**Pharmaceutical Science and Technology**
2023; 7(1): 1-4
http://www.sciencepublishinggroup.com/j/pst
doi: 10.11648/j.pst.20230701.11
ISSN: 2640-4532 (Print); ISSN: 2640-4540 (Online)

# Panoramic Review on Progress and Development of Molecular Docking

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**To cite this article:**
Kiran Dudhat. Panoramic Review on Progress and Development of Molecular Docking. *Pharmaceutical Science and Technology*. Vol. 7, No. 1, 2023, pp. 1-4. doi: 10.11648/j.pst.20230701.11

**Received**: November 7, 2022; **Accepted**: November 28, 2022; **Published**: March 15, 2023

**Abstract:** In structural molecular biology and computer-assisted drug creation, molecular docking is a crucial tool. Predicting the prevailing binding mode (s) of a ligand with a protein having a known three-dimensional structure is the aim of ligand-protein docking. Effective docking methods use a scoring system that correctly ranks candidate dockings and efficiently explore high-dimensional spaces. Lead optimization benefits greatly from the use of docking to do virtual screening on huge libraries of compounds, rate the outcomes, and offer structural ideas for how the ligands inhibit the target. It can be difficult to interpret the findings of stochastic search methods, and setting up the input structures for docking is just as crucial as docking itself. In recent years, computer-assisted drug design has relied heavily on the molecular docking technique to estimate the binding affinity and assess the interactive mode since it can significantly increase efficiency and lower research costs. The main concepts, techniques, and frequently utilized molecular docking applications are introduced in this work. Additionally, it contrasts the most popular docking applications and suggests relevant study fields. Finally, a brief summary of recent developments in molecular docking, including the integrated technique and deep learning, is provided. Current docking applications are not precise enough to forecast the binding affinity due to the insufficient molecular structure and the inadequacies of the scoring mechanism.

**Keywords:** Molecular Docking, Use, Optimization, Software for Molecular Docking, Virtual Screening

## 1. Introduction

One such structure-based drug design technique is molecular docking [1], which simulates molecular interaction and forecasts the binding mechanism and affinity between receptors and ligands. This method has been extensively employed in the field of drug design research in recent years. In addition to making it easy for researchers to buy, manufacture, and finish further pharmacological experiments, using the compounds database to screen possible pharmacophores also significantly increases efficiency and lowers research costs. Additionally, the development of reverse molecular docking technology has the potential to dramatically enhance the ability of researchers to forecast therapeutic targets and comprehend the underlying molecular mechanisms that underlie drug design [2]. The overview concludes by briefly introducing the most recent developments and uses of molecular docking technology. This review's objective is to analyze the most recent developments in the field of molecular docking as well as the role that structural integration plays in drug discovery and medicinal chemistry.

The number of tools available for structure-based drug design is expanding quickly, driven by improvements in the determination of molecular structure. An appealing alternative to high-throughput random screening is lead discovery using molecular docking techniques to scan ligand databases [1]. When it comes to molecular docking, the scale of commercial databases places severe computational restrictions on the amount of calculational information that is allowed for each potential ligand. We discuss alternate docking philosophies that successfully handle this issue. These strategies fall within a range of models that are constrained by the Lock-and-Key and Induced-Fit theories for ligand binding with regard to the dynamic features of molecular recognition. We investigate the potential of a tolerant model for forecasting absolute ligand binding affinity vs a rigid model for leveraging species specificity.

We emphasize this aspect of the issue throughout our

validation of docking procedures because it is one of the main ways that current molecular docking approaches are constrained. Finding a suitable location and orientation for docking a tiny molecule (ligand) to a bigger receptor molecule is known as the molecular docking problem.

