Overview of the Program in Day 3 and 4

Introduction to MD in NAMD
Intro to Molecular Visualization in VMD

Advanced Modeling Tools

Goal:
Making users comfortable with the software environment

Tutorials — MUST MUST MUST MUST
Molecular Dynamics -
A Key Tool in Biophysics and Beyond

Resource software is employed in **more than half of all MD papers** in Life Sciences

"Molecular Dynamics"
"Molecular Dynamics" in Life Sciences
NAMD + VMD

It takes many years to build a reliable and successful scientific software

**more than 50%** of all MD publications in Life Sciences cited VMD and/or NAMD
NIH Biomedical Technology Resource for Macromolecular Modeling and Bioinformatics

Serving a large and growing community

a) Over 125,000 users of Resource software

b) Over 2.2 million total downloads of Resource software

- 586,319 VMD registered users since initial release
- 181,348 VMD 1.9.3 registered users
- 125,130 users of multiple VMD versions

In 2018–2021 alone, Resource software has enabled over 3,700 publications in states throughout the US

VMD and NAMD are used in a broad range of biological fields

Number of publications enabled by the Resource's software

5-yr statistics: 1.4 million web visitors; 228,000 tutorial views
Serving a large and growing community of biomedical researchers employing molecular modeling and simulation technologies.

Resource's software is cited once every 1 h and 8 min.
Serving a large and growing community of biomedical researchers employing molecular modeling and simulation technologies.
Computational Structural Biology
Describing Biomolecules at Nanoscale

Structure / Dynamics @ nanoscale
Why Structural Biology at **Nanoscale**?

- Mechanisms in Molecular Biology
- Molecular Basis of Disease
- Drug Design
- Nano-biotechnology

Why Structural Biology at Nanoscale?

✦ Mechanisms in Molecular Biology
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✦ Nano-biotechnology
Why Structural Biology at Nanoscale?

0.00 us

Drug binding to a GPCR
Why Structural Biology at **Nanoscale**?

✦ Mechanisms in Molecular Biology
✦ Molecular Basis of Disease
✦ Drug Design
✦ Nano-biotechnology

Structural changes underlying function
M. Moradi & E. T. PNAS 2013
Why Structural Biology at Nanoscale?

✦ Mechanisms in Molecular Biology
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Structural changes underlying function
Nano-biotechnology
Microfluidic Sensing Devices

Functionalized nanosurface with antibodies

Lab Chip 2012

Created by nanoBIO Node tools
Nano-biotechnology
Gold Nanoparticles as Delivery Vehicles

Schematic model with no prediction power

Cartoon representation of lipid Au NPs

Experiment: Murphy Lab

Modeling/Simulation: Tajkhorshid Lab

Yang, J. A.; Murphy, C. J. Langmuir 2012, 28, 5404–5416
Applications of Computational Methodologies to Structural Biology

Simulation of the dynamics of the molecular system (MD)
- Calculating ensemble-averaged properties of microscopic systems to compare to macroscopic measurements
- Providing a molecular basis for function
- Describing the molecular/structural changes underlying function
- ...

Thermal fluctuations of a phospholipid bilayer

Hydration at the interface of viral shell proteins

Membrane binding of a coagulation protein
Lipid Protein Interaction

Characterizing Energy Landscapes Associated with Functional Motions of Proteins

Outward-facing (OF) to Inward-facing (IF) Transition

~70 µs simulations

String method and Bias-exchange umbrella sampling

Moradi and Tajkhorshid PNAS 2013
Moradi, …, Tajkhorshid Nat. Comm. 2015
Verhalen, …, Tajkhorshid, Mchaourab, Nature 2017
Molecular Dynamics Simulations

Solving the Newtonian equations of motion for all particles at every time step

Major limitations:
- Time scale / sampling
- Force field approximations

Major advantage:
- Unparalleled spatial and temporal resolutions, simultaneously

SPEED LIMIT
1 fs
QwikMD—Gateway to Easy Simulation

Applications of Computational Methodologies to Cell-Scale Structural Biology

Using computational methods as “structure-building” tools

All experimental Structural biological approaches heavily rely on computational methods to analyze their data

- NMR
- X-ray
- Electron Microscopy
- …
Molecular Dynamics Flexible Fitting (MDFF)

Electron Microscope

(Ribosome-bound YidC)

APS Synchrotron

cryo-EM density map

Match through MD

Supercomputer

crystallographic structure

Molecular Dynamics Flexible Fitting (MDFF)

Integrating experimental data to produce models of biomolecular complexes with atomic detail

Technology Made Highly Accessible to the Community

Developed primarily for experimental users
Applications of Computational Methodologies to Cell-Scale Structural Biology

Using simulations as a “structure-building” tool

The most detailed model of a chromatophore

Computational model of a minimal cell envelope
Automated Protein Embedding into Complex Membrane Structures

Distribution of proteins across the membrane surface (dense environment)
  • Ability to handle a variety of protein geometries
  • Proper orientation of proteins in relation to the membrane surface
  • Generalizable and automated method for membranes of arbitrary shape

Embedding proteins into the membrane
  • Account for surface area occupied by proteins in inner and outer leaflets
  • Proper lipid packing around embedded proteins
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113 million Martini particles representing 1 billion atoms

**Protein Components**

- Aquaporin Z: 97
- Copper Transporter (CopA): 166
- F1 ATPase: 63
- Lipid Flipase (MsbA): 29
- Molybdenum transporter (ModBC): 130
- Translocon (SecY): 103
- Methionine transporter (MetNI): 136
- Membrane chaperon (YidC): 126
- Energy coupling factor (ECF): 117
- Potassium transporter (KtrAB): 148
- Glutamate transporter (GltTK): 41
- Cytidine-Diphosphate diacylglycerol (Cds): 50
- Membrane-bound protease (PCAT): 57
- Folate transporter (FolT): 134

Total: 1,397

3.7 M lipids (DPPC), 2.4 M Na⁺ & Cl⁻ ions, 104 M water particles (4 H₂O / particle)
Applications of Computational Methodologies to Cell-Scale Structural Biology

Using simulations as a “structure-building” tool

A bioenergetic membrane

Fully detailed model

~ 4,000 proteins

Experimental data
Applications of Computational Methodologies to Cell-Scale Structural Biology

Guided Construction of Membranes from Experimental Data

Experimentally-Derived Membrane of Arbitrary Shape Builder

Terasaki Ramp

\(~4\) Billion Atoms

- Outer Leaflet
- Inner Leaflet
- Cholesterol
- POPC
- POPE
- POPI
- POPS
- Sphingomyelin
- Cardiolipin

Terasaki et al., Cell, 2013.

Applications of Computational Methodologies to Cell-Scale Structural Biology

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Terasaki Ramp
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Terasaki et al., Cell, 2013.