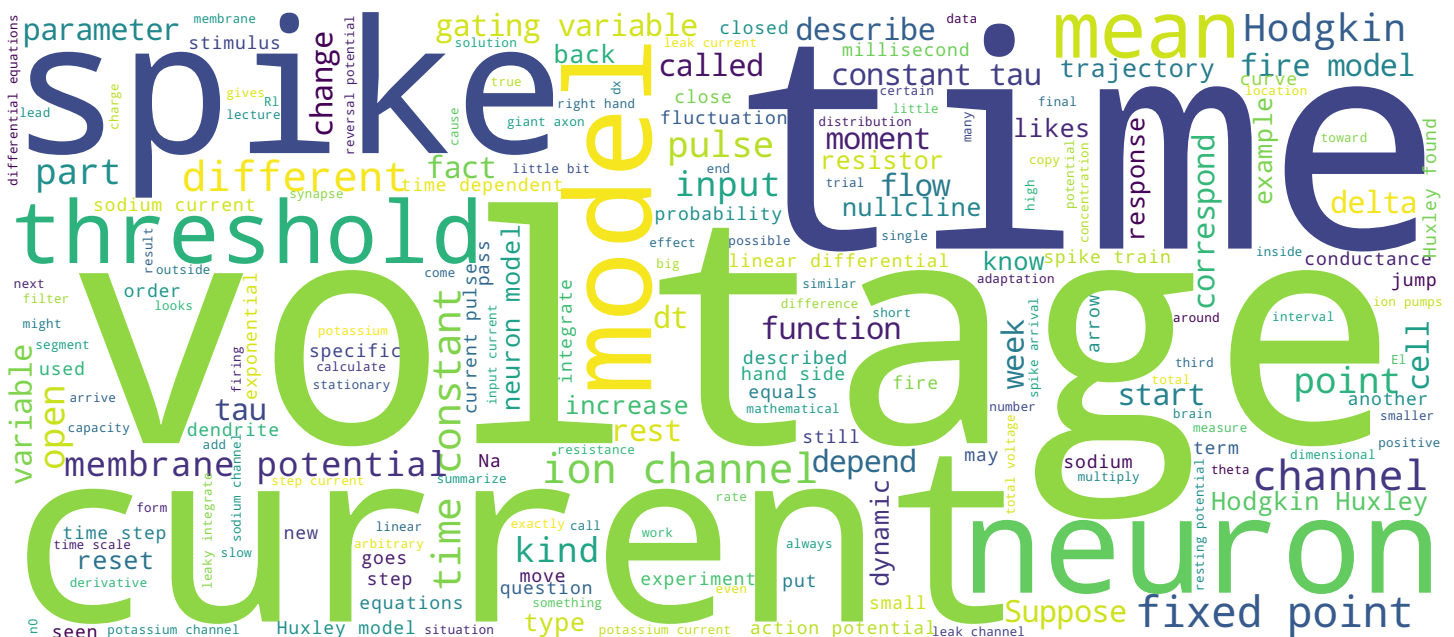


ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

EPFL, Lausanne, Switzerland

- the zoo of ion channels

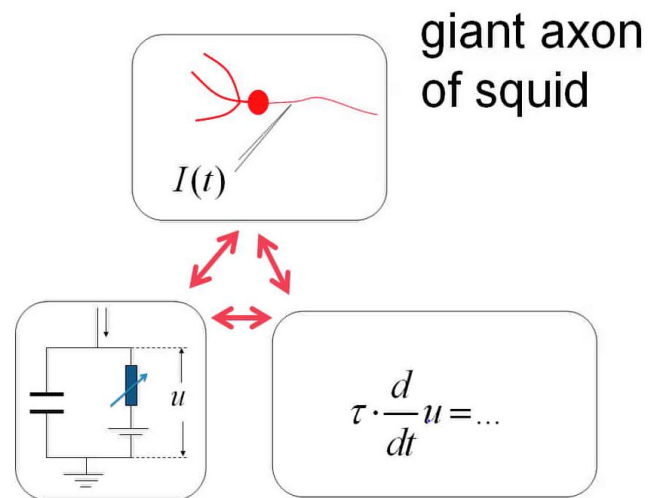


Video



EPFL

Neuronal Dynamics – 2. 3. Hodgkin-Huxley Model



→ Hodgkin-Huxley model

Hodgkin&Huxley (1952)

Nobel Prize 1963

Welcome back to part three of week two. After these preparations, we are now ready to discuss the Hodgkin-Huxley model. Hodgkin and Huxley made experimental recordings on a giant axon of the squid-- a nice experimental preparation where they could inject current directly into the axon. Via a series of very careful measurements, they could deduce a model description. Thus, they went from their experiments first to an equivalent electrical circuit and then to a mathematical model, which I will introduce now.

