Principles of Molecular Dynamics Flexible Fitting (MDFF)

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Molecular Dynamics Flexible Fitting - Theory

Two terms are added to the MD potential

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

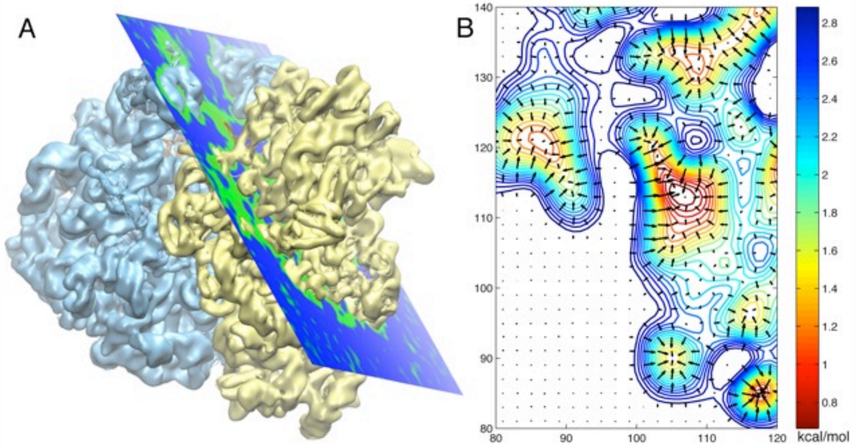
An external potential derived from the EM map is defined on a grid as

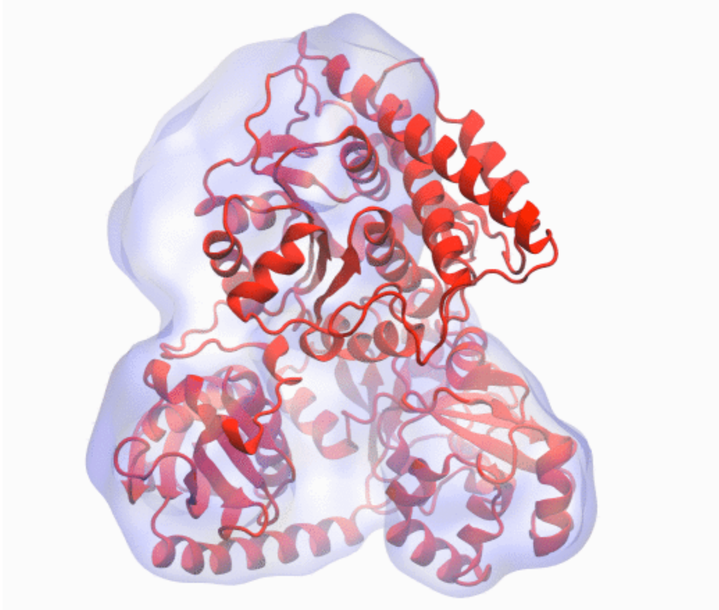
$$U_{EM}(\mathbf{R}) = \sum_j w_j V_{EM}(\mathbf{r}_j)$$

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

A mass-weighted force is then applied to each atom

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



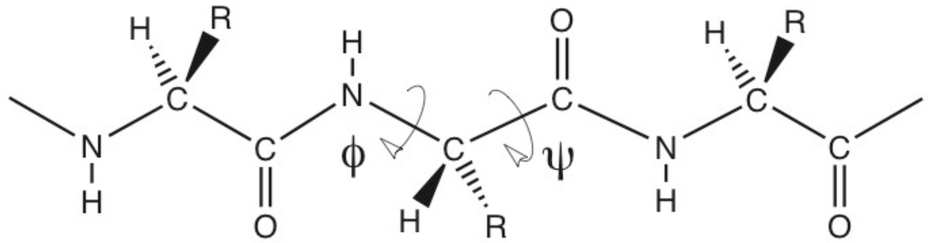


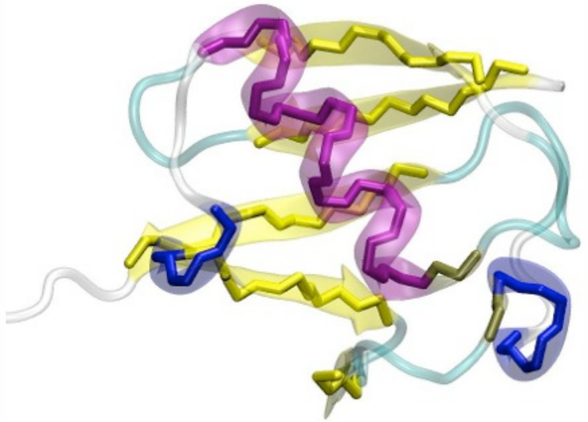
MDFF: Secondary structure restraints

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.





