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# Next Generation Quantum Mechanics for Drug Discovery

David Pearlman

VP Product

QSimulate,  Boston, MA

https://qsimulate.com

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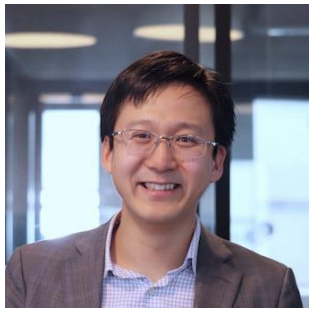
# Making quantum mechanics relevant to the mainstream



**Cofounder & CEO**

**Toru Shiozaki**
Previously a Northwestern Chem Professor developing software

**Cofounder & CSA**

**Garnet Chan**
Bren Professor of Chemistry at Caltech, world leading scientist in quantum

25 People company with branches in Boston, Berkeley, and Ghent (Belgium).

- 20 PhDs in the software and science teams
- Deep computational experience in quantum mechanics
- World renowned scientific advisors

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# Why we *need* quantum mechanics for drug discovery

The two most common sources of simulation error:

1) Insufficient sampling of configurations
    a) Broadly addressed by massive increases in compute
2) Inaccurate energy function
    a) Prevents reliable calculations for many important systems

**Quantum mechanics applicable to pharma problems with pharma-relevant turnaround addresses problem (2) ⟹ A new state-of-the-art**

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# Modern drug discovery is critically dependent on computational chemistry

- Protein structure determination on the modern time-scale would be impossible without methods like MD
- Hit identification is almost always jump-started using virtual screening
- Computational methods, particularly free energy calculations (FEP) are heralded as having helped reduce the time for hit-to-lead by as much as 66%, from 3-5 years to 18 months or shorter

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# Incredible increases in compute fundamentally changed the game

| | Circa 1980 (dawn of modern comp chem) | Circa 2023 |
|---|---|---|
| Machine | Vax 11/780; 1 core | 32+ core 5Ghz+ Linux (local); cloud; GPU |
| Speed | 1 MFLOP | 170,000 MFLOP (cpu workstation); up to ~$10^9$ MFLOPS for supercomputer |
| Memory | 128mb or less | 64gb common; up to 2-3tb |
| Storage | 9-track tape (170mb) | Many TB on fast RAID |
| Price | ~$2M (fully configured, inflation adjusted) | $2-8k |
| Possible to make *reliable* predictions with pharma-relevant turnaround? | No | Yes* |

* When the model and force field are suitable

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# New Generation Quantum Mechanics (QM)

## QSimulate has developed a platform making possible:

1. Unprecedentedly large DFT QM calculations
    - 3000+ atoms, ~1 hour turnaround, ~$10 on cloud
2. Unprecedentedly long QM/MM-based FEP
    - Cloud deployed, fast enough to replace MM

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# Quantum mechanics summary

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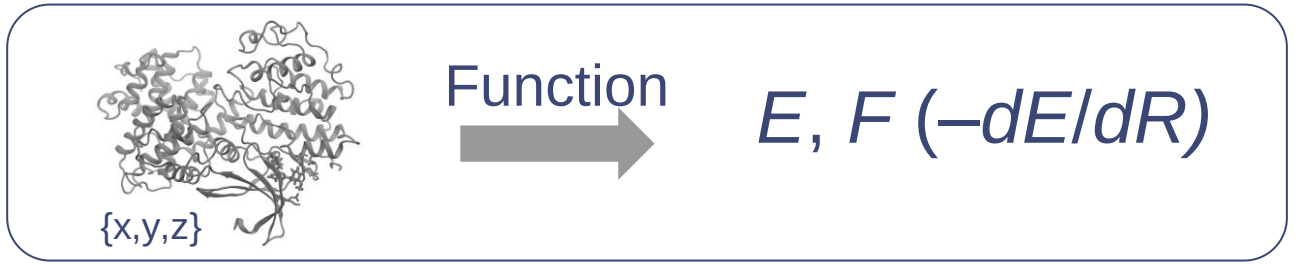
# Quantum mechanics (QM) is the gold standard

Computational work is based on being able to evaluate energies and forces from atomic structure




- QM is best, but, traditionally, too computationally expensive
- Nearly all simulation work has used MM (Molecular Mechanics)
  - MM: Calculate (E, F) rapidly from analytic function with fitted empirical coefficients
  - MM has gotten better over the decades, but suffers serious deficiencies
- Cost aside, everything that can be done with force fields can be done (better) with quantum mechanics.

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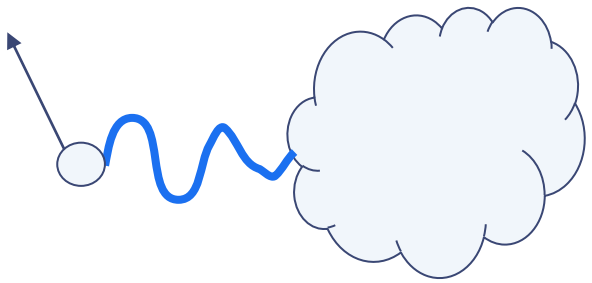
# Quantum mechanics flavors

- Exact:  Impossibly expensive (exponential with number of atoms)
- Hartree-Fock (H-F): Older style. Becomes prohibitively expensive for larger systems
- Density Functional Theory (DFT): Determines properties from density. Can be applied to real-world systems. Very good approximation to exact, but still expensive/slow
- Semi-Empirical: Further approximations, but recent versions based on fit to DFT (e.g. GFNn-xTB) still good, very fast, and applicable to larger systems.



