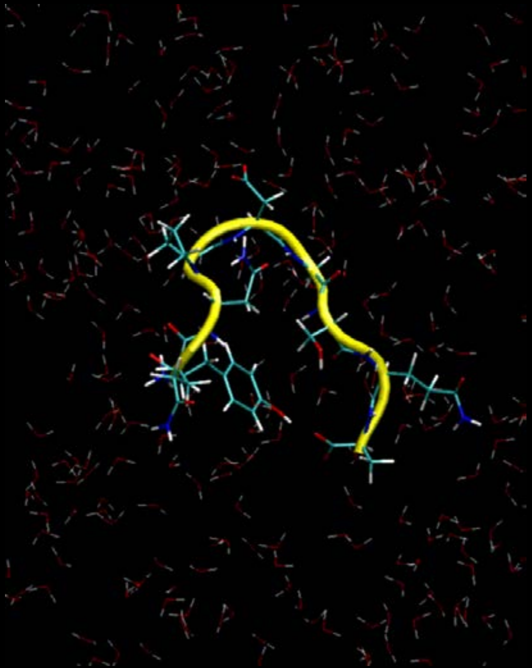
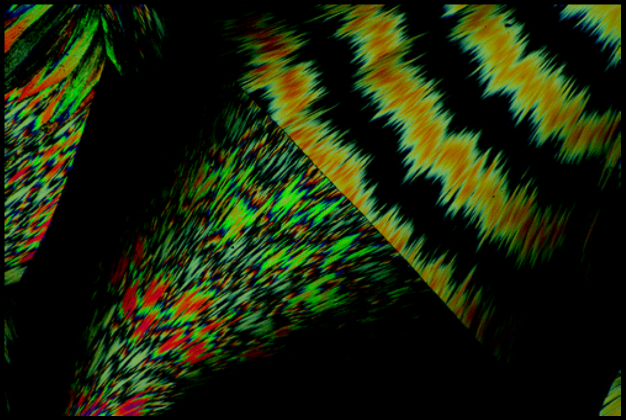
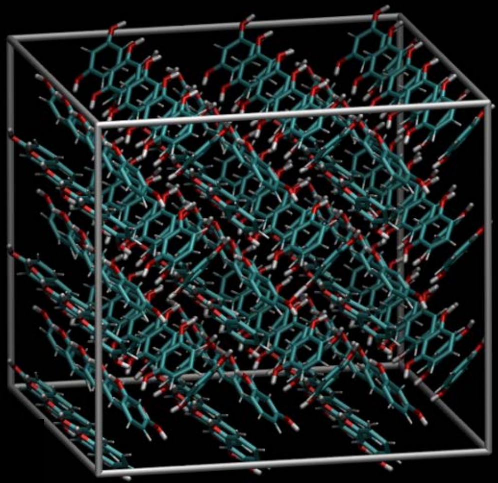
Enhanced sampling via molecular dynamics I: Targeting collective variables

Mark E. Tuckerman
Dept. of Chemistry and Courant Institute of Mathematical Sciences
New York University, 100 Washington Square East, NY 10003







Molecular Dynamics

$$H = \sum_{i=1}^{N} \frac{\mathbf{p}_i^2}{2m_i} + U(\mathbf{r}_1, \ldots, \mathbf{r}_N) \quad : \quad \mathrm{R}^{2dN} \rightarrow \mathrm{R}$$

$$\dot{\mathbf{r}}_i = \frac{\partial H}{\partial \mathbf{p}_i} = \frac{\mathbf{p}_i}{m_i}, \qquad \dot{\mathbf{p}}_i = -\frac{\partial H}{\partial \mathbf{r}_i} = -\frac{\partial U}{\partial \mathbf{r}_i} = \mathbf{F}_i(\mathbf{r}_1, \ldots, \mathbf{r}_N)$$

Solve subject to initial conditions:

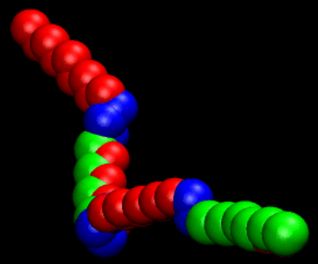
$$(\mathbf{r}_1(0), \ldots, \mathbf{r}_N(0), \mathbf{p}_1(0), \ldots, \mathbf{p}_N(0)) \rightarrow (\mathbf{r}_1(t), \ldots, \mathbf{r}_N(t), \mathbf{p}_1(t), \ldots, \mathbf{p}_N(t))$$

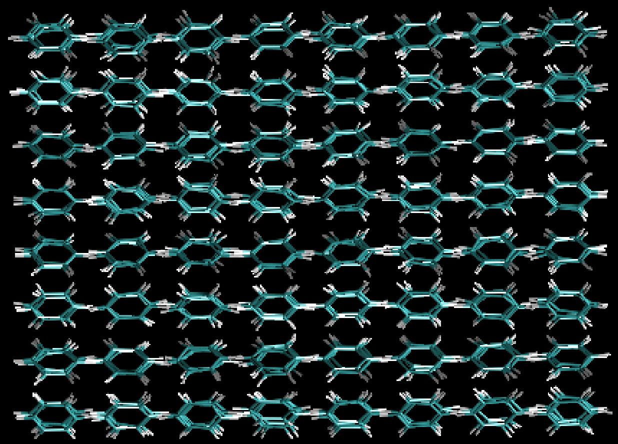
Energy conservation:

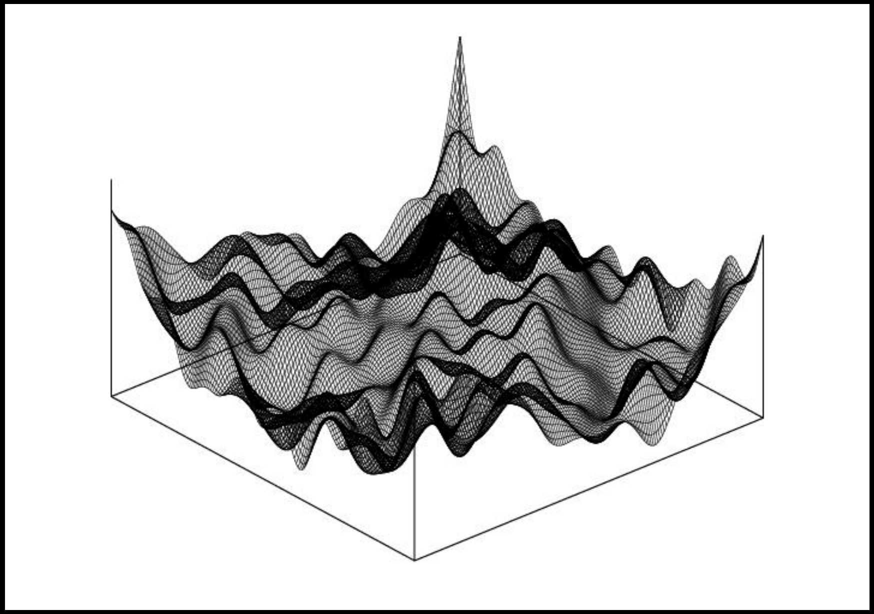
$$\frac{dH}{dt} = 0 \quad \Rightarrow \quad H(\mathbf{r}(0), \mathbf{p}(0)) = H(\mathbf{r}(t), \mathbf{p}(t))$$

$$H(\mathbf{r}(0), \mathbf{p}(0)) \neq H(\mathbf{r}(k\Delta t), \mathbf{p}(k\Delta t))$$

Rough energy landscapes in proteins and crystals



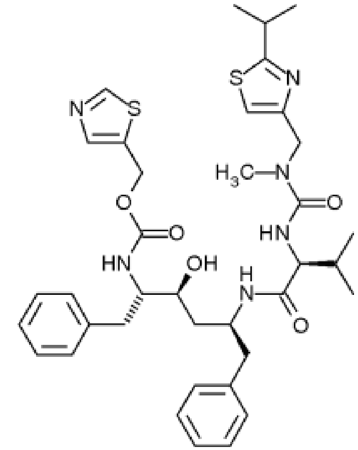




Dunitz and Scheraga
PNAS **101**, 14309 (2004)

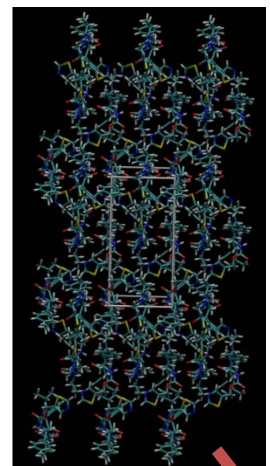
Pharmaceutical polymorphism

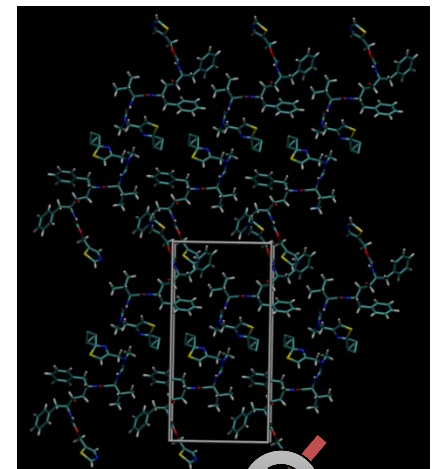
Polymorphism **refers to the ability of a compound to form multiple crystal structures.**

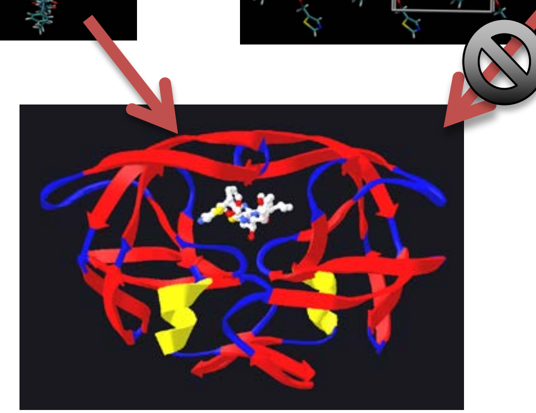


Ritonavir: HIV protease inhibitor

- NIH: $3,500,000 investment
- Abbott Labs: $200,000,000 investment
- Originally dispensed in 1996 as ordinary capsules, no refrigeration required
- Converted to lower energy (hitherto unknown) polymorph (form I to form II) on the shelf
- Form II: Poor solubility, lower bioavailability
- Required recall (1998) and reformulation as gel caps (2002).
- Even a trace of form II causes phase transformation



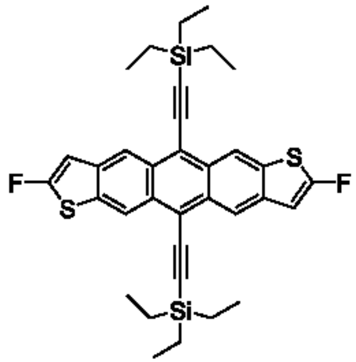


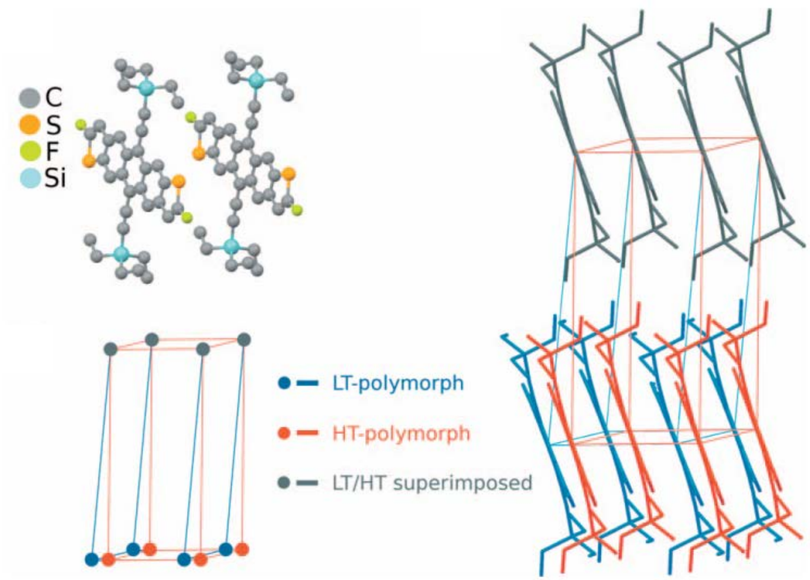


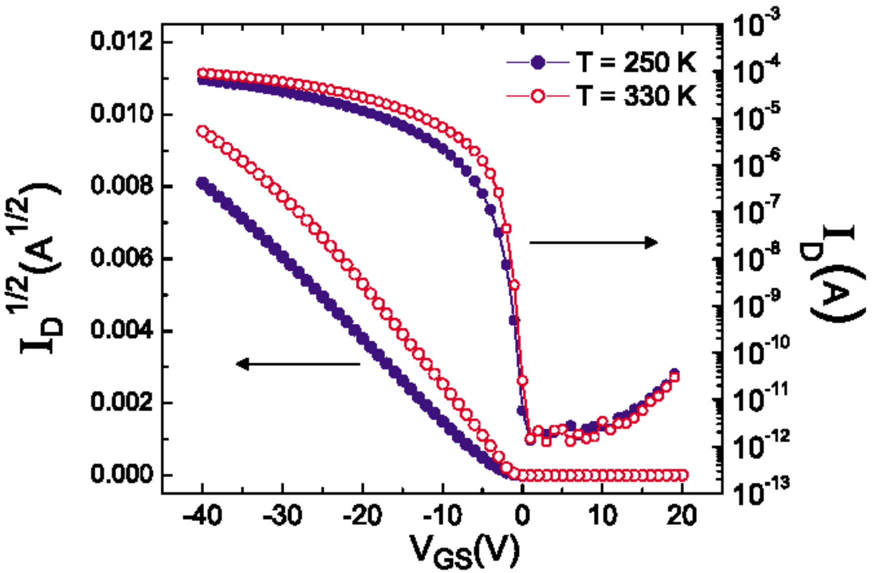
HIV-1 protease

Polymorphism in Organic Semiconductors

- Different crystal packing arrangements can affect electronic coupling between molecules.
- Properties can be affected even by small changes in the crystal structure.
- Example: Difluorinated 5,11-bis(triethylsilylethynyl)anthradithiophene (Jurchescu *et al*. *PRB*, 2009).

