Rare Event Simulation for Molecular Dynamics

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Joint work with :

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ENUMATH Conference 2011

September 8, 2011, Leicester

Introduction

The aim of Molecular Dynamics computations is to evaluate macroscopic quantities from models at the microscopic scale.

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

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

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

Introduction

- A molecular dynamics model $\Leftrightarrow$ a potential V.
- A configuration $x = (x_1, ..., x_n) \Rightarrow$ an energy $V(x_1, ..., x_n)$.
- Consider the over-damped Langevin (or gradient) dynamics

$$dX_t = -\nabla V(X_t)\,dt + \sqrt{2\beta^{-1}}dW_t,$$

where $\beta = 1/(k_B T)$.

- Equilibrium Boltzmann-Gibbs measure

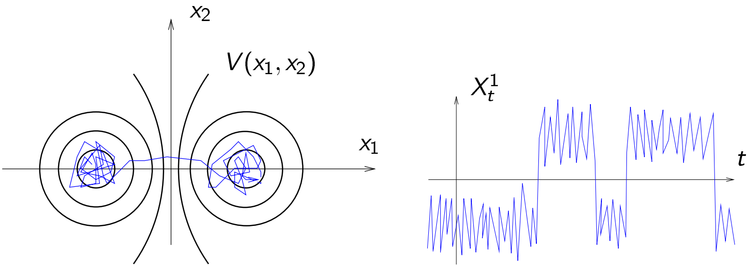
$$d\mu = Z^{-1}\exp(-\beta V(x))\,dx$$

where $Z = \int_{\mathbb{R}^n} \exp(-\beta V(x))\,dx$ is the partition function.

Introduction

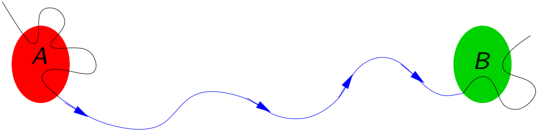
Difficulty: In practice, X_t is a metastable process, so that the convergence to equilibrium is very slow.

$\Rightarrow$ A 2d schematic picture: X_t^1 is a slow variable of the system.



Reactive Trajectories

Let A and B denote two metastable (recurrent) regions in $\mathbb{R}^d$.



- Reactive trajectory: piece of equilibrium trajectory that leaves A and goes to B without going back to A in the meantime.
- Problem: one may wait a long time before the trajectory eventually reaches B.

Reaction Coordinate

- Reaction coordinate: Smooth one-dimensional function

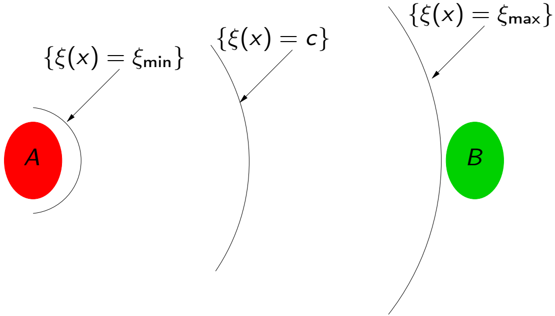
$$\xi : \mathbb{R}^d \to \mathbb{R}$$

with $|\nabla \xi| \neq 0$, and there exist $\xi_{\min} < \xi_{\max}$ such that

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

- Examples: $\xi(x) = \|x - x_A\|$ or $\xi(x) = |x^1 - x_A^1|$.
- Remark: Reaction coordinate in Molecular Dynamics $\Leftrightarrow$ Importance function in Rare Events literature.

Reaction Coordinate



- Example: $\xi(x) = \|x - x_A\|$, where x_A is a configuration in A.
- The level sets $\{\xi(x) = c\}$ are then Euclidean hyperspheres.
- Importance Splitting [Kahn and Harris, 1951]: clone the trajectories approaching B (wrt ξ), kill the other ones.
- Question: what is the best choice for ξ?

