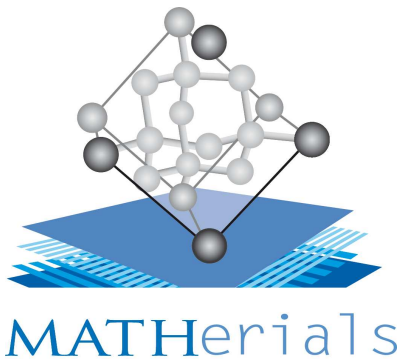
What is a good collective variable? A numerical viewpoint

Tony Lelièvre, Thomas Pigeon, and Gabriel Stoltz

Ecole des Ponts ParisTech and INRIA



Winter school GdR MatBio, 8-12 November 2021, CIRM

Motivation

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

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

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

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

Dynamics

Newton equations of motion:

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

Dynamics

Newton equations of motion + thermostat: Langevin dynamics:

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

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

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

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

Dynamics

Newton equations of motion + thermostat: Langevin dynamics:

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

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

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

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.

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

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

which is also ergodic wrt μ.

Macroscopic quantities of interest

These dynamics are used to compute macroscopic quantities:

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

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

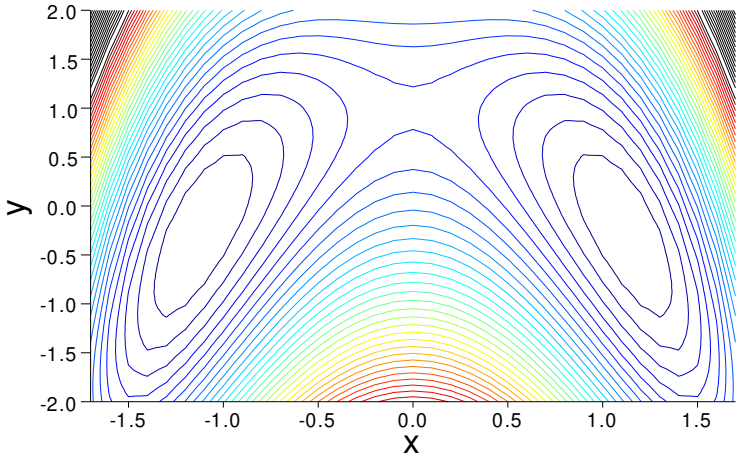
(ii) Dynamical quantities (averages over trajectories): diffusion coefficients, viscosity, transition rates,...

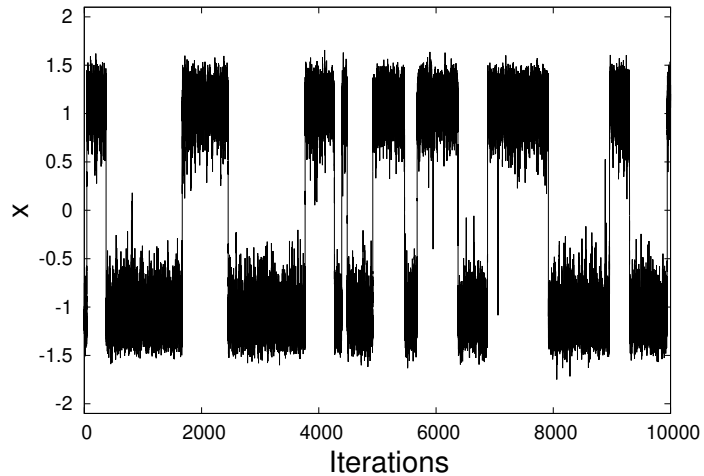
$$\mathbb{E}(\mathcal{F}((\boldsymbol{X}_t)_{t\geq 0})) \simeq \frac{1}{M} \sum_{m=1}^{M} \mathcal{F}((\boldsymbol{X}_t^m)_{t\geq 0}).$$

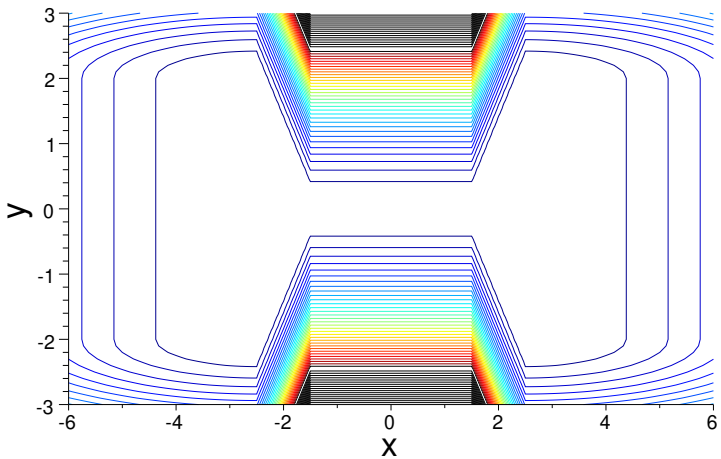
Difficulties: (i) high-dimensional problem ($N \gg 1$); (ii) $\boldsymbol{X}_t$ is a metastable process and μ is a multimodal measure.

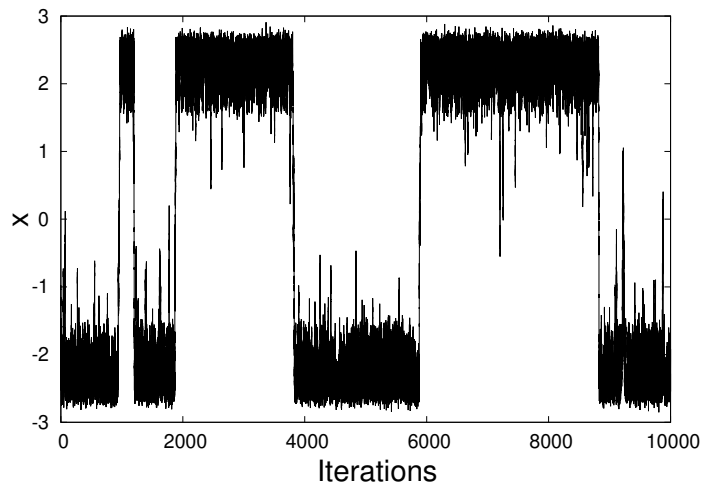
Metastability: energetic and entropic barriers

A two-dimensional schematic picture







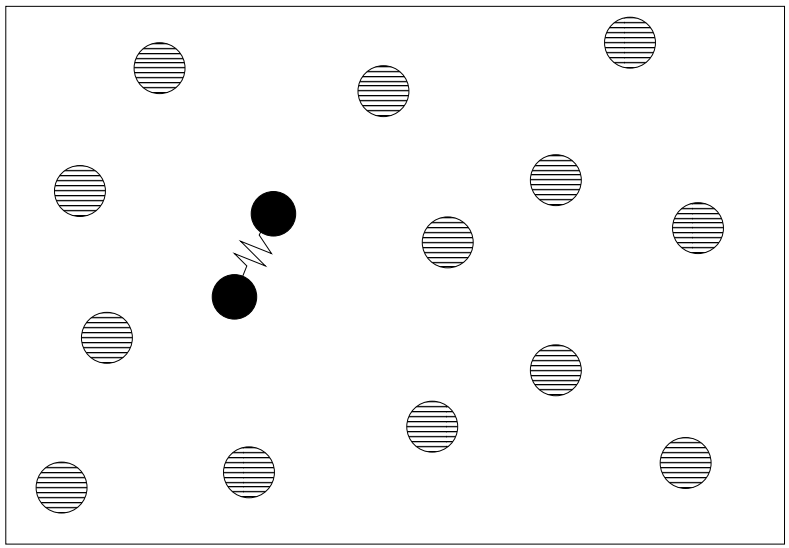


$\longrightarrow$ • Slow convergence of trajectorial averages

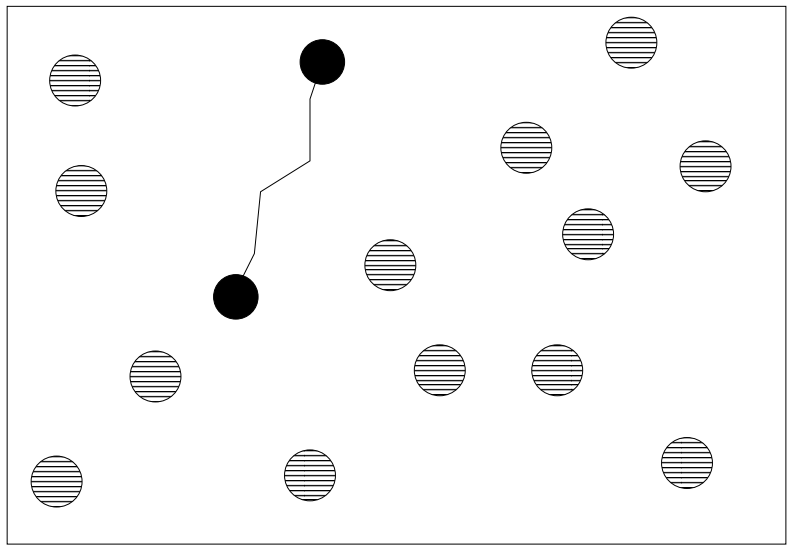
• Transitions between metastable states are rare events

A toy model for solvation

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



Compact state.



