# *(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)

- 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

$$\mathcal{L} = \{\cdot, H\} + \frac{\mathrm{e}^{\beta H}}{\beta} \mathrm{div}_p \left( \gamma \mathrm{e}^{-\beta H} \nabla_p \cdot \right)$$

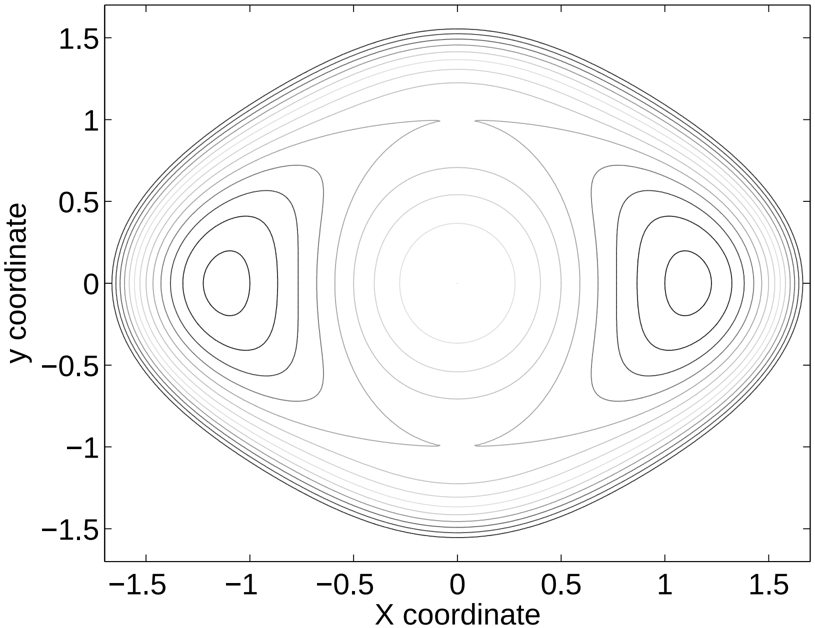
and $\{A_1, A_2\} = (\nabla A_1)^T J \nabla A_2 = (\nabla_q A_1)^T \nabla_p A_2 - (\nabla_p A_1)^T \nabla_q A_2$

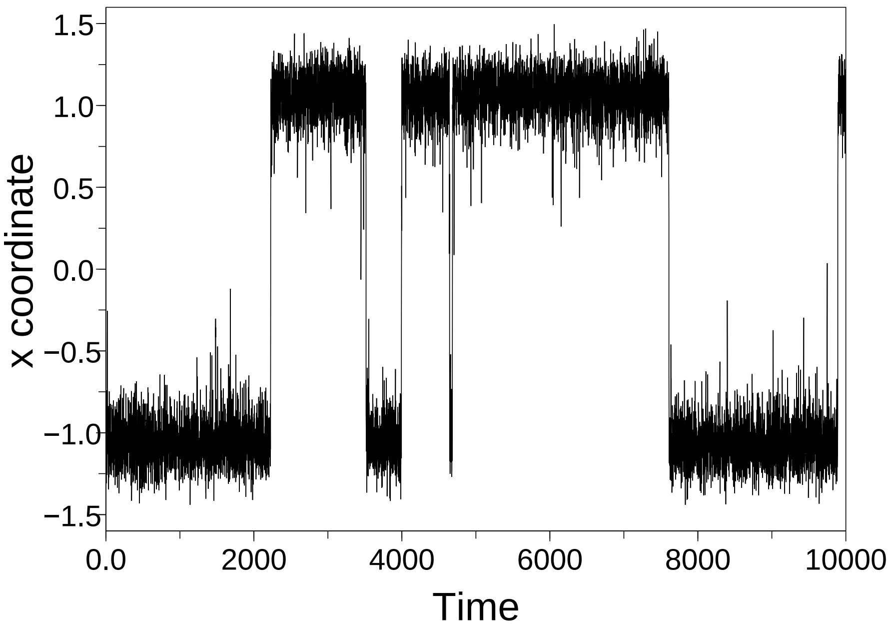
- Irreducibility amounts to controllability (Hörmander condition)
- Numerical schemes obtained by a splitting strategy for instance (Verlet scheme + partial randomization of momenta)

