Enhanced sampling via molecular dynamics II: Unbiased approaches

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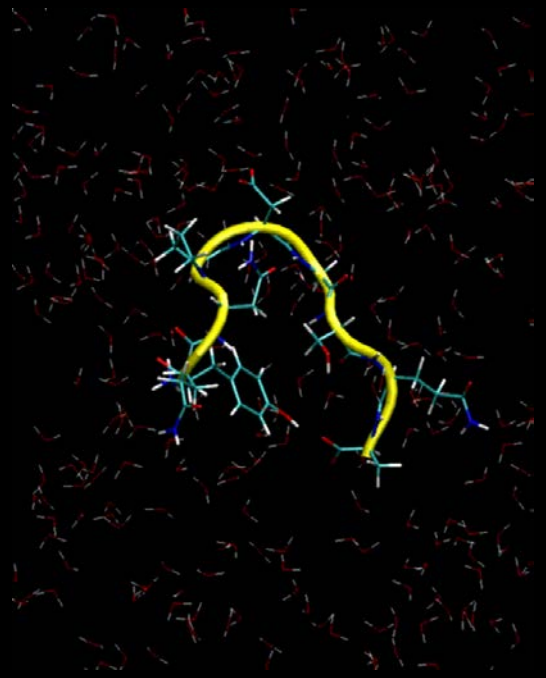
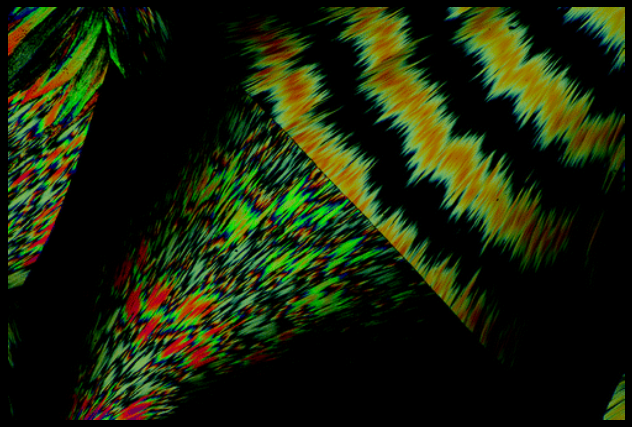
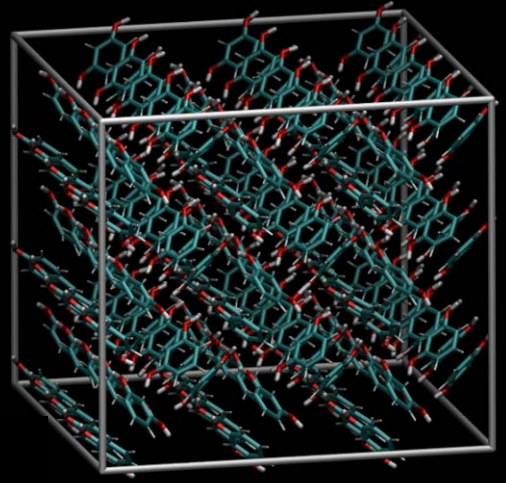
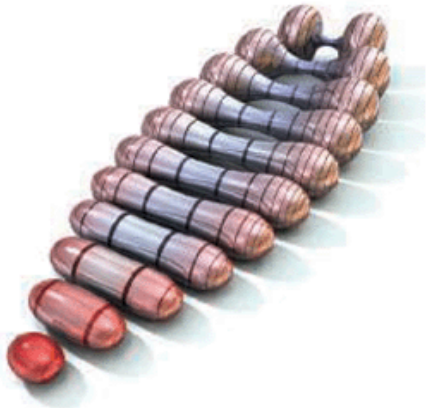




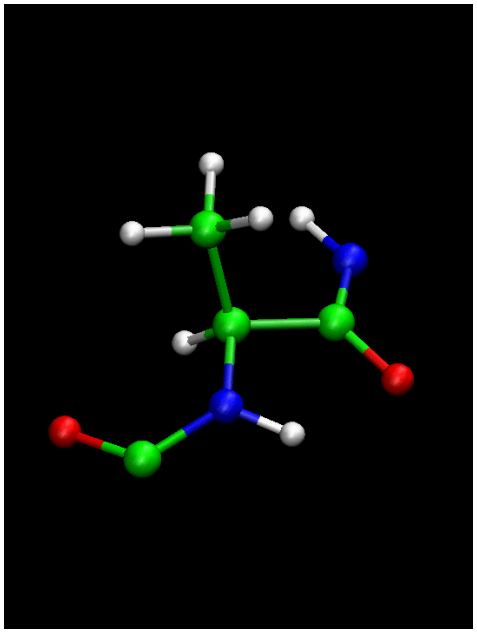


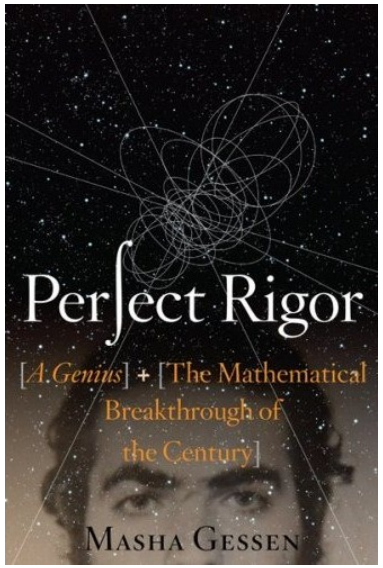
Spatial-Warping Transformations

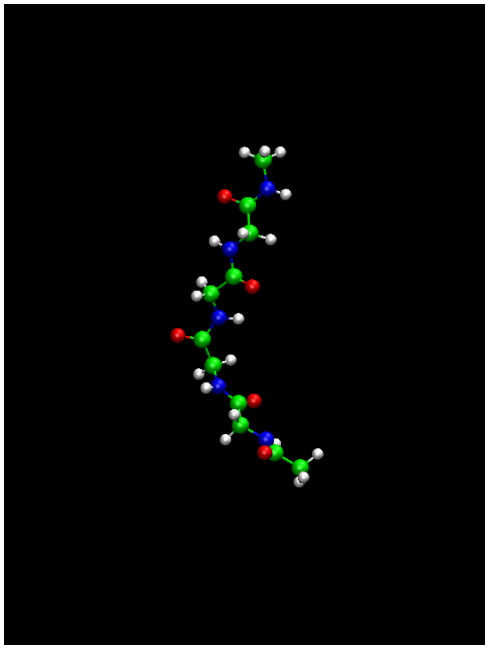
Z. Zhu, MET, S. O. Samuelson, G. J. Martyna, *Phys. Rev. Lett*. **88** 100201 (2002)
P. Minary, MET, G. J. Martyna *SIAM J. Sci. Comput*. **30**, 2055 (2007)



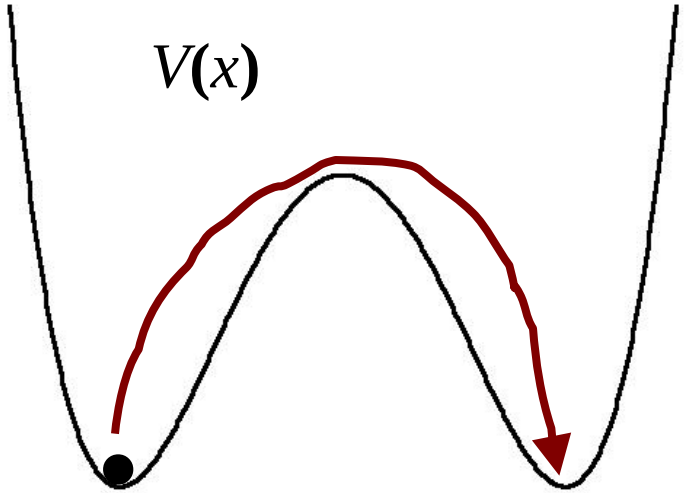
Science, December 22, 2006





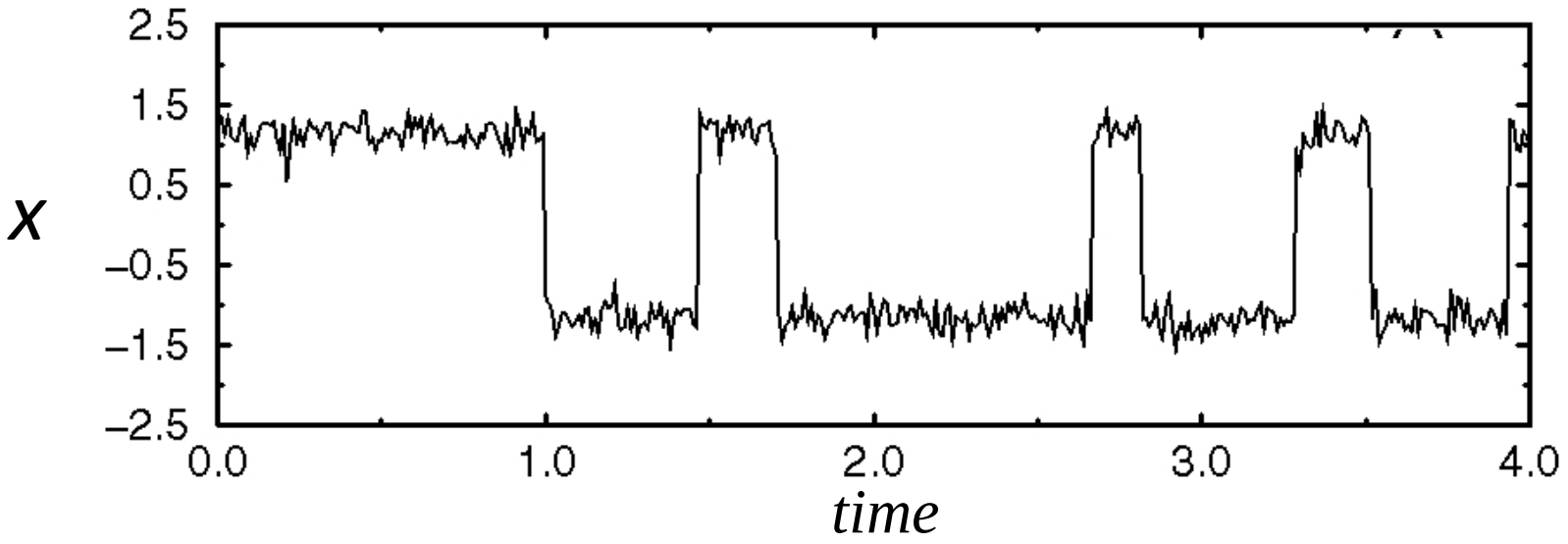


Molecular dynamics in a double well



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

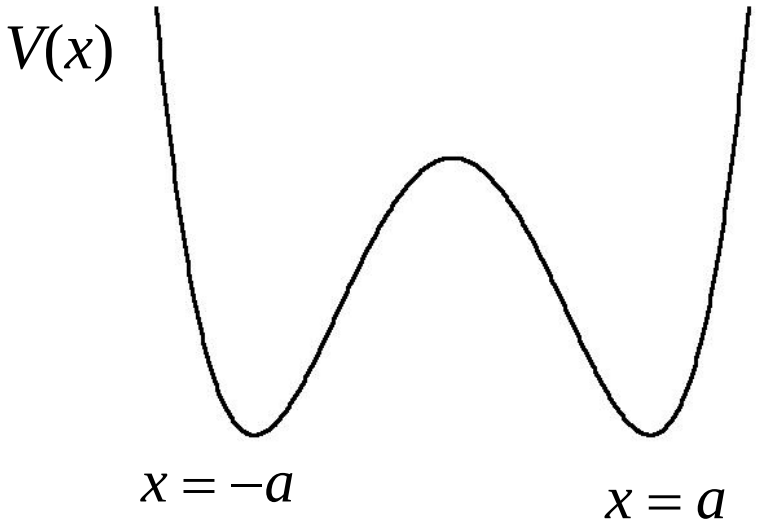
$$\dot{p} = -\frac{dV}{dx} = F(x) + \text{heat bath}$$



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:

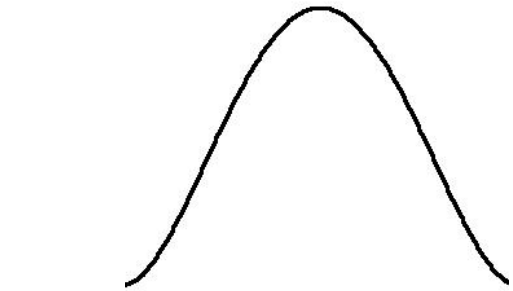
$$Q=\int dp\ du\ \exp\left\{-\beta\left[\frac{p^2}{2m}+V\left(f^{-1}(u)\right)-\tilde{V}\left(f^{-1}(u)\right)\right]\right\}$$

