Accurate and Scalable Free Energy Calculations via Nonequilibrium Chimeric Switching (NEX)

Dominic Rufa[#], Mary Pitman[#], Amogh Sood[#], Lee Huntington[#]

[#]SandboxAQ, Palo Alto, California, USA

Motivations and Objectives

- **Bottleneck:** Accurate and efficient prediction of protein-ligand binding free energies remains a barrier in hit-to-lead and lead optimization drug discovery.
- **Solution:** NEX provides an accurate and scalable free energy framework.
- **Broad Applicability:** Amenable to diverse chemical space and complex transformations (e.g., scaffold hopping, ring-breaking, charge changes)
- **Forward-Compatible:** Seamless integration with machine-learned force fields (MLFFs) and enhanced sampling.

Methodology and Calibration

- Short, 100ps nonequilibrium switches[1] between the physical and nonphysical states are parallelized for scalability.

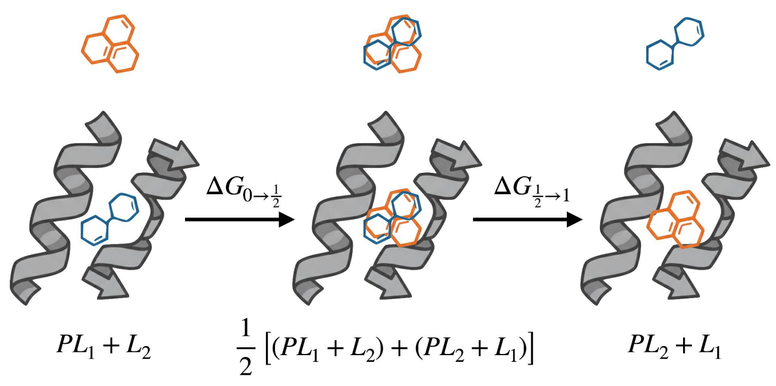

Figure 1. Schematic of a dual-topology NEX transformation.

- One possible realization of NEX, tested here, uses a dual-topology Alchemical Transfer Method (ATM) formulation[2,3], where ligands are translated between the binding pocket and the bulk solvent via a nonphysical intermediate (Figure 1).
- Routing nonequilibrium switches through nonphysical intermediates improves convergence over end-to-end switching (Figure 2).

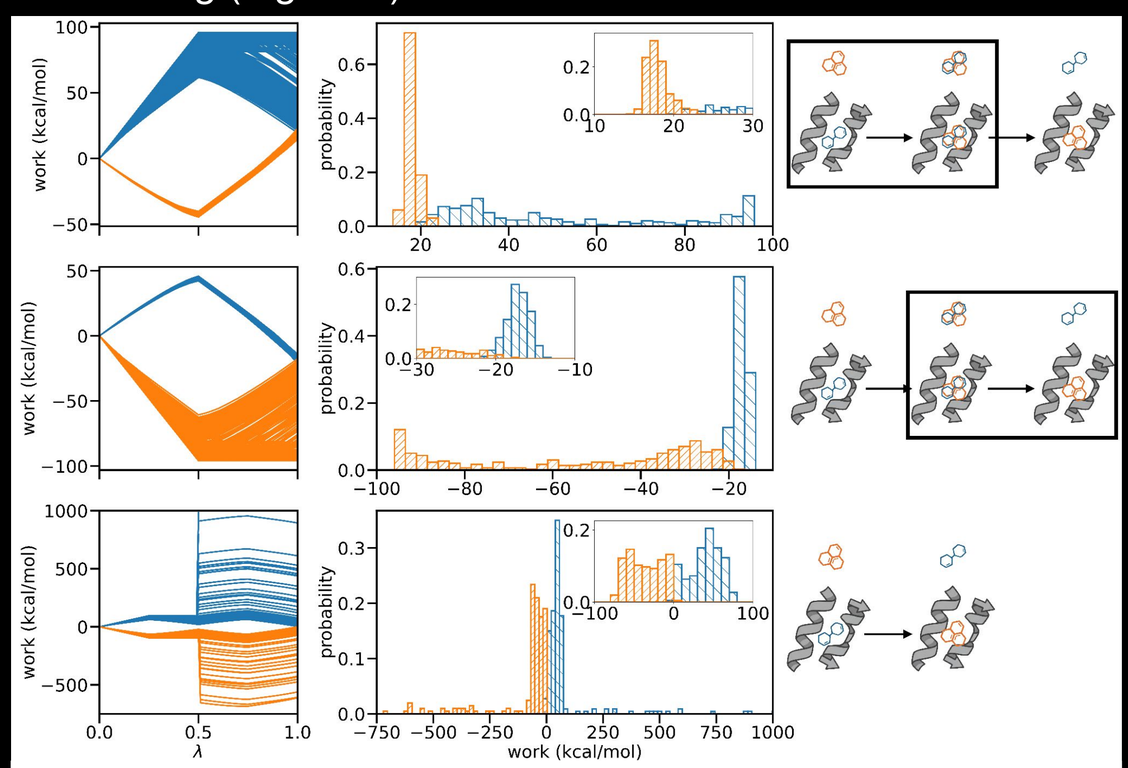

Figure 2. Forward (blue) and backward (orange) nonequilibrium work trajectories and distributions for a representative CDK2 transformation with (row 1, 2) and without (row 3) chimeric intermediate.

Competitive ΔΔG Predictions on Protein:Ligand Benchmarks

- NEX performs competitively across 6 well-studied protein:ligand benchmarks[4] with RMSEs ranging from 0.76 kcal/mol (JNK1) to 1.60 kcal/mol (p38) (Figure 3).

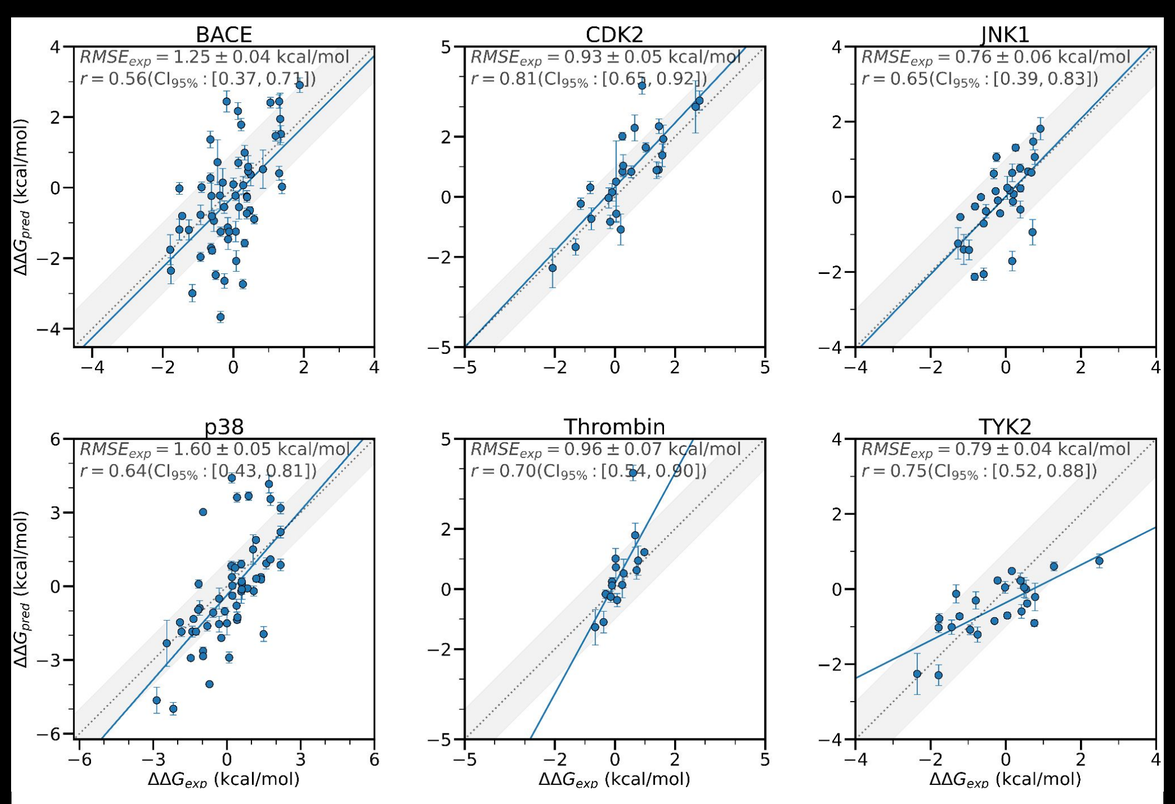

Figure 3. Predicted vs experimental relative binding free energies for six protein targets.

- NEX yields strong correlation on a challenging scaffold-hopping[5] set (BACE1) without protocol tuning (Figure 4).

