D3R Grand Challenge 2

Affinity prediction methods in the pharmaceutical industry

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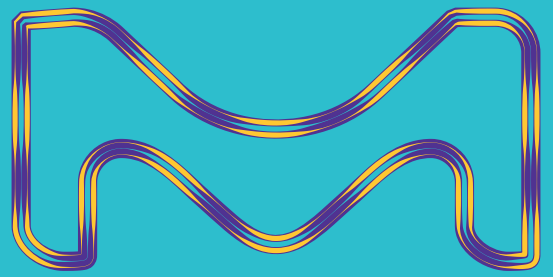
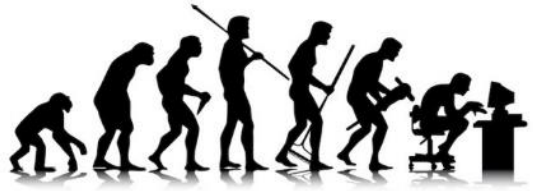


MERCK

Hunting for drugs

Affinity prediction in the pharmaceutical industry



1990 | 2000 | 2010 | 2020

QSAR

Docking & Scoring

Free energy perturbation FEP

My postdoc: explore opportunities and challenges of using FEP in real-life drug design projects at Merck KGaA

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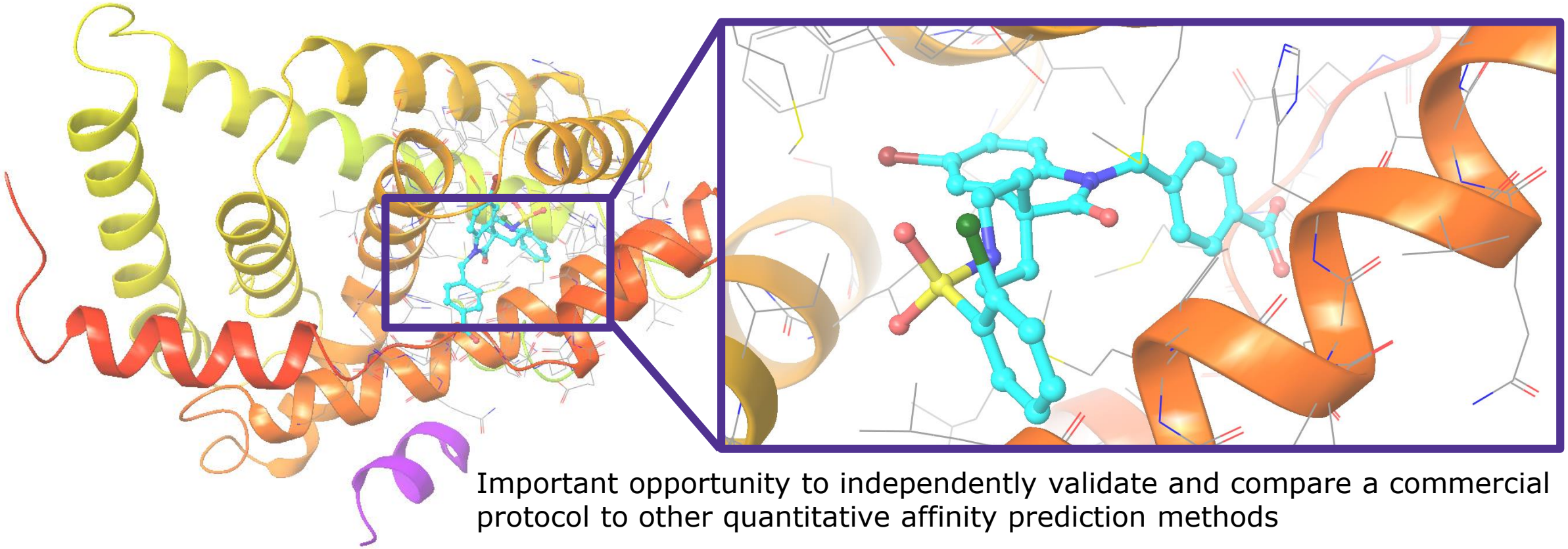
Affinity prediction in real-life drug design projects

Desire to comparatively validate methods independent of vendor

Need to rely on commercial protocols (Schrödinger FEP+)

D3R Challenge Stage 2: Independent assessment of FEP+ performance in comparison to other affinity prediction methods

Community-wide blinded prediction challenge using datasets of one protein and multiple ligands with measured affinity data and co-crystal structures



Important opportunity to independently validate and compare a commercial protocol to other quantitative affinity prediction methods