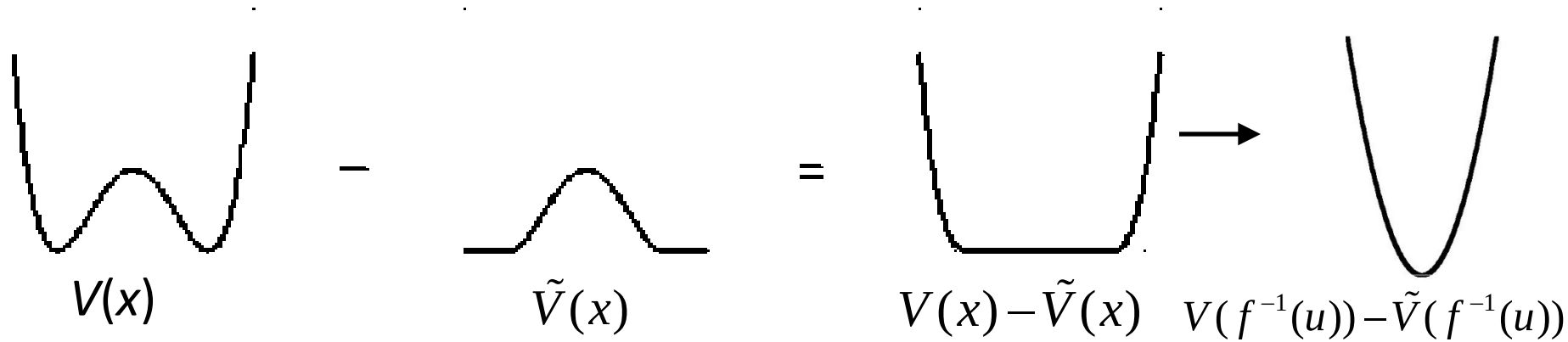
Spatial-warping transformations (cont'd)

$\tilde{V}(x)$

Choosing the transformation:

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

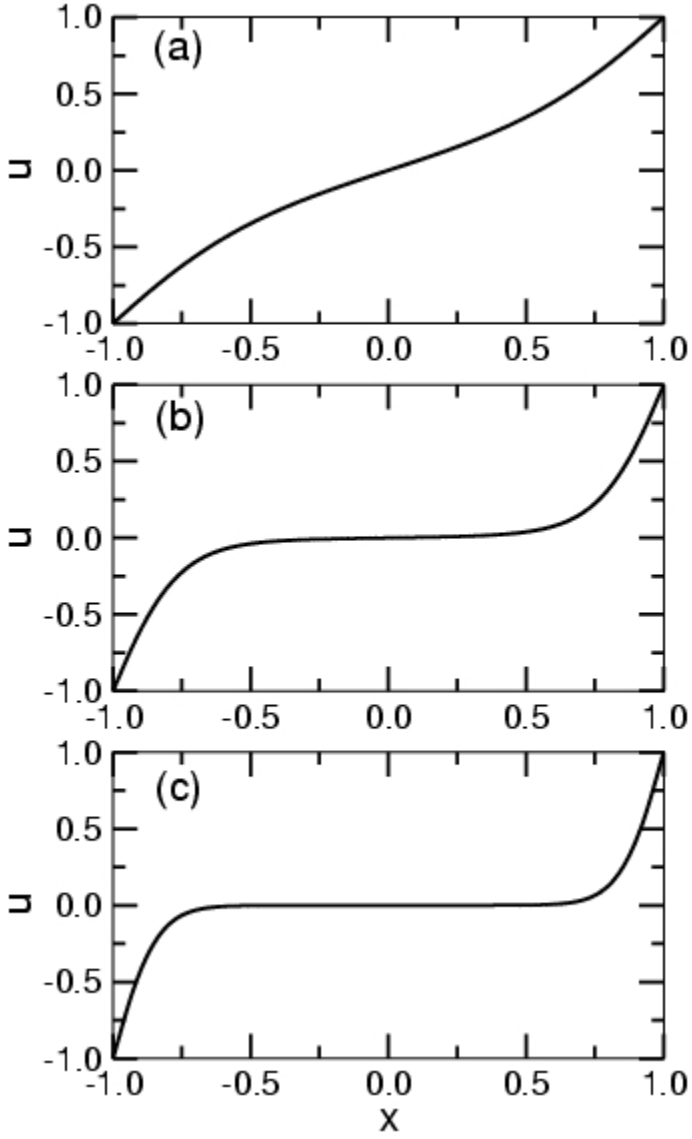




MD: $\dot{u} = \frac{p}{m}$ $\dot{p} = F(u) + \text{heat bath}$

Reference potential spatial warping (REPSWA)

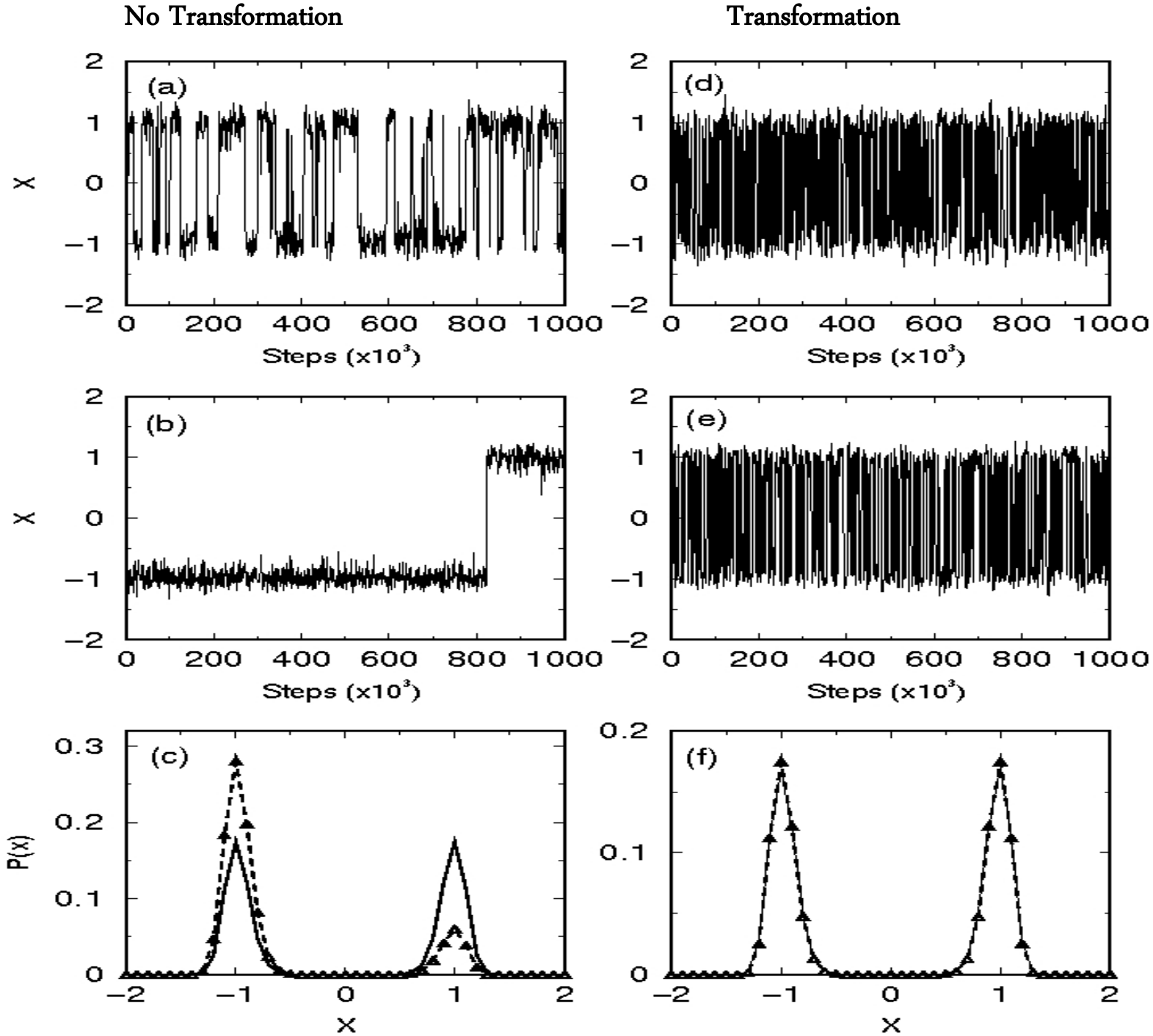
How is the space “warped”?



Barrier: $k_B T$

Barrier: $5k_B T$

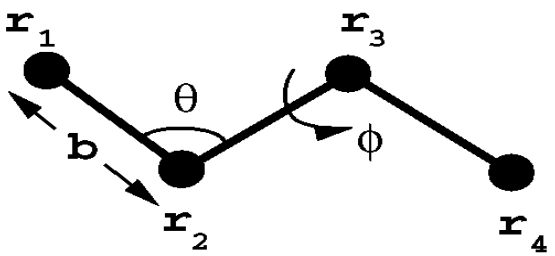
Barrier: $10k_B T$


No Transformation
Transformation
(a)
(b)
(c)
(d)
(e)
(f)
X
P(x)
Steps (x10³)
0
200
400
600
800
1000
2
1
0
−1
−2
0.3
0.2
0.1
0.2
0.1
−2
−1
0
1
2

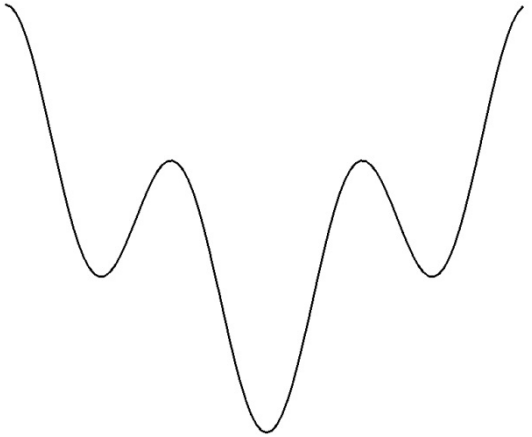
How to do biomolecules and polymers

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

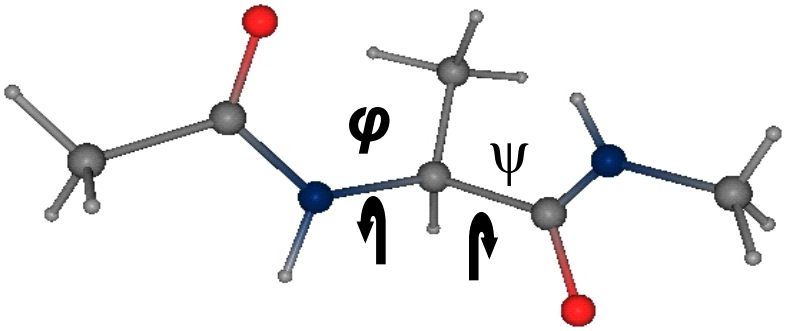
Sampling hindered by barriers in the dihedral angles:

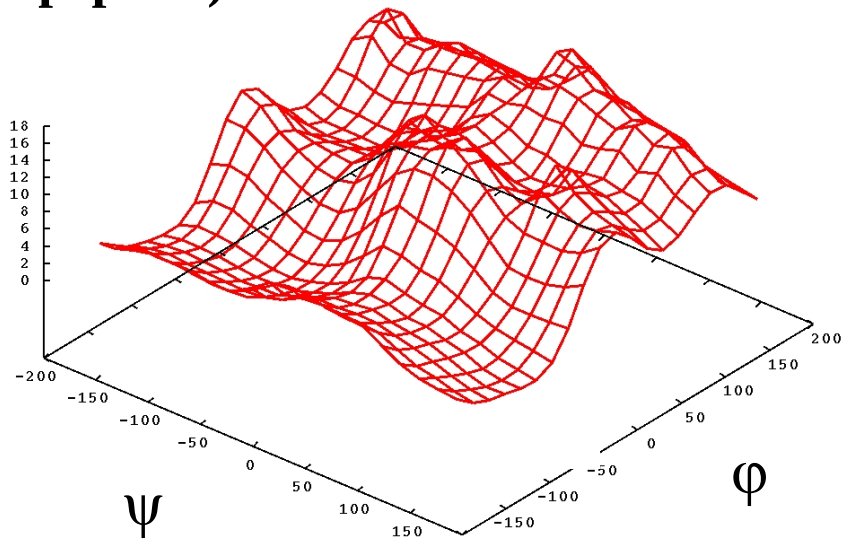


$V(\phi)$

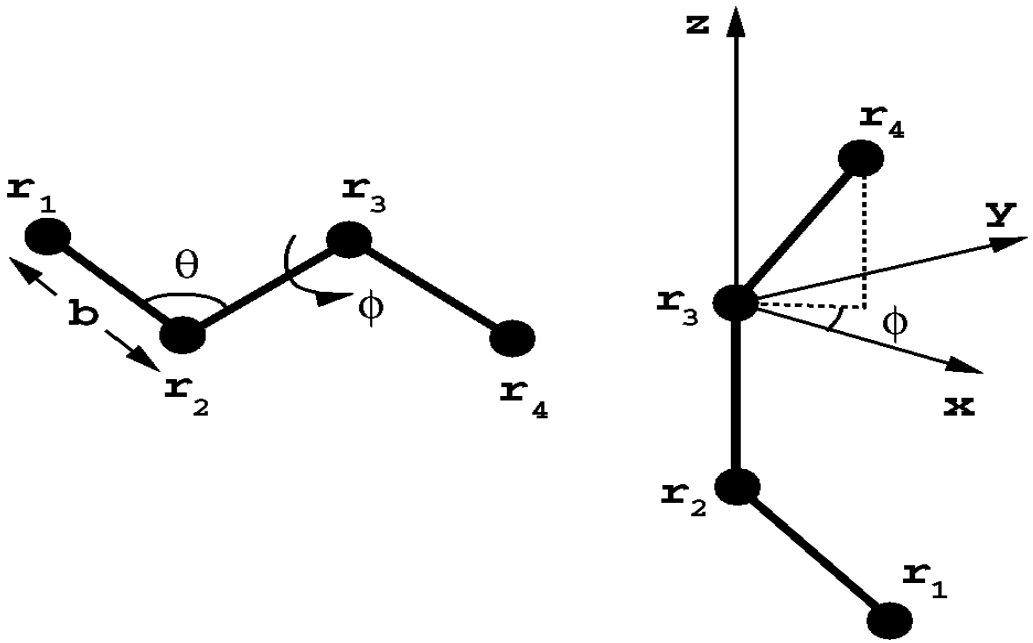


Ramachandran dihedral angles (alanine dipeptide):



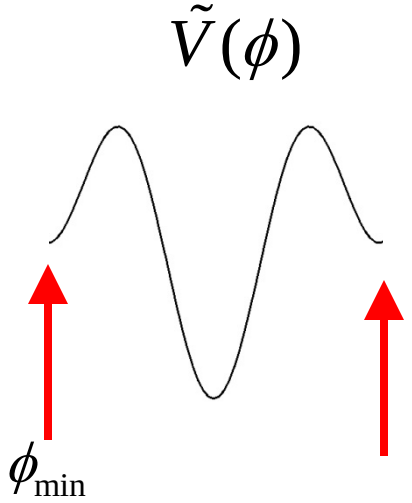


Dihedral angle transformations



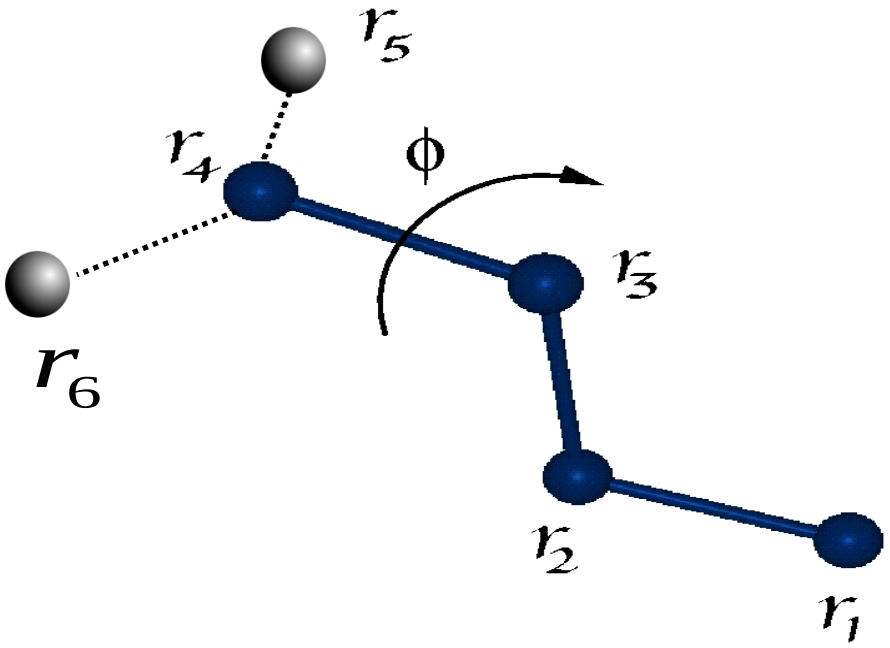
Transformed angle:

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



Dynamic Transformations

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



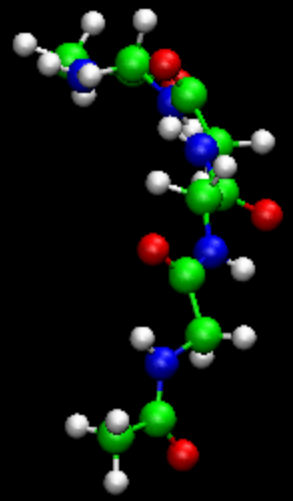
Reference potential:

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

Transformation

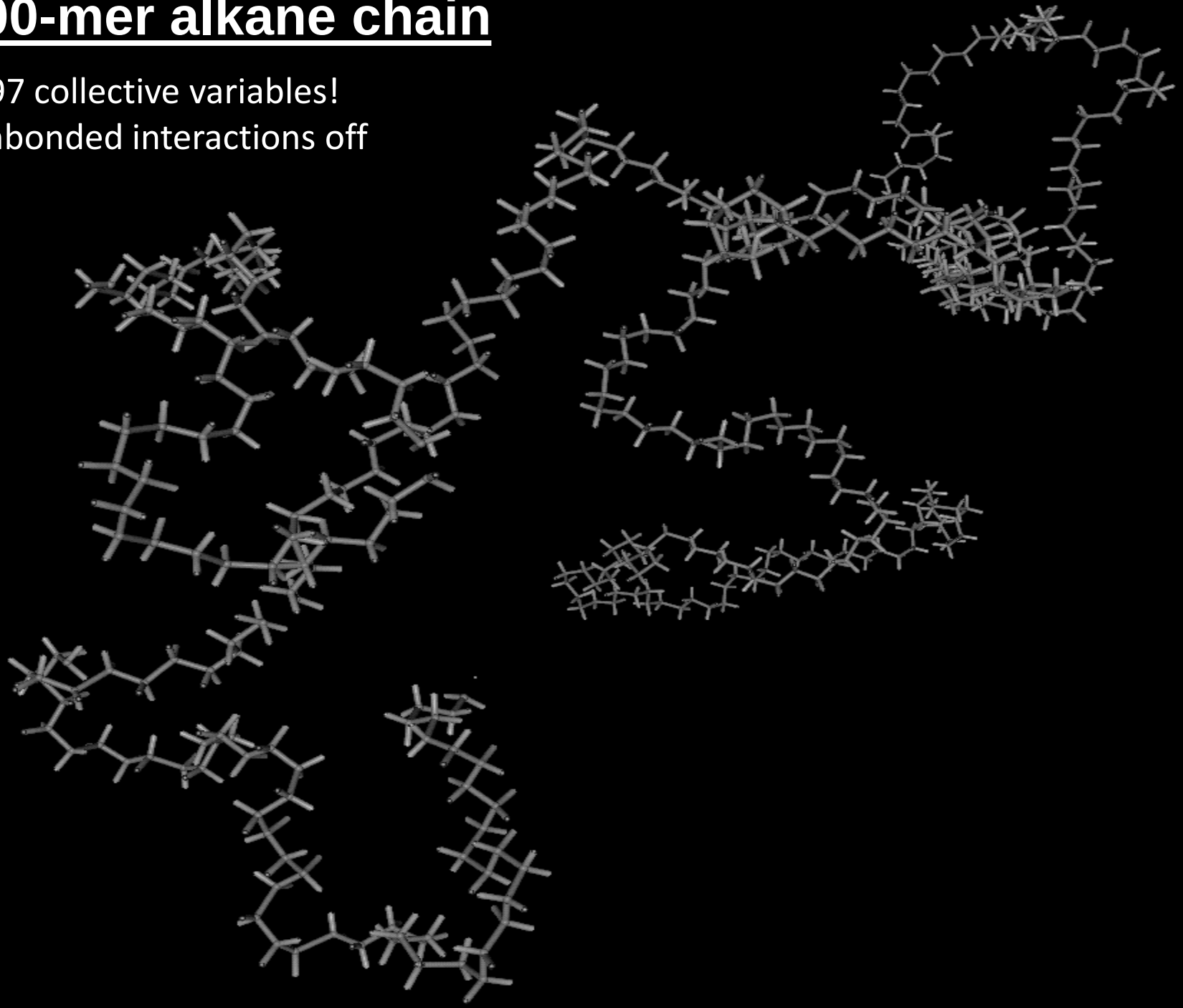
$$\phi_u(\{\mathbf{r}\}) = \phi_{\min}(\{\mathbf{r}\}) + c(\{\mathbf{r}\}) \int_{\phi_{\min}(\{\mathbf{r}\})}^{\phi(\{\mathbf{r}\})} d\phi'\; e^{-\beta V_{\text{ref}}(\phi',\{\mathbf{r}\})}$$

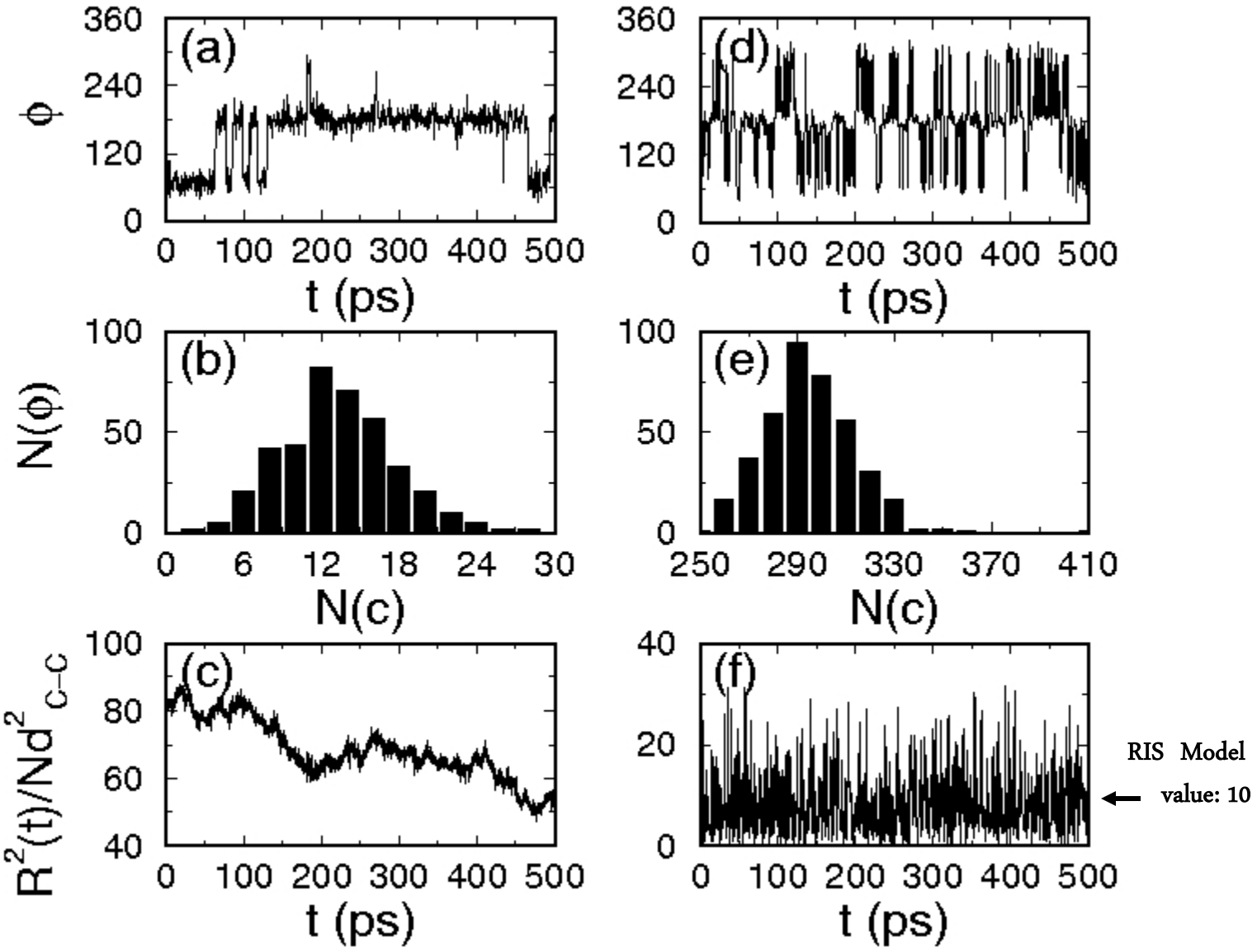
Additional force contributions from $\partial\phi_u/\partial\mathbf{r}_i$.

