How to Build a Synapse with MCell/CellBlender: An Environment for Spatially Realistic Simulation of Cellular Microphysiology

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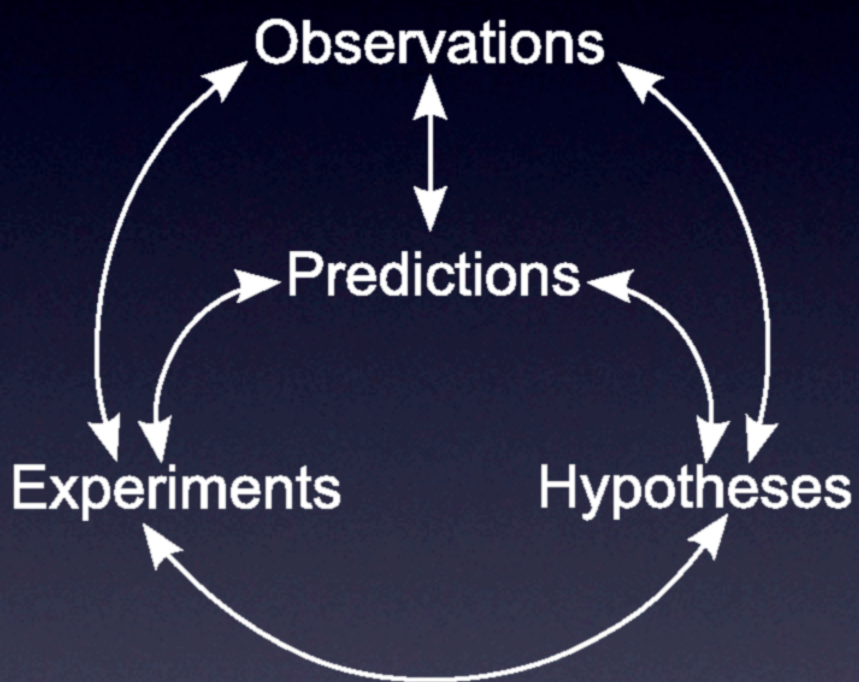
Scientific Computing Enables The Scientific Discovery Cycle

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*

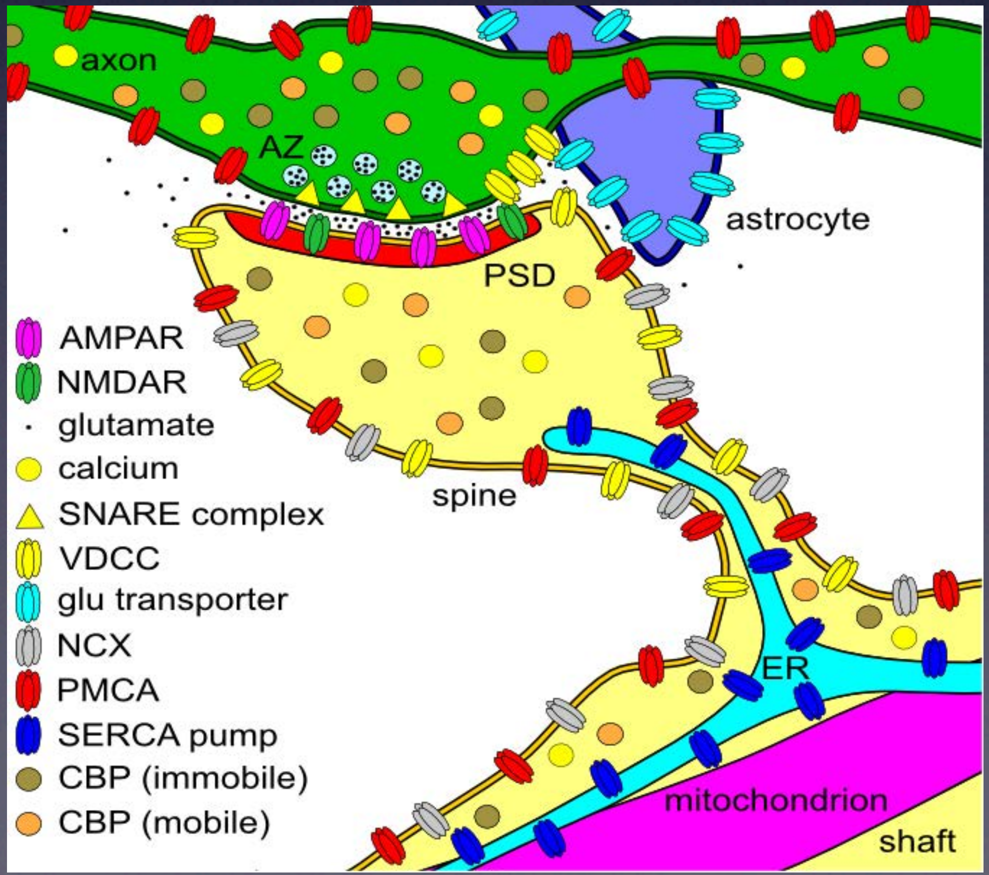
Philosophical Approach: Understanding through simulation

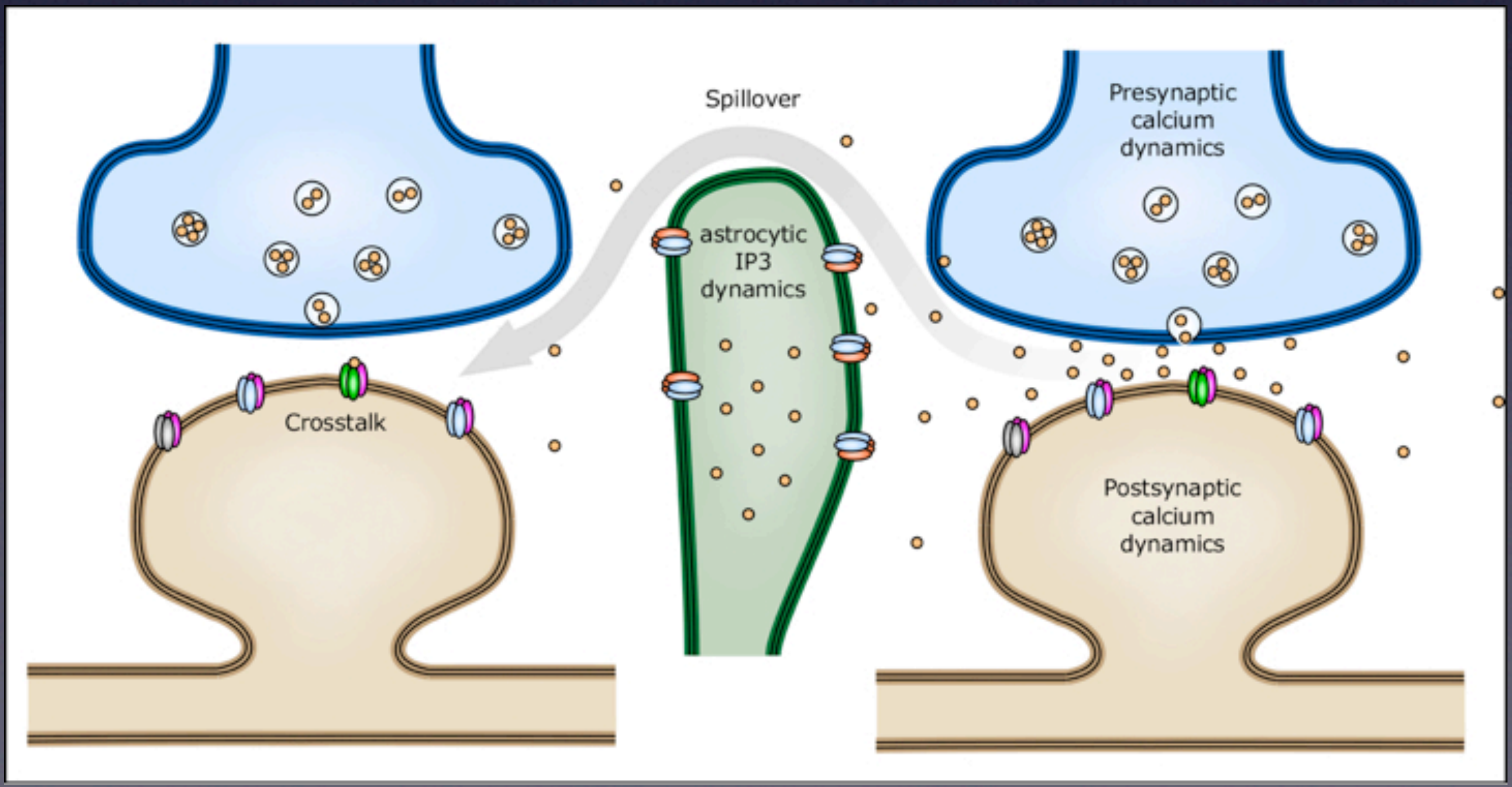
Motivation

How do synapses work?

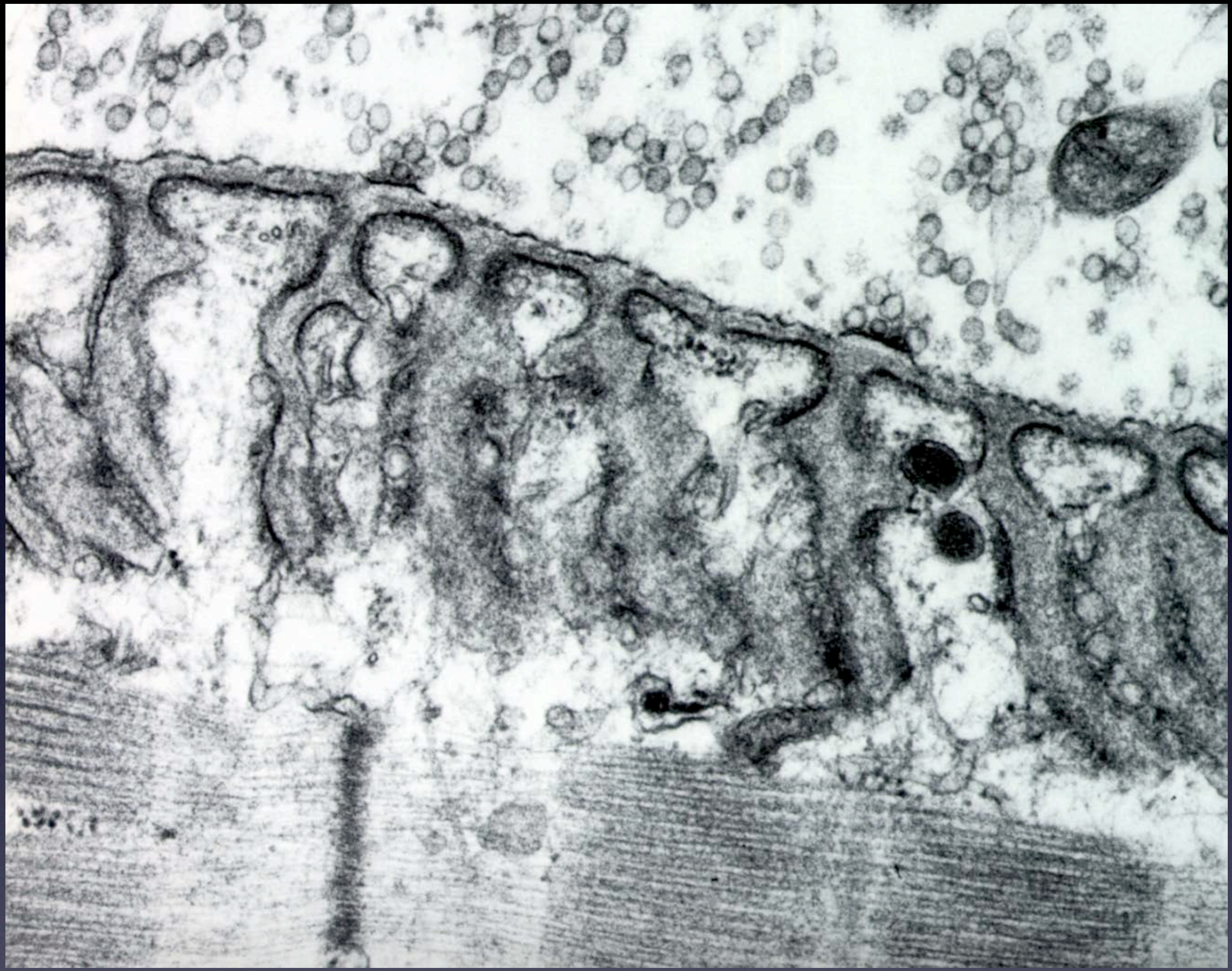
How does synaptic structure influence synaptic function?

- 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





Cells are Not Well Mixed Bags of Cytoplasm



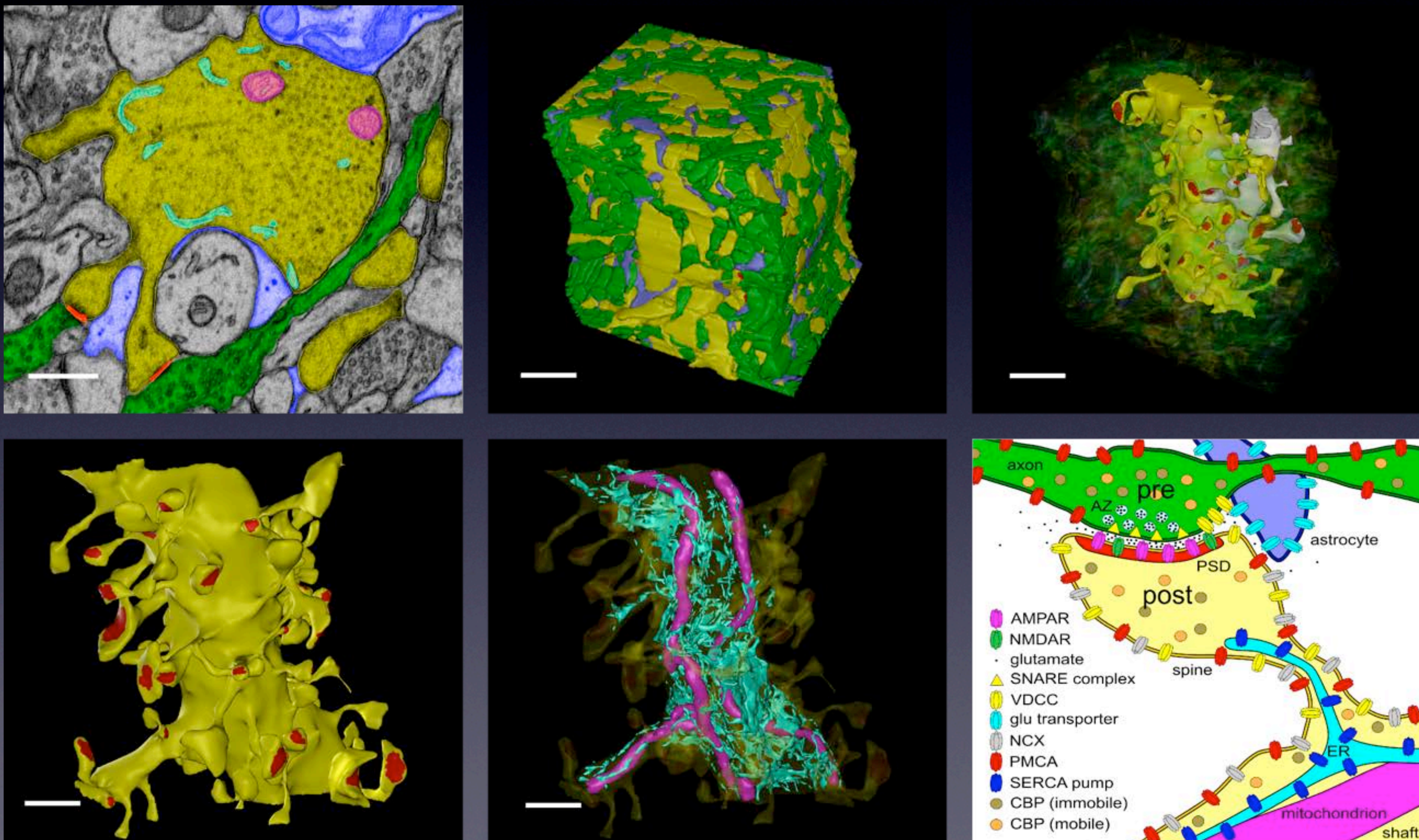
Biochemistry should be explored using 3D reaction/diffusion simulation to put reaction networks in their natural context.

