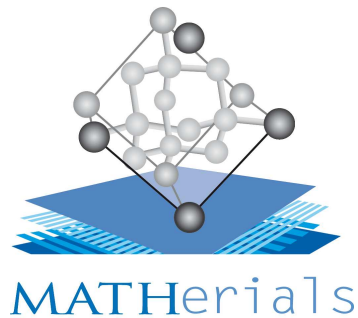
Metastability: a journey from stochastic processes to semi-classical analysis

Tony Lelièvre

CERMICS - Ecole Nationale des Ponts et Chaussées & INRIA



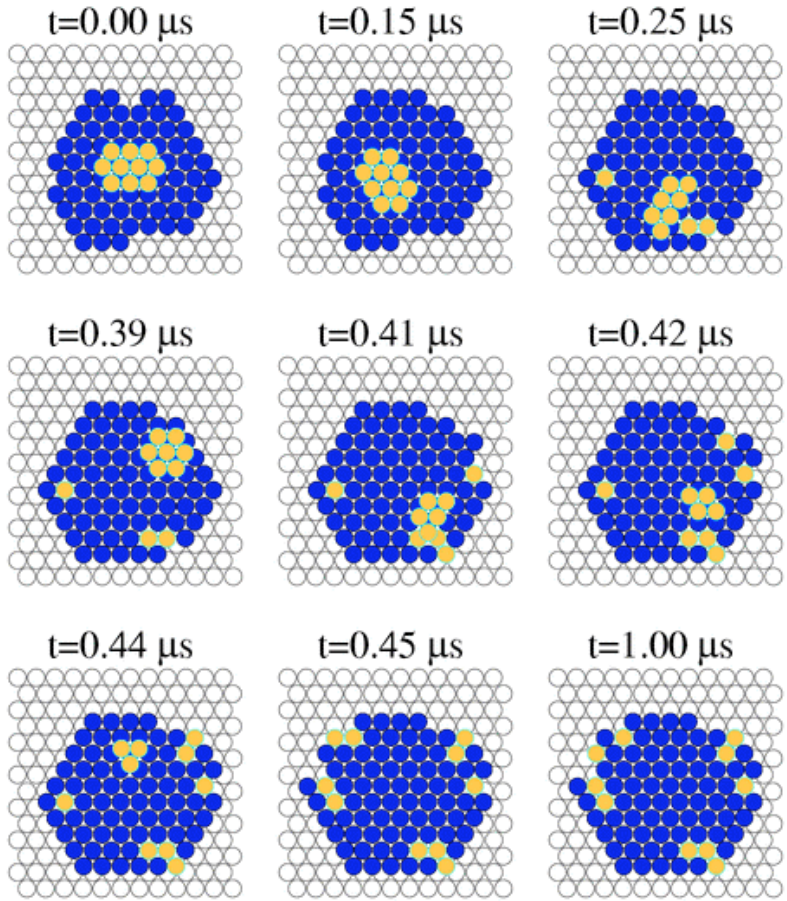
SMAI conference, Carcans-Maubuisson, June 2nd 2025

On the quasi-stationary distribution approach to metastability

Special thanks to:

- Arthur Voter, Danny Perez
- Francis Nier, Dorian Le Peutrec, Giacomo Di Gesù, Boris Nectoux
- Florent Hédin, Mouad Ramil, Mohamad Rachid, Noé Blassel, Thomas Normand, Louis Carillo, Julien Reygner, Gabriel Stoltz, and Urbain Vaes

Molecular dynamics



Diffusion of adatoms on a surface (Courtesy of A. Voter, Los Alamos National Laboratory)

Molecular dynamics

Molecular dynamics consists in simulating on the computer the evolution of atomistic systems, as a numerical microscope:

- Understand the link bewteen macroscopic properties and microscopic ingredients
- Explore matter at the atomistic scale
- Simulate new materials, new molecules
- Interpret experimental results

Applications: chemistry, biology, materials science

Molecular dynamics comes of age:

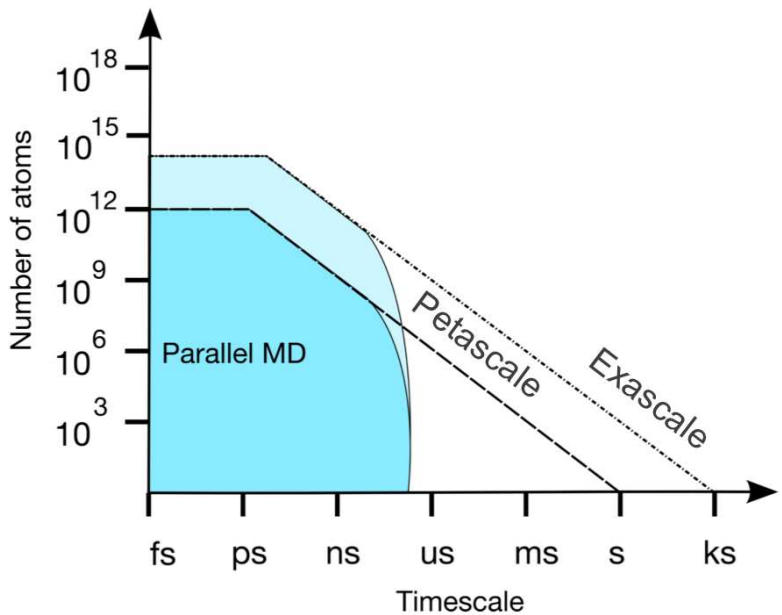
- 1/4 of CPU time worldwide is devoted to computations at the molecular scale
- 2013 Chemistry Nobel prize: Arieh Warshel, Martin Karplus and Michael Levitt. "Today the computer is just as important a tool for chemists as the test tube. Simulations are so realistic that they predict the outcome of traditional experiments."

Challenges

Main challenges:

- Improve models (force fields, coarse-grained force fields): polarisability, water, chemical reactions
- Incorporate data: Bayesian approaches, data sciences
- Improve sampling methods (access long time scales): thermodynamic quantities, and dynamical properties

Spatial parallelism is very effective, but temporal reach of heroic brute force MD is limited to $1\mu s$ or less.



Courtesy of Danny Perez (LANL)

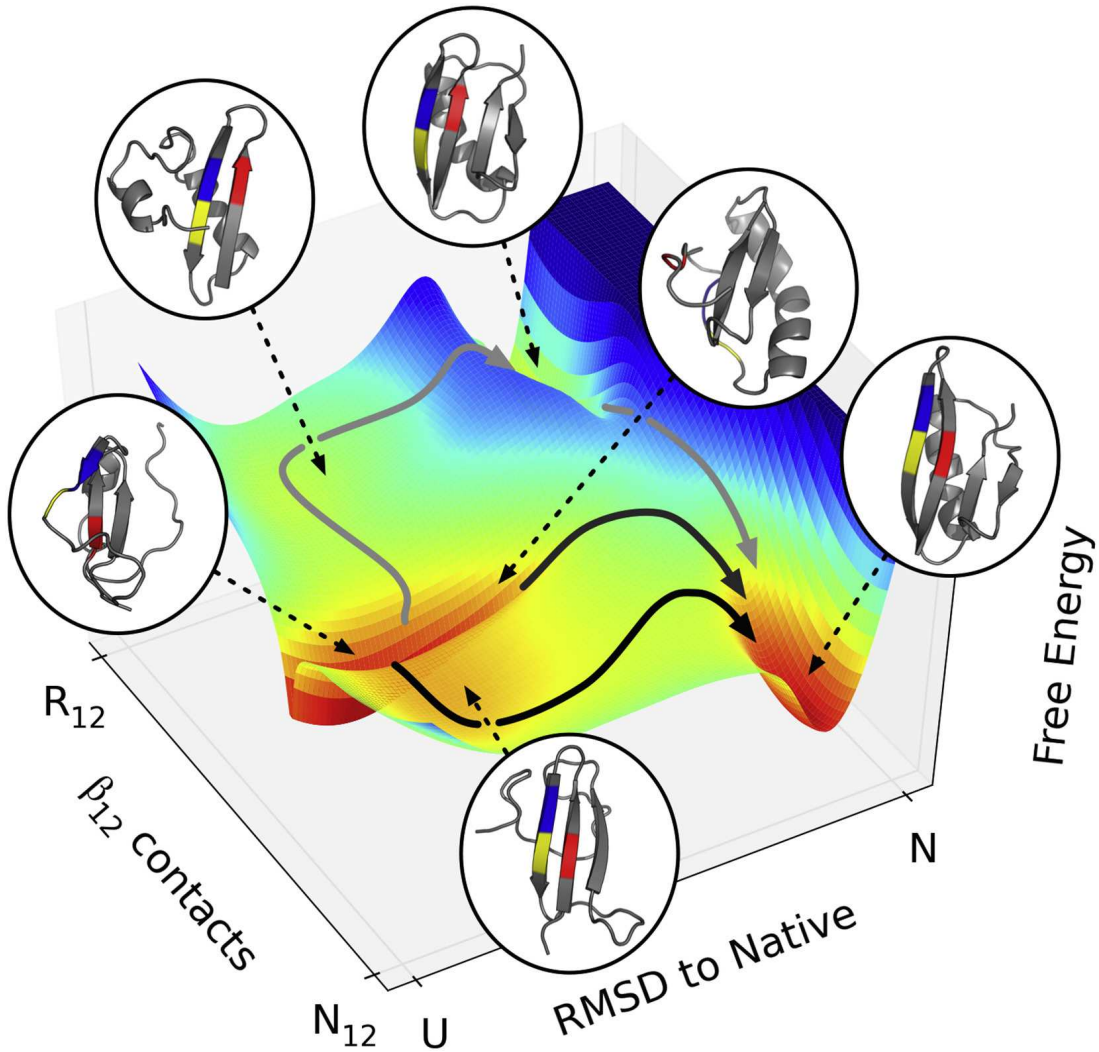
Challenges

Examples of hot topics in mathematics for MD:

- Sampling of reactive trajectories, rare event sampling (A. Guyader, C. Hartmann, TL, C. Schuette, E. Vanden Eijnden, J. Weare, ...)
- Sampling of probability measures on manifolds, constrained MD (P. Breiding, P. Diaconis, J. Goodman, C. Hartmann, TL, ...)
- Effective dynamics, Mori-Zwanzig (L. Delle Site, T. Hudson, F. Legoll, TL, P. Monmarché, C. Schuette, W. Zhang, ...)
- Sampling of non equilibrium stationary state, non-reversible dynamics (J. Bierkens, G. Stoltz, ...)
- Towards better force fields (G. Csanyi, C. Ortner, A.V. Shapeev, ...)

