ASSIGNMENT #2

ECBM E4070, Professor Aurel A. Lazar

Deadline: 11:59AM Noon, Monday, February 24, 2020

In this assignment you will be experimenting with the Input/Output (I/O) characteristics of the OTP-BSG cascade shown in Figure. 1. Particularly, you will first explore the I/O of the two individual components and then connect them.

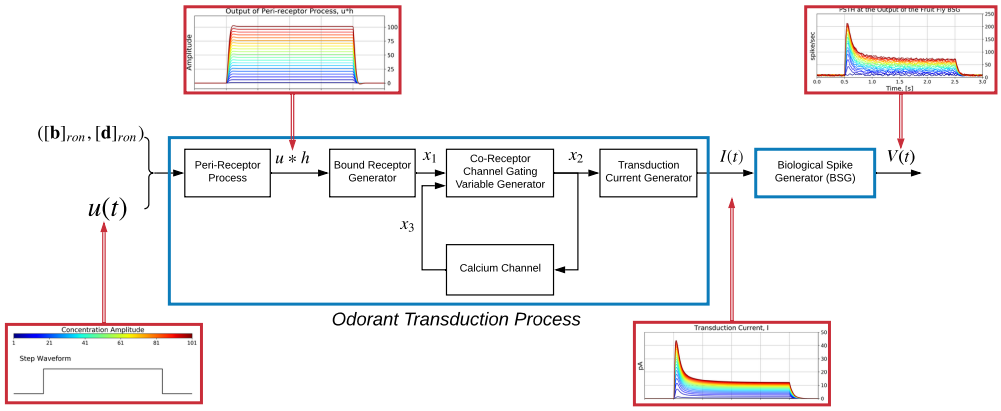

Figure 1: OTP-BSG Cascade with step input. Figure insets show example traces for a few variables of interest. Note that the BSG's (point neuron's) output is labeled by its membrane voltage $V(t)$ while the corresponding trace (above) shows the PSTH of the neuron, a measure of the frequency at which the neuron is firing. See below for details.

Task #1: (OTP) You are given an implementation of the OTP model and are asked to explore its input/output behavior. For your reference, the equations for the OTP model are given below.

$$[\mathbf{v}]_{ron} = Re\left(\int_{\mathbb{R}} h(t-s)u(s)ds + [\gamma]_{ron}\int_{\mathbb{R}} h(t-s)du(s)\right)$$

$$\begin{bmatrix}\dot{\mathbf{x}}_1\\ \dot{\mathbf{x}}_2\\ \dot{\mathbf{x}}_3\end{bmatrix}_{ron} = \begin{bmatrix}[\mathbf{b}]_{ron}\cdot[\mathbf{v}]_{ron}\cdot(1-[\mathbf{x}_1]_{ron}) - [\mathbf{d}]_{ron}\cdot[\mathbf{x}_1]_{ron}\\ \alpha_2\cdot[\mathbf{x}_1]_{ron}(1-[\mathbf{x}_2]_{ron}) - \beta_2\cdot[\mathbf{x}_2]_{ron} - \kappa\cdot[\mathbf{x}_2]_{ron}^{2/3}\cdot[\mathbf{x}_3]_{ron}^{2/3}\\ \alpha_3\cdot[\mathbf{x}_2]_{ron} - \beta_3\cdot[\mathbf{x}_3]_{ron}\end{bmatrix}$$

$$[\mathbf{I}]_{ron} = \frac{[\mathbf{x}_2]_{ron}^p}{[\mathbf{x}_2]_{ron}^p + c^p}\cdot I_{max}$$

Please complete the following:

- Setting binding and dissociation rates to $b = 1, d = 132$, replicate part of Figure. 4 shown in the red box. Particularly, simulate the OTP model with a parabola input waveform $u = u_p$ as described by equations in Eqn. 2 with concentration levels $c = [1, 20, 40, 60, 80, 100]$ ppm. Generate result as in the boxed region in Fig. 4, showing $(u, u * h, v, x_1, x_2, x_3, I)$ which includes the input waveform u at various concentration amplitude levels.
- Repeat the step above for 5 different pairs of values (b, d) under step input u_s, comment on the results.

