Predicting protein-protein dissociation rates from spontaneous association trajectories

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PRESENTATION OUTLINE

1 **Data collection**

2 **Data analysis**

a setting up the simulation box

a finding a reaction coordinate

b running molecular dynamics

b building a stochastic model

c assessing the quality of the simulations

c getting physico-chemical properties

SETTING UP THE SIMULATION BOX

Our system

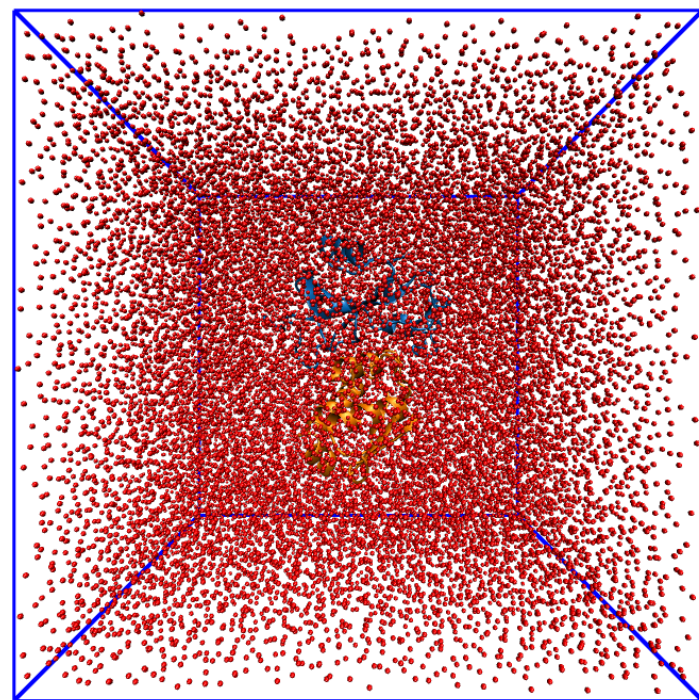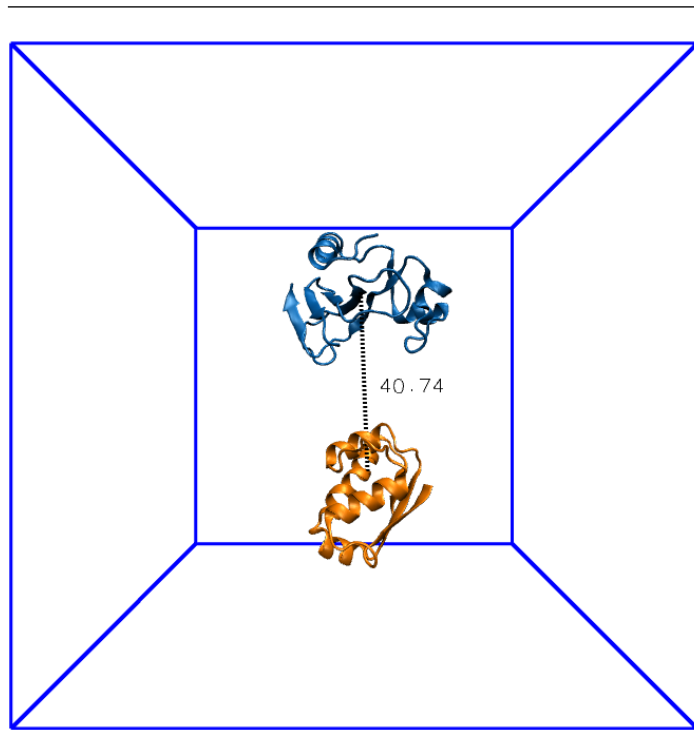Ribonuclease **Barnase** and its inhibitor **Barstar**

