Computation of free energy differences

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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):

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

- For instance, $\mathcal{E} = \mathcal{M} \times \mathbb{R}^{3N}$ with $\mathcal{M} = \mathbb{R}^{3N}$ or $\mathbb{T}^{3N}$
- More complicated situations can be considered... (constraints defining submanifolds of the phase space)
- Hamiltonian

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

- All the physics is contained in V
- For instance, pair interactions $V(q_1, \ldots, q_N) = \sum_{1 \le i < j \le N} V_0(\mid q_j - q_i \mid)$

Extracting macroscopic properties: Statistical physics

- Given the structure and the laws of interaction of the particles, what are the macroscopic properties of the matter composed of these particles?
- Equilibrium thermodynamic properties (pressure,...):

$$\langle A \rangle = \int_{\mathcal{E}} A(q,p)\, d\mu(q,p)$$

- Integral in a high dimensional space...
- Choice of thermodynamic ensemble $\equiv$ choice of probability measure $d\mu$:
  - microcanonical (NVE, constant energy) ;
  - canonical (NVT, "constant temperature") : Boltzmann measure

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

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

Sampling the canonical ensemble: Overdamped Langevin dynamics

- SDE on the configurational part only (momenta trivial to sample)

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

where $(W_t)_{t\geq 0}$ is a standard Wiener process of dimension dN

- Invariance of the canonical measure

$$d\pi(q) = Z^{-1}\mathrm{e}^{-\beta V(q)}\,dq, \qquad Z = \int_{\mathcal{M}} \mathrm{e}^{-\beta V(q)}\,dq$$

if steady state of Fokker-Planck equation $\partial_t \psi_t = \mathrm{div}\left(\nabla V \psi_t + \frac{\sigma^2}{2}\nabla \psi_t\right)$

- Fluctuation/dissipation relation $\sigma = (2/\beta)^{1/2}$
- Invariance + irreducibility (elliptic process):

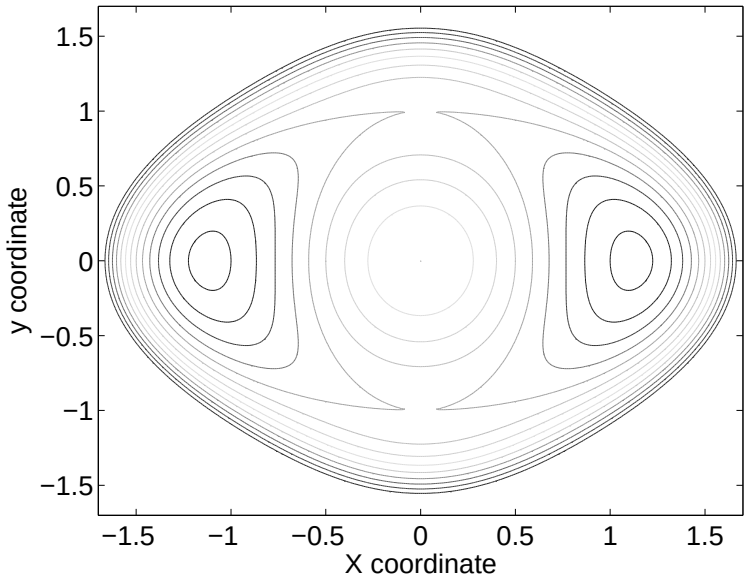
$$\lim_{T\to\infty} \frac{1}{T}\int_0^T A(q_t^x)\,dt = \int_{\mathcal{M}} A(q)d\pi \quad \text{a.s.}$$

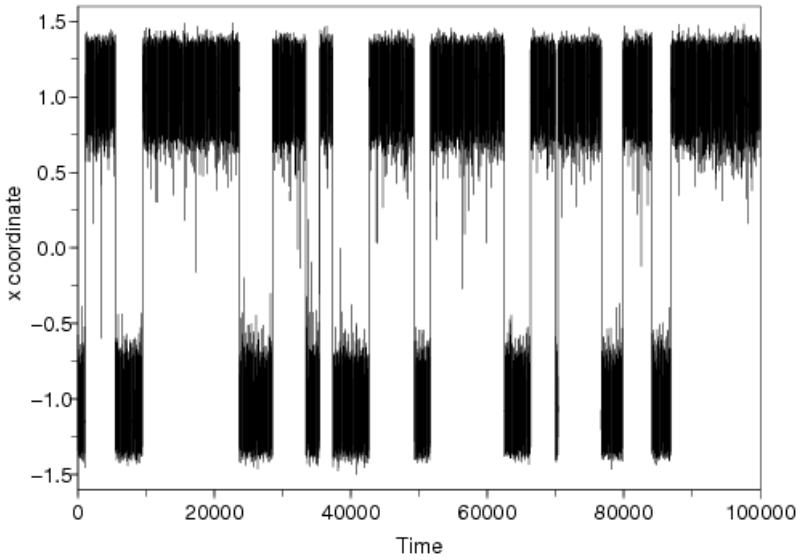
Metastability (1)

