(Non)equilibrium computation of equilibrium properties

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Outline of the talk

- Computation of static properties
  - Presentation of some mixed stochastic/molecular dynamics methods
  - Application to rare gases
- Computation of dynamical properties
  - Equilibrium or nonequilibrium methods (steady/transient)
  - Example: computation of thermal conductivity
- Computation of free energy differences
  - Static methods (thermodynamic integration)
  - Out of equilibrium dynamics (Jarzynski)
  - Equilibration of the out of equilibrium dynamics

Computation of static properties

Description of a classical system

- Microscopic description of a classical system (N particles):

$$(q,p) = (q_1, \ldots, q_N,\ p_1, \ldots, p_N) \in T^*\mathcal{M}$$

- Usually, $T^*\mathcal{M} = \mathbb{R}^{3N} \times \mathbb{R}^{3N}$ or $\mathbb{T}^{3N} \times \mathbb{R}^{3N}$
- More complicated situations can be considered... (submanifolds)
- Positions q (configuration)
- Momenta $p = M\dot{q}$ (M mass matrix)
- Energy

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

- All the physics is contained in V

Computation of observables (static)

- Equilibrium thermodynamic properties (elastic moduli,. . .):

$$\langle A \rangle = \int_{\mathcal{M} \times \mathbb{R}^{3N}} A(q,p)\, d\mu(q,p)$$

- Choice of a thermodynamic ensemble $\equiv$ choice of a measure $d\mu$:
  - microcanonical (NVE, constant energy) ;
  - canonical (NVT, "constant temperature") : Boltzmann measure

$$d\mu_{NVT} = \frac{1}{Z_{NVT}} \exp(-\beta H(q,p))\, dq\, dp, \quad \beta = 1/(k_B T)$$

  - Other choices are possible (grand-canonical, constant pressure,. . .)
  - Certain properties can not be computed this way (free energy, entropy)!

Some observables

- Pressure:

$$A(q,p) = \frac{1}{3|\mathcal{M}|} \sum_{i=1}^{N} \left(\frac{p_i^2}{m_i} - q_i \cdot \nabla_{q_i} V(q) \right)$$

- Temperature: $\langle A \rangle_{NVT} = T$ with

$$A(q,p) = \frac{1}{3N k_{\mathrm{B}}} \sum_{i=1}^{N} \frac{p_i^2}{m_i}$$

.

- Specific heat:

$$C_V = \frac{\mathcal{N}_{\mathrm{a}}}{N k_{\mathrm{B}} T^2} (\langle H^2 \rangle - \langle H \rangle^2)$$

Problem and methods

- $A(q,p)$ and $d\mu(q,p)$ are given by physics
- Question: how to compute $\langle A \rangle = \int A(q,p)\, d\mu(q,p)$?
- Difficulty: large dimension: $(q,p) \in \Omega \times \mathbb{R}^{3N} \subset \mathbb{R}^{6N}$ with $N \geq 10^5$
- Different methods:
  - purely stochastic methods: generate random points (q_n, p_n) i.i.d. according to $d\mu$ and resort to the Law of Large Numbers:

$$\lim_{N_{\text{iter}} \to \infty} \frac{1}{N_{\text{iter}}} \sum_{n=1}^{N_{\text{iter}}} A(q^n, p^n) = \langle A \rangle$$

  - Markov chain based techniques: consider one or several realizations (q_n, p_n) of a Markov chain letting $d\mu$ invariant + "LLN".
  - (extended) molecular dynamics methods (Nosé-hoover and beyond).

Mixed stochastic/déterministic methods

- Hamiltonian dynamics on the manifold

$$T^*\mathcal{M}(E_0) = \{(q,p) \in T^*\mathcal{M}; H(q,p) = E_0\}$$

  with initial energy $E_0 = H(q_0, p_0)$

- Need for perturbations to sample all the submanifolds $T^*\mathcal{M}(E_0)$ of $\mathcal{M}$
- Several types of perturbations:
  1. strong but at discrete times (HMC)
  2. continuous ((overdamped) Langevin)

Hybrid Monte Carlo (HMC), Duane et al. 1987, Schuette et al. 1999

Markov chain on the positions q. Starting from q^n:

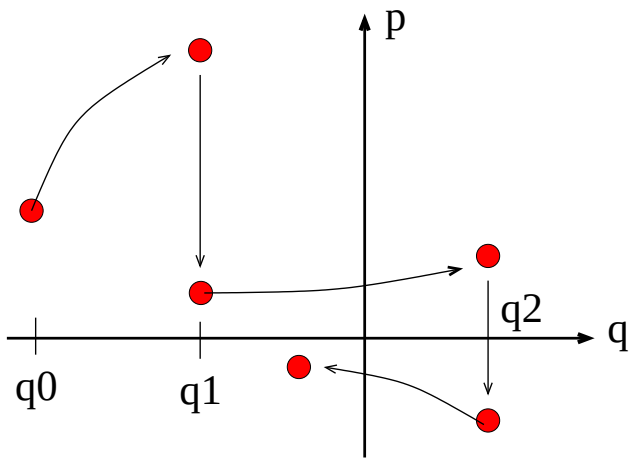
- generate momenta p^n for all particles according to $\mathcal{P}(p)dp = 1/Z_p \; e^{-\beta p^2/2m} dp$
- compute (an approximation of) the flow $\Phi_\tau(q^n, p^n) = (\tilde{q}^{n+1}, \tilde{p}^{n+1})$ of Newton equation = integrate

$$\dot{q}_i = \frac{p_i}{m_i}, \quad \dot{p}_i = -\nabla_{q_i} V(q)$$

on a time τ starting from (q^n, p^n).

- accept $\tilde{q}^{n+1}$ and set $q^{n+1} = \tilde{q}^{n+1}$ with a probability $\min\Big(1, \exp -\beta(\tilde{E}_{n+1} - E_n)\Big)$; otherwise set $q^{n+1} = q^n$.

Two parameters : τ and Δt.



Convergence theorems for Markov chains

Denoting by $P(q, B)$ the probability to reach $B \subset \Omega$ starting from q,

Theorem (convergence on a single realization)[a] : For a Markov chain $P(q, \cdot)$ such that

$$d\pi \text{ is an invariant probability measure of the chain,} \qquad \text{(Inva)}$$

$$\forall q \in \Omega, \quad \forall B \in \mathcal{B}_{\text{Borel}}(\Omega), \quad \lambda^{\text{Leb}}(B) > 0 \;\Rightarrow\; P(q, B) > 0. \qquad \text{(Access)}$$

then, for all $A \in L^1(\pi)$, and π-a.s $q^0 \in \Omega$,

$$\lim_{N \to \infty} \frac{1}{N} \sum_{n=1}^{N} A(q^n) = \int_{\Omega} A(q) d\pi \quad \text{a.s.}$$

[a] S.P. Meyn et R.L. Tweedie, *Markov Chains and Stochastic Stability*, Springer (1993)

Convergence of HMC

- Invariant measure $d\pi(q) = f(q)dq = \frac{1}{Z_q} e^{-\beta V(q)} dq$.
- It is enough to show some accessibility property of the form

$$\forall q_1, q_2,\ \forall \mathcal{V}_2 \text{ neighbourhood of } q_2,\quad P(q_1, \mathcal{V}_2) > 0$$

with transition kernel $P(q_1, \mathcal{V}_2) = \int_{\mathbb{R}^d} \mathbf{1}_{\{\Pi_q \Phi_\tau(q_1,p) \in \mathcal{V}_2\}} \mathcal{P}(p)\, dp.$

- Non-trivial: $V(q) = \frac{1}{2}q^2$ and $\tau = 2\pi$:

$$\Phi_\tau(q_1, p) = (q_1, p) \quad \Rightarrow \quad \Pi_q \Phi_\tau(q_1, p) = q_1 \quad \Rightarrow \quad P(q_1, \mathcal{V}_2) = 0 \text{ si } q_1 \notin \mathcal{V}_2.$$