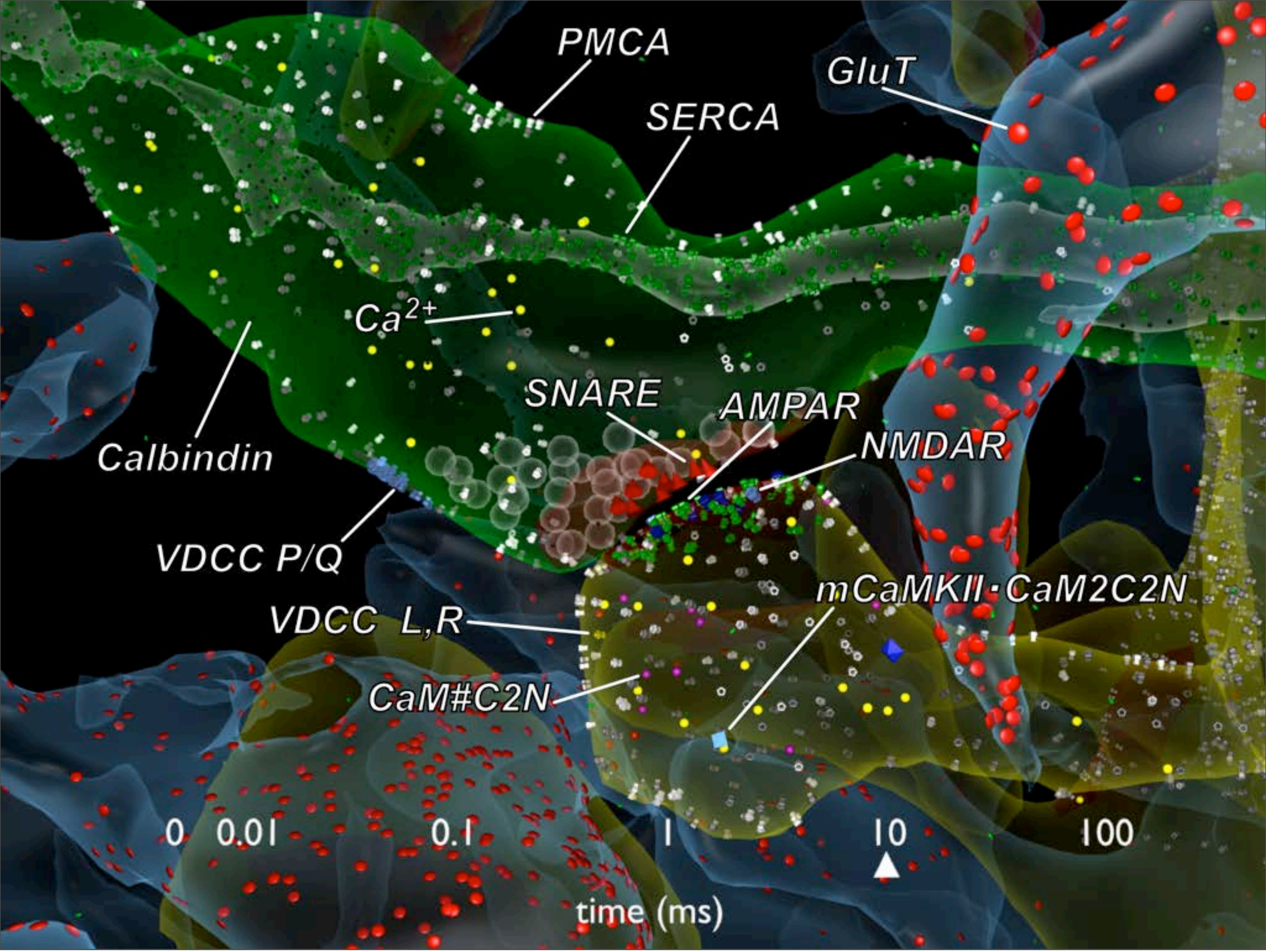
MCell: Monte Carlo Simulator of Cellular Microphysiology

- 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
- New model building, visualization and analysis environment -- CellBlender

Realistic Model of Synaptic Signaling in Neuropil

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




PMCA
GluT
SERCA
Ca2+
SNARE
AMPAR
NMDAR
Calbindin
VDCC P/Q
mCaMKII·CaM2C2N
VDCC L,R
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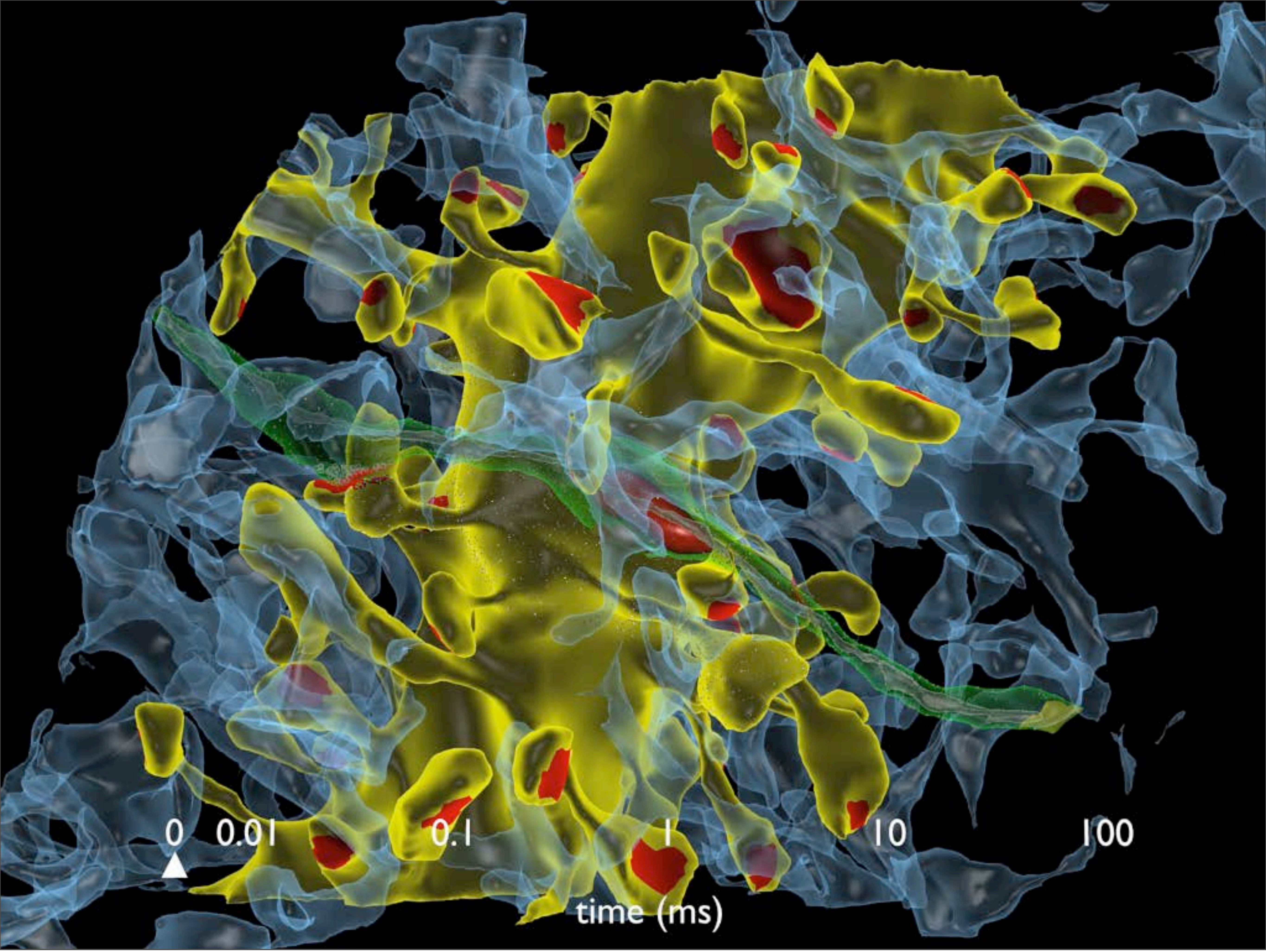
10
100
time (ms)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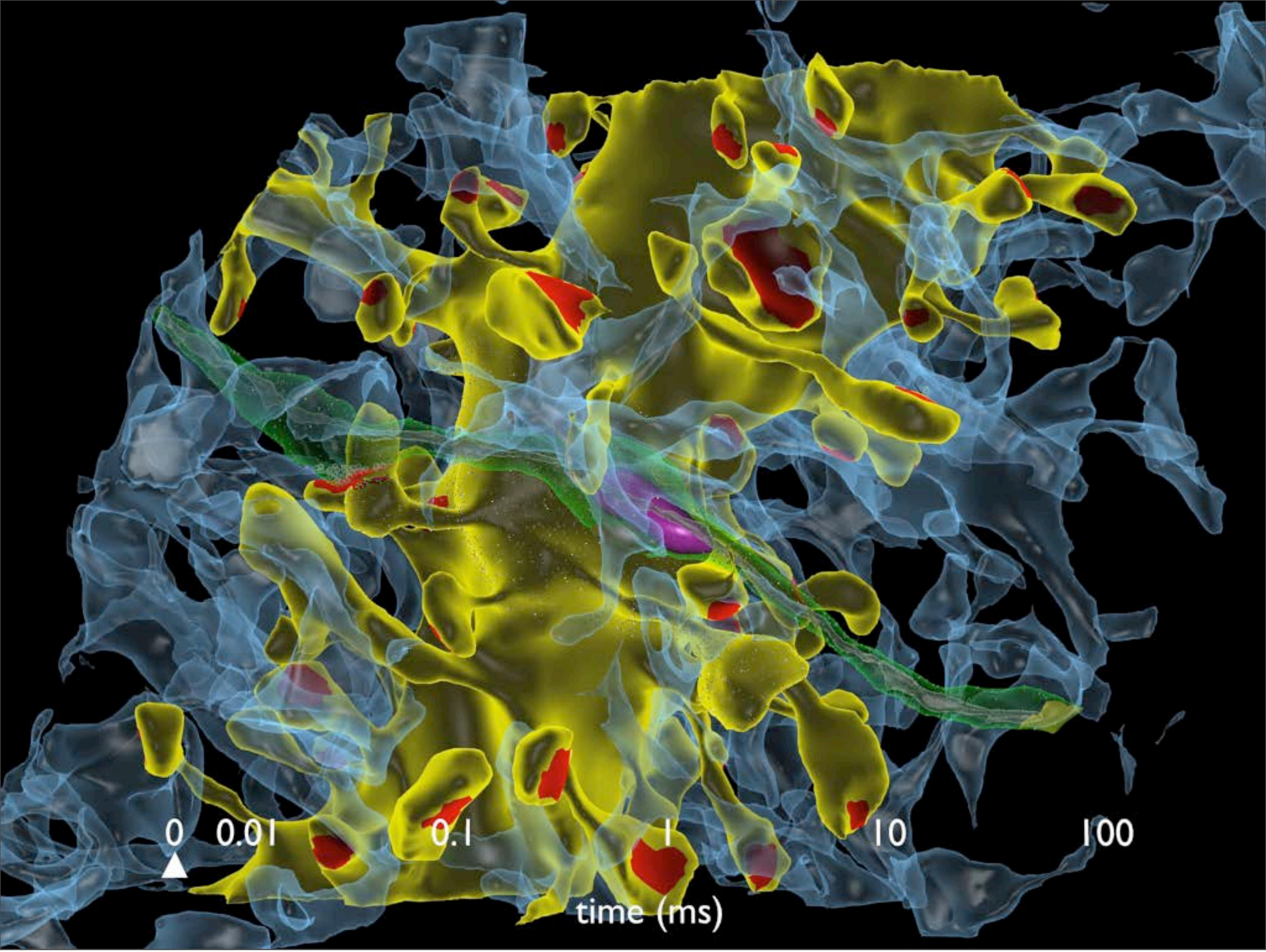
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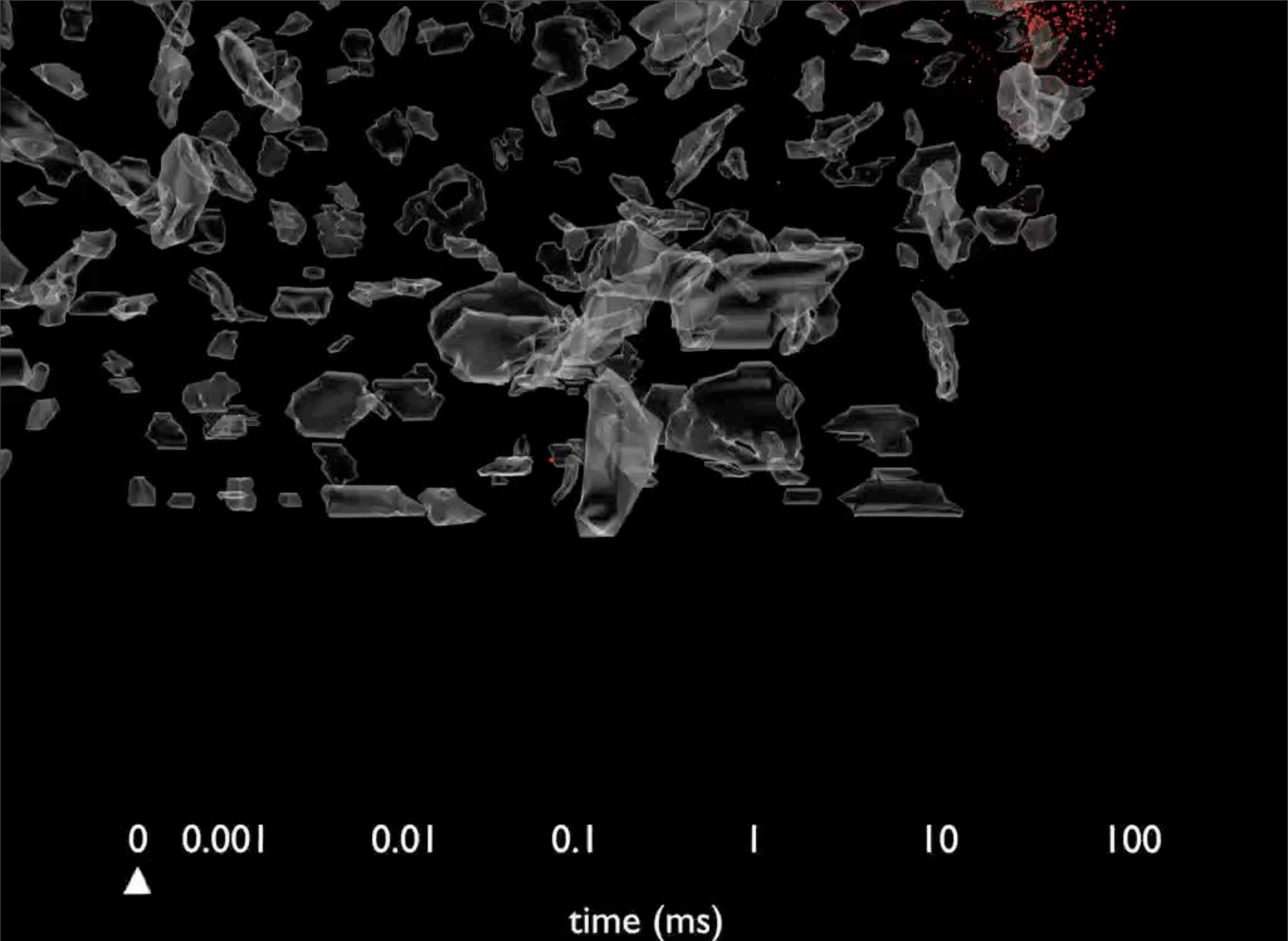