## 2. Molecular Docking Technology

*The Fundamental Concepts of Molecular Docking*

In order to predict and determine the binding affinity and interactive mode between ligand and receptor, molecular docking simulates the ideal conformation in accordance with complementarity and pre-organization [1]. The original "lock-and-key model", which makes reference to rigorous docking of receptors and ligands to determine the best orientation for the "key" to open the "lock," is depicted in Figure 1A. The significance of geometric complementarity is emphasized by this model [3]. In structural molecular biology and computer-assisted drug creation, molecular docking is a crucial tool. Predicting the dominant binding mode (s) of a ligand with a protein having a known three-dimensional structure is the aim of ligand-protein docking. Effective docking methods use a scoring system that correctly ranks candidate dockings and efficiently explore high-dimensional spaces. Lead optimization benefits greatly from the use of docking to do virtual screening on huge libraries of compounds, rate the outcomes, and offer structural ideas for how the ligands inhibit the target [3]. It can be difficult to interpret the findings of stochastic search methods, and setting up the input structures for docking is just as crucial as docking itself.

However, the actual docking procedure is so adaptable that ligands and receptors must alter their conformation to fit one another well. We create a "induced fit model" as a result (Figure 1B) [3]. The energy complementarity and pre-organization, which are based on geometric complementarity, ensure that receptors and ligands will achieve the most stable structure while minimizing the free energy [4].

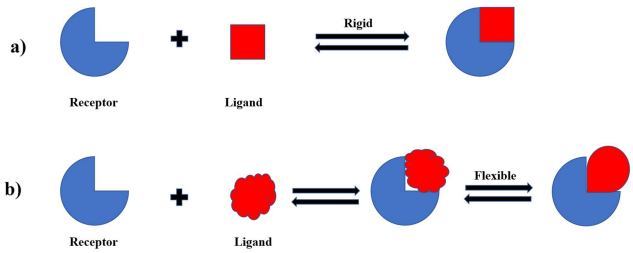


***Figure 1.*** *Molecular docking models a) Lock and Key Model b) Fit- Induced Model.*

Molecular docking software can help us find the optimal conformation and orientation in accordance with a certain algorithm, as shown in Figure 2. The binding affinity can then be predicted using a scoring method, and the interactive mode can be assessed. using Autodock Vina to dock proteins and DNA [5]. To explore intricate biological and chemical systems, pharmaceutical research has effectively incorporated a wide range of molecular modelling techniques into a number of drug development initiatives. The creation of new, promising chemicals has greatly benefited from the merging of computational and experimental methodologies. Molecular docking techniques, which are widely utilized in contemporary drug design, investigate the ligand conformations taken within the binding sites of macromolecular targets [6]. By analyzing crucial aspects of the intermolecular recognition process, this method also calculates the ligand-receptor binding free energy. Since there are numerous docking algorithms available nowadays, it is essential to comprehend the benefits and drawbacks of each algorithm before developing efficient tactics and producing pertinent outcomes.