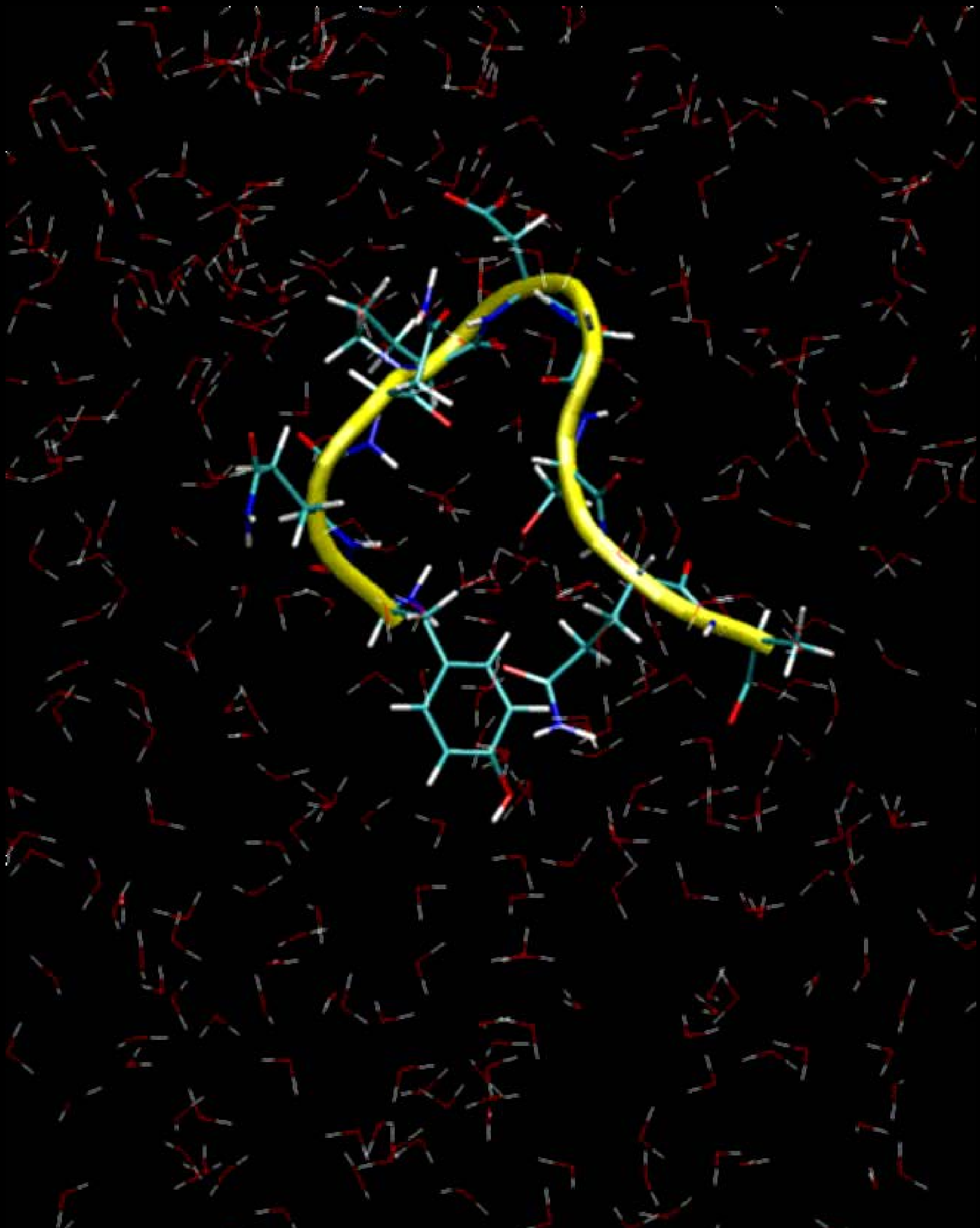






Sequence:
YQPDGSQA

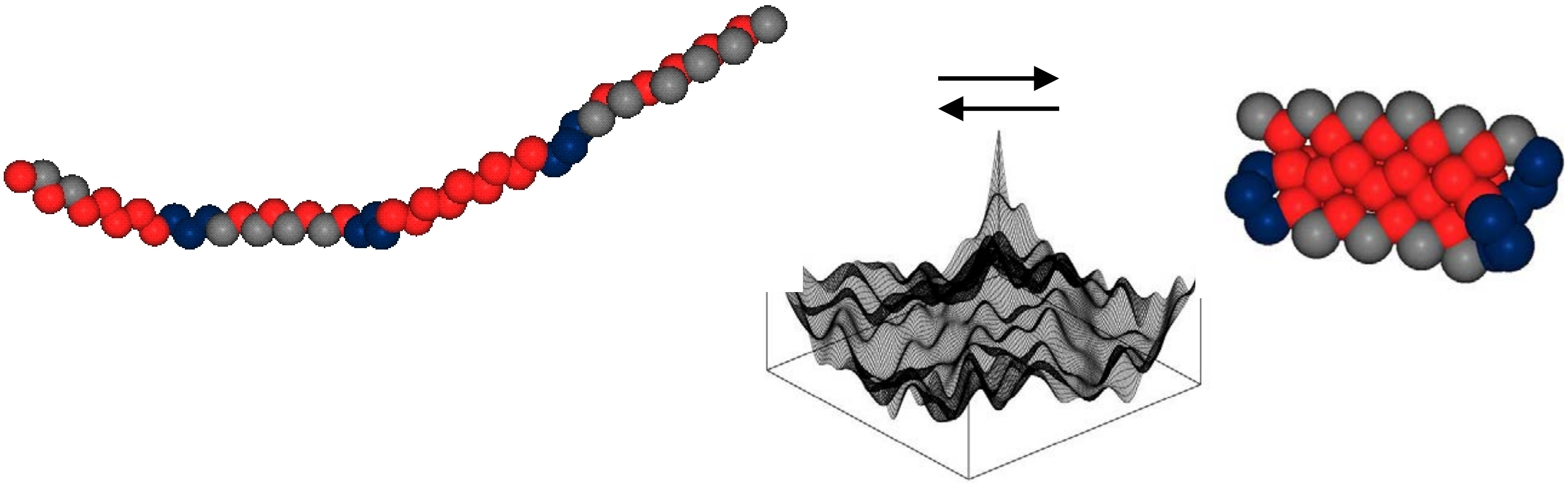
I.-C. Lin and MET
J. Phys. Chem. B
(2010)



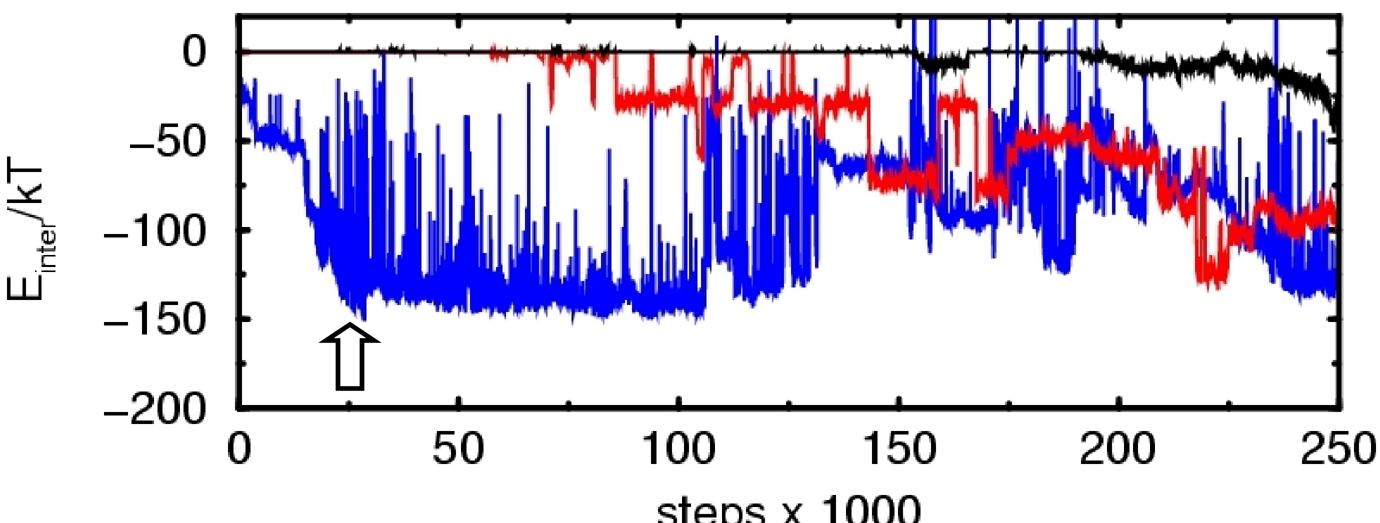
Solvent
mass scaling
0.1

Side-chain
mass scaling
0.6

Conformational equilibrium



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

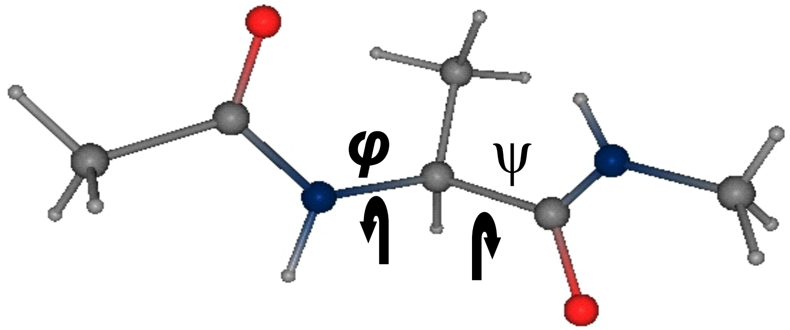


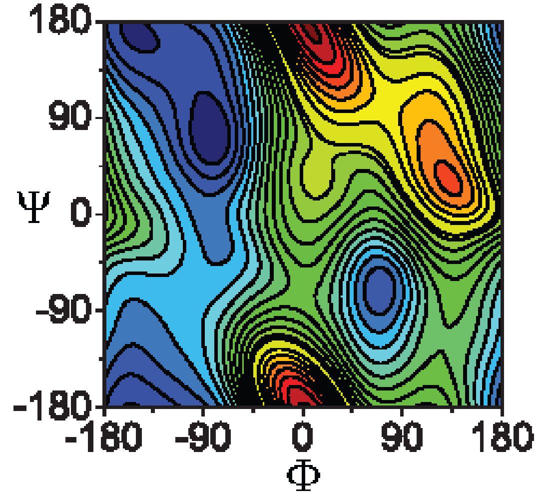
Collective variables in molecular simulation

Let $\mathbf{r}_1,\ldots,\mathbf{r}_N$ denote the Cartesian coordinates of N atoms in a system.
Suppose n collective variables (CVs) characterize a process of interest

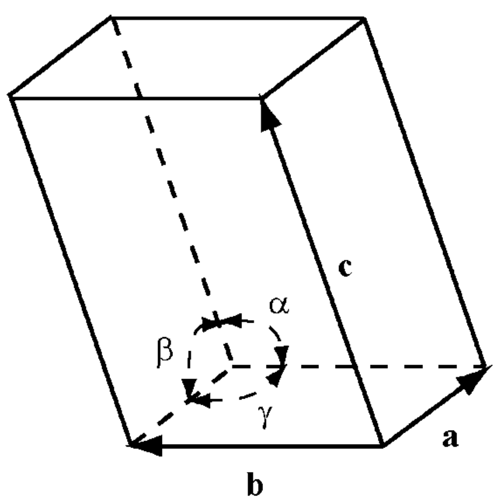
$$q_\alpha = q_\alpha(\mathbf{r}_1,\ldots,\mathbf{r}_N) \equiv q_\alpha(\mathbf{r}) \qquad \alpha = 1,\ldots,n$$

Peptides:





Crystals:



$$\mathbf{h} = \begin{pmatrix} a_x & b_x & c_x \\ a_y & b_y & c_y \\ a_z & b_z & c_z \end{pmatrix}$$

(Box matrix)

Calculation of free energies in CVs

Given a classical Hamiltonian

$$H(\mathbf{p},\mathbf{r}) = \frac{1}{2}\mathbf{p}^T M^{-1}\mathbf{p} + U(\mathbf{r}_1,...,\mathbf{r}_N)$$

and a set of $n << 3N$ collective variables

$$q_\alpha = q_\alpha(\mathbf{r}_1,...,\mathbf{r}_N) \qquad \alpha = 1,...,n$$

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

$$= \left\langle \prod_{\alpha=1}^{n}\delta(q_\alpha(\mathbf{r}) - s_\alpha)\right\rangle$$

Free-energy surface:

$$A(s_1,...,s_n,T) = -kT\ln P(s_1,...,s_n,T)$$

Thermodynamic integration in the blue moon ensemble

M. Sprik and G. Ciccotti, *J. Chem. Phys*. **109**, 7737 (1998)

Suppose we have a canonical transformation to generalized coordinates and momenta:

$$q_\alpha(\mathbf{r}), \qquad \pi_\alpha = \frac{\partial L}{\partial \dot{q}_\alpha}$$

such that $q_1(\mathbf{r})$ is the reaction coordinate.

Hamiltonian:

$$H(\pi, q) = \frac{1}{2}\pi^{\mathrm{T}} K(q)\pi + U\left(\mathbf{r}_1(q), \ldots, \mathbf{r}_N(q)\right)$$

$$K_{\alpha\beta}(q) = \sum_{i=1}^{N} \frac{1}{m_i}\left(\frac{\partial q_\alpha}{\partial \mathbf{r}_i}\right)\cdot\left(\frac{\partial q_\beta}{\partial \mathbf{r}_i}\right)$$

Probability distribution:

$$P(s_1, \ldots, s_n) = \int d^{3N}\pi\, d^{3N}q\ e^{-\beta H(\pi, q)} \prod_{\alpha=1}^{n} \delta(q_\alpha - s_\alpha)$$

Thermodynamic integration in the blue moon ensemble

Free energy derivative:

$$\frac{\partial A}{\partial s_\mu} = -\frac{1}{\beta P(s)}\frac{dP}{ds} = -\frac{1}{\beta P(s)}\int d^{3N}\pi d^{3N}q\ e^{-\beta H(\pi,q)}\frac{\partial}{\partial s_\mu}\prod_{\alpha=1}^{n}\delta(q_\alpha - s_\alpha)$$

$$= \frac{1}{\left\langle \prod_{\alpha=1}^{n}\delta(q_\alpha - s_\alpha)\right\rangle}\left\langle \frac{\partial H}{\partial q_\mu}\prod_{\alpha=1}^{n}\delta(q_\alpha - s_\alpha)\right\rangle \equiv \left\langle \frac{\partial H}{\partial q_\mu}\right\rangle_s^{\text{cond}}$$

If we just transform coordinate space, leaving the momenta untouched:

$$\frac{\partial A}{\partial s_\mu} = \left\langle \left[\frac{\partial U(q)}{\partial q_\mu} - k_B T\frac{\partial}{\partial q_\mu}\ln J(q)\right]\right\rangle_s^{\text{cond}}$$

Thermodynamic integration in the blue moon ensemble

Implementation via constrained MD (practical for n = 1):

$$\dot{\mathbf{r}}_i = \frac{\mathbf{p}_i}{m_i}, \qquad \dot{\mathbf{p}}_i = -\frac{\partial U}{\partial \mathbf{r}_i} + \lambda \frac{\partial q}{\partial \mathbf{r}_i}$$

Conditional average:

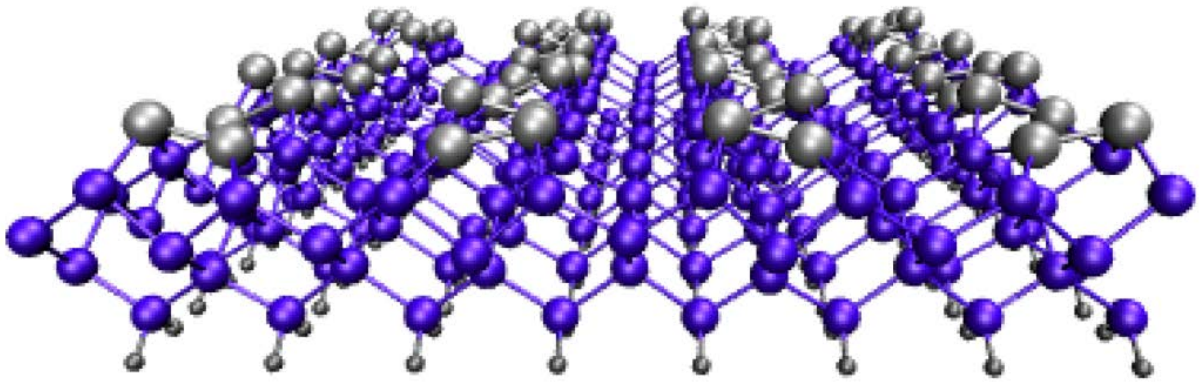
$$\left\langle O(\mathbf{r}) \right\rangle_s^{\text{cond}} = \frac{\left\langle z^{-1/2}(\mathbf{r}) O(\mathbf{r}) \right\rangle_s^{\text{constr}}}{\left\langle z^{-1/2}(\mathbf{r}) \right\rangle_s^{\text{constr}}}, \qquad z(\mathbf{r}) = \sum_{i=1}^{N} \frac{1}{m_i} \left(\frac{\partial q}{\partial \mathbf{r}_i} \right)^2$$

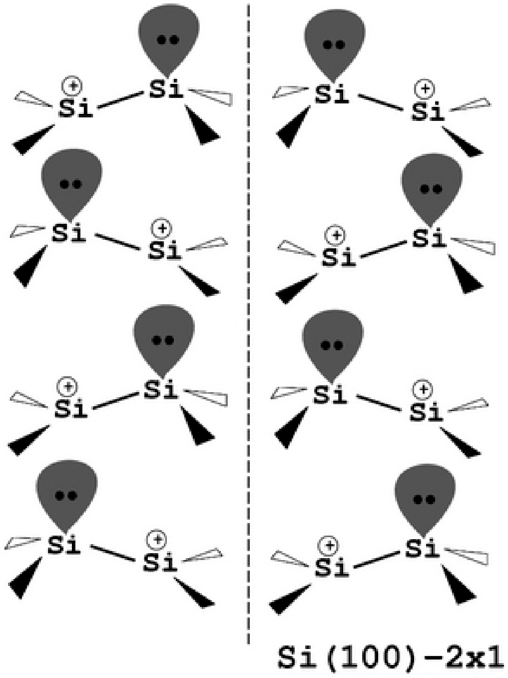
When using constraints:

$$\frac{dA}{ds} = \left\langle \left[\lambda + k_B T G \right] \right\rangle_s^{\text{cond}}, \qquad G = \frac{1}{z^2(\mathbf{r})} \sum_{i,j} \frac{1}{m_i m_j} \frac{\partial q}{\partial \mathbf{r}_i} \cdot \frac{\partial^2 q}{\partial \mathbf{r}_i \partial \mathbf{r}_j} \cdot \frac{\partial q}{\partial \mathbf{r}_j}$$

Reactions on the Si(100)-2x1 Surface

- Formation of surface dimers
- Buckled dimer structure.





