Simulation of Geometrically Accurate, Multibillion Atom Cellular Membrane Structures

Experimental Mesh   Atomistic Model
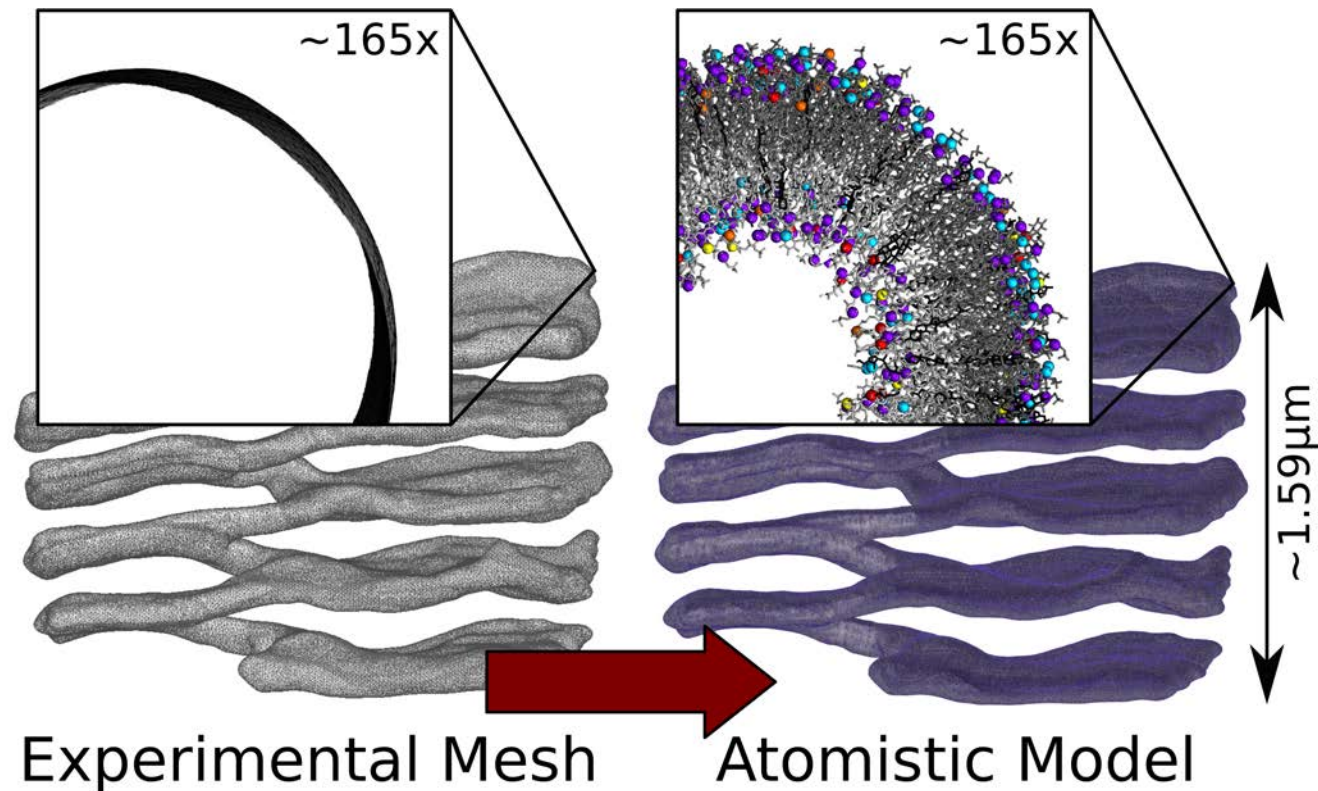
Noah Trebesch[1,2,3] and Emad Tajkhorshid[1,2,3,4]

[1]Center for Biophysics and Quantitative Biology
[2]NIH Center for Macromolecular Modeling and Bioinformatics
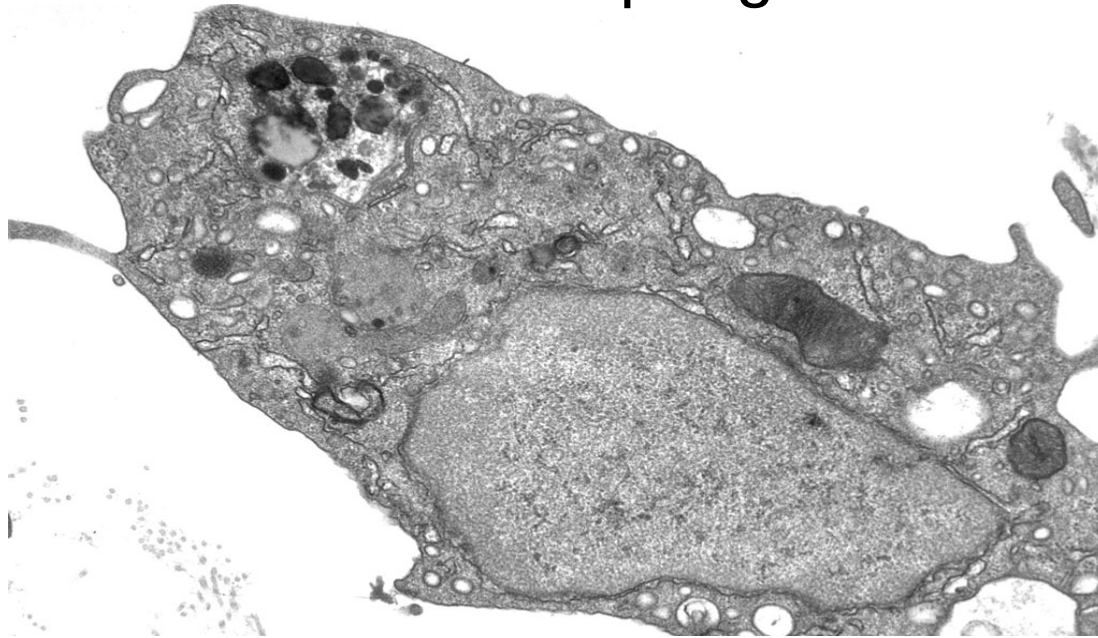[3]Beckman Institute for Advanced Science and Technology
[4]Department of Biochemistry

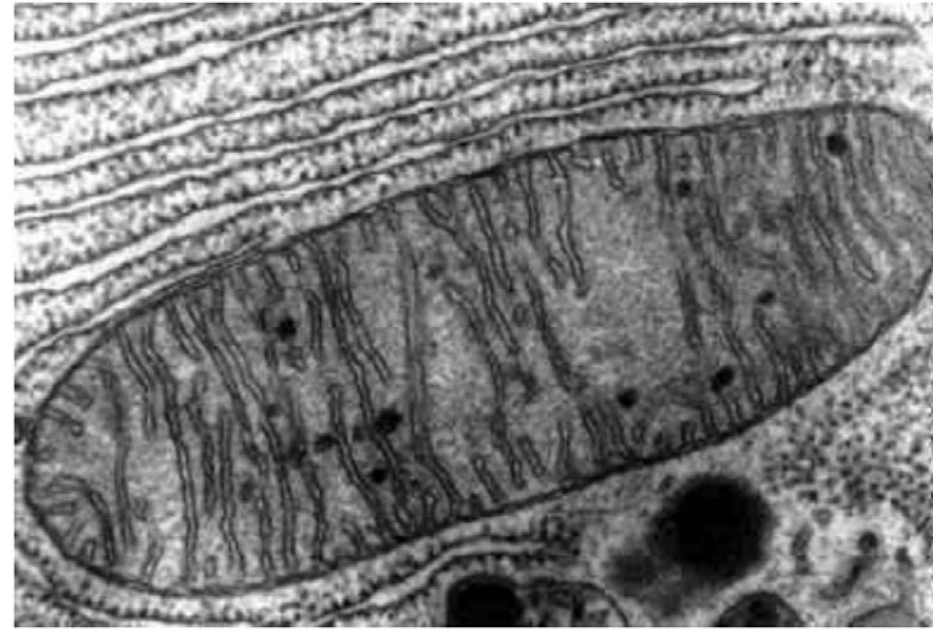University of Illinois at Urbana-Champaign
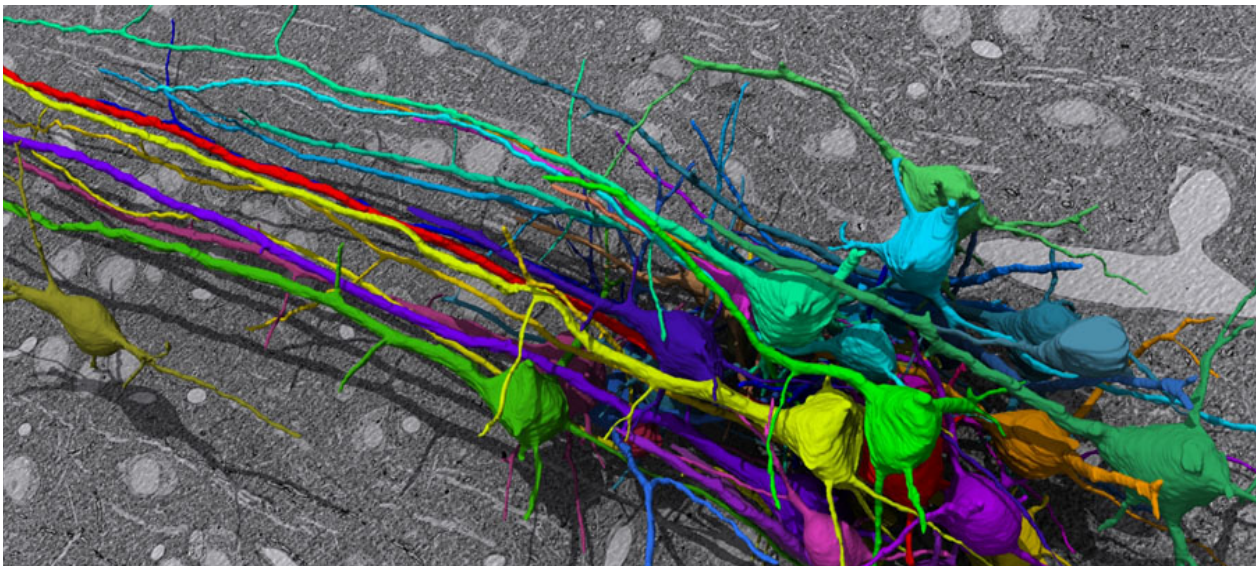
Cellular Membranes are Highly Complex

Macrophage

Yale University

Mitochondrion

G. Angus McQuibban

Neurons

Daniel Berger

Golgi Apparatus

Yale University

Classical Molecular Dynamics (MD) Simulations

Terasaki Ramp
(1240nm)³

Photosynthetic
Chromatophore
(100nm)³

HIV Capsid

Preliminary
Protocell
(200nm)³

ATP Synthase

Aquaporin

(2nm)³

Lysozyme

STMV

Ribosome

Number of Atoms

10^{11}
10^{10}
10^9
10^8
10^7
10^6
10^5

1990 1994 1998 2002 2006 2010 2014 2018 TBD

Year

Define Potential Energy Function (Force Field)

$$U_{CHARMM} = \begin{aligned} &U_{bond} + U_{angle} + U_{UB} + \\ &U_{dihedral} + U_{improper} + U_{CMAP} + \\ &U_{LJ} + U_{elec} \end{aligned}$$