Task #2: (BSG) For this exercise, you will implement a point neuron model for BSG.

Please complete the following:

- You are given an implementation of the Hodgkin-Huxley(HH) Neuron model (`e4070_library.py`) and are asked to implement the Connor-Stevens (CS) model in `Python` (see the Appendix for the set of CS equations).
- Demonstrate that, for a constant input current $I(t) = c$ with appropriately chosen amplitude c, the Connor-Stevens model exhibit periodic spiking. Plot the time-series of the output voltage as well as the spike-timing sequence as in Fig. 2. To compute the spike-timing, calculate the time when the membrane voltage waveform $V(t)$ reaches its peaks.
- You'll next compute the Frequency-Current Curve (F-I curve) of the Connor-Stevens neuron. This will give you an estimate of how fast will the neuron be spiking given an input current. Particularly, for a range of constant current input amplitude values, calculate the number of spikes produced over 1 second in time, which will give you the firing frequency. Plot the Frequency-Current current as shown in Figure. 3. Note that you only need to implemented the noise-less Connor-Stevens and therefore you only need to show the blue-est line in Figure. 3.

Task #3: (OTP-BSG) Finally, let's put the two together. This part should be easy!

- Replicate Figure. 5 by doing the following:
  1. Set affinity value b/d to a given value, you can fix $b = 1$ and change d or vice versa.
  2. Set the input concentration waveform $u(t) = c$ to be a constant waveform, and simulate the OTP model for sufficiently long time such that it reaches the steady-state (output current does not change anymore). Record final current $I(t)$.
  3. Use $I(t)$ and the F-I curve of the Connor-Stevens neuron to estimate the steady-state BSG spike rate.

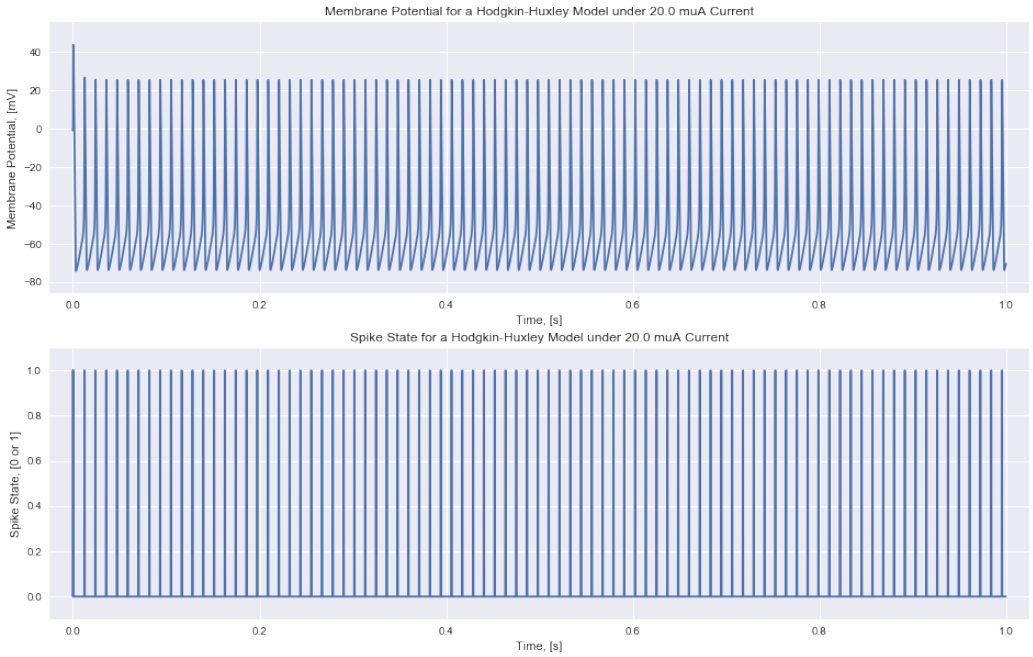

Figure 2: (*Top*) Examples of Time Series traces that you are asked to show for the Hodgkin-Huxley neuron model. (*Bottom*) From the time series result shown above, you can find the time at which the neuron spikes (timing for the peak of each spike).

