

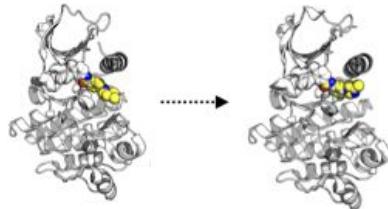
Large-Scale Collaborative Assessment of Binding Free Energy Calculations for Drug Discovery using OpenFE

Alyssa Travitz

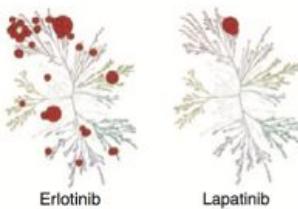
MDAnalysis UGM 2025

November 10, 2025

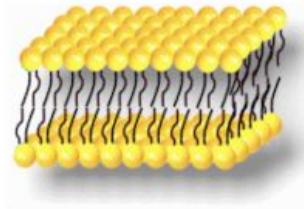
Calculating free energies is key to understanding biological processes



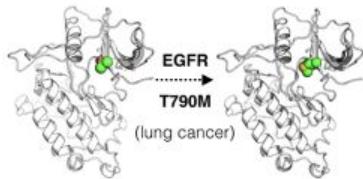
Driving affinity and potency



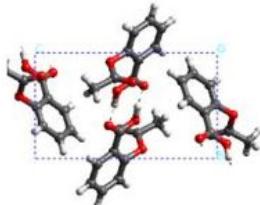
Driving selectivity



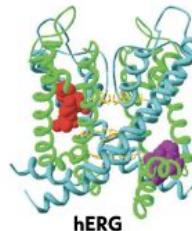
Partition coeffs and permeability



Predicting drug resistance

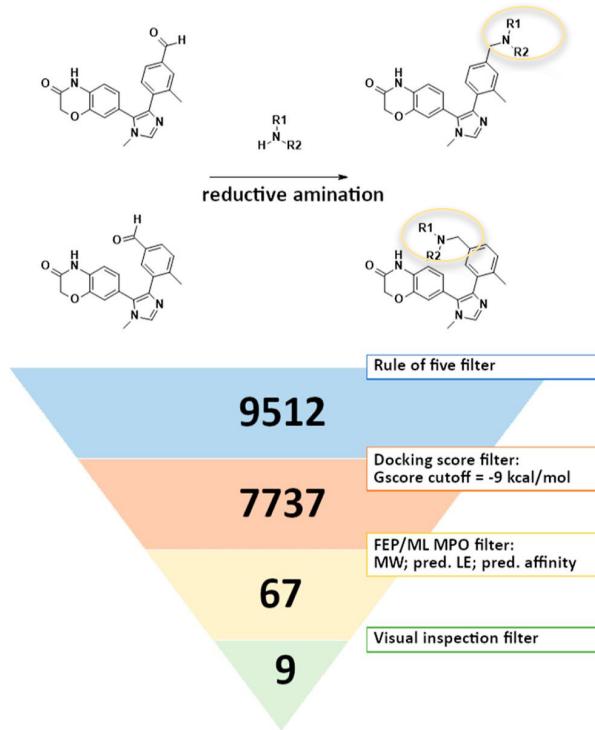
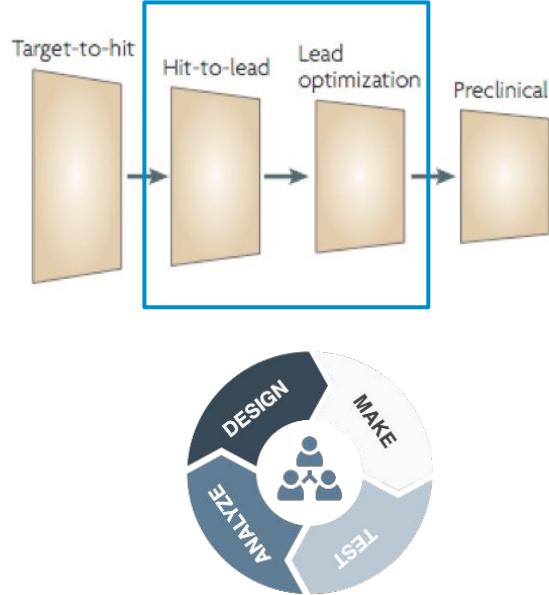