Stretched state.

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

$\longrightarrow$ simulation

Limitation of direct molecular dynamics

Direct molecular dynamics is a very powerful technique to sample atomistic trajectories, in order to compute thermodynamic or dynamical quantities.

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

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

For thermodynamic quantities: variance reduction methods (stratification, importance sampling, control variate, ...)
For dynamic quantities: effective dynamics, rare event sampling methods, ...

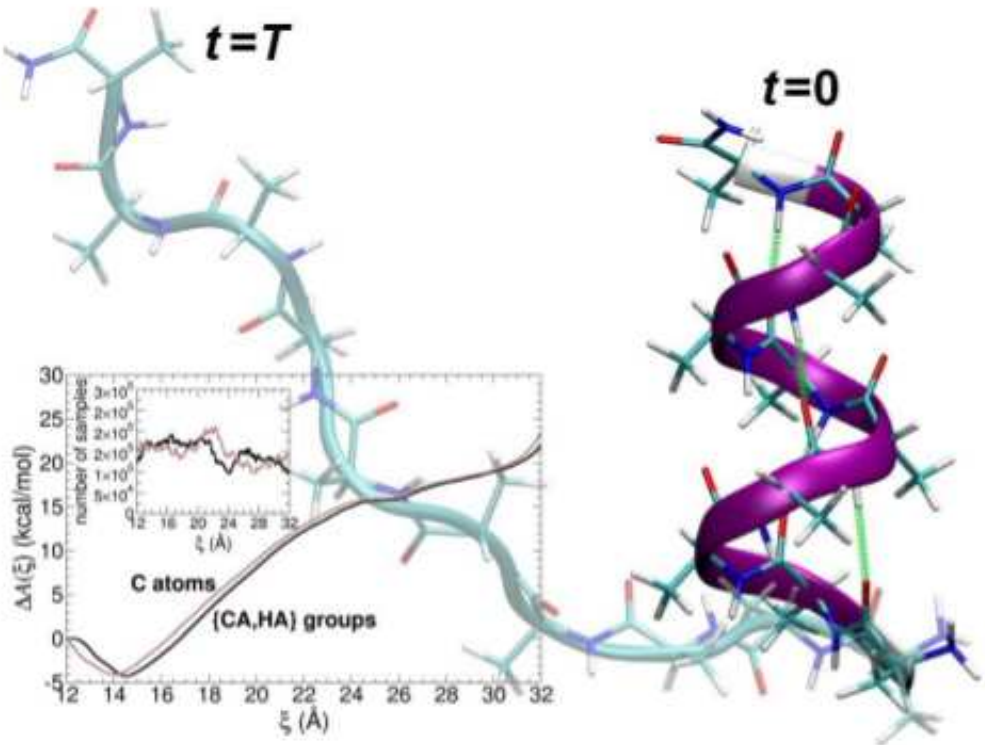
All these techniques require a collective variable.

Outline

Outline of this presentation:

1. Definition of the free energy associated with a collective variable.
2. Using a collective variable to estimate thermodynamics quantities: adaptive biasing techniques.
3. Using a collective variable to access dynamical quantites: effective dynamics.
4. Conclusion and discussion: what is a good collective variable?

Collective variable and free energy



Collective variable

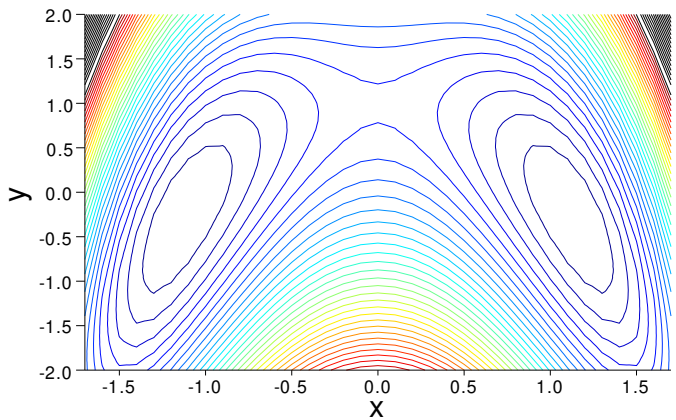
Generally speaking, a collective variable is a low dimensional function $\xi : \mathbb{R}^d \to \mathbb{R}^k$ (with $k \ll d$), which summarizes, in some sense, the state of the system. In the following, for simplicity, we assume that ξ is periodic and of dimension 1:

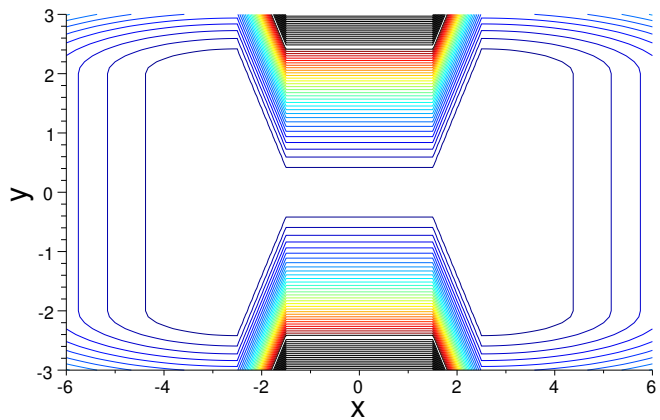
$$\xi : \mathbb{R}^d \to \mathbb{T}.$$

If well chosen, this collective variable can be used to address the metastability issues.

The free energy associated with ξ will play a central role.

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





Free energy

Let us introduce two probability measures associated with 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 $\xi(\boldsymbol{x}) = z$:

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

Free energy (2d case)

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

- The image of the measure μ by ξ:

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

where the free energy A is defined by:

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

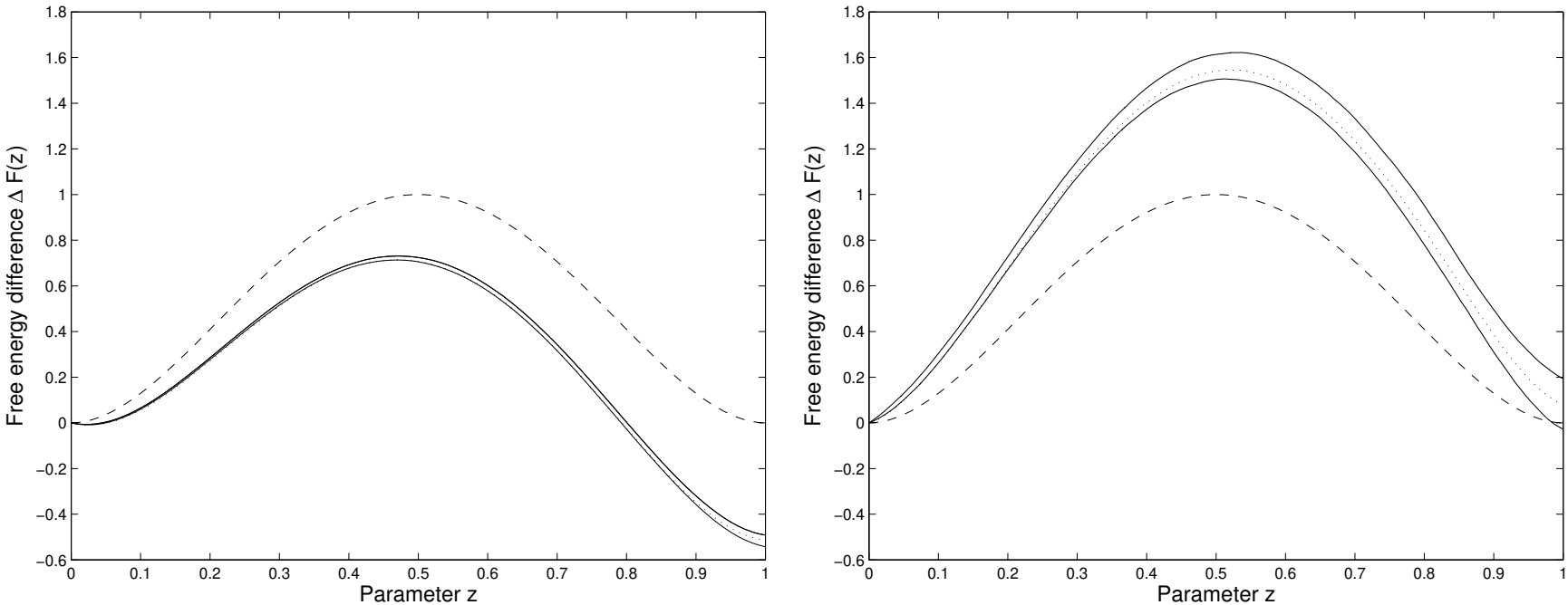
and $\Sigma(x) = \{(x, y),\ y \in \mathbb{R}\}$.

