V = E + IR$$

$$V = E - RC \frac{dV}{dt}$$

$$V = E_K (1 - e^{-t/\tau})$$

Cellular Mechanisms of Brain Function

And together they define the membrane potential and its dynamics. We then have a potassium reversal potential, and we have a resistor or a conductor, depending on how we want to think about it. We know from capacitors equations that  $Q$  is equal to  $CV$ , and that the current flowing in the capacitor is a derivative, the rate of change of charge over time:  $C, dV$  by  $dt$ . We also know that the membrane potential, from considering this arm of the equation, that the membrane potential is equal to  $E + IR$ . That's simply just the Ohm's law here, if we consider this as a resistor here, just for the sake of simplicity. Now this current that's flowing through here, in this particular case that we're thinking about, is actually the capacitive current. We can therefore rewrite this equation as  $V$  equals  $-RC, dv$  by  $dt$ , and the minus sign is because they're flying in opposite directions, in terms of the electrical circuit diagram. You can solve this equation, and because it's a differential equation you expect to find exponentials present in it, and you find out that the solution can be written in this form. Here  $\tau$  (tau) is a membrane time constant, which is equal to the resistance times the capacitance.

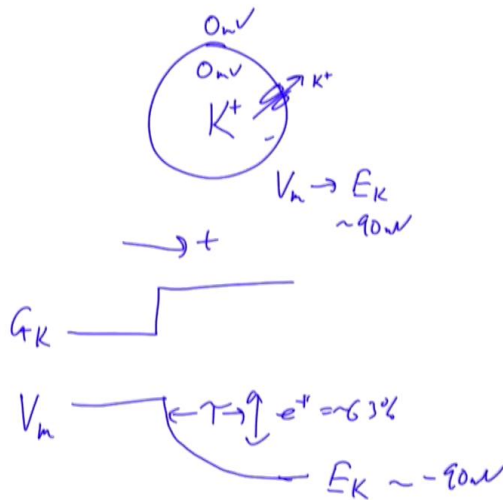
Notes

Summary



# Some numbers – K<sup>+</sup> conductance and V<sub>m</sub>

What happens to V<sub>m</sub> if K<sup>+</sup> channels increase their open probability?



$$Q = CV$$

$$I = \frac{dQ}{dt} = C \frac{dV}{dt}$$

$$V = E + IR$$

$$V = E - RC \frac{dV}{dt}$$

$$V = E_K (1 - e^{-t/\tau})$$

$$\tau = RC = C/G_K$$

Cellular Mechanisms of Brain Function

You can check this equation, of course, by plugging it in and seeing that it comes out correct. So what we see, from this equation here, is that at times zero, the membrane potential is indeed 0. At time infinite, this disappears, and we reach the reversal potential for potassium, and in between we have an exponential time course that then brings us to the reversal potential of potassium, and that is characterized by a time scale  $\tau$  (tau), over which it goes to 1 over E of the membrane potential, so that's about 63 percent. That time course,  $\tau$  (tau), is given by the resistance times the capacitance, which is also the capacitance divided by the conductance. So the rate of change of membrane potential in a cell is determined by a number of different factors. If the cell has a high resistance, a low conductance, then the time course is long, it takes a long time to change. If the capacitance is high, then it also takes a long time to change, and both of those factors make sense. If there's very little conductance then it takes time to move sufficient charge to change the membrane potential. If the capacitor's very large, we need a lot of ions to change the membrane potential. This equation, then, tells us also that membrane potential can't change instantaneously, rather it changes with a time scale that is equal to RC, the membrane time constant.

Notes

Summary



21m 50s

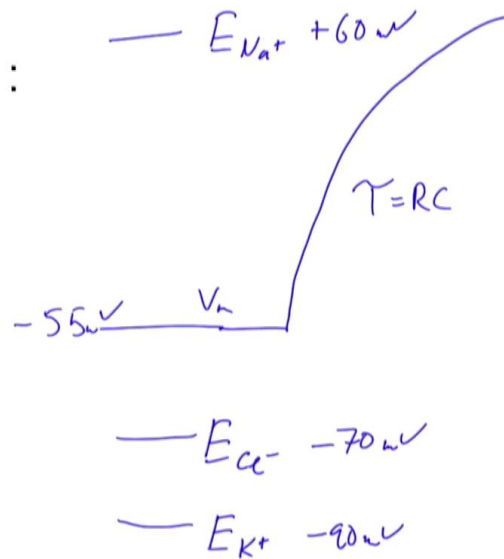
# Some numbers – $K^+$ , $Na^+$ , $Cl^-$ conductances and $V_m$

