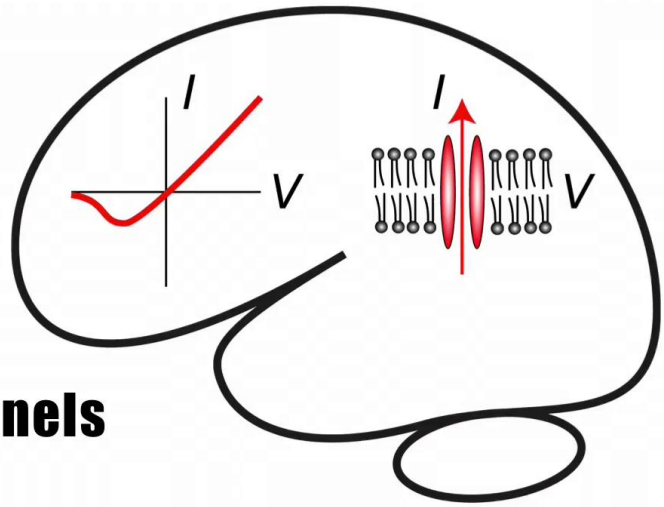
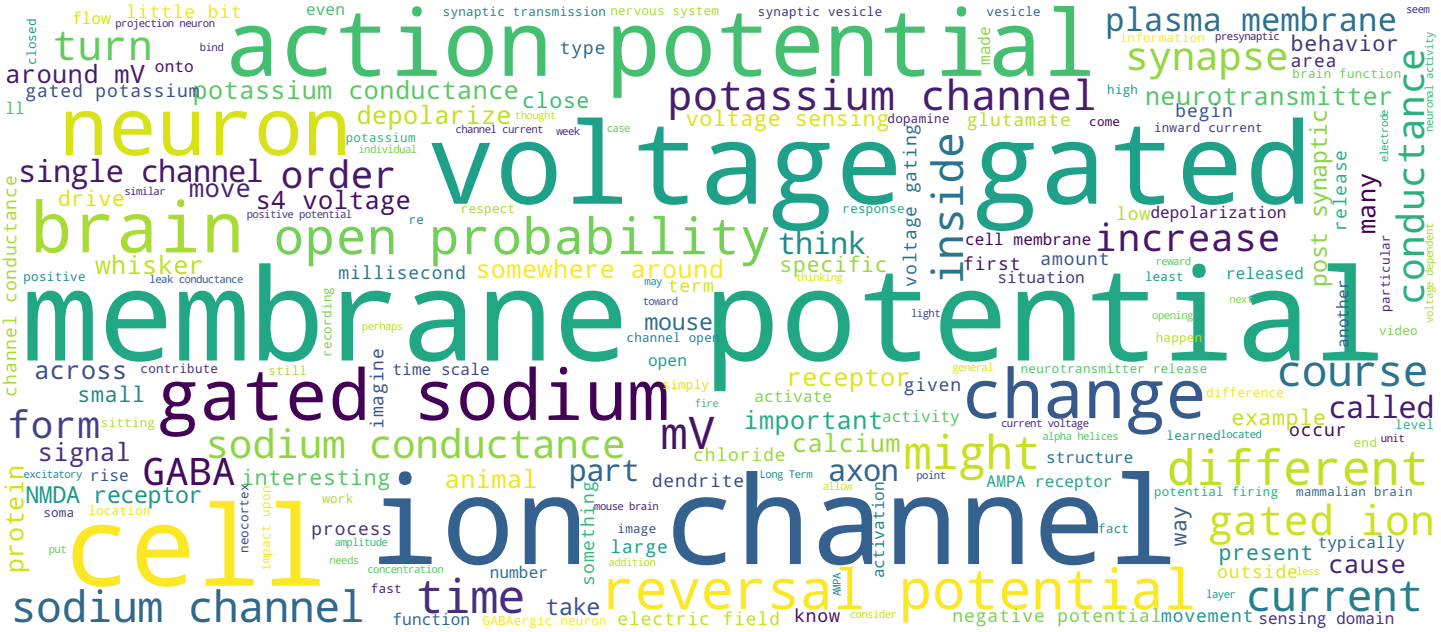


2.1 Voltage-gated channels

Cellular Mechanisms of Brain Function

Prof. Carl Petersen



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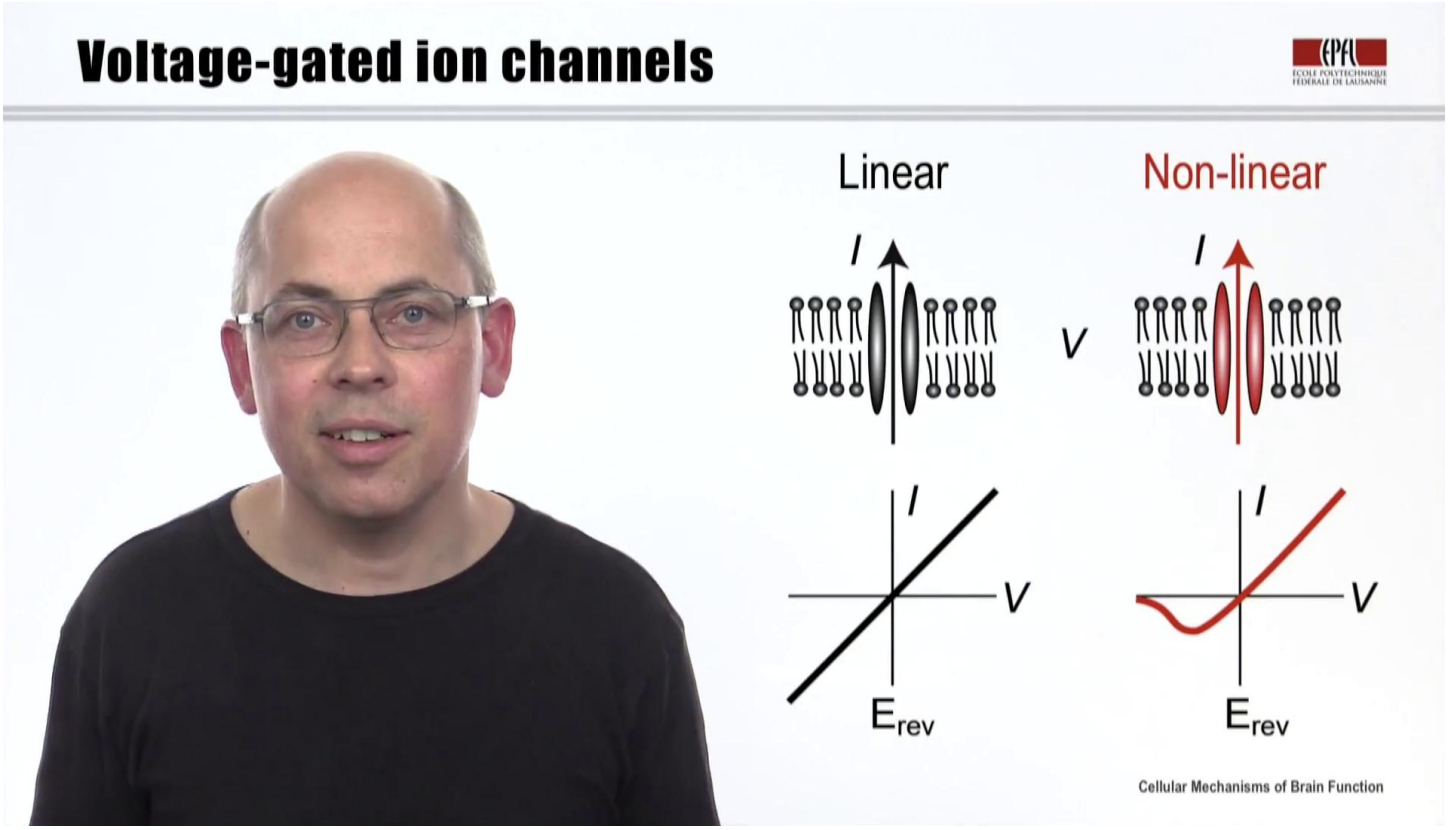
Voltage-gated ion channels

Welcome to week two of cellular mechanisms of brain function. Last week, we learned about the phospholipid bilayer that forms the cell membrane and electrically acts as a capacitor. We also learned about ion channeled proteins that span the plasma membrane and form conductors with specific reversal potentials given by the ionic species for which that iron channel is permeable to. These reversal potentials were given by the Nernst equation calculating from the concentration gradients distributed across the plasma membrane. We also learned that membrane potential was signaled in a complicated way across the extended neuronal operizations of real neurons. Changes in membrane potential in one part of a neuron were signaled to other parts of a neuron, but only after spatial and temporal filtering. Temporal filtering occurred approximately on the ten millisecond timescale given by the membrane time constant. The length constant of the cell on the order of several hundredths of microns defines the length scale over which steady state voltage differences are propagated across neuronal operizations. Now, in real neurons, and in the real mammalian brain signals need to traverse much longer distances.