Committor Function

For the estimation of transition probabilities, it is well known that the optimal reaction coordinate is the committor function

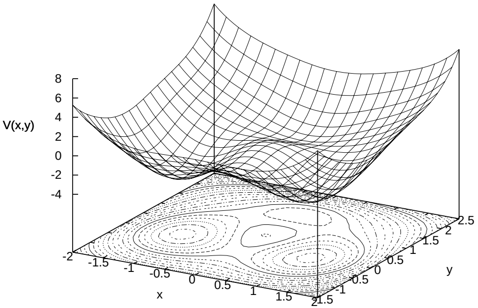
$$q(x) \triangleq \mathbb{P}(\tau_B(x) < \tau_A(x)) = \mathbb{P}\left(X_t^x \text{ reaches } B \text{ before } A\right)$$

solution of the following PDE

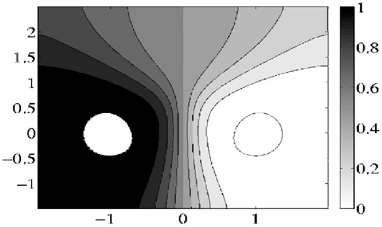
$$\begin{cases} -\nabla V \cdot \nabla q + \beta^{-1}\Delta q = 0 \text{ in } \mathbb{R}^d \setminus (\overline{A} \cup \overline{B}), \\ q = 0 \text{ on } \partial A \text{ and } q = 1 \text{ on } \partial B. \end{cases}$$

2D Example [Metzner, Schütte and Vanden-Eijnden (2006)]

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



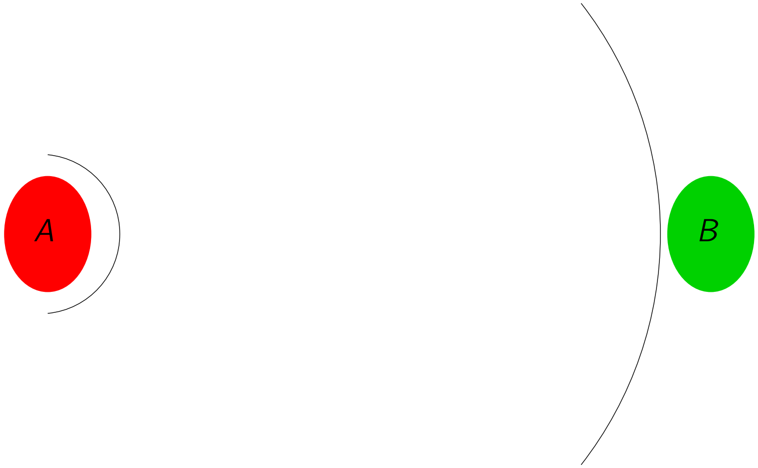
2D Example [Metzner, Schütte and Vanden-Eijnden (2006)]



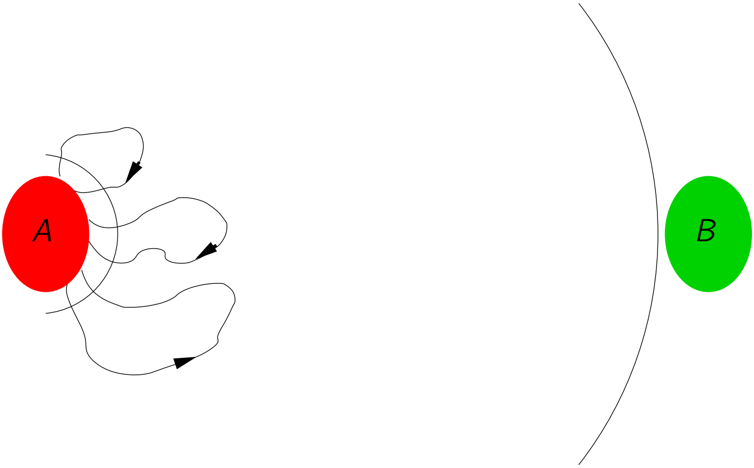
- Level Sets of the Committor Function q for $\beta = 1.67$.
- Difficulty: in general, finding these level sets is too hard...

$\Rightarrow$ Use another reaction coordinate, *e.g.* $\xi(x) = \|x - x_A\|$.

