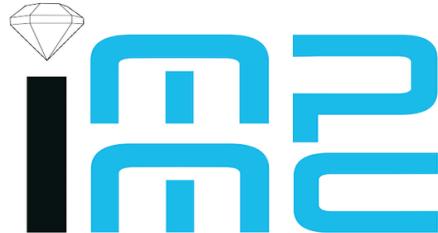


Modelling the dynamics of complex systems using stochastic processes and machine-learned coordinates

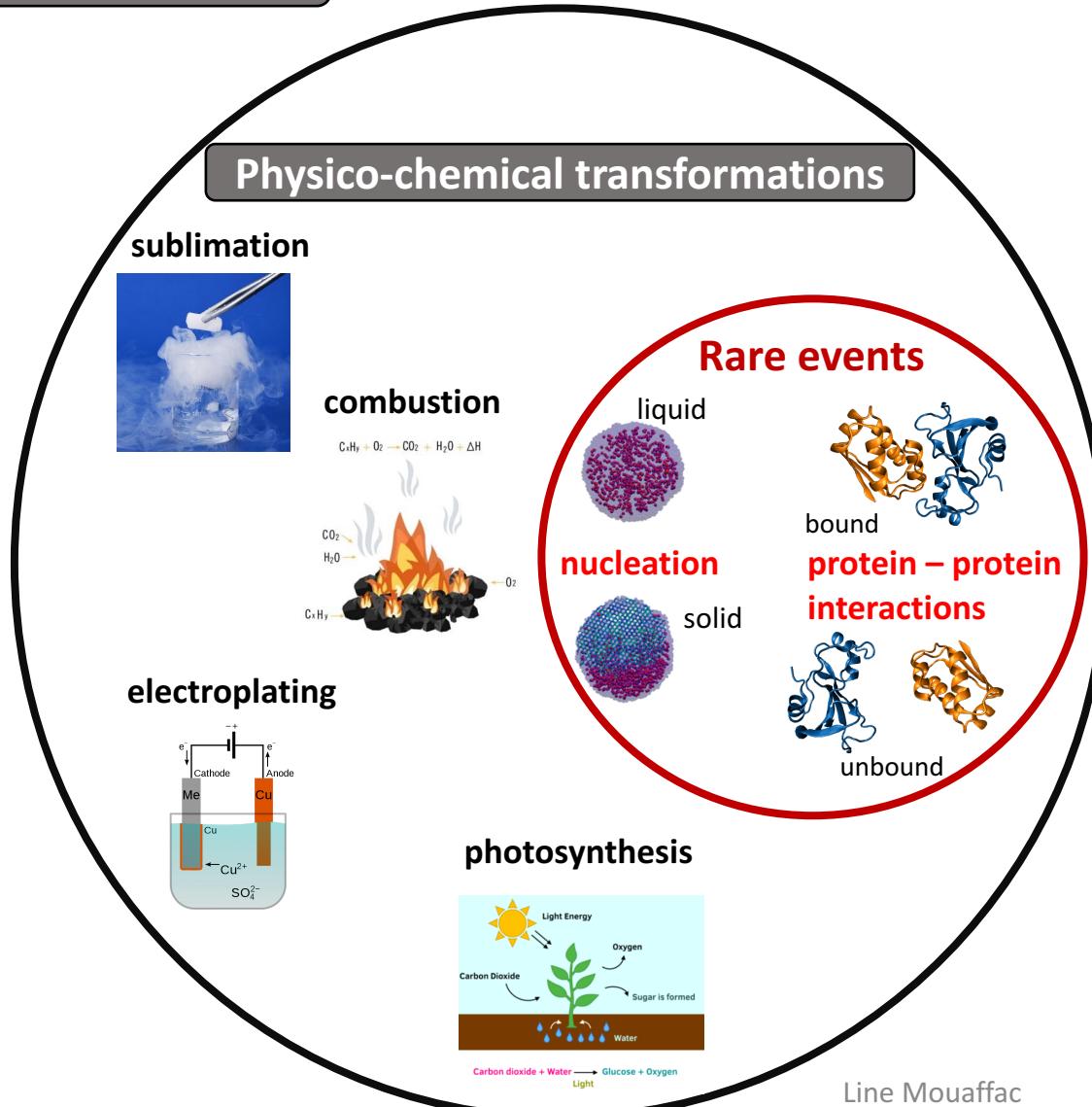
Line MOUAFFAC, Fabio Pietrucci

Institut de Minéralogie et de Physique des Matériaux et de Cosmochimie (IMPMC)