DFT

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# First, something else amazing: Ligand/protein scoring using DFT for the full ligand/protein interaction

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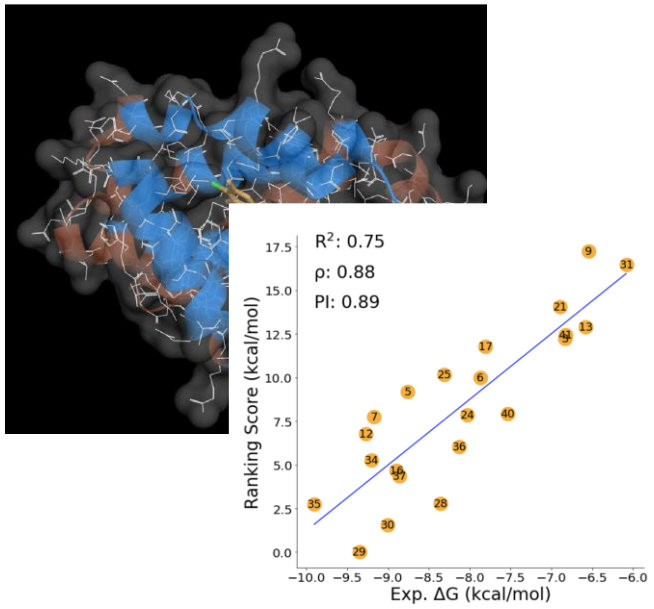
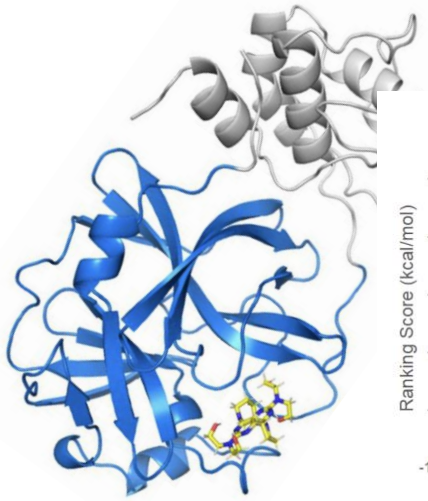
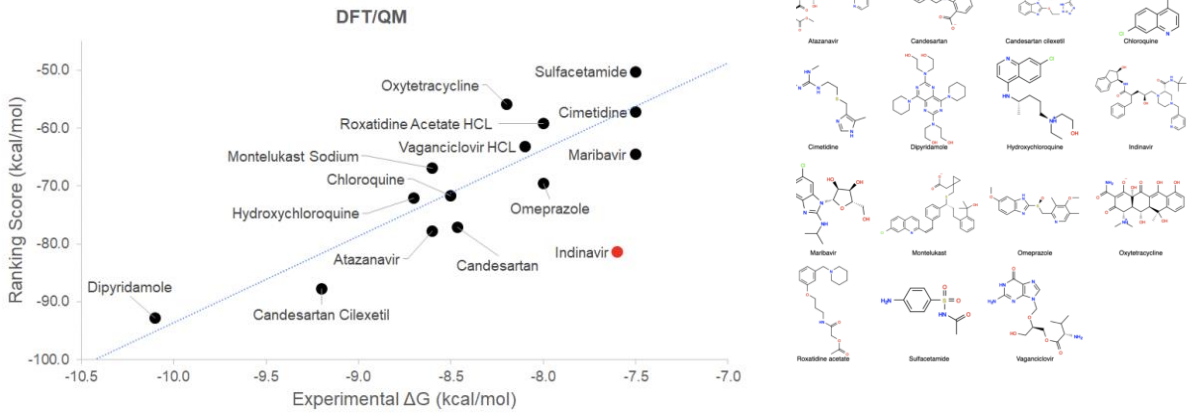
# Direct evaluation of ΔH for ligand binding using DFT

ΔH of binding evaluated by full protein/ligand DFT (revPBE-D3(BJ); def2-SVP)








MCL1
https://arxiv.org/abs/2004.08725

COVID Mpro with diverse set of ligands
J. Comput. Aided Mol. Des. 35, 963–971 (2021)

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# We (re)learned a lesson in a hard way

The results were very good–amazingly so–for some systems, but not all

- Very sensitive to the choice of protein models and simulation protocols
- Sometimes, entropy is important

Lesson (re)learned: ‘there is no easy way around proper sampling of configurations.’

We decided to pursue QM-based FEP

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# QUantum Enhanced Lead Optimization (QUELO)
# The first viable QM/MM FEP

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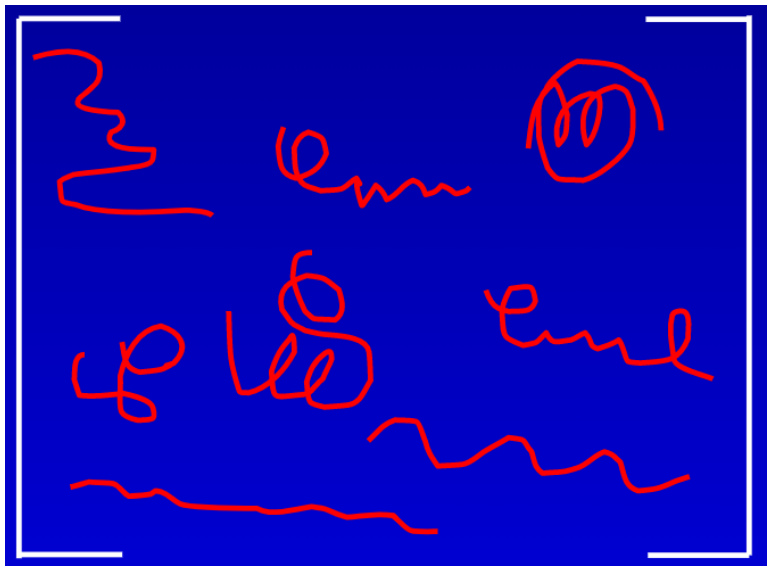
# Free energy calculations (ΔΔG) can direct lead optimization

Question: How does a moderate structural change affect binding?

