Simulating protein flexibility with the Backrub motion

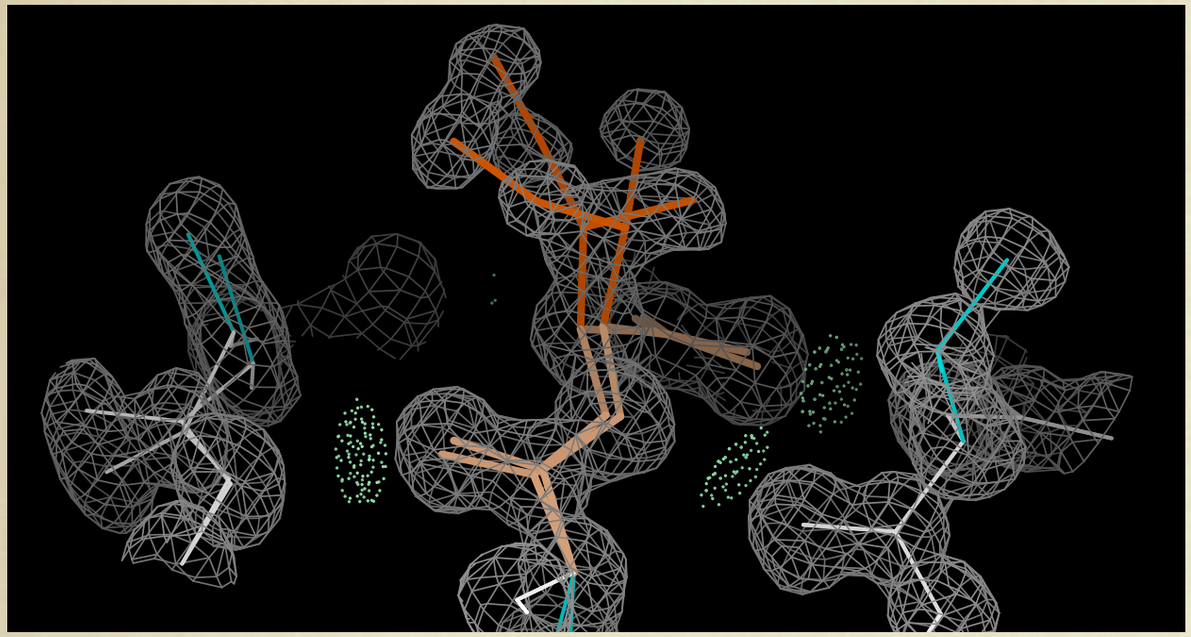
Colin A. Smith
UCSF Kortemme & Jacobson Labs
Wednesday, July 23
RosettaCon 2008