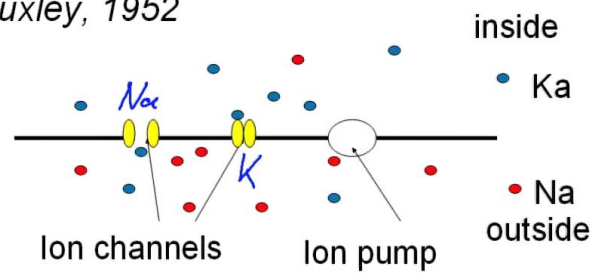
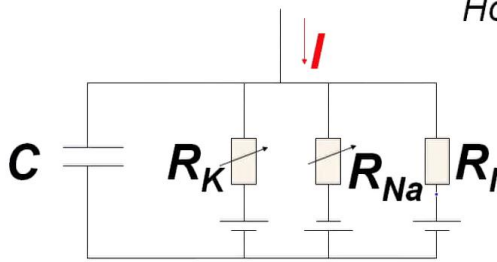
Notes

Summary



Neuronal Dynamics – 2.3. Hodgkin-Huxley Model

Hodgkin and Huxley, 1952



The giant axon of the squid, just like any other cell, has ion channels embedded in the cell membrane, as well as ion pumps. In the case of the giant axon of the squid, Hodgkin and Huxley found that there are two dominant channel types. One channel is specific for sodium. And another channel type is specific for potassium. Now if the channel is closed, it has a very, very high resistance. Basically, ions cannot pass through. If a channel is open, it's easier for the ions to pass through. However, there is still a resistance-- a pore. The opening is of a finite size. Hodgkin and Huxley found that the sodium channel, potassium channel together with a third channel, which they called leak channel-- which really is a summary of all the other channels that might give minor contributions-- they could arrive at a very nice description using this equivalent circuit. So the idea is that the potassium channel corresponds to a certain resistance, which may change. The error indicates that this may change, depending on the current situation, depending on the weather the channel is opened or closed. Similarly, the sodium channel corresponds to a certain resistance. And the remaining channels are summarized in some kind of leak channel.

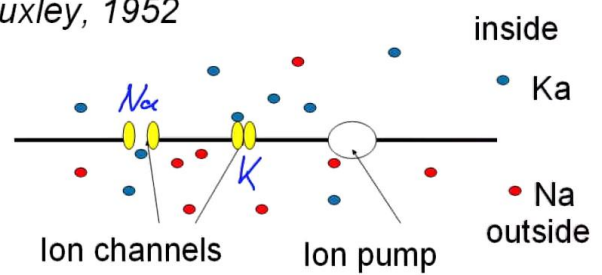
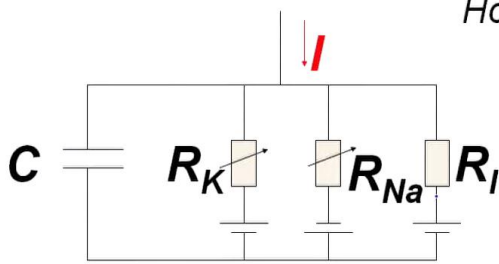
Notes

Summary



Neuronal Dynamics – 2.3. Hodgkin-Huxley Model

Hodgkin and Huxley, 1952



*Mathematical
derivation*

Based on this diagram, I'm now able to introduce the model of Hodgkin and Huxley.

