IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Process Of Molecular Docking

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❖ ABSTRACT

Molecular docking is a key computational technique in drug discovery, used to predict the interaction between small molecules and target proteins. Over the past decade, significant progress has been made in improving docking algorithms, scoring functions, and integrating artificial intelligence (AI) to enhance predictive accuracy.

❖ INTRODUCTION

Molecular docking [1] is such a structure-based drug design method that simulates the molecular interaction and predicts the binding mode and affinity betwee receptors and ligands. In recent years, this technology has been widely used in drug design research field. Using the compounds database to screen the potential pharmacophores is not only convenient for researchers to purchase, synthesize and complete follow-up pharmacological tests, but also greatly improves the efficiency and reduces the research cost. In addition, the emergence of the reverse molecular docking technology [2] could significantly improve the drug target predictive capacity and under stand the related molecular mechanism for drug design. Finally, this review briefly introduces the latest progress and applications of molecular docking technology.

Keywords: molecular docking; numerical analysis; optimization; data mining

❖ THE INTRODUCTION OF MOLECULAR DOCKING TECHNOLOGY

The basic theory of molecular docking Molecular docking is to simulate the optimal conforma according to the complementarity and pre-organization which could predict and obtain the binding affinity and interactive mode between ligand and receptor [1].Figure 1A shows the first proposed"lock-and-key model" [3], which refers to the rigid docking of receptors and ligands to find the correct orientation for the"key" toopen up the"lock". This model emphasizes the importance of geometric complementarity.