- Time τ can be randomized to account for ergodicity failures

Convergence of HMC

- Convergence of the empirical mean under rather intricate assumptions : C. Schütte, Habilitation thesis (1998).
- A simplified result:

  Theorem 1 (Cancès, Legoll, Stoltz (2005)) *Assume that $V \in C^1(\mathcal{M})$ is bounded from above and ∇V is globally Lipschitz. Consider a sequence of points (q_n) generated by the HMC algorithm. Then, for almost all starting points $q^0 \in \mathcal{M}$,*

$$\frac{1}{N} \sum_{n=0}^{N-1} A(q^n) \to \int_{\mathcal{M}} A(q)\, \pi(dq) \quad \text{a.s.}$$

- Ingredients of the proof: least-action principle, continuity of the flow, Hausdorff measure

Langevin dynamics

- Hypo-elliptic SDE (noise on p only)

$$\begin{cases} dq_t = M^{-1} p_t \, dt \\ dp_t = -\nabla V(q_t) \, dt - \xi M^{-1} p_t \, dt + \sigma \, dW_t \end{cases}$$

  where $(W_t)_{t \geq 0}$ standard Wiener process of dimension dN and fluctuation/dissipation relation $\sigma = (2\xi/\beta)^{1/2}$.

- In this case, $d\mu(q,p) = \frac{1}{Z} \exp\left(-\beta H(q,p)\right) dqdp$ is an invariant measure (cf. Fokker-Planck equation)

- Irreducibility property $\Rightarrow$ ergodicity on a trajectory/realization (starting from x)

$$\lim_{T \to \infty} \frac{1}{T} \int_0^T A(q_t^x, p_t^x) \, dt = \int_{\mathcal{M} \times \mathbb{R}^{3N}} A(q,p) d\mu \quad \text{p.s.}$$

- Various discretizations have been proposed

Overdamped Langevin dynamics

- Limit $M \to 0$ of the Langevin dynamics
- SDE on the configurational part only

$$dq_t = -\nabla V(q_t)dt + \sigma dW_t,$$

where $(W_t)_{t\geq 0}$ is a standard Wiener process of dimension dN and with $\sigma = (2/\beta)^{1/2}$.

- Canonical measure $d\pi$ is invariant (steady solution of the associated Fokker-Planck equation) + irreducibility (elliptic process):

$$\lim_{T\to\infty} \frac{1}{T} \int_0^T A(q_t^x)\, dt = \int_{\mathcal{M}} A(q) d\pi \quad \text{a.s.}$$

- Only one parameter in practice: Δt !

Application: rare gases

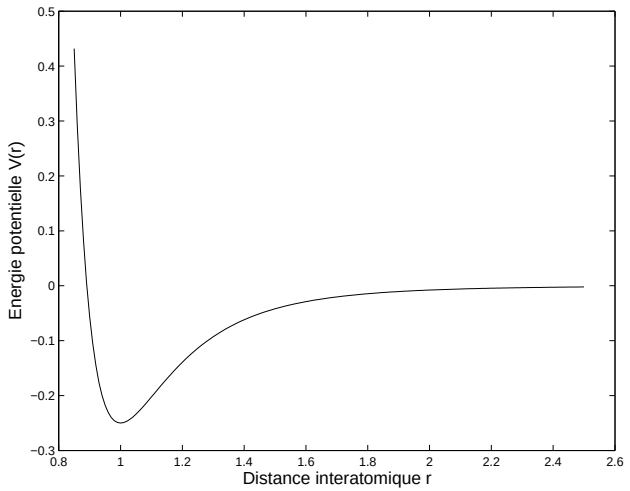
- Pair potential:

$$V(q_1, \ldots, q_N) = \sum_{1 \leq i < j \leq N} V_0(\mid q_j - q_i \mid)$$

- Lennard-Jones potential

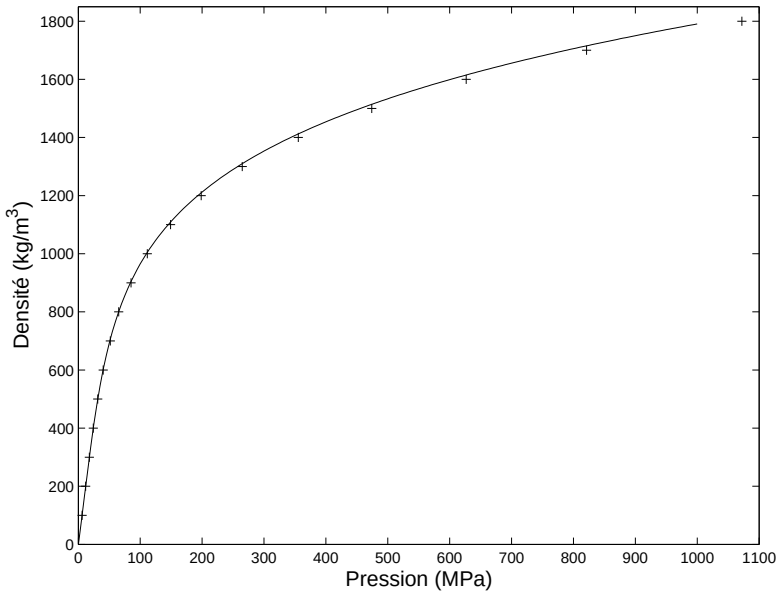
  For a distance $r = |q_1 - q_2|$

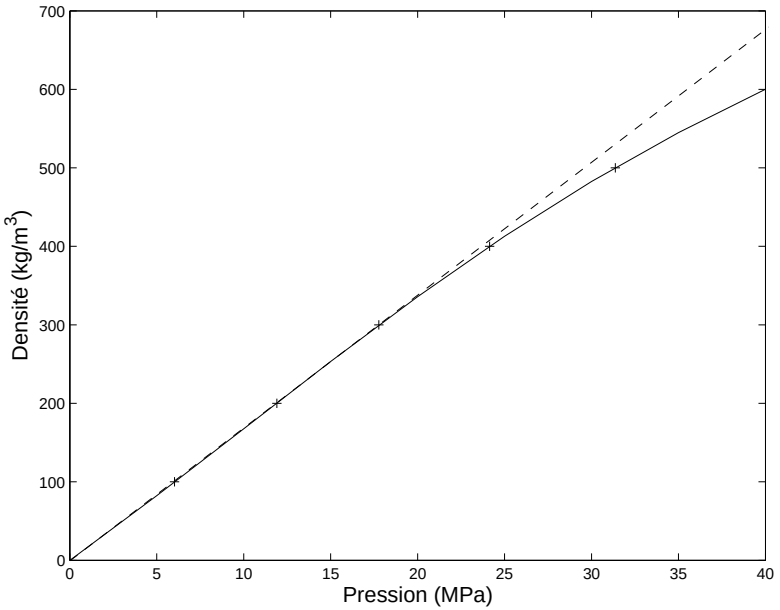
$$V_0(r) = 4\epsilon \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^{6} \right]$$



- Parameters : $\sigma = 3.405 \times 10^{-10}$ m, $\epsilon / k_{\mathrm{B}} = 119.8$ K
- Long-range part $\equiv$ Van der Waals interactions

Application: rare gases (2)





Density as a function of pressure: comparison between experimental data at $T = 300$ K (solid line) and simulation results (STAMP code, CEA/DAM). Ideal gas behaviour at low densities ($\rho \leq \rho_c = 350$ kg/m^3):

$$\rho = \frac{M}{RT} p.$$

Computation of dynamical properties

Usual methods

- Equilibrium fluctuations: Green-Kubo formula (time integration of some autocorrelation function)
- Steady state nonequilibrium molecular dynamics (linear response assumption)
- Example: thermal conductivity