$$U_{bond} = \sum_{bonds} K_b(b - b^0)^2$$

$$U_{angle} = \sum_{angles} K_\theta(\theta - \theta^0)^2$$

$$U_{UB} = \sum_{Urey-Bradley} K_{UB}(b^{1-3} - b^{1-3,0})^2$$

$$U_{dihedral} = \sum_{dihedrals} K_\varphi((1 + \cos(n\varphi - \delta)))$$

$$U_{improper} = \sum_{impropers} K_\omega(\omega - \omega^0)^2$$

$$U_{CMAP} = \sum_{residues} u_{CMAP}(\Phi, \Psi)$$

$$U_{LJ} = \sum_{nonb.pairs} \varepsilon_{ij}\left[\left(\frac{r_{ij}^{min}}{r_{ij}}\right)^{12} - 2\left(\frac{r_{ij}^{min}}{r_{ij}}\right)^6\right]$$
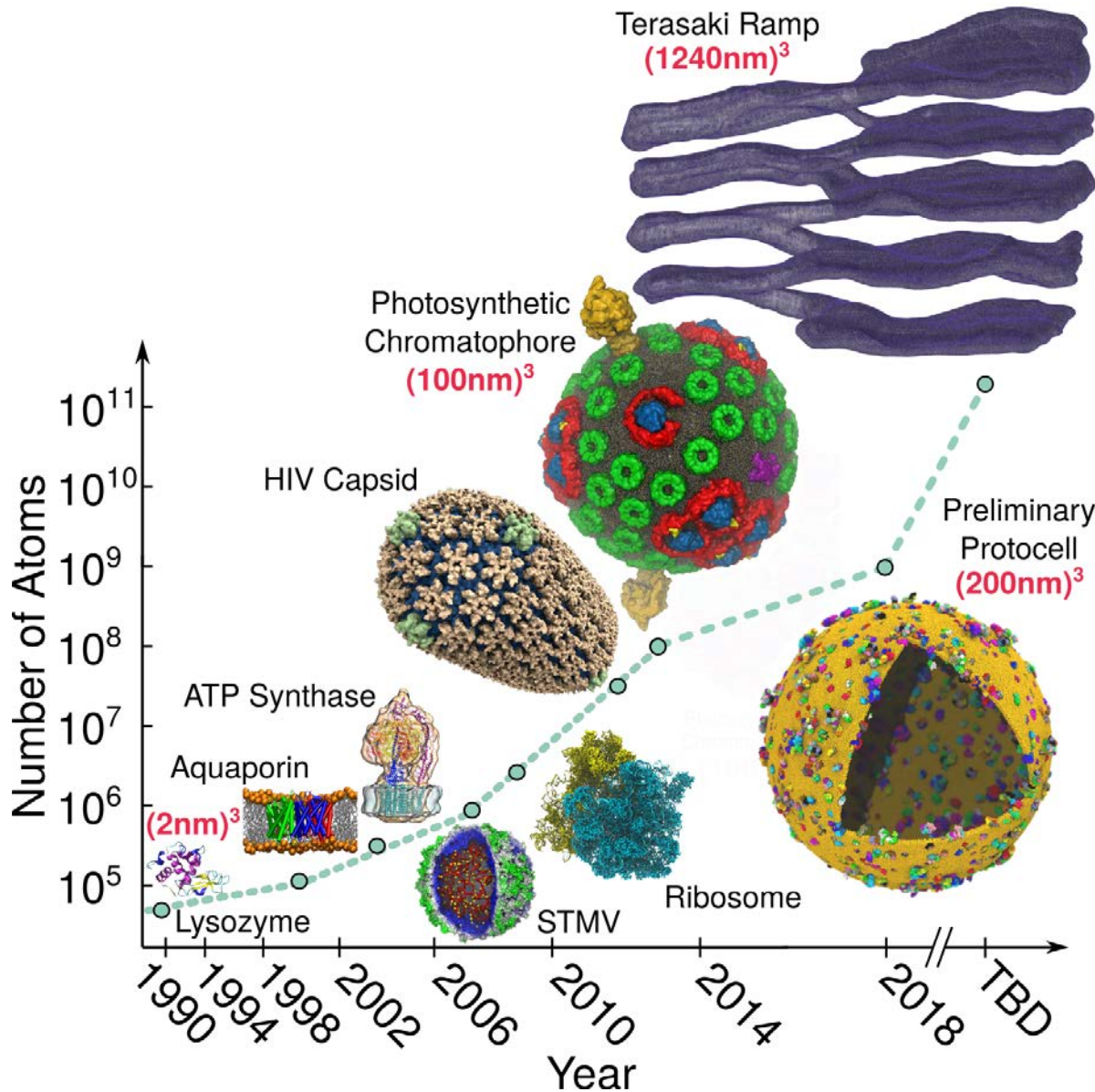
$$U_{elec} = \sum_{nonb.pairs} \frac{q_i q_j}{\epsilon r_{ij}}$$

Integrate Newton's Equations of Motion (Velocity Verlet)

$$\vec{r}_i(t + \delta t) = \vec{r}_i(t) + \vec{v}_i(t)\delta t + \tfrac{1}{2}\vec{a}_i(t)(\delta t)^2$$

$$\vec{a}_i(t + \delta t) = \frac{\vec{F}_i(t+\delta t)}{m_i} = -\frac{1}{m_i}\vec{\nabla}_i U(\vec{r}_i(t + \delta t))$$
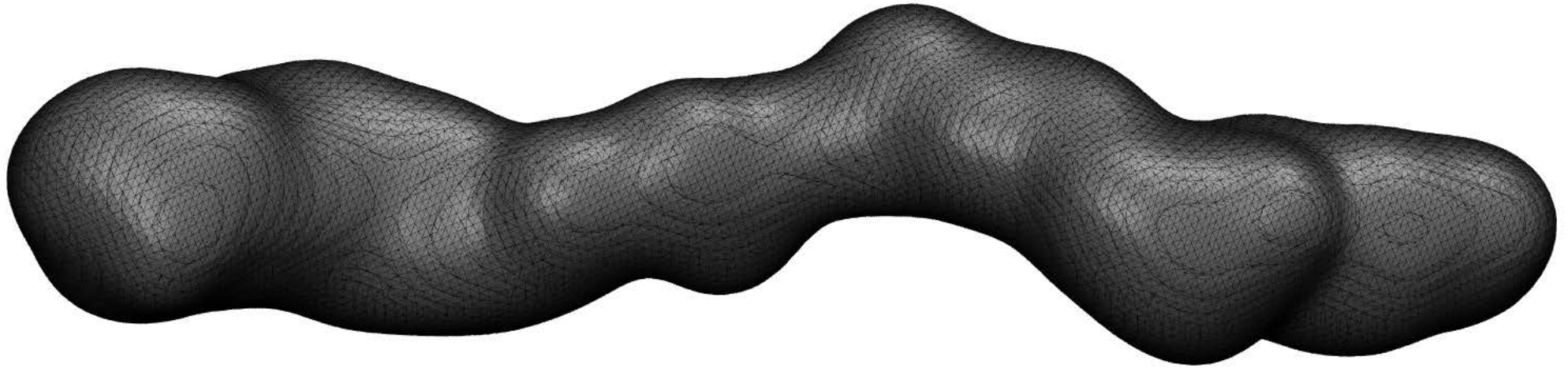
$$\vec{v}_i(t + \delta t) = \vec{v}_i(t) + \tfrac{1}{2}(\vec{a}_i(t) + \vec{a}_i(t + \delta t))\delta t$$

Classical MD Simulations Performed by the NIH Center for Macromolecular Modeling and Bioinformatics at the University of Illinois at Urbana-Champaign
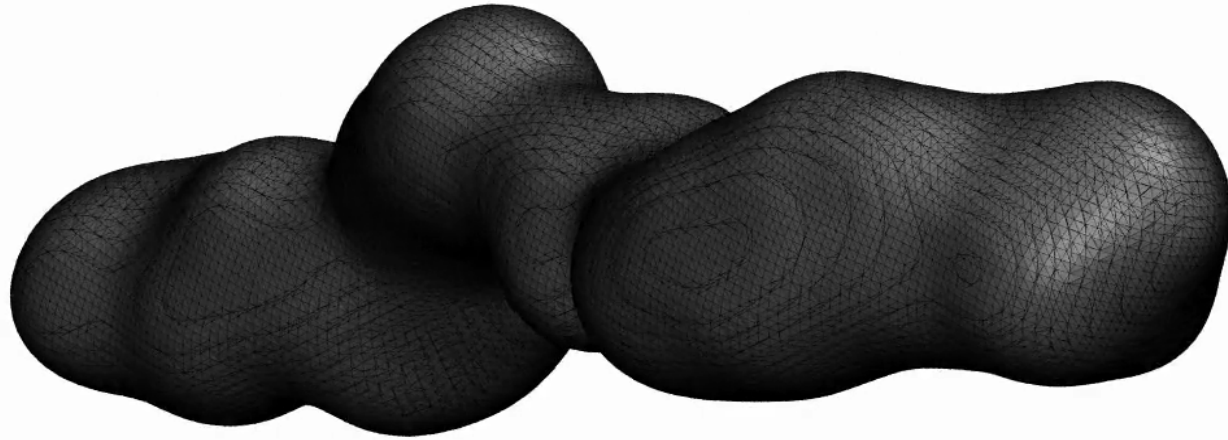
Methodological Overview of xMAS Builder
(E**x**perimentally-Derived **M**embranes of **A**rbitrary **S**hape)

Obtain 3D mesh from an experimental technique

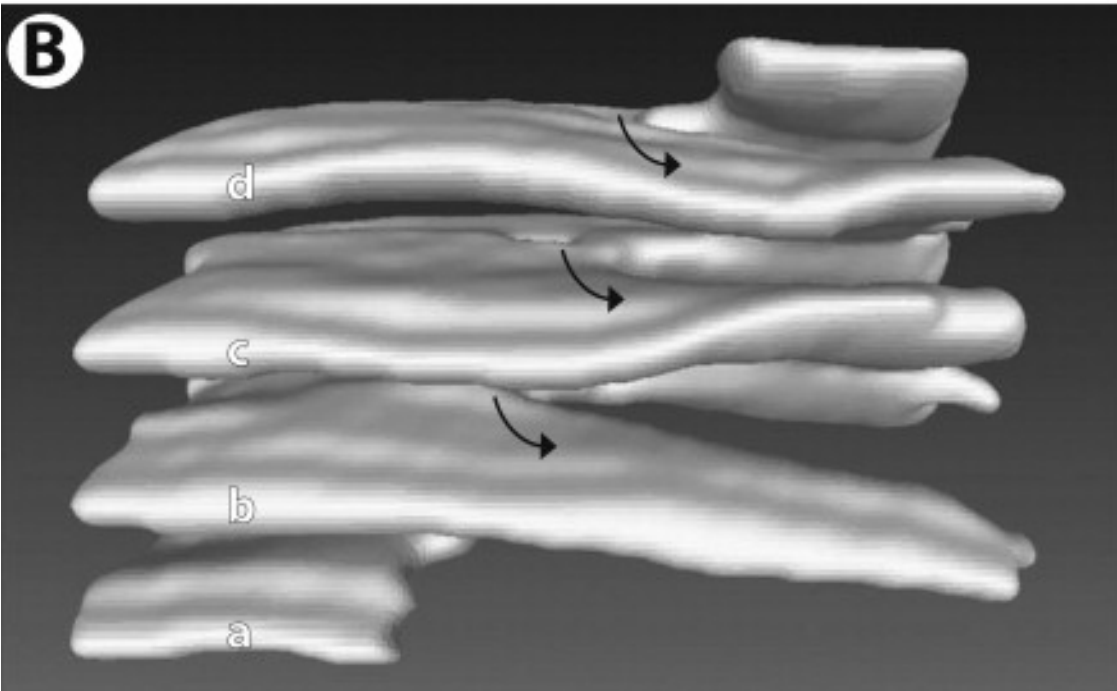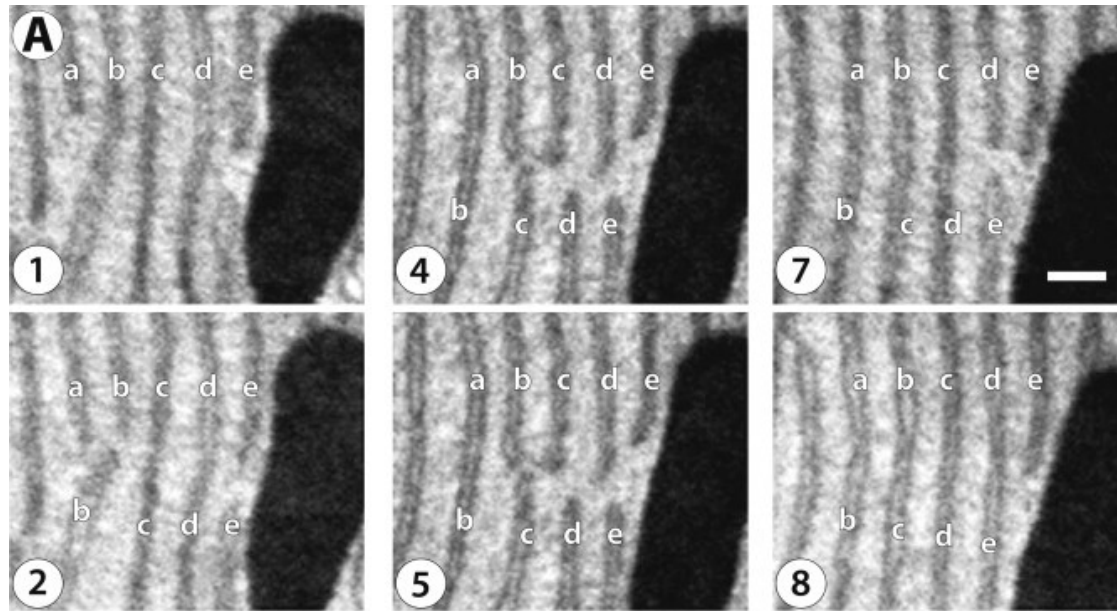# Methodological Overview of xMAS Builder
(E**x**perimentally-Derived **M**embranes of **A**rbitrary **S**hape)

Obtain 3D mesh from an experimental technique

ER Consists of Representative Cell Membranes
Structure: Electron Microscopy

Lipid Composition: Chromatography

14.19% —— Cholesterol

49.65% ⬤ POPC

23.01% ⬤ POPE

4.38% ⬤ POPI

3.46% ⬤ POPS

5.21% ⬤ Sphingomyelin

0.09% ⬤ Cardiolipin

Keenan and Huang. *J Dairy Sci*. **55**:11, 1586-1596 (1972).

