Impact of probability of vesicle release on neuronal firing
Tom Gillespie, BGGN260, December 16, 2012

One well established phenomenon in the CNS is every action potentials does not trigger neurotransmitter release from a single presynaptic terminal. Observations in hippocampal slice and from two photon calcium imaging in vivo suggest that probability of release at a single excitatory synapse is significantly less than .5. We wanted to examine the impact of the probability of release and variance in probability of release on synaptic input to pyramidal neurons. To accomplish this we modeled inputs from probabilistically speaking upstream neurons, varying the mean and variance of the probability of vesicle release for the same upstream spiking pattern and distribution of synapses and examined the impact on spiking in a single downstream layer 2/3 pyramidal neuron. We used NEURON to model this biophysically realistic downstream pyramidal cell.

Methods

Our model has three parts: an upstream population of neurons, synapses from upstream neurons on to our downstream neuron, and the downstream neuron itself. Upstream here is used loosely since many neurons in cortex in fact have recurrent connectivity.

The upstream population of 1000 neurons was modeled as probabilistically spiking neurons where the probability of a spike in a given interval was drawn from a lognormal distribution of firing rates with a mean of 4.9 Hz drawn from Hromadka et al. 2008 [1]. Stimulation events were created by setting average upstream firing rates of a random subset of cells to 50Hz for 50ms.

The connections between the synapses and the upstream neurons was generated by drawning from a binomial distribution n=6 p=.5 to reproduce the mean number of synaptic connections per upstream neuron to downstream neuron observed by Sakmann et al. 2006 [2]. On average there will thus be 3000 synapses onto the pyramidal neuron, and some upstream neurons will not have any connections. The connection matrix was kept the same across all patterns of firing used.

The synapses themselves were modeled using NEURON's AlphaSynpapse with gmax=.002, tau=.5, and a reversal potential of zero. We choose gmax to fit observations by Song et al. 2005 showing that on average EPSP amplitudes were on average about .8mV [3]. Synapses locations were uniformly distributed across the dendritic tree. Vesicle release was determined by spike times and a probability of release for each synapse. The variance of the probability of release was controlled using a beta distribution with a mean equal to the fixed probability of release.

Using realistic time courses for synaptic events with currents lasting tens of milliseconds is problematic in this model and we found it more important to preserve the observed phenomena that synaptic events must occur within narrow time windows in order for a postsynaptic cell to generate an action potential. This does lead to interesting questions about mismatches in our understanding of the properties of synaptic potentials and the importance of synchrony of input events.

The L2/3 pyramidal neuron was a multicompartment HH model from Sejnowski et al. 1996 [4]. The exact setup for running the code requires Python(x,y) version 2.7.3.0 and Jeff Bush's pyneuron installation [5].

Each experiment was run for 500ms, stimulation was applied between 200 ms and 250 ms. We varied the strength of the stimulation by activating 0, 50, 200, or 500 upstream neurons. Stimulation spiking rates are calculated from within that window and baseline is calculated from the rest of the trace. Threshold for spike detection was set to -55 mV.

Results

Interestingly our results suggest that at least for this particular downstream neuron variance in the probability of vesicle release has a small effect on baseline firing rate, different variances seem to have little effect on spike timing for different upstream firing patterns.

