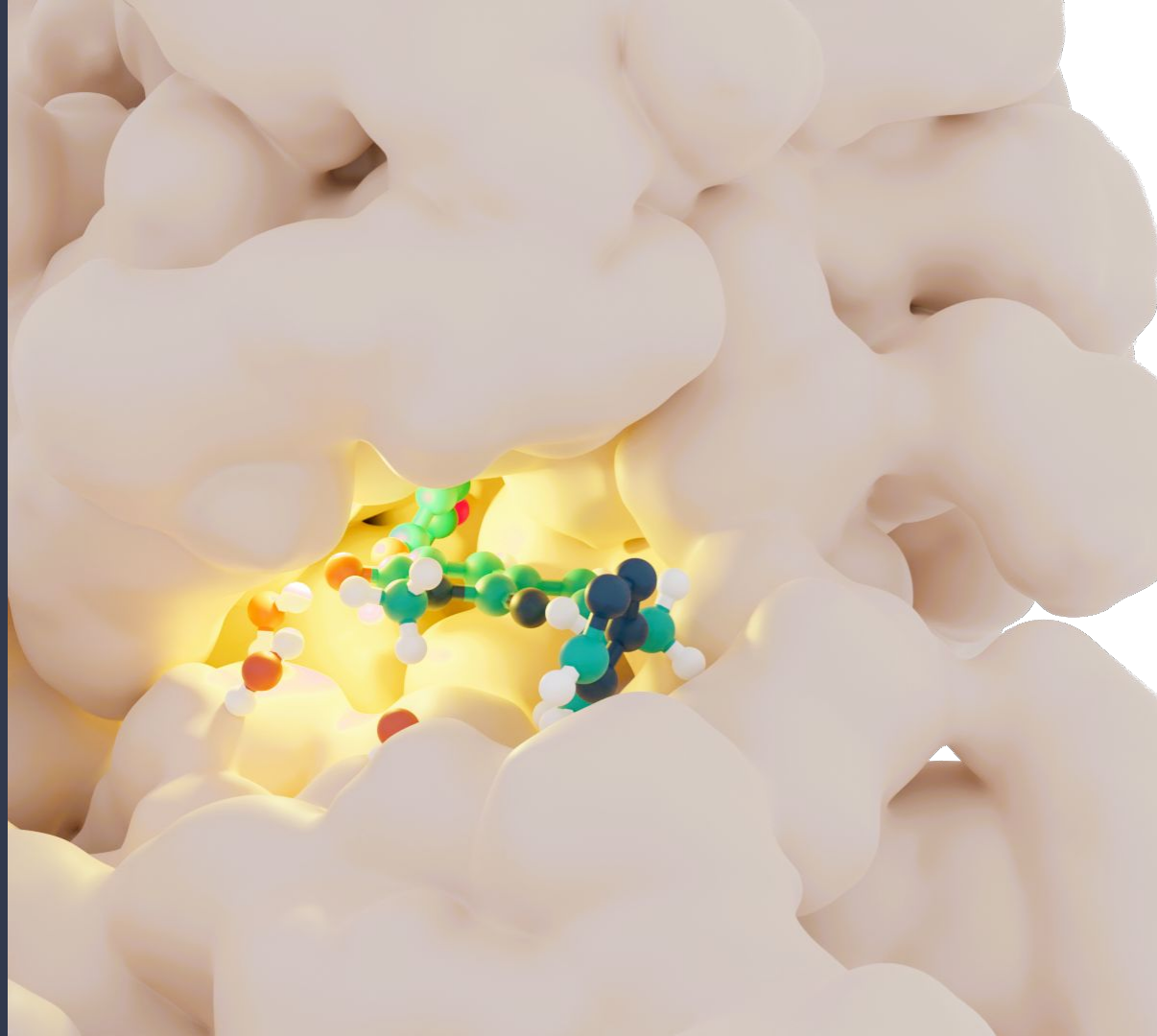
Open Free Energy: An open source ecosystem for alchemistry