Notes

Summary

0m 04s

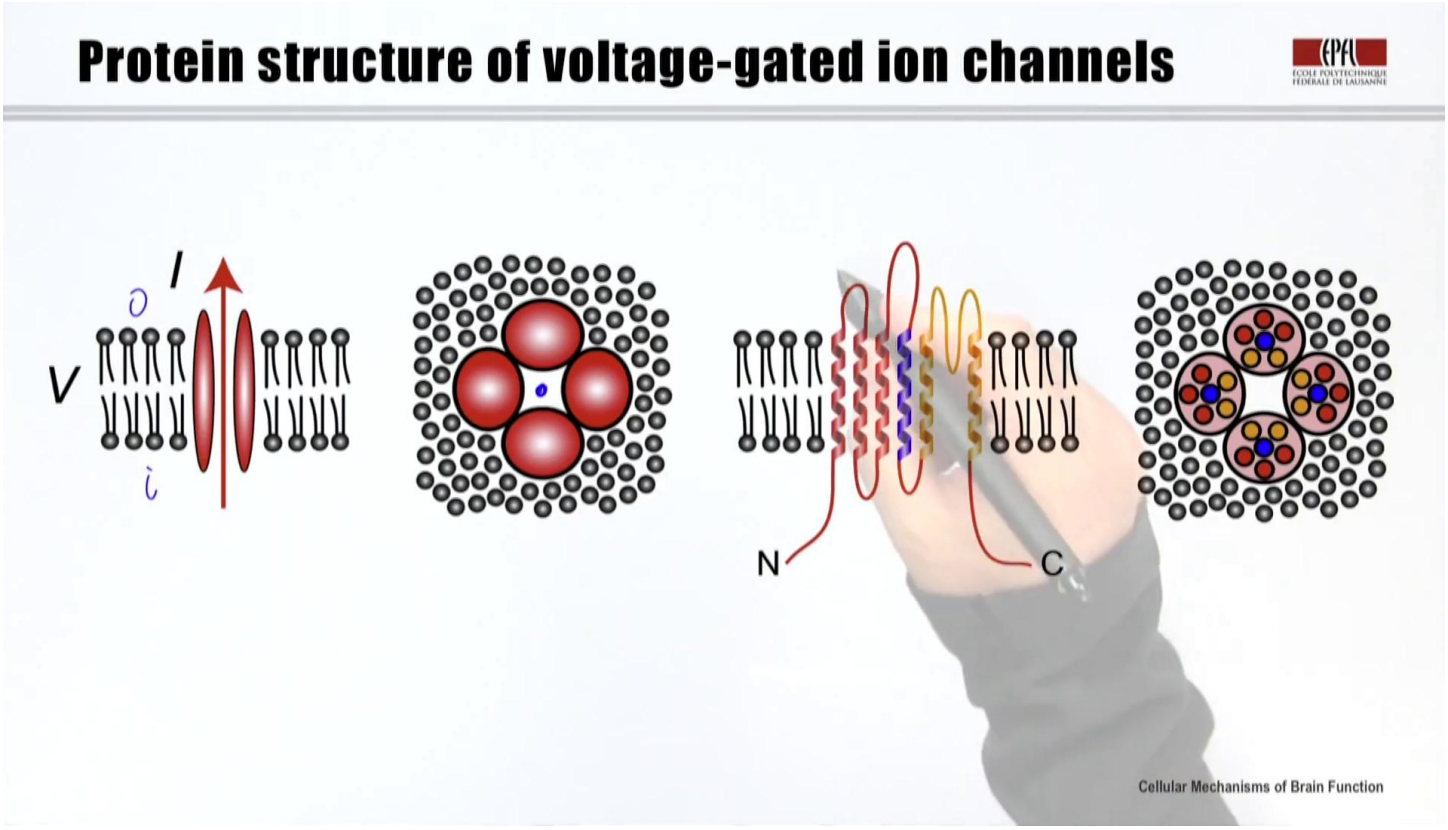


One part of the brain needs to be able to communicate with another part of the brain spanning some 20 centimeters. And some parts of the brain need to be able to communicate down the spinal cord extending meters. Given that we know that membrane potential is filtered significantly by the cable properties of neurons, how then do reliable signals arise in the nervous system? The answer comes in the form of the action potential, a digital all or none signal that's actively propagated across the neuronal operizations through voltage gated ion channels. Today we'll study the biophysics of these voltage gated ion channels. Last week we discussed linear channels. These are ion channels where the conductance is independent of the membrane potential. And this then allow us to plot linear current voltage relations- so-called ohmic conductances. Today we'll think about non-linear conductances where the permeation of cations through the ion channel depends upon the membrane potential. This gives rise to non-linear IV plots where the conductance at one potential might be very far from its linear counterpart. Such non-linear conductances give the nervous system enormous computational power.

Notes

Summary

1m 44s

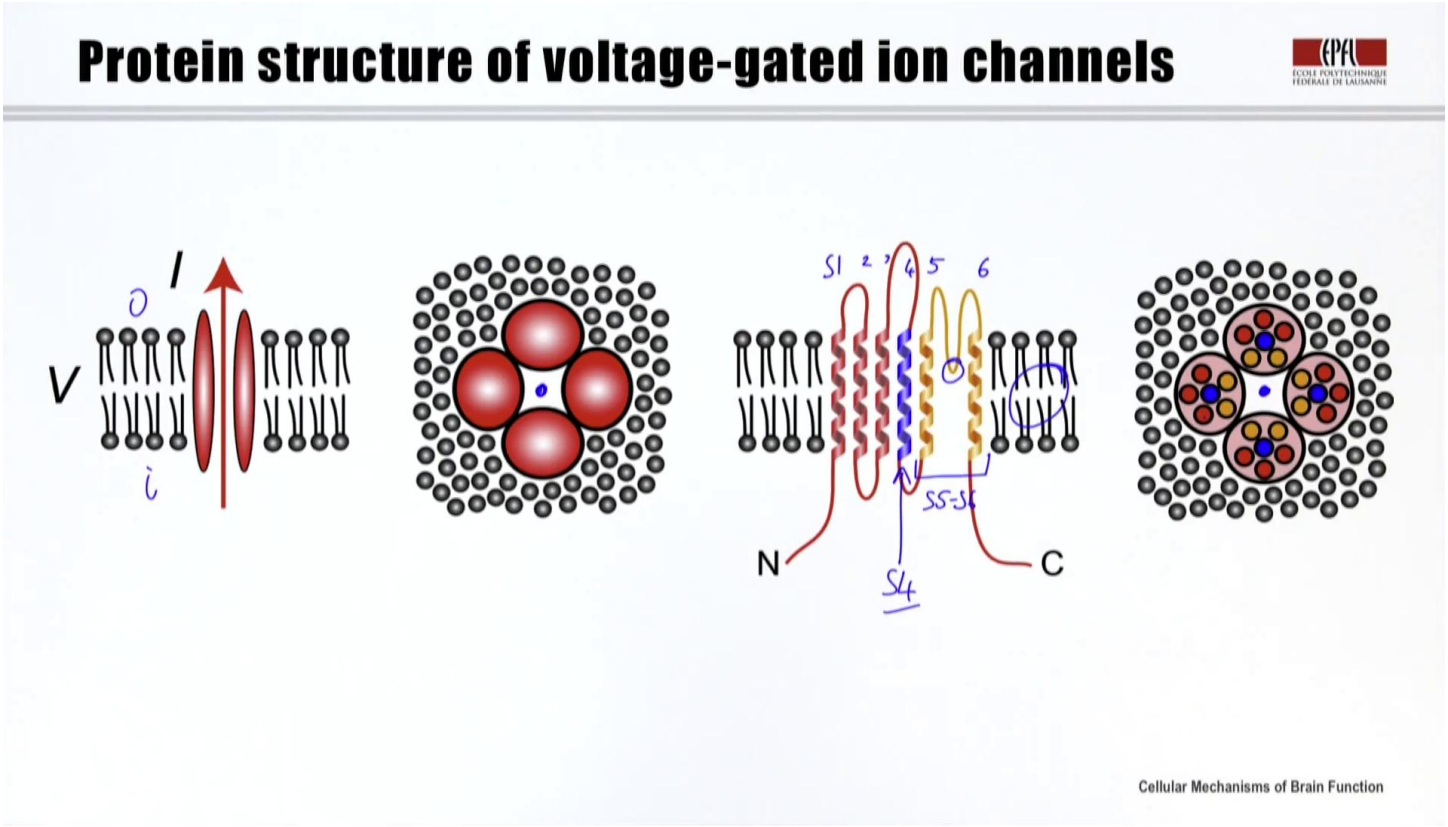


How can an ion channel be voltage dependent? Let's return to look at the protein structure of voltage gated ion channels. The ion channel is made out of a chain of amino acids that span from the inside to the outside of the plasma membrane meeting the lipid bilayer in parts and in other parts meeting an aqueous inter-cell channel, aqueous channel that allows the ions to permeate across the plasma membrane. If we look down upon the face of the plasma membrane and see the phospholipid head groups and the ion channel from the outside we would see a view something like this. Here are the phospholipid head groups Here are the red sub-units of the ion channel. Voltage gated ion channels are composed of four similar sub-units. Sometimes they're part of the same protein sometimes they're part of different proteins that come together. In any case, they form a tight association, these four sub-units and down the middle, of course is the ion conducting pole. Each of these sub-units is composed of multiple trans-membrane segments. Here you see an example ion channel with the typical six trans-membrane alpha helices. We have alpha helix one, two, three, four, five, and six.

Notes

Summary

3m 25s



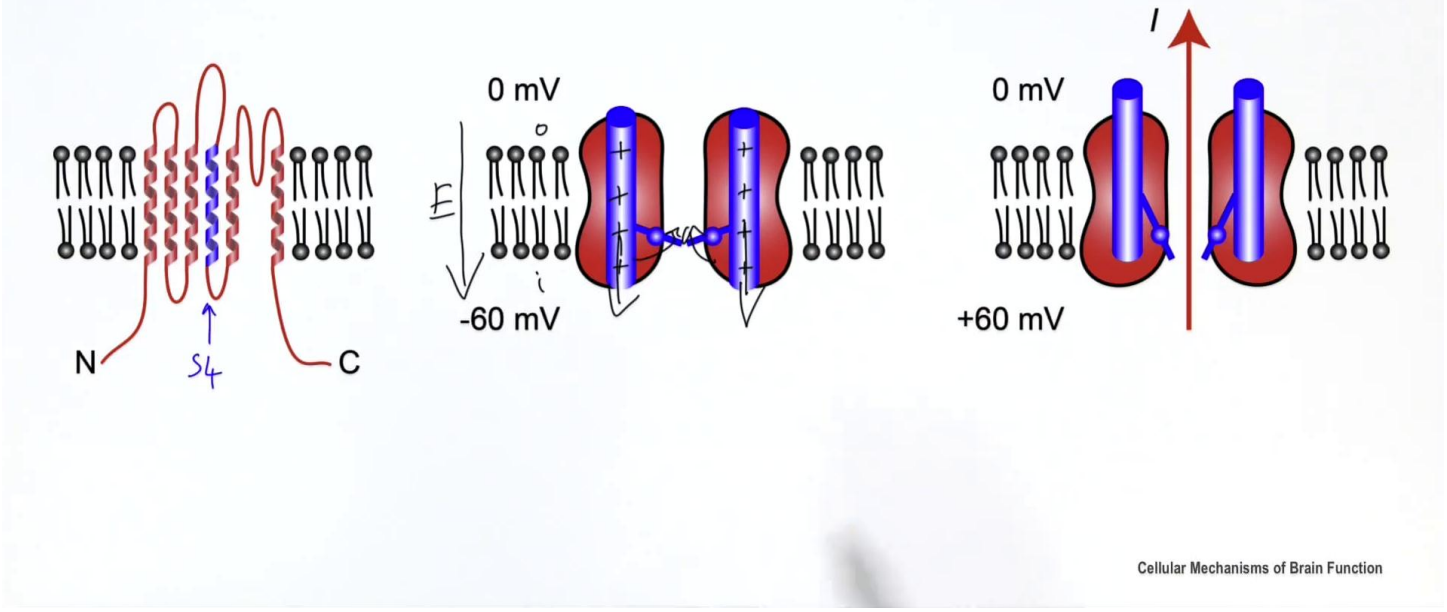
There's a color-coding of these trans-membrane alpha helices and you'll see that there's a yellow part here composed of s5 to s6 and that turns out to form the pole-lining region of the ion channel. So, next to these alpha-helices, we have the aqueous pole. And, in fact, this turns out to be where the selectivity filter is located. The red alpha helices s1 to s3 are here on the outside of the protein. They need to interact with the phospholipid bilayers the lipophilic part of the ion channel. And here, colored in blue, is a special part of the ion channel for voltage gating, the so-called s4 voltage sensing region.

