Simulation moléculaire : modèles, calcul d'énergie libre et aspects dynamiques

2- Echantillonnage de la distribution canonique

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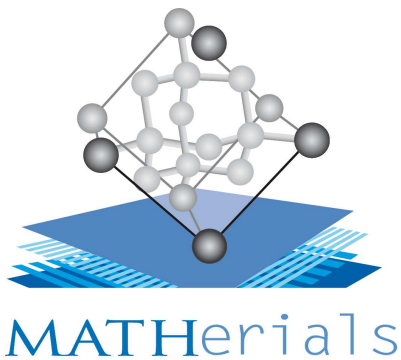

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Motivation

The aim of molecular dynamics simulations is to understand the relationships between the macroscopic properties of a molecular system and its atomistic features. In particular, one would like to evaluate numerically macroscopic quantities from models at the microscopic scale.

Many applications in various fields: biology, physics, chemistry, materials science.

Various models: discrete state space (kinetic Monte Carlo, Markov State Model) or continuous state space (Langevin).

The basic ingredient: a potential V which maps a configuration $(\boldsymbol{x}_1, ..., \boldsymbol{x}_N) = \boldsymbol{x} \in \mathbb{R}^{3N_{atom}}$ to an energy $V(\boldsymbol{x}_1, ..., \boldsymbol{x}_{N_{atom}})$. The dimension $d = 3N_{atom}$ is large (a few hundred thousand to millions).

Dynamics

Newton equations of motion:

$$\begin{cases} d\boldsymbol{X}_t = M^{-1}\boldsymbol{P}_t\,dt \\ d\boldsymbol{P}_t = -\nabla V(\boldsymbol{X}_t)\,dt \end{cases}$$

Dynamics

Newton equations of motion + thermostat: Langevin dynamics:

$$\begin{cases} d\boldsymbol{X}_t = M^{-1}\boldsymbol{P}_t\,dt \\ d\boldsymbol{P}_t = -\nabla V(\boldsymbol{X}_t)\,dt - \gamma M^{-1}\boldsymbol{P}_t\,dt + \sqrt{2\gamma\beta^{-1}}d\boldsymbol{W}_t \end{cases}$$

where $\gamma > 0$. Langevin dynamics is ergodic wrt $\nu(d\boldsymbol{x}) \otimes Z_p^{-1} \exp\left(-\beta \frac{\boldsymbol{p}^t M^{-1}\boldsymbol{p}}{2}\right) d\boldsymbol{p}$ with

$$d\nu = Z^{-1}\exp(-\beta V(\boldsymbol{x}))\,d\boldsymbol{x}$$

where $Z = \int \exp(-\beta V(\boldsymbol{x}))\,d\boldsymbol{x}$ is the partition function and $\beta = (k_B T)^{-1}$ is proportional to the inverse of the temperature.

Dynamics

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In the following, we focus on the *overdamped Langevin* (or gradient) dynamics

$$d\boldsymbol{X}_t = -\nabla V(\boldsymbol{X}_t)\,dt + \sqrt{2\beta^{-1}}d\boldsymbol{W}_t,$$

which is also ergodic wrt ν.

Macroscopic quantities of interest

These dynamics are used to compute macroscopic quantities:

(i) Thermodynamic quantities (averages wrt ν of some observables): stress, heat capacity, free energy,...

$$\mathbb{E}_\nu(\varphi(\boldsymbol{X})) = \int_{\mathbb{R}^d} \varphi(\boldsymbol{x})\, \nu(d\boldsymbol{x}) \simeq \frac{1}{T} \int_0^T \varphi(\boldsymbol{X}_t)\, dt.$$

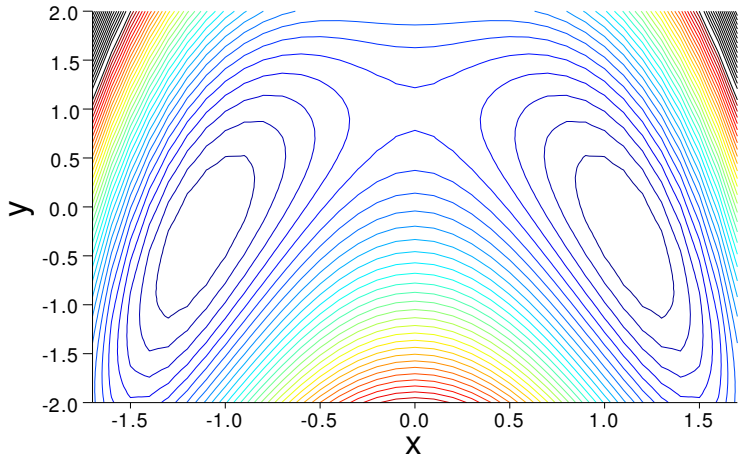
(ii) Dynamical quantities (averages over trajectories): diffusion coefficients, viscosity, transition rates,...

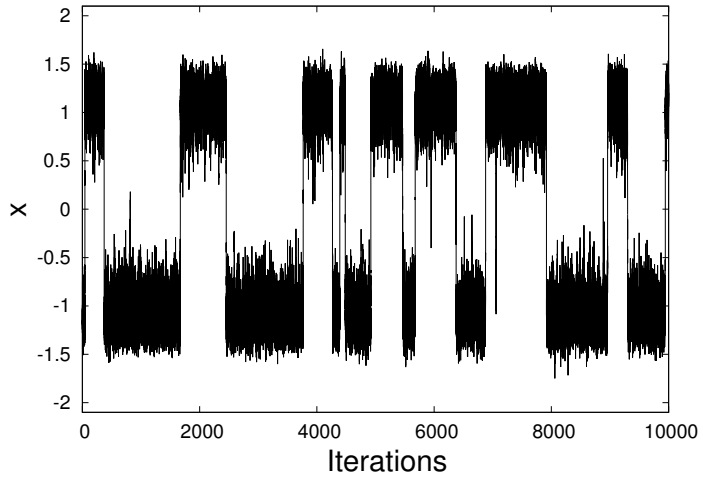
$$\mathbb{E}(\mathcal{F}((\boldsymbol{X}_t)_{t\geq 0})) \simeq \frac{1}{M} \sum_{m=1}^{M} \mathcal{F}((\boldsymbol{X}_t^m)_{t\geq 0}).$$

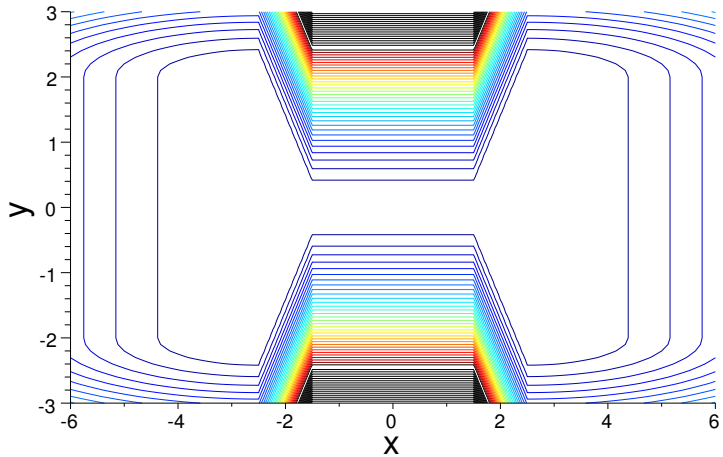
Difficulties: (i) high-dimensional problem ($N \gg 1$); (ii) $\boldsymbol{X}_t$ is a metastable process and ν is a multimodal measure.

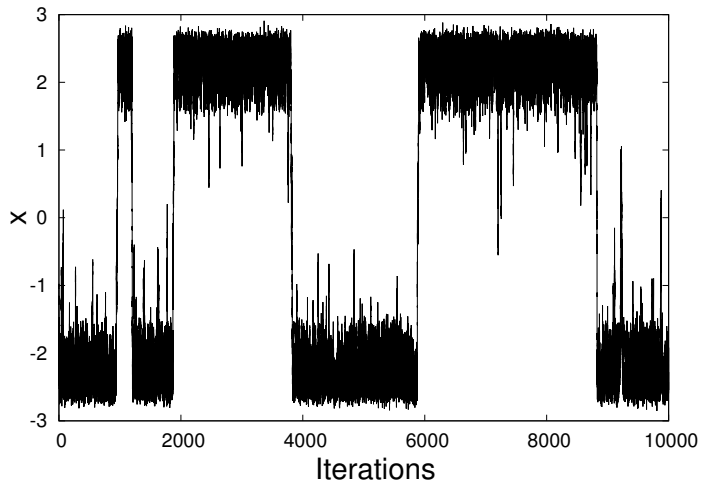
Metastability: energetic and entropic barriers

A two-dimensional schematic picture







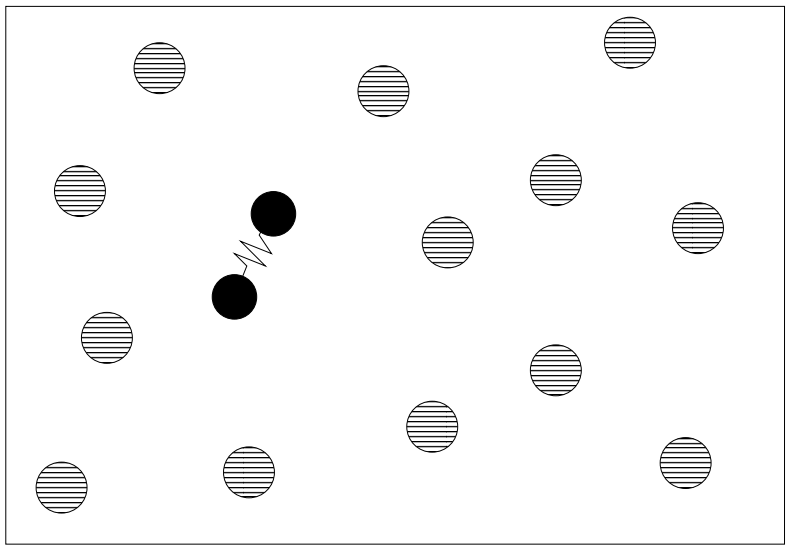


$\longrightarrow$ • Slow convergence of trajectorial averages

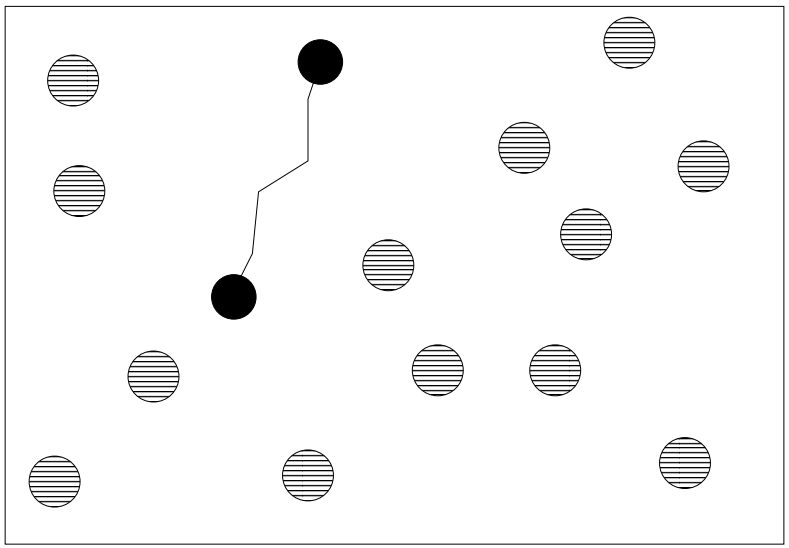
• Transitions between metastable states are rare events

A toy model for solvation

Influence of the solvation on a dimer conformation [Dellago, Geissler].



Compact state.

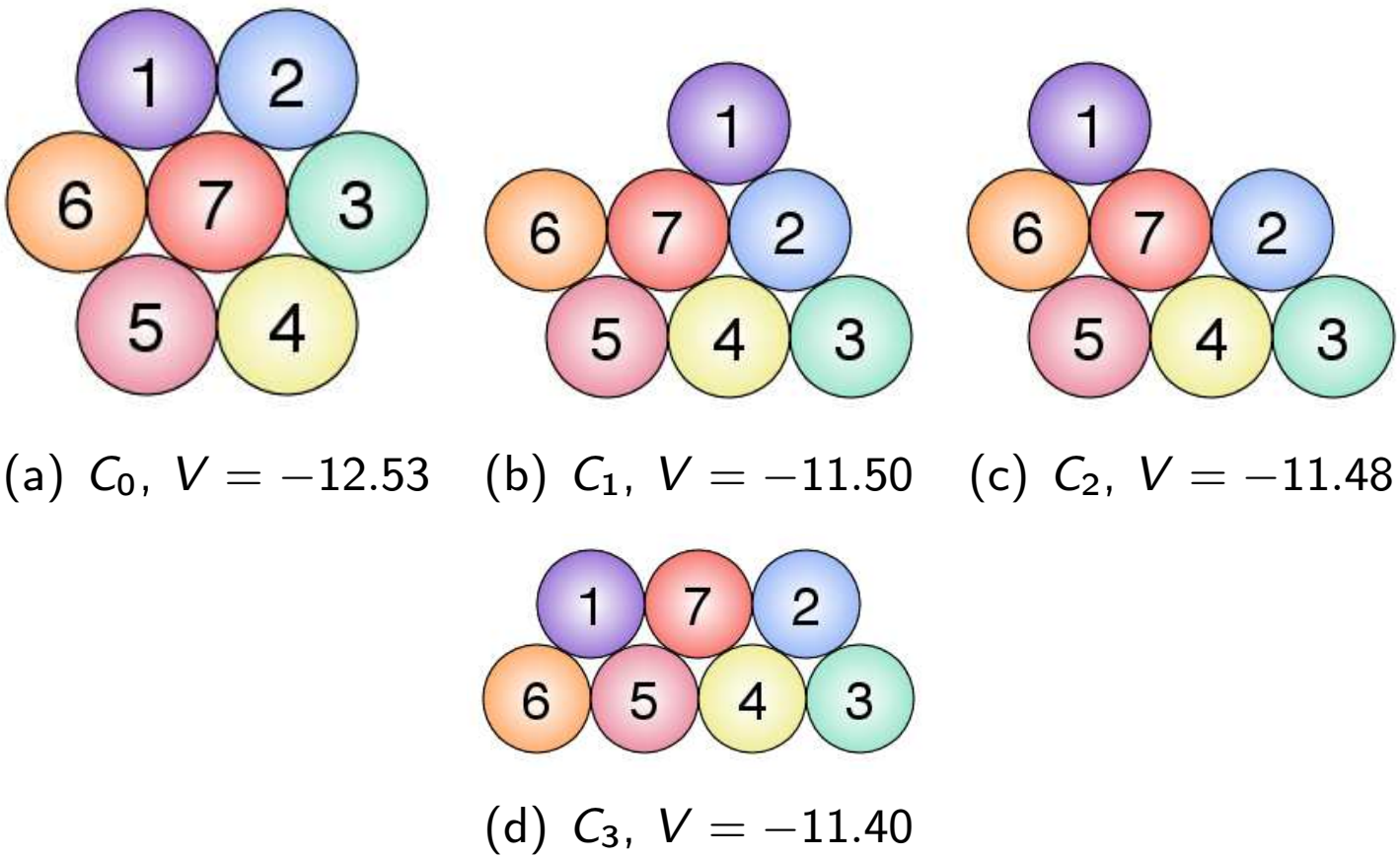


Stretched state.

