Scaling Binding Affinity Prediction with Cofolding and Free Energy Calculations: Application to E3 Ligase Modulators

Ly Le[#], Alex Brueckner[#], Benjamin Shields[#], Jordan Crivelli-Decker[#], Andrea Bortolato[#]

[#]SandboxAQ, Palo Alto, California, USA

Introduction to 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, facilitates its application in virtual screening of extensive ligand libraries, ranging from thousands to millions.

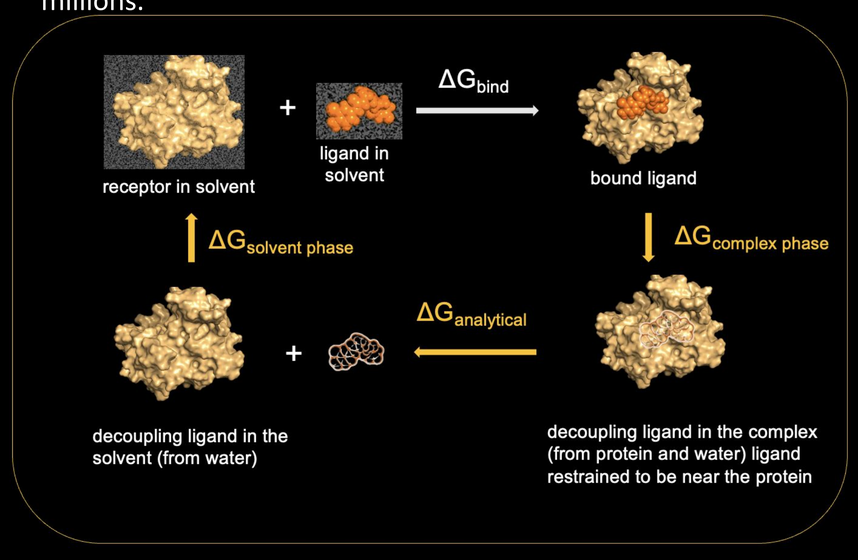


Figure 1: Thermodynamic cycle utilized by AQFEP to compute binding energy predictions.

AQFEP Enables Use of Data Driven Surrogate to Guide Search

- Standard VS workflows have a primary screen of molecular docking, but this is poorly correlated with potency [3]
- Instead, we use a bayesian optimization strategy combined with machine learning surrogate to approximate AQFEP function [4,5]
- Select compounds to calculate AQFEP on based on surrogate model predictions

