Accurate Binding Pose Prediction with Induced-fit posing (IFP)

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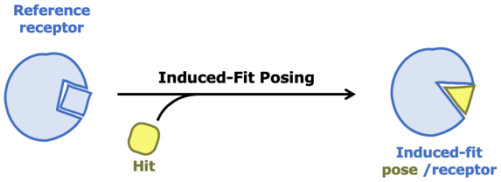
Summary:

- Pose prediction in hit-to-lead is challenging due to high chemical diversity between series
- IFP provides new pose prediction functionality combining docking with short trajectory MD to sample both ligand and protein binding site conformations
- Accuracy is substantially better than standard docking (rate of successful prediction improved by > 20%)

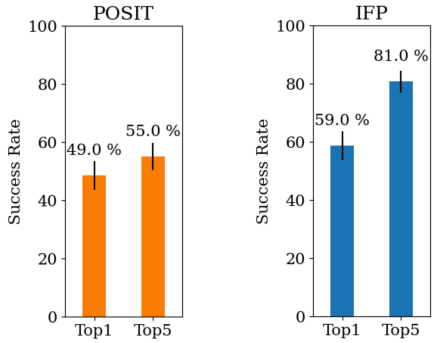
Product Keywords: Orion, Short Trajectory MD, OE Affinity, Induced Fit Posing

Abstract:

Accurate prediction of binding poses is a fundamental requirement in structure-based design. High accuracy can be easily achieved in lead optimization, where most molecules of interest share significant similarities in shape and chemical features with a known crystallographic ligand. However, in the hit-to-lead stage, multiple chemotypes are often pursued, many of which may not be 3D similar to known ligands, thus reducing the reliability and accuracy of pose prediction.



We have recently introduced Induced-Fit Posing (IFP) to enhance pose prediction accuracy in hit-to-lead scenarios. In the initial step, binding site residues are pruned to create more space for docked molecules. Binding hypotheses are then generated in both pruned and unpruned receptors using standard docking protocols,



When compared to standard docking (POSIT) on hit-to-lead datasets, IFP demonstrates approximately a 20% increase in pose prediction accuracy.

taking advantage of the presence of a bound ligand to maximize pose reliability. High-scoring poses from docking undergo a short trajectory MD simulation (STMD), allowing for side chain adjustments and ligand repositioning. Clustering trajectories from STMD yields representative, low-energy binding site conformations with ligand poses. These conformations are then scored using a consensus method that integrates MM-PBSA, docking scores, and knowledge-based protein-ligand interaction assessment.

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