

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

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

- All the physics is contained in  $V$
- **Canonical** probability measure:

$$\mu(dq dp) = Z^{-1} e^{-\beta H(q,p)} dq dp, \quad \beta = \frac{1}{k_B T}$$

- 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**:

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

- 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  $\sigma \sigma^T = \frac{2}{\beta} \gamma$
- Invariance of the canonical measure when it is a stationary solution of the **Fokker-Planck equation**  $\partial_t \psi = \mathcal{L}^* \psi$  with

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

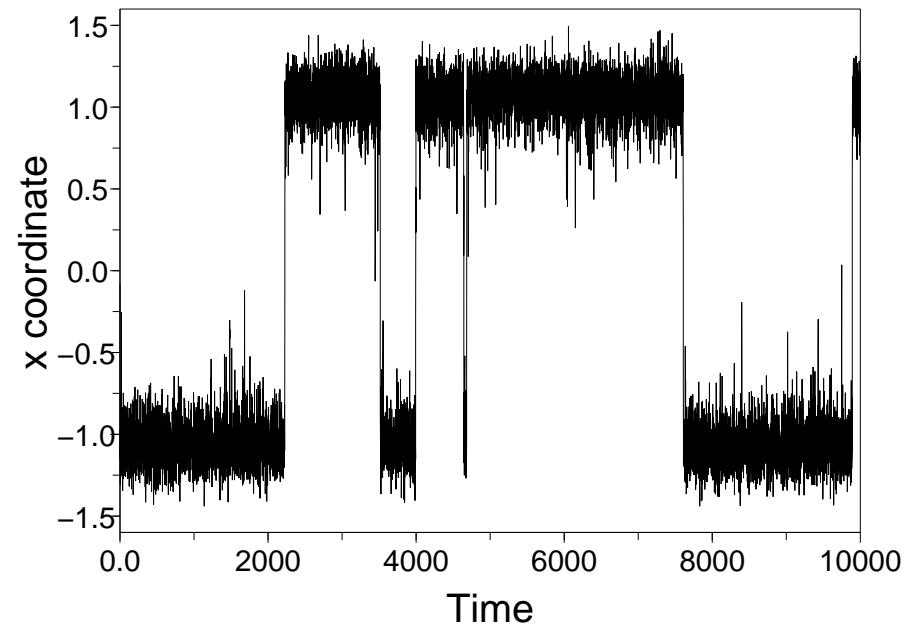
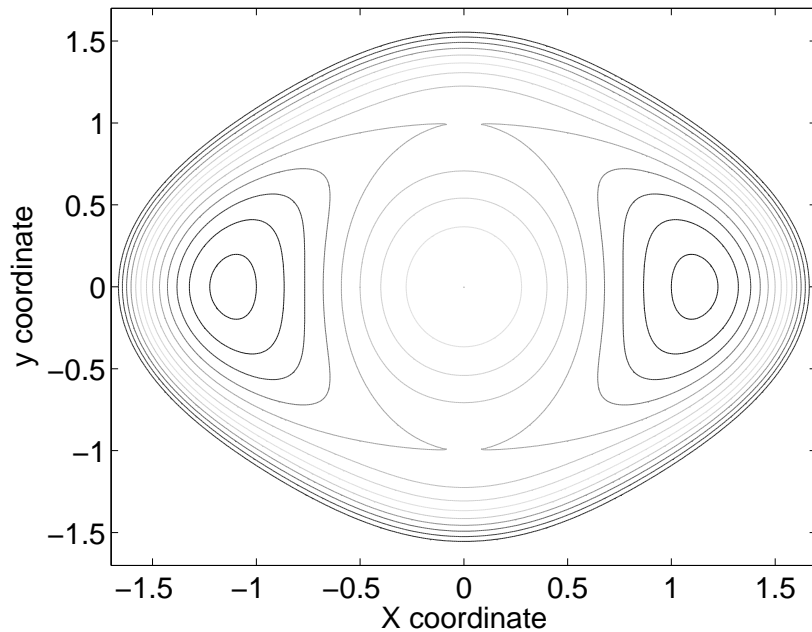
and  $\{A_1, A_2\} = (\nabla A_1)^T J \nabla A_2 = (\nabla_q A_1)^T \nabla_p A_2 - (\nabla_p A_1)^T \nabla_q A_2$

- 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:

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

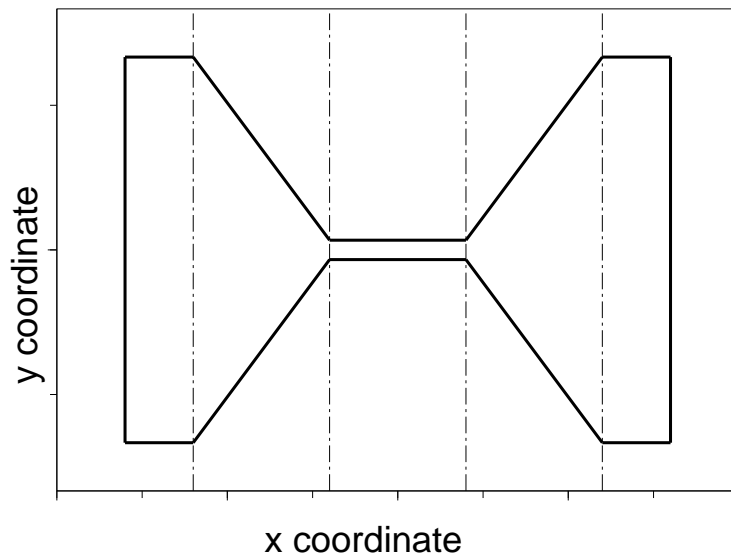
where  $\mathcal{G}^n \sim \mathcal{N}(0, \text{Id}_{dN})$  i.i.d.



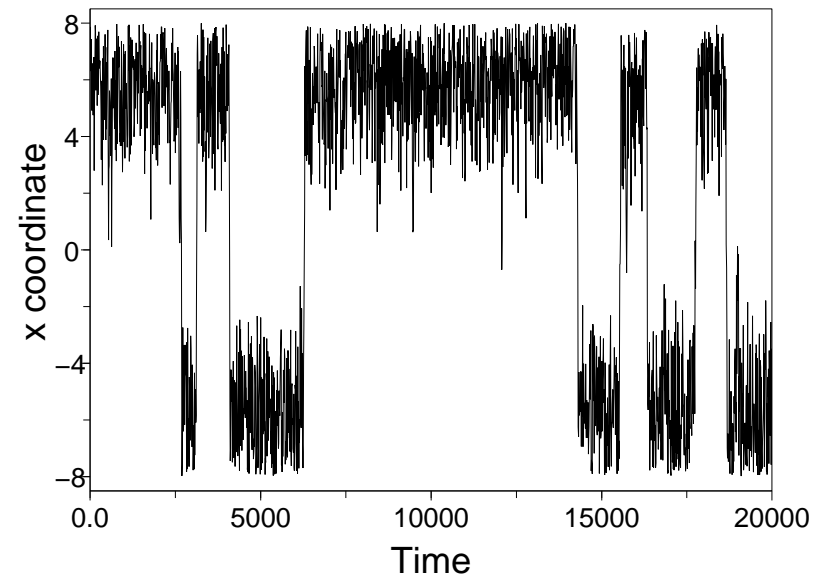
Projected trajectory in the  $x$  variable for  $\Delta t = 0.01$ ,  $\beta = 8$ .

## Metastability (2)

- 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.