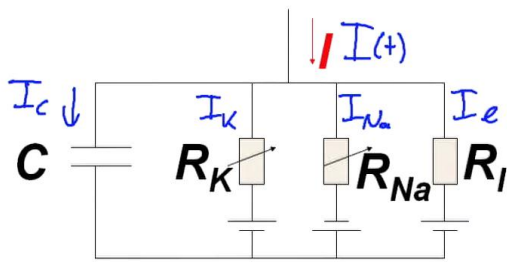
Notes

Summary



2m 34s

Neuronal Dynamics – 2.3. Hodgkin-Huxley Model



$$C = \frac{Q}{U}$$

$$C \frac{dU}{dt} = \frac{dQ}{dt} = I_C$$

$$I(t) = I_C(t) + I_K + I_{Na} + I_l$$



So Hodgkin and Huxley found the three different ion channels. And each ion channel can be in a state, open or closed. If it's open, ions can pass through. If it's closed, the resistance is very high. So we have a time-dependent resistance, indicated here as an arrow. This is true for potassium. This is true for sodium. The leak current, however, is assumed to be constant. It's a phenomenological current that summarizes all other ion channels and all other effects that are not studied in detail. In their experiments, Hodgkin and Huxley injected a stimulating current into the neuron. Now in the circuit diagram, this current has to go somewhere. It can go on the capacitor. It can go through the leak channel. Or it can go through one of the other channels-- potassium or sodium. So the total current is the sum of all these. It's the capacity of current plus the potassium current plus the sodium current plus the leak current. Now for the capacity, we know already from the definition C equals Q over U . I multiply by it U . C times U equals Q . I take derivative. $d/dt U$, $d/dt Q$. This is the capacity of current that I have already discussed last week. So let's put this in here. I have $C du/dt$ for I_C .

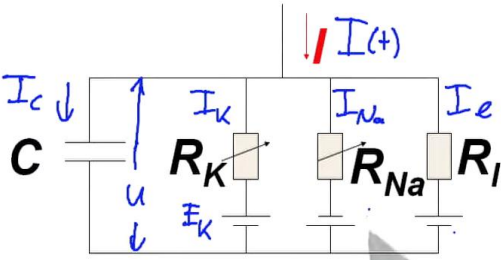
Notes

Summary



2m 42s

Neuronal Dynamics – 2.3. Hodgkin-Huxley Model



Handwritten notes and equations:

$$C = \frac{Q}{U}$$

$$C \frac{dU}{dt} = \frac{dQ}{dt} = I_c$$

$$U = R \cdot I_R$$

$$I_R = \frac{1}{R} \cdot U$$

$$I(t) = I_c(t) + I_k + I_{Na} + I_l$$

$$C \cdot \frac{dU}{dt} = -I_k - I_{Na} - I_l + I(t)$$

And $C \frac{dU}{dt}$. $C \frac{dU}{dt}$ is equal to the stimulating current. And then I shift the three other ion currents to the other side. So I have minus I_k , minus I_{Na} minus I_l . Now what can we say about the currents passing through the channels? In the model, this corresponds to currents passing through the resistors. Let's take one of the resistors. From Ohm's law, we know U , voltage, equals resistance times resistive current-- the current passing through the resistor. We are interested in the resistive current. So we have IR equals $\frac{1}{R}$ times U . Now the total voltage is the voltage across the capacitance. This is U . So the total voltage, U , has actually two components. I have noted here batteries. This is the battery of the potassium channel. Where does this battery come from? Well, this is exactly the reversal potential calculated from the Nernst equation for potassium. Because of the ion pumps, the concentration is different outside the cell than inside the cell. This leads to a potential E_K . It acts like a battery. Because of the ion pumps, the concentration is different inside and outside the cell for sodium, which corresponds to a sodium reversal potential, E_{Na} .