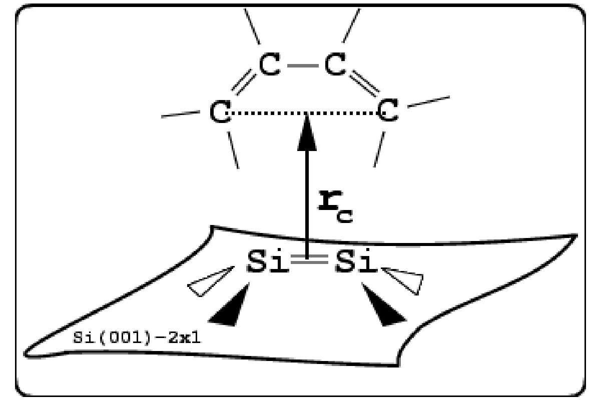
C(4x2)

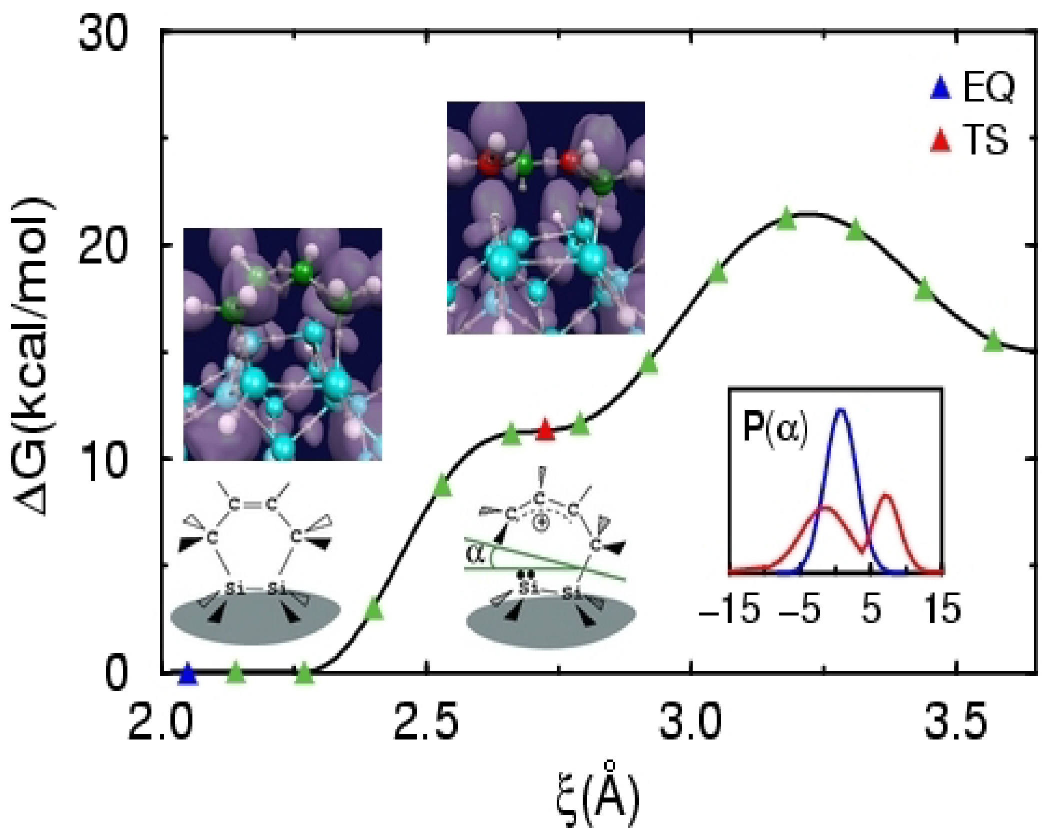
Free energy profile of [4+2] reaction

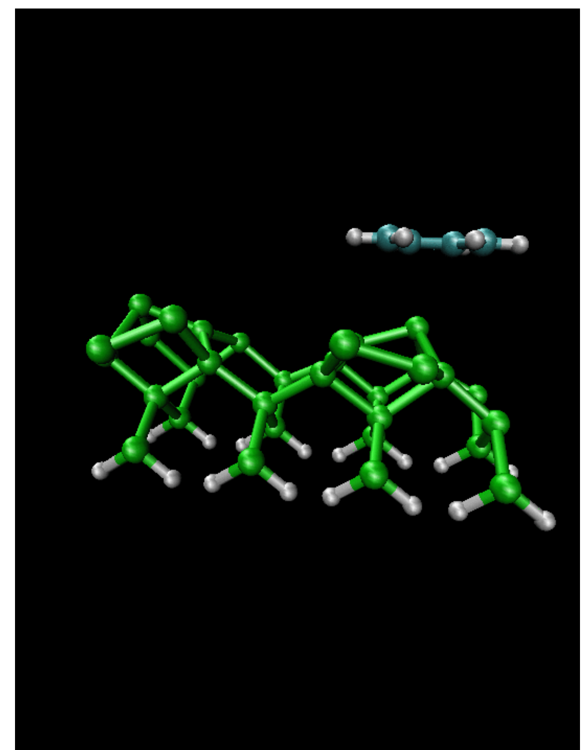
P. Minary and MET *J. Am. Chem. Soc*. (Comm.) **126**, 13920 (2004)

$$\xi = \left| \frac{1}{2}\left(\mathbf{R}_{Si_1} + \mathbf{R}_{Si_2}\right) - \frac{1}{2}\left(\mathbf{R}_{C_1} + \mathbf{R}_{C_4}\right) \right|$$

$$\Delta G(\xi) = \int_{\xi_0}^{\xi} d\xi' \left\langle \frac{\partial H}{\partial \xi'} \right\rangle_{\text{cond}}$$

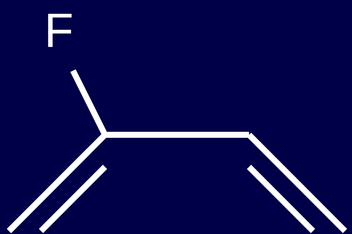




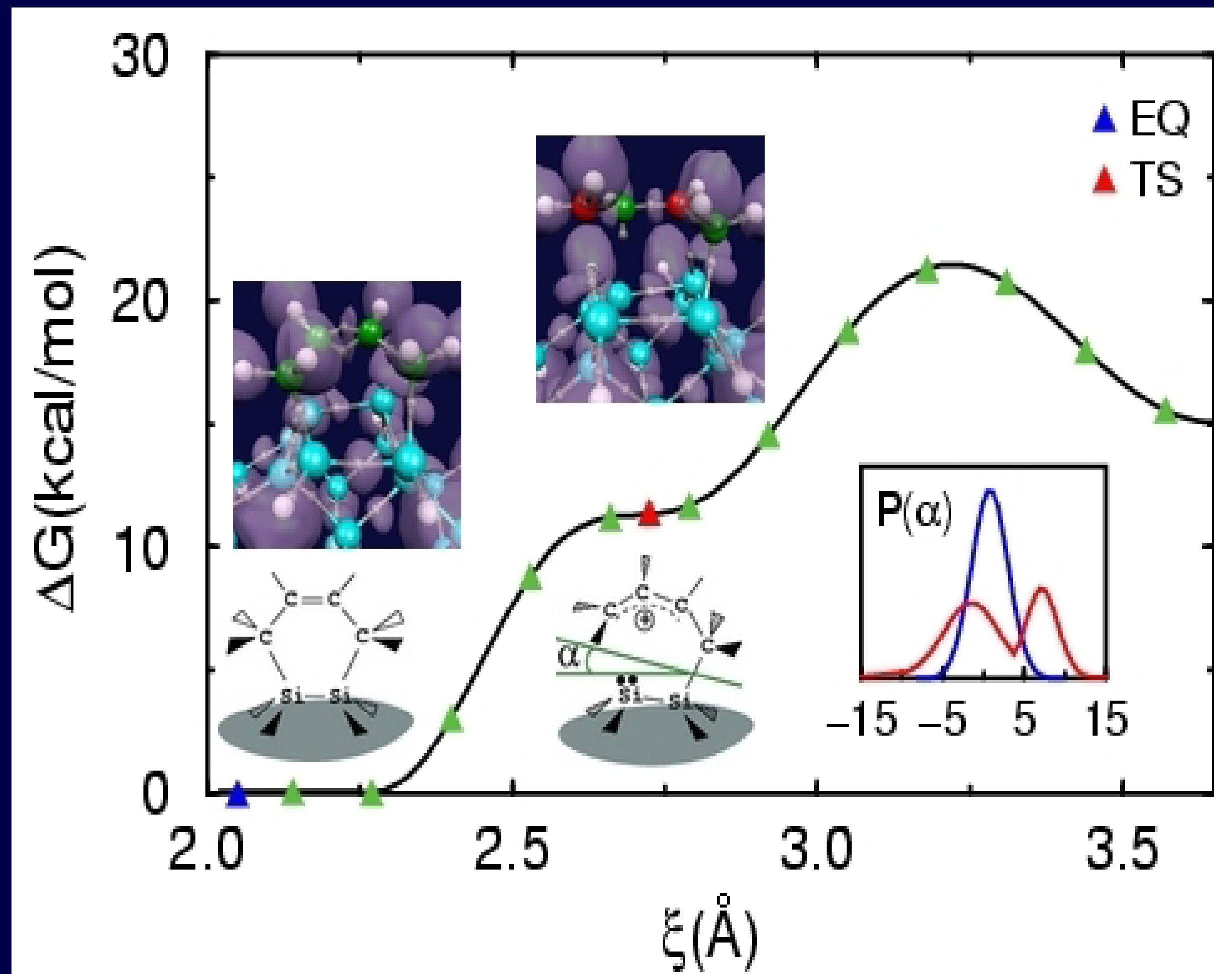


Comparing free energy for fluorinated 1,3-butadiene

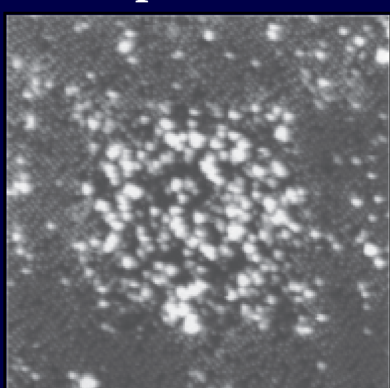
Goal: Design a molecule with a lower free energy barrier for the “retro” Diels-Alder reaction.



Minary, Iftimie, MET
Proc. Natl. Acad. Sci. (2005).



Surface patterning via STM tip



Wolkow and coworkers

Adiabatic free-energy dynamics (AFED)

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:

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

Suppose first n are of particular interest.

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

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

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

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

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

Free energies via adiabatic free energy dynamics (*JCP* 2002, *Mol. Sim.* 2002)

Free energy surface: Given a general interaction potential $U(\mathbf{r}_1,\ldots,\mathbf{r}_N)$

$$A(q_1,\ldots,q_n) = -kT\ln\int d^N\mathbf{r}\; e^{-\beta U(\mathbf{r}_1,\ldots,\mathbf{r}_N)}\prod_{\alpha=1}^{n}\delta(q_\alpha(\mathbf{r})-q_\alpha)$$

Equations of motion in generalized coordinates:

$$m_\alpha\ddot{q}_\alpha = -\frac{\partial\tilde{U}}{\partial q_\alpha} + \text{ Heat Bath}(T_s), \qquad i=1,\ldots,n$$

$$m_\alpha\ddot{q}_\alpha = -\frac{\partial\tilde{U}}{\partial q_\alpha} + \text{ Heat Bath}(T), \qquad i=n+1,\ldots,3N$$

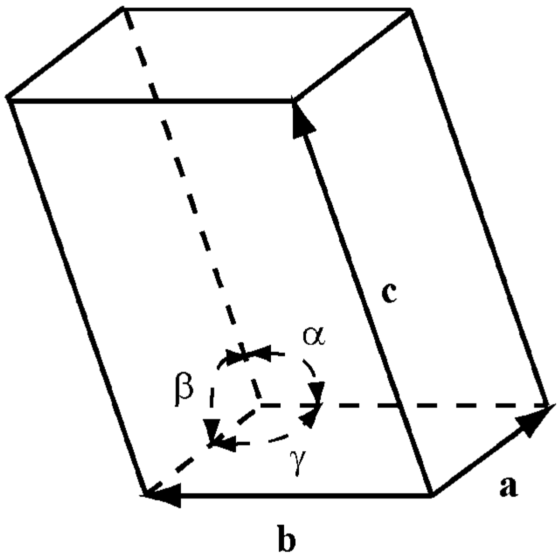
Generalized potential: $\tilde{U}(q) = U(\mathbf{r}(q)) - kT\ln J(q)$

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

In this limit,

$$m_\alpha\ddot{q}_\alpha = -\frac{\partial}{\partial q_\alpha}A(q_1,\ldots,q_n) + \text{ Heat Bath}(T_s), \qquad i=1,\ldots,n$$

Crystal-AFED [T. Q. Yu and MET *Phys. Rev. Lett.* (2011)]



$$\mathbf{h} = \begin{pmatrix} a_x & b_x & c_x \\ a_y & b_y & c_y \\ a_z & b_z & c_z \end{pmatrix}$$

$$V = \mathbf{a}\cdot\left(\mathbf{b}\times\mathbf{c}\right) = \det(\mathbf{h})$$

$$\dot{\mathbf{r}}_i = \frac{\mathbf{p}_i}{m_i} + \frac{\mathbf{p}_\mathbf{g}}{W}\mathbf{r}_i, \qquad \dot{\mathbf{p}}_i = \mathbf{F}_i - \frac{\mathbf{p}_\mathbf{g}}{W}\mathbf{p}_i - \frac{1}{N_f}\frac{\mathrm{Tr}\left[\mathbf{p}_\mathbf{g}\right]}{W}\mathbf{p}_i + \text{heat bath}(T)$$

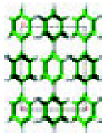
$$\dot{\mathbf{h}} = \frac{\mathbf{p}_\mathbf{g}\mathbf{h}}{W}, \qquad \dot{\mathbf{p}}_\mathbf{g} = \det(\mathbf{h})\left(\mathbf{P}^{(\mathrm{int})} - P\mathbf{I}\right) + \frac{1}{N_f}\sum_{i=1}^{N}\frac{\mathbf{p}_i^2}{m_i}\mathbf{I} + \text{heat bath}(T_\mathbf{h})$$

