NIH Biomedical Technology Research Center for Macromolecular Modeling and Bioinformatics

Overview of the Program in Day 3 and 4

Introduction to MD in NAMD
Intro to Molecular Visualization in VMD

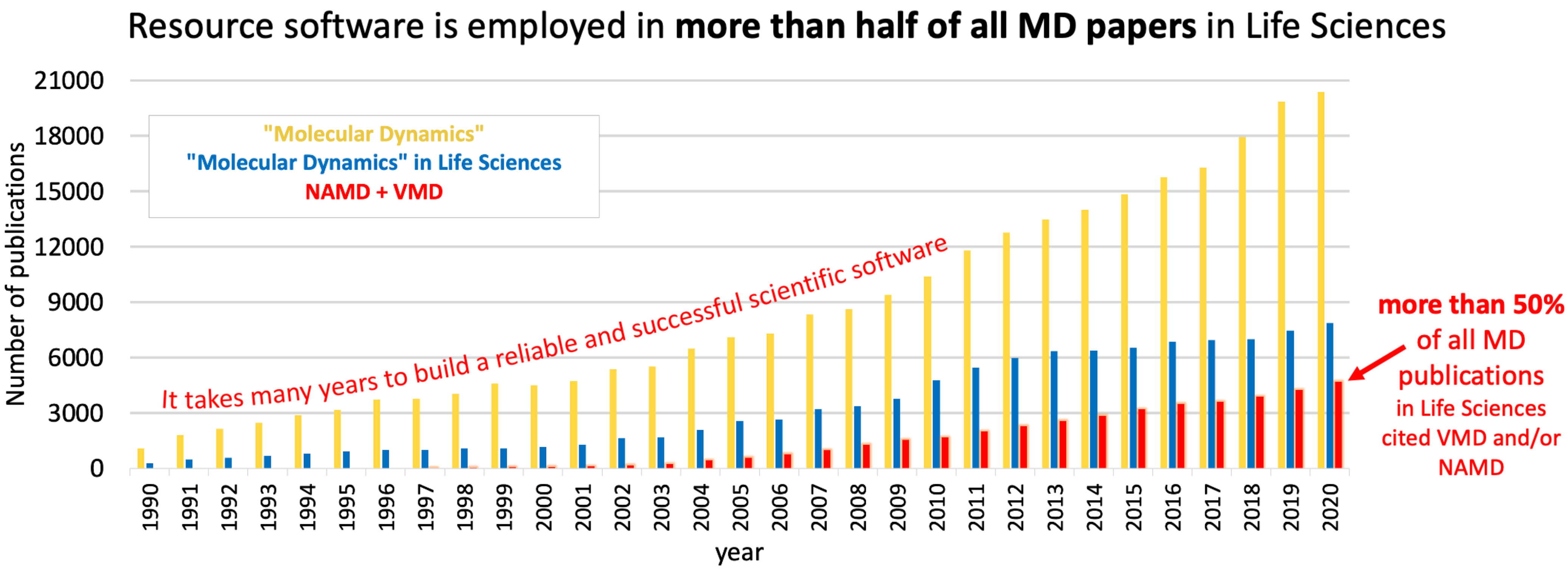
Advanced Modeling Tools

Goal:
Making users comfortable with the software environment

Tutorials — MUST MUST MUST

Emad Tajkhorshid
NIH Center for Macromolecular Modeling and Bioinformatics
Beckman Institute for Advanced Science and Technology
University of Illinois at Urbana-Champaign

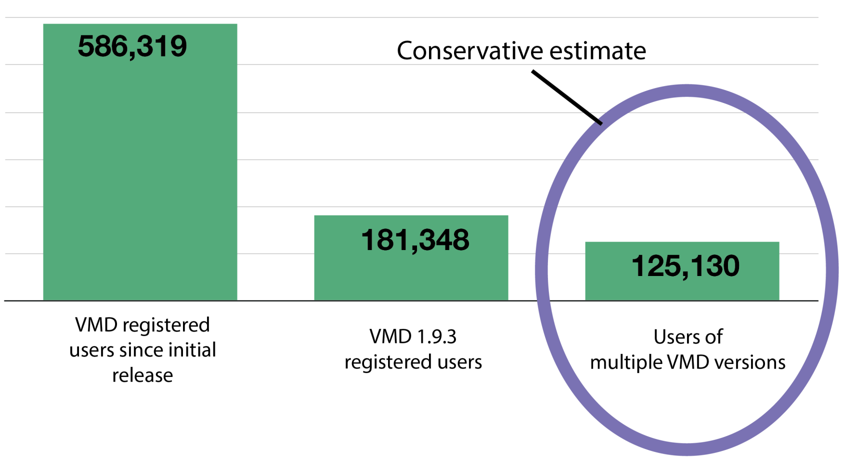
Molecular Dynamics - A Key Tool in Biophysics and Beyond



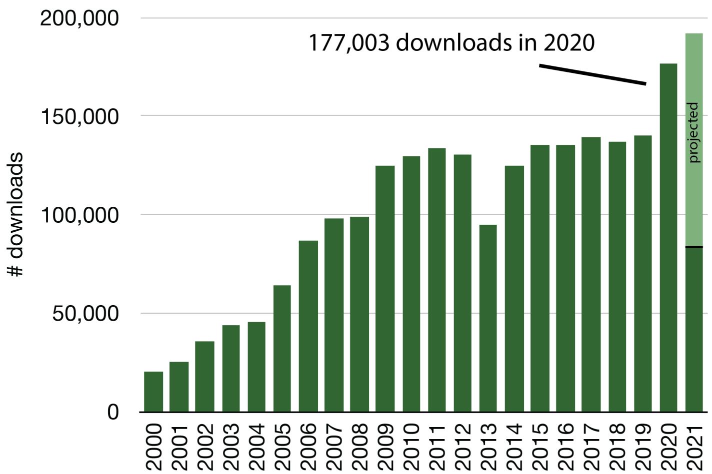
NIH Biomedical Technology Resource for Macromolecular Modeling and Bioinformatics

Serving a large and growing community

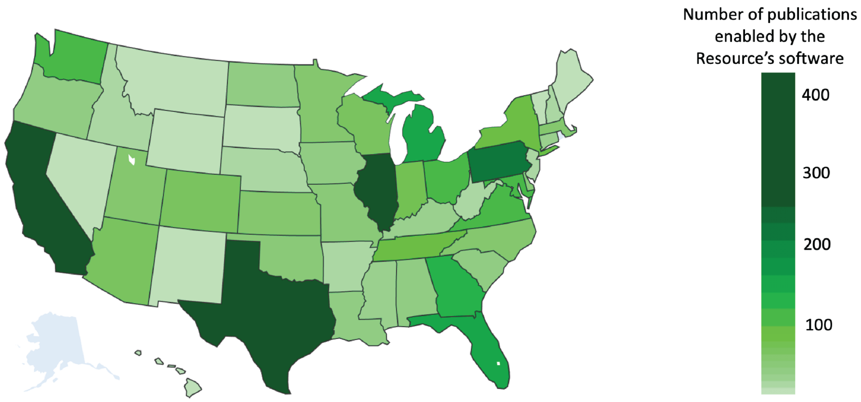
a) Over 125,000 users of Resource software



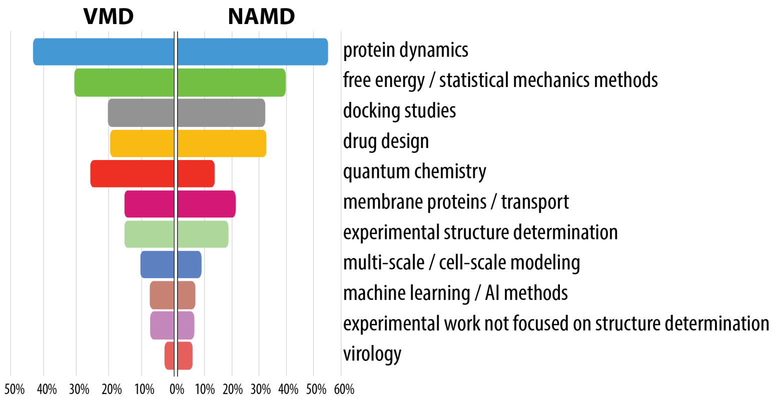
b) Over 2.2 million total downloads of Resource software



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

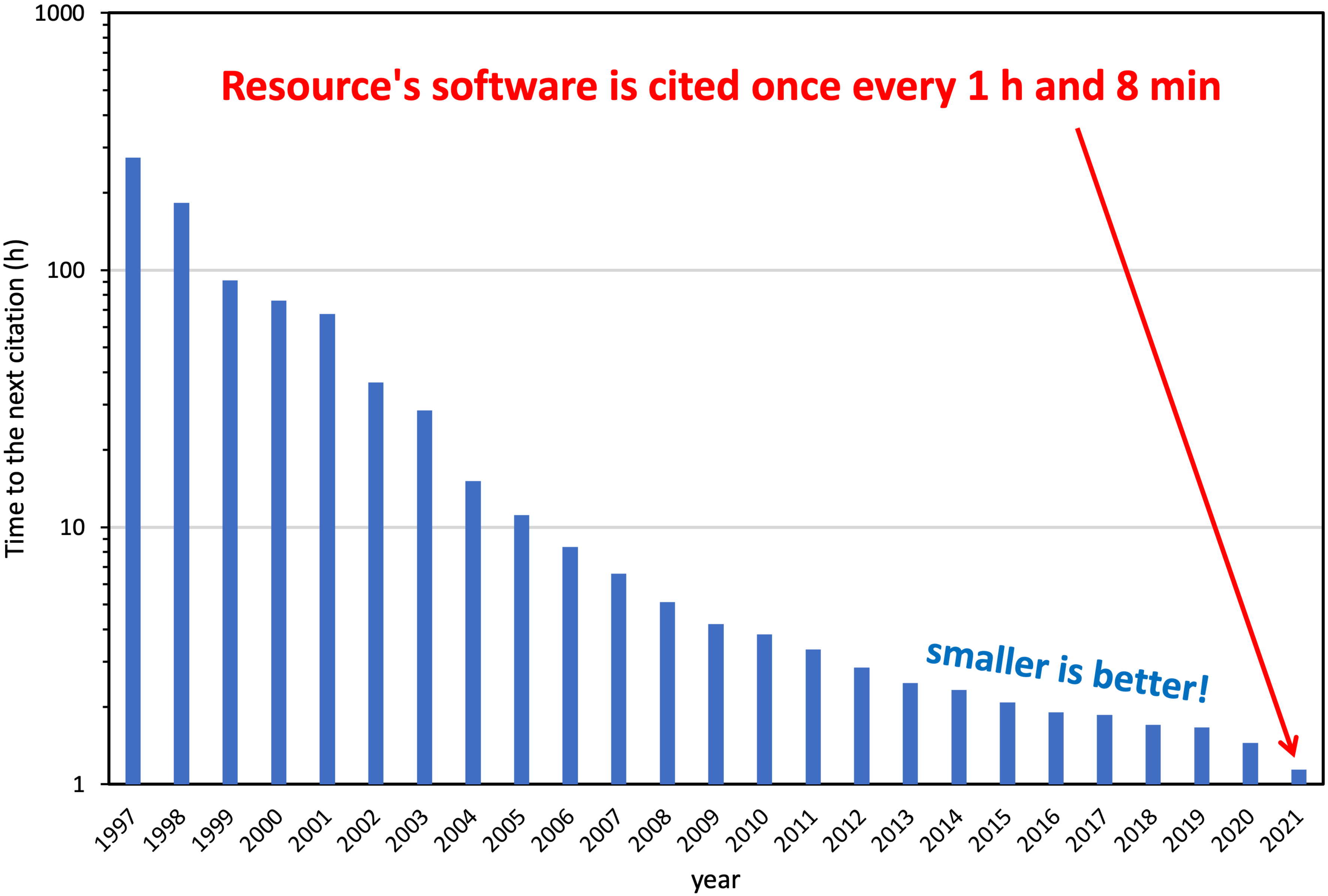


d) VMD and NAMD are used in a broad range of biological fields

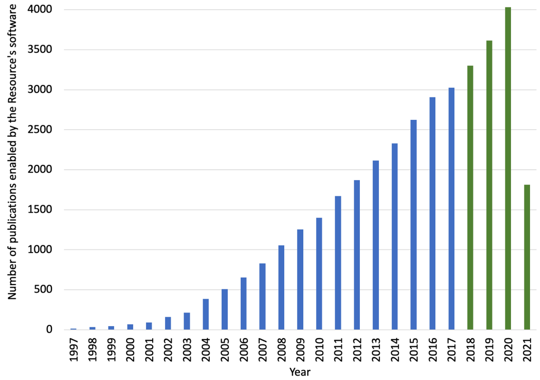


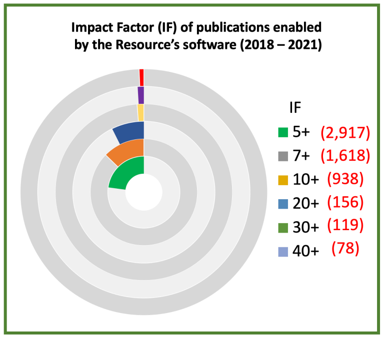
5-yr statistics: **1.4 million** web visitors; **228,000** tutorial views

Serving a large and growing community
of biomedical researchers employing molecular modeling and simulation technologies

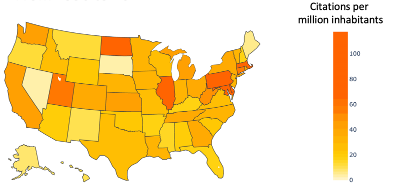


Serving a large and growing community
of biomedical researchers employing molecular modeling and simulation technologies

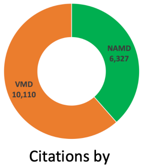



Impact Factor (IF) of publications enabled by the Resource's software (2018 – 2021)