The particles interact through a pair potential: truncated LJ for all particles except the two monomers (black particles) which interact through a double-well potential. A slow variable is the distance between the two monomers.

A toy example in material sciences

The 7 atoms Lennard Jones cluster in 2D.



(a) C_0, $V = -12.53$ (b) C_1, $V = -11.50$ (c) C_2, $V = -11.48$

(d) C_3, $V = -11.40$

Figure: Low energy conformations of the Lennard-Jones cluster.

$\longrightarrow$ simulation

Limitation of direct molecular dynamics

Direct molecular dynamics is a very powerful technique to generate atomistic trajectories. These trajectories can be useful in themselves (dynamical quantities) or to get ensemble averages (thermodynamic quantities).

Orders of magnitude: LJ potential costs $\sim 2\mu s$/atom/timestep; EAM potential costs $\sim 5\mu s$/atom/timestep; AIMD costs (at least) 1 min/atom/timestep.

Thus, molecular dynamics' reach is limited in terms of time and length scales. $\longrightarrow$ Depending on the quantity of interest, MD is combined with other algorithms to get better sampling.

Thermodynamic quantities: variance reduction methods (stratification, importance sampling, control variate, ...)
Dynamic quantities: rare event sampling methods, accelerated dynamics (using Markov State models)

Outline

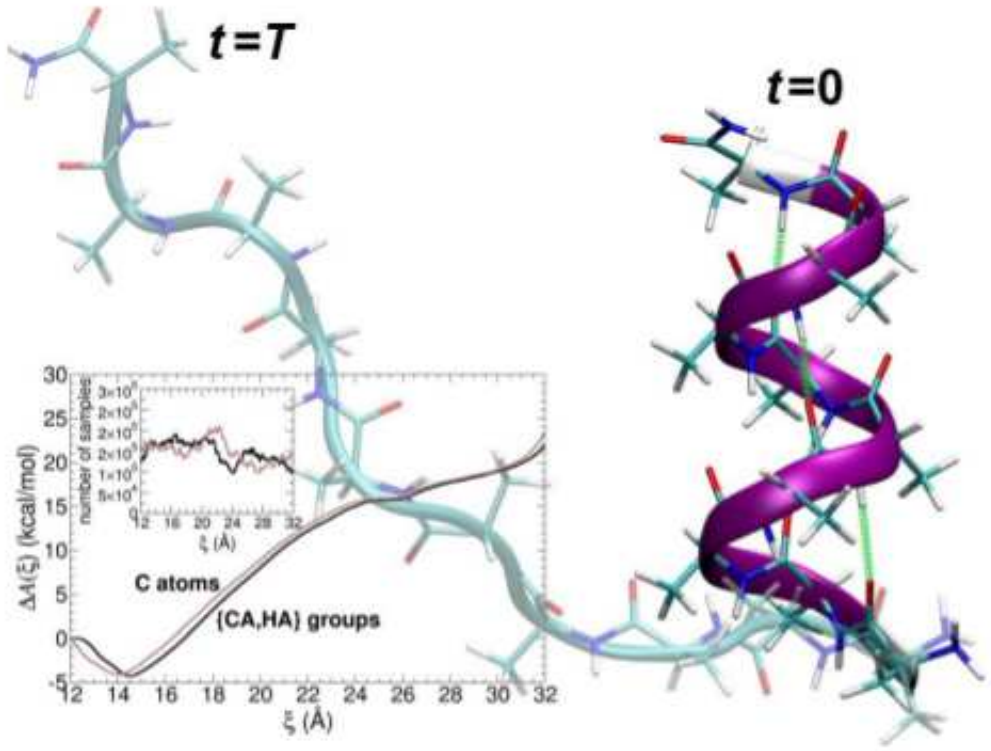
Outline of this part:

1. Definition of the free energy associated with a reaction coordinate.
2. Thermodynamics integration: A free energy computation method based on stochastic processes with constraints.
3. Adaptive biasing techniques: Free energy computation methods based on biased stochastic processes.

Mathematical tools: delta measure and co-area formula, Entropy techniques and Logarithmic Sobolev Inequalities.

Underlying question: how to properly define and quantify metastability ? Various answers: (i) rate of convergence to equilibrium; (ii) exit time from metastable states; (iii) decorrelation time; (iv) asymptotic variance of estimators.

Reaction coordinate and free energy



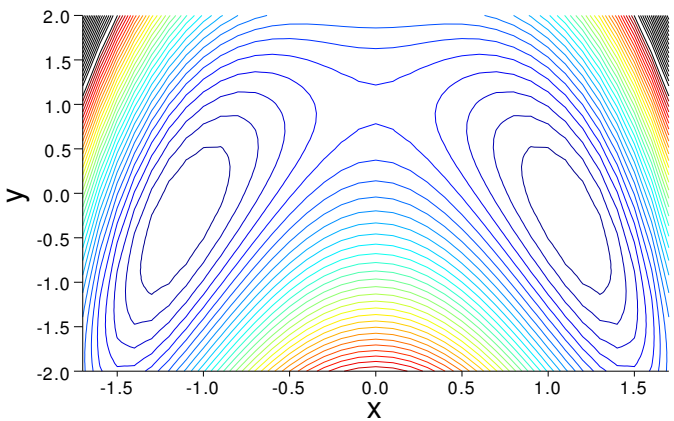
Reaction coordinate

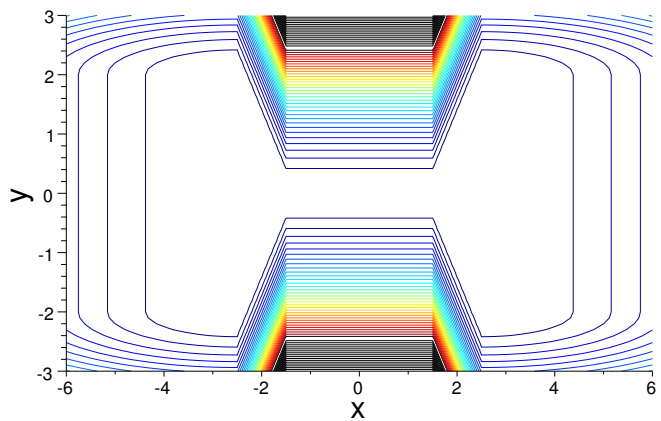
We suppose in the following that we know a slow variable of dimension 1: $\xi(\boldsymbol{X}_t)$, where $\xi : \mathbb{R}^d \to \mathbb{T}$ is a so-called reaction coordinate.

This reaction coordinate will be used to efficiently sample the canonical measure using two techniques: (i) constrained dynamics (thermodynamic integration) or (ii) biased dynamics (adaptive importance sampling technique).

Free energy will play a central role.

For example, in the 2D simple examples: $\xi(x, y) = x$.





Free energy

Let us introduce two probability measures associated with ν and ξ:

- The image of the measure ν by ξ:

$$\xi_* \nu\,(dz) = \exp(-\beta A(z))\,dz$$

where the free energy A is defined by:

$$A(z) = -\beta^{-1} \ln \left(\int_{\Sigma(z)} e^{-\beta V} \delta_{\xi(\boldsymbol{x})-z}(d\boldsymbol{x}) \right),$$

with $\Sigma(z) = \{\boldsymbol{x},\, \xi(\boldsymbol{x}) = z\}$ is a (smooth) submanifold of $\mathbb{R}^d$, and $\delta_{\xi(\boldsymbol{x})-z}(d\boldsymbol{x})\,dz = d\boldsymbol{x}$.

- The probability measure ν conditioned to $\xi(\boldsymbol{x}) = z$:

$$\nu_{\Sigma(z)}(d\boldsymbol{x}) = \frac{\exp(-\beta V(\boldsymbol{x}))\,\delta_{\xi(\boldsymbol{x})-z}(d\boldsymbol{x})}{\exp(-\beta A(z))}.$$

Free energy (2d case)

In the simple case $\xi(x, y) = x$, we have:

- The image of the measure ν by ξ:

$$\xi_* \nu\,(dx) = \exp(-\beta A(x))\,dx$$

where the free energy A is defined by:

$$A(x) = -\beta^{-1} \ln \left(\int_{\Sigma(x)} e^{-\beta V(x,y)} dy \right)$$

and $\Sigma(x) = \{(x, y),\ y \in \mathbb{R}\}$.

- The probability measure ν conditioned to $\xi(x, y) = x$:

$$\nu_{\Sigma(x)}(dy) = \frac{\exp(-\beta V(x, y))\,dy}{\exp(-\beta A(x))}.$$

The delta measure and the co-area formula

- The measure $\delta_{\xi(\boldsymbol{x})-z}$ is defined by: for all test functions $\varphi : \mathbb{T} \to \mathbb{R}$ and $\psi : \mathbb{R}^d \to \mathbb{R}$,

$$\int_{\mathbb{R}^d} \varphi \circ \xi(\boldsymbol{x}) \psi(\boldsymbol{x}) \, d\boldsymbol{x} = \int_{\mathbb{T}} \varphi(z) \left(\int_{\Sigma(z)} \psi(\boldsymbol{x}) \delta_{\xi(\boldsymbol{x})-z}(d\boldsymbol{x}) \right) dz.$$

- The measure $\delta_{\xi(\boldsymbol{x})-z}$ can be understood using a regularization procedure: for any test function $\psi : \mathbb{R}^d \to \mathbb{R}$,

$$\int_{\Sigma(z)} \psi(\boldsymbol{x}) \delta_{\xi(\boldsymbol{x})-z}(d\boldsymbol{x}) = \lim_{\epsilon \to 0} \int_{\mathbb{R}^d} \psi(\boldsymbol{x}) \delta^\epsilon(\xi(\boldsymbol{x}) - z) \, d\boldsymbol{x}$$

  where $\lim_{\epsilon \to 0} \delta^\epsilon = \delta$ (Dirac mass at zero).
- The measure $\delta_{\xi(\boldsymbol{x})-z}$ is related to the Lebesgue measure on $\Sigma(z)$ through:

$$\delta_{\xi(\boldsymbol{x})-z} = |\nabla \xi|^{-1} d\sigma_{\Sigma(z)}.$$

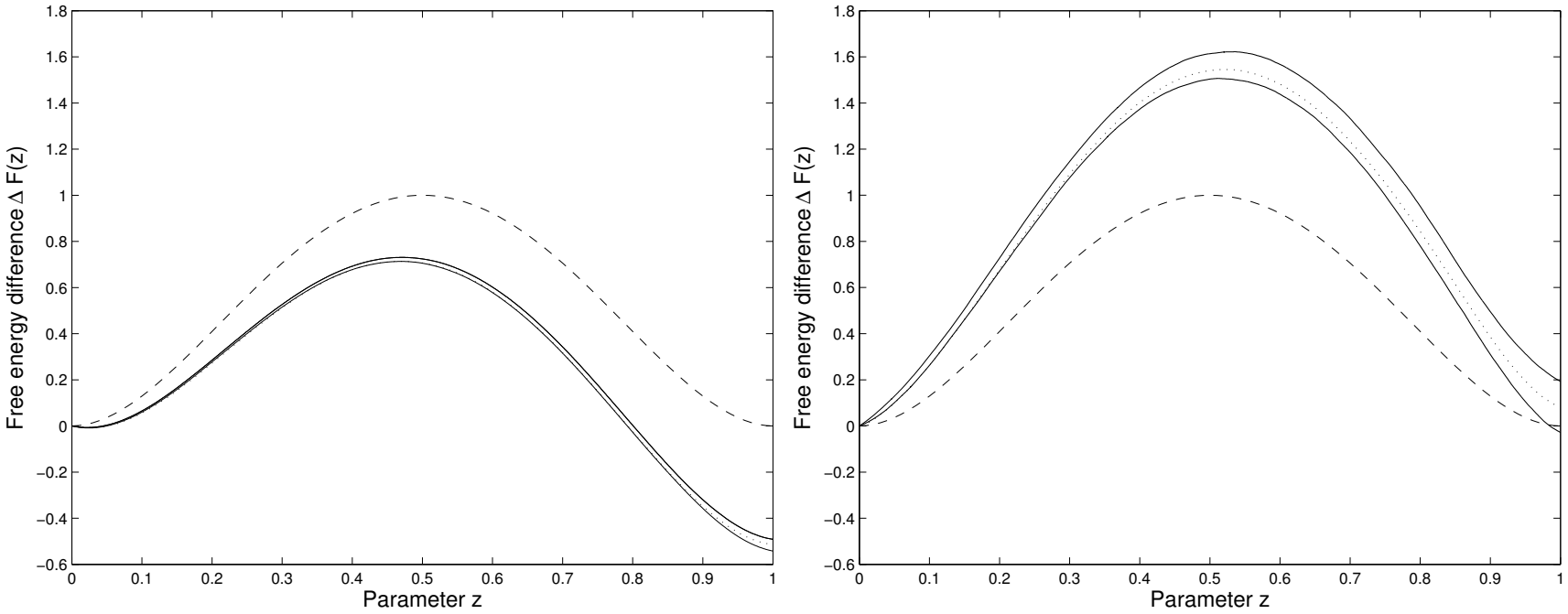
  This is the co-area formula. We thus have: $A(z) = -\beta^{-1} \ln \left(\int_{\Sigma(z)} e^{-\beta V} |\nabla \xi|^{-1} d\sigma_{\Sigma(z)} \right)$.

