

(Non)Equilibrium computation of free energy differences

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- Microscopic description of a system of N particles

$(q, p) = (q_1, \dots, q_N, p_1, \dots, p_M)$ at inverse temperature $\beta = (k_B T)^{-1}$

- Energy

$$H(q, p) = \sum_{i=1}^M \frac{p_i^2}{2m_i} + V(q_1, \dots, q_N)$$

- Free energy (not an average !) = "available phase space"

$$F = -\beta^{-1} \ln \left(\frac{1}{N!} \int_{\mathcal{M}} e^{-\beta V(q)} dq \right)$$

- Can be computed directly only in certain cases (ideal gas, solids at low temperature, ...)
- Free energy differences are easier to compute
 - 'Alchemical' transition (external parameter in the Hamiltonian)
 - Reaction coordinate (internal)

'Alchemical' transitions

- Potential energy $V_\lambda(q_1, \dots, q_N)$: **external parameter** λ
- Free-energy difference

$$\Delta F(\lambda) = -\beta^{-1} \ln \left(\frac{\int_{\mathcal{M}} e^{-\beta V_\lambda(q)} dq}{\int_{\mathcal{M}} e^{-\beta V_0(q)} dq} \right)$$

- Some examples :
 - External field (magnetic field for spin systems)
 - Change of **temperature** from β to β' :

$$V_\lambda(q) = \frac{(1 - \lambda)\beta + \lambda\beta'}{\beta} V(q)$$

- **Widom insertion** (insertion of a particle in a fluid)

$$V_\lambda(q) = (1 - \lambda)V(q_1, \dots, q_{N-1}) + \lambda V(q_1, \dots, q_N),$$

The reaction coordinate case

- Reaction coordinate $\xi(q) \simeq$ **reduced** (relevant) degrees of freedom
- Examples : conformational changes, dissociation reactions
($\xi(q) = |q_1 - q_2|$)
- **Potential of mean force** : different definitions can be considered ! Most general form

$$F_f(z) = -\beta^{-1} \ln \left(Z^{-1} \int_{\Sigma_z} e^{-\beta V(q)} f(q) d\sigma_{\Sigma_z}(q) \right)$$

with $\Sigma_z = \{q \in \mathcal{M} \mid \xi_z(q) = 0\}$ and $Z = \int e^{-\beta V(q)} dq$.

- Intrinsic version $f \equiv 1$
- Non-intrinsic choice ($f = |\nabla \xi_z(q)|^{-1}$)

$$F(z) = -\beta^{-1} \ln \left(Z^{-1} \int_{\Sigma_z} e^{-\beta V(q)} \delta_{\xi_z(q)} dq \right)$$

- 'Alchemical' transitions can be considered as a particular case (extended variable $Q = (\lambda, q)$)
- General methods :
 - Thermodynamic integration^a
 - Free-energy perturbations^b and its refinements (Umbrella sampling^c)
 - Recent alternative: Jarzynski's nonequilibrium dynamics^d

^aJ.G. Kirkwood, *J. Chem. Phys.* **3**, 300 (1935)

^bR. Zwanzig, *J. Chem. Phys.* **22**, 1420 (1954)

^cG.M. Torrie and J.P. Valleau, *J. Comp. Phys.* **23**, 187 (1977)

^dC. Jarzynski, *Phys. Rev. E* **56**(5) 5018 (1997)

- Nonequilibrium dynamics ('Alchemical' transition)
 - Jarzynski's equality
 - A birth/death process to maintain equilibrium
- The reaction coordinate case
 - Thermodynamical integration
 - The corresponding nonequilibrium dynamics
- Some perspectives

Nonequilibrium dynamics:

Jarzynski's equality

The thermodynamical integration point of view

- Free energy difference as an integral

$$\Delta F = \int_0^1 F'(\lambda) d\lambda \simeq \sum_{i=1}^M (\lambda_i - \lambda_{i-1}) F'(\lambda_{i-1/2})$$

with mean force

$$F'(\lambda) = \frac{\int_{\mathcal{M}} \partial_{\lambda} V_{\lambda}(q) e^{-\beta V_{\lambda}(q)} dq}{\int_{\mathcal{M}} e^{-\beta V_{\lambda}(q)} dq} \simeq \frac{1}{n} \sum_{i=0}^n \frac{\partial V_{\lambda}}{\partial \lambda}(q_{\lambda}^n)$$

when (q_{λ}^n) samples the canonical measure associated with V_{λ}

- For example, overdamped Langevin dynamics for a **fixed value λ** (algorithmic time s)

$$dq_{\lambda,s} = -\nabla V_{\lambda}(q_{\lambda,s}) ds + \sqrt{\frac{2}{\beta}} dW_s$$

- Alternative: single long trajectory with λ switched "infinitely" slowly

The nonequilibrium dynamics point of view

- Why not switch λ at an arbitrary rate? Schedule $\Lambda(t)$ such that $\Lambda(0) = 0$, $\Lambda(T) = 1$, $0 < T < +\infty$, and canonical initial conditions $q_0 \sim d\mu_0(q)$
- Time inhomogeneous Markovian evolution (the potential energy changes!)

$$dq_{\Lambda,t} = -\nabla V_{\Lambda(t)}(q_{\Lambda,t}) dt + \sqrt{\frac{2}{\beta}} dW_t$$

- Define the work $\mathcal{W}_T = \int_0^T \frac{\partial V_{\Lambda(t)}}{\partial \Lambda}(q_{\Lambda,t}) \Lambda'(t) dt$
- Jarzynski's equality (Feynman-Kac formula^a)

$$\mathbb{E}(e^{-\beta \mathcal{W}_t}) = e^{-\beta(F(\lambda(t)) - F(0))}$$

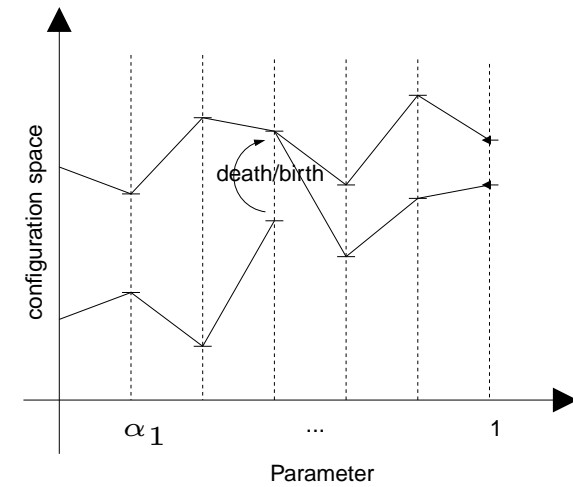
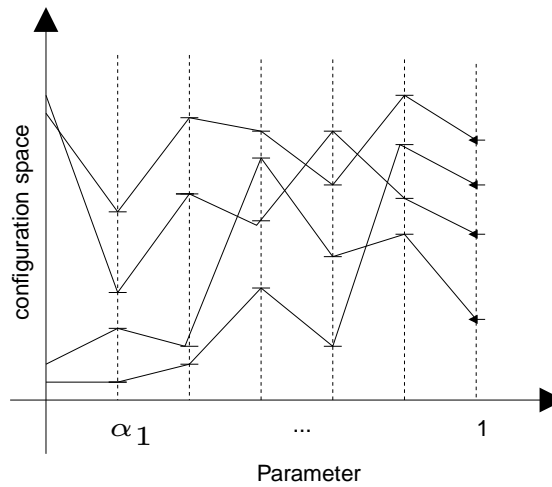
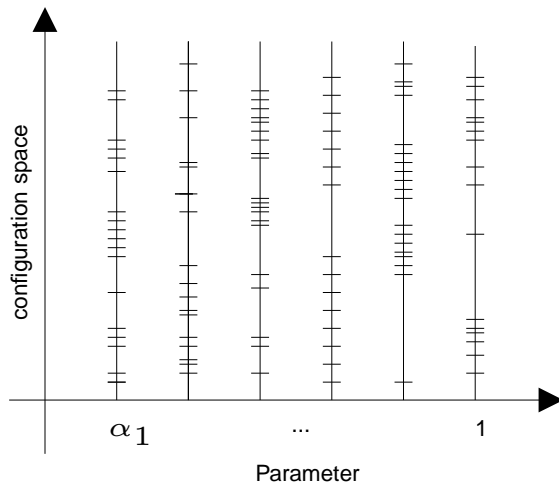
- Consequence $\Delta F \geq \mathbb{E}(\mathcal{W}_t)$ (second law of thermodynamics)