Notes

Summary

5m 05s

Voltage-gating mechanisms



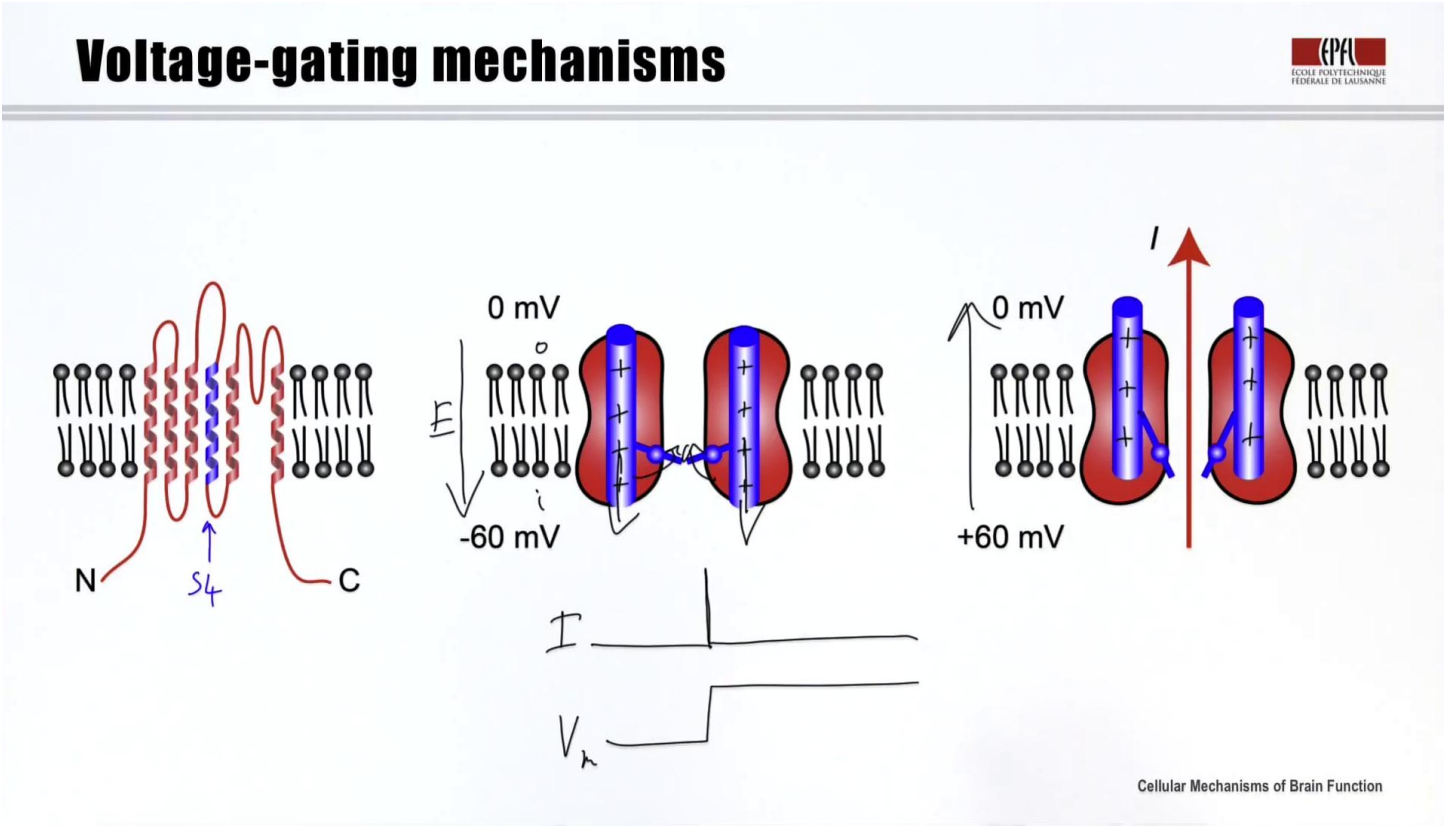
Cellular Mechanisms of Brain Function

The s4 voltage sensing domain that you see again here in blue is interesting and forms a sort of unit that can move and is relatively mobile within the structure of the ion channel. The s4 voltage sensing region is interestingly, positively charged. It's full of arginine amino acids that have positive charge on them. The ability of the s4 region to be relatively mobile and that it's charged allows it to interact with the electric field across the plasma membrane. At hyper-polarized potentials, there's a strong electric field that is from the outside to the inside. That electric field acts upon the charges of the s4 voltage sensing domain and pushes it downward towards the inside of the cell. The s4 voltage sensing domain is attached to a gating mechanism, the voltage gate. When these positive ions are pushed in towards the inside of a cell the gate swings up, and it's closed. the ion channel cannot open, and cannot permeate ions. If, on the other hand, we switch to a positive membrane potential the positive charges on the s4 voltage sensing region are moved out in the electric field, they act upon the voltage gate of the ion channel, open it, and allow the ions to flux when the ion channel opens and closes in its random stochastic manner.

Notes

Summary

6m 00s

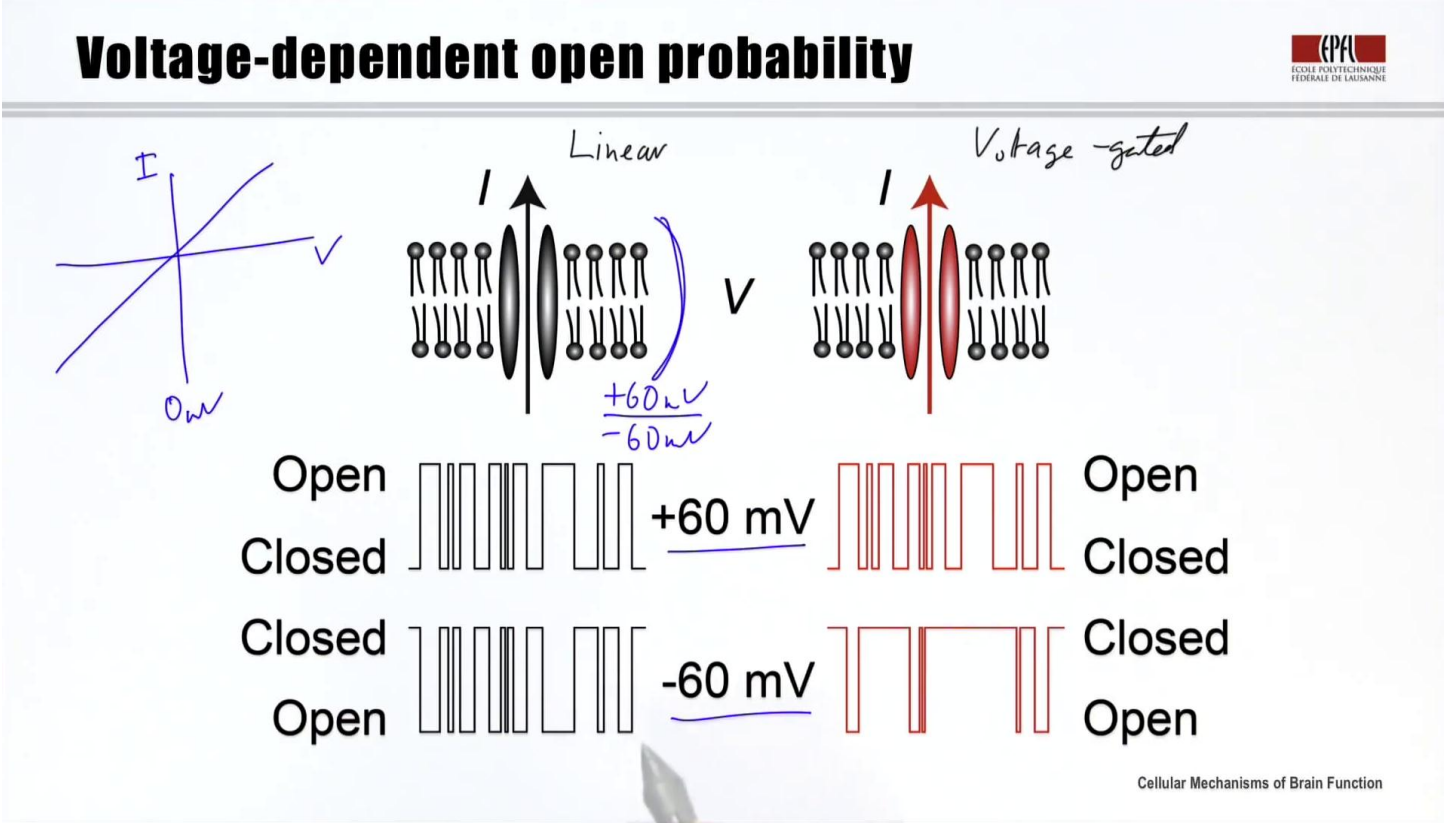


So the movement of the s4 voltage sensing domain gates the open probability of a voltage gated channel in a membrane potential fashion. We know that there's a physical reality to the movement of these charges on the s4 voltaging domain, because, even in the absence of any ion flux through the ion channel, you can measure the gating charge if you change the membrane potential rapidly to a positive value you can see that there's a capacitative current very brief, very fast, in the microsecond time-scale that indicates the capacitative movement of these positive charges on the s4 voltage sensing domain as it moves out.

