QwikMD: Making Molecular Dynamics Simulations of Biological Systems Easy

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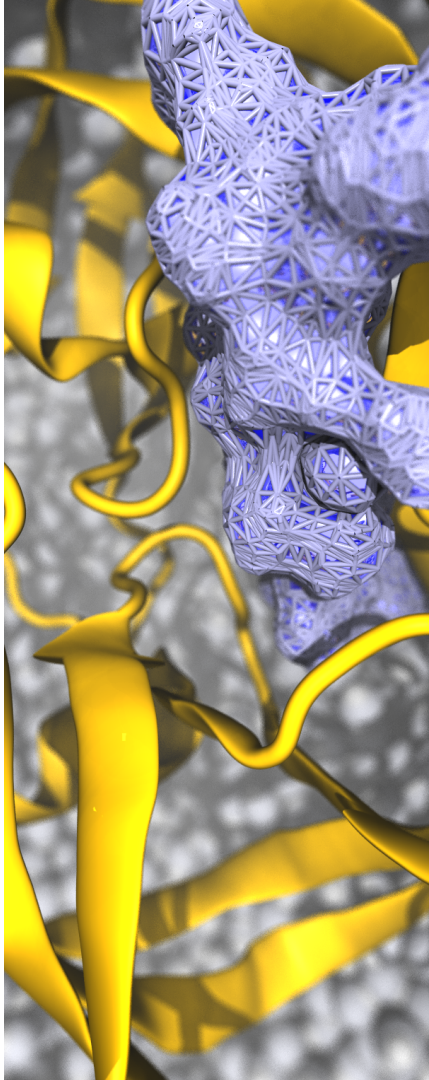


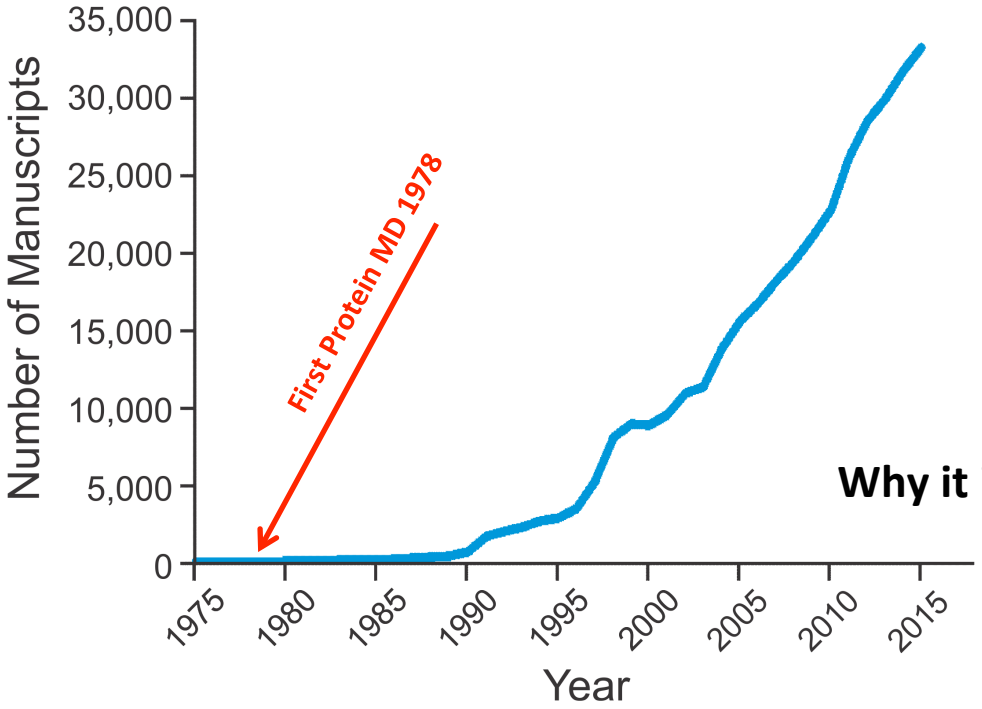
What is Molecular Dynamics?

"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)

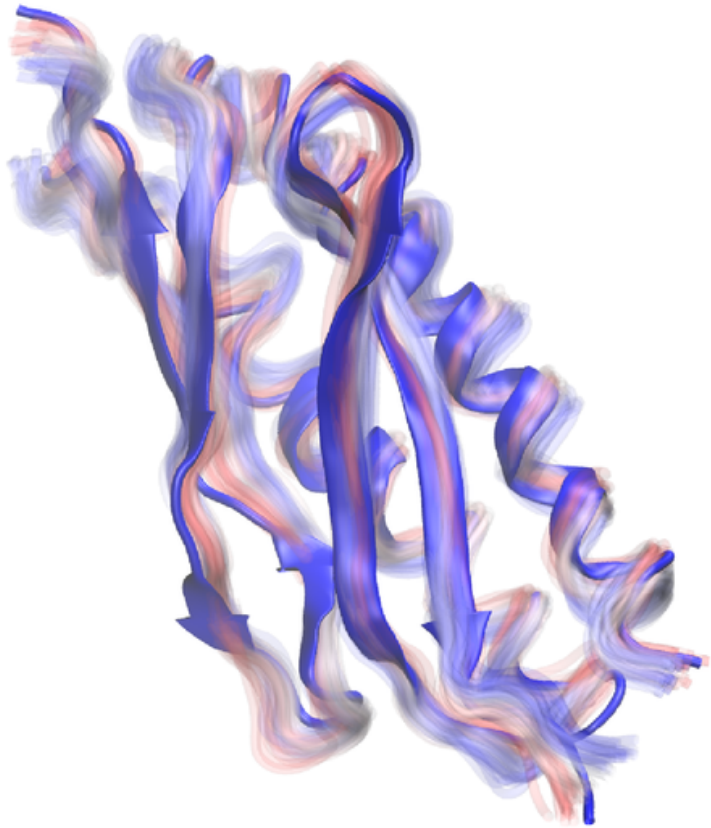
Development of Molecular Dynamics over the past decades:



Why it is so Important?

