

kallisto: A command-line interface to simplify computational modelling and the generation of atomic features

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DOI: [10.21105/joss.03050](https://doi.org/10.21105/joss.03050)

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Submitted: 05 February 2021

Published: 15 April 2021

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Statement of Need

Machine learning (ML) has recently become very popular within pharmaceutical industry ([Roy et al., 2015](#); [Sprous et al., 2010](#)). Tasks as, e.g., building predictive models, performing virtual screening, or predicting compound activities are potential use cases for such ML applications ([Li et al., 2021](#); [Simm et al., 2018](#)). Traditionally, ML models often rely on the quantitative structure-activity relationship (QSAR) that has been popularized by medicinal chemists and statisticians to relate bioactivities to specific functional group manipulations ([Dudek et al., 2006](#); [Verma et al., 2010](#)). This QSAR approach decreases the dimensionality of the underlying problem and projects the molecular structure into a space spanned by the physicochemical features. While early approaches relied more on linear regression, modern approaches combine such features with non-linear ML algorithms.

Cheminformatic packages like RDKit ([Landrum & others, 2006](#)) enable the fast calculation of atomic/molecular features based on structural information like the molecular graph, while recently an extended Hueckel package has been added as well ([Landrum, 2019](#)). However, frequently we want to go beyond a structure-only approach thus incorporating electronic structure effects as obtained, e.g., by a (higher-level) quantum mechanical (QM) treatment. The calculation of QM-based features relies often on well-established quantum chemistry methods like Kohn-Sham density functional theory (DFT) that is currently the workhorse of computational chemistry ([Kohn, 1999](#); [Parr, 1980](#)). However, generating the feature space by DFT is computationally demanding and can become the computational bottleneck especially when aiming for high-throughput experiments with several hundred to thousands of molecules.

Since there exists a critical need for an efficient yet accurate featurizer, we developed the `kallisto` command-line interface that is able to calculate QM-based atomic features for atoms and molecules efficiently (whole periodic table up to Radon). The features are either interpolating high-level references (e.g., static/dynamic polarizabilities with time-dependent DFT data) or are parametrized ([Caldeweyher et al., 2019](#)) to reproduce QM references (e.g., DFT Hirshfeld ([Hirshfeld, 1977](#)) atomic partial charges). Molecular geometries need to have an `xmol` or a `Turbomole` like format to be processed by `kallisto`. Besides, we implemented several computational modelling helpers to simplify the development of high-throughput procedures. Some of those modelling helpers depend on the open-source `xtb` tight-binding scheme that has been developed by Stefan Grimme and co-worker ([Bannwarth et al., 2020](#)). The `kallisto` software depends on the scientific libraries Numpy ([Harris et al., 2020](#)) and SciPy ([Virtanen et al., 2020](#)). The [online documentation](#) covers all high-level functionalizations of this software mostly in terms of copy-paste recipes. Furthermore, we cover bits of the underlying theory and compare to experimental data as well as to other modern deep learning models.

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Atomic and Molecular Features

The following atomic and molecular features are available for all atoms up to Radon

- Coordination numbers (Caldeweyher et al., 2019; Grimme et al., 2010)
- Proximity shells
- Environment-dependent electronegativity equilibration partial charges (Caldeweyher et al., 2019)
- Environment- and charge-dependent dynamic polarizabilities (Caldeweyher et al., 2019; Grimme et al., 2010)
- Environment- and charge-dependent van-der-Waals radii (Fedorov et al., 2018; Mantina et al., 2009; Rahm et al., 2017)
- Sterimol descriptors (L, Bmin, Bmax) (Brethome et al., 2019)

Modelling Helpers

The following modelling helper are implemented

- Breadth first sorting
- Root mean squared deviation (quaternions) (Coutsias et al., 2004)
- Substructure identifier
- Substructure exchanger

Acknowledgements

EC acknowledges contributions from Philipp Pracht (@pprcht) and thanks Kjell Jorner (@kjel1jorner) for sharing his Sterimol algorithm.

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