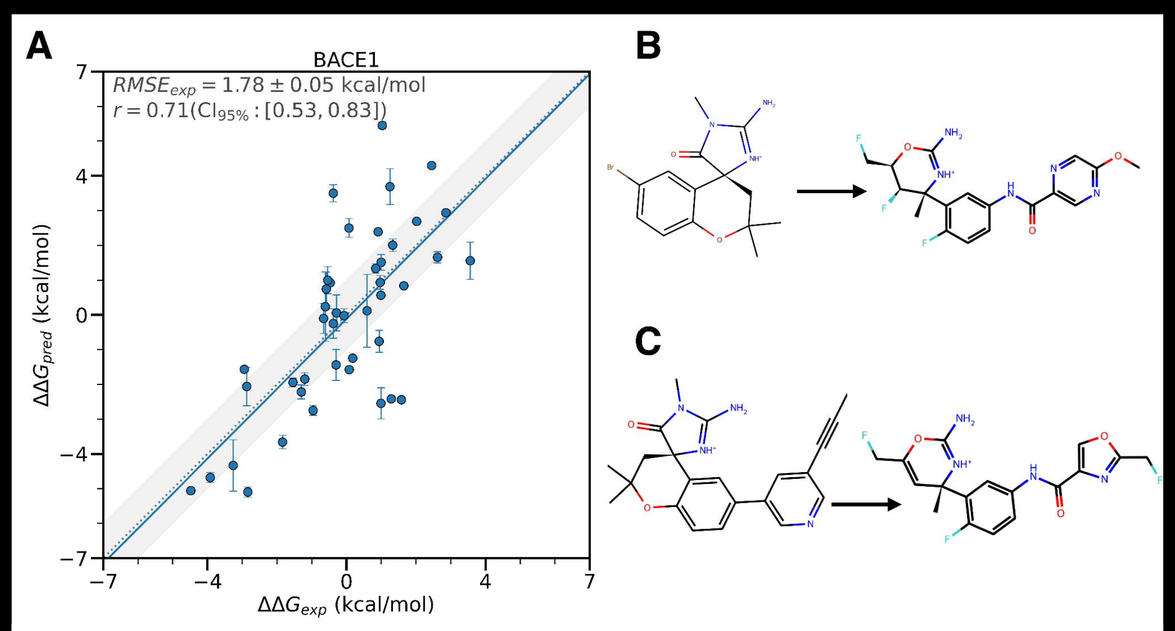

Figure 4. (A) Predicted vs. experimental free energies for 45 transformations. **(B, C)** Representative edges illustrating scaffold-hopping

Future Directions

- **Protocol Optimization:** Improving efficiency via protocol optimization and new rapid NEX innovations.
- **AI-Driven Sampling:** Accelerating calculations by consuming endpoint ensembles generated via deep learning emulators rather than MD simulations.
- **Machine-Learned Potentials:** Enhancing accuracy by deploying NEX with machine learning force fields (MLFFs).
- **Broader Applications:** Expanding to highly flexible, complex systems like peptides and biologics.

References

1. *Jarzynski, C. (1997). A nonequilibrium equality for free energy differences. Phys Rev Lett 78, 2690.*
2. *Wu, J. Z., et al. (2021). Alchemical Transfer Approach to Absolute Binding Free Energy Estimation. J. Chem. Theory Comput., 17(6), 3309–3319.*
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5. *Baumann, H. M., et al. (2023). Broadening the Scope of Binding Free Energy Calculations Using a Separated Topologies Approach. J. Chem. Theory Comput., 19(15), 5058–5076.*
6. *Pitman, M., et al. (2026). Nonequilibrium Chimeric Switching (NEX) Stabilizes Binding Free Energy Calculations Across Chemical Space. ChemRxiv. doi:10.26434/chemrxiv.15001585/v2*

It Takes Two to Tango: A software-suite of custom dual topology methods for binding free energy predictions

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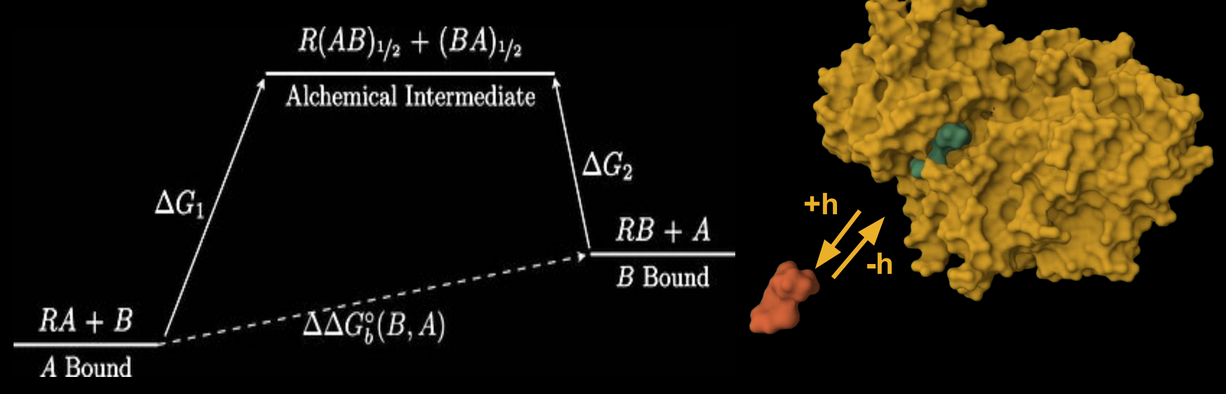

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Towards 1 click lead-optimization

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- We provide computational chemists with a one-click, cloud-native solution to run massive RBFE campaigns on distributed systems.
- We provide a developer friendly pythonic API for rapid feature deployment.
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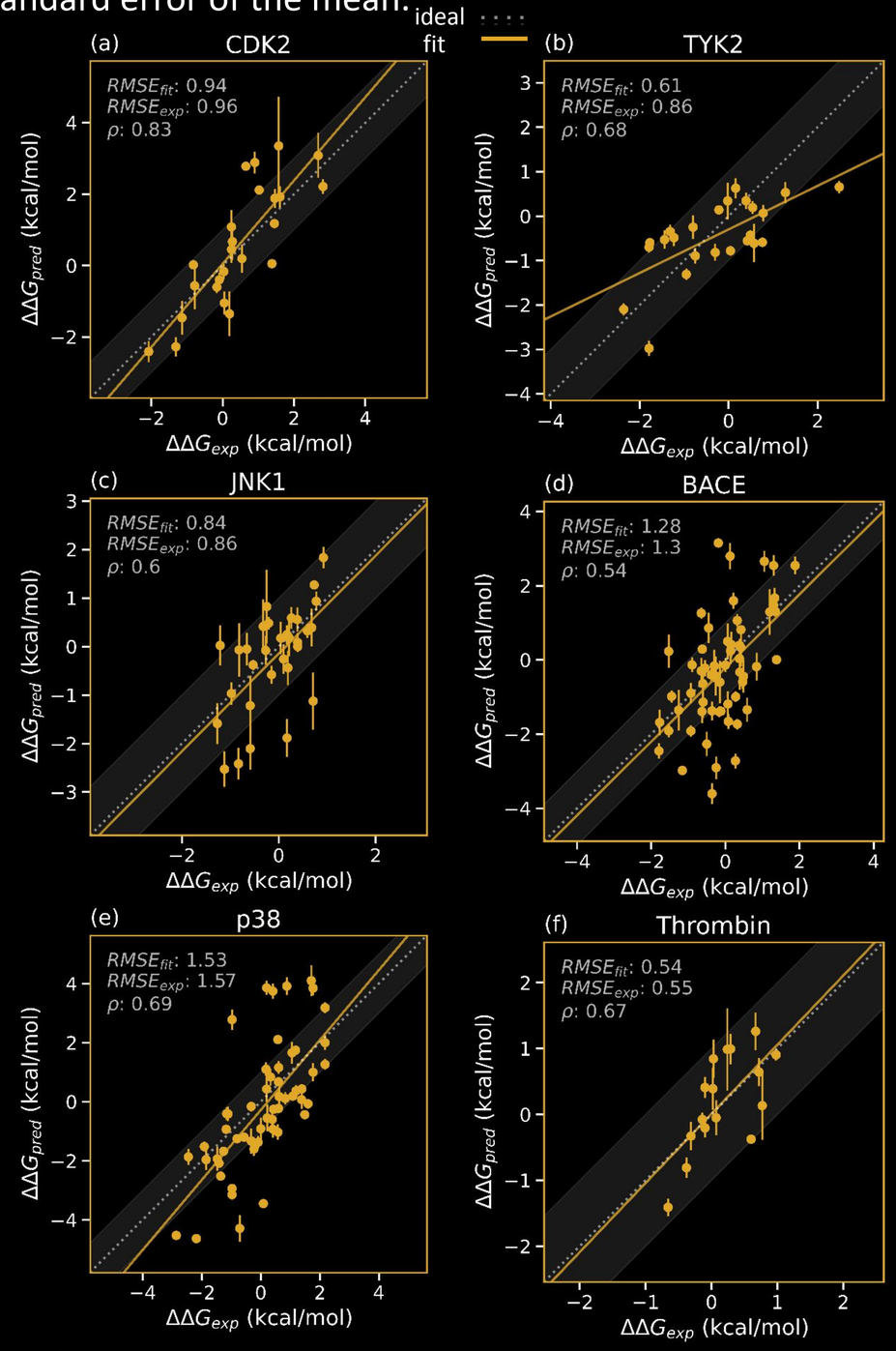

