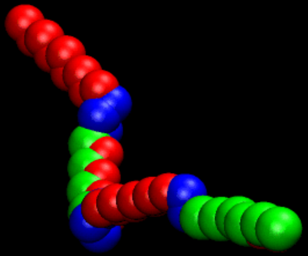
New developments in enhanced conformational sampling using molecular dynamics



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NSF

THE CAMILLE
& HENRY DREYFUS
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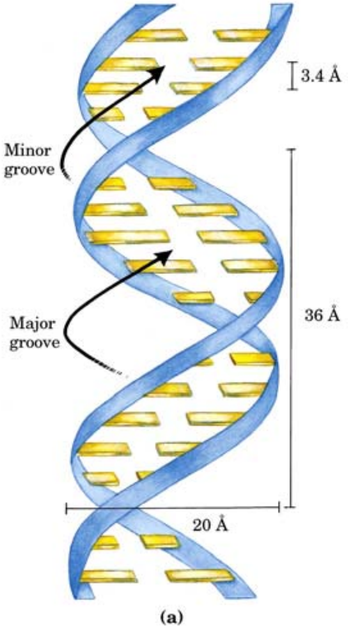
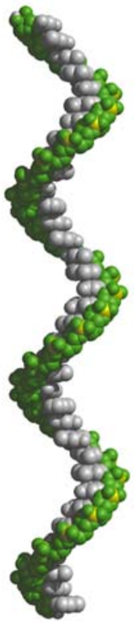
DNA



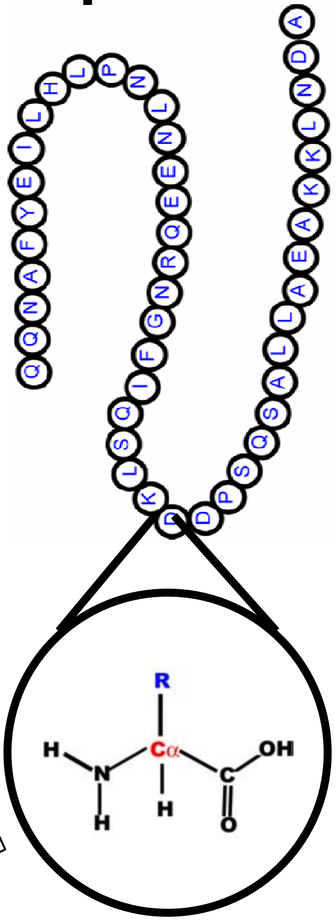
Translation

RNA

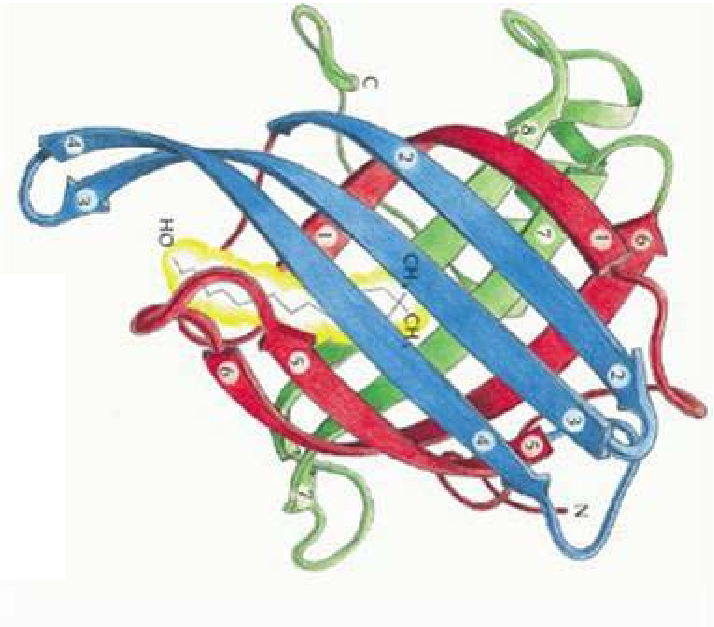


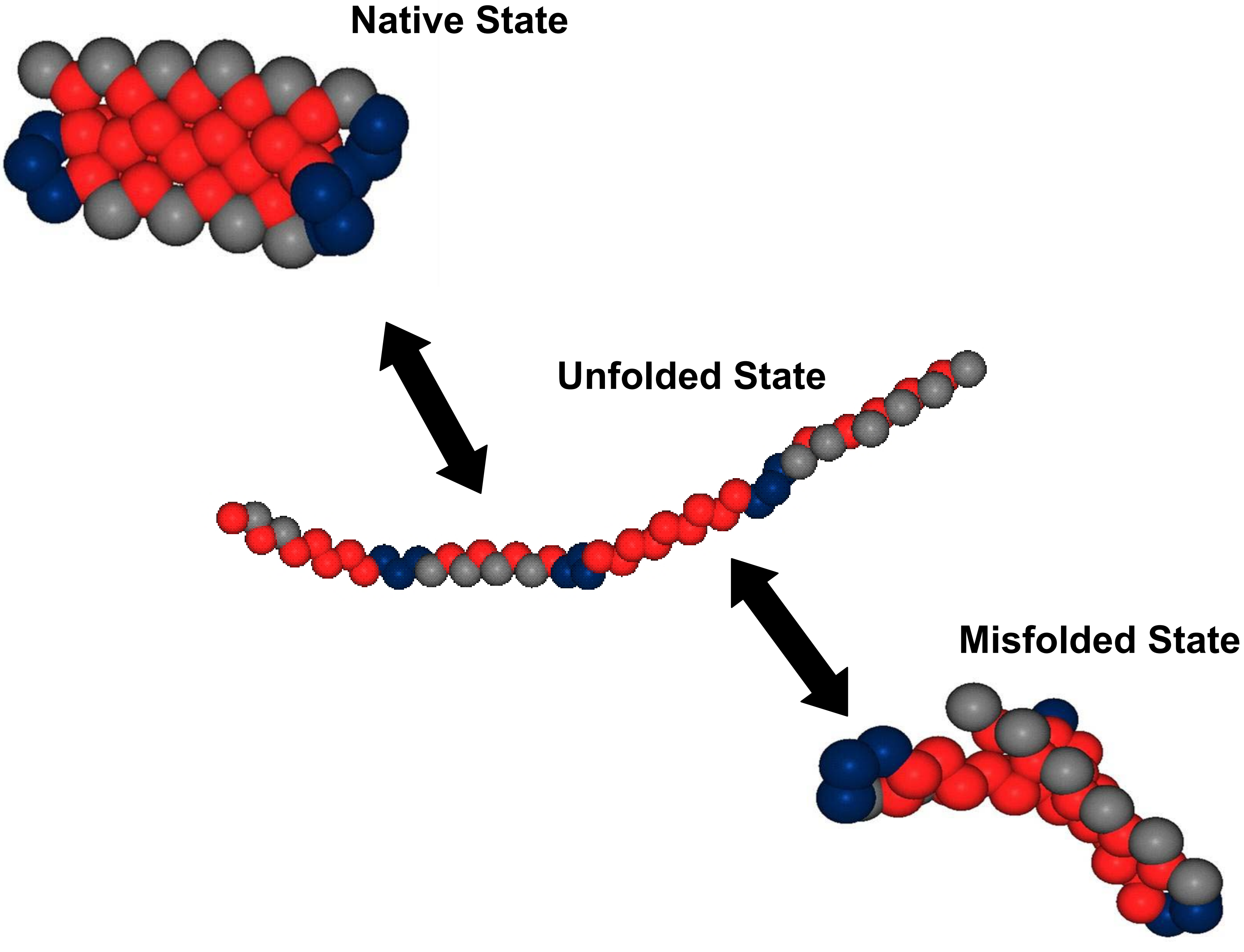
Transcription

Protein Sequence



FOLDING





Native State

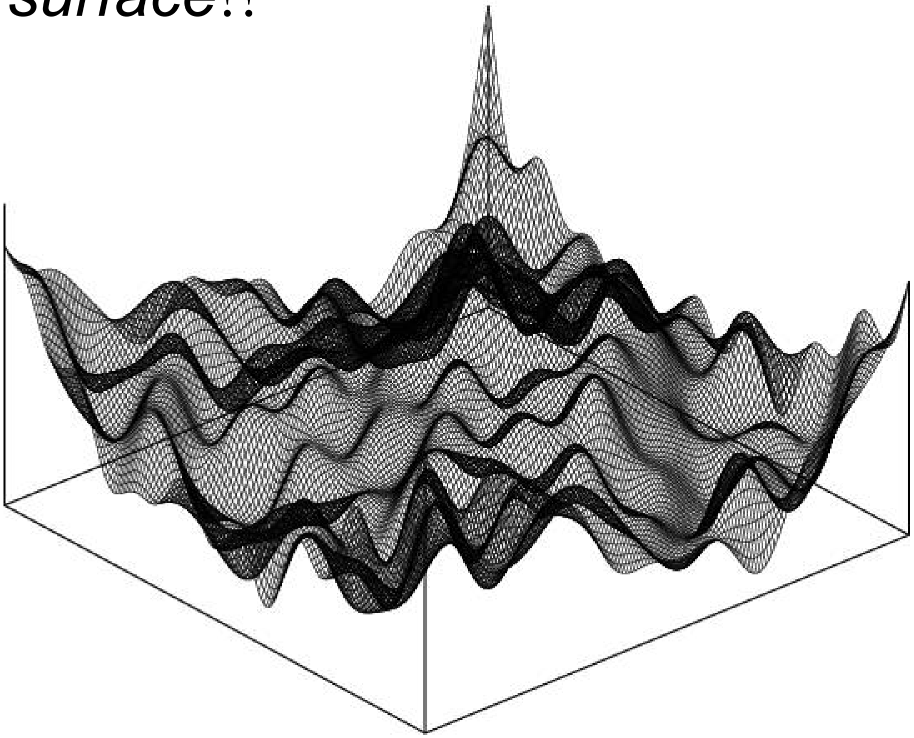
Unfolded State

Misfolded State

Why we cannot sample conformations

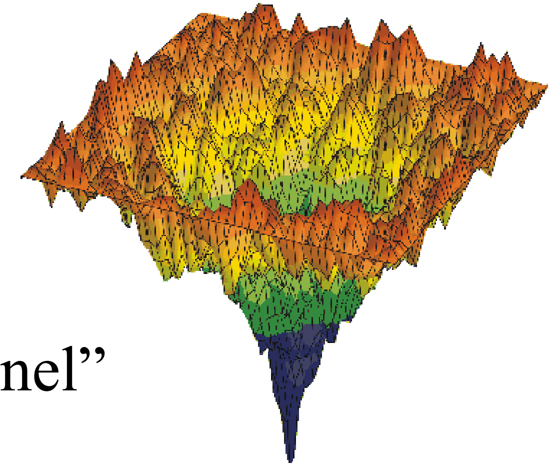
This is our potential energy surface!!

"Rough" energy landscape



Levinthal paradox:

Protein with 100 amino acids has 10^{50} possible conformations!