Terasaki *et al*. Cell. **154**:2, 285-296 (2013).

Atomistic Model of an ER Terasaki Ramp

- Outer Leaflet
- Inner Leaflet
- Cholesterol
- POPC
- POPE
- POPI
- POPS
- Sphingomyelin
- Cardiolipin
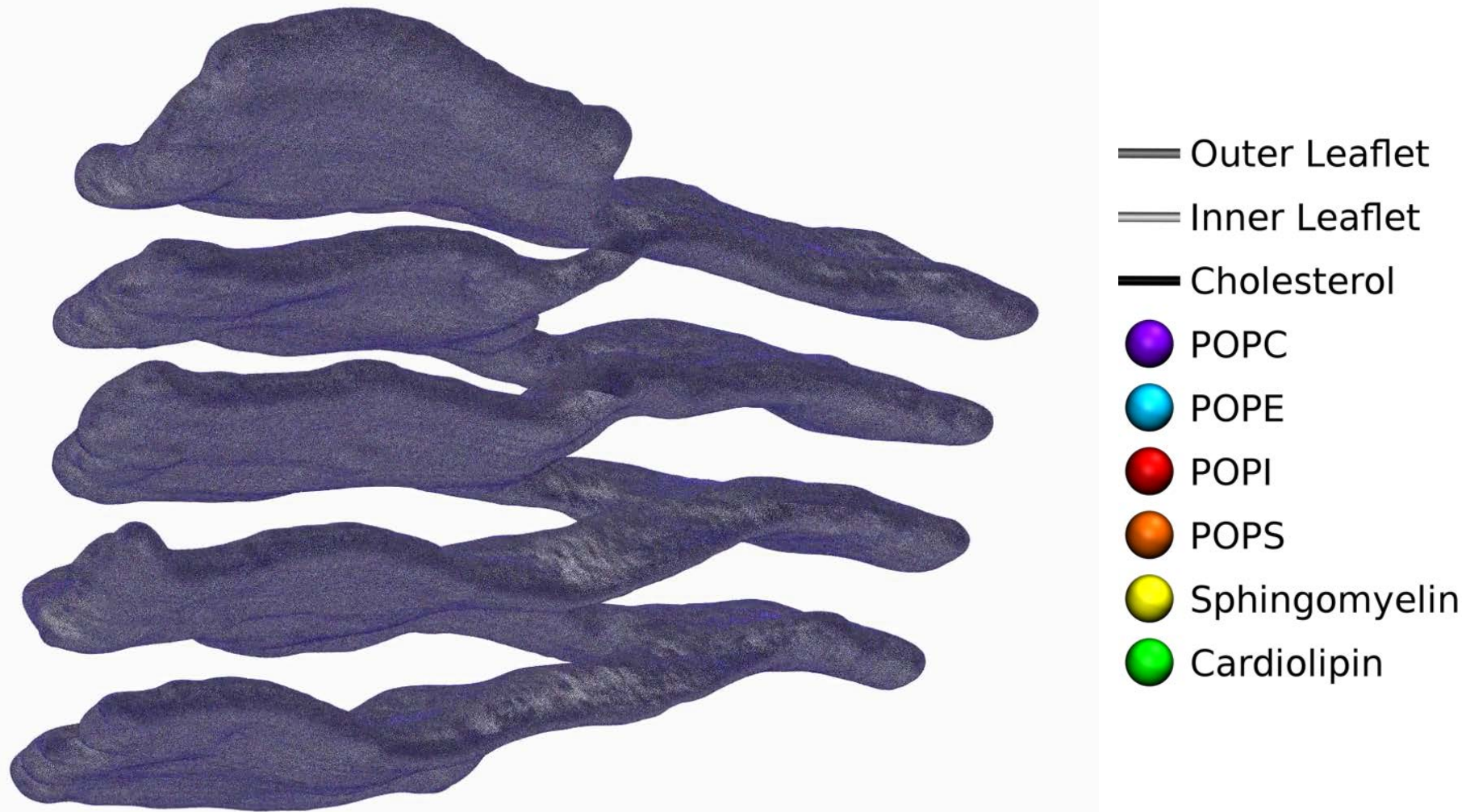
- 1.97μm x 1.59μm x 0.61μm
- Hypothetical Water Box: ~200 Billion Atoms
- ~36.6 Million Lipids
- Lipid Model: ~4.5 Billion Atoms

Methodological Overview of xMAS Builder
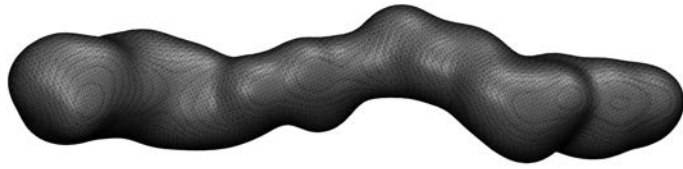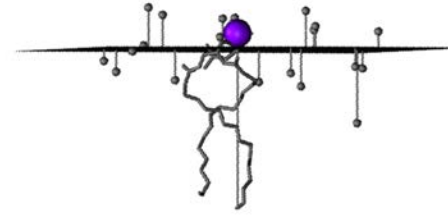
Obtain 3D mesh from an experimental technique

Replace particles with atomistic lipids
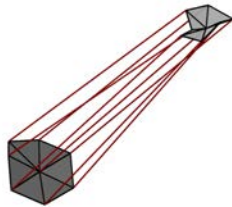
Construct inner leaflet mesh
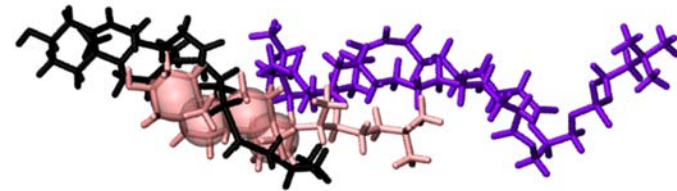
Fix ring piercings
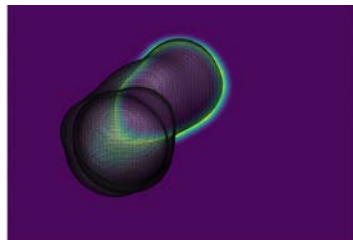
Generate attractive grid densities from inner and outer leaflet meshes
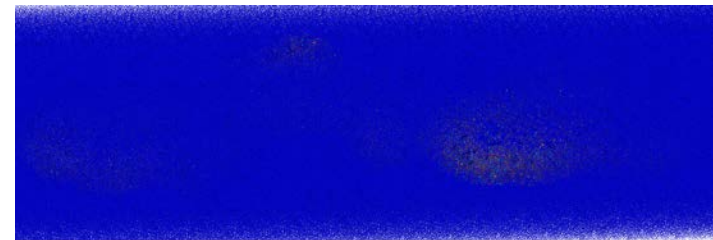
Solvate bilayer
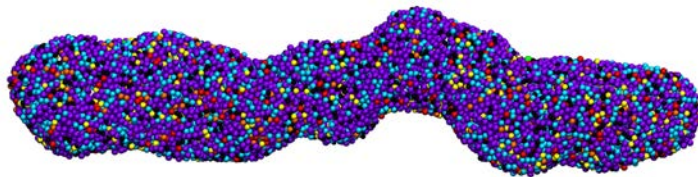
Optimize lipid placement
Simulate particles while restrained to attractive densities
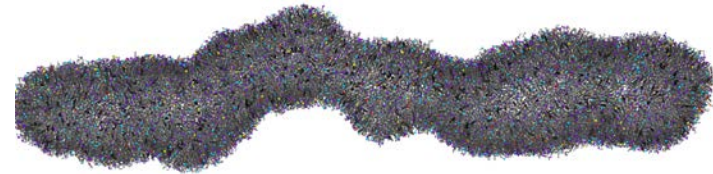
Run simulation