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BACE	0.54	0.99	0.42	1.2	0.61	0.80
p38	0.69	1.2	0.71	1.2	0.79	0.80
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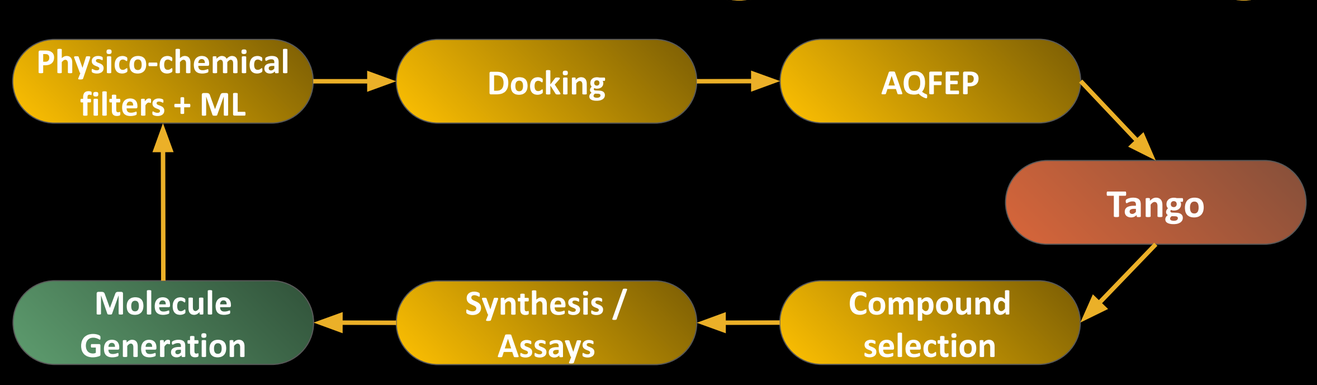

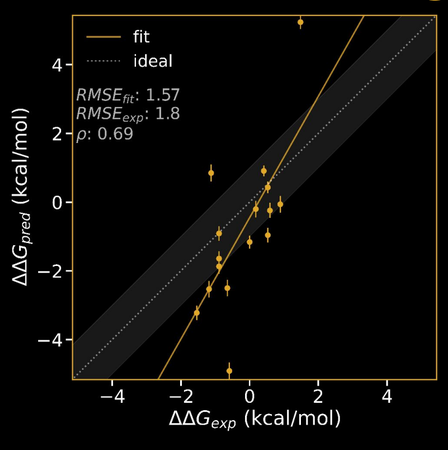

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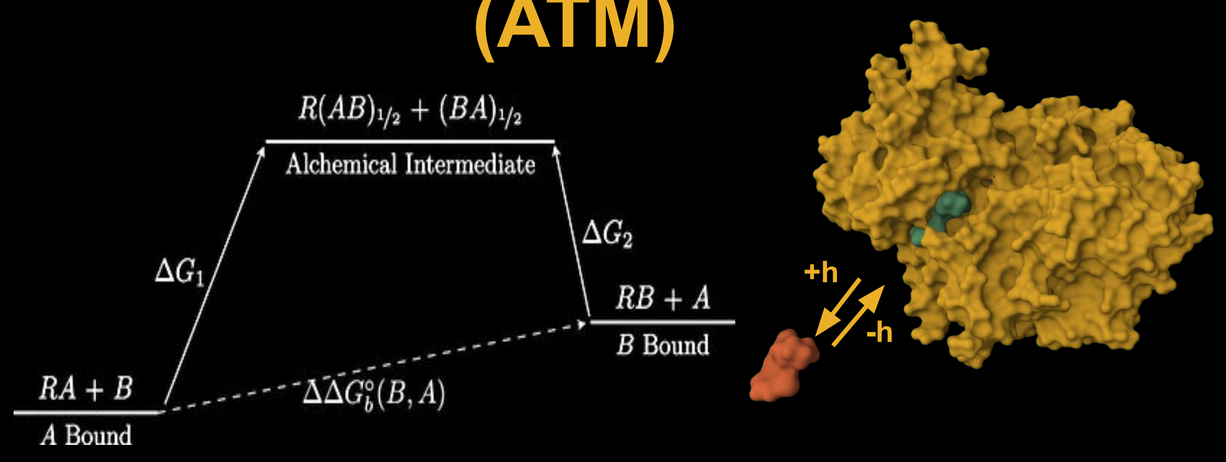

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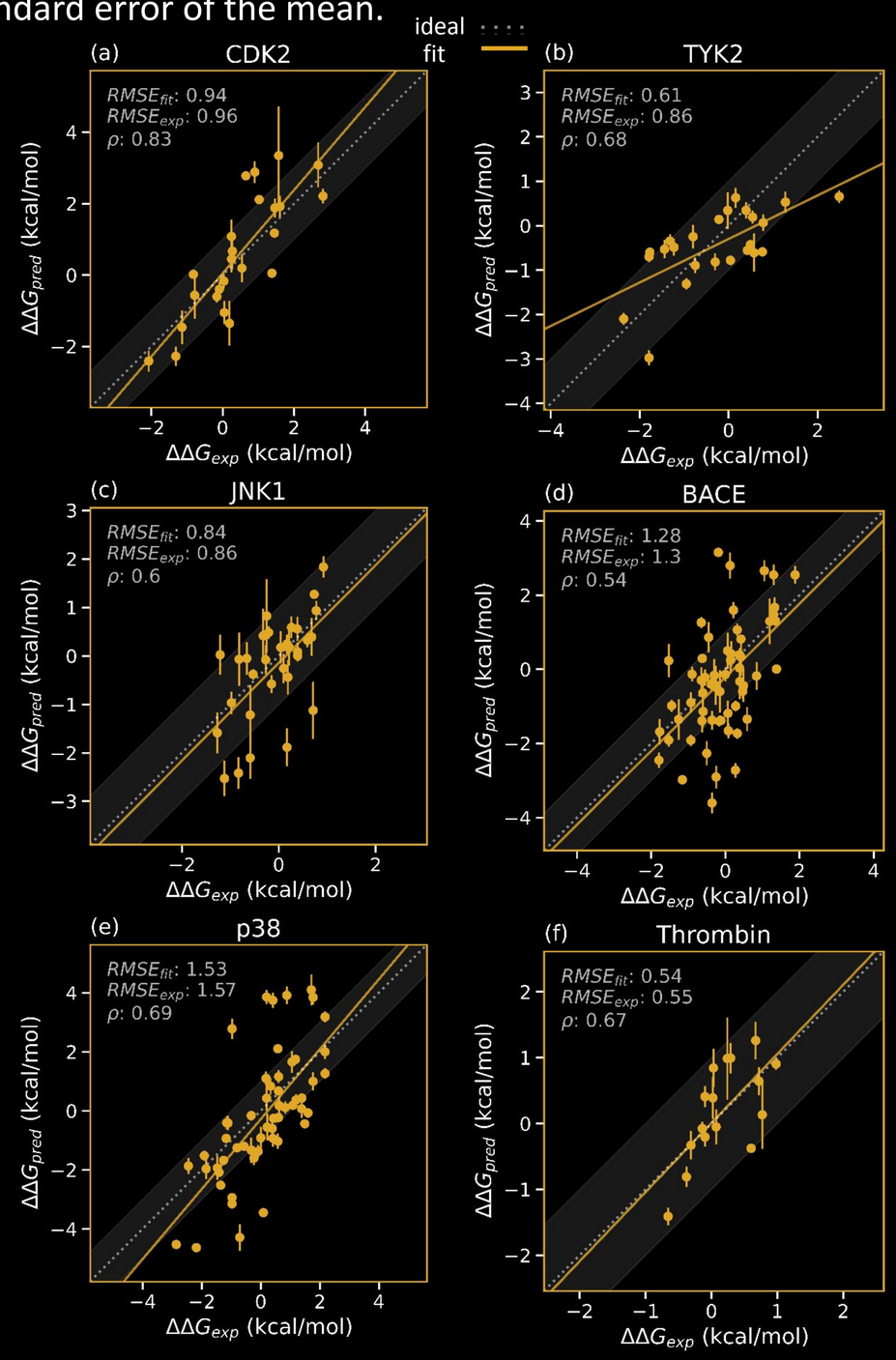

