Free energy computations

Monte Carlo methods in molecular dynamics

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1 Free energy and metastability

The aim of molecular dynamics computations is to evaluate numerically macroscopic quantities from models at the microscopic scale.

Some examples of macroscopic quantities:

- thermodynamics quantities: stress, heat capacity, free energy;
- dynamical quantities: diffusion coefficients, viscosity, transition rates.

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

1 Free energy and metastability

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 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.

Aim: compute averages with respect to μ.

1 Free energy and metastability

Examples of quantities of interest:

- specific heat

$$C \propto \langle V^2 \rangle_\mu - \langle V \rangle_\mu^2$$

- pressure

$$P \propto -\langle q \cdot \nabla V(q) \rangle_\mu$$

1 Free energy and metastability

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

$$V = \sum_{i<j} V_1(\boldsymbol{x}_i, \boldsymbol{x}_j) + \sum_{i<j<k} V_2(\boldsymbol{x}_i, \boldsymbol{x}_j, \boldsymbol{x}_k) + \sum_{i<j<k<l} V_3(\boldsymbol{x}_i, \boldsymbol{x}_j, \boldsymbol{x}_k, \boldsymbol{x}_l).$$

For example, $V_1(\boldsymbol{x}_i, \boldsymbol{x}_j) = V_{LJ}(|\boldsymbol{x}_i - \boldsymbol{x}_j|)$ 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.

1 Free energy and metastability

To sample μ, Markov Chain Monte Carlo methods are used.

A typical example is the *over-damped Langevin* (or gradient) dynamics:

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

Under suitable assumption, we have the ergodic property: for μ-a.e. $\boldsymbol{X}_0$,

$$\lim_{T\to\infty} \frac{1}{T} \int_0^T \phi(\boldsymbol{X}_t) dt = \int \phi(\boldsymbol{x}) d\mu(\boldsymbol{x}).$$

1 Free energy and metastability

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,

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

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 $\mathcal{U}((0,1))$.

1 Free energy and metastability

Proof (invariant measure): One needs to show that if the law of $\boldsymbol{X}_0$ is μ, then the law of $\boldsymbol{X}_t$ is also μ. Let us denote $\boldsymbol{X}_t^{\boldsymbol{x}}$ the solution to (GD) such that $\boldsymbol{X}_0 = \boldsymbol{x}$. Let us consider the function $u(t,\boldsymbol{x})$ solution to:

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

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

$$\frac{d}{dt} \int \mathbb{E}(\phi(\boldsymbol{X}_t^{\boldsymbol{x}})) d\mu(\boldsymbol{x}) = Z^{-1} \int \partial_t u(t,\boldsymbol{x}) \exp(-\beta V(\boldsymbol{x})) d\boldsymbol{x}$$

$$= Z^{-1} \int \left(-\nabla V \cdot \nabla u + \beta^{-1} \Delta u\right) \exp(-\beta V) = 0.$$

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

1 Free energy and metastability

Probabilistic insert (2): Feynman-Kac formula.

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

$$du(t-s,\boldsymbol{X}_s^{\boldsymbol{x}}) = -\partial_t u(t-s,\boldsymbol{X}_s^{\boldsymbol{x}})\,ds + \nabla u(t-s,\boldsymbol{X}_s^{\boldsymbol{x}}) \cdot d\boldsymbol{X}_s^{\boldsymbol{x}}$$

$$+\beta^{-1}\Delta u(t-s,\boldsymbol{X}_s^{\boldsymbol{x}})\,ds,$$

$$= \Big(-\partial_t u(t-s,\boldsymbol{X}_s^{\boldsymbol{x}}) - \nabla V(\boldsymbol{X}_s^{\boldsymbol{x}}) \cdot \nabla u(t-s,\boldsymbol{X}_s^{\boldsymbol{x}})$$

$$+ \beta^{-1}\Delta u(t-s,\boldsymbol{X}_s^{\boldsymbol{x}})\Big)\,ds + \sqrt{2\beta^{-1}}\nabla u(t-s,\boldsymbol{X}_s^{\boldsymbol{x}}) \cdot d\boldsymbol{W}_s.$$

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

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

$$= 0.$$

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):

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

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

$$+\beta^{-1}(G_n)^2 u''(X_n)\Delta t + o(\Delta t).$$

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

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

$$+\beta^{-1}\int_0^t u''(X_s)\,ds.$$

1 Free energy and metastability

In practice, (GD) is discretized in time, and Cesaro means are computed: $\lim_{N_T\to\infty} \frac{1}{N_T}\sum_{n=1}^{N_T} \phi(\boldsymbol{X}_n)$.

Remark: Practitioners do not use over-damped Langevin dynamics but rather *Langevin dynamics*:

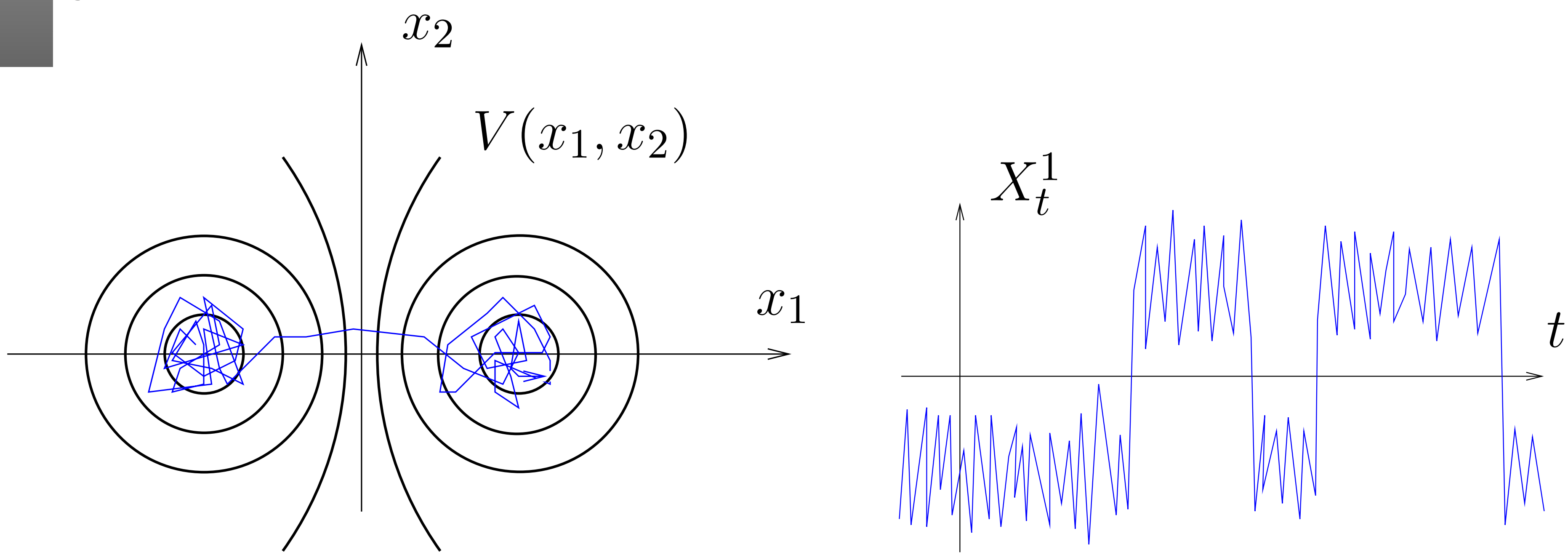
$$\begin{cases} d\boldsymbol{X}_t = M^{-1}\boldsymbol{P}_t\,dt, \\ d\boldsymbol{P}_t = -\nabla V(\boldsymbol{X}_t)\,dt - \gamma M^{-1}\boldsymbol{P}_t\,dt + \sqrt{2\gamma\beta^{-1}}d\boldsymbol{W}_t, \end{cases}$$

where M is the mass tensor and γ is the friction coefficient. In the following, we mainly consider over-damped Langevin dynamics.

1 Free energy and metastability

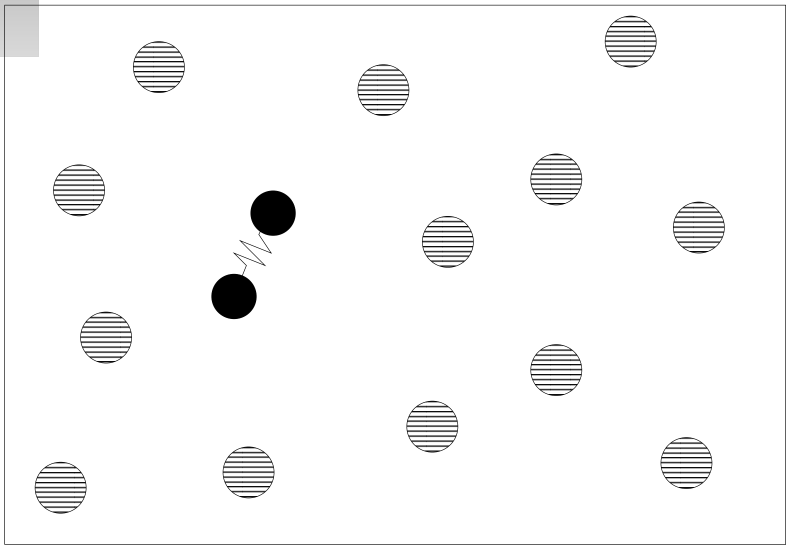
Problem: In practice, $\boldsymbol{X}_t$ is a metastable process, so that the convergence of the ergodic limit is very slow.

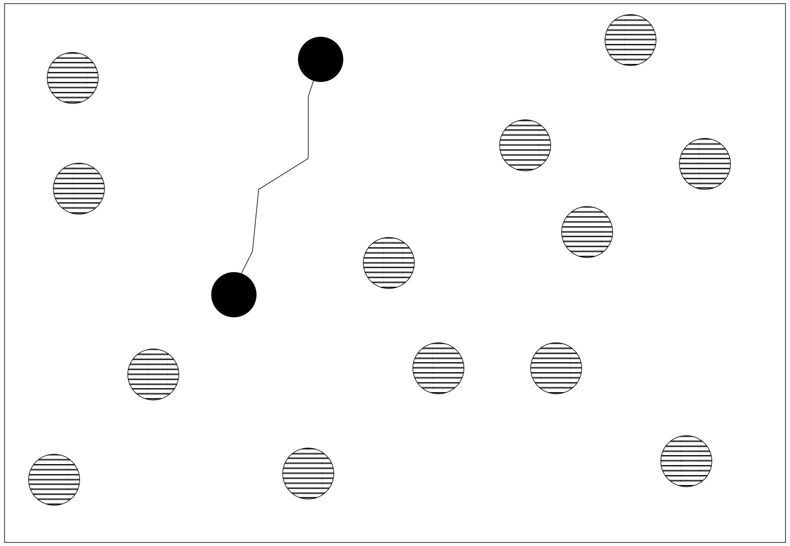
A bi-dimensional example: X_t^1 *is a slow variable of the system.*



1 Free energy and metastability

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



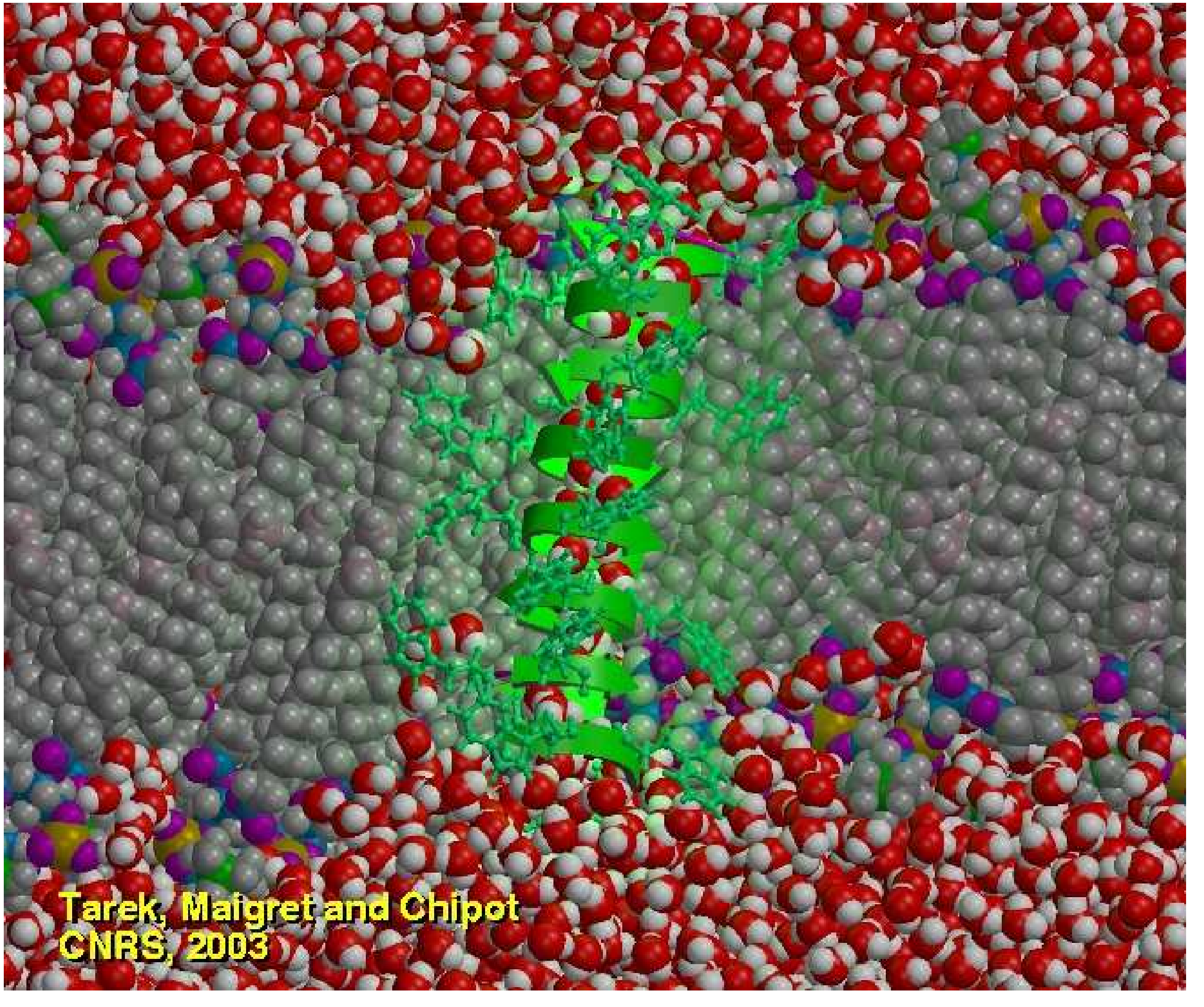


Left: compact state $(\xi = d_0)$. Right: stretched state $(\xi = d_1)$.

A slow variable is $\xi(\boldsymbol{X}_t)$ where $\xi(\boldsymbol{x}) = |\boldsymbol{x}_1 - \boldsymbol{x}_2|$ is a so-called reaction coordinate.

1 Free energy and metastability

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



1 Free energy and metastability

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 criterium.

1 Free energy and 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):

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

1 Free energy and metastability

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

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 $E(t) \leq C \exp(-2\beta^{-1} R t)$ and thus ψ converges to ψ_∞ exponentially fast with rate $\beta^{-1} R$.

Metastability $\iff$ small R

1 Free energy and metastability

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 $\xi : \mathbb{R}^n \to \mathbb{T}$.

