Computational Neuroscience
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Lecture – 45

Lecture 45: Short Term Plasticity - II

Welcome everybody. We have been discussing our short term plasticity and the last class we had covered the particular model of showing or depression in synapses. So let us just recollect what we had. So in the presynaptic terminal if we draw like this then we have vesicles that are there and we call these as the recovered pool of vesicles. Then there is some that is in the effective pool. So this is actually neurotransmitters in the recovered pool.

This is the effective pool and then there is some inactivated or ineffective pool that is not being used by the postsynaptic side that is endocytose and carried back into the endosome and then we have a new vesicles being packed with neurotransmitter. So essentially we had the three states that is the recovered state, the effective state and the ineffective or inactive state. So and with the three differential equations we could describe how the receptor I mean how the neurotransmitters would be in the different states if we have activity and how with more activity this kind of a model where we have DRDT, DEDT and DIDT show the behavior that we see with depression synaptic depression and that is where we have with a spike in the presynaptic side with every subsequent spike we see decrease in the size of synapses until saturation such I mean until an asymptotic size is reached. So however, this particular model where we have three time constants that is the effect that is the recovery to effective that tau_{RE} which is very small of the order of 1 milliseconds that is we have tau_{RE} here and it is taking from the recovered state out into the effective state only when there is a spike we mark that with a U or this can also be written as a delta function where summation delta function where each t_j is the spike time and we will assume that the delta function is 1 or I mean it is not a direct delta function it is 1 over a narrow period around t_j or just after t_j and R is being replenished by from the inactive state with the time constant tau_{IR} and this tau_{IR} the time constant here is extremely large of the order of seconds or 1000 milliseconds.

So, this discrepancy in the time constants and here this time constant is tau_{EI} which is of the order of tens or 100 milliseconds which it is this discrepancy in the time constants between the recovered to effective and the I to R that is tau_{IR}

these two determine whether basically based on activity if we have more and more activity we will have depression it is pretty easy to show and . So, now, we move to the other aspect which is short term facilitation I mean. So, in order to explain short term facilitation and also in in the same kind of model if we need to represent depression as well then we have to modify this model in a particular manner. So, if we think about it let us say that n over a period of time over as a function of time is the neurotransmitter pool which was the entire neurotransmitter pool. So, and this and so some of it is that is in the releasable region.

So, this is the entire neurotransmitter pool that is releasable and so in a simpler model $1 - n(t)$ is the pool that is driving the process to go towards into $n(t)$ that is from non releasable pool to the releasable pool. So, in our earlier three state model this particular state was divided into two parts one is the effective part and the other is the ineffective or inactive part. So, we will now just for the sake of simplicity we will combine these two and keep it in as one pool and consider only a single time constant of recovery that is tau_r. However, there is nothing that will stop us from including the ineffective and effective pool also in whatever we are talking about or whatever model we are saying. So, that can still be done.

So, but just for simplicity we are taking a two state model that is the releasable pool and the non releasable that is it is not in the pool that is going to be released and it can be ineffective or ineffective state ah. So, essentially the the same model becomes $\frac{dn(t)}{dt} = \frac{1-n(t)}{tau_r}$ and this is what is driving ah the tau recovery into to go into the releasable pool. And our usage is based on let us say summation $\delta(t - t_j)$ that is ah from the releasable pool it is going into the effective ah into the non releasable pool and that is this multiplied by $n(t)$ ah. So, this also will be showing ah depression if we make tau_r large ah and I mean kind of like depression, but in order to bring in the facilitation aspect as we have discussed the facilitation is brought about by one of the important hypothesis is the ah build up of calcium. And there are lots of experiments in support of build up of calcium ah that leads to facilitation.

And we will say so basically we need the internal calcium concentration ah to come into play ah in this whole picture in the presynaptic side. So, internal calcium concentration in the presynaptic side ah and this is going to be proportional to the probability of release. So, the probability of release in the terminal is can be a proxy for the calcium and we can simply put a probability of release in front of the $n(t)$. So, depending on ah so this is the this this probability of release the way we have written here is not going to lead to facilitation. What we need to do is make this probability of release ah probability of release ah as a function of time.