What is Molecular Dynamics?

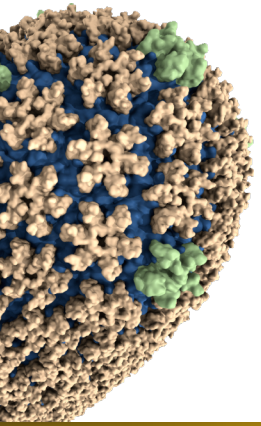
Myoglobin Structure
Kendrew (1962 Chemistry Nobel Prize)

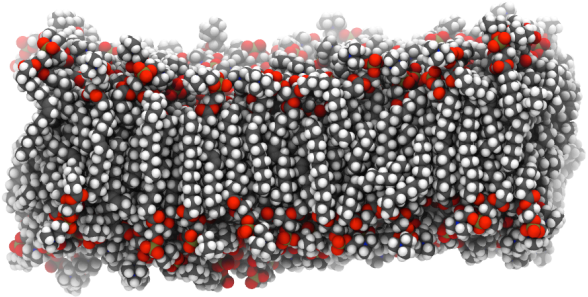


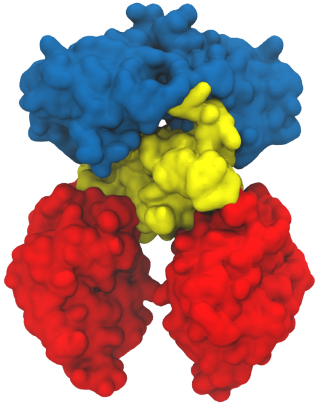
Dynamics plays an important role.

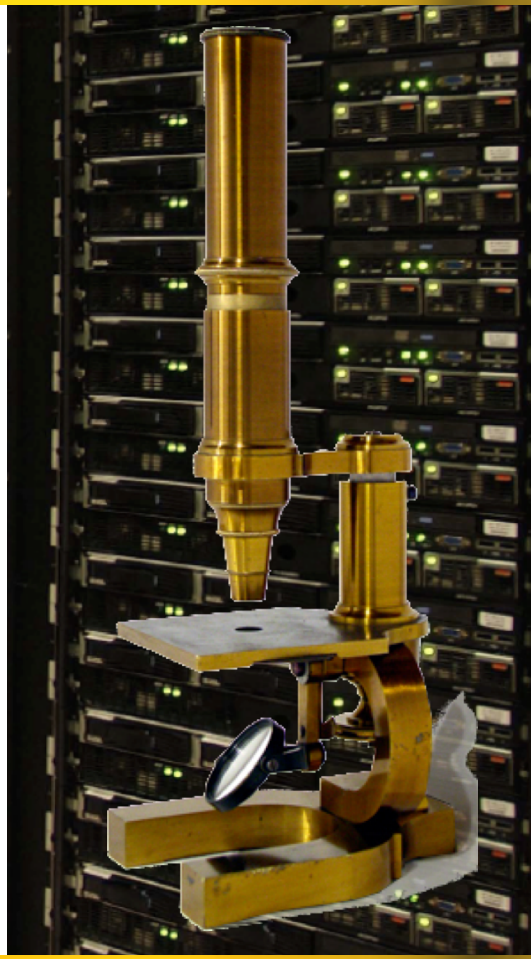
The Computational Microscope

What our microscope is made of?



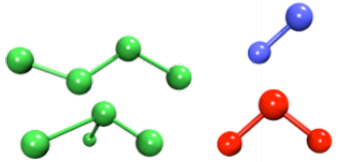






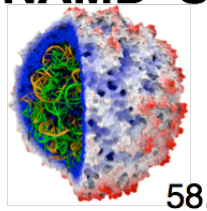
Molecular Dynamics Simulations - Theory

Chemistry

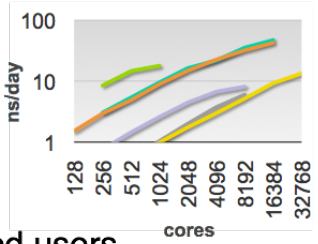


$$U(\vec{R}) = \underbrace{\sum_{bonds} k_i^{bond}(r_i - r_0)^2}_{U_{bond}} + \underbrace{\sum_{angles} k_i^{angle}(\theta_i - \theta_0)^2}_{U_{angle}} + \underbrace{\sum_{dihedrals} k_i^{dihe}[1 + \cos(n_i\phi_i + \delta_i)]}_{U_{dihedral}} + \underbrace{\sum_i \sum_{j \neq i} 4\epsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12}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