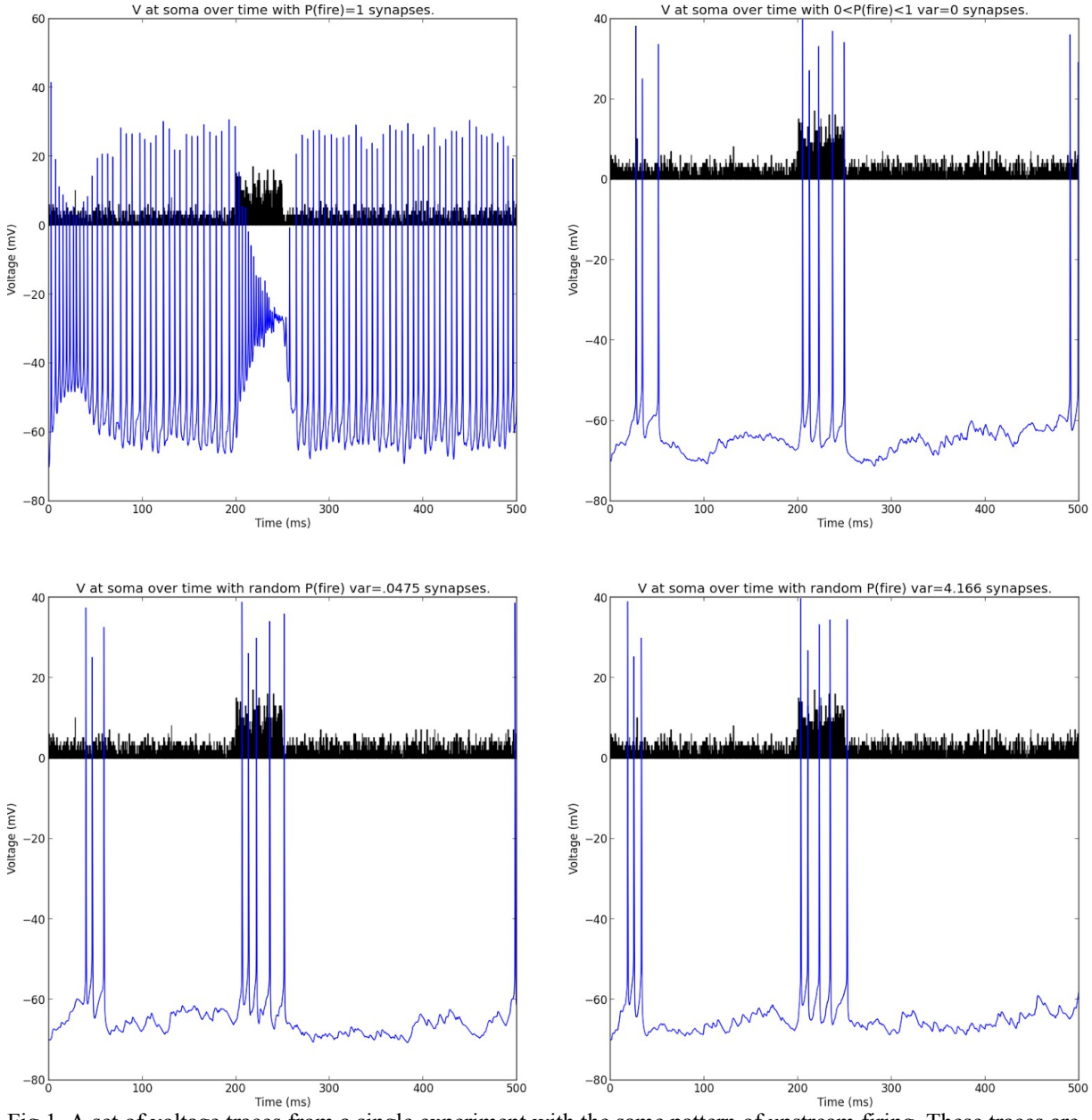


Fig 1. A set of voltage traces from a single experiment with the same pattern of upstream firing. These traces are from trials with 200 stimulated neurons. TL: P(vesicle release)=1. TR: P(vesicle release)=.05 Var=0. LR: P(vesicle release)=.05 Var=.0475. BR: P(vesicle release)=.05 Var=4.166. Black traces show the histogram of upstream spikes (same for all traces).

Average firing rates taken from 6 simulations run for all four stimulus levels, yielding 24 traces in total show a consistent increase in baseline firing rate with increased variance. Is seen in Figure 2 baseline firing increases from 14.5 Hz to 15.7 Hz to 16.9 Hz as variance increased from 0 to .0475 to 4.166. It should be noted that these baseline firing rates are still on the high side for spontaneous cortical rates (4.9 Hz being the average for the upstream neurons). Changes in firing rate as the result of a stimulus are less consistent.