Numerical discretization of the overdamped Langevin dynamics:

$$q^{n+1} = q^n - \Delta t \nabla V(q^n) + \sigma \sqrt{\Delta t}\, U^n$$

where $U^n \sim \mathcal{N}(0,1)$ i.i.d.

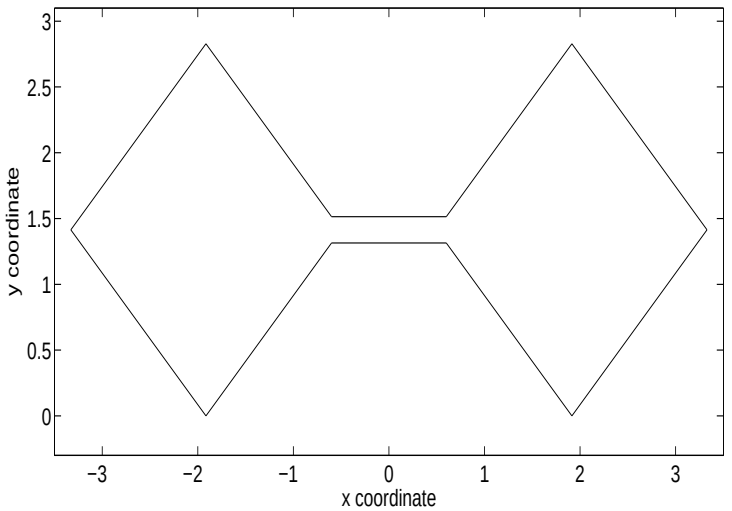




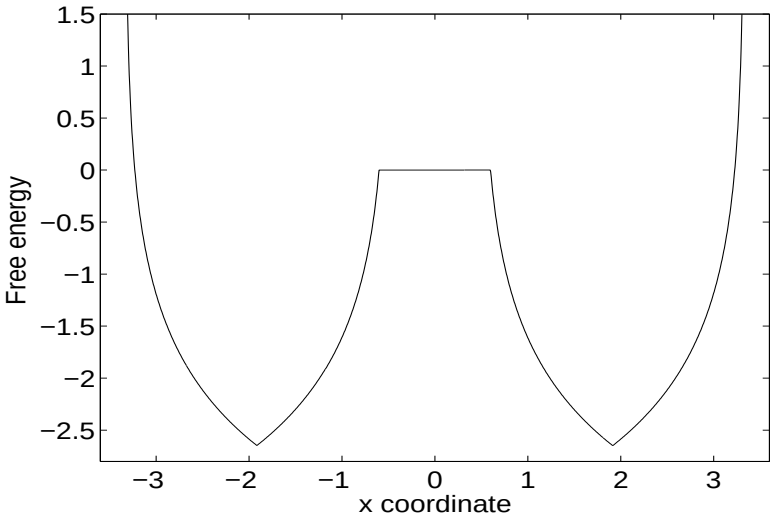
Projected trajectory in the x variable for $\Delta t = 0.01$, $\beta = 8$.

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
- Two origins : energetic or entropic barriers (in fact, free energy barrier)



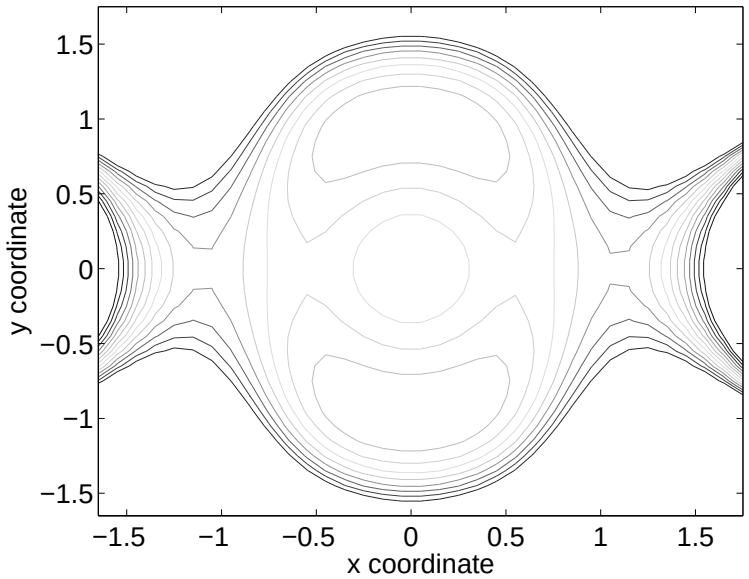
(a) Entropic barrier.

