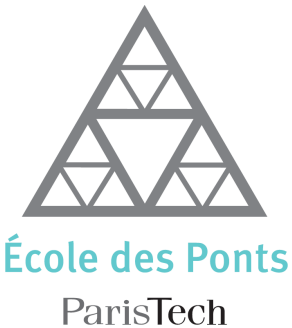
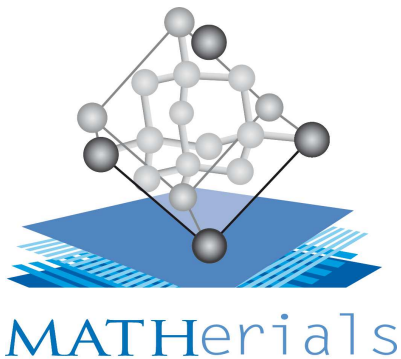
Sampling efficiently metastable dynamics: algorithms and mathematical analysis

T. Lelièvre

CERMICS - Ecole des Ponts ParisTech & Matherials project-team - INRIA





IPAM, September 2017

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).

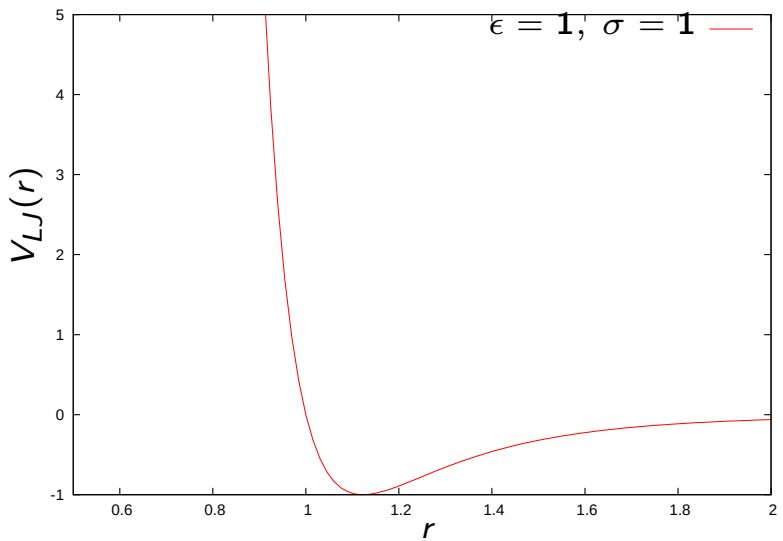
The basic ingredient: a potential V which associates to a configuration $(\boldsymbol{x}_1, ..., \boldsymbol{x}_N) = \boldsymbol{x} \in \mathbb{R}^{3N_{atom}}$ an energy $V(\boldsymbol{x}_1, ..., \boldsymbol{x}_{N_{atom}})$. The dimension $d = 3N_{atom}$ is large (a few hundred thousand to millions).

Empirical force field

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.



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:

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

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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.

Introduction

These dynamics are used to compute macroscopic quantities:

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

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

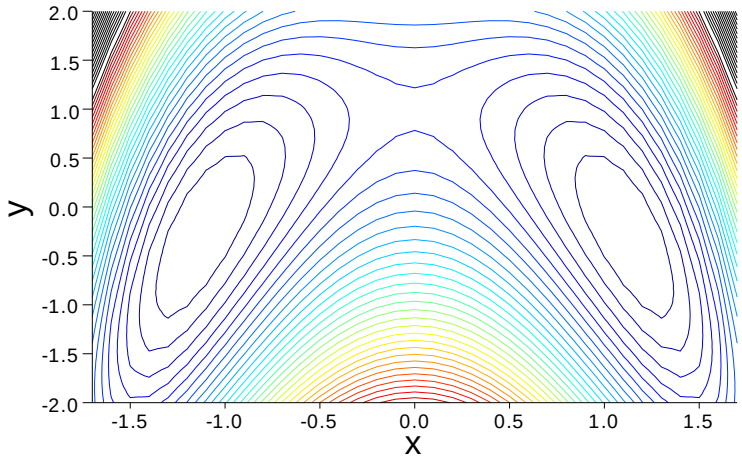
(ii) Dynamical quantities (averages over trajectories): diffusion coefficients, viscosity, transition rates,...

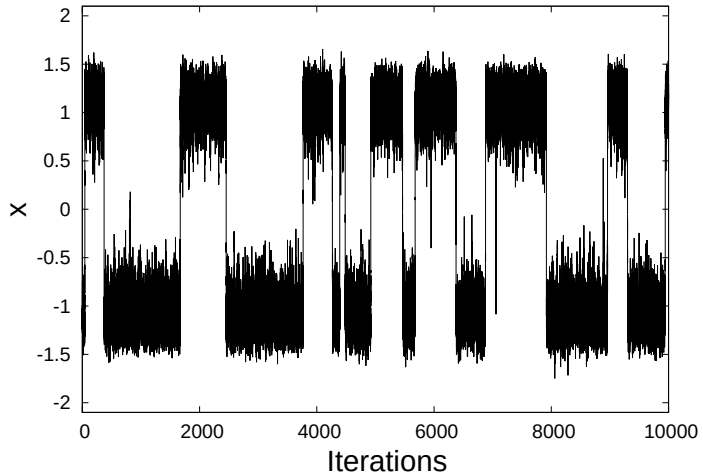
$$\mathbb{E}(\mathcal{F}((\boldsymbol{X}_t)_{t\geq 0})) \simeq \frac{1}{M} \sum_{m=1}^{M} \mathcal{F}((\boldsymbol{X}_t^m)_{t\geq 0}).$$

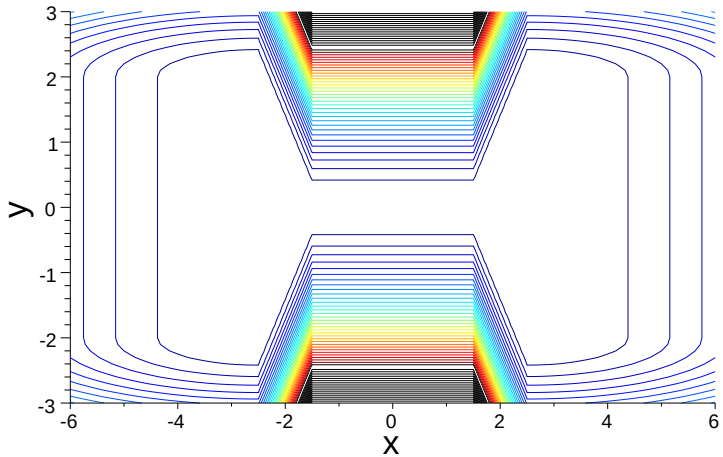
Difficulties: (i) high-dimensional problem ($N \gg 1$); (ii) $\boldsymbol{X}_t$ is a metastable process and μ is a multimodal measure.

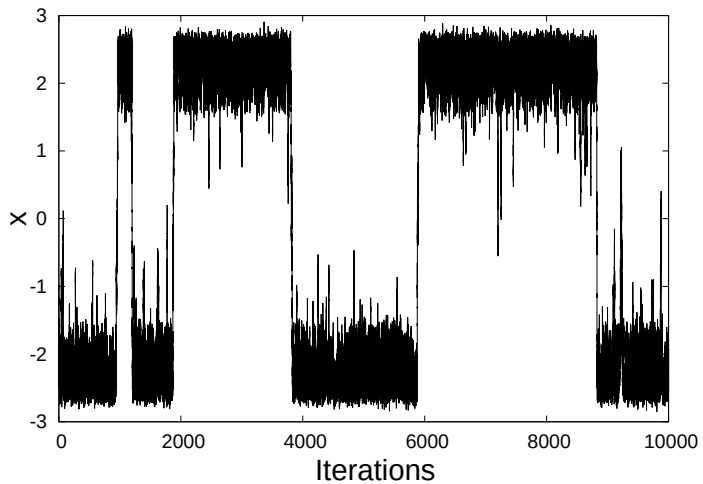
Metastability: energetic and entropic barriers

A two-dimensional schematic picture







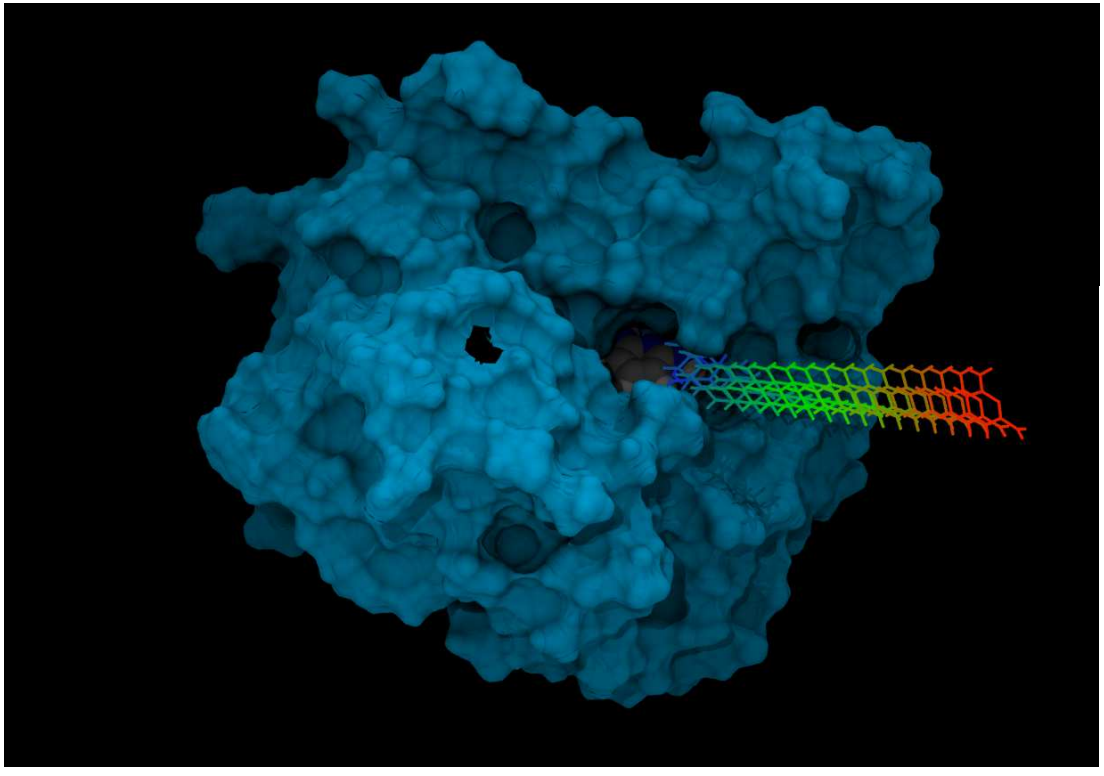


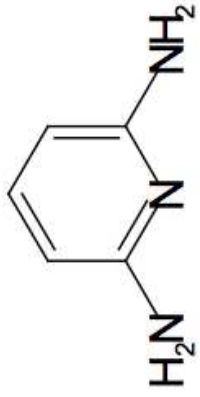
$\longrightarrow$
- Slow convergence of trajectorial averages
- Transitions between metastable states are rare events

Simulations of biological systems

Unbinding of a ligand from a protein

(Diaminopyridine-HSP90, Courtesy of SANOFI)





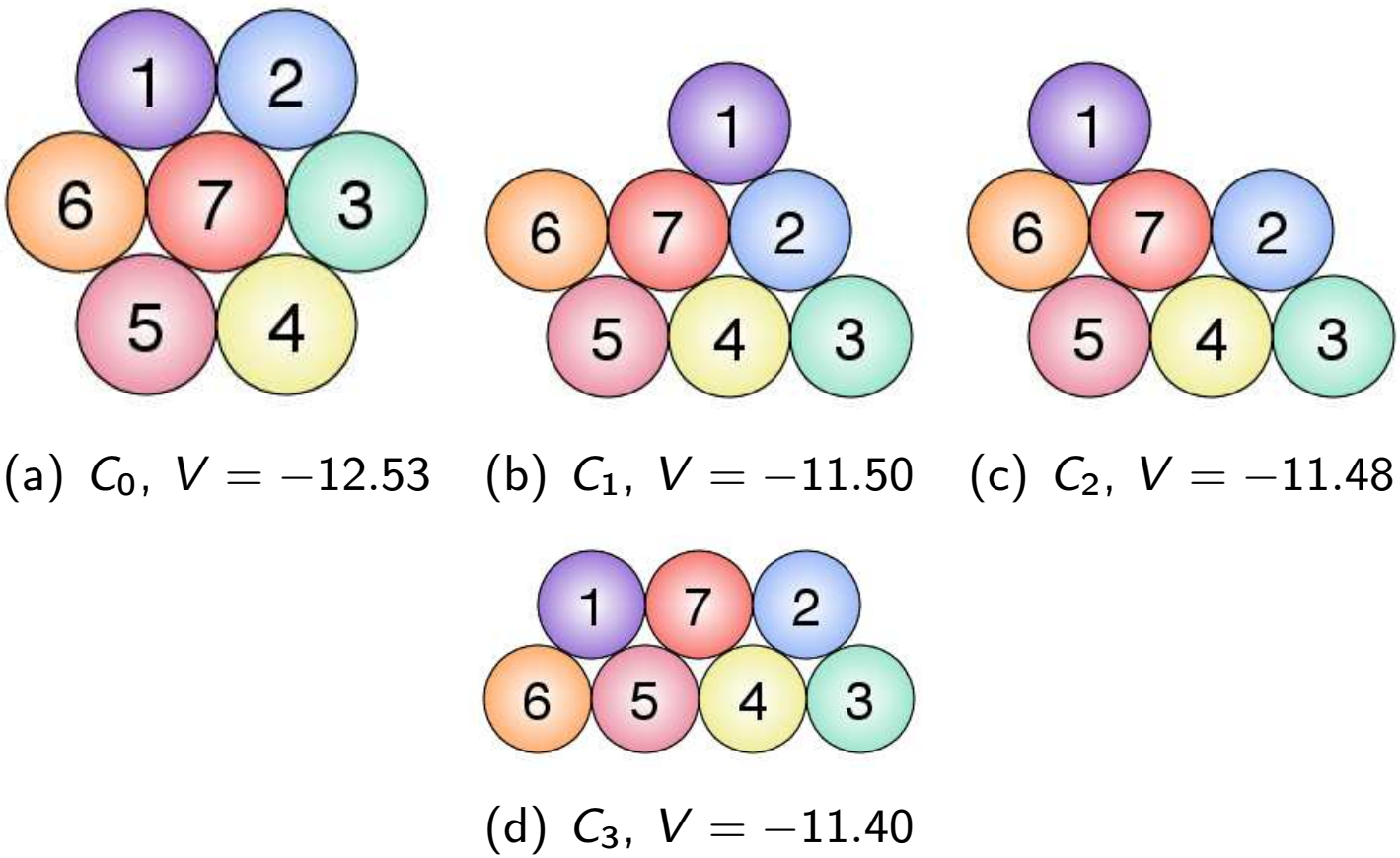
Elementary time-step for the molecular dynamics $= 10^{-15}\,\mathrm{s}$

Dissociation time $= 0.5\,\mathrm{s}$

Challenge: bridge the gap between timescales

A toy example in material sciences

The 7 atoms Lennard Jones cluster in 2D.



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

(d) C_3, $V = -11.40$

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

$\longrightarrow$ simulation

Introduction

For computing thermodynamics quantities, there is a clear classification of available methods, and the difficulties are now well understood (in particular for free energy computations, see for example [TL, Rousset, Stoltz, 2010]). On the opposite, computing efficiently dynamical quantities remains a challenge.

Outline of the lectures:

1. Is free energy enough ?: Approximating transition times using free energy. *Coarse-graining, entropy techniques.*
2. Adaptive Multilevel Splitting methods: Towards efficient sampling of reactive paths. *Rare event simulation.*
3. Accelerated dynamics: These methods have been proposed by A.F. Voter to generate efficiently metastable dynamics. *Kinetic Monte Carlo approximation and Quasi Stationary Distributions.*

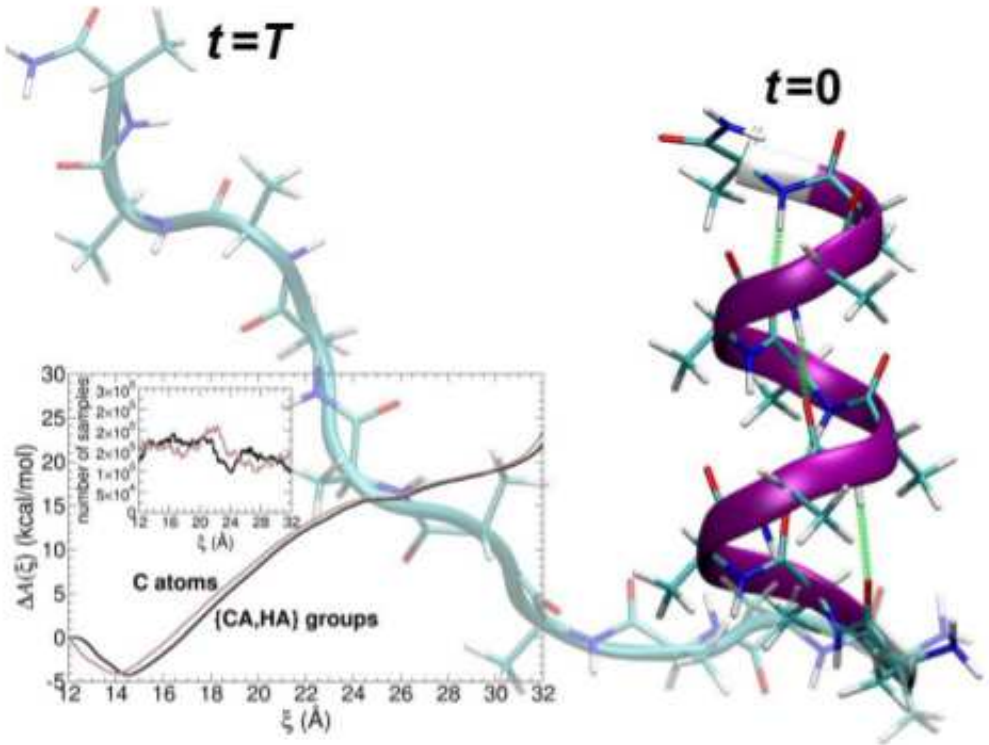
Introduction

Underlying mathematical questions: How to analyze a metastable process ? How to properly define and quantify metastability ?

Various approaches:

- Rate of convergence to equilibrium: entropy techniques [Otto, Villani, TL]; spectral analysis of the underlying Fokker-Planck operator [Schuette, Helffer, Nier, Pavliotis]; potential theoretic approaches [Bovier, Schuette, Hartmann,...].
- Exit time from metastable states versus decorrelation time: large deviation techniques [Freidlin, Wentzell, Dupuis, Spiliopoulos, Vanden-Eijnden, Weare, Touchette,...], quasi stationary distributions [Gaudillière, TL,...].
- Asymptotic variance of trajectory averages: central limit theorems, convergence analysis for stochastic approximation algorithms [Borkar, Dama, TL, ...].

Free energy, effective dynamics and transition times



Free energy, effective dynamics and transition times

Recall the original dynamics

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

with invariant measure $d\mu = Z^{-1} \exp(-\beta V(\boldsymbol{x}))\, d\boldsymbol{x}$. Let us be given a smooth one dimensional function $\xi : \mathbb{R}^d \to \mathbb{R}$. Let $A : \mathbb{R} \to \mathbb{R}$ be the free energy associated with ξ.

Question: What is the dynamical content of A ? Can it be used to build a surrogate dynamics for $(\xi(\boldsymbol{X}_t))_{t\geq}$? Does it make sense to estimate transition times based on A, using the Arrhenius law:

$$\text{transition time} \simeq \exp(\beta \Delta A)?$$

Free energy

The free energy $A : \mathbb{R} \to \mathbb{R}$ is defined by:

$$\exp(-\beta A(z)) = Z^{-1} \int_{\{\boldsymbol{x},\, \xi(\boldsymbol{x})=z\}} \exp(-\beta V(\boldsymbol{x}))\, \delta_{\xi(\boldsymbol{x})-z}(d\boldsymbol{x}).$$

By construction, for any test function φ,

$$\int \varphi \circ \xi d\mu = \int \varphi(z) \exp(-\beta A(z))\, dz.$$

Question: Is the effective dynamics

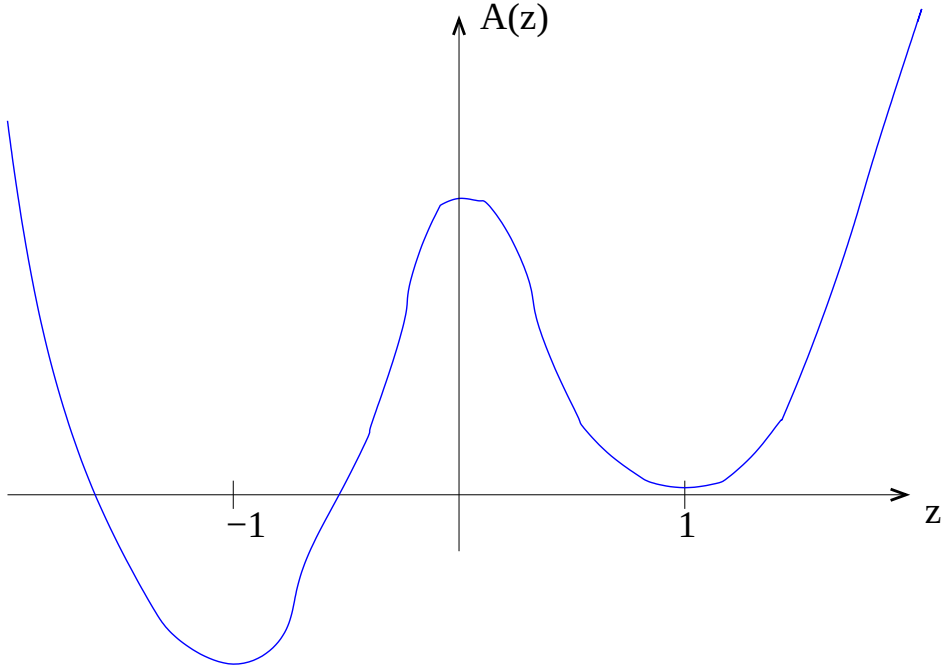
$$dz_t = -A'(z_t)\, dt + \sqrt{2\beta^{-1}} dB_t$$

close to $(\xi(\boldsymbol{X}_t))_{t\geq 0}$? It is indeed thermodynamically consistent (the invariant measure is $\exp(-\beta A(z))\, dz = \xi * \mu$) but is it dynamically consistent ?

From free energy to transition times (1/2)

If the stochastic differential equation $dz_t = -A'(z_t)\,dt + \sqrt{2\beta^{-1}}dB_t$ is a good approximation of the dynamics of $(\xi(\boldsymbol{X}_t))_{t\geq 0}$, then one can deduce the Arrhenius law.

Let us consider a simple 1d case.



First hitting time of the right well: for $z_0 \leq 1$,
$\tau_1 = \inf\{t \geq 0, z_t \geq 1\}$.

From free energy to transition times (2/2)

Let us introduce the mean transition time to the right well, starting from $z_0 = z$: for $z \leq 1$,

$$u(z) = \mathbb{E}^z(\tau_1).$$

Then u satisfies:

$$\begin{cases} A'(z)u'(z) - \beta^{-1}u''(z) = 1 \text{ for } z \in (-\infty, 1), \\ u'(-\infty) = 0 \text{ and } u(1) = 0. \end{cases}$$

Thus

$$u(z) = \beta \int_z^1 \left(\int_{-\infty}^y \exp(\beta(A(y) - A(x))\, dx \right) dy.$$

Using the 2d Laplace's method, one then gets: for all $z < 0$, in the limit $\beta \to \infty$ (A being fixed):

$$u(z) \simeq \frac{2\pi}{\sqrt{-A''(0)A''(-1)}} \exp(\beta(A(0) - A(-1))).$$

Construction of an effective dynamics

By Itô, one has

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

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

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

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

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 an effective dynamics

By Itô, one has

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

The effective dynamics:

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

with

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

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

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

Link with the free energy

- It can be checked that $b = -\sigma^2 A' + \beta^{-1}\partial_z(\sigma^2)$ so that the effective dynamics rewrites:

$$dz_t = \sigma^2(z_t)\left(-A'(z_t) + \beta^{-1}\partial_z(\ln \sigma^2)(z_t)\right)\, dt + \sqrt{2\beta^{-1}}\sigma(z_t)\, dB_t.$$

  In particular (i) the effective dynamics is reversible wrt $\xi * \mu$ and (ii) if $|\nabla \xi(x)| = 1$, then $\sigma(z) = 1$, and $b(z) = -A'(z)$.

- Let us replace ξ by

$$\zeta(x) = h(\xi(x))$$

  where $h'(z) = 1/\sigma(z)$. Then, the effective dynamics associated to $\zeta(x)$ is

$$dz_t = -\mathcal{A}'(z_t)\, dt + \sqrt{2\beta^{-1}}\, dB_t$$

  where $\mathcal{A}$ is the free energy associated to ζ.

Error analysis: trajectories

Assume $\xi(x_1, \ldots, x_n) = x_1$ for simplicity and:

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

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

(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 $\frac{d\mu_0}{d\mu} \in L^\infty$,

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

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

Proof of a weaker result (1/2)

Assume that $\boldsymbol{X}_0 \sim \mu$. Since $\xi(x_1, \ldots, x_n) = x_1$, we have

$$dX_t^1 = -\partial_1 V(\boldsymbol{X}_t)\, dt + \sqrt{2\beta^{-1}} dW_t^1$$

$$dz_t = -A'(z_t)\, dt + \sqrt{2\beta^{-1}} dW_t^1$$

and thus

$$\frac{d(X_t^1 - z_t)}{dt} = -(A'(X_t^1) - A'(z_t)) + e_t$$

where $e_t = A'(X_t^1) - \partial_1 V(\boldsymbol{X}_t)$. Thus, by Gronwall, since $\xi(\boldsymbol{X}_0) = z_0$, $\mathbb{E}(e_t) = \mathbb{E}(e_0)$ and $A'' \geq -L_b$ by (H3):

$$\begin{aligned}\frac{1}{2}\mathbb{E}\left(\sup_{s \leq t} |X_s^1 - z_s|\right) &\leq \mathbb{E}\int_0^t e^{L_b(t-s)}|e_s|\, ds \\ &= \frac{e^{L_b t} - 1}{L_b}\mathbb{E}(|e_0|).\end{aligned}$$

Proof of a weaker result (2/2)

Now, using (H1) and (H2),

$$\begin{aligned}
\mathbb{E}(|e_0|)^2 &\leq \mathbb{E}(|e_0|^2) \\
&= \int |\partial_1 V(\boldsymbol{x}) - A'(x^1)|^2 \mu(d\boldsymbol{x}) \\
&= \int \int |\partial_1 V(\boldsymbol{x}) - A'(x^1)|^2 \mu(d\boldsymbol{x}|\xi(\boldsymbol{x}) = z) \exp(-\beta A(z)) dz \\
&\leq \frac{1}{\rho} \int \int |\partial_{2,\dots n} \partial_1 V(\boldsymbol{x})|^2 \mu(d\boldsymbol{x}|\xi(\boldsymbol{x}) = z) \exp(-\beta A(z)) dz \\
&\leq \frac{\kappa^2}{\rho}.
\end{aligned}$$

This yields

$$\mathbb{E}\left(\sup_{s \leq t} |X_s^1 - z_s|\right) \leq C \frac{\kappa}{\sqrt{\rho}}$$

with $C = \frac{e^{L_b t} - 1}{L_b}$.

