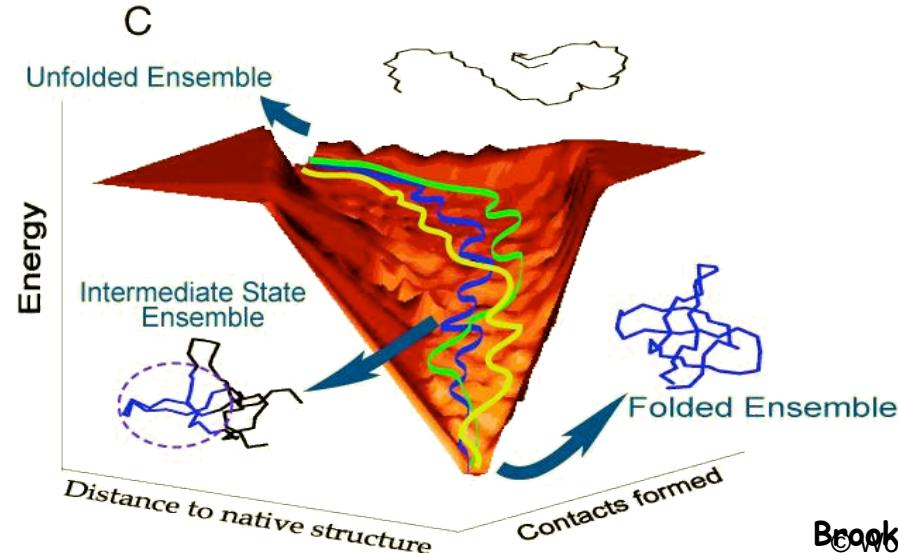
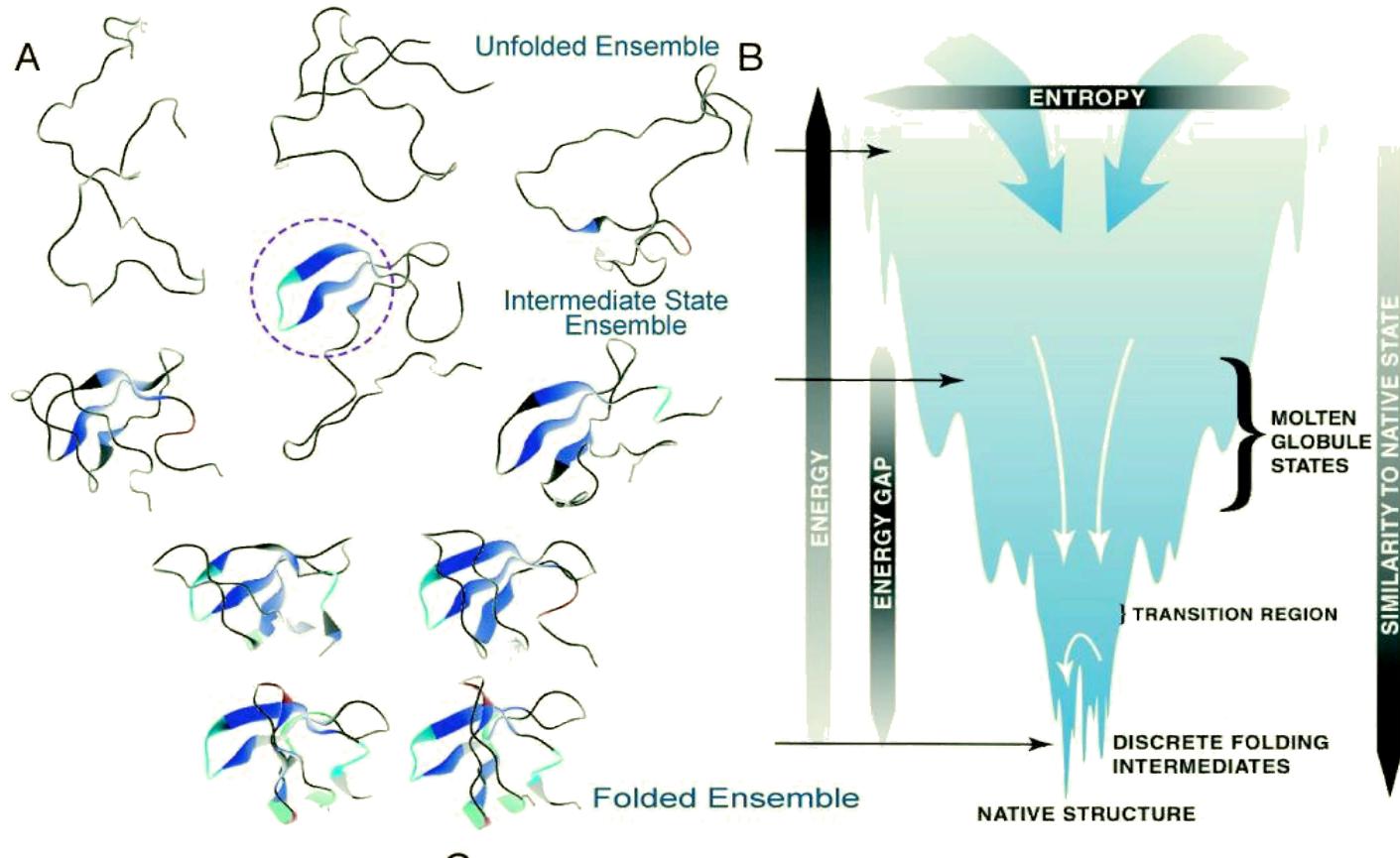


REX-MD with CHARMM and MMTSB

Wonpil Im and Jianhan Chen
MMTSB/CTBP
2006 Summer Workshop



Replica Exchange Simulations

$t = 0$

T_1 $\textcolor{red}{S}_1(T_1)$

T_2 $\textcolor{blue}{S}_2(T_2)$

T_3 $\textcolor{teal}{S}_3(T_3)$

T_4 $\textcolor{orange}{S}_4(T_4)$

T_5 $\textcolor{black}{S}_5(T_5)$

Replica Exchange Simulations

$t = 0$

$t = 1 \text{ ps}$

T_1 $\textcolor{red}{S}_1(T_1)$

$\textcolor{red}{S}_1(T_1)$

T_2 $\textcolor{blue}{S}_2(T_2)$

$\textcolor{blue}{S}_2(T_2)$

T_3 $\textcolor{teal}{S}_3(T_3)$

$\textcolor{teal}{S}_3(T_3)$

T_4 $\textcolor{orange}{S}_4(T_4)$

$\textcolor{orange}{S}_4(T_4)$

T_5 $\textcolor{black}{S}_5(T_5)$

$\textcolor{black}{S}_5(T_5)$

Replica Exchange Simulations

	$t = 0$	$t = 1 \text{ ps}$
T_1	$S_1(T_1)$	$S_1(T_1)$
T_2	$S_2(T_2)$	$S_2(T_2)$
T_3	$S_3(T_3)$	$S_3(T_3)$
T_4	$S_4(T_4)$	$S_4(T_4)$
T_5	$S_5(T_5)$	$S_5(T_5)$

$$\Delta = \left(1/kT_j - 1/kT_i\right) \cdot (E_i - E_j)$$

$$p_{i \leftrightarrow j} = \begin{cases} 1 & \Delta \leq 0 \\ \exp(-\Delta) & \Delta > 0 \end{cases}$$

