M2 Biology **7/10/21**

TD3: Synapses

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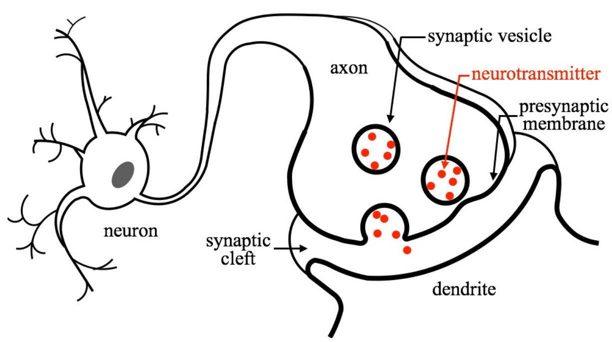
TD material is available at:

`https://github.com/Elieoriol/2122_UlmM2_ThNeuro/tree/master/TD3`

In previous tutorials, we have developed models of point neurons responding to injection of currents. Biologically, these currents correspond to synaptic inputs from other neurons, making the synapse a key element of the communication between neurons. Importantly, synapses are thought to be the substrate of learning, as the modulation of their strength, or plasticity, modifies the interaction between neurons. Plasticity can obey different rules depending on the structure of synapses. In this tutorial, we propose to model two phenomena related to plasticity at the level of the synapse: short-term depression (STD) and spike-timing dependent plasticity (STDP).

1 Short-term synaptic depression

Some chemical synapses undergo activity-dependent reduction of their transmission capabilities, called short-term synaptic depression (STD). This corresponds to having a limited number x of neurotransmitter vesicles available in a synapse. When a spike arrives at the synapse, vesicles are released into the synaptic cleft with probability p_r. The amount of vesicles $x \in [0; 1]$ is then replenished back to 1 with time constant τ_D.



1. Suppose that the synapse receives spikes at a rate ν. Compare the amount of vesicles x available at the synapse at time t and at time $t + \delta t$ to obtain a differential equation on x. Under what condition does this equation hold?

2. When vesicles are released into the cleft, they cause ion channels to open within the postsynaptic neuron. These channels close with a time constant τ_I. An amount 1 of vesicle released causes a current I_0 (absolute synaptic efficacy). Give an equation relating the postsynaptic current to $\nu(t)$ and $x(t)$, considering the system at a slow time scale ($\gg \tau_I$).

3. Suppose the input firing rate is constant, $\nu(t) = \nu_0$.

- What is the time course of x and I?
- What are the values x_∞ and I_∞ at equilibrium?
- Give the limits of x_∞ and I_∞ for $\nu_0 \to 0$ and $\nu_0 \to \infty$. In both of these limits, over what time scale does I reach its equilibrium value?
- Contrast this to the case without STD.

4. The postsynaptic neuron then integrates this current according to

$$\tau_m \dot{V} = -V + RI(t) \tag{1}$$

and emits a spike whenever the voltage reaches the threshold V_{th}. Show that there is a critical threshold θ such that, whatever the input firing rate, the neuron eventually stops spiking.

5. Consider now the following situation. The pre-synaptic cell has been firing at a steady rate $\nu(t) = \nu_0$, with ν_0 large, long enough for x to reach the steady state. At $t = 0$, the pre-synaptic firing rate instantaneously changes to $\nu_1 = \nu_0 + \Delta\nu$ and then stays constant.

- What does ν_0 large mean?
- What is the input current just after $t = 0$?
- What is the minimal step in input rate $\Delta\nu$ necessary to make the postsynaptic neuron spike?

