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Artificial Intelligence-based Molecular Docking in Drug Discovery

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Abstract

Molecular docking is a technique in structural molecular biology and computer-aided drug design that predicts the binding affinity of ligands to the targeted disease-causing proteins. Even after years of progress, there are difficulties in reliably spotting the right ligands and predicting how they fit inside a target's binding site. The field of drug development is changing rapidly due to introduction of Artificial Intelligence (AI) in molecular docking. This method addresses the limitations in traditional docking. Key improvements include handling large datasets, scoring functions, exploring conformational spaces of ligands and receptors. This article explains how AI has enhanced molecular docking at every step for drug discovery.

Keywords: Artificial Intelligence, Drug Discovery, Molecular Docking, Virtual Screening

Introduction

Since AI has proven to be accurate and quick in molecular docking, its usage in drug discovery has grown during the last ten years. Molecular docking is a computer-aided drug discovery tool that represents a major advancement in the field of AI-based drug development. Its advantages over conventional screening methods are evident. It makes use of sophisticated machine learning architectures like deep neural networks to estimate the binding affinity and has high precision. These models are able to operate a lot of data and it is challenging in the traditional methods. Virtual Screening (VS) methods have become necessary in the process of identifying potential drug candidates and enhancing them as a prompt and more streamlined method compared to traditional high-throughput screening (HTS). The virtual screening process, including compound selection and ranking, can be automated with the help of AI-based tools that save time and resources by limiting the amount of manual work. In contrast to classical docking algorithms, which do not deal with protein and ligand flexibility well, AI algorithms are able to model the changes, which lead to more precise and realistic prediction. This article explains how artificial intelligence (AI) is used in molecular docking for drug discovery and discusses potential future directions for using these techniques to advance drug development.

Molecular Docking

Molecular docking is a computer-based methodology, which is used to determine and optimize possible therapeutic agents. The main goal of molecular docking is to predict how small molecules (ligand) will bind to a target protein in order to determine the direction of binding and affinity. This knowledge is essential in the study of the biological processes and in the development of useful medications. Docking modules are customized based on conventional methods that utilize physics, chemistry and computational algorithms. Such methods were not always fast and effective, but AI is capable of processing large volumes of data and making quicker and more accurate forecasts (Bhagat *et al.*, 2021).

Traditional Docking

Traditional molecular docking methods include deterministic, stochastic and hybrid approaches. Deterministic methods use stepwise search algorithms and scoring functions to find the most stable ligand-protein binding, often assuming rigid structures (rigid docking). But it may give false predictions

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due to biological flexibility. Stochastic methods employ probabilistic algorithms to handle ligand and protein flexibility, which is suitable for complex docking. But this method poses limitations such as high computational cost and implementation challenges. Hybrid methods combine both approaches to balance accuracy and efficiency, improving prediction of binding poses and affinities, though they still inherit some complexity and computational demands.

AI-based Molecular Docking

In AI-based molecular docking, ligand-receptor interactions are predicted by sampling multiple ligands pose in the protein's active site and scoring them based on forces like electrostatic, van der Waals and hydrophobic interactions. The best-scoring pose indicates the most likely binding mode and estimates binding affinity (Agu *et al.*, 2023).

Virtual screening (VS) identifies potential drug candidates by computationally screening compound libraries against biological targets. AI improves VS using machine learning (ML) and deep learning (DL), with methods like SVMs classifying compounds and convolutional neural networks (CNNs) and recurrent neural networks (RNNs), analysing 3D structures and binding sites to predict drug-target interactions.

AI-based ligand and protein binding site identification predicts likely ligand binding regions on a protein. Methods like CNNs, graph neural network (GNNs) and point cloud algorithms analyse the protein's 3D structure or surface to detect geometrical patterns of ligand-binding sites (LBSs).

AI-based binding pose prediction models include ligand pose generation and protein-ligand co-generation, which models both structures simultaneously. Ligand pose prediction uses sampling-based methods, to rank multiple conformations, or regression-based methods, to directly predict the most likely pose (Sim *et al.*, 2025).

AI-based scoring functions predict a ligand's binding strength to a target protein using machine learning models, trained on processed datasets of known binding information. Once trained, the model can accurately estimate binding strengths for new molecules and present the results in a user-friendly format (Zhang *et al.*, 2021).

For target proteins, AI can predict a 3D structure from a FASTA sequence or use an existing Protein Data Bank (PDB) structure. Ligands are provided as Simplified Molecular Input Line Entry System (SMILES) strings or 3D formats and their structures are generated accordingly. Blind docking is the technique by which AI uses these inputs to forecast the intensity of ligand binding to the protein without having any prior knowledge of the binding location (Fadahunsi *et al.*, 2024).

Advantages of AI-based Docking Process

1. Learning Complex Patterns

Artificial intelligence algorithms are trained with large amounts of experimentally verified ligand-receptor interactions. This training enables them to interpret complicated patterns and relationship that conventional method may not be able to recognize resulting in better predictions.

2. Enhanced Scoring Functions

A key aspect is the improvement of scoring functions through AI. These algorithms learn from large datasets, leading to more accurate evaluations of binding affinities than traditional docking.

3. Handling Molecular Flexibility

The AI-based methods embrace the diversity of ligands and protein targets and can simulate conformational changes and dynamism during interactions which are usually challenging in the rigid docking method.

4. Pose Prediction

The ideal binding position (pose) and the binding affinity between the ligand and the target protein are predicted by the AI models.

5. Output

Several ranked poses of the docked ligand, each representing a possible binding conformation, are usually produced using AI-based molecular docking technologies. Molecular visualization tools can be used to show these ranking poses, enabling researchers to thoroughly evaluate the binding interactions and choose the most promising candidates to undergo further experimental confirmation (Fadahunsi *et al.*, 2024).

Future Perspectives

AI-driven molecular docking is revolutionizing how proteins are investigated and drugs are developed. Recent models such as AlphaFold 3 enhance predictions of large complexes, individual biomolecules and the use of AI alongside experiments in results makes predictions more precise. Such tools are capable of accelerating drug discovery, assisting in personalizing medicine and disclosing the interaction of molecules in cells. More effective predictions are obtained with integrated AI methods, such as AlphaFold with DiffDock, which makes the research more expeditious, inexpensive and enlightening.

Conclusion

By improving the speed and precision of molecular interaction prediction, AI-based molecular docking algorithms offer an innovative approach to improving computational drug development. Physiochemical and computational algorithm-based traditional docking methods cannot easily scale to large datasets and are rarely able to capture the complexity of molecular interactions and changes in conformation. To overcome major limitations of the traditional methods, AI-based molecular docking enhances scoring capabilities and comprehensively investigates the ligand and the receptor conformations. Deep learning models have the ability to pick up complex patterns of large datasets and this increases the accuracy of the predictions of binding.

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