Today: Sampling metastable dynamics on complex energy landscapes

From Langevin to kinetic Monte Carlo



C.R. Schwantes, D. Shukla, V.S.Pande, Biophysical Journal, vol. 110, 2016

Two models for dynamics

The basic modeling ingredient in molecular dynamics: a potential function V which associates to a configuration $\boldsymbol{x} = (\boldsymbol{x}_1, ..., \boldsymbol{x}_{N_{atom}}) \in \mathbb{R}^d$ $(d = 3N_{atom})$ an energy $V(\boldsymbol{x}) \in \mathbb{R}$.

From V, two kinds of dynamics are considered:

- Langevin and overdamped Langevin dynamics: Markov processes with values in continuous state space ;
- kinetic Monte Carlo model or Markov state model (first order kinetics): Markov processes with values in discrete state space (jump Markov process).

Question: Can a mathematically rigorous link be made between these two kinds of models ?

Langevin and overdamped Langevin dynamics

Let us introduce the inverse temperature: $\beta^{-1} = k_B T$

The *Langevin dynamics* write: ($\gamma > 0$ is the damping parameter)

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

We will (very often) consider the *overdamped Langevin dynamics*

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

In the following $\boldsymbol{X}_t = (\boldsymbol{Q}_t, \boldsymbol{P}_t) \in \mathbb{R}^d \times \mathbb{R}^d$ or $\boldsymbol{X}_t = \boldsymbol{Q}_t \in \mathbb{R}^d$ denotes the associated Markov process

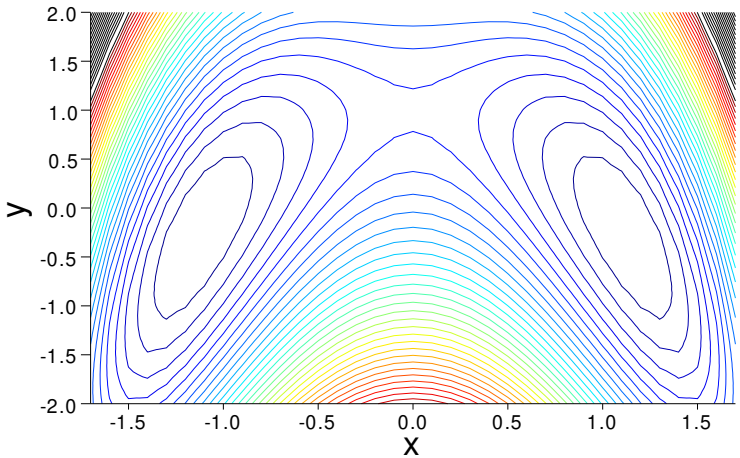
These dynamics are both ergodic wrt the canonical measure: $\lim_{t\to\infty} \frac{1}{t} \int_0^t \varphi(\boldsymbol{Q}_s) ds = \int_{\mathbb{R}^d} \varphi d\mu$ where

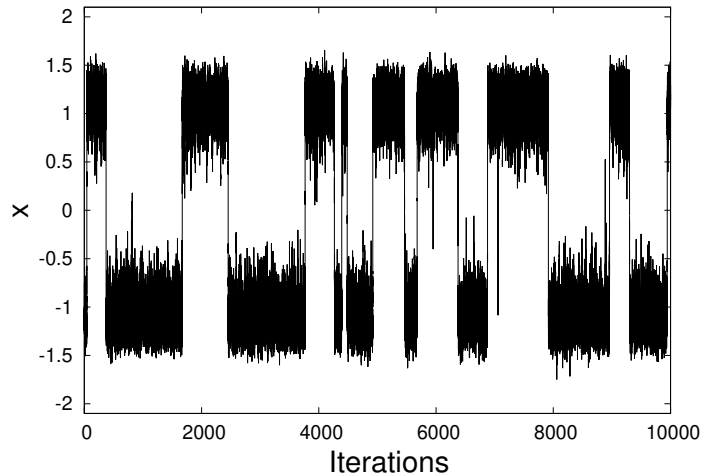
$$\mu(d\boldsymbol{x}) = Z^{-1} \exp(-\beta V(\boldsymbol{x})) d\boldsymbol{x}$$

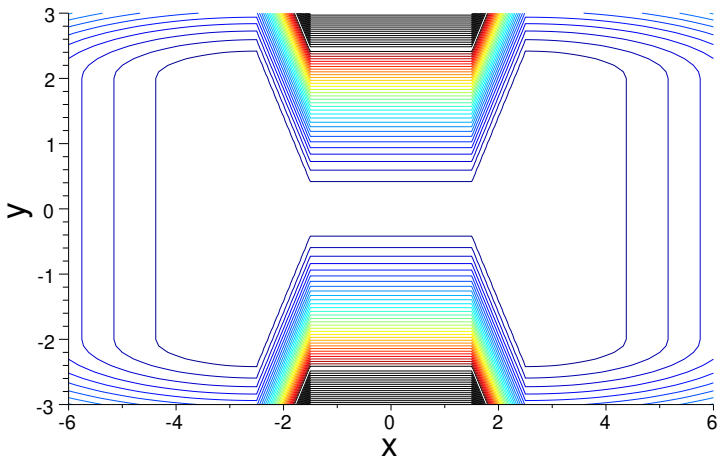
Main practical challenge: these dynamics are metastable

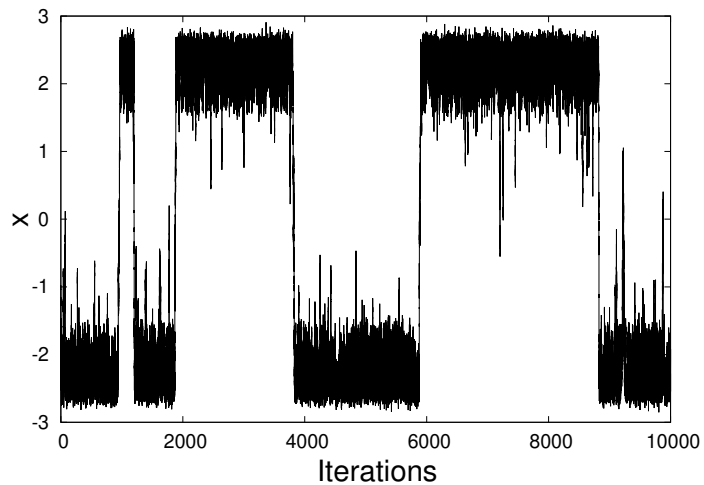
Metastability: energetic and entropic barriers

A two-dimensional schematic picture





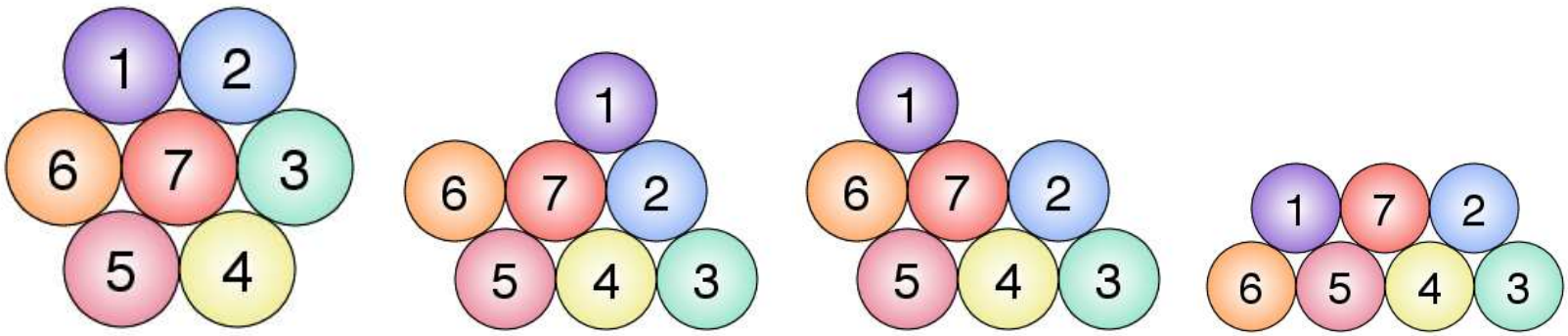




$\longrightarrow$ • Slow convergence of trajectorial averages

• Transitions between metastable states are rare events

Metastability: a toy example



(a) $V = -12.53$ (b) $V = -11.50$ (c) $V = -11.48$ (d) $V = -11.40$

Figure: Low energy conformations of the 7 atoms Lennard-Jones cluster.

