Computational Neuroscience
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Lecture – 19

Lecture 19 : Analysing HHE with Phase Plane Analysis -I

Welcome. We have been discussing the Hodgkin-Huxley equations and phase plane analysis and with that we discussed how action potentials show all or none behavior or how the Hodgkin-Huxley system of equations have what we call true threshold. We also discussed how to find in the phase plane whether limit cycle exists in the system or not or whether the system can go into oscillations or not. And basically those two are very important features of non-linear systems and plays an important role in defining action potentials and in fact saying that they are all or none events. And similarly oscillations we will see also play an important role in many other factors when we discuss more of the network level phenomena to understand the behavior of neural systems. Now among other things some of the important things that Hodgkin-Huxley equations allowed us to show as mentioned last time is anode break excitation or we will call it in short a b e and the other we mentioned is the relative refractory phenomena.

So what are these things? So anode break excitation as the name suggests is that if we I mean first these were experimentally observed and then the Hodgkin-Huxley equations actually were able to explain this behavior. So if we inject negative current that is if we hyperpolarize a neuron for a relatively long period of time few hundred milliseconds with maybe even a small current for the Hodgkin-Huxley equations about a 3 micro ampere per centimeter square current is sufficient to show that. So then if we release the negative current or stop the negative current following that stopping there is a excitation that causes action potential at the end or after the end of the hyperpolarizing current. So here is how it would look like let us say this axis is the current and this axis is time and so if let us say this is zero current and we have a current clamp that would look somewhat like this that is we are injecting a negative current let us say minus 3 micro ampere per centimeter square and we are measuring the and so the at this point which is a few hundred milliseconds later we are stopping the negative current and making it zero.

So we have a current clamp of minus 3 microamp for the this intervening period and then we come back to the zero current level. The corresponding voltage that we are measuring so at the zero current level it is supposed to be at V rest this is the voltage now and because of the negative current we are basically injecting negative ions effectively into the neuron there will be a hyper polarization as expected. Hyper polarization meaning that the voltage will go down and basically stabilize to some negative value for that particular current and it will stay on like that up to the point of release of the current clamp of the negative current clamp. Now after this because that negative current is gone obviously the system will again try to go back to its resting state. So this is our V rest level as on the left hand side so this will try to go back into the resting state and try to stay on to the V rest.

So this is not exactly what happens and we will show in the model in the Hodgkin-Nuxley model as well as experimental data shows that here it actually overshoots beyond the V rest and there is an action potential produced and then it goes to V rest. So this phenomena is the anode break excitation or ABE that is when we release a neuron from hyper polarization for I mean if it is there for a long period of time then it produces an action potential at the end. So to understand why this happens we can think about the Hodgkin-Huxley equations and what happens to the different gating variables at this particular region of time. So as we know let us say we have our let us say this is V and M infinity curve M infinity as a function of voltage let us say this is our V rest equals minus 60 milli volts. We know that our M infinity goes like this and reaches about 1 then if we draw the N infinity V on top of it it is somewhat like this with a higher value at V rest around 0.3 and now the inactivation gates whose gating variable is H they at V rest remain at around 0.6 and then go down back down to 0. So this is H infinity V. So this value here is about 0.6. So when the neuron is at rest our M values are very small this is about 0.1 or so or even less our N values are around 0.3 here and H is around 0.6. So with these values of M, N and H which essentially implies certain probability of sodium channels and potassium channels being open these values provide the equilibrium condition where the net current is 0.

That is the I_{sodium}, I_K and I_{leak} together sum to 0. So remember that is the V resting and any fluctuations from here would try to I mean would be not at equilibrium. So they may go on to other gate they may produce different phenomena. So what we also know is if you recollect we have M is very fast and as we did for the VM system to understand threshold behavior we take N and H at the value what they at what they were when we initialize the system when we consider the VM system and we in the VM system we can understand threshold phenomena because it is the model is valid only for the beginning few milliseconds. So in this case we keep again N and H we can consider N and H to be fixed to the initial value but now instead of at V rest we will now consider the situation in this particular scenario that is when the current clamp is being ended that is shown with the green line.