Free energy: Remarks

- A is the free energy associated with the reaction coordinate or collective variable ξ (angle, length, ...). The aim of many molecular dynamic simulations is to compute A.
- A is defined up to an additive constant, so that it is enough to compute free energy differences, or the derivative of A (the mean force).
- $A(z) = -\beta^{-1} \ln Z_{\Sigma(z)}$ and $Z_{\Sigma(z)}$ is the partition function associated with the conditioned probability measures: $\nu_{\Sigma(z)} = Z_{\Sigma(z)}^{-1} e^{-\beta V} |\nabla \xi|^{-1} d\sigma_{\Sigma(z)}$.
- If $U = \displaystyle\int_{\Sigma(z)} V \, Z_{\Sigma(z)}^{-1} e^{-\beta V} \delta_{\xi(\boldsymbol{x})-z}(d\boldsymbol{x})$ and $S = -k_B \displaystyle\int_{\Sigma(z)} \ln \left(Z_{\Sigma(z)}^{-1} e^{-\beta V} \right) Z_{\Sigma(z)}^{-1} e^{-\beta V} \delta_{\xi(\boldsymbol{x})-z}(d\boldsymbol{x})$, then $A = U - TS$ (since $\beta^{-1} = k_B T$).

Free energy on a simple example

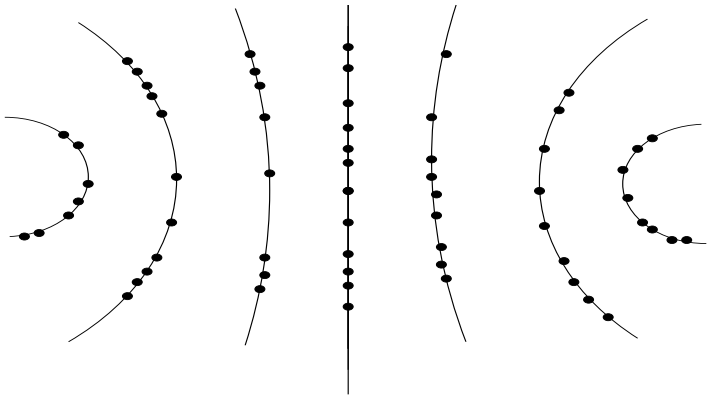
What is free energy ? The simple example of the solvation of a dimer. (Profiles computed using thermodynamic integration.)



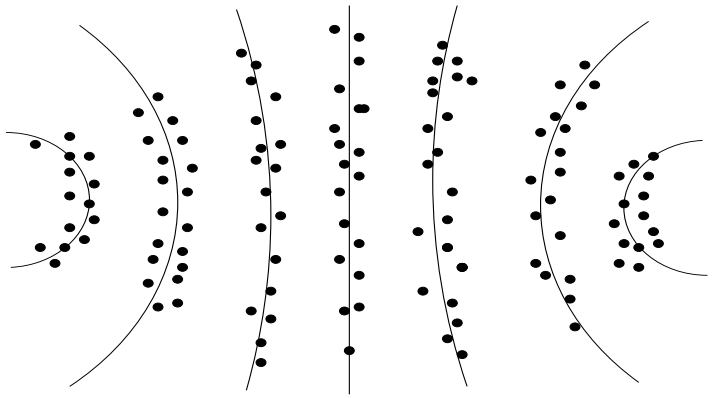
The density of the solvent molecules is lower on the left than on the right. At high (resp. low) density, the compact state is more (resp. less) likely. The "free energy barrier" is higher at high density than at low density. Related question: interpretation of the free energy barrier in terms of dynamics ?

Free energy calculation techniques

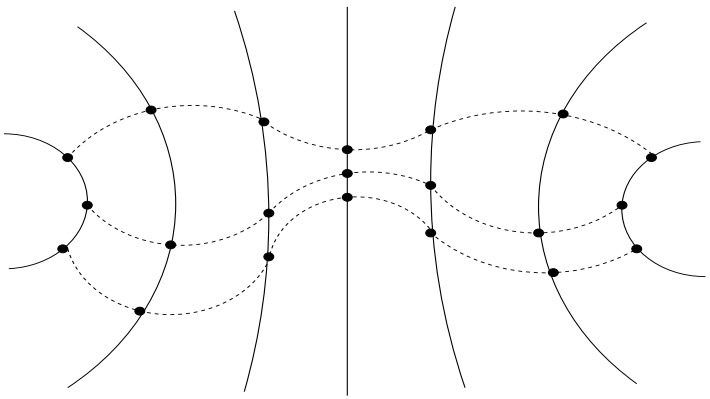
There are many free energy calculation techniques:



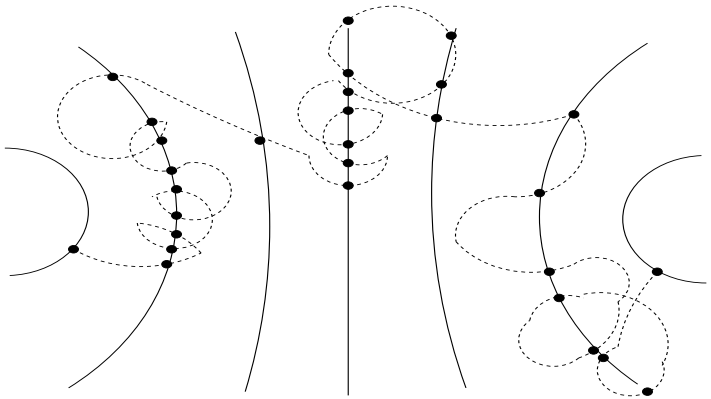
(a) Thermodynamic integration.



(b) Histogram method.

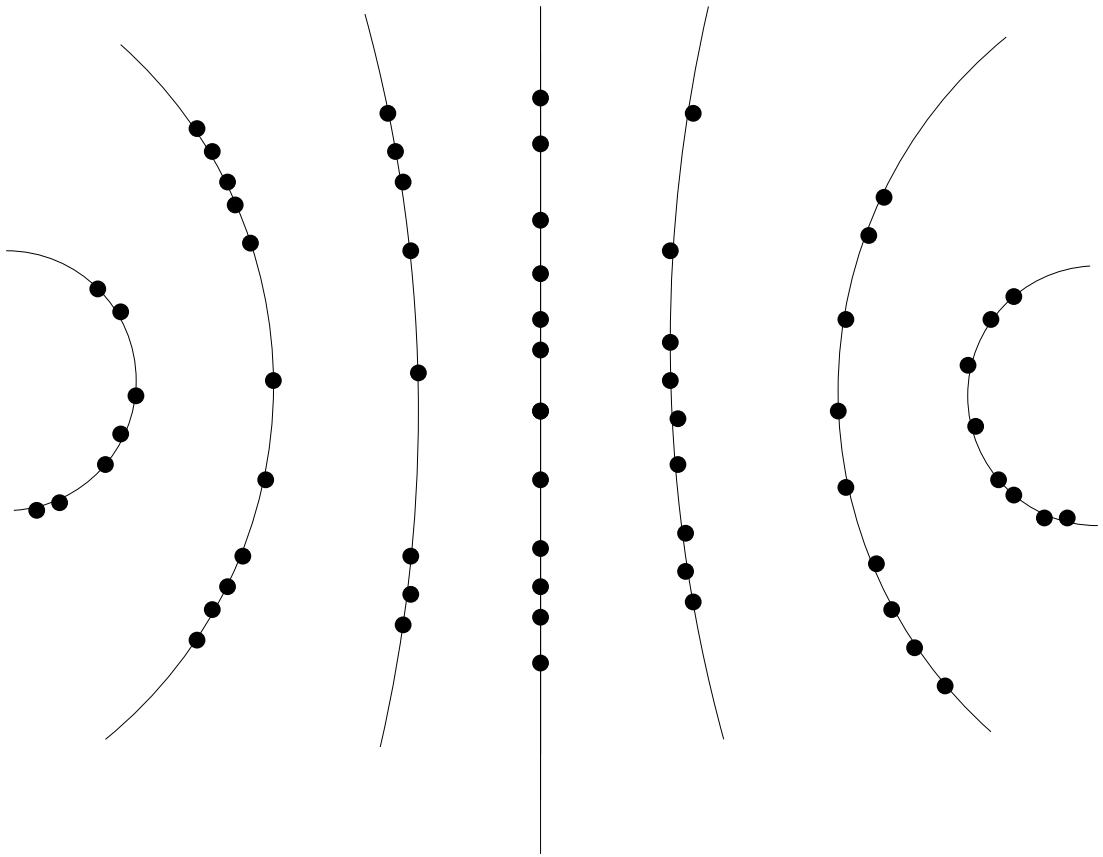


(c) Non equilibrium dynamics.



(d) Adaptive dynamics.

Thermodynamic integration



Ingredient 1: the mean force

Thermodynamic integration is based on two ingredients:
Ingredient 1: The derivative $A'(z)$ can be obtained by sampling the conditional probability measure $\nu_{\Sigma(z)}$ *(Sprik, Ciccotti, Kapral, Vanden-Eijnden, E, den Otter, ...)*

$$A'(z) = Z_{\Sigma(z)}^{-1} \int_{\Sigma(z)} \left(\frac{\nabla V \cdot \nabla \xi}{|\nabla \xi|^2} - \beta^{-1} \mathrm{div} \left(\frac{\nabla \xi}{|\nabla \xi|^2} \right) \right) e^{-\beta V} |\nabla \xi|^{-1} d\sigma_{\Sigma(z)}$$

$$= \int_{\Sigma(z)} f \, d\nu_{\Sigma(z)}$$

where $f = \frac{\nabla V \cdot \nabla \xi}{|\nabla \xi|^2} - \beta^{-1} \mathrm{div} \left(\frac{\nabla \xi}{|\nabla \xi|^2} \right)$. Another equivalent expression:

$$A'(z) = Z_{\Sigma(z)}^{-1} \int_{\Sigma(z)} \frac{\nabla \xi}{|\nabla \xi|^2} \cdot \left(\nabla \tilde{V} + \beta^{-1} \boldsymbol{H} \right) \exp(-\beta \tilde{V}) d\sigma_{\Sigma(z)}$$

where $\tilde{V} = V + \beta^{-1} \ln |\nabla \xi|$ and $\boldsymbol{H} = -\nabla \cdot \left(\frac{\nabla \xi}{|\nabla \xi|} \right) \frac{\nabla \xi}{|\nabla \xi|}$ is the mean curvature vector.

Ingredient 1: the mean force

In the simple case $\xi(x,y) = x$, remember that

$$A(x) = -\beta^{-1} \ln \left(\int_{\Sigma(x)} e^{-\beta V(x,y)} dy \right),$$

so that

$$\begin{aligned} A'(x) &= \frac{\displaystyle\int_{\Sigma(x)} \partial_x V \, e^{-\beta V(x,y)} \, dy}{\displaystyle\int_{\Sigma(x)} e^{-\beta V(x,y)} \, dy} \\ &= \int_{\Sigma(x)} \partial_x V \, d\nu_{\Sigma(x)}. \end{aligned}$$

Ingredient 1: the mean force

Proof in the general case : $A'(z) = -\beta^{-1} \frac{\frac{d}{dz} \int_{\Sigma(z)} \exp(-\beta V) \delta_{\xi(\boldsymbol{x})-z}(d\boldsymbol{x})}{\int_{\Sigma(z)} \exp(-\beta V) \delta_{\xi(\boldsymbol{x})-z}(d\boldsymbol{x})}$

and

$$\int_{\mathbb{T}} \left(\int_{\Sigma(z)} \exp(-\beta V) \delta_{\xi(\boldsymbol{x})-z}(d\boldsymbol{x}) \right)' \phi(z)\, dz$$

$$= - \int_{\mathbb{T}} \int_{\Sigma(z)} \exp(-\beta V) \delta_{\xi(\boldsymbol{x})-z}(d\boldsymbol{x}) \phi'\, dz$$

$$= - \int_{\mathbb{T}} \int_{\Sigma(z)} \exp(-\beta V) \phi' \circ \xi\, \delta_{\xi(\boldsymbol{x})-z}(d\boldsymbol{x})\, dz$$

$$= - \int_{\mathbb{R}^d} \exp(-\beta V) \phi' \circ \xi d\boldsymbol{x} = - \int_{\mathbb{R}^d} \exp(-\beta V) \nabla(\phi \circ \xi) \cdot \frac{\nabla \xi}{|\nabla \xi|^2} d\boldsymbol{x}$$

$$= \int_{\mathbb{R}^d} \nabla \cdot \left(\exp(-\beta V) \frac{\nabla \xi}{|\nabla \xi|^2} \right) \phi \circ \xi\, d\boldsymbol{x}$$

$$= \int_{\mathbb{T}} \int_{\Sigma(z)} \left(-\beta \frac{\nabla V \cdot \nabla \xi}{|\nabla \xi|^2} + \nabla \cdot \left(\frac{\nabla \xi}{|\nabla \xi|^2} \right) \right) \exp(-\beta V) \delta_{\xi(\boldsymbol{x})-z}(d\boldsymbol{x}) \phi(z)\, d$$

Ingredient 2: constrained dynamics

Ingredient 2: It is possible to sample the conditioned probability measure $\nu_{\Sigma(z)} = Z_{\Sigma(z)}^{-1} \exp(-\beta \tilde{V}) d\sigma_{\Sigma(z)}$ by considering the following rigidly constrained dynamics:

$$\text{(RCD)} \quad \begin{cases} d\boldsymbol{X}_t = -\nabla \tilde{V}(\boldsymbol{X}_t)\, dt + \sqrt{2\beta^{-1}} d\boldsymbol{W}_t + \nabla \xi(\boldsymbol{X}_t) d\Lambda_t \\ d\Lambda_t \text{ such that } \xi(\boldsymbol{X}_t) = z \end{cases}$$

The Lagrange multiplier writes $d\Lambda_t = d\Lambda_t^{\mathrm{m}} + d\Lambda_t^{\mathrm{f}}$, with $d\Lambda_t^{\mathrm{m}} = -\sqrt{2\beta^{-1}} \frac{\nabla \xi}{|\nabla \xi|^2}(\boldsymbol{X}_t) \cdot d\boldsymbol{W}_t$ and

$$d\Lambda_t^{\mathrm{f}} = \frac{\nabla \xi}{|\nabla \xi|^2} \cdot \left(\nabla \tilde{V} + \beta^{-1} \boldsymbol{H} \right)(\boldsymbol{X}_t)\, dt = f(\boldsymbol{X}_t)\, dt$$

Ingredient 2: constrained dynamics

Equivalently, the rigidly constrained dynamics writes:

$$\text{(RCD)} \quad d\boldsymbol{X}_t = P(\boldsymbol{X}_t)\left(-\nabla \tilde{V}(\boldsymbol{X}_t)\,dt + \sqrt{2\beta^{-1}}\,d\boldsymbol{W}_t\right) + \beta^{-1}\boldsymbol{H}(\boldsymbol{X}_t)\,dt$$

where $P(\boldsymbol{x})$ is the orthogonal projection operator on $T_x(\Sigma(\xi(x)))$:

$$P(\boldsymbol{x}) = \mathrm{Id} - \boldsymbol{n}(\boldsymbol{x}) \otimes \boldsymbol{n}(\boldsymbol{x}),$$

with $\boldsymbol{n}$ the unit normal vector: $\boldsymbol{n}(\boldsymbol{x}) = \dfrac{\nabla \xi}{|\nabla \xi|}(\boldsymbol{x})$.

