A Monte Carlo Based Simulation of the Effect of Action Potential Broadening on Neurotransmitter Release

Rhys Adams¹, Jon Pattillo², and Joel Stiles²

¹Bioinformatics Department, University of Texas, El Paso.
²Pittsburgh Supercomputing Center, Pittsburgh

I. Introduction

Calcium plays an important role in triggering synaptic transmission. At the action potential (AP) peak, voltage gated calcium channels (VGCC) are opened within an area of the presynaptic portions of the neuron known as the Active Zone (AZ). Ca²⁺ begins to diffuse into the cell at a rate affected by both the membrane potential, and the number of VGCC that are open. VGCCs will close as membrane potential repolarizes, while Ca²⁺ will be more inclined to diffuse into the cell as the AP repolarizes. Once inside the cell, Ca²⁺ activates synaptic fusion of synaptic vesicles (SV) by binding to synaptotagmin proteins. Calcium also activates calcium activated potassium channels, which allow K⁺ to leave the neuron more quickly.

It would be expected that the inhibition of calcium activated potassium channels would slow down the rate at which potassium diffuses out of the cell and would broaden the AP. The membrane potential would fall more slowly, and would become more repulsive towards Ca²⁺ ions. Experiments have shown contradicting amounts of SV release based on these different AP curves (Pattillo et al, 2001). In addition, the timing of
broadening (reflective of the effect inhibiting Ca$^{2+}$-activation) may also change the total amount of calcium influx (Pattillo et al, 2001).

II. Method

We propose to use MCell to perform a Monte Carlo simulation of the presynaptic AZ to test the effects of AP broadening on transmitter release. In this experiment we will generate 4-10 AP curves with differing levels of broadening and run a series of simulations based on these synthetic AP curves. Our test will look at changes in the amount of Ca$^{2+}$ flux, calcium-release relationship (CRR), and SV release. CRR will be defined as the slope of a log-log plot of SV release events as a function of [Ca$^{2+}$] (Pattillo et al. unpublished). We will be using models previously constructed for AZ and SV geometries and positions (Pattillo et al. unpublished). Data generated will be compared against results generated in previous simulations with unbroadened AP curves.

Data will be generated within MCell’s framework, and data mining techniques will be used to extract relevant data.

III. Results

While the overall mechanisms of calcium signaling within the AZ are thought to be well understood, there is still some uncertainty in the details involved. We are especially interested in CRR and SV release rates. Previous work has said that an increase in SV release is associated with a decrease in CRR and conversely, a decrease in
SV release is associated with an increase in CRR. We expect our current model to predict with fair accuracy what experimental evidence tells us, but we are sensitive to changes that may provide a better fit to current models. Our results will help confirm or reject current models of calcium’s role in neurotransmitter release.

From a practical standpoint, a broader understanding of calcium’s role in NMJ signaling may further our understanding of potassium channel blockers and their affects on neuromuscular diseases.

IV. Summary

We would like to simulate calcium ion concentration within the Active Zone found in the neuromuscular junction using MCell. We will be simulating Calcium Activated Potassium Channel inhibitors by creating artificially constructed active potential curves.

V. References


