(Non)equilibrium computation of free-energy differences

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Outline of the talk

- Computation of equilibrium properties
- Computation of free energy differences
  - Free energy perturbation
  - Thermodynamic integration
  - Nonequilibrium dynamics (Jarzynski) and its equilibration
  - Adaptive methods (biasing force or potential)
- Reduced dynamics...?

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

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

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

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/deterministic 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)

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)

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

- Various discretizations have been proposed

Overdamped Langevin dynamics

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

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

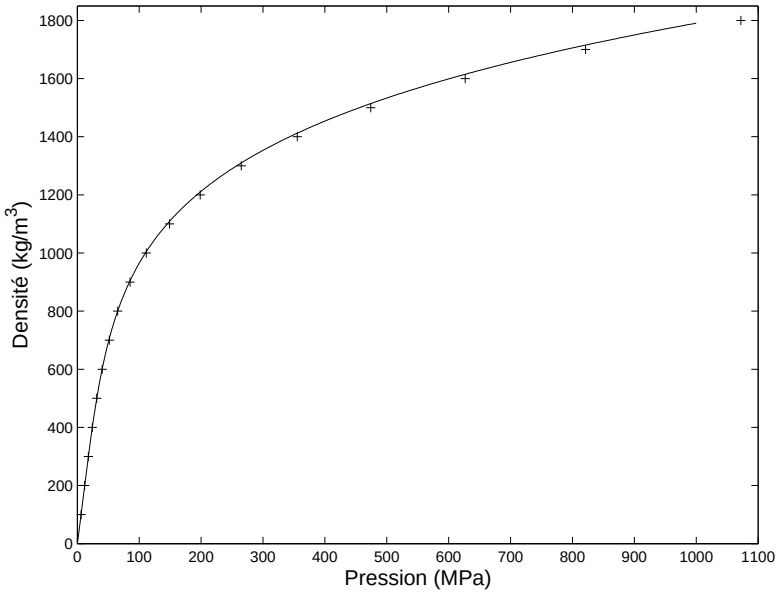
where $(W_t)_{t\geq 0}$ is a standard Wiener process of dimension dN and with $\sigma = (2/\beta)^{1/2}$.

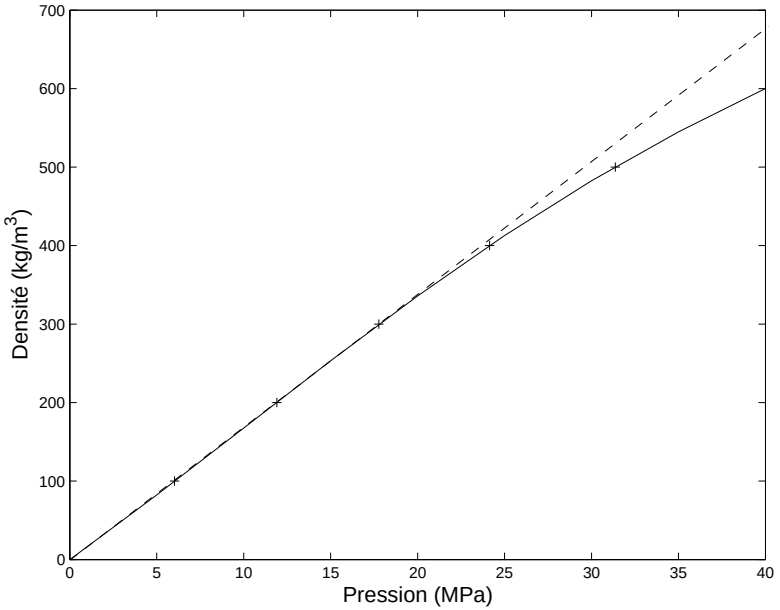
- Canonical measure $d\pi$ is invariant (steady solution of the associated Fokker-Planck equation) + irreducibility (elliptic process):

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

- Only one parameter in practice: Δt !

Application: equation of state for rare gases





Lennard-Jones potential pairwise additive interaction potential. Pressure:

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

Density as a function of pressure: experimental data at $T = 300$ K (solid line) and simulation results (STAMP code). Ideal gas behaviour at low densities.