PHYSICAL CONTEXT AND OBJECTIVES

CONTEXT

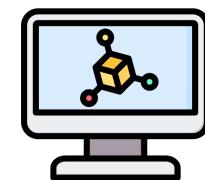


OBJECTIVE

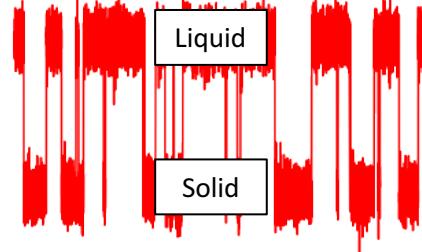
model & characterize rare events



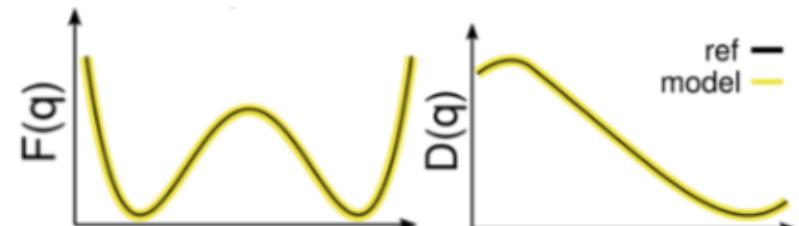
using computer simulations (molecular dynamics) & stochastic processes



Good coordinate q



get thermodynamic properties (free energy & diffusion profiles) and kinetic rates



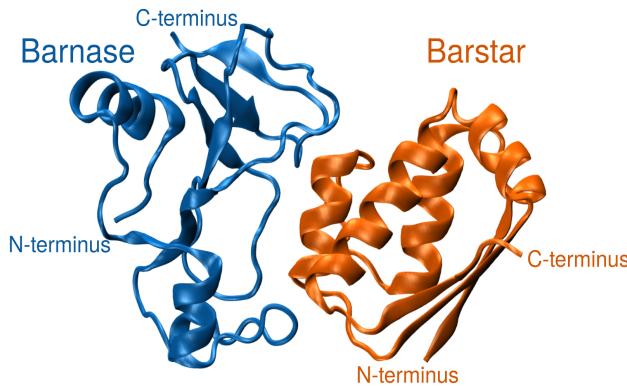
depends on q :
the reaction coordinate

SETTING UP THE SIMULATION BOX

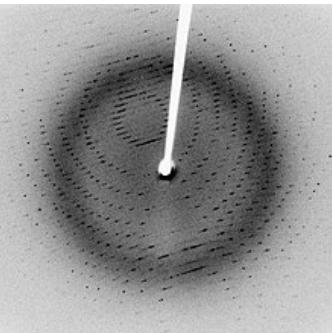
Our system

Ribonuclease Barnase and its inhibitor

Barstar



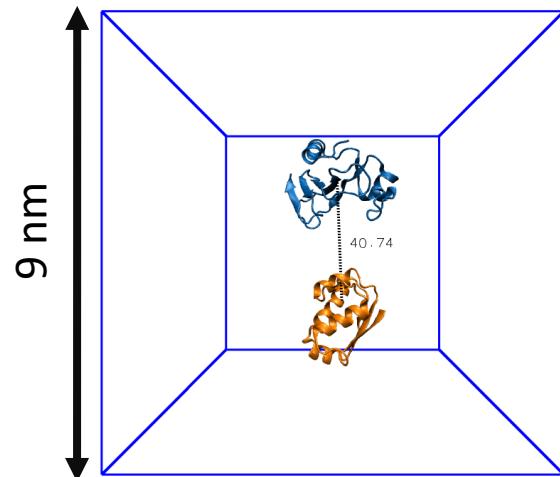
- 1 Get initial structures from experimental data