NAMD Software



Virus

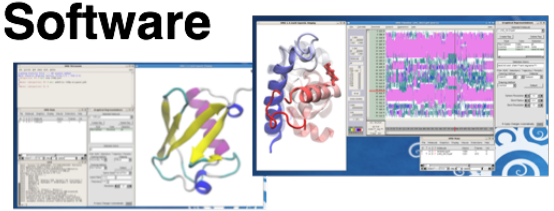


58,000 registered users

Physics

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

VMD Software



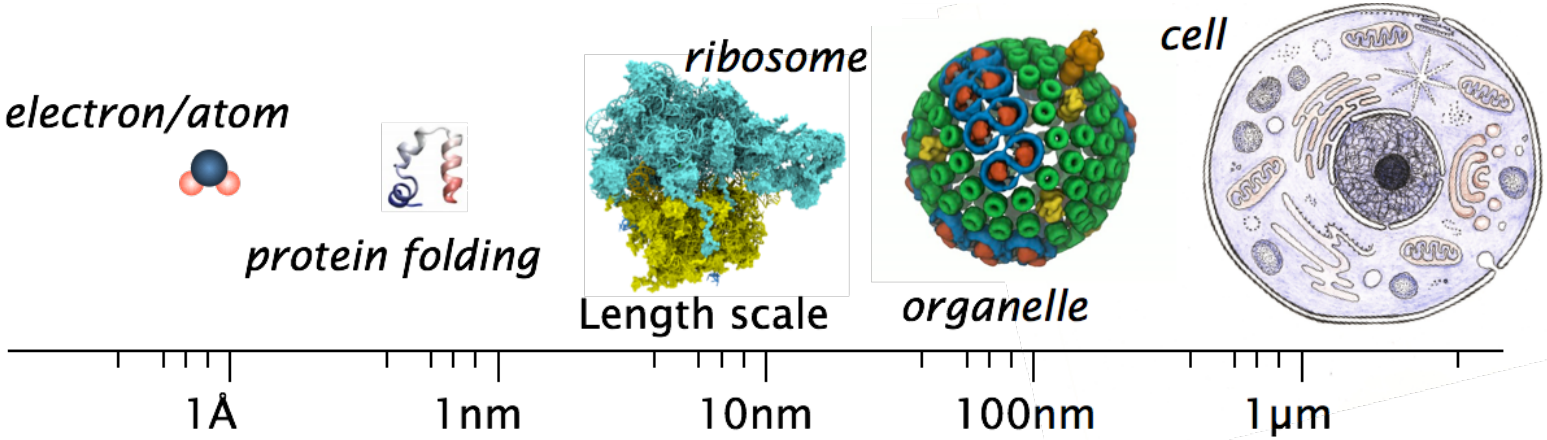
240,000 registered users

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)

… Views Living Systems from Electron to Cell



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

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

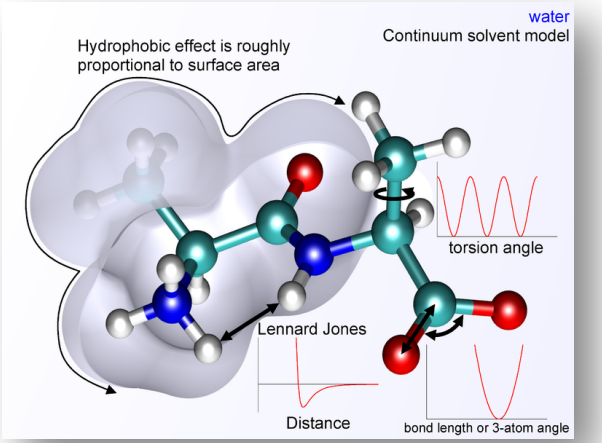
$$V_{vdW,ij} = \varepsilon_{IJ}\left[\left(\frac{R_{IJ}}{R_{ij}}\right)^{12} - 2\left(\frac{R_{IJ}}{R_{ij}}\right)^{6}\right]$$

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

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

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

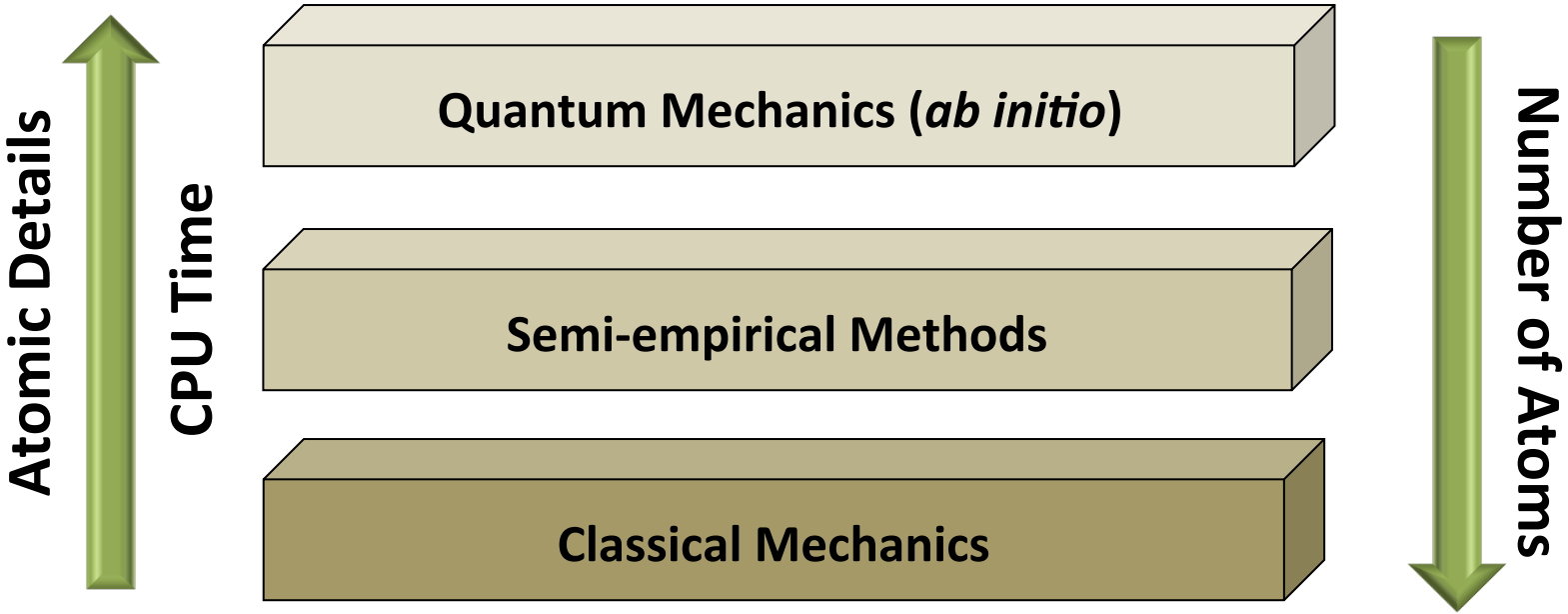
$$V_{str,ij} = \frac{1}{2} k_{IJ}\left(l_{ij} - l^0{}_{IJ}\right)^2$$



