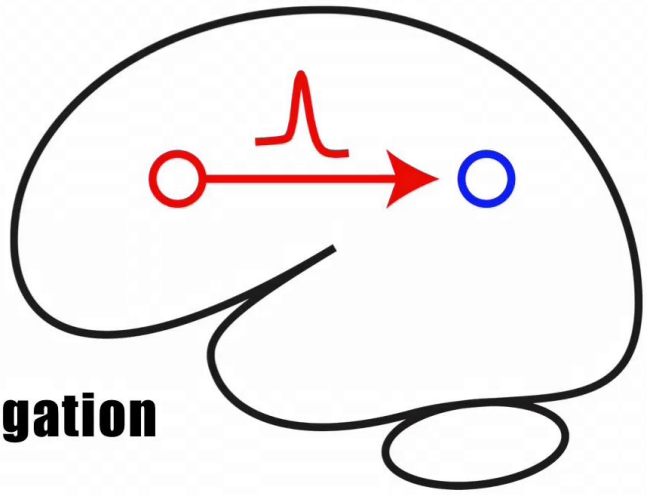
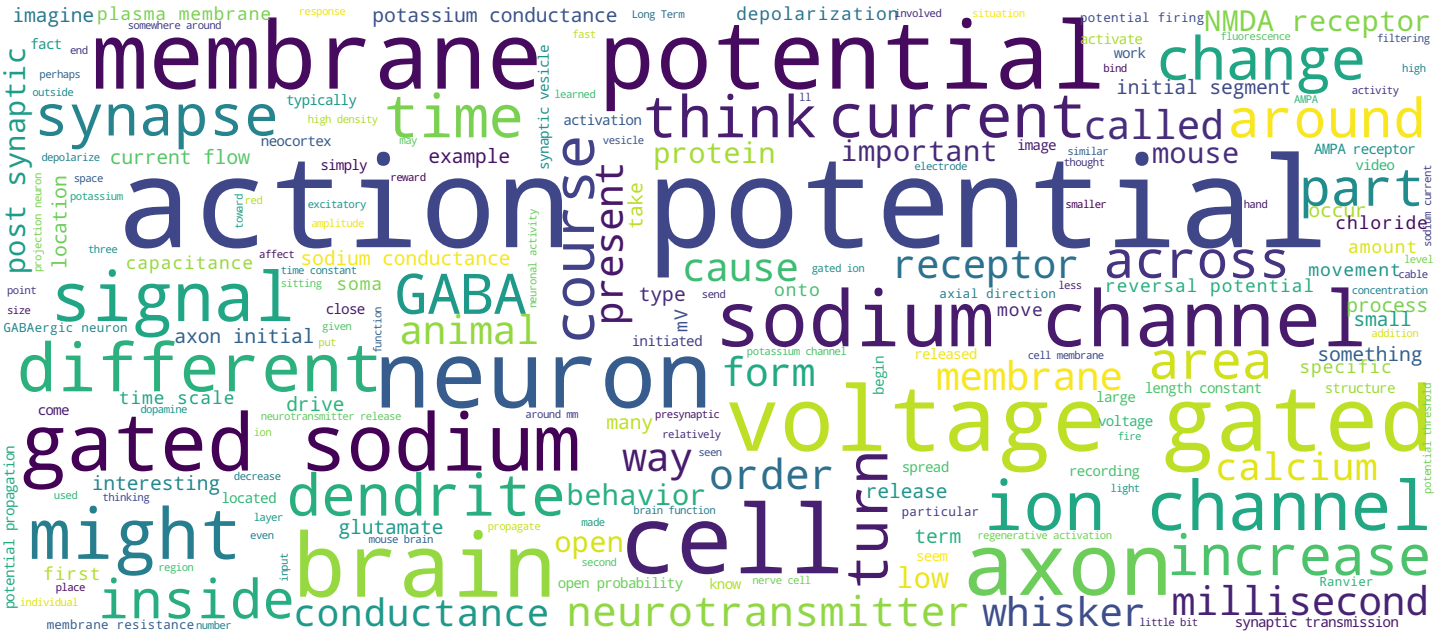


2.4 Action potential propagation

Cellular Mechanisms of Brain Function

Prof. Carl Petersen



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Digital communication

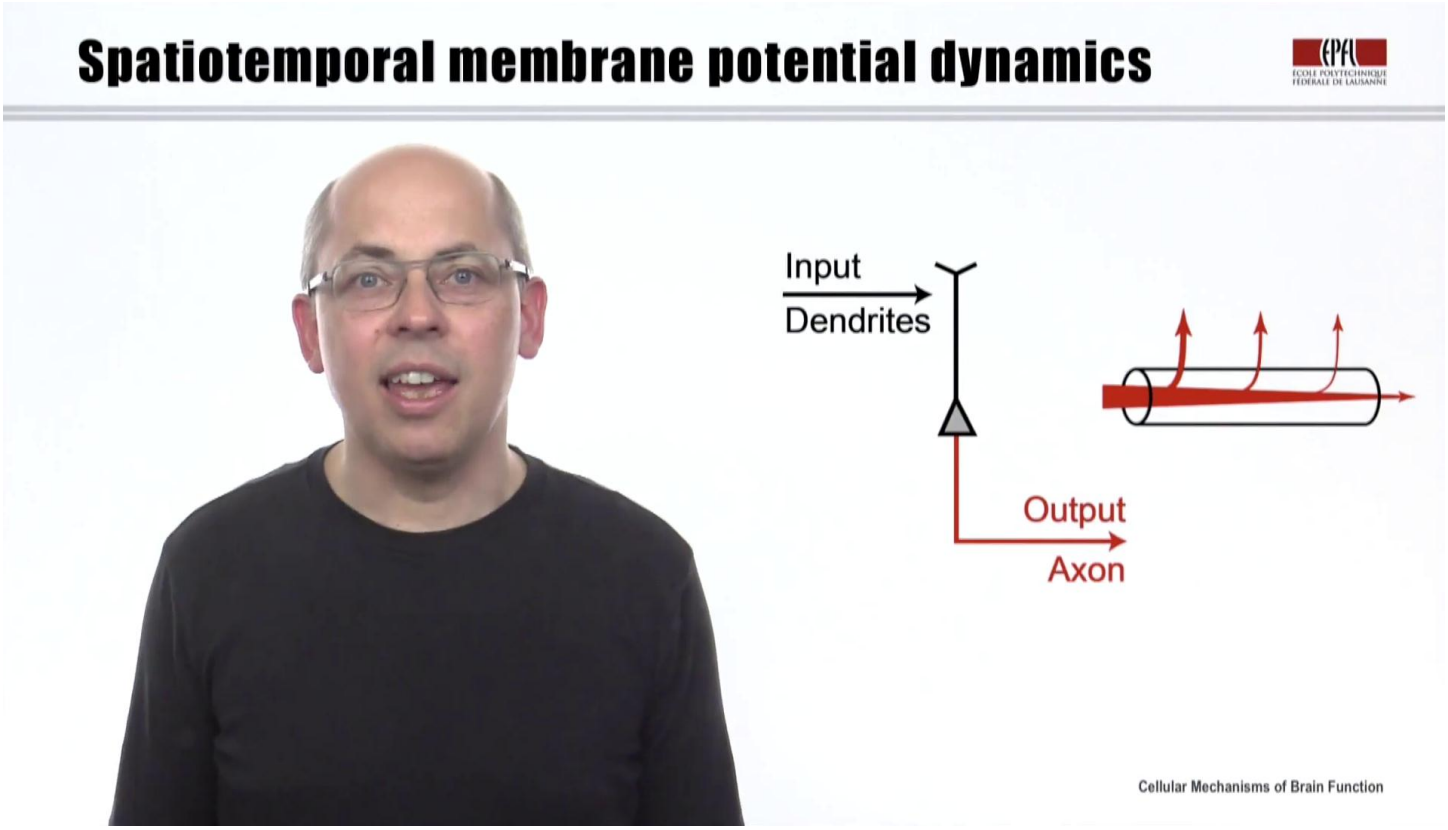
Cellular Mechanisms of Brain Function

Last week we learned about the action potential, an all-or-none signal driven by the explosive positive feedback activation of voltage-gated sodium channels. The action potential is thus a digital, all-or-none binary signal, and the brain apparently, therefore, uses digital information signalling. Digital communications are also important in modern everyday life. Computers, telephones, and all forms of information-processing systems use digital signalling. The reason for using digital signalling is that we can use much higher information rates for reliable information transfer. If we imagine trying to send a signal down a transmission line, and some noise is being introduced, it's easy to restore that if it's a digital signal. We simply have very large signal amplitude, and noise makes very little difference, and we can restore the signal easily through a regenerative amplifier of digital signals. The same processing for an analog signal would be very difficult. Digital signalling in modern telecommunications therefore allows high information transfer rates and reliable signalling. It turns out that the digital signal of the action potential fulfills a very similar role for the brain.

