Monte Carlo methods in molecular dynamics

Part 1: Sampling the canonical distribution and computing free energy differences.

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Introduction

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 to evaluate numerically macroscopic quantities from models at the microscopic scale.

Some examples of macroscopic quantities:

(i) Thermodynamics quantities (average of some observable wrt an equilibrium measure): stress, heat capacity, free energy,...

$$\mathbb{E}_\mu(\varphi(\boldsymbol{X})) = \int_{\mathbb{R}^d} \varphi(\boldsymbol{x})\, \mu(d\boldsymbol{x}).$$

(ii) Dynamical quantities (average over trajectories at equilibrium): diffusion coefficients, viscosity, transition rates,...

$$\mathbb{E}(\mathcal{F}((\boldsymbol{X}_t)_{t\geq 0})) = \int_{\mathcal{C}^0(\mathbb{R}_+,\mathbb{R}^d)} \mathcal{F}((\boldsymbol{x}_t)_{t\geq 0}))\, \mathcal{W}(d((\boldsymbol{x}_t)_{t\geq 0})).$$

Introduction

Many applications in various fields: biology, physics, chemistry, materials science. Molecular dynamics computations consume today a lot of CPU time.

A molecular dynamics model amounts essentially in choosing a potential V which associates to a configuration $(\boldsymbol{x}_1, ..., \boldsymbol{x}_N) = \boldsymbol{x} \in \mathbb{R}^{3N}$ an energy $V(\boldsymbol{x}_1, ..., \boldsymbol{x}_N)$.

In the canonical (NVT) ensemble, configurations are distributed according to the Boltzmann-Gibbs probability measure:

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

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.

Introduction

Typically, V is a sum of potentials modelling interaction between two particles, three particles and four particles:

$$V = \sum_{i<j} V_1(x_i, x_j) + \sum_{i<j<k} V_2(x_i, x_j, x_k) + \sum_{i<j<k<l} V_3(x_i, x_j, x_k, x_l).$$

For example, $V_1(x_i, x_j) = V_{LJ}(|x_i - x_j|)$ where $V_{LJ}(r) = 4\epsilon \left(\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6} \right)$ is the Lennard-Jones potential.

Difficulties: (i) high-dimensional problem ($N \gg 1$) ; (ii) μ is a multimodal measure.

Introduction

To sample μ, ergodic dynamics wrt to μ are used. A typical example is the *over-damped Langevin* (or gradient) dynamics:

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

It is the limit (when the mass goes to zero or the damping parameter to infinity) of the *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 M is the mass tensor and γ is the friction coefficient.

To compute dynamical quantities, these are also typically the dynamics of interest. Thus,

$$\mathbb{E}_\mu(\varphi(\boldsymbol{X})) \simeq \frac{1}{T}\int_0^T \varphi(\boldsymbol{X}_t)\, dt \text{ and } \mathbb{E}(\mathcal{F}((\boldsymbol{X}_t)_{t\geq 0})) \simeq \frac{1}{N}\sum_{m=1}^{N} \mathcal{F}((\boldsymbol{X}_t^m)_{t\geq 0})$$

In the following, we mainly consider the over-damped Langevin dynamics.

Introduction

Probabilistic insert (1): discretization of SDEs.

The discretization of (GD) by the Euler scheme is (for a fixed timestep Δt):

$$\boldsymbol{X}_{n+1} = \boldsymbol{X}_n - \nabla V(\boldsymbol{X}_n)\,\Delta t + \sqrt{2\beta^{-1}\Delta t}\,\boldsymbol{G}_n$$

where $(G_n^i)_{1\leq i\leq 3N, n\geq 0}$ are i.i.d. random variables with law $\mathcal{N}(0,1)$. Indeed,

$$(\boldsymbol{W}_{(n+1)\Delta t} - \boldsymbol{W}_{n\Delta t})_{n\geq 0} \overset{\mathcal{L}}{=} \sqrt{\Delta t}(\boldsymbol{G}_n)_{n\geq 0}.$$

In practice, a sequence of i.i.d. random variables with law $\mathcal{N}(0,1)$ may be obtained from a sequence of i.i.d. random variables with law $\mathcal{U}((0,1))$.

Introduction

μ in invariant for (GD) Proof: One needs to show that if the law of X_0 is μ, then the law of X_t is also μ. Let us denote X_t^x the solution to (GD) such that $X_0 = x$. Let us consider the function $u(t,x)$ solution to:

$$\begin{cases} \partial_t u(t,x) = -\nabla V(x) \cdot \nabla u(t,x) + \beta^{-1} \Delta u(t,x), \\ u(0,x) = \phi(x) (+ \text{ assumptions on decay at infinity}), \end{cases}$$

then, $u(t,x) = \mathbb{E}(\phi(X_t^x))$. Thus, the measure μ is invariant:

$$\begin{aligned} \frac{d}{dt} \int \mathbb{E}(\phi(X_t^x)) d\mu(x) &= Z^{-1} \int \partial_t u(t,x) \exp(-\beta V(x)) dx \\ &= Z^{-1} \int \left(-\nabla V \cdot \nabla u + \beta^{-1} \Delta u\right) \exp(-\beta V) = 0. \end{aligned}$$

Therefore, $\int \mathbb{E}(\phi(X_t^x)) d\mu(x) = \int \phi(x) d\mu(x)$.

Introduction

Probabilistic insert (2): Feynman-Kac formula.

Why $u(t,x) = \mathbb{E}(\phi(\boldsymbol{X}_t^x))$? For $0 < s < t$, we have (*characteristic method*):

$$\begin{aligned} du(t-s, \boldsymbol{X}_s^x) &= -\partial_t u(t-s, \boldsymbol{X}_s^x)\, ds + \nabla u(t-s, \boldsymbol{X}_s^x) \cdot d\boldsymbol{X}_s^x \\ &\quad + \beta^{-1} \Delta u(t-s, \boldsymbol{X}_s^x)\, ds, \\ &= \Big(- \partial_t u(t-s, \boldsymbol{X}_s^x) - \nabla V(\boldsymbol{X}_s^x) \cdot \nabla u(t-s, \boldsymbol{X}_s^x) \\ &\quad + \beta^{-1} \Delta u(t-s, \boldsymbol{X}_s^x) \Big)\, ds + \sqrt{2\beta^{-1}} \nabla u(t-s, \boldsymbol{X}_s^x) \cdot d\boldsymbol{W}_s. \end{aligned}$$

Thus, integrating over $s \in (0,t)$ and taking the expectation:

$$\begin{aligned} \mathbb{E}(u(0, \boldsymbol{X}_t^x)) - \mathbb{E}(u(t, \boldsymbol{X}_0^x)) &= \sqrt{2\beta^{-1}} \mathbb{E}\left(\int_0^t \nabla u(t-s, \boldsymbol{X}_s^x) \cdot d\boldsymbol{W}_s \right) \\ &= 0. \end{aligned}$$

Introduction

Probabilistic insert (3): Itô's calculus. (in 1d.)

Where does the term Δu come from ? Starting from the discretization:

$$X_{n+1} = X_n - V'(X_n)\,\Delta t + \sqrt{2\beta^{-1}\Delta t}\,G_n,$$

we have (for a time-independent function u):

$$\begin{aligned} u(X_{n+1}) &= u\left(X_n - V'(X_n)\,\Delta t + \sqrt{2\beta^{-1}\Delta t}\,G_n\right), \\ &= u(X_n) - u'(X_n)V'(X_n)\,\Delta t + \sqrt{2\beta^{-1}\Delta t}\,u'(X_n)G_n \\ &\quad +\beta^{-1}(G_n)^2 u''(X_n)\Delta t + o(\Delta t). \end{aligned}$$

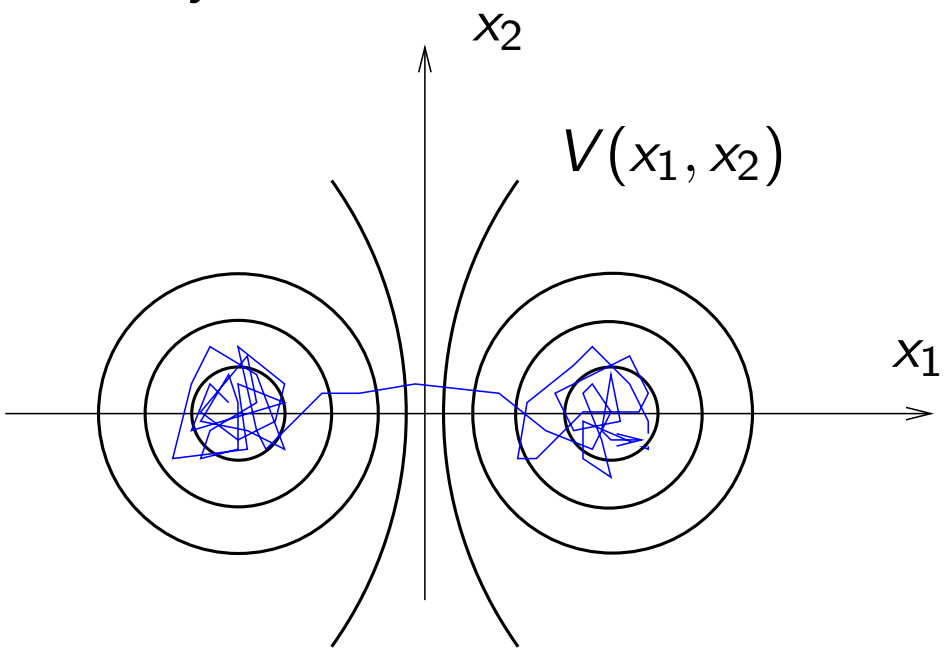
Thus, summing over $n \in [0 \ldots t/\Delta t]$ and taking the limit $\Delta t \to 0$,

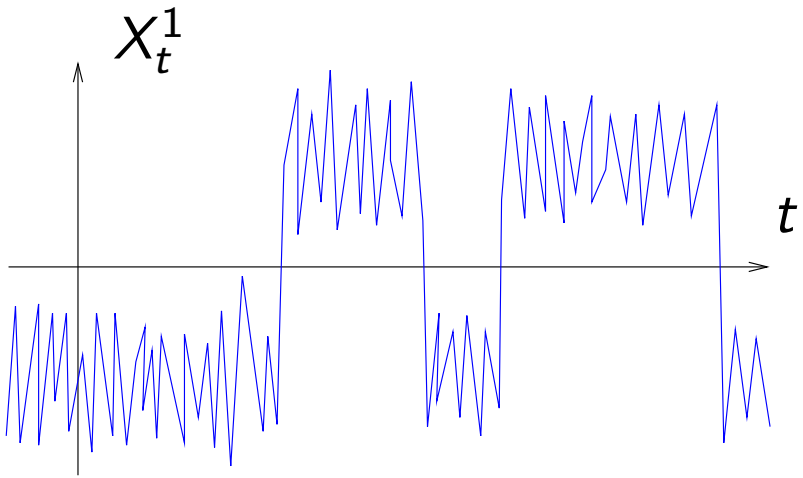
$$u(X_t) = u(X_0) - \int_0^t V'(X_s)u'(X_s)\,ds + \sqrt{2\beta^{-1}}\int_0^t u'(X_s)dW_s$$
$$+\beta^{-1}\int_0^t u''(X_s)\,ds.$$

Introduction: metastability

Difficulty: In practice, $\boldsymbol{X}_t$ is a metastable process, so that the convergence to equilibrium is very slow.

