

ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

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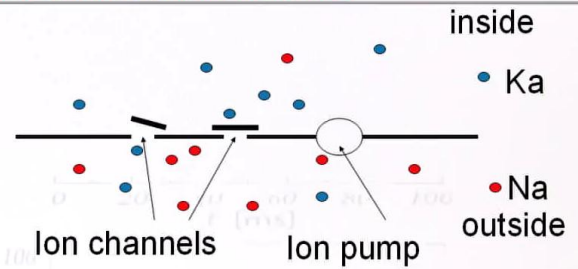
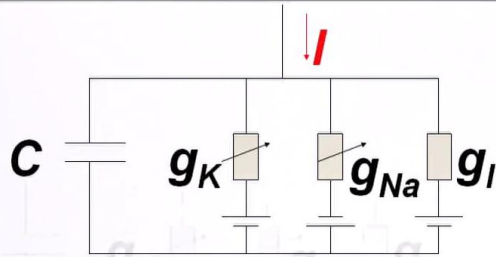
- ✓ 2.1 **Biophysics of neurons**
 - Overview
- ✓ 2.2 **Reversal potential**
 - Nernst equation
- ✓ 2.3 **Hodgin-Huxley Model**
- 2.4 **Threshold in the Hodgkin-Huxley Model**
 - where is the firing threshold?
- 2.5. **Detailed biophysical models**
 - the zoo of ion channels



Video



Neuronal Dynamics – 2.4. Threshold in HH model

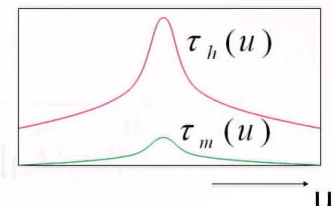
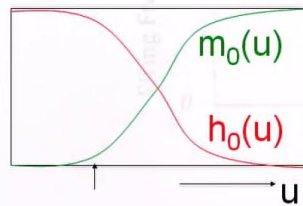


$$C \frac{du}{dt} = -g_{Na} m^3 h (u - E_{Na}) - g_K m^4 (u - E_K) - g_l (u - E_l) + I(t)$$

$$\frac{dm}{dt} = \frac{m_\infty(u) - m}{\tau_m(u)}$$

$$\frac{dh}{dt} = \frac{h_\infty(u) - h}{\tau_h(u)}$$

Where is the threshold for firing?



Welcome to part four of the second week of the class Neuronal Dynamics. In part three, I introduced the Hodgkin-Huxley model. This is a complicated mathematical model consisting of four coupled nonlinear differential equations. And therefore, it would be rather difficult to just sit down with a piece of paper and a pencil and work out what happens in a step by step fashion. However, it's possible to assimilate a model and indeed, Hodgkin and Huxley already in the 1950s, simulate the model on a computer. Or rather, maybe I should say a calculator, a calculator of that time, where they typed in the parameters, and then, step by step, got an output time step by time step of the evolution of the membrane potential and the other variables. So this complicated model of four differential equations has a first equation for the voltage, a second equation for m , a third equation for h , and a fourth equation for n , which is sort of similar to that of h . And the question is, does this model indeed generate action potentials? And yes, it does. But can this say something about the conditions for finding an action potential? Is there something like a threshold for firing? This is one of the questions we'll address in this part four.

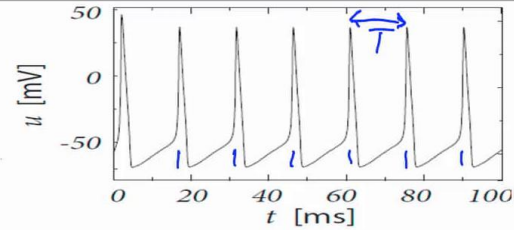
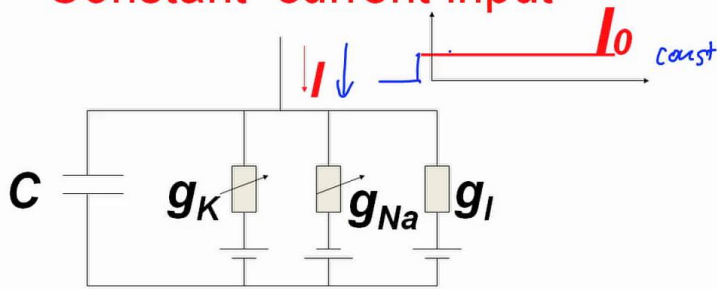
Notes

Summary

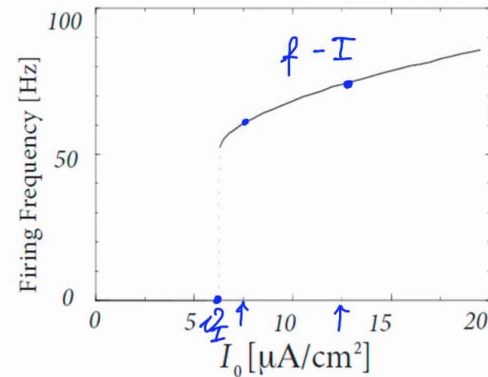


Neuronal Dynamics – 2.4. Threshold in HH model

Constant current input



$$\nu = \frac{1}{T}$$



Threshold?
for repetitive firing
(**current threshold**)

So if we simulate the model by injecting a constant current into the circuit, if the current is sufficiently strong, what we'll find is a sequence of action potentials that is generated at some regular intervals. There's an interspike interval-- the difference in time between two spikes-- which is the period of the regular firing. And now I can talk about the firing frequency as $1/T$. And I can plot for different values of the constant current. Each time it's a constant. For example, I take the current of 12.5, I get a certain firing frequency. That's this value here, say. I do it for a different current, I get a different result. And this way I can plot the $f-I$ curve-- the frequency current curve-- for the Hodgkin-Huxley model. And what you observe is, that there's a minimal current. A threshold current, I_0 . If we are above this minimal current, the model generates regular firing. If you're below this threshold current, then the model shows constant firing. This threshold corresponds to the current that I need if I switch from zero input to the new current I_0 . So at first glance we may say, OK, so now we have found a threshold. There is something like a threshold for repetitive firing, and this threshold corresponds to a minimal current. In that sense, it's a current threshold. So does the model really have a current threshold?

