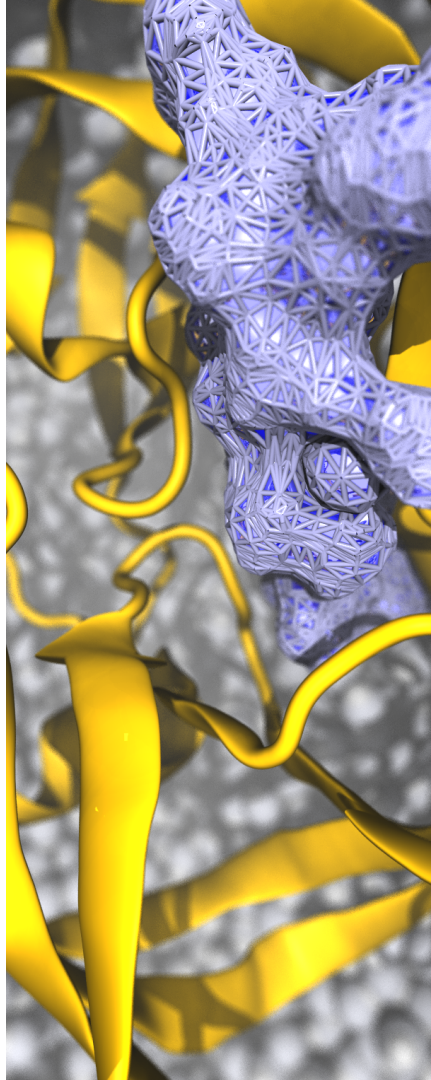
Hands-On Workshop
on Cryo-EM Modeling Based on X-ray Crystallography
Juelich 2016

Introduction to Molecular Dynamics



Till Rudack
trudack@ks.uiuc.edu
www.ks.uiuc.edu/~trudack

Klaus Schulten Group - Theoretical and Computational Biophysics Group
Beckman Institute for Advanced Science and Technology
University of Illinois at Urbana-Champaign
Urbana, IL

Theoretical and Computational Biophysics Group

NIH Center for Macromolecular Modeling and Bioinformatics

NSF Center for the Physics of Living Cells

Prof. Klaus Schulten

Development of NAMD & VMD:

- 320k+ Registered Users;
- Available for Free;
- Most used Software in Supercomputer Centers;

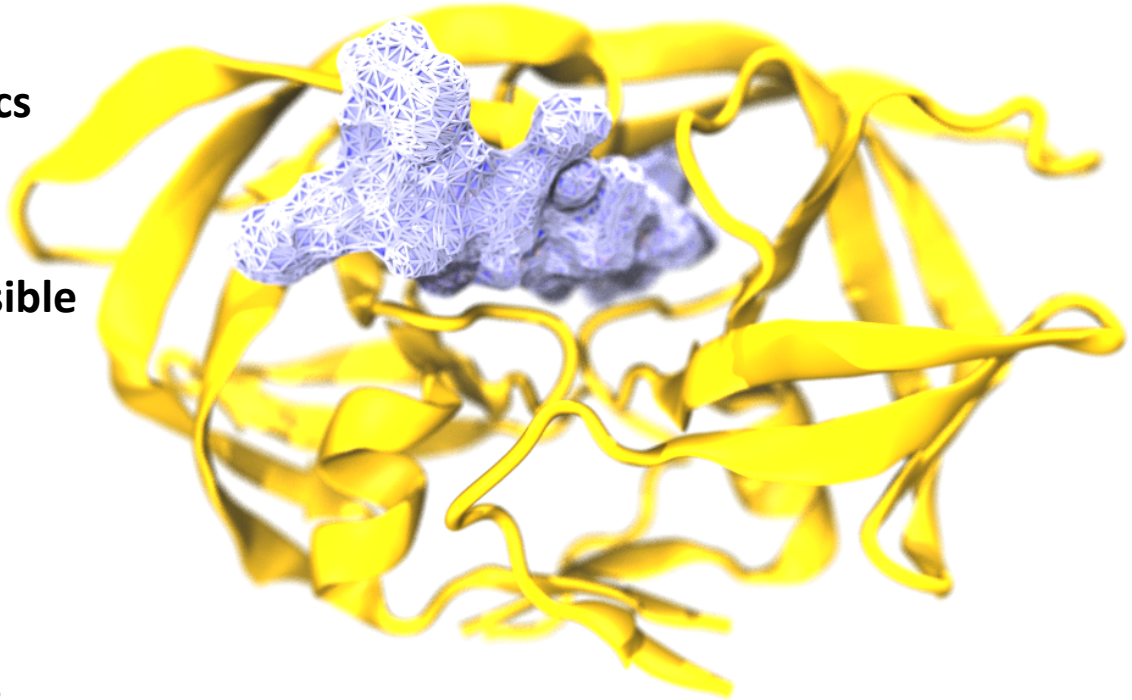
TAs:

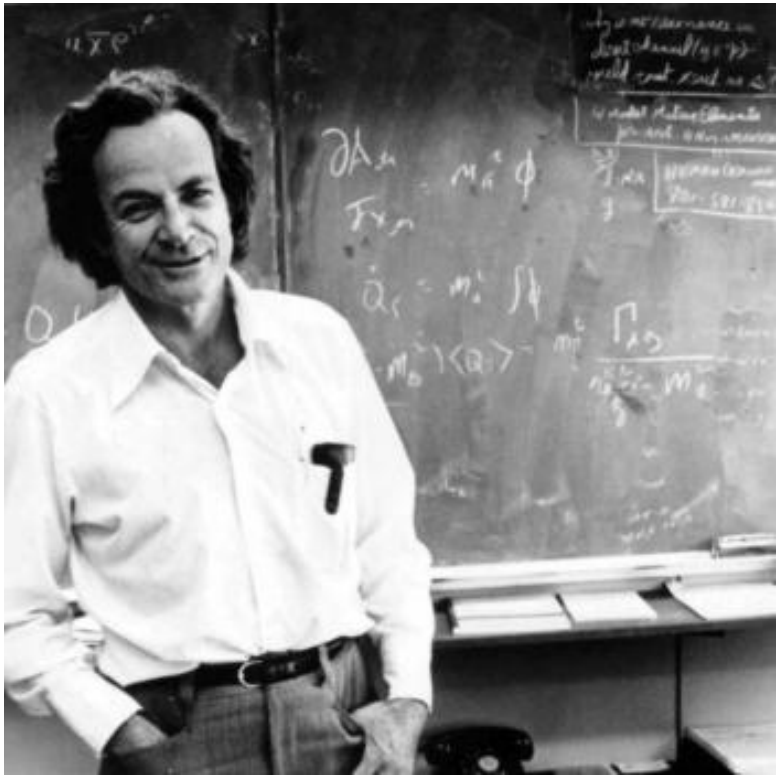
Ryan McGreevy

Rafael C. Bernardi

Till Rudack

- Motivation for Molecular Dynamics
- Molecular Dynamics Theory
- Molecular Dynamics What is possible
- Molecular Dynamics Examples
- Molecular Dynamics Software
- Overview of Tutorials
- Live Demo of Molecular Dynamics





What is Molecular Dynamics?

"Certainly no subject or field is making more progress on so many fronts at the present moment than biology, and if we were to name the most powerful assumption of all, which leads one on and on in an attempt to understand life, it is that ***all things are made of atoms, and that everything that living things do can be understood in terms of the jigglings and wigglings of atoms****."*

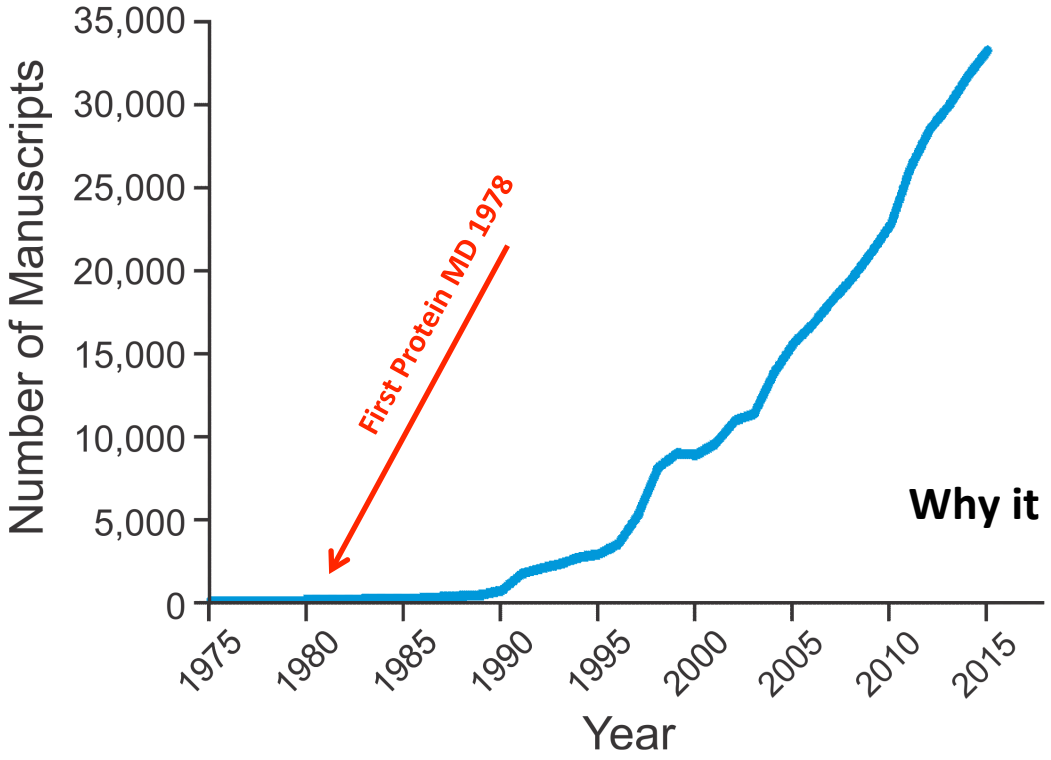
Richard Feynman

The Feynman Lectures on Physics: Mainly Mechanism, Radiation and Heat (1963)

What is Molecular Dynamics?

- Developed as a simple method in **the late 1950's**, MD algorithms evolved greatly.
- MD assists investigation of **atomic motion** as does no other methodology.
- The trajectories of molecules are determined mostly by numerically **solving Newton's equations of motion** for a system of interacting particles.
- The forces between the atoms and their potential energies are calculated from interatomic potentials in **molecular mechanics force fields** that are, in effect, huge data bases of molecular properties.

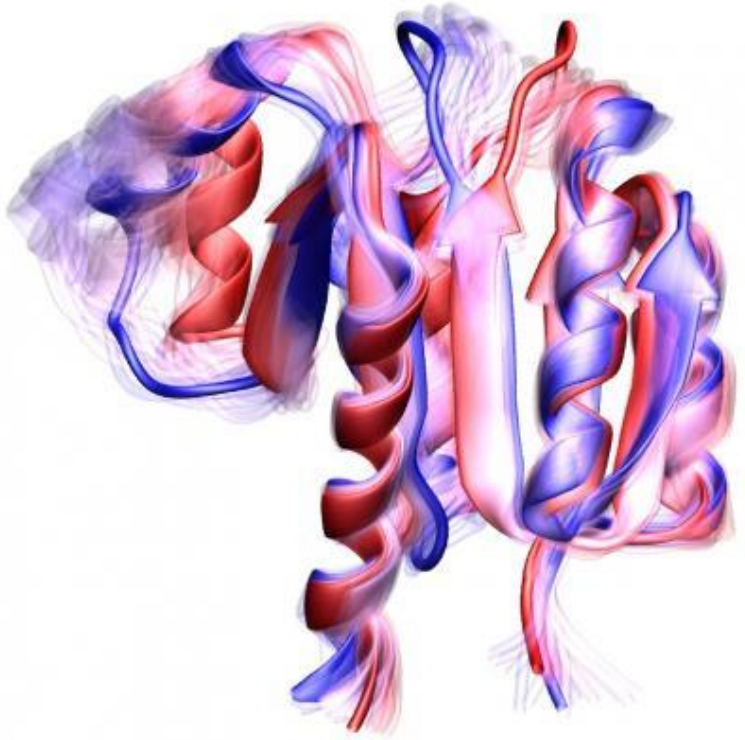
Development of Molecular Dynamics over the past decades:



Why it is so Important?

Not only structure but also dynamics is important

Myoglobin Structure
Kendrew (1962 Chemistry Nobel Prize)



Dynamics plays an important role.

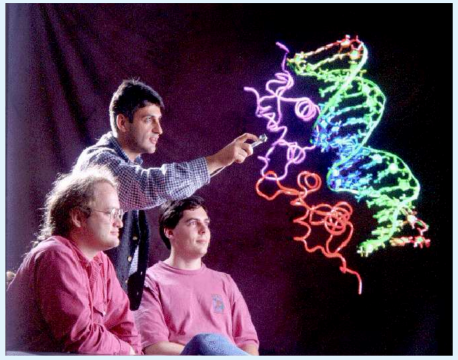
Protein Structure Determination:

- X-Ray Crystallography
- Nuclear Magnetic Resonance (NMR)
- Cryo-Electron Microscopy
- Homology Modeling and *ab initio* Modeling

Structure of Large Complexes are usually solved combining two or more methods.