So we have the all the M, N and H gates held at some lower value than V rest. So at this particular time our H value is $H_{infinity}(V_R - delta)$. So here if we consider the curve we have moved the system down to $V_R - delta$ and so here at the same point N is at $N_{infinity}(V_R - delta)$ that is the steady state value of H and N at that particular voltage since we are holding it for a long period of time we will we can say that they have reached their H has reached its steady state value and N has reached its steady state value and obviously M is very fast it must be at its steady state value that is $M_{infinity}(V_R - delta)$. So what are those values at this point we have a situation something like this where my $M_{infinity}(V)$ is hardly changing because there is a small change in the $M_{infinity}$ values with that delta change because initially itself our sodium activation gates opening probability is very low. However there is a larger change in terms of the values of N and in terms of the values of H.

So this turns out to be around 0.7 and this turns out to be around 0.23. So now if we consider the so think of the system now we have H N and M at these particular values the voltage has shifted to $V_R - delta$ and we suddenly remove that $I_{external}$. So the system will now try to go in the direction that the net current will drive it towards and that is it will try to go towards V_R and in doing so if you if you think about it $M_{infinity}$ is very fast and so the voltage can be increased by the sodium channels activation gates we have H as high H is high here and N is low and these can be considered as fixed to the values we are starting the system with at the end of the current clamp.

So H is very slow it stays at $H_{infinity}(V_R - delta)$ that is it is going to change very slowly so by the time $M_{infinity}$ has gone to $M_{infinity}(V)$ from $M_{infinity}(V_R - delta)$ that is it has changed to $M_{infinity}(V)$ by this time it has changed to $M_{infinity}(V)$ H is still at $H_{infinity}(V_R - delta)$ effectively and N is still at $N_{infinity}(V_R - delta)$ because of their long time constants or large time constants. So now what happens is that our V has reached so this is I am sorry V_R, V has reached V_R so let us consider it here V has reached V_R so that is the resting membrane potential. We know that at this stage the system is in equilibrium or the net current is 0 only if our h is at $h_i nfinity(V_R)$ and n is at $n_i nfinity(V_R)$ and m is at $m_i nfinity(V_R)$. However we do not have that h is larger than the resting value and n is lower than the resting value. So we have a net current that is not 0.

Remember as we said at the $V_r est$ the net current should be 0 but in this scenario although the voltage reaches V_R in this particular point voltage has reached

V_R but the corresponding values for h and n required for the neuron to have no net current and V at V_R we do not have that and H is larger than that N is smaller than that and H being larger than that means that more sodium current will be flowing in as expected from its gradient. So sodium conductance is proportional to M^3H of which this H has increased so 0.59 to 0.7 so 0.7 to 0.6 so that means that more sodium channels are open at this point which means that there will be sodium influx trying to make the membrane potential go towards E_{sodium} as we know. Similarly N which is the potassium activation gate is lower that is our N^4 has decreased and now the role of N is to make the potassium current potassium ions go out and so at equilibrium or at V_{rest} the number of potassium channels available to remove from the inside is getting lowered in comparatively in this case because N is lower. So the potassium ions which would naturally supposed to be outside are now inside and do not have that much conductance to flow out and this is basically effectively another positive additional net positive current into the neuron. These two currents together this net balance current left when the membrane potential is at V_{rest} but H and N are not at the steady state value for V_{rest} we get increase keep on increasing the membrane potential and the same phenomena that we observe during action potential generation that same thing is repeated and we get an action potential. So this phenomena explains is explained by the Hodgkin-Huxley equation so in the code provided for Hodgkin-Huxley equation you will run this and see for yourself that this is what the model shows and this is also what was observed in real neurons and this was the first time it was explained by Hodgkin and Huxley how an outbreak excitation happens.