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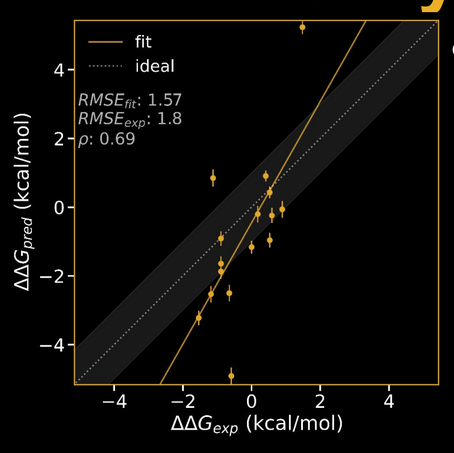
Physico-chemical filters + ML → Docking → AQFEP → Tango → Compound selection → Synthesis / Assays → Molecule Generation



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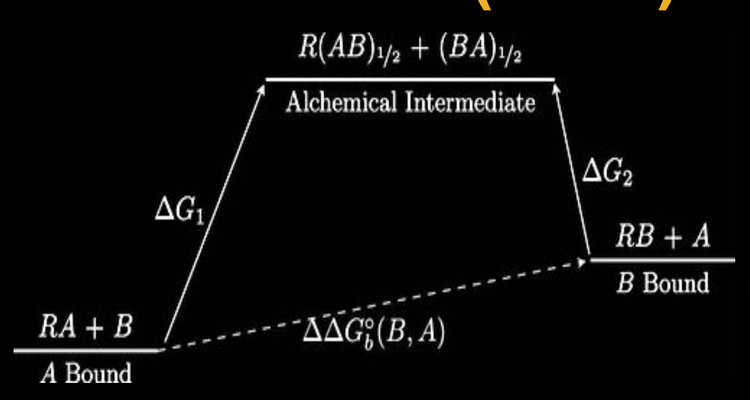

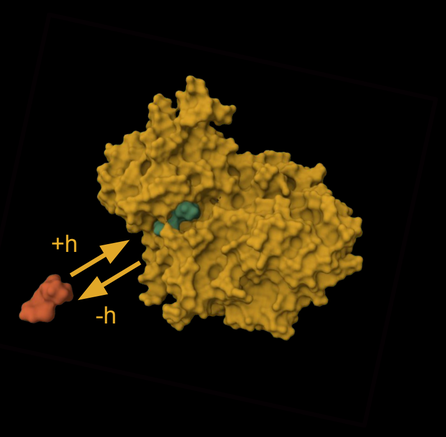

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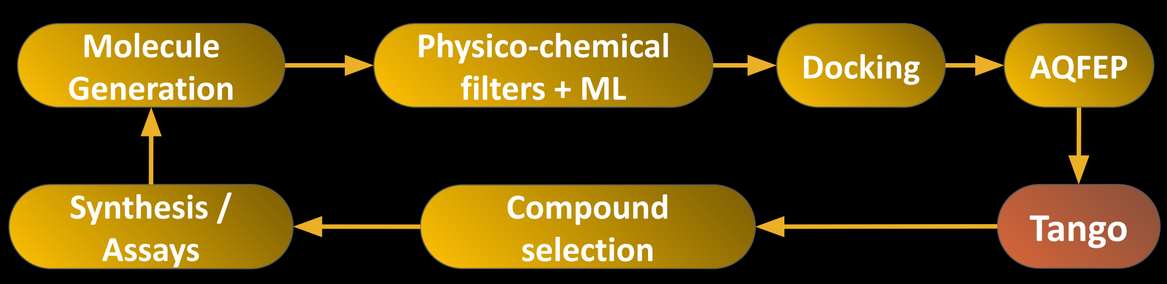

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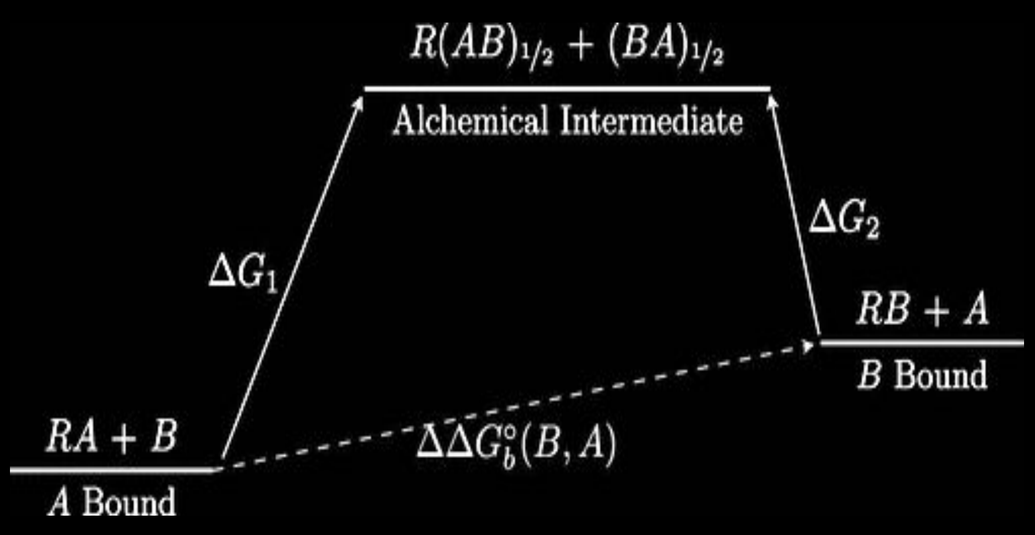

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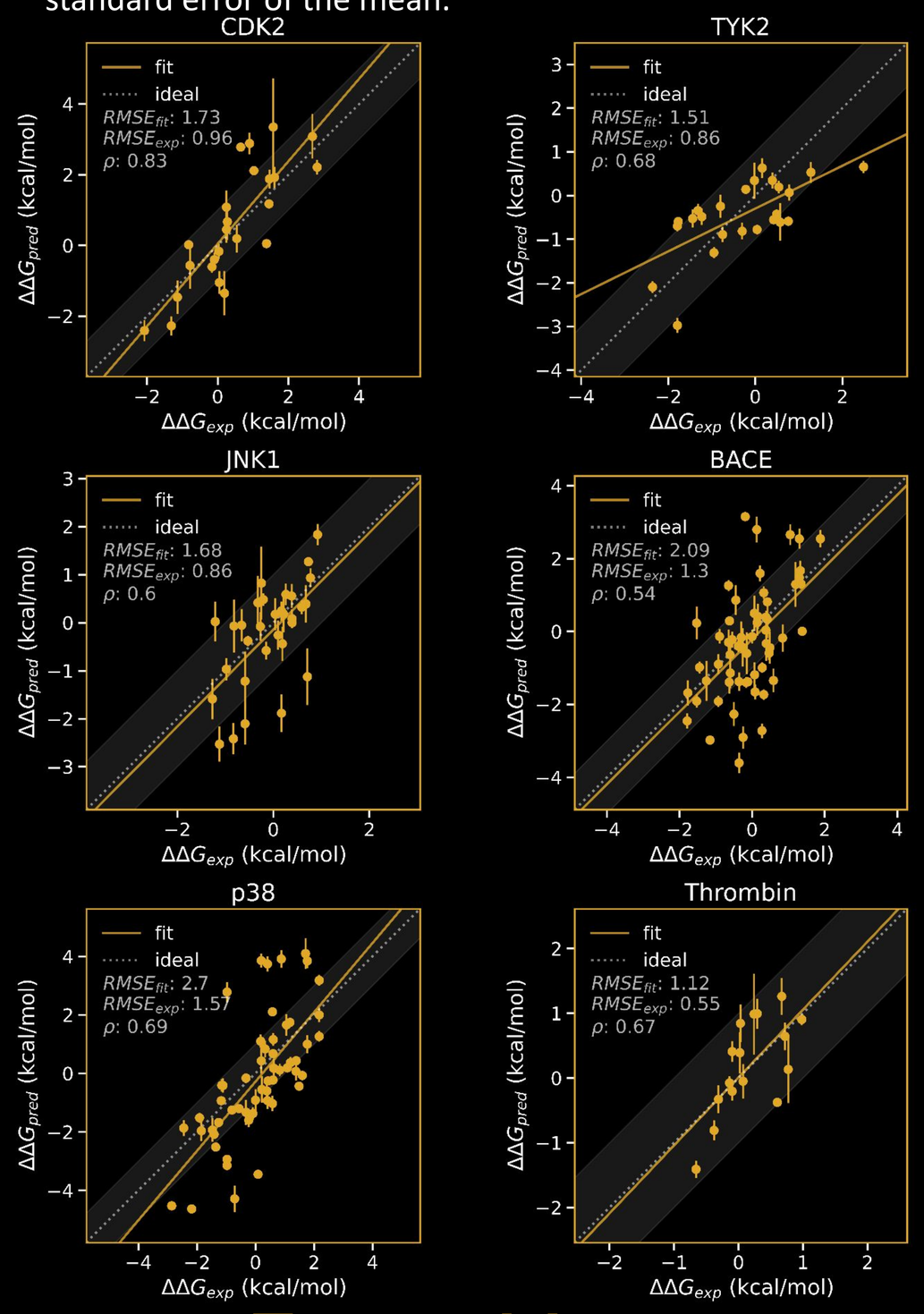