Predicting crystal polymorphs, solubility



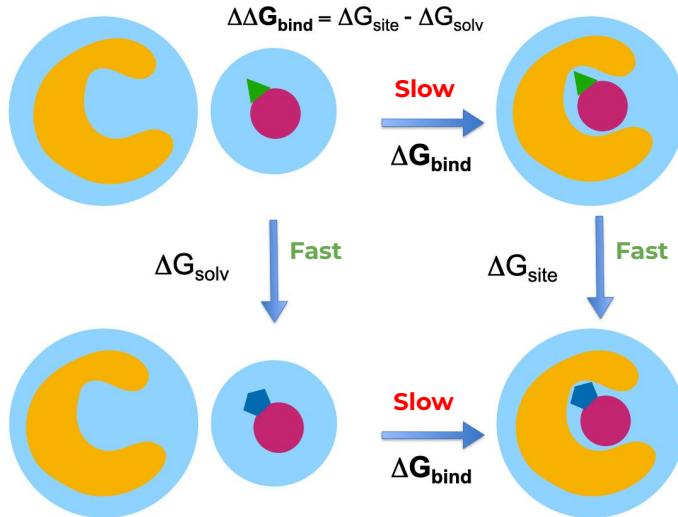
Structure-enabled ADME/Tox targets

Free energy calculations are becoming integral to drug discovery

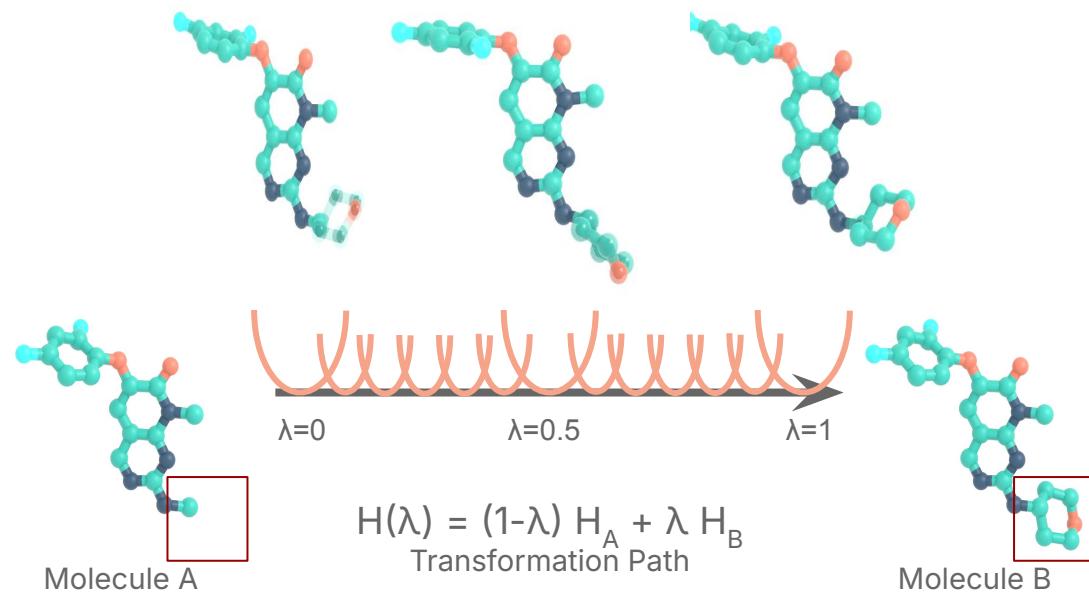
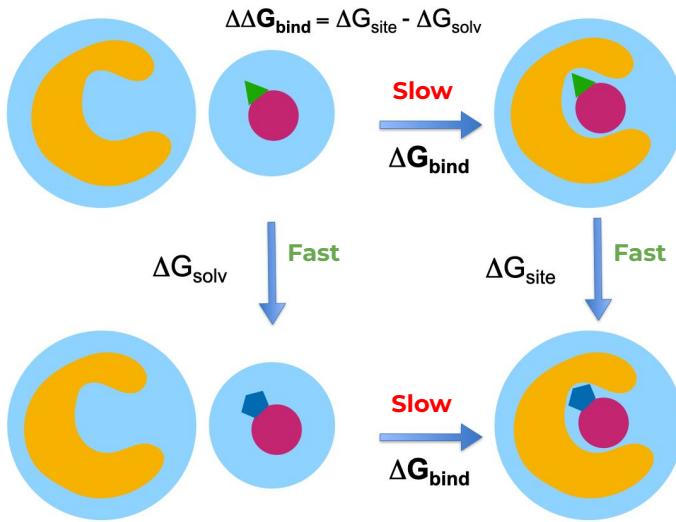


Identification of Novel Potent NSD2-PWWP1 Ligands Using Structure-Based Design and Computational Approaches, J. Med. Chem. 2024, 67, 11, 8962–8987

Alchemical Free Energies: a rigorous way to compute binding affinities



Alchemical Free Energies: a rigorous way to compute binding affinities



A need for open and free alchemical tooling

Blockers to large-scale adoption:



Money

- Proprietary software can be expensive
- Hardware



Infrastructure

- Tools for setup, execution, analysis of complex workflows



Domain specific knowledge

- You need to hire your own alchemical wizard

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OpenFE's priorities:



Free

Permissive open source (MIT) license



Easy to Use

Designed for simple, large scale deployment



Robust

Built and maintained to industry standards



Extensible

Clear API to allow reuse and adaptation of components



Accurate

Guide pharmaceutical drug design and discovery

openfe's CLI makes free energy calculations routine

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
```



protein + ligands



ligand	DG(MLE) (kcal/mol)	uncertainty (kcal/mol)
lig_ejm_31	-0.09	0.05
lig_ejm_42	0.7	0.1
lig_ejm_46	-0.98	0.05
lig_ejm_47	-0.1	0.1
lig_ejm_48	0.53	0.09
lig_ejm_50	0.91	0.06
lig_ejm_43	2.0	0.2
lig_jmc_23	-0.68	0.09
lig_jmc_27	-1.1	0.1
lig_jmc_28	-1.25	0.08

results

Basic customization with the CLI, even more with the Python API



protein
+
ligands



ligand	DG(MLE) (kcal/mol)	uncertainty (kcal/mol)
lig_ejm_31	-0.89	0.05
lig_ejm_42	0.7	0.1
lig_ejm_46	-0.98	0.05
lig_ejm_47	0.8	0.1
lig_ejm_48	0.93	0.09
lig_ejm_58	0.91	0.06
lig_jmc_21	2.0	0.2
lig_jmc_23	-0.68	0.09
lig_jmc_27	-1.1	0.1
lig_jmc_28	-1.25	0.08



results

openfe is the entrypoint to the larger OpenFE ecosystem

openfe

central framework and entrypoint for FE calculations

gufe

custom data models

konnektor

network construction



LOMAP