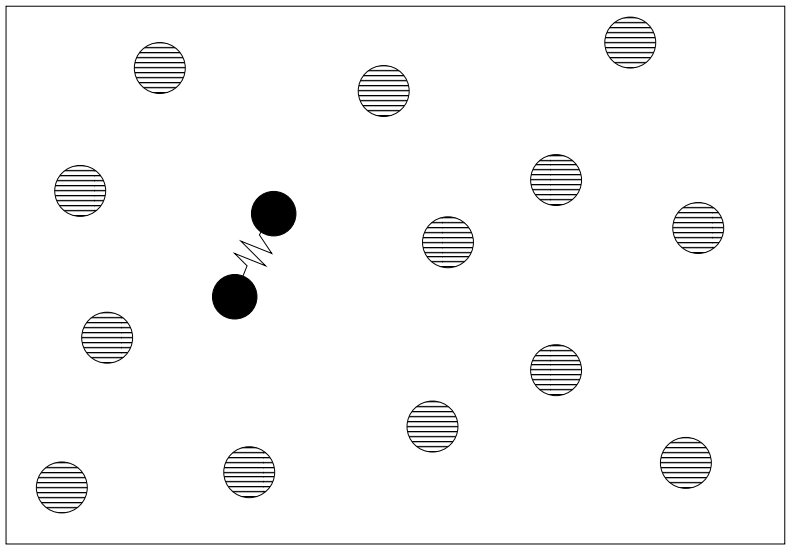
A 2d schematic picture: X_t^1 is a slow variable (a metastable dof) of the system.



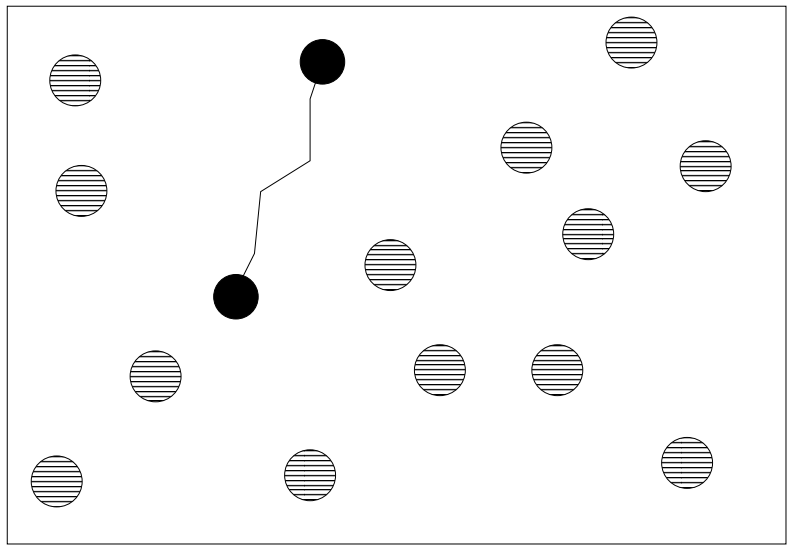


Introduction: metastability

A more realistic example (Dellago, Geissler): Influence of the solvation on a dimer conformation.



Compact state.

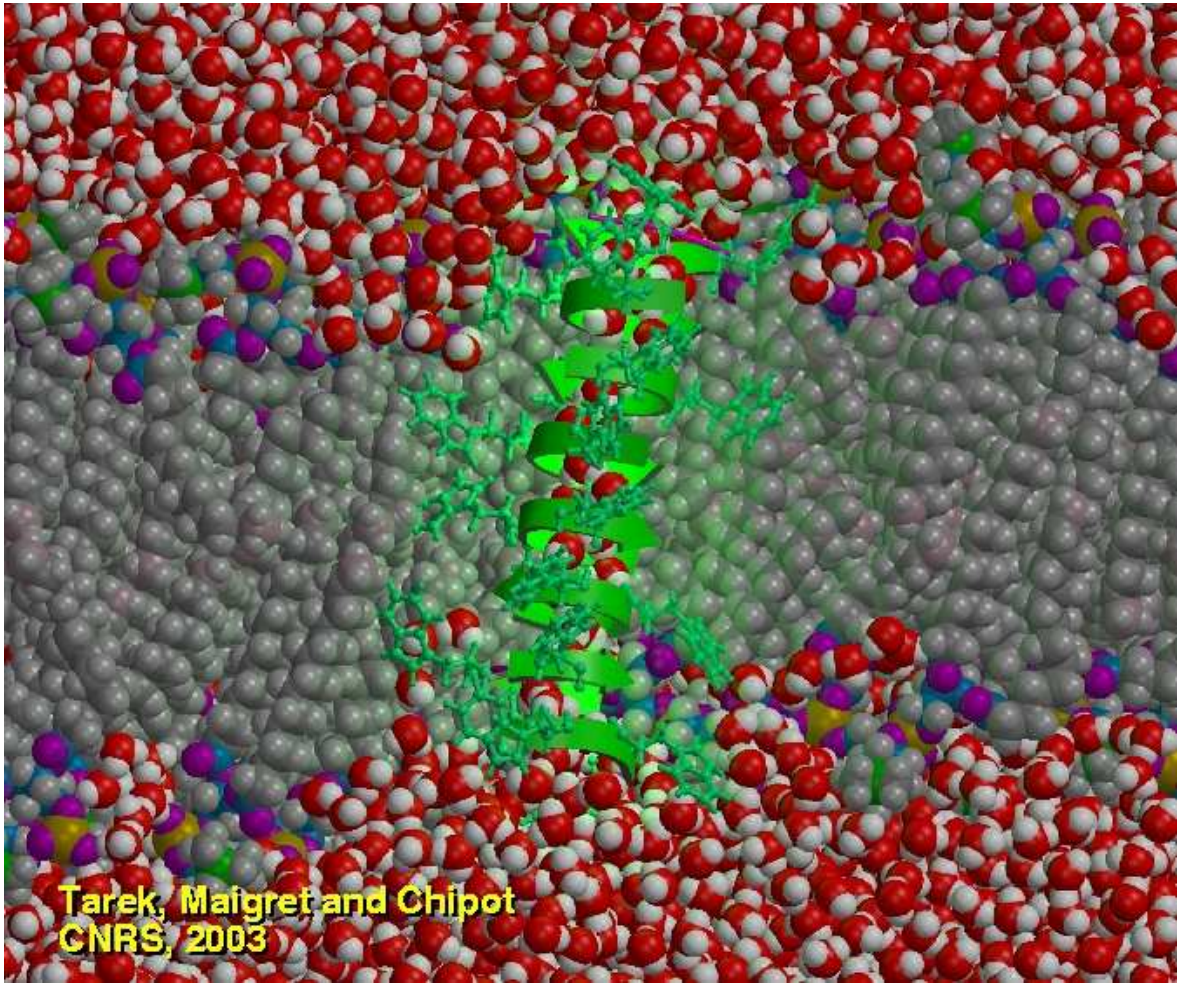


Stretched state.

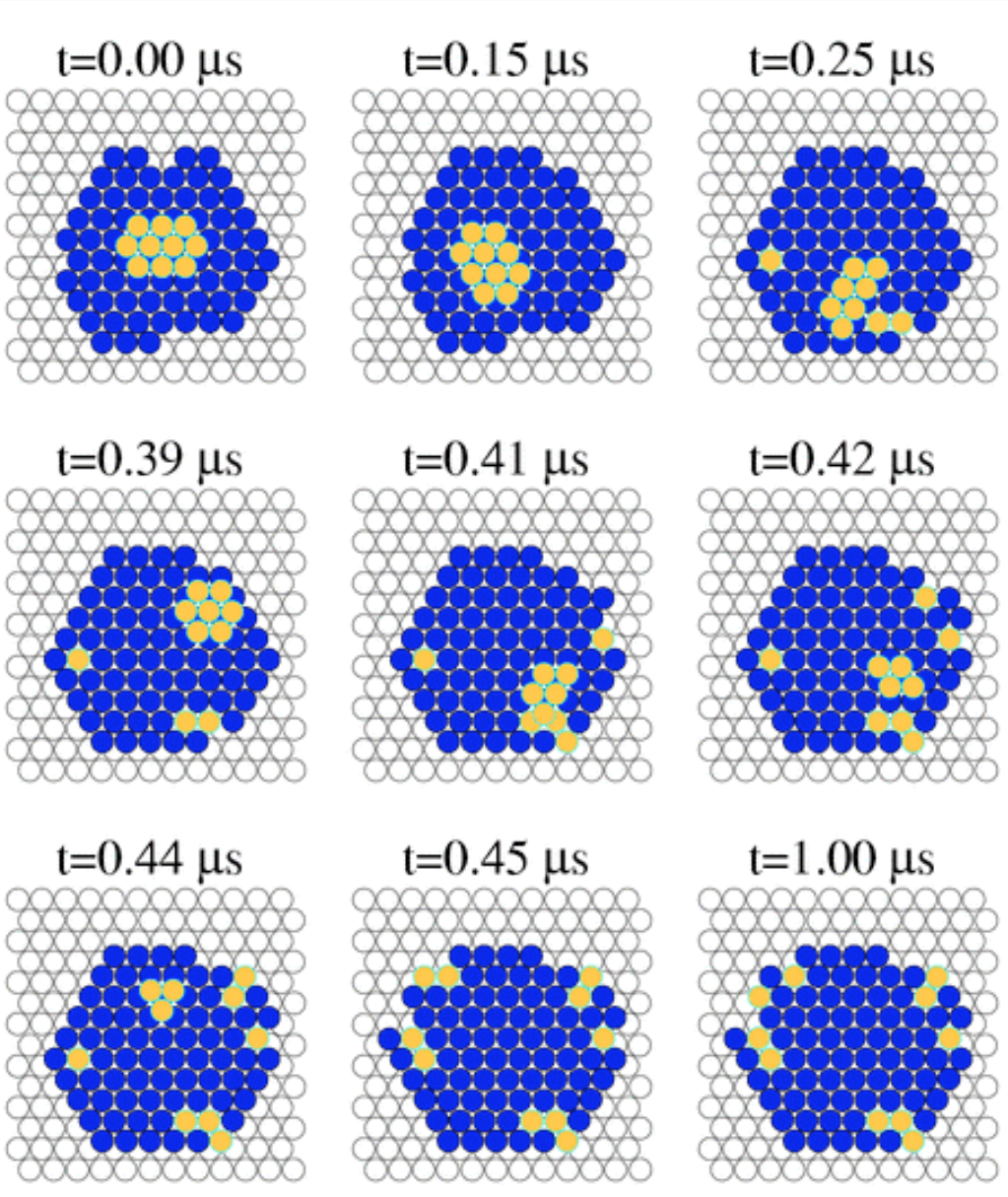
The particles interact through a pair potential: truncated LJ for all particles except the two monomers (black particles) which interact through a double-well potential. A slow variable is the distance between the two monomers.

Introduction: metastability

A "real" example: ions canal in a cell membrane. *(C. Chipot)*.



A second "real" example: Diffusion of adatoms on a surface. *(A. Voter)*.



Introduction: metastability

One central numerical difficulty is thus metastability. How to quantify this bad behaviour ?

1. Escape time from a potential well.
2. Asymptotice variance of the estimator.
3. "Decorrelation time".
4. Rate of convergence of the law of $\boldsymbol{X}_t$ to μ.

In the following we use the fourth criterion.

Introduction: metastability

The PDE point of view: convergence of the pdf $\psi(t, \boldsymbol{x})$ of $\boldsymbol{X}_t$ to $\psi_\infty(\boldsymbol{x}) = Z^{-1} e^{-\beta V(\boldsymbol{x})}$. ψ satisfies the Fokker-Planck equation

$$\partial_t \psi = \mathrm{div}\,(\nabla V \psi + \beta^{-1} \nabla \psi),$$

which can be rewritten as $\partial_t \psi = \beta^{-1} \mathrm{div}\,\left(\psi_\infty \nabla \left(\frac{\psi}{\psi_\infty}\right)\right)$.

