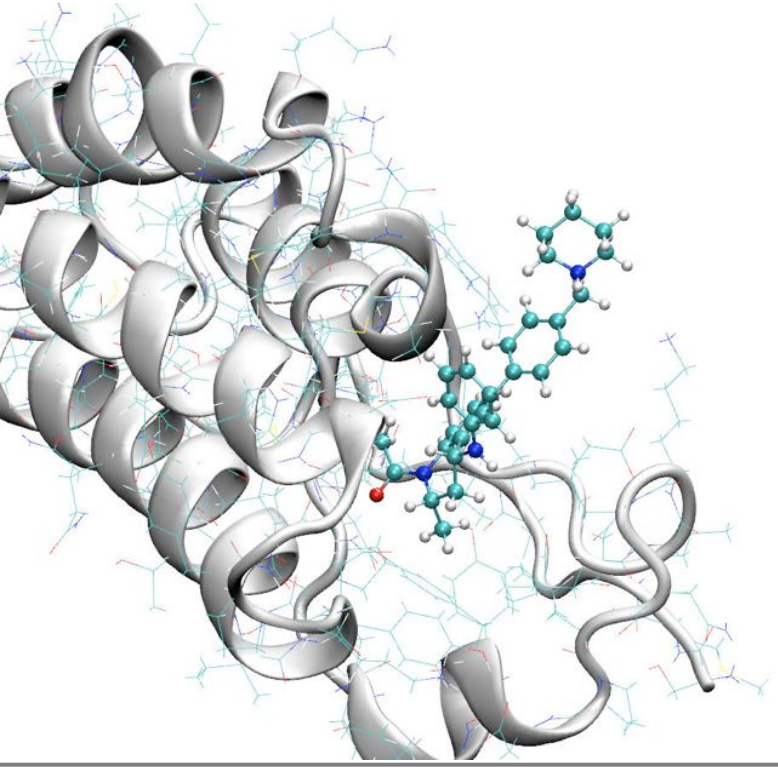
Portability and scalability of molecular dynamics codes for alchemical binding free energy calculations

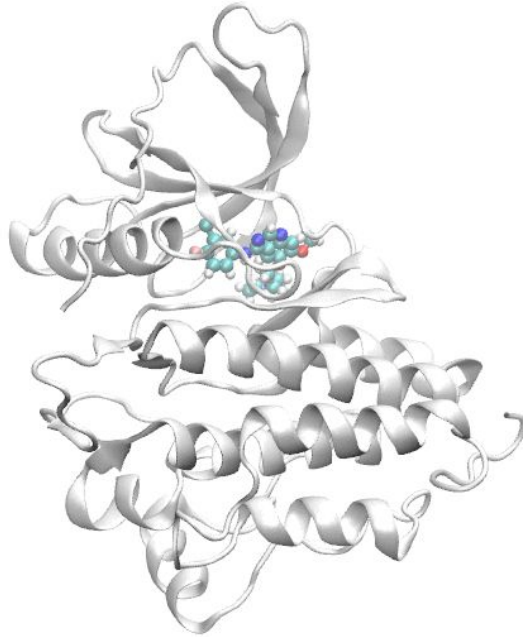


TIES

Alex Wade, Mateusz K. Bieniek, Agastya P. Bhati, Shunzhou Wan, Peter V. Coveney

Drug-protein Binding Affinities

- Drugs are designed to act on specific proteins within the body.
- The protein shape or configuration can also change between patients.
- We can use computer programs to determine the best drug for a specific protein in a given patient