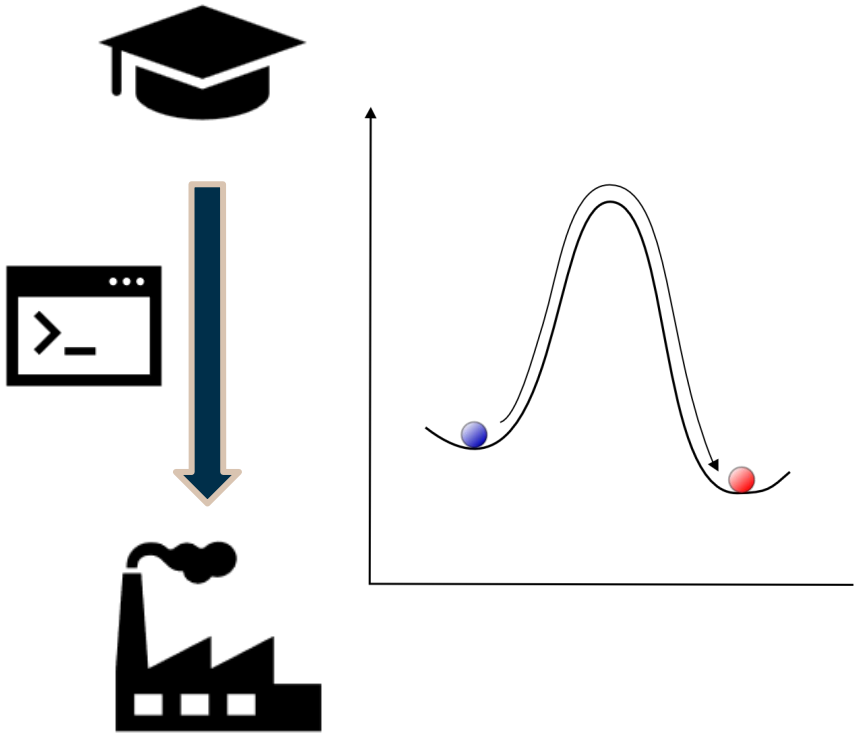
free software free energies

https://openfree.energy/



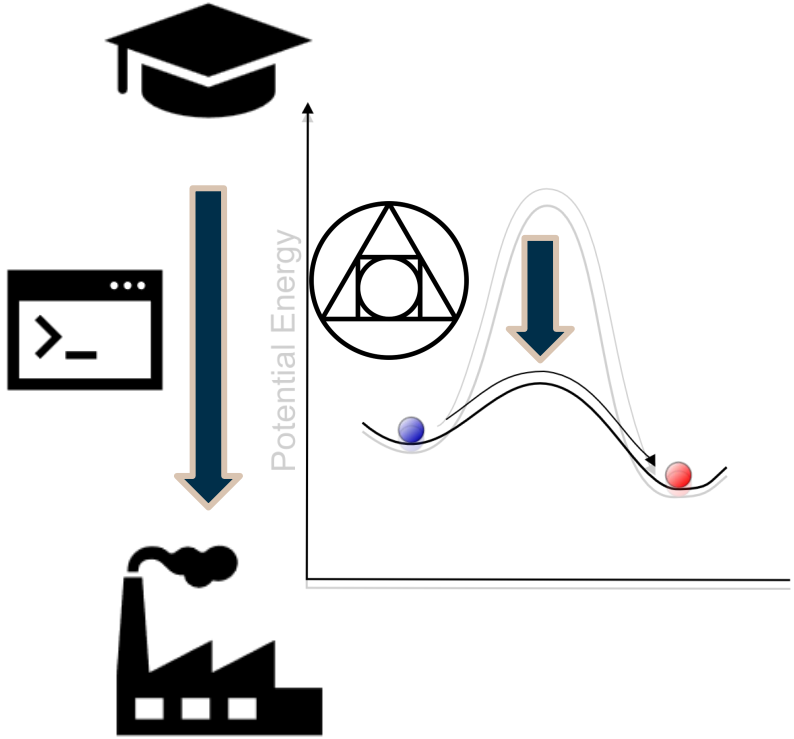
Problem: Gap between methods developed in academia and their application in industry

- Alchemical methods are successfully used in drug discovery projects
- Academia is continuously producing new methods for free energy calculations
- Academia is not incentivised to provide well tested & maintained tooling
    - “Lifetime of a postdoc” tooling
- Industry needs out of the box methods for large scale applications



The Open Free Energy project aims to bridge that gap

- Bridge the **application delivery** and **maintenance** gap
- reduce costs & duplication of efforts
- ensure a sustainable and competitive future for developed tools

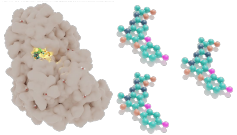


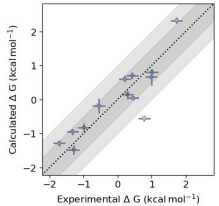
Our vision is to create a decentralized ecosystem of interchangeable components

We are working with **academic groups** to enable their software to be compatible with this ecosystem.

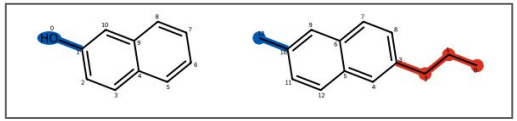
Benefits to them are:
a) software engineering support in packaging/testing/performance
b) visibility of their methods to a wider user base

OpenFE is leveraging different software tools and helps maintain software packages

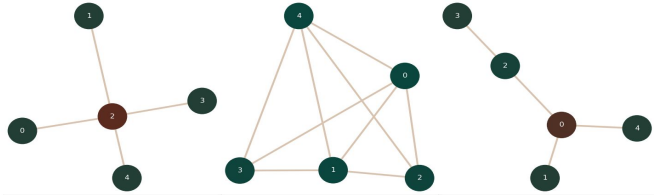




Atom mappers
- LOMAP | Kartograf



Ligand networks:
- Radial | LOMAP | Minimal spanning tree



Different methods:
- OpenFF | GAFF
- OpenMM/Perses | OpenMM/ABFE

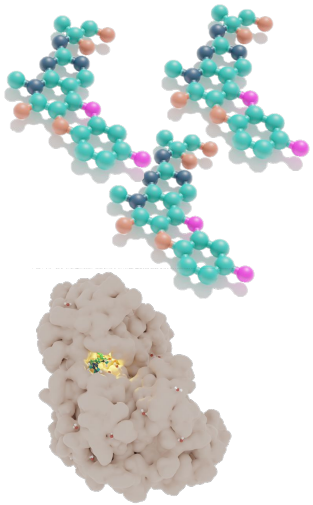
Your fancy new method?!

OpenMM

Perses

openff toolkit

Easy free energy calculations



1. **Plan** the calculations

```
openfe plan-rbfe-network -m ligands.sdf -p protein.pdb
```

2. **Run** the calculations

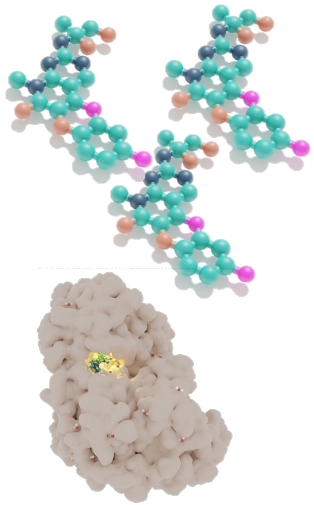
```
openfe quickrun transformation -d ./ -o results/result.json
```

3. **Analyze** the calculations

```
openfe gather results/ –report dg -o final_results.csv
```

ligand	DG(MLE) (kcal/mol)	uncertainty (kcal/mol)
lig_ejm_31	0.05	0.05
lig_ejm_42	0.54	0.09
lig_ejm_46	-0.68	0.07
lig_ejm_47	0.1	0.1
lig_ejm_48	0.5	0.2
lig_ejm_50	0.98	0.08
lig_ejm_43	1.7	0.1
lig_jmc_23	-1.07	0.08
lig_jmc_27	-1.3	0.1
lig_jmc_28	-0.80	0.08