0 0.001 0.01 0.1 1 10 100
time (ms)

MMBioS National Center for Multiscale Modeling of Biological Systems

Our 5 year mission:

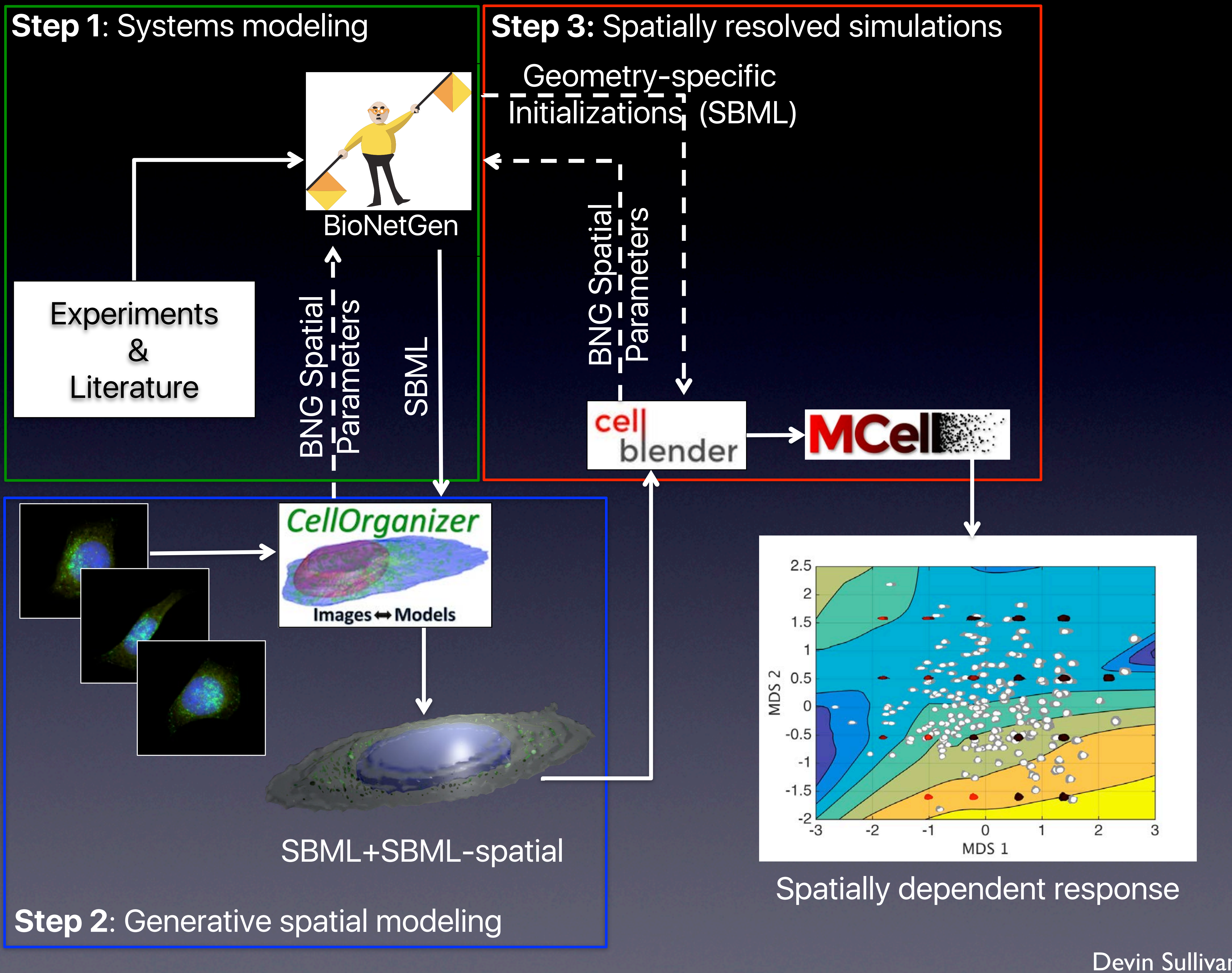
Technology Research and Development to link (at least) 3 Scales:

- 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)
- Tissue: Image processing and analysis, with an emphasis on analysis of cell and tissue organization in support of modeling (AlignTK, CellOrganizer)

Challenges in Spatially Realistic Cell Modeling

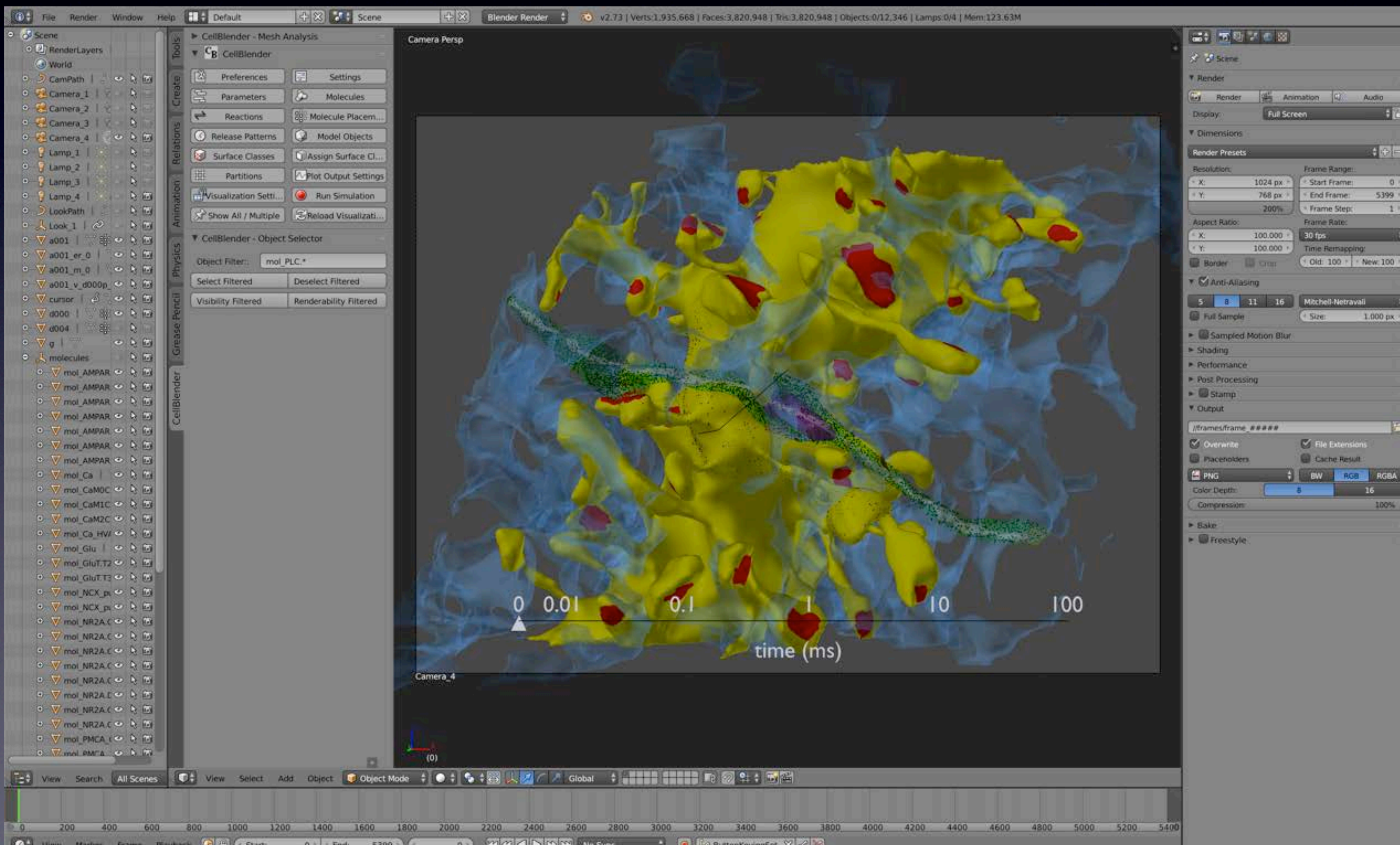
- Creation of computational quality 3D models is too hard
- Managing the complexity of reaction pathways is too hard
- Managing simulations, data, analysis, and visualization in high-dimensional parameter space is too hard

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


Step 1: Systems modeling
Step 3: Spatially resolved simulations
Geometry-specific
Initializations (SBML)
BioNetGen
BNG Spatial Parameters
SBML
Experiments & Literature
BNG Spatial Parameters
cell blender
MCell
CellOrganizer
Images ⟺ Models
SBML+SBML-spatial
Step 2: Generative spatial modeling
MDS 2
MDS 1
Spatially dependent response
Devin Sullivan

CellBlender Addon for Blender

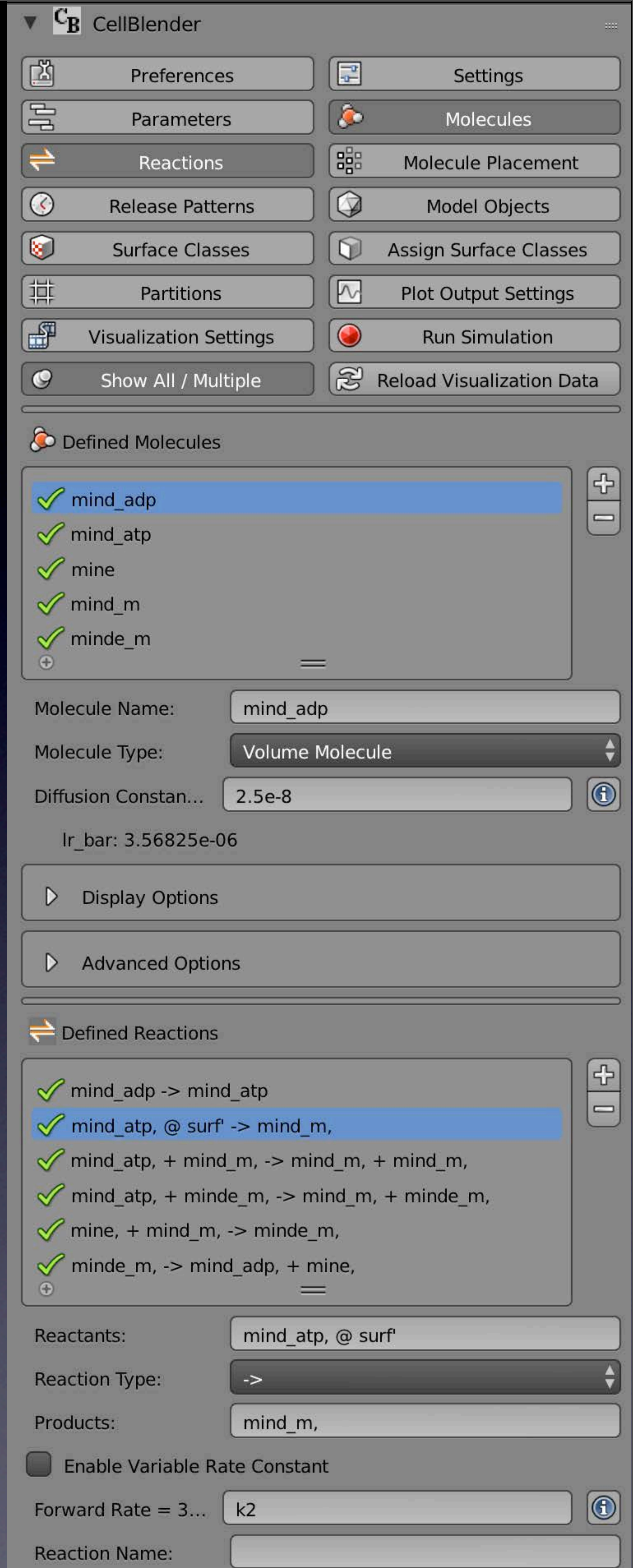
- A complete IDE for realistic reaction-diffusion modeling
- MCell acts as external Physics Engine for data-driven visualization
- We envision/hope that others in community will plugin as well