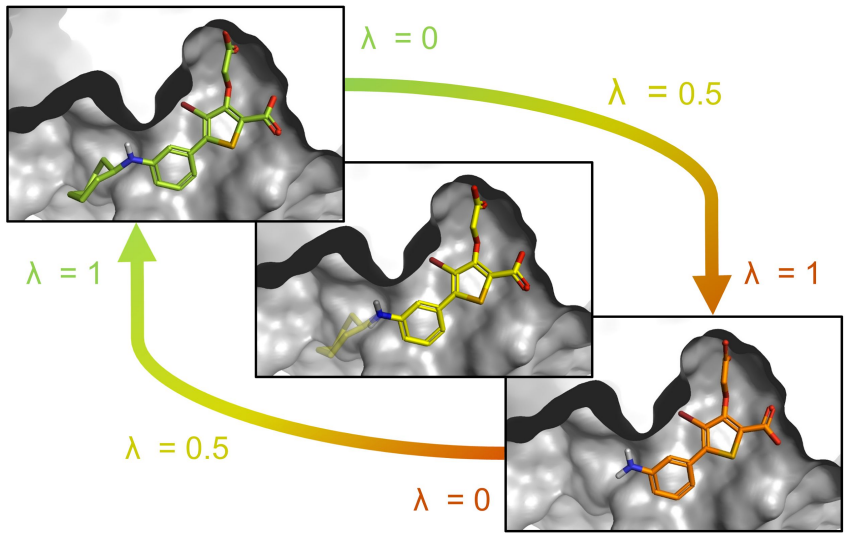


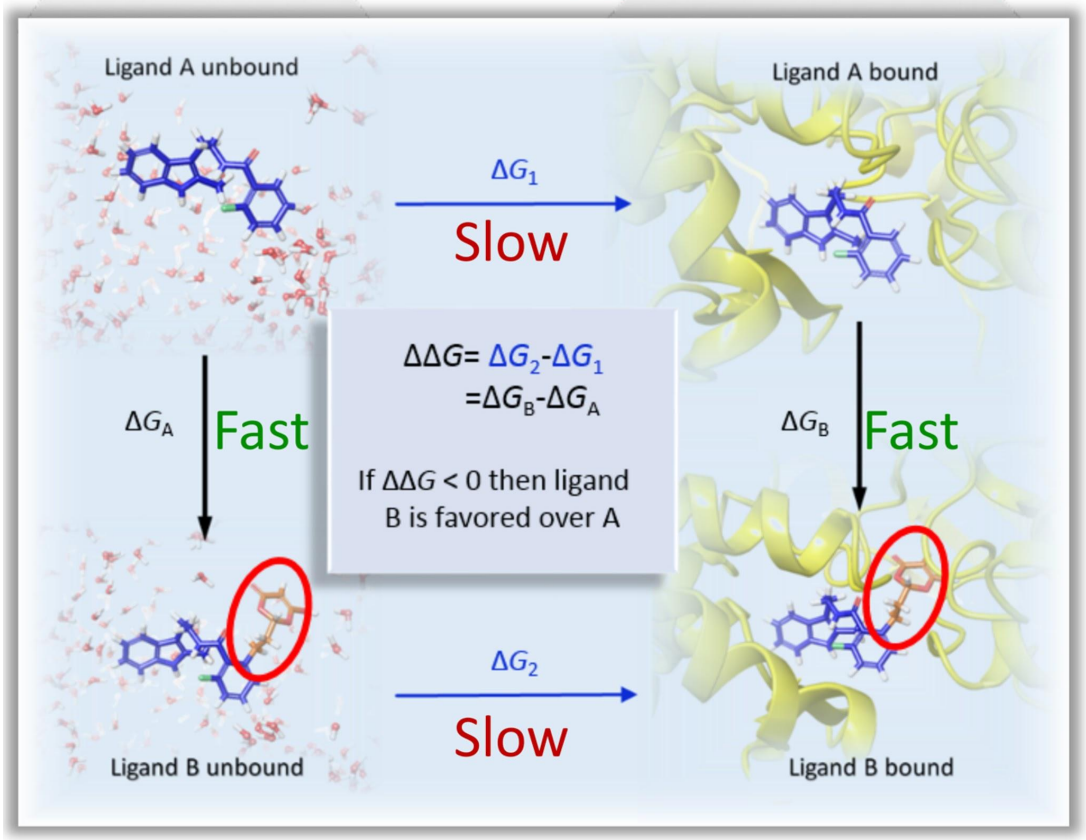
Alchemical Methods

- Mutating Ligand A into Ligand B

$$\frac{\partial \mathrm{G}(\lambda)}{\partial \lambda} = \left\langle \frac{\partial V(\lambda, x)}{\partial \lambda} \right\rangle_{\lambda}$$

$$\text{whence } \Delta \mathrm{G} = \int_0^1 \left\langle \frac{\partial V(\lambda, x)}{\partial \lambda} \right\rangle_{\lambda} d\lambda,$$





Max Kuhn, https://www.cresset-group.com/about/news/flare-alchemical-fep/

Cournia, Z., Allen, B., & Sherman, W. (2017). *JCIM*, *57*(12), 2911–2937. https://doi.org/10.1021/acs.jcim.7b00564

TIES Previous Work

Rapid, Accurate, Precise, and Reliable Relative Free Energy Prediction Using Ensemble Based Thermodynamic Integration

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Rapid and Reliable Binding Affinity Prediction of Bromodomain Inhibitors: A Computational Study

Shunzhou Wan†, Agastya P. Bhati†, Stefan J. Zasada†, Ian Wall‡, Darren Green‡, Paul Bamborough‡, and Peter V. Coveney*†

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Ensemble-Based Replica Exchange Alchemical Free Energy Methods: The Effect of Protein Mutations on Inhibitor Binding

Agastya P. Bhati, Shunzhou Wan, and Peter V. Coveney*

Concurrent and Adaptive Extreme Scale Binding Free Energy Calculations

Publisher: IEEE | Cite This | PDF

Authors

ADVANCED THEORY AND SIMULATIONS

Full Paper | Open Access

Accuracy and Precision of Alchemical Relative Free Energy Predictions with and without Replica-Exchange

Shunzhou Wan,

First published:

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TIES 20: Relative Binding Free Energy with a Flexible Superimposition Algorithm and Partial Ring Morphing