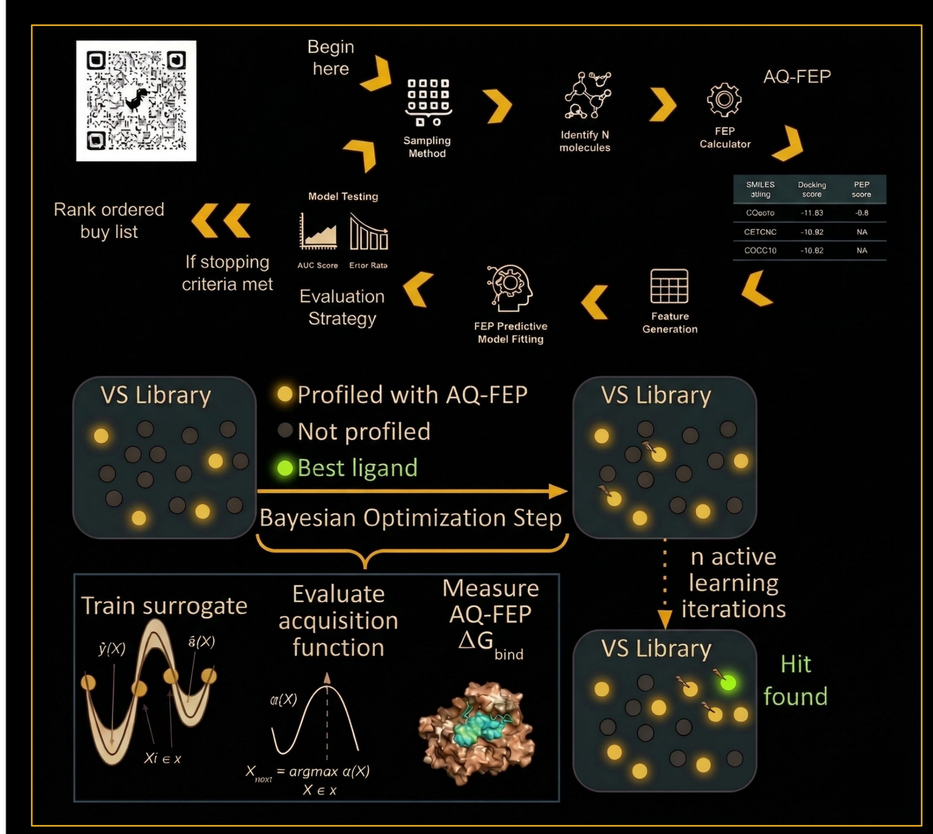
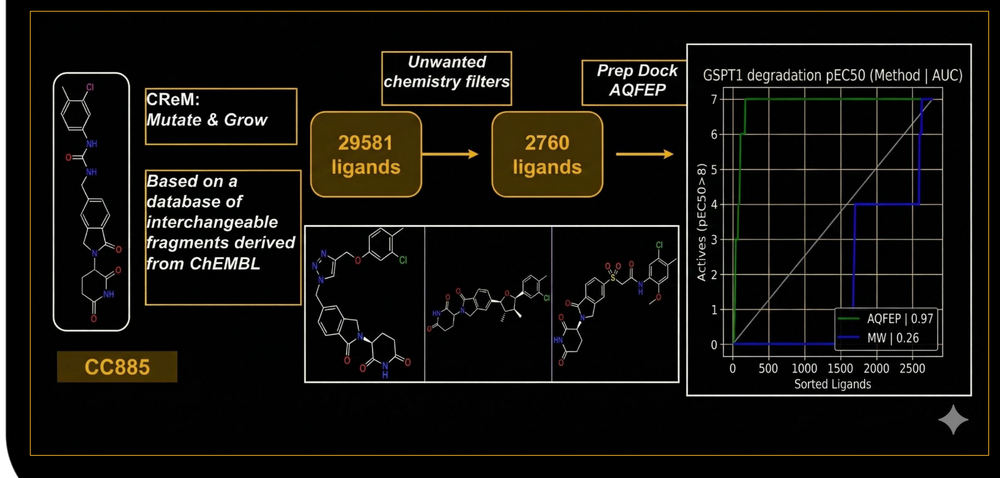


Figure 2: Machine learning guided AQFEP process

Hit expansion and Retrospective example on molecular glues



Overcome Structural Limitations: Physics-Informed AI

- **The Problem:** Initial ternary complex predictions failed due to biologically irrelevant and flexible residues in intrinsically disordered regions
- **The Solution:** Algorithmic truncation of low-confidence regions
- **The Result:**
  - Near-perfect alignment of the ternary complex to the experimental structure (7PI4)
  - VHL binding mode preserved and PROTAC trajectory corrected
  - FAK aligns correctly without additional restraints

