(Non)Equilibrium computation of free energy differences using Langevin dynamics

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Outline of the talk

- A brief presentation of methods to compute free energy differences
- Thermodynamic integration using Langevin dynamics
- Nonequilibrium Langevin dynamics

Computing free energy differences

Microscopic description of a classical system

- Positions q (configuration), momenta $p = M\dot{q}$ (M diagonal mass matrix)
- Microscopic description of a classical system (N particles):

$$(q,p) = (q_1, \dots, q_N,\ p_1, \dots, p_N) \in \mathcal{E}$$

- For instance, $\mathcal{E} = T^*\mathcal{D} = \mathcal{D} \times \mathbb{R}^{3N}$ with $\mathcal{D} = \mathbb{R}^{3N}$ or $\mathbb{T}^{3N}$
- More complicated situations can be considered... (constraints defining submanifolds of the phase space)
- Hamiltonian $H(q,p) = \displaystyle\sum_{i=1}^{N} \frac{p_i^2}{2m_i} + V(q_1, \dots, q_N)$
- All the physics is contained in V
- Canonical probability measure:

$$\mu(dq\,dp) = Z^{-1}\,\mathrm{e}^{-\beta H(q,p)}\,dq\,dp, \qquad \beta = \frac{1}{k_\mathrm{B}T}$$

- The aim is to compute an approximation of the high dimensional integral

$$\langle A \rangle = \int_{T^*\mathcal{D}} A(q,p)\,\mu(dq\,dp)$$

- Restated as a one-dimensional integral using ergodic properties of an irreducible dynamics for which the canonical measure is invariant:

$$\lim_{T\to+\infty} \frac{1}{T}\int_0^T A(q_t,p_t)\,dt = \int_{T^*\mathcal{D}} A(q,p)\,\mu(dq\,dp) \qquad \text{a.s.}$$

- Overdamped Langevin dynamics (momenta trivial to sample)

$$dq_t = -\nabla V(q_t)\,dt + \sqrt{\frac{2}{\beta}}\,dW_t$$

- Zero mass limit of the Langevin dynamics or the limit of the Langevin dynamics when the friction goes to infinity (with suitable time rescaling)

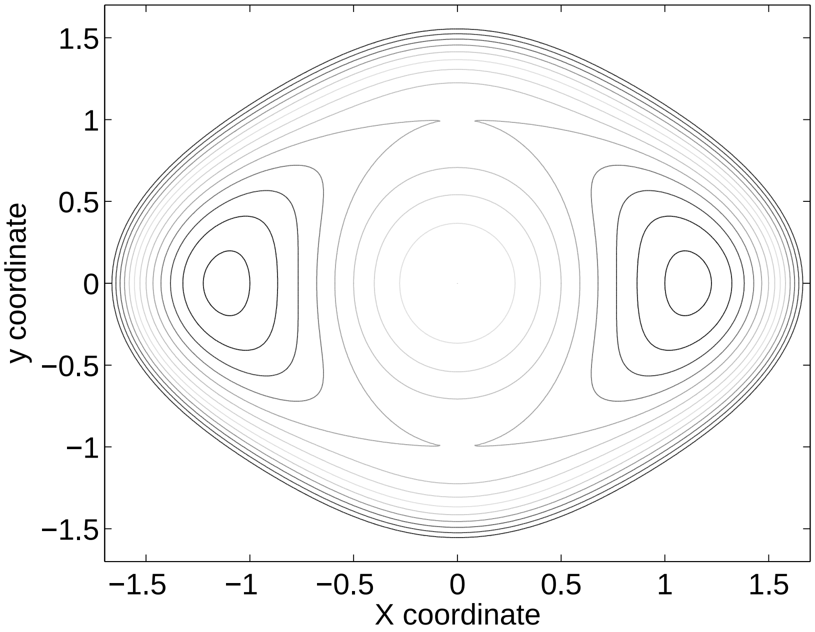
Langevin dynamics

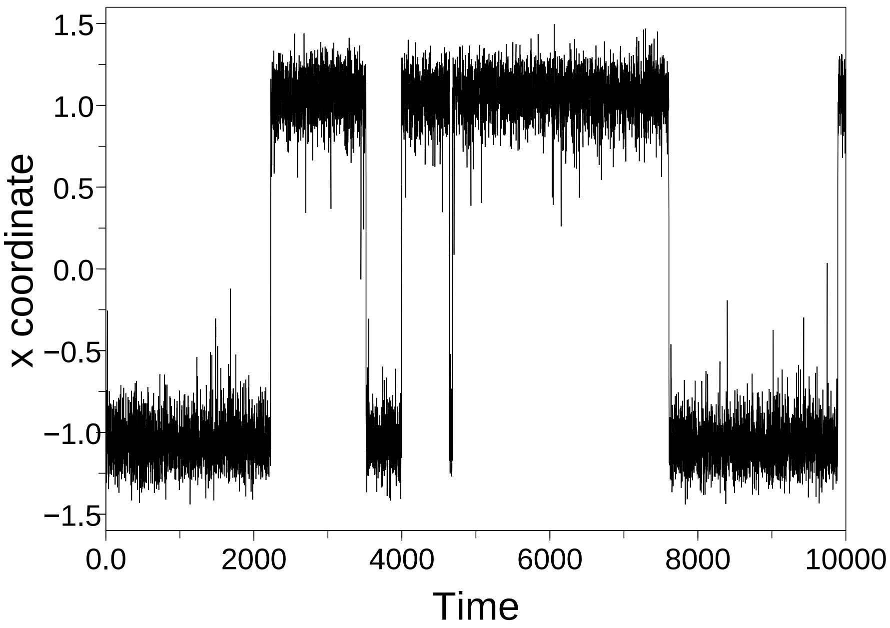
- Stochastic perturbation of the Hamiltonian dynamics
$$\begin{cases} dq_t = M^{-1} p_t \, dt \\ dp_t = -\nabla V(q_t)\, dt - \gamma(q_t) M^{-1} p_t \, dt + \sigma(q_t)\, dW_t \end{cases}$$
- Fluctuation/dissipation relation $\sigma\sigma^T = \dfrac{2}{\beta}\gamma$
- Invariance of the canonical measure when it is a stationary solution of the Fokker-Planck equation $\partial_t \psi = \mathcal{L}^* \psi$ with
$$\mathcal{L} = \{\cdot, H\} + \frac{\mathrm{e}^{\beta H}}{\beta} \mathrm{div}_p \left(\gamma \mathrm{e}^{-\beta H} \nabla_p \cdot \right)$$
and $\{A_1, A_2\} = (\nabla_q A_1)^T \nabla_p A_2 - (\nabla_p A_1)^T \nabla_q A_2$
- Irreducibility amounts to controllability (Hörmander condition)
- Numerical schemes obtained by a splitting strategy for instance (Verlet scheme + partial randomization of momenta)