Mateusz K. Bieniek, Agastya P. Bhati, Shunzhou Wan, and Peter V. Coveney*

Cite this: *J. Chem. Theory Comput.* 2021, 17, 2, 1250–1265

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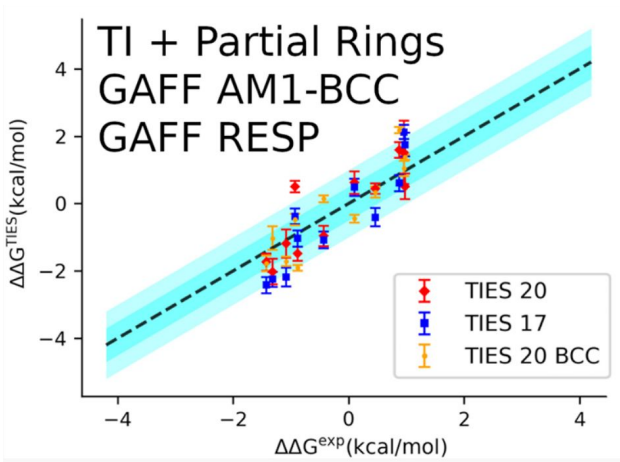
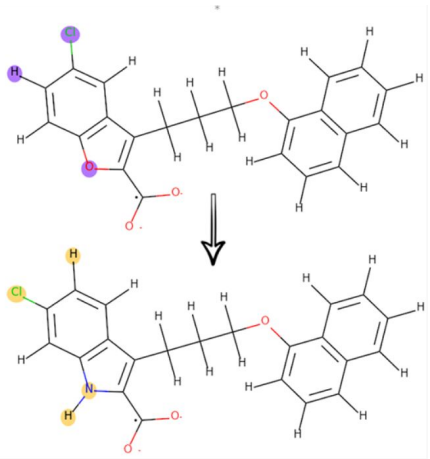
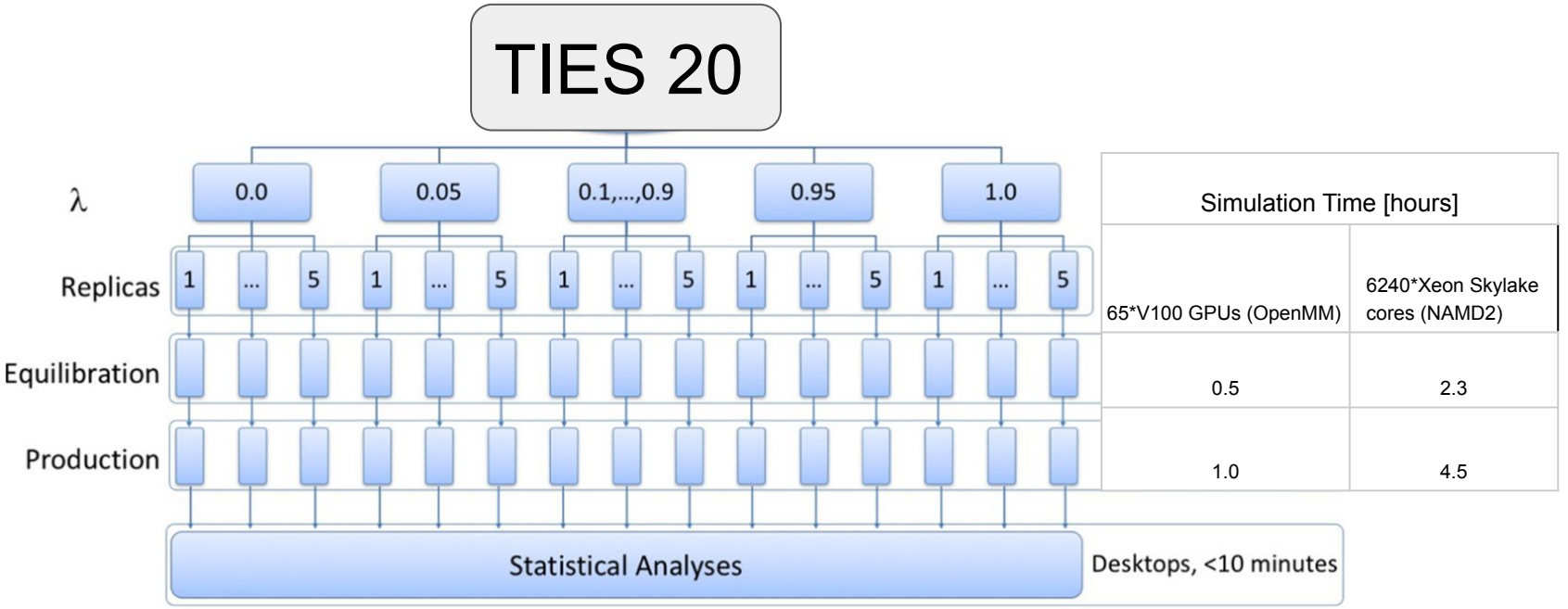




TIES Compute Patterns



	Simulation Time [hours]	
	65*V100 GPUs (OpenMM)	6240*Xeon Skylake cores (NAMD2)
Equilibration	0.5	2.3
Production	1.0	4.5

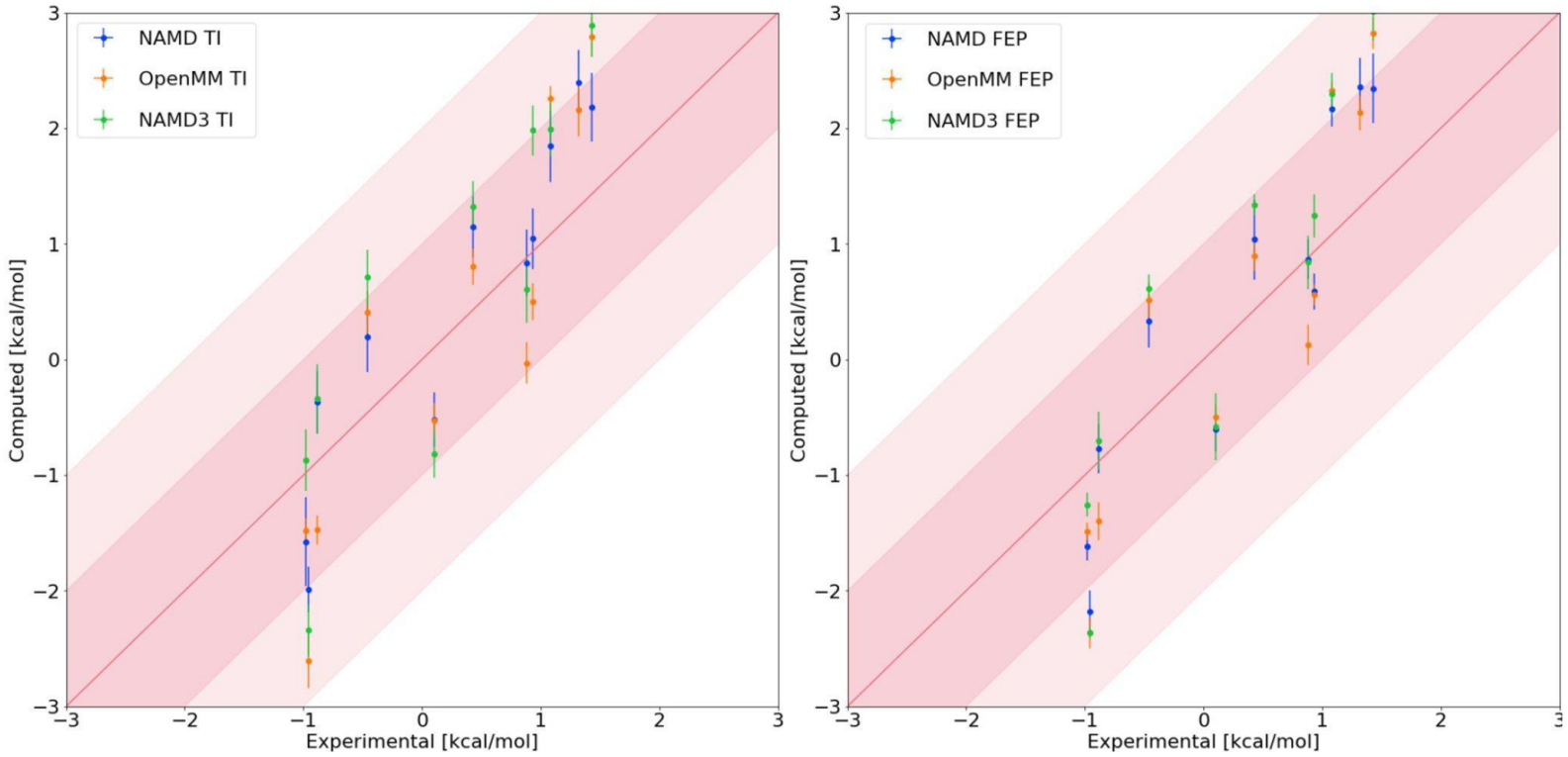
- Embarrassingly parallel
- Can be run on CPU and GPU

