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RECENT ADVANCEMENTS IN FLEXIBLE MOLECULAR DOCKING

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ABSTRACT :

Molecular docking is a fundamental technique in drug discovery, enabling the prediction of interactions between ligands and receptors. The orientation of bound molecules offers crucial insights into predicting energy profiles, such as binding free energy, and evaluating the strength and stability of molecular complexes, including binding affinity and binding constants. This information aids in understanding molecular interactions and optimizing binding efficiency in various applications. Recent progress has aimed to enhance accuracy and computational efficiency by incorporating flexibility into both molecular components. Key advancements include GPU-accelerated flexible docking, which utilizes parallel processing for increased speed, and diffusion-based flexible docking models that apply generative AI for improved conformational sampling. Furthermore, meta-docking protocols combine multiple docking approaches to enhance prediction reliability, while virtual reality-based interactive flexible-receptor docking offers an immersive and intuitive method for structure-based drug design. Collectively, these innovations advance molecular docking, providing more precise and scalable solutions for biomedical applications.

Keywords: Molecular docking, GPU-accelerated flexible docking, Diffusion-based flexible docking, Meta-docking protocols, Virtual reality-based interactive flexible-receptor docking.

INTRODUCTION :

Background

Molecular docking is a key computational technique in drug discovery, used to predict interactions between small molecules (ligands) and biological targets (receptors) [1]. Docking is essential for understanding molecular recognition, optimizing drug candidates, and expediting the drug development process [2]. However, conventional docking methods often assume rigid receptor structures, which can limit their effectiveness when dealing with highly flexible targets [3]. To address these challenges, recent innovations have incorporated flexibility in both ligands and receptors, improving binding predictions. Notable advancements include GPU-accelerated flexible docking, Diffusion-based flexible docking, Meta-docking, and Virtual reality-based interactive flexible-receptor docking. These techniques improve the accuracy, efficiency, and accessibility of molecular docking, making it an increasingly valuable tool in structure-based drug design. This study examines these recent developments and their role in advancing molecular docking for biomedical applications [4].

Goals

The main goals of this study are: [5]

- ✓ To provide a thorough review of the importance of molecular docking in drug discovery.
- ✓ Cost-efficient and highly effective screening.
- ✓ It is a reliable method for identifying and optimizing lead compounds.
- ✓ It increases the hit rate i.e. finding active compounds that have therapeutic potential.

APPROACHES :

(a) GPU-Accelerated Flexible Docking [6]

MedusaDock, a widely used docking software framework, is employed to explore GPU acceleration in molecular docking. Predominantly Docking software supports only rigid receptor docking, MedusaDock accommodates flexible docking by accounting for receptor side-chain flexibility. The latest version, MedusaDock13, incorporates experimental constraints to enhance accuracy. MedusaDock conducts docking in three main steps:

- Generating a stochastic rotamer library for ligands.
- Repacking the protein's side chains.
- Performing rigid body docking.

The first two steps prepare the input for the final rigid body docking stage. MedusaDock identifies multiple minimum energy complexes for further conformation prediction, with lower energy complexes considered more stable. The process is divided into three phases: Preparation for coarse docking, Coarse docking, and Fine docking. In the preparation phase create a set of candidate poses. In the coarse docking phase, MedusaDock searches for the best-fitting poses within a defined docking box, iteratively repacking the side chain of the protein for rigid docking. The coarse docking phase selects a top group of low-energy poses for the fine docking step. During fine docking, both the ligand and receptor side chain rotamers are sampled simultaneously. Ligand conformations in each group are adjusted within 2 Å to refine the ligand diversity. A small number of final candidates are selected.

(b) Diffusion-based Flexible Docking Model

PackDock operates in two stages. Stage 1, utilizes a diffusion model, Packpocket, to explore potential side-chain conformations of empty pockets, adhering to the conformational selection hypothesis. In Stage 2, the diverse conformations generated are employed as receptors for the docking process. Packpocket can simultaneously consider the conformational selection mechanism and induced fit mechanism simultaneously [7].

FlexiDock is a specialized docking system in computational biology, consisting of two independently trained score-based diffusion generative models. Each model is responsible for capturing the conformational flexibility of the receptor (r) and the ligand (l), respectively. This approach enables accurate modeling of molecular docking by accounting for the dynamic nature of both the receptor and ligand. On the other hand, "Flexidock" as used in the context of marine applications refers to flexible, modular, and floating platforms designed for docking boats, ships, or other watercraft. These systems are adaptable in size, shape, and layout, providing versatility for marine environments [8].

Diffdock is a diffusion generative model (DGM) used for molecular docking, focusing on generating ligand poses.

Left: The model receives the individual structures of the ligand and protein as input.

Center: Initial random poses are sampled and refined through a reverse diffusion process, which operates across the translational, rotational, and torsional degrees of freedom.

Right: The generated poses are then ranked by a confidence model, which provides a final prediction along with a confidence score [9].

(c) Meta-docking protocols

The Meta-docking protocol integrates results from AutoDock4.2, LeDock, and rDOCK, which are freely available, user-friendly, and well-suited for large-scale analysis. These programs have demonstrated superior performance in benchmarking studies [10].. It provides a superior alternative for the scientific community that cannot afford expensive commercial packages. It exhibited markedly better performance in scoring, posing, and screening protein-ligand complexes than the reference programs. To overcome these limitations, a comprehensive protein-protein docking meta-approach has been developed, integrating multiple available software tools to predict and analyze pairwise protein-protein complexes. To examine the docking performance of the new meta-approach, individual clustering component analysis was carried out. The approach could become more effective by incorporating a larger number of models generated by each docking engine for further refinement and clustering [11].

(d) Interactive Flexible-Receptor Docking in Virtual Reality:

Interactive docking enables the guidance and control of the docking process of two biomolecules into a binding pose. This method is used to assess the docking of various candidate drug molecules. DockIT integrates virtual reality (VR) with the use of a VR headset and hand-held controllers. Using molecular dynamics simulations, DockIT can capture both global and local conformational changes within the receptor caused by ligand interactions. Its most distinctive feature is the ability to model receptor flexibility using the linear response method. The method enables the quick calculation of hydrogen bonds between receptor and ligand molecules and includes tools for swiftly rendering graphical models, such as ball-and-stick, backbone, space-filling, and molecular surface [12].

CONCLUSION:

Recent advancements in flexible molecular docking have significantly improved the precision and efficiency of predicting ligand-receptor interactions. Advancements such as GPU-accelerated docking, Diffusion-based models, Meta-docking protocols, and Interactive virtual reality interfaces have revolutionized the approach to drug discovery. These advancements accelerate the docking process and enhance its accuracy, offering more realistic simulations. As these technologies continue to evolve, they accelerate the discovery of novel therapeutics, providing powerful tools to design more effective and personalized treatments for a wide range of diseases.

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