OpenDUck: a python library for steered MD

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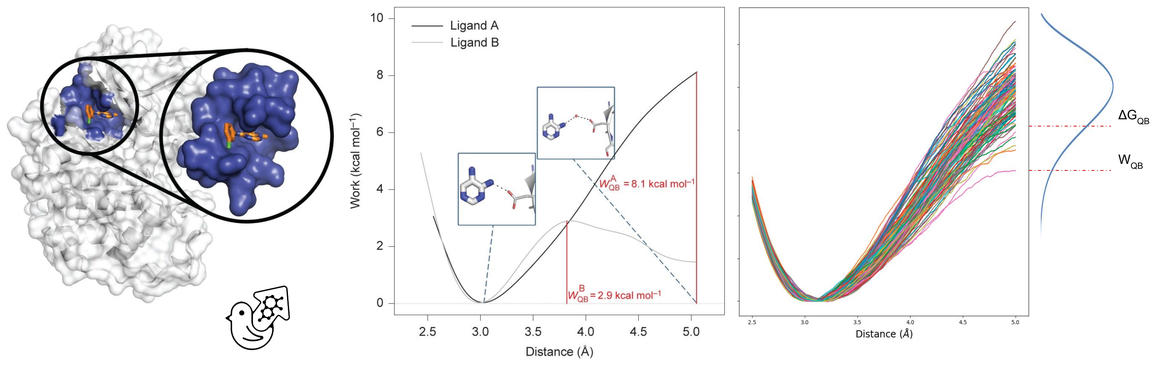
https://github.com/CBDD/openduck

https://github.com/CBDD/openduck-tutorial

Introduction

Dynamic Undocking (DUck)[1] is a particular application of steered molecular dynamics (SMD) where the work needed to break the main H-bond (W_{QB}) of a complex is evaluated. This measure represents the height of the first dissociation barrier and the structural stability of the complex. DUck has shown good results as post-docking filtering step[1], in binding mode determination[2] and stability of protein-protein ternary complexes with molecular glues[3]. However, it relies on several licensed programs and its application is very rigid. OpenDUck is an open-source python library implementation of DUck, aimed to facilitate the creation of SMD pipelines with AMBER and OpenMM.



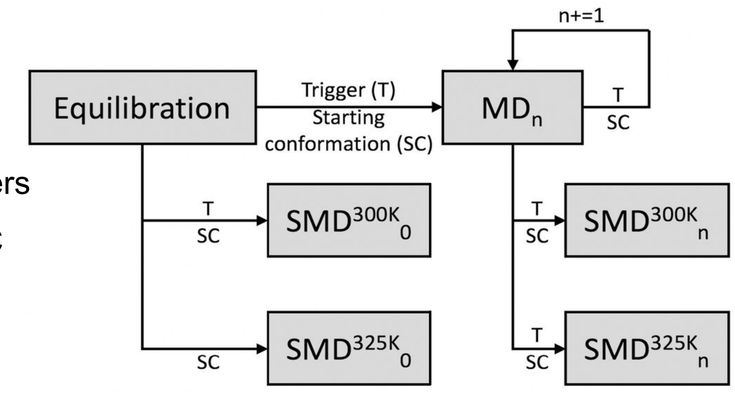
CLI Implementation

System preparation

- Multiple input formats
- Receptor chunking
- Parameterization of receptor, ligands, co-factors, solvents

Production

- Flexible CV definition
- Customizable vector parameters
- Templating for inputs and HPC
- OpenMM and AMBER implementations

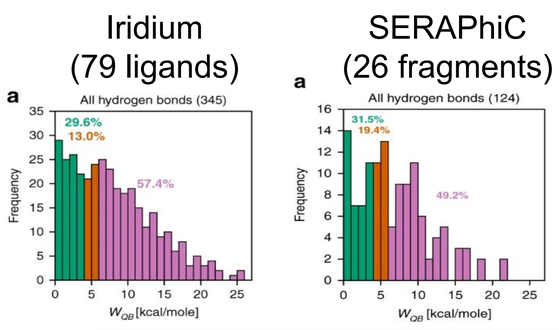


Analysis and report

- Reports and plotting
- ΔG_{QB} calculations
  - Jarzynski equality (JE)
  - Crooks Gaussian Intersection (CGI)
- Hysteresis analysis