Let us introduce the entropy

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

We have (Csiszár-Kullback inequality):

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

Introduction: metastability

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

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

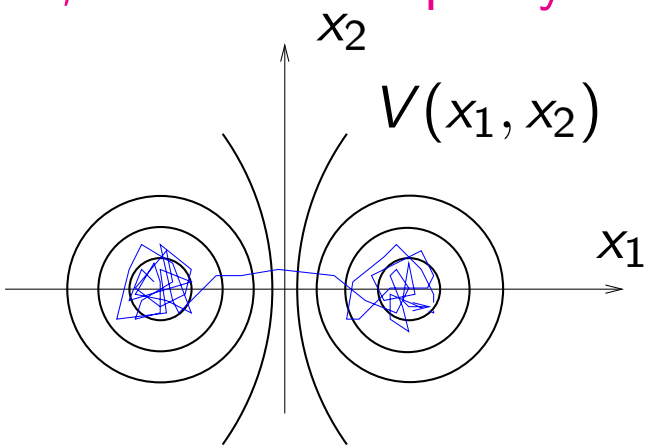
$$H(\psi|\psi_\infty) \leq \frac{1}{2R}I(\psi|\psi_\infty)$$

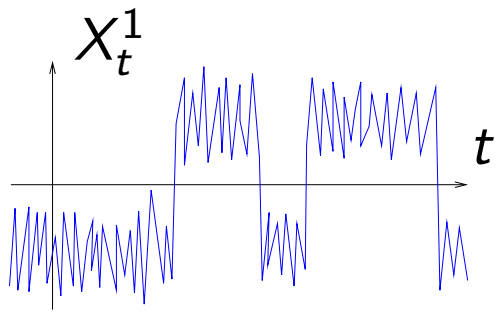
then $E(t) \leq E(0)\exp(-2\beta^{-1}Rt)$ and thus ψ converges to ψ_∞ exponentially fast with rate $\beta^{-1}R$ (and the converse is true).

Metastability $\iff$ small R

Introduction: reaction coordinate and free energy

Metastability: How to attack this problem ?
We suppose in the following that the slow variable is of dimension 1 and known: $\xi(\boldsymbol{X}_t)$, where $\xi : \mathbb{R}^n \to \mathbb{T}$.
For example, in the 2d simple system, $\xi(x_1, x_2) = x_1$.





We will use this knowledge to build efficient sampling techniques.
Two ideas:

- Conditioning (constrained dynamics),
- Importance sampling (biased dynamics).

Free energy will play a central role.

Introduction: reaction coordinate and free energy

Let us introduce two probability measures associated to μ and ξ:

- The image of the measure μ by ξ:

$$\xi * \mu\,(dz) = \exp(-\beta A(z))\,dz$$

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 μ conditioned to $\xi(\boldsymbol{x}) = z$:

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

Introduction: reaction coordinate and free energy

In the simple case $\xi(x_1, x_2) = x_1$, we have:

- The image of the measure μ by ξ:

$$\xi * \mu\,(dx_1) = \exp(-\beta A(x_1))\,dx_1$$

where the free energy A is defined by:

$$A(x_1) = -\beta^{-1} \ln\left(\int e^{-\beta V(x_1,x_2)} dx_2\right),$$

and $\Sigma(x_1) = \{(x_1, x_2),\, x_2 \in \mathbb{R}\}$.

- The probability measure μ conditioned to $\xi(x_1, x_2) = x_1$:

$$\mu_{\Sigma(x_1)}(dx_2) = \frac{\exp(-\beta V(x_1, x_2))\,dx_2}{\exp(-\beta A(x_1))}.$$

Introduction: reaction coordinate and free energy

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:

$$A(z) = -\beta^{-1} \ln \left(\int_{\Sigma(z)} e^{-\beta V} |\nabla\xi|^{-1} d\sigma_{\Sigma(z)} \right).$$

General statement: Let X be a random variable with law $\psi(x)\,dx$ in $\mathbb{R}^n$, then $\xi(X)$ has law $\int_{\Sigma(z)} \psi\,|\nabla\xi|^{-1}\,d\sigma_{\Sigma(z)}\,dz$, and the law of X conditioned to a fixed value z of $\xi(X)$ is

$$d\mu_{\Sigma(z)} = \frac{\psi\,|\nabla\xi|^{-1}\,d\sigma_{\Sigma(z)}}{\int_{\Sigma(z)} \psi\,|\nabla\xi|^{-1}\,d\sigma_{\Sigma(z)}}.$$

Indeed, for any two bounded functions f and g,

$$\begin{aligned}
\mathbb{E}(f(\xi(X))g(X)) &= \int_{\mathbb{R}^n} f(\xi(x))g(x)\psi(x)\,dx, \\
&= \int_{\mathbb{R}^p} \int_{\Sigma(z)} f \circ \xi\, g\, \psi\, |\nabla\xi|^{-1} d\sigma_{\Sigma(z)}\,dz, \\
&= \int_{\mathbb{R}^p} f(z) \frac{\int_{\Sigma(z)} g\,\psi\,|\nabla\xi|^{-1} d\sigma_{\Sigma(z)}}{\int_{\Sigma(z)} \psi\,|\nabla\xi|^{-1} d\sigma_{\Sigma(z)}} \int_{\Sigma(z)} \psi\,|\nabla\xi|^{-1} d\sigma_{\Sigma(z)}\,dz.
\end{aligned}$$

Introduction: reaction coordinate and free energy

Remarks:

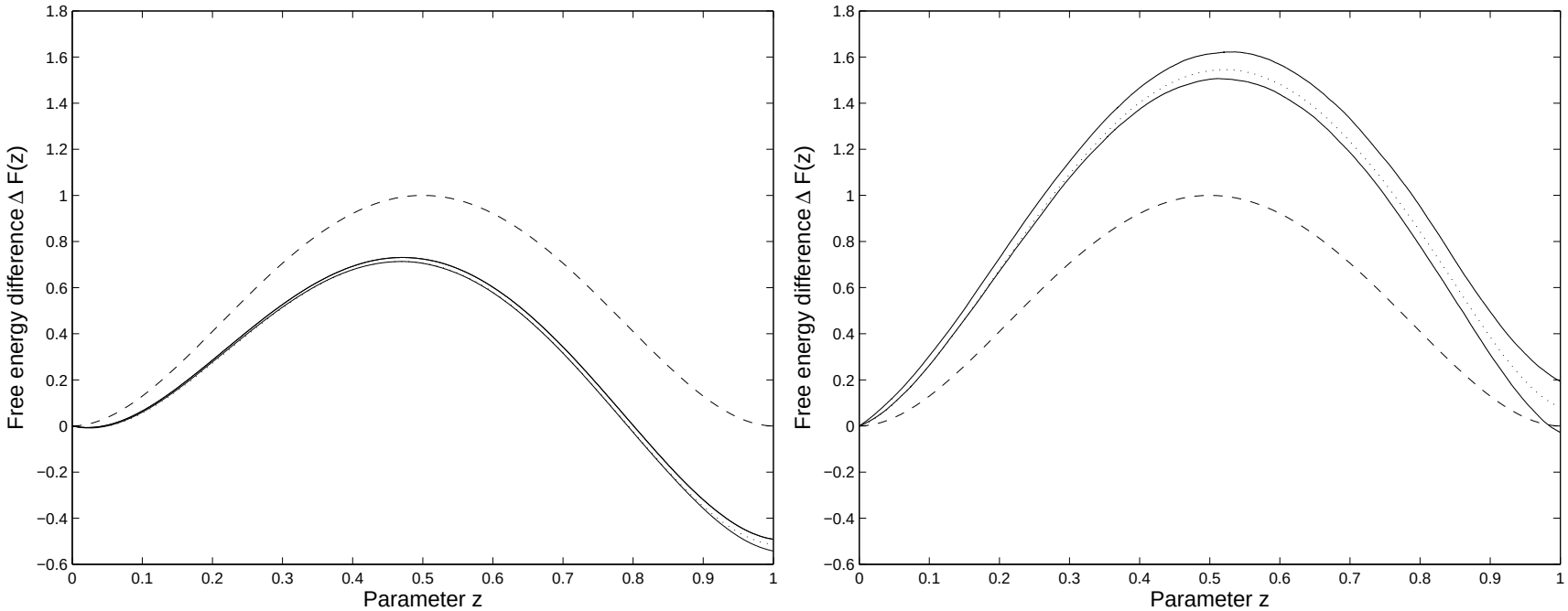
- A is the free energy associated with the reaction coordinate or collective variable ξ (angle, length, ...). A is defined up to an additive constant, so that it is enough to compute free energy differences, or the derivative of A (the mean force).

- $A(z) = -\beta^{-1} \ln Z_{\Sigma(z)}$ and $Z_{\Sigma(z)}$ is the partition function associated with the conditioned probability measures: $\mu_{\Sigma(z)} = Z_{\Sigma(z)}^{-1} e^{-\beta V} |\nabla \xi|^{-1} d\sigma_{\Sigma(z)}$.

- If $U = \displaystyle\int_{\Sigma(z)} V \, Z_{\Sigma(z)}^{-1} e^{-\beta V} \delta_{\xi(x)-z}(dx)$ and $S = -k_B \displaystyle\int_{\Sigma(z)} \ln \left(Z_{\Sigma(z)}^{-1} e^{-\beta V} \right) Z_{\Sigma(z)}^{-1} e^{-\beta V} \delta_{\xi(x)-z}(dx)$ (and $\beta^{-1} = k_B T$), then $A = U - TS$.

Introduction: reaction coordinate and free energy

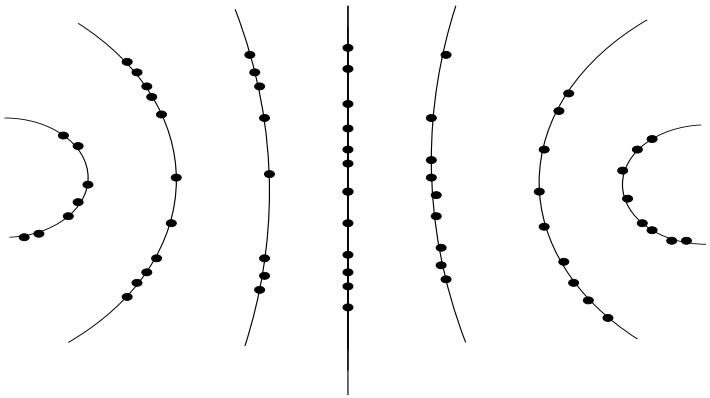
What is free energy ? The simple example of the solvation of a dimer. (Profiles computed using thermodynamic integration.)