Test influence of time constraints in close to real-life drug design setting

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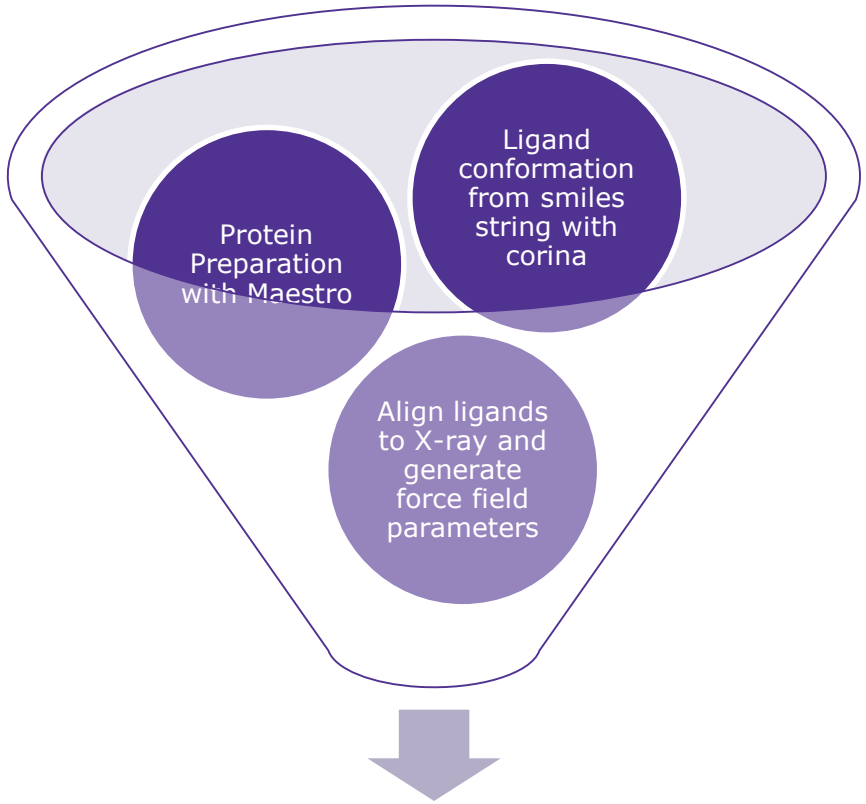
Protocol



Run Schrödinger FEP+ calculations on in-house GPU cluster with default settings

(5ns per window)

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
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Accurate and Reliable Prediction of Relative Ligand Binding Potency in Prospective Drug Discovery by Way of a Modern Free-Energy Calculation Protocol and Force Field

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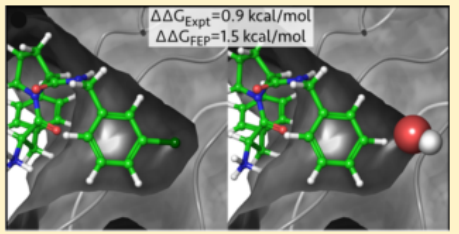
Supporting Information

ABSTRACT: Designing tight-binding ligands is a primary objective of small-molecule drug discovery. Over the past few decades, free-energy calculations have benefited from improved force fields and sampling algorithms, as well as the advent of low-cost parallel computing. However, it has proven to be challenging to reliably achieve the level of accuracy that would be needed to guide lead optimization (~5× in binding affinity) for a wide range of ligands and protein targets. Not surprisingly, widespread commercial application of free-energy simulations has been limited due to the lack of large-scale validation coupled with the technical challenges traditionally associated with running these types of calculations. Here, we report an approach that achieves an unprecedented level of accuracy across a broad range of target classes and ligands, with retrospective results encompassing 200 ligands and a wide variety of chemical perturbations, many of which involve significant changes in ligand chemical structures. In addition, we have applied the method in prospective drug discovery projects and found a significant improvement in the quality of the compounds synthesized that have been predicted to be potent. Compounds predicted to be potent by this approach have a substantial reduction in false positives relative to compounds synthesized on the basis of other computational or medicinal chemistry approaches. Furthermore, the results are consistent with those obtained from our retrospective studies, demonstrating the robustness and broad range of applicability of this approach, which can be used to drive decisions in lead optimization.



