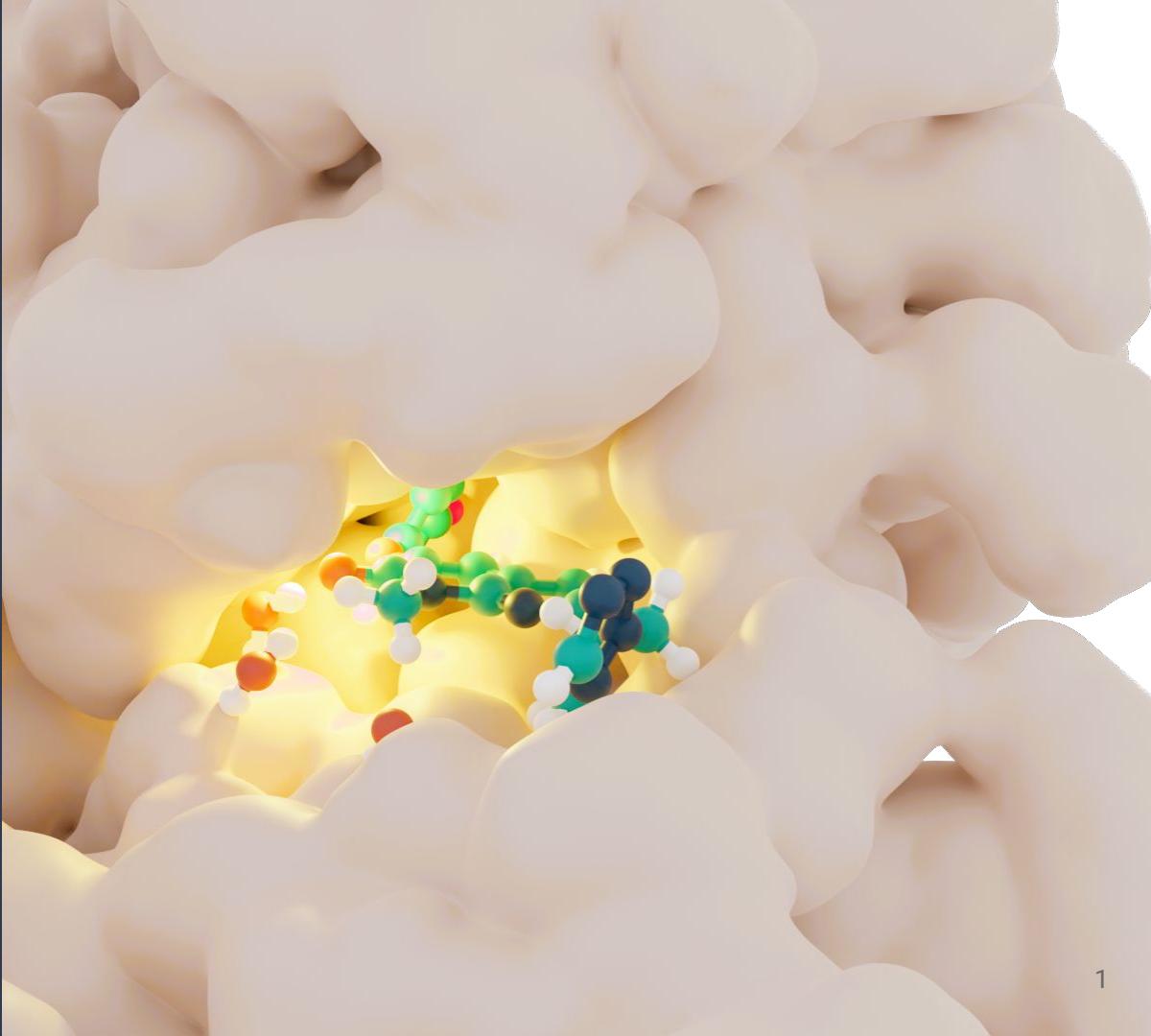


Open Free Energy: OMSF 2024



<https://openfree.energy/>





Open Free Energy

“How do we best share our tools and failures”
- Anonymous (Alchemistry 2019)

“We’ve been talking about these things for over 20 years”
- Anonymous (Alchemistry 2024)

“If only we had spoken to <redacted> earlier on”
- Anonymous (Alchemistry 2024)

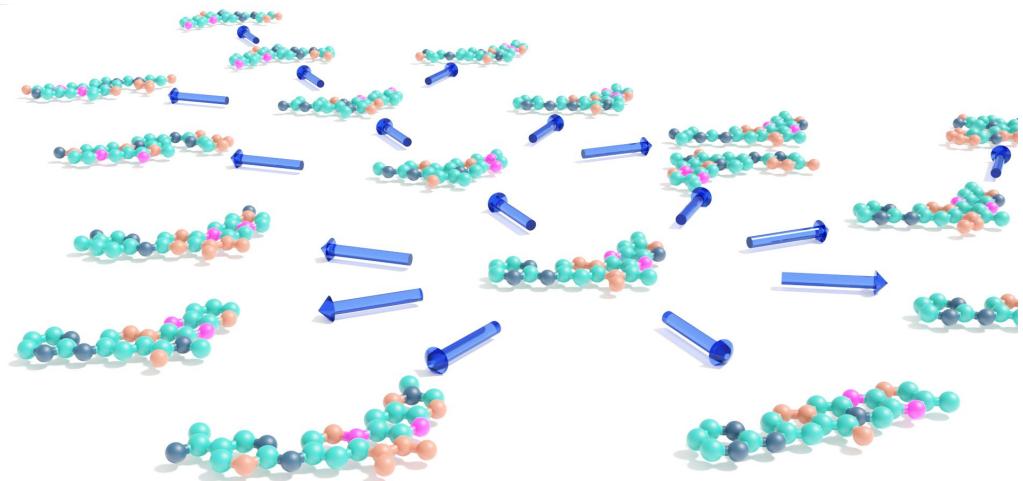
“It’s difficult to always have to re-implement the same things”
- Anonymous (Alchemistry 2024)

“We need to see the code to understand its behaviour”
- Anonymous (Alchemistry 2024)



Open Free Energy

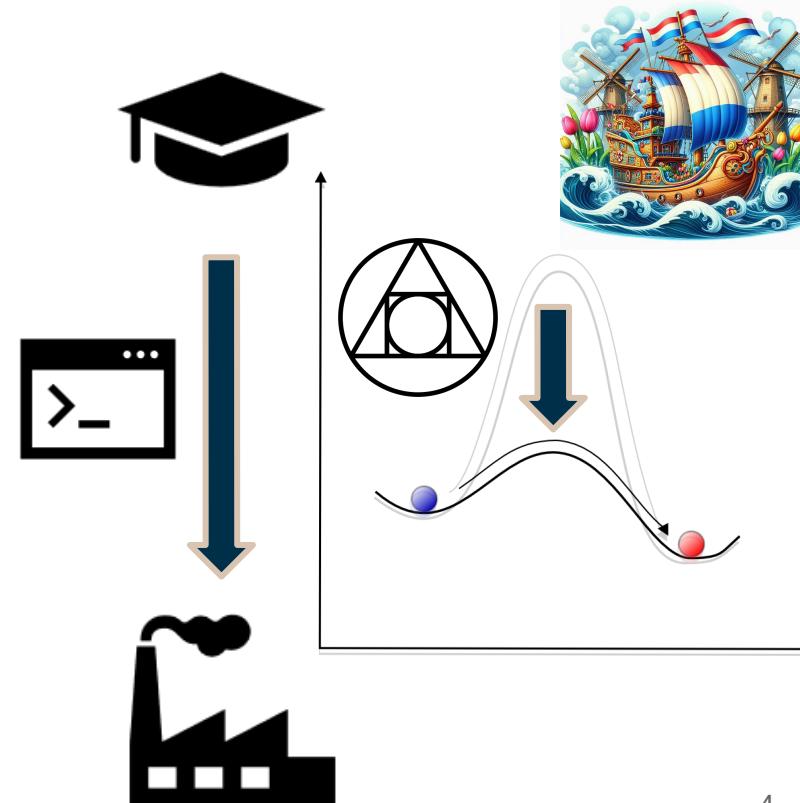
We do Alchemy!





Open Free Energy

- Increase **access** to methodology.
- Bridge the **application delivery** and **maintenance** gap.
- Reduce **costs** & duplication of efforts.
- Ensure a **sustainable** and **competitive** future for developed tools.



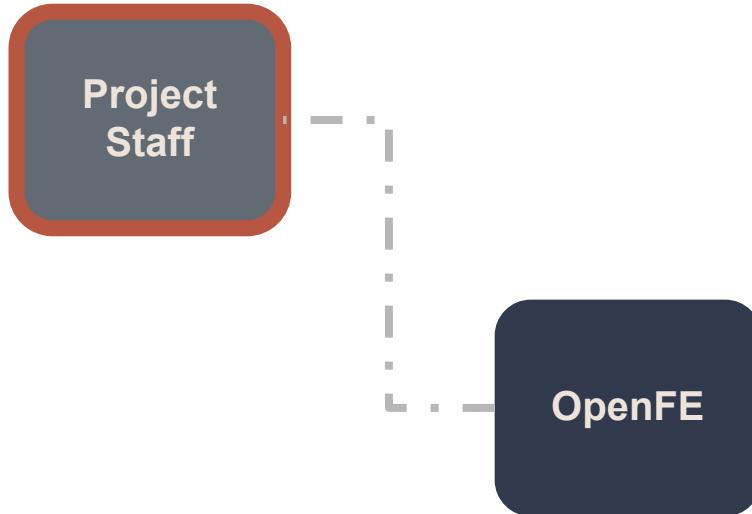


Open Free Energy: who are we?

OpenFE



Open Free Energy: who are we?





Project Staff

Project Staff



Irfan
Alibay



Richard
Gowers



James
Eastwood



Hannah
Baumann



Mike
Henry



Benjamin
Ries

Emeriti



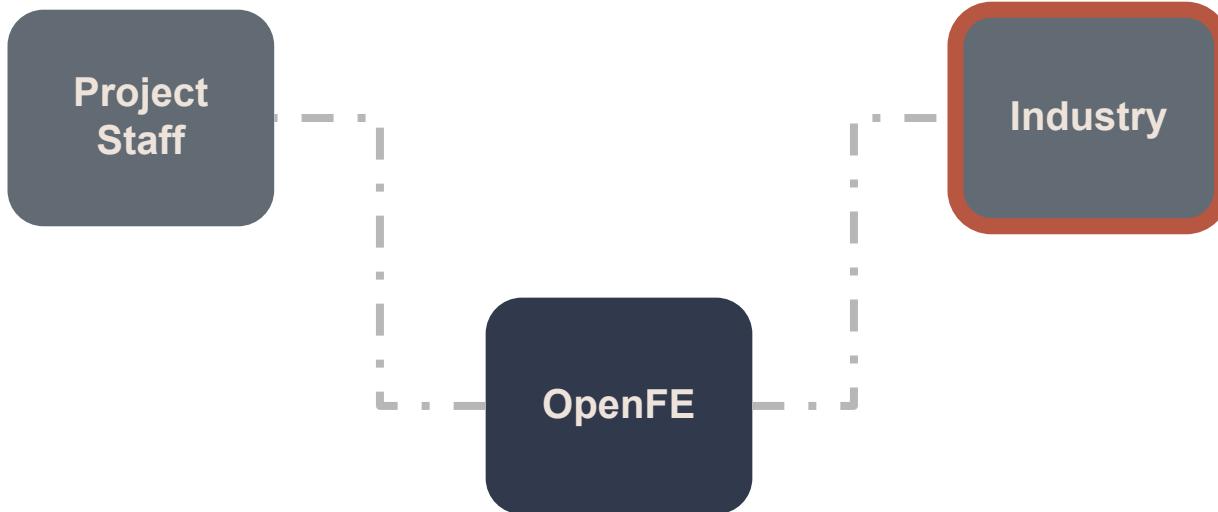
David
Swenson



Josh
Mitchell



Open Free Energy: who are we?





