

Synapse Models Synaptic conductances.

10-1. Today we will talk about how synaptic inputs, specifically how synaptic conductances are represented in models. To do so we shall review the process of synaptic transmission, determine the relevant variables, and make the appropriate equations.

The way that chemical neurotransmission works is that the action potential invades the synaptic terminal and opens calcium channels. Calcium entry is necessary and sufficient for neurotransmitter release. At the synapse, there are synaptic vesicles that contain neurotransmitter and neurotransmission occurs through the release of neurotransmitter from vesicles into the synaptic cleft. How do we know this happens? From quantal analysis and EM studies with freeze-fracture techniques. Vesicles are embedded in an actin matrix in the terminal and are freed from this matrix by synapsin. Remember how this process works? Remember the role of CaMKII to phosphorylate synapsin and when phosphorylated, synapsin releases vesicles so that they are free to move to the release site? Anyhow, vesicles move to the release site and become docked when a SNARE complex forms between the vesicle and the membrane. When calcium enters, the vesicle undergoes final fusion and then there is exocytosis of the neurotransmitter into the cleft. After this happens, the vesicles are recycled, refilled and ready for action!

But what happens to the neurotransmitter that is released? It diffuses in the cleft and into the extracellular space. It can bind to a receptor (typically post-synaptic, but not necessarily so, here we are interested specifically with post-synaptic receptors). When bound to a receptor it causes the opening of an ion channel. When neurotransmitter unbinds, it can diffuse away, be taken back up into the neuron or into glia by re-uptake processes or it can be degraded by enzymes.

There have been a number of models of this process through the years. Perhaps the first was by Wathey in 1978. He modeled acetylcholine at the Neuromuscular junction with differential equations for the various processes. In 1995 I did the same for glutamate binding to AMPA or NMDA receptors. The differential equations models follow the concentration of neurotransmitter in the cleft, here labeled C , as it diffuses—the first term here is diffusion in 1, 2, or 3 dimensions—plus other terms for binding and uptake. There have also been what are called Monte Carlo models of this process. What do you think of when you hear “Monte Carlo”? Race cars and gambling, right, not necessarily in that order. In these models the movement of neurotransmitter in the cleft is stochastic and the binding to receptors is stochastic. Each neurotransmitter molecule does a random walk in the cleft. Faber did a model of GABA and glycine at an inhibitory synapse. Bartol did a Monte Carlo approach to acetylcholine in the NMJ. Bartol and Stiles have developed a software program MCell which is freely available for doing stochastic models of this type. We will say more about this later.

10-2. Given what you know about neurotransmission, what are some of the variables that might be important for a model? 1) The number of neurotransmitter molecules released. Could be 500-10000. With a vesicle 30 nm in diameter (but 5nm thick membrane) and NT concentration in the vesicle of 220 μM , maybe 2000 molecules? 2) The number of postsynaptic receptors. At the NMJ, the number of ACh receptors is large. At glu synapses you might see 100 AMPA receptors and 20 NMDA receptors, but the number can vary widely. 3) What is the affinity of

the receptor for the transmitter. What is the binding rate? What is the unbinding rate? Is there receptor saturation? We need to know something about the kinetics of the process. 4) what is the rate of disappearance of transmitter from the cleft by diffusion (what is D for glu, for example), reuptake (density of uptake transporters and kinetics of removal), or enzymatic breakdown. 5) What is the conductance of a single channel? AMPA 8 pS, NMDA 50 pS for example. These are some of the important variables and I'm sure you can think of others.

The GOAL of transmitter diffusion models is to determine the number of open channels as a function of time when there is release of transmitter. So for example if the synaptic current is represented by $I_{syn} = g_{syn}(V - V_{syn})$ we need to know g_{syn} where g_{syn} = the number of open channels multiplied by the conductance of a single channel. If the number of open channels is 80 and the single channel conductance is 10 pS, then $g_{syn} = 80 * 10 = 800$ pS. Of course g_{syn} is a function of time, so we need to know how many channels are open at every time point.

