

Tensorized Adaptive Biasing Force method for molecular dynamics

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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.

Example: Compute the pressure of a liquid at a given density and temperature.

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

Consider a system composed of N atoms whose positions are denoted by a vector

$$(\mathbf{x}_1, \dots, \mathbf{x}_N) = \mathbf{x} \in (\mathbb{R}^3)^N.$$

For the sake of simplicity, we are going to assume here that **periodic boundary conditions** are imposed on the system so that

$$\mathbf{x} \in (\mathbb{T}^3)^N,$$

where \mathbb{T} denotes the periodic torus \mathbb{R}/\mathbb{Z} .

Basic ingredient to describe the atomistic system: Interaction potential

$$V : \begin{cases} \mathbb{T}^{3N} & \rightarrow \mathbb{R} \\ \mathbf{x} := (\mathbf{x}_1, \dots, \mathbf{x}_N) & \mapsto V(\mathbf{x}_1, \dots, \mathbf{x}_N) \end{cases}$$

which associates to a **configuration** $\mathbf{x} := (\mathbf{x}_1, \dots, \mathbf{x}_N) \in \mathbb{T}^{3N}$ an **energy** $V(\mathbf{x}_1, \dots, \mathbf{x}_N)$, and characterizes the interactions between the different atoms in the system.

Overdamped Langevin dynamics

The evolution of the positions of the atoms is assumed to satisfy the following stochastic dynamics (called *over-damped Langevin* dynamics).

At time $t > 0$, denoting by $\mathbf{X}_t \in \mathbb{T}^{3N}$ the positions of the N atoms in the molecular system at time t , \mathbf{X}_t is solution to the following stochastic differential equation:

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

where $\beta = (k_B T)^{-1}$ is proportional to the inverse of the temperature, and \mathbf{W}_t is a $3N$ -dimensional Brownian motion.

Time discretization (Euler-Maruyama scheme): $\Delta t > 0$, $t_n = n\Delta$

$$\mathbf{X}_{t_{n+1}} = \mathbf{X}_{t_n} - \nabla V(\mathbf{X}_{t_n}) \Delta t + \sqrt{2\Delta t \beta^{-1}} \mathbf{G}_n$$

where $\mathbf{G}_0, \dots, \mathbf{G}_n, \dots$ are independent gaussian variables $\sim \mathcal{N}(0, \text{Id})$.

The over-damped Langevin dynamics is **ergodic with respect to the Gibbs measure** $\mu(d\mathbf{x})$ with

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

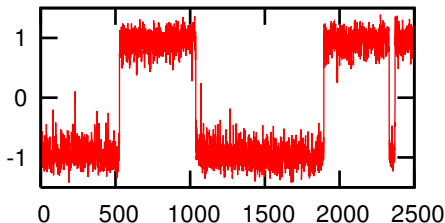
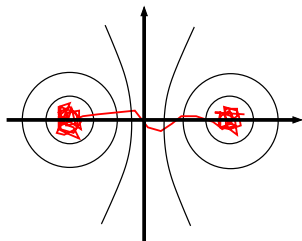
where $Z := \int_{\mathbb{T}^{3N}} \exp(-\beta V(\mathbf{x})) d\mathbf{x}$.

This property is extremely important to compute macroscopic quantities, in particular **thermodynamic quantities** (examples: stress, heat capacity...), which read as averages with respect to μ of some functions $\varphi : \mathbb{T}^{3N} \rightarrow \mathbb{R}$.

Indeed,

$$\begin{aligned} \mathbb{E}_\mu [\varphi(\mathbf{X})] &= \int_{\mathbb{T}^{3N}} \varphi(\mathbf{x}) \mu(d\mathbf{x}) = \frac{1}{Z} \int_{\mathbb{T}^{3N}} \varphi(\mathbf{x}) \exp(-\beta V(\mathbf{x})) d\mathbf{x} \\ &= \lim_{t \rightarrow +\infty} \frac{1}{t} \int_0^t \varphi(\mathbf{X}_s) ds. \end{aligned}$$

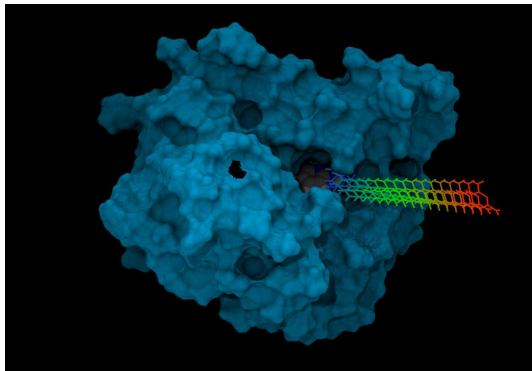
- **Difficulty:** the potential V has several local minima in practice.
- As a consequence, the dynamics is **metastable**: the stochastic process \mathbf{X}_t stays a long time close to a well (a local minimizer) of V before jumping to another well.