Industry partners

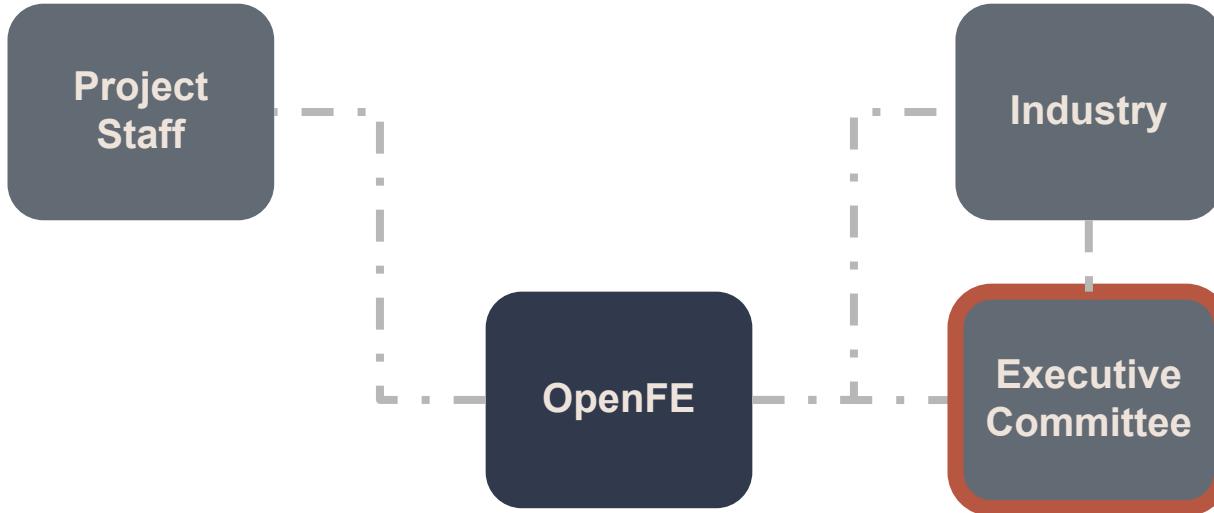
OpenFE is funded and led by a pre-competitive consortium of **17 industrial partners.**

They **advise, validate, and promote** OpenFE's tools and mission.

- AbbVie
- AstraZeneca
- Bayer
- Boehringer Ingelheim
- Bristol Myers Squibb
- Confo Therapeutics
- Eli Lilly
- Genentech, a member of the Roche Group
- GSK
- Janssen Pharmaceutica NV
- Merck KGaA
- Nurix Therapeutics
- And others!



Open Free Energy: who are we?





Executive Committee



Kira
Campbell



Kaushik
Lakkaraju



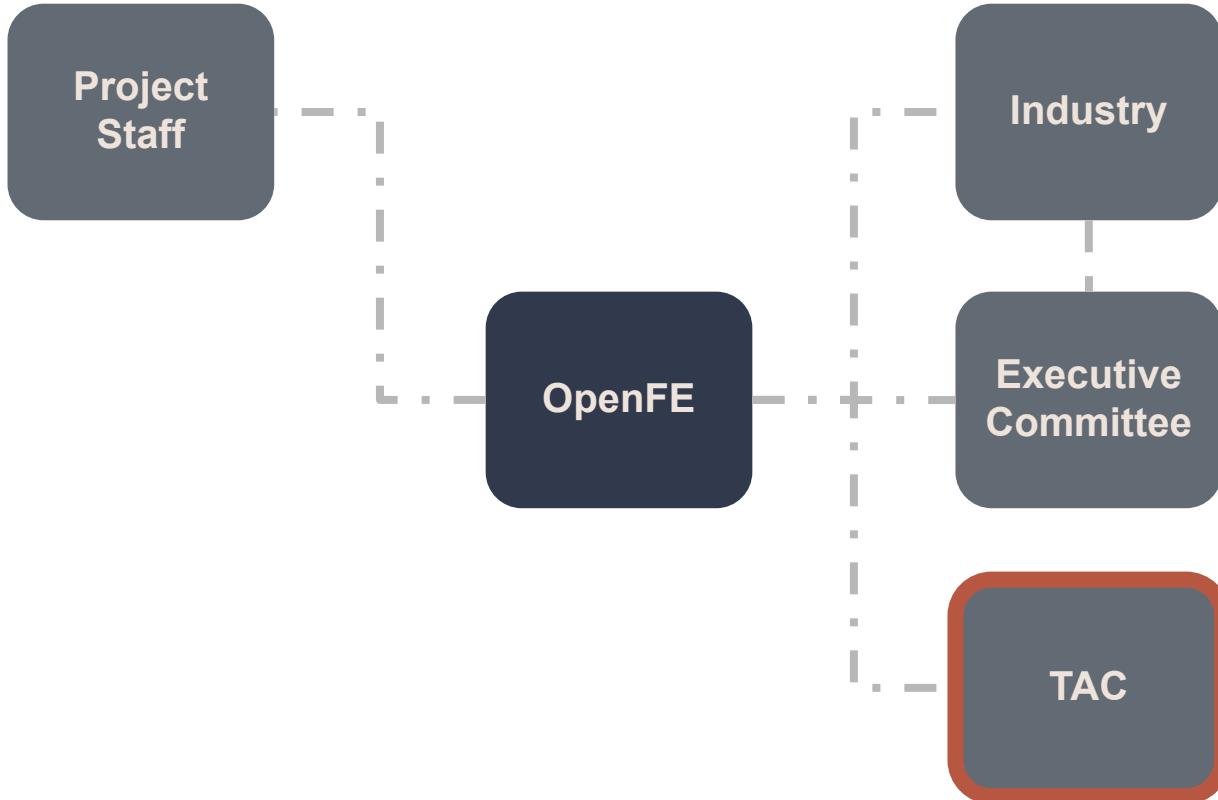
Joseph
Bluck



Vytas
Gapsys



Open Free Energy: who are we?





Open Free Energy: TAC

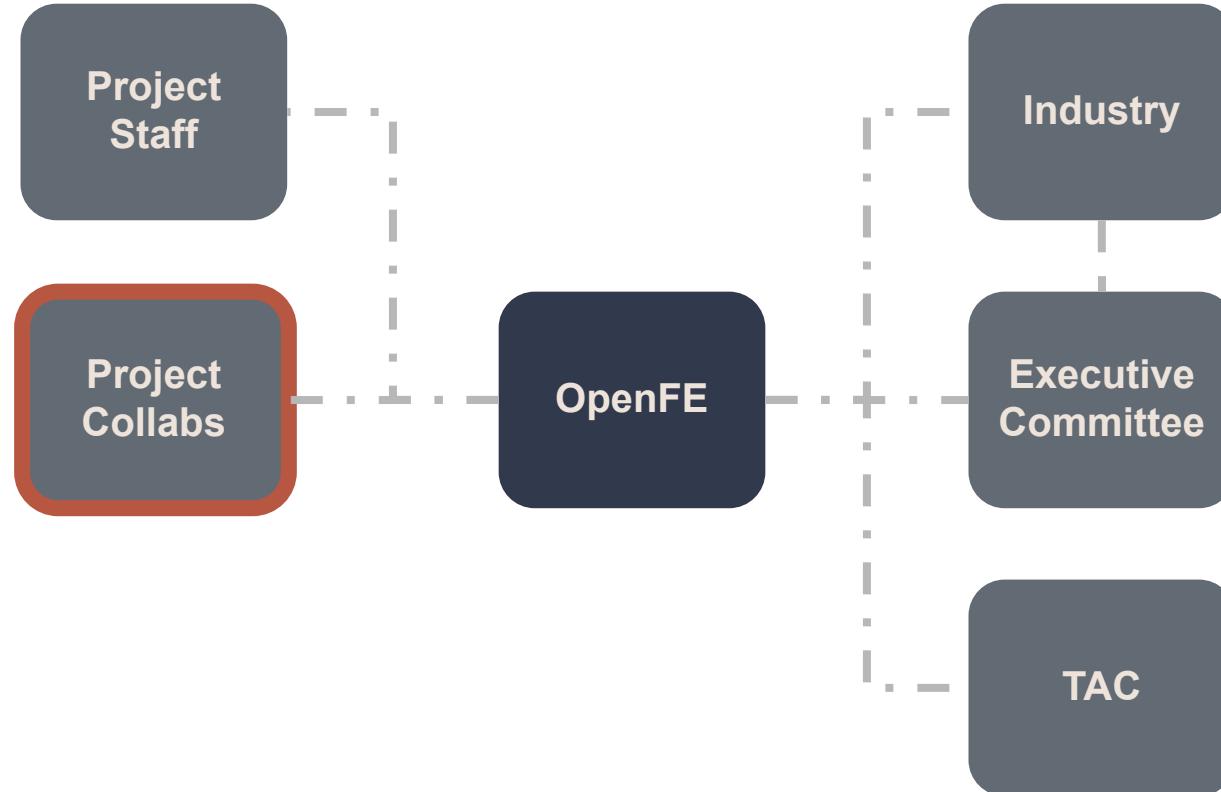


Oliver Beckstein - Arizona State University
Phil Biggin - University of Oxford
John Chodera - Memorial Sloan Kettering
Zoe Cournia - Academy of Athens
Peter Eastman - Stanford University
Antonia Mey - University of Edinburgh
Julien Michel - University of Edinburgh
David Mobley - University of California, 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



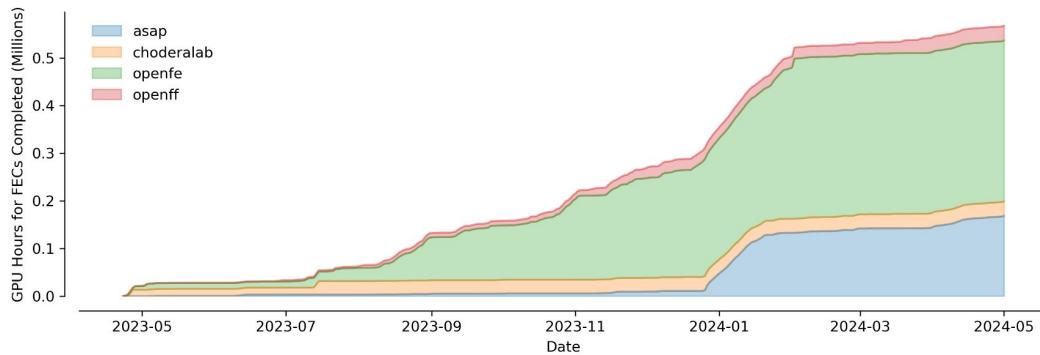


Open Free Energy: who are we?