So to look at it in more details so this was less quantitative in the sense that it was a qualitative description but we can have a quantitative description in the sense of using our numerical simulation methods and using phase plane analysis. So let us say we have this as V and we are considering another state variable in this case it is M. So since we are looking at threshold crossing phenomena again we will have M as our other state variable and as discussed in the previous slide we are keeping H as fixed to $H_{infinity}(V - V_R - delta)$ and N is fixed at $N_{infinity}(V_R - delta)$ which is the steady state value at the end of the current clamp. So we have our $C\frac{dV}{dt}$ equation and our $\frac{dM}{dt}$ equation these two will define our systems behaviour as least in the initial few milliseconds which will show us the anode break phenomena. So here we have $I_{external}$ remember this $I_{external}$ is now 0 when the clamp is released and minus we have our $G_{sodium}barM^3H_{infinity}(V_R - delta) - G_K barN^4$ the value at $V_R - delta$ minus G_{leak} and $V - E_{leak}$.

I am sorry we have one more term here that is this is this is N at this and then we have V minus E_K. Let me erase this fully so we have V minus E_K so remember that this is N as a function of or a function of $V_R - delta$ in the sense that this is a constant and to the power 4. Similarly this is also a constant not $V_R - delta$ is not being multiplied. We will have here V I am sorry let me just erase this and rewrite this. So we have $M^3 H_{infinity}(V_R - delta) \times (V - E_{NA})$ I missed this minus $G_K bar N(V_{infinity} at V_R - delta)^4 \times (V - E_K) - G_{leak}(V - E_{leak})$.

So now from this we can get the $\frac{dM}{dt} = 0$ that is the M null line which is the same as what we have seen before which is it is going to be something like this just the same curve or the $m_i nfinity$ curve as a function of voltage. But we are actually plotting the m value here and this curve is like the $m_i nfinity$ curve. Similarly we can have the $\frac{dV}{dt} = 0$ set out as m as a function of m and V equation which we had earlier shown to look somewhat like this where we have two particular point two steps two nodes here. So this one is the resting membrane potential which is our V_R which is around minus 60 millivolts this is a saddle node and this is again a stable node. So this is a saddle this is again a stable node.

So this resting membrane potential resting point is also a stable node and we have a stable manifold coming in to this particular saddle node which is what is providing us the threshold phenomena that is we if we start with a voltage somewhere along this line then beyond this point where is where we get threshold. So now the same thing is the same phase plane can be plotted with these values of h and n. So this was plotted with $h_i nfinity(V_R)$ as h and $n_i nfinity(V_R)$ as the n value. When we change this to $V_R - delta$ the phase plane the nullclines will change. As you can see if we change this the dm dt or equal to 0 which is the m-nullcline is not going to change.

However because of the change in $h_i nfinity$ and $n_i nfinity$ the $\frac{dV}{dt}$ nullcline is going to change and what happens in this case is that we are now starting the system also at a lower slightly lower value of m from point one and $V_R - delta$ somewhere here. We are starting the system somewhere at this point. This is where the system is the green dot at the end of the current clamp which we had shown by the circle at the end of the current clamp in green. And now the $\frac{dV}{dt}$ nullcline which is this one $\frac{dV}{dt} = 0$ or V nullcline that changes to a different shape moving vertically downwards and becoming like this. So now what happens is that there are no equilibrium points in this region.

The two equilibrium points one that is that was the initial stable node which was the resting membrane potential and the saddle node which provided the threshold because of the stable manifold those two nodes are gone those two equilibrium points are not there anymore and we have the system starting at that green dot. So what happens is that the system follows along this route and goes up to this particular stable node because that is the only stable node present and the direction of flow will take it on to there. And that is essentially that the m has reached up to plus one which is the basically the upstroke of the action potential that we are seeing here. The action potential the complete action potential obviously cannot be shown here because we again need the changes in n and h to be incorporated to bring back the membrane potential down. But we are showing that it indeed it is the voltage is going towards the or making the upstroke of the action potential which is sufficient in this case with the V-m reduced system.

So we have qualitatively explained the anode break excitation with the help of the Hodgkin-Huxley system of equations. We model the anode break excitation with the Hodgkin-Huxley system of equations and with the phase plane analysis with a V-m reduced system we can show the anode break excitation and the reason behind anode break excitation. So next in our next lecture we will consider the issue of refractory or relative refractory following the spike which is also an important phenomena that can be shown by the or understood by the Hodgkin-Huxley equations. Thank you.