NIH Biomedical Technology Research Center for Macromolecular Modeling and Visualization

Overview of the Program

Introduction to MD in NAMD
Introduction to Molecular Visualization in VMD

Free Energy Calculations
Advanced Modeling Tools

Goal:
Making users comfortable with the software environment

Tutorials — MUST MUST MUST

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

Monday, July 17:

09:00	Application of molecular dynamics to biomolecular modeling	Emad Tajkhorshid NIH Resource for Macromolecular Modeling and Visualization University of Illinois at Urbana-Champaign
10:30	Coffee Break	
10:45	Ab initio protein structure modeling with Alphafold in VMD	Rafael Bernardi Department of Physics, Auburn University
11:45	Quick setup and analysis of NAMD simulations with QwikMD	Rafael Bernardi Department of Physics, Auburn University
12:15	Q & A	
12:30	Lunch Break	
14:00	Hands-on tutorial session I: VMD and NAMD tutorial	
15:30	Coffee Break	
15:45	Hands-on tutorial session II: QwikMD tutorial	

Tuesday, July 18:

09:00	Enhanced sampling and free energy calculations in NAMD - Part I	Chris Chipot NIH Resource for Macromolecular Modeling and Visualization University of Illinois at Urbana-Champaign
10:30	Coffee Break	
10:45	Enhanced sampling and free energy calculations in NAMD - Part II	Chris Chipot NIH Resource for Macromolecular Modeling and Visualization University of Illinois at Urbana-Champaign
11:30	Free energy calculations at QM/MM level	Rafael Bernardi Department of Physics, Auburn University
12:10	Q & A	
12:30	Lunch Break	
14:00	Hands-on tutorial session I: Free energy and enhanced sampling tutorial	
15:30	Coffee Break	
15:45	Hands-on tutorial session II: Free energy and enhanced sampling tutorial	

Dr. M. Moradi replaces Dr. Chipot.

Wednesday, July 19:

09:00	VMD+ Special features and capabilities	John Stone NIH Resource for Macromolecular Modeling and Visualization University of Illinois at Urbana-Champaign
10:00	Advanced visualization, figures and movies in VMD	Mariano Spivak NIH Resource for Macromolecular Modeling and Visualization University of Illinois at Urbana-Champaign
10:30	Coffee Break	
10:45	NAMD 3.0 features, performance and capabilites	David Hardy NIH Resource for Macromolecular Modeling and Visualization University of Illinois at Urbana-Champaign
11:45	Force field parameterization with FFTK	Mariano Spivak NIH Resource for Macromolecular Modeling and Visualization University of Illinois at Urbana-Champaign
12:15	Q & A	
12:30	Lunch Break	
14:00	Hands-on tutorial session I: FFTK tutorial	
15:30	Coffee Break	
15:45	Hands-on tutorial session II: PMF tutorial	

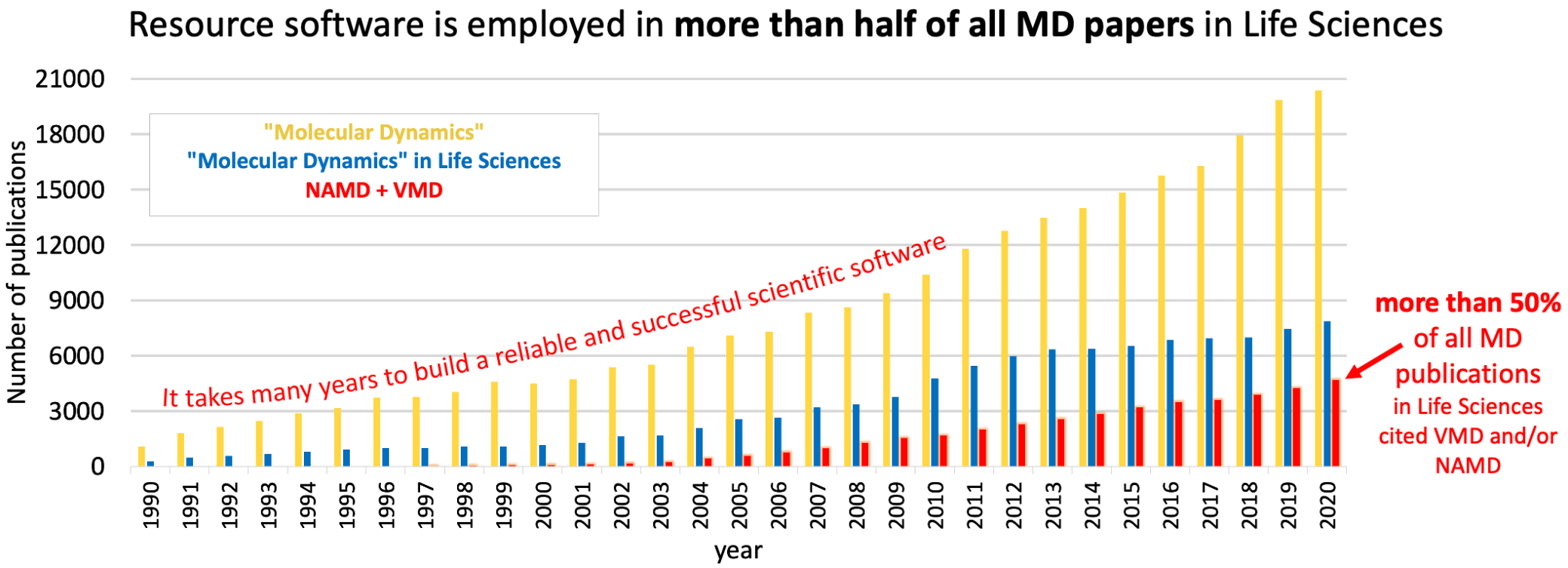
Thursday, July 20:

09:00	Molecular simulation at the interface of biology and nanotechnology	Aleksei Aksimentiev NIH Resource for Macromolecular Modeling and Visualization University of Illinois at Urbana-Champaign
10:30	Coffee Break	
10:45	Multi-resolution simulations with ARBD	Christopher Maffeo NIH Resource for Macromolecular Modeling and Visualization University of Illinois at Urbana-Champaign
12:15	Q & A	
12:30	Lunch Break	
14:00	Hands-on tutorial session I: Modeling nanopores for sequencing DNA	
15:30	Coffee Break	
15:45	Hands-on tutorial session II: Other tutorial	

Friday, July 21:

09:00	TBD	Rafael Bernardi Department of Physics, Auburn University
10:30	Coffee Break	
10:45	Introducing Cybershuttle: A platform to launch and control simulation jobs in HPC	Suresh Marru Cyberinfrastructure Integration Research Center, Indiana University
12:15	Q & A	
12:30	Lunch Break	
14:00	Hands-on tutorial session I: Cybershuttle tutorial	
15:30	Coffee Break	
15:45	Hands-on tutorial session II: Other tutorial	

Molecular Dynamics -
A Key Tool in Biophysics and Beyond

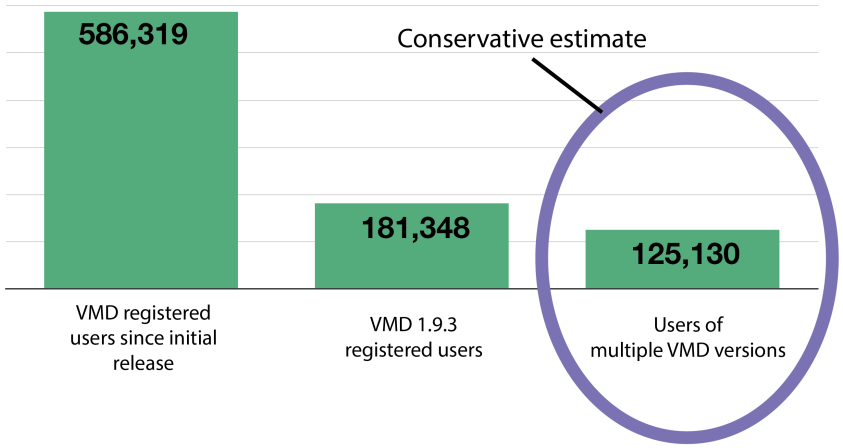


NIH Resource Center for Macromolecular Modeling and Visualization

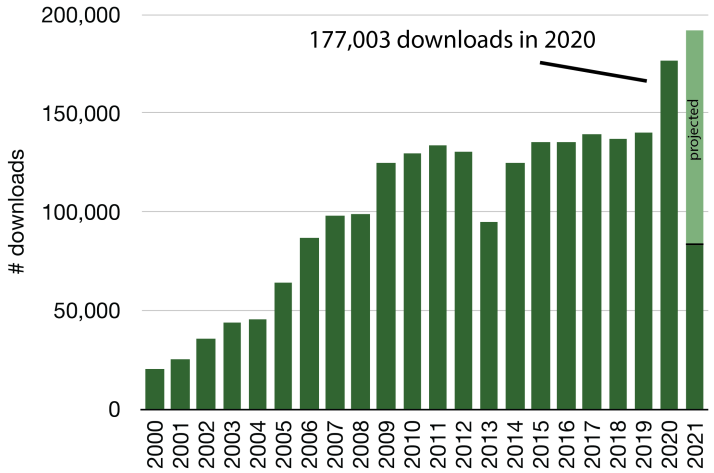
NIH Biomedical Technology Resource for Macromolecular Modeling and Visualization

Serving a large and growing community

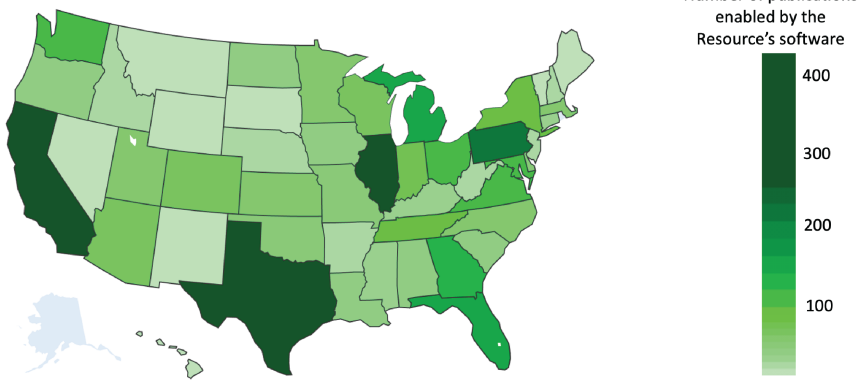
a) Over 125,000 users of Resource software