Notes

Summary

0m 04s

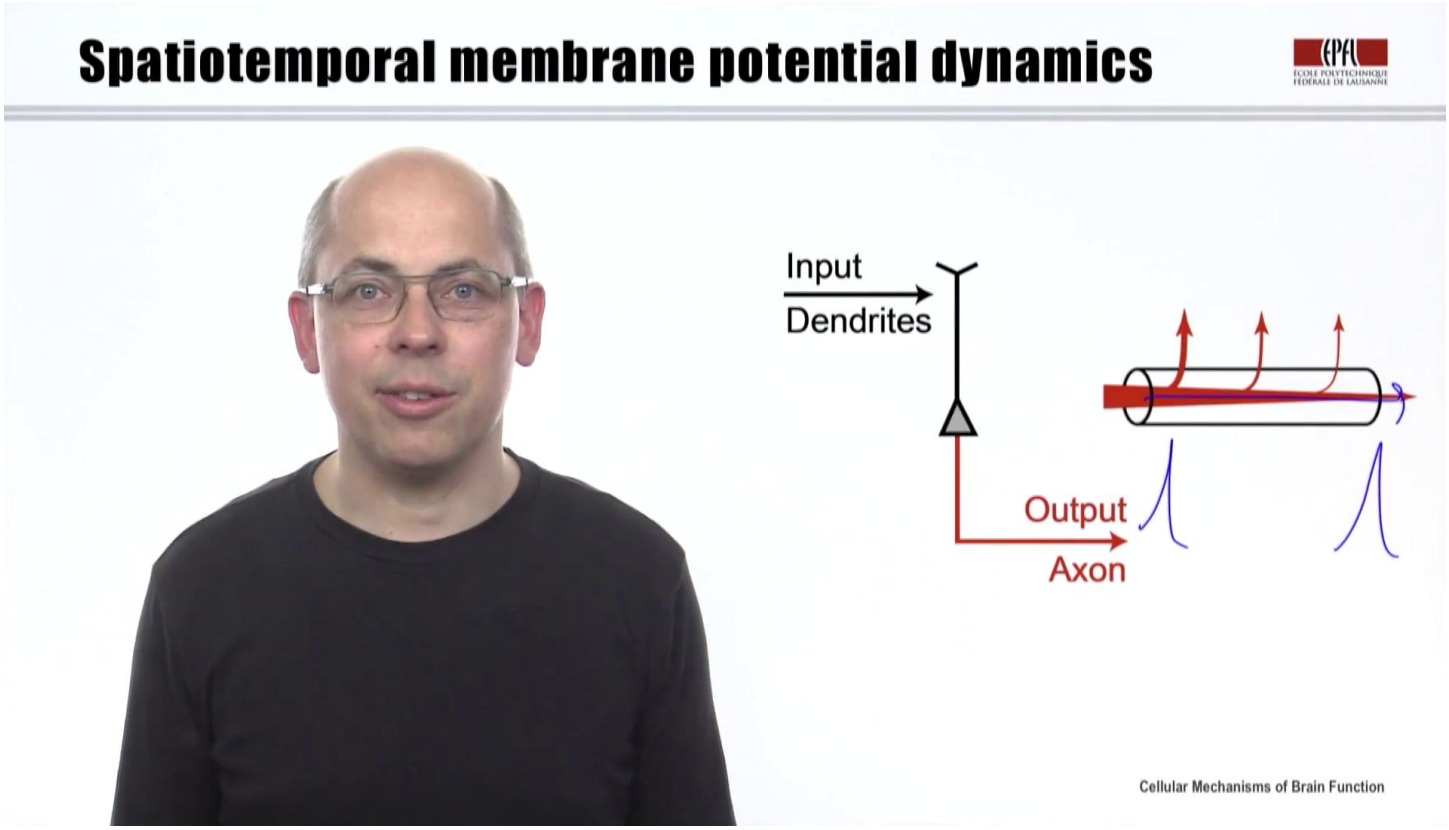


We've already studied some of the issues of passive spread of membrane potential, and the complexity of membrane potential distributions across the arborizations on real neurons. We saw that the thin cables of neurons in the dendrites and axons, were associated with a considerable amount of spatial and temporal filtering. There was a length scale of around 1 mm, which is about the size of the dendritic arborizations in a neuron, which filter the signal -- a steady-state membrane voltage -- so that one voltage up here might be half of its size by the time it reaches the soma. There were also membrane time constants that were on the order of several milliseconds that further filtered the rapid signals that could occur in the dendritic arborizations. The dendrites are on a scale of around 1 mm, and so the length constant of around 1 mm, or several hundred microns, poses a considerable and a real problem for information transfer. The problem is, in fact, much larger when we begin to think about the output of a neuron that is transmitted down the axon of cells. The axon of cells can travel for many centimeters, and even meters; and under these circumstances, the length constants of around 1 mm become so problematic that basically no signal would be transferred passively down an axon.

Notes

Summary

1m 34s

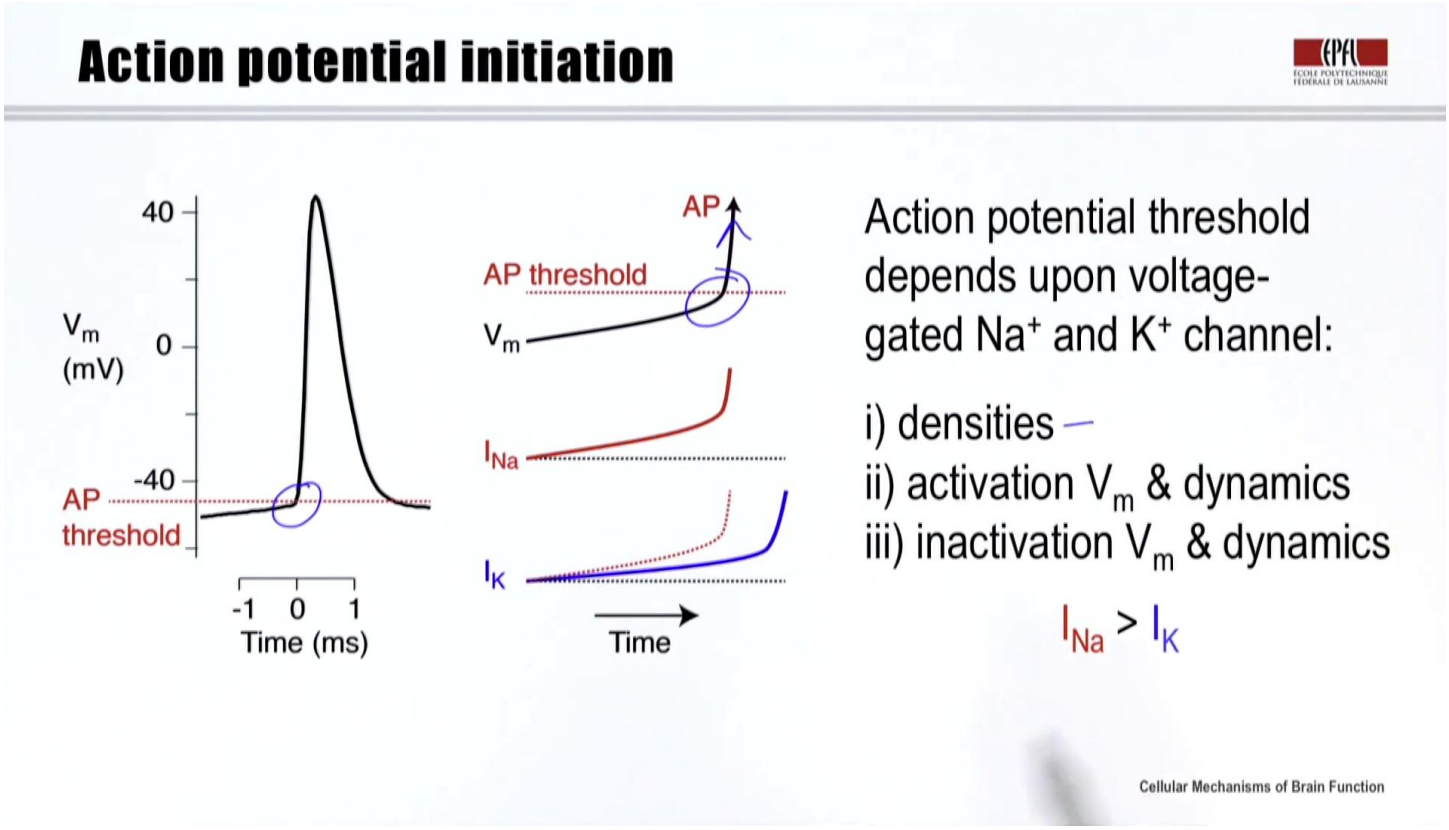


As we'll learn today, the regenerative nature of the all-or-none, explosive amplification of the action potential allows it to propagate down axons faithfully; so that when we have an axon potential at one location, it's faithfully transmitted to an other location because of the regenerative, explosive activation of those voltage-gated sodium channels.

