Computational Neuroscience

Dr. Sharba Bandyopadhyay

Department of Electronics and Electrical Communication Engineering

Indian Institute of Technology Kharagpur

Week – 02

Lecture - 09

Lecture 09 : Current injection: Synapses

Welcome. We continue with our lectures on excitable membranes in week 2 in order to understand how neuronal activity is created, in order to understand the background of how neuronal activity is created. So we have talked about ion channels of different kinds and we have mentioned voltage gated ion channels that are involved in production of action potentials. And we also said that there are ligand gated ion channels that are present which actually provide the necessary tool to allow current injection at the level of synapses. So as we have mentioned earlier that we need the neurons to talk to each other and that action potentials are the currency of this communication. And so whenever there is an action potential on one neuron it gets transmitted along its axon and reaches the synaptic terminal or rather axon terminal which is formed on a synapse on the next neuron.

And as we had discussed there may be thousands of synapses on a neuron as you can see on the left as we have also discussed before it is every green dot on the neurons then right here are locations of synapses basically on the spines. And these are locations of what we call chemical synapses. However, there is also another kind of synapse and that is electrical synapses as shown in the diagram here. In these are synapses as we have mentioned which are based on gap junctions and gap junction proteins particularly the proteins Connexin and the family of proteins of Connexin.

And here the membrane is touching each other and the gap junction proteins sort of sit on face to face with each other allowing making a pore and connecting the inside to the connecting the inside of one neuron to the inside of the other neuron. And these electrical synapses are required for synchronization of activity as you can see if the potential here and the potential here will try to be the same. And so as we have said the membrane potential will be is the measure of activity what this will do is basically synchronize the activity in the two neurons that are connected through gap junctions. And as we have discussed in chemical synapses we have what we call release of

neurotransmitters. So when an action potential occurs and travels through the synaptic travels to the axon terminal what first happens is that there is a phenomena called not phenomena whether there is a voltage gated calcium channel opening that allows calcium to come into the neuron.

And this calcium on coming into the neuron through a series of steps allows the neurotransmitter to be released. And as you can see here in the green dots are the neurotransmitters that are being released from inside of the presynaptic side on to the synaptic cleft here in the middle here. And on the other end there are receptors on that is on the spine or on the postsynaptic side we have these ligand gated receptors as we saw when this neurotransmitter goes and binds to these receptors they have a conformational chain and open and that allows the ion to flow through depending on the kind of receptor that is. So these are what we will call chemical synapses. So our discussions later on also and for most part will be limited to the chemical synapses where the current injection on the postsynaptic neuron because of the action potential on the presynaptic side is due to these release of neurotransmitter into the synaptic cleft and opening up of the ion channel receptors on the receptors of neurotransmitters that are ion channels and that allows the ion to go through and produce the necessary current injection in the postsynaptic neuron.

So if we look further there are now two types of receptors and they are essentially the ionotropic receptors ionotropic receptors or metabotropic receptors. What we mean by that is that as shown in the example here these are the ion channel receptor or these are the neurotransmitter receptors neurotransmitter receptors and if the neurotransmitter goes and binds to the binding site here as described with this indentation on the diagram the receptor is opening and that allows the ions to flow through. Now this means that this is an extremely fast process and in this case the receptor itself is an ion channel as opposed to what we see on the right hand side which is a metabotropic receptor here the receptor is not an ion channel but it has a binding site so the neurotransmitter goes and binds to this binding site and then it is this particular receptor is coupled with other proteins inside of the neuron in the postsynaptic sites. This is particularly the most important kind of such receptors are G protein coupled receptors. So what actually happens here is that on binding it activates the G protein inside and that releases this alpha subunit or other messengers on to some effector proteins which in turn may activate other proteins and further another set of proteins which finally go and act on ion channel that allows the ion to flow through.

So this is an indirect form of current injection and it is called the metabotropic neurotransmission and in this case the current that the changes or the current that is caused is slow as opposed to the fast current injection that we see in the ionotropic case

