Affinity (Free Energy) Prediction in Structure-Based Lead Optimization

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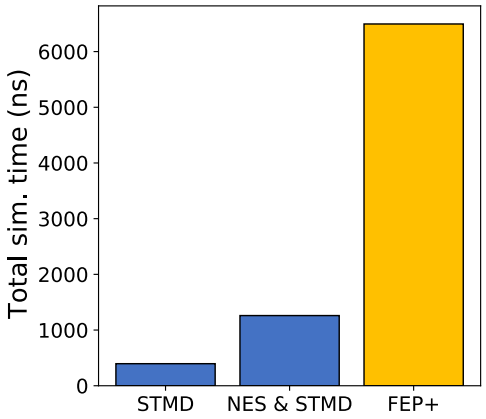
Summary:

- Prediction of protein-ligand binding affinity is a key task in lead optimization
- Non-equilibrium switching (NES) promises to be substantially faster than other methods for relative binding affinity prediction
- NES provides state-of-the-art performance in classifying ligands by activity

Product Keywords: Orion®, MD, OE Affinity

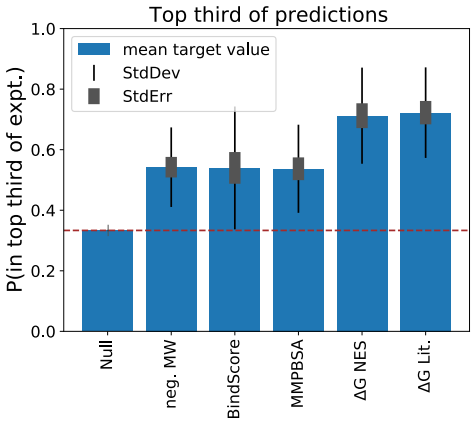
Abstract:

The prediction of the binding affinity of a small molecule to a protein target is among the most significant contributions that computation can offer to the lead optimization process. As part of a cascade of methods for molecule profiling in OpenEye's cloud-native modeling platform, Orion® - encompassing structure-based virtual screening, pose prediction, and pose stability assessment - we have implemented Non-Equilibrium Switching (NES) for predicting relative binding affinity.



Non-equilibrium switching (NES) method is more efficient than FEP+ method for affinity prediction

NES stands out for its substantial computational efficiency compared to other commonly used methods such as free energy perturbation (FEP) or thermodynamic integration (TI). Furthermore, NES is highly parallelizable, enabling exceptionally high throughput on Orion.



NES predicted free energies (ΔG NES) is comparable in accuracy to other published literatures methods (ΔG Lit.)

In extensive comparisons with other methods, we have demonstrated that OpenEye's implementation of NES method in Orion can provide meaningful correlation with experimental binding affinity and offers actionable guidance for classifying molecules as high or low affinity.

Source: OpenEye miniCUP Presentation, October 2023, San Francisco

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