Introduction to Computational Neuroscience (Fall 2023)

Models for Synaptic Transmission

The response to a presynaptic action potential and subsequent neurotransmitter release is given by a postsynaptic current (I_{syn}) produced in response to a presynaptic impulse at time t_{s}. For $t \geq t_{\text{s}}$:

$$I_{\text{syn}}(t) = g_{\text{syn}}(t)(V_{\text{post}}(t) - V_{\text{syn}}) \tag{1}$$

where V_{post} is the postsynaptic membrane potential and V_{syn} is the reversal potential of the ion channel that mediates the synaptic current.

Phenomenological Postsynaptic Conductance Models

- The simplest way to describe postsynaptic conductance is to use a function that looks like what would happen in response to a presynaptic release of a vesicle of neurotransmitter. These are **phenomenological models** in that they are agnostic about mechanism, they just give a conductance that looks right. In each case, $\bar{g}_{\text{syn}}$ is a parameter describing the maximum presynaptic conductance. The *exponential decay model* is

$$g_{\text{syn}}(t) = \bar{g}_{\text{syn}} \exp\left(-\frac{t - t_{\text{s}}}{\tau}\right) \quad . \tag{2}$$

  The *alpha function* description is

$$g_{\text{syn}}(t) = \bar{g}_{\text{syn}} \frac{t - t_{\text{s}}}{\tau} \exp\left(-\frac{t - t_{\text{s}}}{\tau}\right) \quad . \tag{3}$$

  The *dual exponential* description is

$$g_{\text{syn}}(t) = \bar{g}_{\text{syn}} \frac{\tau_1 \tau_2}{\tau_1 - \tau_2} \left(\exp\left(-\frac{t - t_{\text{s}}}{\tau_1}\right) - \exp\left(-\frac{t - t_{\text{s}}}{\tau_2}\right)\right) \quad . \tag{4}$$

  The latter is used when you wish to allow for separate control of rise and fall times.
- These functions can be hard to use in networks since they require that you keep track of the separate conductance time courses. An alternative is to solve the following differential equation numerically, noting that the solution $g(t)$ corresponds to g_{syn} for the exponential decay function when $\tau_1 = 0$, and the alpha function when $\tau_1 = \tau_2 = \tau$:

$$\tau_1 \tau_2 \frac{d^2 g}{dt^2} + (\tau_1 + \tau_2)\frac{dg}{dt} + g = \bar{g}_{\text{syn}} x(t) \tag{5}$$

  where $x(t) = 1$ when there is a spike and 0 otherwise.

Kinetic Models for Postsynaptic Conductance

- A kinetic model describes the activation of a postsynaptic receptor/ion channel that is activated upon binding of a neurotransmitter molecule. It therefore has a dependence on the neurotransmitter concentration (T) in the synaptic cleft. This is a *mechanistic model* that models what actually happens at the postsynaptic terminal, unlike the models described above. The simplest description is a two-state scheme in which receptors can be either closed, C, or open O. This kinetic scheme is:

$$\mathrm{C} \underset{\beta_a}{\overset{\alpha_a[T]}{\rightleftharpoons}} \mathrm{O}$$

and using the **Law of Mass Action** this can be converted to a single differential equation for the fraction of postsynaptic receptors that are open (a):

$$\frac{da}{dt} = \alpha_a[T](1-a) - \beta_a a \tag{6}$$

noting that $1-a$ is the fraction of receptors that are closed. Then

$$g_{\mathrm{syn}} = \bar{g}_{\mathrm{syn}} a(t) \tag{7}$$

- Since neurotransmitter is released only when the presynaptic cell fires an action potential, one can model the transmitter concentration as a step-like function of the presynaptic voltage. Then there is release only when V is above a threshold:

$$[T] = \frac{1}{1+\exp\left(\frac{V_{th}-V}{k_v}\right)} \tag{8}$$

- Many neurotransmitter receptors **desensitize**, meaning that the receptor can enter a desensitized state and not move from the closed to the open state. A kinetic scheme for this is

$$\begin{array}{ccccccc} \mathrm{C}_0 & \underset{R_{u1}}{\overset{R_b[T]}{\rightleftharpoons}} & \mathrm{C}_1 & \underset{R_{u2}}{\overset{R_b[T]}{\rightleftharpoons}} & \mathrm{C}_2 & \underset{\mathrm{R}_c}{\overset{\mathrm{R}_o}{\rightleftharpoons}} & \mathrm{O} \\ & & & & \mathrm{R}_r \Big\Uparrow \Big\Downarrow \mathrm{R}_d & & \\ & & & & \mathrm{D} & & \end{array}$$

where D is the desensitized state, R_d is the desensitization rate, R_r is the recovery rate, R_o is the channel opening rate, and R_c is the closing rate. Using the law of mass action and a conservation rule, this can be written as a system of 4 ordinary differential equations for the receptor states.