Optimizing Initial Lipid Placement

Motivation
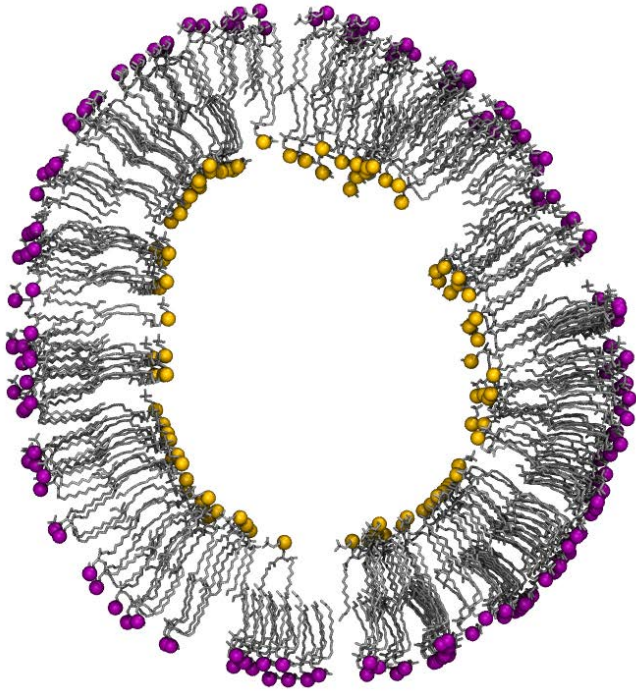
Strategy

Represent Lipids as Particles
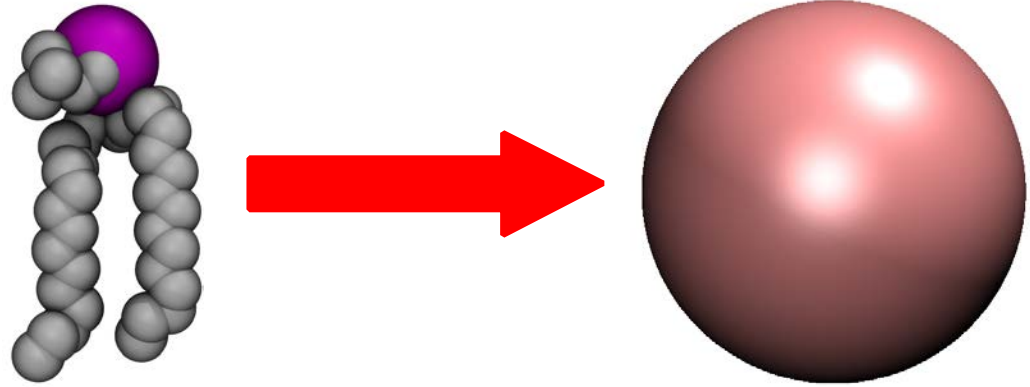
Convert Mesh to Grid-Based Potential
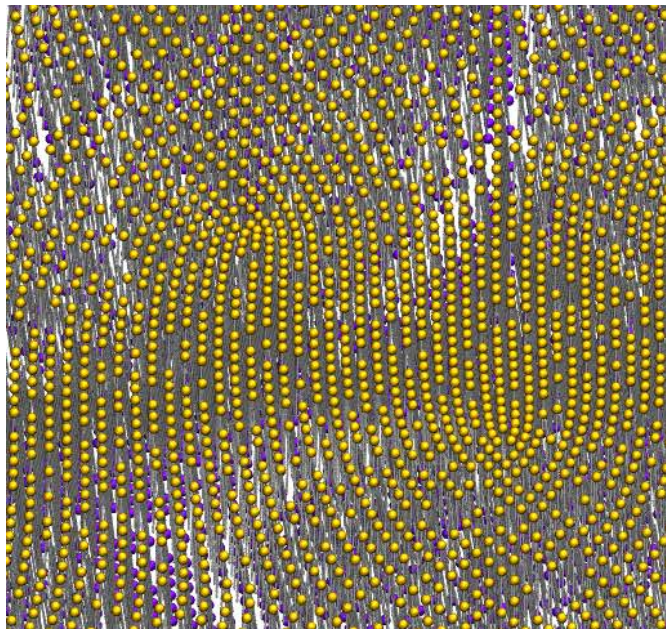
Attractive Potential: More — Less
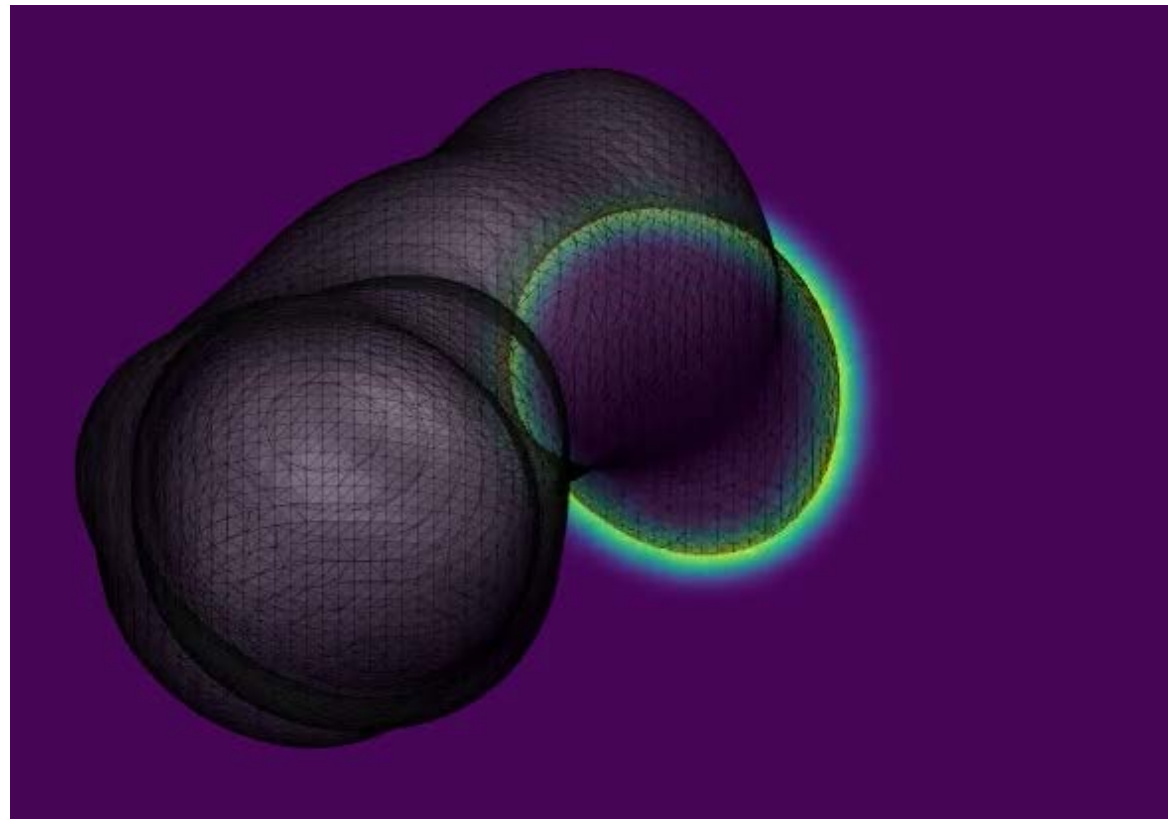
Application to Synthetic System
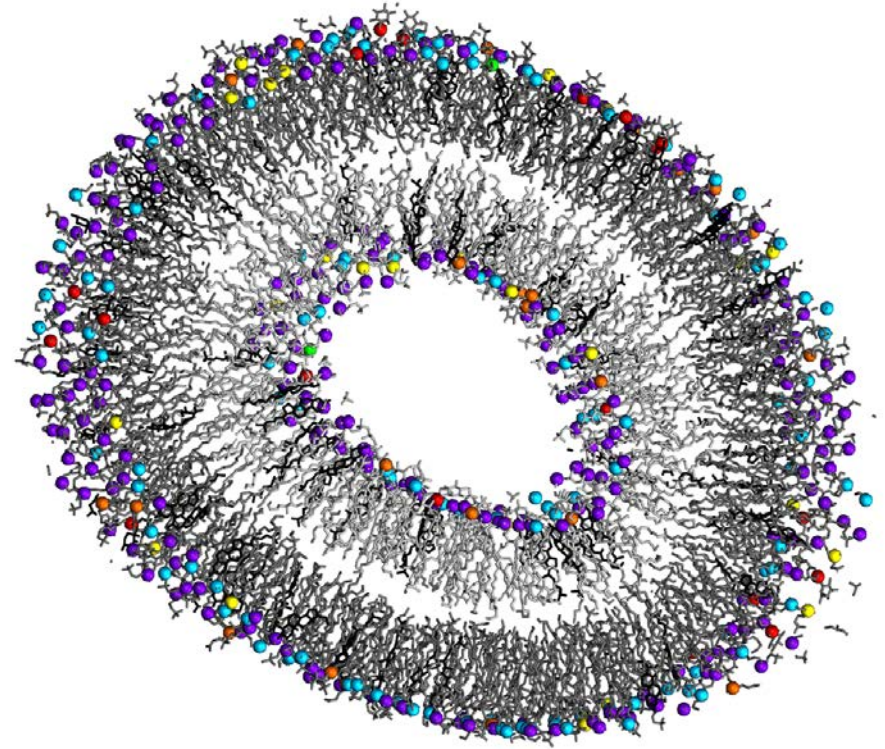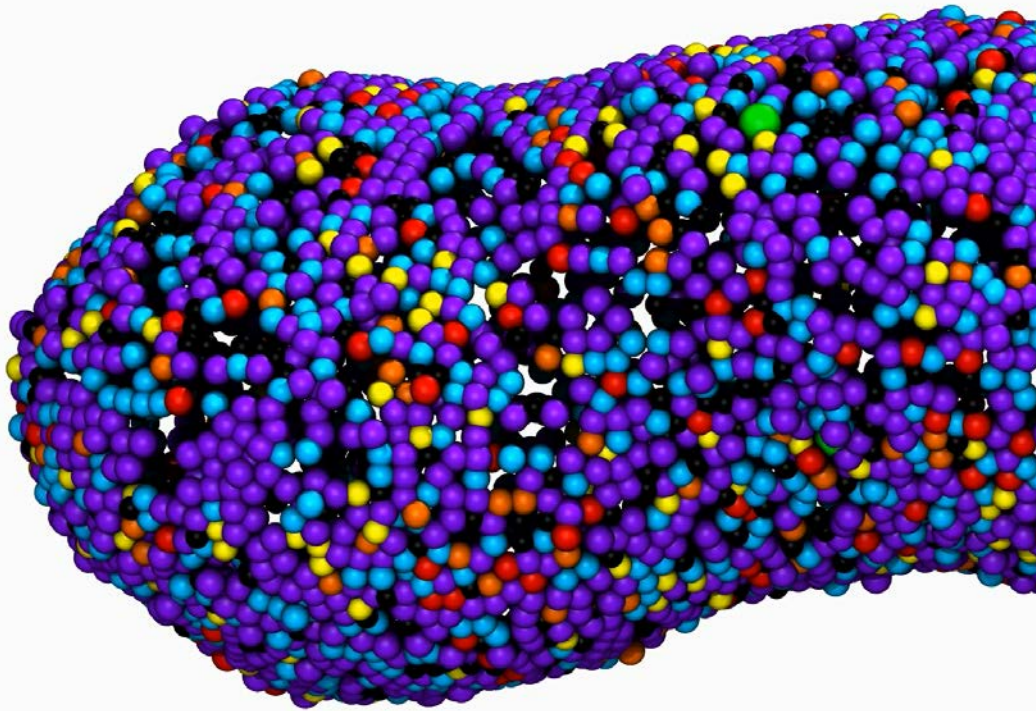
Stage 1
20ps Velocity Quenching
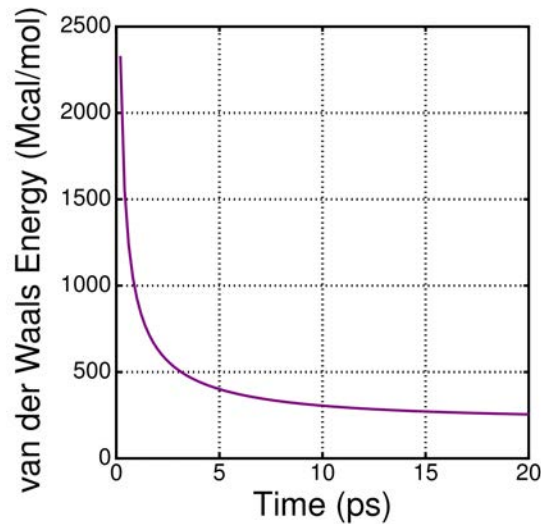
Stage 2A
40ps Equilibration
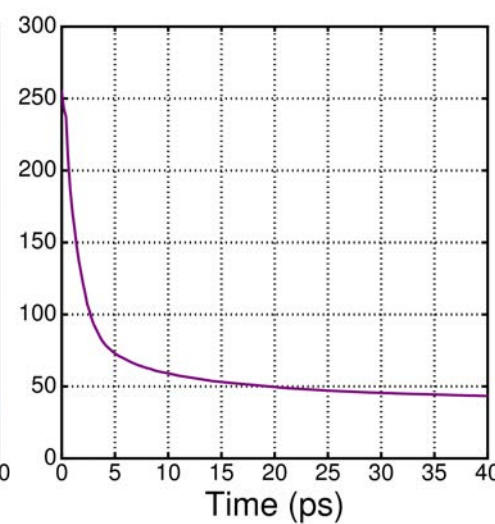
Stage 2B
4.96ns Equilibration
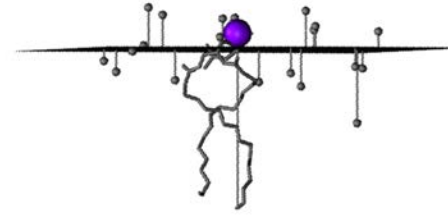### (100x Speed in Movie)
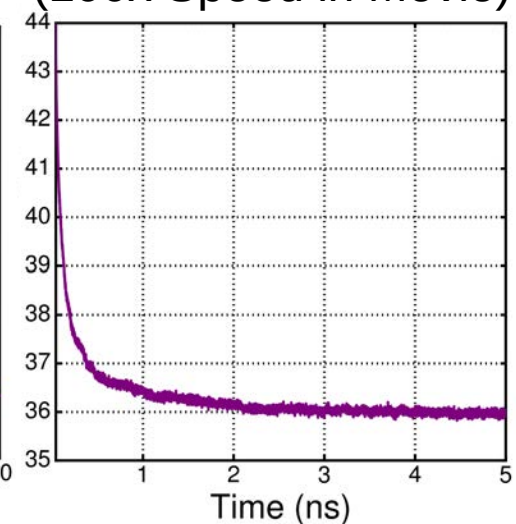
Simulation Details
16,754 Lipids/Particles
1,177Å x 320Å x 310Å
5ns Simulation

Application to ER Terasaki Ramp
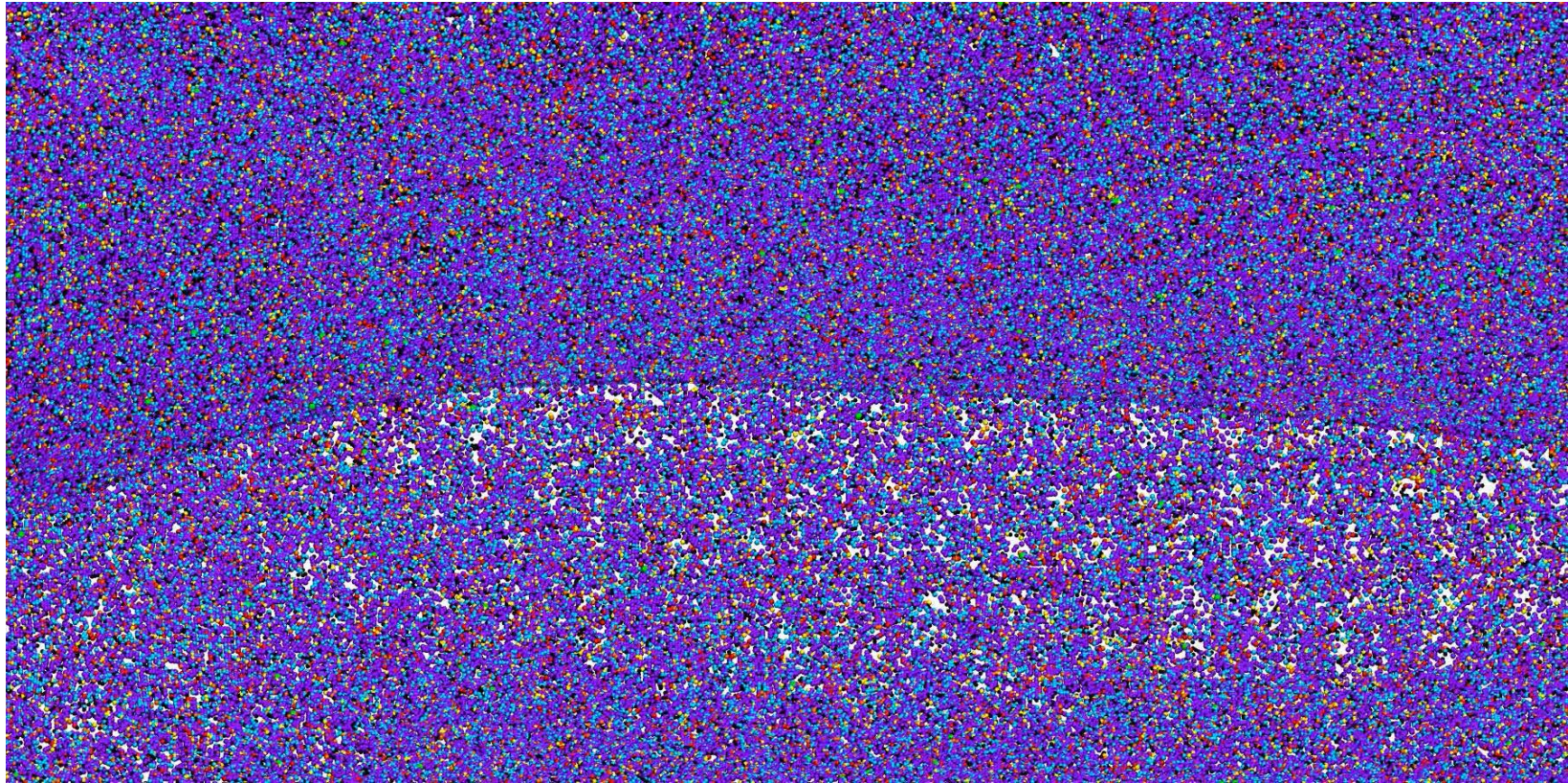
Stage 1
20ps Velocity Quenching