Numerical discretization of the overdamped Langevin dynamics:

$$q^{n+1} = q^n - \Delta t \nabla V(q^n) + \sqrt{\frac{2\Delta t}{\beta}}\, \mathcal{G}^n$$

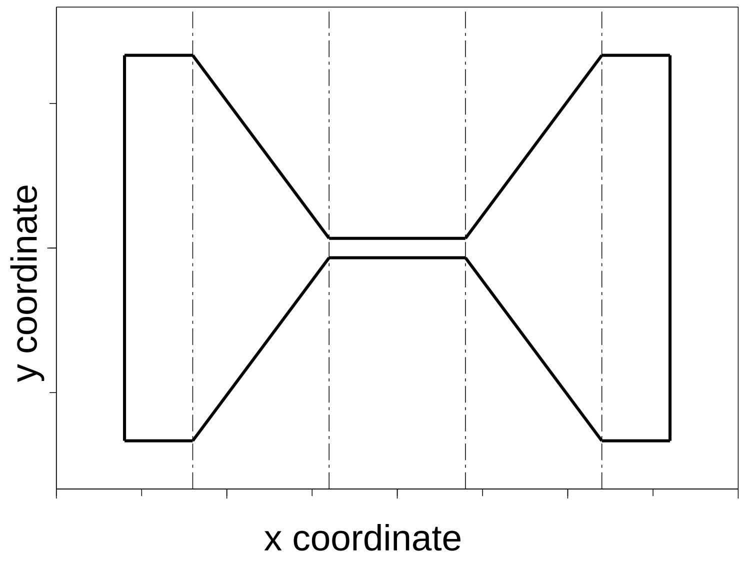
where $\mathcal{G}^n \sim \mathcal{N}(0, \mathrm{Id}_{dN})$ i.i.d.



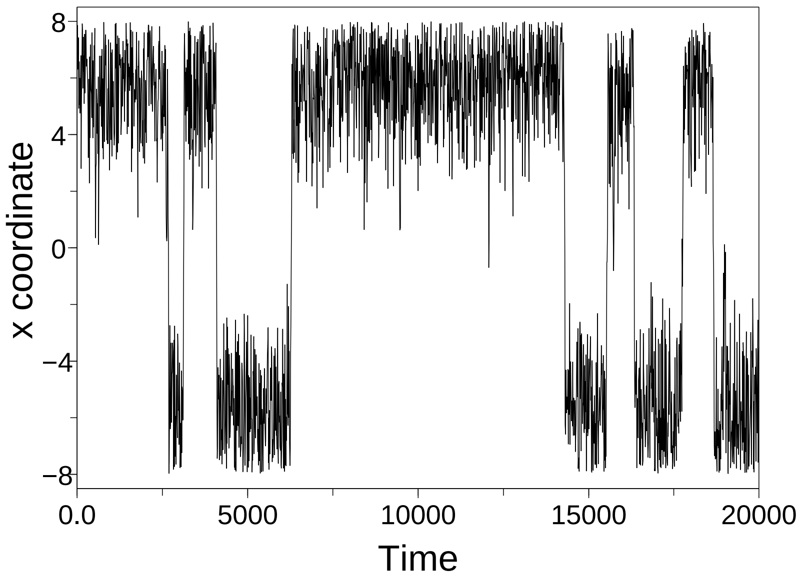


Projected trajectory in the x variable for $\Delta t = 0.01$, $\beta = 8$.

- Although the trajectory average converges to the phase-space average, the convergence may be slow...
- Slowly evolving macroscopic function of the microscopic degrees of freedom: reaction coordinate $\xi(q) \in \mathbb{R}^m$ with $m \ll N$
- Two origins : energetic or entropic barriers (in fact, free energy barriers)

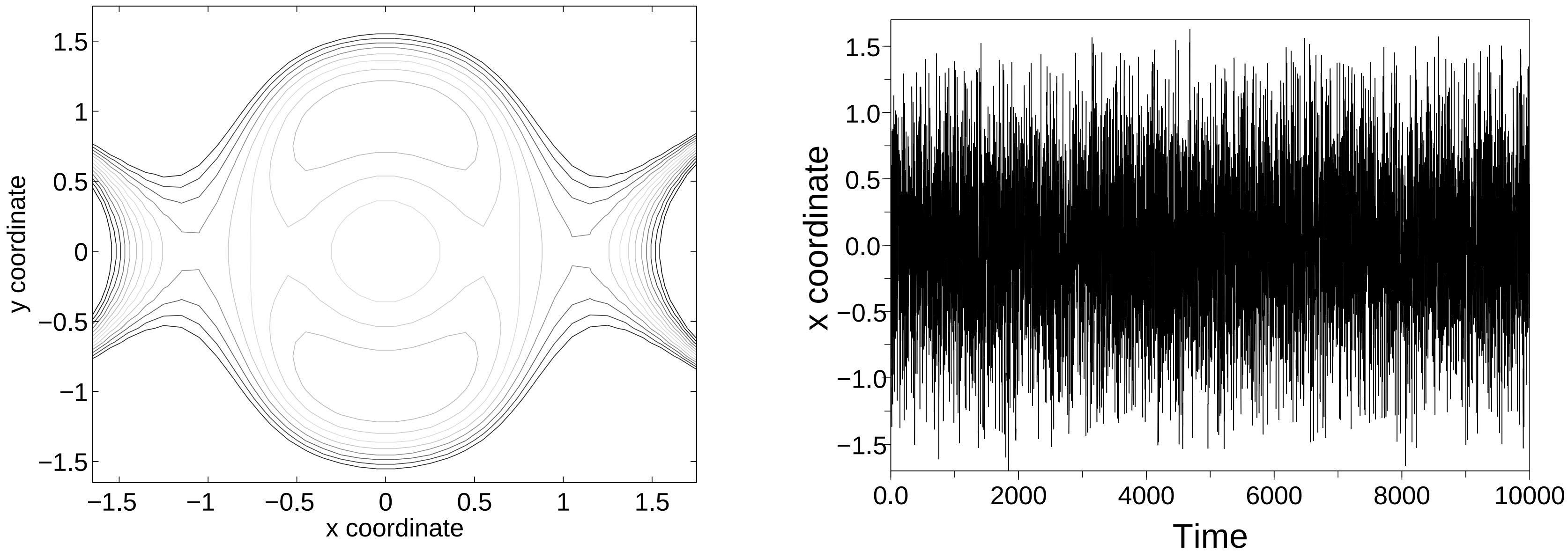


(a) Entropic barrier.