Replica Exchange Simulations

	$t = 0$	$t = 1 \text{ ps}$	$t = 2 \text{ ps}$
T_1	$\mathbf{S}_1(T_1)$	$\mathbf{S}_1(T_1)$	$\mathbf{S}_2(T_1)$
T_2	$\mathbf{S}_2(T_2)$	$\mathbf{S}_2(T_2)$	$\mathbf{S}_1(T_2)$
T_3	$\mathbf{S}_3(T_3)$	$\mathbf{S}_3(T_3)$	$\mathbf{S}_4(T_3)$
T_4	$\mathbf{S}_4(T_4)$	$\mathbf{S}_4(T_4)$	$\mathbf{S}_3(T_4)$
T_5	$\mathbf{S}_5(T_5)$	$\mathbf{S}_5(T_5)$	$\mathbf{S}_5(T_5)$

Replica Exchange Simulations

	$t = 0$	$t = 1 \text{ ps}$	$t = 2 \text{ ps}$
T_1	$\mathbf{S}_1(T_1)$	$\mathbf{S}_1(T_1)$	$\mathbf{S}_2(T_1)$
T_2	$\mathbf{S}_2(T_2)$	$\mathbf{S}_2(T_2)$	$\mathbf{S}_1(T_2)$
T_3	$\mathbf{S}_3(T_3)$	$\mathbf{S}_3(T_3)$	$\mathbf{S}_4(T_3)$
T_4	$\mathbf{S}_4(T_4)$	$\mathbf{S}_4(T_4)$	$\mathbf{S}_3(T_4)$
T_5	$\mathbf{S}_5(T_5)$	$\mathbf{S}_5(T_5)$	$\mathbf{S}_5(T_5)$

$$\Delta = \left(1/kT_j - 1/kT_i\right) \cdot (E_i - E_j)$$

$$p_{i \leftrightarrow j} = \begin{cases} 1 & \Delta \leq 0 \\ \exp(-\Delta) & \Delta > 0 \end{cases}$$

Replica Exchange Simulations

	$t = 0$	$t = 1 \text{ ps}$	$t = 2 \text{ ps}$
T_1	$\mathbf{S}_1(T_1)$	$\mathbf{S}_1(T_1)$	$\mathbf{S}_2(T_1)$
T_2	$\mathbf{S}_2(T_2)$	$\mathbf{S}_2(T_2)$	$\mathbf{S}_1(T_2)$
T_3	$\mathbf{S}_3(T_3)$	$\mathbf{S}_3(T_3)$	$\mathbf{S}_4(T_3)$
T_4	$\mathbf{S}_4(T_4)$	$\mathbf{S}_4(T_4)$	$\mathbf{S}_3(T_4)$
T_5	$\mathbf{S}_5(T_5)$	$\mathbf{S}_5(T_5)$	$\mathbf{S}_5(T_5)$

Replica Exchange Simulations

$H_2(T_1)$	$\textcolor{blue}{S_2}(T_1)$	
$H_1(T_2)$	$\textcolor{red}{S_1}(T_2)$	$\textcolor{orange}{S_4}(T_2) \quad H_4(T_2)$
$H_4(T_3)$	$\textcolor{orange}{S_4}(T_3)$	$\textcolor{red}{S_1}(T_3) \quad H_1(T_3)$
$H_3(T_4)$	$\textcolor{teal}{S_3}(T_4)$	$\textcolor{teal}{S_3}(T_4) \quad H_3(T_4)$
$H_5(T_5)$	$\textcolor{gray}{S_5}(T_5)$	$\textcolor{gray}{S_5}(T_5) \quad H_5(T_5)$

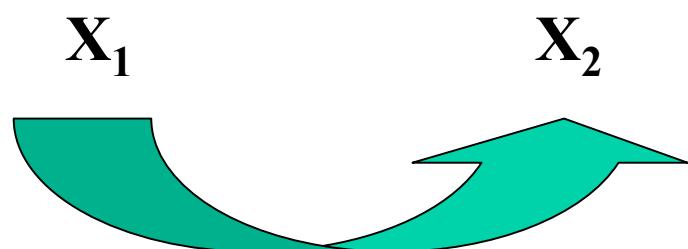
$H_2(T_1) = K_1 + E_2$
 $= \frac{3}{2} k_B T_1 + E_2$

$$W(\mathbf{X}_1) \propto \exp\left[-\frac{H_2(T_1)}{k_B T_1}\right] \exp\left[-\frac{H_1(T_2)}{k_B T_2}\right] \exp\left[-\frac{H_4(T_3)}{k_B T_3}\right] \exp\left[-\frac{H_3(T_4)}{k_B T_4}\right] \exp\left[-\frac{H_5(T_5)}{k_B T_5}\right]$$

$$W(\mathbf{X}_2) \propto \exp\left[-\frac{H_2(T_1)}{k_B T_1}\right] \exp\left[-\frac{H_4(T_2)}{k_B T_2}\right] \exp\left[-\frac{H_1(T_3)}{k_B T_3}\right] \exp\left[-\frac{H_3(T_4)}{k_B T_4}\right] \exp\left[-\frac{H_5(T_5)}{k_B T_5}\right]$$

Replica Exchange Simulations

$H_2(\tau_1)$	$\mathbf{S}_2(\tau_1)$	$\mathbf{S}_2(\tau_1)$	$H_2(\tau_1)$	
$H_1(\tau_2)$	$\mathbf{S}_1(\tau_2)$	$\mathbf{S}_4(\tau_2)$	$H_4(\tau_2)$	$H_2(T_1) = K_1 + E_2$
$H_4(\tau_3)$	$\mathbf{S}_4(\tau_3)$	$\mathbf{S}_1(\tau_3)$	$H_1(\tau_3)$	$= \frac{3}{2} k_B T_1 + E_2$
$H_3(\tau_4)$	$\mathbf{S}_3(\tau_4)$	$\mathbf{S}_3(\tau_4)$	$H_3(\tau_4)$	
$H_5(\tau_5)$	$\mathbf{S}_5(\tau_5)$	$\mathbf{S}_5(\tau_5)$	$H_5(\tau_5)$	



$$W(\mathbf{X}_1) w(\mathbf{X}_1 \rightarrow \mathbf{X}_2) = W(\mathbf{X}_2) w(\mathbf{X}_2 \rightarrow \mathbf{X}_1)$$

$$\frac{w(\mathbf{X}_1 \rightarrow \mathbf{X}_2)}{w(\mathbf{X}_2 \rightarrow \mathbf{X}_1)} = \frac{W(\mathbf{X}_2)}{W(\mathbf{X}_1)}$$