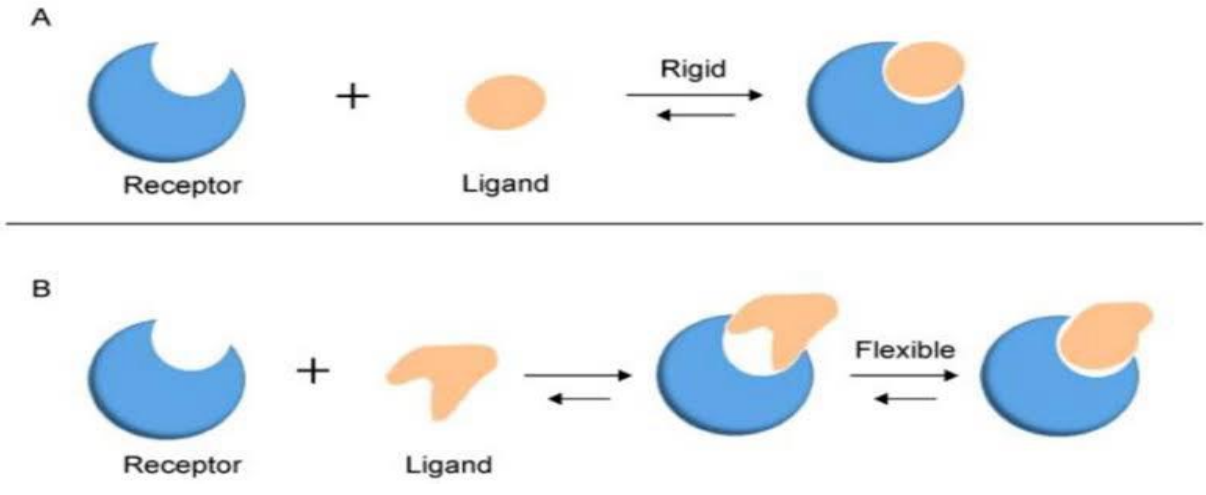
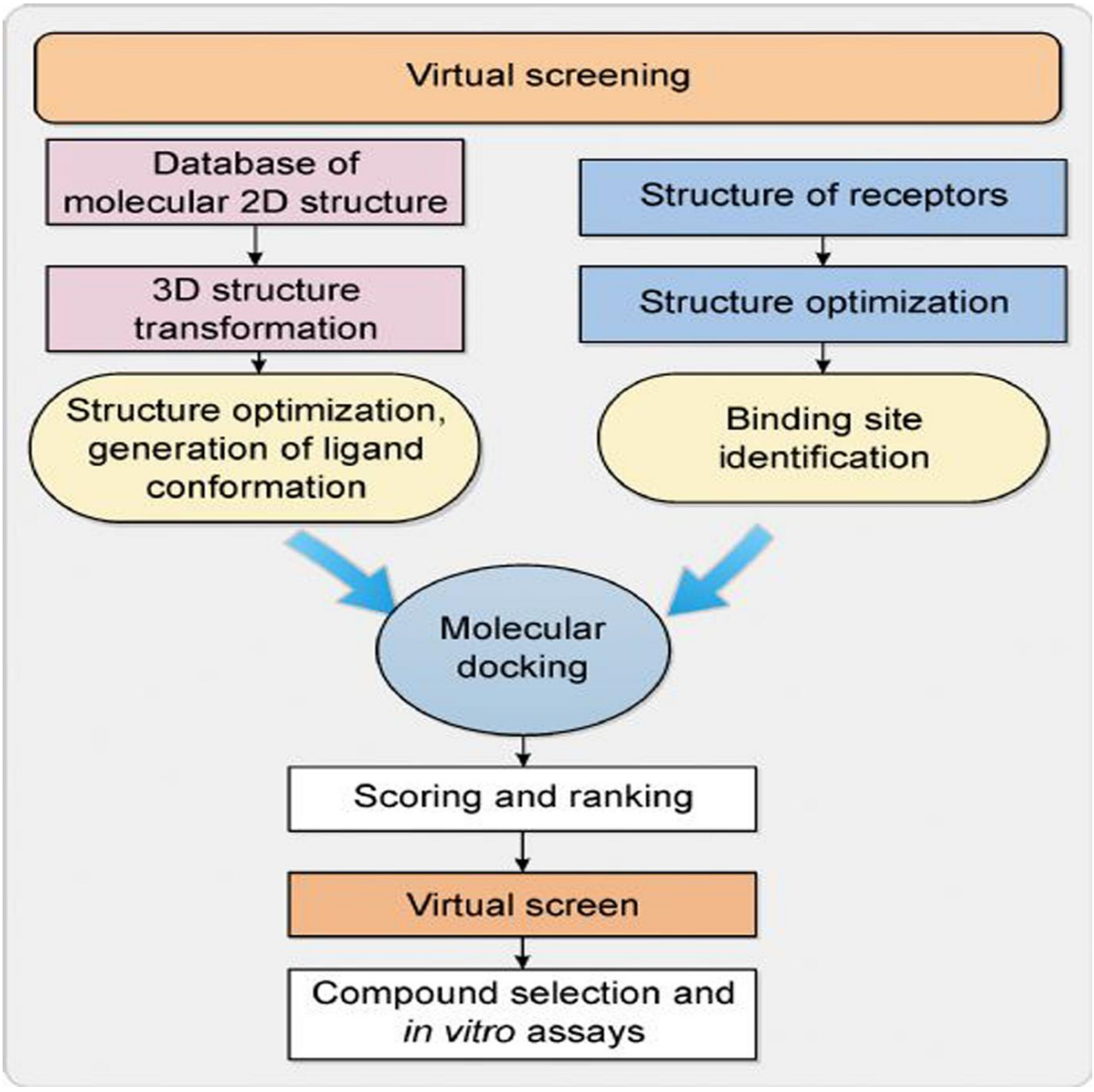


Figure Figure 1. Two models of molecular docking. (A) A lock-and-key model. (B) Induced fit model.

However, the real docking process is so flexible that receptors and ligands have to change their conformationto fit each other well. Thus, we develop“induced fit model” (Figure 1B) [4]. Based on geometric comple- mentarity, the energy complementarity and pre-organiza- guarantee that receptors and ligands would obtain themost stable structure in such a manner that minimizes the free energy [5]. As shown in Figure 2, the molecular docking softwarecan help us to find the optimal conformation and orientation according to complementarity and pre-organization with specific algorithm, followed by applying a scoring function to predict the binding affinity and analyse the interactive mode. Figure 3 shows the protein-DNA docking with Auto dock Vina [6] displayed

Figure 2. Molecular docking processing .