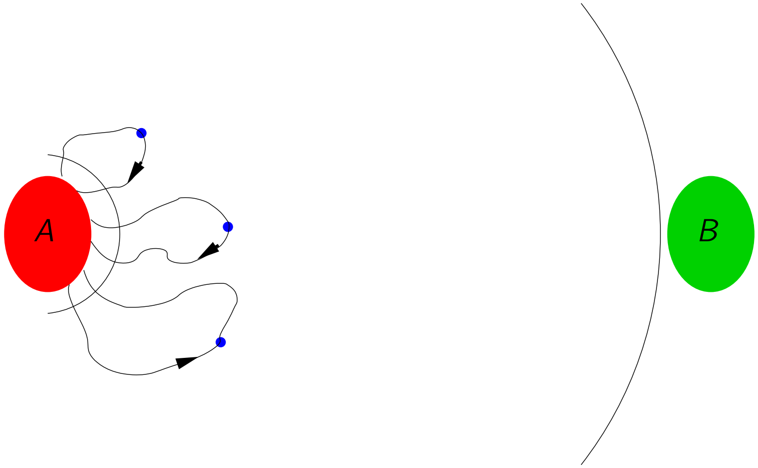
Algorithm



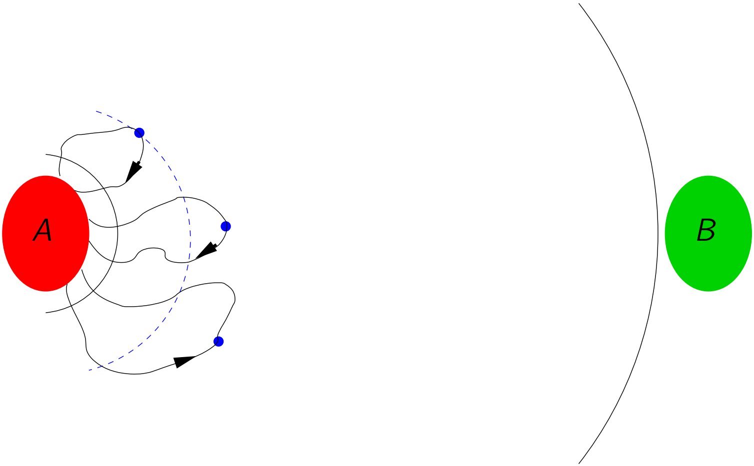
Algorithm



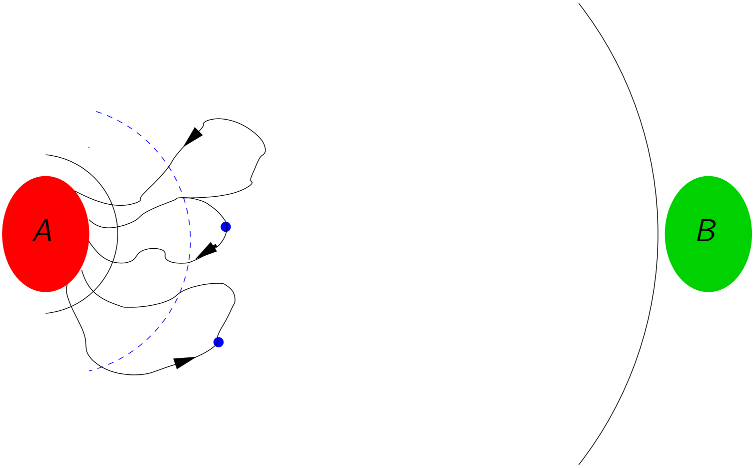
Algorithm



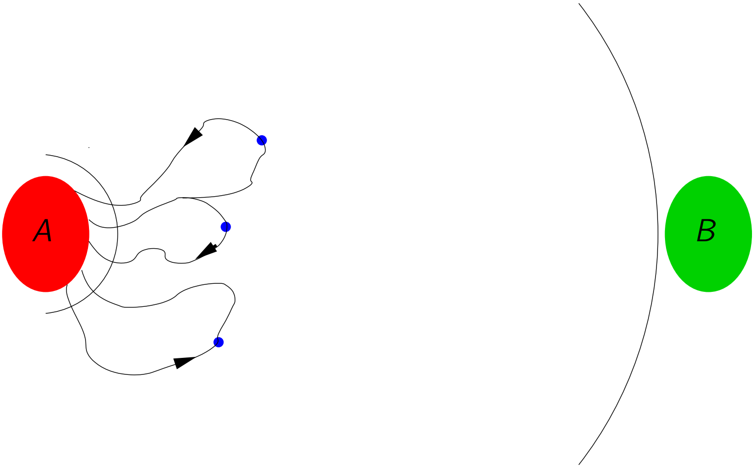
Algorithm



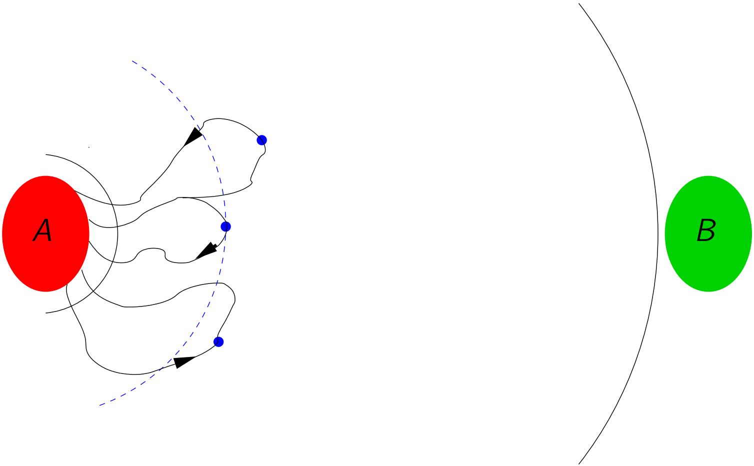
Algorithm



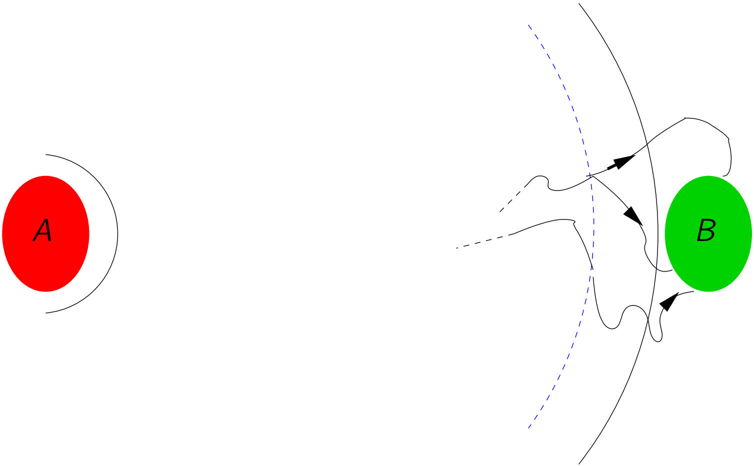
Algorithm



Algorithm



Algorithm



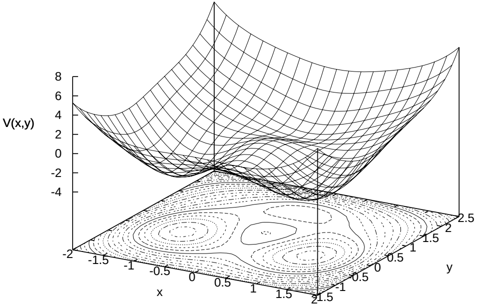
Algorithm

- Stopping Rule: iterate until step $k_{\max}$ when all the paths reach $\{\xi(x) = \xi_{\max}\}$, keep only those which reach B (proportion r).
- Estimation: The probability

$$\hat{p} = r \left(1 - \frac{1}{N}\right)^{k_{\max}}$$

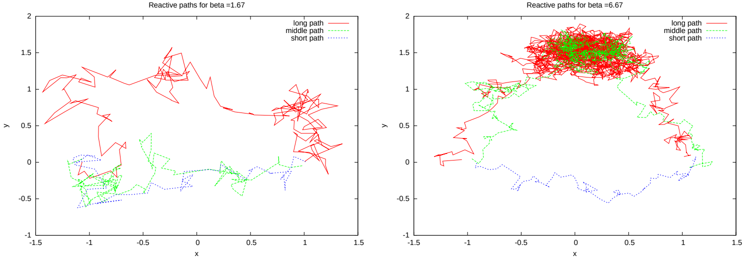
  is the "probability of observing a reactive trajectory".
- Remark: The algorithm can be seen as a kind of adaptive Forward Flux Sampling [Allen, Valeriani, Ten Wolde, 2009]. It is also related to the Interface Sampling Method [Bolhuis, van Erp, Moroni 2003] and the Milestoning Method [Elber, Faradjian 2004].