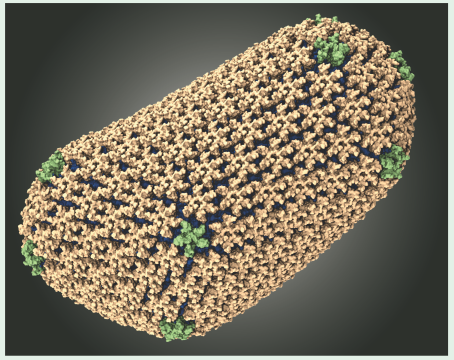
1958

Manual Construction of Structural Models



1996

Computer-aided Construction of Structural Models with Manual Positioning of Atoms



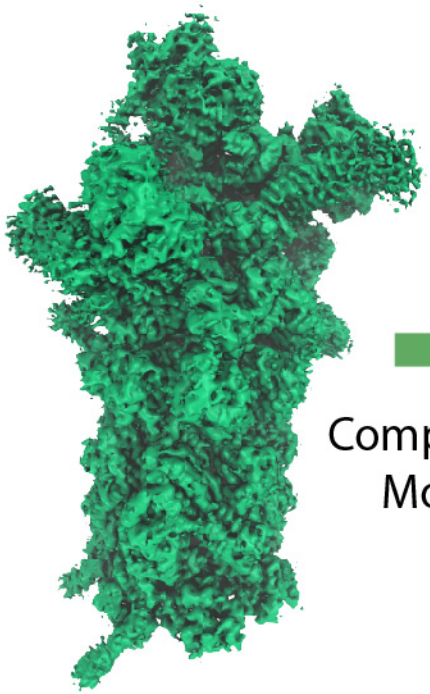
2013

Computational Construction of Structural Models with Automated Positioning of Atoms

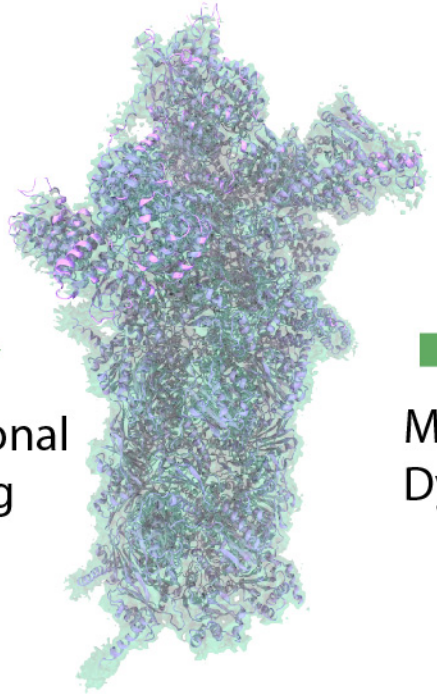
Density

Structure

Function

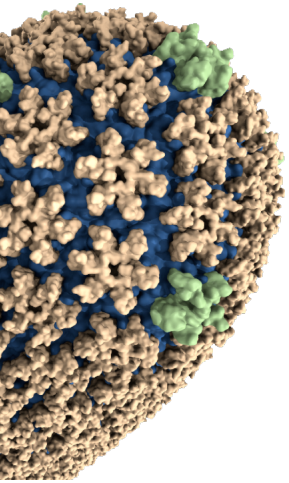


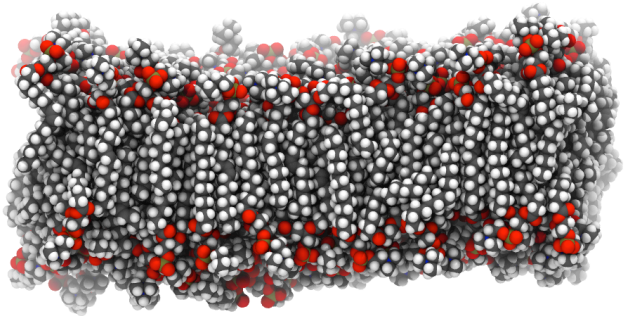
Computational Modeling

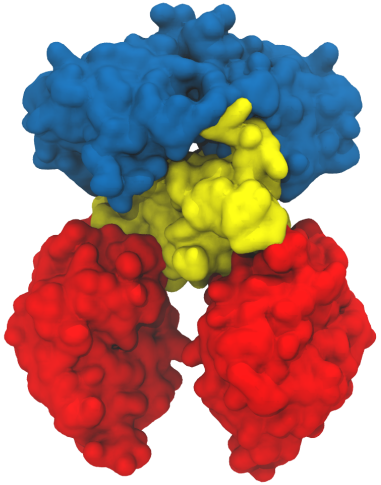


Molecular Dynamics

The Computational Microscope

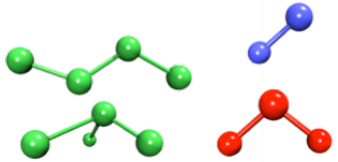






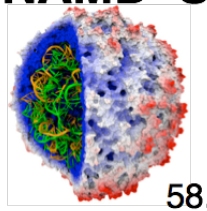
Molecular Dynamics Simulations - Theory

Chemistry

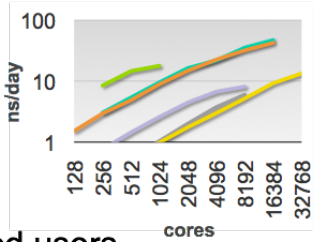


$$U(\vec{R}) = \underbrace{\sum_{bonds} k_i^{bond}(r_i - r_0)^2}_{U_{bond}} + \underbrace{\sum_{angles} k_i^{angle}(\theta_i - \theta_0)^2}_{U_{angle}} + \underbrace{\sum_{dihedrals} k_i^{dihe}[1 + \cos(n_i\phi_i + \delta_i)]}_{U_{dihedral}} + \underbrace{\sum_i \sum_{j \neq i} 4\epsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] + \sum_i \sum_{j \neq i} \frac{q_i q_j}{\epsilon r_{ij}}}_{U_{nonbond}}$$

NAMD Software



Virus

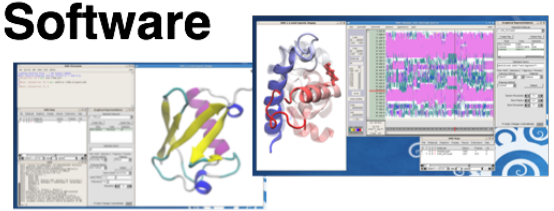


58,000 registered users

Physics

$$m_i \frac{d^2\vec{r}_i}{dt^2} = \vec{F}_i = -\vec{\nabla}U(\vec{R})$$

VMD Software



240,000 registered users

Math

$$\vec{r}_i(t + \Delta t) = 2\vec{r}_i(t) - \vec{r}_i(t - \Delta t) + \frac{\Delta t^2}{m_i}\vec{F}_i(t)$$

(repeat ***one billion times*** = microsecond)

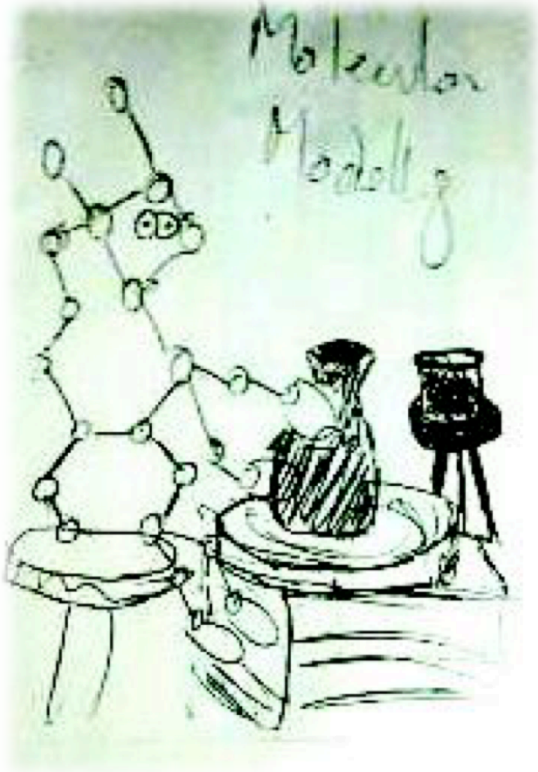
Uses simple Physics concepts of Classical Mechanics.

$$V = V_{str} + V_{bend} + V_{oop} + V_{tors} + V_{vdW} + V_{es}$$

$$\vec{F}_i = -dV / d\vec{r}_i$$

$$\vec{a}_i = \vec{F}_i / m$$

$$\vec{s}_i = \vec{s}_{0i} + \vec{v}_i t + \frac{1}{2}\vec{a}_i t^2$$



$$V = V_{str} + V_{bend} + V_{oop} + V_{tors} + V_{vdW} + V_{es}$$

$$V_{es,ij} = Q_i Q_j / \varepsilon_r R_{ij}$$

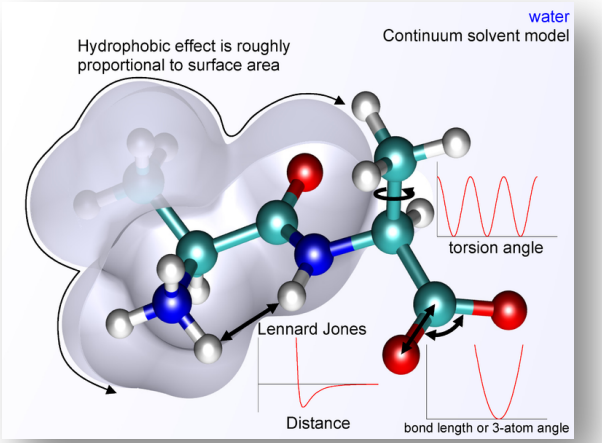
$$V_{vdW,ij} = \varepsilon_{IJ}\left[\left(\frac{R_{IJ}}{R_{ij}}\right)^{12} - 2\left(\frac{R_{IJ}}{R_{ij}}\right)^{6}\right]$$

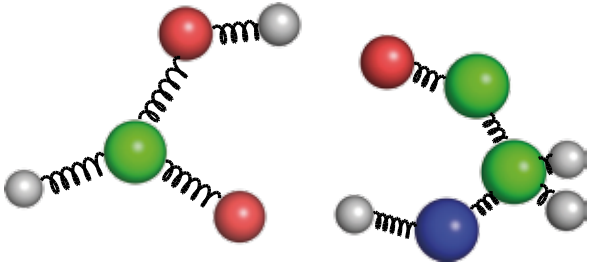
$$V_{tors,ijkl} = \frac{1}{2}\left[V_1(1+\cos\varphi) + V_2(1-\cos 2\varphi) + V_3(1+\cos 3\varphi) + \ldots\right]$$

$$V_{oop} = \frac{1}{2} k_{oop} \omega_{oop}^2$$

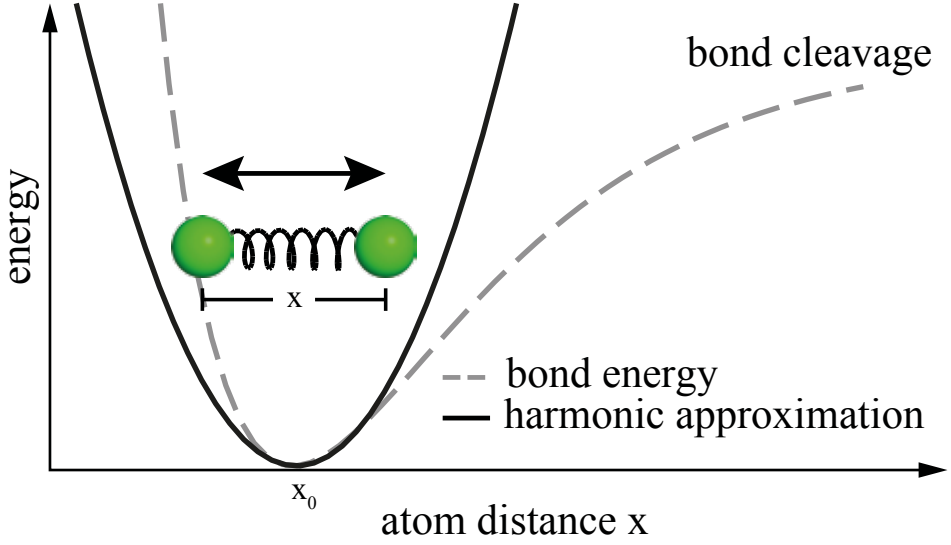
$$V_{bend,ijk} = \frac{1}{2} k_{IJK}\left(\theta_{ij} - \theta^0{}_{IJK}\right)^2$$