Alchemiscale

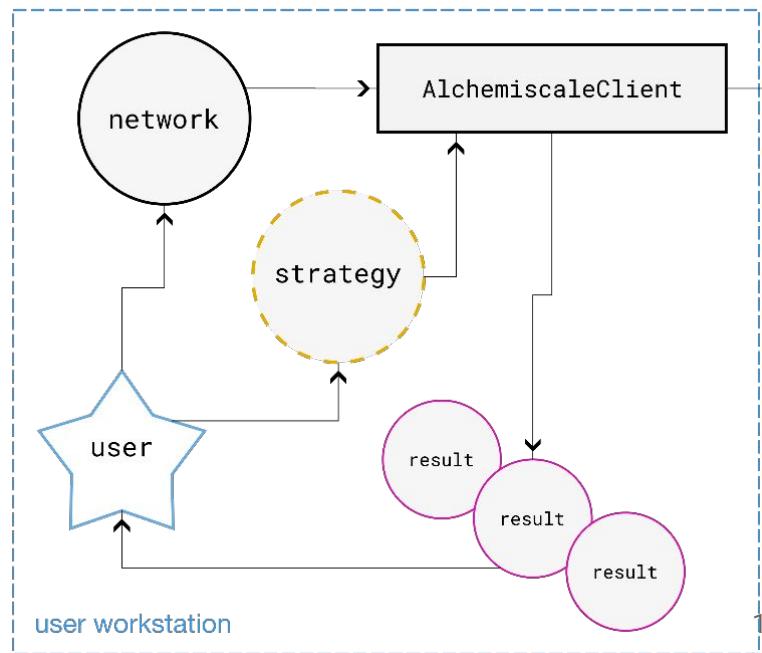


David Dotson



Ian Kenney

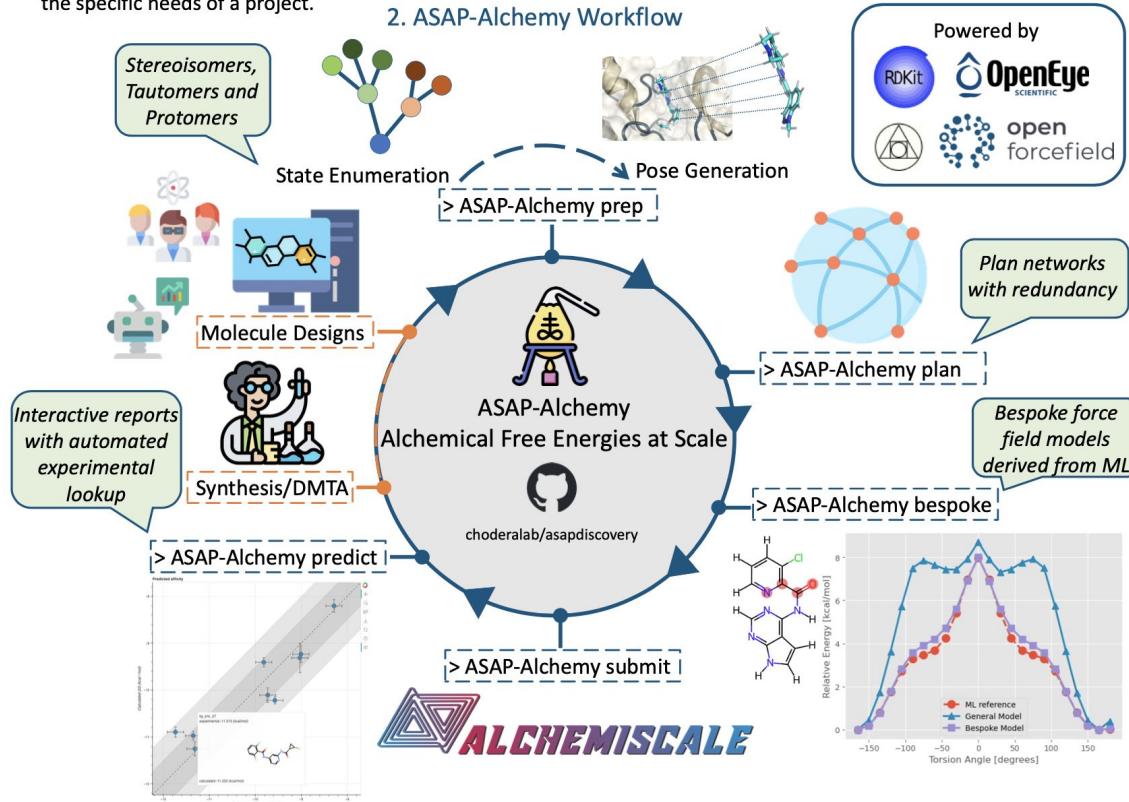
Over **0.5 million GPU hours** of OpenFE testing in the **last year!**





ASAP-Alchemy

the specific needs of a project.



Josh Horton



Jenke Scheen



Hugo!



TAC: Chodera lab

Perses team:

- **Iván Pulido**
- Julie Behr
- Hannah Bruce
- Macdonald
- Andrea Rizzi
- **John Chodera**
- Patrick Grinaway
- Mike Henry
- Jaime Rodríguez-Guerra
- Dominic Rufa
- **Ivy Zhang**



Iván Pulido

FEFlow



<https://github.com/choderalab/feflow>

Community Protocol development.



TAC: Mobley lab



Meghan Osato

- OpenFE benchmarking and validation
- Exploring partial charge issues
- Alchemiscale testing



OMSF Consortia

Open Force Field

- Alchemiscale
- OpenMMForceFields
- Interchange adoption
- NAGL validation
- Benchmarking



Jeff Wagner



Matt Thompson



Lily Wang

OMSF Infrastructure

- Improved testing frameworks
- Plugin systems
- And other ongoing projects...



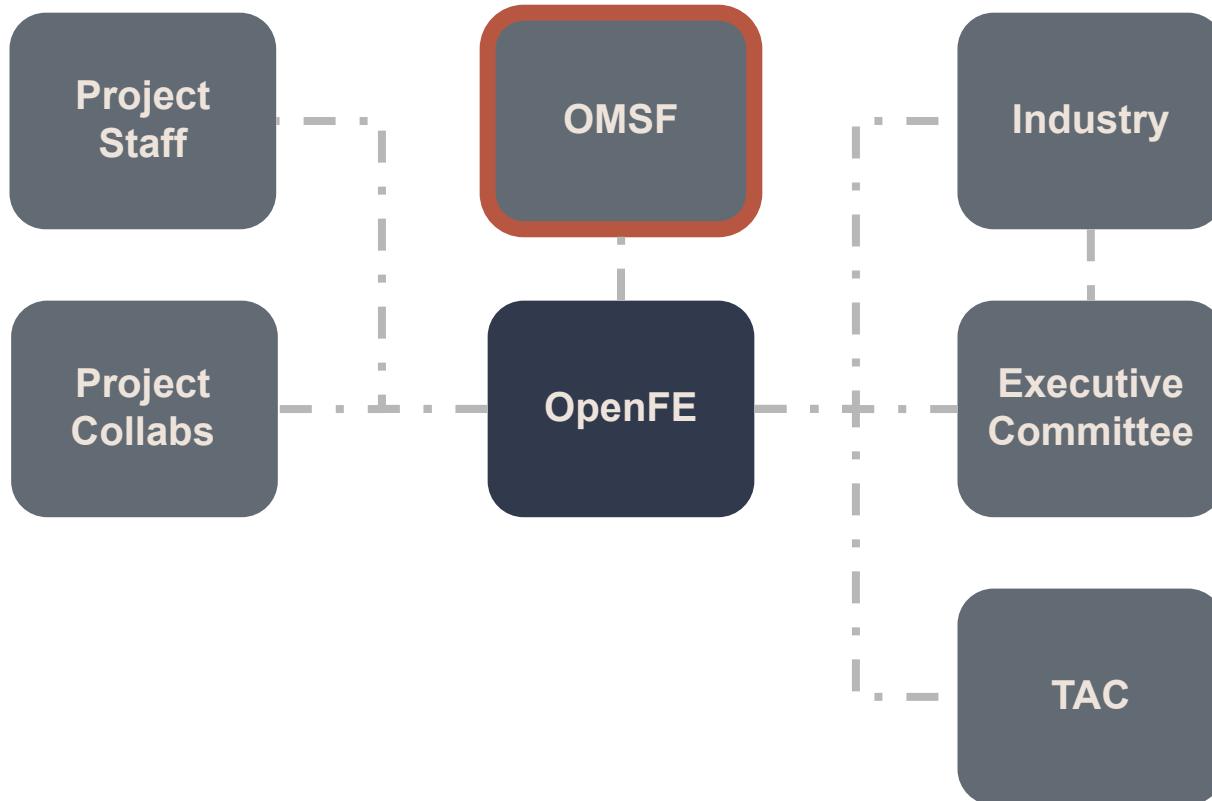
David Swenson



Ethan Holz



Open Free Energy: who are we?





OMSF



**David
Mobley**



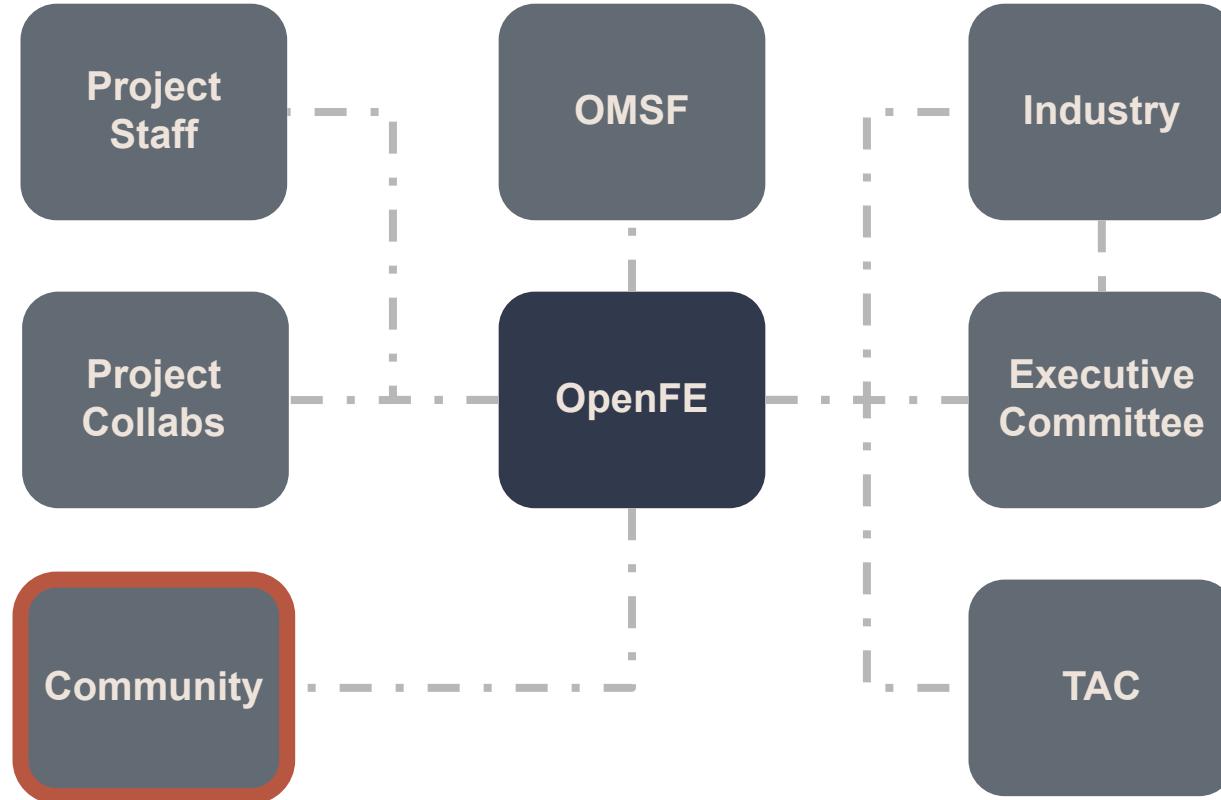
**Zachary
Baker**



**Karmen
Codic-Jurkic**



Open Free Energy: who are we?