Computation of free energy differences

Free energy

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

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

- 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 description through relevant (macroscopic) degrees of freedom
- Examples:
  - conformational changes, such as variation of a dihedral angle ($r_{i,j} = q_j - q_i$) :

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

    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... but (co-area formula)

$$\int_{\mathcal{M}} A(\xi(q)) \mathrm{e}^{-\beta V(q)} \, dq = \int_0^1 A(z) \, \mathrm{e}^{-\beta F(z)} \, dz.$$

A simplified model for solvatation effects on conformational changes

- N particles interacting through the purely repulsive WCA potential

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

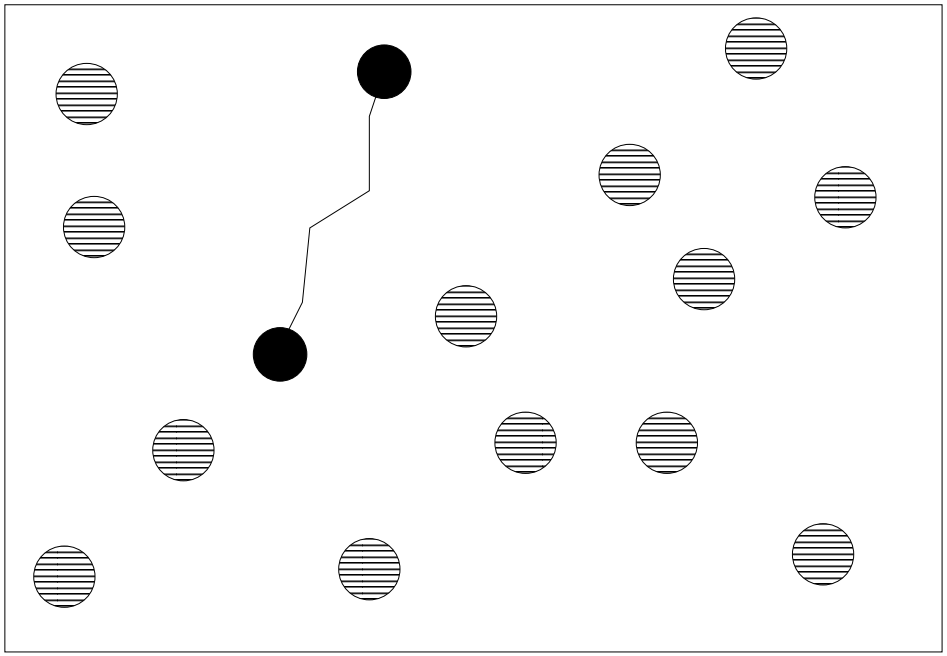
- Two solute particles interact via the double-well potential

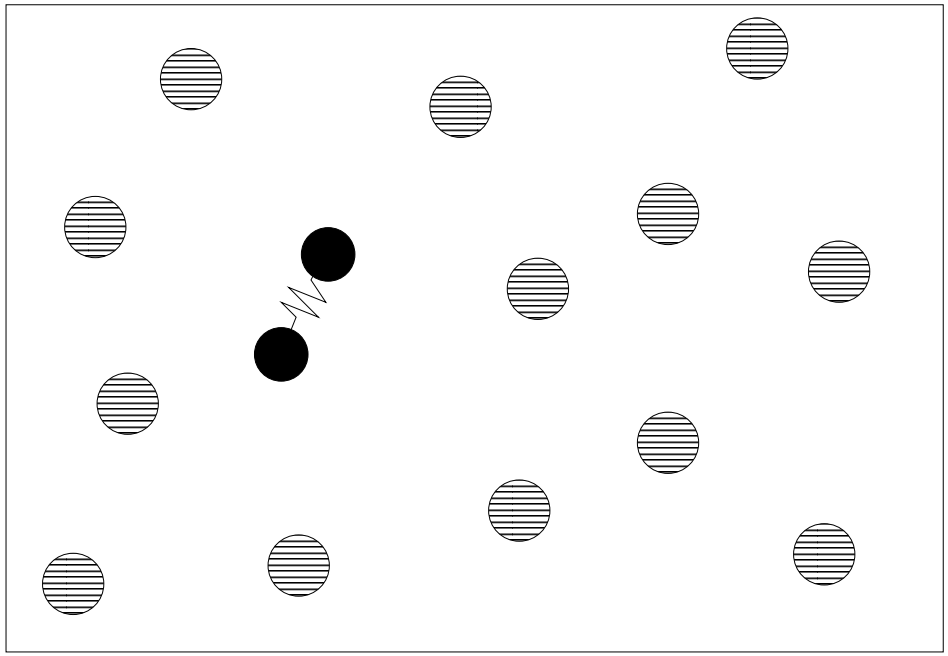
$$V_{\mathrm{S}}(r) = h\left[1 - \frac{(r-\sigma-w)^2}{w^2}\right]^2,$$