Stage 2A
40ps Equilibration

Stage 2B
4.96ns Equilibration

Simulation Details
18,610,625
Lipids/Particles

1.97μm x 1.59μm x
0.61μm
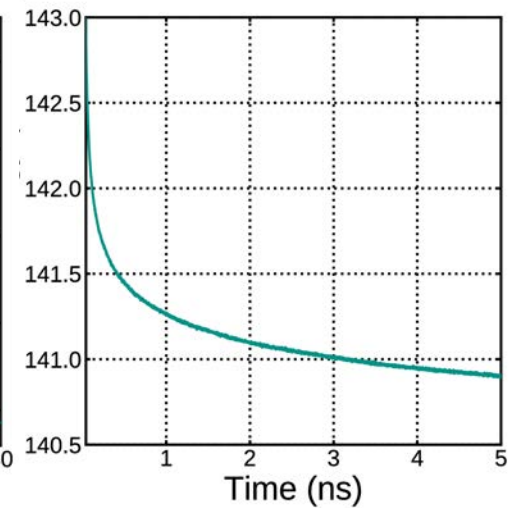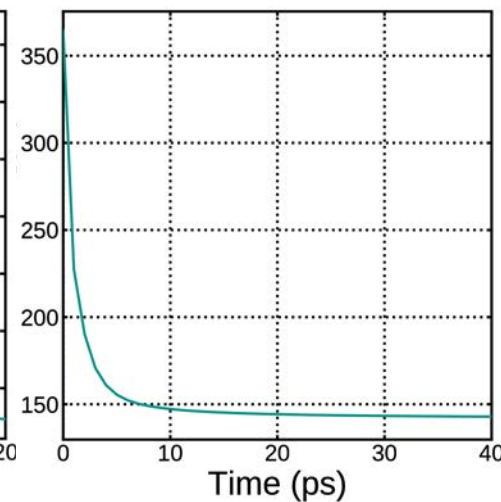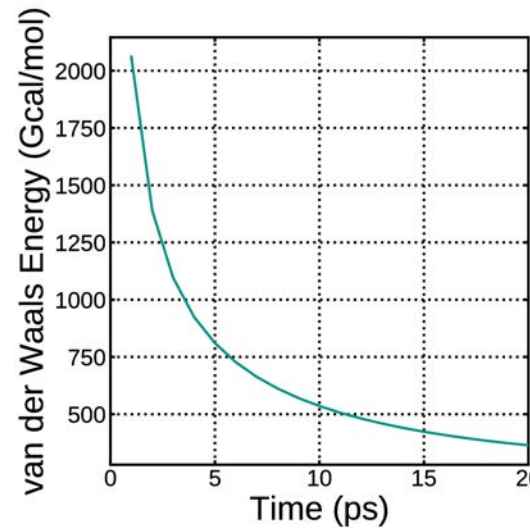
5ns Simulation

Methodological Overview of xMAS Builder
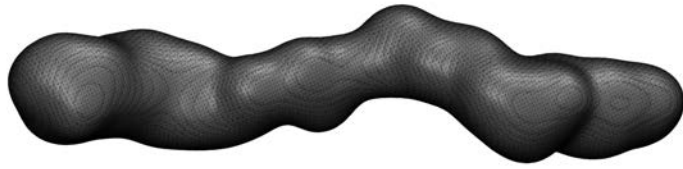
Obtain 3D mesh from an experimental technique

Replace particles with atomistic lipids
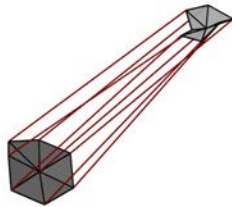
Construct inner leaflet mesh
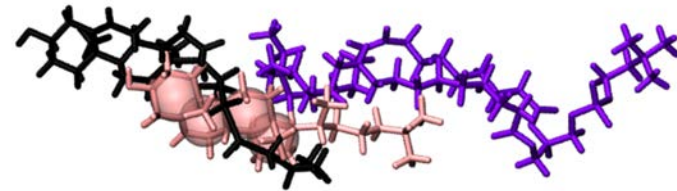
Fix ring piercings
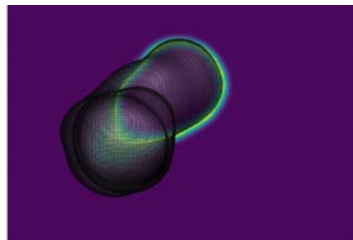
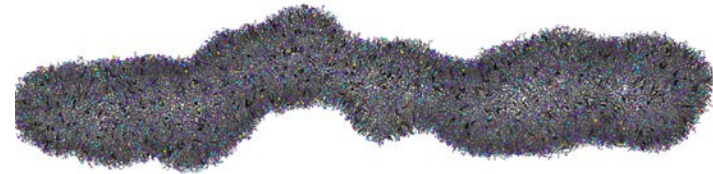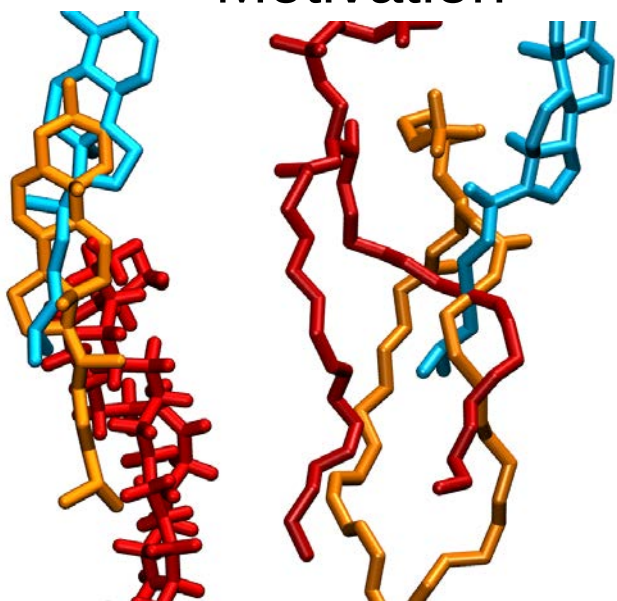Generate attractive grid densities from inner and outer leaflet meshes
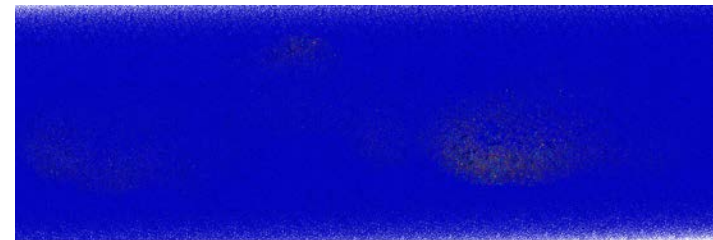
Solvate bilayer
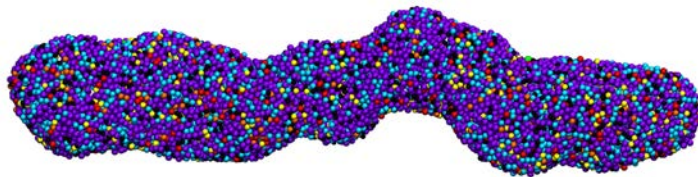
Optimize lipid placement
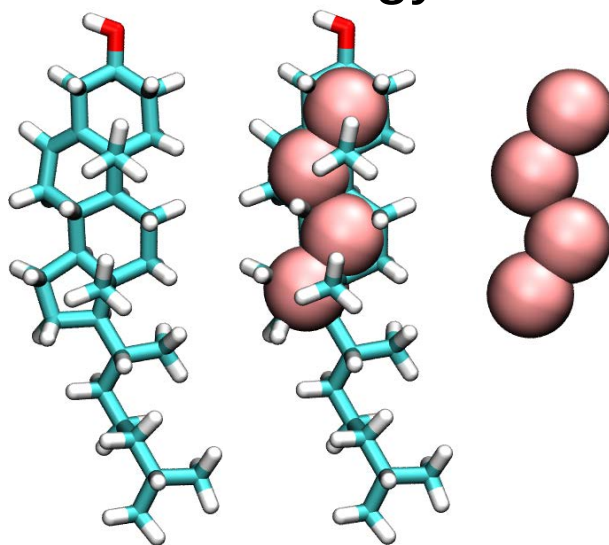Simulate particles while restrained to attractive densities

Run simulation

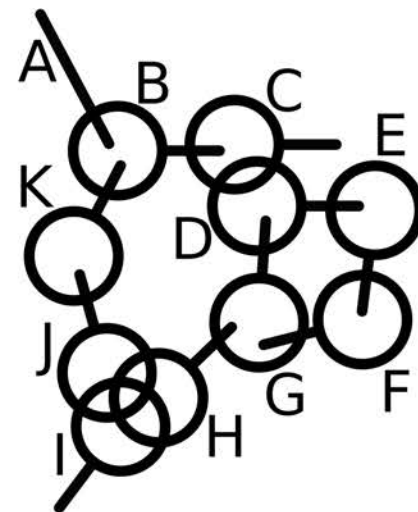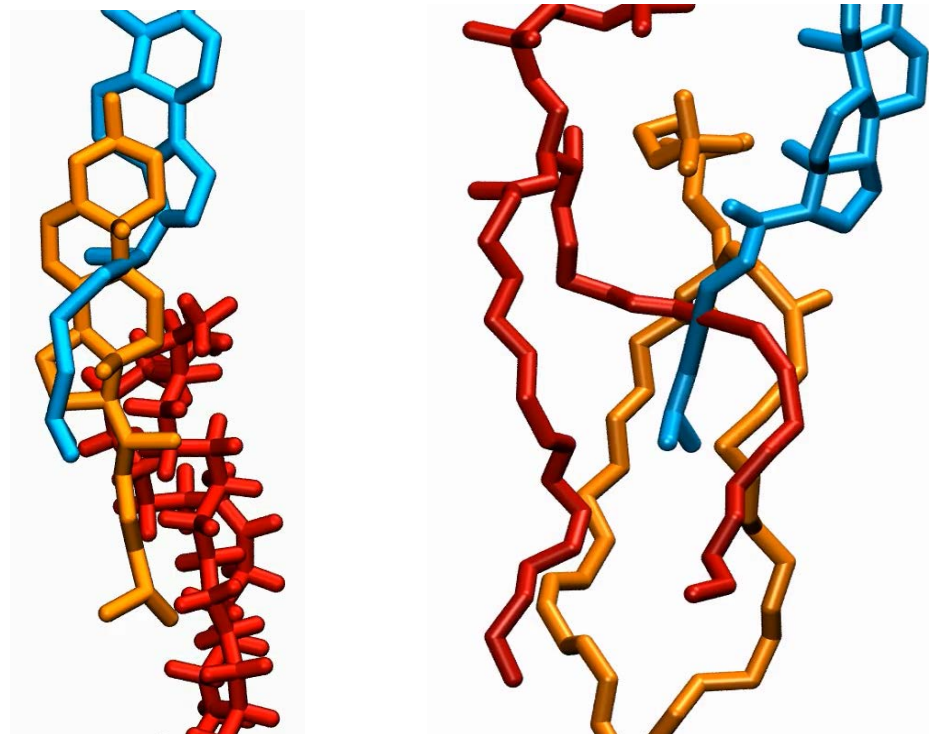# Automatically Correcting Complex Lipid Clashes

