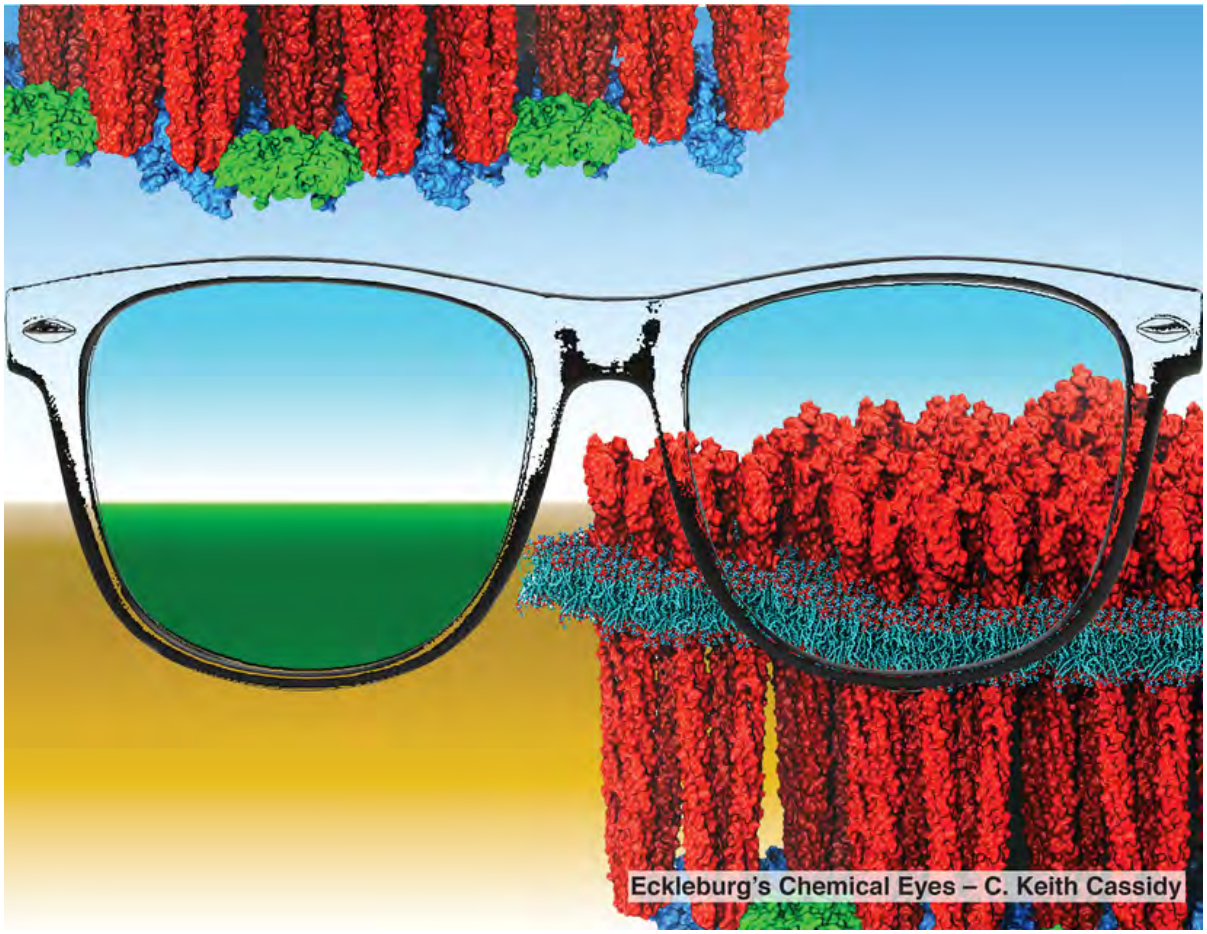
Hands-on Workshop on Computational Biophysics

May 13 -17, 2019

Pittsburgh Supercomputing Center



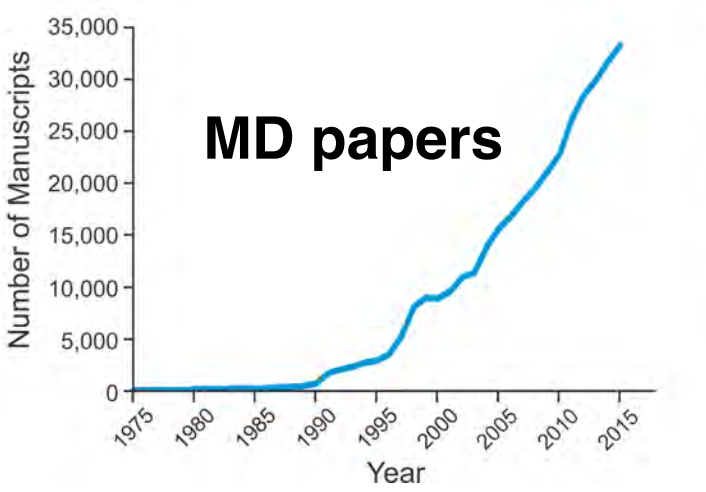
Emad Tajkhorshid

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

NIH P41 Center for Macromolecular Modeling and Bioinformatics

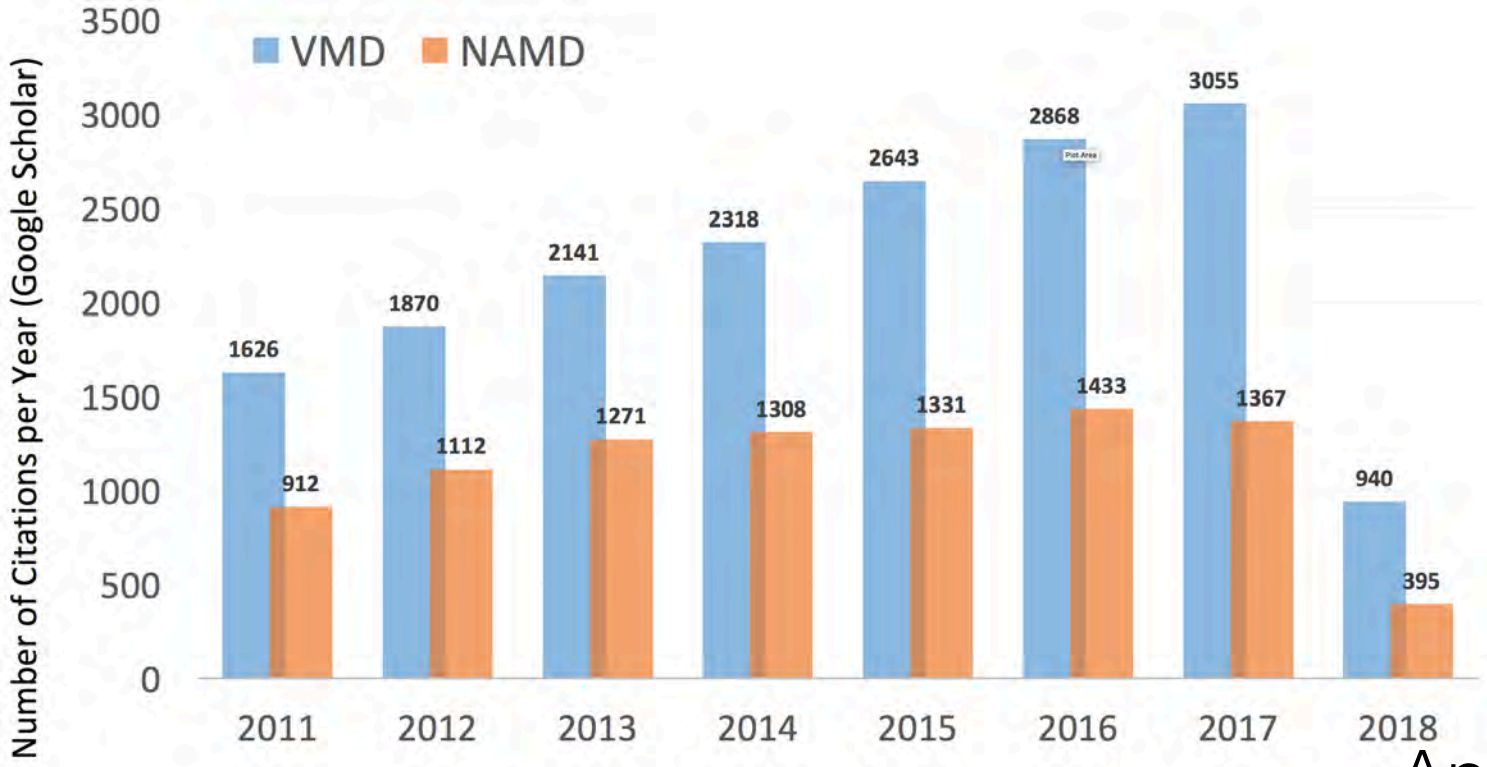
University of Illinois at Urbana-Champaign

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



103,000 VMD users
19,000 NAMD users
17,000 NIH funded
1.4 million web visitors
228,000 tutorial views

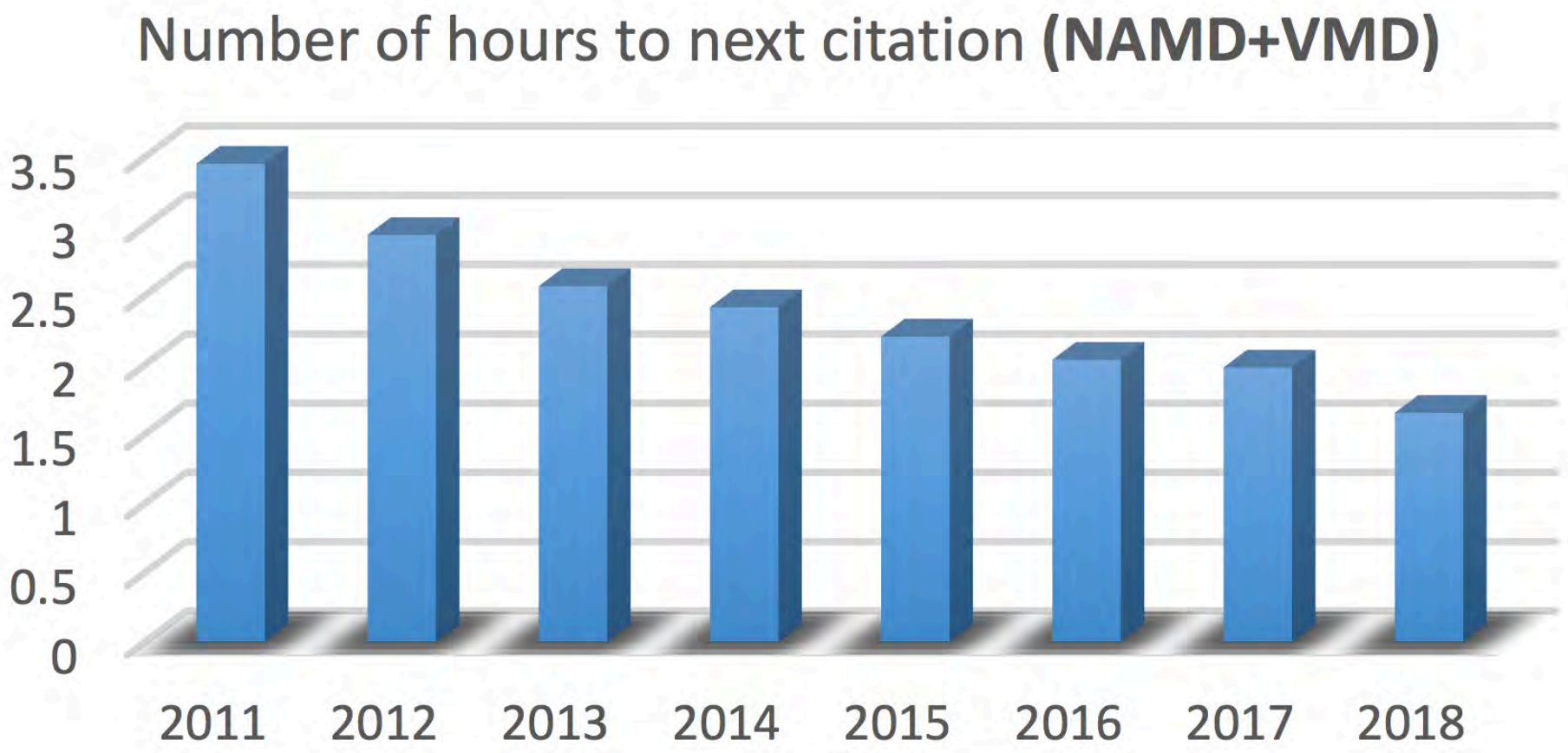
Serving a large and growing community
of biomedical researchers employing molecular modeling and simulation technologies



Apr 2018

Serving a large and growing community

of biomedical researchers employing molecular modeling and simulation technologies

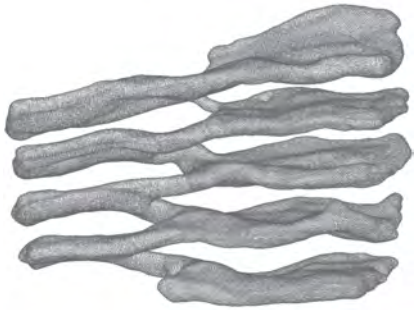


Serving a Large and Fast Growing Community

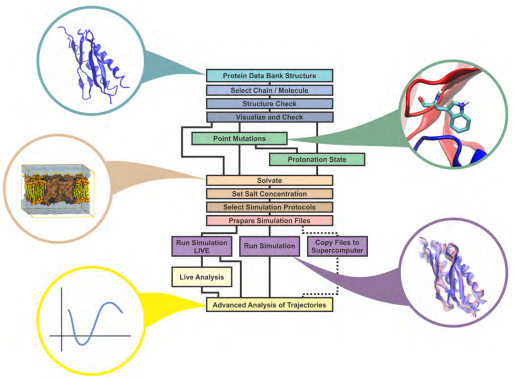
- Deploying Center's flagship programs NAMD and VMD on all major computational platforms from commodity computers to supercomputers

- Consistently adding user-requested features
    - simulation, visualization, and analysis