Numerical discretization of the overdamped Langevin dynamics:

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

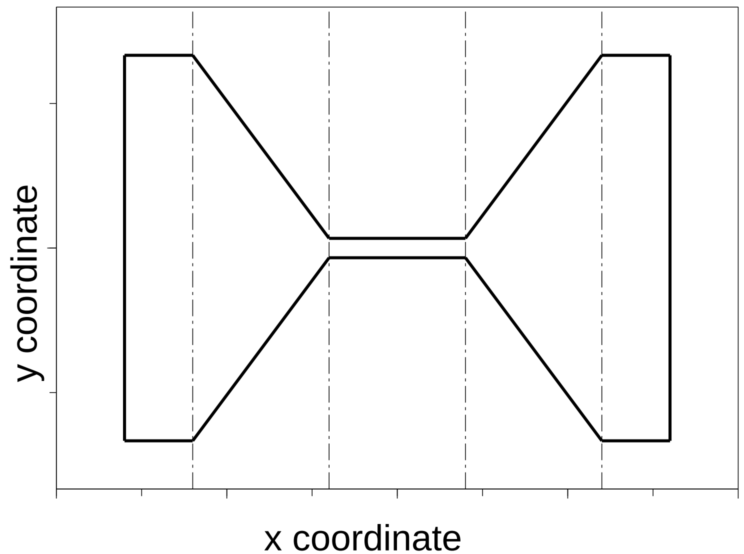
where $\mathcal{G}^n \sim \mathcal{N}(0, \mathrm{Id}_{dN})$ i.i.d.



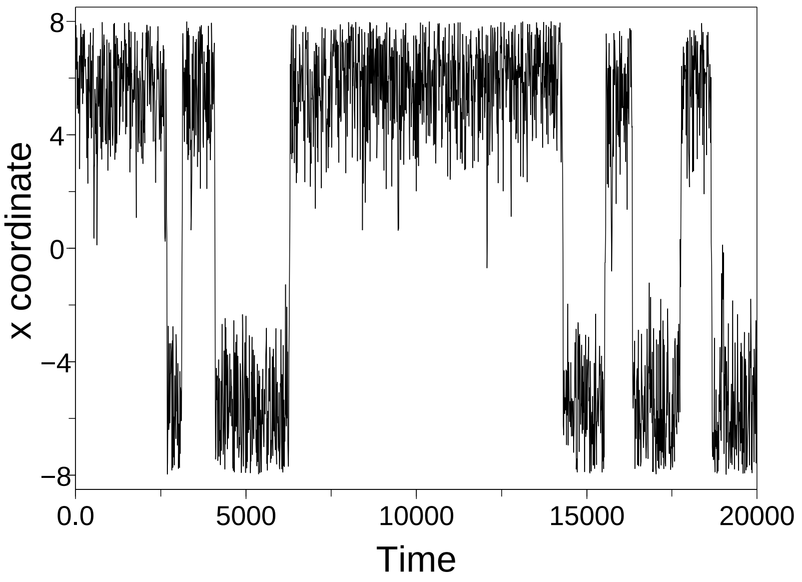




Projected trajectory in the $x$ variable for $\Delta t = 0.01$, $\beta = 8$.

- 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)