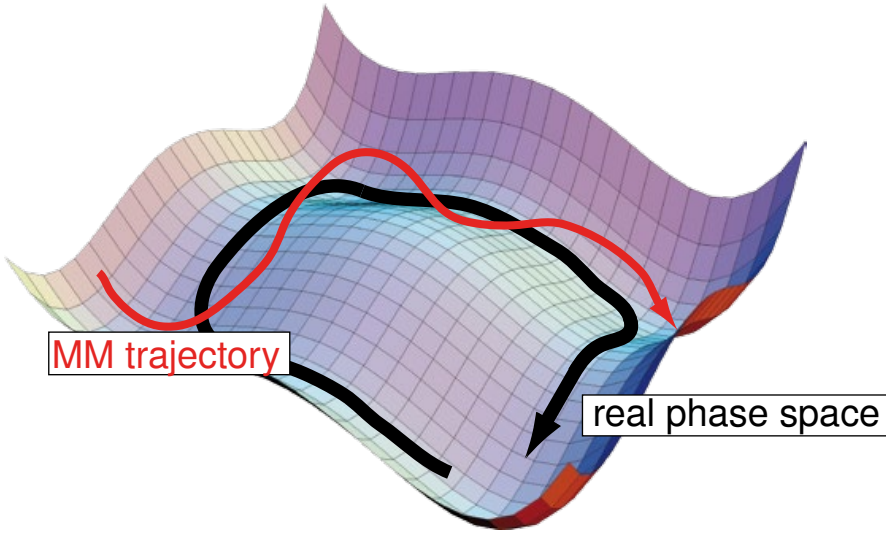
$$V_{str,ij} = \frac{1}{2} k_{IJ}\left(l_{ij} - l^0{}_{IJ}\right)^2$$





$$V_{stretch} = k_{st}\left(r_{ij} - r_0\right)^2$$



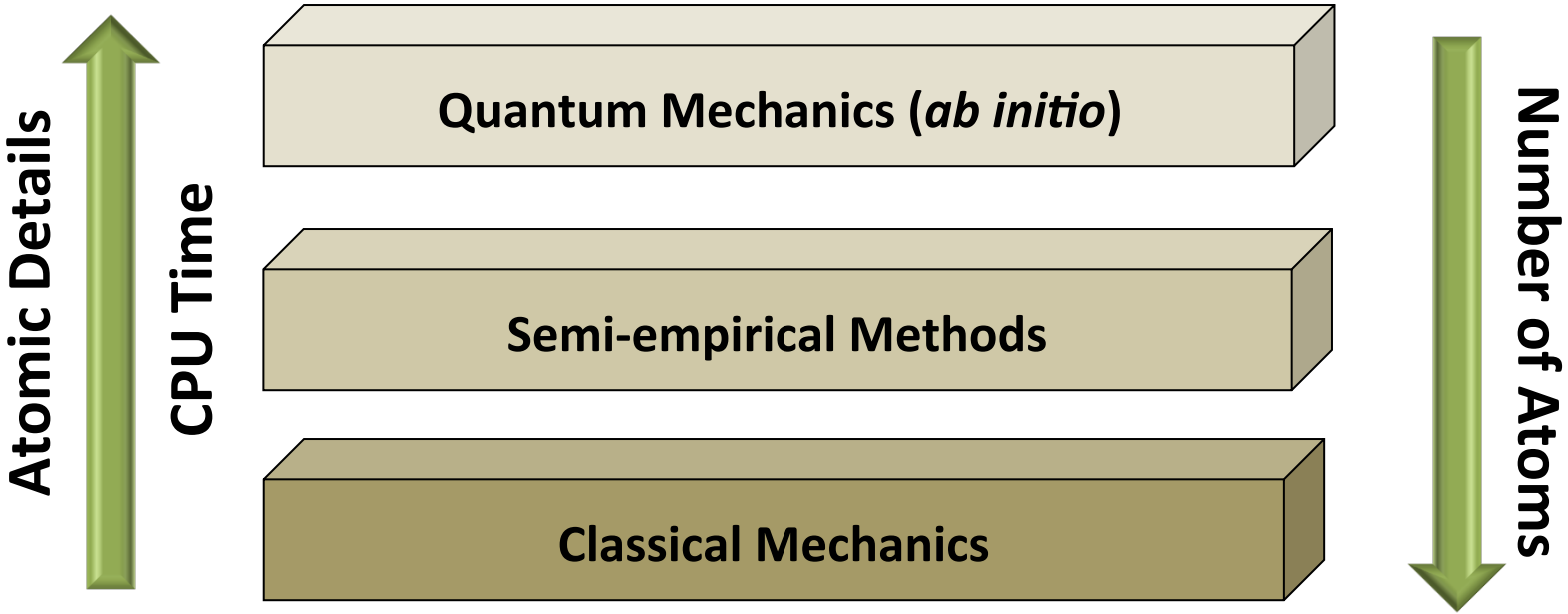


Problem: Bonds cannot break!

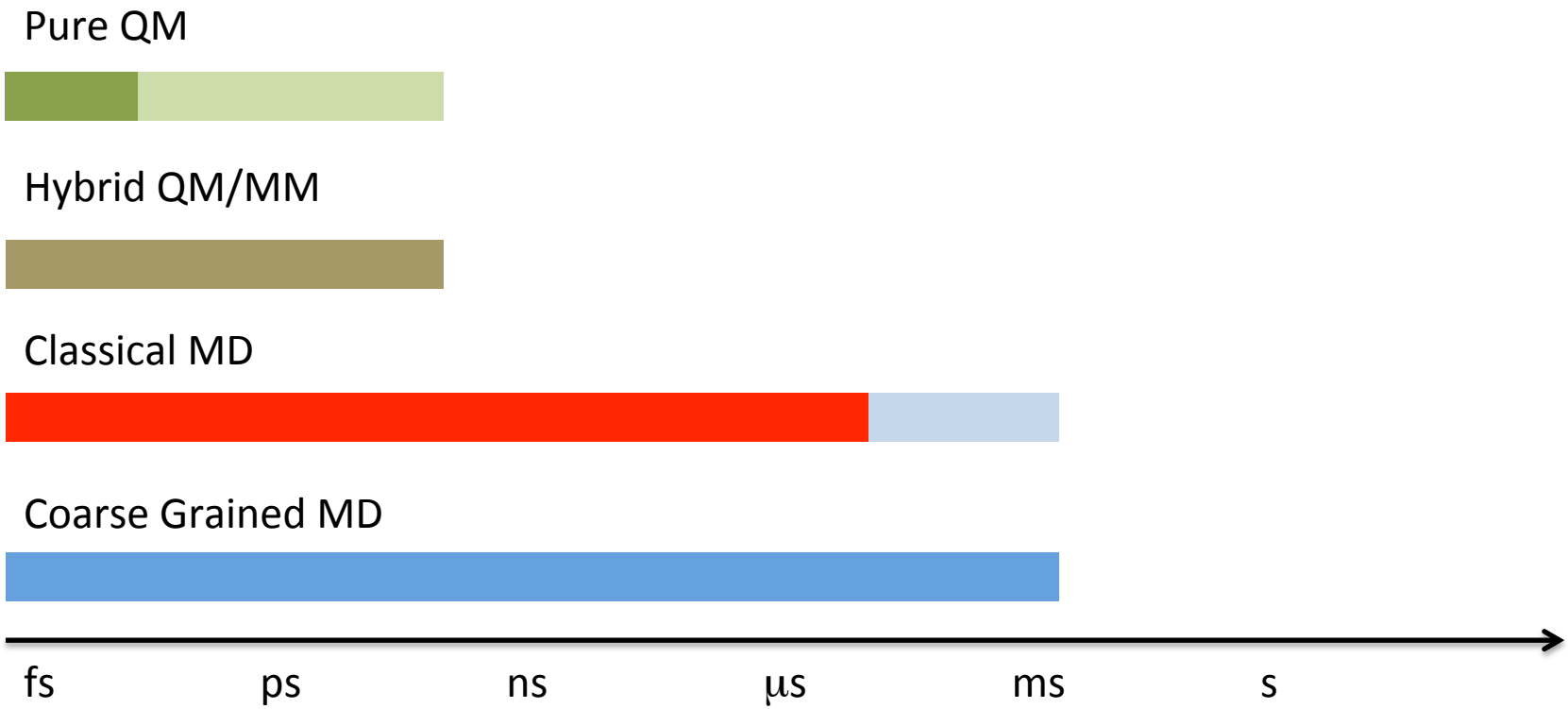
Why not use Quantum Mechanics?

$$\frac{-\hbar^2}{2m}\frac{\partial^2\Psi(x,t)}{\partial x^2} + U(x)\Psi(x,t) = i\hbar\frac{\partial\Psi(x,t)}{\partial t}$$

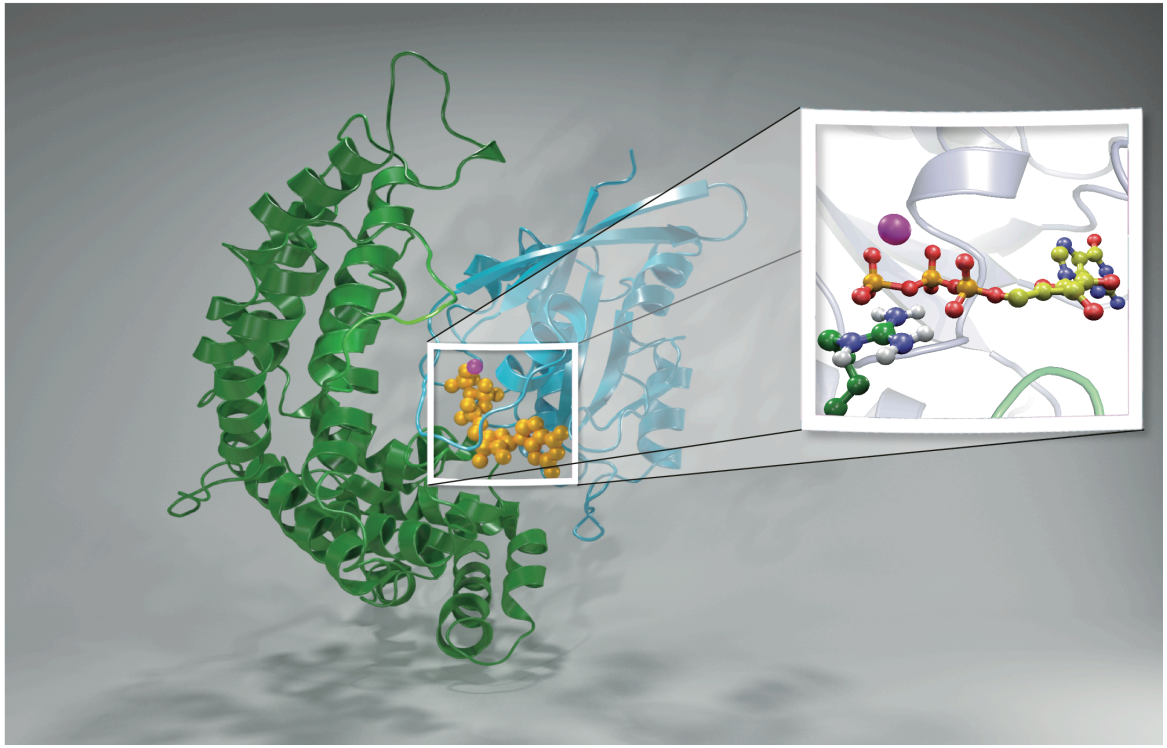
Classical Mechanics vs. Quantum Mechanics



