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# dcTMD: a python package for performing dissipation-corrected targeted molecular dynamics

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## Summary

dcTMD is a Python package designed to extract free-energy and nonequilibrium friction estimates from targeted molecular dynamics (TMD) simulations.
The method implemented here is called *dissipation-corrected targeted molecular dynamics* (dcTMD) by Wolf & Stock (2018).

Given a set of nonequilibrium simulations where, for example, a ligand is pulled from a binding site via a velocity constraint, this tool performs automated post-processing of the bias-force time traces to estimate the underlying free-energy landscape and the friction (dissipation) along the unbinding coordinate.

The method is based on a second-order cumulant expansion of *Jarzynski's equality* (Jarzynski, 1997), which connects nonequilibrium work distributions to equilibrium free-energy differences. Combined with a Markovian Langevin Equation, dcTMD further allows the extraction of *position- and velocity-dependent friction coefficients* from the same nonequilibrium data. This has been done succesfully in multiple studies (Jäger et al. (2022) Wolf et al. (2020) Tänzel et al. (2024) Jäger & Wolf (2025)) Milster et al. (2025) The resulting free-energy and friction profiles can subsequently be used to estimate *binding and unbinding rate constants* following Wolf et al. (2020).

The software is intended for molecular dynamics practitioners interested in ligand–protein unbinding, mechanistic interpretation of binding kinetics, and quantitative modeling of non-equilibrium effects in condensed matter and biomolecular systems.

## Statement of need

Ligand unbinding from proteins is of fundamental interest in computational biophysics Schuetz et al. (2017). In many cases, the unbinding event is rare and requires enhanced-sampling or biased-simulation strategies to observe within computationally feasible timescales. dcTMD-based workflows have been shown to yield accurate free energy and non-equilibrium friction coefficients from velocity-constrained pulling simulations. The dcTMD package builds on this work by offering a unified, documented, and extensible implementation (including pathway separation analysis, see Wolf et al. (2023)) that is currently not available, thereby lowering the barrier for applying dcTMD to new biomolecular systems and for reproducing published dcTMD studies. The *dcTMD* tool offers:

- automatic parsing of Gromacs pulling simulation outputs,
- estimation of work distributions from trajectory ensembles,

- estimation of free-energy profiles along the biasing coordinate,
- estimation of non-equilibrium friction coefficients along the same coordinate,
- force autocorrelation analysis.

By providing a dedicated Python framework with an `scikit-learn`-style API, `dcTMD` enables users to integrate dissipation-corrected analysis into existing workflows, ensuring reproducibility and broad accessibility.

The software has already been successfully applied in several studies (e.g. (Tänzel et al., 2024), (Jäger & Wolf, 2025)), and is expected to promote the wider adoption of the dissipation-corrected targeted MD approach in computational chemistry and biophysics.

## Implementation and architecture

The code is written in Python (versions 3.9–3.14) and is available under the MIT license.
**Repository:** https://github.com/moldyn/dcTMD

Key architectural features include:

- A modular API following `fit`/`transform` conventions familiar from *scikit-learn*, easing integration into analysis pipelines.
- Input support for *GROMACS* pulling trajectories.
- Core functionality for computing free energy and non-equilibrium friction profiles along the biasing coordinate.
- Support for analysis of multiple unbinding pathways.
- Force correlation analysis for non-equilibrium friction analysis.
- Continuous integration and testing via GitHub Actions; documentation hosted at https://moldyn.github.io/dcTMD.

## Use case

A typical workflow begins with the user performing at least 100 independent velocity-constraint pulling simulations. `dcTMD` provides two analysis routes, both following the same workflow pattern:

1. Work-based analysis using a `WorkSet` and `WorkEstimator`
2. Force-correlation analysis using a `ForceSet` and `ForceEstimator`

Both methods yield free-energy and friction profiles but differ in how these properties are estimated.

1. Load trajectories into a `WorkSet` or `ForceSet`

The user loads all pulling trajectories into an appropriate container:

- `WorkSet` for the work-based route, which is computationally cheaper, as the resolution of the trajectories can be reduced after integration.
- `ForceSet` for the force-correlation route.

Each trajectory contains the constraint force $f(t)$ along a pulling coordinate $x(t) = x_0 + vt$ with a constraint velocity $v$. The work along each trajectory is computed as $W(x) = \int_{x_0}^{x} \mathrm{d}x'\, f(x')$.

