Molecular Dynamics Flexible Fitting

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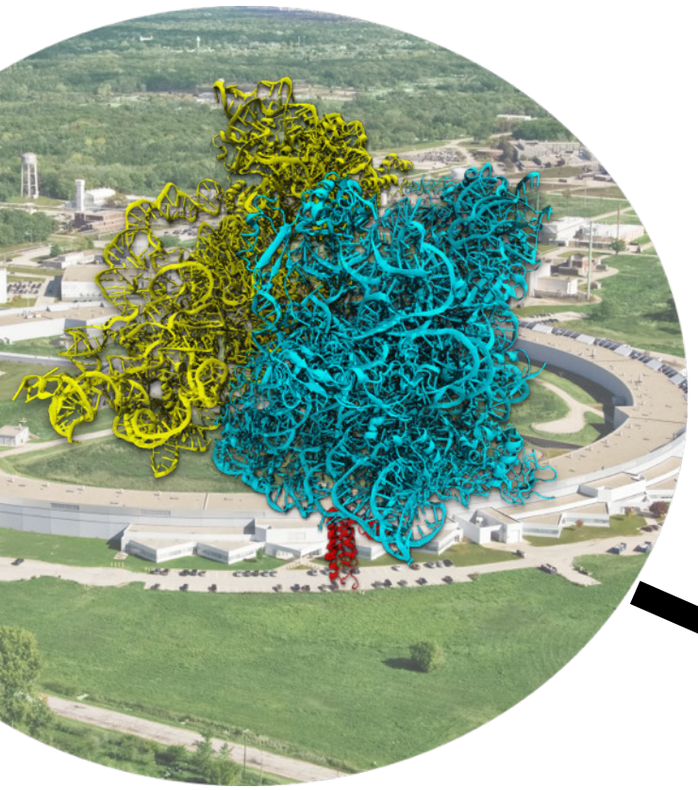
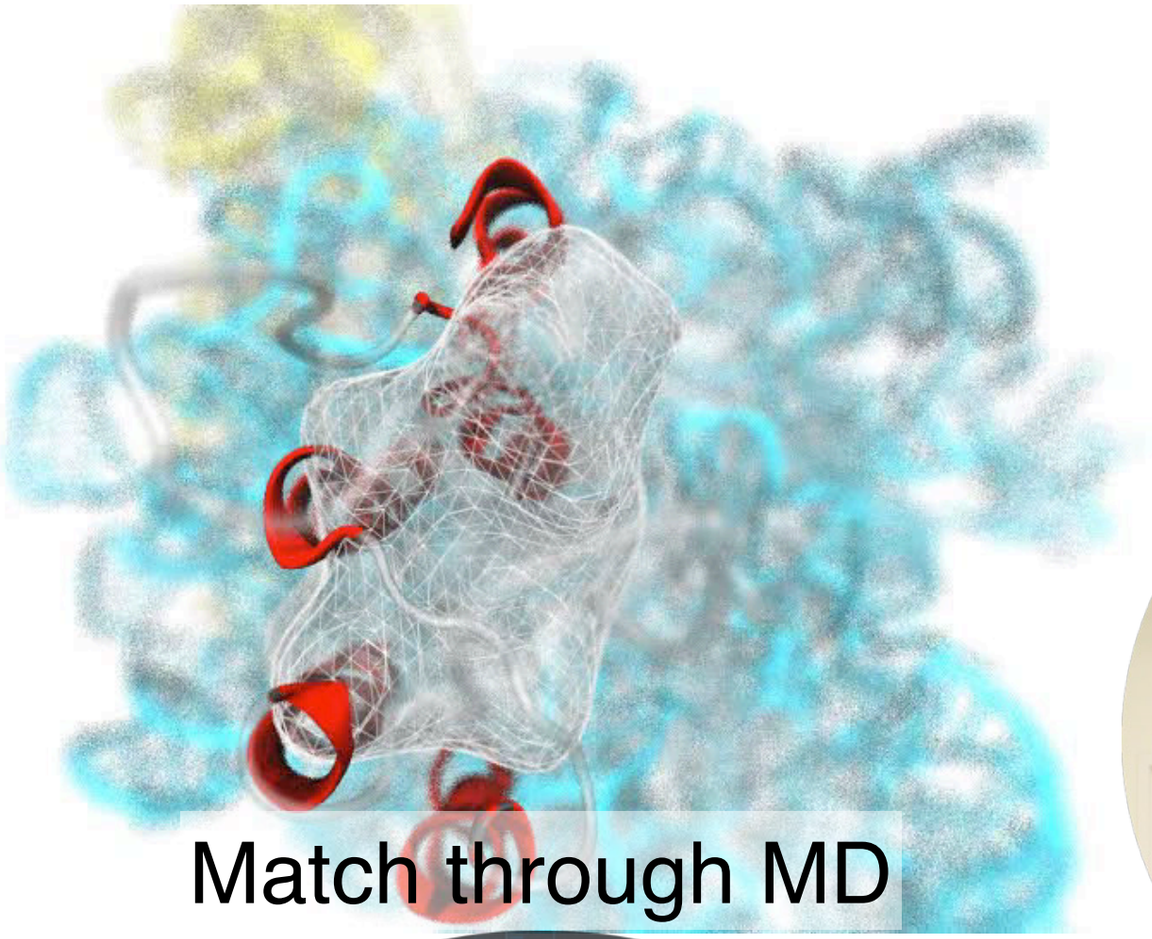
Molecular **D**ynamics **F**lexible **F**itting

(Ribosome-bound YidC)