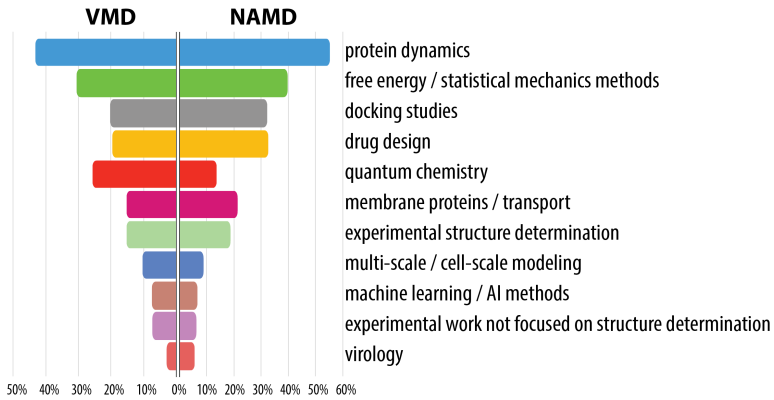
b) Over 2.2 million total downloads of Resource software



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



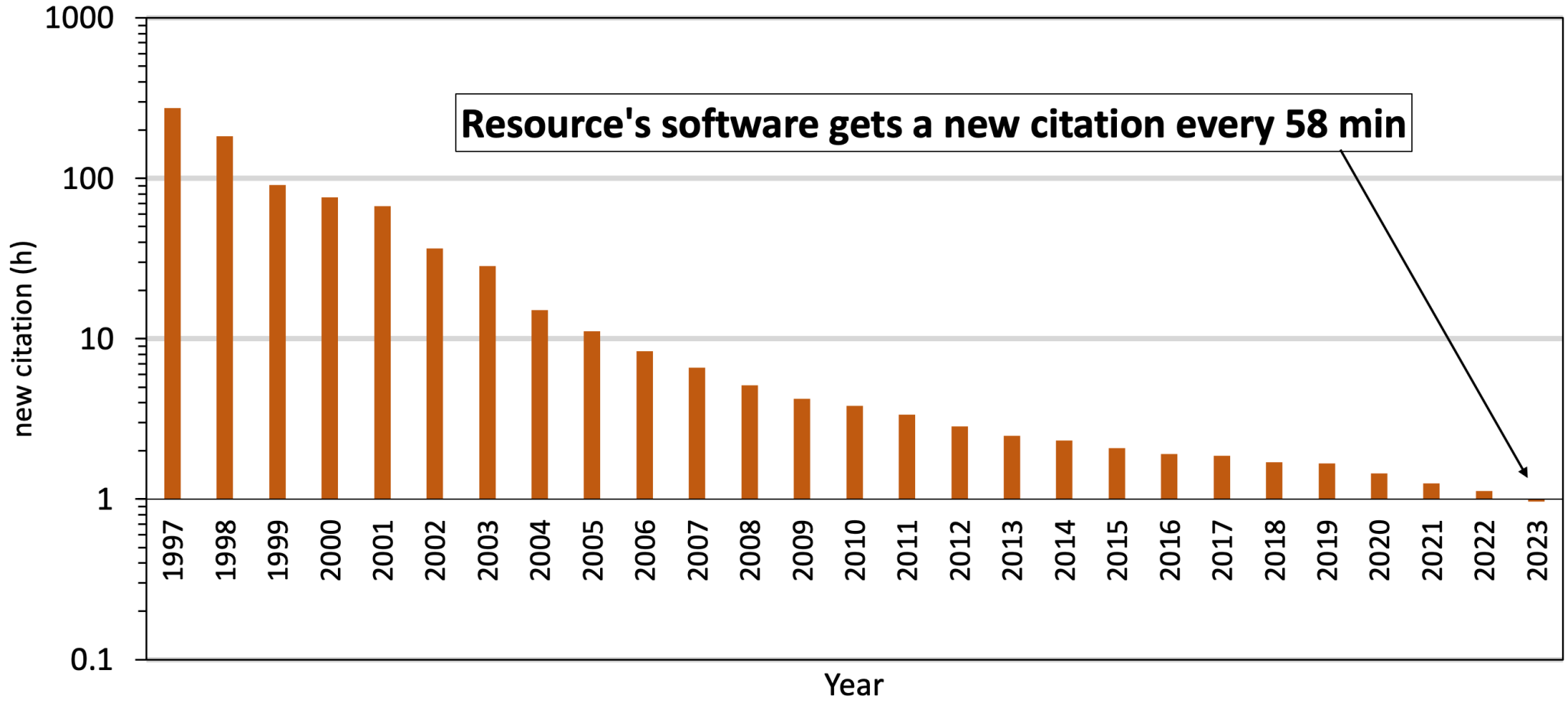
d) VMD and NAMD are used in a broad range of biological fields



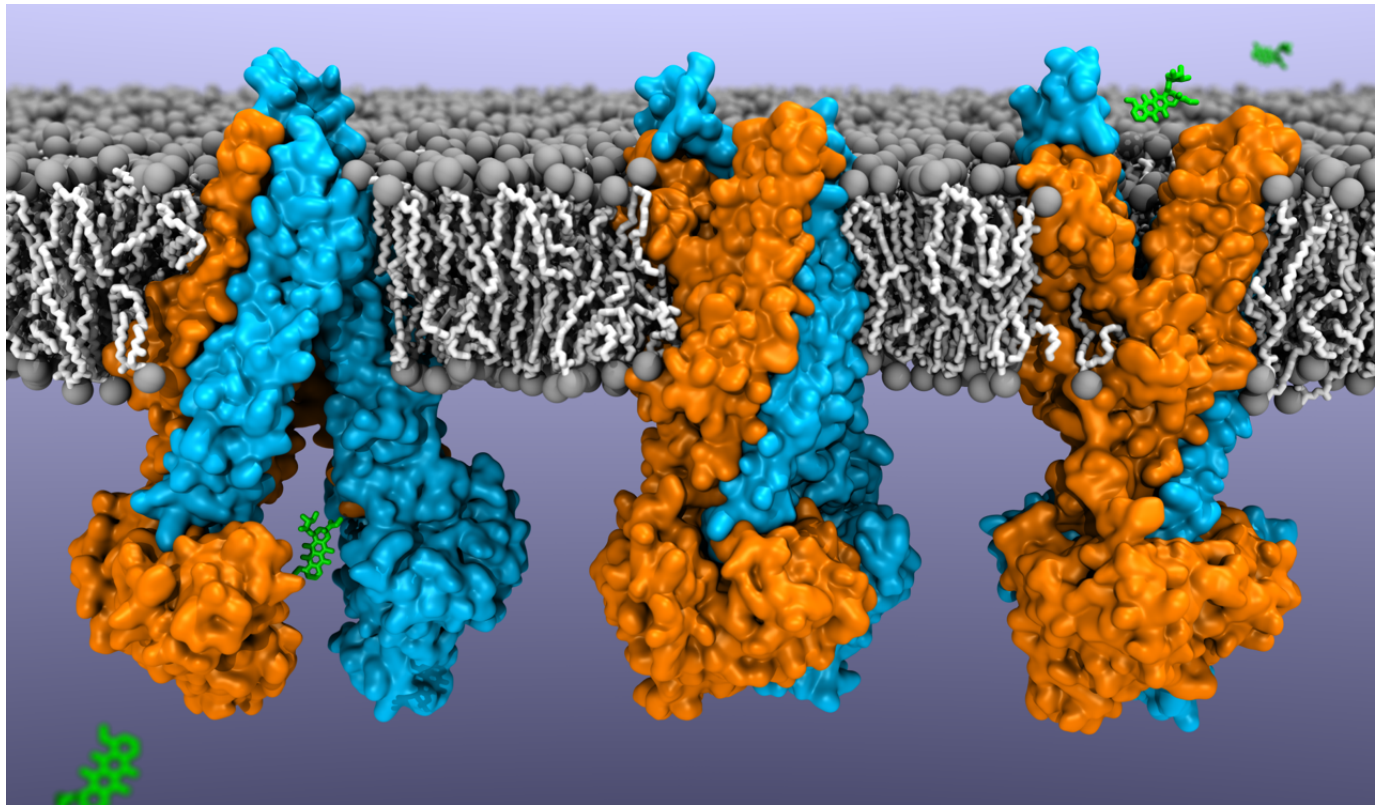
5-yr statistics: **1.4 million** web visitors; **228,000** tutorial views

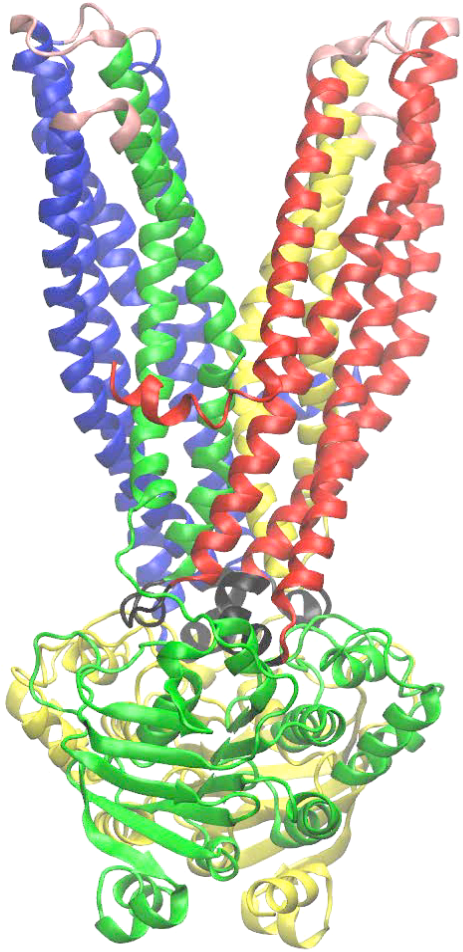
Serving a large and growing community

of biomedical researchers employing molecular modeling and simulation technologies