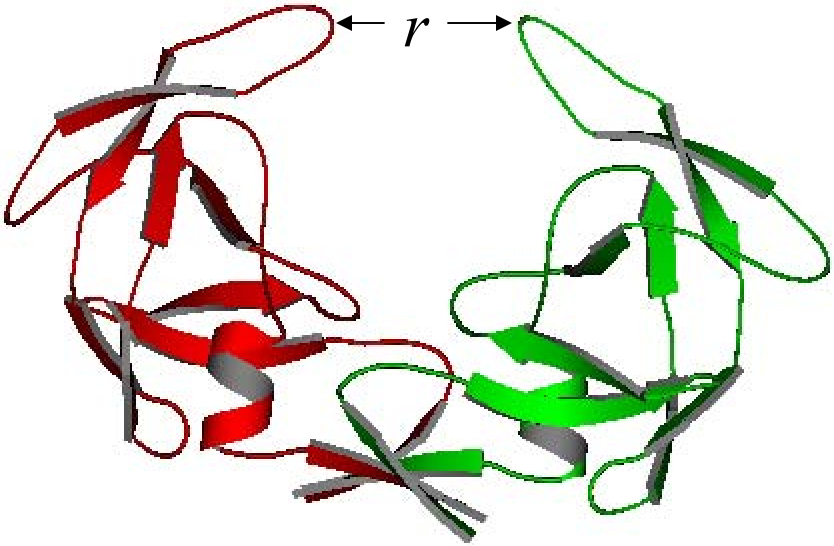
"Folding funnel"

Adiabatic free-energy dynamics (AFED)

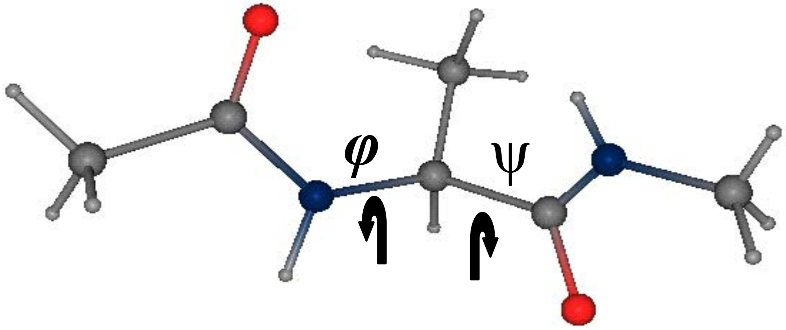
With: **Lula Rosso** (Imperial College) and **Jerry B. Abrams** (BU)

Small subset of collective variables of interest

Distances



Dihedral angles:



Denote these coordinates as

$$q_\alpha(\mathbf{r}) \qquad \alpha = 1,\ldots,n$$

Adiabatic free-energy dynamics

L. Rosso and MET *Mol. Simulat.* **28**, 91 (2002); L. Rosso, P. Minary, Z. Zhu, MET *J. Chem. Phys.* **116**, 4389 (2002)

In a transformation to generalized coordinates:

$$q_\alpha = q_\alpha(\mathbf{r}_1,\ldots,\mathbf{r}_N) \qquad \alpha = 1,\ldots,3N \quad ; \qquad \mathbf{r}_i = \mathbf{r}_i(q_1,\ldots,q_{3N})$$

Suppose first *n* are of particular interest.

$$P(s_1,\ldots,s_n) = \int d^N\mathbf{p}\,d^N\mathbf{r}\; e^{-\beta H(\mathbf{p},\mathbf{r})}\prod_{\alpha=1}^{n}\delta(q_\alpha(\mathbf{r})-s_\alpha)$$

$$= \int d^N\mathbf{p}\,d^{3N}q\; e^{-\beta\tilde{H}(\mathbf{p},q)}\prod_{\alpha=1}^{n}\delta(q_\alpha-s_\alpha)$$

$$H = \frac{1}{2}\mathbf{p}^T M^{-1}\mathbf{p} + V(\mathbf{r}) \qquad \tilde{H} = \frac{1}{2}\mathbf{p}^T M^{-1}\mathbf{p} + V(\mathbf{r}(q)) - kT\ln J(q)$$

Adiabatic and temperature conditions: $m_{1,\ldots,n} \gg m_{n+1,\ldots,3N}$ $\qquad T_s \gg T$

Free-energy surface: $$A(s_1,\ldots,s_n,T) = -kT_s\ln P_{\text{adb}}(s_1,\ldots,s_n)$$

Adiabatic Free-Energy Dynamics

L. Rosso and MET *Mol. Simulat*. **28**, 91 (2002); L. Rosso, P. Minary, Z. Zhu, MET *J. Chem. Phys*. **116**, 4389 (2002)

Equations of motion:

$\alpha = 1,\ldots,n$	$\alpha = n+1,\ldots.,3N$
$m_\alpha \ddot{q}_\alpha = F_\alpha(q) + \text{ heat bath}(T_s)$	$m_\alpha \ddot{q}_\alpha = F_\alpha(q) + \text{ heat bath}(T)$

Analysis using the Liouville operator:

S. Samuelson and G. J. Martyna, *J. Chim. Phys*. **94**, 1503 (1997)
D. Marx, MET, G. J. Martyna, *Comput. Phys. Comm*. **118**, 166 (1999)
L. Rosso, P. Minary, Z. Zhu, MET *J. Chem. Phys*. **116**, 4389 (2002)
L. Rosso and MET *Mol. Simulat*. **28**, 91 (2002)
J. B. Abrams, L. Rosso and MET *J. Chem. Phys*. **125**, 074115 (2006) (solvation free energy)
J. B. Abrams and MET *J. Phys. Chem. B* **112**, 15742 (2008)

Adiabatic Free-Energy Dynamics

Free energy surface at temperature *T*:

$$e^{-\beta A(q_1,\ldots,q_n;\beta)} = \int d^{3N-n}q \; e^{-\beta\tilde{V}(q_1,\ldots,q_{3N})}$$

Free energy surface at temperature T_s:

$$e^{-\beta_s A(q_1,\ldots,q_n;\beta)} = \left[e^{-\beta A(q_1,\ldots,q_n;\beta)} \right]^{\beta_s/\beta}$$

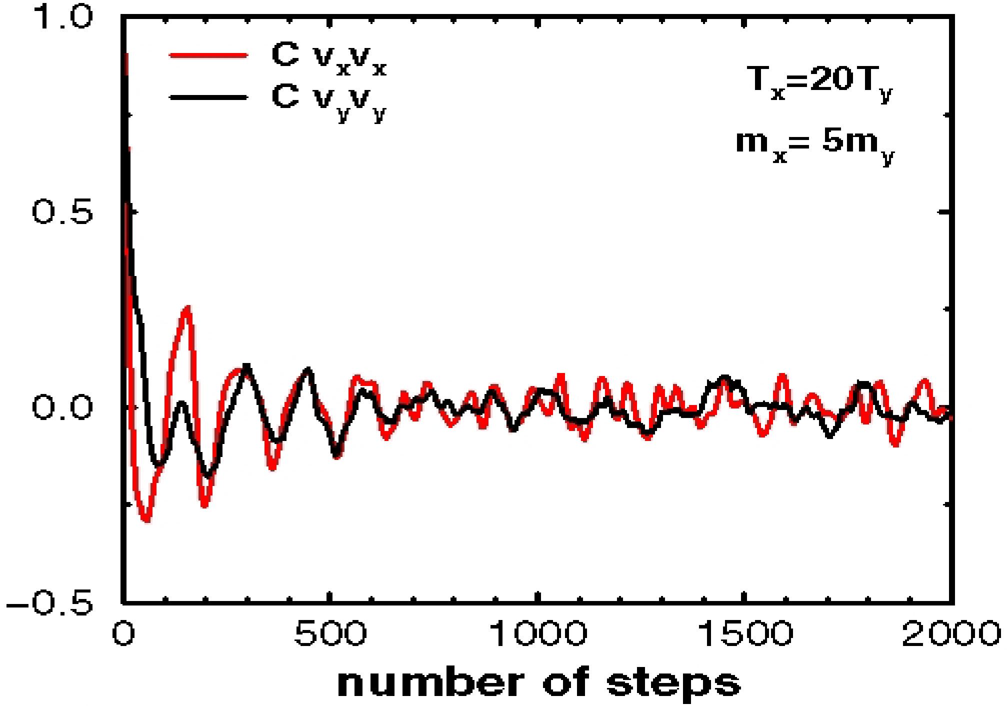
$$= \left[\int d^{3N-n}q \; e^{-\beta\tilde{V}(q_1,\ldots,q_{3N})} \right]^{\beta_s/\beta}$$

$$= P_{\text{adb}}(q_1,\ldots,q_n;\beta,\beta_s)$$

Free energy profile given by:

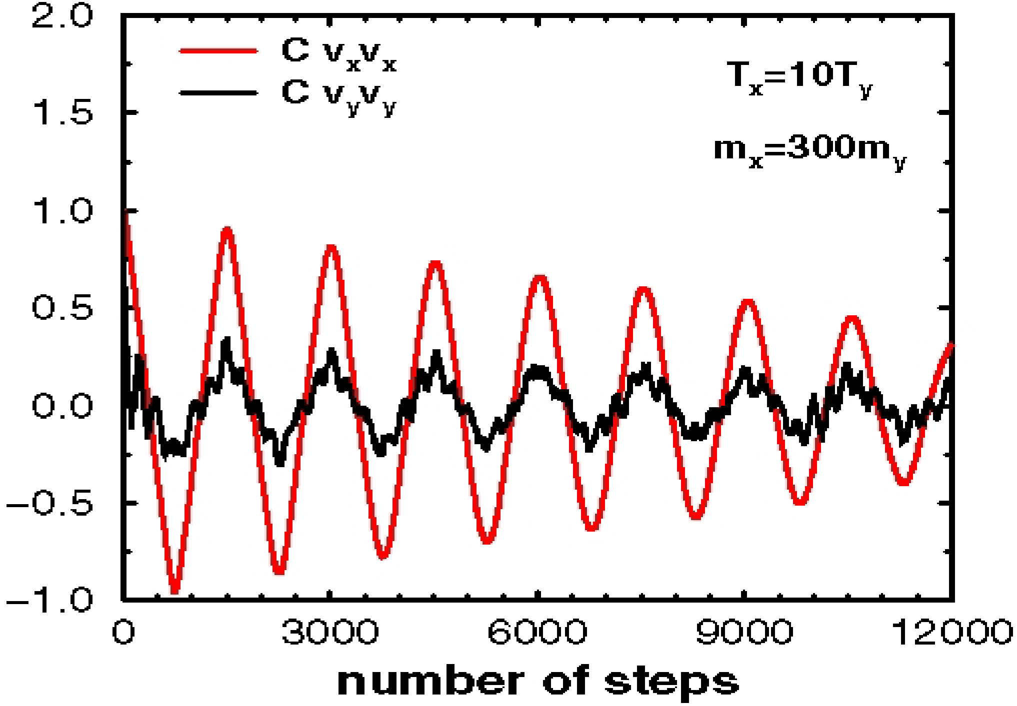
$$\boxed{A(q_1,\ldots,q_n;\beta) = -kT_s \ln P_{\text{adb}}(q_1,\ldots,q_n;\beta,\beta_s)}$$

L. Rosso, P. Minary, Z. Zhu, MET
J. Chem. Phys. **116**, 4389 (2002)



Toy model:

$$V(x,y)=D_0\left(x^2-a^2\right)^2 +\frac{1}{2}ky^2+\lambda xy$$

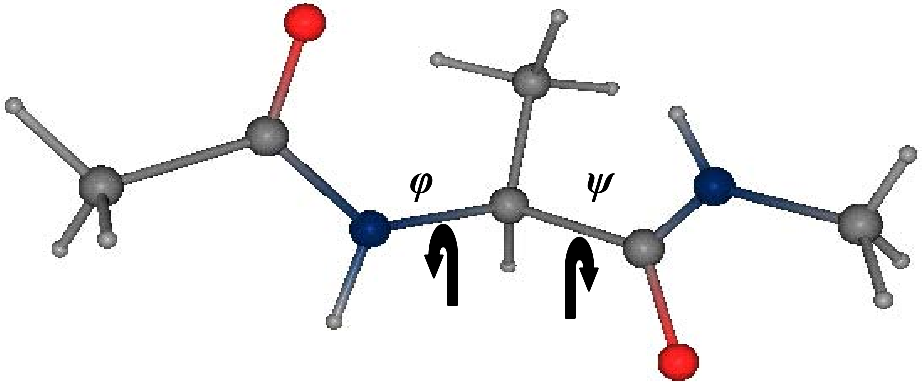


$$C_{v_xv_x}(t)=\left\langle \dot{x}(0)\dot{x}(t)\right\rangle$$

$$C_{v_yv_y}(t)=\left\langle \dot{y}(0)\dot{y}(t)\right\rangle$$

Conformational sampling of the solvated alanine dipeptide

[L Rosso, J. B. Abrams and MET J. Phys. Chem. B **109**, 2099 (2005)]