atom mapping
(originating from the
Mobley Lab)

kartograf

atom mapping
focused on
3D geometries

feflow

Community-contributed
Protocols for FE
calculations

alchemiscale

distributed execution across
heterogeneous compute



cinnabar

Free energy networks
analysis and best
practices

and many more!

OpenFE is powered by open-source software



FeFlow



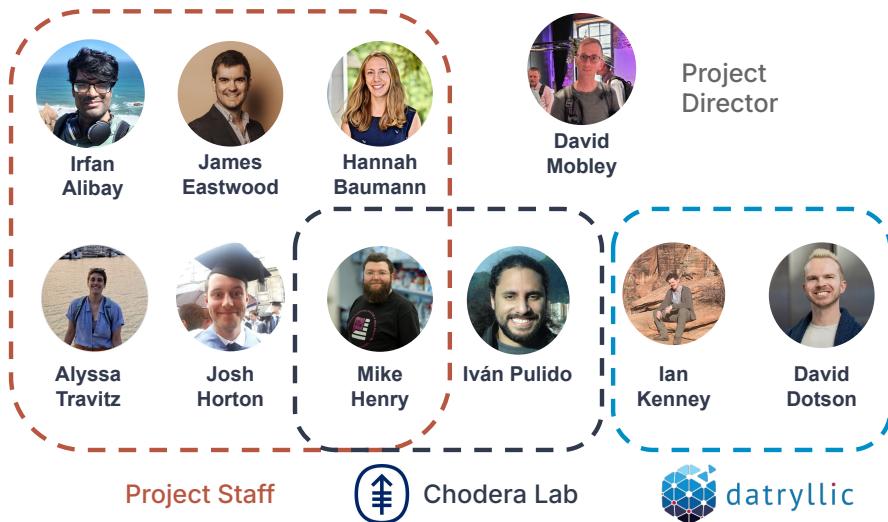
pymbar



- **openfe-analysis**
- Boresch restraints
- COM
- RMSD

OpenFE works with both industry and academic partners

Core Developers



Technical Advisory Committee

14 academic members

Oliver Beckstein
Phil Biggin
John Chodera
Zoe Cournia
Sukrit Singh
Antonia Mey
Julien Michel

David Mobley
Bharath Ramsundar
Michael Shirts
Jonah Vilseck
Emilio Gallicchio
Stefan Boresch
Sereina Riniker

Industry Partner Members

18 companies

Achira
Amgen
AstraZeneca
Bayer
Biogen
Boehringer Ingelheim
Bristol Myers Squibb
Charm Therapeutics
Confo Therapeutics
Cresset
Deep Origin
Eli Lilly
Genentech (Roche Group)
GSK
Janssen
Merck KGaA
Neomorph
Pfizer

Open Free Energy Roadmap

OpenMM RBFEs

OpenFE v0.7

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

First Stable Release

OpenFE v1.0

- Improved validation
- Charge changes