Notes

Summary

3m 15s

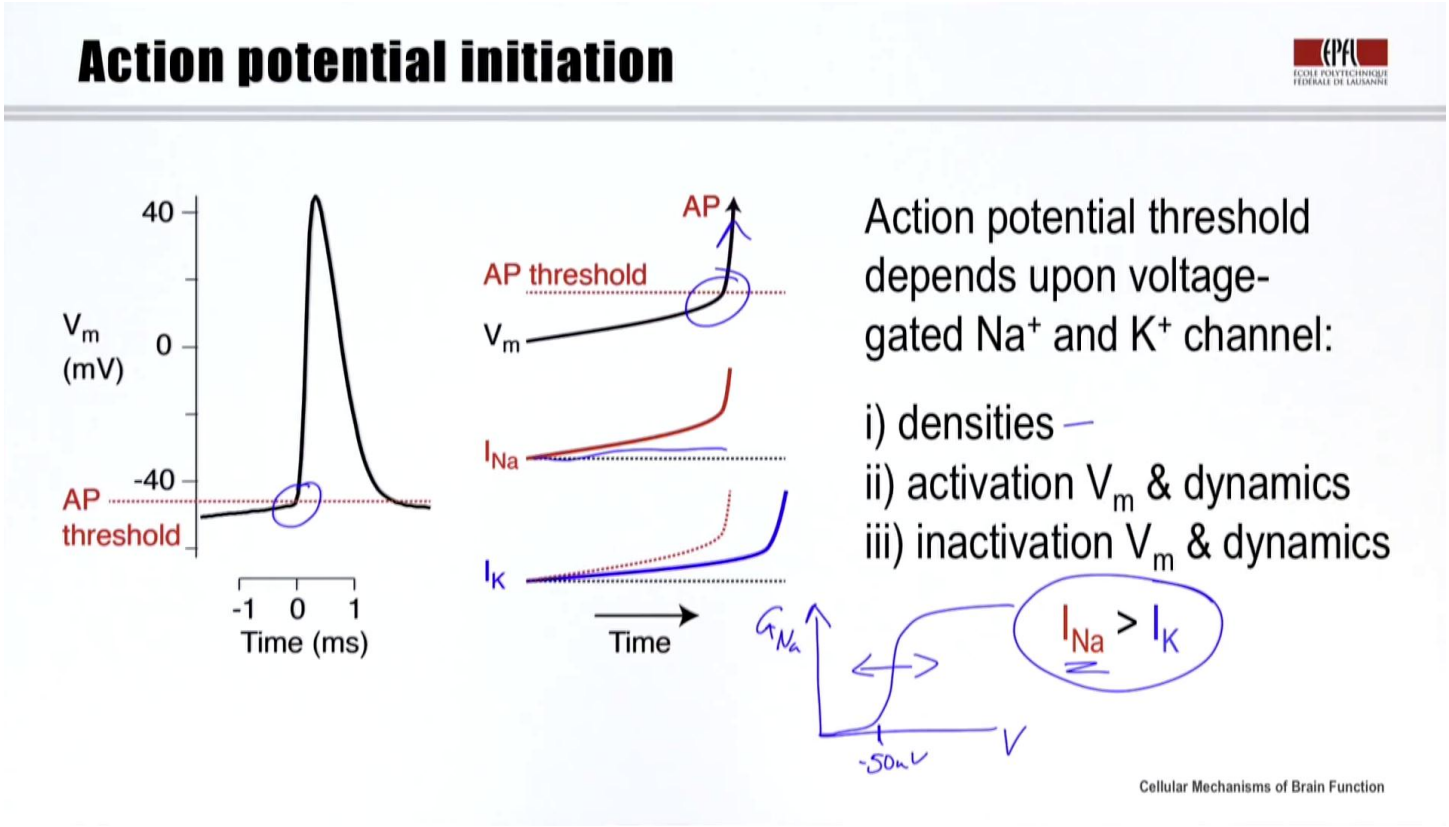


Before we can think about the propagation of the action potential, we must first find out where and how it's initiated. Here is a recording of an action potential. On the millisecond timescale, the membrane potential depolarizes; on a certain point, we hit the action potential threshold, and the voltate shoots up towards positive potentials driven by the activation of the voltage-gated sodium conductance. If we zoom in on a portion here close to the action potential initiation, we see, of course, the depolarizing membrane potential; we see the increase in the sodium current that outpaces the increase in the potassium current. And that's the key feature: the sodium conductance must be larger than the potassium conductance, and then eventually we hit threshold, and then action potential is initiated: a point of no return. And the precise location of that action potential initiation of the action potential threshold will then depend upon how much sodium current there is. So, the sodium current density is one important feature. Another important feature is the activation voltage.

Notes

Summary

3m 40s

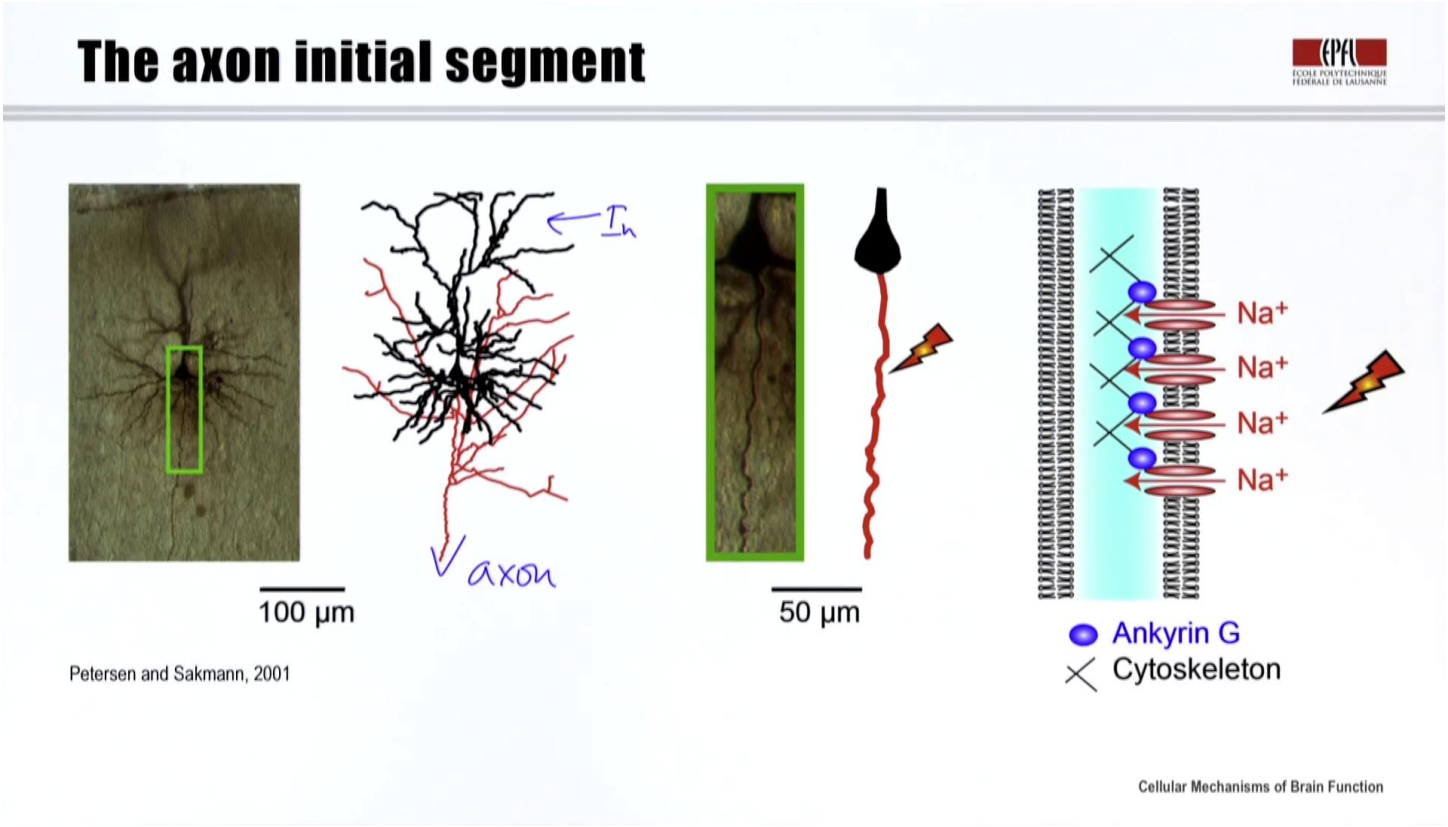


You'll remember that there's a voltage-gated activation curve of the sodium, and also of the potassium conductance, where, at a certain voltage, the sodium conductance begins to become activated: somewhere above +50mV. And so, shifting the activation threshold of the voltage-gated sodium channel is another way in which the AP threshold can be moved. And similiarly, the inactivation of the voltage-gated sodium channel can make a difference: basically, if we inactivate the sodium channel, then we might never reach threshold, because the voltage-gated potassium conductance might out-compete it. And the condition that we need to fulfill is a large sodium current.

Notes

Summary

4m 58s



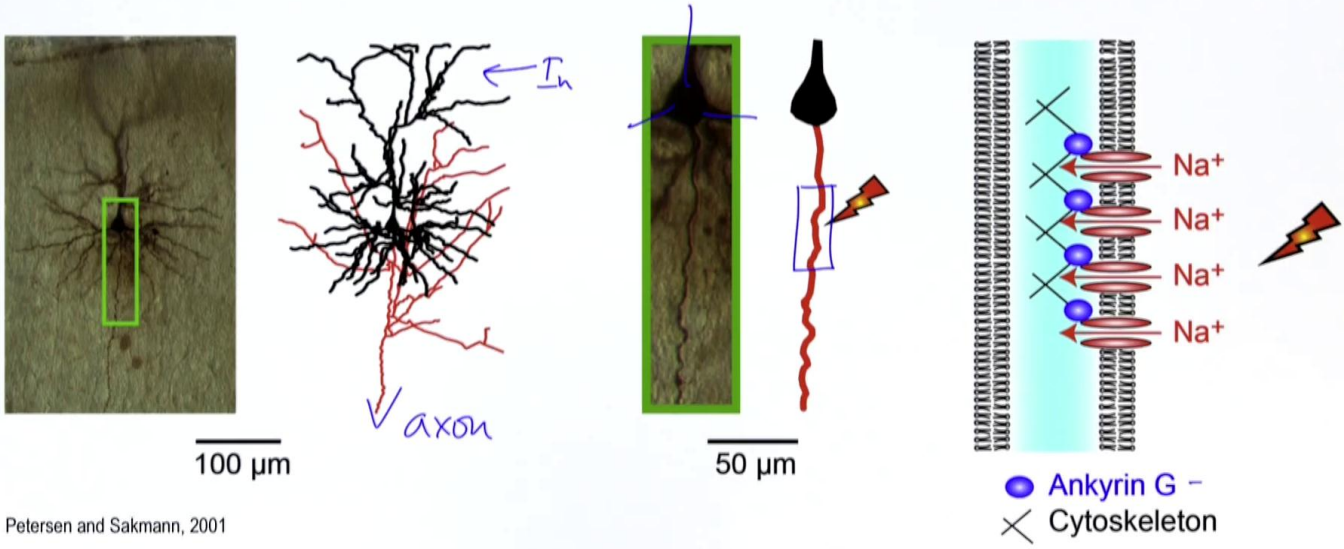
And so, there's a variety of ways in which we can get low action potential thresholds; but the one that appears to be most relevant in terms of the initiation of action potentials in the mammalian nervous system is the density of voltage-gated sodium channels. In fact, in most mammalian neurons, the action potential is always initiated at one unique location: the axon initial segment. Here is an image of an excitatory pyramidal neuron in the neocortex. The dendrites that you can see here, filled in black with a dye and reconstructed here in black for you, are the places where signals from other neurons arrive; so, there's an input end of the neuron; and these are the so-called dendritic arborizations. Thinner, and only visible in part, and only reconstructed in part here in red, is the axon, which is the output end of the neuron. So, signals come in, into the dendrites; it's processed; and there's an output on the axon, where the signals are transmitted to other nerve cells. If we zoom in on this area, region in the green box, you can see at higher magnification the cell body, where the DNA of the cell is located.