Functionals to be averaged are typically functions of this slow variable.
Let us introduce the free energy A which is such that the image of the measure μ by ξ is $Z^{-1} \exp(-\beta A(z))\, dz$.
From the co-area formula, one gets:

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

where $\Sigma(z) = \{\boldsymbol{x}, \, \xi(\boldsymbol{x}) = z\}$ is a (smooth) submanifold of $\mathbb{R}^n$, and $\sigma_{\Sigma(z)}$ is the Lebesgue measure on $\Sigma(z)$.

Co-area formula: 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 bounded functions f and g,

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

Remarks:

- The measure $|\nabla \xi|^{-1} d\sigma_{\Sigma(z)}$ is sometimes denoted $\delta_{\xi(\boldsymbol{x})-z}$ in the literature.

- 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).

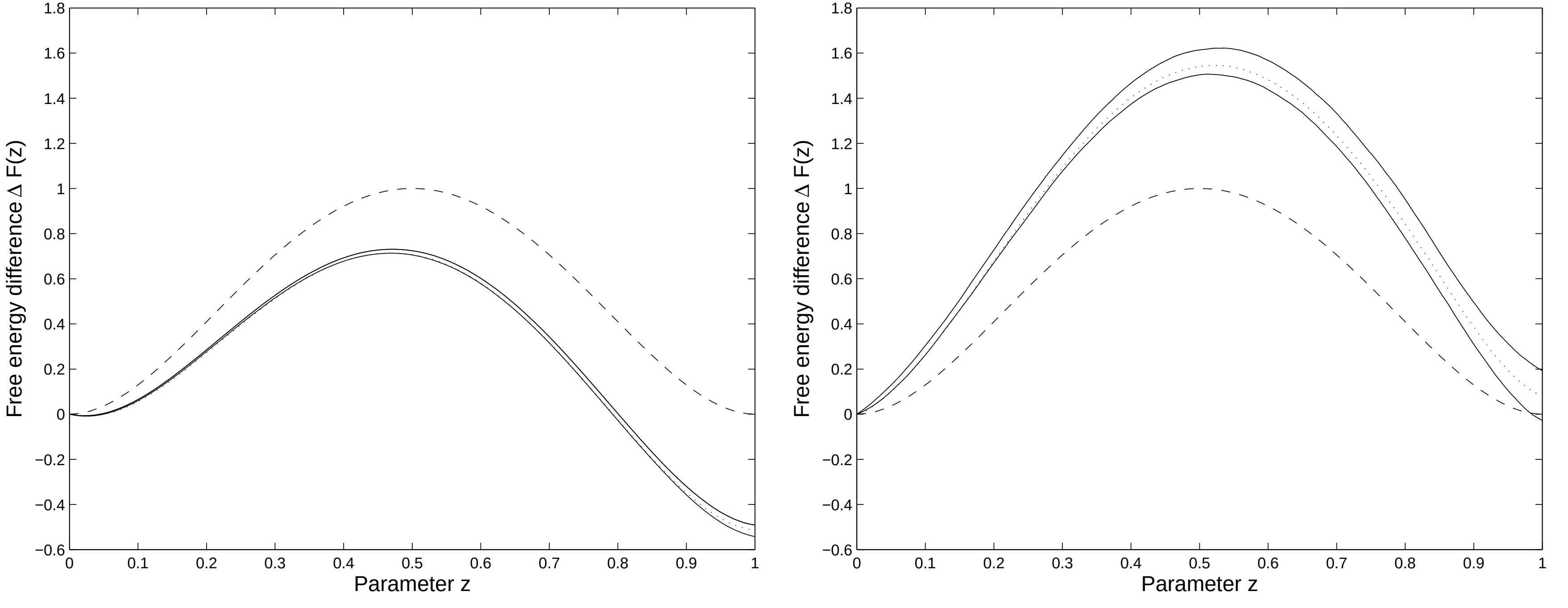
- $A(z) = -\beta^{-1} \ln Z_{\Sigma(z)}$ and $Z_{\Sigma(z)}$ is the partition function associated with the conditioned probability measures:

$$\mu_{\Sigma(z)} = Z_{\Sigma(z)}^{-1} e^{-\beta V} |\nabla \xi|^{-1} d\sigma_{\Sigma(z)}.$$

1 Free energy and metastability

Example of a free energy profile (solvation of a dimer)

(Profiles computed using TI)

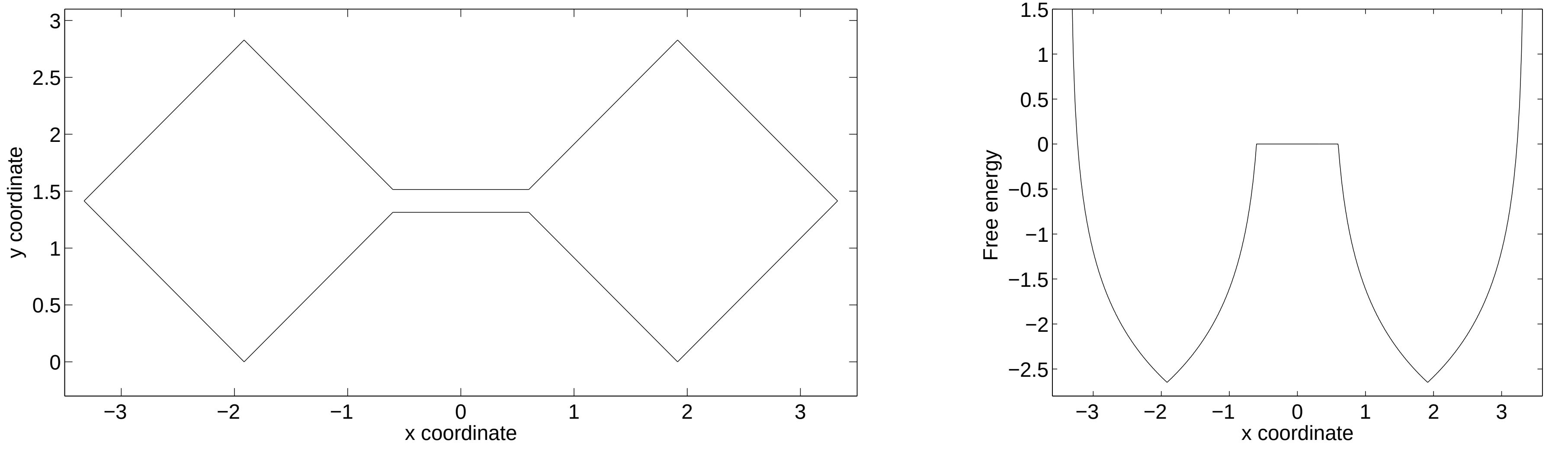


The density of the solvent molecules is lower on the left than on the right. At high (resp. low) density, the compact state is more (resp. less) likely. The “free energy barrier” is higher at high density than at low density. Related question: interpretation of the free energy barrier in terms of dynamics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

1 Free energy and metastability

Some direct numerical simulations...

Remark: Free energy is not energy !



Left: The potential is 0 in the region enclosed by the curve, and $+\infty$ outside.

Right: Associated free energy profile when the x coordinate is the reaction coordinate ($\beta = 1$).

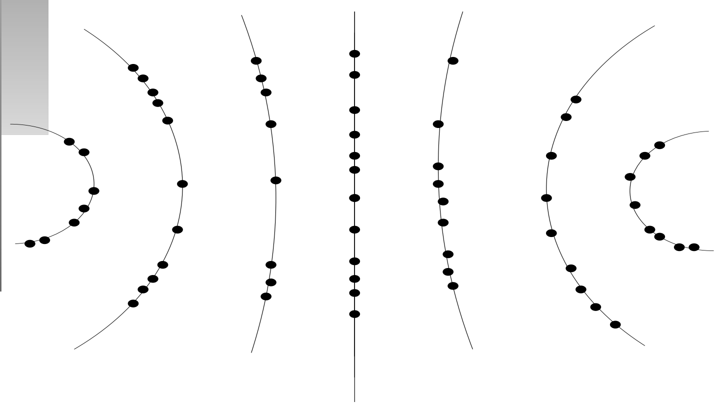
1 Free energy and metastability

Examples of methods to compute free energy differences $A(z_2) - A(z_1)$:

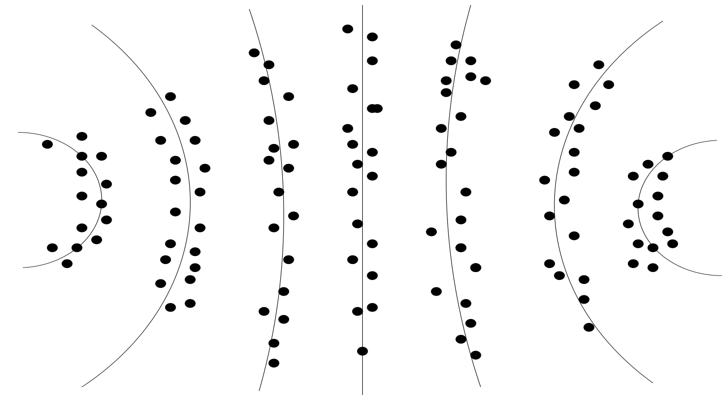
- Thermodynamic integration *(Kirkwood)* (homogeneous Markov process),
- Perturbation methods *(Zwanzig)* and histogram methods,
- Out of equilibrium dynamics *(Jarzynski)* (non-homogeneous Markov process),
- Adaptive methods *(ABF, metadynamics)* (non-homogeneous and non-linear Markov process).

Numerically, this amounts to: (i) sampling efficiently a multi-modal measure in high dimension, (ii) computing the marginal law of such a measure along a given low-dimensional function.

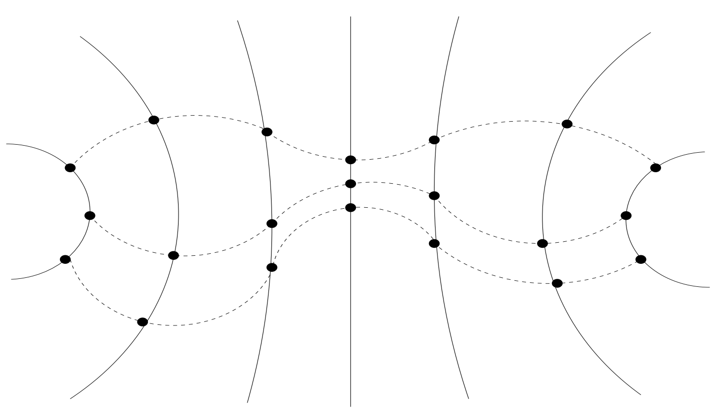
1 Free energy and metastability



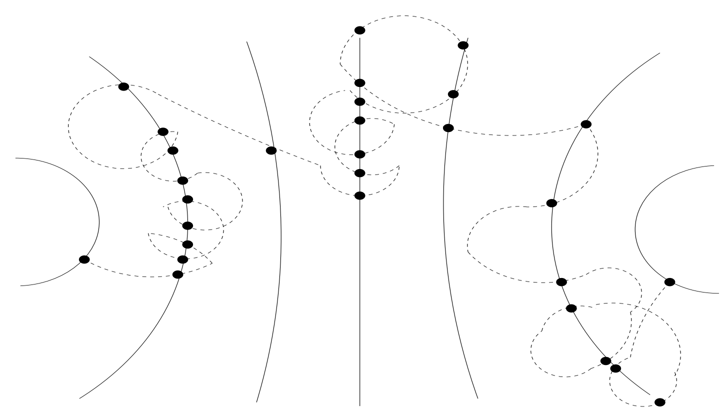
(a) Thermodynamic integration.



(b) Histogram method.



(c) Out of equilibrium dynamics.



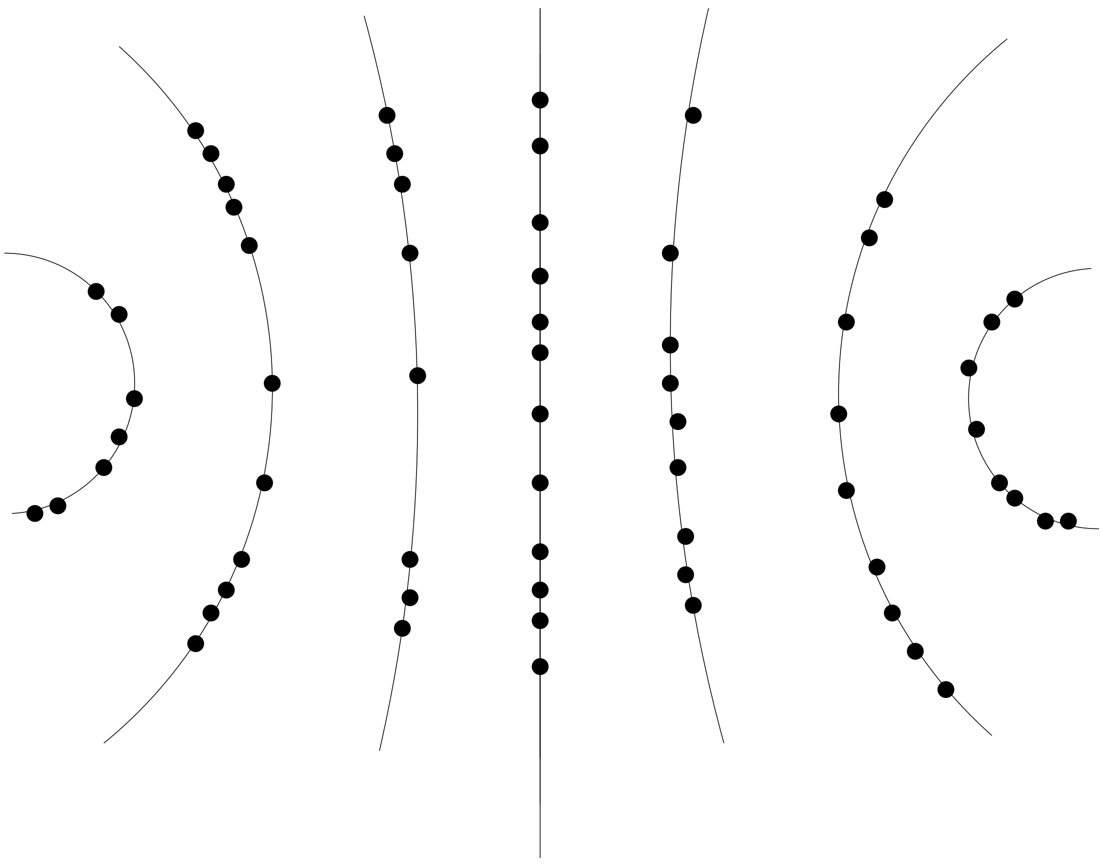
(d) Adaptive dynamics.

2 Constrained dynamics

- Thermodynamic integration *(Kirkwood)*
- Perturbation methods *(Zwanzig)* and histogram methods,
- Out of equilibrium dynamics *(Jarzynski)*,
- Adaptive methods *(ABF, metadynamics)*.

2.1 Thermodynamic integration

Thermodynamic integration



2.1 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, ...)*

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

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

$$= \int f \, d\mu_{\Sigma(z)},$$

where $\tilde{V} = V + \beta^{-1} \ln |\nabla \xi|$, $f = \frac{\nabla V \cdot \nabla \xi}{|\nabla \xi|^2} - \beta^{-1} \mathrm{div} \left(\frac{\nabla \xi}{|\nabla \xi|^2} \right)$

and $\boldsymbol{H} = -\nabla \cdot \left(\frac{\nabla \xi}{|\nabla \xi|} \right) \frac{\nabla \xi}{|\nabla \xi|}$ is the mean curvature vector.