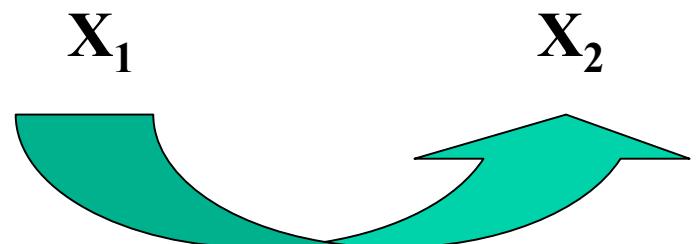
Replica Exchange Simulations

$$\frac{w(\mathbf{X}_1 \rightarrow \mathbf{X}_2)}{w(\mathbf{X}_2 \rightarrow \mathbf{X}_1)} = \frac{W(\mathbf{X}_2)}{W(\mathbf{X}_1)}$$

$$\begin{aligned} &= \frac{\exp\left[-\frac{H_2(T_1)}{k_B T_1}\right] \exp\left[-\frac{H_4(T_2)}{k_B T_2}\right] \exp\left[-\frac{H_1(T_3)}{k_B T_3}\right] \exp\left[-\frac{H_3(T_4)}{k_B T_4}\right] \exp\left[-\frac{H_5(T_5)}{k_B T_5}\right]}{\exp\left[-\frac{H_2(T_1)}{k_B T_1}\right] \exp\left[-\frac{H_1(T_2)}{k_B T_2}\right] \exp\left[-\frac{H_4(T_3)}{k_B T_3}\right] \exp\left[-\frac{H_3(T_4)}{k_B T_4}\right] \exp\left[-\frac{H_5(T_5)}{k_B T_5}\right]} \\ &= \exp\left[-\frac{T_3 H_4(T_2) - T_2 H_4(T_3)}{k_B T_2 T_3}\right] \exp\left[-\frac{T_2 H_1(T_3) - T_3 H_1(T_2)}{k_B T_2 T_3}\right] \\ &= \exp\left[-\frac{T_3 - T_2}{k_B T_2 T_3} E_4\right] \exp\left[-\frac{T_2 - T_3}{k_B T_2 T_3} E_1\right] \\ &= \exp\left[-\left(\frac{1}{k_B T_3} - \frac{1}{k_B T_2}\right)(E_1 - E_4)\right] \end{aligned}$$

Replica Exchange Simulations

$H_2(\tau_1)$	$\mathbf{S}_2(\tau_1)$		$\mathbf{S}_2(\tau_1)$	$H_2(\tau_1)$
$H_1(\tau_2)$	$\mathbf{S}_1(\tau_2)$		$\mathbf{S}_4(\tau_2)$	$H_4(\tau_2)$
$H_4(\tau_3)$	$\mathbf{S}_4(\tau_3)$		$\mathbf{S}_1(\tau_3)$	$H_1(\tau_3)$
$H_3(\tau_4)$	$\mathbf{S}_3(\tau_4)$		$\mathbf{S}_3(\tau_4)$	$H_3(\tau_4)$
$H_5(\tau_5)$	$\mathbf{S}_5(\tau_5)$		$\mathbf{S}_5(\tau_5)$	$H_5(\tau_5)$



$$\frac{w(\mathbf{X}_1 \rightarrow \mathbf{X}_2)}{w(\mathbf{X}_2 \rightarrow \mathbf{X}_1)} = \exp\left[-\left(\frac{1}{k_B T_3} - \frac{1}{k_B T_2}\right)(E_1 - E_4)\right]$$

Replica Exchange Simulations

$H_1(T_1)$ **S**(T_1)

$H_2(T_2)$ **S**(T_2)

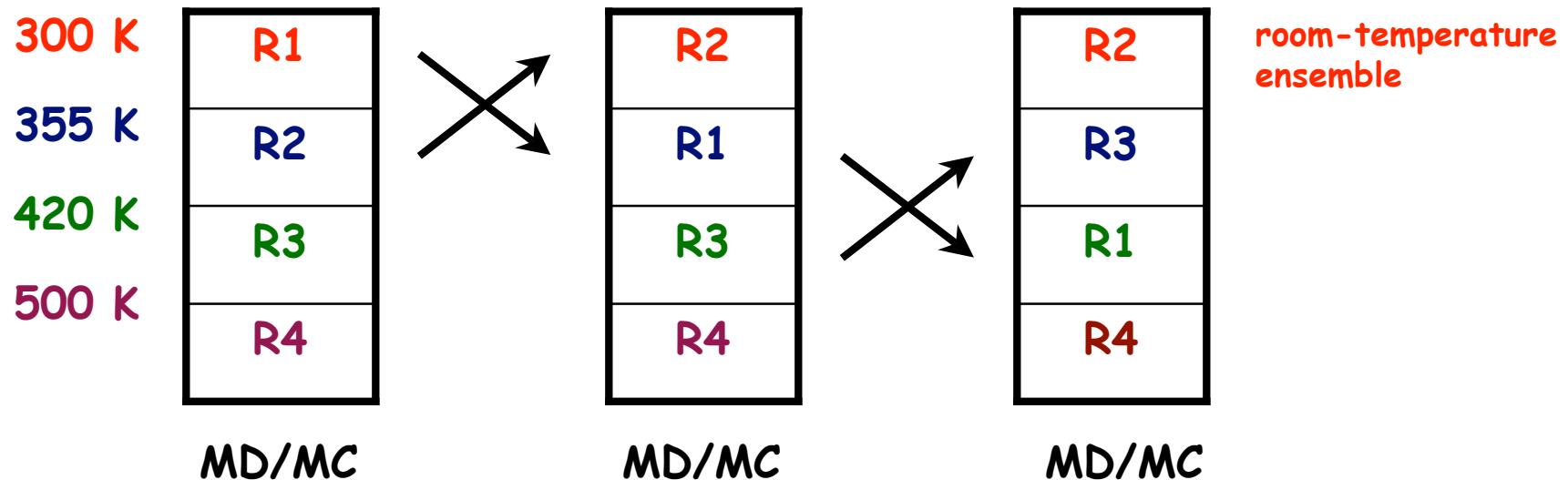
$H_3(T_3)$ **S**(T_3)

$H_4(T_4)$ **S**(T_4)

$H_5(T_5)$ **S**(T_5)

$$p_{2 \leftrightarrow 3} = \exp\left[-\left(\frac{1}{k_B T_3} - \frac{1}{k_B T_2}\right)(E_2 - E_3)\right]$$

Replica Exchange Simulations



- Exchange based on Metropolis criterion
- Ideal sampling with 20~30% acceptance
- REX calculations using the Multiscale Modeling Tools in Structural Biology (MMTSB) tool set (<http://mmtsbs.scripps.edu>).