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

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

Cartoon picture of the system





Usual techniques

- Thermodynamic integration
- Free-energy perturbations[a]

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

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

$\rightarrow$ usual sampling techniques + many extensions and refinements (e.g. Umbrella sampling[b])

$\rightarrow$ but restricted to alchemical transitions. . .

- Nonequilibrium dynamics
- Adaptive Dynamics

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

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

Thermodynamic integration

- Free energy = integral[a]

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

where the mean force is

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

if (q_λ^n) are sampled from 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)

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

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 (Itô interpretation)

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

with projection operator $P(q) = \mathrm{Id} - P^{\perp}(q) = \mathrm{Id} - \mathbf{n}(q) \otimes \mathbf{n}(q)$ 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] G. Ciccotti, T. Lelièvre and E. Vanden-Eijnden, to appear in *Comm. Pure Appl. Math.* (2007)

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 (Hamiltonian case)

- Hamiltonian case

$$\begin{cases} \dot{q}_i(t) = \dfrac{\partial H_{\Lambda(t)}}{\partial p_i}(q(t),p(t)), \\ \dot{p}_i(t) = -\dfrac{\partial H_{\Lambda(t)}}{\partial q_i}(q(t),p(t)). \end{cases}$$

- Work $W(q,p) = \displaystyle\int_0^T \frac{\partial H_{\Lambda(t)}}{\partial \Lambda}(\Phi_t^T(q,p))\,\Lambda'(t)\,dt = H_1(\Phi_T^T(q,p)) - H_0(q,p)$
- Then

$$\int_{T^*\mathcal{M}} \mathrm{e}^{-\beta W(q,p)}\,d\mu_0(q,p) = Z_0^{-1}\int_{T^*\mathcal{M}} \mathrm{e}^{-\beta H_1(\Phi_T^T(q,p))}\,dq\,dp$$

so that

$$\frac{Z_1}{Z_0} = \mathrm{e}^{-\Delta F} = \int_{T^*\mathcal{M}} \mathrm{e}^{-\beta W(q,p)}\,d\mu_0(q,p).$$

Nonequilibrium dynamics (Diffusion)

- 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) :

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

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

Nonequilibrium dynamics (The Jarzynski equality)

- 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"[b]

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

- Consequence ("second law of thermodynamics"):

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

- There are experimental validations

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

[b] C. Jarzynski, *Phys. Rev. Lett.* **78** (1997) 2690-2693

Nonequilibrium dynamics (Implementation)

- 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

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

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.* projection of $\tilde{X}_{t+dt} = X_t - \nabla V(X_t)dt + \sqrt{2\beta^{-1}}dW_t$.
- Dynamics

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

Nonequilibrium dynamics: The reaction coordinate case (2)

- The "right" dynamics to consider is

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

  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)