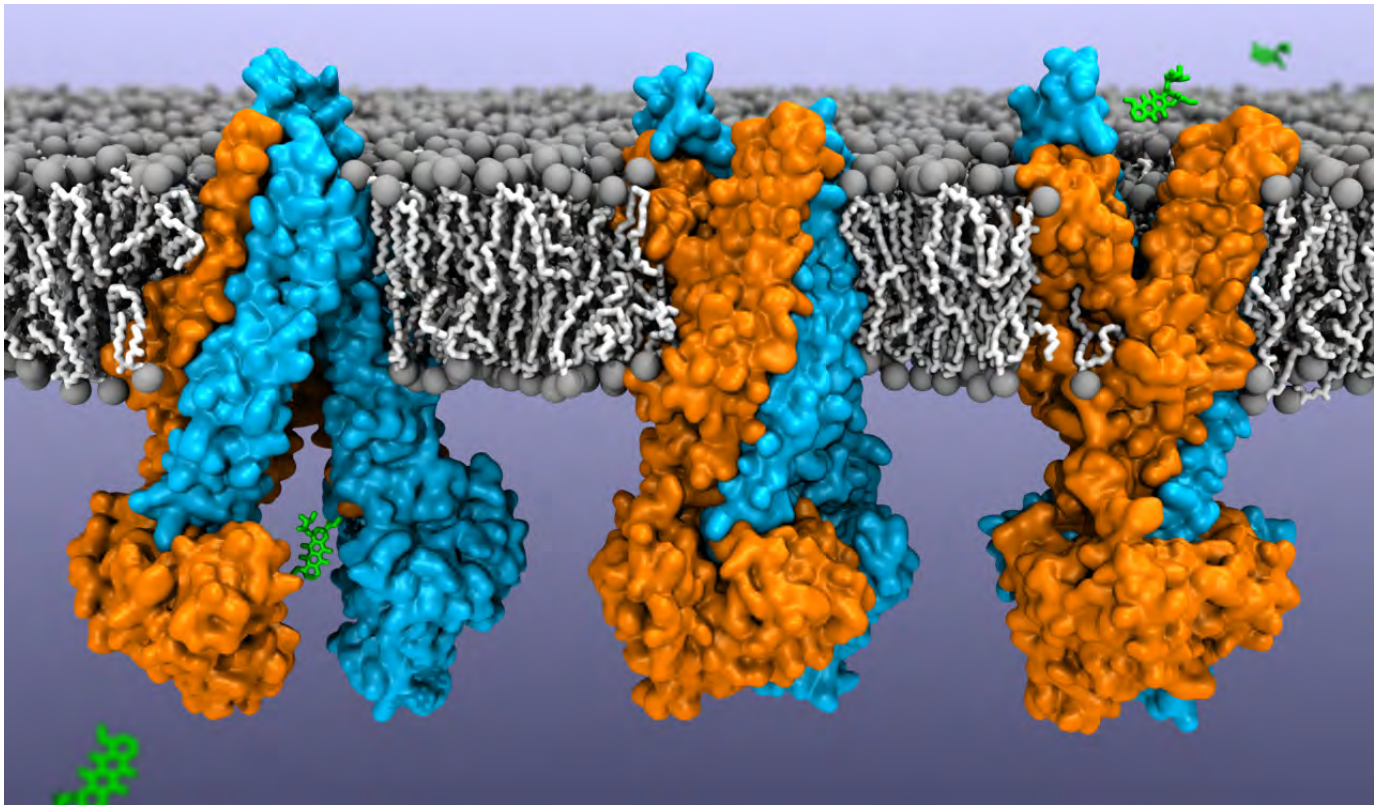
- Covering broad range of scales (orbitals to cells) and data types

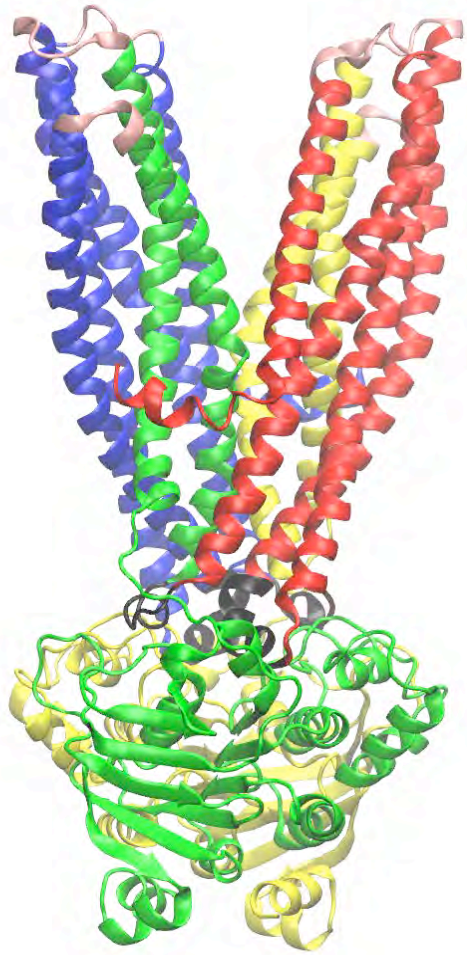


- Enhanced software accessibility
    - QwikMD, interactive MDFF, ffTk, simulation in the Cloud, remote visualization



Computational Structural Biology Describing Biomolecules at Nanoscale

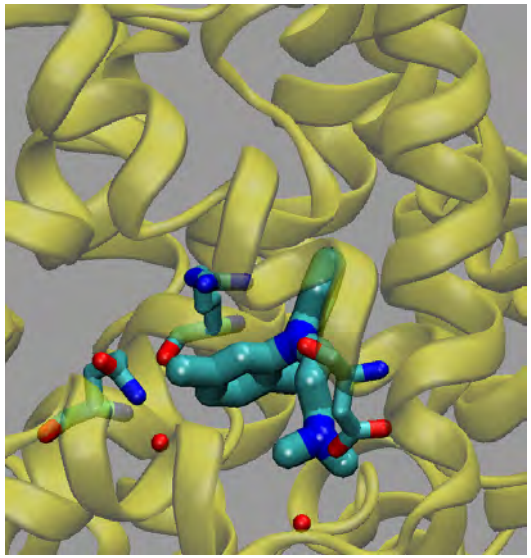


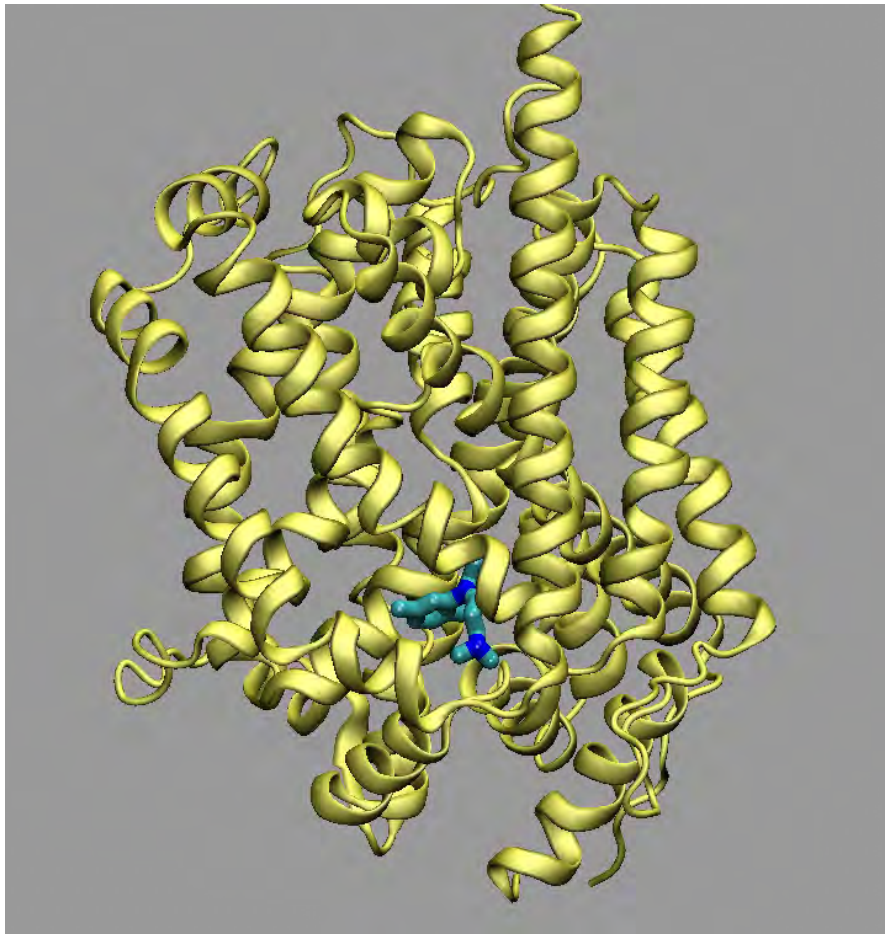


Structure / Dynamics
@ nanoscale

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)

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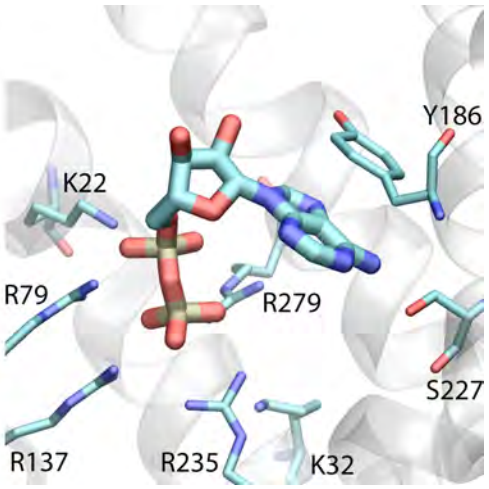
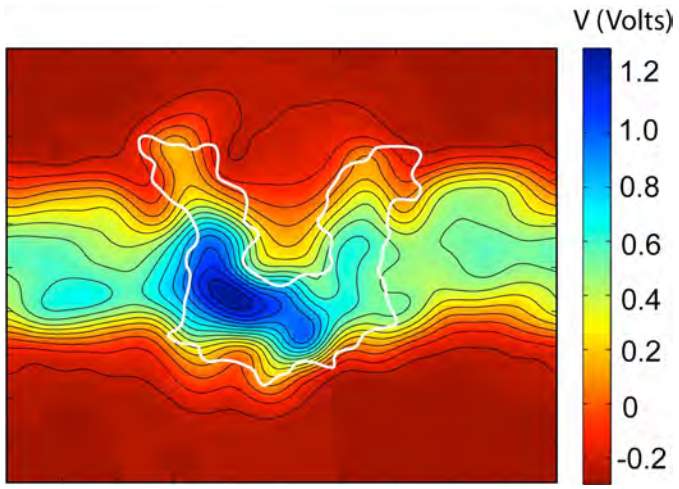
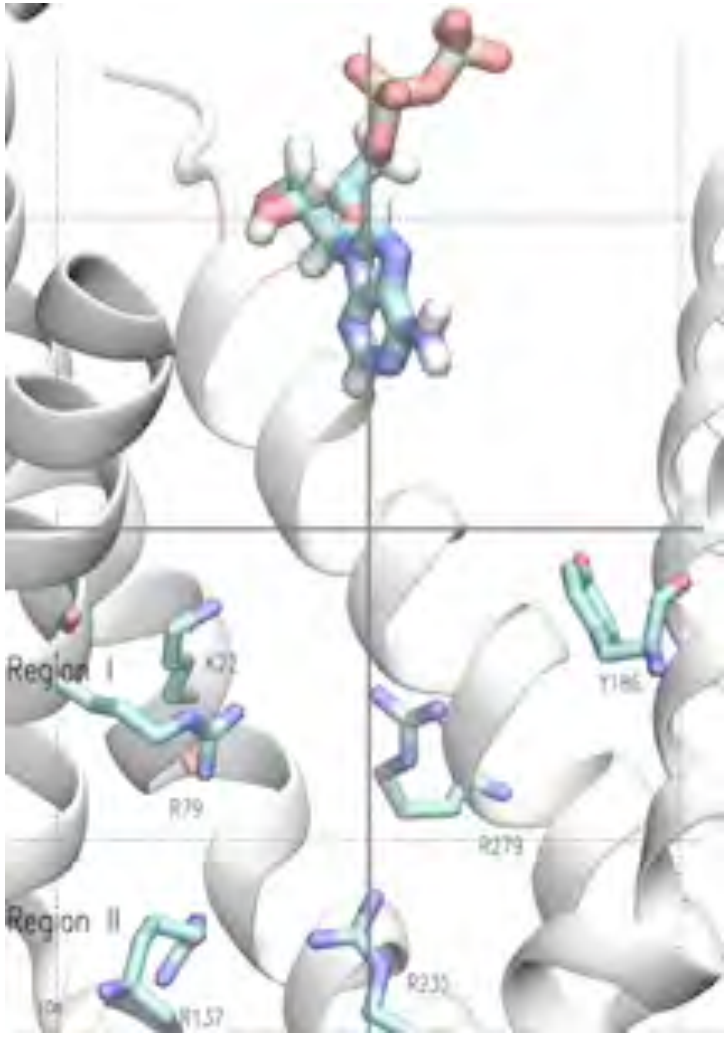
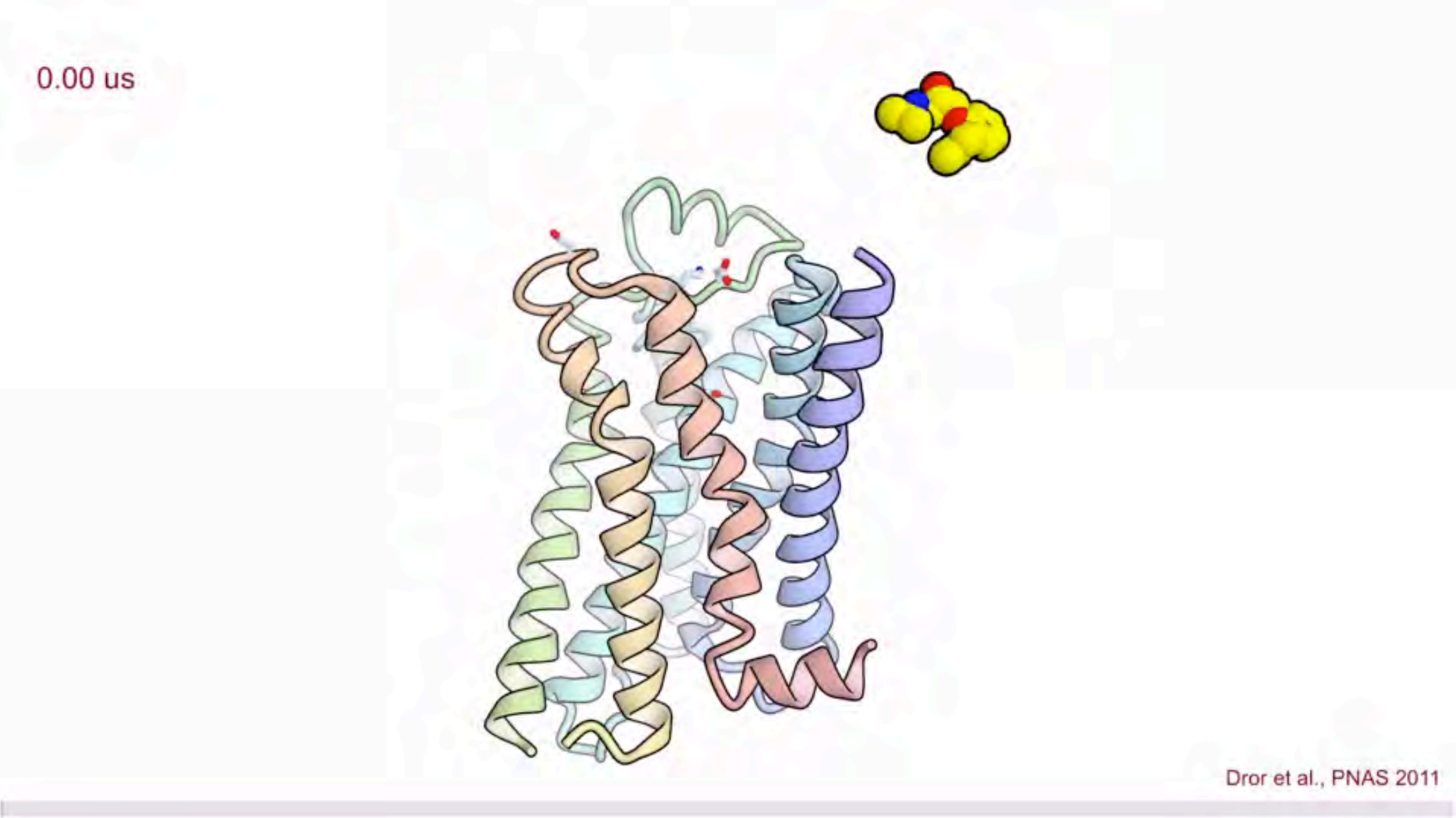






