Practical and Accurate Free Energy Calculations using Neural Network Potentials

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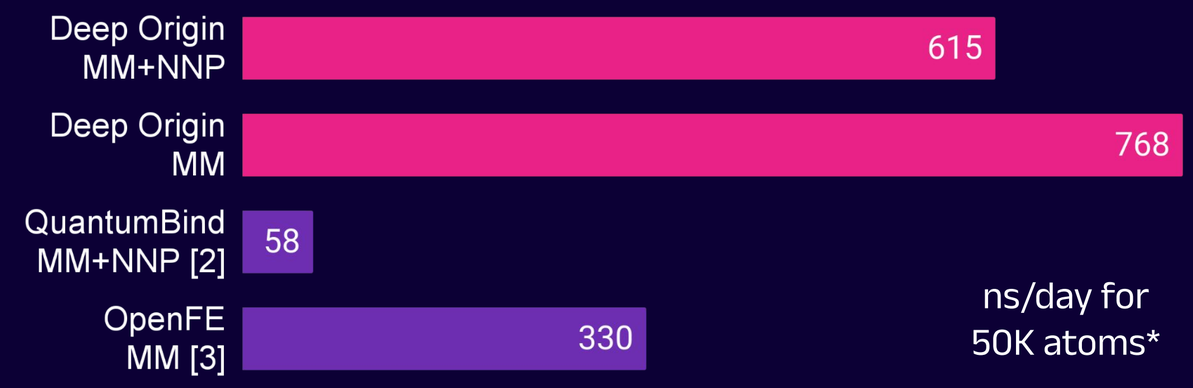
We introduce Deep Origin's Neural Network Potential (NNP)-based force field for small molecules and demonstrate its effectiveness in Free Energy Perturbation (FEP) calculations. By training neural networks on Density Functional Theory (DFT) calculations, we achieve quantum-level accuracy for intramolecular potentials of small molecules. This NNP force field is integrated with classical Molecular Mechanics (MM) force fields within our proprietary MD engine, enabling both conventional Molecular Dynamics (MD) and efficient FEP simulations. Benchmarking reveals high accuracy for solvation and absolute binding free energy calculations. Our combined MM/NNP CPU implementation is an order of magnitude more efficient than similar methods in the literature with a speed of 600ns/day on a complex with 50K atoms*. This makes NNP-based methods practical and scalable for routine use in drug discovery projects. We plan to release these models and tools through Deep Origin's computational drug discovery platform.

