Estimation of Kinetic Rates and Collective Variable Quality from Time-Dependent Biased Simulations

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INTRODUCTION

A **central challenge** in **molecular dynamics** (MD) simulations is the prediction of **kinetic rates**, due to the gap between the time scales accessible with MD and those of **rare events**[1]. Methods aiming to estimate kinetics from **enhanced sampling** techniques such as metadynamics[2,3], require intensive **computer effort** and/or rely on ideal **collective variables** (CVs). We developed an efficient methodology for the prediction of rates from time-dependent biased simulations. This strategy only require sets of **short simulations** as input data. Additionally, it allows to **assess the quality of CVs** in **post-processing**, avoiding the need of new expensive MD simulations.

OUR GOALS

1

Metadynamics[2] trajectories and **Kramers' theory** to estimate transition **rates** and assess the **CV quality**.

2

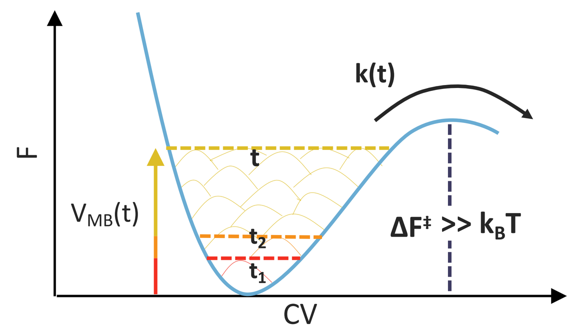
Barrier-crossing statistics in **post-processing** with **reliability tests** at **high computational efficiency.**

METHODS AND THEORY

Kramers' theory and **likelihood maximization** allow to estimate **kinetic rates** and measure the **CV quality** from single-transition **metadynamics** trajectories.

Metadynamics (MetaD)

The barrier decreases with increasing bias, thus the **effective rate k(t)** increases with time.



Kramers' time-dependent rate (KTR)

True barrier and **maximum bias**

$$k(t) = k_{pre}\, e^{-\beta\Delta F^\ddagger + \beta\gamma V_{MB}(t)}$$

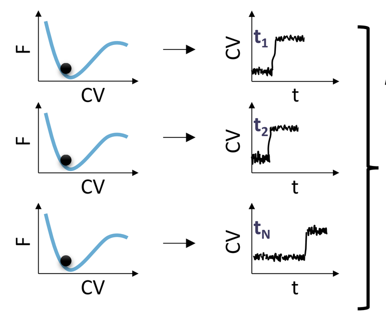
Measure of the CV quality: $\gamma \in [0,1]$

$$k(t) = k_0\, e^{\beta\gamma V_{MB}(t)}$$

Parameters to optimize

Survival probability S(t)[4]

Escape from a single free energy well.



$$S(t) = \exp\left(-k_0 \int_0^t e^{\beta\gamma V_{MB}(t')} dt'\right)$$

N parallel replicas biased with metadynamics.

Likelihood function

$$\mathcal{L} = \prod_{i\,\in\,\mathrm{events}}^{M} -\frac{dS(t)}{dt}\bigg|_{t=t_i} \prod_{j\,\in\,\mathrm{non-events}}^{N-M} S(t_j)$$