Presynaptic Plasticity

- **Synaptic facilitation** occurs when the probability of transmitter release, p, increases when a presynaptic spike comes shortly after one or more previous spikes. It often occurs in synapses onto muscle (*neuromuscular junctions*), but also in central synapses. A simple phenomenological model for this is to increment p by $\Delta p(1-p)$ at each action potential, with decay back to baseline p_0 with a time constant τ_f:

$$\frac{dp}{dt} = -\frac{(p-p_0)}{\tau_f} + \sum_s \Delta p(1-p)\delta(t-t_s) \tag{9}$$

  where $\delta(t-t_s)$ is the Dirac delta function and t_s is the time of a spike. Between spikes, p will return towards p_0 by a fractional amount $1-\exp(-\Delta t/\tau_f)$ from its value immediately following the previous action potential. Because Eq. 9 is linear except at the time of spikes, one can solve it and derive formulas such as p_j where j is the jth spike, or the equilibrium p_∞ if the spike train is periodic. The transmitter release is $T = pn\nu$ where ν is a number reflecting the concentration of neurotransmitter molecules within a synaptic vesicle.
- Another approach to model facilitation is to keep track of the facilitated release sites using a kinetic scheme like the following:

$$\mathrm{U} \underset{\beta_f}{\overset{\alpha_f[T]}{\rightleftharpoons}} \mathrm{f}$$

  where U is the fraction of unfacilitated release sites and f is the fraction of facilitated release sites. Then the transmitter release function T is multiplied by $(f_0 + f)$ where $f_0 \in [0,1]$ reflects release without facilitation.
- **Synaptic depression** is due to the depletion of vesicles in the RRVP, and often occurs in small central neuron synapses. One way to simulate this, called a *vesicle-state model*, is to keep track of the vesicles in the two vesicle pools:

$$\mathrm{V}_r \underset{k_r}{\overset{k_n}{\rightleftharpoons}} \mathrm{V}_p \xrightarrow{p} \mathrm{T}$$

  where V_r are the vesicles in the reserve pool and V_p are those in the RRVP, and p is the probability of release (which will be higher when there is a presynaptic spike). The reserve pool is usually very large, so V_r can be considered to be a constant. Then:

$$\frac{dn}{dt} = k_n^* - k_r n - pn \tag{10}$$

  where $n = \mathrm{Prob}(V_p)$ and $k_n^* = k_n n_r$ is a constant. If the presynaptic spike train is periodic with frequency ψ, then the equilibrium number of vesicles in the RRVP is:

$$n_\infty = \frac{k_n^*}{k_r + \psi p_s} \tag{11}$$

  where p_s is the probability of vesicle release when a presynaptic spike occurs.

- An alternative method is to define a **presynaptic efficacy** variable, $s \in [0,1]$, which is the probability that a release site is not depressed (i.e., not lacking an associated vesicle). Then the dynamics of s can be described by the following first-order kinetic scheme:

$$\mathrm{D} \underset{\beta_s[T]}{\overset{\alpha_s}{\rightleftharpoons}} \mathrm{s}$$

where D is the fraction of depressed release sites. The transmitter release function is then multiplied by s, so that transmitter release becomes $s[T]$.

Long-lasting Synaptic Plasticity

- The plasticity discussed so far is short-term, lasting only seconds or tens of seconds. Lasting memories are encoded through long-term synaptic plasticity, and typically involve an increase or decrease in the number of postsynaptic receptors in the membrane in response to a high-frequency presynaptic stimulation. **Long-term potentiation** occurs when the number of receptors (typically AMPA-type glutamate receptors) is increased and **long-term depression** occurs when the number decreases. In a model, either of these would change $\bar{g}_{\mathrm{syn}}$.
- **Spike-timing-dependent plasticity** is a form of long-term plasticity in which the timing of presynaptic and back-propagating postsynaptic action potentials determine whether the synaptic strength is increased or decreased. The simplest model determines $\Delta t = t^{\mathrm{post}} - t^{\mathrm{pre}}$, and then:

$$\Delta w_{ij} = A^{\mathrm{LTP}} \exp(-\Delta t/\tau^{\mathrm{LTP}}) \quad \text{if} \;\; \Delta t \geq 0 \tag{12}$$

$$\Delta w_{ij} = -A^{\mathrm{LTD}} \exp(-\Delta t/\tau^{\mathrm{LTD}}) \quad \text{if} \;\; \Delta t < 0 \tag{13}$$

where w_{ij} is the *synaptic weight* between neuron i and neuron j, A^{LTP} and A^{LTD} are positive parameters, and τ^{LTP} and τ^{LTD} are positive time constant parameters (usually between 10 and 40 ms). Then $\bar{g}_{\mathrm{syn}}$ at the synapse between neurons i and j would be proportional to the synaptic weight.

Electrical Synapses

- Some neurons (and most endocrine cells) are coupled together through **gap junctions**, which are made up of connexin proteins. These form an electrical bridge from one cell to its neighbor since ions and small molecules can flow through these junctions. The simplest, and most used, model for this electrical coupling is purely ohmic:

$$I_1 = g_c(V_2 - V_1) \tag{14}$$

$$I_2 = g_c(V_1 - V_2) \tag{15}$$

where V_1 and V_2 are membrane potential of the coupled neurons and g_c is the constant gap junctional conductance.

- Because the coupling is direct, electrical coupling is faster than synaptic coupling. Also, it is bidirectional and often tends to synchronize the activity of the coupled cells. In neurons, electrical coupling most often couples dendrites to dendrites, or axons to axons.
- Gap-junctional coupling can exhibit short-term plasticity through the action of G-proteins, which can act to close or open gap junctions. They can also exhibit long-term plasticity through the insertion of new gap junctions between cells.