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

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

Free energy on a simple example

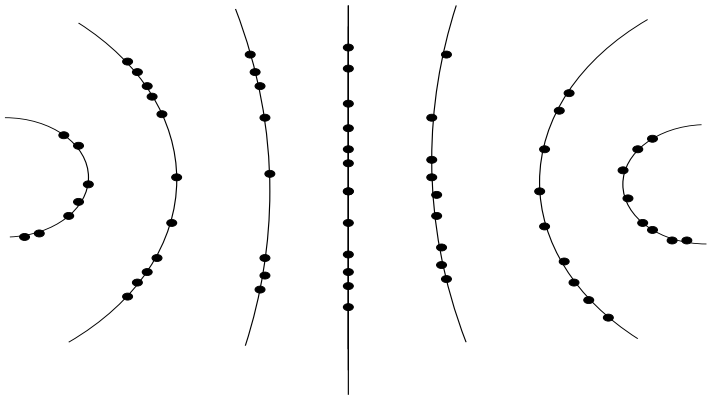
What is free energy ? The simple example of the solvation of a dimer. (Profiles computed using thermodynamic integration.)



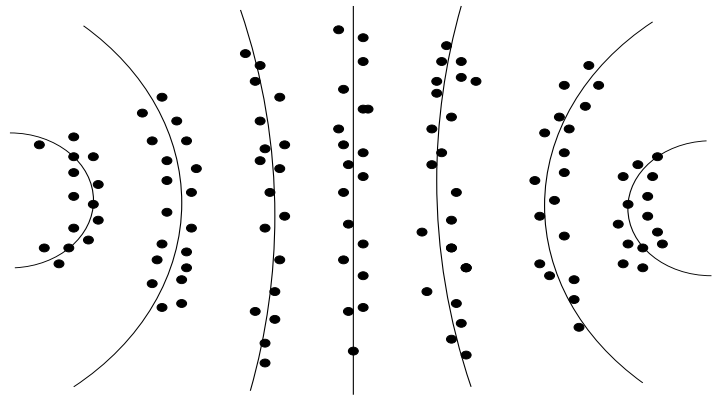
The density of the solvent molecules is lower on the left than on the right. At high (resp. low) density, the compact state is more (resp. less) likely. The "free energy barrier" is higher at high density than at low density. Related question: interpretation of the free energy barrier in terms of dynamics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

Free energy calculation techniques

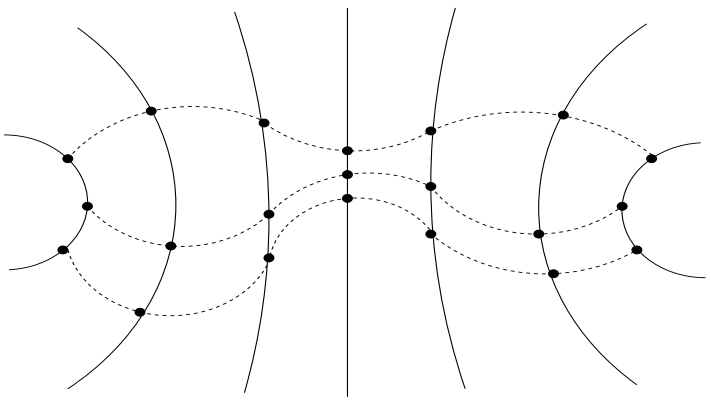
There are many free energy calculation techniques:



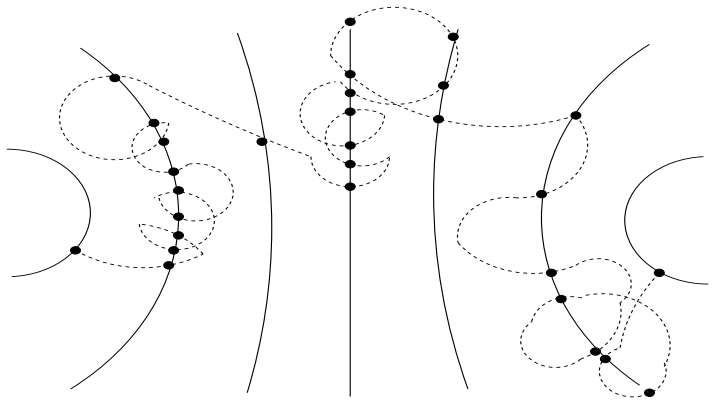
(a) Thermodynamic integration.



(b) Histogram method.

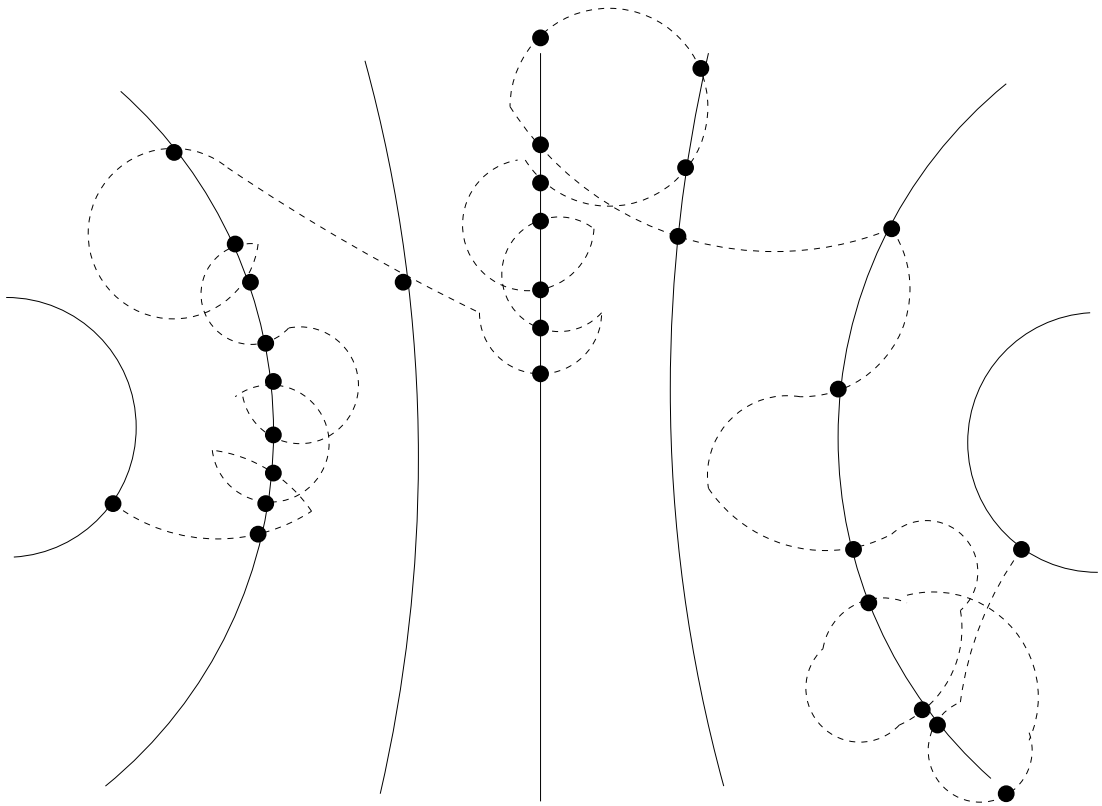


(c) Non equilibrium dynamics.



