Computational Neuroscience

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Week – 03

Lecture – 13

Welcome. So, we were discussing our Hodgkin-Huxley system of equations that describe the spiking behaviour of neurons. Hodgkin-Huxley type models exist for a variety of neurons, as researchers have derived them based on the types of ion channels present or the density of these channels. These models have stood the test of time, and we know a lot more today in terms of actual gating of ion channels like the sodium and potassium channels, as we have discussed in our ion channels lectures. They seem to corroborate with what Hodgkin and Huxley proposed back in the middle of the last century.

We said that ultimately the circuit model for the neuron is a point model, where a single voltage describes the entire neuron. We have the external current (I_{external}) under our control. The membrane is described by a membrane capacitor. The different ion channels we have include (G_{Na})as a function of (V), then we have our (E_{Na}), which is the battery representing the reversal potential of sodium, that is, when the voltage ($V_{\text{in}} - V_{\text{out}}$) is equal to ($E_{\text{Na}}$), there is no net flow (i.e., (I_{Na}) is 0).

Similarly, for the potassium branch, we are assuming only one type of sodium channel and one type of potassium channel, which describe the Hodgkin-Huxley equations and are adequate to explain the spiking behaviour of neurons.

Additionally, we have ($\square_{\text{leak}}$)and the corresponding (E_{leak}), and our (E_{K}). So, we are essentially trying to determine what our (G_{Na}) and (G_{K})as functions of (V) should be. As we have discussed, one of the governing equations of the system is:

$$C\frac{dV}{dt} = I_{\text{external}} - G_{\text{Na}}(V)(V - E_{\text{Na}}) - G_{\text{K}}(V)(V - E_{\text{K}}) - G_{\text{leak}}(V - E_{\text{leak}})$$

For a voltage clamp, we described how we can determine the sodium current for different voltages by blocking one channel of the sodium and potassium channels. This sodium current can then be converted into obtaining (G_{Na})as a function of (V) and (T) for a particular clamp.

And so from this, we can derive this because we know what (V) and (E_{Na}) are when we are blocking the potassium channel, and the(G_{leak}) and (E_{leak}) are known and (I_{external}) is basically corresponding to the sodium current that is going because we are in clamp mode as we have discussed in the patch clamp lecture. So, from this (G_{Na}) what we saw is that we have two components of the sodium conductance: one that is an activation part and another that is an inactivation part. And potassium has only activation when we clamp it to a particular voltage; the potassium conductance increases and stops at a particular value, the current increases and stops at a particular value, and so the conductance also increases and stops at a particular value. And that peak value is what we will say as the steady-state value of the conductance for that particular voltage. And what Hodgkin and Huxley then came up with is the idea that let us represent that sodium channel gating, voltage gating, with different gates where there are 4 gates, 3 activation gates and 1 inactivation gate.

So, why exactly the numbers 3 and 1 came about we will just briefly mention that it essentially came about empirically and that is with the other equations that we will see these explain the data the best and that I mean they came up with this with certain insight of course, which is the most important thing and then with the numbers that fitted the data best. And now from other studies, more than 60 years later, 50 years later we now know that indeed there are 3 activation gates and 1 inactivation gate in sodium channels and 4 activation gates in potassium channels. So, this is for sodium channels and this is for the potassium channel 4 activation gates. So, as we mentioned the gates are activation gates are such that when voltage increases that is as voltage increases the peak value of the conductance increases. So, this (G_{Na}\) peak at that particular voltage as we saw last time.

Similarly, for the inactivation gate, it is the opposite: that it with increasing voltage it has to come down. So, now as we also saw that if we repeat those voltage clamp experiments, we see stochastic behavior that is they are not always the ion channels all of them are not always opening or whatever fraction of them are supposed to open on average they do not always open in every trial. And so what that means is that there is a probability or stochasticity associated with the opening and closing of these gates or opening and closing hence opening and closing of these ion channels. So, what Hodgkin and Huxley then proposed is that let us represent the 3 probability of the 3 activation gates being open is represented by 'm'. So, this is the probability of sodium channel activation gate open that is represented by 'm'.