Method:



Thermodynamic ensembles of conformations

Ensembles generated using long Molecular Dynamics simulations

statistical mechanics → ΔΔG

Changes in affinity/binding

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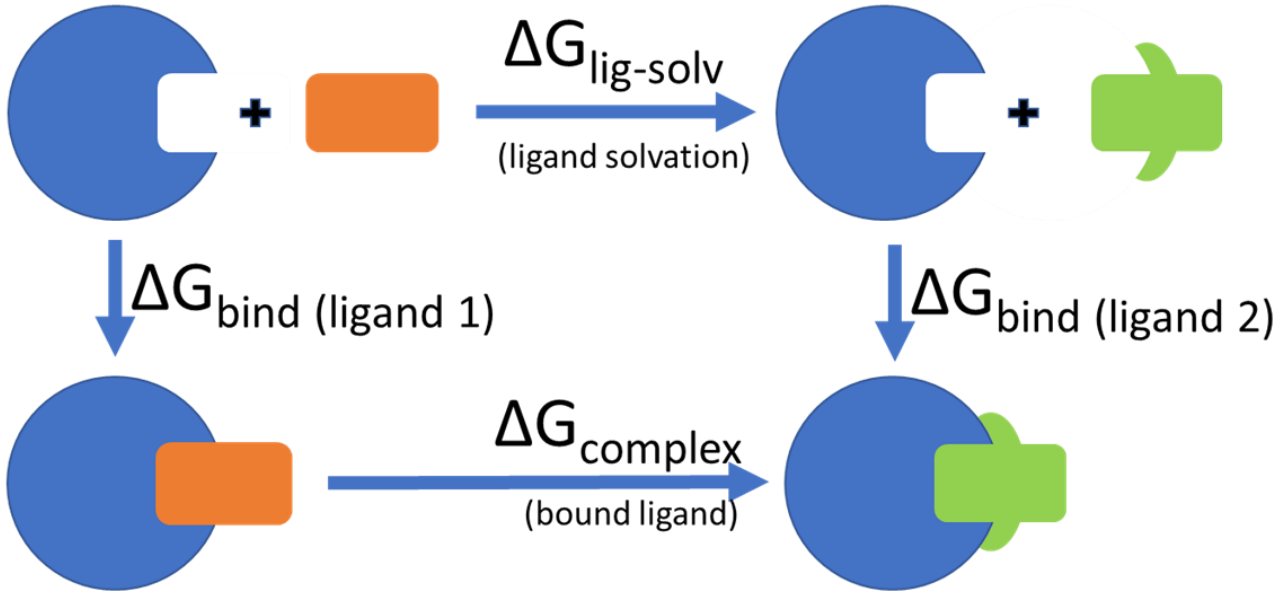
# Connecting calculation with experiment: The thermodynamic cycle




$$\Delta\Delta G_{binding} = (\Delta G_{lig\text{-}solv} - \Delta G_{complex}) \quad | \text{ Computed}$$

$$= (\Delta G_{bind\ (ligand\ 1)} - \Delta G_{bind\ (ligand\ 2)}) \quad | \text{ Experimental}$$

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# What is QUELO?

Performs FEP (ΔΔG) calculations using QM/MM

- Same established protocol as MM–no shortcuts!
- Reproduces standard MM FEP when QM region is null
- QM calculated using state-of-the-art semiempirical GFNn-xTB
- MM calculated using Amber FF (ff14SB)

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# Why QUELO QM/MM-FEP?

If (semi-empirical) QM/MM is a better energy function than MM force fields, which we believe is the case, QM/MM FEP should provide better accuracy for prediction.

