Comprehensively Benchmarking AQFEP: Assessing the Accuracy and Generalizability Across Diverse Chemical Space

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AFEP for Virtual Screening

- **Free Energy Perturbation (FEP)** calculates free energy differences (ΔG) using simulations with nonphysical intermediates and can predict binding affinities (K_d).
- AFEP, Absolute FEP, can predict ΔGs of diverse ligands, enabling virtual screening campaigns for hit identification and lead optimization *in silico*.
- However, variation within druggable chemical space poses a significant challenge, making it difficult for any single computational tool to consistently achieve accurate predictions.
- This research investigates the applicability of AQFEP, an absolute FEP method, across a broad range of biochemical targets, and employs Bayesian Optimization to refine and adapt its parameters for improved accuracy.

The AQFEP Method

- Employing a double decoupling approach, AQFEP provides more accurate binding affinity predictions compared to conventional docking scoring methods.
- AQFEP is exceptionally fast, achieving predictions in just 1-2 hours per ligand on a single T4 GPU.
- AQFEP's speed facilitates its application in virtual screening of extensive ligand libraries, ranging from thousands to millions.

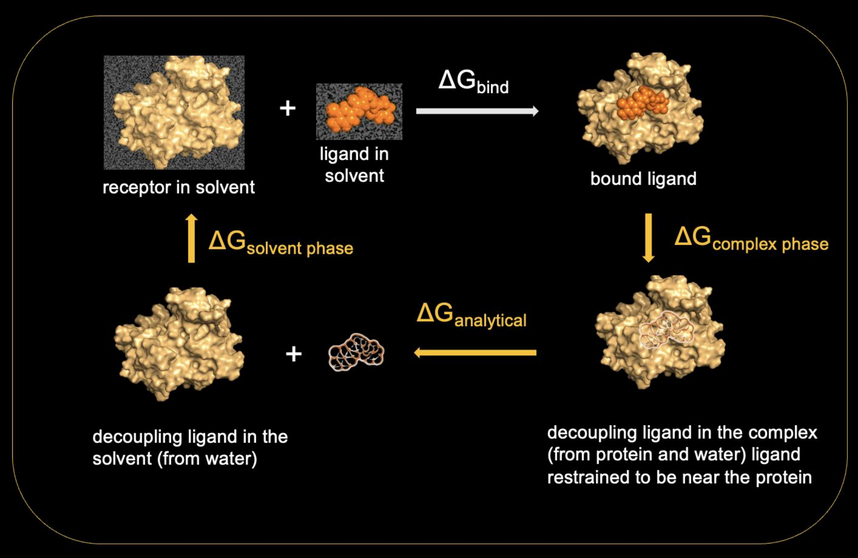
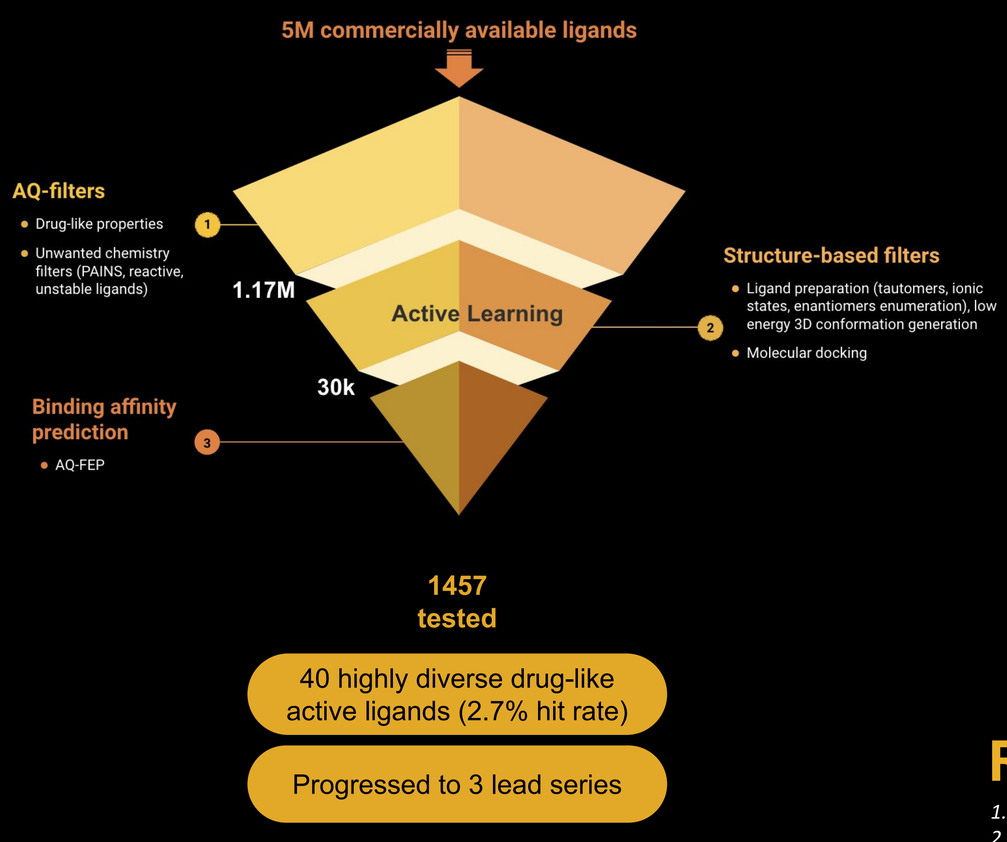


