9.16 Problem Set #4

In the final problem set you will combine the pieces of knowledge gained in the previous assignments to build a full-blown model of a plastic synapse. You will investigate the effects of presynaptic stimulation at different frequencies on synaptic potentiation and depression.

Part 1 – Presynaptic Spiking

First, to make the presynaptic neuron fire at an arbitrary frequency, you need to inject a series of square current pulses, instead of just changing the amplitude of a long depolarizing current, as done previously. This is because with one depolarizing pulse, you cannot evoke repetitive firing at an arbitrarily low frequency (Why? Try it and comment.)

To set this up you can use the following Matlab script:

```
t = 0:TMax;
I = 40*(mod(t, 50) == 0);
```

This script will produce a series of pulses of amplitude 40 nA, duration 1ms, recurring every 50 ms.

Feed this through the presynaptic model you built in Assignment #2. In Part 3, change the mean number of vesicles in the readily releasable pool (m) to 10, as central synapses generally have small number of vesicles (you need to change the initial condition to $RP_0 = 10$).

Plot the vesicle fusion rate for trains of action potentials at 20 Hz and 100 Hz. (Fig. 1)

Part 2 - Glutamate Concentration Profile

Next, you need to calculate the concentration profile of glutamate evoked by the action potential trains at the postsynaptic receptors. Each vesicle release generates glutamate profile given by the equation

$$A(t) = A_{MAX}\left(3.2\exp^{-t/0.1} + 0.5\exp^{-t/2.1}\right) * \left(1 - \exp^{-t/0.2}\right), \qquad (1)$$

with $A_{MAX} = 300$. To do the calculation right, you would need to simulate the fusion of individual vesicles, which is a stochastic process governed by the fusion rate FR. For simplicity, it will suffice to simulate the average behavior. To obtain the average glutamate profile, you need to convolve the concentration profile due to the release of a single vesicle (Eq. 1) with the average fusion rate (FR).

In Matlab this can be done with the command `conv`:

```
Glut = conv(FR, A);
TGlut = 0:dt:(length(FR)+length(A)-2)*dt;  % time vector
plot(Tglut, Glut);
```

(you have to make sure that FR and A are sampled at the same resolution, to ensure this, keep `dt` constant in all simulations. To see how to control sampling, look at the solutions to the previous assignments posted on the web).

Plot the concentration of glutamate for the trains of action potentials at 20 Hz and 100 Hz. (Fig. 2)

Part 3 – Receptor Activation

Feed the glutamate concentration calculated in the previous section into the model for AMPA and NMDA receptors given in Assignment #3. (Fig. 3)

Part 4 – Postsynaptic Activation

Now use the HH equations to simulate the postsynaptic membrane potential. To do this rigorously, you would have to simulate the effects of both AMPA and NMDA currents on the membrane potential, while at the same time calculating the effects of the membrane potential on the NMDA current by modulating the Mg^{++} block, and the effects on both type of currents through the change in the driving force. To avoid this complication, you can assume that the NMDA current does not significantly contribute to the membrane potential (this is true for most time, since except during an action potential, NMDA receptor is largely blocked), and a constant driving force for AMPA receptors. That way, you can use the HH equations in the form from Assignment #1 without modification.

To calculate the AMPA current, use the following equation:

$$I_{AMPA} = E_{AMPA} * g_{AMPA} * N_{AMPA} * A_2 R^*_{AMPA}$$

where E_{AMPA} is the driving force, g_{AMPA} is the single channel conductance and N_{AMPA} is the number of AMPA receptors. For simplicity, take $g_{Ampa} * E_{Ampa} = 1$, $N_{AMPA} = 50$. (Fig. 4)

Part 5 –Internal calcium

Now you are in the position to calculate the Ca^{2+} flux through the NMDA receptors, and the resulting change in the postsynaptic $[Ca^{2+}]$ concentration.

To model the Ca^{2+} current through the NMDA receptor, you can use the equation:

$$I_{Ca} = -A_2 R^*_{NMDA} * (V - E_{Ca}) * g_{Mg}$$

$$g_{Mg} = \frac{e^{(V+30)/10}}{e^{(V+30)/10} + 1}$$

$E_{Ca} = 60$ mV,

where g_{Mg} is the voltage-dependent conductance modulated by the Mg^{2+} block, and V is the membrane potential calculated in Part 4. Plot I_{Ca}. (Fig. 5)

Explain the qualitative differences between I_{Ca} and NMDA activation. Why is Ca flux correlated better with AMPA activation rather than NMDA activation? Why are there two spikes on the I_{Ca} trace for each postsynaptic spike?