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

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

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

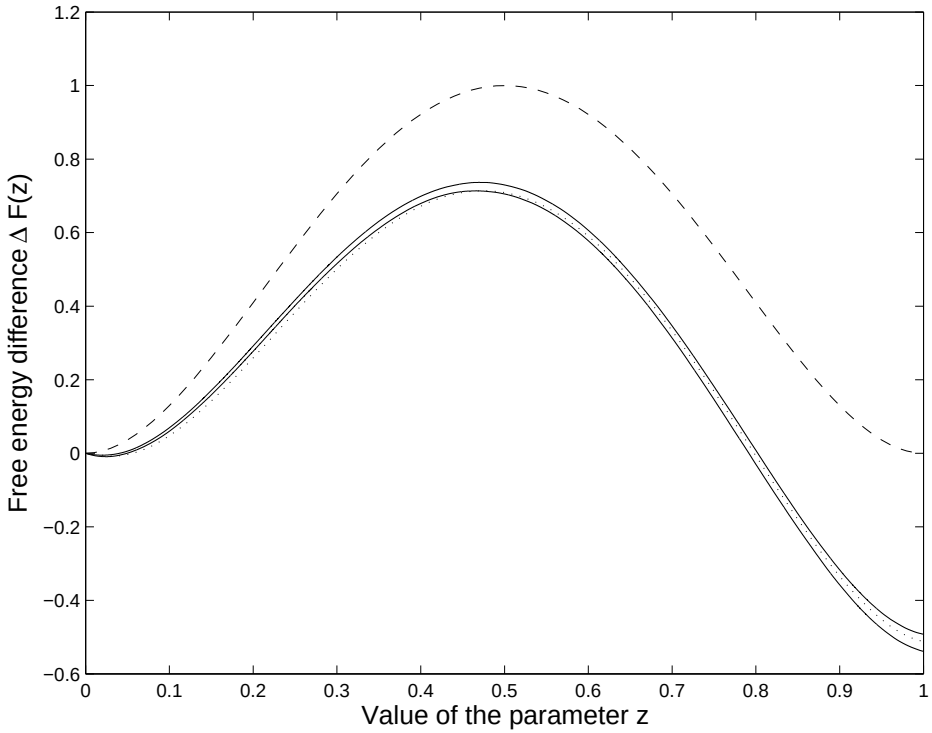
- For example, discretization of the dynamics and computation of the work according to

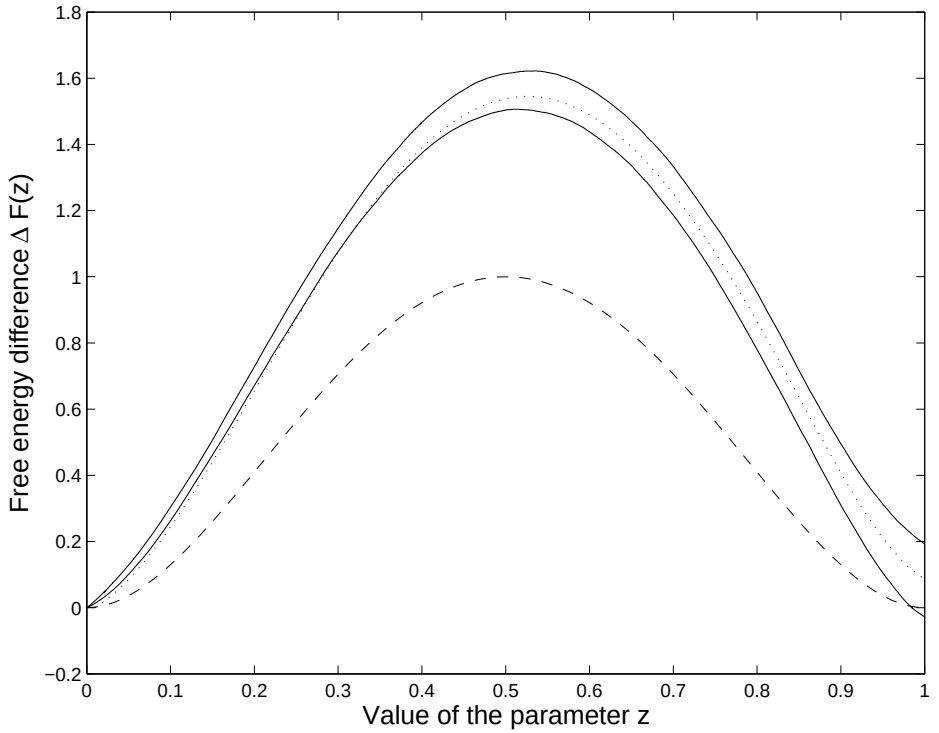
$$\mathcal{W}_n = \mathcal{W}_{n-1} + \frac{z(t_n) - z(t_{n-1})}{t_n - t_{n-1}} \lambda_{n+1}^{\mathrm{f}},$$

with

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

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).