2D Example



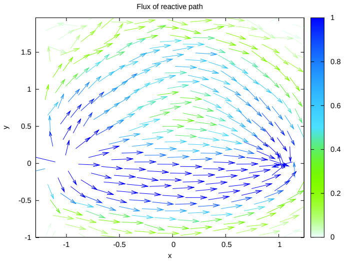
- 2 Deep Minima: $H_\pm = (\pm 1, 0) \Rightarrow A\&B = \mathcal{B}(H_\pm, 0.05)$.
- 1 Shallow Minimum: $M = (0, 1.5)$.
- 3 Saddle Points: $U_\pm = (\pm 0.6, 1.1)$ and $L = (0, -0.4)$.
- 2 Channels $\Rightarrow$ 2 scenarii, depending on the temperature.

A Few Reactive Trajectories



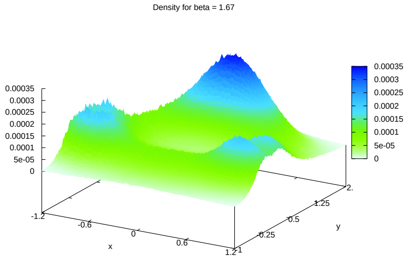
- Subsamplings of the generated trajectories.
- Reaction coordinate: $\xi(x) = \|x - x_A\|$.
- $\beta = 1.67$ (high temperature): shallow is shallow.
- $\beta = 6.67$ (low temperature): shallow becomes deep...

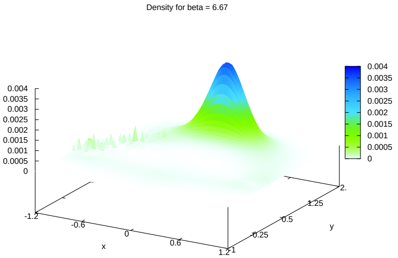
Flux of Reactive Trajectories



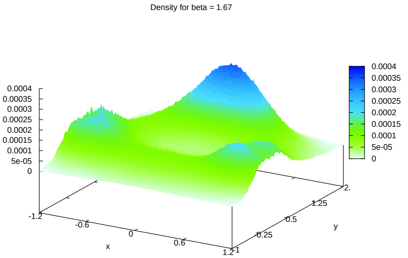
- The color indicates the norm of the flux.
- Reaction coordinate: $\xi(x) = \|x - x_A\|$.
- $\beta = 1.67$: the lower channel is preferred (entropic effect).
- $\beta = 6.67$: the upper channel is preferred (lower energy barrier).

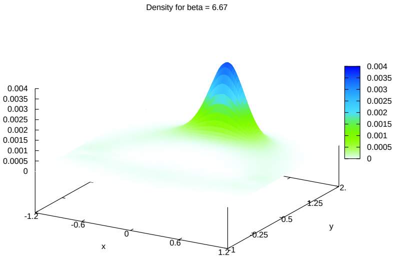
Density of Reactive Paths: : $\xi(x) = \|x - x_A\|$



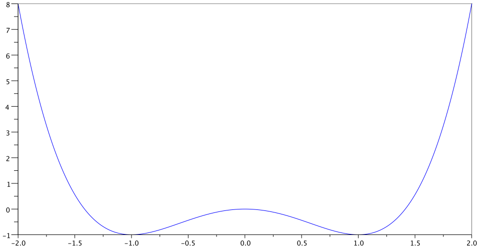


Density of Reactive Paths: : $\xi(x) = |x^1 - x_A^1|$



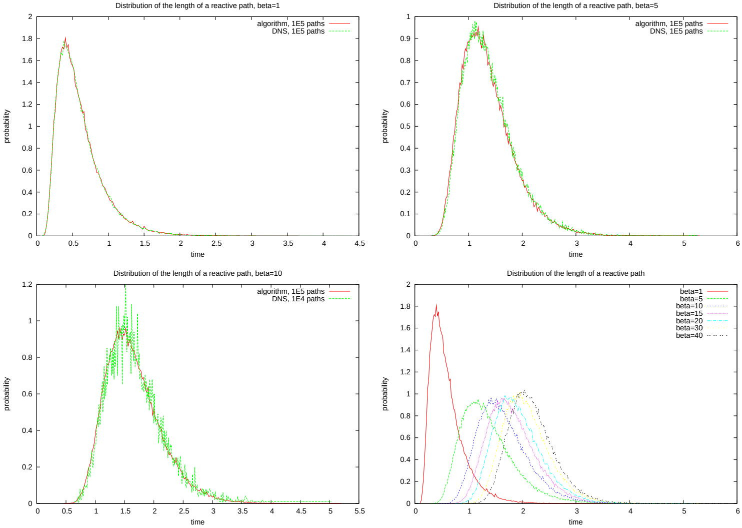


1D Example : $V(x) = x^4 - 2x^2$.