2.1 Thermodynamic integration

Proof: (based on the co-area formula)

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

$$\begin{aligned}
&= -\int \int \exp(-\beta \tilde{V}) \phi' \circ \xi \, d\sigma_{\Sigma(z)} \, dz, \\
&= -\int \exp(-\beta \tilde{V}) \phi' \circ \xi |\nabla \xi| d\boldsymbol{x}, \\
&= -\int \exp(-\beta \tilde{V}) \nabla (\phi \circ \xi) \cdot \frac{\nabla \xi}{|\nabla \xi|^2} |\nabla \xi| d\boldsymbol{x}, \\
&= \int \nabla \cdot \left(\exp(-\beta \tilde{V}) \frac{\nabla \xi}{|\nabla \xi|} \right) \phi \circ \xi \, d\boldsymbol{x},
\end{aligned}$$

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

2.1 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:

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

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:

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

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

2.1 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: $\boldsymbol{n}(\boldsymbol{x}) = \frac{\nabla\xi}{|\nabla\xi|}(\boldsymbol{x})$.

(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).

2.1 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 : $\forall \boldsymbol{\phi} \in \mathcal{C}^1(\mathbb{R}^{3N}, \mathbb{R}^{3N})$,

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

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

2.1 Thermodynamic integration

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

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

2.1 Thermodynamic integration

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

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

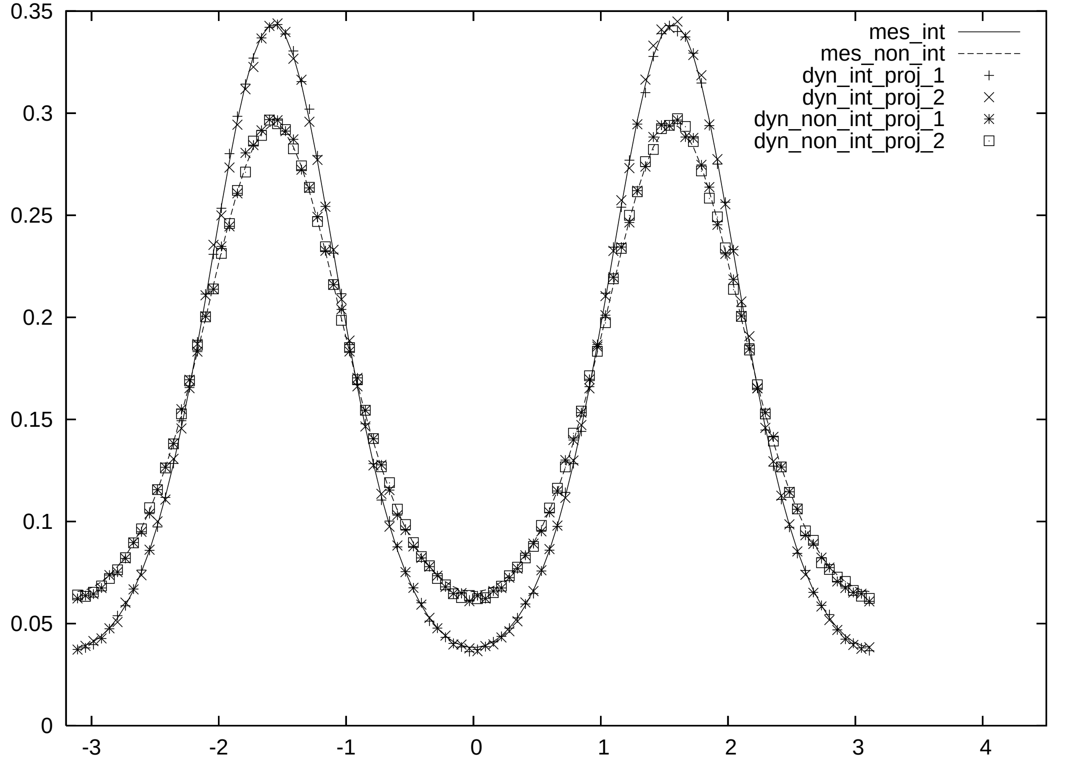
$$\begin{cases} \boldsymbol{X}_* = \boldsymbol{X}_n - \nabla \tilde{V}(\boldsymbol{X}_n)\Delta t - \sqrt{2\beta^{-1}}\Delta \boldsymbol{W}_n + \lambda_* \nabla \xi(\boldsymbol{X}_*), \\ \text{with } \lambda_* \in \mathbb{R} \text{ such that } \xi(\boldsymbol{X}_*) = 0, \end{cases}$$

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.

2.1 Thermodynamic integration

An over-simplified illustration: in dimension 2,
$V(\boldsymbol{x}) = \frac{\beta^{-1}}{2}|\boldsymbol{x}|^2$ and $\xi(\boldsymbol{x}) = \frac{x_1^2}{a^2} + \frac{x_2^2}{b^2} - 1$.



Measures samples theoretically and numerically (as a function of the angle θ), with $\beta = 1$, $a = 2$, $b = 1$, $\Delta t = 0.01$, and 50 000 000 timesteps.

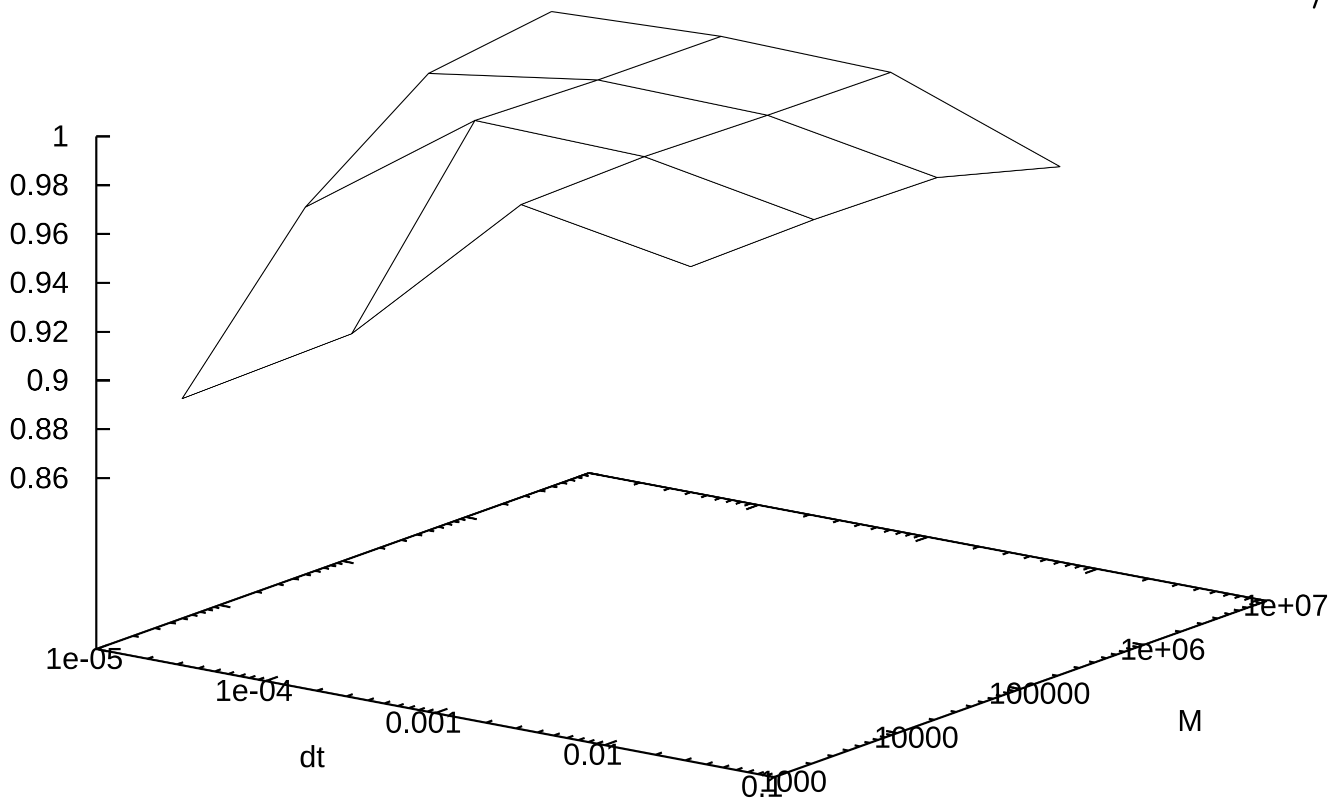
2.1 Thermodynamic integration

Computation of the mean force: $\beta = 1$, $a = 2$, $b = 1$. The exact value is: 0.9868348150. The numerical result (with $\Delta t = 0.001$, $M = 50000$) is: $[0.940613\,;\,1.03204]$.

The variance reduction method reduces the variance by a factor 100. The result (with $\Delta t = 0.001$, $M = 50000$) is: $[0.984019\,;\,0.993421]$.

2.1 Thermodynamic integration

App. mean force as a function of Δt and $M = T/\Delta t$:



A balance needs to be find between the discretization error ($\Delta t \to 0$) and the convergence in the ergodic limit ($T \to \infty$).

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

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

2.1 Thermodynamic integration

Metastability issue: Using TI, we have to 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.

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.

2.1 Thermodynamic integration

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,...)*.

2.1 Thermodynamic integration

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

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

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

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

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

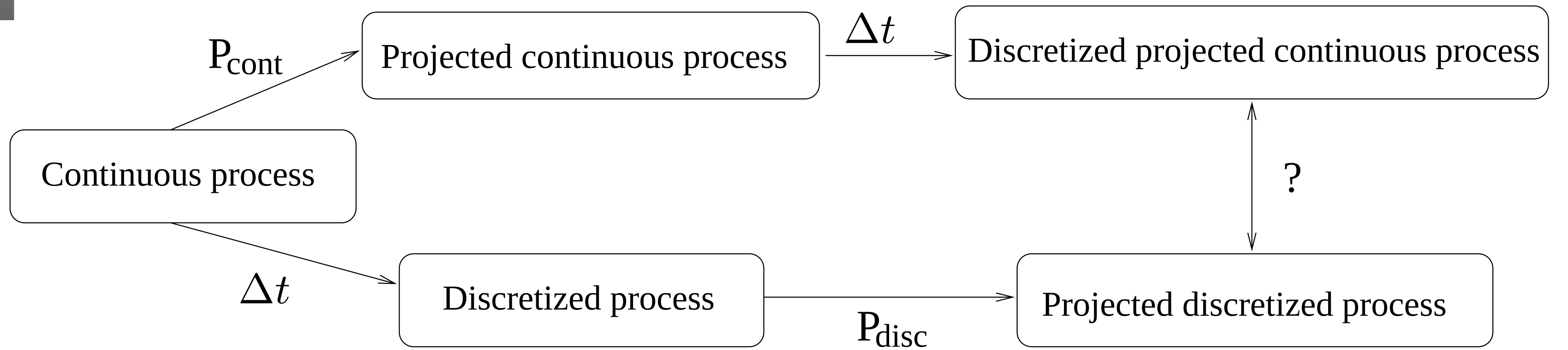
with $\Sigma(z) = \{\boldsymbol{x}, \, \xi(\boldsymbol{x}) = z\}$,

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

$\mu_{\Sigma(z)} = e^{-\beta V} |\nabla \xi|^{-1} d\sigma_{\Sigma(z)} / \int_{\Sigma(z)} e^{-\beta V} |\nabla \xi|^{-1} d\sigma_{\Sigma(z)}$.

2.1 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:



2.1 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.

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

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

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

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

2.1 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.

2.1 Thermodynamic integration

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

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

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

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

2.1 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

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

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 has not simple analytical expression.

2.1 Thermodynamic integration

Moreover, 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).

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 scheme writes:

2.1 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:

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

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

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

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

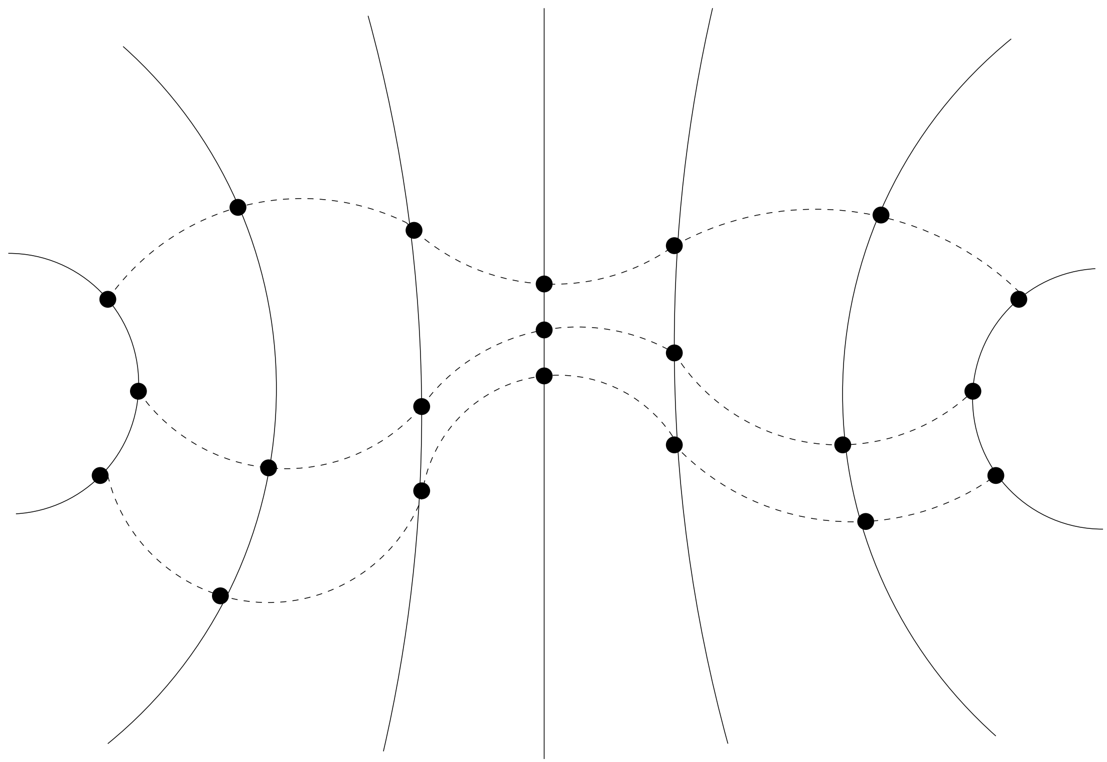
Proposition: The probability measure

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

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

2.2 Non-equilibrium dynamics

Non-equilibrium dynamics



2.2 Non-equilibrium dynamics

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

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

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

2.2 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 $d\Lambda_t^{\mathrm{ext}} = \frac{z'(t)}{|\nabla \xi(\boldsymbol{X}_t)|^2}\, dt$.

2.2 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):

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

2.2 Non-equilibrium dynamics

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

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

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

$$\int \varphi \exp(-\beta \tilde{V}) d\sigma_{\Sigma_{z(t)}} = \exp(-\beta A(z(0)))\mathbb{E}\left(\int \varphi(\boldsymbol{X}_t) \exp\left(-\beta \int_0^t f(\boldsymbol{X}_r) z'(r)\, dr\right)\right).$$

2.2 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: $q_0^f \sim \mu_{\Sigma(z(0))}$, $q_0^b \sim \mu_{\Sigma(z(T))}$,

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

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

2.2 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].

2.2 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:

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

2.2 Non-equilibrium dynamics

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

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

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 $-\beta^{-1}\ln\left(\frac{1}{M}\sum_{m=1}^M \exp\left(-\beta\mathcal{W}_{T/\Delta t}^m\right)\right)$.

2.2 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...

