Metropolis Hastings Monte Carlo simulations with RosettaScripts

Colin A. Smith - Kortemme Lab
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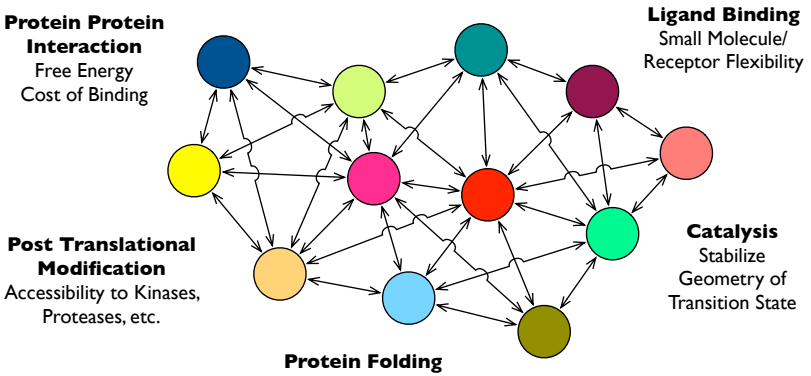
Predicting Flexibility With Monte Carlo Simulations



Rigorous Monte Carlo Must Preserve Detailed Balance

Analogous to the Law of Mass Action:

$A \Leftrightarrow B$

$$K_{eq} = \frac{[B]}{[A]} = \frac{k_{forward}}{k_{reverse}}$$

Solution #2:

$$a_{AB} = \frac{1}{q_{AB}} e^{(E_A - E_B)/kT}$$

$$p_{AB} = q_{AB} a_{AB}$$

$$\frac{\pi_B}{\pi_A} = \frac{p_{AB}}{p_{BA}} = \frac{q_{AB} a_{AB}}{q_{BA} a_{BA}}$$