Motivation

Strategy

Complication

Results

System Size
16,754 Lipids
3,111 Ringed Lipids

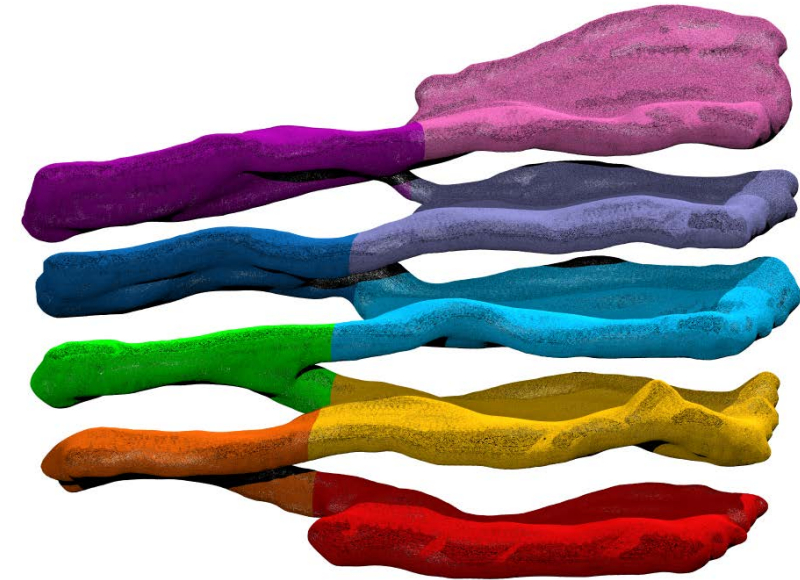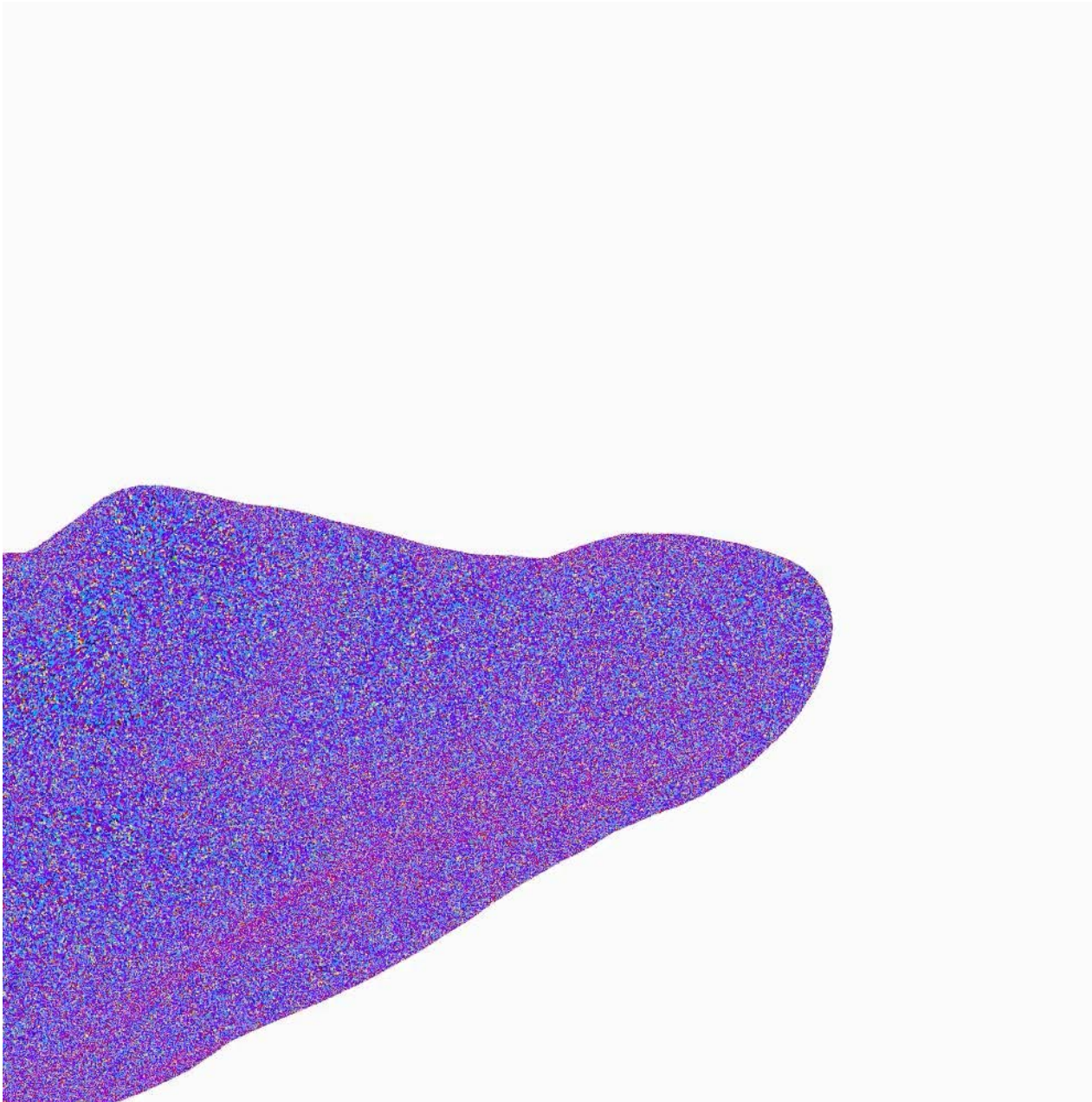### Entanglements
6 Entanglements

Ring Piercings

Iteration 1:
880 Ring Piercings
517 Lipids Frozen

Iteration 3:
2 Ring Piercings
1 Lipid Frozen

Iteration 2:
12 Ring Piercings
7 Lipids Frozen

Iteration 4:
1 Ring Piercings
1 Lipid Frozen

Application to ER Terasaki Ramp

System Size
Full Upper Leaflet:
18,610,625 Lipids
3,456,671 Ringed Lipids

Simulated Piece (Red):
2,476,460 Lipids
459,037 Ringed Lipids

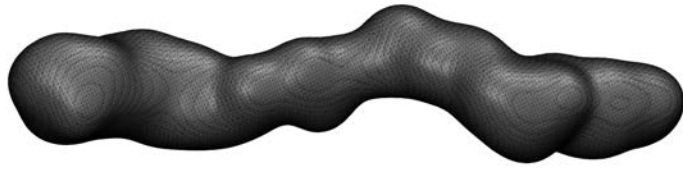### Ring Piercings
Iteration 1:
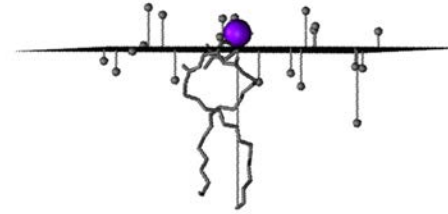139,815 Ring Piercings
73,046 Lipids Frozen

Iteration 2:
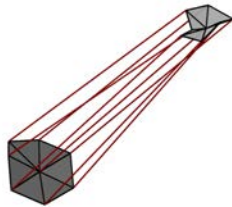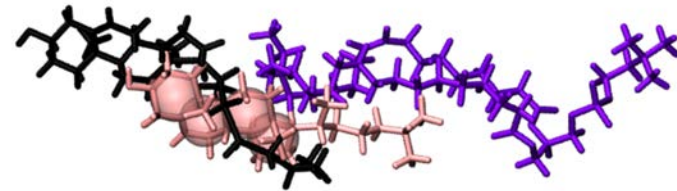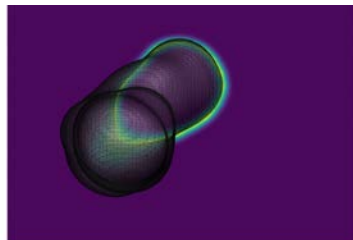11,722 Ring Piercings

Methodological Overview of xMAS Builder

Obtain 3D mesh from an experimental technique
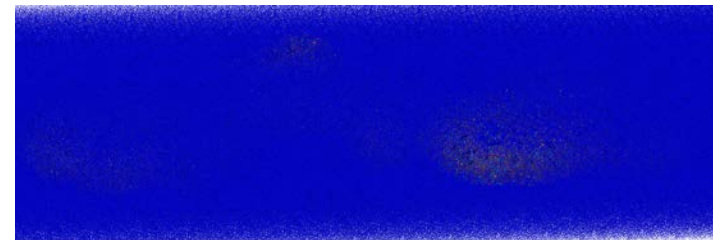

Replace particles with atomistic lipids
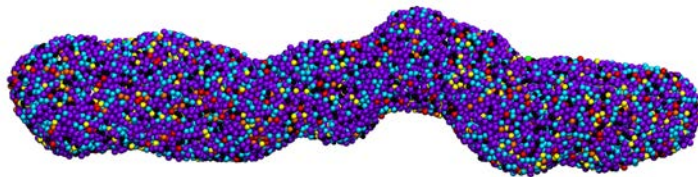

Construct inner leaflet mesh

Fix ring piercings

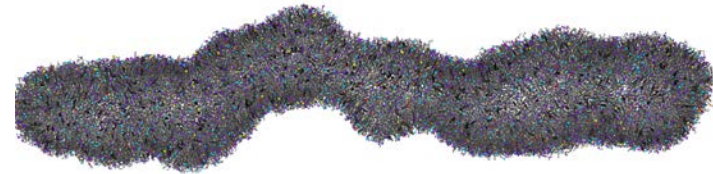Generate attractive grid densities from inner and outer leaflet meshes

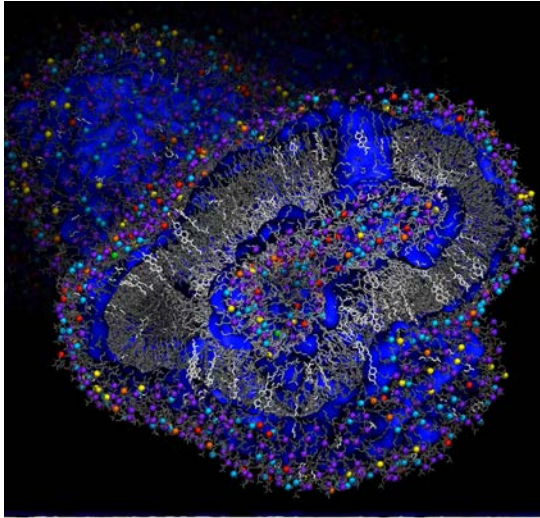Solvate bilayer

Optimize lipid placement
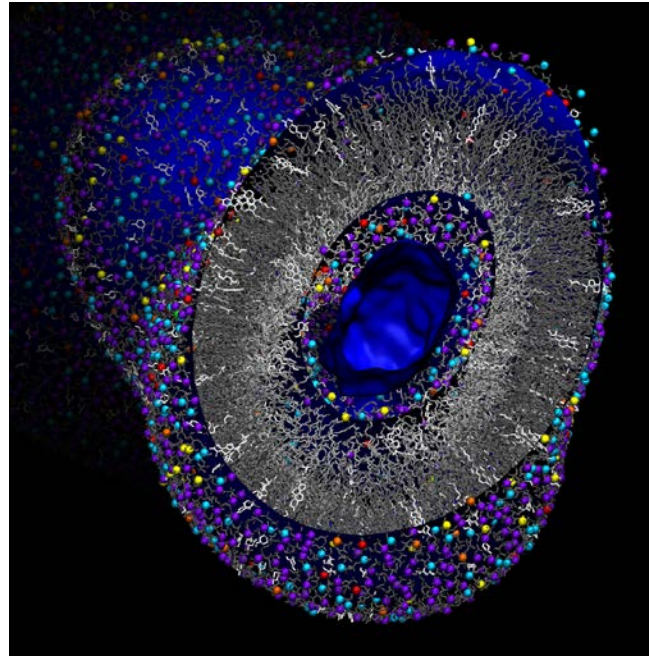Simulate particles while restrained to attractive densities