(d) Adaptive biasing techniques.

Adaptive biasing techniques



Adaptive biasing techniques

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

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

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

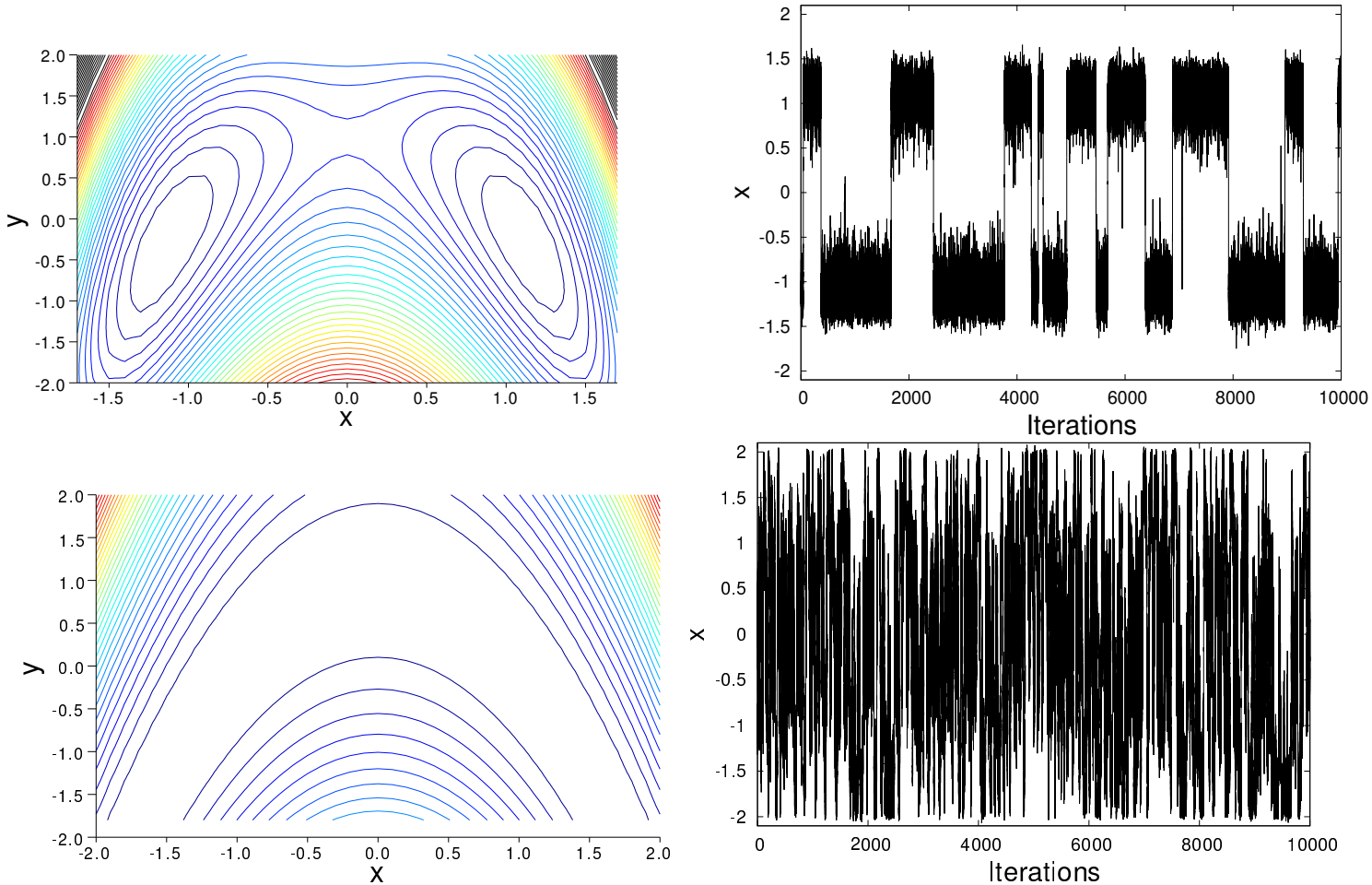
where A_t is an approximation at time t of A, given the configurations visited so far.

Hopes:

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

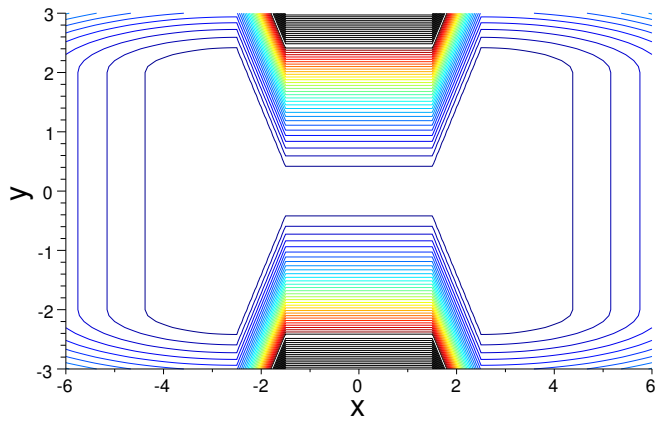
Wang-Landau, ABF, metadynamics: *Darve, Pohorille, Hénin, Chipot, Laio, Parrinello, Wang, Landau,...*

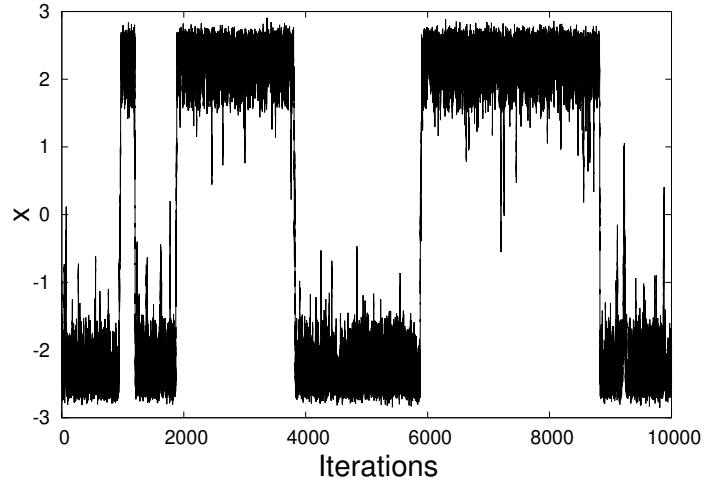
Free energy biased dynamics (1/2)

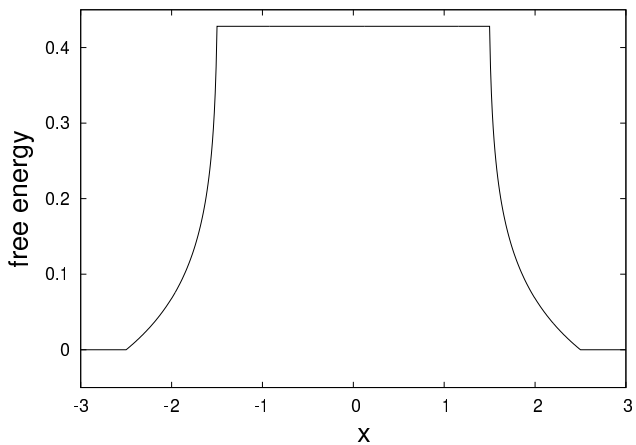


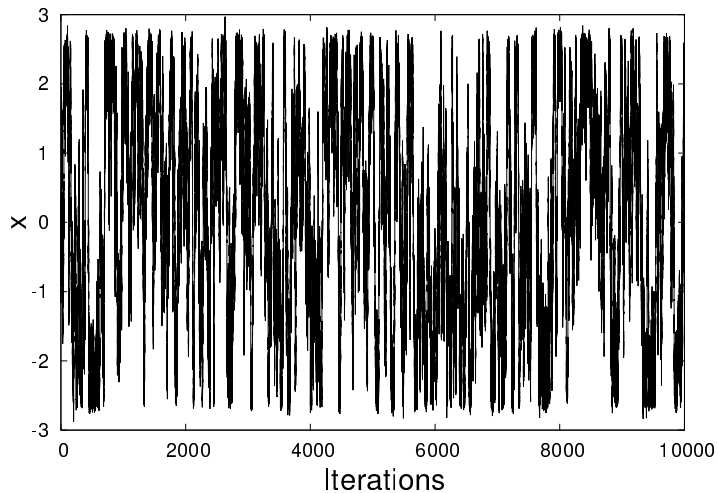
A 2d example of a free energy biased trajectory: energetic barrier.