Customizable settings



1. Plan the calculations

```
openfe plan-rbfe-network -m ligands.sdf -p protein.pdb -s settings.yaml
```

settings.yaml

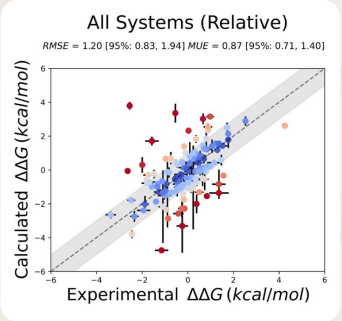
```
network:
  method: generate_radial_network
  settings:
    central_ligand: CHEMBL1078774
```

ligand	DG(MLE) (kcal/mol)	uncertainty (kcal/mol)
lig_ejm_31	0.05	0.05
lig_ejm_42	0.54	0.09
lig_ejm_46	-0.68	0.07
lig_ejm_47	0.1	0.1
lig_ejm_48	0.5	0.2
lig_ejm_50	0.98	0.08
lig_ejm_43	1.7	0.1
lig_jmc_23	-1.07	0.08
lig_jmc_27	-1.3	0.1
lig_jmc_28	-0.80	0.08

Open Free Energy Roadmap

Open Free Energy Fund founded

- Pre-competitive consortium
- Founded with backing of 13 industrial partners



First Stable Release

OpenFE v1.0

- Improved validation
- Absolute free energies
- Spectator molecules
- Charge changes
- Automated trajectory analysis

Advanced methods

OpenFE v2.0

- **Scaffold hopping** (Separated Topologies)
- **GROMACS / PMX** support
- Custom OpenFF parameter fitting

2022 2023 2024

OpenMM RBFEs

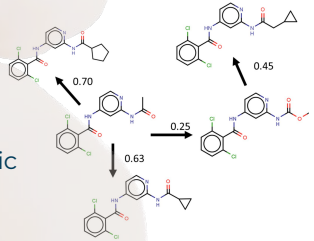
OpenFE v0.7

- GPU powered workflow based on **perses**
- Common reusable “free energy language"
- Full **OpenFF** support

Supporting tooling

Kartograf v1.0

- **Kartograf** - geometric atom mapper
- **LOMAP**v2 - Ligand network planning
- **Cinnabar** - simulation analysis and reporting



Industry benchmarking

- Large scale benchmarking of OpenFE methods conducted with our industry partners

Outline

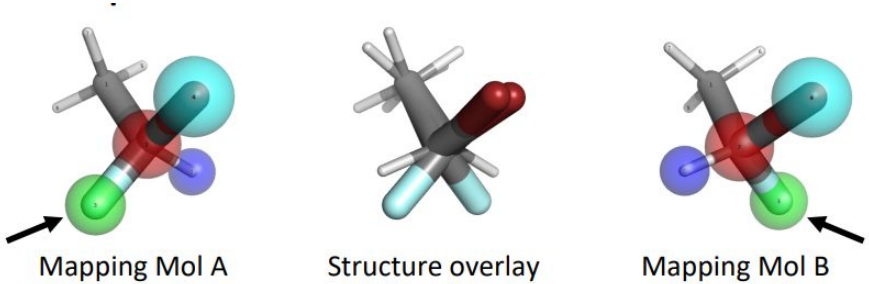
1. New tooling: Kartograf, a geometrically-accurate atom mapper