NAMD
Scalable Molecular Dynamics

OpenMM

Reproducibility in TIES - Parametric

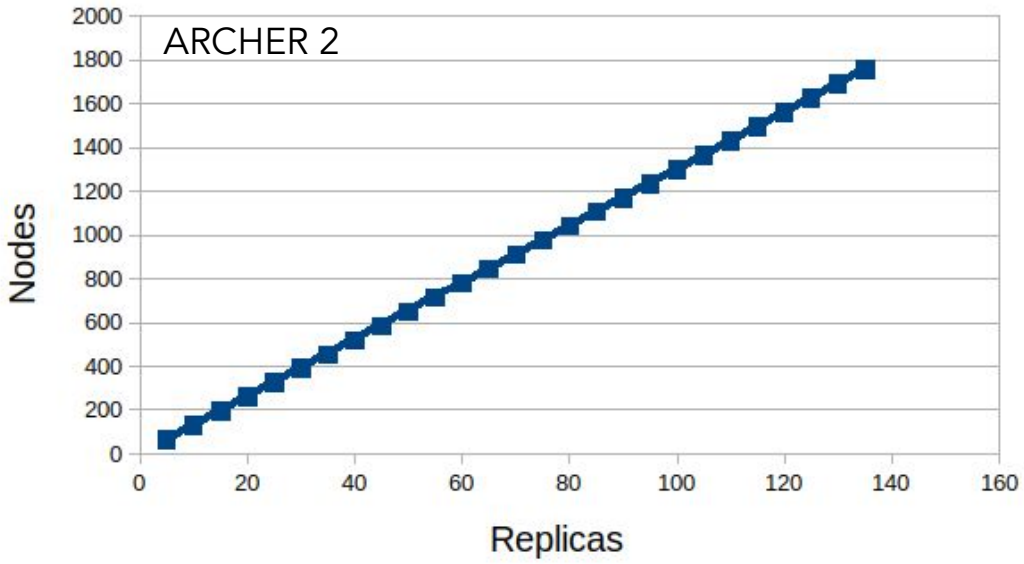
- Computational results obtained with different molecular dynamics engines
- Using replicas there is good agreement between MD engines (OpenMM/NAMD)
- Excellent agreement is seen between the different free energy estimators TI (left) and FEP (right)