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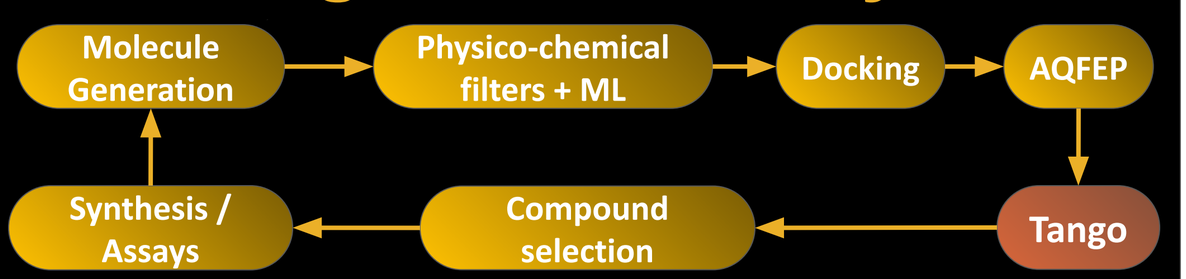

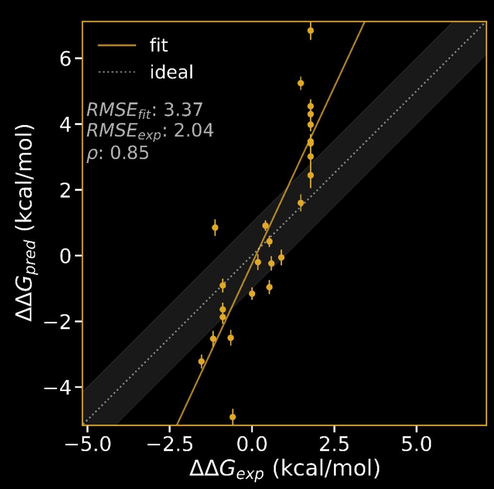

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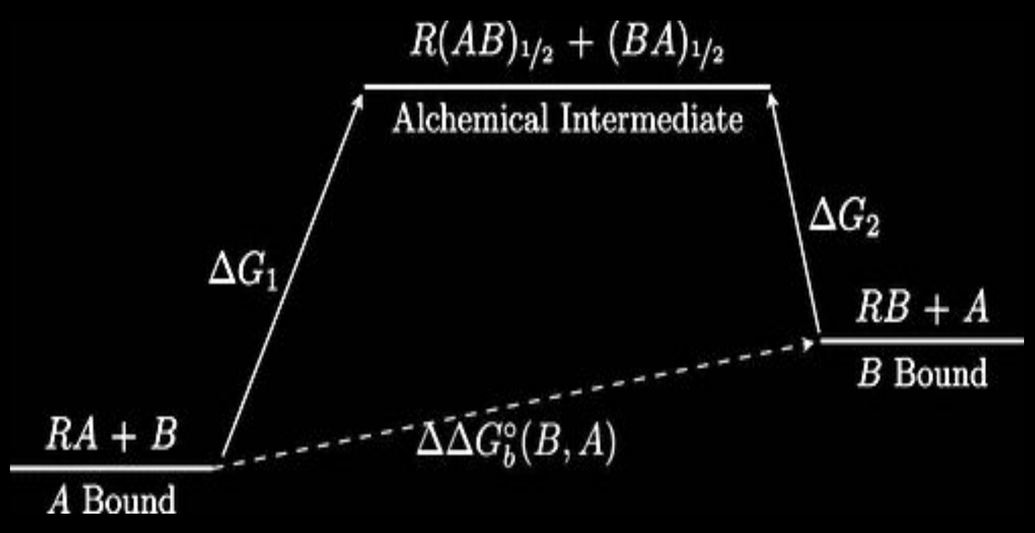

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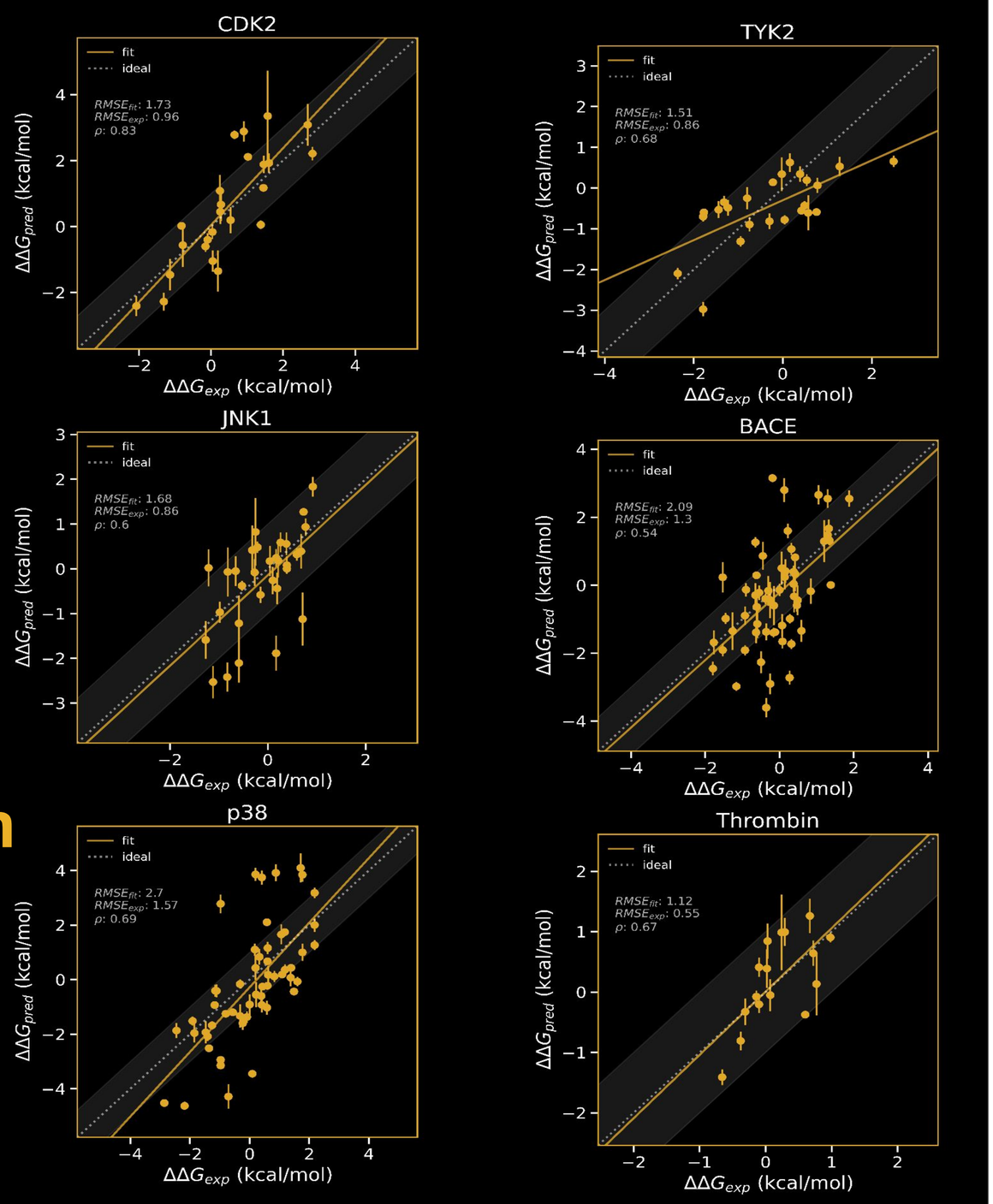

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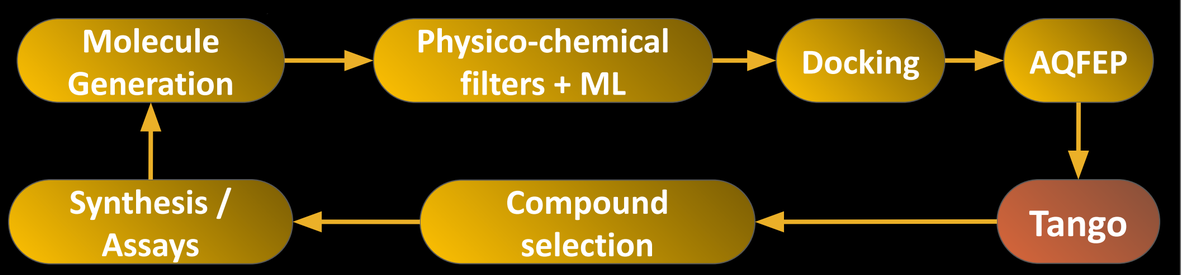
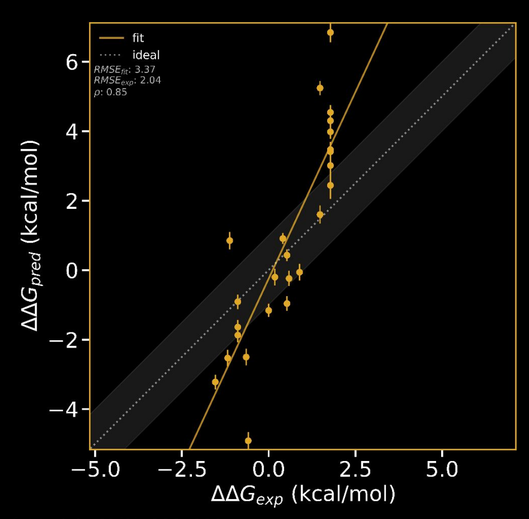