Barnase
C-terminus
N-terminus

Barstar
C-terminus
N-terminus
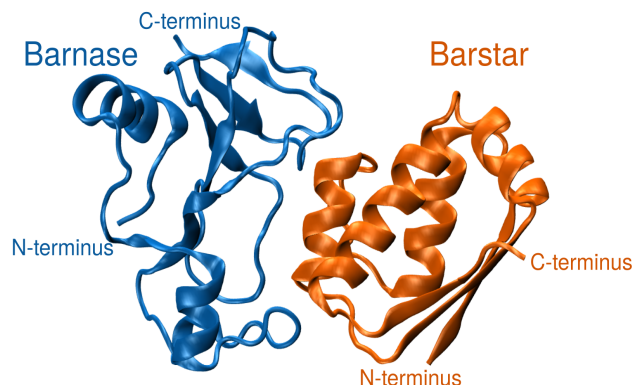
1 Get initial structures from experimental data
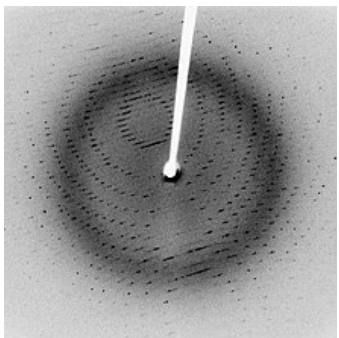
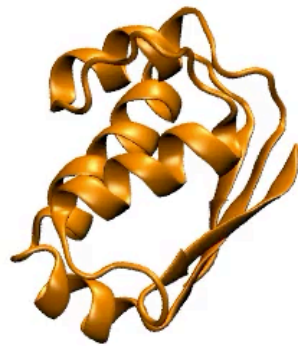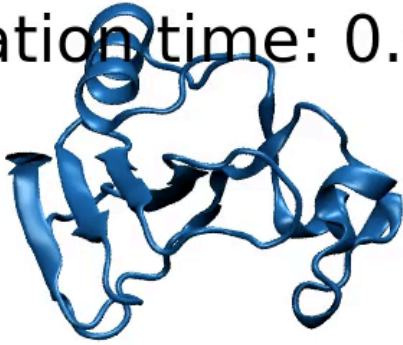**2** Place the proteins far apart and solvate

9 nm

40.74

3 Equilibrate with thermostat & barostat

4 Run **molecular dynamics**

RUNNING MOLECULAR DYNAMICS

Simulation time: 0.0 ns

Computer time: 0 hours

Timescale barrier

| 10^{-15} femto | 10^{-12} pico | 10^{-9} nano | 10^{-6} micro | 10^{-3} milli | 1 sec | >1 sec |

bond vibration

side chain rotation
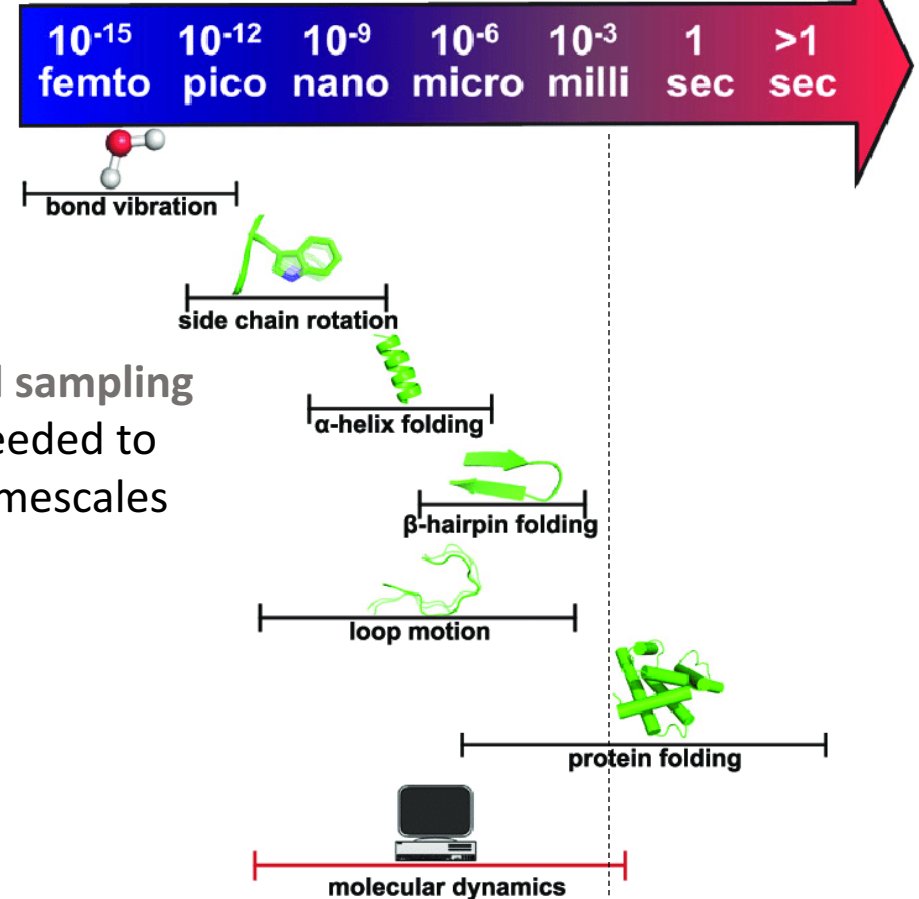
Usually **enhanced sampling** techniques are needed to access relevant timescales