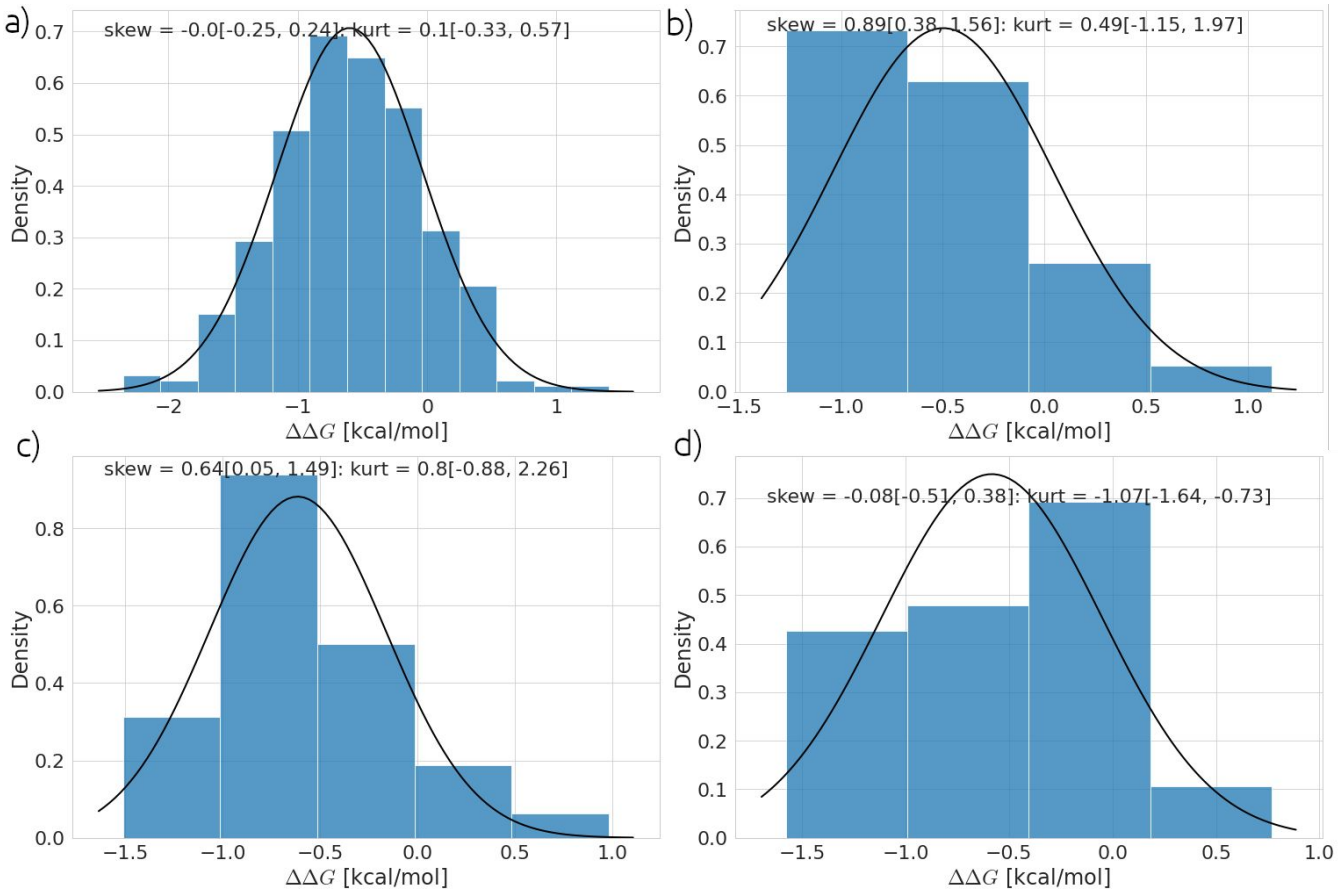


Wade, Alexander, et al. J. Chem. Theory Comput. (2021). DOI:10.1021/acs.jctc.2c00114

Large Replica Simulations - Aleatoric

- Distributions of binding free energies can vary widely
- Many simulations needed to characterise these distributions.
- Accurate reporting and understanding of these distributions key for actionable results.