(b) Associated trajectory.

- Assume the free energy F associated with the slow direction x has been computed, and sample the modified potential $\mathcal{V}(x, y) = V(x, y) - F(x)$.



Projected trajectory in the x variable for $\Delta t = 0.01$, $\beta = 8$.

- Many more transitions! The variable x is uniformly distributed.
- Reweighting with weights $\mathrm{e}^{-\beta F(x)}$ to compute canonical averages
- Compute efficiently the free energy?

- Alchemical transition: indexed by an external parameter λ (force field parameter, magnetic field,...)

$$\Delta F = -\beta^{-1} \ln \left(\frac{\displaystyle\int_{T^*\mathcal{D}} \mathrm{e}^{-\beta H_1(q,p)}\, dq\, dp}{\displaystyle\int_{T^*\mathcal{D}} \mathrm{e}^{-\beta H_0(q,p)}\, dq\, dp} \right) \; ;$$

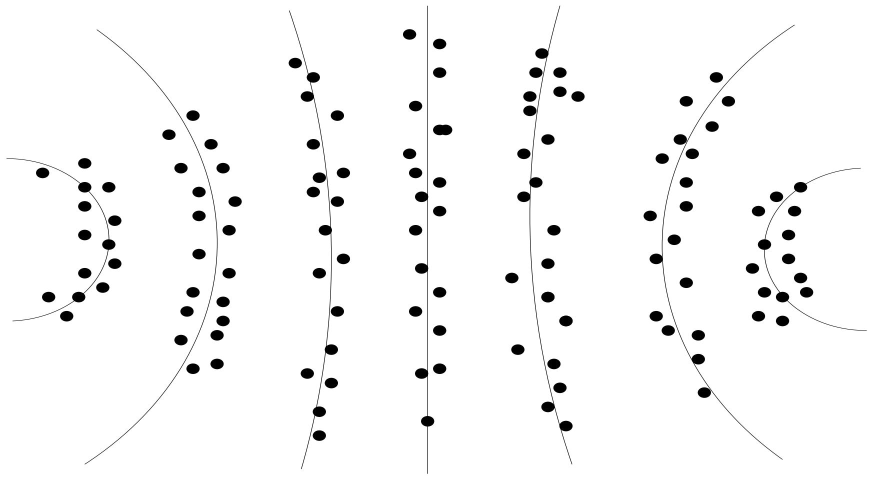
Typically, $H_\lambda = (1-\lambda)H_0 + \lambda H_1$

- (given) reaction coordinate $\xi : \mathbb{R}^{3N} \to \mathbb{R}^m$ (angle, length,...):

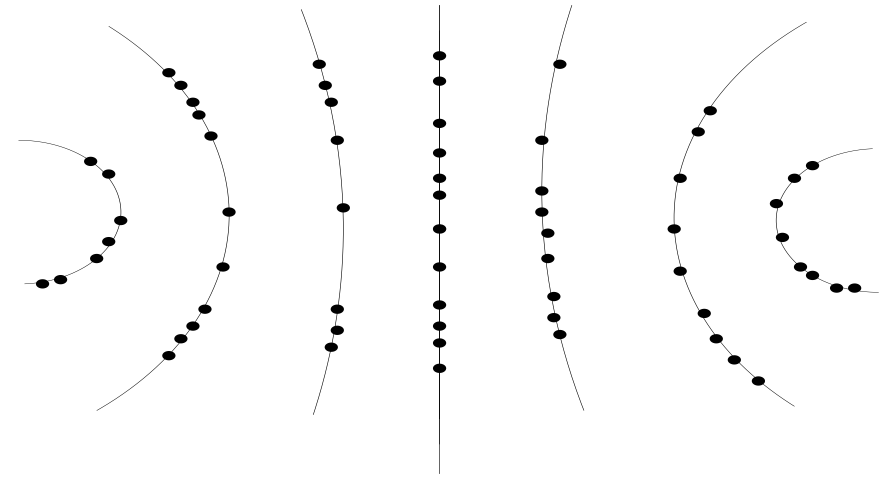
$$\Delta F = -\beta^{-1} \ln \left(\frac{\displaystyle\int_{T^*\Sigma_z} \mathrm{e}^{-\beta H(q,p)}\, \delta_{\xi(q)-z_1}(dq)\, dp}{\displaystyle\int_{T^*\Sigma_z} \mathrm{e}^{-\beta H(q,p)}\, \delta_{\xi(q)-z_0}(dq)\, dp} \right).$$

with $\Sigma_z = \left\{ q \in \mathcal{D} \,\middle|\, \xi(q) = z \right\}$. Recall $\delta_{\xi(q)-z} = |\nabla \xi|^{-1} d\sigma_{\Sigma_z}$.

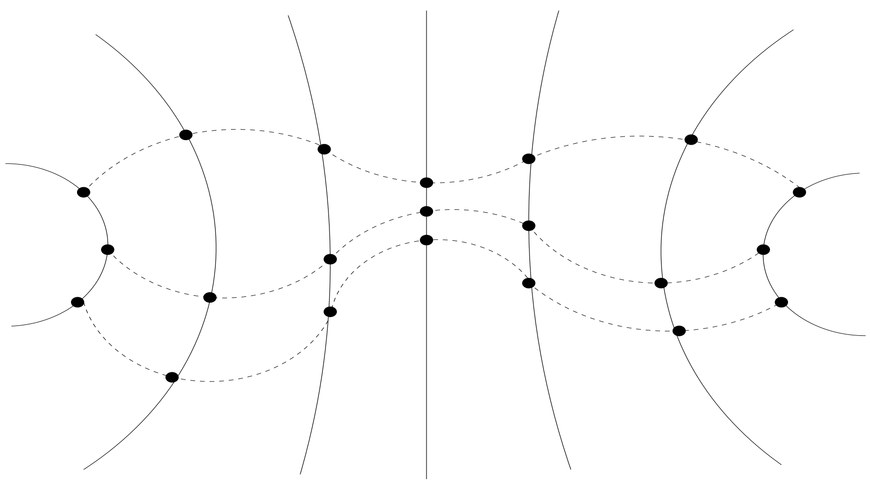
Cartoon comparison of the methods (reaction coordinate case)