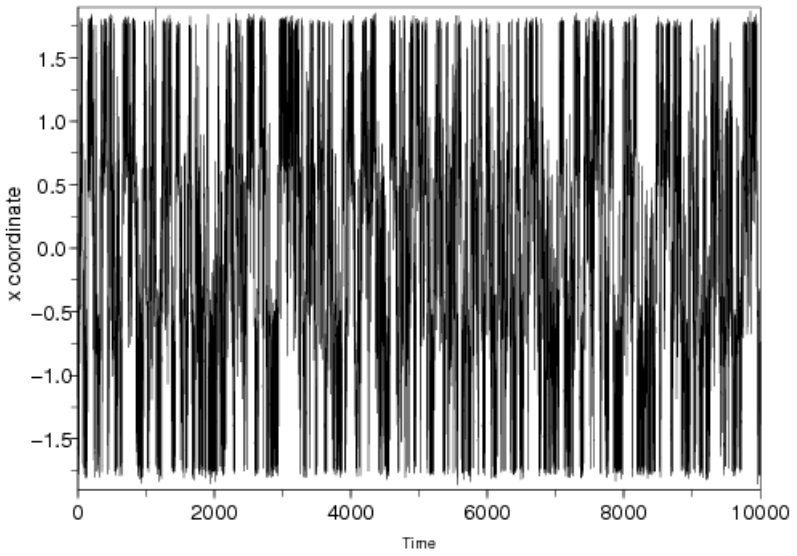


(b) Associated free energy.

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

Computation of free energy differences (1)

- Absolute free energy

$$F = -\frac{1}{\beta} \ln Z, \qquad Z = \int_{\mathcal{E}} \mathrm{e}^{-\beta H(q,p)} \, dq \, dp$$

- Motivation (Gibbs, 1902):
  - canonical measure $\mu(q,p) = Z^{-1} \exp(-\beta H(q,p))$
  - start from the thermodynamic identity $F = U - TS$
  - average energy $U = \int H \mu$
  - entropy $S = -k_{\mathrm{B}} \int \mu \ln \mu$
- Can be computed for ideal gases, and solids at low temperature
- Usually only free energy differences matter!

Computation of free energy differences (2)

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

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

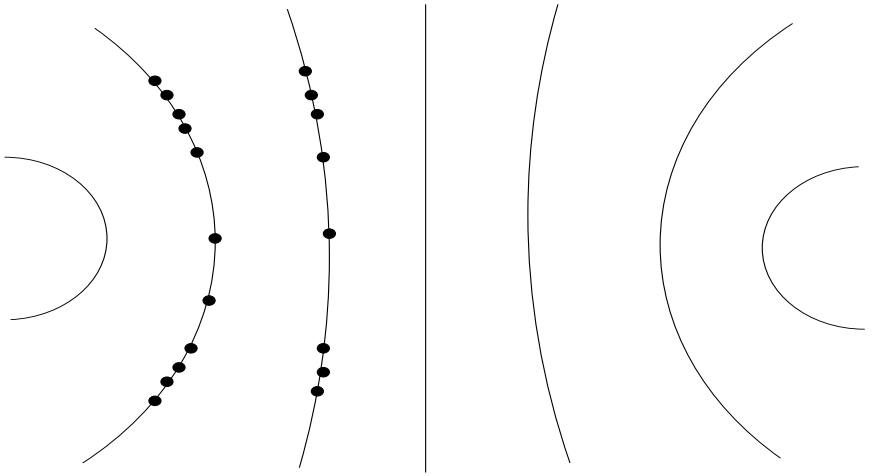
  Typically, $H_\lambda = (1-\lambda)H_0 + \lambda H_1$