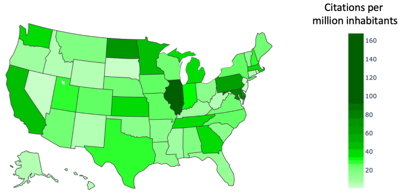
From 1996 to 2021



VMD

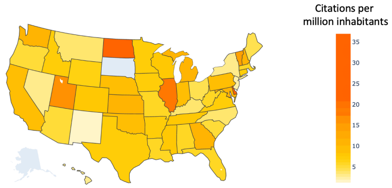


Citations by
US researchers

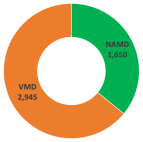


NAMD

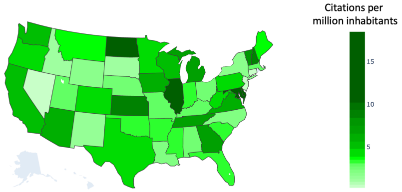
From 2018 to 2021



VMD

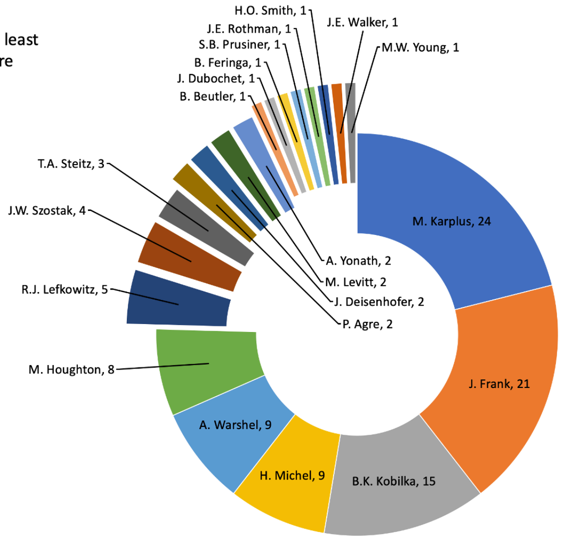


Citations by
US researchers

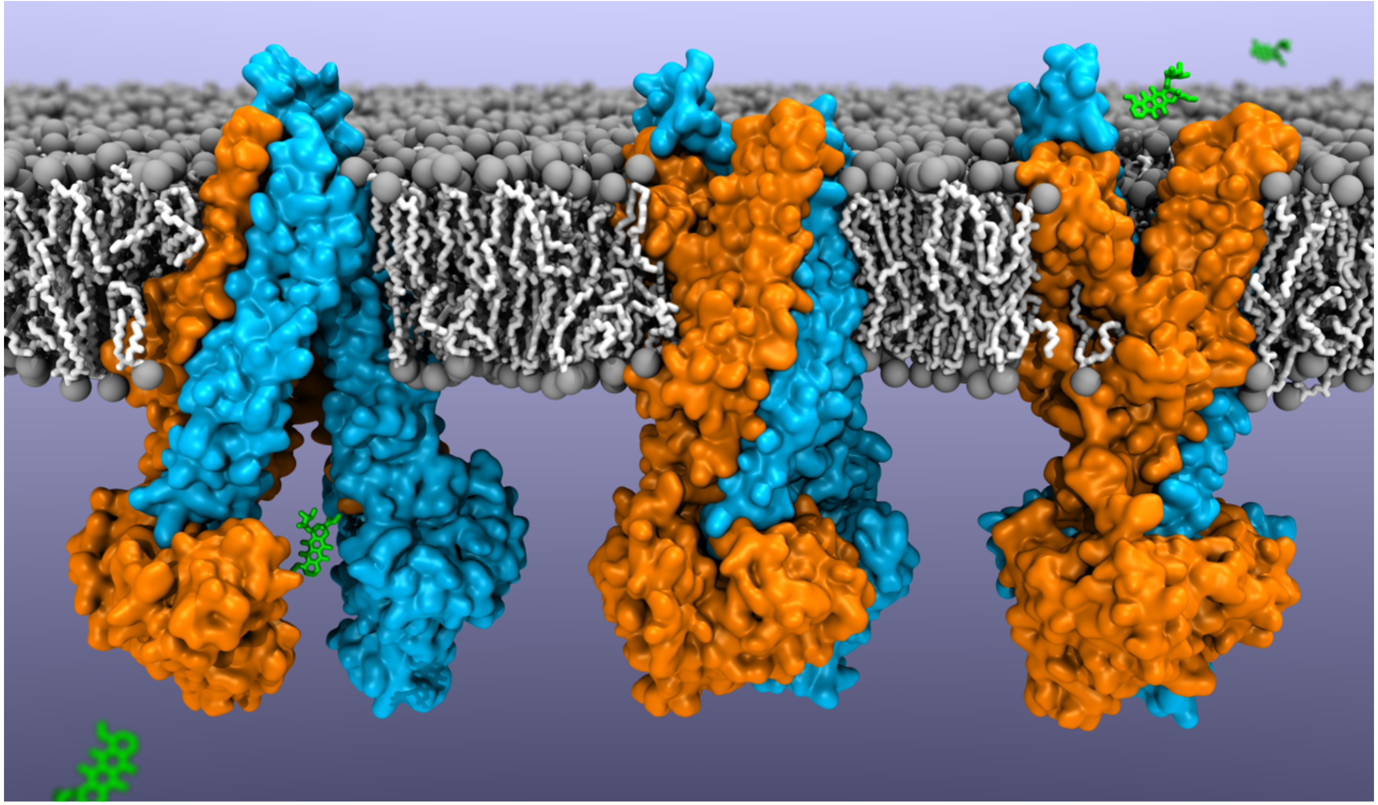


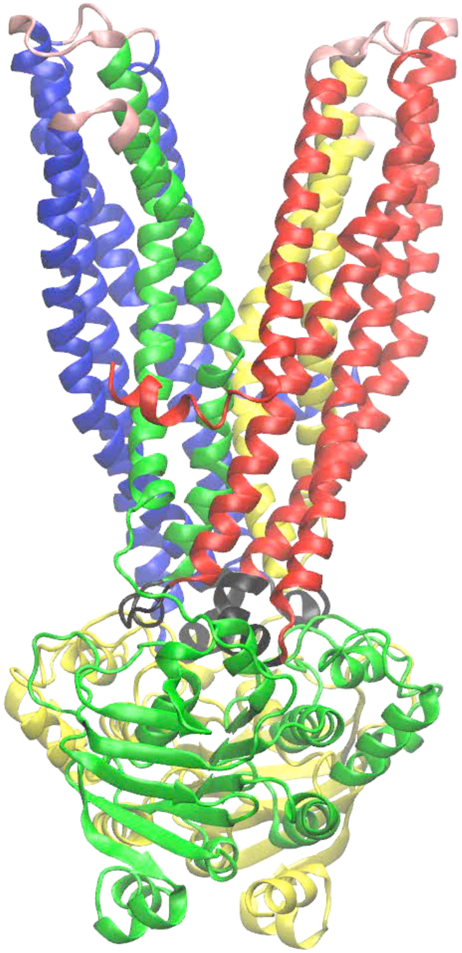
NAMD

Over 20 Nobel Prize laureates have published at least 114 papers employing our resource's software



Computational Structural Biology
Describing Biomolecules at Nanoscale

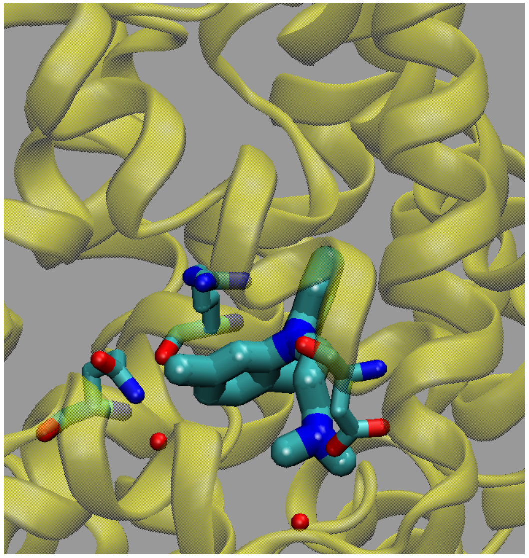


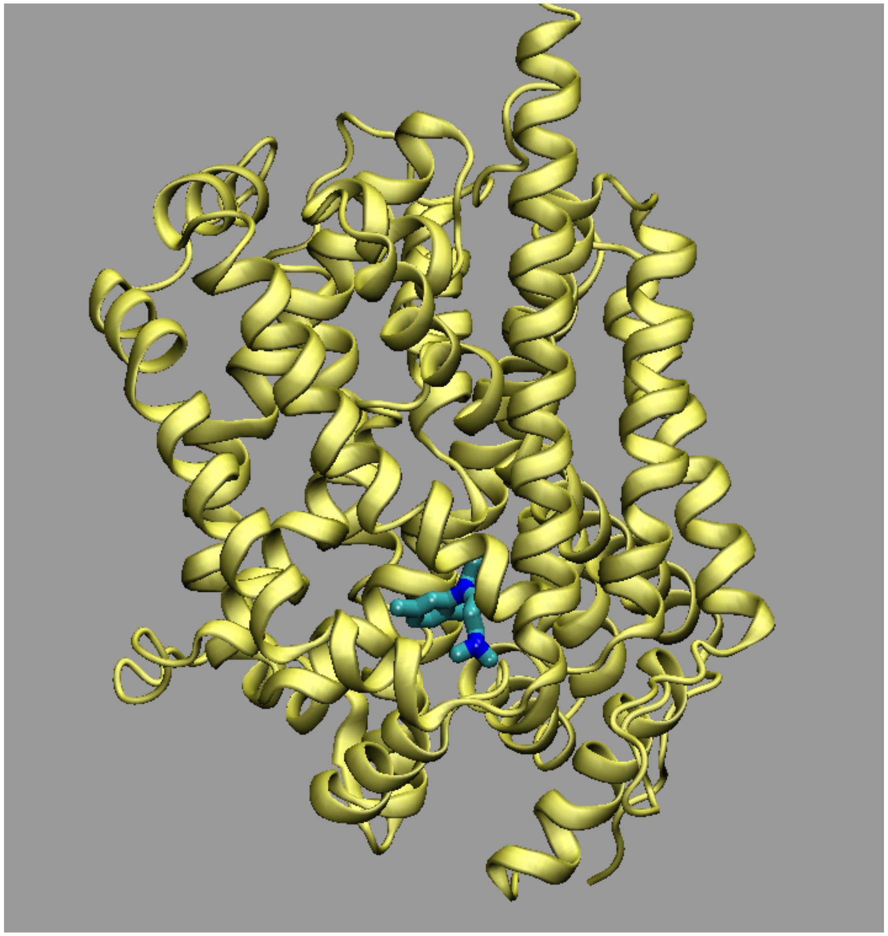


Structure / Dynamics
@ nanoscale

Why Structural Biology at Nanoscale?

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

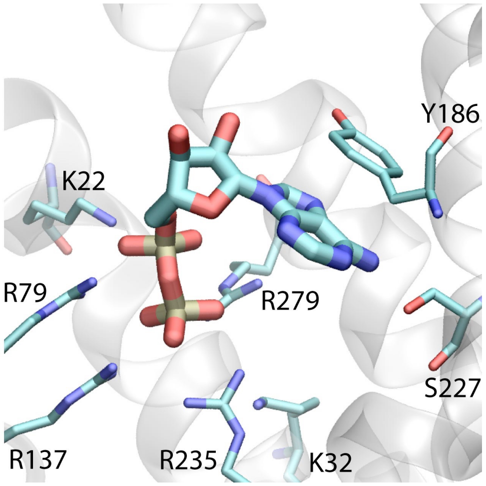


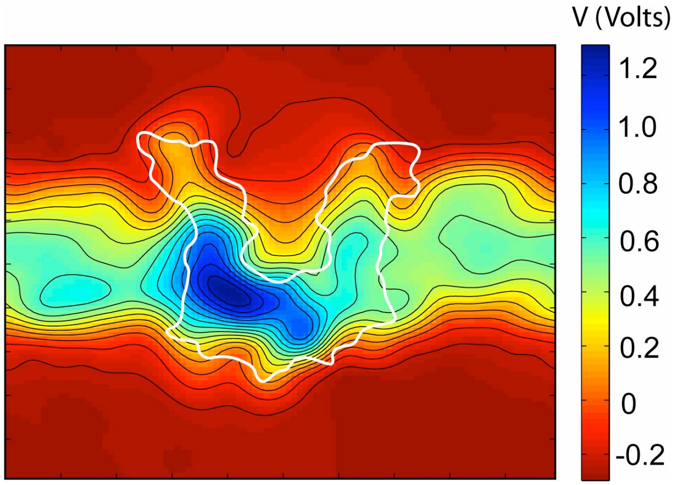


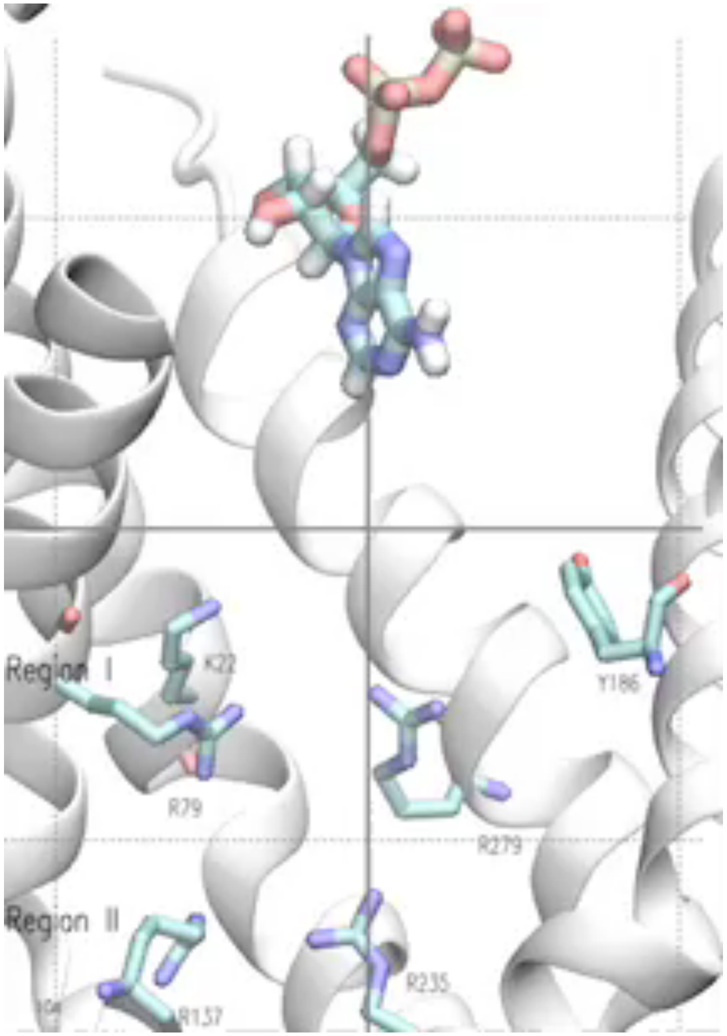
Antidepressant binding site in a neurotransmitter transporter.
Nature 448: 952-956 (2007)

Why Structural Biology at Nanoscale?

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

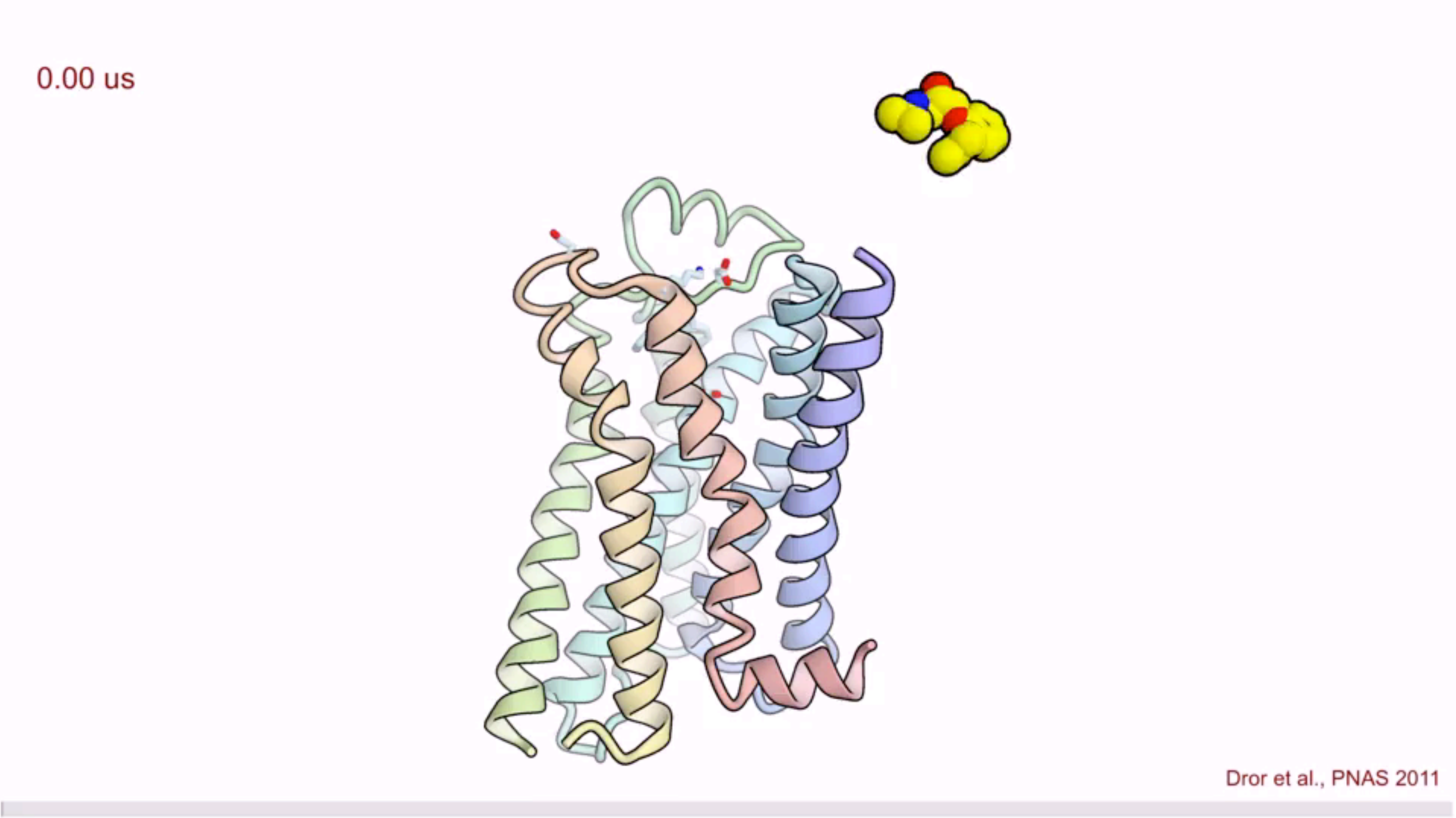






Binding of a small molecule to a binding site
Y. Wang & E.T. PNAS 2010

Why Structural Biology at Nanoscale?