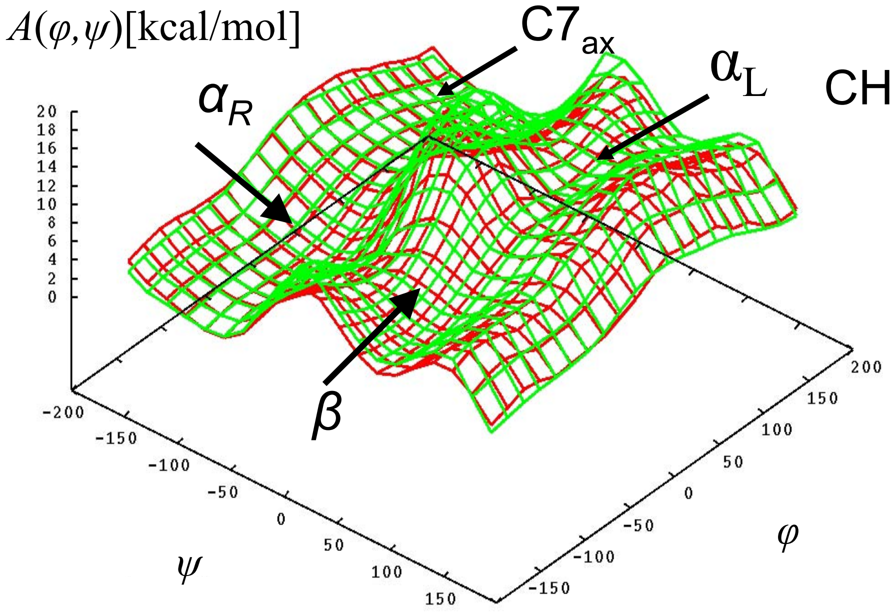


	Time	FF	β	α_R	$C7_{ax}$	α_L
Meta[1]	5 ns	CHm27	1.0	0.0	4.8	7.4
US	400 ns	CHm22	0.3	0.0	3.9	4.4
AFED	4.7 ns	CHm22	0.2	0.0	4.6	8.2

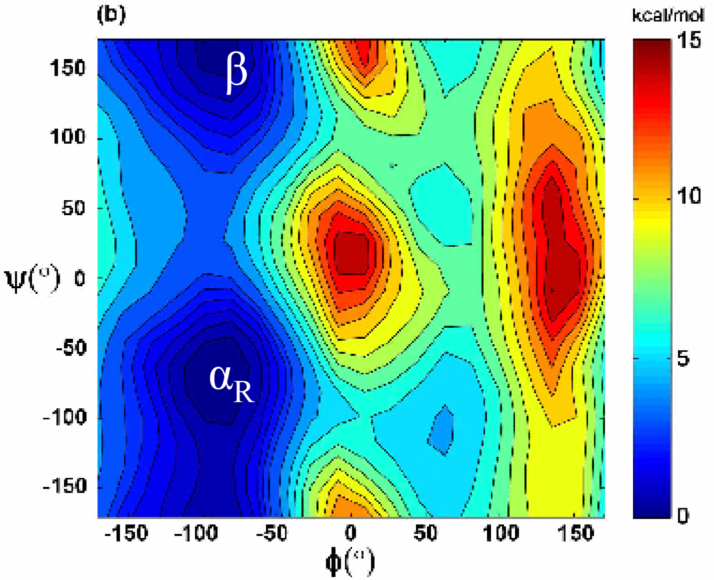
🟥 AFED $T_{\varphi,\psi} = 5T$, $M_{\varphi,\psi} = 50M_C$ 4.7 ns

🟩 Umbrella Sampling 50 ns

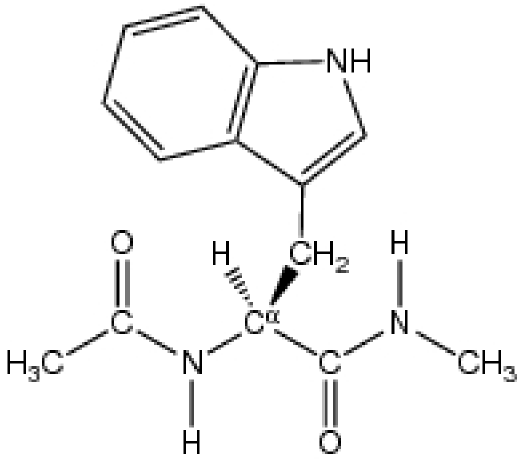
1. Laio and Parrinelli, PNAS (2002)
   Ensing, et al. ACR **39**, 73 (2005)

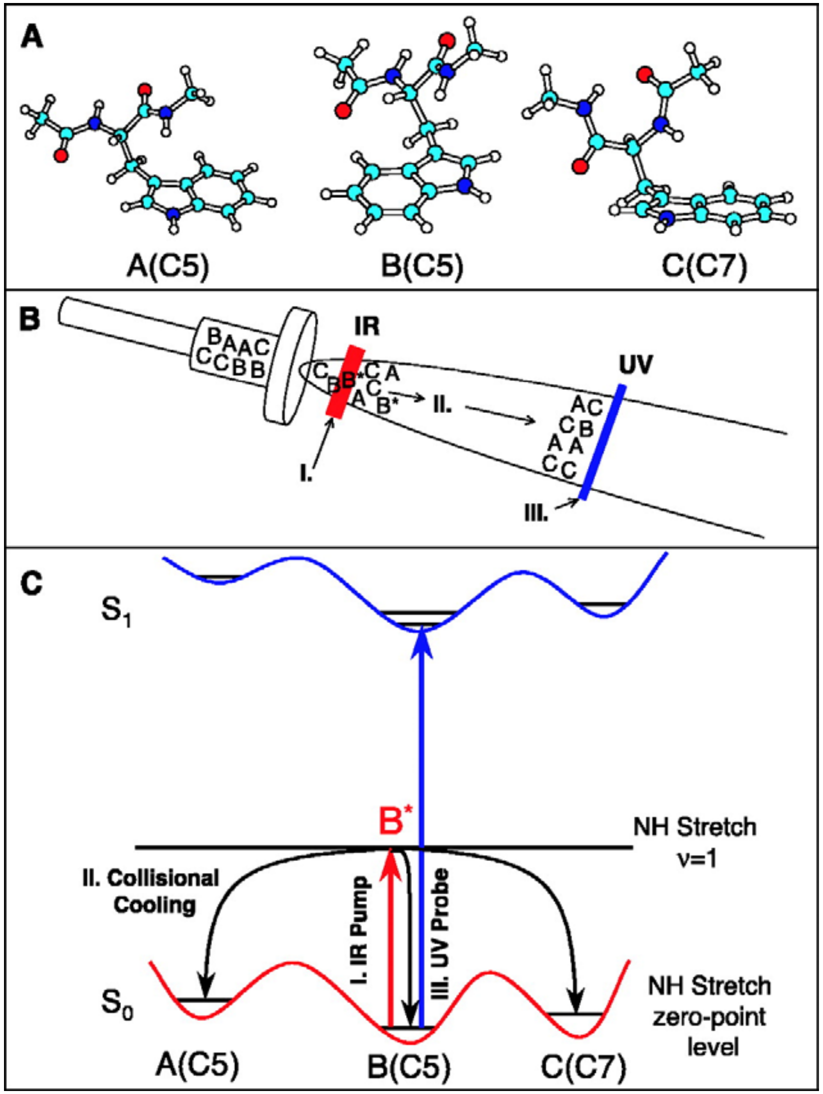


CHARMm22



N-acetyl-tryptophan-methylamide (NATMA)





- Selective IR excitation of molecules from jet gives molecules excess energy.
- Excess energy causes isomerization.
- Collisions lead to cooling.
- UV Probe collision-free cooled populations.

Dian, *et al*. *Science* **296**, 2369 (2002)
Dian, *et al*. *JCP* **117**, 10688 (2002)
Dian, *et al*. *JCP* **120**, 133 (2004)
Dian, *et al*. *JCP* **120**, 9033 (2004)

Ramachandran Surfaces

J. B. Abrams and MET (in preparation)

Simulation Details

$T = 423$ K

$T_{\phi,\psi} = 5T$

$M_{\phi,\psi} = 50M_C$

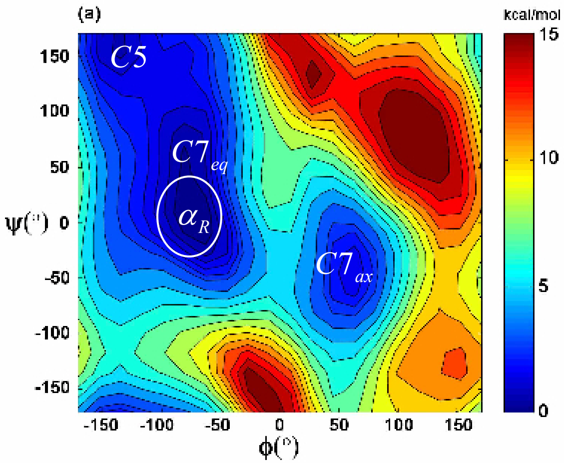
$\Delta t = 2.0$ fs with r-RESPA

Simulation time = 5 ns

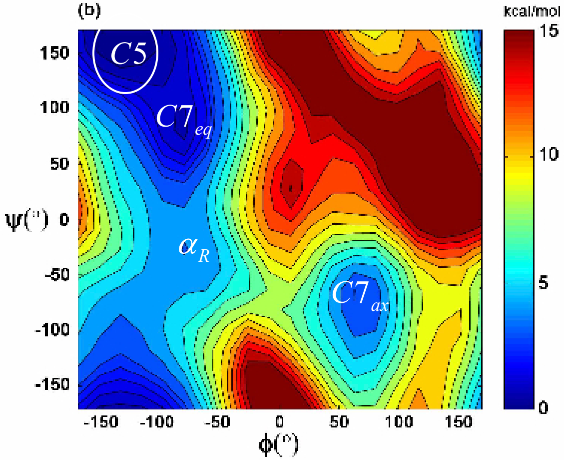
FFs: CHARMM22, AMBER95, OPLS-AA

GGMT Thermostats

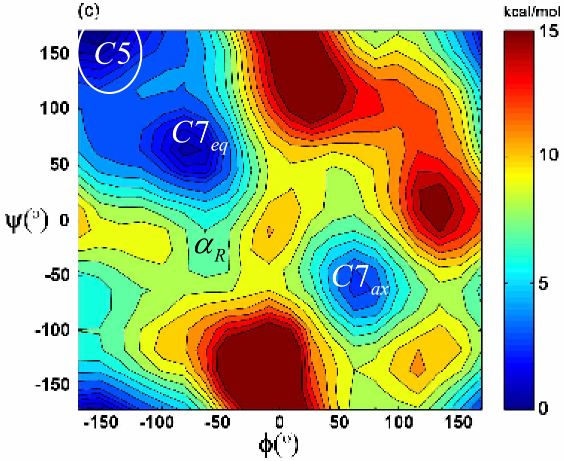
[Liu, et al. JCP **112**, 1685 (2000)]



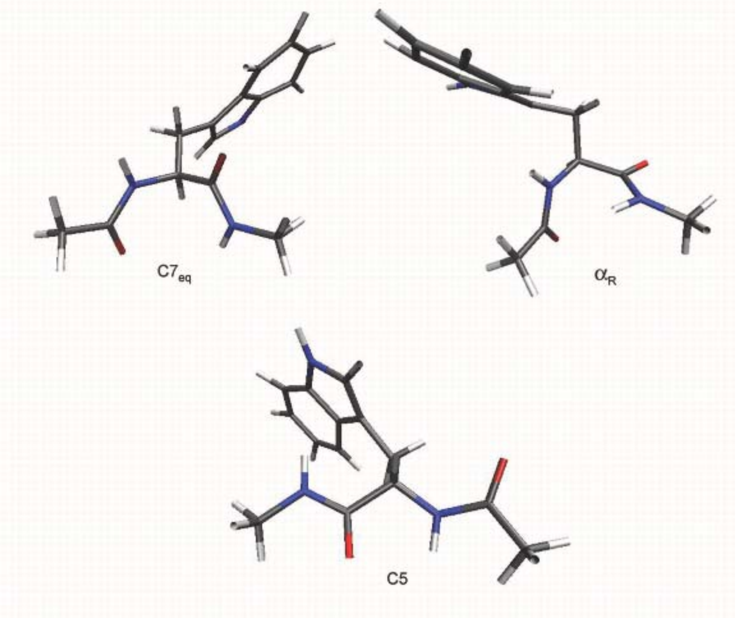
AMBER95



CHARM22



OPLS-AA



Expt. C5 (0.0), C7eq (0.73 kcal/mol)

AFED without transformations/TAMD

Margliano and Vanden-Eijnden, *Chem. Phys. Lett.* **426**, 168 (2006)
J. B. Abrams and MET, *J. Phys. Chem. B* **112**, 14752 (2008)

$$P(s_1,\ldots,s_n) = \int d^N\mathbf{p}\,d^N\mathbf{r}\;e^{-\beta H(\mathbf{p},\mathbf{r})}\prod_{\alpha=1}^{n}\delta(q_\alpha(\mathbf{r})-s_\alpha)$$

Write δ-functions as product of Gaussians:

$$P(s_1,\ldots,s_n) = \lim_{\kappa\to\infty}\left(\frac{\beta\kappa}{2\pi}\right)^{n/2}\int d^N\mathbf{p}\,d^N\mathbf{r}\;e^{-\beta H(\mathbf{p},\mathbf{r})}\prod_{\alpha=1}^{n}\exp\left[-\frac{\beta\kappa}{2}\left(q_\alpha(\mathbf{r})-s_\alpha\right)^2\right]$$