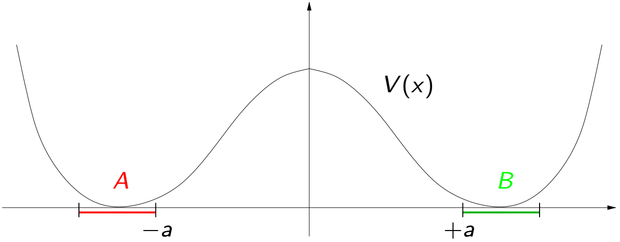
- Metastable States: $A = (-1.1; -0.9)$ and $B = (0.9; 1.1)$.
- Reaction Coordinate: $\xi(x) = x$.
- Application: distribution of the duration of the reactive paths.

1D Example



Distribution of the length of a reactive path, beta=1
algorithm, 1E5 paths
DNS, 1E5 paths
probability
time
Distribution of the length of a reactive path, beta=5
algorithm, 1E5 paths
DNS, 1E5 paths
probability
time
Distribution of the length of a reactive path, beta=10
algorithm, 1E5 paths
DNS, 1E4 paths
probability
time
Distribution of the length of a reactive path
beta=1
beta=5
beta=10
beta=15
beta=20
beta=30
beta=40
probability
time

Framework

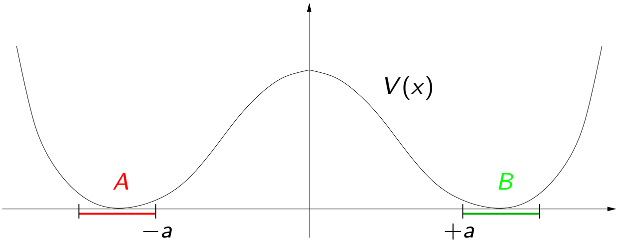


- Recall:

$$dX_t = -V'(X_t)\,dt + \sqrt{2k_B T}dW_t$$

- Assumption: V is an even double well potential, $V''(0) = -1$.
- Metastable States: A and B.
- Question: knowing $T_a < T_{-a}$, what is the law of $T_{-a \to a}$?

An Asymptotic Expansion



Theorem

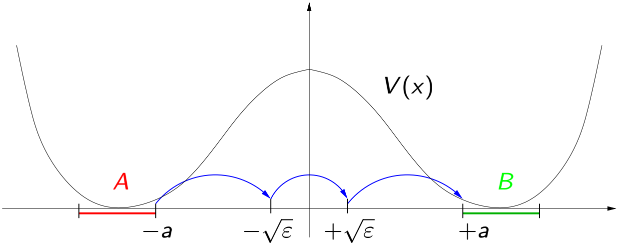
On the set $\{T_a < T_{-a}\}$, one has

$$T_{-a\to a} \underset{T\to 0}{\sim} -\log(k_B T) + 2\log a - 2H_a(0) + G$$

where G is a standard Gumbel random variable and

$$H_a(s) = \int_s^a \frac{t + V'(t)}{tV'(t)}\, dt.$$

Sketch of the Proof (1)

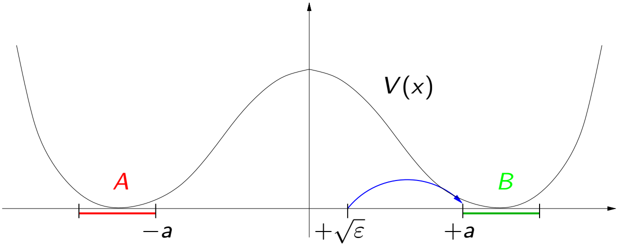


Denote $\varepsilon = k_B T$, and decompose the reactive path in 3 parts

$$T_{-a \to a} = T_{-a \to -\sqrt{\varepsilon}} + T_{-\sqrt{\varepsilon} \to +\sqrt{\varepsilon}} + T_{\sqrt{\varepsilon} \to a}$$

on the event $\{T_a < T_{-a}\}$.