Binding of a small molecule to a binding site
Y. Wang & E.T. PNAS 2010

Why Structural Biology at Nanoscale?



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

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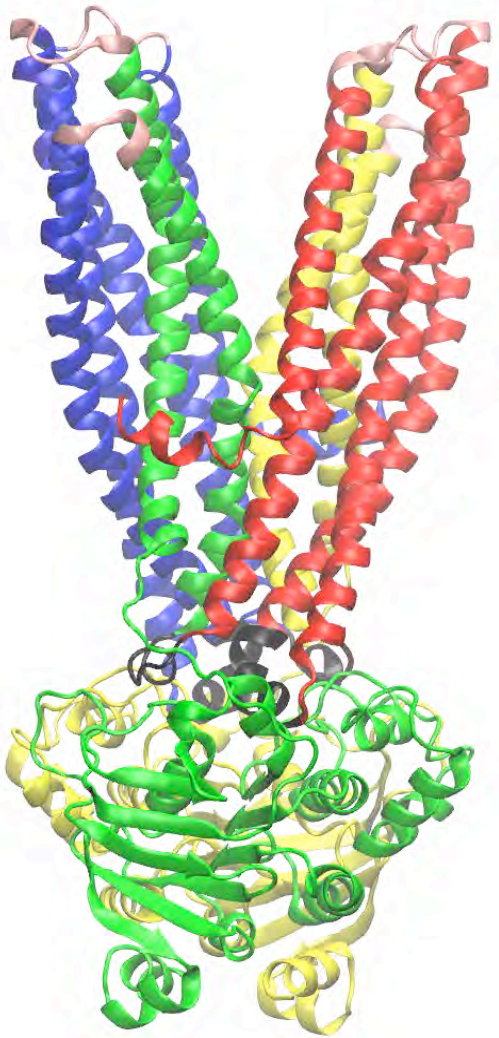
- ✦ Nano-biotechnology



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

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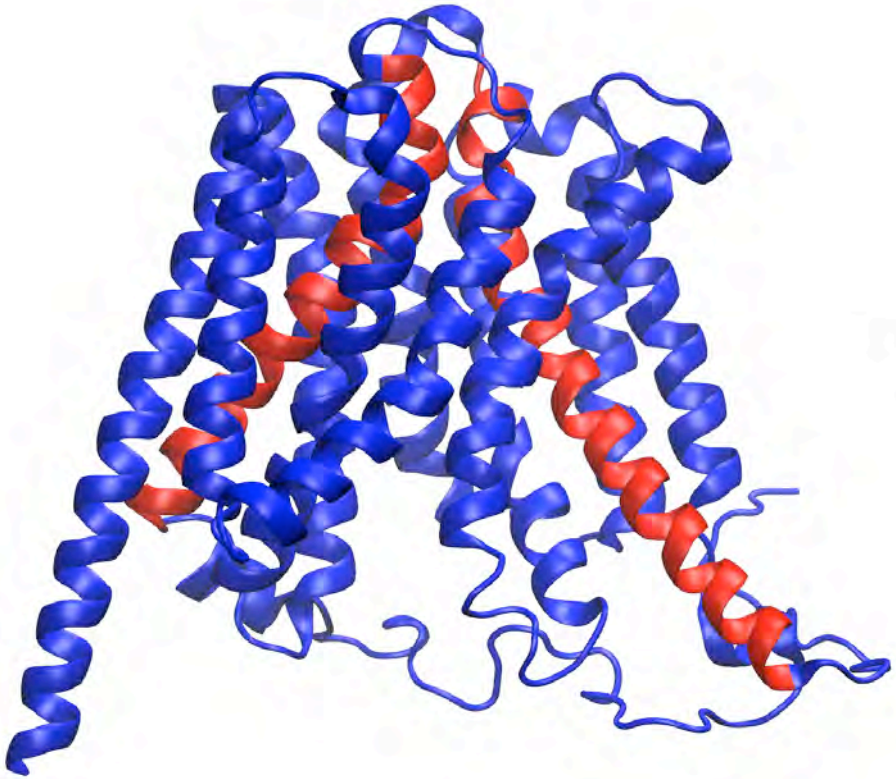
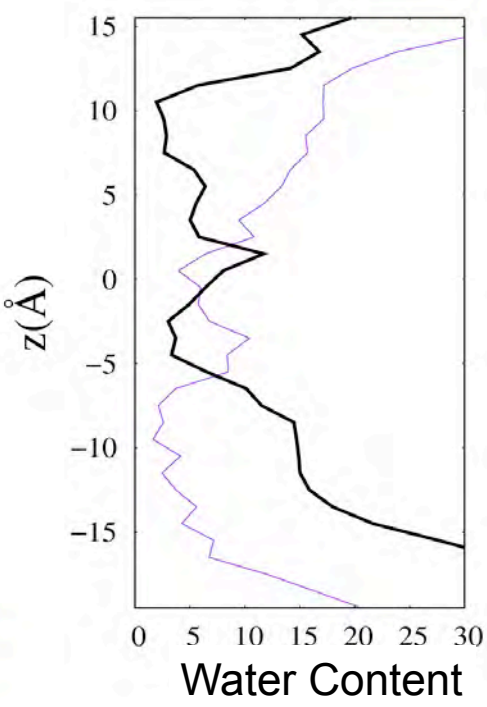
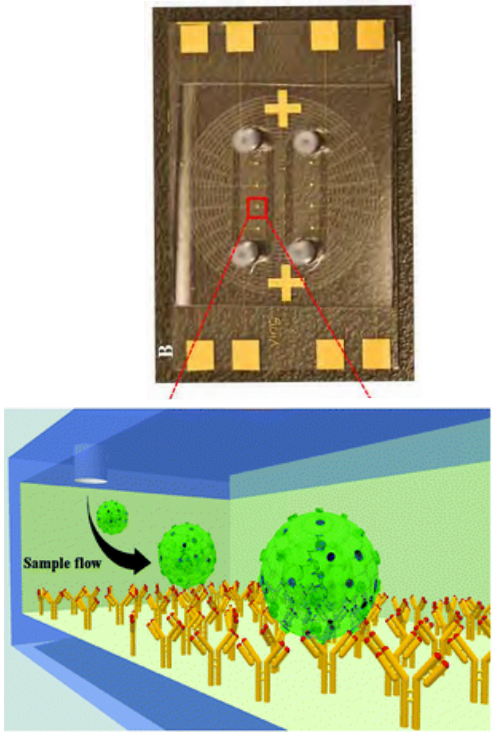




Structural changes underlying function
M. Moradi, G. Enkavi, & E. T. Nature Comm. 2015

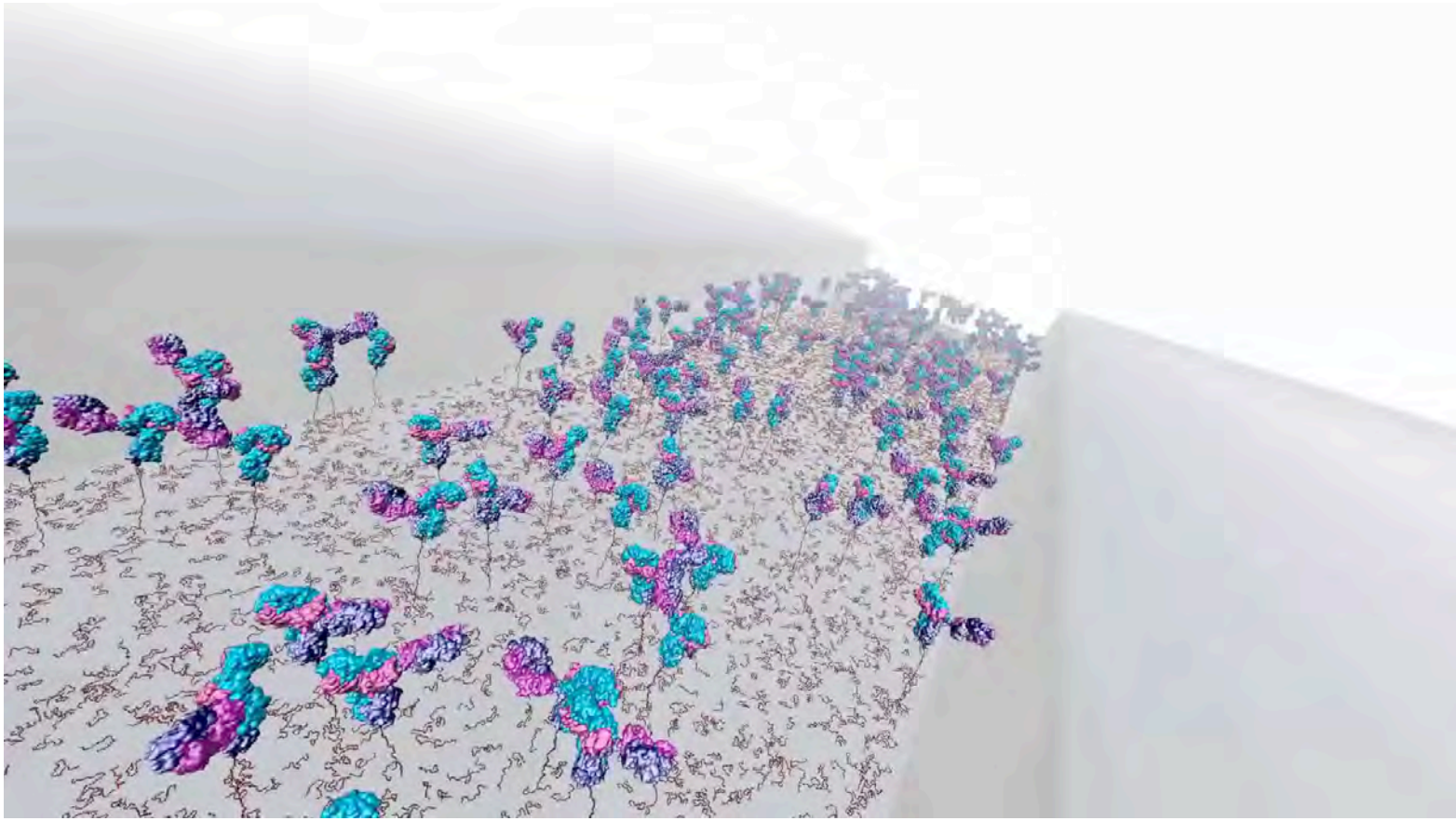
Nano-biotechnology
Microfluidic Sensing Devices



HIV subtype identification

Lab Chip 2012

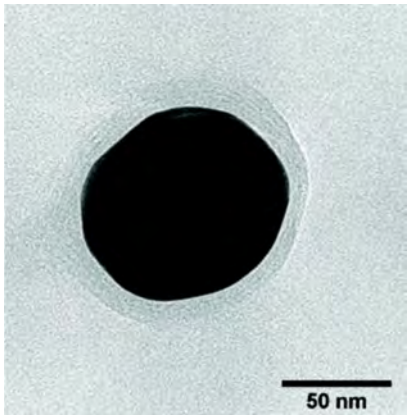
Functionalized nanosurface with antibodies



Created by **nanoBIO Node** tools

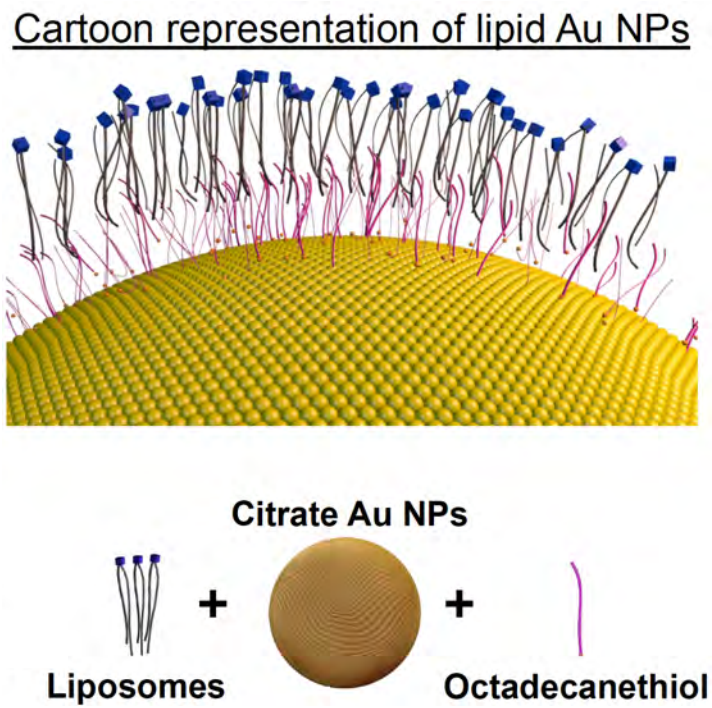
Nano-biotechnology
Gold Nanoparticles as Delivery Vehicles