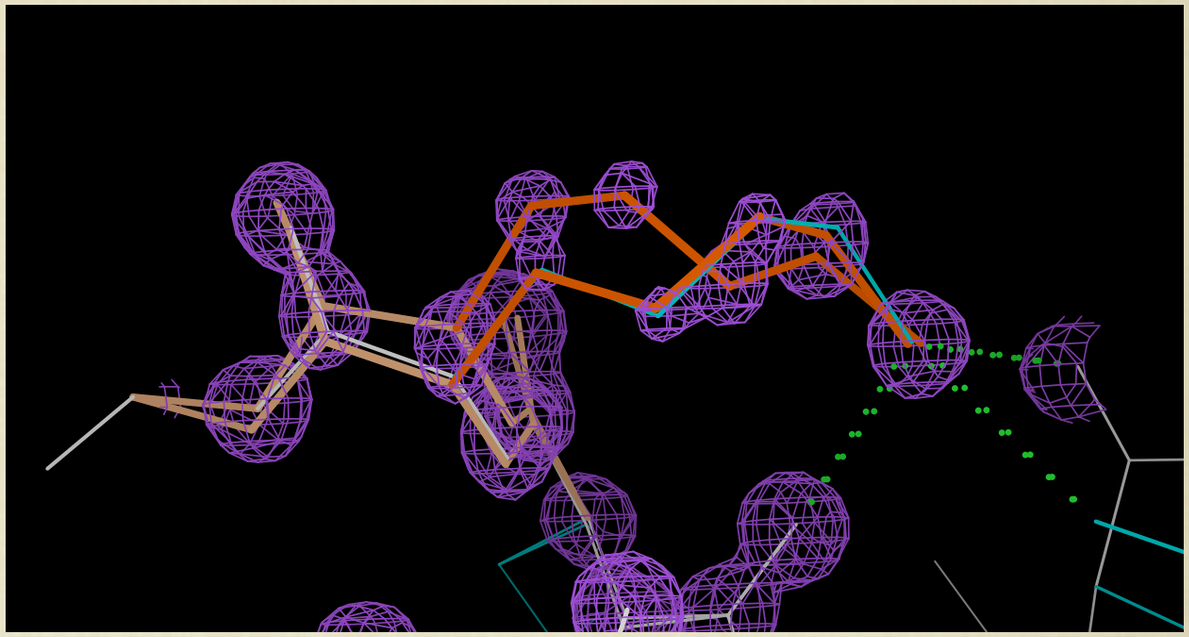
Overview

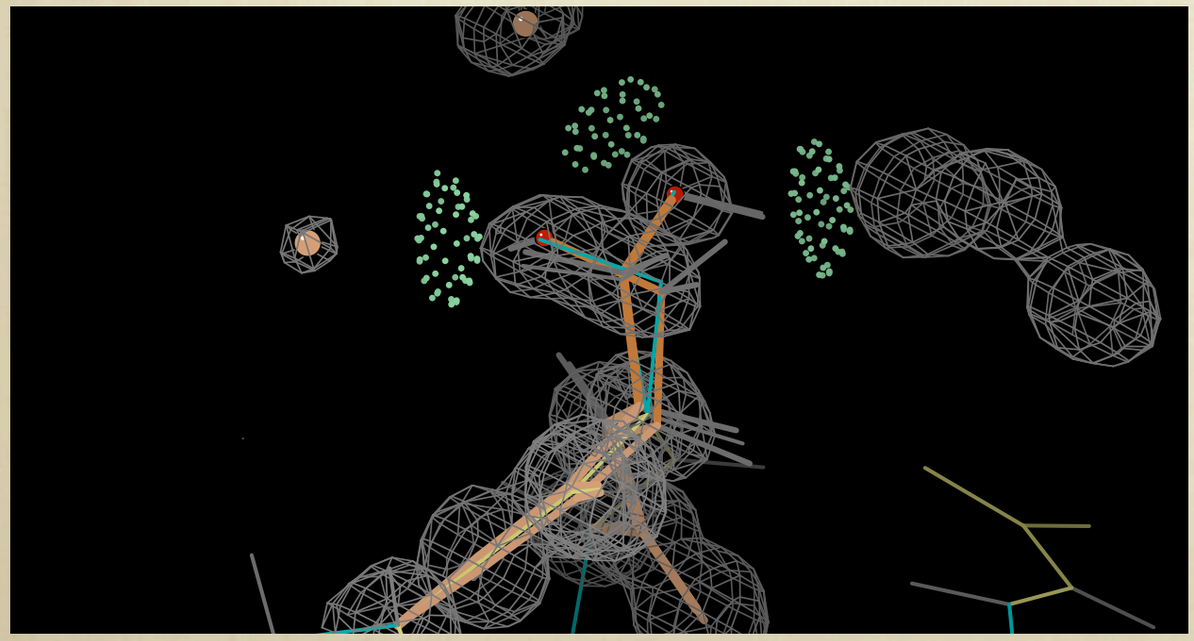
- Background
- New Applications
- Miniaturization

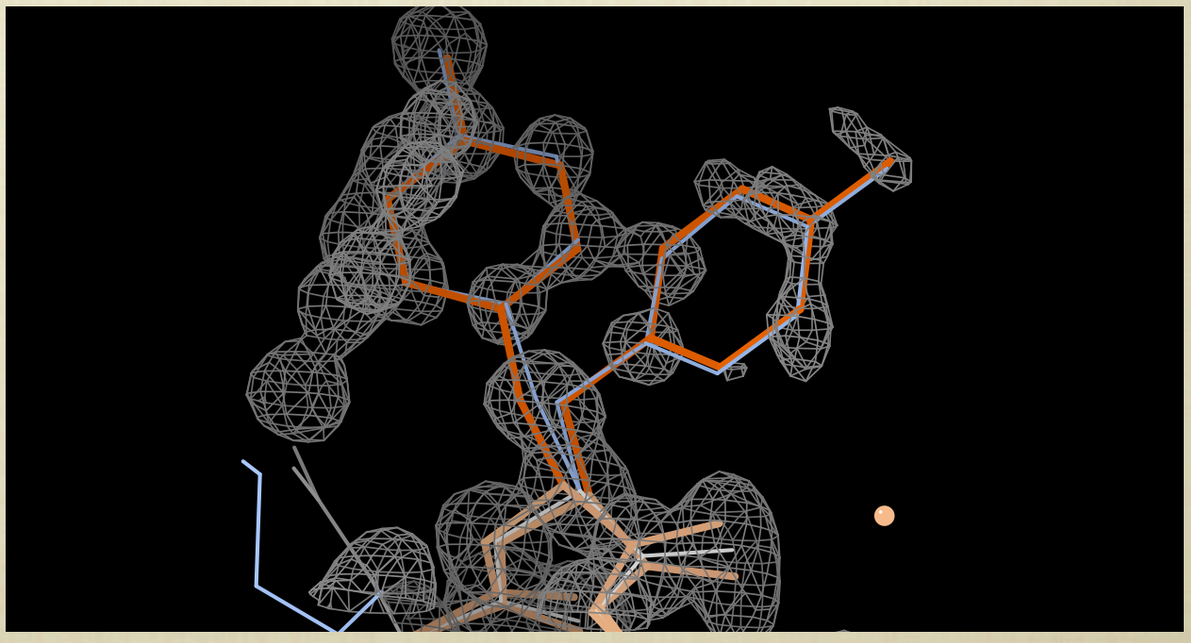
Structure *14*, 265–274, February 2006 DOI 10.1016/j.str.2005.10.007