Run simulation
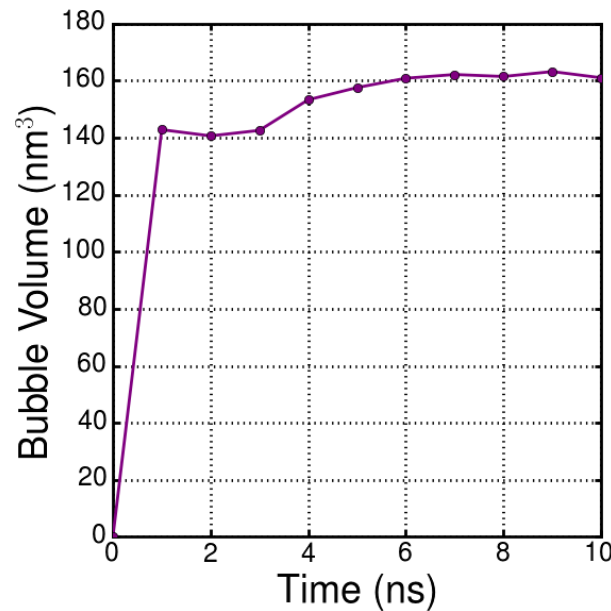
Simulating the Membrane Structures

Problem: Equilibration

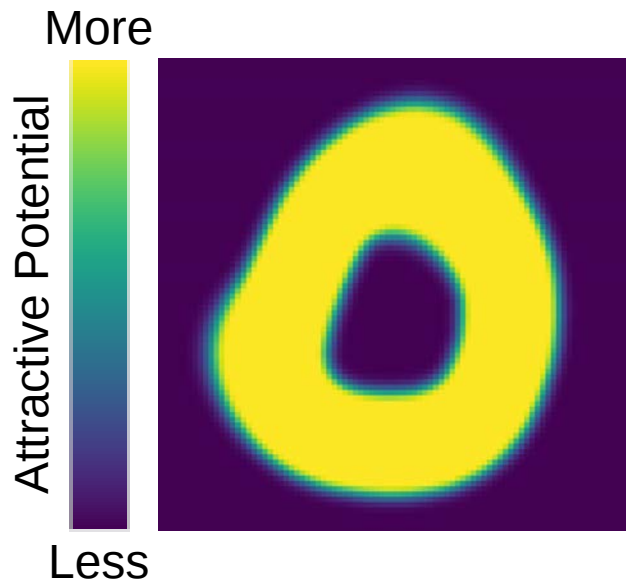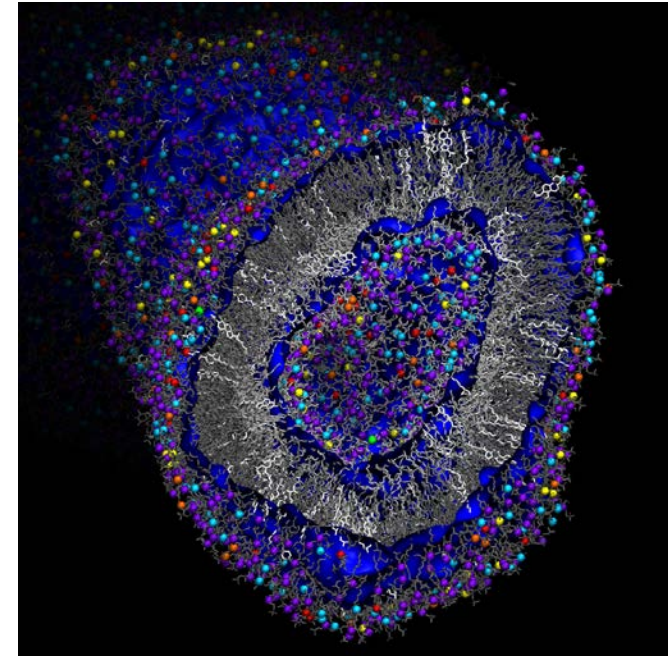

Problem: Bubbles

Final Result

Attractive Potential — More / Less
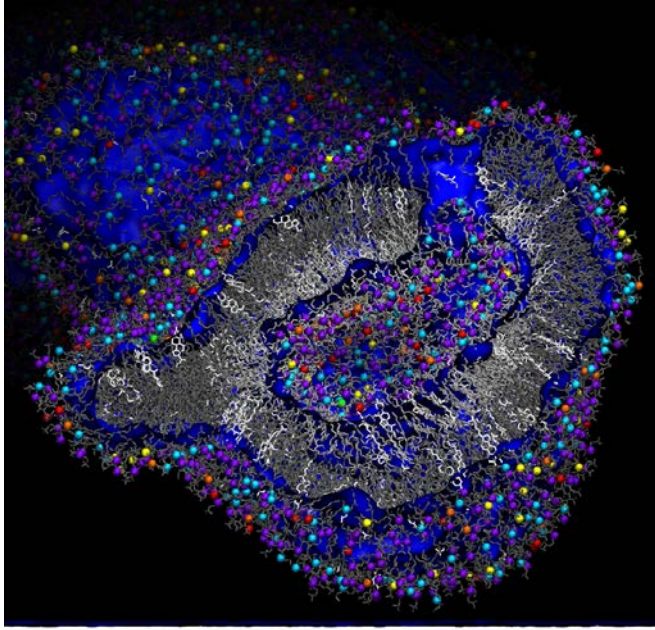

Bubble Volume (nm³) vs Time (ns)

Simulation Details

16,754 Lipids
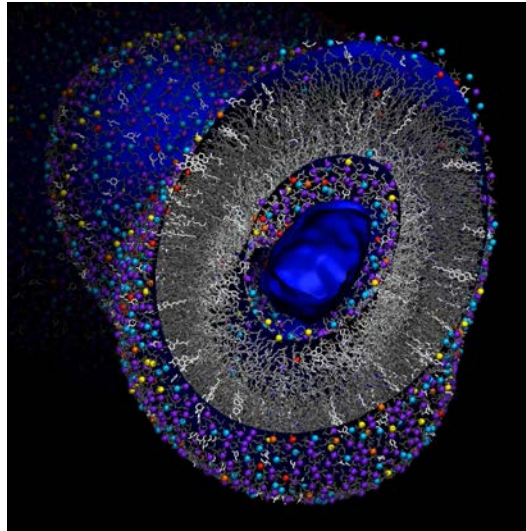~2.1 Million Lipid Atoms
~11.9 Million Atoms Total
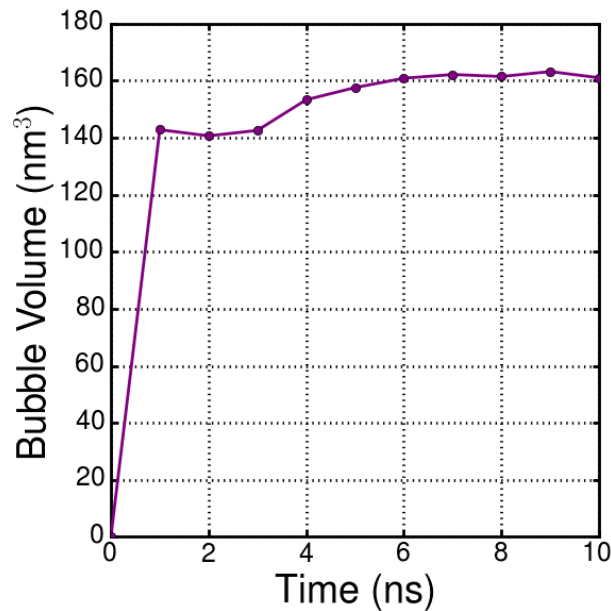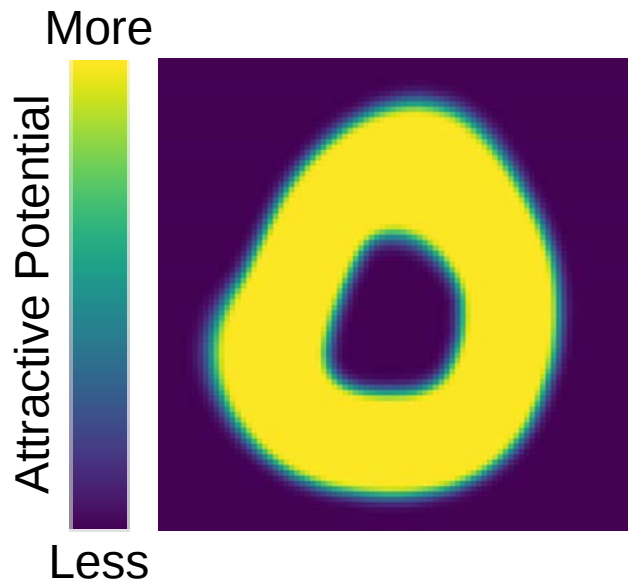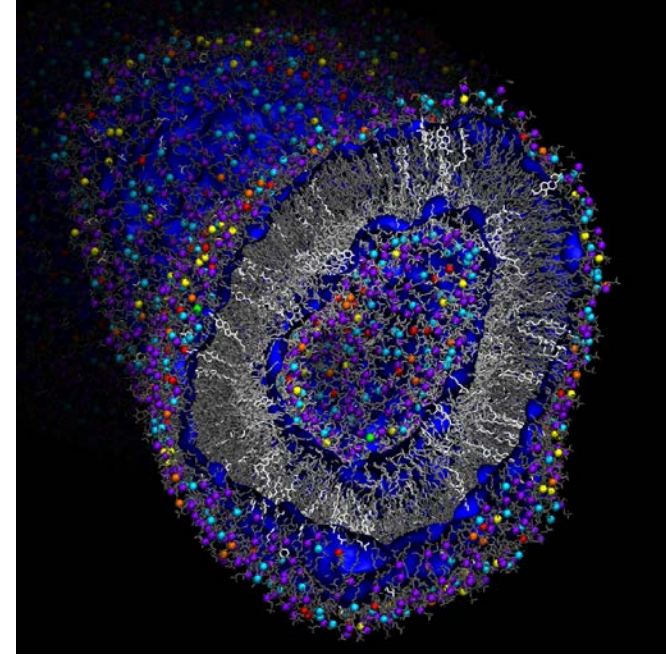
10ns Simulation

Simulating the Membrane Structures

Problem: Equilibration

Problem: Bubbles

Final Result

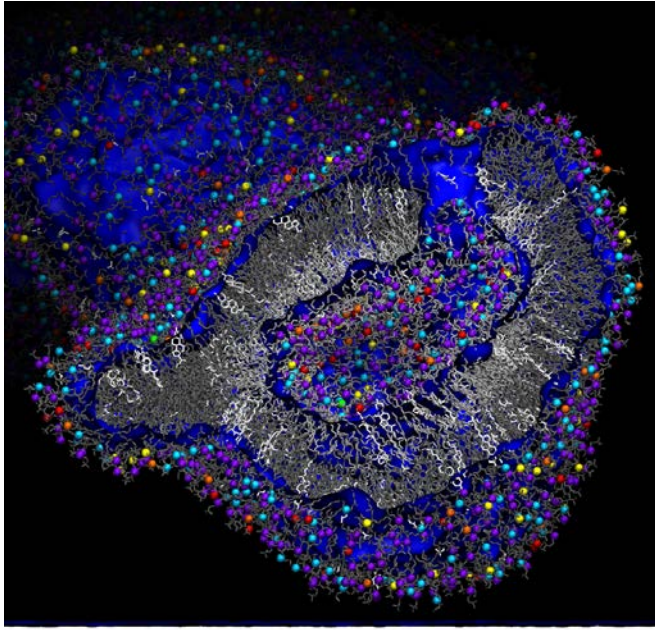Attractive Potential

More

Less

Simulation Details

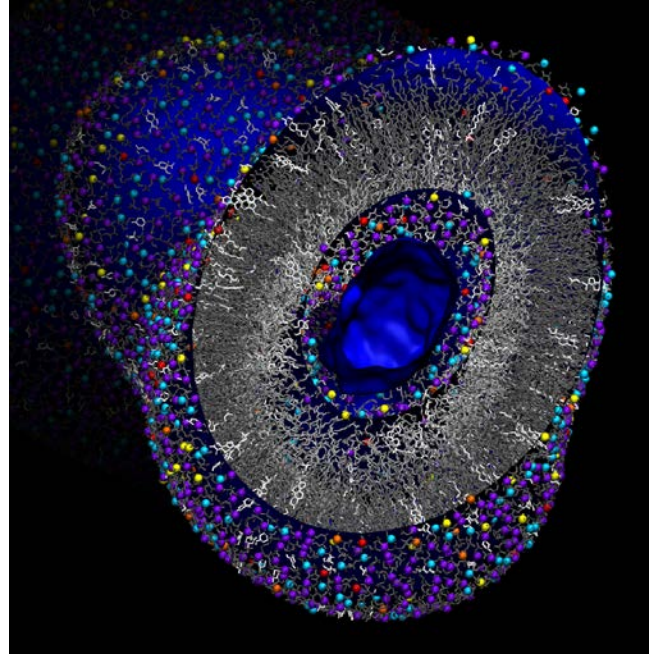16,754 Lipids
~2.1 Million Lipid Atoms
~11.9 Million Atoms Total
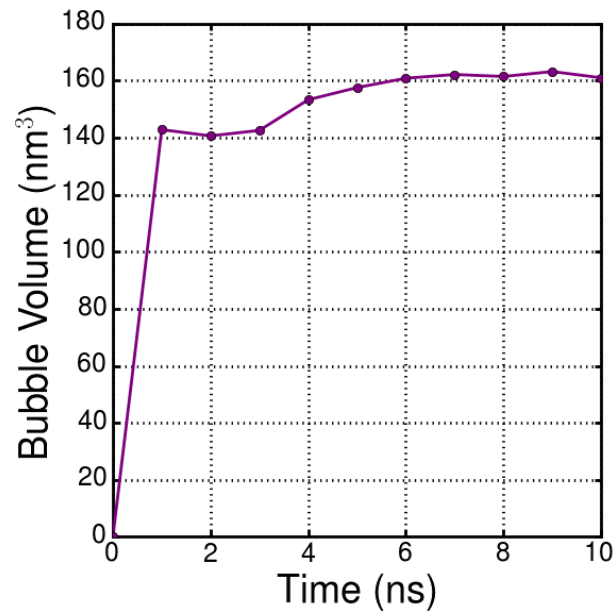
10ns Simulation