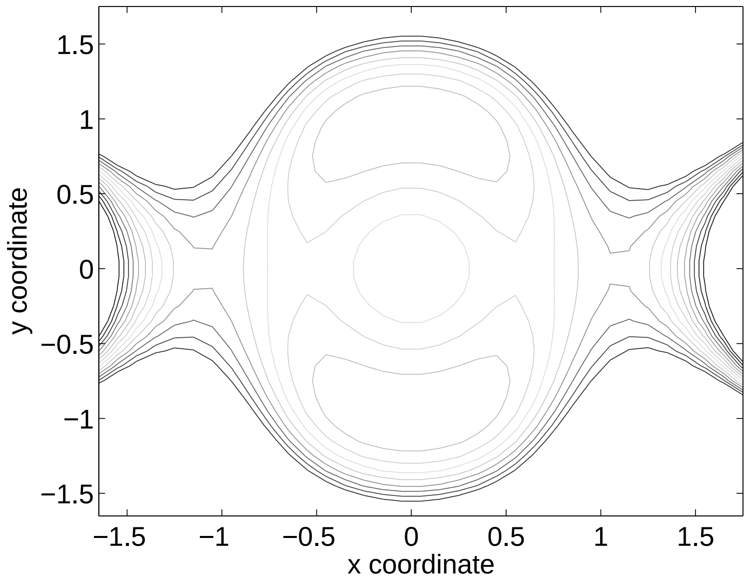

(a) Entropic barrier.

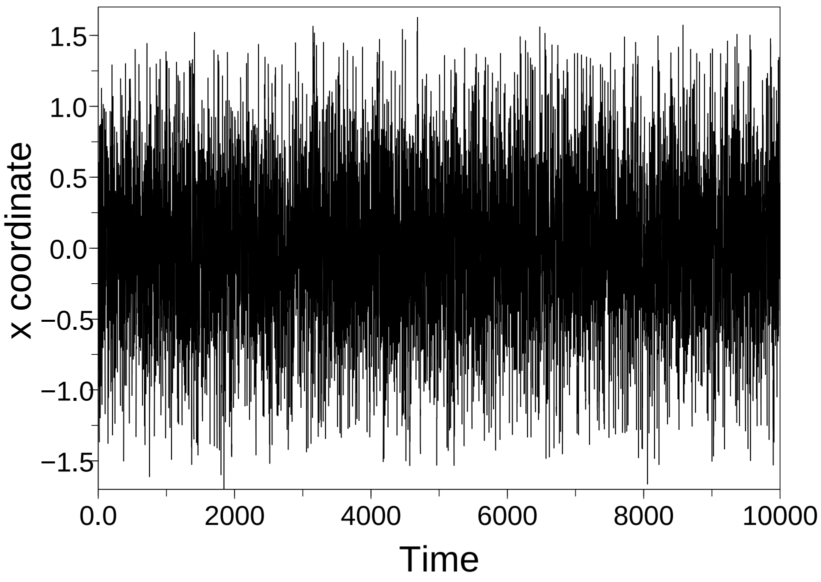



(b) Associated trajectory.

# *Metastability (3)*

- 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?

## Computation of free energy differences

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

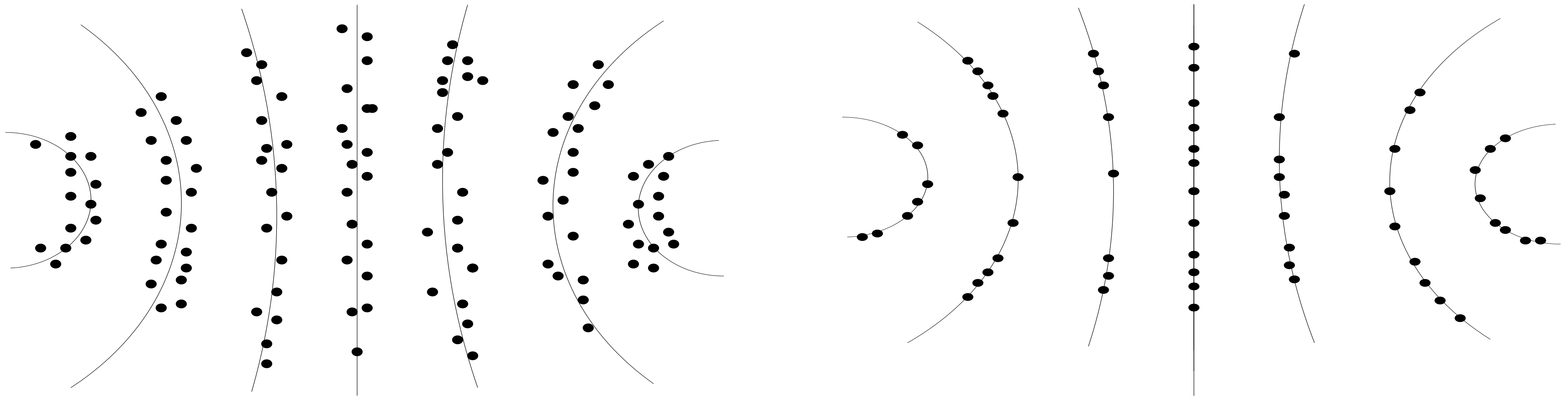
$$\Delta F = -\beta^{-1} \ln \left( \frac{\displaystyle\int_{T^*\mathcal{D}} \mathrm{e}^{-\beta H_1(q,p)}\, dq\, dp}{\displaystyle\int_{T^*\mathcal{D}} \mathrm{e}^{-\beta H_0(q,p)}\, dq\, dp} \right) ;$$