And the inactivation gates probability of being open is represented by 'h' and the activation gates of the potassium channel being open that probability is represented by 'm'. With the assumption that these gates work independently and that they are a function of voltage what we find is that the with 3 activation gates and 1 inactivation gates the probability of a sodium ion channel being open would be (m^3h) where actually (m) is a function of voltage again the cube of that and (h) as a function of voltage again and this is assumed power 1 as there is 1 inactivation gate. So, if we assume that there are a large number of gates then on average we can say that the conductance of the sodium ion channels in the entire neuron can be given by a fraction of the total conductance. So, if we can measure the total sodium conductance of the neuron, that is the conductance of sodium when all the sodium ion channels are open, the conductance of the ion channels when all the sodium ion channels are open. If that is ($G_{\bar{\text{Na}}}$) then it simply means that for a particular value of (m) and (h), on average, we will have the sodium conductance to be ($G_{\bar{\text{Na}}} \times m^3 h$) where implicitly these are functions of voltage.

So, this ($G_{\bar{\text{Na}}}$) is the overall sodium conductance of the neuron, the conductance of all the sodium channels put together, and ($m^3 h$) is the probability of each of those channels being open. So, with the law of large numbers, we can say that the conductance of the sodium channels on average is going to be this ($G_{\bar{\text{Na}}} \times m^3 h$\), again assuming independence between the different gates. Similarly, for the potassium we have a total potassium conductance of ($G_{\bar{\text{K}}} \times n^4$) that will describe the behavior of the conductance of the potassium channels. So, we can now rewrite this same equation that we have using these terms ($G_{\bar{\text{Na}}}$)and ($G_{\bar{\text{K}}}$) and get a new equation where we have:

$$C\frac{dV}{dt} = I_{\text{external}} - G_{\text{Na}}^{\text{bar}} m^3 h(V - E_{\text{Na}}) - G_{\text{K}}^{\text{bar}} n^4 (V - E_{\text{K}}) - G_{\text{leak}}(V - E_{\text{leak}})$$

So, how do (m), (h), and (n) change with voltage? We only saw so far what the steady-state value of these (n)'s may be at a particular voltage or maybe the (m)'s can be at the particular voltage, that is, if we allow the (m) gates to be held at a particular voltage whatever is the probability of the (m) gates being opened that is the steady-state value of (m) at that voltage. What Hodgkin and Huxley did was that they the whole thing came about together, that with that equation and assuming that there is first-order kinetics of the gates they describe that for each of the gating variables (m), (n), and (h). These are the gating variables they are as we said are the probabilities, but they are also dynamically changing based on the voltage since they are a function of voltage. So, what we have is then essentially first-order kinetics:

$$\frac{dM}{dt} = \frac{M_\infty(V) - M}{\tau_M(V)}$$

There are a few terms here that need explanation. What we are saying here is that as if we hold the system at a particular voltage (V) for a very long period of time, so that steady state is reached, in other words, this ($\frac{dM}{dt}$) goes to 0 in steady state, then obviously (M) will reach ($M_\infty(V)$) as the ($\frac{dM}{dt}$)goes to 0 at steady state. So, if we are holding it for a very long period of time, ultimately (m) has to become ($m_\infty(V)$) and how fast it is reaching that($m_\infty(V)$)is this time constant \(

$\tau_m(V)$). The more complicating factor here is that (τ_m) is also a function of voltage and (m_∞) is also a function of voltage and this ($m_\infty(V)$) is sort of the steady-state value that we were referring to when we were plotting the conductance curves for or the sodium current curves for with a voltage clamp or the potassium ($n_\infty(V)$) would be the potassium current curves that that peak value corresponding ah voltage like corresponding conductance and obviously, the associated fraction in that case that is the probability value of (n). So, similarly, ($\frac{dn}{dt}$) is also described in the same way which is ($n_\infty(V) - n$), divided by ($\tau_n(V)$) and ($\frac{dh}{dt} = h_\infty(V) - h$), divided by ($\tau_h(V)$). So, we have now a set of 4 variables ($V, m, n,$) and (h) and we have 4 differential equations governing their dynamics that is our ($C\frac{dV}{dt}$) equation with the($I_{\text{external}}, -G_{\text{Na}}^{\text{bar}} m^3 h(V - E_{\text{Na}})$) and the rest of the terms now you are completely familiar with. So, and this is the first equation here this would be the second equation third equation and the fourth equation.