Figure 1: Thermodynamic cycle utilized by AQFEP to compute binding energy predictions.

Prospective Virtual Screening AQFEP Example

- Shown below is the virtual screening pipeline followed for an active collaboration focused on identifying potential binders for an undruggable oncology target.
- A rigorous filtering process, incorporating AQ-filters, Active Learning, and AQFEP calculations, was employed to refine the initial dataset from 5M commercially available ligands to 1457 promising ligands.
- The virtual screen achieved a 2.7% hit rate with 3 ligands advancing to lead series.



Application of AQFEP to Hit-to-Lead Optimization with GLP1R

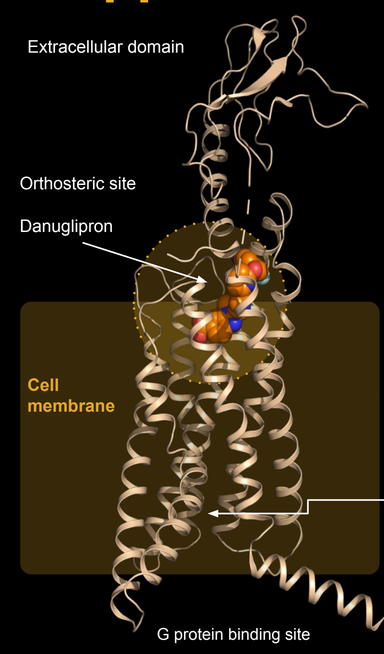


Figure 4: Structure of the GLP1R in complex with dangulipron, showing the ligand's positioning within the receptor's transmembrane domain.