Green-Kubo formula

- Microscopic heat flux j :

$$j(t) = \sum_i \frac{p_i}{m_i}\,\epsilon_i + \sum_{i \neq j} \frac{1}{2}\,q_{ij}\,\left(F_{ij} \cdot \frac{p_i}{m_i}\right),$$

with $q_{ij} = q_i - q_j$, $F_{ij} = \partial_{q_i} V(|q_i - q_j|)$, and ϵ_i internal energy of the i-th particle

$$\epsilon_i = \frac{p_i^2}{2m_i} + \frac{1}{2}\sum_{i \neq j} V(r_{ij}).$$

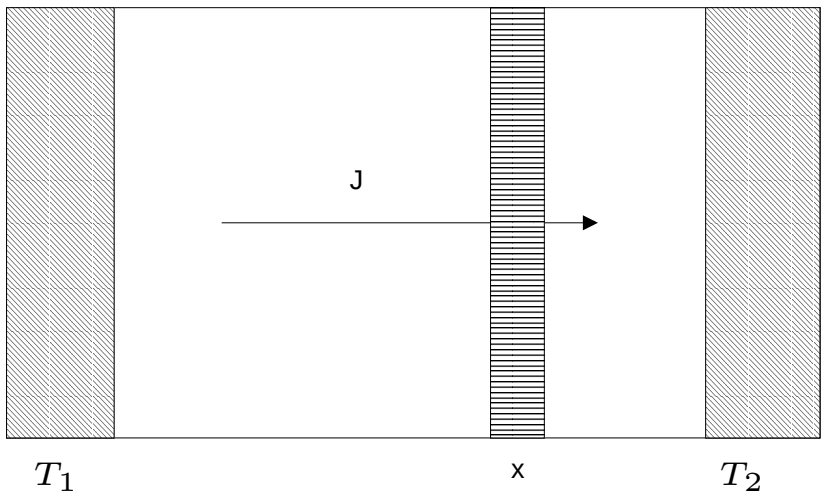
- Thermal conductivity λ

$$\lambda = \frac{1}{3|\mathcal{M}|k_{\mathrm{B}}T^2}\int_0^{+\infty} \langle j(t)\, j(0)\rangle\, dt.$$

- In practice, one long simulation

Steady state NEMD

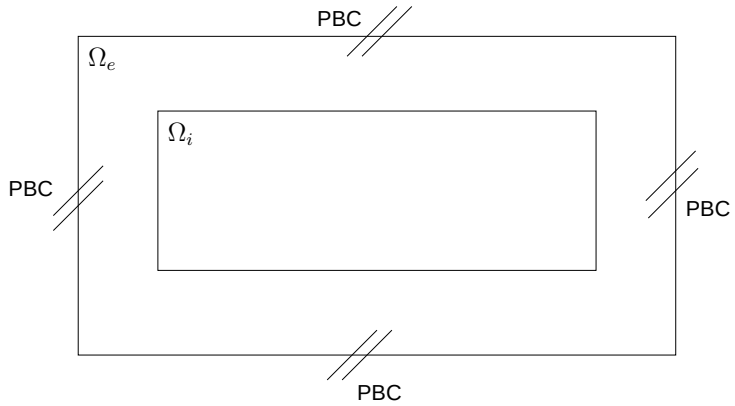
- Linear response $J = -\lambda \nabla T \left(= \dfrac{T_1 - T_2}{L} \right)$
- J macroscopic heat flux = spatial average



- In practice, one long simulation

Transient NEMD

- Langevin dynamics in $\Omega_e = \{x \in \Omega \mid \mathrm{d}(x, \partial\Omega) < r_\mathrm{c}\}$, NVE dynamics in Ω_i



- Dynamics

$$\left\{ \begin{array}{rcl} dq_t^i &=& \dfrac{p_t^i}{m^i}\, dt, \\ dp_t^i &=& -\nabla V(q_t^i)\, dt - \gamma(q_t^i)\dfrac{p_t^i}{m^i}\, dt + \sqrt{\dfrac{2\gamma(q_t^i)}{\beta}}\, dW_t, \end{array} \right. \tag{1}$$

- For example, $\gamma(\cdot) = \gamma_1 \cos\left(\dfrac{\pi \mathrm{d}(\cdot, \partial\Omega)}{2r_\mathrm{c}}\right) \mathbf{1}_{\mathrm{d}(\cdot,\partial\Omega)\leq r_\mathrm{c}}$.
- Preservation of canonical measure

Transient NEMD (3)

- Heating from $T = T_1$ to $T = T_2$
- Fourier law on $\Omega_i = (O, L)^3$

$$\rho C_v \partial_t T = \lambda \Delta T,$$

- Setting $A = \pi^2 L^{-2} \dfrac{\lambda}{\rho C_v}$, it follows

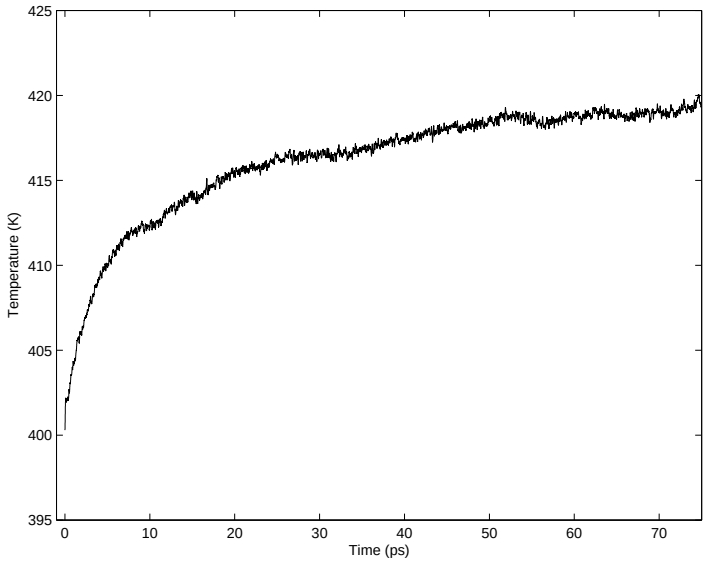
$$\frac{\bar{u}(t)}{\bar{u}(t_0)} \sim \mathrm{e}^{-3A(t-t_0)} \quad \text{with} \quad \bar{u}(t) = \int_{\Omega_i} \frac{T_2 - T(x,t)}{T_2 - T_1}\, dx$$

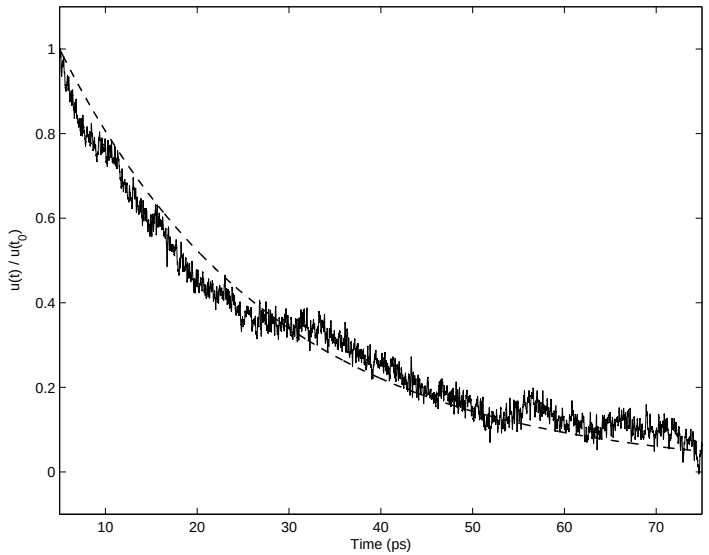
- In practice

$$\int_{\Omega_i} T(x,t)\, dx := T_{\mathrm{kin}}(t) = \frac{2}{3N_i k_{\mathrm{B}}} \sum_{n=1}^{N_i} \frac{p_n(t)^2}{2m_n}.$$

Numerical results

- Dense argon fluid at $T = 400$ K, with
- Averaging over 30 independent realizations:





- Gives $\lambda = 0.1509$ W/m/K, in fair agreement with experimental value $\lambda = 0.1557$ W/m/K at $T = 400$ K (3 % error).