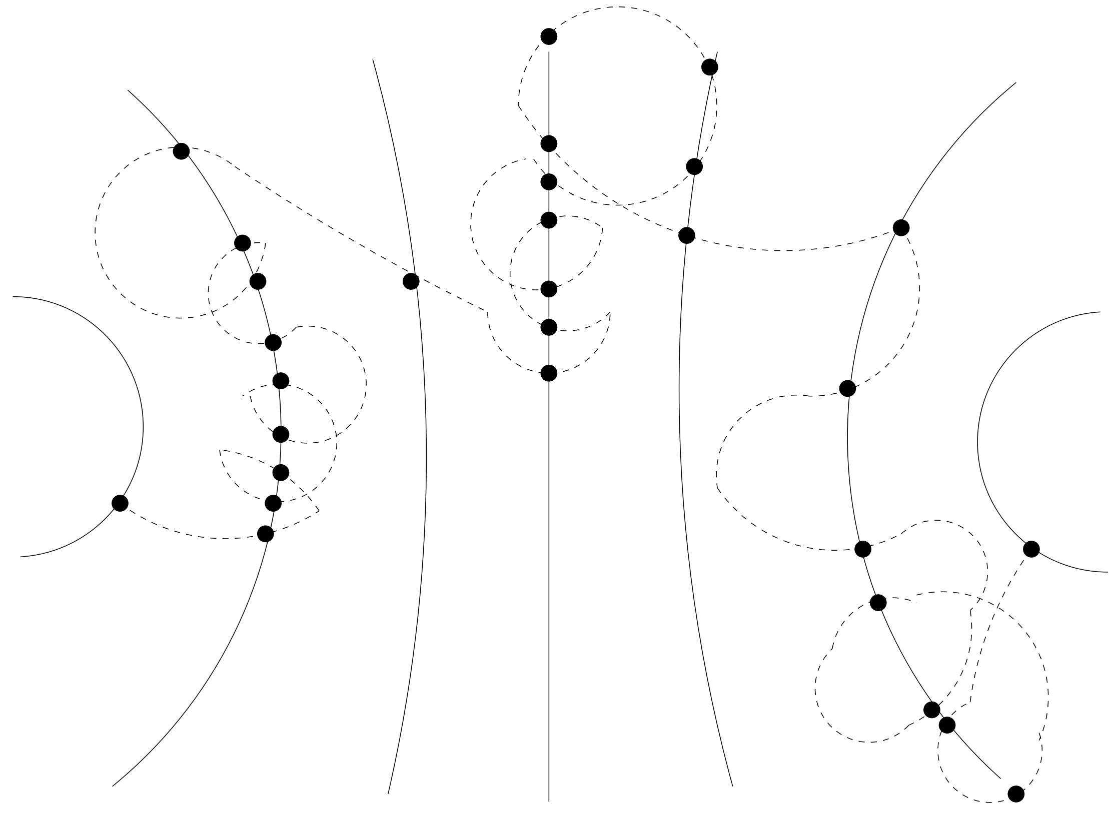
Ideas: (i) combine forward and backward trajectories, (ii) add selection mechanisms [M. Rousset, G. Stoltz, 2006] or (iii) use importance sampling to help the transition (escorting) [Vaikuntanathan, Jarzynski, 2008].

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

3 Adaptive methods

- Thermodynamic integration *(Kirkwood)*
- Perturbation methods *(Zwanzig)* and histogram methods,
- Out of equilibrium dynamics *(Jarzynski)*,
- Adaptive methods *(ABF, metadynamics)*.

Adaptive methods



3.1 Adaptive methods: algorithms

The bottom line of adaptive methods is the following: for “good” ξ the potential $V - A \circ \xi$ is less metastable than V. But A is unknown !

Principle: 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,...*

3.1 Adaptive methods: algorithms

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 method, the idea is to use the formula

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

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

The mean force $A'(z)$ is the mean of f with respect to $\mu_{\Sigma(z)} = Z_{\Sigma(z)}^{-1} e^{-\beta V} |\nabla \xi|^{-1} d\sigma_{\Sigma(z)}$.

3.1 Adaptive methods: algorithms

Important remark: whatever A_t, the mean force associated with the Gibbs distribution

$$\psi^{\rm eq} \propto \exp(-\beta \mathcal{V}_t)(\boldsymbol{x})\, d\boldsymbol{x} = \exp(-\beta(V - A_t \circ \xi))(\boldsymbol{x})\, d\boldsymbol{x}$$

is the original mean force A':

$$\frac{\displaystyle\int f \psi^{\rm eq} |\nabla \xi|^{-1} d\sigma_{\Sigma(z)}}{\displaystyle\int \psi^{\rm eq} |\nabla \xi|^{-1} d\sigma_{\Sigma(z)}} = A'(z).$$

Thus, use as an approximation of $A'(z)$:

$$A'_t(z) = \mathbb{E}(f(\boldsymbol{X}_t) | \xi(\boldsymbol{X}_t) = z).$$

3.1 Adaptive methods: algorithms

A typical ABF dynamics is thus:

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

The associated (nonlinear) Fokker-Planck equation writes:

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

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

3.1 Adaptive methods: algorithms

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. A typical example is:

$$\begin{cases} d\boldsymbol{X}_t = -\nabla(V - A_t \circ \xi)(\boldsymbol{X}_t)\, dt + \sqrt{2\beta^{-1}} d\boldsymbol{W}_t, \\ \dfrac{\partial A_t}{\partial t}(z) = -\dfrac{1}{\tau}\beta^{-1} \ln \Big(\mathbb{E}\left(\delta(\xi(\boldsymbol{X}_t) - z)\right) \Big). \end{cases}$$

3.1 Adaptive methods: algorithms

- 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).

3.1 Adaptive methods: algorithms

[TL, M. Rousset, G. Soltz, J Chem Phys, 2007] 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

3.1 Adaptive methods: algorithms

Consistency of the method : the stationary state yields the mean force. Indeed, if the system reaches a stationary state

$$(\psi_t(\boldsymbol{x}), A_t(z)), \longrightarrow (\psi_\infty(\boldsymbol{x}), A_\infty(z)),$$

then

$$\psi_\infty = Z^{-1} \exp(-\beta(V - A_\infty \circ \xi))$$

and we have:

- for (ABP), $0 = -\beta^{-1} \ln \int \psi_\infty |\nabla \xi|^{-1} d\sigma_{\Sigma(z)}$,
- for (ABF), $0 = \frac{\int f \, \psi_\infty |\nabla \xi|^{-1} d\sigma_{\Sigma(z)}}{\int \psi_\infty |\nabla \xi|^{-1} d\sigma_{\Sigma(z)}} - A'_\infty(z)$,

and thus, in both cases, (up to an additive constant),

$$A_\infty = A.$$

3.2 Adaptive methods: convergence

Let us now study the rate of convergence of the ABF methods:

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

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

3.2 Adaptive methods: convergence

A fundamental remark. Let us consider the problem in a simple situation: $n = 2$, the configuration space is $\mathbb{T} \times \mathbb{R}$, and $\xi(x, y) = x$.

$$\begin{cases} \partial_t \psi = \mathrm{div}\ \left(\nabla V \psi + \beta^{-1} \nabla \psi\right) - \partial_x (A_t' \psi), \\ A_t'(x) = \dfrac{\int \partial_x V(x,y) \psi(t,x,y)\, dy}{\int \psi(t,x,y)\, dy}. \end{cases}$$

Let $\overline{\psi}(t,x) = \int \psi(t,x,y)\, dy$. Then

$$\begin{aligned} \partial_t \overline{\psi} &= \beta^{-1} \partial_{x,x} \overline{\psi} + \partial_x \int \partial_x V \psi \, dy - \partial_x (A_t' \overline{\psi}) \\ &= \beta^{-1} \partial_{x,x} \overline{\psi}. \end{aligned}$$

The metastability along the reaction coordinate direction has been eliminated.

3.2 Adaptive methods: convergence

Theorem: Suppose

(H1) ergodicity of the microscopic variables: the conditioned probability measures $\mu_{\Sigma(z)}$ satisfy a logarithmic Sobolev inequality 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 $\overline{\psi} = \int \psi |\nabla \xi|^{-1} \, d\sigma_{\Sigma(z)}$ to $\overline{\psi_\infty}$, at the macroscopic level,
- the constant ρ of LSI at the microscopic level.
  $\longrightarrow$ The real limitation.

3.2 Adaptive methods: convergence

Main ingredients of the proof in the simple setting ($n = 2$ on $\mathbb{T} \times \mathbb{R}$, with $\xi(x,y) = x$).

Ingredient 1: $\overline{\psi}(t,x) = \int \psi(t,x,y)\, dy$ satisfies a closed PDE

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

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

Ingredient 2: Decomposition of entropy: $E = E_M + E_m$. "Total entropy = macroscopic entropy + microscopic entropy."

Cf. works by F. Otto *et al.*

3.2 Adaptive methods: convergence

Equilibrium is $\psi_\infty = Z^{-1} \exp(-\beta(V - A \circ \xi))$.

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

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

The microscopic entropy is

$$\begin{aligned} E_m(t) &= \int H\left(\psi(\cdot|\xi(x)=z)\middle|\psi_\infty(\cdot|\xi(x)=z)\right)\overline{\psi}(z)\,dz \\ &= \int H\left(\frac{\psi(t,x,.)}{\overline{\psi}(t,x)}\middle|\frac{\psi_\infty(x,.)}{\overline{\psi_\infty}(x)}\right)\overline{\psi}(t,x)\,dx. \end{aligned}$$

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

3.2 Adaptive methods: convergence

Notice that

$$\partial_t \psi = \beta^{-1} \mathrm{div} \left(\psi_\infty \nabla \left(\frac{\psi}{\psi_\infty} \right) \right) + \partial_x ((A' - A'_t) \psi).$$

Ingredient 3: We have (algebraïc miracle)

$$\partial_t E_m = \partial_t E - \partial_t E_M$$

$$\leq -\beta^{-1} \iint \left| \partial_y \ln \left(\frac{\psi}{\psi_\infty} \right) \right|^2 \psi - \int \partial_x \ln \left(\frac{\overline{\psi}}{\overline{\psi_\infty}} \right) \overline{\psi} (A'_t - A').$$

Using (H1) the conditioned prob. measures $\frac{\psi_\infty(x,y)}{\overline{\psi_\infty}(x)}\, dy$ satisfy a logarithmic Sobolev inequality LSI(ρ), then

$$-\beta^{-1} \iint \left| \partial_y \ln \left(\frac{\psi}{\psi_\infty} \right) \right|^2 \psi \leq -2\rho\beta^{-1} E_m.$$

3.2 Adaptive methods: convergence

(H1) also implies a Talagrand inequality (Ingredient 4):

$$
\begin{aligned}
&\left|A_t'(x) - A'(x)\right| \\
&= \left| \int \partial_x V(x,y) \frac{\psi(t,x,y)}{\int \psi(t,x,y)\,dy}\,dy - \int \partial_x V(x,y) \frac{\psi_\infty(x,y)}{\int \psi_\infty(x,y)\,dy}\,dy \right| \\
&\leq \|\partial_{x,y} V\|_{L^\infty} \int \left|y - y'\right| \pi_{t,x}(dy, dy') \\
&\leq \|\partial_{x,y} V\|_{L^\infty} \sqrt{\frac{2}{\rho} H\left(\frac{\psi(t,x,.)}{\overline{\psi}(t,x)} \middle| \frac{\psi_\infty(x,.)}{\overline{\psi_\infty}(x)} \right)},
\end{aligned}
$$

where $\pi_{t,x}$ is any coupling measure:

$$
\int (f(y) + g(y'))\pi_{t,x}(dy, dy') = \int f(y) \frac{\psi(t,x,y)}{\int \psi(t,x,y)\,dy}\,dy + \int g(y') \frac{\psi_\infty(x,y')}{\int \psi_\infty(x,y)\,dy}\,dy'.
$$

This requires (H2) $\partial_{x,y} V \in L^\infty$.

3.2 Adaptive methods: convergence

Thus, we have

$$-\int \partial_x \ln\left(\frac{\overline{\psi}}{\overline{\psi_\infty}}\right)\overline{\psi}(A'_t - A') \leq \sqrt{\int |A'_t - A'|^2\,\overline{\psi}}\sqrt{\int \left|\partial_x \ln\left(\frac{\overline{\psi}}{\overline{\psi_\infty}}\right)\right|^2 \overline{\psi}}$$

$$\leq \|\partial_{x,y}V\|_{L^\infty}\sqrt{\frac{2}{\rho}E_m}C\exp(-4\pi^2\beta^{-1}t).$$

We have proved that

$$\partial_t E_m \leq -2\rho\beta^{-1}E_m + \|\partial_{x,y}V\|_{L^\infty}\sqrt{\frac{2}{\rho}E_m}C\exp(-4\pi^2\beta^{-1}t),$$

and this yields $\sqrt{E_m}(t) \leq C\exp(-\beta^{-1}\min(\rho, 4\pi^2)t)$.

3.2 Adaptive methods: convergence

These arguments can be generalized to prove the theorem in the following frameworks:

- $\xi : \mathbb{R}^n \to \mathbb{T}$ (with a slight modification of the dynamics),
- $\xi : \mathbb{R}^n \to \mathbb{R}$ (with a slight modification of the dynamics and a constraining potential on $\xi(\boldsymbol{x})$),
- $\xi : \mathbb{R}^n \to \mathbb{T}^m$ or $\xi : \mathbb{R}^n \to \mathbb{R}^m$ with a suitable modification of the dynamics,
- $\xi : \mathbb{R}^n \to \mathbb{T}^m$ or $\xi : \mathbb{R}^n \to \mathbb{R}^m$ with the original ABF dynamics, if the coupling is small enough.

3.2 Adaptive methods: convergence

The case $\xi : \mathbb{R}^n \to \mathbb{R}$: the convergence result holds for the following adaptive dynamics:

$$d\boldsymbol{X}_t = -\nabla\Big(V - \beta^{-1}\ln(|\nabla\xi|^{-2}) - A_t \circ \xi + \Pi \circ \xi\Big)(\boldsymbol{X}_t)|\nabla\xi|^{-2}(\boldsymbol{X}_t)\,dt + \sqrt{2\beta^{-1}}|\nabla\xi|^{-1}(\boldsymbol{X}_t)\,dW_t,$$

$$A_t'(z) = \mathbb{E}\left(\left(\frac{\nabla V \cdot \nabla\xi}{|\nabla\xi|^2} - \beta^{-1}\mathrm{div}\left(\frac{\nabla\xi}{|\nabla\xi|^2}\right)\right)(\boldsymbol{X}_t)\Big|\xi(\boldsymbol{X}_t) = z\right).$$

The blue terms are required to obtain a closed parabolic PDE on $\overline{\psi}(t,z) = \int_{\Sigma(z)} |\nabla\xi|^{-1}\psi(t,.)d\sigma_{\Sigma(z)}$:

$$\partial_t\overline{\psi} = \partial_z(\Pi'\,\overline{\psi} + \beta^{-1}\partial_z\overline{\psi}).$$

The green term is required for $\overline{\psi}$ to converge to a stationary state.

3.2 Adaptive methods: convergence

In summary [TL, G. Stoltz, M. Rousset, Nonlinearity 2008] :

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

If ξ is well chosen, $\rho \gg R$.

