Problem set #1, Part 2. Oscillations, John Huguenard

We discussed in class 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, through a process of voltage-dependent inactivation. The channels can be primed by hyperpolarizing neurons, i.e. bringing their membrane potentials to values more negative than rest (~ -65 mV). This can occur through 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.

Launch the program SimCC, and load the parameter file ps1_exp2.cc5, provided. Start the simulation via the menu Run->Begin, or command B. You can ignore the voltage transients occurring within the first 100 ms, which mainly reflect the system coming into equilibrium from the initial conditions set in the model.

This simulation mimics an IPSP with an underlying synaptic current (IPSC) with 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 receptors are modified in their gating by drugs such as alcohol, anesthethics, hypnotics, muscle relaxants, etc, to produce exactly these kind of kinetic changes. To explore the parameter space, 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 Y to generate an overlaid trace.

Q1) what difference in response do you see between these two situations?
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? 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.
Q4) What is optimal oscillation frequency of this network?
Q5) Extra credit. Instead of modifying kinetics, instead modify the number of IPSCs, and compare results with Q3. Why is the result not the same?

Exercise 2. Intrinsic oscillations and neural state changes. You may have read about ultra slow (<1Hz) oscillations in neocortical circuits with up (plateau with AP firing) and down (hyperpolarized, little firing) states in individual neurons, which these

states especially common during sleep. To explore a cellular mechanism of up and down states, load parameter file latch1.cc5. Run it with command B. Now change the protocol, using Parameters->Protocol->Starting Vm, and modify this value to -89. Overlay with command Y. Modify protocol to make injected current -0.007, and overlay again. Describe the response. Now, reset Starting Vm to -67.5 mV and overlay one more time, still with injected current at -0.007. Overlay the response one more time, and note the strange non-linearity. You are seeing a transition from one state to another. To explore this fully examine the relationship between steady injected current, "Base current" and equilibrium membrane potential. You might start with a value of -0.005 nA and then a series of linear changes in base current. Note that the membrane potential is initially unstable with some settings but eventually it should stabilize to an equilibrium value, given sufficient time. Plot a V/I plot for this cell at equilibrium. Given what you know about the V/I relationship expected for a passive neuron, can you explain, in one paragraph, what is going on here? One hint: "window current".