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 of 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. Such hyperpolarization can occur through slow, steady-state changes in membrane potential, as occur through neuromodulatory mechanisms that open resting potassium channels, or through transient hyperpolarization, as through inhibitory post-synaptic potentials mediated by GABA receptors.

We will use the modeling software provided in class to examine the relationship between synaptic inhibition and burst firing in thalamic relay neurons.

Problem set 1, part 2, experiment 1. Launch the program SimCC, and load the parameter file ps1_pt2_exp1.cc5, provided. Start the simulation via the menu Run->Begin, or command B (mac) or alt B (PC). Note that 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 ion channels) set in the model.

This simulation mimics an IPSP at 300 ms with an underlying synaptic current (IPSC) that has fast kinetics, as can be seen in the bottom trace. Now take this simulation and modify it to alter the kinetics of the IPSC, via the menu tree Parameters->Synaptic Currents->IPSC kinetics. Note that the initial value is 4, which is scaling the decay kinetics of the IPSC to be 4-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. To explore the parameter space of IPSC kinetics and the effects on neuronal excitability, use log steps to modify this value (e.g. by two-fold at each trial). For example, you might try a new value of 2. Hit OK, and the command (or Alt) Y to generate an overlaid trace.

Q1) What difference in response do you see between these two situations? As the IPSP, initated at 300ms decays, what is the subsequent membrane potential response. How is it different with a kinetic factor of 4 vs 2? Do you see quantitative or qualitative changes? Now continue to modify the kinetics parameter, while overlaying more simulations with command Y.
Q2) What is the relationship between IPSC kinetics and output of this neuron? Output could be measured by the presence or absence of a rebound membrane

potential response and/or the generation of fast action potentials. Be sure to explore the complete range of kinetics until you have reached the limit of neural output at each extreme of slow and fast kinetics.
Q3) Plot the relationship, and explain the result. Is there a monotonic relationship between IPSC duration (as governed by decay rate), and post-inhbitory response? If not, what are some potential explanations for this finding?
Q4) Extra credit. Instead of modifying kinetics, instead modify the number of IPSCs, and compare and contrast results with those obtained in Q3.

Problem set 1, part 2, experiment 1. Intrinsic oscillations and neural state changes. You may be familiar with the concept of slow sleep related oscillations in neocortical circuits -- with up (plateau with AP firing) and down (hyperpolarized, little firing) states in individual neurons, with these states especially common during sleep. To explore a cellular mechanism of up and down states, load parameter file ps1_pt2_exp2.cc5. Run it with command B. Now change the protocol, using Parameters->Protocol->Injected Current, and double to value to .01 nA. Produce an overlaid response with command Y. Continue to modify the project to increase the injected current until a final value is reached of 0.02 nA, while overlaying additional responses. Estimate from the screen the Vm values obtained in the steady state as the membrane potential stabilizes following current injection. Plot to V-I curve and estimate the input resistance of the cell from the slope. Now modify the protocol to invert the injected current, starting with -0.05 nA. Note difference in the response to hyperpolarizing current injection. Is a stable Vm obtained? Now modify the protocol to inject -0.01 nA, and note response during and after the current injection. How is this different from all the other responses? Does the cell have two stable states, i.e. Vms that are reached in the absence of injected current? Does the apparent input resistance (from the slope of the V-I curve) depend on the initial state of the cell? You can see the underlying biophysical basis of the simulation by examining the parameter dialog box for Conductances.