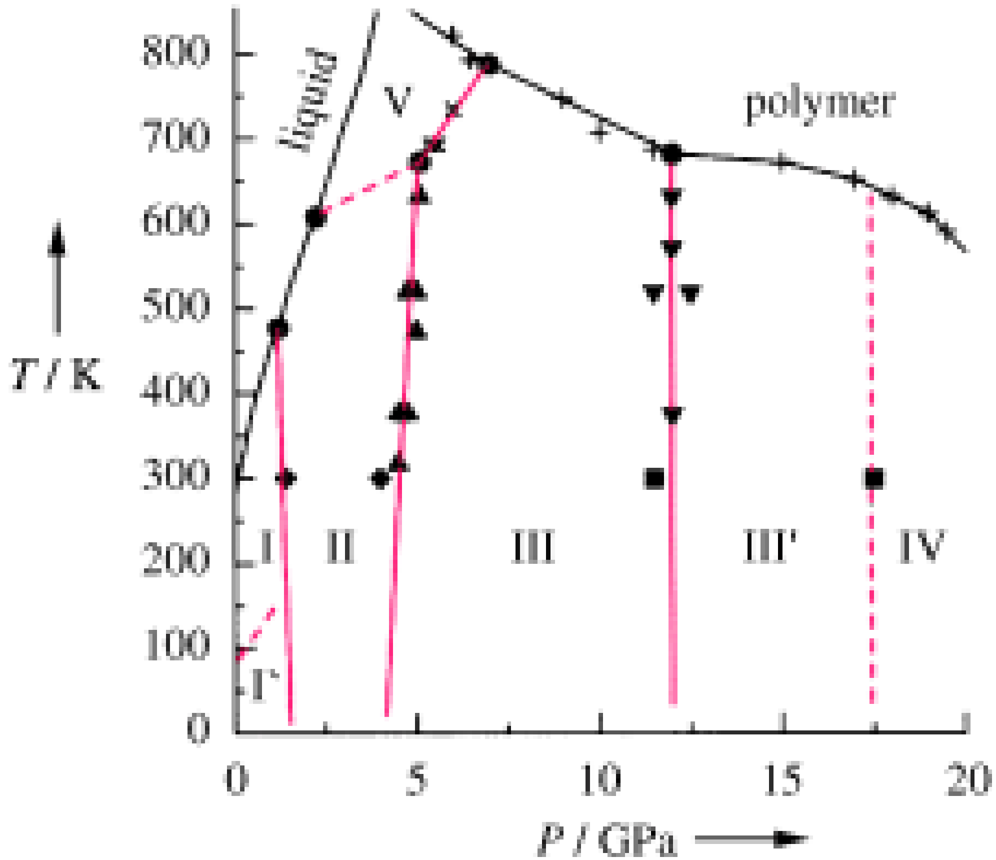
$$\text{Large } W, \qquad T_\mathbf{h} \gg T$$

"Phase diagram" of benzene

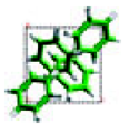
Raiteri, Martonak, Parrinello *Angew. Chem. Intl. Ed.* **44**, 3769 (2005)

I

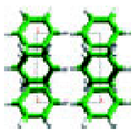




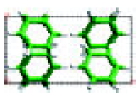
II



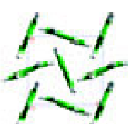
III



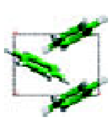
III′



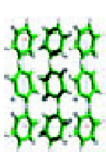
IV



V



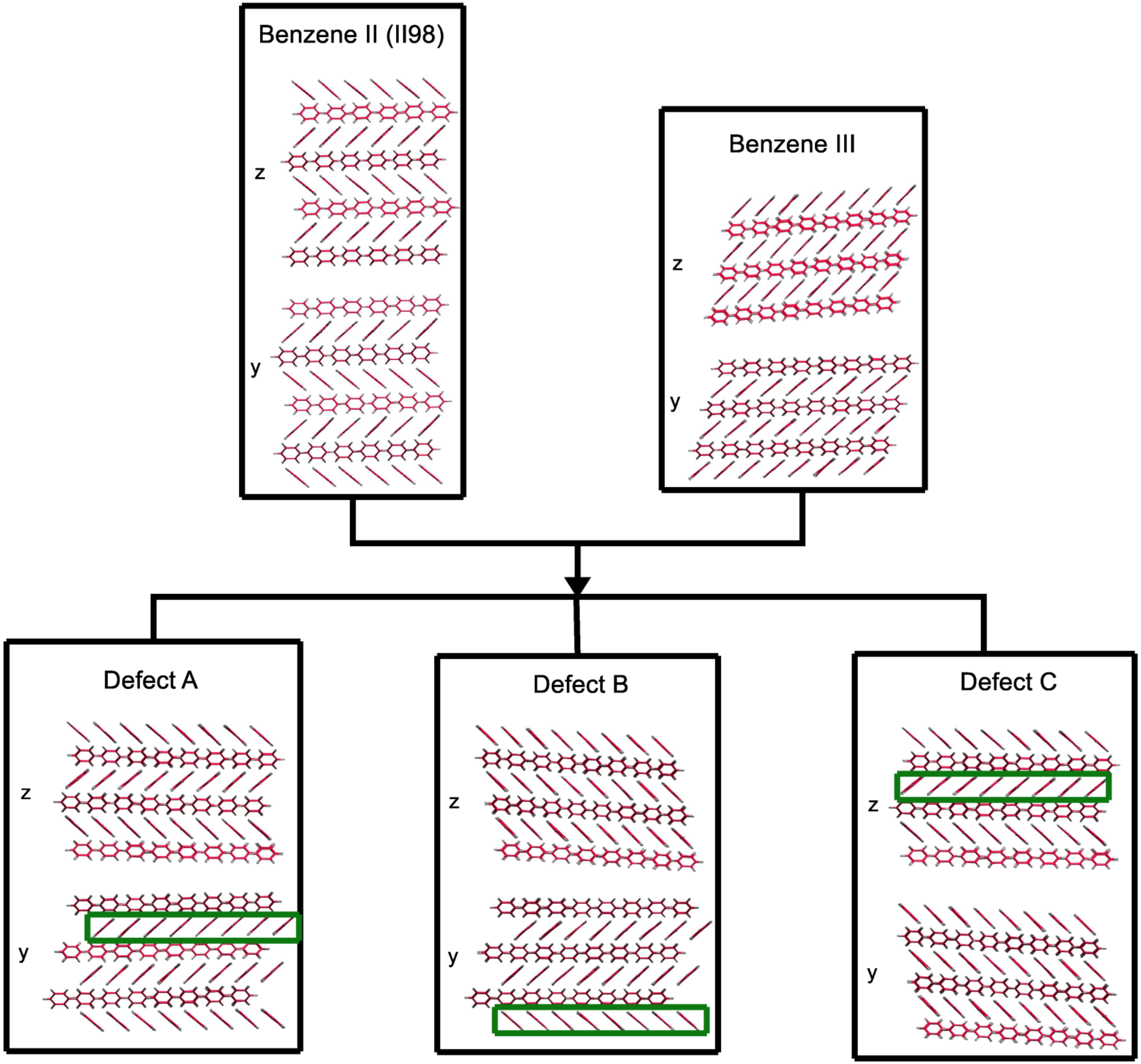
I′

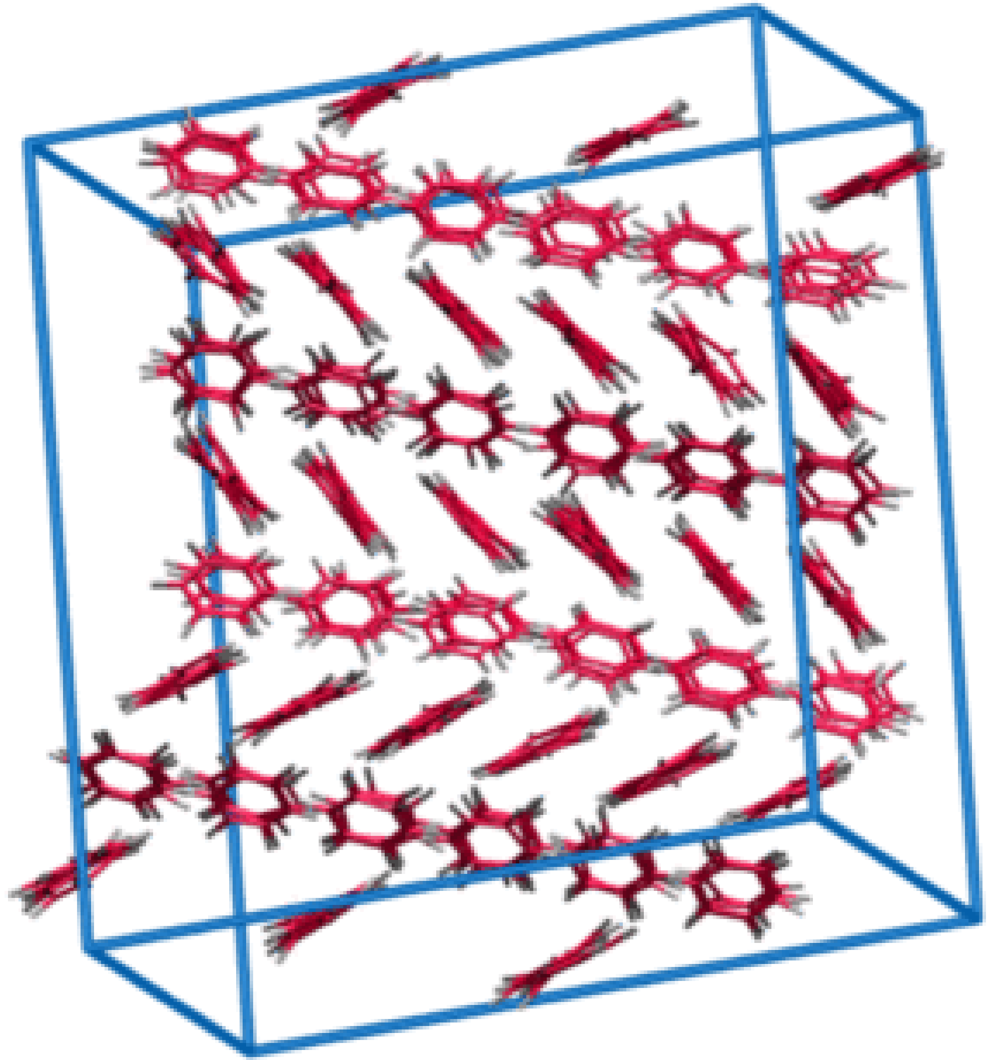


$P2_1/c$ (II96) $P4_32_12$(II98) II01

I, II, III, III′, IV known from X-ray and Raman scattering

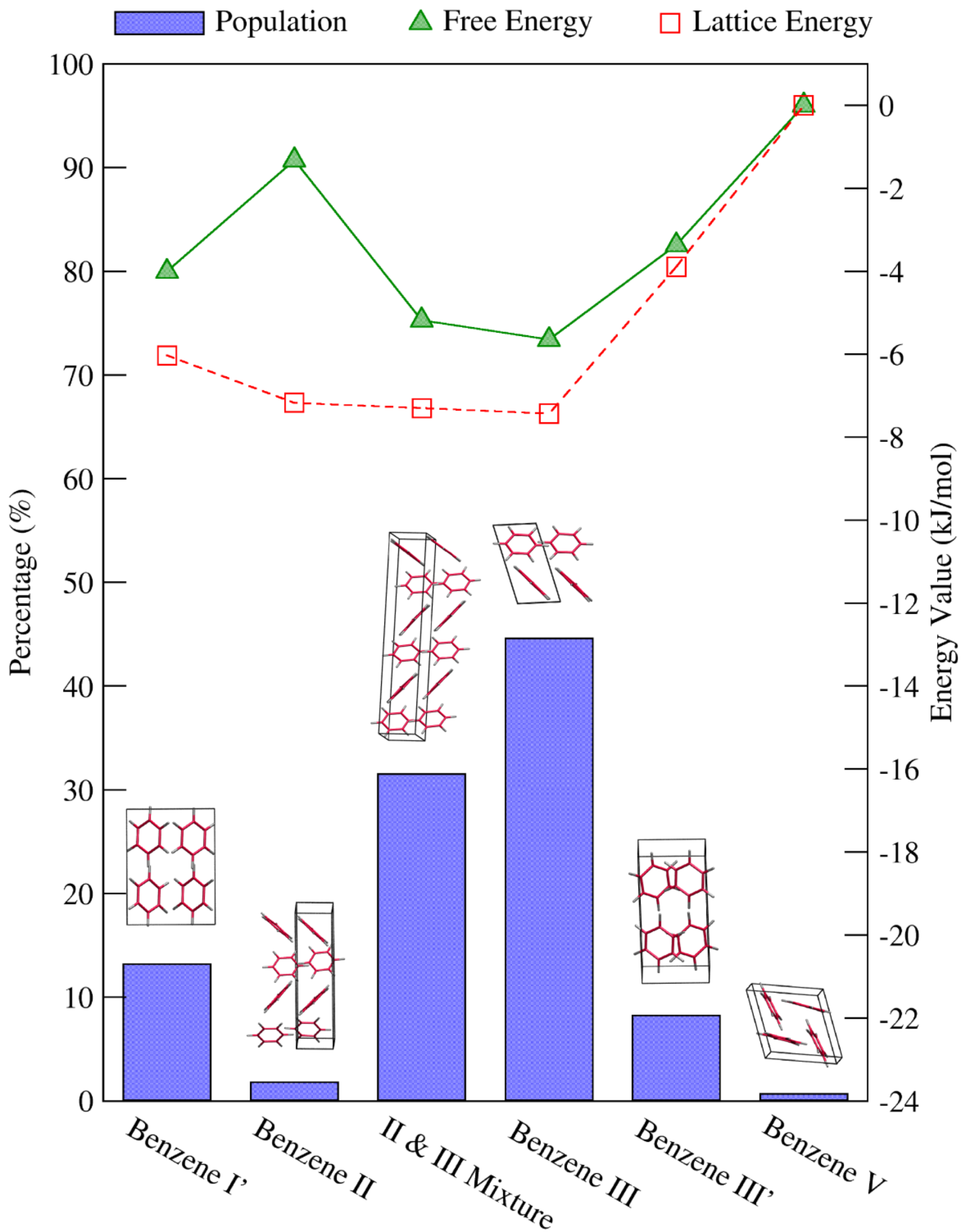
I′ and V more speculative


Benzene II (II98)
z
y
Benzene III
z
y
Defect A
z
y
Defect B
z
y
Defect C
z
y



GROMOS FF, $T = 100$ K, $T_{\mathbf{h}} = 32,000 - 40,000$ K

$N = 216$ $(3 \times 3 \times 3)$, $P = 2$ GPa, Total run time = 500 ps, 5 ns


Population
Free Energy
Lattice Energy
Percentage (%)
Energy Value (kJ/mol)
100
90
80
70
60
50
40
30
20
10
0
-2
-4
-6
-8
-10
-12
-14
-16
-18
-20
-22
-24
Benzene I'
Benzene II
II & III Mixture
Benzene III
Benzene III'
Benzene V

Driven Adiabatic Free Energy Dynamics (d-AFED)

L. Rosso, P. Minary, Z. Zhu, MET *J. Chem. Phys.* **116**, 4389 (2002)
Margliano and Vanden-Eijnden, *Chem. Phys. Lett.* **426**, 168 (2006)
J. B. Abrams and MET, *J. Phys. Chem. B* **112**, 14752 (2008)

Suppose *n* collective variables characterize a free energy landscape of interest

$$q_\alpha = q_\alpha(\mathbf{r}_1,...,\mathbf{r}_N) \qquad \alpha = 1,...,n$$

Canonical probability distribution:

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

Write δ-functions as product of Gaussians:

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

Introduce uncoupled Gaussian integrations:

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

Effective Hamiltonian:

$$\mathcal{H}(\mathbf{p},\mathbf{r},s,p_s) = H(\mathbf{p},\mathbf{r}) + \sum_{\alpha=1}^{n}\frac{p_{s_\alpha}^2}{2m_\alpha} + \sum_{\alpha=1}^{n}\frac{\kappa_\alpha}{2}\left(q_\alpha(\mathbf{r}) - s_\alpha\right)^2$$

Driven Adiabatic Free Energy Dynamics (d-AFED)

Introduce high temperature $T_s \gg T$ for extended variables and high masses $m_\alpha \gg m_i$

Adiabatically decoupled equations of motion:

$$m_i \ddot{\mathbf{r}}_i = -\frac{\partial H}{\partial \mathbf{r}_i} + \sum_\alpha \kappa_\alpha \left(s_\alpha - q_\alpha(\mathbf{r}) \right) \frac{\partial q_\alpha}{\partial \mathbf{r}_i} + \text{heat bath}(T)$$