Computational Structural Biology Describing Biomolecules at Nanoscale

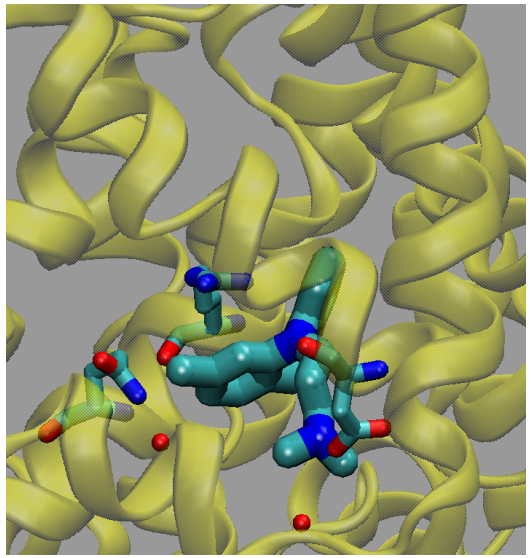


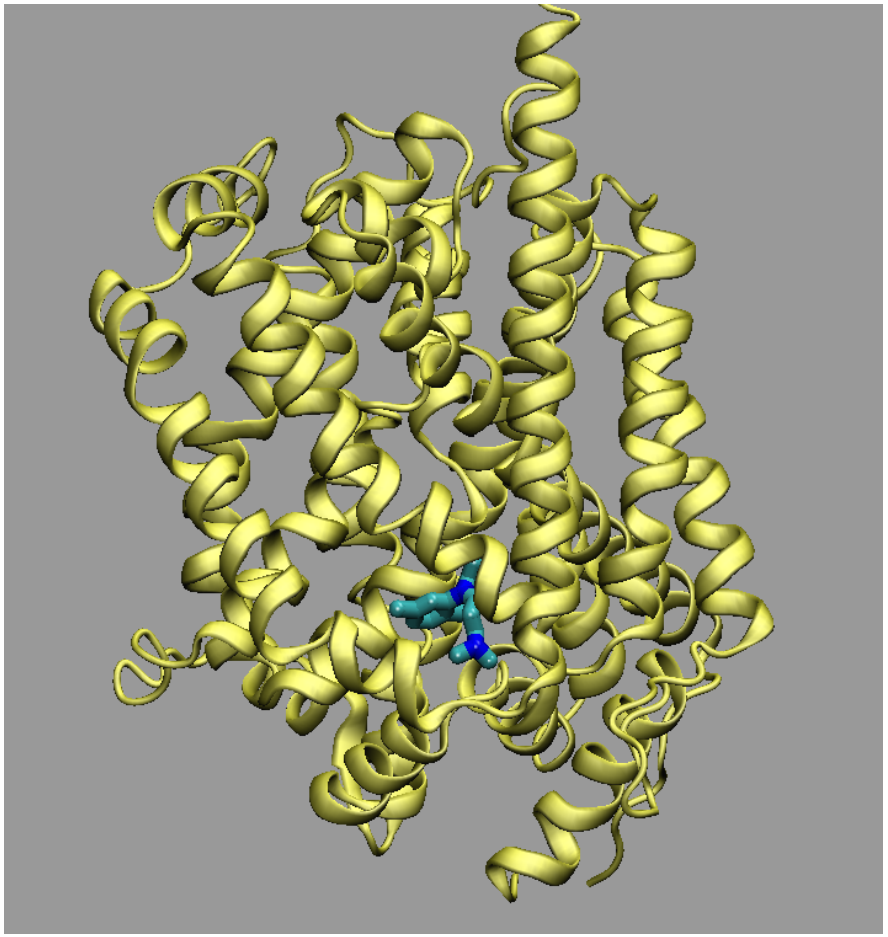


Structure / Dynamics
@ nanoscale

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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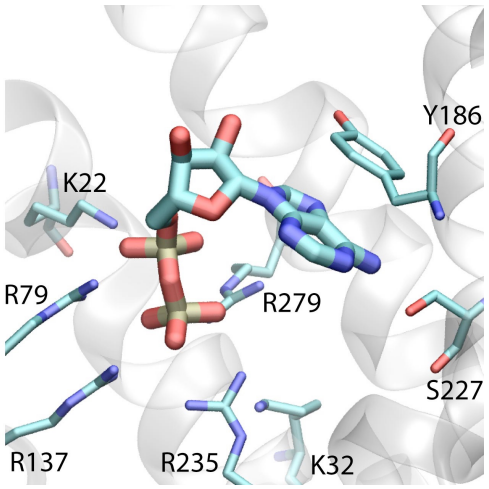
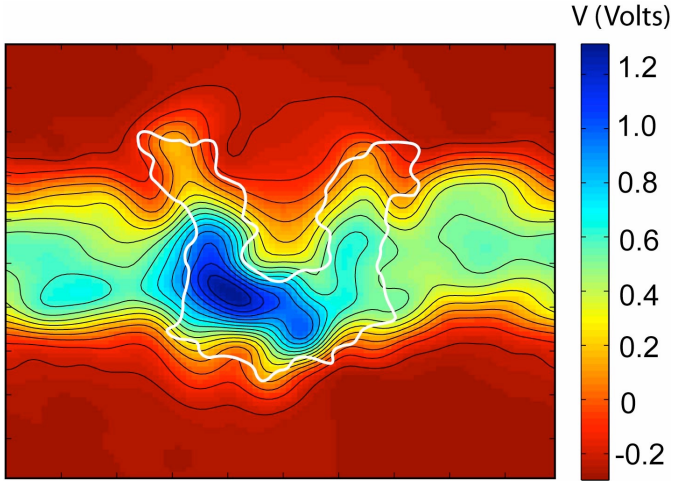
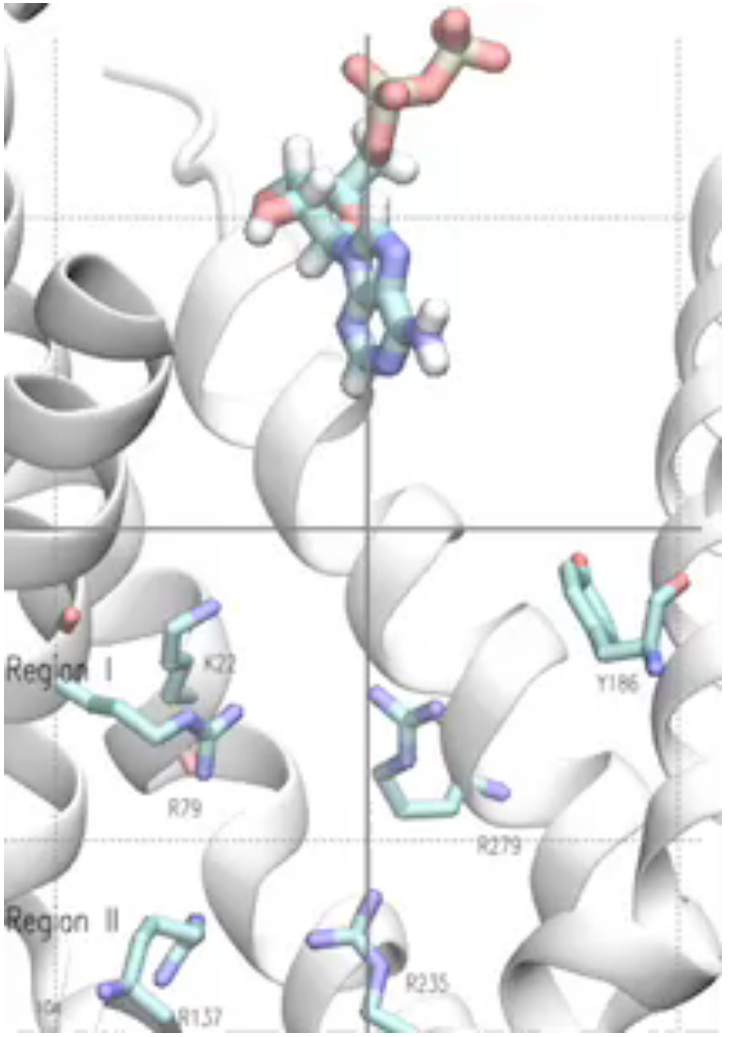
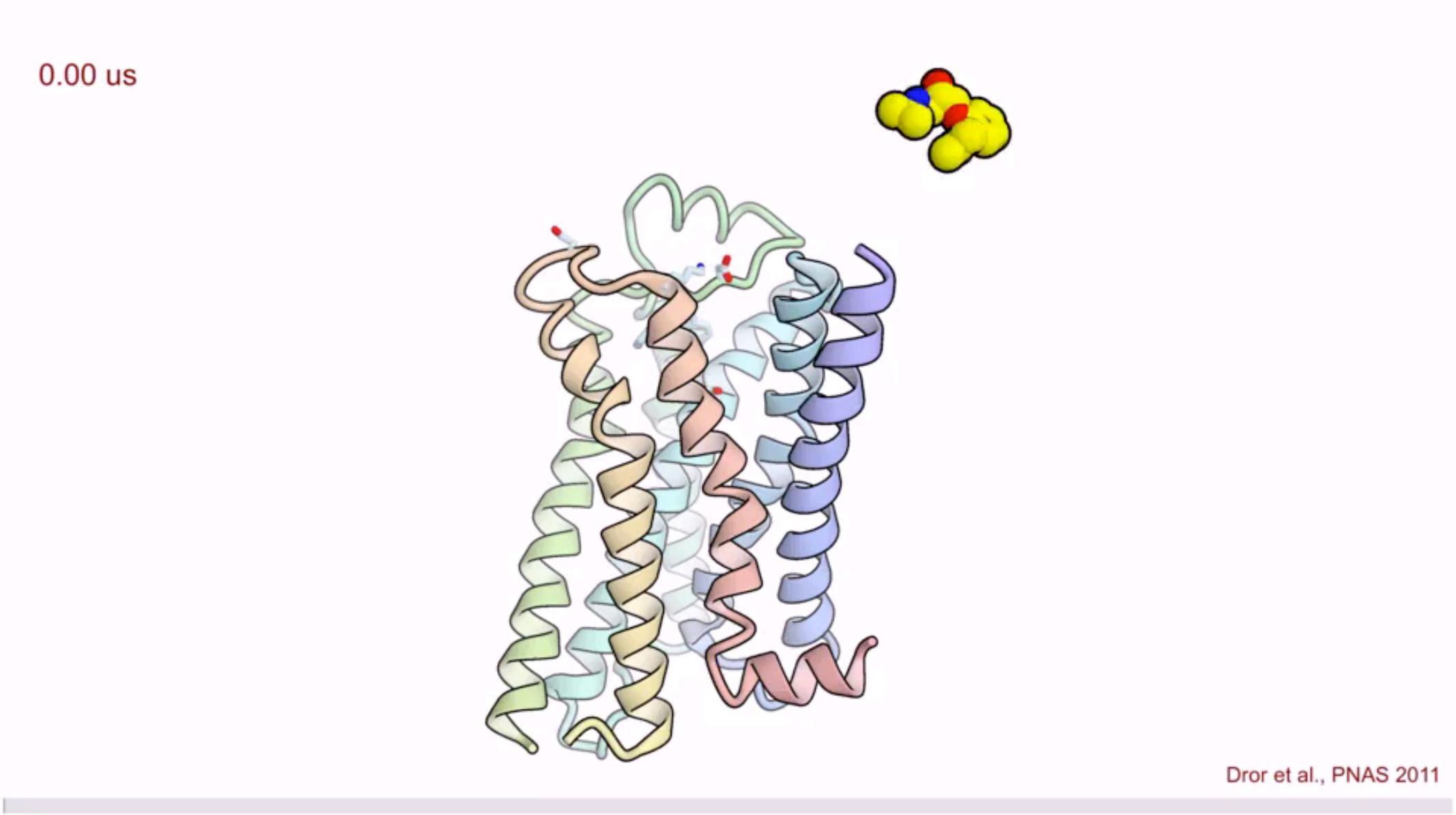






Binding of a small molecule to a binding site
Y. Wang & E.T. PNAS 2010

Why Structural Biology at Nanoscale?