Population

Transition Probability

Mover Proposal Density

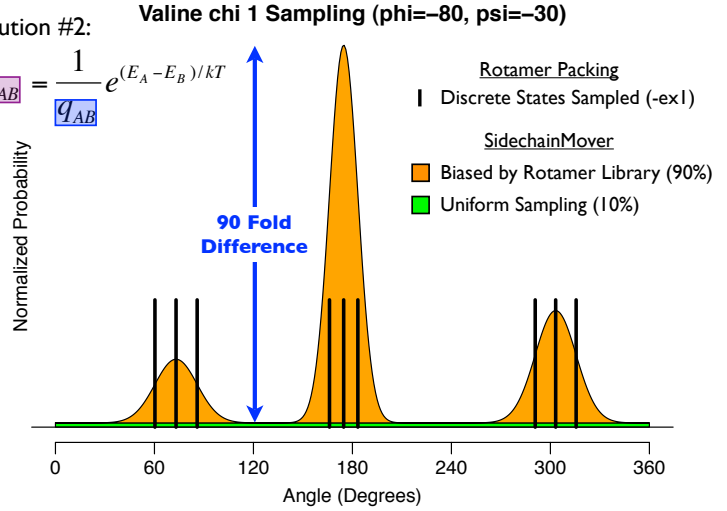
Metropolis Criterion

Problem: $q_{AB} \neq q_{BA}$ Solution #1: $q_{AB} = q_{BA}$

Rotamer Packing vs. SidechainMover

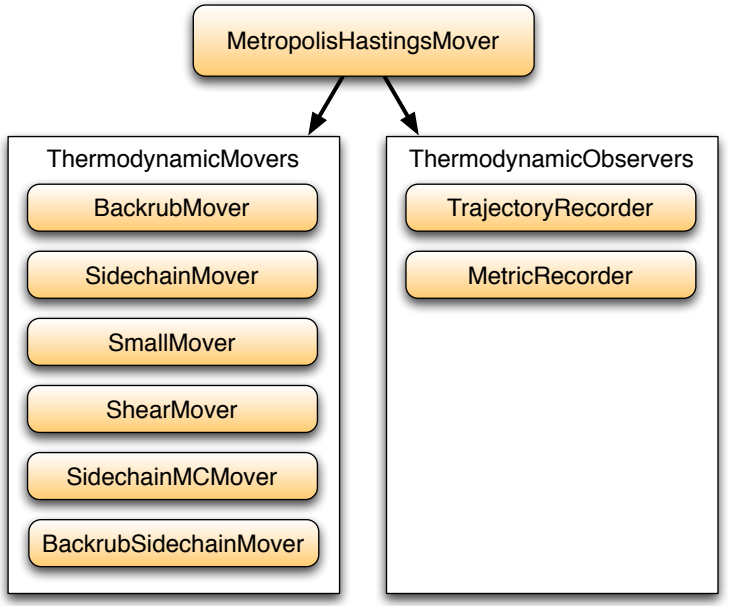
Solution #2:

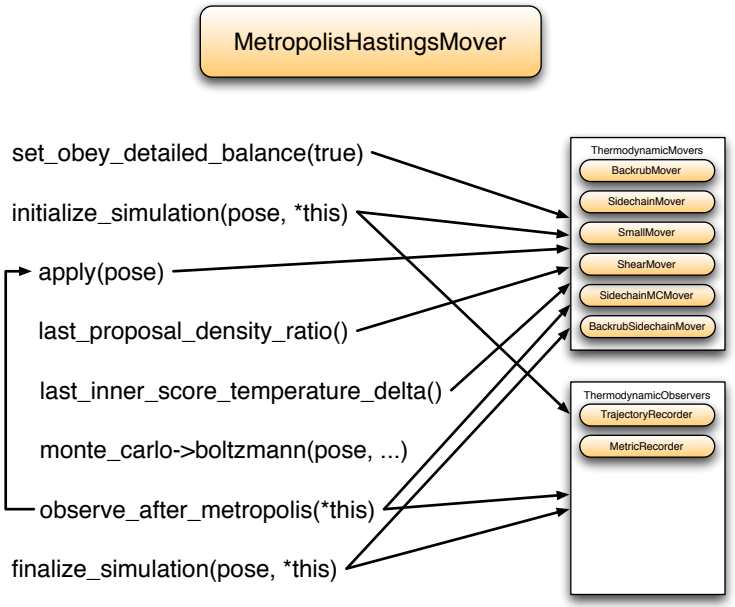
$$a_{AB} = \frac{1}{q_{AB}} e^{(E_A - E_B)/kT}$$



Problems with the backrub app

- Can't upweight sampling of certain regions, only on/off
- No way to automatically use movers others implement
- Many movers have overlapping command line flags
- Difficult to combine with other movers in a larger protocol
- Side chains use PDB numbering, backbone uses absolute Rosetta numbering
- Doesn't support JD2





MetropolisHastingsMover

```
<SCOREFXNS>
   <score12_mh weights=score12_full>
      <Reweight scoretype=mm_bend weight=1/>
   </score12_mh>
</SCOREFXNS>
```

```
<MetropolisHastings name=metropolis_hastings
                    scorefxn=score12_mh
                    temperature=4.8
                    trials=10000000>
```

Including Movers

Traditional

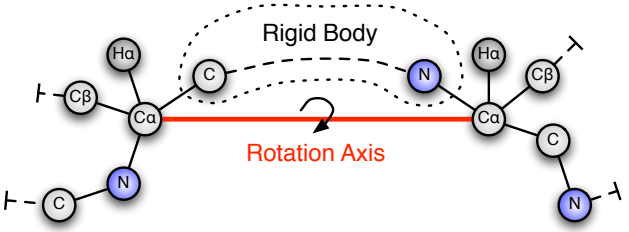
```
<Backrub name=backrub .../>
<MetropolisHastings name=metropolis_hastings ...>
  <Add mover_name=backrub sampling_weight=(1 &Real)/>
</MetropolisHastings>
```

