1. Synaptic Depression

Consider the following model of synaptic transmission. Let \( I(t) = \sum_i \delta(t - t_i) \) be a presynaptic action potential train and assume that the presynaptic neuron make \( M \) synaptic contacts on a postsynaptic neuron. Let \( 0 \leq m(t) \leq M \) be the number of available vesicles at time \( t \) with \( 0 \leq w_i \leq m(t) \) being the total number of vesicles released by presynaptic spike \( i \). The total number of vesicles released at time \( t \) is \( N_x(t) = \sum_{t < t_j} w_j \) with

\[
x(t) = \frac{dN_x}{dt} = \sum_i w_i \delta(t - t_i).
\]

Let each vesicle release with a probability \( p_r \) and a vesicle recovers as a Poisson process with rate \( 1/\tau_u \). Take the release and recovery at each contact to be independent of release and recovery events at all other contacts. Under these assumptions we have

\[
dm(t) = -dN_x(t) + dN_u(t).
\]

Here \( N_u(t) \) is the recovery count and is an inhomogeneous Poisson process with rate conditioned on the number of currently depleted vesicles.

\[
\langle dN_u(t) | m(t) \rangle = \left( \frac{M - m(t)}{\tau_u} \right) dt.
\]

Here \( \langle \cdot \rangle \) denotes the expectation over vesicle release and uptake. Given a realization of vesicle release \( \{w_i\} \), the synaptic conductance is simply

\[
g(t) = \bar{g} \sum_i w_i \alpha^2 (t - t_i) e^{-\alpha(t-t_i)} \theta(t - t_i),
\]

with \( 1/\alpha \) being the synaptic timescale and \( \theta(\cdot) \) the standard Heaviside function.

(a) Synaptic physiologists often characterize synapses by recording many trials of postsynaptic response to a fixed presynaptic \( I(t) \) (i.e it is the same \( I(t) \) during each trial). Show that \( \langle m(t) \rangle \) obeys

\[
d\langle m \rangle = -dN_x(t) + \frac{M - \bar{m}}{\tau_u} dt,
\]

\[
dN_x = p_r \langle m \rangle dI(t).
\]
(b) Let \( I(t) = \sum_i \delta(t - iT) \) and use the result in the previous question to give an analytic expression for \( \langle g(t) \rangle \). Write a MATLAB code to simulate the full stochastic synapse model. Compare your analytic and the trial averaged simulation results with \( M = 5 \), \( p_r = 0.5 \), \( \tau_u = 500 \text{ ms} \), and \( 1/\alpha = 5 \text{ ms} \). Do this for ten pulses of \( I(t) \) with \( T = 10, 100, 1000 \text{ ms} \). For each case plot the numeric (in red) and analytic (in blue) \( \bar{g} \) on top of one another.

(c) Let \( I(t) = \sum_i \delta(t - t_i) \) with \( \{t_i\} \) coming from a Poisson process with rate intensity \( \lambda \). Let \( \langle \cdot \rangle \) now denote expectations over vesicle release, uptake, and presynaptic input realizations. Derive

\[
\frac{d\langle m \rangle}{dt} = \frac{M}{\tau_u} - \left( 1 + \frac{p_r \lambda \tau_u}{\tau_u} \right) \langle m \rangle, \\
\frac{d\langle N(x) \rangle}{dt} = p_r \lambda \langle m \rangle.
\]

Compare simulations of the stochastic synapse with the above trial averaged Poisson theory. Take synaptic parameters to be those in question 2 with \( 1/\lambda = 10, 100, 1000 \text{ ms} \). For each case plot the dynamics for \( 10\tau_u \).

(d) Consider the long time behavior of the synapse in part (c) and show that

\[
\langle g \rangle_\infty \equiv \lim_{t \to \infty} \langle g(t) \rangle = \frac{\bar{g} \lambda p_r M}{1 + p_r \tau_u \lambda}.
\]

Compare and discuss the gain \( \frac{d\langle g \rangle}{d\lambda} \) for probabilistic \( (p_r < 1) \) and the unrealistic case of perfect synaptic transmission \( (p_r = 1) \).

2. Synaptic balance and fluctuation driven activity

In this question you will explore how the variability of mixed excitatory and inhibitory synaptic inputs translates to the variability of the neural response.