2. Benchmarking: Comparison of different ligand networks

3. Exploring reproducibility problems: Partial charges

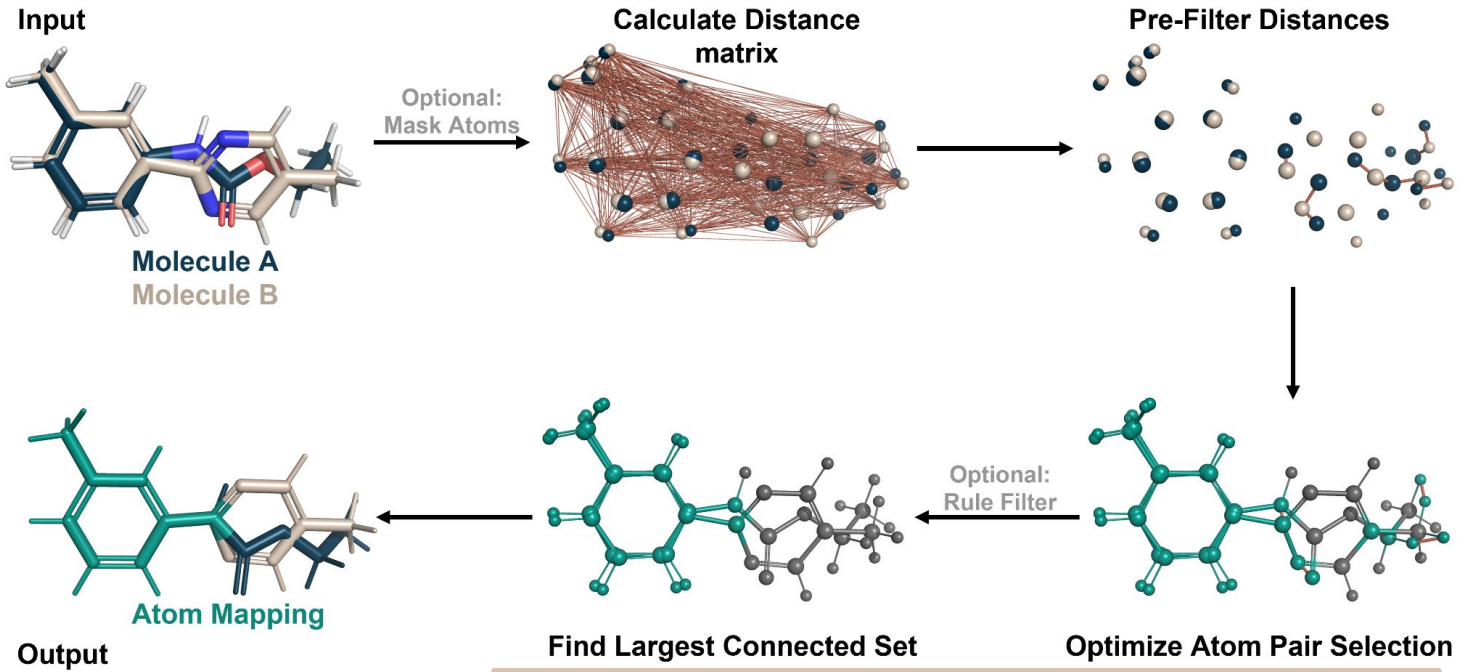
Atom mapping is a challenging problem

- MCS (2D) approaches can sometimes poorly handle things like stereochemistry
  - Manual inspections of mappings required → costly!
  - Need for better 3D aware mappers
- MCS algorithms can become very slow as the number of ligands becomes large
  - Need for faster algorithms



Ries et al., JCTC, 2024

Kartograf: geometrically accurate mappings



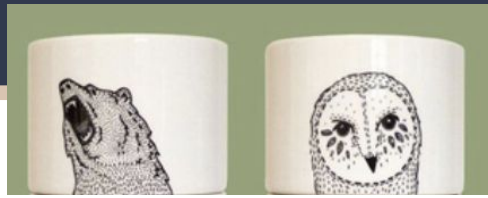
Filters to add alchemical "knowledge"

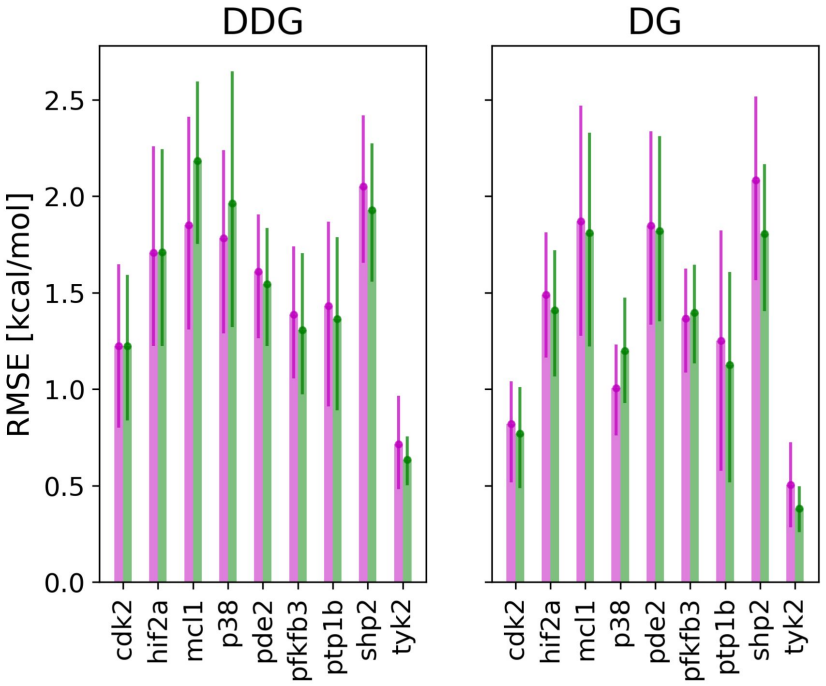
- Avoid disconnected mappings, prevent ring breaking, etc.