Streamlined

```
<MetropolisHastings name=metropolis_hastings ...>
  <Backrub sampling_weight=(1 &Real) .../>
</MetropolisHastings>
```

BackrubMover

```
<Backrub  sampling_weight=0.6
          pivot_residues=54A,...,130A
          pivot_atoms=CA (default)
          require_mm_bend=1 (default)/>
```

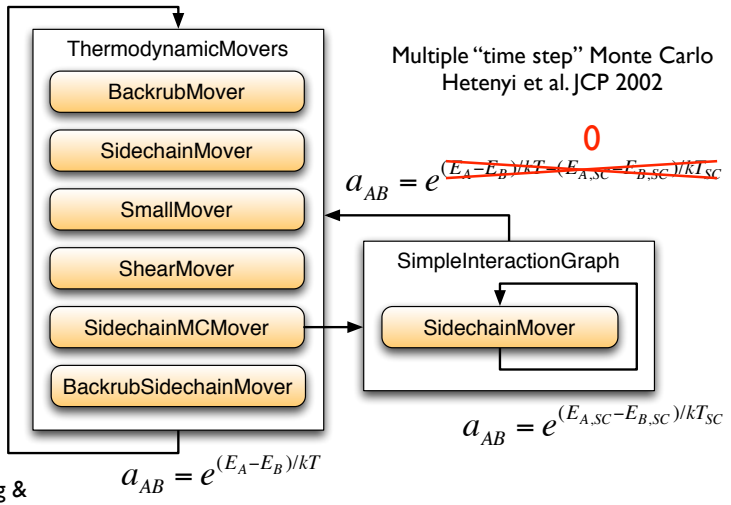


SidechainMover

```
<TASKOPERATIONS>
   <DesignAround name=da repack_on=0 design_shell=0
                 resnums=8A,...,156A/>
   <RestrictToRepacking name=rtrp/>
   <PreserveCBeta name=pcb/> (important for backrub)
</TASKOPERATIONS>
```

```
<Sidechain sampling_weight=0
           task_operations=da,rtrp,pcb
           prob_uniform=0.1
           prob_withinrot=0.2/>
```

SidechainMCMover



Liz Kellogg &
Andrew Leaver-Fay

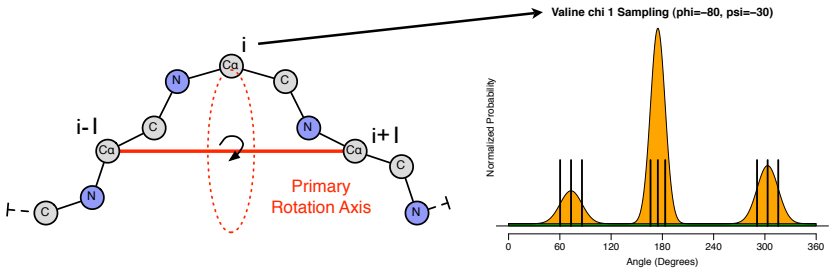
SidechainMCMover

```
<SidechainMC sampling_weight=0.1
             task_operations=da,rtrp,pcb
             prob_uniform=0.1
             prob_withinrot=0.2
             ntrials=1000
OR           scorefxn=score12_mh
             temperature=4.8
             inherit_scorefxn_temperature=1/>
```

Liz Kellogg &
Andrew Leaver-Fay

BackrubSidechainMover

```
<BackrubSidechain sampling_weight=0.3
                  pivot_residues=112A,113A,114A
                  task_operations=da,rtrp,pcb/>
```



ThermodynamicObservers

TrajectoryRecorder

```
<TrajectoryRecorder stride=5000
                    filename=traj.pdb.gz/>
```