Notes

Summary

5m 45s

The axon initial segment



Petersen and Sakmann, 2001

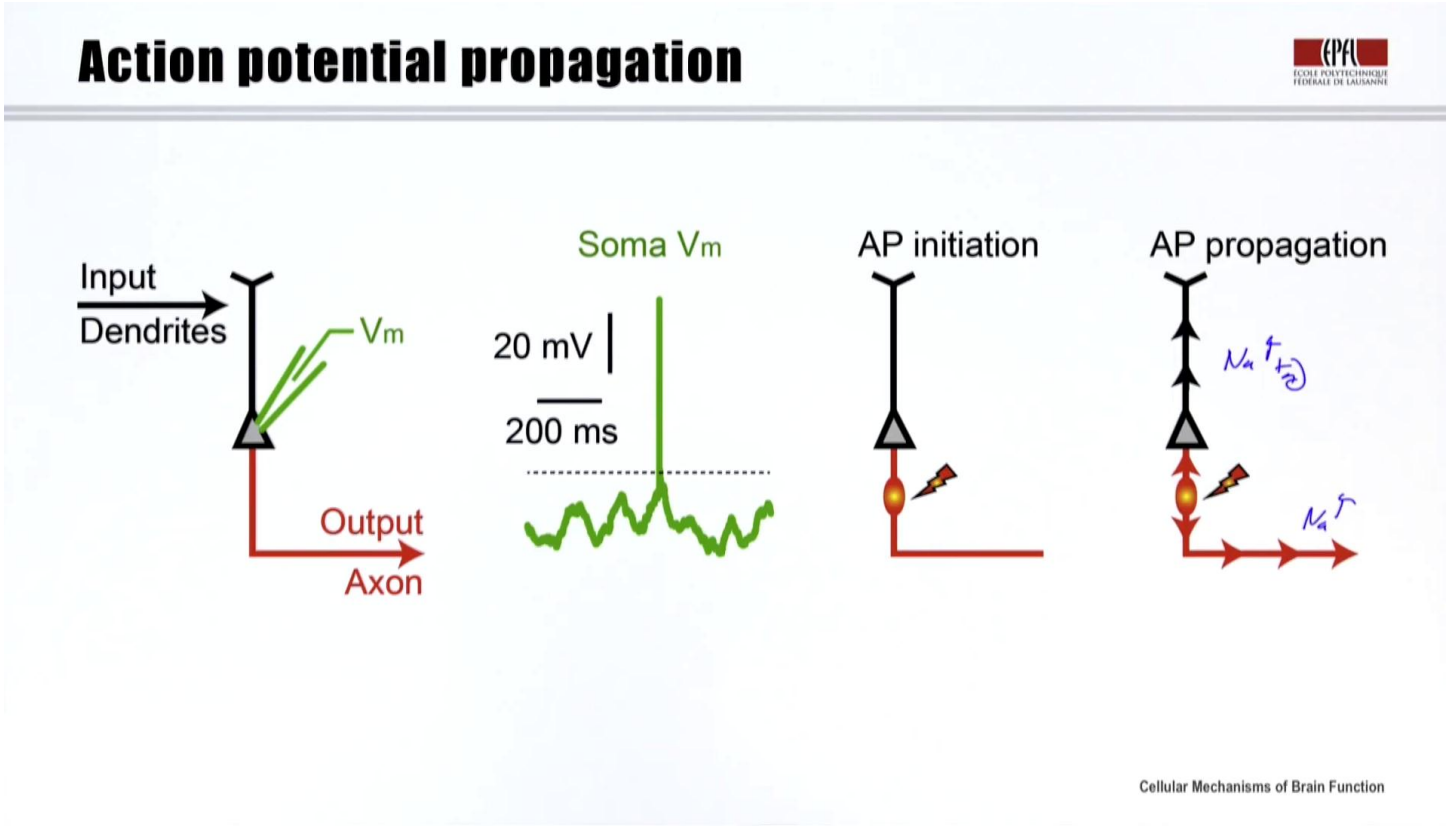
Cellular Mechanisms of Brain Function

We have the dendritic processes that stick out from here; and in the thin, you see a smooth structure here: the axon, that descends in towards the depths of the brain. This unique process, the axon, is thinner than the dendrites and somewhere around 50 µm away from the cell body is an interesting specific location called the axon initial segment. And at that area, we find a very high density of voltage-gated sodium channels. Many times, more sodium channels are located in this part of the cell membrane than anywhere else. The voltage-gated sodium channels are clustered here by molecular scaffolds. The voltage-gated sodium channels bind to another protein called Ankyrin G that binds to the cytoskeleton; and that anchoring process is involved in clustering the voltage-gated sodium channels here at a high density. And that high density of sodium channels means that this is the point of the neuron that has the lowest voltage activation threshold for the action potential. Action potentials are initiated right here, in the axon initial segment.

Notes

Summary

7m 14s

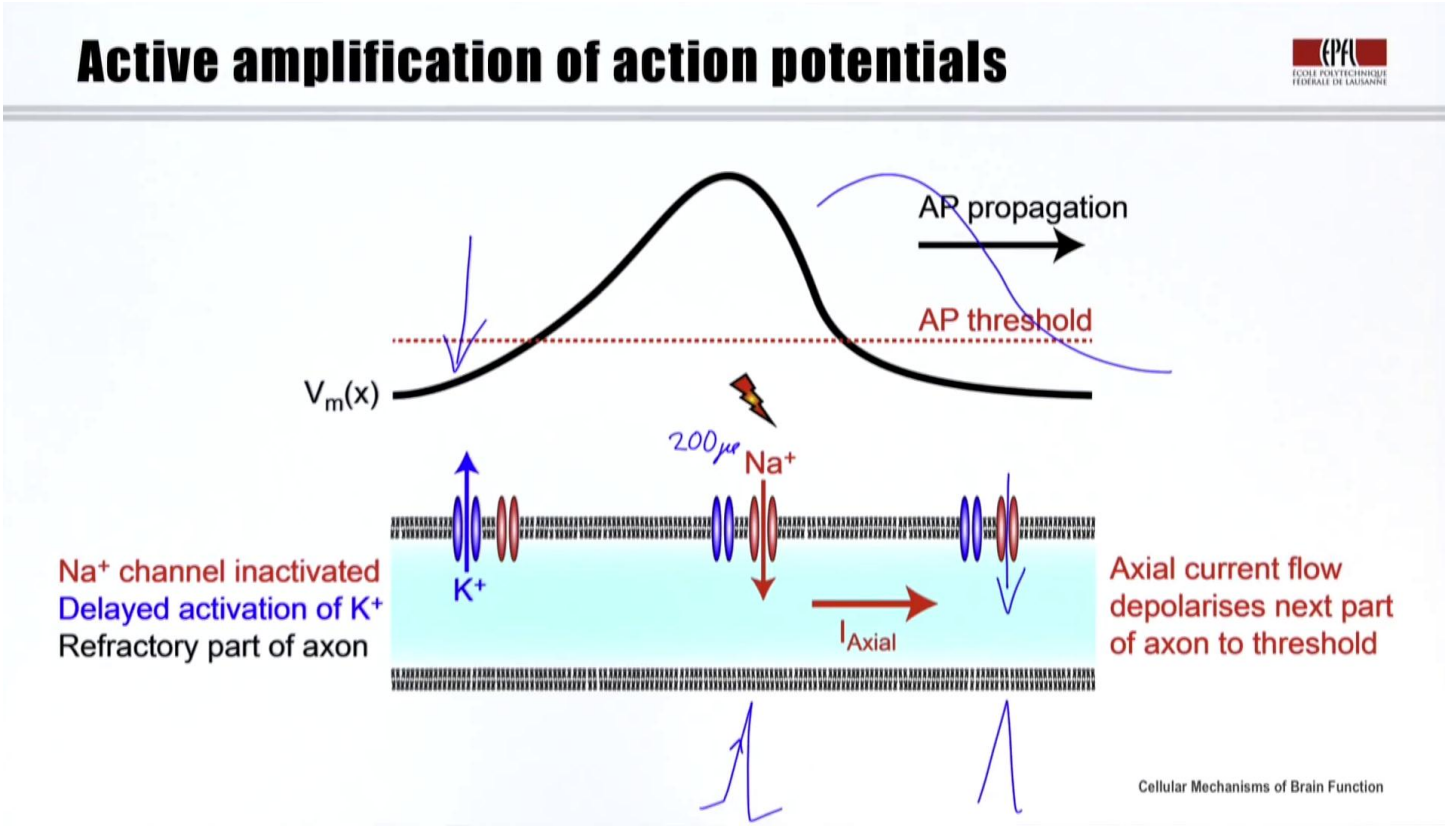


So, if you were recording the membrane potential of a neuron here at the soma, and there's input arriving from other neurons across the dendrites, we'll see that the membrane potential fluctuates; and if the input is sufficiently large, that drives the membrane potential to cross threshold, and an action potential is initiated. We now know that the action potential initiation occurs at the axon initial segment, some 50 µm away from the recording site. From the axon initial segment, the action potential propagates actively, through the regenerative activation of voltage-gated sodium channels that are distributed, not only at the axon initial segment, but across all neuronal membranes. The action potential, therefore, is initiated here; but, through regenerative activation, it propagates down the axon. It also propagates back up towards the soma, which is where we record this action potential; and it also propagates back into the dendrites. And again, voltage-gated sodium channels are present here, and they can regeneratively amplify the signal in a positive-feedback way. Somewhere across these dendrites, sodium channel density drops below a critical number, and the action potential stops propagating. That's not true of the axon; the action potential is faithfully propagated throughout the extent of the axon of real mammalian nerve cells.