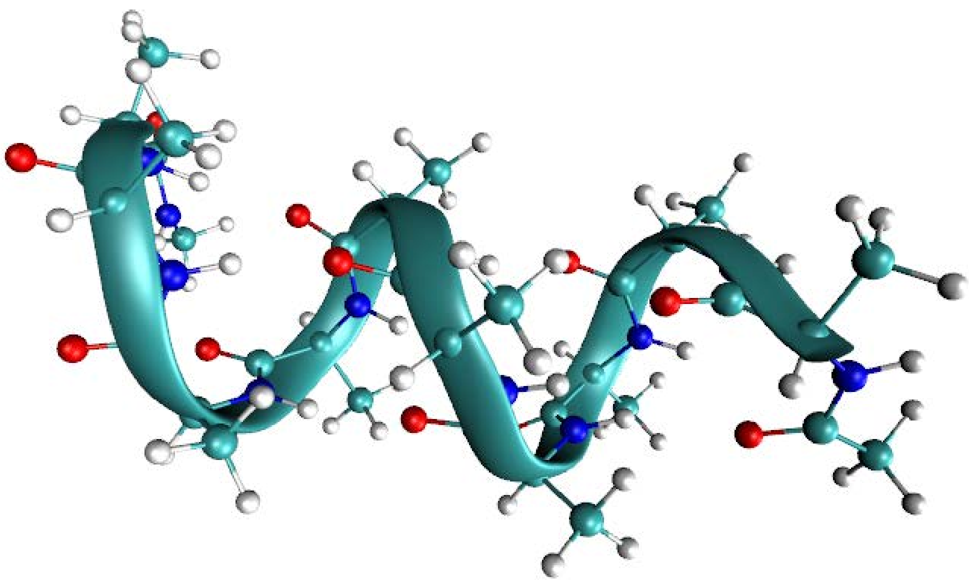
$$m_\alpha \ddot{s}_\alpha = -\kappa_\alpha \left(s_\alpha - q_\alpha(\mathbf{r}) \right) + \text{heat bath}(T_s)$$

Under adiabatic conditions, we generate a distribution $P_{\text{adb}}^{(\{\kappa\})}(s_1,...,s_n,T_s,T)$

$$P_{\text{adb}}^{(\{\kappa\})}(s_1,...,s_n,T_s,T) = \tilde{C}_{\{\kappa\}} \int d^n p e^{-\beta_s \sum_\alpha \frac{p_\alpha^2}{2m_\alpha}} \left[P_{\{\kappa\}}(s_1,...,s_n,T) \right]^{T/T_s}$$

$$\lim_{\{\kappa \to \infty\}} \left[-kT_s \ln P_{\text{adb}}^{(\{\kappa\})}(s_1,...,s_n,T_s) \right] = A(s_1,...,s_n,T)$$

Alanine Decamer (gas phase)



Force field: CHARMM22

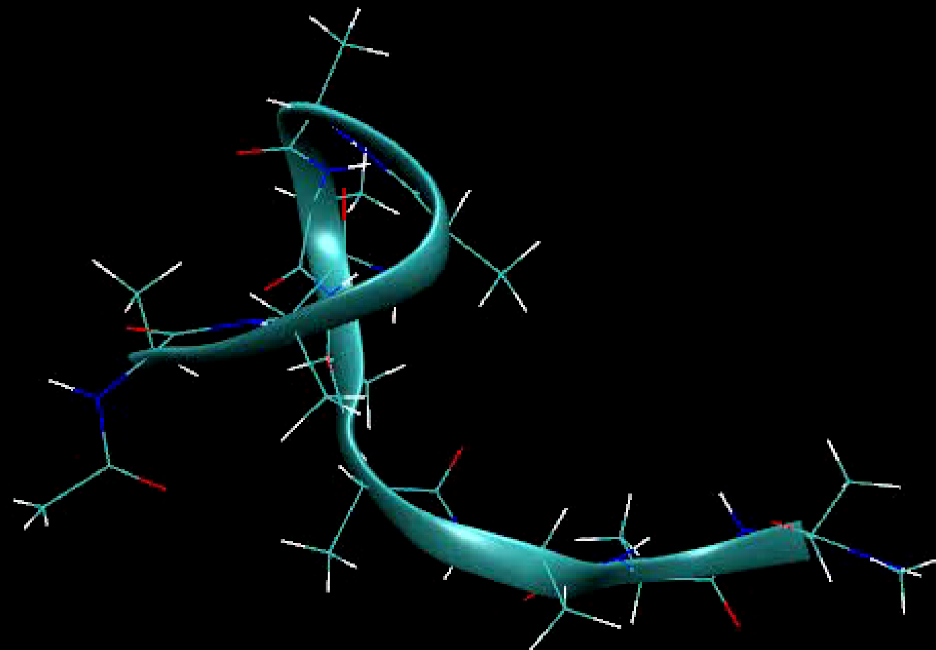
20 CVs: All (φ,ψ) pairs

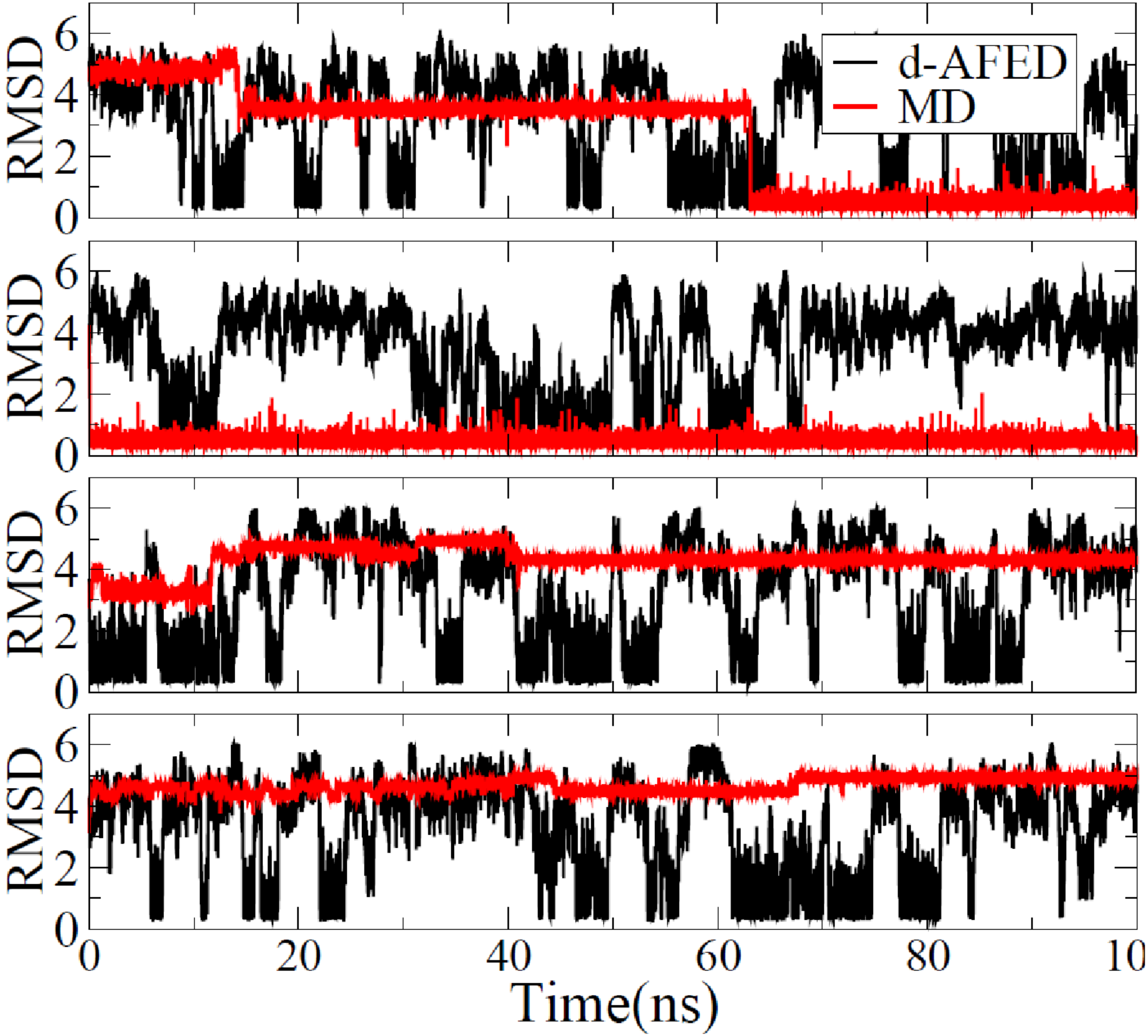
CV Temperature: T_s = 900 K

Physical Temp: T = 300 K

CV mass: $m_{(\psi,\varphi)} = 600 m_H$

Harmonic coupling: 300.5 kcal/mol/rad^2




d-AFED
MD
RMSD
RMSD
RMSD
RMSD
0
2
4
6
0
20
40
60
80
10
Time(ns)

Metadynamics

A. Laio and M. Parrinello, *PNAS* **99**, 12562 (2002)

Suppose we have n reaction coordinates or collective variables $q_\alpha(\mathbf{r})$, $\alpha=1,\ldots,n$ of interest, and we wish to generate the multidimensional free energy hypersurface

$$P(s_1,\ldots,s_n) = \left\langle \prod_{\alpha=1}^{n} \delta(q_\alpha(\mathbf{r}) - s_\alpha) \right\rangle \approx \left\langle \prod_{\alpha=1}^{n} C_\alpha \exp\left[-\frac{1}{2\sigma_\alpha^2}\left(q_\alpha(\mathbf{r}) - s_\alpha\right)^2\right] \right\rangle$$

$$A(s_1,\ldots,s_n) = -k_B T \ln P(s_1,\ldots,s_n)$$

<u>Ergodic hypothesis</u>:

$$\langle O(\mathbf{r}) \rangle = \lim_{\tau\to\infty} \frac{1}{\tau} \int_0^\tau O(\mathbf{r}(t))\,dt$$

<u>Applying to probability distribution</u>:

$$P(s_1,\ldots,s_n) = \lim_{\tau\to\infty} \lim_{\{\sigma\}\to 0} \frac{1}{\tau} \int_0^\tau \prod_{\alpha=1}^{n} C_\alpha e^{-\left(q_\alpha(\mathbf{r}(t)) - s_\alpha\right)^2/2\sigma_\alpha^2}\,dt$$

Metadynamics

Write time integral in discrete form:

$$P(s_1,\ldots,s_n) \approx \frac{1}{M}\sum_{k=0}^{M-1}\prod_{\alpha=1}^{n} C_\alpha e^{-\left(q_\alpha(\mathbf{r}(k\Delta t))-s_\alpha\right)^2/2\sigma_\alpha^2}$$

Consider a bias potential of the form

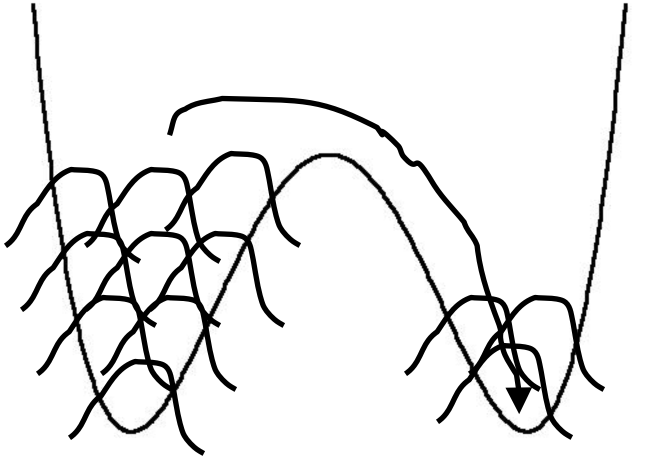
$$U_G(q_1(\mathbf{r}),\ldots,q_n(\mathbf{r}),t) = \sum_{t=\tau_G,2\tau_G,\ldots}\prod_{\alpha=1}^{n} W_\alpha e^{-\left(q_\alpha(\mathbf{r})-q_\alpha(\mathbf{r}_G(t))\right)^2/2\sigma_\alpha^2}$$

$\mathbf{r}_G(t)$ is the evolution of positions under the action of a potential $U + U_G$.

Free energy hypersurface:

$$A(s_1,\ldots,s_n) = -\lim_{t\to\infty} U_G(s_1,\ldots,s_n,t)$$

Metadynamics

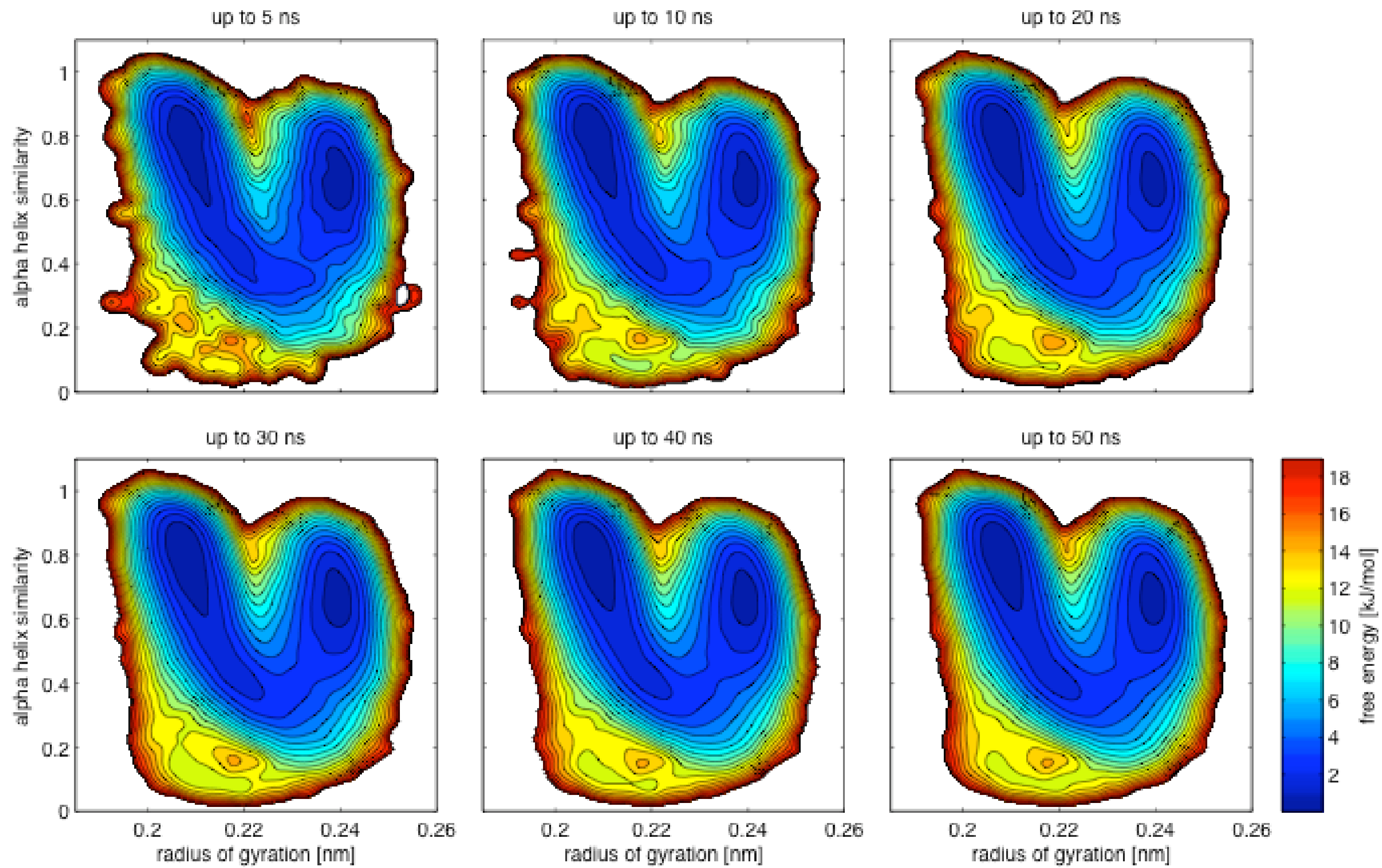


Metadynamics:
(Laio and Parrinello, *PNAS*)
Time-dependent potential periodically adds Gaussians.