α-helix folding

β-hairpin folding

loop motion

protein folding

molecular dynamics
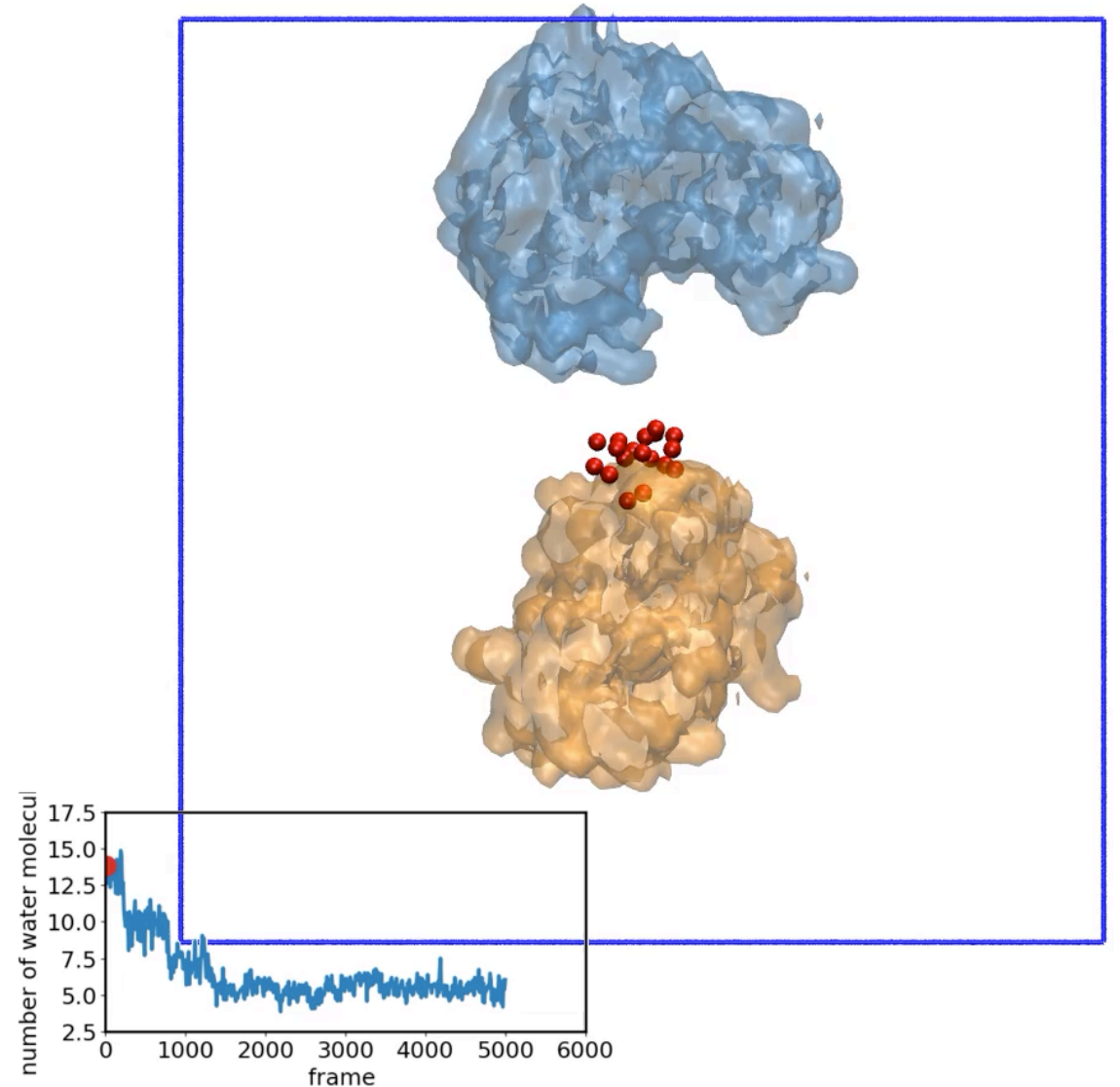
ASSESSING THE QUALITY OF THE SIMULATIONS