- Tango facilitated several key analyses on this client project: evaluating compound series across a wide potency range, eliminating false positives identified through docking studies, accurately distinguishing between active and inactive compounds, and enabling the investigation of activity cliffs

References

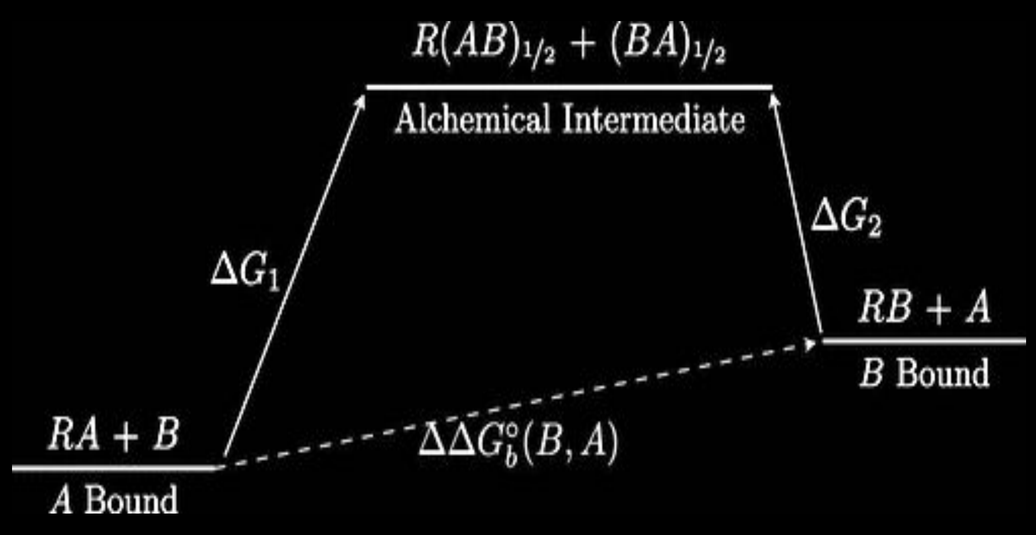
1. *Wu, J. Z., et al. (2021). Alchemical Transfer Approach to Absolute Binding Free Energy Estimation. J. Chem. Theory Comput., 17(6), 3309–3319.*
2. *Azimi, S., et al. (2022). Relative Binding Free Energy Calculations for Ligands with Diverse Scaffolds with the Alchemical Transfer Method. J. Chem. Inf. Model., 62(2), 309–323.*
3. *Zariquiey, F. S., et al., (2023) Validation of the Alchemical Transfer Method for the Estimation of Relative Binding Affinities of Molecular Series, J. Chem. Inf. Model, 63 (8), 2438-2444*
4. *Crivelli-Decker, J. E., et al. (2024). Machine Learning Guided AQFEP: A Fast and Efficient Absolute Free Energy Perturbation Solution for Virtual Screening. J. Chem. Theory Comput, 20 (16), 7188-7198*

It Takes Two to Tango: A software-suite of custom dual topology methods for binding free energy predictions

Amogh Sood[#], Lee Huntington[#], Sheenam Khuttan[#], Dominic Rufa[#], Emilio Gallicchio[⊥], Andrea Bortolato[#], Mary Pitman[#]

[#]SandboxAQ, Palo Alto, California, USA , [⊥]Department of Chemistry, Brooklyn College of the City University of New York, USA

The Alchemical Transfer Method (ATM)



- Tango, a software suite of methods based on dual topology methods.
- Herein, we present a relative binding free energy (RBFE) computation protocol adapted from the alchemical transfer method (ATM).
- We place ligand A in solution and ligand B in the binding site. We then construct the potential of the final state by swapping the positions of the two ligands: $U_{RB+A}(x_a, x_b) = U_{RA+B}(x_a\text{-}h, x_b\text{+}h)$.
- The alchemical transformation is carried out via energy interpolation rather than parameter interpolation, streamlining alchemical binding free energy computations with arbitrary energy functions.

Towards 1 click lead-optimization

- Robust and accurate *in silico* RBFE predictions are the cornerstone of lead optimization phases in structure-based drug discovery.
- Our software-solution provides computational chemists with a one-click, cloud-native solution to undertake massive RBFE campaigns on distributed systems
- In addition, our software also provides a developer friendly pythonic API for rapid prototyping and feature deployment.
- Using a single on-demand T4 GPU, we estimate a cost of $10 per prediction per edge. Using spot instances, we estimate costs as low as $6 per prediction.

protein.pdb, ligands.sdf, config.yml + 1-click submission

Automated perturbation map planning

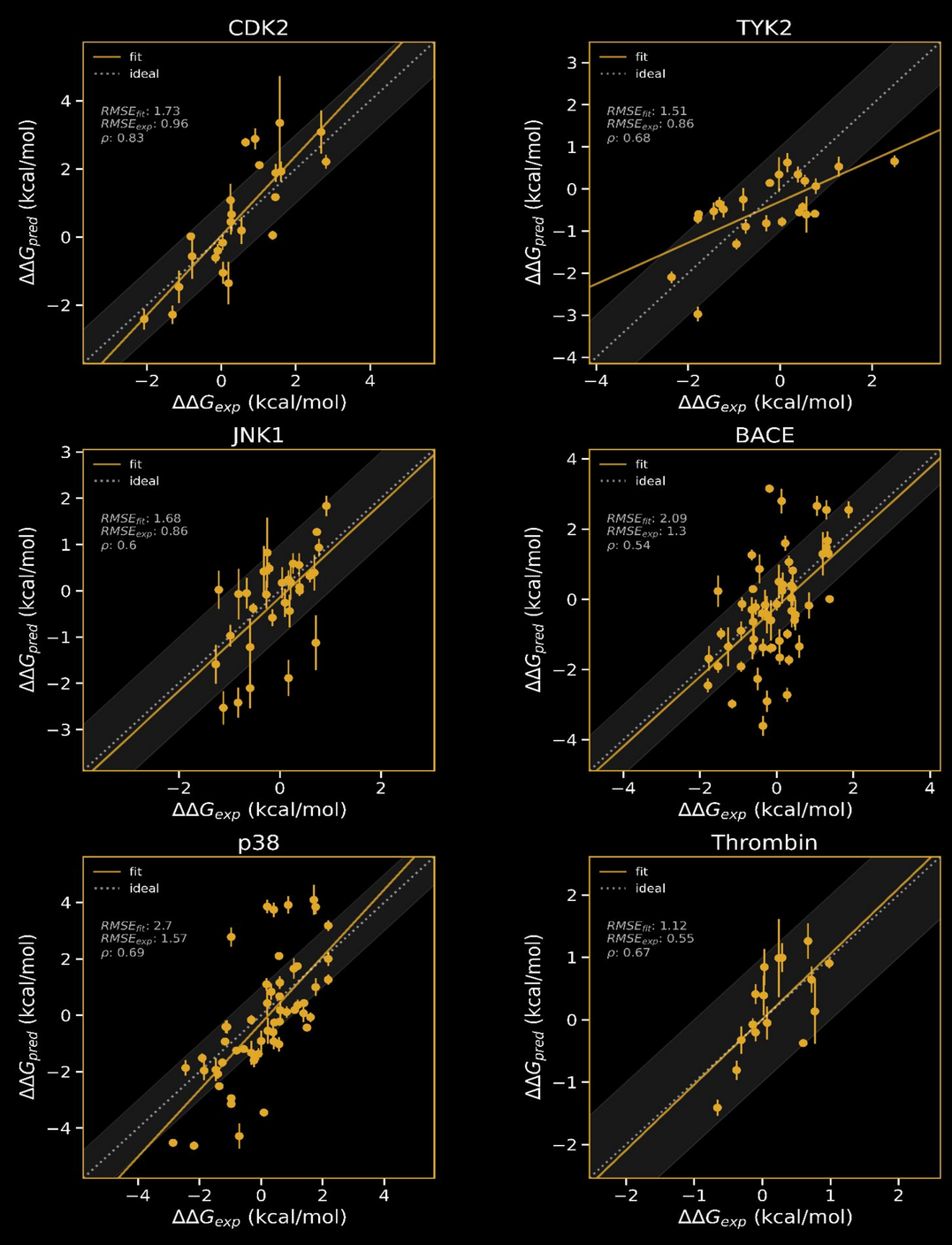
Automated atom selection for alignment restraints (*NP*-hard) using a greedy algorithm

MD simulations and Hamiltonian replica exchange deployed at scale on Google Cloud Platform (GCP)

Convergence information, ΔΔG, ΔG

Competitive ΔΔG predictions on protein-ligand benchmarks

- All simulations were run in triplicate and error bars represent standard error of the mean.