Remarks:

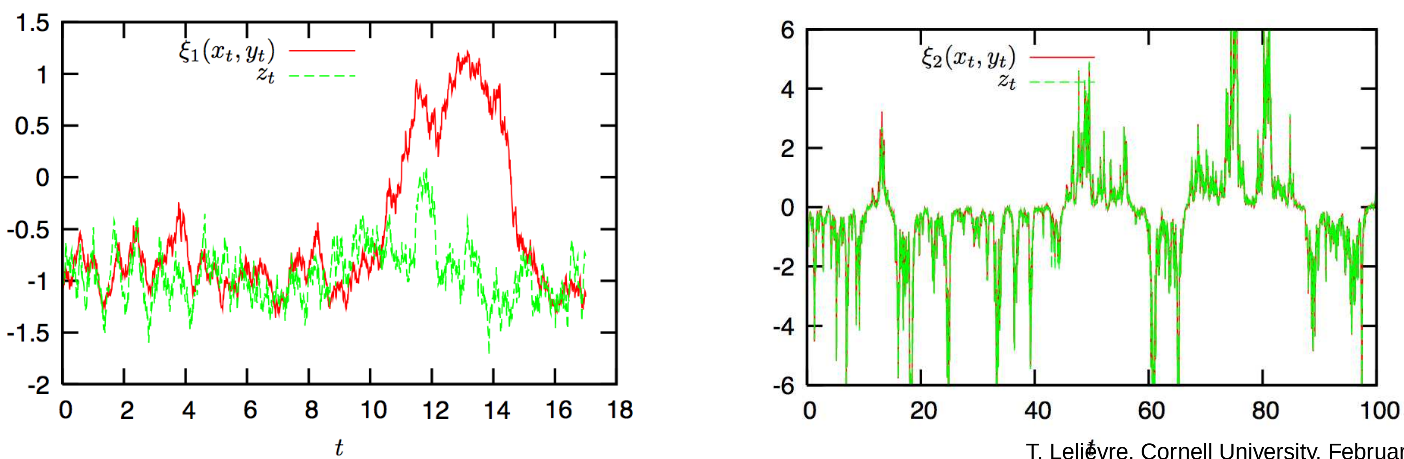
- if there are metastabilities in $\mu_{\Sigma(z)}$, only “local LSI” is needed (work in progress with K. Minoukadeh)
- the ABP case is not understood so far...

3.2 Adaptive methods: convergence

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 ($\|\nabla_{\Sigma(z)} f\|_{L^\infty} < \infty$) $\implies$ LSI for μ.
- [F. Legoll, TL, 2009] Effective dynamics for $\xi(\boldsymbol{X}_t)$. Uniform control in time:

$$H(\mathcal{L}(\xi(X_t))|\mathcal{L}(z_t)) \leq C \left(\frac{\|\nabla_{\Sigma(z)} f\|_{L^\infty}}{\rho} \right)^2 H(\mathcal{L}(X_0)|\mu).$$



3.3 Multiple replicas implementations

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):

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

3.3 Multiple replicas implementations

Interest of a discretization using an interacting particle system:

- Very efficient parallelization.
- Better sampling of all reactive paths.
- A selection mechanism may be added to duplicate “innovative particles” and kill “redundant particles”.

$\longrightarrow$ We propose a selection mechanism which accelerates the convergence “at the macroscopic level” (increase r). [TL, G. Stoltz, M. Rousset, J Chem Phys 2007].

3.3 Multiple replicas implementations

Numerical analysis of the particle system [B. Jourdain, TL, R. Roux, M2AN, 2010]

Theorem: We suppose that the configuration space is $\mathbb{T}^d$, V is smooth, and $\xi(\boldsymbol{x}) = x^1$. We consider the following particle approximation:

$$d\boldsymbol{X}_{t,n,N} = \left(-\nabla V(\boldsymbol{X}_{t,n,N}) + \frac{\sum_{m=1}^N \phi_\epsilon^\alpha(X^1_{t,n,N} - X^1_{t,m,N}) \partial_1 V(\boldsymbol{X}_{t,m,N})}{\sum_{m=1}^N \phi_\epsilon^\alpha(X^1_{t,n,N} - X^1_{t,m,N})} \mathbf{e}_1 \right) dt + \sqrt{2} d\boldsymbol{W}_t^n$$

where $\phi_\epsilon^\alpha = \alpha + \epsilon^{-1}\phi(\epsilon^{-1}\cdot)$. Then we have,

$$\mathbb{E} \int_0^T \left\| \frac{\sum_{m=1}^N \phi_\epsilon^\alpha(\cdot - X^1_{t,m,N}) \partial_1 V(\boldsymbol{X}_{t,m,N})}{\sum_{m=1}^N \phi_\epsilon^\alpha(\cdot - X^1_{t,m,N})} - A'_t \right\|_{L^\infty_{\mathbb{T}}} dt$$

$$= O\left(\alpha + \sqrt{\epsilon} + \frac{\exp\left(\frac{K}{\alpha\epsilon^2}\right)}{\sqrt{N}} \right).$$

3.3 Multiple replicas implementations

The selection mechanism

On the ABF dynamics, a selection mechanism can enhance the diffusion at the “macroscopic“ level.

$$\left\{\begin{aligned} &\partial_t\psi = \mathrm{div}\;\left(|\nabla\xi|^{-2}\left(\nabla(V - A_t\circ\xi)\psi + \beta^{-1}\nabla\psi\right)\right) + W_{\overline{\psi}}\circ\xi\,\psi,\\ &A_t'(z) = \int_{\Sigma(z)}\left(\frac{\nabla V\cdot\nabla\xi}{|\nabla\xi|^2} - \beta^{-1}\mathrm{div}\;\left(\frac{\nabla\xi}{|\nabla\xi|^2}\right)\right)|\nabla\xi|^{-1}\psi(t,.)d\sigma_{\Sigma(z)}\\ &\qquad\times\left(\int_{\Sigma(z)}|\nabla\xi|^{-1}\psi(t,.)d\sigma_{\Sigma(z)}\right)^{-1}. \end{aligned}\right.$$

Then, we have: $\partial_t\overline{\psi} = \beta^{-1}\partial_{z,z}\overline{\psi} + W_{\overline{\psi}}\,\overline{\psi}$.

3.3 Multiple replicas implementations

How to choose W? A typical choice :

$$W_{\overline{\psi}} = c\frac{\partial_{z,z}\overline{\psi}}{\overline{\psi}}$$

so that

$$\partial_t \overline{\psi} = (\beta^{-1} + c)\partial_{z,z}\overline{\psi}.$$

The rate of convergence of $\overline{\psi}$ to $\overline{\psi_\infty}$, at the "macroscopic" level, is thus enhanced.

Numerically, it amounts to associate a weight

$$w_{n,N}(t) = \exp\left(\int_0^t W_{\overline{\psi}}(\xi(\boldsymbol{X}_{s,n,N}))\,ds\right)$$

to the n-th replica trajectory, and to make weighted means to compute A'_t.

3.3 Multiple replicas implementations

We use an histogram to discretize $\overline{\psi}$ and thus

$$W_{\overline{\psi}}(z) \simeq c\frac{\overline{\psi}(z+\delta z) - 2\overline{\psi}(z) + \overline{\psi}(z-\delta z)}{\overline{\psi}(z)\delta z^2}$$

$$\simeq \frac{3c}{\overline{\psi}(z)\delta z^2}\left(\frac{\overline{\psi}(z+\delta z) + \overline{\psi}(z) + \overline{\psi}(z-\delta z)}{3} - \overline{\psi}(z)\right)$$

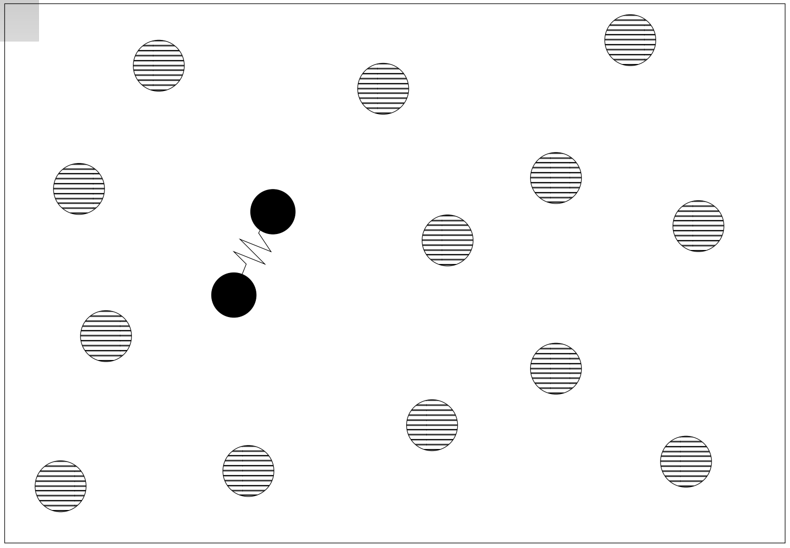
Weights of particles in locally under-explored regions are increased.

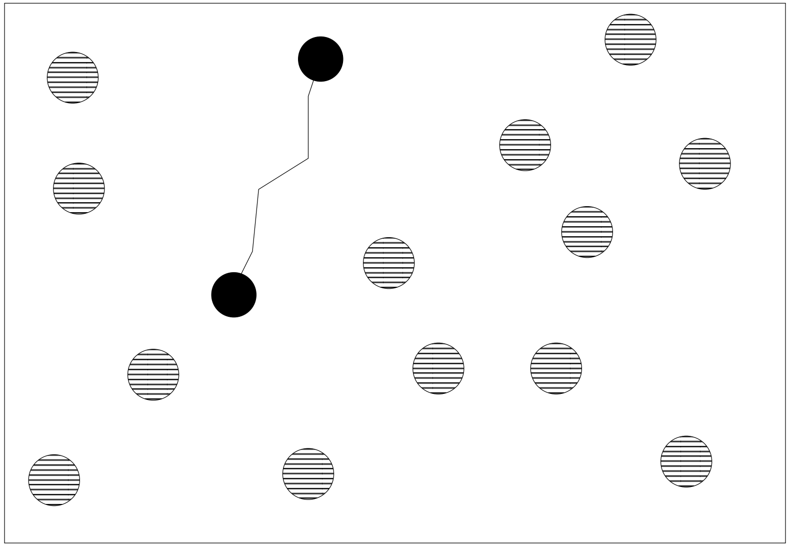
An adequate selection process can then be implemented, using these weights (like in genetic algorithm).

This should help to efficiently detect and take advantage of rare events.

3.3 Multiple replicas implementations

Numerical illustration on the example of the solvation of a dimer.





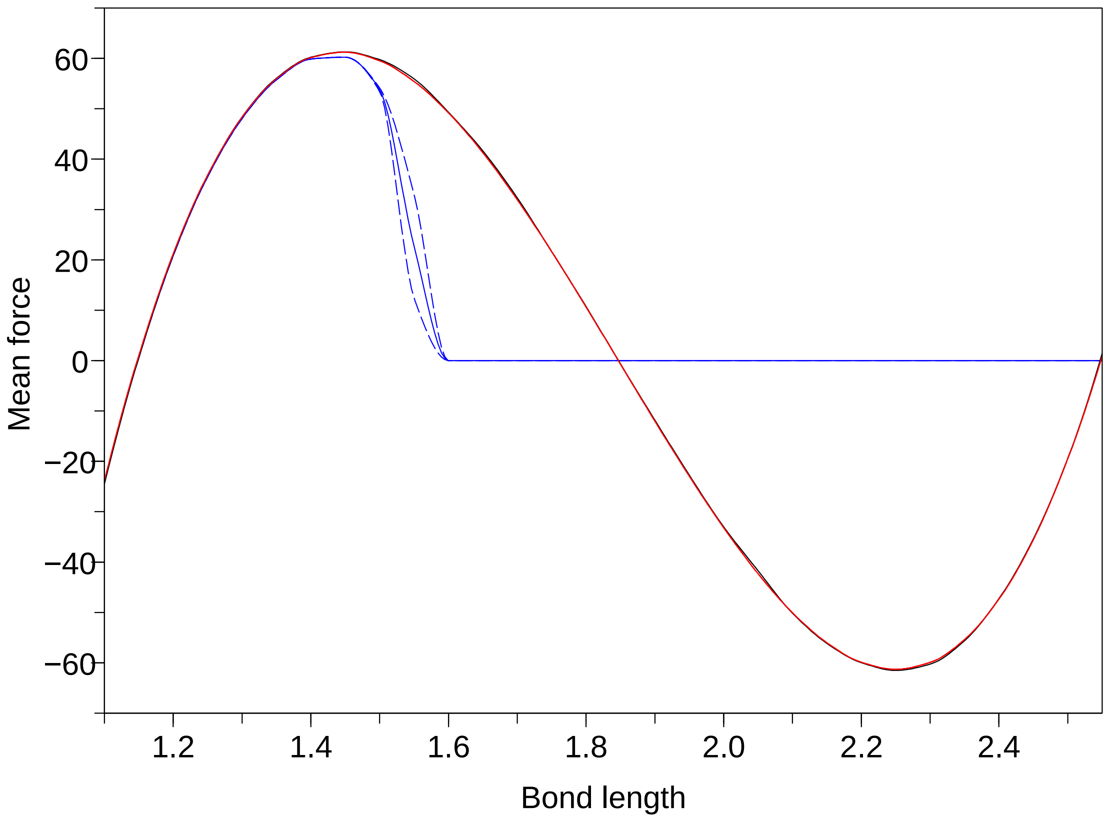
Left: compact state

Right: stretched state.

Recall the reaction coordinate is $\xi(x) = |x_1 - x_2|$.

3.3 Multiple replicas implementations

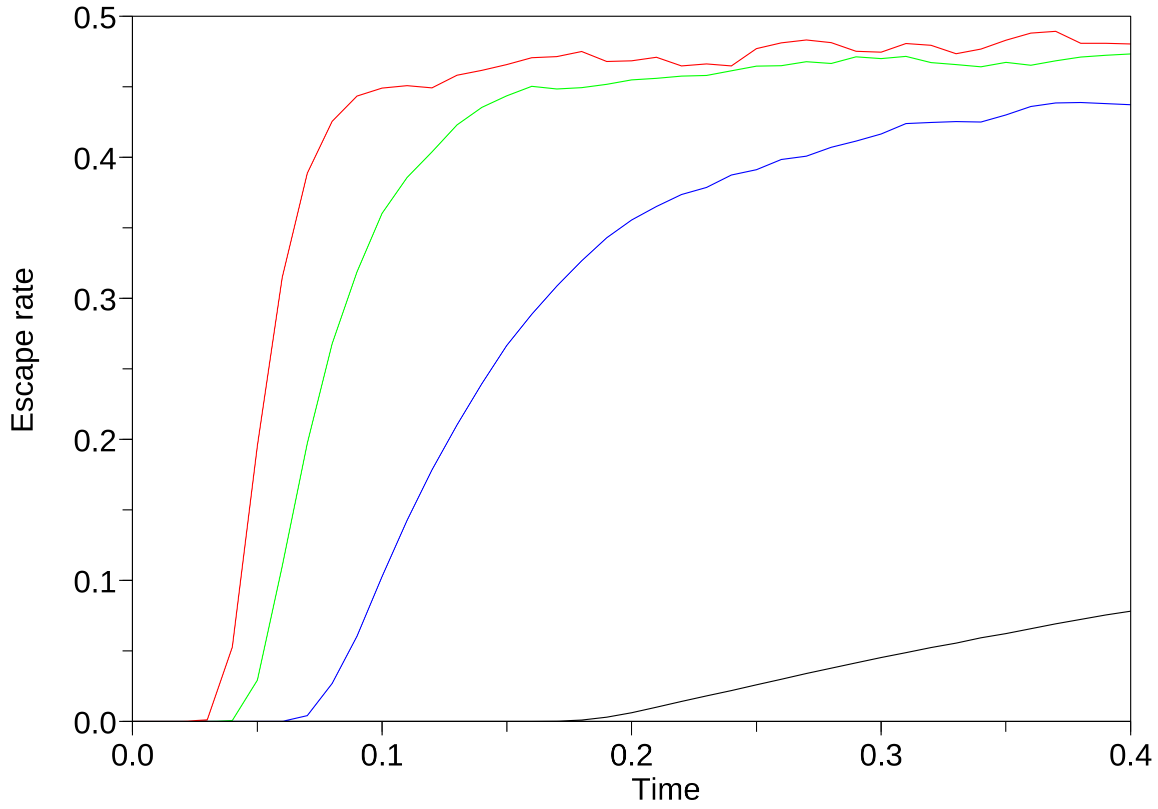
Free energy profile with parallel ABF obtained at t = 0.1, with 2000 replicas.