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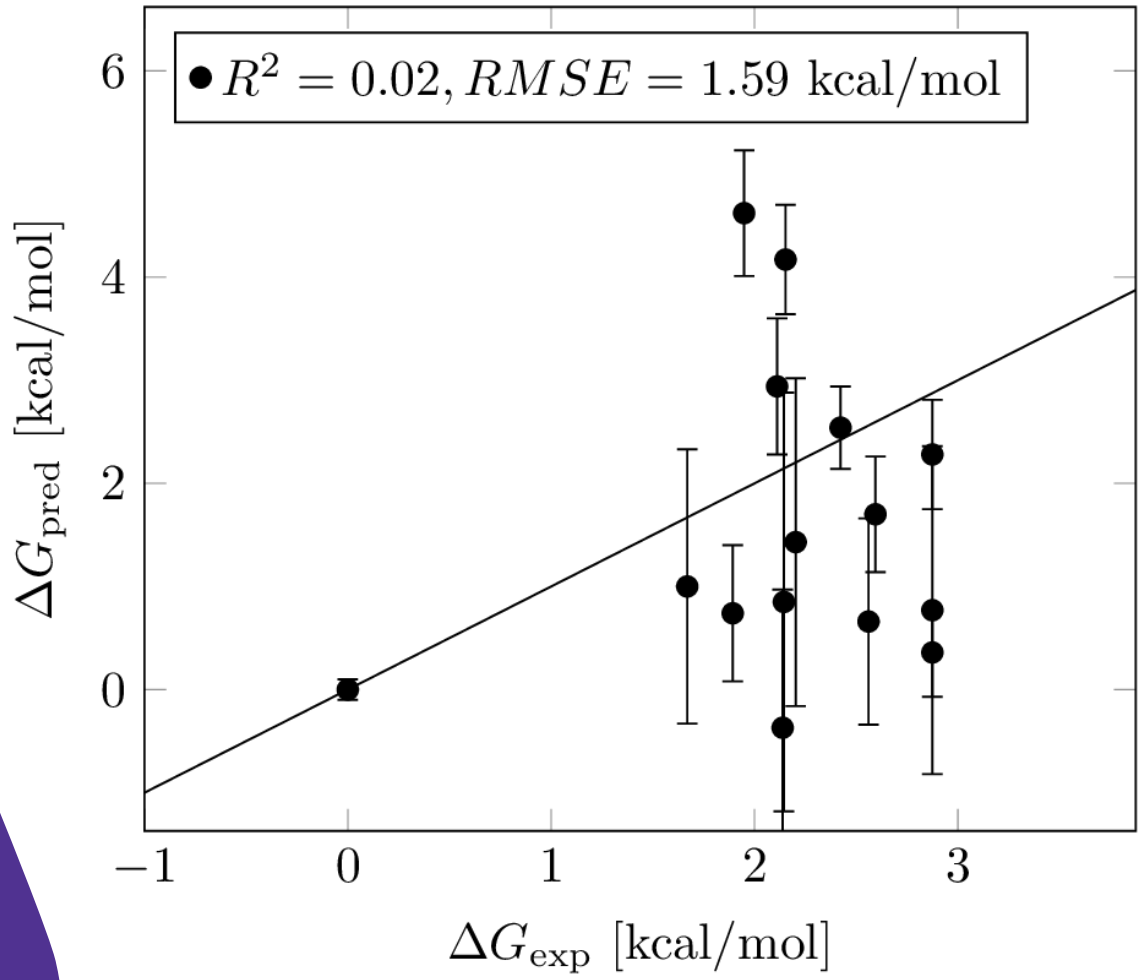
Results: Free Energy Prediction Set 1

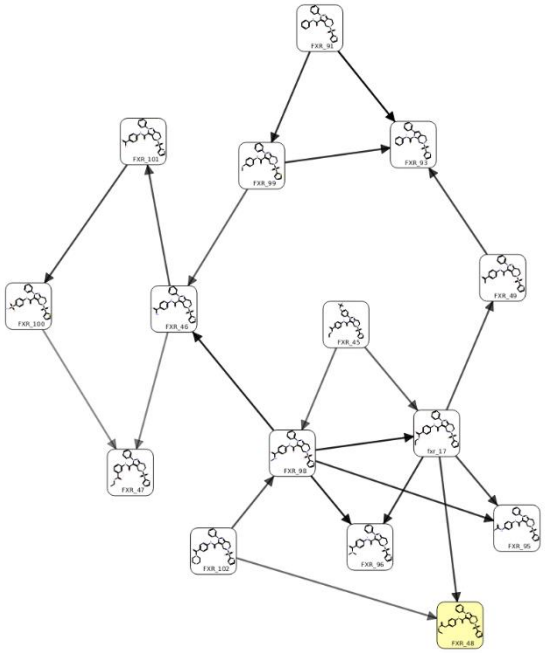


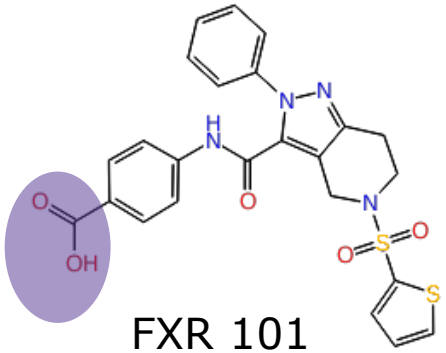
Reference X-ray: 1hqmf

All ligands were assumed to be not charged to fit them into one FEP map (no charge change).

