Abstract View

MONTE CARLO MODEL OF BACKGROUND GLUTAMATE SPILLOVER IN THE HIPPOCAMPUS

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The goal of this study was to explore the activation of extrasynaptic AMPA and NMDA receptors by diffusion of glutamate in extracellular space following fast excitatory synaptic release. Conclusive results from analytical models are hampered by the difficulty of integrating information about the time course of glutamate concentration profiles in the synaptic cleft with diffusion profiles in the complex geometry of the neuropil. Furthermore, experimental measurements of critical model parameters are difficult to obtain, such as the fine structure of 3-D morphology of the neuropil on the sub-micron scale. We have used MCell, a Monte Carlo simulator of molecular signaling, to study the release of hippocampal glutamate and diffusion in 3-D geometrical reconstructions of the neuropil. Our simplified 3-D model contains repeating motifs with the appropriate design and spacing to replicate experimentally measured values for hippocampal tortuosity. The model simulates, on the microsecond time scale, the random walk of every glutamate molecule in a synapse after vesicular release. We have focused on the effects of background glutamate concentrations on the levels of receptor activation due to spillover.
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MONTE CARLO SIMULATION OF GLUTAMATE SPILLOVER

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I. Introduction

The goal of this project is to construct a simplified realistic 3D model of the hippocampal neuropil and use it in a Monte Carlo computer simulation of synaptic neurotransmitter release to characterize the effect of biophysical parameters of hippocampal neuropil on glutamate spillover. This parameter space will have three dimensions and will be explored as follows:

Specific Aim #1: determine how quantal size affects spillover by simulating synaptic release of 3000 and 5000 glutamate molecules per vesicle.

Specific Aim #2 and #3: determine how neuronal firing pattern affects spillover. The spatial configuration and temporal pattern of synaptic release of glutamate will be varied to simulate a diverse array of single burst release of the neurotransmitter.

In all cases, the time course of postsynaptic AMPA and NMDA receptor occupancy will serve as a measure of the spatiotemporal profile of spillover.

II. Methods

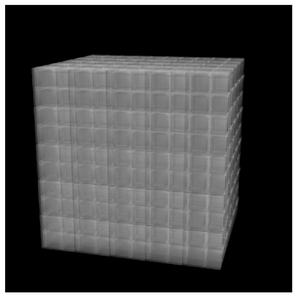
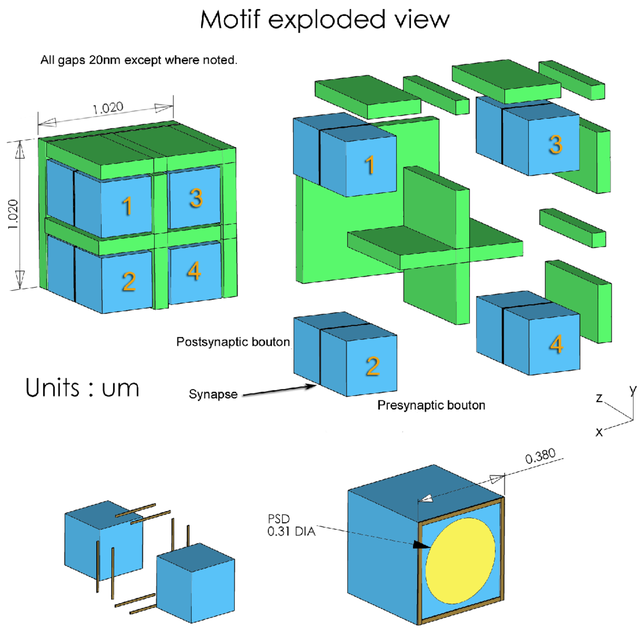


Figure 1. Neuropil model as motif array. A three dimensional model with tortuosity of 1.4 has been constructed in MCell. A cubic volume of neuropil 5 µm on a side is built by assembling 125 one µm cubic motifs in a 5 x 5 x 5 array. The extracellular volume ratio, which is equal to the extracellular volume divided by total volume, is approximately 0.177. The glial surface area-to-total volume ratio is 10.65 μm^2 per μm^3. Computer simulations as in Figure 3 were performed using MCell with a time step of one microsecond and glutamate diffusivity of 2E-6 cm^2 per sec, thus the mean radial diffusion length of glutamate per time step is 35 nm.

Figure 2. Motif design and synapse detail. Each motif contains 4 independent synapses surrounded by glial processes. Thus, the model contains 500 synapses total. The gap between synapses is 20 nm narrowing to 10 nm at edges. Each postsynaptic density (PSD) contains 80 AMPARs and 20 NMDARs. Glial surfaces contain glutamate transporters with a surface density of 1600 per μm^2.



