Unraveling GPCR Complexity: A Hybrid Machine Learning and Physics-Based Approach for GPCR Profiling

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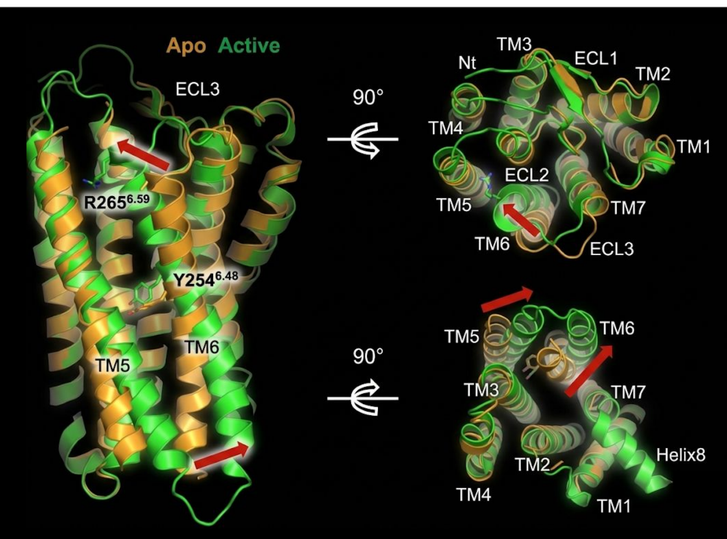
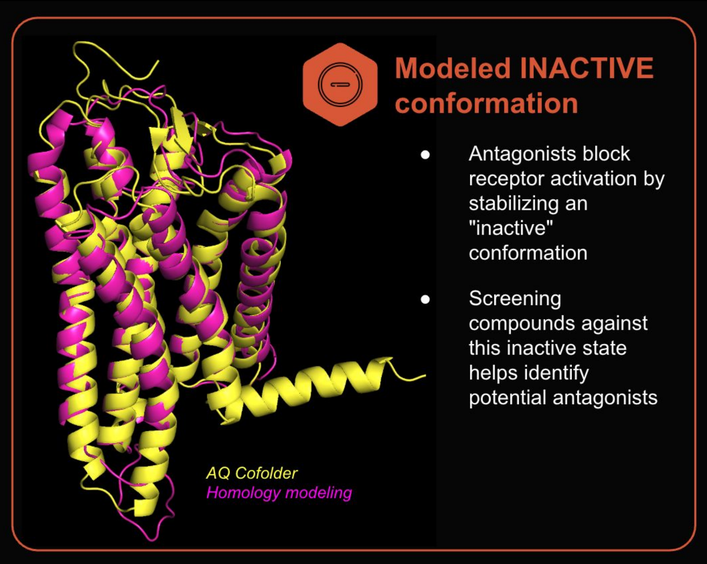
From GPCR Challenges to Mechanism-Aware In-Silico Solutions

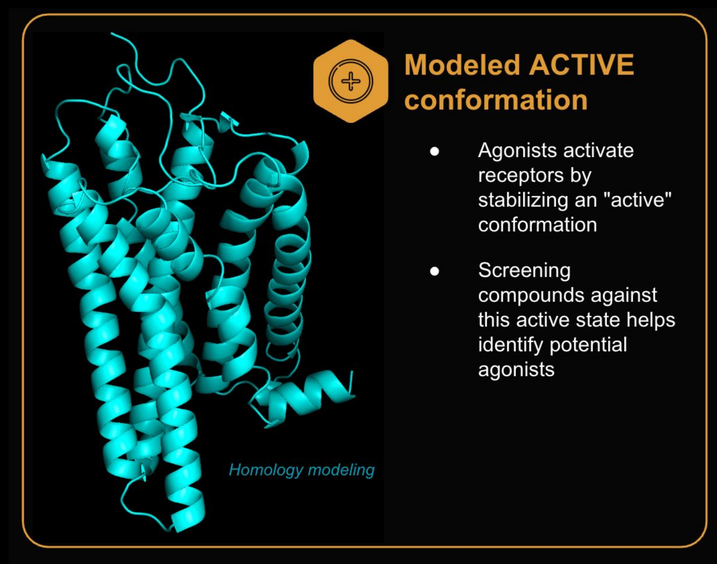
- The Challenge: Predicting GPCR Mechanism of Action (MoA) is challenging because distinguishing agonists from antagonists requires capturing state-dependent energetics rather than binding affinity alone.
- The Approach: We integrated ML-based affinity prediction with Absolute Free Energy Perturbation (AQFEP), utilizing multi-state receptor models to capture the dynamic microswitch rearrangements essential for signaling.
- The Results: Evaluation on proprietary datasets demonstrates that this hybrid workflow enables scalable ligand prioritization and clear functional characterization via free energy differences.This accelerates drug discovery through faster, more confident decisions and reduces experimental cost.