Free energy biased dynamics (2/2)









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

Updating strategies

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

To avoid geometry problem, an extended configurational space $(\boldsymbol{x}, z) \in \mathbb{R}^{n+1}$ may be considered, together with the meta-potential:

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

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

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

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

The mean force

For the Adaptive Biasing Force (ABF) method, the idea is to directly compute an approximation of the mean force $A'(z)$.

Main ingredient: the derivative $A'(z)$ can be obtained as an average wrt $\mu(d\boldsymbol{x}|\xi(\boldsymbol{x}) = z)$ [Sprik, Ciccotti, Kapral, Vanden-Eijnden, E, den Otter, ...]:

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

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

Notice that actually, for any biasing potential $V_b(\xi(x))$,

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

The mean force (2d case)

In the simple case $\xi(x,y) = x$, this writes:

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

so that

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

And for any biasing potential $V_b(x)$,

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

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:

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

The ABF method

The ABF dynamics is then:

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

The associated (nonlinear) Fokker-Planck equation writes:

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

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

The ABF method

The ABF dynamics is then:

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

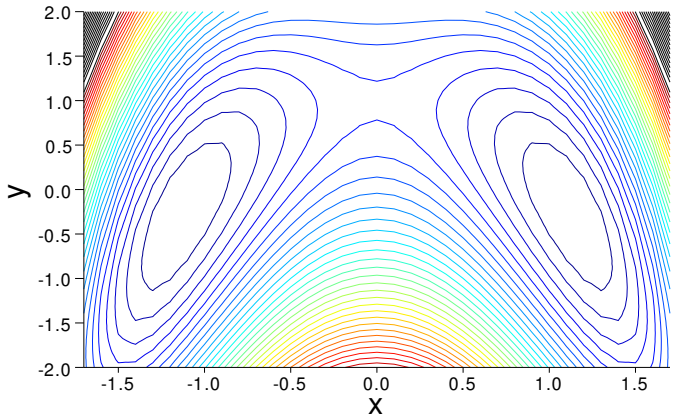
The associated (nonlinear) Fokker-Planck equation writes:

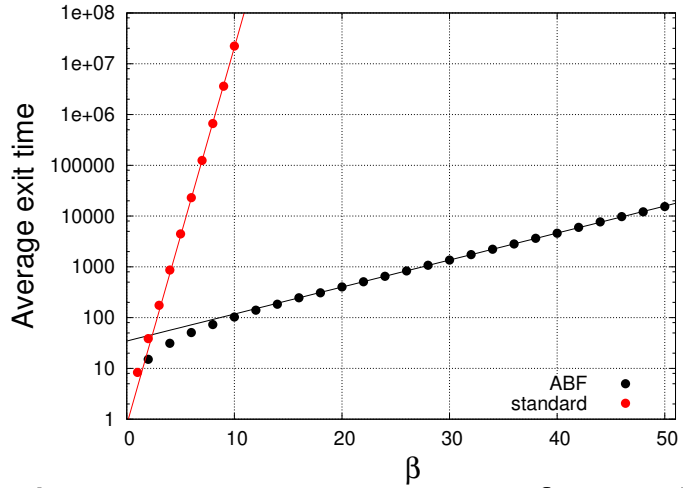
$$\begin{cases} \partial_t \psi = \operatorname{div}\left(\nabla(V - A_t \circ \xi)\psi + \beta^{-1}\nabla\psi\right), \\ A_t'(z) = \dfrac{\displaystyle\int f\, \psi\, \delta_{\xi(\boldsymbol{x})-z}(d\boldsymbol{x})}{\displaystyle\int \psi\, \delta_{\xi(\boldsymbol{x})-z}(d\boldsymbol{x})}, \end{cases}$$

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

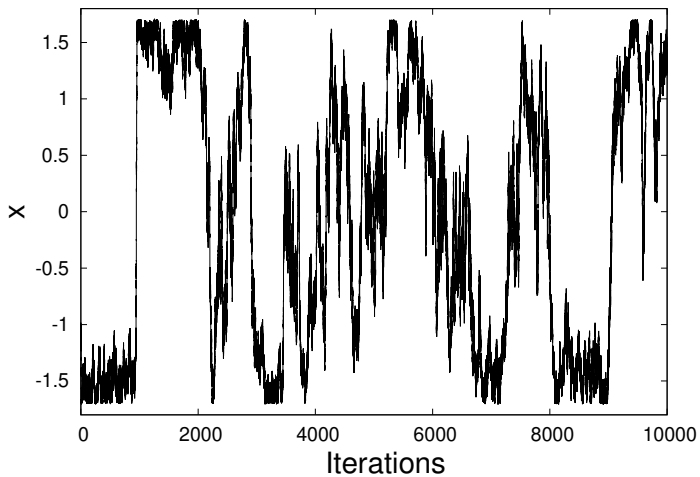
Questions: Does A_t' converge to A' ? What did we gain compared to the original gradient dynamics ?

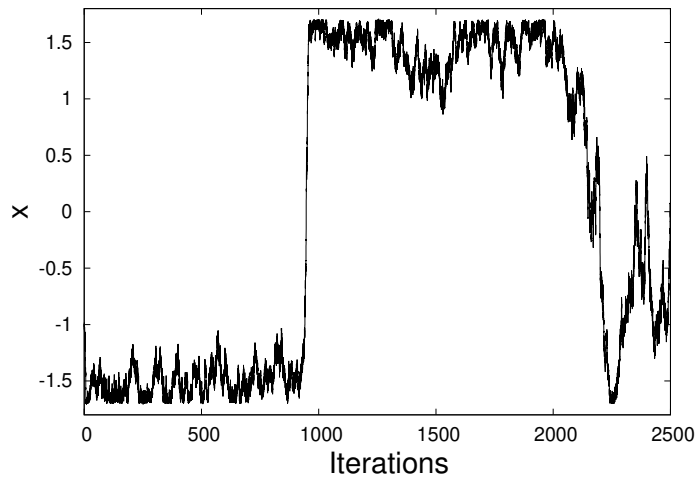
Back to the 2d example





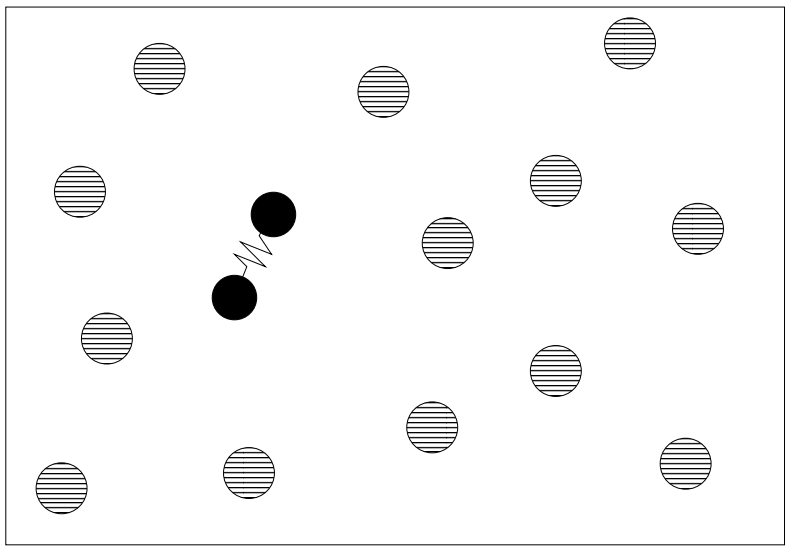
Left: the 2d potential – energetic barrier; Right: average exit time from the left well