Notes

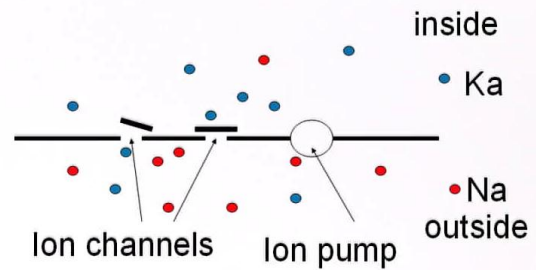
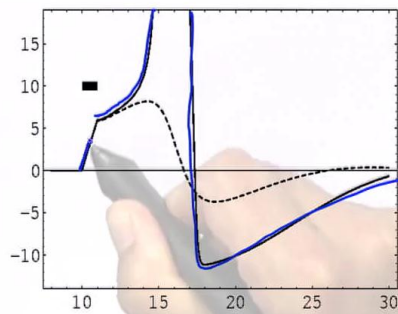
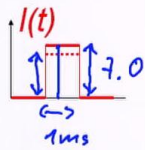
Summary



1m 43s

Neuronal Dynamics – 2.4. Threshold in HH model

pulse input



Threshold?

- AP if amplitude 7.0 units
 - No AP if amplitude 6.9 units
- (pulse with 1ms duration)
(and pulse with 0.5 ms duration?)

Well, that's not exactly true because if you change the paradigm we find something completely different. Now, instead of a constant current, you have a short pulse current of, say, one millisecond duration. And if the pulse has an amplitude which is sufficiently high, then an action potential is generated, which is completely out of balance. It goes up-- if zero here is the resting value, it goes up to about 100 millivolts. And then it comes down again and returns slowly back to the resting potential. Now, if I decrease the current just a tiny little bit, just really-- just a little bit less stimulation, then I get the other trace-- the dash trace-- and there's no action potential. So you may say that, in these current units-- for example, a current of seven-- gives an action potential, whereas a current of 6.9 does not. So does this mean that now we have, again, a current threshold? Well, think about it. This cannot be true because if I now use a current that does not have a duration of 1 millisecond, but which has a duration of 0.5 milliseconds-- so I take my current of amplitude 7. But I stop at 0.5 milliseconds. Then it only works up here. The first 0.5 milliseconds are the same.

Notes

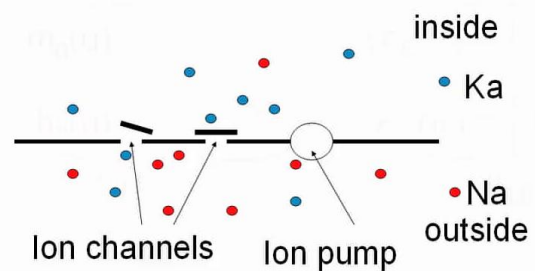
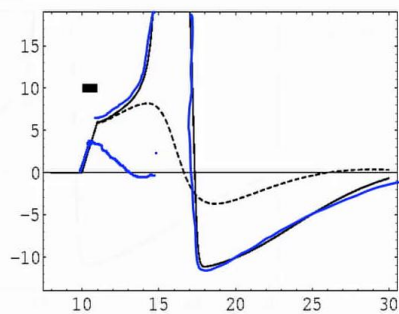
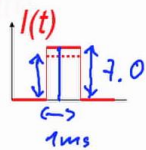
Summary



3m 46s

Neuronal Dynamics – 2.4. Threshold in HH model

pulse input



Threshold?

- AP if amplitude 7.0 units
 - No AP if amplitude 6.9 units
- (pulse with 1ms duration)
(and pulse with 0.5 ms duration?)

The voltage will only increase for the first 0.5 seconds. And then it's left alone. And it will do something which I don't want to assimilate. But it will return back. So the value 7.0 is completely uninformative because it depends on the shape of the pulse and the duration of a pulse, and many other things.

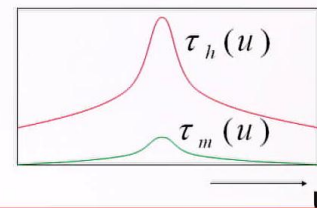
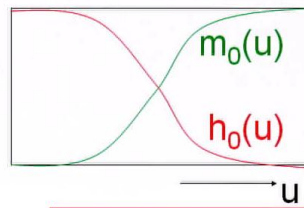
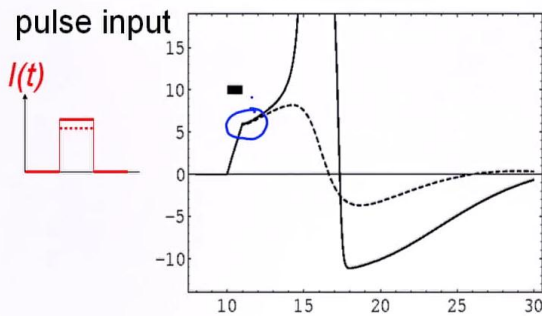
Notes

Summary



5m 32s

Neuronal Dynamics – 2.4. Threshold in HH model



Mathematical explanation

$$C \frac{du}{dt} = -g_{Na} m^3 h (u - E_{Na}) - g_K n^4 (u - E_K) - g_l (u - E_l) + I(t)$$

$$\frac{dm}{dt} = -\frac{m - m_0(u)}{\tau_m(u)}$$

$$\frac{dh}{dt} = -\frac{h - h_0(u)}{\tau_h(u)}$$

So what can we say? We can say that we have a system consisting of four differential equations. There's a sodium current, there's a potassium current, there's a leak current, and this is my stimulation. And I don't really see a threshold. But nevertheless, this threshold effect that we have observed in simulations must be somehow hidden in the equations. So can we get a more mathematical explanation of the things we observe in the simulations?