Typically, $H_\lambda = (1-\lambda)H_0 + \lambda H_1$. Other parametrizations possible (see Gelman and Meng, *Stat. Sci.*, 1998)

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

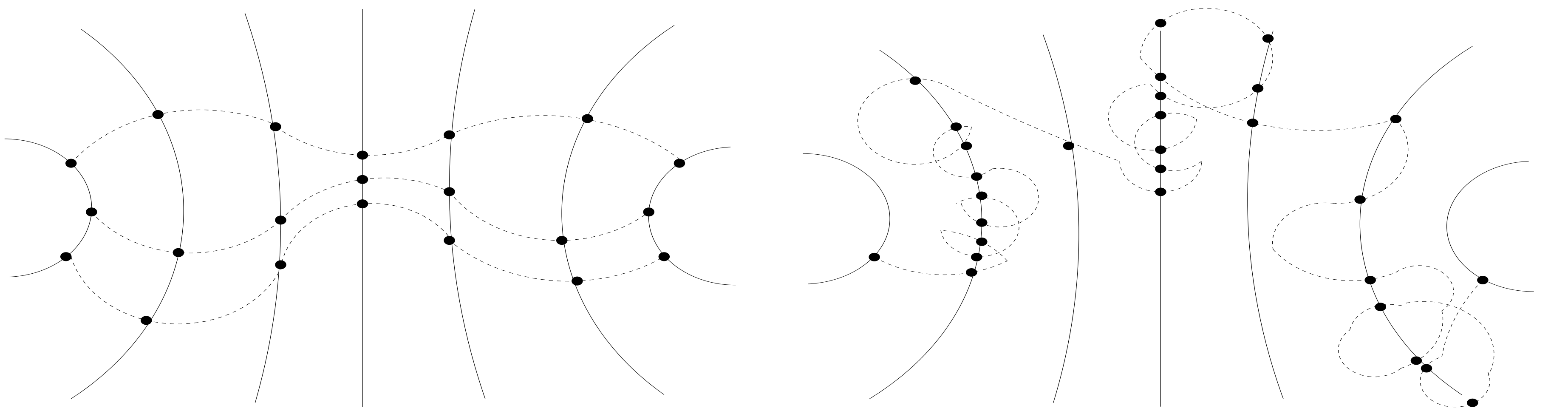
$$\Delta F = -\beta^{-1} \ln \left( \frac{\displaystyle\int_{\Sigma(z)\times\mathbb{R}^{3N}} \mathrm{e}^{-\beta H(q,p)}\, \delta_{\xi(q)-z_1}(dq)\, dp}{\displaystyle\int_{\Sigma(z)\times\mathbb{R}^{3N}} \mathrm{e}^{-\beta H(q,p)}\, \delta_{\xi(q)-z_0}(dq)\, dp} \right) .$$

with $\Sigma(z) = \left\{ q \in \mathcal{D} \,\middle|\, \xi(q) = z \right\}$



(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) and HMC (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), Wang-Landau, self-healing umbrella sampling (Marsili *et al.*, Dickson *et al.*), etc
- 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

