**Computational Neuroscience**

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**Week – 02**

**Lecture - 12**

Lecture 12 : Hodgkin Huxley Equations - I

Welcome. So, we start with our Hodgkin Huxley equations today. So, you learnt about the integrate and fire model, actually to be more correct leaky integrate and fire model. And we will change this into the basically the spiking model with using the Hodgkin Huxley equations. So, as we have discussed, we need now what the incorporation of sodium ion channels which are voltage dependent and potassium ion channels which are also voltage dependent. So, if we think about the go back to our circuit again, if we have this I_external as before, we have the capacitor, the membrane capacitance on this side, this is the inside, this is the outside, this difference $V_{in} - V_{out}$ is our V that is the membrane potential and we had this $G_{leak}$ and $E_{leak}$ that makes up the leaky integrate and fire neuron.

Now, we had said that the path of current is across the membrane and so that is why we have the $G_{leak}$ and $E_{leak}$ in parallel to the capacitor. And now, we also know that the ion channels, the voltage gated sodium channels and the voltage dependent potassium channels, they are also transmembrane proteins and as you remember from the lecture on ion channels, there is a pore that allows the flow of ion through the membrane. And if we were to consider the ion channels, the sodium ion channels all together, then that is simply going to be an additional branch in this circuitry, a parallel branch. So, what we will have here if this branch is going to be the sodium channel branch and then if we incorporate the potassium that is going to be the potassium channel branch.

So, this is because of the sodium, I am drawing it as a box, we will describe what is going to be inside in a little bit, this is for the potassium ion. If we have to have more ion channels, more other kinds of ion channels which can be again potassium channels, but with different properties, not the kind of voltage gated potassium channels that we will be using here, then those will be additional parallel branches that can be added on here. We can have calcium channels, we can have chloride channels and so on. So, what as we have been mentioning that to explain the behavior of action potentials, the sodium and potassium channels are sufficient and that is what Hodgkin Huxley did in their experiment with the squid giant axon, where they did patch clamp experiments on the squid giant axon. And with a variety of measurements came up with the exact properties that govern this circuitry with the properties of the, what the properties of these two boxes should be.

So, let us start considering just by the sodium channel branch and so what we have in this branch, what we should have in this branch is that because of the flow of the sodium, there is essentially a conductance present for the sodium ion and this conductance is variable. So, I am drawing this block here. So, we have what we can call that conductance is $G_{Na}$ as a function of the voltage which is across the membrane. This is if you recollect our discussions on the voltage gated channels, this is this essentially must capture the behavior of the ion channel as the voltage changes throughout when there is some current injection. Now, as you know that sodium ions have some equilibrium potential based on the concentration of sodium inside and outside the neuron and that equilibrium potential or reversal potential is let us say $E_{Na}$.

So, sodium reversal potential. So, what we mean by reversal potential just to recollect what we had studied early on in this course. So, it is if there if the membrane potential is at $E_{Na}$, that is V is at $E_{Na}$ , then there will be no net sodium ions flowing through the membrane or also if the voltage is different from $E_{Na}$and there are paths for sodium available to flow through the membrane, then the sodium will flow in such a direction so that the voltage is pulled towards $E_{Na}$. Similarly, we will have the same thing for potassium its reversal potential and so it is dependent on the potassium concentration outside and inside. So, given from our previous lectures, this $E_{Na}$ is close to plus 40 millivolts and this $E_K$ is close to minus 85 millivolts.

These are approximate values, they also can vary, but when you will be actually calculating those, you will be provided with the actual concentrations to be able to calculate them. So, for now we will assume these are the nearby values to understand the system. So, now as we introduce the idea of $E_{Leak}$ earlier, similarly here we will have now $E_{Na}$because if this voltage V across the membrane or in this case here this V is equal to $E_{Na}$, then there will be no flow of current through this membrane because the current through this branch is essentially $G_{Na}(V)\times(V - E_{Na})$, where $G_{Na}$(V) is the sodium channel conductance as a function of voltage and so if V equals $E_{Na}$, this $I_{sodium}$

is 0. So, here now we have the new components $I_{Na}$ that is $I_{sodium}$ and $I_K$ or $I_{potassium}$ and we have our old $I_{leak}$ and $I_{capacitor}$. So, similarly the branch for the potassium is simply going to be is $G_K$ as a function of V followed by this battery $E_K$.