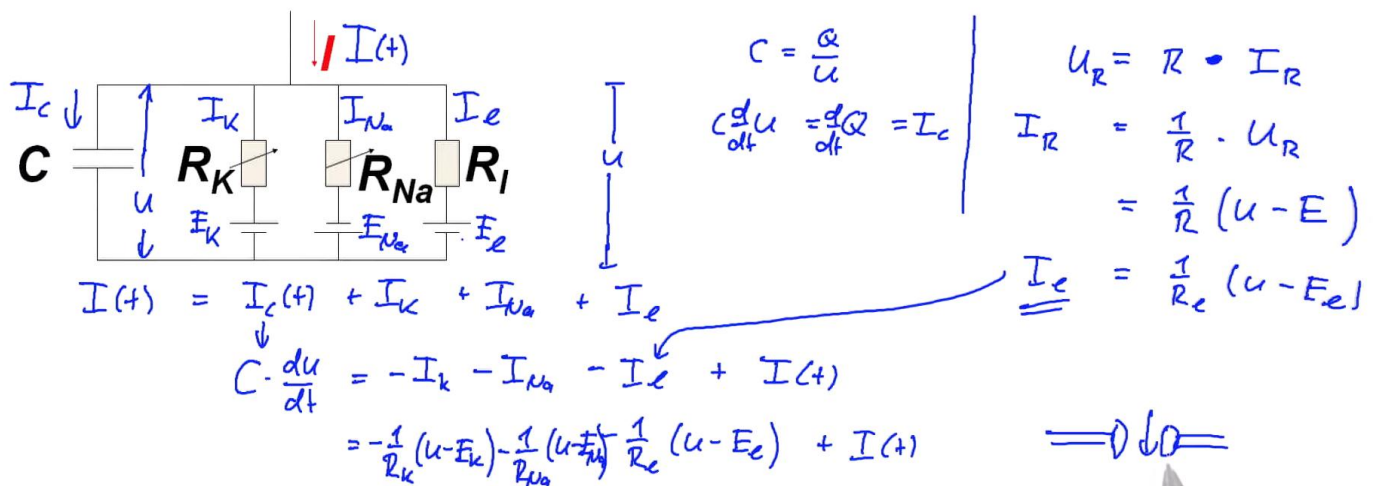
Notes

Summary



4m 53s

Neuronal Dynamics – 2.3. Hodgkin-Huxley Model



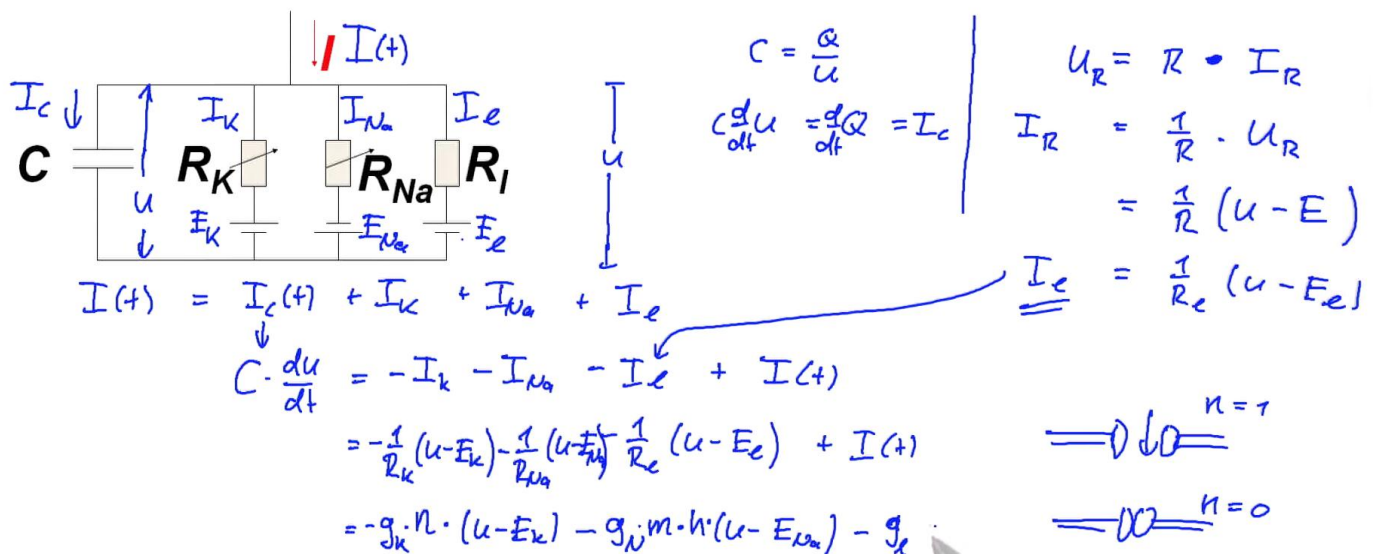
And analogously, I have a leak potential, E_l . So in Ohm's law, the voltage is the voltage at the resistor. The voltage at the resistor is the total voltage minus the battery power. Now let's use this first for the leak current. So I would have I_l equals 1 over R_l U minus E_l , which I can plug in here. So I have minus 1 over R_l U minus E_l . The same reasoning can be applied to any other current. So for the potassium current, I have minus 1 over R_K U minus E_K . For the sodium current, I have 1 over R_{Na} U minus E_{Na} . This is sometimes called the first Hodgkin-Huxley equation. However, in fact, this equation simply represents the conservation of current. And every first-year electricity student can write down this type of equation. The difficulty for Hodgkin and Huxley arose from the fact that the resistors-- R_K , R_{Na} -- are not constant. They change. The change depends on the surrounding effects. It depends on the voltage. It depends on the history, so how can we describe these changes? Suppose I have a channel. And this channel is open, which means ions can flow through the channel. Even if the channel is open, it has some finite width. That means even if the channel is open, it has some resistance.