To calculate the change in the postsynaptic [Ca], you can use a simple integrator model with a diffusion constant D (this captures both the diffusion through the cytoplasm, and the effects of buffers). The corresponding equation is

$$\frac{d}{dt}[Ca] = I_{Ca} - D * [Ca]$$

The solution can be computed directly (without simulating) by convolving the impulse response function e^{-Dt} of the system with the input I_{Ca}. Plot [Ca]. (Fig. 6)

Part 6 – Ca Mediated Plasticity

Now, into the final stage. The simplest model of Ca^{2+} modulated synaptic plasticity is the one in which high concentration of Ca^{2+} triggers receptor insertion and potentiation, while low concentration of Ca^{2+} triggers receptor internalization and depression.

This mechanism can be modeled by a differential equation

$$\frac{d}{dt} N_{AMPA} = \frac{1}{\tau}([Ca] - [Ca]_\theta) * (1 - e^{-[Ca]/[Ca]_\theta}) * \frac{(N_{MAX} - N_{AMPA})}{N_{MAX}} * \frac{N_{AMPA}}{N_{MAX}},$$

where N_{AMPA} is the number of AMPA receptors in the synapse, and $[Ca]_\theta$ is the critical [Ca] concentration above and below which the synapse gets potentiated or depressed respectively. Note that this equation guarantees that 0 [Ca] has no effect on N_{AMPA}, and that N_{AMPA} stays bounded between 0 and N_{MAX}.

Simulate N_{AMPA} with the initial value 50, $N_{MAX} = 100$, $[Ca]_\theta = 50$, $\tau = 10$, and two different presynaptic action potential trains, one at 20 Hz, the other at 100 Hz.

What happens to N_{AMPA} in the two cases?

Experiment with different frequencies of presynaptic potentials. At what frequency is the change in the synaptic strength minimal? (there is one obvious solution to this question, what is the other one?)

Part 7 – Congratulation

You have just completed a model of two coupled neurons and reproduced frequency dependent synaptic plasticity *in silico*.

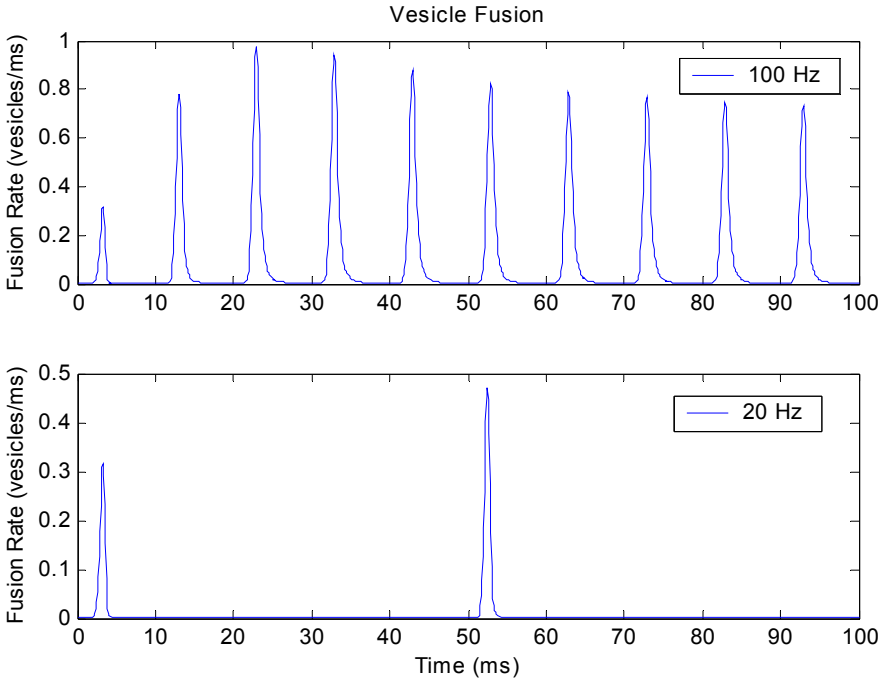
Vesicle Fusion
Fusion Rate (vesicles/ms)
100 Hz
Fusion Rate (vesicles/ms)
20 Hz
Time (ms)