$\longrightarrow$ simulation

The exit event

Let us consider a domain $\mathcal{O} \subset \mathbb{R}^d$ defined in position space. The associated state is $\mathcal{S} = \mathcal{O} \times \mathbb{R}^d$ for the Langevin dynamics and $\mathcal{S} = \mathcal{O}$ for the overdamped Langevin dynamics. The exit event from $\mathcal{O}$ is given by

$$(\tau_{\mathcal{O}}, \boldsymbol{X}_{\tau_{\mathcal{O}}})$$

where $\tau_{\mathcal{O}} = \inf\{t > 0,\ \boldsymbol{Q}_t \notin \mathcal{O}\} = \inf\{t > 0,\ \boldsymbol{X}_t \notin \mathcal{S}\}$

Typically, $\mathcal{O}$ is the basin of attraction of one of the local minima of V for the steepest descent dynamics: $\dot{\boldsymbol{x}} = -\nabla V(\boldsymbol{x})$

Objective: build a jump Markov model to simulate the exit event $(\tau_{\mathcal{O}}, \boldsymbol{X}_{\tau_{\mathcal{O}}})$

This is useful theoretically (justification of Markov state models and Eyring-Kramers laws) and numerically (accelerated dynamics *à la* Voter)

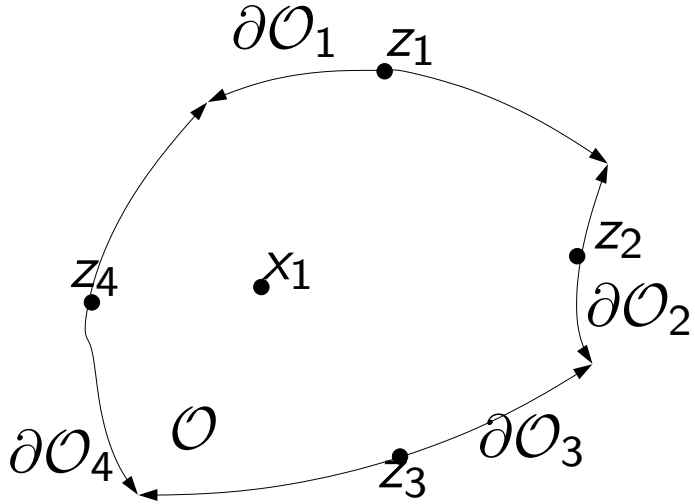
Kinetic Monte Carlo

Kinetic Monte Carlo (or Markov state) models are built as follows:

- define exit regions from $\mathcal{O}$: $\partial\mathcal{O} = \cup_{j=1}^{J} \partial\mathcal{O}_j$
- associate a rate k_j with an exit through $\partial\mathcal{O}_j$

and then (jump Markov model)

- the exit time $\tau_{\mathcal{O}}^{kMC}$ is exponentially distributed with parameter $\sum_{j=1}^{J} k_j$
- the exit region is $I_{\mathcal{O}}^{kMC}$ with law $\mathbb{P}(I_{\mathcal{O}}^{kMC} = i) = \frac{k_i}{\sum_{j=1}^{J} k_j}$
- $I_{\mathcal{O}}^{kMC}$ and $\tau_{\mathcal{O}}^{kMC}$ are independent random variables



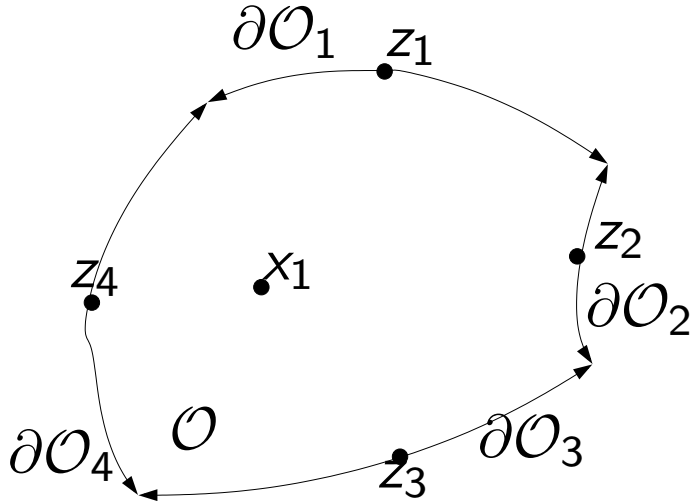
Energetic barriers and Eyring-Kramers laws

Formulas for transition rates. Let us introduce the local minima $(z_j)_{j=1,\dots,J}$ of V on $\partial\mathcal{O}$, and associated exit regions $(\partial\mathcal{O}_j)_{j=1,\dots,J}$. If $\mathcal{O}$ is the basin of attraction of a local minimum x_1, the z_j's are saddle points of V

The parameters k_j are computed using the Eyring-Kramers formula (Transition State Theory):

$$k_j^{TST} = \nu_j \, \mathrm{e}^{-\beta[V(z_j)-V(x_1)]}$$

where ν_j is an explicit prefactor and $x_1 = \arg\min_{\mathcal{O}} V$



A theoretical question

Question: can we relate the exit event $(\tau_{\mathcal{O}}, \boldsymbol{X}_{\tau_{\mathcal{O}}})$ for the original dynamics with the exit event $(\tau_{\mathcal{O}}^{kMC}, I_{\mathcal{O}}^{kMC})$ for the jump Markov process?

$\longrightarrow$ Python simulations

Two steps:

- Step 1: Introduce the Quasi-Stationary Distribution
  (both for overdamped Langevin and Langevin)
  $\longrightarrow$ justify the use of a kMC model
- Step 2: Consider the small temperature regime $\beta \to \infty$
  (only for the overdamped Langevin)
  $\longrightarrow$ justify the use of the Eyring-Kramers laws to parametrize the kMC model

Step 1: The Quasi-Stationary Distribution

Definition of the QSD: A probability measure ν with support $\mathcal{S}$ is a QSD for the Markov process $(\boldsymbol{X}_t)_{t\geq 0}$ iff for all $t > 0$,

$$\boldsymbol{X}_0 \sim \nu \Longrightarrow \mathcal{L}(\boldsymbol{X}_t | \tau_{\mathcal{O}} > t) = \nu$$

Existence, uniqueness, convergence: Assume $\mathcal{O}$ is bounded. For the Langevin and the overdamped Langevin dynamics, there exists a unique QSD ν in $\mathcal{S}$. Moreover, for any $\boldsymbol{X}_0$ in $\mathcal{S}$,

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

Remark: Quantitative definition of a metastable exit:

local equilibration time $\ll$ exit time

Existence of Quasi-Stationary Distributions

The QSD is the first eigenfunction of (the adjoint of) the infinitesimal generator of the dynamics with absorbing boundary conditions [Collet, Martinez, San Martin, 2013]: proofs rely on spectral analysis

Remarks:

- For overdamped Langevin, see [Le Bris, TL, Luskin, Perez, 2012] and [Gong, Qian, Zhao 1988] for non-gradient forces
- For Langevin, the result is non trivial since $\mathcal{O} \times \mathbb{R}^d$ is unbounded and the infinitesimal generator is hypoelliptic and non-reversible [TL, Ramil, Reygner, 2021] [Guillin, Nectoux, Wu, 2021]
- Other approaches use Lyapunov functions and Doeblin-like conditions [Champagnat, Villemonais, 2017-2018]

Fundamental properties of the QSD

Assume $\boldsymbol{X}_0 \sim \nu$, then:

- the first exit time $\tau_{\mathcal{O}}$ is exponentially distributed since:

$$\begin{aligned}\mathbb{P}_\nu(\tau_{\mathcal{O}} > s+t) &= \mathbb{P}_\nu(\tau_{\mathcal{O}} > s+t | \tau_{\mathcal{O}} > s)\, \mathbb{P}_\nu(\tau_{\mathcal{O}} > s) \\ &= \mathbb{P}_\nu(\tau_{\mathcal{O}} > t)\, \mathbb{P}_\nu(\tau_{\mathcal{O}} > s)\end{aligned}$$

- and $\tau_{\mathcal{O}}$ is independent of the first hitting point $\boldsymbol{X}_{\tau_{\mathcal{O}}}$ since:

$$\begin{aligned}\mathbb{P}_\nu(\boldsymbol{X}_{\tau_{\mathcal{O}}} \in A, \tau_{\mathcal{O}} > s) &= \mathbb{P}_\nu(\boldsymbol{X}_{\tau_{\mathcal{O}}} \in A | \tau_{\mathcal{O}} > s)\, \mathbb{P}_\nu(\tau_{\mathcal{O}} > s) \\ &= \mathbb{P}_\nu(\boldsymbol{X}_{\tau_{\mathcal{O}}} \in A)\, \mathbb{P}_\nu(\tau_{\mathcal{O}} > s)\end{aligned}$$

Consequence: Starting from ν, the exit event from $\mathcal{O}$ can be exactly written as one jump of a kinetic Monte Carlo model with rates

$$k_j = \frac{\mathbb{P}_\nu(\boldsymbol{X}_{\tau_{\mathcal{O}}} \in \partial\mathcal{O}_j)}{\mathbb{E}_\nu(\tau_{\mathcal{O}})}$$