Introduce uncoupled Gaussian integrations:

$$P_\kappa(s_1,\ldots,s_n) = C_\kappa\int d^N\mathbf{p}\,d^N\mathbf{r}\;d^n p_s\,\exp\left\{-\beta\left[H(\mathbf{p},\mathbf{r})+\sum_{\alpha=1}^{n}\frac{p_{s_\alpha}^2}{2m_\alpha}+\frac{\kappa}{2}\sum_{\alpha=1}^{n}\left(q_\alpha(\mathbf{r})-s_\alpha\right)^2\right]\right\}$$

AFED without transformations/TAMD

Now impose adiabatic conditions on $\{s, p_s\}$: $T_s \gg T, \quad m_\alpha >> m$

Distribution generated:

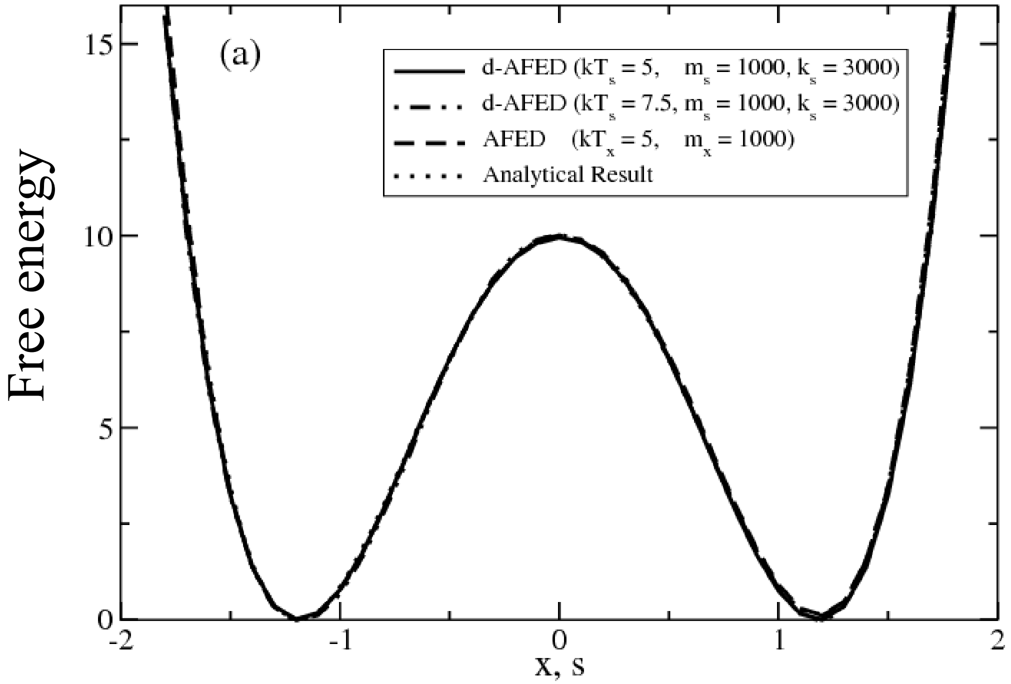
$$P_\kappa^{(\mathrm{adb})}(s_1,\ldots,s_n) \propto \int d^n p_s \exp\left[-\beta_s \sum_{\alpha=1}^{n} \frac{p_{s_\alpha}^2}{2m_\alpha}\right]\left[Z_\kappa(s_1,\ldots,s_n)\right]^{\beta_s/\beta}$$

$$Z_\kappa(s_1,\ldots,s_n) = \int d^N\mathbf{p}\,d^N\mathbf{r}\ \exp\left\{-\beta\left[H(\mathbf{p},\mathbf{r}) + \sum_{\alpha=1}^{n}\frac{p_{s_\alpha}^2}{2m_\alpha} + \frac{\kappa}{2}\sum_{\alpha=1}^{n}\left(q_\alpha(\mathbf{r}) - s_\alpha\right)^2\right]\right\}$$

Free energy surface:

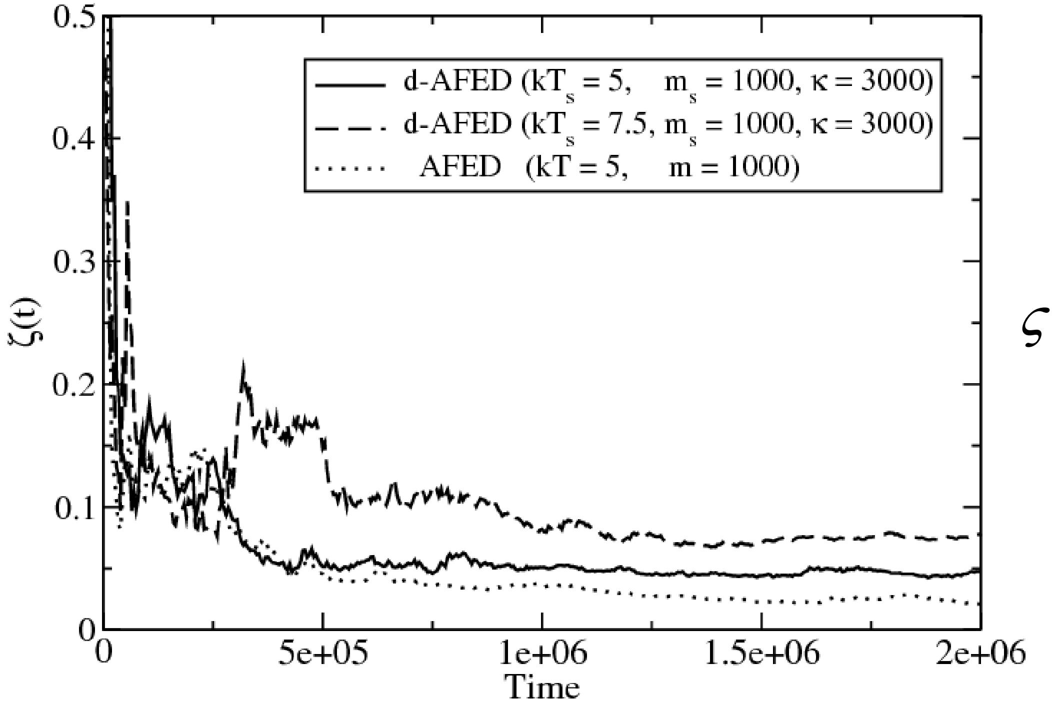
$$A_\kappa(s_1,\ldots,s_n) = -kT_s \ln P_\kappa^{(\mathrm{adb})}(s_1,\ldots,s_n)$$

$$A(s_1,\ldots,s_n) = \lim_{\kappa\to\infty} A_\kappa(s_1,\ldots,s_n)$$



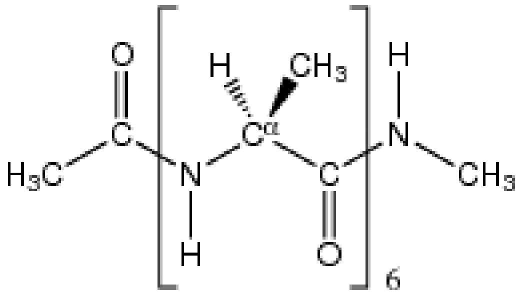
Toy model:

$$V(x,y) = D_0\left(x^2 - a^2\right)^2 + \frac{1}{2}ky^2 + \lambda xy$$



$$\varsigma(t) = \frac{1}{N_{\text{bins}}}\sum_{i=1}^{N_{\text{bins}}}\left[P(x_i;t) - P_{\text{exact}}(x_i)\right]$$

Preliminary results for N-acetyl-(AAAAAA)-methylamide



Simulation Details

$T = 300$ K, $T_s = 600$ K

$m_s = 150 m_C$

$\kappa = 5.4\times10^6\,\mathrm{K}\bullet(\mathrm{A})^{-2}$

(5 r-RESPA steps used for harmonic coupling)

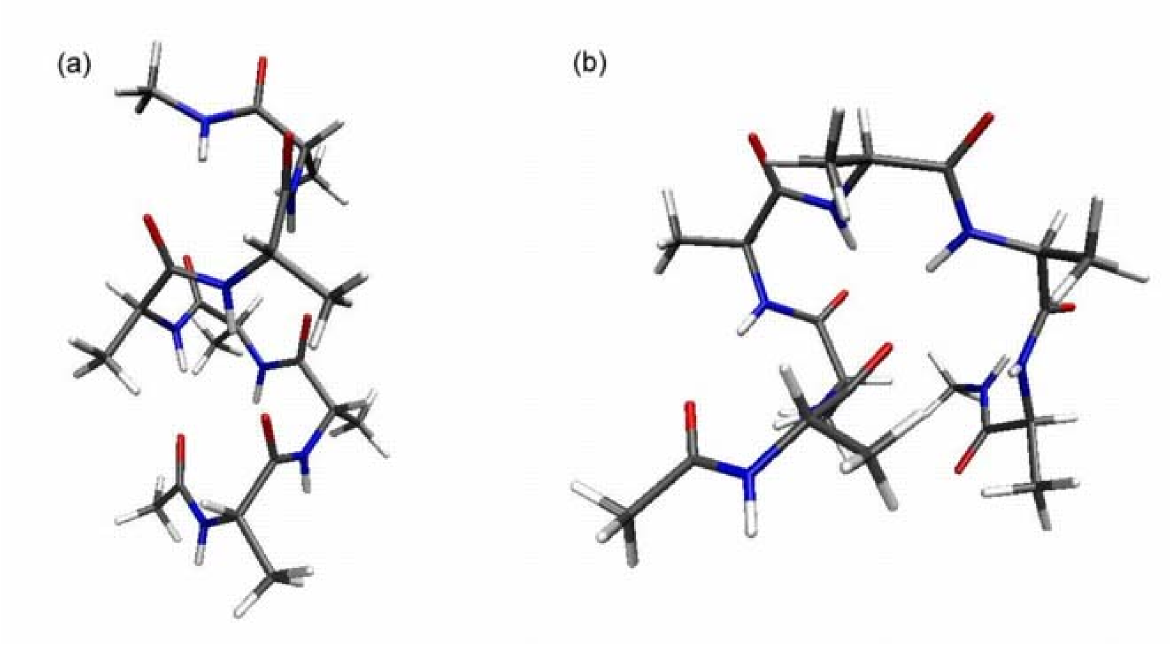
$\Delta t = 6.0$ fs

FF: AMBER95, 698 TIP3P waters

GGMT Thermostats

Run length = 5 ns

Minimum: α_R



Collective variables:

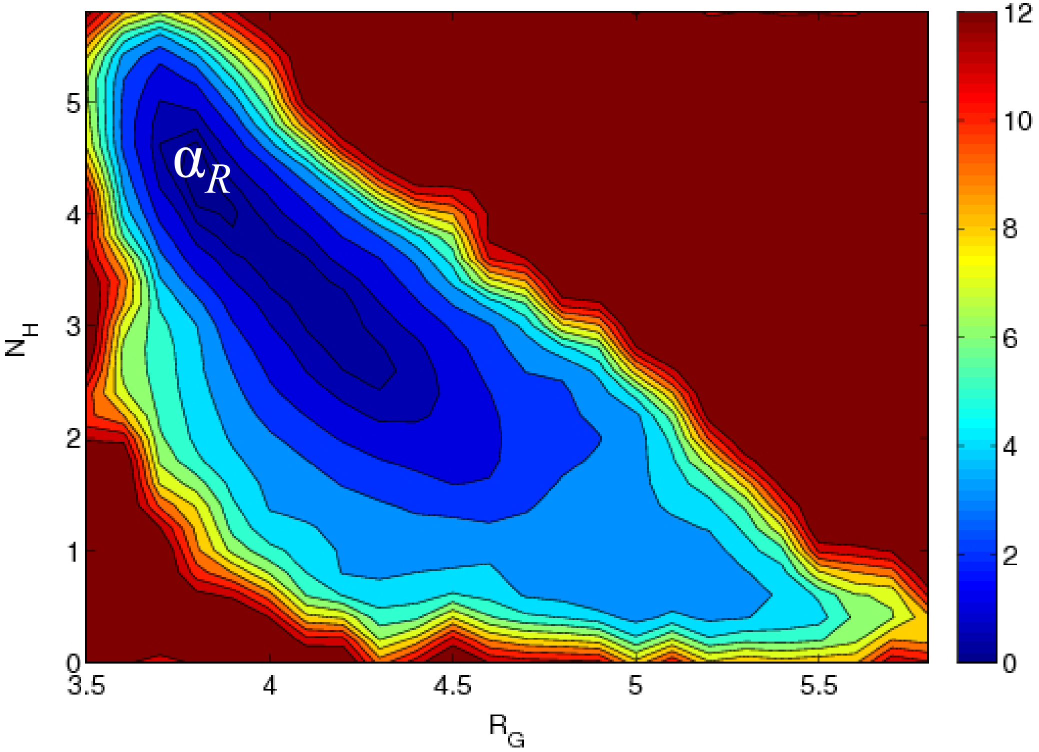
Radius of gyration of backbone:

$$R_G = \sqrt{\frac{1}{N_b}\sum_{i=1}^{N_b}\left(\mathbf{r}_i - \frac{1}{N_b}\sum_{j=1}^{N_b}\mathbf{r}_j\right)^2}$$