Notes

Summary

7m 49s

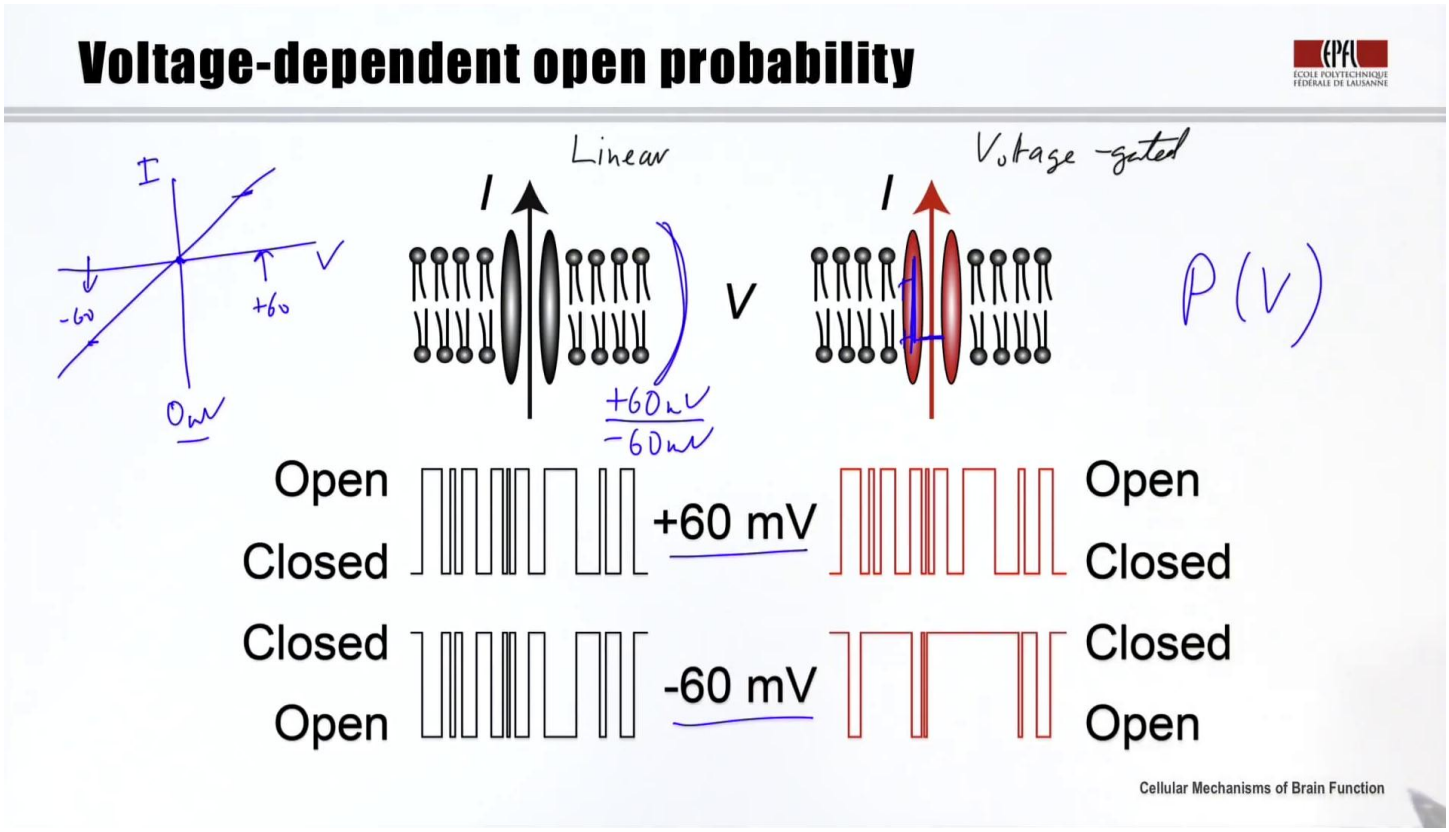


So, at the level of an individual ion channel, where we'll now consider the difference between a linear and a voltage gated ion channel, on the right. For a linear ion channel, the open probability of that ion channel doesn't depend upon the electric field that we have. The open probability will be the same if there's a membrane potential of +60 mV or -60 mV. And here, we imagine for example an ionic conductance that has a reversal potential at 0 mV. This would be the current, the voltage and we have a linear conductance. And so, at a membrane potential of +60 mV we have a certain amount of time that the ion channel spends in the open state, compared to the closed state, in this case maybe it's in the open state about half of the time. If you go to negative hyper-polarized potentials the open probability of a standard linear ohmic ion channel doesn't change. The open probability is still about 50%. But now, of course, when the ion channel opens then the currents flow in, because we're in this symmetric situation here where we have +60 and -60 mV the amount of current here is the same at both ends in an ohmic ion channel with reversal at 0 mV.

Notes

Summary

8m 37s

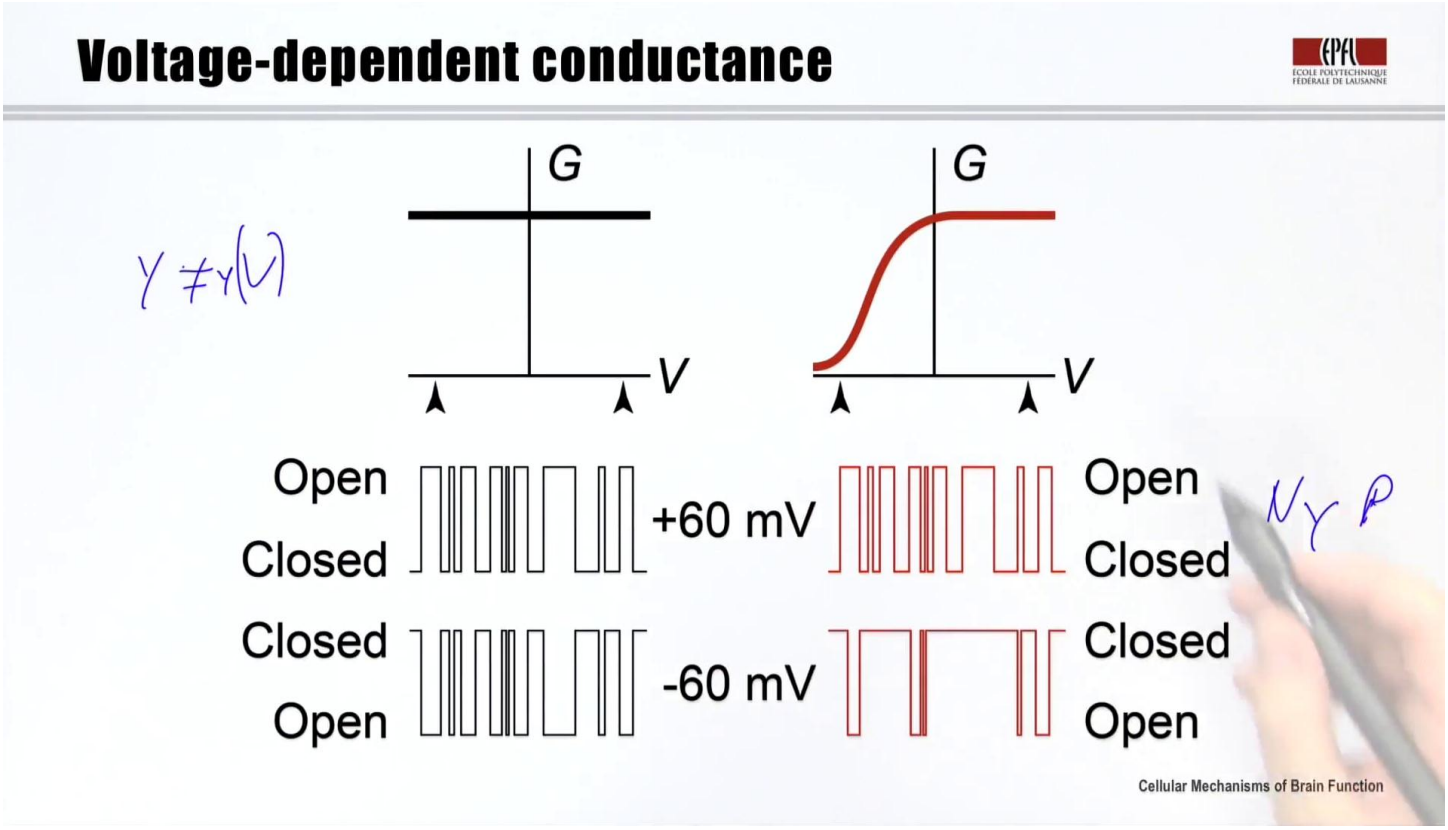


For the voltage gated ion channel, the situation is very different. At negative potentials, the ion channel has a low open probability. Remember, the s4 gating area here is positive, and the gate is closed at negative potentials. So, this channel spends relatively little time in the open state. When it does open, however, we get the full normal single channel currents, just as we would in the linear situation. What changes through the voltage dependance of voltage gated ion channels is the open probability. The probability is a function of the membrane potential.