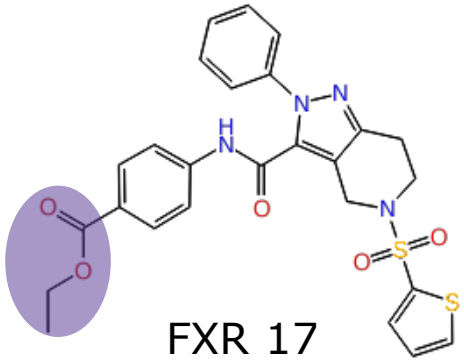
Expected R2 for ligand set: 0.19+-0.17

Predicted correct sign of ΔΔ G : 13 out of 14



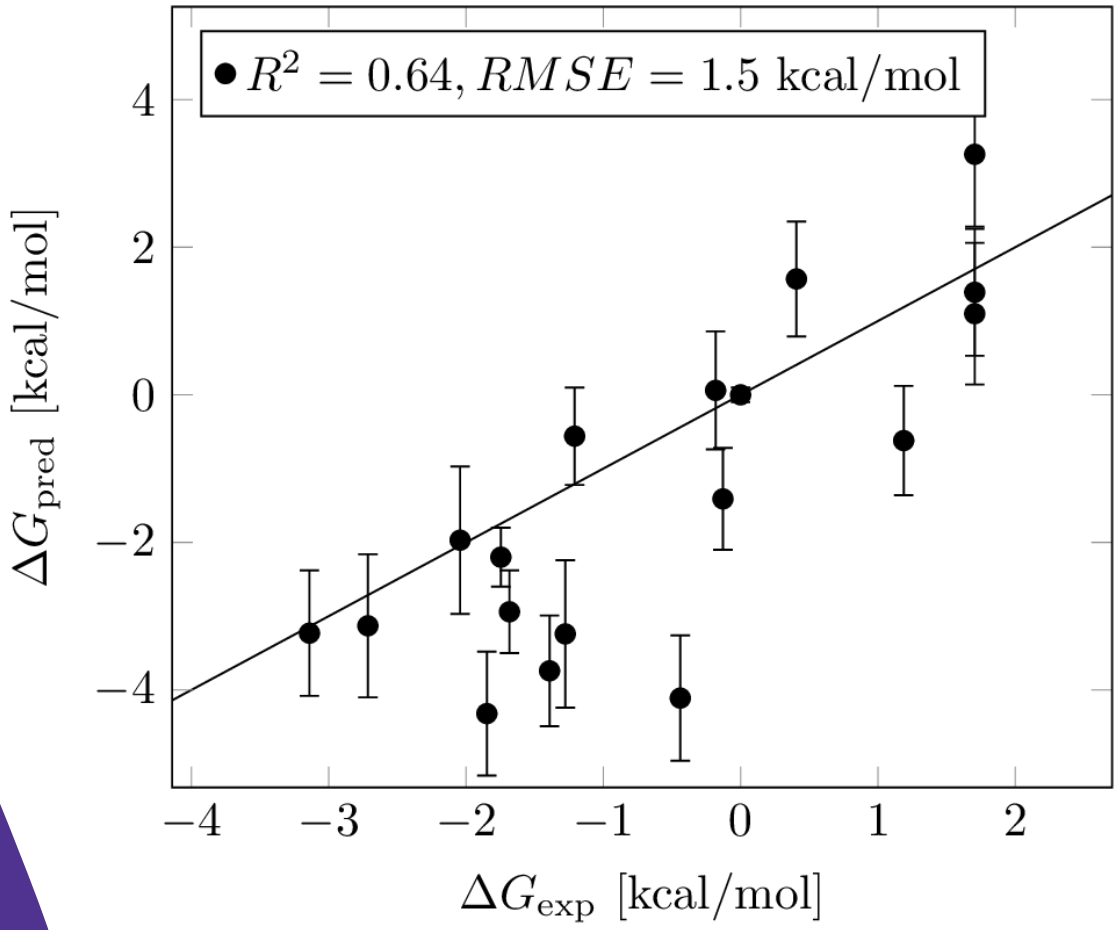


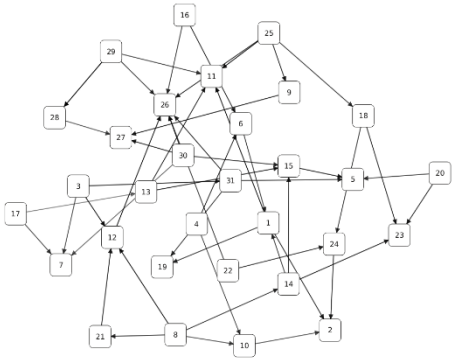
FXR 101



FXR 17

Results: Free Energy Prediction Set 2



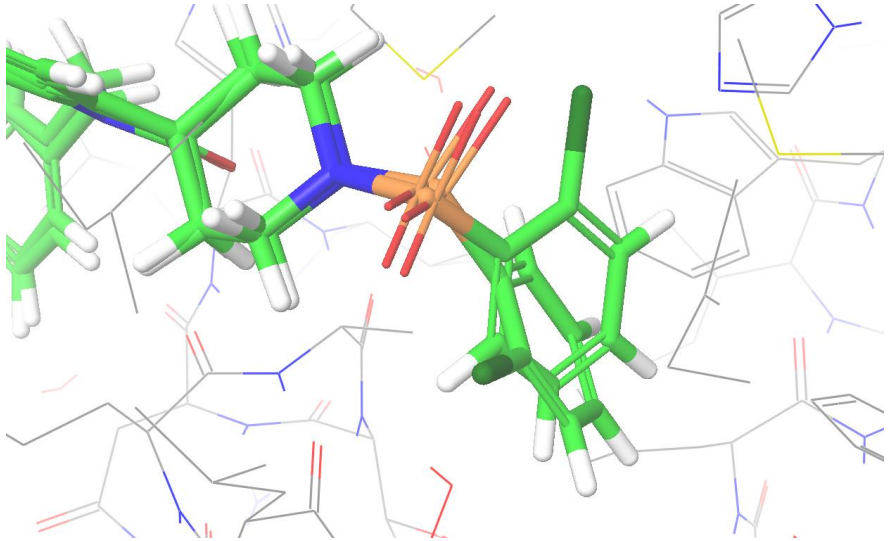


