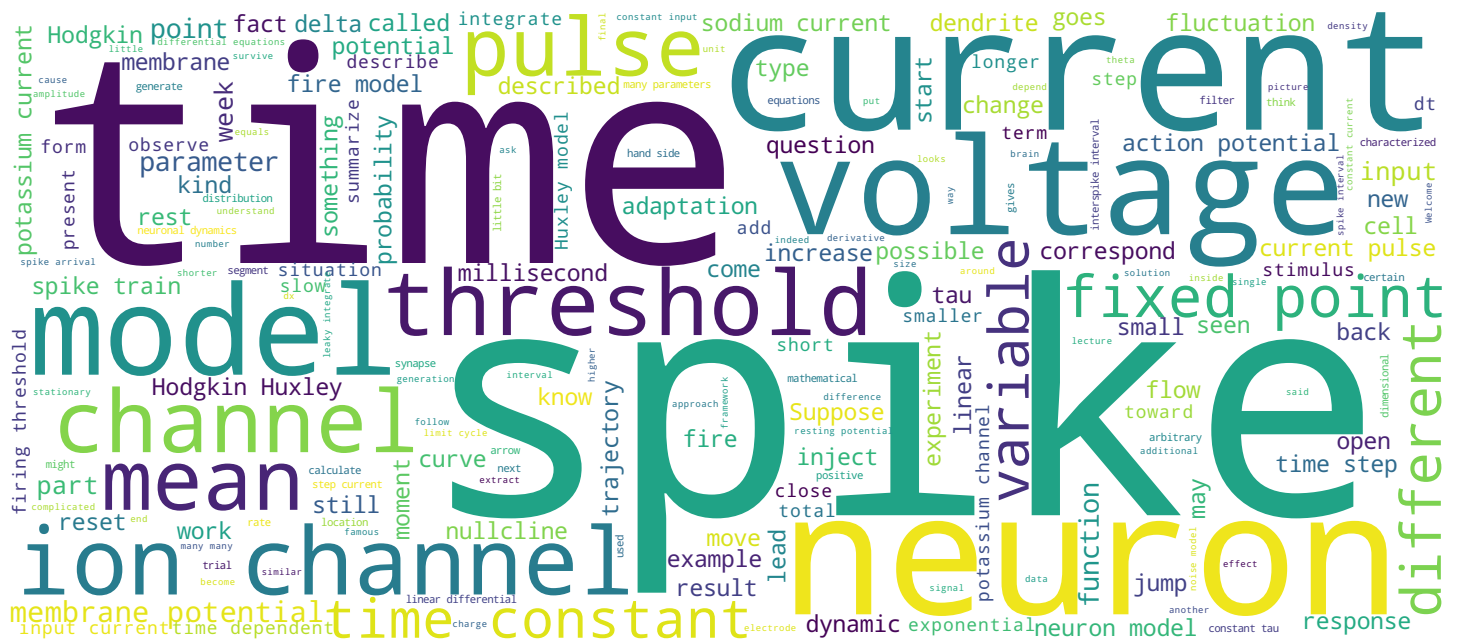


ÉCOLE POLYTECHNIQUE
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EPFL, Lausanne, Switzerland

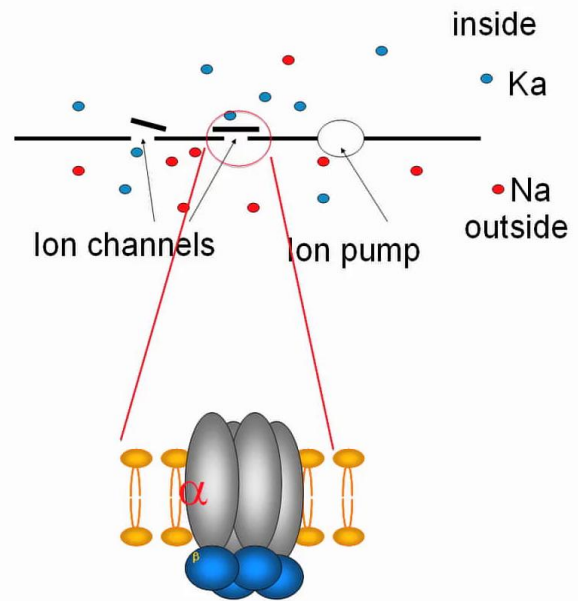
- ✓ 2.1 **Biophysics of neurons**
 - Overview
- ✓ 2.2 **Reversal potential**
 - Nernst equation
- ✓ 2.3 **Hodgin-Huxley Model**
- 2.4 **Threshold in the Hodgkin-Huxley Model**
 - where is the firing threshold?
- 2.5. **Detailed biophysical models**
 - the zoo of ion channels



