9.16 Problem Set #2

In this assignment you will build a simulation of the presynaptic terminal.

The simulation can be broken down into three parts: simulation of the arriving action potential (based on the Hodgkin-Huxley equations from the last assignment); simulation of the calcium current influx; and, finally, simulation of the vesicle release dynamics.

Part 1 – Simulation of the Action Potential

For simplicity, you may assume that the calcium current does not change the shape of the action potential dramatically; hence, you can use the action potential waveform from the previous assignment as the starting point. Look for the solution to the previous assignment posted on the web.

You will need to take the voltage output from this simulation and feed it as an input to the next part of the assignment. For all subsequent simulations assume a constant current of 20 nA injected for 100 ms. Plot the resulting action potentials here.

Part 2 – Simulation of the Calcium Current Influx

Since the Ca^{2+} concentration inside the cell varies, you will need to use the Goldmann-Hodgkin-Katz (GHK) equation to calculate the Ca^{2+} current:

$$I_{Ca} = P_{Ca} V \left(\frac{e^{\varepsilon V} [Ca]_{in} - [Ca]_{out}}{e^{\varepsilon V} - 1} \right) \qquad \varepsilon = 0.07788 \text{ mV}^{-1}$$

To model the Ca^{2+} channel kinetics, you may adopt a simplified model (from Borst and Sakmann, *J. Phys.*, 1998), which consolidates the effects of different calcium channels present in the terminal into a single activation parameter (c):

$$\alpha_c = 1.78 e^{V/23.3}$$
$$\beta_c = 0.14 e^{-V/15}$$
$$\frac{d}{dt} c = \alpha_c (1-c) - \beta_c c$$
$$P_{Ca} = P_{max} c^2 \qquad\qquad P_{max} = 8.2650 \cdot 10^{-5}$$

Simultaneously, you will need to solve for $[Ca]_{in}$, which changes due to the influx of Ca^{2+} ions into the terminal through the Ca^{2+} current. The synaptic terminal can be modeled as a single compartment with a calcium buffer (B) and diffusion of free Ca^{2+} away from the release site (diffusion of the calcium buffer is a relatively slow process and can therefore be omitted from the model). The dynamics of the Ca^{2+} buffering and diffusion can be summarized in the following kinetic scheme:
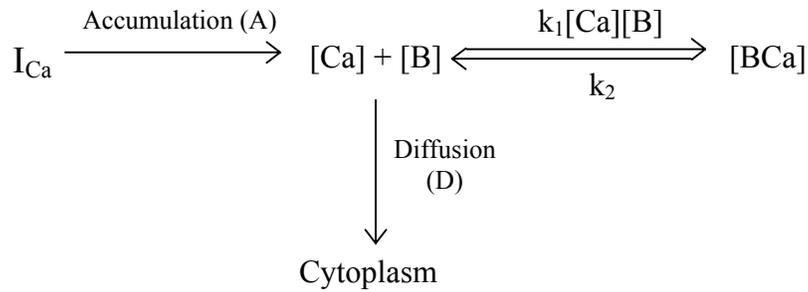
This corresponds to the following equations:

$$[B] = [B_{Tot}] - [BCa]$$

$$\frac{d}{dt}[Ca] = I_{Ca} A + k_2 [BCa] - k_1 [Ca][B] - D[Ca]$$

$$\frac{d}{dt}[BCa] = k_1 [Ca][B] - k_2 [BCa]$$

The relevant constants are:

$[Ca]_{out} = 2000$ μM; $[B_{Tot}] = 500$ μM; $k_1 = 0.01$ ms^{-1}; $k_2 = 0.1$ ms^{-1}; $A = 100$; $D = 1$

a)   Run the simulation and plot the calcium current influx in the same graph with the action potentials. Observe that the peak calcium influx coincides with the repolarizing phase of the action potential. Why?
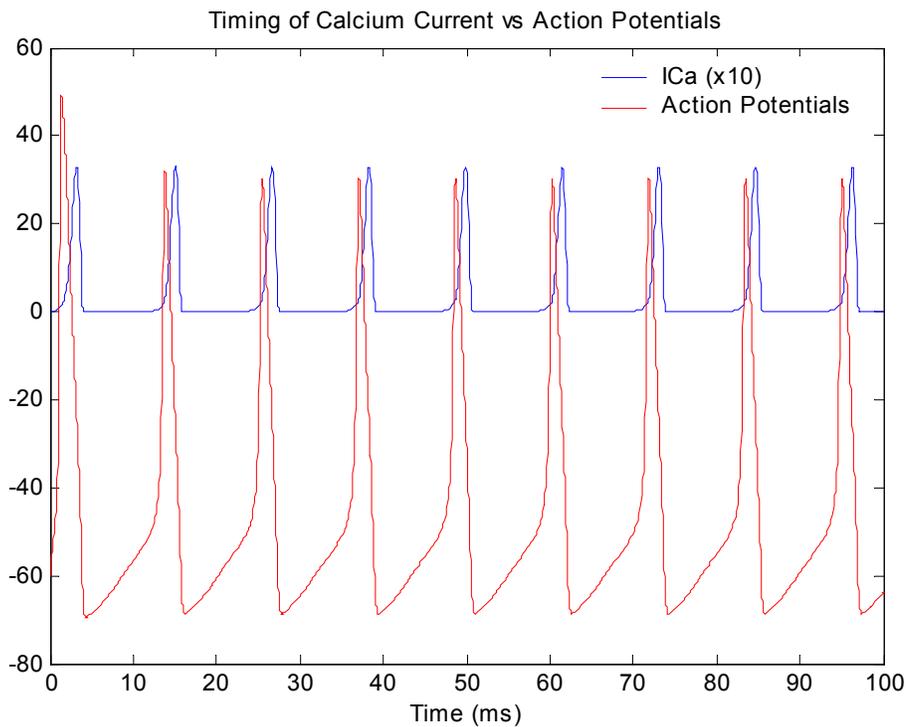
Start the simulation with the following initial conditions:
c = 0.017; $[Ca]_{in}$ = 0.24; [BCa] = 0

b)   Plot the free $[Ca]_{in}$ in the same graph with the buffered calcium [BCa]. Note that as the buffer saturates, the concentration of free Ca^{2+} increases. Accumulation of free Ca^{2+} in the presynaptic terminal results in the enhancement of vesicle fusion, and causes a form of short-term synaptic plasticity called *paired-pulse facilitation*. (This will be explored further in Part 3).
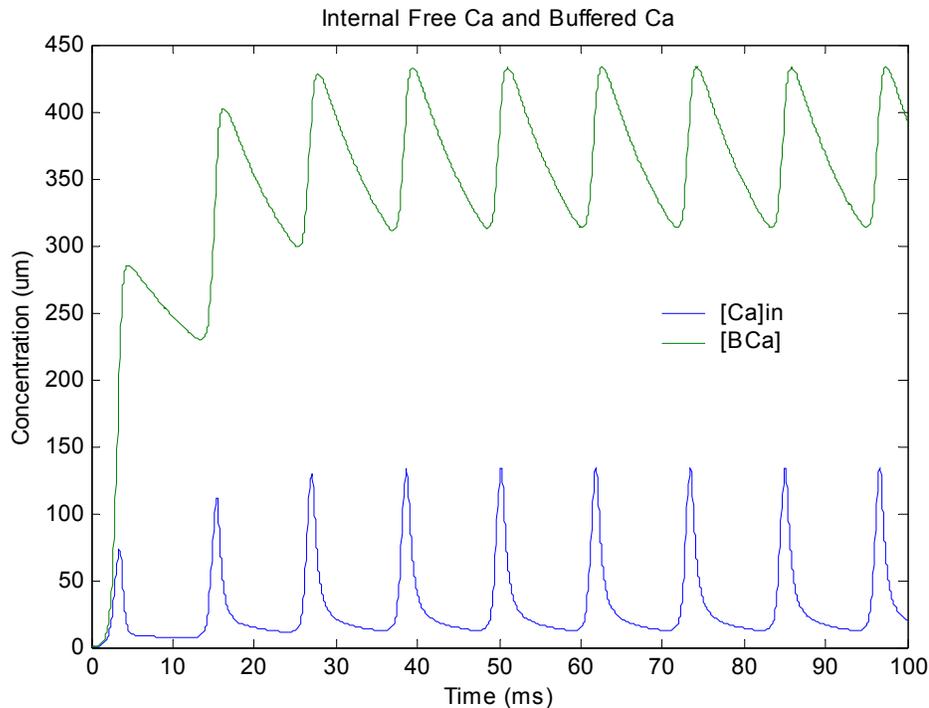
c)   Explore the effects of buffer concentration $[B_{Tot}]$ on the extent of paired-pulse facilitation.
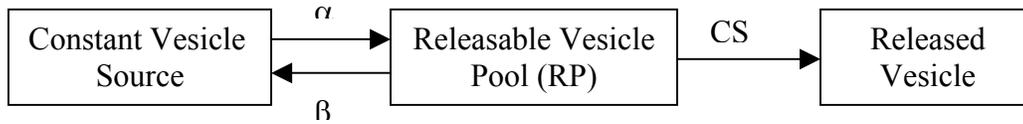
Part 3- Simulation of the Vesicle Release