Reference X-ray: 1kjyp

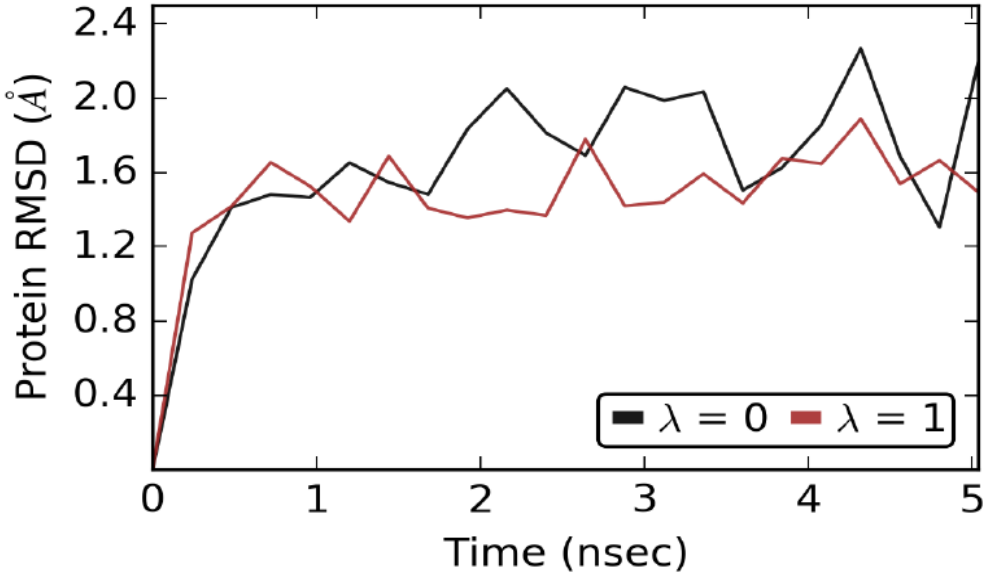
All ligands were assumed to be not charged.

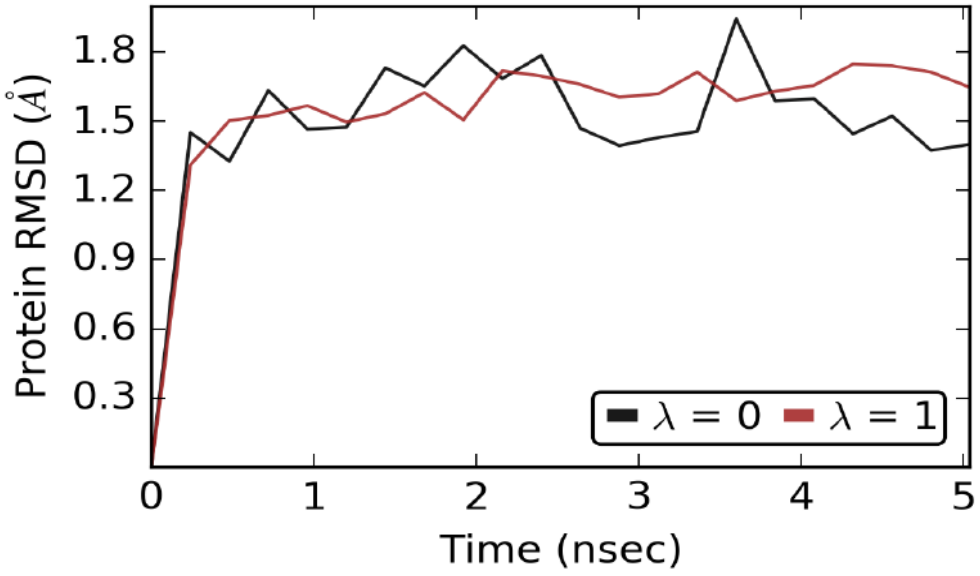
Both binding modes observed in reference X-ray were considered (if applicable). The more favorable free energy change was considered for the final prediction.