^aG. Hummer and A. Szabo, *PNAS* **98**(7) (2001) 3658-3661.

- Exponential averaging = degeneracy of weights and the law of $q_{\Lambda,t}$ is **not** the canonical measure!
- Birth/death process (jump/diffusion) to restore equilibrium at all times^a: process $\bar{q}_{\Lambda,t}$
 - simulate several replicas of the system in parallel [diffusion process]
 - to each replica, two exponentially distributed random times are attached (birth/death times)
 - if the current work performed on the replica is lower than the average, decrease the birth time, otherwise decrease the death time
 - if the birth time of the k -th replica is zero, select another replica l at random, and set $q^l = q^k$ (id death process) [jump process]
- The law of $\bar{q}_{\Lambda,t}$ is the **canonical measure at all times** and $\mathbb{E}(\bar{W}_T) = \Delta F$

^aM. Rousset and G. Stoltz (2005)

A cartoon comparison

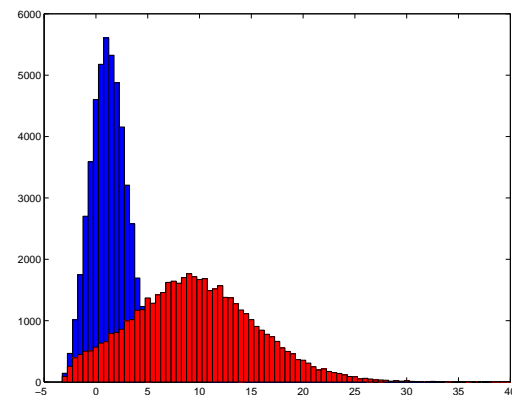
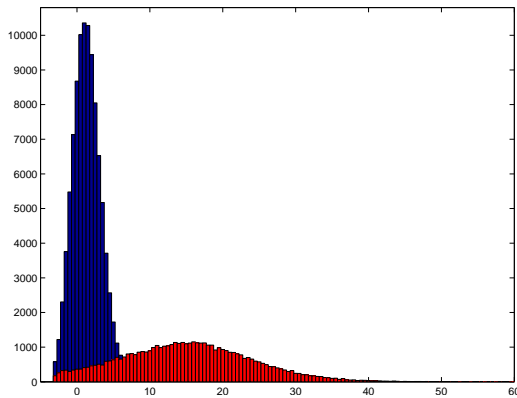


Left: Thermodynamic integration (adiabatic).

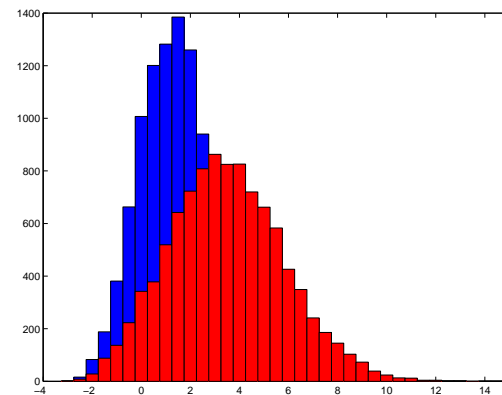
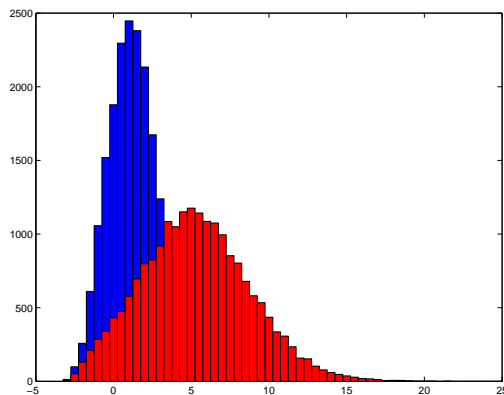
Middle: Jarzynski nonequilibrium dynamics (canonical initial conditions, reweighting).