EPFL



Neuronal Dynamics – 2.5 Biophysical models



Welcome to part five of week two of the class Neuronal Dynamics. Hodgkin and Huxley were the first to describe neuronal dynamics on the level of ion channels. The model is not just a classic reference, but it's still in use today as a framework to describe many, many other ion channels. In fact, when Hodgkin and Huxley did their experiments, it was not possible to follow the dynamics of individual channels. However, nowadays, using patch recordings, it's possible to look just at a few channel at a time. Those channels that are sitting just below the electrode.

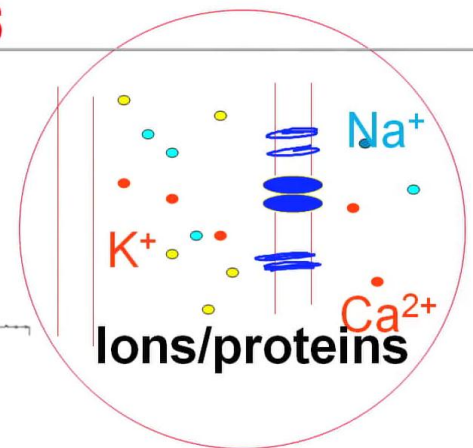
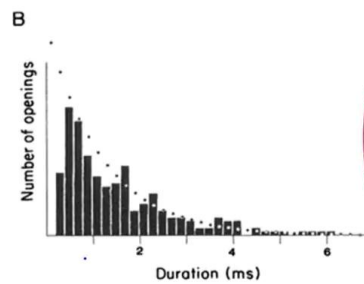
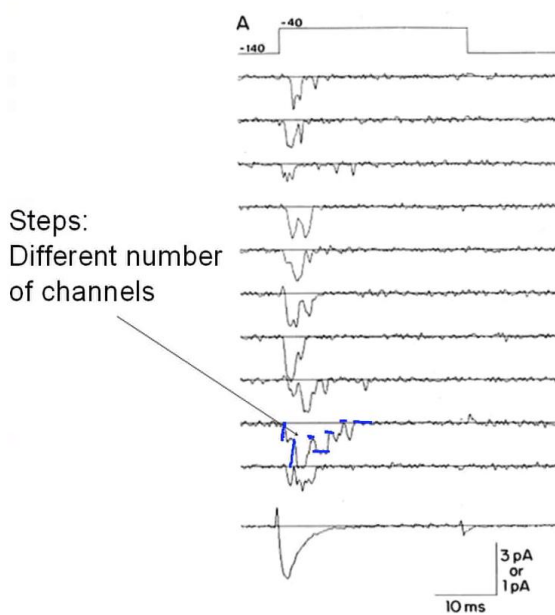
Notes

Summary



0m 04s

Neuronal Dynamics – 2.5 Ion channels



Na⁺ channel from rat heart (*Patlak and Ortiz 1985*)
A traces from a patch containing several channels.
Bottom: average gives current time course.
B. Opening times of single channel events

Now, here's a classic experiment. Suppose you have something like three channels in the membrane that you observe at the same time. So it could be possible that all three are closed, one is open, two are open, three are open. The experimentalist injects a voltage step and observes the current. And, for example here, you see nine steps. There's a first step, maybe one channel is open, big step, maybe two other channels are open, three in total. Then only one, then two, then one, and, again, zero, zero. Now this is just one run. If you repeat the experiment, the result is, each time, different. If you add up the results of many, many of these experiments, you get a smooth current curve. And this is the one described by the formalism of Hodgkin and Huxley. Individual channels, however, open and close stochastically, and they have a mean duration time, in that case, of about 2 milliseconds which you can extract from these experiments.