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

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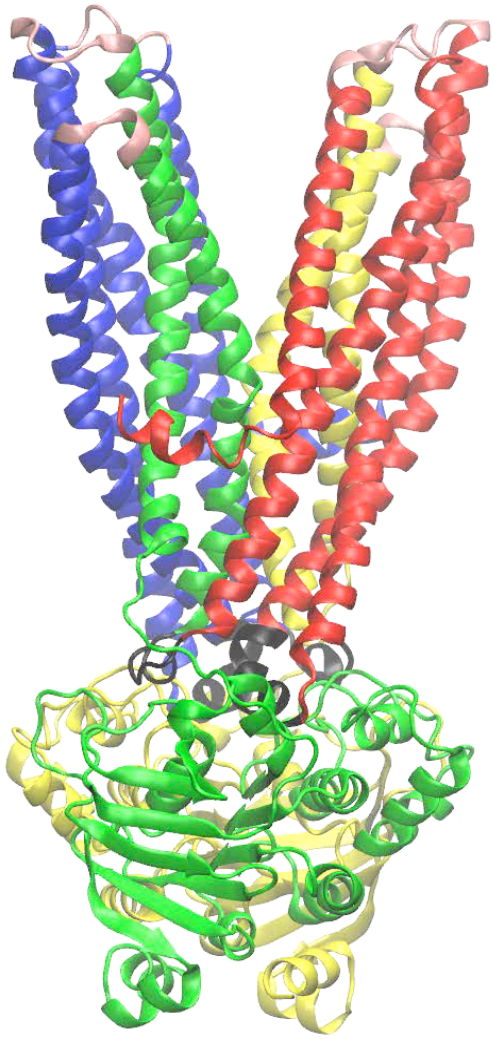
- ✦ Drug Design
- ✦ Nano-biotechnology



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

Why Structural Biology at Nanoscale?

- ✦ Mechanisms in Molecular Biology
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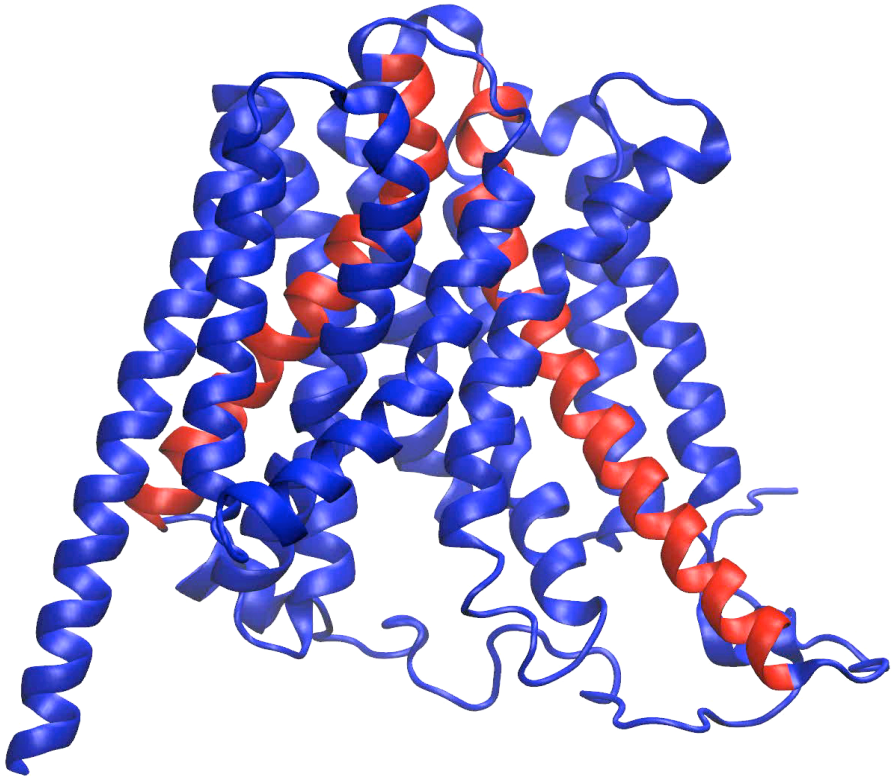
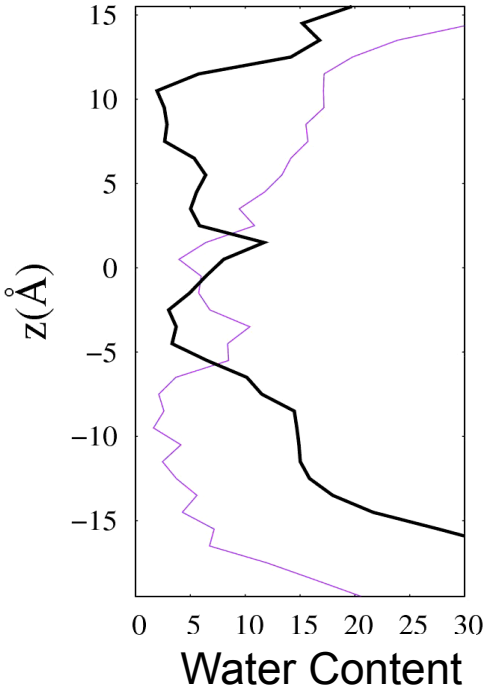
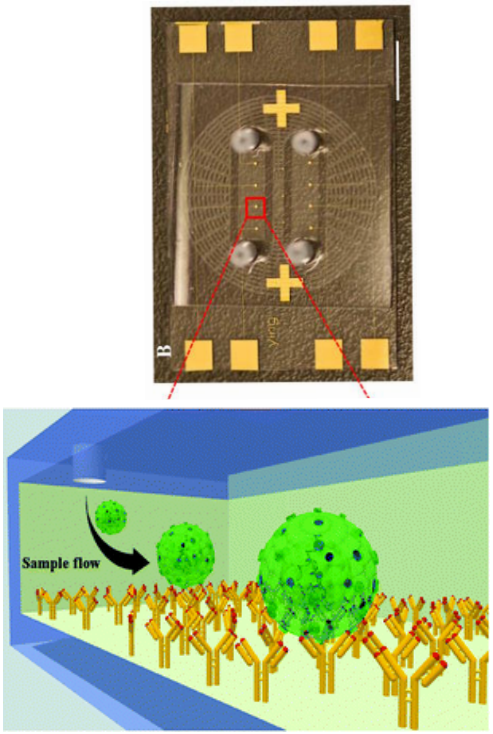
- ✦ Drug Design
- ✦ Nano-biotechnology





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

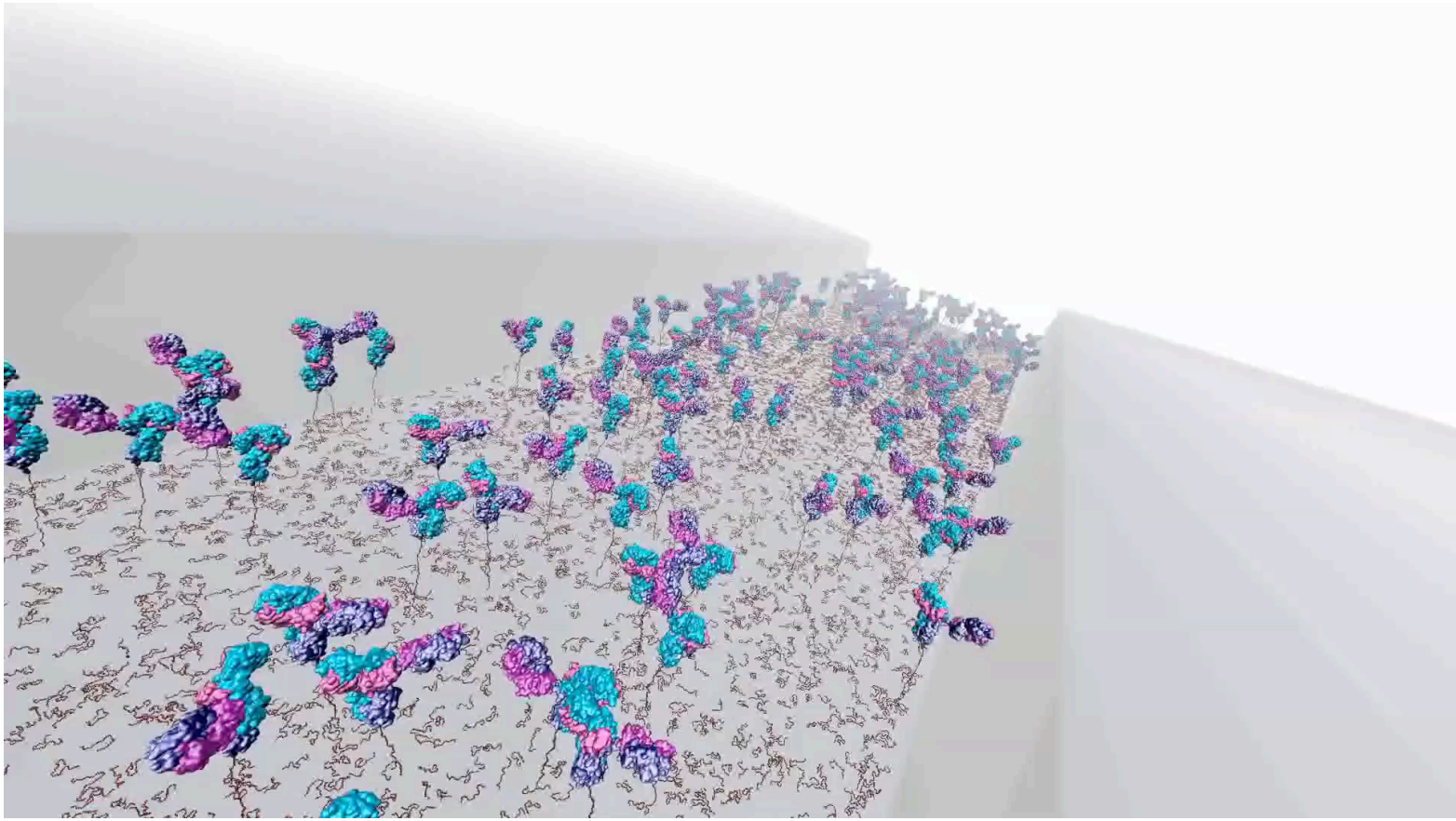
Nano-biotechnology
Microfluidic Sensing Devices