crystallographic structure

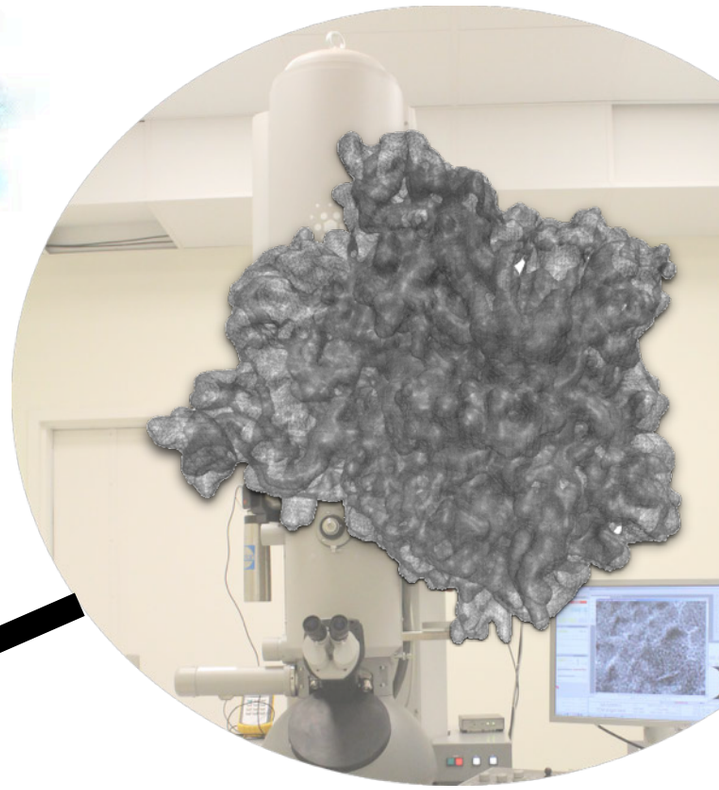


APS Synchrotron

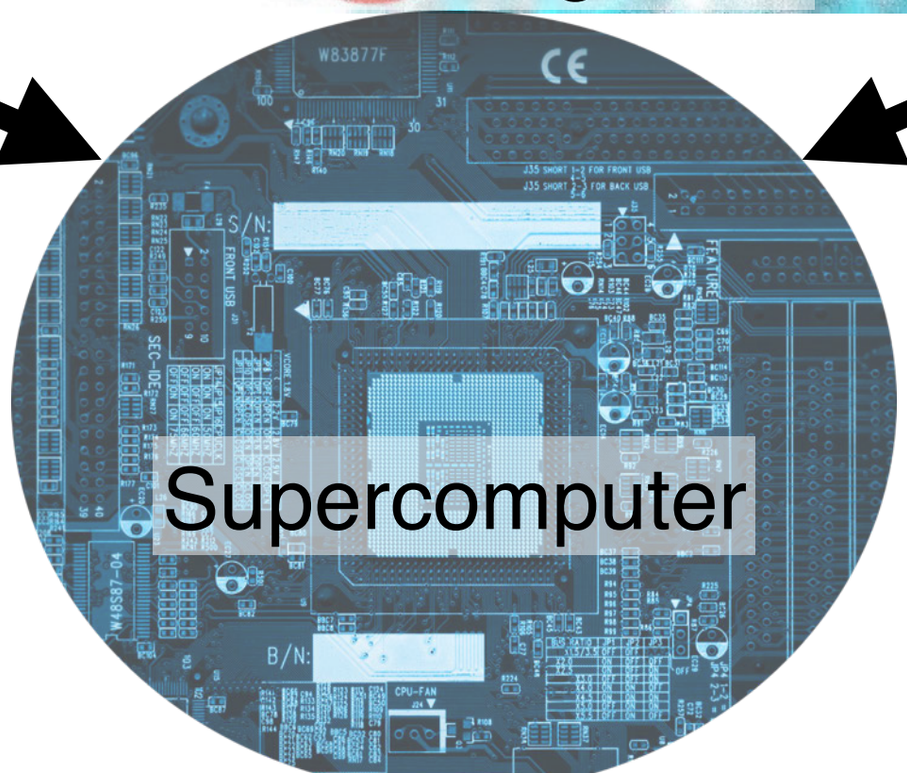


Match through MD

cryo-EM density map



Electron Microscope



Supercomputer

Molecular Dynamics Flexible Fitting - Theory

Two terms are added to the MD potential

$$U_{total} = U_{MD} + U_{EM} + U_{SS}$$

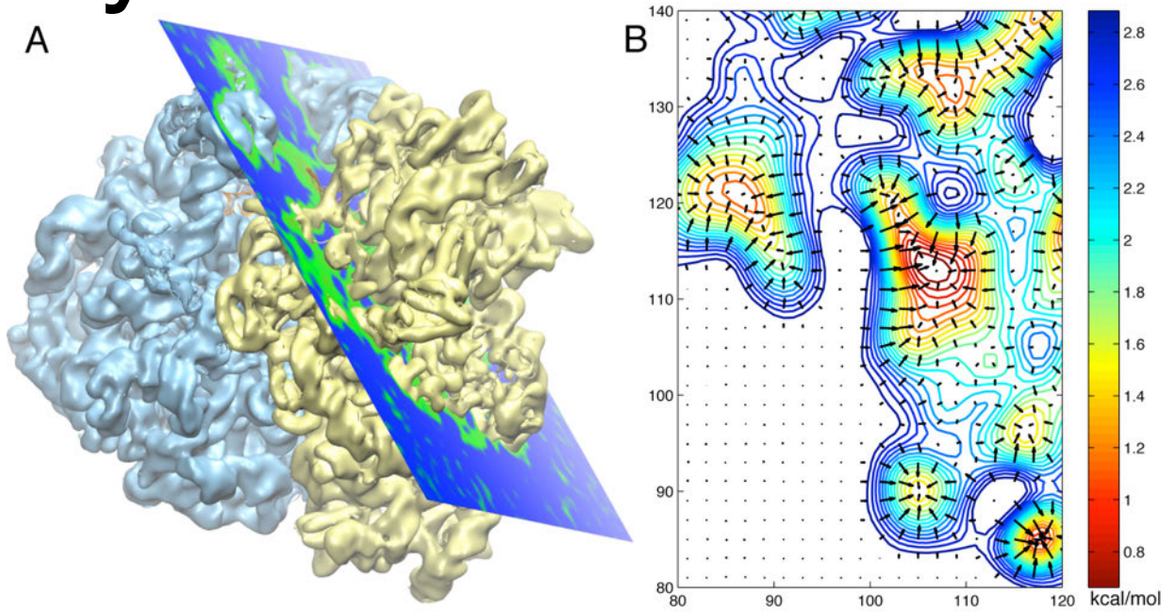
An external potential derived from the EM map is defined on a grid as

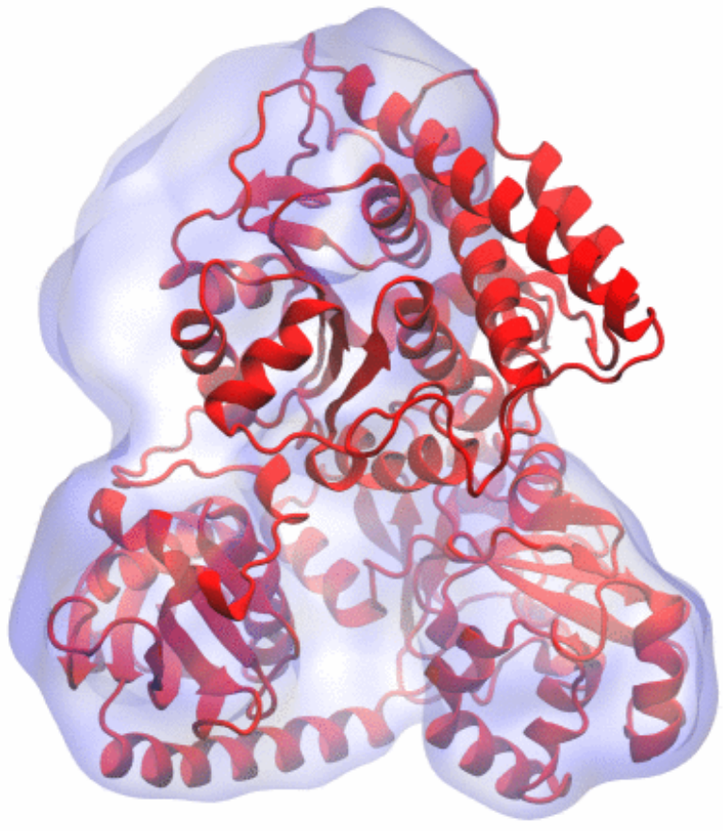
$$U_{EM}(\mathbf{R}) = \sum_j w_j V_{EM}(\mathbf{r}_j)$$

$$V_{EM}(\mathbf{r}) = \begin{cases} \xi \left(1 - \frac{\Phi(\mathbf{r}) - \Phi_{thr}}{\Phi_{max} - \Phi_{thr}}\right) & \text{if } \Phi(\mathbf{r}) \geq \Phi_{thr}, \\ \xi & \text{if } \Phi(\mathbf{r}) < \Phi_{thr}. \end{cases}$$

A mass-weighted force is then applied to each atom

$$\mathbf{f}_i^{EM} = -\nabla U_{EM}(\mathbf{R}) = -w_i \partial V_{EM}(\mathbf{r}_i)/\partial r_i$$





Acetyl – CoA Synthase

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

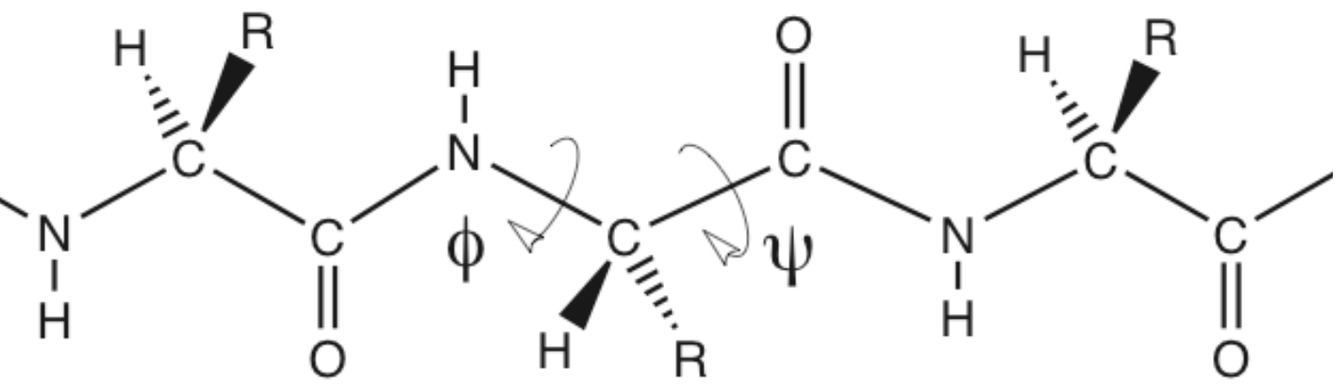
[2] Trabuco et al. *Methods* (2009) 49:174-180.