Notes

Summary



Neuronal Dynamics – 2.3. Hodgkin-Huxley Model



One of the resistance is a conductance. So even if the channel is open, it has a conductance-- $1 \text{ over } R_K$ equals g_K . I copy the U minus E_K , but I leave a little bit of space in here. Because the channel may not always be open. The channel can also be closed. The conductance in that case is very, very different. Hodgkin and Huxley introduced a gating variable that describes the state of the gate. A gating variable, n , is time dependent. Suppose n equal 1. That means the channel is open. The current, x , with its maximal conductance-- it allows potassium ions to flow through, and the conductance is g_K . However, sometimes the channel is closed. And this is represented by a activation variable n equals 0. If I multiply g times 0, the total conductance is 0. No current can flow through. The same kind of reasoning can be applied to the sodium current. It has a maximum conductance. It depends on the voltage. And again, there is a gating variable. In fact, there is a first one, called m , and the second one, called h . And then I have to copy the rest. $1 \text{ over } R_l$ is g_l . It's the conductance of the leak channel, U minus E_l plus I , the applied current.

Notes

Summary



Neuronal Dynamics – 2.3. Hodgkin-Huxley Model

$C = \frac{Q}{U}$
 $C \frac{dU}{dt} = \frac{dQ}{dt} = I_c$
 $U_R = R \cdot I_R$
 $I_R = \frac{1}{R} \cdot U_R$
 $= \frac{1}{R} (U - E)$
 $I_e = \frac{1}{R_e} (U - E_e)$

$I(t) = I_c(t) + I_K + I_{Na} + I_l$
 $C \cdot \frac{dU}{dt} = -I_K - I_{Na} - I_l + I(t)$
 $= -\frac{1}{R_K} (U - E_K) - \frac{1}{R_{Na}} (U - E_{Na}) - \frac{1}{R_l} (U - E_l) + I(t)$
 $\Rightarrow \frac{dU}{dt} = \dots$

$(1) \quad C \cdot \frac{dU}{dt} = -g_K \cdot n^4 \cdot (U - E_K) - g_{Na} \cdot m^3 \cdot h \cdot (U - E_{Na}) - g_l \cdot (U - E_l) + I_c(t)$

for n, m, h
 $\frac{dX}{dt} = - \frac{X - X_0(U)}{\tau(U)}$

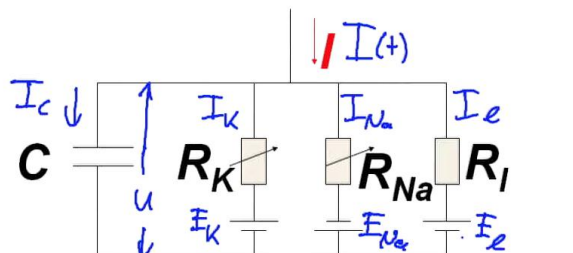
Now Hodgkin and Huxley found a description for the dynamics of these gating variables, n , m , and h . For each of the gating variables, they wrote down an equation of the form $\frac{dX}{dt} = \frac{X - X_0}{\tau}$. X minus X_0 with a minus sign means X likes to go towards X_0 . X_0 is a fixed point. This fixed point is stable, because of the minus sign. X likes to go towards X_0 exponentially fast, with the time constant τ . So this is a simple linear differential equation. There's one of these equations for n , another one for m , yet another one for h . The simple linear differential equation worked. However, Hodgkin and Huxley found that the value X_0 that X likes to take-- the stationary value X_0 depends on the voltage. Moreover, the time constant τ depends on the voltage. This linear equation described the behavior nicely, except that some of the delayed activations were not correctly described. And therefore, Hodgkin and Huxley proposed to use the equation for n , n equals n_∞ minus n_0 of U [INAUDIBLE] τ . And put n to the power of 4. Similarly, in order to describe the experiments, m is to the power of 3. So $C \frac{dU}{dt}$ -- this is the first equation. The voltage is on the right-hand side. So the [?]