HIV subtype identification

Lab Chip 2012

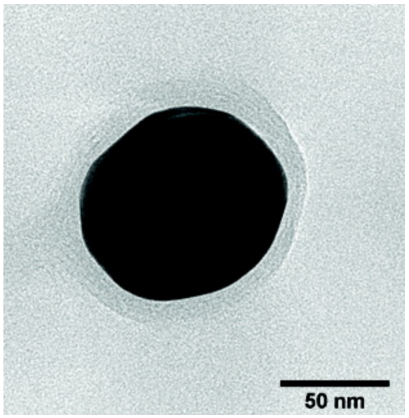
Functionalized nanosurface with antibodies



Created by **nanoBIO Node** tools

Nano-biotechnology
Gold Nanoparticles as Delivery Vehicles

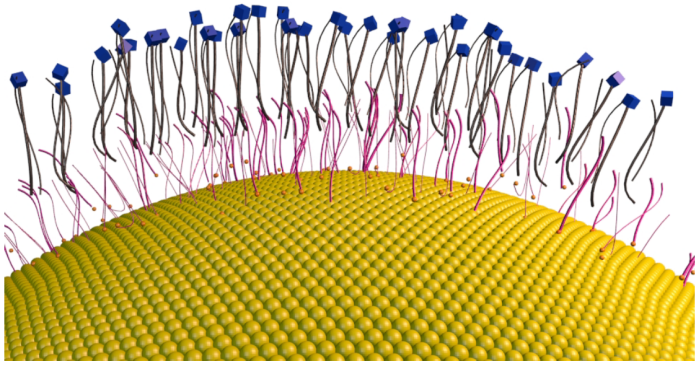
Transmission Electron Micrograph

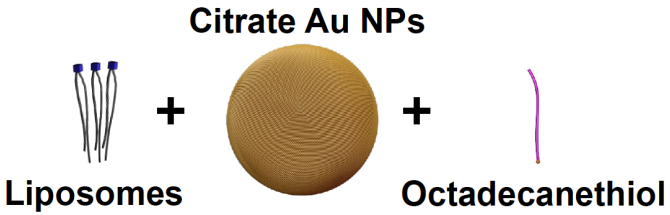


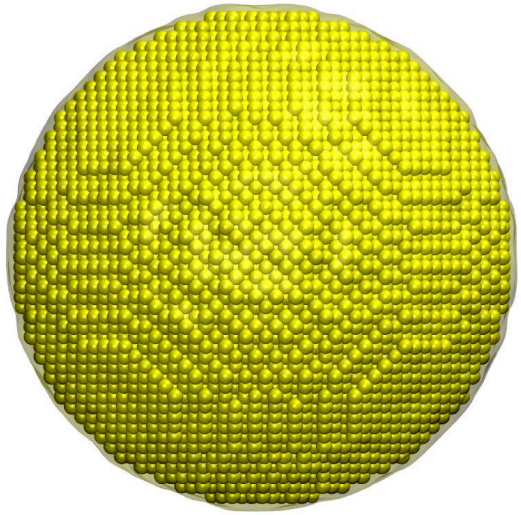
Yang, J. A.; Murphy, C. J. Langmuir 2012, 28, 5404–5416

Schematic model with no prediction power

Cartoon representation of lipid Au NPs







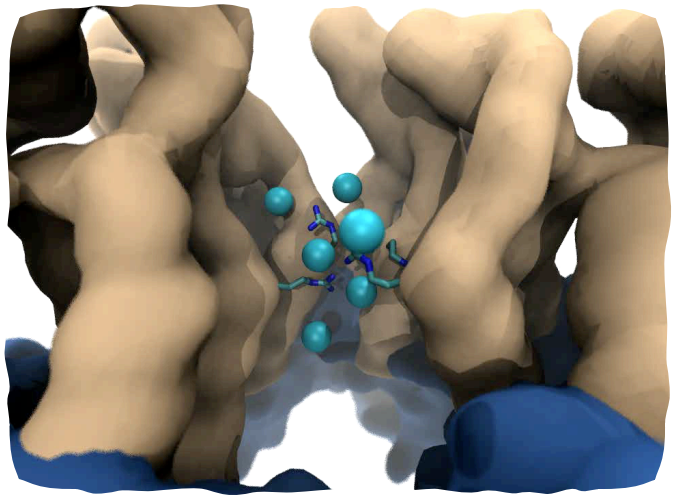
Experiment:
Murphy Lab

Modeling/Simulation:
Tajkhorshid Lab

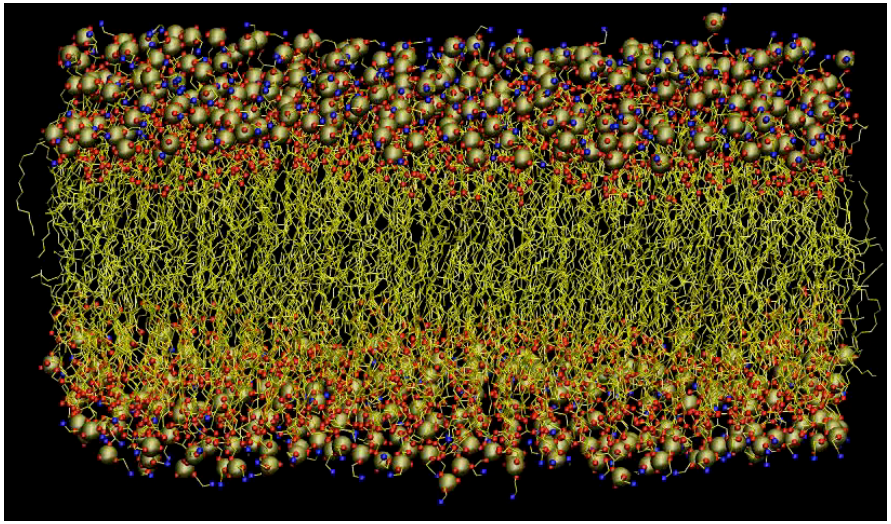
Applications of Computational Methodologies to Structural Biology

Simulation of the dynamics of the molecular system (MD)

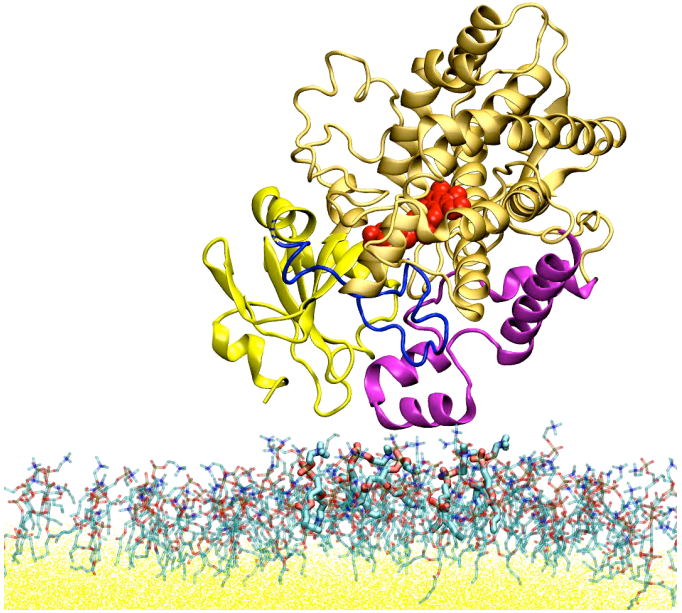
- Calculating ensemble-averaged properties of microscopic systems to compare to macroscopic measurements
- Providing a molecular basis for function
- Describing the molecular/structural changes underlying function
- …