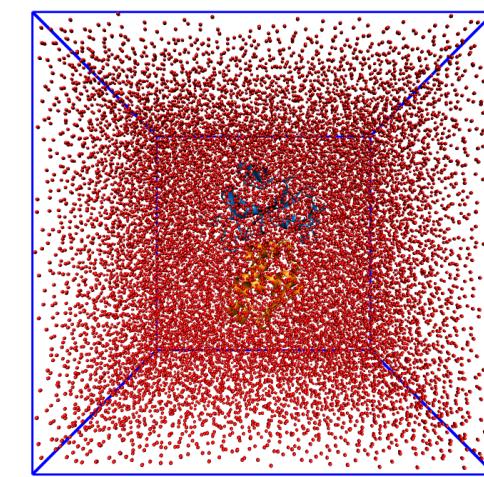
RCSB **PDB**
PROTEIN DATA BANK

2

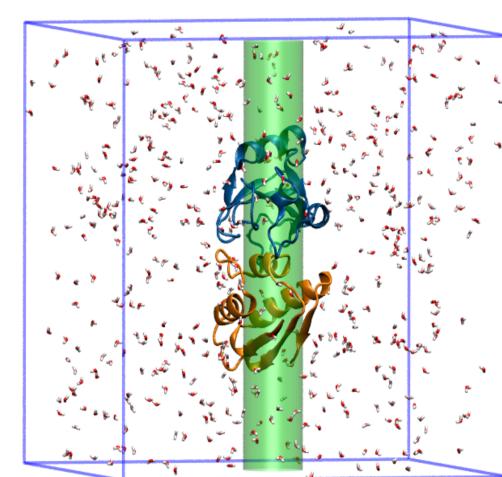
- Place the proteins far apart



- Add ions & water molecules



- Add a cylindrical wall to restrict rotation



~ 120K atoms

Box dimensions: $9.33 \times 9.33 \times 9.33 \text{ nm}^3$

3

- Equilibrate with thermostat & barostat

4

- Run molecular dynamics