Secondary structure restraints

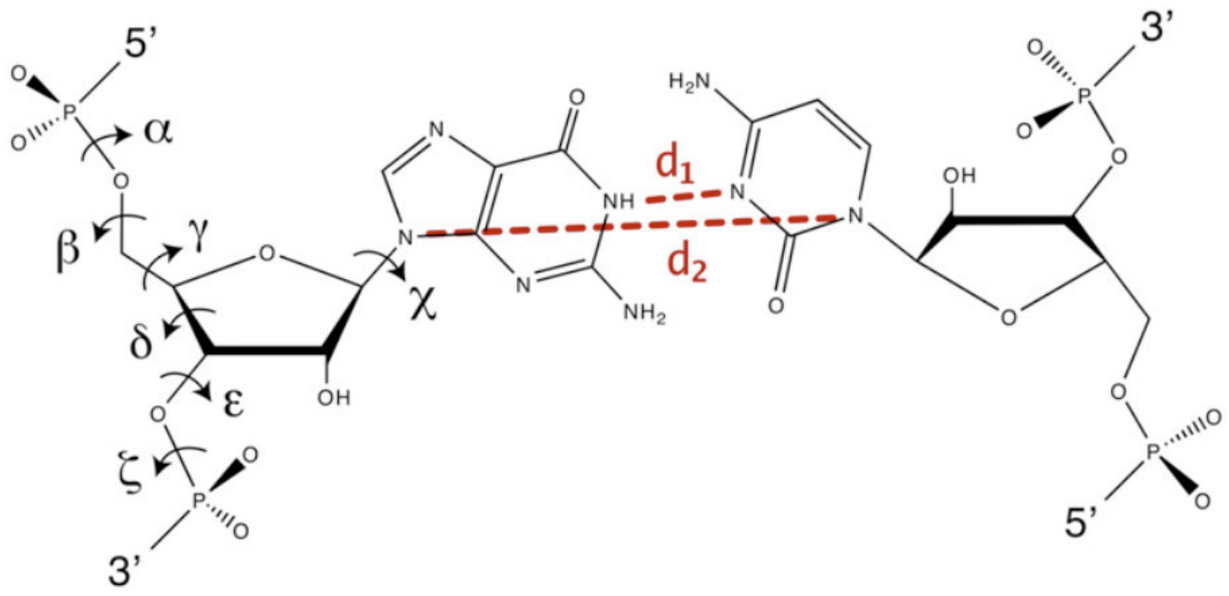
Harmonic restraints are applied to preserve secondary structure of proteins and nucleic acids, avoiding “overfitting.”

$$U_{SS} = \sum_{restraints} k_\mu(\mu - \mu_0)^2$$

For proteins, ϕ and ψ dihedral angles of residues within helices or beta strands are restrained.



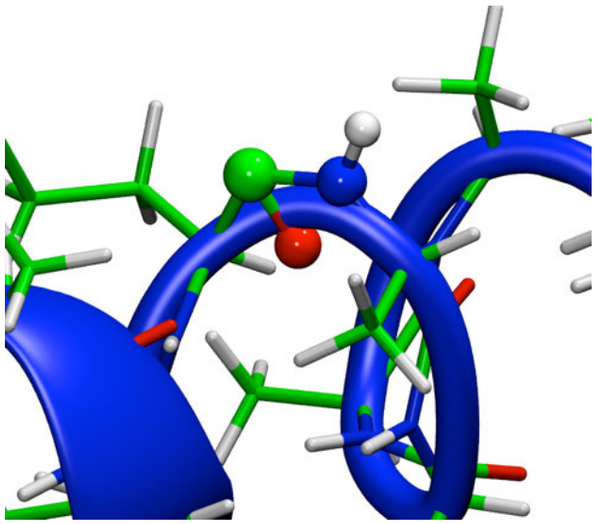
For nucleic acids, distance and dihedral restraints are applied to a selected set of base pairs.