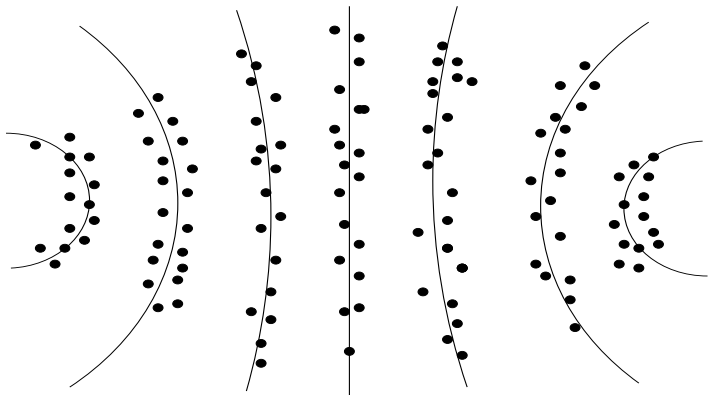
The density of the solvent molecules is lower on the left than on the right. At high (resp. low) density, the compact state is more (resp. less) likely. The "free energy barrier" is higher at high density than at low density. Related question: interpretation of the free energy barrier in terms of dynamics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

Introduction: reaction coordinate and free energy

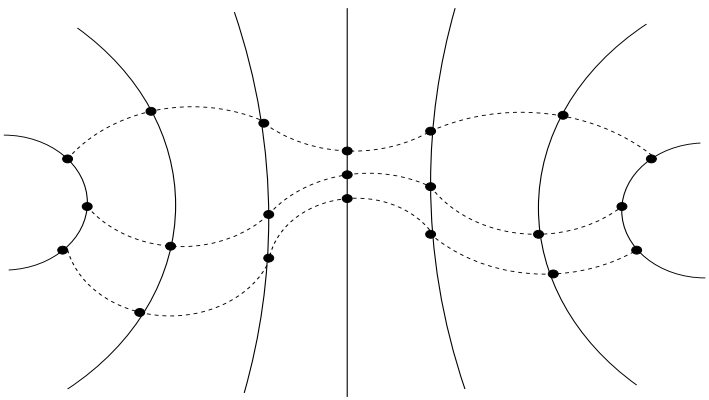
There are many free energy calculation techniques:



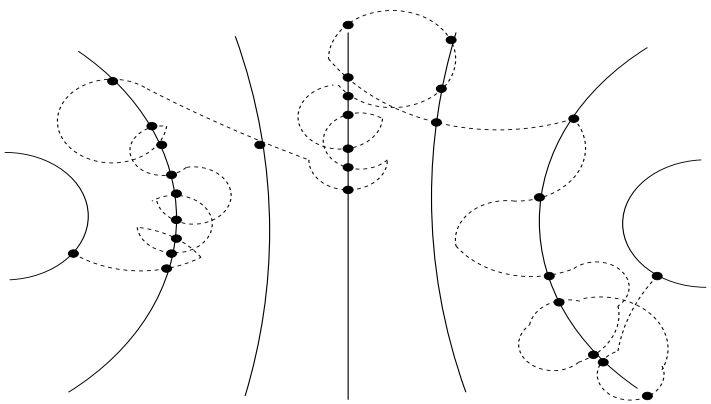
(a) Thermodynamic integration.



(b) Histogram method.

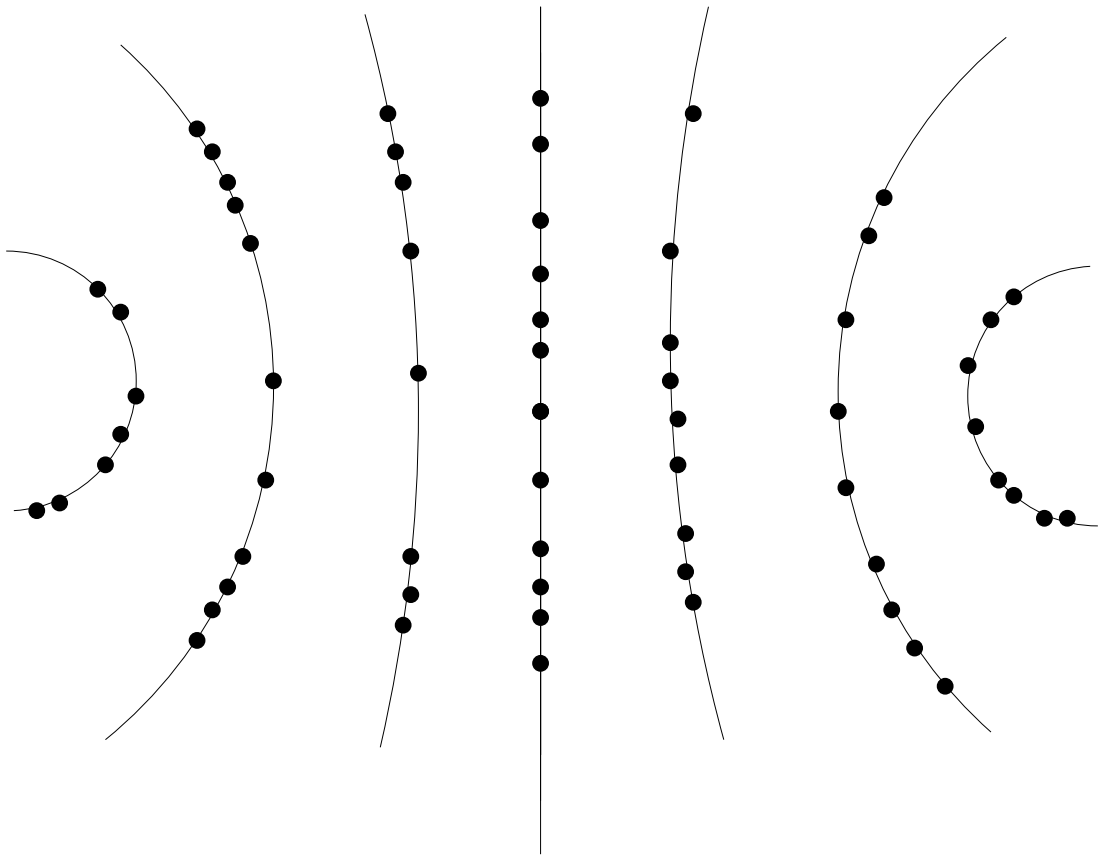


(c) Non equilibrium dynamics.



(d) Adaptive dynamics.

Thermodynamic integration



Thermodynamic integration

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

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

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

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

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.

Thermodynamic integration

In the simple case $\xi(x_1, x_2) = x_1$, remember that

$$A(x_1) = -\beta^{-1} \ln \left(\int e^{-\beta V(x_1, x_2)} dx_2 \right),$$

so that

$$\begin{aligned} A'(x_1) &= \frac{\displaystyle\int \partial_{x_1} V \, e^{-\beta V(x_1, x_2)} \, dx_2}{\displaystyle\int e^{-\beta V(x_1, x_2)} \, dx_2} \\ &= \int \partial_{x_1} V \, d\mu_{\Sigma(x_1)}. \end{aligned}$$

Thermodynamic integration

Proof in the general case : (based on the co-area formula)

$$\int \left(\int \exp(-\beta \tilde{V}) d\sigma_{\Sigma(z)} \right)' \phi(z)\, dz = - \iint \exp(-\beta \tilde{V}) d\sigma_{\Sigma(z)} \phi'\, dz,$$

$$= - \int \int \exp(-\beta \tilde{V}) \phi' \circ \xi \, d\sigma_{\Sigma(z)}\, dz,$$

$$= - \int \exp(-\beta \tilde{V}) \phi' \circ \xi |\nabla \xi| d\boldsymbol{x},$$

$$= - \int \exp(-\beta \tilde{V}) \nabla(\phi \circ \xi) \cdot \frac{\nabla \xi}{|\nabla \xi|^2} |\nabla \xi| d\boldsymbol{x},$$

$$= \int \nabla \cdot \left(\exp(-\beta \tilde{V}) \frac{\nabla \xi}{|\nabla \xi|} \right) \phi \circ \xi \, d\boldsymbol{x},$$

$$= \int \int \left(-\beta \frac{\nabla \tilde{V} \cdot \nabla \xi}{|\nabla \xi|^2} + |\nabla \xi|^{-1} \nabla \cdot \left(\frac{\nabla \xi}{|\nabla \xi|} \right) \right) \exp(-\beta \tilde{V}) d\sigma_{\Sigma(z)} \phi(z)\, dz.$$

Thermodynamic integration

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

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

Thus, $A'(z) = \lim_{T \to \infty} \frac{1}{T} \int_0^T f(\boldsymbol{X}_t)\, dt$.

The free energy profile is then obtained by thermodynamic integration:

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

Thermodynamic integration

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

Indeed, we have $d\Lambda_t = d\Lambda_t^{\mathrm{m}} + d\Lambda_t^{\mathrm{f}}$, 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

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

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

Of course, this comes at a price: essentially, we are using the fact that

$$\lim_{M\to\infty}\lim_{\Delta t\to 0}\frac{1}{M\Delta t}\sum_{m=1}^{M}\left[\xi\left(q+\sqrt{\Delta t}\,G^m\right) - 2\xi(q) + \xi\left(q-\sqrt{\Delta t}\,G^m\right)\right] = \Delta\xi(q),$$

and this estimator has a non zero variance.

Thermodynamic integration

More explicitly, the rigidly constrained dynamics writes:

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

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

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

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

It is easy to check that $\xi(\boldsymbol{X}_t) = \xi(\boldsymbol{X}_0) = z$ for $\boldsymbol{X}_t$ solution to (RCD).

Thermodynamic integration

[G. Ciccotti, TL, E. Vanden-Einjden, 2008] Assume wlg that $z = 0$. The probability $\mu_{\Sigma(0)}$ 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 $\mu_{\Sigma(0)}$. Then, for all smooth function ϕ and for all time $t > 0$,

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

Proof: Introduce the infinitesimal generator and apply the divergence theorem on submanifolds : $\forall \boldsymbol{\phi} \in \mathcal{C}^1(\mathbb{R}^{3N}, \mathbb{R}^{3N})$,

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

where $\text{div}_{\Sigma(0)}(\boldsymbol{\phi}) = \text{tr}(P \nabla \boldsymbol{\phi})$.

Thermodynamic integration

Discretization: These two schemes are consistent with (RCD):

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

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

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). The discretization of $A'(0) = \lim_{T\to\infty} \frac{1}{T}\int_0^T d\Lambda_t$ is:

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

Thermodynamic integration

In practice, the following variance reduction scheme may be used:

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

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

and $\lambda_n = (\lambda + \lambda_*)/2$.

The martingale part $d\Lambda_t^{\mathrm{m}}$ (*i.e.* the most fluctuating part) of the Lagrange multiplier is removed.

Thermodynamic integration

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

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

Metastability issue: Using TI, we sample the conditional measures $\mu_{\Sigma(z)}$ rather than the original Gibbs measure μ. The long-time behaviour of the constrained dynamics (RCD) will be essentially limited by the LSI contant $\rho(z)$ of the conditional measures $\mu_{\Sigma(z)}$ (to be compared with the LSI constant R of the original measure μ). For well-chosen ξ, $\rho(z) \gg R$, which explains the efficiency of the whole procedure.

Thermodynamic integration

Remarks:

- There are many ways to constrain the dynamics (GD). We chose one which is simple to discretize. We may also have used, for example (for $z = 0$)

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

where the constraint is penalized. 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 penalized dynamics.