Equilibrating the nonequilibrium dynamics

- Problems with the usual approach: exponential weights = only the lower tail of the work distribution counts (statistical confidence?)
  $\longrightarrow$ **Path sampling** approaches
- 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

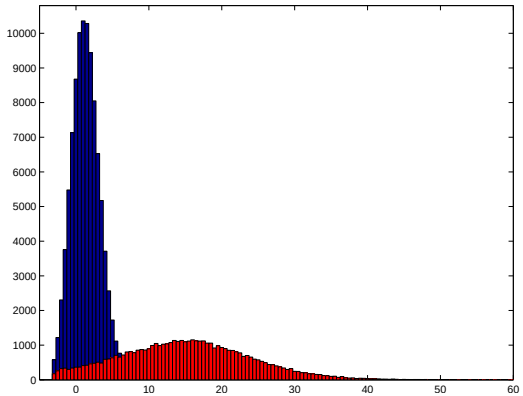
$$W^{k,\mathrm{ex}}_{T^{k,d}_{n+1}} - W^{k,\mathrm{ex}}_{T^{k,\mathrm{ex}}_n} = \tau_n^{k,\mathrm{ex}} \sim \mathcal{E}(\beta^{-1})$$

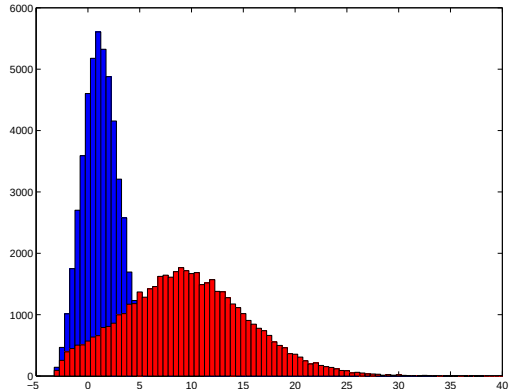
  the k-th configuration is replaced by a configuration $l \in \{1, \ldots, M\}$ chosen at random;
- [Birth] At random times $T_n^{k,de}$ such that

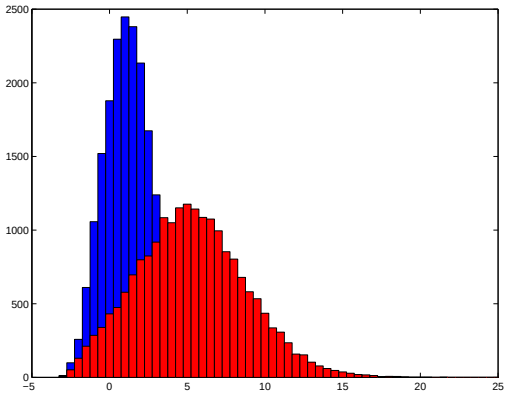
$$W^{k,\mathrm{de}}_{T^{k,\mathrm{de}}_{n+1}} - W^{k,\mathrm{de}}_{T^{k,\mathrm{de}}_n} = \tau_n^{k,\mathrm{de}} \sim \mathcal{E}(\beta^{-1})$$

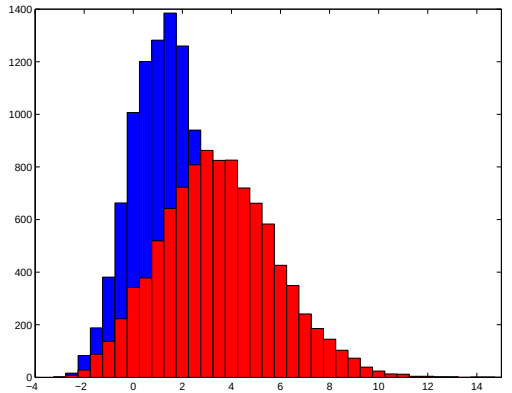
  a configuration $l \in \{1, \ldots, M\}$ chosen at random is replaced by the k-th configuration.