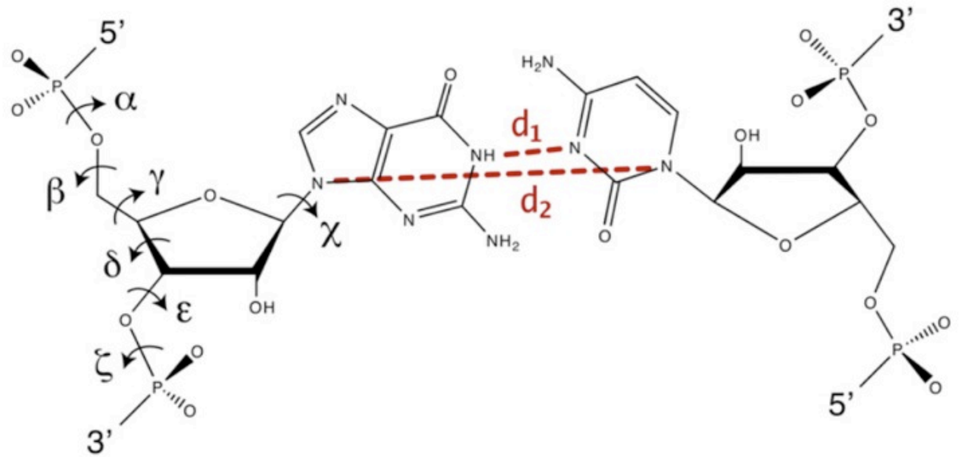
[1] Trabuco et al. *Structure* (2008) 16:673-683.
[2] Trabuco et al. *Methods* (2009) 49:174-180.

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



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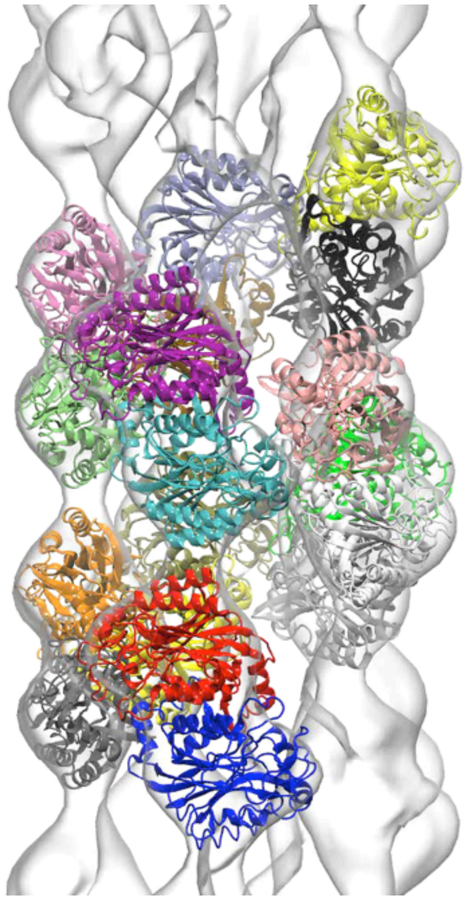
Symmetry restrained MDFF

- Many biological systems have structural symmetry (e.g., microbial nitrilase)
- Include symmetry information to improve MDFF results
- Improve quality of fit for low-resolution data



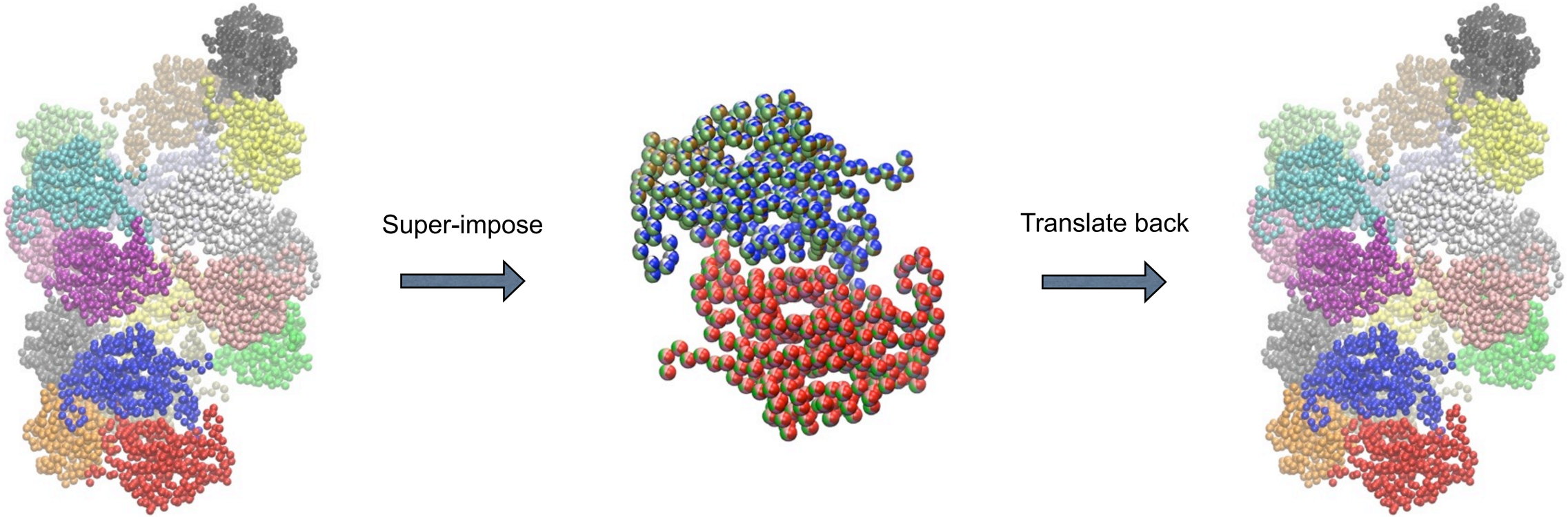
B. pumilus cyanide dihydratase

Collaboration with Trevor Sewell from U. of Cape Town

Chan et al. *Structure* (2011) 19:1211-1218.