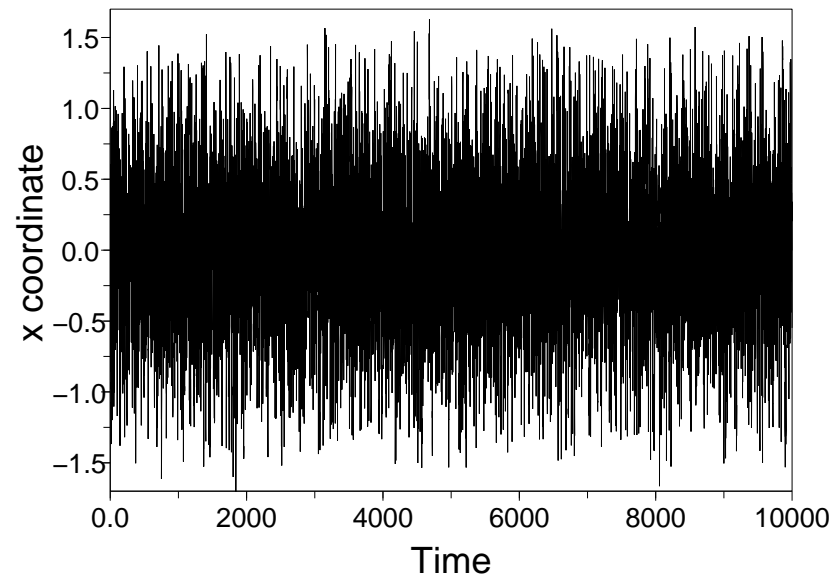
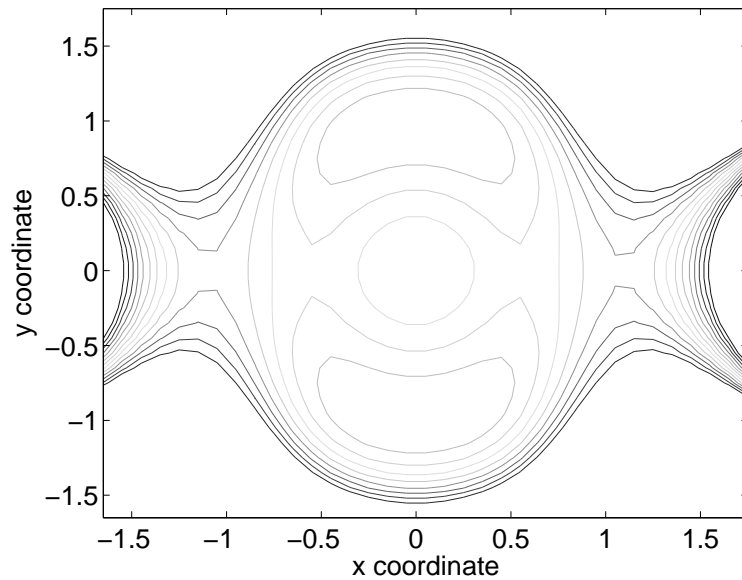


(b) Associated trajectory.



## 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  $e^{-\beta F(x)}$  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,...)

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

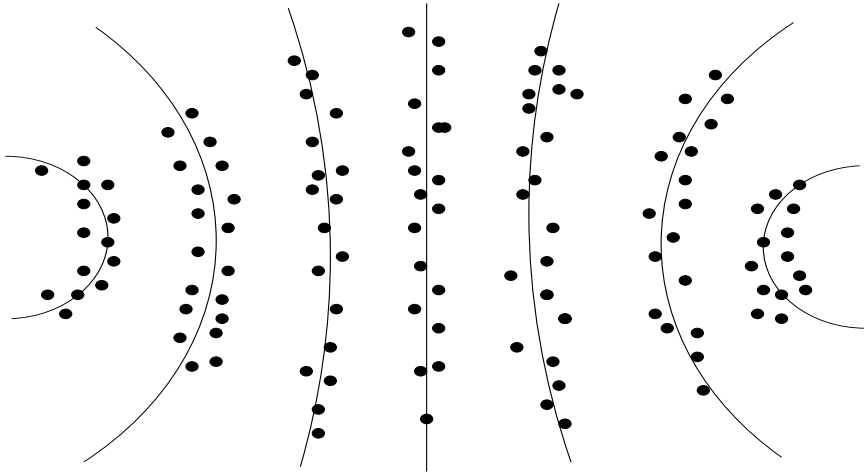
Typically,  $H_\lambda = (1 - \lambda)H_0 + \lambda H_1$ . Other parametrizations possible (see Gelman and Meng, *Stat. Sci.*, 1998)

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

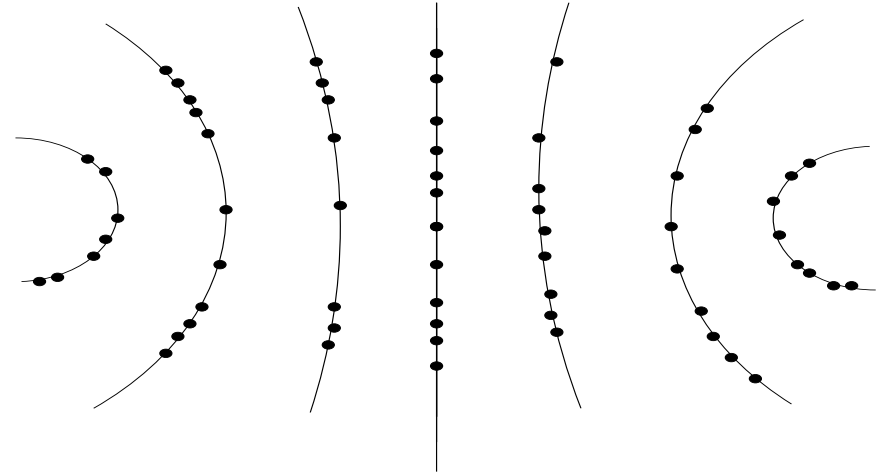
$$\Delta F = -\beta^{-1} \ln \left( \frac{\int_{\Sigma(z) \times \mathbb{R}^{3N}} e^{-\beta H(q,p)} \delta_{\xi(q)-z_1} (dq) dp}{\int_{\Sigma(z) \times \mathbb{R}^{3N}} e^{-\beta H(q,p)} \delta_{\xi(q)-z_0} (dq) dp} \right) .$$