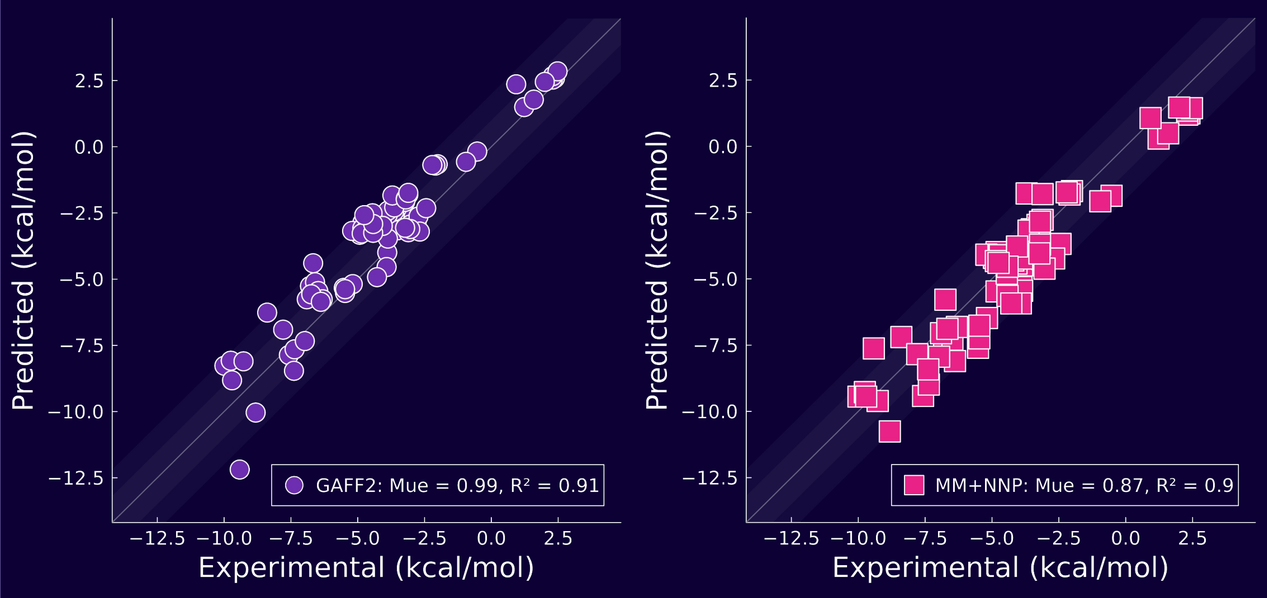
Practical Binding FEP Performance



Deep Origin MM+NNP uses MTS simulations with 4fs timesteps the MM system and 1fs for NNP-driven small molecule. [2] use 2fs timesteps. MM-only approaches use 4fs timesteps.

*Assuming 96-core CPUs for Deep Origin's FEP. [2-3] use an RTX 4090 GPU.

Accurate Solvation Free Energy Benchmark



Solvation free energy simulations on a random subset of FreeSolv [1].

About Deep Origin

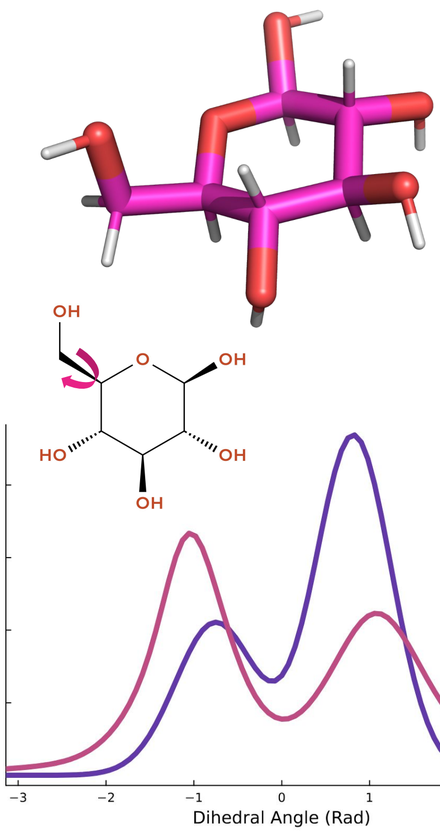
We help scientists solve disease and extend health-span by building tools that simplify R&D, simulate biology, and untangle the complexity of life. We provide our tools as software and work in partnership with others to design better therapeutics faster. You can also try our AI assistant Balto at https://www.deeporigin.com/.

Solvation FEP Case Studies

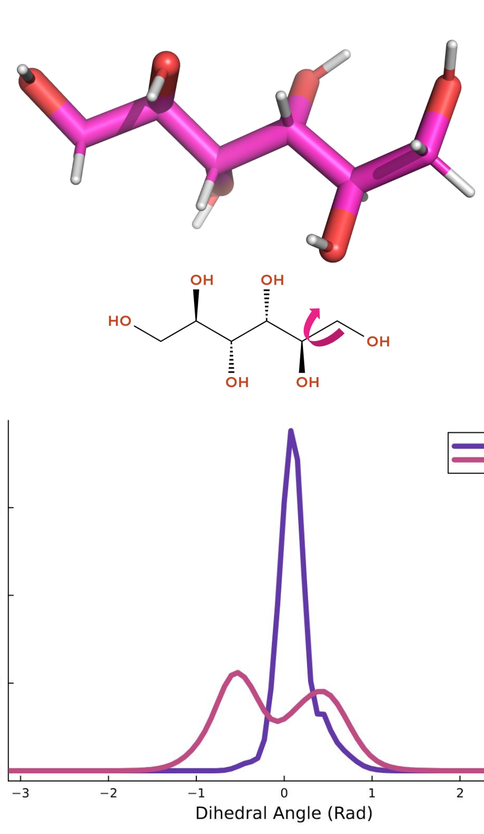
Molecule	Exp. dG	FEP with NNP	FEP with GAFF2
9534740	-25.33	-28.91	-15.39
4587267	-23.61	-26.05	-16.03