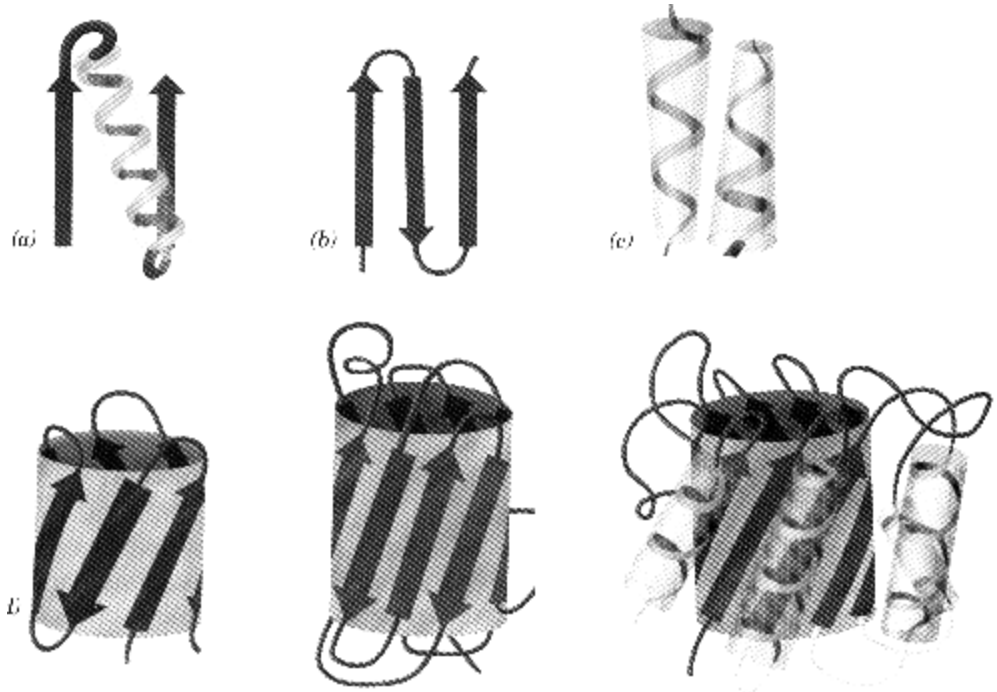


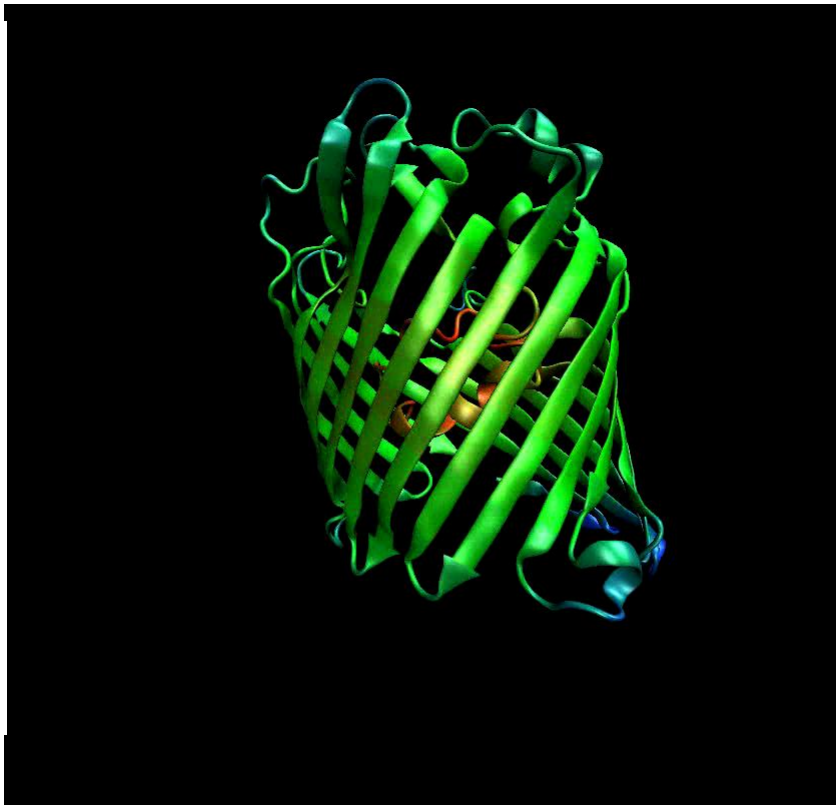
A 400-mer alkane chain

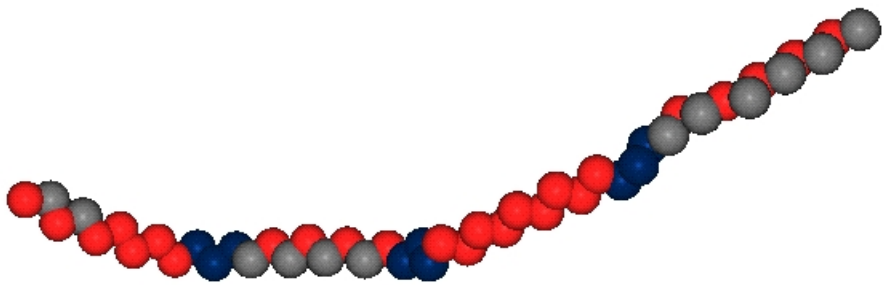
397 collective variables!
Nonbonded interactions off

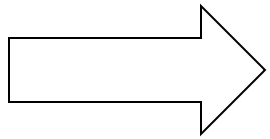


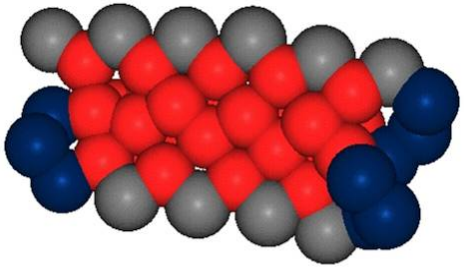

No Transformation
REPSWA Transformations
(a)
(b)
(c)
(d)
(e)
(f)
φ
N(φ)
$R^2(t)/Nd^2_{c-c}$
t (ps)
N(c)
RIS Model
value: 10


(a)
(b)
(c)









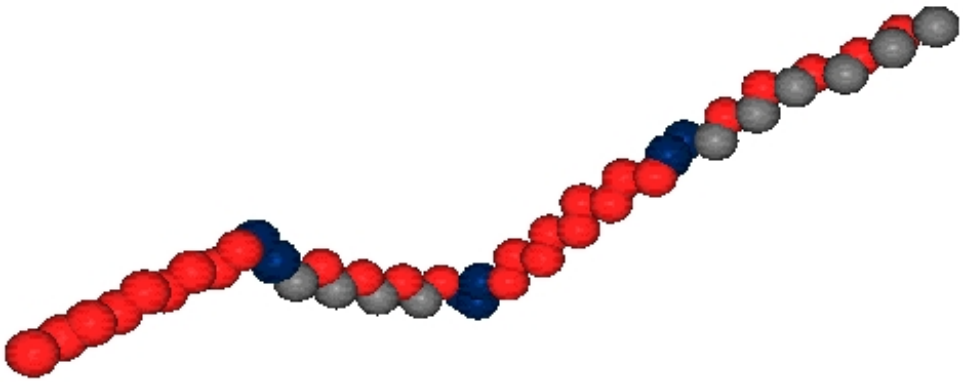
A model β-sheet protein

Honeycutt and Thirumalai PNAS **87**, 3526 (1990)

- 48 residue protein
- Types of residues:
  - B: *hydrophobic*
  - L: *hydrophilic*
  - N: *neutral*
- The model:

$$
\begin{aligned}
V &= \sum_{i=1}^{45} \frac{k_i}{2} \left(r_{i,i+1} - r_{0,i}\right)^2 + \sum_{i=1}^{44} \frac{\kappa_i}{2} \left(\theta_i - \theta_{0,i}\right)^2 \\
&+ \sum_{i=1}^{43} \left[A_i \left(1 + \cos\phi_i\right) + B_i \left(1 + \cos 3\phi_i\right)\right] \\
&+ \sum_{i,j>i+3} V_{\mathrm{nb}}(r_{ij})
\end{aligned}
$$

- Given sequence: $\mathrm{B_9N_3(LB)_4N_3B_9N_3(LB)_5L}$
- Initial Structure:

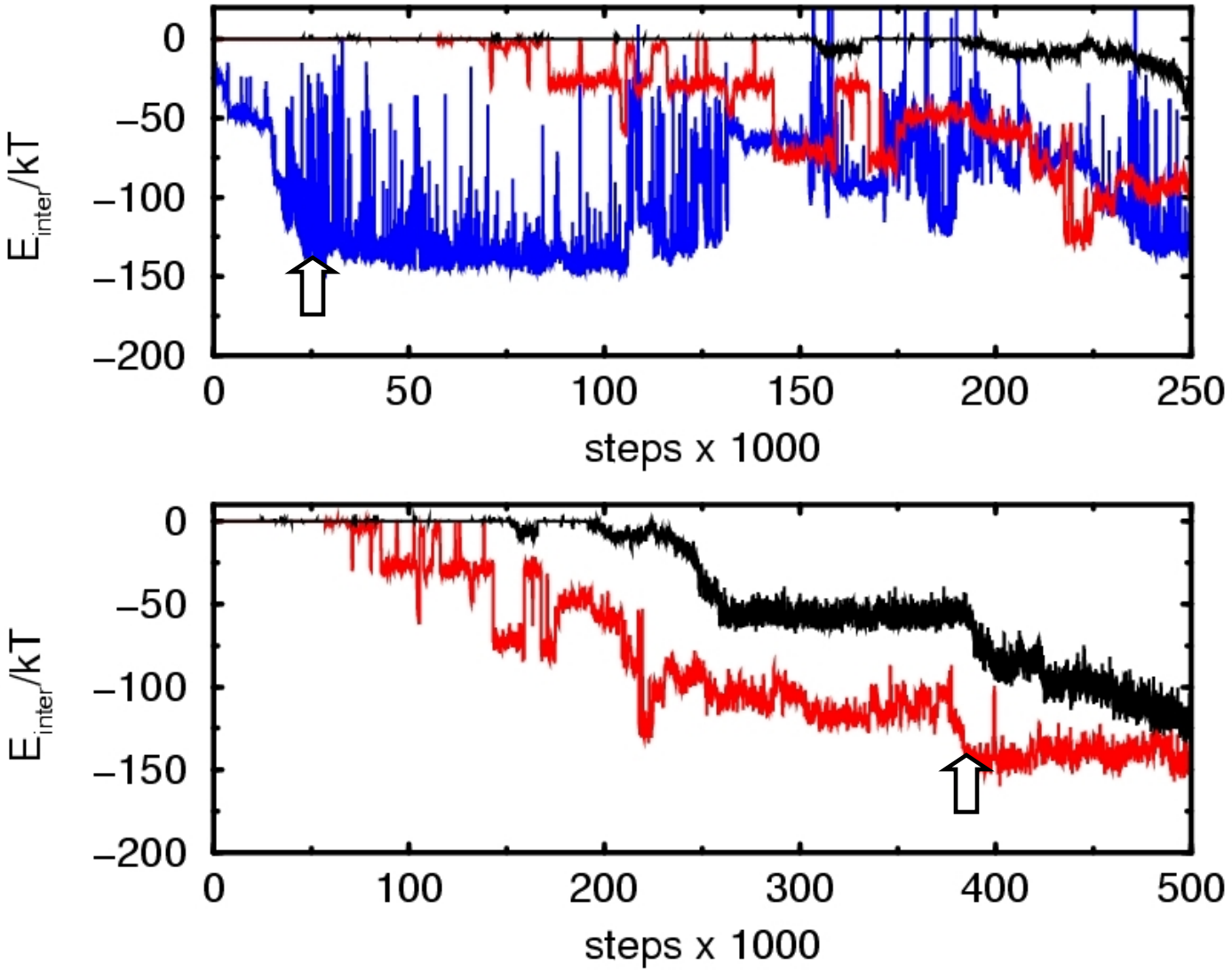


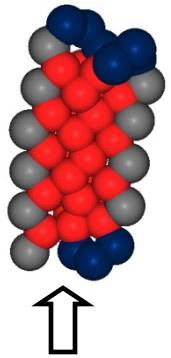
MD

REMC

Transformations

PT replicas = 16





Integrators in molecular dynamics

Equations of motion:

$$\dot{q} = \frac{p}{m}, \qquad \dot{p} = F(q)$$

Time evolution:

$$\begin{pmatrix} q(\Delta t) \\ p(\Delta t) \end{pmatrix} = e^{iL\Delta t} \begin{pmatrix} q(0) \\ p(0) \end{pmatrix}$$