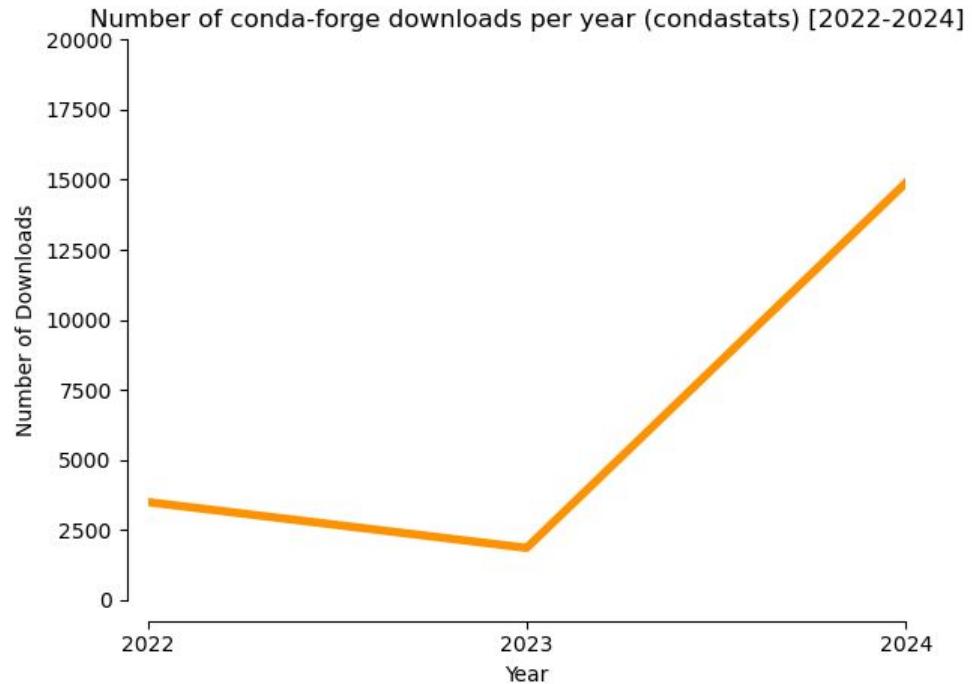


A growing user community

This years has seen a **threefold** increase in download activity.

We are seeing a growing number of industry and academic parties testing out OpenFE tooling.

Caveat: does not exclude CI downloads.





Open Free Energy: what do we do?

Infrastructure

FE Tooling

OpenFE

Validation

Free Energy
Protocols



Open Free Energy: what do we do?

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GUFE is our fundamental
**common language for free
energy** simulations.

Defines various **building
blocks** for expressing
concepts related to free
energies.

Continued development as
we expand our domain of
applicability.

**GUFE Abstract
layer**

Application Layer

AtomMapper

LOMAP

Kartograf



Command-line interface

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



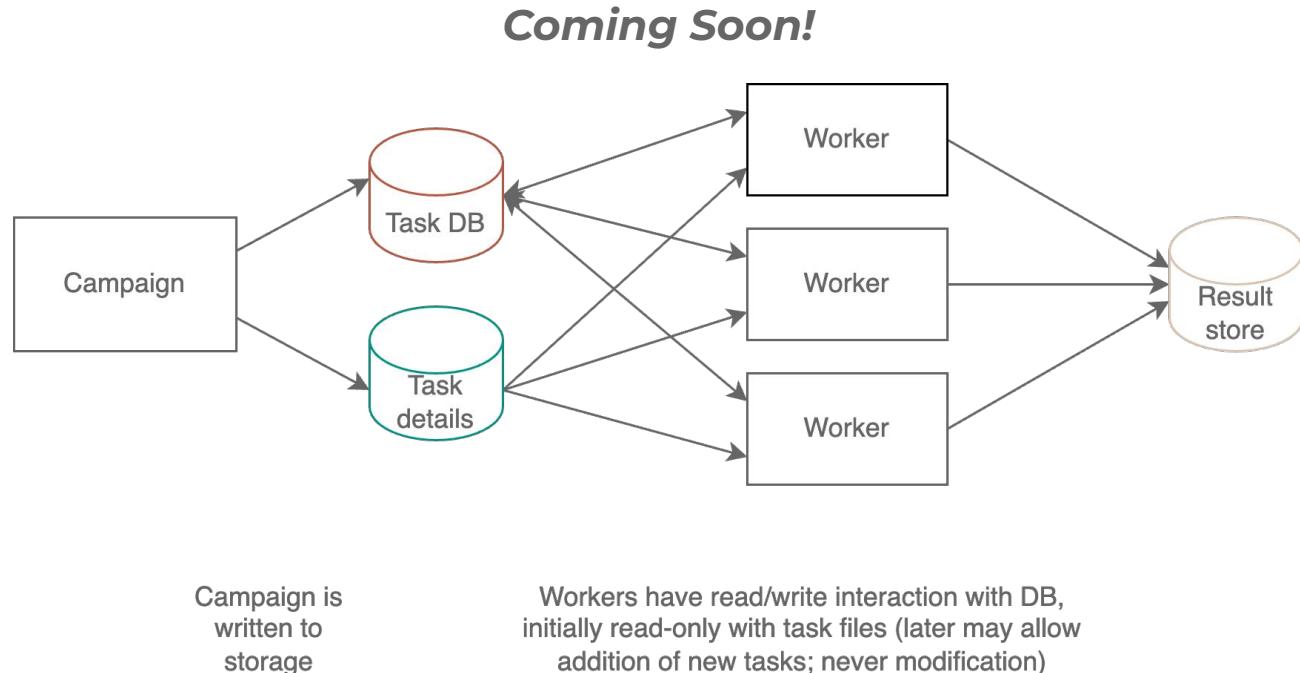
Towards improved simulation execution

A framework for
daemonless task execution.

Improved **file storage** and
modular DAG unit
execution.



**David
Swenson**





Open Free Energy: what do we do?

Infrastructure

FE Tooling

OpenFE

Validation

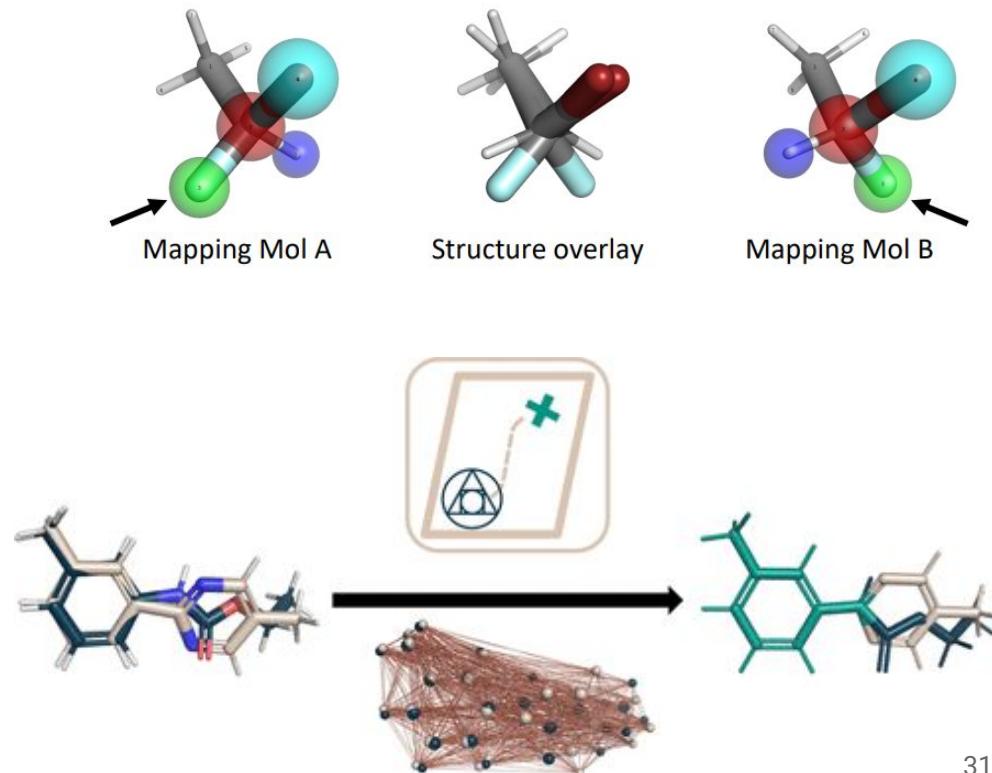
Free Energy
Protocols



Kartograf: atom mapper

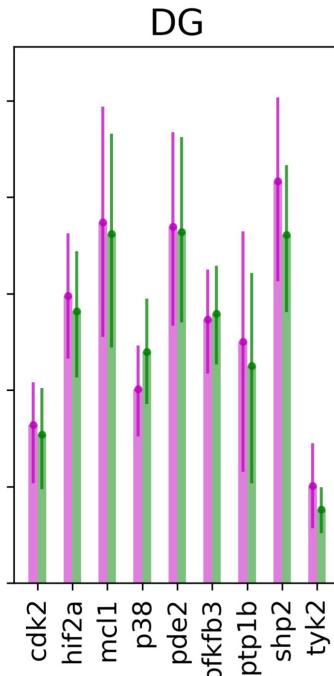
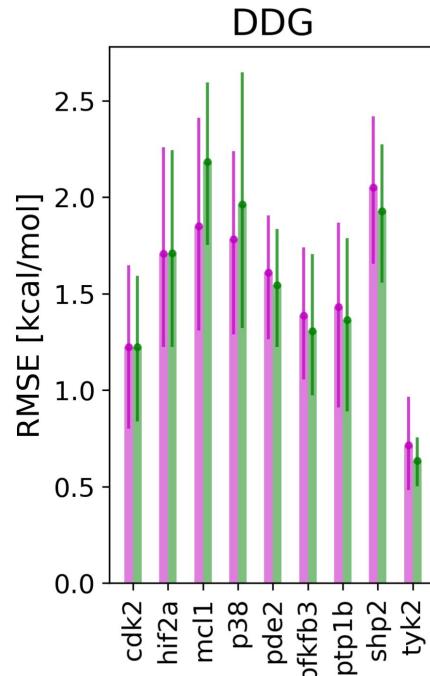
Kartograf, a geometrically accurate atom mapper.