MetricRecorder

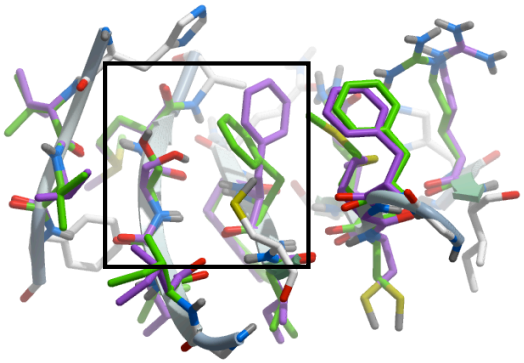
```
<MetricRecorder stride=100 filename=metrics.txt>
    <Torsion rsd=99A type=CHI torsion=1 name="Ser 99 Chi 1"/>
    <Torsion rsd=113A type=CHI torsion=1 name="Phe 113 Chi 1"/>
    <Torsion rsd=113A type=CHI torsion=2 name="Phe 113 Chi 2"/>
</MetricRecorder>
```

Crystallography shows alternate conformations at room temperature

Most of the alternate conformations occur in the 2 beta sheets of the beta sandwich

Fraser et al. *Nature* 2009

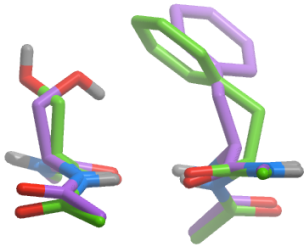
Crystallography shows alternate conformations at room temperature



Major Conformation (A)
Minor Conformation (B)

Fraser et al. *Nature* 2009

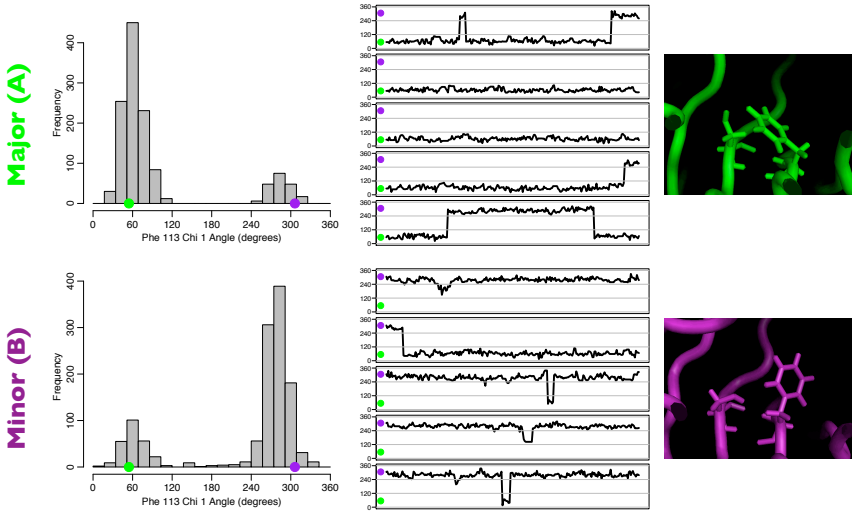
Crystallography shows alternate conformations at room temperature



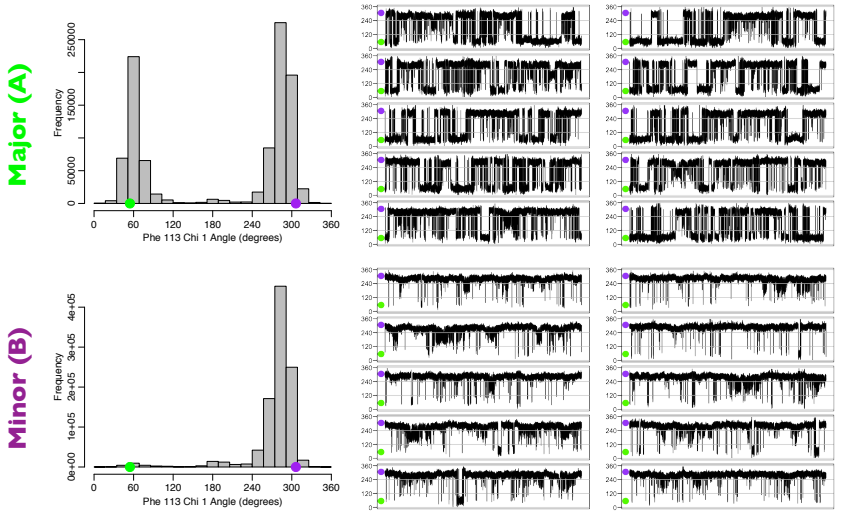
Major Conformation (A)
Minor Conformation (B)