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

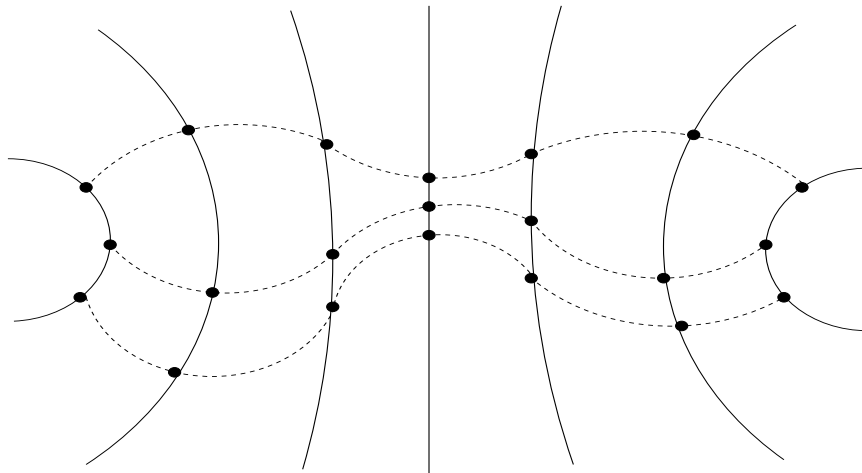
# Cartoon comparison of the methods (reaction coordinate case)



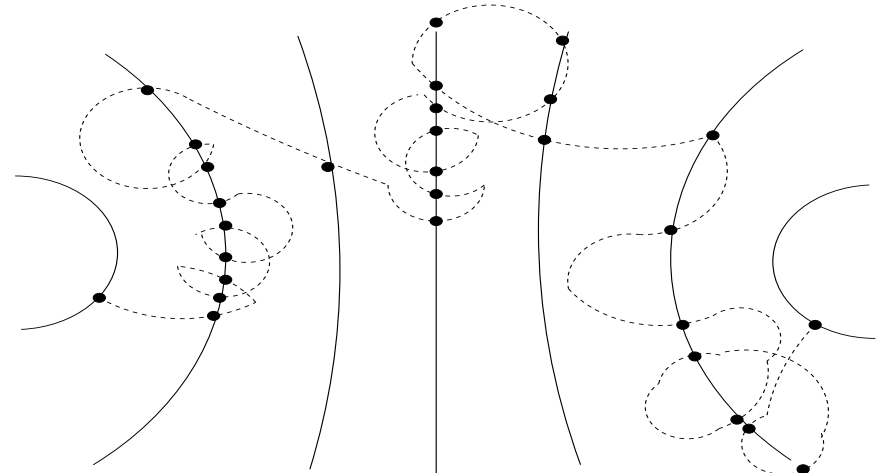
(a) Histogram method



(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) and **HMC** (Hartmann/Schütte) or for **overdamped Langevin** dynamics (Ciccotti/Lelièvre/Vanden-Eijnden)
- Nonequilibrium methods: **overdamped case** (Lelièvre/Rousset/Stoltz) or **steered versions** (potentials  $V_\lambda(q) = V(q) + K(\xi(q) - \lambda)^2$ )
- Adaptive 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

- 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

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

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

## Constrained Langevin dynamics (2)

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

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

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

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

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

- Thermodynamic integration through the computation of the **mean force**

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

- **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)

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

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

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



- Longtime (a.s.) convergence

$$\lim_{T \rightarrow +\infty} \frac{1}{T} \int_0^T d\lambda_t = \nabla_z F_{\text{rgd}}^M(z)$$

