Cognition and its Computation

Prof. Rajlakshmi Guha
Prof. Sharba Bandyopadhyay
Biotechnology and Bioengineering
Indian Institute of Technology, Kharagpur

Lecture - 12

Currency of Computation in Neurobiology - Action Potential

Welcome. We have been discussing about the Action Potential in the introduction to computation in terms of computation in the brain. And so, in order to go into more detail about the computation performed by neurons, we have to understand the spiking in a little more detail or the way the action potentials are generated. So, as we had said that, previous stage neurons project through axons.

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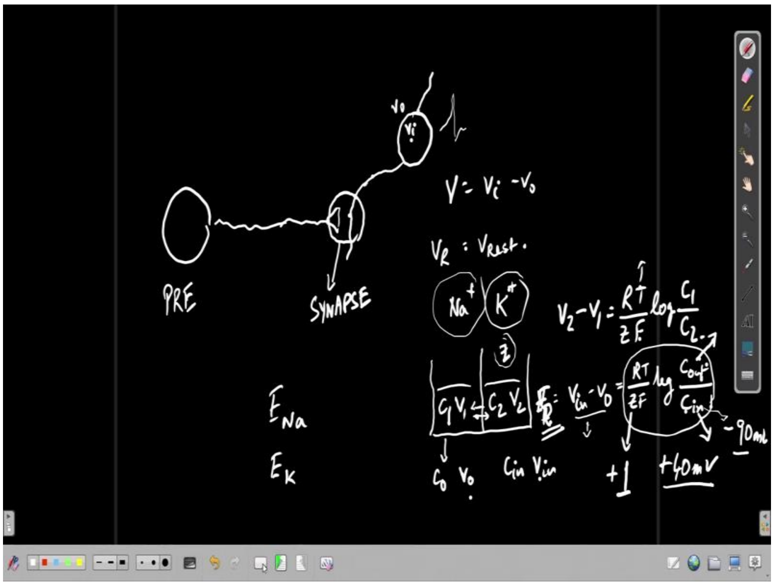

So, this is a pre neuron let us say or a previous stage neuron, whose action axon goes and projects through a synapse on the dendrite of the next neuron and through a process of neurotransmission to be covered in detail at this synapse, the there is a current injection into the next neuron that carries forward into the soma and then this neuron may or may not produce an action potential.

Please remind yourself that if we could somehow record the voltage inside the neuron and outside the neuron, which we call V equals V in minus V out it when there are no inputs coming in it is at V R or V rest or the resting membrane potential. So, as we had discussed this resting membrane potential is because of the ionic concentrations at in the inside and the outside of the neuron.

And it is primarily governed by the equilibrium potentials, the respective equilibrium potentials or reversal potentials of the neurons. To understand the action potential we primarily need the two key players, two key ions that is sodium and potassium. The rest can be lumped together as separate in terms of leak currents and so on. But it is really the sodium ions and potassium ions that can determine the main behavior of neurons in terms of spiking.

And this was shown in the 1950s or earlier a little earlier by Hodgkin and Huxley, how this action potential happens they had actually modeled it. So, when this when we have a sodium ion or any ion, with two different concentrations on two sides of a semi-permeable membrane, let us say a concentration C 1 and concentration C 2. Or here in our case it will be C out and C in let us say and this is potential V out and V in.

So, this is at V 2 and V 1. So, there is one particular ion with charge Z, could be plus 1 for sodium and plus 2 for calcium minus 1 for chloride. So, to generalize that we are saying that the charge is Z and that ion is present in concentration C 1 and V 1 C 2 and V 2 on the two sides at equilibrium, that is there is no net charge flow across the membrane.

So, in order for the ion to be at equilibrium, that is it will the net flow across the membrane is 0, in that case from the Nernst equation we know that the V 1 minus V 1 equals RT by ZF, where R, T is the temperature and R and F have their usual meanings the they are constants basically these Faraday's constant R is the universal gas constant RT by ZF, log of it is going to be V 2 minus V in.