In this part of the assignment, you will take the internal calcium concentration computed in Part 2, and use it to drive the vesicle release machinery.

First, you will have to simulate the binding of Ca^{++} to a Ca^{++} sensor (CS) located on the docked vesicles. For simplicity, you may assume that binding to the sensor is instantaneous, in which case the fraction of sensors binding 4 Ca^{++} molecules (remember that vesicle release obeys a 4th order Ca^{++} dependency) is given by the dose response relationship:

$$CS = \left(\frac{[Ca]}{[Ca] + K_D} \right)^4 \qquad K_D = 100 \ \mu M$$

To model the vesicle population dynamics, you may assume a constant source of vesicles inside the cell, a rate constant α of vesicle docking, and a rate constant β of vesicle undocking. The rate of fusion of docked vesicles depends on CS. The setup for the problem is the following:

$$\boxed{\begin{array}{c}\text{Constant Vesicle}\\\text{Source}\end{array}}\xrightarrow{\alpha}\xleftarrow{\beta}\boxed{\begin{array}{c}\text{Releasable Vesicle}\\\text{Pool (RP)}\end{array}}\xrightarrow{CS}\boxed{\begin{array}{c}\text{Released}\\\text{Vesicle}\end{array}}$$

The corresponding model equation is:

$$\frac{d}{dt}RP = -\beta \cdot RP + \alpha - RP \cdot CS$$

Fusion Rate $= RP \cdot CS$

$\tau = 50;$ (vesicle relaxation time constant)
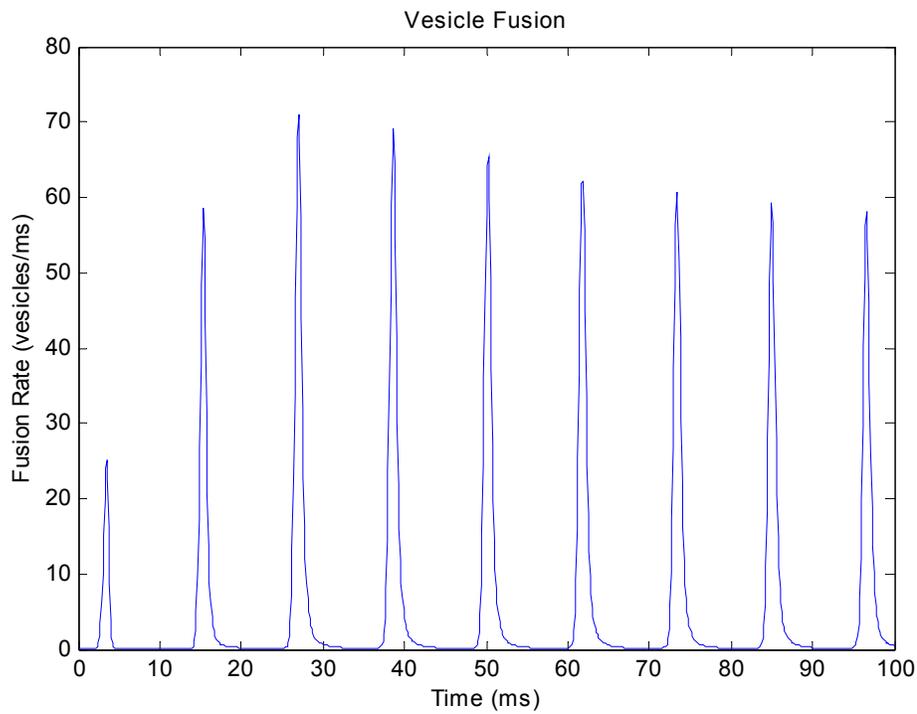$m = 800;$ (mean number of vesicles in the readily releasable pool)
$\beta = 1/\tau;$ $\alpha = m/\tau;$

    a)   Run the simulation with the initial condition $RP_0 = 800$, and plot the size of the readily releasable vesicle pool as a function of time. Observe that the vesicle pool depletes fast. Explore the effects of the vesicle relaxation time constant on the extent of vesicle pool depletion.

Vesicle Pool Depletion
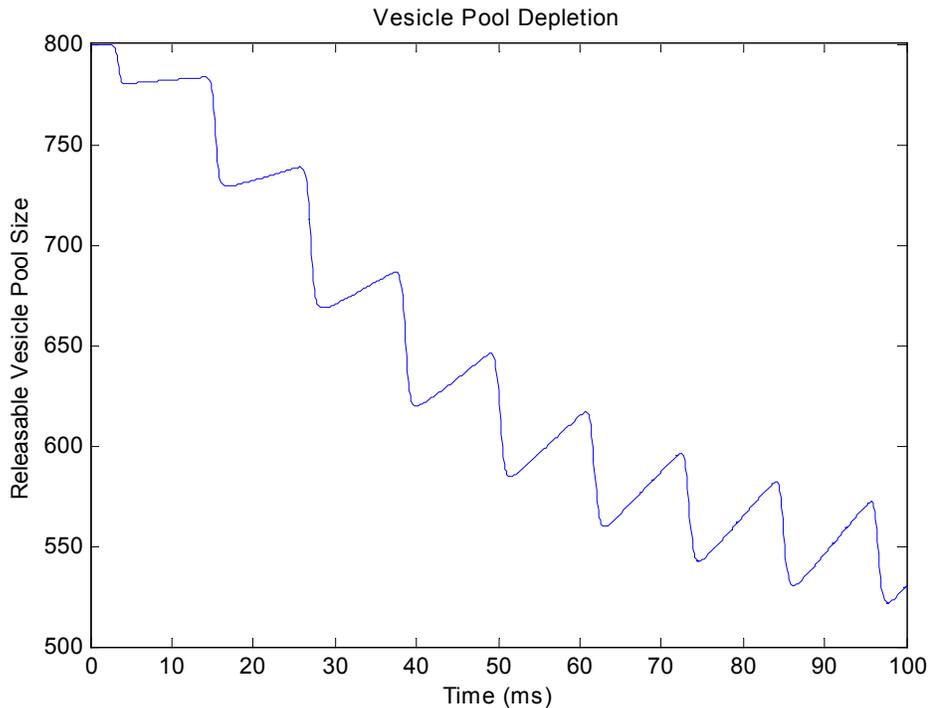
b)   Finally, combine the effects of internal calcium concentration and the vesicle pool size on the rate of vesicle release. Plot the vesicle fusion rate as a function of time.

Vesicle Fusion

Comment on what you see.