Notes

Summary

10m 05s

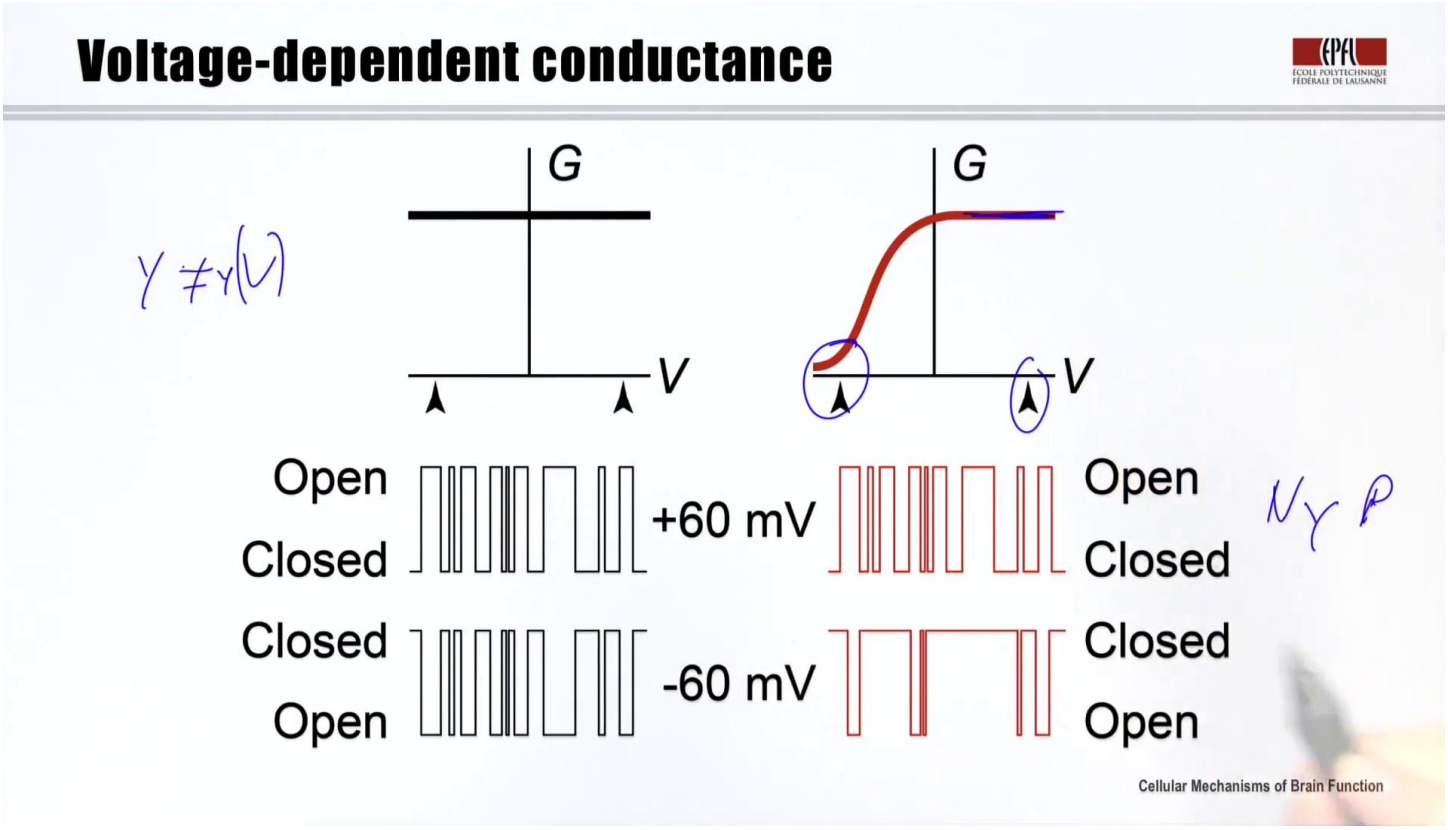


At positive potentials, the gating of the s4 voltage gating region is then changed. The s4 region moves out, the gate is then opened, and ions can flux. The open probability then increases at positive membrane potentials for a voltage gated ion channel. These changes in open probability can then be either summated over time where we take a mean current flux across a stochastic opening and closings of the ion channel, or we can think of many ion channels on the cell membrane that are opening and closing independently of each other and we then have a mean conductance, that's of course composed of the single channel conductance times the number of ion channels and of course, together with the open probability of that ion channel. And so, for a linear conductance, the conductance is independent of membrane potential, so it's a flat line. The conductance is the same at positive and negative potentials because the open probability is the same at open and negative potentials. And we've agreed that the single channel conductance is not a function of voltage. For the voltage gated scenario, we have a change in open probability in voltage.

Notes

Summary

10m 51s

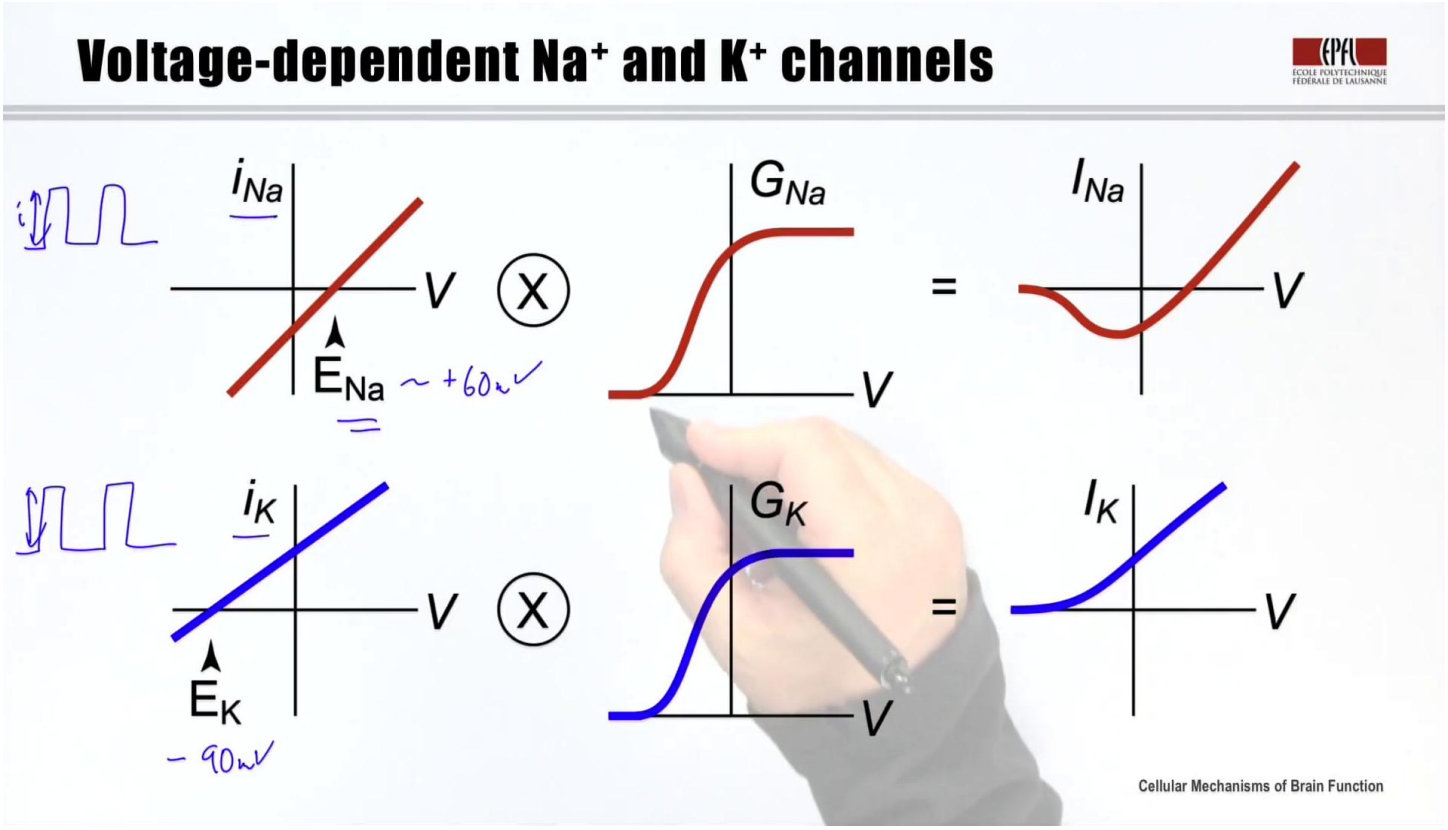


At negative potentials, the open probability is low, and the conductance, is therefore, also low. As we depolarize, we move the s4 voltage gating region out, the voltage gate opens, and the open probabilty of the ion channel increases and we move up here on the conductance until we reach some sort of steady state region here, where the ion channel is saturated with respect to its voltage dependence.

Notes

Summary

12m 25s

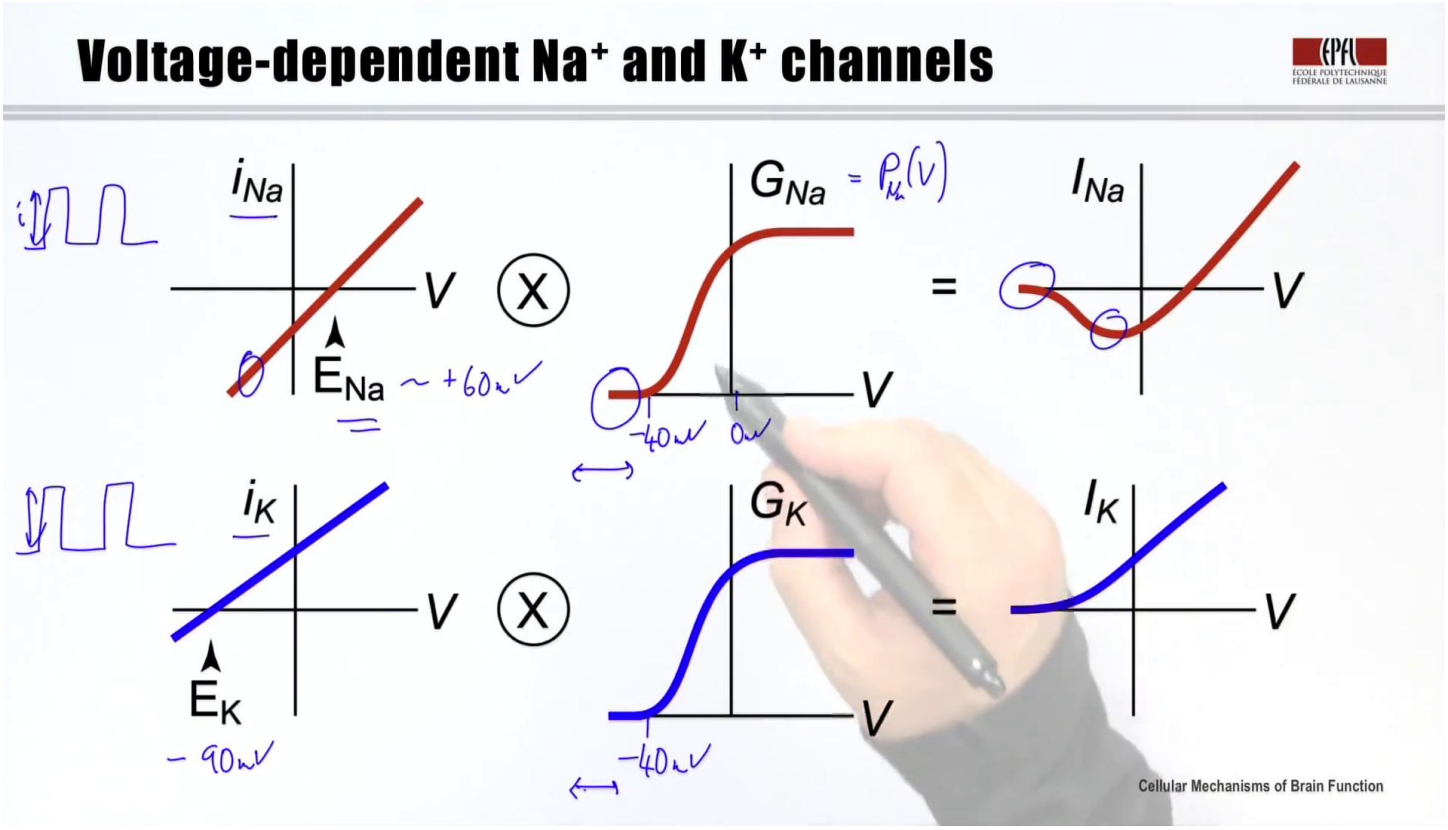


If we now think specifically about sodium and potassium channels, and voltage dependent sodium and potassium channels are amongst the most important voltage gated channels in the nervous system, we now need to think for the sodium and potassium channels, about their reversal potentials. And we know that sodium has a positive reversal potential, somewhere around +60 mV and potassium has a negative reversal potential somewhere around -90 mV. And so, the single channel currents all would be flowing through a single sodium channel at different membrane potentials as the ion channel opens and closes so this single channel sodium current will then be linear, and reversing of course, at the sodium reversal potential. Similarly, the single channel potassium currents as the ion channel opens and closes will also be linear with respect to voltage, and will of course reverse at the reversal potential for potassium. For voltage gated sodium and potassium channels in general, they become activated at relatively similar membrane potentials. And so, somewhere around -40 mV and more positive to that the ion channels begin to open, the voltage gate sodium channels increase their conductance above -40 mV and the same is true for the voltage gated potassium currents.