❖ **Molecular Dolphins Software**

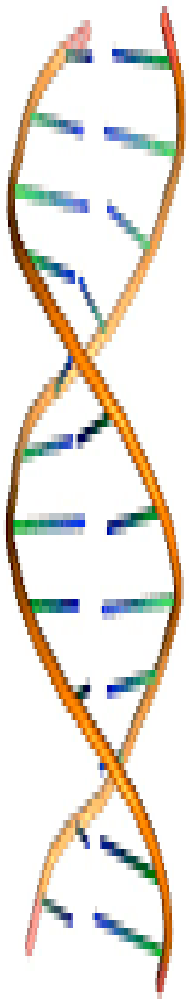


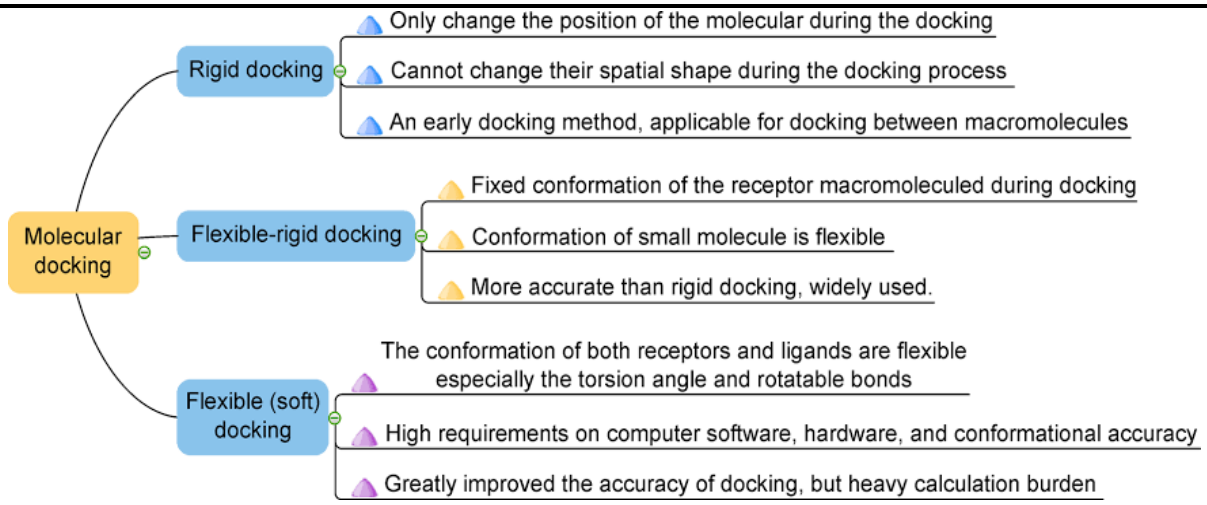
Figure 4 lists the main three types of software for molecular docking. Flexible-rigid docking has been widely used. However, since flexible docking is usually more accurate, the relevant researches have become the hot studying spot in recent years. Table 1 lists the widely- used molecular docking software and its algorithms, evaluation methods, features and application areas.

❖ **Molecular Docking Databases**

The most popular protein structure database is the public database Protein Data Bank (PDB) [8]. Also, the public databases such as PubChem Compound Database [9] and ZINC [10] are free to use. Besides, there are many important commercial databases, such Compound Database (AcD) [11], Cambridge Structural Database (CSD) [12].

❖ **THE APPLICATIONS OF MOLECULAR DOCKING**

Virtual screening to discover the lead compounded hit compoun. Virtual screening [13] is to find the lead compound and hit compound from the molecular databases according to the scoring function, which has tremendously improved the screening efficiency compared with the traditional screen method (Figure 5). The applications of virtual screening are commonlyused. Notably, given the exponential growth of high throughput [14], high-performance computing [15],machine learning [16] and deep learning [17] techniques, the integrated method flourishes quickly. For example, Pereira at. al.[18]applied deep learning approach in virtual screening, which extracts relevant features from molecular docking data to create the distributed vector representations for protein-ligand complexes. Also, Pyzerknapp et al. [19] proposed the virtual high-throughput screening.



Prediction of potential targets.