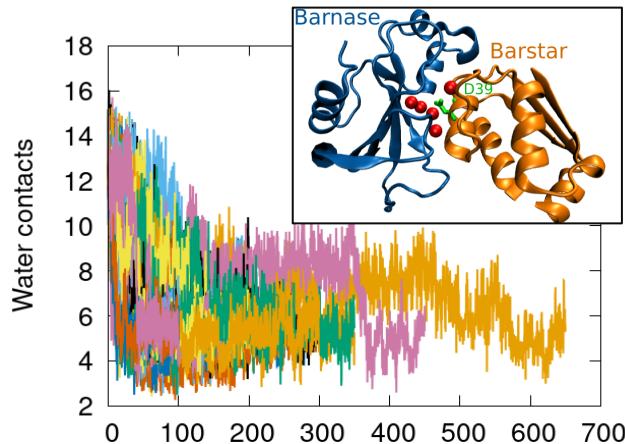


Output: atomic positions & velocities at each time step

EXTRACTING REACTION COORDINATES

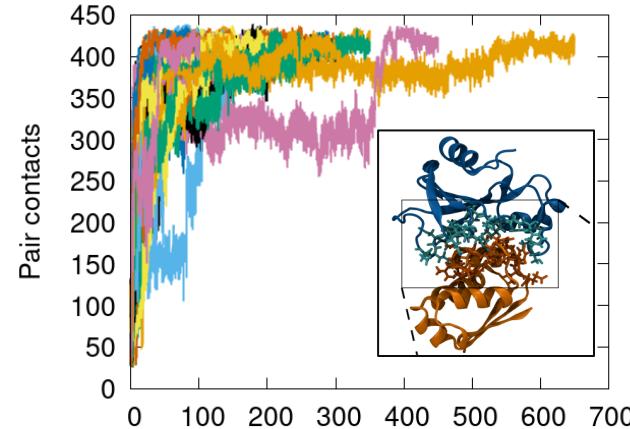
1

Protein-water contacts



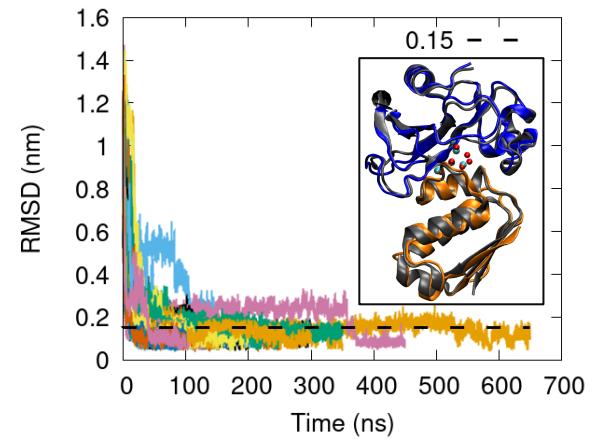
2

Barnase-Barstar contacts



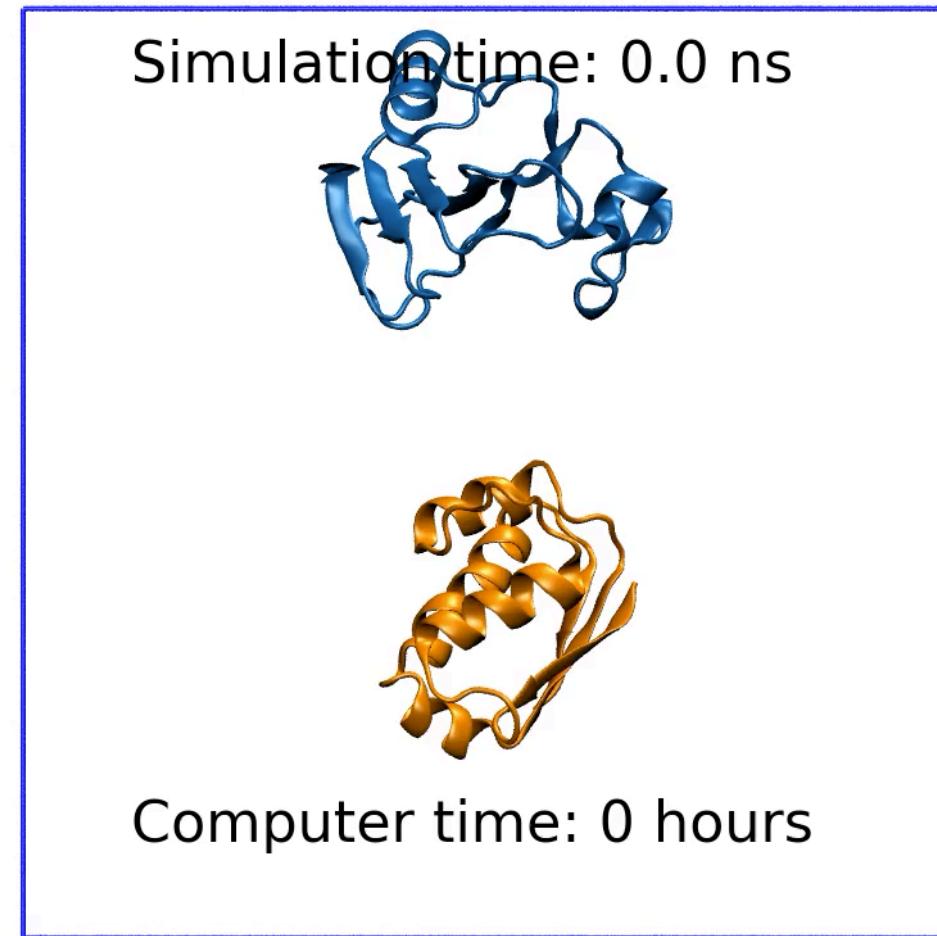
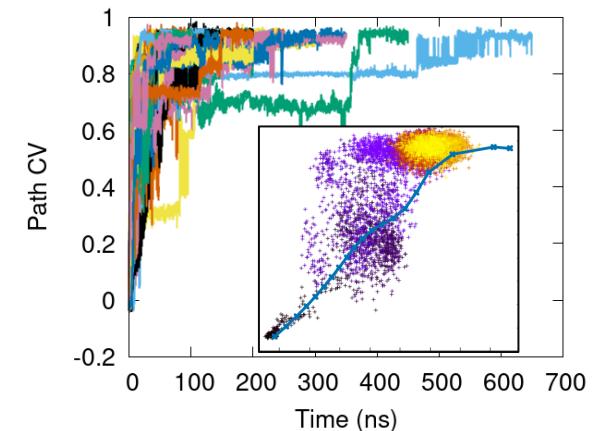
3