The quality of the model depends on the quality of the data

Is the transition captured by the simulations?

Is the end structure the experimentally determined bound state?
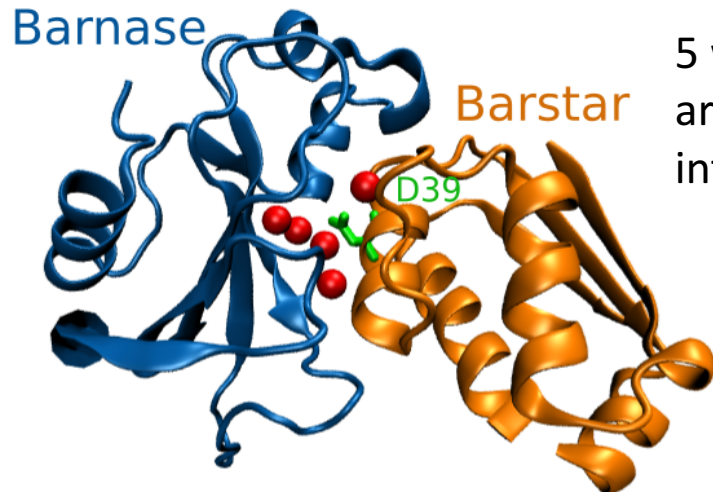
5 water molecules are buried inside the interface

THE REACTION COORDINATE

Atomic coordinates of 100 000 atoms in 3 dimensions

$\Longrightarrow$ $3 \times 100\ 000$ degrees of freedom

Is there a way to reduce the **high dimensionality** all while keeping the system's **accuracy**?
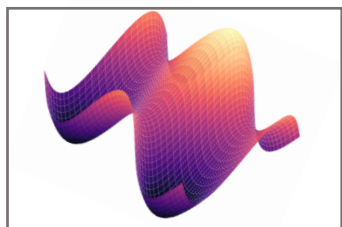
Use **reaction coordinates** (RC)

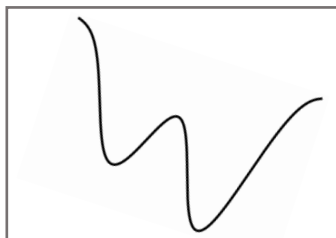Order parameter tracking progress of a reaction

Generic function of atomic coordinates

$3N$ dimensions

1 dimension

RC

How can we find such reaction coordinates?