It is noted that the aforementioned methods are all general docking methods which use the different ligands in the database to dock with the same receptor. However, current commonly used reverse docking technique is different from them. Here, we employed Figure 6 describe the reverse docking technique [2].

Molecular docking databases

The most popular protein structure database is the public database Protein Data Bank (PDB) [8]. Also, the public

Table 1 Representative software for molecular docking.

Sr. No.	Name	Evaluation method	Features & Application areas
1	Flex X [33]	Semi-empirical calculation on free energy	Flexible-rigid docking. It can be used for virtual screening of small molecule databases by using incremental construction strategy
2	Gold [34	Semi-empirical calculation on free energy	Flexible docking. It is a GA-based docking program. The accuracy and reliability of this software have been highly evaluated
3	Glide [35	Semi-empirical calculation on free energy	Flexible docking. This software uses domain knowledge to narrow the searching range and has XP(extra precision), SP (standard precision) and high throughout virtual

			screen modes
4	AutoDock [36]	Semi-empirical calcu-lation on free energy	Flexible-rigid docking. This software is always used with Autodock-tools and it is free for academic use
5	ZDOCK [37]	Molecular force field	Rigid docking. Chen et al. [37] propose a new scoring function which combines pairwise shape complementarity(PSC) with desolvation and electrostatic and develop the ZDOCK server [38]
6	RDOCK [39]	Molecular force field	Rigid docking. The CHARMm-based procedure for refinement and scoring. Besides predicting the binding mode, it is especially designed for high throughput virtual screening (HTVS) campaigns
7	LeDOCK [40]	Molecular force fie	Flexible docking. LeDock is a new molecular docking program. From the results of the present study [41], since it is fast and exhibits a high accuracy, it is recommended for the virtual screen task
8	Dock [42]	Molecular force field	Flexible docking. It is widely applicable and is always used in docking between flexible proteins and flexible ligands
9	Autodock Vina [6]	Semi-empirical calcu-lation on free energy	Flexible-rigid docking.

			AutoDock Vina employs an iterated local search global optimizer and it is faster than the AutoDock 4

docking technique identifies the novel targets by assign-ing a single small-molecule ligand as the probe to dock with multiple receptors to discover potential binding cavities. In this way, the potential targets of drug can be predicted. For example, Grinter et al. [20] explored the potential target oxidized squalene cyclase (OSC) of PRIMA-1 by using the reverse docking software package Mdock. Also, Chen et al. [21] applied reverse docking technique to discover targeted proteins of marine compounds with anti-tumor activity. Furthermore, Chenet al. [21] also indicated that reverse docking can be complementary with in vitr assays as an effective method of target fishing. Finally, we considered that exploring relevant mechanism of action or side effect profile by structural biology analysis [22] such as the pocket analysis [23], could significantly benefit the novel drug design.

CONCLUSION

Considering the approximation capacity of the scoring function and incomplete collection of conformations,molecular docking score of inactive molecules will be improperly so high that implicates false positive [24–26]. Furthermore, if the actual compound and the compound in database are significantly different in physical properties, the molecular docking score will be abnormal [27]. Therefore, it is necessary to take thermodynamic features into account [28], or use retrospective verification to evaluate the reliability of the prediction of affinity [29]. In addition, as the three-dimensional. structure used for molecular docking will be away from its original environment resulting in a change in conformation, the docking result cannot truly reflect the state of the experimental docking. In the distant future, we are optimizing the conformational search algorithm by taking more flexible bonds, solvent states and integrating recent biological data mining algorithms [30–32] in considera-tion. In general, we believe that molecular docking technique will become such a reliable drug-design tool that integrate the big biological data by optimizing the scoring function and upgrading the relevant search-algorithms

ACKNOWLEDGEMENTS

This study was supported by the National Natural Science Foundation of China (No. 61372138) and the National Science and Technology Major Project of China (No. 2018ZX10201002).

COMPLIANCE WITH ETHICS GUIDELINES

The authors Jiya Fan, Ailing Fu and Le Zhang declare that they have no conflict of interests. This article is a review article and does not contain any studies with human or animal subjects performed by any of the authors.

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