The Backrub Motion: How Protein Backbone Shrugs When a Sidechain Dances



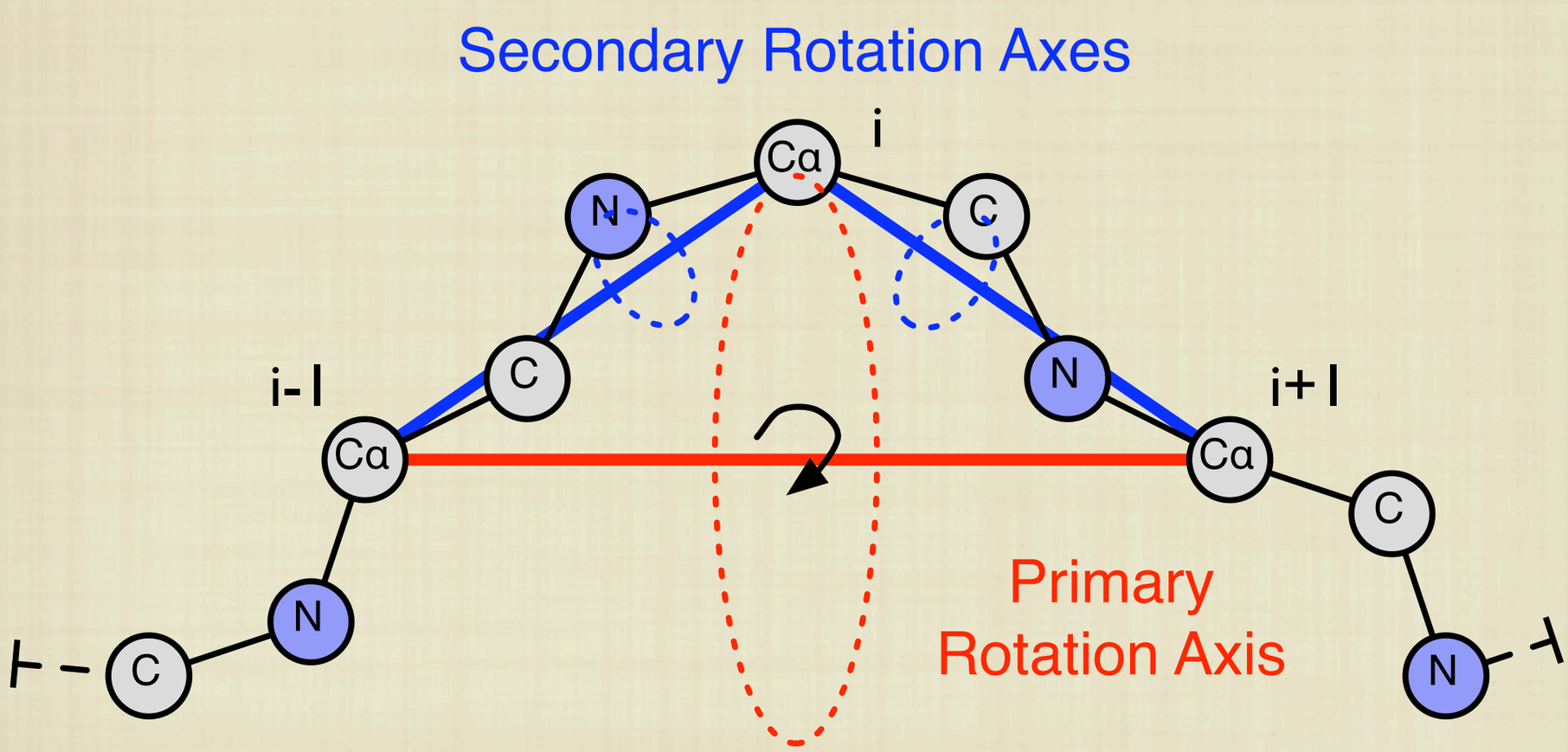






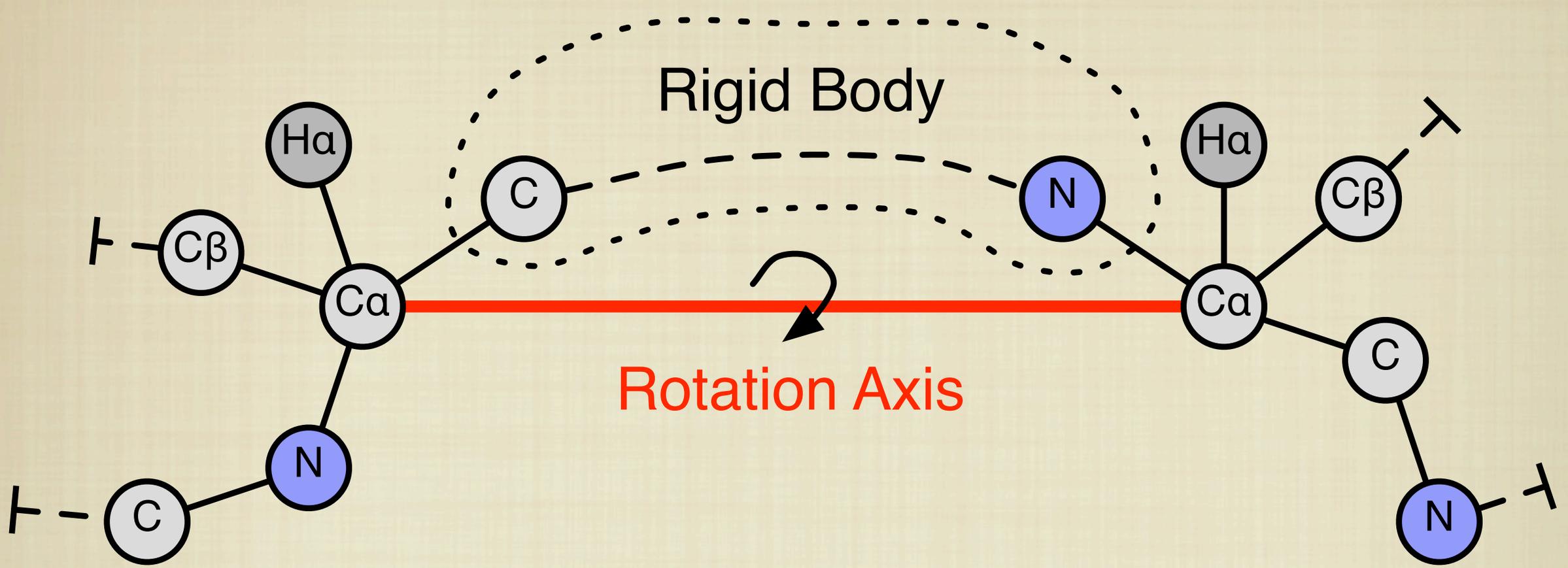
Structure *14*, 265–274, February 2006 DOI 10.1016/j.str.2005.10.007