Right: Interacting Particle Strategy (Birth/death process).

Application: Computation of chemical potential (Widom insertion)



IPS = birth/death process, SA = plain Jarzynski. Left: $\mu_{\text{IPS}} = 1.37$ (blue), $\mu_{\text{SA}} = 1.32$ (red), $\tau = 1$. Right: $\mu_{\text{IPS}} = 1.35$, $\mu_{\text{SA}} = 1.29$ ($\tau = 2$). Reference (Zwanzig, 10^8 points): $\mu_{\text{ex}} = 1.31$.



Left: $\mu_{\text{IPS}} = 1.29$, $\mu_{\text{SA}} = 1.33$ ($\tau = 5$). Right: $\mu_{\text{IPS}} = 1.34$, $\mu_{\text{SA}} = 1.36$ ($\tau = 10$).

The reaction coordinate case

The thermodynamical integration setting

- Reaction coordinate $\xi_z(q)$ and associated free energy

$$F_f(z) = -\beta^{-1} \ln \left(Z^{-1} \int_{\Sigma_z} e^{-\beta V(q)} f(q) d\sigma_{\Sigma_z}(q) \right)$$

- Projected SDE^a on the submanifold Σ_z

$$dq_{z,s} = P(q_{z,s}) \left(-\nabla V(q_{z,s}) ds + \sqrt{\frac{2}{\beta}} dW_s \right) - \frac{1}{\beta} (\nabla \cdot \mathbf{n}(q_{z,s})) \mathbf{n}(q_{z,s}) ds$$

with $P(q) = \text{Id} - \mathbf{n}(q) \otimes \mathbf{n}(q)$ and $\mathbf{n}(q) = \frac{\nabla \xi_z(q)}{|\nabla \xi_z(q)|}$

- Lagrange multiplier formulation

$$dq_{z,s} = -\nabla V(q_{z,s}) ds + \sqrt{\frac{2}{\beta}} dW_s + dr_{z,s}$$

with $r_{z,s}$ directed along $\nabla \xi_z(q_{z,s})$ and such that $\xi_z(q_{z,s}) = 0$.

^aC. Le Bris, T. Lelièvre and E. Vanden-Eijnden, in preparation

- Free energy difference computed as $\Delta F_f = \int_0^1 F'_f(z) dz$
- **Mean force**: analytical expression not practical!

$$F'_f(z) = \int_{\Sigma_z} \left[\frac{\nabla V_f(q) \cdot \nabla \xi_z(q)}{|\nabla \xi_z(q)|^2} - \frac{1}{\beta |\nabla \xi(q)|} \nabla \cdot \left(\frac{\nabla \xi_z(q)}{|\nabla \xi_z(q)|} \right) \right] d\mu_{\Sigma_z, f}$$

where $V_f = V - \beta^{-1} \ln f$ and $\mu_{\Sigma_z, f} = Z_{z, f}^{-1} f(q) e^{-\beta V(q)} dq$

- Averaging over the Lagrange multipliers

$$\lim_{n \rightarrow +\infty} \frac{1}{n \Delta s} \sum_{m=1}^n r_z^m = F'_f(z) + o(\Delta s)$$

where r_z^{n+1} is such that $\xi_z(q_z^{n+1}) = 0$, using the discretization

$$q_z^{n+1} = q_z^n - \nabla V_f(q_z^n) \Delta s + \sqrt{\frac{2\Delta s}{\beta}} U^n + r_z^{n+1} \nabla \xi_z(q_z^{n(+1)})$$