(RCD) can also be written using the Stratonovitch product:
$d\boldsymbol{X}_t = -P(\boldsymbol{X}_t)\nabla \tilde{V}(\boldsymbol{X}_t)\,dt + \sqrt{2\beta^{-1}}P(\boldsymbol{X}_t) \circ d\boldsymbol{W}_t$.

One can check that $\xi(\boldsymbol{X}_t)$ is constant if $\boldsymbol{X}_t$ satisfies (RCD).

Ingredient 2: constrained dynamics

[G. Ciccotti, TL, E. Vanden-Einjden, 2008] Assume wlg that $z = 0$. The probability $\nu_{\Sigma(0)}$ is the unique invariant measure with support in $\Sigma(0)$ for (RCD).

Proposition: Let $\boldsymbol{X}_t$ be the solution to (RCD) such that the law of $\boldsymbol{X}_0$ is $\nu_{\Sigma(0)}$. Then, for all smooth function ϕ and for all time $t > 0$,

$$\mathbb{E}(\phi(\boldsymbol{X}_t)) = \int \phi d\nu_{\Sigma(0)}.$$

Proof: Introduce the infinitesimal generator and apply the divergence theorem on submanifolds : $\forall \boldsymbol{\phi} \in \mathcal{C}^1(\mathbb{R}^d, \mathbb{R}^d)$,

$$\int \text{div}_{\Sigma(0)}(\boldsymbol{\phi})\, d\sigma_{\Sigma(0)} = -\int \boldsymbol{H} \cdot \boldsymbol{\phi}\, d\sigma_{\Sigma(0)},$$

where $\text{div}_{\Sigma(0)}(\boldsymbol{\phi}) = \text{tr}(P\nabla\boldsymbol{\phi})$. Notice that this rewrites:

$$\int \text{div}_{\Sigma(0)}(P\boldsymbol{\phi})\, d\sigma_{\Sigma(0)} = 0.$$

Thermodynamic integration

Using the two ingredients above, $A'(z) = \lim_{T\to\infty} \frac{1}{T}\int_0^T f(\boldsymbol{X}_t)\,dt$, where $\boldsymbol{X}_t$ satisfies (RCD) and $\xi(\boldsymbol{X}_0) = z$. The free energy profile is then obtained by thermodynamic integration:

$$A(z) - A(0) = \int_0^z A'(z)\,dz \simeq \sum_{i=0}^{K} \omega_i A'(z_i).$$

Notice that there is actually no need to compute f in practice since the mean force can be obtained by averaging the Lagrange multipliers:

$$A'(z) = \lim_{T\to\infty} \frac{1}{T}\int_0^T d\Lambda_t = \lim_{T\to\infty} \frac{1}{T}\int_0^T d\Lambda_t^{\mathrm{f}}$$

since $d\Lambda_t = d\Lambda_t^{\mathrm{m}} + d\Lambda_t^{\mathrm{f}}$, with $d\Lambda_t^{\mathrm{m}} = -\sqrt{2\beta^{-1}}\frac{\nabla\xi}{|\nabla\xi|^2}(\boldsymbol{X}_t)\cdot d\boldsymbol{W}_t$ and $d\Lambda_t^{\mathrm{f}} = f(\boldsymbol{X}_t)\,dt$.

Discretization of (RCD)

The two following schemes are consistent with (RCD):

$$(S1)\begin{cases} \boldsymbol{X}_{n+1} = \boldsymbol{X}_n - \nabla\tilde{V}(\boldsymbol{X}_n)\Delta t + \sqrt{2\beta^{-1}}\Delta\boldsymbol{W}_n + \lambda_n\nabla\xi(\boldsymbol{X}_{n+1}), \\ \text{with } \lambda_n \in \mathbb{R} \text{ such that } \xi(\boldsymbol{X}_{n+1}) = 0, \end{cases}$$

$$(S2)\begin{cases} \boldsymbol{X}_{n+1} = \boldsymbol{X}_n - \nabla\tilde{V}(\boldsymbol{X}_n)\Delta t + \sqrt{2\beta^{-1}}\Delta\boldsymbol{W}_n + \lambda_n\nabla\xi(\boldsymbol{X}_{n}), \\ \text{with } \lambda_n \in \mathbb{R} \text{ such that } \xi(\boldsymbol{X}_{n+1}) = 0, \end{cases}$$

where $\Delta\boldsymbol{W}_n = \boldsymbol{W}_{(n+1)\Delta t} - \boldsymbol{W}_{n\Delta t}$. The constraint is exactly satisfied (important for longtime computations). An approximation of $A'(0) = \lim_{T\to\infty} \frac{1}{T}\int_0^T d\Lambda_t$ is:

$$\lim_{T\to\infty}\lim_{\Delta t\to 0}\frac{1}{T}\sum_{n=1}^{T/\Delta t}\lambda_n = A'(0).$$

Error analysis

[Faou,TL, Mathematics of Computation, 2010] Using classical techniques (Talay-Tubaro like proof), one can check that the ergodic measure $\nu_{\Sigma(0)}^{\Delta t}$ sampled by the Markov chain $(\boldsymbol{X}_n)_{n\geq 0}$ is an approximation of order one of $\nu_{\Sigma(0)}$: for all smooth functions $g : \Sigma(0) \to \mathbb{R}$,

$$\left| \int_{\Sigma(0)} g \, d\nu_{\Sigma(0)}^{\Delta t} - \int_{\Sigma(0)} g \, d\nu_{\Sigma(0)} \right| \leq C \Delta t.$$

Rigidly and softly constrained dynamics

Another way to constrain the overdamped Langevin dynamics to $\Sigma(0)$ is to add a constraining potential (soft constraint):

$$d\boldsymbol{X}_t^\eta = -\nabla V(\boldsymbol{X}_t^\eta)\,dt - \frac{1}{2\eta}\nabla(\xi^2)(\boldsymbol{X}_t^\eta)\,dt + \sqrt{2\beta^{-1}}d\boldsymbol{W}_t$$

One can show that $\lim_{\eta\to 0} \boldsymbol{X}_t^\eta = \boldsymbol{X}_t$ (in $L^\infty_{t\in[0,T]}(L^2_\omega)$-norm) where $\boldsymbol{X}_t$ satisfies (RCD). Notice that we used V and not $\tilde{V}$ in the softly constrained dynamics.

The statistics associated with the dynamics where the constraints are rigidly imposed and the dynamics where the constraints are softly imposed are different: "a stiff spring $\neq$ a rigid rod" *(van Kampen, Hinch,...)*.

Back to the sampling of ν

TI yields a way to compute $\int_{\mathbb{R}^d} \phi d\nu$:

$$\begin{aligned}
\int_{\mathbb{R}^d} \phi d\nu &= Z^{-1} \int_{\mathbb{R}^d} \phi e^{-\beta V} d\boldsymbol{x} \\
&= Z^{-1} \int_{\mathbb{T}} \int_{\Sigma(z)} \phi e^{-\beta V} \delta_{\xi(\boldsymbol{x})-z}(d\boldsymbol{x}) \\
&= Z^{-1} \int_{\mathbb{T}} \frac{\int_{\Sigma(z)} \phi e^{-\beta V} \delta_{\xi(\boldsymbol{x})-z}(d\boldsymbol{x})}{\int_{\Sigma(z)} e^{-\beta V} \delta_{\xi(\boldsymbol{x})-z}(d\boldsymbol{x})} \int_{\Sigma(z)} e^{-\beta V} \delta_{\xi(\boldsymbol{x})-z}(d\boldsymbol{x})\, dz \\
&= \left(\int_{\mathbb{T}} e^{-\beta A(z)}\, dz \right)^{-1} \int_{\mathbb{T}} \left(\int_{\Sigma(z)} \phi d\nu_{\Sigma(z)} \right) e^{-\beta A(z)}\, dz
\end{aligned}$$

where, we recall, $\Sigma(z) = \{\boldsymbol{x},\, \xi(\boldsymbol{x}) = z\}$,
$A(z) = -\beta^{-1} \ln \left(\int_{\Sigma(z)} e^{-\beta V} \delta_{\xi(\boldsymbol{x})-z}(d\boldsymbol{x}) \right)$ and
$\nu_{\Sigma(z)} = e^{-\beta V} \delta_{\xi(\boldsymbol{x})-z}(d\boldsymbol{x}) / \int_{\Sigma(z)} e^{-\beta V} \delta_{\xi(\boldsymbol{x})-z}(d\boldsymbol{x})$.

Generalization to Langevin dynamics

Interests: (i) Newton's equations of motion are more "natural"; (ii) is less sensitive to choice of the timestep choice; (iii) leads to numerical schemes which sample the constrained measure without time discretization error (Metropolis-Hastings);

$$\begin{cases} dq_t = M^{-1} p_t \, dt \\ dp_t = -\nabla V(q_t) \, dt - \gamma M^{-1} p_t \, dt + \sqrt{2\gamma\beta^{-1}} dW_t + \nabla\xi(q_t) \, d\lambda_t \\ \xi(q_t) = z. \end{cases}$$

The probability measure sampled by this dynamics is

$$\mu_{T^*\Sigma(z)}(dqdp) = Z^{-1} \exp(-\beta H(q,p)) \sigma_{T^*\Sigma(z)}(dqdp)$$

where $H(q,p) = V(q) + \frac{1}{2} p^T M^{-1} p$.

Generalization to Langevin dynamics

The marginal of $\mu_{T^*\Sigma(z)}(dqdp)$ in q writes:

$$\nu^M_{\Sigma(z)} = \frac{1}{Z}\exp(-\beta V(q))\sigma^M_{\Sigma(z)}(dq) \neq \frac{1}{Z}\exp(-\beta V(q))\delta_{\xi(q)-z}(dq).$$

Thus, the "free energy" which is naturally computed by this dynamics is

$$A^M(z) = -\beta^{-1}\ln\left(\int_{\Sigma(z)}\exp(-\beta V(q))\sigma^M_{\Sigma(z)}(dq)\right).$$

The original free energy may be recovered from the relation: for $G_M = \nabla\xi^T M^{-1}\nabla\xi$,

$$A(z) - A^M(z) = -\beta^{-1}\ln\left(\int_{\Sigma(z)}\det(G_M)^{-1/2}d\nu^M_{\Sigma(z)}\right).$$

Generalization to Langevin dynamics

Moreover, one can check that:

$$\lim_{T\to\infty} \frac{1}{T} \int_0^T d\lambda_t = (A^M)'(z).$$

Discretization of the constrained Langevin dynamics

For simplicity, let us consider $\beta = 1$, $M = \mathrm{Id}$ and let us denote $\mathcal{M} = \Sigma(0)$. Let us rewrite the extended measure in phase space:

$$\mu(dq\,dp) = Z_\mu^{-1} \mathrm{e}^{-H(q,p)}\, \sigma_{T^*\mathcal{M}}(dq\,dp)$$

where $H(q,p) = V(q) + \frac{|p|^2}{2}$ and $\sigma_{T^*\mathcal{M}}(dq\,dp)$ is the phase space Liouville measure on

$$T^*\mathcal{M} = \left\{(q,p) \in \mathbb{R}^d \times \mathbb{R}^d,\ \xi(q) = 0 \text{ and } [\nabla\xi(q)]^T\, p = 0\right\}.$$

The marginal of μ in q is $\nu = Z_\nu^{-1} \exp(-\beta V(q))\sigma_{\mathcal{M}}(dq)$. Indeed, the measure μ rewrites:

$$\mu(dq\,dp) = \nu(dq)\,\kappa_q(dp)$$

where

$$\kappa_q(dp) = (2\pi)^{\frac{m-d}{2}} \mathrm{e}^{-\frac{|p|^2}{2}} \sigma_{T_q^*\mathcal{M}}(dp)$$

with $T_q^*\mathcal{M} = \left\{p \in \mathbb{R}^d,\ [\nabla\xi(q)]^T\, p = 0\right\} \subset \mathbb{R}^d$.

The constrained Langevin dynamics

The constrained Langevin dynamics ($\gamma > 0$ is the friction parameter)

$$\begin{cases} dq_t = p_t\, dt \\ dp_t = -\nabla V(q_t)\, dt - \gamma p_t\, dt + \sqrt{2\gamma} dW_t + \nabla\xi(q_t)\, d\lambda_t \\ \xi(q_t) = 0 \end{cases}$$

is ergodic with respect to μ. Notice that $[\nabla\xi(q_t)]^T p_t = 0$.
It can be seen as the composition (operator splitting) of:

- the constrained Hamiltonian dynamics:

$$\begin{cases} dq_t = p_t\, dt \\ dp_t = -\nabla V(q_t)\, dt + \nabla\xi(q_t)\, d\lambda_t \\ \xi(q_t) = 0. \end{cases}$$

- the Ornstein-Uhlenbeck process on momenta:

$$\begin{cases} dq_t = 0 \\ dp_t = -\gamma p_t\, dt + \sqrt{2\gamma} dW_t + \nabla\xi(q_t)\, d\lambda_t \\ [\nabla\xi(q_t)]^T p_t = 0. \end{cases}$$

.

The Ornstein-Uhlenbeck part

Discretization of the Ornstein-Uhlenbeck process on momenta: midpoint Euler leaves the measure κ_{q^n} and thus μ invariant:

$$\begin{cases} p^{n+1} = p^n - \dfrac{\Delta t}{2}\gamma\,(p^n + p^{n+1}) + \sqrt{2\gamma\Delta t}\,G^n + \nabla\xi(q^n)\,\lambda^n, \\ \nabla\xi(q^n)^T p^{n+1} = 0, \end{cases}$$

In the following, we denote one step of this dynamics by $\Psi^{OU}_{\Delta t} : T^*\mathcal{M} \to T^*\mathcal{M}$:

$$\Psi^{OU}_{\Delta t}(q^n, p^n) = (q^n, p^{n+1}).$$

Remark: The projection is always well defined, and easy to implement:

$$p^{n+1} = \Pi^*(q^n)\left(\frac{(1 - \Delta t\gamma/2)p^n + \sqrt{2\gamma\Delta t}\,G^n}{1 + \Delta t\gamma/2}\right)$$

where $\Pi^*(q) = \mathrm{Id} - \nabla\xi(q)G^{-1}(q)[\nabla\xi(q)]^T$ is the orthogonal projector from $\mathbb{R}^d$ to $T^*_q\mathcal{M}$.