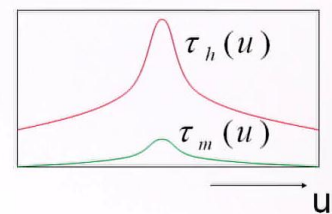
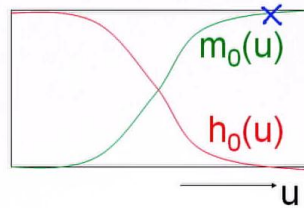
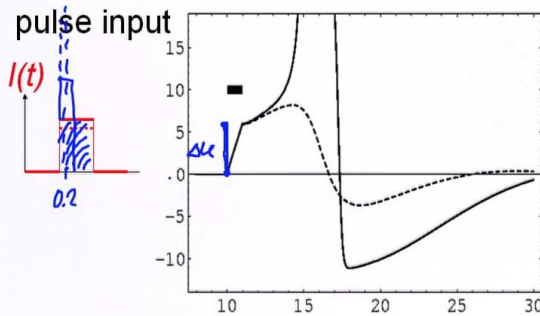
Notes

Summary



5m 56s

Neuronal Dynamics – 2.4. Threshold in HH model



$$C \frac{du}{dt} = -g_{Na} m^3 h (u - E_{Na}) - I_K - I_{leak} + I(t)$$

I_{Na}

Stim. ↓

$$\frac{dm}{dt} = -\frac{m - m_0(u)}{\tau_m(u)}$$

$= q \delta(t - t_0)$

$$\frac{dh}{dt} = -\frac{h - h_0(u)}{\tau_h(u)}$$

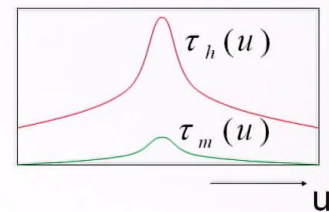
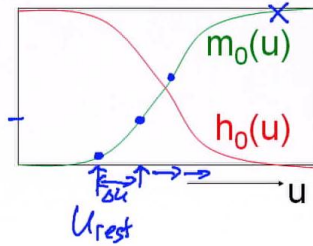
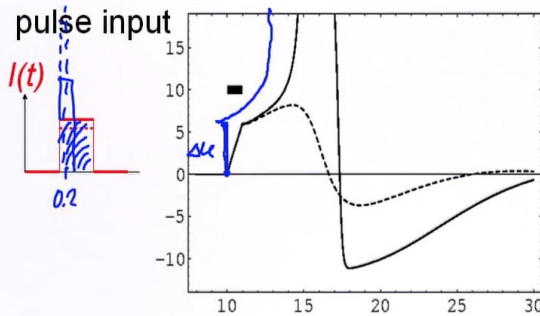
Well, let's go step by step. So I'm mostly interested in the sodium current. So the potassium current and leak current have been reduced to a more compressed form so that I have more space on the left hand side. And now, this is my stimulation. I've talked about pulses. This is a pulse current of one millisecond duration. I can consider a pulse current of half a millisecond duration, but twice as high. Or I even can take the limit. I can take a pulse current of 0.2 millisecond duration, but 5 times as high. So it's really a short current pulse. Imagine a charge q delivered at time t_0 . Now, this charge q , it's a delta pulse. It causes a jump of the membrane potential. So if I have now the same area as the one over here, but I deliver the pulse in a very short time-- 0.2 milliseconds or 0.1 milliseconds-- then, as we are saying last week, you essentially just have a jump. You just have to jump by an amount Δu which I can calculate from q and the capacity c . So now I know the membrane potential is higher. Now let's look at the graph. This is for m . m likes to go towards m_0 , and the m_0 curve is the green curve here. At rest. Rest is denoted as 0 so we have adjusted the voltage scale for this plot that at rest is at 0.

Notes

Summary



Neuronal Dynamics – 2.4. Threshold in HH model



$$\begin{aligned}
 C \frac{du}{dt} &= -\overbrace{g_{Na} m^3 h}^{I_{Na}} (u - E_{Na}) - \underbrace{I_K}_{\checkmark} - \underbrace{I_{leak}}_{\checkmark} + \overset{\text{Stim.}}{\downarrow} I(t) \\
 \frac{dm}{dt} &= -\frac{m - m_0(u)}{\tau_m(u)} \\
 \frac{dh}{dt} &= -\frac{h - h_0(u)}{\tau_h(u)}
 \end{aligned}$$