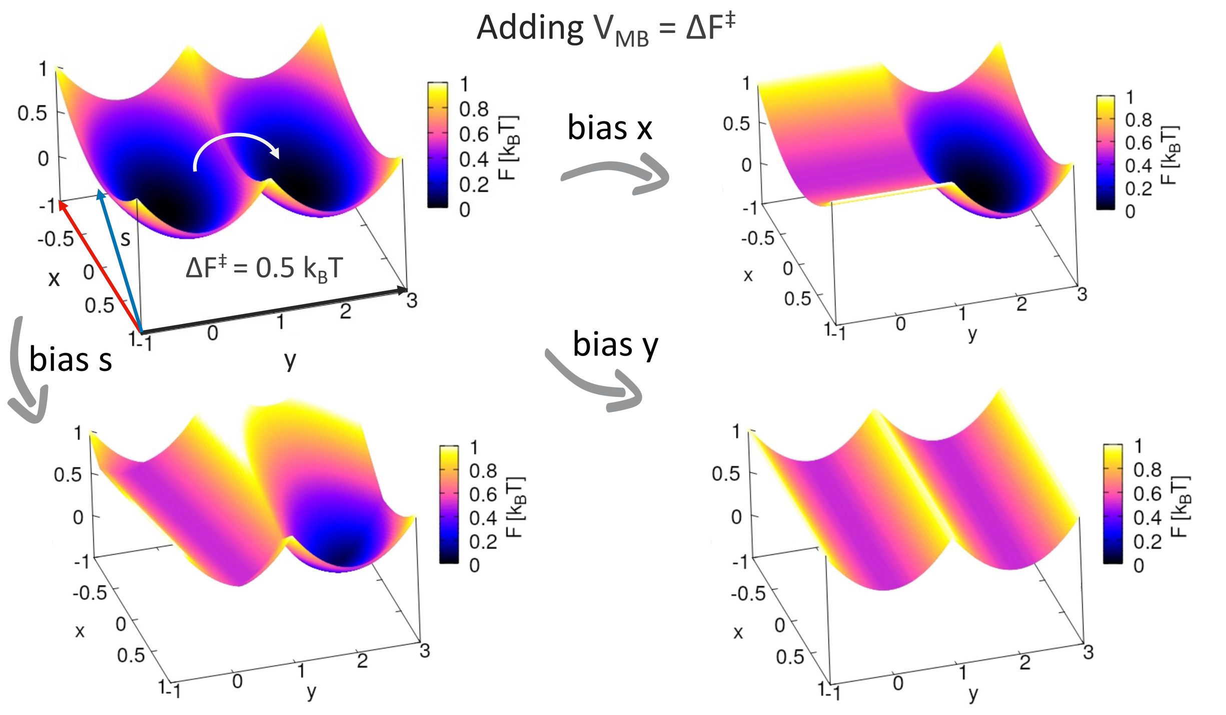
Extract γ and k_0 that maximize the likelihood. Perform KS-tests with the empirical and predicted CDFs[5].

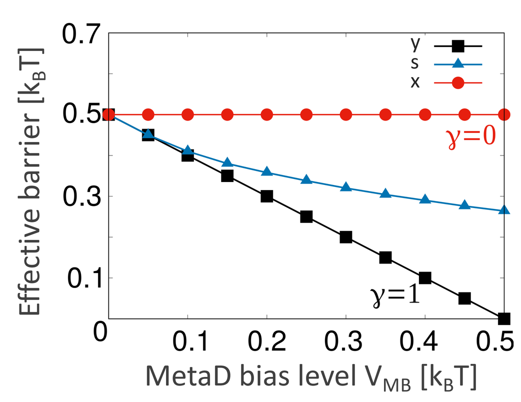
RESULTS

How does it work?

In MetaD, the time-dependent effective barrier depends on the CV being biased. We estimated the effective barrier for a $V_{MB} \le \Delta F^\ddagger$ in a 2D potential energy surface. γ estimates how much of the bias is helping to accelerate the transition.