So, it is going to be C 1 minus C 2 so; that means, we have V 2 minus V 1 is in our case V in minus V out ok. So, that is our V in minus V out, that is our V equals RT by ZF, for our case this z for sodium and potassium is plus 1 and log of this is C 1 is C out concentration outside and C in is concentration inside ok.

So, when we mean V in minus V out, that is our V or rather E equilibrium, E I or E ion or E R that is at equilibrium, the ion will not flow across the membrane if the voltage V in minus V out is this particular value. So, for sodium, this particular value for the given concentration outside and inside. So, as we have mentioned sodium concentration outside is very high and inside is very low and this is of the order of 10, 1 1 order of magnitude.

And so this turns out to be around plus 40 plus 50 milli volts, I am I would not depend on the exact concentration values, but it is a large positive value. So; that means, that when the potential across the membrane is at this particular value that is for sodium whatever we get as C out by C in and calculate this let us say it comes out to be plus 40 millivolt. Then if the membrane is at plus 40 millivolt at that time there will be no net flow of sodium across the membrane.

Even if there is a path available for sodium to flow in or out of the cell of the neuron, sodium will not be able to flow because the electrochemical potential is equal on both sides. Similarly for potassium this as we said that inside potassium is of very high concentration and outside it is of very low concentration and the exact values lead to a reversal potential or equilibrium potential of potassium to be around minus 90 milli volts.

As you can see is C in is greater than C out. So, it has to be negative and C out is greater than C in for sodium so it is positive. So, it is around minus 90 milli volts for potassium and that means, that when the potential difference across the membrane is about minus 90 milli volts. Then even if there is a path available for potassium to go into the neuron or out of the neuron it will not be able to do it because potassium is in equilibrium.

So, these two values E Na for sodium and E K for potassium play a big role in terms of the formation of the action potential.

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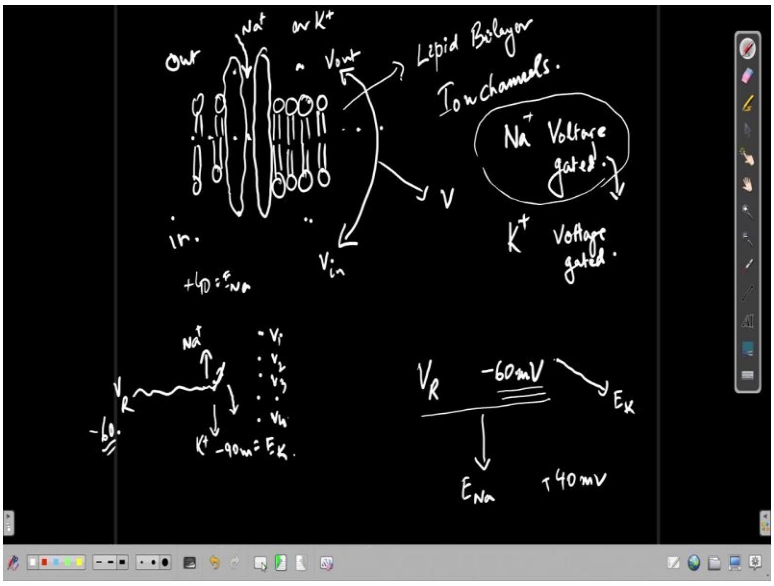

So, if we go further, now in we had talked about the membrane being a lipid bilayer and so the there are phospholipids with two tails and a polar head group, that make up the membrane. And if we consider, if we artificially form this lipid bilayer then and try to measure the impedance across the membrane, then it is extremely high, very high value of the lipid bilayers impedance.

But in real neurons actually there are conductances present that allow ions to flow into the neuron or out of the neuron and these are what we know as ion channels. So, ion channels are essentially proteins, they are transmembrane proteins arranged in such a way that they can be selective to a particular ion and so they have structures embedded in the membrane. So, this is the lipid bilayer and an ion channel has proteins that are embedded in the membrane like this.