An examination of multiple voltage traces in Figure 3 seems to suggest that increased variance in vesicle release probability has some impact on shortening the refractory period following stimulation. Another interpretation is that increased variability impacts spike timing under no stimulation in such a way as to give the appearance of a shorter refractory period, a conclusion supported by the general increased firing rate observed at baseline with higher variance.

Individual traces for other runs of the experiment would normally be found with the accompanying material, unfortunately the version of python used was 32bit and ran out of memory while trying to generate all the figures.

Discussion

Interestingly the number of excitatory synapses that actually drive spiking in pyramidal neurons sensory cortex has been estimated to be less than 5-10% of the total synapses on a dendritic tree. Unfortunately much of the data for this study has been compiled from both hippocampal and cortical data. There may be significant differences in the connectivity and activity between these areas as well as variability between the species the data was drawn from.

It seems surprising that increased variance in probability of vesicle release seems to lead to slight increases in the baseline firing rates of downstream neurons. Such a phenomenon seems to warrant further investigation since coordinated control to decrease the variance of presynaptic release probability by postsynaptic neurons might be one mechanisms for affecting synaptic homeostasis.

Acknowledgments

I would like to thank Jeff Bush for his help in working with the monstrosity that is NEURON.

Fig 2. Histograms of firing rates as a function of variance, data is taken from all stimulation levels. X axis is spike rate in Hz, Y axis is the number of individual voltage traces (out of 24 total) that had a spike rate in a given bin.