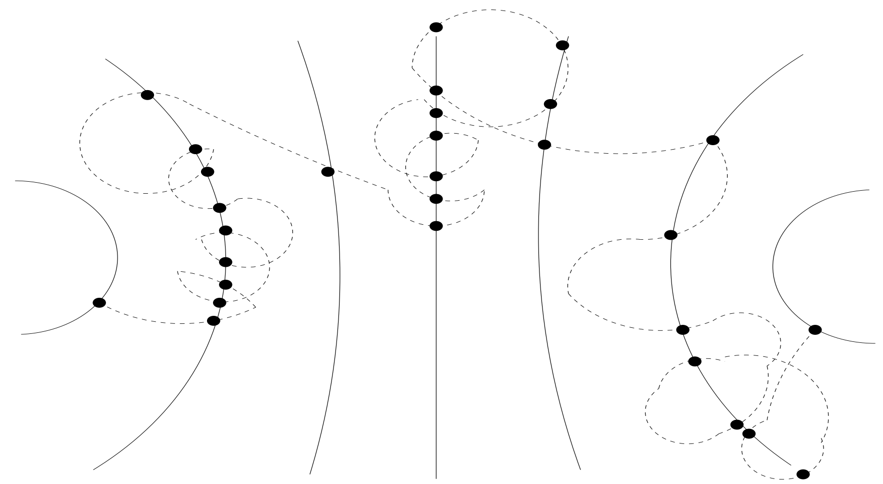
(a) Histogram method



(b) Thermodynamic integration



(c) Nonequilibrium switching dynamics



(d) Adaptive dynamics

Some elements on the scientific landscape

- We focus on the reaction coordinate case
- Histogram methods: WHAM (Kumar *et al.*), MBAR (Chodera/Shirts)
- Thermodynamic integration in the Hamiltonian case (Carter *et al.*, den Otter/Briels, Sprik/Ciccotti, Hartmann/Schütte) or for overdamped Langevin dynamics (Ciccotti/Lelièvre/Vanden-Eijnden)
- Nonequilibrium methods: overdamped case (Lelièvre/Rousset/Stoltz) or steered versions (potentials $V_\lambda(q) = V(q) + K(\xi(q) - \lambda)^2$)
- Adpative methods: adaptive biasing force (Darve/Pohorille, Chipot/Hénin), nonequilibrium metadynamics (Bussi/Laio/Parrinello), self-healing umbrella sampling (Marsili *et al.*, Dickson *et al.*)
- Aims of this work:
  - Thermodynamic integration with Langevin dynamics
  - Nonequilibrium Langevin dynamics

Thermodynamic integration with Langevin dynamics

Constrained Langevin dynamics (1)

- Consider the following Langevin process:

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

- Standard fluctuation/dissipation relation $\sigma \sigma^T = \frac{2}{\beta} \gamma$
- Hidden velocity constraint: $\frac{d\xi(q_t)}{dt} = v_\xi(q_t, p_t) = \nabla \xi(q_t)^T M^{-1} p_t = 0$
- The corresponding phase-space is $\Sigma_{\xi, v_\xi}(z, 0)$ where

$$\Sigma_{\xi, v_\xi}(z, v_z) = \left\{ (q, p) \in \mathbb{R}^{6N} \;\middle|\; \xi(q) = z, \; v_\xi(q, p) = v_z \right\}$$

- An explicit expression of the Lagrange multiplier can be found by computing the second derivative in time of the constraint

Constrained Langevin dynamics (2)

- Reformulation of the constrained Langevin dynamics as

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

- Projected fluctuation/dissipation matrices

$$(\sigma_P, \gamma_P) := (P_M \, \sigma, P_M \, \gamma \, P_M^T)$$

where $P_M(q) = \mathrm{Id} - \nabla\xi(q) G_M^{-1}(q) \nabla\xi(q)^T M^{-1}$

- Constraining force (projection of the conservative force + centrifugal term)

$$f_{\mathrm{rgd}}^M(q,p) = G_M^{-1}(q) \nabla\xi(q)^T M^{-1} \nabla V(q) - G_M^{-1}(q) \mathrm{Hess}_q(\xi)(M^{-1}p, M^{-1}p)$$

where $G_M(q) = \nabla\xi(q)^T M^{-1} \nabla\xi(q)$

Properties of the projected Langevin dynamics

- Generator of the dynamics: $\mathcal{L} = \mathcal{L}^{\mathrm{ham}} + \mathcal{L}^{\mathrm{thm}}$ with

$$\mathcal{L}^{\mathrm{thm}} = \frac{1}{\beta}\, \mathrm{e}^{\beta H} \mathrm{div}_p\Big(\mathrm{e}^{-\beta H}\, \gamma_P\, \nabla_p \,\cdot\,\Big)$$

- Invariant measure

$$\mu_{\Sigma_{\xi,v_\xi}(z,0)}(dq\,dp) = Z_{z,0}^{-1}\, \mathrm{e}^{-\beta H(q,p)}\, \sigma_{\Sigma_{\xi,v_\xi}(z,0)}(dq\,dp),$$

where $\sigma_{\Sigma_{\xi,v_\xi}(z,v_z)}(dq\,dp)$ is the phase space Liouville measure of $\Sigma_{\xi,v_\xi}(z,v_z)$ induced by the symplectic matrix J

- Reversibility: $\mathrm{Law}(q_t, p_t; 0 \le t \le T) = \mathrm{Law}(q_{T-t}, -p_{T-t}; 0 \le t \le T)$
- Ergodicity (longtime trajectorial convergence)
- The normalizing constant of this canonical distribution defines a rigid free energy (more on this later)

Numerical discretization (1)

- Splitting in a Hamiltonian part + constrained Ornstein-Uhlenbeck process
- Midpoint scheme for the momenta (reversible for the canonical measure with constraints)

$$p^{n+1/4} = p^n - \frac{\Delta t}{4}\gamma\, M^{-1}(p^n + p^{n+1/4}) + \sqrt{\frac{\Delta t}{2}}\,\sigma\,\mathcal{G}^n + \nabla\xi(q^n)\,\lambda^{n+1/4},$$

with the constraint $\nabla\xi(q^n)^T M^{-1} p^{n+1/4} = 0$

- RATTLE scheme (symplectic)

$$\left\{\begin{array}{rcl} p^{n+1/2} & = & p^{n+1/4} - \dfrac{\Delta t}{2}\nabla V(q^n) + \nabla\xi(q^n)\,\lambda^{n+1/2}, \\ q^{n+1} & = & q^n + \Delta t\, M^{-1}\, p^{n+1/2}, \\ p^{n+3/4} & = & p^{n+1/2} - \dfrac{\Delta t}{2}\nabla V(q^{n+1}) + \nabla\xi(q^{n+1})\,\lambda^{n+3/4}, \end{array}\right.$$

with $\xi(q^{n+1}) = z$ and $\nabla\xi(q^{n+1})^T M^{-1} p^{n+3/4} = 0$

- Metropolization of the RATTLE part to eliminate the time-step error
- Overdamped limit (exact sampling)