Symmetry restrained MDFF

Iterative MDFF process



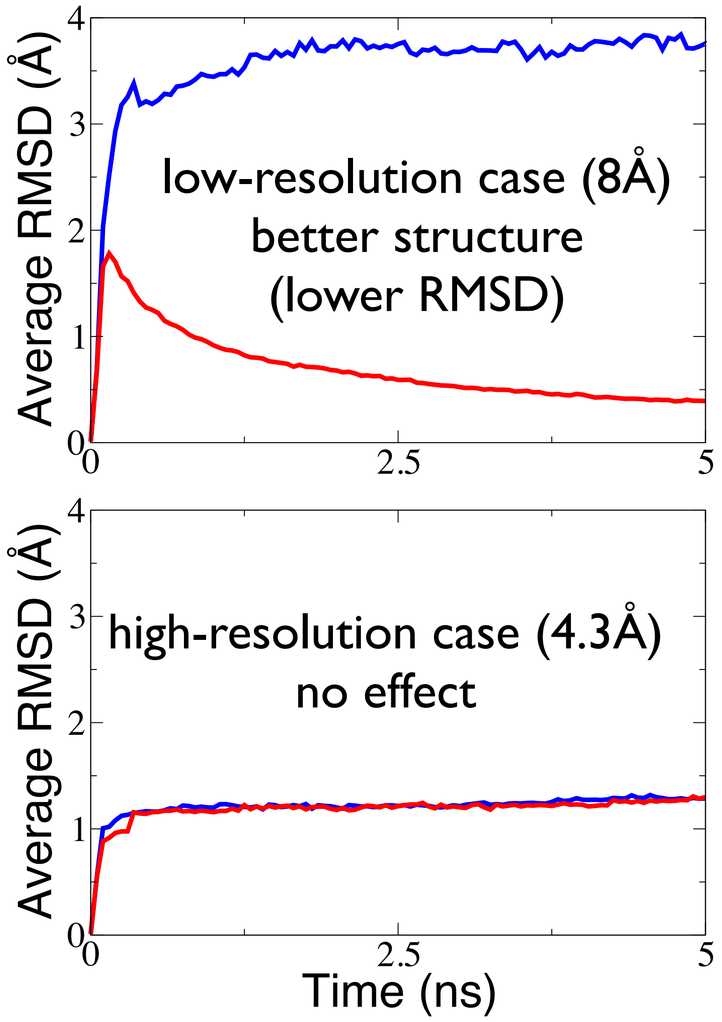
Harmonic restraints

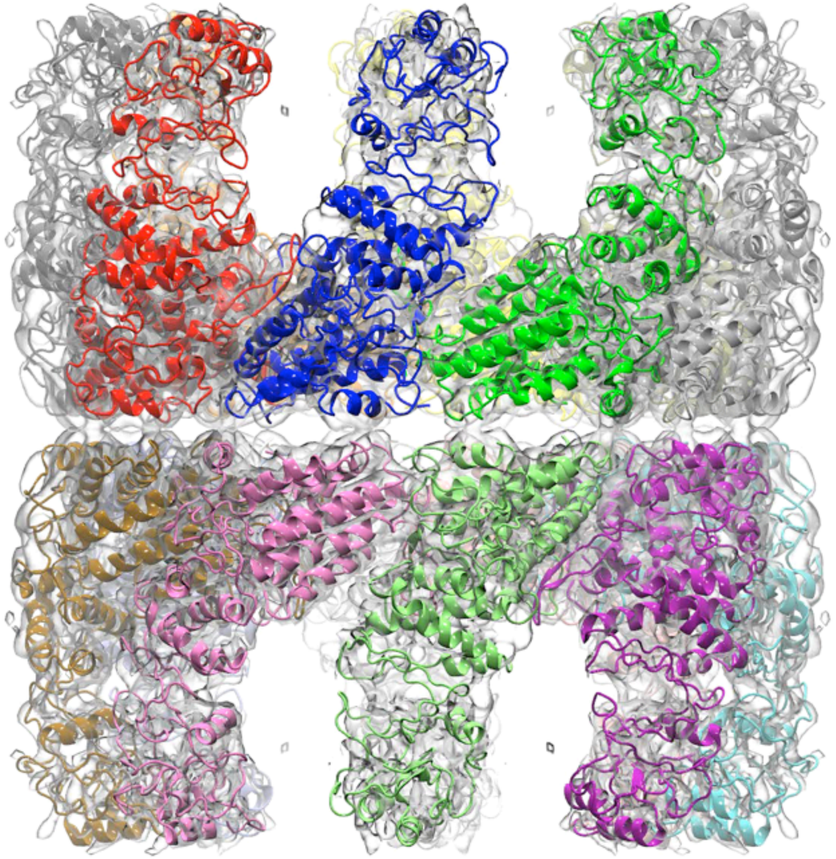
(strength increasing over simulation for convergence)

Chan et al. *Structure* (2011) 19:1211-1218.