The Backrub Motion: How Protein Backbone Shrugs When a Sidechain Dances



- Rotation around an axis defined by 2 Cα atoms (i-1, i+1)
- Compensating rotation around (i-1, i) and (i, i+1) axes

Generalization



A generalized backrub move is a continuous rotation around a single axis

Predicting Point Mutant Sidechains

Pre-Mutation PDB

Repack 6 Å

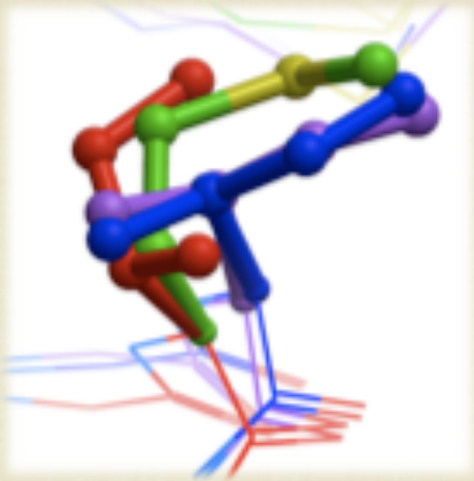
10K Moves

Fixed BB Prediction

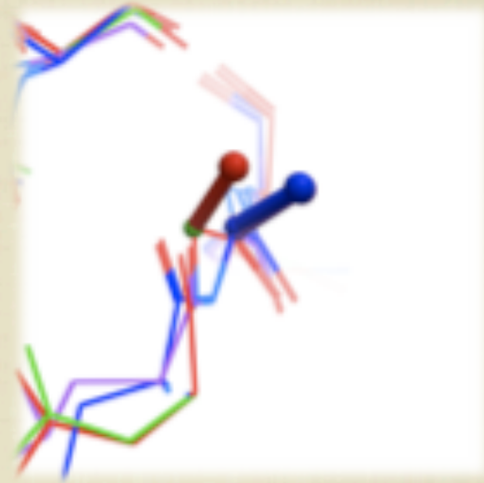
Backrub Prediction

Post-Mutation PDB

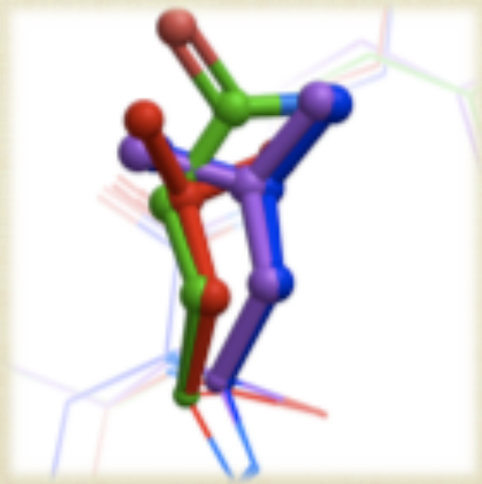
2,023 Pairs of Structures



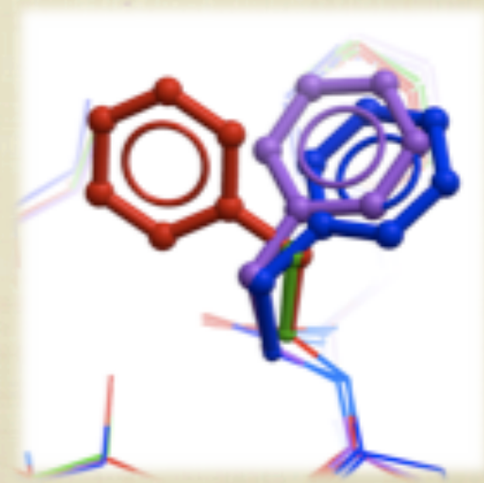