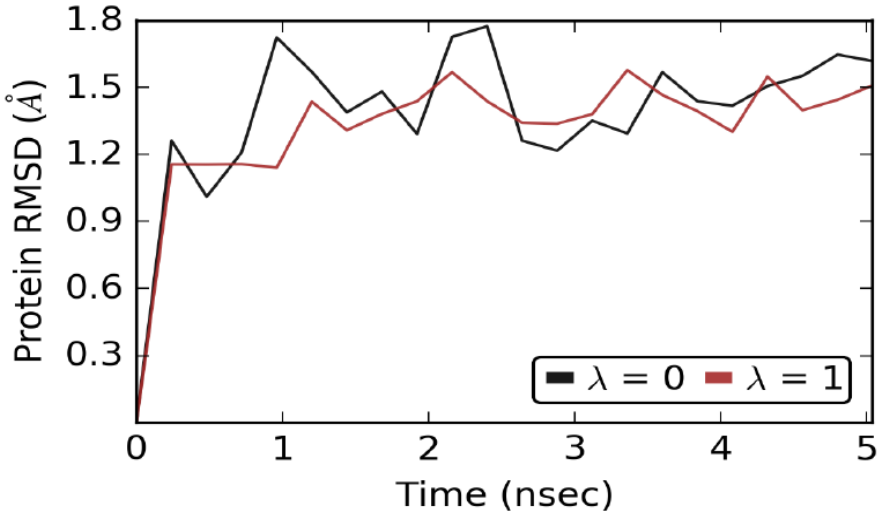
Expected R2: 0.55 +- 0.14



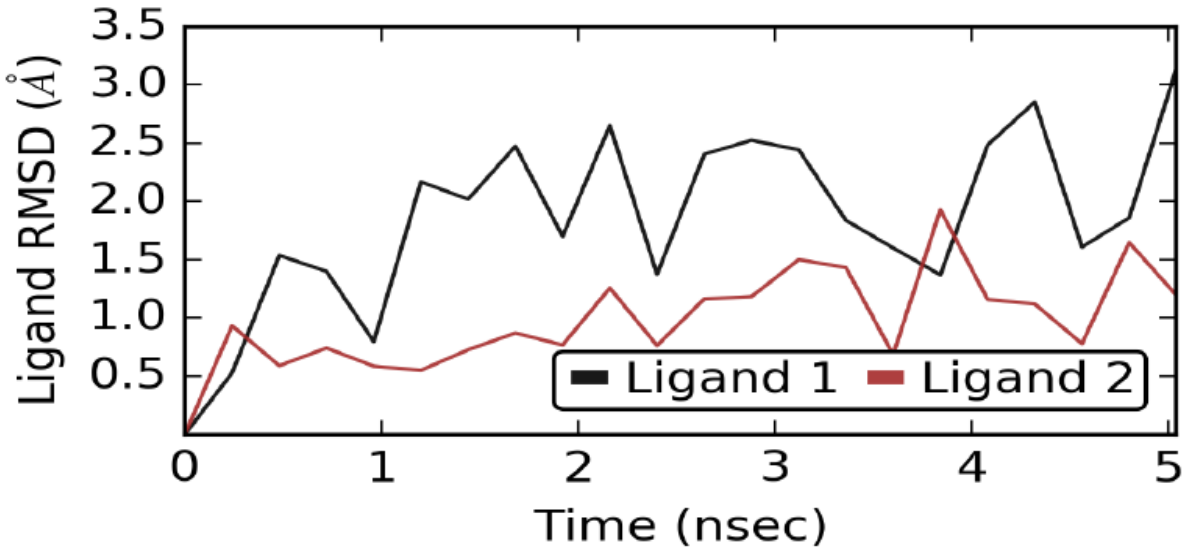
Quality of simulations: stable protein conformation