Notes

Summary

12m 58s

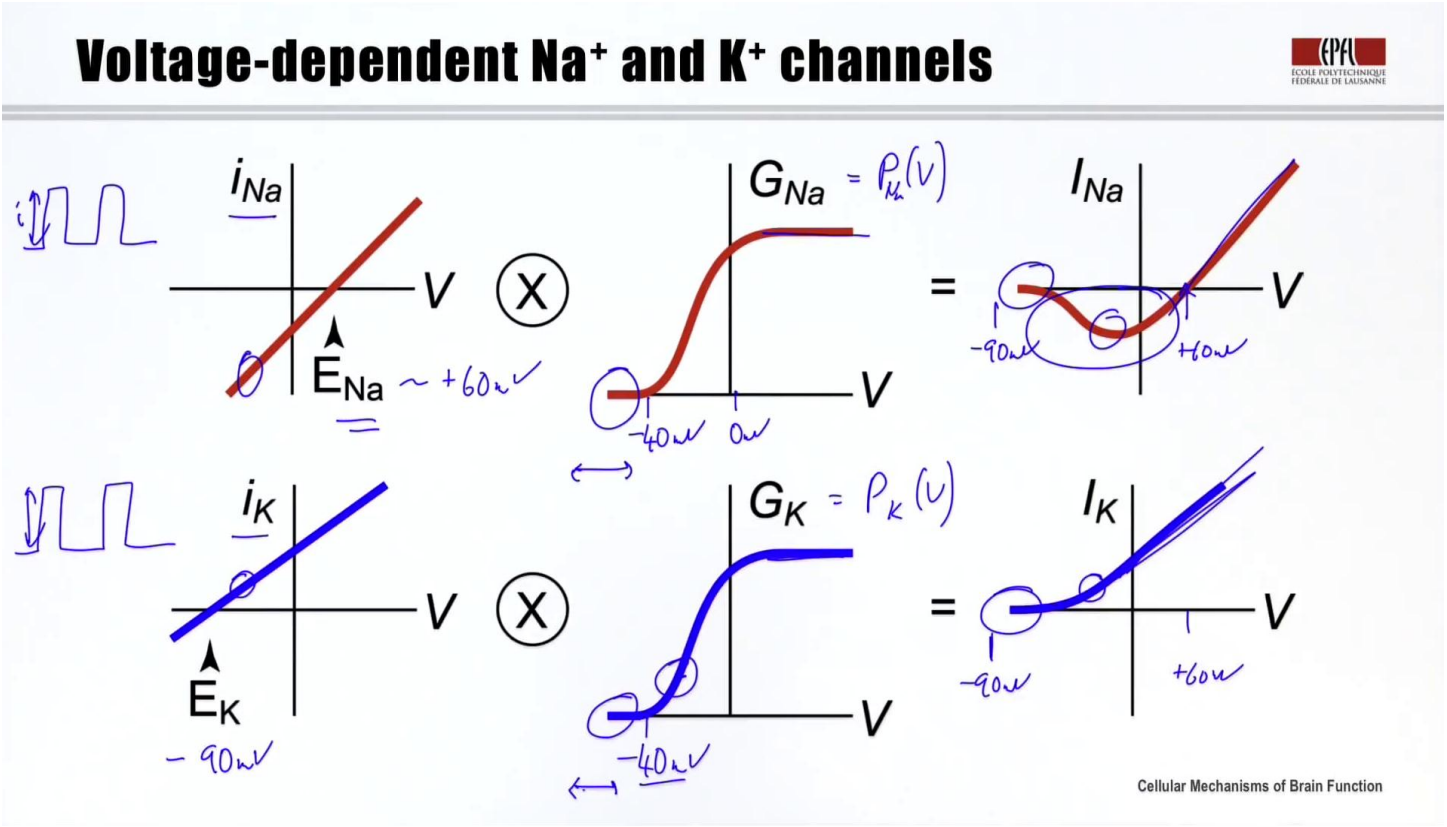


And so, there's a regime here hyper-polarized to -40 mV in which there's very little conduction through the voltage gated sodium and potassium channels. They're closed at most resting membrane potentials. And at more positive potentials to -40 they begin to become activated in a strong and steep manner becoming almost fully activated around 0 mV. If we then convolve this voltage gating the change in the open probability of the voltage gated sodium channel with respect to voltage we convolve that open probability with the single channel currents and the reversal potential at the sodium reversal potential we see that we get a current voltage relationship that looks something like this. At negative potentials the ion channel is closed and therefore, there's no current that flows as we move through the -40 mV and the open probability begins to become significant we then get single channel conductances that are substantial then give rise to an inward current. As we keep depolarizing, the voltage gating saturates we hit the reversal potential for sodium and we enter the linear conduction regime.

Notes

Summary

14m 43s

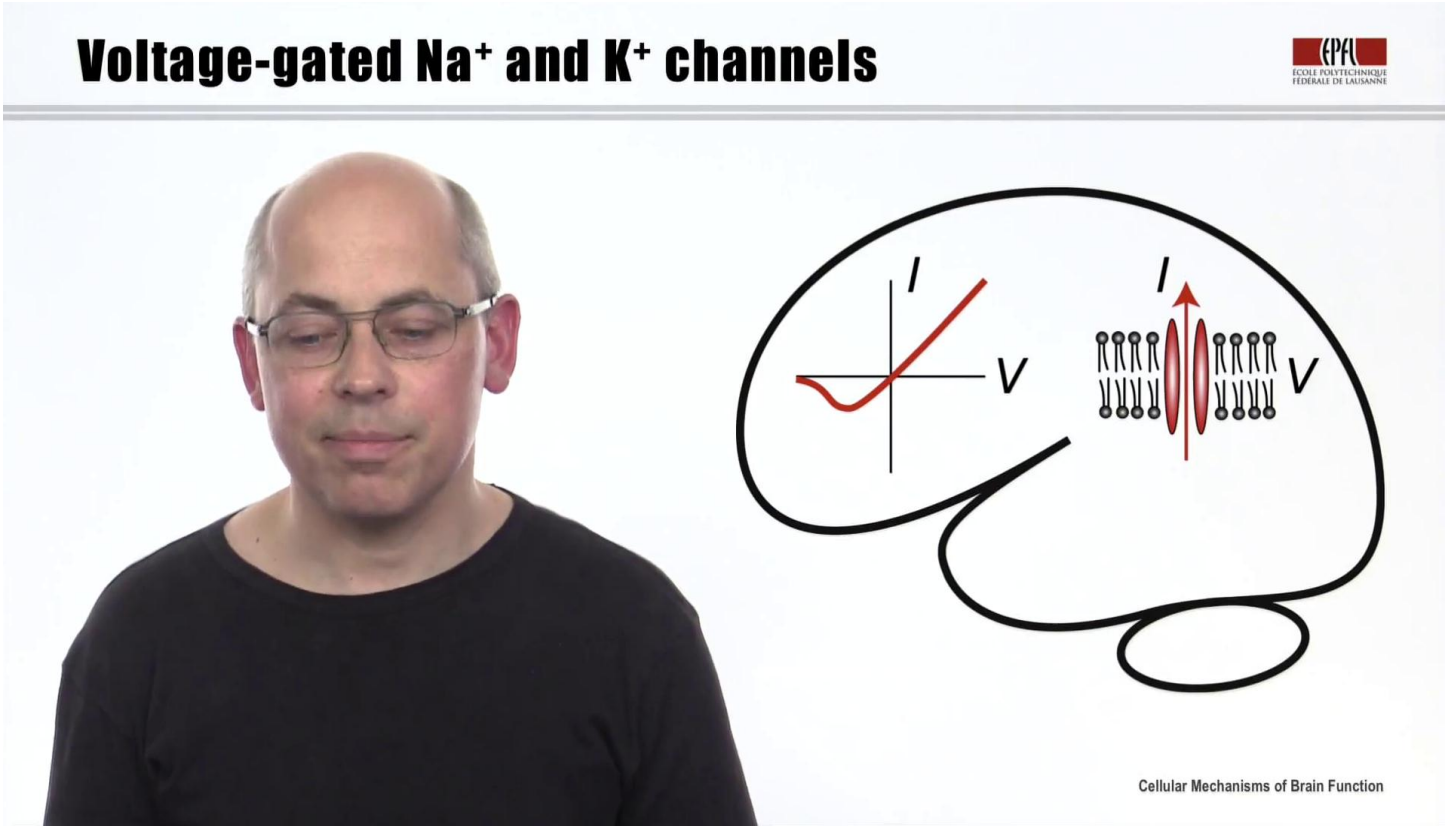


And so we have this interesting biphasic situation where between the physiological range of membrane potentials from -90 to around +60 mV we have an inward current that's generated by the voltage gated sodium channel. For the voltage gated potassium channels the situation is very similar. At negative potentials the conductance is basically closed. And so, there's nothing carried by the voltage gated potassium conductance. As we depolarize beyond -40 mV it activates, and we see now that there's an outward current that we can then compute by multiplying the overall open probability of the potassium with respect to voltage and the single channel currents that go through it. As we keep depolarizing the more and more conductance is activated until we hit this linear regime, and that's what we see here, we end up in this linear regime here and interestingly, again in this range of the physiologically relevant membrane potentials from -90 to +60 mV here, we always have an outward current in terms of what can be carried by the potassium channels.