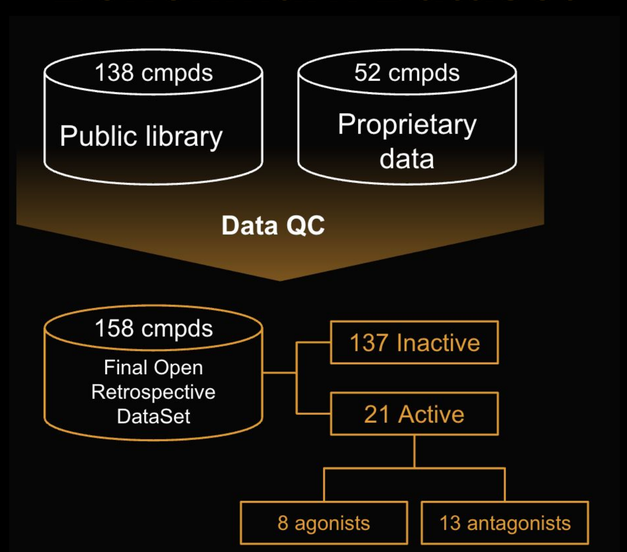
Apo to active transition: Intracellular opening (TM5–TM6 outward, TM7 inward). Coupled with extracellular pocket contraction (TM1–TM2–TM7 tightening around the ligand-binding site). Microswitch rearrangements that stabilize a G-protein–binding conformation.[1]

Modeled GPCR ACTIVE & INACTIVE STATES

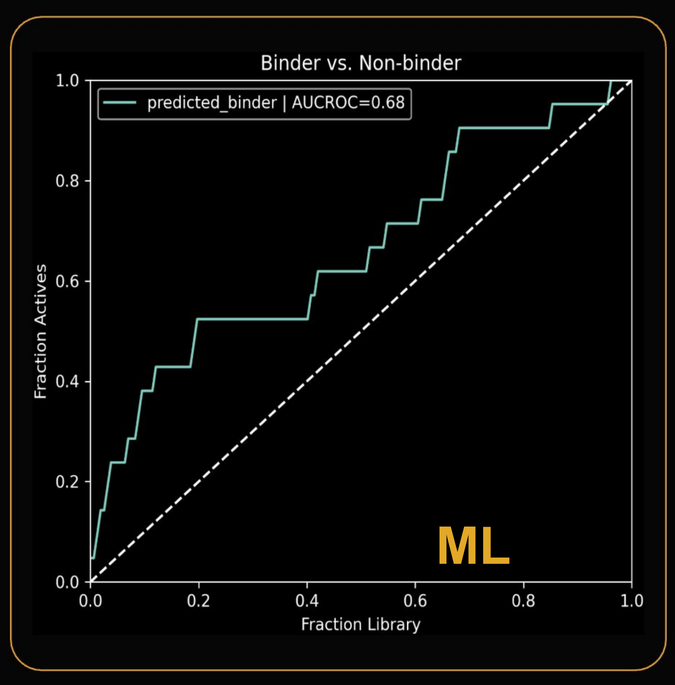


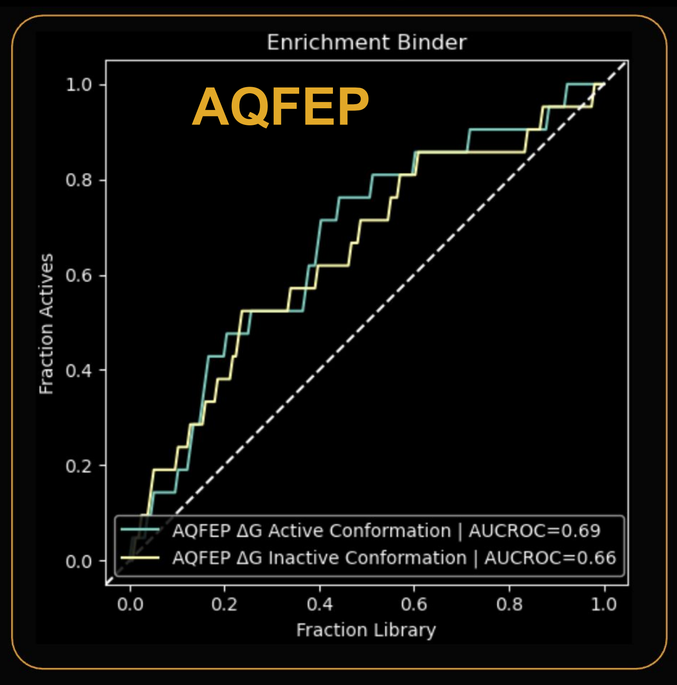


Benchmark Dataset



Binder vs. Non-Binder Classification Using ML and Physics-based Methods





Method	Frac Lib	Accuracy	Sensitivity	Specificity
ML	0.22	0.79	0.52	0.83
AQFEP	0.44	0.63	**0.76**	0.61