2D potential | **Potential felt by the system** | **Effective barrier**



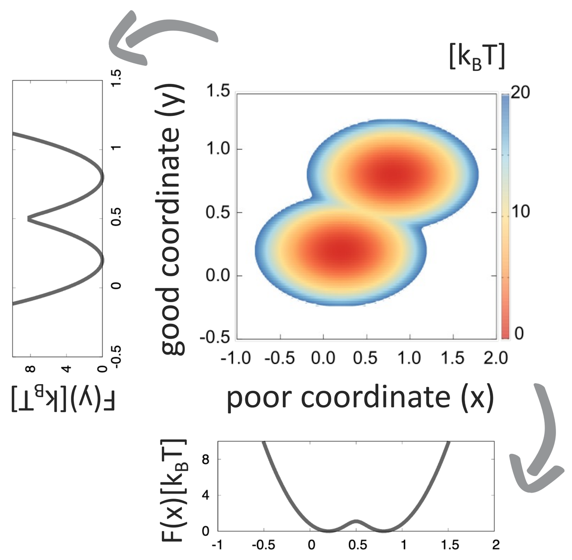


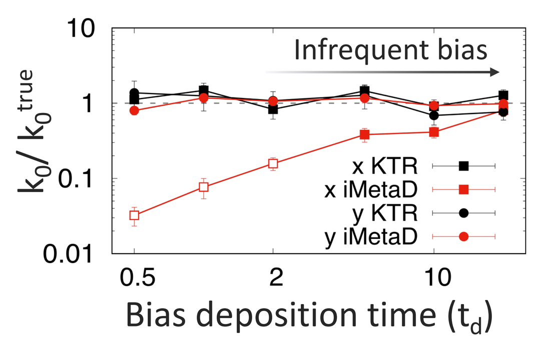
For equal deposited bias, the better the CV, the smaller the effective barrier. γ scales the maximum bias allowing us to work with sub-optimal CVs.

2D double-well landscape

Benchmark system that allows assessing the effect of the CV quality. We compare the rate estimated by our method (KTR) and that of the state-of-the-art infrequent metadynamics[3] (iMetaD) method.

Free energy profiles | **Kinetic rate (k_0)** | **Cumulative distribution functions**

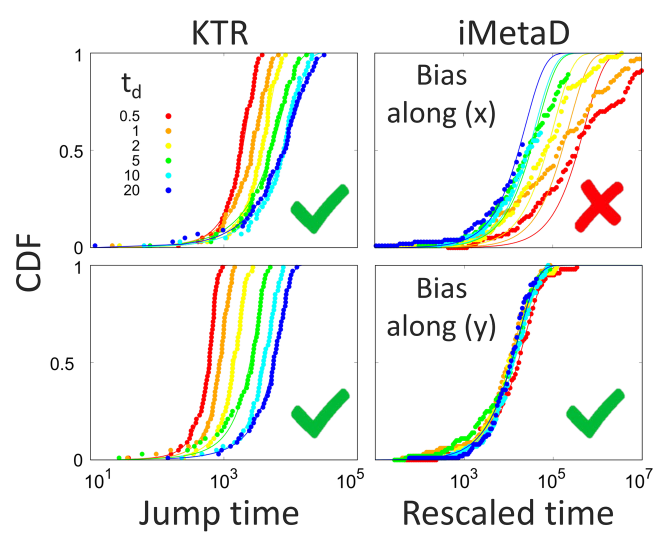




Quality of CV (γ)

γ_x = 0.38 ± 0.12 γ_y = 0.84 ± 0.13

CDF = 1-S(t)

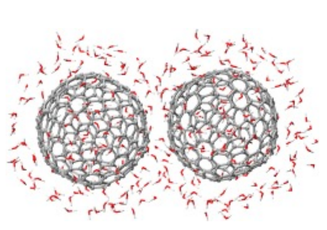


KTR outperforms iMetaD even for poor CVs. γ corrects the effect of poor biasing directions and gives indication of the CV quality.

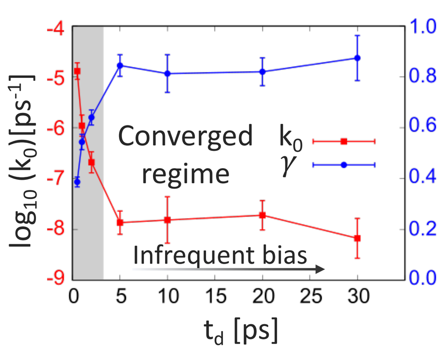
Fullerene dimerization

C_{240} dimer in water displays a single-well free energy landscape with a dissociation barrier of ~14 k_BT.