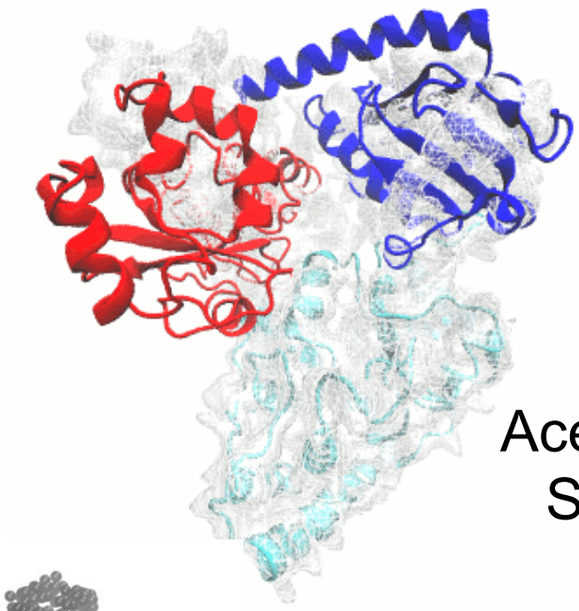
Additional Restraints

Cis-peptide and Chirality

Eduard Schreiner, et al. BMC Bioinformatics, 12, 190, 2011

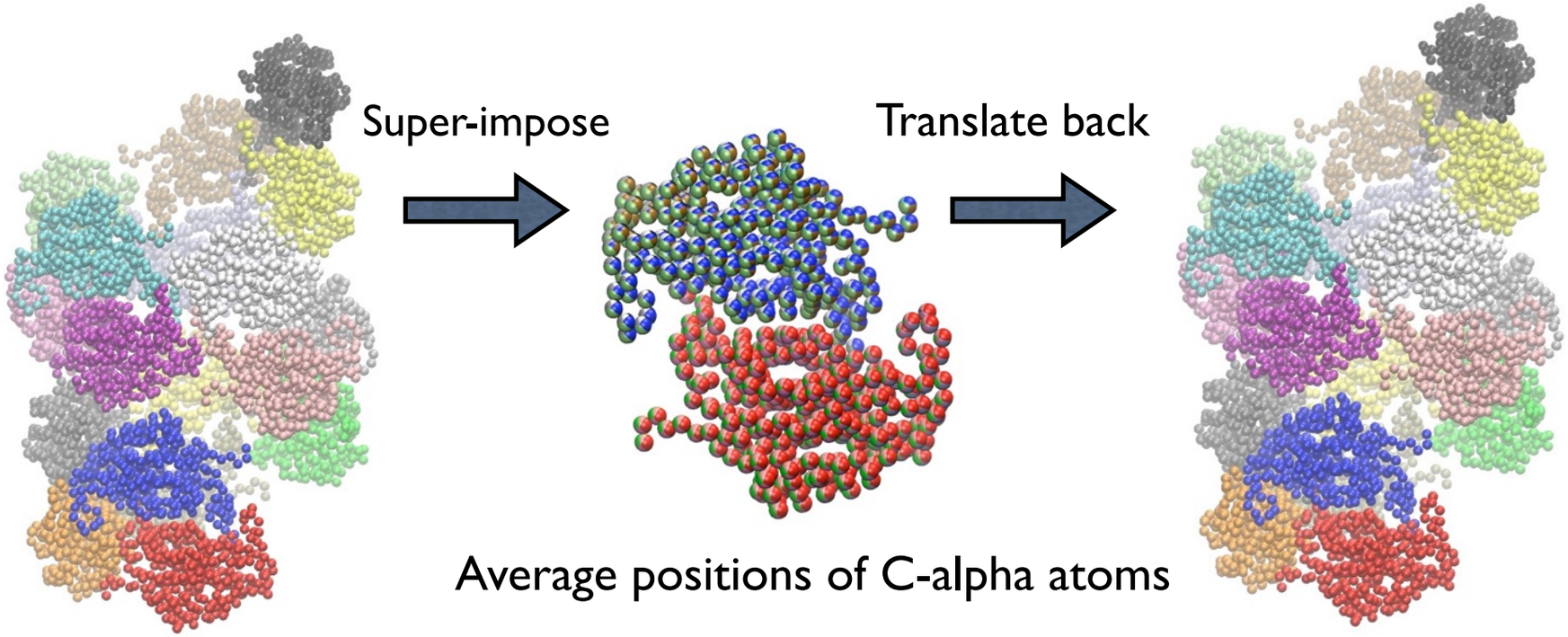


Domain-wise

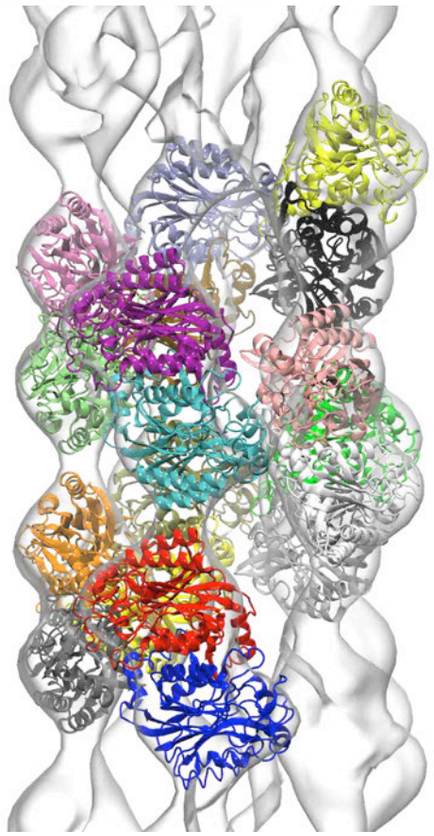


Acetyl – CoA Synthase

Symmetry



Kwok-Yan Chan, et al. Structure, 19, 1211-1218, 2011

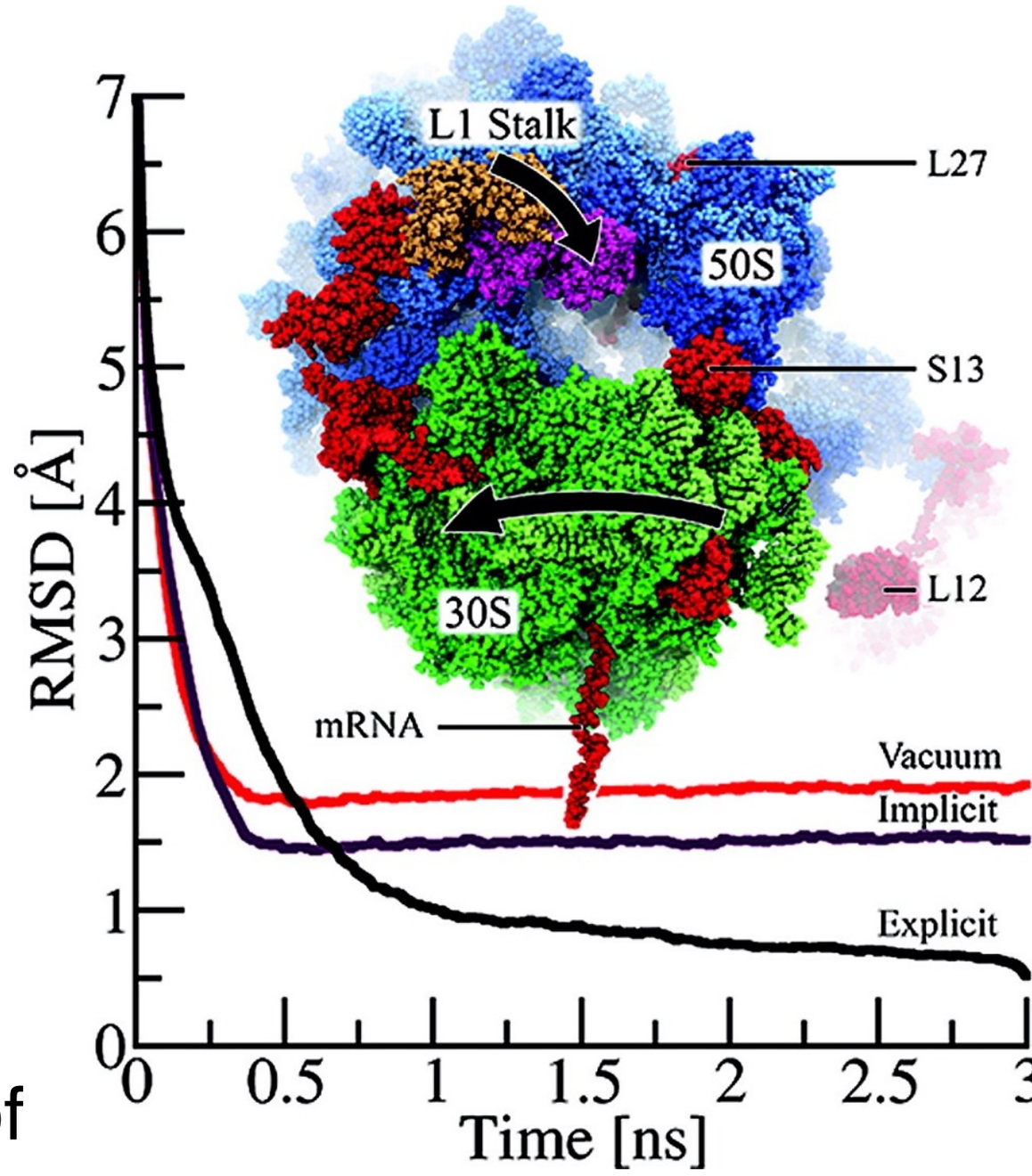


B. pumilus cyanide dihydratase

Simulation Environment

MDFF can be run in different environments:

1. <u>Vacuum</u>
   - No water molecules
   - Fastest but potentially inaccurate
2. <u>Explicit Solvent</u>
   - Explicit atomic detail water molecules
   - Computationally slow and introduces effects of viscous drag
3. <u>Implicit Solvent</u>
   - generalized Born approximation of electrostatics
   - Compromise between speed and accuracy