Thermodynamic integration (1)

- The free energy can be estimated from constrained samplings as

$$\begin{aligned} F(z) &= -\frac{1}{\beta}\ln\int_{\Sigma(z)\times\mathbb{R}^{3N}} \mathrm{e}^{-\beta H(q,p)}\delta_{\xi(q)-z}(dq)\,dp \\ &= F^M_{\mathrm{rgd}}(z) - \frac{1}{\beta}\ln\int_{T^*\Sigma(z)} (\det G_M)^{-1/2} d\mu_{\Sigma_{\xi,v_\xi}(z,0)} + \mathrm{C} \end{aligned}$$

with the rigid free energy (constraints on both q and p)

$$F^M_{\mathrm{rgd}}(z) = -\frac{1}{\beta}\ln\int_{\Sigma_{\xi,v_\xi}(z,0)} \mathrm{e}^{-\beta H(q,p)} d\mu_{\Sigma_{\xi,v_\xi}(z,0)}$$

- Extension to the case of molecular constraints
- Thermodynamic integration through the computation of the mean force

$$\nabla_z F^M_{\mathrm{rgd}}(z) = \int_{\Sigma_{\xi,v_\xi}(z,0)} f^M_{\mathrm{rgd}}(q,p)\,\mu_{\Sigma_{\xi,v_\xi}(z,0)}(dq\,dp)$$

Thermodynamic integration (2)

- Longtime (a.s.) convergence

$$\lim_{T \to +\infty} \frac{1}{T} \int_0^T d\lambda_t = \nabla_z F^M_{\mathrm{rgd}}(z)$$

- Variance reduction: keep only the Hamiltonian part of λ_t
- Numerical discretization: approximate the mean force using only the Lagrange multipliers from the RATTLE part:

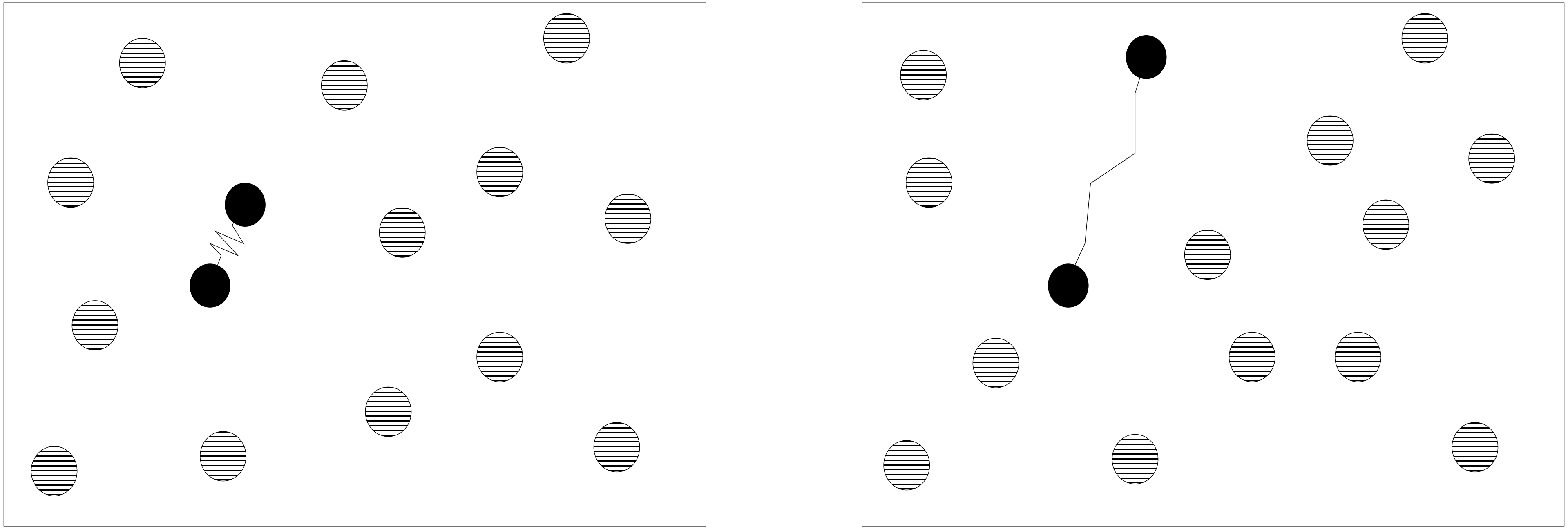
$$\nabla_z F^M_{\mathrm{rgd}}(z) \simeq \frac{1}{N} \sum_{n=0}^{N-1} f^M_{\mathrm{rgd}}(q^n, p^n) \simeq \frac{1}{N\Delta t} \sum_{n=0}^{N-1} (\lambda^{n+1/2} + \lambda^{n+3/4})$$

- Consistency result

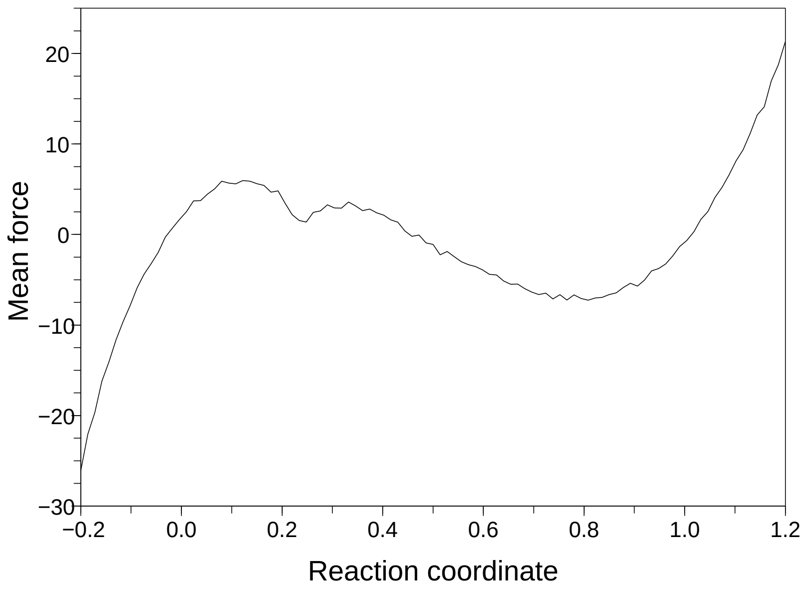
$$\lambda^{n+1/2} + \lambda^{n+3/4} = \frac{\Delta t}{2} \Big(f^M_{\mathrm{rgd}}(q^n, p^{n+1/2}) + f^M_{\mathrm{rgd}}(q^{n+1}, p^{n+1/2}) \Big) + \mathrm{O}(\Delta t^3)$$