Notes

Summary



Neuronal Dynamics – 2.3. Hodgkin-Huxley Model



$C = \frac{Q}{U}$
 $C \frac{dU}{dt} = \frac{dQ}{dt} = I_c$

$U_R = R \cdot I_R$
 $I_R = \frac{1}{R} \cdot U_R$
 $= \frac{1}{R} (U - E)$
 $I_e = \frac{1}{R_e} (U - E_e)$

$I(t) = I_c(t) + I_K + I_{Na} + I_l$
 $C \cdot \frac{du}{dt} = -I_K - I_{Na} - I_l + I(t)$
 $= -\frac{1}{R_K} (u - E_K) - \frac{1}{R_{Na}} (u - E_{Na}) - \frac{1}{R_l} (u - E_l) + I(t)$

$(1) \quad C \cdot \frac{du}{dt} = -g_K n^4 (u - E_K) - g_{Na} m^3 h (u - E_{Na}) - g_l (u - E_l) + I(t)$

$\text{for } n \quad (2) \quad \frac{dn}{dt} = -\frac{n - n_\infty(u)}{\tau(u)}$

4 equations

evolution ?] depends on the voltage. It also depends on n, on m, and on h. And for n, there is an equation of this kind. For m, there is an equation of this kind. For h, there is an equation of this kind. So in total, there are four equations which describe the Hodgkin and Huxley model.

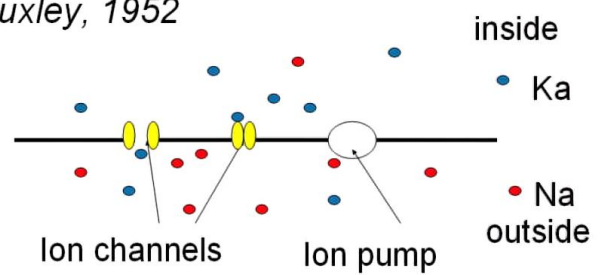
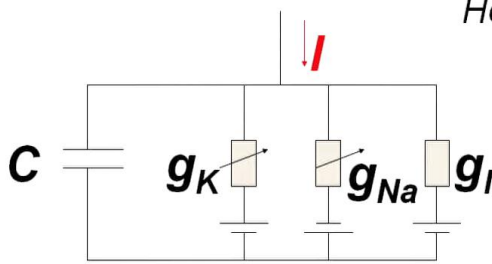
Notes

Summary



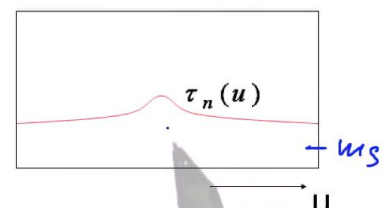
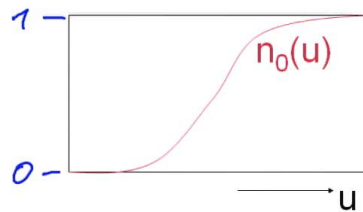
Neuronal Dynamics – 2.3. Hodgkin-Huxley Model

Hodgkin and Huxley, 1952



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

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



In the Hodgkin-Huxley model, we have four equations. There's a first equation, which represents the conservation of current. The first term on the right-hand side represents the sodium current, the current that can pass through sodium channels, channels that are specific, that allow sodium ions to pass through if open. The second current corresponds to potassium channels. The third current is an effective leak current, and the whole thing is driven by the stimulus I of t . Now for each of these gating variables-- m , or h , or n -- I have an equation. m likes to approach m_0 , with the time constant τ_m , which depends on U . h likes to approach h_0 , with the time constant τ_h . Both h_0 and τ_h depend on U . n approaches n_0 , which depends on U , with the time constant τ_n , which depends on U . Now typically, a typical shape of these functions is shown here. This is hand-drawn n_0 of U . This would be a gating variable that controls the potassium current. So if the voltage is high, n_0 is close to 1. Therefore, the channel can open. If n is 1, I have a maximal conductance. But it takes some time for the channel to open. And the time is a few milliseconds. So the time scale here is milliseconds. The scale here is between 0 and 1. So n likes to approach n_0 -- this is n_0 -- with a time constant of a few milliseconds, which also depends on the momentary voltage.