Extension to nonequilibrium dynamics

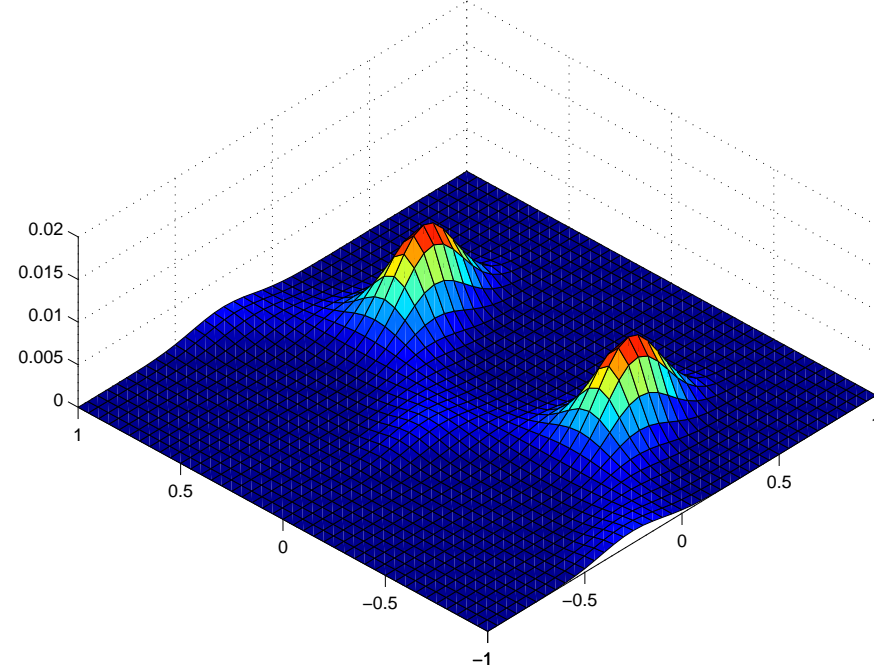
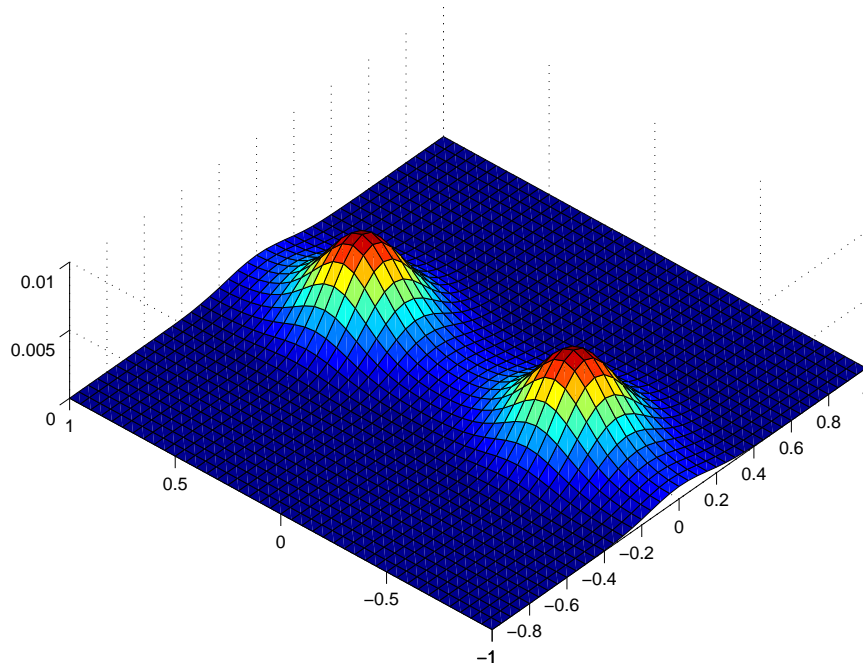
- Schedule $z(t)$ such that $z(0) = 0, z(T) = 1$
- Starting from canonical initial conditions on Σ_0
- Discretization

$$q^{n+1} = q^n - \nabla V(q^n) \Delta t + \sigma \sqrt{\Delta t} U^n + r_{z^{n+1}}^{n+1} \nabla \xi_{z^n}(q^{n(+1)})$$

with $z^n = \frac{n\Delta t}{T}$ for example

- Exponential average of the work \mathcal{W}_T , defined using the Lagrange multipliers (work still in progress...)
- Variance reduction techniques can be used for thermodynamic integration: extension?