Fullerene C_{240} dimer in explicit solvent

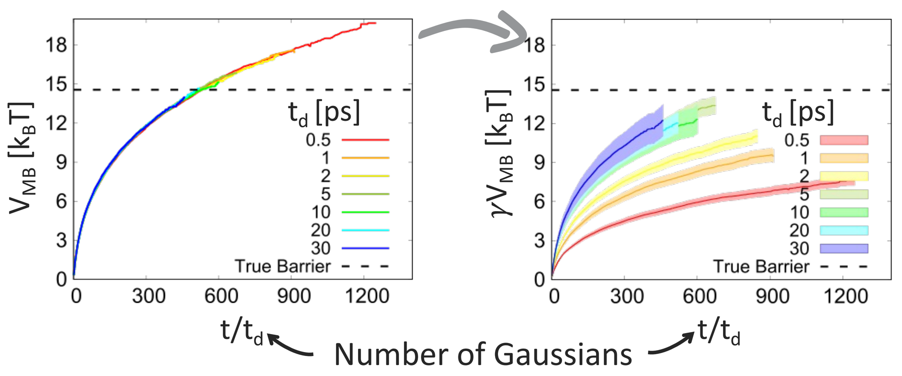


γ gets lower to compensate overbias



When t_d is small the system is overbiased

γV_{MB} is the same for all acceptable values of t_d

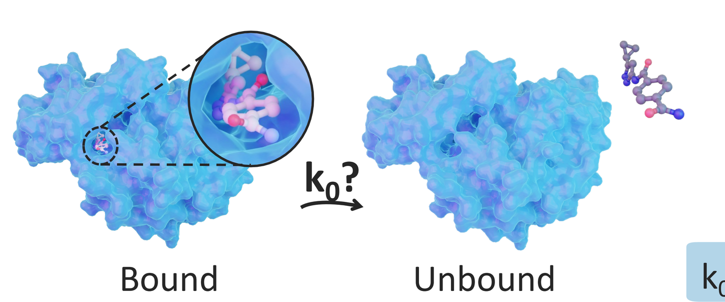


As a reliability test, we can plot γV_{MB} for different t_d: at convergence, γ and k_0 do not depend on t_d and the graphs overlap.

Protein-ligand unbinding

CDK2 is involved in cell cycle and has been a target for anti-cancer drugs. CDK2-ligand unbinding displays a complex multi-state landscape.

Cyclin-dependent kinase 2 (CDK2) bound to ligand 03K in explicit solvent



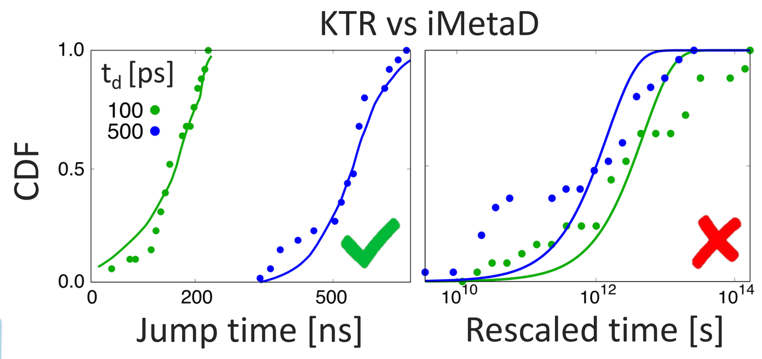
Unbinding rate

t_d = 100 ps
k_0 = 8 ± 6 s^{-1}
γ = 0.65 ± 0.06

t_d = 500 ps
k_0 = 5 ± 3 s^{-1}
γ = 0.61 ± 0.11

k_0^{exp} = 0.26 ± 0.05 s^{-1}

CDFs



We recover unbinding rate up to one order of magnitude accuracy using non-optimal CVs

CONCLUSIONS

At convergence, **KTR** yields **accurate rates.** γ simultaneously gives insights about the **efficacy of the CV** and corrects the height of the barrier.

Limitations: i) The method is **restricted to single transitions**, extension to multi-state systems required. ii) The **accuracy depends on t_d**.

Advantages: Only **single-transition** trajectories required: the **CV quality** can be assessed in post-processing. **Useful for CV optimization.**

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4. Hummer, & Szabo. *Biop. J.*, (2003).
5. Salvalaglio, Tiwary, & Parrinello. *JCTC.* (2014).

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kpalaciorodr/KTR