Step 2: The small temperature regime

We need explicit formulas for $\mathbb{E}(\tau_{\mathcal{O}})$ and the distribution of $\boldsymbol{X}_{\tau_{\mathcal{O}}}$

Let us consider the overdamped Langevin dynamics. The first eigenstate (λ_1, u_1) of the infinitesimal generator, with Dirichlet boundary conditions on $\partial\mathcal{O}$ is:

$$\begin{cases} -\nabla V \cdot \nabla u_1 + \beta^{-1}\Delta u_1 = -\lambda_1 u_1 & \text{on } \mathcal{O} \\ u_1 = 0 & \text{on } \partial\mathcal{O} \end{cases}$$

Then, the QSD is $d\nu = \frac{1_{\mathcal{O}}(\boldsymbol{x})u_1(\boldsymbol{x})e^{-\beta V(\boldsymbol{x})}d\boldsymbol{x}}{\int_{\mathcal{O}} u_1 e^{-\beta V}}$

$$\mathbb{E}_\nu(\tau_{\mathcal{O}}) = \frac{1}{\lambda_1} \quad \text{and} \quad \mathbb{P}_\nu(\boldsymbol{X}_{\tau_{\mathcal{O}}} \in \partial\mathcal{O}_j) = -\frac{\int_{\partial\mathcal{O}_j} \partial_n u_1 e^{-\beta V}\, d\sigma}{\beta\lambda_1 \int_{\mathcal{O}} u_1 e^{-\beta V}}$$

Thus, $k_j = -\frac{\int_{\partial\mathcal{O}_j} \partial_n u_1 e^{-\beta V}\, d\sigma}{\beta \int_{\mathcal{O}} u_1 e^{-\beta V}}$. Can we then show that $k_j \simeq k_j^{TST}$?

Justifying Eyring-Kramers laws

Theorem [TL, Le Peutrec, Nectoux, 2022, to appear in JEP]
Let $\mathcal{O}$ be the basin of attraction of a local minimum x_1 of V.
Under some geometric assumptions, starting from the QSD, in the limit $\beta \to \infty$, the exit rates for the overdamped Lang dyn are

$$k_j = \nu_j^{OL} \, \mathrm{e}^{-\beta[V(z_j)-V(x_1)]} \, (1 + O(\beta^{-1/2}))$$

where

$$\nu_j^{OL} = \frac{|\mu_{z_j}|}{\pi} \sqrt{\frac{\det(\nabla^2 V)(x_1)}{|\det(\nabla^2 V)(z_j)|}}$$

with μ_{z_j} the negative eigenvalue of $\nabla^2 V(z_j)$

Assumptions

- V is a Morse function
- $\mathcal{O}$ is the basin of attraction of a local minimum x_1 of V (one may need to regularize the basin of attraction)
- Deep well: $V(z_1) - V(x_1) > V(z_J) - V(z_1)$
- $\forall j \in \{1, \dots, J\}$, consider B_{z_j} the basin of attraction of z_j for the dynamics $\dot{x} = -\nabla_T V(x)$ and assume that

$$\inf_{z \in B_{z_j}^c} d_a(z, z_j) > \max(V(z_J) - V(z_j), V(z_j) - V(z_1))$$

where d_a is the Agmon distance

Sketch of the proof (1/2)

Main difficulty: find a precise approximation of $\int_{\partial\mathcal{O}_j} \partial_n u_1$. One has

$$\begin{cases} L^{(0)} u_1 = \lambda_1 u_1 & \text{on } \mathcal{O} \\ u_1 = 0 & \text{on } \partial\mathcal{O} \end{cases}$$

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 $\nabla u_1 \cdot n$, and ∇u_1 satisfies

$$\begin{cases} L^{(1)} \nabla u_1 = \lambda_1 \nabla u_1 & \text{on } \mathcal{O} \\ \nabla_T u_1 = 0 & \text{on } \partial\mathcal{O} \\ (-\beta^{-1}\mathrm{div} + \nabla V \cdot)\nabla u_1 = 0 & \text{on } \partial\mathcal{O} \end{cases}$$

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 (2/2)

Let $\pi^{(p)}$ be the spectral projection operator on eigenvalues of $L^{(p)}$ smaller than some well-chosen constant c_0
For β large, $\dim(\mathrm{Ran}\pi^{(0)}) = 1$ and $\dim(\mathrm{Ran}\pi^{(1)}) = J$ [Helffer, Sjöstrand]:

$$\mathrm{Ran}\pi^{(0)} = \mathrm{Span}(u_1)$$

$$\mathrm{Ran}\pi^{(1)} = \mathrm{Span}(\psi_1, \ldots, \psi_J)$$

Since $\nabla u_1 \in \mathrm{Ran}\pi^{(1)}$,

$$\int_{\partial\mathcal{O}_j} \partial_n u_1 \, e^{-\beta V} = \sum_{\ell=1}^{J} \langle \nabla u_1, \psi_\ell \rangle_{L^2(e^{-\beta V})} \int_{\partial\mathcal{O}_j} \psi_\ell \cdot n \, e^{-\beta V}$$

The proof then consists in building quasi-modes which approximate $\mathrm{Ran}\pi^{(0)}$ and $\mathrm{Ran}\pi^{(1)}$ when $\beta \to \infty$

Eyring-Kramers formulas: quick review of other results

Global approaches:

- Analysis of the the spectrum in the small temperature regime: potential theoretic approaches [Bovier, Klein, Landim, Miclo, Seo,...], semiclassical analysis [Helffer, Nier, Simon, Sjöstrand,...]
- Compare kMC and (overdamped) Langevin in terms of spectrum: Time-lagged transition operator, Koopman operator [Schuette, Bornemann, Klus, Noe, Hartmann, Zhang, Koltai,...]

$\longrightarrow$ No information on the exit point distribution

Local approaches: Analysis of the exit event in the small temperature regime

- Large deviations [Freidlin, Wentzell, Day, Vanden-Eijnden, Sugiura, Weare, Touchette, Bouchet, Reygner,...]
- PDE techniques [Borisov, Ishii, Kamin, Perthame, Souganidis, Sultanov,...]

About large deviations

Another approach to study the exit problem from a domain: Large deviations techniques

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

Typical result [Freidlin, Wentzell, 2012, Theorem 5.1]: $\forall \mathcal{O}' \subset\subset \mathcal{O}$, $\forall \gamma, \delta > 0$, $\exists \delta_0 \in (0, \delta]$, $\exists \beta_0 > 0$, $\forall \beta \geq \beta_0$, $\forall x \in \mathcal{O}'$ s.t. $V(x) < V(z_1)$, $\forall y \in \partial\mathcal{O}$,

$$e^{-\beta[V(y)-V(z_1)+\gamma]} \leq \mathbb{P}_x(\boldsymbol{X}_{\tau_{\mathcal{O}}} \in \mathcal{V}_{\delta_0}(y)) \leq e^{-\beta[V(y)-V(z_1)-\gamma]}$$

Generalizations and perspectives

If the state is metastable, the QSD is a good intermediate between continuous-state space dynamics and jump Markov models

The mathematical analysis gives the proper geometric setting under which the kinetic Monte Carlo model can be built and the Eyring-Kramers formulas can be used to parameterize it

Beyond Eyring-Kramers laws for overdamped Langevin:

- Broader geometric setting (in particular purely entropic barriers)
- Langevin dynamics: one expects the same results with the prefactor

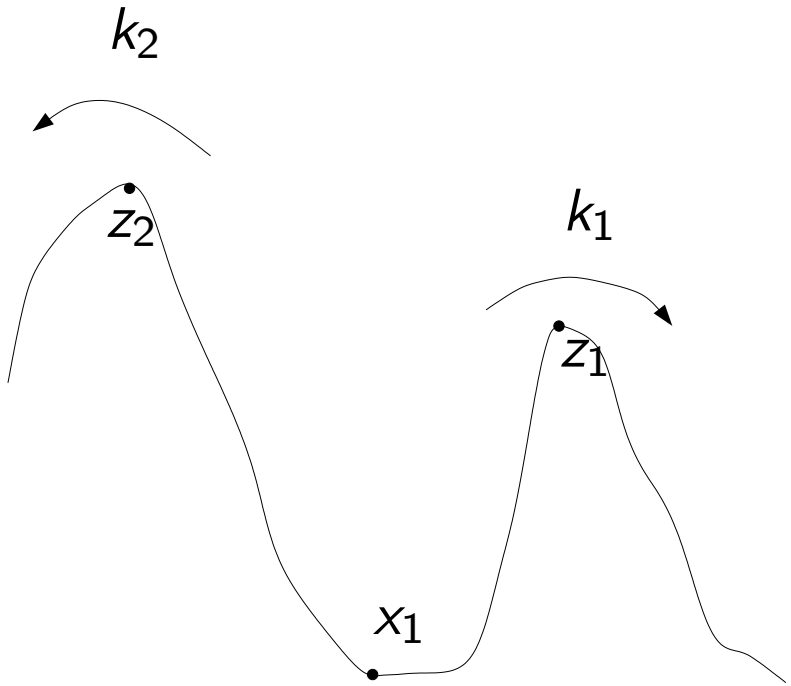
$$\nu_j^L = \frac{1}{2\pi}\left(\sqrt{\gamma^2 + 4|\mu_{z_j}|} - \gamma\right) \frac{\sqrt{\det(\nabla^2 V)(x_1)}}{\sqrt{|\det(\nabla^2 V)(z_j)|}}$$