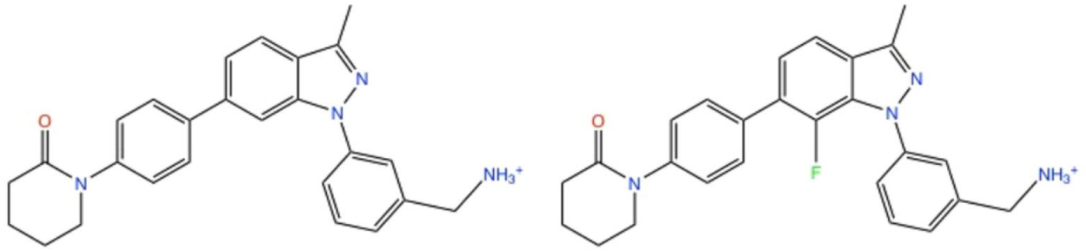




a) 320 replica simulation b) c) and d) same system with 32 replicas

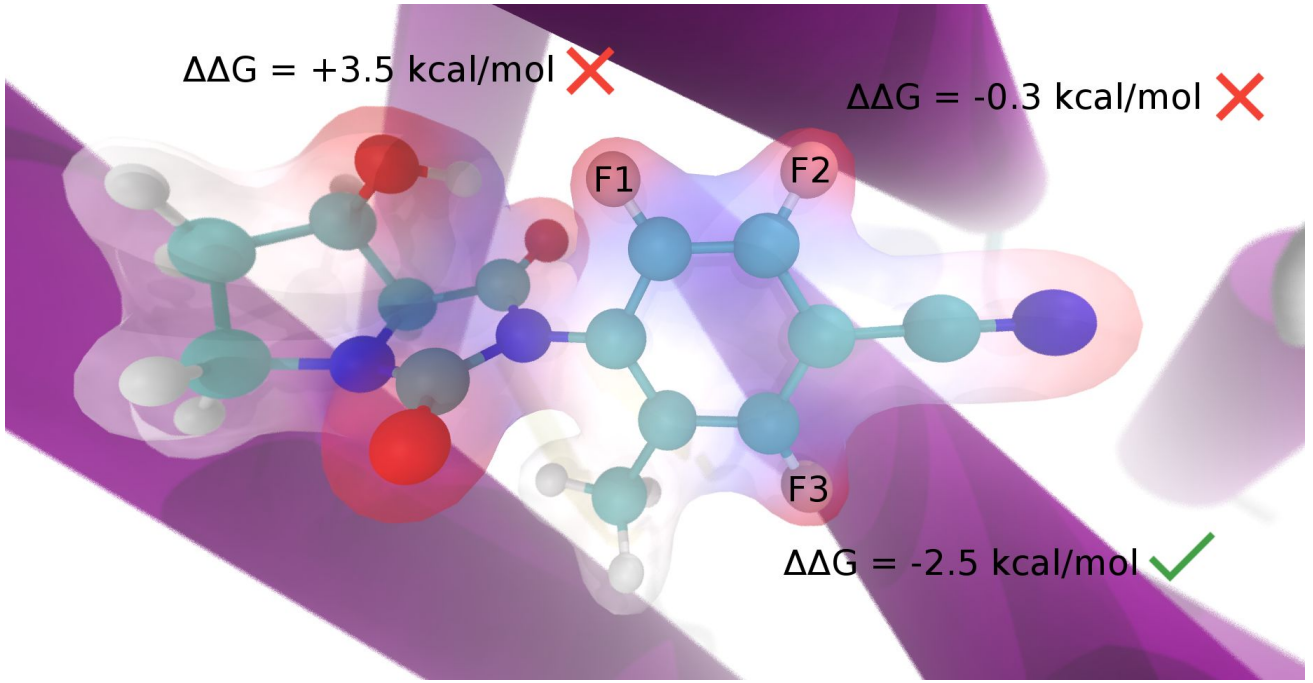
Fluorine Scanning - Methodological

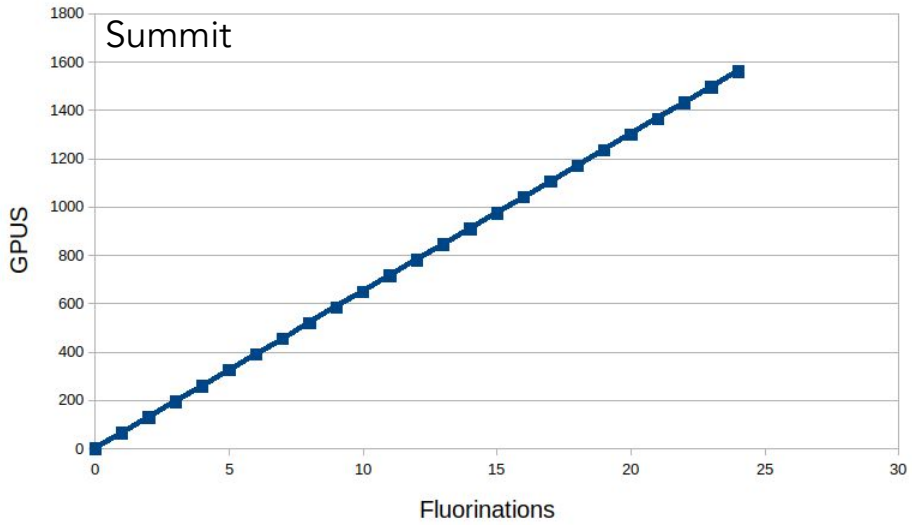
- Fluorine scanning is a common technique in medicinal chemistry
- Involves systematic replacement of hydrogen with fluorine.
- It can improve binding affinity as well as ADME properties
- One fluorination could improve binding affinity 55-fold (see 1->2)



1 Factor Xa K_i = 6850 nM

2 Factor Xa K_i = 124 nM





TIES API

```
1.from ties import Pair, Config, Protein, MD

#Settings for simulation
2.config = Config()
3.config.workdir = 'ties20'
4.config.md_engine = 'openmm'
5.config.protein = 'protein.pdb'

#load the two ligands and create a hybrid
6.pair = Pair('102.mol2', '103.mol2',
              ligand_net_charge=-1, config)
7.pair.make_atom_names_unique()
8.hybrid = pair.superimpose()

#setup ligand simulation
9.hybrid.prepare_inputs()

#add protein and setup complex simulation
10.protein = Protein(config.protein, config)
11.hybrid.prepare_inputs(protein=protein)

#run ligand and complex simulations
12.for leg in ['lig', 'com']:
13.    MD('./ties20/ties-102-103/{}'.format(leg), fast=True)

#run the analysis of these simulations
14.exp_data = {'ties20': {'ties-102-103': [1.0, 0.50]}}
15.MD.analysis(exp_data, legs)
```

- Pipeline can be used on command line or as API.
- Allow us to easily set up simulations with large numbers of inputs or replicas.
- New software release