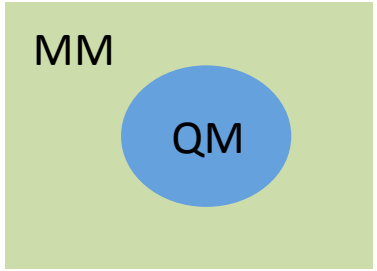
Why not to use Quantum Mechanics?

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

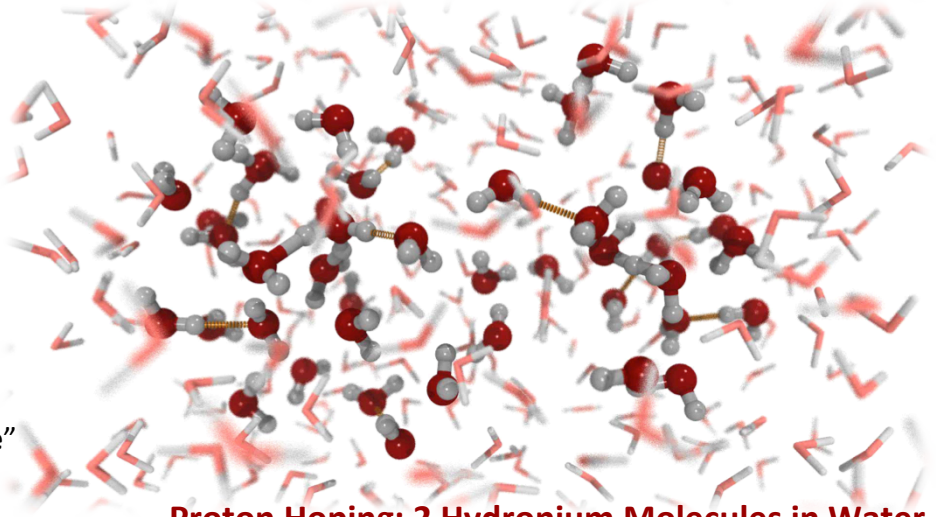
Classical Mechanics vs. Quantum Mechanics



NAMD QM/MM – The Most Complete Hybrid Interface



QM/MM allows precise study of chemical reactions in MD simulations.



Proton Hoping: 2 Hydronium Molecules in Water

Main Features

Interface to ORCA, MOPAC, and "**Generic Interface to any QM Software**"
Multiple Charge Redistribution Schemes
PME for Long-Range Electrostatics
Solvent Molecule Switcher (necessary for long timescale QM/MM simulations)
Multiple Independent QM Regions
Easy Setup Interface with QwikMD
Mix and Match (**Combine with any other NAMD Feature**):

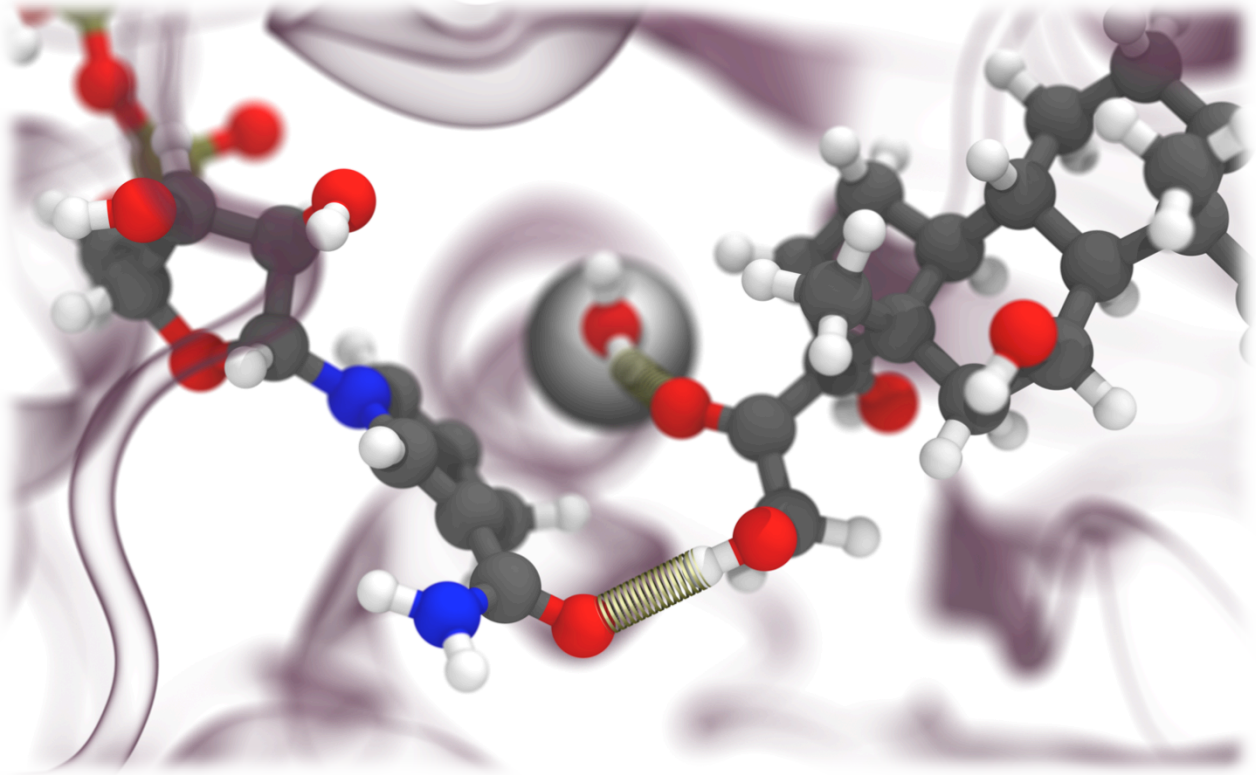
- Polarizable Force Field in MM Region
- Replica Exchange Molecular Dynamics
- Adaptive Biasing Force
- Steered Molecular Dynamics