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

Thermodynamic integration

- TI yields a way to compute $\int \phi(\boldsymbol{x}) d\mu(\boldsymbol{x})$:

$$\int \phi(\boldsymbol{x}) d\mu(\boldsymbol{x}) = Z^{-1} \int \phi(\boldsymbol{x}) e^{-\beta V(\boldsymbol{x})} d\boldsymbol{x},$$

$$= Z^{-1} \int_z \int_{\Sigma(z)} \phi e^{-\beta V} |\nabla \xi|^{-1} d\sigma_{\Sigma(z)}\, dz, \qquad \text{(co-area formula)}$$

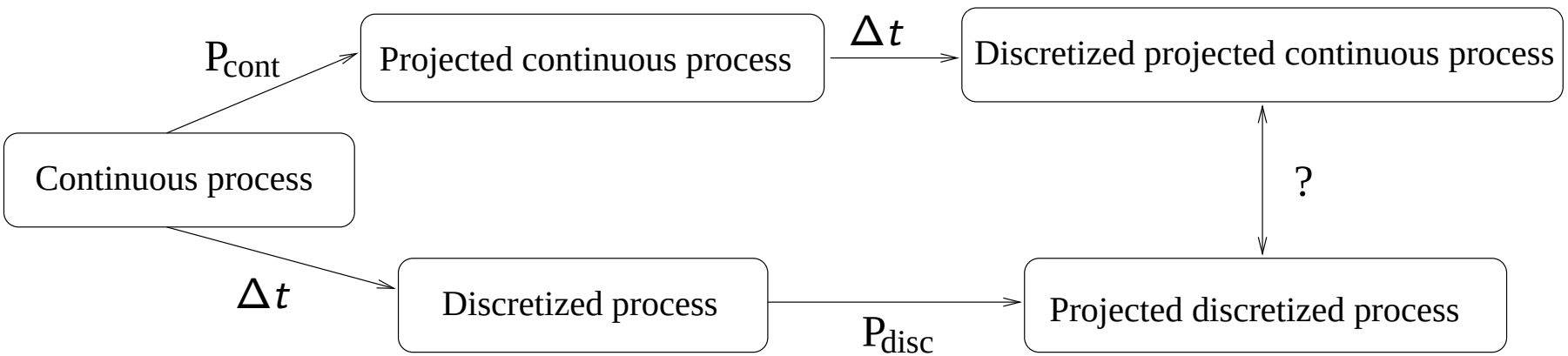
$$= Z^{-1} \int_z \frac{\int_{\Sigma(z)} \phi e^{-\beta V} |\nabla \xi|^{-1} d\sigma_{\Sigma(z)}}{\int_{\Sigma(z)} e^{-\beta V} |\nabla \xi|^{-1} d\sigma_{\Sigma(z)}} \int_{\Sigma(z)} e^{-\beta V} |\nabla \xi|^{-1} d\sigma_{\Sigma(z)}\, dz,$$

$$= \left(\int_z e^{-\beta A(z)}\, dz \right)^{-1} \int_z \left(\int_{\Sigma(z)} \phi d\mu_{\Sigma(z)} \right) e^{-\beta A(z)}\, dz.$$

with $\Sigma(z) = \{\boldsymbol{x},\, \xi(\boldsymbol{x}) = z\}$,
$A(z) = -\beta^{-1} \ln \left(\int_{\Sigma(z)} e^{-\beta V} |\nabla \xi|^{-1} d\sigma_{\Sigma(z)} \right)$ and
$\mu_{\Sigma(z)} = e^{-\beta V} |\nabla \xi|^{-1} d\sigma_{\Sigma(z)} / \int_{\Sigma(z)} e^{-\beta V} |\nabla \xi|^{-1} d\sigma_{\Sigma(z)}$.

Thermodynamic integration

- [C. Le Bris, TL, E. Vanden-Einjden, CRAS 2008] For a general SDE (with a non isotropic diffusion), the following diagram does not commute:



Thermodynamic integration

Generalization to Langevin dynamics. Interests: (i) Newton's equations of motion are more "natural"; (ii) leads to numerical schemes which sample the constrained measure without time discretization error; (iii) seems to be more robust wrt the timestep choice.

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

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

Thermodynamic integration

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 $G_M = \nabla\xi^T M^{-1}\nabla\xi$,

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

Thermodynamic integration

Moreover, one can check that:

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

Discretization: A natural numerical scheme is to use a splitting:

- 1/2 midpoint Euler on the fluctuation-dissipation part,
- 1 Verlet step on the Hamiltonian part (RATTLE scheme) and
- 1/2 midpoint Euler on the fluctuation-dissipation part.

Thermodynamic integration

$$
\begin{cases}
p^{n+1/4} = p^n - \dfrac{\Delta t}{4}\gamma\, M^{-1}(p^n + p^{n+1/4}) + \sqrt{\dfrac{\Delta t}{2}}\,\sigma\, G^n + \nabla\xi(q^n)\,\lambda^{n+1/4}, \\
\nabla\xi(q^n)^T M^{-1} p^{n+1/4} = 0,
\end{cases}
$$

$$
\begin{cases}
p^{n+1/2} = p^{n+1/4} - \dfrac{\Delta t}{2}\nabla V(q^n) + \nabla\xi(q^n)\,\lambda^{n+1/2}, \\
q^{n+1} = q^n + \Delta t\, M^{-1}\, p^{n+1/2}, \\
\xi(q^{n+1}) = z, \\
p^{n+3/4} = p^{n+1/2} - \dfrac{\Delta t}{2}\nabla V(q^{n+1}) + \nabla\xi(q^{n+1})\,\lambda^{n+3/4}, \\
\nabla\xi(q^{n+1})^T M^{-1} p^{n+3/4} = 0,
\end{cases}
$$

$$
\begin{cases}
p^{n+1} = p^{n+3/4} - \dfrac{\Delta t}{4}\gamma\, M^{-1}(p^{n+3/4} + p^{n+1}) + \sqrt{\dfrac{\Delta t}{2}}\,\sigma\, G^{n+1/2} \\
\qquad\qquad + \nabla\xi(q^{n+1})\,\lambda^{n+1}, \\
\nabla\xi(q^{n+1})^T M^{-1} p^{n+1} = 0,
\end{cases}
$$

and $\lim_{T\to\infty}\lim_{\Delta t\to 0}\frac{1}{T}\sum_{n=1}^{T/\Delta t}\left(\lambda^{n+1/2} + \lambda^{n+3/4}\right) = (A^M)'(z)$.

Thermodynamic integration

Using the symmetry of the Verlet step, it is easy to add a Metropolization step to the previous numerical scheme, thus removing the time discretization error. For this modified scheme, it is easy to prove that

$$\lim_{\Delta t \to 0} \lim_{T \to \infty} \frac{1}{T} \sum_{n=1}^{T/\Delta t} \left(\lambda^{n+1/2} + \lambda^{n+3/4} \right) = (A^M)'(z).$$

By choosing $M = \Delta t \gamma / 4 = \mathrm{Id}$, this leads to an original sampling scheme in the configuration space (generalized Hybrid Monte Carlo scheme).

Notice that it is not clear how to use such a Metropolization step for the constrained dynamics (RCD) since the proposal kernel is not symmetric, and does not admit any simple analytical expression.

Thermodynamic integration

Algorithm: Let us introduce $R_{\Delta t}$ which is such that, if $(q^n, p^n) \in T^*\Sigma(z)$, and $|p^n|^2 \leq R_{\Delta t}$, one step of the RATTLE scheme is well defined (*i.e.* there exists a unique solution to the constrained problem).

Then the GHMC scheme writes ($M = \Delta t \gamma / 4 = \mathrm{Id}$):

Thermodynamic integration

Consider an initial configuration $q^0 \in \Sigma(z)$. Iterate on $n \geq 0$,

1. Sample a random vector in the tangent space $T_{q^n}\Sigma(z)$ ($\nabla\xi(q^n)^T\, p^n = 0$):

$$p^n = \beta^{-1/2}\, P(q^n) G^n,$$

where $(G^n)_{n\geq 0}$ are i.i.d. standard random Gaussian variables, and compute the energy $E^n = \frac{1}{2}|p^n|^2 + V(q^n)$ of the configuration (q^n, p^n);

2. If $|p^n|^2 > R_{\Delta t}$, set $E^{n+1} = +\infty$ and go to (3); otherwise perform one integration step of the RATTLE scheme:

$$\begin{cases} p^{n+1/2} = p^n - \dfrac{\Delta t}{2}\nabla V(q^n) + \nabla\xi(q^n)\,\lambda^{n+1/2}, \\ \widetilde{q}^{n+1} = q^n + \Delta t\, p^{n+1/2}, \\ \xi(\widetilde{q}^{n+1}) = z, \\ \widetilde{p}^{n+1} = p^{n+1/2} - \dfrac{\Delta t}{2}\nabla V(\widetilde{q}^{n+1}) + \nabla\xi(\widetilde{q}^{n+1})\,\lambda^{n+1}, \\ \nabla\xi(\widetilde{q}^{n+1})^T\,\widetilde{p}^{n+1} = 0; \end{cases}$$

Thermodynamic integration

3. If $|\widetilde{p}^{n+1}|^2 > R_{\Delta t}$, set $E^{n+1} = +\infty$; otherwise compute the energy $E^{n+1} = \frac{1}{2}|\widetilde{p}^{n+1}|^2 + V(\widetilde{q}^{n+1})$ of the new phase-space configuration. Accept the proposal and set $q^{n+1} = \widetilde{q}^{n+1}$ with probability

$$\min\Big(\exp(-\beta(E^{n+1} - E^n)), 1\Big);$$

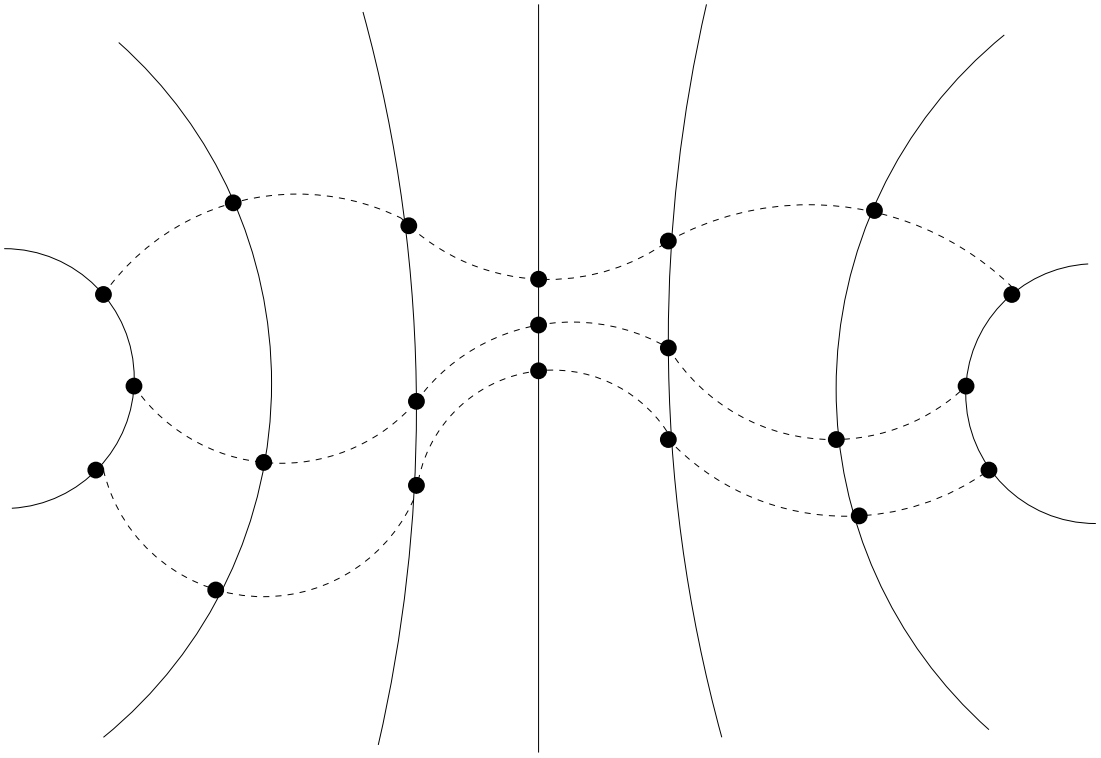
otherwise, reject and set $q^{n+1} = q^n$.