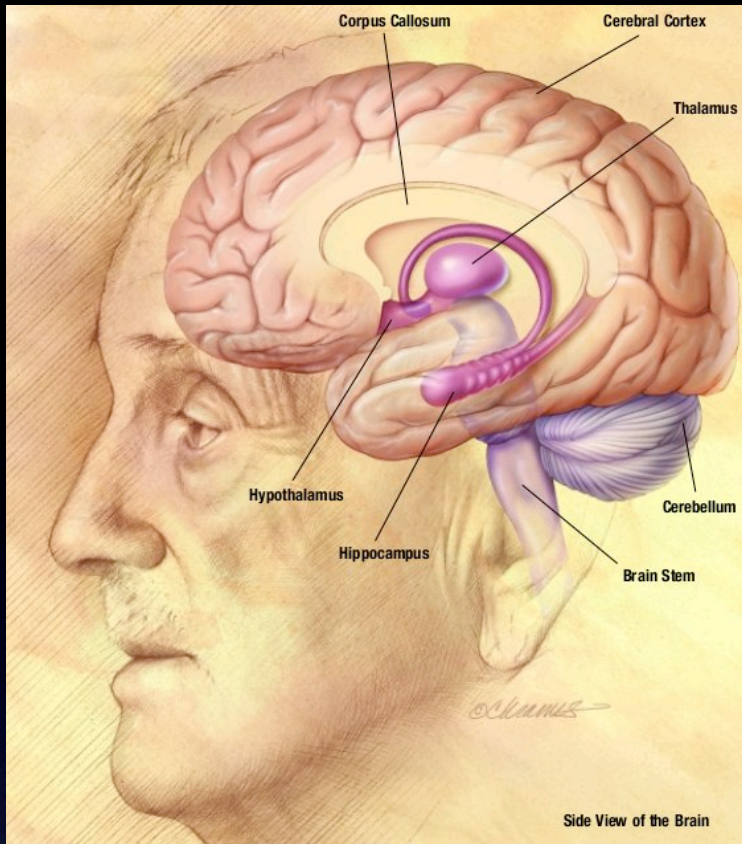
CellBlender Capabilities

All of Blender's features plus:

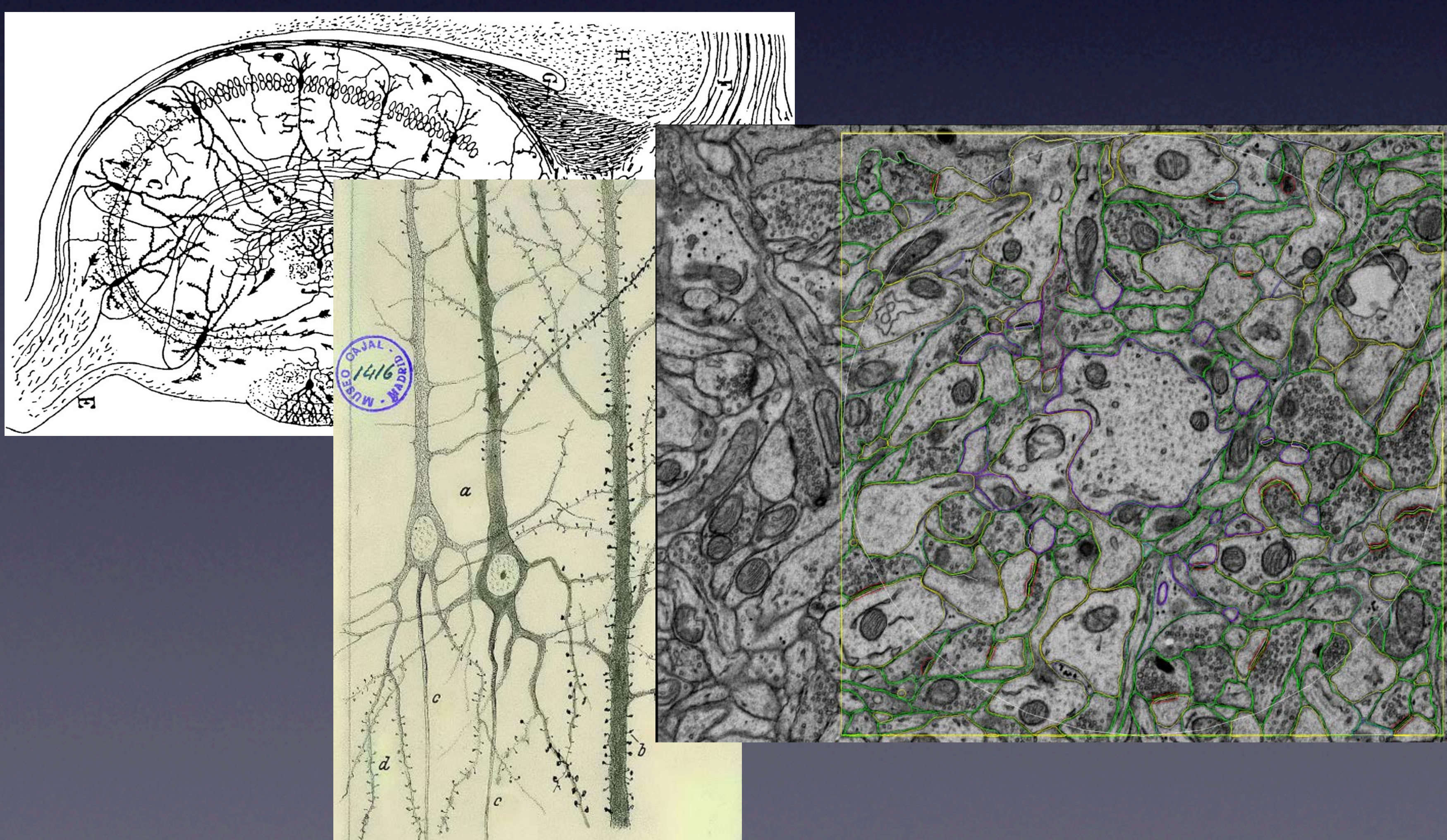
- Model Specification
  - model parameters
  - molecules
  - reactions
  - output options
  - visualization options
  - run-time options
- Import geometry from many sources:
  - CellOrganizer
  - VolRoverN
- Import whole models from:
  - SBML Spatial
  - CellOrganizer as SBML Spatial
  - BioNetGen as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

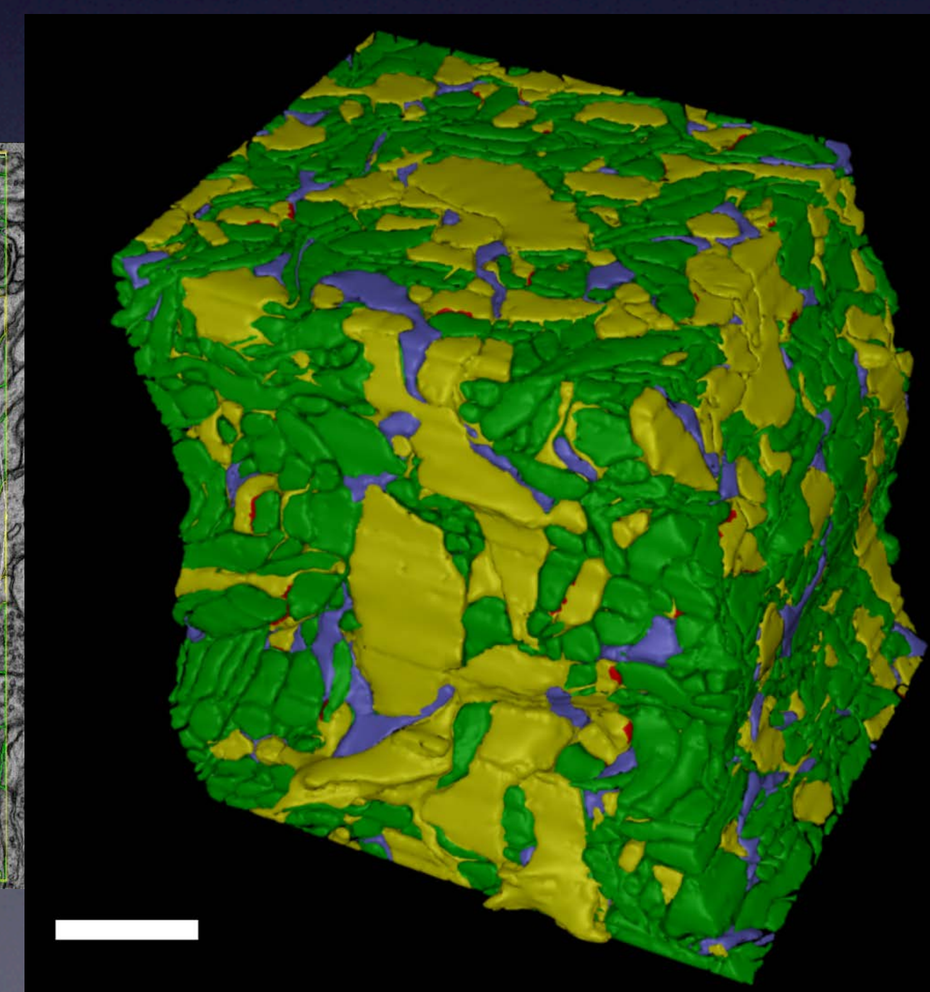


Let's Build the Model: Model Constraints



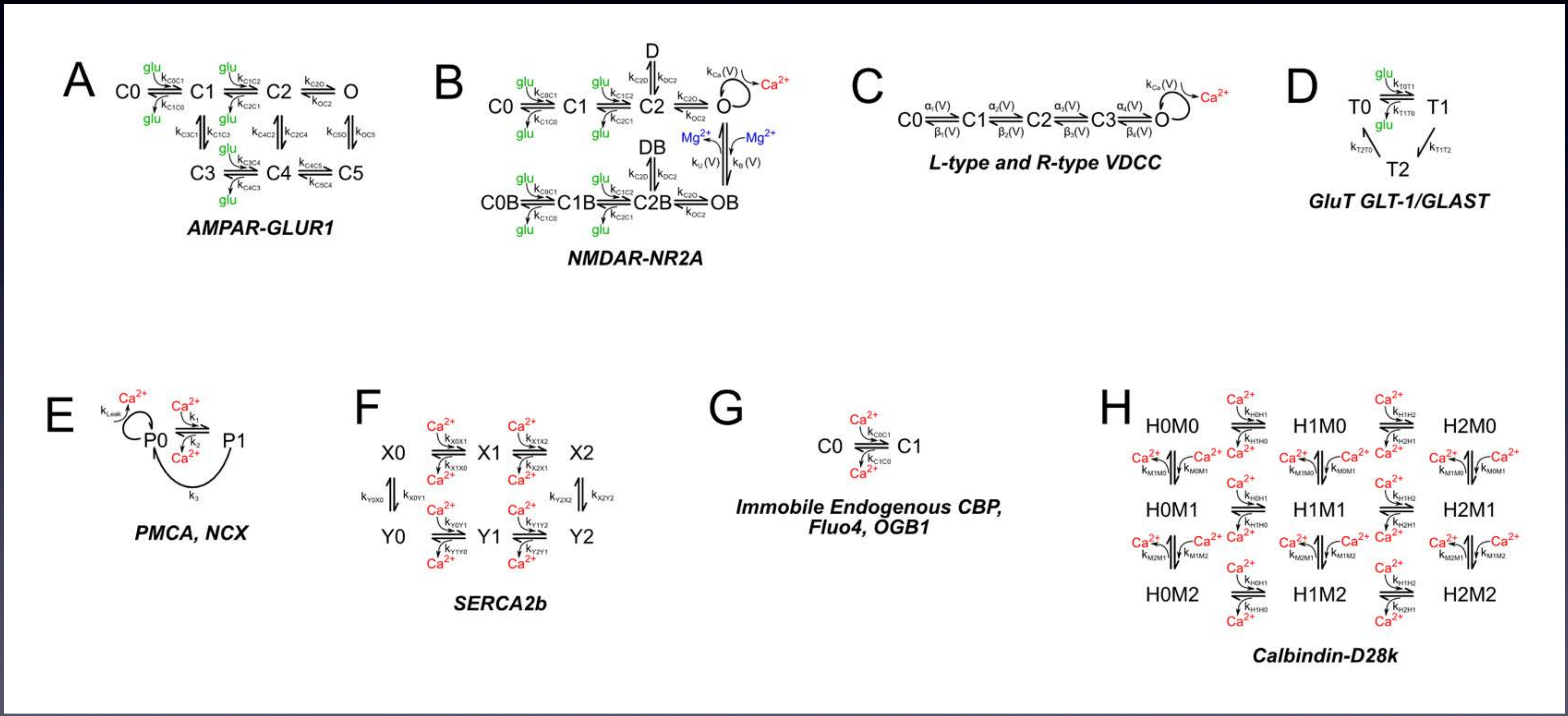
Realistic synaptic morphology from ssTEM reconstruction of hippocampal neuropil (collaboration with Kristen Harris, UT Austin)





Model Constraints

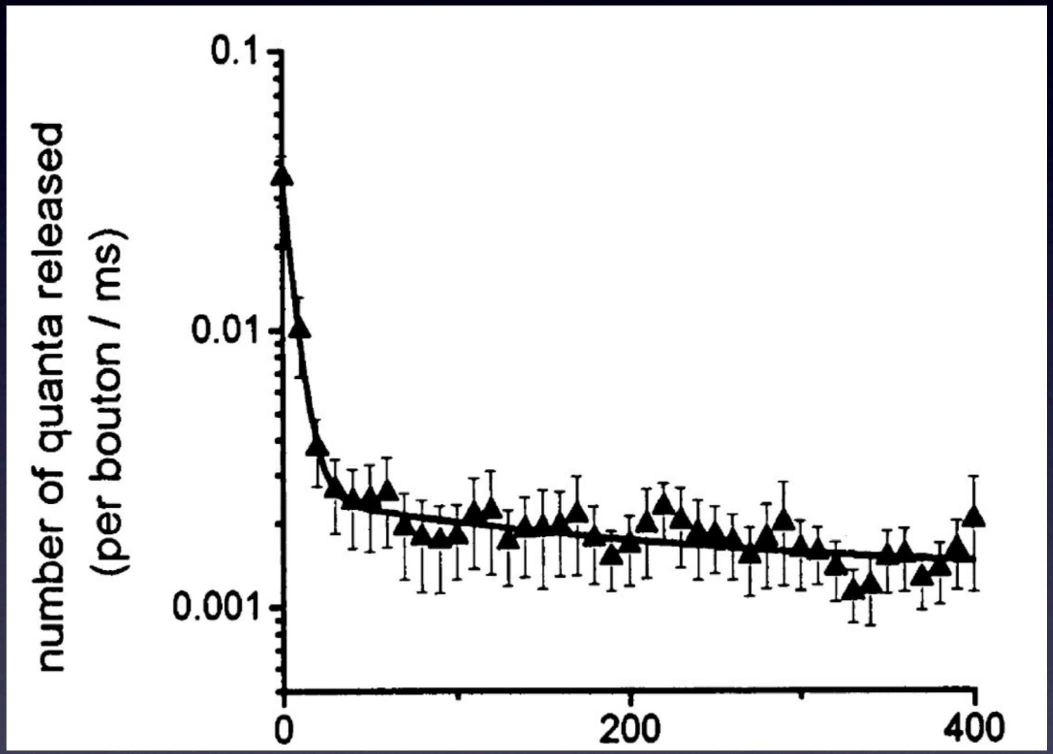
Experimental estimates of reaction kinetics and subcellular distributions for important molecules