Symmetry restrained MDFF - Test Case 1
Improve quality of fit for low-resolution data

Blue: without symmetry restraints
Red: with symmetry restraints





Archaeal group II chaperonin from *M. maripaludis* (Mm-cpn)
8-fold rotational + 2 fold reflection symmetry

homology model (based on PDB 3LOS) fitted into EM map (EMDB 5140)

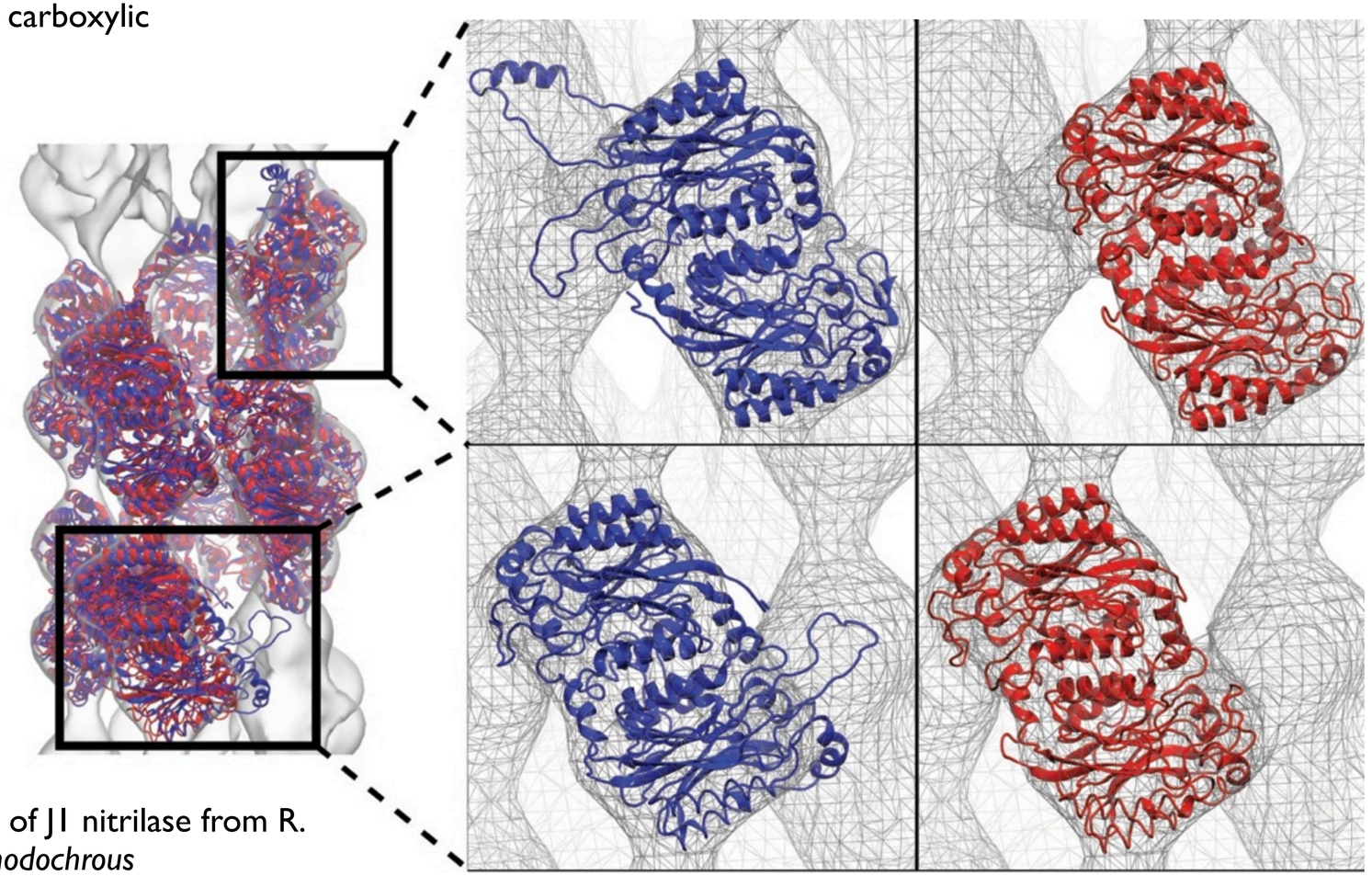
Chan et al. *Structure* (2011) 19:1211-1218.

Symmetry restrained MDFF - Test Case 2
Prevent “edge distortion effect”

nitrilase in bacteria convert nitriles to carboxylic acids and ammonia

helical symmetry

Finite-size Simulation
(9 dimers)



Fitted models of J1 nitrilase from R. *rhodochrous*

homology model and EM map (EMD 1313) from collaborator T. Sewell, U. of Cape Town