So, the ($\frac{dm}{dt}$), ($\frac{dn}{dt}$)and ($\frac{dh}{dt}$). So, and you can see that they are all interconnected with each other. So, (m) is connected to the first equation through this (m^3h)is connected to the first equation with (n^4)here (h) is connected to the first equation through this (h) and each of this ($m, n,$) and (h \) are connected with voltage because our ($m_\infty(V)$) and ($\tau_m(V)$) and the other gating variables are all dependent on voltage the similar equations. So, this set of differential equations cannot be solved analytically as you can imagine even if we first of all well the(m_∞) as a function of voltage this relationship needs to be known in order to solve this system of equations. Similarly, ($\tau_m(V)$) also needs to be known in order to solve these equations and so for the all the other gating variables.

So, let us say even if we know them still let us say we have functional forms of them still these system of equations cannot be solved analytically and has to be simulated numerically in order to understand the behavior of the system. So, the way ($m_\infty(V)$), ($\tau_m(V)$) and the other ones that is ($h_\infty(V)$) and ($\tau_h(V)$) and ($n_\infty(V)$) and ($\tau_n(V)$) are obtained are with those voltage clamp experiments that we described. So, essentially with fitting the curves you Hodgkin and Huxley estimated empirically what the ($m_\infty(V)$) function would look like with voltage and all the others by fitting the time constants with the correct powers with the observed traces. And what they found is essentially the description is like this that if we have a voltage in this way and this is the ($m_\infty(V)$) as a function of (V) then if the resting membrane potential is around minus 60 milli volt then there is a small value of ($m_\infty(V)$) and then it rises and reaches 1. So, the exact figures will be given in your handouts.

Here we want to understand the system simply in terms of the characteristics and the real actual numbers will go into the simulation. So, they reach 1 at a particular voltage close to plus 20 milli volt or plus 40 milli volts. And ($n_\infty(V)$) also has a similar shape that is if we have this (ah)($n_\infty(V)$) as a function of voltage it is also an activation gate for potassium channels this was also an activation gate for potassium channels and so the steady state. So, potassium gate opening probability is also increasing as a function of voltage just like the (m) gates. And obviously, as we have described earlier also the (h) in ($h_\infty(V)$) changes from a value of 1 and at around minus 60 milli volt it is around a 0.6 value that is all the a lot of the activation gates are open and then it drops down and reaches 0 as in voltage increases. So, Hodgkin and Huxley also came up with from this empirical data they came up with functional forms, I mean they are not obviously, theoretically derived, but something that explained the functions that really fit the data very well. And based on those functions you can actually put those (m_∞) and (n_∞) and in these equations to solve them further. Obviously, we also need the ($\tau_m(V)$) and all the other time constants as a function of voltage. And what they showed that what they found in fact is that for the (τ_s) if we plot the (τ_m) as a function of voltage, this is the voltage then it is more like a bell-shaped thing where it is at rest it is somewhere at the peak value near close to the peak value.

And again the exact plots are available for you in your reading material and essentially the nature would be something like this that is sort of a bell-shaped thing. So, this is ($\tau_h(V)$) and this is voltage and this is (V_r) or minus 60 millivolts. So, notice something that they all look similar, but a very important point is this scale here. So, these values (τ_m) values are very small, that is in the order of 0.2 millisecond and less or less than half a millisecond.

(τ_n) is of the order of 2 to 5 milliseconds and (τ_h) is of the order of 10 to 20 milliseconds. So, as you can see there is from $(m) to (n) to (h)$ these gating variables the or rather not the gating the time constant of each of the gating variables change almost an order of magnitude from $(m) to (n)$ and then from $(n) to (h \backslash)$. And this essentially is the most important point in terms of describing an action potential using the Hodgkin-Huxley equations this difference in the time constants. So, what are we saying that the (m) gates or the sodium channel activation gates open extremely fast and similarly the potassium channels are slower than the sodium channel activation gates and the so (n) opens slowly and (h) the activation gates they are opening and closing is further slower almost. So, these are all in almost multiples of 5 to 10 as we go from one to the other.

This as if we now put all this together if now let us say we have the (m) here and we are at (V_{rest})which is equal to minus 60 millivolts and we have ($m_\infty(V)$)and we have a small sodium activation gate open and a lot of that is point around 0.6 of the inactivation gates being open. So, here what we have is (m) is small, (V) equal $to(V_{\text{rest}}\backslash)$, very small, (h) is of the order of 0.6. So, that means that (m^3h)is also going to be small and so a very little sodium current is present at rest which is balanced out by whatever potassium current is there at rest based on the small value of (n).