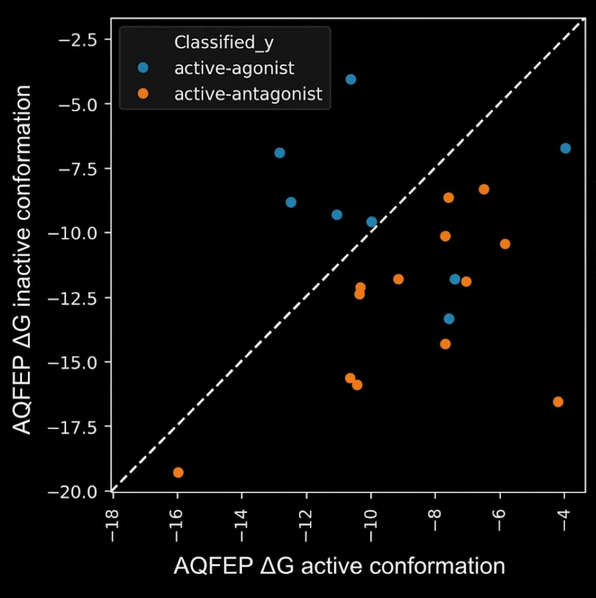
ML-Based Method

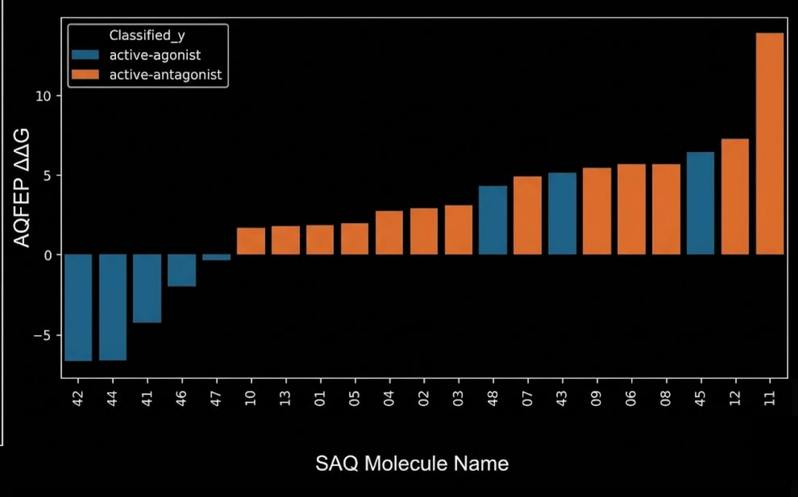
- ~22% screening achieves balanced performance (79% accuracy, 83% specificity), enabling efficient prioritization.
- Consistently classifies binders vs. non-binders across the dataset.

Physics-Based (AQFEP) Method 2

- ~44% screening increases sensitivity, improving discovery rate (~+24%) with manageable specificity trade-off.
- Enhances binder detection → higher overall discovery rate.

Mechanism of Action: Agonist vs. Antagonist Prediction





- ML and physics-based models demonstrated strong performance.
- AQFEP ΔΔG is a strong predictor, clearly separating agonists and antagonists.
- Perfect antagonist recall: ΔΔG > 0 reliably indicates antagonist behavior.
- Minor gaps remain: three agonists misclassified, highlighting room for improvement.

Summary

Binder vs. Non-Binder

- Selected GPCR retrospective successfully classified binders vs. non-binders.
- ML and physics-based models demonstrated strong performance.

Agonist vs. Antagonist

- AQFEP ΔΔG reliably predicts agonist vs. antagonist mechanisms.
- Future improvements include additional data and receptor modeling.

Scalable two-step screening
ML accelerates selection → AQFEP refines accuracy & mechanism

References:

1. *Choi, C., Bae, J., Kim, S. et al. Understanding the molecular mechanisms of odorant binding and activation of the human OR52 family. Nat Commun 14, 8105 (2023).*
2. *Crivelli-Decker, J. E., Beckwith, Z., Tom, G., Le, L., Khuttan, S., Salomon-Ferrer, R., Beall, J., Gómez-Bombarelli, R. & Bortolato, A. Machine Learning Guided AQFEP: A Fast and Efficient Absolute Free Energy Perturbation Solution for Virtual Screening. Molecular Mechanics (2024).*