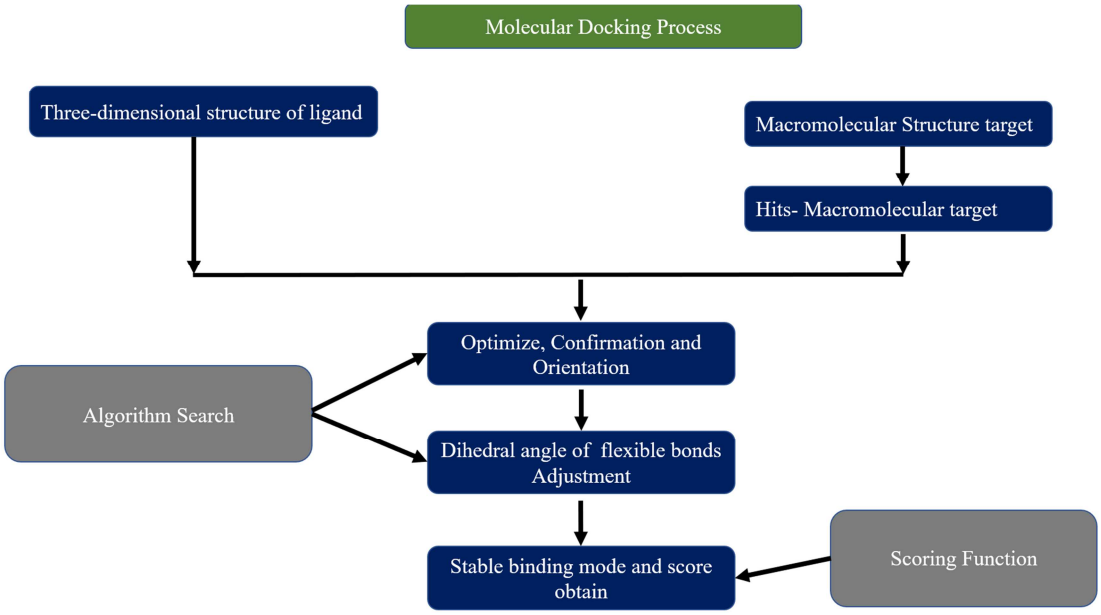


***Figure 2.*** *Molecular Docking Process.*

## 3. Software for Molecular Docking

Figure 3 lists the three main types of molecular docking software. Flexible-rigid docking is frequently used. But because flexible docking is usually more accurate, there has been an increase in research in this field in recent years [7]. Using machine-learning techniques, several new, or at least revitalized, advancements were made in fields such nonlinear scoring functions. The recent developments in drug design, particularly in virtual screening and fragment-based drug design, are the main focus of this study. The behavior of tiny molecules at the binding site of a target protein is investigated by molecular docking methods. Molecular docking is utilized more frequently as a method in drug development as more protein structures are discovered experimentally using X-ray crystallography or nuclear magnetic resonance (NMR) spectroscopy. It also becomes possible for proteins whose structures are unknown to dock to homology-modeled targets [7]. For subsequent lead optimization procedures, the druggability of the compounds and their specificity against a certain target can be determined using the docking techniques.