- Avoids MCS limitations (e.g. stereochemistry)
- Fast: can **scale to whole proteins!**
- Flexible: easily add more filter rules as necessary.
- Significantly reduces manual intervention!
- Caveat: requires well aligned molecules

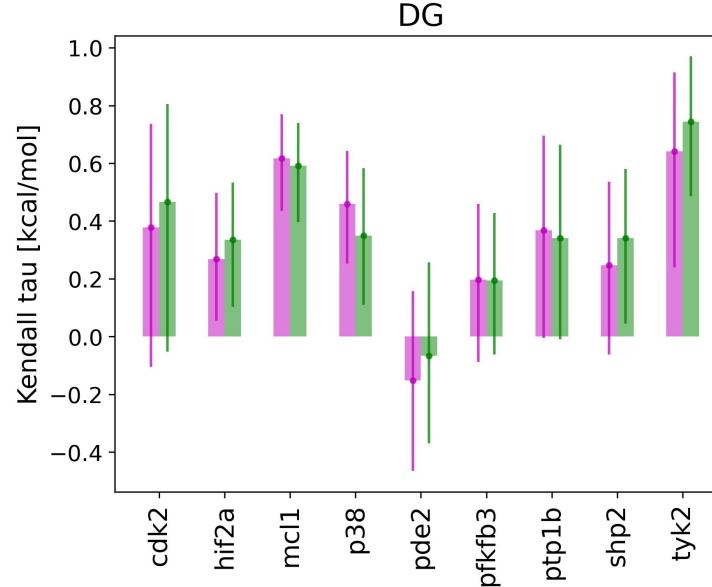




LOMAP vs Kartograf atom mapper comparison



Statistically similar results over 9 systems.

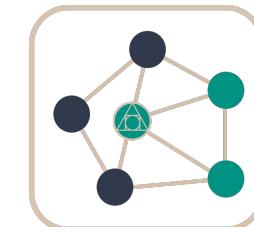




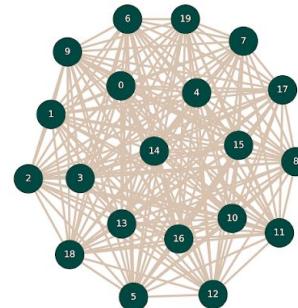
Setup Tooling: Konnektor

Konnektor, a tool for largescale free energy perturbation network planning..

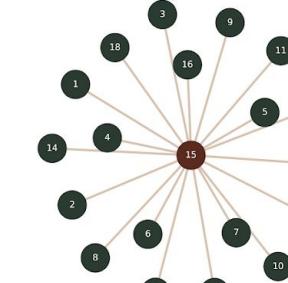
- Allows users to create diverse networks
- Offers a variety of features for **network handling and analysis**
- Allows us to aim for a future where we construct and use **complex perturbation network topologies**.



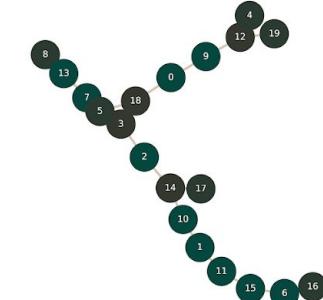
Maximal Network



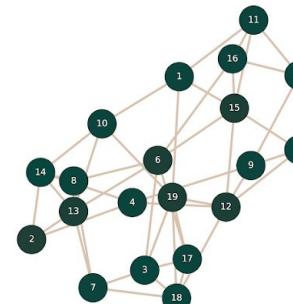
Star Network



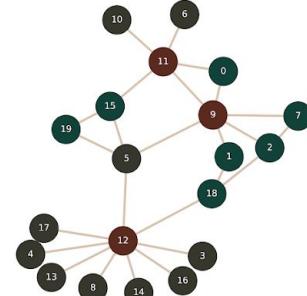
Minimal Spanning Tree Network



Cyclic Network



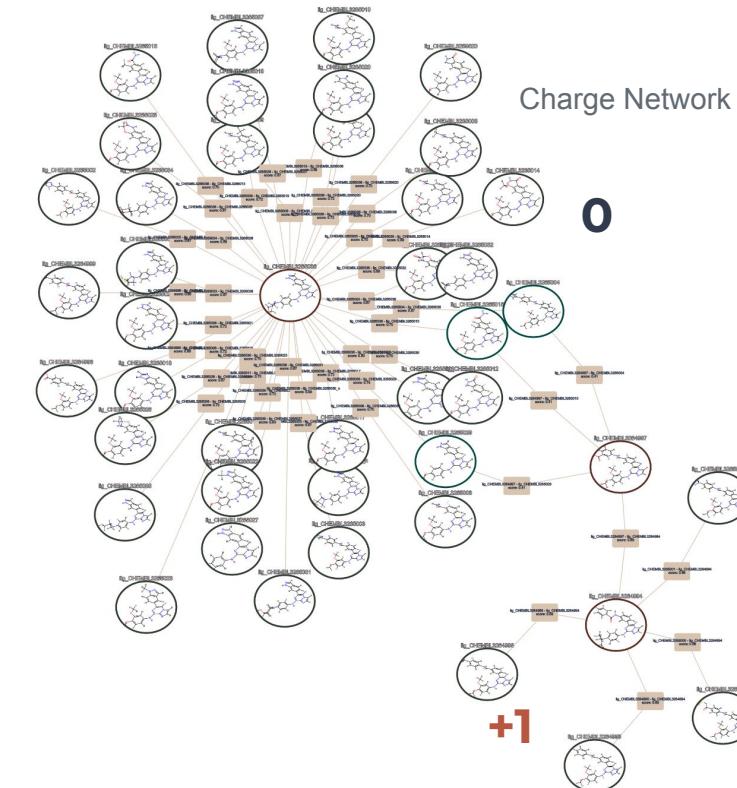
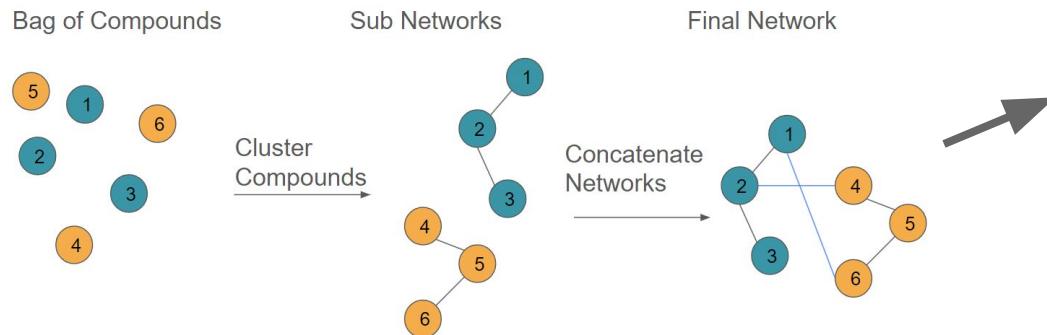
Starry Sky Network





Setup Tooling: Konnektor

An example of advanced Network Planning





Open Free Energy: what do we do?

Infrastructure

FE Tooling

OpenFE

Validation

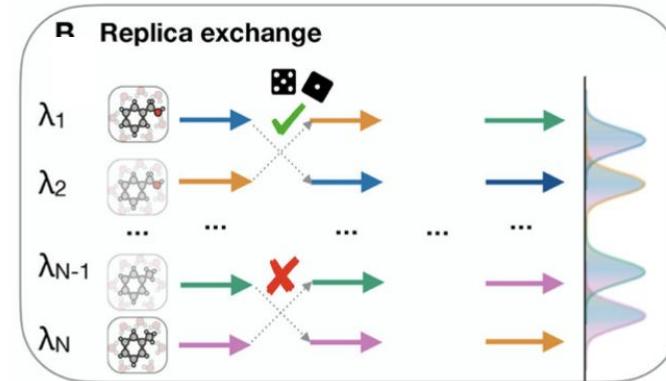
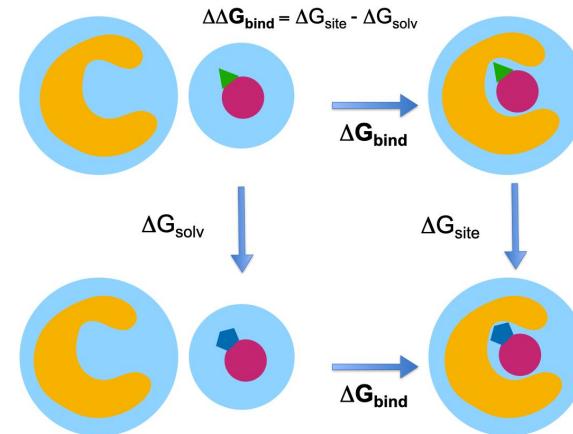
Free Energy
Protocols



Protocols: Relative Free Energies

OpenFE offers an MVP **relative free energy** Protocol.

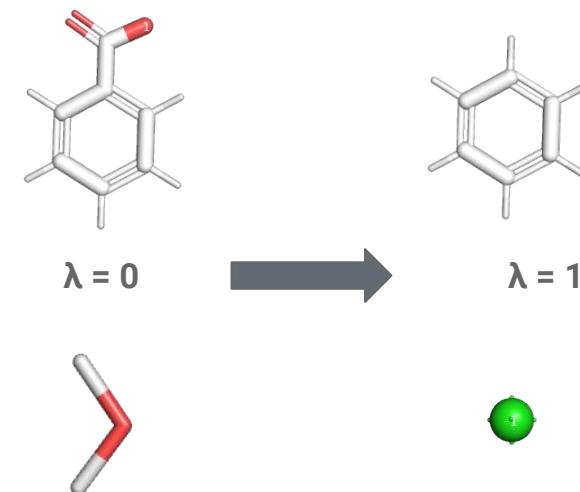
- Based on the **Perse**s hybrid topology methodology
- Variety of **samplers**; HREX, SAMS, independent sampling
- Continually updated to extend domain of applicability.