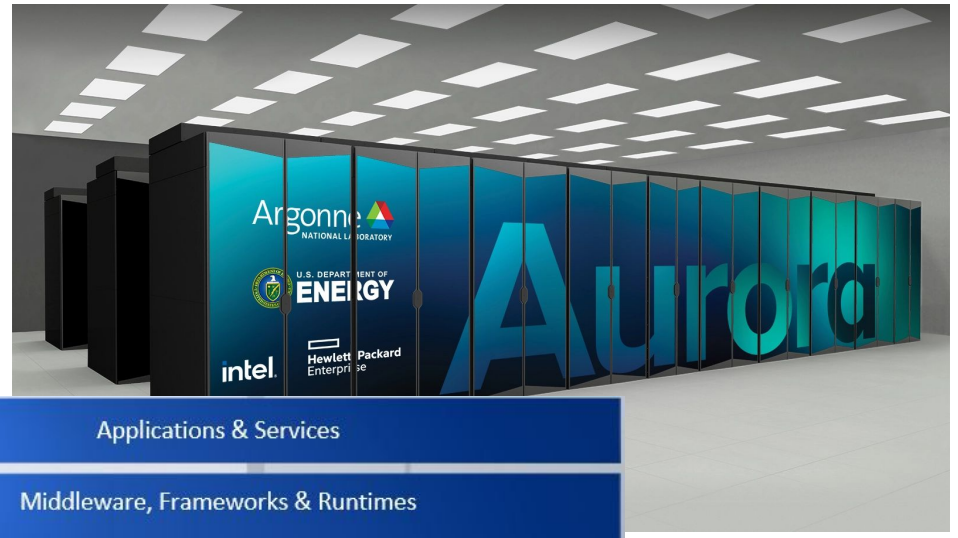
TIES

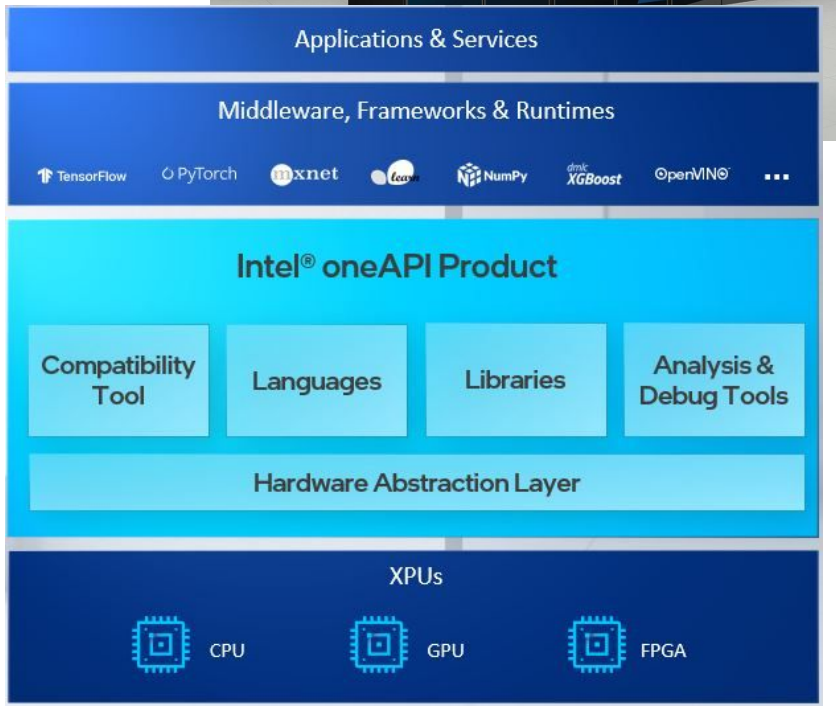
GitHub

https://github.com/UCL-CCS/TIES_MD

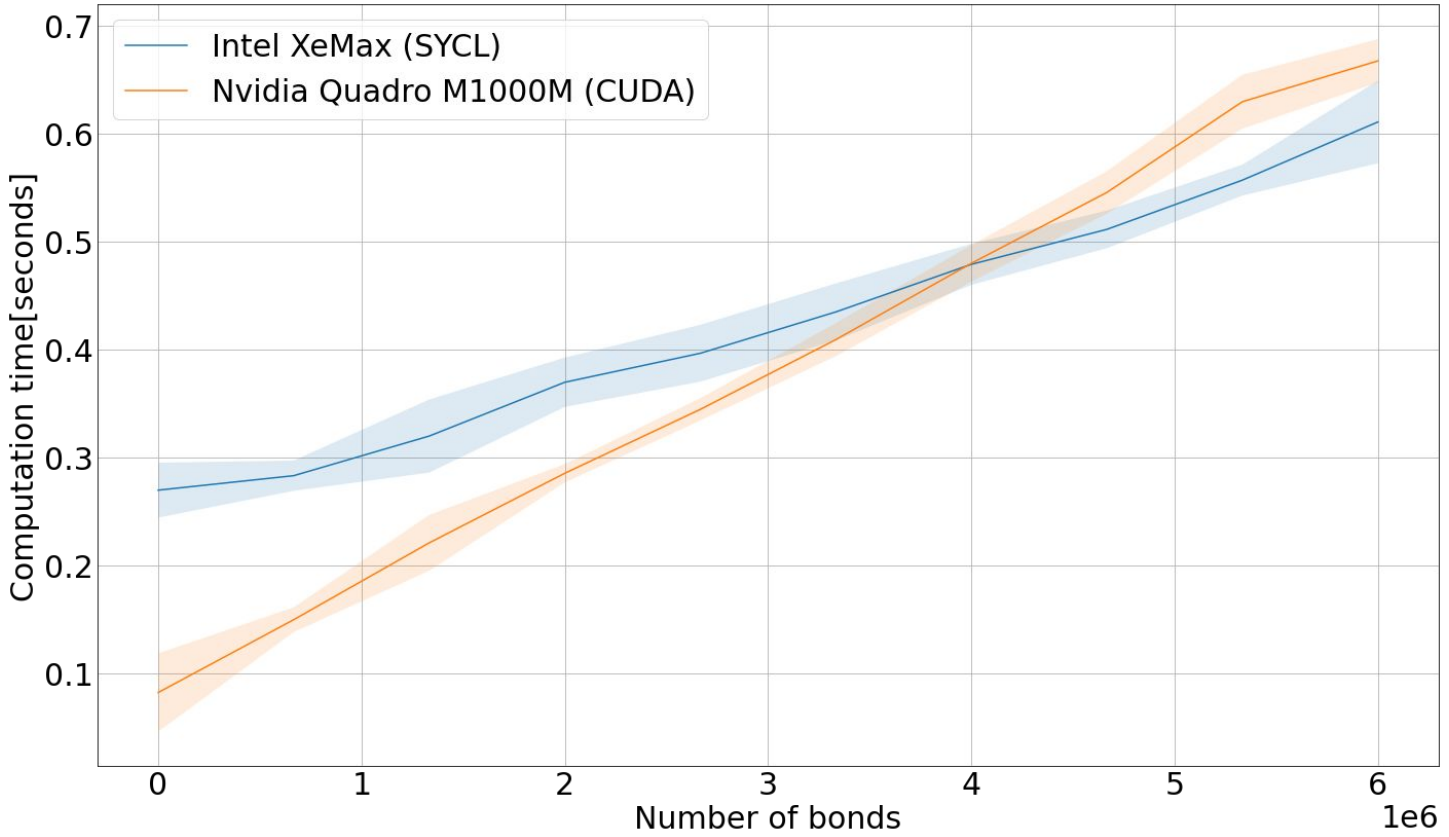
Intel OneAPI

- Unifies programing for CPU/GPU/FPGAs improving portability.
- Intel GPUs will power many of the upcoming top 500 HPCs.
- GPU programing is handled through non proprietary SYCL 2020 standard.