Computation of free energy differences

Free energy

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

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

- 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 $V_\lambda(q_1, \ldots, q_N)$: external parameter λ
- Initial state: $\lambda = 0 \rightarrow$ final state: $\lambda = 1$
- Free energy differences

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

- Alchemical transition = particular reaction coordinate ($Q = (\lambda, q)$)

Some examples of "alchemical" transitions

- Intensity/orientation of a magnetic filed for a spin system
- 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 Lennard-Jones fluid)

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

Free energy difference = excess chemical potential

The reaction coordinate case

- reaction coordinate $\xi(q) \simeq$ reduced dynamics for relevant degrees of freedom
- Examples:
  - conformational changes, such as variation of a dihedral angle ($r_{ij} = q_j - q_i$) :

    $$\xi(q) = \phi$$

    varies from ϕ_0 to ϕ_1 with

    $$\cos\phi = -\frac{(r_{0,1} \times r_{1,2}) \cdot (r_{1,2} \times r_{2,3})}{|(r_{0,1} \times r_{1,2})| \cdot |(r_{1,2} \times r_{2,3})|} \; ;$$

  - dissociation of a molecule AB: distance between center of masses

    $$\xi(q) = |q_A - q_B|.$$

The reaction coordinate case (2)

- Potential of mean force: different definitions... Most general form

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

where the manifold $\Sigma_z = \{q \in \mathcal{M} \,|\, \xi(q) = z\}$ and $Z = \int \mathrm{e}^{-\beta V(q)} \, dq$.

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

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

The free energy also depends on the local values of the gradient of the reaction coordinate...

Usual techniques

- Thermodynamic integration[a]
- Free-energy perturbations[b]

$$\Delta F(\lambda) = -\beta^{-1} \ln \left\langle \mathrm{e}^{-\beta(V_\lambda(q) - V_0(q))} \right\rangle_0$$

where $\langle \cdot \rangle_0$ denotes a canonical average w.r.t. $d\mu_0(q) = Z^{-1} \mathrm{e}^{-\beta V_0(q)}\, dq$
$\longrightarrow$ usual sampling techniques

- Many extensions and refinements (e.g. Umbrella sampling[c])
- Recent alternative: nonequilibrium dynamics[d]

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[a] J.G. Kirkwood, *J. Chem. Phys.* **3**, 300 (1935)

[b] R. Zwanzig, *J. Chem. Phys.* **22**, 1420 (1954)

[c] G.M. Torrie and J.P. Valleau, *J. Comp. Phys.* **23**, 187 (1977)

[d] C. Jarzynski, *Phys. Rev. E* **56**(5) 5018 (1997)

Thermodynamic integration

- Free energy = integral

$$\Delta F = \int_0^1 F'(\lambda)\, d\lambda \simeq \sum_{i=1}^{M} (\lambda_i - \lambda_{i-1}) \left(\frac{F'(\lambda_{i-1}) + F'(\lambda_i)}{2} \right)$$

where the mean force is

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

if (q_λ^n) the Boltzmann measure associated with V_λ

- Ergodic stochastic dynamics for a fixed value λ_i, and consider a sequence $\lambda_i \in [0, 1]$
- Alternative: average over a single long trajectory with λ varying "infinitely" slowly (quasi-static transformation)

Thermodynamic integration (2)

- Reaction coordinate $\xi(q)$
- Associated free energy

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

- Free energy difference

$$\Delta F_f = \int_0^1 F_f'(z) \, dz$$

- Mean force = canonical average on a submanifold
- Analytical expression not practical...

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

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

Thermodynamic integration (3)

- 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 projection operator $P(q) = \mathrm{Id} - \mathbf{n}(q) \otimes \mathbf{n}(q)$ and $\mathbf{n}(q) = \frac{\nabla \xi(q)}{|\nabla \xi(q)|}$

- Lagrange multiplier formulation

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

where $r_{z,s}$ is directed along $\nabla \xi(q_{z,s})$ and is such that $\xi(q_{z,s}) = z$.

[a] C. Le Bris, T. Lelièvre and E. Vanden-Eijnden, in preparation

Thermodynamic integration (4)

- In practice, for a fixed value z, discretization (algorithmic time step Δs)

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

with r_z^{n+1} such that the constraint

$$\xi(q_z^{n+1}) = z$$

is satisfied.

- Mean force = average over Lagrange multipliers

$$\lim_{n\to+\infty} \frac{1}{n\Delta s} \sum_{m=1}^{n} r_z^m = F_f'(z) + \mathrm{o}(\Delta s)$$

- Then, free energy difference = integration of mean force

Nonequilibrium dynamics (alchemical case)

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

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

- In particular, the law of $q_{\Lambda,t}$ is not $Z_{\Lambda(t)}^{-1}\, \mathrm{e}^{-\beta V_{\Lambda(t)}}$... (distribution lags behind...)

Nonequilibrium dynamics (2)

- Definition: virtual work exerted on a trajectory

$$\mathcal{W}_T = \int_0^T \frac{\partial V_{\Lambda(t)}}{\partial \Lambda}(q_{\Lambda,t})\,\Lambda'(t)\,dt$$

- Feynman-Kac formula[a], usually known as the "Jarzynski equality"

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

- Consequence ("second law of thermodynamics"):

$$\Delta F(\Lambda(t)) \geq \mathbb{E}(\mathcal{W}_t)$$

- Remark: NVE dynamics also possible
- Remark: there are experimental validations

[a] G. Hummer and A. Szabo, *PNAS* **98**(7) (2001) 3658-3661.

Nonequilibrium dynamics (3)

- Denote by $\Pi_{\Lambda(t)}(f) = \int_{\mathcal{M}} f(q)\, \mathrm{e}^{-\beta V_{\Lambda(t)}(q)}\, dq$
- Infinitesimal generator L

$$L_\Lambda \varphi = \frac{1}{\beta}\Delta_q \varphi - \nabla V_\Lambda(q) \cdot \nabla_q \varphi.$$

with balance property (invariance of the measure) :

$$\forall \varphi, \quad \mu_{\Lambda(t)}(L_{\Lambda(t)}(\varphi)) = 0.$$

- Deriving w.r.t. t,

$$\partial_t \Pi_{\Lambda(t)}(\phi) = \Pi_{\Lambda(t)} \left(L_{\Lambda(t)}(\phi) - \beta \frac{\partial V_{\Lambda(t)}}{\partial \Lambda} \Lambda'(t) \phi \right).$$

- Associated PDE (Fokker-Planck) $\partial_t f = L^* f - \beta \frac{\partial V_{\Lambda(t)}}{\partial \Lambda} \Lambda'(t)\, f$

Nonequilibrium dynamics (4)

- Practical implementation ($\lambda^0 = 0, \lambda^N = 1, N = T/\Delta t$) for $0 \leq i \leq M$ systems
  - update the parameter (for example $\lambda^n = \lambda^{n-1} + 1/N$)
  - one-step diffusion (overdamped Langevin)

$$q^{i,n+1} = q^{i,n} - \Delta t \, \nabla V_{\lambda^{n+1}}(q^{i,n}) + \sqrt{\frac{2\Delta t}{\beta}} \, R^{i,n}$$