The Hamiltonian part

Discretization of the constrained Hamiltonian dynamics (RATTLE):

$$\begin{cases} p^{n+1/2} = p^n - \dfrac{\Delta t}{2} \nabla V(q^n) + \nabla \xi(q^n)\, \lambda^{n+1/2}, \\ q^{n+1} = q^n + \Delta t\, p^{n+1/2}, \\ \xi(q^{n+1}) = 0, & (C_q) \\ p^{n+1} = p^{n+1/2} - \dfrac{\Delta t}{2} \nabla V(q^{n+1}) + \nabla \xi(q^{n+1})\, \lambda^{n+1}, \\ \left[\nabla \xi(q^{n+1})\right]^T p^{n+1} = 0, & (C_p) \end{cases}$$

where $\lambda^{n+1/2} \in \mathbb{R}^m$ are the Lagrange multipliers associated with the position constraints (C_q), and $\lambda^{n+1} \in \mathbb{R}^m$ are the Lagrange multipliers associated with the velocity constraints (C_p).

In the following, we denote one step of the RATTLE dynamics by $\Psi_{\Delta t}^{RATTLE} : T^*\mathcal{M} \to T^*\mathcal{M}$:

$$\Psi_{\Delta t}^{RATTLE}(q^n, p^n) = (q^{n+1}, p^{n+1}).$$

Discretization by a Strang splitting

Discretization of the constrained Langevin dynamics (Strang splitting):

$$\begin{cases} (q^n, p^{n+1/4}) = \Psi^{OU}_{\Delta t/2}(q^n, p^n) \\ (q^{n+1}, p^{n+3/4}) = \Psi^{RATTLE}_{\Delta t}(q^n, p^{n+1/4}) \\ (q^{n+1}, p^{n+1}) = \Psi^{OU}_{\Delta t/2}(q^{n+1}, p^{n+3/4}) \end{cases}$$

But there is a bias due to time discretization...

Unbiasing using Hastings-Metropolis

Let us denote by

$$S(q,p) = (q,-p)$$

the momentum reversal map and

$$\Psi_{\Delta t}(q,p) = S\left(\Psi_{\Delta t}^{RATTLE}(q,p)\right).$$

Fundamental properties of RATTLE: for Δt small enough,

- $\Psi_{\Delta t}\left(\Psi_{\Delta t}(q,p)\right) = (q,p)$
- $\Psi_{\Delta t}$ is a symplectic map, which thus preserves $\sigma_{T^*\mathcal{M}}$

[Hairer, Lubich, Wanner, 2006] [Leimkuhler, Reich, 2004] [Leimkuhler, Skeel, 1994].

One can thus add a Metropolis Hastings rejection step to get unbiased samples: if $(q',p') = \Psi_{\Delta t}(q,p)$, the MH ratio writes:

$$\frac{\delta_{\Psi_{\Delta t}(q',p')}(dq\,dp)\,\mathrm{e}^{-H(q',p')}\,\sigma_{T^*\mathcal{M}}(dq'\,dp')}{\delta_{\Psi_{\Delta t}(q,p)}(dq'\,dp')\,\mathrm{e}^{-H(q,p)}\,\sigma_{T^*\mathcal{M}}(dq\,dp)} = \mathrm{e}^{-H(q',p')+H(q,p)}.$$

The constrained GHMC algorithm

Constrained Generalized Hybrid Monte Carlo algorithm ([TL, Rousset, Stoltz 2012], constrained version of [Horowitz 1991]):

$$
\left\{
\begin{array}{l}
(q^n, p^{n+1/4}) = \Psi^{OU}_{\Delta t/2}(q^n, p^n) \\
(\tilde{q}^{n+1}, \tilde{p}^{n+3/4}) = \Psi_{\Delta t}(q^n, p^{n+1/4}) \\
\quad \text{If } U^n \leq \mathrm{e}^{-H(\tilde{q}^{n+1},\tilde{p}^{n+3/4})+H(q^n,p^{n+1/4})} \\
\qquad \text{accept the proposal: } (q^{n+1}, p^{n+3/4}) = (\tilde{q}^{n+1}, \tilde{p}^{n+3/4}) \\
\qquad \text{else reject the proposal: } (q^{n+1}, p^{n+3/4}) = (q^n, p^{n+1/4}) \\
\tilde{p}^{n+1} = -p^{n+3/4} \\
(q^{n+1}, p^{n+1}) = \Psi^{OU}_{\Delta t/2}(q^{n+1}, \tilde{p}^{n+1})
\end{array}
\right.
$$

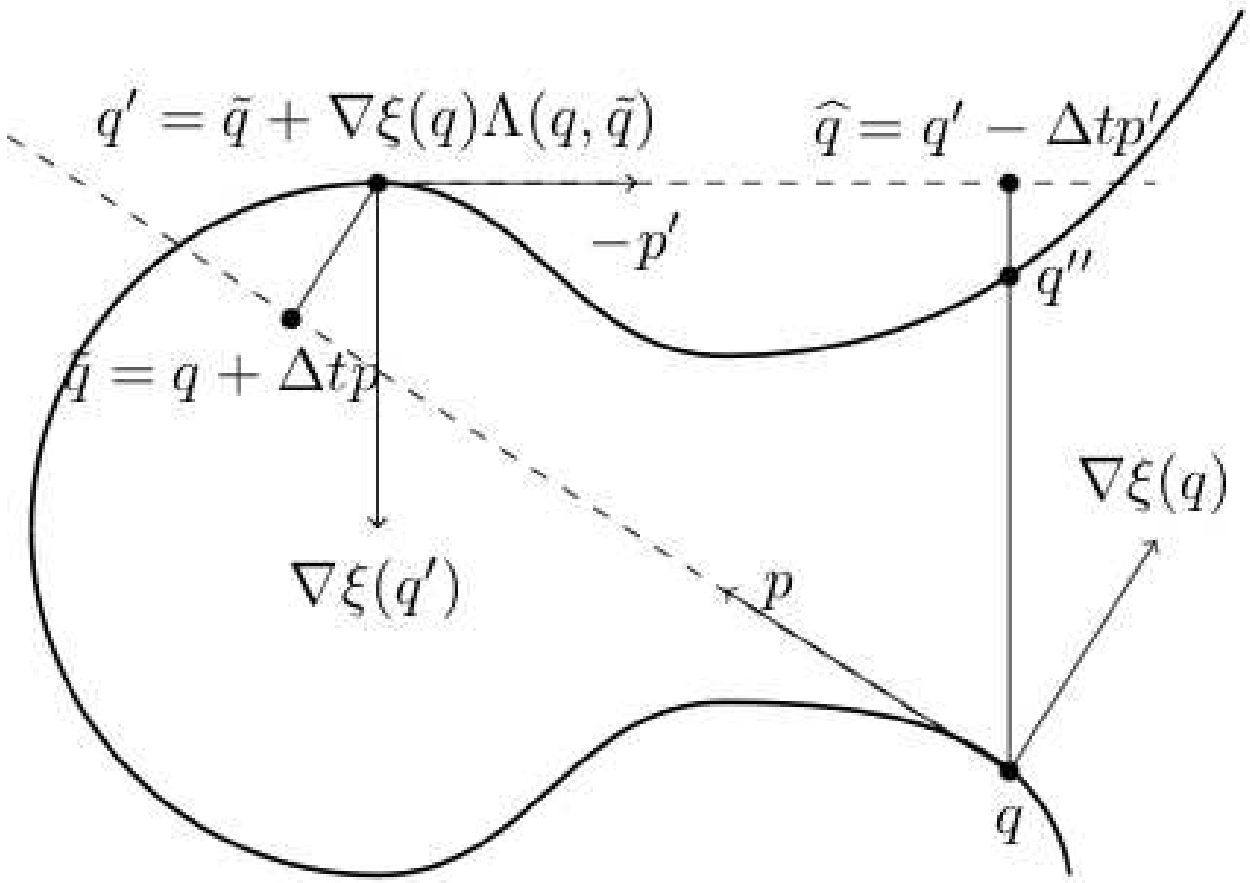
where $U^n \sim \mathcal{U}(0,1)$.

Is it really reversible in practice?

Problem: RATTLE is only well defined and reversible for locally small timesteps. Three possible difficulties:

- $\Psi_{\Delta t}(q,p)$ may not be defined;
- If $\Psi_{\Delta t}(q,p)$ is well defined, $\Psi_{\Delta t}\left(\Psi_{\Delta t}(q,p)\right)$ may not be defined;
- If $\Psi_{\Delta t}(q,p)$ and $\Psi_{\Delta t}\left(\Psi_{\Delta t}(q,p)\right)$ are well defined, one may have $\Psi_{\Delta t}\left(\Psi_{\Delta t}(q,p)\right) \neq (q,p)$.

An example where $\Psi_{\Delta t}\left(\Psi_{\Delta t}(q,p)\right) \neq (q,p)$



Here, $V = 0$ and the projection is defined as the closest point to $\mathcal{M}$. Notice that $q'' \neq q$!

The Lagrange multiplier function

In order to introduce the the set of positions and momenta from which RATTLE is well defined, let us rewrite the RATTLE dynamics as follows:

$$\begin{cases} q^{n+1} = q^n + \Delta t \left[p^n - \dfrac{\Delta t}{2} \nabla V(q^n) \right] + \Delta t \nabla \xi(q^n)\, \lambda^{n+1/2} \\ p^{n+1} = \Pi^*(q^n) \left(p^n - \dfrac{\Delta t}{2} \left(\nabla V(q^n) + \nabla V(q^{n+1}) \right) + \nabla \xi(q^n)\, \lambda^{n+1/2} \right) \end{cases}$$

where

$$\Delta t \lambda^{n+1/2} = \Lambda \left(q^n, q^n + \Delta t \left[p^n - \frac{\Delta t}{2} \nabla V(q^n) \right] \right).$$

The function $\Lambda : \mathcal{D} \to \mathbb{R}^m$, where $\mathcal{D}$ is an open set of $\mathcal{M} \times \mathbb{R}^d$ is the Lagrange multiplier function which satisfies:

$$\forall (q, \tilde{q}) \in \mathcal{D},\ \tilde{q} + \nabla \xi(q) \Lambda(q, \tilde{q}) \in \mathcal{M}.$$

Local well-posedness

The function Λ is only defined on $\mathcal{D}$ and thus $\Psi_{\Delta t}^{RATTLE}$ is only defined on the open set:

$$A = \left\{ (q,p) \in T^*\mathcal{M}, \quad \left(q, q + \Delta t\, M^{-1} \left[p - \frac{\Delta t}{2} \nabla V(q) \right] \right) \in \mathcal{D} \right\}$$

and likewise, $\Psi_{\Delta t} = S \circ \Psi_{\Delta t}^{RATTLE}$ is defined on A.

Properties ([TL, Rousset, Stoltz 2018])

If Λ is C^1, then $\Psi_{\Delta t} : A \to T^*\mathcal{M}$ is a C^1 local diffeomorphism, locally preserving the phase-space measure $\sigma_{T^*\mathcal{M}}(dq\, dp)$.

How to build such a Lagrange multiplier function? Theoretically: Implicit Function Theorem. Numerically: Newton algorithm, root finding algorithms. In general, it is only locally well-defined.

The reverse projection check

Let us now introduce the RATTLE dynamics with momentum reversal and reverse projection check: for any $(q,p) \in T^*\mathcal{M}$,

$$\Psi_{\Delta t}^{\mathrm{rev}}(q,p) = \Psi_{\Delta t}(q,p) 1_{\{(q,p)\in B\}} + (q,p) 1_{\{(q,p)\notin B\}}$$

where the set $B \subset A \subset T^*\mathcal{M}$ is defined by

$$B = \left\{ (q,p) \in A,\ \Psi_{\Delta t}(q,p) \in A \text{ and } \Psi_{\Delta t} \circ \Psi_{\Delta t}(q,p) = (q,p) \right\}.$$

Properties ([TL, Rousset, Stoltz 2018])

Let us assume that Λ is C^1 and satisfies the non-tangential condition: $\forall (q,\tilde{q}) \in \mathcal{D}$,

$$\left[\nabla\xi\left(\tilde{q} + \nabla\xi(q)\Lambda(q,\tilde{q})\right)\right]^T \nabla\xi(q) \in \mathbb{R}^{m\times m} \text{ is invertible.}$$

Then, the set B is the union of path connected components of the open set $A \cap \Psi_{\Delta t}^{-1}(A)$. It is thus an open set of $T^*\mathcal{M}$. Moreover, $\Psi_{\Delta t}^{\mathrm{rev}} : T^*\mathcal{M} \to T^*\mathcal{M}$ is globally well defined, preserves globally the measure $\sigma_{T^*\mathcal{M}}(dq\,dp)$ and satisfies $\Psi_{\Delta t}^{\mathrm{rev}} \circ \Psi_{\Delta t}^{\mathrm{rev}} = \mathrm{Id}$.

The globally well-defined constrained GHMC

The constrained GHMC algorithm writes:

$$
\begin{cases}
(q^n, p^{n+1/4}) = \Psi^{OU}_{\Delta t/2}(q^n, p^n) \\
(\tilde{q}^{n+1}, \tilde{p}^{n+3/4}) = \Psi^{rev}_{\Delta t}(q^n, p^{n+1/4}) \\
\text{If } U^n \leq \mathrm{e}^{-H(\tilde{q}^{n+1}, \tilde{p}^{n+3/4}) + H(q^n, p^{n+1/4})} \\
\qquad \text{accept the proposal: } (q^{n+1}, p^{n+3/4}) = (\tilde{q}^{n+1}, \tilde{p}^{n+3/4}) \\
\qquad \text{else reject the proposal: } (q^{n+1}, p^{n+3/4}) = (q^n, p^{n+1/4}) \\
\tilde{p}^{n+1} = -p^{n+3/4} \\
(q^{n+1}, p^{n+1}) = \Psi^{OU}_{\Delta t/2}(q^{n+1}, \tilde{p}^{n+1})
\end{cases}
$$

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

Properties ([TL, Rousset, Stoltz 2018])

The Markov chain $(q^n, p^n)_{n \geq 0}$ admits μ as an invariant measure.

To prove ergodicity, it remains to check irreducibility [Hartmann, 2008].