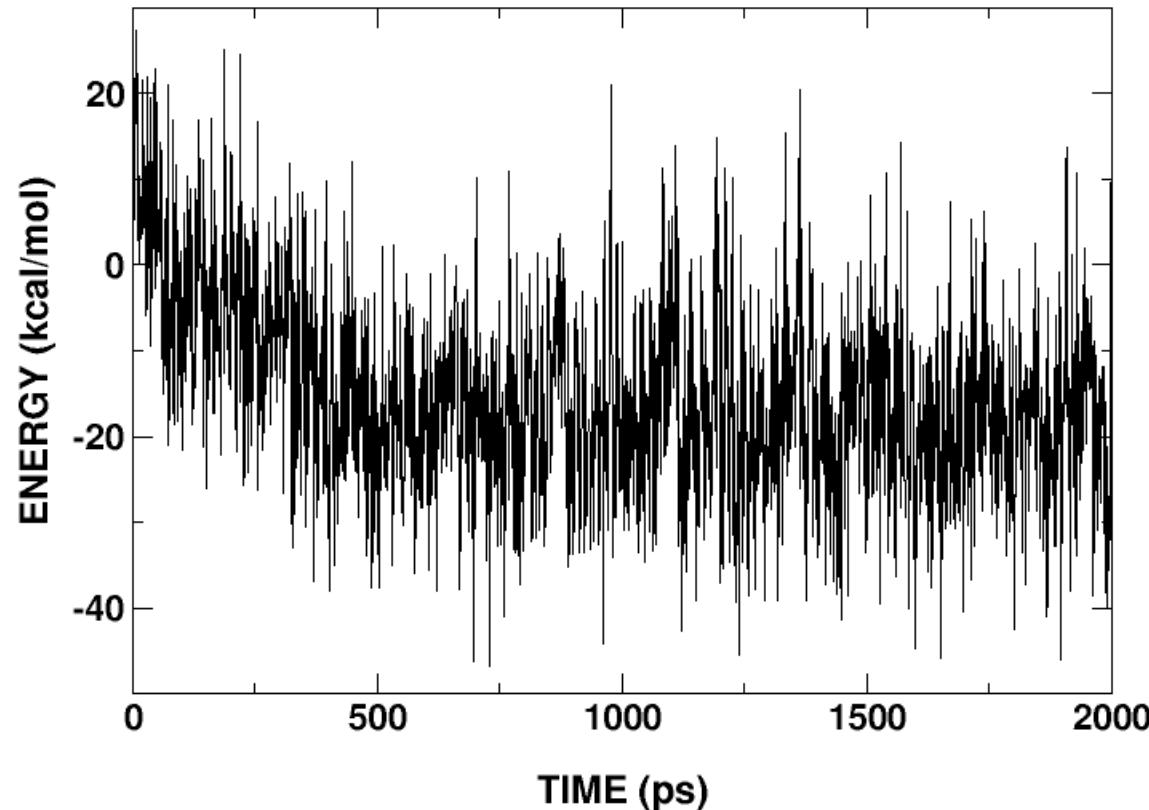
$$\Delta = (1/kT_j - 1/kT_i) \cdot (E_i - E_j)$$

$$p_{i \leftrightarrow j} = \begin{cases} 1 & \Delta \leq 0 \\ \exp(-\Delta) & \Delta > 0 \end{cases}$$

Replica Exchange Simulations

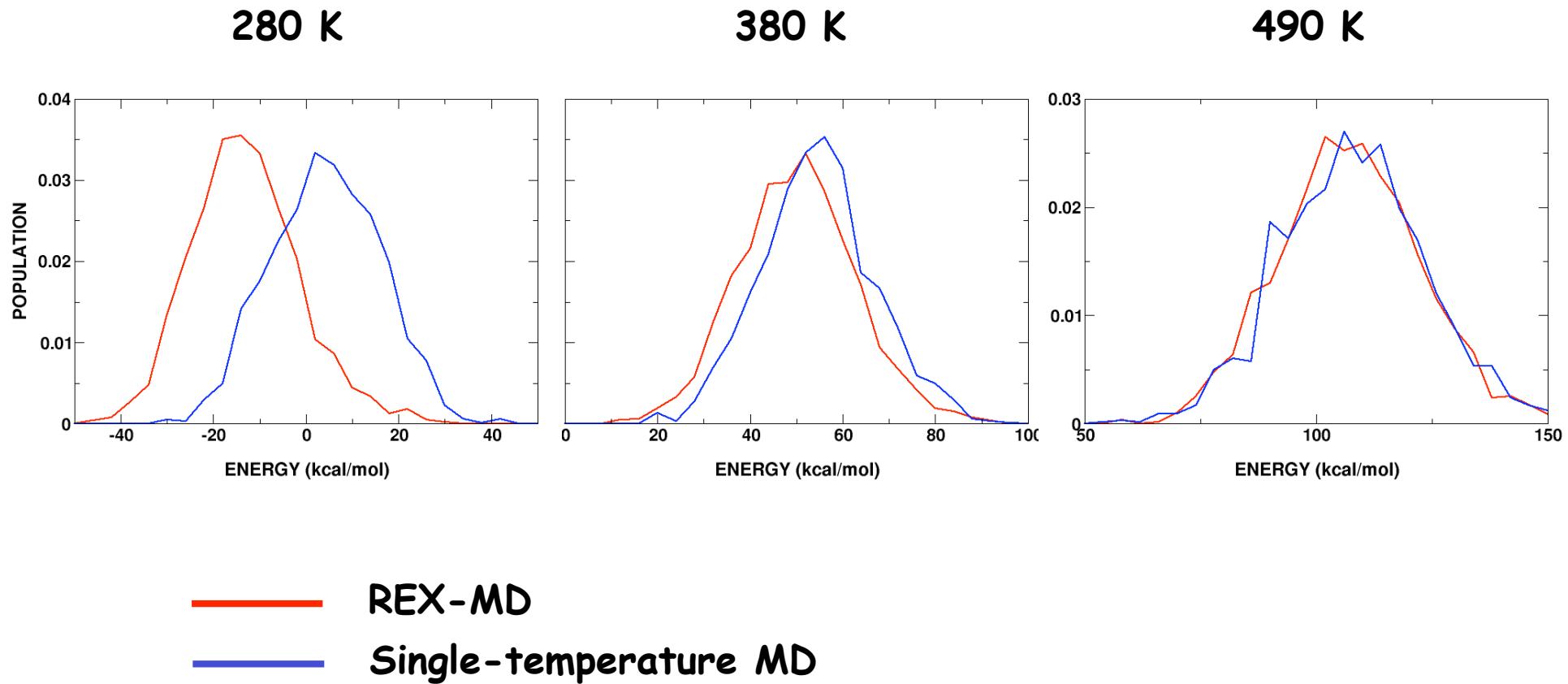
Is the simulation converged?

- look at the energy profile at the lowest temperature



Replica Exchange Simulations

Is the REX-MD better than a single-temperature MD?