Computation of chemical potentiel (Widom insertion)









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

Adaptive Dynamics

- Zoology
  - Adaptive Biasing Force[a]
  - Wang-Landau dynamics[b]
  - Nonequilibrium metadynamics[c]

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[b] F. Wang and D.P. Landau, *Phys. Rev. E* **64**, 056101 (2001)

[c] G. Bussi, A. Laio, and M. Parinello, *Phys. Rev. Lett.* **96**, 090601 (2006); P. Raiteri, A. Laio, F. Luigi Gervasio, C. Micheletti, and M. Parinello, *J. Phys. Chem. B* **110**, 3533 (2006)

Definition of the bias

- Dynamics $t \mapsto Q_t$, ergodic with respect to the Boltzmann measure
- Consider an ensemble of realizations, description through $\psi_t(q)$
- Define the marginal

$$\psi_t^\xi(z) = \int \psi_t(q)\, \delta_{\xi(q)-z}$$

- Biasing potential added: $\mathcal{V}_t(q) = V(q) - F_{\text{bias}}(t, \xi(q))$
- Recall that

$$F(z) = -\beta^{-1} \ln \int \exp(-\beta V(q))\, \delta_{\xi(q)-z},$$

and

$$F'(z) = \frac{\displaystyle\int f^V(q)\, \exp(-\beta V(q))\, \delta_{\xi(q)-z}}{\displaystyle\int \exp(-\beta V(q))\, \delta_{\xi(q)-z}}, \qquad f^V = \frac{\nabla V \cdot \nabla \xi}{|\nabla \xi|^2} - \beta^{-1} \mathrm{div}\left(\frac{\nabla \xi}{|\nabla \xi|^2}\right)$$

- Question: how to update the bias? (Fixed point strategy)

Biasing potential

- At equilibrium $\psi_t^{\mathrm{eq}}(q) = Z_t^{-1} \exp(-\beta \mathcal{V}_t(q))$, so that, in this case,

$$-\beta^{-1} \ln \int \psi_t^{\mathrm{eq}}(q)\, \delta_{\xi(q)-z} = F(z) - F_{\mathrm{bias}}(t,z) + \beta^{-1} \ln Z_t.$$

  and exponential convergence $F_{\mathrm{bias}}(t) \to F$ (up to a constant) for the update

$$\partial_t F_{\mathrm{bias}}(t,z) = -\frac{\beta^{-1}}{\tau} \ln \int \psi_t^{\mathrm{eq}}(q)\, \delta_{\xi(q)-z}$$

- General case: observed potential of mean force

$$F_{\mathrm{pot,obs}}(t,z) = -\beta^{-1} \ln \int \psi_t(q)\, \delta_{\xi(q)-z},$$

  and update

$$\boxed{\text{(ABP)} \qquad \partial_t F_{\mathsf{bias}}(t,z) = g_t(F_{\mathrm{pot,obs}}(t,z)).}$$

Biasing force

- At equilibrium $\psi_t^{\mathrm{eq}}(q) = Z_t^{-1} \exp(-\beta \mathcal{V}_t(q))$, so that

$$\frac{\int f^{\mathcal{V}_t}(q)\, \psi_t^{\mathrm{eq}}(q)\, \delta_{\xi(q)-z}}{\int \psi_t^{\mathrm{eq}}(q)\, \delta_{\xi(q)-z}} = F'(z) - F'_{\mathrm{bias}}(t,z)$$

  and exponential convergence $F'_{\mathrm{bias}}(t) \to F'$ for the update

$$\partial_t F'_{\mathrm{bias}}(t,z) = \frac{1}{\tau} \frac{\int f^{\mathcal{V}_t}(q)\, \psi_t^{\mathrm{eq}}(q)\, \delta_{\xi(q)-z}(dq)}{\int \psi_t^{\mathrm{eq}}(q)\, \delta_{\xi(q)-z}(dq)}$$

- General case: observed mean force

$$F'_{\mathrm{force,obs}}(t,z) = \frac{\int f^{\mathcal{V}_t}(q)\, \psi_t(q)\, \delta_{\xi(q)-z}}{\int \psi_t(q)\, \delta_{\xi(q)-z}} = \frac{\int f^{V}(q)\, \psi_t(q)\, \delta_{\xi(q)-z}}{\int \psi_t(q)\, \delta_{\xi(q)-z}} - F'_{\mathrm{bias}}(t,z)$$

  and update

$$\text{(ABF)} \qquad \partial_t F'_{\mathrm{bias}}(t,z) = h_t(F'_{\mathrm{force,obs}}(t,z)).$$

