Journal Club

Consequences of Molecular-Level Ca\(^{2+}\) Channel and Synaptic Vesicle Colocalization for the Ca\(^{2+}\) Microdomain and Neurotransmitter Exocytosis: A Monte Carlo Study

What We’re Looking At!

- In the neuromuscular junction, calcium plays a crucial role in synaptic signaling.
- Calcium ion channels open up and calcium diffuses in.
- Synaptic vesicles are located very close to these ion channels, and will fuse into the synapse if triggered by calcium ions.
- An understanding of this area may facilitate neuromuscular drug research.
The Neuromuscular Junction

The Active Zone
Question:

- How does vesicle placement affect local concentration, and how does that affect transmitter release?

Method:

- This paper looked at calcium kinetics using Monte Carlo simulations.
- Synaptic vesicles were moved and changed to see what the resulting “concentrations” would be.
- Calcium binding rates were manipulated.
- Buffers were manipulated.
- Amount of calcium influx was changed.
Monte Carlo Analysis

- Because Monte Carlo methods are random, many different runs are performed, and the averages are taken.
- Monte Carlo parameters: 2ms over 500 runs.
- Does not give a precise solution, but may give a more realistic solution.

Monte Carlo Discrete Steps

- If Calcium ions flutter around tighter crevices, the time steps will need to be reduced to allow them to flow through tiny cracks.
- Large time steps tend to distort and clump reactions.
- 1 time step was 10 ns in this paper.

The time step chosen is important!
Many of the simulations looked at the vesicle’s geometry and how it interfered with calcium diffusion.

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Only 1 calcium binding site used, two methods of binding considered:

- $X \leftrightarrow XCa_1 \leftrightarrow XCa_2 \leftrightarrow XCa_3 \leftrightarrow XCa_4 \leftrightarrow F$
- $X \leftrightarrow XCa_1 \leftrightarrow XCa_2 \leftrightarrow XCa_3 \leftrightarrow XCa_4 \leftrightarrow XCa_5 \leftrightarrow XCa_5 \leftrightarrow F$

4 Calciums bind, and 5 calciums bind.

Buffers will also bind and unbind to calcium at preset rates.
Results

- Barriers caused increased concentrations of Calcium
- Synaptic fusion was largely unaffected by buffering.
- Slight changes in calcium influx had major affects.

Vesicles and Calcium Concentration

- Calcium tended to be concentrated against the vesicle.
- The author’s results say that a larger vesicle would increase the calcium concentration one side and decrease concentration on the other side.
Calcium Detection

- The position of the calcium sensor can affect the amount of calcium detected 13-fold.

The Relative Impacts of Multiple Vesicles

- Vesicle 3 increases release probability by 25%.
- Vesicle 2 has no significant effect on calcium release.
Conclusion

- The average concentration of calcium diffusion will be increased if a barrier is placed near the diffusion point.

Discussion

- Synaptic vesicles have 8 proteins at the base. It has been hypothesized that 3 are needed to cause synaptic fusion. If calcium concentration is high against a barrier, would this system get rid of the need for directionality.
- Concentrations discussed were at very low levels. How can concentration be used and not used.
Issues

- The calcium diffusion coefficient is critical to this simulation.
- The concentrations reported were 0.18 ions within 10 nm and 1.23 within 30 nm.
- At these concentrations, the effects of the calcium sensors becomes very large.
- What would be the effects of multiple ion channels and multiple vesicles?
- Fluctuations were not looked at!

Summer work

- Our work will be very similar.
- We will be using MCell to model calcium and synaptic vessel release.
- We will be adjusting the amount of polarization to see how the active zone responds.
As the active potential peaks, calcium channels open up, but calcium is unwilling to diffuse into the positively charged cell.

As the active potential repolarizes, calcium diffuses in as calcium channels start to shut down.

Certain medicines/poisons i.e. Scorpion venom can change the shape of this curve.

Synaptic vesicle release is affected, though we don’t have a good model of how.