Proposition: The probability measure

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

is invariant for the Markov Chain $(q^n)_{n\geq 1}$.

Non-equilibrium dynamics



Non-equilibrium dynamics

Let us consider a stochastic process such that $\boldsymbol{X}_0 \sim \mu_{\Sigma_{z(0)}}$ and

$$\begin{cases} d\boldsymbol{X}_t = -P(\boldsymbol{X}_t)\nabla\tilde{V}(\boldsymbol{X}_t)\,dt + \sqrt{2\beta^{-1}}P(\boldsymbol{X}_t)\circ d\boldsymbol{W}_t \\ \qquad\qquad +\nabla\xi(\boldsymbol{X}_t)d\Lambda_t^{\mathrm{ext}}, \\ d\Lambda_t^{\mathrm{ext}} = \dfrac{z'(t)}{|\nabla\xi(\boldsymbol{X}_t)|^2}\,dt, \end{cases}$$

where $z : [0, T] \to [0, 1]$ is a fixed deterministic evolution of the reaction coordinate ξ, such that $z(0) = 0$ and $z(T) = 1$.
One can check that

$$\xi(\boldsymbol{X}_t) = z(t).$$

Non-equilibrium dynamics

The dynamics can also be written using a Lagrange multiplier:

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

And we have

$$d\Lambda_t = d\Lambda_t^{\mathrm{m}} + d\Lambda_t^{\mathrm{f}} + d\Lambda_t^{\mathrm{ext}},$$

where $d\Lambda_t^{\mathrm{m}} = -\sqrt{2\beta^{-1}} \frac{\nabla\xi}{|\nabla\xi|^2}(\boldsymbol{X}_t) \cdot d\boldsymbol{W}_t$, $d\Lambda_t^{\mathrm{f}} = f(\boldsymbol{X}_t)\, dt$ and $d\Lambda_t^{\mathrm{ext}} = \frac{z'(t)}{|\nabla\xi(\boldsymbol{X}_t)|^2}\, dt$.

Non-equilibrium dynamics

How to get equilibrium quantities (like the free energy) through non-equilibrium simulations ?

The idea is to associate to each trajectory $\boldsymbol{X}_t$ a weight

$$\mathcal{W}(t) = \int_0^t f(\boldsymbol{X}_s) z'(s)\, ds = \int_0^t z'(s) d\Lambda_s^{\mathrm{f}}.$$

and to compute free energy differences by a Feynman-Kac formula (Jarzynski identity):

$$A(z(t)) - A(z(0)) = -\beta^{-1} \ln \left(\mathbb{E} \left(\exp(-\beta \mathcal{W}(t)) \right) \right).$$

Non-equilibrium dynamics

[TL, M. Rousset, G. Stoltz, 2007]. The proof consists in introducing the semi-group associated with the dynamics

$$u(s,x) = \mathbb{E}\left(\varphi(X_t^{s,x}) \exp\left(-\beta \int_s^t f(X_r^{s,x}) z'(r)\, dr\right)\right)$$

and to show that $\frac{d}{ds} \int u(s,.) \exp(-\beta \tilde{V}) d\sigma_{\Sigma_{z(s)}} = 0$ using the divergence theorem on submanifolds. Then

$$\int u(t,.) \exp(-\beta \tilde{V}) d\sigma_{\Sigma_{z(t)}} = \int u(0,.) \exp(-\beta \tilde{V}) d\sigma_{\Sigma_{z(0)}}$$

is equivalent to

$$\int \varphi \exp(-\beta \tilde{V}) d\sigma_{\Sigma_{z(t)}}$$

$$= \exp(-\beta A(z(0))) \mathbb{E}\left(\int \varphi(X_t) \exp\left(-\beta \int_0^t f(X_r) z'(r)\, dr\right)\right).$$

Non-equilibrium dynamics

A more general relation is the so-called Crooks identity which is a more general formula relating the free energy to the work of forward and backward switched processes. Let q_t^f and q_t^b satisfy: $q_0^f \sim \mu_{\Sigma(z(0))}$, $q_0^b \sim \mu_{\Sigma(z(T))}$,

$$\begin{cases} dq_t^f = -\nabla \tilde{V}(q_t^f)\, dt + \sqrt{2\beta^{-1}} dW_t^f + \nabla \xi(q_t^f) d\Lambda_t^f, \\ \xi(q_t^f) = z(t), \end{cases}$$

$$\begin{cases} dq_{t'}^b = -\nabla \tilde{V}(q_{t'}^b)\, dt' + \sqrt{2\beta^{-1}} dW_{t'}^b + \nabla \xi(q_{t'}^b) d\Lambda_{t'}^b, \\ \xi(q_{t'}^b) = z(T - t'). \end{cases}$$

Non-equilibrium dynamics

Then, for any $\theta \in [0,1]$, for any path functional ϕ,

$$\exp\Big(-\beta(A(z(T))-A(z(0))\Big)\,\mathbb{E}\Big(\phi(\{q^b_{T-s}\}_{0\le s\le T})\exp(-\beta\theta\mathcal{W}^b(T))\Big)$$
$$=\mathbb{E}\Big(\phi(\{q^f_s\}_{0\le s\le T})\exp(-\beta(1-\theta)\mathcal{W}^f(T))\Big),$$

where $\mathcal{W}^f(T)=\int_0^t f(q^f_s)z'(s)\,ds$ and
$\mathcal{W}^b(T)=-\int_0^t f(q^b_s)z'(T-s)\,ds$.

This identity can be used to combine forward and backward processes to get better estimates of the free energy difference, see for example bridge sampling methods [Bennett, Meng and Wong, Shirts].

Non-equilibrium dynamics

The discretization of the constrained process is (as before):

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

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

To extract λ_n^{f} from λ_n, one can *e.g.* compute:

$$\lambda_n^{\mathrm{f}} = \lambda_n - \frac{z(t_{n+1}) - z(t_n)}{|\nabla\xi(\boldsymbol{X}_n)|^2} + \sqrt{2\beta^{-1}}\frac{\nabla\xi}{|\nabla\xi|^2}(\boldsymbol{X}_n)\cdot\Delta\boldsymbol{W}_n.$$

Non-equilibrium dynamics

Another method to compute λ_n^{f} consists in:

$$\left\{ \begin{array}{l} \boldsymbol{X}_{n+1}^R = \boldsymbol{X}_n - \nabla \tilde{V}(\boldsymbol{X}_n)\Delta t - \sqrt{2\beta^{-1}}\Delta \boldsymbol{W}_n + \lambda_n^R \nabla \xi(\boldsymbol{X}_{n+1}^R), \\ \text{with } \lambda_n^R \text{ such that } \frac{1}{2}\left(\xi(\boldsymbol{X}_{n+1}^R) + \xi(\boldsymbol{X}_{n+1})\right) = \xi(\boldsymbol{X}_n). \end{array} \right.$$

We then have $\lambda_n^{\mathrm{f}} = \frac{1}{2}\left(\lambda_n + \lambda_n^R\right)$.
The weight is then approximated by

$$\left\{ \begin{array}{l} \mathcal{W}_0 = 0, \\ \mathcal{W}_{n+1} = \mathcal{W}_n + \frac{z(t_{n+1}) - z(t_n)}{t_{n+1} - t_n} \lambda_n^{\mathrm{f}}, \end{array} \right.$$

and a (biased) estimator of the free energy difference $A(z(T)) - A(z(0))$ is $-\beta^{-1} \ln\left(\frac{1}{M}\sum_{m=1}^{M} \exp\left(-\beta \mathcal{W}_{T/\Delta t}^m\right)\right)$.

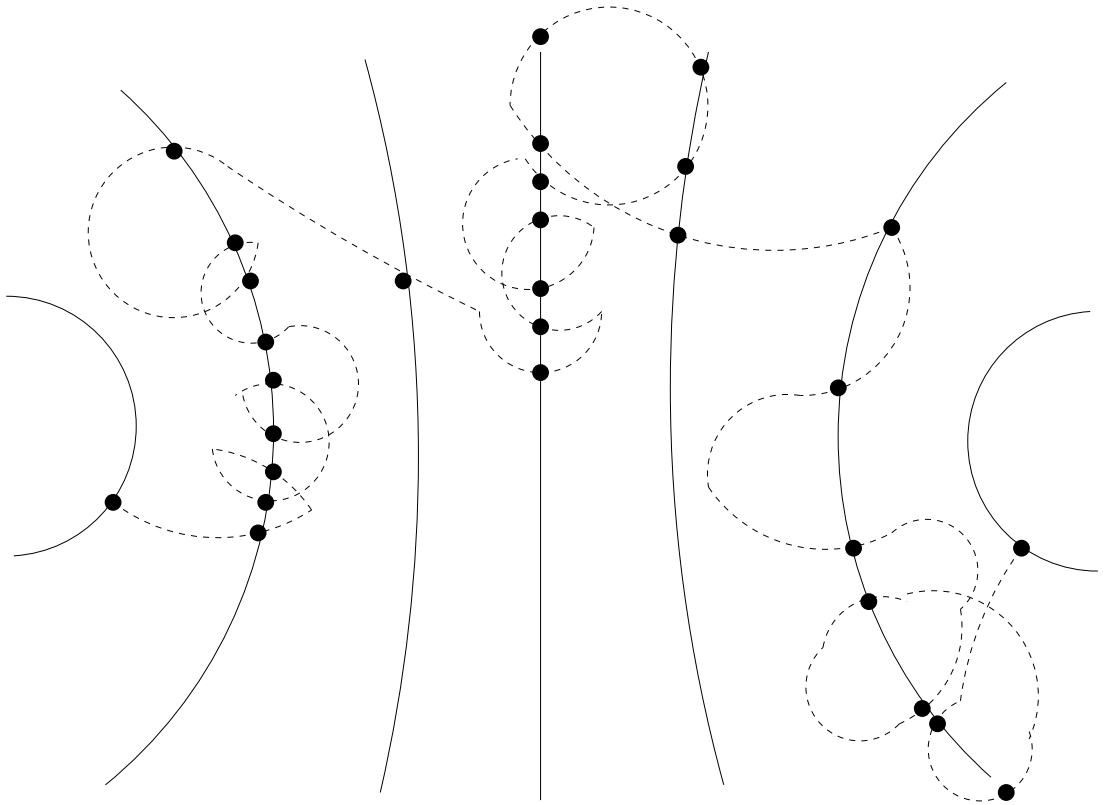
Non-equilibrium dynamics

In practice, the efficiency of this numerical method is not clearly demonstrated. If the transition is too fast, the variance of the estimator is very large. If the transition is slow, we are back to thermodynamic integration...

Ideas: (i) combine forward and backward trajectories, (ii) add selection mechanisms [M. Rousset, G. Stoltz, 2006] or (iii) use importance sampling to help the transition (escorting) [Vaikuntanathan, Jarzynski, 2008].

All this can be generalized to Langevin (phase-space) dynamics, with the additional difficulty that generalized free energies with constraints on both positions and momenta are obtained.

Adaptive biasing techniques



Adaptive biasing techniques

Recall that the original gradient dynamics (GD)

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

is metastable. We want to use the information that $\xi(\boldsymbol{X}_t)$ is a slow variable, where $\xi : \mathbb{R}^n \to \mathbb{T}$ to have better sampling.

We will use the free energy

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

to bias the dynamics.