Numerical parameters and generalizations

- In $\Psi^{rev}_{\Delta t}$, one can use any potential V! Choosing the potential V of the target measure $d\nu = Z_\nu^{-1} e^{-V} d\sigma_{\mathcal{M}}$ is good to increase the acceptance probability.
- If $\Delta t \gamma / 4 = 1$, one obtains a HMC (or MALA) algorithm. If $\Delta t \gamma / 4 = 1$ and $V = 0$ in $\Psi^{rev}_{\Delta t}$, this is a constrained random walk MH algorithm [Goodman, Holmes-Cerfon, Zappa, 2017].
- In pratice, one can use K steps of RATTLE within Ψ^{rev} to get less correlated samples. [Bou-Rabee, Sanz Serna]
- If $\Psi^{rev}_{\Delta t}(q^n, p^{n+1/4}) = \Psi_{\Delta t}(q^n, p^{n+1/4})$ (reverse projection check OK), one obtains a consistent discretization of the constrained Langevin dynamics.
- Similar ideas can be used to enforce inequality constraints.
- It may be interesting for numerical purposes to consider non identity mass matrices.

Beyond reverse projection check

Work with G. Stoltz and W. Zhang following discussions with P. Breiding

In many situations, one is able to compute if not all, many solutions to the problem: for $(q, \tilde{q}) \in \mathcal{M} \times \mathbb{R}^d$,

$$\text{find } \Lambda(q, \tilde{q}) \in \mathbb{R}^m \text{ s.t. } \tilde{q} + \nabla\xi(q)\Lambda(q, \tilde{q}) \in \mathcal{M}.$$

Let us assume that there exists $\mathcal{D} \subset \mathcal{M} \times \mathbb{R}^d$ such that for all $(q, \tilde{q}) \in \mathcal{D}$, there exists $n(q, \tilde{q}) \in \mathbb{N}$ which is locally constant, and $n(q, \tilde{q})$ C^1 functions $(\Lambda^i(q, \tilde{q}) : \mathcal{D} \to \mathbb{R}^m)_{1 \le i \le n(q,\tilde{q})}$ such that

$$\forall (q, \tilde{q}) \in \mathcal{D},\ \tilde{q} + \nabla\xi(q)\Lambda^i(q, \tilde{q}) \in \mathcal{M}.$$

How to use this additional information ?

Multiple projection constrained GHMC (1/2)

Let us assign a probability $\pi^i(q, \tilde{q})$ to each of the solutions $(\Lambda^i(q, \tilde{q}))_{1 \leq i \leq n(q,\tilde{q})}$:

$$\pi^i(q, \tilde{q}) \geq 0 \text{ and } \sum_{i=1}^{n(q,\tilde{q})} \pi^i(q, \tilde{q}) = 1.$$

For example, $\pi^i(q, \tilde{q}) = \frac{1}{n(q,\tilde{q})}$.

Then choose one of the solution at random, and adapt the constrained GHMC algorithm.

Remark: If all the solutions can be computed, then there is no need of a reverse projection check.

Multiple projection constrained GHMC (2/2)

1. Update momenta: $(q^n, p^{n+1/4}) = \Psi^{OU}_{\Delta t/2}(q^n, p^n)$
2. Compute the Lagrange multipliers $(\Lambda^i(q^n, \tilde{q}^n))_{1 \leq i \leq n(q^n, \tilde{q}^n)}$, where $\tilde{q}^n = q^n + \Delta t \left[p^{n+1/4} - \frac{\Delta t}{2} \nabla V(q^n) \right]$. Choose index $i^n \in \{1, \ldots, n(q^n, \tilde{q}^n)\}$ with probability $\pi^{i^n}(q^n, \tilde{q}^n)$.
3. Compute the move $(\tilde{q}^{n+1}, \tilde{p}^{n+3/4}) = \Psi_{\Delta t}(q^n, p^{n+1/4})$, where $\Psi_{\Delta t}$ uses in the RATTLE step the Lagrange multiplier Λ^{i^n}.
4. Check if one of the Lagrange multipliers (denoted by Λ^{j^n}) $(\Lambda^j(\tilde{q}^{n+1}, \bar{q}^{n+1}))_{1 \leq j \leq n(q^{n+1}, \bar{q}^{n+1})}$ brings back to $(q^n, -p^{n+1/4})$, where $\bar{q}^{n+1} = \tilde{q}^{n+1} + \Delta t \left[\tilde{p}^{n+3/4} - \frac{\Delta t}{2} \nabla V(\tilde{q}^{n+1}) \right]$. If not, set $(q^{n+1}, p^{n+3/4}) = (q^n, p^{n+1/4})$, and go to Step 6.
5. Accept the move $(q^{n+1}, p^{n+3/4}) = (\tilde{q}^{n+1}, \tilde{p}^{n+3/4})$ with probability

$$1 \wedge \left(\frac{\pi^{j^n}(\tilde{q}^{n+1}, \bar{q}^{n+1})}{\pi^{i^n}(q^n, \tilde{q}^n)} \mathrm{e}^{-H(\tilde{q}^{n+1}, \tilde{p}^{n+3/4}) + H(q^n, p^{n+1/4})} \right)$$

   else reject $(q^{n+1}, p^{n+3/4}) = (q^n, p^{n+1/4})$.
6. $\tilde{p}^{n+1} = -p^{n+3/4}$ and $(q^{n+1}, p^{n+1}) = \Psi^{OU}_{\Delta t/2}(q^{n+1}, \tilde{p}^{n+1})$

Theoretical result

One can adapt the arguments of the work [TL, Rousset, Stoltz 2018] to show that

Properties ([TL, Stoltz, Zhang 2020])

The Markov chain $(q^n, p^n)_{n\geq 0}$ *admits* μ *as an invariant measure.*

Same remarks as before apply: change V or the number of steps in $\Psi_{\Delta t}$, MALA version if $\Delta t \gamma/4 = 1$, inequality constraints, change the mass matrix, ...

See the preprint [TL, Stoltz, Zhang 2020] for numerical experiments: this algorithm can be useful to converge quicker to equilibrium.

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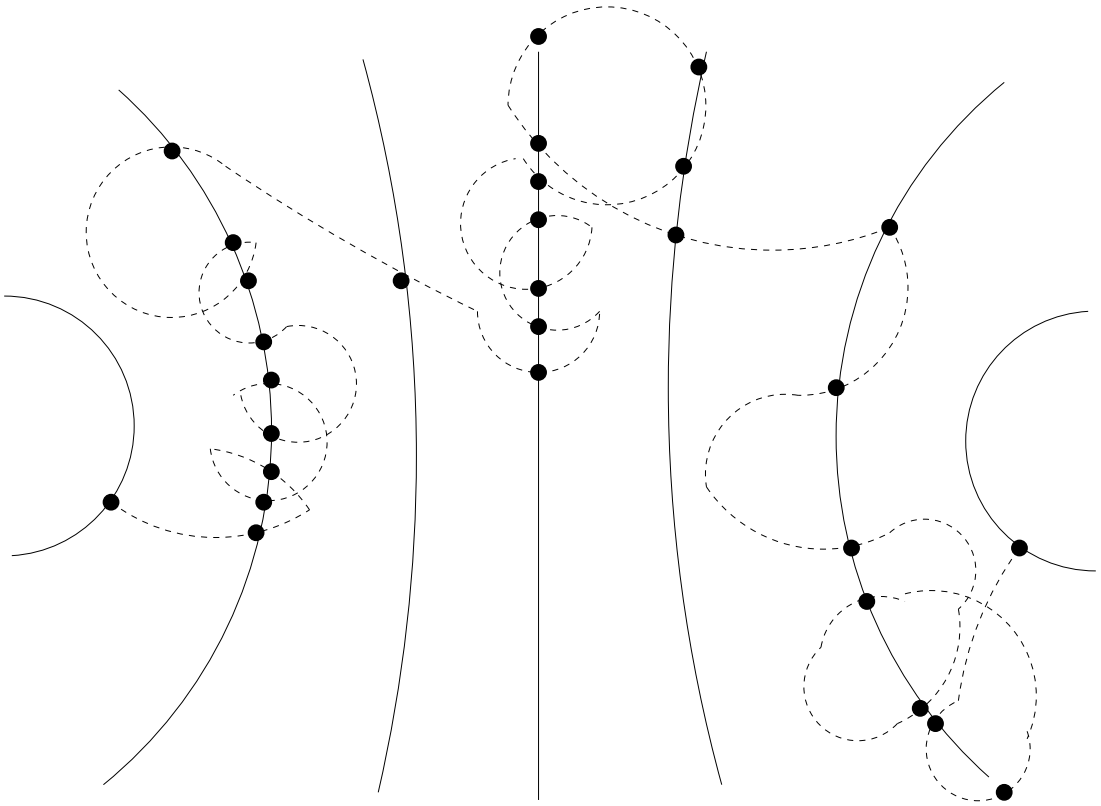
Adaptive biasing techniques

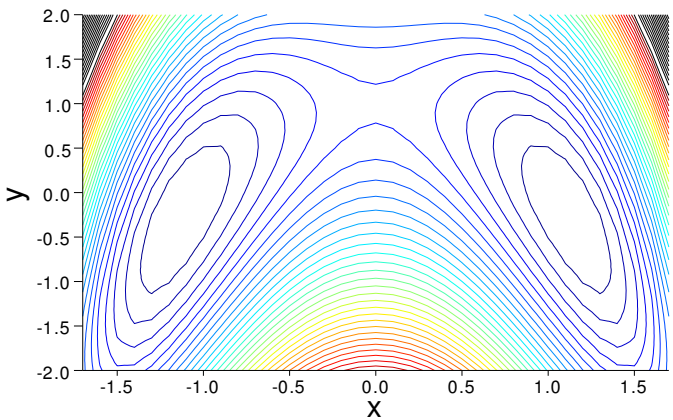


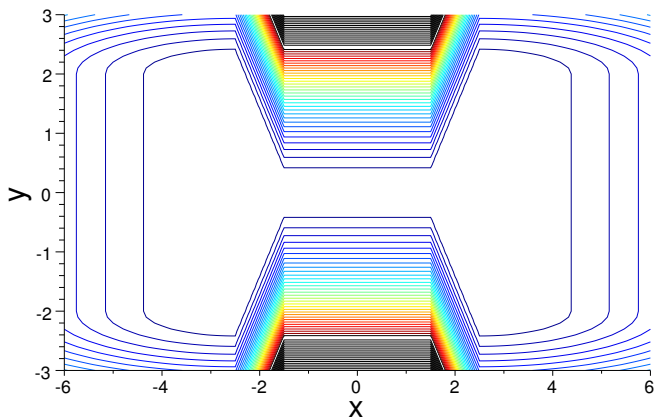
Adaptive biasing techniques

We suppose again that we know a slow variable of dimension 1: $\xi(\boldsymbol{X}_t)$, where $\xi : \mathbb{R}^d \to \mathbb{T}$ is a so-called reaction coordinate.

This reaction coordinate will be used to bias the dynamics (adaptive importance sampling technique), using the free energy A associated with the reaction coordination ξ.

For example, in the 2D simple examples: $\xi(x, y) = x$.





Adaptive biasing techniques

The bottom line of adaptive methods is the following: for "well chosen" ξ the potential $V - A \circ \xi$ is less rugged than V. Indeed, by construction $\xi_* \exp(-\beta(V - A \circ \xi)) = 1_{\mathbb{T}}$.

Problem: A is unknown ! Idea: use a time dependent potential of the form

$$\mathcal{V}_t(\boldsymbol{x}) = V(\boldsymbol{x}) - A_t(\xi(\boldsymbol{x}))$$

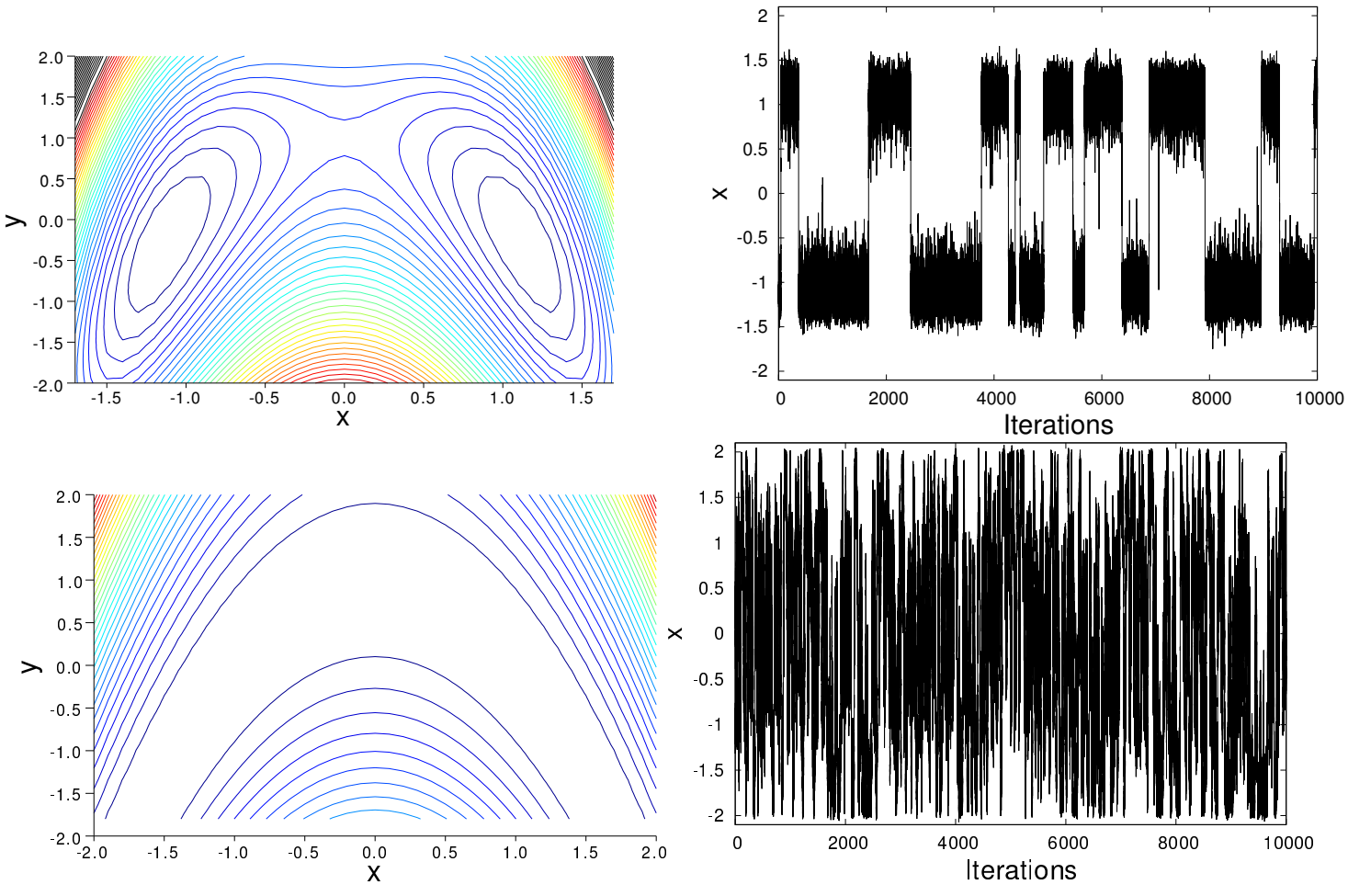
where A_t is an approximation at time t of A, given the configurations visited so far.