Number of hydrogen bonds:

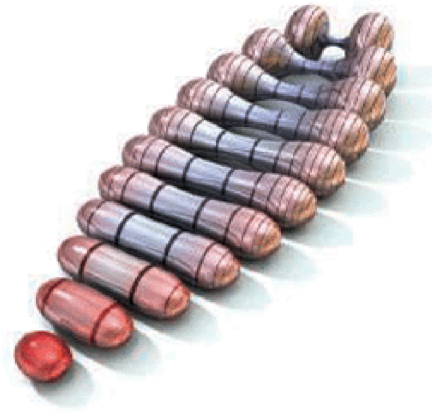
$$N_H = \sum_{i=1}^{N_O}\sum_{j=1}^{N_N}\frac{1-\left(\left|\mathbf{r}_i - \mathbf{r}_j\right|/d_0\right)^6}{1-\left(\left|\mathbf{r}_i - \mathbf{r}_j\right|/d_0\right)^{12}}$$

Free-energy surface of alanine hexamer

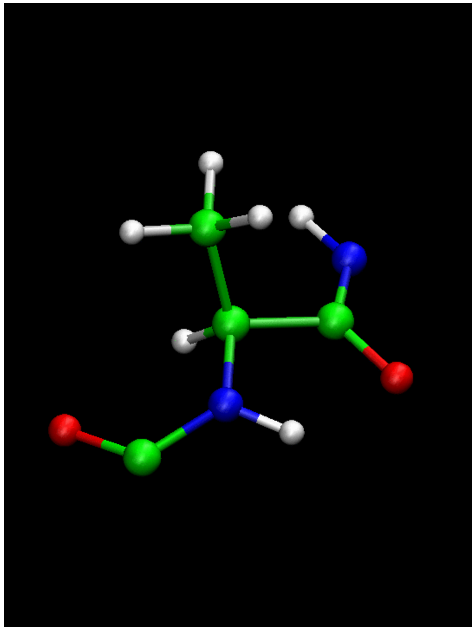


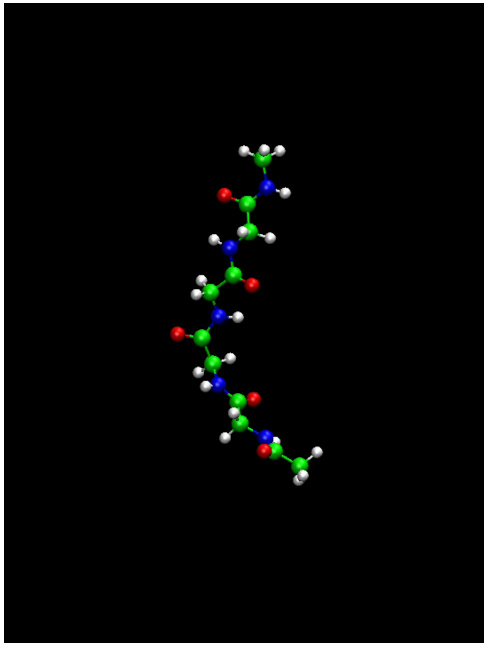
Spatial-Warping Transformations

With: **Glenn J. Martyna** (IBM), **Zhongwei Zhu (**Wall Street**)**, **Peter Minary** (Stanford)

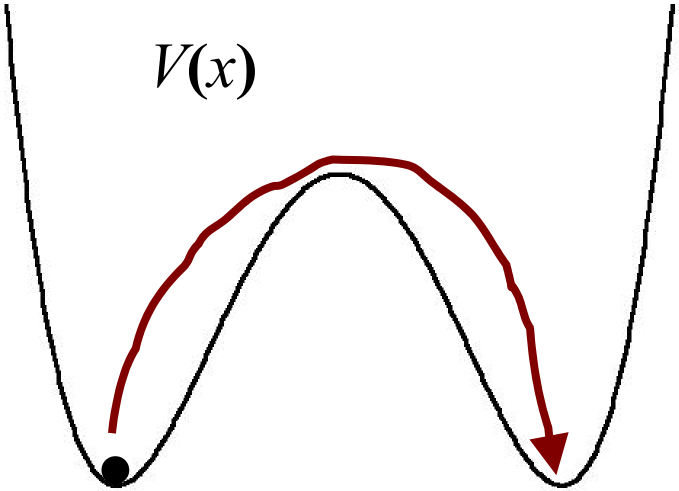


Science, December 22, 2006



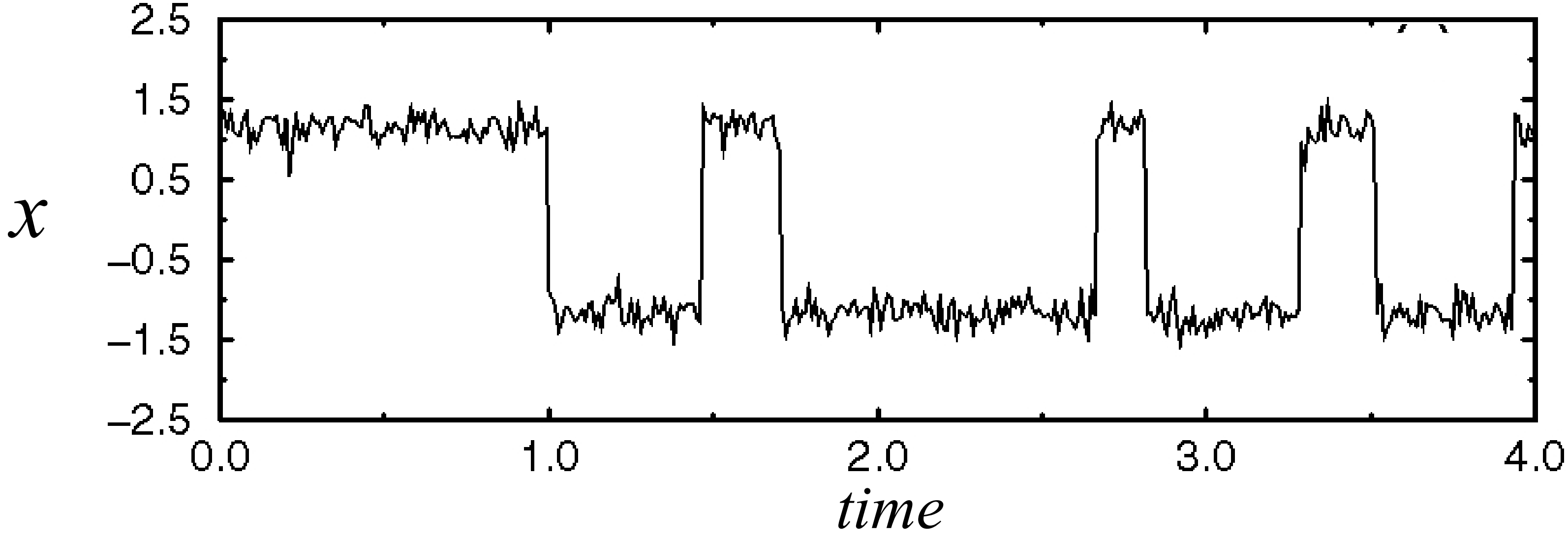


Molecular dynamics in a double well



$$\dot{x} = \frac{p}{m}$$

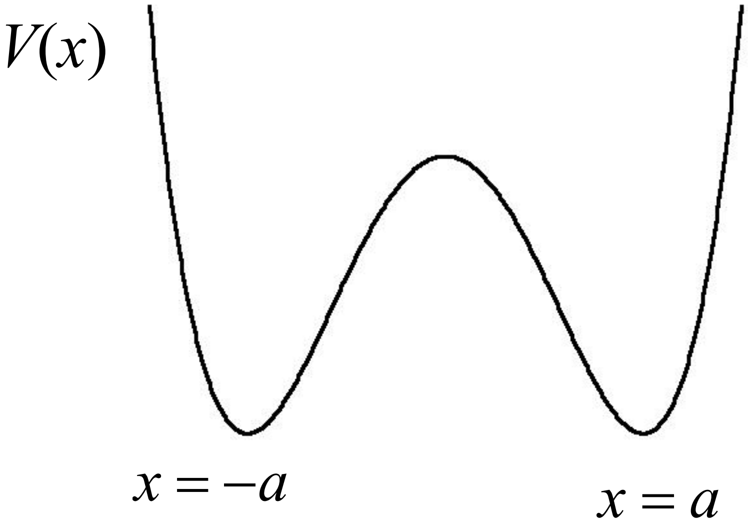
$$\dot{p} = -\frac{dV}{dx} = F(x) + \text{heat bath}$$



Crossing the barrier is a rare event!

Spatial-warping transformations

Z. Zhu, MET, S. O. Samuelson, G. J. Martyna, *Phys. Rev. Lett*. **88** 100201 (2002)



Hamiltonian:

$$H(x,p)=\frac{p^2}{2m}+V(x)$$

Canonical partition function:

$$Q=\int dp\ dx\ \ \exp\left\{-\beta\left[\frac{p^2}{2m}+V(x)\right]\right\}$$

Change the integration variables:

$$u=f(x)=-a+\int_{-a}^{x}dy\ e^{-\beta\tilde{V}(y)}$$

$$dx=e^{\beta\tilde{V}(f^{-1}(u))}du$$

Transformed partition function:

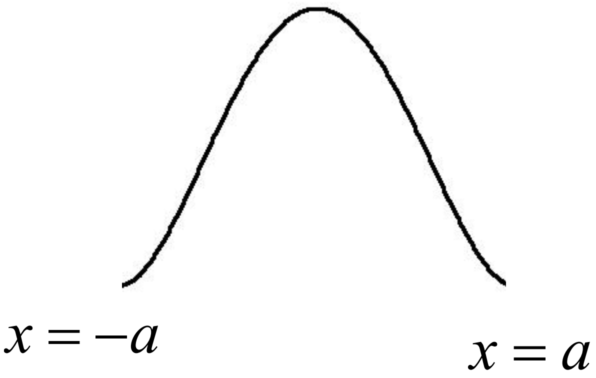
$$Q=\int dp\ du\ \ \exp\left\{-\beta\left[\frac{p^2}{2m}+V\left(f^{-1}(u)\right)-\tilde{V}\left(f^{-1}(u)\right)\right]\right\}$$

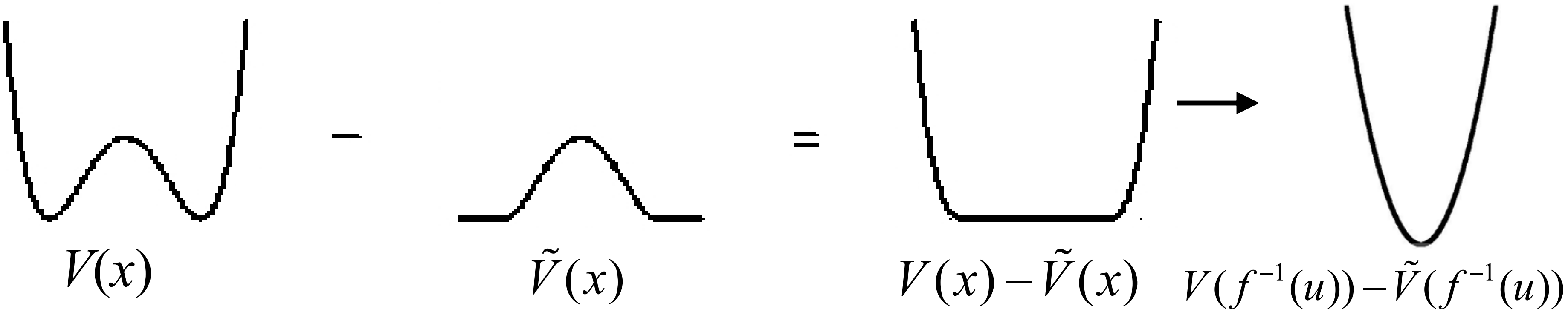
Spatial-warping transformations (cont'd)

$\tilde{V}(x)$

Choosing the transformation:

$$\tilde{V}(x) = \begin{cases} V(x) & -a < x < a \\ 0 & \text{Otherwise} \end{cases}$$





MD: $\dot{u} = \frac{p}{m}$ $\dot{p} = F(u) + \text{heat bath}$

Reference potential spatial warping (REPSWA)

Difference from bias potential methods

Bias potential needs the unbiasing factor:

$$Q = \int dp\ dx\ \exp\left\{-\beta\left[\frac{p^2}{2m} + V\left(x\right) - \tilde{V}\left(x\right)\right]\right\}\exp[-\beta\tilde{V}(x)]$$

Spatial-warping transformations:

$$Q = \int dp\ du\ \exp\left\{-\beta\left[\frac{p^2}{2m} + V\left(f^{-1}(u)\right) - \tilde{V}\left(f^{-1}(u)\right)\right]\right\}$$

System *naturally* moves on the smoother surface. No unbiasing needed.