Model Constraints

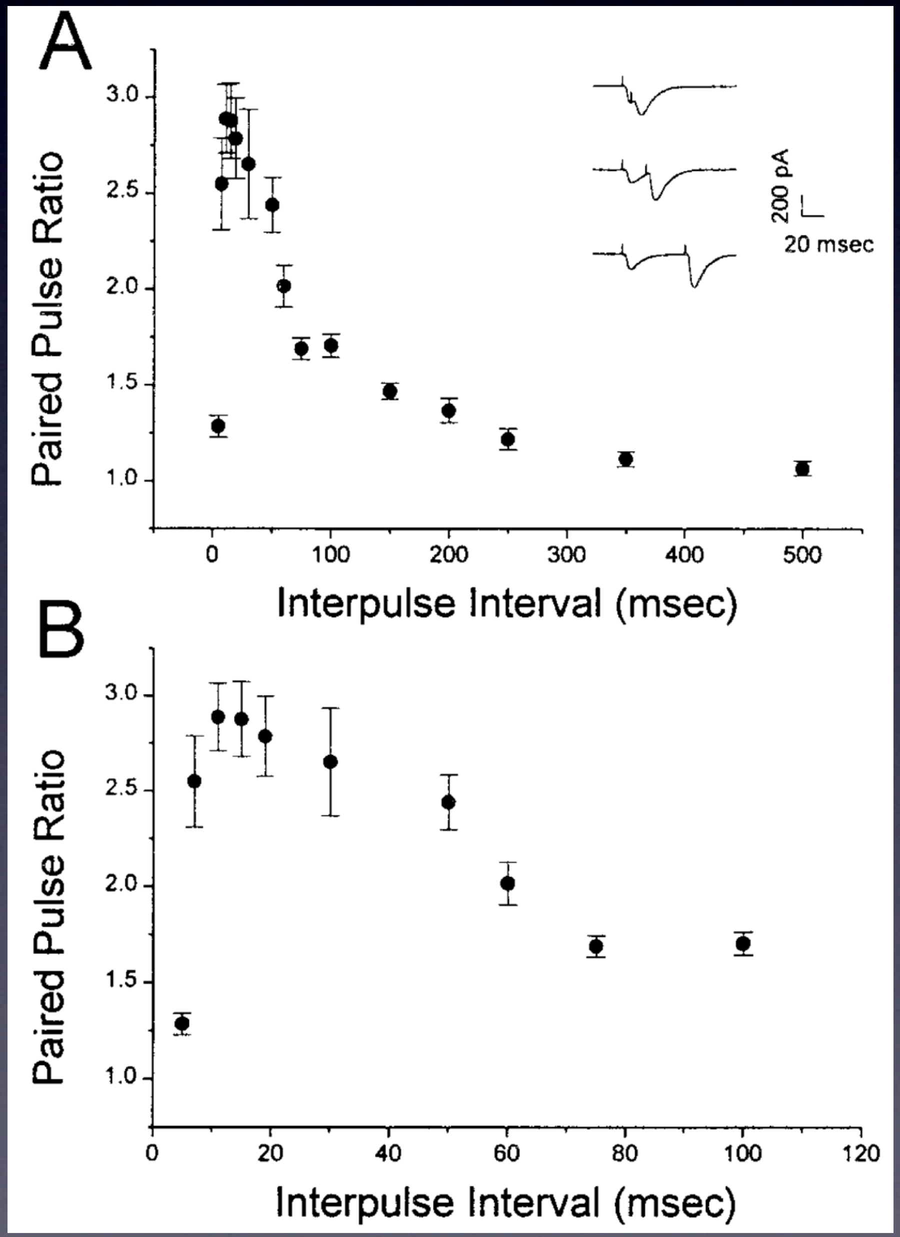
Experimental observations of evoked vesicular release:

single stimulus



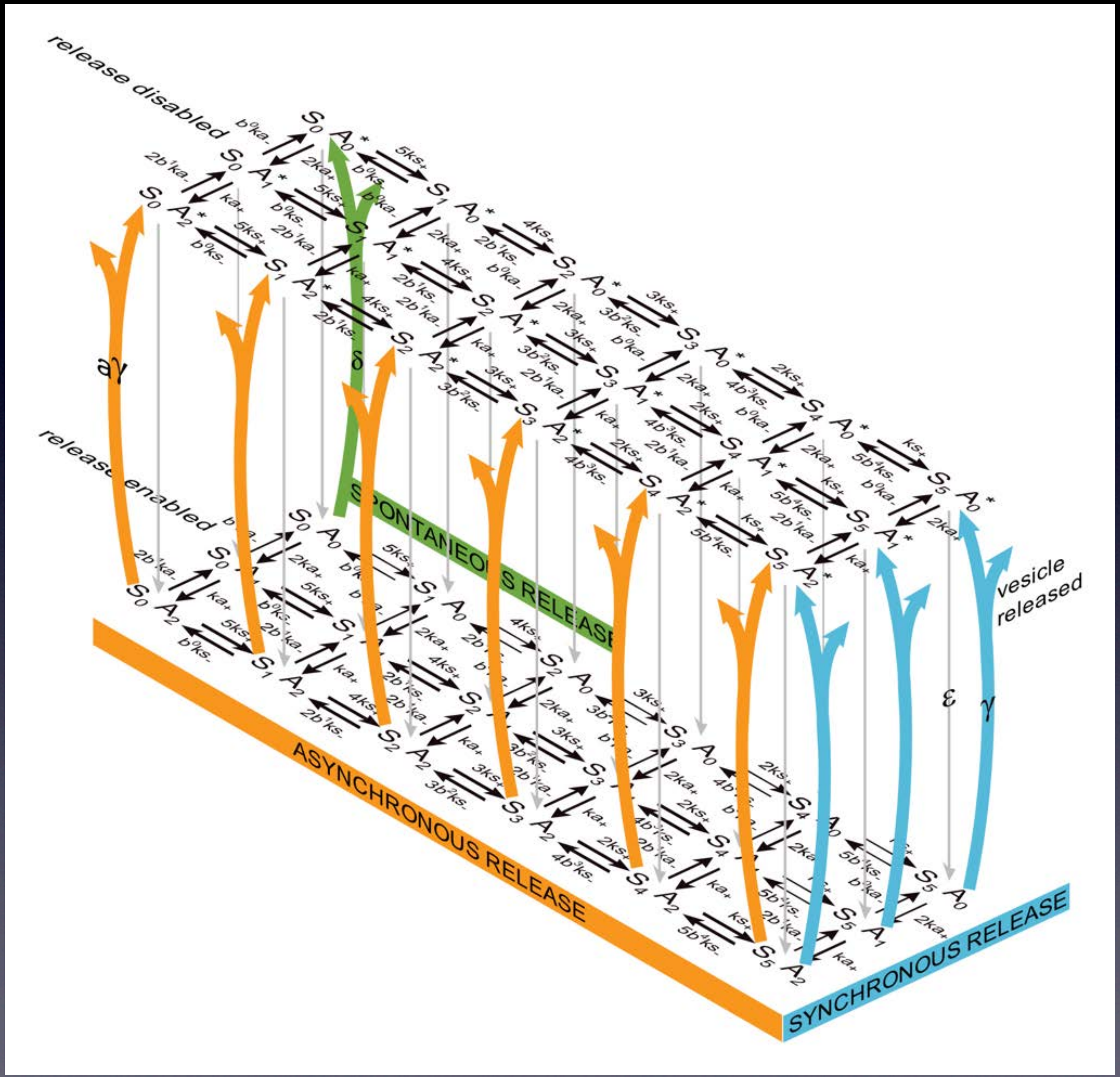
Goda & Stevens, PNAS, 1994

paired-pulse stimulus



Dobrunz, Huang & Stevens, PNAS, 1997

Model Constraint: kinetics of calcium sensor in SNARE complex



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

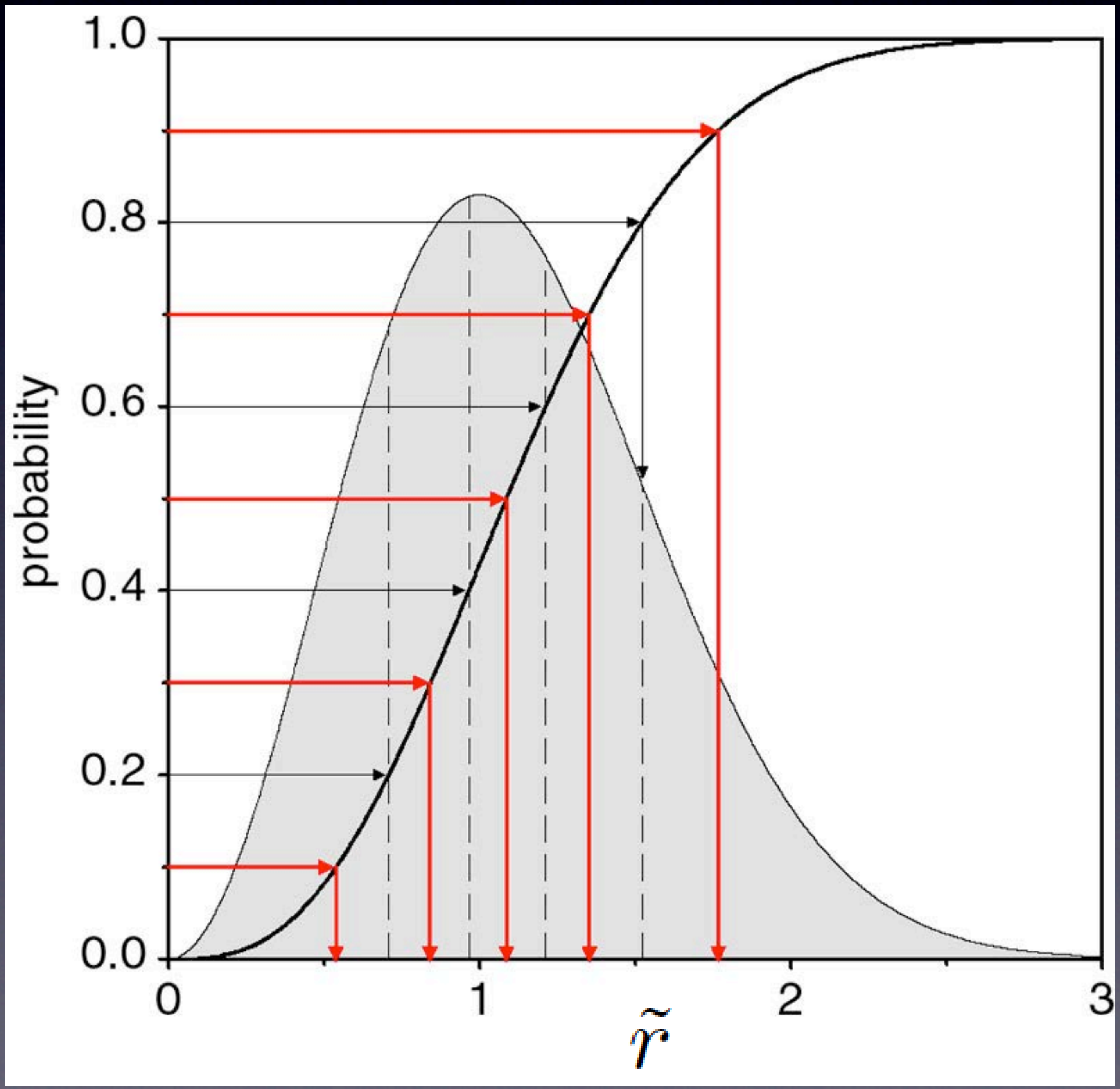
Applies when concentration in volume is changing in time (i.e. $J_{in} \neq J_{out}$)