- Non-reversible dynamics

Energetic vs entropic trap

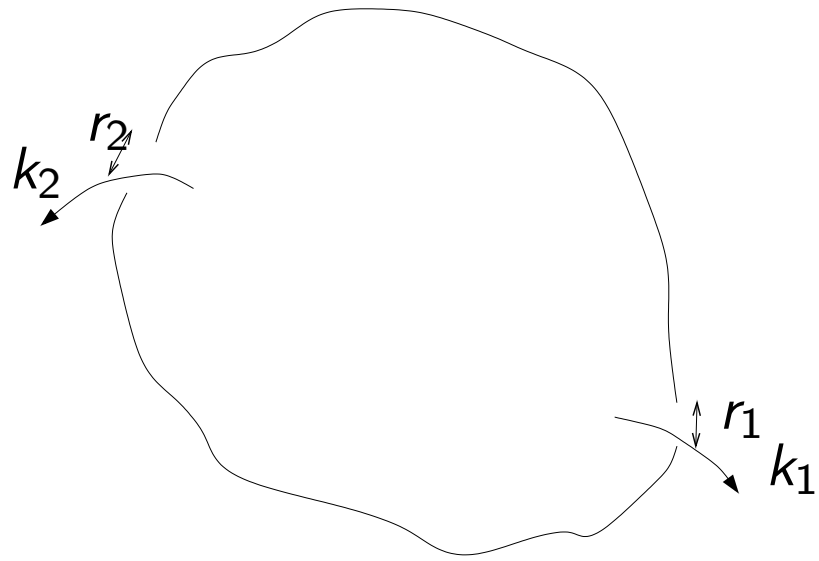
(work in progress [Carillo, Normand, TL, Stoltz, Vaes])

$\beta \to \infty$



$$k_j = \nu_j \, \mathrm{e}^{-\beta[V(z_j)-V(x_1)]}$$

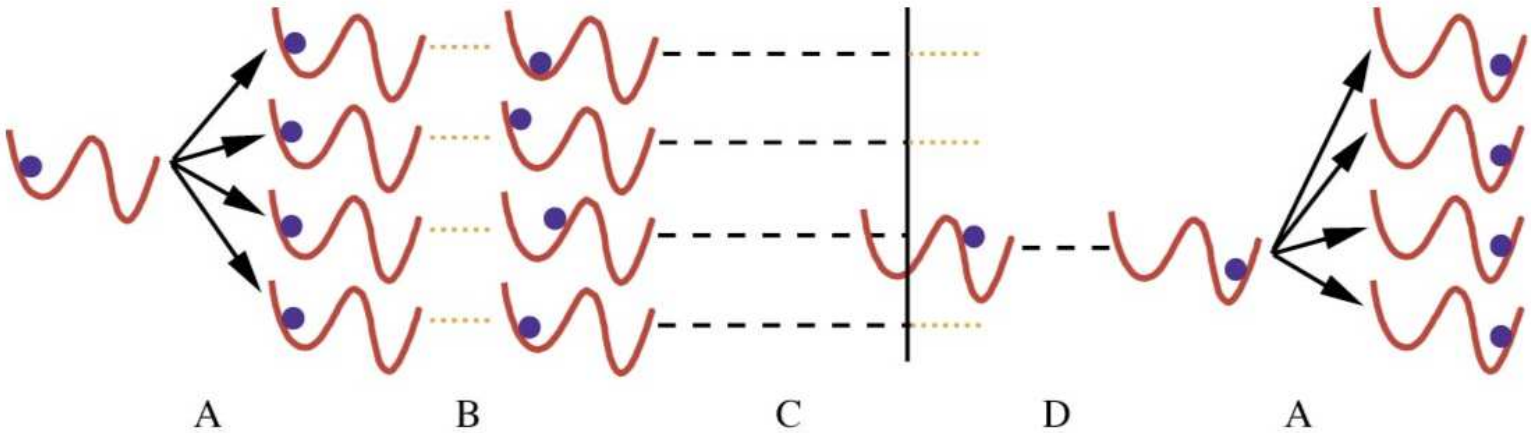
$$\max_j(r_j) \to 0$$



$$k_j = -\frac{1}{\ln r_j} \ (d = 2)$$

$$k_j = r_j^{d-2} \ (d > 2)$$

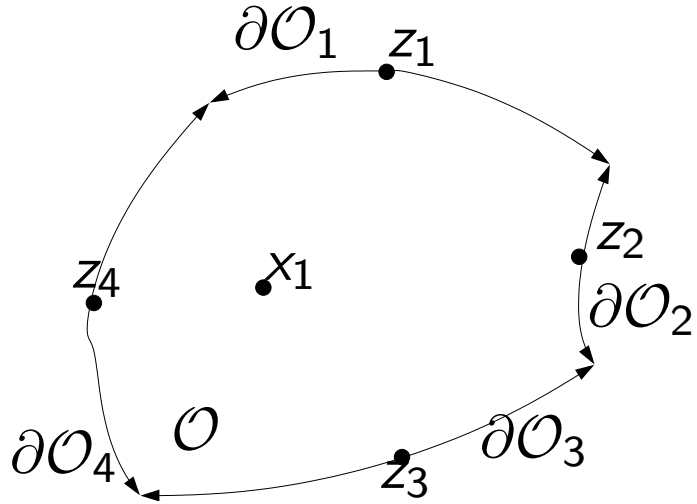
From theory to algorithms



A.F. Voter, Annu. Rev. Mater. Res., vol. 32, 2002

How to sample efficiently the exit event?

If the process remains sufficiently long in a state, the exit event can be modeled by one jump of a Markov state model. This can be used to simulate efficiently the exit event: accelerated dynamics *à la* A.F. Voter



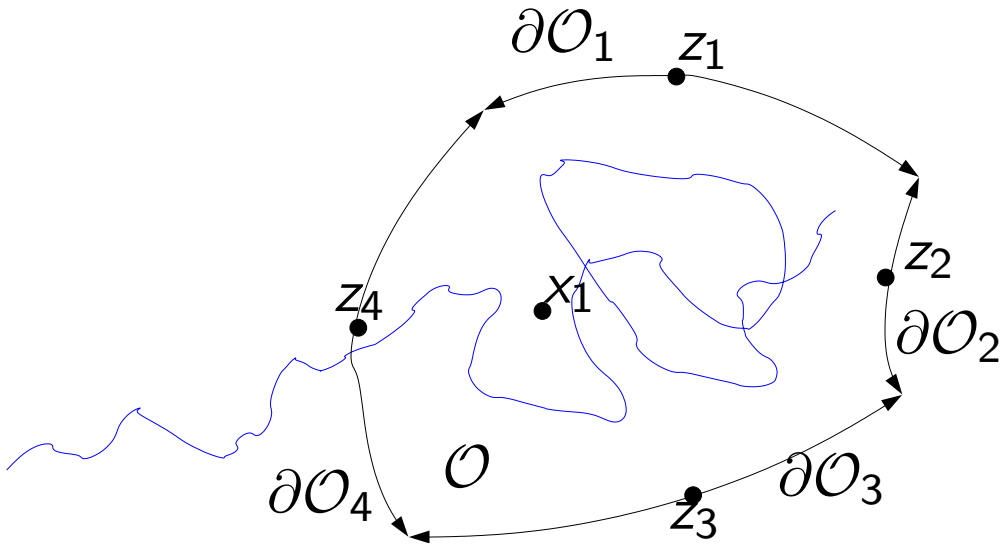
Two steps:

- Estimate the decorrelation time, namely the time to reach the QSD
- Use the underlying jump Markov process to efficiently sample the exit event

Decorrelation time

How long should we wait in practice so that $\mathcal{L}(\boldsymbol{X}_t|\tau_{\mathcal{O}} > t)$ is close to the QSD ν?

- Theoretically: exponential decay
  $\|\mathcal{L}(\boldsymbol{X}_t|\tau_{\mathcal{O}} > t) - \nu\|_{TV} \leq C(\mathcal{L}(\boldsymbol{X}_0)) \exp\left(-(\lambda_2 - \lambda_1)t\right)$
- Numerically: simulate $\mathcal{L}(\boldsymbol{X}_t|\tau_{\mathcal{O}} > t)$ via an interacting particle system (Fleming-Viot particle system), and test stationarity to estimate the convergence time to the QSD (Gelman-Rubin convergence diagnostic)



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 [Villemonais]

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

satisfies:

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

Accelerated dyamics

Once the QSD has been reached, there are three ideas to efficiently sample $(\tau_{\mathcal{O}}, \boldsymbol{X}_{\tau_{\mathcal{O}}})$:

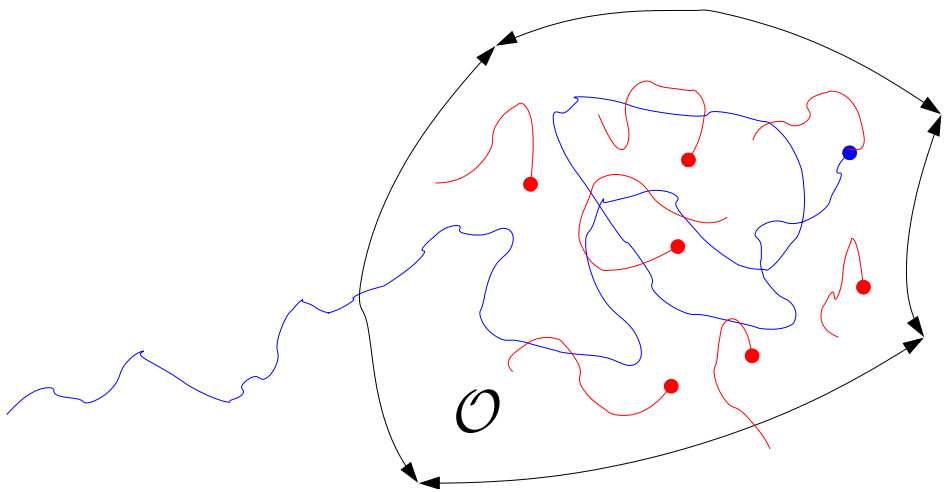
- use parallel architectures to accelerate the sampling: Parallel Replica, ParSplice
- raise the minimum of the potential inside the state $\mathcal{O}$ (but not on $\partial\mathcal{O}$): Hyperdynamics
- raise the temperature: Temperature Accelerated Dynamics

The Parallel Replica Algorithm

Perform many independent exit events in parallel [Voter, 1998]

Two steps:

- Distribute N independent initial conditions in $\mathcal{O}$ according to the QSD ν
- Evolve N replicas from these initial conditions, consider the first exiting replica, and multiply the first exit time by the number of replicas



The Parallel Replica Algorithm

Why is it consistent?

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

$$N \min(\tau_{\mathcal{O}}^1, \ldots, \tau_{\mathcal{O}}^N) \stackrel{\mathcal{L}}{=} \tau_{\mathcal{O}}^1$$

- Exit time is independent of exit point so that

$$\boldsymbol{X}^{I_0}_{\tau_{\mathcal{O}}^{I_0}} \stackrel{\mathcal{L}}{=} \boldsymbol{X}^1_{\tau_{\mathcal{O}}^1}$$

where $I_0 = \arg\min_i(\tau_{\mathcal{O}}^i)$

Remark: For this algorithm, one just needs two properties: $\tau_{\mathcal{O}}$ is exponentially distributed, and independent of the exit point $\boldsymbol{X}_{\tau_{\mathcal{O}}}$. The Eyring-Kramers formulas for the exit rates are not used

The generalized Parallel Replica algorithm

[Binder, Hédin, TL, Simpson, 2015]

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 generalized Parallel Replica algorithm

- The algorithm does not require a partition of the state space but only an ensemble of states
- The time to reach the QSD is estimated each time the process enters a new state using the Gelman-Rubin convergence diagnostic: it depends on the state and on the initial condition within the state

Numerical results

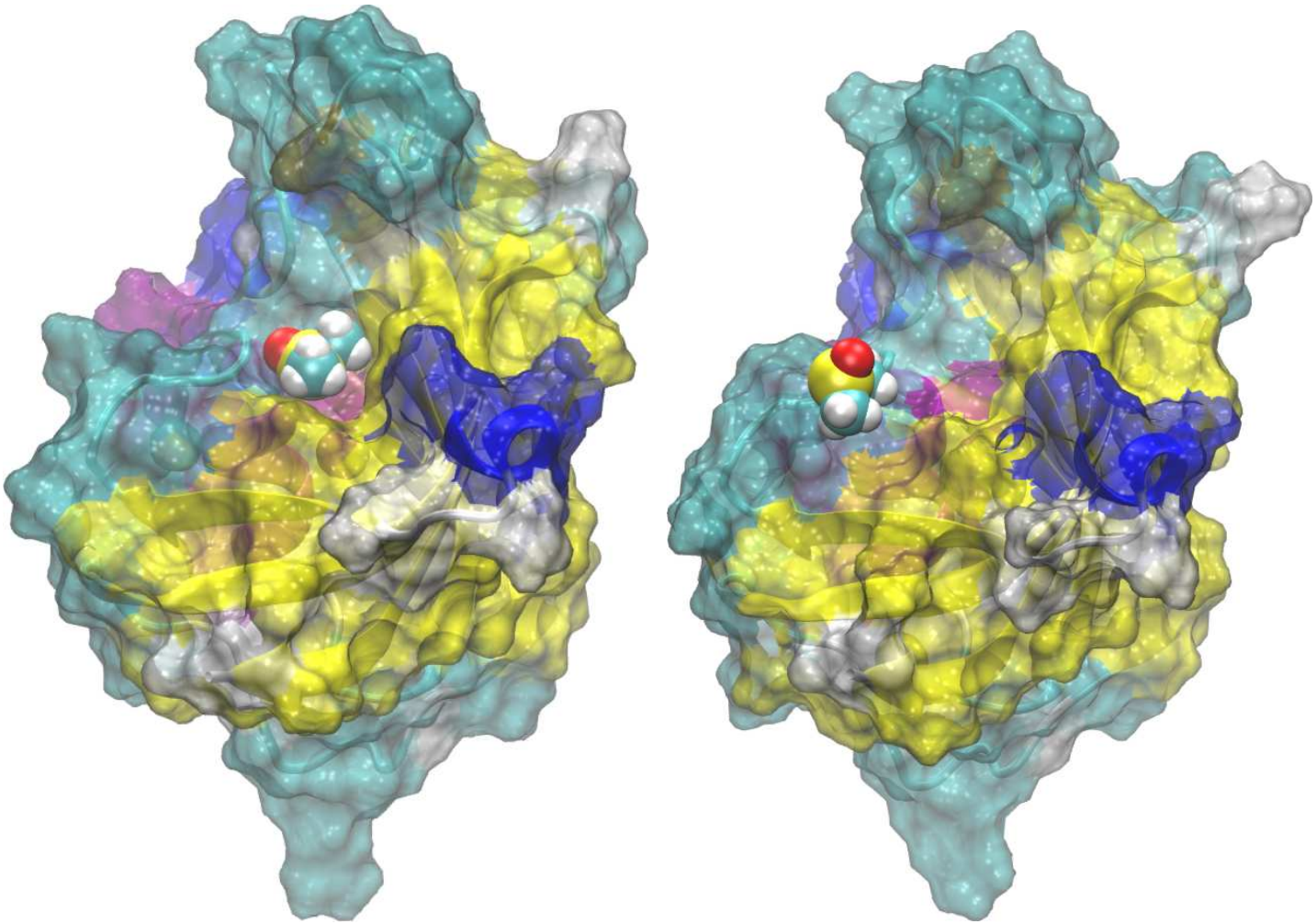
We tested the generalized Parallel Replica algorithm applied to biological systems [Hédin, TL, 2019]:

- Conformational equilibrium of the alanine dipeptide
- Dissociation of the FKBP-DMSO protein-ligand system

Main differences with materials science: definition of the states using collective variables; the states do not define a partition; much more rugged energy landscapes

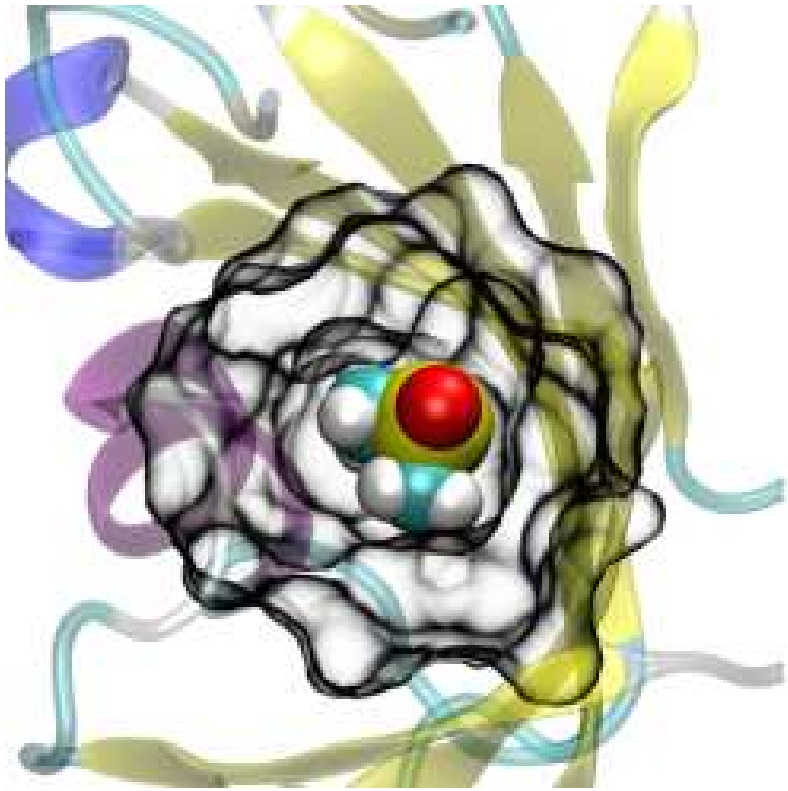
Implementation within OpenMM, see
`https://gitlab.inria.fr/parallel-replica`

FKBP-DMSO: the model (1/4)