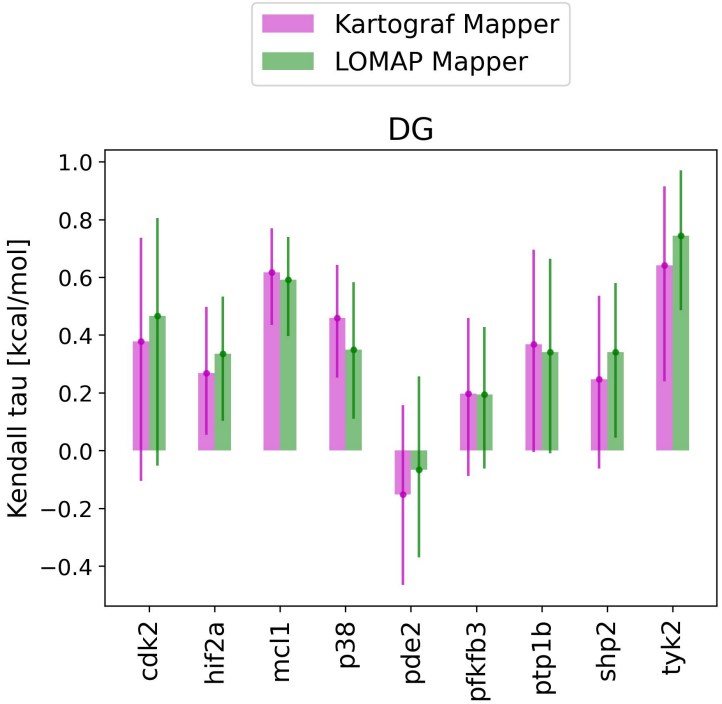
Ries et al., JCTC, 2024

Benjamin Ries

LOMAP and Kartograf atom mappers gave similar results for 9 systems







Outline

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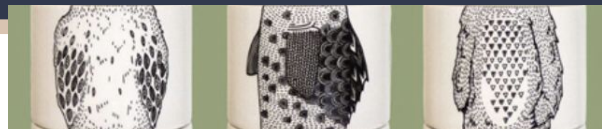
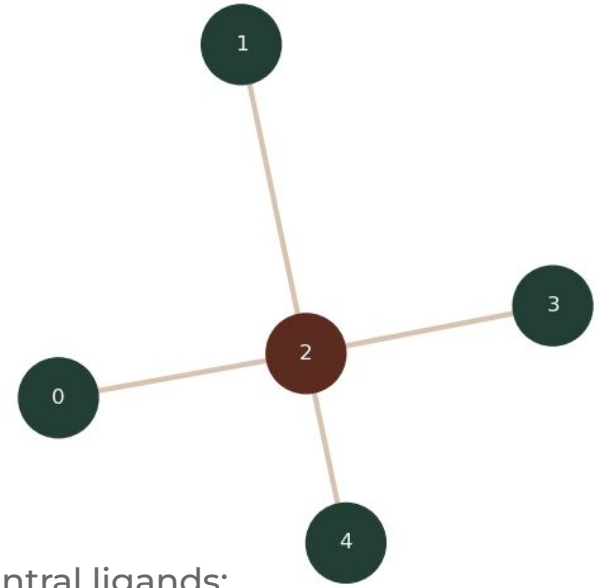
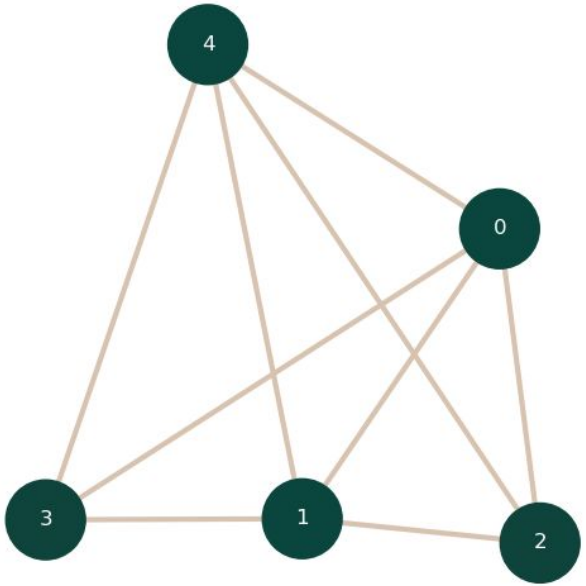
Benchmarking:
Comparing different ligand networks