Simulating the Membrane Structures

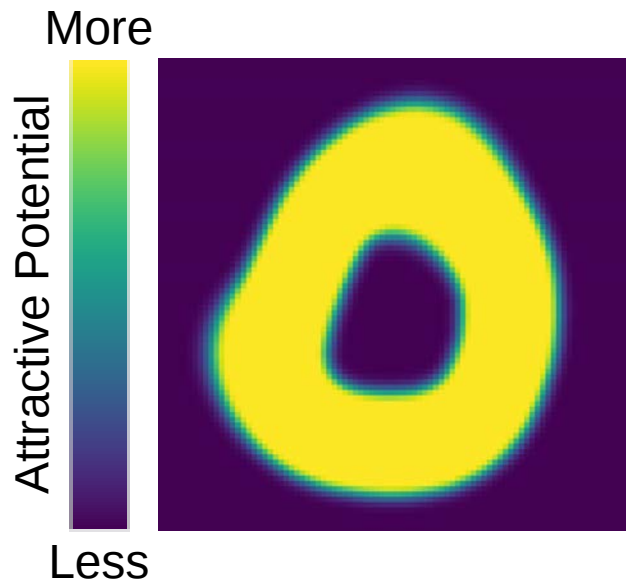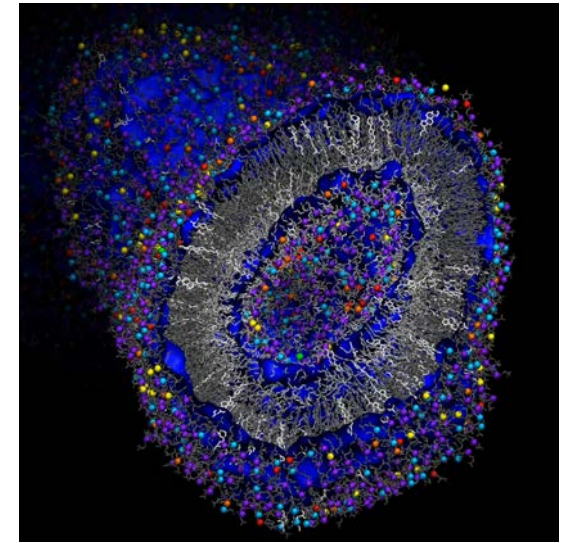## Problem: Equilibration

Problem: Bubbles

Final Result

More

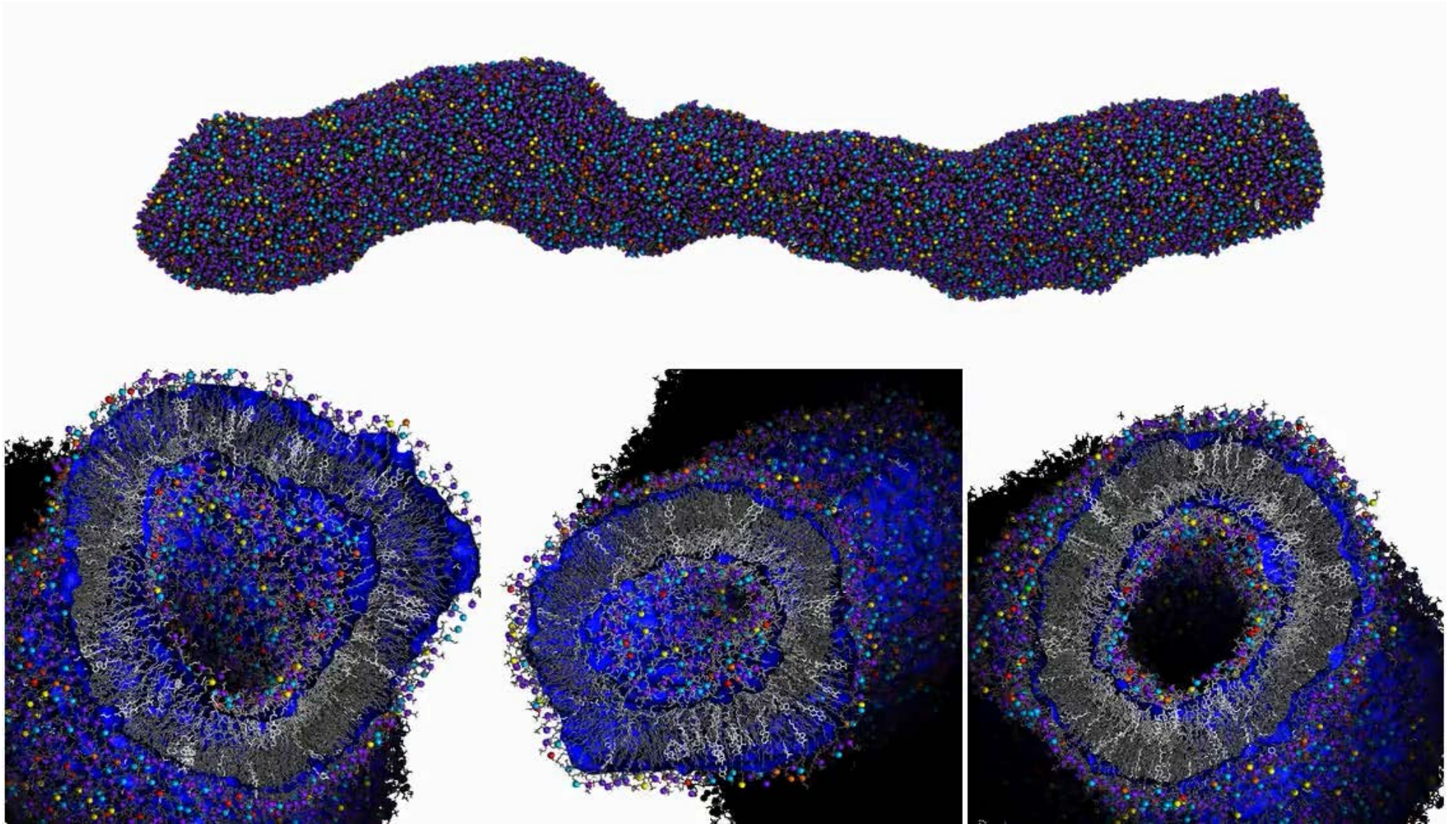Attractive Potential

Less

Simulation Details

16,754 Lipids
~2.1 Million Lipid Atoms
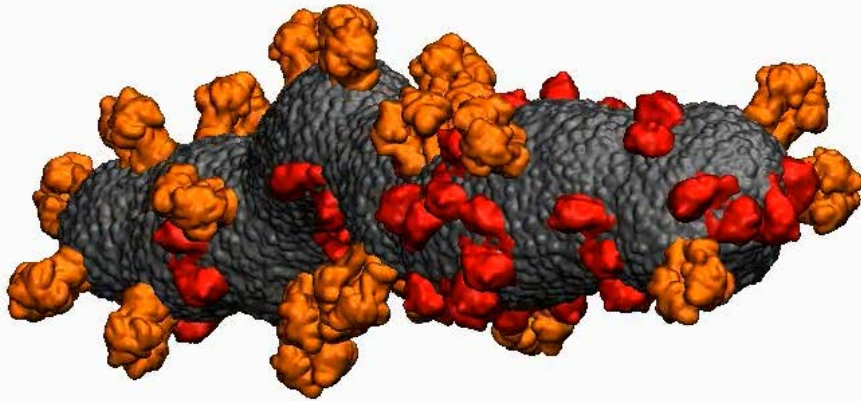~11.9 Million Atoms Total

10ns Simulation

Membrane Stable During Unbiased Simulation

16,754 Lipids
~2.1 Million Lipid Atoms
~12.0 Million Atoms Total

~50ns Simulation

Concluding Remarks

Future Work

Add support for proteins

Add support for other modeling features

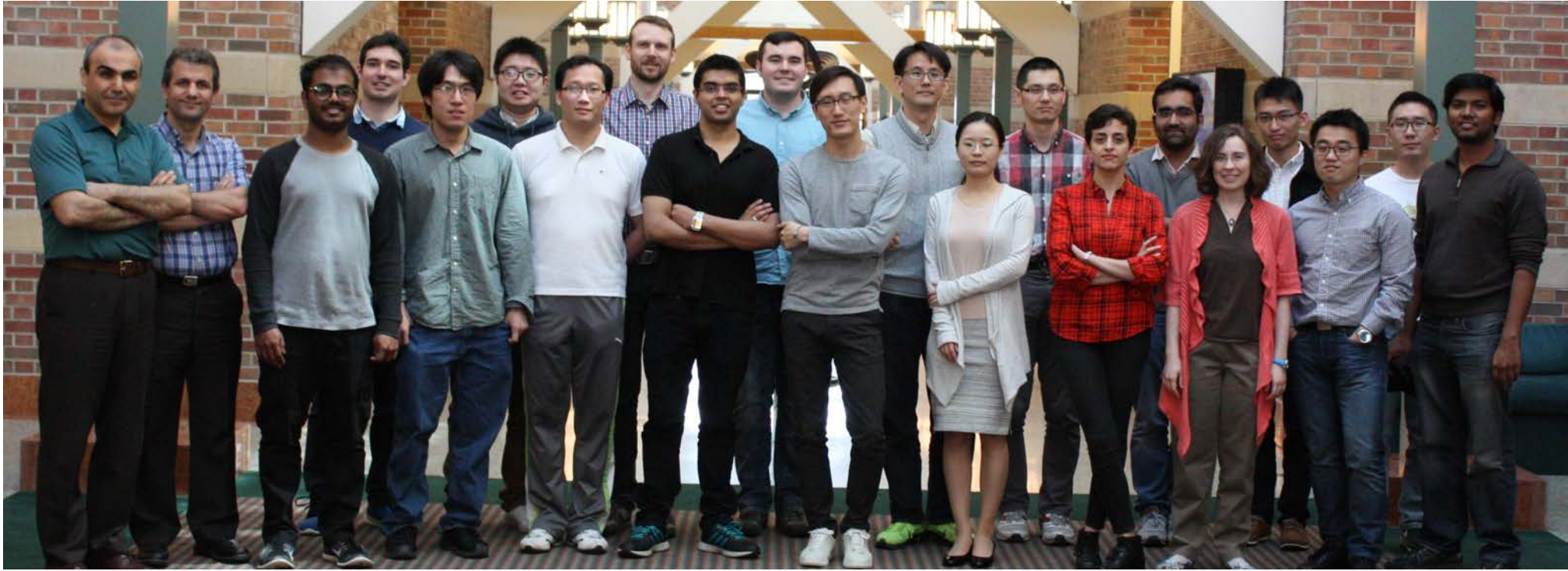Make xMAS Builder more user friendly

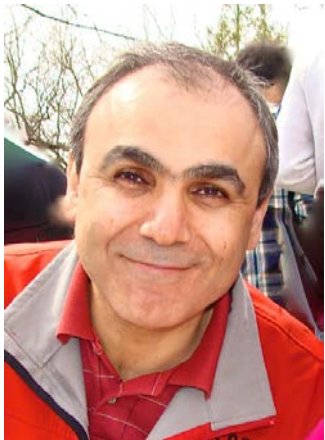Apply xMAS Builder to a more biomedically relevant system

Model Details

Red/Blue:
25 copies VcINDY

Orange/Purple:
25 copies MsbA

Acknowledgements

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