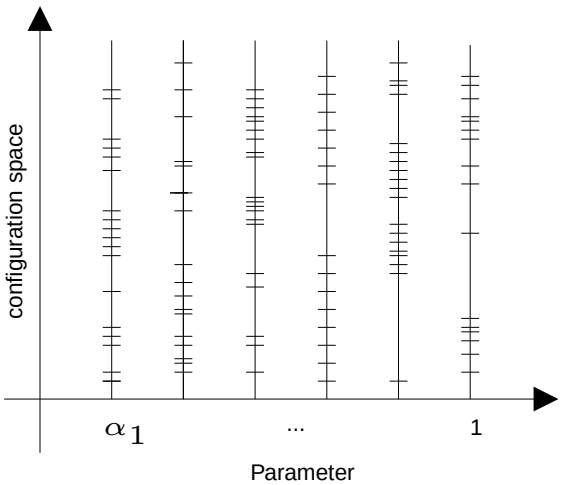
  - update the work

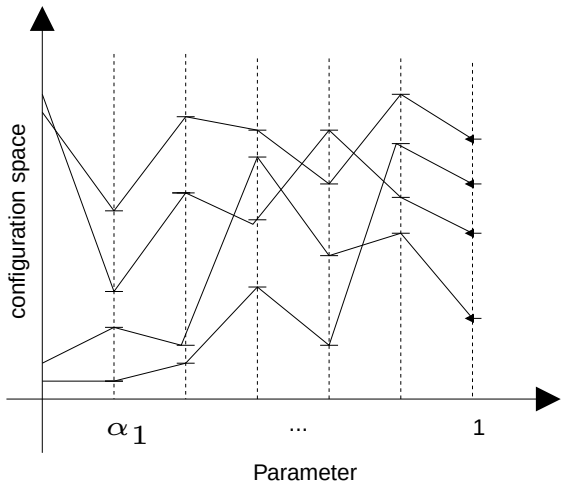
$$\mathcal{W}^{i,n+1} = \mathcal{W}^{i,n} + \frac{1}{2}\left(\frac{\partial V_{\lambda^n}}{\partial \lambda}(q^{i,n}) + \frac{\partial V_{\lambda^{n+1}}}{\partial \lambda}(q^{i,n+1})\right)(\lambda^{n+1} - \lambda^n).$$

- (Biased) free-energy estimator

$$\Delta F = -\beta^{-1} \ln\left(\frac{1}{M}\sum_{i=1}^{M} \mathcal{W}^{i,N}\right)$$

Before going on...





Left: Thermodynamic integration (adiabatic).

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

Nonequilibrium dynamics: The reaction coordinate case

- Geometric extension: reaction coordinate $\xi(q)$
- Variation of the constraint $z(t)$ such that $z(0) = 0, z(T) = 1$
- Formal properties
  - $X_0 \sim \mu_{\Sigma_{z(0)}}$
  - for all $t \in [0, T]$, X_{t+dt} is the orthogonal projection onto $\Sigma_{z(t+dt)}$ of the diffusion leaving the Boltzmann measure invariant, *i.e.* $\tilde{X}_{t+dt} = X_t - \nabla V(X_t)dt + \sqrt{2\beta^{-1}}dW_t$.
- Dynamics

$$\left\{ \begin{array}{rcl} X_0 & \sim & \mu_{\Sigma_{z(0)}} \\ dX_t & = & -P(X_t)\nabla V(X_t)dt + \sqrt{2\beta^{-1}}P(X_t) \circ dW_t + \nabla\xi(X_t)\, d\Lambda_t^{\mathrm{d}} \\ d\Lambda_t^{\mathrm{d}} & = & \frac{1}{|\nabla\xi(X_t)|^2} z'(t)dt \end{array} \right.$$

Nonequilibrium dynamics: The reaction coordinate case (2)

- The "right" dynamics to consider is

$$\left\{ \begin{array}{rcl} X_0 & \sim & \mu_{\Sigma_{z(0)}} \\ dX_t & = & -\nabla V(X_t)dt + \sqrt{2\beta^{-1}}dW_t + \nabla\xi(X_t)\, d\Lambda_t \end{array} \right.$$

  with $d\Lambda_t$ such that $d[\xi(X_t)] = z'(t)dt$.

- Decomposition of the Lagrange multiplier as $\Lambda_t = \Lambda_t^{\mathrm{d}} + \Lambda_t^{\mathrm{m}} + \Lambda_t^{\mathrm{f}}$ with
  - martingale part $\nabla\xi(X_t)\, d\Lambda_t^{\mathrm{m}} = -\sqrt{2\beta^{-1}}P^{\perp}(X_t)\, dW_t$,
  - local force part

$$\nabla\xi(X_t)\, d\Lambda_t^{\mathrm{f}} = \left(P^{\perp}(X_t)\, \nabla V(X_t) \; - \beta^{-1}\nabla \cdot \left(\frac{\nabla\xi(X_t)}{|\nabla\xi(X_t)|} \right) \frac{\nabla\xi(X_t)}{|\nabla\xi(X_t)|} \right) dt = f(X_t)\, dt$$

  - forcing term (bias allowing a finite time switch)

$$\nabla\xi(X_t)d\Lambda_t^d = \frac{\nabla\xi(X_t)}{|\nabla\xi(X_t)|^2}\, z'(t)dt = P^{\perp}(X_t)dX_t.$$

Nonequilibrium dynamics: The reaction coordinate case (3)

- Definition of the work

$$\mathcal{W}_t = \int_0^t f(X_s)\, z'(s)\, ds = \int_0^t z'(s) d\Lambda_s^{\mathrm{f}}$$

- Feynman-Kac formula

$$\mathrm{e}^{-\beta(F(z(t))-F(z(0)))} = \mathbb{E}\left(\mathrm{e}^{-\beta \mathcal{W}_t}\right).$$

- For example, discretization of the dynamics and computation of the work according to

$$\mathcal{W}_n = \mathcal{W}_{n-1} + \frac{z(t_n) - z(t_{n-1})}{t_n - t_{n-1}} \lambda_{n+1}^{\mathrm{f}},$$

with

$$\lambda_{n+1}^{\mathrm{f}} = \lambda_{n+1} - \frac{z(t_{n+1}) - z(t_n)}{|\nabla\xi(q_n)|^2} + \sqrt{\frac{2\Delta t}{\beta}} \frac{\nabla\xi(q_n)}{|\nabla\xi(q_n)|^2} \cdot U_n.$$

Equilibrating the nonequilibrium dynamics

- Problems with the usual approach: exponential weights = only the lower tail of the work distribution counts (statistical confidence?)
- Source term in Fokker/Planck equation is reinterpreted in a probabilistic way through a birth/death process ($\simeq$ elegant continuous resampling)
- Jump/diffusion process $\bar{q}_{\Lambda,t}$ enhancing works lower than the average (and penalizing works larger than the average) in order to maintain equilibrium at all times
  - "Interacting Particle System" (genetic algorithm: mutation = diffusion)
  - the law of $\bar{q}_{\Lambda,t}$ is the canonical measure at all times
  - $\mathbb{E}(\bar{\mathcal{W}}_T) = \Delta F$
- "Simulated annealing" strategy (comparison with parallel tempering)

Equilibrating the nonequilibrium dynamics (2)

- M replicas of the sytem
- Evolution in a mean-field sense: empirical mean force

$$\mathcal{F}^M_{\Lambda(t)} = \frac{1}{M}\sum_{k=1}^{M} \frac{\partial V_{\Lambda(t)}}{\partial \Lambda}(q^k_{\Lambda,t})$$

- Selection mechanism favors replicas sampling lower virtual works $\rightarrow$ 'self-organization' to keep closer to a quasi-static transformation

$$\Delta F = \mathbb{E}\left(\mathrm{e}^{-\beta(W_t^{\mathrm{ex}} - W_t^{\mathrm{de}})}\right)$$

with excess (penalized) / deficit (enhanced) works

$$W_t^{k,\mathrm{ex/de}} = \int_0^t \left(\frac{\partial V_{\Lambda(s)}}{\partial \Lambda}(q^k_{\Lambda,t}) - \mathcal{F}^M_{\Lambda(s)}\right)^{+/-} \Lambda'(s)\, ds$$

Equilibrating the nonequilibrium dynamics (3)

Algorithm Initial distribution $(q_0^1, \ldots, q_0^M) \sim d\pi_0(q)$, initial jump times $T_0^{k,d} = 0, T_0^{k,b} = 0$.