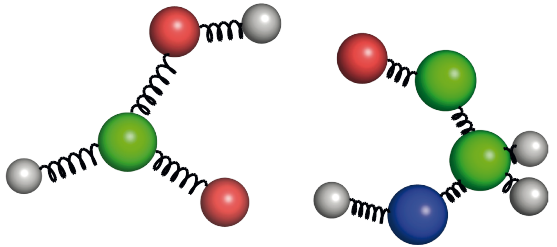
The Time Scale Problem



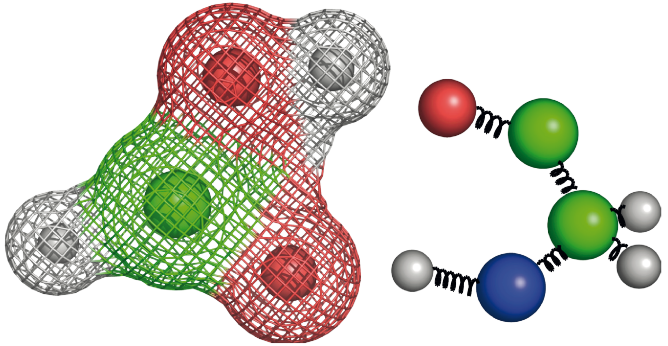
Hybrid QM/MM



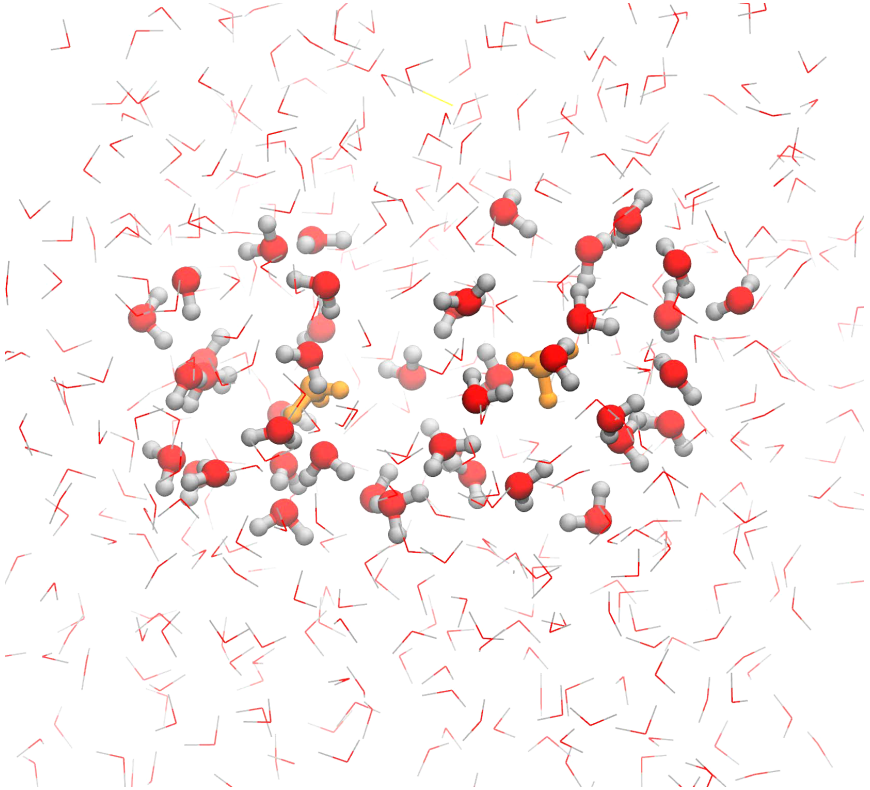
MM



QM / MM



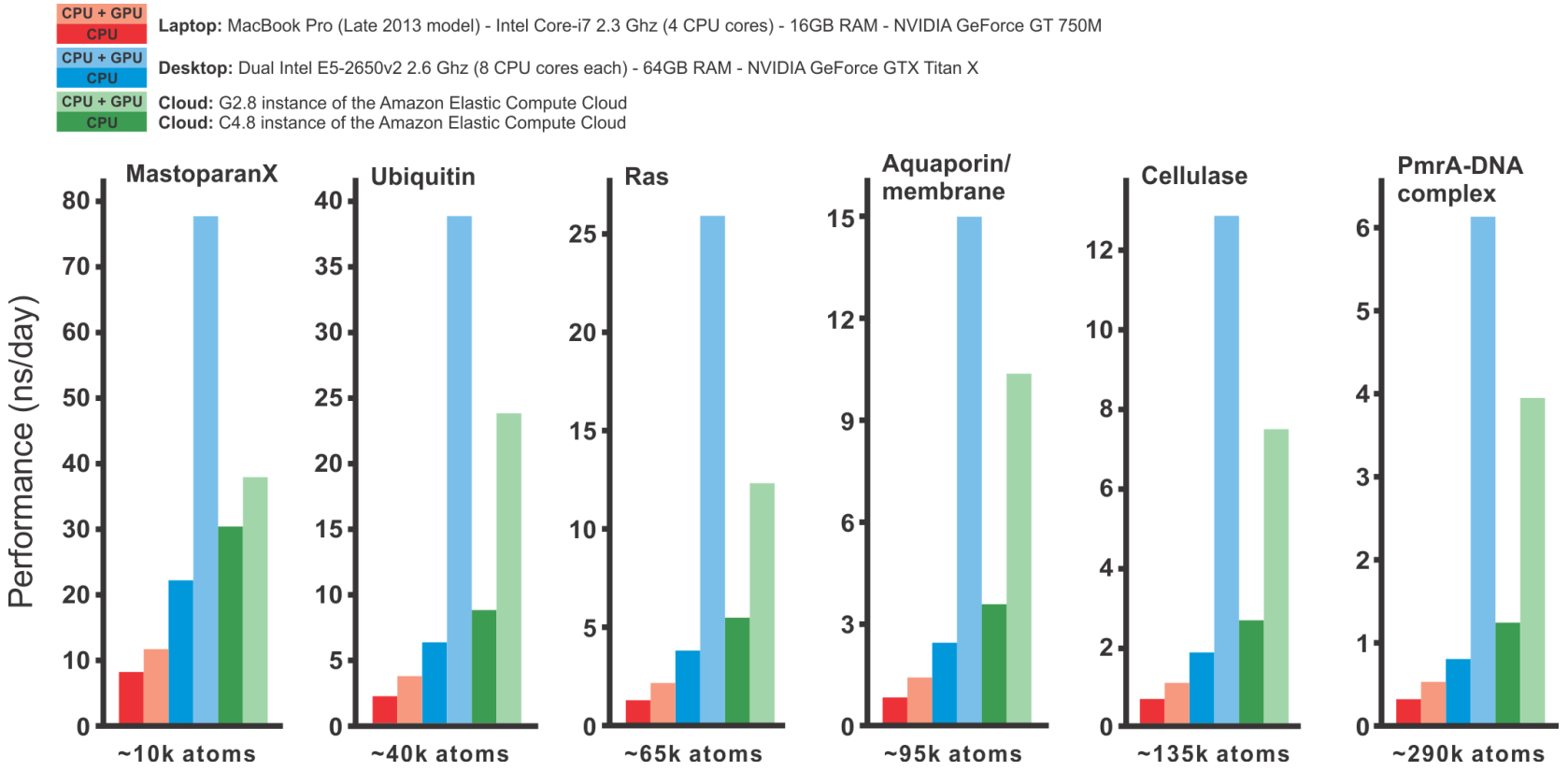
Now bonds can break!



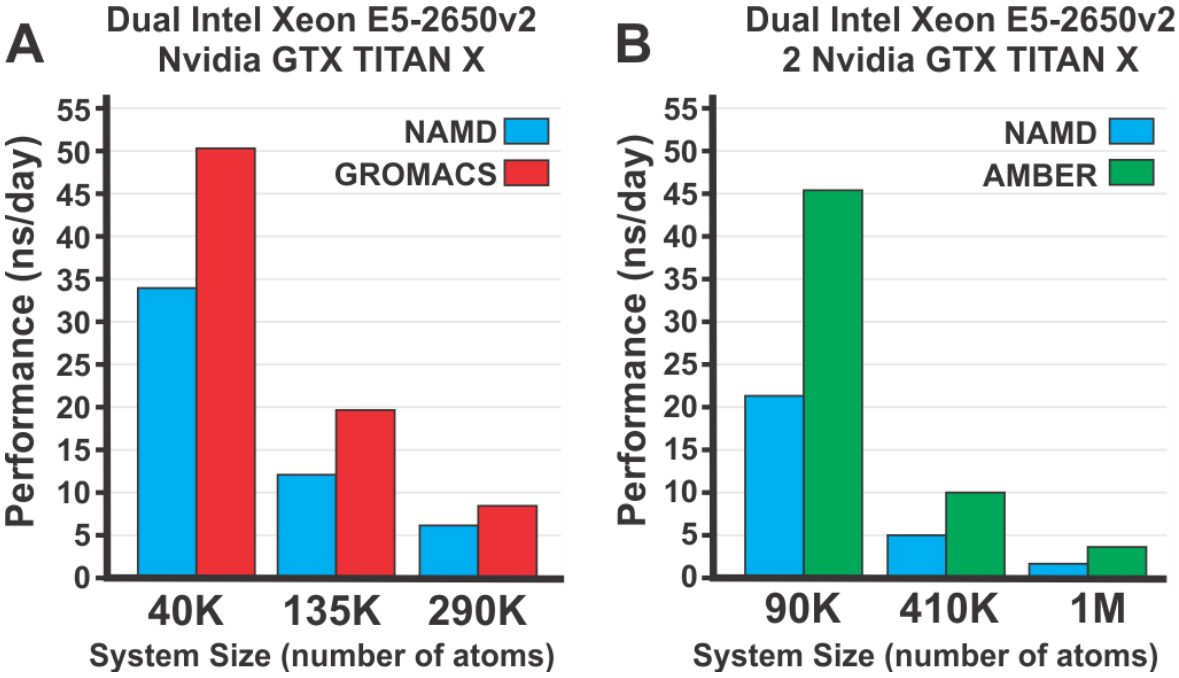
New NAMD QM/MM interface is ready and will be released soon.

What timescales are accessible using classical Molecular Dynamics?

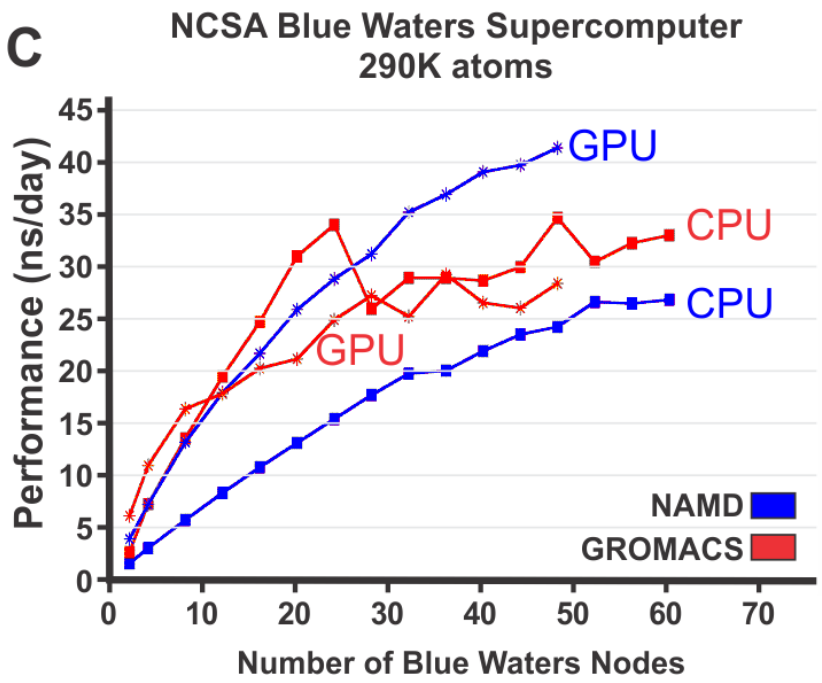
Performance of NAMD simulations on different computer platforms

