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Molecular docking: A powerful tool for predicting protein-ligand interactions

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Abstract

Molecular docking is a computational method used in molecular biology, structural biology and therapeutic discovery to predict how candidate molecules bind with target molecules. While predicting the binding patterns and conformations of the molecules, hardware, software, algorithm, molecule databases and models are widely used. Molecular docking processes consist of the generation and analysis of different possible conformations and orientations of the ligand within the binding site of the receptor/target. The goal is to predict the most favorable binding position or configuration, as well as the strength of the binding affinity between the ligand and receptor. The key elements of molecular docking consist of molecule preparations and using proper scoring parameters. With the help of previous knowledge and advancing technology, it is possible to expand diversity of potent therapeutics with low cost. In this proceeding review, we will focus on molecular docking as a powerful tool to predict protein-ligand interactions.

Introduction

Concept of the molecular docking is trying to determine the affinity between ligand and its receptor by using computational methods [1]. Molecular docking is the most popular SBDD (Structure Based Drug Design) method [2]. Foreseeing the binding type, binding degree and binding sites between molecules helps drug discovery and development area significantly. At first this technique designed to be used between ligand and protein which are small molecule and target molecule but in the last ten years protein-protein docking, ligand-nucleic acid docking and protein-nucleic acid-ligand docking concepts are highly popular with the growing interest in area and because of the developments of computational methods [2].

The most important elements of molecular docking include sampling and scoring [1]. Sampling represents prediction of the conformation of the ligand and its orientation and position together with the protein binding site. Scoring represents determining the quality of the binding and interactions between those molecules [2].

Molecular docking procedure basically includes these 4 steps:

1. Target selection and preparation: Target structure could be detected experimentally with using X-ray crystallography or NMR (nuclear magnetic resonance) spectroscopy ideally [3]. In some cases, target structure can be modeled by using 3D modeling programs. The structure model should be prepared in good quality and well tested with specialized software [3]. While molecules binding, the bond between them can be affected by other factors such as water molecules and side chains [2, 3]. So, removing those components till the target becomes biologically active and stable is as important as preparing the main structure [3].

2. Ligand selection and preparation: Ligand selection depends on the aim of the study. The information and structure about the molecule can be acquired from many different databases on the other hand it can be modeled by using 3D modeling programs [3]. Ligands can be bind with various types of molecules so eliminating by filtering the molecules that ligand may has affinity is important for the success of the procedure.

3. Binding/Docking: When ligand is bound to the active site of the receptor, the docking is completed. Investigating and detecting the interactions between molecules is the important step of this procedure [2, 3].

4. Analyzing Docking: The generated dockings are visualized and ranked based on their predicted binding affinity or binding energy scores. The scoring function quantitatively evaluates the strength of the ligand-receptor interaction, helping identify the most suitable binding for the aim of the study [3].

There are various of molecular docking software that can be used for predicting favorable fittings within the molecules [4]. They can be classified as ''Rigid-docking'' software which refers when both ligand and receptor are considered as rigid bodies and the fitting pattern is suited for ''lock and key'' model; ''Flexible-rigid docking'' softwares which refers when ligand is flexible and receptor is rigid and the fitting pattern is suited to ''induced fit'' model partially; and lastly ''Flexible-docking'' software when both ligand and receptor considered as flexible/soft bodies and the fitting pattern is suited to ''induced fit'' model (Table 1) [4, 5].

Table 1. Classification of molecular docking software and their main properties (adapted from [3])

Rigid Docking Software	Flexible-Rigid Docking Software	Flexible Docking Software
Early method, can be applied for macromolecules	Widely used, more reliable than rigid model	The most reliable, requires much more calculation
Only positions can be changed	Receptor molecules conformation is fixed	Conformation of the ligand and receptor is highly flexible
Rigidity does not allow to spatial shapes	Conformation of the ligands and small molecules is flexible	Software and hardware for accuracy and calculation are exceptionally needed

Results and Discussion

Molecular docking is a computational technique used in the field of molecular biology and drug discovery. It involves predicting the proper orientation or binding mode of a ligand within a target receptor to form a stable complex. With molecular docking softwares, it is possible to find and analyze the most suitable binding between the molecules with the help of specific algorithms [4].

Scientist from İstanbul University published a study which they performed molecular dynamic and molecular docking tests on the L-Glycyl-L-Glutamic Acid Dipeptide (Gly-Glu-dipeptide) by using suitable docking software. In some neurodegenerative diseases such as Alzeimer's Disease, this molecule plays an important role in preventing neuronal degeneration with its anti-apoptotic behavior. Firstly, with the help of molecular dynamic calculations, they explored the conformational variation of the dipeptide molecule then they determined and analyzed the most stable 3D structure possibly. Molecular docking procedure applied for Caspase 3 and dipeptide. As a result of molecular docking dipeptide linked to the Caspase 3's active site and showed the stability degree and locations of the bonding. Lastly, scientist tried to determine the drug ability of the dipeptide by using specialized software and calculations. As a result, they reported that L-Glycyl-L-Glutamic Acid Dipeptide could be an active drug candidate for Alzeimer's Disease [1].

In another study, scientists generated and reported various of DNA gyrase inhibitor candidates as an antibacterial treatment. DNA gyrase is a bacteria originated enzyme which unvinds bacterial DNA. With the help of software and calculations, scientists investigated some binding patterns with the known inhibitors of the enzyme. They observed how inhibitors and enzyme exchange hydrogen bonds and the necessity of the lipophilic interactions during the binding. With those information and models, scientist revealed a various number of molecules which fit this binding model and can be potent inhibitor for the DNA gyrase enzyme [5, 6].

Scientists from Ahmadu Bello University studied binding patterns between 2,4-Disubstitued Quiloline derivatives and Lipoate Protein B (LipB) by using molecular docking tools. LipB protein is the *Mycobacterium tuberculosis* receptor and has a potential as a target for anti-tuberculosis treatments [7]. Tuberculosis still needs better treatment method since current vaccines such as BCG is not efficient enough. For this study LipB protein selected as a target antigen and binding patterns and affinities of derivatives detected and compared with eachother and other known drugs. They reported that Ligand 8 and Ligand 17 were able to bind LipB target better than other derivatives and known drugs and they have a potential to be more suitable anti-tuberculosis drug candidates [7].

As another example of molecular docking study, scientist tried to find biopolymer adjuvant carriers for treatment of Dengue disease. Dengue disease is caused by dengue virus (DENV) and its incidence is highly increased in the last decade. They used monomer units of CS (chitosan), PVP (polyvinylprrolidone), and CS/TPP/CS [chitosan-tripylphosphate-chitosan) as ligands and E protein of the virus as a target. With the help of suitable softwares and algorithms, molecular docking patterns and affinities detected. They reported that each biopolymer has great affinity to E protein and they can be used as potent adjuvants for dengue virus vaccines [3].

Conclusion

Molecular docking has emerged as a pivotal tool in the field of computational drug discovery [4]. The molecular docking concept allows for efficient screening of compound libraries, coherent optimization of molecules and comprehensive understanding of ligand-target interactions [2]. As computational methods continue to develop and our knowledge of protein structures and dynamics expands [4,5], molecular docking plays an important role in the development of novel therapeutics such as inhibitors, adjuvants, blockers or catalysts etc; benefiting patients worldwide at last. On the other hand, there is still a room for progress in molecule libraries, algorithms and more accessible hardware and software for the molecular docking studies.

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