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

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

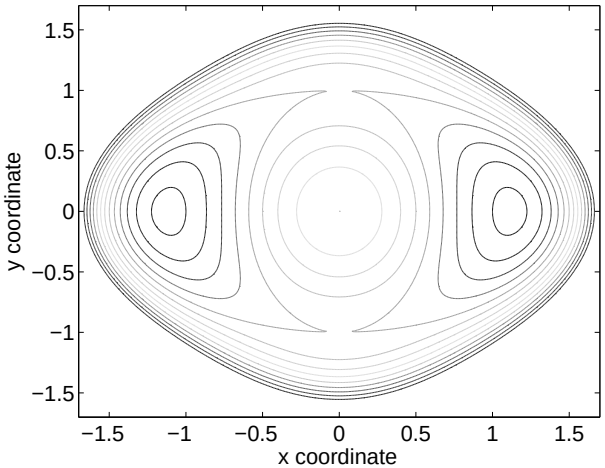
where A_t is an approximation at time t of A, given the configurations visited so far.

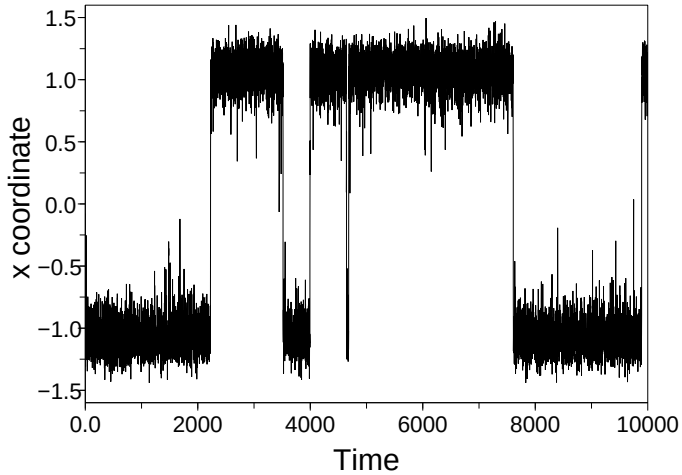
Hopes:

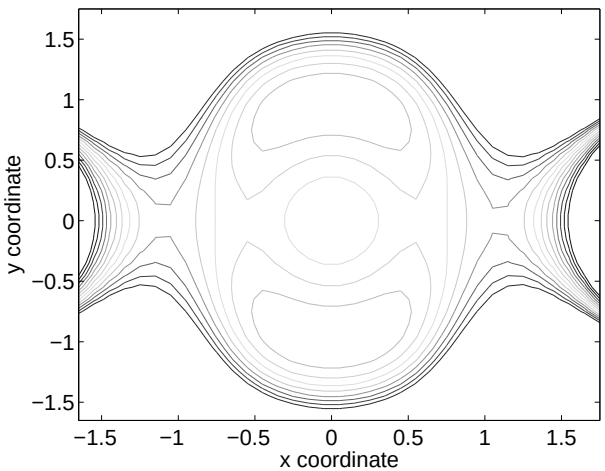
- build a dynamics which goes quickly to equilibrium,
- compute free energy profiles.

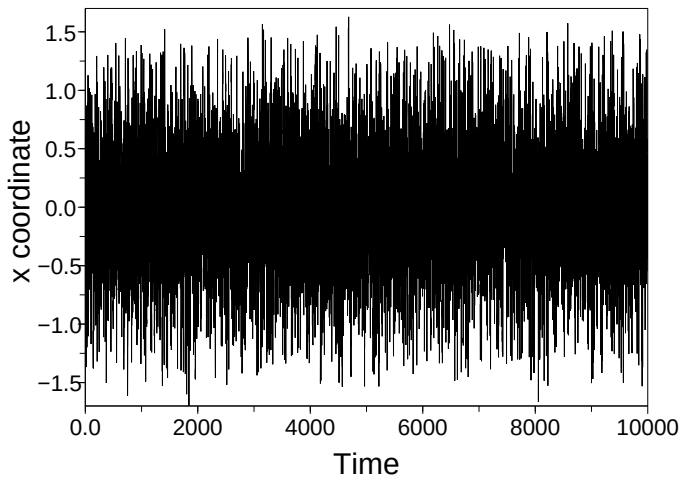
Wang-Landau, ABF, metadynamics: *Darve, Pohorille, Hénin, Chipot, Laio, Parrinello, Wang, Landau,...*

Adaptive biasing techniques



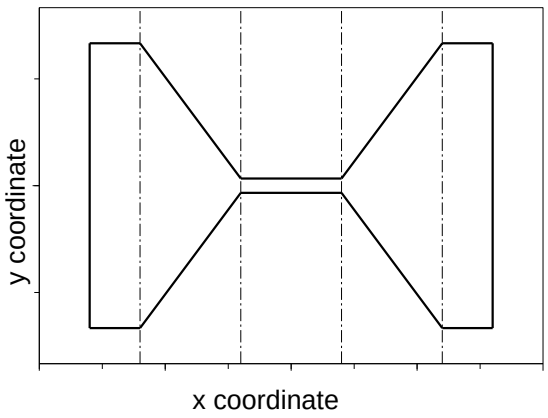


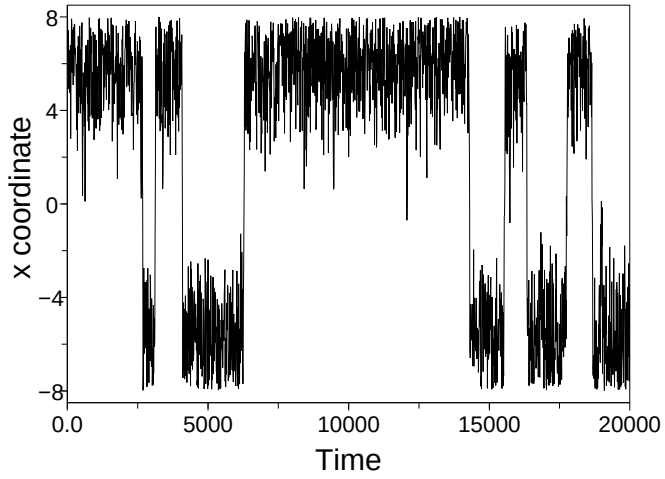


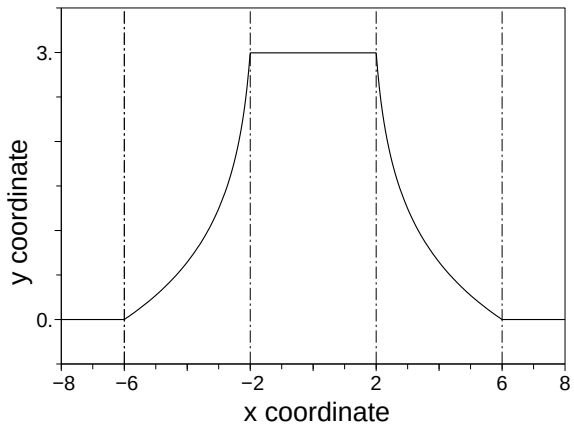


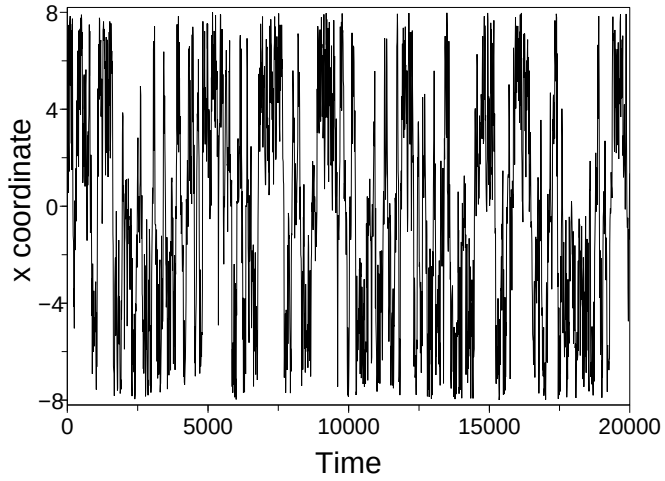
A 2d example of a free energy biased trajectory: energetic barrier.

Adaptive biasing techniques









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

The ABF method

How to update A_t ? Two methods depending on wether A'_t (Adaptive Biasing Force) or A_t (Adaptive Biasing Potential) is approximated.

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

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

$$= \int f \, d\mu_{\Sigma(z)} = \mathbb{E}_\mu(f(\boldsymbol{X})|\xi(\boldsymbol{X}) = z).$$

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

The ABF method

Notice that actually, whatever A_t is,

$$A'(z) = \frac{\int f e^{-\beta(V - A_t \circ \xi)} \, \delta_{\xi(x)-z}(dx)}{\int e^{-\beta(V - A_t \circ \xi)} \, \delta_{\xi(x)-z}(dx)}.$$

Thus, if the bias is fixed:

$$d\boldsymbol{X}_t = -\nabla(V - A_{t_0} \circ \xi)(\boldsymbol{X}_t)\, dt + \sqrt{2\beta^{-1}} d\boldsymbol{W}_t,$$

we obtain the free energy at equilibrium:

$$\lim_{t \to \infty} \mathbb{E}(f(\boldsymbol{X}_t) | \xi(\boldsymbol{X}_t) = z) = A'(z).$$

Of course, we will adapt A_t as time goes...

The ABF method

Thus, we would like to simulate:

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

but A is unknown...

The ABF method

The ABF dynamics is then:

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

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The associated (nonlinear) Fokker-Planck equation writes:

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

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

The ABF method

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

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

Adaptive methods (1)

Two variants:

- A may be approximated instead of A', using the formula

$$A(z) = -\beta^{-1} \ln \left(\int_{\Sigma_z} e^{-\beta V} |\nabla \xi|^{-1} d\sigma_{\Sigma_z} \right).$$

  This leads to Adaptive Biasing Potential (ABP) methods.

- To avoid geometry problem, an extended configurational space $(\boldsymbol{x}, z) \in \mathbb{R}^{n+1}$ is 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 methods (2)

Adaptive algorithms used in molecular dynamics fall into one of these four possible combinations:

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

Longtime convergence and entropy (1)

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 μ, which can be quantified through the rate of convergence of ϕ to $\phi_\infty = Z^{-1} \exp(-\beta V)$.

Longtime convergence and entropy (2)

Recall that exponential convergence to equilibrium of the entropy is equivalent to LSI(R).

Exponential convergence to equilibrium: For any initial condition, $E(t) \leq E(0) \exp(-2\beta^{-1} R t)$ where
$E(t) = H(\phi(t,\cdot)|\phi_\infty) = \int \ln\left(\frac{\phi}{\phi_\infty}\right)\phi$.

Logarithmic Sobolev inequality (LSI(R)): For all probability density function ϕ,

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

We thus measure metastability through LSI constants:

$$\text{Metastability} \iff \text{small } R$$

What did we gain compared to the original gradient dynamics (GD) ?

Convergence of ABF (1)

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) "Strong mixing" of the microscopic variables: the conditional probability measures $\mu_{\Sigma(z)}$ 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)

In summary:

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

If ξ is well chosen, $\rho \gg R$: the free energy can be computed very efficiently. Once the free energy is known, there are classical techniques to compute averages wrt μ (unbiasing, conditioning).

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)

(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

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

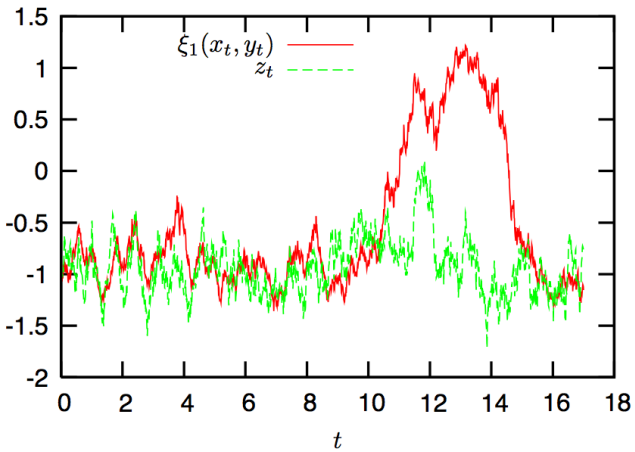
We already know that E_M goes to zero: it remains only to consider E_m...