So, here also (n) is also small. So, and so basically the$(I_{\text{Na}} + I_{\text{K}} + I_{\text{leak}}) and (I_{\text{external}})$is obviously 0 and at rest in steady state (dV/dt) is 0. So, this is making the overall current across the membrane to be 0 at this point. And now we saw that we have synaptic inputs which are the current injections into the neurons or in other words let us say that (I_{external})is we inject a small current. If we are patched on to a neuron let us say we inject a small current in there.

So, what that does is if we inject a current (I) into the neuron. So, let us say this is outside and this is inside which means positive ions have gone in that means if this is our $\backslash(V\_\{"\{in\}\}) and (V\_\{"\{out\}\})$. So, this is the membrane since positive ions have gone in this

$(V_{\text{in}} - V_{\text{out}})$ increases. So, (ΔV) is increasing which is this axis here in this curve. So, from (V_{rest}) because of the current injection the system moves to the right slightly let us say.

So, what happens is that because of this movement to the right this small depolarization which is the increase in voltage there is an increase in value of (m) that is the probability of the sodium channels being open increases from this particular value to that value. So, this is the change in the $(\mathrm{m}_{\infty}(V))$ and since \(m \) is extremely fast the (m) value reaches the $(\mathrm{m}_{\infty}(V))$ value almost instantaneously. So, what that does now is that (h) is starting to change it has not changed within that less than half a millisecond period.

So, (h) is still very close to 0.6. So, more sodium channels have opened up potassium channels are also slow they also have not moved so much they also have not opened so much more with this small change in voltage because they also have a time constant of 2 to 5 millisecond that is they are they will also open, but very slowly. So, with this increase in voltage and there is an opening of more sodium channels and as you know that if the membrane potential is different from (E_{Na}) then the sodium and if there is a path available for sodium to flow across the membrane then sodium will flow in a direction such that the potential is pulled towards (E_{Na}). So, we are at minus 60 millivolts if you remember our (E_{Na}) is at plus 40 millivolts. So, sodium will flow inwards that is trying to pull the membrane potential towards plus 40 millivolts or this (E_{Na}). So, what that does is that that increases the voltage a little further because now positive sodium ions are going in.

So, the voltage is further moved to the right I am exaggerating this in the plot, but it can move to the right and then so more sodium channels open and then more sodium comes in and this increases the voltage and more sodium channels open and goes on in a very fast time scale less than half a millisecond or so. So, what that does is that there is a shoot up in the voltage there is a small catch here which we will mention at the end that if you increase the voltage the the sodium activation gates reaches saturation that is all of them are open and by then the potassium channels have caught up that is they have started opening and there are lots of them are open because as you saw that the time constant curves are bell shaped. So, as the voltage moves to the right the potassium time constants are also decreasing. So, by the time all the (m) gates have opened the potassium channels have all started to open and so the potassium conductance increases and so potassium channels being open would mean that the potassium ions will flow in such a manner that the membrane potential will be pulled towards (E_{K}) that is the reversal potential of potassium and so it will go towards the minus 80 millivolt. So, if we look at the voltage what happens is that you are at (V_{rest}) with that current injection there is a sudden shoot up in the voltage and then they drop down and by now essentially the (h) −gates have all closed because they are the slowest ones they are all closed and so the sodium channels are inactivated that is (h) is 0 and then briefly they after a period of time they will return the the all and the entire system would return to rest.

So, here it is I have explained this very qualitatively this needs to be simulated to fully understand it and there is as I said there is something that we mean as threshold which I did not mention while describing the the behavior of action potential as we will show that indeed there is a particular value of voltage which needs to be crossed when the current injection is happening that particular voltage needs to be crossed only then there will be an action potential otherwise if the if it is the depolarization is not large enough it is going to come back down and not produce an action potential. So, that we will describe in later lectures how we model that phenomena or how we understand that phenomena. So, in short, we have the Hodgkin Huxley equations that can describe the formation of action potentials and we will then go into this how to analyze the Hodgkin Huxley system of equations to understand the behavior of the action potential in the next lectures. Thank you.