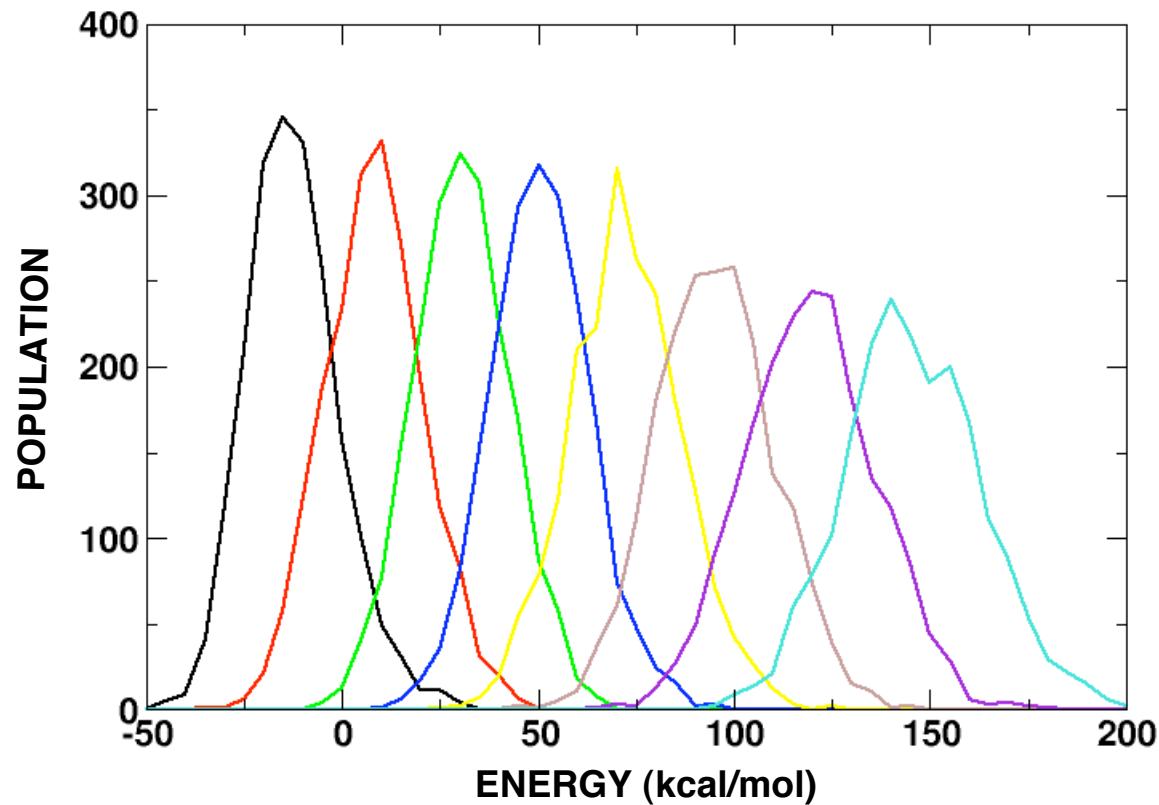


Replica Exchange Simulations

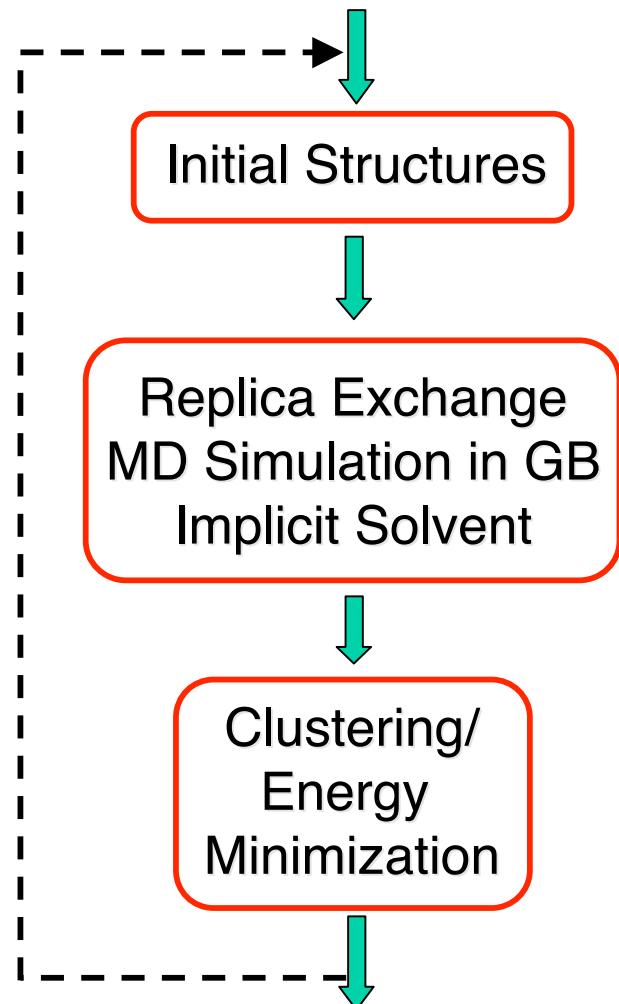
Why the temperature gaps increase?

- look at the energy distribution
- in MMTSB (`rexserver.cond`),

$$T_n = T_i \times f^n \quad \text{where } f = \sqrt[N]{T_f / T_i}$$

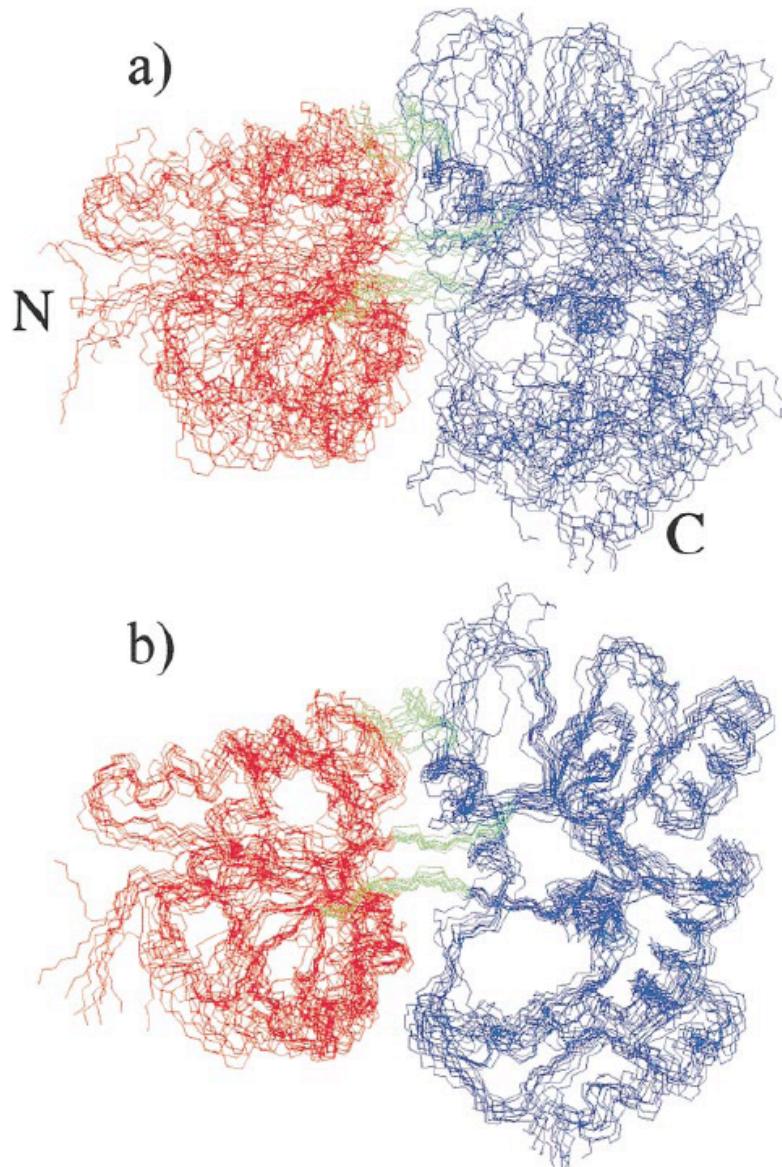


A Simple REX/GB Protocol



- from experiment or prediction
- in presence of restraints, derived either from experiments or prediction
- weakly imposed for stability and flexibility
- hierarchical clustering
- rank by population of clusters
- repeat for recursive restraint assignments or for convergence