Remark: Application to the averaging principle

These techiques can be used to obtain quantitative limiting results for two-timescale systems such as:

$$\begin{cases} dX_t^{1,\varepsilon} = -\partial_1 V(X_t^\varepsilon)\, dt + \sqrt{2\beta^{-1}} dW_t^1 \\ dX_t^{i,\varepsilon} = -\dfrac{\partial_i V(X_t^\varepsilon)}{\varepsilon}\, dt + \sqrt{\dfrac{2\beta^{-1}}{\varepsilon}} dW_t^i \qquad \text{for } i = 2, \dots, n \end{cases}$$

Then, under the assumptions of the former result:

$$\mathbb{E}\left(\sup_{0 \le t \le T} \left| X_t^{1,\varepsilon} - z_t \right| \right) \le C \sqrt{\beta\varepsilon}\, \frac{\kappa}{\rho}.$$

Notice that we do not assume b globally Lipschitz.

Error analysis: time marginals

Assume that $\xi(x_1, \ldots, x_n) = x_1$ for simplicity and:

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

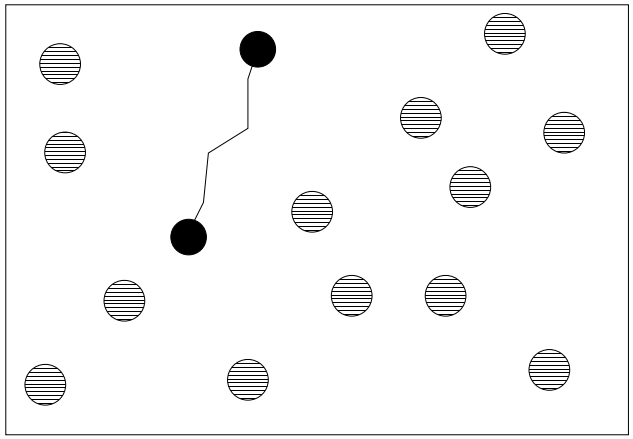
(H2') Bounded coupling: $\|\partial_1 \partial_{2,\ldots,n} V\|_{L^\infty} \leq \kappa$.

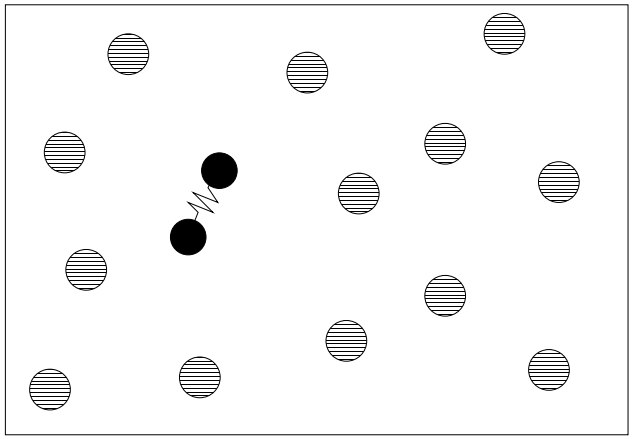
Then, $\exists C > 0$, $\forall t \geq 0$,

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

The proof [Legoll, TL] is based on a decomposition of the entropy proposed in [Grunewald/Otto/Villani/Westdickenberg], and relies on entropy estimates.

Numerical illustration: dimer in a solvant





- Solvent-solvent, solvent-monomer: truncated LJ for $\|x_i - x_j\|$,
- Monomer-monomer: double well potential for $\|x_1 - x_2\|$.

ξ is the distance between the two monomers: $\xi(x) = \|x_1 - x_2\|$.

Transition times from the compact to the stretched state:

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

Conclusion

Back to our question: Can we justify the use of the free energy to estimate transition times ?

We have:

- Short time analysis on trajectories
- Long time analysis on marginals

$\longrightarrow$ This is not enough !

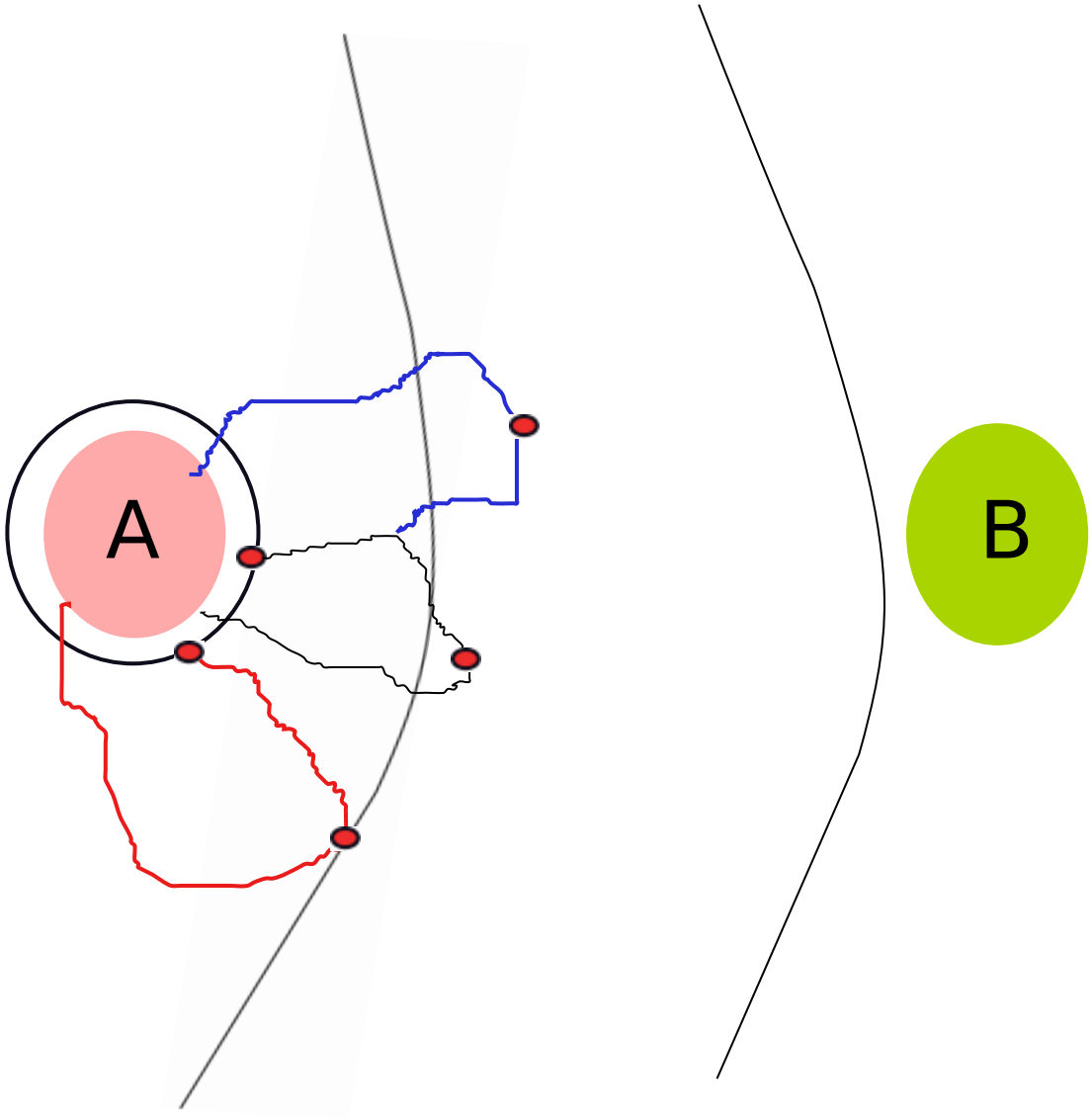
See however the recent work [W. Zhang, C. Hartmann and C. Schuette, *Effective dynamics along given reaction coordinates, and reaction rate theory*, Faraday Discussion, **195**, 365-394, 2016].

How to efficiently simulate metastable dynamics ?

There are many approaches:

- Going from state A to state B:
  - *Local search*: the string method [E, Ren, Vanden-Eijnden], max flux [Skeel], transition path sampling methods [Chandler, Bolhuis, Dellago],
  - *Global search, ensemble of trajectories*: AMS [Cérou, Guyader, TL], transition interface sampling [Bolhuis, van Erp], forward flux sampling [Allen, Valeriani, ten Wolde], milestoning techniques [Elber, Schuette, Vanden-Eijnden]
- Importance sampling approaches on paths, reweighting [Dupuis, Vanden-Einjden, Weare, Schuette, Hartmann]
- State-to-state dynamics, adaptive kMC [Voter, Perez, Henkelman]
- Saddle point search techniques [Mousseau, Henkelman, Wales] and graph exploration [Cameron]
- Starting from a long trajectory, extract states: clustering, Hidden Markov chain [Schuette]

Splitting strategies



Multilevel splitting

We would like to sample trajectories between two given metastable states A and B. The main assumption is that we are given a smooth one dimensional function $\xi : \mathbb{R}^d \to \mathbb{R}$ (s.t. $|\nabla \xi| \neq 0$) which "indexes" the transition from A to B in the following sense:

$$A \subset \{x \in \mathbb{R}^d, \xi(x) < z_{\min}\} \text{ and } B \subset \{x \in \mathbb{R}^d, \xi(x) > z_{\max}\},$$

where $z_{\min} < z_{\max}$, and $\Sigma_{z_{\min}}$ (resp. $\Sigma_{z_{\max}}$) is "close" to ∂A (resp. ∂B).

Example: $\xi(x) = \|x - x_A\|$ where $x_A \in A$ is a reference configuration in A. We are interested in the event $\{\tau_A < \tau_B\}$, starting from an initial condition on $\Sigma_{z_{\min}}$, where

$$\tau_A = \inf\{t > 0, \boldsymbol{X}_t \in A\}, \quad \tau_B = \inf\{t > 0, \boldsymbol{X}_t \in B\}$$

and

$$\tau_z = \inf\{t > 0, \xi(\boldsymbol{X}_t) > z\}.$$

Multilevel splitting

Question: How to compute dynamical quantities using ξ ? More precisely, we consider: (a) Reactive trajectories and (b) Transition times between the two metastable states A and B.

We propose a multilevel splitting approach [Kahn, Harris, 1951] [Rosenbluth, 1955] to discard failed trajectories and branch trajectories approaching the rare set. We focus on an adaptive variant [Cérou, Guyader, 2007] [Cérou, Guyader, TL, Pommier, 2011]: the Adaptive Multilevel Splitting (AMS) algorithm.

Remark: The algorithm can be seen as a kind of adaptive Forward Flux Sampling [Allen, Valeriani, Ten Wolde, 2009]. It is also related to the Interface Sampling Method [Bolhuis, van Erp, Moroni 2003] and the Milestoning method [Elber, Faradjian 2004]. See the review paper [Bolhuis, Dellago, 2009]. Another splitting technique in MD: weighted ensemble method [Zuckerman, 2010].

Reactive trajectory

A reactive trajectory between two metastable sets A and B is a piece of equilibrium trajectory that leaves A and goes to B without going back to A in the meantime [Hummer,2004] [Metzner, Schütte, Vanden-Eijnden, 2006].

Difficulty: A trajectory leaving A is more likely to go back to A than to reach B.

Splitting algorithm: basic idea

The idea of splitting algorithms (FFS, TIS, RESTART, ...) is to write the rare event

$$\{\tau_B < \tau_A\}$$

as a sequence of nested events: for $z_{\min} < z_1 < \ldots < z_{\max}$,

$$\{\tau_{z_1} < \tau_A\} \supset \{\tau_{z_2} < \tau_A\} \supset \ldots \supset \{\tau_{z_{\max}} < \tau_A\} \supset \{\tau_B < \tau_A\}$$

and to simulate the successive *conditional events*: for $q = 1, 2, \ldots,$

$$\{\tau_{z_q} < \tau_A\} \text{ knowing that } \{\tau_{z_{q-1}} < \tau_A\}.$$

It is then easy to build an unbiased estimator of

$$\mathbb{P}(\tau_B < \tau_A) = \mathbb{P}(\tau_{z_1} < \tau_A)\mathbb{P}(\tau_{z_2} < \tau_A | \tau_{z_1} < \tau_A) \ldots \mathbb{P}(\tau_B < \tau_A | \tau_{z_{\max}} < \tau_A)$$

Splitting algorithm: adaptive level computation

Problem: How to choose the intermediate levels $(z_q)_{q\geq 1}$?

It is easy to check that, for a given number of intermediate levels, the optimum in terms of variance is attained if

$$\mathbb{P}(\tau_{z_q} < \tau_A | \tau_{z_{q-1}} < \tau_A) \text{ is constant .}$$

This naturally leads to adaptive versions (AMS, nested sampling) where the levels are determined by using *empirical quantiles*: choose $k < n$, and given n trajectories $(\boldsymbol{X}^m_{t\wedge\tau_A})_{t>0,m=1,\ldots,n}$ in the event $\{\tau_{z_{q-1}} < \tau_A\}$, choose z_q so that

$$\mathbb{P}(\tau_{z_q} < \tau_A | \tau_{z_{q-1}} < \tau_A) \simeq \left(1 - \frac{k}{n}\right).$$

The level z_q is the k-th order statistics of $\sup_{t\geq 0} \xi(\boldsymbol{X}^m_{t\wedge\tau_A})$:

$$\sup_{t\geq 0} \xi(\boldsymbol{X}^{(1)}_{t\wedge\tau_A}) < \ldots < \sup_{t\geq 0} \xi(\boldsymbol{X}^{(k)}_{t\wedge\tau_A}) =: z_q < \ldots < \sup_{t\geq 0} \xi(\boldsymbol{X}^{(n)}_{t\wedge\tau_A}).$$

AMS: estimator of the rare event probability (1/2)

Let Q_{iter} be the number of iterations to reach the level $z_{\max}$:

$$Q_{\mathrm{iter}} = \min\{q \geq 0, z_q > z_{\max}\}$$

(where z_0 is the k-th order statistics of the n initial trajectories). Then, one obtains the estimator:

$$\left(1 - \frac{k}{n}\right)^{Q_{\mathrm{iter}}} \simeq \mathbb{P}(\tau_{z_{\max}} < \tau_A).$$

AMS: estimator of the rare event probability (2/2)

At iteration Q_{iter}, one has an ensemble of n trajectories starting from $\Sigma_{z_{\min}}$ and such that $\tau_{z_{\max}} < \tau_A$. Thus

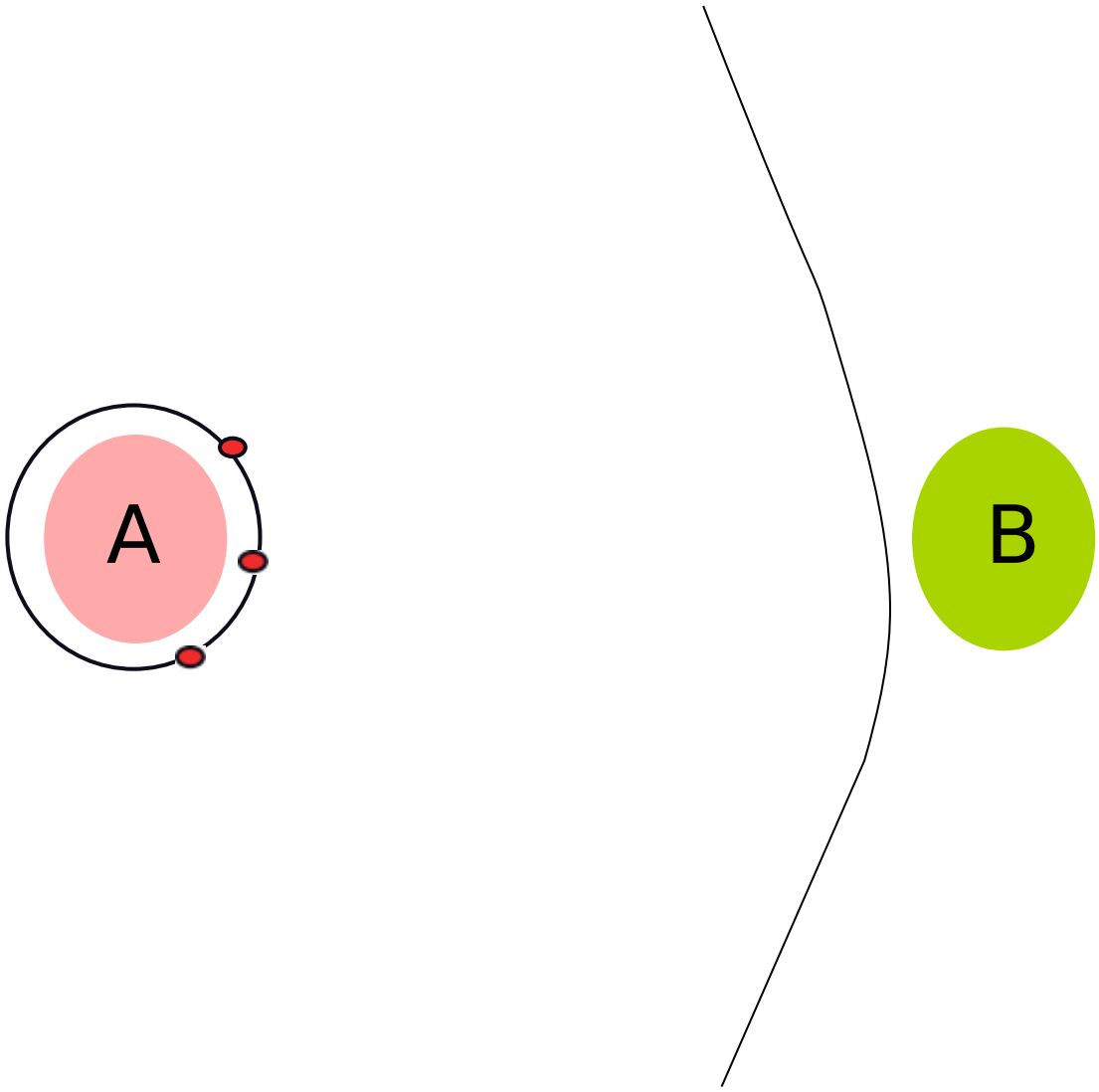
$$\hat{p}_{\mathrm{corr}} := \frac{1}{n} \sum_{\ell=1}^{n} 1_{\{T_B(\boldsymbol{X}^{\ell,Q_{\mathrm{iter}}}) < T_A(\boldsymbol{X}^{\ell,Q_{\mathrm{iter}}})\}} \simeq \mathbb{P}(\tau_B < \tau_A | \tau_{z_{\max}} < \tau_A).$$

$\hat{p}_{\mathrm{corr}}$ is the proportion of trajectories reaching B before A at the last iteration Q_{iter}.

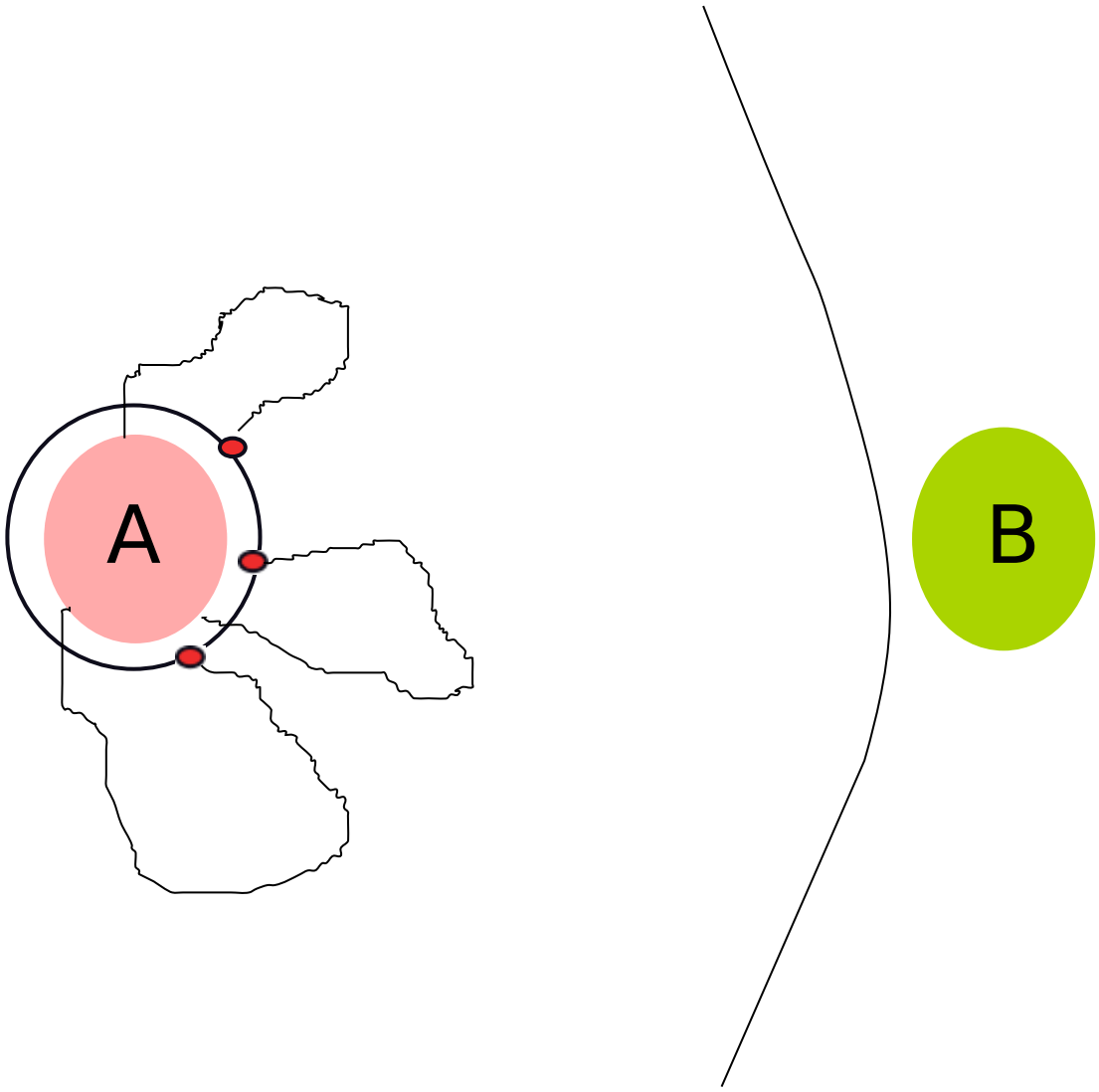
Therefore, an estimator of $\mathbb{P}(\tau_B < \tau_A)$ is