Red: with selection (c = 10); Blue: without selection
Dashed lines: 95 % confidence interval.

3.3 Multiple replicas implementations

Proportion of replicas which have crossed the free energy barrier.



Black: without selection; Blue: c=2; Green: c=5; Red: c=10.

3.4 Application to Bayesian statistics

Adaptive methods can be seen as adaptive importance sampling methods rather than free energy calculation methods. $\longrightarrow$ compute a bias adaptively, and then unbias.

Compare to classical importance sampling methods, only ξ is provided and a “good” bias function of ξ is then computed. Only ξ has to be chosen, and not the whole importance biasing function.

3.4 Application to Bayesian statistics

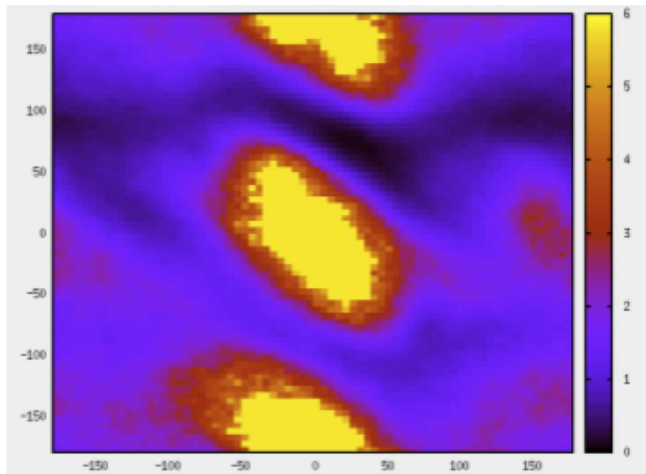
This gives many freedom in the way to use them. For example:

- Instead of computing the complicated local mean force $f = \frac{\nabla V \cdot \nabla \xi}{|\nabla \xi|^2} - \beta^{-1} \mathrm{div} \left(\frac{\nabla \xi}{|\nabla \xi|^2} \right)$, use simpler expressions, like $\frac{\nabla V \cdot \nabla \xi}{|\nabla \xi|^2}$.
- Use ABF for high dimensional reaction coordinates by postulating a separated representations of the mean force:

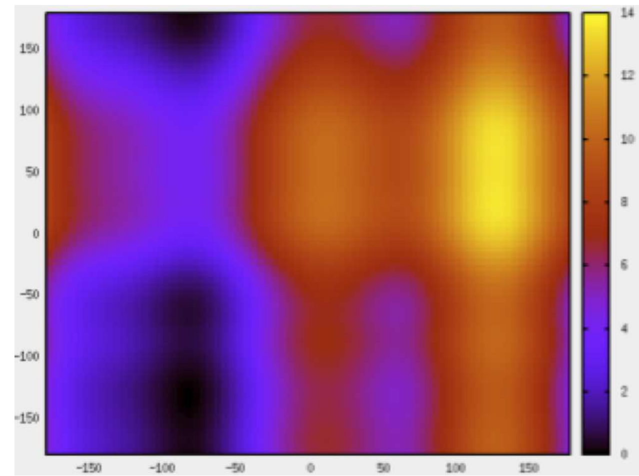
$$A(z_1, \ldots, z_N) = A_1(z_1) + A_{2,3}(z_2, z_3) + A_4(z_4) + \ldots$$

3.4 Application to Bayesian statistics

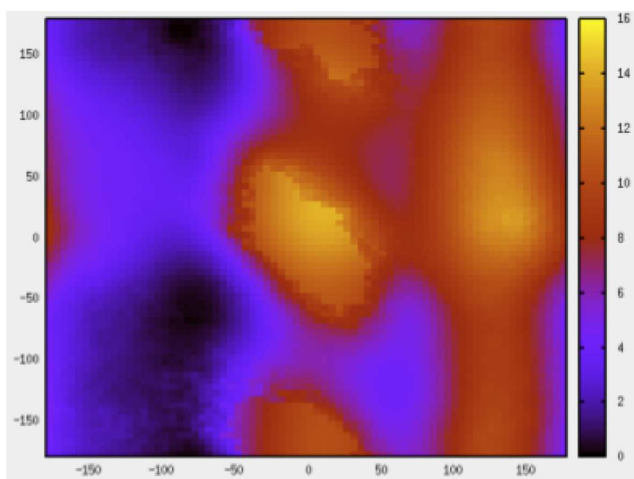
Preliminary results on the alanine dipeptide: $A_1(\phi) + A_2(\psi)$.



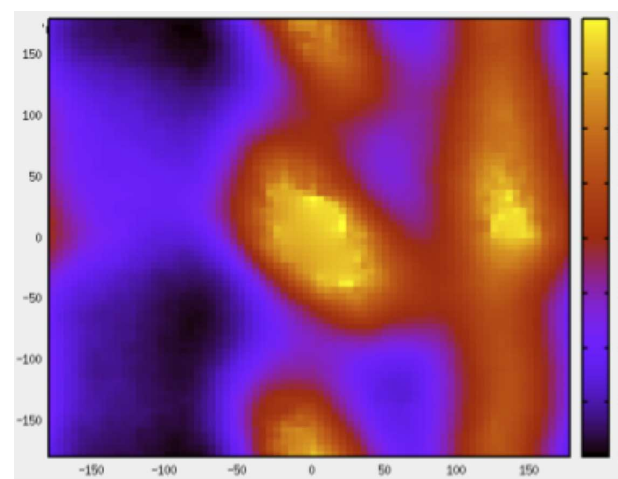
$-kT \ln(\mathbb{P}(\delta_{(\phi,\psi)(\boldsymbol{X}_t)-(\phi_0,\psi_0)}))$



Tensor product of the bias



Reconstructed PMF



Reference PMF

Work in progress with C. Chipot and J. Hénin.

3.4 Application to Bayesian statistics

Application to Bayesian statistics [N. Chopin, TL, G. Stoltz]: Sampling of posterior distributions using a MCMC ABF algorithm.

- The fishery problem: the size of $N_{\rm data} = 256$ fishes are measured, and the corresponding histogram is approximated by a mixture of N Gaussians:

$$f(y\,|\,x) = \sum_{i=1}^{N} q_i \sqrt{\frac{v_i}{2\pi}} \exp\left(-\frac{v_i}{2}(y-\mu_i)^2\right),$$

- parameters describing the mixture ($q_N = 1 - \sum_{i=1}^{N-1} q_i$): $x = \big(q_1,\ldots,q_{N-1},\mu_1,\ldots,\mu_N,v_1,\ldots,v_N\big) \in \mathcal{S}_{N-1} \times [\mu_{\min},\mu_{\max}]^N \times [v_{\min},+\infty) \subset \mathbb{R}^{3N-1}$, where $\mathcal{S}_{N-1} = \left\{(q_1,\ldots,q_{N-1}) \,\middle|\, 0 \le q_i \le 1,\ \sum_{i=1}^{N-1} q_i \le 1\right\}$.

3.4 Application to Bayesian statistics

- given the parameters, the likelihood of observing the data $\{y_i, 1 \le i \le N_{\rm data}\}$ is

$$\Pi(y \,|\, x) = \prod_{d=1}^{N_{\rm data}} f(y_d \,|\, x).$$

- the prior on the parameters is: $\mu_i \sim \mathcal{N}(M, R^2/4)$, $v_i \sim \mathrm{Gamma}(a, \beta)$ with $\beta \sim \mathrm{Gamma}(g, h)$ and $(q_1, \ldots, q_N) \sim \mathrm{Dirichlet}_N(1, \ldots, 1)$ for fixed values (M, R, a, g, h) (random beta model).

So actually $x = (q_1, \ldots, q_{N-1}, \mu_1, \ldots, \mu_N, v_1, \ldots, v_N, \beta)$.

Objective: sample the posterior distribution (distribution of the parameters given the observations):

$$\Pi(x|y) = \frac{\Pi(y|x)\,\mathrm{Prior}(x)}{\int \Pi(y|x)\,\mathrm{Prior}(x)\,dx}.$$

3.4 Application to Bayesian statistics

The potential associated with the posterior (posterior is proportional to $\exp(-V)$) is

$$V = V_{\text{prior}} + V_{\text{likelihood}}$$

with $V_{\text{prior}} = \frac{2}{R^2} \sum_{i=1}^N (\mu_i - M)^2 - N\alpha \ln \beta + \beta \sum_{i=1}^N v_i - (a-1) \sum_{i=1}^N \ln v_i + h\beta - (g-1) \ln \beta$ and $V_{\text{likelihood}} = \sum_{d=1}^{N_{\text{data}}} \ln \left[\sum_{i=1}^N q_i \sqrt{v_i} \exp\left(-\frac{v_i}{2} (y_d - \mu_i)^2 \right) \right]$.

The posterior distribution is a metastable (multimodal) measure. In particular, the invariance by permutation of the Gaussians leads to a metastability.

Idea: use ABF within a MCMC Metropolis Hastings algorithm. The biasing potential modifies the target probability measure in the acception-rejection step.

3.4 Application to Bayesian statistics

Algorithm: Metropolis Hastings-ABF.

Iterate on $n \geq 0$

1. Update the biasing potential by computing and then integrating $(A^{n+1})'$ (the conditional expectation of f at a fixed value of ξ).
2. Propose a move from x^n to $\bar{x}^{n+1}$ according to $T(x^n, \bar{x}^{n+1})$.
3. Acceptance ratio

$$r^n = \min\left(\frac{\pi_{A^{n+1}}(\bar{x}^{n+1})\, T(\bar{x}^{n+1}, x^n)}{\pi_{A^{n+1}}(x^n)\, T(x^n, \bar{x}^{n+1})}, 1 \right),$$

   where the biased probability is $\pi_{A^{n+1}}(x) \propto \pi(x) \exp(A^{n+1}(\xi(x)))$.
4. Draw a random variable U^n uniformly distributed in $[0, 1]$ ($U^n \sim \mathcal{U}[0, 1]$).
   (a) if $U^n \leq r^n$, accept the move and set $x^{n+1} = \bar{x}^{n+1}$;
   (b) if $U^n > r^n$, reject the move and set $x^{n+1} = x^n$.

3.4 Application to Bayesian statistics

More precisely, the results below have been obtained with the following ingredients:

- The proposal density kernel $T(x, x')$ is a fixed Gaussian centered on x.
- Binning procedure and trajectorial average: mean force and bias in bin (z_i, z_{i+1})

$$\Gamma_n^{\Delta z}(z) = \frac{\displaystyle\sum_{j=0}^{n} f(x_j)\, \mathbf{1}_{z_i \le \xi(x^j) \le z_{i+1}}}{\displaystyle\sum_{j=0}^{n} \mathbf{1}_{z_i \le \xi(x^j) \le z_{i+1}}}, \quad A_n^{\Delta z}(z) = \sum_{k=0}^{i-1} \Delta z\, \Gamma_n^{\Delta z}\left(k + \frac{1}{2}\Delta z\right)$$

- M is the mean of the data, R is the range of the data, $\alpha = 2$, $g = 0.2$ and $h = 100g/(\alpha R^2)$.

The question is now: Is there a good “reaction coordinate” $\xi(x)$?

3.4 Application to Bayesian statistics

Methodology: (i) choose a reaction coordinate, (ii) compute the associated free energy, (iii) use the free energy to bias the MCMC sampler.

Measures of the efficiency of the whole procedure:

- Sampling efficiency: observation of mode switchings;
- Relevance of the samples generated by the biased dynamics: efficiency factor EF. The effective sample size is $EF\,N$.

3.4 Application to Bayesian statistics

For $w(x) = \exp(-A(\xi(x)))$, the efficiency factor is

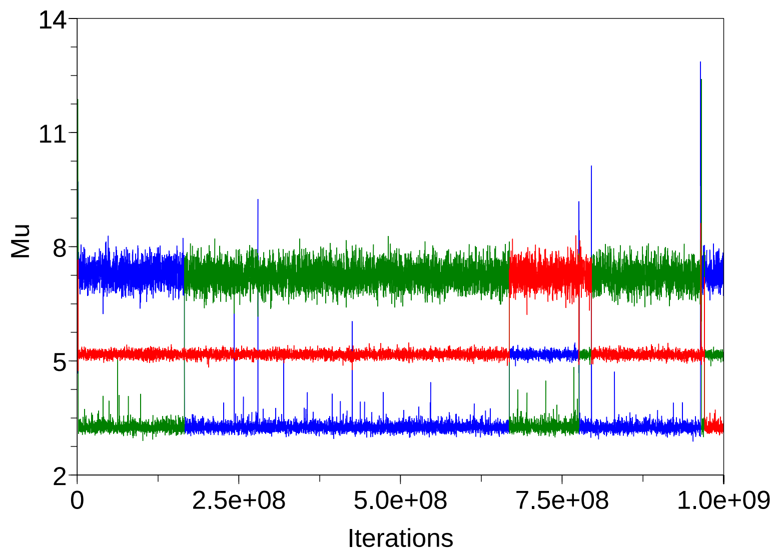
$$EF = \frac{\left(\sum_{n=1}^N w(x^n)\right)^2}{N \sum_{n=1}^N w^2(x^n)}.$$

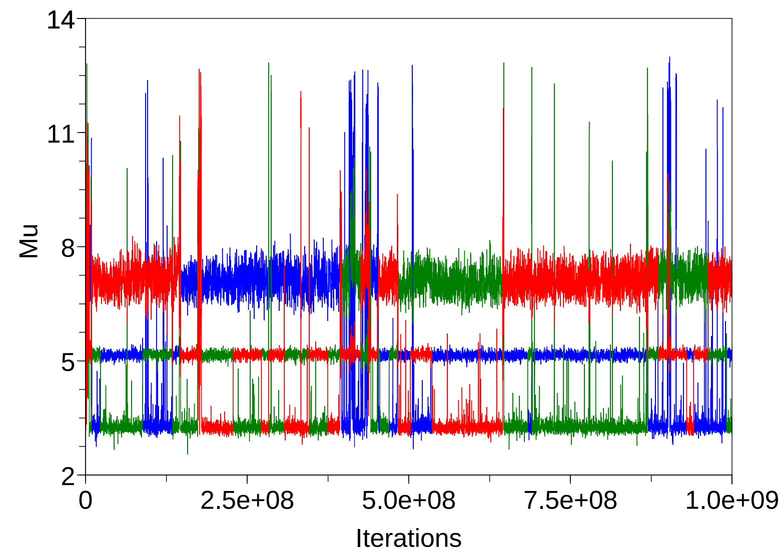
Using the fact that $\xi(x^n)$ are approximately uniformly distributed over $(z_{\min}, z_{\max})$, one obtains:

$$EF \simeq \frac{\left(\int_{z_{\min}}^{z_{\max}} \exp(-A(z))\, dz\right)^2}{(z_{\max} - z_{\min}) \int_{z_{\min}}^{z_{\max}} \exp(-2A(z))\, dz}.$$

Thus, EF is close to one $\iff \max A - \min A$ is small.