(a) Consider a mixed excitatory-inhibitory synaptic drive where the excitatory and inhibitory synaptic current is given by \( I_E(t) = \bar{a}_E x_E(t) \) and \( I_I(t) = \bar{a}_I x_I(t) \). A reasonable model for the time course of a single synaptic input is a difference of exponential terms:

\[
x(t) = \left[ e^{-\frac{t-\hat{t}}{\tau_1}} - e^{-\frac{t-\hat{t}}{\tau_2}} \right] \theta(t - \hat{t}),
\]
where $\tau_1 > \tau_2$, $\theta(x)$ is a Heaviside function, and $t$ is the time of a presynaptic spike. Show that a convenient differential equation treatment for this two-timescale synaptic current is given by:

$$\frac{dx}{dt} = y,$$
$$\frac{dy}{dt} = -\frac{x}{\tau_1 \tau_2} - \left(\frac{1}{\tau_1} + \frac{1}{\tau_2}\right)y + \left(\frac{1}{\tau_2} - \frac{1}{\tau_1}\right)\sum_i \delta(t - t_i).$$

and initial conditions $x(0) = y(0) = 0$. Here $t_i$ is the time of the $i^{th}$ presynaptic spike.

(b) Let the sequences $\{t_iE\}_i$ and $\{t_iI\}_i$ be Poisson point process with distinct firing rates $\lambda_E$ and $\lambda_I$. Find the mathematical expression relating $a_E > 0$, $a_I < 0$, $\lambda_E > 0$, and $\lambda_I > 0$ such that the mean total current $\langle I(t) \rangle_t = \langle I_E(t) + I_I(t) \rangle_t = 0$, i.e is 'balanced'. Write a MATLAB code to simulate $I(t)$ with $a_E = 1 \mu A/cm^2$, $\lambda_E = \lambda_I = 500$ Hz, and $a_I$ such that $I$ is balanced. Let $\tau_{1E} = 4$ ms, $\tau_{2E} = 0.4$ ms, $\tau_{1I} = 6$ ms, and $\tau_{2I} = 1.75$ ms. Use your simulation to verify that $\langle I \rangle_t \approx 0$.

(c) Consider the exponential integrate and fire neuron model with current based synapses:

$$C \frac{dV}{dt} = -g_L(V - V_L) + \phi(V) + I_E(t) + I_I(t),$$
$$I_E(t) = a_E x_E(t),$$
$$I_I(t) = a_I x_I(t),$$

where $\phi(V) = g_L \Delta \exp \left(\frac{V - V_T}{\Delta}\right)$. Supplement the model dynamics with the spike-reset rule $V(t) = V_{\text{peak}}$ implies $V(t^+) = V_{\text{reset}}$. Let $C = 1 \mu F/cm^2$, $g_L = 0.1$ mS/cm$^2$, $V_L = -65$ mV, $V_T = -60$ mV, $V_{\text{reset}} = -70$ mV, $V_{\text{peak}} = -45$ mV and $\Delta = 2$ mV. Let $x_E(t)$ and $x_I(t)$ be synaptically filtered inputs as in part (b) with $a_E = 0.2 \mu A/cm^2$, $\lambda_E = 500$ Hz, and set inhibition to zero. Write a MATLAB code to simulate the above system and plot a 1s realization of $V(t)$ and $I(t)$. Run 1000 1s realizations and report the Fano factor $FF = \frac{\text{Var}}{\text{M}^2}$, where

\footnote{For a stochastic process we denote the mean as $\langle x(t) \rangle_t = \lim_{T \to \infty} \frac{1}{T} \int_0^T x(t)dt$}
\footnote{Hint: For a Poisson process we have $\langle y(t) \rangle_t = \lambda$. For a filtered Poisson process, say through a synapse, $\langle x(t) \rangle_t = \lambda \int_0^\infty x_1(t)dt$ where $x_1(t)$ is the synaptic response to a single input at time 0 (this is called Campbell’s theorem).}
\footnote{see Fourcaud-Trocmé N, Hansel D, van Vreeswijk C, Brunel N. How spike generation mechanisms determine the neuronal response to fluctuating inputs. J Neurosci. 2003, 23: 11628-40.}
\[ M = \frac{1}{1000} \sum_i n_i \text{ and } Var = \frac{1}{1000} \sum_i (n_i - M)^2, \text{ with } n_i \text{ being the spike count in realization } i. \]

(d) The firing rate for the inhibition free post-synaptic cell in c) should be about 13 Hz. Set \( \lambda_E = \lambda_I = 500 \text{ Hz} \) and use the balance relation calculated in b) to determine \( a_I \). This gives an effective line in \((a_E, a_I)\) space. Explore this line to determine the point where the output firing rate from the postsynaptic cell is approximately 13 Hz. For these values of \( a_E \) and \( a_I \) compare a 1s realization of \( V(t) \) and \( I(t) \) to that in c). Compute the Fano factor and compare it to that in c).