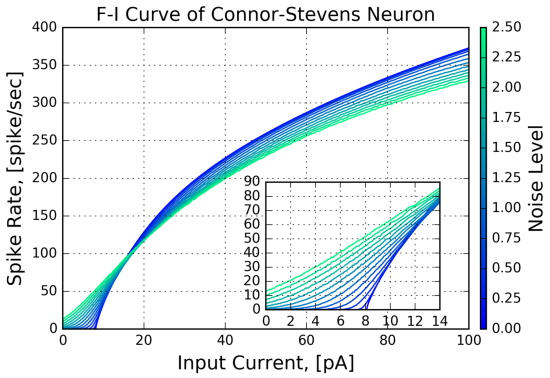

Figure 3: Frequency-Current curve of the Connor-Stevens neuron model. Note that you are only asked to implement the noise-less version of the model, therefore you only need to show the blue-est line!

4. Repeat 2-3 for a set of concentration values $u(t) \in [10^{-3}, 10^{3}]$ppm, record all resulting spike rates which will give you data for a single line in Fig. 5.
5. Change affinity values to be the same as shown in the inset in Figure.5 and repeat the steps above.

Submission Instructions: Your submission must include

1. A `pdf` file clearly documenting your code, figures, and results.

Name your write-up `assignment2_YOURUNI.pdf` (replace YOURUNI with your UNI) and submit the file to the **Assignments** section of ECBM E4070 on Courseworks.

Please post any questions regarding this assignment on the **Piazza discussion forum**. Your questions and the answers may also benefit the other students in class. If you have any other questions, please do not hesitate to contact the CAs using their emails in the course website.

GOOD LUCK!

A Appendix

A.1 Notes on Numerical Simulation

Simulating neural circuits (with biophysical models of neurons and synapses like the OTP model) is equivalent to solving Initial Value Problems (IVPs) for systems of nonlinear 1st order Ordinary Differential Equations (ODEs). These ODEs can be solved using a variety of solvers (see `scipy.integrate.solve_ivp` for example), and solvers generally trade computational complexity for error. The way ODEs are solved inside the reference file `e4070_library.py` use Forward Euler Method, the simplest kind of ODE solver which we implement directly. In another word, for systems like $\frac{dx}{dt} = f(x)$, we solve it numerically like:

$$x_{n+1} \leftarrow x_n + \Delta_t f(x_n), \quad x_1 \leftarrow x_0 + \Delta_t f(x_0) \tag{1}$$

where x_0 is the initial condition, and Δ_t is the step-size at which we are integrating the ODE. Euler's Method is simple but tends to have a large error at every step, which needs to be mitigated by a smaller time-step, which we recommend setting to a value less than 10^{-5} sec.

A.2 Models

A.2.1 Hodgkin-Huxley Model (Given)

$$\begin{aligned}
C\frac{dV}{dt} &= -\overline{g}_{Na}m^3h(V - E_{Na}) - \overline{g}_K n^4(V - E_K) - \overline{g}_L(V - E_L) + I(t) \\
\frac{dn}{dt} &= \alpha_n(V)(1 - n) - \beta_n(V)n \\
\frac{dm}{dt} &= \alpha_m(V)(1 - m) - \beta_m(V)m \\
\frac{dh}{dt} &= \alpha_h(V)(1 - h) - \beta_n(V)h
\end{aligned}$$

where the external input current $I(t) = b + I^{net}_{syn}(t)$ for this problem, where b is the bias and $I^{net}_{syn}(t)$ is the sum of incoming synaptic currents. Furthermore,

$$\alpha_n(V) = \frac{0.01(V + 55)}{1 - e^{-\frac{V+55}{10}}} \qquad \alpha_m(V) = \frac{0.1(V + 40)}{1 - e^{-\frac{V+40}{10}}} \qquad \alpha_h(V) = 0.07e^{-\frac{V+65}{20}}$$

$$\beta_n(V) = 0.125e^{-\frac{V+65}{80}} \qquad \beta_m(V) = 4e^{-\frac{V+65}{18}} \qquad \beta_h(V) = \frac{1}{1 + e^{-\frac{V+35}{10}}},$$