So, now if we draw the full circuit and write out the entire set of equation or the entire equation, we have this is our I_external, we have the capacitor C, we have $G_{Na}$ as a function of V followed by $E_{Na}$, then $G_K$ as a function of V followed by $E_K$ and this is $G_{leak}$ which is passive, which are not the voltage gated, which is not like the voltage gated conductance conductances and this $E_{leak}$ which stops the flow of the ions around those branches those branch that branch sorry. So, capacitor so and this is inside and outside. So, exactly in the same way as we did for the leaky integrate and fire, if this is $I_{Na}$ and this is $I_K$, we have I_external is equal to I_capacitor plus $I_{Na} + I_K + I_L$. So, our $I_{capacitor}$ turns out to be $I_{external} - I_{Na} - I_K - I_{Leak}$ and so we have $C\frac{dV}{dt} = I_{external} - G_{Na}(V)\left(V - E_{Na}\right) - G_K(V)\left(V - E_K\right) - G_{Leak}(V - E_{Leak})$ So, in now like we were earlier saying we would simulate this differential equation with a starting point and then see how the voltage changes with time for a given I_external over time. We will have let us if we enforce a V_threshold, we can find out where the spiking is going to happen and so on.

But in order to do that in this case now we have a very very difficult problem and that is what is the nature of this $G_{Na}$ and $G_K$. That is what Hodgkin and Huxley with their immense amount of work and inside showed us how to model the $G_{Na}$ and $G_K$ the voltage gated potassium conductances and voltage gated sodium channels. So, if you recollect when we talked about the patch clamp recordings, we had done this little experiment that was similar to what Hodgkin and Huxley did. I mean we had discussed the experiment that is we do a voltage clamp that is we are at $V_{rest}$, this $V_{rest}$ is let us say minus 60 milli volts around there and we go up to minus 20 milli volts and we clamp it there this is our $V_{clamp}$ and we bring it down some 10-15 milliseconds later. Now if you remember with variety of other information by putting in cesium ions by and that blocks the potassium channels and now we are left with only the sodium channels.

If we assume that it is only the sodium and potassium channels that are involved in this and actually turns out to be sufficient for the squid giant axon. So, for this we show that the current that we get that we measure goes up or in magnitude and then goes down and stays at 0. So, this is 0 current, this is the I axis and this is the time. So, at this particular point there is an inward current that is positive ions going into the neuron which is why this is negative sign in our convention and then it goes back up to 0. And again on the similarly on the other side if we block the sodium channel and plot the potassium current with the same kind of voltage clamp we get the potassium current to increase and saturate at a particular value until the clamp is held and then it goes back down to 0.

So, these 2 observations actually tell us how to go about or start thinking about modeling these $G_{Na}$ and $G_K$. So, let us say somehow we have blocked this sodium channels and we know because of the integrated and fired model this $G_{leak}$ and $E_{leak}$ we can have measurements to get $G_{leak}$ and $E_L$. $G_L$ and $E_L$ and so that can be that is not of not a problem to estimate. Then what we have here is if we remove with this from this equation we have $C\frac{dV}{dt} = I_{external} - G_{Na}(V)\left(V - E_{Na}\right)$. So, if we can measure the currents during this period where the sodium channels are not working or if it is close if we can manage to close them this is in here it was with t t x as you may remember from our previous lectures. So, what are we doing essentially in this experiment we are clamping the voltage at a particular value which means that our $C\frac{dV}{dt}$ is set to 0 because the voltage is fixed it cannot be changed experimenter is controlling the voltage exactly at the particular V that we want that the experimenter wants.

So, if this is 0 by measuring the current we can easily get basically $I_{external}$ that is what is the profile of the $G_K$ into V. $G_K$ as a function of V - $E_K$. And so by using different clamp values let us say this is $V_{rest}$ and back to V_rest here and we clamp it to some V_1 here we clamp it to some $V_2$ here some $V_3$ here some $V_4$ here some $V_5$ here and so on. So, essentially what we are describing each of these are different experiments just like what we did here only the voltage clamp value the clamp value is different in the different experiments. So, in each case for the voltage clamp in each case for the clamp value to be V_1 V_2 and so on we are measuring our $I_{external}$ is equal to the $G_K$ as a function of V, $V - E_K$. So, we know what $E_K$ is we know what V is it is in our control and we are measuring $I_{external}$ because of the patch clamp.

So, from that profile what we are essentially we can determine is how $G_K$ is changing over time when we fix the voltage at a particular value which may be $V_1$ which may be $V_2$ which may be $V_3$ and so on. So, what we will see if this experiment is done if the potassium current by itself if this is let us say we will have each experiment for a clamp at $V_1$, $V_2$ and so on is described by the successive lines here. So, at the lowest V what we see so this is time what we see is and we are having a clamp for this period and this value is our $V_{clamp}$ which is our $V_1$ etcetera that is this case is for $V_1$ this case is for $V_2$ and this case is for $V_n$. And the current is the $I_K$ or $I_{potassium}$ which we will see is increases to a particular value and stays there till the clamp till the clamp is removed and it drops down and goes back down to 0 current. So, this each of these is 0 current and this axis is current if we go.