$$\left(1 - \frac{k}{n}\right)^{Q_{\mathrm{iter}}} \hat{p}_{\mathrm{corr}}.$$

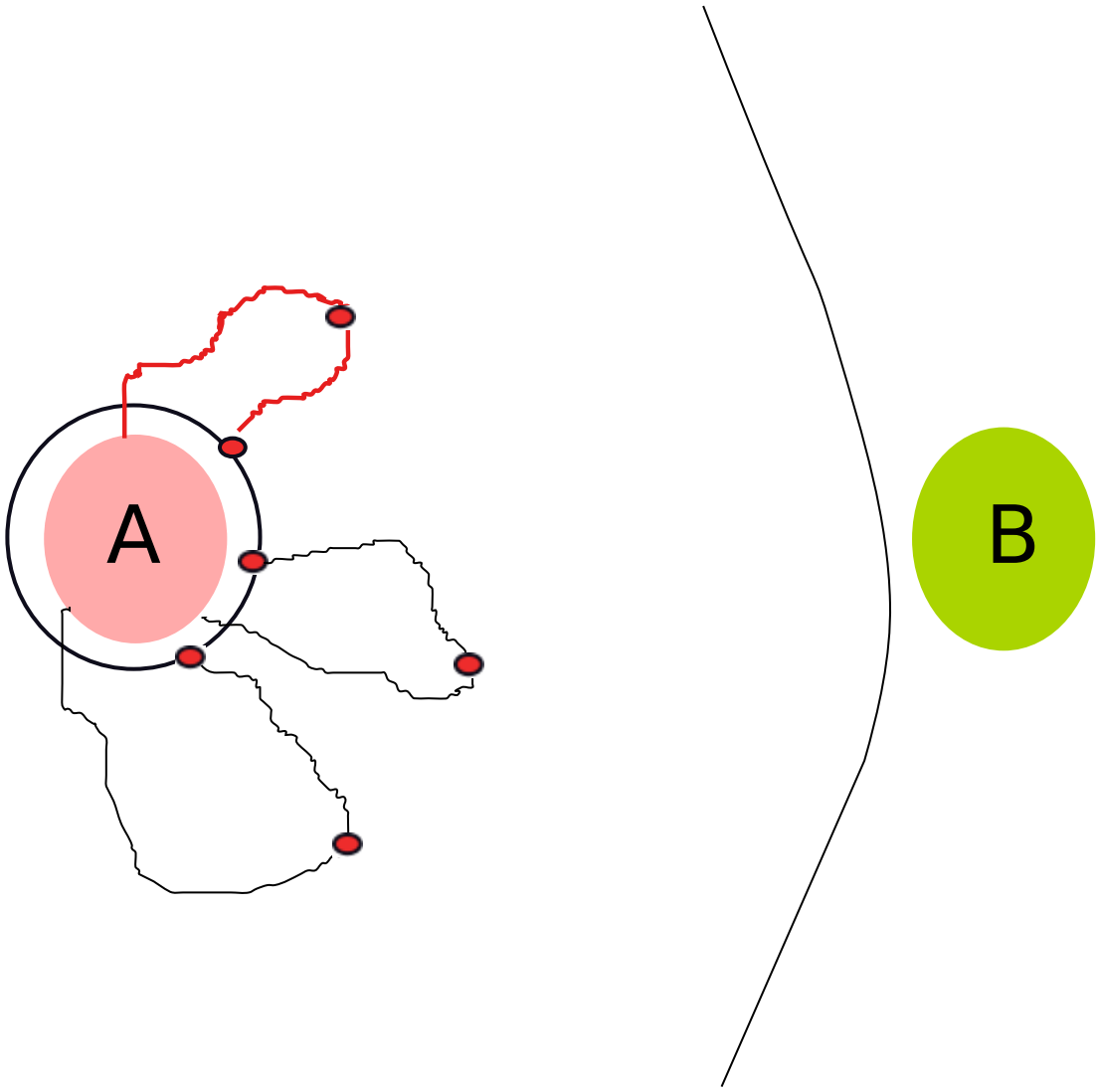
AMS Algorithm



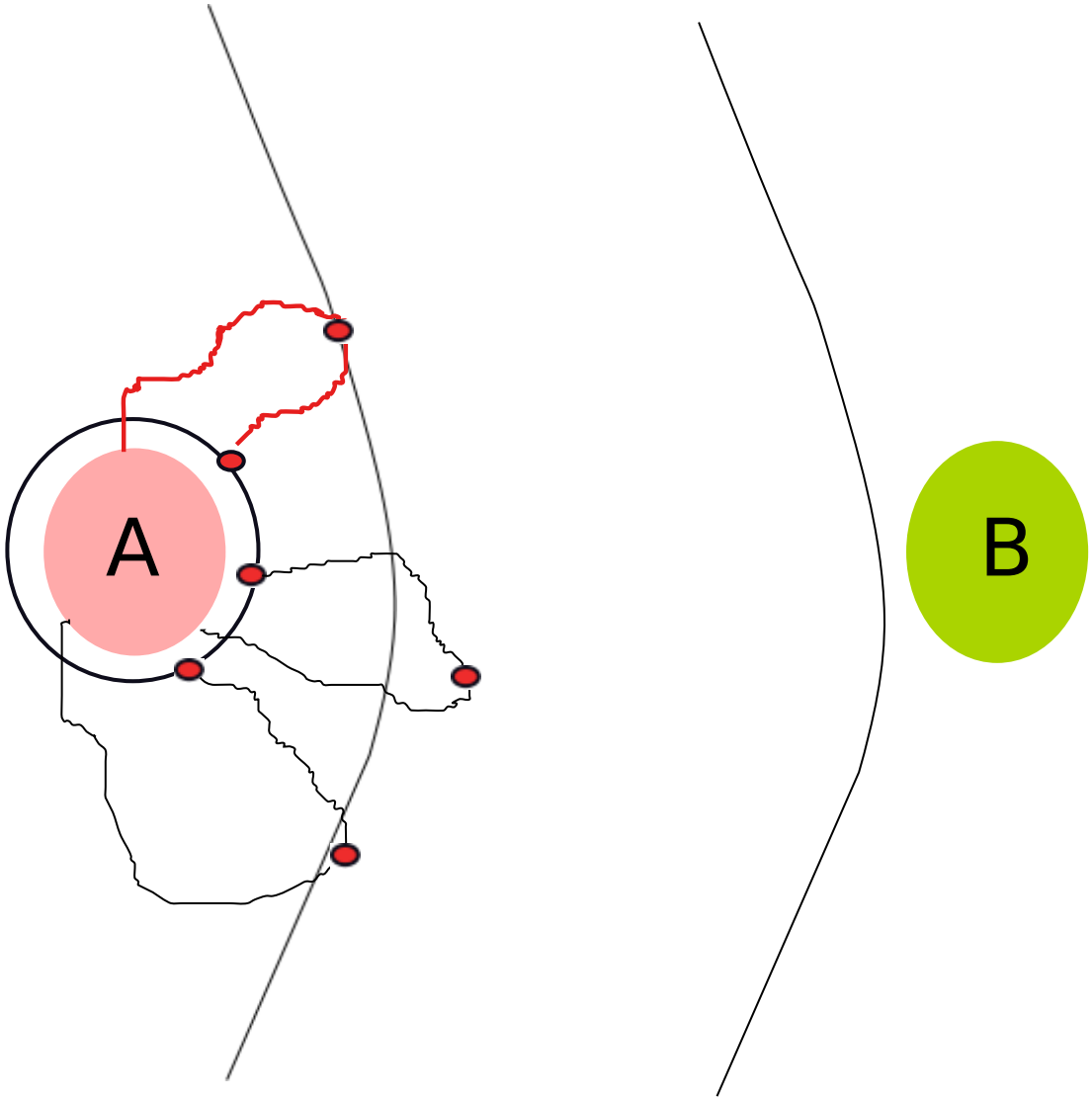
AMS Algorithm



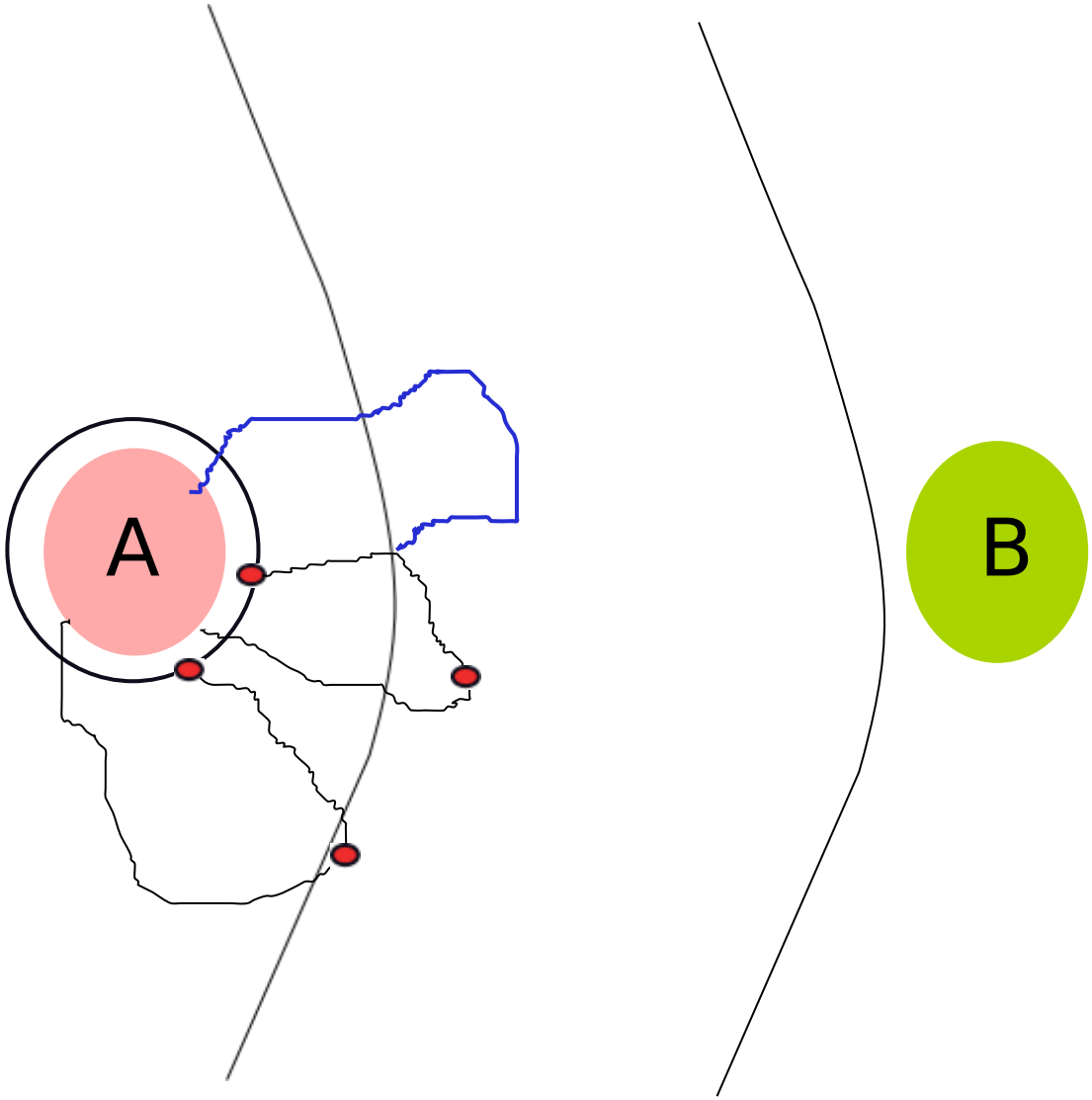
AMS Algorithm



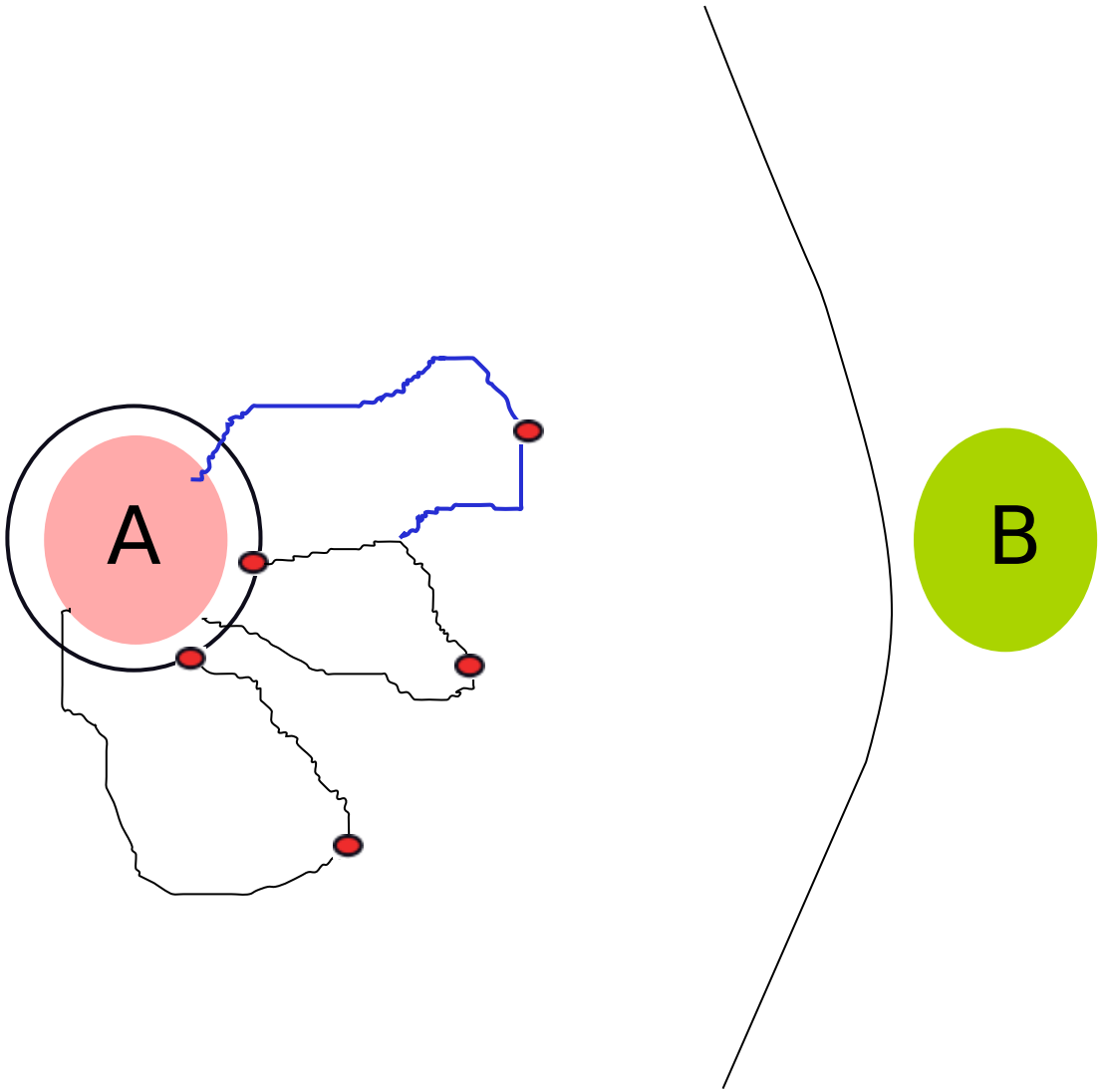
AMS Algorithm



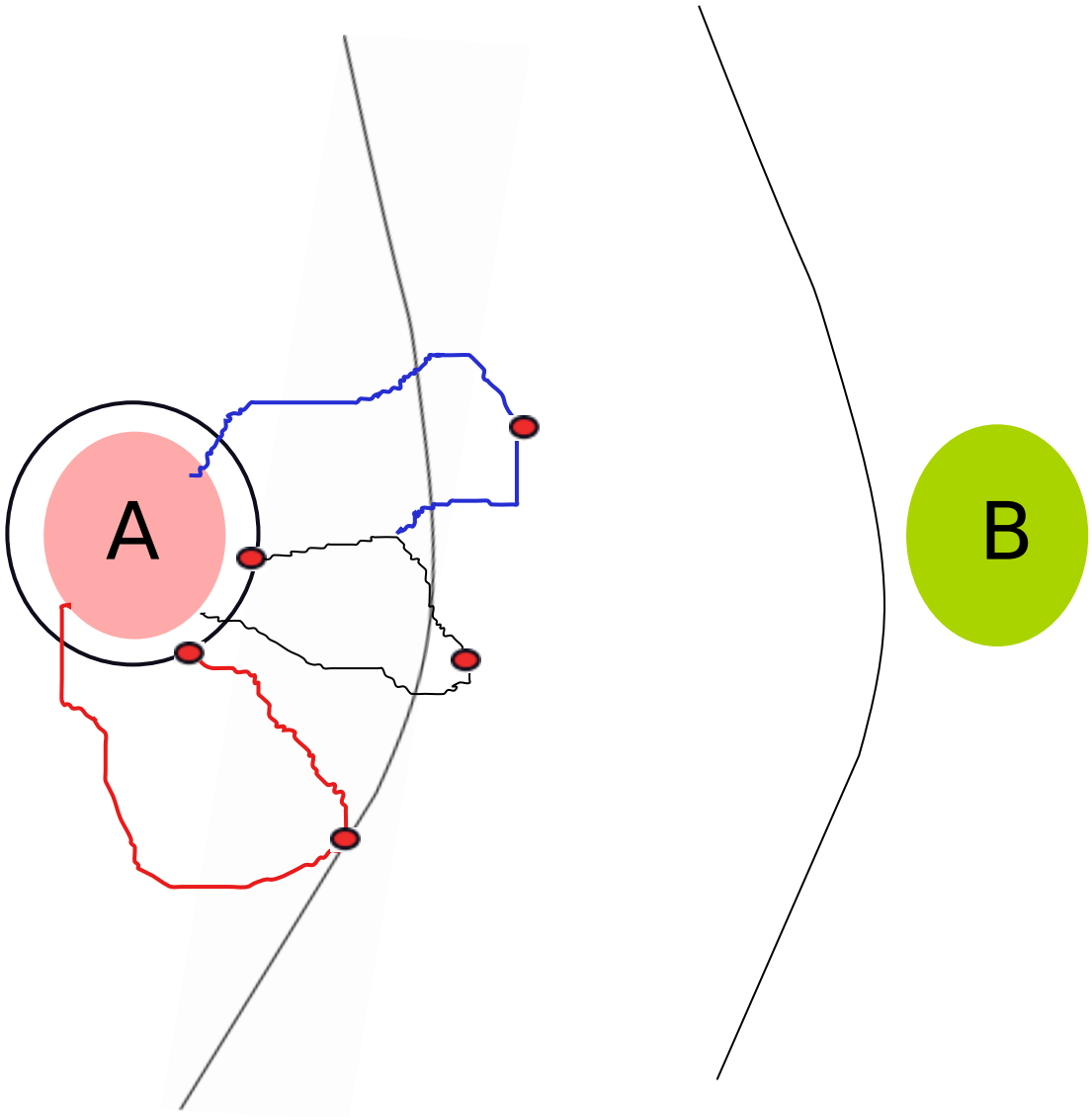
AMS Algorithm



AMS Algorithm



AMS Algorithm



AMS Algorithm: the case of Markov chains

In practice, the dynamics are *discrete in time* and thus, it may happen that more than k trajectories are such that

$$\sup_{t\geq 0} \xi(\boldsymbol{X}^{\ell}_{t\wedge\tau_A}) \leq \sup_{t\geq 0} \xi(\boldsymbol{X}^{(k)}_{t\wedge\tau_A}) =: z_q$$

In this case, all the trajectories with maximum level smaller or equal than z_q should be discarded.

The actual estimator of $\mathbb{P}(\tau_B < \tau_A)$ thus reads:

$$\hat{p} = \left(1 - \frac{K_1}{n}\right) \dots \left(1 - \frac{K_{Q_{\mathrm{iter}}}}{n}\right) \hat{p}_{\mathrm{corr}}$$

instead of $\left(1 - \frac{k}{n}\right)^{Q_{\mathrm{iter}}} \hat{p}_{\mathrm{corr}}$, where $K_q \geq k$ is the effective number of discarded trajectories at iteration q.

AMS Algorithm: unbiasedness

Theorem [C.-E. Bréhier, M. Gazeau, L. Goudenège, TL, M. Rousset, 2016]: For any choice of ξ, n and k,

$$\mathbb{E}(\hat{p}) = \mathbb{P}(\tau_B < \tau_A).$$

The proof is based on Doob's stopping theorem on a martingale built using filtrations indexed by the level sets of ξ. Actually, this result is proved for general path observables and in a much more general setting.

Practical counterparts:

- The algorithm is easy to parallelize.
- One can compare the results obtained with different reaction coordinates ξ to gain confidence in the results.

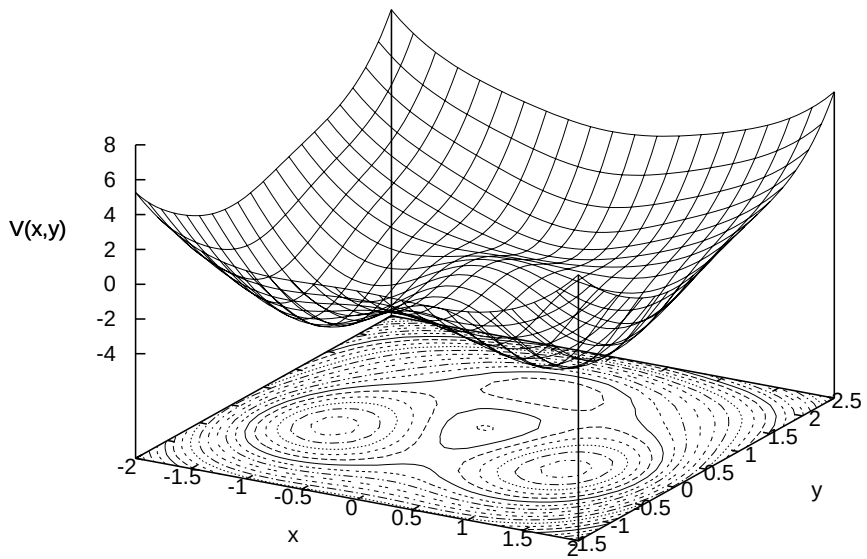
Numerical results: a 2D example

Time-discretization of the overdamped Langevin dynamics:

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

with a deterministic initial condition $\boldsymbol{X}_0 = \boldsymbol{x}_0$ and the 2D potential

[Park, Sener, Lu, Schulten, 2003] [Metzner, Schütte and Vanden-Eijnden, 2006]



$$V(x,y) = 3\mathrm{e}^{-x^2-(y-\frac{1}{3})^2} - 3\mathrm{e}^{-x^2-(y-\frac{5}{3})^2} - 5\mathrm{e}^{-(x-1)^2-y^2}$$
$$- 5\mathrm{e}^{-(x+1)^2-y^2} + 0.2x^4 + 0.2\left(y-\frac{1}{3}\right)^4.$$

A 2D example

The interest of this "bi-channel" potential is that, depending on the temperature, one or the other channel is prefered to go from A (around $H_- = (-1, 0)$) to B (around $H_+ = (1, 0)$).

Three reaction coordinates: $\xi^1(x, y) = \|(x, y) - H_-\|$, $\xi^2(x, y) = C - \|(x, y) - H_+\|$ or $\xi^3(x, y) = x$.

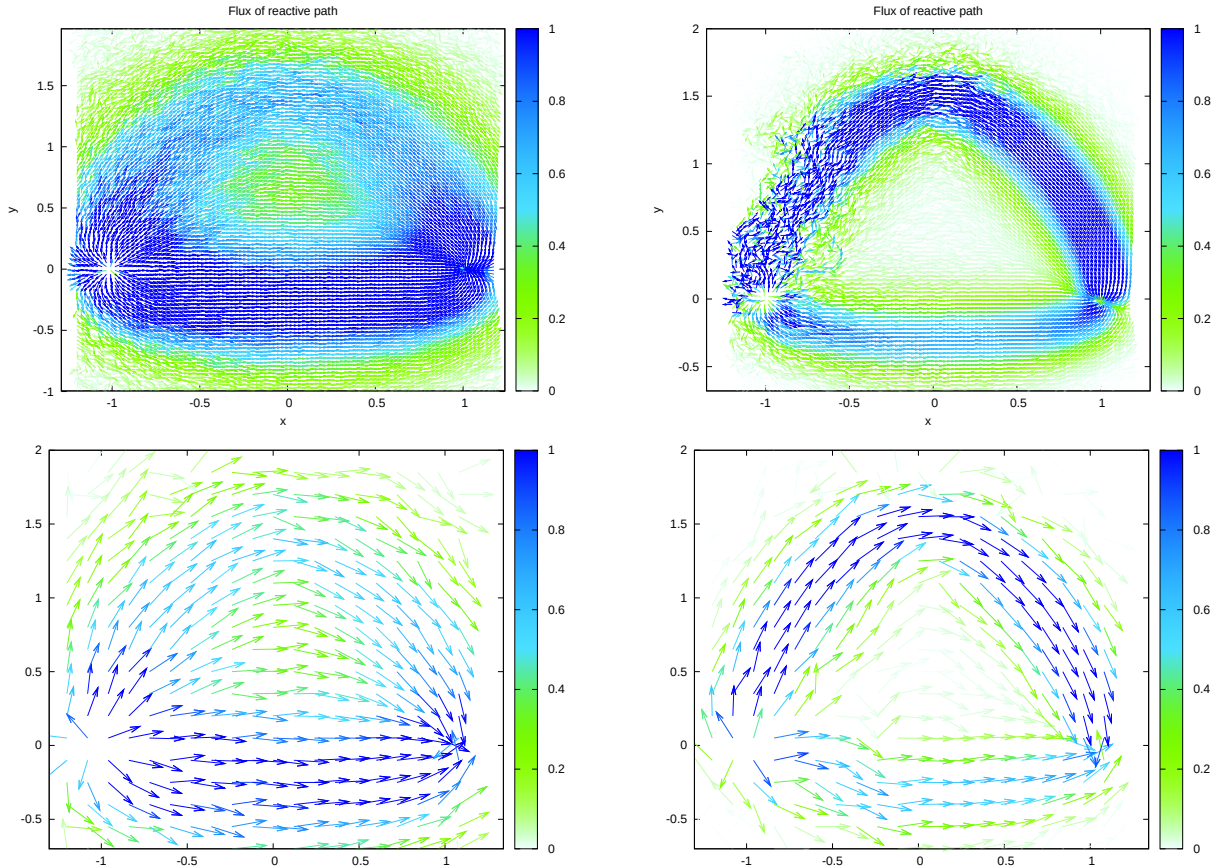
We plot as a function of the number N of independent realizations of AMS, the empirical average

$$\overline{p}_N = \frac{1}{N} \sum_{m=1}^{N} \hat{p}_m$$

together with the associated empirical confidence interval: $[\overline{p}_N - \delta_N/2, \overline{p}_N + \delta_N/2]$ where

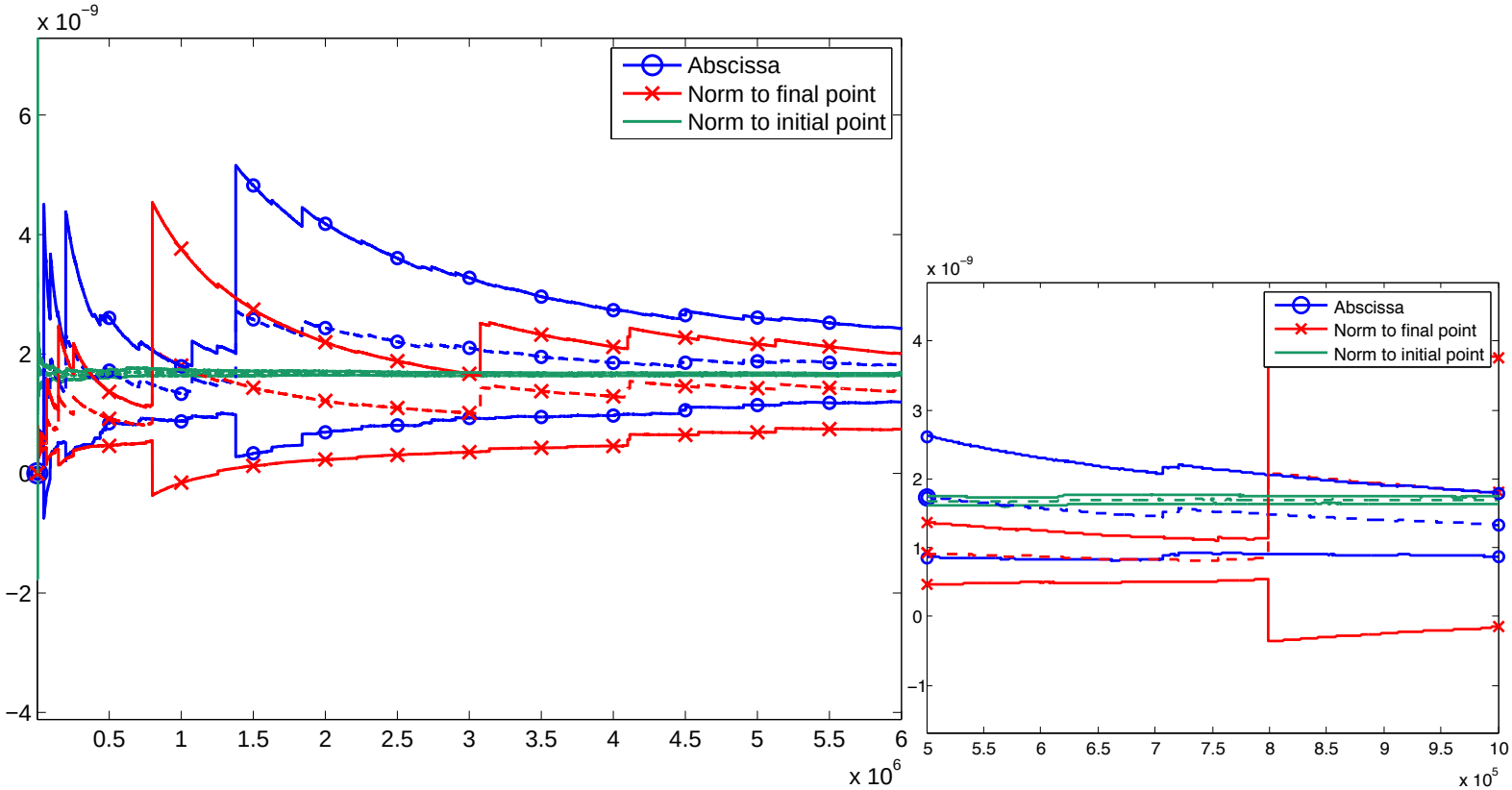
$$\delta_N = 2 \frac{1.96}{\sqrt{N}} \sqrt{\frac{1}{N} \sum_{m=1}^{N} (\hat{p}_m)^2 - (\overline{p}_N)^2}$$