where V is the membrane potential and n, m, h are the gating variables. Here $C = 1\mu F/cm^2$ and

$$\overline{g}_{Na} = 120 \text{ (mS/cm}^2), \overline{g}_K = 36 \text{ (mS/cm}^2), \overline{g}_L = 0.3 \text{ (mS/cm}^2),$$

$$E_{Na} = 50(\text{mV}), E_K = -77(\text{mV}), E_L = -54.387(\text{mV}).$$

For this assignment, you can assume that at $t = 0$ (start of the simulation) we have $n(0) = 0$, $m(0) = 0$ and $h(0) = 1$.

A.2.2 Connor-Stevens Model (To Be Implemented)

The Connor-Stevens model is an extension of the Hodgkin-Huxley model with an additional term, A, for modeling K^+:

$$C\frac{dV}{dt} = -\bar{g}_A a^3 b(V-E_A) - \bar{g}_{Na} m^3 h(V-E_{Na}) - \bar{g}_K n^4 (V-E_K) - \bar{g}_L (V-E_L) + I(t)$$

$$\begin{aligned}
\frac{da}{dt} &= \frac{\alpha_\infty(V) - a}{\tau_a(V)} \\
\frac{db}{dt} &= \frac{b_\infty(V) - b}{\tau_b(V)} \\
\frac{dm}{dt} &= \frac{m_\infty(V) - m}{\tau_m(V)} \\
\frac{dn}{dt} &= \frac{n_\infty(V) - n}{\tau_n(V)} \\
\frac{dh}{dt} &= \frac{h_\infty(V) - h}{\tau_h(V)}.
\end{aligned}$$

Furthermore,

$$\begin{aligned}
\alpha_m(V) &= \frac{0.1(V+35+m_s)}{1-e^{-\frac{V+35+m_s}{10}}} & \alpha_n(V) &= \frac{0.01(V+50+n_s)}{1-e^{-0.1(V+50+n_s)}} & \alpha_h(V) &= 0.07e^{-0.05(V+60+h_s)} \\
\beta_m(V) &= 4e^{-(V+60+m_s)/18} & \beta_n(V) &= 0.125e^{-(V+60+ns)/80} & \beta_h(V) &= \frac{1}{1+e^{-\frac{V+30+h_s}{10}}},
\end{aligned}$$

$$\begin{aligned}
\alpha_m(V) &= \frac{0.1(V+35+m_s)}{1-e^{-\frac{V+35+m_s}{10}}} & \alpha_n(V) &= \frac{0.01(V+50+n_s)}{1-e^{-0.1(V+50+n_s)}} & \alpha_h(V) &= 0.07e^{-0.05(V+60+h_s)} \\
\beta_m(V) &= 4e^{-(V+60+m_s)/18} & \beta_n(V) &= 0.125e^{-(V+60+ns)/80} & \beta_h(V) &= \frac{1}{1+e^{-\frac{V+30+h_s}{10}}} \\
m_\infty &= \frac{\alpha_m}{\alpha_m+\beta_m} & n_\infty &= \frac{\alpha_n}{\alpha_n+\beta_n} & h_\infty &= \frac{\alpha_h}{\alpha_h+\beta_h} \\
\tau_m &= \frac{1}{3.8(\alpha_m+\beta_m)} & \tau_n &= \frac{2}{3.8(\alpha_n+\beta_n)} & \tau_h &= \frac{1}{3.8(\alpha_h+\beta_h)}
\end{aligned}$$

$$\begin{aligned}
a_\infty(V) &= \left[\frac{0.0761e^{(V+94.22)/31.84}}{1+e^{(V+1.17)/28.93}}\right]^{1/3} & b_\infty(V) &= \left[\frac{1}{1+e^{(V+53.3)/14.54}}\right]^4 \\
\tau_a(V) &= 0.3632 + 1.158/(1+e^{(V+55.96)/20.12}) & \tau_b(V) &= 1.24 + 2.678/(1+e^{(V+50)/16.027})
\end{aligned}$$