$= q \delta(t - t_0)$

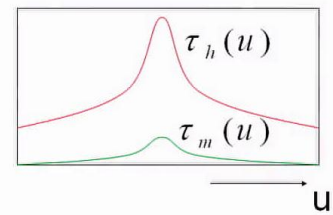
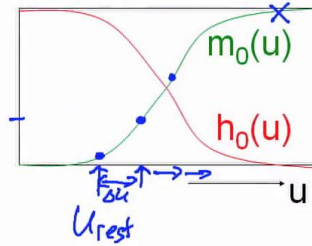
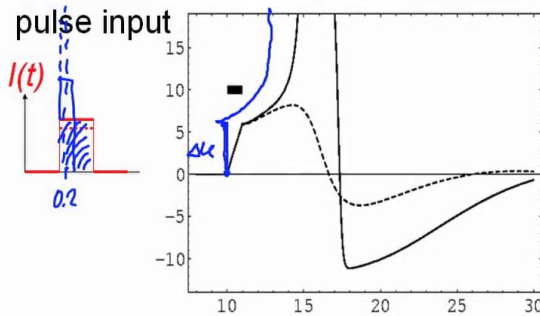
At rest, m has a certain value. But now, because of my pulse, I get this jump in the voltage, which means I'm now here. This is the difference Δu . But, at this new voltage value, m_0 is higher. So now m will go to this higher value. But if m is higher then the total conductance of the channel has increased. This is sodium. Sodium is a positive ion that will flow from the outside into the cell. If it flows into the cell, then the voltage will increase further. But now, m is even bigger, and the voltage will yet increase further. So we see that this m dynamics leads to an instability. A first voltage step causes a blow up, like an explosion. And you see it here. It really will move up rapidly to a very high value. So we have a sort of explosive behavior. Now, the question is, if it explodes, while it cannot go to infinity, why does it stop? Where does it stop? Well, the biologists who have read already some introduction to neuroscience will immediately say, well, it stops because of the potassium current. Which is true, and we'll see that in a minute. But I will claim that, even if there is no potassium current, even if there is no potassium current, then it will still not go to infinity.

Notes

Summary



Neuronal Dynamics – 2.4. Threshold in HH model



$$\begin{aligned}
 C \frac{du}{dt} &= -\overbrace{g_{Na} m^3 h}^{I_{Na}} (u - E_{Na}) - \cancel{I_K} - I_{leak} + \text{Stim.} \downarrow I(t) \\
 \frac{dm}{dt} &= -\frac{m - m_0(u)}{\tau_m(u)} \quad \uparrow +30\text{mV} \\
 \frac{dh}{dt} &= -\frac{h - h_0(u)}{\tau_h(u)} \quad \uparrow = q \delta(t - t_0)
 \end{aligned}$$

Well, another possibility is that it stopped because of h . Well, if the voltage gets high then h gets low, but h also enters here. If h goes to 0, the channel closes again. So h is important. But even without h , it would still not explode. Well, it would not explode for the simple fact that I have a reversal potential here which is about 30 millivolt for sodium, as we have calculated at beginning of this week's sessions. In these units, this would mean about 100 millivolt above the resting potential. With a standard normalization it's around plus 30 millivolt. Therefore, if the voltage gets close to 30 millivolt, then this term will be 0, will be close to 0. And therefore, this additional sodium current-- this sodium current influx of ions into the cell-- this sodium current will stop.

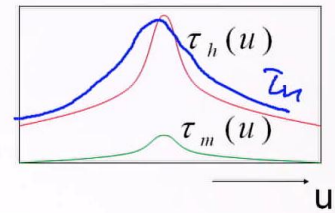
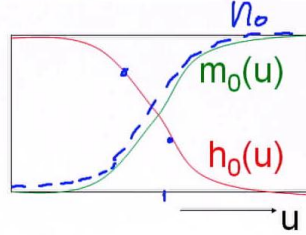
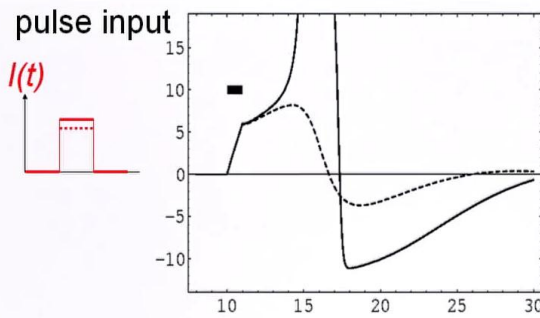
Notes

Summary



10m 44s

Neuronal Dynamics – 2.4. Threshold in HH model



Why start the explanation with m and not h ?

$$C \frac{du}{dt} = \underbrace{I_{Na}}_{\substack{\uparrow \\ \text{more slowly}}} - \underbrace{g_{Na} m^3 h (u - E_{Na})}_{\substack{\uparrow \\ \text{slow}}} - \underbrace{g_K n^4 (u - E_K)}_{\substack{\uparrow \\ \text{slow}}} - \underbrace{g_l (u - E_l)}_{\substack{\uparrow \\ \text{slow}}} + \underbrace{I(t)}_{\text{Stim.} \downarrow}$$

$$\frac{dm}{dt} = - \frac{m - m_0(u)}{\tau_m(u)} \quad \parallel \quad \frac{dn}{dt} = - \frac{n - n_0(u)}{\tau_n(u)} \quad \text{slow}$$

$$\frac{dh}{dt} = - \frac{h - h_0(u)}{\tau_h(u)} \quad \text{more slowly}$$

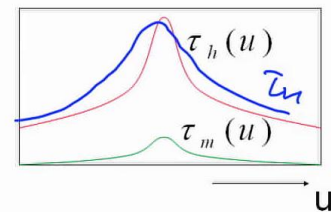
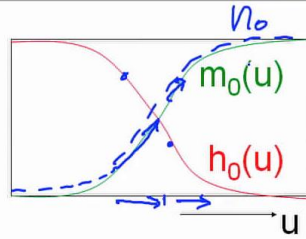
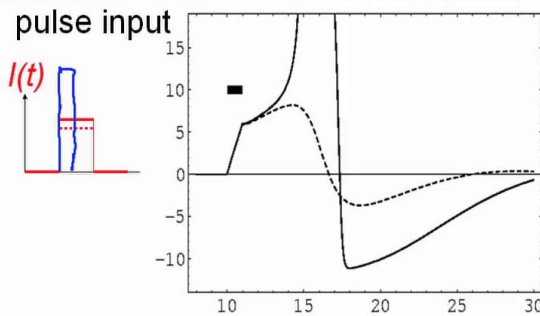
So now here are, again, the summary. I have my three currents, the sodium current-- this gives this blow up, the rapid rise of the membrane potential. I have a potassium current, I have the leak current, I have the stimulation. Now, for my mathematical explanation, I started with m I started with m , with this variable. Why did I start with m and not with h ? Imagine I start the same explanation with h . I increase the voltage, the voltage increase changes h from an initial value to a lower value, therefore, the channel inactivates and there's no explosive effect at all. Well, what's the reason to start with m and not with h ? The reason can be found here on the right-hand side. The time constant that controls the gating variable m is much, much quicker. And therefore, dynamics is faster than the dynamics of h . h is slow compared to m . Therefore, my explanation started with m . m reacts first. And h reacts more slowly, and therefore, comes in later. There's a similar plot for the n_0 and the tile n . And indeed, the n_0 looks sort of similar to the one of m_0 with a time constant that's more similar to that of h , which means it's also slow. I started the explanation with m because m is the fast variable.