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

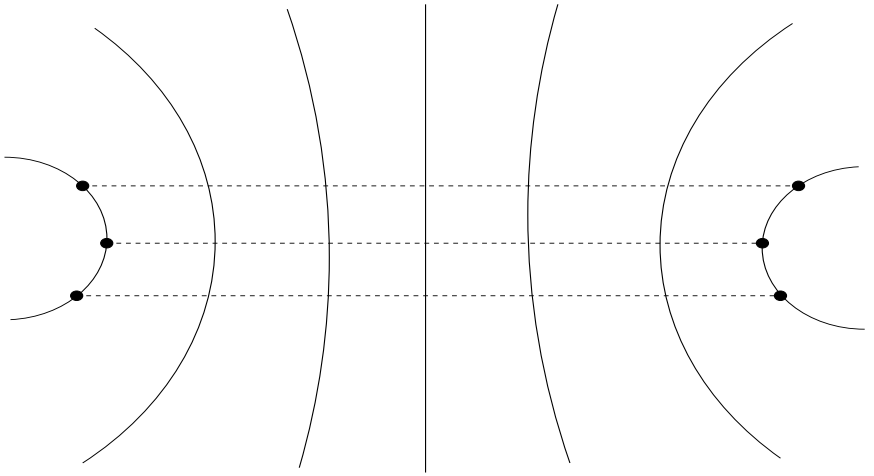
$$\Delta F = -\beta^{-1} \ln \left(\frac{\int_{\mathcal{E}} \mathrm{e}^{-\beta H(q,p)}\, \delta_{\xi(q)-z_1}\, dq\, dp}{\int_{\mathcal{E}} \mathrm{e}^{-\beta H(q,p)}\, \delta_{\xi(q)-z_0}\, dq\, dp} \right) .$$

  Recall $\delta_{\xi(q)-z} = |\nabla \xi|^{-1} d\sigma_{\Sigma_z}$.

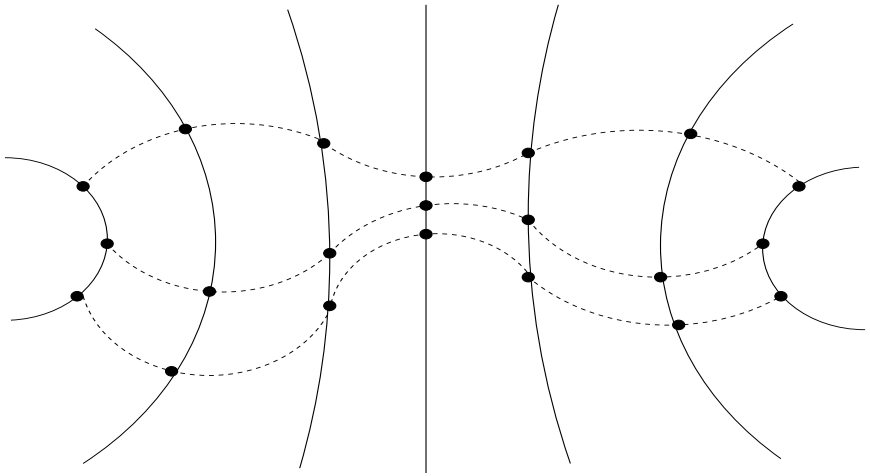
Cartoon comparison of the methods



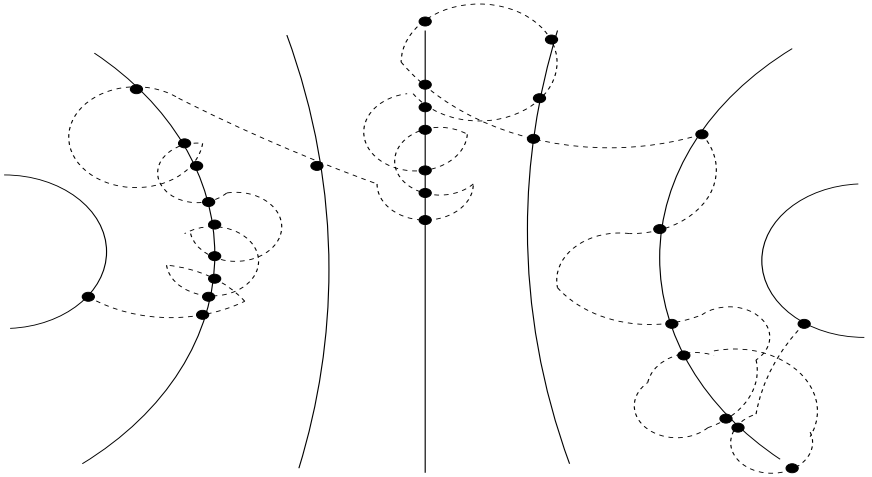
(a) Thermodynamic integration



(b) Free energy perturbation



(c) Nonequilibrium switching dynamics



(d) Adaptive dynamics

Mathematical classification (april 2008)