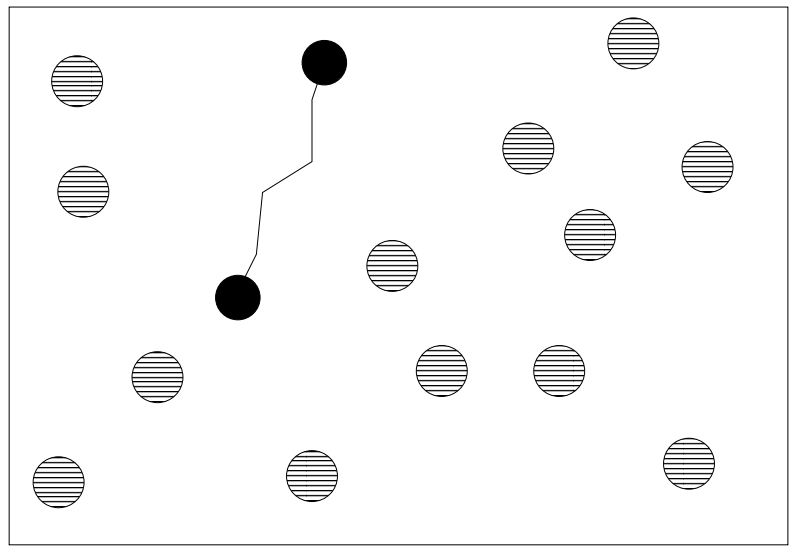


The ABF trajectory (right: zoom on the first 2500 iterations)

Back to the toy example for solvation



Compact state.



Stretched state.

The collective variable ξ is the distance between the two monomers. $\longrightarrow$ simulation

Longtime convergence and entropy (1/3)

Recall the original gradient dynamics:

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

The associated (linear) Fokker-Planck equation writes:

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

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

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

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

Longtime convergence and entropy (2/3)

Notice that the Fokker-Planck equation rewrites

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

Let us introduce the entropy:

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

We have (Csiszár-Kullback inequality):

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

Longtime convergence and entropy (3/3)

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

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

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

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

Metastability $\iff$ Small R

Convergence of ABF (1/3)

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

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

Suppose:

(H1) "Ergodicity" of the microscopic variables: the conditional probability measures $\mu(dx|\xi(x) = z)$ 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 (2/3)

In summary:

- Original gradient dynamics: $\exp(-\beta^{-1}Rt)$ 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 $\mu(d\boldsymbol{x}|\xi(\boldsymbol{x}) = z)$.

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

Two ingredients of the proof:

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

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

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

Convergence of ABF (3/3)

(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

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

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

Discretization of ABF

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

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

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

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

- Use trajectorial averages along a single path:

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

  The longtime behavior is much more difficult to analyze.

ABF: extensions and open problems

Numerical aspects:

- Multiple walker ABF [C. Chipot, TL, K. Minoukadeh]
- Projection on a gradient of the mean force (Helmholtz decomposition) [J. Hénin, TL, 2016-2017]
- collective variables in larger dimension: exchange bias, separated representations [Ehrlacher, TL, Monmarché, 2019], learning techniques.

Theoretical aspects:

- Analysis when the mean force (or the free energy) is approximated using time averages [M. Benaïm, G. Fort, B. Jourdain, TL, P. Monmarché, G. Stoltz, P.A. Zitt, 2014-2021]
- Extension of the analysis to the Langevin dynamics [M. Benaïm, P. Monmarché, 2018]

References on ABF

- J. Comer, J.C. Gumbart, J. Hénin, TL, A. Pohorille and C. Chipot, *The adaptive biasing force method: everything you always wanted to know, but were afraid to ask*, The Journal of Physical Chemistry B 119(3), 2015.
- E. Darve and A. Pohorille, *Calculating free energies using average force*, The Journal of Chemical Physics 115(20), 2001.
- J. Hénin and C. Chipot, *Overcoming free energy barriers using unconstrained molecular dynamics simulations*, J. Chem. Phys. 121, 2004.
- TL, M. Rousset and G. Stoltz, *Long-time convergence of an Adaptive Biasing Force method*, Nonlinearity 21, 2008.

CV for enhanced sampling: take-home message

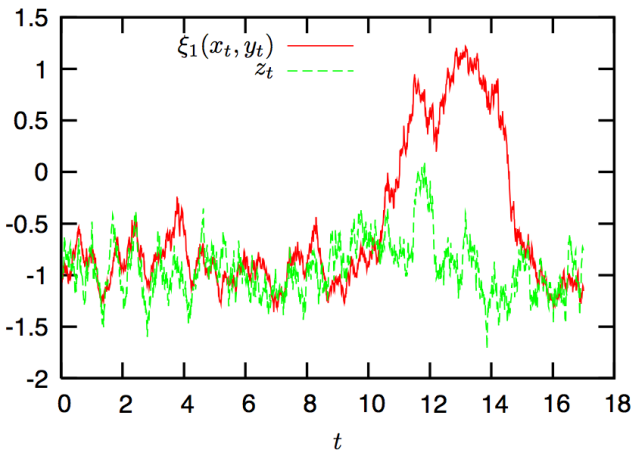
Free energy adaptive biasing techniques require a (low-dimensional) collective variable. They force the system to visit all the values of the collective variable.

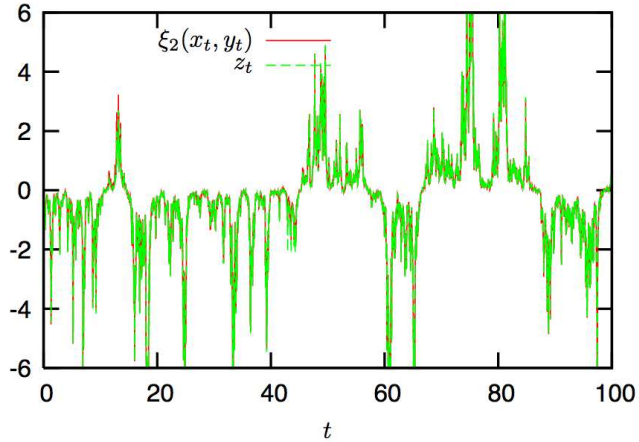
A good collective variable is thus such that if $\xi(\boldsymbol{X})$ is well sampled, than $\boldsymbol{X}$ is well sampled.

A prototypical example of a bad collective variable is when the law of $\boldsymbol{X}$ given $\xi(\boldsymbol{X}) = z$ is difficult to sample (multimodal). This is consistent with the mathematical analysis of the convergence of ABF using entropy techniques.

A prototypical example of a good collective variable is when $\boldsymbol{X}$ is almost fully determined when $\xi(\boldsymbol{X})$ is known. For example a quantitative estimate is: the smaller $\mathbb{E}\left(\mathrm{Var}(\boldsymbol{X}|\xi(\boldsymbol{X}))\right)$, the better.

Effective dynamics





General setting

Consider the stochastic dynamics

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

This dynamics is ergodic with respect to

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

Assume we are given a smooth one dimensional function $\xi : \mathbb{R}^d \to \mathbb{R}$.

Objective: build a closed Markov dynamics that approximates the dynamics $(\xi(\boldsymbol{X}_t))_{t \geq 0}$.

Side question: is it true that the mean transition time can be computed using an Eyring-Kramers formula of the form $C \exp(\beta \Delta A)$?

Construction of the effective dynamics

By Itô, one has

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

First attempt:

$$d\tilde{z}_t = \tilde{b}(t,\tilde{z}_t)\,dt + \sqrt{2\beta^{-1}}\tilde{\sigma}(t,\tilde{z}_t)\,dB_t$$

with $dB_t = \frac{\nabla\xi(\boldsymbol{X}_t)}{|\nabla\xi(\boldsymbol{X}_t)|}\cdot dW_t$,

$$\tilde{b}(t,\tilde{z}) = \mathbb{E}\left((-\nabla V\cdot\nabla\xi + \beta^{-1}\Delta\xi)(\boldsymbol{X}_t)\middle|\xi(\boldsymbol{X}_t) = \tilde{z}\right)$$

$$\tilde{\sigma}^2(t,\tilde{z}) = \mathbb{E}\left(|\nabla\xi|^2(\boldsymbol{X}_t)\middle|\xi(\boldsymbol{X}_t) = \tilde{z}\right).$$

Then, for all time $t \geq 0$, $\mathcal{L}(\xi(\boldsymbol{X}_t)) = \mathcal{L}(\tilde{z}_t)$! But $\tilde{b}$ and $\tilde{\sigma}$ are untractable numerically...