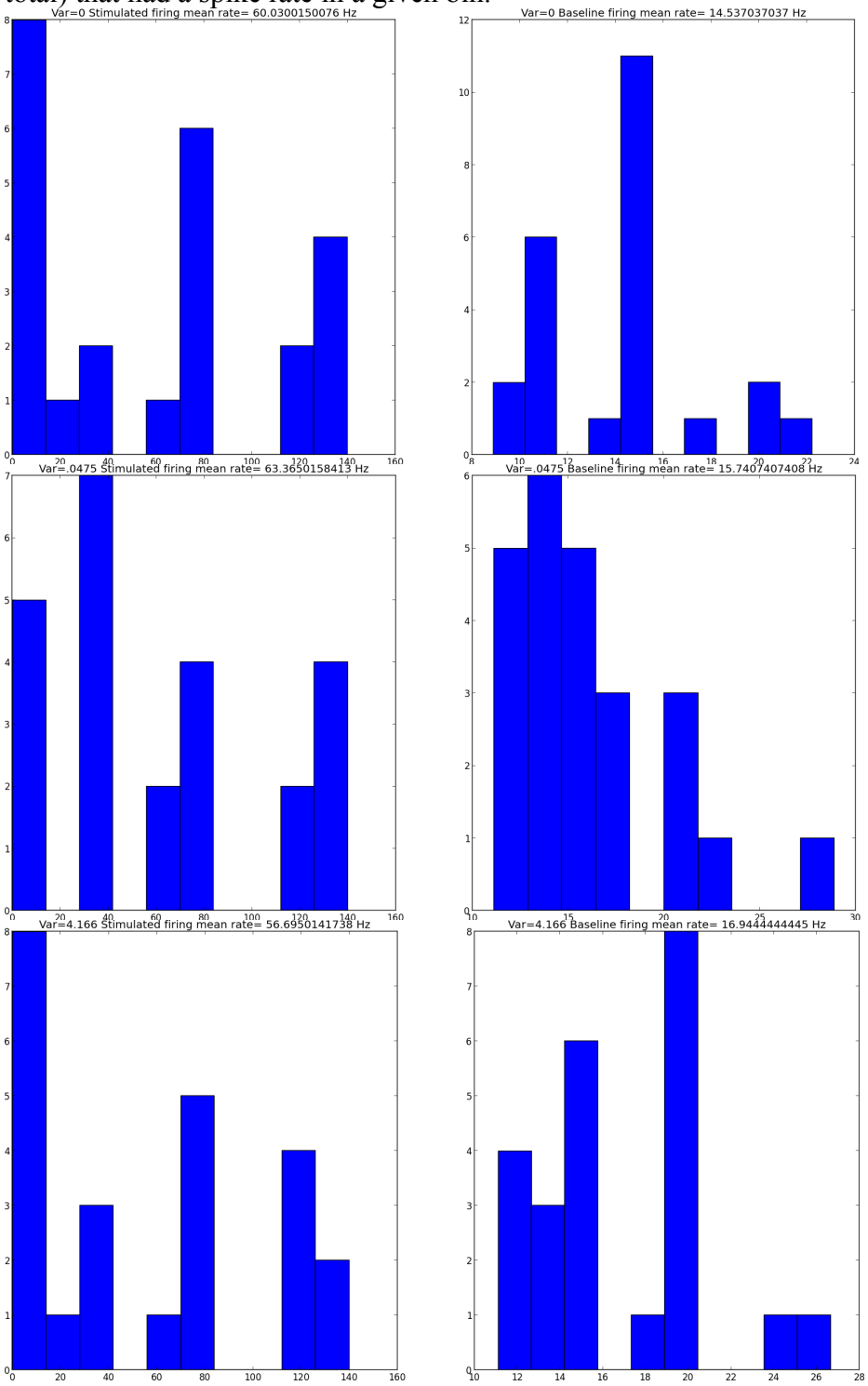
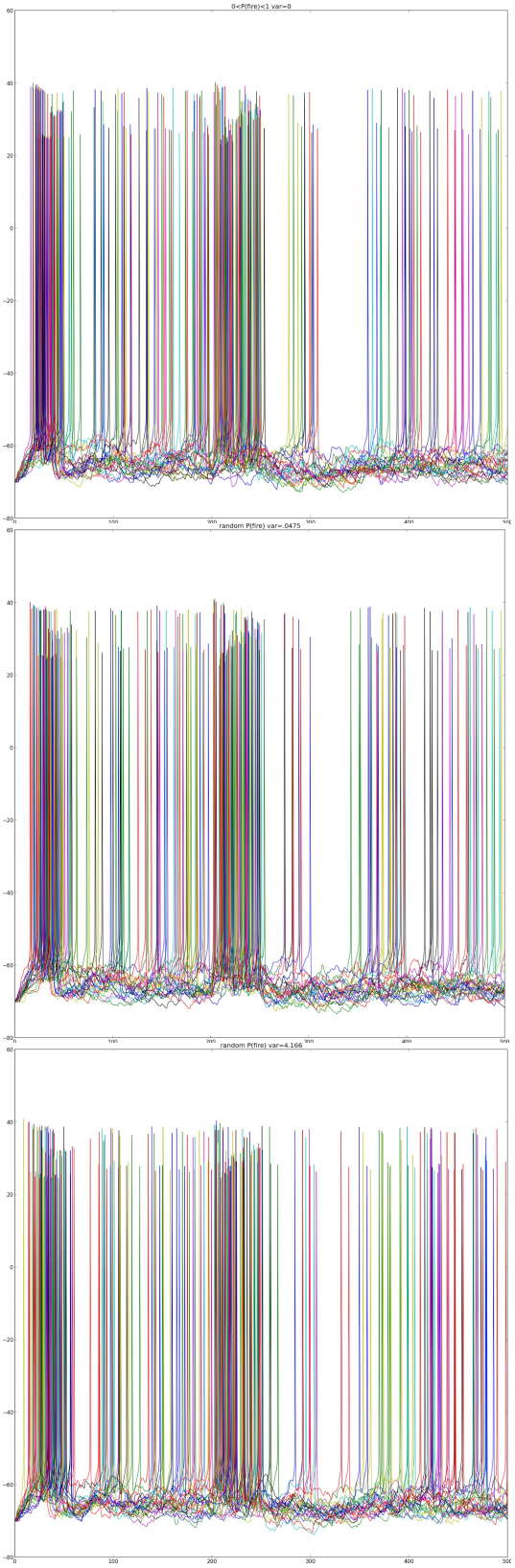


Fig 3. Plots of voltage traces for a given stimulus level. X axis is time in ms, Y axis is voltage in mV.



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5. See week 5 at: http://www.isn.ucsd.edu/courses/beng260/complab/