Tutorial: Simulating protein flexibility with the Backrub motion

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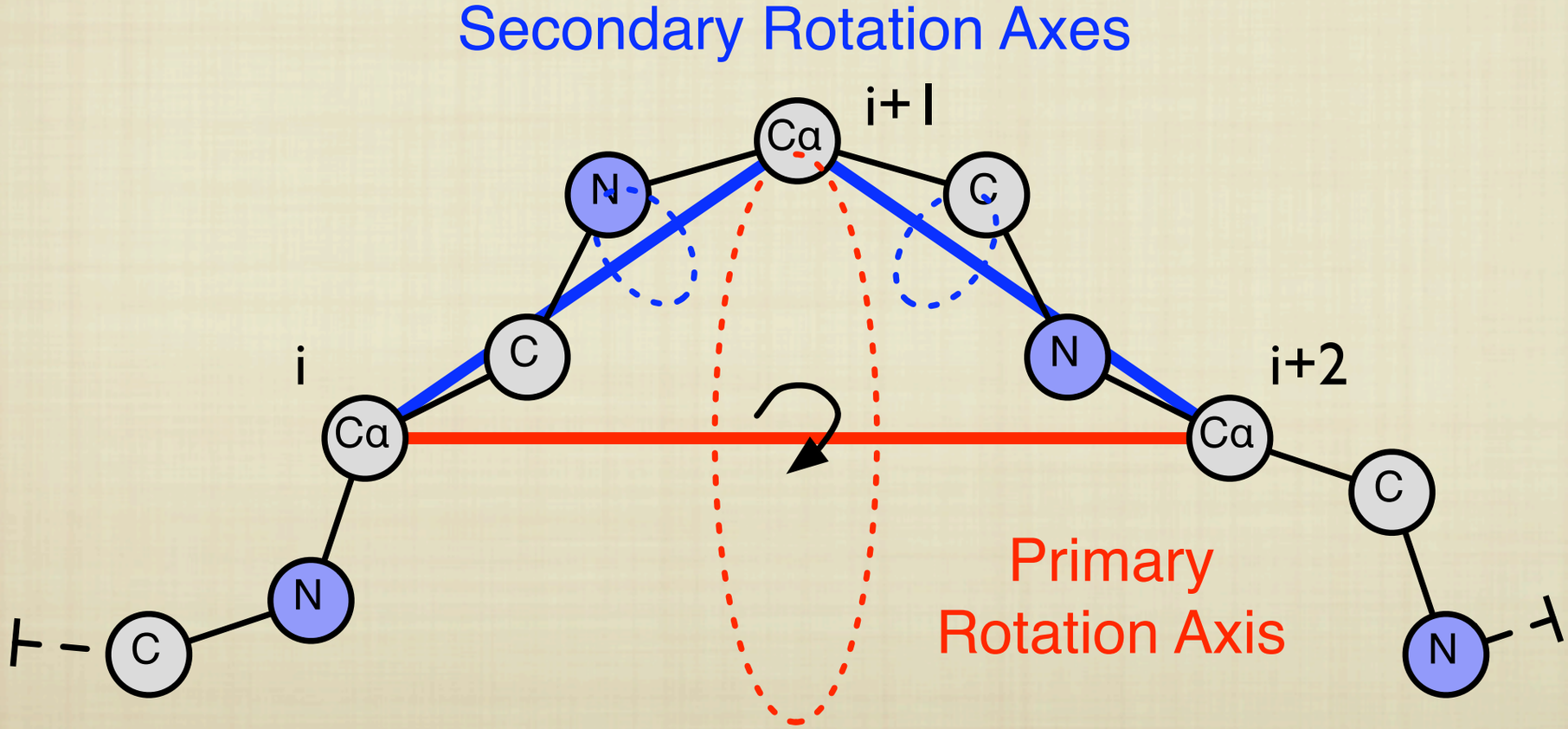
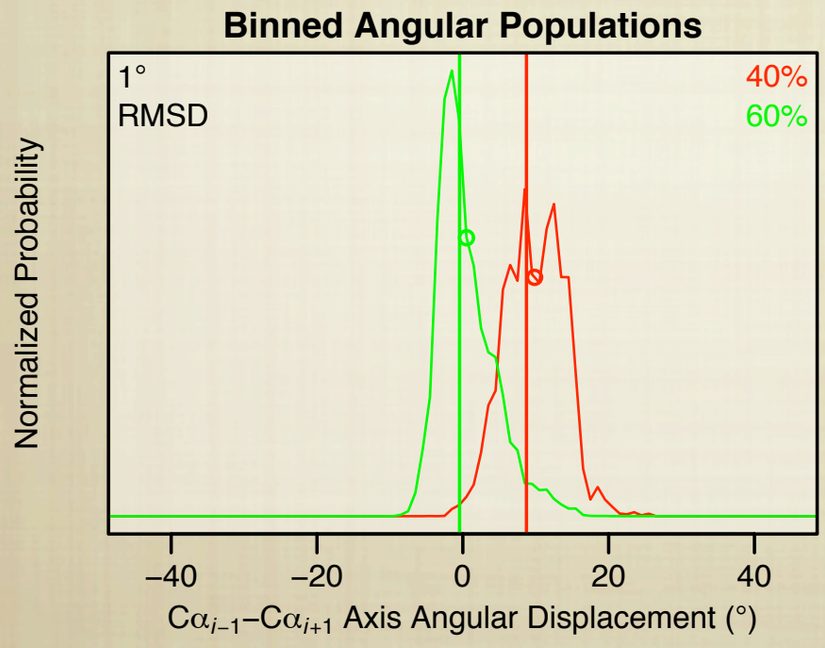
The Backrub Motion: How Protein Backbone Shrugs When a Sidechain Dances