Convergence

- Consistency of the method (stationary state is $\propto \exp(-\beta(V - F \circ \xi))$)
- No general convergence result – especially, no result/strategy in the ABP case at the moment...
- Convergence for ABF in some limiting case, using entropy estimates
- Sketch of proof in a simplified geometrical setting: $\mathcal{M} = \mathbb{T} \times \mathbb{R}$ and $\xi(x, y) = x$
- Limit $\tau \to 0$ and overdamped Langevin dynamics: Fokker-Planck equation reads

$$\begin{cases} \partial_t \psi = \operatorname{div}(\nabla V \psi + \nabla \psi) - \partial_x (F_t' \psi), \\ F_t'(x) = \dfrac{\displaystyle\int \partial_x V(x, y) \psi(t, x, y) dy}{\overline{\psi}(t, x)}, \end{cases}$$

where $\overline{\psi}(t, x) = \int \psi(t, x, y) dy$

The entropy method in a simple case

- Consider $dX_t = -\nabla V(X_t)\,dt + \sqrt{2/\beta}\,dW_t$
- With $\psi_\infty(q) = Z^{-1}\mathrm{e}^{-\beta V(q)}$, rewrite the Fokker-Planck equation as

$$\partial_t \psi = \frac{1}{\beta}\nabla\cdot\left(\psi_\infty \nabla\left(\frac{\psi}{\psi_\infty}\right)\right)$$

- Entropy ($f = \psi/\psi_\infty$)

$$E(t) = -\int \psi \ln\left(\frac{\psi}{\psi_\infty}\right) = -\int f \ln f\, \psi_\infty$$

is such that

$$\partial_t E(t) = -\frac{1}{\beta}\int \frac{|\nabla f|^2}{f}\,\psi_\infty \le -\frac{1}{2\rho\beta}E(t)$$

provided ψ_∞ satisfies a logarithmic Sobolev inequality

- Since $E(t) \ge 0$ (Jensen inequality), this shows that $E(t) \to 0$ exponentially fast, and so, $\psi \to \psi_\infty$.

The entropy method in the ABF case

- Additivity $E(t) = E_M(t) + E_m(t)$ with

$$E_M(t) = \int \ln\left(\frac{\overline{\psi}(t,x)}{\overline{\psi_\infty}(t,x)}\right)\overline{\psi}(t,x)\,dx$$

$$E_m(t) = \int e_m(t,x)\,\overline{\psi}(t,x)\,dx, \qquad e_m(t,x) = \int \ln\left(\frac{\psi/\overline{\psi}}{\psi_\infty/\overline{\psi_\infty}}\right)\frac{\psi}{\overline{\psi}}\,dy$$

- Notice

$$\partial_t\overline{\psi} = \beta^{-1}\partial_{xx}\overline{\psi},$$

  which implies convergence of macroscopic entropy

- Convergence of $E_m = E - E_M$ done assuming that the conditioned measures $\psi_\infty(x,\cdot)/\overline{\psi_\infty}(x)$ satisfy LSI(ρ) (plus some algebra...)
- Global convergence rate given by the infimum of macroscopic and microscopic convergence rates