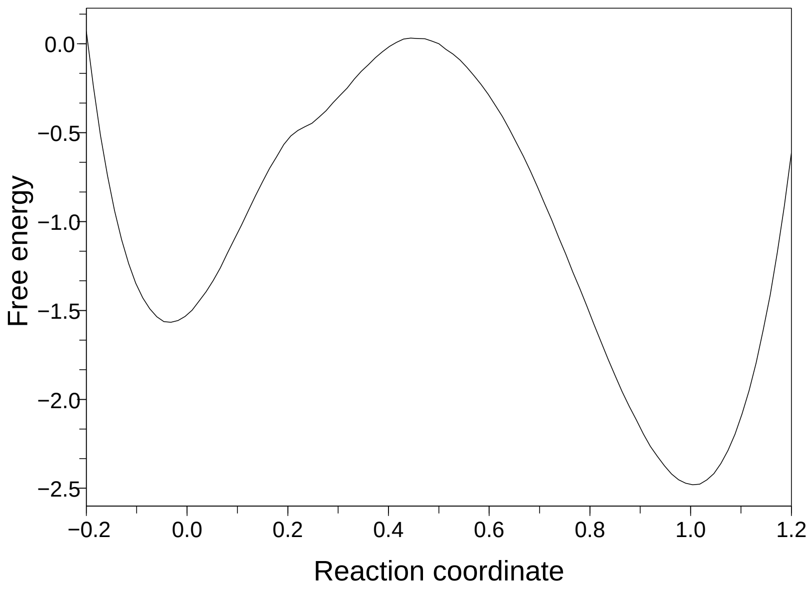
Application: Solvatation effects on conformational changes (1)

- Two particules (q_1,q_2) interacting through $V_{\mathrm{S}}(r) = h\left[1 - \frac{(r-r_0-w)^2}{w^2}\right]^2$
- Solvent: particules interacting through the purely repulsive potential $V_{\mathrm{WCA}}(r) = 4\epsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right] + \epsilon$ if $r \leq r_0$, 0 if $r > r_0$
- Reaction coordinate $\xi(q) = \frac{|q_1 - q_2| - r_0}{2w}$, compact state $\xi^{-1}(0)$, stretched state $\xi^{-1}(1)$



Application: Solvatation effects on conformational changes (2)





Left: Estimated mean force. Right: Corresponding potential of mean force.

Parameters: $\beta = 1$, $N = 100$ particles, solvent density $\rho = 0.436$, WCA interactions $\sigma = 1$ and $\varepsilon = 1$, dimer $w = 2$ and $h = 2$. Mean force estimated at the values $z_i = z_{\min} + i\Delta z$, with $z_{\min} = -0.2$, $z_{\max} = 1.2$ and $\Delta z = 0.014$, by ergodic averages obtained with the projected dynamics with Metropolis correction (time $T = 2 \times 10^4$, step size $\Delta t = 0.02$, scalar friction $\gamma = 1$).

Nonequilibrium Langevin dynamics

Presentation of the dynamics (1)

- Idea: start at equilibrium and perform a switching from the initial to the final state in a finite time T
- Schedule $z(t)$ for $t \in [0,T]$ and dynamics

$$\left\{ \begin{array}{rcl} dq_t & = & M^{-1} p_t \, dt, \\ dp_t & = & -\nabla V(q_t)\, dt - \gamma_P(q_t) M^{-1} p_t \, dt + \sigma_P(q_t)\, dW_t + \nabla \xi(q_t)\, d\lambda_t, \\ \xi(q_t) & = & z(t), \end{array} \right. \qquad (C_q(t))$$

with initial conditions $(q_0, p_0) \sim \mu_{\Sigma_{\xi, v_\xi}(z(0), \dot{z}(0))}(dq\, dp)$

- Projected fluctuation/dissipation relation $(\sigma_P, \gamma_P) := (P_M\, \sigma, P_M\, \gamma\, P_M^T)$ so that the noise act only in the direction orthogonal to $\nabla \xi$
- Hidden constraint on the reaction coordinate velocity $v_\xi(q,p) = \dot{z}(t)$

- Backward dynamics: start at equilibrium for the final value of the schedule, switching with a time-reversed schedule $t' \mapsto z(T-t')$
- Initial conditions $(q_0^{\mathrm{b}}, p_0^{\mathrm{b}}) \sim \mu_{\Sigma_{\xi,v_\xi}(z(T),\dot{z}(T))}(dq\,dp)$ and evolution

$$\begin{cases} dq_{t'}^{\mathrm{b}} = -M^{-1}p_{t'}^{\mathrm{b}}dt', \\ dp_{t'}^{\mathrm{b}} = \nabla V(q_{t'}^{\mathrm{b}})\,dt' - \gamma_P(q_{t'}^{\mathrm{b}})M^{-1}p_{t'}^{\mathrm{b}}\,dt' + \sigma_P(q_{t'}^{\mathrm{b}})\,dW_{t'}^{\mathrm{b}} + \nabla\xi(q_{t'}^{\mathrm{b}})\,d\lambda_{t'}^{\mathrm{b}}, \\ \xi(q_{t'}^{\mathrm{b}}) = z(T-t') \end{cases}$$

- The generator of the forward dynamics is (Gram matrix $\Gamma = \{\Xi, \Xi\}$, $\zeta = (z, \dot{z})$)

$$\mathcal{L}_t^{\mathrm{f}} = \{\,\cdot\,, H\}_\Xi + \mathcal{L}_\Xi^{\mathrm{thm}} + \{\cdot, \Xi\}\,\Gamma^{-1}\dot{\zeta}(t)$$

while the generator of the backward dynamics is $\mathcal{L}_{t'}^{\mathrm{b}} = \mathcal{R}\,\mathcal{L}_{T-t'}^{\mathrm{f}}\,\mathcal{R}$ (where $\mathcal{R} : \phi \mapsto \phi \circ S$ is the momentum flip operator with $S(q,p) = (q,-p)$)