$V^{\ddagger}$

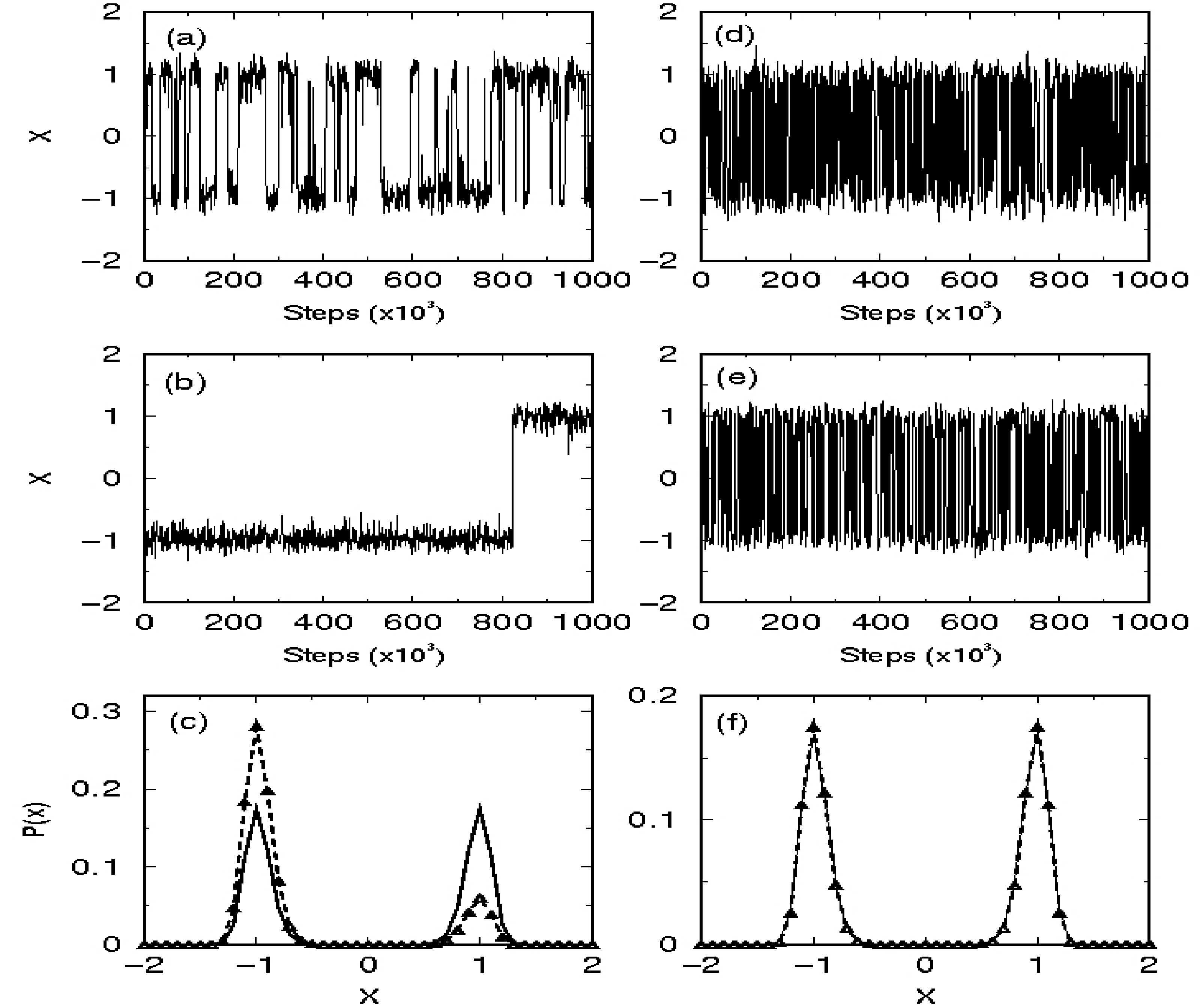
No Transformation

Transformation

5kT

10kT

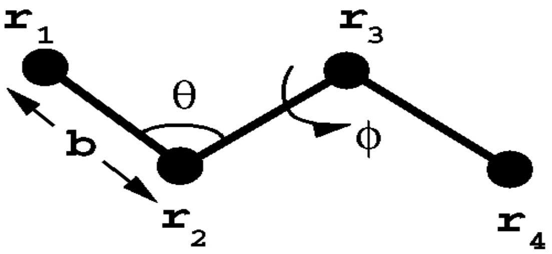
10kT

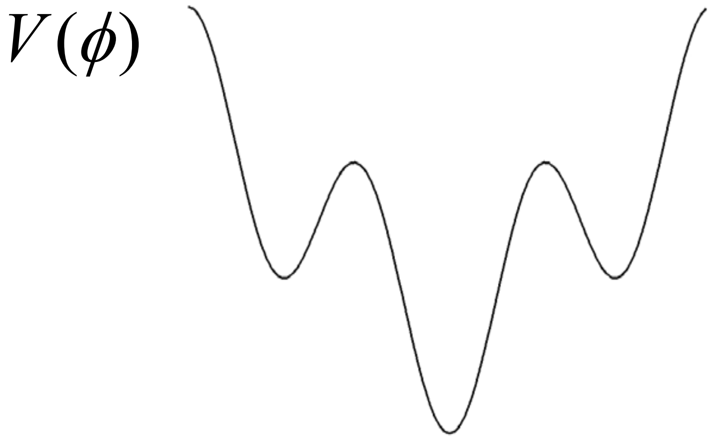


How to do biomolecules and polymers

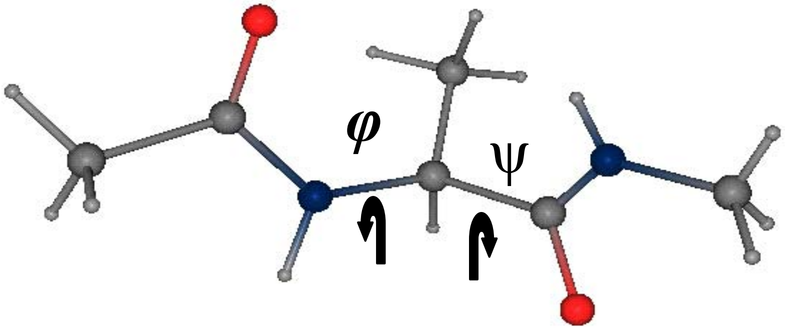
P. Minary, MET, G. J. Martyna *SIAM J. Sci. Comput.* **30**, 2055 (2007)

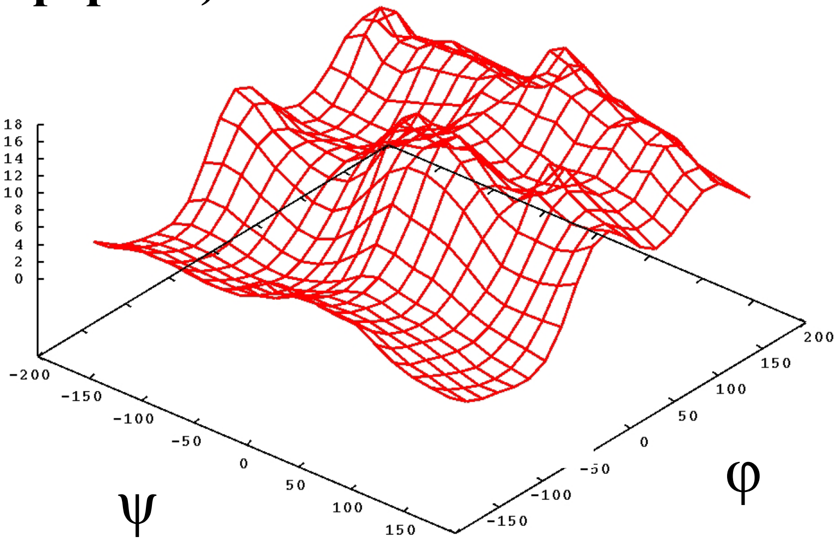
Sampling hindered by barriers in the dihedral angles:



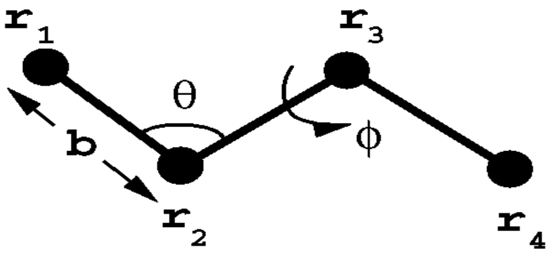


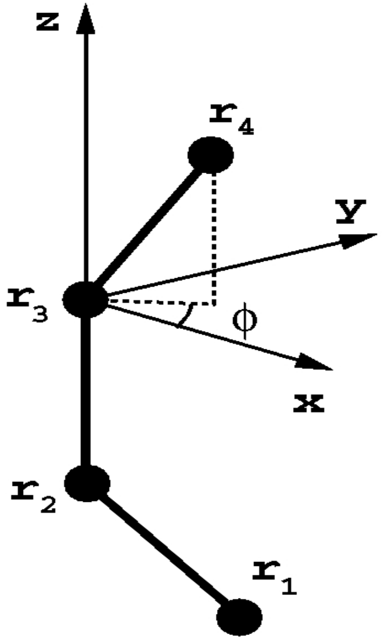
Ramachandran dihedral angles (alanine dipeptide):





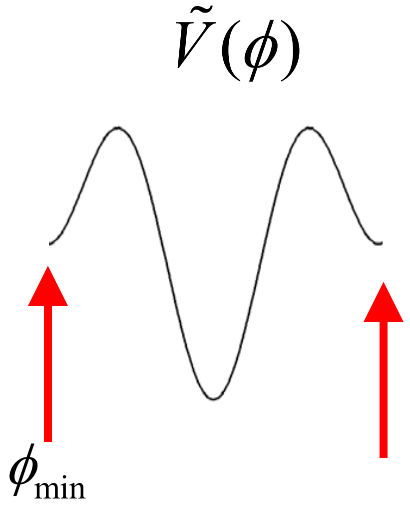
Dihedral angle transformations





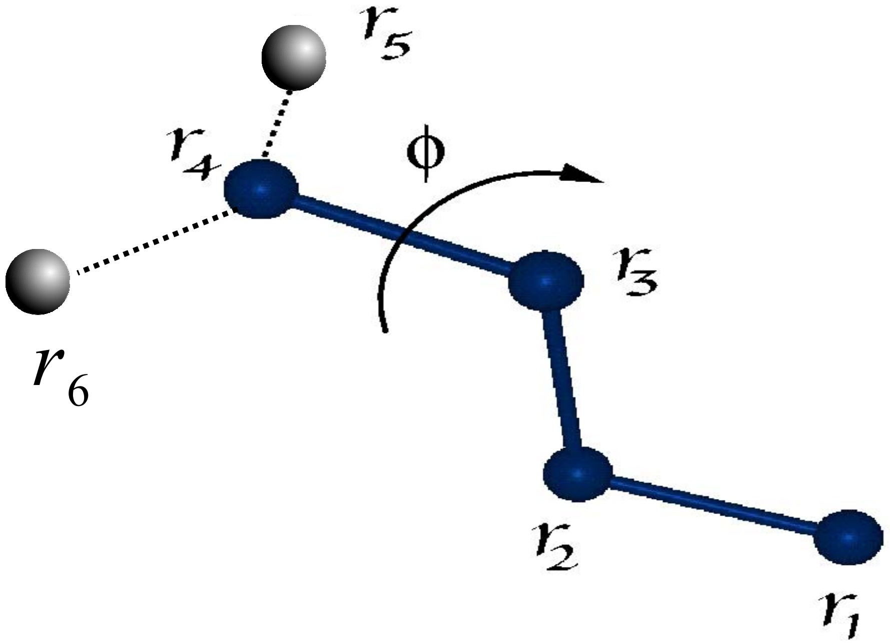
Transformed angle:

$$\phi_u = \phi_{\min} + \int_{\phi_{\min}}^{\phi} d\chi \; e^{-\beta \tilde{V}(\chi)}$$