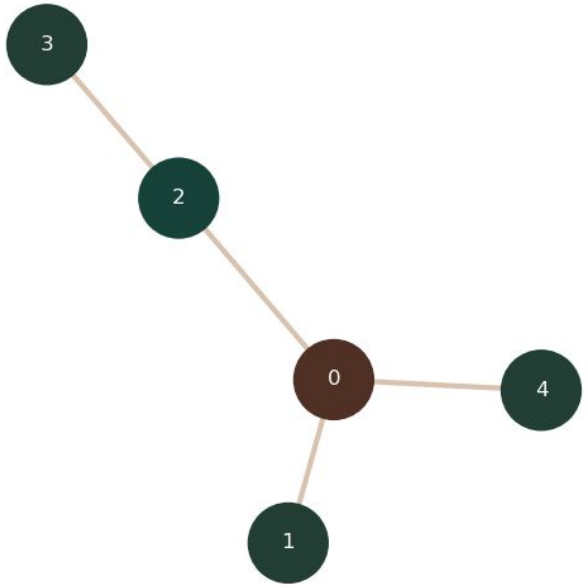
Radial Networks



LOMAP Network

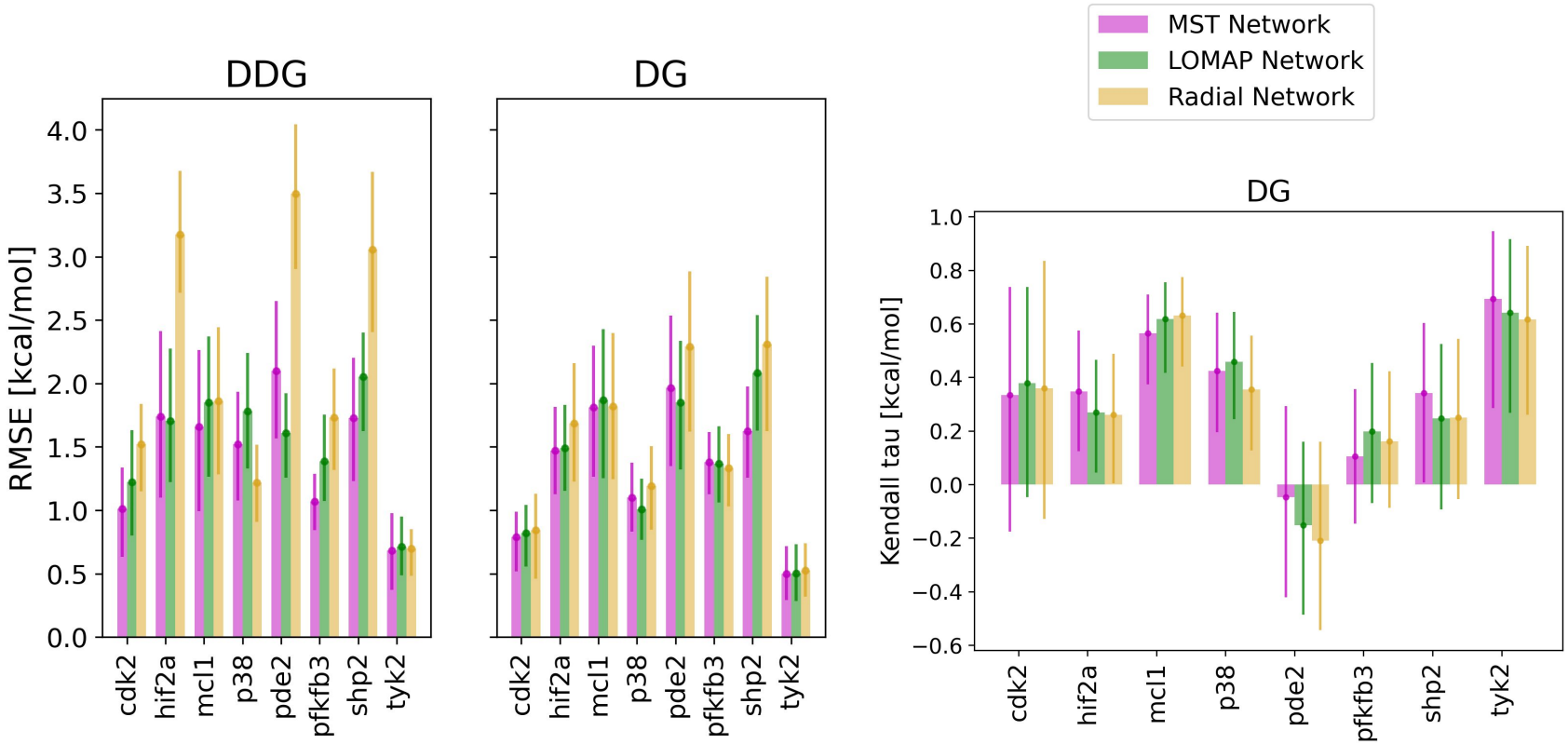


Minimal Spanning Network



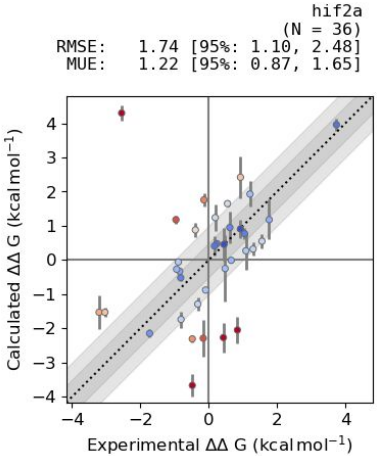
Central ligands:
ligand with least amount of heavy atoms

MST and LOMAP networks gave comparable results, while radial networks performed poor on some systems

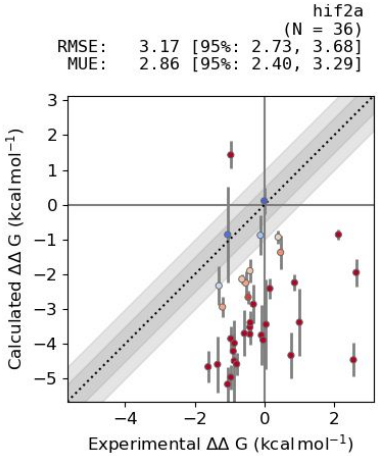


In some radial networks, transformation were very large, resulting in poor performance

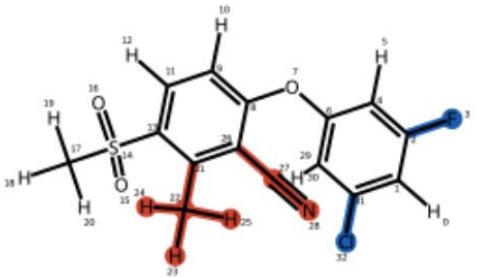
MST network

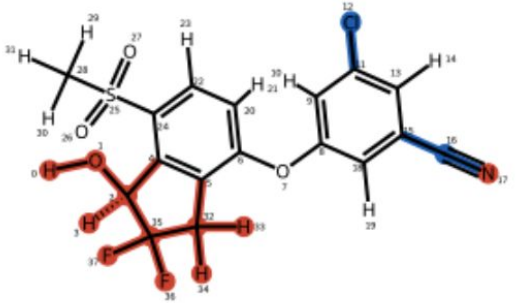


Radial network



Large transformations in the radial network





- Use as central ligand the ligand with highest similarity to all other ligands?
- Cluster ligands and run multiple radial networks

Outline

1. New tooling: Kartograf, a geometrically-accurate atom mapper

2. Benchmarking: Comparison of different ligand networks

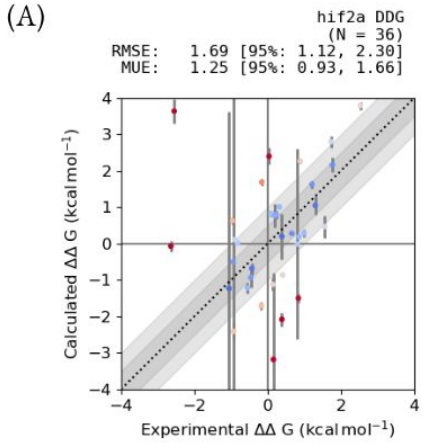
3. Exploring reproducibility problems: Partial charges

Partial charges impact free energies

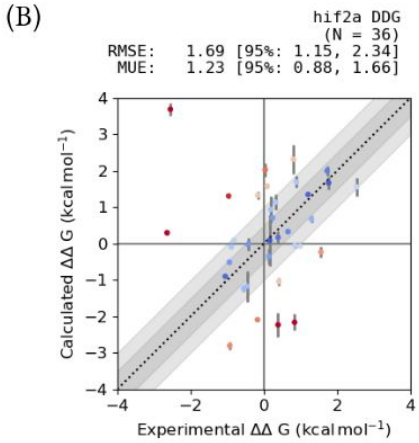
- Partial charge generation known to be sensitive to input conformation
  - But how bad can small fluctuations really be?
- Default OpenFF Tk: pseudo-random conformer selection