Test cases exemplify similar structures and results across multiple examples. dGs shown are in Kcal/mol, experimental results are from [4]

FreeSolv 9534740



FreeSolv 4587267



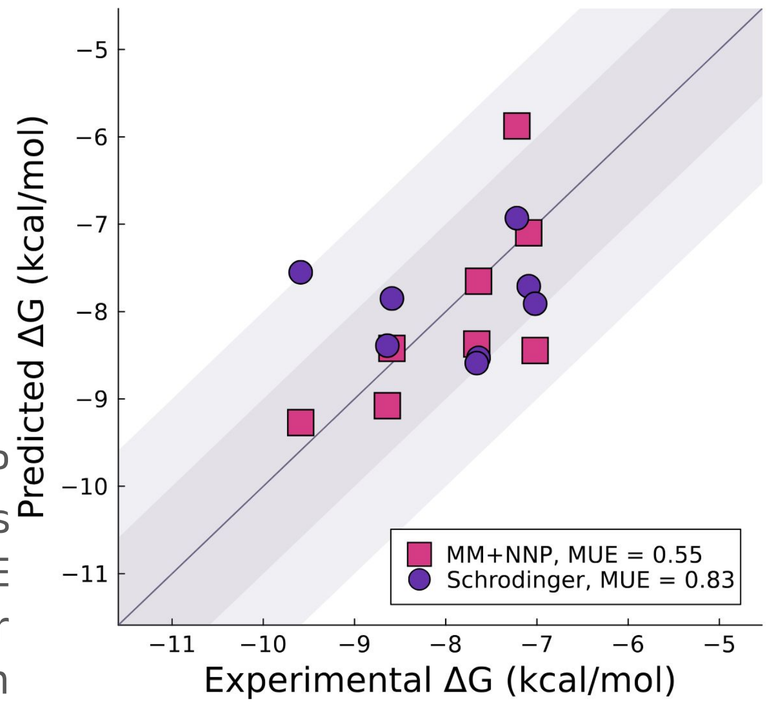
Mono-substituted cyclohexanes showed significant improvement, which we hypothesize to be leading to better sampling, here to the hydroxyl group on the tail.

Straight chains also showed significant improvement, here the dihedral of interest is the hydroxyl group on either end of the chain.

Highly hydrophilic molecules show improved experimental dG proximity, which we theorize is partially due to improved sampling of hydroxyl groups.

Sneak Peek on further results: NNPs with ABFE

Our absolute binding FEP calculations with NNPs outperform FEP+ RBFE calculations together with cycle closure on BRD4 [5].



Future Directions

- Benchmark expansion to include harder and more complicated systems
- New NNP revisions for more accurate results
- Prospective study testing and usage

References

[1] Mobley, David L., et al. J Comput Aided Mol Des 28, no. 7 (2014): 711–20.
[2] Sabanés Zariquiey, F. et al. J. Chem. Inf. Model. 2025, 65 (8), 4081–4089.
[3] https://openfree.energy/
[4] Geballe, M.T. et al. J Comput Aided Mol Des 24, 259–279 (2010).
[5] Ross, G. A.; et al. Commun Chem 2023, 6 (1), 1–12.

Get in touch!

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