Fraser et al. *Nature* 2009

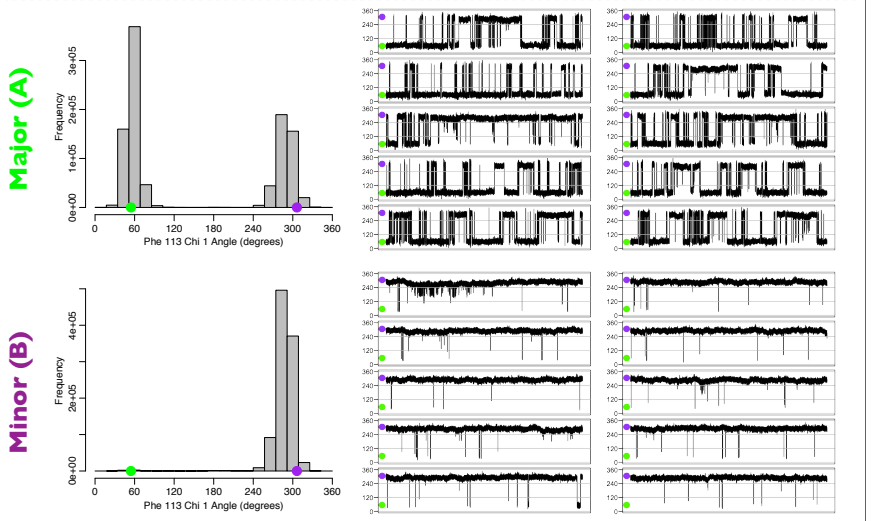
Phenylalanine Intraconverts at 4.8 kT



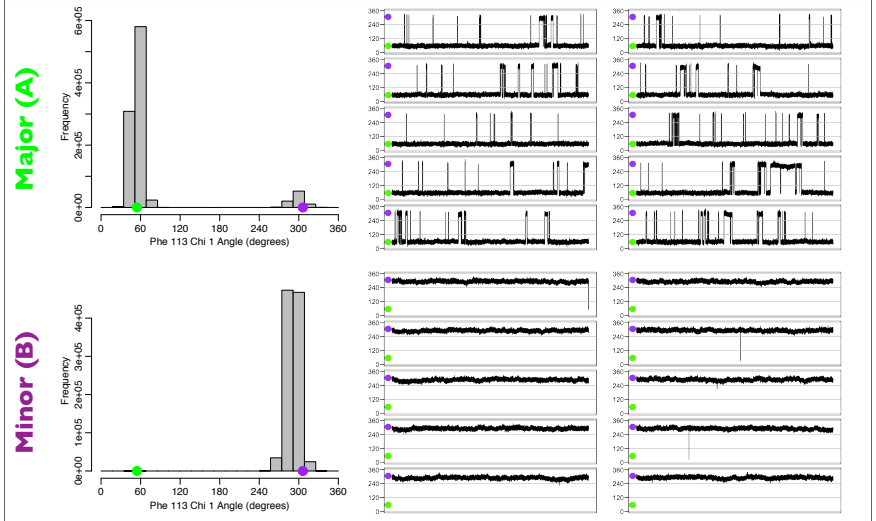

```
<MetropolisHastings temperature=4.8 trials=10000000 ...>
 <Backrub sampling_weight=0.6 pivot_residues=54A,...,130A pivot_atoms=CA/>
 <BackrubSidechain sampling_weight=0.3 pivot_residues=112A,113A,114A .../>
 <SidechainMC sampling_weight=0.1 ntrials=1000 .../>
```