Proof (2): Going Down Is Easy



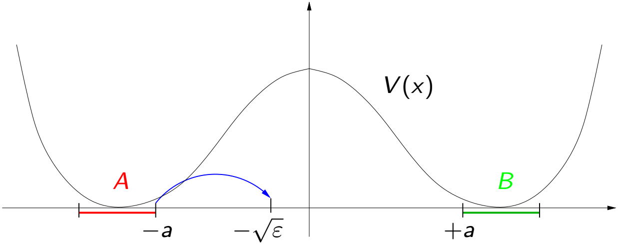
Thanks to Gronwall's Lemma

$$T_{\sqrt{\varepsilon}\to a} - t_{\sqrt{\varepsilon}\to a} \xrightarrow[\varepsilon\to 0]{a.s.} 0$$

with $t_{\sqrt{\varepsilon}\to a}$ the time for the unnoised process to reach a from $\sqrt{\varepsilon}$:

$$t_{\sqrt{\varepsilon}\to a} = -\int_{\sqrt{\varepsilon}}^{a} \frac{1}{V'(s)}\, ds \underset{\varepsilon\to 0}{\sim} \log\sqrt{\varepsilon} - \log a + H_a(0)$$

Proof (3): The Climbing Part



Freidlin-Wentzell's theory ensures that

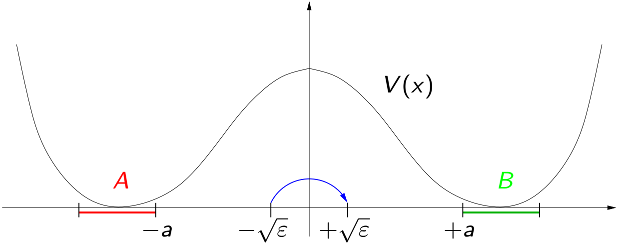
$$T_{-a \to -\sqrt{\varepsilon}} - t_{-\sqrt{\varepsilon} \to -a} \xrightarrow[\varepsilon \to 0]{a.s.} 0$$

and since V is even

$$t_{-\sqrt{\varepsilon} \to -a} = -\int_{-\sqrt{\varepsilon}}^{-a} \frac{1}{V'(s)}\, ds = t_{\sqrt{\varepsilon} \to a}$$

A reactive path doesn't need more time to go up than to go down!

Proof (4): The Middle Earth



Things happen "almost" like for a repulsive Ornstein-Uhlenbeck

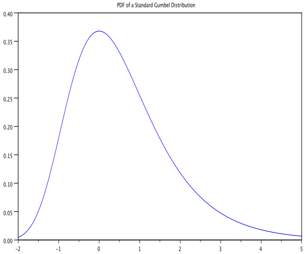
$$dX_t = X_t \, dt + \sqrt{2\varepsilon} dW_t$$

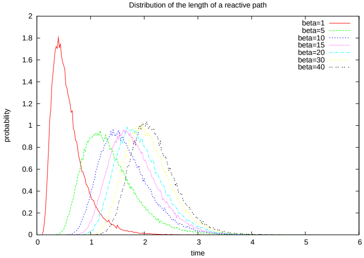
On the set $\{T_{\sqrt{\varepsilon}} < T_{-\sqrt{\varepsilon}}\}$, one can prove that

$$T_{-\sqrt{\varepsilon} \to \sqrt{\varepsilon}} \underset{\varepsilon \to 0}{\sim} -\log(\varepsilon) + G + o_\varepsilon(1).$$

where G is a standard Gumbel random variable.

Recall: The Gumbel Distribution





- PDF: $\forall x \in \mathbb{R},\ f(x) = e^{-x-e^{-x}}$.
- Extreme Value Theory: if $X_1, \ldots, X_n$ are i.i.d. $\mathcal{E}(1)$, then

$$\max(X_1, \ldots, X_n) - \log n \xrightarrow[n\to\infty]{\mathcal{L}} G$$

Conclusion

A new adaptive multilevel splitting type algorithm with a random number of levels. Other possible applications:

- Estimation of the transition times between metastable states.
- Exploration of the energy landscape without any *a priori*.

References:

1. A. Guyader, N.W. Hengartner and E. Matzner-Løber, *Simulation and Estimation of Extreme Quantiles and Extreme Probabilities*, Applied Mathematics & Optimization, 2011.
2. F. Cérou, A. Guyader, T. Lelièvre and D. Pommier, *A Multiple Replica Approach to Simulate Reactive Trajectories*, Journal of Chemical Physics, 2011.
3. F. Cérou, A. Guyader, T. Lelièvre and F. Malrieu, *On the Length of a Reactive Path*, preprint, 2011.