Synaptic Drive: Questions

• Q1. Channel Noise

Though not directly related to synaptic drive, it is instructive to look at the level of noise in a group of N channels that spontaneously open at a rate α and close at a rate β. Use $x_k = 1$ to signify channel k is open and $x_k = 0$ to signify it is closed.

[Q] By considering the total opening and closing rates of channels, calculate $\langle x \rangle$ the probability that a channel is open in the steady state.

[A] The average opening rate is $(1 - \langle x \rangle)\alpha$; the average closing rate $\langle x \rangle \beta$. In the steady state, these will be balanced, so

$$(1 - \langle x \rangle)\alpha = \langle x \rangle \beta \quad \text{requires} \quad \langle x \rangle = \frac{\alpha}{\alpha + \beta}. \tag{1}$$

Let γ be the conductance of a single channel, and E_x be its reversal potential. Assume that the voltage V remains constant: the voltage of a cell can be fixed using the *voltage clamp* mode of intracellular voltage recording.

[Q] Write down a form for the instantaneous current flowing through all N channels as a function of the x_ks.

[A] $I_x = \gamma \left(\sum_{k=1}^{N} x_k \right) (V - E_x)$

[Q] What is the average current?

[A] $\langle I_x \rangle = \gamma N \langle x \rangle (V - E_x)$. Here it is important that the voltage was assumed constant. If the voltage was free to vary under the influence of the noisy current, its fluctuations would also have to be taken into account.

Let X be equal to the total number of open channels

$$X = \sum_{k=1}^{N} x_k. \tag{2}$$

You have already calculated its average value $\langle X \rangle = \sum_{k=1}^{N} \langle x_k \rangle = N \langle x \rangle$. The aim now will be to calculate its variance, so we can examine the strength of the current fluctuations through the opening and closing channels.

[Q] First calculate the average value of X^2. Assume that different channels are uncorrelated. It is also useful to note that $x_k^2 = x_k$ for the values that x_k can take.

[A]

$$\langle X^2 \rangle = \sum_j \sum_k \langle x_j x_k \rangle = \sum_k \langle x_k^2 \rangle + \sum_{j \neq k} \langle x_j \rangle \langle x_k \rangle = N \langle x \rangle + N(N-1) \langle x \rangle^2. \tag{3}$$

The variance σ_I^2 of the current is defined as $\sigma_I^2 = \langle I_x^2 \rangle - \langle I_x \rangle^2$.

[Q] Use the results of $\langle X^2 \rangle$ and $\langle X \rangle$ to calculate the current variance.

[A] The variance of X is $\langle X^2 \rangle - \langle X \rangle^2 = N \langle x \rangle (1 - \langle x \rangle)$. And

$$\sigma_I^2 = \gamma^2 (\langle X^2 \rangle - \langle X \rangle^2)(V - E_x)^2 \quad \text{and so} \quad \sigma_I^2 = \gamma^2 N \langle x \rangle (1 - \langle x \rangle)(V - E_x)^2 \tag{4}$$

The standard deviation σ_I has units of current. A convenient dimensionless measure of the noise strength is $\sigma_I / \langle I \rangle$.

[Q] Calculate this quantity.

[A]

$$\frac{\sigma_I}{\langle I \rangle} = \sqrt{\frac{1 - \langle x \rangle}{N \langle x \rangle}} \sim \frac{1}{\sqrt{N}} \tag{5}$$

[Q] How does the relative strength of fluctuations scale with the channel number?
[A] They decrease with the reciprocal of the root of N.
[Q] If the total conductance $N\gamma$ remains constant, so the current is constant, how does the variance scale with the single channel conductance γ? What are the implications?
[A] Variance scales linearly with γ at constant conductance. Hence a small number of high conductance ion channels will give rise to a very noisy current.

• Q2. Shunting Inhibition
In this question we will examine the role of inhibition and see if it is subtractive or divisive. First we consider the voltage response to injected current. The voltage equation is

$$C\frac{dV}{dt} = g_L(E_L - V) + I \tag{6}$$

The current is initially zero but at time $t = 0$ jumps to a constant value I_0.
[Q] After a long time has passed, what is the voltage increase $\Delta V = V - E_L$?
[A] $\Delta V = I_0/g_L$
[Q] What quantity in equation (6) determines the excitability of the cell (i.e. how easy it is to increase the voltage)?
[A] It is inversely proportional to the conductance g_L, so the more channels that are open, the less responsive is the cell.
The amplitude of a weak post-synaptic potential (PSP) is proportional to the difference between the resting potential E_L and the reversal potential of the synapse E_s, i.e. to $(E_s - E_L)$. The resting potential is typically around -65mV and for excitation $E_e = 0$mV, giving an amplitudinal factor of 65mV. For inhibition E_i is around -70mV giving an amplitudinal factor over 10 times weaker. In fact in many cases $E_i = E_L$ and so inhibitory synapses have zero amplitude. Nevertheless, the presence of inhibition can significantly reduce the response of the neuron to exctitatory synaptic drive. Consider the extreme case where $E_i = E_L$. The voltage equation is