Alchemical water net charge correction

- Alchemical water to ion perturbation
 - $\text{LIG_A}[+1] \rightarrow \text{LIG_B}[0]$
 - water $\rightarrow \text{Na}^+$
 - $\text{LIG_A}[-1] \rightarrow \text{LIG_B}[0]$
 - water $\rightarrow \text{Cl}^-$
- Needs longer simulations
 - 20 ns / window (from 5 ns)
 - 22 windows (from 11 windows)



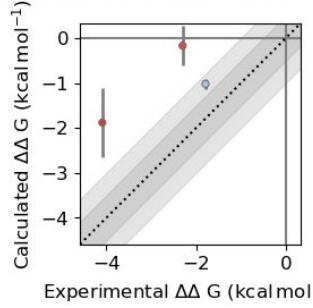
Ivy Zhang
(Perses)



Comparable results on key test cases

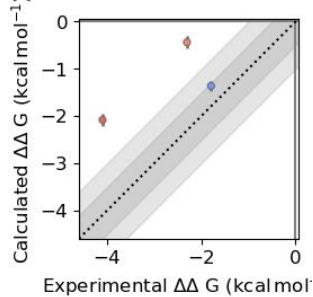
OpenFE

PTP1B
RMSE: 1.83 [95%: 0.77, 2.21]
MUE: 1.70 [95%: 0.77, 2.21]



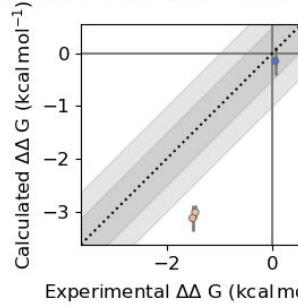
FEP+

CDK2
RMSE: 1.60 [95%: 0.43, 2.01]
MUE: 1.44 [95%: 0.43, 2.01]



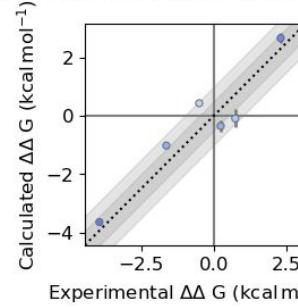
CDK2

TYK2
RMSE: 1.30 [95%: 0.20, 1.61]
MUE: 1.12 [95%: 0.20, 1.61]



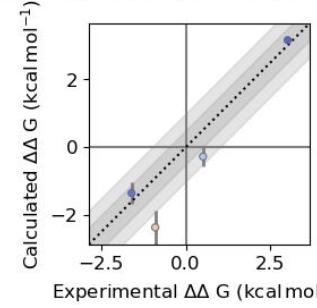
TYK2

EPHX2
RMSE: 0.64 [95%: 0.45, 0.81]
MUE: 0.60 [95%: 0.42, 0.79]



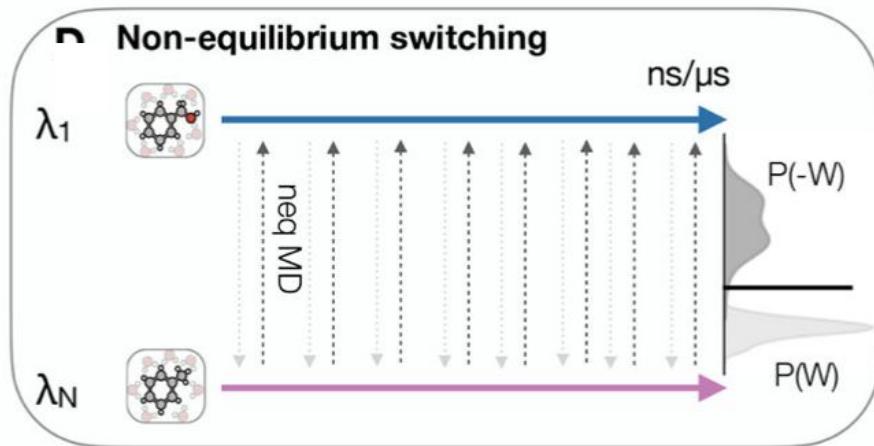
EPHX2

(N = 4)
RMSE: 0.84 [95%: 0.21, 1.27]
MUE: 0.66 [95%: 0.20, 1.13]





Extending to new samplers



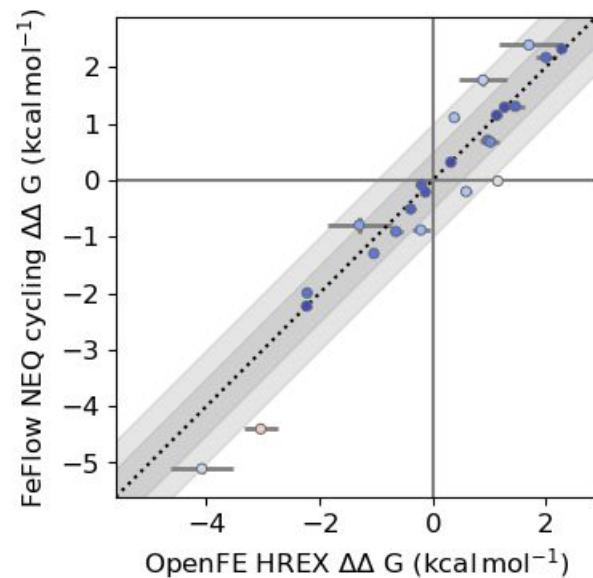
FEFlow



Iván Pulido

<https://github.com/choderalab/feflow>

mcl1
(N = 24)
RMSE: 0.57 [95%: 0.40, 0.72]
MUE: 0.41 [95%: 0.26, 0.59]



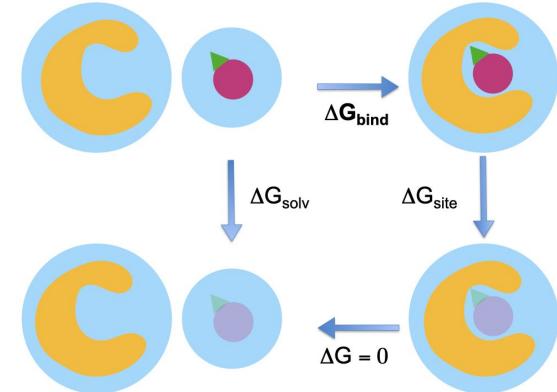
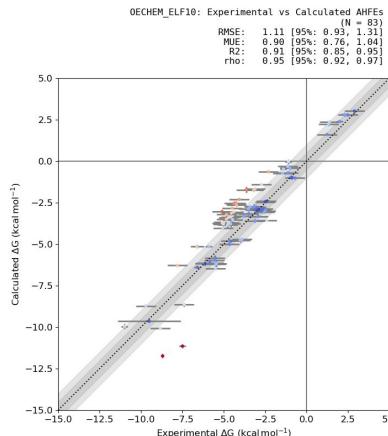


Towards absolute

We are currently developing
absolute free energy calculation
Protocols

Aim to deliver a stable version
within the next couple of months!

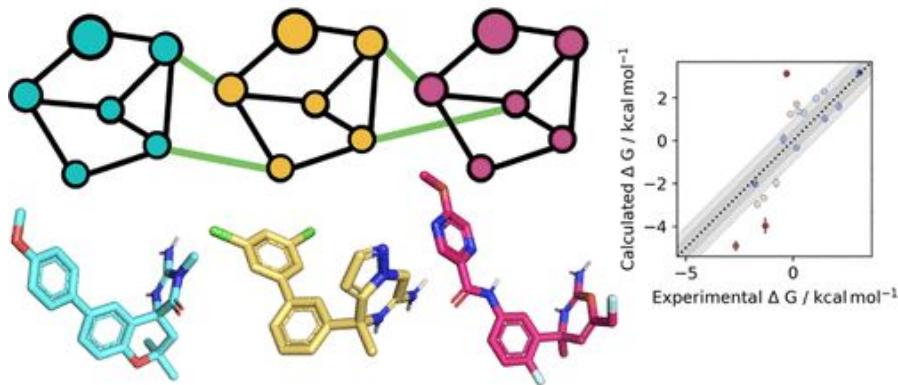
AHFE calculations





Near future Protocols

Separated Topologies



RBFE calculations in Gromacs

GROMACS
FAST. FLEXIBLE. FREE.



pmx



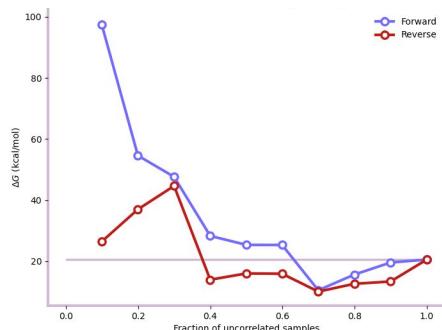
Towards automated analysis

Delivering on a promise from the last OMSF workshop!

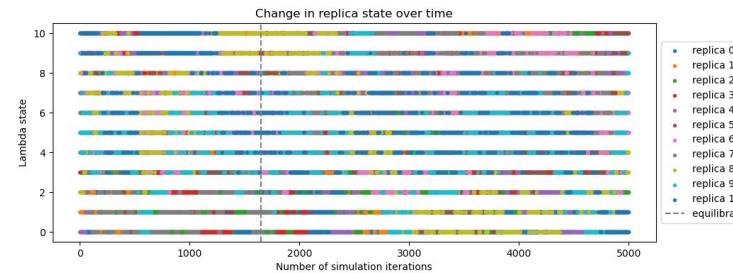
MBAR overlap matrix

λ	0	1	2	3	4	5	6	7	8	9	10
0	.88	.12	.00	.00	.00	.00	.00	.00	.00	.00	.00
1	.12	.78	.10	.00	.00	.00	.00	.00	.00	.00	.00
2	.00	.10	.81	.09	.00	.00	.00	.00	.00	.00	.00
3	.00	.00	.09	.77	.14	.00	.00	.00	.00	.00	.00
4	.00	.00	.00	.14	.63	.16	.07	.00	.00	.00	.00
5	.00	.00	.00	.00	.16	.66	.17	.01	.00	.00	.00
6	.00	.00	.00	.00	.07	.17	.58	.18	.00	.00	.00
7	.00	.00	.00	.00	.00	.01	.18	.66	.15	.00	.00
8	.00	.00	.00	.00	.00	.00	.00	.15	.70	.15	.00
9	.00	.00	.00	.00	.00	.00	.00	.00	.15	.69	.15
10	.00	.00	.00	.00	.00	.00	.00	.00	.00	.15	.84