- 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:

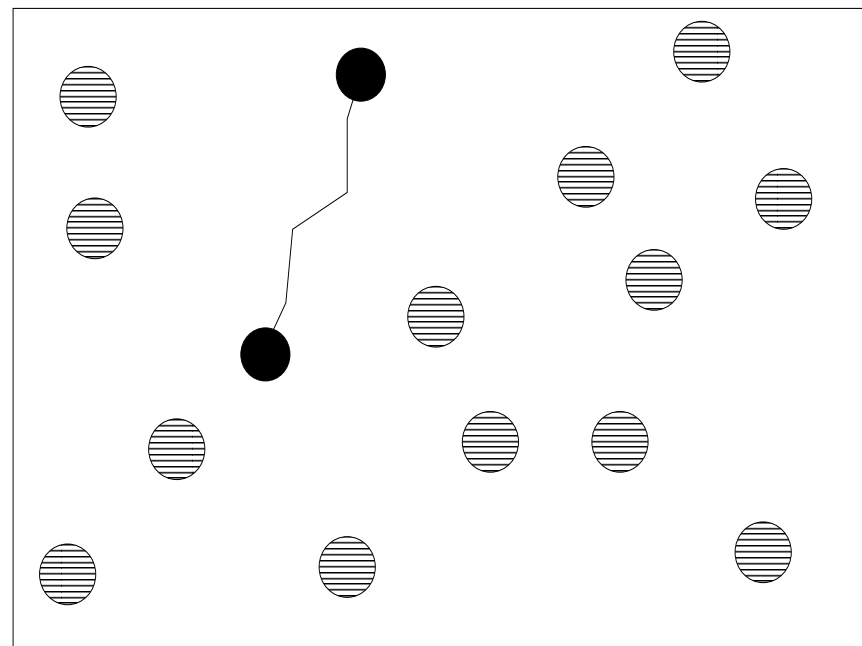
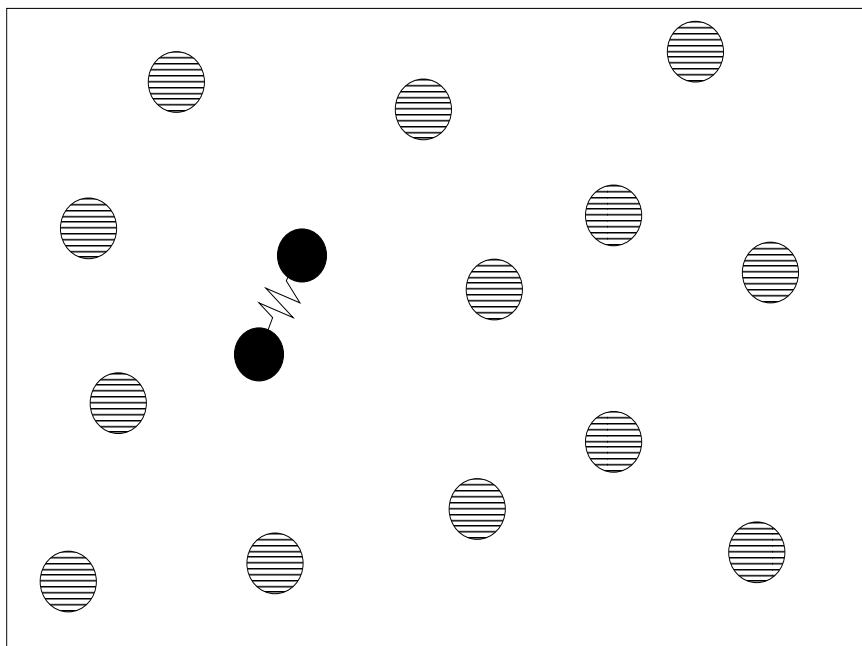
$$\nabla_z F_{\text{rgd}}^M(z) \simeq \frac{1}{N} \sum_{n=0}^{N-1} f_{\text{rgd}}^M(q^n, p^n) \simeq \frac{1}{N\Delta t} \sum_{n=0}^{N-1} (\lambda^{n+1/2} + \lambda^{n+3/4})$$