and these currents are also longer lasting because the activation of the intermediate proteins or molecules that are involved in indirectly going and modulating or opening the ion channel they will take some time to deactivate because there are processes that come into play that go and deactivate these molecules and since this activation is not one to one always it can be one to many that is many other molecules from one particular molecule get activated. Let us say in the path there is one A so if we have from the G protein one particular subunit goes and some effector protein is activated this may activate another protein which may activate multiple other proteins that is many of the B's it is not a one to one. So B may also activate many other and so you can see there can be a huge amplification in the process where the final molecule goes and binds to the ion channel that is shown here on the right hand side. So that means that once activated unless these intermediate molecules or intermediate proteins are not deactivated or not stopped the effect on the ion channel keeps on staying and so these are long lasting effects whereas in the ionotropic case once the ion goes through and that is a very fast process in which it ends fast also as we will see in the shape of the current injection that we measure when we have a presynaptic spike. So now if we look I mean if we think of the synapses or the current injection the way we will measure is that if we have a presynaptic neuron let us say and this is the axon that is going and projecting on to the spine of the next presynaptic neuron this is an exaggerated drawing of the dendrite and the synapse and this is the dendrite and the presynaptic neuron whose axon is going out.

So if in this kind of scenario if we can stimulate the axon here or bundles of axons that project on to the neurons that we know and let us say we are patched on to the postsynaptic neuron. So in other words we can control the spiking here through stimulation by titrating the strength of the current so this is basically like a stimulating electrode if we put it on a fiber bundle and we gradually reduce the current we can make sure that we have the minimal kind of effect on the postsynaptic neuron. Minimal effect on the postsynaptic neuron and so that way we can be sure that there is only actually one action potential that is coming on to the postsynaptic neuron. In other ways also we can do it by if we can patch on to the presynaptic neuron and also the postsynaptic neuron if they happen to be connected then we can do a more direct control of the spiking of the previous neuron. So either way we will think of it in this way that we can produce a presynaptic action potential like this so let us say this is V_{rest} of the presynaptic side this is time and this is the spike or action potential as we have mentioned in the presynaptic side and based on this action potential if we are measuring the voltage on the postsynaptic side through a current clamp then what we will see is if this is the voltage then at a different scale is a change in potential like this.

If this is an excitatory synapse then we have a depolarization so the postsynaptic neuron this is the postsynaptic neuron stress we have the postsynaptic neuron at its v rest when

we have an action potential with a slight delay we will get a change in the membrane potential of the next neuron and this amplitude is maybe 2 millivolts 4 millivolts or of that order of a few millivolts and this range here as we know is of the order of a 100 millivolts. So just to make sure that you do not confuse the scales on the two different plots. So what this is this is reflecting is that because of the receptors here the ion channel receptors of the neurotransmitters which are ion channels let us say there is current flow into the postsynaptic neuron and that depolarizes the postsynaptic neuron if this positive ions going in then the inside of the postsynaptic neuron voltage increases and goes towards 0 towards the towards spiking threshold and so this is what we call the excitatory postsynaptic potential or EPSP. So in this particular case if we also alternatively measure the current that is being injected into the postsynaptic side through a voltage clamp by keeping the membrane potential at V_{rest} and if we measure current here and what we will see is at similar stage so this is 0 current in the beginning and then we see EPSP excitatory postsynaptic current this is of the order of picoamps to few hundreds of picoamps may be for large cases can go up to nanoamps. So in this case what we are measuring is the effect of the spike in the presynaptic side as measured by the current in the postsynaptic side the current injection in the postsynaptic side and in this case for the EPSP what we are doing is we are measuring the effect of the presynaptic spike through the voltage change in the postsynaptic side.

So depending on the type of synapsities it is excitatory postsynaptic potential or excitatory postsynaptic current that we will measure and if it is of the other kind that is inhibitory in nature that is in this case the membrane potential is brought lower than the resting membrane potential. So let us say if we have a inhibitory synapse and the presynaptic side is acting is producing an action potential which is in our control and then if we align that and measure the postsynaptic potential on the by through the patch recordings then we will see a decrease in the membrane potential. So this is again a few millivolts. So this is at the rest of the postsynaptic neuron and this is what we will call the IPSP or inhibitory postsynaptic potential. Similarly if we measure the current instead of the voltage in the postsynaptic neuron then this is the zero current at the baseline and then we will have inhibitory postsynaptic current that we will measure on the electrode.

So these are for excitatory synapses, these are when the synapse is inhibitory or rather effect of the receptor is inhibitory effect of the receptor on the postsynaptic side is excitatory. So what we mean by that is that even with the same neurotransmitter at the same synapse we can have an effect of excitation as well as inhibition. It depends on the types of the different kinds of receptors that are present. Let us say for example glutamate has AMPA receptors which are the main ionotropic receptors for them and there are some metatrophic glutamate receptors also that can be inhibitory in nature. So it is really the property of the receptor that provides the nature of the current, not just the

neurotransmitter itself.