Gas-phase CHARMM27 alanine dipeptide: d-AFED (Ts = 350 K)

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

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



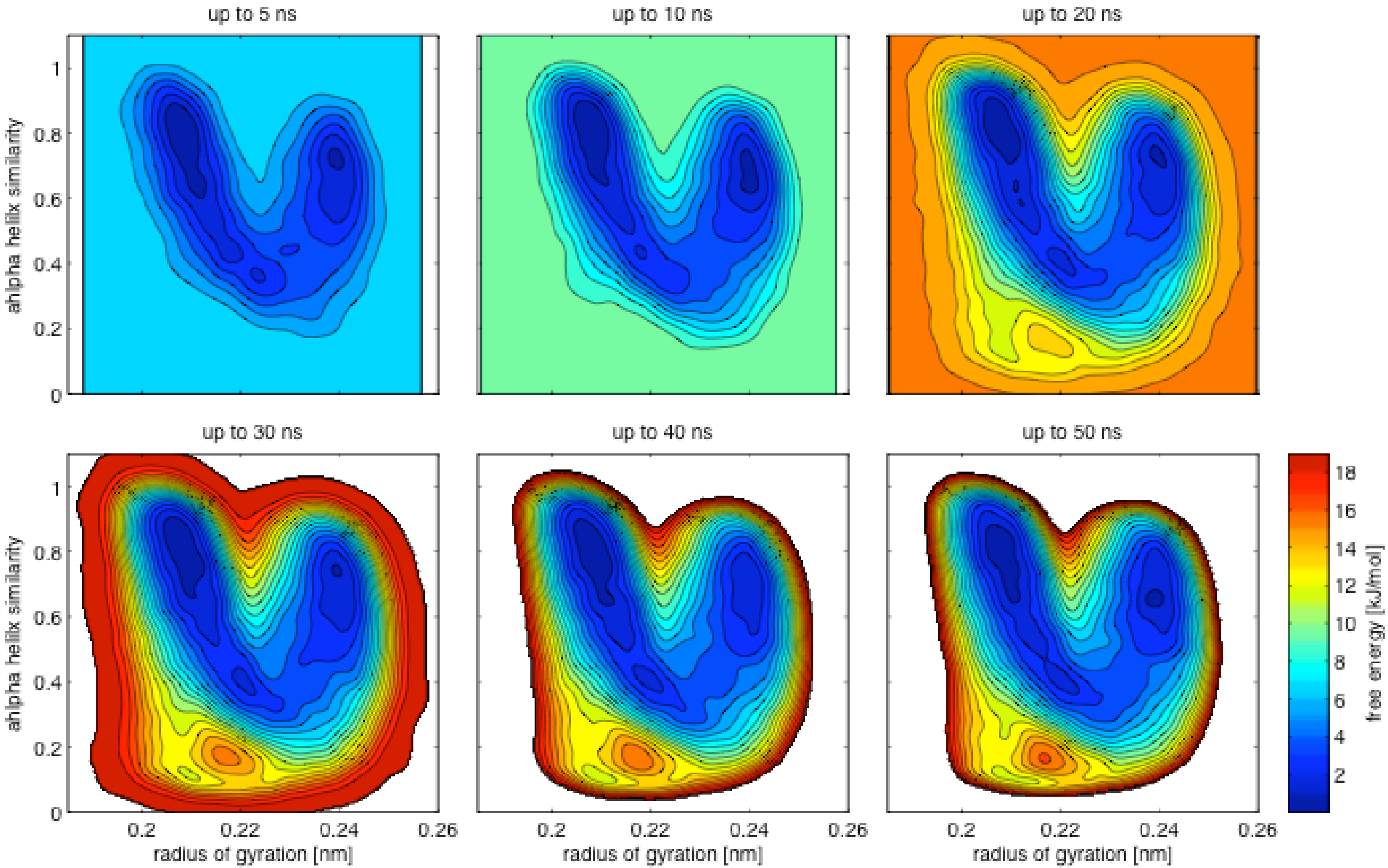
Gas-phase CHARMM27 alanine dipeptide: Metadynamics

Sigma(R_{gyr}) = 0.002 nm

Sigma (N_H) = 0.03

Hill height = 0.05 kJ/mol

Deposition rate = 1/ps



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

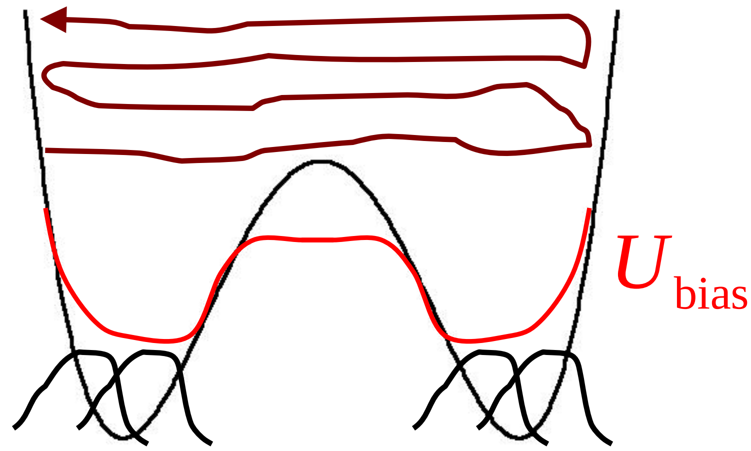
d-AFED with a bias potential

M. Chen, M. Cuendet, and MET *J. Chem. Phys.* **137**, 024102 (2012)

Suppose a bias potential $U_{\text{bias}}(s_1,\ldots,s_n)$ is applied in the extended phase space.

Apply metadynamics-like bias in the extended-variable space:

$$U_{\text{bias}}(s) = \sum_i A e^{-\sum_\alpha \left\| s_\alpha - s_\alpha(t_i) \right\|^2 / 2\sigma^2}$$



Effective Hamiltonian:

$$H(\mathbf{p},\mathbf{r},s,p_s) = H(\mathbf{p},\mathbf{r}) + \sum_{\alpha=1}^{n} \frac{p_{s_\alpha}^2}{2m_\alpha} + \frac{1}{2}\sum_{\alpha=1}^{n} \kappa_\alpha \left(q_\alpha(\mathbf{r}) - s_\alpha\right)^2 + U_{\text{bias}}(s)$$

<u>Important limits:</u>

When $T_s = T$, reduces to metadynamics in an extended space.

When $A = 0$, reduces to standard TAMD/d-AFED

Using the free energy gradient

Free energy surface:

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

If the space of CVs is not too large, then we can employ free energy gradients:

$$F_\alpha(s_1,\ldots,s_n) = -\frac{\partial A}{\partial s_\alpha} = \left\langle \kappa_\alpha \left(q_\alpha(\mathbf{r}) - s_\alpha \right) \right\rangle$$

Manifestly independent of T_s and can be shown to be independent of bias.

Free energy reconstruction:

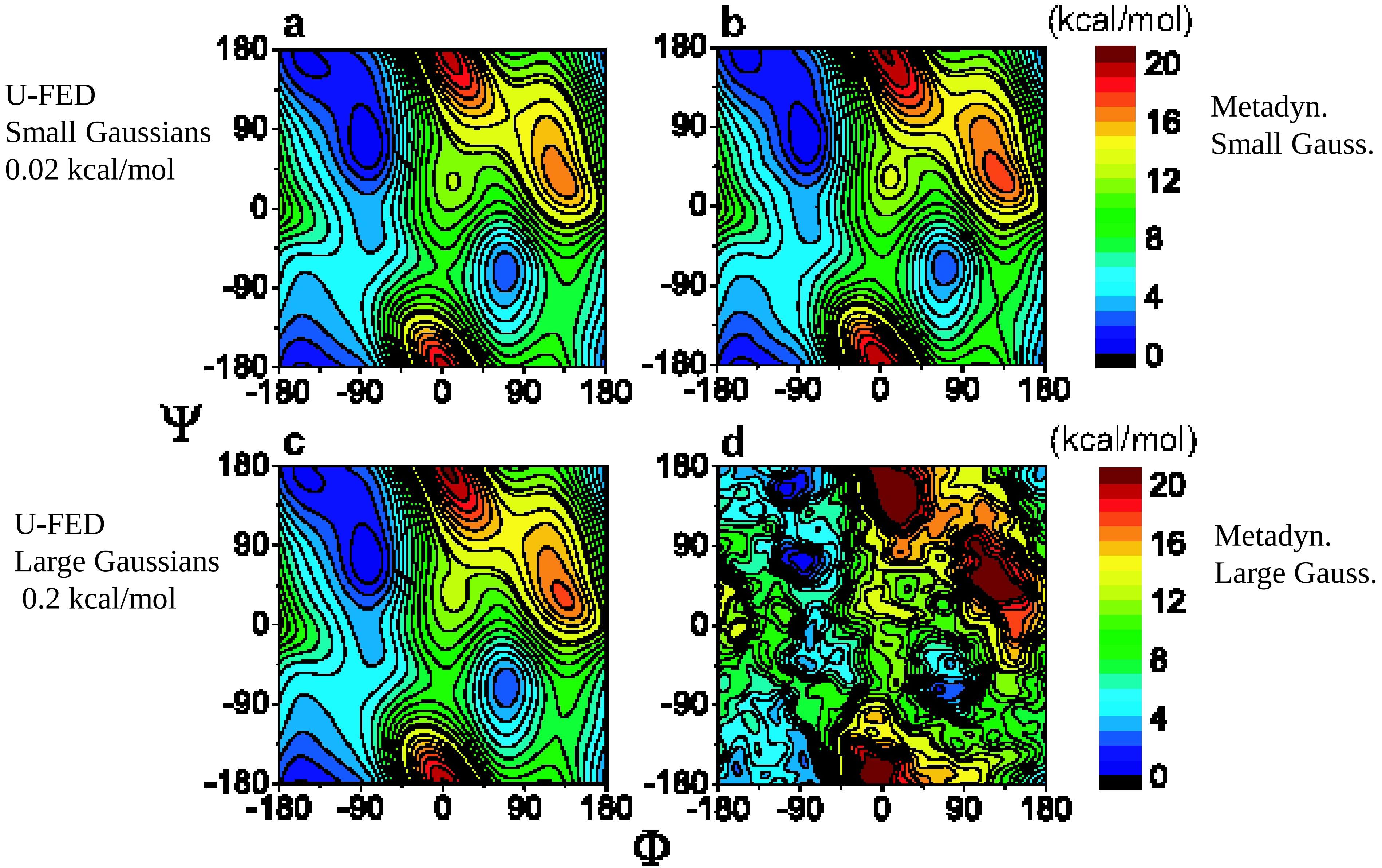
1. Expand free energy in a basis set: $A(\{s\}) = \sum_i C_i \psi_i(\{s\})$
2. Minimize gradient expansion on a grid:

$$f(\{C\}) = \sum_k \sum_\alpha \left| \partial_\alpha A(\{s^{(k)}\}) + F_\alpha(\{s^{(k)}\}) \right|^2$$

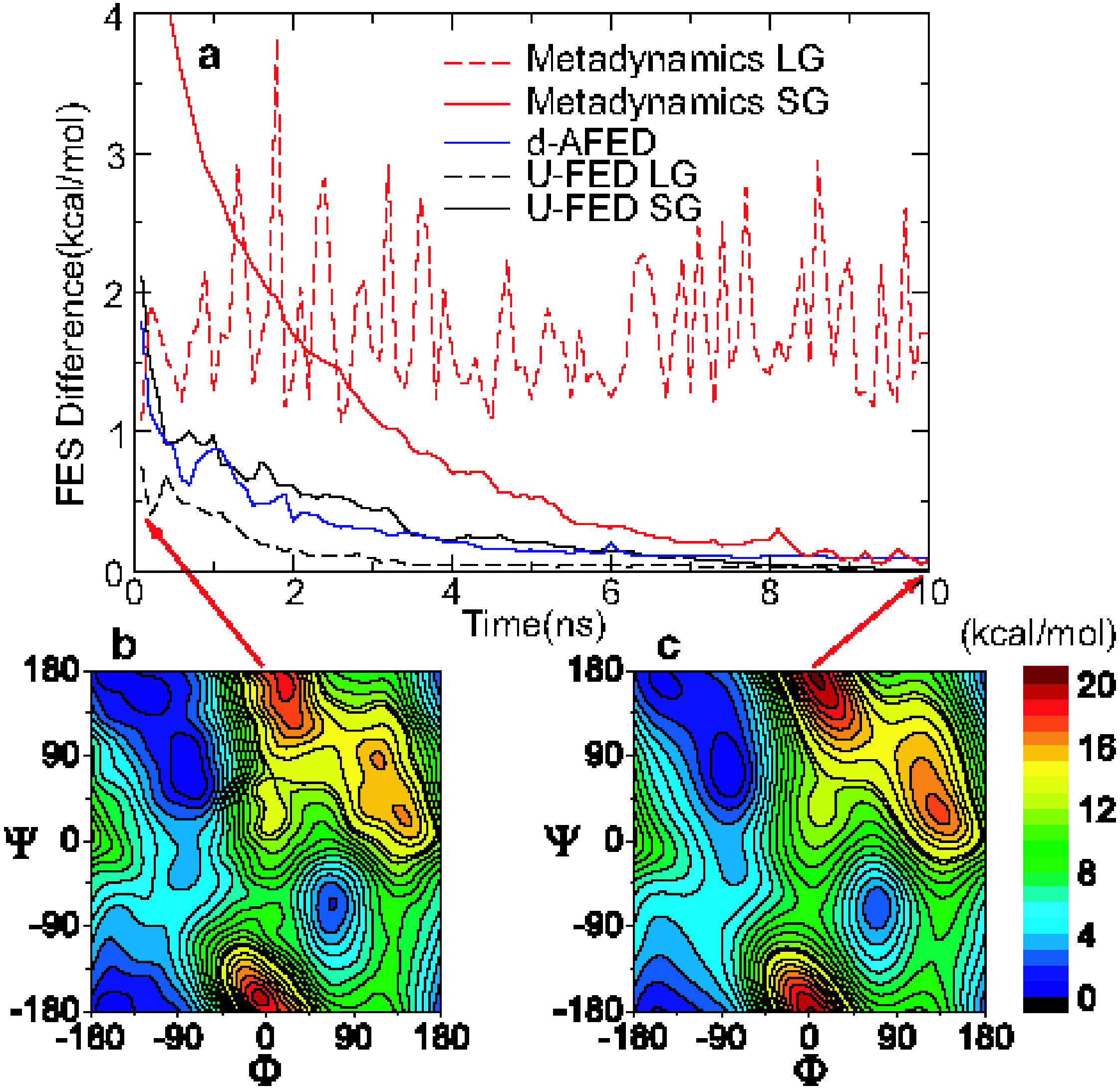
3. Gives a set of linear equations

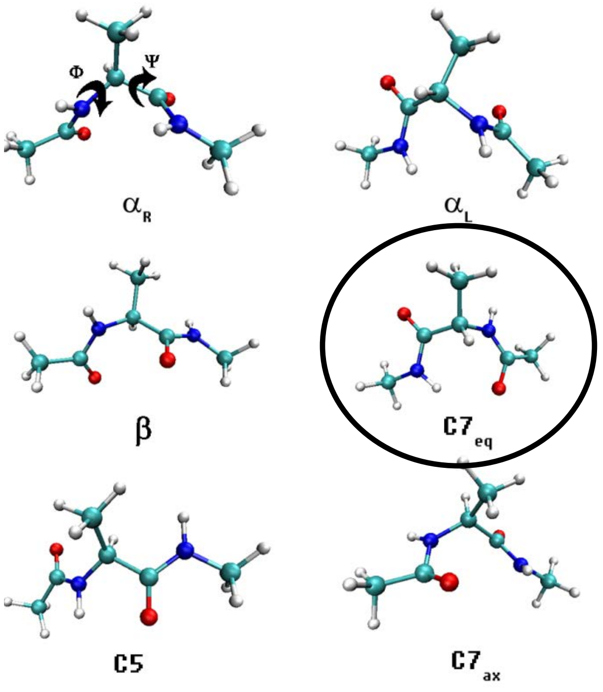
Overall scheme: Adiabatic dynamics, high T_s, gradients, bias – termed U-FED (unified FED).
[see, also, L. Maragliano and E. Vanden-Eijnden *J. Chem. Phys.* **128**, 184110 (2008)]