Notes

Summary

16m 13s

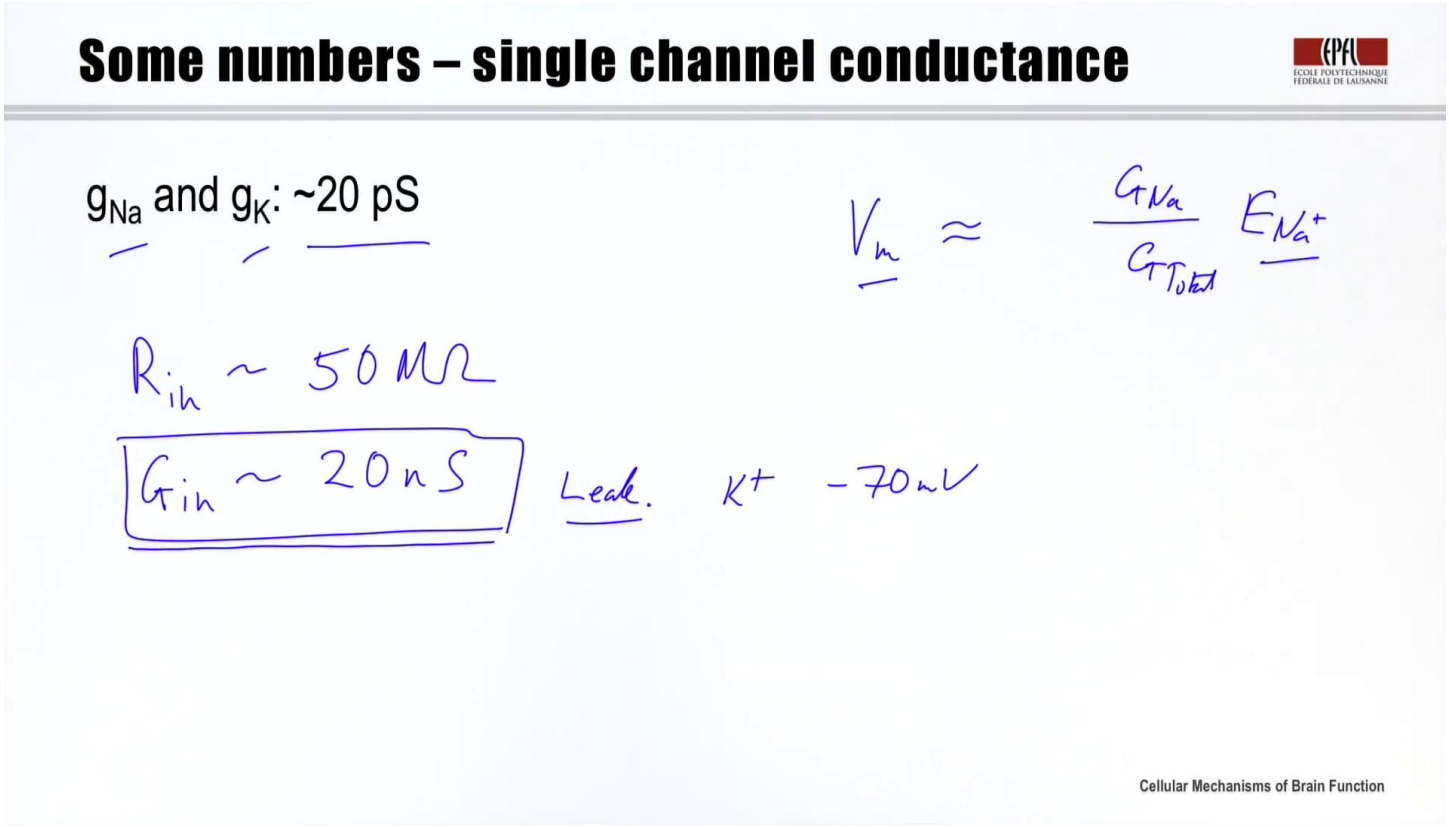


So, we've seen some interesting features of voltage gated ion channels. They're largely closed at resting membrane potentials. Membrane potential is normally somewhere in the range from -70 to -50 mV. In this range, the open probability of voltage gated sodium and potassium channels is very low, and they'll make very little contribution to the overall conductance of the membrane. At more positive potentials to -40 mV the open probability increases sharply, and the voltage gated ion channels then begin to conduct and can contribute to the overall conductance of the cell membrane. The change in conductance of the voltage gated ion channels is not because of a change in the single channel conductance but it is a change in the overall open probability. Let's see how voltage gated ion channels can contribute to changing membrane potential in neurons.

Notes

Summary

17m 38s

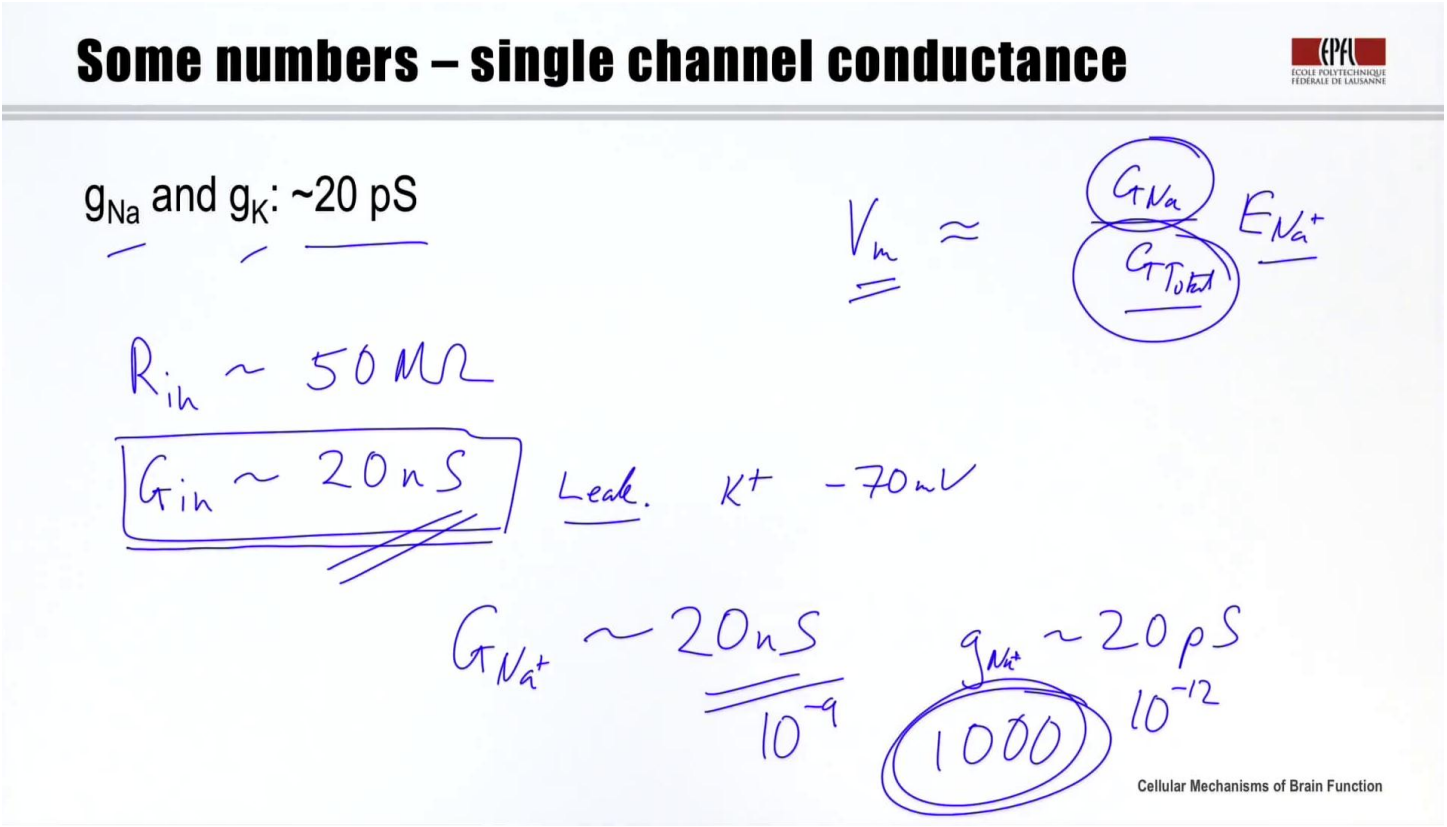


Let's consider a cell that has voltage gated sodium and potassium channels, each of which has a single channel conductance of roughly 20 pS. The input resistance of a cell, it's total input resistance is somewhere around 50 mΩ, typically, and that corresponds to an input conductance of something like 20 nS. So, this is the leak conductance of a typical neuron. And it's dominated by a leak potassium conductance that keeps membrane potential somewhere around -70 mV on average. In order for the voltage gated sodium or potassium channels to have a major impact upon membrane potential, we need for these conductances to get close, at least in the same ballpark, as these leak conductances. Remember that the membrane potential goes something like the sodium conductance divided by the total conductance and the reversal potential for sodium. So, if the total conductance is dominated by sodium conductance the membrane potential will tend towards the reversal potential for sodium. So, if we want the voltage gated sodium channel to make a considerable impact upon the overall membrane potential, the overall sodium conductance must somehow at least get close to the total conductance of the cell.

Notes

Summary

18m 46s



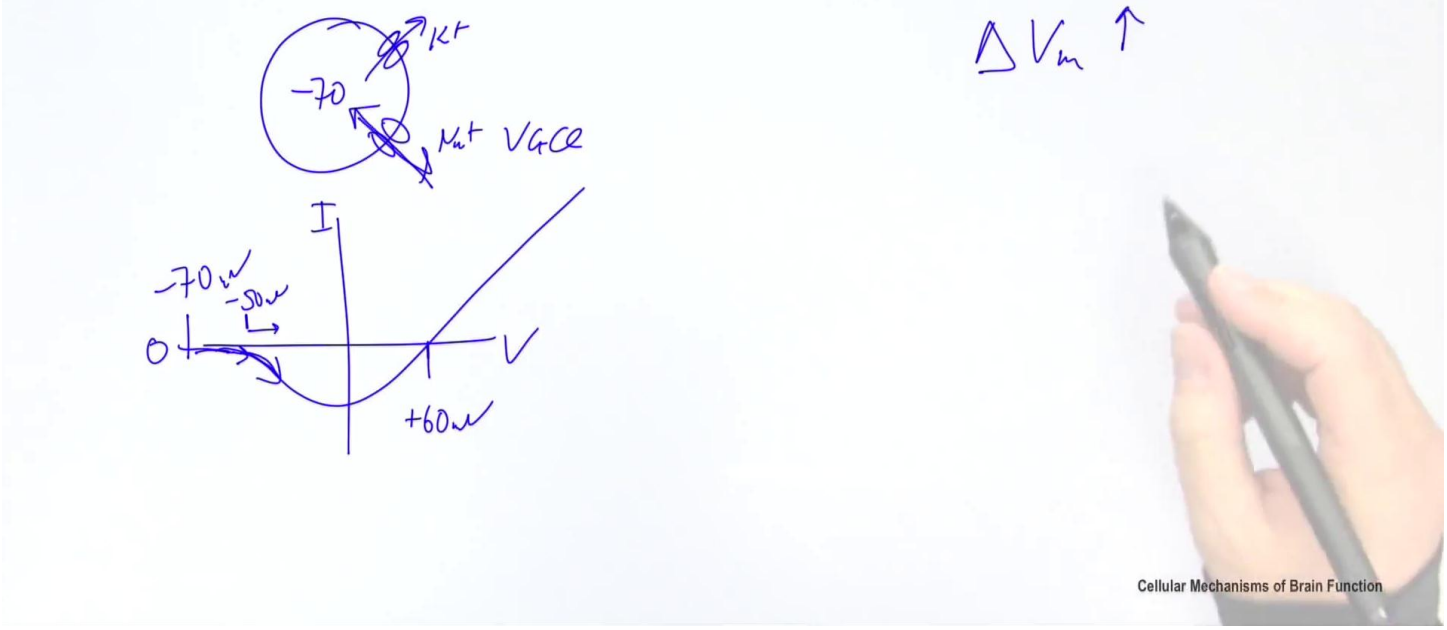
And we said that the lead conductance is somewhere around 20 nS. And so, if we want the voltage gated sodium conductance to make a considerable impact upon membrane potential the total voltage gated sodium conductance also needs to be somewhere around 20 nS. The single channel conductance is around 20 pS. This is 10 to the minus 9, this is 10 to the minus 12, there's a factor of 1,000. So, something like 1,000 sodium channels are needed in order to make a substantial impact upon the membrane potential of a cell. And, indeed, most neurons have high concentrations of voltage gated sodium and potassium channels, so that exactly this, they can change the membrane potential rapidly in a voltage dependent manner in order to perform non-linear computations.