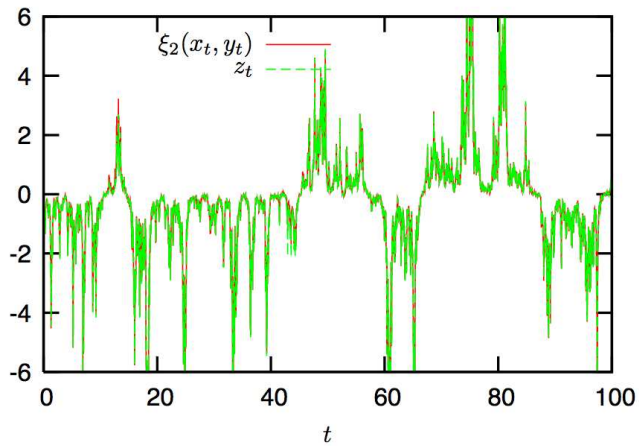
Convergence of ABF (4)

Other results based on this set of assumptions:

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

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





Discretization of ABF (1)

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

- Use trajectorial averages along a single path:

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

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

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

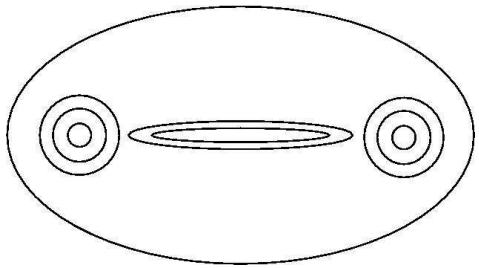
Discretization of ABF (2)

Interest of a discretization using an interacting particle system:

- Convergence can be more easily analyzed !
- Very efficient parallelization.
- A selection mechanism may be added to duplicate "innovative particles" and kill "redundant particles". [TL, M. Rousset, G. Stoltz, J Chem Phys 2007].
- Better sampling of all reactive paths.

Multiple channel cases

In some practical cases (multi-channel case), ρ may be small... Are these convergence results optimal ?

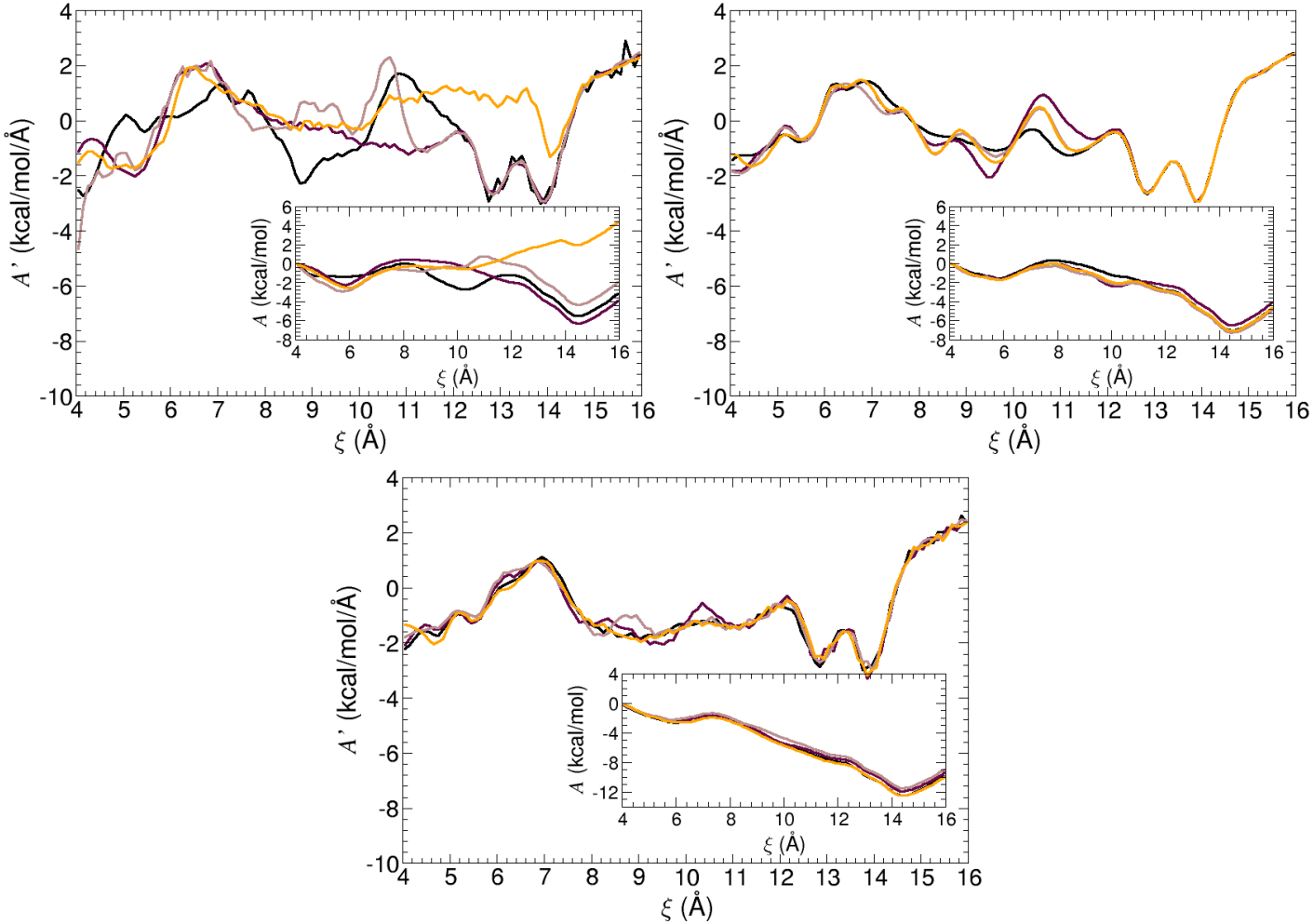


Numerically, it is observed [C. Chipot, TL, K. Minoukadeh, 2010] that in such a situation, the ABF method actually converges rapidly, in particular when using implementations using many replicas.

Test case: Compact configurations of a deca-alanine peptide. It appears that using many replica in parallel and empirical means yields better sampling, even at fixed CPU time.

Multiple channel cases

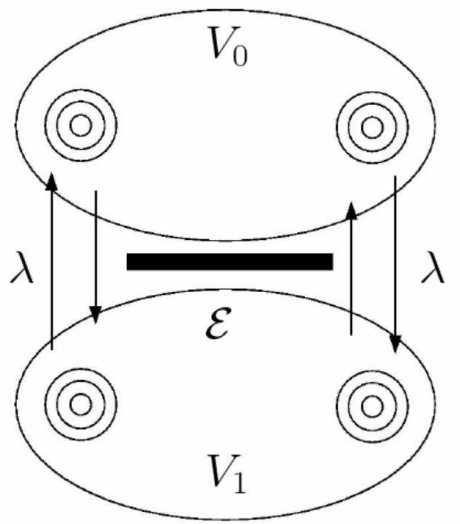
Mean force and free energy profiles obtained with 4 independent runs.



Top left: 1 walker, T=100 ns ; Top right: 32 walkers, T=100ns ;
Bottom: 32 walkers, T=3ns.

Convergence of ABF in a bi-channel case

Theoretically, it can be shown [TL, K. Minoukadeh, 2010] that, in a bi-channel situation, the ABF method actually converges with a rate limited by the LSI constants of the conditional measures in each channel (2d, $\xi(x,y) = x$ and $\beta = 1$ for simplicity).



$$\begin{cases} dX_t = -\nabla(V_{I_t} - A_t \circ \xi)(X_t)dt + \sqrt{2}dB_t, \\ A_t'(x) = \mathbb{E}\left[\partial_x V_{I_t}(X_t) | \xi(X_t) = x\right], \\ I_t \in \{0,1\} \text{ is a jump process changing value} \\ \quad \text{with intensity } \lambda(\xi(X_t))\, dt. \end{cases}$$

$$\exists\, \mathcal{E} \subset \mathbb{T}, \lambda = \lambda_0 \mathbf{1}_{\mathbb{T}\setminus\mathcal{E}} \text{ and } \forall x \in \mathbb{T} \setminus \mathcal{E},\, V_0(x,\cdot) = V_1(x,\cdot)$$

The process (X_t, I_t) has law with density $\psi(t,x,y,i)$ satisfying $\partial_t \psi = \mathrm{div}(\nabla(V_i - A_t \circ \xi)\psi + \nabla\psi) - \lambda \circ \xi(\psi - \psi_{1-i})$.

Convergence of ABF in a bi-channel case

The non-linear Fokker-Planck equation writes:

$$\begin{cases} \partial_t \psi = \mathrm{div}\ \left(\nabla(V_i - A_t \circ \xi)\psi + \nabla\psi\right) - \lambda \circ \xi(\psi - \psi_{1-i}), \\ A_t'(x) = \dfrac{\displaystyle\sum_{i=0}^{1} \int \partial_x V_i\, \psi\, dy}{\displaystyle\sum_{i=0}^{1} \int \psi\, dy}. \end{cases}$$

A convergence result in a bi-channel case [TL, K. Minoukadeh, 2010]:
Suppose that in each channel, the conditional measures satisfy LSI(ρ), and that the free energy is a good bias in each channel.
Then, exponential convergence of A_t' to A' at a rate close to ρ can be proven.

Adaptive biasing techniques

Coming back to the original aim: how to use free energy to compute canonical averages $\int \varphi d\mu = \int \varphi Z^{-1} e^{-\beta V}$?

- Importance sampling:

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

- Conditioning:

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

This requires the sampling of the conditional probability measure $\mu_{\Sigma(z)}$ which can be done using projected Langevin dynamics [TL, M. Rousset, G. Stoltz, 2011].

Adaptive biasing techniques: conclusions

Interesting features of the algorithm: parallelization and adaptivity.

Entropy approaches are powerful techniques to investigate multimodal measures, metastable dynamics and analyze sampling algorithms.

These techniques can be used whenever the sampling of a multimodal measure is involved, for example for statistical inference in Bayesian statistics [N. Chopin, TL, G. Stoltz, 2011].

Conclusion

To efficiently sample multimodal distributions, we have introduced:

- methods based on constraints (TI, non-equilibrium dynamics),
- importance sampling techniques (free energy biasing methods).

All these techniques (constraining / importance sampling) do not apply when the drift is not a gradient (non reversible dynamics). How to treat efficiently such cases (sampling of Non Equilibrium Steady States) ?

Conclusion

A few references:

- G. Ciccotti, TL and E. Vanden-Eijnden *Projection of diffusions on submanifolds: Application to mean force computation*, CPAM, 61(3), 371-408, (2008).
- C. Chipot, TL and K. Minoukadeh, *Potential of mean force calculations: a multiple-walker adaptive biasing force approach*, JCTC, 6(4), 1008-1017, (2010).
- TL, M. Rousset and G. Stoltz, *Long-time convergence of an Adaptive Biasing Force method*, Nonlinearity, 21, 1155-1181, 2008.
- TL, M. Rousset et G. Stoltz, *Langevin dynamics with constraints and computation of free energy differences*, Math. of Comp., 2012.
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