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

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

Free Diffusion: Concentration in Space and Time

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



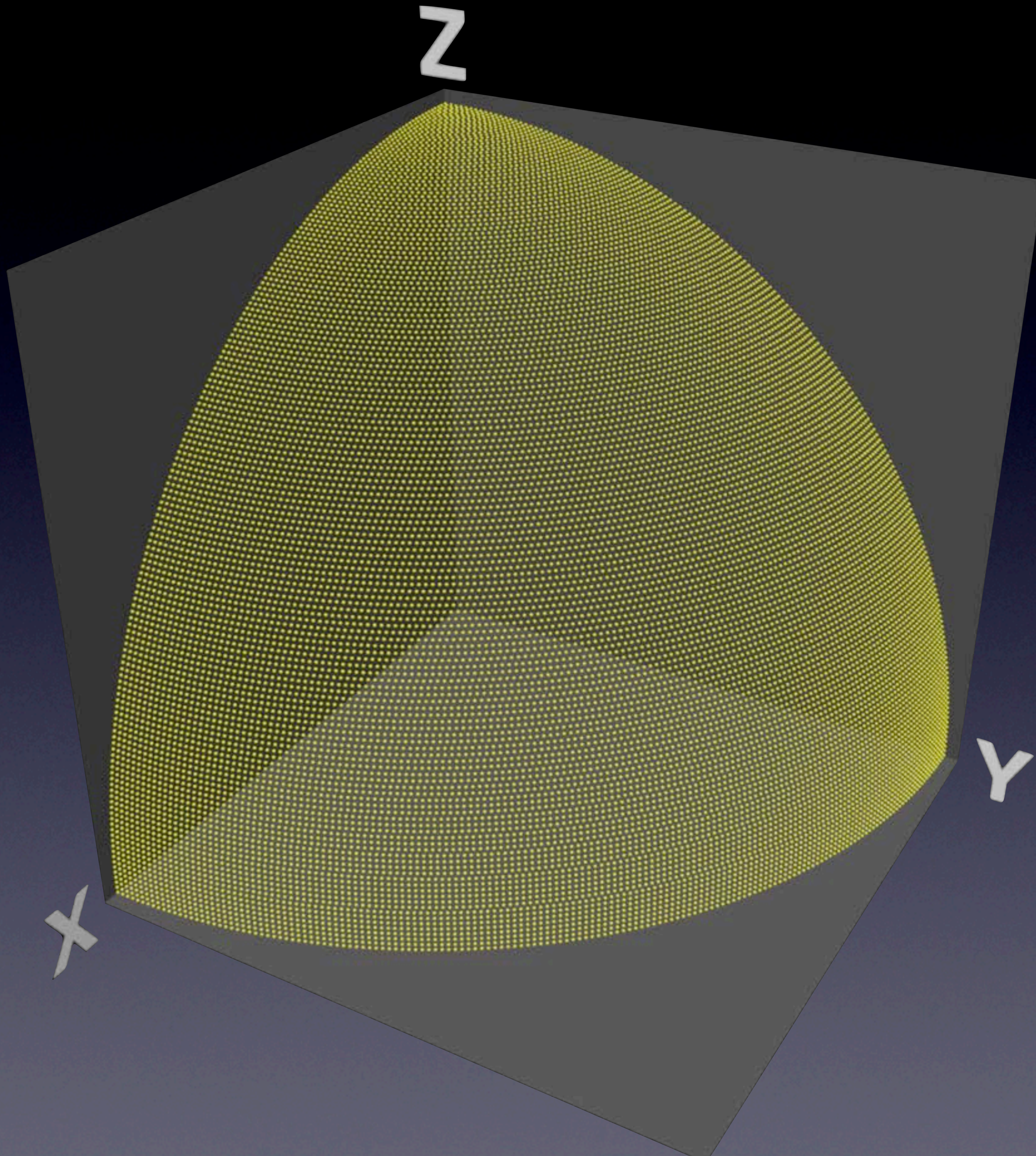
$$\lambda = \sqrt{4Dt}$$

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

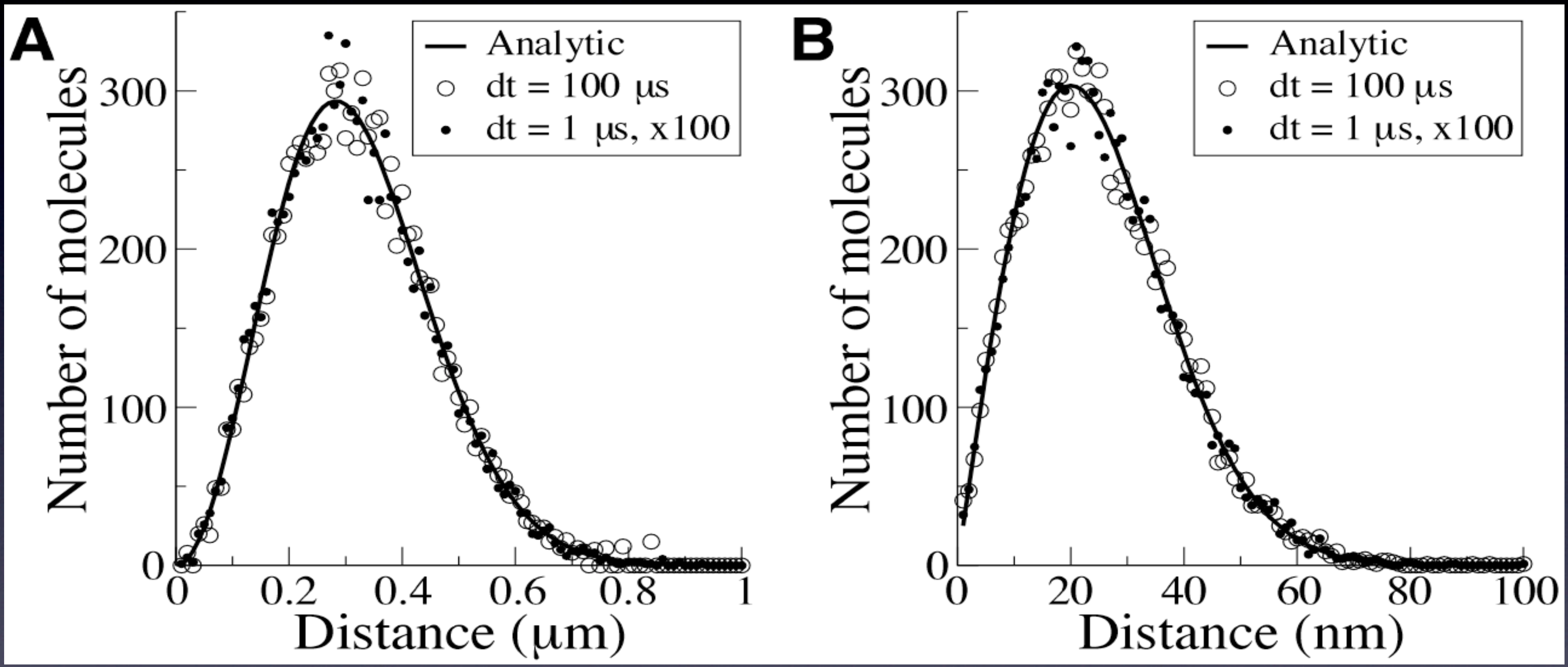
$$\bar{l}_r = 2\sqrt{\frac{4D\Delta t}{\pi}}$$

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

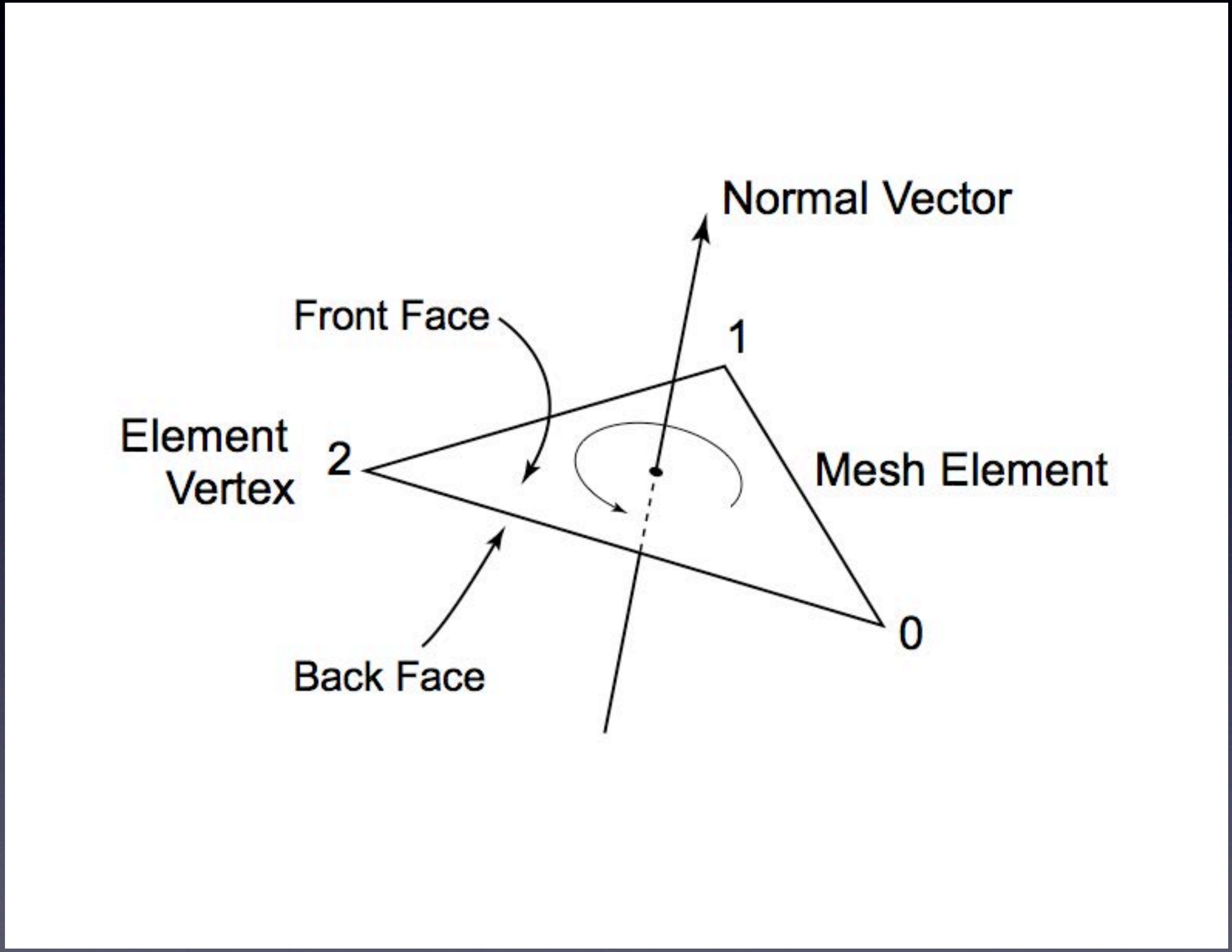
Diffusion: Random Directions



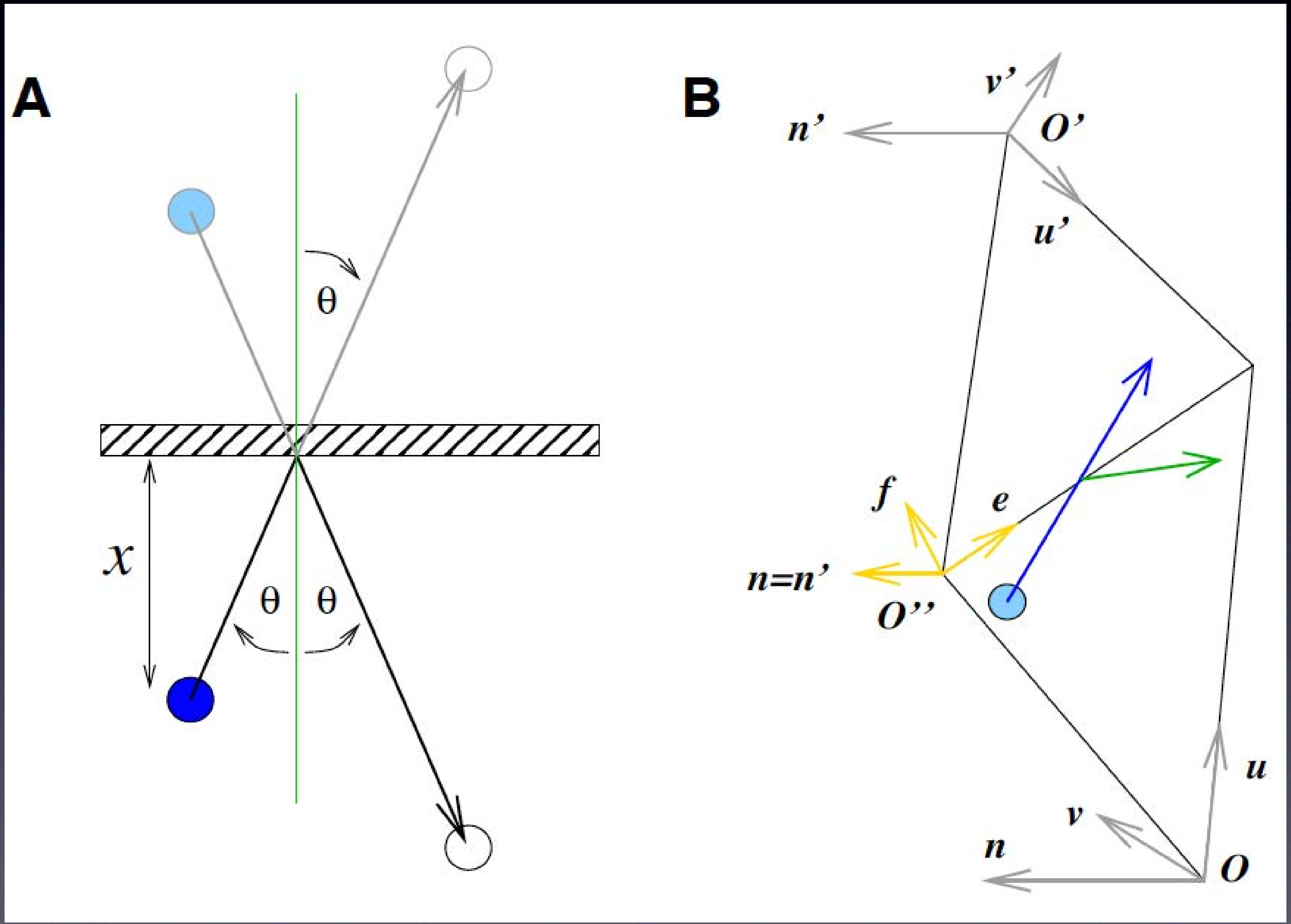
Grid-Free Random Walk Diffusion



Surface Mesh Representation



Diffusion with Boundaries



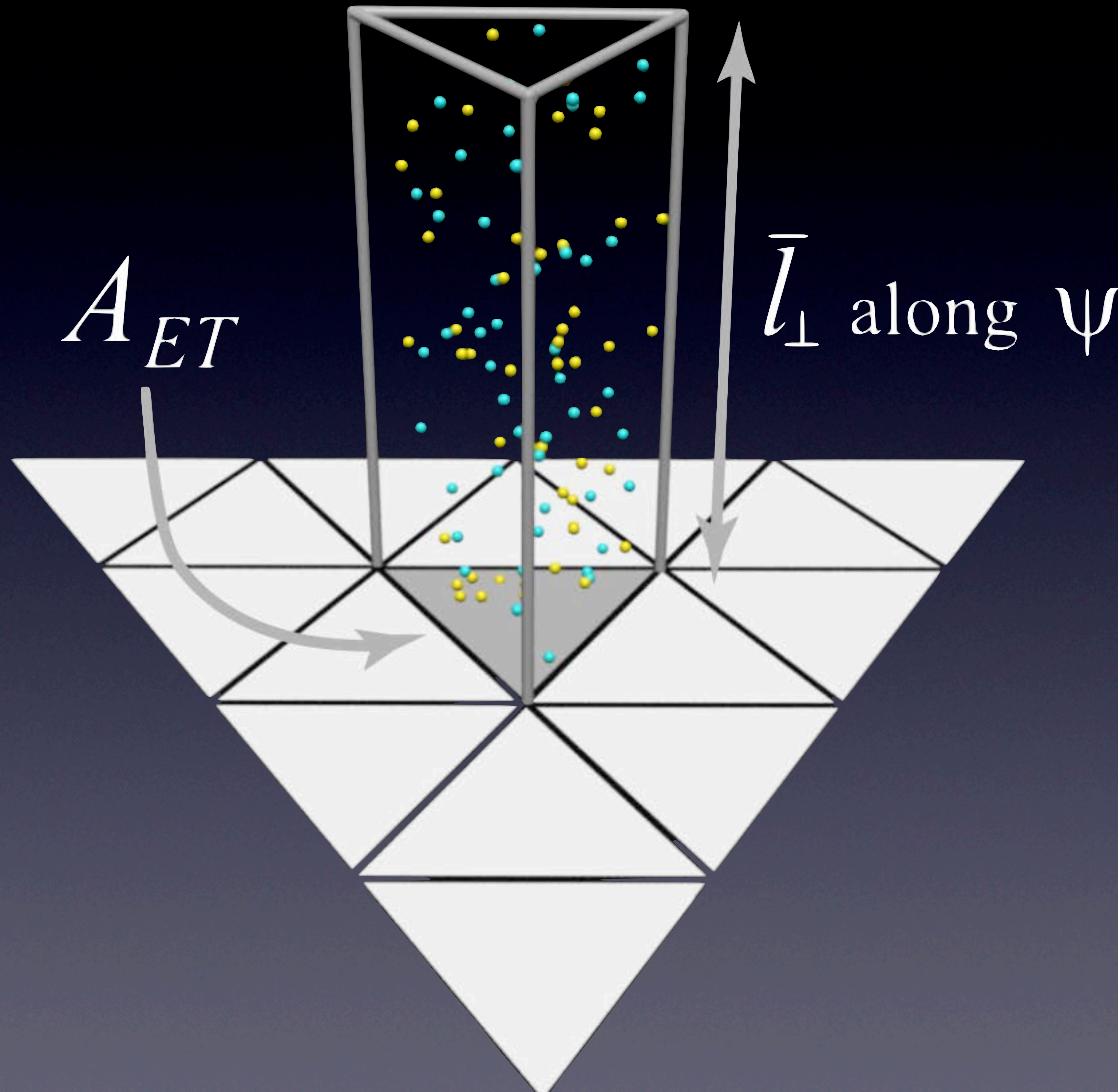
Unimolecular Reactions

$$A \xrightarrow{k} B$$

Distribution of first-order decay lifetimes is:

$$\rho(t) = \frac{1}{k} e^{-kt}$$

Bimolecular Reactions: Rate of Encounter



Bimolecular Reactions: Volume/Surface

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

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

From rate of encounter:

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

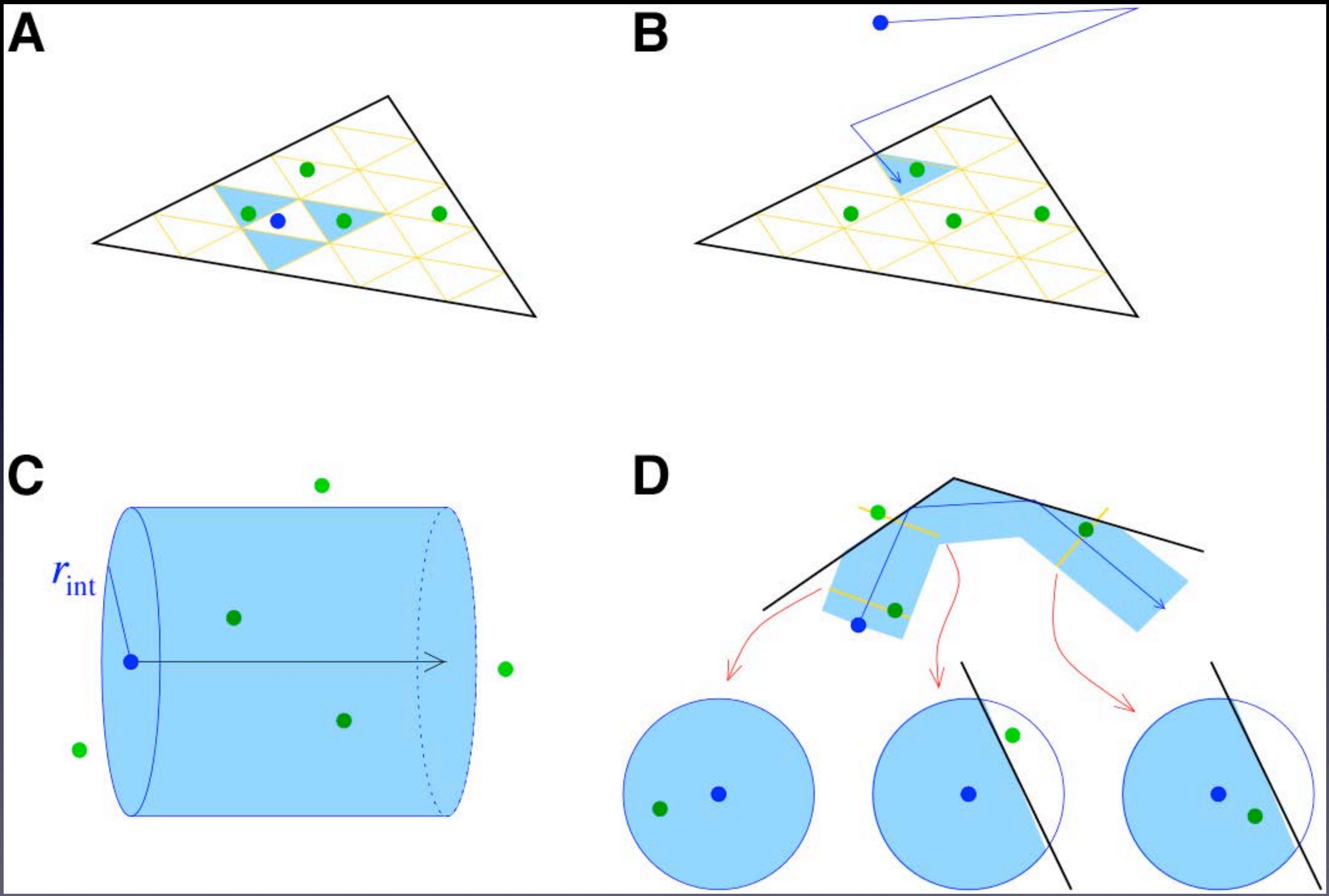
$$N_H = N_A \bar{l}_\perp A_{ET} [A]_o$$

From Mass Action:

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

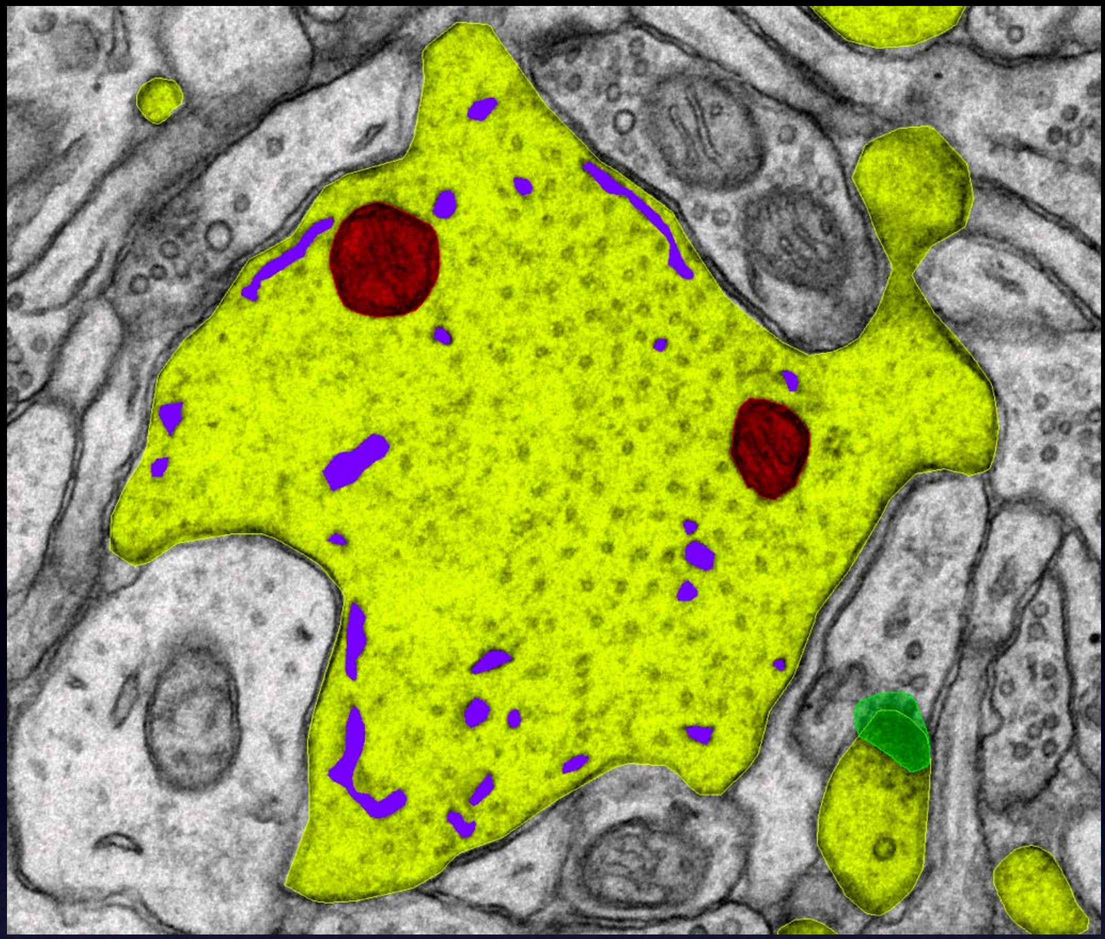
$$p_b = \frac{k}{N_A A_{ET}} \sqrt{\frac{\pi \Delta t}{D}}$$

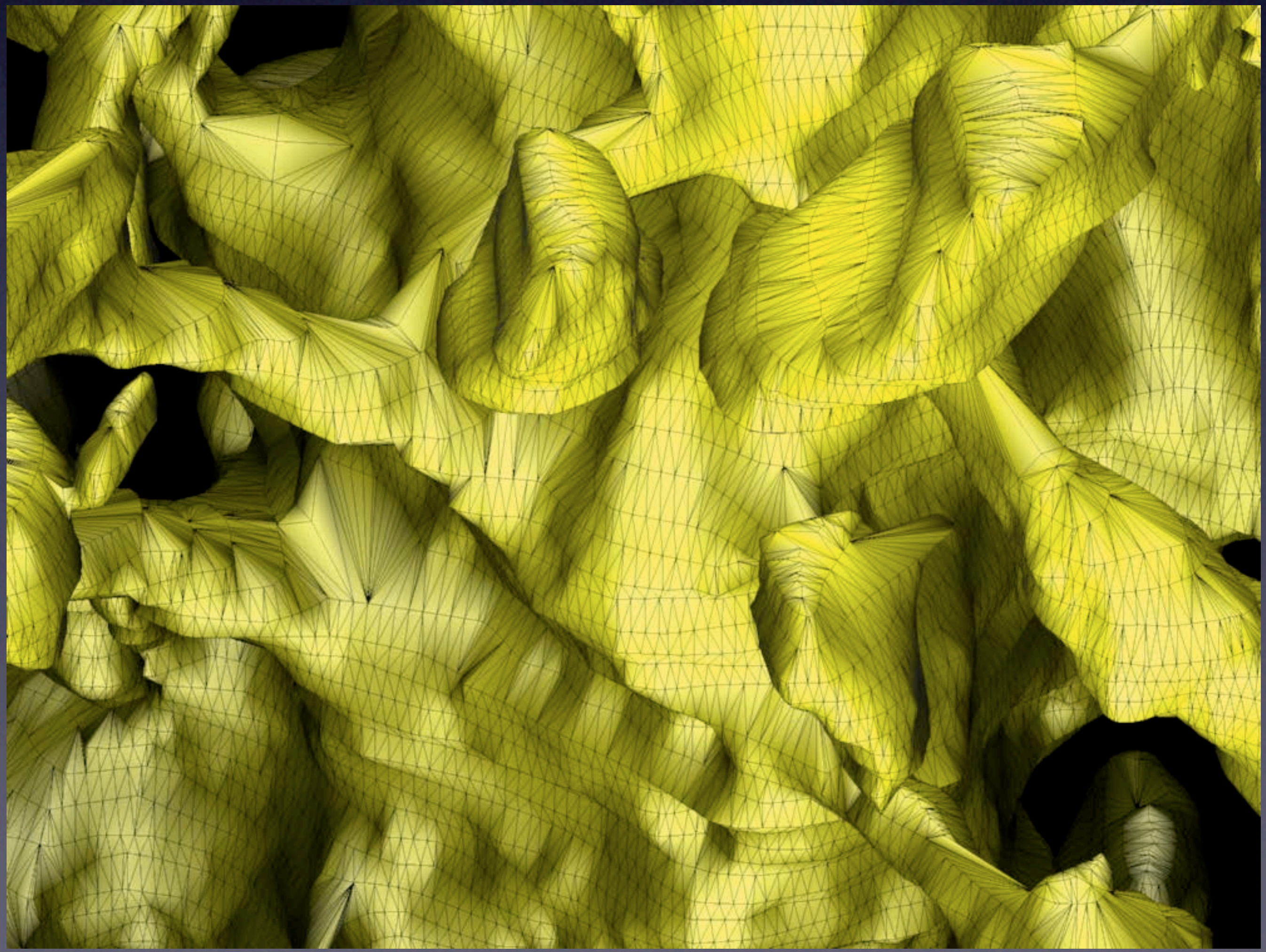
Bimolecular Reactions: Collision Detection