So, they are transmembrane proteins. So, this is outside and this is inside and they have they may be selective to only particular ions going through, like just sodium or just potassium. And they are opening and closing, that is when they allow the ion to go through can be dependent on various factors and in our case we will we will consider the types of ion channels that are there, whose opening and closing are dependent on the membrane potential itself across the membrane, that is our V in minus V out.

So, the amount of ion that goes through the ion channels, the number of ions that can go through the ion channel is actually determined by this V in and V out. So, when we mean through the ion channel we mean that overall in the cell there are many many such ion channels and they are stochastic in nature and overall there is a certain probability of the ion channels being open, which is dependent on this voltage V ok.

And that determines how much current will flow through and so there are ion channels that are sodium selective Na plus selective and are voltage-gated. So, they are what we call voltage-gated sodium channels, that is when we when the voltage across the membrane determines the probability of the ion channels, the sodium ion channels being open or not that those kind of ion channels are what we called sodium ion voltage-gated sodium ion channels.

Similarly, we have voltage-gated potassium ion channels that are voltage gated and they behave in a similar manner and when a ion channel let us say a sodium ion channel is open; that means, there is a path available for sodium to go into the neuron or out of the neuron. Some ion channels can allow flow in both directions and some who cannot flow in some ion channels do not allow flow in both directions.

So, for our purposes let us consider that at V rests if a sodium ion channel is open. So, our V rest is minus 60 milli volts, if somehow a voltage gated sodium ion channel is open at and the membrane potential is this millivolt, what we learned from the Nernst equation is that when the path is available it will try to make the sodium ion flow in such a direction across the membrane through that ion channel so that the membrane potential is pulled towards E Na.

And we said that E Na is about plus 40 millivolts or some positive value here. So, basically the membrane potential V R, that we had fluctuating at rest if a sodium ion channel is open it will try to get the membrane potential higher towards the plus 40 this is minus 60.

Now, whether a sodium ion channel would be open or not at this stage, that is dependent on the properties of the voltage-gated sodium channels, that is what is the probability of the sodium ion channels being open at minus 60 millivolt, that determines how much how many of the ion channels sodium ion channels are open and that will determine how much current will finally, flow through.

So, similarly if let us say potassium ion channel is open, we know at let us say minus 60 millivolt, if a potassium ion channel is open it will try to pull this membrane potential towards E K or. So, in this case sodium ion channel it is pulling upwards towards 40 millivolts that is E Na and in this case it is the potassium ion channels will if it is open it will try to pull it towards minus 90 millivolts or minus 90 millivolts equal to E K.

So, depending on where my potential is, at whatever voltage that is V in minus V out, V 1, V 2, V 3, V 4 and what kind of ion channels are open at that particular voltage and in what probability they are open, that will determine which way the potential is going to change or how it is going to change. So, that or these all together come into a good put into a full description and this is how it is represent.

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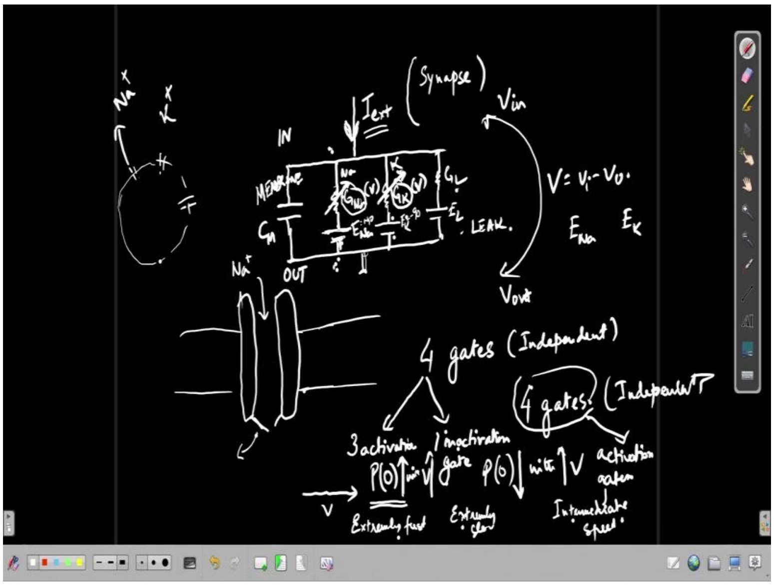

So, let us see the there is a current coming in to the soma, which we will call I external. And remember where this current is coming in, we have been saying in an actual neuron it is coming in through a synapse from the previous stage neuron. Or rather totally non-linearly weighted sum or amalgamation I would not even say sum of currents finally, reaches the soma and let us say we call it I external.