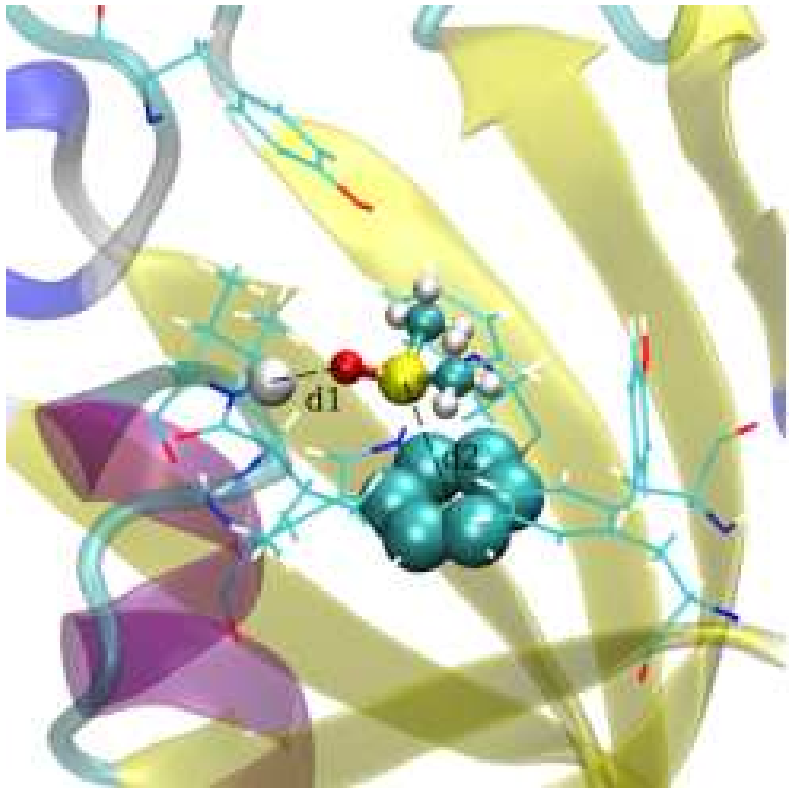


FKBP-DMSO complex,
corresponding to the RCSB-PDB entry “1D7H”

FKBP-DMSO: the model (2/4)

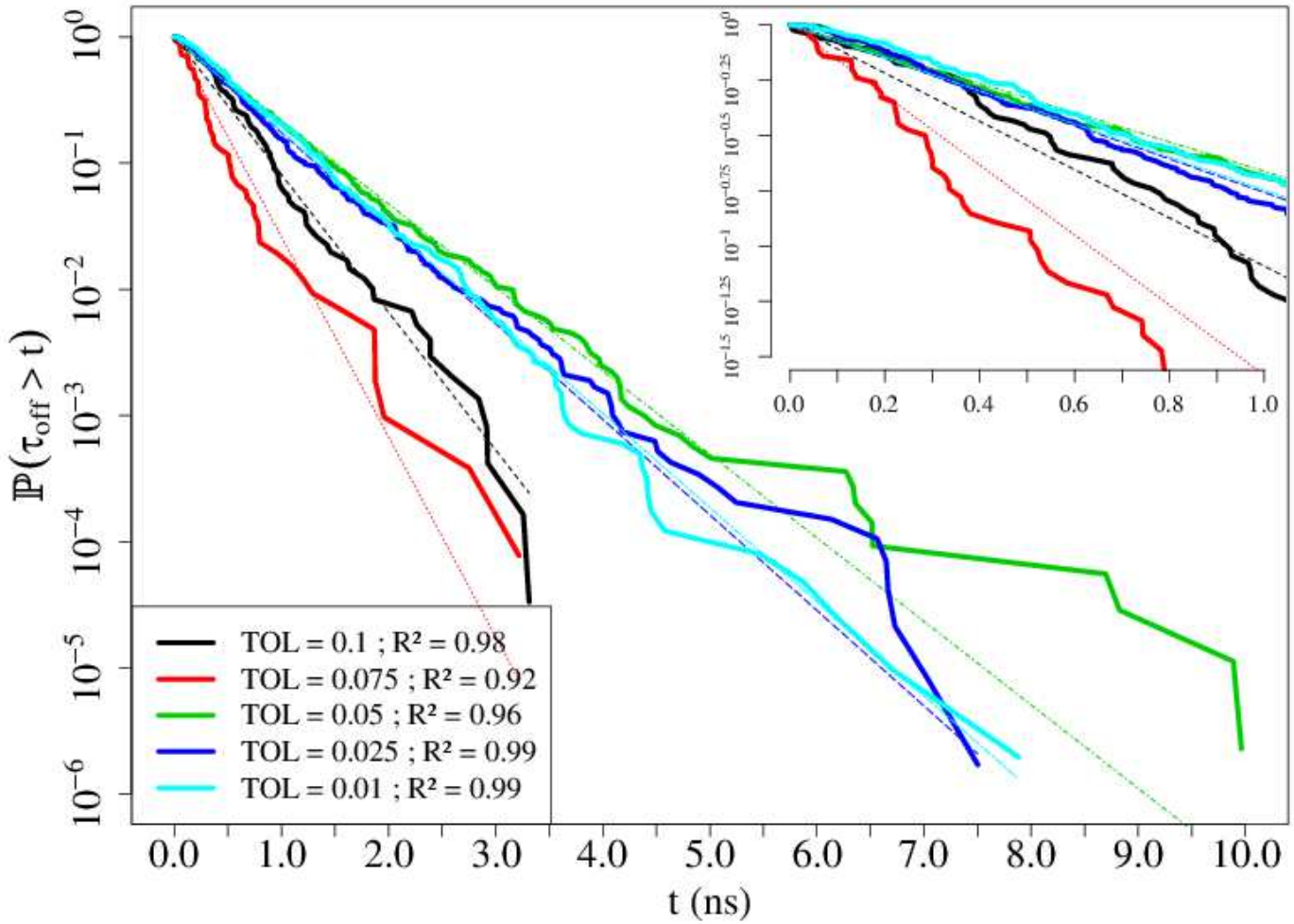


DMSO in its binding cavity



Distances used to define the cavity

FKBP-DMSO: accuracy of ParRep (3/4)



Cumulative distribution function of the dissociation times

FKBP-DMSO: parallel efficiency (4/4)

TOL	Speed (ns/day)	Eff. speedup	(Eff./Max)
0.05	493.4	95.8	68.4%
0.025	496.8	96.5	68.9%
0.01	409.4	79.5	56.8%

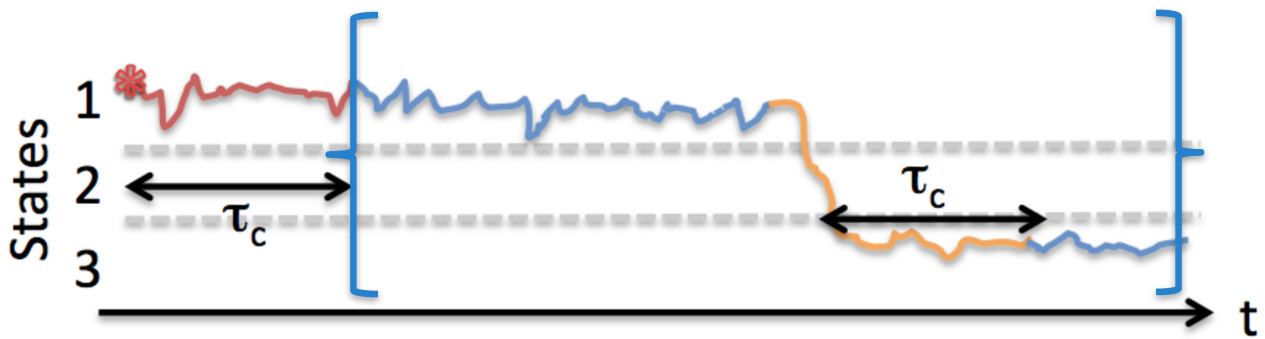
Effective speed-up as a function of the tolerance, for $N = 140$ replicas run in parallel (speed of a reference Langevin dynamics is 5.15 ns/day)

The Parallel Trajectory Splicing algorithm

Precompute the exit events [Perez, Cubuk, Waterland, Kaxiras, Voter, 2015]

Algorithm:

- 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

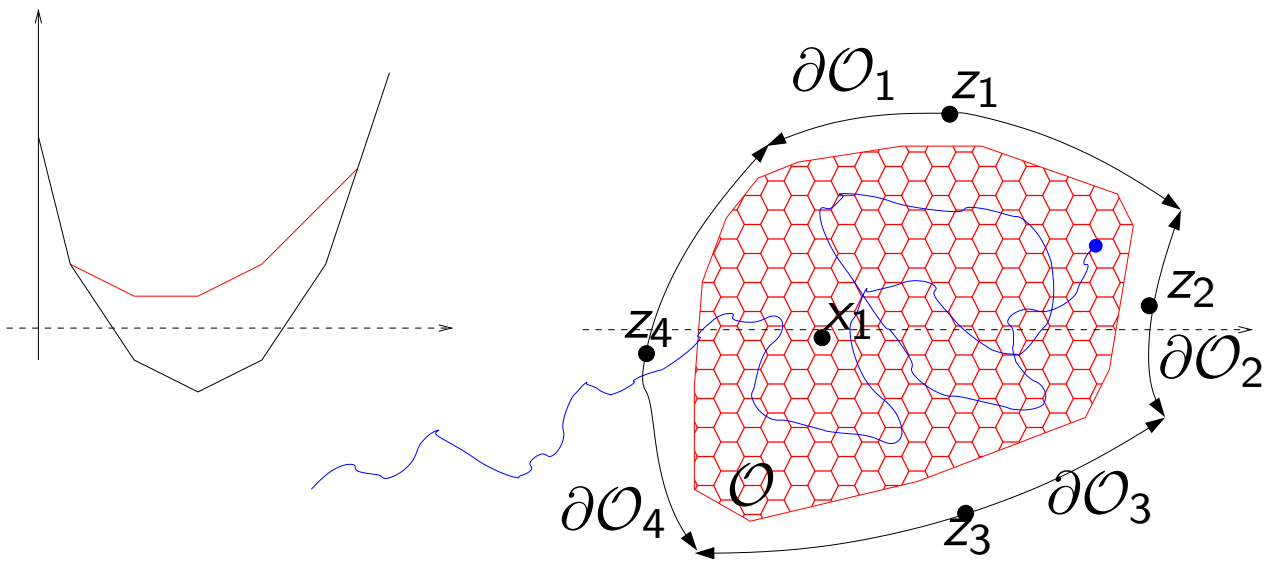


Hyperdynamics (1/2)

Raise the potential in $\mathcal{O}$ to reduce the exit time [Voter, 1997]

Two steps:

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



Hyperdynamics (2/2)

Why is it consistent ?