Ramachandran Surfaces of alanine-dipeptide in gas phase



Convergence of the FES for gas-phase alanine dipeptide

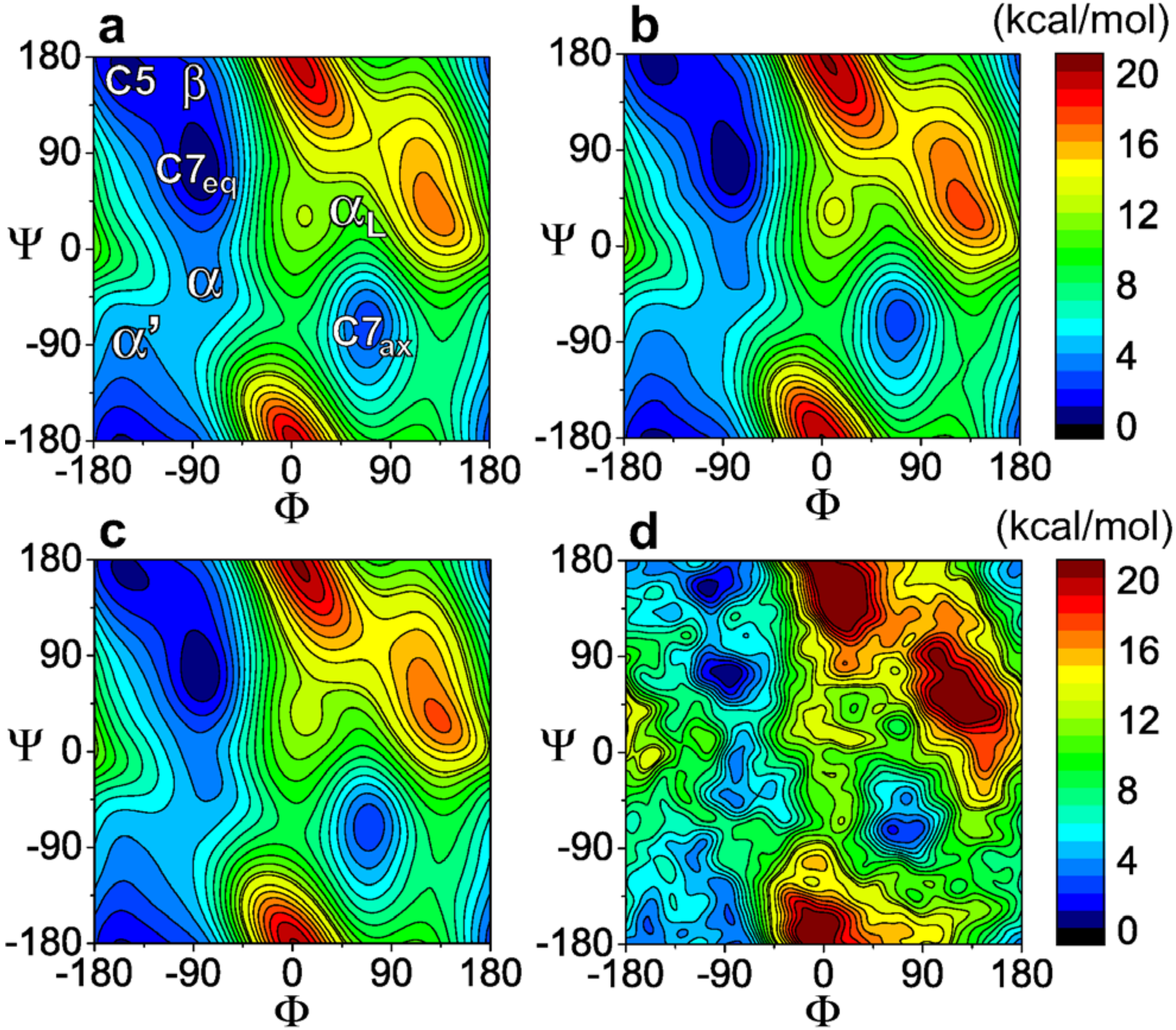




Biased d-AFED 500 ps Large Gauss. Biased d-AFED 10 ns Large Gauss.

Convergence of FESs for alanine dipeptide in solution

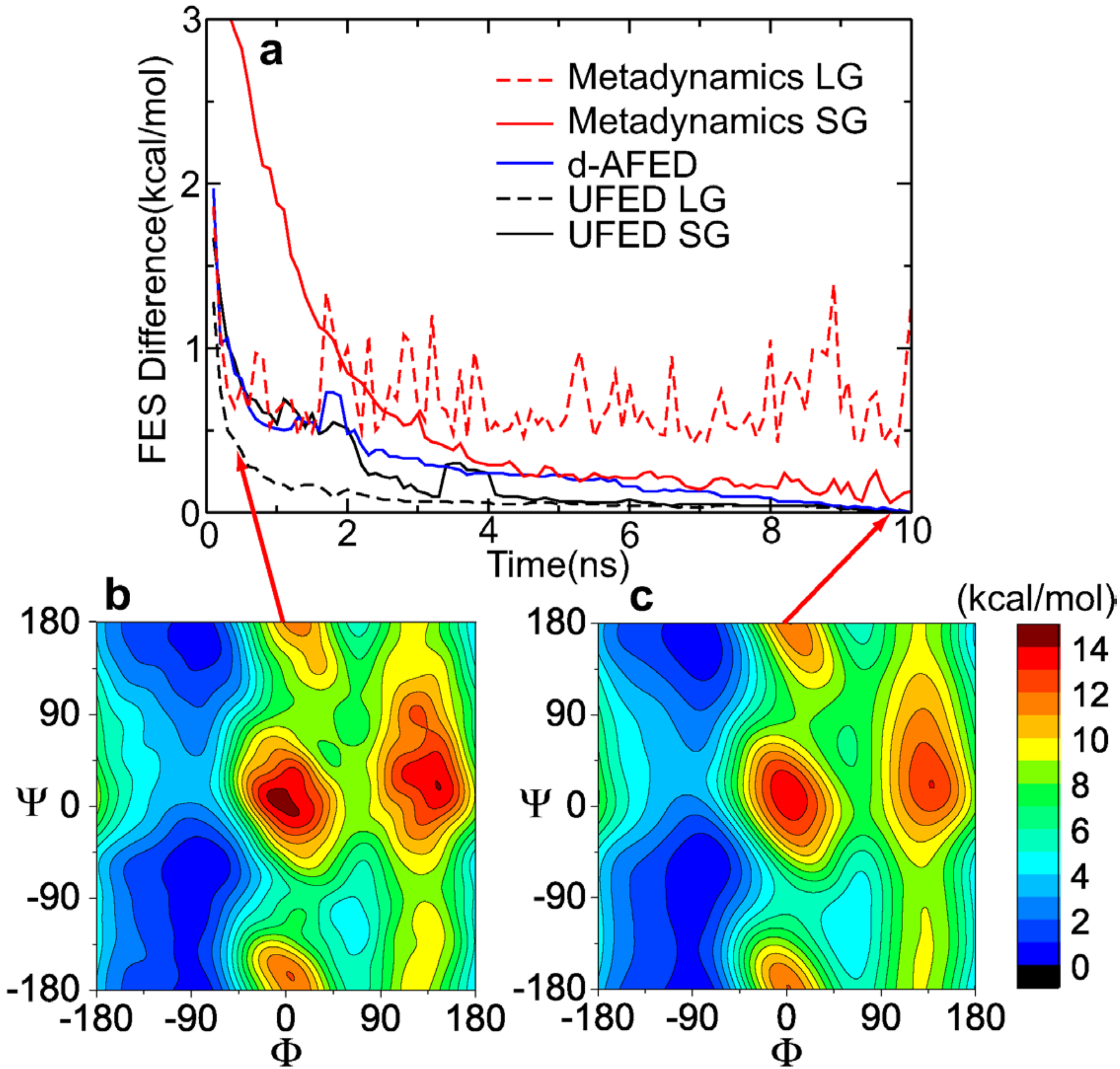
U-FED
Small Gaussians
0.02 kcal/mol



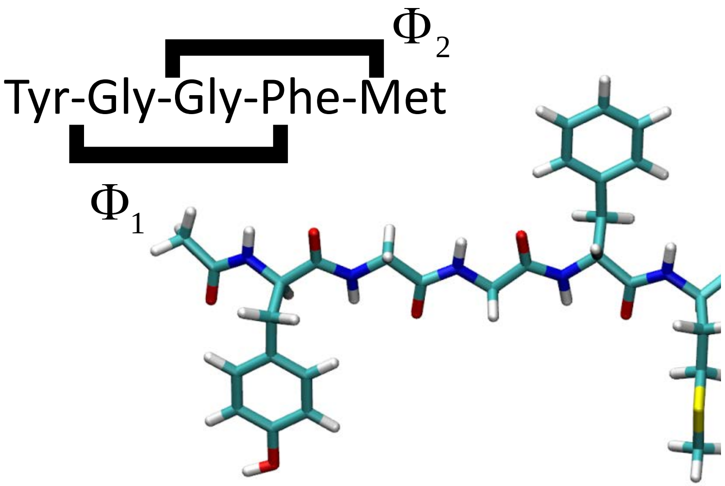
Metadyn.
Small Gauss.

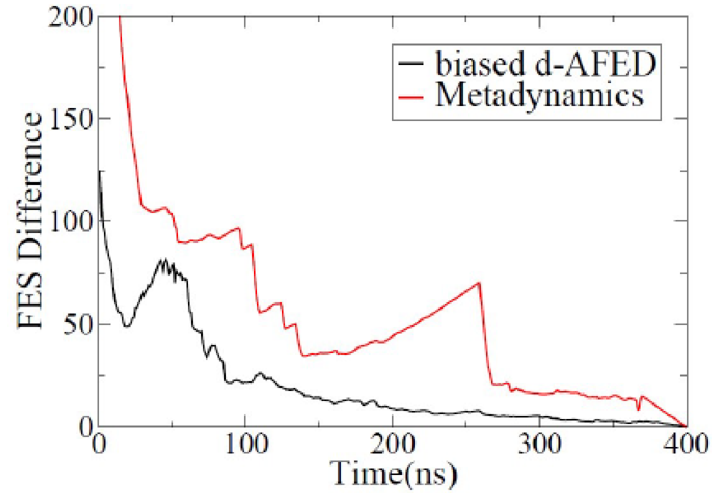
U-FED
Large Gaussians
0.2 kcal/mol

Metadyn.
Large Gauss.

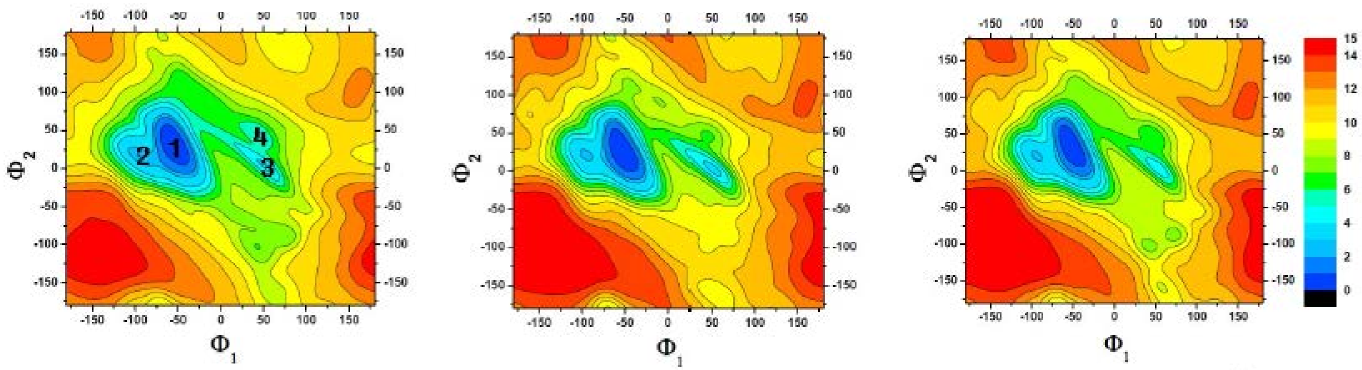

a
Metadynamics LG
Metadynamics SG
d-AFED
UFED LG
UFED SG
FES Difference(kcal/mol)
Time(ns)
0
1
2
3
0
2
4
6
8
10
b
c
(kcal/mol)
180
90
Ψ 0
-90
-180
-180
-90
0
90
180
Φ
180
90
Ψ 0
-90
-180
-180
-90
0
90
180
Φ
14
12
10
8
6
4
2
0