- Consistency result

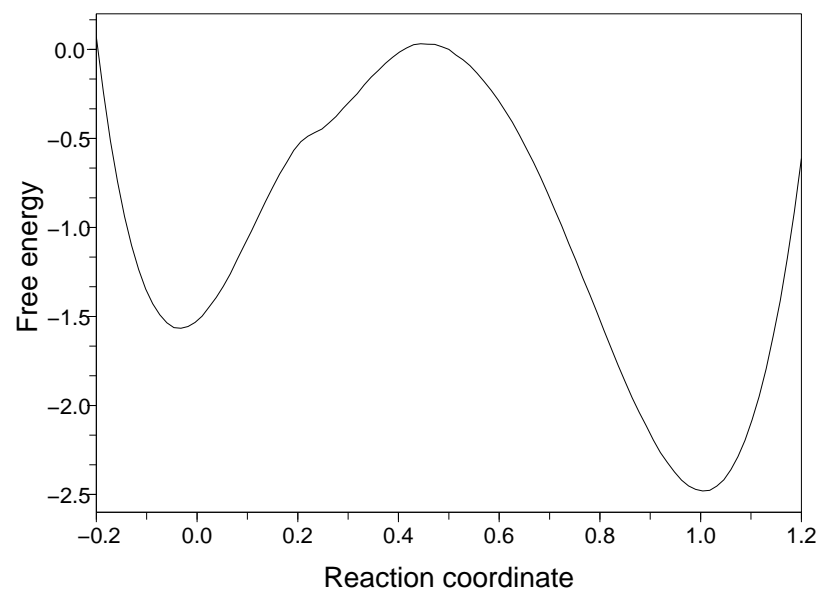
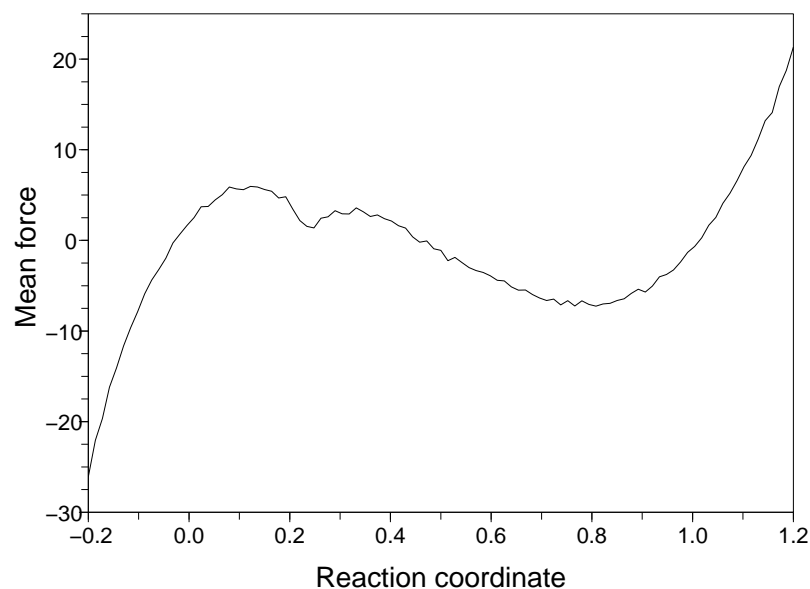
$$\lambda^{n+1/2} + \lambda^{n+3/4} = \frac{\Delta t}{2} \left( f_{\text{rgd}}^M(q^n, p^{n+1/4}) + f_{\text{rgd}}^M(q^{n+1}, p^{n+3/4}) \right) + O(\Delta t^3)$$

## Application: Solvation effects on conformational changes (1)

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

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

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  $d\lambda_t = f_{\text{rgd}}^M(q_t, p_t) dt + G_M^{-1}(q_t) \ddot{z}(t) dt$
- Not the same dynamics as in Latorre/Hartmann/Schütte

- **Rigid** free energy  $F_{\text{rgd}}^M(z, v_z) = -\frac{1}{\beta} \ln \int_{\Sigma_{\xi, v_{\xi}}(z, v_z)} e^{-\beta H(q, p)} d\mu_{\Sigma_{\xi, v_{\xi}}(z, v_z)}$

- Actual free energy recovered from the difference  $F(z) - F_{\text{rgd}}^{\xi, v_{\xi}}(z, v_z)$ , 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:**  $\mathcal{W}_{0,T}(\{q_t, p_t\}_{0 \leq t \leq T}) = \int_0^T \dot{z}(t)^T d\lambda_t$