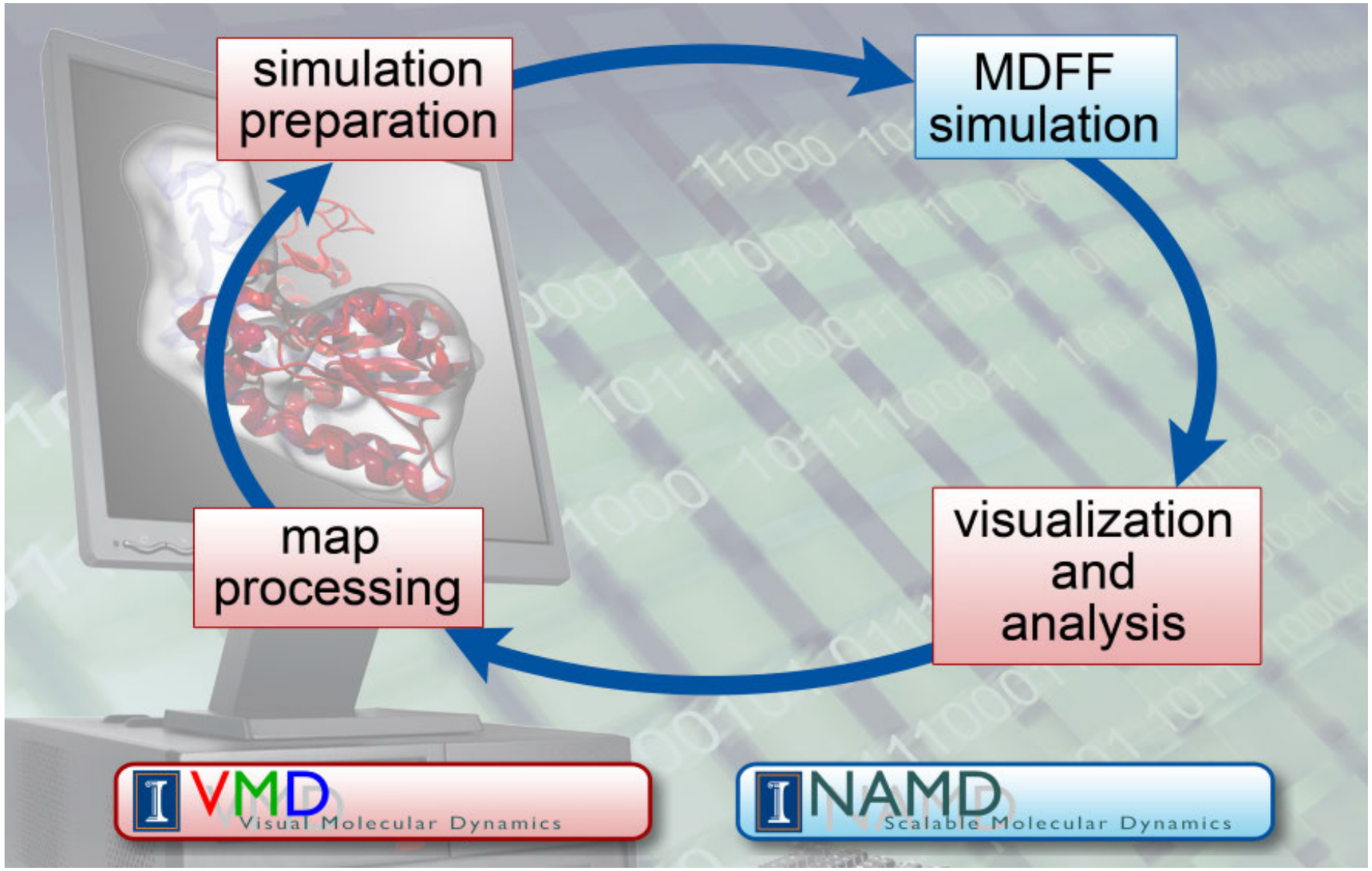


Tanner, et al. *Journal of Chemical Theory and Computation* 7(11) 3635–3642, 2011.

MDFF Software Suite

- NAMD and VMD used together to run MDFF

- Every NAMD and VMD feature is available in MDFF



Fitting time is dependent on:

- system size
- map and structure quality
- Generally need ~ 1ns or less (much shorter than MD)

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

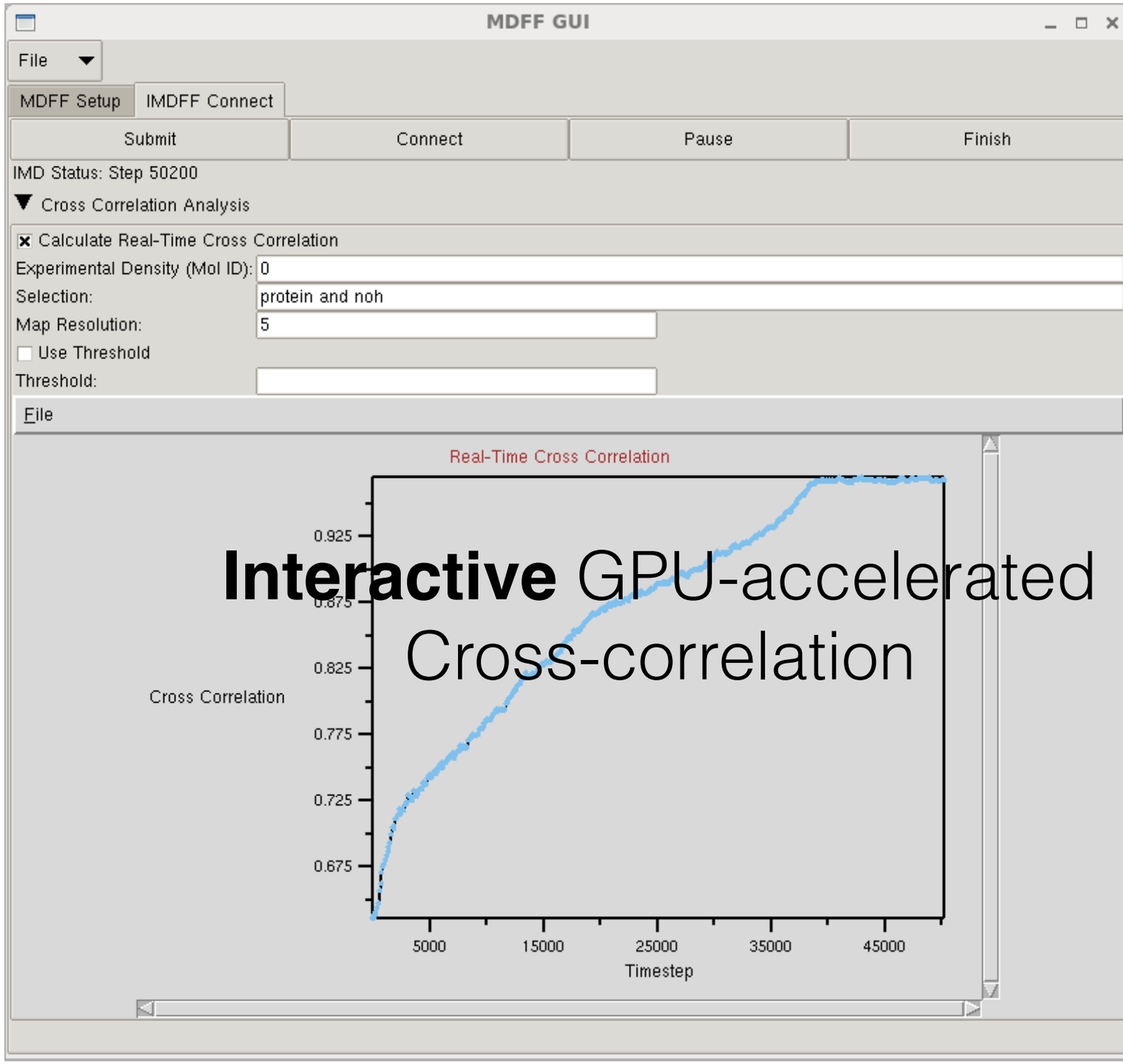
Input: MDFF only requires a PDB, PSF, and density map

Output: produces simulation trajectory from which an ensemble of structures can be extracted

MDFF Software Suite

- system sizes up to 100 million atoms (viruses, chromatophore)
- maps from 3 to 15 Å
- runs on laptops to petascale computing resources (Blue Waters, Titan)

New MDFF GUI (VMD 1.9.3) makes setting up, running, and analyzing fitting simulations even easier