Validation

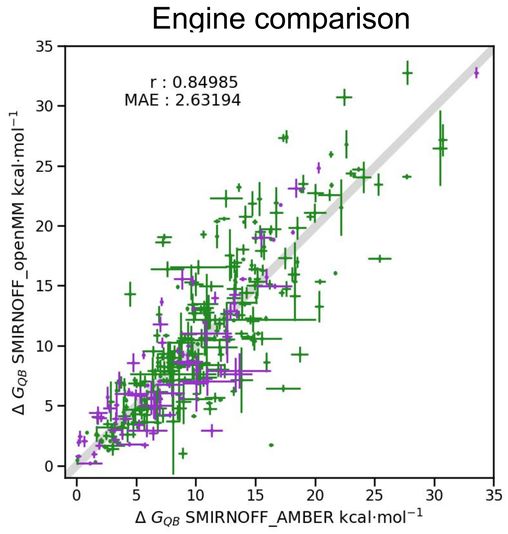
Benchmark datasets[4]



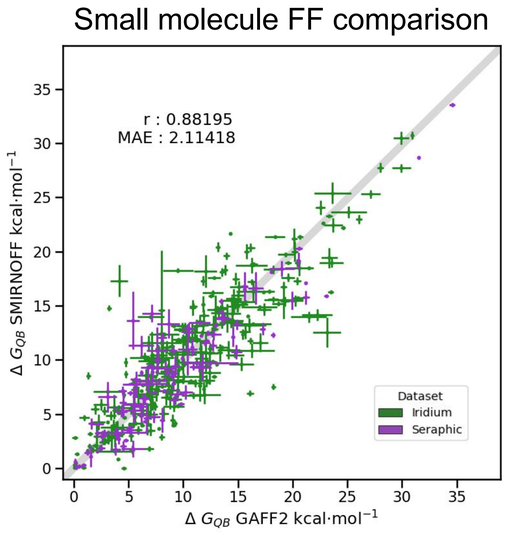
Conditions surveyed

- MD engine
- Small-molecule forcefield
- System conditions (box size, ionic strength, water model, HMR)
- Convergence