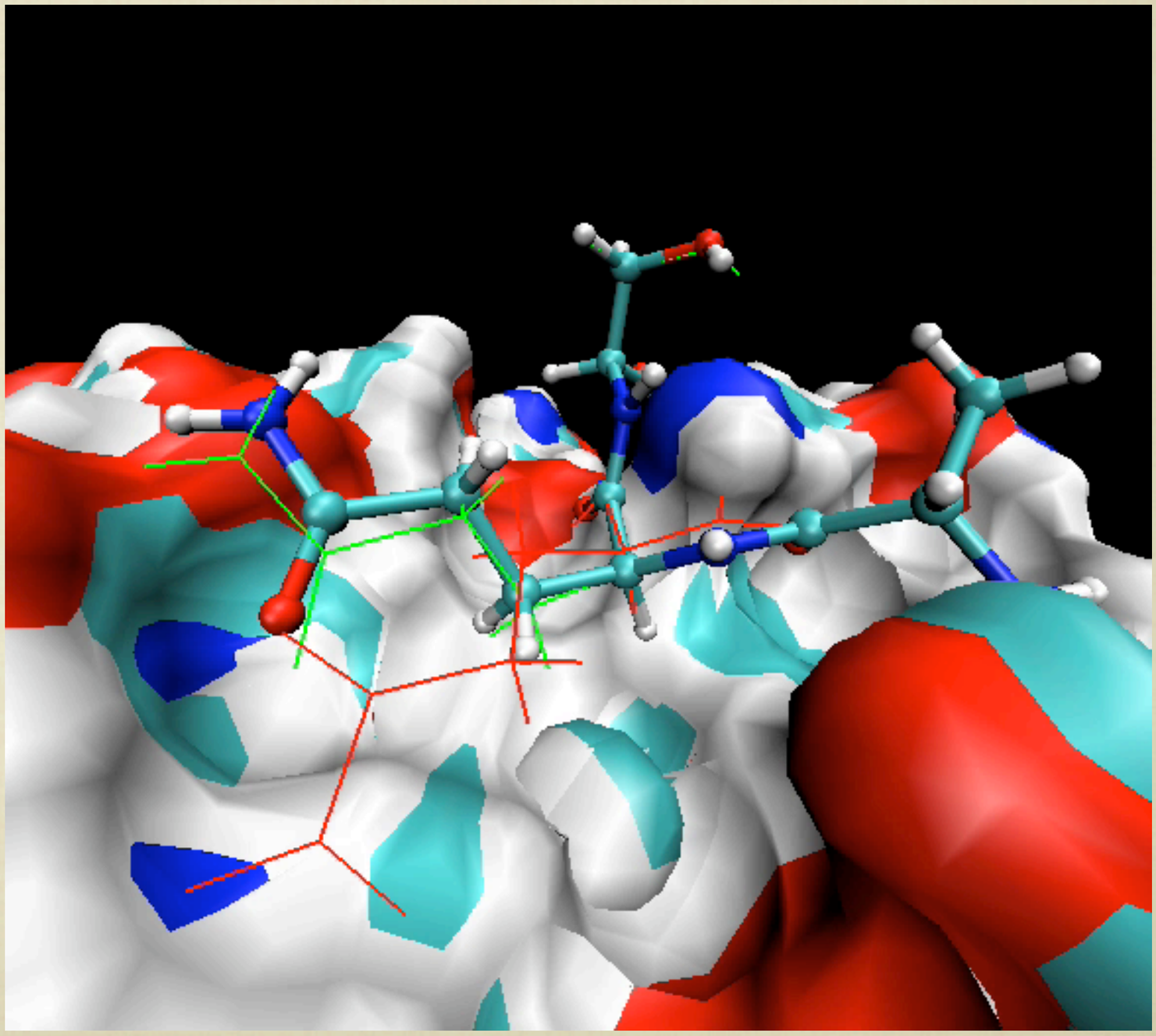
- Rotation around an axis defined by 2 Cα atoms (i, i+2)
- Compensating rotation around (i, i+1) and (i+1, i+2) axes