Forward and Reverse convergence



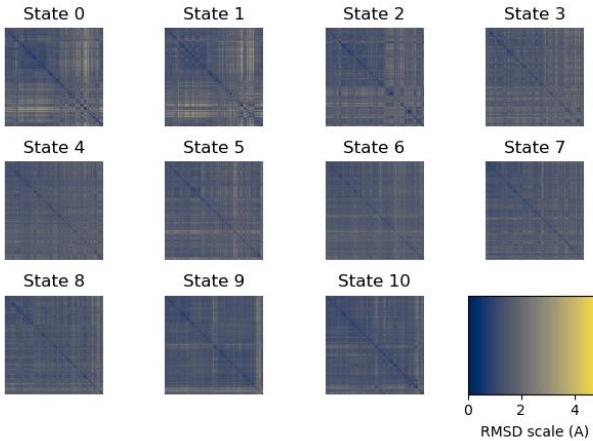
Replica exchange transitions



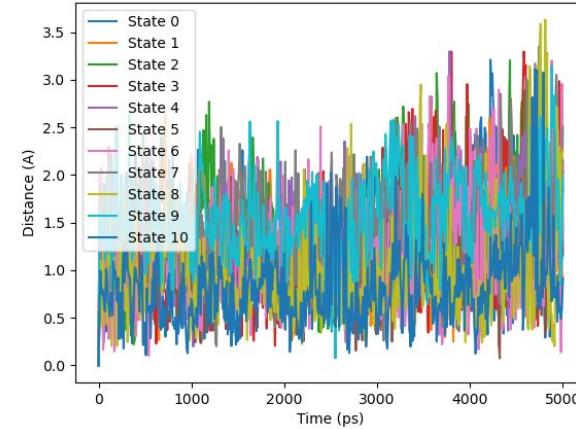


Towards automated analysis

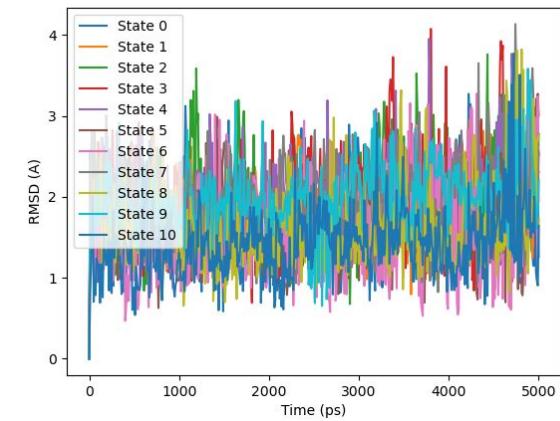
Protein 2D RMSD



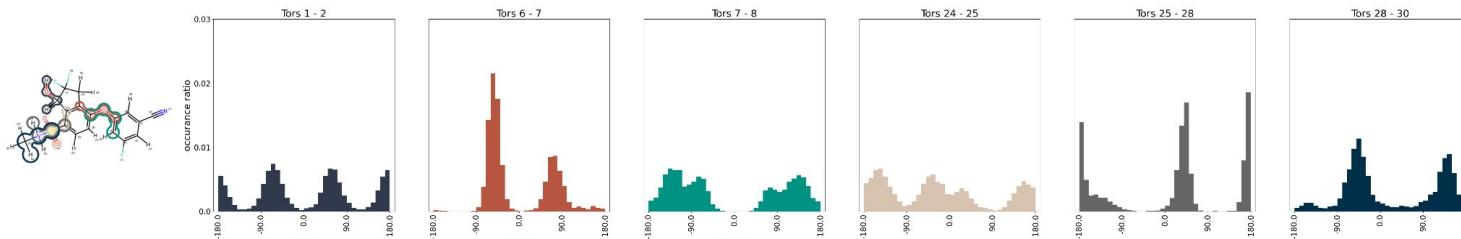
Ligand COM drift



Ligand RMSD



Dihedral analysis





Open Free Energy: what do we do?

Infrastructure

FE Tooling

OpenFE

Validation

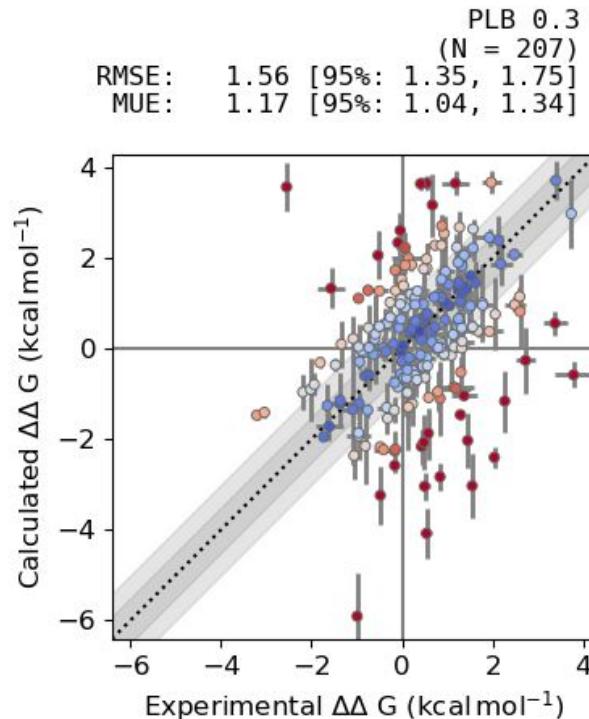
Free Energy
Protocols



Release benchmarking

OpenFE **continually benchmarks** and **validates** its releases on protein-ligand benchmark datasets.

The v0.3 release of the Protein-Ligand benchmark is imminent!



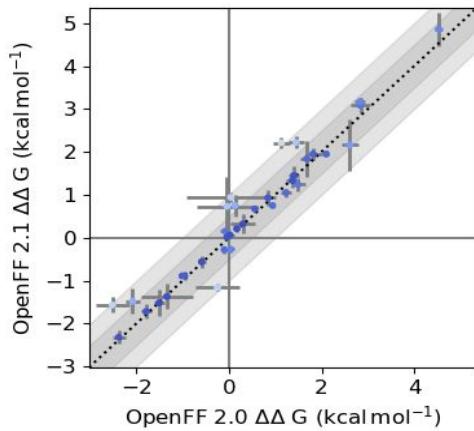


OFF Benchmarking

We are helping to validate new OpenFF versions.

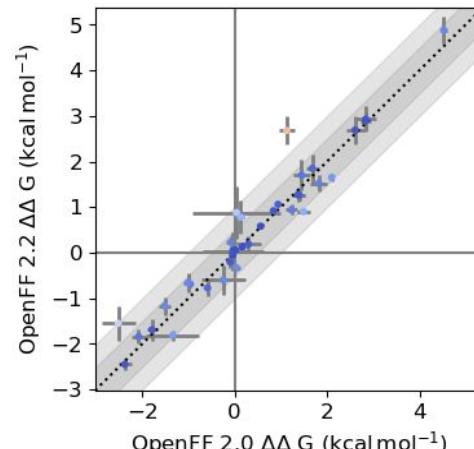
2.0 vs 2.1

HIF2a
(N = 36)
RMSE: 0.43 [95%: 0.30, 0.54]
MUE: 0.29 [95%: 0.20, 0.39]



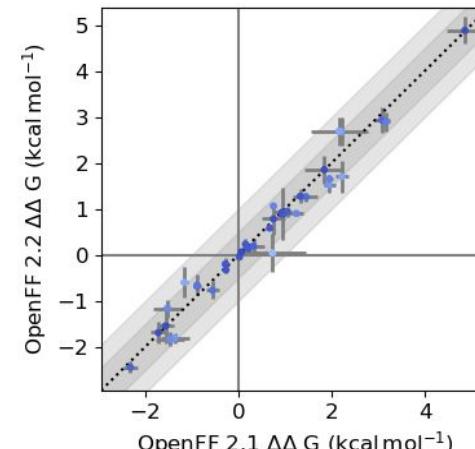
2.0 vs 2.2

HIF2a
(N = 36)
RMSE: 0.43 [95%: 0.26, 0.58]
MUE: 0.29 [95%: 0.20, 0.41]



2.1 vs 2.2

HIF2a
(N = 36)
RMSE: 0.28 [95%: 0.21, 0.34]
MUE: 0.21 [95%: 0.15, 0.28]



Meghan Osato



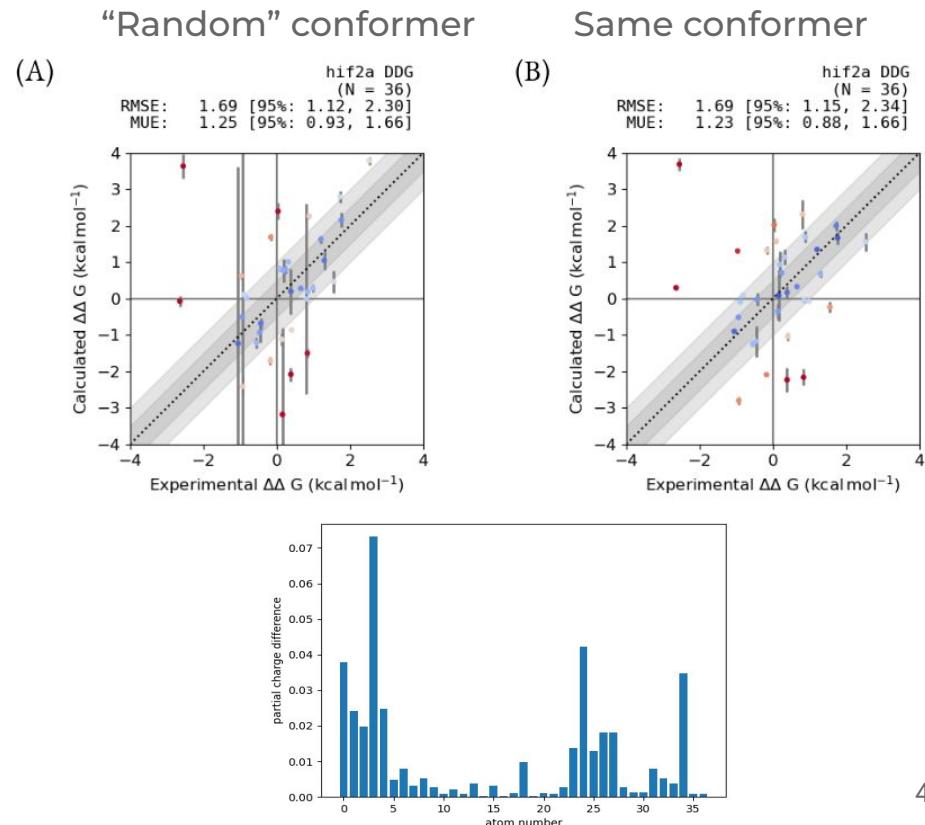
Partial charges impact free energies

Finding the limits of partial charge assignment in free energy outcomes.