...

Collaborators

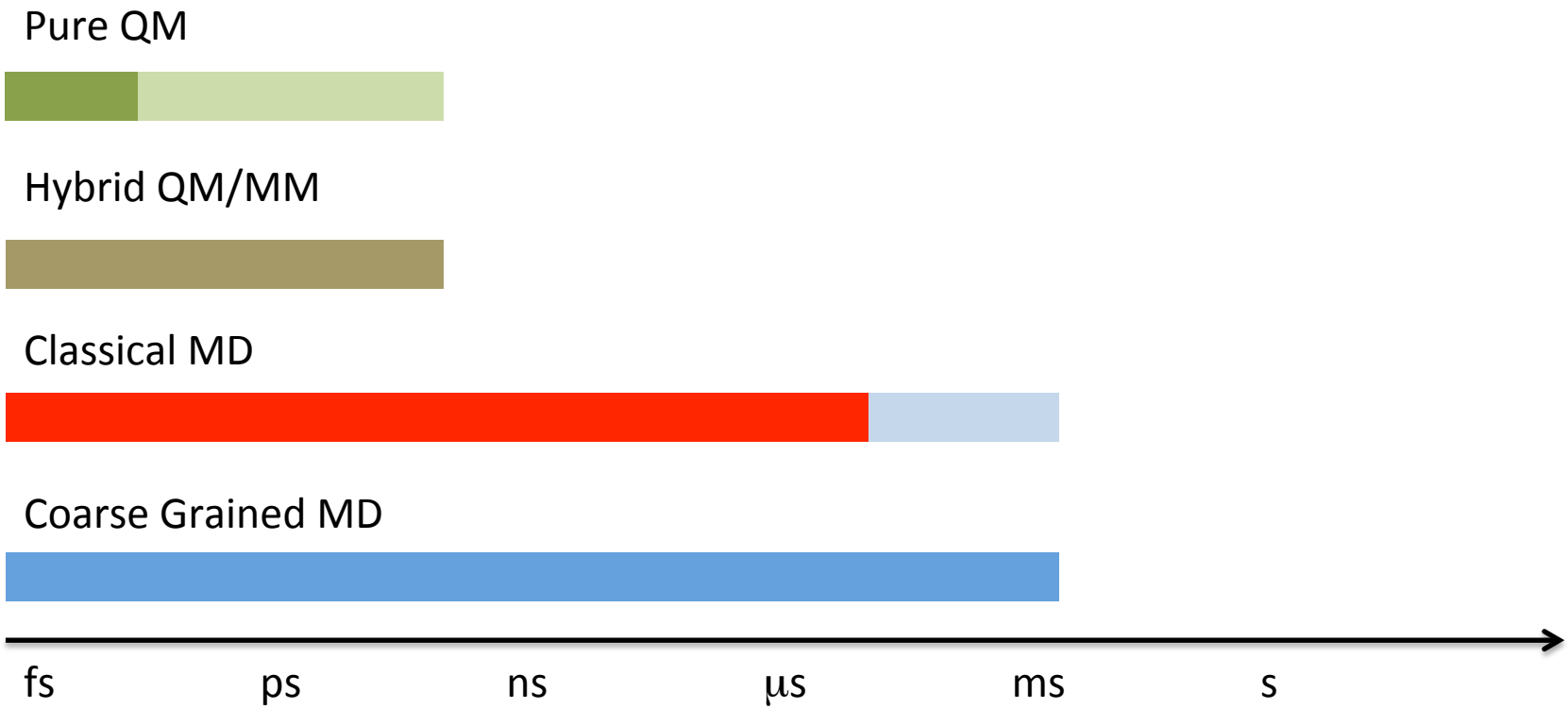
Frank Neese (ORCA)
Max Planck Institute for
Chemical Energy Conversion
Mülheim an der Ruhr, Germany

Gerd Rocha (MOPAC-GPU)
Theoretical Quantum Chemistry Group
UFPB - João Pessoa, Brazil