6. Could this model be a good model of learning?

2 Spike-timing dependent plasticity

We consider a synapse connecting two neurons. The pre-synaptic neuron emits a train of n_{pre} pre-synaptic spikes $(t_{\text{pre},1}, t_{\text{pre},2}, \ldots, t_{\text{pre},n_{pre}})$, while the post-synaptic neuron emits a train of n_{post} post-synaptic spikes $(t_{\text{post},1}, t_{\text{post},2}, \ldots t_{\text{post},n_{post}})$. The synaptic weight w is modified according to the following rule: each pair of *nearest-neighbor* spikes $(t_{\text{pre},i}, t_{\text{post},j})$ induces a modification $\Delta w = f(t_{\text{post},j} - t_{\text{pre},i})$, with

$$\begin{aligned} f(s) = &\quad A^+ e^{-s/\tau^+} \quad \text{if } s \geq 0 &(2)\\ = &\quad -A^- e^{s/\tau^-} \quad \text{if } s < 0 &(3)\end{aligned}$$

where A^+, A^-, τ^+ and τ^- are positive real parameters. Pairs of spikes are considered *nearest-neighbor* if and only if there is no other (pre-synaptic or post-synaptic) spike in the interval between the two spikes $]t_{\text{pre},i}, t_{\text{post},j}[$ (or $]t_{\text{post},j}, t_{\text{pre},i}[$). The synaptic modification is the sum of all modifications induced by the individual nearest-neighbor pairs.

2.1 Regular firing

Both neurons fire n spikes periodically with a frequency $F = 1/T$ (where T is the inter-spike interval), with a fixed interval ΔT between the spikes, $\Delta T = t_{\text{post},i} - t_{\text{pre},i}$ for all $i = 1, \ldots n$.

1. Compute the total synaptic modification W induced by these spike trains for ΔT in $[-T/2, T/2]$.
2. Compute the synaptic modification W when the inter-spike interval T is much longer than the widths of the STDP windows τ^+ and τ^-, for both $\Delta T > 0$ and $\Delta T < 0$. Sketch how W depends on ΔT.

3. Compute the synaptic modification when the inter-spike interval T is much shorter than the widths of the STDP windows. Sketch again the dependence of W on ΔT.
4. Could this model be a good model of learning?

2.2 Poisson process

An experimenter can record the times at which a neuron emits spikes in response to a given stimulus. However, repeating the same stimulus, one observes that the spikes don't occur at the same time; the number of spikes is not even conserved. One way to describe these spike trains is therefore to use a random process with a given rate of spike occurrence R.

The simplest random process is the Poisson process, in which all events (here spikes) are independent, such that the mean number of spikes in an interval of duration T is RT, and the actual number of spikes on a given trial in one interval is independent of the number of spikes in any other interval.

5. This property of independence is enough to obtain the full probability distribution of the number of spikes in any given interval. A way to obtain it is to divide the interval into M bins of length $\Delta T \ll 1/R$ such that there is at most one spike per bin (for instance ΔT can correspond to the absolute refractory period of the neuron). What is the probability of observing n spikes in the total interval?
6. What is the distribution of interspike intervals?
7. Let X be a random variable with probability density $P(X)$. We define:
$$G_X(\alpha) = \int e^{\alpha X} P(x) \, \mathrm{d}X = \langle e^{\alpha X} \rangle_X \tag{4}$$
Show that:
$$\left. \frac{\mathrm{d}^n G_X}{\mathrm{d}\alpha^n} \right|_{\alpha=0} = \langle X^n \rangle \tag{5}$$
G_X is called the **moment-generating function** of the random variable X. We have a similar definition with sums instead of integrals in the case of a discrete probability distribution.
8. Use the moment-generating function to compute the mean and variance of the number of spikes generated by a homogeneous Poisson process of rate R in a window of size T.

2.3 STDP with Poisson input

We now consider random, alternating spike trains. The spike trains of both neurons are generated as follows: the total (pre+post-synaptic) spike train is generated according to a Poisson process, with frequency $R = 1/T$. Then each spike is assigned to a neuron in an alternating fashion: 1st spike to neuron 1, 2nd to neuron 2, 3rd to neuron 1, etc. In total, $2n$ spikes are generated, n per neuron.

9. What is the average total synaptic modification W at the end of the spike trains, as a function of n, R, A^+, A^-, τ^+ and τ^-?
10. What are the limits of W in the low ($R \to 0$) and high ($R \to \infty$) frequency limits?
11. Is it possible for the total modification to be negative at low frequencies, and positive at high frequencies (as in the BCM rule)? Write down the conditions on parameters for this to occur. Sketch the shape of the function f when these conditions hold. What is the frequency at which the total synaptic modification changes sign?