A 2D example: flux of reactive trajectories

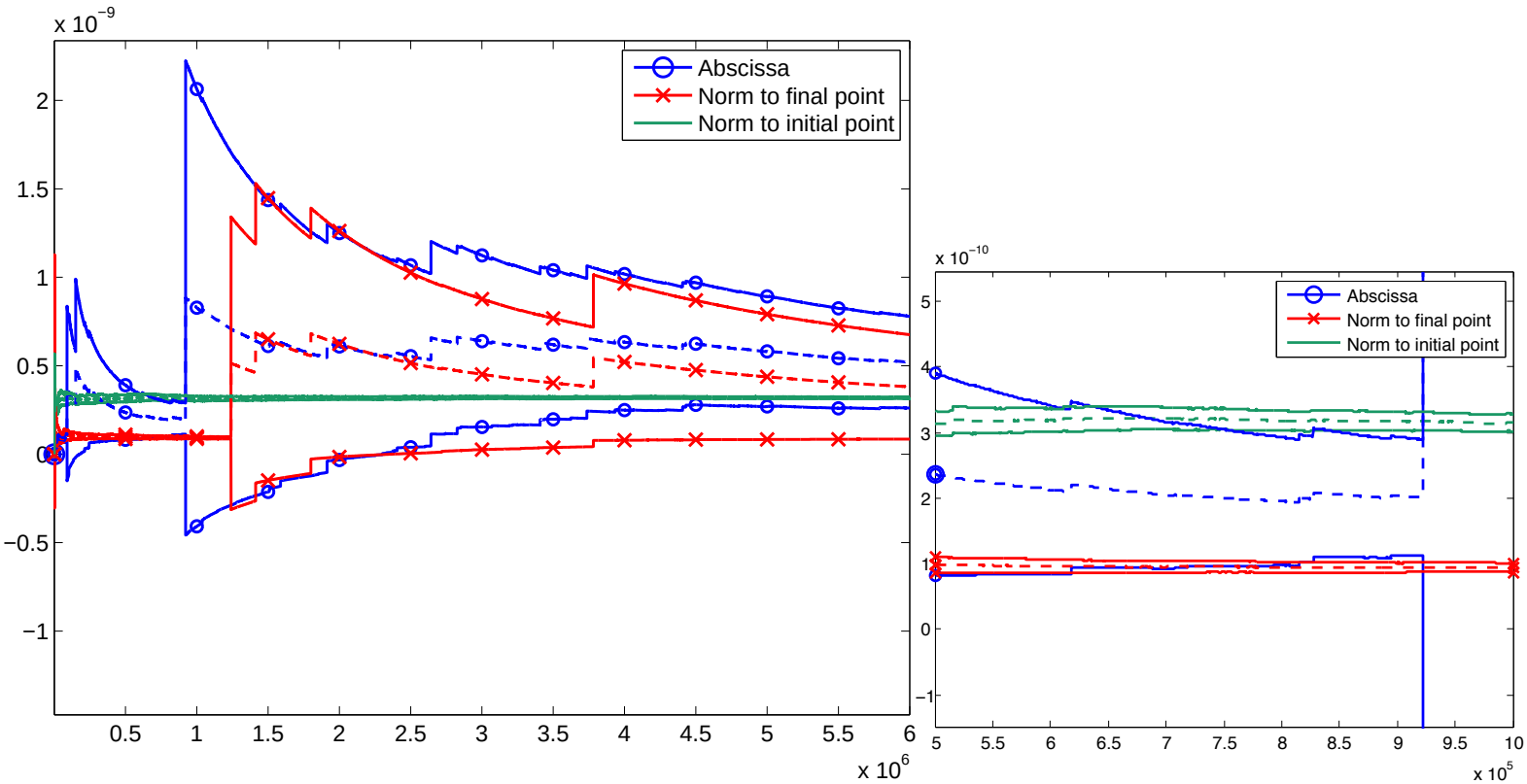


Flux of reactive trajectories, at $\beta = 1.67$ on the left, and $\beta = 6.67$ on the right.

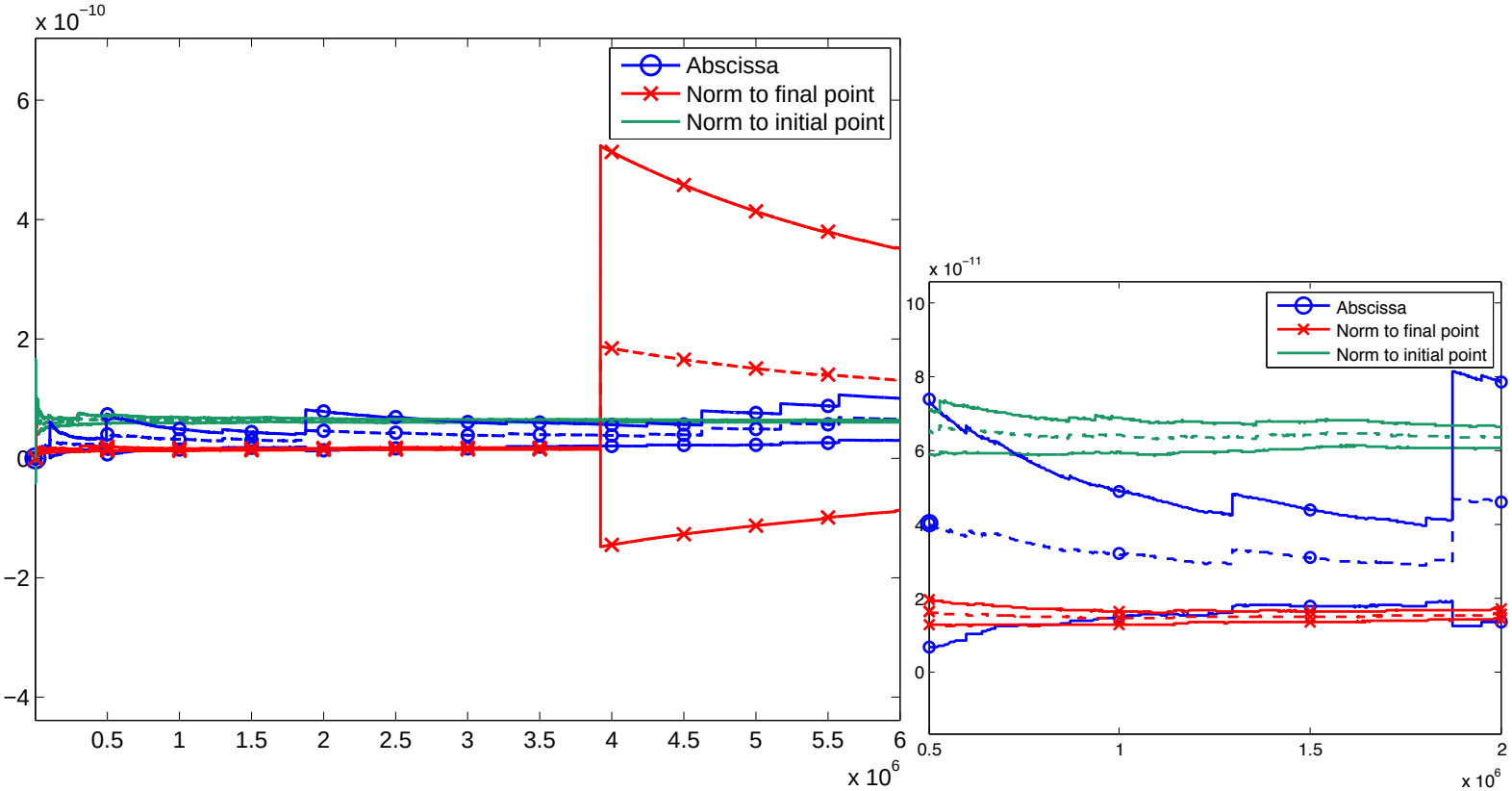
A 2D example: $k = 1$, $n = 100$, $\beta = 8.67$



A 2D example: $k = 1$, $n = 100$, $\beta = 9.33$



A 2D example: $k = 1$, $n = 100$, $\beta = 10$



A 2D example

Observations:

- When N is sufficiently large, confidence intervals overlap.
- For too small values of N, "apparent bias" is observed [Glasserman, Heidelberger, Shahabuddin, Zajic, 1998].
- Fluctuations depend a lot on ξ.

$\longrightarrow$ To gain confidence in the results, check that the estimated quantity is approximately the same for different ξ's.

"Apparent bias" phenomenon

The apparent bias is due to the fact that [Glasserman, Heidelberger, Shahabuddin, Zajic, 1998]:

- Multiple pathways exist to go from A to B.
- Conditionally to reach Σ_z before A, the relative likelihood of each of these pathways depends a lot on z.

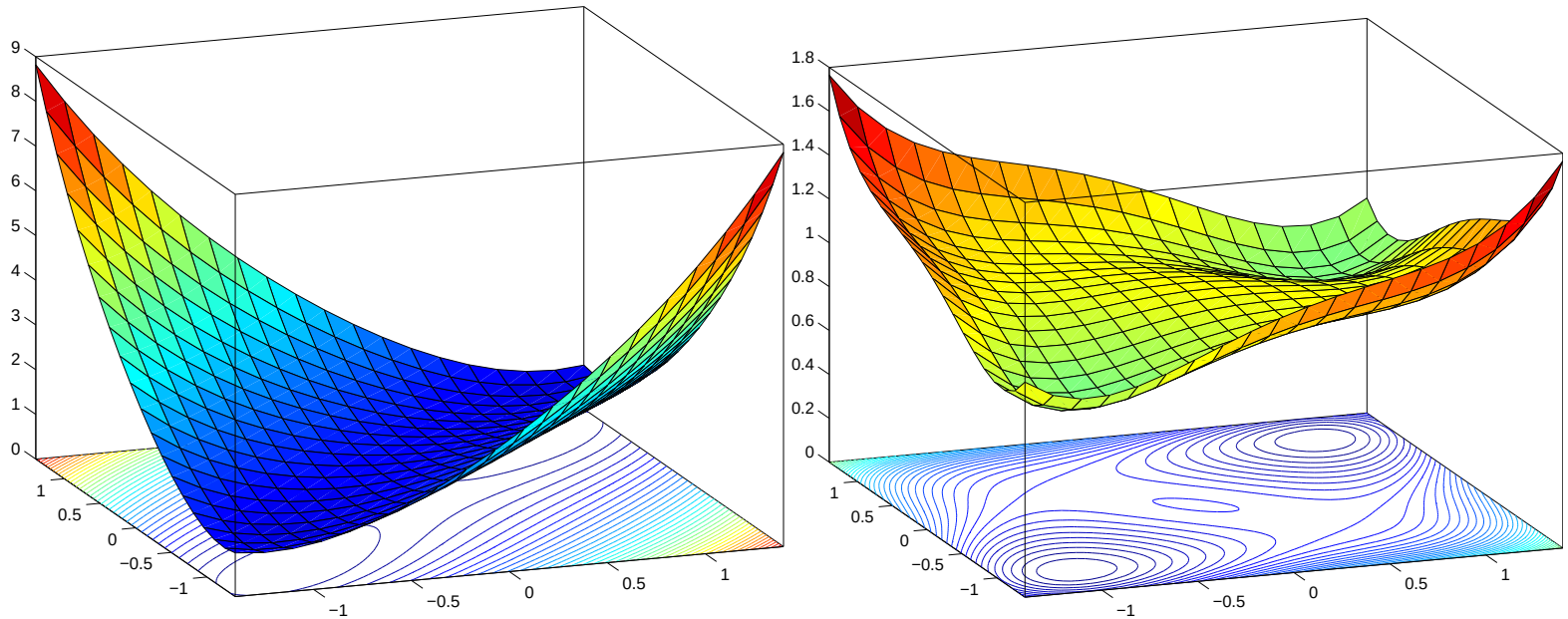
On our example, for small n, we indeed observe that (for ξ^3):

- Most of the time, all replicas at the end go through only one of the two channels (two possible scenarios).
- One of this scenario is rare.
- The values of $\hat{p}$ associated to each of these two scenarios are very different.

This explains the large fluctuations.

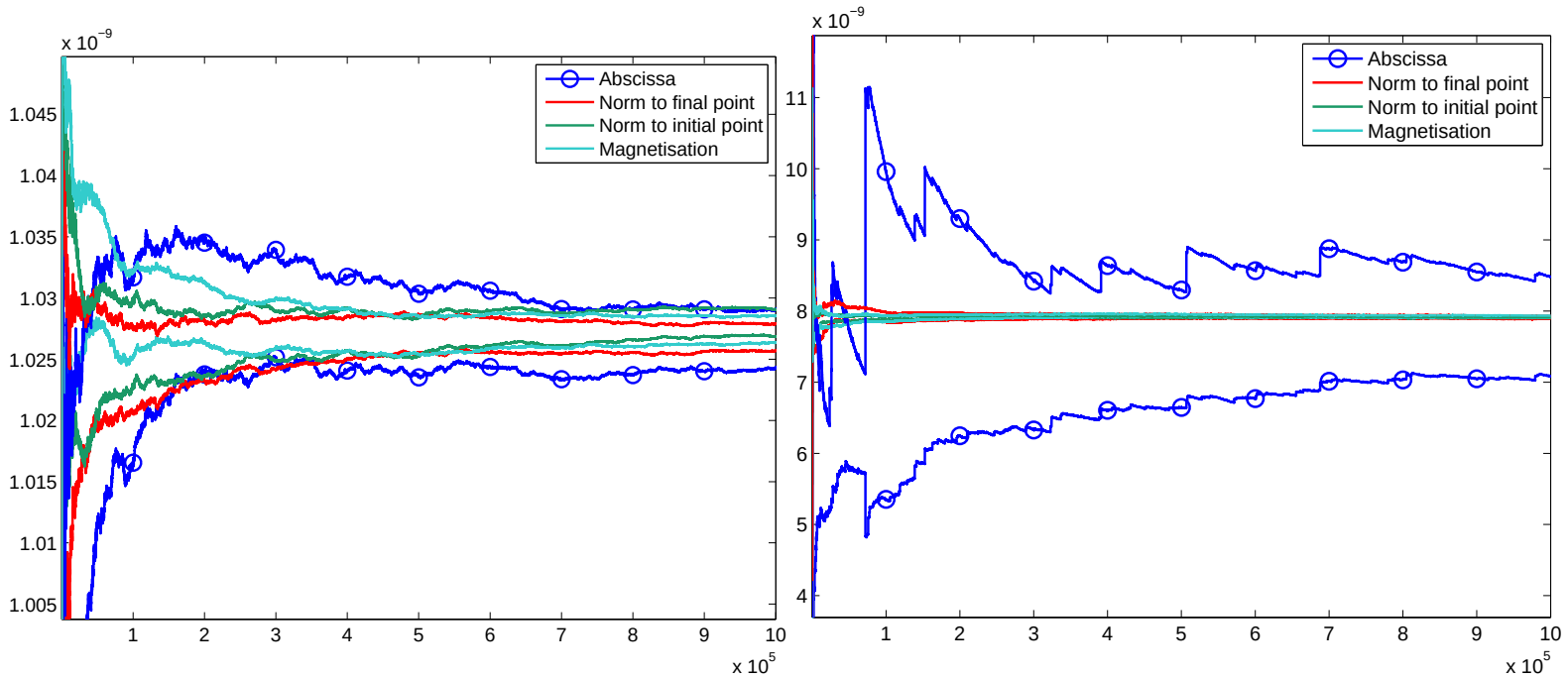
"Apparent bias" phenomenon

Another 2D test case:



Potential $V_\gamma(x, y)$.
Left: $\gamma = 1$ (one channel); right: $\gamma = 0.1$ (two channels).

"Apparent bias" phenomenon



Parameters: $k = 1$, $n = 100$ and $\beta = 80$.

Left: $\gamma = 1$ (one channel). Right: $\gamma = 0.1$ (two channels).

Computing transition times

To use the algorithm to compute transition times, we split a transition path from A to B into: excursions from ∂A to $\Sigma_{z_{\min}}$ and then back to ∂A, and finally an excursion from ∂A to $\Sigma_{z_{\min}}$ and then to B. Assuming that A is metastable ($p \ll 1$), one obtains that the mean transition time is:

$$\mathbb{E}(T) = \left(\frac{1}{p} - 1\right) \mathbb{E}(T_1 + T_2) + \mathbb{E}(T_1 + T_3)$$

where:

- p is the probability, once $\Sigma_{z_{\min}}$ has been reached, to go to B rather than A (approximated by $\hat{p}_N$) ;
- $\mathbb{E}(T_1 + T_2)$ is the mean time for an excursion from ∂A to $\Sigma_{z_{\min}}$ and then back to ∂A (approximated by DNS) ;
- $\mathbb{E}(T_1 + T_3)$ is the mean time for an excursion from ∂A to $\Sigma_{z_{\min}}$ and then to B (approximated by the AMS algorithm).

A 1D example

We consider the double-well potential:

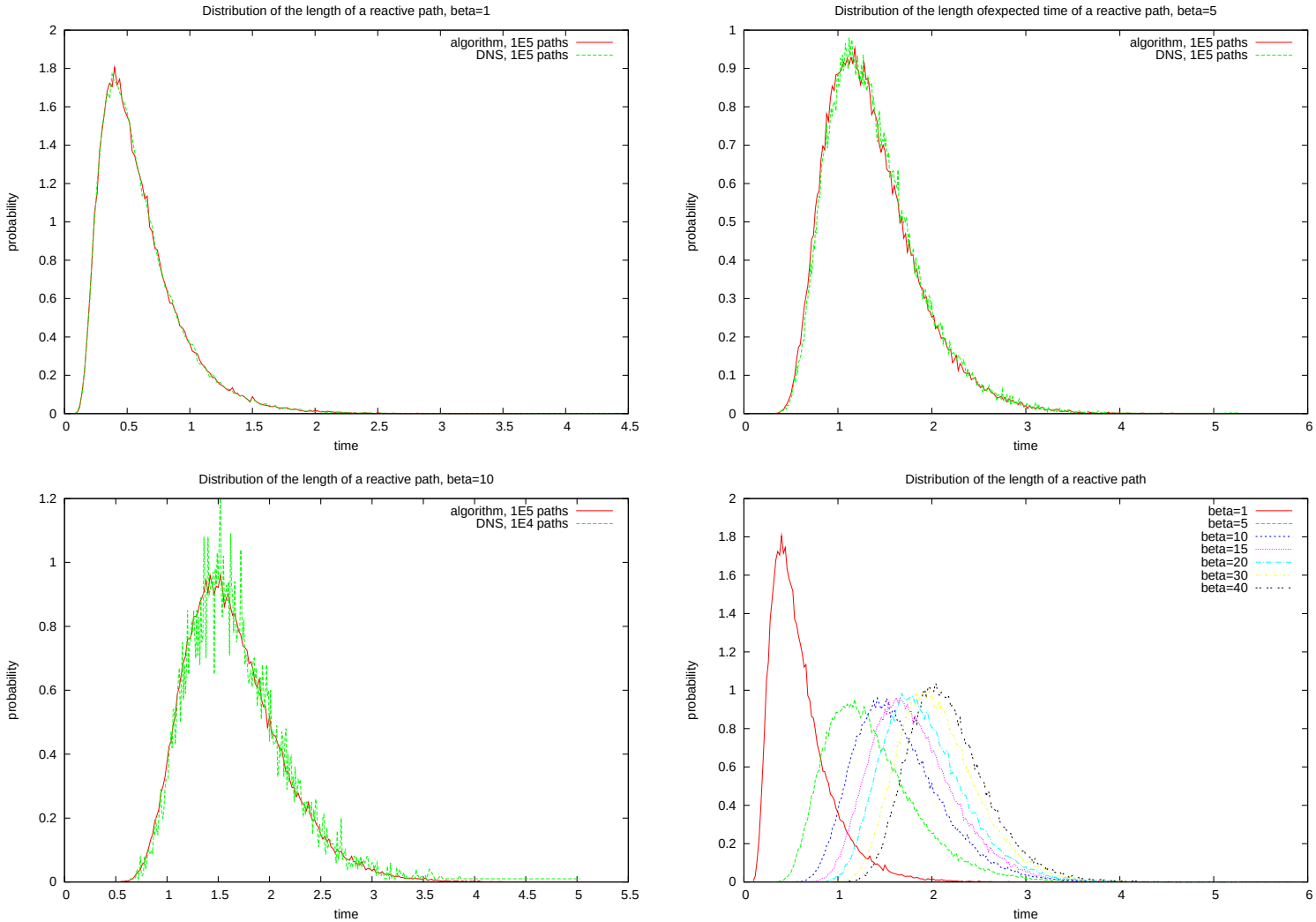
$$V(x) = x^4 - 2x^2,$$

which has two minima at ± 1 and one saddle point at 0.
In this simple one dimensional setting, we set as metastable states $A = \{-1\}$ and $B = \{+1\}$, and the reaction coordinate is taken to be simply

$$\xi(x) = x.$$

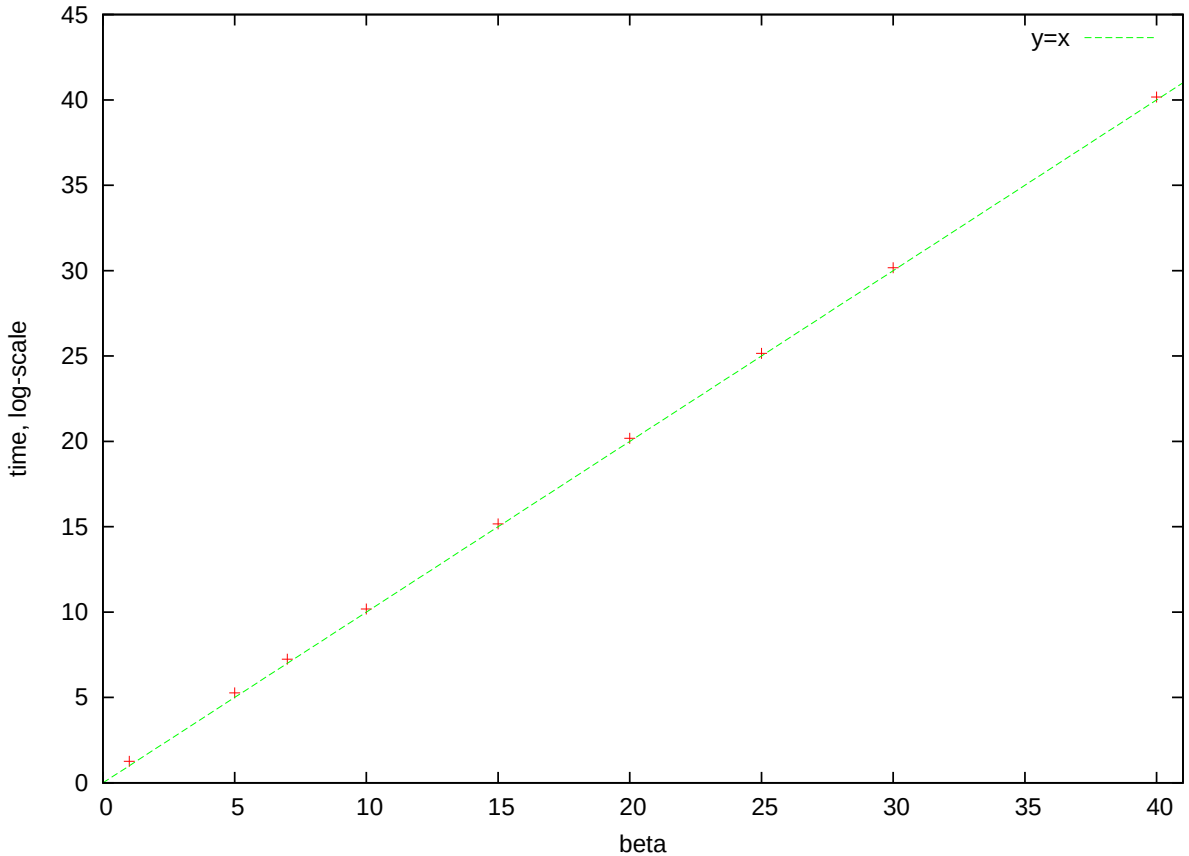
To test the consistency of the algorithm, we compute the distribution of the time-lengths of the reactive paths and compare to DNS (when possible).

A 1D example



Distributions of time-lengths of reactive paths. Comparison with DNS for $\beta = 1, 5, 10$ and distributions for $\beta = 1, 5, 10, 15, 20, 30, 40$.

A 1D example



Comparison of the estimated mean transition times as a function of β with the asymptotic law from large deviation theory:

$$\mathbb{E}(T) \propto \exp(\beta \Delta V)$$

where $\Delta V = 1$ is the height of the energy barrier.

The 2D case

N $\times 10^3$	β	k_{AB} (AMS)	C.I. on k_{AB} (AMS)
2	1.67	$2.03\ 10^{-2}$	$[1.83; 2.22]\ 10^{-2}$
10	1.67	$1.84\ 10^{-2}$	$[1.82; 1.86]\ 10^{-2}$
50	1.67	$1.88\ 10^{-2}$	$[1.87; 1.88]\ 10^{-2}$
100	1.67	$1.89\ 10^{-2}$	$[1.89; 1.90]\ 10^{-2}$
2	6.67	$9.97\ 10^{-8}$	$[7.74; 12.2]\ 10^{-8}$
10	6.67	$9.20\ 10^{-8}$	$[7.71; 10.7]\ 10^{-8}$
50	6.67	$8.88\ 10^{-8}$	$[8.42; 9.34]\ 10^{-8}$
100	6.67	$9.32\ 10^{-8}$	$[9.08; 9.57]\ 10^{-8}$

Estimates of the reaction rate $k_{AB} = 2/\mathbb{E}(T)$, with $\xi = \xi_2$. Values from [Metzner, Schütte, Vanden-Eijnden, 2006] are $k_{AB} = 1.912\ 10^{-2}$ for $\beta = 1.67$ and $k_{AB} = 9.47\ 10^{-8}$ for $\beta = 6.67$.

Recent results using NAMD

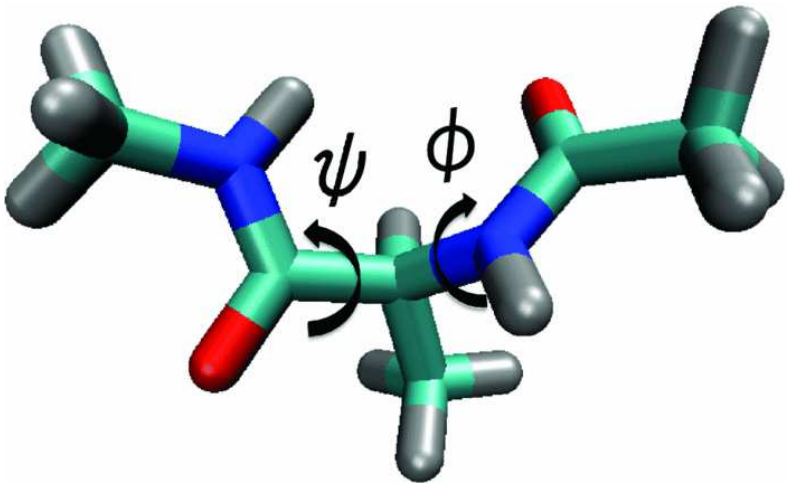
We are currently implementing AMS in the NAMD software

(collaboration with SANOFI, C. Mayne and I. Teo, PhD of L. Silva Lopes).