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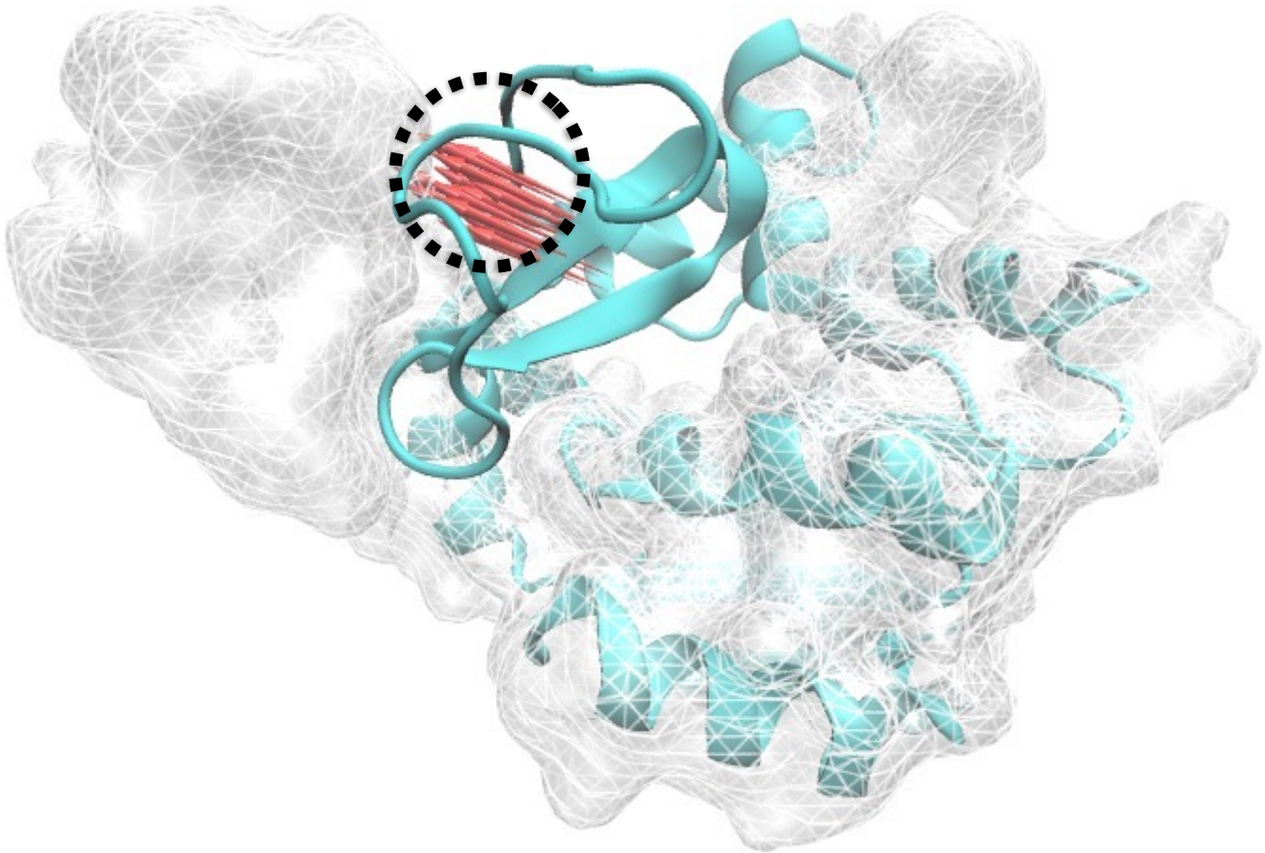
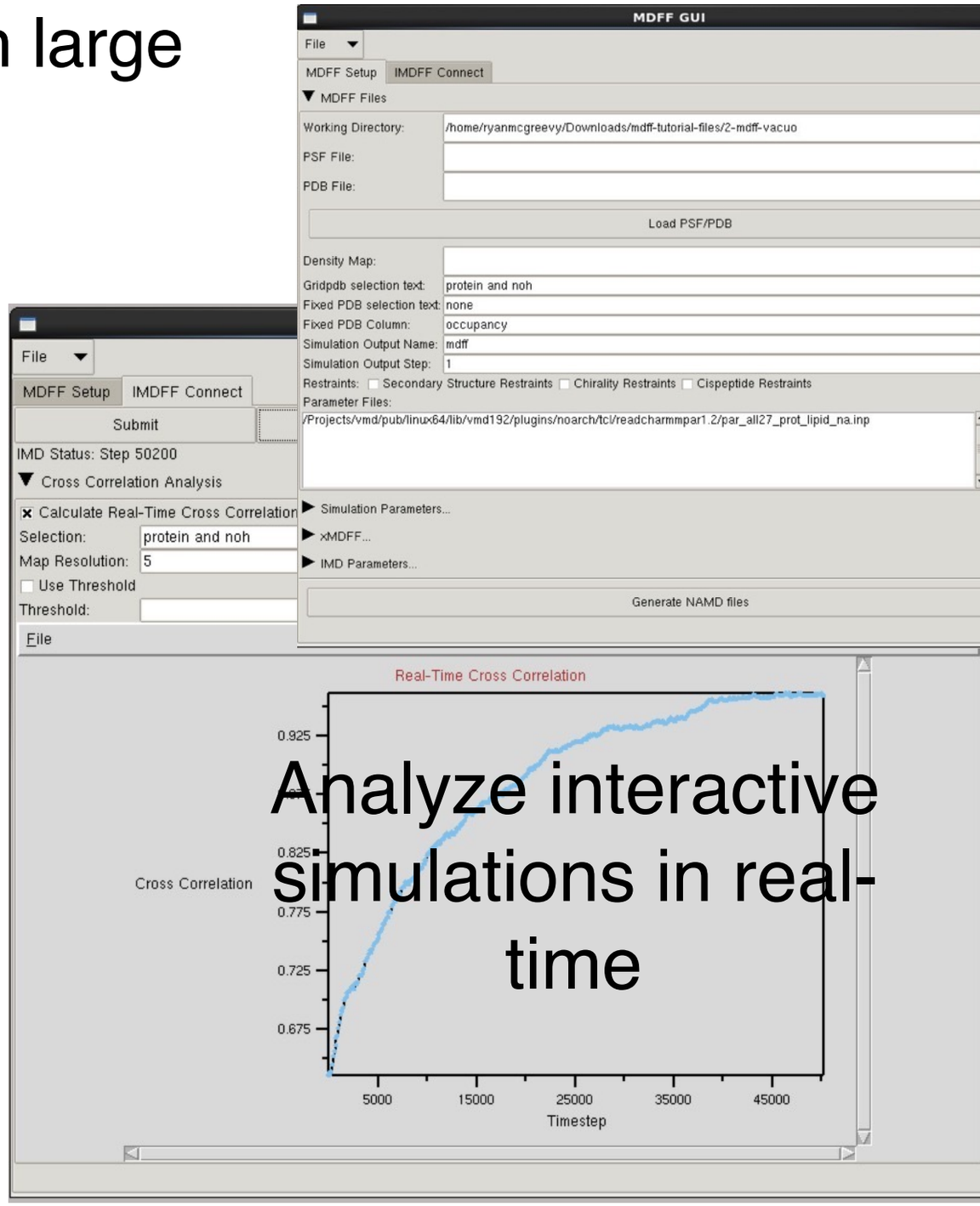
Interactive Modeling with MDFF GUI

- Apply forces to manually manipulate structure into the density
- Useful for difficult to fit structures with large conformational changes