Construction of the effective dynamics

By Itô, one has

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

The effective dynamics:

$$dz_t = b(z_t)\,dt + \sqrt{2\beta^{-1}}\sigma(z_t)\,dB_t$$

with $dB_t = \frac{\nabla\xi(\boldsymbol{X}_t)}{|\nabla\xi(\boldsymbol{X}_t)|}\cdot dW_t$,

$$b(z) = \mathbb{E}_\mu\left((-\nabla V\cdot\nabla\xi + \beta^{-1}\Delta\xi)(\boldsymbol{X})\middle|\xi(\boldsymbol{X}) = z\right)$$

$$\sigma^2(z) = \mathbb{E}_\mu\left(|\nabla\xi|^2(\boldsymbol{X})\middle|\xi(\boldsymbol{X}) = z\right).$$

Related approaches: Mori-Zwanzig and projection operator formalism [E/Vanden-Eijnden, ...], asymptotic approaches [Papanicolaou, Freidlin, Pavliotis/Stuart, ...].

Link with the free energy

Let us introduce the free energy A associated with ξ.
The effective dynamics is:

$$dz_t = b(z_t)\,dt + \sqrt{2\beta^{-1}}\sigma(z_t)\,dB_t$$

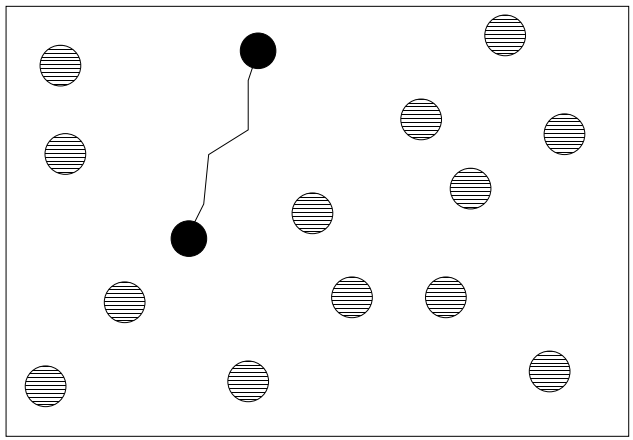
with

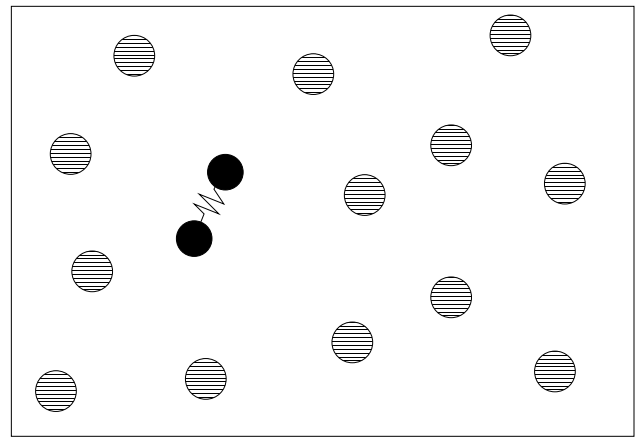
$$b(z) = -A'(z)\sigma^2(z) + \beta^{-1}\partial_z(\sigma^2).$$

It is thus the reversible dynamics wrt $\exp(-A(z))\,dz$, with a metric tensor defined by $\sigma^2(z)$.

If the effective dynamics is correct and if the metastable states of interest are defined in terms of ξ, in the limit $\beta \to 0$, one can thus justify the use of an Eyring-Kramers formula to estimate the mean transition time.

Illustration on the toy model for solvation





The collective variable is the distance between the two black particles. Here, $\sigma^2 = 2$ (and thus $b = -2A'$).

β	Reference	Eff. dyn.	Eff. dyn. with $b = -A'$ and $\sigma = 1$
0.5	262 ± 6	245 ± 5	504 ± 11
0.25	1.81 ± 0.04	1.68 ± 0.04	3.47 ± 0.08

Error analysis

Three mathematical results on the error introduced by the closure approximation:

- weak: error analysis on the time marginals
- strong: error analysis on the trajectories
- intermediate: error analysis on the reaction rate

Error analysis on the time marginals

Theorem Under the assumptions ($\xi(x_1, \ldots, x_n) = x_1$ for simplicity):

(H1) The conditional probability measures $\mu(\cdot|\xi(\boldsymbol{x}) = z)$ satisfy a Logarithmic Sobolev Inequality with constant ρ,

(H2) Bounded coupling assumption: $\|\partial_1 \partial_{2,\ldots,n} V\|_{L^\infty} \leq \kappa$.

Then, $\exists C > 0$, $\forall t \geq 0$,

$$H(\mathcal{L}(\xi(\boldsymbol{X}_t))|\mathcal{L}(z_t)) \leq C\frac{\kappa}{\rho}\Big(H(\mathcal{L}(\boldsymbol{X}_0)|\mu) - H(\mathcal{L}(\boldsymbol{X}_t)|\mu)\Big),$$

where $H(\phi|\psi) = \displaystyle\int \ln\left(\frac{\phi}{\psi}\right)\phi$ is the relative entropy.

If ρ is large (timescale decoupling assumption), the error is small.

The proof [Legoll, TL] is based on entropy techniques, logarithmic Sobolev inequalities and a micro-macro separation of the total entropy in the spirit of [Grunewald, Otto, Reznikoff, Villani].

Error analysis on the trajectories

Theorem Under the assumptions ($\xi(x_1, \ldots, x_n) = x_1$ for simplicity):

(H1') The conditional probability measures $\mu(\cdot|\xi(\boldsymbol{x}) = z)$ satisfy a Poincaré inequality with constant ρ,

(H2') Bounded coupling assumption: $\|\partial_1 \partial_{2,\ldots,n} V\|_{L^2(\mu)} \leq \kappa$,

(H3) b is one-sided Lipschitz ($-b' \leq L_b$) and such that

$$\int_{\mathbb{R}^d} \left(\sup_{y \in [-|x|,|x|]} |b'(y)| \right)^2 \mu(dx) < \infty.$$

Then, if $z_0 = \xi(\boldsymbol{X}_0)$ is distributed according to a measure μ_0 such that $\frac{d\mu_0}{d\mu} \in L^\infty$,

$$\mathbb{E}\left(\sup_{t \in [0,T]} |\xi(\boldsymbol{X}_t) - z_t| \right) \leq C \frac{\kappa}{\rho}$$

The proof [Legoll, TL, Olla] uses probabilistic arguments (Poisson equations, and Doob's martingale inequality).

Error analysis on the transition times

Let us assume that we are given two states $\mathcal{A}$ and $\mathcal{B}$ which can be defined thanks to ξ: $\boldsymbol{x} \in \mathcal{A}/\mathcal{B} \iff \xi(\boldsymbol{x}) \in \bar{\mathcal{A}}/\bar{\mathcal{B}}$.
Let us define the committor function for the original dynamics:

$$q(\boldsymbol{x}) = \mathbb{P}^{\boldsymbol{x}}(\tau_{\mathcal{B}} < \tau_{\mathcal{A}})$$

and for the effective dynamics:

$$\bar{q}(z) = \mathbb{P}^{z}(\tau_{\bar{\mathcal{B}}} < \tau_{\bar{\mathcal{A}}}).$$

Let us consider the equilibrium reaction rates ν and $\bar{\nu}$ for the original and effective dynamics.
Theorem One has:

$$\bar{\nu} = \nu + \beta^{-1} \int_{(A \cup B)^c} |\nabla(q - \bar{q} \circ \xi)|^2 d\mu.$$

The proof [Hartmann, Schütte, Zhang] is based on the formula which defines the reaction rate as a function of the committor function [E, Vanden Eijnden].