Notes

Summary



Neuronal Dynamics – 2.4. Threshold in HH model



Why start the explanation with m and not h ?

What about n ?

Where is the threshold?

$$C \frac{du}{dt} = \underbrace{-g_{Na} m^3 h (u - E_{Na})}_{I_{Na}} - \underbrace{g_K n^4 (u - E_K)}_{I_K} - \underbrace{g_l (u - E_l)}_{I_{leak}} + \underbrace{I(t)}_{\text{Stim.}}$$

$$\frac{dm}{dt} = -\frac{m - m_0(u)}{\tau_m(u)} \quad \text{fast}$$

$$\frac{dn}{dt} = -\frac{n - n_0(u)}{\tau_n(u)} \quad \text{slow}$$

$$\frac{dh}{dt} = -\frac{h - h_0(u)}{\tau_h(u)} \quad \text{more slowly}$$

So m is first. h and n come roughly at the same time, but a bit later. Now we are back at our threshold. Where is the threshold? In fact, there is no threshold. There cannot be a threshold in this system of coupled non-linear differential equations. Everything is smooth. For a given stimulation paradigm, like the one I discussed with very short pulses--yes, for given stimulation paradigm I can define a threshold. And that's then more like a voltage threshold. That's the moment when this m dynamics becomes unstable. And the voltage will automatically reinforce itself. You have this kind of explosive behavior. However, if I choose a different stimulation paradigm, not the pulse paradigm, then the threshold, I determined, would be completely different.

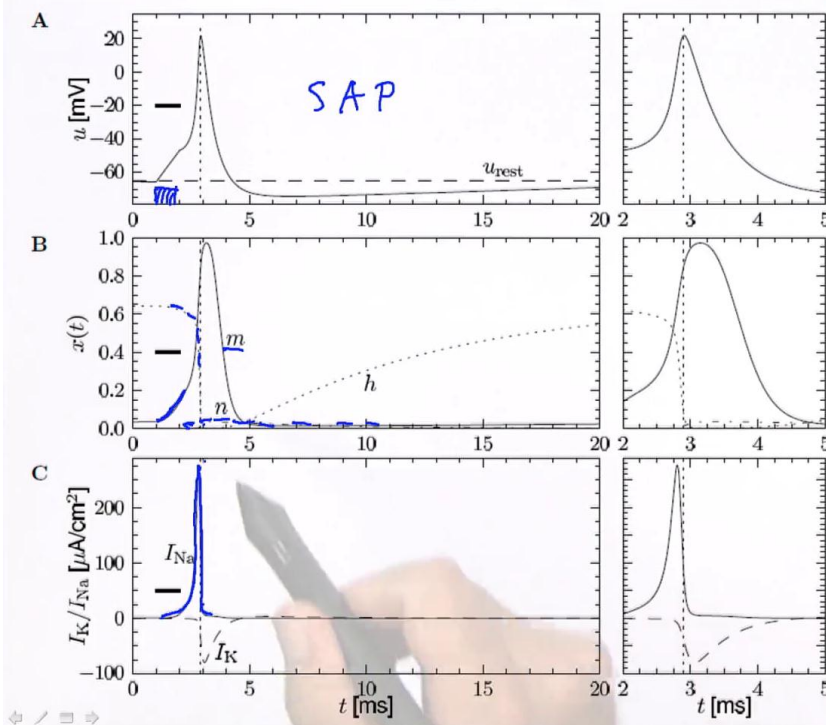
Notes

Summary



14m 04s

Neuronal Dynamics – 2.4. Threshold in HH model



$$C \frac{du}{dt} = -g_{Na} m^3 h (u - E_{Na}) - g_K n^4 (u - E_K) - g_l (u - E_l) + I(t)$$

So with this discussion of the dynamics of m and h , we can now follow and understand the formation of action potentials. So here, a short current has been applied during this time here. This is my current pulse for one second. And afterwards the voltage explodes, it goes up to nearly plus 30-- here it stops at plus 20, then goes down again-- and then you see we have this long, long, long spike after potential. S-A-P-- Spike After Potential. This long spike after potential, it takes a long time before the voltage comes back to the normal value, the normal resting potential. Now here's the plot for the three different gating variables. And indeed, you see that m -- right at the beginning, m is the one to start first. h follows a bit later. This is h . h goes down, but with a delay. The combination of h and m makes that the sodium current is short, and then it's stopped. Indeed, the current is stopped by h . The voltage would be stopped, in any case, even without h because of the reversal potential here. Now, for the sodium current, I have the variable n . n starts about here, and in this scale, n only reacts slightly. But we have a bump about here. This bump is multiplied with the power of four.