Notes

Summary



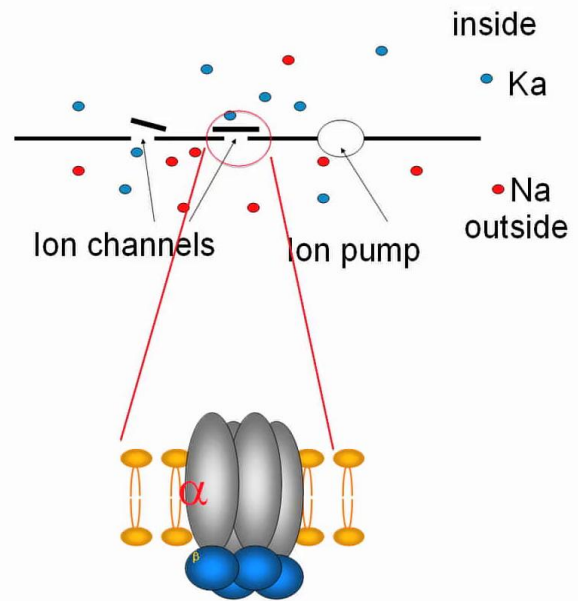
0m 51s

Neuronal Dynamics – 2.5 Biophysical models

There are about 200 identified ion channels

<http://channelpedia.epfl.ch/>

How can we know
which ones are present
in a given neuron?



Now, nowadays, we know about 200 identified ion channels. Each of these ion channels has its own dynamics, each of these ion channels can be described by the framework of the Hodgkin and Huxley equations. Now, if there are so many ion channels, how would we know which ones are present in a given neuron?

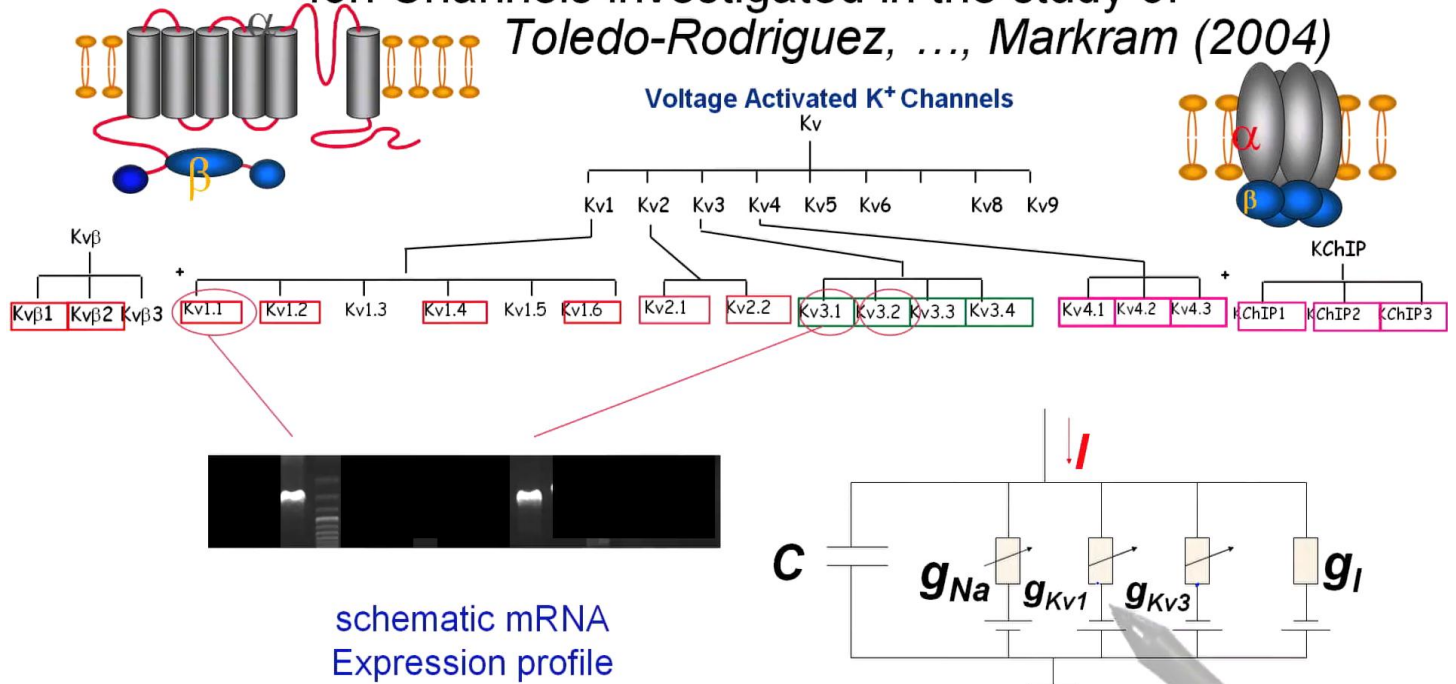
Notes

Summary



1m 59s

Ion Channels investigated in the study of Toledo-Rodriguez, ..., Markram (2004)