Three test cases:

- Alanine di-peptide (test case)
- β-cyclodextrin (in progress)
- benzamidine-trypsin dissociation rate

Alanine di-peptide (1/5)

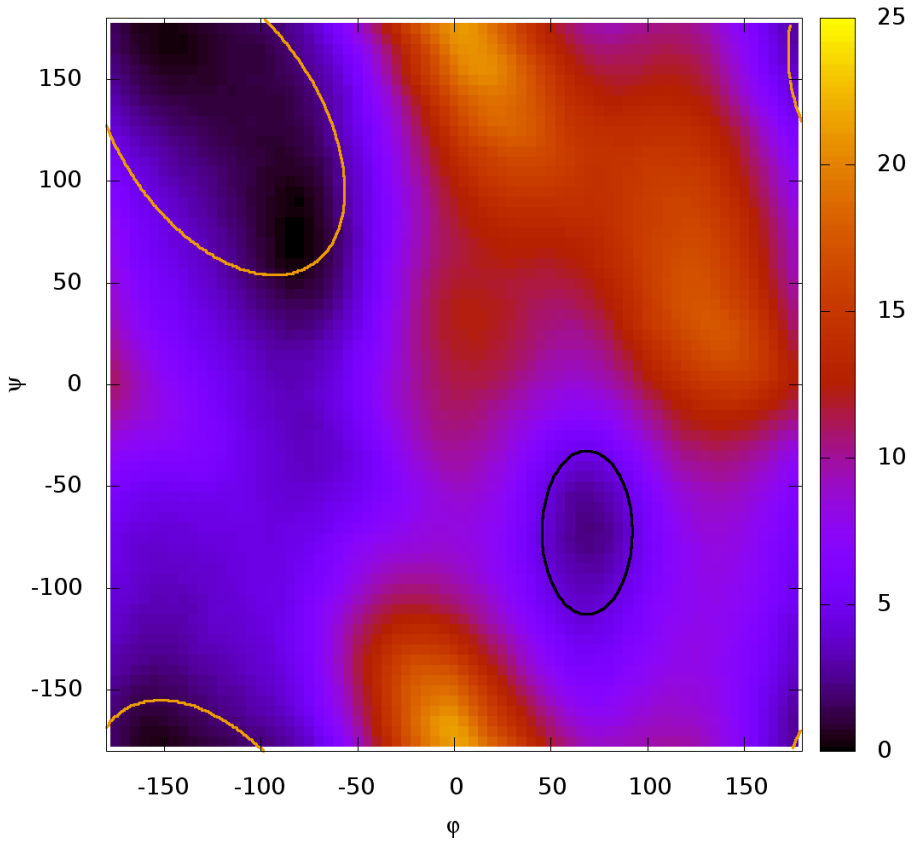


Two reaction coordinates:

- ξ_1 is a continuous piecewise affine function of φ
- $\xi_2(\varphi, \psi) = \min(d_A(\varphi, \psi), 6.4) - \min(d_B(\varphi, \psi), 3.8)$

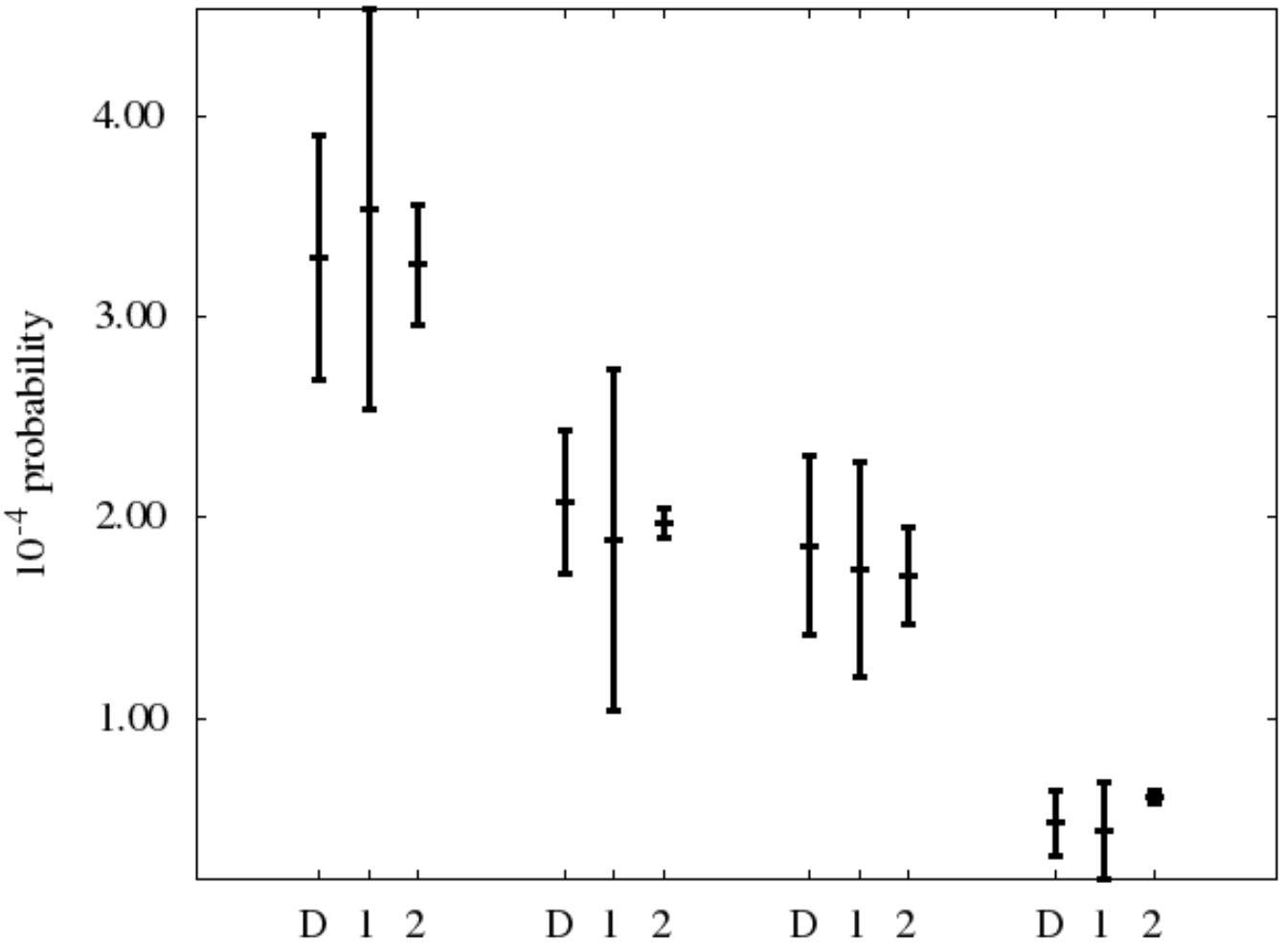
Computational setting: no solvent, force field: CHARMM27. AMS with $n = 500$ to 1000 replicas and $k = 1$.

Alanine di-peptide (2/5)



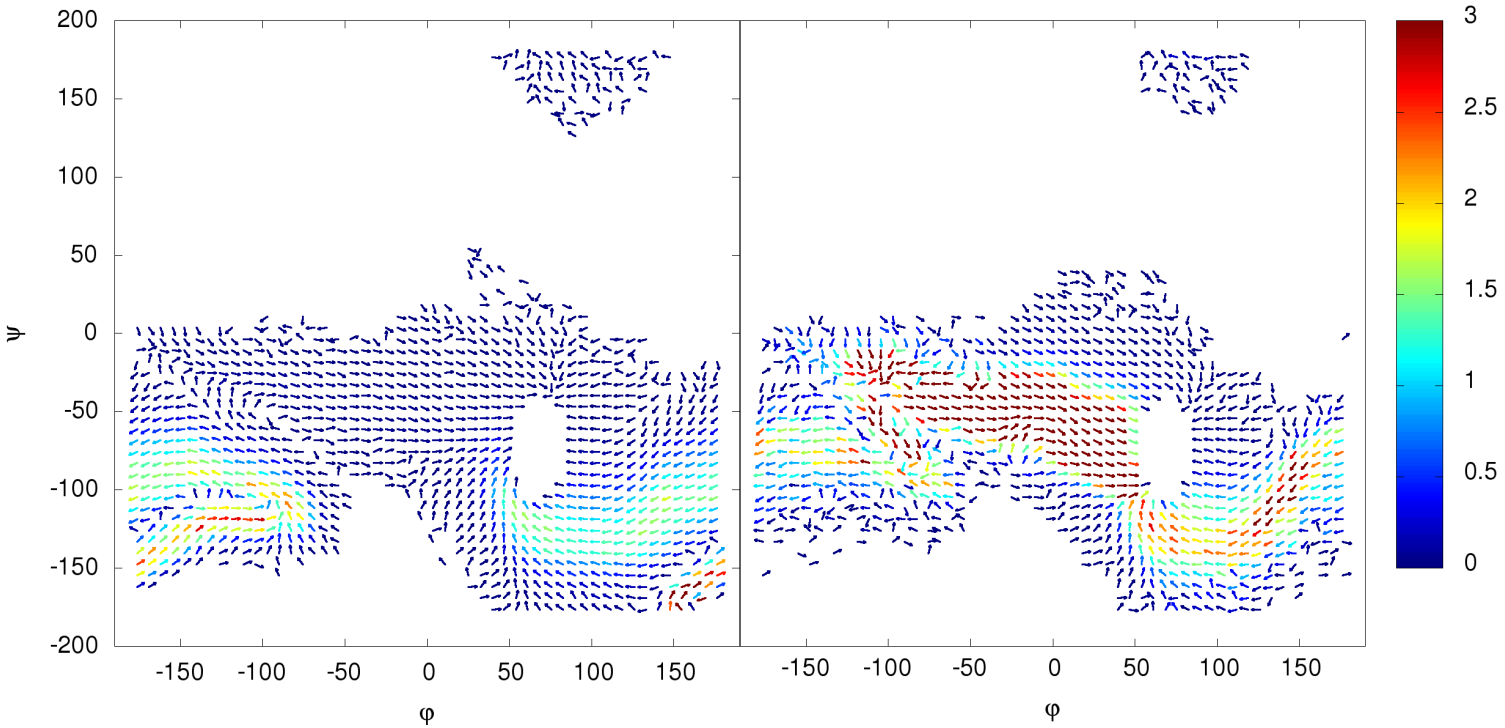
Free energy landscape and zones A (yellow) and B (black).

Alanine di-peptide (3/5)



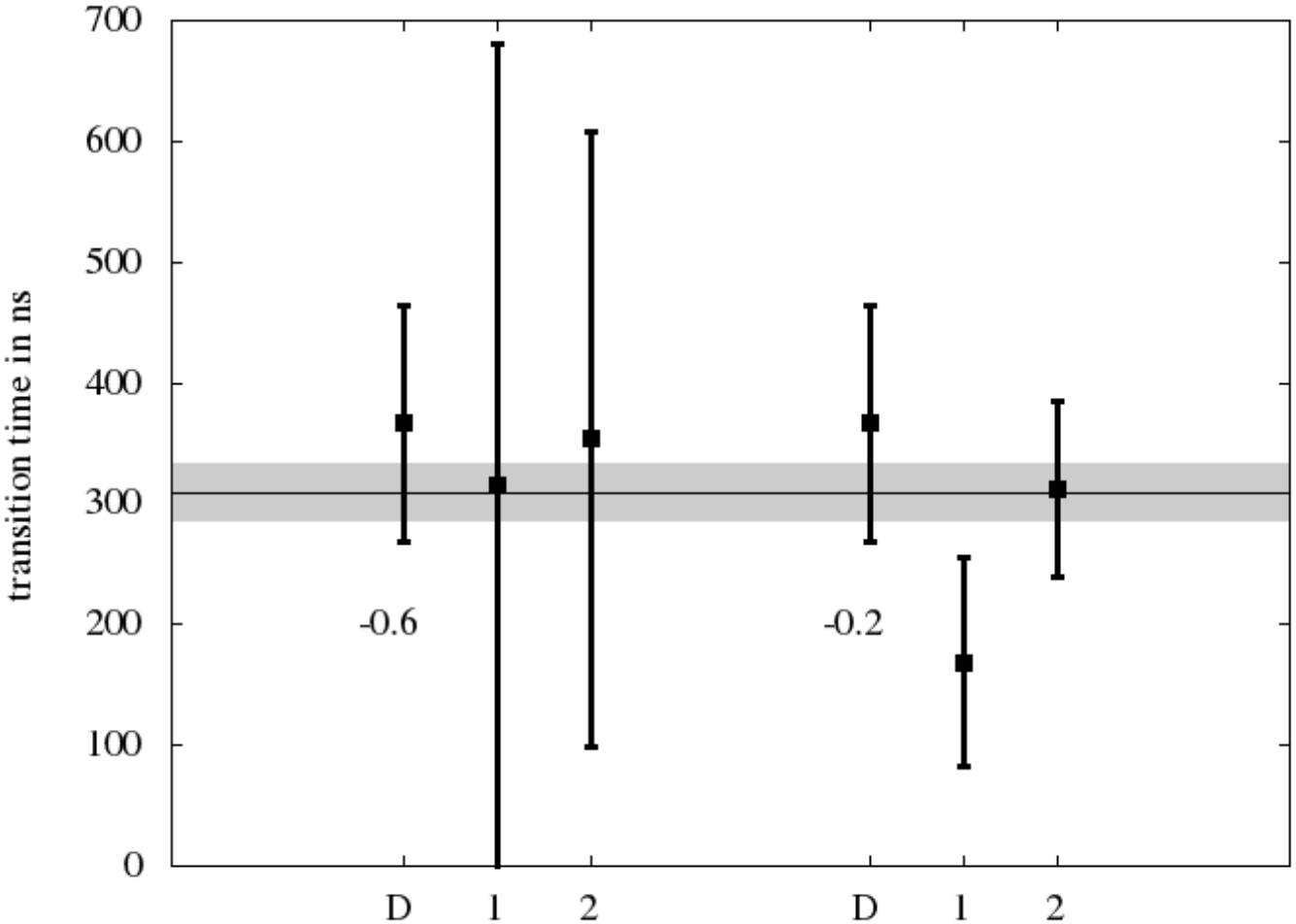
Probability estimations using different initial conditions: D=DNS, 1=ξ_1, 2=ξ_2.

Alanine di-peptide (4/5)



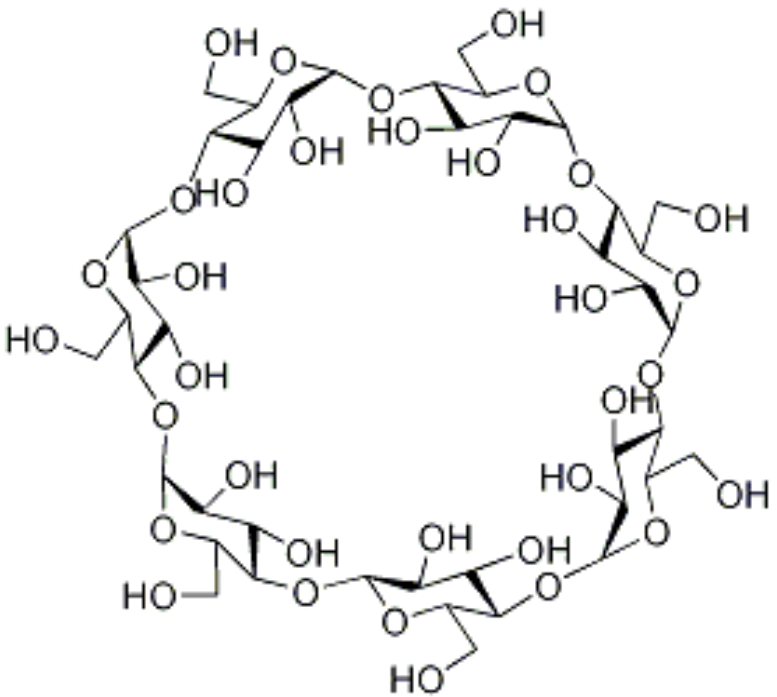
Flux of reactive trajectories, starting from two different initial conditions.

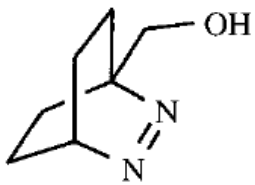
Alanine di-peptide (5/5)



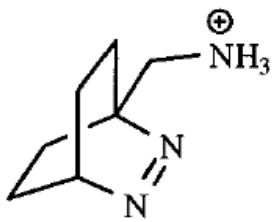
Transition time obtained for two values of z_{min}: D=DNS, 1=ξ_1, 2=ξ_2. Reference value obtained by DNS over a 97 DNS simulations of $2\mu s$.

β-cyclodextrin (1/3)





1d



1f

The β-cyclodextrin with ligands d and f.

β-cyclodextrin (2/3)

$\longrightarrow$ One reactive path obtained using AMS of the ligand 1f leaving the cyclodextrin.

Computational setting: explicit solvent, about 6000 atoms, 2fs time step, AMBER force field, parametrization with GAFF. AMS with $n = 50$ replicas and $k = 1$.

β-cyclodextrin (3/3)

Estimate of the dissocation rate with AMS:

- ligand d: 1.36e+08 ($\pm$ 1.e+08) fs (30 runs of AMS)
- ligand f: 2.65e+06 ($\pm$ 6.23+05) fs (57 runs of AMS)

Experimental values (from [X. Zhang, G. Gramlich, X. Wang and W. M. Nau, J. Am. Chem. Soc., 124 (2) 2002]):

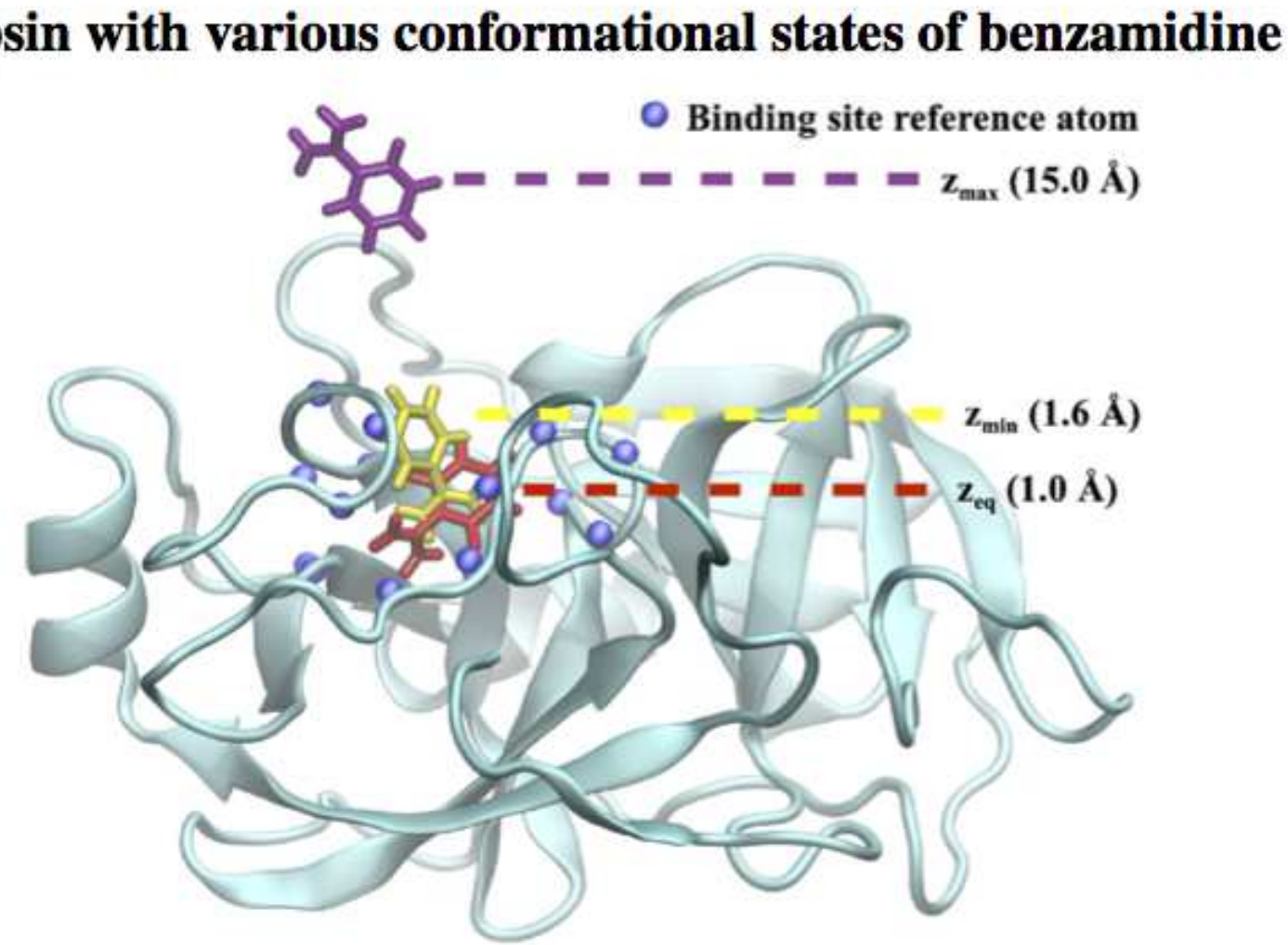
- ligand d: $5.55e+08$ fs
- ligand f: $8.33e+07$ fs

Computational times: AMS gives 50 trajectories, with a total simulation time = 4.4e+07 fs (d) ; 3.5e+07 fs (f).

... to be continued

Benzamidine-trypsin (1/2)

We recently used AMS to estimate the off rate of benzamidine from trypsin [I. Teo, C. Mayne, K. Schulten and TL, 2016].



Benzamidine-trypsin (2/2)

We obtain a dissociation rate $k_{\text{off}} = (260 \pm 240) s^{-1}$ within the same order of magnitude as the experimentally measured rate $(600 \pm 300) s^{-1}$.

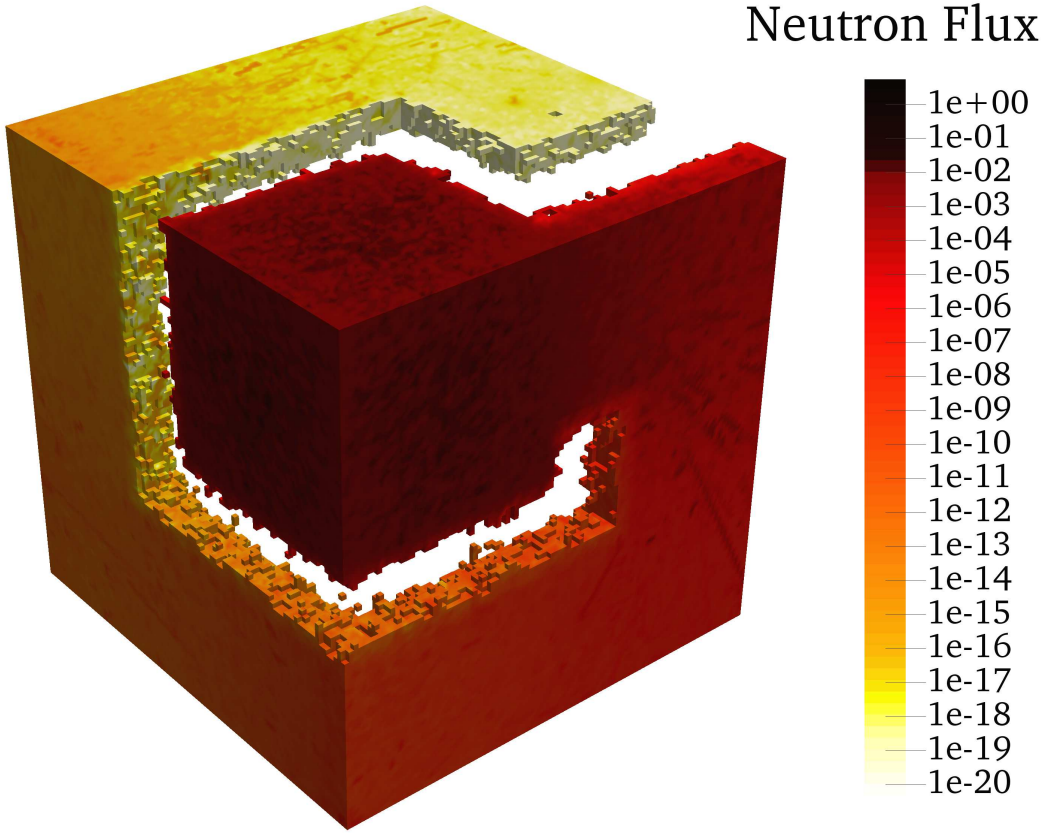
The overall simulation time taken, summed over all 1000 replicas, was $2.1 \mu s$ ($2.3 \mu s$ after including direct MD and steered MD simulations), which is four orders of magnitude shorter than the estimated dissociation time of one event.

The main practical difficulty seems to be the determination of a 'good' domain A.

Computational setting: 68 789 atoms, with 21 800 water molecules, 62 sodium ions, and 68 chloride ions. Water: TIP3P model. CHARMM36 force field, with parameters for benzamidine obtained from the CGenFF force field. NPT conditions, at 298 K and 1 atm Langevin thermostat and barostat settings, using 2 fs time steps. AMS with $n = 1000$ replicas and $k = 1$.

Another application

The AMS algorithm in other context: in collaboration with CEA, AMS is currently implemented in the Tripoli code for nuclear safety application.



Conclusions (1/2)

Practical recommendations:

- A careful implementation of the splitting step leads to unbiased estimators for non-normalized quantities.
- Perform many independent realizations of AMS.
- Use ξ as a numerical parameter.

The algorithm is very versatile:

- Non-intrusivity: the MD integrator is a black box.
- Can be applied both to entropic and energetic barriers.
- Can be adapted to generate trajectories of any stopped process.
- Other models: non-homogeneous Markov process, random fields, ...
- Algorithmic variants: other resampling procedure, additional selection, ...