Notes

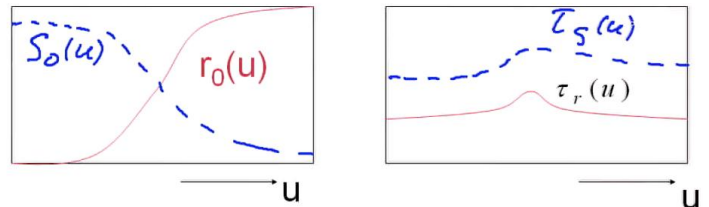
Summary



14m 32s

Neuronal Dynamics – 2.3. Ion channel

$$C \frac{du}{dt} = - \sum_k I_{ion,k} + I(t)$$



$$I_{ion} = -g_{ion} \underline{r}^{n_1} \underline{s}^{n_2}$$

$$\frac{dr}{dt} = - \frac{r - r_0(u)}{\tau_r(u)} \quad \frac{ds}{dt} = - \frac{s - s_0(u)}{\tau_s(u)}$$

✎ ✎ ✎ ✎

The beauty of the experiments of Hodgkin and Huxley consisted in the fact that they were able to measure for each gating variable the stationary value-- for example n_0 of U for potassium-- together with a time constant, τ_n of U for potassium, m_0 and h_0 for sodium. A very careful set of experiments, including some pharmacological blocking, enabled them to extract all of these parameters. Now these experiments were the basis for the mathematical model. And in order to connect the two, Hodgkin and Huxley went through an equivalent electrical circuit summarized by the diagram that I have used in this part. So far for the Hodgkin-Huxley model, why is it so successful? In fact, it tells a story. It tells us for each possible ion channel how we could possibly write down an equation. There are gating variables. Let's call them r and s . These gating variables will be described by a linear differential equation, which is coupled to the voltage. An activation variable is one which increases with the voltage. An inactivation variable would be the other way around. For example, this could be s_0 of U , with some time constant, τ_s of U . Nowadays, hundreds of ion channels are known.

Notes

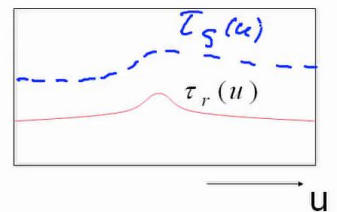
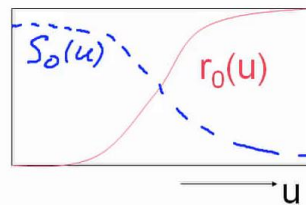
Summary

16m 36s



Neuronal Dynamics – 2.3. Ion channel

$$C \frac{du}{dt} = - \sum_k I_{ion,k} + I(t)$$



$$I_{ion} = -g_{ion} \underline{r}^{n_1} \underline{s}^{n_2}$$

$$\frac{dr}{dt} = - \frac{r - r_0(u)}{\tau_r(u)} \quad \frac{ds}{dt} = - \frac{s - s_0(u)}{\tau_s(u)}$$

And in theory, it's possible to describe each of these ion channels using the framework provided by Hodgkin and Huxley. Now in order for you to get used to the description of ion channels, I invite you now to our next exercise, where we have simplified the dependence on voltage.

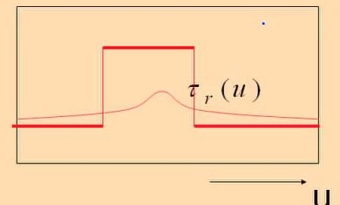
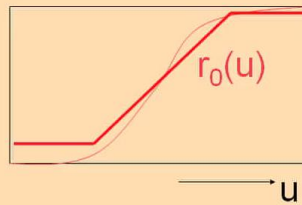
Notes

Summary



18m 43s

Neuronal Dynamics – Exercise 2.3. Ion channel



$$C \frac{du}{dt} = -g_{ion} r^{n_1} s^{n_2} (u - E_{Na}) + I(t)$$

$$\frac{dr}{dt} = -\frac{r - r_0(u)}{\tau_r(u)}$$

Instead of some smooth function, we have a piecewise linear function, which allows you to really address the dynamics of individual ion channels. Once we have done this, we come back for part four.

Notes

Summary