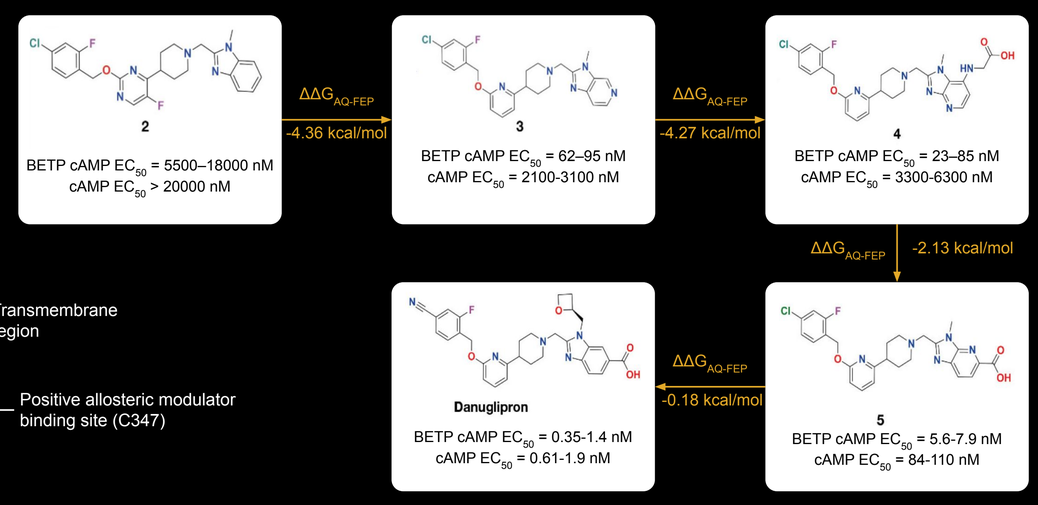


Figure 5: Flow chart summarizing the binding characteristics of Danuglipron derivatives to GLP1R. Each molecule is accompanied by measured EC_{50} values (BETP cAMP and cAMP) as well as calculated $\Delta\Delta G_{AQFEP}$ values between related molecules.

Key Takeaways

- AQFEP reliably predicts the relative functional activity of GLP1R agonists, aligning with experimental data.
- AQFEP effectively recapitulates Pfizer's published hit-to-lead development, showcasing its hit-to-lead optimization capabilities.

Refining Parameters for Improved Accuracy Utilizing Bayesian Optimization

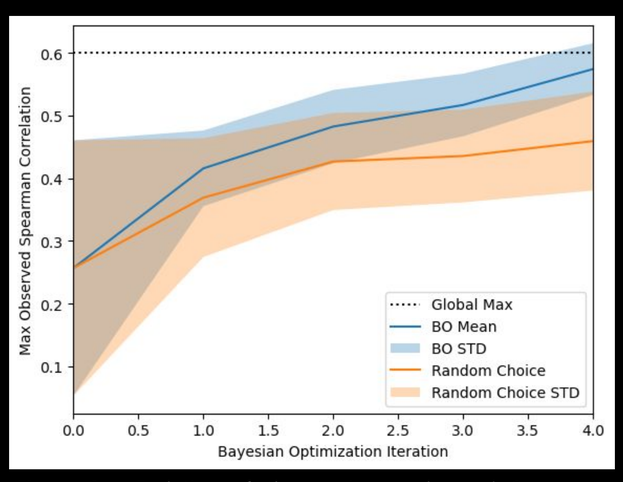


Figure 6: Evolution of the maximum observed Spearman correlation coefficient during Bayesian optimization of the TYK2 system, demonstrating the convergence towards higher correlation values.

What is Bayesian Optimization?

- Bayesian Optimization minimizes costly function evaluations by building a probabilistic model to guide the search for optimal solutions.
- It balances exploring new possibilities with exploiting promising areas, using an acquisition function to decide where to sample next.
- Ideal for complex problems where the objective function is unknown or expensive to evaluate, such as multi parameter tuning for AQFEP.

System	Spearman Rank Correlation (Default Parameters)	Spearman Rank Correlation (Optimized Parameters)
TYK2	0.14	0.60
EGFR	0.23	0.43
PTP1B	0.32	0.43
CRBN	0.43	0.70

Table 1: The table displays the Spearman rank correlation (ρ) values, used to assess the degree of correlation between calculated and experimental binding energies for three systems tested. The two Spearman rank correlation coefficients reported for each system indicate the ranking of calculated binding energies with default and optimized parameters.

Key Takeaway: Bayesian Optimization effectively addresses the challenge of multi-parameter optimization for FEP calculations. By predicting optimal, system-specific settings for AQFEP, this approach yields substantial improvements, with Spearman Rank Correlations demonstrating up to 4-fold enhancement.

Summary & Conclusions

- **Diverse systems pose a challenge:** Correctly predicting binding free energies across the diverse biochemical landscape remains difficult for generalizable computational tools. Robust, adaptable methods are needed to address the unique complexities of different systems.
- **AQFEP shows target breadth:** AQFEP accurately ranks ligands in a variety of retrospective studies, including challenging cases like molecular glues and complex targets such as GLP1R. This underscores its versatility and potential for broader applications in drug discovery and development.
- **Bayesian Optimization for tailored parameters:** Optimal FEP parameters can vary significantly across systems, impacting the accuracy of predictions. Bayesian Optimization offers an efficient solution by systematically exploring the parameter space and identifying ideal combinations for each specific system. This tailored approach maximizes AQFEP's performance and ensures reliable results across diverse targets.

References

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