- Between each jump time, evolve independently the replicas $q_{\Lambda,t}^k$ according to the chosen dynamics;
- [Death] At random times $T_n^{k,\mathrm{ex}}$ such that

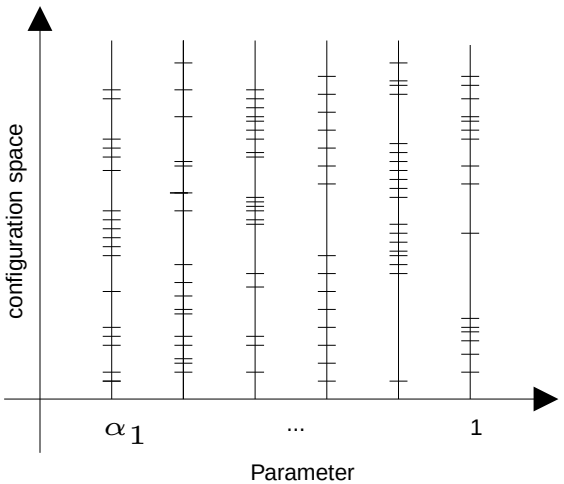
$$W^{k,\mathrm{ex}}_{T^{k,d}_{n+1}} - W^{k,\mathrm{ex}}_{T^{k,\mathrm{ex}}_n} = \tau_n^{k,\mathrm{ex}} \sim \mathcal{E}(\beta^{-1})$$

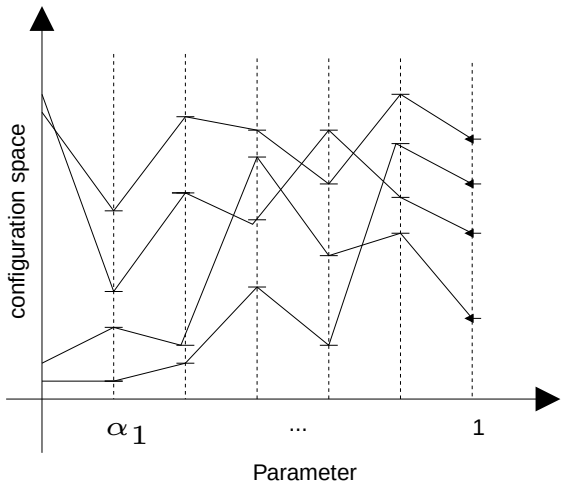
  the k-th configuration is replaced by a configuration $l \in \{1, \ldots, M\}$ chosen at random;
- [Birth] At random times $T_n^{k,de}$ such that

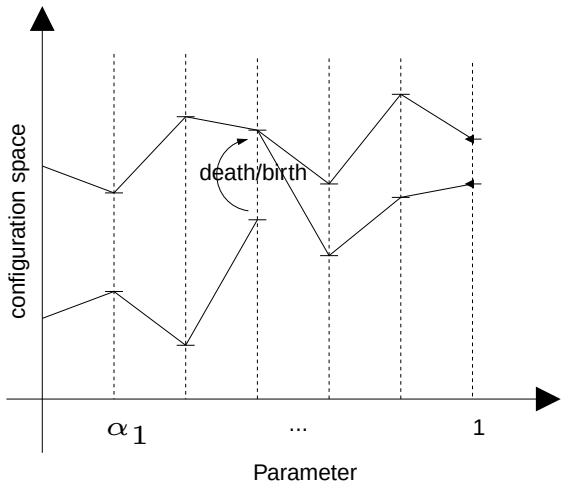
$$W^{k,\mathrm{de}}_{T^{k,\mathrm{de}}_{n+1}} - W^{k,\mathrm{de}}_{T^{k,\mathrm{de}}_n} = \tau_n^{k,\mathrm{de}} \sim \mathcal{E}(\beta^{-1})$$

  a configuration $l \in \{1, \ldots, M\}$ chosen at random is replaced by the k-th configuration.

Final cartoon comparison...





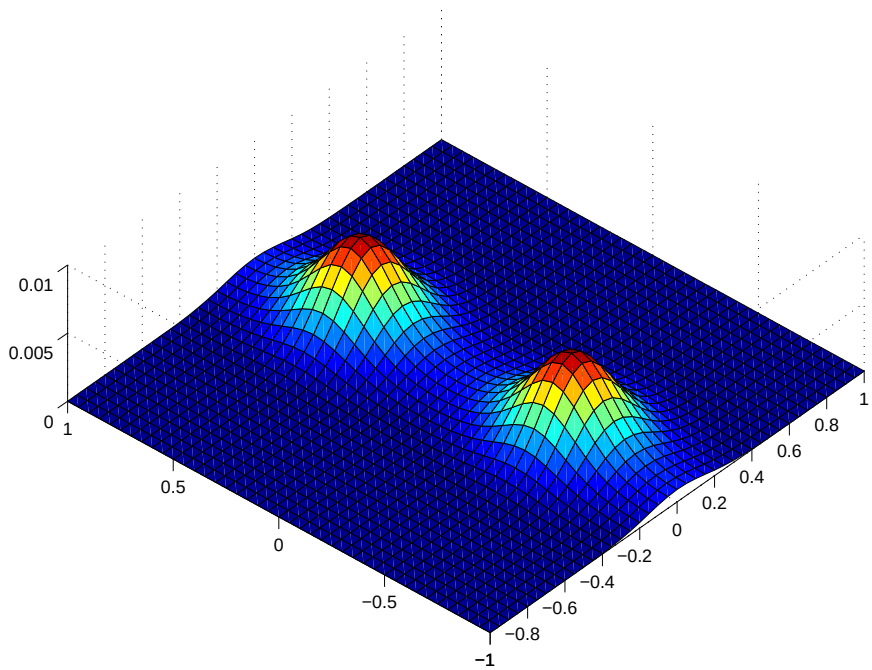


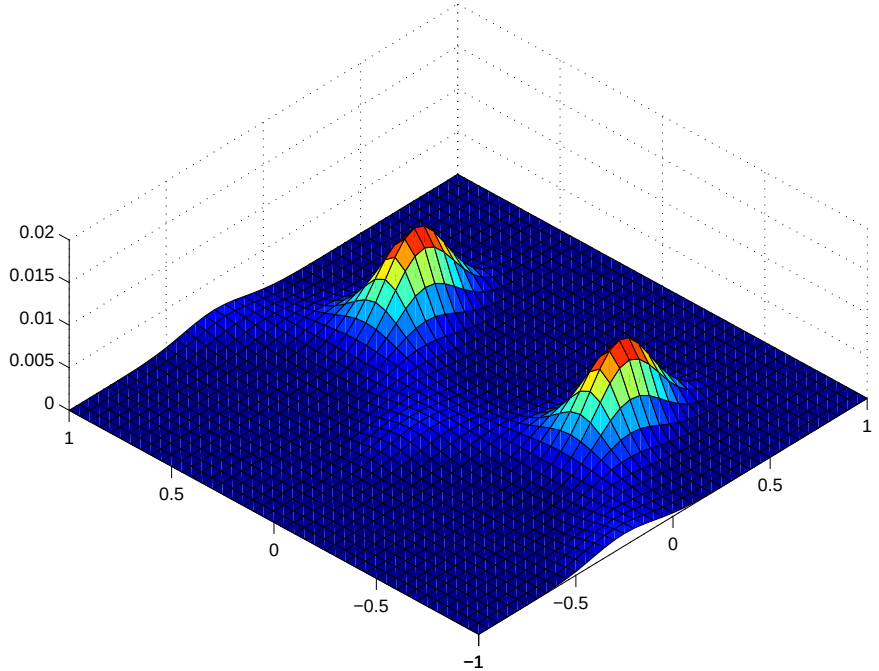
Left: Thermodynamic integration (adiabatic).