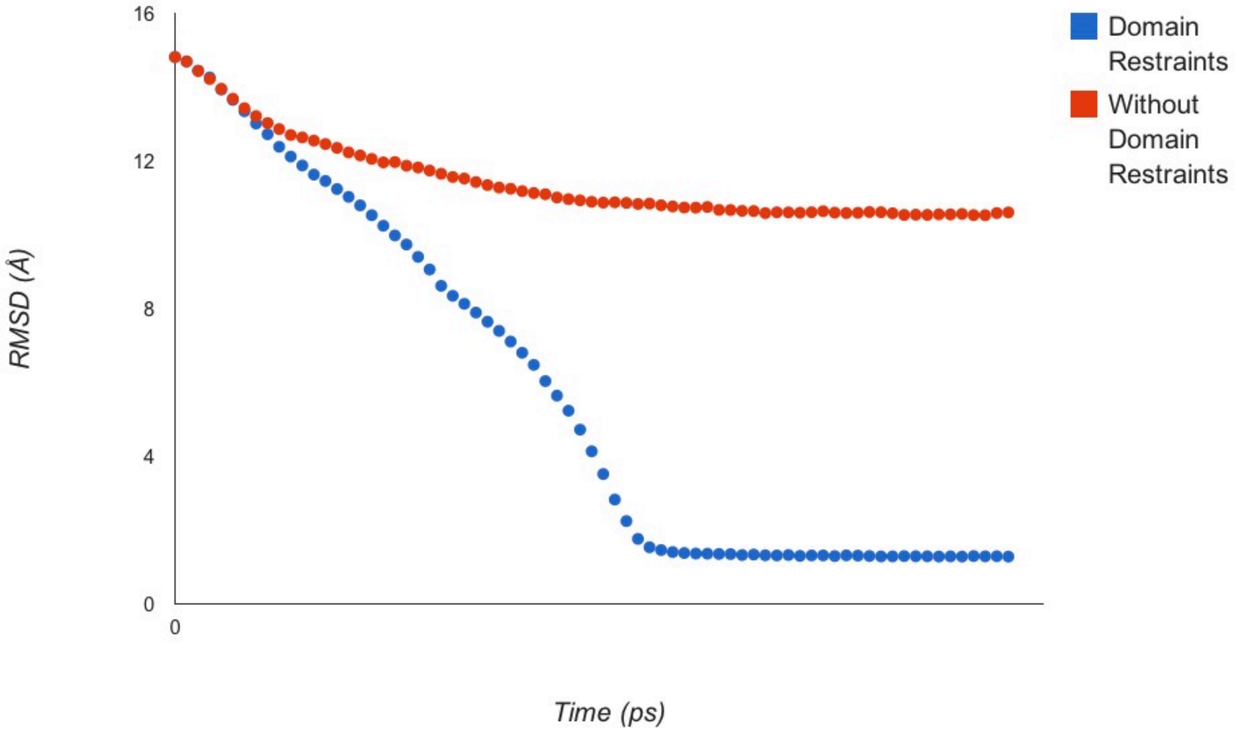
Without Symmetry Restraints

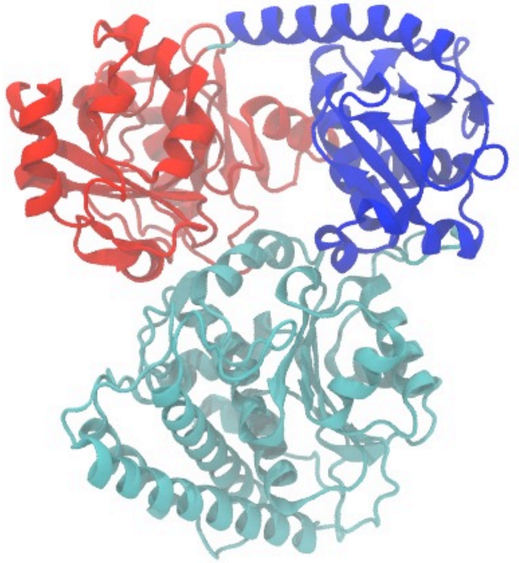
With Symmetry Restraints

Chan et al. *Structure* (2011) 19:1211-1218.

Domain restrained MDFF

Use Targeted MD (TMD) feature of NAMD to restrain non-overlapping groups of atoms to maintain rigid domains