Hydration at the interface of viral shell proteins

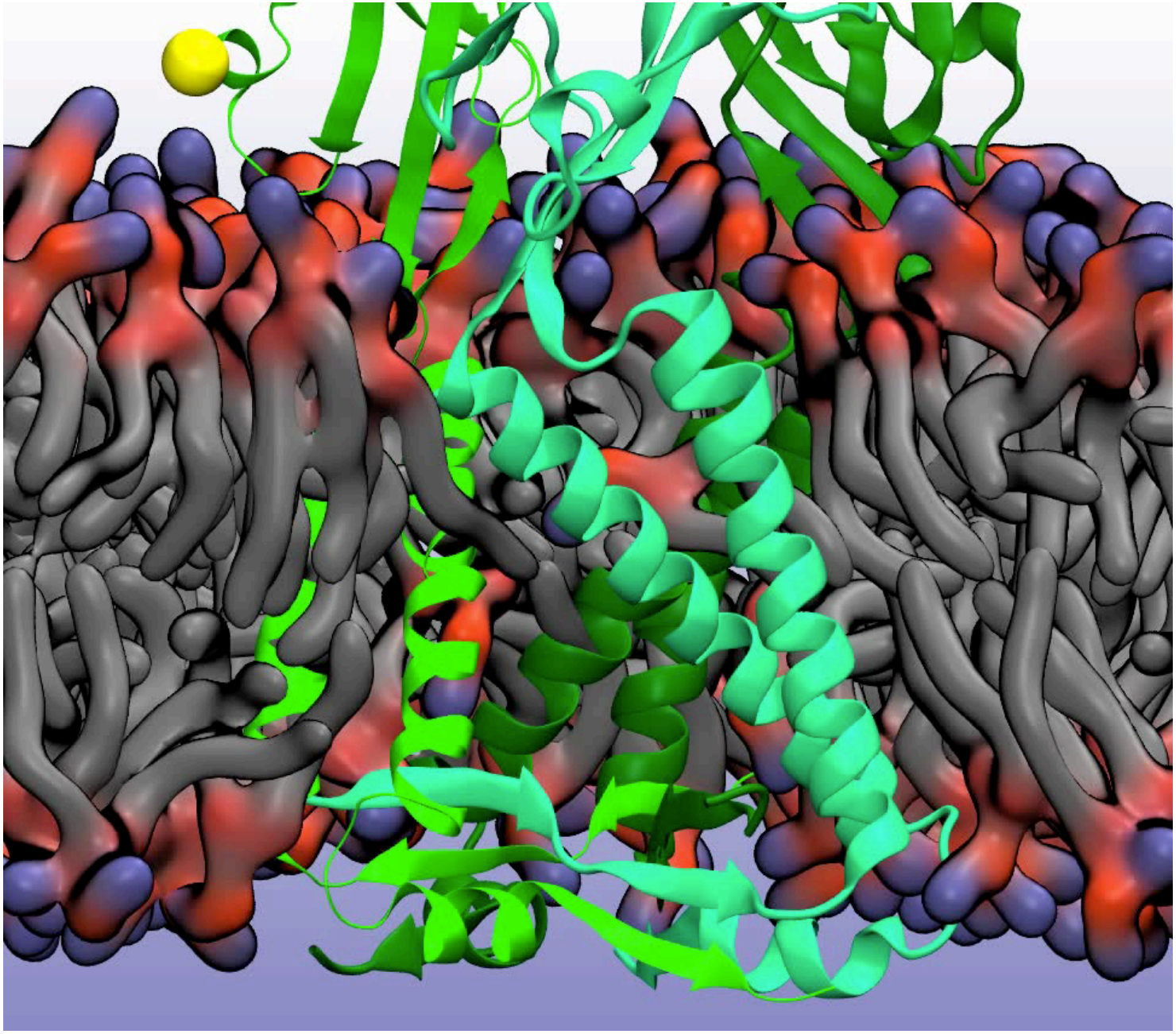


Thermal fluctuations of a phospholipid bilayer



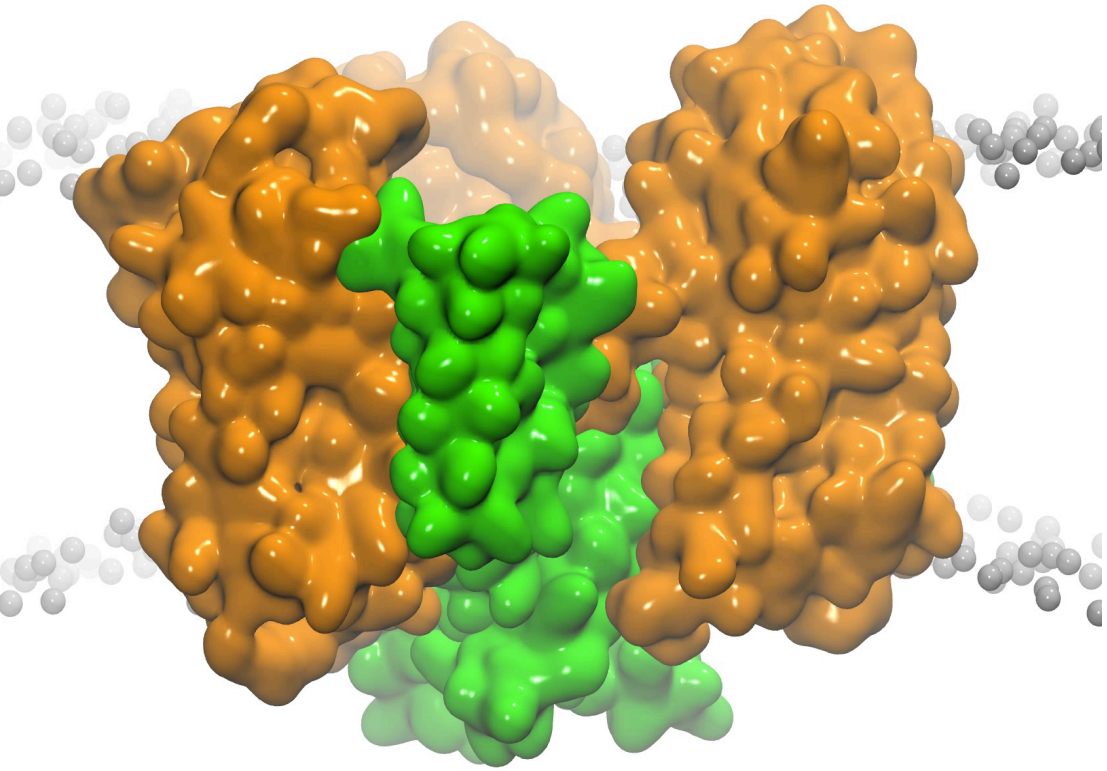
Membrane binding of a coagulation protein

Lipid Protein Interaction

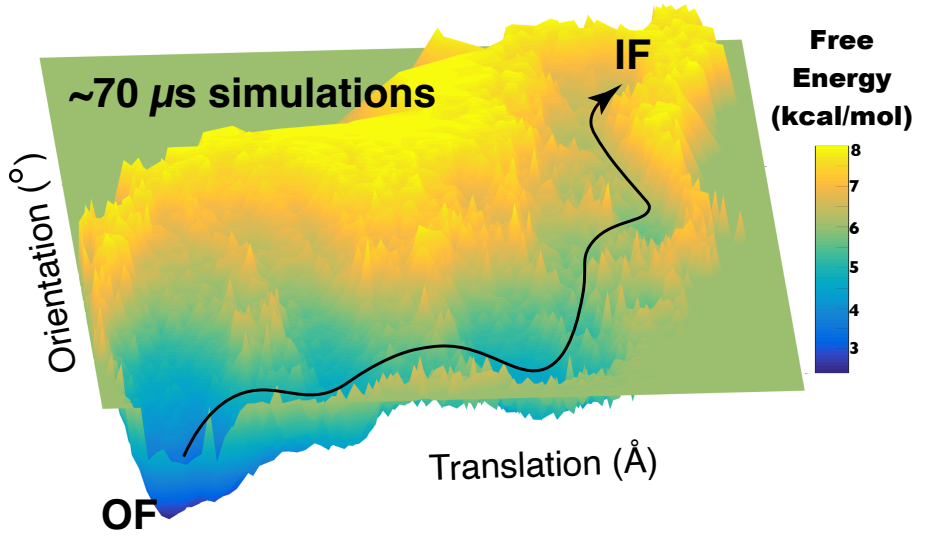


S. Mansoor, …, E. Tajkhorshid, E. Gouaux, Nature, 2016.

Characterizing Energy Landscapes Associated with Functional Motions of Proteins



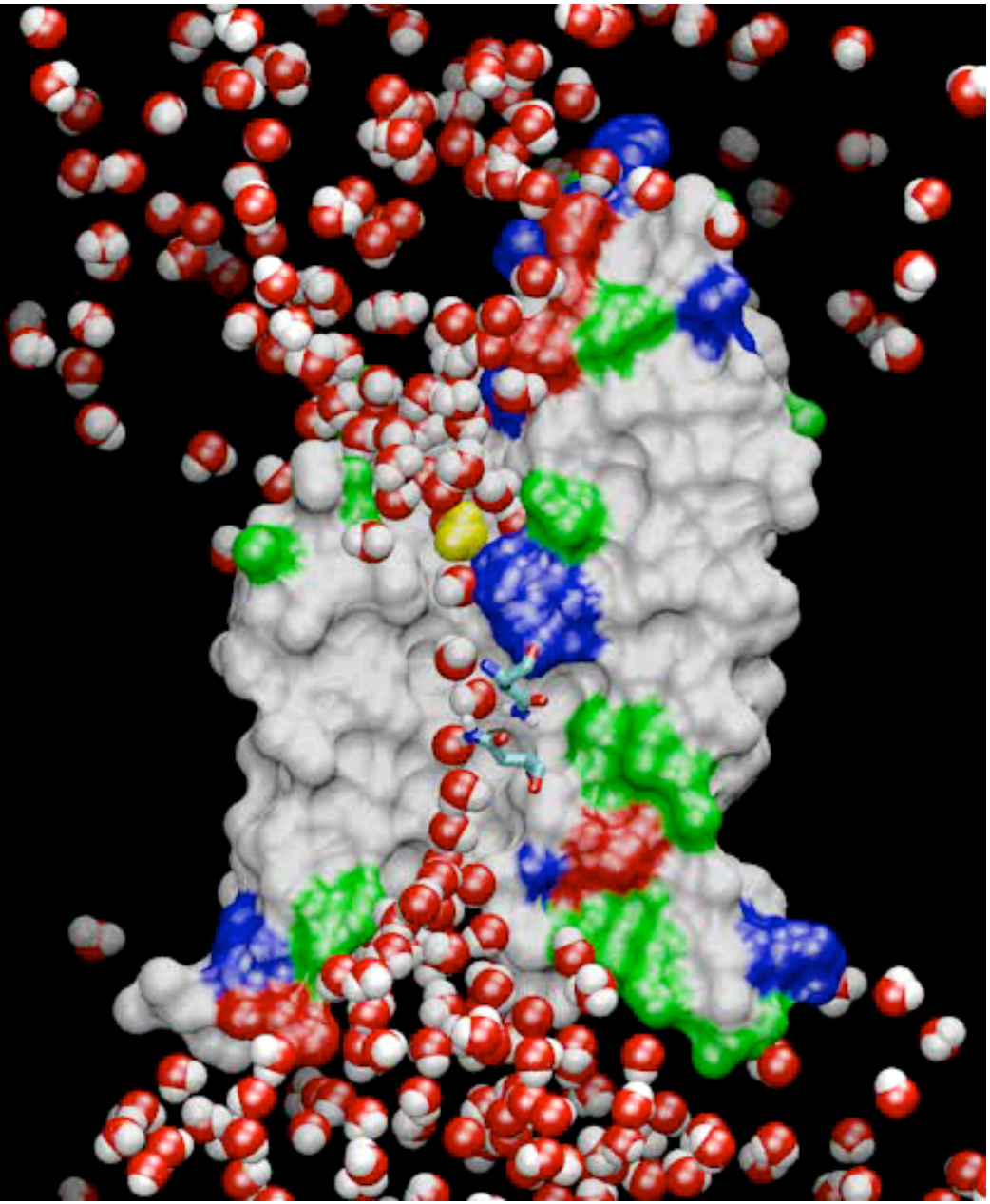
Outward-facing (OF) to Inward-facing (IF) Transition