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

Right: Interacting Particle Strategy (canonical initial conditions, birth/death process).

A 2D toy model





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

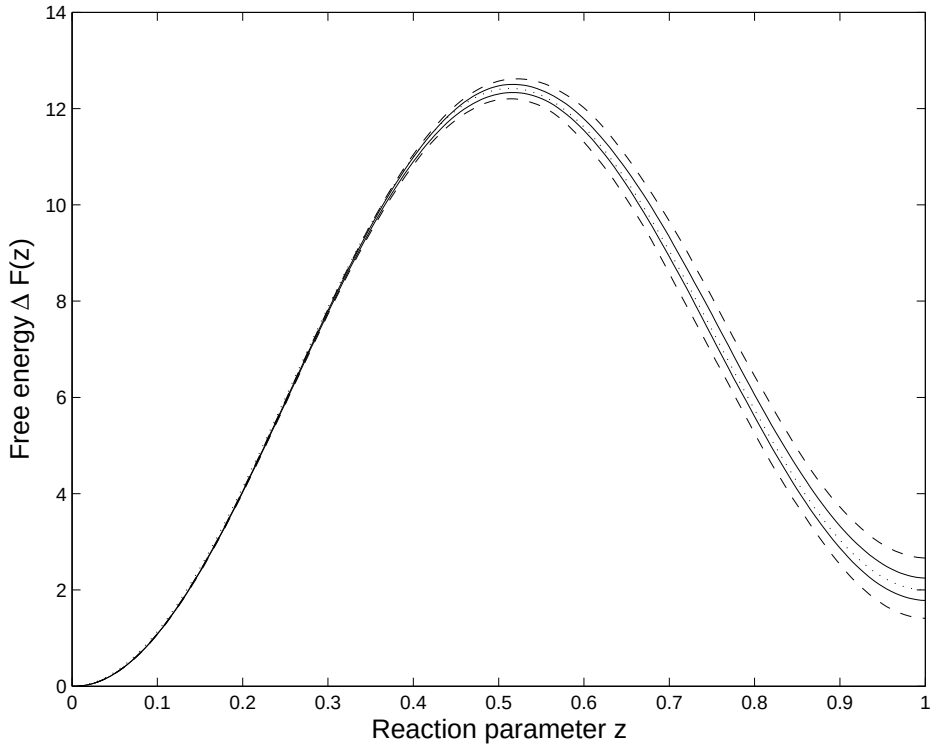
Plot of the probability density ($\beta = 1, d_2 = 1$). Left: $d_1 = 0$. Right: $d_1 = 10$.

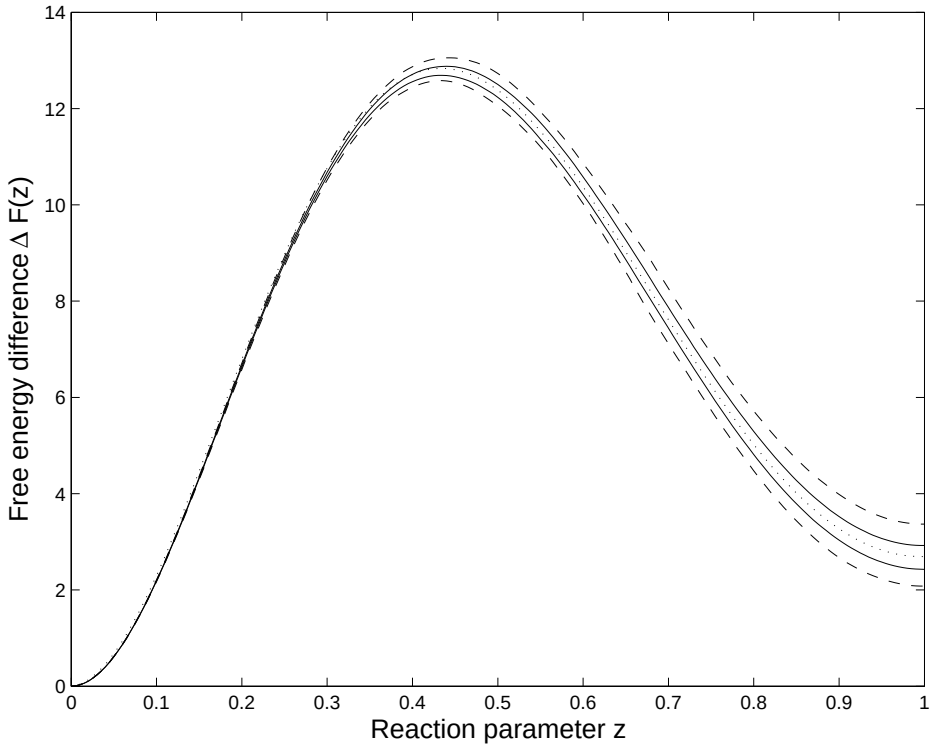
Free energy difference profiles between $x_0 = -\frac{1}{2}$ and $x_1 = 0$.

Reaction coordinate: $\xi(x,y) = \frac{x - x_0}{x_1 - x_0} - z$ ($0 \leq z \leq 1$).

[a] A. Voter (1997)

Free energy difference profiles (toy 2D case)





Free energy difference profile for $d_1 = 30, d_2 = 1$ and $\beta = 1$.
Dotted line: analytical reference. Solid lines: 95 $\%$ confidence interval (variance estimated over $K = 100$ simulations) for a nonequilibrium dynamics with $T = 1$ and $M = 10^4$. Dashed lines: id with $M = 10^3$.

A simplified model for solvatation effects on conformational changes

- N particles interacting through the purely repulsive WCA potential

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

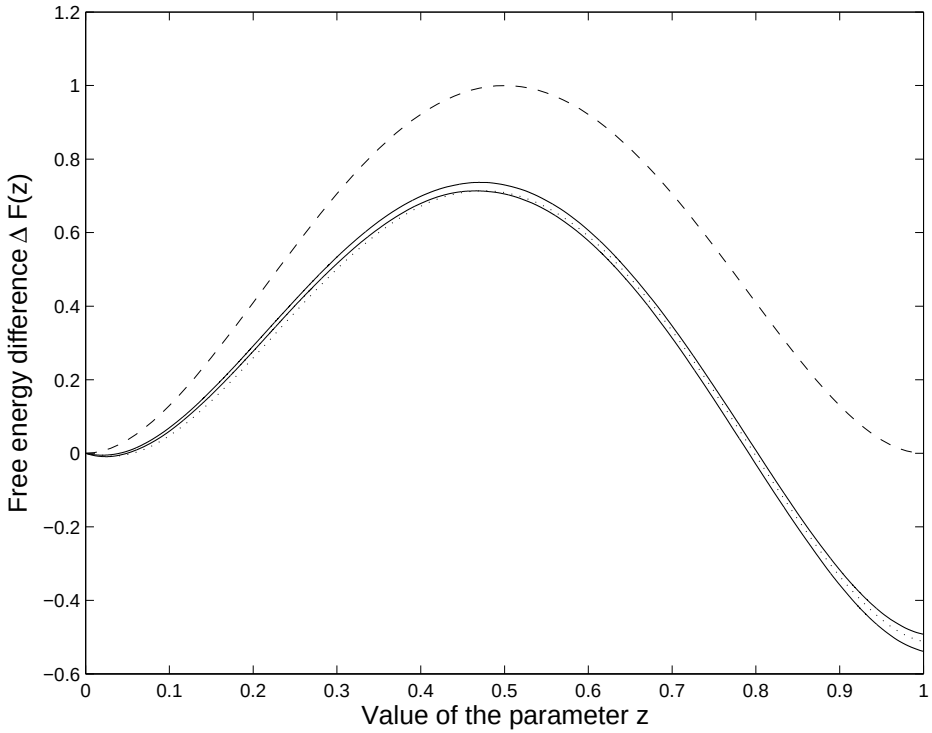
- Two solute particles interact via the double-well potential