Free energy perturbation	$\longrightarrow$	Homogeneous MCs and SDEs
Thermodynamic integration	$\longrightarrow$	Projected MCs and SDEs
Nonequilibrium dynamics	$\longrightarrow$	Nonhomogenous MCs and SDEs
Adaptive dynamics	$\longrightarrow$	Nonlinear SDEs and MCs
Selection procedures	$\longrightarrow$	Particle systems and jump processes

Free energy perturbation

- Express ΔF as an average[a]

$$\Delta F(\lambda) = -\beta^{-1} \ln \frac{\displaystyle\int_{\mathcal{M}} \mathrm{e}^{-\beta(V_\lambda(q)-V_0(q))}\, d\pi_0(q)}{\displaystyle\int_{\mathcal{M}} d\pi_0(q)} = -\beta^{-1} \ln \frac{\displaystyle\int_{\mathcal{M}} \mathrm{e}^{-\beta(V_\lambda - W)} d\pi_W}{\displaystyle\int_{\mathcal{M}} \mathrm{e}^{-\beta(V_0 - W)} d\pi_W},$$

  with $d\pi_0(q) = Z^{-1}\mathrm{e}^{-\beta V_0(q)}\, dq$

- All usual sampling techniques can be used to sample from $d\pi_0$ (or $d\pi_W$)
- Many extensions and refinements to deal with the numerical issues (in particular, Umbrella sampling[b] $\equiv$ importance sampling)
- Restricted to alchemical transitions. . .

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[a] 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 of an average force [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 average force is

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

- Extension to the case of reaction coordinates using projected SDEs, mean force = average Lagrange multiplier of the constraint[b]

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

[b] Ciccotti, Lelièvre, Vanden-Eijnden, Comm. Pure Appl. Math. **61**(3) 371-408 (2008)

Nonequilibrium dynamics (1)

- Hamiltonian case: a priori evolution $\Lambda(t)$ of the alchemical parameter ($\Lambda(0) = 0$, $\Lambda(T) = 1$)

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

- 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

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

so that finally

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

Nonequilibrium dynamics (2)

- Jarzynski equality[a] $\boxed{\mathbb{E}(\mathrm{e}^{-\beta W}) = \mathrm{e}^{-\beta \Delta F}}$ (starting from equilibrium)
- Average taken over initial conditions and realizations of the noise
- Proof: Feynman-Kac formula in the stochastic case
- An interesting consequence: $\mathbb{E}(W) \geq \Delta F$ (second principle of thermodynamics)
- Various extensions/improvements :
  - Variance reduction using interacting particle systems[b] = reequilibration to avoid degeneracy of weights
  - Reaction coordinate case using switched projected SDEs[c] (average the Lagrange multipliers along the trajectory, up to some correction)
  - Path sampling strategies

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[a] Jarzynski, *Phys. Rev. Lett.* (1997)

[b] M. Rousset and G. Stoltz, *J. Stat. Phys.* (2006)

[c] T. Lelièvre, M. Rousset and G. Stoltz, *J. Comput. Phys.* (2007)

Adaptive dynamics (1)

- Adaptive methods (*Adaptive biasing force*[a], *nonequilibrium metadynamics*[b], etc)
  - General framework[c]
  - Convergence proof in a limiting case[d]
- Simplified setting: $\lambda \in \mathbb{R}/\mathbb{Z}$, $V_\lambda(q) \equiv V(q,\lambda)$

$$\left\{ \begin{array}{l} dq_t = -\nabla_q V(q_t,\lambda_t)\,dt + \sqrt{2\beta^{-1}}\,dW_t^q \\ d\lambda_t = -\partial_\lambda V(q_t,\lambda_t)\,dt + \sqrt{2\beta^{-1}}\,dW_t^\lambda \end{array} \right.$$

so that $F(\lambda_2) - F(\lambda_1) = -\beta^{-1} \ln \dfrac{\overline{\psi}_{\rm eq}(\lambda_2)}{\overline{\psi}_{\rm eq}(\lambda_1)}$, with $\overline{\psi}_{\rm eq}(\lambda) = \displaystyle\int_{\mathcal{M}} \mathrm{e}^{-\beta V(q,\lambda)}\,dq$

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[a] Darve and Pohorille, *J. Chem. Phys.* (2001)

[b] Bussi, Laio and Parrinello, *Phys. Rev. Lett.* (2006)

[c] T. Lelièvre, M. Rousset and G. Stoltz, *J. Chem. Phys.* (2007)

[d] T. Lelièvre, M. Rousset and G. Stoltz, *Nonlinearity* (2008)

Adaptive dynamics (2)