- Invariant measure (reversibility and detailed balance up to momentum reversal, ergodicity)

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

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 $J$

- The free energy can be estimated from constrained samplings as

$$F(z) = F_{\mathrm{rgd}}^{M}(z) - \frac{1}{\beta}\ln\int_{\Sigma_{\xi,v_\xi}(z,0)} (\det G_M)^{-1/2} d\mu_{\Sigma_{\xi,v_\xi}(z,0)} + \mathrm{C}$$

with rigid free energy $F_{\mathrm{rgd}}^{M}(z) = -\dfrac{1}{\beta}\ln\displaystyle\int_{\Sigma_{\xi,v_\xi}(z,0)} \mathrm{e}^{-\beta H(q,p)} d\mu_{\Sigma_{\xi,v_\xi}(z,0)}$

- Thermodynamic integration through the computation of the mean force

$$\nabla_z F_{\mathrm{rgd}}^{M}(z) = \int_{\Sigma_{\xi,v_\xi}(z,0)} f_{\mathrm{rgd}}^{M}(q,p)\,\mu_{\Sigma_{\xi,v_\xi}(z,0)}(dq\,dp)$$

# *Numerical discretization*

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

- Overdamped limit obtained when $\dfrac{\Delta t}{4}\gamma = M \propto \mathrm{Id}$
- Metropolization of the RATTLE part to eliminate the time-step error

- Longtime (a.s.) convergence

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

- No second order derivatives of $\xi$ needed!
- Variance reduction: keep only the Hamiltonian part of $\lambda_t$
- Numerical discretization: approximate the mean force using only the Lagrange multipliers from the RATTLE part:

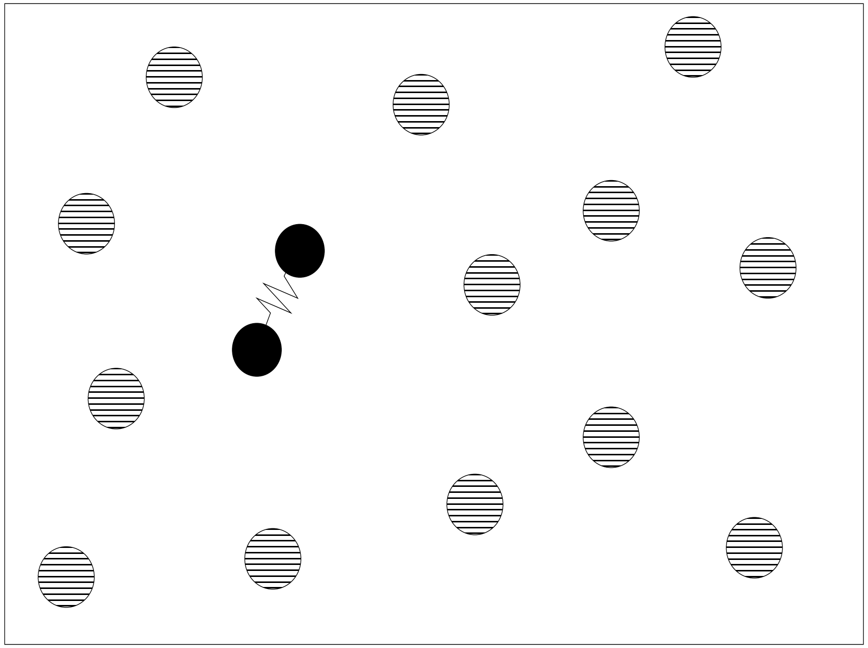
$$\nabla_z F^M_{\mathrm{rgd}}(z) \simeq \frac{1}{N} \sum_{n=0}^{N-1} f^M_{\mathrm{rgd}}(q^n, p^n) \simeq \frac{1}{N \Delta t} \sum_{n=0}^{N-1} (\lambda^{n+1/2} + \lambda^{n+3/4})$$