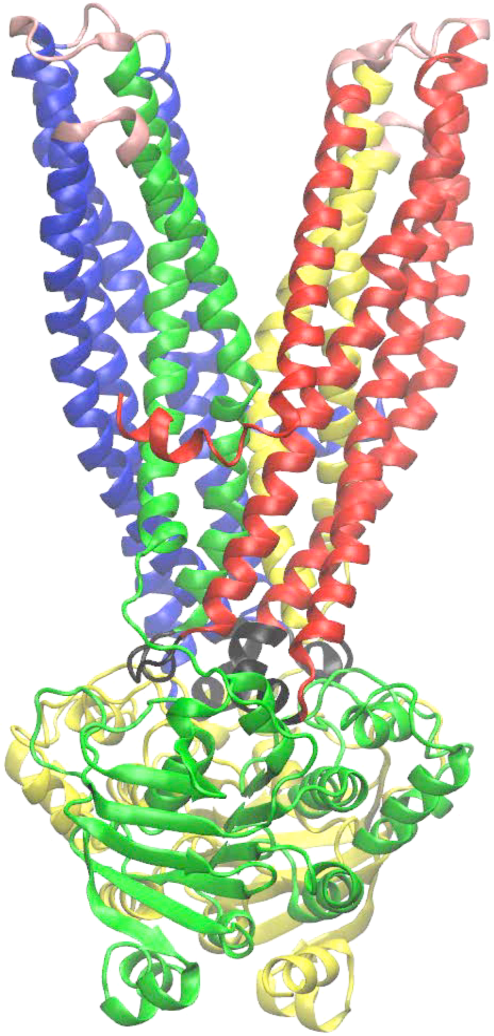


Dror et al., PNAS 2011

Drug binding to a GPCR
Dror, …, Shaw, PNAS, 108:13118–13123 (2011)

Why Structural Biology at Nanoscale?

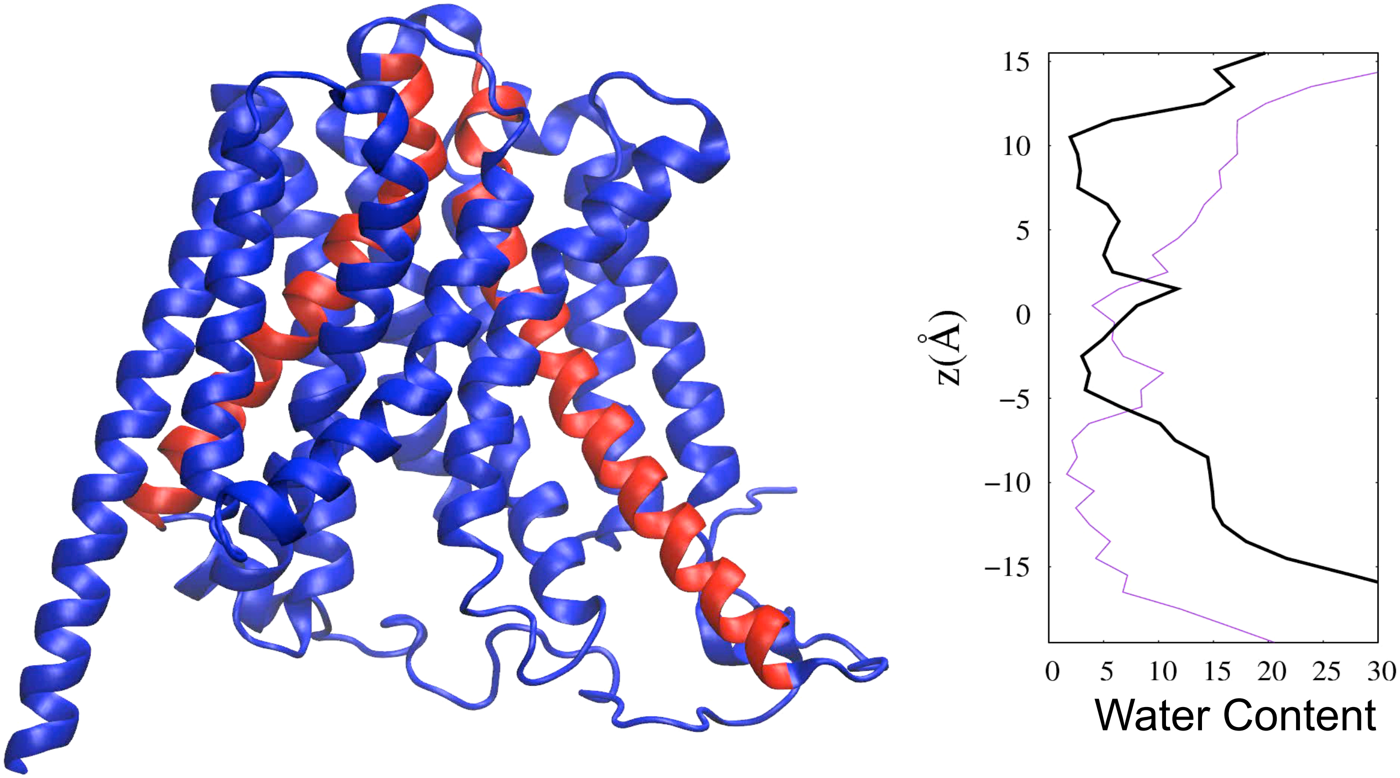
- ✦ Mechanisms in Molecular Biology
- ✦ Molecular Basis of Disease
- ✦ Drug Design
- ✦ Nano-biotechnology



Structural changes underlying function
M. Moradi & E. T. PNAS 2013

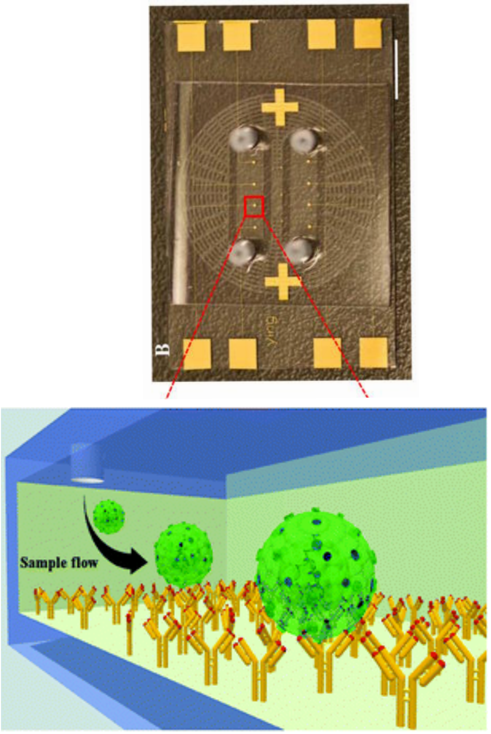
Why Structural Biology at Nanoscale?

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



Structural changes underlying function
M. Moradi, G. Enkavi, & E. T. Nature Comm. 2015

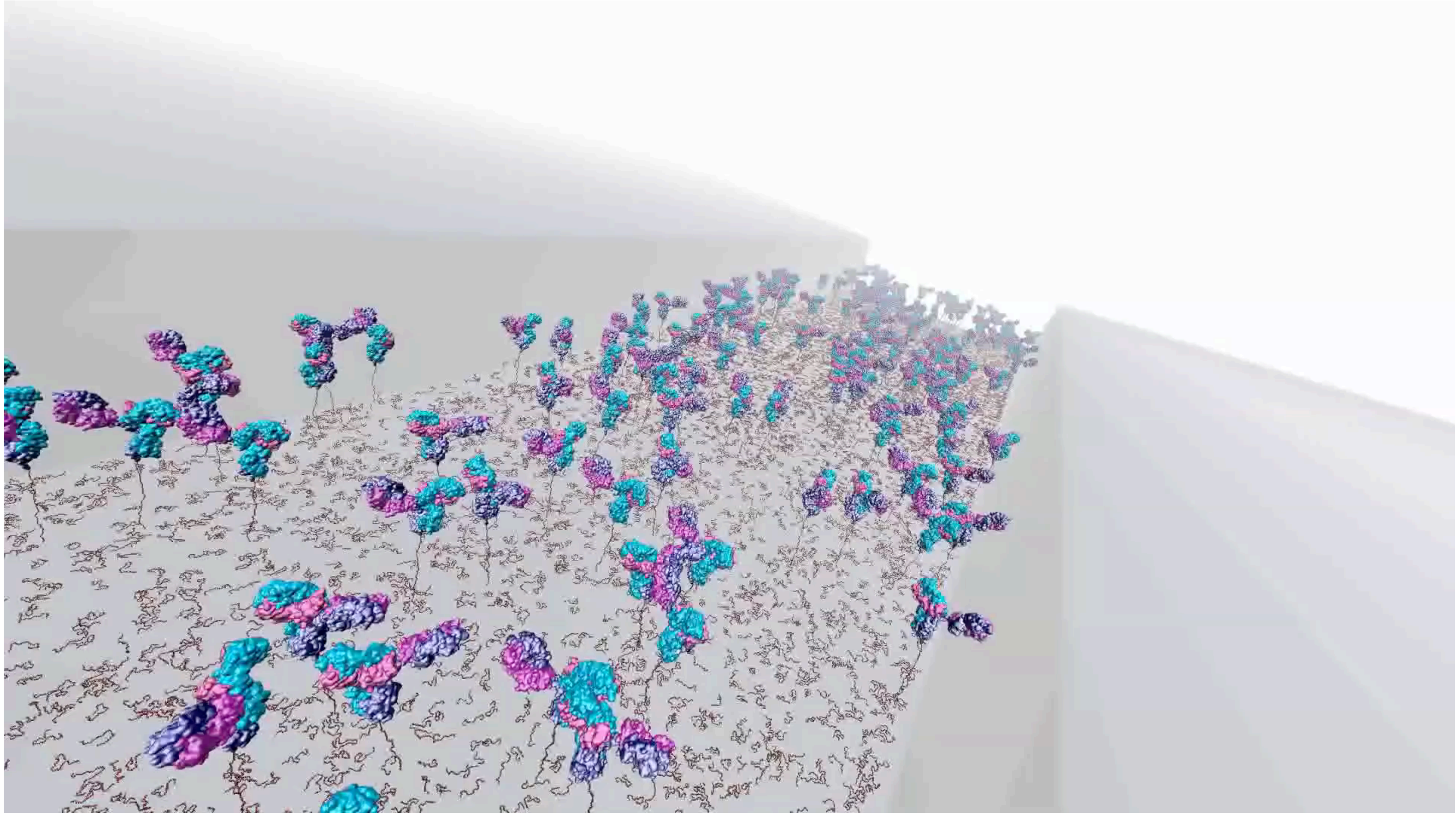
Nano-biotechnology
Microfluidic Sensing Devices



HIV subtype identification

Lab Chip 2012

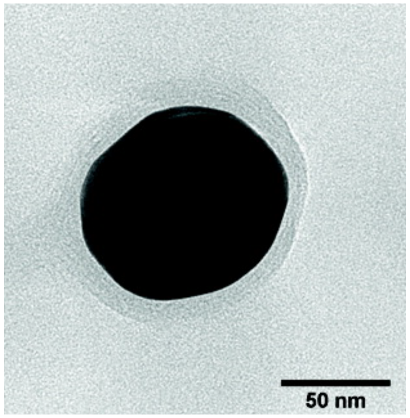
Functionalized nanosurface with antibodies



Created by **nanoBIO Node** tools

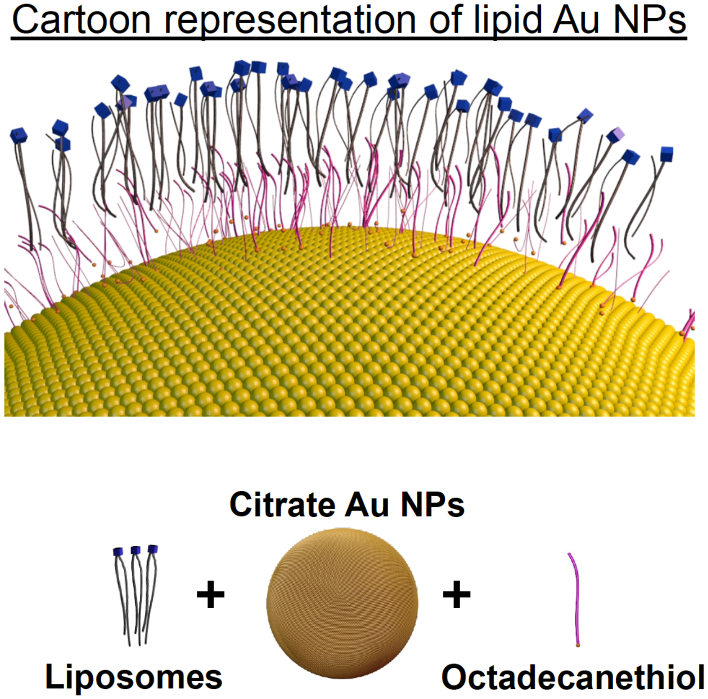
Nano-biotechnology
Gold Nanoparticles as Delivery Vehicles