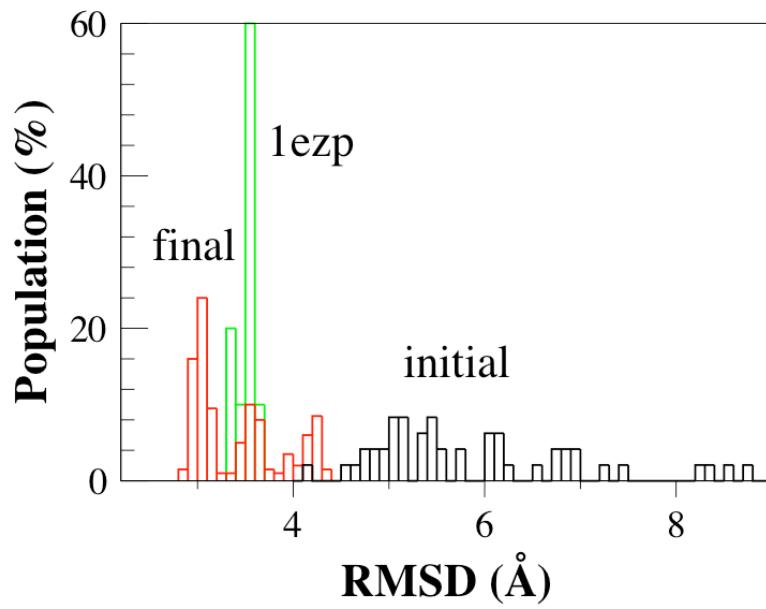
Refinement of Maltose-Binding Protein



- 370 residues, 42 kDa
- 1943 NOE
- 45 hydrogen bonding
- 555 dihedral angle restraints.
- Average backbone RMSD to X-ray structure is 5.5 Å (a).
- Improved to 3.3 Å with 940 additional dipolar coupling (b)

REX/GB Refinement Results

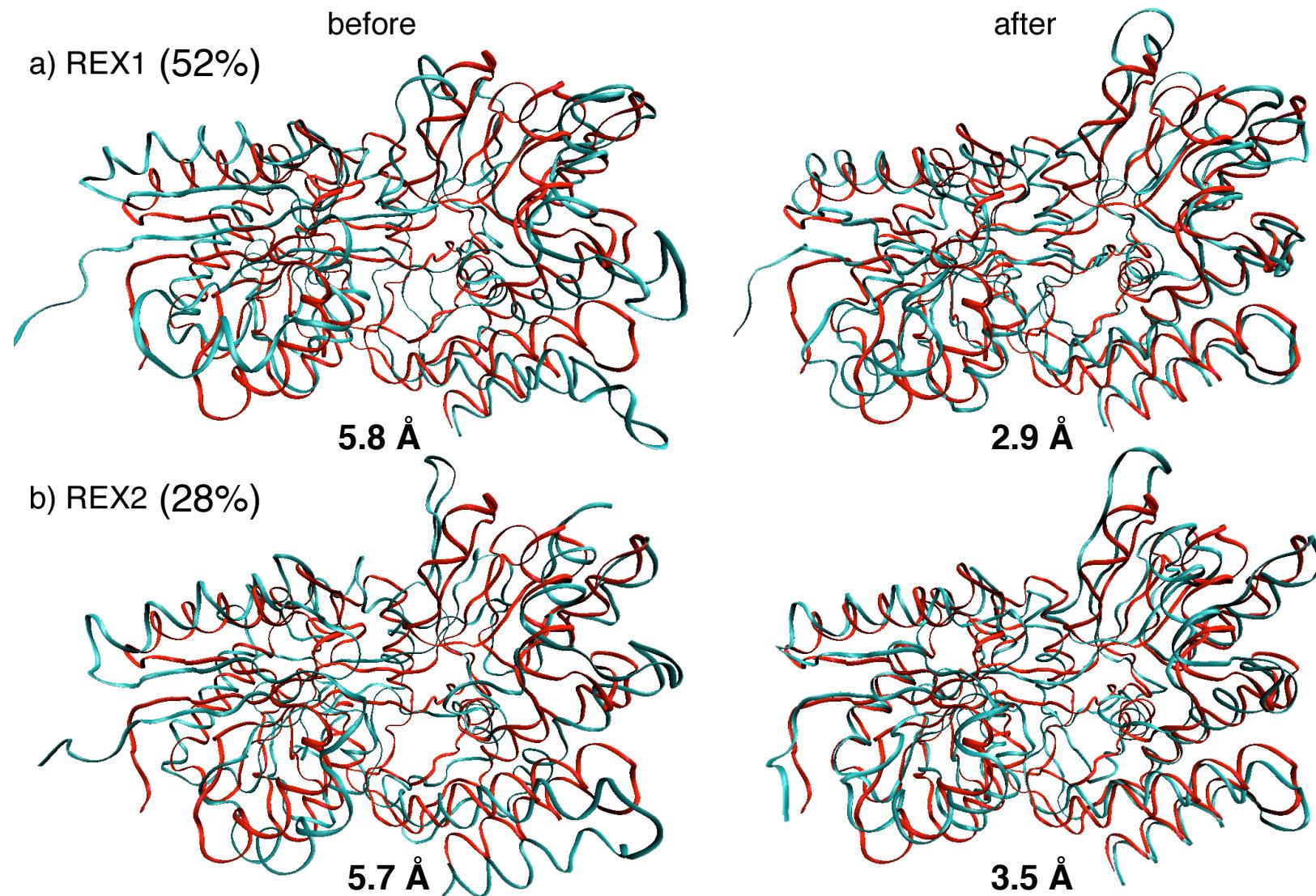
- All NOE and dihedral angle restraints were used.
- 48 replicas were simulated at 300 to 800 K until converged.
- Total of 1.0 ns REX/GB simulation.



	Initial	Final
RMSD to X-ray (Å) ^a		
Global	4.3±4.1	2.3±2.6
N-domain	2.5±2.1	2.2±1.4
C-domain	3.0±3.2	2.0±1.9
φ/ψ space: residues (%)		
Most favored	72.2	84.3
Additionally allowed	22.8	13.3
Generously allowed	3.8	1.6
Disallowed	1.2	0.8
Violation statistics		
RMSD of NOEs (Å)	0.0047	0.014
NOE violations (> 0.2 Å)	2.85	4.42
RMSD of angles (in degrees)	0.53	6.25