Conclusions (2/2)

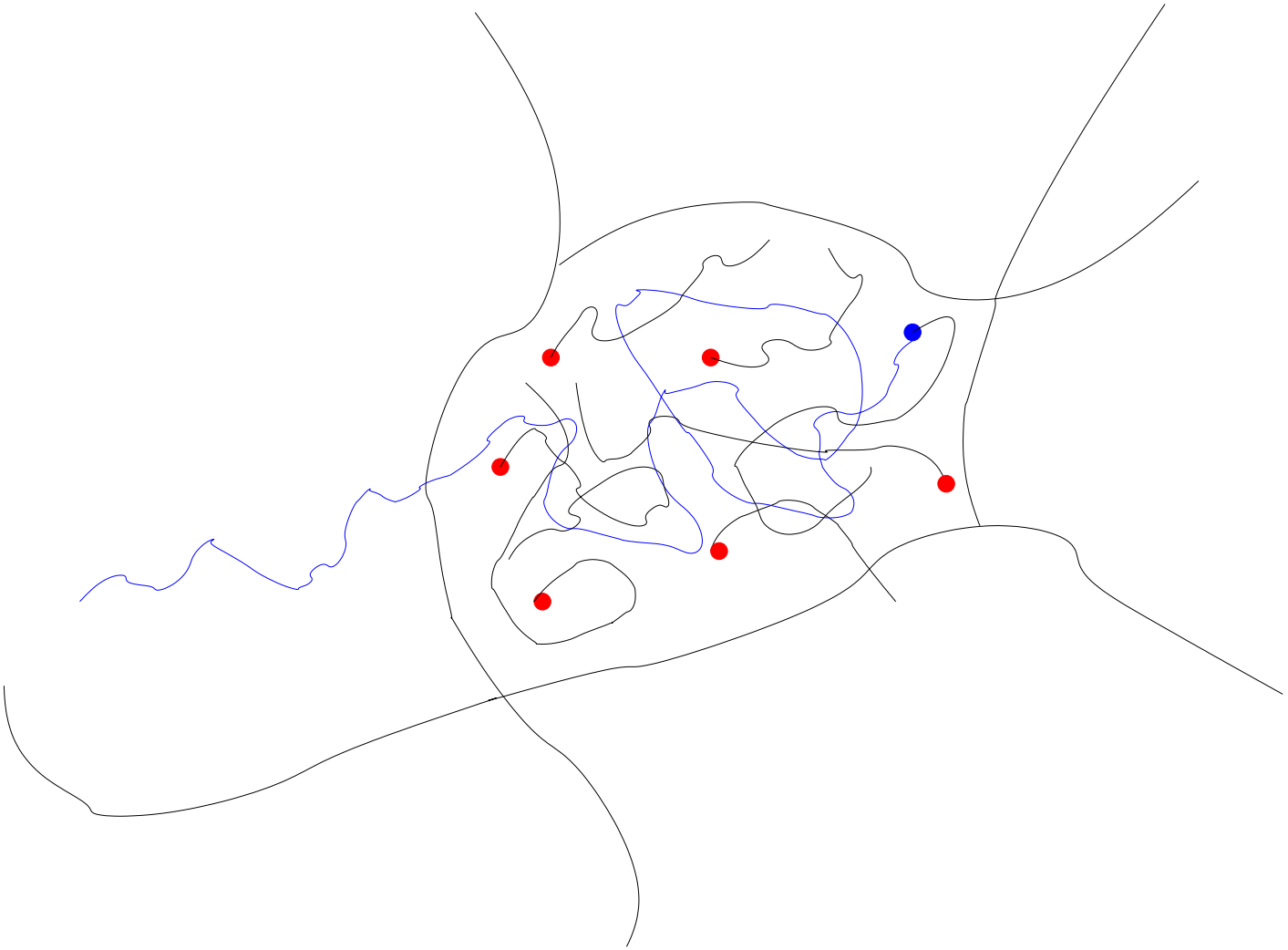
Works in progress:

- Implementation in the NAMD software (collaboration with SANOFI, C. Mayne and I. Teo), and in TRIPOLI (collaboration with CEA).
- Computation of the committor function and adaptive algorithm for the reaction coordinate ξ.
- Analysis of the efficiency as a function of ξ. For optimal choice of ξ, the cost of AMS is (for n large)

$$\left((\log p)^2 - \log p\right)$$

much better than the cost of naive Monte Carlo: $\frac{1-p}{p}$. How does this degrade when ξ departs from the optimal case ?

Accelerated dynamics



Accelerated dynamics

The aim of this part is twofold:

- First, discuss numerical methods to efficiently sample metastable dynamics: the accelerated dynamics algorithms proposed by A. Voter, D. Perez and collaborators.
- Second, justify rigorously kinetic Monte Carlo models which are used to simulate metastable dynamics over long times using a jump process between metastable states.

Both analysis will be based on the notion of quasi-stationary distribution.

Outline of this part:

- Introduction of the quasi-stationary distribution.
- Accelerated dynamics: Parallel Replica, Parsplicing, Hyperdynamics and Temperature Accelerated Dynamics.
- Precise asymptotic results of the first exit point density: justifying kinetic Monte Carlo models, the Harmonic Transition State Theory and the Eyring-Kramers formulas.

Accelerated dynamics

The bottom line of the accelerated dynamics proposed by A. Voter in the late 90's is to get efficiently the state-to-state dynamics. Three algorithms: Parallel replica, Hyperdynamics, Temperature Accelerated Dynamics.

Let us consider the overdamped Langevin dynamics:

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

and let assume that we are given a mapping

$$\mathcal{S} : \mathbb{R}^d \to \mathbb{N}$$

which to a configuration in $\mathbb{R}^d$ associates a state number. Think of a numbering of the wells of the potential V.

Objective: generate very efficiently a trajectory $(S_t)_{t\geq 0}$ which has (almost) the same law as $(\mathcal{S}(\boldsymbol{X}_t))_{t\geq 0}$.

The Quasi-Stationary Distribution

How to take advantage of metastability to build efficient sampling techniques ?

Let us consider a metastable state W, and

$$T_W = \inf\{t \geq 0, \boldsymbol{X}_t \notin W\}.$$

Lemma: Let $\boldsymbol{X}_t$ start in the well W. Then there exists a probability distribution ν with support W such that

$$\lim_{t\to\infty} \mathcal{L}(\boldsymbol{X}_t | T_W > t) = \nu.$$

Remark: Quantitative definition of a metastable state:

exit time $\gg$ local equilibration time

The Quasi-Stationary Distribution

Property 1: $\forall t > 0$, $\forall A \subset W$,

$$\nu(A) = \frac{\displaystyle\int_W \mathbb{P}(\boldsymbol{X}_t^{\boldsymbol{x}} \in A,\, t < T_W^{\boldsymbol{x}})\, \nu(d\boldsymbol{x})}{\displaystyle\int_W \mathbb{P}(t < T_W^{\boldsymbol{x}})\, \nu(d\boldsymbol{x})}.$$

If $\boldsymbol{X}_0 \sim \nu$ and if $(\boldsymbol{X}_s)_{0 \leq s \leq t}$ has not left the well, then $\boldsymbol{X}_t \sim \nu$.

Property 2: Let $L = -\nabla V \cdot \nabla + \beta^{-1}\Delta$ be the infinitesimal generator of $(\boldsymbol{X}_t)$. Then the density u_1 of ν ($d\nu = u_1(\boldsymbol{x})d\boldsymbol{x}$) is the first eigenfunction of $L^* = \operatorname{div}(\nabla V + \beta^{-1}\nabla)$ with absorbing boundary conditions:

$$\begin{cases} L^* u_1 = -\lambda_1 u_1 \text{ on } W, \\ \quad u_1 = 0 \text{ on } \partial W. \end{cases}$$

The Quasi-Stationary Distribution

Property 3: If $\boldsymbol{X}_0 \sim \nu$ then,

- the first exit time T_W from W is exponentially distributed with parameter λ_1 ;
- T_W is independent of the first hitting point $\boldsymbol{X}_{T_W}$ on ∂W ;
- the exit point distribution is proportional to $-\partial_n u_1$: for all smooth test functions $\varphi : \partial W \to \mathbb{R}$,

$$\mathbb{E}^\nu(\varphi(\boldsymbol{X}_{T_W})) = -\frac{\displaystyle\int_{\partial W} \varphi\, \partial_n u_1 \, d\sigma}{\beta\lambda_1 \displaystyle\int_W u_1(x)\, dx}.$$

Link with kinetic Monte Carlo models (1/2)

Starting from the QSD in W, the exit event from W is Markovian: it can be rewritten as one step of a Markov jump process (kinetic Monte Carlo or Markov state model):

Link with kinetic Monte Carlo models (2/2)

Let us introduce $\lambda_1 = 1/\mathbb{E}(T_W)$ and

$$p(i) = \mathbb{P}(\boldsymbol{X}_{T_W} \in \partial W_i) = -\frac{\displaystyle\int_{\partial W_i} \partial_n u_1 \, d\sigma}{\beta\lambda_1 \displaystyle\int_W u_1(x)\, dx}.$$

To each possible exit region ∂W_i is associated a rate $k(i) = \lambda_1 p(i)$.
If $\tau_i \sim \mathcal{E}(k(i))$ are independent, then

- The exit time is $\min(\tau_1, \ldots, \tau_I)$;
- The exit region is $\arg\min(\tau_1, \ldots, \tau_I)$.

Escaping from a metastable state

How to use these properties to design efficient algorithms ?

Assume that the stochastic process remained trapped for a very long time in a metastable state W. How to accelerate the escape event from W, in a statistically consistent way ?

Remark: In practice, one needs to:

- Choose the partition of the domain into (metastable) states;
- Associate to each state an equilibration time (a.k.a. *decorrelation time*).

These are not easy tasks... we will come back to that.

Remark: All the algorithms below equally apply to the Langevin dynamics. The extensions of the mathematical results to the Langevin dynamics are not straightforward though...

The accelerated dynamics

Four numerical methods:

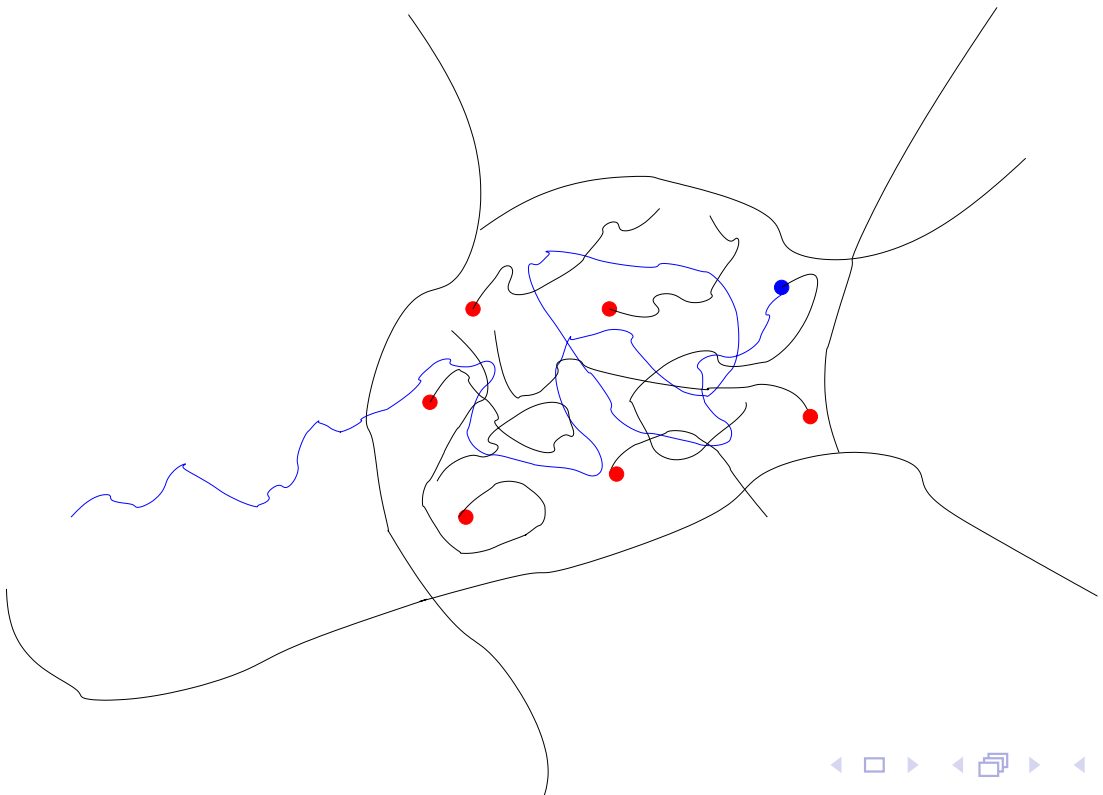
- The parallel replica algorithm
- The parsplicing algorithm
- The hyperdynamics
- The Temperature Accelerated Dynamics

The Parallel Replica Algorithm

Idea [Voter, 1998]: perform many independent exit events in parallel.

Two steps:

- Distribute N independent initial conditions in W according to the QSD ν ;
- Consider the first exit event, and multiply it by the number of replicas.



The Parallel Replica Algorithm

Why is it consistent ?

- Exit time is independent of exit point so that

$$\boldsymbol{X}^{I_0}_{T_W^{I_0}} \overset{\mathcal{L}}{=} \boldsymbol{X}^{1}_{T_W^{1}},$$

  where $I_0 = \arg\min_i(T_W^i)$;

- Exit times are i.i.d. exponentially distributed so that, for all N,

$$N \min(T_W^1, \ldots, T_W^N) \overset{\mathcal{L}}{=} T_W^1.$$

Remark: In practice, discrete time processes are used. Exponential laws become geometric, and one can adapt the algorithm by using the identity [Aristoff, TL, Simpson, 2014]: if τ_i i.i.d. with geometric law,

$$N[\min(\tau_1, \ldots, \tau_N) - 1] + \min[i \in \{1, \ldots, N\}, \tau_i = \min(\tau_1, \ldots, \tau_N)] \overset{\mathcal{L}}{=} \tau_1.$$

The Parallel Replica Algorithm

This algorithm is very versatile: it works for entropic barriers, and for any partition of the state space into states. But it requires some a priori knowledge on the system: the local equilibration time τ_{corr} attached to each state S.

Two questions: How to choose τ_{corr} ? How to sample the QSD ?

One can use a generalized Parallel Replica algorithm [Binder, TL, Simpson, 2014] to solve these issues. It is based on two ingredients:

- the Fleming-Viot particle process
- the Gelman-Rubin statistical test

The Fleming-Viot particle process

Start N processes i.i.d. from μ_0, and iterate the following steps:

1. Integrate (in parallel) N realizations ($k = 1, \ldots, N$)
$$d\boldsymbol{X}_t^k = -\nabla V(\boldsymbol{X}_t^k)\, dt + \sqrt{2\beta^{-1}} d\boldsymbol{W}_t^k$$
until one of them, say $\boldsymbol{X}_t^1$, exits;
2. Kill the process that exits;
3. With uniform probability $1/(N-1)$, randomly choose one of the survivors, $\boldsymbol{X}_t^2, \ldots, \boldsymbol{X}_t^N$, say $\boldsymbol{X}_t^2$;
4. Branch $\boldsymbol{X}_t^2$, with one copy persisting as $\boldsymbol{X}_t^2$, and the other becoming the new $\boldsymbol{X}_t^1$.

It is known that the empirical distribution

$$\mu_{t,N} \equiv \frac{1}{N} \sum_{k=1}^{N} \delta_{\boldsymbol{X}_t^k}$$

satisfies:

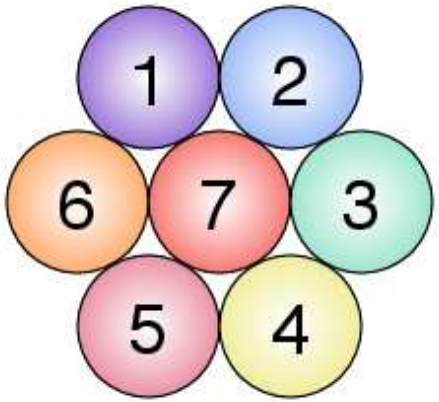
$$\lim_{N\to\infty} \mu_{t,N} = \mathcal{L}(\boldsymbol{X}_t | t < T_W).$$

The generalized Parallel Replica algorithm

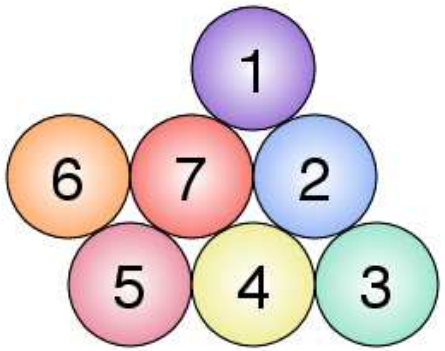
1. Run a reference walker, using standard MD.
2. Each time the reference walker enters a state, start a Fleming-Viot particle process (with N replicas simulated in parallel) with initial condition the entering point.
3. If the reference walker exits before the Fleming Viot particle process reaches stationarity go back to 1. Else go to the parallel step.
4. Parallel step: Starting from the end points of the Fleming-Viot particle process (approximately i.i.d. with law the QSD), run independent MD and consider the first exit event. Multiply the first exit time by N and go back to 1, using the first exit point as initial condition.

The time at which the Fleming-Viot particle process becomes stationary is determined using the Gelman-Rubin statistical test.

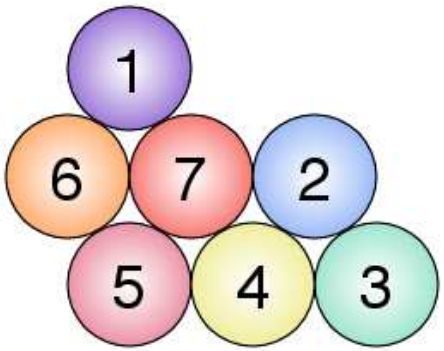
Numerical test case: the 7 atoms LJ cluster



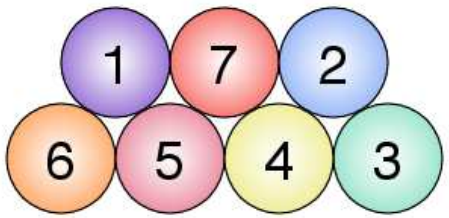
(a) C_0, $V = -12.53$



(b) C_1, $V = -11.50$



(c) C_2, $V = -11.48$



(d) C_3, $V = -11.40$

We study the escape from the configuration C_0 using overdamped Langevin dynamics with $\beta = 6$. The next visited states are C_1 or C_2.

Numerical test case: the 7 atoms LJ cluster

Method	TOL	$\langle T \rangle$	$\mathbb{P}[C_1]$	$\mathbb{P}[C_2]$
Serial	–	17.0	(0.502, 0.508)	(0.491, 0.498)
ParRep	0.2	19.1	(0.508, 0.514)	(0.485, 0.492)
ParRep	0.1	18.0	(0.506, 0.512)	(0.488, 0.494)
ParRep	0.05	17.6	(0.505, 0.512)	(0.488, 0.495)
ParRep	0 .01	17.0	(0.504, 0.510)	(0.490, 0.496)

Method	TOL	$\langle t_{\mathrm{corr}} \rangle$	$\langle$Speedup$\rangle$	% Dephased
Serial	–	–	–	–
ParRep	0.2	0.41	29.3	98.5%
ParRep	0.1	.98	14.9	95.3%
ParRep	0.05	2.1	7.83	90.0%
ParRep	0 .01	11	1.82	52.1%

Numerical test case: the 7 atoms LJ cluster

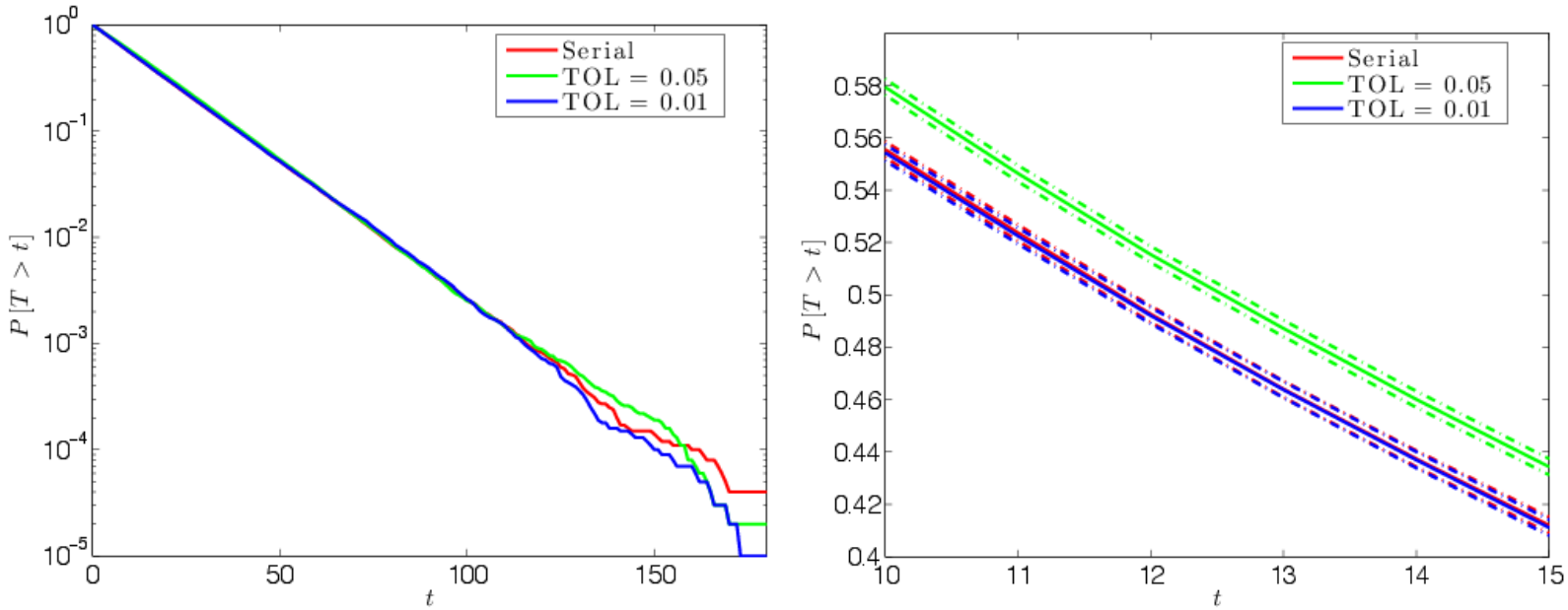
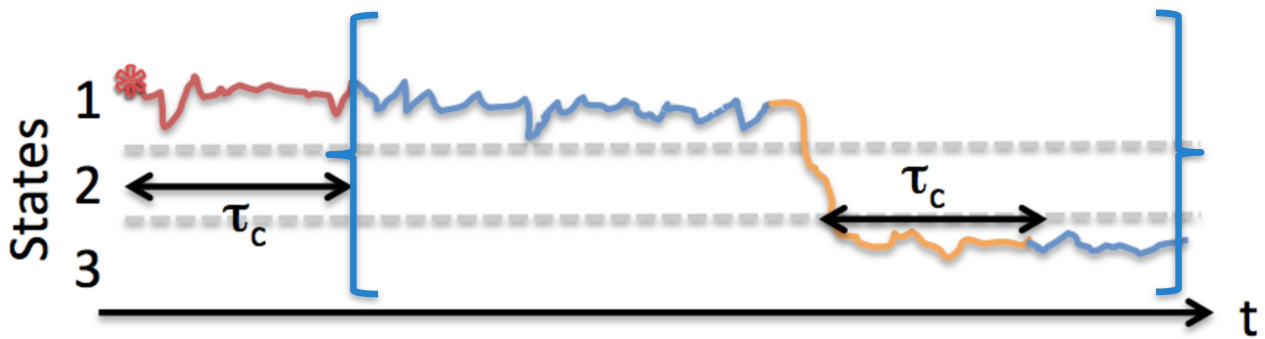


Figure: $\mathrm{LJ}_7^{\mathrm{2D}}$: Cumulative distribution function of the escape time from C_0.

The Parallel Trajectory Splicing algorithm

Idea [Perez, Cubuk, Waterland, Kaxiras, Voter, 2015]:

- Simulate in parallel short trajectories which start from the QSD in a state, and end at the QSD in a state.
- Glue together these short trajectories to build the full dynamics.

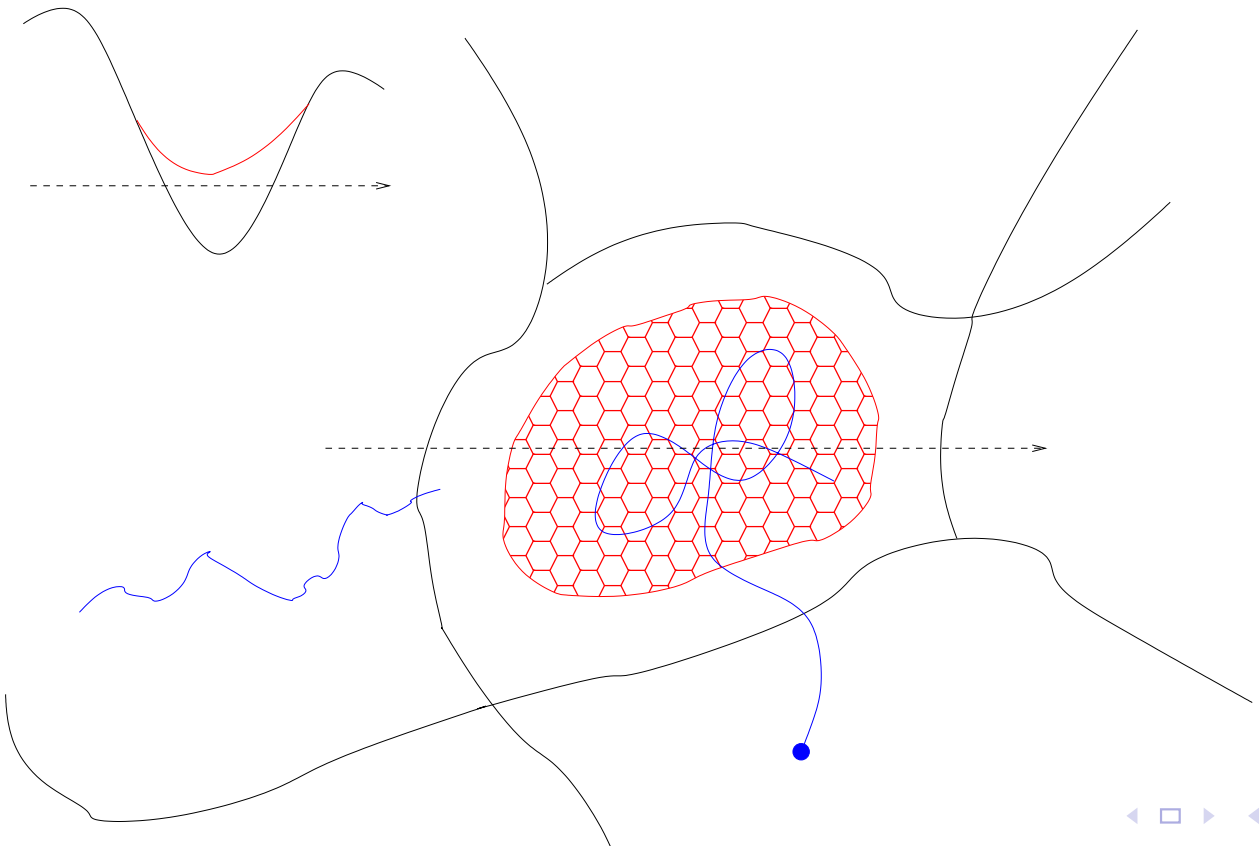


The Hyperdynamics

Idea [Voter, 1997]: raise the potential in W to reduce the exit time.