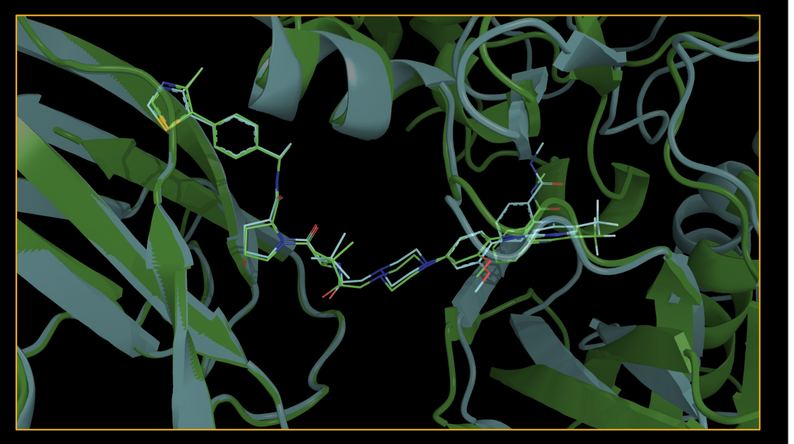
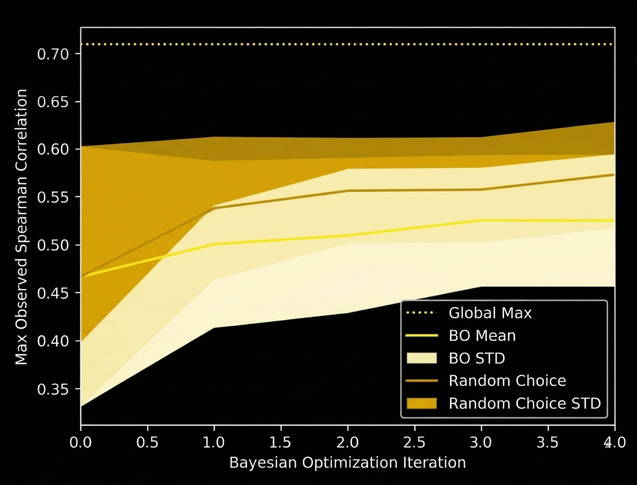


Figure 3:. Superimposed cofolding and experimental structures (7PI4)

Key Takeaways: System definition matters as much as the algorithm. Our platform diagnoses and corrects for structural interference.

Bayesian Optimization in E3 systems



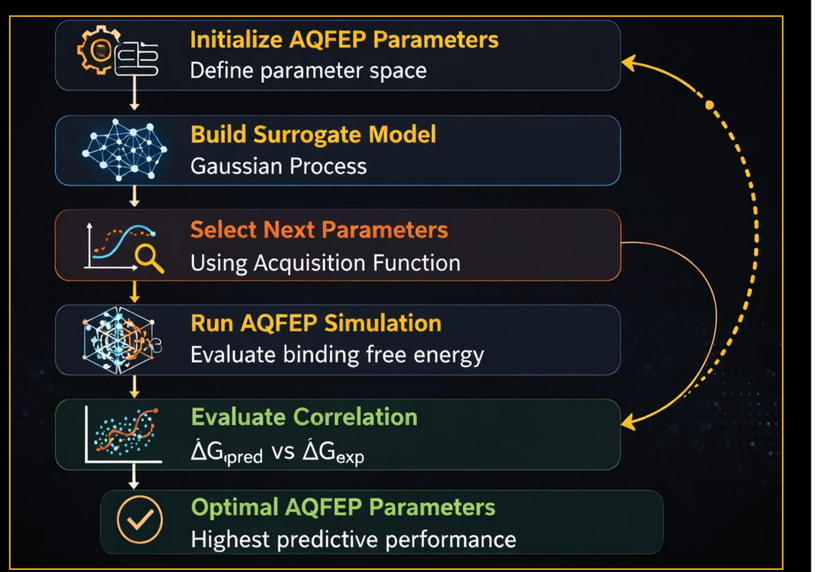


Figure 6: Evolution of the maximum observed Spearman correlation coefficient during Bayesian optimization of the CRBN system

System	Spearman Rank Correlation (Default Parameters)	Spearman Rank Correlation (Optimized Parameters)
CRBN	0.41	0.70
CRBN-AIOLOS	0.1	0.32
CRBN-GSPT1	0.56	0.61

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

- AQFEP provides rigorous and efficient binding affinity predictions suitable for large-scale screening.
- Integration of physics-based simulations with AI enables scalable exploration of chemical space and improved ligand prioritization.
- Bayesian optimization enhances system-specific performance, significantly improving correlation with experimental data.
- Prospective virtual screening demonstrates strong predictive power, effectively narrowing large libraries to high-quality candidates for challenging targets, highlighting its potential in drug discovery.

References

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