And a point model of the neuron is such that we will represent the neuron with one voltage, that is the entire neuron the V in minus V out is same, which is not true, but for the purposes of explaining the action potential we will assume that and it is not too bad.

So, this is the synaptic current coming in let us say and we have. So, this side is our inside and this side is our outside and we will represent the membrane with one branch.

So, remember the whole neuron has a membrane all around it and embedded in them are the ion channels ok. So, let us say there are Na a plus voltage-gated ion channels and K plus voltage gated ion channels. So, these are present in parallel so this is the membrane, representation of the membrane, this branch and the this is the branch for the sodium flow and this is the branch for the potassium flow. And there are some leakage currents and the all the rest of them, that we will consider as going through another branch that is the leak currents.

So, this will finally balance everything out. So, this is the sodium current branch and this is the potassium current branch, I hope that this idea is clear that we have everything in parallel here. So, the membrane is acting like a path for the external current and in it there are sodium channels, that is basically creating another parallel path for the I external and then in it there are potassium channels for the potassium current and that is creating another parallel path.

So, in this kind of a scenario as we said the membrane acts really like a capacitor. So, we will put in a capacitance here, which is C let us say or membrane capacitance C M and here we have the sodium branch so; that means, that there is some conductance of sodium. So, there is some the ion channels are providing a path and they may be open they may be closed and so there is some conductance value of sodium that is how much sodium is allowed to go through the membrane, that is present here.

And similarly, there is a potassium branch where there is a potassium conductance which is G K let us say and here it is G Na. And let us say we have another branch which is E leak V sorry which is G leak G L. So, if we draw the circuit like this with branches, there is as you can see there if we have an external current, then this G Na, will allow some sodium to go through some potassium to go through the direction is dependent on. So that should point out what is missing in this circuit.

So, the direction remember is determined by the voltage V in minus V out which is equal to V ok. And if you remember now from the earlier slides there is a reversal potential for sodium and a reversal potential for potassium which act like batteries in this branch. So, if I remove this branch and add this battery here, the potential that this battery is providing is E Na. So, which means that remember the voltage across here is V in minus V out.

We said that when V equals E Na, there will be no current flowing in the sodium ion channels. So, the battery has to be in this direction that is the positive side, this is the negative side with E Na and this is plus 40, which means when the voltage is equal to E Na, the there will be no net current in this branch. Similarly, in the potassium branch there will be a E K. So, and this is actually this is the negative positive side, this is the negative side. So, we will write this E K as the minus 90 millivolts.

And similarly, there is a corresponding E leak with this branch to actually represent the leak channels. So, this completes the overall point model of the neuron where we have sodium ion channels, potassium ion channels and the branch for leak currents and the membrane capacitance. And this I external is representing our synaptic input and this is the V out on the other side.

So, the critical thing now that we have to go through is how this G Na and G K change with the voltage. As we said that the sodium channels and the potassium channels are the probability of them being open is dependent on the voltage itself, that is the membrane potential across them. So, if we know that dependence, then we can actually see how the current flows when a synaptic input of I external comes into a neuron and what happens in the circuit.

So, this G Na. So, these G Nas and G Ks are actually variable as they are functions of voltage. So, we will put in an arrow and that is they can change, but the G leak is fixed. And this dependence Hodgkin Huxley showed that this dependence is because of the characteristics of gating of the sodium channels and potassium channels, with the probability of the gates being open or closed being determined experimentally and there are empirical relations of how the those probabilities change with voltage. With and another important aspect of that is how fast these changes happen.