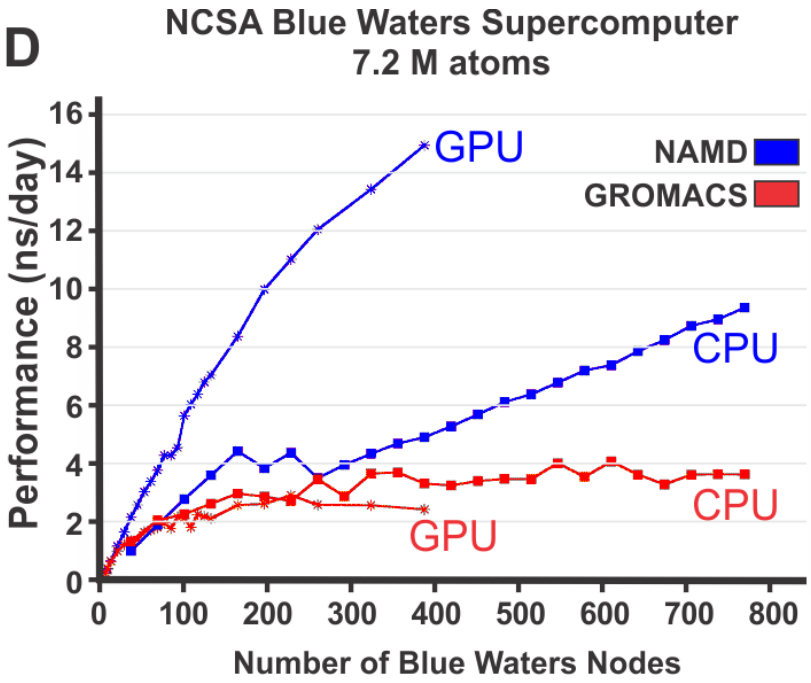


NAMD vs AMBER vs GROMACS

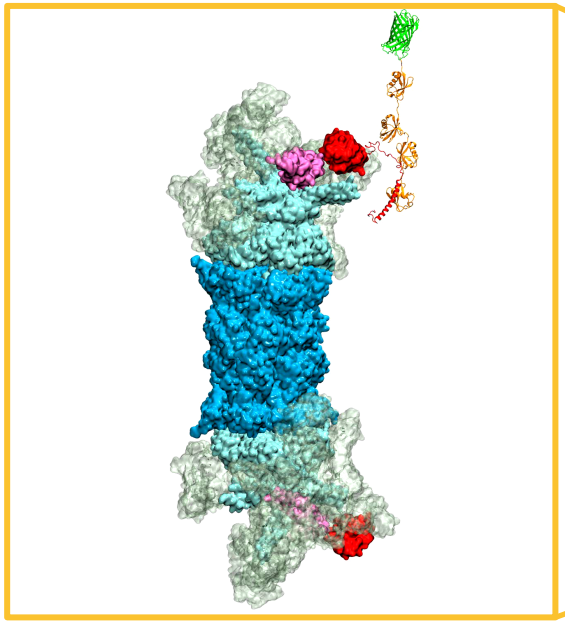


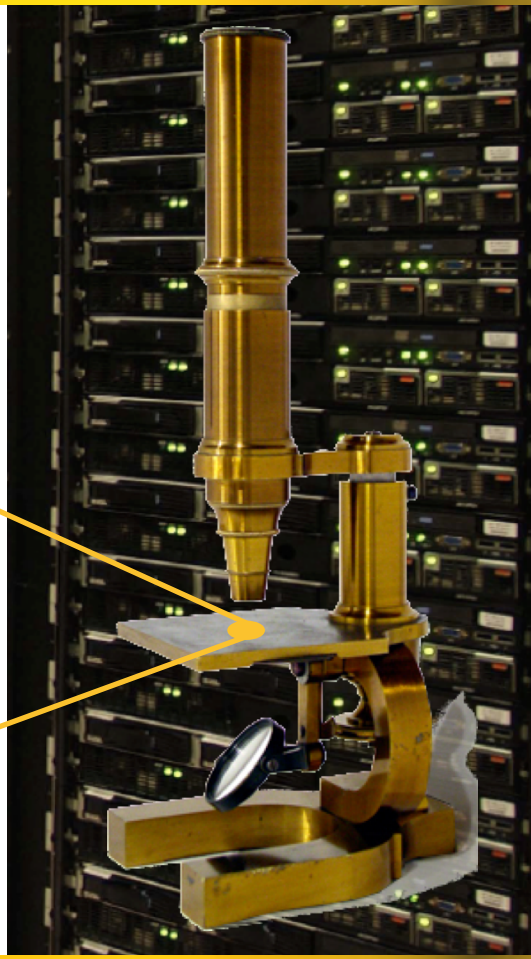
NAMD vs GROMACS



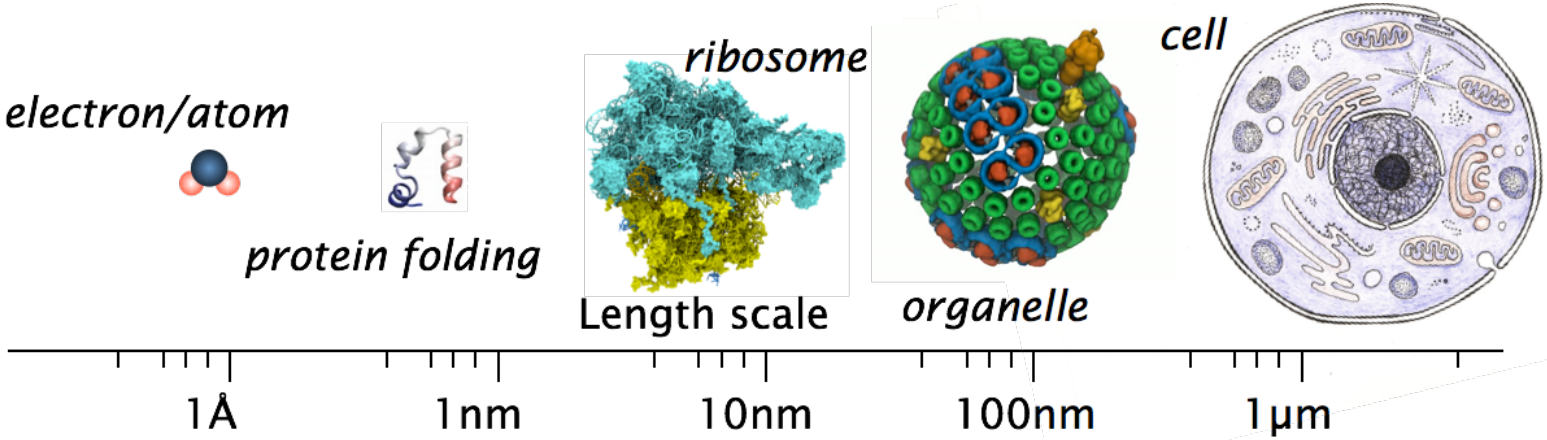


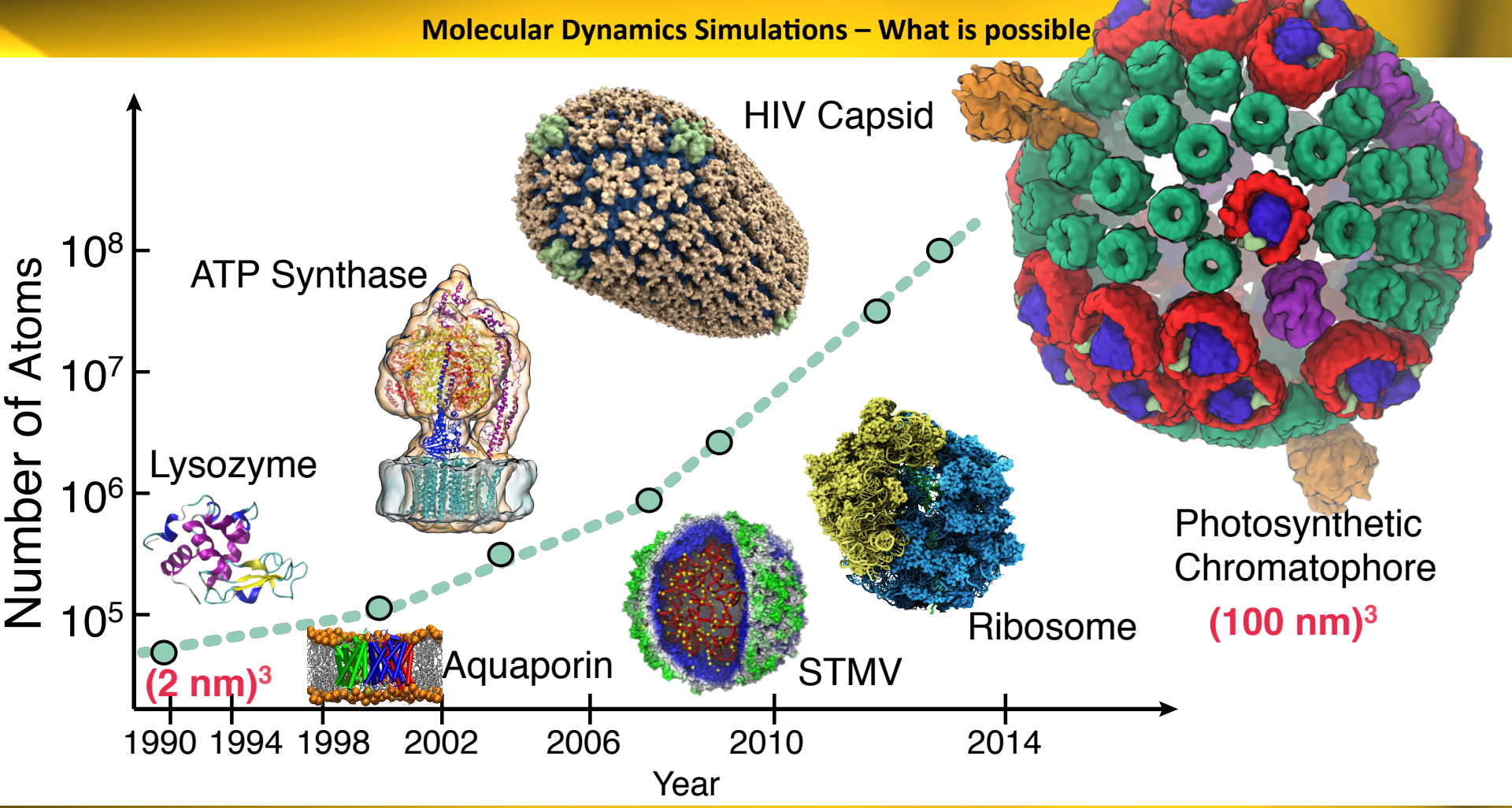
What can we study with the Computational Microscope?





... Views Living Systems from Electron to Cell

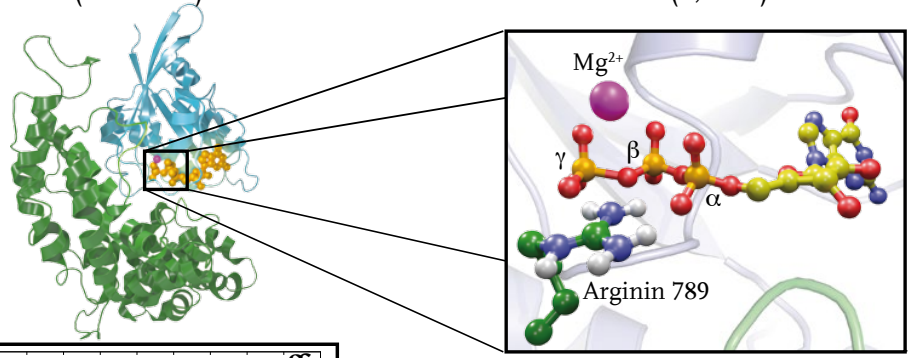


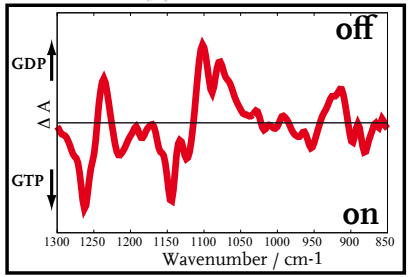

HIV Capsid
ATP Synthase
Lysozyme
Aquaporin
STMV
Ribosome
Photosynthetic Chromatophore
(100 nm)3
(2 nm)3
Number of Atoms
10^8
10^7
10^6
10^5
1990
1994
1998
2002
2006
2010
2014
Year

Not only size but also detail matters

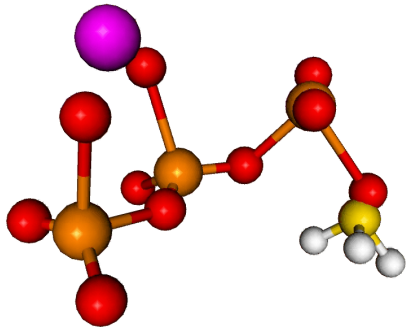
Experiment
X-ray Crystallography
(1.6-2.5 Å)

Theory
MD Simulations
(0,01 Å)





FTIR-Spectroskopy ($\Delta\nu$ = 1.0 cm^{-1}; 10^{-4} Å)

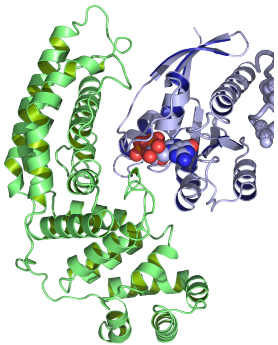


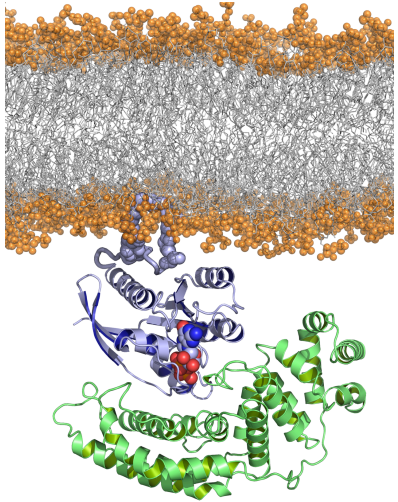
Protein
In Solvent

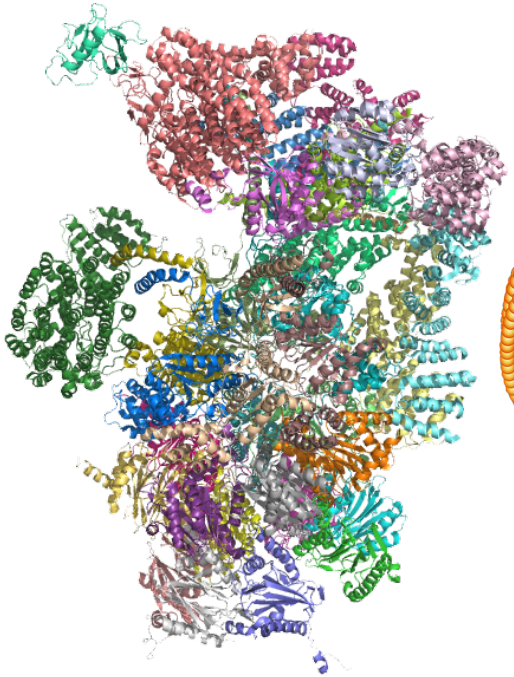
Protein
+ Membrane

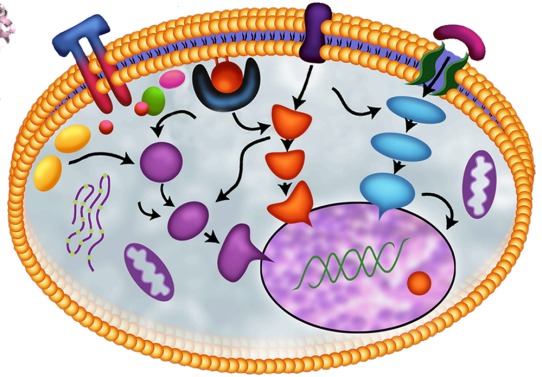
Multi-Protein
Complex

Cell









Molecular dynamics simulations connect **function** and **dynamics** to **structural data** from diverse **experimental sources** to investigate critical cellular processes occurring at the **sub-Ångstrom** level up to the **macromolecular** level.