1CV1:A M111I



1CWU:B G138A

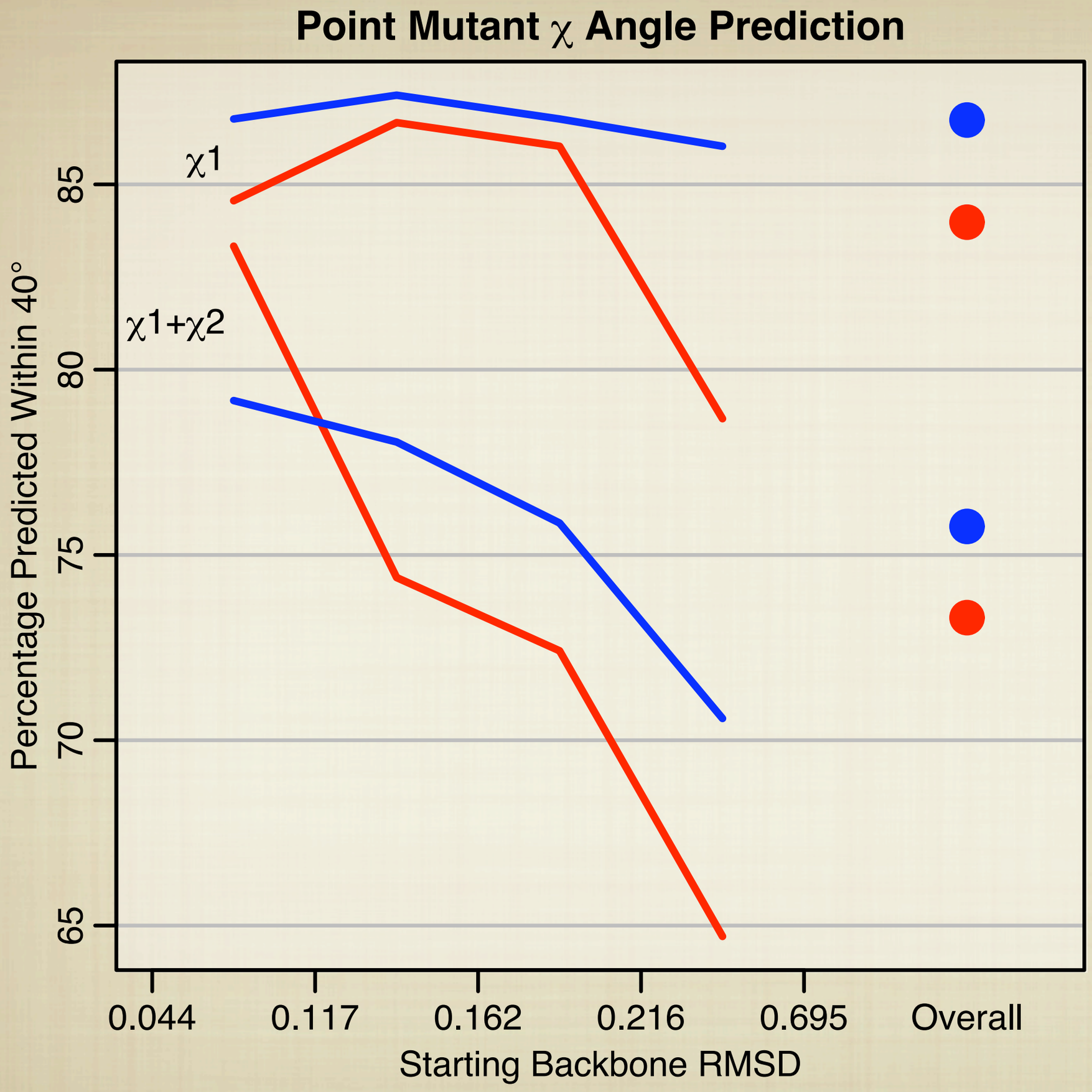


1LVE:A Q89L



2HEC:A A56F

Smith, C. A., & Kortemme, T. (2008) *J Mol Biol* 380, 742-756.



Backrub Prediction

Fixed BB Prediction

SASA < 5%

χ1: 543
χ1 + χ2: 326

Smith, C. A., & Kortemme, T. (2008) *J Mol Biol* 380, 742-756.

Triosephosphate isomerase loop 6 Simulations

- 11 residue loop that maintains the same internal conformation in open and closed states

- Reason: Exclude waters and avoid toxic byproducts

- Several residues move over 7 Å

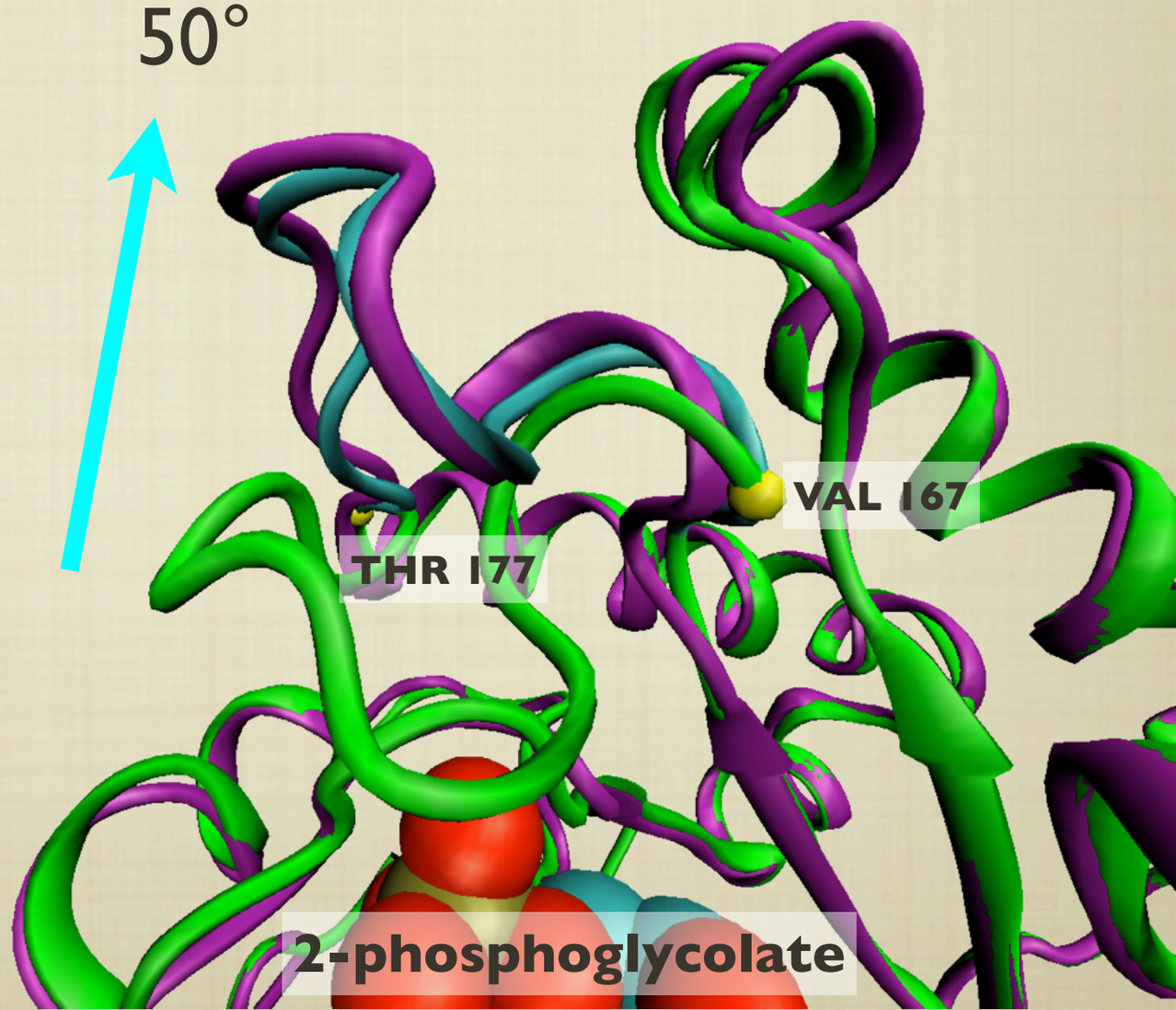
- Opening/closing on the 100 μs–ms time scale