Hopes:

- build a dynamics which goes quickly to equilibrium,
- compute free energy profiles.

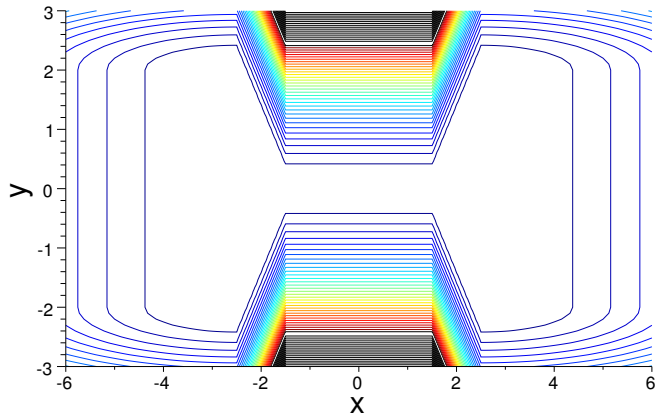
Wang-Landau, ABF, metadynamics: *Darve, Pohorille, Hénin, Chipot, Laio, Parrinello, Wang, Landau,...*

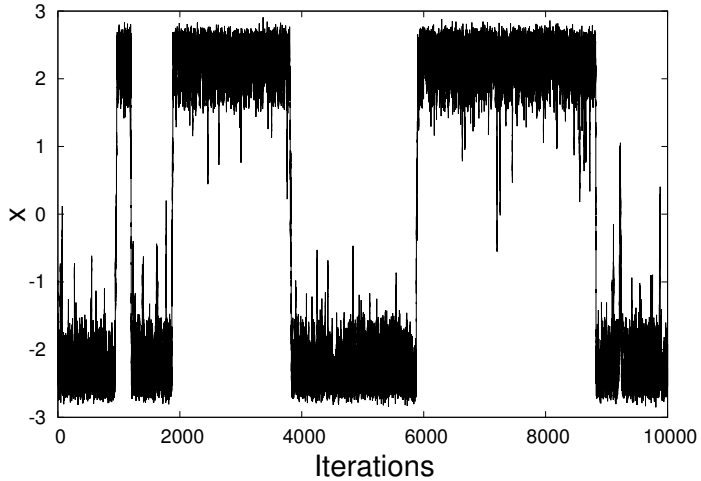
Free energy biased dynamics (1/2)

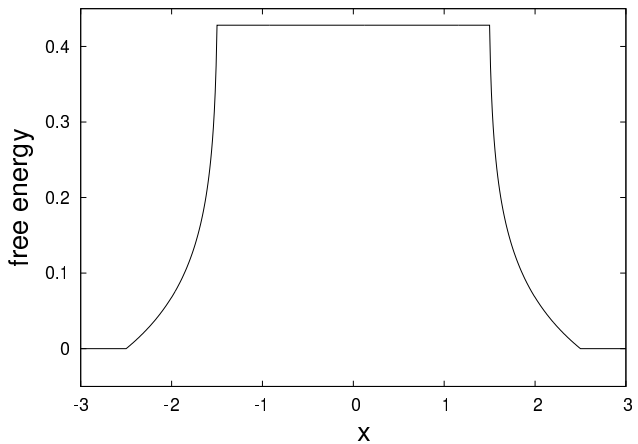


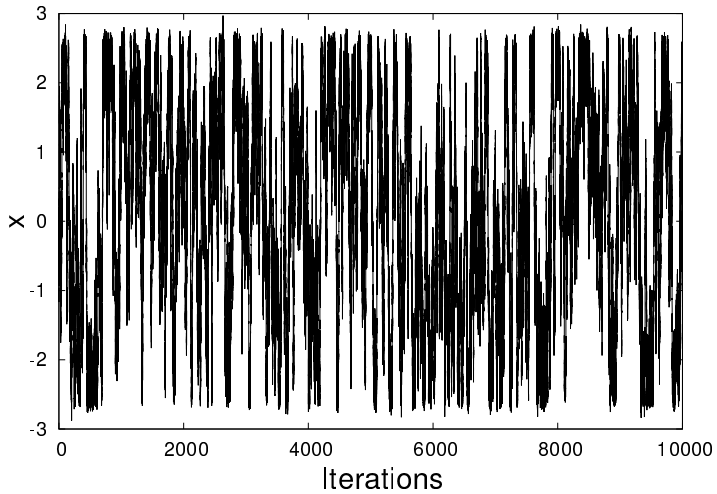
A 2D example of a free energy biased trajectory: energetic barrier.

Free energy biased dynamics (2/2)









A 2D example of a free energy biased trajectory: entropic barrier.

Updating strategies

How to update A_t ? Two methods depending on wether A'_t (Adaptive Biasing Force) or A_t (Adaptive Biasing Potential) is approximated.
To avoid geometry problem, an extended configurational space $(\boldsymbol{x}, z) \in \mathbb{R}^{n+1}$ may be considered, together with the meta-potential:

$$V^k(\boldsymbol{x}, z) = V(\boldsymbol{x}) + k(z - \xi(\boldsymbol{x}))^2.$$

Choosing $(\boldsymbol{x}, z) \mapsto z$ as a reaction coordinate, the associated free energy A^k is close to A (in the limit $k \to \infty$, up to an additive constant).

Adaptive algorithms used in molecular dynamics fall into one of these four possible combinations [TL, M. Rousset, G. Stoltz, J Chem Phys, 2007]:

	A'_t	A_t
V	ABF	Wang-Landau
V^k	...	metadynamics

The ABF method

For the Adaptive Biasing Force (ABF) method, the idea is to use the formula

$$A'(z) = \frac{\displaystyle\int_{\Sigma(z)} \left(\frac{\nabla V \cdot \nabla \xi}{|\nabla \xi|^2} - \beta^{-1} \mathrm{div} \left(\frac{\nabla \xi}{|\nabla \xi|^2} \right) \right) e^{-\beta V} \, \delta_{\xi(\boldsymbol{x})-z}(d\boldsymbol{x})}{\displaystyle\int_{\Sigma(z)} e^{-\beta V} \, \delta_{\xi(\boldsymbol{x})-z}(d\boldsymbol{x})}$$

$$= \int_{\Sigma(z)} f \, d\nu_{\Sigma(z)} = \mathbb{E}_\nu(f(\boldsymbol{X})|\xi(\boldsymbol{X}) = z).$$

The mean force $A'(z)$ is the average of f with respect to $\nu_{\Sigma(z)}$.

The ABF method

In the simple case $\xi(x,y) = x$, remember that

$$A(x) = -\beta^{-1} \ln \left(\int e^{-\beta V(x,y)} dy \right),$$

so that

$$A'(x) = \frac{\displaystyle\int_{\Sigma(x)} \partial_x V \, e^{-\beta V(x,y)} \, dy}{\displaystyle\int_{\Sigma(x)} e^{-\beta V(x,y)} \, dy}$$

$$= \int \partial_x V \, d\nu_{\Sigma(x)}.$$

Notice that actually, whatever A_t is,

$$A'(z) = \frac{\displaystyle\int_{\Sigma(z)} f \, e^{-\beta(V - A_t \circ \xi)} \, \delta_{\xi(\boldsymbol{x})-z}(d\boldsymbol{x})}{\displaystyle\int_{\Sigma(z)} e^{-\beta(V - A_t \circ \xi)} \, \delta_{\xi(\boldsymbol{x})-z}(d\boldsymbol{x})}.$$

The ABF method

Thus, we would like to simulate:

$$\begin{cases} d\boldsymbol{X}_t = -\nabla(V - A \circ \xi)(\boldsymbol{X}_t)\, dt + \sqrt{2\beta^{-1}} d\boldsymbol{W}_t, \\ A'(z) = \mathbb{E}_\nu \left(f(\boldsymbol{X}) | \xi(\boldsymbol{X}) = z \right) \end{cases}$$

but A is unknown...

The ABF method

The ABF dynamics is then:

$$\begin{cases} d\boldsymbol{X}_t = -\nabla(V - A_t \circ \xi)(\boldsymbol{X}_t)\, dt + \sqrt{2\beta^{-1}} d\boldsymbol{W}_t, \\ A_t'(z) = \mathbb{E}\left(f(\boldsymbol{X}_t) | \xi(\boldsymbol{X}_t) = z\right). \end{cases}$$

The ABF method

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The associated (nonlinear) Fokker-Planck equation writes:

$$\begin{cases} \partial_t \psi = \operatorname{div}\left(\nabla(V - A_t \circ \xi)\psi + \beta^{-1}\nabla\psi\right), \\ A_t'(z) = \dfrac{\displaystyle\int f\, \psi\, \delta_{\xi(\boldsymbol{x})-z}(d\boldsymbol{x})}{\displaystyle\int \psi\, \delta_{\xi(\boldsymbol{x})-z}(d\boldsymbol{x})}, \end{cases}$$

where $\boldsymbol{X}_t \sim \psi(t, \boldsymbol{x})\, d\boldsymbol{x}$.

The ABF method

The ABF dynamics is then:

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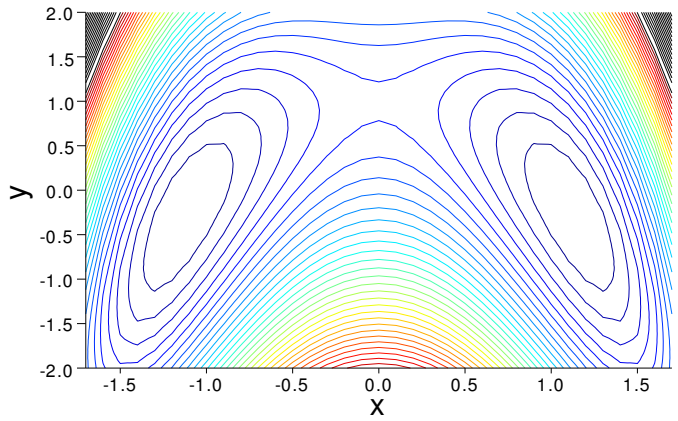
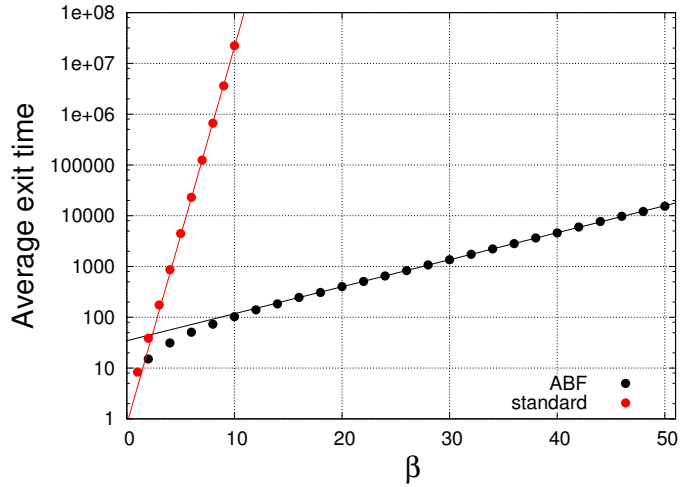
where $\boldsymbol{X}_t \sim \psi(t, \boldsymbol{x})\, d\boldsymbol{x}$.

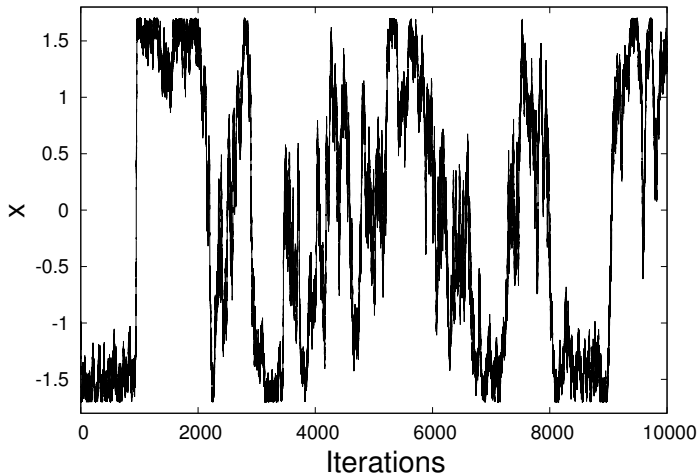
Questions: Does A_t' converge to A' ? What did we gain compared to the original gradient dynamics ?