So, that is ah essentially $p(t)$ and ah for the facilitation the idea is that there is

for every spike there is some leftover ah calcium that is going to be present and be released into the that is going to drive more neurotransmitter to be released into the synaptic cleft. So, ah in other words what we have is now if we modify that if we additionally have another differential equation let us repeat the $\frac{dn(t)}{dt} = \frac{1-n(t)}{tau_r}$ this is the recovery time constant and our usage is based on the sum over j $\delta(t - t_j)$ ah times $p(t)$ times $n(t)$. So, given that we have certain concentration of $n(t)$ multiplied by the probability is going to be the one that is ah released for each and every spike and that is how the $n(t)$ is being ah reduced. Now in terms of ah the idea of ah $p(t)$ be reflecting calcium we essentially need to make $p(t)$ we need to have a dynamics of $p(t)$ ah that is the $\frac{dp(t)}{dt}$. So, we will have we will have to have a baseline probability of release when there is no activity going on then there is a certain probability of release that is p_0.

So, p_0 is baseline release probability and ah so that is what the probability of release will try to reach with a facilitator time constant let us say tau_f this is that the or this is opposite of the facilitation actually. So, ah $p(t)$ is trying to go down to p_0 if it is ah facilitator and tau_f is the time constant that is pulling ah the probability of release to the baseline probability of release. And now the thing is that with we need a ah jump in the probability of release for every presynaptic spike ah essentially reflecting the buildup of calcium. So, that is given by j. So, that is the probability of release $\delta(t - t_j)$ there is a factor that we can put in a p times ah $1 - p(t)$ ah.

So, that is ah the maximum the probability can go up to is our $p(t)$ and for every time there is a jump ah proportional to the possible ah probability increase ah and that is how the $p(t)$ is being modulated with every spike. And so with the proper sign of a p or we can ah I mean this this a p is not provided ah as ah or ah as a I mean a particularly a negative number here because we want a general model ah because ah in we can have the same thing in the short term depression also by changing the a p or we can even make p_0 with no change in probability of release that is $p(t)$ would be constantly at p_0. So, depending on the situation we can ah have a p ah represent different things ah. So, now as you can see that if the probability of release with every delta ah every spike is ah kept on increasing then in subsequent spikes there will be a larger probability of release which will be reflected here and the larger $n(t)$ release ah ah ah ah larger reduction in $n(t)$. And so this $n(t)$ is also ah going to be ah the probability t times $n(t)$ is going to be finally, what ah is seen by the post synaptic side and with may be a factor that ah is let us call it a d for now that finally, is reflected in the post synaptic current due to the neurotransmitter it is not that all the neurotransmitter is going to drive

a current ah.

So, this can be represented representative of the post synaptic neurons conductance g_s as a function of time that is post synaptic neurons synaptic conductance. So, since this is a fraction the maximum conductance can be taken as g_m and it is a d times $p(t)$ times $n(t)$ is going to be our $g(t)$ and that conductance is going to be what we will take as driving the current based on the voltage change in the post synaptic side just like we have done earlier. And simply there also will be a equilibrium potential in the ah given the equilibrium potential represented as a battery in the branch that is the synaptic current and that can ah that can be ah that that is based on the ions that is being ah that is being transported or rather ions that are being ah allowed to go out or into the post synaptic neuron by the synapse. So, essentially what we are saying is that we have ah our post synaptic neuron instead of an I external current I mean this can also be there ah for let us say our patch clamp and so on. This is the capacitor then ah this is the sodium channel ah this is the potassium channel branch.

So, this is E_{Na} E_k g_{Na} as a function of time g_k as a function of time then let us say we have g_{leak} we have E_{leak} and we can have a $g_{synapse}$ g_s and similarly an equilibrium potential this will be called E_{syn} in this side. And this g_s whenever there is a spike would become ah I mean it will follow the ah I mean whenever there is a spike after a resting ah stage it will produce a current that will be driven into this circuit. So, it is ah sort of ah acting like ah almost like ah source. In the other words if we make the conductance ah equal to the this term here that we have put and accordingly put in $p(t)$ and $n(t)$ and drive the system now with our summation $\delta(t - t_j)$ with a finite width I mean do not I would not want you to confuse this $\delta(t - t_j)$ as ah derived delta function, but just a very narrow pulse ah. So, now this with this we have connected what we had learnt in the very first ah section ah of our course in computational neuroscience where ah we were talking of ah ah models of neurons and here ah with the explaining action potentials of the postsynaptic sides with g_k and g_{Na} and g_l n capacitor.

And we had assumed that a synaptic current is simply an I external here we have explicitly put in the synaptic current and we still have an I external for an additional component that may be driving it. So, that is the other one. So, here we are including only one particular synapse ah in the model. So, there may be many other types of synapses that still is reflected in the I external or if we are doing a patch clamp ah that would be reflected in the I external. So, as with this ah A p ah or ah the jump in the probability of release we have achieved the facilitation part and we have also shown that we with the same model we can do depression.