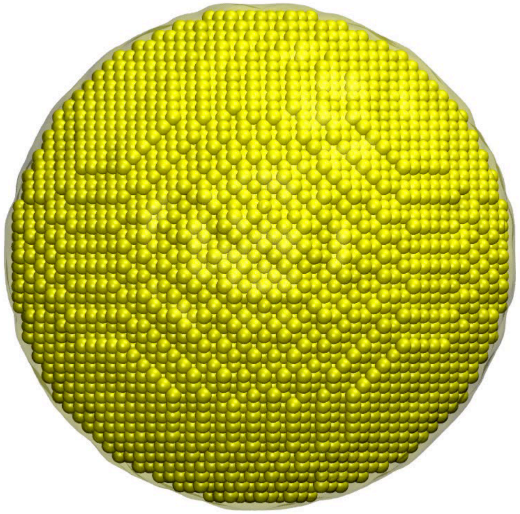
Transmission
Electron Micrograph



Yang, J. A.; Murphy, C. J. Langmuir 2012, 28, 5404–5416

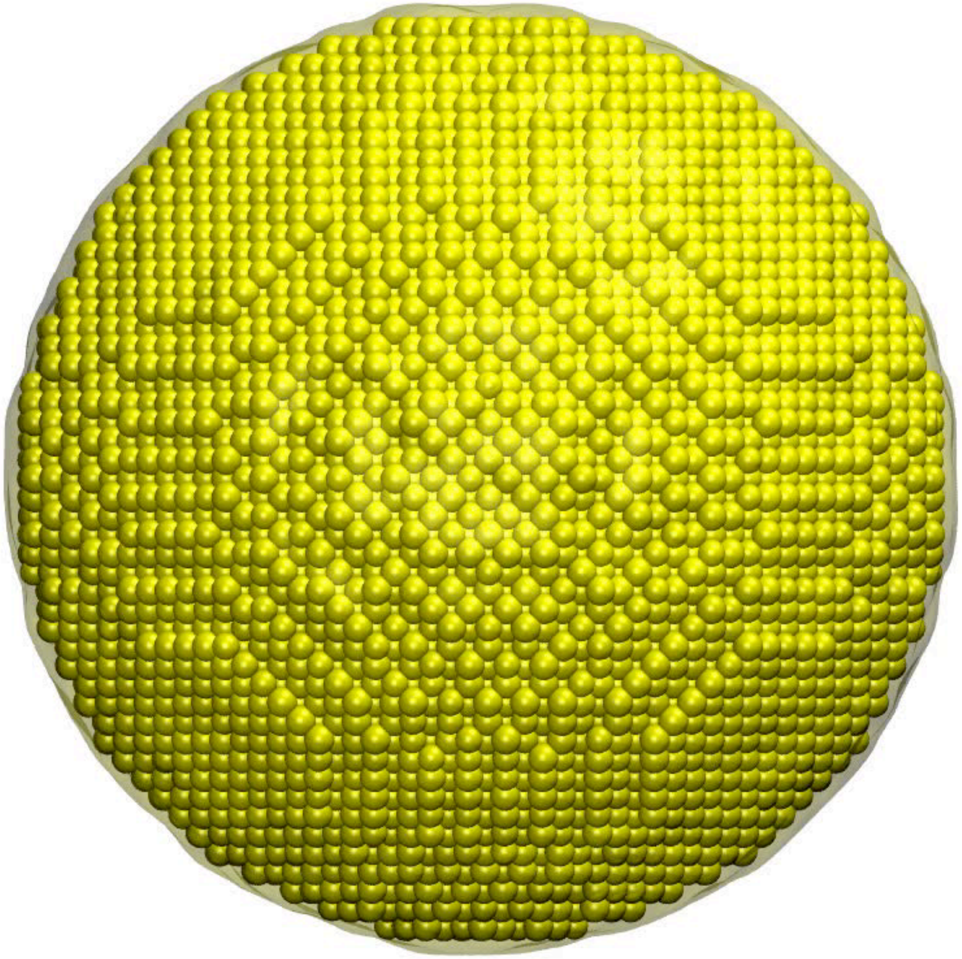
Schematic model with
no prediction power





Experiment:
Murphy Lab

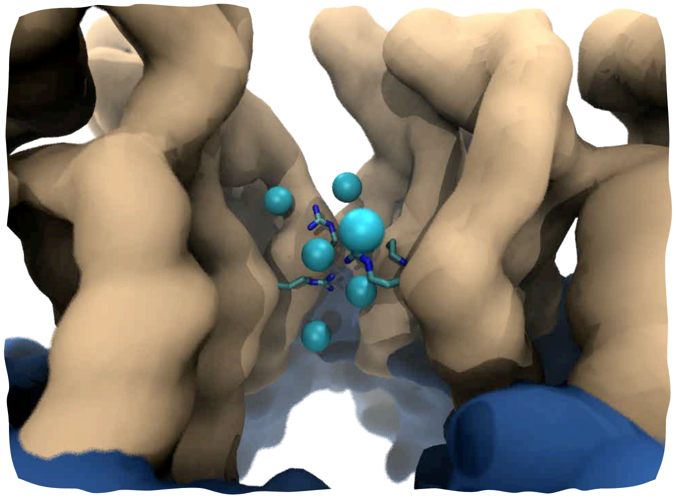
Modeling/Simulation:
Tajkhorshid Lab



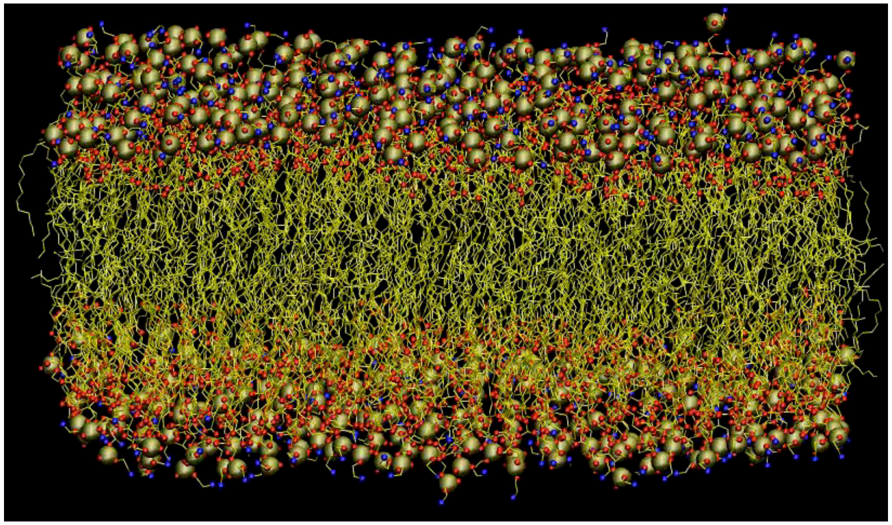
Applications of Computational Methodologies to Structural Biology

Simulation of the dynamics of the molecular system (MD)

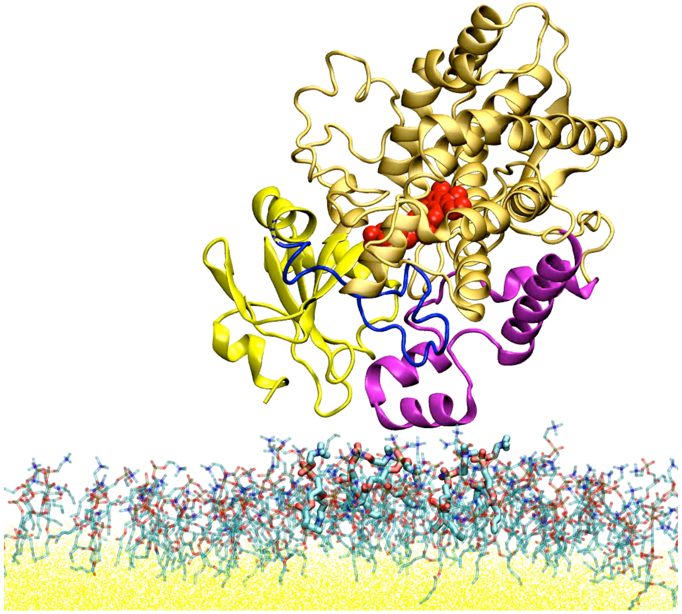
- Calculating ensemble-averaged properties of microscopic systems to compare to macroscopic measurements
- Providing a molecular basis for function
- Describing the molecular/structural changes underlying function
- …



Hydration at the interface of viral shell proteins

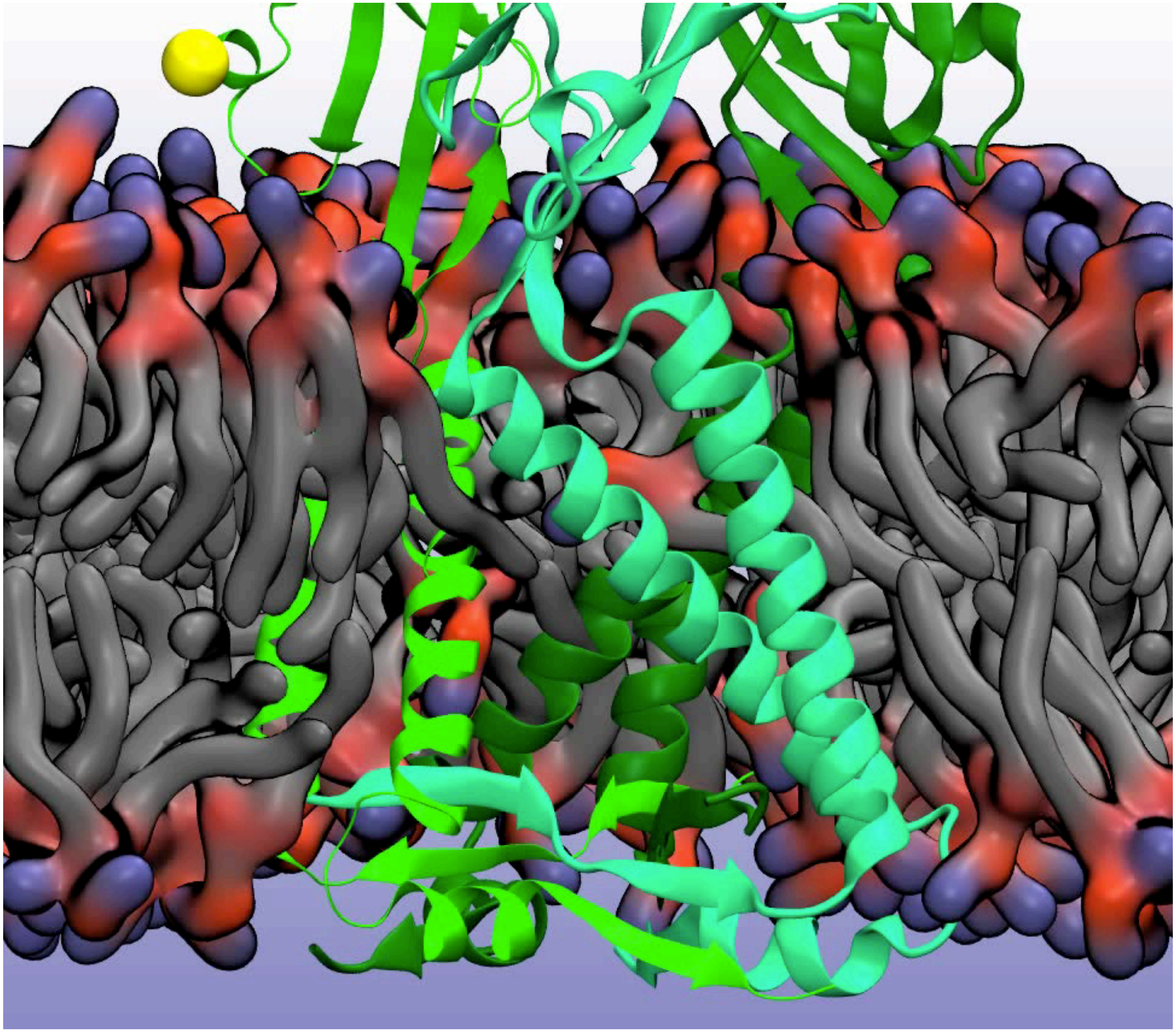


Thermal fluctuations of a phospholipid bilayer



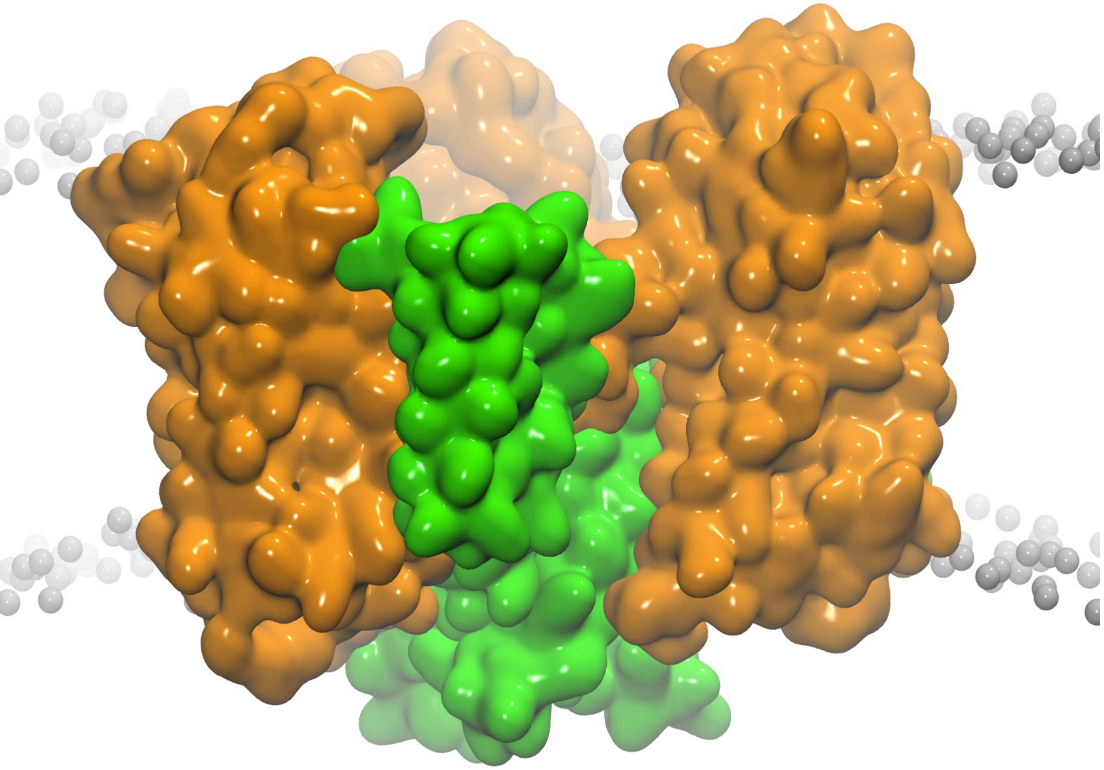
Membrane binding of a coagulation protein