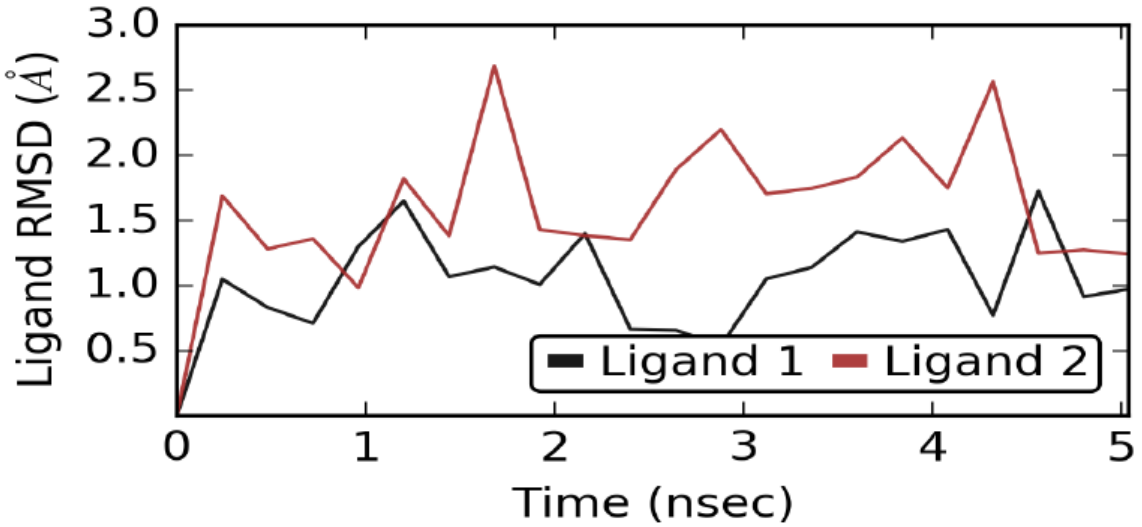


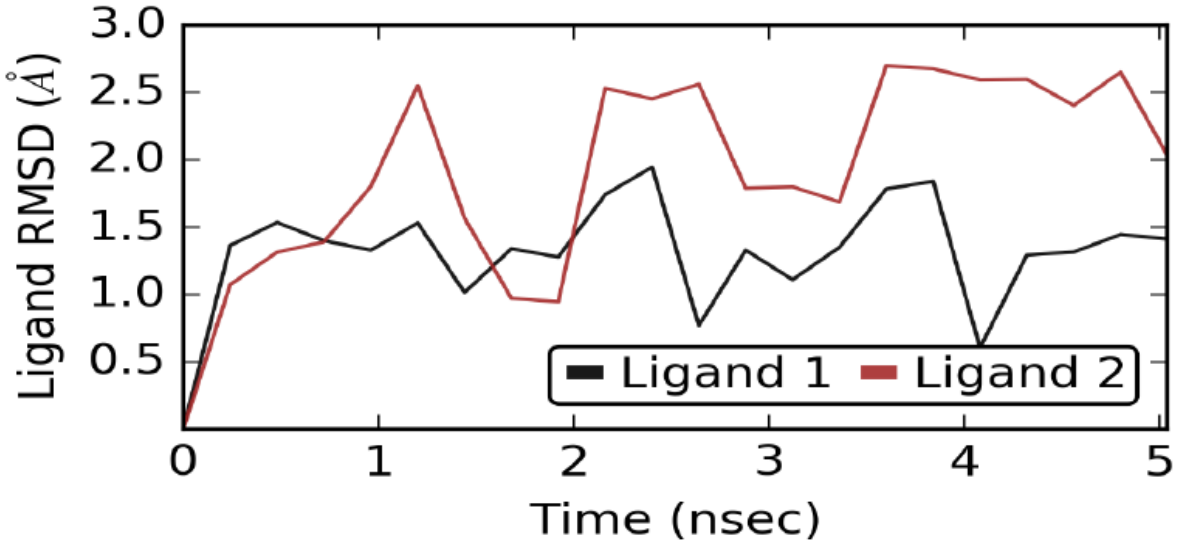




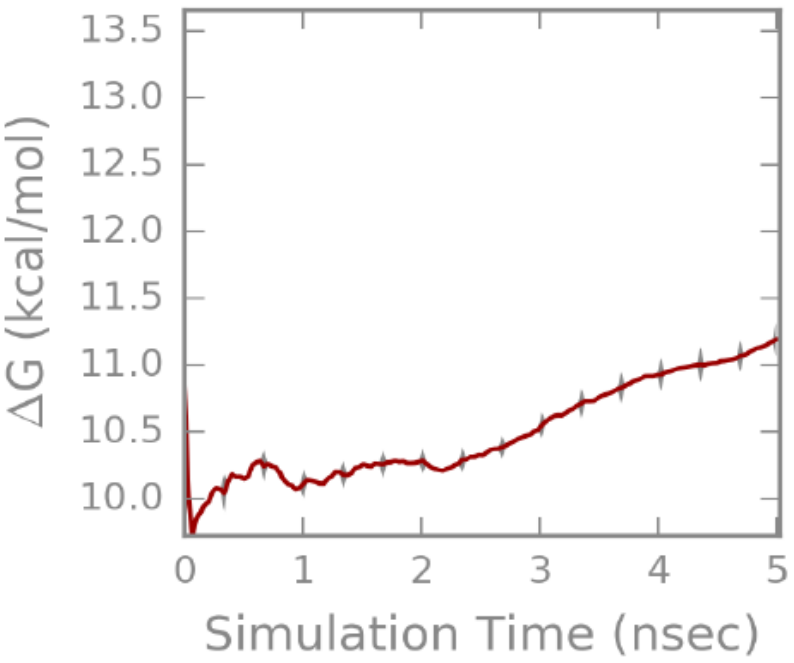
Quality of simulations: larger-than-usual changes in ligand conformation