Simulation of a known backrub from Davis et al

- The glutamine $\chi 1$ angle prefers to be ~ 60° when the backbone is closer to the protein.





Why Use Backrub?

- Modeling local backbone flexibility
  - Increases sampling in the area of interest
  - Reduces energy function noise coming from distant conformational changes
- Applications
  - Generation of ensembles for: design, docking, flexibility prediction
  - High-resolution structure prediction of small perturbations (mutation, binding)

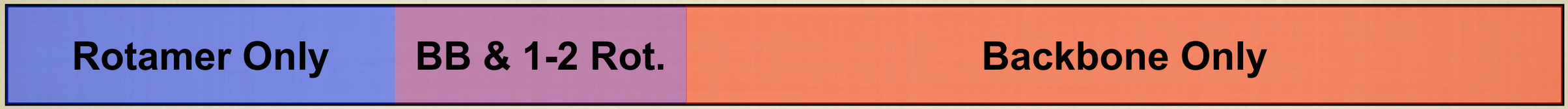
```
rosetta -pose1 -backrub_mc -s filename.pdb
        -resfile filename.resfile
```

```
This file specifies which residues will be varied

 Column      2: chain
 Column    4-7: sequential residue number
 Column   9-12: pdb residue number
 Column  14-18: id (described below)
 Column     19: [ ] fixed backbone [B] flexible backbone
 Column  20-40: amino acids to be used

 NATAA  => use native amino acid
 ALLAA  => all amino acids

 A  161  162 NATRO
 A  162  163 NATRO
 A  163  164 NATAA
 A  164  165 NATAAB
 A  165  166 NATROB
 A  166  167 NATAAB
```

Additional Parameters

-only_rot [0, 1]

Default: 0.25



Default: 0.75

Move Type Selection

-only_bb [0, 1]

-bond_angle_weight (1.0)

-bond_angle_params

bond_angle_amber[_rosetta]

Default

or

bond_angle_charmm[_rosetta]

-mc_temp (0.6)

-min_res (2)

-max_res (12)

Generating many structures

Required Arguments:

```
-chain <chain>
-series <two characters>
-protein <name>
```

Optional:

```
-nstruct (1000)
-read_all_chains
```

Recording Trajectories

- Specify the name of the trajectory file:

```
-moviefile <moviefile>
```

- Turn on trajectory output:

```
-trajectory
```

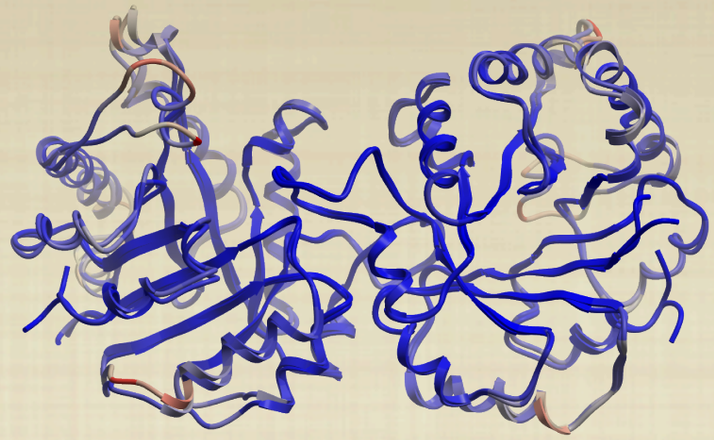
- write out a frame after N MC trials:

```
-movie_frame_skip (1)
```

- compress trajectory files with gzip:

```
-output_pdb_gz
```

Example Command



250K Step TIM Trajectory

```
rosetta -pose1 -backrub_mc -s 1YPIalign.pdb
        -resfile all_core_dimer.resfile
        -chain A -series 00 -protein alld_1YPI
        -read_all_chains -use_pdb_numbering
        -nstruct 1 -ntrials 250000
        -ex1 -ex1aro -ex2 -ex2aro -extrachi_cutoff 0
        -try_both_his_tautomers
        -moviefile 00alld_1YPI -trajectory
        -movie_frame_skip 2500 -output_pdb_gz
        -bond_angle_params bond_angle_amber
```