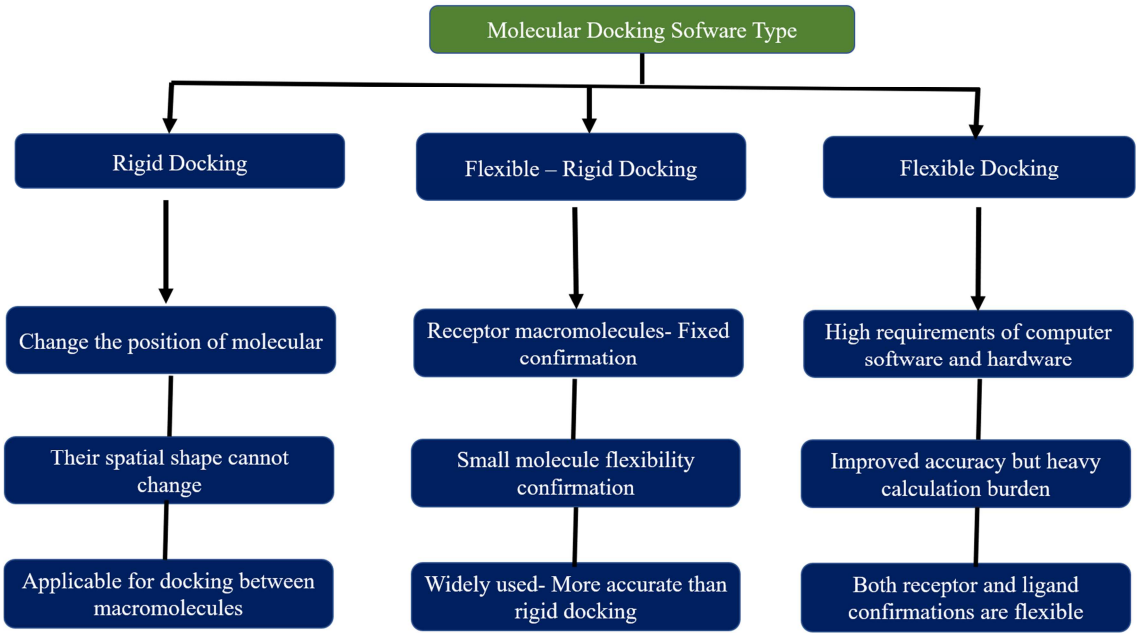


***Figure 3.*** *Molecular Docking Software Type.*

## 4. Use Cases for Molecular Docking

*To Find the Lead Compound and the Hit Compound Via Virtual Screening*

Through the use of molecular databases and the scoring system, virtual screening has greatly outperformed traditional screening in terms of screening efficiency [8].

Applications for virtual screening are often used. Notably, the rapid growth of high-throughput, high performance computing, machine learning, and deep learning methodologies has contributed to the success of the integrated strategy [9, 10, 11, 12, 13]. For instance, Pereira et al deep's learning approach was used in virtual screening to construct distributed vector representations of protein-ligand complexes by extracting pertinent features from molecular docking data. Another suggestion was made by Pyzerknapp et al. [14] for virtual high-throughput screening.

## 5. Prediction of Targets' Potential

The above methods all use general docking strategies that use different ligands from the database to dock with the same receptor. Although different from them, the reverse docking technique now in use [9, 15]. By using a single small-molecule ligand as the probe to dock with various receptors to find potential binding holes, the reverse docking approach identifies novel targets [16, 17]. In this way, the likely targets of a medication can be predicted. Last but not least, we believed that using structural biology analysis, such as the pocket analysis, to examine relevant mechanisms of action or side effect profiles, could significantly help in the creation of innovative medications [6, 18, 19].

Molecular docking is more and more taken into account for lead discovery as the structures of more and more proteins and nucleic acids become known. Recent research takes into account the improvement of docking screens' hit rates and the precision of docking structure forecasts. As more experimentally defined protein structures are discovered, more proteins can be docked against homology-modeled targets.

One important molecular docking statistic is the enrichment of ligands among top-ranking hits. Decoys should be physically similar to ligands in order to prevent bias and ensure that enrichment is more than just the separation of superficial features, but chemically different from them in

order to make it less likely that they are binders. A directory of usable decoys (DUD) with 2950 ligands for 40 different targets has been put together by us. A database of 98266 compounds is produced by the 36 decoy molecules that each ligand contains, which are physically identical but topologically distinct. With uncorrected databases like the MDDR, enrichment was at least half a log better for the majority of targets than with DUD, showing bias in the latter. These calculations also enabled 40×40 cross-docking, allowing a specificity metric for the docking screens by comparing the enrichments of each ligand set for each of the 40 targets.

## 6. Conclusion

Due to the scoring function's approximation capacity and an insufficient array of conformations, the molecular docking score of inactive molecules will be incorrectly so high that it implies a false positive. Additionally, if there is a significant difference between the physical characteristics of the chemical in question and the compound in the database, the molecular docking score will be abnormal. As a result, one must either use retrospective verification or take into account thermodynamic properties in order to evaluate the correctness of the forecast of affinity. Additionally, since the three-dimensional structure would have changed conformation as a result of being taken out of its native context, the molecular docking result cannot precisely reflect the state of the actual docking.

By taking into account more flexible bonds, solvent conditions, and contemporary biological data mining tools, we are enhancing the conformational search approach in the distant future. In general, we believe that the molecular docking technique will evolve into a reliable drug-design tool that incorporates the substantial amount of biological data by enhancing the scoring function and modernizing the applicable search algorithms.

## Authors' Contributions

All the authors have contributed to the research work and preparation of the final manuscript.

## Conflict of Interests

All the authors do not have any possible conflicts of interest.

## Acknowledgements

No acknowledgments.

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