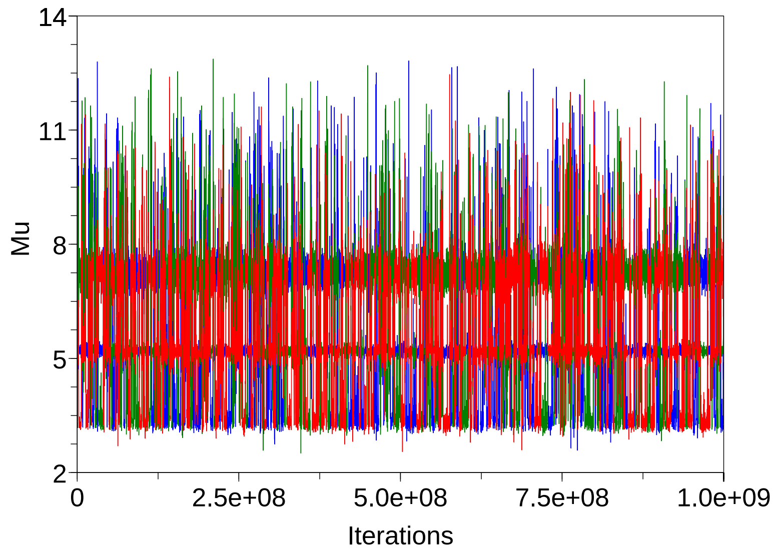
Some results for $N = 3$.

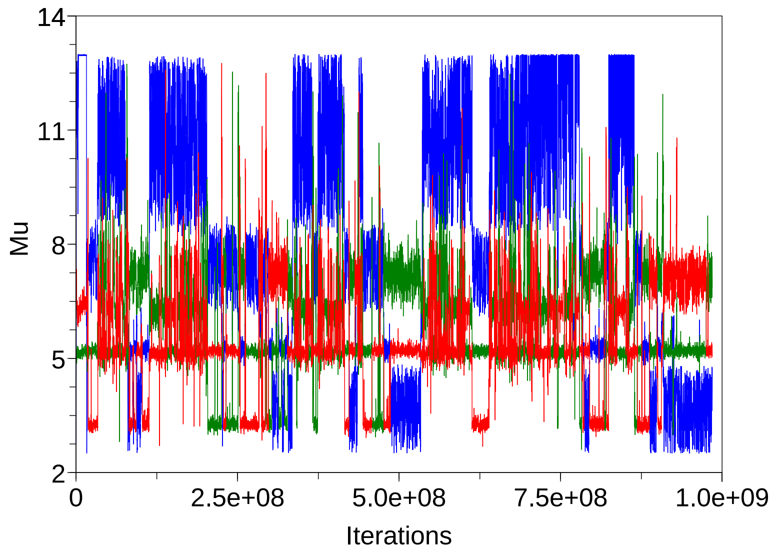




Left: evolution of the averages μ_i without bias.
Right: evolution of the averages μ_i with $\xi = q_1$.

3.4 Application to Bayesian statistics

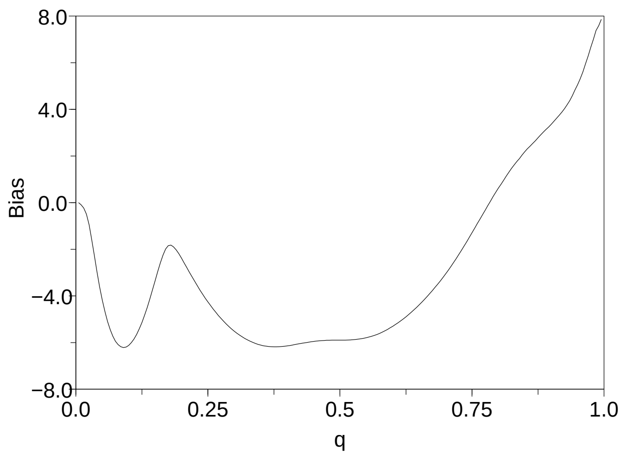


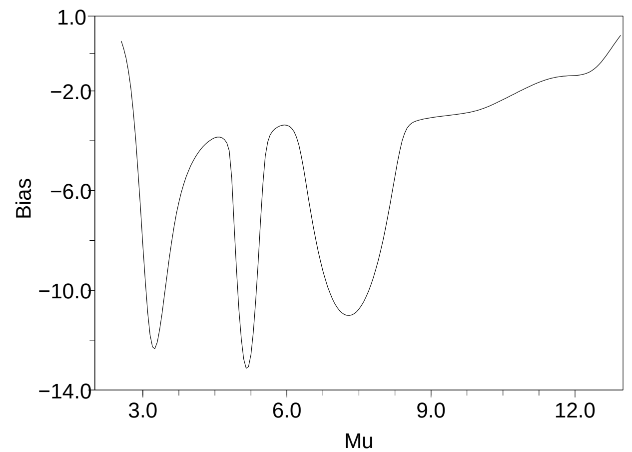


Left: evolution of the averages μ_i with $\xi = \beta$.
Right: evolution of the averages μ_i with $\xi = \mu_1$.

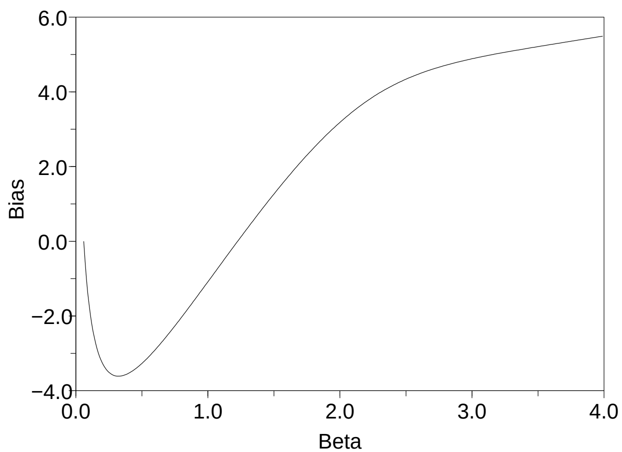
A good reaction coordinate seems to be $\xi = \beta$.

3.4 Application to Bayesian statistics





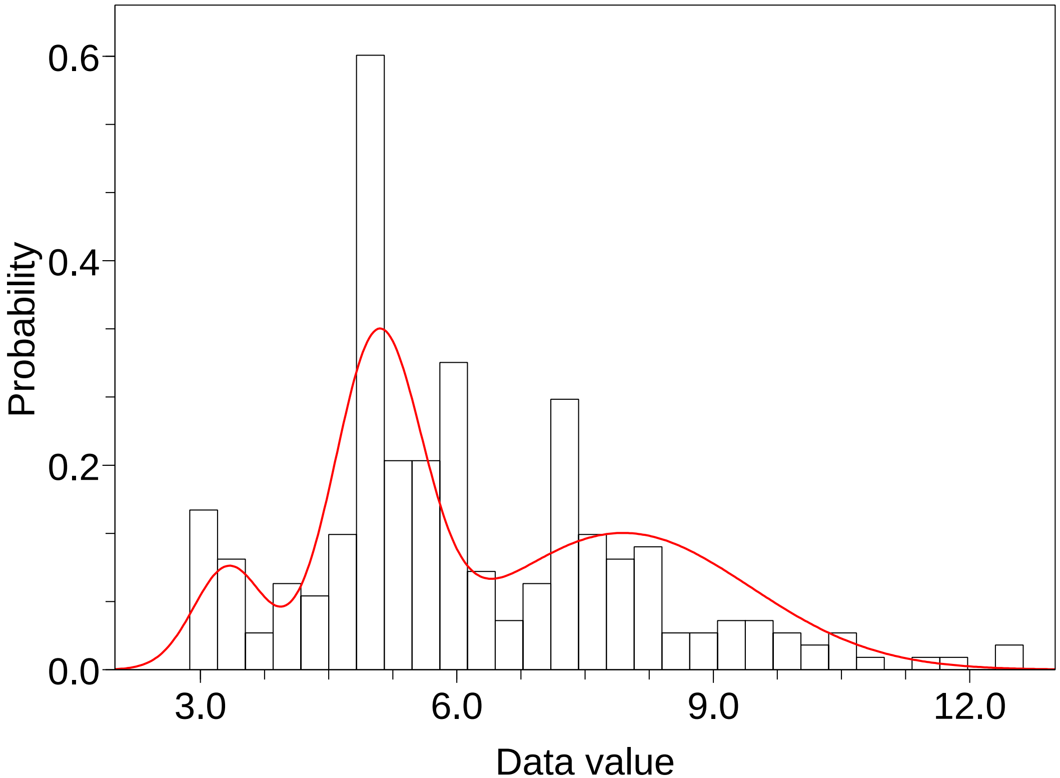
Converged bias.



The efficiency factor for $\xi = \beta$ is approximately 0.18.

3.4 Application to Bayesian statistics

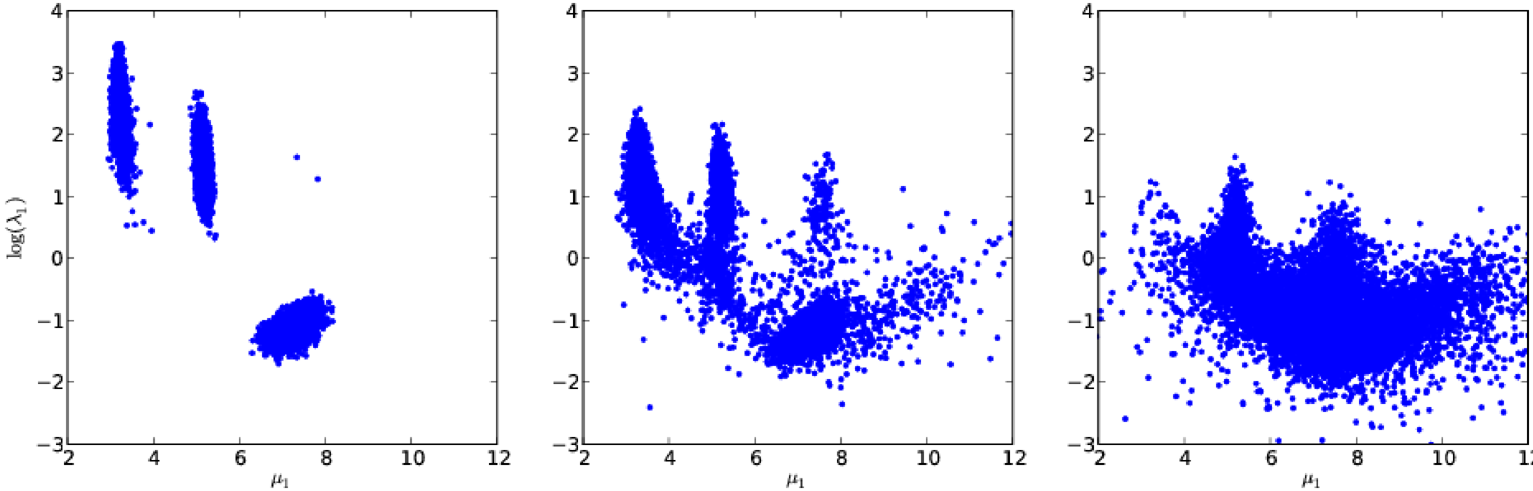
Comparison of the mixture with the datas.



$$q_1 = 0.42227 \quad q_2 = 0.118506$$
$$\mu_1 = 5.1818 \quad \mu_2 = 3.29704 \quad \mu_3 = 7.79154$$

3.4 Application to Bayesian statistics

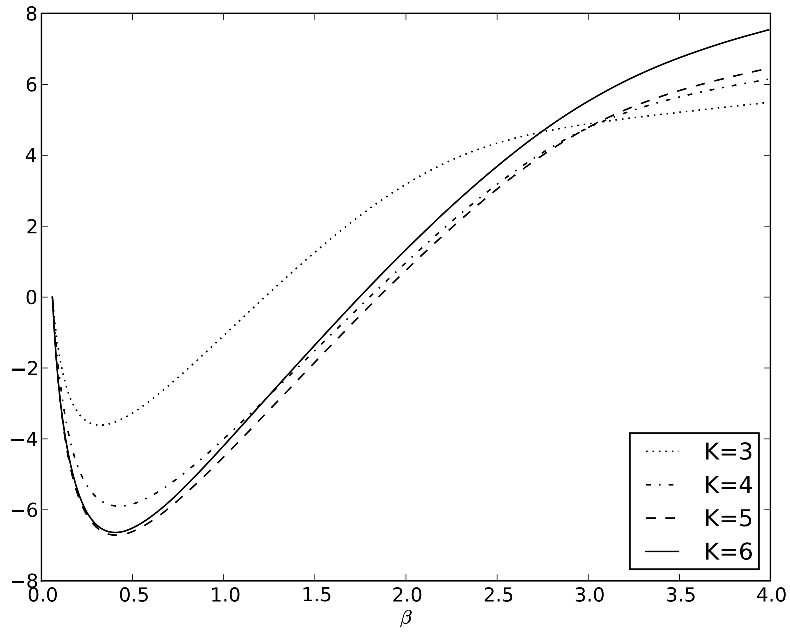
Why does it work with $\xi = \beta$? The bias is relatively small; forcing large values of β is forcing large values of the variances, which allows for a mixing of the components.



Samples of (μ_1, λ_1) conditional on (from left to right) $\beta \in [0, 0.5]$, $\beta \in [1.5, 2]$ and $\beta \in [3.5, 4]$.

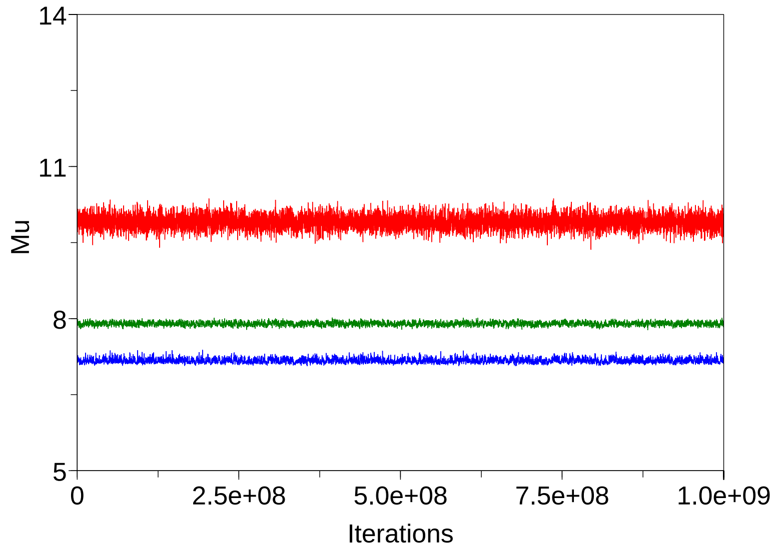
3.4 Application to Bayesian statistics

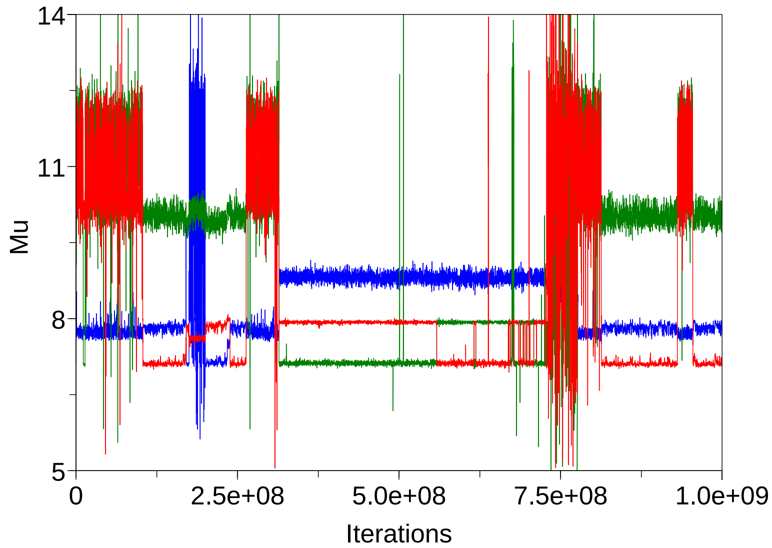
Extension: Bayesian model choice. Look for the best number of components. It seems that the bias (for $\xi = \beta$) for $K = 3$ is also a good bias for $K = 4$ and $K = 5$.