- Metastable sampling in the λ variable... Introduction of a bias in the dynamics of λ to force the exploration while computing the free energy difference

$$\begin{cases} dq_t = & -\nabla_q V(q_t, \lambda_t)\, dt + \sqrt{2\beta^{-1}}\, dW_t^q \\ d\lambda_t = & -\partial_\lambda \left[V(q_t, \lambda_t) - F_{\text{bias}}(t, \lambda_t)\right]\, dt + \sqrt{2\beta^{-1}}\, dW_t^\lambda \end{cases}$$

- Distribution of the configurations $X_t = (q_t, \lambda_t)$ according to $\psi_t(q, \lambda)$
- Variables λ_t distributed according to the marginals $\overline{\psi}_t(\lambda) = \displaystyle\int_{\mathcal{M}} \psi_t(q, \lambda)\, dq$
- If the biasing term $F_{\text{bias}}(t, \lambda)$ converges to $F(\lambda)$, then, at equilibrium,
  - $X_t \sim \psi_\infty(q, \lambda) = Z_\infty \mathrm{e}^{-\beta(V(q,\lambda) - F(\lambda))}$,
  - $\lambda_t \sim \overline{\psi}_\infty(\lambda) = \displaystyle\int_{\mathcal{M}} \exp(-\beta[V(q, \lambda) - F(\lambda)])\, dq = 1$
- Update of the bias? (potential or force)

Adaptive dynamics (3)

- Assume that the dynamics is instantaneously at equilibrium in the q variable at fixed λ, *i.e.* the conditioned measure

$$\psi_t^{\mathrm{eq}}(q,\lambda) = Z_t^{-1}\,\mathrm{e}^{-\beta\mathcal{V}_t(q,\lambda)}\,dq, \qquad \mathcal{V}_t(q,\lambda) = V(q) - F_{\mathrm{bias}}(t,\lambda).$$

  Then, an update of the form

$$\partial_t F'_{\mathrm{bias}}(t,\lambda) = \frac{1}{\tau}\,\frac{\displaystyle\int_{\mathcal{M}} \partial_\lambda \mathcal{V}_t(q,\lambda)\,\psi_t^{\mathrm{eq}}(q,\lambda)\,dq}{\displaystyle\int_{\mathcal{M}} \psi_t^{\mathrm{eq}}(q,\lambda)\,dq}$$

  implies $\partial_t F'_{\mathrm{bias}}(t,\lambda) = \dfrac{1}{\tau}\left(F(\lambda) - F'_{\mathrm{bias}}(t,\lambda)\right)$ hence the convergence.

- In general,

$$\partial_t F'_{\mathrm{bias}}(t,\lambda) = \frac{1}{\tau}\,\frac{\displaystyle\int_{\mathcal{M}} \partial_\lambda \mathcal{V}_t(q,\lambda)\,\psi_t(q,\lambda)\,dq}{\displaystyle\int_{\mathcal{M}} \psi_t(q,\lambda)\,dq}$$

Adaptive dynamics (4)

- In practice, the following conditional expectation is required for the update of the bias:

$$\mathbb{E}(\partial_\lambda V|\lambda) = \frac{\displaystyle\int_{\mathcal{M}} \partial_\lambda V(q,\lambda)\,\psi_t(q,\lambda)\,dq}{\displaystyle\int_{\mathcal{M}} \psi_t(q,\lambda)\,dq}$$

- There are two (complementary) strategies to compute it:
  - using a large number of replicas $(Q_t^{i,M}, \lambda_t^{i,M})_{i=1,\dots,M}$ of the system which all contribute to the same free energy profile

$$\psi_t(q,\lambda) \simeq \frac{1}{M}\sum_{i=1}^{M} \delta^{\varepsilon}{}_{(Q_t^{i,M},\lambda_t^{i,M})-(q,\lambda)};$$

  - resorting to some time average

$$\psi_t(q,\lambda) \simeq \frac{1}{T}\int_{t-T}^{t} \delta^{\varepsilon}{}_{(q_s,\lambda_s)-(q,\lambda)}\,ds.$$