Forced Open

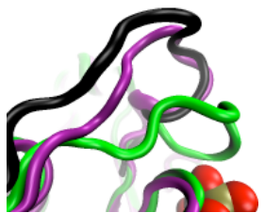
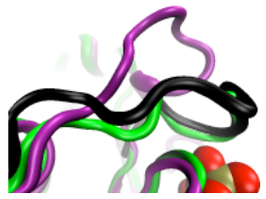
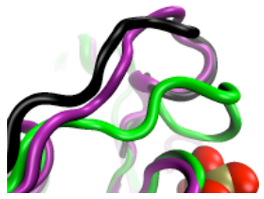
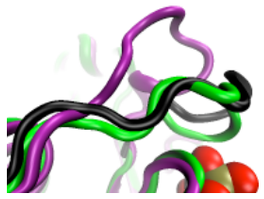
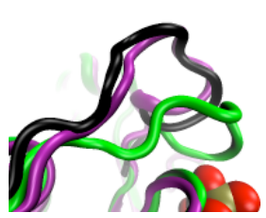
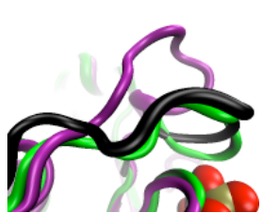
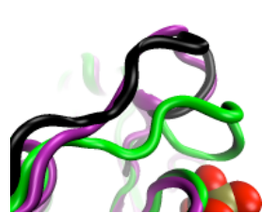
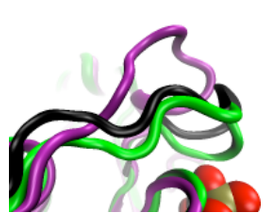
Open (1YPI) **Closed (2YPI)**

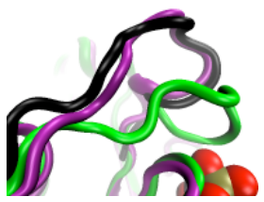
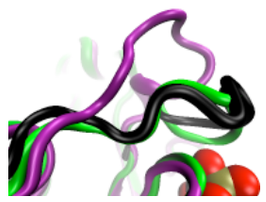
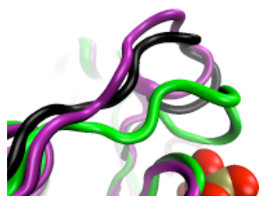
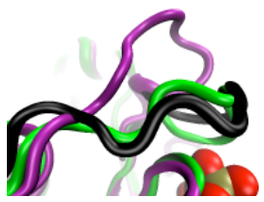
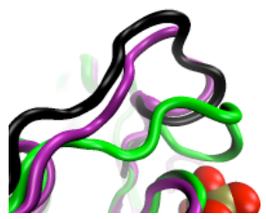
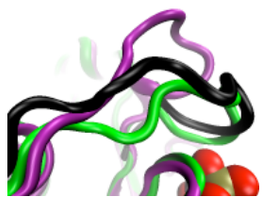
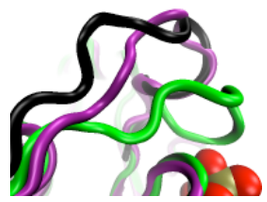
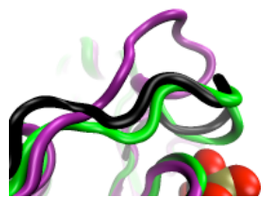
V167-T177 Rotated 50°

Cα RMSD from Open: 4.7 → 1.1



Triosephosphate isomerase loop 6 Simulations

	1	2	3	4	5	6	7	8
								
$RMSD_{open}$	2.49	4.90	1.74	4.51	1.76	4.75	1.73	3.71
$RMSD_{closed}$	5.12	1.73	4.35	1.66	4.19	2.36	4.71	1.68
Difference	2.64	-3.17	2.61	-2.84	2.42	-2.39	2.97	-2.03

	9	10	11	12	13	14	15	16
								
$RMSD_{open}$	1.57	5.02	1.77	5.02	2.20	4.39	1.96	4.14
$RMSD_{closed}$	4.34	1.74	3.50	2.04	4.22	2.22	4.85	1.38
Difference	2.77	-3.28	1.73	-2.99	2.01	-2.17	2.89	-2.76

1.5M Step Simulation
Starting from Open Conformation

Smith, C. A., & Kortemme, T. (2008) *J Mol Biol* 380, 742-756.