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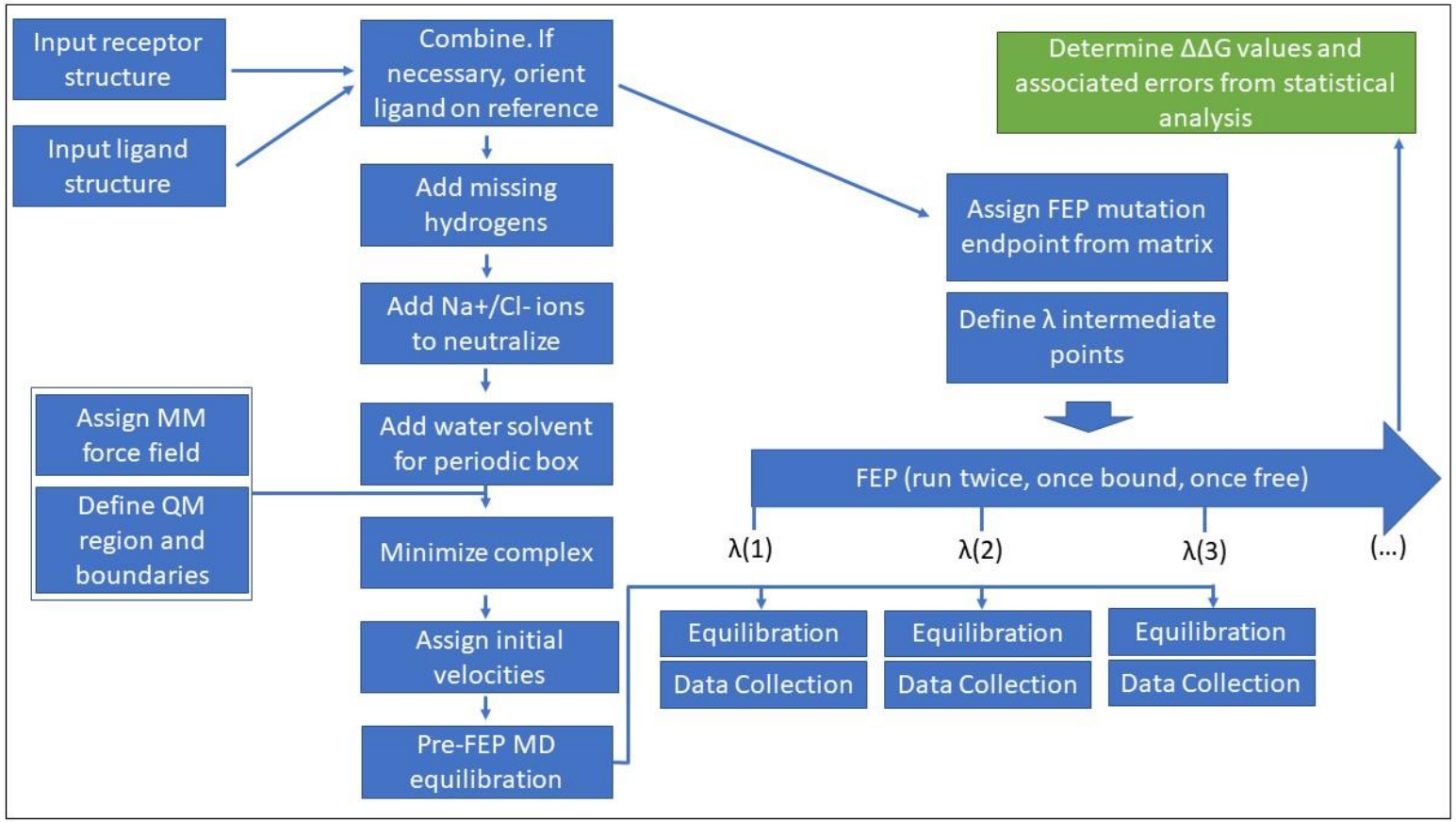
# QUELO makes it trivial to run a complex workflow




- Fully automated
- It as simple to run a quantum FEP simulation as a classical simulation.

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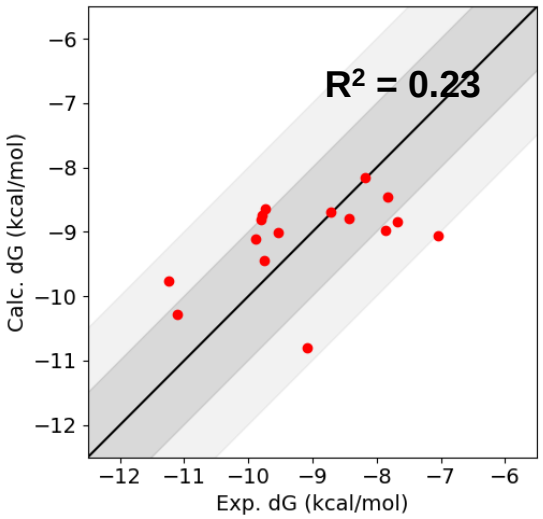
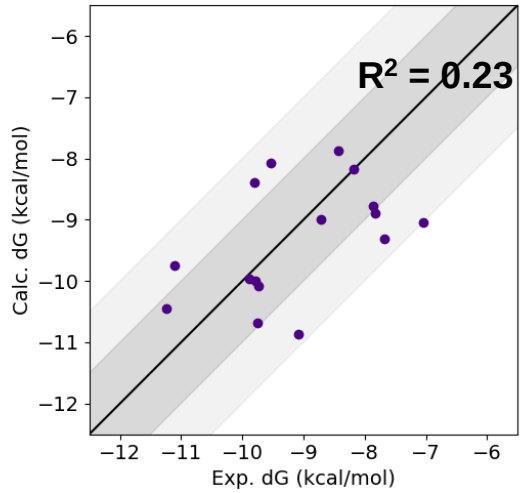
# QM/MM FEP raises the bar substantially