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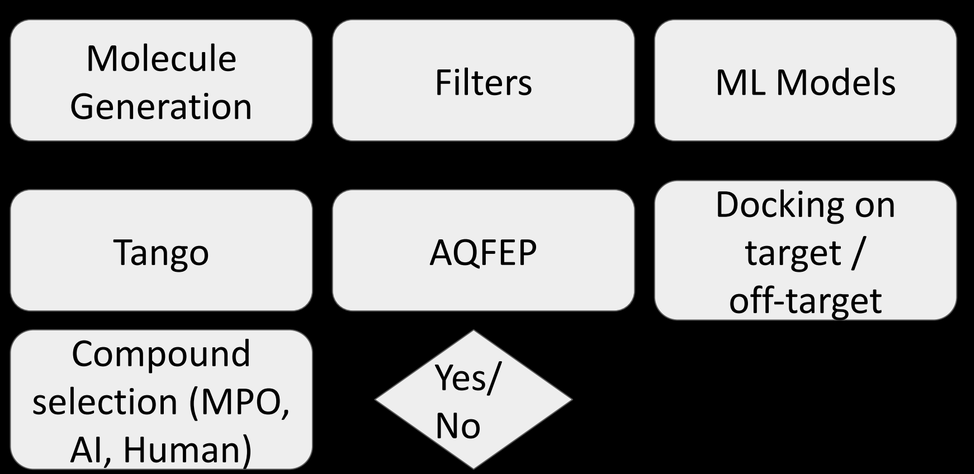

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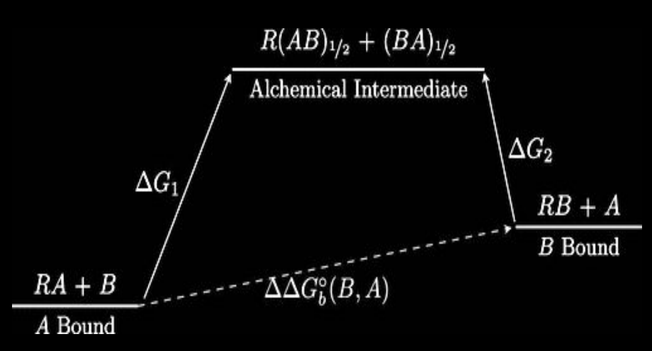
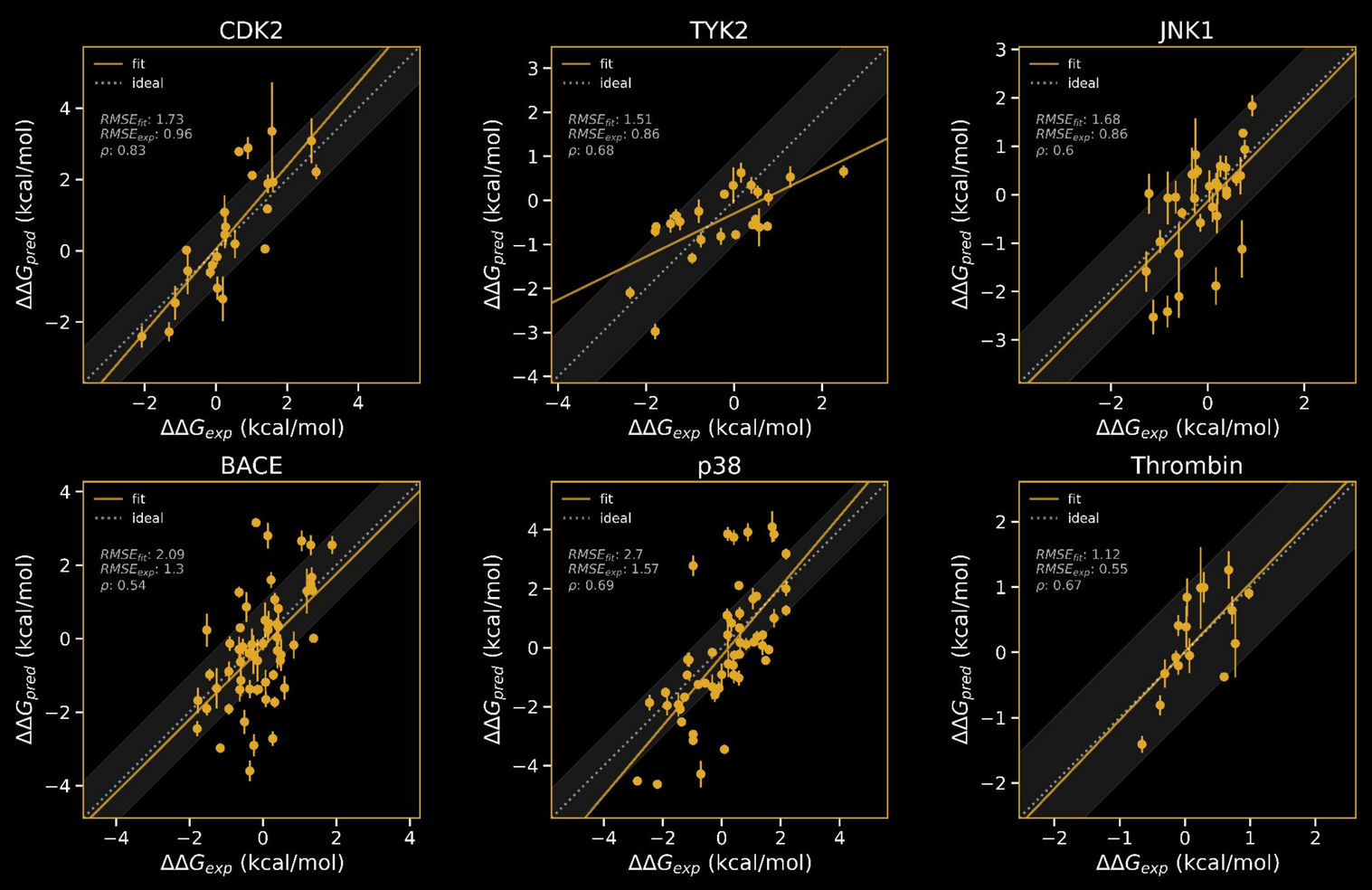


Benchmarks



1-click Relative binding free energy campaigns

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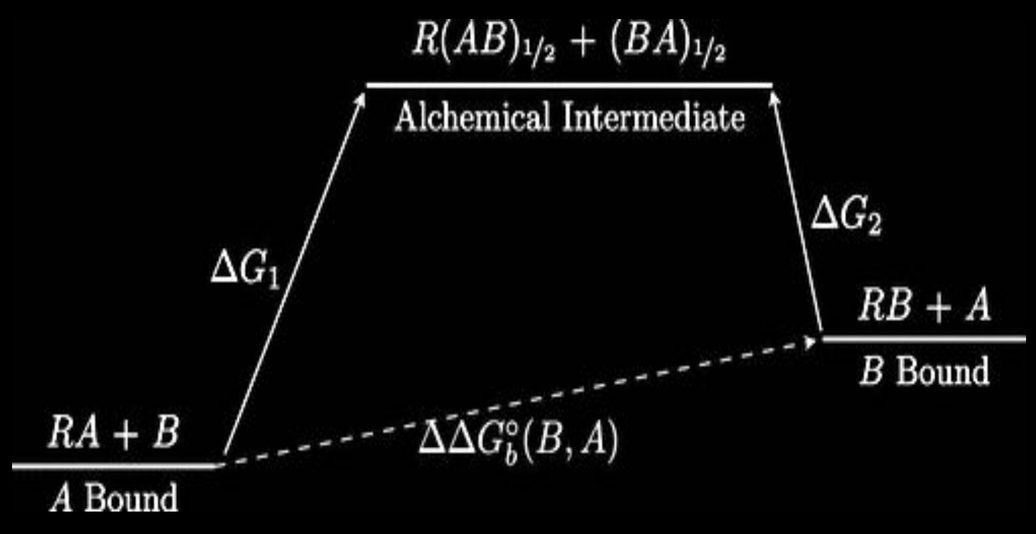