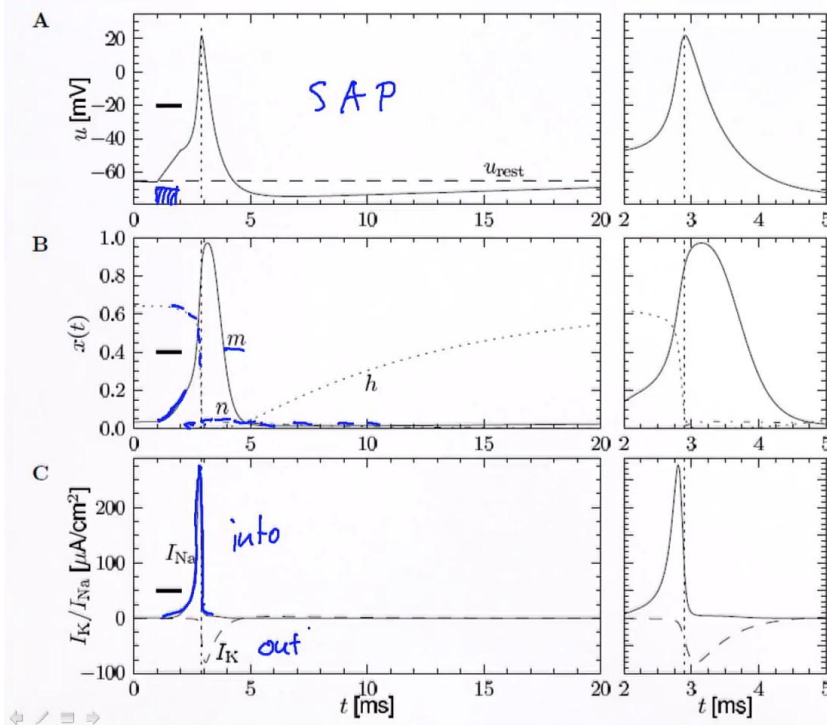
Notes

Summary



15m 09s

Neuronal Dynamics – 2.4. Threshold in HH model



$$C \frac{du}{dt} = -g_{Na} m^3 h (u - E_{Na}) - g_K n^4 (u - E_K) - g_l (u - E_l) + I(t)$$

This little gives rise to the K current, to the potassium current, which is plotted here in the opposite direction. This is-- sodium is flowing into the cell, potassium is flowing out of the cell.

Notes

Summary



16m 57s

Neuronal Dynamics – 2.4. Threshold in HH model

There is no strict threshold:

Coupled differential equations

'Effective' threshold
in simulations?

So let me summarize what we have seen so far. A Hodgkin-Huxley model consists of four coupled non-linear differential equations. There is no strict threshold, there is no strict voltage threshold, there is no strict current threshold. When you look for a threshold, the results you get will depend on the stimulation paradigm that you use, and the result is different for short current pulses, it's different for step currents, it's different for slow current ramps, and so forth. Nevertheless, in practice, it's well versed talking about a threshold. So there's something like an effective threshold, because there's a regime where the differential equations are very, very, very sensitive to small changes in the input. And this is what gives, effectively, rise to a threshold. So let's look at some other simulation paradigms.

Notes

Summary

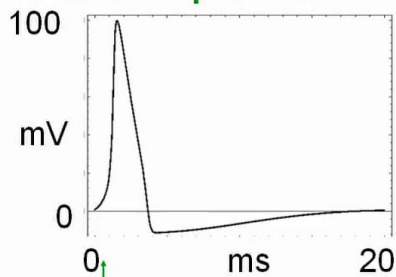


17m 15s

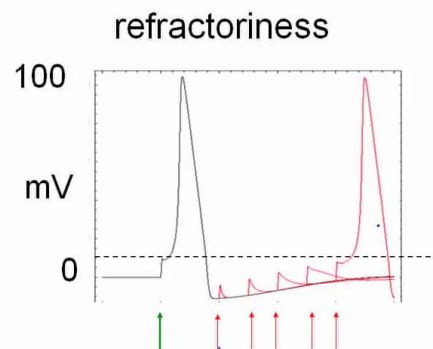
Neuronal Dynamics – 2.4. Refractoriness in HH model

Where is the firing threshold?

Action potential



Strong stimulus



Strong stimuli

Refractoriness! Harder to elicit a second spike

For example, here I've used a short current pulse, which is just enough to generate a spike. Now if I use a first current pulse to generate the spike, and then I use the same pulse again a few milliseconds later-- say, five milliseconds later-- this same pulse will no longer generate an action potential. Or, if I use the same pulse strength, the same pulse form, 10 milliseconds later, it will not generate an action potential. It remains below threshold, and only if I use the same strong stimuli much later again, I can generate a further spike. This phenomenon is called refractoriness. It's more difficult to elicit a second spike during a few milliseconds after the first spike.