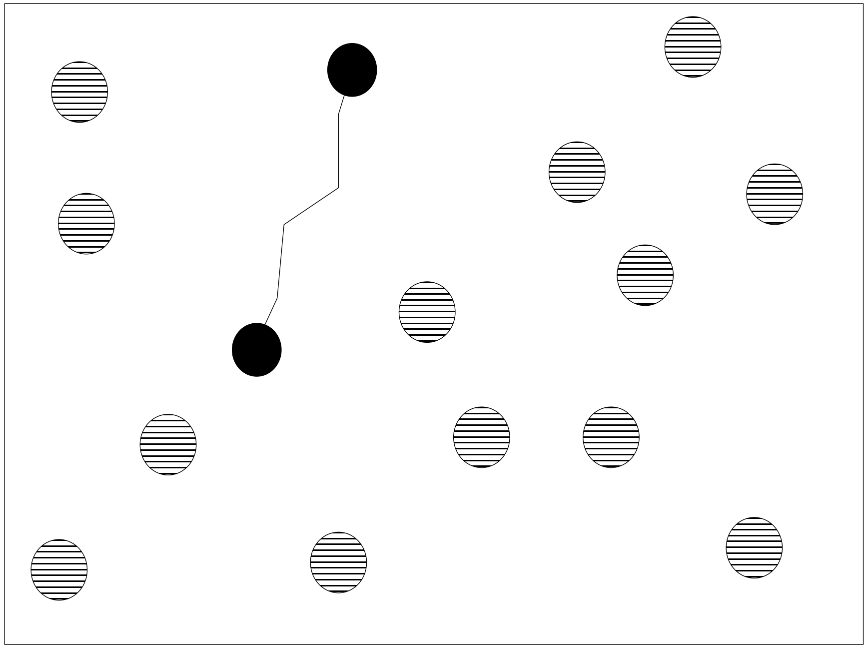
- Consistency result

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

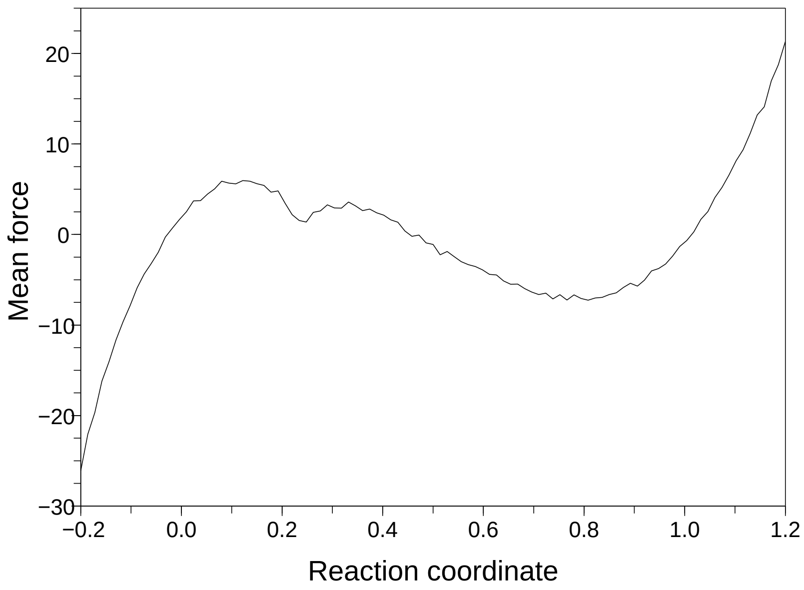
# Application: Solvatation effects on conformational changes (1)