- Timescale of the microscopic process: 10^{-15} sec.
- Timescale of the macroscopic process: from 10^{-6} to 10^2 sec.
- **Slow convergence with respect to t of $\lim_{t \rightarrow +\infty} \frac{1}{t} \int_0^t \varphi(\mathbf{X}_s) ds$.**

Unbinding of a ligand from a protein

(Diaminopyridine-HSP90, Courtesy of SANOFI)



3,258 atoms without solvent. 41,091 atoms with solvent. 1 to 2 Angstroms.

Elementary time-step for the molecular dynamics = 10^{-15} s

Dissociation time = 0.5 s

The aim of the **Adaptive Biasing Force (ABF)** method is to **adaptively modify the stochastic dynamics** along a given time trajectory so as to **accelerate the convergence** of long-time averages of the form $\lim_{t \rightarrow +\infty} \frac{1}{t} \int_0^t \varphi(\mathbf{X}_s) ds$ with respect to t .

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

In the ABF method, it is assumed that an appropriate **collection of slow variables** associated to the molecular system is given. More precisely, let us assume that there exists a function

$$\xi : \mathbb{T}^{3N} \rightarrow \mathbb{T}^d,$$

so that $d \ll 3N$ and $\xi(\mathbf{x})$ enables to properly characterize coarse-grained degrees of freedom of the system for a configuration $\mathbf{x} \in \mathbb{T}^{3N}$.

Example: $\xi(\mathbf{x})$ may represent the length between two particular atoms in the system, or some particular bond angles...

Reaction coordinates

Such a vector $\xi(\mathbf{x})$ is called a vector of **reaction coordinates** or **collective variables**, and will be used to bias the dynamics.

Such reaction coordinates can either be intuited by chemists or physicists, or be identified by **machine learning** techniques (diffusion maps, nonlinear manifold learning...)

Kevrekidis, Goldsmith, Arroyo, Clementi, ...

For the sake of simplicity of the presentation, we are going to assume in the rest of the talk that

$$\xi(\mathbf{x}) = (\mathbf{x}_1, \dots, \mathbf{x}_p)$$

for some $p \in \mathbb{N}$ such that $p \ll N$, so that $d = 3p$.

We will also denote by $D := 3N - 3p = 3N - d$ and write any $\mathbf{x} \in \mathbb{T}^{3N}$ as

$$\mathbf{x} = (z, q) \text{ with } z \in \mathbb{T}^d \text{ and } q \in \mathbb{T}^D.$$

Then, for the above choice of reaction coordinates, it holds that

$$\xi(\mathbf{x}) = \xi(z, q) = z.$$

(based on works by T. Lelièvre, F. Legoll, M. Rousset and G. Stoltz)

The **free energy** $A : \mathbb{T}^d \rightarrow \mathbb{R}$ of the molecular system associated to the reaction coordinates $\xi(\mathbf{x}) = \xi(z, q) = z$ is defined as follows:

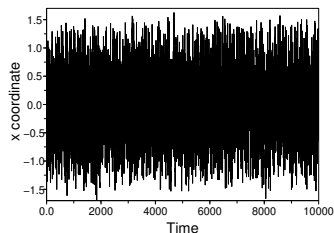
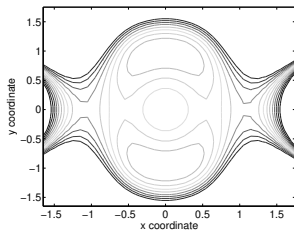
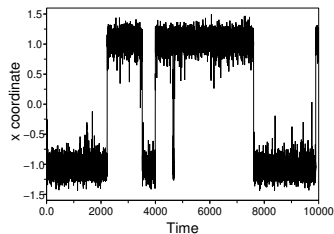
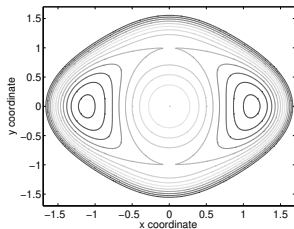
$$\forall z \in \mathbb{T}^d, \quad A(z) = -\beta^{-1} \ln \left(\int_{\mathbb{T}^D} e^{-\beta V(z, q)} dq \right).$$

The bottom line of the ABF method is the following: for a “well chosen” set of reaction coordinates ξ , the potential $\mathcal{V} = V - A \circ \xi$ is “has less local minima” than V .