10-3. How should we model binding reactions? The classic binding scheme for the NMJ given by Magleby and Stevens (1972) is $A + R \xrightleftharpoons[k_{-1}]{k_1} AR \xrightleftharpoons[\alpha]{\beta} AR_{open}$. Here A is the neurotransmitter or Agonist, R is receptors, k_1 and k_{-1} are the binding and unbinding rates of transmitter to receptor in units of $M^{-1}s^{-1}$ and s^{-1} , AR is the transmitter-receptor complex, and β and α are the channel opening and closing rates respectively in units of s^{-1} . Note that $\alpha = 1/\text{mean open time}$.

Now we could write down the differential equations for this scheme and try to solve them. To make our lives easier, we can make a simplifying assumption. We assume that neurotransmitter crosses the cleft and binds instantly to a certain number of receptors. Then all unbound neurotransmitter disappears (so no rebinding). This is actually a pretty reasonable assumption. Transmitter concentration directly over the post-synaptic density (PSD) drops sharply over 100-200 ns, so any NT that doesn't bind in this time is probably lost. What this assumption does is it allows us to start with a certain number of AR complexes without having to account for the k_1 reaction. We have just $A + R \xrightleftharpoons[k_{-1}]{\beta} AR \xrightleftharpoons[\alpha]{} AR_{open}$ where the system starts with $AR(0) =$ some number of receptors bound with neurotransmitter.

10-4. So how does this make things easier. Let's write the differential equations now for AR and AR_{open} . They are $\frac{dAR}{dt} = -k_{-1}AR - \beta AR + \alpha AR_{open}$ and $\frac{dAR_{open}}{dt} = \beta AR - \alpha AR_{open}$.

There are many ways to solve this system of 2 differential equations. Perhaps the easiest is to convert the system into a single equation (2nd order) with constant coefficients. To do this we can differentiate the first and substitute the 2nd into the result. I won't go into the details. I'll leave this as an exercise for those interested.

The solution (assuming that the number of open channels is initially 0) is

$$AR_{open}(t) = \frac{AR(0)\beta}{(r_1 - r_2)} \{ \exp(r_1 t) - \exp(r_2 t) \} \text{ where } r_1 = -a + \sqrt{a^2 - b}, r_2 = -a - \sqrt{a^2 - b}, \text{ and}$$

$a = (k_{-1} + \alpha + \beta)/2$ and $b = k_{-1}\alpha$. Then $g_{syn}(t) = AR_{open}(t) * \text{single channel conductance}$.

Often this solution is given with $r_1=1/\tau_1$ and $r_2=1/\tau_2$.

10-5. Now suppose $r_1=r_2$ in the previous expression $AR_{open}(t) = \frac{AR(0)\beta}{(r_1 - r_2)} \{ \exp(r_1 t) - \exp(r_2 t) \}$.

This will happen if $a^2=b$ so that the square root in the definitions of r_1 and r_2 disappear. Note that this condition places constraints on combinations of the rate constants.

If this condition holds, the solution reduces to what is called the α -function. There is one slight problem. Note that the above expression has a $(r_1 - r_2)$ in the denominator, and this will be zero. However the numerator will also be zero. (Go ahead and check this). Sounds like another occasion to use L'Hopital's rule.

Let $x=r_1 - r_2$, then $r_1 = x+r_2$ and $r_2=r_1-x$. Substituting in we get

$$AR_{open}(t) = AR(0)\beta \left\{ \frac{\exp(xt + r_2 t) - \exp(r_1 t - xt)}{x} \right\}.$$

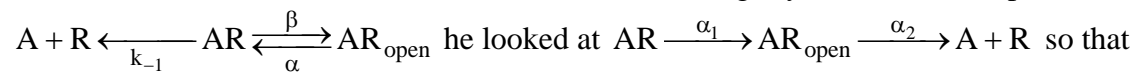
Now take the derivative of the numerator and denominator with respect to x to get

$$AR_{open}(t) = AR(0)\beta \left\{ \frac{t \exp(xt + r_2 t) - (-t) \exp(r_1 t - xt)}{1} \right\}$$

and let x go to 0. Then $AR_{open}(t)=2AR(0) \beta t \exp(-\alpha t)$ where $\alpha=-r_1 = -r_2$