Lipid Protein Interaction

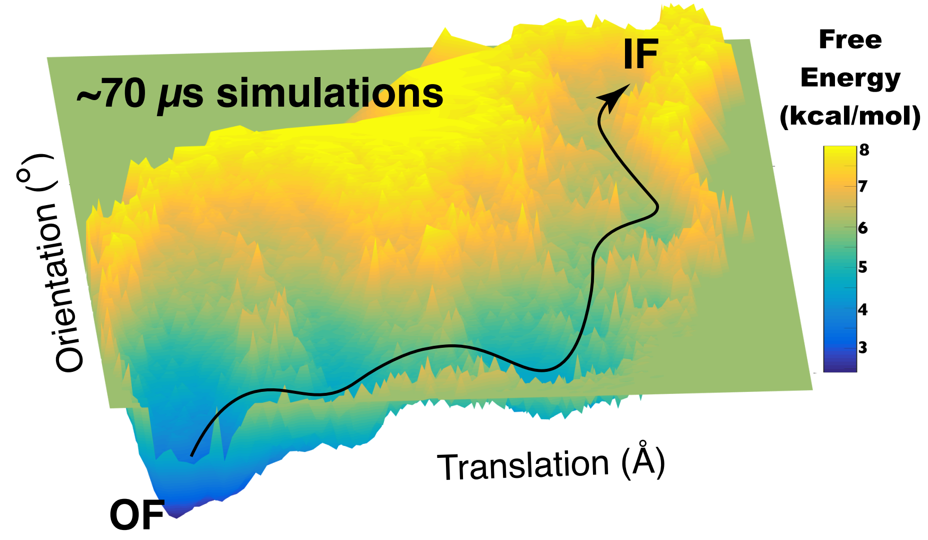


S. Mansoor, …, E. Tajkhorshid, E. Gouaux, Nature, 2016.

Characterizing Energy Landscapes Associated with Functional Motions of Proteins



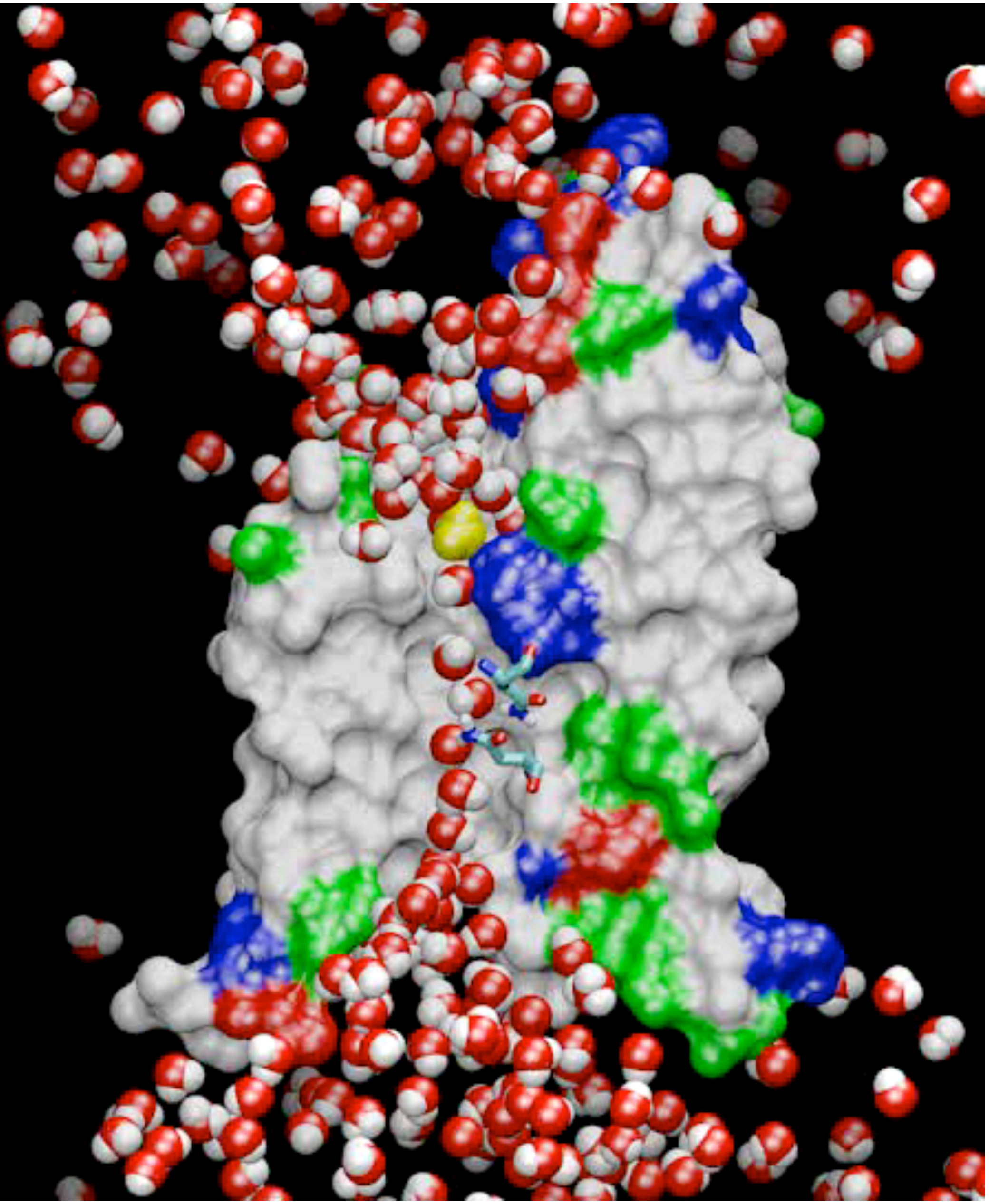
Outward-facing (OF) to Inward-facing (IF) Transition



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

String method and Bias-exchange umbrella sampling

Molecular Dynamics Simulations



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

Major limitations:

- Time scale / sampling
- Force field approximations

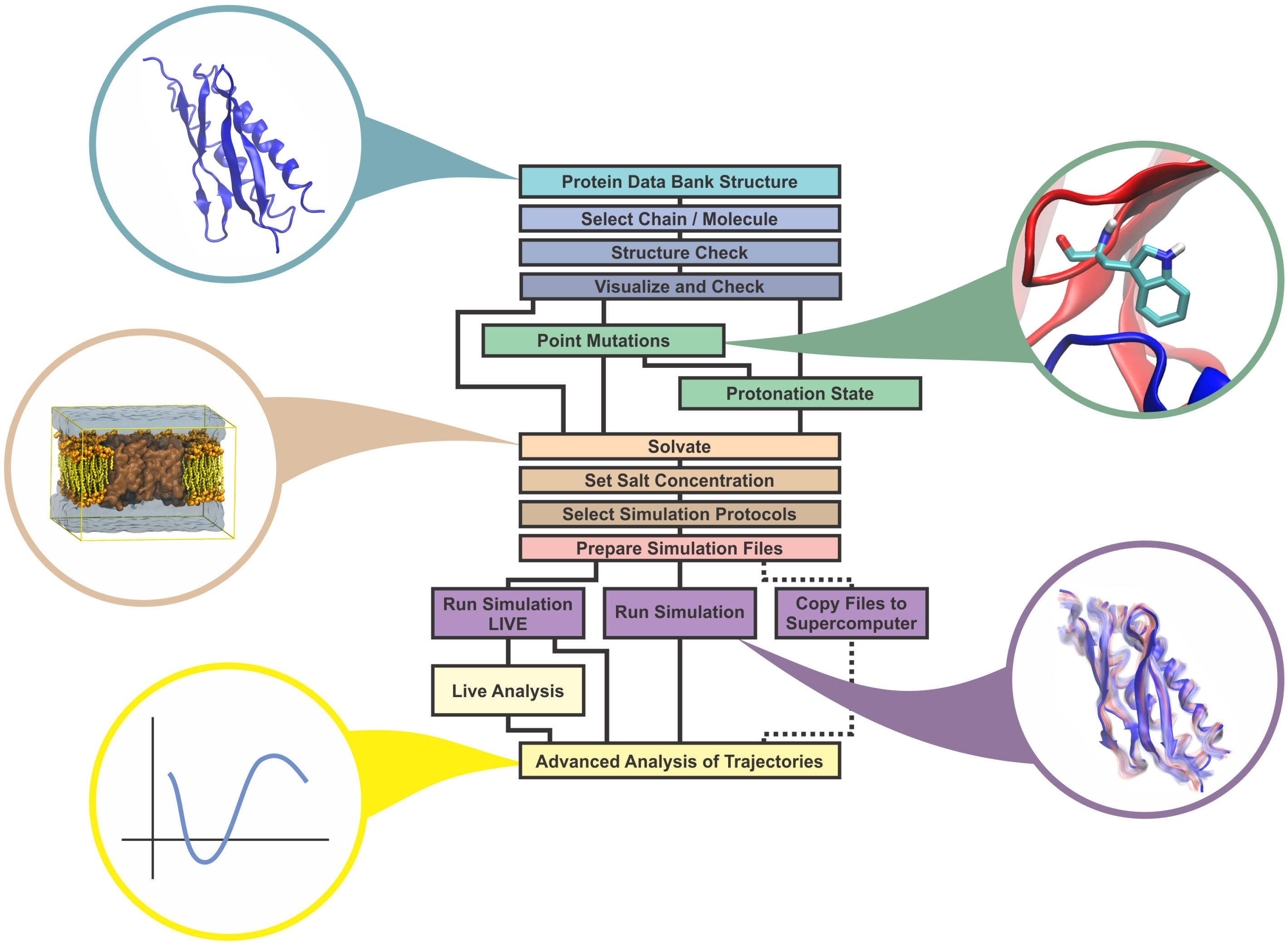
SPEED LIMIT

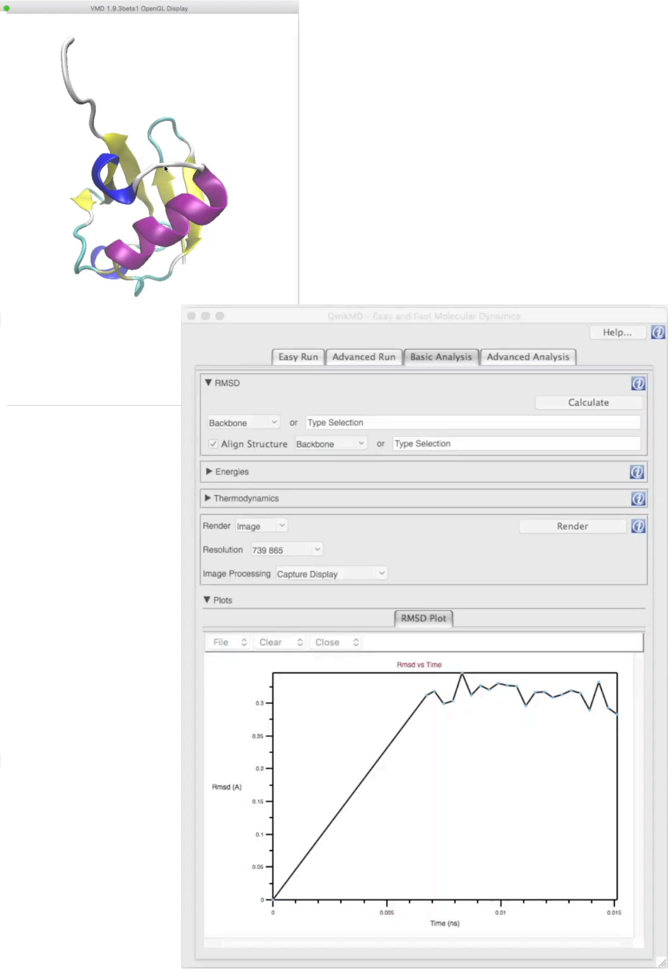
1 fs

Major advantage:

- Unparalleled spatial and temporal resolutions, simultaneously

QwikMD- Gateway to Easy Simulation





Backbone or Type Selection

☑ Align Structure Backbone or Type Selection

Render Image

Resolution 739 865

Image Processing Capture Display

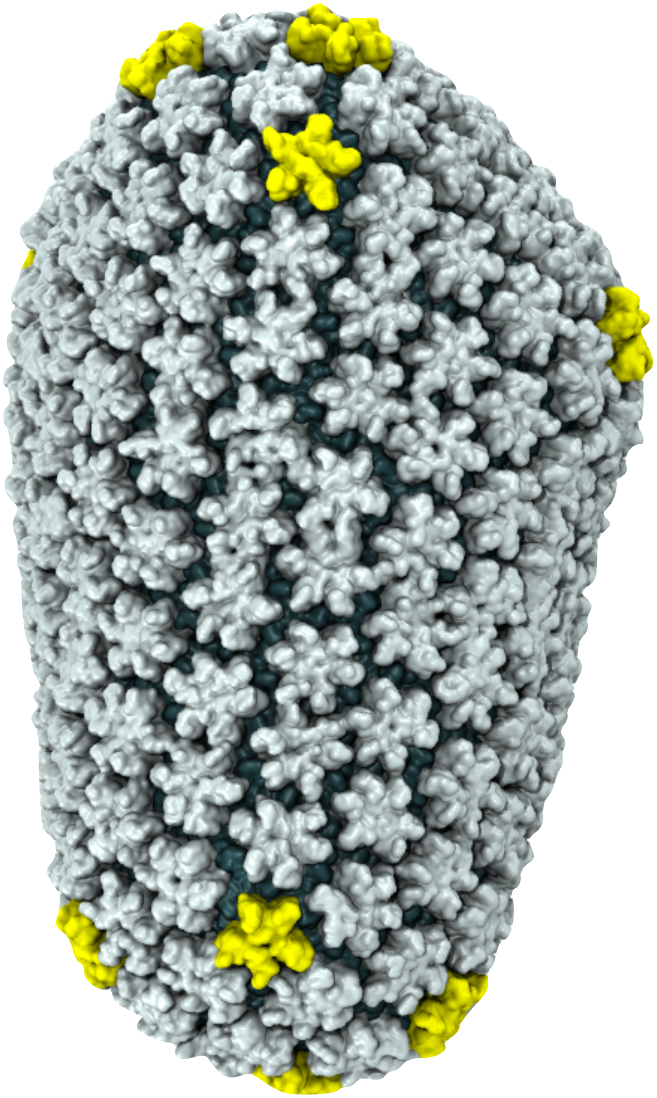
Ribeiro, J. V., …, Schulten, K.. QwikMD — Integrative Molecular Dynamics Toolkit for Novices and Experts. ***Sci. Rep***. 6, 26536; doi: 10.1038/srep26536 (**2016**)

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

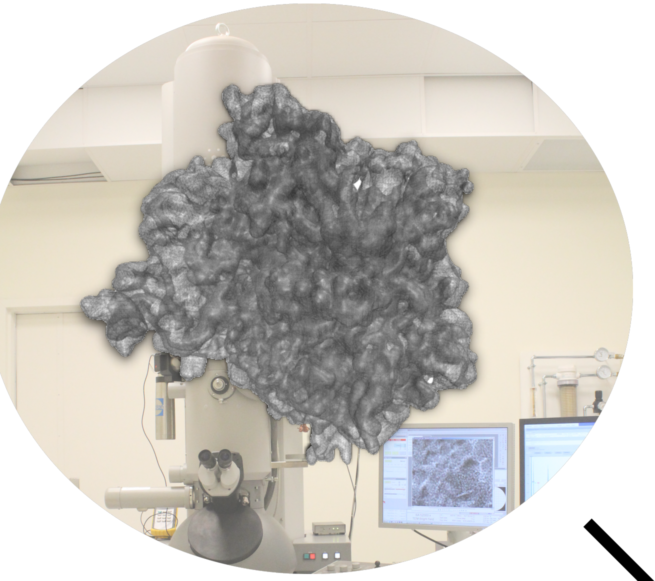
- NMR
- X-ray
- Electron Microscopy
- …



Structural model of HIV virus

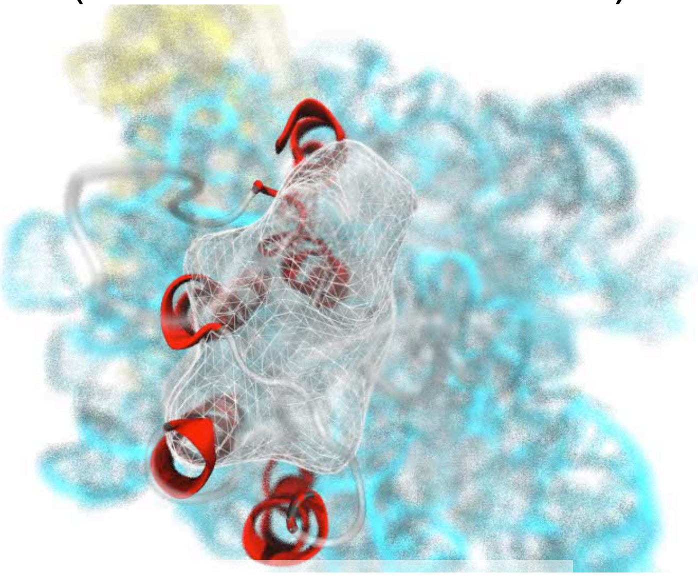
Molecular Dynamics Flexible Fitting (MDFF)

