# Structure-Based Lead Optimization with Non-Equilibrium Switching (NES)

Chris Neale[1], Gaetano Calabró[1], and Christopher Bayly[1]

[1]*OpenEye, Cadence Molecular Sciences, 9 Bisbee Court Suite D, Santa Fe, NM 87508*

**Summary:**

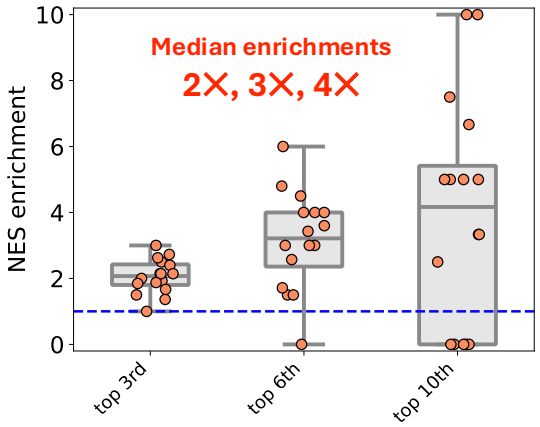
- OpenEye NES predicts, within hours, ligand affinities with useful rank-order relations
- For DMTA cycles, selection enrichment is more important than correlation or rank ordering
- NES achieves 2- to 4-fold enrichments across a broad spectrum of protein targets and ligand chemistries

**Product Keywords:** Orion®, OE Affinity, MD, Non-Equilibrium Switching

Computational estimates of ligand-protein binding free energies are widely utilized in both industry and academia. Non-Equilibrium Switching (NES) is faster and more cost-effective than alternative methods for computing binding free energy, such as free energy perturbation or lambda dynamics, which require sampling closer to equilibrium.

OpenEye's implementation of NES on our Orion® platform enables automated calculations to complete within hours, even for a large number of ligands, making NES suitable for use in iterative lead optimization.

The impact of affinity estimation on lead optimization cycles is best measured by selection enrichment, which emphasizes practical outcomes. When choosing which ligands to synthesize and test, what matters most is that the selected group includes a larger number of strong binders than would be picked randomly. We quantify enrichment by NES as the number of top experimentally ranked ligands found in the top predicted ligands, divided by the random expectation. The figure below illustrates NES' performance on various literature datasets, showing that it can be effective for ranking and selecting active ligands.




*OpenEye's NES provides 2- to 4-fold enrichment, across a broad spectrum of protein targets and ligand chemistries, within hours. Blue line is no enrichment. Data sets originally curated in [1, 2].*

Although outcomes vary for different ligand-protein datasets, NES median enrichments of 2-fold, 3-fold, and 4-fold for the top 1/3rd, 1/6th, and 1/10th ligands, respectively, demonstrate NES's ability to provide actionable guidance across a spectrum of protein targets.

[1] Wang et al., 2015, *J. Am. Chem. Soc.*, 137: 2695.
[2] Schindler et al., 2020, *J. Chem. Inf. Model.*, 60: 5457.

Source: OpenEye CUP Presentation, March 2024, Santa Fe

info@eyesopen.com