- Automated trajectory analysis
- Absolute hydration free energies
- "Vanilla" MD simulations

New Protocols

- Separated Topologies and ABFEs
- Protein **mutation**
- Improved **performance** and **file storage**
- Bespoke parameter support

Protocol Refinement

- Membrane support.
- Improvements to **dummy atoms** handling
- New parameterization pipeline
- Continual **benchmarking**

2022

2023

2024

2025

2026

RFE support tooling

Kartograf v1.0

- **Kartograf** - geometric atom mapper
- **LOMAPv2** - Ligand network planning
- **Cinnabar** - simulation analysis and reporting

Improved Setup

- **Konnektor** - network generation tooling
- Custom ligand parameter support
- Non-cubic solvation
- Improved CLI
- **Gromacs MD Protocol**

Industry Benchmarks

- Large scale collaborative benchmark of OpenFE tools with industry partners on private and public datasets

Enhanced Usability

- Improved **HPC execution**
- **Simulation Continuations**
- **User documentation** and **API usability** drive.
- Developer documentation.

Large scale benchmarking to demonstrate real world performance



Participants

- 15 companies involved in this study



Public dataset

- Inputs taken from Ross et al.
(Schrödinger's latest FEP+ study)
- 59 datasets: **876** ligands



Private datasets

- In-house datasets
- 37 datasets: **864** ligands

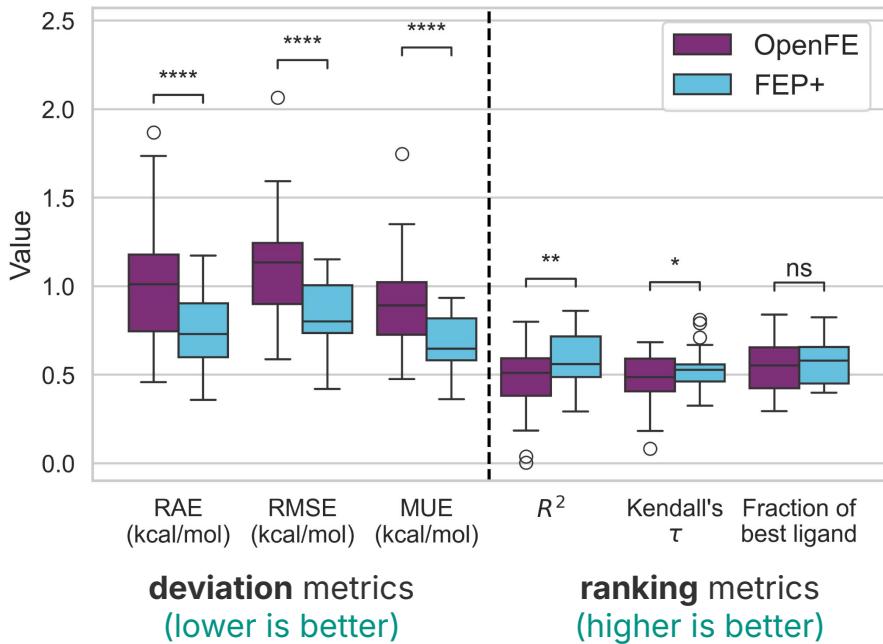
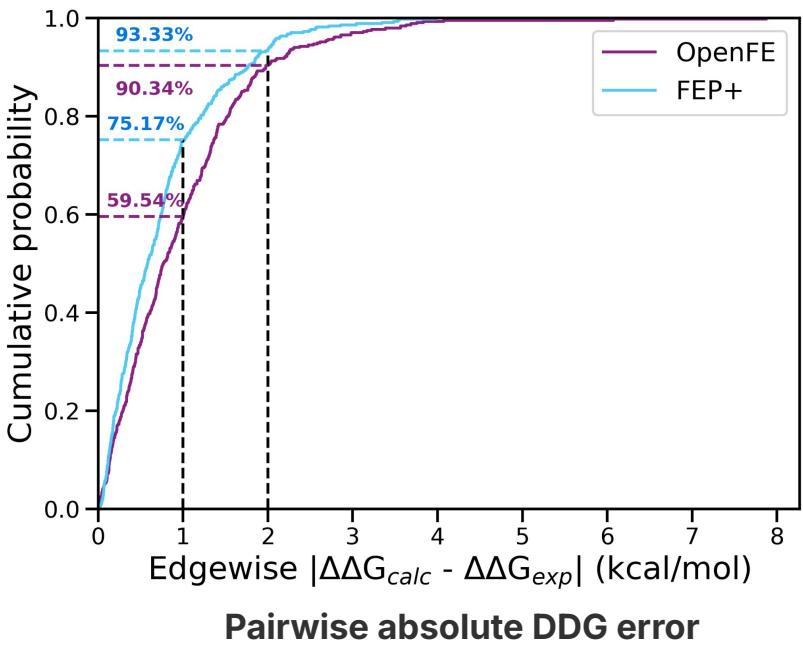
Data from:

Abbvie
ASAP
AstraZeneca
Bayer
Biogen
BMS
Boehringer Ingelheim
Deep Origin
Eli Lilly
Genentech
GSK
Johnson & Johnson
Merck KGaA
Odyssey
Roche

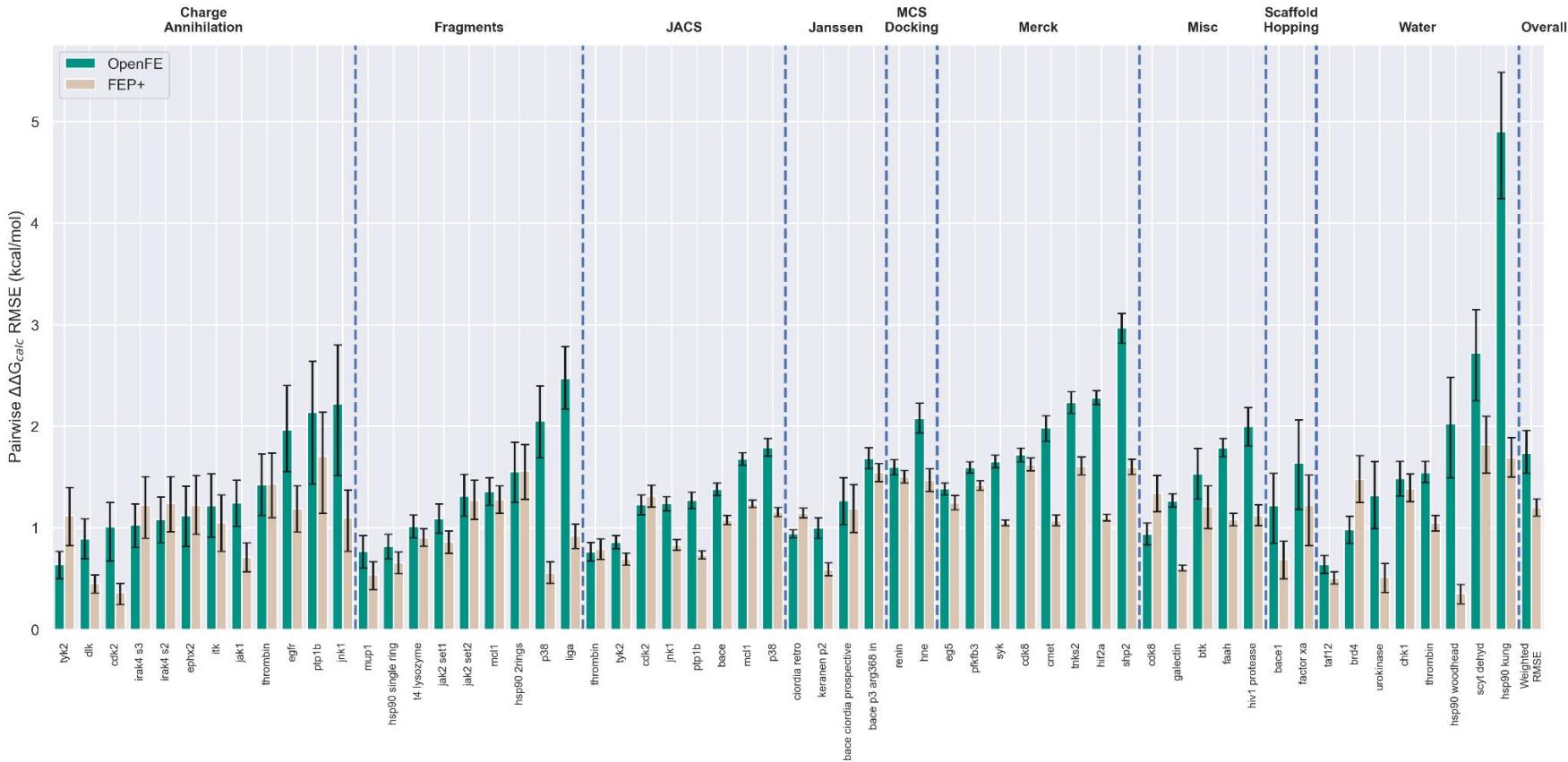
We benchmark with default settings and compare to the state-of-the-art

	OpenFE	Ross et al. (FEP+)
Automation	Full default protocol with no manual tuning of settings	Manual tuning of atom mappings and settings to improve performance
Simulation length	5ns neutral edges 20 ns charge changes	20 ns
Lambda schedule	11 windows neutral edges 22 windows charge changes	12 windows for simple transformations 24 windows charge changes 16 windows scaffold hopping and macrocyclization
Repeats	Triplicates	Single simulation
Sampling	Hamiltonian replica exchange	Replica exchange with solute tempering (REST2) GCMC water sampling
Force field	OpenFF-Sage-2.2.0 ligands TIP3P water FF14SB protein	OPLS4 ligands with custom torsions SPC water

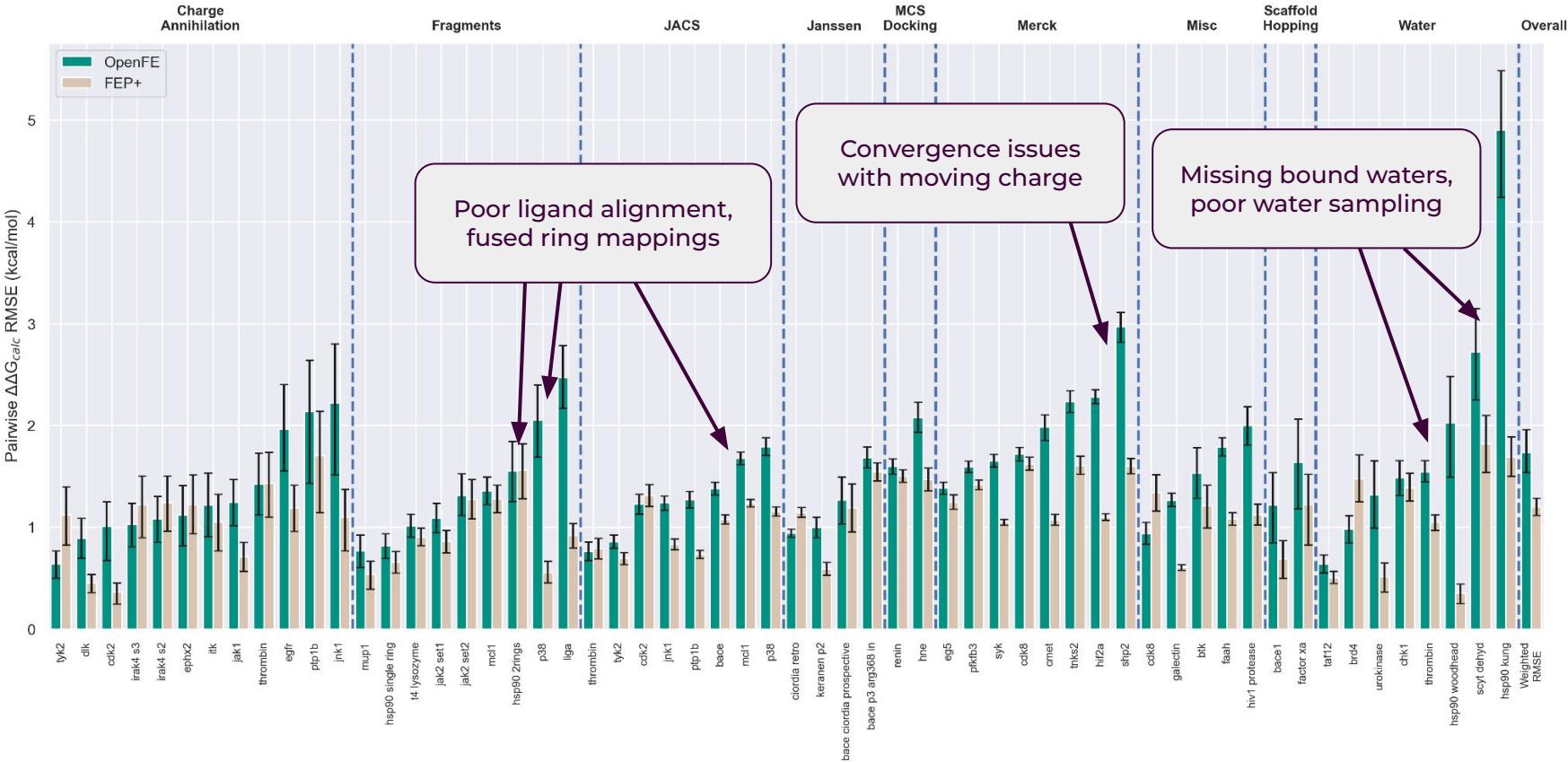
Public dataset results: comparison to FEP+



OpenFE is competitive with state-of-the-art protocols



