How to Build a Synapse with MCell/CellBlender: A Computational Microscope for Spatially Realistic Simulation of Cellular Microphysiology

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Scientific Computing Enables The Scientific Discovery Cycle

Scientific Discovery Cycle

Types of Experiments & Models

Thought Experiments
Mental Models

Bench Experiments
Physical World
Model Systems
Model Organisms

Computational Experiments
Computational Models

"What I cannot create, I do not understand" -- *Richard Feynman*

Philosophical Approach: Understanding through simulation

Motivation

How do synapses work?
How does synaptic structure influence synaptic function?

- Topology of synaptic and perisynaptic space (neuropil !!!)
- Organization of pre- and postsynaptic cytoplasmic organelles
- Distributions of receptors, ion channels, enzymes, transporters...
- Biochemical reaction networks and their dynamics
- Cells are not well mixed & numbers of molecules can be small
- Simulations must include stochastic spatiotemporal dynamics

MCell: Monte Carlo Simulator of Cellular Microphysiology

- Models realistic 3D reaction/diffusion systems
- Rigorously validated and highly optimized stochastic Monte Carlo methods
- Tracks Brownian dynamics diffusion and reaction of individual particles in 3D volumes and on 2D surfaces embedded in 3D
- Arbitrarily complex 3D geometry -- triangle surface meshes
- Arbitrarily complex reaction networks -- Markov processes and Network-free rule-based specification modeled as discrete event-driven point processes
- High-level, flexible Model Description Language
- Sophisticated model building, visualization and analysis environment -- CellBlender

Diffusion: Brownian Motion

Thermal Velocity:

$$\bar{v} \approx \sqrt{\frac{3kT}{m}}$$

For Water:

$$\bar{v} \approx \sqrt{\frac{3(1.3807\times10^{-23})(298)}{3\times10^{-26}}} \approx 640\, ms^{-1}$$

Diffusion: Brownian Motion

But, how far do the water molecules go between collisions?

1. Density of water ≅ 1g/cc or 1000g/liter.
2. Molecular weight of water ≅ 18g/mole.
3. From 1 and 2, the molarity of water = 1000/18 = 55.56 moles/liter
4. 55.56 x 6.022 x 10^{23} molecules/mole =
   3.3458 * 10^{25} or 3.3458 * 10^{22} molecules/cc
5. Average volume of each molecule is:
   1/ 3.3458 * 10^{22} ≅ 3.0 * 10^{-23} cc/molecule
6. Assuming that each molecule corresponds to a spherical space:

$$\frac{4\pi r^3}{3} = 3.0 \times 10^{-23}$$
$$r = 0.2\,nm$$

in 0.3 ps !!!

Diffusion: Fick's Second Law

Applies when concentration in volume is changing in time (i.e. $J_{in} \neq J_{out}$)

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2}$$

$$\frac{\partial c}{\partial t} = D \nabla^2 c$$

Free Diffusion: Concentration in Space and Time

$$\rho(r,t) = \frac{1}{\pi^{d/2}\lambda^d} e^{-r^2/\lambda^2}$$

$$\lambda = \sqrt{4Dt}$$

$$\tilde{r} = r/\lambda$$

$$\bar{l}_r = 2\sqrt{\frac{4D\Delta t}{\pi}}$$

$$\bar{l}_\perp = \sqrt{\frac{4D\Delta t}{\pi}}$$

Diffusion: Random Directions

Grid-Free Random Walk Diffusion

Surface Mesh Representation

Diffusion with Boundaries

Unimolecular Reactions

$$A \xrightarrow{k} B$$

Distribution of first-order decay lifetimes is:

$$\rho(t) = ke^{-kt} \qquad t_l = \frac{-\ln(R)}{k}$$

Bimolecular Reactions: Rate of Encounter

$$A + B \xrightarrow{k} C$$

$$N_H = N_A \bar{l}_{\perp} A_{ET} [A]_o$$

Bimolecular Reactions: Volume/Surface

$$A + B \xrightarrow{k} C$$

Probability of reaction between diffusing volume molecule and a surface molecule:

<u>From rate of encounter:</u>

$$p_{bt} = 1 - (1 - p_b)^{N_H} \approx N_H p_b$$

$$N_H = N_A \bar{l}_\perp A_{ET} [A]_o$$

<u>From Mass Action:</u>

$$p_{bt} = k[A]_o \Delta t$$

$$p_b = \frac{k}{N_A A_{ET}} \sqrt{\frac{\pi \Delta t}{D}}$$

Bimolecular Reactions: Collision Detection

Model Constraints

Realistic synaptic morphology from ssTEM reconstruction of hippocampal neuropil (collaboration with Kristen Harris, UT Austin)

Realistic Model of Synaptic Signaling in Neuropil

Realistic synaptic morphology from ssTEM reconstruction of hippocampal neuropil (collaboration with Kristen Harris, UT Austin)

Model Constraints

Experimental estimates of reaction kinetics and subcellular distributions for important molecules (collaboration with Mary Kennedy, CalTech)