What happens to  $V_m$  if :

i)  $G_{K^+}$  increases

ii)  $G_{Na^+}$  increases

iii)  $G_{Cl^-}$  increases



Cellular Mechanisms of Brain Function

In general, of course, potassium conductances aren't the only important conductance in a cell, and we have to consider both potassium, sodium, and chloride conductance changes if we want to understand how the membrane potential moves. We know that at equilibrium membrane potential will be driven towards the potassium reversal potential, if the potassium conductance increases it'll be driven towards the sodium reversal potential. If sodium conductance increases it'll be driven towards the chloride reversal potential, if a chloride conductance increases. And, typically, this is sitting at  $+60mV$  minus  $90mV$  for potassium and around  $-70mV$  for chloride. If we then begin with a membrane potential sitting at  $-55mV$ , and that's our membrane potential, and we open a sodium conductance then with an exponential time cross we head towards the sodium reversal potential. Again, this membrane potential doesn't occur instantaneously, but depends upon the membrane time constant  $RC$ . If we open a chloride conductance then the membrane potential tends towards the chloride reversal potential, and so on, also, for the potassium conductance.

Notes

Summary



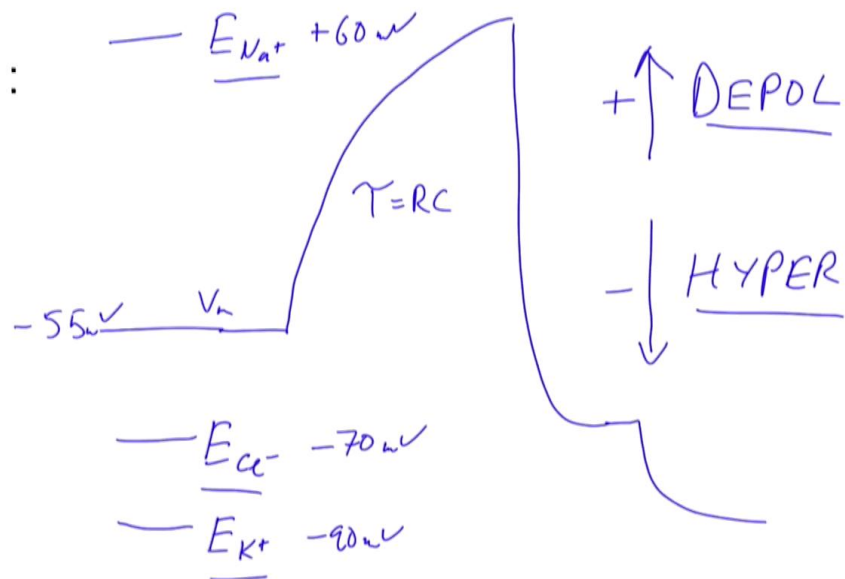
# Some numbers – $K^+$ , $Na^+$ , $Cl^-$ conductances and $V_m$

What happens to  $V_m$  if :

i)  $G_{K^+}$  increases

ii)  $G_{Na^+}$  increases

iii)  $G_{Cl^-}$  increases



Cellular Mechanisms of Brain Function

So we can move membrane potential by simply opening the conductance for sodium, and then it goes towards the sodium reversal potential, towards the chloride reversal potential, or towards the potassium reversal potential. In general, if we make the membrane potential more positive, this is called a depolarization. And if we make the membrane potential more negative, then it's called a hyperpolarization, and these are terminologies that we'll consider and talk about a lot in the next lessons. Depolarization for more positive membrane potentials, and hyperpolarization for more negative potentials. And so if you want to hyperpolarize a neuron we need to open a chloride or a potassium conductance, and if you want to depolarize a neuron we want to open a sodium conductance.

Notes

Summary



25m 23s



# Membrane potential



- Electrochemical diffusion describes ion flow through ion channels and defines Nernst equilibrium potentials.
- Independently regulated ion channel conductances with selective permeability control membrane potential.

Cellular Mechanisms of Brain Function

In this lesson we've learned a number of important biophysical principals that ultimately lead us to find out how the membrane potential of a cell is determined. We've seen that electrochemical diffusion describes ion flow through ion channels, and so there are two important forces that act upon ions. There's a concentration gradient, where ions want to move from high concentration to low concentration, and there's an electric field, which also acts upon the individual charged ions. Together, these two forces, electricity and concentration gradients, can mathematically be formulated into the Nernst equilibrium potential, which is the electrical potential that precisely counters the concentration gradient, and leads to no net ion flux. By independently regulating the ion channel conductances with selective permeability we can control the membrane potential. If we open a sodium conductance, the membrane potential will move towards the sodium reversal potential, and depolarize the cell. If we open a chloride, or a potassium conductance we will cause negative charge to accumulate inside the cell causing a hyperpolarization. These basic principals of ionic conductances driving membrane potential changes are fundamental to understanding how neurons work.

Notes

Summary



26m 27s