This α -function was first used by Rall in 1967 to describe synaptic input, although he expressed this simply as $g_{syn}=A\alpha t \exp(-\alpha t)$

10-6. Perkel (Neuroscience 6:827-837, 1981) made a slightly different assumption. Instead of



unbinding occurs from the open state and there is no rebinding. In fact GENESIS and NEURON favor this scheme. The differential equations for AR and AR_{open} are

$$\frac{dAR}{dt} = -\alpha_1 AR \text{ and } \frac{dAR_{open}}{dt} = \alpha_1 AR - \alpha_2 AR_{open}. \text{ The first equation can be solved directly to}$$

yield $AR(t) = AR(0)\exp(-\alpha_1 t)$. We can substitute this into the second equation and get

$$\frac{dAR_{open}}{dt} = \alpha_1 AR - \alpha_2 AR_{open} = \alpha_1 AR(0) \exp(-\alpha_1 t) - \alpha_2 AR_{open}.$$

This can be solved with an integrating factor (left as an exercise to those interested) to get

$$AR_{open}(t) = \frac{\alpha_1 AR(0)}{\alpha_2 - \alpha_1} \{ \exp(-\alpha_1 t) - \exp(-\alpha_2 t) \} + AR_{open}(0) \exp(-\alpha_2 t)$$

where normally $AR_{open}(0)$ is 0 unless there are repetitive inputs.

If $\alpha_1=\alpha_2$ then $AR_{open}(t) = 2\alpha_1 AR(0)t \exp(-\alpha_1 t) + AR_{open}(0) \exp(-\alpha_1 t)$ (after application of L'Hopital's rule again, where the first term is an α function and the second is for repetitive I/P).

10-7. So results with either kinetic form $A + R \xrightleftharpoons[k_{-1}]{\beta} AR \xrightleftharpoons[\alpha]{\beta} AR_{\text{open}}$ or $AR \xrightarrow{\alpha_1} AR_{\text{open}} \xrightarrow{\alpha_2} A + R$ have a similar solution.

If left in the 2-exponential form the solutions are

$$AR_{\text{open}}(t) = \frac{AR(0)\beta}{(r_1 - r_2)} \{ \exp(r_1 t) - \exp(r_2 t) \} \text{ and } AR_{\text{open}}(t) = \frac{\alpha_1 AR(0)}{\alpha_2 - \alpha_1} \{ \exp(-\alpha_1 t) - \exp(-\alpha_2 t) \}$$

(dropping the repetitive input part).

NEURON and GENESIS use $AR_{\text{open}}(t) = \frac{G_{\text{max}} A \tau_2}{\tau_2 - \tau_1} \{ \exp(-t/\tau_2) - \exp(-t/\tau_1) \}$ where $\tau_2 > \tau_1$

Where A is chosen to normalize the maximum to G_{max} . In Exp2Syn in NEURON, the A absorbs the $1/(\tau_2 - \tau_1)$. The time constant τ_1 governs the rising phase and τ_2 governs the falling phase.

10-8. In the α -function form the solutions are

$$AR_{\text{open}}(t) = 2 AR(0) \beta t \exp(-\alpha t) \quad \text{where } \alpha = -r_1 = -r_2 \quad \text{and}$$

$$AR_{\text{open}}(t) = 2 AR(0) \alpha_1 t \exp(-\alpha_1 t) \quad \text{where here } \alpha_1 = \beta$$

NEURON and GENESIS use $g(t) = g_{\text{max}} t/\tau \exp(1-t/\tau)$ called AlphaSynapse in NEURON

Where $\alpha = 1/\tau$ and $2AR(0) \beta = g_{\text{max}} \exp(1)/\tau$. The idea is that the maximum occurs at $t=\tau$ and is equal to g_{max} . The $\exp(1)/\tau$ factor ensures that the maximum occurs at $t=\tau$. You can find the maximum of the function $g(t) = g_{\text{max}} t/\tau \exp(1-t/\tau)$ by taking the derivative and finding the value of t that makes the derivative equal 0. (Try it!).

NOTE: Channel openings are stochastic events. These conductances can be considered to be an average event. If R, the number of receptors, is large these expressions should be OK. If R is small, then a stochastic approach is needed.