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Synergistic Approach of Consensus and Flexible Docking for Accurate Binding Pose Estimation

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Molecular docking plays a pivotal role in early-stage drug discovery, enabling rapid virtual screening and prediction of protein–ligand interactions. However, conventional docking approaches suffer from critical limitations, including reliance on an inaccurate scoring function and insufficient consideration of protein flexibility. These constraints often lead to discrepancies between predicted and experimental binding poses, thereby reducing the reliability of docking-based screening. To overcome these challenges, flexible docking has been introduced to account for conformational changes in target proteins, allowing exploration of more realistic binding poses. Nevertheless, flexible docking alone cannot fully address the inherent bias of individual scoring functions. To complement this, consensus docking has emerged as a strategy to integrate multiple scoring functions, thereby enhancing prediction robustness and mitigating the limitations of single-function evaluation.

In this study, we propose a combined framework termed combined flexible and consensus docking, which sequentially integrates the strengths of flexible docking and consensus scoring. First, flexible docking was employed to generate candidate poses while reflecting target flexibility. Subsequently, consensus scoring across multiple functions was applied to refine and prioritize poses, improving both pose accuracy and scoring stability. To evaluate the effectiveness of this strategy, we applied the method to the Astex Diverse Set, a widely recognized benchmark for docking validation. The results demonstrated superior pose reproduction rates and improved scoring consistency compared with single-method approaches, confirming both the reliability and generalizability of the proposed framework.