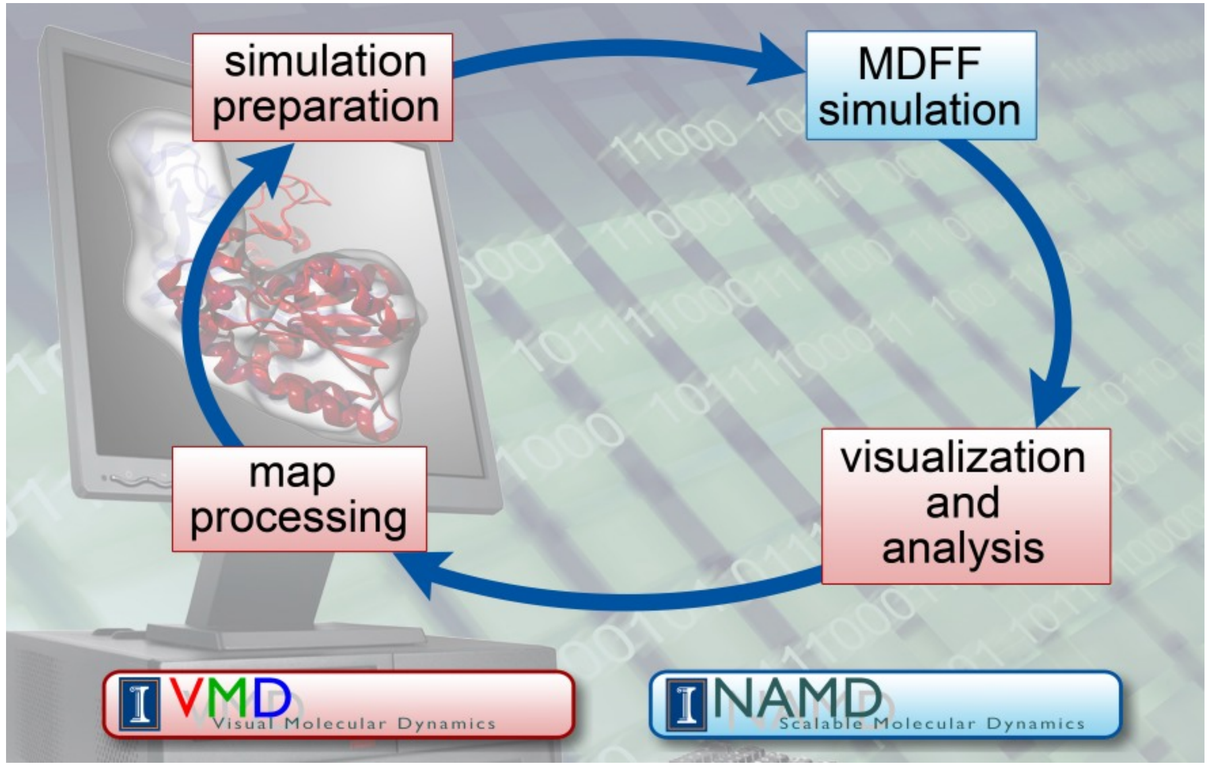




Acetyl CoA Synthase with two domains (red and blue) separately restrained

MDFF Software Suite

NAMD and VMD used together to run MDFF



NAMD Features

- gridforces
- extraBonds
- Implicit Solvent
- Targeted MD (TMD)
- Interactive MD (IMD)
- Replica Exchange

VMD Features

- mdff
- volutil
- ssrestraints
- cispeptide
- chirality
- volmap

...and every other NAMD/VMD feature!

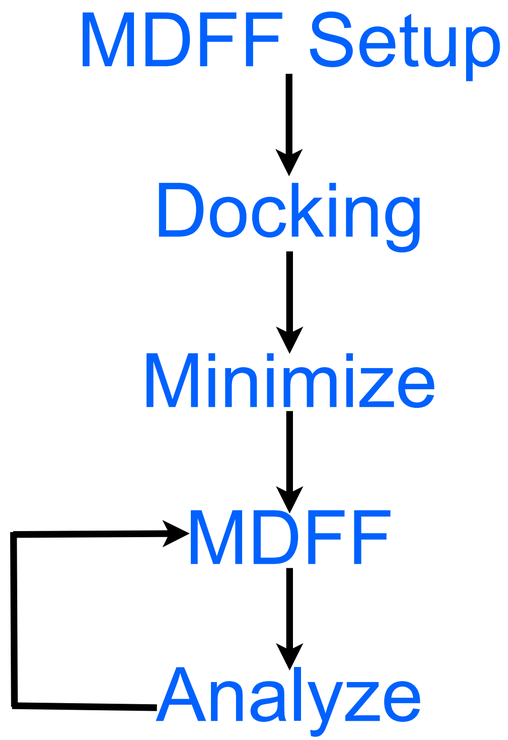
MDFF Required Files and Basic Protocol

What you need:

- Initial Structure (PDB + PSF)
- Target Density (converted to MDFF potential)
- Restraint Files (ssrestraints, chirality, cispeptide)
- “Gridpdb” with per-atom scaling factor

What you do:

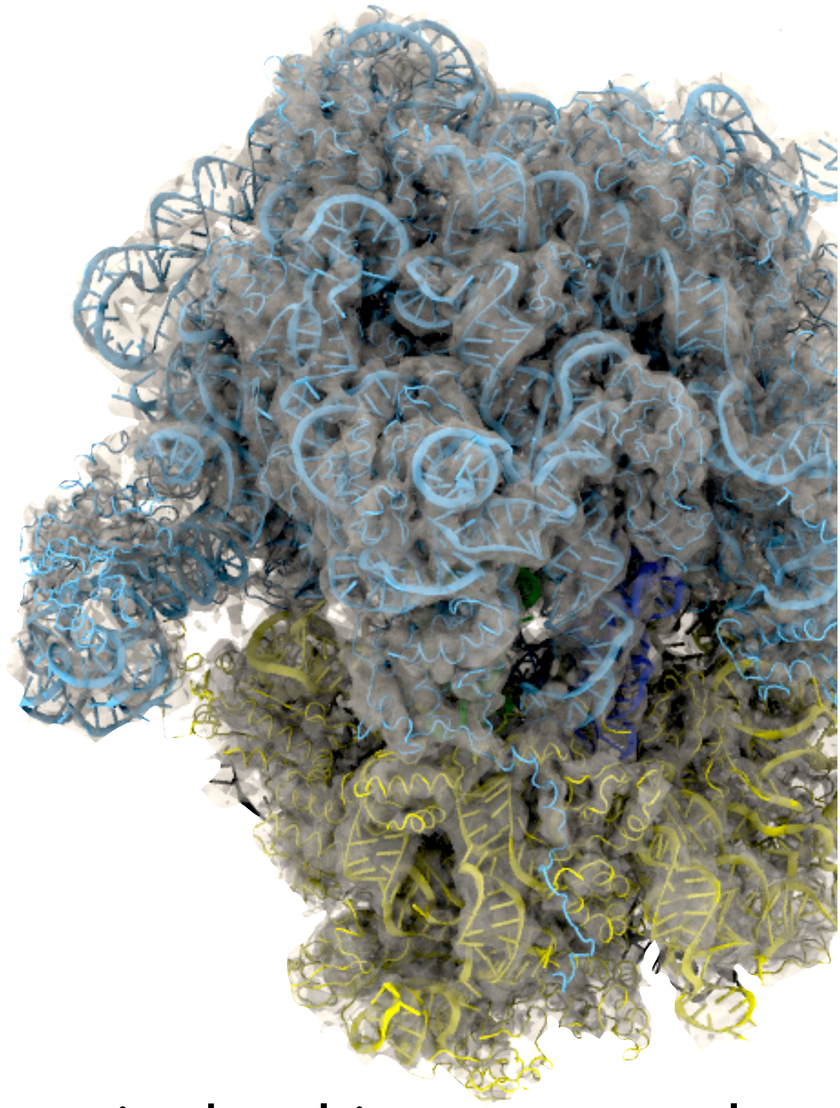
1. Generate all required files (VMD)
2. Rigid body dock structure to density (Situs)
3. Minimization (NAMD)
4. Set appropriate parameters and run MDFF (NAMD)
5. Analyze results (i.e. cross correlation)
6. Adjust parameters and continue MD as needed