Two steps:

- Equilibrate on the biased potential $V + \delta V$;
- Wait for an exit and multiply the exit time $T_W^{\delta V}$ by the boost factor $B = \frac{1}{T_W^{\delta V}} \int_0^{T_W^{\delta V}} \exp(\beta\, \delta V(\boldsymbol{X}_t))\, dt$.



The Hyperdynamics

Why is it consistent ?

Recall property 3 go to Prop3. The underlying mathematical question is: how λ_1 and $\partial_n u_1$ are modified when V is changed to $V + \delta V$?

Recall that

$$\begin{cases} \operatorname{div}\left(\nabla V\, u_1 + \beta^{-1}\nabla u_1\right) = -\lambda_1 u_1 \text{ on } W, \\ u_1 = 0 \text{ on } \partial W. \end{cases}$$

Strategy: change u_1 to $u_1 \exp(V/2)$ and use results from semi-classical analysis for boundary Witten Laplacians in order to characterize $(\lambda_1, \partial_n u_1)$ in terms of V.

The Hyperdynamics: mathematical analysis

Assumptions on V. We assume there exists $W^- \subset\subset W$ such that:

- Regularity: V and $V|_{\partial W}$ are Morse functions ;
- Localization of the small eigenvectors in W^-:
  - (i) $|\nabla V| \neq 0$ in $\overline{W} \setminus W^-$,
  - (ii) $\partial_n V > 0$ on ∂W^- ,
  - (iii) $\min_{\partial W} V \geq \min_{\partial W^-} V$,
  - (iv) $\min_{\partial W^-} V - \mathrm{cvmax} > \mathrm{cvmax} - \min_{W^-} V$ where $\mathrm{cvmax} = \max\{V(x), x \text{ s.t. } |\nabla V(x)| = 0\}$;
- Non degeneracy of exponentially small eigenvalues: The critical values of V in W^- are all distinct and the differences $V(y) - V(x)$, where $x \in \mathcal{U}^{(0)}$ ranges over the local minima of $V|_{W^-}$ and $y \in \mathcal{U}^{(1)}$ ranges over the critical points of $V|_{W^-}$ with index 1, are all distinct.

Assumptions on δV.

- $V + \delta V$ satisfies the same assumptions as V ;
- $\delta V = 0$ on $\overline{W} \setminus W^-$.

The Hyperdynamics: mathematical analysis

Result [TL, Nier, 2013]: Under the above assumptions on the potentials V and $(V + \delta V)$, there exists $c > 0$ such that, in the limit $\beta \to \infty$,

$$\frac{\lambda_1(V+\delta V)}{\lambda_1(V)} = \frac{\int_W e^{-\beta V}}{\int_W e^{-\beta(V+\delta V)}}(1+\mathcal{O}(e^{-\beta c}))\,,$$

$$\frac{\partial_n\left[u_1(V+\delta V)\right]\big|_{\partial W}}{\|\partial_n\left[u_1(V+\delta V)\right]\|_{L^1(\partial W)}} = \frac{\partial_n\left[u_1(V)\right]\big|_{\partial W}}{\|\partial_n\left[u_1(V)\right]\|_{L^1(\partial W)}} + \mathcal{O}(e^{-\beta c}) \quad \text{in} \quad L^1(\partial W)\,.$$

Remark: We indeed have

$$\begin{aligned} B &= \frac{1}{T_W^{\delta V}} \int_0^{T_W^{\delta V}} \exp(\beta\,\delta V(\boldsymbol{X}_t))\,dt. \\ &\simeq \frac{\int_W \exp(\beta\delta V)\exp(-\beta(V+\delta V))}{\int_W \exp(-\beta(V+\delta V))} \\ &= \frac{\int_W \exp(-\beta V)}{\int_W \exp(-\beta(V+\delta V))}. \end{aligned}$$

The Hyperdynamics: idea of the proof

Use semi-classical analysis for boundary Witten laplacians ($f = V$, $h = 2/\beta$).

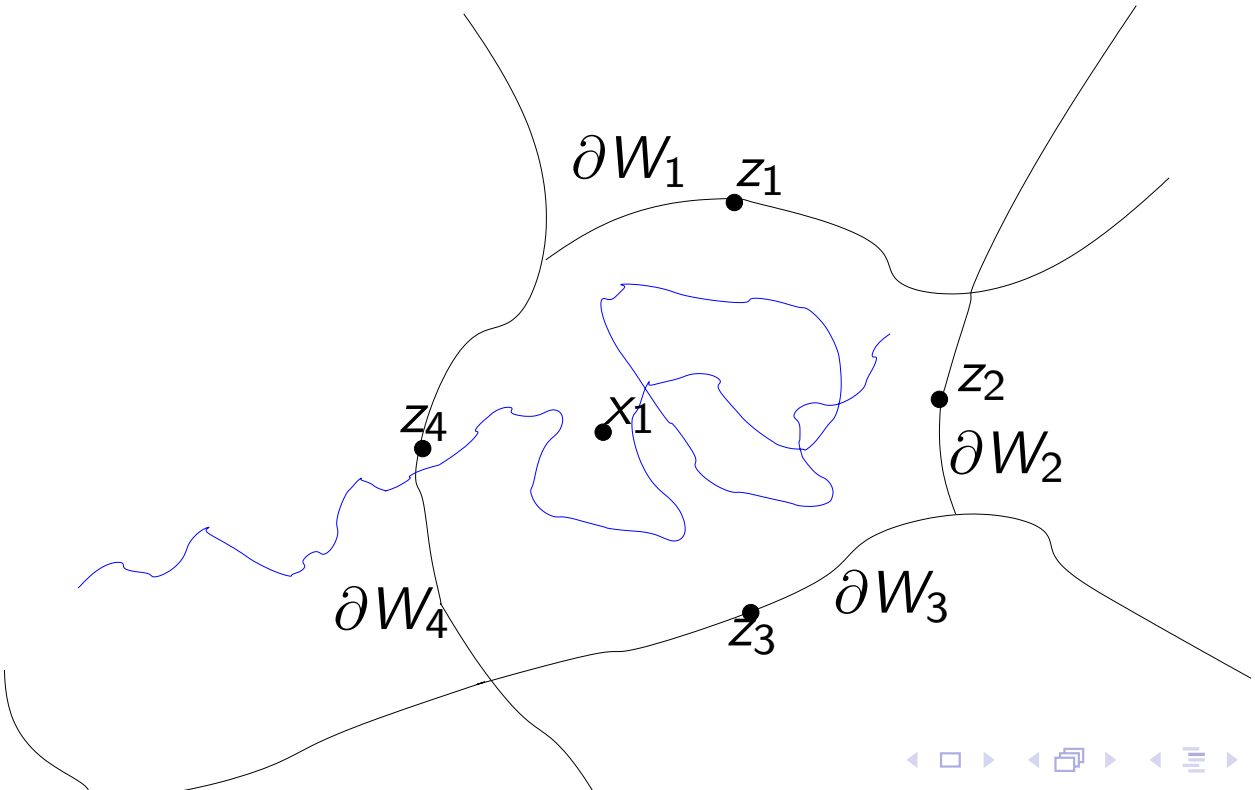
- Build quasimodes for $\Delta_{f,h}^{D,(p)}(W)$ $(p = 0, 1)$ using eigenvectors of $\Delta_{f,h}^{N,(p)}(W^-)$ $(p = 0, 1)$ and of $\Delta_{f,h}^{D,(1)}(W \setminus \overline{W^-})$.
- Analyze the asymptotics of the singular values of the restricted differential ($\nu(h) \leq h$ and $\lim_{h\to 0} h \log(\nu(h)) = 0$)
  $d_{f,h} : F^{(0)} \to F^{(1)}$ where $F^{(p)} = \mathrm{Ran}\left(1_{[0,\nu(h)]}\left(\Delta_{f,h}^{D,(p)}(W)\right)\right)$.
  This is a finite dimensional linear operator.
- Show that, up to exponentially small terms,
  $\lambda_1(V) = \frac{A}{\int_W \exp(-\beta V)}(1 + \mathcal{O}(e^{-\frac{c}{h}}))$ and $\frac{\partial_n u_1}{\|\partial_n u_1\|} = B + \mathcal{O}(e^{-\frac{c}{h}})$
  where A and B only depends on the eigenvectors of $\Delta_{f,h}^{D,(1)}(W \setminus \overline{W^-})$, and are thus not modified when changing V to $V + \delta V$.

The Temperature Accelerated Dynamics

Idea [Sorensen, Voter, 2000]: increase the temperature to reduce the exit time.

Algorithm:

- Observe the exit events from W at high temperature ;
- Extrapolate the high temperature exit events to low temperature exit events.



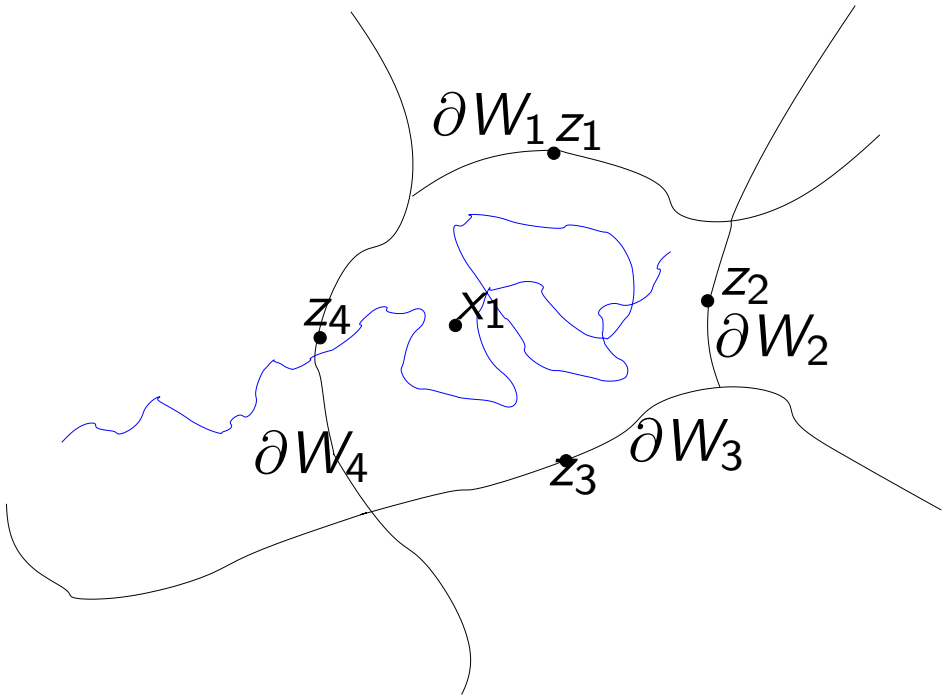
Extrapolation procedure (1/2)

Recall that, starting from the QSD, the exit event from a given state W can exactly be modelled using a kinetic Monte Carlo model with rates

$$k(i) = \lambda_1 p(i)$$

where $\lambda_1 = 1/\mathbb{E}(T_W)$ is the exit rate and

$$p(i) = \mathbb{P}(\boldsymbol{X}_{T_W} \in \partial W_i) = -\frac{\int_{\partial W_i} \partial_n u_1 \, d\sigma}{\beta\lambda_1 \int_W u_1(x)\, dx}.$$



Extrapolation procedure (2/2)

Extrapolating from high temperature to low temperature:

The extrapolation procedure is based on the empirical Eyring-Kramers law (HTST): for large β,

$$k(i) = \lambda_1 p(i) \simeq A_i \exp(-\beta(V(z_i) - V(x_1)))$$

where A_i is independent of β, which yields

$$\frac{k^{lo}(i)}{k^{hi}(i)} = \frac{\lambda_1^{lo} p^{lo}(i)}{\lambda_1^{hi} p^{hi}(i)} \simeq \exp(-(\beta^{lo} - \beta^{hi})(V(z_i) - V(x_1))).$$

Algorithm: observe exit events at high temperature, extrapolate the rates to low temperature, stop when the extrapolated event will not modify anymore the low temperature exit event.

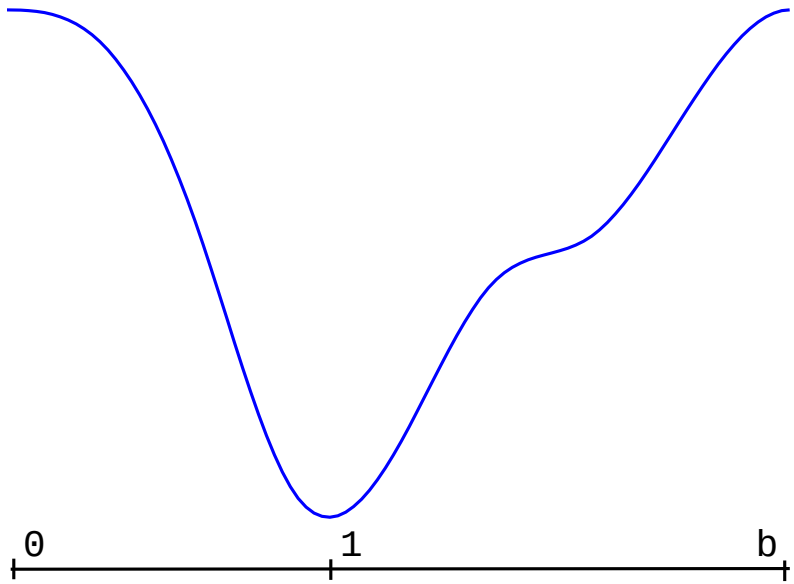
Remark: TAD can be seen as a smart saddle point search method.

Eyring-Kramers law

If the Eyring-Kramers law is exactly satisfied, one can show that the temperature accelerated dynamics method is exact.

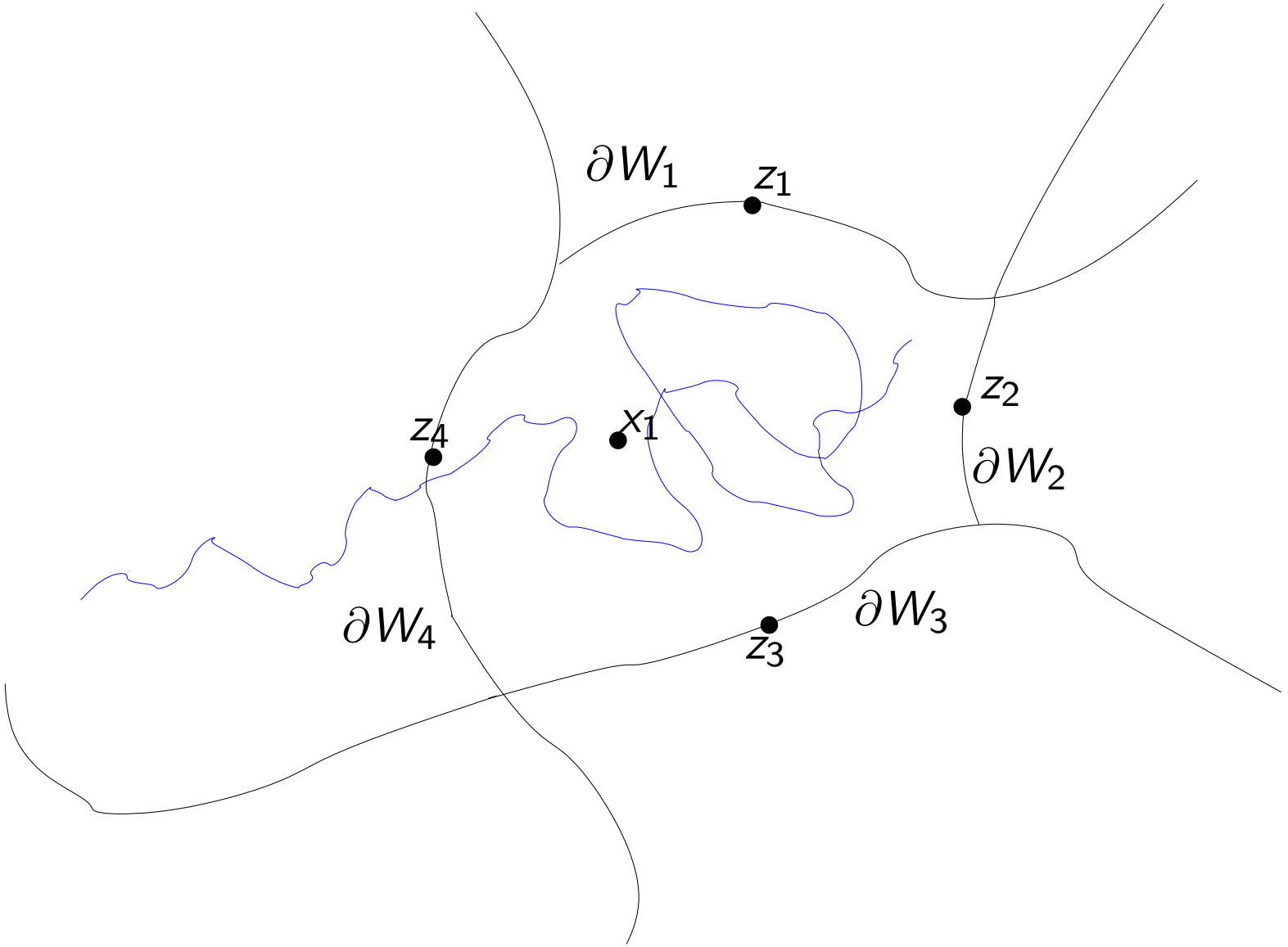
Mathematical question: Under which assumptions is the Eyring-Kramers law satisfied ? This is again a semi-classical analysis problem...

In 1D, this can be done. In the limit $\beta^{hi}, \beta^{lo} \to \infty$, $\beta^{lo}/\beta^{hi} = r$, under appropriate assumptions, one has [Aristoff, TL, 2014]:



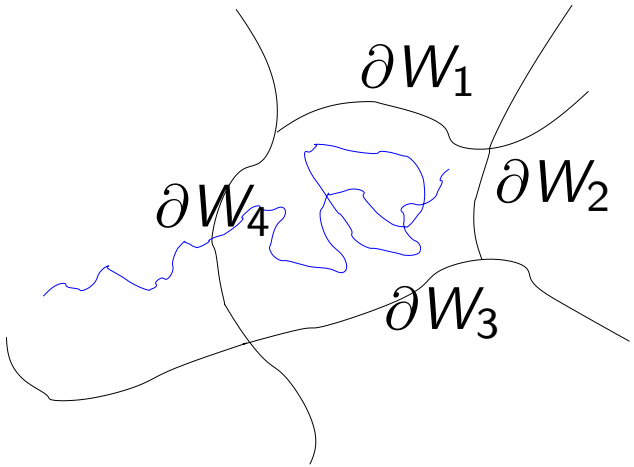
$$\frac{\lambda^{hi} p_i^{hi}}{\lambda^{lo} p_i^{lo}} = e^{-(\beta^{hi}-\beta^{lo})(V(z_i)-V(x_1))} \left(1 + O\left(\frac{1}{\beta^{hi}} - \frac{1}{\beta^{lo}}\right)\right)$$

kinetic Monte Carlo and Harmonic Transition State Theory



kMC models

Let us go back to the kinetic Monte Carlo model.



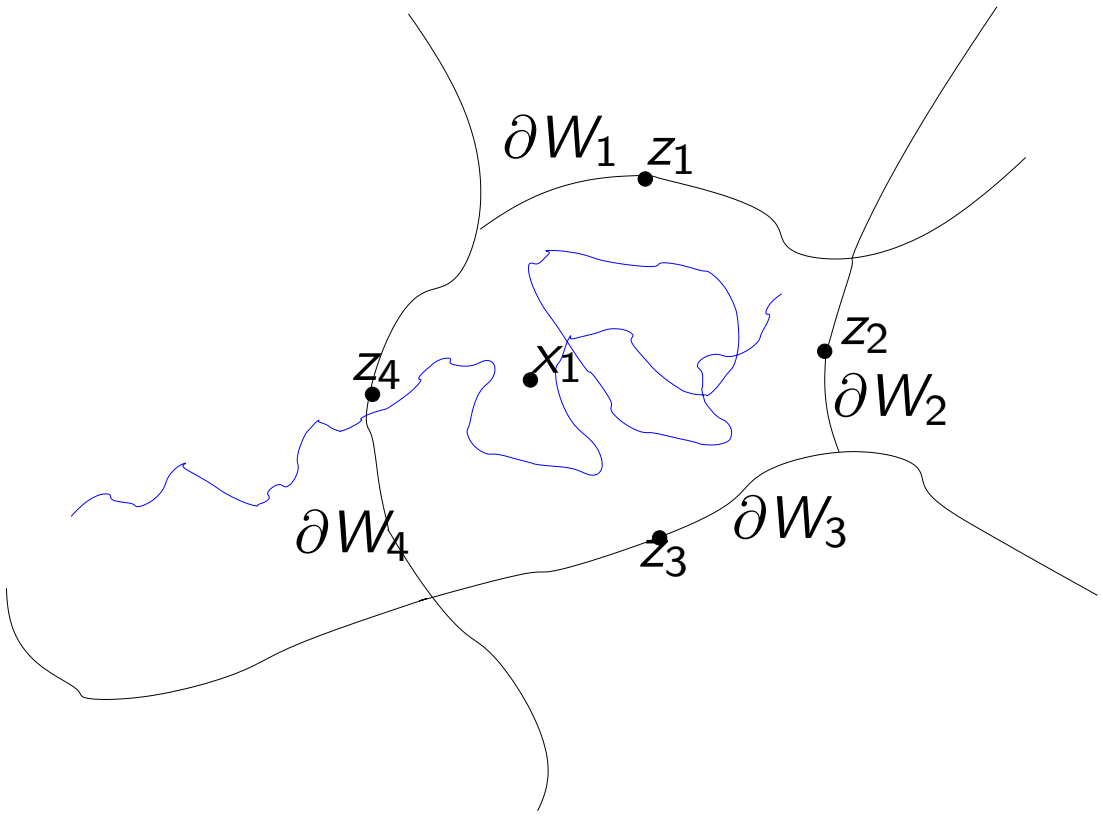
To each exit region ∂W_i is associated a rate $k(i)$. Let $\tau_i \sim \mathcal{E}(k(i))$ be independent exponential random variables. And then,

- The exit time is $\min(\tau_1, \ldots, \tau_I)$;
- The exit region is $\arg\min(\tau_1, \ldots, \tau_I)$.

Thus, (i) exit time and exit region are independent r.v. ; (ii) exit time is $\mathcal{E}(k(1) + \ldots + k(I))$; (iii) exit region is i with prob. $\frac{k(i)}{k(1)+\ldots+k(I)}$.

The Eyring Kramers law and HTST

In practice, kMC models are parameterized using HTST.



We assume in the following $V(z_1) < V(z_2) < \ldots < V(z_I)$.

Eyring Kramers law (HTST): $k(i) = A_i \exp\left(-\beta(V(z_i) - V(x_1))\right)$
where A_i is a prefactor depending on V at z_i and x_1.

kMC and HTST

Thus, one obtains the following law for the exit event:

- exit time and exit region are independent r.v.
- exit time is $\mathcal{E}(k(1) + \ldots + k(I))$ and, when β is large

$$k(1) + \ldots + k(I) \simeq k(1) = A_1 \exp\left(-\beta(V(z_1) - V(x_1))\right)$$

- exit region is i with probability $\frac{k(i)}{k(1)+\ldots+k(I)}$ and, when β is large,

$$\frac{k(i)}{k(1) + \ldots + k(I)} \simeq \frac{k(i)}{k(1)} = \frac{A_i}{A_1} \exp\left(-\beta(V(z_i) - V(z_1))\right)$$

Our aim: justify these formulas.

Back to overdamped Langevin and the QSD

Starting from the QSD $d\nu = u_1(x)dx$, we already know that

- the exit time T_W and the exit point X_{T_W} are independent r.v.
- the exit time is exponentially distributed with parameter λ_1
- the exit region is ∂W_i with probability

$$p(i) = \mathbb{P}(\boldsymbol{X}_{T_W} \in \partial W_i) = -\frac{\displaystyle\int_{\partial W_i} \partial_n u_1 \, d\sigma}{\beta\lambda \displaystyle\int_W u_1(x)\, dx}.$$

We thus need to prove that

$$\lambda_1 \simeq A_1 \exp\left(-\beta(V(z_1) - V(x_1))\right)$$

and

$$-\frac{\displaystyle\int_{\partial W_i} \partial_n u_1 \, d\sigma}{\beta\lambda_1 \displaystyle\int_W u_1(x)\, dx} \simeq \frac{A_i}{A_1} \exp\left(-\beta(V(z_i) - V(z_1))\right).$$

Small temperature regime

The question is thus: consider (λ_1, u_1) such that (first eigenvalue eigenfunction pair)

$$\begin{cases} \operatorname{div}\left(\nabla V u_1 + \beta^{-1}\nabla u_1\right) = -\lambda_1 u_1 \text{ on } W, \\ u_1 = 0 \text{ on } \partial W. \end{cases}$$

We assume wlg $u_1 > 0$ and $\int u_1^2 e^{\beta V} = 1$.
In the small temperature regime ($\beta \to \infty$), prove that

$$\lambda_1 \simeq A_1 \exp\left(-\beta(V(z_1) - V(x_1))\right)$$

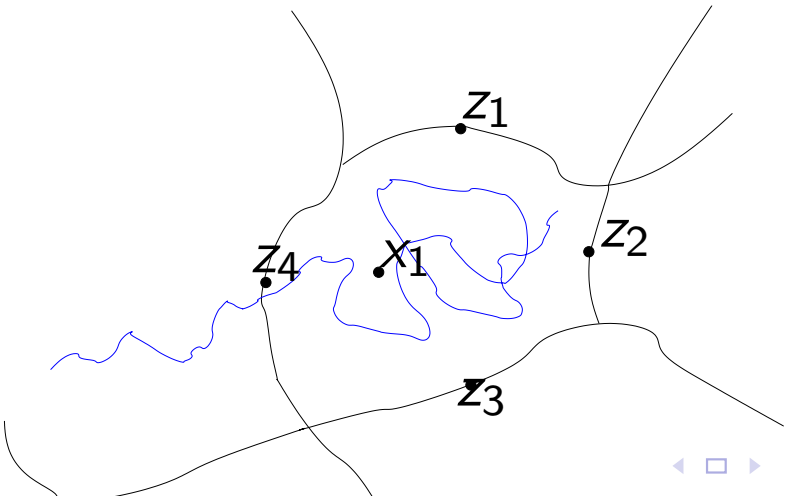
and

$$-\frac{\displaystyle\int_{\partial W_i} \partial_n u_1 \, d\sigma}{\beta\lambda_1 \displaystyle\int_W u_1(x)\, dx} \simeq \frac{A_i}{A_1} \exp\left(-\beta(V(z_i) - V(z_1))\right).$$

Assumptions

- W is an open bounded smooth domain in $\mathbb{R}^d$.
- $V : \overline{W} \to \mathbb{R}$ is a Morse function with a single critical point x_1. Moreover, $x_1 \in W$ and $V(x_1) = \min_{\overline{W}} V$.
- $\partial_n V > 0$ on ∂W and $V|_{\partial W}$ is a Morse function with local minima reached at $z_1, \ldots, z_I$ with $V(z_1) < \ldots < V(z_I)$.
- $V(z_1) - V(x_1) > V(z_I) - V(z_1)$
- $\forall i \in \{1, \ldots I\}$, consider B_{z_i} the basin of attraction for the dynamics $\dot{x} = -\nabla_T V(x)$ and assume that

$$\inf_{z \in B_{z_i}^c} d_a(z, z_i) > V(z_I) - V(z_1)$$



Agmon distance

Here, d_a is the Agmon distance:

$$d_a(x,y) = \inf_\gamma \int_0^1 g(\gamma(t))|\gamma'(t)|\,dt$$

where $g = \begin{cases} |\nabla V| \text{ in } W \\ |\nabla_T V| \text{ in } \partial W \end{cases}$, and the infimum is over all Lipschitz paths $\gamma : [0,1] \to \overline{W}$ such that $\gamma(0) = x$ and $\gamma(1) = y$. A few properties:

- One has $\forall x, y \in \overline{W}$, $|V(x) - V(y)| \leq d_a(x,y) \leq C|x-y|$
- On a neighborhood $\mathcal{V}$ of a local minima z_i, the function $x \mapsto d_a(x, z_i)$ satisfies the eikonal equation: $|\nabla \Phi|^2 = |\nabla V|^2$ on $\mathcal{V}$ with boundary conditions $\Phi = V$ on $\mathcal{V} \cap \partial W$, and $\Phi \geq V(z_i)$.