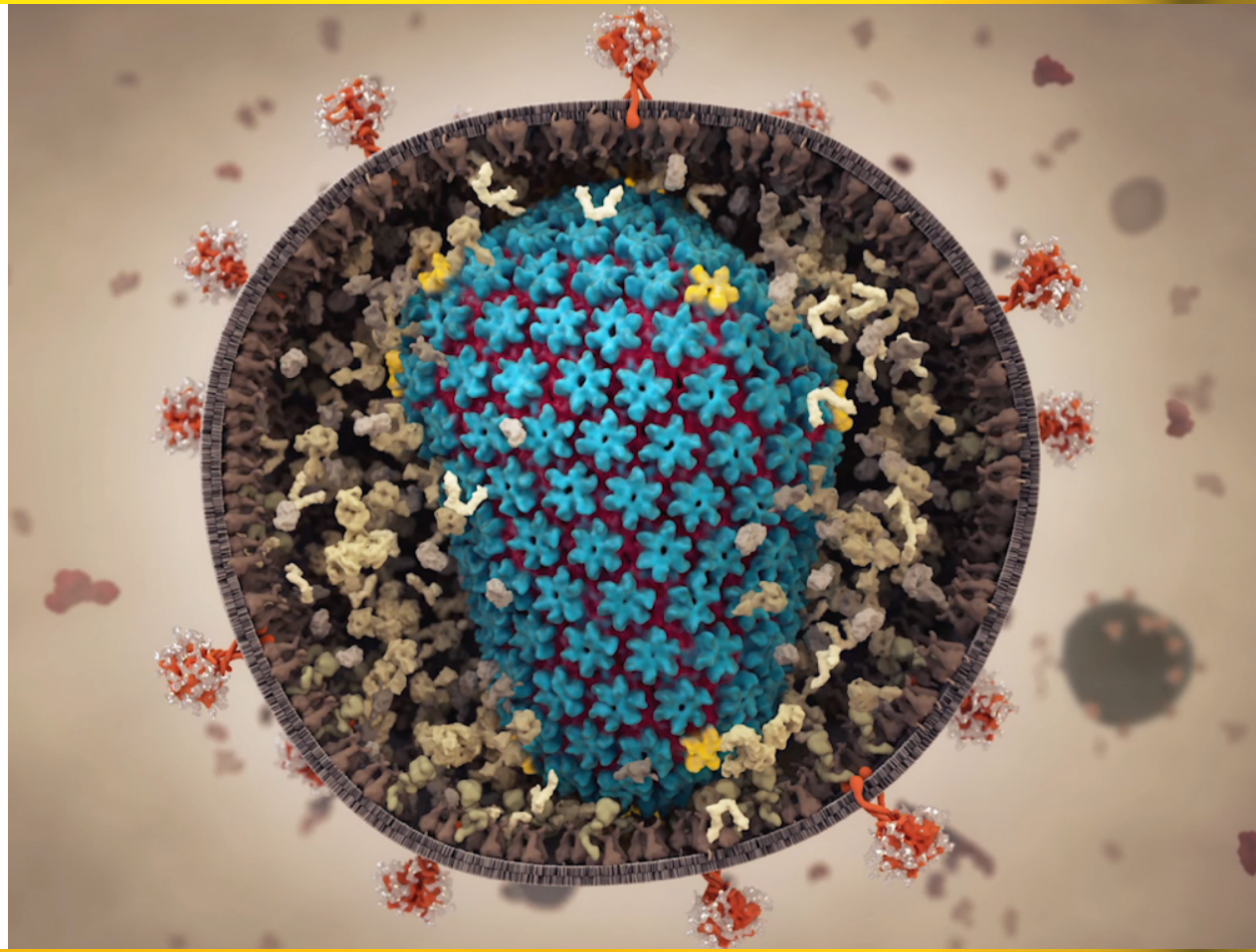
Some selected examples of Molecular Dynamics simulation studies

MD helps to solve complex structures

Structure of the HIV Capsid

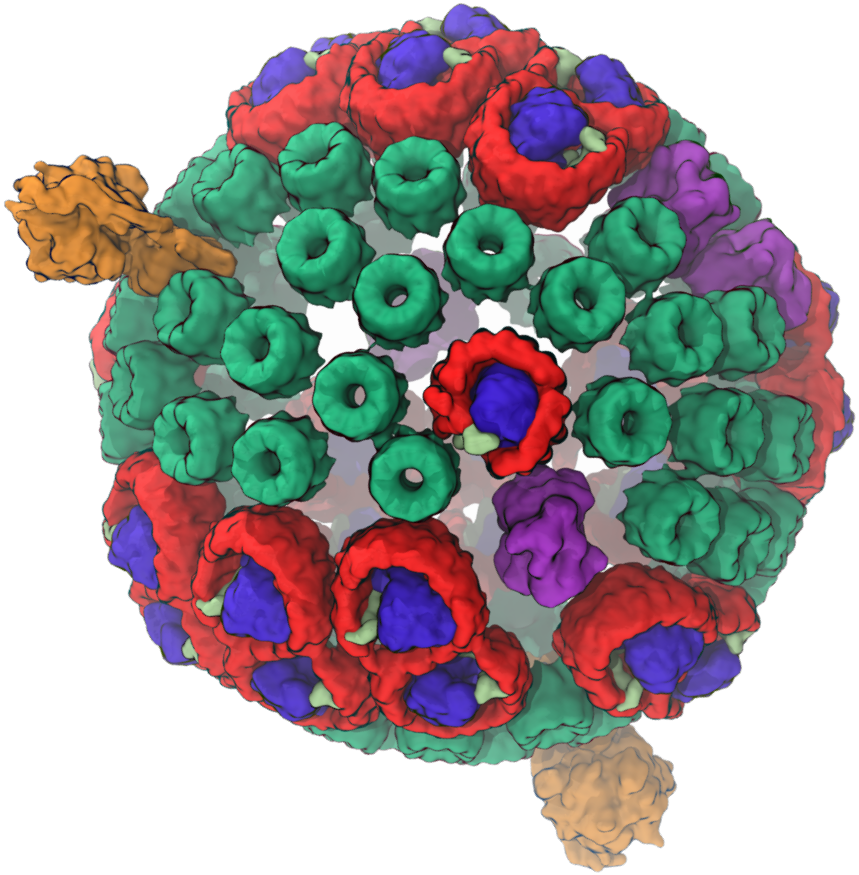
64 million atoms

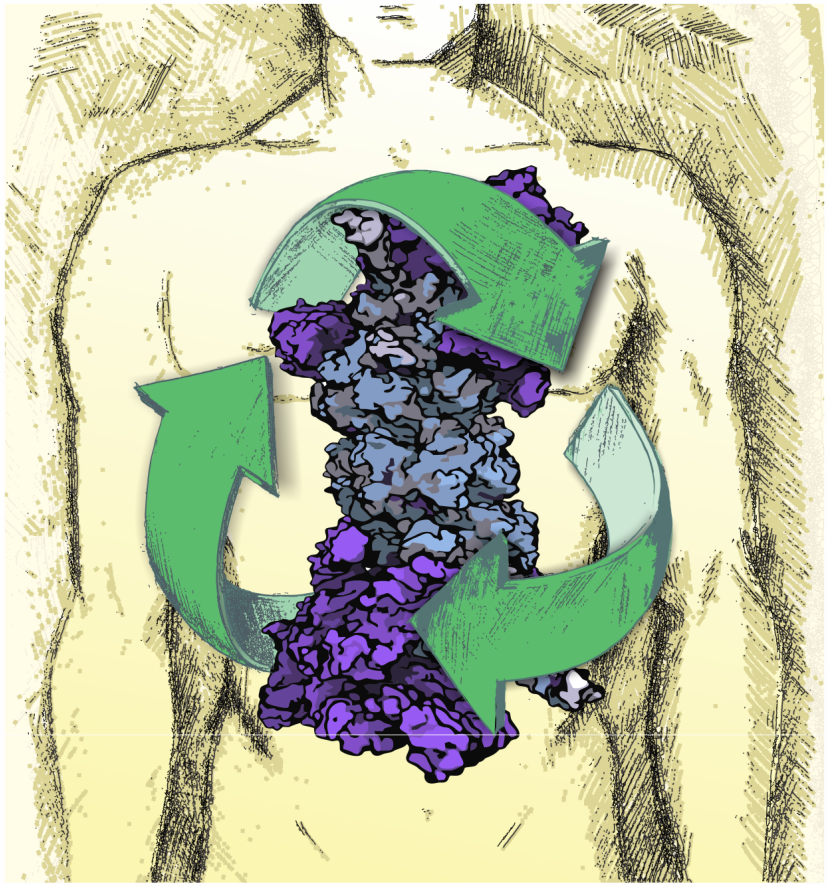
Juan Perilla



MD helps to investigate the function of small organelles like the photosyntetic chromatophore

100 million atoms





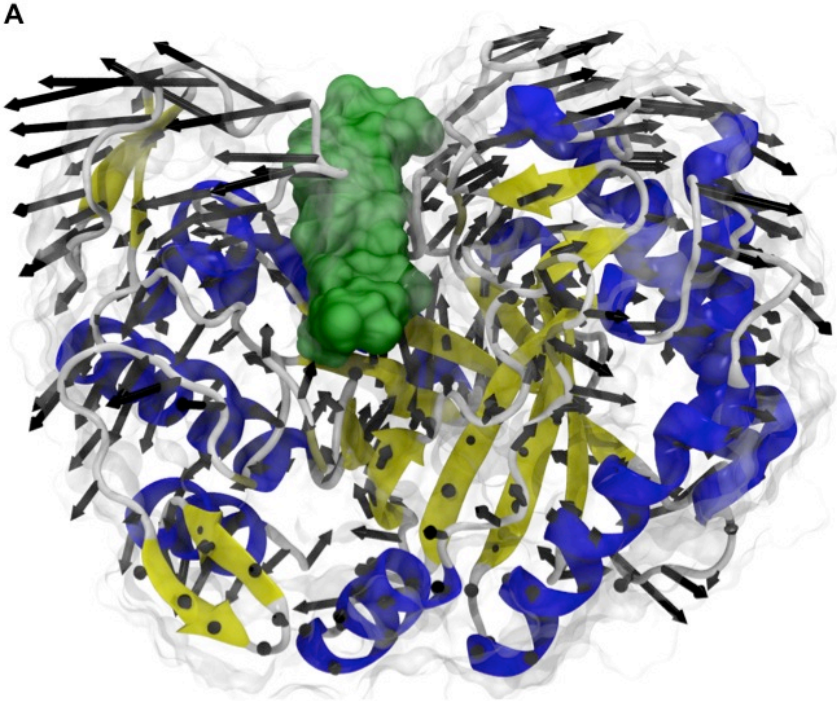
26S Proteasome
The Recycling System of the Cell

A complex clockwork
of over 30 different proteins

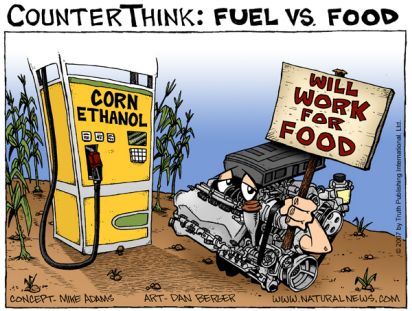
5 million atoms

Collaboration with Wolfgang Baumeister MPI Munich

Biofuels



Enzymatic Activity of Cellulases

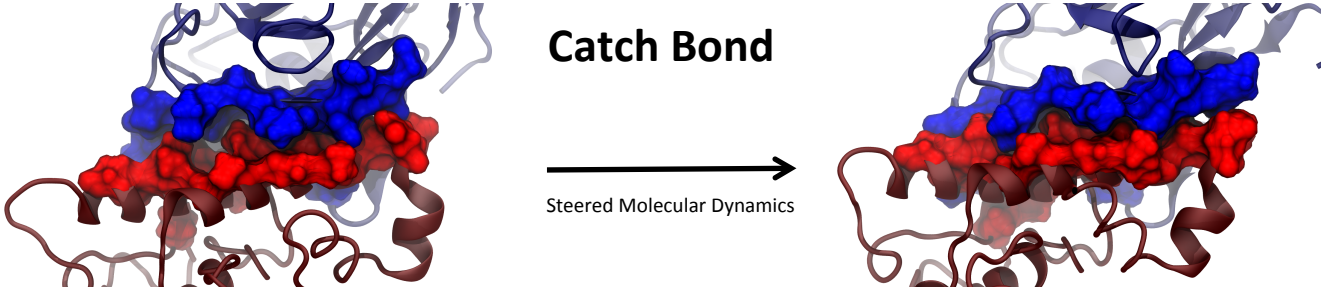


Rafael C. Bernardi

Ultrastable Protein complexes

Challenging environments have guided nature in the development of ultrastable protein complexes. Specialized bacteria produce discrete multi-component protein networks called cellulosomes to effectively digest lignocellulosic biomass.

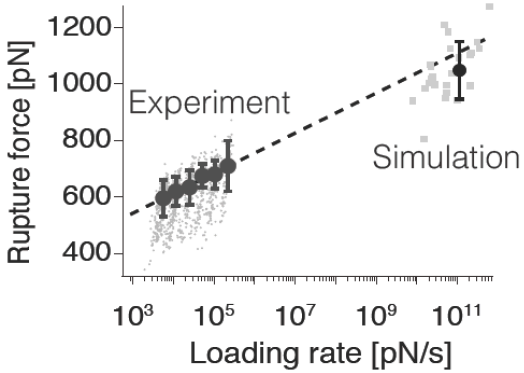
Certain cellulosomal ligand–receptor interactions exhibit extreme resistance to applied force.