Electron
Microscope



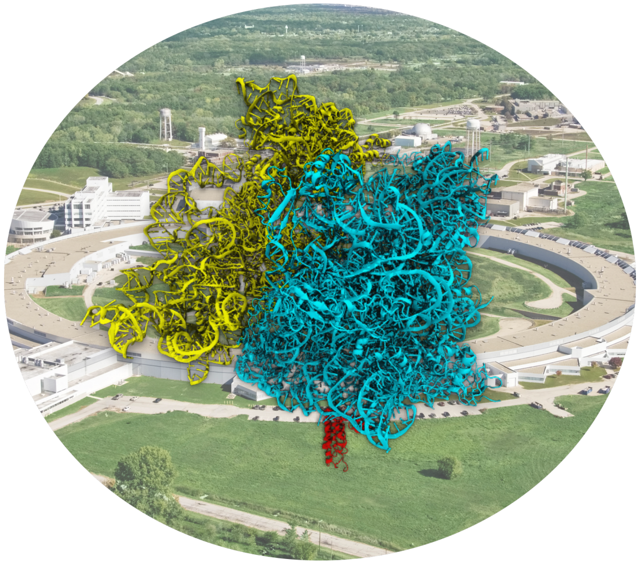
cryo-EM density
map

(Ribosome-bound YidC)

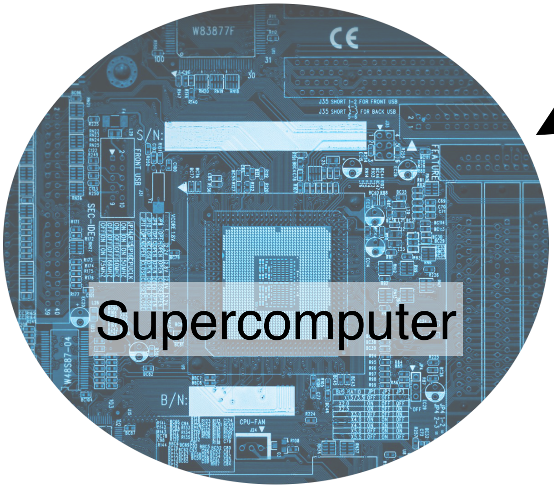


Match through MD

APS
Synchrotron



crystallographic
structure

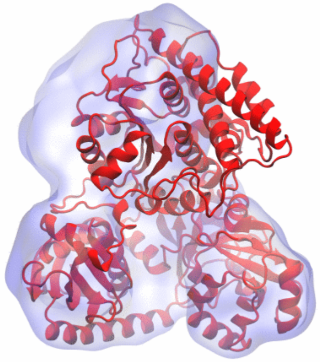


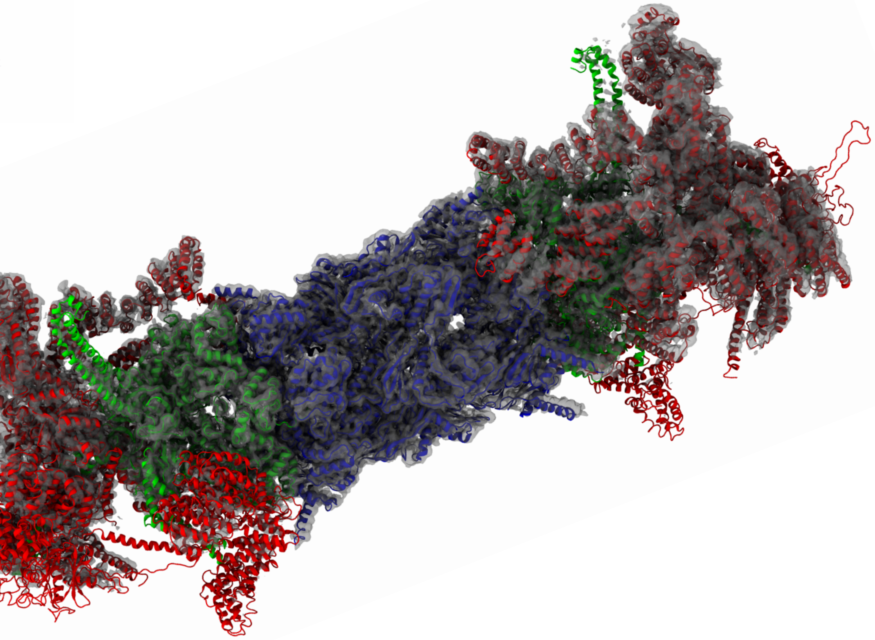
Supercomputer

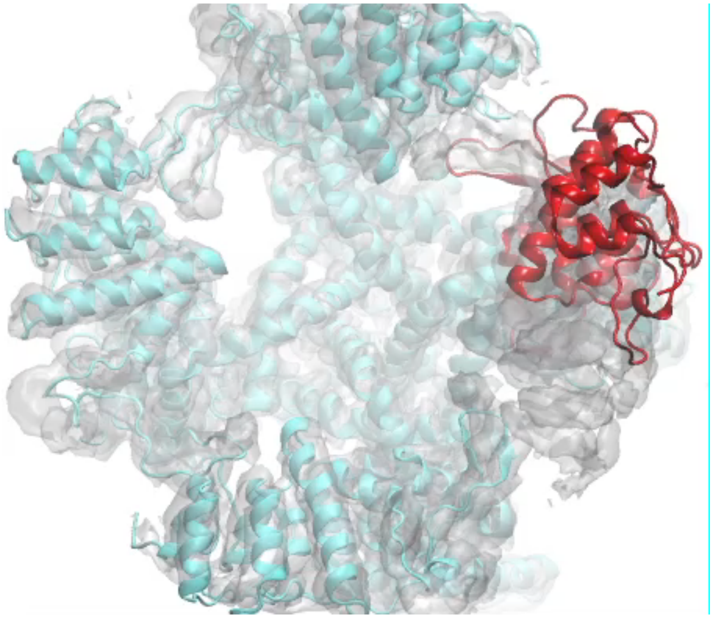
[1] Trabuco et al. *Structure* (2008) 16:673-683.
[2] Trabuco et al. *Methods* (2009) 49:174-180.

Molecular Dynamics Flexible Fitting (MDFF)

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





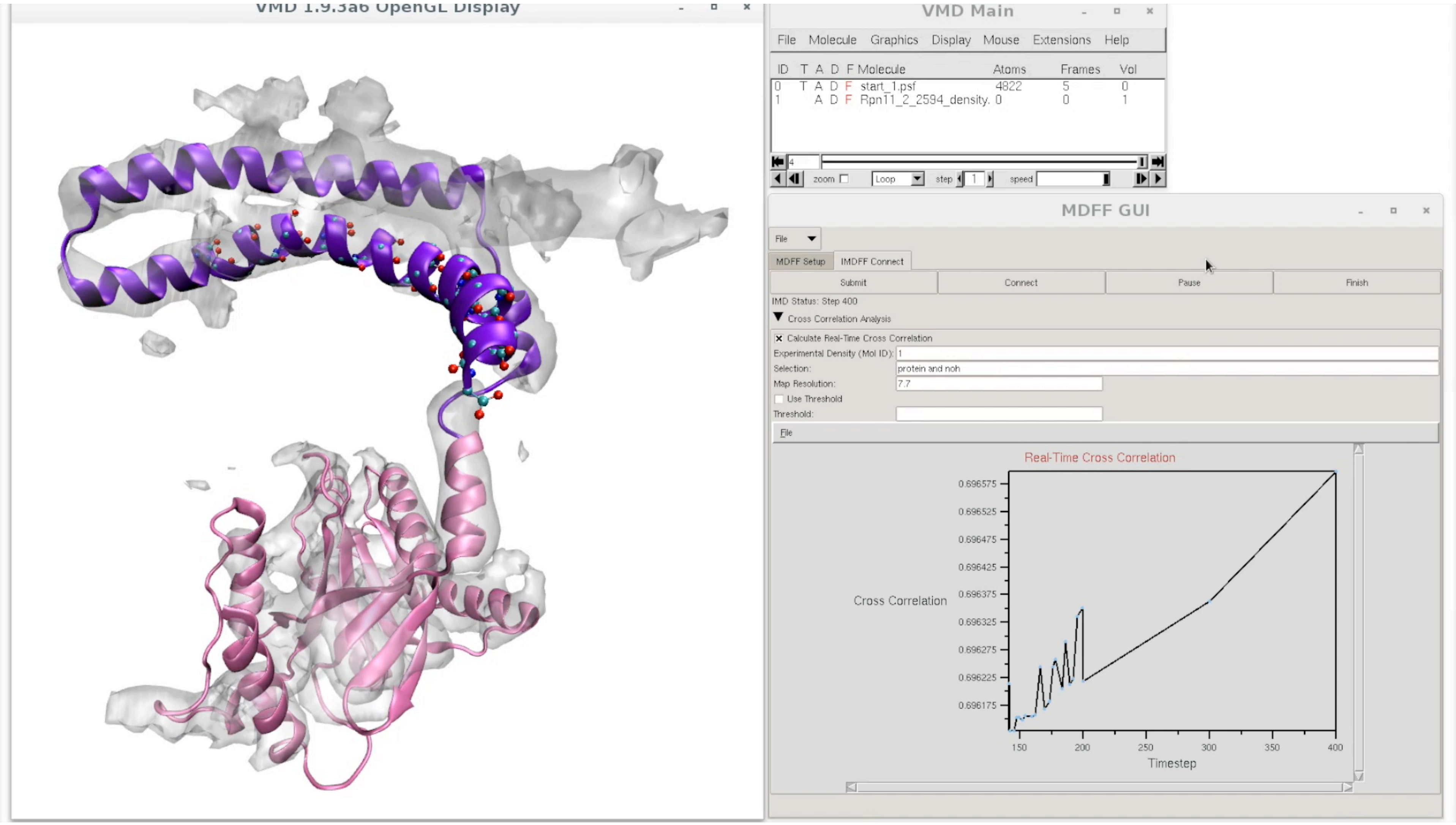


[1] Trabuco et al. *Structure* (2008) 16:673-683.

[2] Trabuco et al. *Methods* (2009) 49:174-180.

Technology Made Highly Accessible to the Community

interactive MDFF



ID	T	A	D	F	Molecule	Atoms	Frames	Vol
0	T	A	D	F	start_1.psf	4822	5	0
1		A	D	F	Rpn11_2_2594_density.	0	0	1

IMD Status: Step 400

Cross Correlation Analysis

☒ Calculate Real-Time Cross Correlation

Experimental Density (Mol ID): 1

Selection: protein and noh

Map Resolution: 7.7

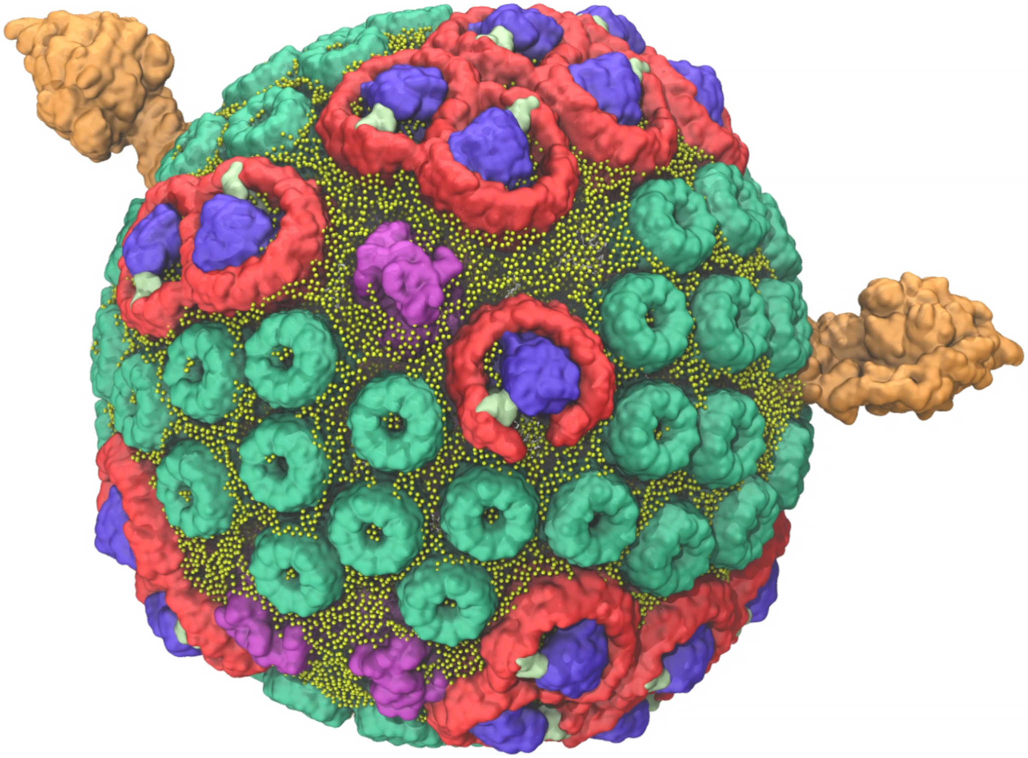
☐ Use Threshold

Threshold:

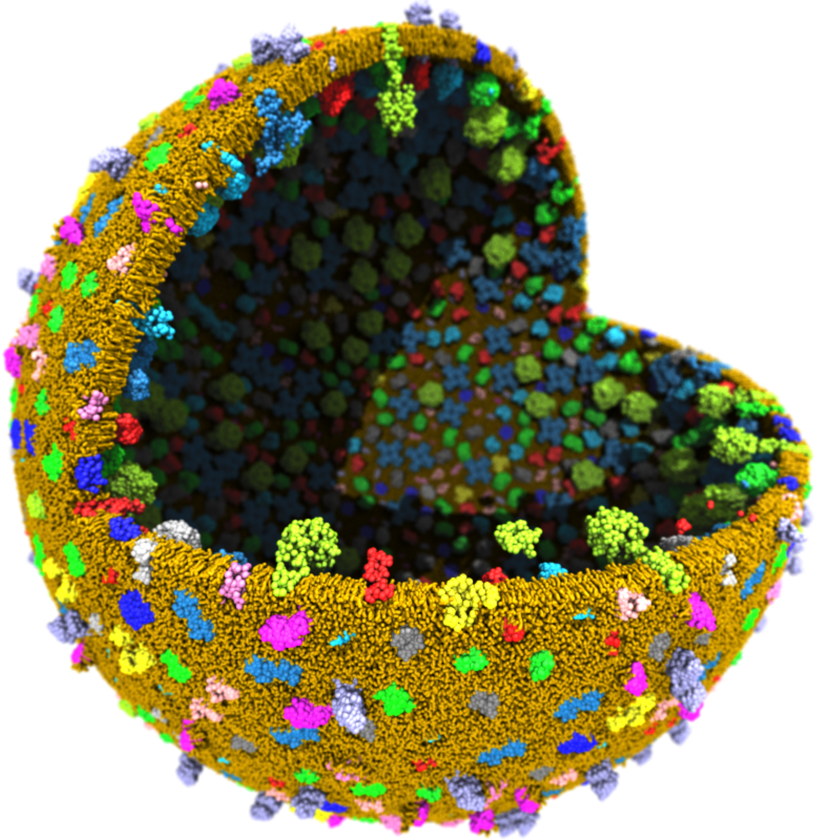
Developed primarily for experimental users