Investigating outliers

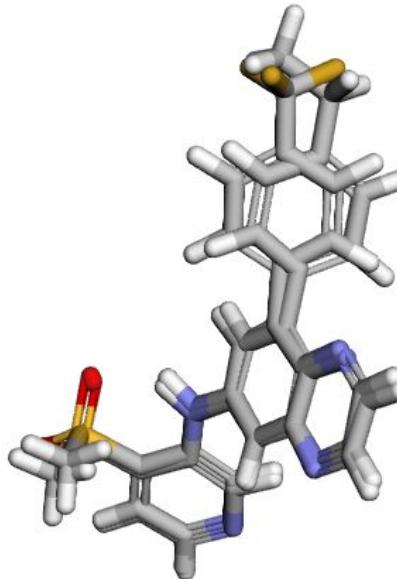
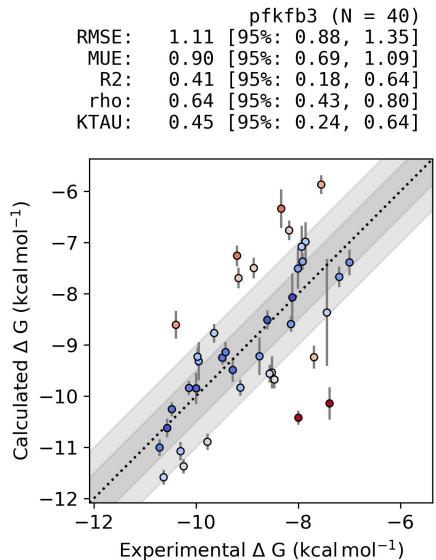
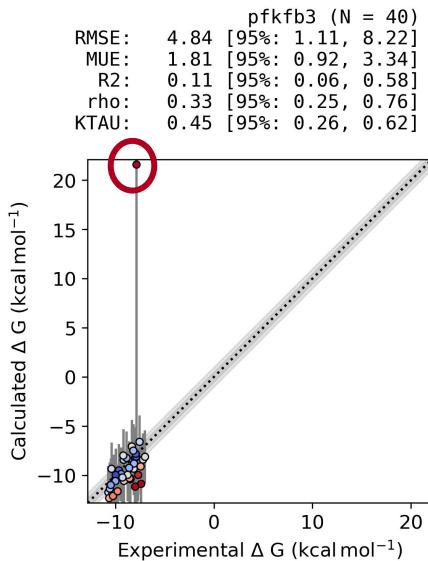


Benchmarking helped us identify a bug in the atom mapper

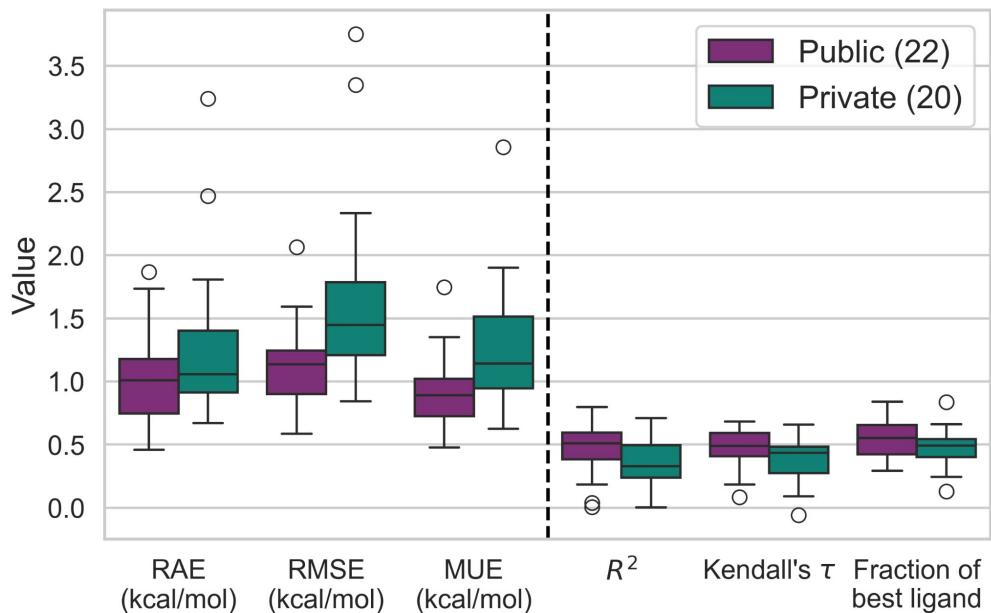
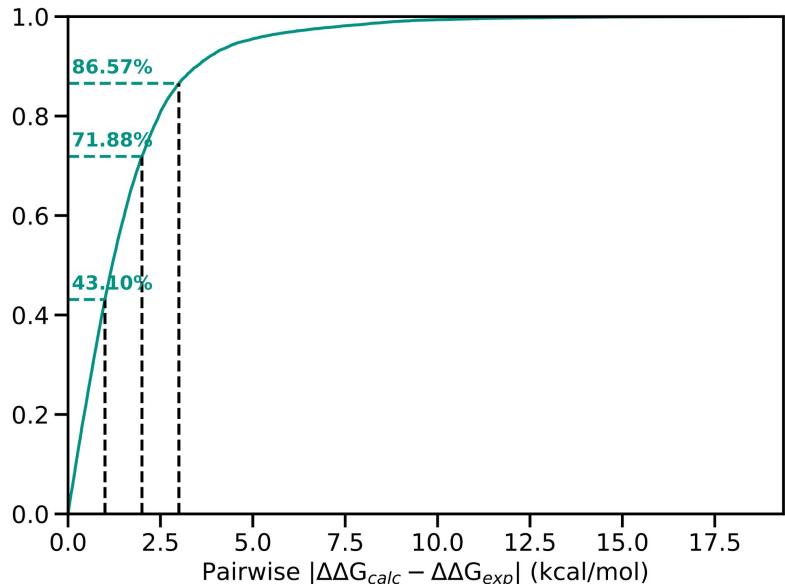
PFKFB3

- Absolute error: 28 kcal/mol
- Standard deviation in the complex: 73 kcal/mol

This mapping accidentally introduces a **bond breaking transformation**, resulting in very poor performance.



Private datasets represent real-world performance



deviation metrics
(lower is better)

ranking metrics
(higher is better)

Key Takeaways:

- OpenFE's **default performance is competitive** with state-of-the-art tooling (FEP+).
- Application to **real world systems** (i.e. private datasets) demonstrates reduced accuracy, but retains **predictive power** on most submitted systems.
- Our industry benchmarking results offer a wealth of **feedback** to help us define **future developments**.
- **Look for our preprint in the next month or so!**

What's next for OpenFE?

- Membrane support
- Community-contributed protocols
- Usability Drives
- Enhanced simulation execution system
- More benchmarking!