Adaptive dynamics: convergence

- Adaptive biasing force in the limiting regime $\tau \to 0$= nonlinear PDE

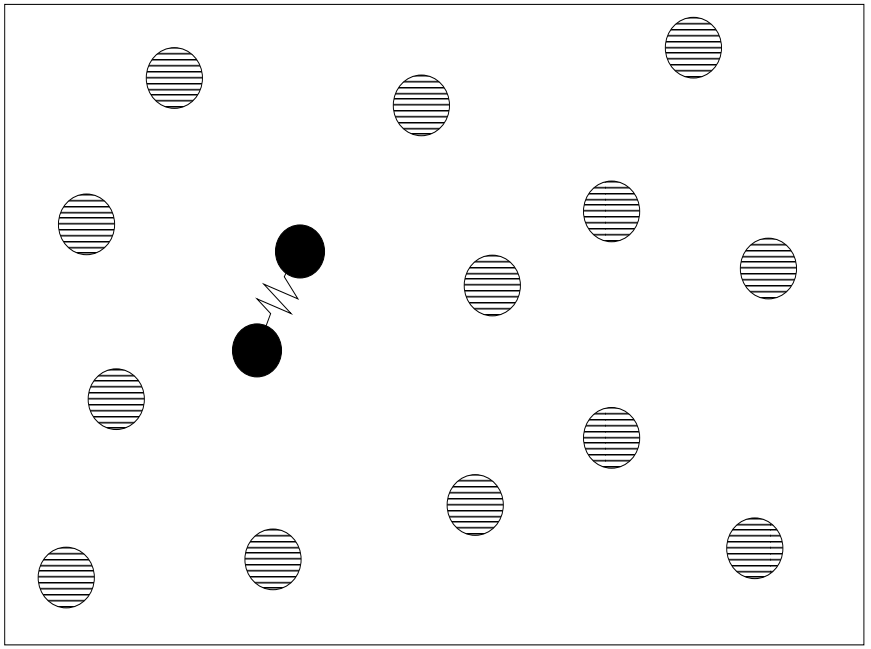
$$\begin{cases} \partial_t \psi_t = \operatorname{div}\left(\nabla(V - F_{\rm bias}(t,\lambda))\psi_t + \beta^{-1}\nabla\psi_t\right), \\ F'_{\rm bias}(t,\lambda) = \dfrac{\displaystyle\int_{\mathcal{M}} \partial_\lambda V(q,\lambda)\,\psi_t(q,\lambda)\,dq}{\displaystyle\int_{\mathcal{M}} \psi_t(q,\lambda)\,dq}. \end{cases}$$

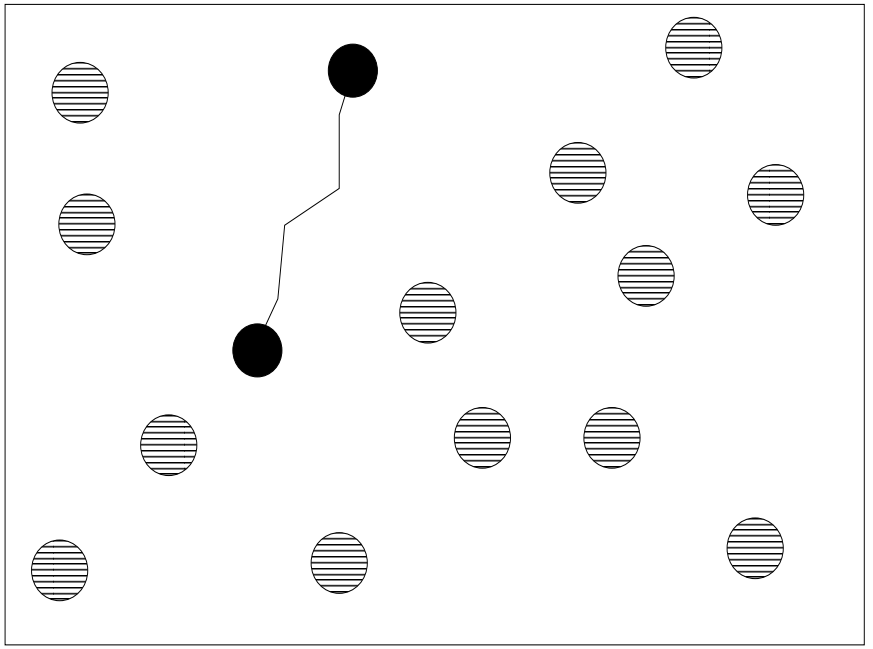
- Simple diffusion for the marginals $\partial_t \overline{\psi}_t = \partial_{\lambda\lambda}\,\overline{\psi}_t$
- Entropic method: decomposition[a] of the total entropy $H(\psi_t \,|\, \psi_\infty) = \displaystyle\int_{\mathcal{M}\times\mathbb{T}} \ln\left(\frac{\psi_t}{\psi_\infty}\right)\psi_t$ into a macroscopic contribution (marginals in λ) and a microscopic one (conditioned measures)
- Convergence of the microscopic entropy provided some uniform logarithmic Sobolev inequality on the conditioned measures holds