- **Energy variations:**  $\mathcal{W}_{0,T}(\{q_t, p_t\}_{0 \leq t \leq T}) = \int_0^T w(t, q_t, p_t) dt$  where

$$w(t, q, p) = \dot{\zeta}(t)^T \Gamma^{-1} \{\Xi, H\}(q, p) = \left( \frac{d}{dh} H \circ \Phi_{t, t+h} \right) \Big|_{h=0} (q, p) \text{ with } \Phi$$

the flow of the switched Hamiltonian dynamics

- Work fluctuation relation

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

- More general result involving backward nonequilibrium dynamics and path functionals
- This leads in particular to the following **free energy estimator**

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

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)
- An exact time-discrete version (no time error)

- 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**)

$$\left\{ \begin{array}{l} p^{n+1/2} = p^{n+1/4} - \frac{\Delta t}{2} \nabla V(q^n) + \nabla \xi(q^n) \lambda^{n+1/2}, \\ q^{n+1} = q^n + \Delta t M^{-1} p^{n+1/2}, \\ \xi(q^{n+1}) = z(t_{n+1}), \\ p^{n+3/4} = p^{n+1/2} - \frac{\Delta t}{2} \nabla V(q^{n+1}) + \nabla \xi(q^{n+1}) \lambda^{n+3/4}, \\ \nabla \xi(q^{n+1})^T M^{-1} p^{n+3/4} = \frac{z(t_{n+2}) - z(t_{n+1})}{\Delta t}, \end{array} \right. \quad (C_q)$$

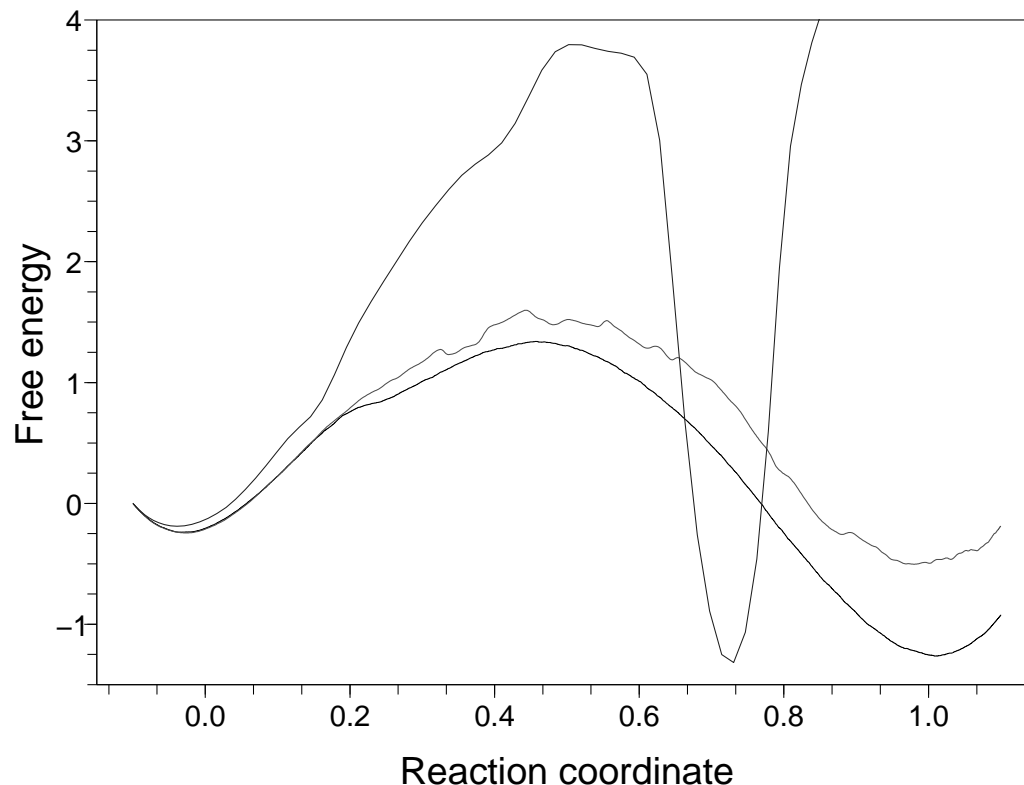
$$\quad (C_p)$$

- 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**  $\frac{\Delta t}{4} \gamma = M = \frac{\Delta t}{2} \text{Id}$



## Application: Solvation 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

- 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)