Dynamic Transformations

P. Minary, G. J. Martyna and MET *SIAM J. Sci. Comp.* **30**, 2055 (2008)



Reference potential:

$$\tilde{V}(\phi,\{\mathbf{r}\}) = V_{\text{tors}}(\phi)S_1(\phi) + \alpha \sum_{i\in \text{nn}} V_{\text{n.b.}}(|\,\mathbf{r}_4(\phi,\{\mathbf{r}\}) - \mathbf{r}_i\,|)S_2(|\,\mathbf{r}_4(\phi,\{\mathbf{r}\}) - \mathbf{r}_i\,|)$$

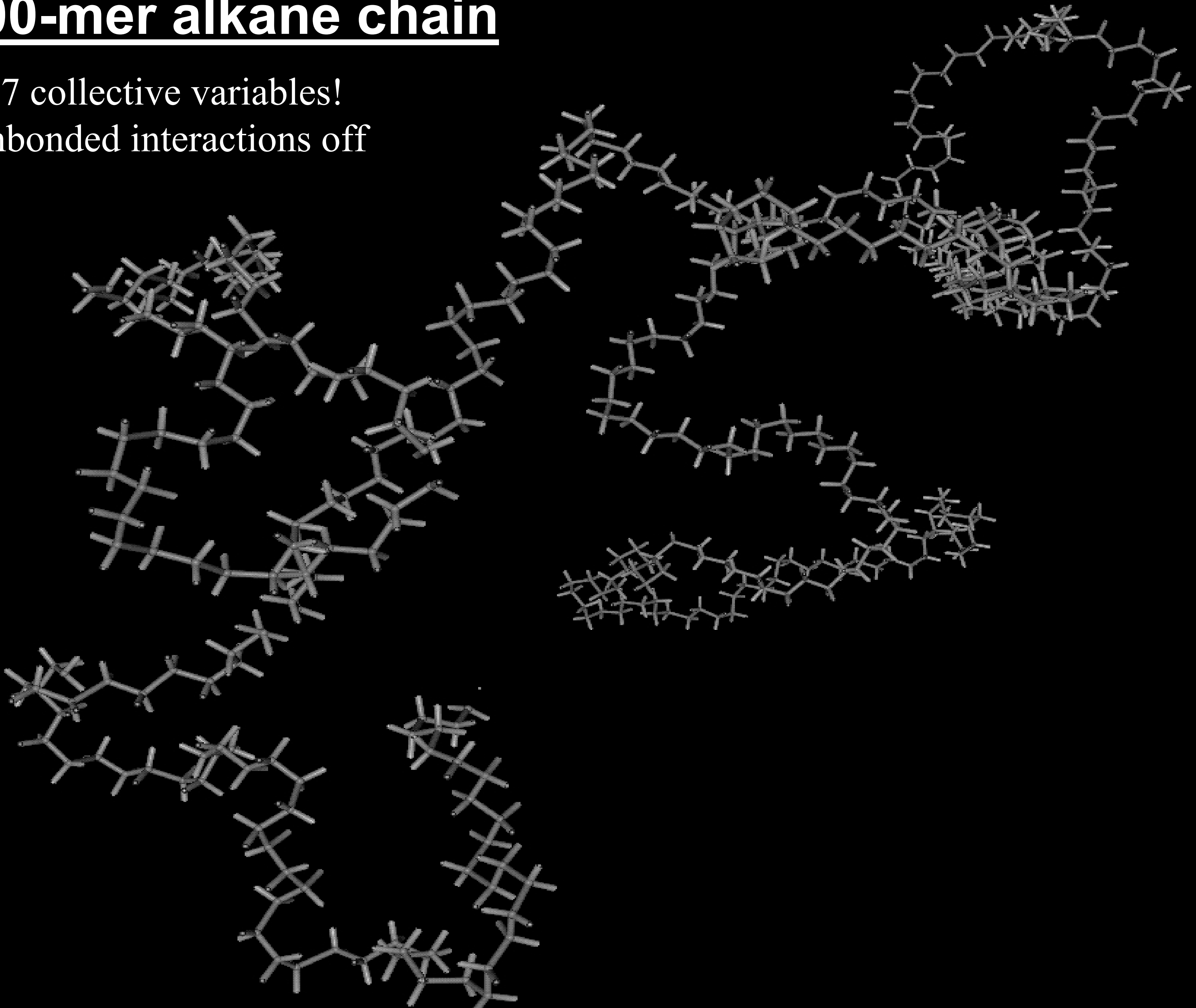
Transformation

$$\phi_u(\{\mathbf{r}\}) = \phi_{\min}(\{\mathbf{r}\}) + c(\{\mathbf{r}\}) \int_{\phi_{\min}(\{\mathbf{r}\})}^{\phi(\{\mathbf{r}\})} d\phi' \; e^{-\beta V_{\text{ref}}(\phi',\{\mathbf{r}\})}$$

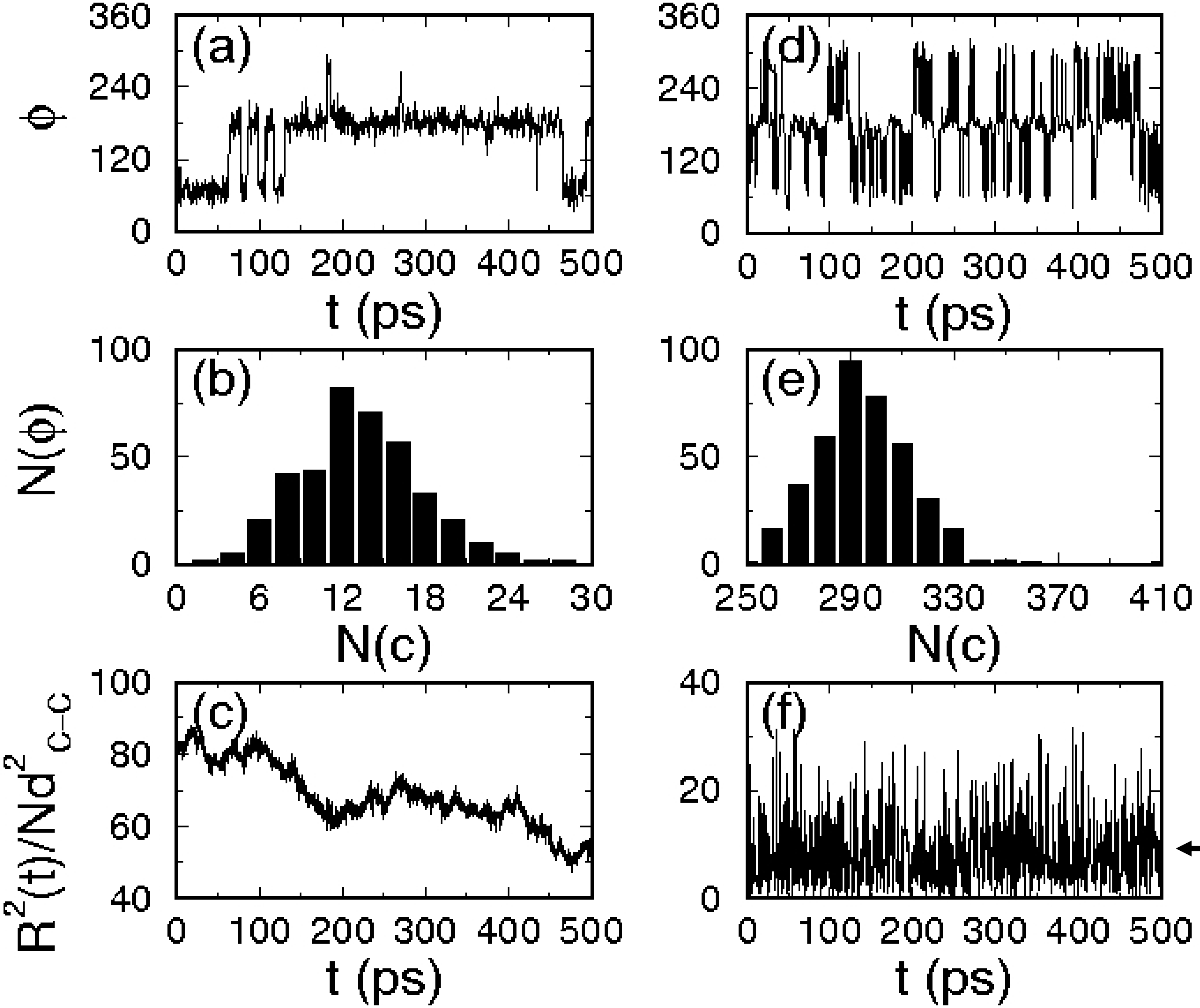
Additional force contributions from $\partial\phi_u/\partial\mathbf{r}_i$.

A 400-mer alkane chain

397 collective variables!
Nonbonded interactions off



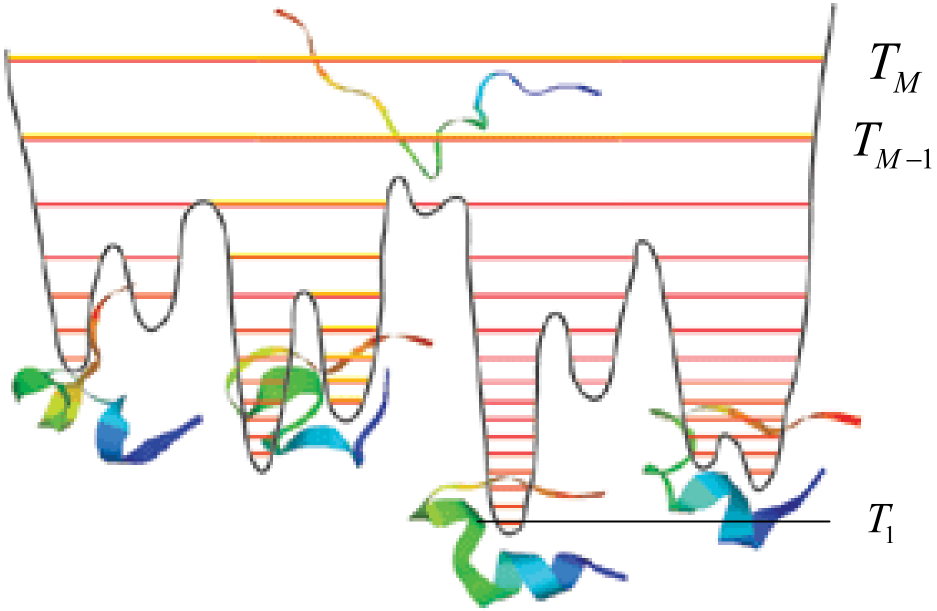
No Transformation **REPSWA Transformations**



RIS Model value: 10

Replica-exchange Monte Carlo (Parallel Tempering)

Swendsen and Wang, *Phys. Rev. Lett.* **57**, 2607 (1986)



Basic Algorithm (Parisi, Whittington, Nemoto)

A. Create M replicas of a system with temperatures $T_1 < T_2 < \cdots T_M$

B. Run molecular dynamics on each replica and periodically attempt neighbor exchanges:

$$A(\mathbf{r}^{k+1}, \mathbf{r}^{k} \mid \mathbf{r}^{k}, \mathbf{r}^{k+1}) = \min\left[1, e^{-\Delta_{k,k+1}}\right]$$

$$\Delta_{k,k+1} = \left(\beta_k - \beta_{k+1}\right)\left[V(\mathbf{r}^{k}) - V(\mathbf{r}^{k+1)})\right]$$