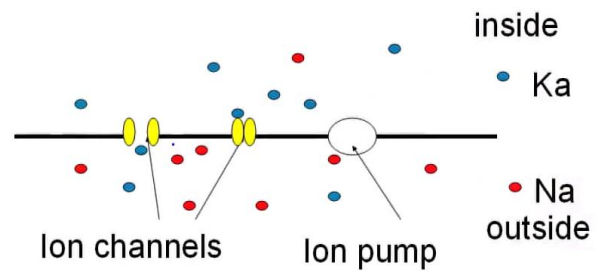
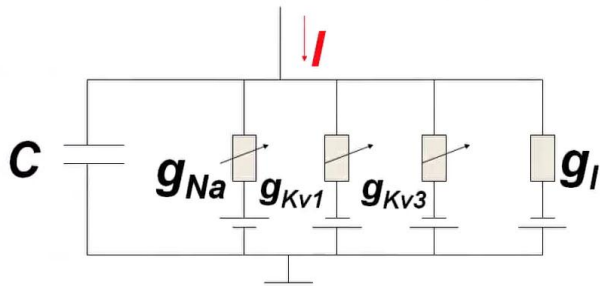
Well, you can extract a little liquid, a little droplet of liquid from the neuron, and analyze the profile of messenger RNA-- the expression profile of messenger RNA. And ion channels are proteins. Proteins can be genetically characterized. For example, for the potassium channels, there are different families. There are voltage dependent potassium channels, voltage activated potassium channels. These come in families Kv1, which has subclasses Kv1.1, Kv1.2, and so forth. Forty or so potassium channels, easily. Now, if you test for all these different ion channels in parallel-- as was done in the study of Toledo-Rodriguez in the Markram lab-- then you see which channels are currently present, or currently in the process of being built inside the neuron. Some are present, some are not present. Now, to keep things simple, suppose that we have a hypothetical neuron where only two of these channels are found. Now we can-- for each of these channels, we will write down a Hodgkin-Huxley type model. Each channel is characterized by its activation and inactivation dynamics if present.

Notes

Summary



Model of a hypothetical neuron



$$C \frac{du}{dt} = -g_{Na} m^3 h (u - E_{Na}) - g_{Kv1} n_{Kv1}^4 (u - E_K) - g_{Kv3} n_{Kv3}^2 (u - E_K) - g_l (u - E_l) + I(t)$$

How many parameters per channel?