Hence, if the set of reaction coordinates ξ is well-chosen, long-time convergence of time averages should be **faster for overdamped Langevin dynamics associated to the potential \mathcal{V}** than for the original overdamped Langevin dynamics associated to the unbiased potential V .

Free energy biased potential

A 2D example of a free energy biased trajectory: **energetic barrier**. $\xi(z, q) = z$



Problem 1: A is unknown ! **Idea:** use a time dependent potential of the form

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

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

Hopes: build a dynamics such that A_t quickly converges to A as t increases.

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

More precisely, the aim of an ABF method is to sample the biased process

$$d\tilde{\mathbf{X}}_t = -\nabla_{\mathbf{x}} \mathcal{V}_t(\tilde{\mathbf{X}}_t) dt + \sqrt{2\beta^{-1}} dW_t,$$

where for all time $t \geq 0$, $\mathcal{V}_t = V - A_t \circ \xi$ and the bias function A_t

- is equal to 0 at time $t = 0$: $A_0 = 0$;
- is easy to compute given the knowledge of the past trajectory $(\tilde{\mathbf{X}}_s)_{0 \leq s \leq t}$;
- converges quickly in the long time limit to an approximation of the free energy A .

In the sequel, we will use the notation for all $t \geq 0$,

$$\tilde{\mathbf{X}}_t = (\tilde{Z}_t, \tilde{Q}_t) \text{ where } \tilde{Z}_t \in \mathbb{T}^d \text{ and } \tilde{Q}_t \in \mathbb{T}^D.$$

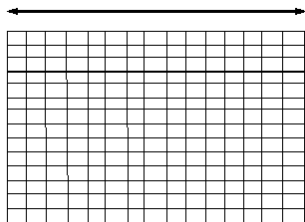
Assuming that A_t converges in the long time limit (in some sense) to a limit function A_∞ , we can recover averages of $\varphi : \mathbb{T}^{3N} \rightarrow \mathbb{R}$ with respect to the Gibbs measure μ using the following debiasing formula:

$$\frac{\frac{1}{t} \int_0^t \varphi(\tilde{X}_s) e^{-\beta A_s \circ \xi(\tilde{X}_s)} ds}{\frac{1}{t} \int_0^t e^{-\beta A_s \circ \xi(\tilde{X}_s)} ds} \xrightarrow{t \rightarrow +\infty} \frac{\int_{\mathbb{T}^{3N}} \varphi(\mathbf{x}) e^{-\beta A_\infty \circ \xi(\mathbf{x})} e^{-\beta(V - A_\infty \circ \xi)(\mathbf{x})} d\mathbf{x}}{\int_{\mathbb{T}^{3N}} e^{-\beta A_\infty \circ \xi(\mathbf{x})} e^{-\beta(V - A_\infty \circ \xi)(\mathbf{x})} d\mathbf{x}}$$
$$= \frac{\int_{\mathbb{T}^{3N}} \varphi(\mathbf{x}) e^{-\beta V(\mathbf{x})} d\mathbf{x}}{\int_{\mathbb{T}^{3N}} e^{-\beta V(\mathbf{x})} d\mathbf{x}}.$$

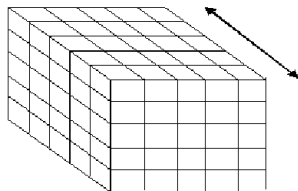
Problem 2: When the number of relevant reaction coordinates d becomes large (say a few dozens), standard ABF methods suffer from the **curse of dimensionality**.

$A(z)$ has to be discretized on a grid whose size scales exponentially with respect to d :

$$DIM = N^2$$



$$DIM = N^3$$



$$DIM = N^d$$

Tensorized Adaptive Biasing Force Method (TABF): Modified ABF method, combined with **tensor approximations**, in order to circumvent the curse of dimensionality in the case where the number of reaction coordinates is large.

Basic idea in this talk: for $t > 0$, an approximation A_t of A will be computed under a tensorized form

$$\forall z = (z_1, \dots, z_d) \in \mathbb{T}^d, \quad A_t(z) \approx \sum_{k=1}^{m_t} r_k^1(t, z_1) \cdots r_k^d(t, z_d)$$

with m_t small (hopefully).