So, if we think about a sodium channel without going into too much details, we can say that if this is the pore of the sodium channel, this represents the pore of the sodium channel where sodium is going in, then there are gates on this end of the sodium channel that actually open, physically open and allow ions to flow through.

So, they are through a link or protein and so on and they actually push the inside of the ion channels closed together or pull out and allow the ion to go through. So, there are 4 such gates independent, they are independent of each other that are present in sodium channels and 4 gates in potassium channels that are also independent. The difference between the two being that here there are 3 that are activation gates and 1 that is an inactivation gate.

What we mean by activation and inactivation is that with activation means that with increasing voltage, the probability of the gate being open increases and inactivation gate means that with increasing voltage the probability of the gate being open actually decreases. So, probability of the gate being open of open decreases with increase in voltage for the inactivation gate.

And here the probability of the activation gate being open, increases with increase in voltage. And 4 potassium channel gates they are all activation gates. So, the other big difference here is that these activation gates of sodium channels are extremely fast, less than half a millisecond time constant of open. And the inactivation gates are extremely slow.

Similarly, the potassium activation gates are of intermediate speed. So, these difference in time constant of how fast the sodium channels open, activation gets open, how fast the inactivation gets open and how fast the potassium activation gets open all these things together come into play in determining this G Na and the behavior of the neuron.

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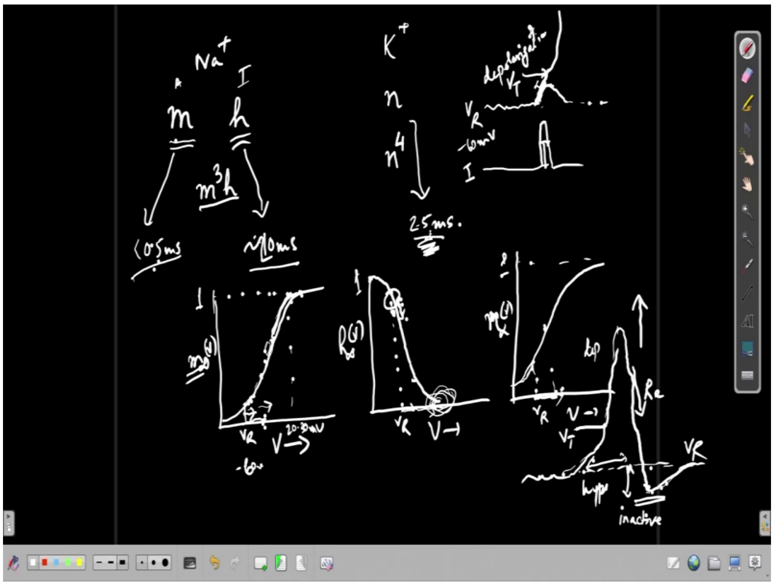

So, the sodium activation gates are called represented by m gates and their probability of being open is considered as m a variable and that is dependent on voltage.

So, the inactivation gates, so these are activation gates; the inactivation gates of a sodium channel is represented by h or h gates and the probability of them being open is given by h. And so since they are independent, the probability of the sodium channels being open is m cube h, because there are 3 m gates and 1 h gate and all of them together the probability is m cube h as they are all independent.

And for k plus the 4 activation gates, the probability of them being open is represented by n and the probability of the potassium gate being open is n to the power 4 that is the 4 of them independently act together. And the, so m we said has a time constant of opening that is extremely fast, less than 0.5 milliseconds through for all voltages, h is the slowest and its nearly like or order of 10 to 20 milliseconds, actually around 20 milliseconds and n has a time constant of opening and closing of the order of 2 to 3 milliseconds.

So, as you can see, this is the fastest, this is intermediate, this is the slowest, the sluggish ones. And so the way the m changes with voltage is there being activation gates is like this, this is how the steady state value of m as a function of voltage. What I mean is that a particular voltage V, if I hold the if the neuron is at that voltage for a long time then the value of m at steady state which we call m infinity at a particular voltage V is looks somewhat like this, where it reaches one at some voltages here this around here is the resting membrane potential V rest equals minus 60 millivolt.