$$\frac{dn_1}{dt} = - \frac{n_1 - n_{0,1}(u)}{\tau_{n,1}(u)}$$

$$\frac{dn_3}{dt} = - \frac{n_3 - n_{0,3}(u)}{\tau_{n,3}(u)}$$

Erisir et al, 1999

Hodgkin and Huxley, 1952

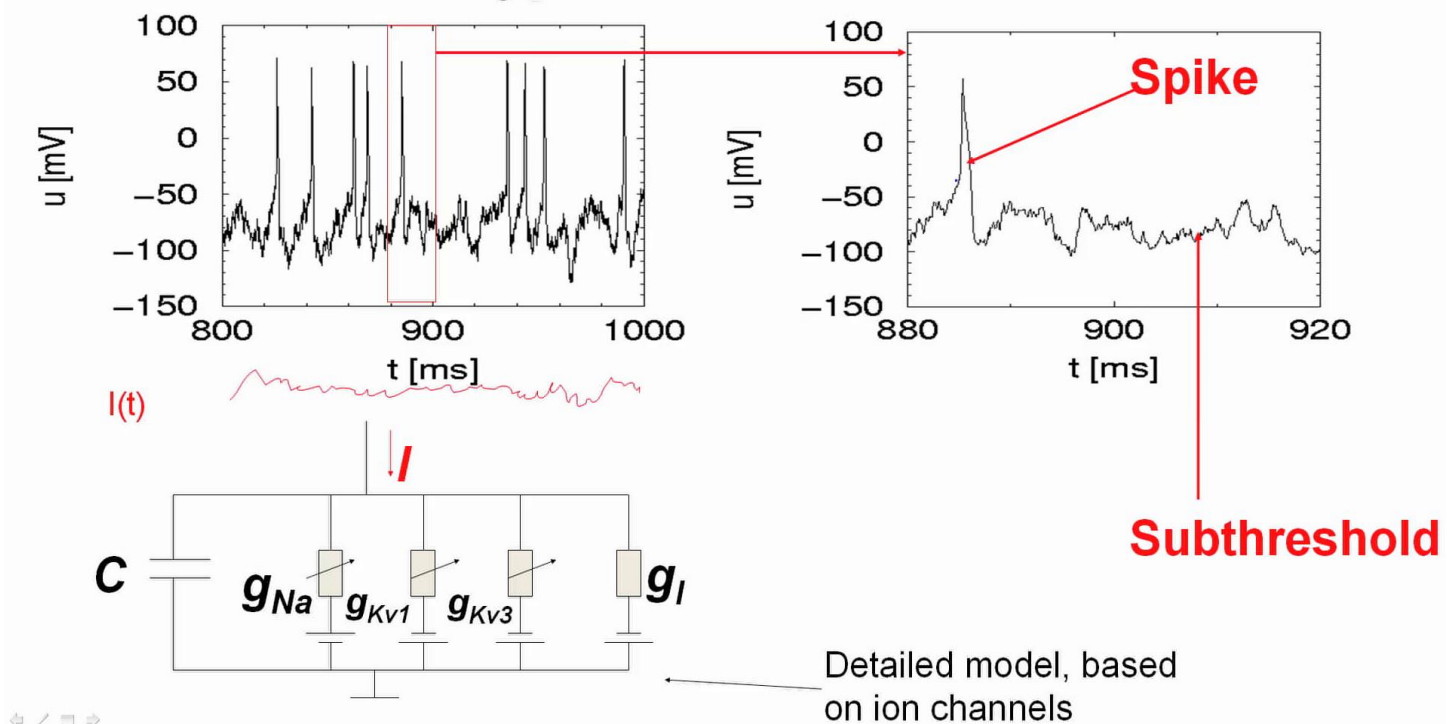
And the model, therefore, will have, say, a sodium current as before, plus a potassium current of type Kv1, another potassium current of type Kv3. Each of these channels has its membrane dynamics and gating dynamics. The sodium current has an m variable and h variable. The potassium currents have an n variable for the first current, it's another n variable for the second current. So, how many channels do we have per current? How many parameters do we have per channel? Well, each channel is characterized by a time constant. But the time constant is not a constant, but voltage dependent. You need at least two or three parameters for the time constant. Similarly, the stationary value needs at least two or three parameters. Finally, the maximum conductance is not a parameter. So we have, easily, five, six, seven, or more parameters for each of the ion channels. If the parameters of each ion channel are known, then we can build an arbitrarily complex model once we know the presence and the density of ion channels in the membrane.

Notes

Summary



Model of a hypothetical neuron



Now if you take our hypothetical model, inject the time dependent current, as we will probably observe in cortex, again, we see spikes, we see a sub threshold fluctuation.