Generated Files

Initial Conformation after Cβ/Hα Optimization:

00alld_1YPI_initial.pdb

```
ATOM      1  N   ALA A   2     104.518  36.178  70.075  1.00 49.53
ATOM      2  CA  ALA A   2     103.430  35.183  70.422  1.00 50.07
...
ATOM   7549 1HB  ASN B 248      41.699  26.671  46.560  1.00 50.09
ATOM   7550 2HB  ASN B 248      40.108  27.084  47.243  1.00 50.09
TER
SCORE -197.002 RAMACHANDRAN 189.128 FA_ATR -1353.76 FA_REP 186.017
FA_SOL 682.754 FA_ELEC 0 FA_PAIR -31.6002 FA_REF 88.9998 FA_DUN
418.777 FA_PROB -77.1309 FA_H2O 0 HB_SRBB -131.145 HB_LRBB -91.2992
HB_SC -29.0766 FA_INTRA 0.684673 GB 0 PLANE 0 BOND_ANGLE 175.81
BARCODE 0 BAR_ENRG 0 CST 0
```

Generated Files

Last Conformation from Simulation:

00alld_1YPIlast_0001.pdb

```
REMARK   99 SAMPLE   250000
REMARK   99 SCORE    -265.831
REMARK   99 CA_RMSD 1.32876
ATOM      1  N   ALA A   2      104.518  36.178  70.075  1.00 49.53
...
```

Low Conformation from Simulation:

00alld_1YPIlow_0001.pdb

```
REMARK   99 SAMPLE   123660
...
```

Generated Files

Output Trajectory

00alld_1YPIT.pdb.gz

```
MODEL         1
REMARK   99 2500
REMARK   98 483.056
ATOM      1  N   ALA A   2      104.518  36.178  70.075  1.00 49.53
...
ATOM   7550 2HB  ASN B 248       40.310  27.003  47.194  1.00 50.09
TER
ENDMDL
MODEL         2
REMARK   99 5000
...
```

Rosetta Output

```
command executed: rosetta -pose1 -backrub_mc -s
...
Loading design/repack settings from resfile
                                    all_core_dimer.resfile
Allowed Backrub Moves (<size>: <start res> ...)
2: 1 2 3 4 5 8 9 10 11 12 13 14 15 16 17 18 19 20...
3: 1 2 3 4 8 9 10 11 12 13 14 15 16 17 18 19 20...
...
11: 8 9 10 11 12 13 14 15 16 17 18 19 20 21 23 24...
12: 8 9 10 11 12 13 14 15 16 17 18 19 20 22 23 24...
...
```

Rosetta Output

```
Reading rosetta_database/bond_angle_amber


Initial Scores:
SCORE 1871.43 RAMACHANDRAN 252.178 FA_ATR -1805.71
FA_REP 845.92 FA_SOL 964.968...BOND_ANGLE 984.875...


Scores After CB/HA Optimization:
SCORE 2232.97 RAMACHANDRAN 252.178 FA_ATR -1790.37
FA_REP 1871.11 FA_SOL 973.05...BOND_ANGLE 276.145...
...
```

Rosetta Output

```
Running 250000 Monte Carlo trials


backrub_02_0 trials=  13021 accepts= 0.3504...
backrub_02_1 trials=   3372 accepts= 0.1234...
backrub_02_2 trials=    706 accepts= 0.0255...
backrub_03_0 trials=  12742 accepts= 0.2990...
...
backrub_12_0 trials=  12657 accepts= 0.2117...
backrub_12_1 trials=   3202 accepts= 0.0656...
backrub_12_2 trials=   1100 accepts= 0.0336...
 backrub_rot trials=   62868 accepts= 0.2519...
```

Rosetta Output

```
Trial Statistics (N-CA-C Deviation from Ideal):
   Degrees     1.0     2.0     3.0     4.0     5.0...
    Trials    3964   11263   17207   21703   23933...
Acc. Ratio   0.343   0.324   0.303   0.284   0.245...

Trial Statistics (Angular Displacement):
   Degrees     4.0     8.0    12.0    16.0    20.0...
2   Trials    2397    2254    2161    2002    1893...
Acc. Ratio   0.701   0.526   0.366   0.256   0.179...
3   Trials    4514    4041    3498    2770    2122...
Acc. Ratio   0.576   0.256   0.100   0.054   0.028...
```