- Rigid free energy $F_{\rm rgd}^{M}(z,v_z) = -\frac{1}{\beta}\ln\int_{\Sigma_{\xi,v_\xi}(z,v_z)} \mathrm{e}^{-\beta H(q,p)}d\mu_{\Sigma_{\xi,v_\xi}(z,v_z)}$
- Actual free energy recovered from the difference $F(z) - F_{\rm rgd}^{\xi,v_\xi}(z,v_z)$, which equals, up to an unimportant additive constant:

$$-\frac{1}{\beta}\ln\int_{\Sigma_{\xi,v_\xi}(z,v_z)} (\det G_M(q))^{-1/2}\exp\left(\frac{\beta}{2}v_z^T G_M^{-1}(q)v_z\right)\,\mu_{\Sigma_{\xi,v_\xi}(z,v_z)}(dq\,dp)$$

- Work performed during the switching: several expressions
  - Force times displacement: $\mathcal{W}_{0,T}\left(\{q_t,p_t\}_{0\le t\le T}\right) = \int_0^T \dot z(t)^T d\lambda_t$
  - Energy variations: $\mathcal{W}_{0,T}\left(\{q_t,p_t\}_{0\le t\le T}\right) = \int_0^T w(t,q_t,p_t)\,dt$ where $w(t,q,p) = \dot\zeta(t)^T\Gamma^{-1}\{\Xi,H\}(q,p) = \left(\frac{d}{dh}H\circ\Phi_{t,t+h}\right)\Big|_{h=0}(q,p)$ with Φ the flow of the switched Hamiltonian dynamics

Jarzynski-Crooks relation

- For any bounded path functional $\varphi_{[0,T]}$,

$$\frac{Z_{z(T),\dot{z}(T)}}{Z_{z(0),\dot{z}(0)}} = \frac{\mathbb{E}\left(\varphi_{[0,T]}\left(\{q_t,p_t\}_{0\le t\le T}\right)\, \mathrm{e}^{-\beta\mathcal{W}_{0,T}\left(\{q_t,p_t\}_{t\in[0,T]}\right)}\right)}{\mathbb{E}\left(\varphi^{\mathrm{r}}_{[0,T]}\left(\{q^{\mathrm{b}}_{t'},p^{\mathrm{b}}_{t'}\}_{0\le t'\le T}\right)\right)}$$

where $(\,\cdot\,)^{\mathrm{r}}$ denotes the composition with the operation of time reversal of paths:

$$\varphi^{\mathrm{r}}_{[0,T]}\left(\{q^b_{t'},p^b_{t'}\}_{0\le t'\le T}\right) = \varphi_{[0,T]}\left(\{q^b_{T-t},p^b_{T-t}\}_{0\le t\le T}\right)$$

- This leads in particular to the following free energy estimator

$$F(z(T)) - F(z(0)) = -\frac{1}{\beta}\ln\frac{\mathbb{E}\left(\mathrm{e}^{-\beta\left[\mathcal{W}_{0,T}\left(\{q_t,p_t\}_{t\in[0,T]}\right)+C(T,q_T)\right]}\right)}{\mathbb{E}\left(\mathrm{e}^{-\beta C(0,q_0)}\right)}$$

with the corrector $C(t,q) = \dfrac{1}{2\beta}\ln\Big(\det G_M(q)\Big) - \dfrac{1}{2}\dot{z}(t)^T G_M^{-1}(q)\dot{z}(t)$

- Standard methods can then be used (bridge estimators, etc)

Some elements on the proof

- The proof relies on the following balance condition

$$\int_{\Sigma_{\xi,v_\xi}(z(t),\dot z(t))} \left(\varphi_1 \mathcal{L}_t^{\mathrm{f}}(\varphi_2) - \varphi_2 \mathcal{L}_{T-t}^{\mathrm{b}}(\varphi_1)\right) \mathrm{e}^{-\beta H} \, d\sigma_{\Sigma_{\xi,v_\xi}(z(t),\dot z(t))}$$
$$= \int_{\Sigma_{\xi,v_\xi}(z(t),\dot z(t))} \beta w(t,\cdot) \varphi_1 \varphi_2 \mathrm{e}^{-\beta H} \, d\sigma_{\Sigma_{\xi,v_\xi}(z(t),\dot z(t))}$$
$$+ \frac{d}{dt}\left(\int_{\Sigma_{\xi,v_\xi}(z(t),\dot z(t))} \varphi_1 \varphi_2 \mathrm{e}^{-\beta H} \, d\sigma_{\Sigma_{\xi,v_\xi}(z(t),\dot z(t))} \right)$$

- Left-hand side: detailed balance contribution
- Right-hand side: evolution of the measure and work correction

- Fluctuation/dissipation part (no Lagrange multiplier needed)

$$p^{n+1/4} = p^n - \frac{\Delta t}{4}\gamma_P(q^n) M^{-1}(p^{n+1/4} + p^n) + \sqrt{\frac{\Delta t}{2}}\sigma_P(q^n)\mathcal{G}^n$$

- Hamiltonian part for the forward evolution

$$\begin{cases} p^{n+1/2} = p^{n+1/4} - \dfrac{\Delta t}{2}\nabla V(q^n) + \nabla\xi(q^n)\lambda^{n+1/2}, & \\ q^{n+1} = q^n + \Delta t \ M^{-1} p^{n+1/2}, & \\ \xi(q^{n+1}) = z(t_{n+1}), & (C_q) \\ p^{n+3/4} = p^{n+1/2} - \dfrac{\Delta t}{2}\nabla V(q^{n+1}) + \nabla\xi(q^{n+1})\lambda^{n+3/4}, & \\ \nabla\xi(q^{n+1})^T M^{-1} p^{n+3/4} = \dfrac{z(t_{n+2}) - z(t_{n+1})}{\Delta t}, & (C_p) \end{cases}$$

which defines a symplectic map

$$\Phi^n \ : \ \Sigma_{\xi,v_\xi}\left(z(t_n), \frac{z(t_{n+1}) - z(t_n)}{\Delta t}\right) \to \Sigma_{\xi,v_\xi}\left(z(t_{n+1}), \frac{z(t_{n+2}) - z(t_{n+1})}{\Delta t}\right)$$