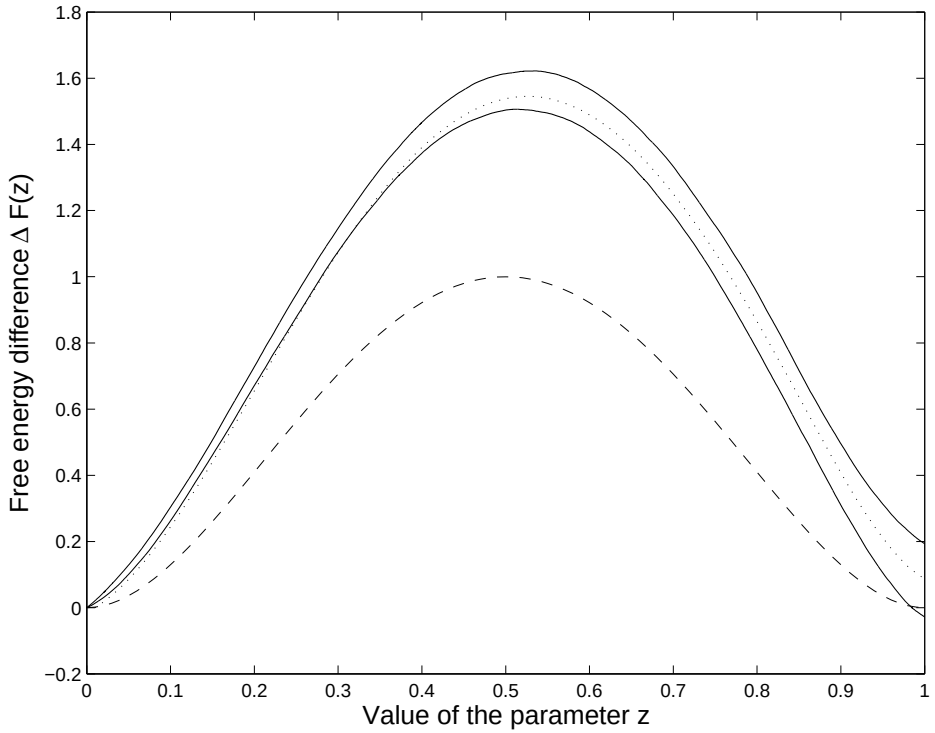
$$V_{\mathrm{S}}(r) = h\left[1 - \frac{(r-\sigma-w)^2}{w^2}\right]^2,$$

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

$$\xi(q) = \frac{|q_1 - q_2| - r_0}{2w}$$

Influence of solvent density on free energy profiles





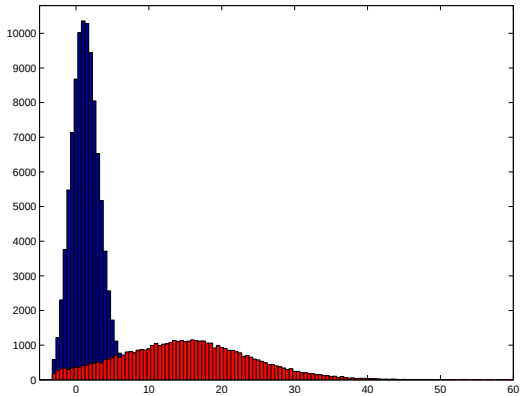
Density $\rho = a^{-2}$. Left: $a = 3$. Right: $a = 1.3$.

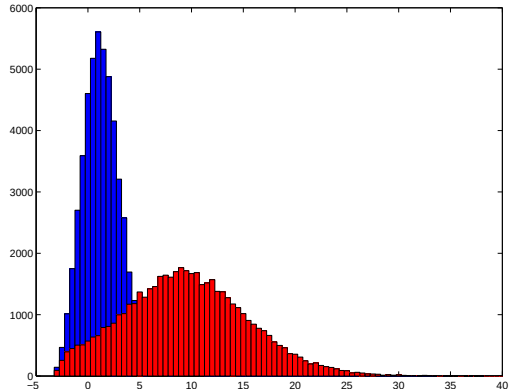
Solid line: Free-energy profiles computed using a nonequilibrium method ($T = 10$, $M = 100$, averaged over 50 realizations).

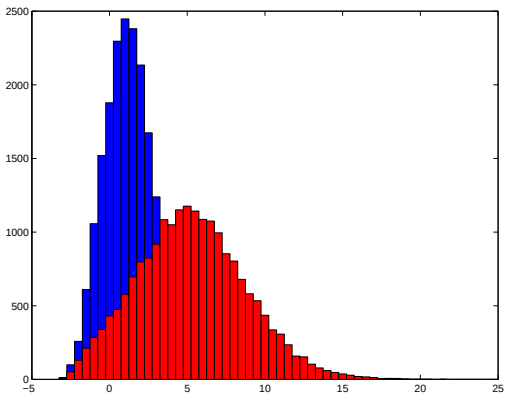
Dotted line: reference TI computation (101 points for $z \in [0, 1]$, averages taken over time $T = 2500$).

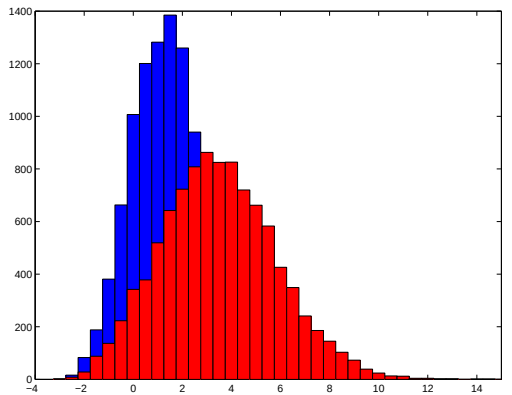
Dashed line: Energy difference for the bond (double well potential).

Computation of chemical potentiel (Widom insertion)









Work distribution for a widom insertion (blue = IPS, red = Jarzynski) for increasing switching times ($T = 1, 2, 5, 10$).

Conclusion and prospects

References

- **Equilibrium sampling**: E. Cancès, F. Legoll, and G. Stoltz, Theoretical and numerical comparison of some sampling methods, submitted to M2AN (2005)
- **Thermodynamic integration (projected SDE)**: C. Le Bris, T. Lelièvre, and E. Vanden-Eijnden, Sampling measures on a manifold with stochastic differential equations, in preparation.
- **Nonequilibrium computation of free energy differences**:
  - *Reaction coordinate case*: Tony Lelièvre, Mathias Rousset, and Gabriel Stoltz, Computation of free energy differences through nonequilibrium dynamics: The reaction coordinate case, in preparation.
  - *Equilibration of the nonequilibrium dynamics*: M. Rousset and G. Stoltz, Equilibrium sampling from nonequilibrium dynamics, accepted for publication in *J. Stat. Phys.* (2006)

Perspectives : Path sampling

- 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)

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[a] C. Dellago, P.G. Bolhuis, F.S. Csajka, and D. Chandler (1998)

[b] C. Dellago, P.G. Bolhuis, and P.L. Geissler (2002)

[c] D. Zuckermann and M. Ytreberg (2004)

[d] P. Geissler and C. Dellago (2004)