Notes

Summary

20m 26s

Some numbers – explosive Na^+ conductance



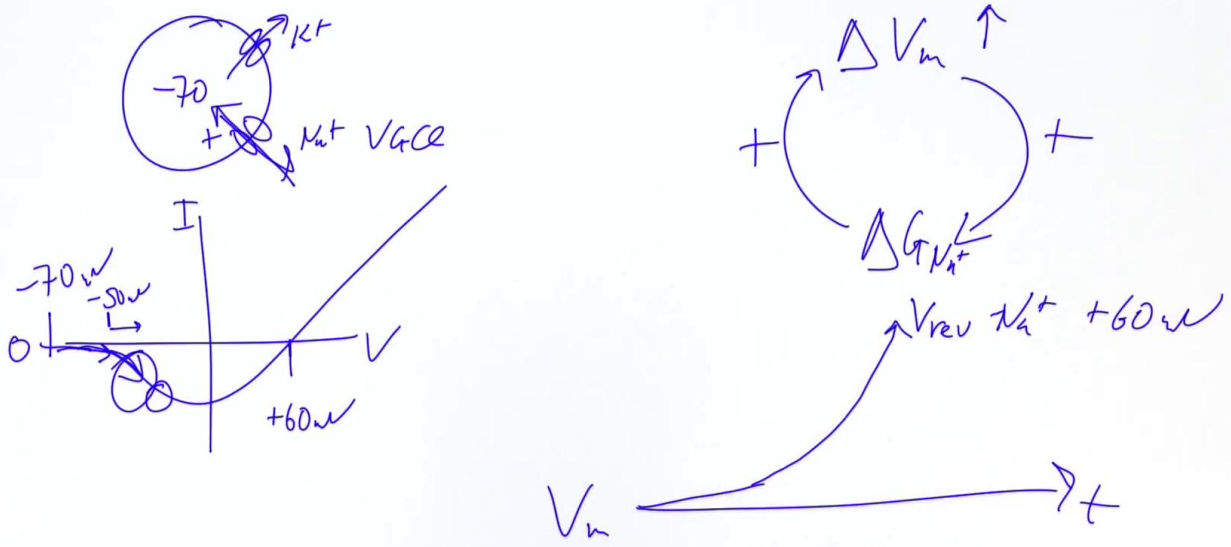
Let's see what happens if we open a voltage gated sodium conductance on a cell. Let's imagine we have a neuron that has some leak conductance and it's largely governed by potassium. In addition, we can then add a voltage gated sodium conductance. We also have the current/voltage relationships for the voltage gated sodium conductance and it looks something like this, with the reversal potential for sodium somewhere at around +60 mV and the typical cell is sitting somewhere around here at -70 mV, a time where the current flux through the voltage gated sodium channel is basically is basically zero. What if we were now to depolarize the cell a little bit, and we'll take it a little bit in this direction, we'll take the membrane potential to -50 mV. At this stage, there's still very little current that flows through the voltage gated sodium channels, and they probably wouldn't contribute very much. But as we depolarize just a little bit more the current flux begins to flow in. There's a considerable influx of sodium into the cell as we open the voltage gated sodium channel. So, we depolarize the membrane potential a little bit. That opens a voltage gated sodium conductance.

Notes

Summary

21m 27s

Some numbers – explosive Na^+ conductance



Cellular Mechanisms of Brain Function

That voltage gated sodium conductance leads to an inward current. That inward current will bring more positive charge inside the cell and will cause the membrane potential to further depolarize. Depolarizing the membrane potential further will lead to an even larger inward current, which in turn, will depolarize some membrane potential even more, and so on, we get into a positive spiral, where depolarization increases the voltage gated sodium conductance that further increases the charge influx further depolarizing the cell. And if we think about membrane potential with respect to time we depolarize it a little bit, and suddenly the voltage gated sodium channels begin to participate and we're in this explosive situation where membrane potential has this positive feedback loop that takes us toward the reversal potential for sodium, somewhere around +60 mV depending upon the strength of the leak conductances. So, voltage gated sodium channels give rise to an explosive sodium conductance where a small bit of depolarization will give rise to a positive feedback loop taking the membrane potential toward a sodium reversal potential.

Notes

Summary

23m 00s

Some numbers – stabilising K⁺ conductance

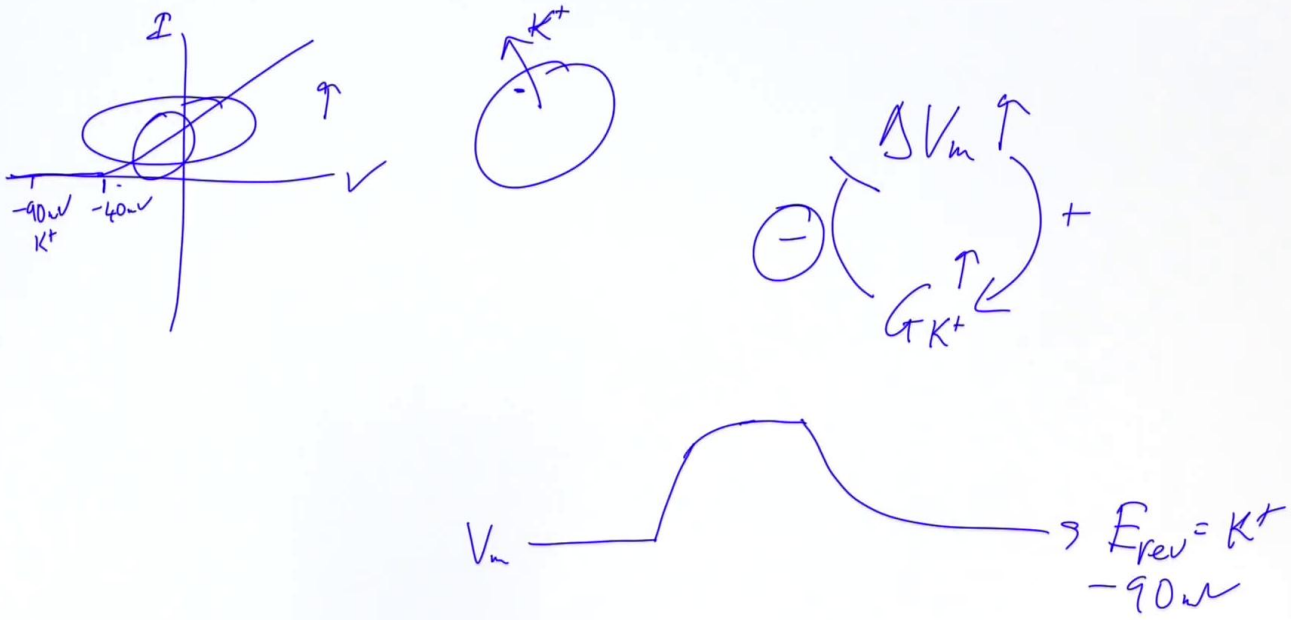
Let's now consider voltage gated potassium conductance. The current/voltage relation has similar features. We have reversal potential at -90 mV for the potassium reversal potential. We have the activation of the potassium conductance at around -40 mV. So it's zero conductance here, this is the current. This is the voltage, and then somewhere around -40 it begins to conduct, and we end up with the linear IV relationship here with potassium always forming an outward current, potassium will then always want to leave a cell, and will then always make things more negative inside the cell. So, in contrast to what we saw with the potassium conductance, the sodium conductance, rather, where we had the positive explosive feedback here, as we depolarize the cell, we increase the potassium conductance but that makes it more negative on the inside, and will then be a stabilizing influence. So if we depolarize the membrane potential that will certainly lead to an increase in the potassium conductance but an increase in the potassium conductance will, on the other hand lead to a reduction in the membrane potential, and so we have a stabilizing influence of voltage gated potassium conductances.

Notes

Summary

24m 22s

Some numbers – stabilising K⁺ conductance



Cellular Mechanisms of Brain Function

For a given membrane potential, if we perturb it by depolarizing it a little bit the activation of voltage gated potassium channels will tend to hyper-polarize the membrane potential and take it towards the reversal potential for potassium, around -90 mV.

Notes

Summary

25m 50s

Voltage-gated ion channels

- The open probability of a voltage-gated ion channel depends strongly upon the membrane potential (V_m).
- Voltage-gated Na^+ channels drive explosive depolarisation. Voltage-gated K^+ channels stabilise hyperpolarised V_m.

Cellular Mechanisms of Brain Function

So, in today's lesson, we've learned a number of interesting features about voltage gated ion channels. Voltage gated ion channels have a specific voltage sensing domain, the s4 region that's highly charged, and is very sensitive to the electric field across the plasma membrane. At positive potentials, the gate opens allowing ion channel permeation and high open probability. At negative potentials the s4 voltage sensing domain swings in, the gate shuts, and open probability is low. Open probability is therefore the key feature that's regulated by the voltage dependent gating of ion channels, whereas the single channel conductance remains unchanged. The voltage gating of the sodium channel, because of its positive reversal potential leads to an explosive depolarization once you get into that voltage gating activation regime of the sodium channel. On the other hand, voltage activation of the potassium channel acts to stabilize membrane potential, hyper-polarizing the membrane potential towards the potassium reversal potential. It turns out that a dynamic interplay in terms of the kinetics of the opening and closing of sodium and potassium channels underlies the generation of the action potential. And in the next lesson, we're going to look at the voltage gating kinetics of the sodium and potassium channels.

Notes

Summary

26m 10s