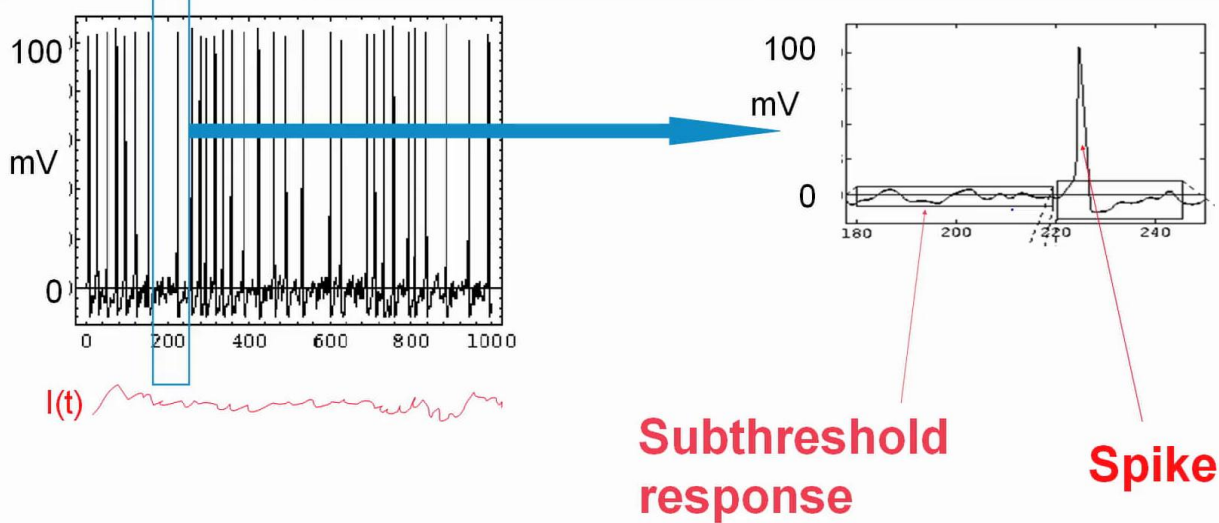
Notes

Summary



18m 10s

Neuronal Dynamics – 2.4. Simulations of the HH model



Now let's look at some other paradigm. In vivo, a neuron sitting somewhere in the cortex is expected to receive some time dependent current which represents the input of thousands of other spikes that arrive from other neurons. Now, with this kind of current, the Hodgkin-Huxley model generates a spike train which looks irregular. And this spike train has a sub threshold behavior where it just fluctuates. This fluctuations represent the fluctuations in the input, and occasionally there's a spike.

Notes

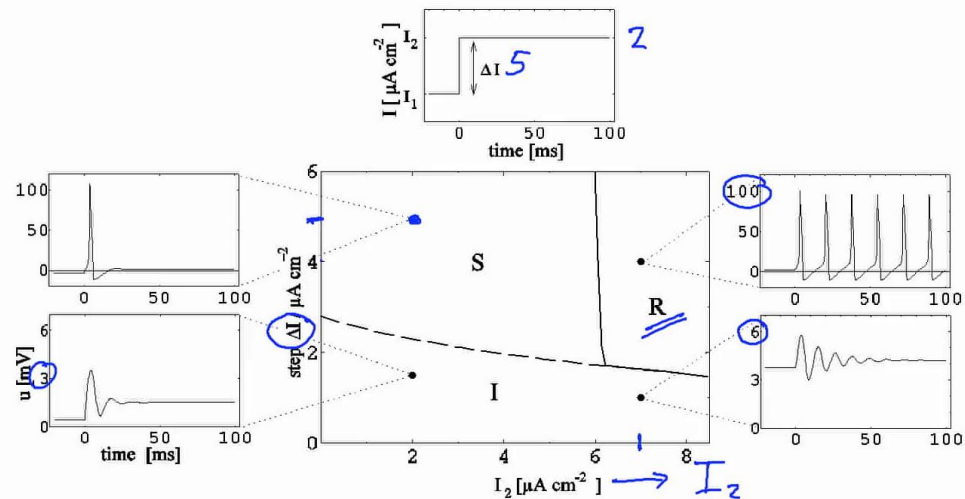
Summary



19m 06s

Neuronal Dynamics – 2.4. Threshold in HH model

Step current input I_1 I_2



Now, yet another paradigm often used in experiment is this step current. Now the notation here is that I start with a certain value I_1 . And now there's a step and we land at a new value I_2 . So this axis here is I_2 , that's the final value of the step. The vertical axis is ΔI , it's the step size. So let's look at large values of I_2 . We have seen before that we get repetitive firing. However, you get the repetitive firing only if there is a step. So here we get repetitive firing, for example, at a final value of 7 current units, and a step size of 4. With a step size of 1-- so we land at the same final current-- but the step is much smaller, you don't get repetitive firing. You just get some auxiliary response to the change. Note the scale. 6 millivolt, 100 millivolt. This is very different. This is not a spike. So this is a regime of repetitive firing, R. Now let's go over here. I land at a final value of 2, using a step of amplitude 5. So my final value is 2, the step is 5. What I get is a single spike in response to the current step. If I land at 2, but the step size is only 2, then I only get this three millivolt little undulation. Thus, for step current, it's not just the final current that plays a role, it's the final current just as well as the step size that come into account.

Notes

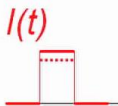
Summary

19m 48s



Neuronal Dynamics – 2.4. Threshold in HH model

Where is the firing threshold?

pulse input 

step input 

ramp input 

There is no threshold

- no current threshold
- no voltage threshold

‘effective’ threshold

- depends on typical input

$$C \frac{du}{dt} = -g_{Na} m^3 h (u - E_{Na}) - \dots$$

So let's summarize. There is no final threshold, it depends on the input what you get as a result, and in addition to the pulse currents and step currents, you can also look at ramp currents and would get, yet another different result. Now, the reason is that it's four coupled differential equations. And it's not just the voltage threshold, it's not just the current threshold. The m has its own dynamics. And if you make a longer pulse, m can react, but also h . If you make a short pulse, it's only m which can react. If it's a very short pulse, even m reacts only with a delay. So it's really the interaction of the different variables of the differential equations that cause spike generation.

Notes

Summary



22m 00s

Neuronal Dynamics – 2.4. Type I and Type II

Hodgkin-Huxley model
with other parameters
(e.g. for cortical pyramidal
Neuron)

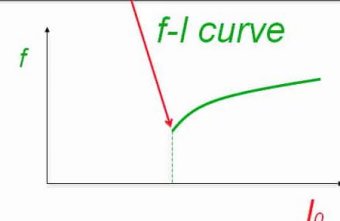
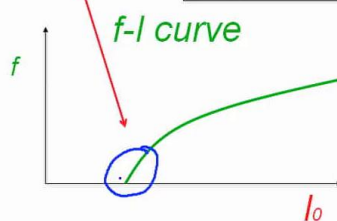
Hodgkin-Huxley model
with standard parameters
(giant axon of squid)

Response at firing threshold?

