Development of a Flexible Protein–Ligand Docking Approach for Virtual Screening, Applied to the Nuclear Receptor Family

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This study explores nuclear receptors, key proteins involved in the regulation of gene expression and representing important therapeutic targets. Their activity relies on highly specific interactions with ligands characterized by diverse pharmacological profiles, such as agonists or antagonists. These interactions are associated with significant conformational rearrangements, which make their structural modeling particularly challenging.

Conventional molecular docking approaches based on rigid receptor structures fail to capture this structural variability, leading to inaccurate prediction of ligand–receptor interactions. While ensemble docking has been proposed to address this limitation, it often remains insufficient to fully represent the dynamic behavior of nuclear receptors and may lead to poor predictive performance.

In this work, we propose an alternative flexible docking strategy that focuses on biologically relevant structural adaptations rather than global conformational sampling. A baseline is first established using rigid docking.

Subsequently, local flexibility is introduced by targeting key binding site residues (Arg228, Ser277, Arg266, and His381) and by explicitly modeling different conformations of helix H12, a critical element of receptor activation. This approach aims to better capture ligand-induced conformational changes that are not adequately represented by classical methods.

Different docking protocols, including GNINA, Smina, Boltz-2, and AutoDock-GPU, will be systematically evaluated and compared to assess their ability to capture receptor flexibility and improve ligand discrimination. Docking performance will then be assessed using pose RMSD, enrichment metrics (AUC, EF), and advanced rescoring approaches such as MM-GBSA and CNN-based scoring.

This framework is expected to provide a comprehensive evaluation of docking strategies and to assess the impact of incorporating targeted flexibility on binding mode prediction and ligand discrimination.