Rosetta Output

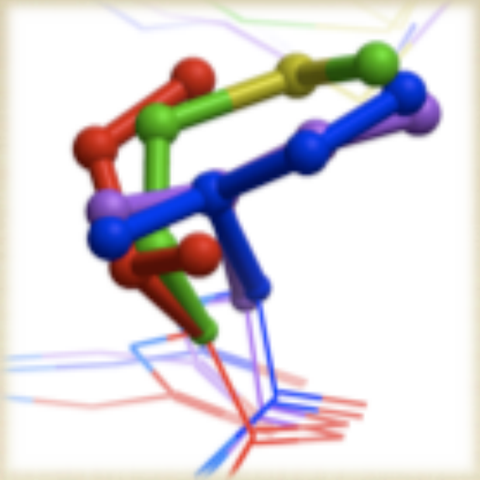
```
N-CA-C Bond Angle Statistics:
Res     Ideal Initial-Ideal    Last-Ideal
A1     109.70  106.60 -3.10   113.70   4.00...
R2     109.70  100.81 -8.89   102.00 -7.70...
T3     109.70  109.09 -0.62   111.75   2.05...
```

```
...    Low-Ideal    Mean-Ideal     SD Th SD
...115.10  5.40   113.25  3.54   3.26  3.63
...104.56 -5.14   105.95 -3.75   2.07  3.63
...108.68 -1.02   110.08  0.38   1.83  3.63
```

Rosetta Output

```
Last Scores:
SCORE -265.831 RAMACHANDRAN 186.514 FA_ATR -1526.19
FA_REP 207.752 FA_SOL 770.436 FA_ELEC 0 FA_PAIR
-36.5424 FA_REF 88.9998 FA_DUN 443.509 FA_PROB
-75.0048 FA_H2O 0...BOND_ANGLE 186.509...

Low Scores:
SCORE -317.897 RAMACHANDRAN 161.706 FA_ATR -1545.51
FA_REP 204.67 FA_SOL 779.633 FA_ELEC 0 FA_PAIR
-35.9939 FA_REF 88.9998 FA_DUN 426.758 FA_PROB
-76.0363 FA_H2O 0...BOND_ANGLE 183.184...
```

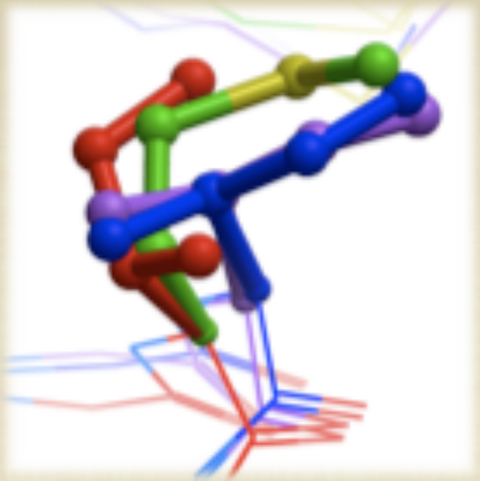
Example Command



1CV1:A M111I Point Mutant Prediction

```
rosetta -pose1 -backrub_mc -s 1CV1.pdb.gz
        -resfile 1CV1_A_M111I.resfile
        -chain A -series 00 -protein 1CV1_A_M111I
        -read_all_chains -use_pdb_numbering
        -nstruct 10 -ntrials 10000
        -ex1 -ex2 -extrachi_cutoff 0
        -bond_angle_params bond_angle_amber
```

Example Resfile



1cv1:A M111I Point Mutant Prediction

```
...
  A    98    98 NATRO
  A    99    99 NATAAB
  A   100   100 NATRO
  A   101   101 NATRO
  A   102   102 NATAAB
  A   103   103 NATAAB
  A   104   104 NATRO
  A   105   105 NATRO
  A   106   106 NATAAB
  A   107   107 NATAAB
  A   108   108 NATAAB
  A   109   109 NATAAB
  A   110   110 NATAAB
  A   111   111 PIKAAB I
  A   112   112 NATAAB
  A   113   113 NATAAB
  A   114   114 NATAAB
  A   115   115 NATAAB
...
```

```
#include "pose_backrub_controller.h"

   pose_ns::Backrub_controller backcontrol;

   backcontrol.set_pose(&pose);
   backcontrol.init_with_args();

   float  bond_angle_weight;
   realafteroption("bond_angle_weight", 1.0, bond_angle_weight);
   weight_map.set_weight(pose_ns::BOND_ANGLE, bond_angle_weight);

   backcontrol.trial(pose, mc);

   backcontrol.trial(pose, mc, weight_map, min_type, nmoves,
                     try_rotamers, energycut, tag_suffix);
```

Rotamer Trials & Minimization