Type I

type II

ramp input/
constant input



Now, if you use this very slow ramp input on a Hodgkin-Huxley model, we find an f-I curve with a jump. This is called a type II or class II behavior. If you use the frame variable of Hodgkin-Huxley models but change parameters so it's more adapted to cortical neurons, then you can make it a smooth response with very low frequencies. This would be called type I or class I firing behavior.

Notes

Summary



22m 52s

Neuronal Dynamics – 2.4. Hodgkin-Huxley model



- 4 differential equations
- no explicit threshold
- effective threshold depends on stimulus
- BUT: voltage threshold good approximation

Giant axon of the squid

→ cortical neurons

- Change of parameters
- More ion channels
- Same framework

So let's summarize. There are four differential equations, they are coupled to each other, they are non-linear, you can solve these equations on the computer. The model generates action potentials but there's no strict firing threshold. However, for practical purposes, the notion of the threshold remains, indeed, very useful. Now, this model was originally designed and parameterized for this giant axon of this squid. However, it provides a framework instead of just the two ion channels that we have for the giant axon of this squid. A cortical neuron will have many more ion channels, but the framework, the mathematical arguments to describe these channels, is exactly the same.

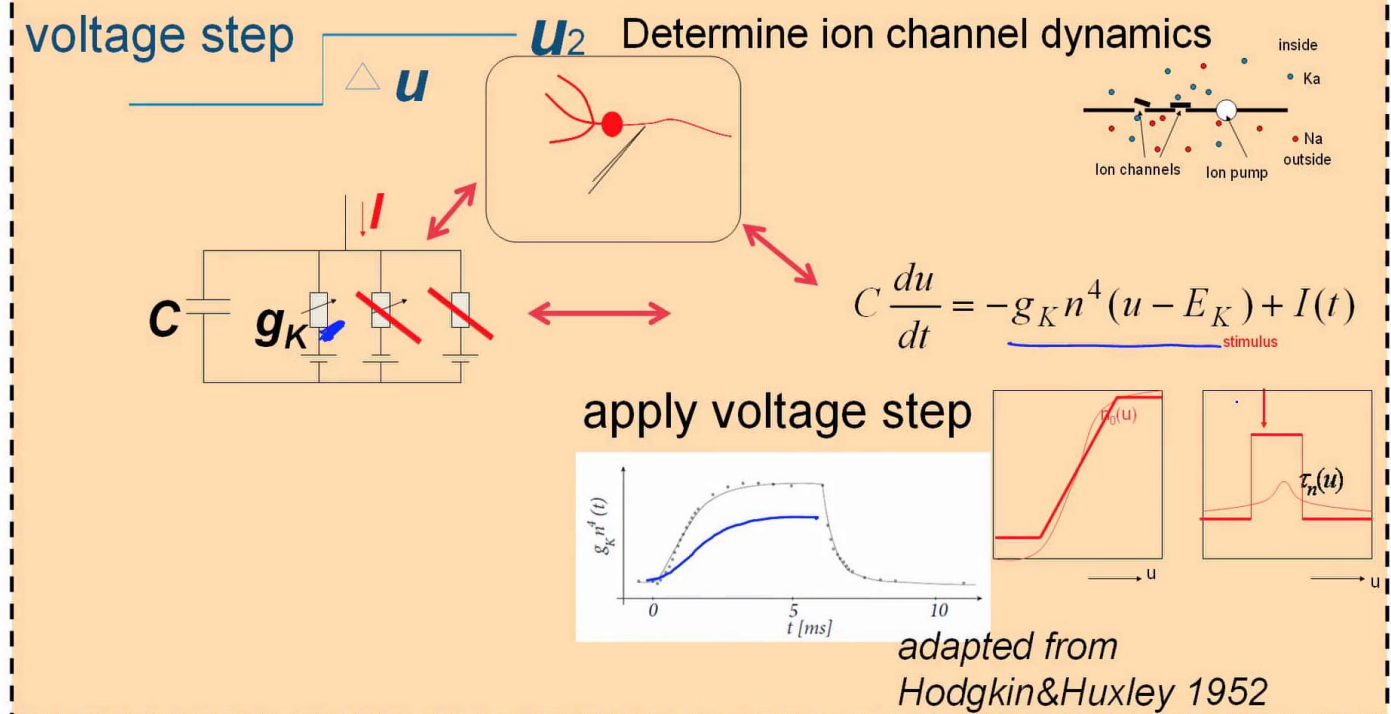
Notes

Summary



23m 30s

Exercise – 2.4. Hodgkin-Huxley model – ion channel



Now, in order for you to understand how Hodgkin and Huxley found their equations and the parameterization of their equations, let me walk you a little bit through this diagram. Hodgkin and Huxley applied a voltage step on the giant axon of this grid, and they were able to block channels. Let us suppose that we can block channels so that only the potassium channel remains. In this case, we only need to keep here the term for the potassium current. And what Hodgkin and Huxley did is, in the experiments, they observed the total current through the membrane. And that's the kind of results they found. And then they repeated this for different step sizes. And if you change the step size you get different results. And out of that, they were able to extract the time constant, how n , as well as the function of n_0 of u . Now, in order for you to understand how this works, we will use simplified time constants and n_0 of u .

Notes

Summary



24m 21s

Exercise – 2.4. Hodgkin-Huxley model – ion channel



Determine ion channel dynamics

$$C \frac{du}{dt} = -g_K n^4 (u - E_K) + I(t)$$

stimulus

apply voltage step

adapted from
Hodgkin&Huxley 1952

And you now have the chance to work through that. Please work on this exercise. It's a slightly longer exercise. It's their first assignment for week two, and by doing this assignment you will be really able to understand how Hodgkin-Huxley extracted ion channel dynamics from experiments. And indeed, in many labs worldwide, every week people do these kinds of experiments and this type of analysis in order to characterize electrical properties of channels.

Notes

Summary



25m 41s