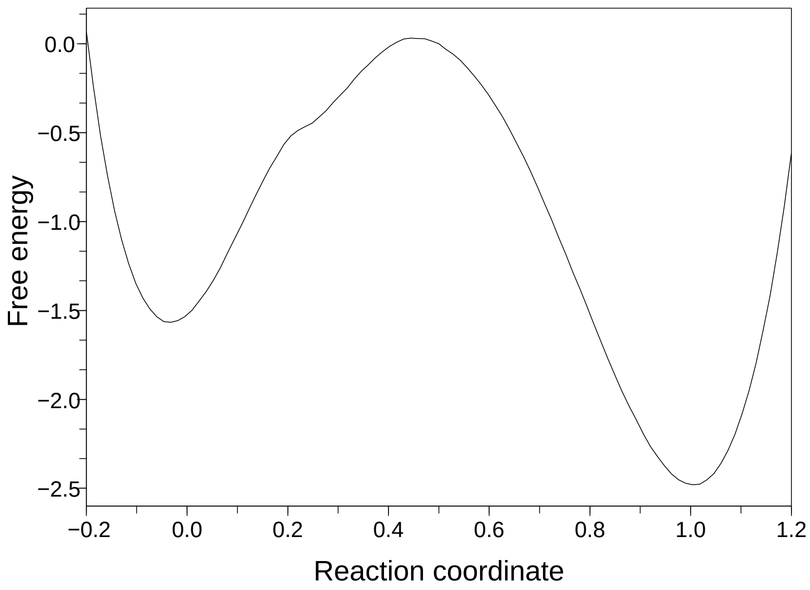
- Two particules ($q_1$,$q_2$) interacting through $V_S(r) = h\left[1 - \frac{(r - r_0 - w)^2}{w^2}\right]^2$
- Solvent: particules interacting through the purely repulsive potential $V_{WCA}(r) = 4\epsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^6\right] + \epsilon$ if $r \leq r_0$, 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

- 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 nonequilibrium dynamics

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

with equilibrium 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 $v_\xi(q,p) = \dot{z}(t)$
- A computation shows $d\lambda_t = f_{\mathrm{rgd}}^M(q_t, p_t)\, dt + G_M^{-1}(q_t) \ddot{z}(t)\, dt$
- Not the same dynamics as in Latorre/Hartmann/Schütte

- Rigid free energy $F_{\mathrm{rgd}}^{M}(z,v_z) = -\frac{1}{\beta}\ln \int_{\Sigma_{\xi,v_\xi}(z,v_z)} \mathrm{e}^{-\beta H(q,p)} d\mu_{\Sigma_{\xi,v_\xi}(z,v_z)}$
- Actual free energy recovered from the difference $F(z) - F_{\mathrm{rgd}}^{\xi,v_\xi}(z,v_z)$, 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 $\Phi$ the flow of the switched Hamiltonian dynamics

# *Jarzynski-Crooks relation*

- Work fluctuation relation

$$\frac{Z_{z(T),\dot{z}(T)}}{Z_{z(0),\dot{z}(0)}} = \mathbb{E}\left(\mathrm{e}^{-\beta \mathcal{W}_{0,T}\left(\{q_t,p_t\}_{t\in[0,T]}\right)}\right)$$

- More general result involving backward nonequilibrium dynamics and path functionals
- 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 $C(t,q) = \frac{1}{2\beta}\ln\left(\det G_M(q)\right) - \frac{1}{2}\dot{z}(t)^T G_M^{-1}(q)\dot{z}(t)$

- Standard methods can then be used (bridge estimators, etc)
- Exact time-discrete version (no time error)

# Numerical schemes: splitting strategy

- 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 (symplectic map)

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

- Work update $\mathcal{W}^{n+1} = \mathcal{W}^n + H(q^{n+1}, p^{n+3/4}) - H(q^n, p^{n+1/4})$
- Overdamped limit $\dfrac{\Delta t}{4}\gamma = M = \dfrac{\Delta t}{2}\mathrm{Id}$