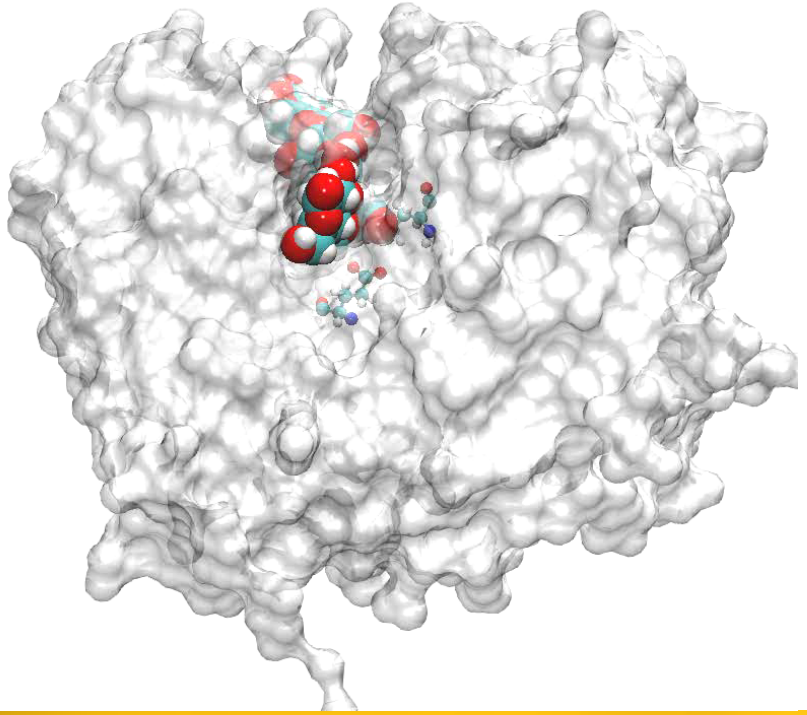


Mechanism of Hydroxysteroid Dehydrogenases

The Time Scale Problem



The Time Scale Problem



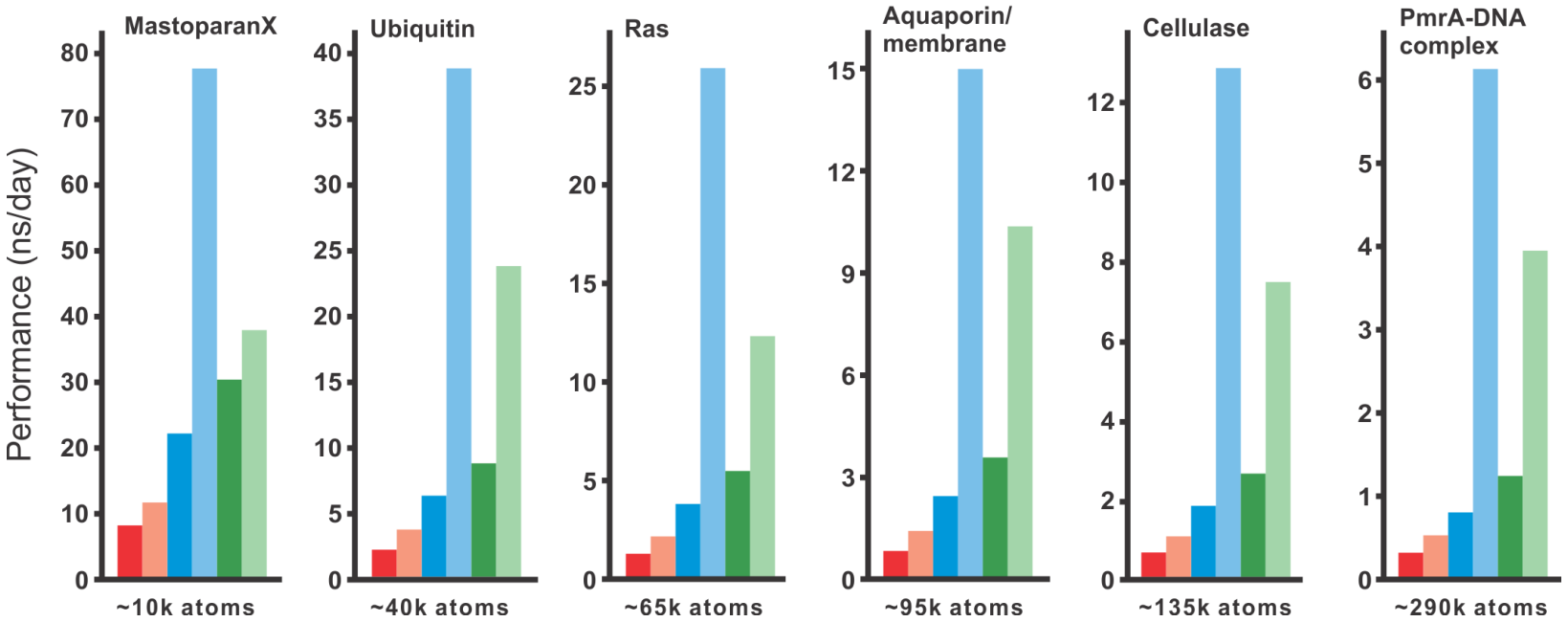
What timescale we can simulate?

Performance of NAMD simulations on different computer platforms

CPU + GPU / CPU — **Laptop:** MacBook Pro (Late 2013 model) - Intel Core-i7 2.3 Ghz (4 CPU cores) - 16GB RAM - NVIDIA GeForce GT 750M