3.4 Application to Bayesian statistics

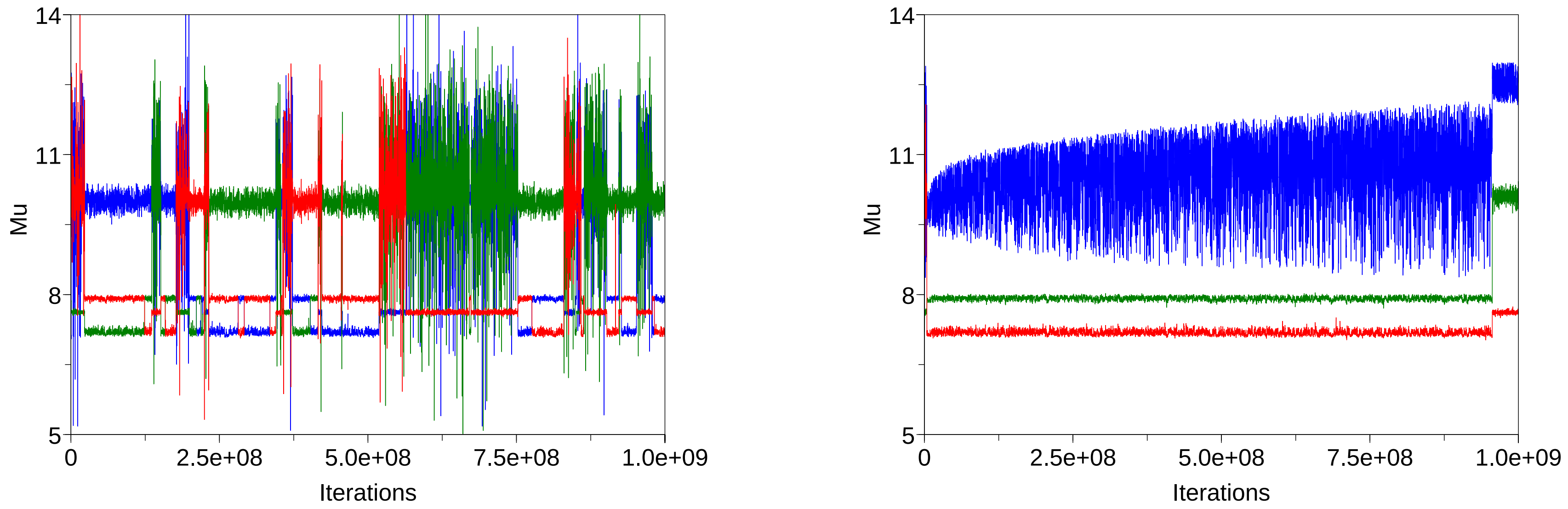
Same computations for another set of data: the Hidalgo stamp problem.





Left: evolution of the averages μ_i without bias.
Right: evolution of the averages μ_i with $\xi = q_1$.

3.4 Application to Bayesian statistics

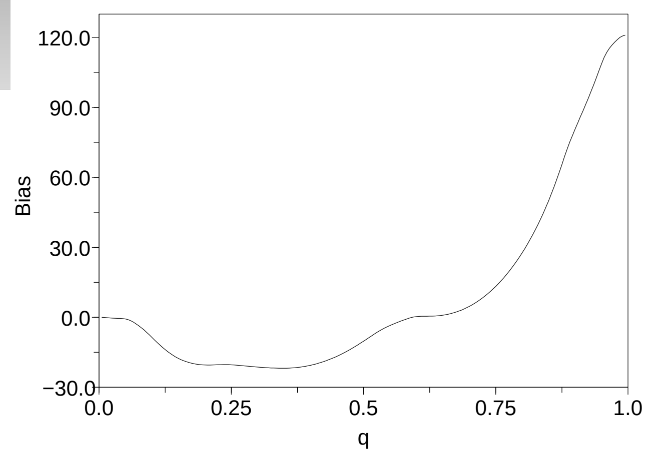


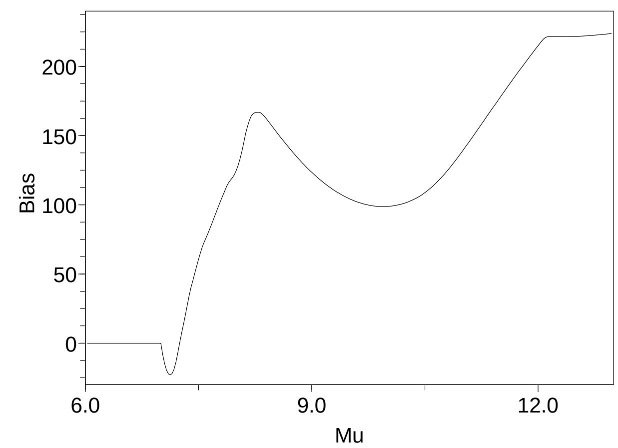
Left: evolution of the averages μ_i with $\xi = \beta$.
Right: evolution of the averages μ_i with $\xi = \mu_1$.

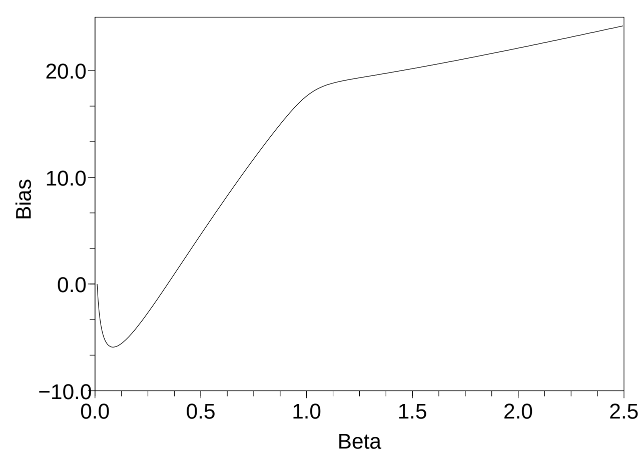
Again, $\xi = \beta$ seems to be a good reaction coordinate.

3.4 Application to Bayesian statistics

Bias for $\xi = q_1$, $\xi = \beta$, $\xi = \mu$.

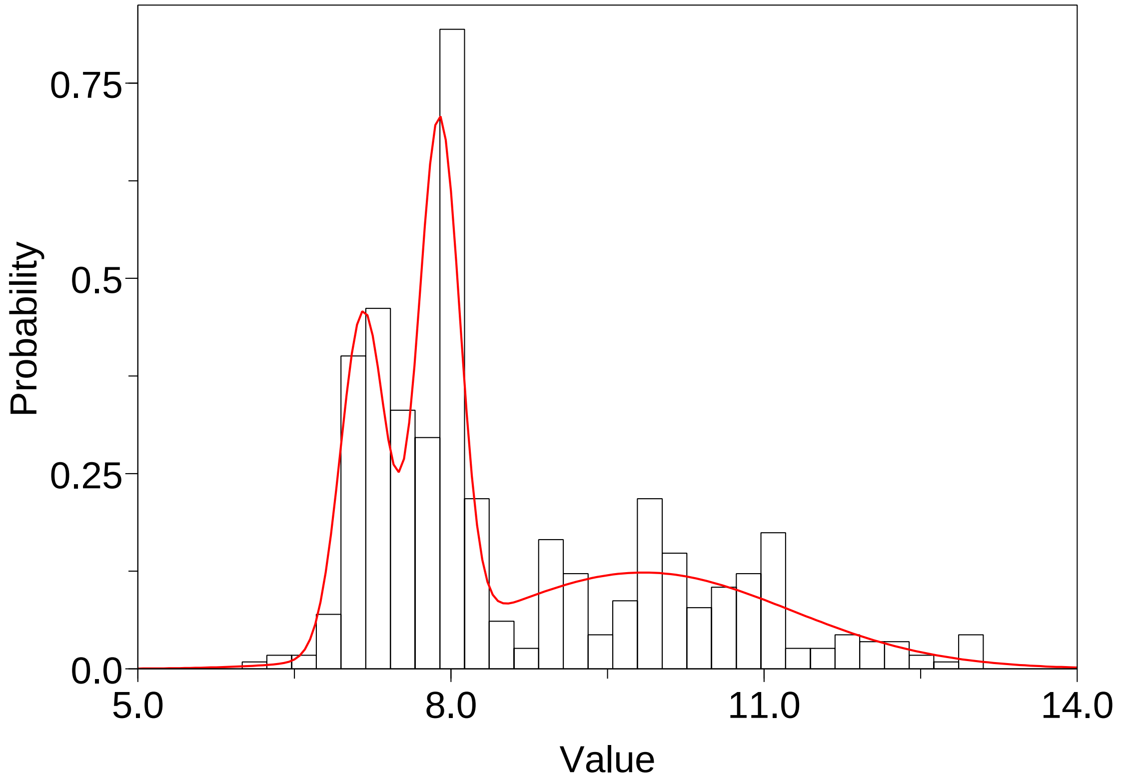






3.4 Application to Bayesian statistics

Comparison of the mixture with the datas.



Conclusion

SDEs with constraints:

- The discretization of the projected dynamics may be different from the projection of the discretized dynamics,
- Constraining the dynamics with “rigid bonds” is different from constraining the dynamics with “very stiff springs”,
- The mean force can be computed by averaging the Lagrange multipliers associated with the constraints,
- Going to phase space enables Metropolis-Hastings algorithms,
- The free energy differences can be obtained by non-equilibrium stochastic dynamics.

Conclusion

Adaptive algorithms:
We proposed a unified formulation of adaptive methods using conditional distributions.

Theoretically, this allows a proof of convergence in the longtime limit for a certain class of algorithm (ABF-like algorithms). The rate of convergence is related to the logarithmic Sobolev inequality constant of the conditioned Boltzmann-Gibbs probability measures at fixed values of the reaction coordinate.

Numerically, the conditional distributions are naturally approximated by empirical means on many replicas. We have shown how a selection mechanism on the replicas can speed up the computation.

These techniques can be seen as adaptive importance sampling methods. They may be applied more generally to the sampling of metastable potentials, as soon as some knowledge of the directions of metastability is assumed.

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- F. Otto (Bonn)
- M. Rousset (INRIA Lille)
- E. Vanden Eijnden (NYU)

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If you can read French,

http://cermics.enpc.fr/~lelievre/rapports/ECODOQUI_notes.pdf

otherwise...

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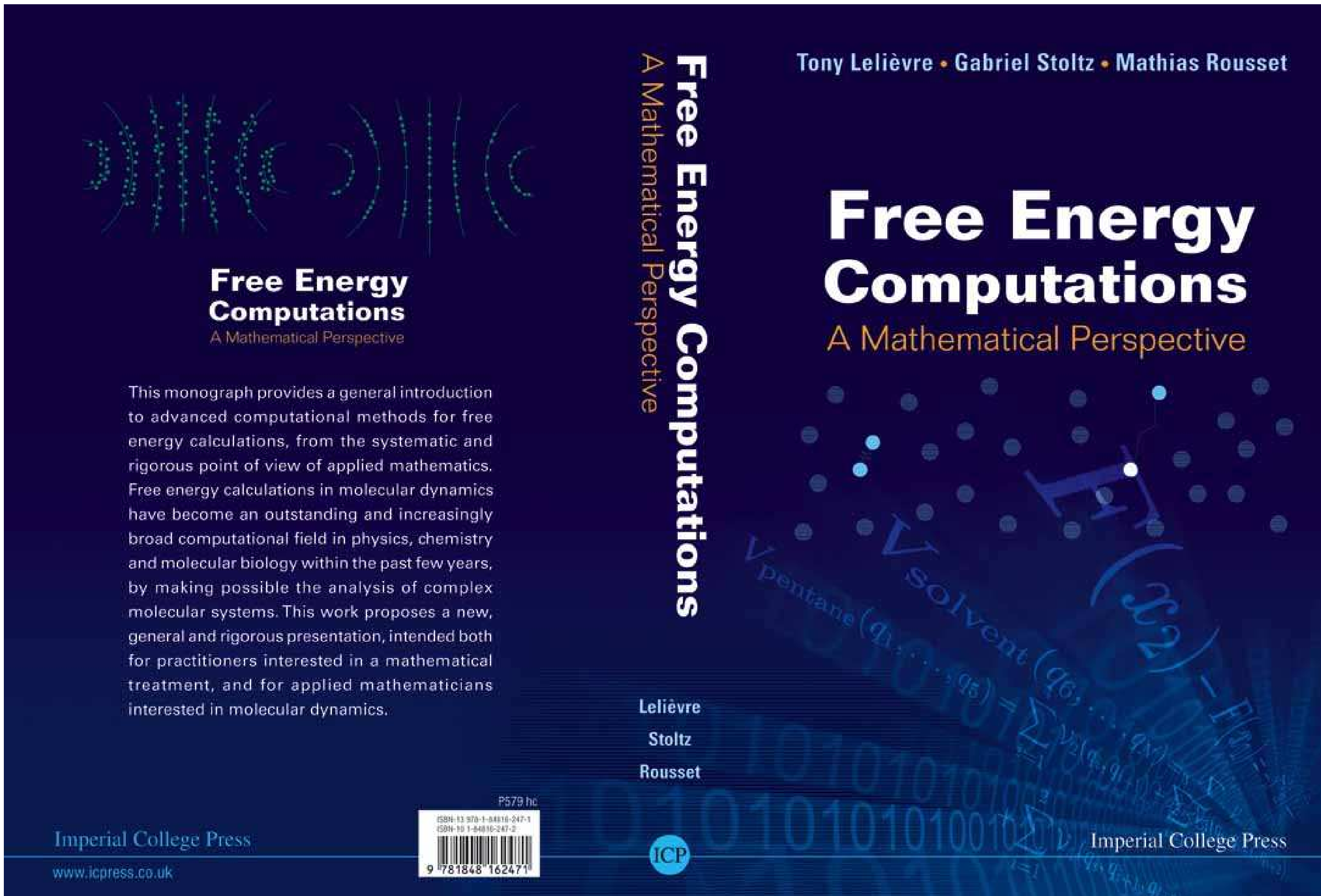
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Free Energy Computations
A Mathematical Perspective
Free Energy Computations
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Free Energy Computations
A Mathematical Perspective
This monograph provides a general introduction to advanced computational methods for free energy calculations, from the systematic and rigorous point of view of applied mathematics. Free energy calculations in molecular dynamics have become an outstanding and increasingly broad computational field in physics, chemistry and molecular biology within the past few years, by making possible the analysis of complex molecular systems. This work proposes a new, general and rigorous presentation, intended both for practitioners interested in a mathematical treatment, and for applied mathematicians interested in molecular dynamics.
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