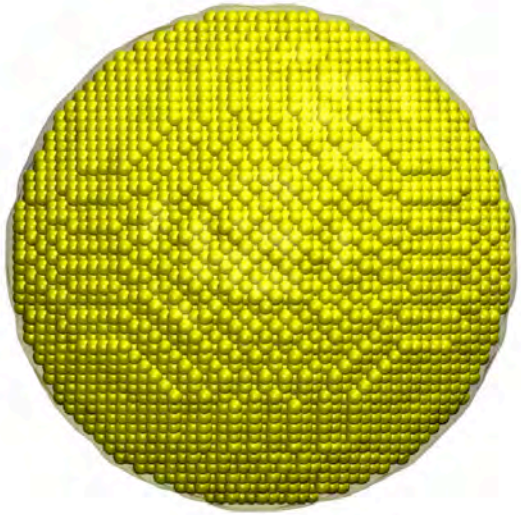
Transmission Electron Micrograph



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

Schematic model with no prediction power





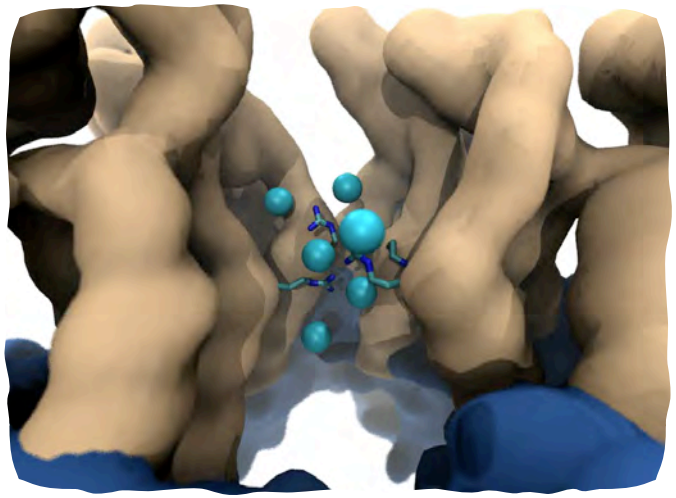
Experiment:
Murphy Lab

Modeling/Simulation:
Tajkhorshid Lab

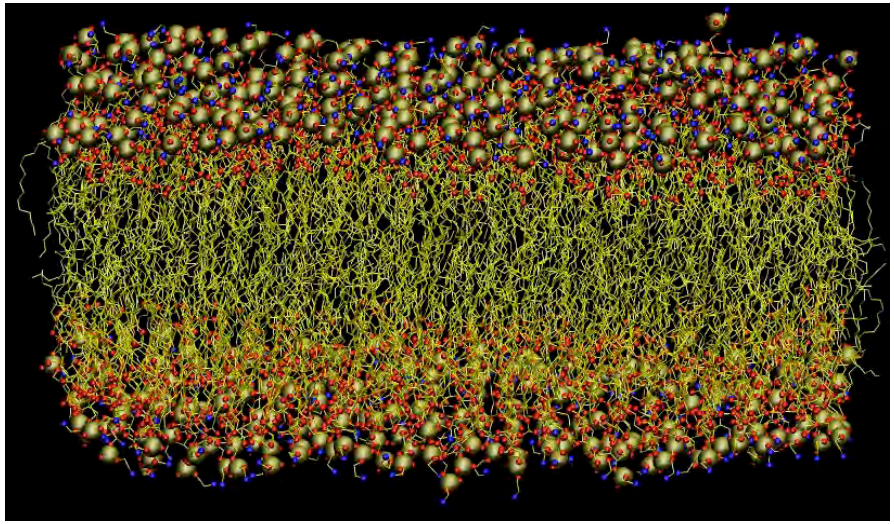
Applications of Computational Methodologies to Structural Biology

Simulation of the dynamics of the molecular system (MD)

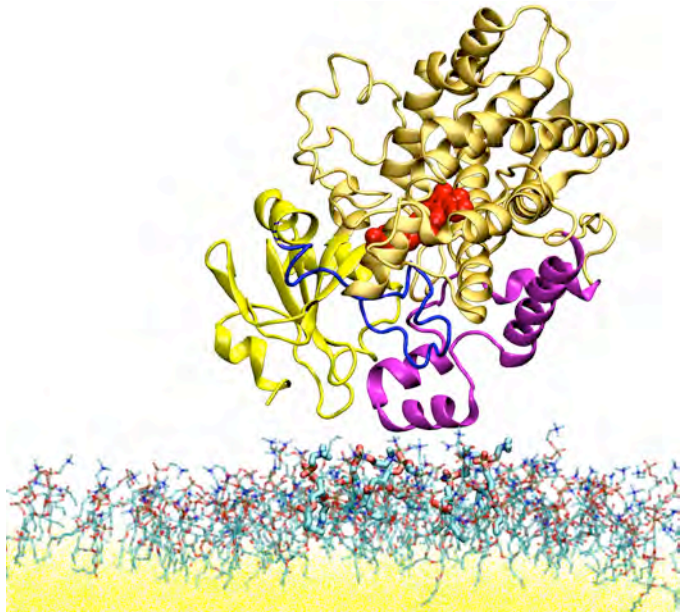
- Calculating ensemble-averaged properties of microscopic systems to compare to macroscopic measurements
- Providing a molecular basis for function
- Describing the molecular/structural changes underlying function
- …



Hydration at the interface of viral shell proteins

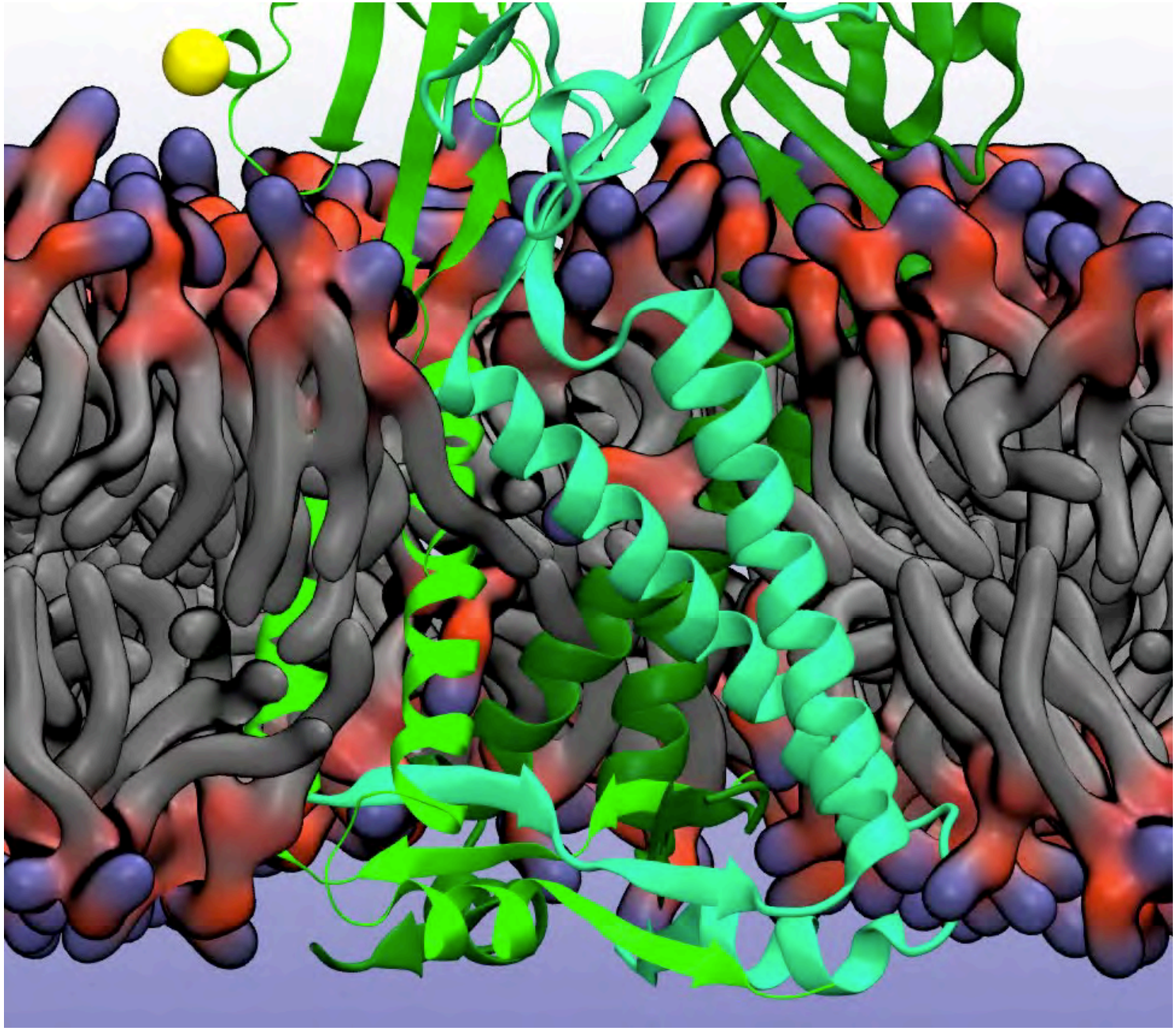


Thermal fluctuations of a phospholipid bilayer



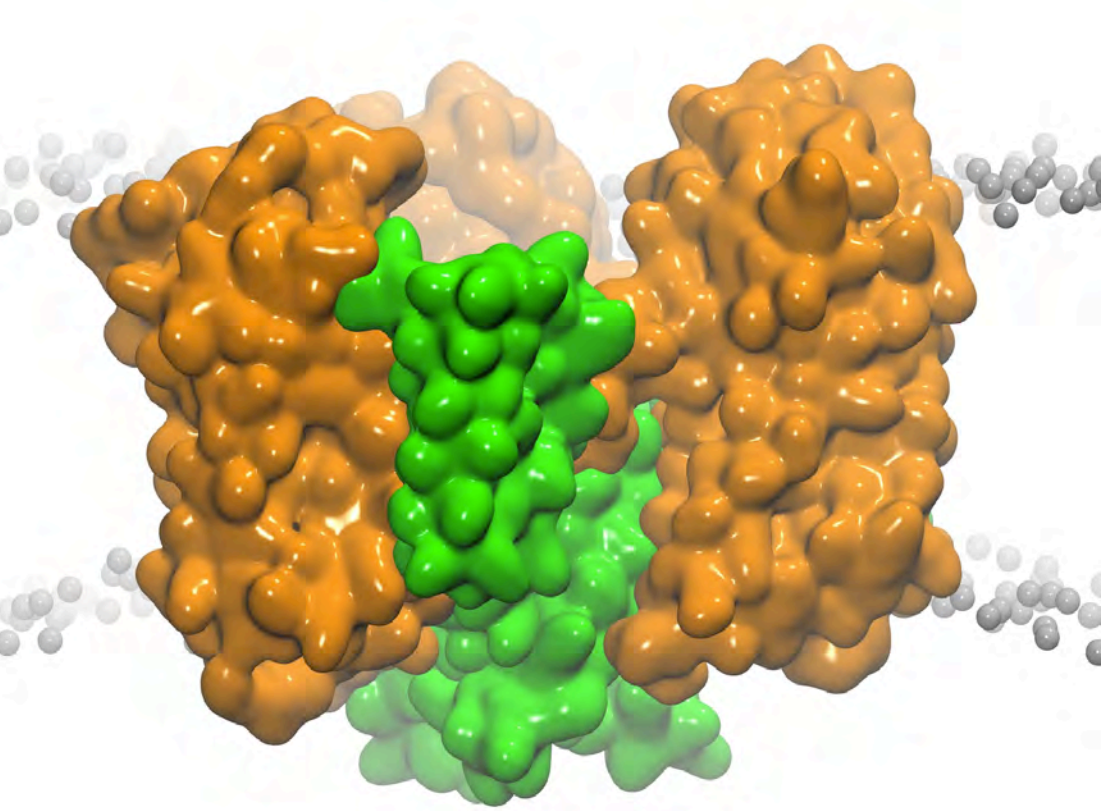
Membrane binding of a coagulation protein