Interface RMSD



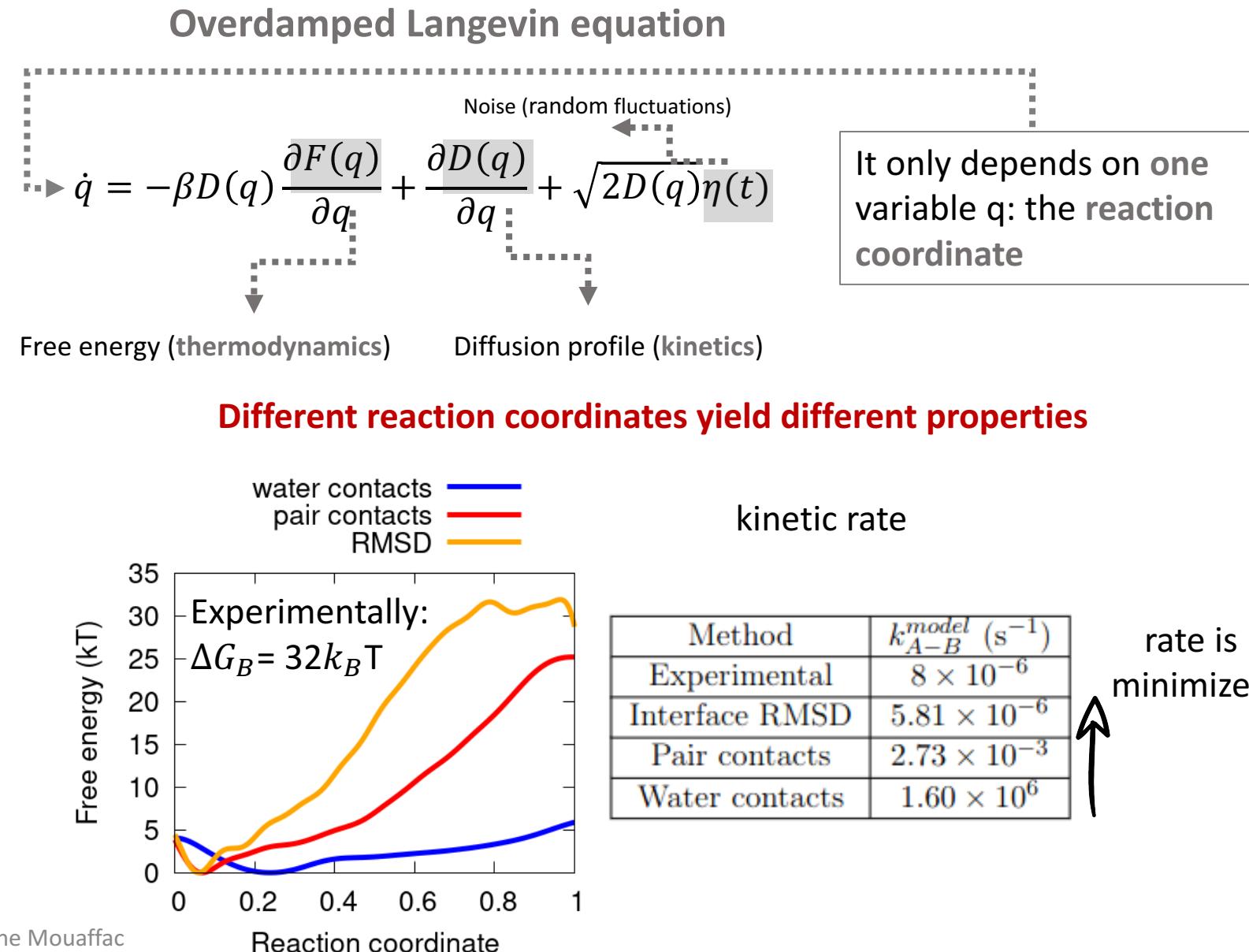
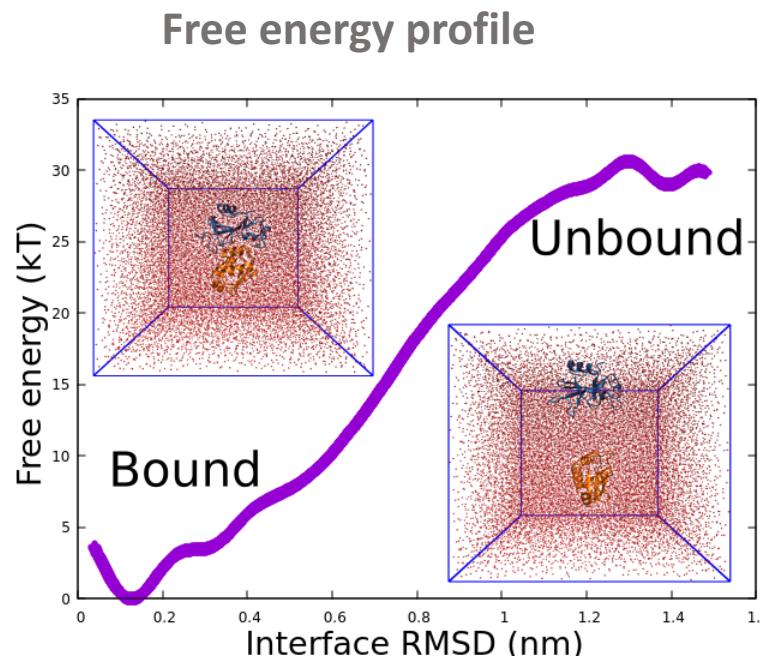
4