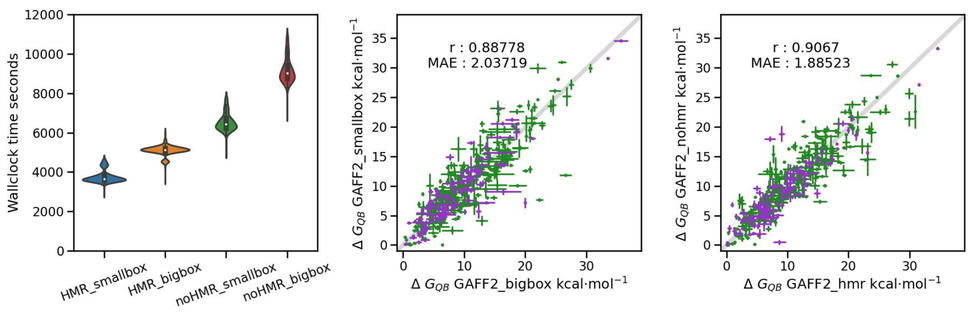
Engine comparison



Small molecule FF comparison

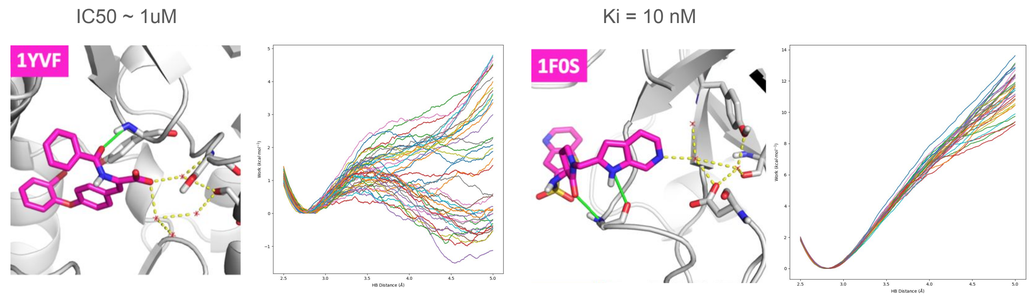


Optimizing simulation time through HMR and smaller box size



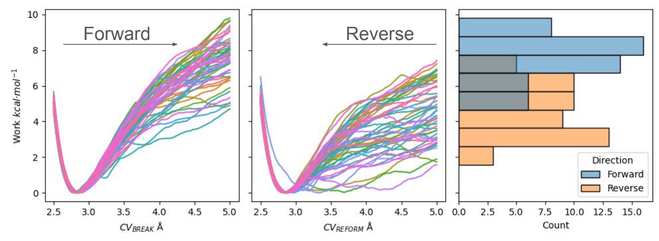
Examples of new applications

Steering water bridges



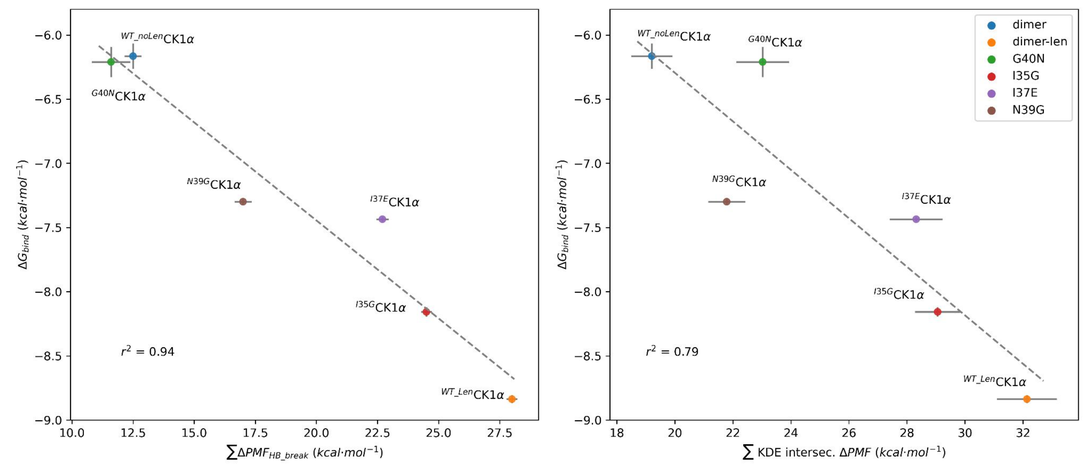
Forward and reverse SMD for CGI

- Can we accelerate convergence using CGI?
- Lower sampling &
- faster simulations
- Test on CRBN-CK1α PPI systems[3]



JE x 100 replicas @ 0.5 Å·ns^{-1}

CGI x 10 replicas @ 5 Å·ns^{-1}



Conclusions

- OpenDUck is able to reproduce the results from the original DUck implementation
- HMR and smaller boxes decrease simulation speed ~70% with no accuracy cost
- New applications of SMD are easily developed using the OpenDUck library, from variants of DUck to drastically different protocols.

References

1. Ruiz-Carmona et al., *Nature Chemistry*. 2017
2. Majewski & Barril, *Journal of Chemical Information and Modelling*. 2020
3. Miñarro et al., *Journal of Medicinal Chemistry*. 2023
4. Majewski et al., *Communications Chemistry*. 2019

Acknowledgements

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