MDFF Protocol is Adaptable

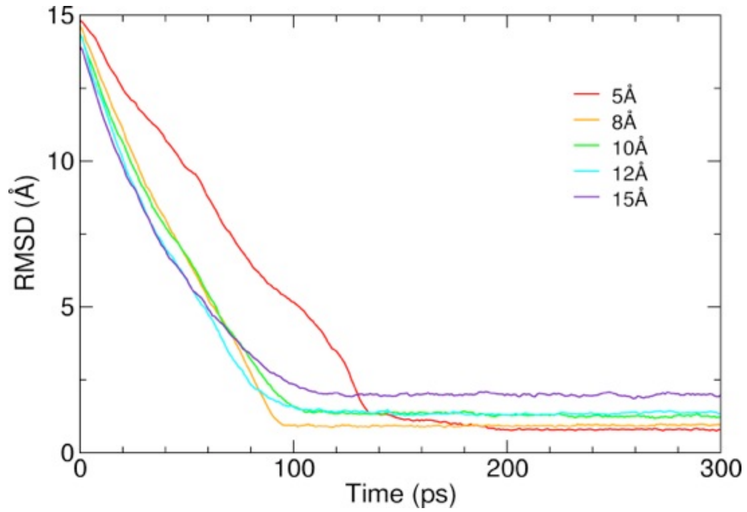
Parameters to change as needed

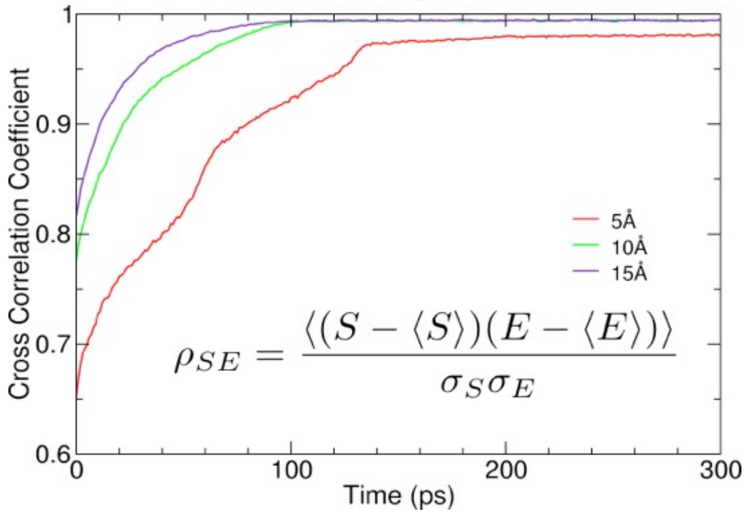
- Per-atom weights
- Global scaling factor
- Temperature
- Map smoothing (low pass filtering)
- Restraint scaling
- Fixed atoms
- Delete density/stepwise fitting

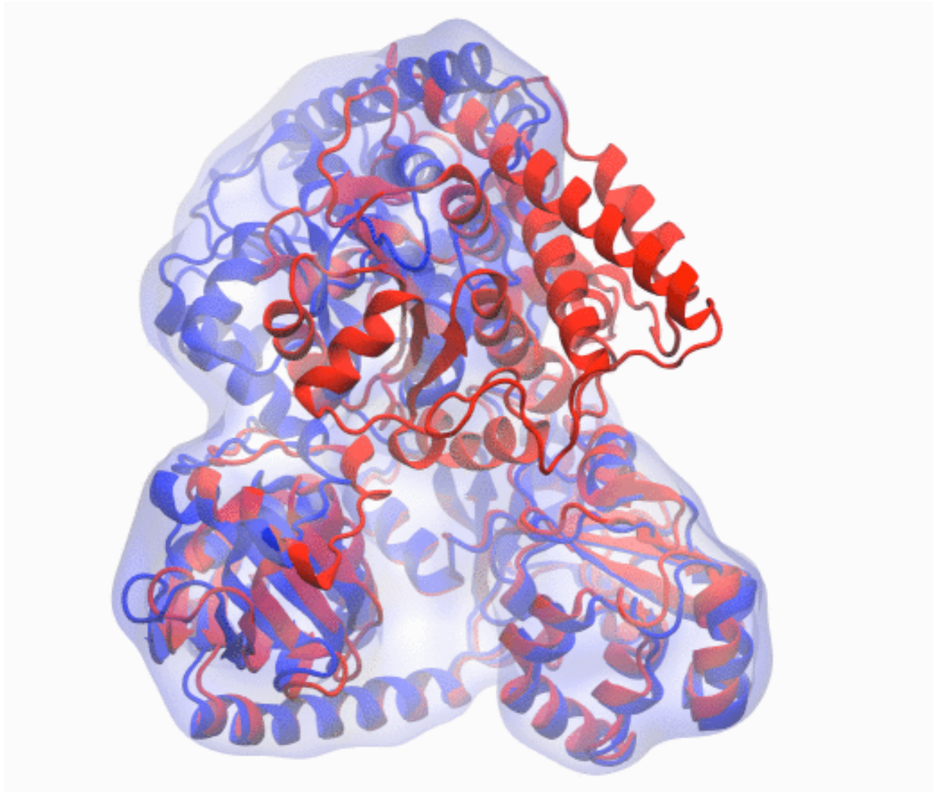


MDFF of ribosome required multi-step protocol to separately fit protein, RNA, and ligands