Lipid Protein Interaction

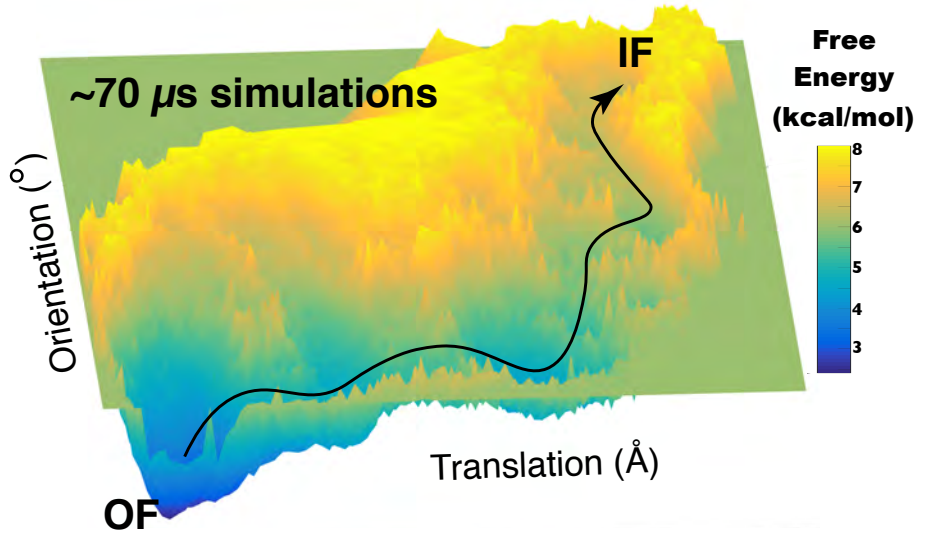


S. Mansoor, …, E. Tajkhorshid, E. Gouaux, Nature, 2016.

Characterizing Energy Landscapes Associated with Functional Motions of Proteins



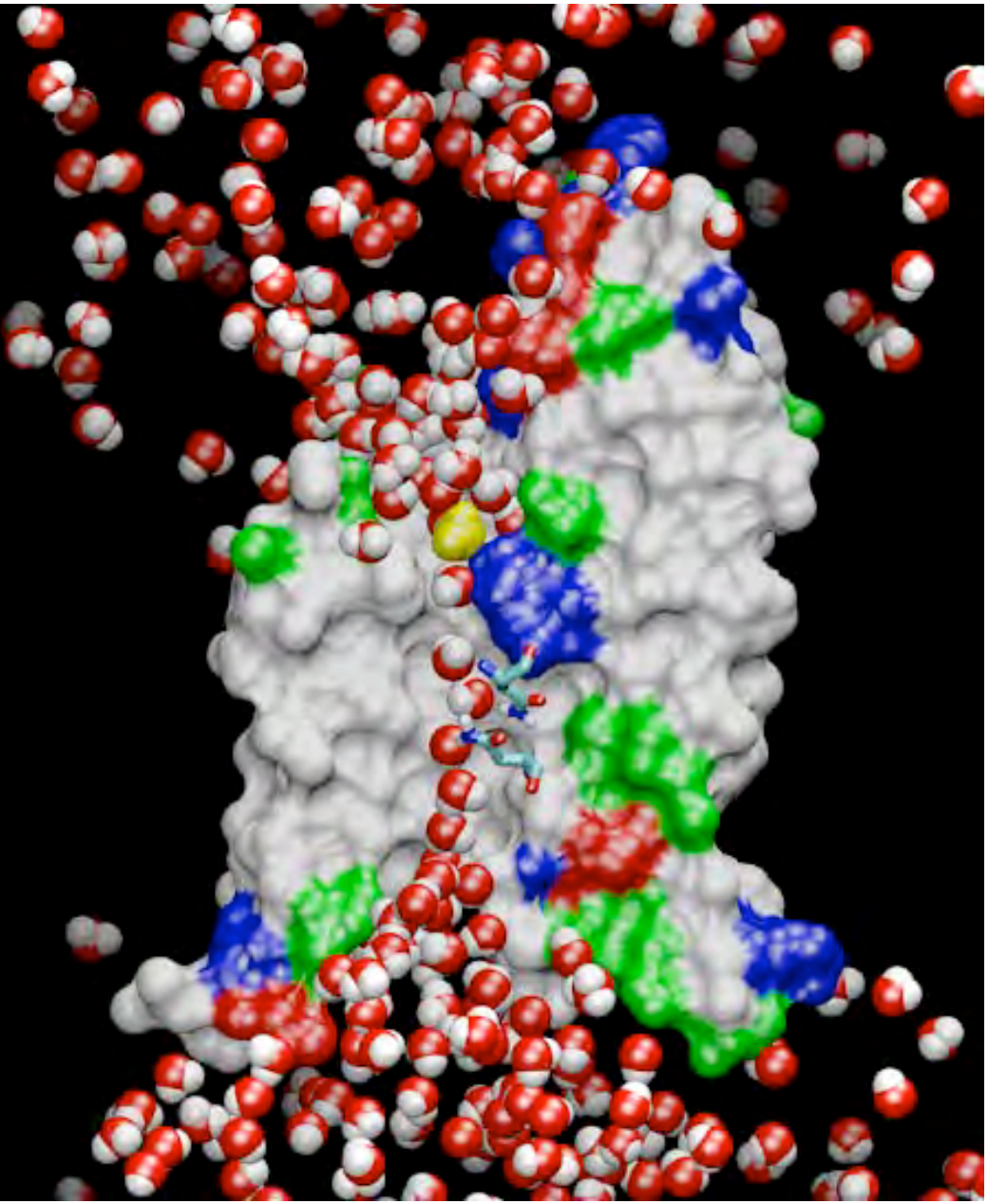
Outward-facing (OF) to Inward-facing (IF) Transition



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

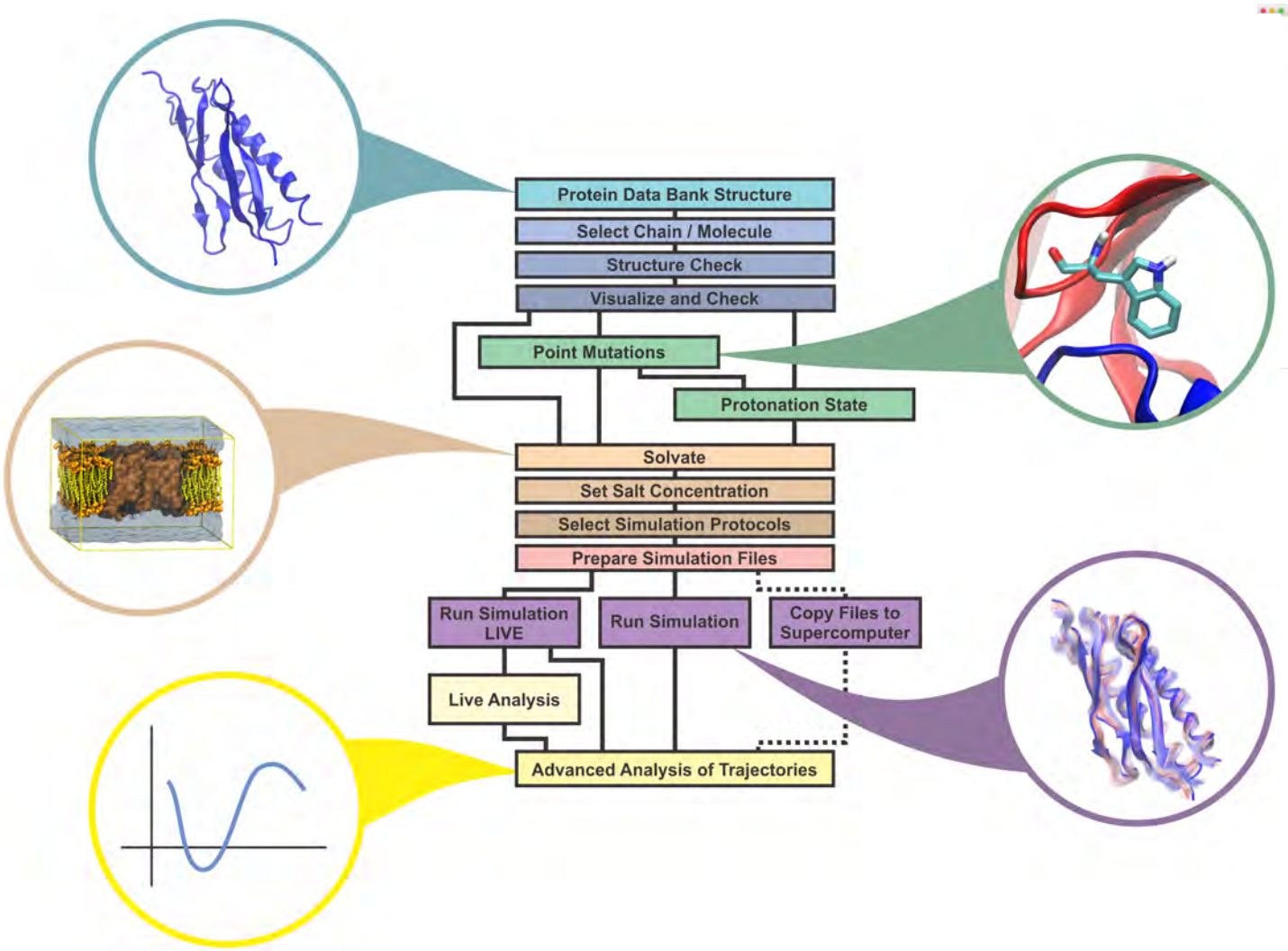
SPEED LIMIT

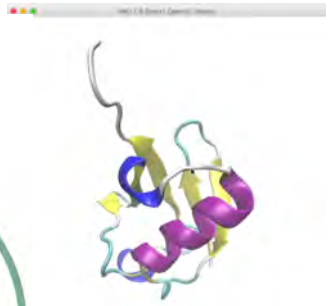
1 fs

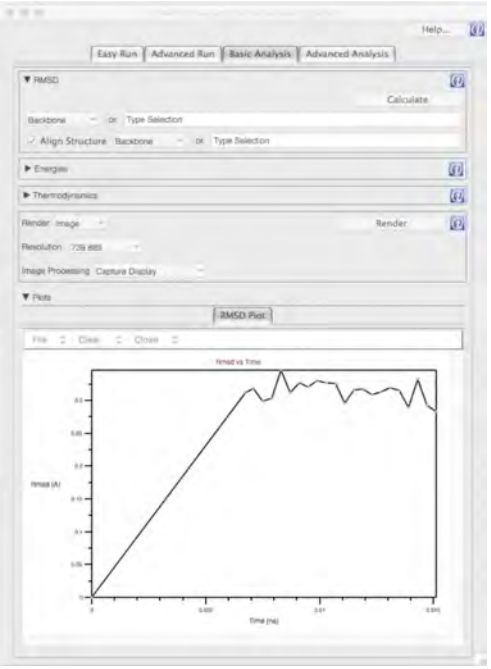
Major advantage:

- Unparalleled spatial and temporal resolutions, simultaneously

QwikMD- Gateway to Easy Simulation







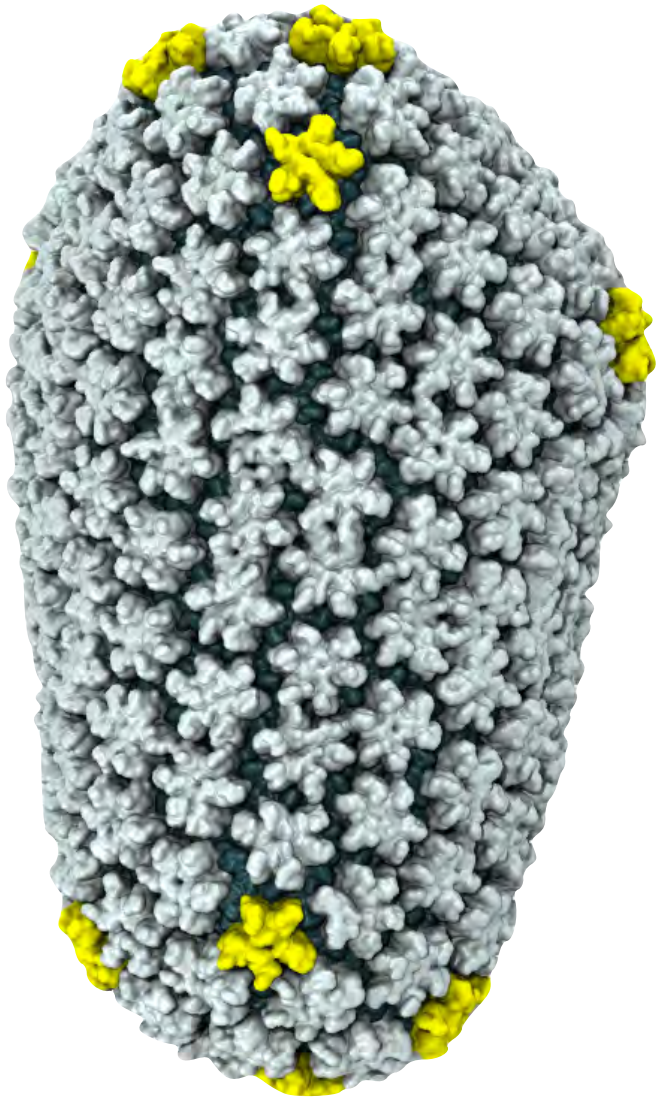
Ribeiro, J. V., …, Schulten, K.. QwikMD — Integrative Molecular Dynamics Toolkit for Novices and Experts. ***Sci. Rep***. 6, 26536; doi: 10.1038/srep26536 (**2016**)

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

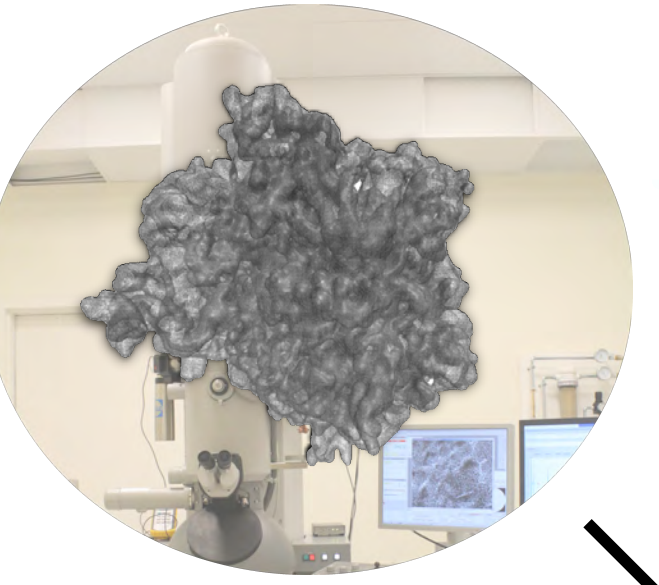
- NMR
- X-ray
- Electron Microscopy
- …



Structural model of HIV virus

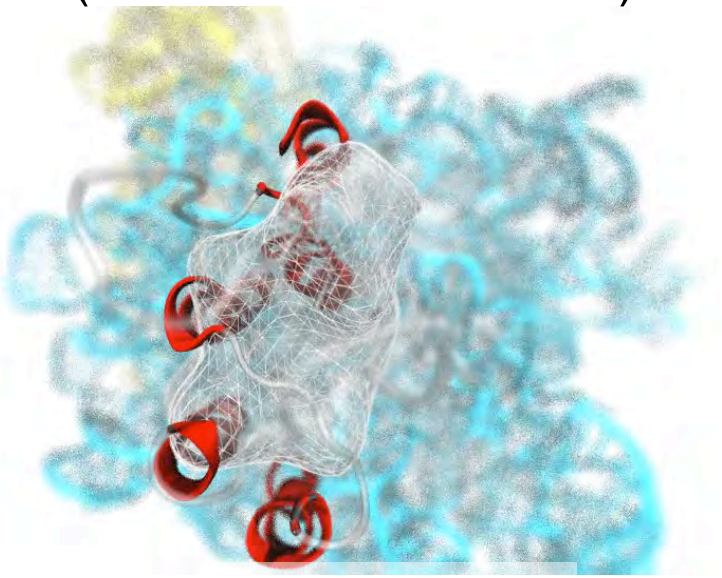
Molecular Dynamics Flexible Fitting (MDFF)