Open problem

No general recipe

Our approach

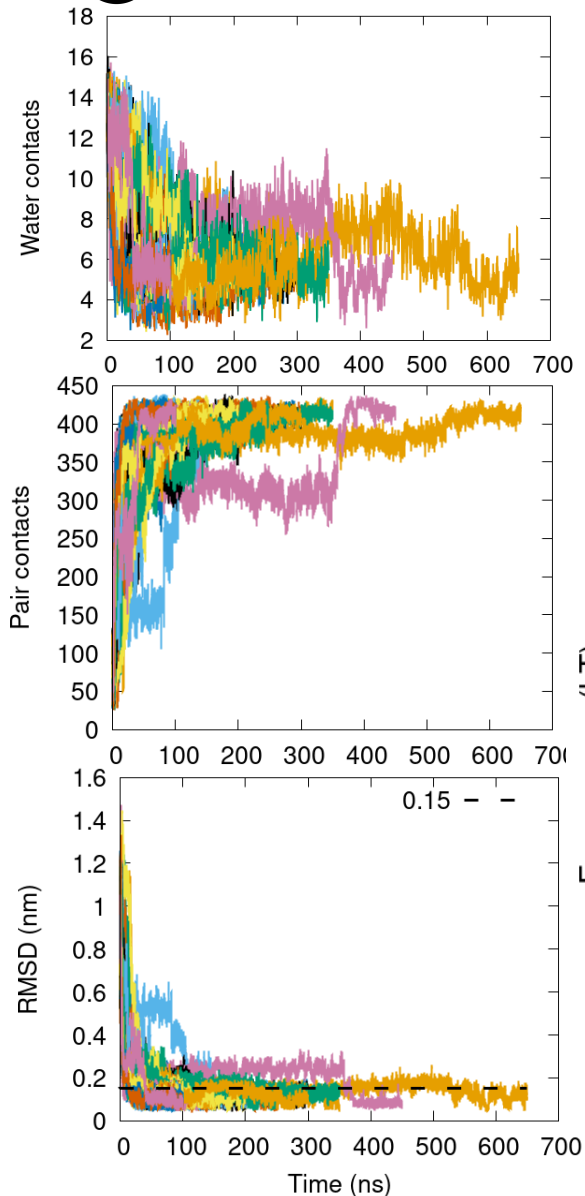**A variational principle**: the optimal coordinate q yields the minimal kinetic rate

$$k_{A \to B} \leq k^{model}{}_{A \to B}$$

Zhang, Hartmann, and Schütte. *Faraday discussions* (2016)

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

GETTING PHYSICO-CHEMICAL PROPERTIES

❶ Reaction coordinates

❷ Overdamped Langevin equation

Noise (random fluctuations)

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

It only depends on **one** variable q: the **reaction coordinate**
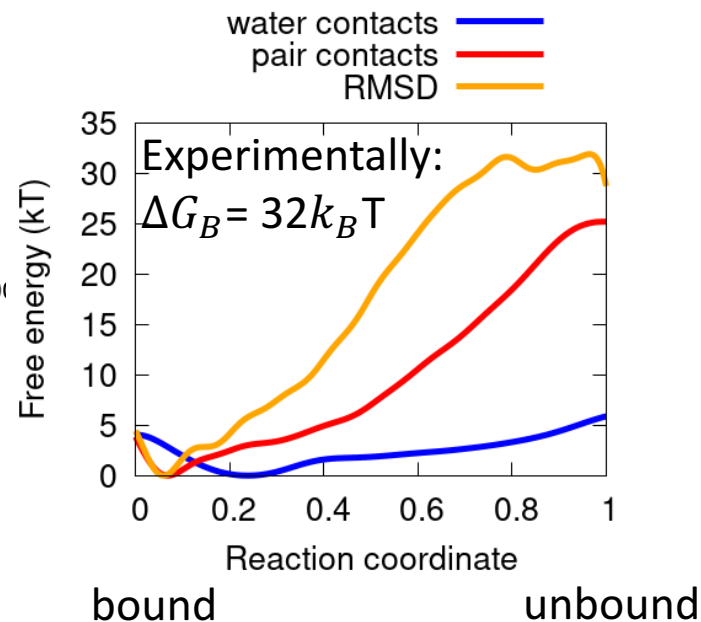
Free energy (**thermodynamics**)   Diffusion profile (**kinetics**)

Experimentally:
$\Delta G_B = 32 k_B T$

- water contacts ——
- pair contacts ——
- RMSD ——

bound   unbound

❸ Dissociation rate

$$\frac{1}{k^{model}_{A \to B}} = \int_{q_0}^{b} dy \frac{e^{\beta F(y)}}{D(y)} \int_a^y dz e^{-\beta F(z)}$$

Method	k^{model}_{A-B} (s^{-1})
Experimental	8×10^{-6}
Interface RMSD	5.81×10^{-6}
Pair contacts	2.73×10^{-3}
Water contacts	1.60×10^{6}

Rate is minimized

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CONCLUSIONS

We need ~ 1 day of simulation time to calculate dissociation rates

This is impossible to compute using classical molecular dynamics

Using our framework we are able to predict dissociation
rates from classical molecular dynamics