This is done here using a **greedy** algorithm, which is an iterative scheme.

Billaud-Friess, Cueto, Chamoin, Chinesta, Huerta, Maday, Ladevèze, Temlyakov, Néron, Nouy, Zahm ...

Remark: More evolved tensor formats such as Tensor Train or Hierarchical Tucker could also be used here in principle.

The idea of the TABF method is to exploit the fact that the free energy A of the system is the solution (up to an arbitrary additive constant) to the minimization problem

$$\operatorname{argmin}_{f \in H^{1,0}(\mathbb{T}^d)} \mathcal{E}(f)$$

where

$$\mathcal{E}(f) := \int_{\mathbb{T}^d \times \mathbb{T}^D} |\nabla_z V(z, q) - \nabla_z f(z)|^2 e^{-\beta V(z, q)} dz dq$$

and

$$H^{1,0}(\mathbb{T}^d) := \left\{ f \in H^1(\mathbb{T}^d), \int_{\mathbb{T}^d} f = 0 \right\}.$$

At some time $t \geq 0$, A_t will be computed as a tensorized approximation of the solution of the minimization problem

$$\underset{f \in H^{1,0}(\mathbb{T}^d)}{\operatorname{argmin}} \mathcal{E}_t(f) \quad (1)$$

where

$$\begin{aligned} \mathcal{E}_t(f) &:= \frac{1}{t} \int_0^t |\nabla_z V(\tilde{Z}_s, \tilde{Q}_s) - \nabla_z f(\tilde{Z}_s)|^2 e^{-\beta A_s \circ \xi(\tilde{X}_s)} ds \\ &= \frac{1}{t} \int_0^t |\nabla_z V(\tilde{Z}_s, \tilde{Q}_s) - \nabla_z f(\tilde{Z}_s)|^2 e^{-\beta A_s(\tilde{Z}_s)} ds \end{aligned}$$

where for all $0 \leq s \leq t$, $\tilde{\mathbf{X}}_s = (\tilde{Z}_s, \tilde{Q}_s) \in \mathbb{T}^d \times \mathbb{T}^D$.

Let $T > 0$ a given time frame and $T_n := nT$ for all $n \in \mathbb{N}$.

- Set $n = 0$, $t_0 = 0$ and $A_0 = 0$;
- Suppose that A_{T_n} has already been computed. Then, sample the biased process \tilde{X}_t with $A_t = A_{T_n}$ for time $T_n \leq t \leq T_{n+1}$.
- At time T_{n+1} , define $A_{T_{n+1}}$ as a tensorized approximation of a minimizer to

$$\operatorname{argmin}_{f \in H^{1,0}(\mathbb{T}^d)} \mathcal{E}_{T_{n+1}}(f) \quad (2)$$

with $\mathcal{E}_{T_{n+1}}$ defined in the previous slide.

- Set $n := n + 1$.

Theorem (VE, Lelièvre, Monmarché, 2021)

Under some additional technical assumptions (regularity on V , ...), assuming that for all $n \in \mathbb{N}$, $A_{T_{n+1}}$ is computed as an *exact minimizer* to

$$\operatorname{argmin}_{f \in H^{1,0}(\mathbb{T}^d)} \mathcal{E}_{T_{n+1}}(f), \quad (3)$$

it holds that

$$\|\nabla_z A_t - \nabla_z A\|_{L^2(\mathbb{T}^d)} \xrightarrow{t \rightarrow +\infty} 0.$$

The main ingredient of the proof is to use the so-called ODE method of [Benaïm, Ledoux, Raimond, 2002].

Computation of the tensorized approximation

Let $t \geq 0$ and let us now explain the method used to compute a tensorized approximation of a solution to the minimization problem

$$\operatorname{argmin}_{f \in H^{1,0}(\mathbb{T}^d)} \mathcal{E}_t(f) \quad (4)$$

Recall that

$$H^{1,0}(\mathbb{T}^d) = \left\{ f \in H^1(\mathbb{T}^d), \int_{\mathbb{T}^d} f = 0 \right\}. \quad (5)$$

and that $H^{1,0}(\mathbb{T}^d) \ni f \mapsto \mathcal{E}_t(f)$ is a **quadratic functional** with respect to f .