Notes

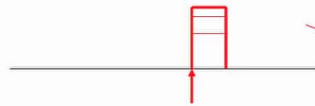
Summary



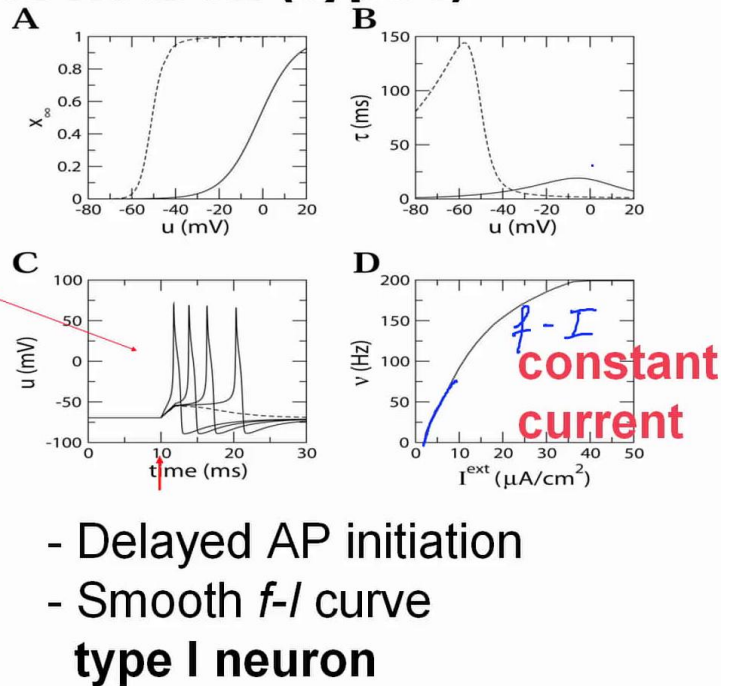
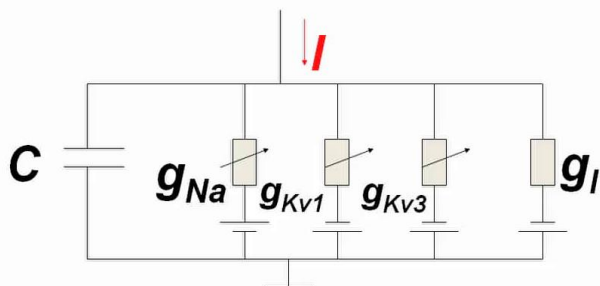
5m 29s

Model of a hypothetical neuron (type I)

Current pulse



Biophysical model, based on ion channels



- Delayed AP initiation
 - Smooth $f-I$ curve
- type I neuron**

If we inject a current pulse, we, again, see some kind of threshold behavior. There's either a pulse or there is no pulse-- the dash line. If we inject a constant current, we see a $f-I$ curve. And this $f-I$ curve is here. Smooth, it goes down smoothly, therefore, it's more like a type one neuron. The time constants for these currents are a little bit more complicated as extracted from experiments.

Notes

Summary

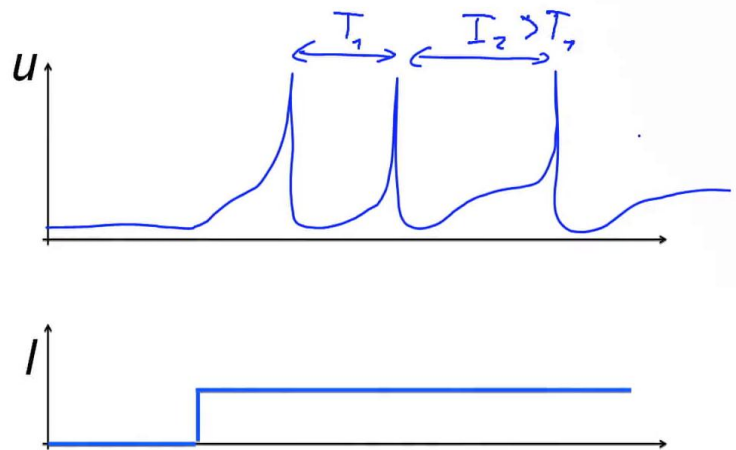


5m 39s

Neuronal Dynamics – 2.5 Adaptation

Functional roles of channels?

- Example: adaptation



So, I said that we have about 200 ion channels. What are they for? Is there any function? Can we assign function to ion channels? Well, sometimes. Partially. Let me give one example. Neurons adapt to constant current, to constant stimulation. So, suppose I have here a constant input current, then the neuron will probably fire a first spike, then a second spike, then a third spike, then a fourth spike. And adaptation means that, in the spike intervals, get longer and longer. Adaptation means that, in the spike intervals, get longer and longer.