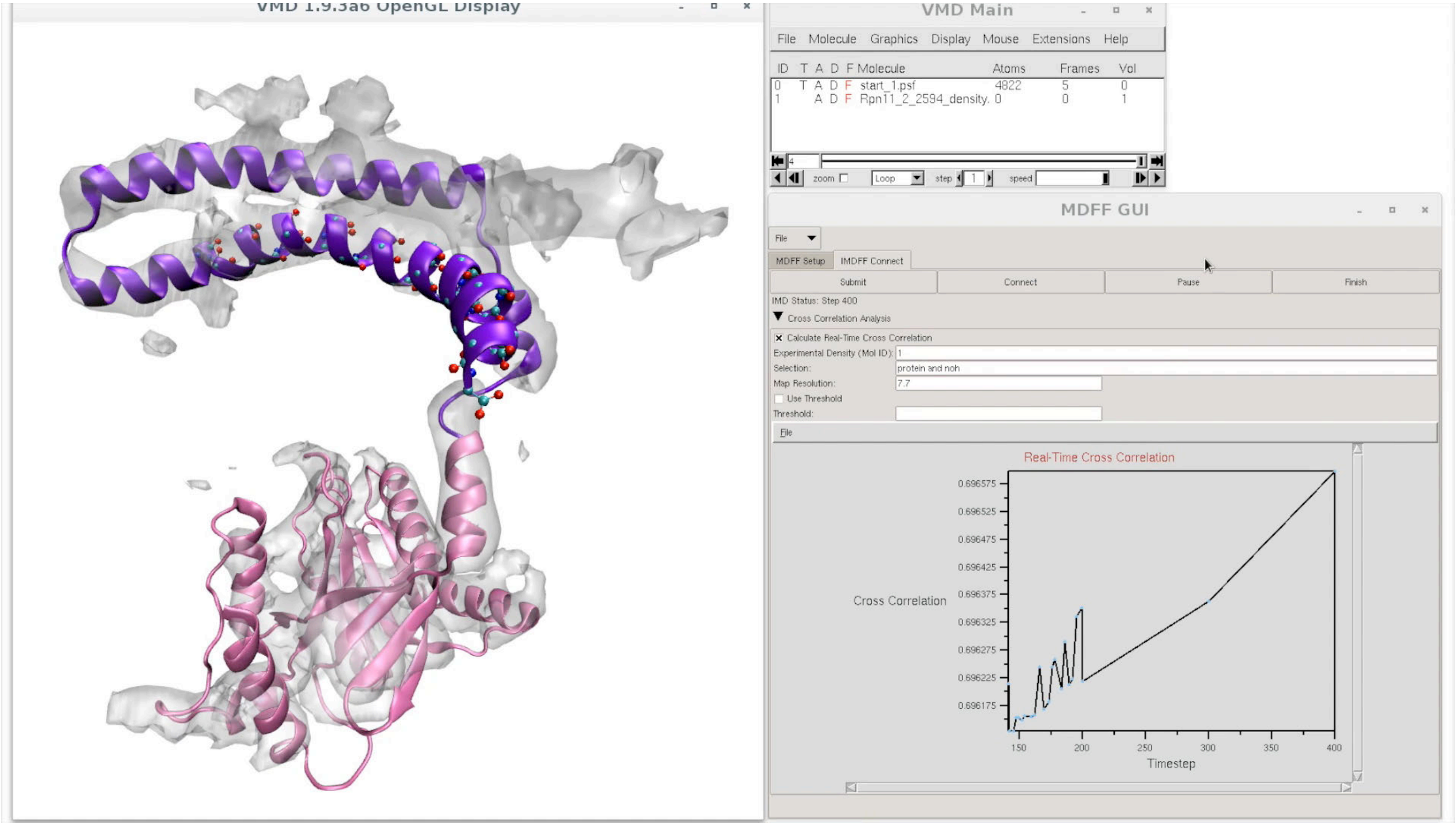
New MDFF GUI in VMD 1.9.3

Set up and run interactive (or traditional) MDFF/xMDFF simulations



Analyze interactive simulations in real-time

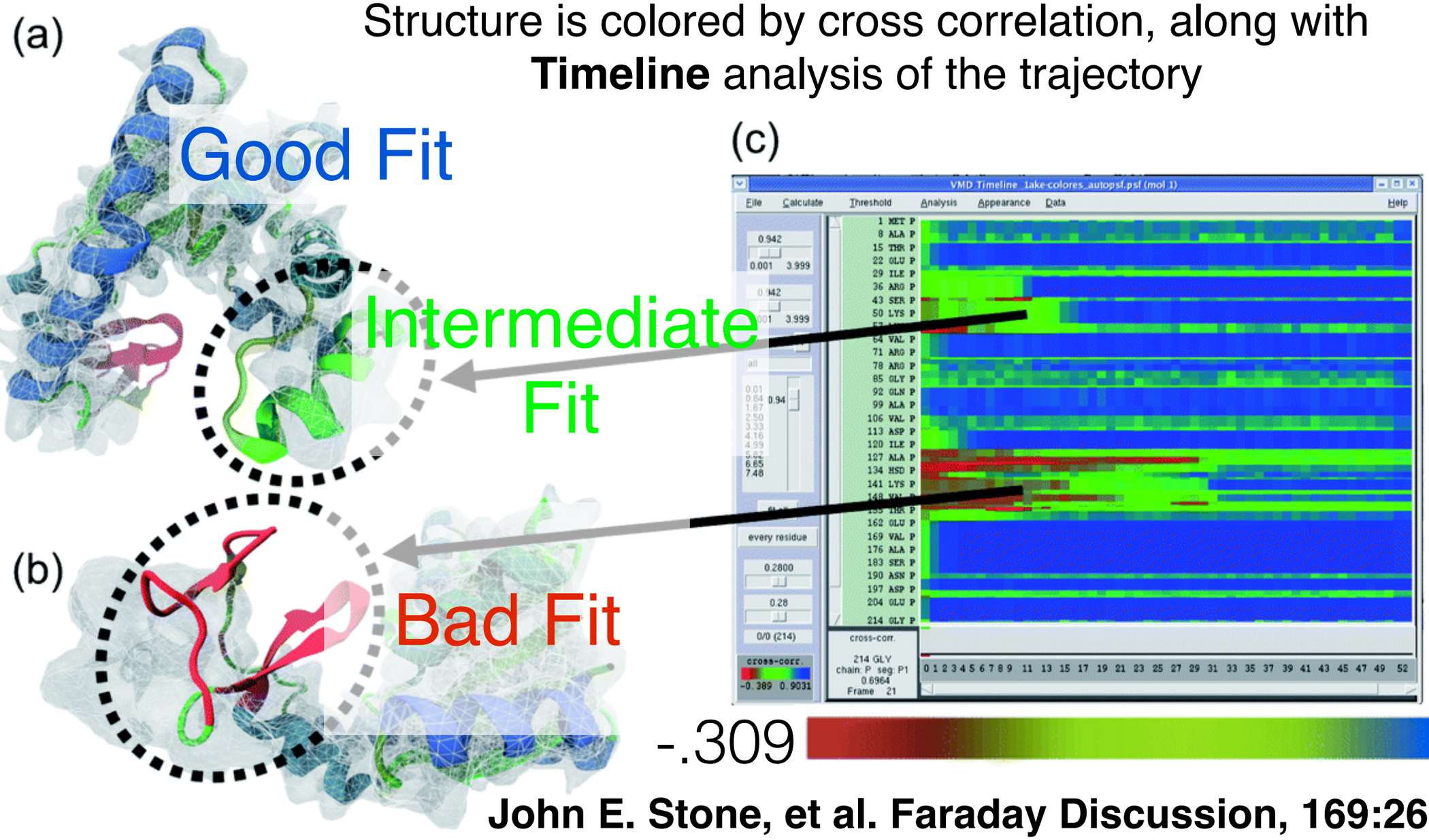
Interactive Modeling Integrates User Expertise



Analyzing MDFF Model Quality: **Local Cross Correlation**

- Local cross correlation indicates quality of fit of specific regions across the entire structure
- New parallel CPU and GPU algorithms provide significant speed up (**25-50x speedup over Chimera**), allowing for fast computation along fitting trajectories

Structure is colored by cross correlation, along with **Timeline** analysis of the trajectory



