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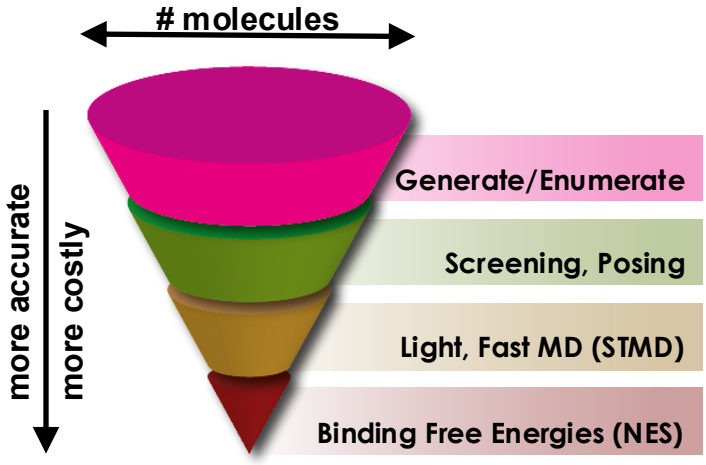
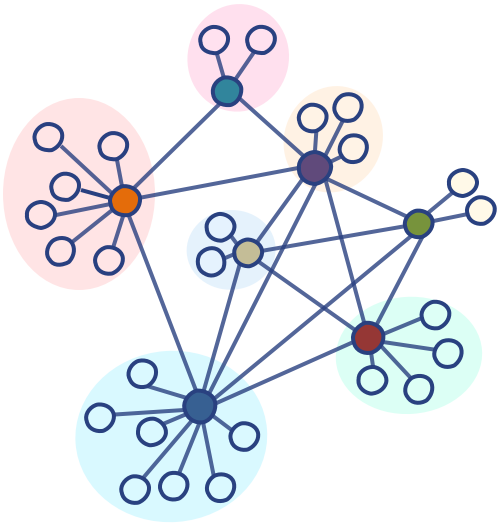
Balancing Accuracy and Throughput in Lead Optimization

Computational chemists require practical solutions for lead optimization that offer substantial flexibility in balancing accuracy and throughput effectively. Here, we assess the accuracy, predictive utility, and computational cost of various methods for ranking ligands by binding affinity. Our implementation of NES offers robust guidance for classifying molecules as high or low affinity across diverse aqueous protein targets. Leveraging the inherent parallelization of NES, we show how computational investments can be reduced by up to 75% while maintaining comparable accuracy in affinity predictions.

Design: Triage in Virtual Lead Optimization



Interactive Edge Mapping for NES



Source: OpenEye miniCUP Presentation, October 2023, San Francisco

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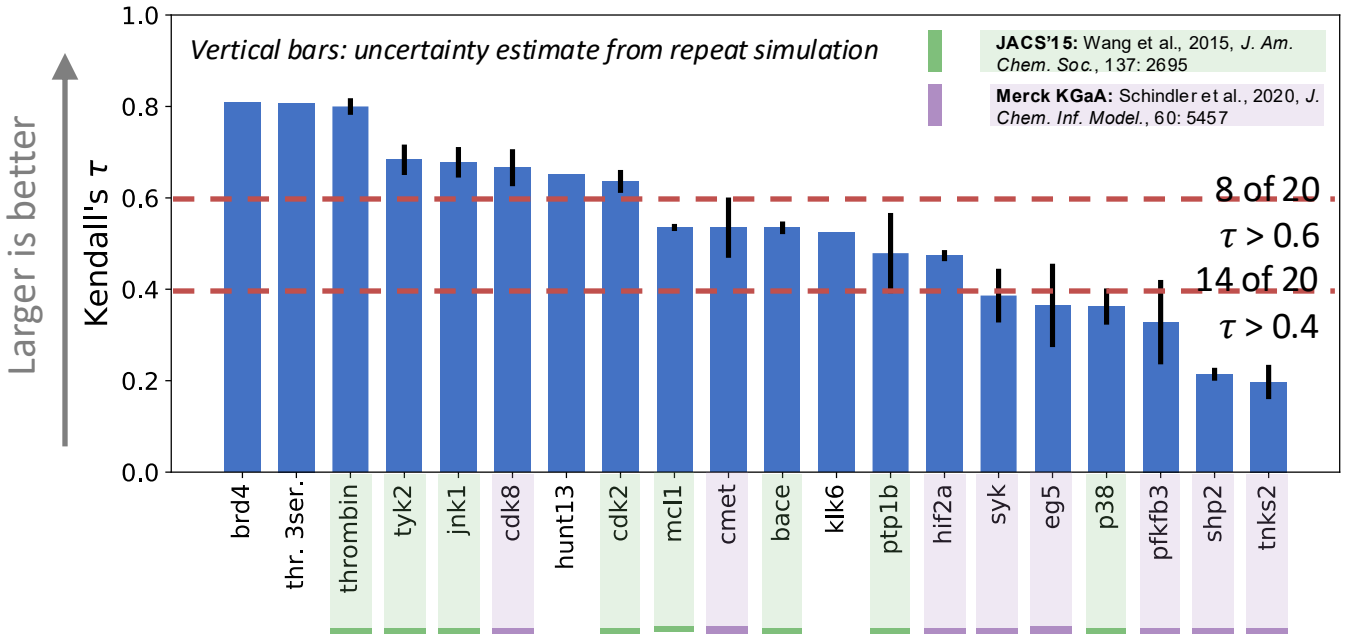
Rank association for NES-predicted binding



Summary:

• NES often provides actionable guidance across diverse targets and ligand chemistries.

• Reducing MD & NES components to ¼ their default values reduces compute costs by 3x while only increasing ligand inaccuracy by ~0.2 kcal/mol.

• Analog triage using docking, MMPBSA, etc. can be effectively followed by rapid NES prior to investing in full-scale NES for detailed ranking.

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