Two difficulties are in order here, with respect to tensor approximations to solutions of (4):

- the functional \mathcal{E}_t is not strongly convex on $H^{1,0}(\mathbb{T}^d)$: this issue is related to **tensor completion problems** but will not be addressed here;
- the **zero-mean condition** in the definition of $H^{1,0}(\mathbb{T}^d)$: numerical instabilities observed in ALS if not taken into account for the resolution of (4).

Greedy algorithm

Let us assume here for the sake of simplicity that \mathcal{E}_t is a strongly convex quadratic functional defined on $H^{1,0}(\mathbb{T}^d)$ and let

$$u = \operatorname{argmin}_{f \in H^{1,0}(\mathbb{T}^d)} \mathcal{E}_t(f). \quad (6)$$

Standard greedy algorithm:

- set $m = 0$ and $u_0 = 0$.
- **Iteration n :** compute $h_{m+1} \in \Sigma$ solution to

$$h_{m+1} \in \operatorname{argmin}_{h \in \Sigma} \mathcal{E}_t(u_m + h).$$

Define $u_{m+1} := u_m + h_{m+1}$ and set $m := m + 1$;

where Σ is a dictionary of pure tensor-product functions:

$$\Sigma = \left\{ \begin{array}{l} w \in H^{1,0}(\mathbb{T}^d), \\ \forall z = (z_1, \dots, z_d), w(z) = r_1(z_1) \cdots r_d(z_d), \\ r_1 \in V_1, \dots, r_d \in V_d \end{array} \right\}$$

where $V_i \subset H^1(\mathbb{T})$ is some Hilbert space of functions depending only on the variable z_i .

What should be a proper choice of spaces V_i to ensure the convergence of the greedy algorithm?

Choices which do **not** work:

- $V_i = H^{1,0}(\mathbb{T}) := \{r \in H^1(\mathbb{T}), \int_{\mathbb{T}} r = 0\}$ for all $1 \leq i \leq d$;
- $V_1 = \{r \in H^1(\mathbb{T}), \int_{\mathbb{T}} r = 0\}$ and $V_i = H^1(\mathbb{T})$ for $i > 1$;

In the present context, d dictionaries have to be introduced:

$$\Sigma_i := \left\{ r_1(z_1) \cdots r_i(z_i) \cdots r_d(z_d), \quad r_i \in H^{1,0}(\mathbb{T}), \quad r_j \in H^1(\mathbb{T}), j \neq i \right\}.$$

Modified greedy algorithm:

- set $m = 0$ and $u_0 = 0$.
- **Iteration m :** set $u_{m,0} = u_m$.
 - For $i = 1, \dots, d$, compute $h_{m+1,i} \in \Sigma_i$ solution to

$$h_{m+1,i} \in \underset{h \in \Sigma_i}{\operatorname{argmin}} \mathcal{E}_t(u_{m,i-1} + h). \quad (7)$$

- Set $u_{m,i} := u_{m,i-1} + h_{m+1,i}$.

Set $u_{m+1} = u_{m,d}$ and $m := m + 1$.

Theorem (VE, Lelièvre, Monmarché, 2021)

Assume that for all $f \in H^{1,0}(\mathbb{T}^d)$, $\mathcal{E}_t(f) = a_t(f, f)$ for some symmetric continuous coercive bilinear form $a_t : H^{1,0}(\mathbb{T}^d) \times H^{1,0}(\mathbb{T}^d) \rightarrow \mathbb{R}$.

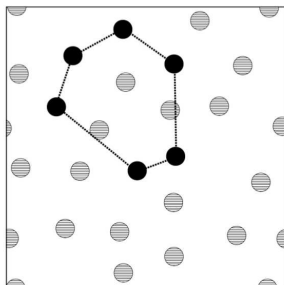
Then, each iteration of the modified greedy algorithm is well-defined in the sense that there always exists at least one minimizer to (7). Besides, *the sequence $(u_m)_{m \in \mathbb{N}^*}$ strongly converges in $H^1(\mathbb{T}^d)$ to u .*

Numerical experiments: polymer ring

$N = 100$ atoms in dimension 2, among which d polymer particles (belonging to a polymer ring) and $N - d$ solvent particles.

Interaction potential:

- Double-well potential between pairs of polymer particles
- Truncated Lennard-Jones repulsion for all other pairs
- Polymer angular potential $-\cos(\theta - \theta_0)$ with $\theta_0 = \pi(1 - 2/d)$



d reaction coordinates: the length between two consecutive polymer particles of the polymer ring

Numerical experiments: polymer ring $d = 3$

Convergence of the tensorized approximation of the free energy with respect to the number of terms in the tensorized approximation in L^2 norm.