Path-RC based on 2



Line Mouaffac

GETTING PHYSICO-CHEMICAL PROPERTIES



CONCLUSIONS & PERSPECTIVES

All properties depend on the reaction coordinate q that is chosen

The optimal reaction coordinate minimizes the kinetic rate *

We are able to predict kinetic rates with experimental accuracy

Come & chat with me
at the poster session

* Mouaffac, Palacio-Rodriguez & Pietrucci , JCTC (2023)

Line Mouaffac

poster

40

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1 INTRODUCTION

While **collective variables** (CV) are ubiquitously used to model physico-chemical transformations, finding **optimal reaction coordinates** (RC) that yield accurate thermodynamic and kinetic properties is a **fundamental challenge** in the field of atomistic simulations. Projecting onto an accurate RC helps to **accurately and efficiently** estimate **reaction rates** and identify the common properties of transition states. Customarily, optimal RCs are defined as monotonic one-to-one functions of the committer [1]. We are proposing an original computationally affordable method to optimize reaction coordinates [2]. It is based on the fact that sub-optimal RCs yield kinetic rates higher than optimal ones.

2 THEORETICAL FRAMEWORK

In 2016, Zhang et. [3] investigated the repercussions on the reaction rate k of **projecting** the full dynamics onto a **low-dimensional space** defined by the CV



The rate of the full dynamics is less than or equal to the one computed using effective dynamics.

The kinetic rate can be used as an optimization criterion for CVs

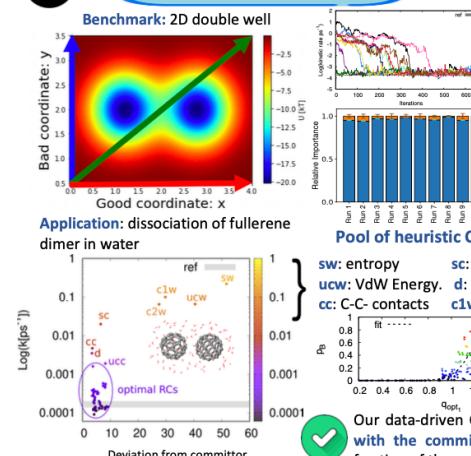
The free energy $F(q)$ and diffusion $D(q)$ are obtained by training an overdamped Langevin model via **likelihood maximization** [4][5].

$$\dot{q} = -\beta D(q) \frac{\partial F(q)}{\partial q} + \frac{\partial D(q)}{\partial q} + \sqrt{2D(q)}\eta(t)$$

Free energy (thermodynamics)

Diffusion profile (kinetics)

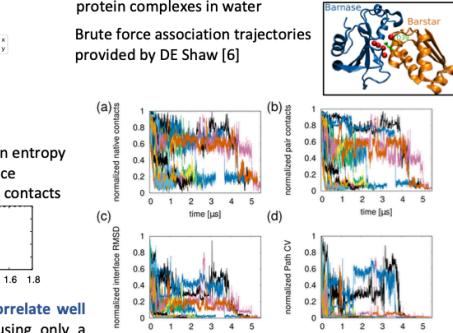
4 METHOD VALIDATION



5 METHOD PERSPECTIVES

Application: predict dissociation rates of protein-protein complexes in water

Brute force association trajectories provided by DE Shaw [6]



REFERENCES

- [1] J. Lu and E. Vanden-Eijnden *JCP*, 2014.
- [2] L. Mouaffac, K. Palacio-Rodriguez, and F. Pietrucci *JCTC*, 2023.
- [3] W. Zhang, C. Hartmann, and C. Schütte *Faraday discuss.*, 2016.
- [4] K. Palacio-Rodriguez and F. Pietrucci *JCTC*, 2022.
- [5] B. Peters, G. Beckham and B. Trout *JCP*, 2007.
- [6] A. Pan, D. Jacobson, K. Yatsenko, D. Sritharan, D. Shaw *PNAS*, 2019.