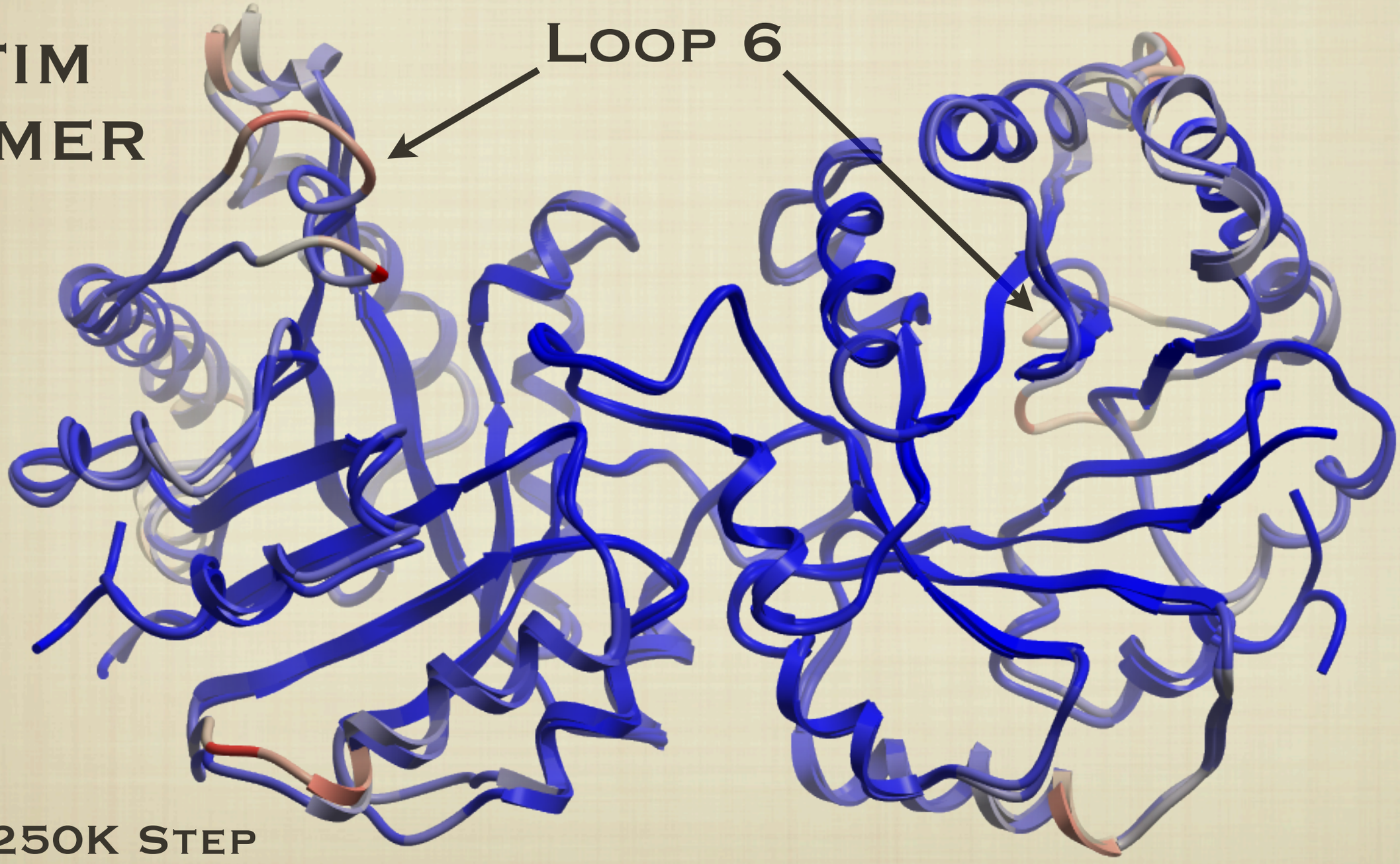
Predicting Backbone Flexibility

Calculated b-factors:

High <-> Low

TIM dimer

Loop 6



20 250K Step Trajectories

Smith, C. A., & Kortemme, T. (2008) *J Mol Biol* 380, 742-756.

Online Help

```
Usage:
bin/backrub.gccrelease [options]
```

Option	Setting	Type	Description
in:path:			
database	~/miniros	(P)	Database file input search paths
in:file:			
s		(F)	Name(s) of single PDB file(s) to process
l		(F)	File(s) containing list(s) of PDB files to process
in:			
ignore_unrec...	false	B	Do not abort if unknown residues are in PDB file
out:			
nstruct	1	I	Number of times to process each input PDB
packing:			
resfile	resfile	F	name of the resfile
backrub:			
pivot_residues		(I)	residues for which contiguous stretches contain segments (internal residue numbers, defaults to all residues)
pivot_atoms	CA	(S)	main chain atoms usable as pivots
min_atoms	3	I	minimum backrub segment size (atoms)
max_atoms	34	I	maximum backrub segment size (atoms)
ntrials	1000	I	number of Monte Carlo trials to run
sc_prob	0.25	R	probability of making a side chain move
sc_prob_uniform	0.1	R	probability of uniformly sampling chi angles
mc_kt	0.6	R	value of kT for Monte Carlo
mm_bend_weight	1	R	weight of mm_bend bond angle energy term

Continuous Side Chain Sampling

- Rotamer wells are chosen according to the Dunbrack probability
- Chi-angles are sampled from a Gaussian distribution with the Dunbrack std. dev.
- Rare conformations can be sampled through occasional uniform chi-angle sampling
- Proline is not sampled
- Class: `protocols::moves::SidechainMover`

Abagyan, R., & Totrov, M. (1994) *J Mol Biol* 235, 983-1002.