2. Perform dcTMD analysis via an estimator

   - **Work-based estimator (`WorkEstimator`)**

     The free-energy profile is estimated as

     $\Delta G(x) = \langle W(x) \rangle - \frac{\beta}{2} \langle \delta W(x)^2 \rangle$, with $\delta W = W - \langle W \rangle$, $\beta = (k_\mathrm{B} T)^{-1}$, and $\langle . \rangle$ denoting a mean over the ensemble of trajectories.

     The dissipated work is $W_\mathrm{diss}(x) = \frac{\beta}{2} \langle \delta W(x)^2 \rangle$.

     The non-equilibrium position-dependent friction is obtained from its derivative:

     $\Gamma(x) = \frac{1}{v} \frac{\mathrm{d}}{\mathrm{d}x} W_\mathrm{diss}(x)$.

   - **Force-correlation-based estimator (`ForceEstimator`)** In this approach the $\Delta G$ and $\Gamma$ are computed directy from the force data:

     $$\Delta G(x) = \int_{x_0}^{x} \mathrm{d}x' \, \langle f(x') \rangle - v \int_{x_0}^{x} \mathrm{d}x' \, \Gamma(x').$$

     $$\Gamma(x) = \beta \int_0^{t(x)} \mathrm{d}\tau \langle \delta f(t(x)) \, \delta f(\tau) \rangle.$$

     Furthermore, the two-time force autocorrelation function $C_t(\tau) = \langle \delta f(t(x)) \, \delta f(\tau) \rangle$, which corresponds to the ''Memory Kernel'' of the dcTMD methodology Post et al. (2022), can be plotted for selected values of $t(x)$ to gain insight into timescales within the ''bath'' degrees of freedom constituting dissipation channels and thus friction sources.

3. Visualize and interpret results

`dcTMD` provides plotting and export tools for:

   - free-energy profiles $\Delta G(x)$
   - friction profiles $\Gamma(x)$
   - work distributions

In addition, the tool supports trajectory separation, enabling analysis of different dissociation routes (see Wolf et al. (2023)).

4. Example

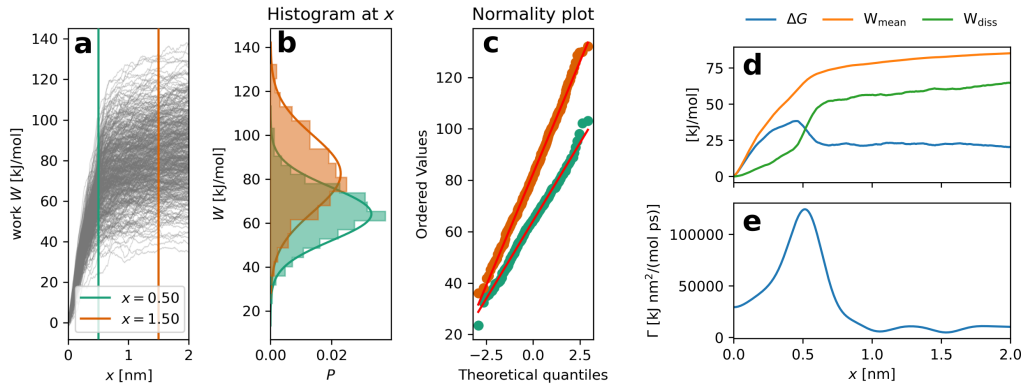


**Figure 1:** Figures crated using data taken from Wolf et al. (2020) of Trypsin Benzamidine unbinding. a)-c) work distribution analysis. d) Decomposition of mean work $W_\mathrm{mean} = \langle W(x) \rangle$ into free energy $\Delta G(x)$ and dissipation work $W_\mathrm{diss}(x)$. e) non-equilibrium friction coefficient $\Gamma(x)$ along the pulling coordinate $x$.

## Impact

By providing an open and reproducible implementation of the dcTMD methodology, the software lowers the barrier for researchers to apply dissipation-corrected targeted molecular dynamics to ligand unbinding problems as well as other condensed soft matter systems. This enables broader exploration of nonequilibrium binding kinetics, supports mechanistic interpretation of frictional contributions, and provides access to position-dependent friction from targeted MD trajectories.

We anticipate the tool will be adopted in academic molecular simulation groups and in pharmaceutical research exploring unbinding free energies and kinetics.

## Acknowledgements

The implementation of dcTMD builds on the Python scientific stack, relying on **NumPy** for numerical operations, **Matplotlib** for visualization, and **Click** for the command-line interface.

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