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

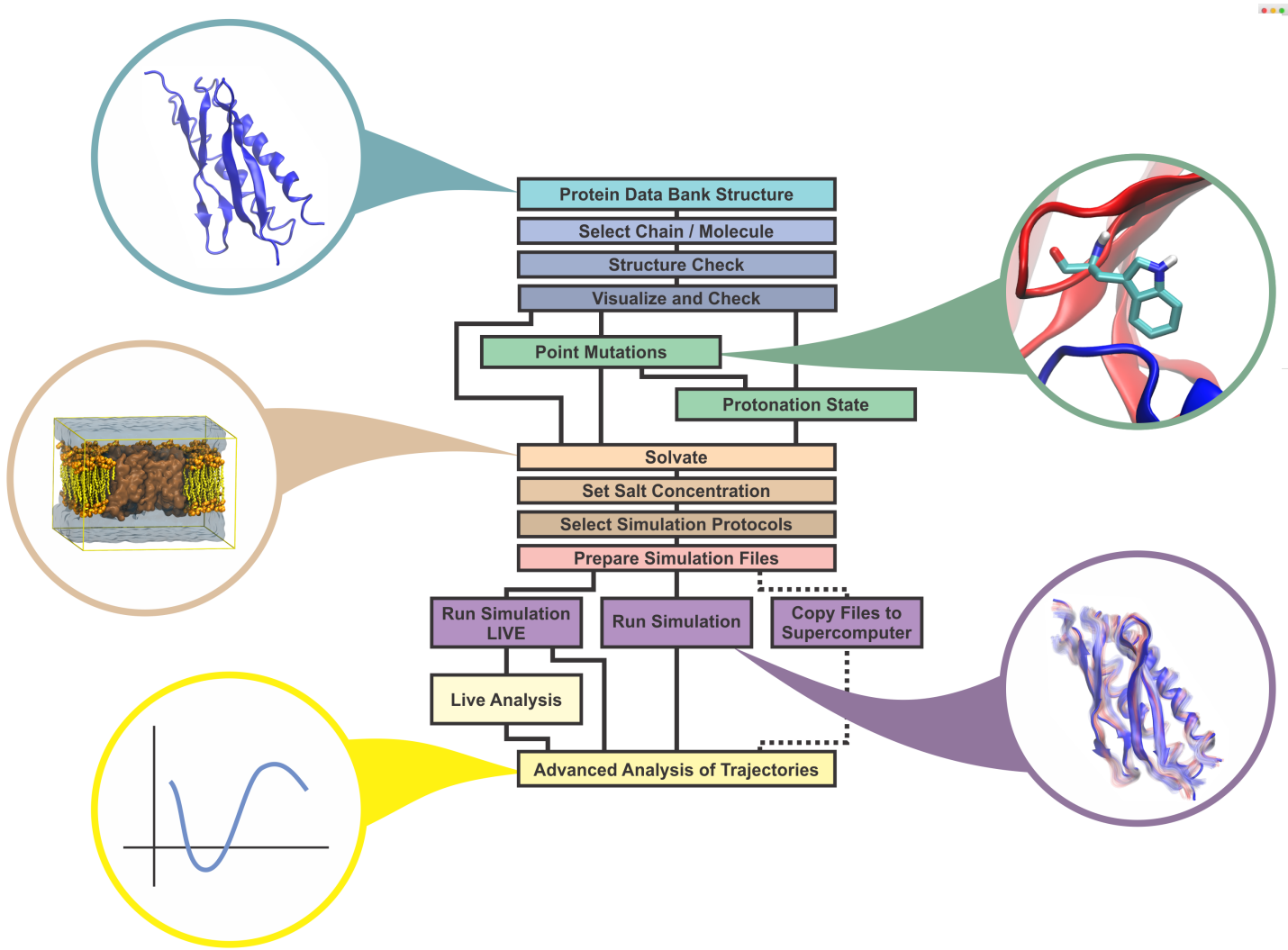
SPEED LIMIT

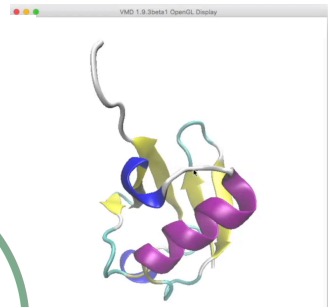
1 fs

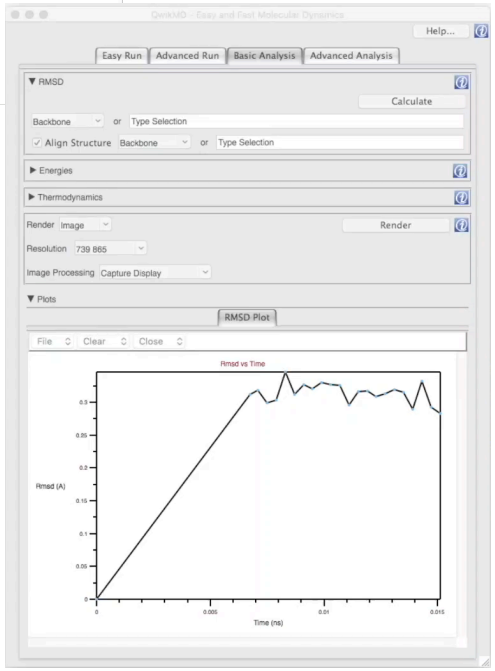
Major advantage:

- Unparalleled spatial and temporal resolutions, simultaneously

QwikMD- Gateway to Easy Simulation







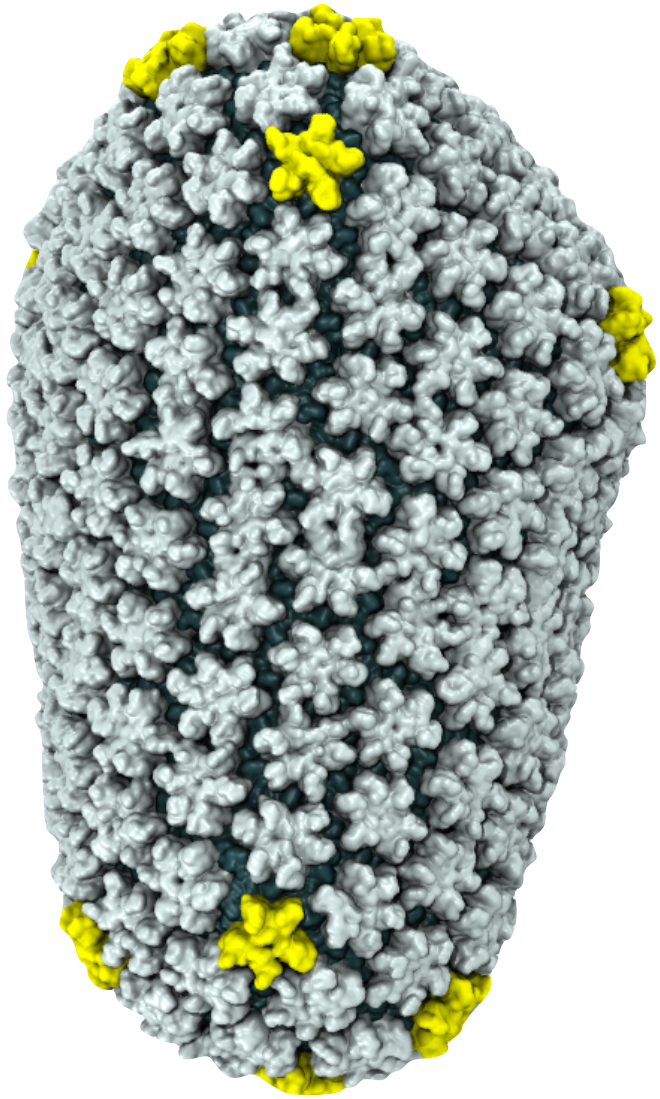
Ribeiro, J. V., …, Schulten, K.. QwikMD — Integrative Molecular Dynamics Toolkit for Novices and Experts. ***Sci. Rep.*** 6, 26536; doi: 10.1038/srep26536 (**2016**)

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

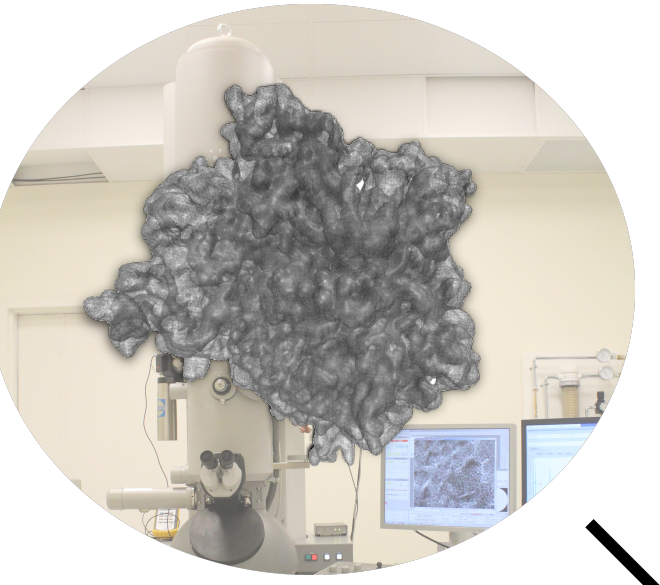
- NMR
- X-ray
- Electron Microscopy
- …



Structural model of HIV virus

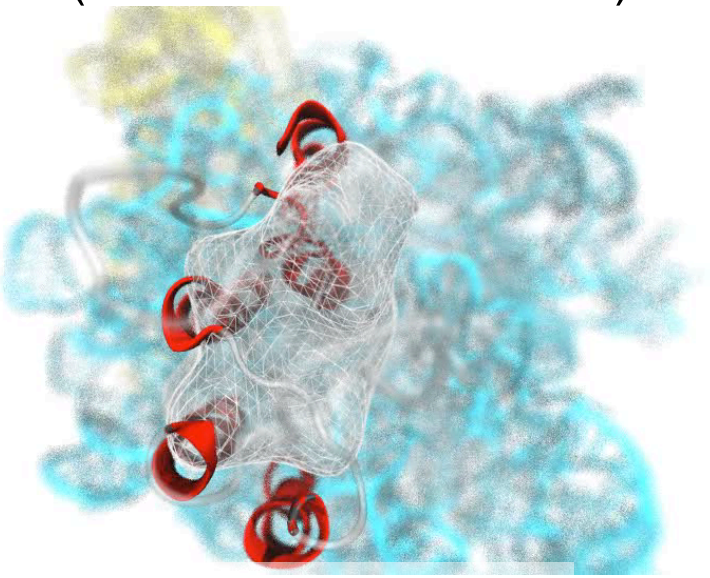
Molecular Dynamics Flexible Fitting (MDFF)