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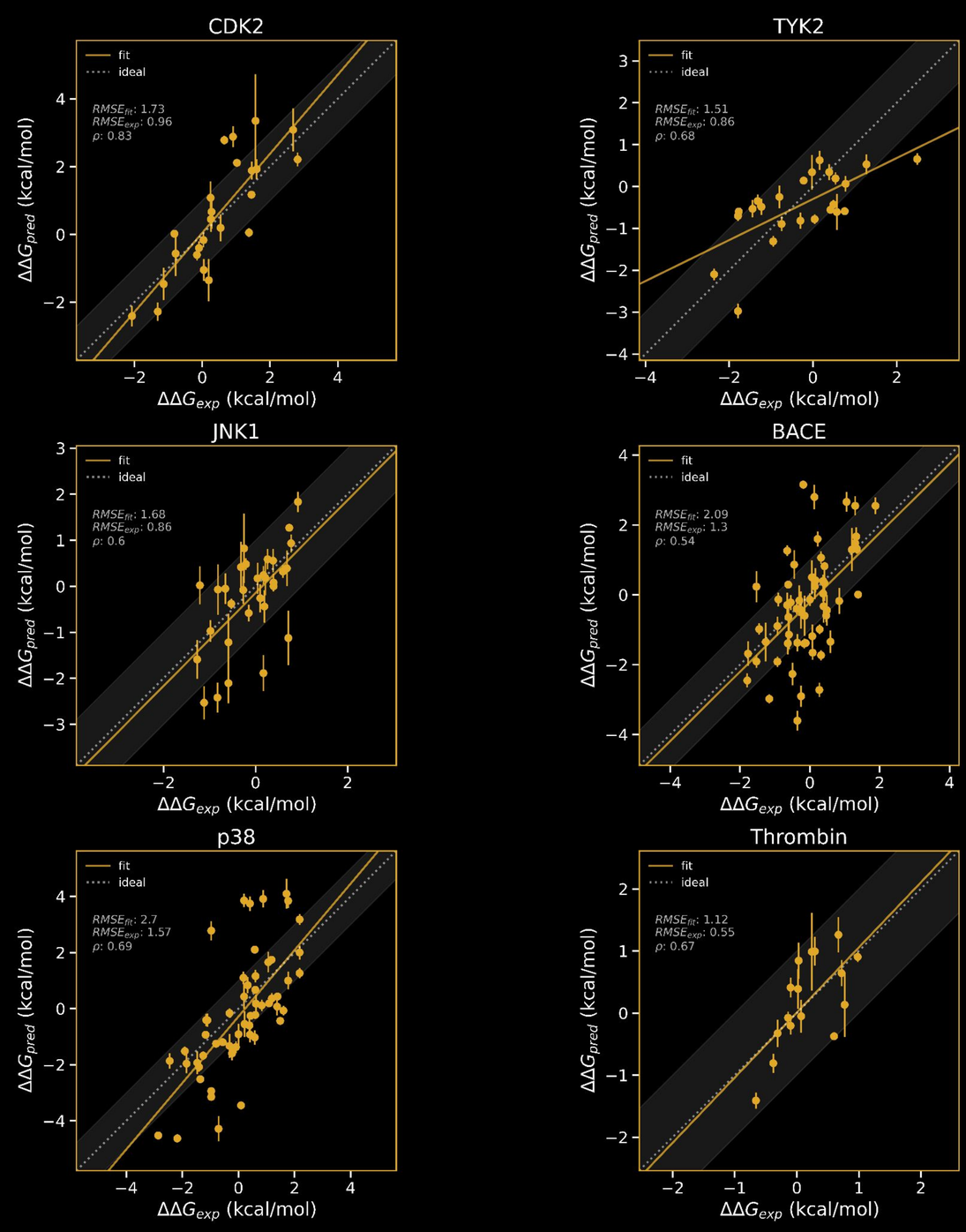

1-click Relative binding free energy campaigns

Inputs: protein.pdb, ligands.sdf, config.yml

Automated perturbation map planning

Automated atom selection for alignment restraints (*NP*-hard), using a greedy algorithm

Molecular dynamical simulations and Hamiltonian replica exchange deployed at scale on Google Cloud Platform (GCP)

Outputs: Convergence information, $\Delta\Delta G$, ΔG (optional)

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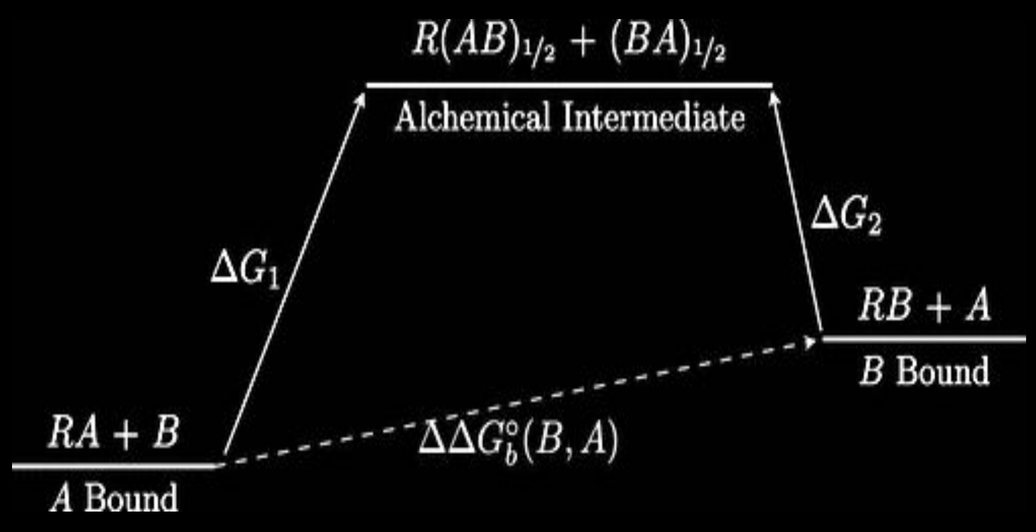

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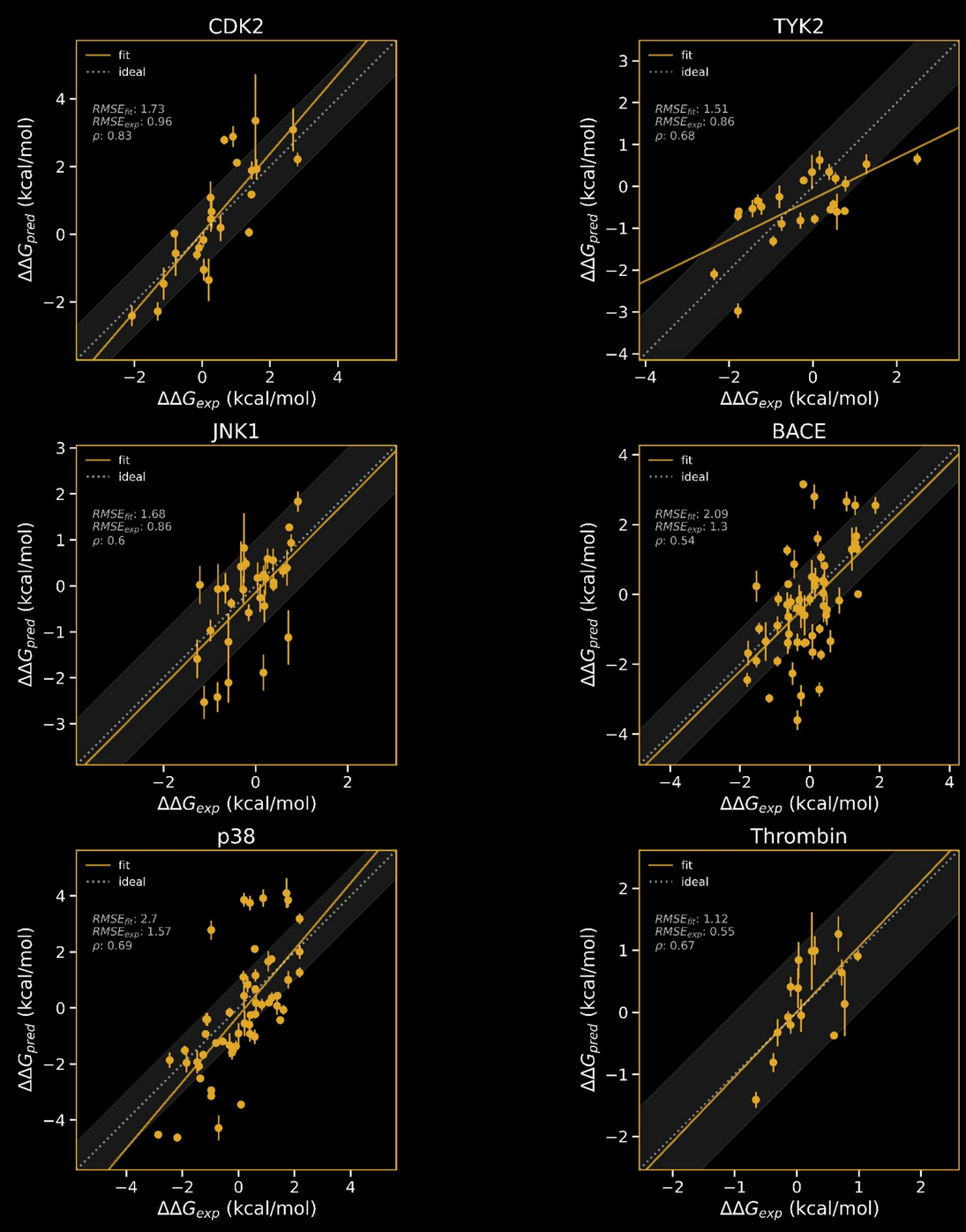

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