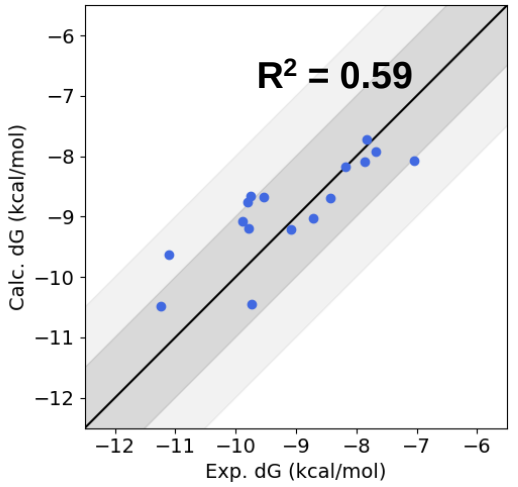
**FEP+**




**MM (QSimulate)**




**QUELO (QSimulate)**




## CDK2

**QM/MM:**

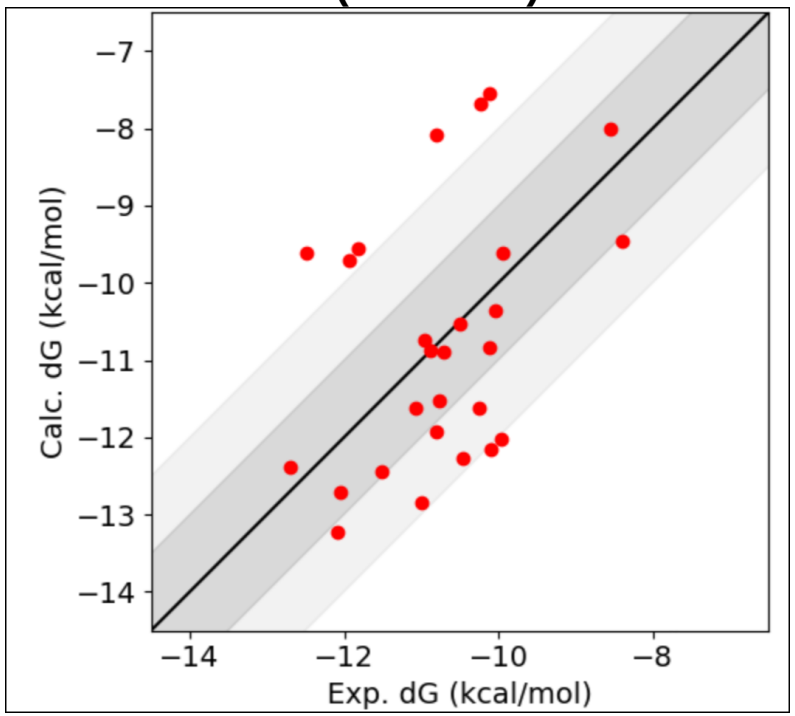
**14 windows per mutation**

**2ns simulation per window**

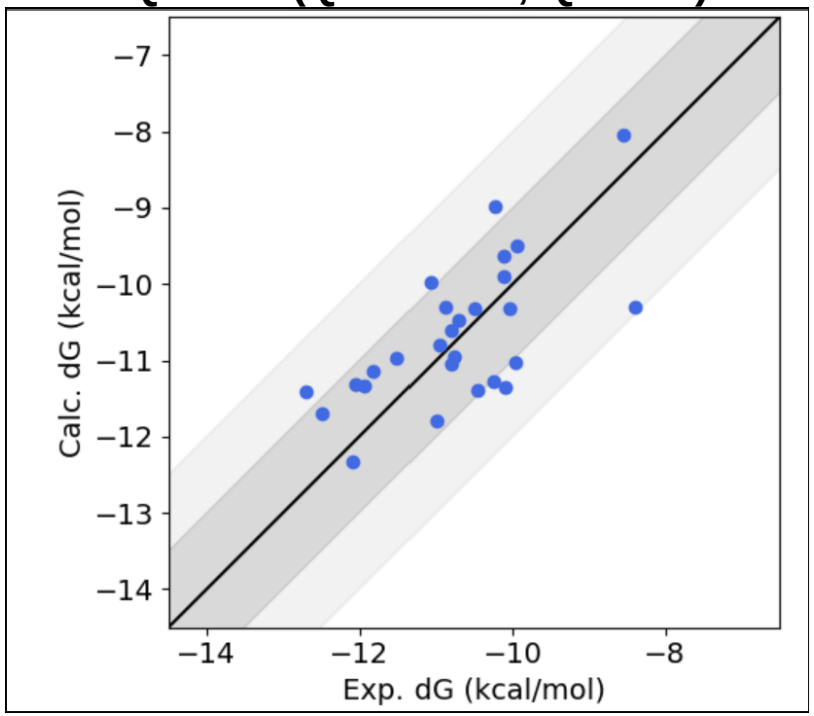
| | Mean Average Error (Kcal/mol) | $R^2$ Linear Regression | $\tau$ Kandall Rank | $\rho$ Pearson Coeff. |
|---|---|---|---|---|
| FEP+ classical (OPLS FF)[68] | 0.88 | 0.23 | 0.28 | 0.41 |
| QSimulate classical FEP (Amber) | 0.93 | 0.23 | 0.20 | 0.42 |
| QSimulate QM/MM FEP | 0.65 | 0.59 | 0.65 | 0.80 |