[a] T. Lelièvre, F. Otto, M. Rousset, G. Stoltz, *arXiv* **0706.1695** (2007)

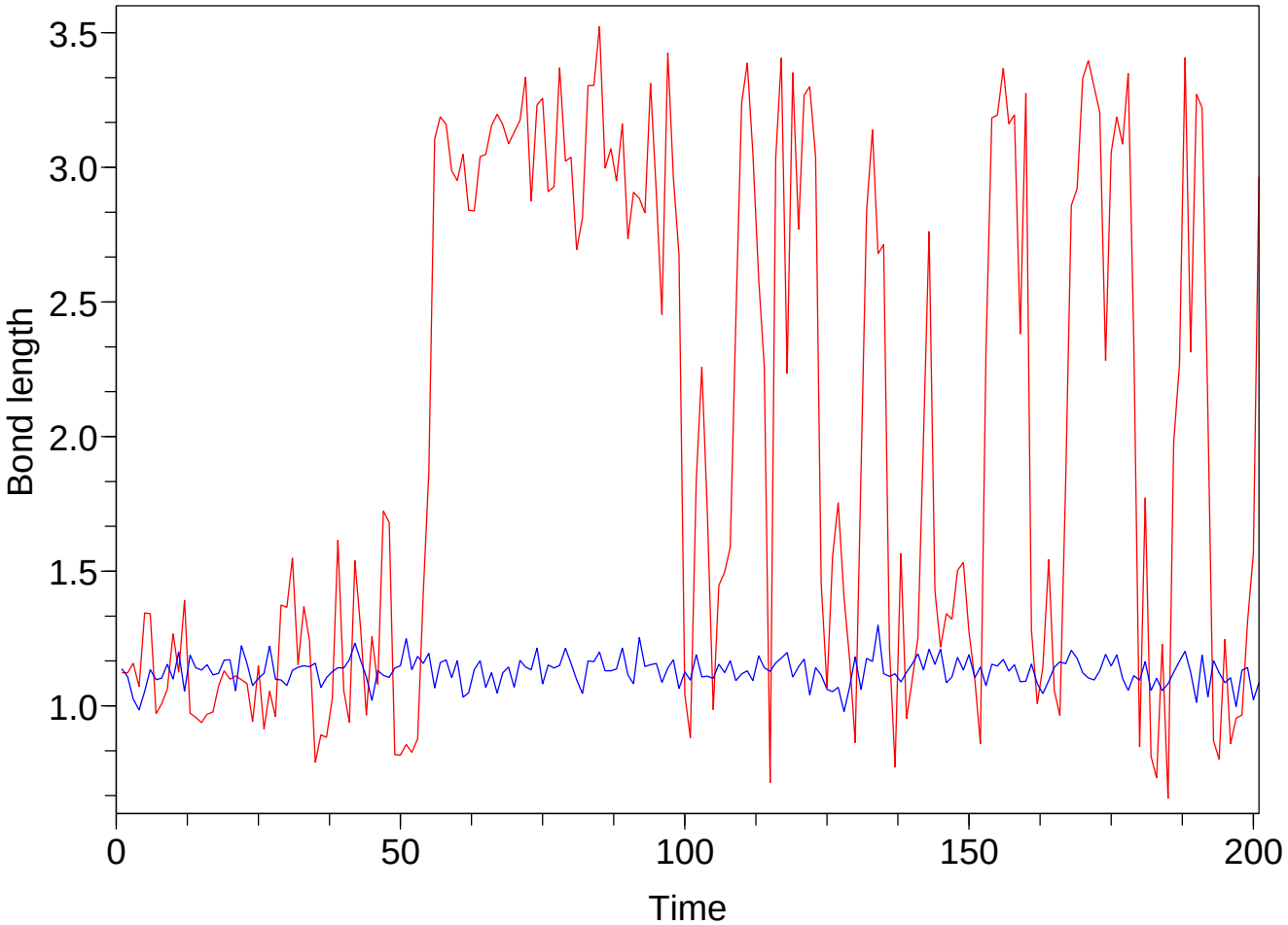
Application: Solvatation effects on conformational changes (1)

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





Application: Solvatation effects on conformational changes (2)



Blue: without biasing term. Red: adaptive biasing force.

Parameters: $h = 10$, density $\rho = 0.25\,\sigma^{-2}$, $w = 1$, $\beta = 3$, $\epsilon = 1$, $\tau = 0.1$

Conclusion – Mathematical classification (april 2008)

Free energy perturbation	$\longrightarrow$	Homogeneous MCs and SDEs
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Which method is the most efficient in practice...?