Notes

Summary

8m 35s



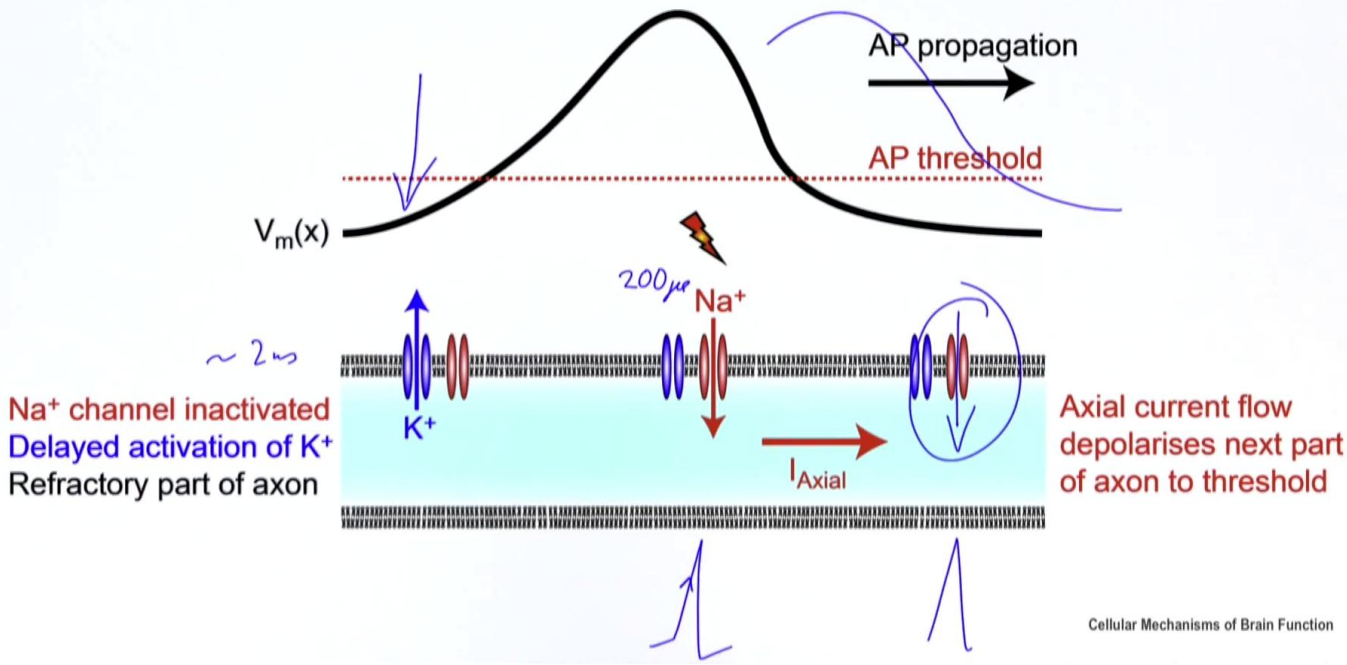
The propagation of the action potential is thus supported by the regenerative activation of voltage-gated sodium channels. Let's imagine we have a snapshot of an area of the axon through which the action potential is propagating. This area of the axon is currently excited. It's depolarized; the voltage-gated sodium channels are open; and there's a large sodium flow coming into the axon. That sodium flow, in part, goes down the axial direction of the axon, causing further depolarization in this area here -- where, in turn, it will activate the voltage-gated sodium conductance, driving a new, regenerative spike in this area, propagating the voltage waveform forwards in this direction. On the tail, the voltage-gated sodium channels become inactivated. Remember, they're only open for a short period of time. They're transiently activated for around 200 μs. Afterwards, they inactivate; and instead, the delayed activation of the potassium conductance takes over, hyperpolarizing the membrane potential on the falling part of the action potential waveform as it propagates down the axon. And so, we have a refractory part of the axon here where the voltage-gated sodium channels are inactivated for a period of some milliseconds.

Notes

Summary

10m 12s

Active amplification of action potentials

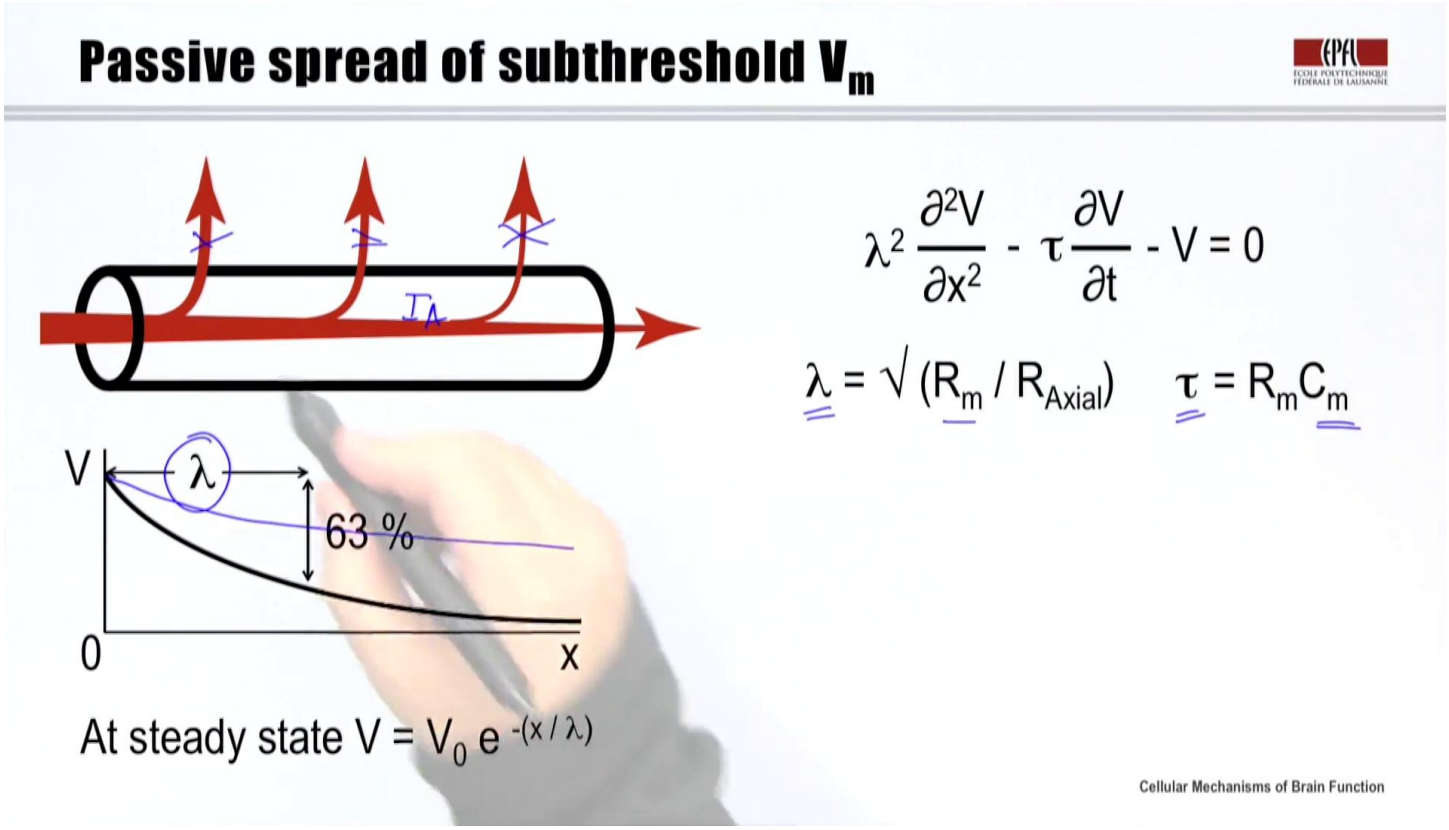


The potassium conductance is open, and no further action potentials can be initiated here for a period of some milliseconds. On the other hand, this wavefront here is propagating rapidly through the spread of current axially, and the activation of the voltage-gated sodium conductance.

Notes

Summary

11m 45s



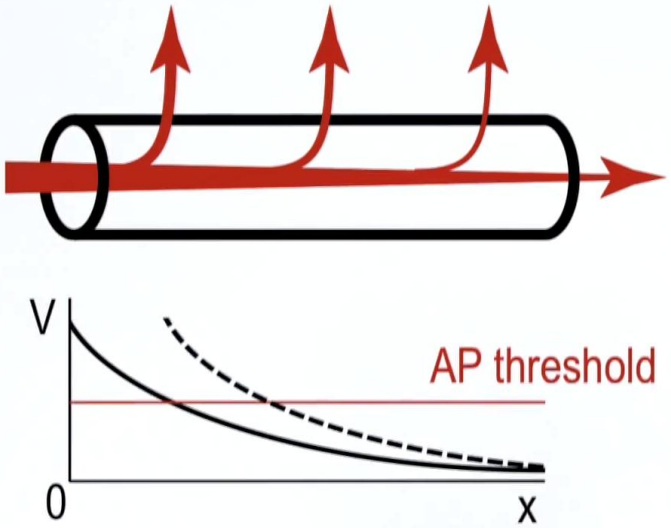
So, the spread of the action potential depends critically upon the axial spread of current flow. And so, let's quickly review what we know about axial current flow in cables. We looked at the cable equation across neurites, and we found that there were key determinants for the filtering of voltage as it tries to propagate down the cable. There was a length constant for the membrane, and there was a membrane time constant. And these have obvious and intuitive ideas about them. The length scale for, say, a steady-state membrane potential drops off with the exponential time-distance factor of λ, and we can intuitively imagine that, if we have a high membrane resistance, we have less leak of current; and we therefore would have a greater spread of current in the axial direction. And so, λ would increase. Equally, if we have a lower axial resistance, that would also, of course, increase the axial current flow. In addition, we have some filtering of the signal through the capacitors. So, some of the axial current flows across the membrane conductances, and another part is used to fill the capacitance.

Notes

Summary

12m 06s

Action potential propagation speed



Action potential propagation speed depends upon axial current flow.