And this is this saturates by about 20 to 30 millivolts, the detailed numbers will be available in the reading material. So, similarly, the h gates have similar a steady state value h infinity V as a function of voltage and they start at the lowest voltage at value of 1, that is they are open. And at resting they are around the value of 0.6 at V rest and then as voltage increases they go down to 0.

This is what the inactivation characteristic is, that is with increasing voltage the probability of the h gate being open decreases and similarly n behaves very much like the m gates, that is our n infinity as a function of voltage this is the voltage here, that behaves somewhat like this where this is 1 and we have a V R value here. So, as you can see at rest there is some sodium channel open some potassium channels open.

And altogether there is net 0 current and those can be computed and shown that with those currents flowing the net current is 0, when the potential is around minus 60 millivolts or that is the V test. Now, when there is a small current injection into the neuron, what happens is that so we are at V rest let us say the voltage goes on like this, there is a small current injection that is a positive current into the neuron that is positive ions are flowing in.

And so what will that do? So, this is at minus 60 milli volts that will cause the neuron to go to positive directions, because positive ions are coming in which is called depolarization. The neuron gets depolarized slightly with a small current injection and if let us say parallel, if I draw the current it is like a pulse let us say, the current injection causes a volt depolarization and then it will come back.

So, what happens with this change in potential is that our V rest is the potential is moving to this direction. So, some sodium channels open up and if the current is sufficient, this is what where I am coming into a territory where we cannot explain this with great computational accuracy in this course. But, we can actually do these calculations and show that there is something called an large enough current and that is when the potential goes across the threshold potential.

So, that is the current is large enough to cause the membrane potential to cross threshold, then there will be an action potential, what happens is that if this is large enough then the potential goes to the right. The m gets, so in all cases the potential goes to the right from here. So, apparently it would mean that h is coming down and m is going up. So, m cube h will come down and similarly the potential is going to the right means n is increasing. So, more potassium channels are open.

And as we know potassium will go out of the neuron and cause the membrane potential to come down, but the thing is that these m gates are extremely fast. So momentarily, these m gates open up and more sodium actually comes into the neuron. And so that causes more depolarization and more sodium channels to open.

Remember the age gates are very slow, they take a long time to close even though the voltage is going in this direction. Similarly, the potassium channels gates are also very slow compared to m, they are an order of magnitude higher here, the time constant. So, momentarily the all the sodium channels open up in a very rapid succession synergistically. So, if I change the voltage here, more depolarization more sodium channels open that is m gates open and h is already high.

It has not, it has started moving in this direction, but very very slowly. So, actually the sodium channels the m gates open up completely, that is all the m gates are open, by then hardly h changes or changes by a little amount. So, that is what causes the first large depolarization of the neuron in the action potential and this happens after a particular voltage V threshold. So, after that, this potassium gets kicked in, I mean they catch up.

So, they start to open and remember the sodium channels are all saturated, that is the m is all open and now it is waiting for the inactivation gates to come close. In the meantime, in between this period the potassium channels are open and as we said the E K is minus 90 millivolts and the potential or V is around plus 20 milli volts.

So, the potassium will go out and try to pull the membrane potential down towards minus 90 millivolts. And so, that is why the membrane potential goes down and after goes into after hyper, into a hyper polarized state that is below the resting membrane potential this is the hyper polarization.

So, and now the h gates catch up and they are all they inactivate all the sodium channels. So, h goes to 0 means or no matter what value of m the sodium channels are closed and that is where we have inactivation of sodium channels and an x absolute refractory period.

That is no matter how much current we put in here there will be no more action potentials hm. So, finally, again hand wave will leave the things will balance out and the current flow, if there are no more no further current injections it will come back to V rest. And that is how the action potential occurs.

This is the depolarization, this is the repolarization repolarization and that pulls the membrane potential below the membrane resting membrane potential and finally, if there are no further currents, they it goes back up and go again goes back to the same original state. So, this happens very fast in scales of few milliseconds, 1 or 2 milliseconds and we will see that this action potential is what causes transmission between neurons, from one neuron to other and is what is the bases of computation in actual neuronal factors.

Thank you.