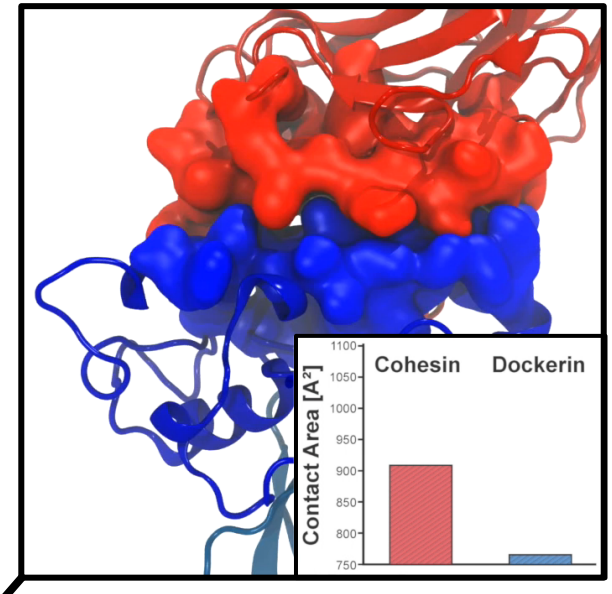


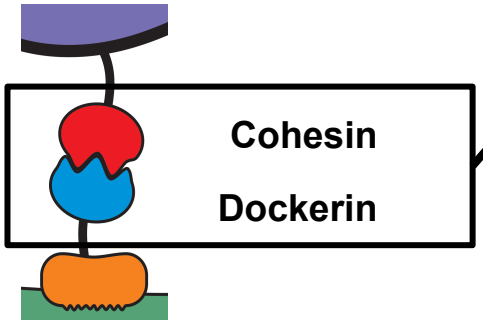
Nature Comm ***5***, 5635 - ***2014***
Nano Lett., 2015, ***15*** (11), 7370 - ***2015***

Ultrastable Protein complexes

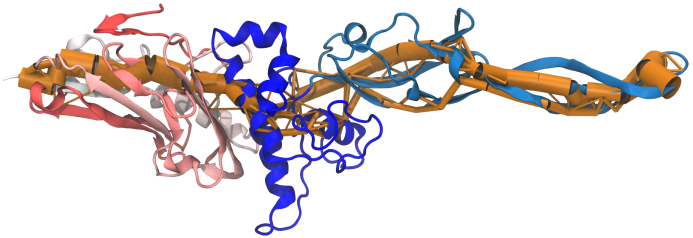
Collaboration w/ Hermann Gaub (Munich)



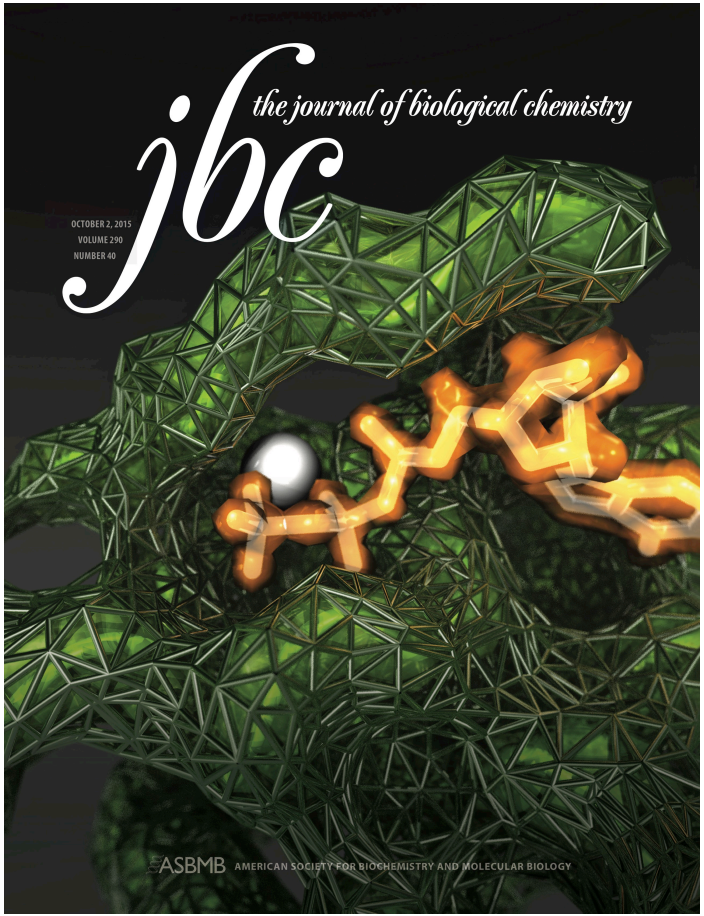




Force Propagation Pathway



Nature Comm. ***5***, 5635 - ***2014***
Nano Lett., 2015, ***15*** (11), 7370 - ***2015***



Enzymatic catalysis

Combining MD, X-ray, and IR-spectroscopy
to explain enzymatic catalysis

JBC ***290, 40*** *24079 -* ***2015***
PNAS ***109****, 15295 -* ***2014***

Molecular Dynamics Simulations

Theory

Software Development

Experiment

Software Application

Disciplines: Physics, Mathematics, Informatics, Chemistry, Biology, Medicine

The Computational Microscope

Software

NAMD – VMD – QwikMD

NAMD – Nanoscale Molecular Dynamics

60,000 users can't all be computer experts.
- 18% are NIH-funded; many in other countries.
- 17,000 have downloaded more than one version.
- 4000 citations of NAMD reference papers.

One program available on all platforms.
- Desktops and laptops – setup and testing
- Linux clusters – affordable local workhorses
- Supercomputers – free allocations on XSEDE
- Blue Waters – sustained petaflop/s performance
- GPUs - next-generation supercomputing

User knowledge is preserved across platforms.
- No change in input or output files.
- Run any simulation on **any number of cores.**

Available free of charge to all.

Hands-On Workshops

Oak Ridge TITAN

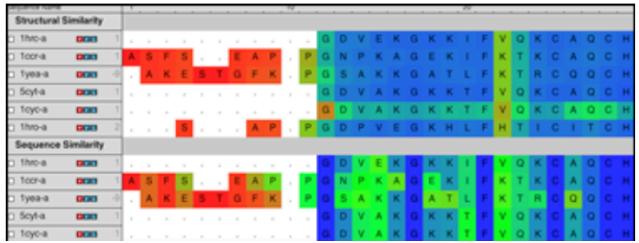
VMD – Visual Molecular Dynamics

Visualization and analysis of:

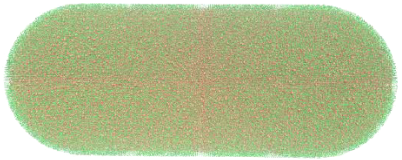
- molecular dynamics simulations
- particle systems and whole cells
- cryoEM densities, volumetric data
- quantum chemistry calculations
- sequence information

User extensible w/ scripting and plugins

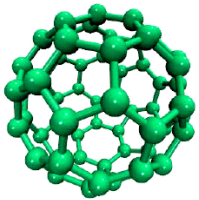
http://www.ks.uiuc.edu/Research/vmd/



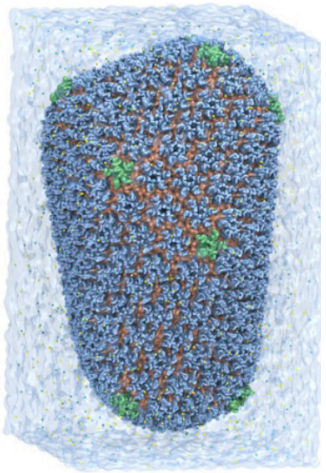
Sequence Data



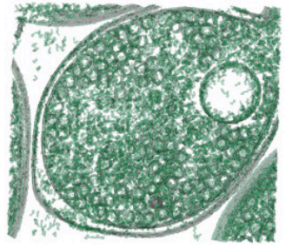
Whole Cell Simulation



Quantum Chemistry



MD Simulations



CryoEM, Cellular Tomography

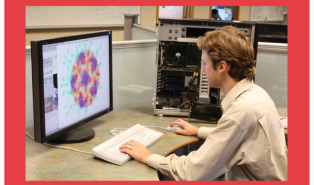
Theoretical investigations of large macromolecular complexes is more than just **running** MD simulations. It also involves **visualization** and **analysis** of Terabytes of data.

Solution: Interactive Remote Visualization and Analysis

Storage

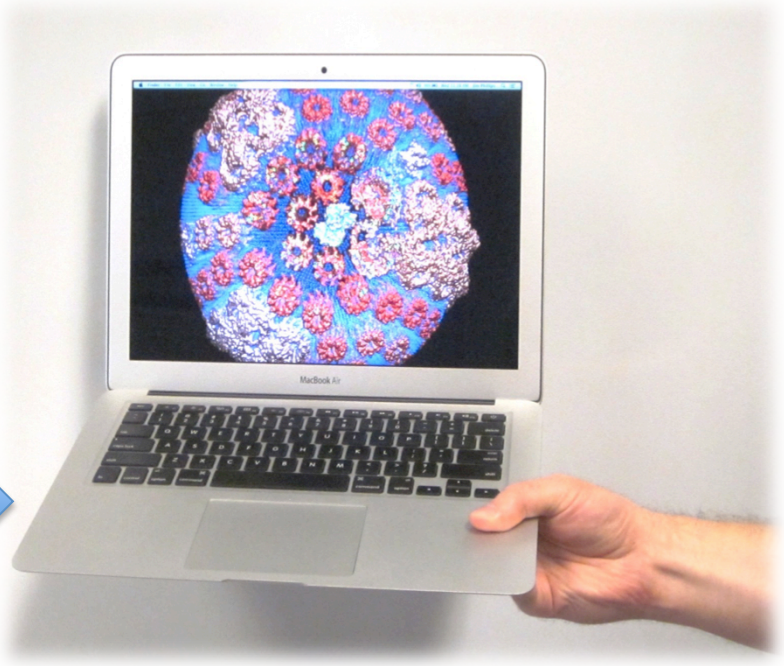
Compute

Visualization



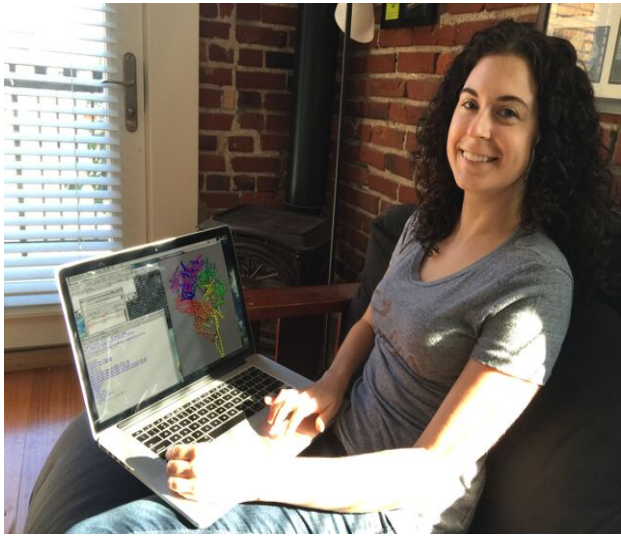
Compressed Video

1 Gigabit Network



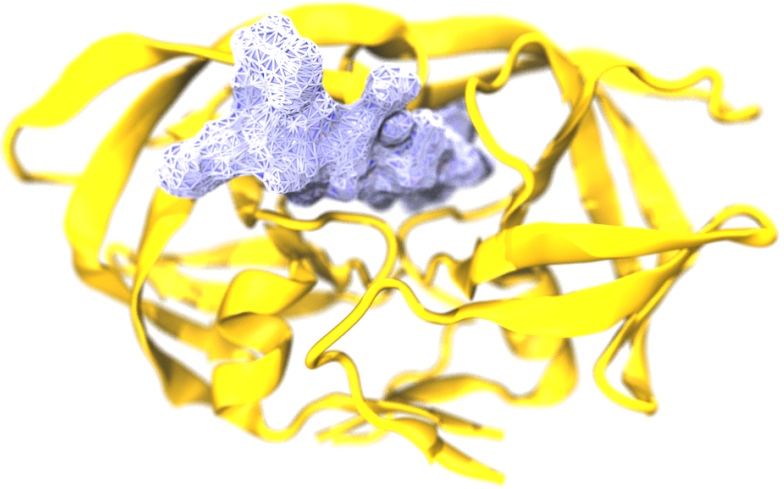
- Enable visualization and analyses not possible with conventional workstations
  - Access data located anywhere in the world
    - Same VMD session available to any device

Bringing supercomputers to your home



QwikMD

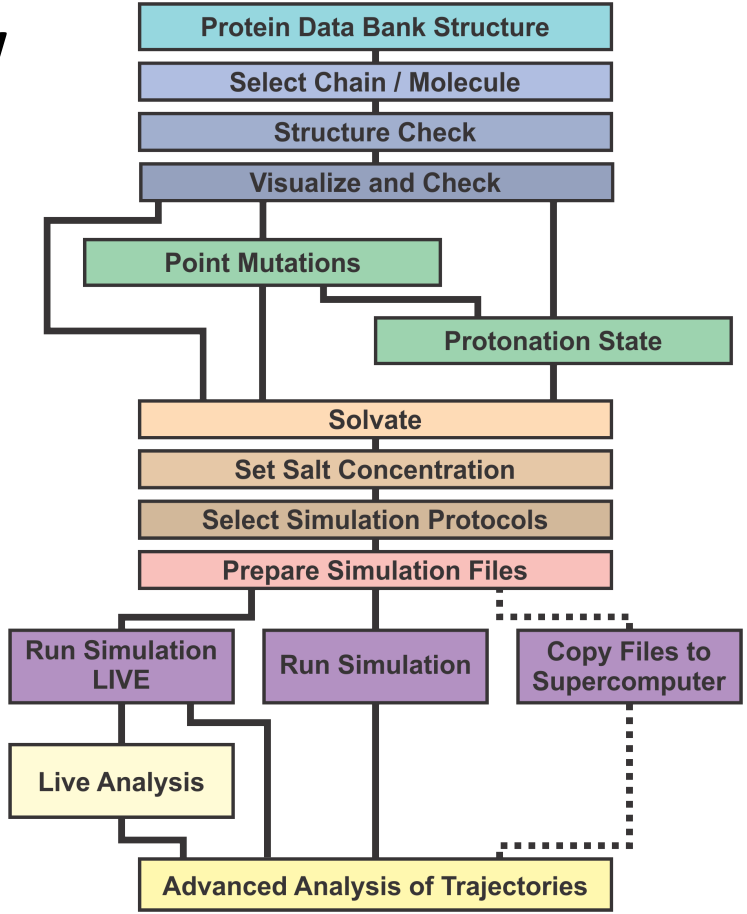
Employing QwikMD, a user is able to prepare an MD simulation in just a few minutes, allowing studies of point mutations, partial deletions and even atomic force microscopy experiments.



