Problem set 1, Part 2. Oscillations

In class we discussed different modes of oscillation in neural networks, some dependent on intrinsic voltage-dependent signaling, some on network interactions, and some on a combination of the two.

Thalamic relay neurons express high levels of T-type calcium channels that promote "burst" firing, in which action potentials will be produced in high frequency clusters. T-channels are silent at rest (~ -65 mV) as a result of a process termed voltage-dependent inactivation. The channels can be primed (deinactivated) by membrane hyperpolarization , i.e. bringing their membrane potentials to values more negative than rest.

As we discussed in class, state changes for ion channel gates have forward and reverse rate constants. For example, T channel inactivation and deinactivation both get faster with voltage. Inactivation becomes faster with strong depolarization, and deinactivation faster with stronger hyperpolarization.

Physiological hyperpolarization that primes or deinactivates T channels and enables burst firing could occur through two mechanisms, as follows: 1) steady change in resting membrane potential through changes in neuromodulatory state. When we are awake and perceptive, neuromodulatory output is high through cholinergic, noradrenergic, etc, mechanisms, and this depolarizes neurons in cortex and thalamus and makes them more responsive. As we drift off towards drowsiness, neuromodulatory output decreases – and this releases what had been a steady depolarizing influence thus causing steady hyperpolarization of resting membrane potential. 2) transient hyperpolarization, as through inhibitory post-synaptic potentials mediated by GABA receptors.

We will inspect screenshots from modeling software to examine the relationship between synaptic inhibition and burst firing in thalamic relay neurons.

The following figure is the output of a simulation that mimics an IPSP at 300 ms. The IPSP transiently hyperpolarizes the membrane potential due to an underlying synaptic current (IPSC) that has fast kinetics, as can be seen faintly in the bottom trace (gGABA).

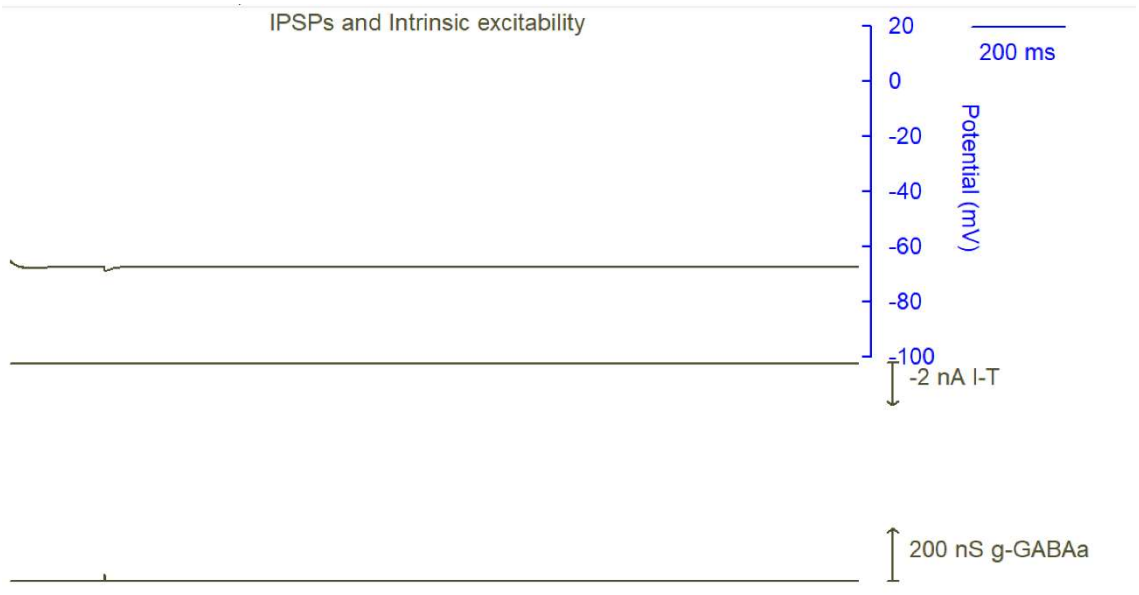

Figure 1: A simulation that mimics an IPSP at 300 ms. The IPSC kinetic scaling factor is 24.

Note the changes in Vm that occur at the onset, within the first 100ms of the simulation. For the purposes of this problem set, you can largely ignore these as they mainly reflect the system coming into equilibrium from the initial conditions (numbers and types of leak and voltage gated ion channels) set in the model.

Also note that the response to synaptic input is similar to what I showed in class. Upon termination of the IPSP, the membrane potential simply returns to the same membrane voltage as that observed before the IPSP. The IPSP was simply too weak to have much of a priming effect on the T channels and no post-inhibitory response is seen.