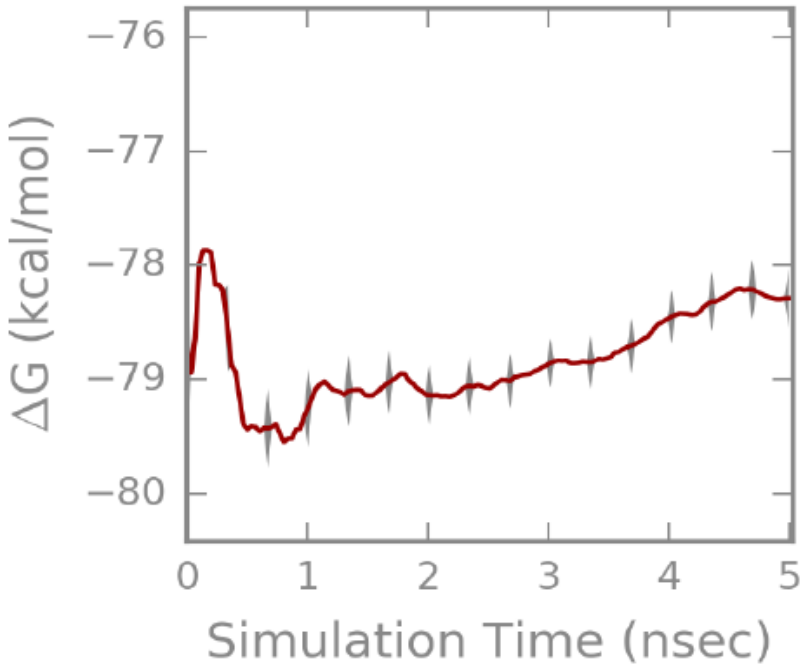


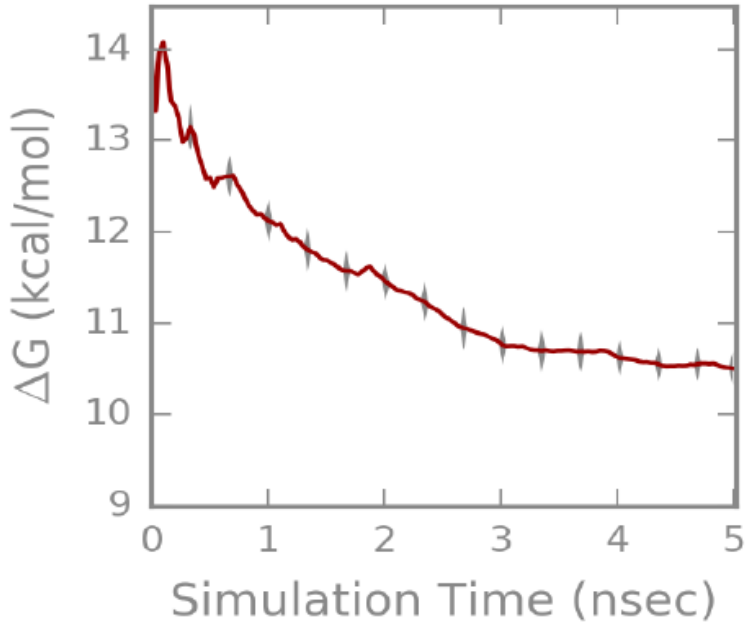




Quality of simulations: protein-ligand complex simulations partly not converged







Simulations in solvent appear well converged.

Extend simulation time beyond 5ns per window to improve sampling.

Conclusion

Current protocol for setting up and running FEP calculations with Schrödinger FEP+ at Merck gives results comparable to state-of-the-art affinity prediction methods.

FEP+ is a robust technique for quantitative affinity prediction.

FEP calculations can be performed to sufficient accuracy even under the time and resources constraints in an industry setting.

More sampling is needed to achieve higher accuracy.

D3R results give confidence to apply FEP to more targets and larger library screens (several hundred compounds).

Acknowledgements

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