Enhancing the convergence through a selection process

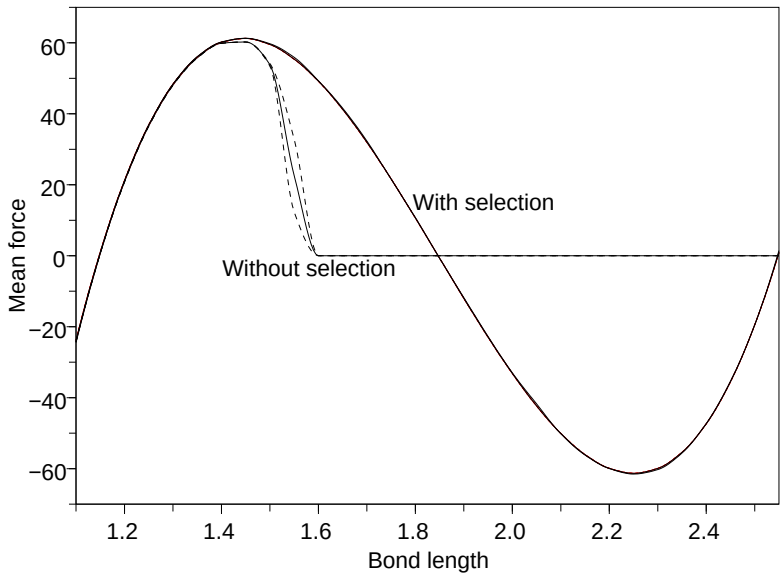
- Discretization though parallel implementation of replicas + possibly some local time averaging
- Selection step to duplicate "innovating" replicas (replicas located in regions where the sampling of the reaction coordinate is not sufficient), and kill "redundant" ones
- Jump process quantified by a field $S(t,z)$ over the reaction coordinate values: replica trajectories weighted by $\exp(\int_0^t S(s,\xi(Q_s^{i,M}))\,ds)$ $\rightarrow$ birth/death probabilities
- For example,

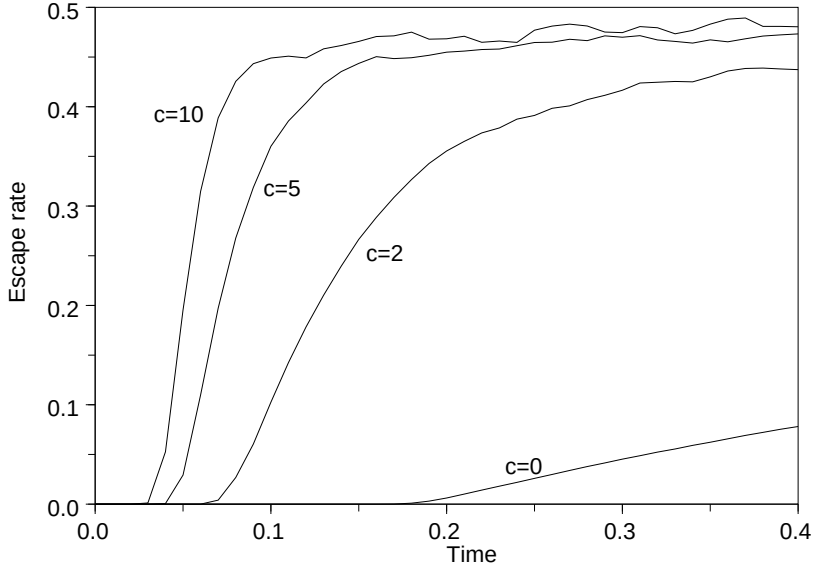
$$S = c\frac{\partial_{zz}\psi_t^\xi}{\psi_t^\xi}$$

- In the above ABF case, it then follows

$$\partial_t\psi_t^\xi = (\beta^{-1}+c)\partial_{zz}\psi_t^\xi.$$

Selection process for adaptive computations





Left: Comparison of mean force profiles computed with ABF dynamics, with and without selection (at time $t_{\mathrm{figure}} = 0.1$ and averaged over $K = 100$ independent realizations).

Right: Escape rates of the first free energy minimum as a function of time (for different values of the selection parameter).

Reduced/effective dynamics for the reaction coordinate?

Reduced dynamics. . . ?

- Mean force $\simeq$ drift for the evolution of the reaction coordinate + non-additive noise

$$d\xi_t = f(\xi_t)\,dt + \sigma(\xi_t)\,dt$$

- Can be obtained
  - from Mori-Zwanzig projection of Hamiltonian dynamics[a] + Markovian assumption
  - using conditional expectations of all-atom overdamped Langevin dynamics[b]
  - by rescaling of the motion in the directions orthogonal to the reaction coordinate[c]
- Drift and diffusion estimated in practice with short all-atom simulations

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[b] Gyongy, Mimicking the one-dimensional marginal distributions... (1986)

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