# Discrete Jarzynski-Crooks equality: The reaction coordinate case

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

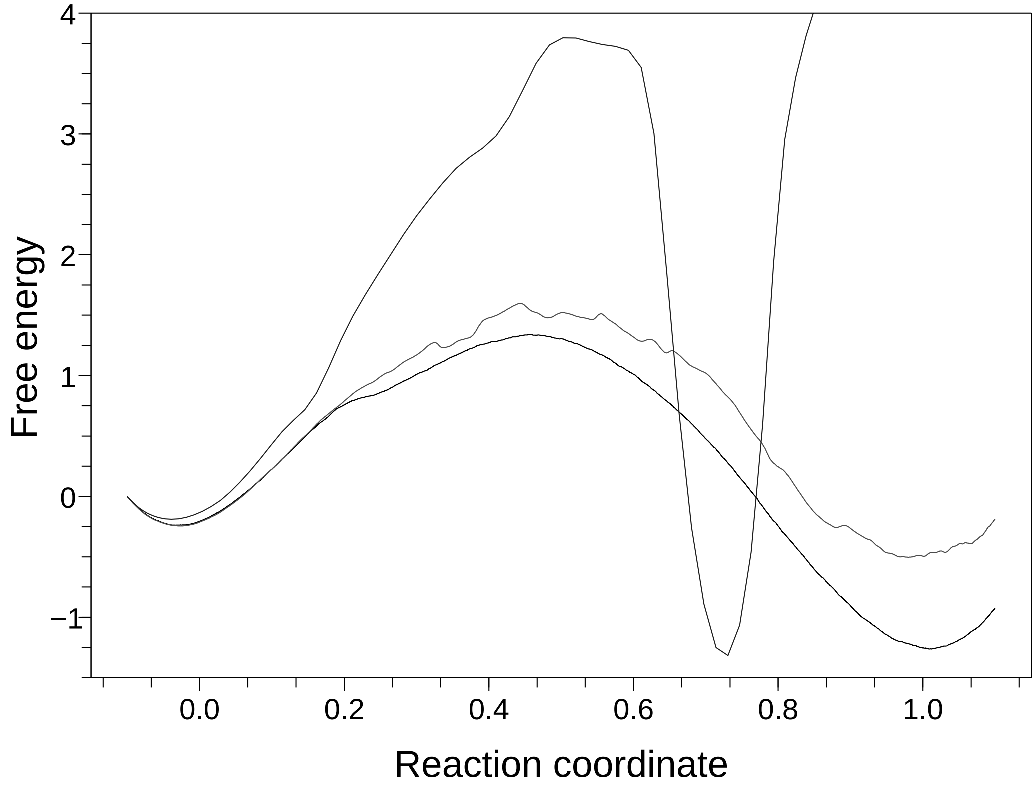
$$\mathcal{W}^{n+1} = \mathcal{W}^n + H(q^{n+1}, p^{n+3/4}) - H(q^n, p^{n+1/4})$$

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

$$\frac{Z_{z(N_T), \frac{z(t_{N_T+1})-z(t_{N_T})}{\Delta t}}}{Z_{z(t_0), \frac{z(t_1)-z(t_0)}{\Delta t}}} = \mathbb{E}\left(\mathrm{e}^{-\beta \mathcal{W}^{N_T}}\right)$$

- Standard free energy upon using a corrector
- More general version with backward dynamics and path functionals
- Overdamped limit $\frac{\Delta t}{4}\gamma = M = \frac{\Delta t}{2}\mathrm{Id}$: no bias due to the finite time-step in the estimator (compare to Lelièvre/Rousset/Stoltz, 2007)

# Application: Solvatation effects on conformational changes




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

- The main references for this work:
  - T. LELIÈVRE, M. ROUSSET AND G. STOLTZ, Langevin dynamics with constraints and computation of free energy differences, *arXiv preprint* **1006.4914** (2010)
  - T. LELIÈVRE, M. ROUSSET AND G. STOLTZ *Free energy computations: A Mathematical Perspective*, Imperial College Press (2010).
- Other recent works on adaptive computation of free energy differences:
  - N. CHOPIN, T. LELIÈVRE AND G. STOLTZ, Free energy methods for efficient exploration of mixture posterior densities, accepted for publication in *J. Stat. Comput.* (2011)
  - B. DICKSON, F. LEGOLL, T. LELIÈVRE, G. STOLTZ AND P. FLEURAT-LESSARD, Free energy calculations: An efficient adaptive biasing potential method, *J. Phys. Chem. B* **114**(17), 5823-5830 (2010)