AP speed increases with:
i) Higher membrane resistance
ii) Lower axial resistance
iii) Lower membrane capacitance

Typical AP speed = ~1 m/s

Cellular Mechanisms of Brain Function

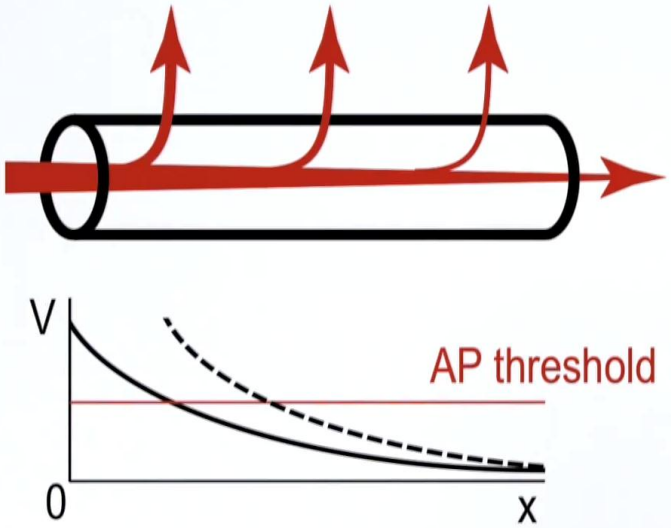
And so, in time, if we imagine that there's a brief signal and membrane potential here, -- a brief current pulse, or a brief voltage pulse -- that will then spread to other locations, but after filtering. And so, at this location, we might see a signal that looks like this; and a bit further away -- it's filtered both in space and in time -- we get slower potentials, and that are smaller, in time, and also delayed. And so, both the temporal filtering and the length-scale filtering will tend to affect the spread of current down the axial direction, and will therefore affect things like the propagation, reliability, and speed of the action potential. And so, if we want to have a rapid and reliable action potential propagation, then we need to have a high membrane resistance -- so that there's little leak, and we get these long length constants -- a low axial resistance -- so, that there's, again, a greater current flow and, again, a longer length constant -- and a low membrane capacitance -- so that there's less of the current flow down the axial direction that's used in charging the membrane, and more of it can propagate down the axon, giving rise to the regenerative activation of voltage-gated sodium channels.

Notes

Summary

13m 28s

Action potential propagation speed



Action potential propagation speed depends upon axial current flow.

AP speed increases with:
i) Higher membrane resistance
ii) Lower axial resistance
iii) Lower membrane capacitance

Typical AP speed = ~1 m/s

~ 1 mm / ms

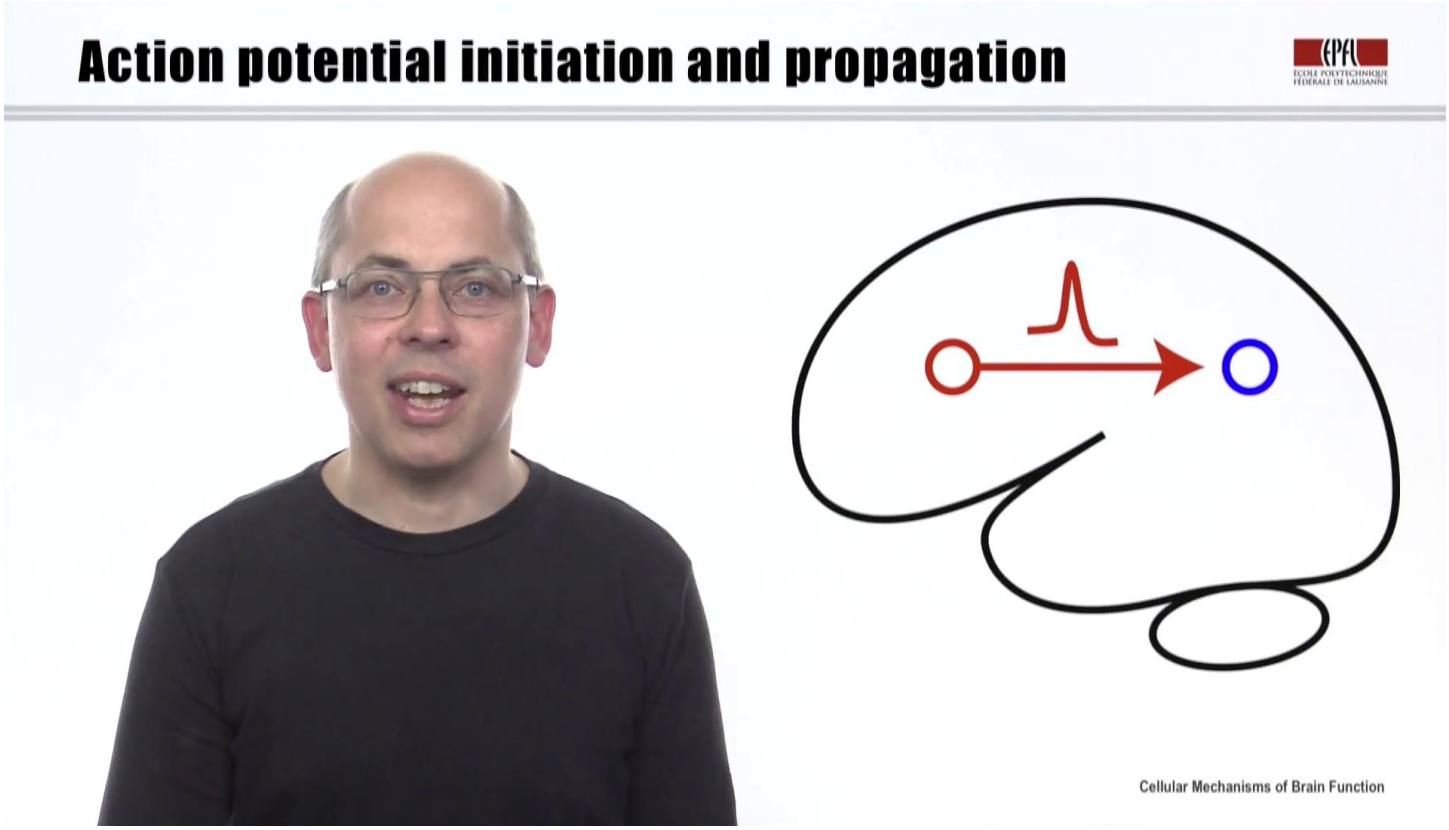
Cellular Mechanisms of Brain Function

In a typical neuron of the mammalian nervous sytem, the action potential propagation speed is around 1 m/s; so, that's around 1 mm/ms. And if we think about neuronal computations that need to take place on the millisecond time scale in order to be compatible with behavior, this then allows local processing in a small cube of brain of around 1 mm³ to take place with high speed and high accuracy. On the other hand, if you need to propagate the signals further, then maybe 1 mm/ms begins to seem a little bit slow. And in particular, last lesson, we learned about the squid giant axon, which had this enormously large, thick-diameter axon that then gives it a very low axial resistance; and for the squid giant axon, this then increases action potential propagation speed to something like 25 m/s: perhaps the difference between life and death for the squid as it tries to escape its predator.

Notes

Summary

14m 51s



So, we've now seen that the digital, all-or-none signal of the action potential in the brain serves a good purpose in terms of reliable information transfer down the axon. The action potential propagates through the regenerative activation of voltage-gated sodium channels, and it propages at around 1 m/s, 1 mm/ms, allowing at least local computations in nearby neurons of the brain to take place on that millisecond time scale. However, some parts of the brain are located much further away than 1 mm; and if we think about, say, controlling our leg movements, then we need to think about distances of around 1 m. And then, the action potential propagation speed of 1 m/s doesn't seem so impressive. It would take one second for a signal from the brain to reach the leg, and if we think about the speed of movements, this is clearly not compatible with our normal behavior. There must be ways in which axon potential propagation can be sped up. And that process is known as myelination.

Notes

Summary

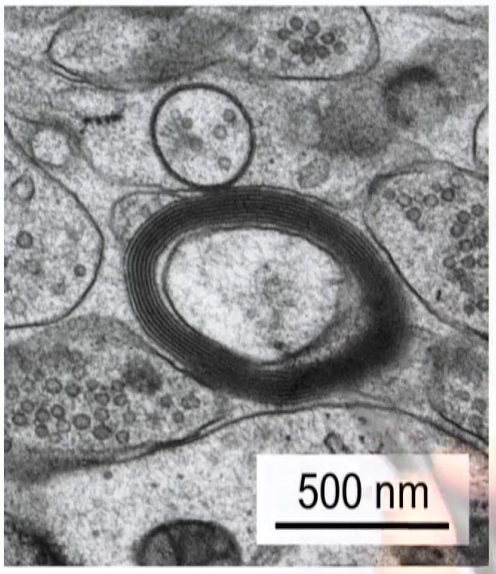
16m 01s

Myelination

Specialised glial cells (oligodendrocytes and Schwann cells) wrap very thin processes around selected axons. The myelin processes contain 80% lipid, which is a good electrical insulator.

Myelination increases axonal membrane resistance by a factor of ~5,000 and decreases axonal capacitance by ~50.

$$\lambda = \sqrt{(R_m / R_{Axial})}$$



Korogod, Petersen and Knott

Cellular Mechanisms of Brain Function

Myelination is a process in which specialized glial cells -- that is, not neurons; so, there are non-excitable cells that are present in the brain. These glial cells -- oligodendrocytes, and Schwann cells in the peripheral nervous system -- they wrap very thin processes around selected axons. And here, in this electron micrograph, you see a large-diameter axon that's somewhere around 500 nm in diameter; and this process, wrapped around it, has this black layers of membrane that are wrapped around, and around, and around. And there's an oligodendrocyte here that sends out this process and wraps it around this membrane many, many times. And these membrane processes -- these myelin processes -- are made largely of lipid. And lipid, as we already know from our consideration of the cell membrane, is a very good electrical insulator; it's a dielectric. And what this wrapping does, around the axon, is actually a little bit similar to what the plastic coating of a cable does in our standard electronical devices. It increases the axonal membrane resistance by a large factor -- something like a factor of 5,000 -- so that there's very little leak that occurs across the myelinated axon.