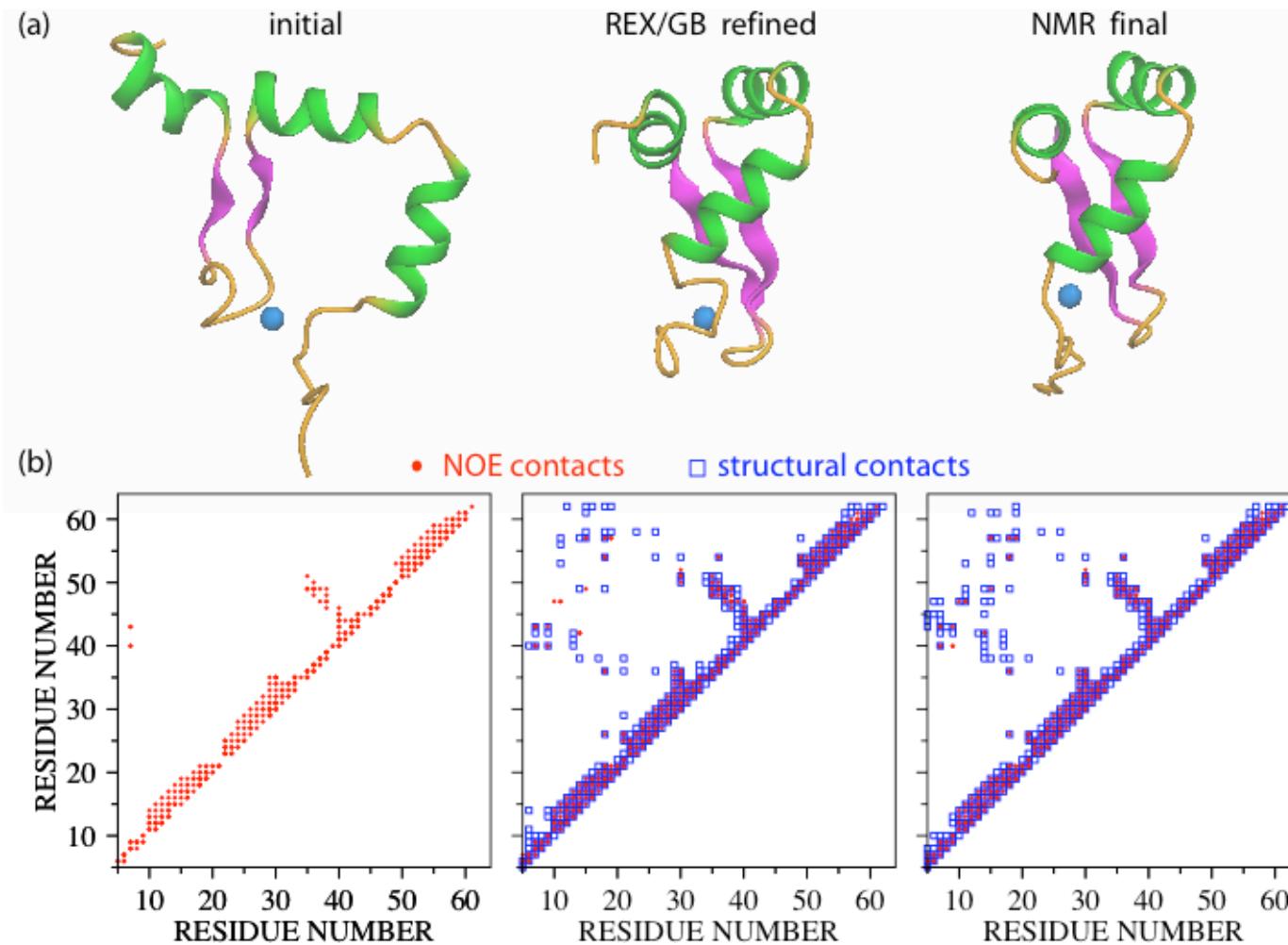
^a Backbone RMSD with respect to PDB:1dmb shown.
Global: residues 6-235 and 241-370;
N-domain: 6-109 and 264-309;
C-domain: 114-235, 241-258 and 316-370.

Representative Structures: MBP



RMSD values: from X-ray (PDB:1dm); backbone atoms of residues 6-235 and 241-370.

REX/GB Refinement for Native-like Models from Limited NMR Data



Cost: ~12h wall time using 16 Intel 2.4GHz CPUs

Membrane Proteins

Excellent Results to Come This Fall !

Excellent Results to Come This Fall !

CASPR Refinement Experiment

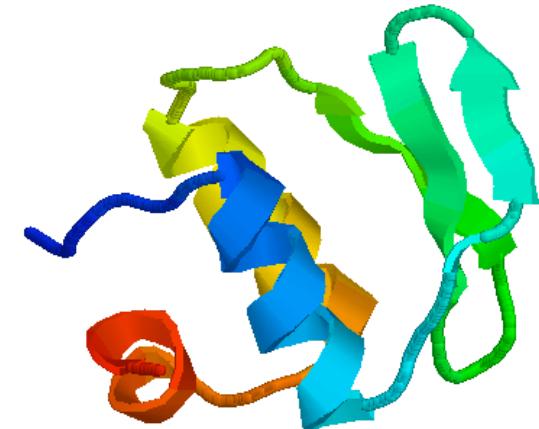
- 5 monomer targets
 - CA RMSD ~ 2-4 Å; GDT_TS ~ 60-80
- Topological Restraints
 - Long secondary structures:
helices and strands

$$E(\theta) = k_\theta \max(0, |\theta - \theta_0| - \Delta_\theta)^2,$$

- Tertiary fold: as defined by residue contacts

$$E(\rho) = k_\rho \max(0, \rho - \rho_0)^2$$

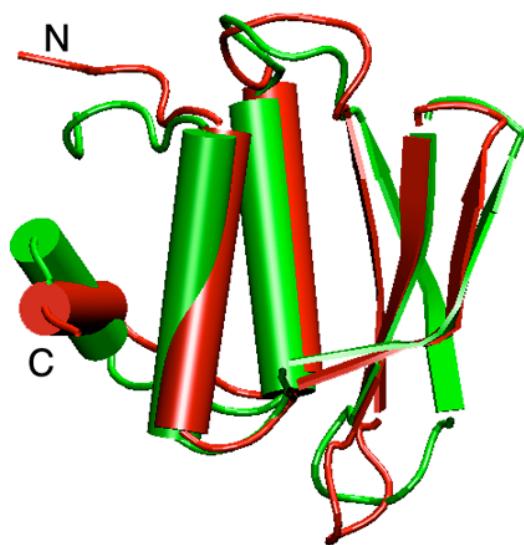
$$\rho = \frac{1}{N_c} \sum_i 1 - \frac{1}{1 + \exp[\gamma (r_i - r_{\text{cutoff}} - 5/\gamma)]}.$$



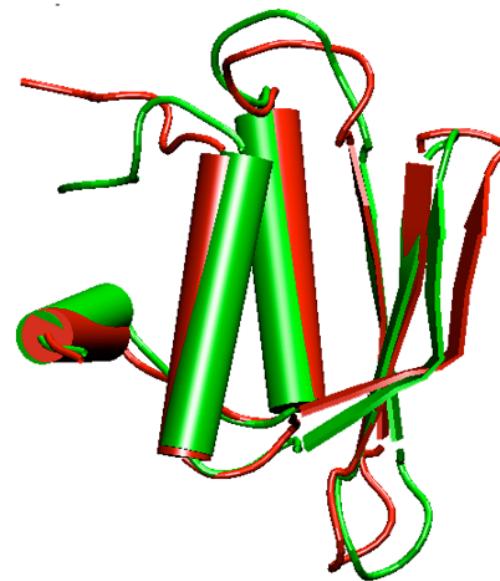
Distance
Matrix
Potential

A Positive Example: TMR04

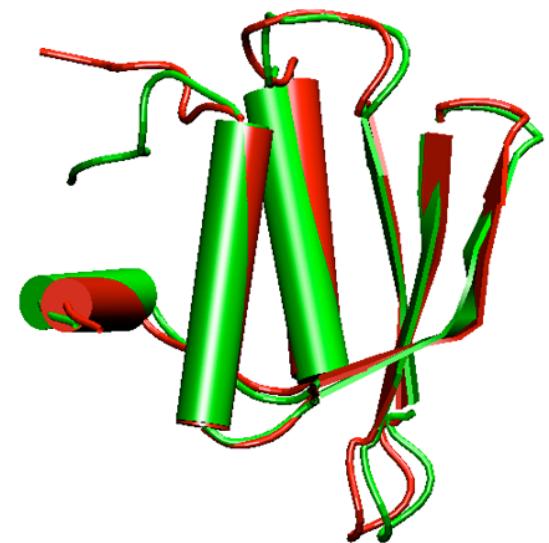
a) Initial Model



b) Ref-1 Model 1



c) Ref-2 Model 1



RMSD (Å) 2.18 (2.04)