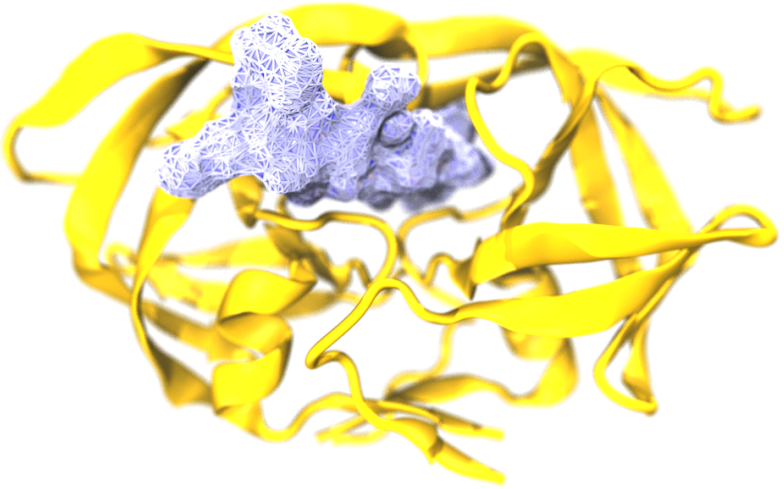
CPU + GPU / CPU — **Desktop:** Dual Intel E5-2650v2 2.6 Ghz (8 CPU cores each) - 64GB RAM - NVIDIA GeForce GTX Titan X

CPU + GPU / CPU — **Cloud:** G2.8 instance of the Amazon Elastic Compute Cloud
Cloud: C4.8 instance of the Amazon Elastic Compute Cloud



QwikMD

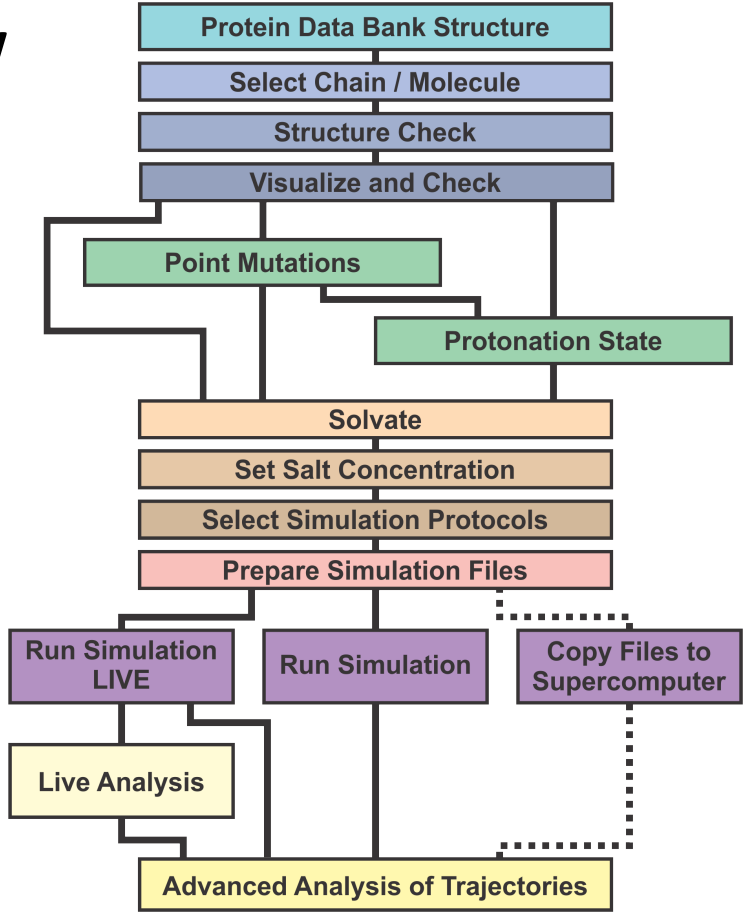
Employing QwikMD, a user is able to prepare an MD simulation in just a few minutes, allowing studies of point mutations, partial deletions and even atomic force microscopy experiments.



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.

Download QwikMD from: www.ks.uiuc.edu/~rcbernardi

QwikMD Workflow



Download QwikMD:
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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

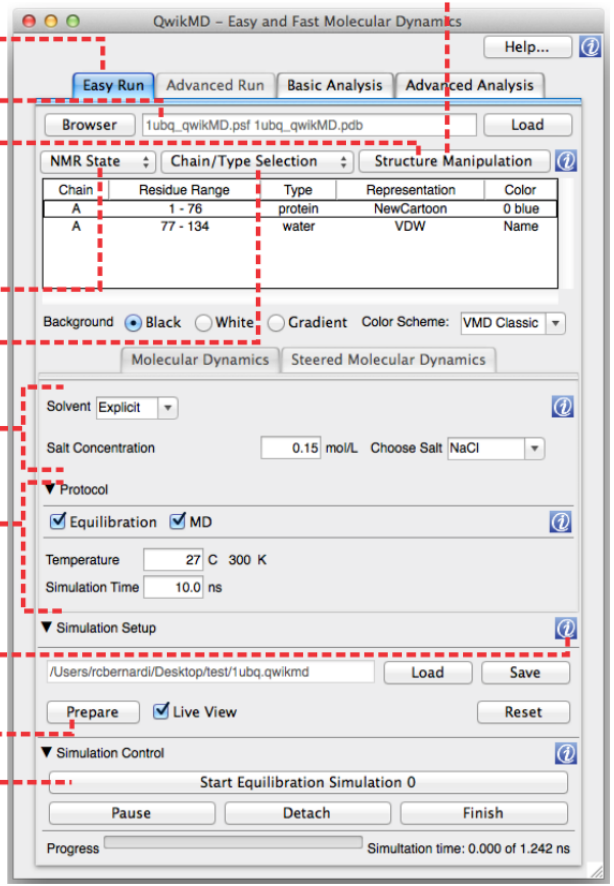
Select the environment: implicit or explicit solvent, and salt concentration