Fig. 1

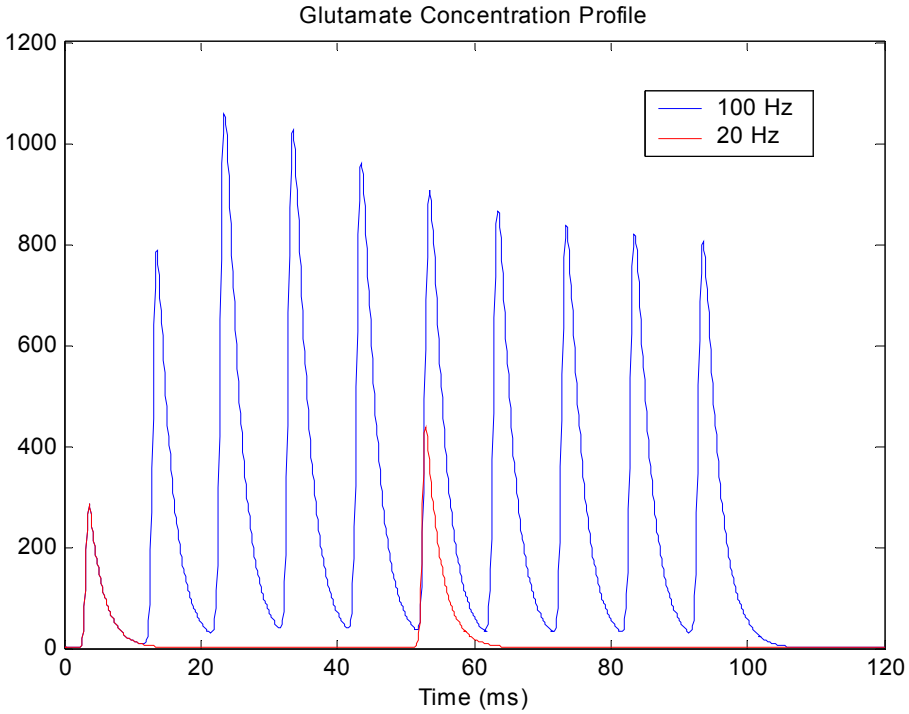
Glutamate Concentration Profile
100 Hz
20 Hz
Time (ms)

Fig. 2

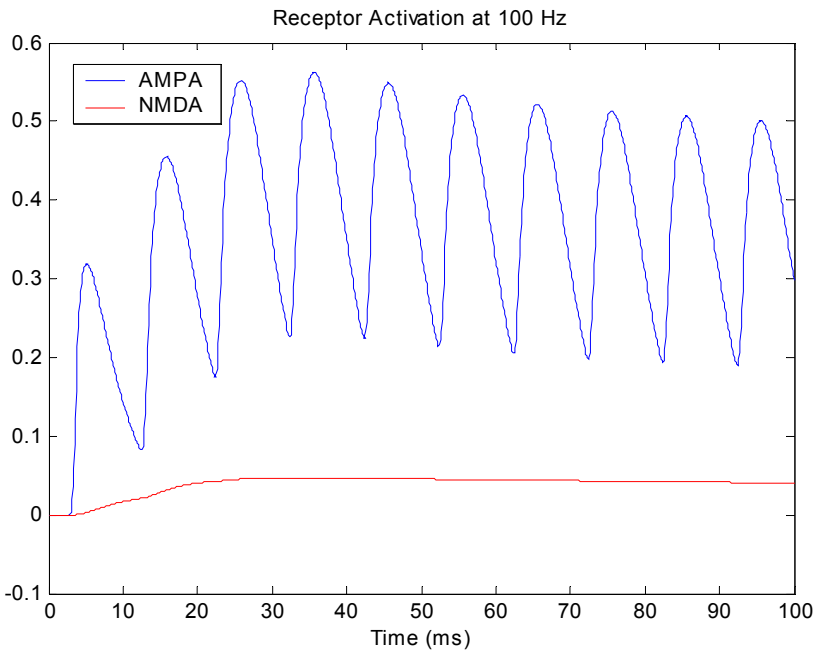
Receptor Activation at 100 Hz
AMPA
NMDA
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
0
10
20
30
40
50
60
70
80
90
100
Time (ms)