A toy 2D example



2D potential^a $V(x, y) = \cos(2\pi x)(1 + d_1 y) + 2d_2 \pi^2 y^2$.

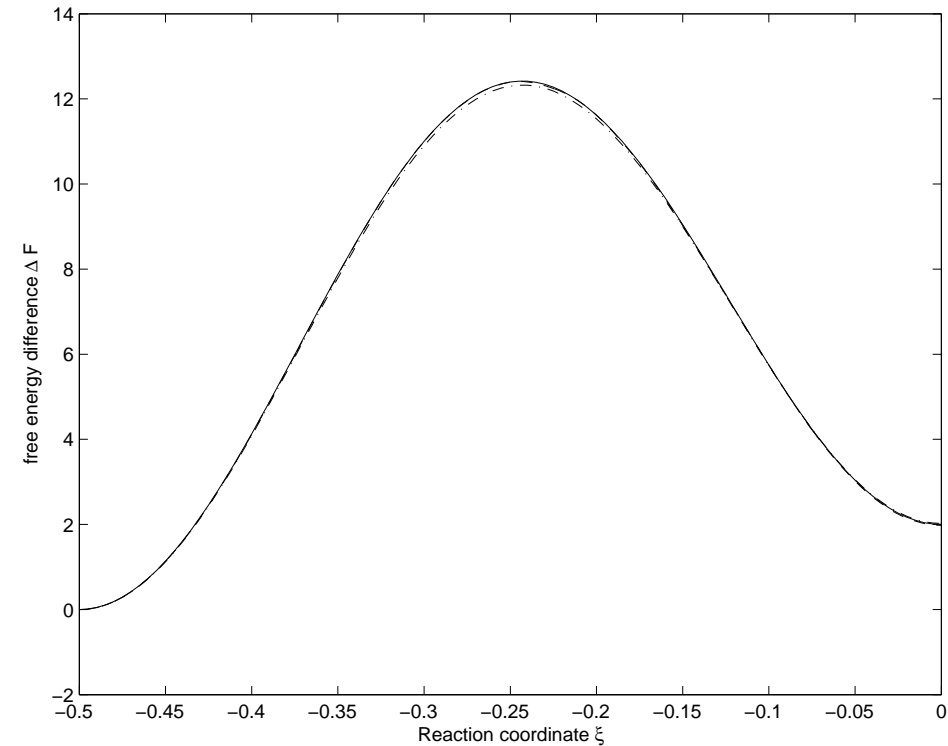
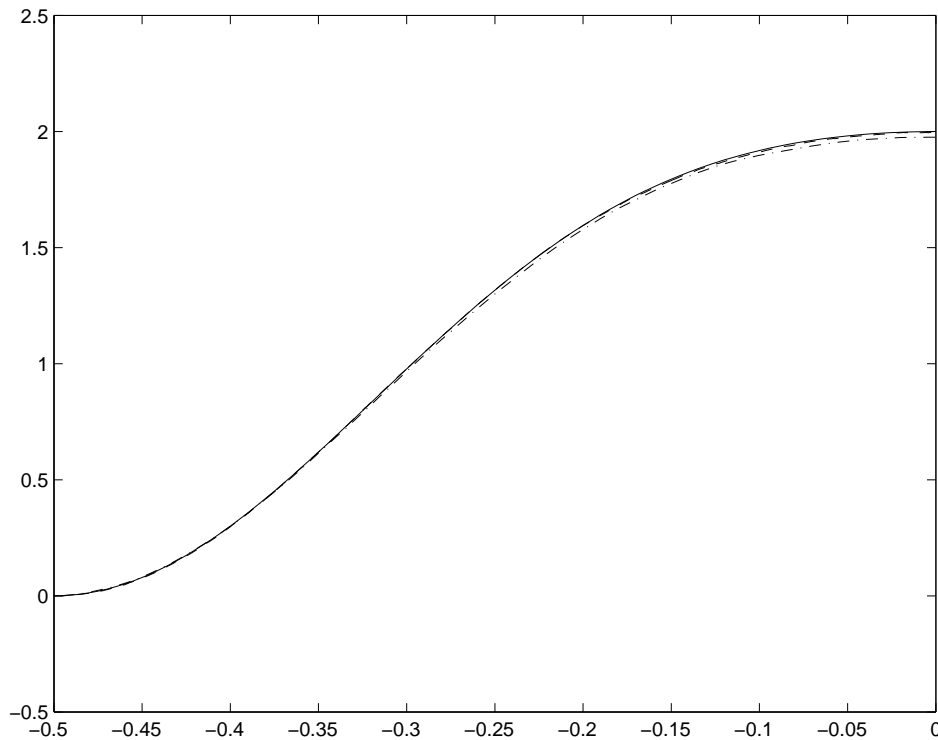
Plot of some probability densities ($\beta = 1, d_2 = 1$). Left: $d_1 = 0$. Right: $d_1 = 10$.