and parameters

$$\overline{g}_{Na} = 120\ (\mathrm{mS/cm^2}), \overline{g}_K = 20\ (\mathrm{mS/cm^2}), \overline{g}_L = 0.3\ (\mathrm{mS/cm^2}), \overline{g}_A = 47.7\ (\mathrm{mS/cm^2}),$$

$$E_{Na} = 55(\mathrm{mV}), E_K = -72(\mathrm{mV}), E_L = -17(\mathrm{mV}), E_A = -75(\mathrm{mV}),$$

$$m_s = -5.3(\mathrm{mV}), n_s = -4.3(\mathrm{mV}), h_s = -12(\mathrm{mV}).$$

Variable	Value	Description
α_1	$1.570 \cdot 10^1$	cutoff frequency of the filter modeling the peri-receptor process
β_1	$8.000 \cdot 10^{-1}$	slope of the transition region of the peri-receptor process filte
γ	$1.750 \cdot 10^{-1}$	scaling factor of the filtered odorant concentration gradient rate
α_2	$8.877 \cdot 10^1$	rate of activation of the gating variable of the co-receptor channel
β_2	$9.789 \cdot 10^1$	rate of deactivation of the gating variable of the co-receptor channel
α_3	$2.100 \cdot 10^0$	rate of increase of the state variable of the calcium channel
β_3	$1.200 \cdot 10^0$	rate of decrease of the state variable of the calcium channel
κ	$7.089 \cdot 10^3$	feedback strength from the calcium channel to the co-receptor channel
c	$7.534 \cdot 10^{-2}$	value achieving the half-activation of the co-receptor channel
p	1	the Hill coefficient of the co-receptor channel
I_{max}	$7.774 \cdot 10^1$	maximum current amplitude generated by the co-receptor channel Methods

Table 1: OTP Parameter Values.

A.3 OTP Parameters and Inputs

$$
\begin{aligned}
u_s(t) &= \begin{cases} c, & 0.5 \leq t \leq 2.5 \\ 0, & otherwise \end{cases} \\
u_r(t) &= \begin{cases} c\frac{1}{1.8}\left(t - 0.5\right), & 0.5 \leq t < 2.3 \\ c\left(1 - 5\left(t - 2.3\right)\right), & 2.3 \leq t \leq 2.5 \\ 0, & otherwise \end{cases} \\
u_p(t) &= \begin{cases} c\left(\frac{1}{1.9}\left(t - 0.5\right)\right)^2, & 0.5 \leq t < 2.4 \\ c\left(1 - 10\left(t - 2.4\right)\right)^2, & 2.4 \leq t \leq 2.5 \\ 0, & otherwise \end{cases}
\end{aligned}
\tag{2}
$$