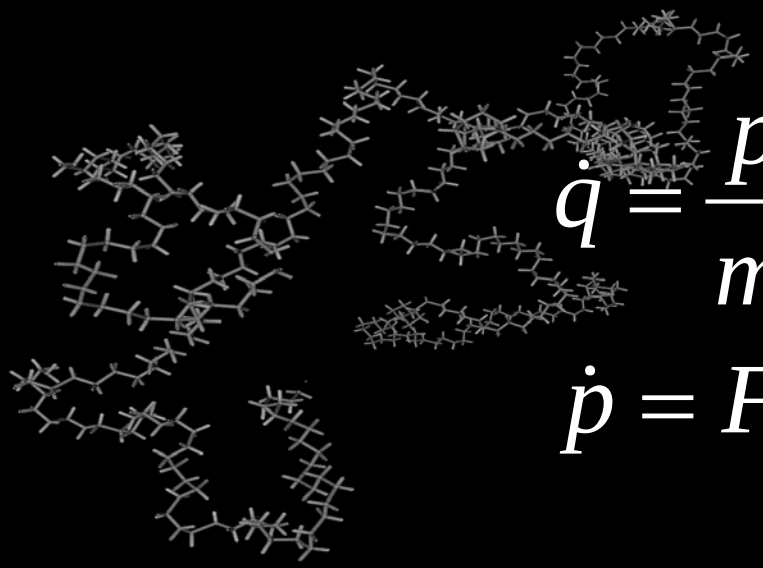
where $iL = \frac{p}{m}\frac{\partial}{\partial q} + F(q)\frac{\partial}{\partial p}$

$$\exp(iL\Delta t) = \exp\left[\frac{\Delta t}{2}F(q)\frac{\partial}{\partial p}\right]\exp\left[\Delta t\frac{p}{m}\frac{\partial}{\partial q}\right]\exp\left[\frac{\Delta t}{2}F(q)\frac{\partial}{\partial p}\right] + O(\Delta t^3)$$

Pseudocode:

Multiple time scale (r-RESPA) integration

MET, G. J. Martyna and B. J. Berne, *J. Chem. Phys*. **97**, 1990 (1992)



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

$$\dot{p} = F_{fast} + F_{slow}$$

$$iL = \left(\frac{p}{m} \frac{\partial}{\partial q} + F_{fast} \frac{\partial}{\partial p} \right) + F_{slow} \frac{\partial}{\partial p} = iL_{ref} + iL_{slow}$$

Multiple Time Scale Integration (cont'd)

Trotter factorized propagator:

$$\exp(iL\Delta t) = \exp(iL_{slow}\Delta t/2)\exp(iL_{ref}\Delta t)\exp(iL_{slow}\Delta t/2) + O(\Delta t^3)$$

$$= \exp(iL_{slow}\Delta t/2)\left[\exp(iL_{ref}\delta t)\right]^n \exp(iL_{slow}\Delta t/2)$$

$$\exp(iL\Delta t) = \exp\left[\frac{\Delta t}{2}F_{slow}\frac{\partial}{\partial p}\right]$$

$$\times\left\{\exp\left[\frac{\delta t}{2}F_{fast}\frac{\partial}{\partial p}\right]\exp\left[\delta t\frac{p}{m}\frac{\partial}{\partial q}\right]\exp\left[\frac{\delta t}{2}F_{fast}\frac{\partial}{\partial p}\right]\right\}^n$$

$$\exp\left[\frac{\Delta t}{2}F_{slow}\frac{\partial}{\partial p}\right]$$

Results for liquid all-atom Butane:

Time scales: Intramolecular/Intermolecular

$$N = 64, \quad T = 267K, \quad V = 159\text{Å}^3/\text{molecule}$$

Energy conservation measure:

$$\Delta E(\Delta t) = \left(\frac{1}{N_{\text{steps}}}\right) \sum_{k=1}^{N_{\text{steps}}} \left| \frac{E(k\Delta t) - E(0)}{E(0)} \right|$$

$\Delta t(fs)$	n	$10^4 \Delta E$
0.5	1	1.616
1.0	4	0.473
2.0	8	0.898
3.0	12	1.753
4.0	16	3.838

From:
G. J. Martyna, MET, D. Tobias,
and M. L. Klein
Mol. Phys. **87**, 1117 (1996).

Illustration of resonance

A. Sandu and T. S. Schlick, *J. Comput. Phys*. **151**, 74 (1999)

$$F_{fast} = -\omega^2 x \qquad F_{slow} = -\Omega^2 x$$

$$p' = p(0) - \frac{\Delta t}{2}\Omega^2 x(0)$$

$$x(\Delta t) = x(0)\cos(\omega\Delta t) + \frac{p'}{\omega}\sin(\omega\Delta t)$$

$$p'' = p(0)\cos(\omega\Delta t) - \omega x(0)\sin(\omega\Delta t)$$

$$p(\Delta t) = p'' - \frac{\Delta t}{2}\Omega^2 x(\Delta t)$$

$$\begin{pmatrix} x(\Delta t) \\ p(\Delta t) \end{pmatrix} = A(\omega, \Omega, \Delta t) \begin{pmatrix} x(0) \\ p(0) \end{pmatrix}$$

Illustration of resonance (cont'd)

$$A(\omega,\Omega,\Delta t)=\begin{pmatrix}\cos(\omega\Delta t)-\dfrac{\Delta t\Omega^2}{2\omega}\sin(\omega\Delta t) & \dfrac{1}{\omega}\sin(\omega\Delta t)\\ \left(\dfrac{\Delta t^2\Omega^4}{4\omega}-\omega\right)\sin(\omega\Delta t)-\Delta t\Omega^2\cos(\omega\Delta t) & \cos(\omega\Delta t)-\dfrac{\Delta t\Omega^2}{2\omega}\sin(\omega\Delta t)\end{pmatrix}$$

Note: det(A) = 1

Depending on Δt, eigenvalues of A are either complex conjugate pairs

$$-2<\mathrm{Tr}(A)<2$$

or eigenvalues are both real

$$|\mathrm{Tr}(A)|\ \geq 2$$

Leads to resonances ($|Tr(A)| \rightarrow 2$) at $\Delta t = n\pi/\omega$

Isokinetic dynamics

Constraint the kinetic energy of a system:

$$\sum_i \frac{\mathbf{p}_i^2}{2m_i} = \frac{3N-1}{2} kT$$

Introduce constraint via a Lagrange multiplier:

$$\dot{\mathbf{r}}_i = \frac{\mathbf{p}_i}{m_i} \qquad\qquad \dot{\mathbf{p}}_i = \mathbf{F}_i - \lambda \mathbf{p}_i$$

Derivative of constraint yields multiplier:

$$\sum_i \frac{\mathbf{p}_i}{m_i} \cdot \dot{\mathbf{p}}_i = \sum_i \frac{\mathbf{p}_i}{m_i} \cdot \left[\mathbf{F}_i - \lambda \mathbf{p}_i \right] = 0 \quad \Rightarrow \quad \lambda = \frac{\sum_i \mathbf{F}_i \cdot \mathbf{p}_i / m_i}{\sum_i \mathbf{p}_i \cdot \mathbf{p}_i / m_i}$$

Partition function generated:

$$\Omega = \int d^N \mathbf{p} \; \delta\left(\sum_i \frac{\mathbf{p}_i^2}{2m_i} - \frac{3N-1}{2} kT \right) \int d^N \mathbf{r} \; e^{-\beta U(\mathbf{r})}$$

Resonance-free but is a poor thermostat.

Resonance-free stochastic isokinetic thermostat

P. Minary, MET, G. J. Martyna *PRL* (2004); B. Leimkuhler, D. Margul, MET *Mol. Phys*. (in press)

Consider the equations of motion:

$$dq = vdt$$

$$dv = \left[\frac{F}{m} - \lambda v\right]dt$$

$$dv_{1,k} = -\lambda v_{1,k}dt - v_{2,k}v_{1,k}dt, \qquad k = 1,\ldots,L$$

$$dv_{2,k} = \frac{G(v_{1,k})}{Q_2}dt - \gamma v_{2,k}dt + \sigma dw_k$$

$$G(u) = Q_1 u^2 - \beta^{-1}$$

Isokinetic constraint: $$mv^2 + \frac{L}{L+1}\sum_{k=1}^{L} Q_1 v_{1,k}^2 = \Lambda(v, v_{1,1}, \ldots., v_{1,L}) = L\beta^{-1}$$

Multiplier: $$\lambda = \frac{vF - \frac{L}{L+1}\sum_{k=1}^{L} Q_1 v_{1,k}^2 v_{2,k}}{\Lambda(v, v_{1,1}, \ldots, v_{1,L})}$$

Multiple time-step integrator

Assume forces have fast and slow components: $F = F_f + F_s$

$$iL = iL_q + iL_v^{(f)} + iL_v^{(s)} + iL_N + iL_{OU}$$

$$iL_q = v\frac{\partial}{\partial q}$$

$$iL_v^{(f)} = \left(\frac{F_f}{m} - \lambda_F^{(f)} v\right)\frac{\partial}{\partial v} - \lambda_F^{(f)} \sum_{k=1}^{L} v_{1,k}\frac{\partial}{\partial v_{1,k}}$$

$$iL_v^{(s)} = \left(\frac{F_s}{m} - \lambda_F^{(s)} v\right)\frac{\partial}{\partial v} - \lambda_F^{(s)} \sum_{k=1}^{L} v_{1,k}\frac{\partial}{\partial v_{1,k}}$$

$$iL_N = -\lambda_N v\frac{\partial}{\partial v} - \lambda_N \sum_{k=1}^{L} v_{1,k}\frac{\partial}{\partial v_{1,k}} - \sum_{k=1}^{L} v_{2,k} v_{1,k}\frac{\partial}{\partial v_{1,k}} + \sum_{k=1}^{L}\frac{G(v_{1,k})}{Q_2}\frac{\partial}{\partial v_{2,k}}$$

$$\lambda_F^{(f)} = \frac{vF_f}{\Lambda}, \qquad \lambda_F^{(s)} = \frac{vF_s}{\Lambda}, \qquad \lambda_N = -\frac{\dfrac{L}{L+1}\displaystyle\sum_{k=1}^{L} Q_1 v_{1,k}^2 v_{2,k}}{\Lambda}$$

Multiple time-step integrator

$$e^{iL\Delta t} = e^{iL_N \Delta t/2} e^{iL_v^{(s)} \Delta t/2} \left[e^{iL_v^{(f)} \delta t/2} e^{iL_q \delta t/2} e^{iL_{OU} \delta t} e^{iL_q \delta t/2} e^{iL_v^{(f)} \delta t/2} \right]^n e^{iL_v^{(s)} \Delta t/2} e^{iL_N \Delta t/2}$$

Solution of the Ornstein-Uhlenbeck process:

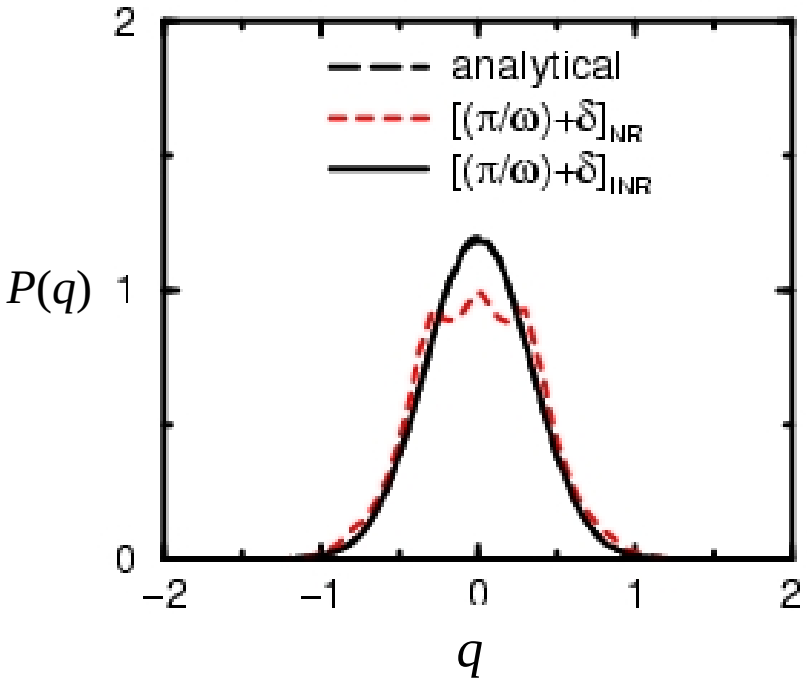
$$e^{iL_{OU} \delta t} v_{2,k} = v_{2,k}(0) e^{-\gamma \delta t} + \sigma R(t) \sqrt{\frac{1 - e^{-2\gamma \delta t}}{2\gamma}}$$