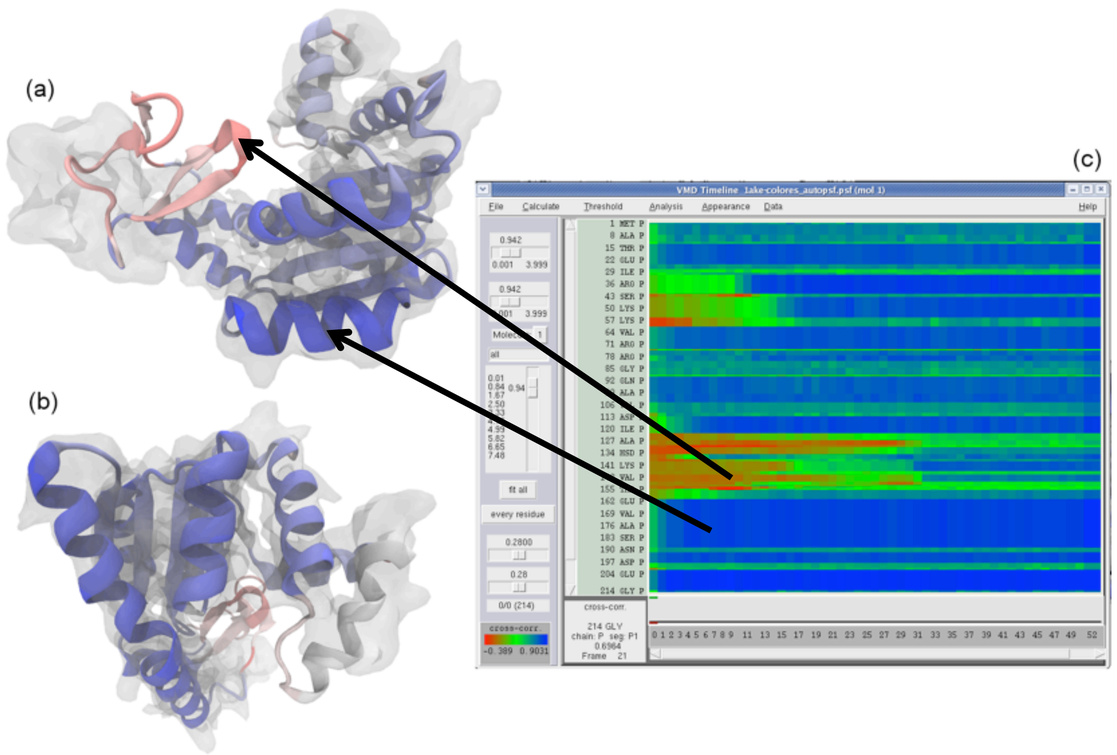
Analysis of MDFF





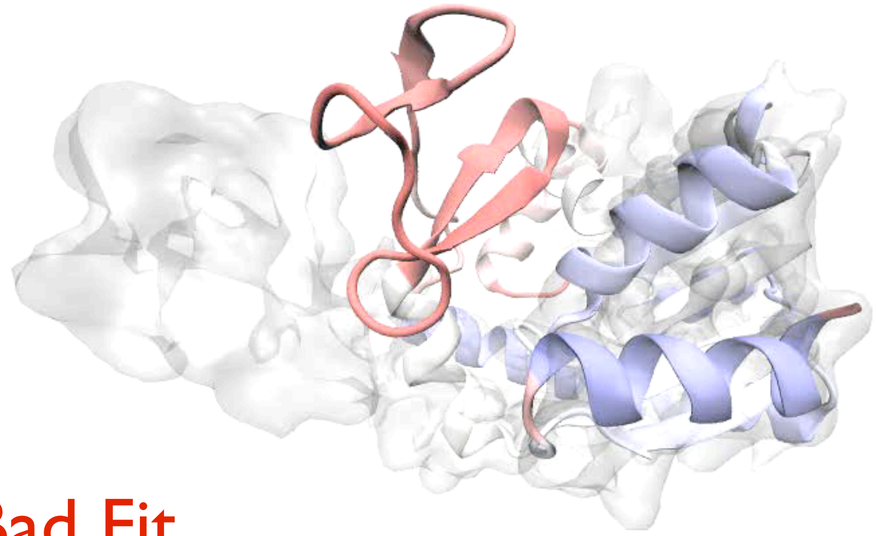


Localized Cross Correlation Provides Good Indicator of Quality of Fit



Quality of fit for MDFF simulation where structure is colored by cross correlation (a,b), along with Timeline analysis (c)

New parallel CPU and GPU algorithms provide significant speed up, allowing the cross correlation to be computed in real-time during Interactive MDFF simulations



Bad Fit

Good Fit

Instant feedback about quality of fit can guide IMD user when manipulating the protein for an improved fit