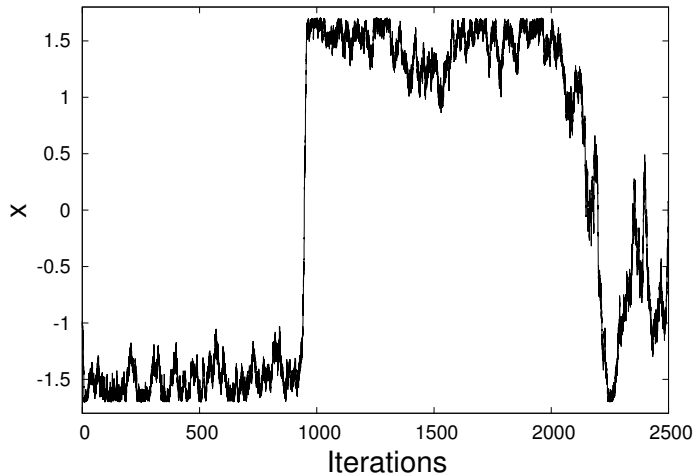
Back to the 2D example





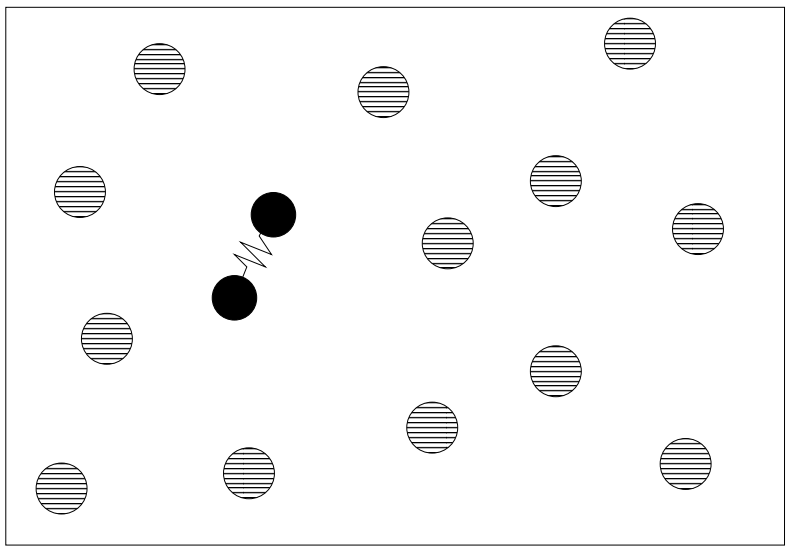
Left: the 2D potential – energetic barrier; Right: average exit time from the left well



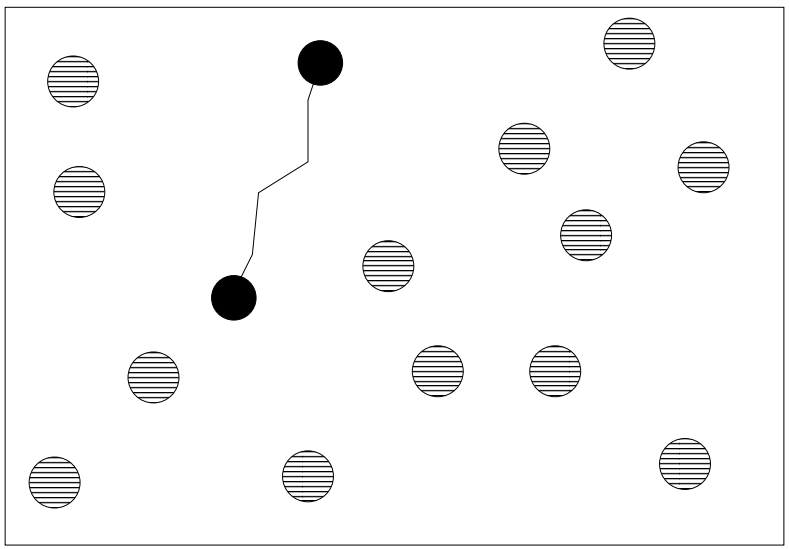


The ABF trajectory (right: zoom on the first 2500 iterations)

Back to the toy example for solvation



Compact state.



Stretched state.

The reaction coordinate ξ is the distance between the two monomers. $\longrightarrow$ simulation

Longtime convergence and entropy (1/3)

Recall the original gradient dynamics:

$$d\boldsymbol{Q}_t = -\nabla V(\boldsymbol{Q}_t)\, dt + \sqrt{2\beta^{-1}} d\boldsymbol{W}_t.$$

The associated (linear) Fokker-Planck equation writes:

$$\partial_t \phi = \mathrm{div}\, \left(\nabla V \phi + \beta^{-1} \nabla \phi\right).$$

where $\boldsymbol{Q}_t \sim \phi(t, \boldsymbol{q})\, d\boldsymbol{q}$.

The metastable behaviour of $\boldsymbol{Q}_t$ is related to the multimodality of ν, which can be quantified through the rate of convergence of ϕ to $\phi_\infty = Z^{-1} \exp(-\beta V)$.

A classical approach for partial differential equations (PDEs): entropy techniques.

Longtime convergence and entropy (2/3)

Notice that the Fokker-Planck equation rewrites

$$\partial_t \phi = \beta^{-1} \mathrm{div} \left(\phi_\infty \nabla \left(\frac{\phi}{\phi_\infty} \right) \right).$$

Let us introduce the entropy:

$$E(t) = H(\phi(t,\cdot)|\phi_\infty) = \int \ln \left(\frac{\phi}{\phi_\infty} \right) \phi.$$

We have (Csiszár-Kullback inequality):

$$\|\phi(t,\cdot) - \phi_\infty\|_{L^1} \leq \sqrt{2E(t)}.$$

Longtime convergence and entropy (3/3)

$$\begin{aligned}\frac{dE}{dt} &= \int \ln\left(\frac{\phi}{\phi_\infty}\right)\partial_t\phi \\ &= \beta^{-1}\int \ln\left(\frac{\phi}{\phi_\infty}\right)\operatorname{div}\left(\phi_\infty\nabla\left(\frac{\phi}{\phi_\infty}\right)\right) \\ &= -\beta^{-1}\int\left|\nabla\ln\left(\frac{\phi}{\phi_\infty}\right)\right|^2\phi =: -\beta^{-1}I(\phi(t,\cdot)|\phi_\infty).\end{aligned}$$

If V is such that the following Logarithmic Sobolev inequality (LSI(R)) holds: $\forall\phi$ pdf,

$$H(\phi|\phi_\infty) \leq \frac{1}{2R}I(\phi|\phi_\infty)$$

then $E(t) \leq E(0)\exp(-2\beta^{-1}Rt)$ and thus ϕ converges to ϕ_∞ exponentially fast with rate $\beta^{-1}R$.

Metastability $\Longleftrightarrow$ small R

Efficiency of thermodynamic integration

With thermodynamic integration, the conditional measures $\nu_{\Sigma(z)}$ are sampled rather than the original Gibbs measure ν. The long-time behaviour of the constrained dynamics (RCD) will be essentially limited by the LSI contant $\rho(z)$ of the conditional measures $\nu_{\Sigma(z)}$ (to be compared with the LSI constant R of the original measure ν). For well-chosen ξ, $\rho(z) \gg R$, which explains the efficiency of the whole procedure.

Convergence of ABF (1/4)

A convergence result [TL, M. Rousset, G. Stoltz, Nonlinearity 2008]: Recall the ABF Fokker-Planck equation:

$$\begin{cases} \partial_t \psi = \mathrm{div}\, \left(\nabla (V - A_t \circ \xi) \psi + \beta^{-1} \nabla \psi \right), \\ A_t'(z) = \dfrac{\int f\, \psi\, \delta_{\xi(x)-z}(dx)}{\int \psi\, \delta_{\xi(x)-z}(dx)}. \end{cases}$$

Suppose:

(H1) "Ergodicity" of the microscopic variables: the conditional probability measures $\nu_{\Sigma(z)}$ satisfy a LSI(ρ),

(H2) Bounded coupling: $\left\| \nabla_{\Sigma(z)} f \right\|_{L^\infty} < \infty$,

then

$$\| A_t' - A' \|_{L^2} \leq C \exp(-\beta^{-1} \min(\rho, r) t).$$

The rate of convergence is limited by:

- the rate r of convergence of $\overline{\psi} = \int \psi\, \delta_{\xi(x)-z}(dx)$ to $\overline{\psi_\infty}$,
- the LSI constant ρ (the real limitation).

Convergence of ABF (2/4)

In summary:

- Original gradient dynamics: $\exp(-\beta^{-1} R t)$ where R is the LSI constant for ν;
- ABF dynamics: $\exp(-\beta^{-1} \rho t)$ where ρ is the LSI constant for the conditioned probability measures $\nu_{\Sigma(z)}$.

If ξ is well chosen, $\rho \gg R$: the free energy can be computed very efficiently.

Two ingredients of the proof:

(1) The marginal $\overline{\psi}(t,z) = \int \psi(t,\boldsymbol{x})\, \delta_{\xi(\boldsymbol{x})-z}(d\boldsymbol{x})$ satisfies a closed PDE:

$$\partial_t \overline{\psi} = \beta^{-1} \partial_{z,z} \overline{\psi} \text{ on } \mathbb{T},$$

and thus, $\overline{\psi}$ converges towards $\overline{\psi_\infty} \equiv 1$, with exponential speed $C \exp(-4\pi^2 \beta^{-1} t)$. (Here, $r = 4\pi^2$).

Convergence of ABF (3/4)

(2) The total entropy can be decomposed as [N. Grunewald, F. Otto, C. Villani, M. Westdickenberg, Ann. IHP, 2009]:

$$E = E_M + E_m$$

where

The total entropy is $E = H(\psi|\psi_\infty)$,

The macroscopic entropy is $E_M = H(\overline{\psi}|\overline{\psi_\infty})$,

The microscopic entropy is

$$E_m = \int H\Big(\psi(\cdot|\xi(\boldsymbol{x}) = z)\Big|\psi_\infty(\cdot|\xi(\boldsymbol{x}) = z)\Big)\,\overline{\psi}(z)\,dz.$$

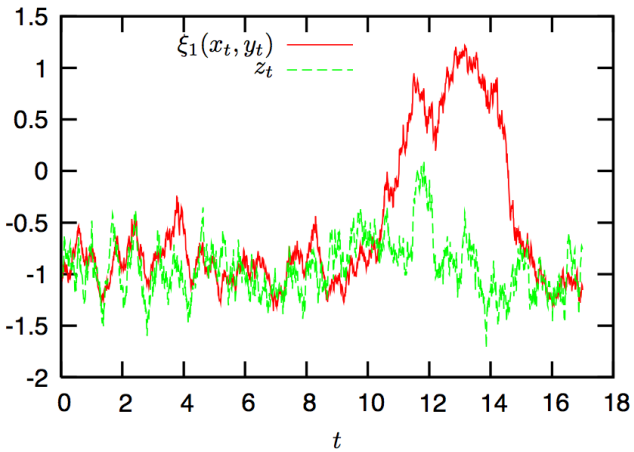
We already know that E_M goes to zero: it remains only to consider E_m...

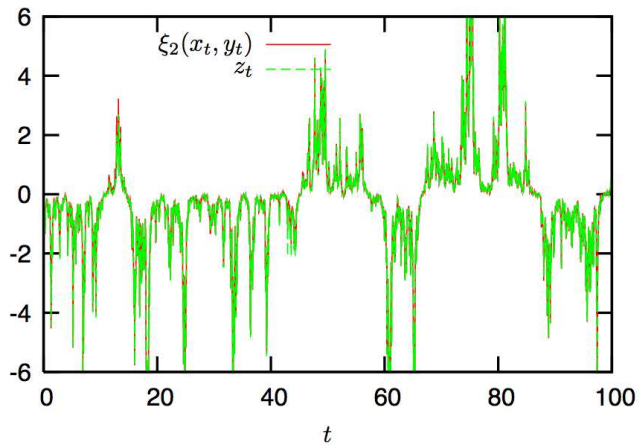
Convergence of ABF (4/4)

Other results based on this set of assumptions:

- [TL, JFA 2008] LSI for the cond. meas. $\nu_{\Sigma(z)}$
  + LSI for the marginal $\overline{\nu}(dz) = \xi_* \nu(dz)$
  + bdd coupling ($\|\nabla_{\Sigma(z)} f\|_{L^\infty} < \infty$) $\Longrightarrow$ LSI for ν.
- [F. Legoll, TL, Nonlinearity, 2010] Effective dynamics for $\xi(\boldsymbol{Q}_t)$. Uniform control in time:

$$H(\mathcal{L}(\xi(\boldsymbol{Q}_t))|\mathcal{L}(z_t)) \leq C \left(\frac{\|\nabla_{\Sigma(z)} f\|_{L^\infty}}{\rho} \right)^2 H(\mathcal{L}(\boldsymbol{Q}_0)|\nu).$$





Discretization of ABF

Discretization of adaptive methods can be done using two (complementary) approaches:

- Use empirical means over many replicas (interacting particle system):

$$\mathbb{E}(f(\boldsymbol{X}_t)|\xi(\boldsymbol{X}_t)=z) \simeq \frac{\sum_{m=1}^N f(\boldsymbol{X}_t^{m,N})\,\delta^\alpha(\xi(\boldsymbol{X}_t^{m,N})-z)}{\sum_{m=1}^N \delta^\alpha(\xi(\boldsymbol{X}_t^{m,N})-z)}.$$

  This approach is easy to parallelize, flexible (selection mechanisms) and efficient in cases with multiple reactive paths. [TL, M. Rousset, G. Stoltz, 2007; C. Chipot, TL, K. Minoukadeh, 2010 ; TL, K. Minoukadeh, 2010]

- Use trajectorial averages along a single path:

$$\mathbb{E}(f(\boldsymbol{X}_t)|\xi(\boldsymbol{X}_t)=z) \simeq \frac{\int_0^t f(\boldsymbol{X}_s)\,\delta^\alpha(\xi(\boldsymbol{X}_s)-z)\,ds}{\int_0^t \delta^\alpha(\xi(\boldsymbol{X}_s)-z)\,ds}.$$

  The longtime behavior is much more difficult to analyze.

Back to the original problem

How to use free energy to compute canonical averages $\int \varphi d\nu = Z^{-1} \int \varphi e^{-\beta V}$?

- Importance sampling:

$$\int \varphi \, d\nu = \frac{\int \varphi e^{-\beta A \circ \xi} \, Z_A^{-1} e^{-\beta(V - A \circ \xi)}}{\int e^{-\beta A \circ \xi} \, Z_A^{-1} e^{-\beta(V - A \circ \xi)}}.$$

- Conditioning:

$$\int \varphi \, d\nu = \frac{\int_z \left(\int_{\Sigma(z)} \varphi \, d\nu_{\Sigma(z)} \right) e^{-\beta A(z)} \, dz}{\int_z e^{-\beta A(z)} \, dz}.$$

ABF: extensions and open problems

Numerical aspects:

- Multiple walker ABF [C. Chipot, TL, K. Minoukadeh]
- Projection on a gradient of the mean force (Helmholtz decomposition) [J. Hénin, TL, 2016-2017]
- Reaction coordinates in larger dimension: exchange bias, separated representations [Ehrlacher, TL, Monmarché, 2019], learning techniques
- Link with Stein Variational Gradient Descent?

Theoretical aspects:

- Analysis when the mean force (or the free energy) is approximated using time averages [G. Fort, B. Jourdain, E. Kuhn, TL, G. Stoltz, P.A. Zitt, 2014-2019]
- Extension of the analysis to the Langevin dynamics?

Other techniques to compute thermodynamic quantities

Other algorithms which are used in MD to sample efficiently ν:

- Umbrella sampling and statistical reconstruction: Histogram methods
- Out of equilibrium methods: fluctuation relations $\tilde{A}$ *la* Jarzynski-Crooks
- Modify the dynamics: Metropolis Hastings algorithms with well-chosen proposals, non-reversible perturbations,...
- Interacting replicas techniques: Parallel tempering, Replica exchange dynamics, ...

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