So in general however we will consider glutamate as the primary excitatory neurotransmitter and we will consider GABA or gamma aminobutyric acid as the inhibitory neurotransmitter. So in these cases what happens is generally AMPA receptors are activated by the binding of glutamate as we saw and that itself is an ion channel and allows cations to flow in particularly sodium and calcium. Similarly for GABA what we will see is that the receptors, the GABA receptors type A and B are also ion channels that are chloride channels and when GABA binds to the GABA receptors then there is a flow of chloride into the neuron and so that lowers the membrane potential, hyperpolarize the membrane potential to produce an IPSP. Now actually if we consider the synapse we should introduce this sort of idea now itself in order to go forward is that it is not that the system is working with an isolated spikes like this artificial experimental case. It is actually trains of action potentials that are occurring as you saw in the diagram there are thousands of synapses and on each synapse there can be a train of action potentials over time that are occurring and there are small current injections in each of those synapses and this current injection is not always the same in the sense that if you have an action potential every time over time that the post synaptic potential is going to be the same it can vary over time and that is because there are multiple steps involved in the neurotransmitter release and current injection.

So here is the detailed process on the presynaptic side where we have these vesicles containing the neurotransmitters. So these are the vesicles on the presynaptic side that contain neurotransmitter which gradually due to many many different synaptic proteins that are present presynaptically are docked on the membrane on the inside of the presynaptic terminal and they are primed and ready to release the neurotransmitter that is present in them. When an action potential occurs in the presynaptic neuron so let us say the neuron is here whose axon ends up into this terminal so up to here it is one scale and from here it is another scale. So the action potential is occurring here at the axon hillock that travels and finally reaches the axon terminal which is drawn in this enlarged manner. What we mean by the action potential reaching the axon terminal is that the voltage takes time to travel from the soma or the axon hillock and travel through the axon and finally the membrane potential depolarization equivalent to the action potential due to the action potential occurs in the presynaptic terminal in the axon terminal.

And that voltage change that depolarization due to the action potential causes voltage gated calcium channels that are present on the presynaptic side to open VGCC is open due to the action potential and that causes calcium to come into the presynaptic terminal and this calcium through again a complicated process by binding to the many synaptic proteins that are involved in the process allows the vesicle to dump the neurotransmitter

through this exocytosis to allow the neurotransmitter to be dumped in the cleft. And that neurotransmitter release then as we know goes on and binds to the receptor on the postsynaptic side. Now the released neurotransmitter that is left over is actually endocytosed in the process over scales of tens of seconds and then finally they again are processed and packed and then reach the endosome which then cause create the vesicles to be released to be created packed with neurotransmitter and this cyclic process goes on. Now as you can see that the time scale of action of this calcium coming in and neurotransmitter release is of the scale of milliseconds. This process of endocytosis is of the scale of seconds and so the overall process is of the scale of minutes.

So depending on how much neurotransmitter is available in the presynaptic side we may or may not get release of neurotransmitter or may get lower or larger amount of neurotransmitter released in the synaptic cleft. So if we have many action potentials occurring then it could be that the neurotransmitter available to be released from the presynaptic side has reduced and so because the probability of release may reduce that means the finally the current injection on the postsynaptic side may also reduce or the membrane potential change may also reduce. And so at a very short time scale in this cases the EPSP or the IPSP or EPSC or IPSC can change and it depends on the previous activity going on in the presynaptic side also. So that tells us that it is one of the ways in which we can control or rather the neurons can control the amount of activity that it can produce on the postsynaptic side. Or amount of influence it can produce on the postsynaptic side.

So while we are studying we like to study the synapses through isolated single action potentials but now itself I would like you to remember that it is not that all the synapses are doing the same all the time the synapses are doing the same thing. It also depends on the activity. Similarly later on we will also see that in the postsynaptic side depending on how much receptors are present that current injection can be different. So with this we would like to conclude our discussions on the synapses and the current injection on postsynaptic neurons. So what we have now in our arsenal is the idea of how the presynaptic side's activity produces a change in membrane potential on the postsynaptic side or on a neuron.

And what we will see is that this is the normal way or the natural way of current injection in neurons and how later on we will see how this current injection finally goes on and adds up and produces action potentials. And we will also model these processes later on in the course where we talked about how synaptic strength is changing or rather how the amount of current injection or the amount of depolarization in the postsynaptic neuron can change which is what we will call plasticity. And depending on the time

scales of those changes it may be or the permanence of those changes it may be a short term plasticity or long term plasticity. Thank you.