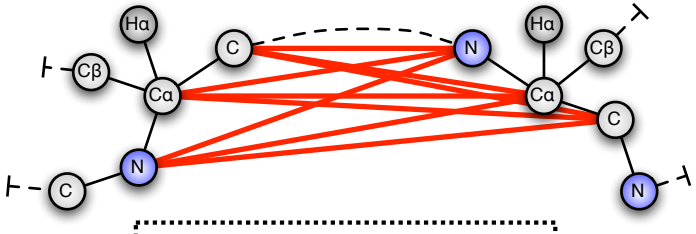
```
<MetropolisHastings temperature=2.4 trials=10000000 .../>
 <Backrub sampling_weight=0.6 pivot_residues=54A,...,130A pivot_atoms=CA/>
 <BackrubSidechain sampling_weight=0.3 pivot_residues=112A,113A,114A .../>
 <SidechainMC sampling_weight=0.1 ntrials=1000 .../>
```




```
<MetropolisHastings temperature=1.2 trials=10000000 .../>
 <Backrub sampling_weight=0.6 pivot_residues=54A,...,130A pivot_atoms=CA/>
 <BackrubSidechain sampling_weight=0.3 pivot_residues=112A,113A,114A .../>
 <SidechainMC sampling_weight=0.1 ntrials=1000 .../>
```

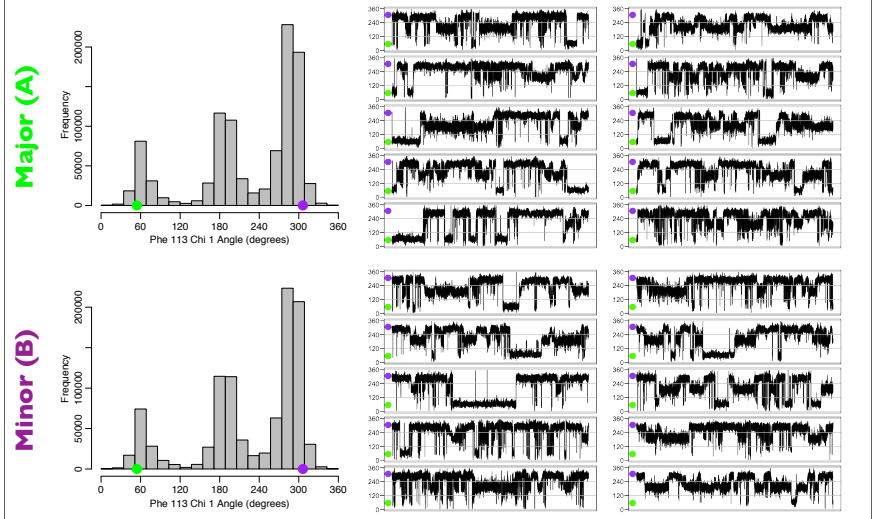


Are unsampled backbone degrees of freedom preventing convergence?




```
<Backrub  ...
          pivot_atoms=N,CA,C/>
```

```
<MetropolisHastings temperature=4.8 trials=10000000 .../>
 <Backrub sampling_weight=0.6 pivot_residues=54A,...,130A pivot_atoms=N,CA,C/>
 <BackrubSidechain sampling_weight=0.3 pivot_residues=112A,113A,114A .../>
 <SidechainMC sampling_weight=0.1 ntrials=1000 .../>
```



Conclusions

- RosettaScripts is awesome. Don't ask why you should use it, ask why you shouldn't.
- Sampling between states at near "room temperature" is still an unsolved issue for long time scale intraconversions like CypA Phe113
- Non-sampled degrees of freedom can bias sampling in important ways

Thanks

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