IV. Results

Figure 5. Distribution of AMPA and NMDA states at steady-state. The distribution of receptor states seen in the figures below are based on 180 measurements taken with 0.5 µM background glutamate concentration. For both AMPA and NMDA, C0 represented the unbound state and O the open state. Receptor kinetic models are shown below right.

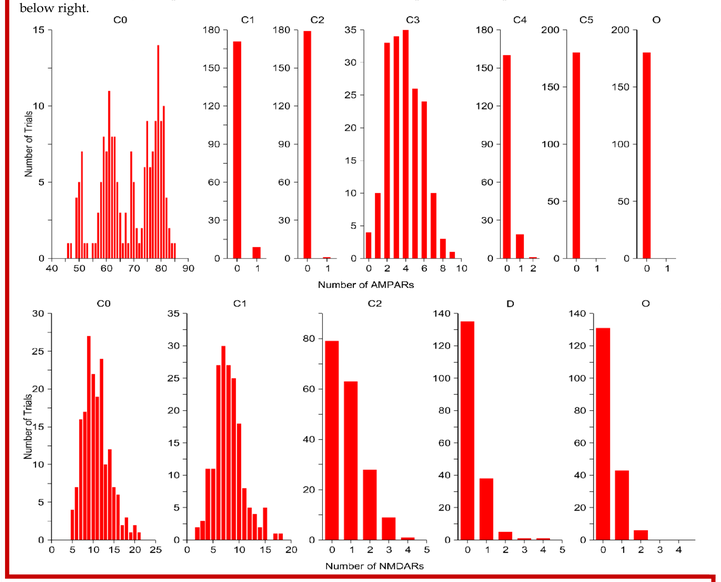


Figure 3. Synaptic release of glutamate. Simultaneous release of one vesicle (4000 molecules) from each of four synapses in a motif demonstrates spillover into the extrasynaptic space. Surrounding motifs are hidden from view. Glutamate transporters were included in this simulation.

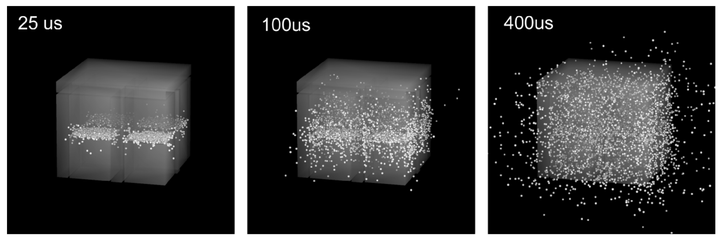


Figure 4. Equilibrium glutamate concentration. Glutamate molecules were released at a steady rate of 5.89 molecules per µsec from extrasynaptic locations with glutamate transporters activated to achieve a spatially-uniform 0.5 µM background concentration. The predicted steady glutamate release rate required to achieve 0.5 µM concentration based on well-mixed system is 6.62 molecules per µsec which agrees well with the actual rate. The steady release drives the system to an equilibrium total glutamate count of 6722, corresponding to 0.5 µM, regardless of the amount of glutamate in the system at the initial condition.

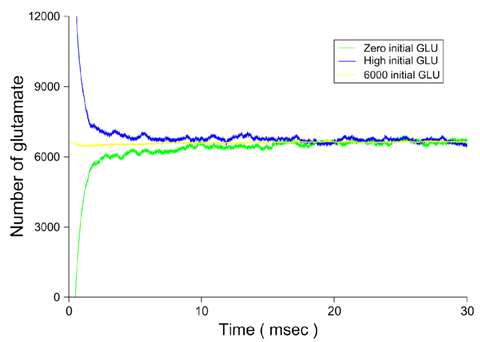
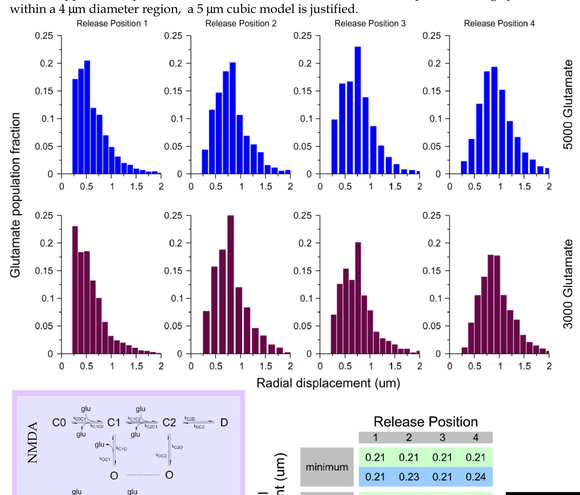


Figure 6. Spatial extent of glutamate spillover . Starting with zero initial background glutamate concentration, vesicles were released one at a time from the cleft center of each of the four synapses in the motif shown in Figure 2. Motif asymmetry causes variation in mean radial diffusion displacement of glutamate from the point of release among the four synapses following synaptic release. The minimum radial diffusion distance of ~0.21 µm reflects the absence of glutamate transporters inside the synapse. The mean radial diffusion distance varied across the four synapses but was approximately the same for the two vesicle sizes. Because the spillover is largely contained within a 4 µm diameter region, a 5 µm cubic model is justified.