Fig. 3

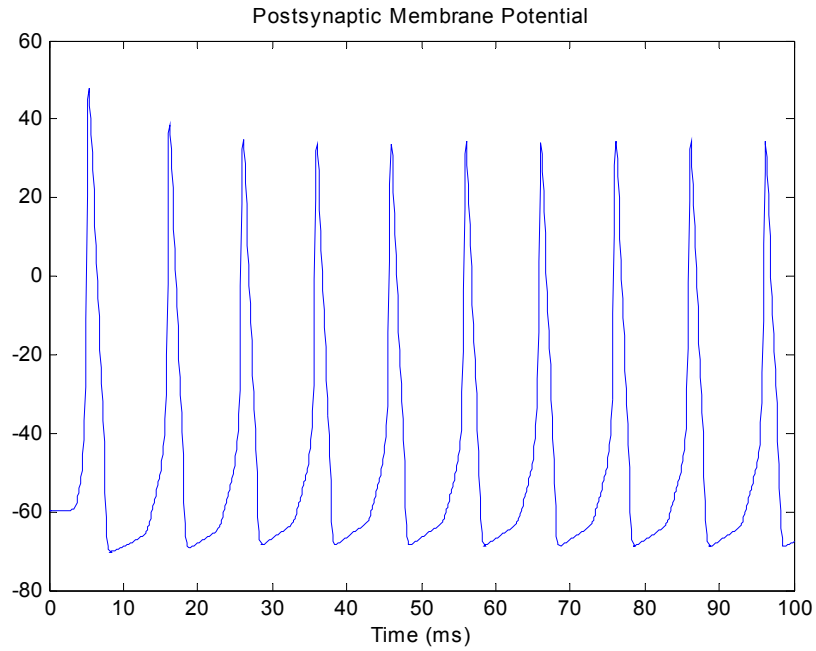
Postsynaptic Membrane Potential
60
40
20
0
-20
-40
-60
-80
0
10
20
30
40
50
60
70
80
90
100
Time (ms)

Fig. 4

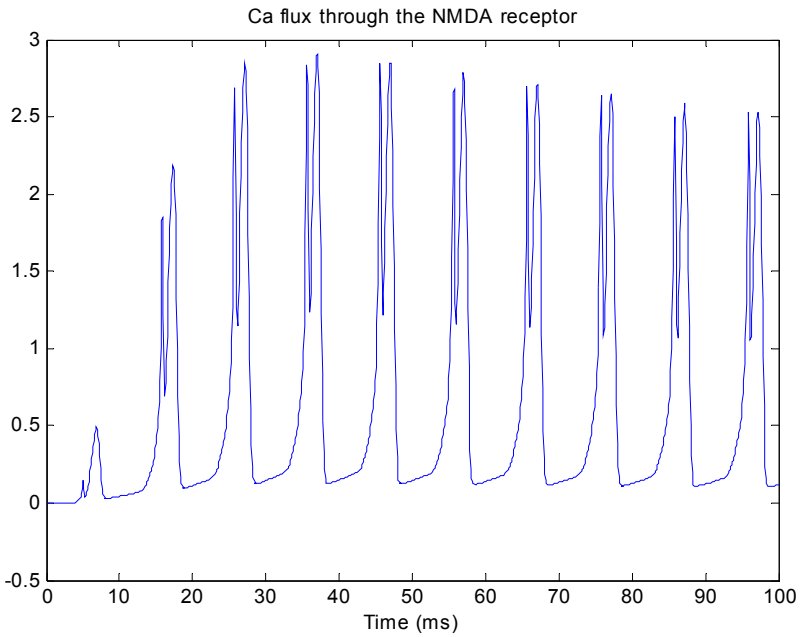
Ca flux through the NMDA receptor
3
2.5
2
1.5
1
0.5
0
-0.5
0
10
20
30
40
50
60
70
80
90
100
Time (ms)

Fig. 5

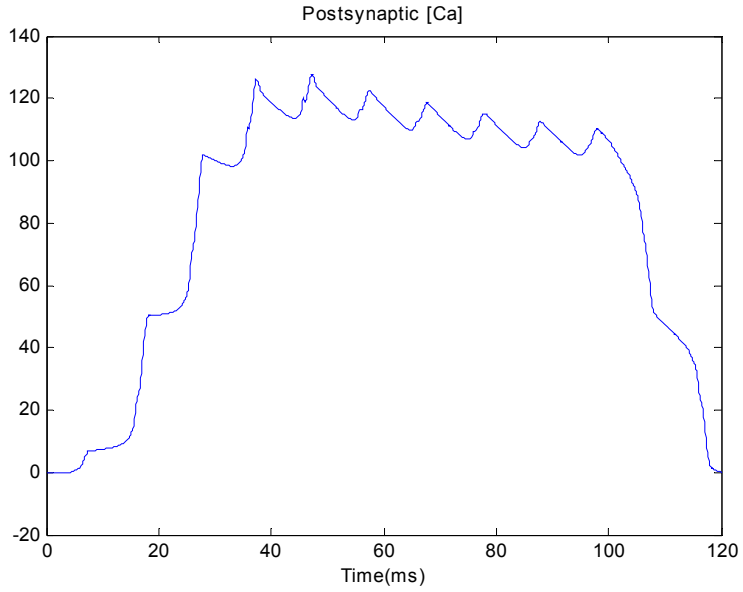
Postsynaptic [Ca]
140
120
100
80
60
40
20
0
-20
0
20
40
60
80
100
120
Time(ms)

Fig. 6