$$C\frac{dV}{dt} = g_L(E_L - V) + g_i(E_i - V) + g_e(E_e - V) \tag{7}$$

[Q] Assume first that $g_i = g_e = 0$. What is the leak time constant τ_L of the neuron?
[A] $\tau_L = C/g_L$.
Now assume that there is a steady barrage of inhibition so $g_i = g_{i0} > 0$.
[Q] What is the total conductance of the neuron now? What is the effective time constant? Is it larger or smaller than τ_L? How will this affect any EPSPs that arrive? How does this affect the neuron as a coincidence detector?
[A] The conductance $g = g_{i0} + g_L$ is larger, the time constant $\tau_{eff} = C/(g_{i0} + g_L)$ is smaller. Any EPSPs will decay away faster. For two EPSPs to sum together they must arrive closer.
Imagine the excitatory input can be modelled as a constant conductance g_{e0}.
[Q] What is the value of $\Delta V = V - E_L$ in the absence of inhibition?
[A] The solution for the voltage is

$$V = \frac{E_L g_L + E_e g_{e0}}{g_L + g_{e0}} \quad \text{so that} \quad V - E_L = \frac{g_{e0}(E_e - E_L)}{g_L + g_{e0}} \tag{8}$$

[Q] What is its average value in the presence of constant inhibition g_{i0}?
[A] The solution is of similar form

$$V = \frac{E_L g_L + E_e g_{e0} + E_i g_i}{g_L + g_{e0} + g_{i0}} \quad \text{so that} \quad V - E_L = \frac{g_{e0}(E_e - E_L)}{g_L + g_{e0} + g_{i0}} \tag{9}$$

where the relation $E_i = E_L$, which is particular to the case considered here, has been used.
[Q] Excitatory drive is largely additive. Does inhibitory drive have a subtractive or divisive effect?
[A] It is largely divisive. The main effects it has are to reduce the time constant of the membrane so that EPSPs are over sooner and to reduce the amplitude of the EPSPs. This effect is called *shunting* inhibition in analogy with a shunt on a railway (where a train is pushed down a side track). In the circuit diagram the opened inhibitory synaptic channels allow excitatory current to escape before it has a chance to increase the voltage of the membrane significantly.

• Q3. Mean-Variance Analysis
We will now review a simple method for extracting, from experiment, the number of vesicle release sites n and the voltage amplitude a (assuming this quantity has no variance) that each released vesicle causes. The total amplitude of the PSP due to the arrival of a presynaptic pulse at the release sites is

$$\mathcal{A} = a \sum_{k=1}^{n} y_k \tag{10}$$

where $y_k = 1$ with probability p (or p_m if this particular event is part of a train of pulses) if a vesicle is released and $y_k = 0$ with probability $1 - p$ if no vesicle is released. Hence $\langle y \rangle = p$.
[Q] What is the mean amplitude $\langle \mathcal{A} \rangle$?
[A]

$$\langle \mathcal{A} \rangle = a \sum_{k=1}^{n} \langle y_k \rangle = anp. \tag{11}$$

[Q] Show that the variance of $\mathcal{A}$ takes the form

$$\sigma^2_{\mathcal{A}} = a^2 np(1-p). \tag{12}$$

[A] First we calculate $\langle \mathcal{A}^2 \rangle$

$$\langle \mathcal{A}^2 \rangle = a^2 \left(\sum_{j=1}^{n} \sum_{k=1}^{n} \langle y_j y_k \rangle \right) = a^2 \left(\sum_{j=1}^{n} \langle y_j^2 \rangle + \sum_{j \neq k} \langle y_j y_k \rangle \right) = a^2 \left(\sum_{j=1}^{n} \langle y_j \rangle + \sum_{j \neq k} \langle y_j \rangle \langle y_k \rangle \right) \tag{13}$$

where in the last result the fact that $y_j^2 = y_j$ has been used, as well as the independence of release sites. On inserting the forms for $\langle y_k \rangle = p$ we have

$$\langle \mathcal{A}^2 \rangle = a^2 \left(np + n(n-1)p^2 \right) \tag{14}$$

so that the variance $\sigma^2_{\mathcal{A}} = \langle \mathcal{A}^2 \rangle - \langle \mathcal{A} \rangle^2$ can be written

$$\sigma^2_{\mathcal{A}} = a^2 np(1-p). \tag{15}$$

[Q] Re-express p as a function of the mean $\mathcal{A}$ and use it to remove the explicit p-dependence of $\sigma^2_{\mathcal{A}}$. What is the functional relationship between the mean and variance?
[A] The mean is related to p by $\langle \mathcal{A} \rangle / an = p$. On substitution we get

$$\sigma^2_{\mathcal{A}} = a \langle \mathcal{A} \rangle \left(1 - \frac{\langle \mathcal{A} \rangle}{an} \right) \tag{16}$$

so the relationship between the two is parabolic.
[Q] How might this result be used to calculate n and a?
[A] For the vesicle run-down experiments, for each of the m steps one can calculate $\langle \mathcal{A} \rangle$ and $\sigma^2_{\mathcal{A}}$. The variance (y-axis) can be plotted as a function of the mean (x-axis) for each of the points and a parabola fitted to through the points. The gradient at zero mean gives a and the non-zero intercept of the x axis is an, giving n. This analysis is, unsurprisingly, called *mean-variance* analysis and is a standard method for quantifying synapses.