Electron Microscope



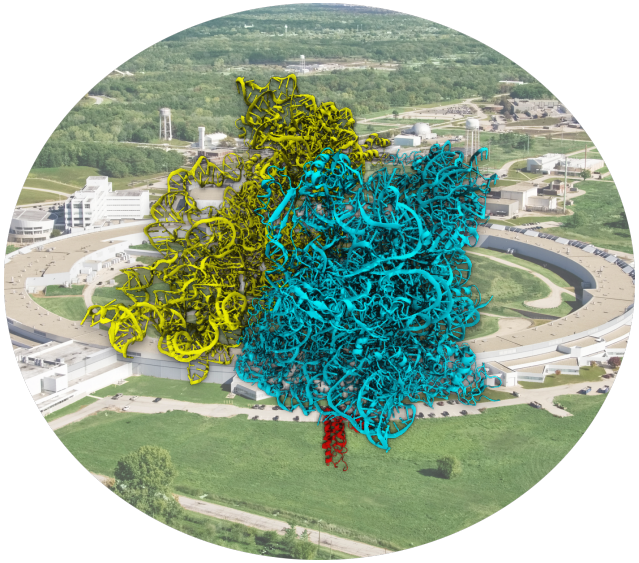
cryo-EM density map

(Ribosome-bound YidC)

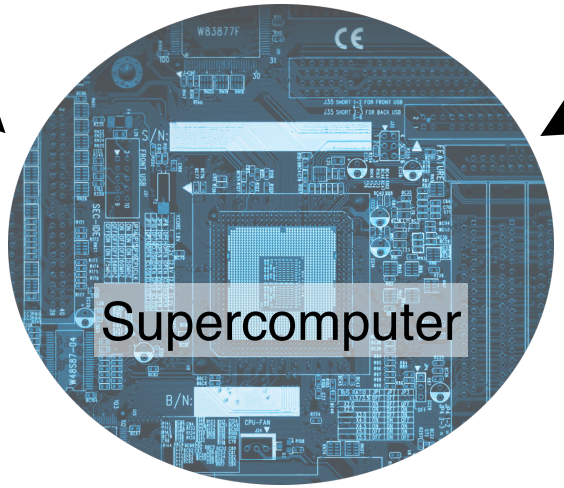


Match through MD

APS Synchrotron



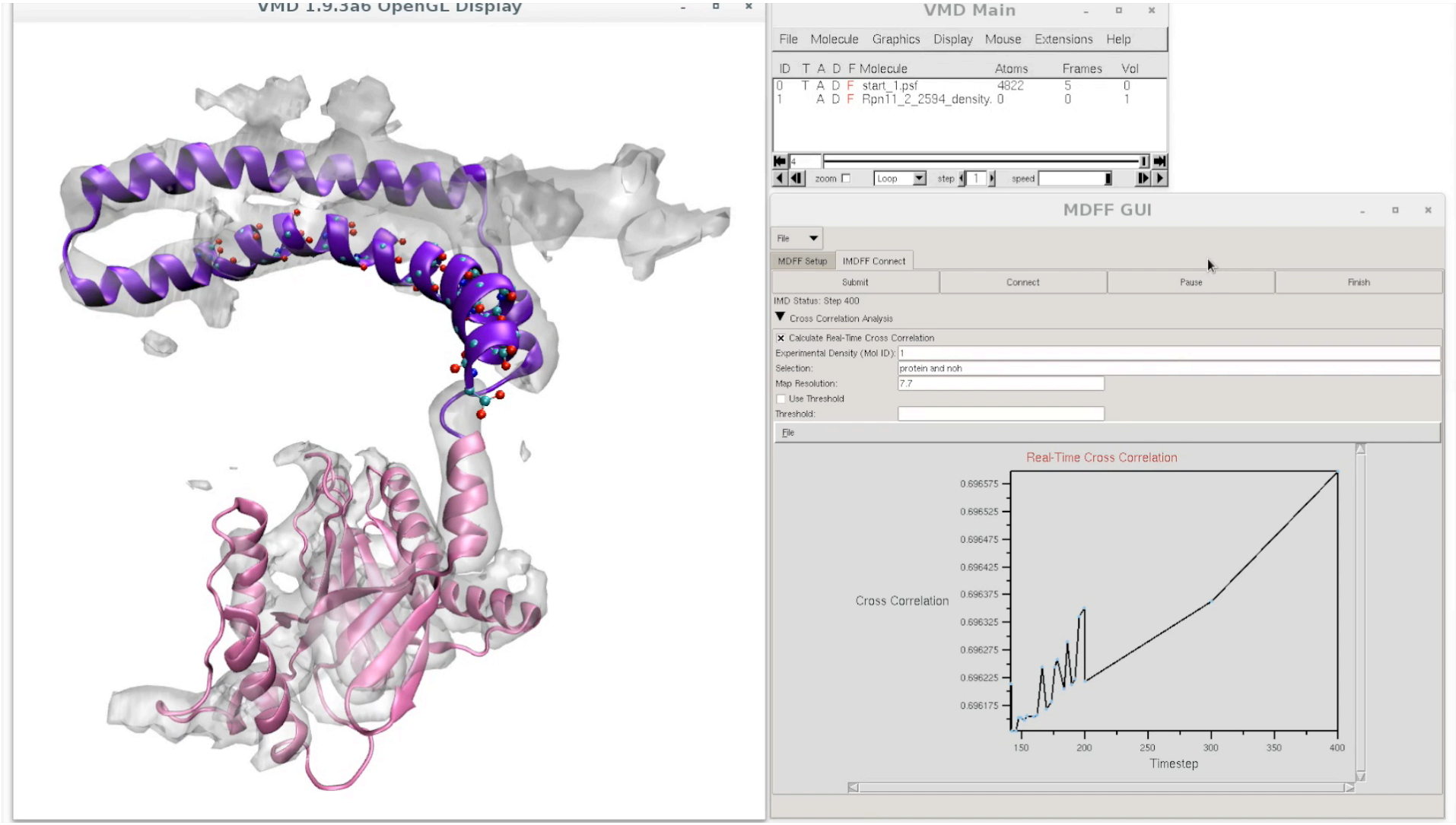
crystallographic structure



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

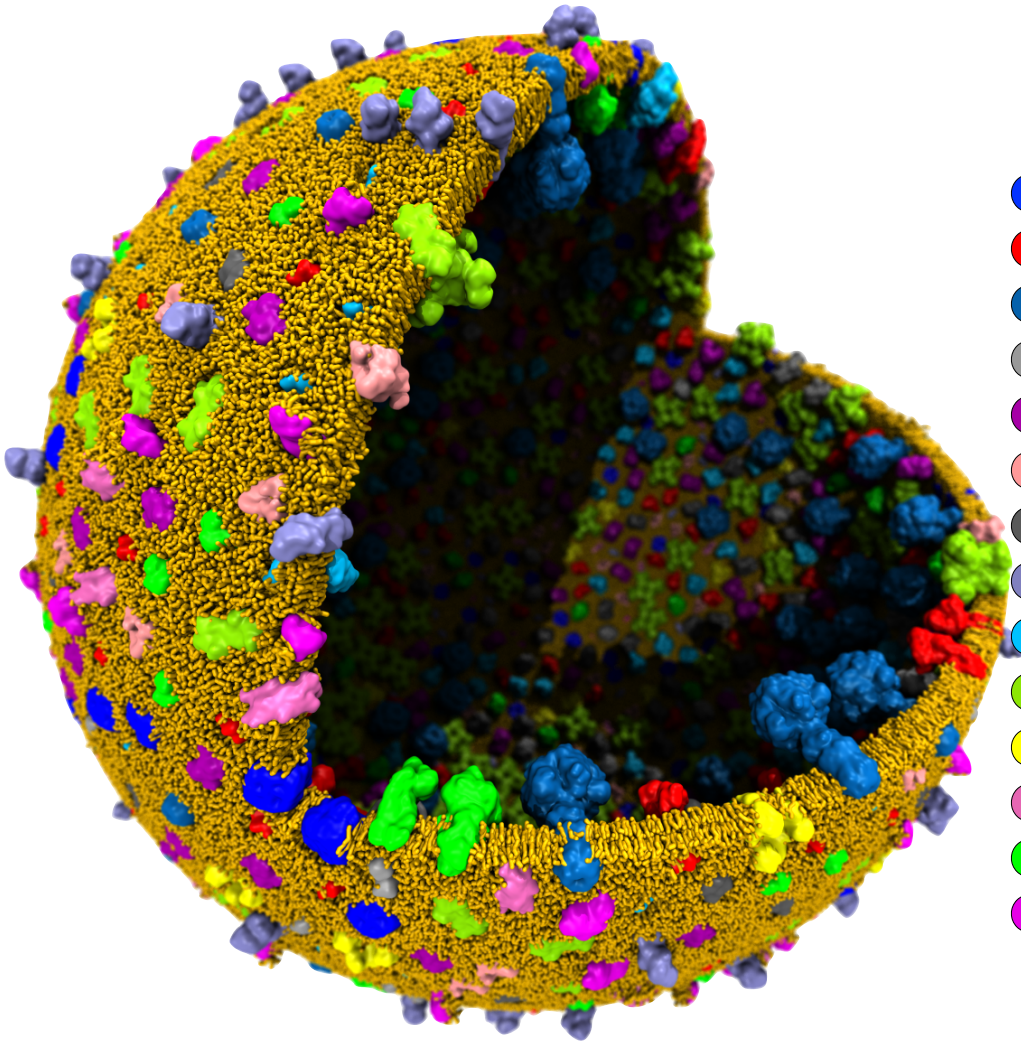
Technology Made Highly Accessible to the Community

interactive MDFF



Developed primarily for experimental users

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)