Now the simulation will be modified to alter the kinetics of the IPSC. The above trace has an initial value of 24, which means the decay kinetics of the IPSC have been scaled to be 24-fold faster than normal. $GABA_A$ receptors are modified in their gating by drugs such as alcohol, anesthetics, hypnotics, muscle relaxants, etc., to produce changes in decay rates and enhance inhibition.

The following image shows the same simulation as above overlaid with a simulation with an ISPC kinetics value of 12 (teal) and another with an ISPC kinetics value of 6 (purple).

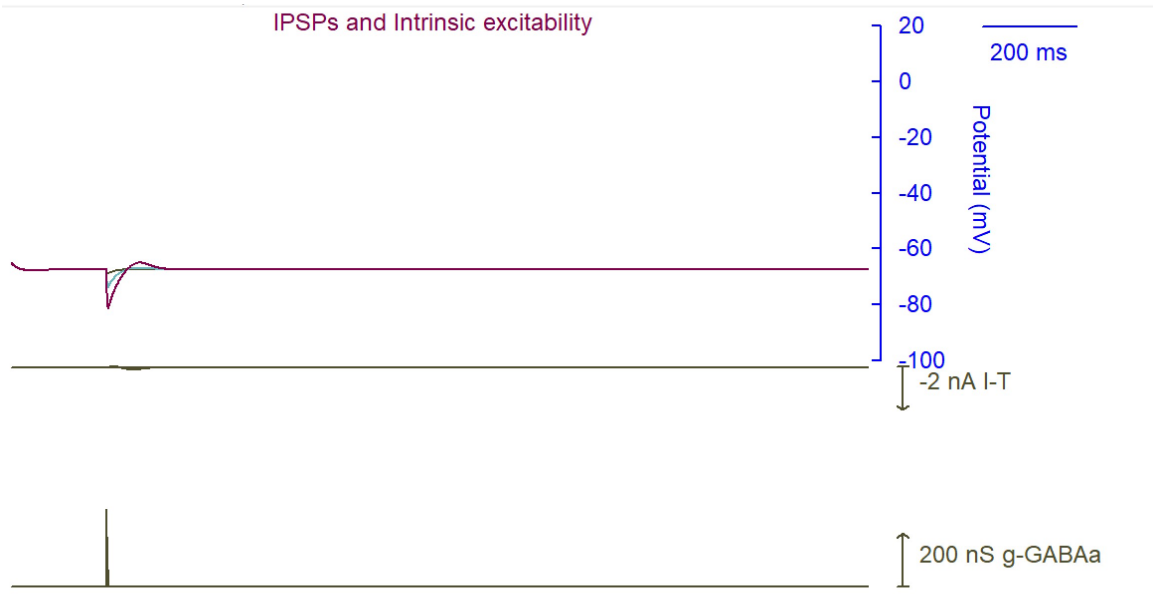

Figure 2: Simulation with ISPC kinetics of 12 (teal) and 6 (purple)

Question 1: What difference in response do you see between these situations? As the IPSP decays what is the subsequent membrane potential response? How is it different with a kinetic factor of 24 vs 6? Do you see quantitative or qualitative changes? For example, do you see a post-inhibitory rebound depolarization that is goes beyond initial resting membrane potential? Do you observe the presence or absence of action potentials, or just changes in the postinhibitory response such as amplitude or duration?

The following image shows a simulation with an ISPC kinetics value of 3 (black) overlaid with a simulation with an ISPC kinetics value of 1.5 (teal).