Notes

Summary

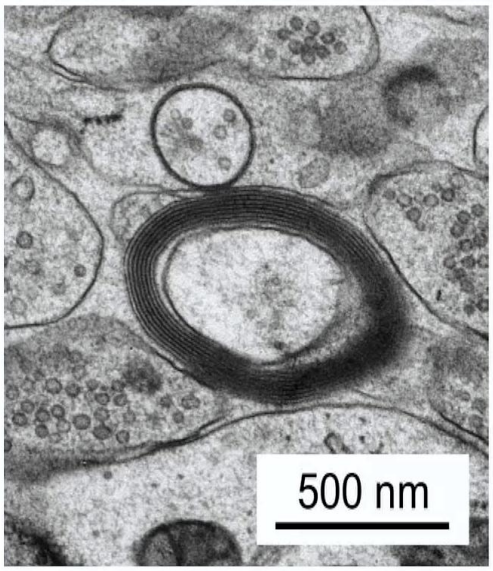
17m 16s

Myelination

Specialised glial cells (oligodendrocytes and Schwann cells) wrap very thin processes around selected axons. The myelin processes contain 80% lipid, which is a good electrical insulator.

Myelination increases axonal membrane resistance by a factor of ~5,000 and decreases axonal capacitance by ~50.

$\lambda = \sqrt{(R_m / R_{Axial})}$



Korogod, Petersen and Knott

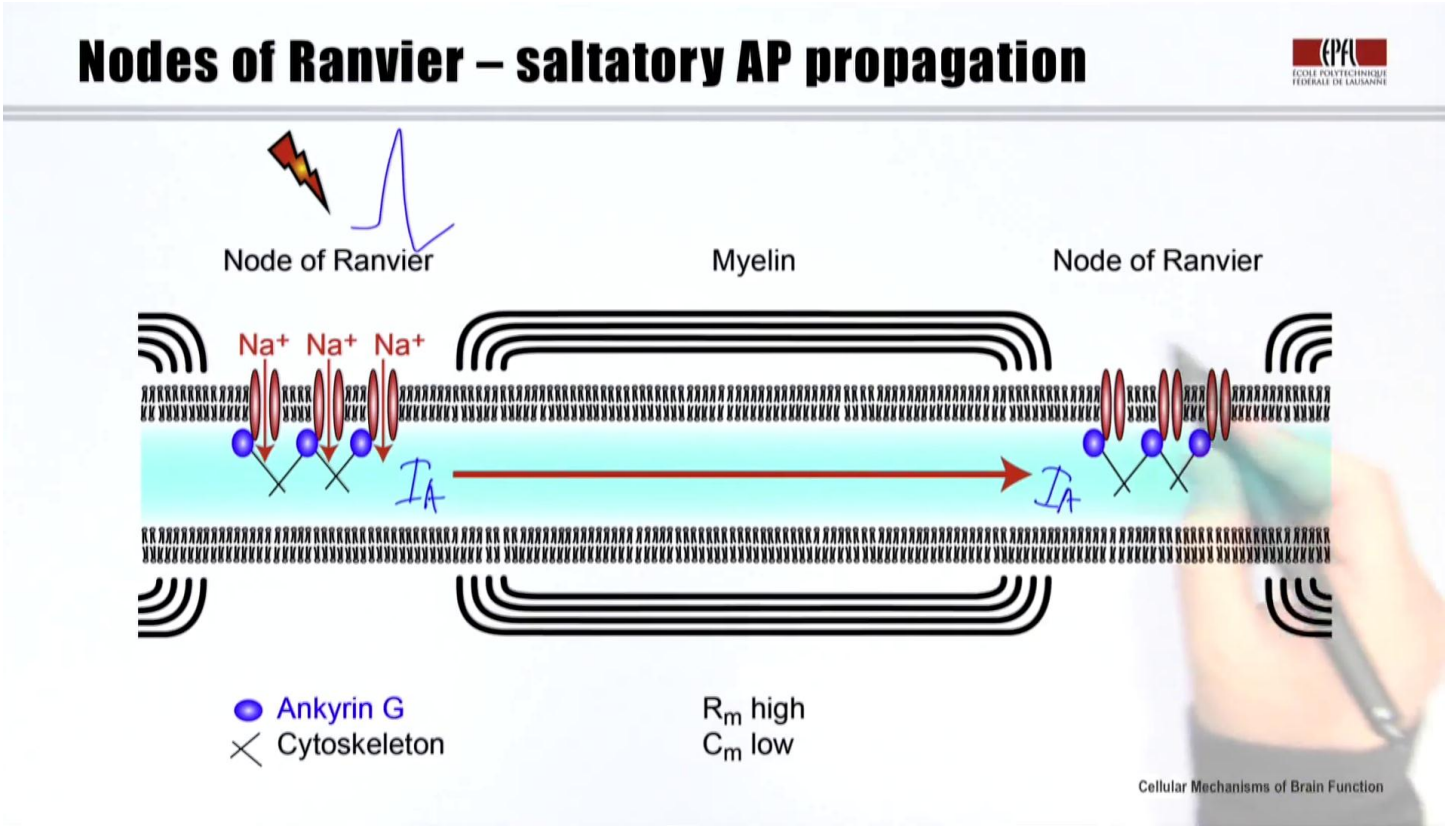
Cellular Mechanisms of Brain Function

And it also decreases the axonal capacitance by a factor of something like 50. This, then, has several effects in terms of the propagation of signals down the axon. By increasing the membrane resistance, we increase the length constant of the membrane; and by decreasing the capacitance, we also decrease the membrane time constants. And so, the signals that are sent inside a myelinated axon travel further and are filtered less in time: both of which are helpful in terms of propagating action potentials down axons.

Notes

Summary

18m 49s

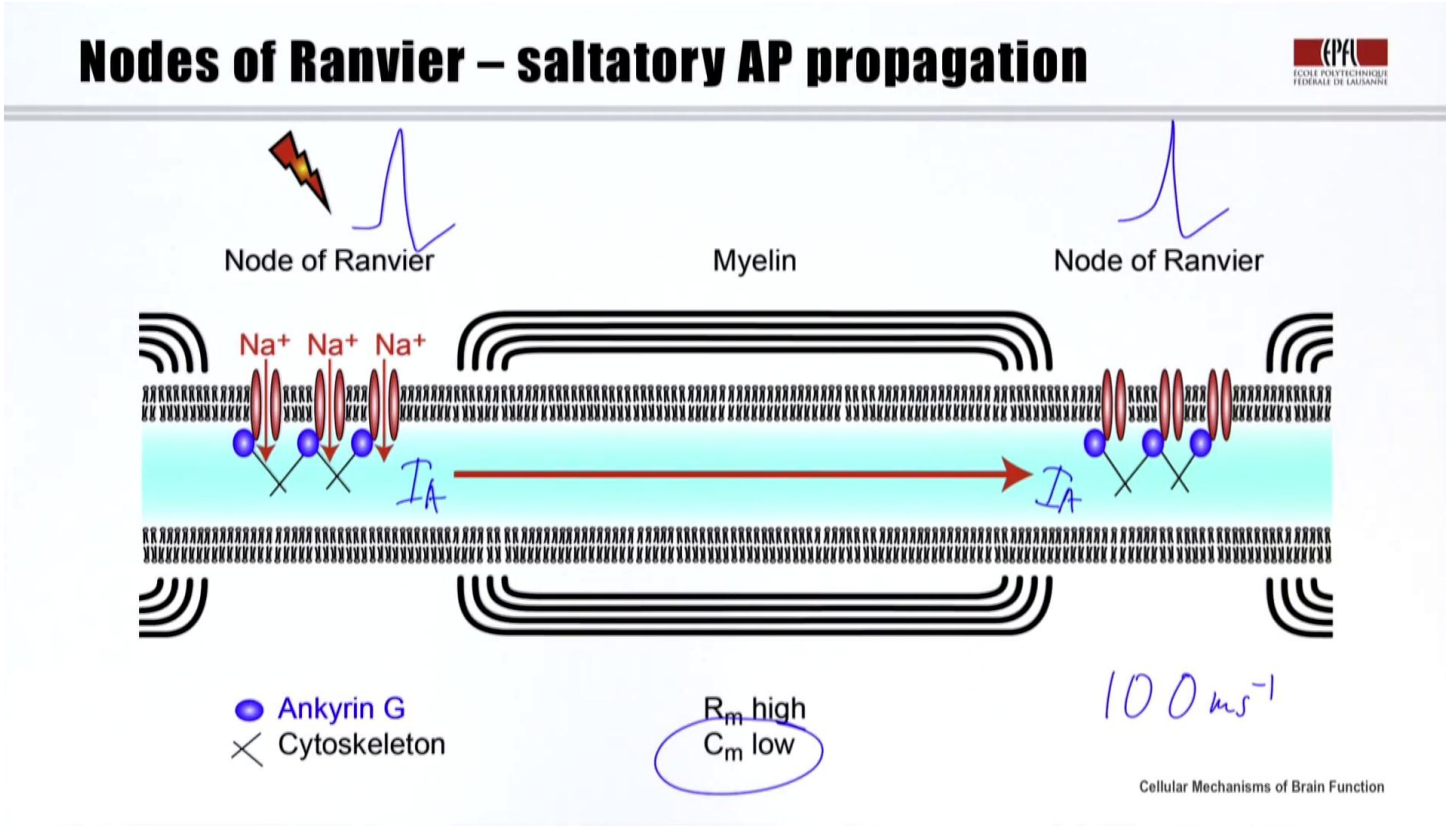


The myelination, it turns out, is not sufficient for propagating action potentials across, say, a meter of space. The action potential is regeneratively amplified at different points called Nodes of Ranvier. At a Node of Ranvier, which is actually very similar molecularly to the axon initial segment, we have a high density of voltage-gated sodium channels. These are clustered and held in place by our scaffolding molecules: Ankylin G, and the cytoskeleton. And so then, this is very similar to the axon initial segment. It's an area where the threshold for action potential is very low. And so, we can imagine an action potential being fired at this location in space; in between, we have 1 mm of myelin. Here, the membrane resistance is high; the membrane capacitance is low; and so we get a faithful transfer of current down the axial direction, across this myelinated bit of axon. The capacitance is low, and so the filtering of the signal is also very little; and so it's a fast transfer of this current. The depolarization then reaches the next Node of Ranvier and fires another action potential.