Results

[G. Di Gesu, TL, D. Le Peutrec and B. Nectoux] In the limit $\beta \to \infty$, the exit rate is

$$\lambda_1 = \sqrt{\frac{\beta}{2\pi}} \partial_n V(z_1) \frac{\sqrt{\det(Hess V)(x_1)}}{\sqrt{\det(Hess V_{|\partial W})(z_1)}} \mathrm{e}^{-\beta(V(z_1)-V(x_1))}(1+O(\beta^{-1})).$$

Moreover, for all open set Σ_i containing z_i such that $\overline{\Sigma}_i \subset B_{z_i}$,

$$\frac{\int_{\Sigma_i} \partial_n u_1 \, d\sigma}{\int_W u_1} = -C_i(\beta) e^{-\beta(V(z_i)-V(x_1))}(1+O(\beta^{-1})),$$

where $C_i(\beta) = \frac{\beta^{3/2}}{\sqrt{2\pi}} \partial_n V(z_i) \frac{\sqrt{\det(Hess V)(x_1)}}{\sqrt{\det(Hess V|_{\partial W})(z_i)}}$. Therefore,

$$\mathbb{P}^\nu(X_{T_W} \in \Sigma_i) = \frac{\partial_n V(z_i) \sqrt{\det \mathrm{Hess}(V|_{\partial W})(z_1)}}{\partial_n V(z_1) \sqrt{\det \mathrm{Hess}(V|_{\partial W})(z_i)}} e^{-\beta(V(z_i)-V(z_1))}(1+O(\beta^{-1})).$$

Related results in the literature (1/3)

The result on λ_1 is well known and actually holds under weaker assumptions. See for example [Helffer Nier] [Le Peutrec].

Similar formulas are obtained concerning the problem on the whole domain to compute the cascade of timescales down to the global minimum.

- Potential theoretic approaches [Bovier, Schuette, Hartmann,...]
- Spectral analysis of the Fokker Planck operator on the whole space and semi-classical analysis [Holley, Kusuoka, Stroock, Miclo, Sjöstrand, Helffer, Nier, Pavliotis, Schuette]

Warning: The exit rate is (1/2) times the transition rate !

Related results in the literature (2/3)

Another approach to study the exit problem from a domain: Large deviation techniques [Freidlin, Wentzell, Day, Vanden Eijnden, Weare, Touchette,...].

Compared to our approach, the assumptions in LD are much less stringent but LD only provides the exponential rates (not the prefactors) and LD does not provide error bounds. (Moreover the fact that the exit time is exponentially distributed and the independance property between exit time and exit point are only obtained when $\beta = \infty$.)

There are also PDE versions of these results see [Matkowsky, Schuss, Maier, Stein] for formal expansions, and [Holley, Kusuoka, Stroock, Kamin, Friedman, Mathieu, Perthame] for precise results.

Typical result [Freidlin, Wentzell, Theorem 5.1]: for all $W' \subset\subset W$, for any $\gamma > 0$, for any $\delta > 0$, there exists $\delta_0 \in (0, \delta]$ and $\beta_0 > 0$ such that for all $\beta \geq \beta_0$, for all $x \in W'$ such that $f(x) < \min_{\partial W} f$ and for all $y \in \partial W$,

$$\exp(-\beta(V(y) - V(z_1) + \gamma)) \leq \mathbb{P}^x(X_{T_W} \in \mathcal{V}_{\delta_0}(y)) \leq \exp(-\beta(V(y) - V(z_1) - \gamma))$$

Related results in the literature (3/3)

Why do we care about prefactors ?

Consider a situation with two local minima on the boundary ($V(z_1) < V(z_2)$). Compare

- the probability to leave through Σ_2 such that $z_2 \in \Sigma_2$, $\overline{\Sigma_2} \subset B_{z_2}$ and
- the probability to leave through Σ such that $\overline{\Sigma} \subset B_{z_1}$ and $\inf_\Sigma V = V(z_2)$.

Then, in the limit $\beta \to \infty$,

$$\frac{\mathbb{P}^\nu(X_{T_W} \in \Sigma)}{\mathbb{P}^\nu(X_{T_W} \in \Sigma_2)} = O(\beta^{-1/2}).$$

Discussion on the assumptions (1/5)

The assumption

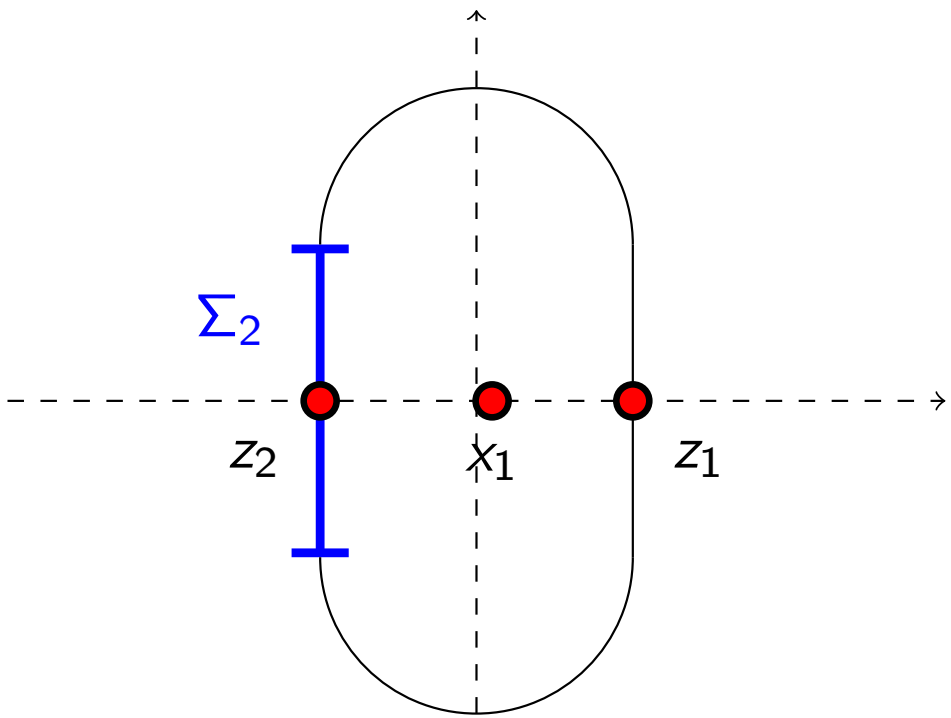
$$\forall i \in \{1, \dots I\}, \inf_{z \in B_{z_i}^c} d_a(z, z_i) > V(z_I) - V(z_1)$$

seems indeed important to get the expected results.

Discussion on the assumptions (2/5)

Let us consider the potential function $V(x, y) = x^2 + y^2 - ax$ with $a \in (0, 1/9)$ on the domain W. Two saddle points: $z_1 = (1, 0)$ and $z_2 = (-1, 0)$ (and $V(z_2) - V(z_1) = 2a$). One can check that the above assumptions are satisfied.

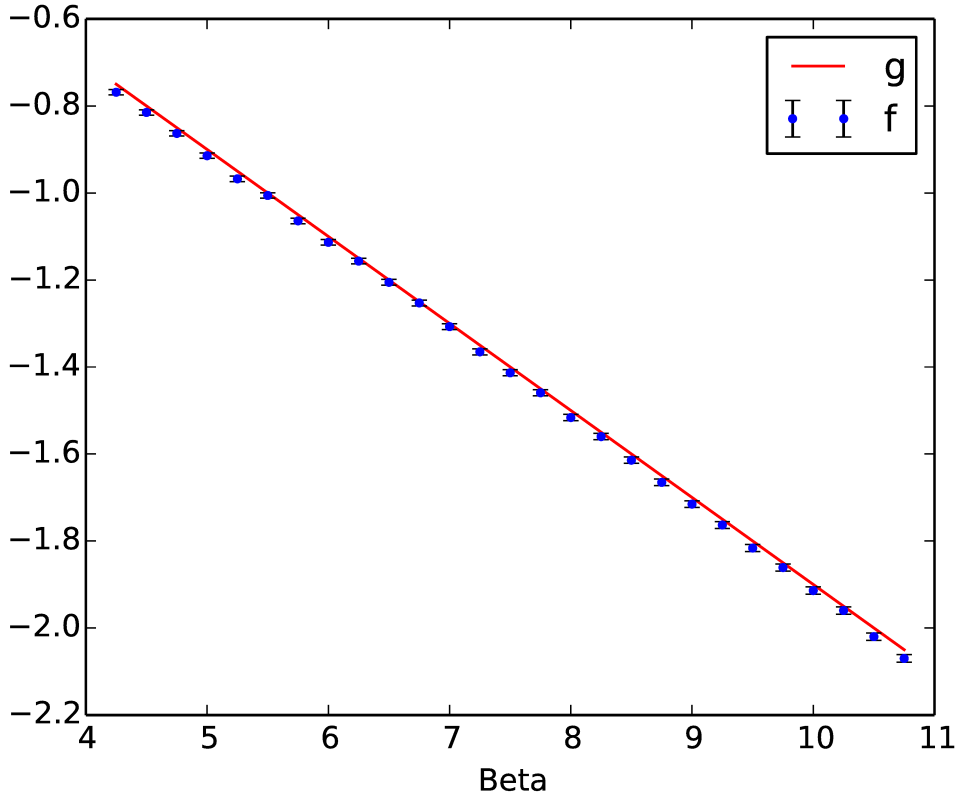
The domain W



Discussion on the assumptions (3/5)

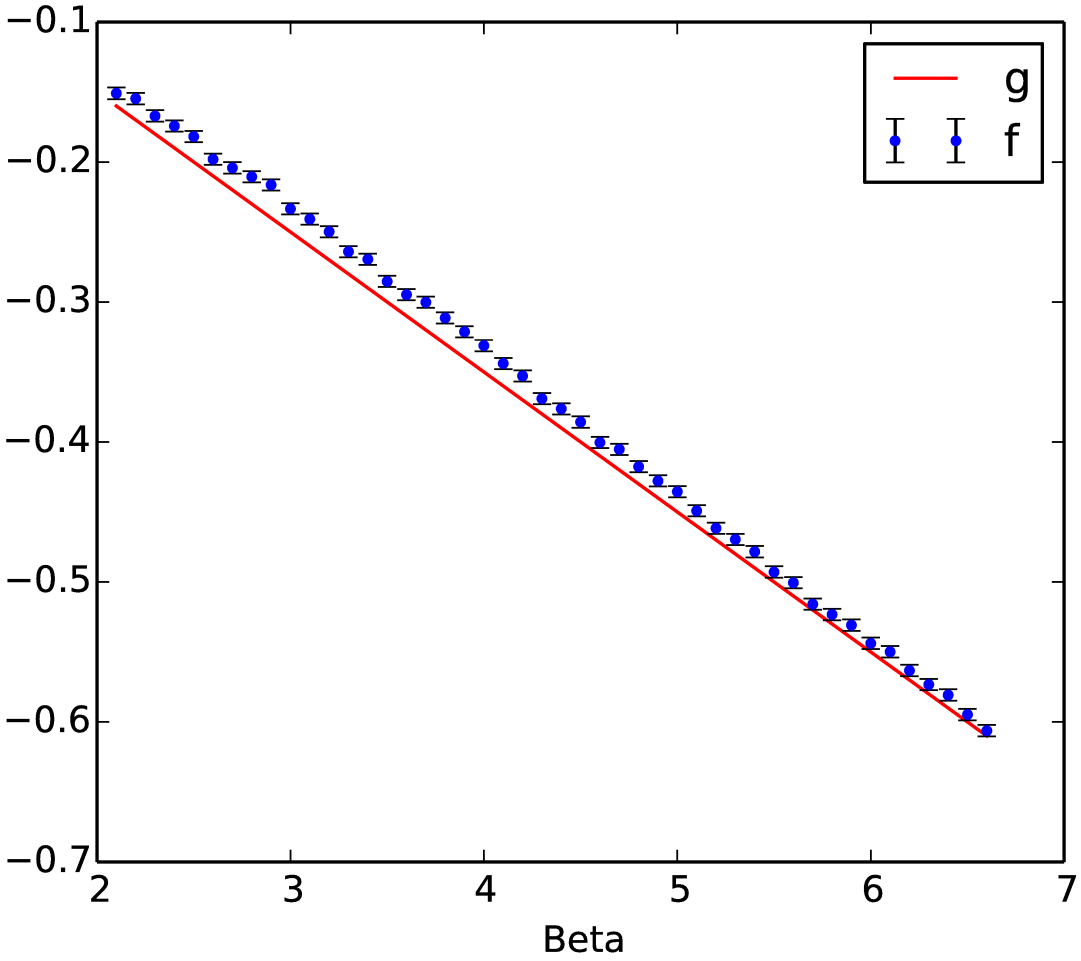
With $a = 1/10$, let us plot

- the numerical results $f : \beta \mapsto \ln\ \mathbb{P}^{\nu}(X_{T_W} \in \Sigma_2)$
- the theoretical result $g : \beta \mapsto \ln B_2 - \beta(V(z_2) - V(z_1))$, where $B_2 = \frac{\partial_n V(z_2)\sqrt{\det\ \mathrm{Hess}(V|_{\partial W})(z_1)}}{\partial_n V(z_1)\sqrt{\det\ \mathrm{Hess}(V|_{\partial W})(z_2)}}$ is the expected prefactor.



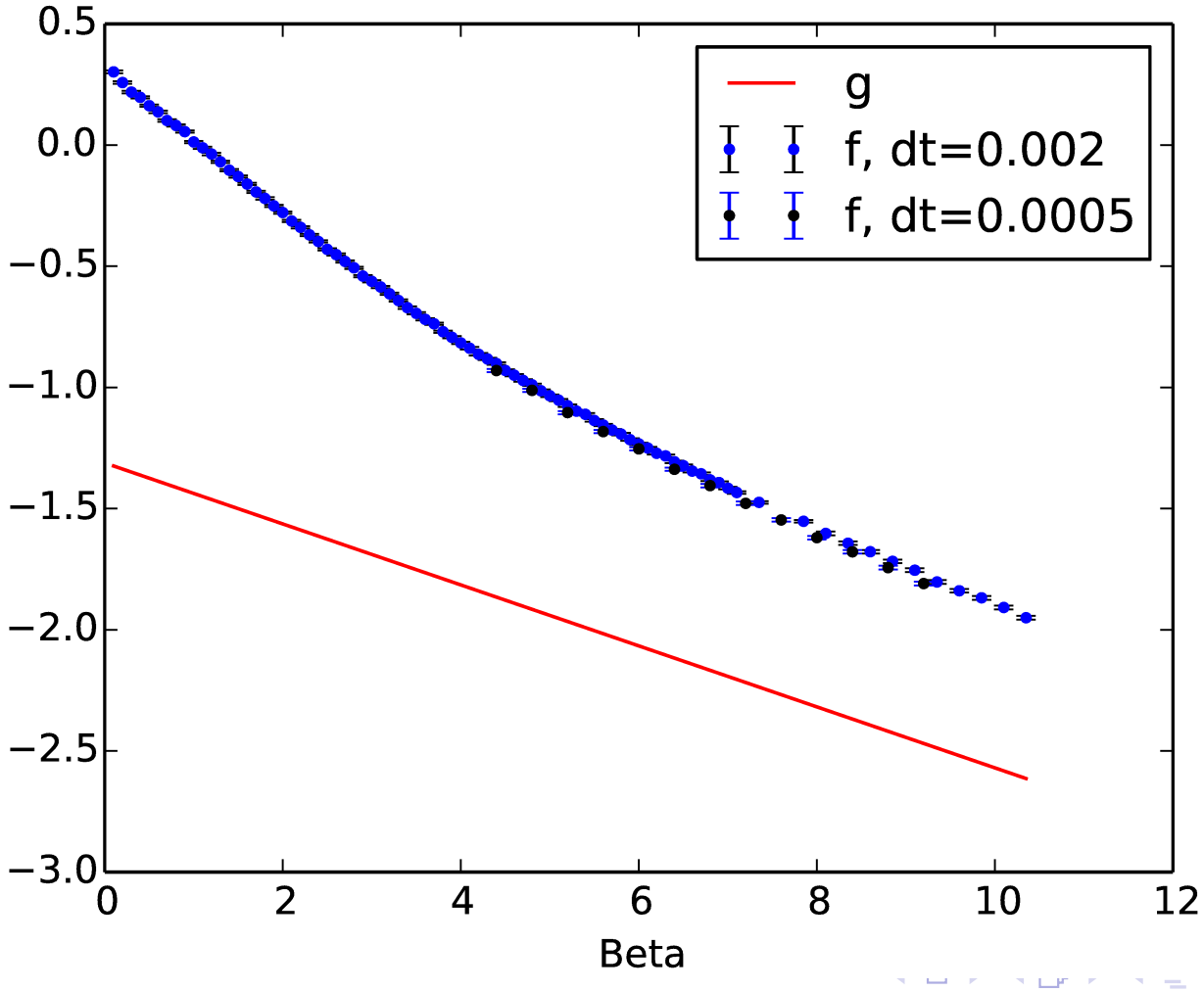
Discussion on the assumptions (4/5)

Same result with $a = 1/20$.



Discussion on the assumptions (5/5)

We now modify the potential such that the assumption on the Agmon distance is not satisfied anymore.



Sketch of the proof

The difficult part is to find an approximation for $\int_{\Sigma_i} \partial_n u_1 d\sigma = \int_{\Sigma_i} \partial_n v_1 e^{-\beta V}$, where $v_1 = u_1 e^{\beta V}$.
We have

$$\begin{cases} L^{(0)} v_1 = -\lambda_1 v_1 \text{ on } W, \\ v_1 = 0 \text{ on } \partial W, \end{cases}$$

where $L^{(0)} = \beta^{-1}\Delta - \nabla V \cdot \nabla$ is a self adjoint operator on $L^2(e^{-\beta V})$. We are interested in $\nabla v_1 \cdot n$, and ∇v_1 satisfies

$$\begin{cases} L^{(1)} \nabla v_1 = -\lambda_1 \nabla v_1 \text{ on } W, \\ \nabla_T v_1 = 0 \text{ on } \partial W, \\ (\beta^{-1}\mathrm{div} \ - \nabla V \cdot) \nabla v_1 = 0 \text{ on } \partial W, \end{cases}$$

where

$$L^{(1)} = \beta^{-1}\Delta - \nabla V \cdot \nabla - \mathrm{Hess}(V).$$

Therefore ∇v_1 is an eigenvector (eigen-1-form) of $-L^{(1)}$ associated with the small eigenvalue λ_1.

Sketch of the proof

Let $\Pi^{(p)} = 1_{[0,\beta^{-3/2}]}(-L^{(p)})$ be the spectral projection operator on small eigenvalues. We know that, for β large, $\dim(\mathrm{Ran}\Pi^{(0)}) = 1$ and $\dim(\mathrm{Ran}\Pi^{(1)}) = I$ [Helffer,Sjöstrand]:

$$\mathrm{Ran}\Pi^{(0)} = \mathrm{Span}(v_1)$$

$$\mathrm{Ran}\Pi^{(1)} = \mathrm{Span}(\psi_1, \ldots, \psi_I).$$

Since $\nabla v_1 \in \mathrm{Ran}\Pi^{(1)}$,

$$\int_{\Sigma_i} \partial_n v_1 \exp(-\beta V) = \sum_{j=1}^{I} \langle \nabla v_1, \psi_j \rangle_{L^2(e^{-\beta V})} \int_{\Sigma_i} \psi_j \cdot n e^{-\beta V}.$$

The idea is now to build so-called quasi-modes which approximate the eigenvectors of $L^{(0)}$ and $L^{(1)}$ associated with small eigenvalues in the regime $\beta \to \infty$, in order to approximate the terms in the sum.

Sketch of the proof

- $\mathrm{Ran}\Pi^{(0)}$: an approximation of v_1 is given by

$$\tilde{v} = Z^{-1} 1_{W'}$$

where $W' \subset\subset W$.

- $\mathrm{Ran}\Pi^{(1)}$: an approximation of $\mathrm{Ran}\Pi^{(1)}$ is $\mathrm{Span}(\tilde{\psi}_1, \ldots, \tilde{\psi}_I)$ where $(\tilde{\psi}_i)_{1 \leq i \leq I}$ are solutions to auxiliary eigenvalue problems, attached to the local minima $(z_i)_{1 \leq i \leq I}$.

Two tools:

- Agmon estimates (the support of $\tilde{\psi}_i$ is essentially in a neighborhood of z_i):

$$\exists N > 0, \ \| e^{\beta d_a(z_i, \cdot)/2} \tilde{\psi}_i \|_{H^1(e^{-\beta V})} = O(\beta^N).$$

- WKB approximations:

$$\exists N > 0, \ \tilde{\psi}_i \simeq Z_i^{-1} d(e^{\beta V/2} e^{-\beta d_a(z_i, \cdot)/2}) \beta^p.$$

Sketch of the proof

The last step consists in projecting the approximation of ∇v_1 on the approximation of $\mathrm{Ran}\Pi^{(1)}$.

Using the assumptions $V(z_1) - V(x_1) > V(z_I) - V(z_1)$ and $\inf_{z \in B_{z_i}^c} d_a(z, z_i) > V(z_I) - V(z_i)$, one can check that $\tilde{v}$ and $(\tilde{\psi}_i)_{i=1\dots I}$ are such that

- [Normalization] $\tilde{v} \in H_0^1(e^{-\beta V})$ and $\|\tilde{v}\|_{L^2(e^{-\beta V})} = 1$. $\forall i$, $\tilde{\psi}_i \in H_T^1(e^{-\beta V})$ and $\|\tilde{\psi}_i\|_{L^2(e^{-\beta V})} = 1$.
- [Good quasimodes]
  - $\forall \delta > 0$

$$\|(1 - \Pi^{(0)})\tilde{v}\|^2_{L^2(e^{-\beta V})} = O(e^{-\beta(V(z_1) - V(x_1) - \delta)}),$$

  - $\exists \varepsilon > 0$, $\forall i$,

$$\|(1 - \Pi^{(1)})\tilde{\psi}_i\|^2_{H^1(e^{-\beta V})} = O(e^{-\beta(V(z_I) - V(z_1) + \varepsilon)})$$

- [Orthonomality of quasimodes] $\exists \varepsilon_0 > 0$, $\forall i < j$

$$\langle \tilde{\psi}_i, \tilde{\psi}_j \rangle_{L^2(e^{-\beta V})} = O\left(e^{-\frac{\beta}{2}(V(z_j) - V(z_i) + \varepsilon_0)} \right).$$

Sketch of the proof

- [Decomposition of $\nabla\tilde{v}$] $\exists C_i, p, \forall i,$

$$\langle \nabla\tilde{v}, \tilde{\psi}_i \rangle_{L^2(e^{-\beta V})} = C_i \ \beta^{-p} e^{-\frac{\beta}{2}(V(z_i)-V(x_1))} \ (1 + O(\beta^{-1}) \ ).$$

- [Normal components of the quasimodes] $\exists B_i, m, \forall i, j$

$$\int_{\Sigma_i} \tilde{\psi}_j \cdot n \, e^{-\beta V} d\sigma = \begin{cases} B_i \ \beta^{-m} \ e^{-\frac{\beta}{2}V(z_i)} \ (\ 1 \ + O(\beta^{-1}) \ ) & \text{if } i = j \\ 0 & \text{if } i \neq j \end{cases}$$

Then for $i = 1, ..., n$, when $\beta \to \infty$

$$\int_{\Sigma_i} \partial_n v_1 \ e^{-\beta V} d\sigma = C_i B_i \ \beta^{-(p+m)} \ e^{-\frac{\beta}{2}(2V(z_i)-V(x_1))} \ (1 + O(\beta^{-1}))$$

Sketch of the proof

The proof of this last estimate is based on the formula:

$$\int_{\Sigma_i} \partial_n v_1 \exp(-\beta V) = \sum_{j=1}^{I} \langle \nabla v_1, \psi_j \rangle_{L^2(e^{-\beta V})} \int_{\Sigma_i} \psi_j \cdot n e^{-\beta V}.$$

Using the fact that $v_1 = \Pi^{(0)} \tilde{v}$ and that $(\psi_1, \ldots, \psi_I)$ can be obtained by a Gram-Schmidt procedure on $(\Pi^{(1)} \tilde{\psi}_1, \ldots, \Pi^{(1)} \tilde{\psi}_I)$, one can rewrite this formula in terms of $\tilde{v}$ and $(\tilde{\psi}_i)_{1 \leq i \leq n}$. Injecting the estimates then yields the result.

Conclusions

- From ParRep (ParSplicing) to Hyper to TAD, the underlying assumptions for the algorithms to be correct are more and more stringent. In particular, TAD is based on the fact that the Eyring-Kramers formula yield a correct approximation of the exit event.
- The QSD is a good intermediate between continuous state dynamics and kMC-like approximations (Markov state models). Transition rates could be defined starting from the QSD.
- The QSD can be used to analyze the validity of kMC models and the Eyring-Kramers law, in the small temperature regime.

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