So, whatever we have so far that can still be modified further to bring in the

three state model ah and still show facilitation. So, implementing these ah differential equations numerically is not that challenging ah in the sense that we can do this by simple ah integration of over small ah time windows that is over ah millisecond or ah one tenth of a millisecond and directly ah make the ah derivative compute the derivative at each point and ah find the next point and simulate these equations because our time constants are not varying ah with the simulation. So, we do not need ah ah stiff solvers in order to simulate these differential equations ah. So, ah so far we have been talking about the short term plasticity from the point of view ah only of the presynaptic . So, we have talked about ah neurotransmitter depletion, we have talked about calcium ah buildup and hence the modulation of probability of release.

Similarly, these can be further extended if our p_0 the baseline probability that is also varying over time ah which is a possibility in real neurons that it is becoming more excitable with time because of plasticity and this p_0 may be varying with time over longer time constants that can also be included in a very similar manner with a similar differential equation and it is activity dependent and it can be made activity dependent by making the differential equation as with a function of the summation $\delta(t - t_j)$'s. We can further have activity dependent replenishment activity dependent replenishment that is essentially in the previous model that we talked about the tau_r has dynamics. So, basically, we have a differential equation with $\frac{dtau_r}{dt}$ and tau_r is now a function of time and this tau_r varies based on activity and there is a lot of evidence about how with very strong activity the replenishment actually becomes faster and the mechanisms of them are moderately understood there are many more experiments to be done and. So, here I mean we are we are trying to inform you about the possible complications or rather complexities that can be put into the presynaptic terminal and still be able to realistically model our previous short term depression and short term facilitation. So, all these actually play a role and in our in our modeling work in our computational neuroscience when you actually go and use these things in the real synaptic data and so on.

There you have to decide on how complex you want your model to be based on the questions that you want to answer and that is true for even the Hodgkin Huxley type of single neuron model also. So, you can have multiple many multiple types of channels . So, and make the model more and more complicated , but those complexities may be required for particular questions that you may be asking and . So, that becomes the important issue. So, so far all that we have done for the short term plasticity are presynaptic changes I mean factors on the presynaptic side.

So, there is one more important thing on the postsynaptic side for short term

plasticity and that is our receptor desensitization. So, this receptor desensitization essentially means that the postsynaptic receptors are less and become less and less sensitive to glutamate or I mean not glutamate necessarily to the neurotransmitter and mainly studied with glutamate and AMPA receptors because of over stimulation. So, the more and more activity there is in the presynaptic side the more the receptors on the postsynaptic side get desensitized that is they are not as much responsive as before that is their probability of getting reduces keeps on reducing and may go to 0. So, that also leads to factor in the short term plasticity and even if the mechanisms in the presynaptic side do not conform to short term plasticity for a particular synapse based on simply the postsynaptic sides receptor desensitization we could see short term plasticity. What I mean is that as we have discussed before there are there can be synapses where the presynaptic mechanism I mean whatever is going on in the presynaptic sides is not producing the short term depression , but we might still be able to see see short term depression because of postsynaptic factors and the primary among them is the receptor desensitization.

If so the again we extend the same kind of differential equations to model that and here we will say that $d(t)$ is the pool of non desensitized receptors. So, let us go to the other page. So, here what we will have is $\frac{dd(t)}{dt}$ equals. So, the $d(t)$ is trying to non desensitized this is trying to go to $1 - d(t)$ by tau_d this is the time constant for the desensitized receptors to become non desensitized that is it is trying to get back its sensitivity. So, that is increasing the pool of non desensitized receptors and with every presynaptic spike we are getting some factor of them being desensitized and that is we will have a decrease in the non desensitized population based on the activity in the presynaptic side which again we will show by $\delta(t - t_j)$ and now how much is it used we have had the discussion before and that is this A_d times $P(t)$ times $N(t)$.

So, that simply here is multiplied by A_d times $P(t)$ times $N(t)$ and now this will be multiplied by the non desensitized neurotransmitter population a receptor population. So, now you can see that we have the factor for facilitation we have the factor for neurotransmitter depletion we have a factor for the desensitization of neurotransmitter all of them included in the model and so based on our requirements and questions we can choose the level of factors that we want to include or the which factors we want to include and accordingly model the synaptic transmission that will reflect short term plasticity that is either depression or facilitation or even if it requires to be constant for periods of time that also can be done by modulating the baseline probability of release accordingly or even bringing in dynamics of these factors also which can also be happening. So, with this we come

to the conclusion about our discussions of short term plasticity and we will later on be discussing along with other things the implications of both long term and short term plasticity and we will be picking this up once more. Thank you.