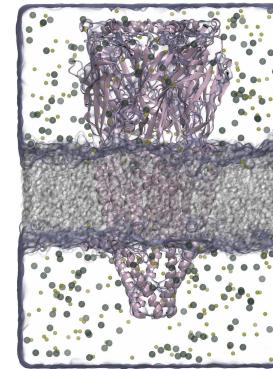
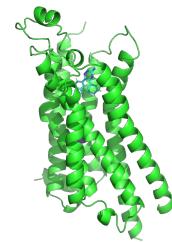


Image credit: Yuxuan Zhuang



A2A receptor
(initial membrane
test system)

Thank you!

OpenFE developers

Hannah Baumann
Josh Horton
Irfan Alibay
Mike Henry
James Eastwood
Ivan Pulido
David Dotson
Ian Kenney
Benjamin Ries
David Mobley

ASAP Discovery

Jenke Scheen
Hugo 🦨!

Chodera lab

Julie Behr
Hannah Bruce Macdonald
John Chodera
Patrick Grinaway
Dominic Rufa
Ivy Zhang
Andrea Rizzi

OMSF Eco-Infra

Ethan Holz
David Swenson

OpenFE TAC

OpenFE Board

Many more!

Matt Thompson,

Contributors in the benchmarking study

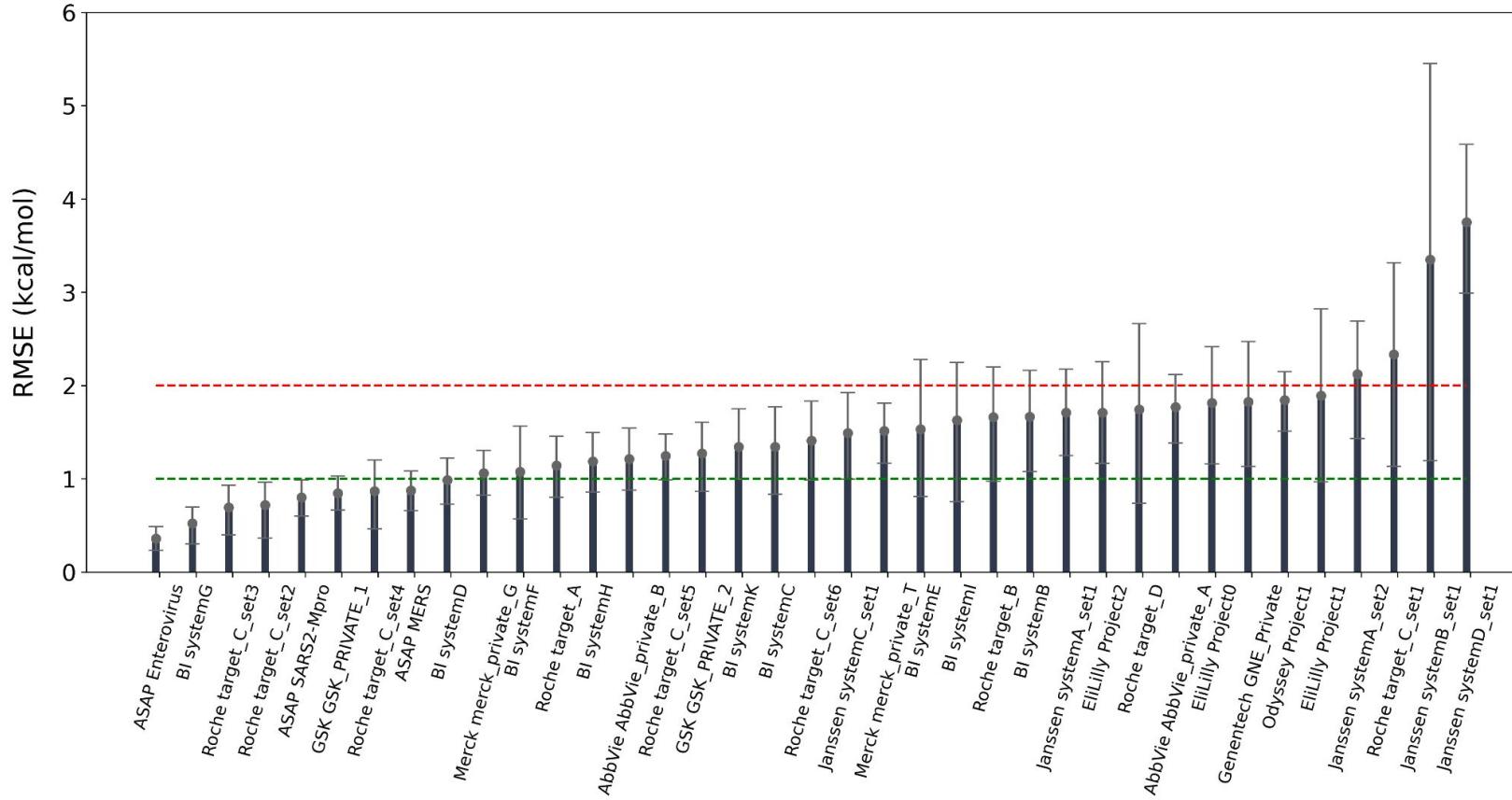
Abbvie
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Bayer
Biogen
BMS
Boehringer Ingelheim
Deep Origin
Eli Lilly
Genentech
GSK
Johnson & Johnson
Merck KGaA
Odyssey
Roche



OpenFE's binding free energy protocols

now available in openfe v1.7.0!

	Hybrid Topology Relative Free Energy	Separated Topologies (SepTop)*	Absolute Binding Free Energy*
Speed	Fast	Medium	Slow
Use case(s)	R-group enumeration	Scaffold hopping	Virtual screening Protein selectivity
Protocol inspired by	Perseus (Chodera Lab)	Mobley Lab Femto (Psivant)	Yank (Chodera Lab)



Private datasets represent real-world performance