Notes

Summary

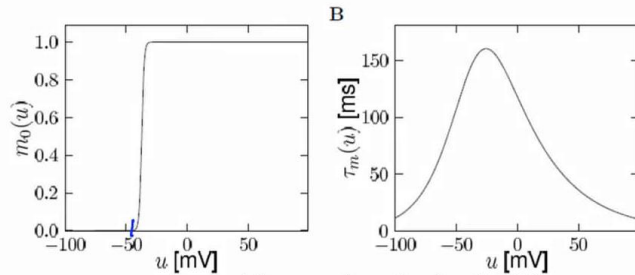


6m 08s

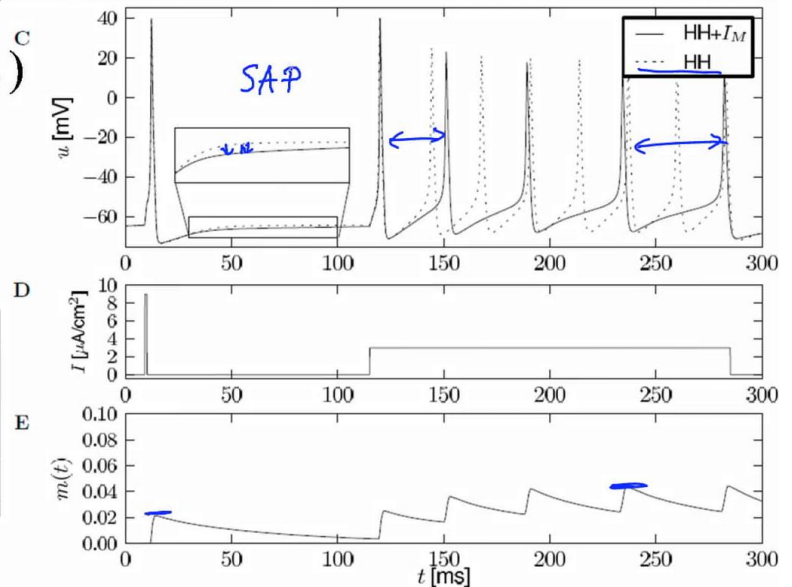
Neuronal Dynamics – 2.5 Adaptation: I_M -current

M current: $I_M = g_M m (u - E_K)^C$

- Potassium current
- Kv7 subunits
- slow time constant



Yamada et al., 1989



I_M current is one of many potential sources of adaptation

So here's a current that's involved in adaptation, the IM current. The IM current has a time constant as a function of voltage-- which is shown here-- and an activation profile which basically starts at minus 45 or minus 40 millivolt. That means this channel is activated early during spikes. The spiking threshold would sit about here. So this current is mainly activated during a spike, but then, because of the slow time constant, it accumulates. So if we give here a first pulse, then we give a step current, and you see that this variable M accumulates, it increases to higher and higher values. It's a potassium current. A potassium current leads to a decrease of the membrane potential. So you see that, in dashed we have a standard Hodgkin-Huxley model. With the solid line, it's the model with the additional IM current-- the M current-- and you see that the voltage is lower. Now this decreased voltage leads to a increase in the spike interval and indeed, what you observe is that the first interspike interval is much shorter than the fourth one. Thus, a current such as IM is one of the potentially many sources of adaptation. It works by lowering the membrane potential, by lowering the spike after potential. Now you can think of a different way of generating adaptation, and it would be not changing the spike after potential, but by increasing the firing threshold.

Notes

Summary

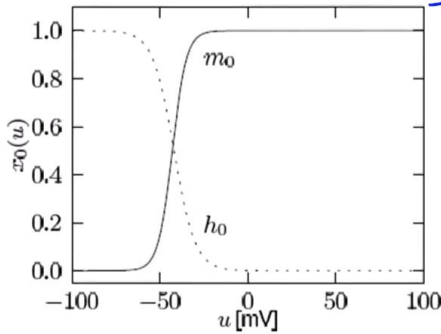


7m 06s

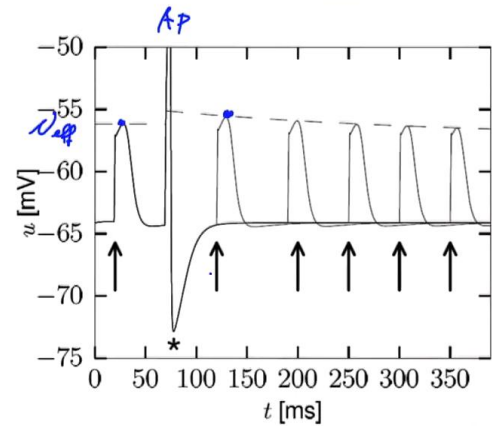
Neuronal Dynamics – 2.5 Adaptation – I_{NaP} current

current: $I_{NaP} = g_{NaP} m h (u - E_{Na})$

- persistent sodium current
- fast activation time constant
- slow inactivation ($\sim 1s$)