# QUELO QM/MM FEP succeeds where classical FEP+ fails

**FEP+ (classical)**




**QUELO (QSimulate; QM/MM)**




TNKS2

Preliminary results

FEP+ data from J. Chem. Inf. Model. 2020, 60, 11, 5457–5474

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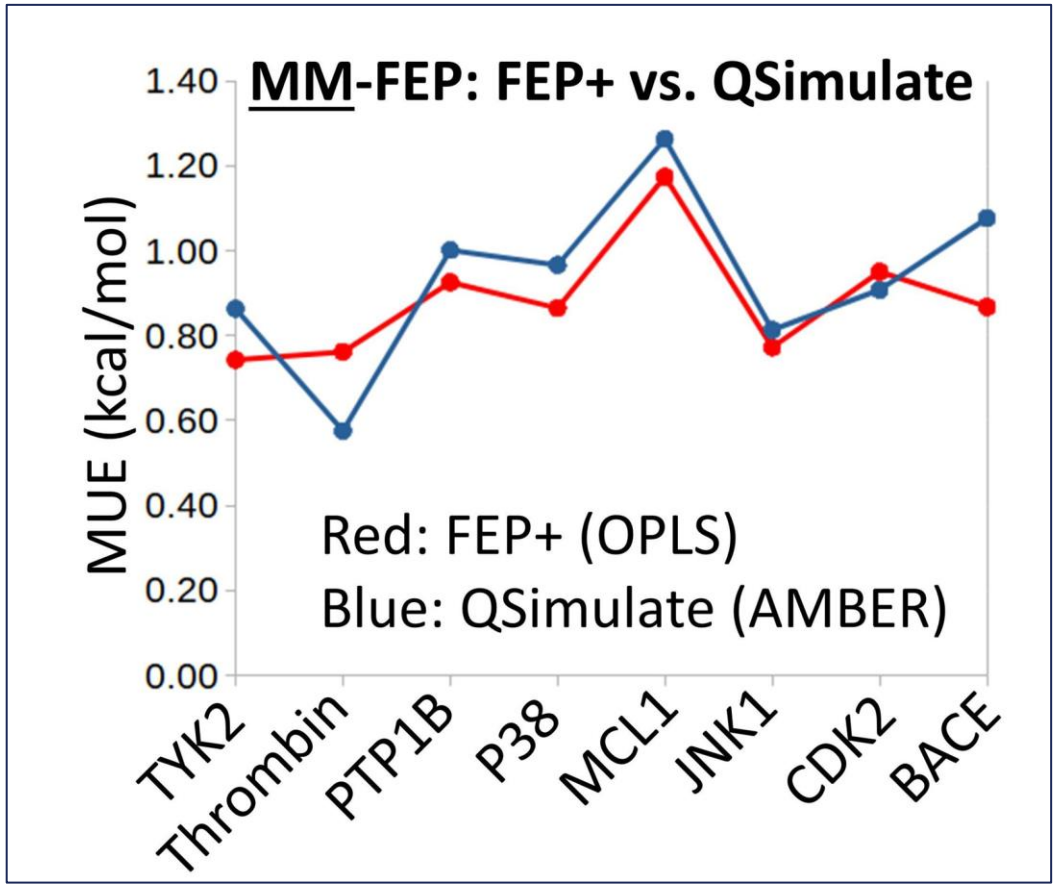
# QUELO can also perform entirely classical (MM) FEP




- **Providing leading edge performance**
- **Cloud extensibility**
- **Attractive cost**

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# Where to Expect Significant Improvements using QUELO?

When ligand can’t easily be described by MM
e.g., when ligand polarization is important

When there are difficult specific interactions
e.g., when there are important halogen bonds, pi-stacking

Where formal charge is changing

Metal interactions

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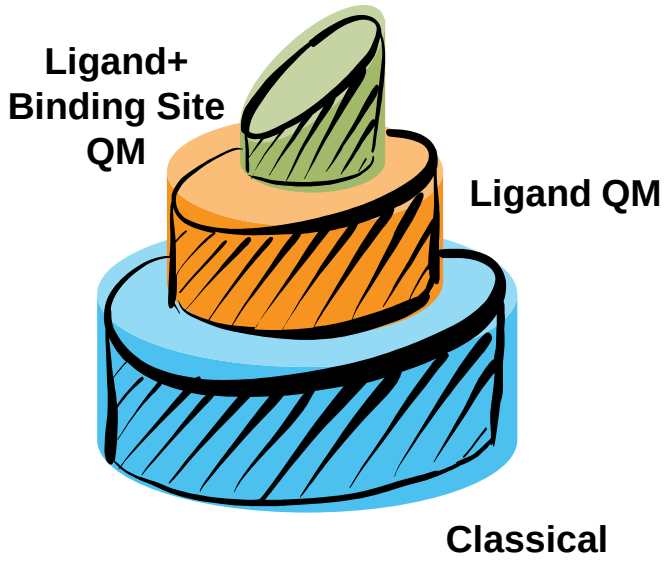
# QUELO beats the competition on science and cost

- Ligand+Binding Site QM:
  - Offers accuracy never before possible for many systems
  - Only available through our platform
  - Speed/cost still commensurate with modern pharmaceutical discovery
- Ligand QM:
  - Better than FEP+, at a similar overall cost
  - Only available through our platform
- Classical:
  - A cheaper drop-in replacement of FEP+