Electron Microscope



cryo-EM density map

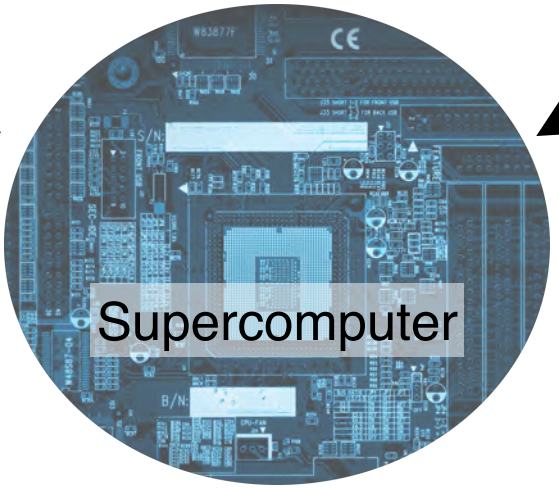
(Ribosome-bound YidC)



Match through MD

APS Synchrotron

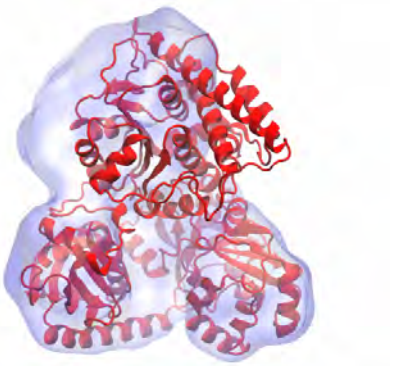
crystallographic structure

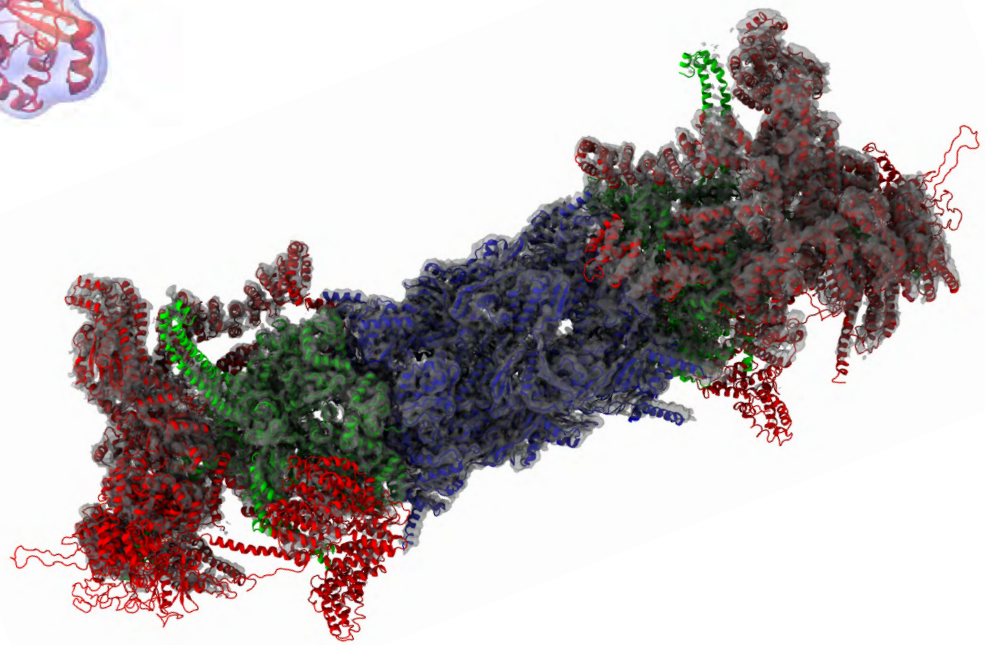


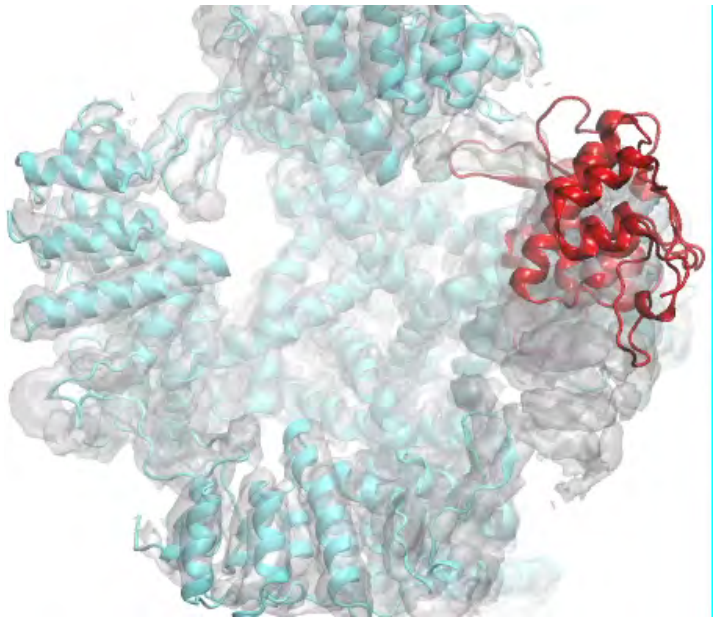
[1] Trabuco et al. *Structure* (2008) 16:673-683.
[2] Trabuco et al. *Methods* (2009) 49:174-180.

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.
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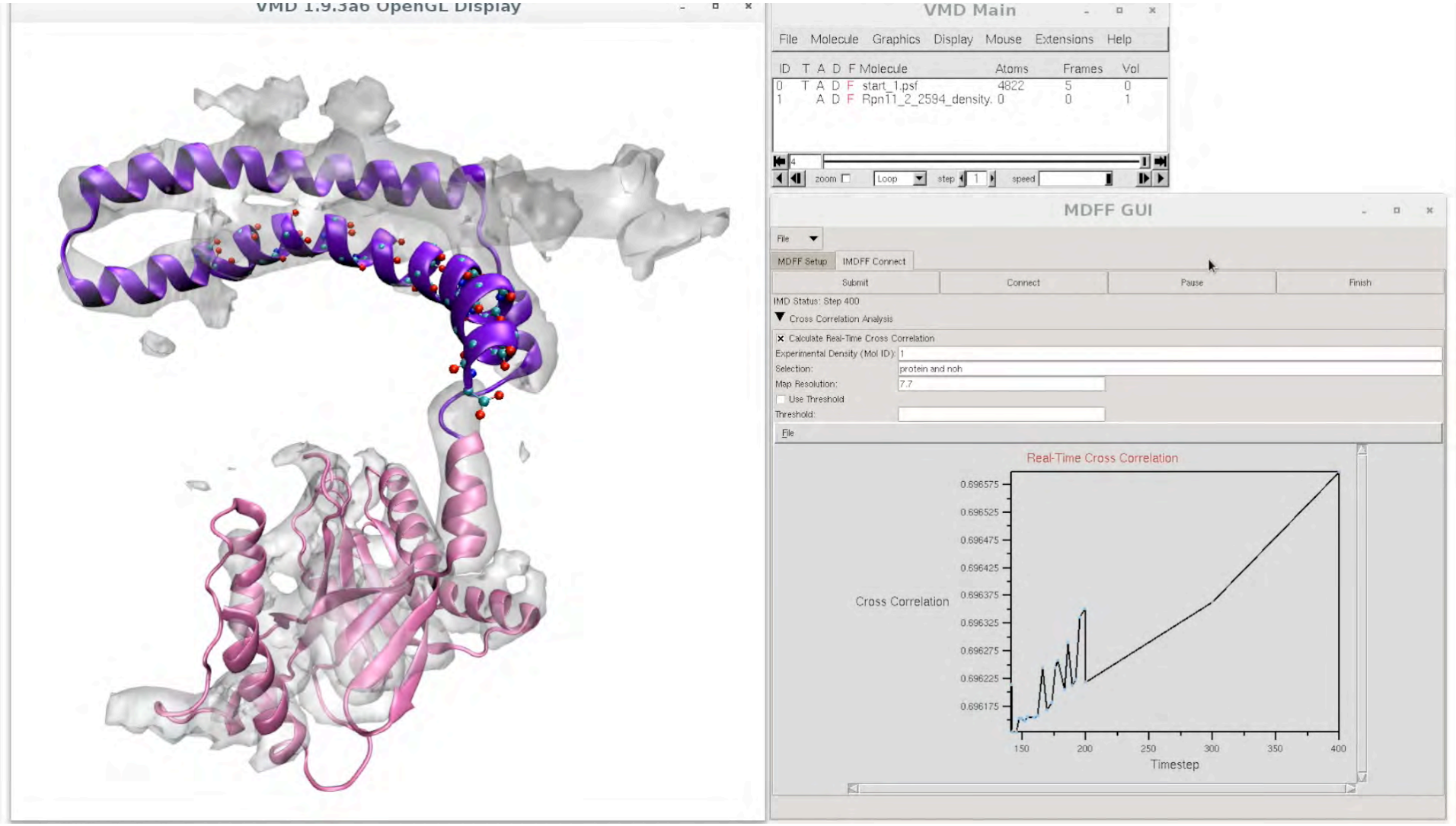
Technology Made Highly Accessible to the Community

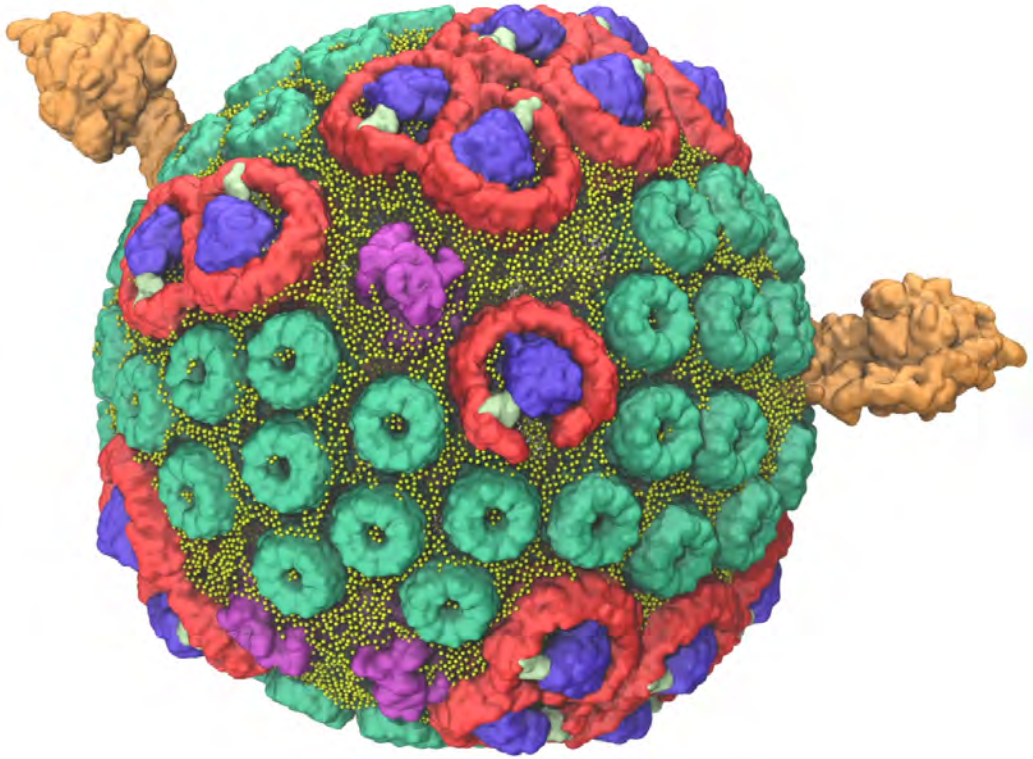
interactive MDFF



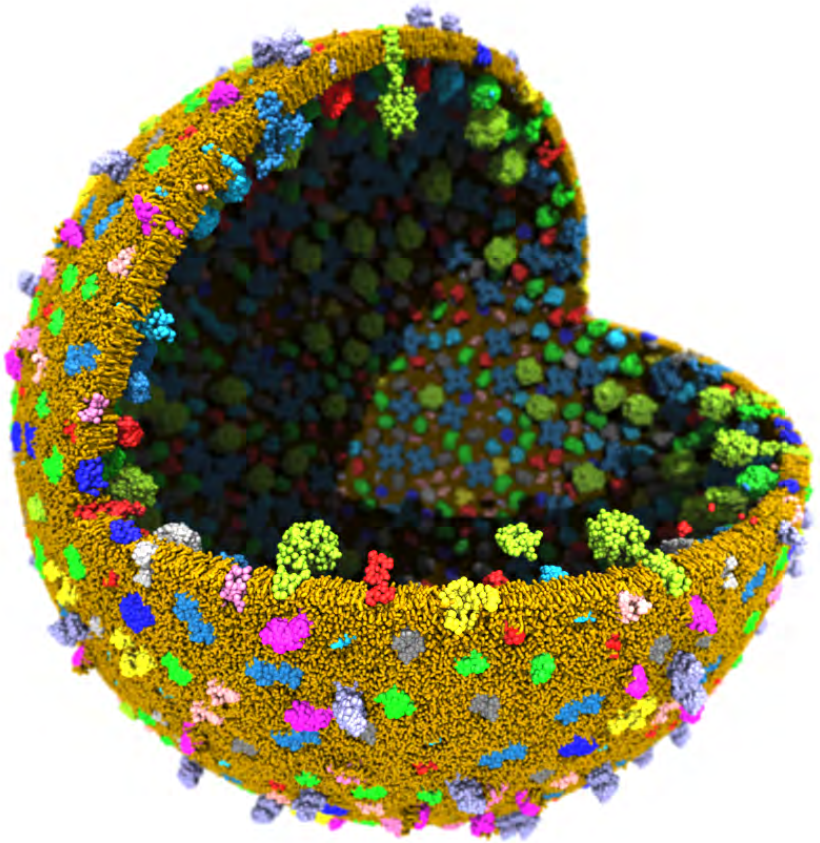
Developed primarily for experimental users

Applications of Computational Methodologies to Cell-Scale Structural Biology

Using simulations as a “structure-building” tool



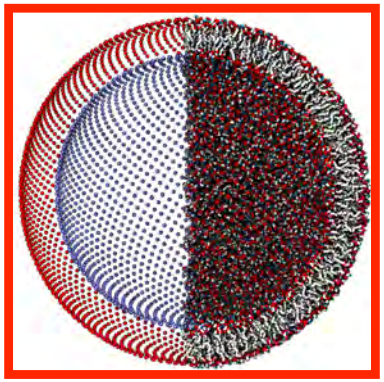
The most detailed model of a chromatophore