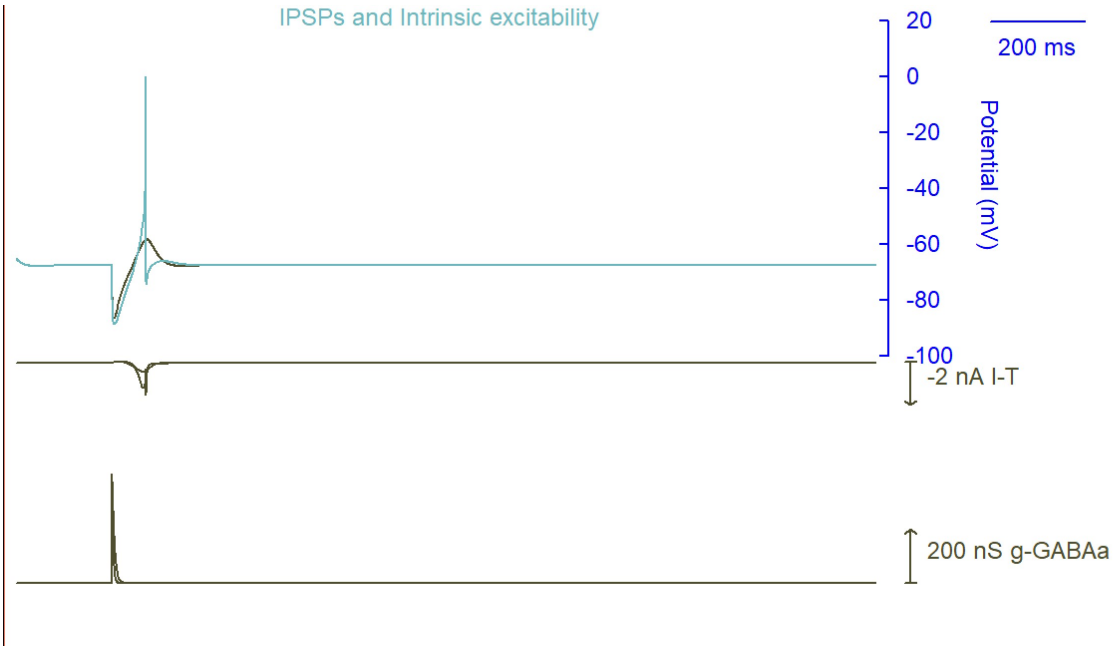

Figure 3: Simulation with ISPC kinetics of 3 (black) and 1.5 (teal)

Question 2: What difference in response do you see between the two simulations in Figure 3 compared to each other and compared to Figure 1? Do you see a post-inhibitory rebound depolarization that is goes beyond initial resting membrane potential? Do you observe the presence or absence of action potentials, or just changes in the postinhibitory response such as amplitude or duration?

The following image shows overlays of five simulations. The simulations have ISPC kinetics values of 3 (black), 1.5 (teal), 0.375 (purple), 0.093 (dark blue), and 0.047 (bright blue).

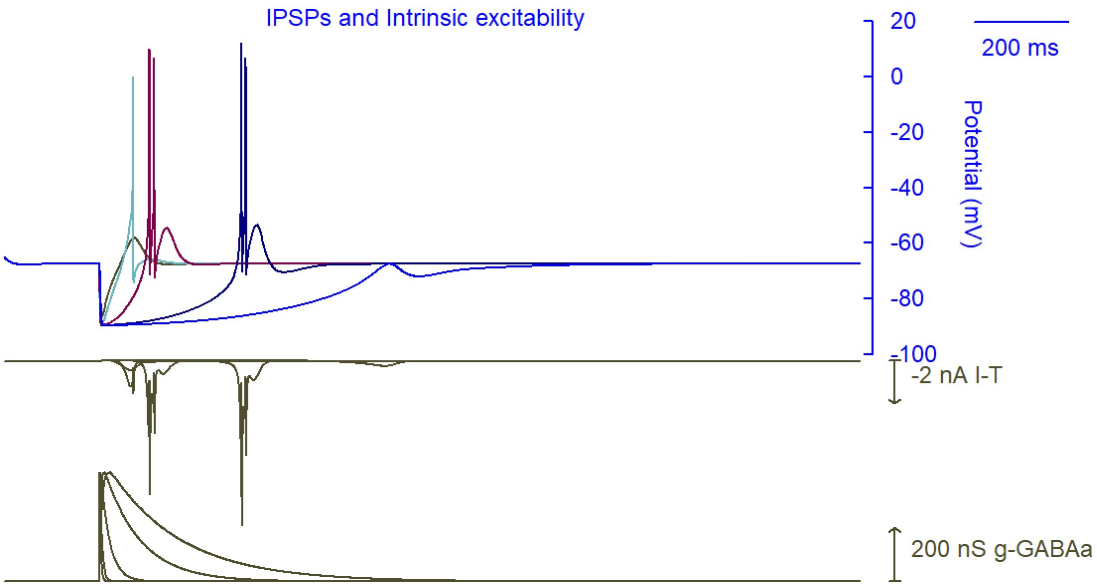

Figure 4: Simulation with ISPC kinetics of 3 (black), 1.5 (teal), 0.375 (purple), 0.093 (dark blue), and 0.047 (bright blue)

Question 3: What is the relationship between IPSC kinetics and output of this neuron? Give a general description of the relationship between post-inhibitory rebound response magnitude (mV of overshoot), and b) number of action potentials produced. What is the mechanism of these results in terms of neuron electrophysiology?

Question 4: Why do you see little response at the extremes of the IPSC kinetics? Is there a monotonic relationship between IPSC duration (as governed by decay rate), and post-inhibitory response? If not, what are some potential explanations for these findings, especially regarding the decreased rebound responses observed with the longest IPSC durations?