John E. Stone, et al. Faraday Discussion, 169:265-283, 2014

MDFF on the Cloud Costs Less than a Cup of Coffee

VMD, NAMD, MDFF now available on Amazon Cloud

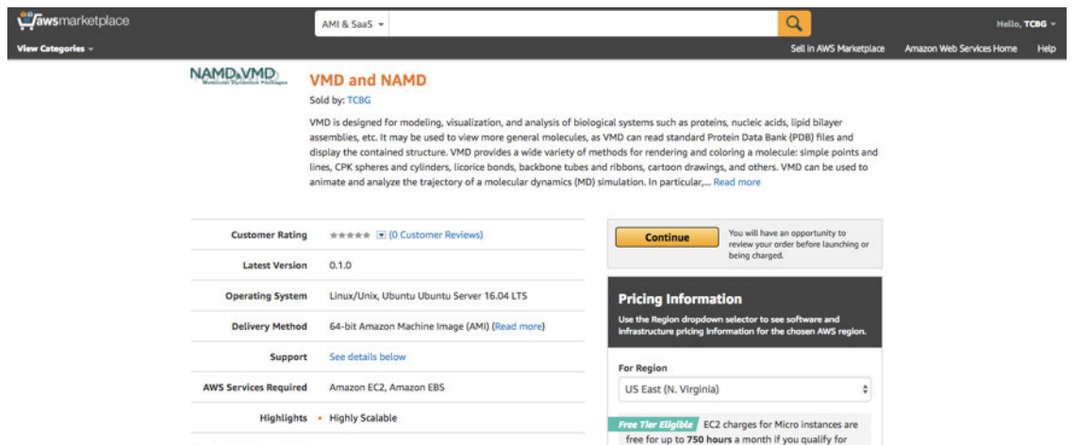
Focus on the scientific challenges of your project without having to worry about local availability and administration of suitable computer hardware and installing or compiling software

Acetyl-CoA Synthase (PDB 1OAO) 11469 atoms, 6 Parallel Replicas

Instance Type	CPU	Performance (ns/day)	Time (hours)	Simulation Cost ($)
c3.8xlarge	30	5.88	0.41	1.68
c3.4xlarge	12	3.33	0.72	0.84
c3.2xlarge	6	1.35	1.78	0.84

Singharoy, *et al*. eLife 2016

Easy, 1-click launch for fast access to MDFF on HPC hardware



MDFF Has a Wide Range of Applications

Over 100 reported MDFF applications:

- ***By intramural Researchers:***

Schweitzer et al. ***PNAS*** (2016): Human 26S Proteasome

Cassidy et al. ***eLife*** (2016): Chemosensory array

Qufei Li et al. ***Nat. Struct. Mol. Biol***. (2014): Structural mechanism of voltage-sensing protein

Zhao et al. ***Nature*** (2013): All-atom structure of HIV-1 capsid

Agirrezabala et al. ***PNAS*** (2012): Ribosome translocation intermediates

- ***By extramural Researchers:***

He et al. ***Nature*** (2016): human pre-initiation complex

Li et al. ***Nature*** (2016): 20S proteasome

Barrio-Garcia et al. ***Nat. Struct. Mol. Biol***. (2016): pre-60S-ribosome remodeling

Gogala et al. ***Nature*** (2014): Ribosome Sec61 complex

Unverdorben et al. ***PNAS*** (2014): 26S proteasome

Bharat et al. ***PNAS*** (2014): Tubular arrays of HIV-1 Gag

Park et al. ***Nature*** (2014)***:*** SecY channel during initiation of protein translocation

Hashem et al. ***Nature*** (2013): *Trypanosoma brucei* ribosome

Becker et al. ***Nature*** (2012): Ribosome recycling complex

Lasker et al. ***PNAS*** (2012): Proteasome

Strunk et al. ***Science*** (2011): Ribosome assembly factors

MDFF/xMDFF Methodological Articles:

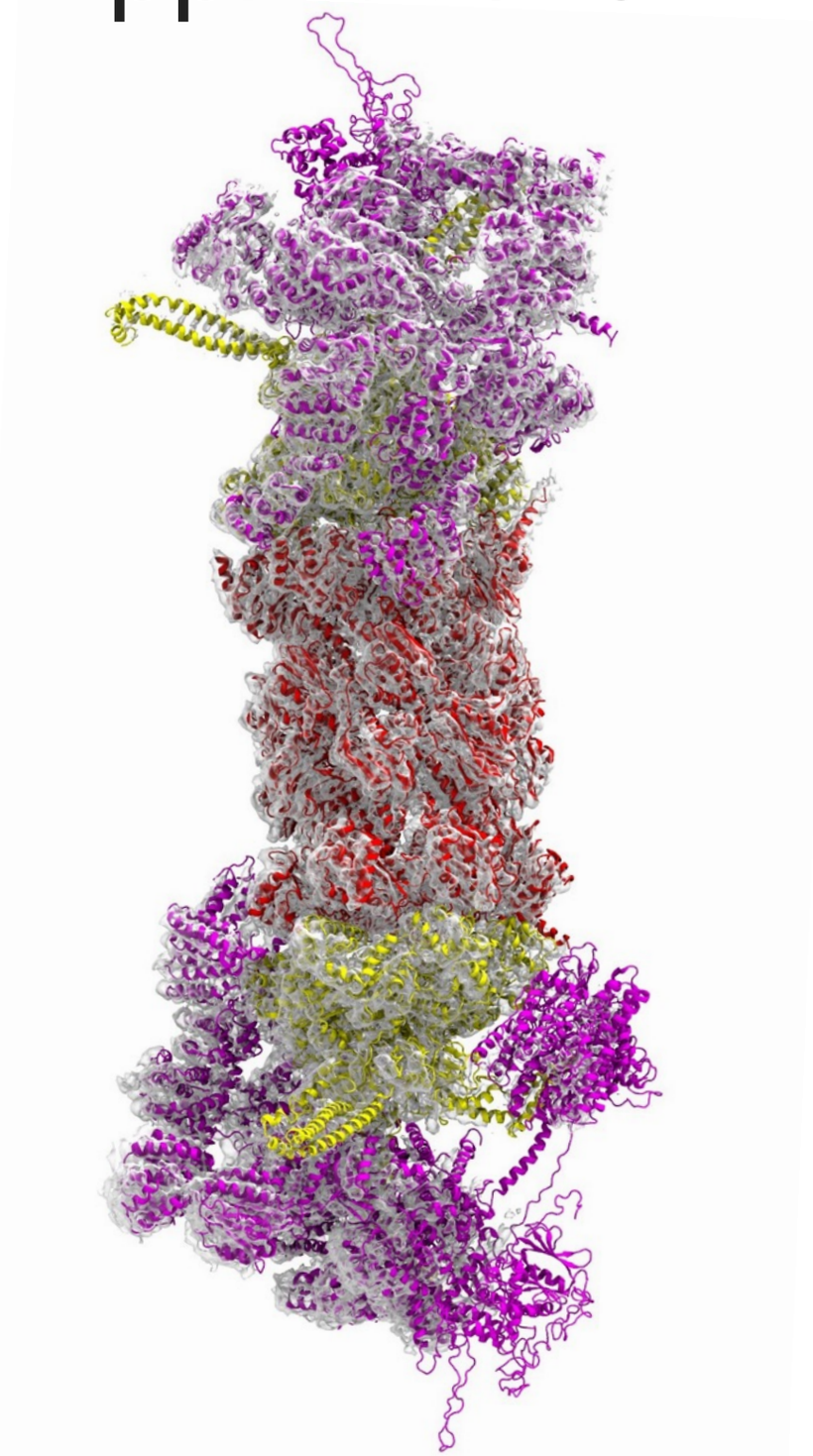
Singharoy*, Teo*, McGreevy*, et al. *eLife* (2016)

McGreevy et al. *Methods* (2016) 100:50-60

McGreevy*, Singharoy*, et al. Acta Crystallographica (2014) D70, 2344-2355

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

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



Full structure of the human 26S Proteasome
Schweitzer et al., ***PNAS.*** 2016

Further Information

Find out more about MDFF including:

- software downloads
- publications
- documentation
- **tutorials**

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