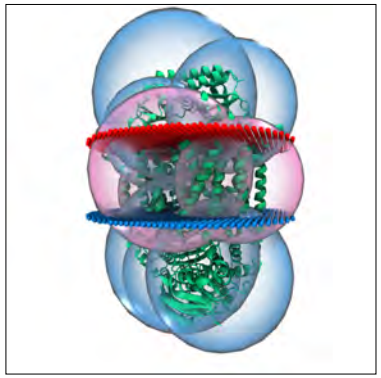
Computational model of a minimal cell envelope

Automated Protein Embedding into Complex Membrane Structures

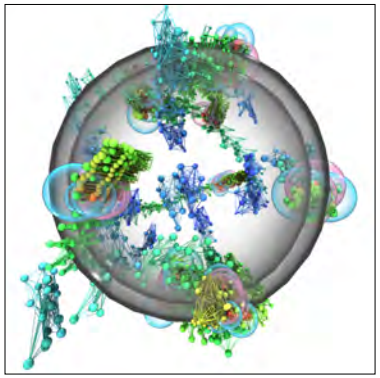
Vesicle Construction



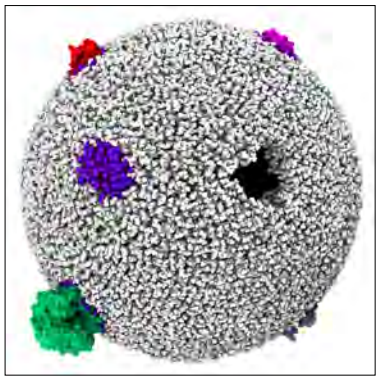
Coarse Grain Protein

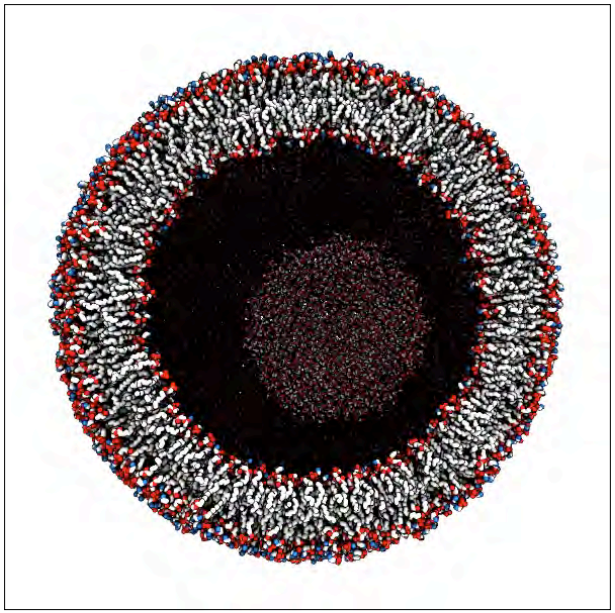


CG Protein Placement



Combine Lipid + Protein





Distribution of proteins across the membrane surface (dense environment)

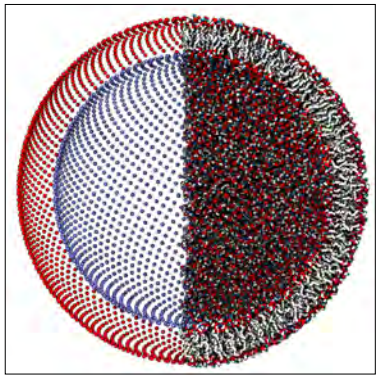
- Ability the handle a variety of protein geometries
- Proper orientation of proteins in relation to the membrane surface
- Generalizable and automated method for membranes of arbitrary shape

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



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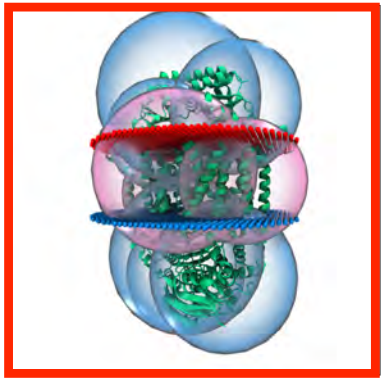
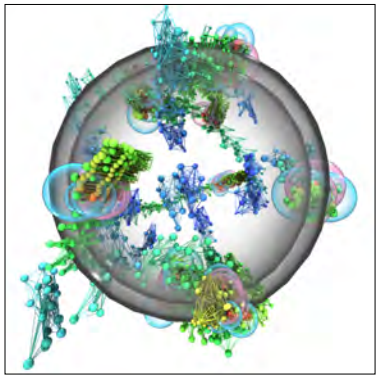
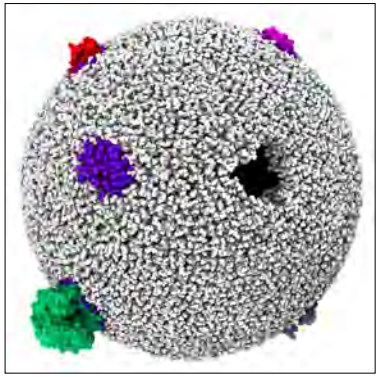
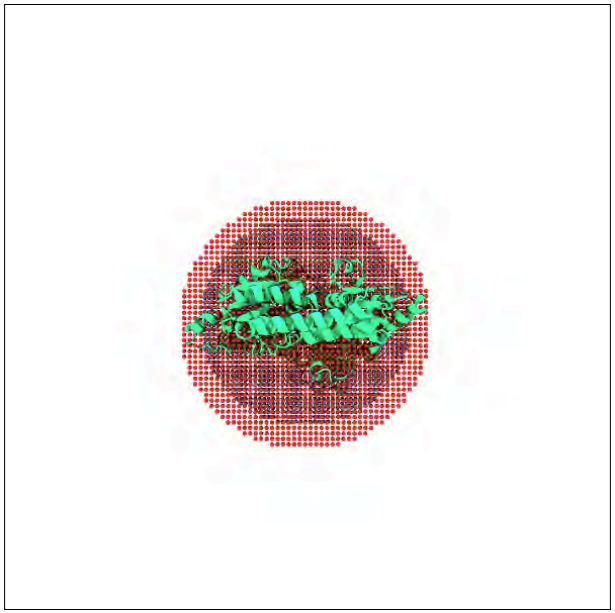


CG Protein Placement



Combine Lipid + Protein





Distribution of proteins across the membrane surface (dense environment)

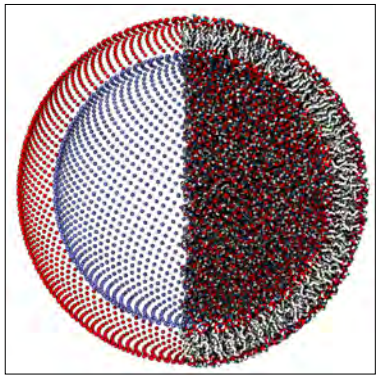
- Ability the handle a variety of protein geometries
- Proper orientation of proteins in relation to the membrane surface
- Generalizable and automated method for membranes of arbitrary shape

Embedding proteins into the membrane

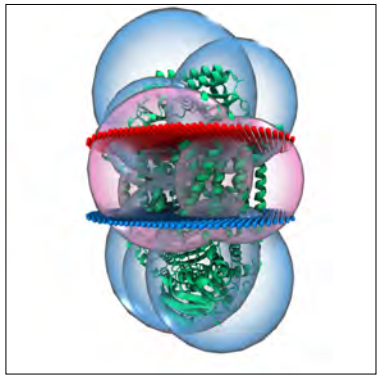
- Account for surface area occupied by proteins in inner and outer leaflets
- Proper lipid packing around embedded proteins

Automated Protein Embedding into Complex Membrane Structures

Vesicle Construction



Coarse Grain Protein



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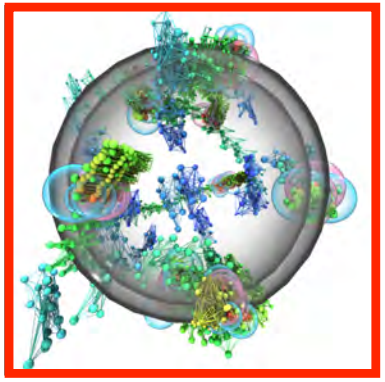

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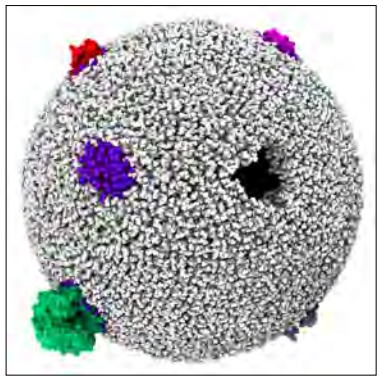

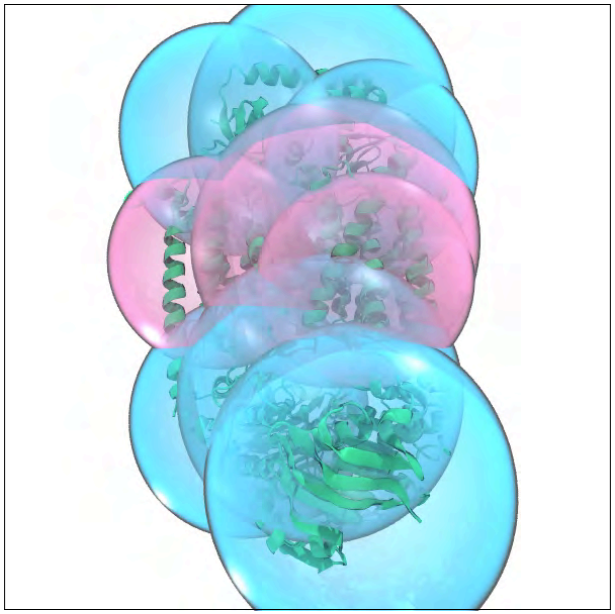

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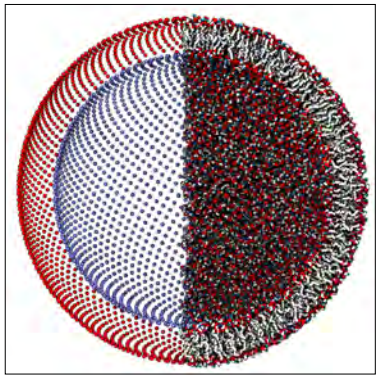

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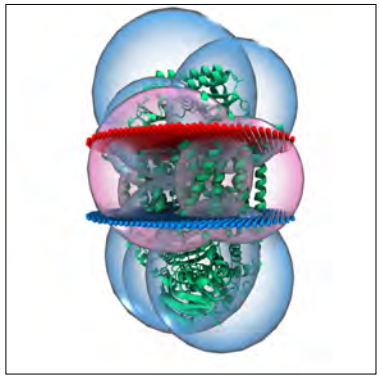

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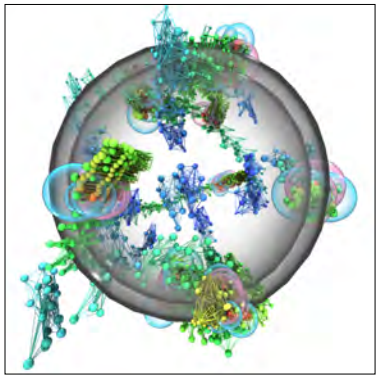

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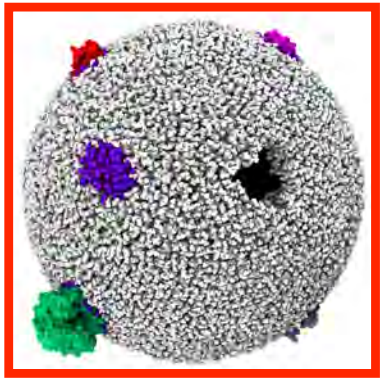

