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 (de-inactivated) 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 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. 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 leak and voltage gated ion channels) set in the model. This simulation mimics an IPSP at 300 ms that transiently hyperpolarizes the membrane potential due to an underlying synaptic current (IPSC) that has fast kinetics, as can be seen in the bottom trace (gGABA). 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 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 64, which is scaling the decay kinetics of the IPSC to be 64-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 32. Hit OK, and the command Run, Overlay (or Alt or CMD Y) to generate an overlaid trace. Q1) What difference in response do you see between these two situations? As the IPSP decays what is the subsequent membrane potential response? How is it different with a kinetic factor of 64 vs 32? Do you see quantitative or qualitative changes? For examples, do you see a post-inhibitory rebound depolarization that is goes beyond initial resting membrane potential? Do presence or absence of action potentials with some simulations, or just changes in the post-inhibitory response such as amplitude or duration? Now continue to modify the IPSC kinetics parameter in log 2 steps al the way down to 0.03125, while overlaying more simulations with command Y. Q2) What is the relationship between IPSC kinetics and output of this neuron? Generate plots showing relationship between IPSC kinetic factor and a) post-inhibitory rebound response magnitude (mV of overshoot), and b) number of action potentials produced. 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) Explain the results shown in Q2. 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? Q4) Instead of modifying kinetics, instead modify the number of IPSCs while keeping kinetics constant (e.g. value of 1), and compare and contrast results with those obtained in Q3.