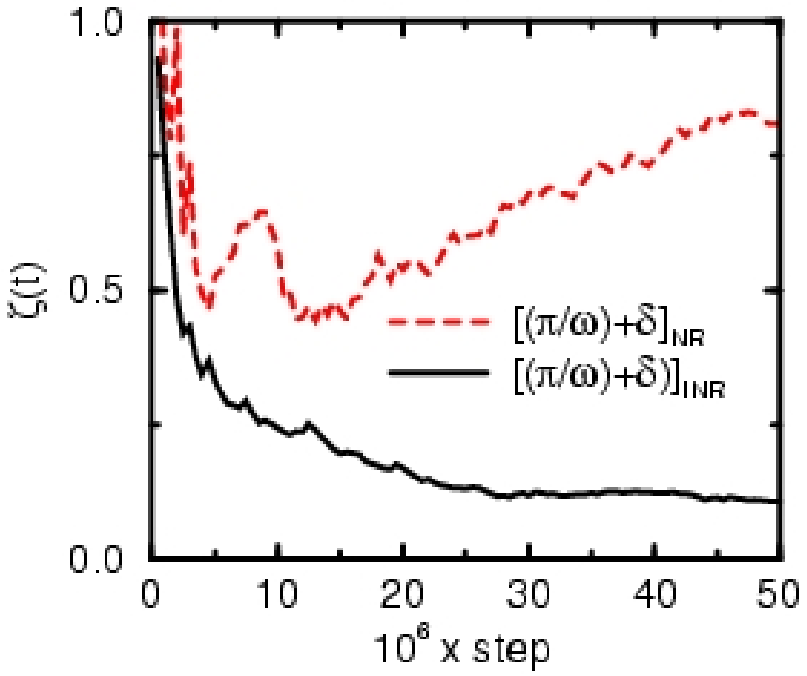
Numerical illustration of resonance

Harmonic oscillator with quartic perturbation

$$U(q) = \frac{9}{2}q^2 + 0.025q^4$$

$$L = 3, \qquad \delta t = \frac{\Delta t}{100} \qquad \varsigma(t) = \frac{1}{N_{\text{bins}}} \sum_{i=1}^{N_{\text{bins}}} \left[P(q_i;t) - P_{\text{exact}}(q_i) \right]$$





Flexible SPC/E water

F. Paesani *et al*. *J. Chem. Phys*. **125**, 184507 (2006)

$$U(\mathbf{r}) = U_{\text{intra}}(\mathbf{r}) + U_{\text{nb}}(\mathbf{r}) = U_{\text{intra}}(\mathbf{r}) + U_{\text{short}}(\mathbf{r}) + U_{\text{long}}(\mathbf{r})$$

$$U_{\text{short}}(\mathbf{r}) = \sum_{ij}\left[U_{\text{LJ}}(r_{ij}) + \frac{q_i q_j \operatorname{erfc}(\alpha r_{ij})}{r_{ij}} \right]$$

$$U_{\text{long}}(\mathbf{r}) = \frac{1}{V} \sum_{\mathbf{k},|\mathbf{k}|<k_{\max}} \frac{4\pi}{|\mathbf{k}|^2} e^{-|\mathbf{k}|^2/4\alpha^2} |S(\mathbf{k})|^2 - \frac{\alpha}{\sqrt{\pi}} \sum_i q_i^2$$

$$S(\mathbf{k}) = \sum_i q_i e^{i\mathbf{k}\cdot\mathbf{r}}$$

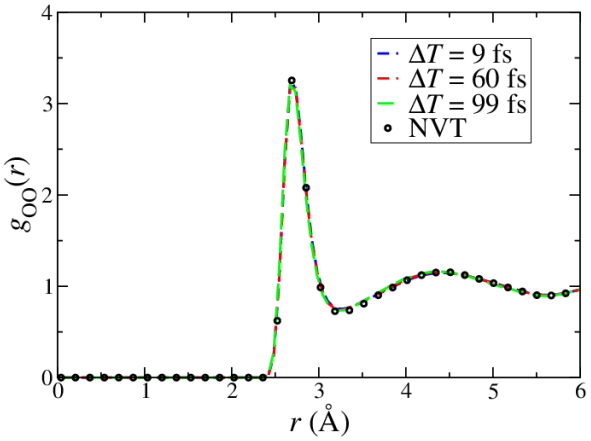
RESPA schemes

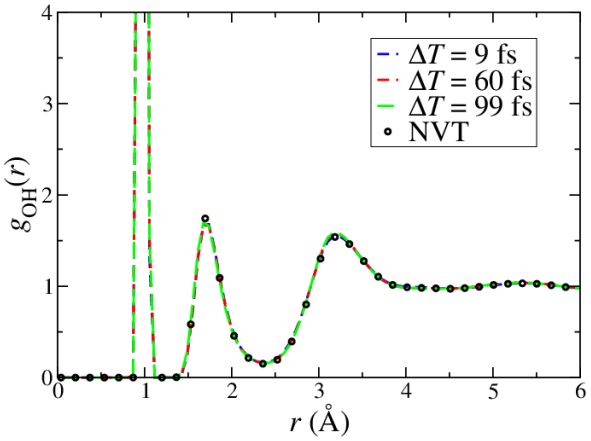
$$U^{(1)}_{\text{long}}(\mathbf{r}) = U_{\text{recip}}(\mathbf{r};\alpha,k_{\text{res}}) + \sum_{i>j}\left(1-\delta_{ij}\right)\theta(r_{ij}-r_{\text{cut}})\frac{q_i q_j \operatorname{erf}(\alpha r_{ij})}{r_{ij}}$$

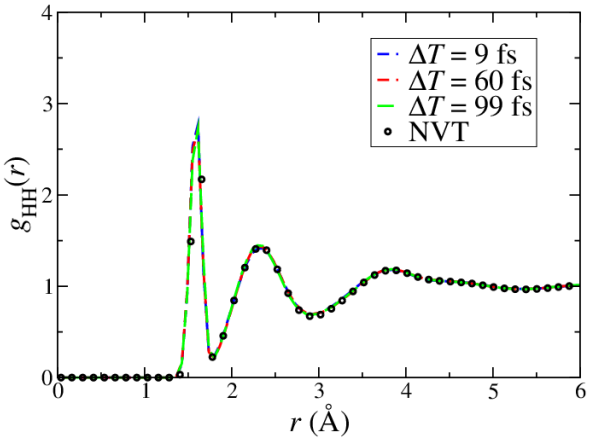
$$U^{(2)}_{\text{long}}(\mathbf{r}) = U_{\text{recip}}(\mathbf{r};\alpha,k_{\max}) - \sum_{i>j}\left(1-\delta_{ij}\right)\left[1-\theta(r_{ij}-r_{\text{cut}})\right]\frac{q_i q_j \operatorname{erf}(\alpha r_{ij})}{r_{ij}}$$

$\delta t = 0.5$ fs $\quad \Delta t = 3$ fs $\quad \Delta T = ?$

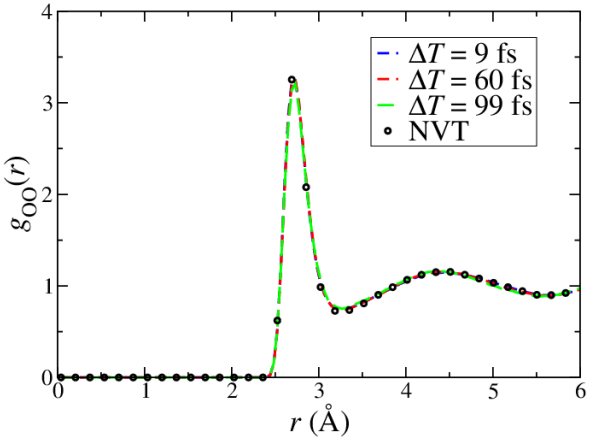
RESPA 1: $L = 4$, $\quad r_{\text{cut}} = 6$ Å

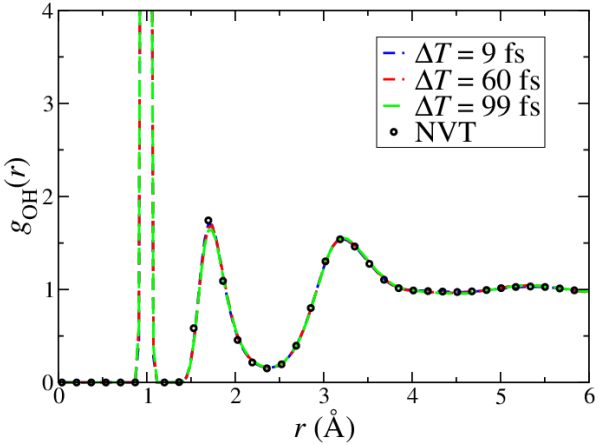


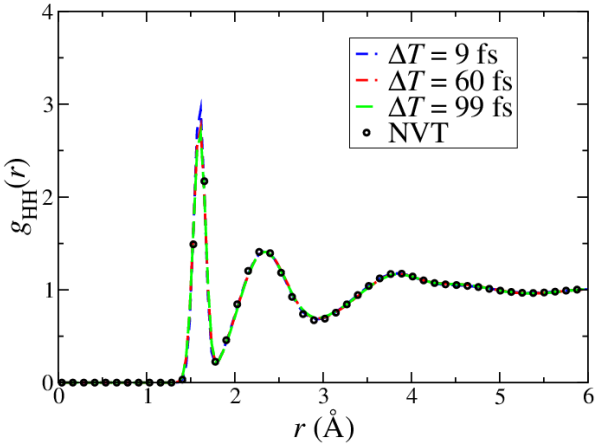




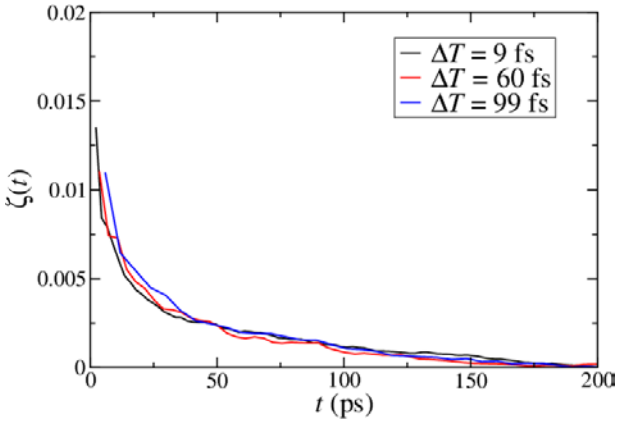
RESPA 2: $L = 4$, $\quad r_{\text{cut}} = 8$ Å