- Small fluctuations can have significant impacts on the free energies
- Conformer generation can be problematic



Meghan Osato



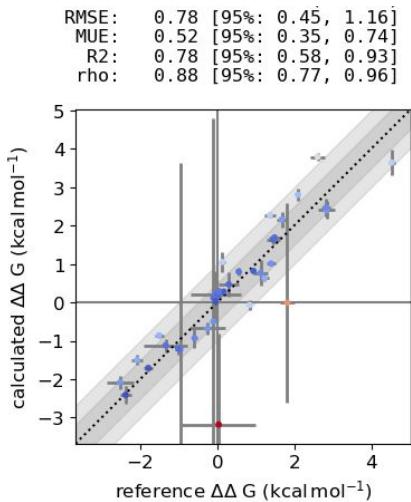


With OpenFE, we can systematically compare different methods for partial charge generation

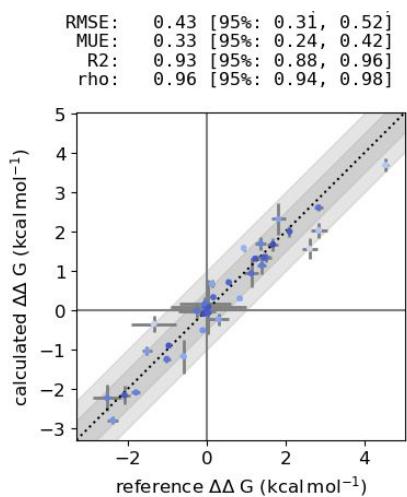
HIF2A: Comparison of different partial charge method against OpenEye ELF10 reference



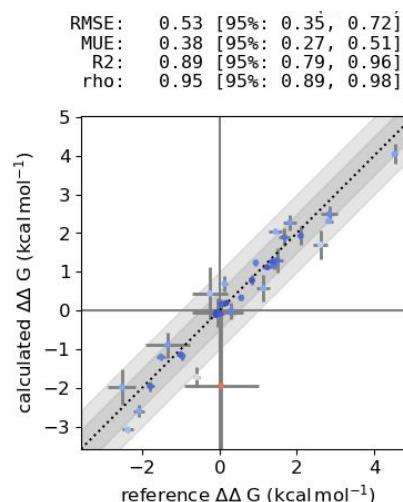
Antechamber:
Random conformer



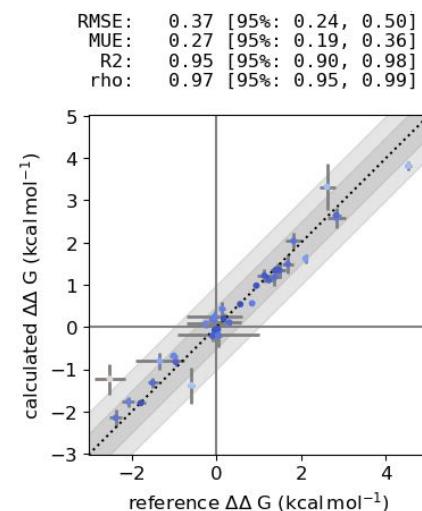
Antechamber:
Single conformer



Antechamber:
ELF10



NAGL 0.1rc1

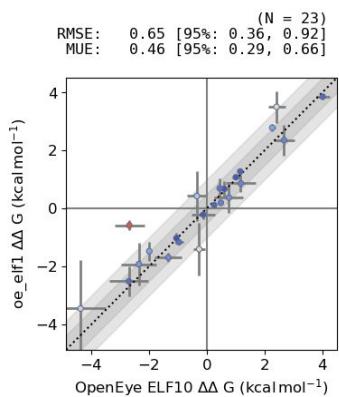




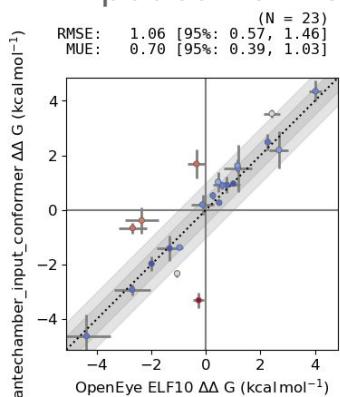
With OpenFE, we can systematically compare different methods for partial charge generation

HIF2A: Comparison of different partial charge methods against OpenEye ELF10

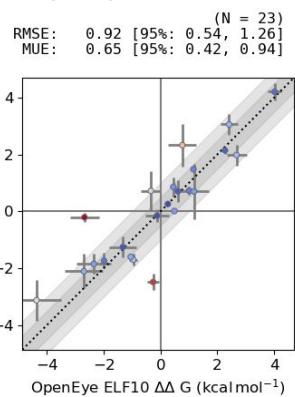
Antechamber
Random conformer



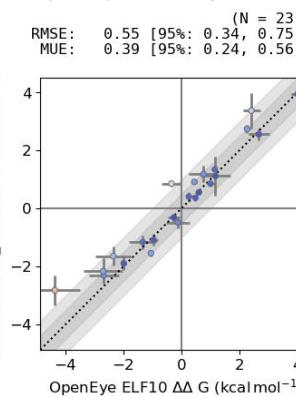
Antechamber
input conformer



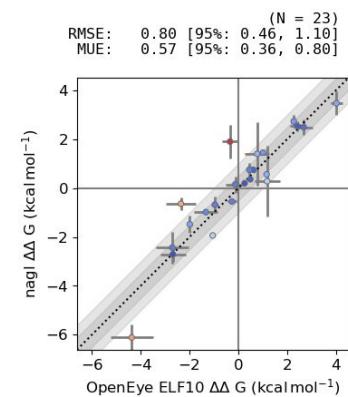
Antechamber/
RdKit ELF1



Antechamber/
RdKit ELF10



NAGL





Major milestone: OpenFE 1.0 release!

First stable release of OpenFE.

Stable user facing API until the next major release.

Ready to be in your hands for production use!

v1.0.0 - First stable release

Latest

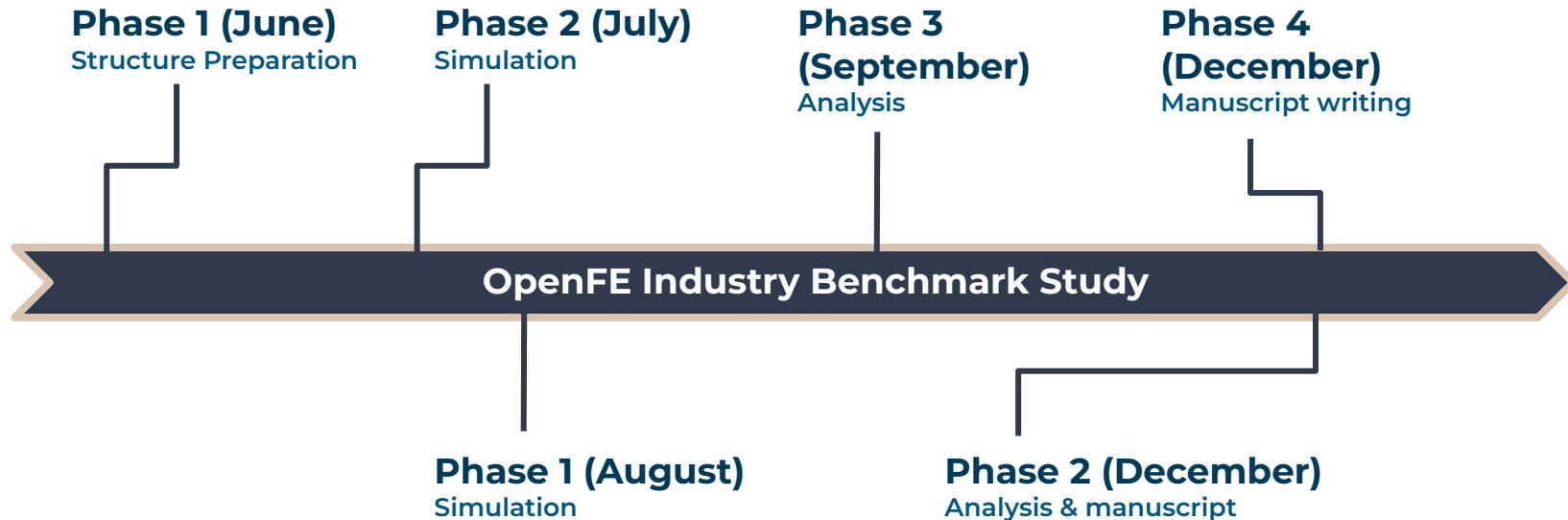
What's Changed

- Fix sing file installer by [@mikemhenry](#) in [#667](#)
- Protocol to run plain MD simulations by [@hannahbaumann](#) in [#516](#)
- Set cache to expire after a day by [@mikemhenry](#) in [#676](#)
- Remove flatten torsions from HTF by [@IAlibay](#) in [#684](#)
- Expand water virtual site tests by [@IAlibay](#) in [#680](#)



Time for production testing

Public datasets



Private datasets

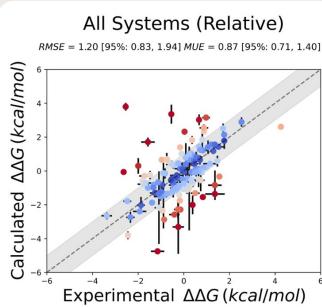


Open Free Energy Roadmap

Open Free Energy Fund founded



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



First Stable Release OpenFE v1.0

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

2022

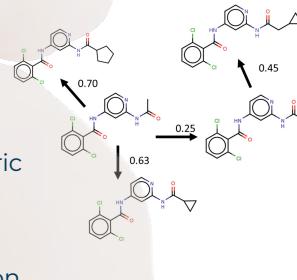


OpenMM RBFEs OpenFE v0.7

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

Supporting tooling Kartograf v1.0

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



Advanced methods OpenFE v2.0

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

2023

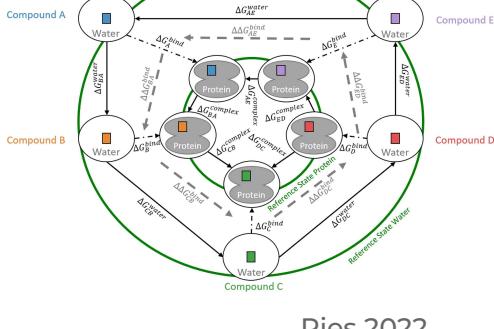
2024

Industry benchmarking

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



Beyond 2024

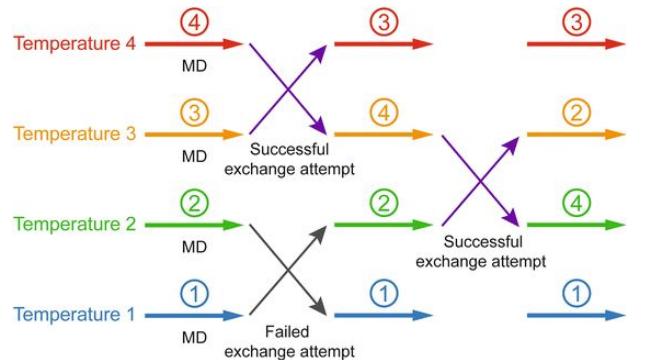


**MultiState
Sampling**

RE-EDS
Sidlera 2016

LadyBugs
Robo2023

A-EDS
Perthold 2020

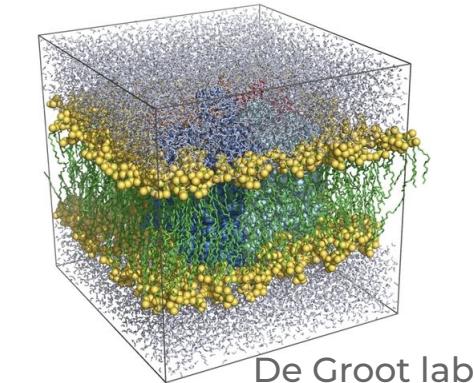


**New Enhanced
Sampling**

ATOM
Solmaz 2022

Times Square Sampling
Predescu 2022

REST
Liu 2005



**Increase Domain
of Applicability**

Membrane Proteins

Protein-Protein
Mutations



Thank you!

Thank you for all our contributors,
collaborators, and upstream
developers!

We look forward to continuing to
work with you.

Try it out!



try.openfree.energy