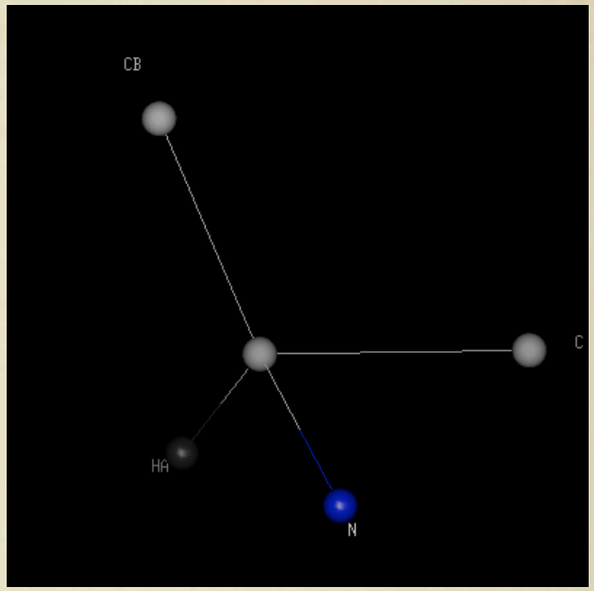
Atom-centric Backrub

- Class: `protocols::moves::BackrubMover`
- Backrubs can be performed between any atom in the atom tree and one of its direct descendants
- Convenience method for backbone segments:

```
BackrubMover::add_mainchain_segments(
    vector1<Size> resnums,
    vector1<string> atomnames,
    Size min_atoms,
    Size max_atoms)
```

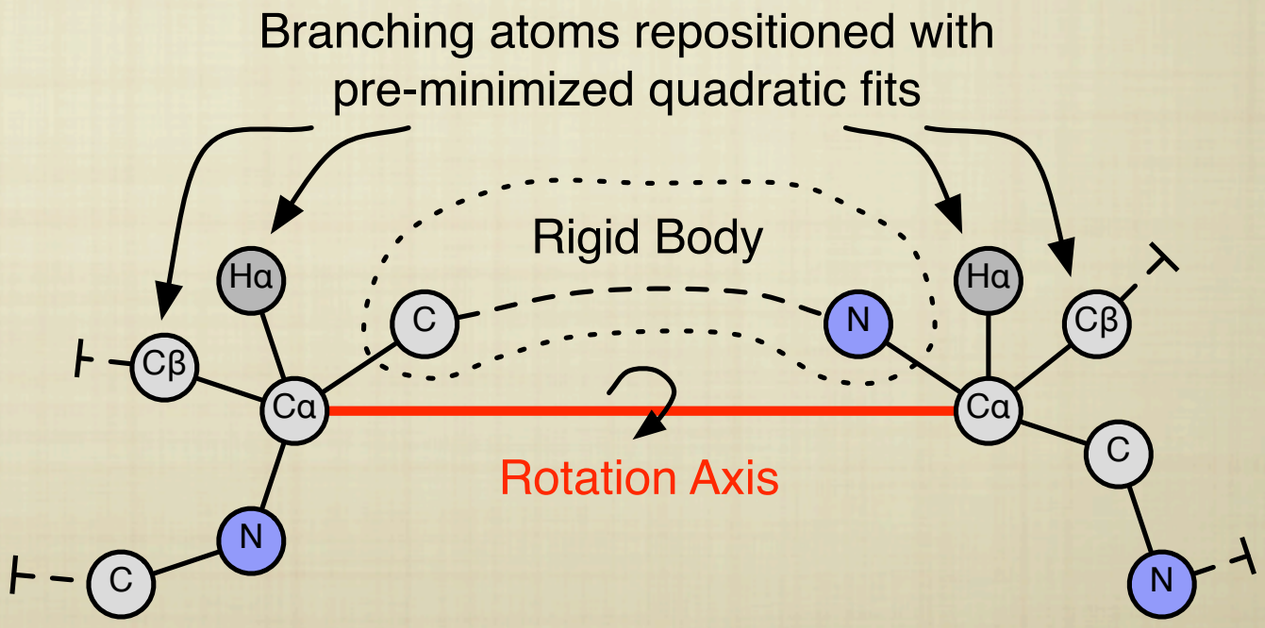
Branch angle optimization

- Class: `protocols::branch_angle::BranchAngleOptimizer`
- Quadratic coefficients determined using an external R script:
  - Run `BranchAngleOptimizer` protocol
  - Run R Script:




```
> source("<mini>/external/R/BranchAngleOptimizer.R")
> process_database("<minirosetta_database>")
```

```
minirosetta_database/
  branch_angle/
    branch_angle_1.txt
    branch_angle_2.txt
    branch_angle_1_undefined.txt
    branch_angle_2_undefined.txt
    branch_angle_1_user.txt
    branch_angle_2_user.txt
```



Caveats

- Performance: Energy evaluation for side chain and backbone sampling not as efficient as it could be

- Sampling in the context of jumps does not necessarily do what you want

- Bond angle potential limited to CHARMM which disagrees with Rosetta/PDB ideal bond angles

- What is room temperature in Rosetta?

Thanks

Kortemme Lab
Tanja
Greg Friedland
Anthony Linares
Elisabeth Humphris
Dan Mandell
Mariana Babor

Jacobson Lab
Matt
Jeremy Nilmeier

Bradley Lab
Phil

Kuhlman Lab
Doug Renfrew

Baker Lab
Andrew Leaver-Fay

Genentech Scholars Program
Department of Defense NDSEG
NSF Synthetic Biology Engineering Research Center