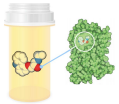
Improving Molecular Modeling through Advances in Force Field Development

Daniel Cabrera, Jessica Maat, Dr. David Mobley

Department of Chemistry, University of California Irvine - Software Engineering Major

Abstract

- Force fields are the underlying technology in molecular simulations that allow for predictive measures of different physical properties
- These molecular simulations have applications in computer aided drug design through accurate predictions of protein and ligand behavior
- Force fields consist of potential energy functions that describe bonded and non-bonded molecular interactions
- In order to improve, benchmark, and train force fields, chemically diverse datasets are important
- DANCE works to generate diverse datasets of molecules using fragment based fingerprints
- This allows for molecules to be filtered for specific molecular substructures and properties for force field development

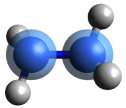


$$W_{AB} = \sum_{\mu \in A} \sum_{\nu \in B} P^2 \mu\nu$$

Wiberg bond order equation
SOURCE: docs.openeye.com

Introduction

- Chemists make use of tools, such as ForceBalance, in order to parameterize force fields
- DANCE aids in this process by providing chemists with diverse datasets for parameterization
- This ultimately allows for improved molecular modeling and increasingly accurate predictions about molecular behavior



Single nitrogen-nitrogen bond
SOURCE: avogadro.cc

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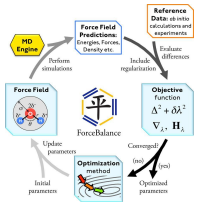
Single nitrogen-nitrogen bond
SMIRKS pattern



Wang et al. *J. Phys. Chem. Lett.*2014511885-1891

- DANCE currently implements fragment based fingerprinting for impropers and select torsion parameters
- This project extends this method to bonds, specifically single nitrogen-nitrogen bonds

Methods

Develop a customizable fingerprint method to filter molecules based on their Wiberg bond order and neighboring atoms

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Curate a diverse dataset of molecules with single nitrogen-nitrogen bonds using the customizable DANCE fingerprint

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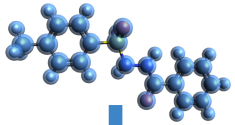
Perform chemical diversity analysis on the resulting datasets using MACCS key fingerprint and bond length



Single Nitrogen-Nitrogen bond: 7-7 (blue)
Neighbor 1: 6 Carbon (dark grey)
Neighbor 2: 16 Sulfur (yellow)
Neighbor 3: 1 Hydrogen (light grey)
Neighbor 4: 1 Hydrogen (light grey)
Wiberg bond order: 0.9447705833913734

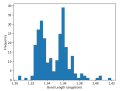
Fingerprinted Cc1ccc(cc1)S(=O)(=O)NNC(=O)c2ccccc2 molecule
SOURCE: avogadro.cc

Results: Bond Length

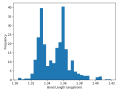
- We have established a customizable fingerprint for molecular bonds
- Used this fingerprint to generate a diverse database of molecules with single nitrogen-nitrogen bonds based on a fingerprint
- Analyzed the diversity of the dataset by comparing against a dataset of randomly selected molecules
- Bond length values appeared relatively similar between the two datasets
- MACCS key fingerprint values varied heavily, with more diverse values in the fingerprinted dataset

Bond Length Comparisons

- Fingerprinted Dataset



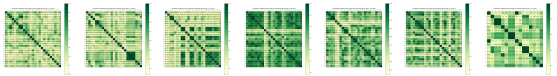
- Random Dataset



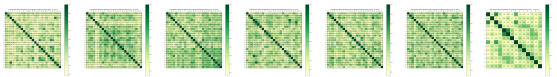
Results: MACCS Key Fingerprint

MACCS Key Fingerprint Comparisons

- Fingerprinted Dataset



- Random Dataset



Outlook

- DANCE proved to be effective at filtering datasets for specific molecular traits and electronic properties
- DANCE also demonstrated the ability to effectively generate diverse datasets using customizable fingerprinting
- Moving forward, we are looking to develop new fingerprinting methods and expand the molecular properties that DANCE is able to fingerprint for

Diagram of the DANCE pipeline steps.
SOURCE: dance.readthedocs.io

Acknowledgements

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