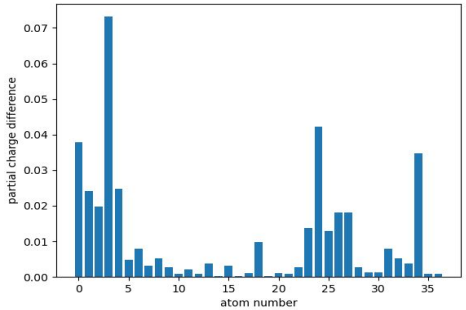
Meghan Osato

"Random" conformer



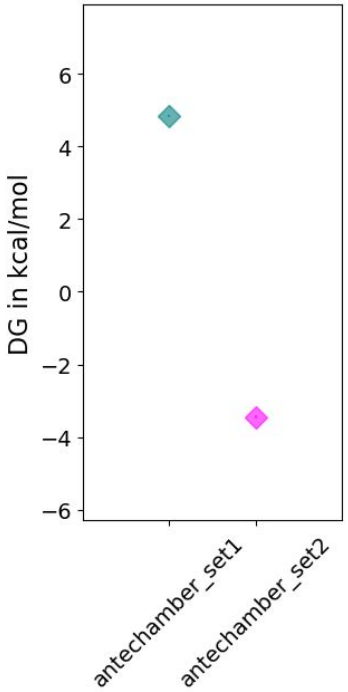
Same conformer



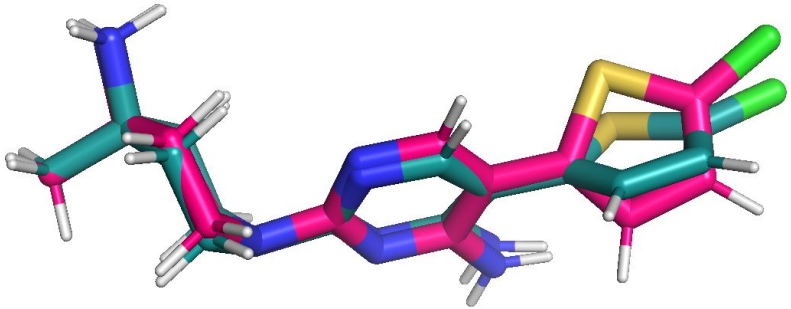


Using the same input conformer, antechamber can converge to different minima

Gas phase transformation ligand E3 → ligand E4

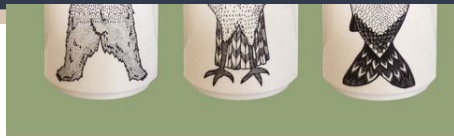


SHP2 ligand E3:
two different conformations from antechamber



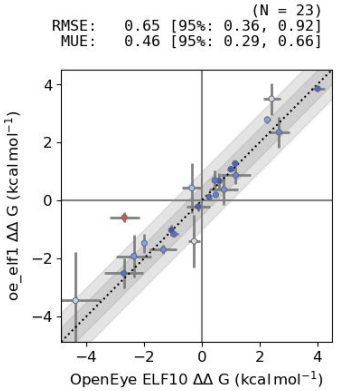
Small change in float accuracy* leading to identification of different optimized conformation.
*(down to choice of antechamber diagonalization routine)

With OpenFE, we can systematically compare different methods for partial charge generation

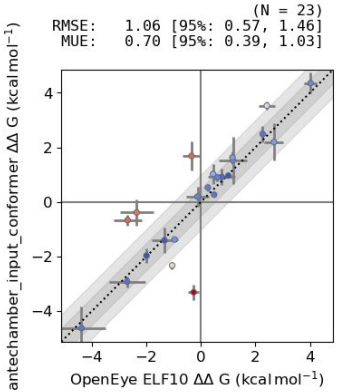


SHP2: Comparison of different partial charge methods **against OpenEye ELF10**

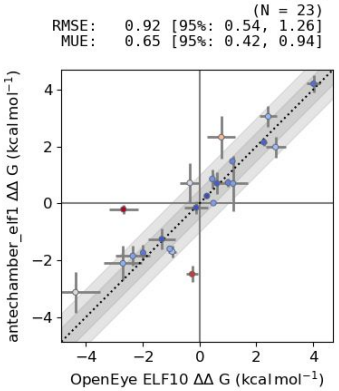
OpenEye ELF1



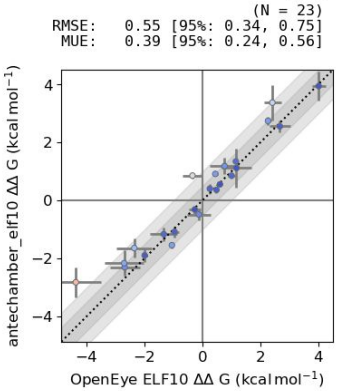
Antechamber input conformer



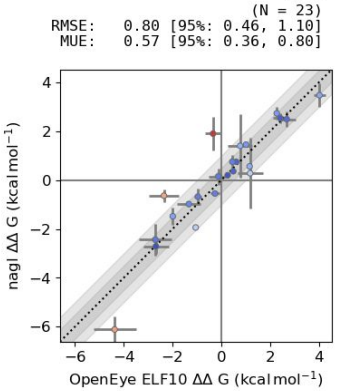
Antechamber/ RdKit ELF1



Antechamber/ RdKit ELF10



NAGL

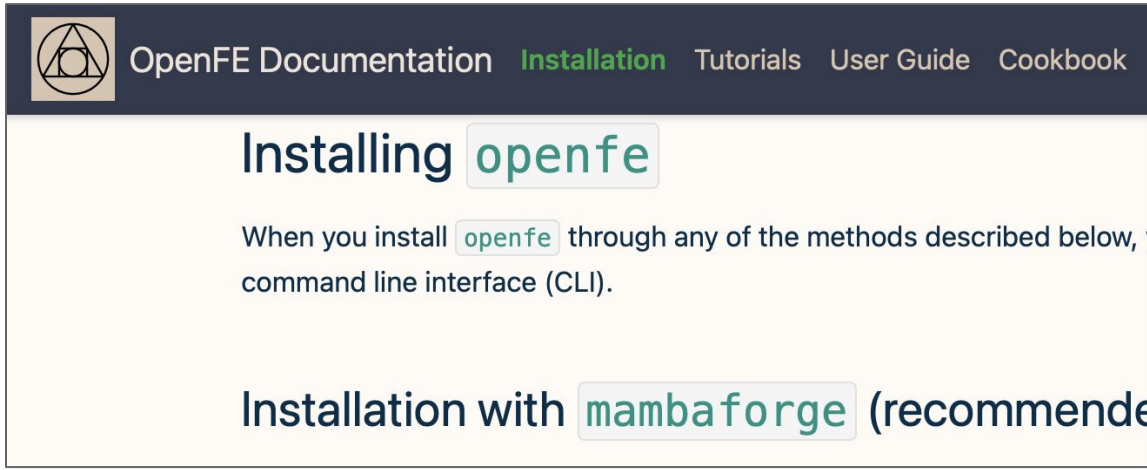


Getting OpenFE into your hands

Getting Started:

- https://docs.openfree.energy
- Click “Installation”
- Next try “Tutorials”
- `openfe fetch rbfe-tutorial`

https://openfree.energy



Open Free Energy is hosted by the non-profit organization OMSF and funded by industry partners

Open Molecular Software Foundation

open forcefield

Open Free Energy

OpenFold

Democratizing AI for Biology

Open Rosetta

Some advertisement ...

Richard Gowers:
Distopia: A molecular geometry analysis MDAKit
Poster Board #1828
08:00pm - 10:00pm EDT - March 19, 2024

James Eastwood:
Open Force Field: Improving the accuracy and applicability of open molecular models
Poster Board #2041
08:00pm - 10:00pm EDT - March 19, 2024

Jenke Scheen:
ASAP Discovery: Open source structure-enabled drug discovery for pandemic preparedness
05:50pm - 06:15pm EDT - March 19, 2024

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- Iván Pulido
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- Dominic Rufa
- Ivy Zhang

Mobley lab

- Meghan Osato
- David Mobley

And many many more

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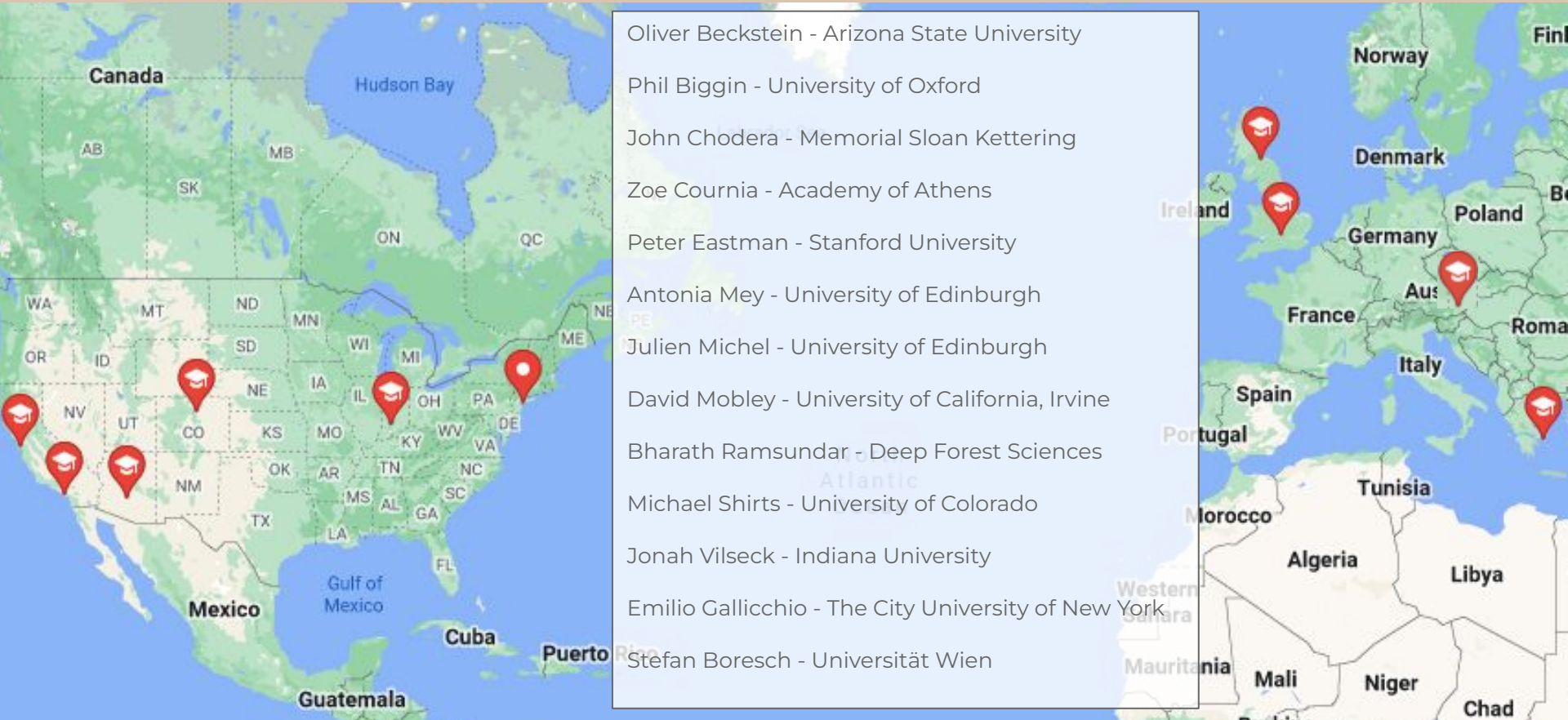
Technical Advisory Committee



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Phil Biggin - University of Oxford

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Zoe Cournia - Academy of Athens

Peter Eastman - Stanford University

Antonia Mey - University of Edinburgh

Julien Michel - University of Edinburgh

David Mobley - University of California, Irvine

Bharath Ramsundar - Deep Forest Sciences

Michael Shirts - University of Colorado

Jonah Vilseck - Indiana University

Emilio Gallicchio - The City University of New York

Stefan Boresch - Universität Wien