Notes

Summary

19m 28s

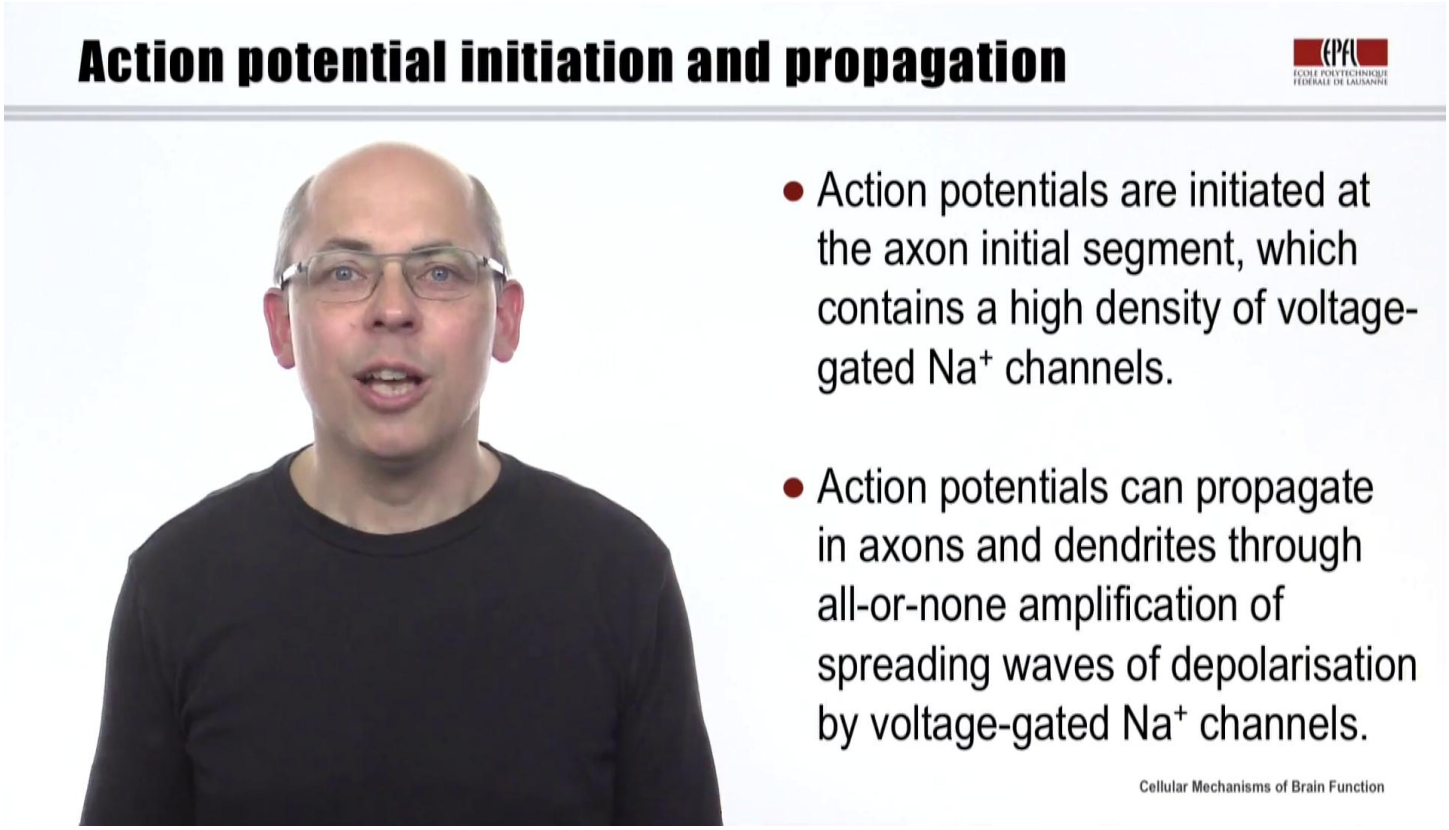


And so, the action potential jumps, from Node of Ranvier to Node of Ranvier; and the jump is fast, because the capacitance is low; and the current reaches faithfully the next Node of Ranvier. In myelinated axons, action potential propagation can occur at speeds of around 100 m/s. And now we can see how the brain can control our legs and allow us to run at high speed.

Notes

Summary

20m 53s

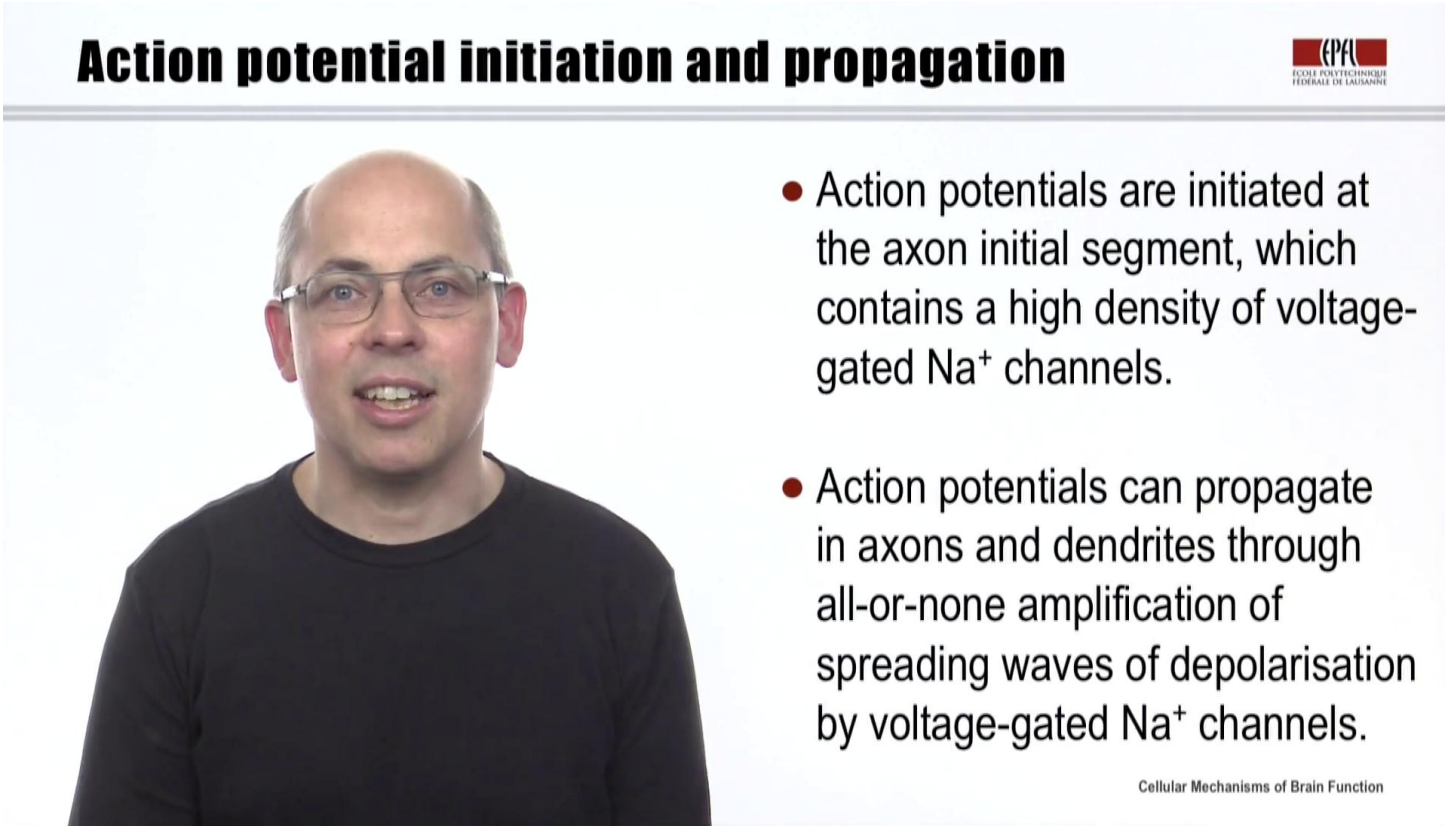


So, in this lesson, we've seen the advantages of the digital, all-or-none action potential signal. The action potential is initiated at the axon initial segment: a location in the cell where there's a very high density of voltage-gated sodium channels. The action potential propagates faithfully down the axon and into the dendrites, through the regenerative activation of voltage-gated sodium channels. There's a spread, a passive spread, of current down the axial direction of the axon; and that, in turn, drives the explosive, positive feedback of activation of voltage-gated sodium channels in the next segment of the axon. Action potential propagation takes place at around 1 m/s, or 1 mm/ms, within unmyelinated axons that dominate local circuit activity within the brain; and, for longer-distance communication across larger parts of the human brain -- for example, the 20 cm that separate the front and back of the brain, or the 1 m that separates the brain from the end of the spinal cord -- for these long distances, myelinated axons are used that have much higher propagation velocities of around 100 m/s. So, the digital signal of the action potential allows reliable and high-speed communication of different nerve cells in the brain.

Notes

Summary

21m 21s



The signal can go from one neuron to the entire extent of that neuron, down its axon, in a very short period of time of just a few milliseconds. When that signal reaches the end of the axon, it releases a signal to talk to the downstream neuron or the downstream muscle. That release of neurotransmitter is called synaptic transmission, and that's what we'll discuss next week.

Notes

Summary

22m 50s