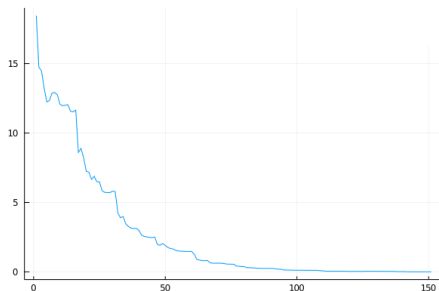


Figure: Error in L^2 norm on the approximation of the gradient of the free energy A as the number of terms in the tensorized approximation

Numerical experiments: polymer ring $d = 3$

$n_{\text{fin}} = 7$, $m_{\text{fin}} = 20$, $T = 10$.

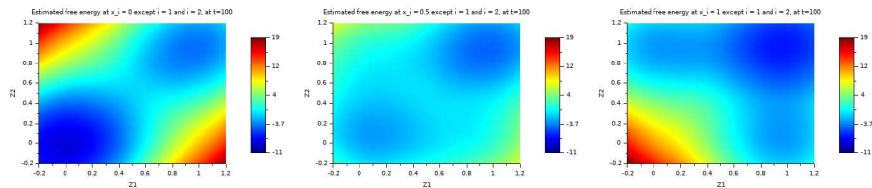


Figure: $(z_1, z_2) \mapsto A(z_1, z_2, z_3)$ for respectively $z_3 = 0, 0.5$ and 1

Numerical experiments: polymer ring $d = 5$

$n_{\text{fin}} = 7$, $m_{\text{fin}} = 20$, $T = 10$.

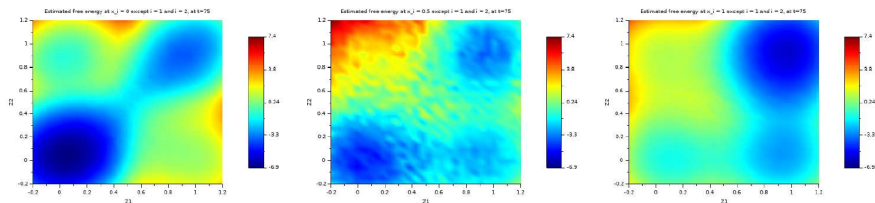


Figure: $(z_1, z_2) \mapsto A(z_1, z_2, z_3, z_4, z_5)$ for respectively $(z_3, z_4, z_5) = (0, 0, 0)$, $(0.5, 0.5, 0.5)$ and $(1, 1, 1)$

Numerical experiments: polymer ring $d = 5$

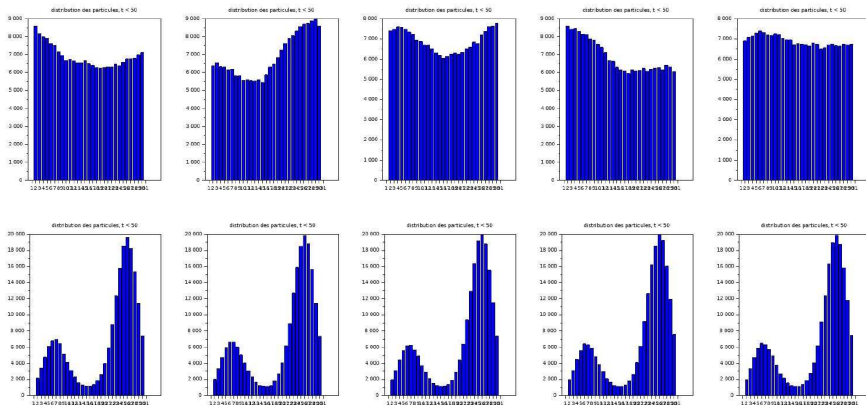


Figure: Cumulative one-dimensional histograms of the five reaction coordinates at $t = 50$ for a TABF algorithm (up) and a non-biased process (down)

We presented here a Tensorized Adaptive Biasing Force (TABF) method for molecular dynamics simulation, which is well-adapted to contexts where the number of reaction coordinates may be large.

The algorithm is based on the adaptation of the Adaptive Biasing Force method together with tensor methods and gave very encouraging preliminary results on toy examples.

- Lots of remaining open theoretical questions!
- Numerical implementation of the algorithm on more realistic molecular systems
- Extension to the use of more evolved tensor formats.

Thank you for your attention!