Applications of Computational Methodologies to Cell-Scale Structural Biology

Using simulations as a "structure-building" tool



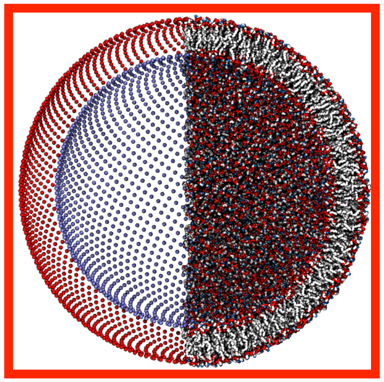
The most detailed model of a chromatophore



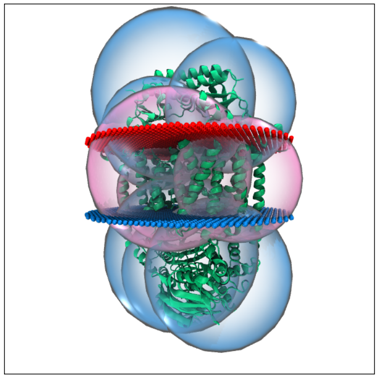
Computational model of a minimal cell envelope

Automated Protein Embedding into Complex Membrane Structures

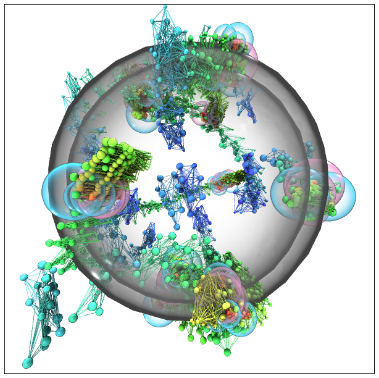
Vesicle Construction



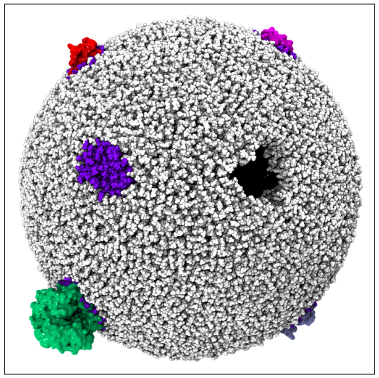
Coarse Grain Protein

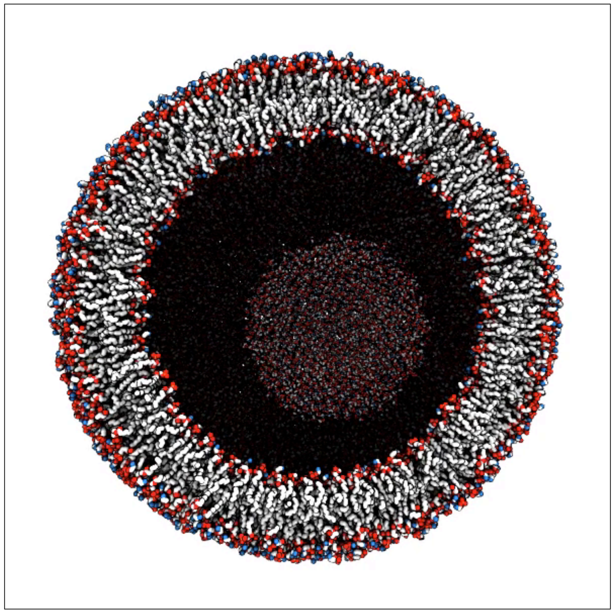


CG Protein Placement



Combine Lipid + Protein





Distribution of proteins across the membrane surface (dense environment)

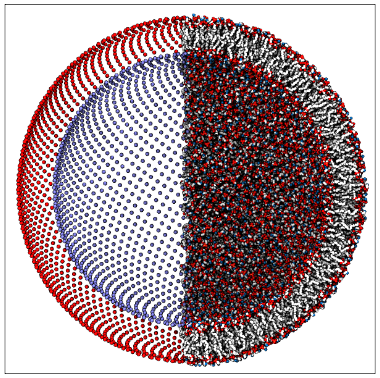
- Ability the handle a variety of protein geometries
- Proper orientation of proteins in relation to the membrane surface
- Generalizable and automated method for membranes of arbitrary shape

Embedding proteins into the membrane

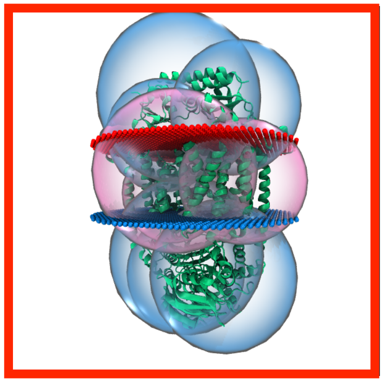
- Account for surface area occupied by proteins in inner and outer leaflets
- Proper lipid packing around embedded proteins

Automated Protein Embedding into Complex Membrane Structures

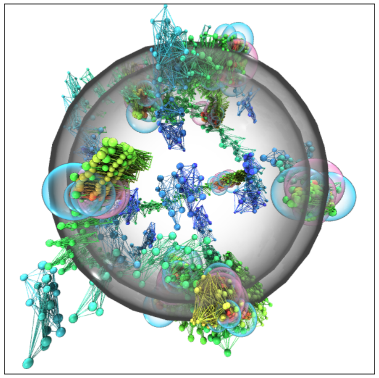
Vesicle Construction



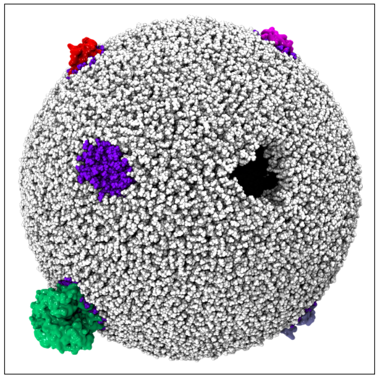
Coarse Grain Protein

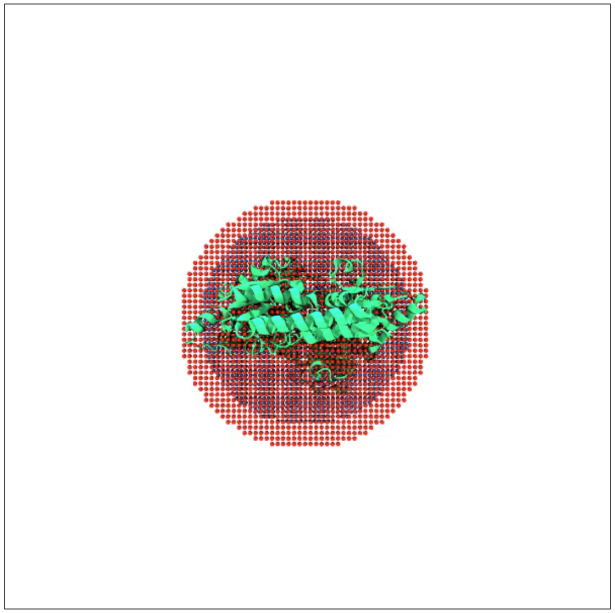


CG Protein Placement



Combine Lipid + Protein





Distribution of proteins across the membrane surface (dense environment)

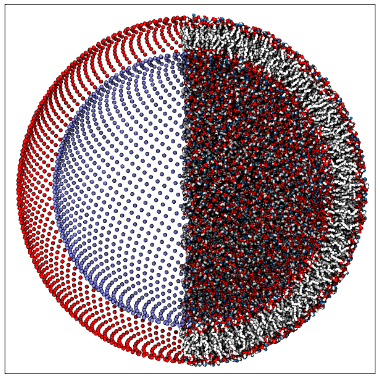
- Ability the handle a variety of protein geometries
- Proper orientation of proteins in relation to the membrane surface
- Generalizable and automated method for membranes of arbitrary shape

Embedding proteins into the membrane

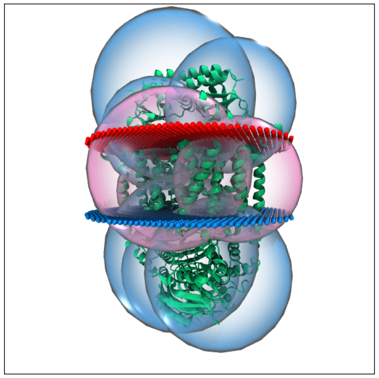
- Account for surface area occupied by proteins in inner and outer leaflets
- Proper lipid packing around embedded proteins

Automated Protein Embedding into Complex Membrane Structures

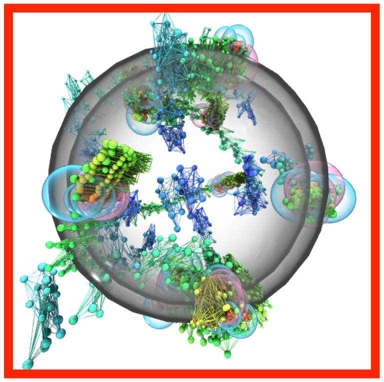
Vesicle Construction



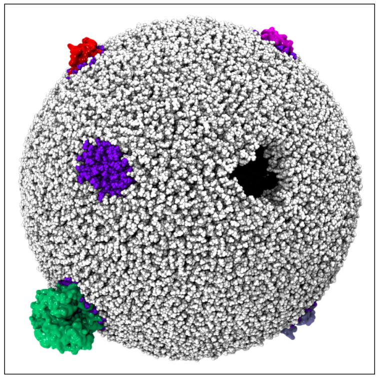
Coarse Grain Protein

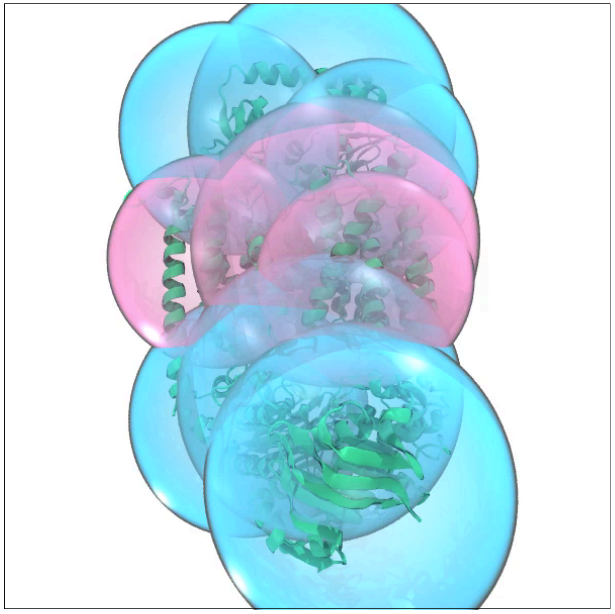


CG Protein Placement



Combine Lipid + Protein





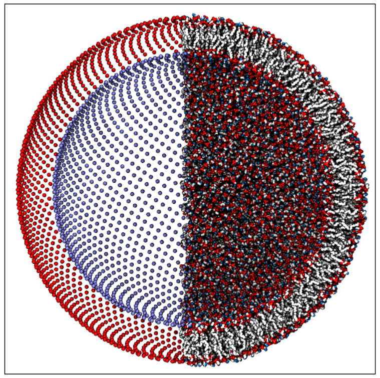
Distribution of proteins across the membrane surface (dense environment)

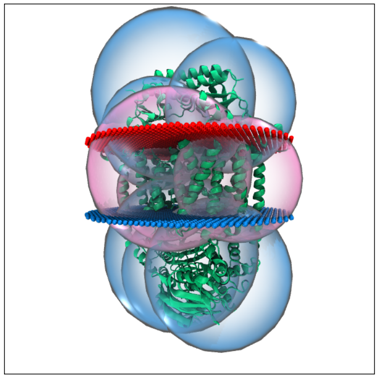
- Ability the handle a variety of protein geometries
- Proper orientation of proteins in relation to the membrane surface
- Generalizable and automated method for membranes of arbitrary shape

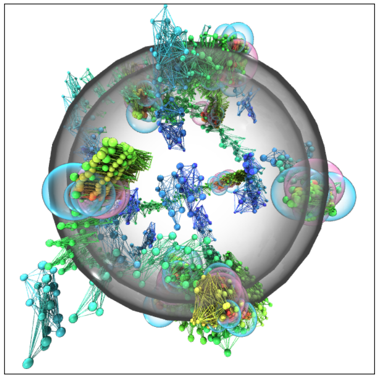
Embedding proteins into the membrane

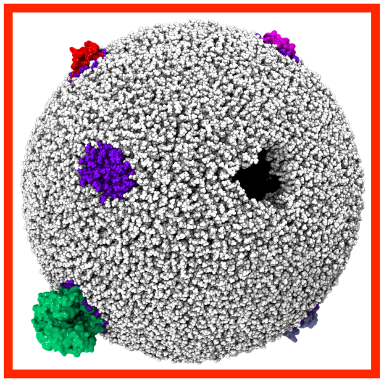
- Account for surface area occupied by proteins in inner and outer leaflets
- Proper lipid packing around embedded proteins

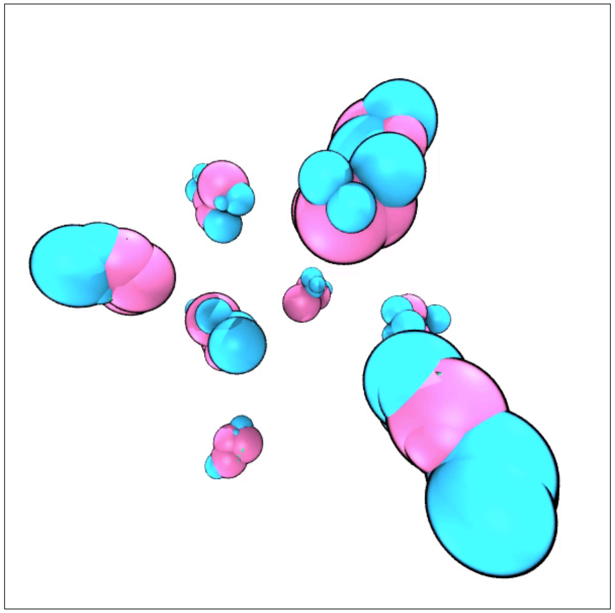
Automated Protein Embedding into Complex Membrane Structures