Met-enkephalin





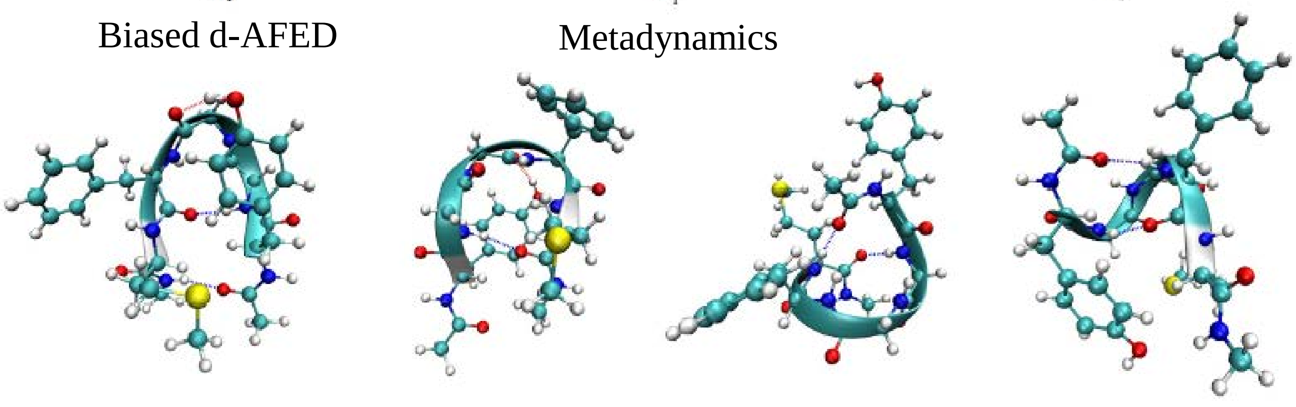
a



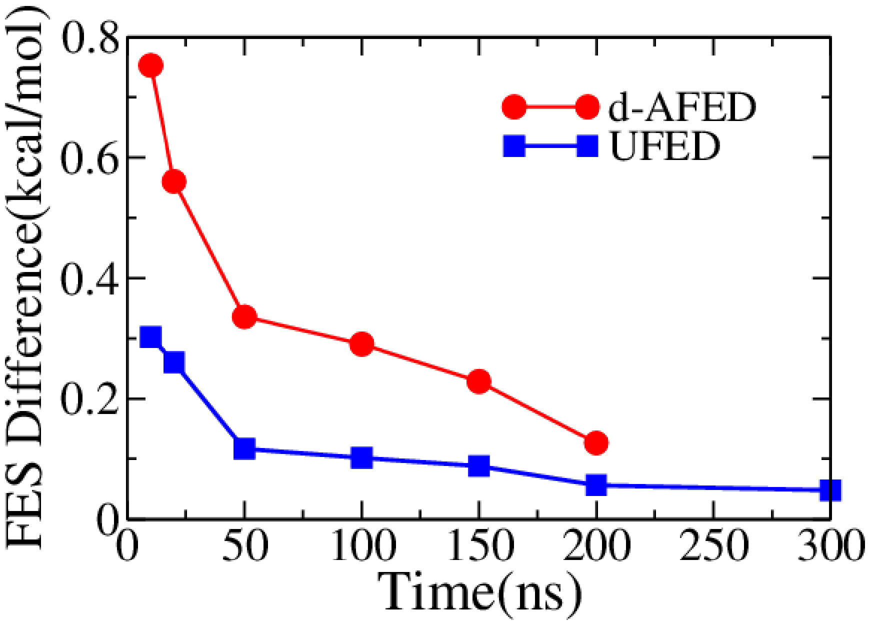
Biased d-AFED

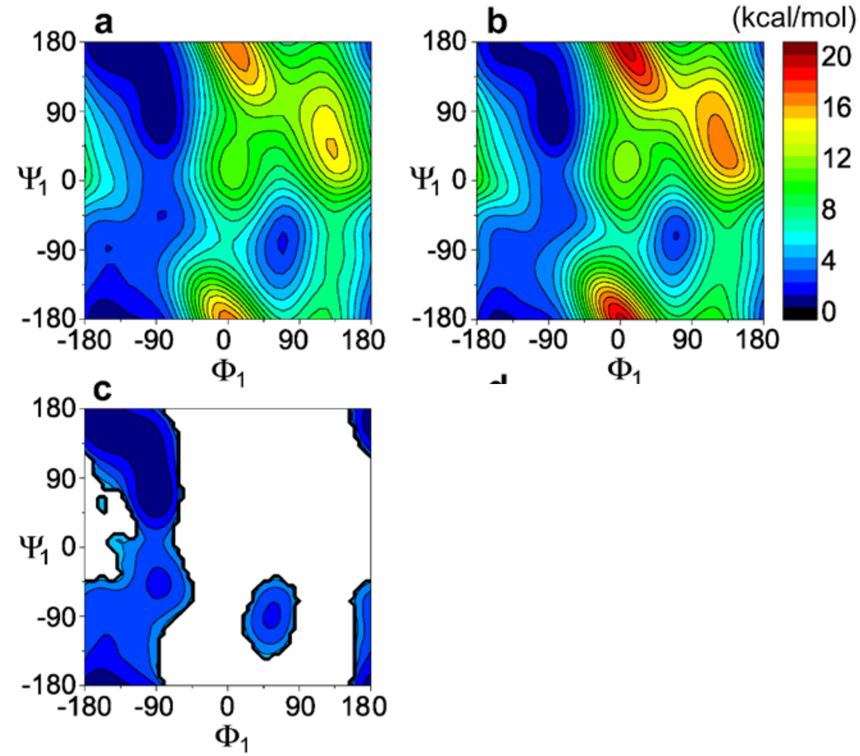
Metadynamics

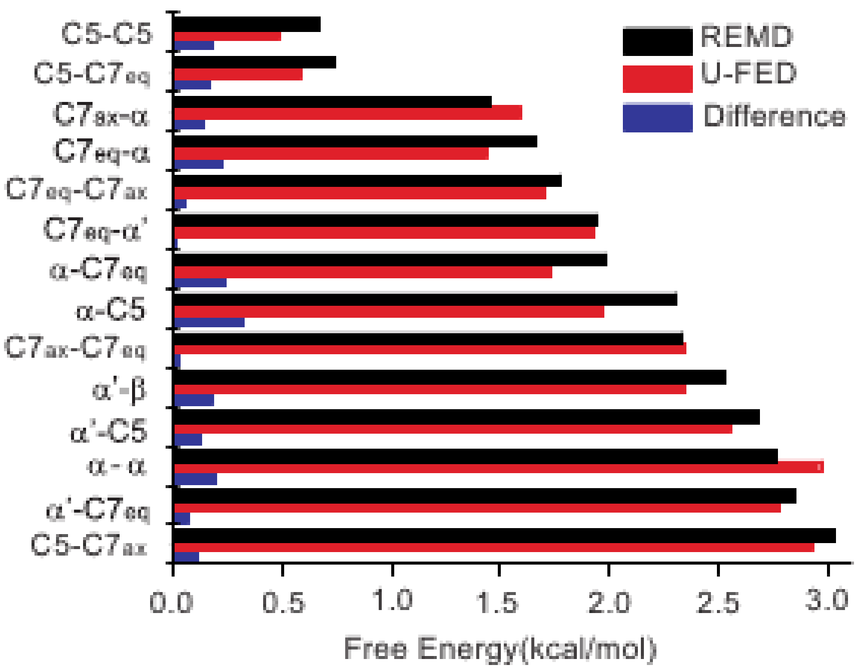
Metadynamics (GROMACS)



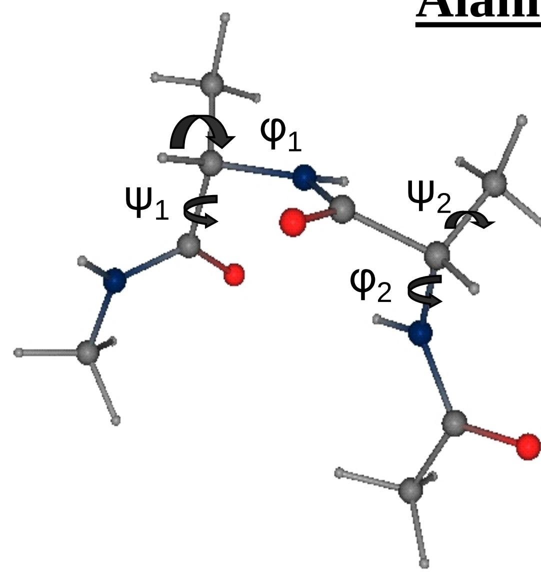
1 2 3 4







Alanine tripeptide



Well-tempered metadynamics

Bonomi *et al.* *Phys. Rev. Lett*. (2008); *J. Comp. Chem*. (2009)

Consider the metadynamics bias potential in the form:

$$U_G(q_1(\mathbf{r}),...,q_n(\mathbf{r}),t,T,\Delta T) = \sum_{t=\tau_G,2\tau_G,...} \prod_{\alpha=1}^{n} W_\alpha(t) e^{-\left(q_\alpha(\mathbf{r})-q_\alpha(\mathbf{r}_G(t))\right)^2/2\sigma_\alpha^2}$$

where the Gaussian heights are scaled according to:

$$W_\alpha(t) = W_\alpha(0) e^{-U_G(s_1,...,s_n,t)/k_B \Delta T}$$

where ΔT is a temperature different from T.

Free energy generated is:

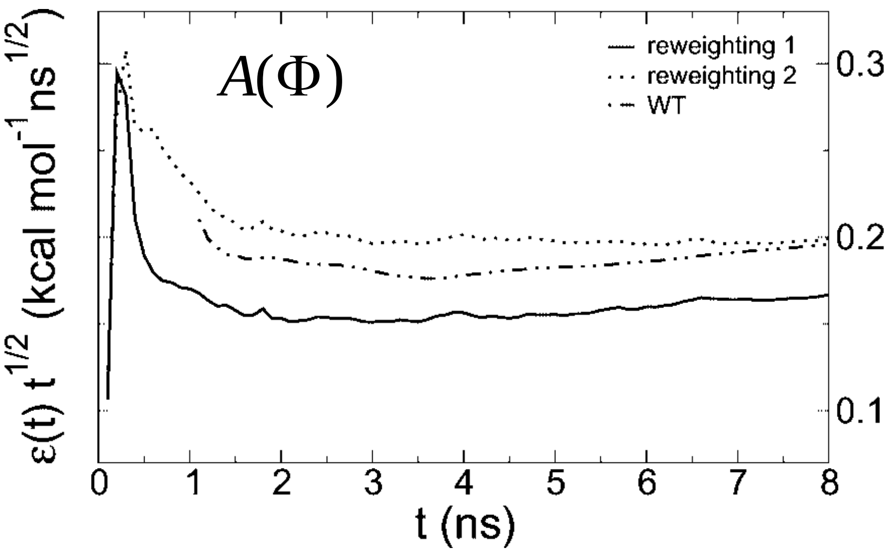
$$A(s_1,...,s_n,T) = -\frac{T+\Delta T}{\Delta T} \lim_{t\to\infty} U_G(s_1,...,s_n,t,T,\Delta T)$$

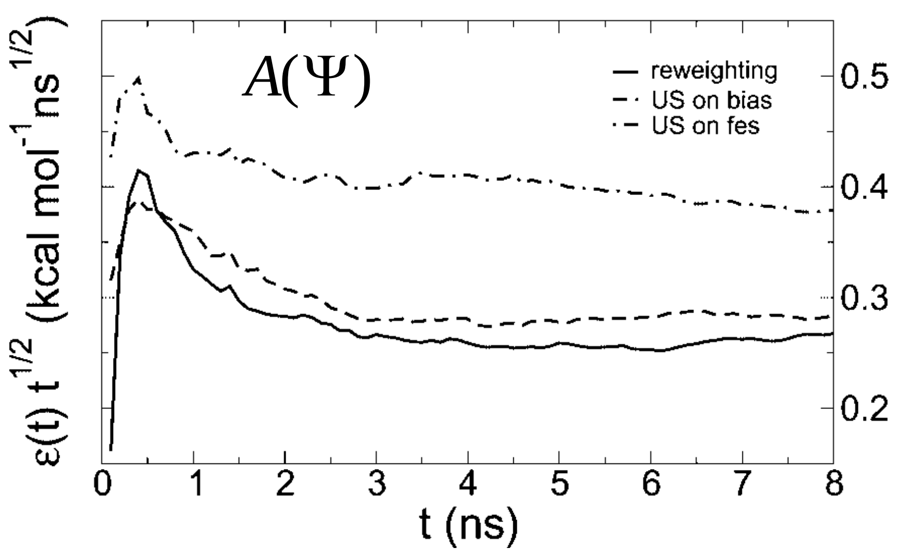
Compare to d-AFED/TAMD free energy:

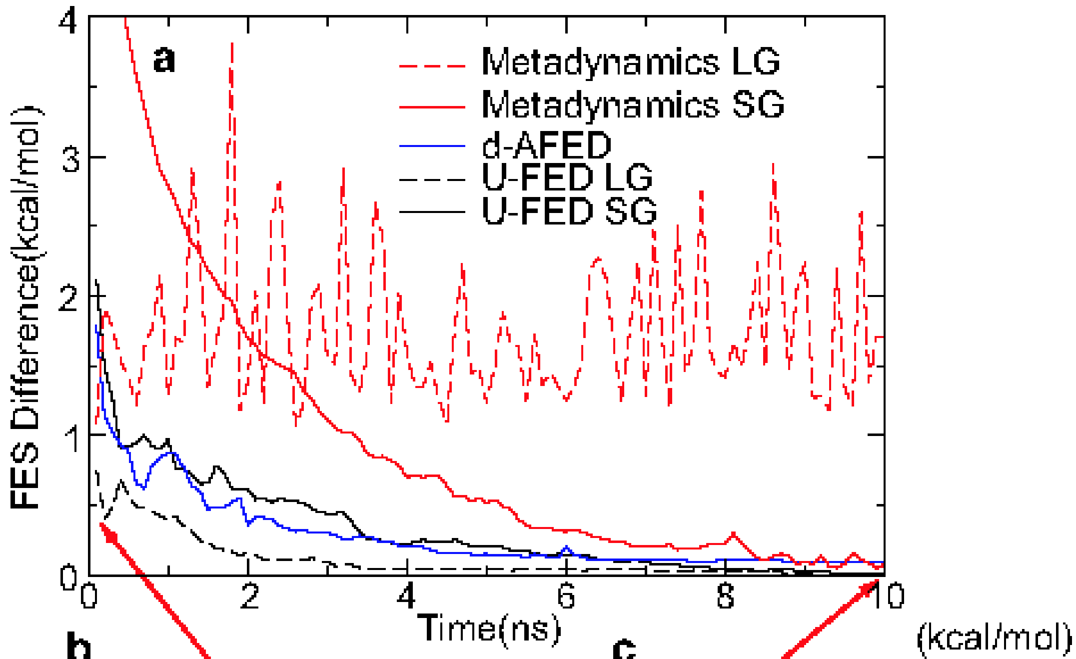
$$A(s_1,...,s_n,T) = -k_B T_s \ln P_{\rm adb}(s_1,...,s_n,T,T_s)$$

Convergence of gas-phase alanine dipeptide

$$T + \Delta T = 6T = 1800\ K$$







Sampling path variables

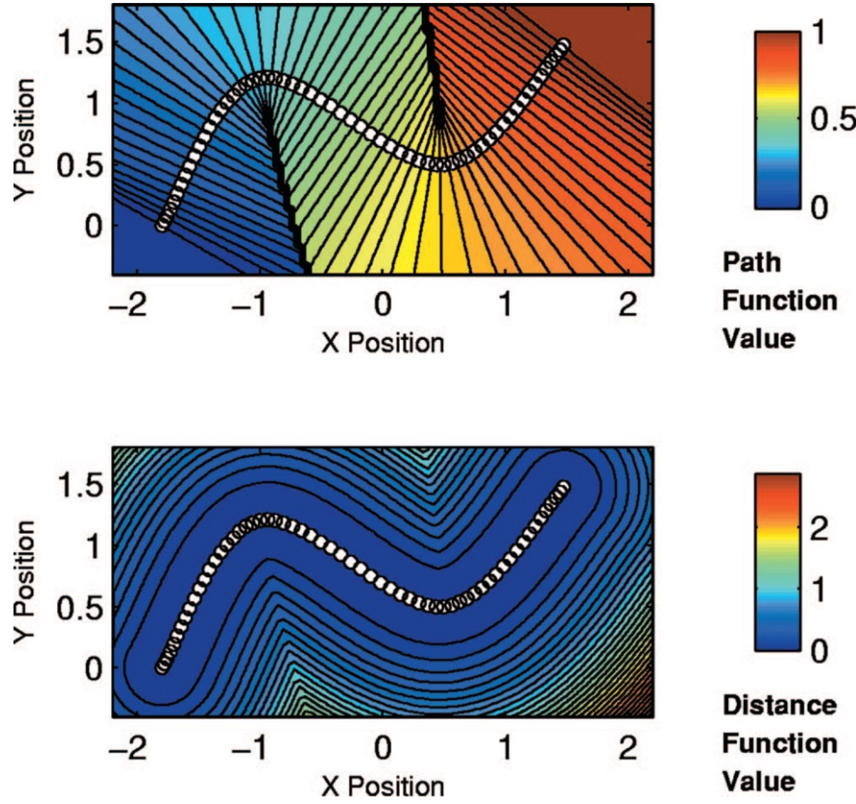
Branduardi et al. *J. Chem. Phys*. (2007)

Consider the two collective variables:

$$q_1(\mathbf{r}) = N^{-1}(\mathbf{r})\sum_{k=1}^{P} k e^{-\lambda D(\mathbf{R}_k,\mathbf{r})} \equiv S(\mathbf{r})$$

$$q_2(\mathbf{r}) = -\frac{1}{\lambda}\ln N(\mathbf{r}) \equiv Z(\mathbf{r})$$

$$N(\mathbf{r}) = \sum_{k=1}^{P} e^{-\lambda D(\mathbf{R}_k,\mathbf{r})}$$



$D(\mathbf{r},\mathbf{r}')$ = Distance metric between configurations $\mathbf{r},\mathbf{r}'$

$\mathbf{R}_1,....\mathbf{R}_P$ is a set of reference structures along a path.

<u>Example: Alanine decamer</u>

Margul, Cuendet, MET (in preparation)

Use path variable with P = 2 to predict free energy difference between α-helix and β-hairpin. Enhance sampling of $S(\mathbf{r})$ with a harmonic restraint $Z(\mathbf{r})$:

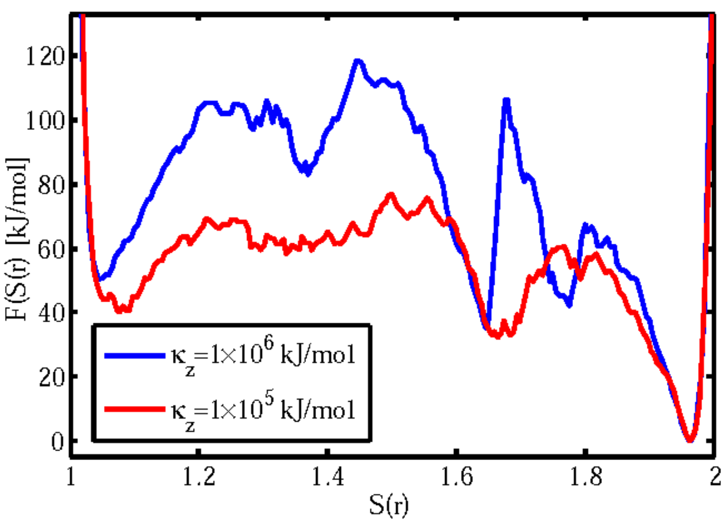
$$V_z(\mathbf{r}) = \frac{1}{2}\kappa_z Z^2(\mathbf{r})$$

Other parameters :

$T_s = 500$ K, $\kappa_s = 10^6$ kJ/mol, $m_s = 10^6$ amu

Gaussian height = 1.0 kJ/mol, $\sigma = 0.01$

Gaussian deposit rate = 2500 steps



$\Delta A \approx 46.5$ kJ/mol