A.4 Reference Figures

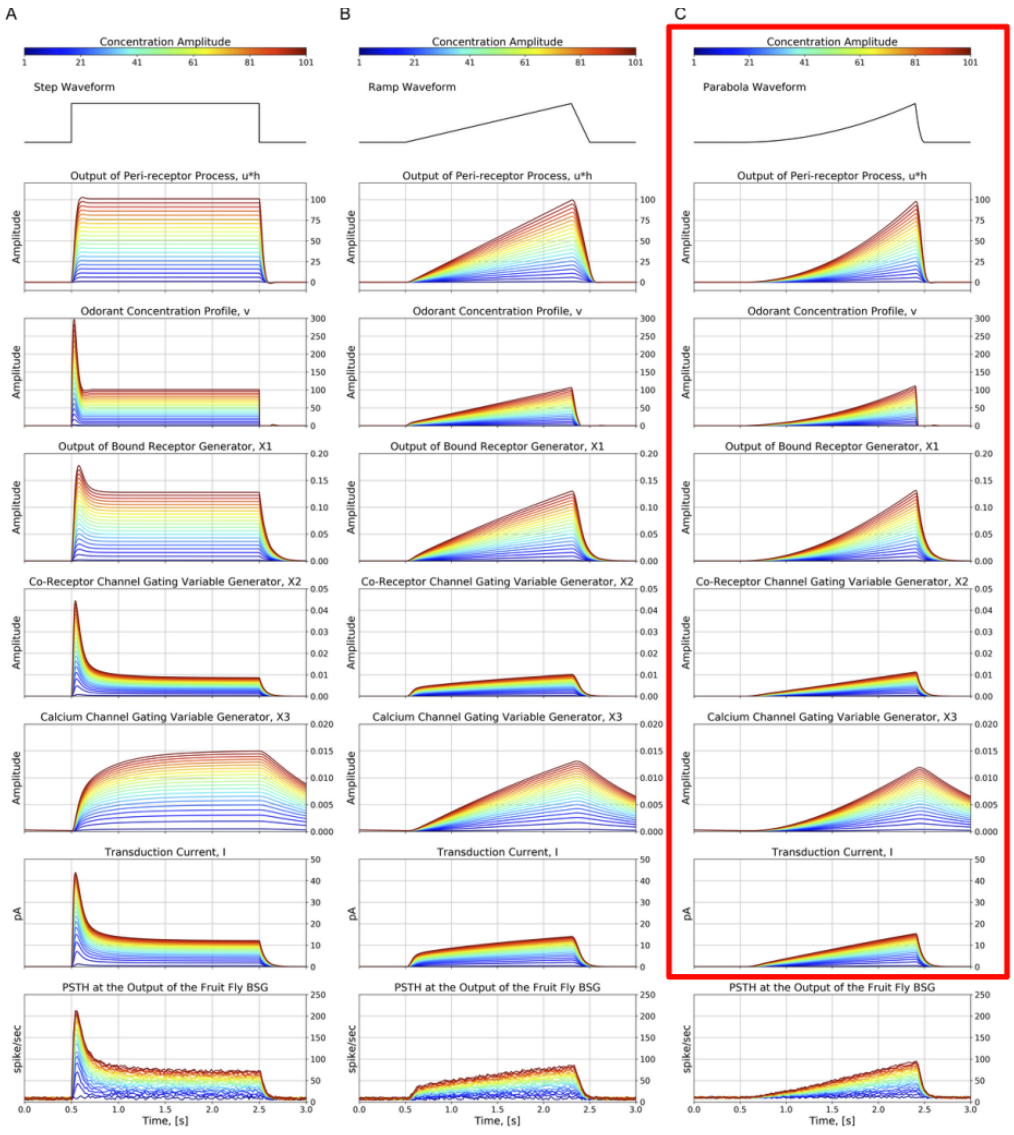

Figure 4: Example figure showing input and output relations of the OTP-BSG cascade. For **Task #1**, you are asked to generate the top 7 rows $(u, u * h, v, x_1, x_2, x_3, I)$ which includes the input waveform (u) for parabola input. Note that the differently colored lines correspond to the waveform at different amplitudes, see **Task#1** for details.

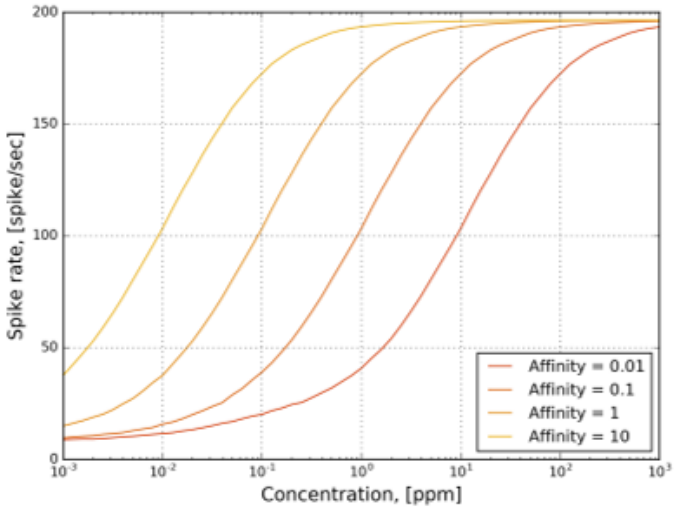

Figure 5: Example steady-state response of OTP-BSG cascade for different affinity values across concentration level. You are asked to generate this figure in **Task #3**.