Bartol et al., Frontiers Synaptic NeuroSci ,2015

Model Constraints

Experimental observations of evoked vesicular release:
(collaboration with Suhita Nadkarni, ISER Pune)

single stimulus

Goda & Stevens, PNAS, 1994

paired-pulse stimulus

Dobrunz, Huang & Stevens, PNAS, 1997

Model Constraint: kinetics of calcium sensor in SNARE complex

Nadkarni et al., PLoSCompBio,2010

PMCA
GluT
SERCA
Ca^{2+}
SNARE
AMPAR
NMDAR
Calbindin
VDCC P/Q
mCaMKII·CaM2C2N
VDCC L,R
CaM#C2N
0
0.01
0.1
1
10
100
time (ms)

0
0.01
0.1
1
10
100
time (ms)

0
0.001
0.01
0.1
1
10
100
time (ms)

Predicted Synaptic Behavior

Bartol et al., Frontiers Synaptic NeuroSci ,2015

Model Constraint: Calcium Buffering Capacity

Bartol et al., Frontiers Synaptic NeuroSci ,2015

Predicted Impact of Exogenous Ca^{2+} Indicators

Bartol et al., Frontiers Synaptic NeuroSci ,2015

But there is a problem with this Model: AMPARs Desensitize but EPSCs Should Not

Problem Solved by AMPAR diffusion and Clustering

(as shown by Constals et al., Neuron, 2015)

C0
glu
k_{C0C1}
k_{C1C0}
glu
C1
glu
k_{C1C2}
k_{C2C1}
glu
C2
k_{C2O}
k_{OC2}
k_{D1C1}
k_{C1D1}
k_{D2C2}
k_{C2D2}
k_{D3O}
k_{OD3}
D1
glu
k_{D3D4}
k_{D4D3}
glu
D2
k_{D4D5}
k_{D5D4}
D3

Maintaining Precise Alignment of Pre- & Post-synaptic Machinery is Critically Important

Haas et al., eLife, in review

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Future Directions

- Advanced simulation control
  - parameter sweep
  - parameter fitting/optimization/estimation
- Integration/coupling of other Physics Engines
  - Cytomechanics
  - Energy Bookkeeping (accounting for ΔG)
  - Electrophysiology/electrodiffusion
  - Hybrid reaction-diffusion: ODE/PDE/SSA
- Space-filling molecules -- macromolecular crowding, self-assembly of filaments, scaffolds etc...
- Dynamic cell geometry
- Multi-scale simulations spanning molecules to neural circuits

Registration, Segmentation, Mesh Generation, and Mesh Improvement

- AlignTK/SWiFT-IR
- RECONSTRUCT
- VolRoverN
- GAMer

Our 5 year mission:
Technology Research and Development to link (at least) 3 Scales:

- Molecular: molecular modeling and simulations, with focus on identifying functional substates and interaction mechanisms for proteins and their complexes (ProDy, GTKDynamo, WESTPA)
- Cellular: cell modeling, with an emphasis on developing tools to handle spatial and molecular complexity inherent to neuronal signal transmission (MCell, CellBlender, BioNetGen, RuleBender)
- Tissue: Image processing and analysis, with an emphasis on analysis of cell and tissue organization in support of modeling (AlignTK/SWiFT-IR, CellOrganizer)

Challenges in Spatially Realistic Cell Modeling

- Creation of computational quality 3D models is too hard
- Managing the complexity of reaction pathways is too hard
- Managing simulations, data, analysis, and visualization in high-dimensional parameter space is too hard

PS: Did I forget to mention, it's too HARD

Blender to the Rescue!

A complete, comprehensive, open-source solution to many of the hardest problems we face:

- Geometry/Mesh creation
  - rich mesh primitives
  - rich geometric representations
- Beautiful interface for editing/manipulating of geometry
- State-of-the-art visualization workflow for 3D production

blender.org

Blender is Extensible

Python and C APIs access a Model/View/Controller framework

- User-defined pluggable Addons to GUI
- User-extensible data model
- Hang user-defined metadata on almost any item:
  - ints, floats, strings, dictionaries
- Metadata viewed in GUI
- Metadata controlled by user-defined operators via GUI
- Metadata updated via callbacks in data dependency graph
- Consistent look-and-feel on all platforms
- Built-in help system
- All metadata automatically saved in blend file

CellBlender Addon for Blender

- A complete IDE for realistic reaction-diffusion modeling
- MCell acts as external Physics Engine for data-driven visualization
- We envision/hope that others in community will plugin as well

CellBlender Capabilities

All of Blender's features plus:

- Model Specification
  - model parameters
  - molecules
  - reactions
  - output options
  - visualization options
  - run-time options
- Import geometry from many sources:
  - CellOrganizer
  - VolRoverN
- Import whole models from:
  - SBML Spatial
  - CellOrganizer as SBML Spatial
  - BioNetGen as reaction network (as rules, coming soon)

Devin Sullivan

Mesh Improvement: MeshMorph

Controlling extracellular space

Assumption

- uniform extracellular width

Fun fact: Less than 2% of ECS is synaptic cleft.