Aracri et al., 2006



I_{NaP} current

- increases firing threshold
- source of adaptation

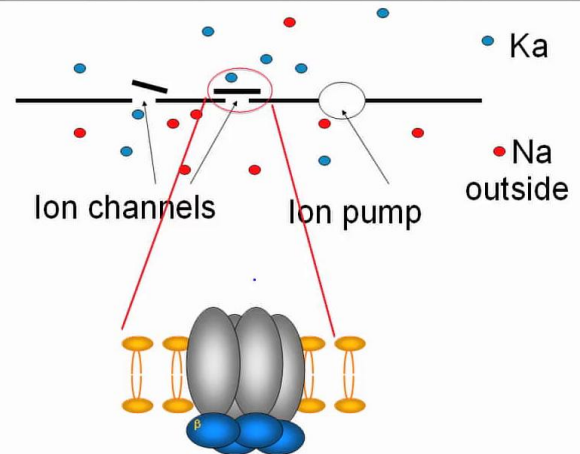
Now, let's look at this current. The persistent sodium current. Na for sodium, p for persistent. It's a current, like any sodium current, that leads to an influx of ions into the cell. So here we give a current pulse that's just not enough to lead to the generation of a spike. So we have something like effective firing threshold, which would sit around here. If we give a pulse that's just a bit stronger, we generate an action potential which is out of balance, which would go up to plus 30 milliseconds. Now after the action potential we adjust the current pulses so that the amplitude is just not sufficient to generate a spike. And you see now that the voltage trajectory goes to a value which is higher than the maximum value here, which means that the effective firing threshold is increased. Therefore, the persistent sodium current is a source of adaptation and it works by increasing the firing threshold. It's a persistent current because, once it's activated, it has a very, very slow inactivation time constant. Therefore, for the second spike, many sodium channels are still in an inactivated state and they cannot participate in the generation of the next action potential.

Notes

Summary



Neuronal Dynamics – 2.5 Biophysical models



Hodgkin-Huxley model
provides flexible framework

Hodgkin&Huxley (1952)
Nobel Prize 1963

So let me summarize. The Hodgkin-Huxley model is a famous model. It's famous for good reasons. It was a breakthrough at the time when Hodgkin and Huxley made the experiments and wrote down the model, but it's also famous because it's still a reference for many experiments done on many ion channels in labs around the world. Sometimes you wonder if a Nobel Prize is well deserved. I think, for Hodgkin and Huxley, the picture is very clear. This is a Nobel Prize that's worth the prize. It has been a highly influential model, and it's still influential today.

Notes

Summary



10m 55s

Exercise – 2.5. Hodgkin-Huxley model – gating dynamics

A) Often the gating dynamics is formulated as

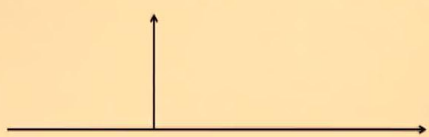
$$\frac{dm}{dt} = \alpha_m(u)(1 - m) - \beta_m(u)m \quad \parallel \quad \longrightarrow \quad \frac{dm}{dt} = -\frac{m - m_0(u)}{\tau_m(u)}$$

Calculate $m_0(u)$ and $\tau_m(u)$

B) Assume a form $\alpha_m(u) = \beta_m(u) = \frac{1}{1 - \exp[-(u + a)/b]}$

How are a and b related to γ and θ in the equations

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


 $m_0(u) = 0.5\{1 + \tanh[\gamma(u - \theta)]\}$

C) What is the time constant $\tau_m(u)$?

Please take some time to work on the assignments. We talked about stochastic ion channels. One way to think about stochastic ion channels is about opening and closing of individual gates which could lead to a dynamics of that form. Convince yourself that you can transform it to this form here, this standard form that we used here. And then, we also ask, well, how many parameters do we need to describe a single channel? Use this form here for alpha and beta, transform it to that form, calculate the time constant, and then answer the questions. How many parameters do we need if a channel just has the activation variable m ? How many parameters are there?

Notes

Summary