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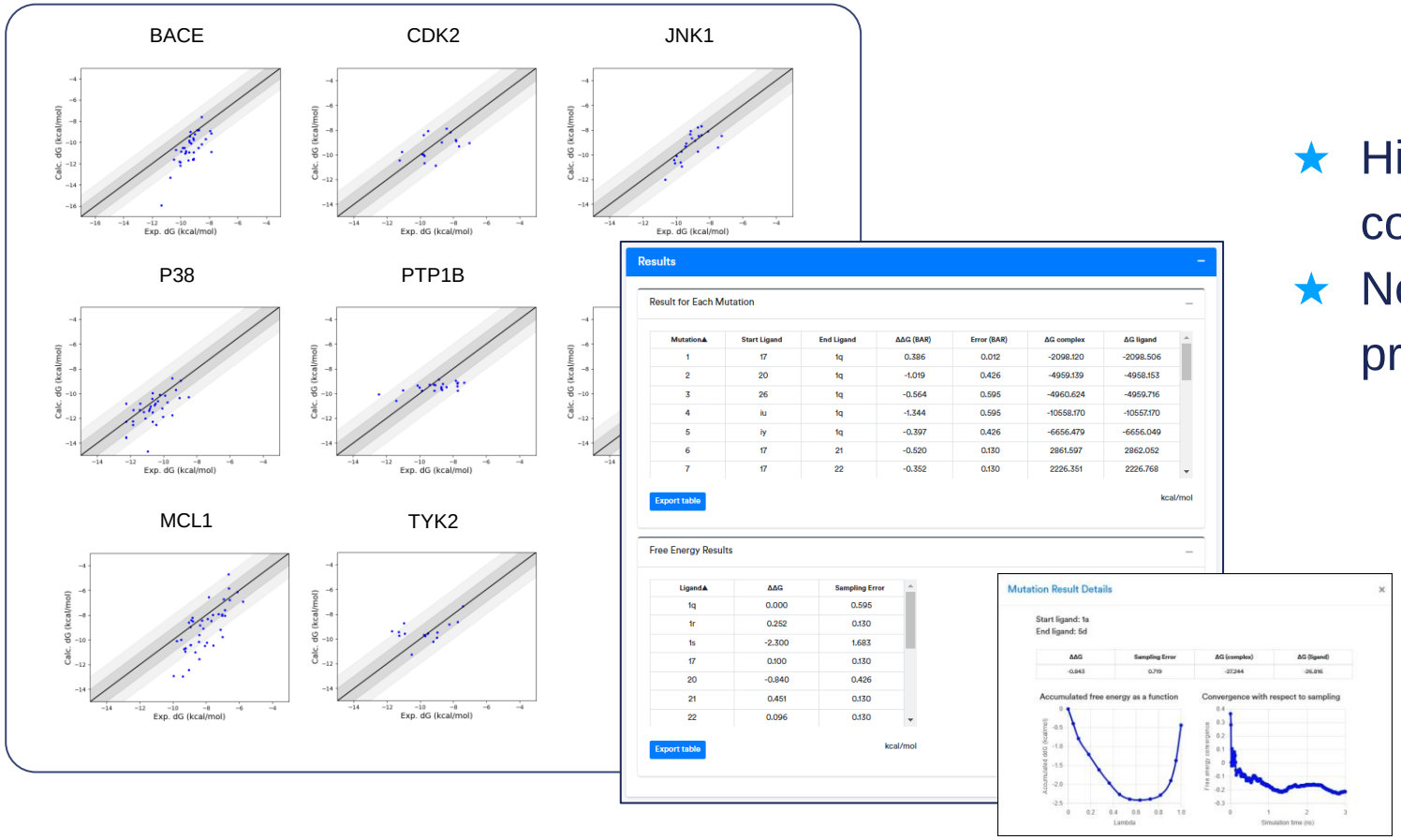
# Evaluate dozens of ligands using classical MM FEP in a day










- ★ High throughput using vast cloud computing resources
- ★ No manual labor, no FTE spent on preparation and post processing