Radial Displacement (um)	Release Position 1	2	3	4
minimum	0.21	0.21	0.21	0.21
	0.21	0.23	0.21	0.24
mean	0.62	0.82	0.76	0.96
	0.58	0.81	0.75	0.95
maximum	2.68	3.01	3.32	3.29
	2.62	3.51	2.66	2.86

Vesicle size: 5000 / 3000

Figure 7. Half-life of glutamate. With 0.5 µM background glutamate concentration vesicles containing 3000 or 5000 glutamate molecules were released singly from each of four synapses in motif. The average half-life was 666 µsec for 5000 glutamate and 591 µsec for 3000 glutamate. Results for zero initial glutamate concentration were comparable. Legend indicates release synapse as defined in Figure 2. On a semi-log plot the profile has a dual exponential decay and exhibits virtually no dependence on which of the four synapses in the motif is chosen for release. Analytical calculation of half-life assuming a well-mixed system predicts a half-life of 700 microseconds, independent of vesicle size. The difference in the half-lives between the 3000 and 5000 glutamate cases is interpreted as arising from local transporter saturation in the latter case.

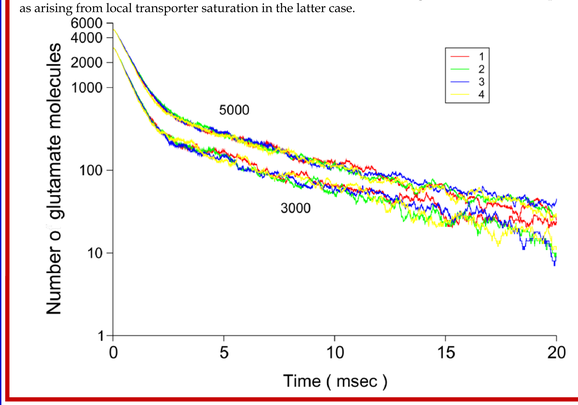
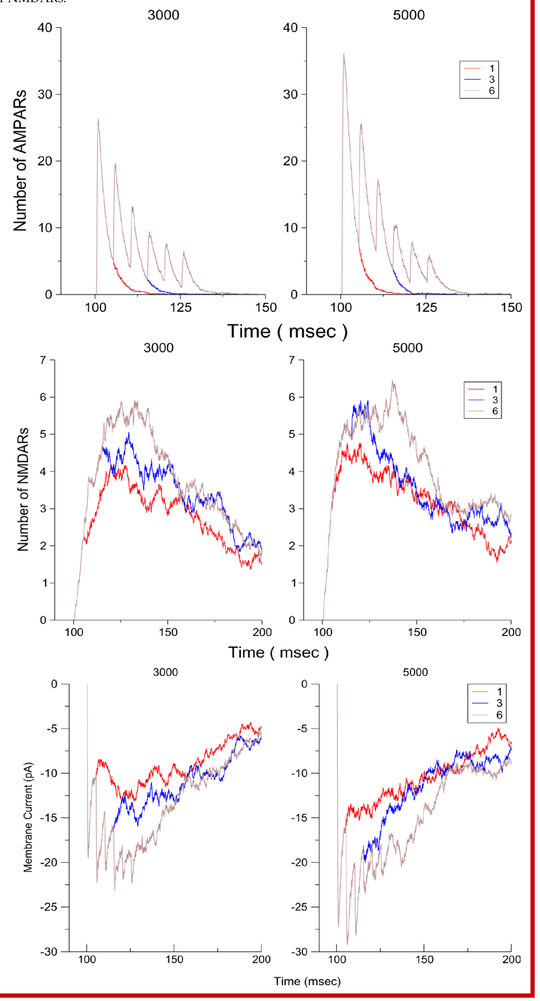


Figure 8. Glutamate release at the test synapse . Synapse 4 in Figure 2 was arbitrarily chosen as the measurement synapse with active AMPA and NMDA receptors. To establish a baseline response, vesicular release at synapse 4 was simulated with vesicles of size 3000 and 5000 with 100 Hz bursts of 1, 3, and 6 releases. The time course of receptors in the open state are plotted below. The excitatory postsynaptic current in the last figure below was calculated by assuming a constant membrane voltage of -70 mV, and single channel conductance values of 10 pS for AMPARs and 45 pS for NMDARs.



V. Future Work

- Include more sophisticated release patterns.
- Improve accuracy of 3D model.

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Acknowledgements

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