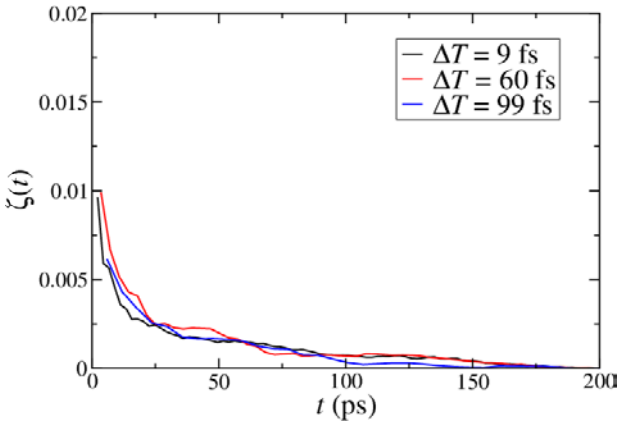


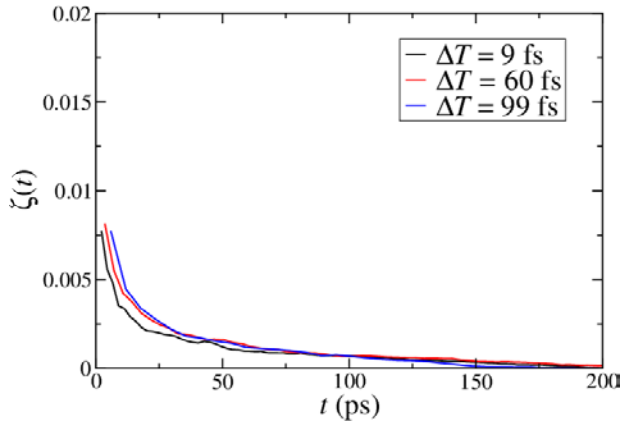


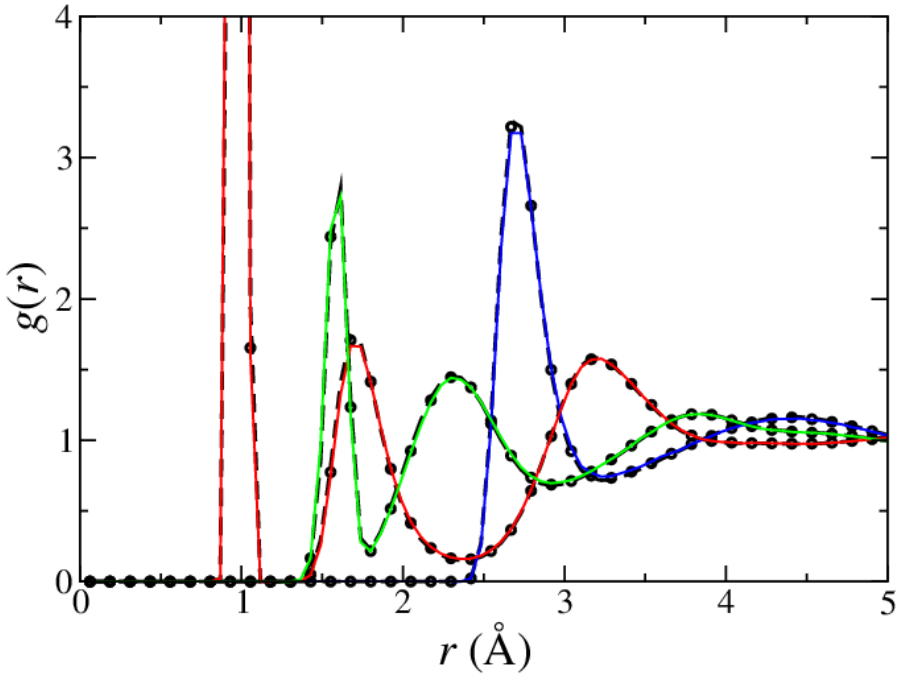


RESPA 1: $L = 4$, $r_{cut} = 6$ Å





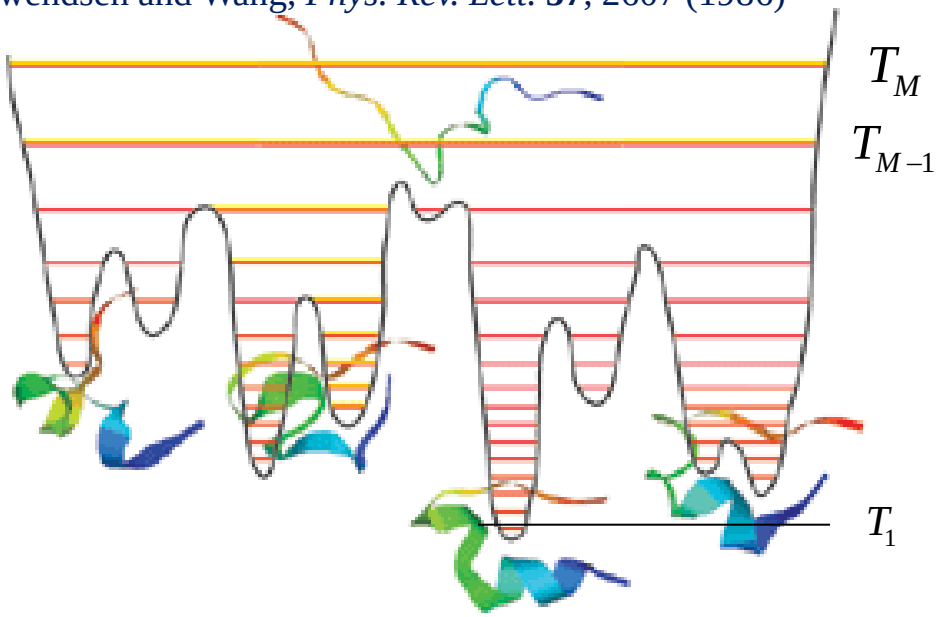




$L = 4$ (colors)
$L = 1$ (dashed)
$L = 2$ (circles)

Parallel Tempering

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



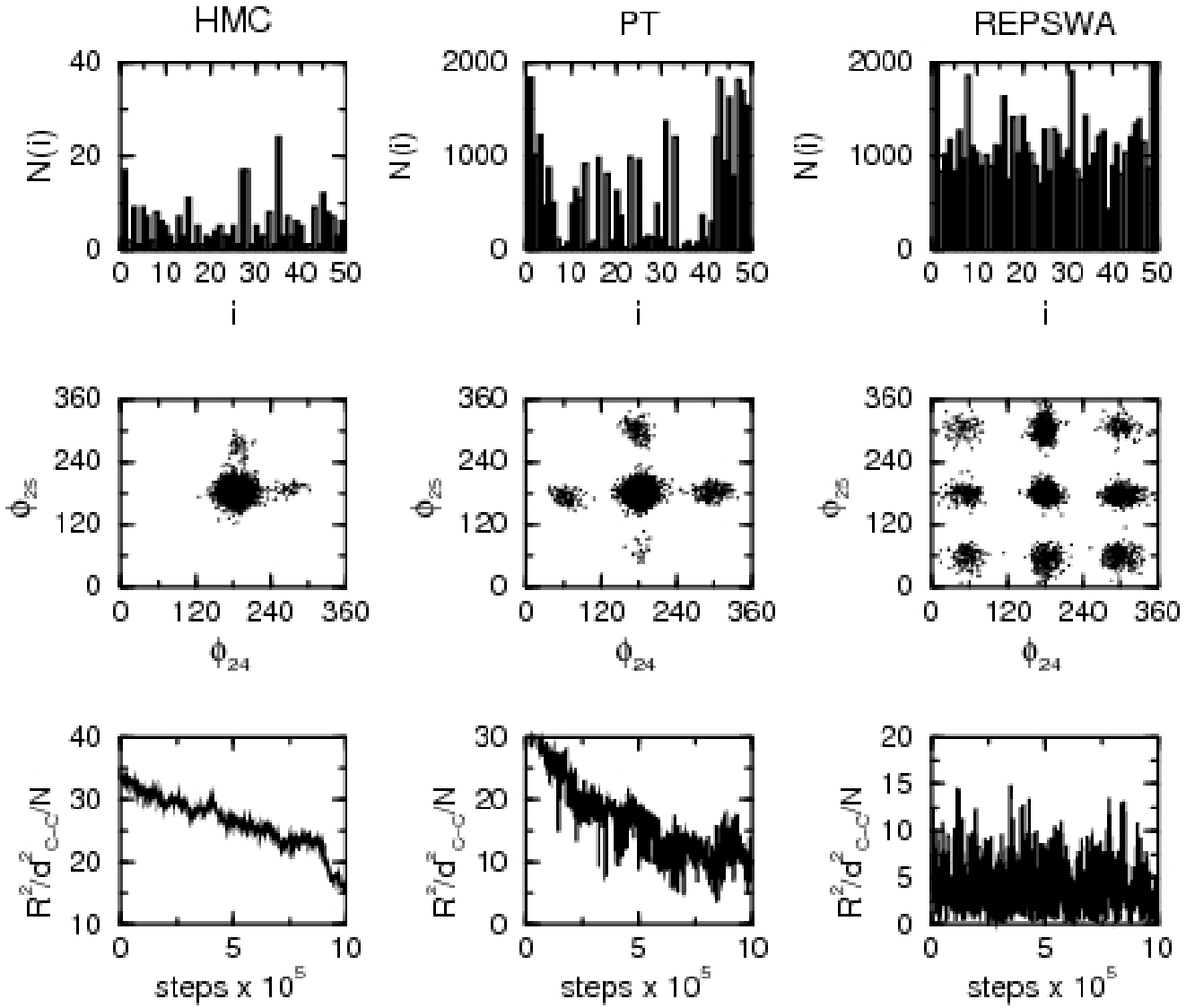
$$f_K(\mathbf{r}^{(K)}) = \frac{e^{-\beta_K U(\mathbf{r}^{(K)})}}{Z(N,V,T_K)} \qquad F(\mathbf{r}^{(1)},\ldots,\mathbf{r}^{(M)}) = \prod_{K=1}^{M} f(\mathbf{r}^{(K)})$$

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

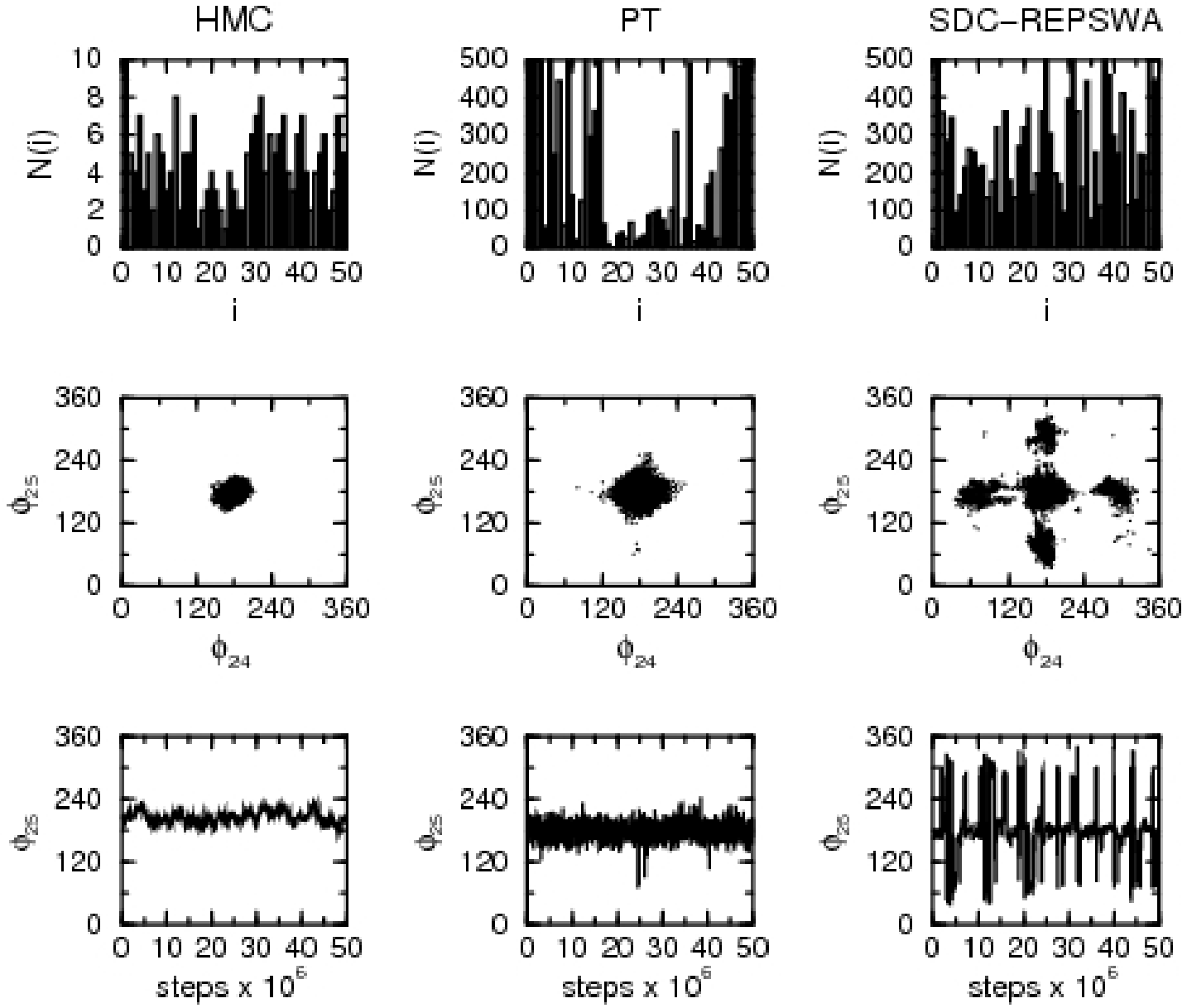
$$\Delta_{K,K+1} = (\beta_K - \beta_{K+1})\left[U(\mathbf{r}^{(K)}) - U(\mathbf{r}^{(K+1)})\right]$$

Comparison for a 50-mer chain using CHARMM22

REMC/PT replicas = 10; 300 < T < 1000, 10 replicas 20% acceptance
Nonbonded interactions off