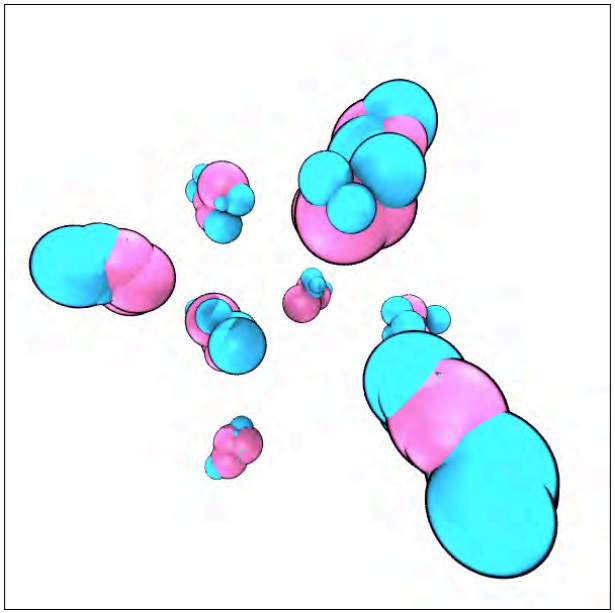

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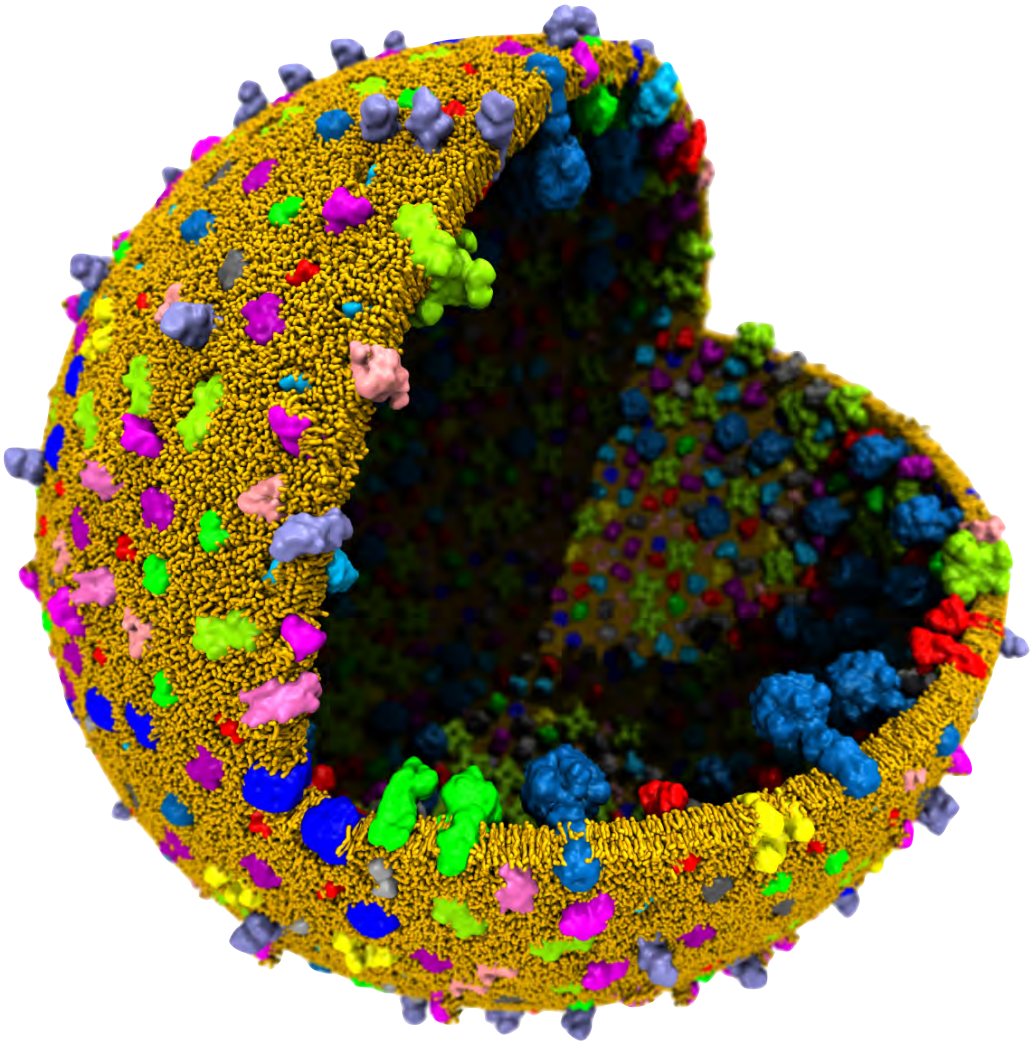
113 million Martini particles representing **1 billion** atoms



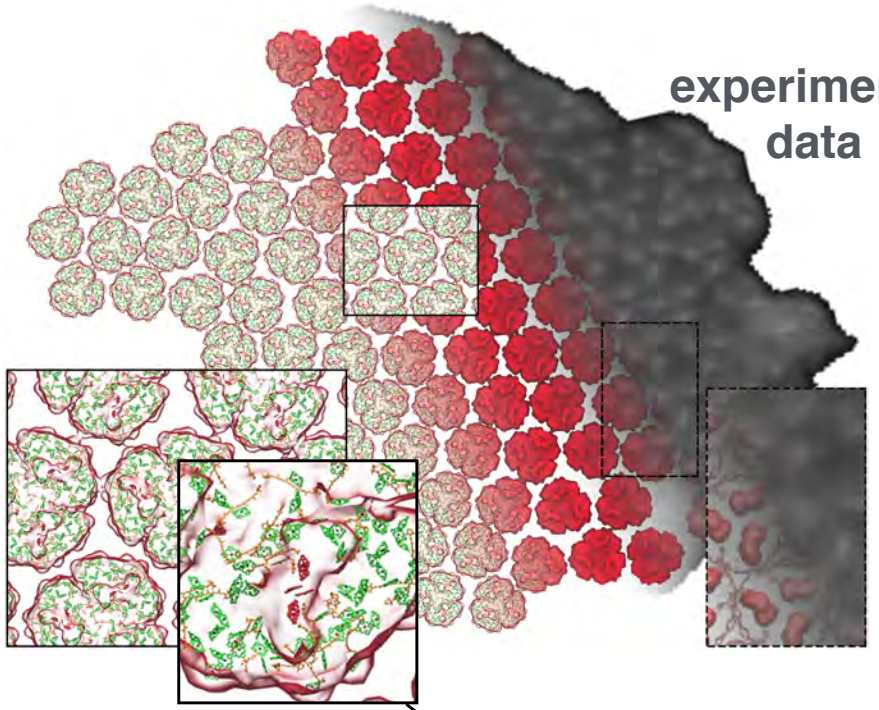
0.4 μm

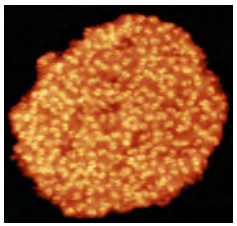
Protein Components	Copy #
Aquaporin Z	97
Copper Transporter (CopA)	166
F1 ATPase	63
Lipid Flipase (MsbA)	29
Molybdenum transporter (ModBC)	130
Translocon (SecY)	103
Methionine transporter (MetNI)	136
Membrane chaperon (YidC)	126
Energy coupling factor (ECF)	117
Potassium transporter (KtrAB)	148
Glutamate 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)

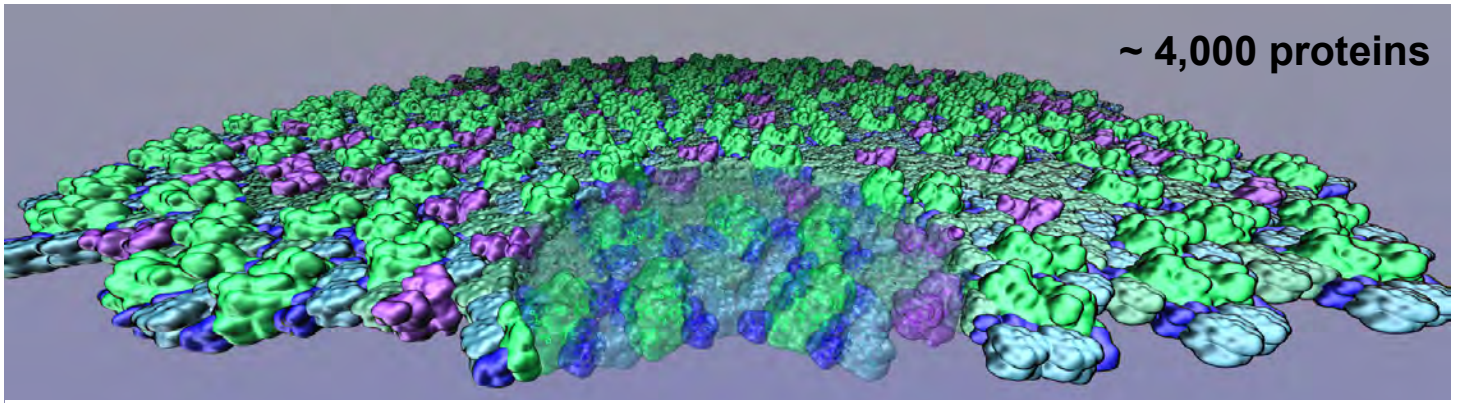
Applications of Computational Methodologies to Cell-Scale Structural Biology

Using simulations as a “structure-building” tool





A bioenergetic membrane

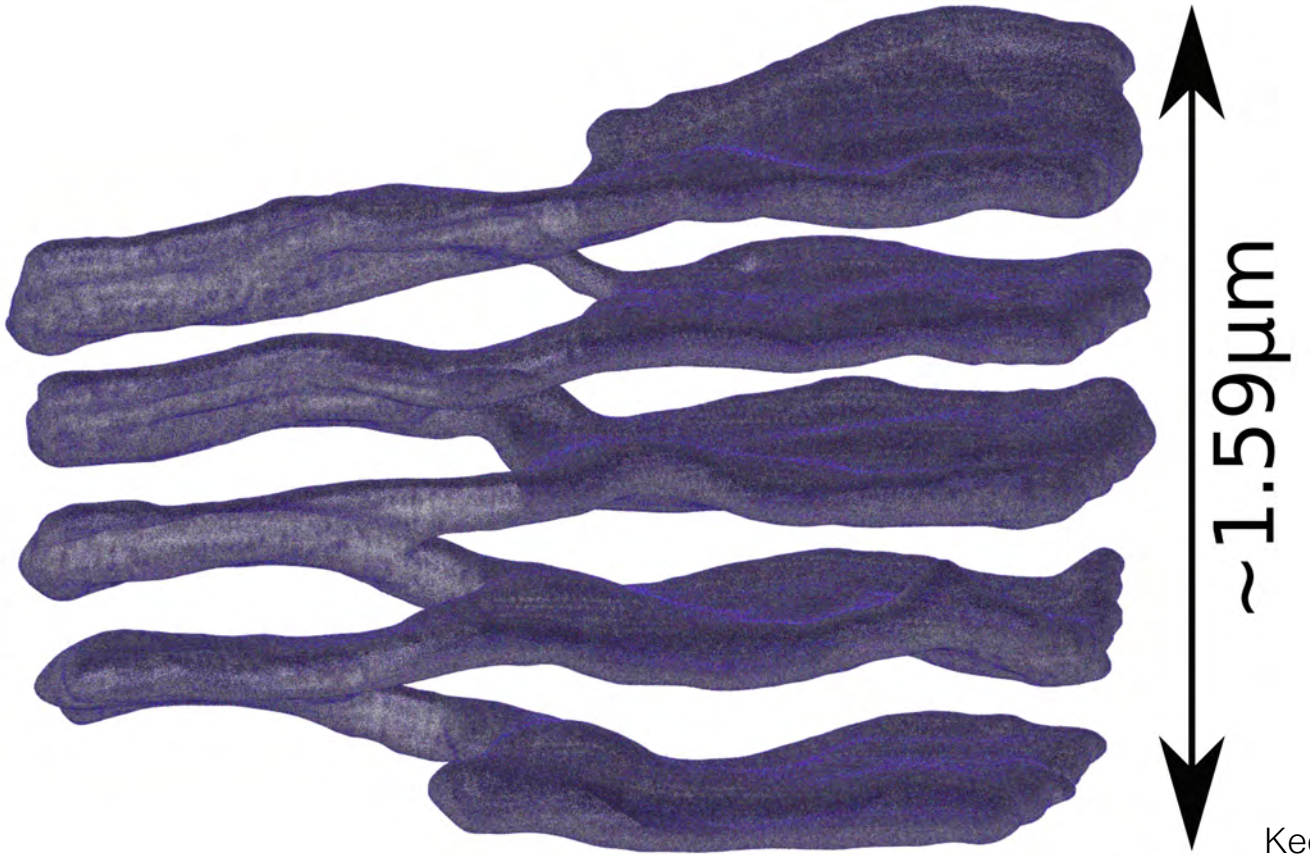


Applications of Computational Methodologies to Cell-Scale Structural Biology

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

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

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

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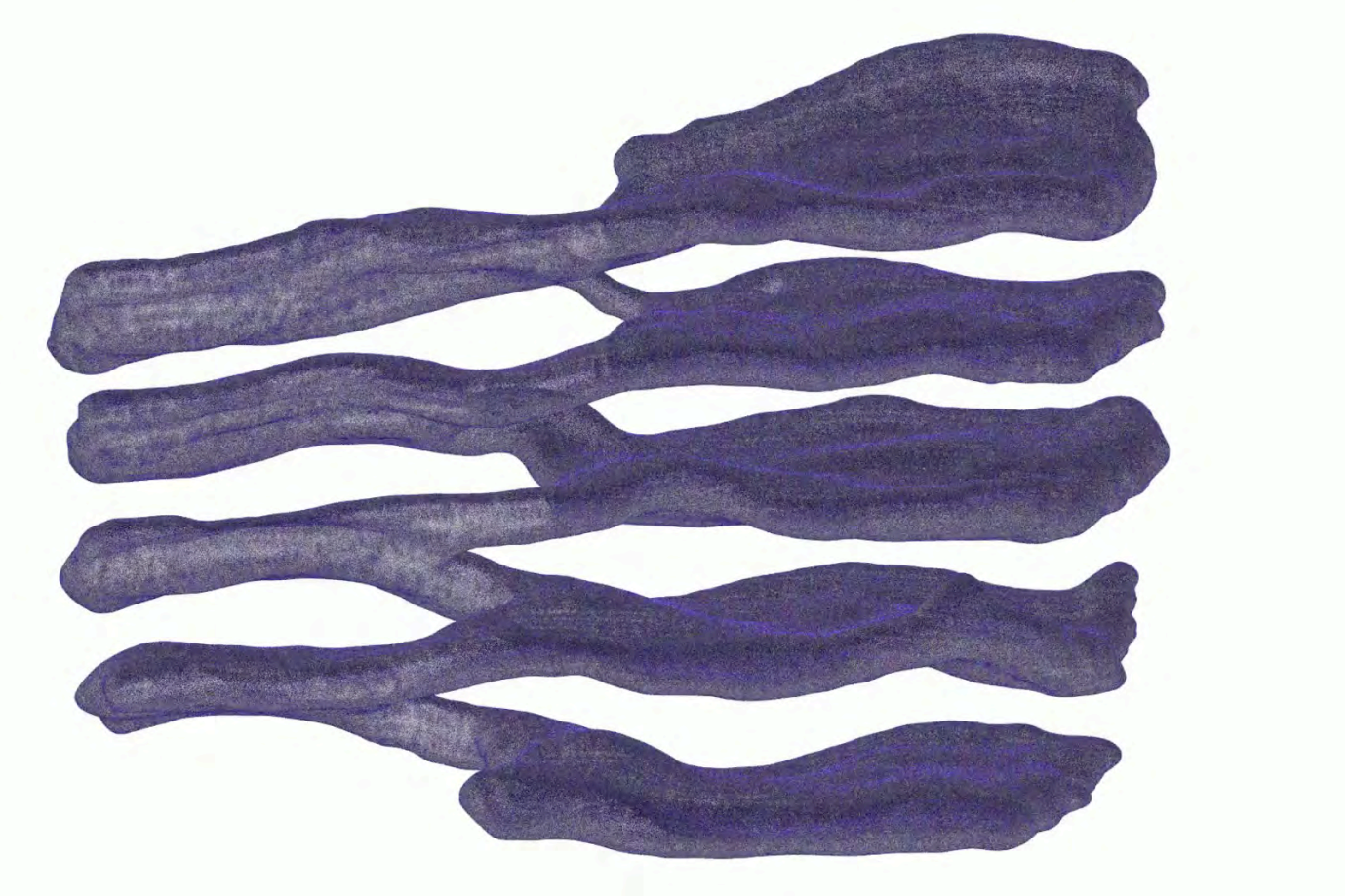

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