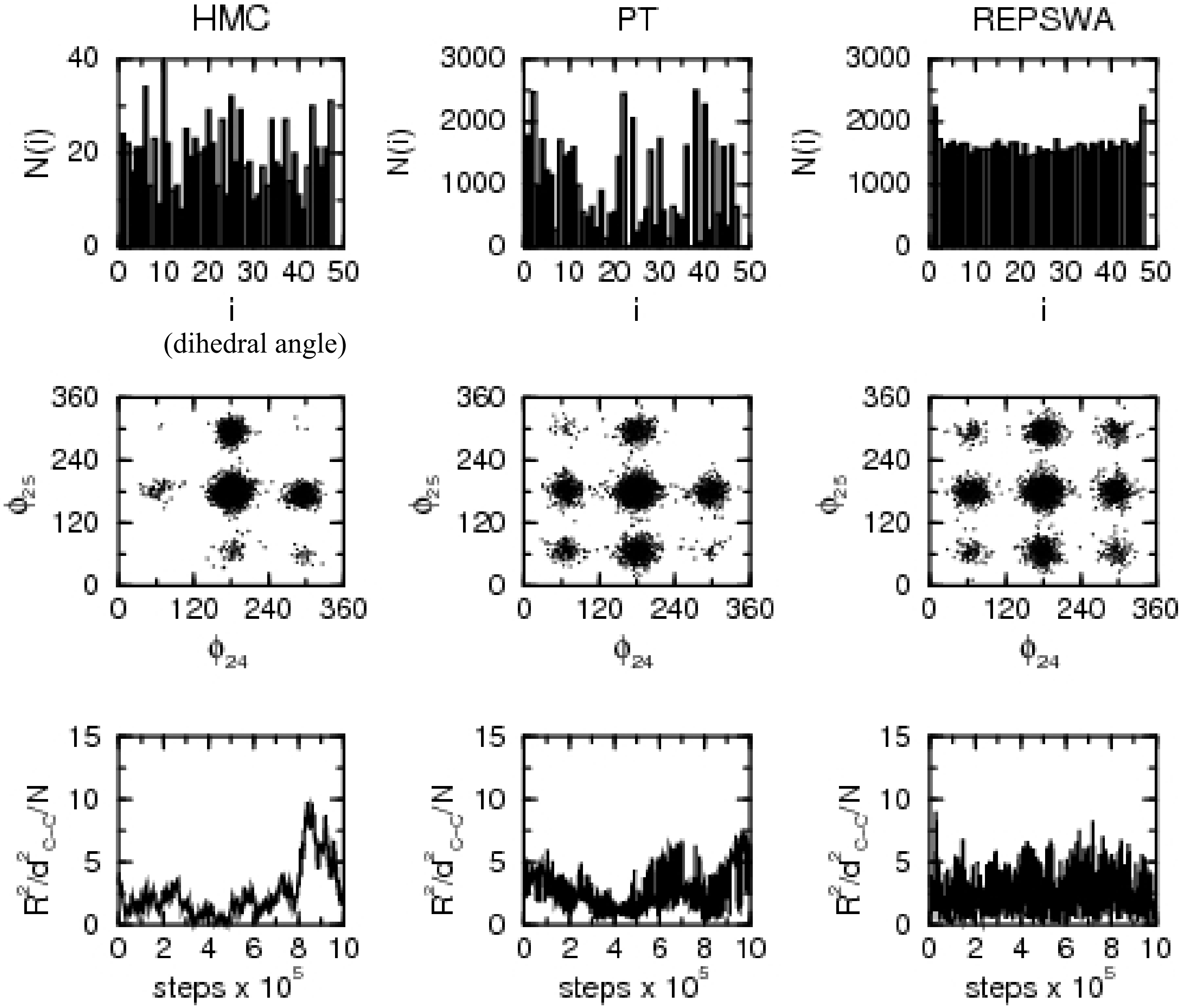
10-20 Replicas
5%-20% Exchange prob.

Comparison for a 50-mer chain using TraPPE

Martin and Siepmann, *J. Phys. Chem. B* **102**, 2569 (1998)

PT replicas = 10; 300 < T <1000 PT exchange prob. = 5%

Nonbonded interactions off

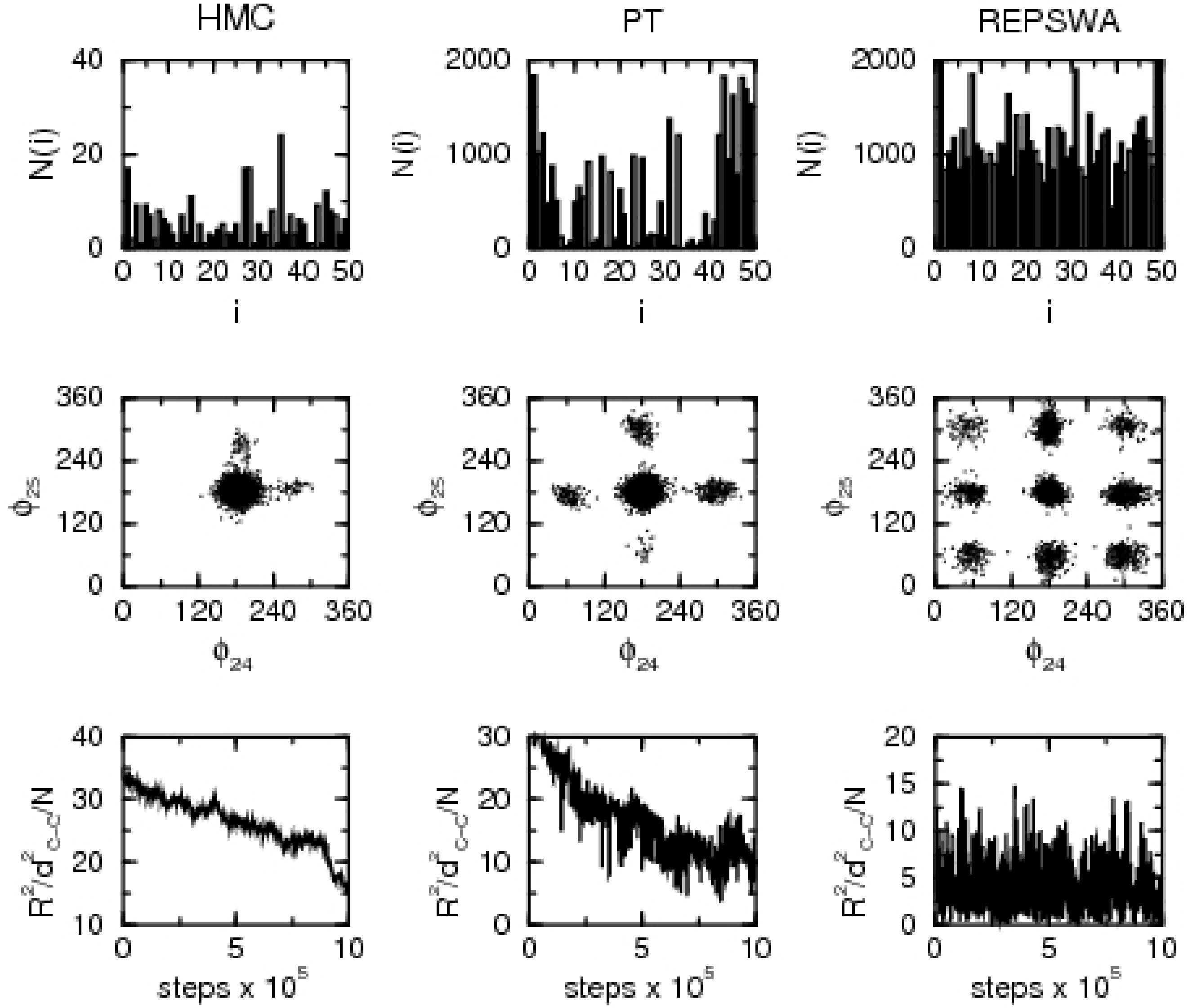


(dihedral angle)

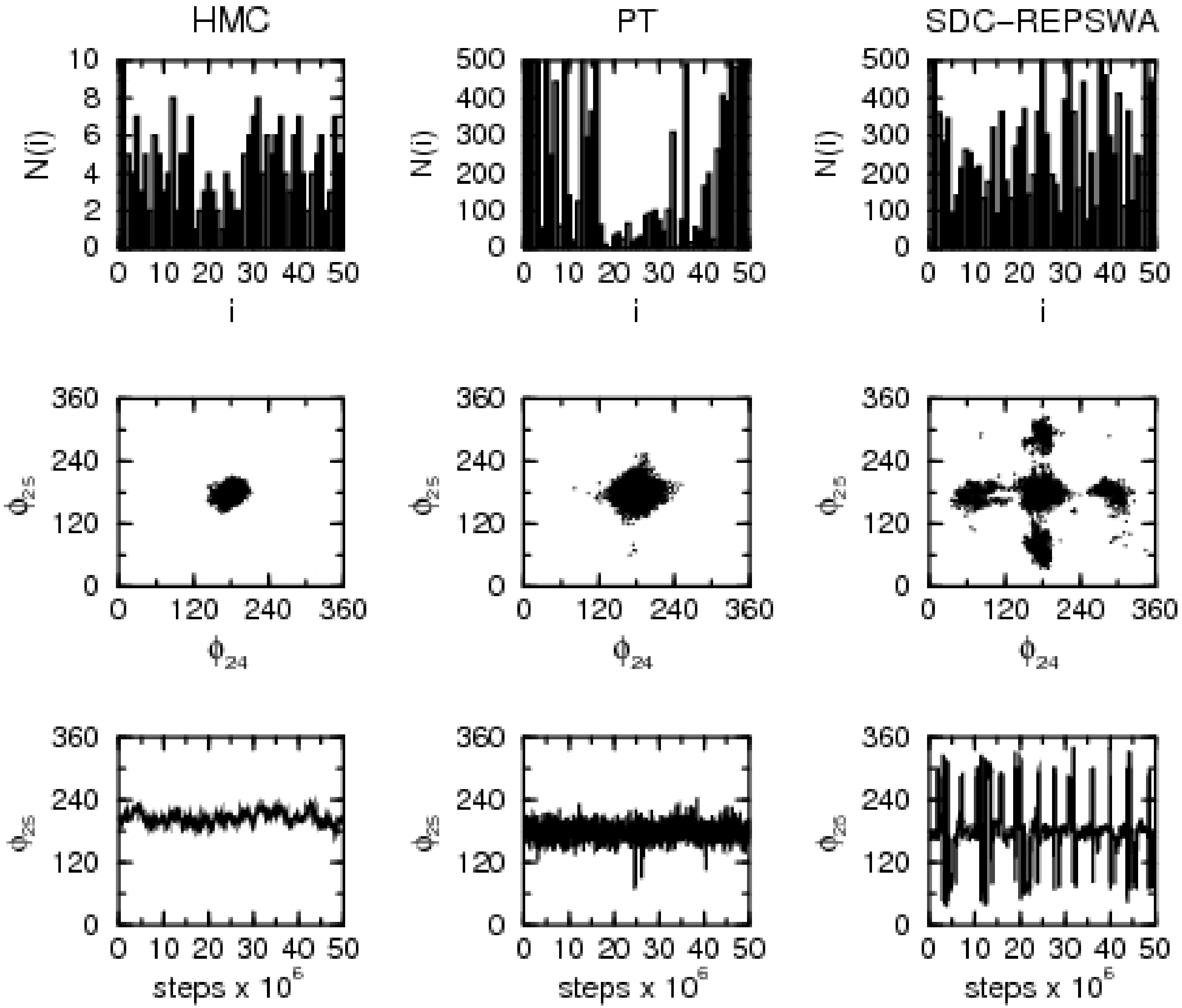
Comparison for a 50-mer chain using CHARMM22

REMC/PT replicas = 10; 300 < T < 1000

Nonbonded interactions off



Comparison for 50-mer using CHARMM22 all interactions



Conclusions and Questions

1. Spatial-warping transformations lead to substantial gains in conformational sampling over ordinary MD and REMC.

   Future: Combine two approaches to gain advantages of both
   Still need transformations for hydrogen bonds.

2. Adiabatic dynamics can be used to explore and generate free-energy hypersurfaces efficiently.

3. Use of external variables [TAMD (Maragliano and Vanden-Eijnden)/ d-AFED (Abrams and Tuckerman)] eliminates the need for explicit variable transformations.

4. Simple mass scaling leads to some enhancement of conformational sampling

Future: Combine REMC with REPSWA – advantages of both (I-Chun Lin).
How does light water help in all of these methods?