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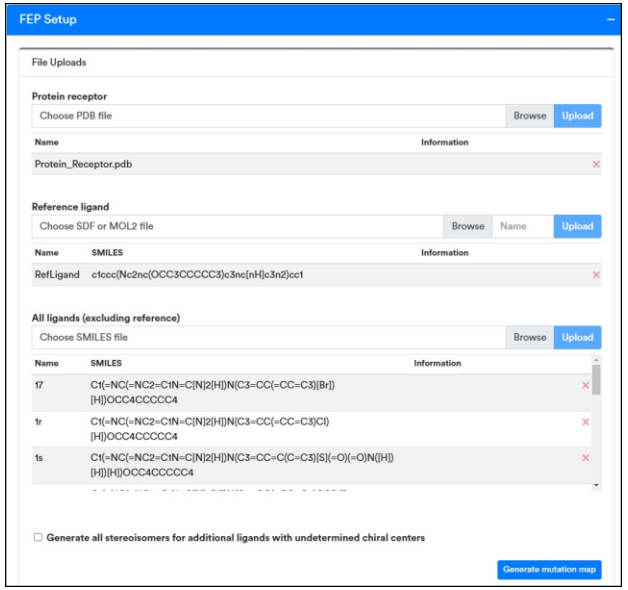
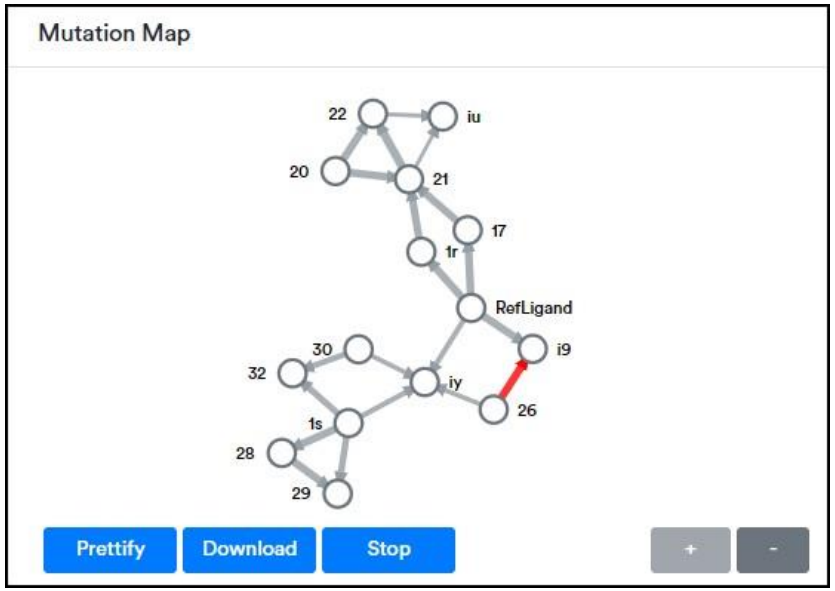
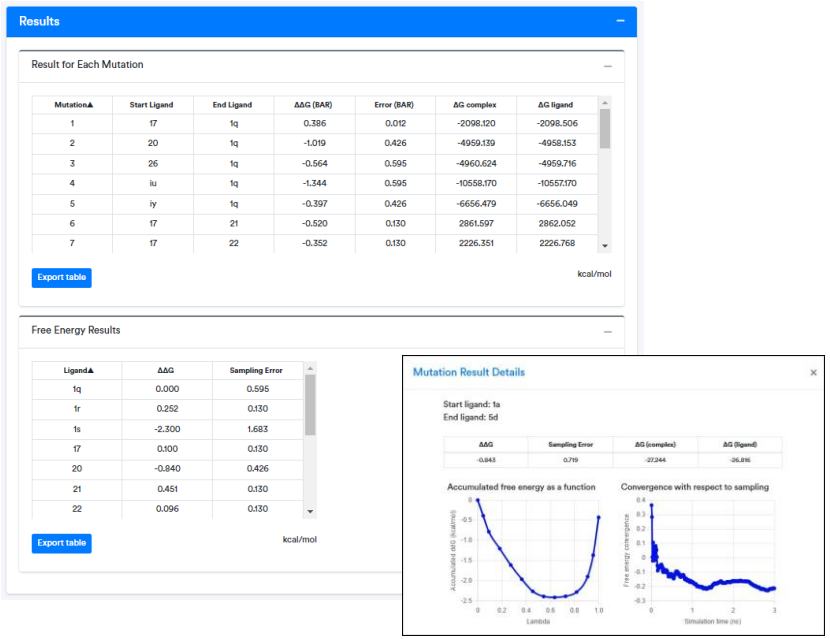
# It’s not just a backend

We automate the FEP workflow on our cloud-based platform (we can probably install this to local environments, but it requires some efforts)



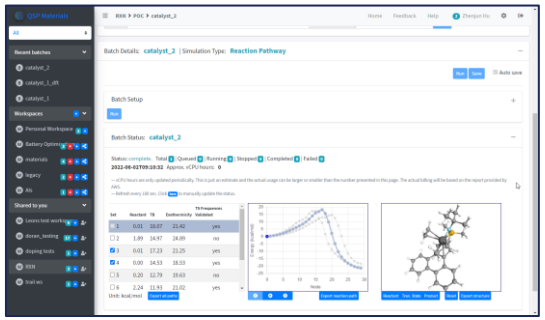

Input panel

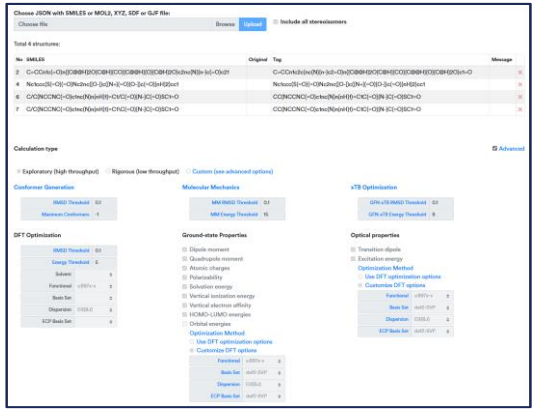
Mutation Map generated

Simulation results

# We’re working broadly to bring QM to drug discovery

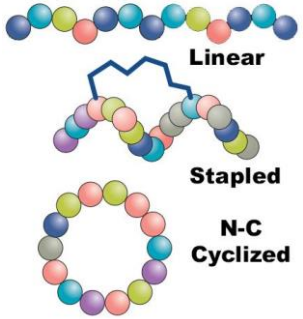
- Automated characterization of covalently bound ligands; warhead tuning





- High-throughput quantum-fingerprinting of molecules for AI/ML/SAR
  - Automatic 3D structure generation and QM assessment
  - Thousands or millions of molecules on the cloud

- Peptide scoring, including non-canonicals and cyclics



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# Summary

1) Never-before: Full DFT on large ligand/protein system
2) Never before: FEP using QM/MM
3) Quantum mechanics is now relevant to drug discovery

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# Without whom…
# Our development effort depends on many smart people

- Jia Chen
- Alec White
- David Reilley
- Klaas Gunst
- Alexander Doran
- Beatrice van der Goetz
- Fredy Aquino
- Leon Freitag
- Zhenjun Hu
- Dan Moberg
- Justin Provazza
- Sébastien Hoyas
- Sruthi Murlidaran
- Csaba Daday
- Jaden Tayag
- Joachim Vandewalle

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# Thank you for your interest!


**QSimulate**

**20 Guest St STE 101**

**Boston, MA 02135**


We are a world-class team, deeply passionate about solving world problems through the application of the most innovative quantum technologies. Join our journey!


Contact: info@qsimulate.com