Choosing the committor as the collective variable

Consequences:

- For given fixed $\mathcal{A}$ and $\mathcal{B}$, the best collective variable minimizes the reaction rate of the effective dynamics.
- If ξ is such that $q(\boldsymbol{x}) = \tilde{q}(\xi(\boldsymbol{x}))$, then $\bar{q} = \tilde{q}$ and $\nu = \bar{\nu}$. In this case, one can check that the mean transition time from $\mathcal{A}$ to $\mathcal{B}$ for the original dynamics is equal to the mean transition time from $\bar{\mathcal{A}}$ to $\bar{\mathcal{B}}$ for the effective dynamics.
- In particular, if one chooses $\xi(\boldsymbol{x}) = q(\boldsymbol{x})$, then the reaction rate and the transition times are exactly reproduced by the effective dynamics.

Recent extensions and on-going works

We recently extended the error analysis on the time marginals and the trajectories to general vectorial reaction coordinates and to non-reversible dynamics (non-gradient forces) (collab. with F. Legoll, U. Sharma and W. Zhang).

From a numerical viewpoint, these coarse-grained dynamics can be used as predictors in predictor-corrector schemes (parareal algorithms) (collab. with F. Legoll and G. Samaey).

Questions:

- How to systematically improve the coarse-grained model (GLE, increase the dimension of the Markov model, ...)?
- Coarse-graining may involve rescaling in time/space.

References on effective dynamics

- F. Legoll and TL, *Effective dynamics using conditional expectations*, Nonlinearity, 2010.
- F. Legoll, TL and S. Olla, *Pathwise estimates for an effective dynamics*, Stochastic Processes and their Applications, 2017.
- TL, W. Zhang, *Pathwise estimates for effective dynamics: the case of nonlinear vectorial reaction coordinates*, SIAM Multiscale Modeling and Simulation, 2019.
- F. Legoll, TL and U. Sharma, *Effective dynamics for non-reversible stochastic differential equations: a quantitative study*, Nonlinearity, 2019.
- W. Zhang, C. Hartmann and C. Schütte, *Effective dynamics along given reaction coordinates, and reaction rate theory*, Faraday Discussions, 2016.

CV for dynamics: take-home message

From a dynamical viewpoint, a good collective variable is such that

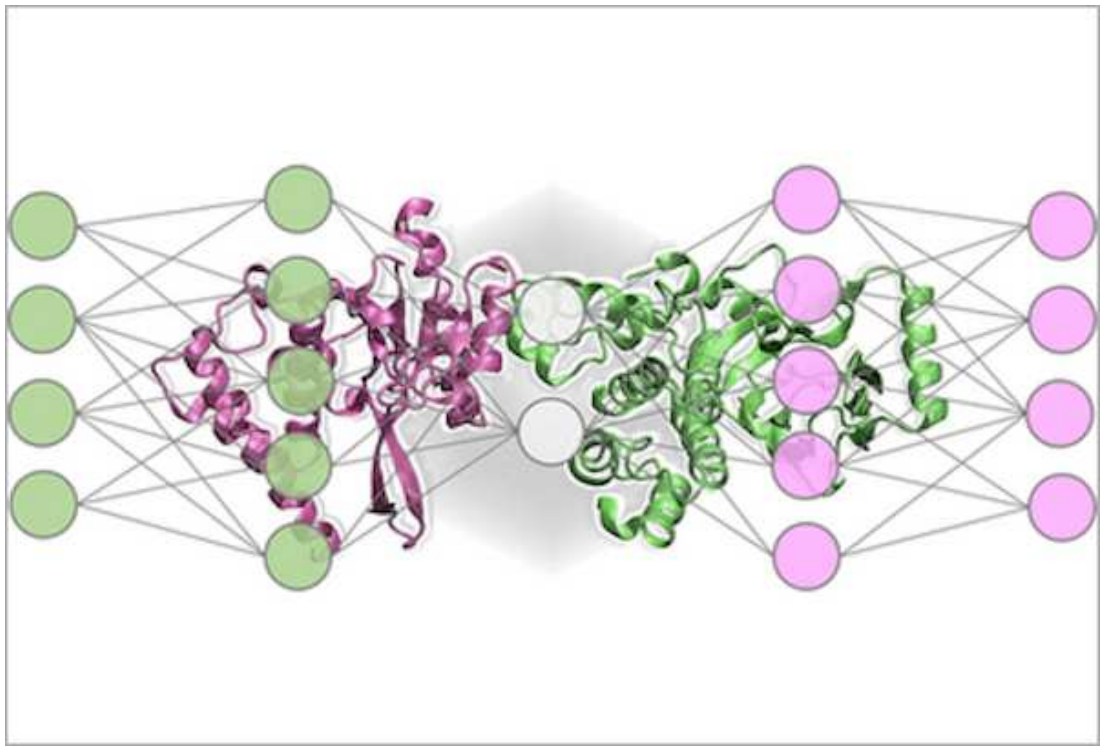
- (i) ξ determines the dynamical quantities we are interested in (e.g. the states, the observables of interest, the transition pathway, ...) and
- (ii) $(\xi(\boldsymbol{X}_t))_{t\geq 0}$ is close to a homogenous Markov process.

In this case, one can consider the effective dynamics $(z_t)_{t\geq 0}$ (in $\mathbb{R}^k$) to estimate dynamical quantities of the original dynamics (in $\mathbb{R}^d$).

The framework used to analyze the efficiency of ABF (functional inequalities) also apply to estimate the error of the effective dynamics.

The committor is a natural collective variable to build a good effective dynamics.

Conclusion



What is a good collective variable?

A collective variable is a low dimensional function $\xi : \mathbb{R}^d \to \mathbb{R}^k$ of the cartesian coordinates.

• The practical viewpoint: physically based collective variable
A good collective variable describes the state of the system: it can be interpreted physically, and measured experimentally.
Examples: angles, distances, coordination number, ...

• The thermodynamic viewpoint: collective variable for efficient sampling of the canonical measure
A good collective variable is such that if $\xi(\boldsymbol{X})$ is well sampled, then $\boldsymbol{X}$ is well sampled.
Examples of numerical methods which require such a good collective variable: umbrella sampling, thermodynamic integration, free energy adaptive biasing methods.
This point of view has been used to build collective variables: MESA [Ferguson], AE-ABF [Belkacemi, Gkeka, TL, Stoltz].

What is a good collective variable?

- The dynamical viewpoint: collective variable to estimate dynamical quantities

A good collective variable is such that (i) ξ determines the dynamical quantities of interest and (ii) $(\xi(\boldsymbol{X}_t))_{t\geq 0}$ is close to a homogenous Markov process.

Examples of numerical methods which require such a good collective variable: Effective dynamics based on free energy, Splitting techniques (AMS, FFS, TIS).

Remark: We focused on continuous collective variables, but the same discussion applies to discrete collective variables (in particular to build Markov State Models).

Some natural candidates

- Energy

The energy can be used as a collective variable to enhance the sampling of the canonical measure (Wang-Landau algorithm).

Difficulty: how to choose the range of energy to be visited? The volume of $\{\boldsymbol{x}, V(\boldsymbol{x}) = z\}$ increases quickly with z.

- Committor function

The committor function is a natural 1d collective variable.

It is the central object of the Transition Path Theory [E, Vanden Einjden].

The effective dynamics on the committor function is exact in terms of reaction rate and transition times [Hartmann, Schütte, Zhang].

The committor function is the optimal importance function for many rare event sampling methods: splitting techniques and importance sampling methods on path space.

Some natural candidates

• Eigenfunctions of the transition operator

Effective dynamics built using the eigenvectors as collective variables have the same leading eigenvalues as the original dynamics [Hartmann, Schütte, Zhang].

In the small temperature regime, eigenfunctions are piecewise constant, the constancy zones being neighborhoods of the local minima of V.

Example of numerical methods to approximate eigenfunctions: diffusion map, Koopman operator approaches (tICA), ...

Remarks:

- In practice, the eigenfunctions can be approximated using the committor functions associated with core sets [Sarich, Schütte]
- The committor and the eigenfunctions are high dimensional functions: approximation by neural networks is natural.

What's next?

How to use the mathematical insights we gain on what characterizes a good collective variable to actually build collective variables?

How to solve the chicken and egg problem: (i) one needs a good sampling to build a collective variable and (ii) a good sampling requires a good collective variable...

- Gabriel Stoltz will present how machine learning techniques can be used to build collective variables.
- Thomas Pigeon will illustrate these techniques during a hands-on session.