Assumptions on δV: (i) $\delta V = 0$ on $\partial\mathcal{O}$ and (ii) δV is sufficiently small so that the Theorem above applies on V and $V + \delta V$

Recall the formula for the exit rates:

$$k_j = \nu_j^{OL}\, \mathrm{e}^{-\beta[V(z_j)-V(x_1)]}\,(1 + O(\beta^{-1}))$$

where $\nu_j^{OL} = \frac{|\mu_{z_j}|}{\pi}\sqrt{\frac{\det(\nabla^2 V)(x_1)}{|\det(\nabla^2 V)(z_j)|}}$

Thus $k_j / \sum_{\ell=1}^J k_\ell$ is independent of δV and

$$\frac{\sum_{\ell=1}^J k_\ell(V+\delta V)}{\sum_{\ell=1}^J k_\ell(V)} = \sqrt{\frac{\det(\nabla^2(V+\delta V))(x_1)}{\det(\nabla^2(V))(x_1)}}\mathrm{e}^{\beta\delta V(x_1)}(1+O(\beta^{-1}))$$

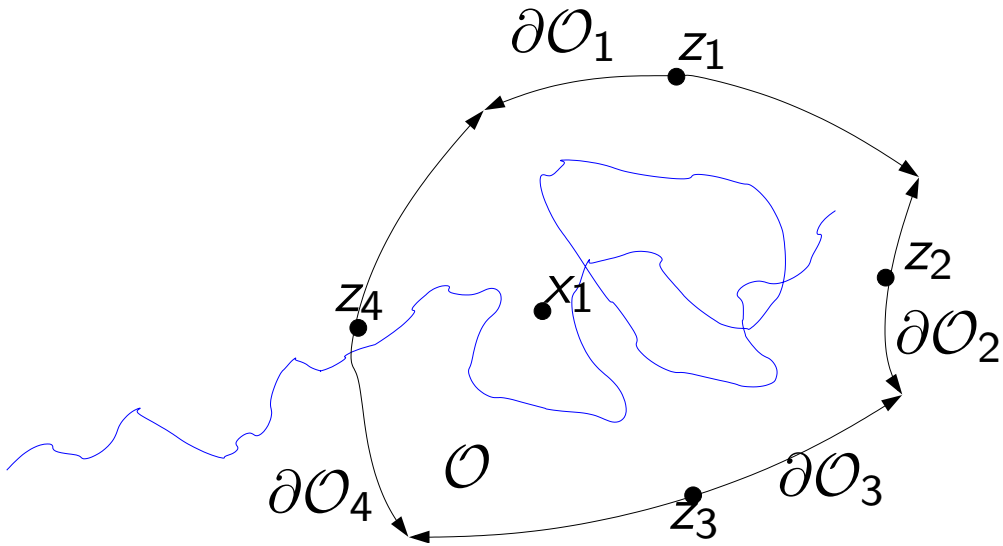
$$= \frac{\int_{\mathcal{O}}\exp(-\beta V)}{\int_{\mathcal{O}}\exp(-\beta(V+\delta V))}(1+O(\beta^{-1})) \simeq B$$

Temperature Accelerated Dynamics (1/2)

Increase the temperature to reduce the exit time [Sorensen, Voter, 2000]

Algorithm:

- Observe the exit events from $\mathcal{O}$ at high temperature
- Extrapolate the high temperature exit events to low temperature exit events



Temperature Accelerated Dynamics (2/2)

Recall that, starting from the QSD, the exit event from a given state $\mathcal{O}$ can exactly be modelled using a kinetic Monte Carlo model with rates

$$k_j = \nu_j^{OL} \, \mathrm{e}^{-\beta[V(z_j)-V(x_1)]} \, (1 + O(\beta^{-1}))$$

where $\nu_j^{OL} = \frac{|\mu_{z_j}|}{\pi} \sqrt{\frac{\det(\nabla^2 V)(x_1)}{|\det(\nabla^2 V)(z_j)|}}$

Thus,

$$\frac{k_j^{lo}}{k_j^{hi}} \simeq \exp(-(\beta^{lo} - \beta^{hi})(V(z_j) - V(x_1)))$$

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

Generalizations and perspectives

- The parallel replica is a very versatile algorithm: it applies *e.g.* to non reversible dynamics, discrete-in-time dynamics, continuous-time Markov Chain [Aristoff, Plechac, Wang]. It does not require estimates for the exit rates
- Hyper and TAD are more efficient, but require the temperature to be sufficiently small so that estimates of the rates by the Eyring-Kramers formulas hold true

All these techniques require "good" metastable states:

$$\text{exit time} > \text{convergence time to the QSD}$$

Generalizations and perspectives

Works in progress:

- How to efficiently estimate the convergence to the QSD?
- How to to optimize the definitions of the states? For example, consider [Blassel, TL, Stoltz]:

$$\max_{\mathcal{O}} \frac{\lambda_2(\mathcal{O}) - \lambda_1(\mathcal{O})}{\lambda_1(\mathcal{O})}$$

- Combine ParRep with Hyper [Adjoua, Gouraud, Lagardère, Monmarché, Plé]

References

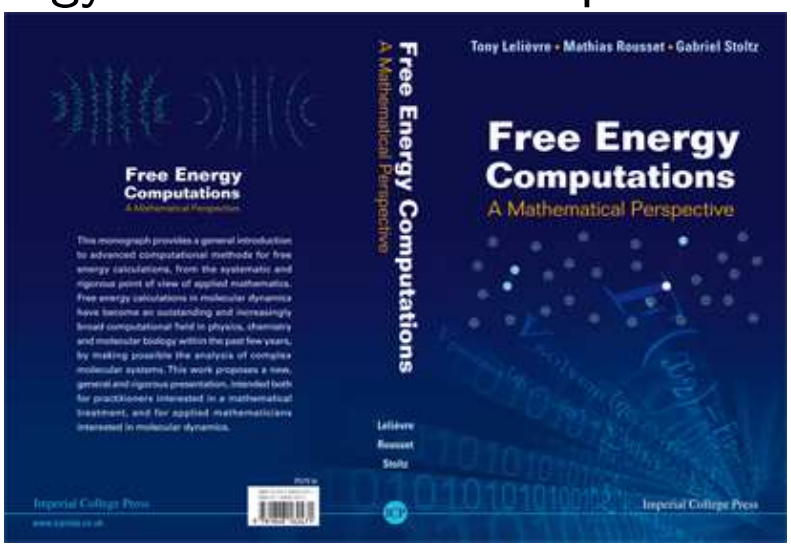
Some papers I mentioned:

- G. Di Gesù, TL, D. Le Peutrec and B. Nectoux, *Jump Markov models and transition state theory: the Quasi-Stationary Distribution approach*, Faraday Discussion, 2016
- C. Le Bris, TL, M. Luskin, and D. Perez, *A mathematical formalization of the parallel replica dynamics*, Monte Carlo Methods and Applications, 2012
- TL, D. Le Peutrec, and B. Nectoux, *Eyring-Kramers exit rates for the overdamped Langevin dynamics: the case with saddle points on the boundary*, Journal de l'Ecole Polytechnique, 2025
- TL, M. Rachid et G. Stoltz, *A spectral approach to the narrow escape problem in the disk*, `arXiv 2401.06903`, 2024
- TL, M. Ramil, and J. Reygner, *Quasi-stationary distribution for the Langevin process in cylindrical domains, part I: existence, uniqueness and long-time convergence*, Stochastic Processes and their Applications, 2022

References

Review works:

- TL and Gabriel Stoltz, *Partial differential equations and stochastic methods in molecular dynamics*. Acta Numerica, 25, 2016
- TL and Danny Perez *Recent advances in Accelerated Molecular Dynamics Methods: Theory and Applications*, In: Comprehensive Computational Chemistry, Vol. 3, 2024
- A book on free energy calculation techniques:



Mini-symposia

If you want to learn more on sampling, particle systems and metastability, join us in the two mini-symposia co-organized with Pierre Monmarché:

- Wednesday 11:00-13:00: Noé Blassel, Marylou Gabrié, Tim Johnston, Oliver Tough
- Thursday 14:30-16:30: Shiva Darshan, Elisa Marini, Mouad Ramil, Adrien Vacher