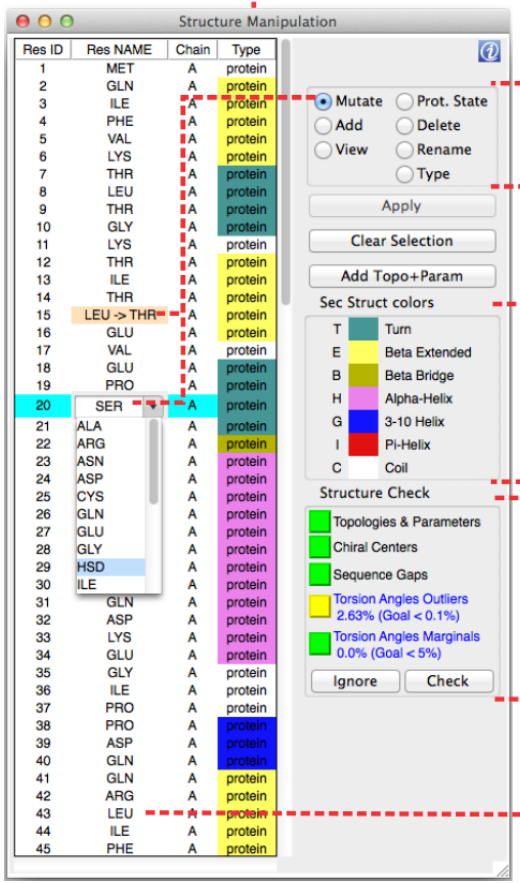
In the Protocol section the user selects temperature and duration of the simulation and also if an equilibration will be performed

"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"





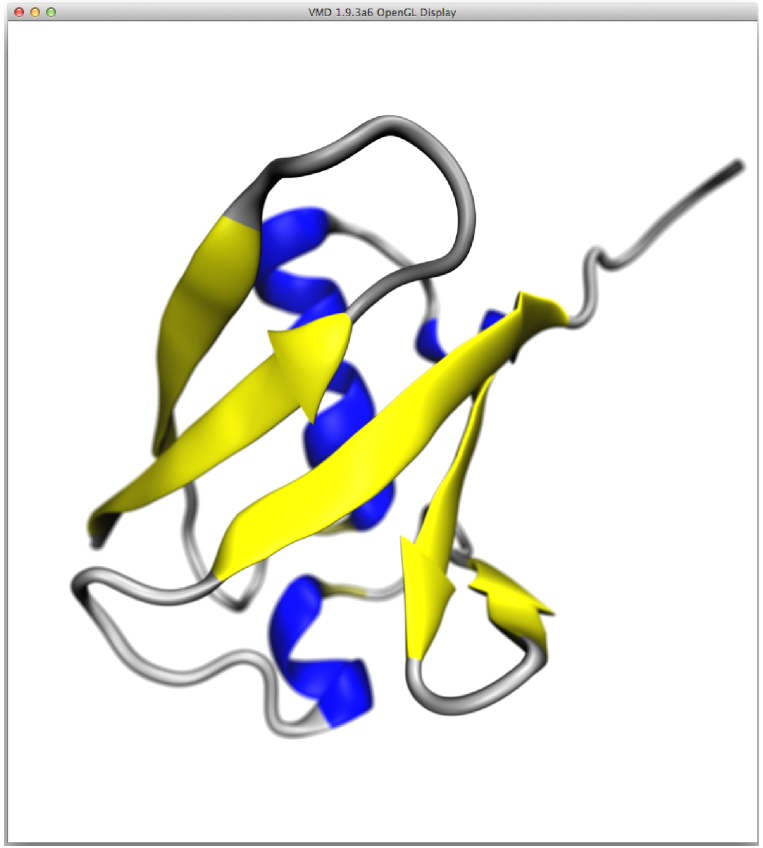
QwikMD user can easily perform point mutations. To do so, select "Mutate" and click on the amino acid from the sequence amino acid table. A list of all possible mutations will allow the user to select the desired mutation.

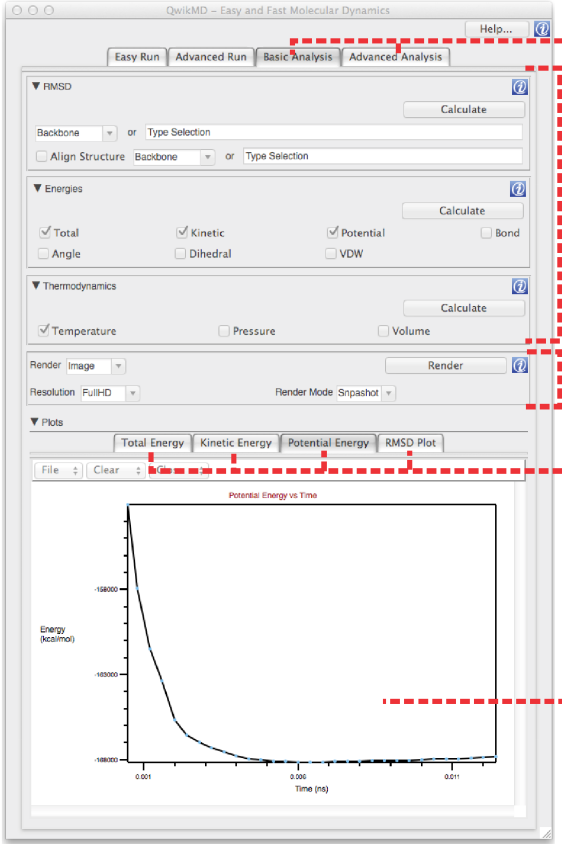
The list of amino acid in the protein sequence is colored according to the secondary structure.

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

HANDS-ON

Let’s open VMD

HIV Protease 1KJF

Aquaporin AQP5

Membrane 2HG0 (98-110)

Thank You

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