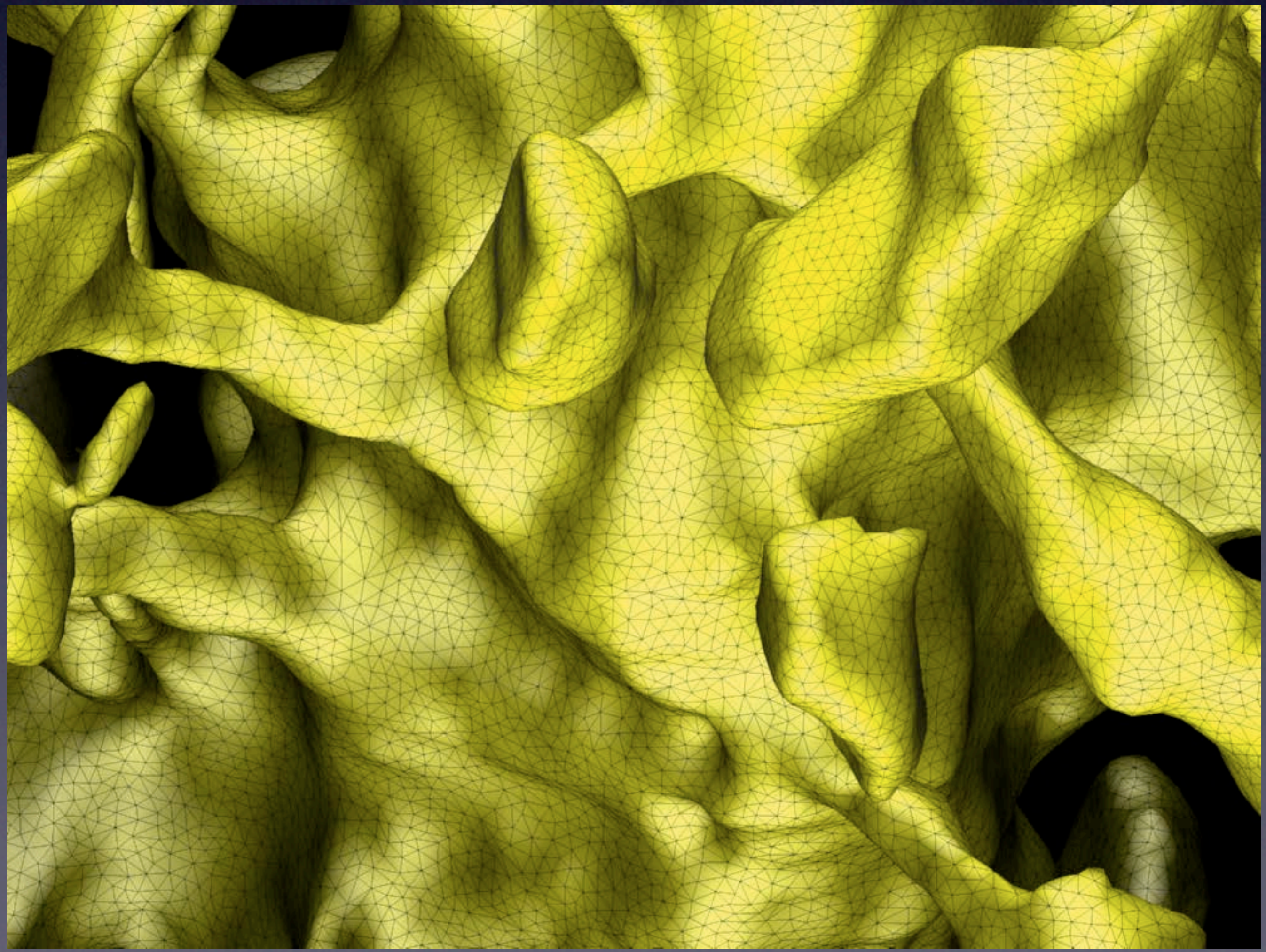


Segmentation, Mesh Generation, and Mesh Improvement

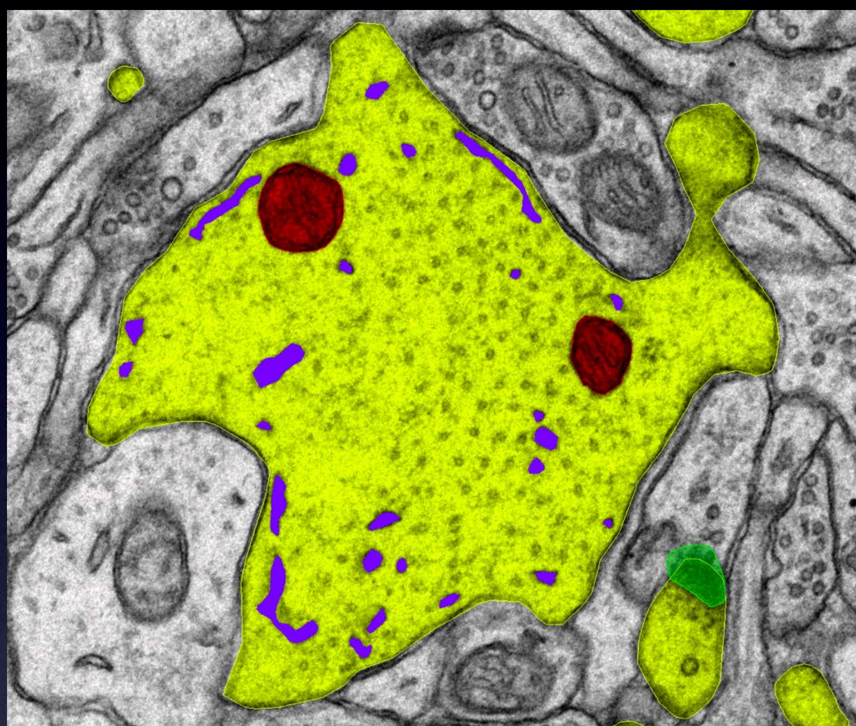
- RECONSTRUCT
- VolRoverN
- GAMer

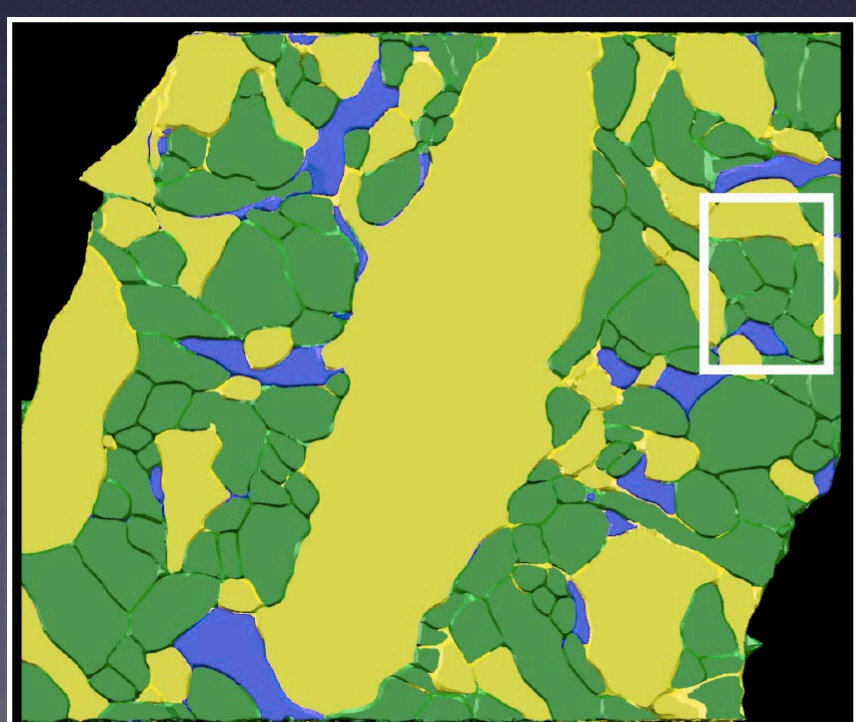


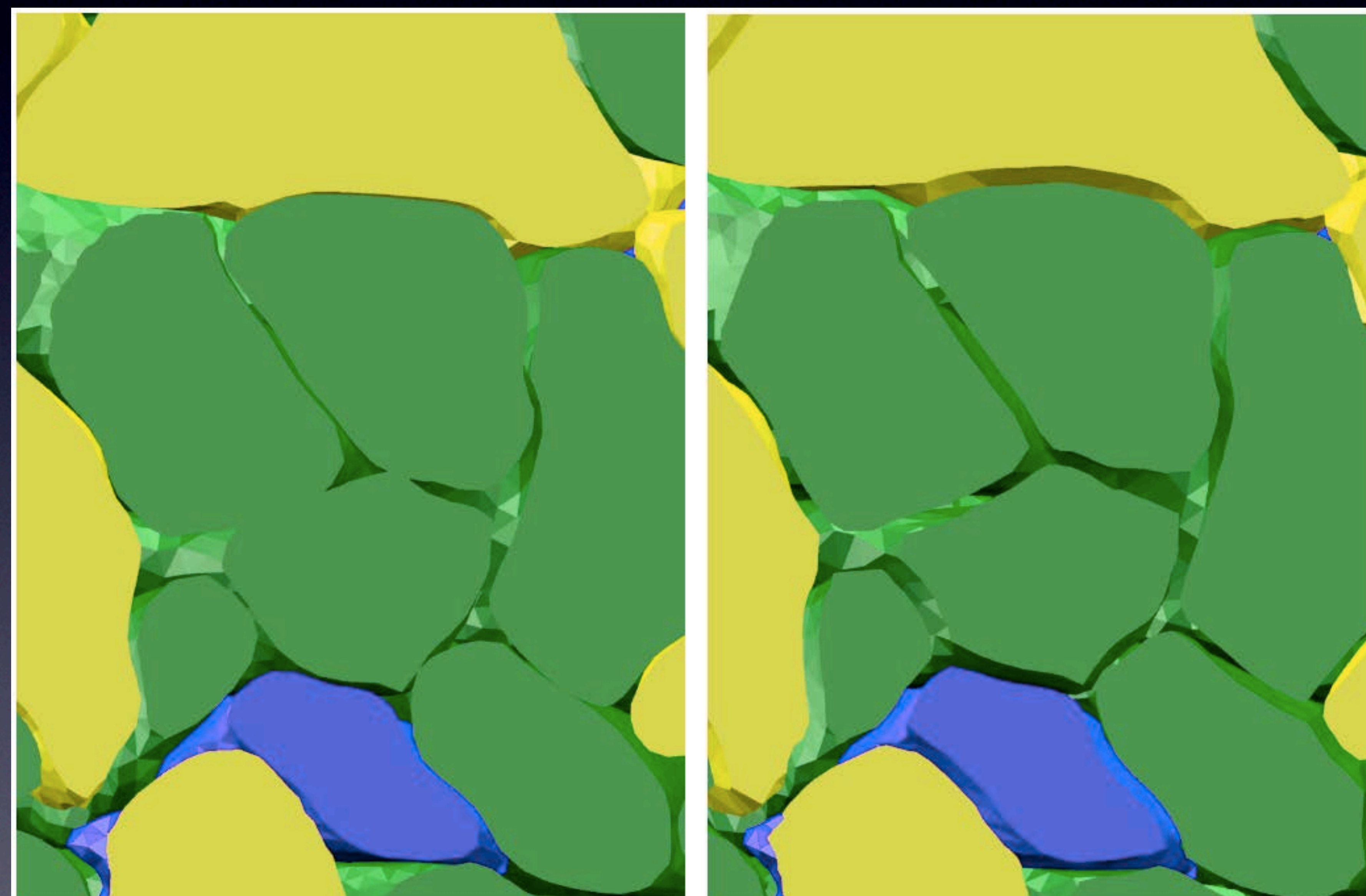




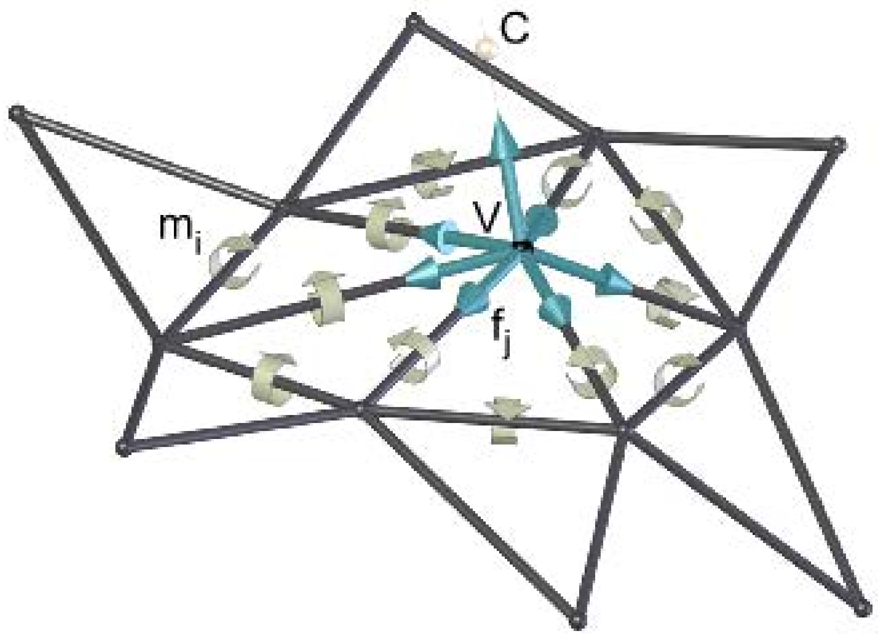
Mesh Improvement

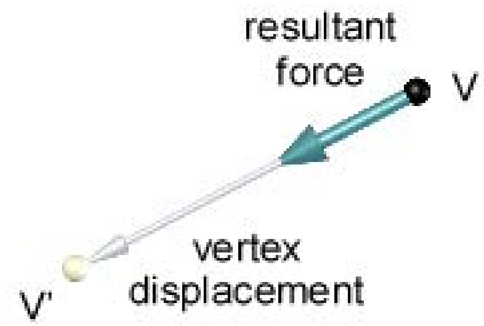


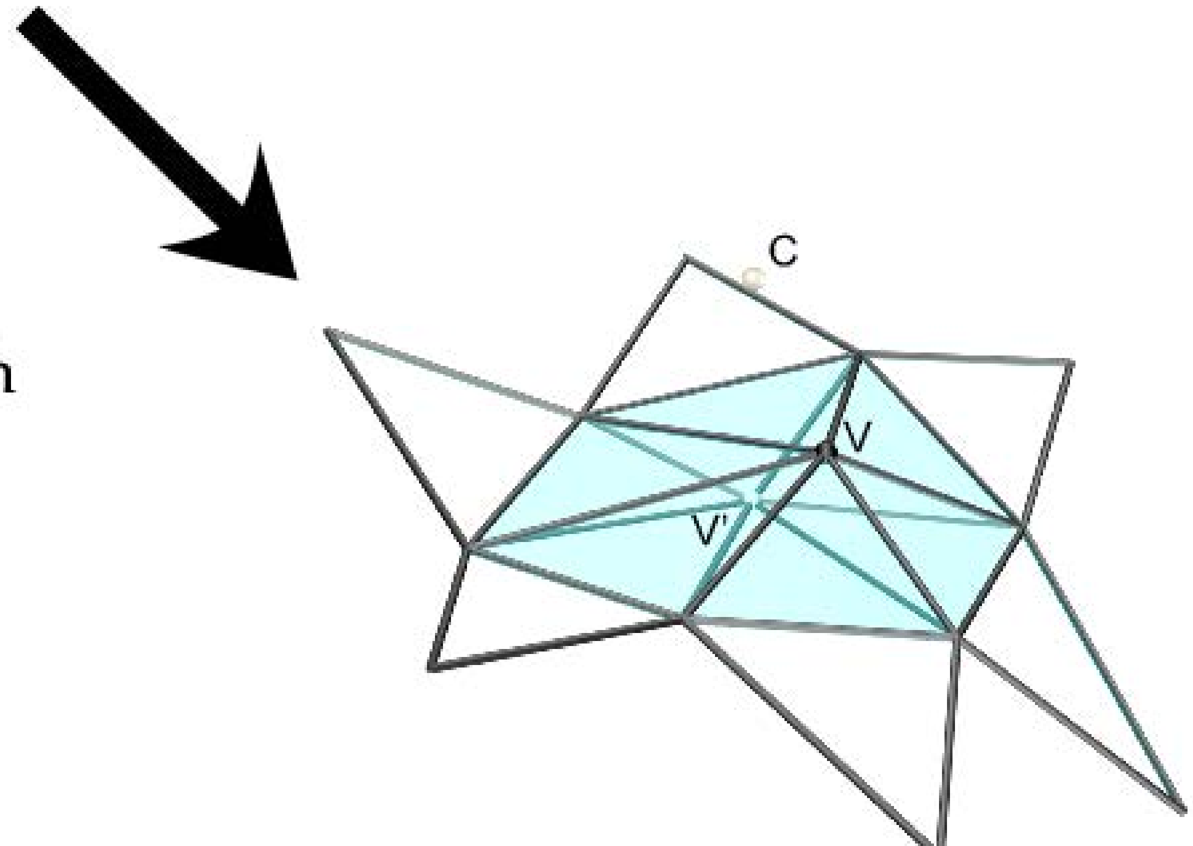




Controlling extracellular space







Assumption

- uniform extracellular width

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

Future Directions

- Advanced simulation control
  - parameter sweep
  - parameter fitting/optimization/estimation
- Integration/coupling of other Physics Engines
  - Cytomechanics
  - 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 -- Blue Brain Project +++

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