Computation of free energy profile between $x = -\frac{1}{2}$ and $x = 0$.

Chosen reaction coordinate: $\xi_z(x, y) = x - \frac{1-z}{2}$ ($0 \leq z \leq 1$).

^aA. Voter (1997)

Free-energy profiles



Free energy profiles for $d_2 = 1$ and $\beta = 1$. Left: $d_1 = 5$. Right: $d_1 = 30$. Notice that both thermodynamic integration and nonequilibrium methods agree with the reference profile.

A simplified model for solvation effects on conformational changes

- N particles interacting through the purely repulsive WCA potential

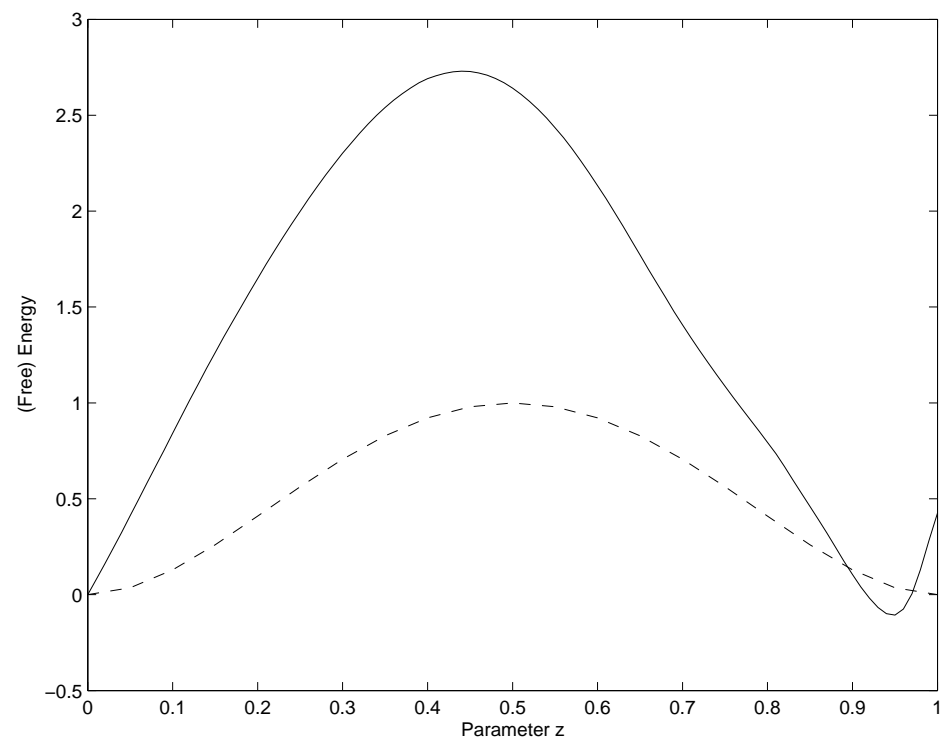
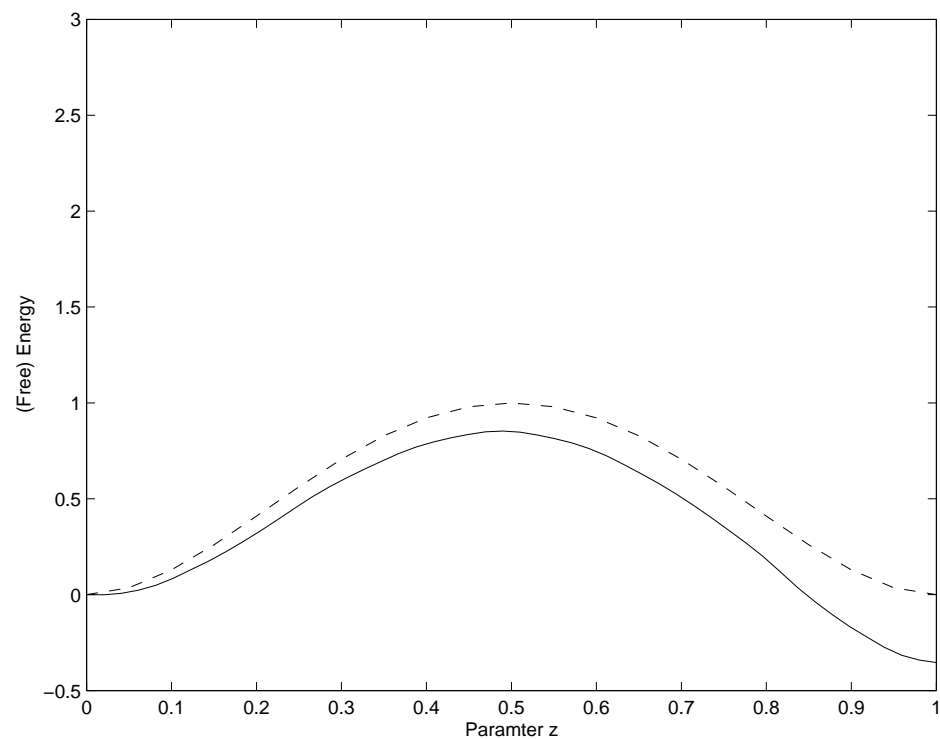
$$V_{\text{WCA}}(r) = \begin{cases} 4\epsilon \left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^6 \right] + \epsilon & \text{if } r \leq \sigma, \\ 0 & \text{if } r > \sigma. \end{cases}$$

- Two solute particles interact via the double-well potential

$$V_S(r) = h \left[1 - \frac{(r - \sigma - w)^2}{w^2} \right]^2,$$

- Two energy minima (compact state $r = r_0 = 2^{1/6}\sigma$, stretched state $r = r_0 + 2w$), energy barrier h
- Reaction coordinate $\xi_z(q) = |q_1 - q_2| - (r_0 + 2zw)$

Influence of solvent density on free energy profiles



Density $\rho = a^{-2}$. Left: $a = 2$. Right: $a = 1.05$. Solid line: Free-energy profiles. Dashed line: Energy difference for the bond.

- Transition path sampling^{a b}
- Path sampling techniques can be used to compute free energy differences^c
- Methods used for the computation of free energy differences can be used for path sampling^d
- Birth/death process for path sampling (work on progress since Workshop II)

^aC. Dellago, P.G. Bolhuis, F.S. Csajka, and D. Chandler (1998)

^bC. Dellago, P.G. Bolhuis, and P.L. Geissler (2002)

^cD. Zuckermann and M. Ytreberg (2004)

^dP. Geissler and C. Dellago (2004)