Discrete Jarzynski-Crooks equality: Alchemical case

- Idea in the alchemical case
- Discrete schedule $\{\lambda(0), \ldots, \lambda(t_{N_T})\}$ with $N_T \Delta t = T$
- Initial conditions $(q^0, p^0) \sim \mu_0(dq\, dp) = Z_0^{-1} \exp\left(-\beta H_{\lambda(0)}(q,p)\right)\, dq\, dp$
- Successive updates of the parameter and the configuration:
  - Change the parameter from $\lambda(n\Delta t)$ to $\lambda((n+1)\Delta t)$
  - Update work: $\mathcal{W}^{n+1/2} = \mathcal{W}^n + H_{\lambda((n+1)\Delta t)}(q^n, p^n) - H_{\lambda(n\Delta t)}(q^n, p^n)$
  - Update the configuration using the Verlet map Φ^{n+1} associated with the Hamiltonian $H_{\lambda((n+1)\Delta t)}$
  - $\mathcal{W}^{n+1} = \mathcal{W}^{n+1/2} + H_{\lambda((n+1)\Delta t)}(q^{n+1}, p^{n+1}) - H_{\lambda((n+1)\Delta t)}(q^n, p^n)$
- Total work: $\mathcal{W}^n = H_{\lambda(n\Delta t)}(q^n, p^n) - H_{\lambda(0)}(q^0, p^0)$
- It can be checked that $\mathbb{E}\left(\mathrm{e}^{-\beta \mathcal{W}^n}\right) = \dfrac{Z_n}{Z_0}$ for any value of Δt such that the Verlet scheme is stable
- Extension to path functionals

Discrete Jarzynski-Crooks equality: The reaction coordinate case

- Discrete schedule $\{z(0), \dots, z(t_{N_T})\}$
- Initial conditions $(q^0, p^0) \sim \mu_{\Sigma_{\xi, v_\xi}\left(z(t_0), \frac{z(t_1)-z(t_0)}{\Delta t}\right)}(dq\, dp)$ and $(q^{\mathrm{b},0}, p^{\mathrm{b},0}) \sim \mu_{\Sigma_{\xi, v_\xi}\left(z(t_{N_T}), \frac{z(t_{N_T+1})-z(t_{N_T})}{\Delta t}\right)}(dq\, dp)$
- Initial work $\mathcal{W}^0 = 0$, and work update

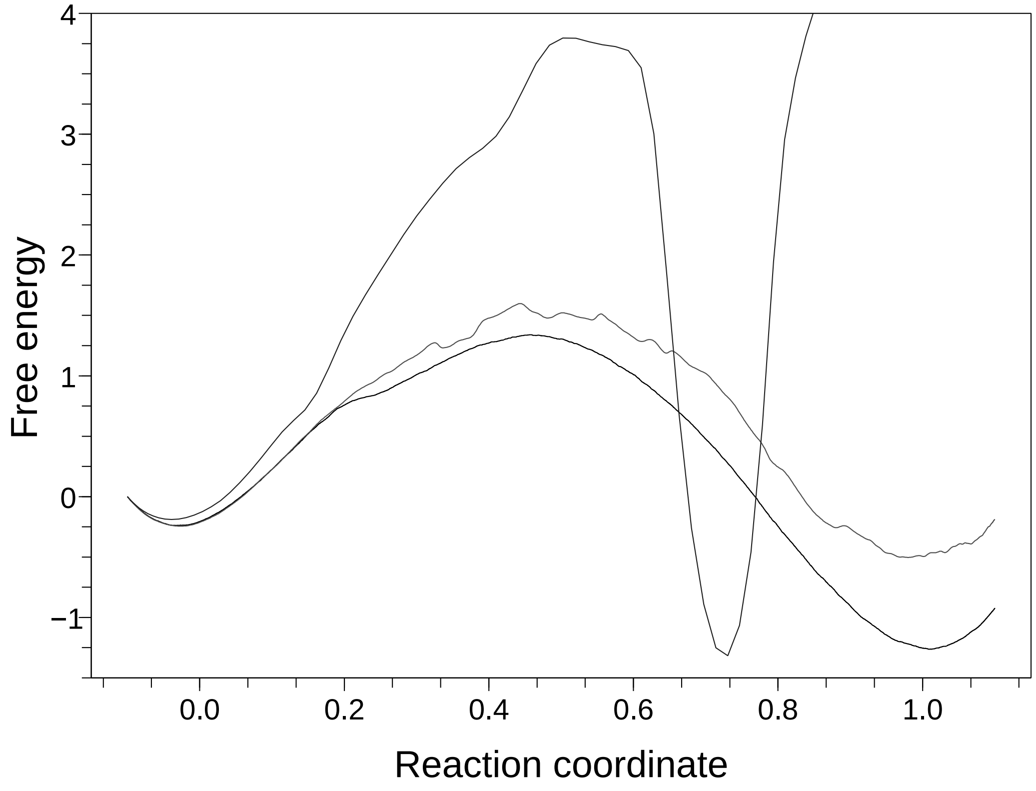
$$\mathcal{W}^{n+1} = \mathcal{W}^n + H(q^{n+1}, p^{n+3/4}) - H(q^n, p^{n+1/4})$$

- Time-step error free estimator of the free energy difference:

$$\frac{Z_{z(N_T), \frac{z(t_{N_T+1})-z(t_{N_T})}{\Delta t}}}{Z_{z(t_0), \frac{z(t_1)-z(t_0)}{\Delta t}}} = \frac{\mathbb{E}\left(\varphi_{[0,N_T]}\left(\{q^n, p^n\}_{0 \le n \le N_T}\right) \mathrm{e}^{-\beta \mathcal{W}^{N_T}}\right)}{\mathbb{E}\left(\varphi^{\mathrm{r}}_{[0,N_T]}\left(\{q^{\mathrm{b},n'}, p^{\mathrm{b},n'}\}_{0 \le n' \le N_T}\right)\right)}$$

- Overdamped limit $\dfrac{\Delta t}{4}\gamma = M = \dfrac{\Delta t}{2}\mathrm{Id}$: no bias due to the finite time-step in the estimator

Application: Solvatation effects on conformational changes



Estimated free energy profiles for $T = 1$ with $M = 10^5$ (top curve), $T = 10$ with $M = 10^4$ and $T = 100$ with $M = 10^3$ (smoothest curve).

Same parameters as before, except $\Delta t = 0.01$. Schedule $z(t) = z_{\min} + (z_{\max} - z_{\min})\frac{t}{T}$ with $z_{\min} = -0.1$ and $z_{\max} = 1.1$.

References

References

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