So, this is for V1 now if we increase the voltage to some other value we will see that it is increases more than in the next case we will see that it rises and goes back to a high value even faster and on a larger value too and then even larger value and drop back. So, as you can see first of all with increasing voltage this is $V_1$, $V_2$, $V_3$, $V_4$ the largest value of the potassium current and hence the conductance at that voltage keeps on increasing and that is as a function of voltage the largest value of the potassium conductance keeps on increasing and then saturates at a particular value. The other observation here is that mostly in this description we have a speed or a time constant that governs the rise of the potassium to that particular voltage. So, this time constant turns out to be decreasing as the voltage increases in this particular depiction of the potassium currents and so from these we can actually if we were to fit let us say an exponential we can derive a time constant or know what the time constant is for each of those cases or each of those voltages. So, as a function of voltage if the maximum $G_{Na}$ that it reaches is of this kind then we have one particular depiction of the behavior of $G_{Na}$ as a function of V.

Remember we have said that this $G_{Na}$ as a function of V needs to be completely described in order to solve that differential equation that we had which is our which is our C dV/dt equals I_external and then we have minus $I_{Na} - I_K - I_L$ where we are now looking at this $I_K$ which is described by this $G_{Na}$ into V minus $E_K$ sorry not $G_{Na}$, $G_K(V - E_K)$. So and here also we are talking of G_K I am sorry for that. Now so we need the entire dynamics of the how the G_K is changing with V. What this experiment has provided us so far at least is the value of G_K I mean we can indirectly infer the value of G_K as a function of V, but what the $G_K$ value is going to be if the potential is held at V for a fairly long period of time. That is if I am holding the voltage at a particular value let us say we were at minus 60 which is the resting membrane potential and then we hold it at minus 40 and if we hold it for a period of time then the potassium conductance finally goes up and to a particular value and stays there for a long time it saturates there.

So, in a sense what we at least have is what the value should be of $G_K$ when the potential is when at steady state essentially. So, if we can measure how this is changing over time to that value and incorporate that dynamics into the $G_K$ then we would be able to solve the differential equation because simply the final value of $G_K$ at that clamp voltage is not sufficient for us to solve this equation to get the voltage across as a function of time. So, in order to do that what we need is to obtain the time constants here. Similarly, for the sodium currents again we see that if you talk that if we have the sodium currents here it is small here actually similarly in parallel here if we are plotting the $I_K$, $I_{Na}$ and correspondingly the at the different V's that we have at different times then what we will see is that there is increase in the magnitude of the sodium current and it reaches its final values faster and faster. So, there is a jump increase in the magnitude as a function of voltage and that there is a hastening of reaching the peak value there.

So, again from here also we can obtain some sort of time constant, but the big difference between the two as we had mentioned is that there is a component that brings the current back to 0. And so with these two observations what Hodgkin and Huxley essentially proposed is that the potassium channels, the potassium ion channels have only activation gates. That is once the channels are I mean as the voltage increases the gates open more and more I mean the number of gates over the probability of ion channels the potassium ion channels being open keeps on increasing. We will get into the why we said probability in the next lecture, but for now let us think of it in this way that more and more potassium channels are going to be open as we increase the voltage on average more opening of potassium channels as voltage increases. But in terms of the sodium gates, sodium channel they propose that sodium will have activation gates as well as inactivation gates.

So, what we mean by inactivation gates is that if the voltage increases the ion channels the sodium ion channels starts to close these particular gates start to close. That is as a function of voltage if we think of the in a probability of opening of inactivation gates, then as a function of voltage they keep on dropping they keep on reducing as the voltage increases where it goes those particular details we will be covering in our next discussion on the Hodgkin and Huxley equations. So, here so far what we have shown is that experimentally the sodium conductance and the potassium conductances as a function of voltage clamp that is different values of voltage clamp those can be obtained and their profile over the duration of the clamp can be obtained. The difference between the potassium and sodium is that potassium goes and reaches the saturation and stays there until the clamp is removed. The sodium goes and reaches some value and then the current or the conductance goes back down to 0.

And what Hodgkin Huxley proposed that this can be modeled by assuming that potassium channel opening is controlled by gates that are activated by voltage that is or activation gates that is with increasing voltage more and more of those gates will open. And sodium channels have two types of gates activation as well as inactivation one that behaves like the potassium channel gates and another that behaves in the opposite way that is as voltage increases their closing chances keep on increasing or their opening increases with decreasing voltage. So, with these ideas we will start off in our next continuation lecture of the Hodgkin Huxley equations and see how this there will be a set of differential equations that will come about by incorporating all these ideas and show action potential behavior. Thank you.