Porting OpenMM to SYCL

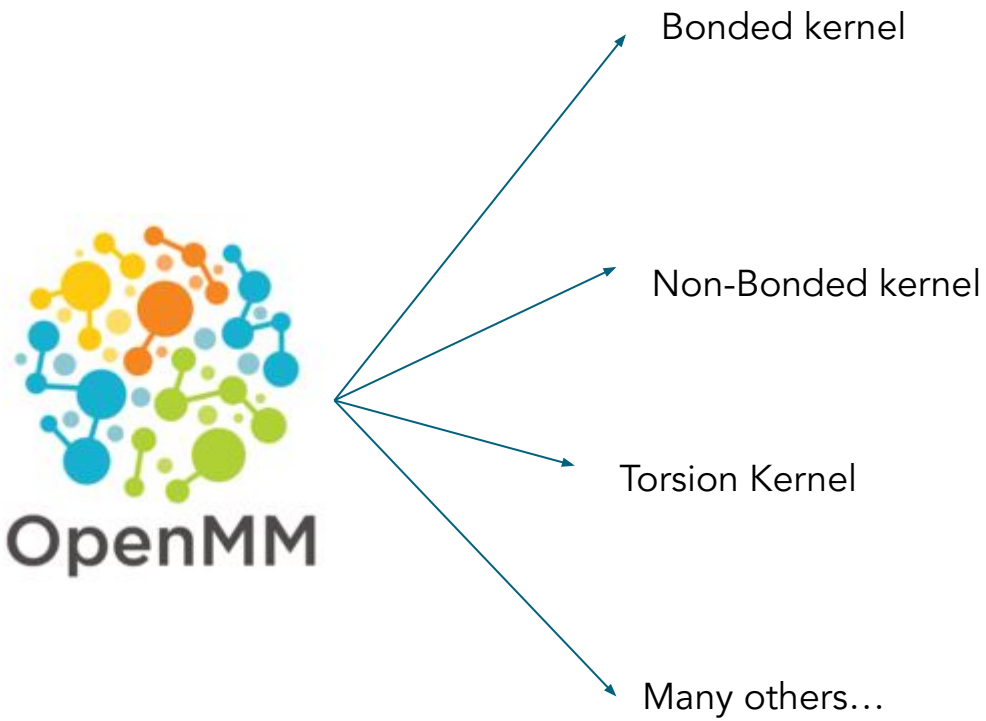


Remaining Challenges

- Runtime compilation is used extensively by OpenMM but is not supported by the compatibility tool.

- Run time compilation is used to provide existing level of portability between AMD and CUDA GPUS.

- Additionally it is integral to user customisable force available in OpenMM .



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Team members:

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- Shunzhou Wan
- Agastya Bhati
- Mat Bieniek
- Maxime Vassaux
- Wouter Edeling
- and many others ...

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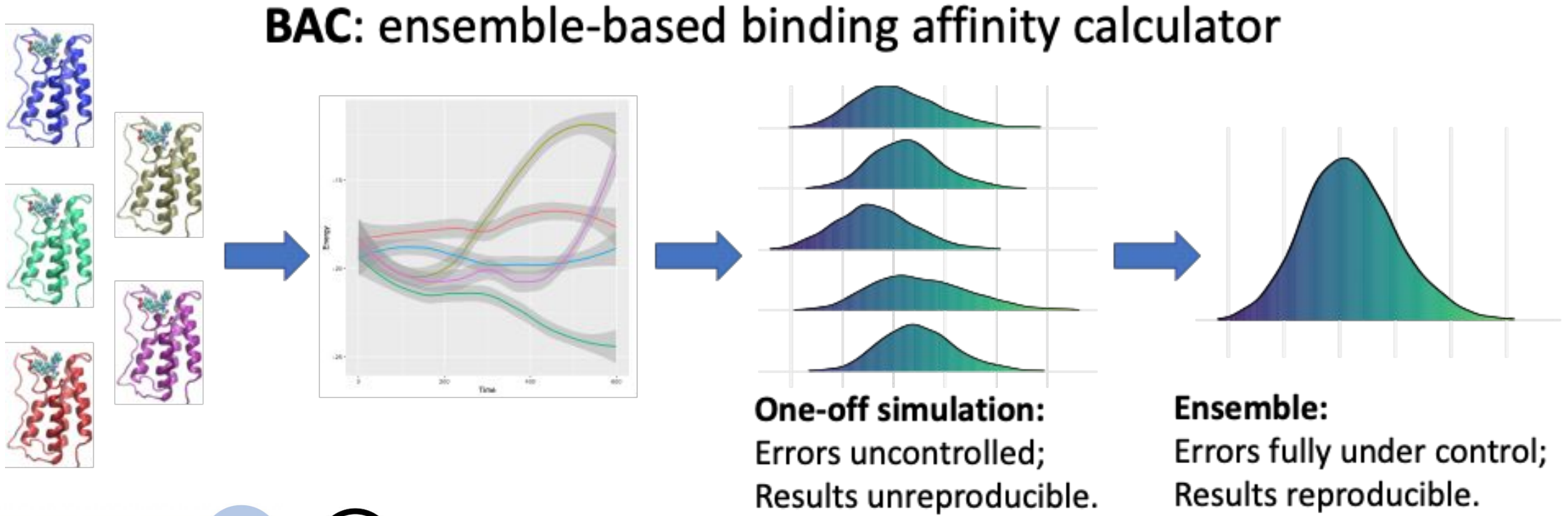
UQ in Molecular Dynamics - Parametric

- Performing ensemble simulations and obtaining averages leads to more reliable results
- Ensemble averaging helps to eradicate aleatoric errors on stochastic simulations, e.g. in drug affinity ranking



Vassaux et al., *J. Chem. Theory Comp.* (2021) 17 (8), 5187–5197