1.88 (1.26)

1.57 (0.98)

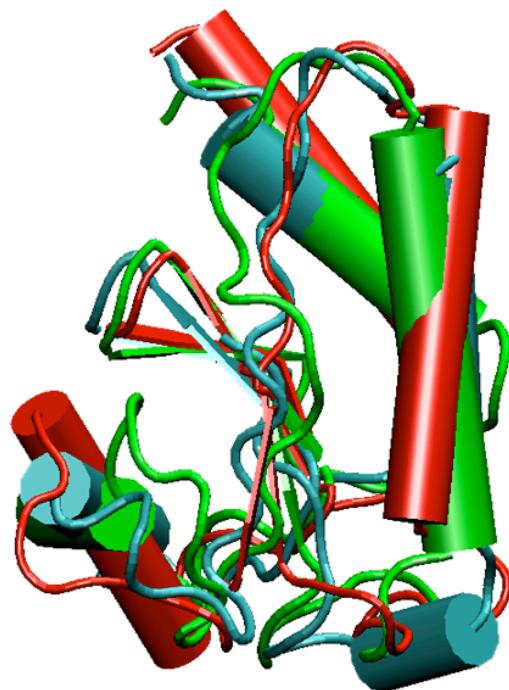
GDT_TS 76.1

85.7

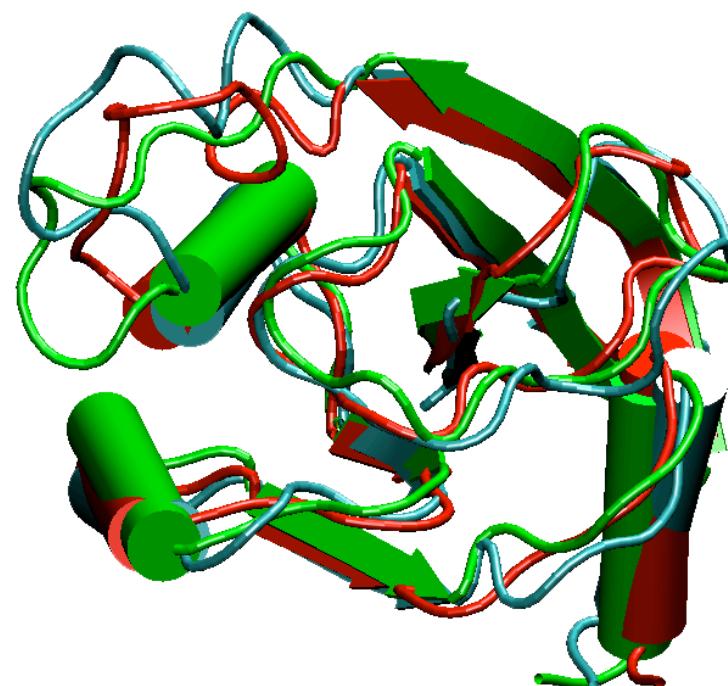
90.0

Where It Fails: Long Loops

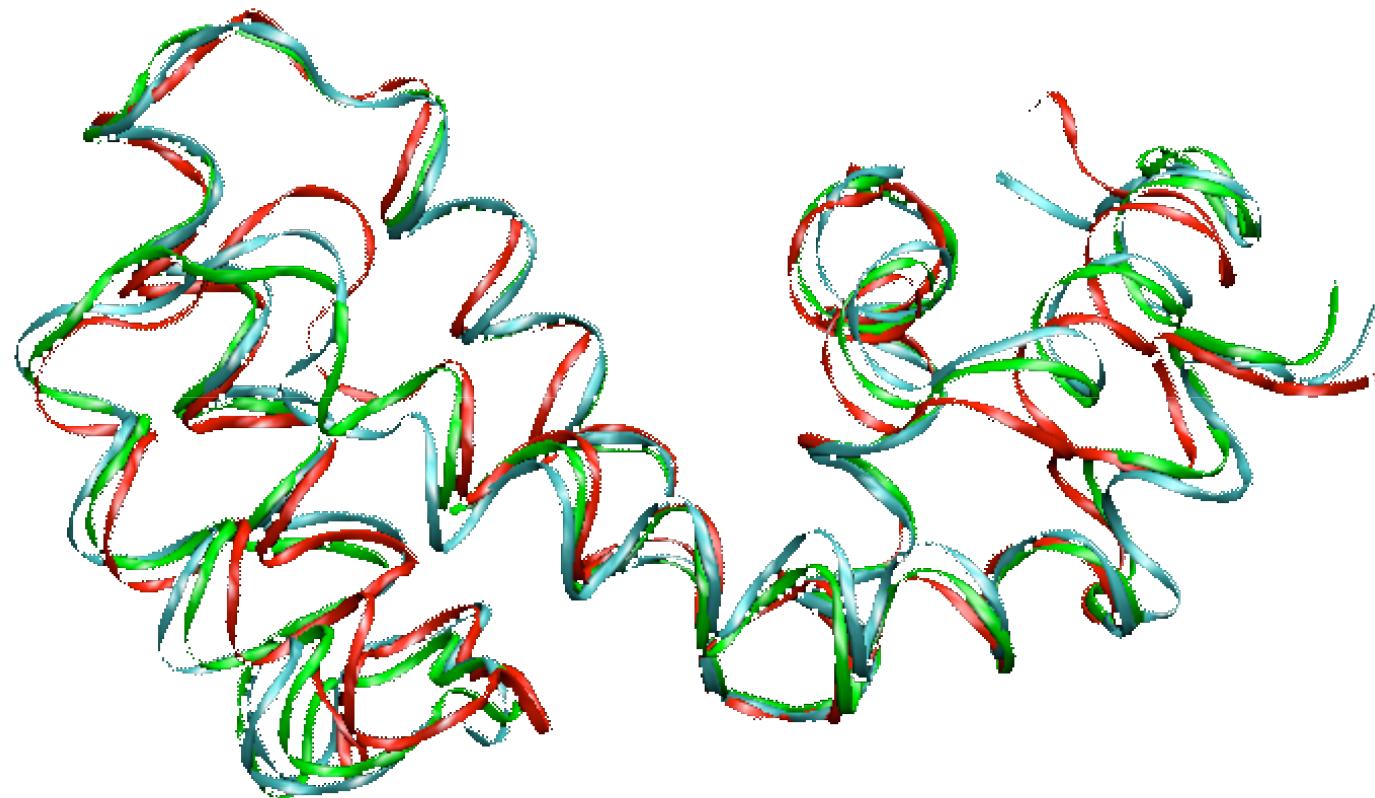
a) TMR06



b) TMR07



A Blind Test: T0302



Red: PDB:2H33

Blue: PROTINFO_TS2

Green: Refined Model 1

RMSD=2.53Å, GDT_TS=72.4 RMSD=1.93Å, GDT_TS=81.1