QwikMD assists a new user in performing MD simulations, while it also servers as a learning tool. Many "info buttons" provide the theoretical background underlying the MD procedures carried out in modern MD simulations.

www.ks.uiuc.edu/Research/qwikmd

QwikMD Workflow



www.ks.uiuc.edu/Research/qwikmd

QwikMD - Integrative Molecular Dynamics Toolkit for Novices and Experts

Select: Easy Run or Advanced Run Analysis Tools can also be selected

Browse for a PDB file or type PDB code

In the structure manipulation window the QwikMD user can delete molecules or parts of a protein sequence; perform point mutations; change protonation states; check the structure; insert membrane model (Advanced mode only)

For structures solved by NMR, select the conformational state

Select the chains and type of molecule to be included in the simulation

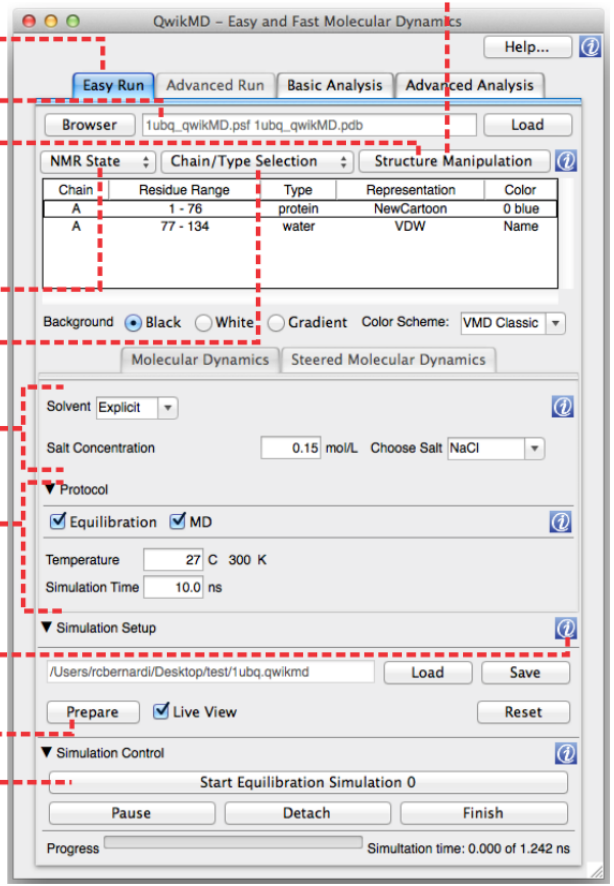
Select the environment: implicit or explicit solvent, and salt concentration

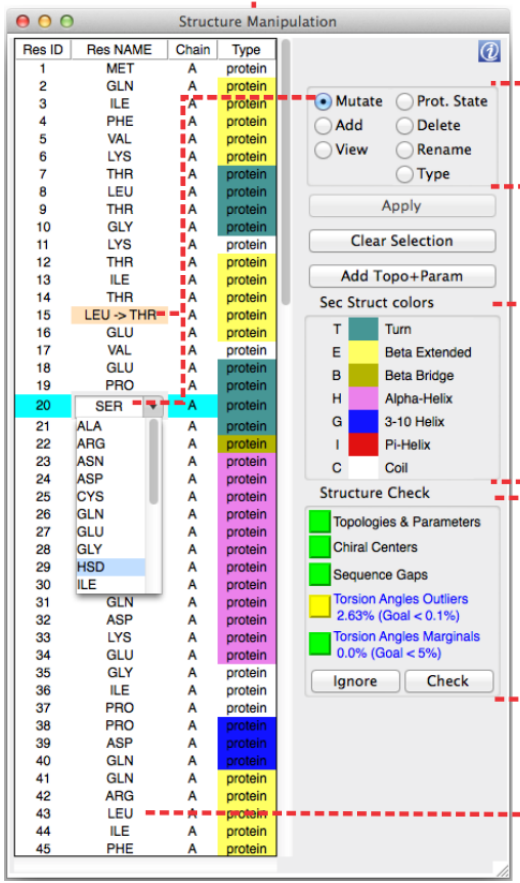
In the Protocol section the user selects temperature and duration of the simulation and also if an equilibration will be performed

"Info Buttons" provide the user with a variety of information, from protocols to a guidance on how to perform simulations and how to check results

When "Prepare" is clicked, QwikMD will invoke several scripts to perform all the operations set before, such as mutations, solvation, ...

Starts the simulation, either in "Live View" mode (if selected) or in "Background"





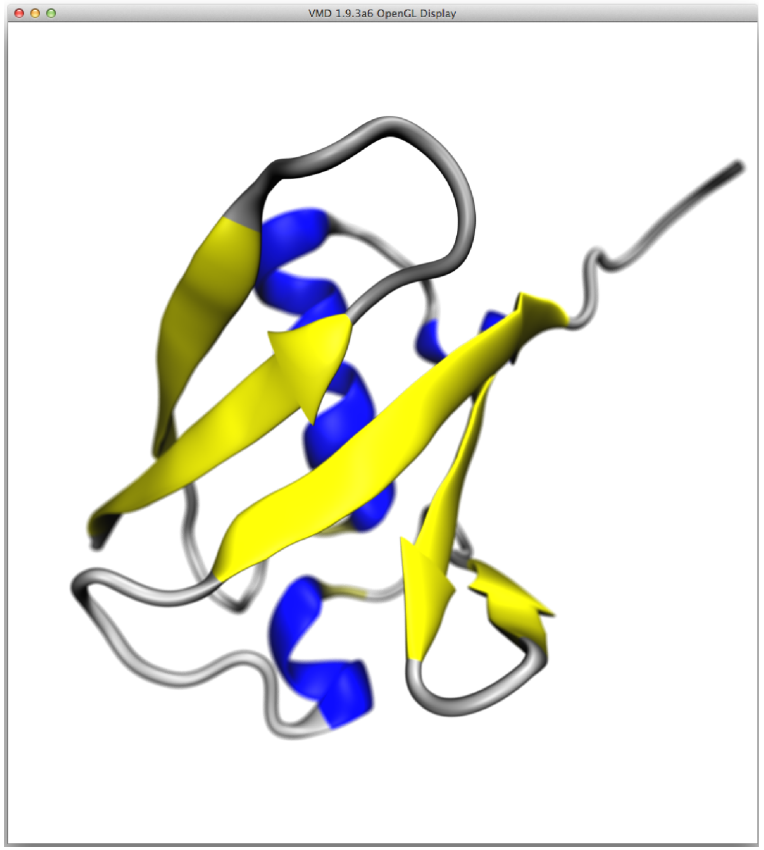
QwikMD user can easily perform point mutations. To do so, select "Mutate" and click on the amino acid from the sequence amino acid table. A list of all possible mutations will allow the user to select the desired mutation.

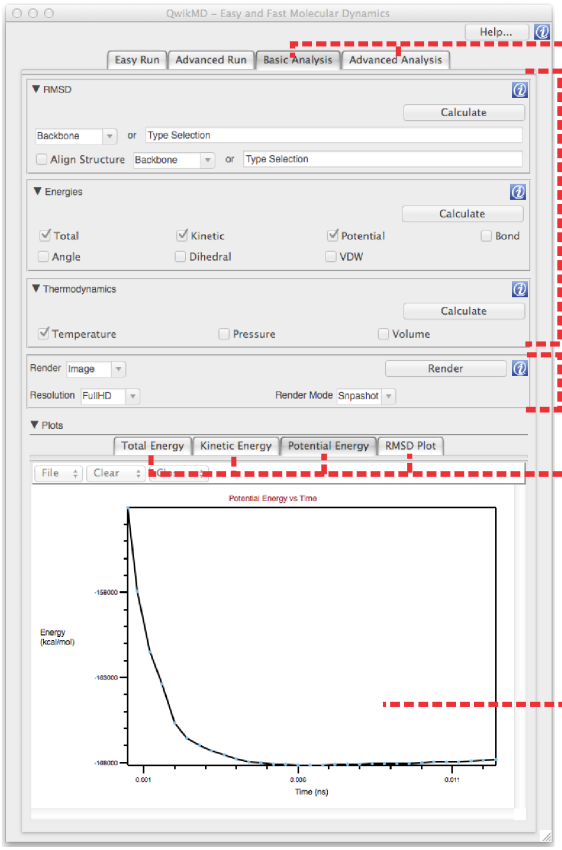
The list of amino acid in the protein sequence is colored according to the secondary structure.

An automated check of the structure is performed when a PDB is loaded by QwikMD. If problems arise they will be marked in the "Structure Check" Tab. The user will be guided on how to fix the problems found.

All molecules of the system are presented in a list an can be separated by *type* or *chain*. The QwikMD user can easily delete parts of structure, change protonation states, perform point mutations, among other actions.

QwikMD - Integrative Molecular Dynamics Toolkit for Novices and Experts





QwikMD users can select between: (1) “Basic Analysis”, which include most common analysis methods used to check how stable is the structure in the simulation; or (2) “Advanced Analysis”, which includes several of the most used analysis tools in VMD, i.e., Hydrogen Bond count, and Solvent Accessible Surface Area (SASA).

Here the user can select the analysis to be performed when “Calculate” is clicked.

VMD is known for its structure image rendering capabilities. In QwikMD a quick-render tab allows for a fast high-quality rendering, employing the most used settings for shadows, colors, materials, ...

Multiple analysis can be performed at the same time. The resulting plots will be presented in different tabs.

In a simulation on *live view* mode the plot will be updated while the simulation is performed

http://www.ks.uiuc.edu/Training/Tutorials/

Using NAMD:
Participants learn how to use NAMD to set up basic molecular dynamics simulations, and to understand typical NAMD input and output files, with an emphasis on such files for protein energy minimization and equilibration in water. Tutorial versions available for Windows, or Mac and Unix/Linux platforms.

http://www.ks.uiuc.edu/Training/Tutorials/

Using VMD:
Participants build an image of ubiquitin while becoming familiar with basic VMD commands. Additionally, participants learn how to look for interesting structural properties of proteins using VMD.

http://www.ks.uiuc.edu/Training/Tutorials/

VMD Images and Movies Tutorial:

This tutorial is designed to give users of VMD an introduction to advanced techniques for making custom images and movies. The first section looks at how to use features such as resolution, color, and material, depth perception, and volumetric data to produce effects and enhancements for still images. The second part demonstrates how to work with trajectories, by using techniques such as smoothing trajectories, showing multiple frames at once, and making atom selections "follow" a trajectory. It also shows how to create a movie file from a trajectory using VMD's Movie Maker plugin.

http://www.ks.uiuc.edu/Training/Tutorials/

Structure Check:

This tutorial describes two VMD plugins that can be used to detect and correct certain structure errors, namely chirality and cis peptide bonds. The plugins can also be used to prevent these errors from occurring in simulations with NAMD. Requires VMD and NAMD.

http://www.ks.uiuc.edu/~trudack/QwikMD/

QwikMD image tutorials:

QwikMD - How to perform HIV-proteases simulations.

QwikMD - How to perform Glycoside Hydrolases simulations.

QwikMD - How to perform simulations of Peptide + Membrane.

QwikMD - How to perform simulations of Aquaporin in Membrane.

QwikMD - How to perform steered molecular dynamics simulations of ultrastable cellulosome components.

Well suited for beginners

http://www.ks.uiuc.edu/Training/Tutorials/

Molecular Dynamics Flexible Fitting (MDFF): This tutorial describes how to flexibly fit atomic structures into density maps using the MDFF method. This method can be used to obtain atomic models of macromolecular complexes by combining X-ray structures and cry-electron microscopy maps. Requires VMD and NAMD.

Tutorial files are provided in your home folder.

http://www.ks.uiuc.edu/Training/Tutorials/

ModelMaker:
This tutorial describes interactive model building with ModelMaker to fill in missing pieces of structures.

http://www.ks.uiuc.edu/~trudack/QwikMDFF/

QwikMD image tutorial:
QwikMD / MDFF GUI - How to perform MDFF of Adenylate Kinase.

YouTube tutorials interactive MDFF:

https://www.youtube.com/watch?v=-KJiH_WF65s

Well suited for beginners

New VMD Release VMD 1.9.3 beta2 available here:

http://www.ks.uiuc.edu/Research/mdff/vmdbeta/

QwikMD Tutorials:

http://www.ks.uiuc.edu/~trudack/QwikMD/

QwikMDFF Tutorial:

http://www.ks.uiuc.edu/~trudack/QwikMDFF/

Slides will be provided here:

http://www.ks.uiuc.edu/Training/Workshop/Juelich2016/


Thank You