Vesicle Construction


Coarse Grain Protein


CG Protein Placement


Combine Lipid + Protein



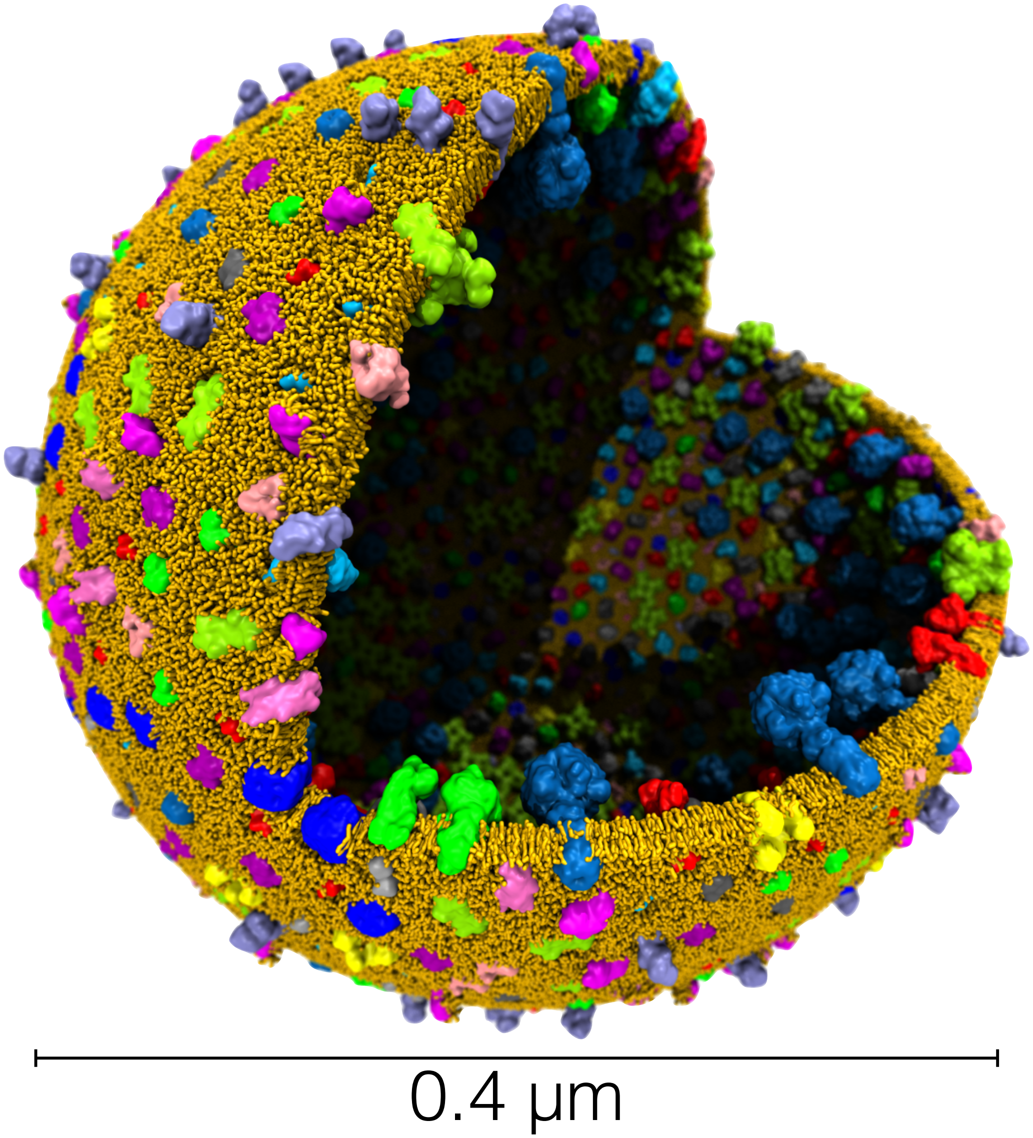
Distribution of proteins across the membrane surface (dense environment)

- Ability the 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

113 million Martini particles
representing **1 billion** atoms

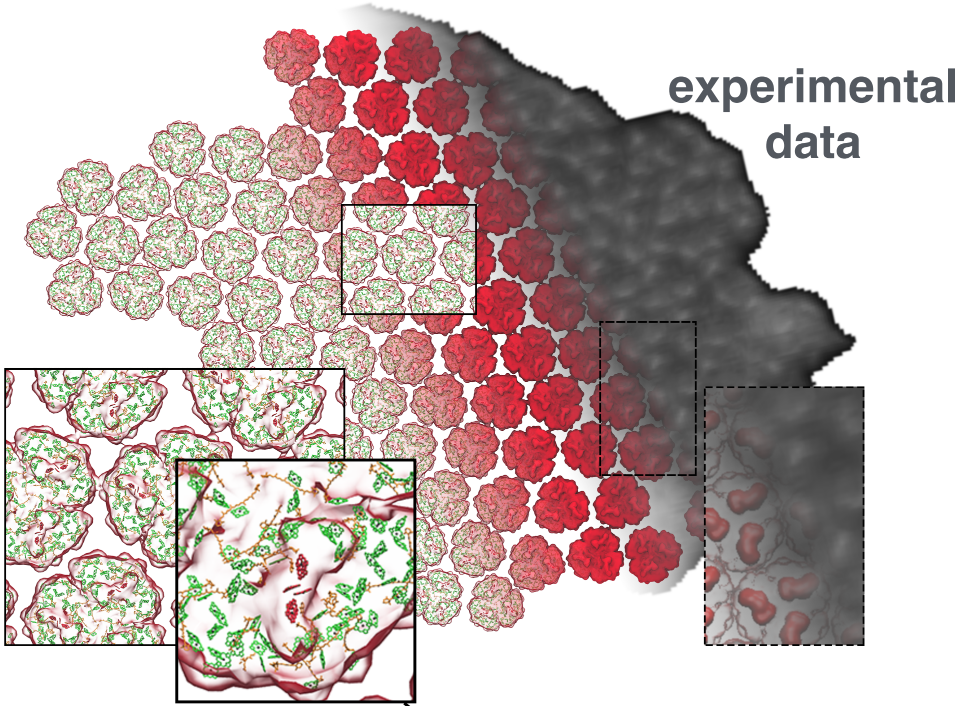


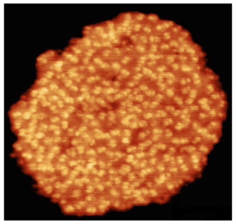
	Protein Components	Copy
●	Aquaporin Z	97
●	Copper Transporter (CopA)	166
●	F1 ATPase	63
●	Lipid Flipase (MsbA)	29
●	Molybdenum transporter (ModBC)	130
●	Translocon (SecY)	103
●	Methionine transporter (MetNI)	136
●	Membrane chaperon (YidC)	126
●	Energy coupling factor (ECF)	117
●	Potassium transporter (KtrAB)	148
●	Glutamate transporter (Glt$_{Tk}$)	41
●	Cytidine-Diphosphate diacylglycerol (Cds)	50
●	Membrane-bound protease (PCAT)	57
●	Folate transporter (FolT)	134
		1,397

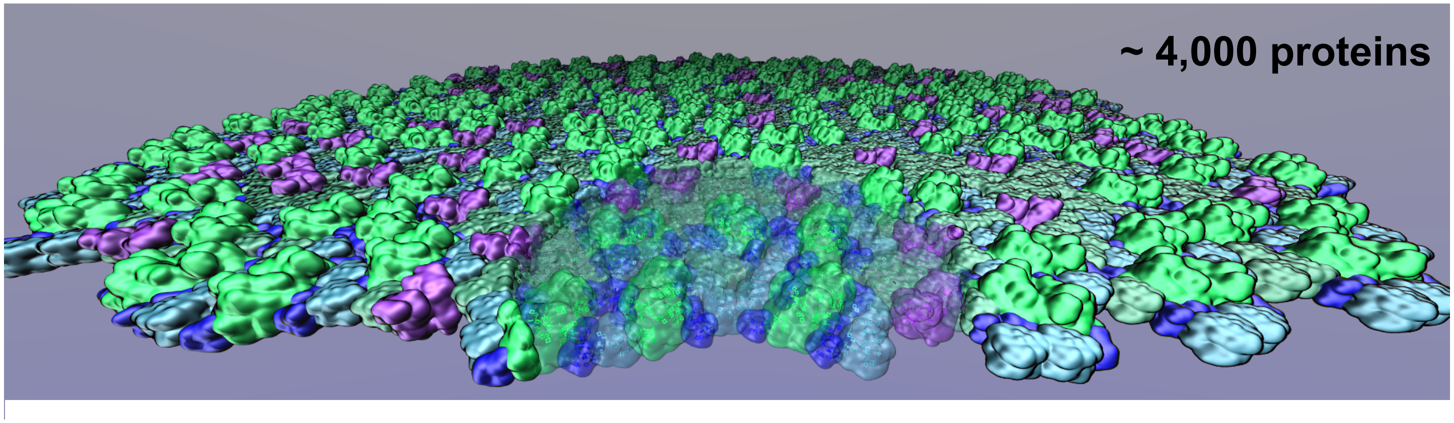
3.7 M lipids (DPPC), 2.4 M Na$^+$ & Cl$^-$ ions,
104 M water particles (4 H_2O / particle)

Applications of Computational Methodologies to Cell-Scale Structural Biology

Using simulations as a “structure-building” tool







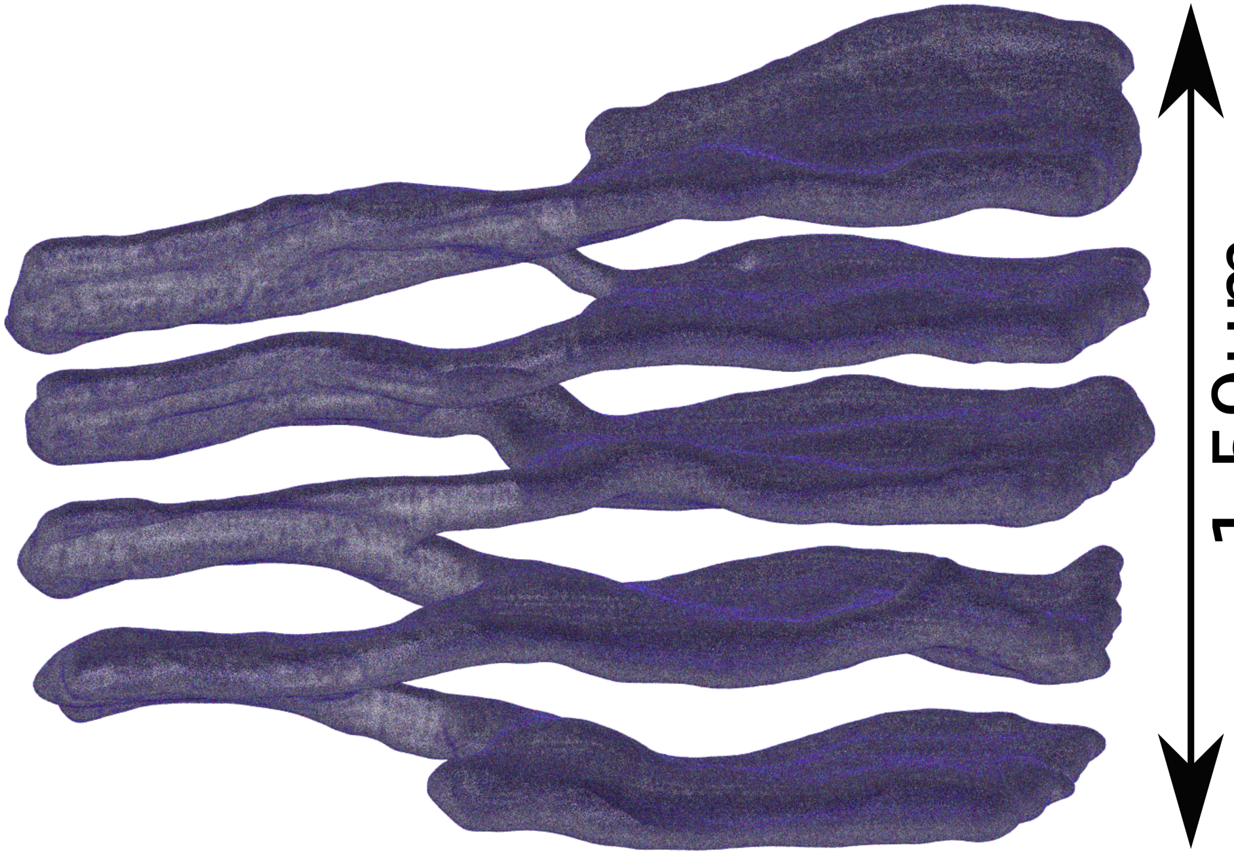
A bioenergetic membrane

Applications of Computational Methodologies to Cell-Scale Structural Biology

Guided Construction of Membranes from Experimental Data

E**x**perimentally-Derived **M**embrane of **A**rbitrary **S**hape Builder

Terasaki Ramp
~4 Billion Atoms



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

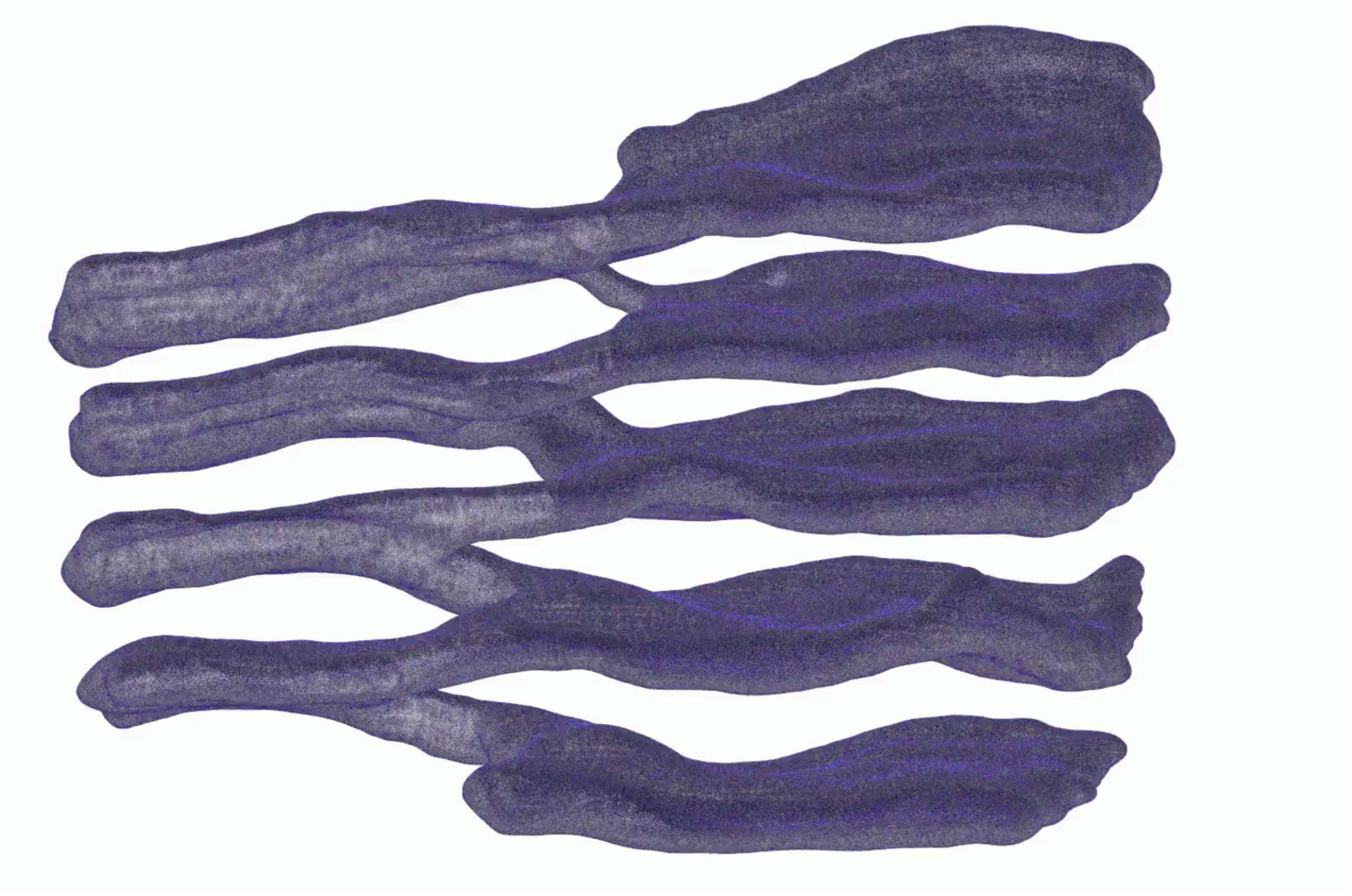
Keenan and Huang, *J. Dairy Sci.*, **1972**.

Terasaki et al., *Cell*, **2013**.

Applications of Computational Methodologies to Cell-Scale Structural Biology

Guided Construction of Membranes from Experimental Data

E**x**perimentally-Derived **M**embrane of **A**rbitrary **S**hape Builder



Terasaki Ramp
~4 Billion Atoms

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

Keenan and Huang, *J. Dairy Sci.*, **1972**.

Terasaki et al., *Cell*, **2013**.