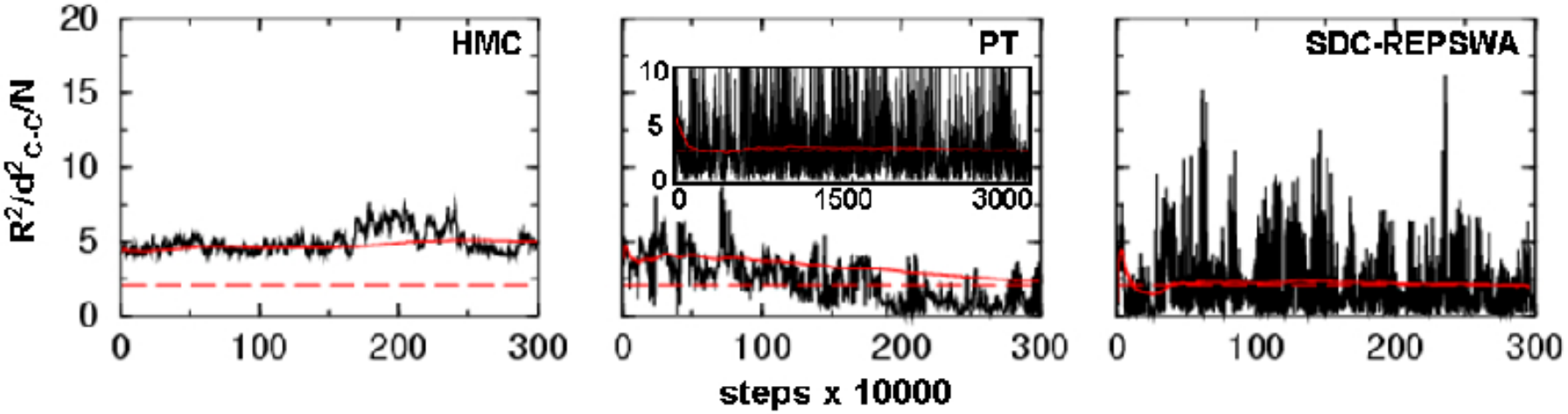


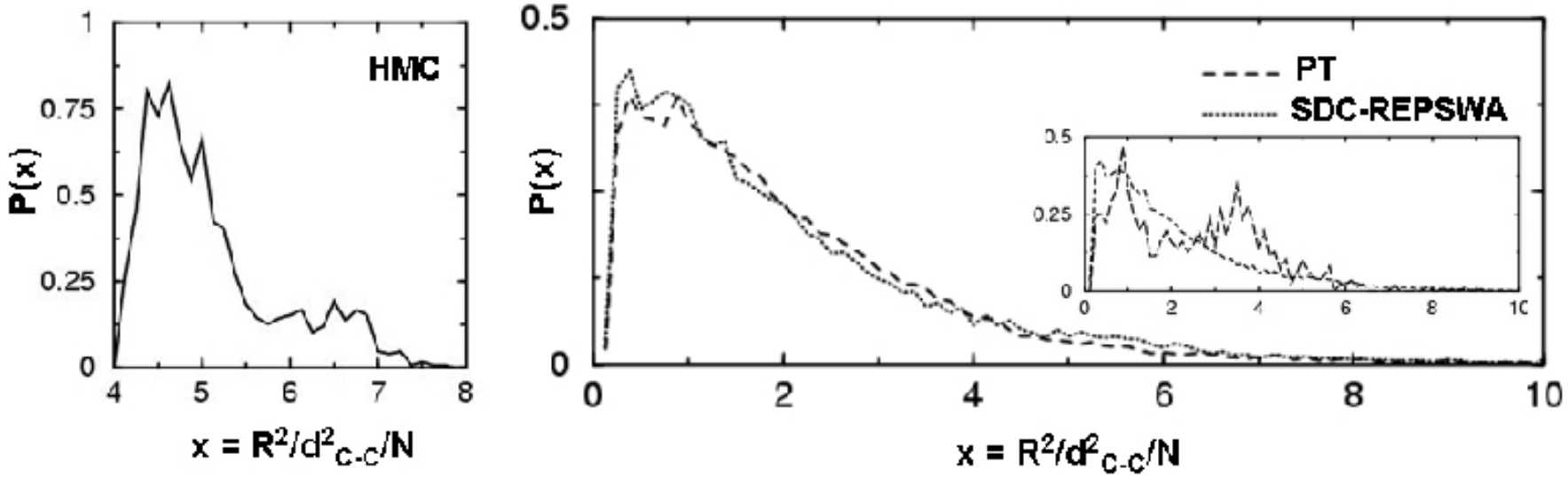
Comparison for 50-mer using CHARMM22 all interactions



Comparison for 50-mer with all interactions

PT replicas = 10; REPSWA α = 0.8; Every 10th dihedral not transformed





Replica exchange with "solute" tempering

P. Liu, B. Kim, R. A. Friesner, B. J. Berne PNAS (2005); L. Wang, R. A. Friesner, B. J. Berne J. Phys. Chem. B (2011)

A downside of replica-exchange is that $U \sim N$, therefore, the energy differences between neighboring replica need to shrink as the system size grows, which means more and more replica are needed in order for the acceptance probability to remain approximately fixed.

Replica exchange with solute tempering (REST) was developed to allow just part of the system (the "solute") to be subject to attempted exchanges. It relies on the idea that different replicas can be subject to different potentials.

$$f_K(\mathbf{r}) = \frac{e^{-\beta_K U_K(\mathbf{r})}}{Z(N,V,T_K)}$$

$$\Delta_{K,K+1} = \beta_K \left(U_K(\mathbf{r}^{(K)}) - U_K(\mathbf{r}^{(K+1)})\right) + \beta_{K+1}\left(U_{K+1}(\mathbf{r}^{(K+1)}) - U_{K+1}(\mathbf{r}^{(K)})\right)$$

If the potential energy of a solute-solvent system is:

$$U_K(\mathbf{r}) = U_s(\mathbf{r}) + U_{sv}(\mathbf{r}) + U_v(\mathbf{r})$$

The latest version of REST (called REST2) uses the following ladder of potentials:

$$U_K(\mathbf{r}) = \frac{\beta_K}{\beta_0} U_s(\mathbf{r}) + \sqrt{\frac{\beta_K}{\beta_0}} U_{sv}(\mathbf{r}) + U_v(\mathbf{r})$$

Replica exchange with “solute” tempering

The ladder of potentials

$$U_K(\mathbf{r}) = \frac{\beta_K}{\beta_0} U_s(\mathbf{r}) + \sqrt{\frac{\beta_K}{\beta_0}} U_{sv}(\mathbf{r}) + U_v(\mathbf{r})$$

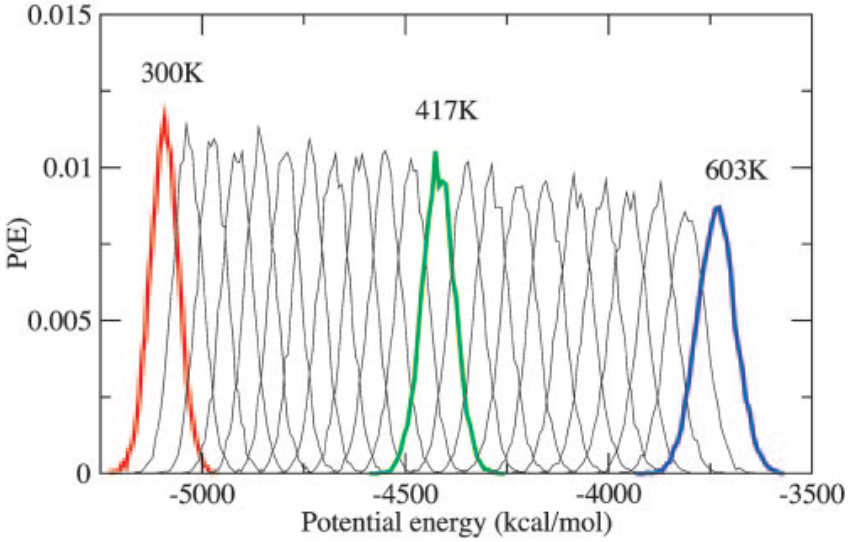
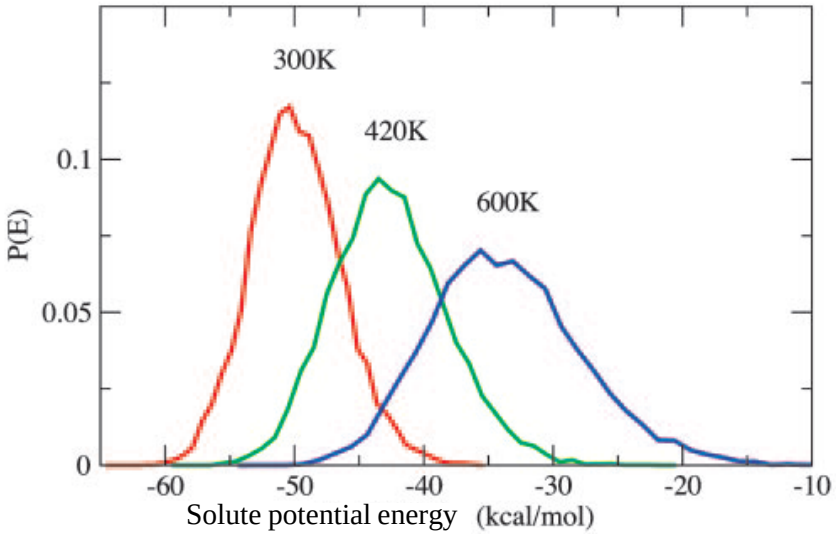
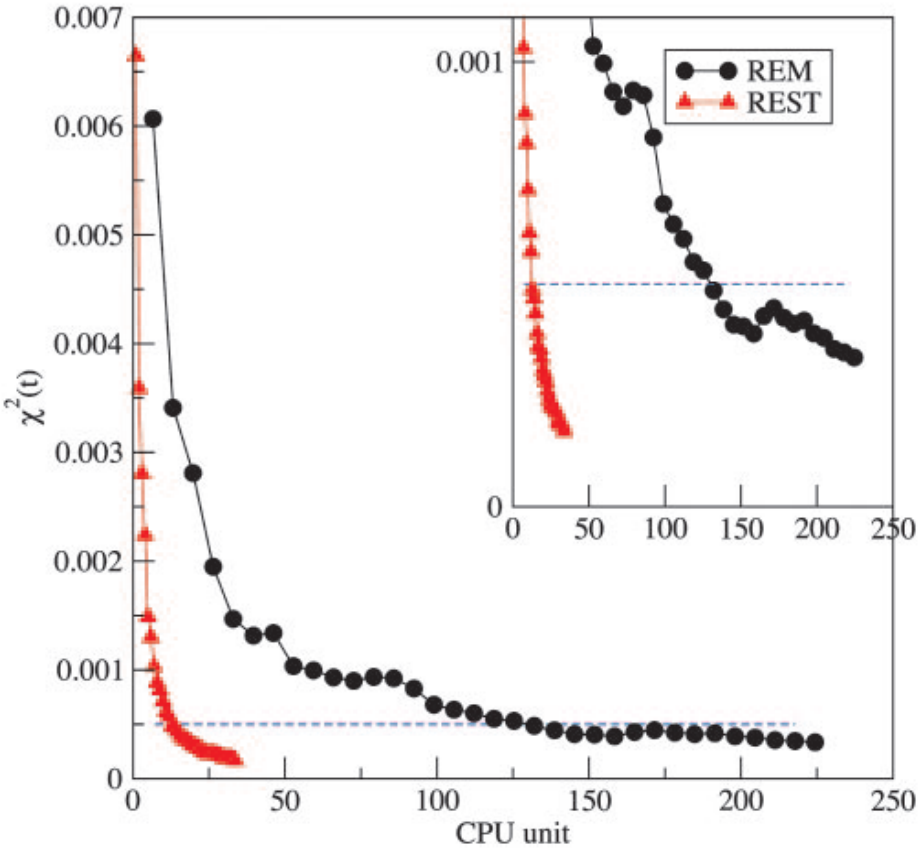
allows each replica to be run at a single temperature T_0 so that the solute probability

$$e^{-\beta_0(\beta_K/\beta_0)U_s(\mathbf{r})} = e^{-\beta_K U_s(\mathbf{r})}$$

For full potential ladder:

$$\beta_0 U_K(\mathbf{r}) = \beta_K U_s(\mathbf{r}) + \sqrt{\beta_0 \beta_K} U_{sv}(\mathbf{r}) + \beta_0 U_v(\mathbf{r})$$

Acceptance probability determined by

$$\Delta_{K,K+1} = (\beta_K - \beta_{K+1}) \left[U_s(\mathbf{r}^{(K)}) - U_s(\mathbf{r}^{(K+1)}) + \frac{\sqrt{\beta_0}}{\sqrt{\beta_K} + \sqrt{\beta_{K+1}}} \left(U_{sv}(\mathbf{r}^{(K)}) - U(\mathbf{r}^{(K+1)}) \right) \right]$$

Convergence of alanine dipeptide in solution