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Review Article
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MOLECULAR DOCKING STIMULATION OF DRUGS

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Abstract
Molecular docking has become an increasingly important tool in drug discovery. In this review, we present a brief introduction to available molecular docking methods, along with their development and applications in drug discovery. Relevant basic theories, including sampling algorithms and scoring functions, are summarized. The differences and performance of available docking software are also discussed. Flexible receptor molecular docking approaches, particularly that involving backbone flexibility in receptors, remain a major challenge for current docking methods. A recently developed Local Move Monte Carlo (LMMC)-based approach is introduced as a potential solution to flexible receptor docking problems. Finally, three application examples of molecular docking approaches in drug discovery are presented.

Keywords: *Molecular docking, Drug discovery, Scoring functions, Flexible receptor docking, Monte Carlo simulation, Docking software.*

INTRODUCTION

The completion of the human genome project has resulted in an increasing number of new therapeutic targets for drug discovery. At the same time, high-throughput protein purification, crystallography and nuclear magnetic resonance spectroscopy techniques have been developed and contributed to many structural details of proteins and protein–ligand complexes. These advances allow the computational strategies to permeate all aspects of drug discovery today, such as the virtual screening (VS) techniques for hit identification and methods for lead optimization. Compared with traditional experimental high-throughput screening (HTS), VS is a more direct and rational drug discovery approach and has the advantage of low cost and effective screening. VS can be classified into ligand-based and structure-based methods. When a set of active ligand molecules is known and little or no structural information is available for targets, the ligand-based methods, such as pharmacophore modeling and quantitative structure activity relationship (QSAR) methods can be employed. As to structure-based drug design, molecular docking is the most common method which has been widely used ever since the early 1980s.Programs based on different algorithms were developed to perform molecular docking studies, which have made docking an increasingly important tool in pharmaceutical research.

Various excellent reviews on docking have been published in the past and many comparison studies were conducted to evaluate the relative performance of the programme. The molecular docking approach can be used to model the interaction between a small molecule and a protein at the atomic level, which allow us to characterize the behavior of small molecules in the binding site of target proteins as well as to elucidate fundamental biochemical processes. The docking process involves two basic steps: prediction of the ligand conformation as well as its position and orientation within these sites (usually referred to as pose) and assessment of the binding affinity. These two steps are related to sampling methods and scoring schemes, respectively, which will be discussed in the theory section.

Knowing the location of the binding site before docking processes significantly increases the docking efficiency. In many cases, the binding site is indeed known before docking ligands into it. Also, one can obtain information about the sites by comparison of the target protein with a family of proteins sharing a similar function or with proteins co-crystallized with other ligands. In the absence of knowledge about the binding sites, cavity detection programs or online servers, e.g. GRID, POCKET, SurfNet, PASS and MMC can be utilized to identify putative active sites within proteins.

Docking without any assumption about the binding site is called blind docking.

History:

1970s–early 1980s: The concept phase

1975: Levinthal's "paradox" highlighted that protein folding couldn't be random search. This pushed the idea of computational prediction.

Early 1980s: First rigid-body docking programs appeared. DOCK was developed by Irwin Kuntz's group at UCSF in 1982. It treated both ligand and protein as rigid and used shape complementarity to fit small molecules into binding pockets.

Late 1980s–1990s: Flexibility + scoring

X-ray crystallography + NMR boom gave real 3D protein structures from the PDB, launched 1971. Docking finally had targets.

AutoDock (1990) by Arthur Olson's lab added ligand flexibility and grid-based energy scoring. Major leap for drug discovery.

1990s: Force fields like AMBER, CHARMM got better. Programs like FlexX, GOLD, and Glide introduced new algorithms. Fragment-based docking and genetic algorithms appeared to handle ligand conformational space.

2000s: Mainstream in pharma

Structure-based drug design became standard. HIV protease inhibitors like saquinavir and indinavir were some of the early success stories where docking guided design.

Virtual screening: Libraries of millions of compounds could be docked to find hits. DOCK, AutoDock Vina (2010), and Glide became workhorses.

Induced fit: Software started allowing protein side-chain and even backbone flexibility, like Schrödinger's Induced Fit Docking protocol.

2010s–now: AI, physics, and scale

GPU acceleration + cloud: Docking millions of compounds became routine. ZINC database + Vina made ultralarge virtual screening possible.

Types of docking

There are two distinct forms of docking.

1. Rigid docking
2. Flexible docking

RIGID DOCKING

Assuming the compounds are inflexible, we are seeking a rearrangement of one of the compounds in three-dimensional space that results in the best match to the other compounds in parameters of a scoring system. The ligand's conformation can be formed with or without receptor binding activity.

Flexible docking

In conjunction with transformation, we evaluate molecular flexibility to identify confirmations for the receptor and ligand molecules as they exist in the complex.

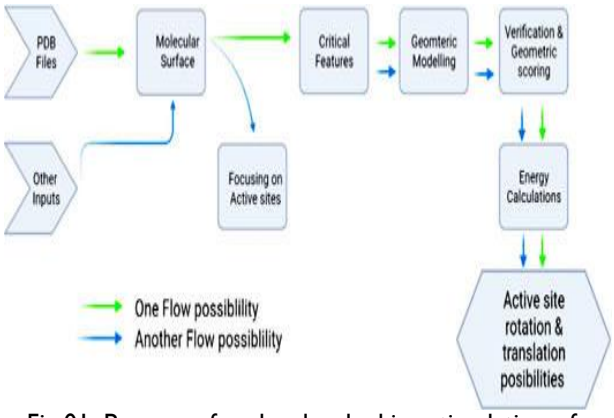

Fig 01: Process of molecular docking stimulation of drugs

LIMITATIONS

There are mainly 7 limitations

- Lack of quality datasets.
- Lack of standardization.
- Accurate scoring functions.
- Model interpretation issues.
- Issues with multi-domain proteins.
- Assessment of multi-drugs effects.

APPLICATIONS

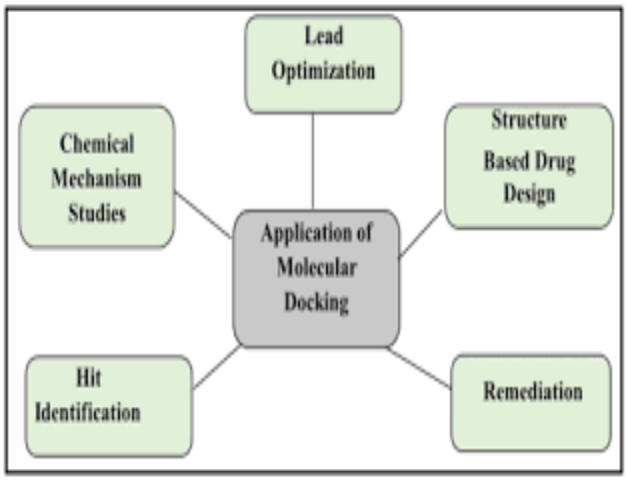

Fig 02:Applications of molecular docking stimulation of drugs

CONCLUSION

Since its first appearance in the mid 1970's, molecular docking has represented a unique in silico tool to assist drug design and discovery. However, beyond the applications for which it was originally developed, docking is now also widely employed to assist a variety of other drug discovery tasks, such as the identification of novel chemical scaffolds within large libraries of compounds, to perform in silico target fishing and profiling for drug repositioning, polypharmacology, prediction of adverse effects and beyond, as described in this review article. Being a versatile tool, docking will certainly find application also in other fields of drug discovery. Moreover, docking has been successfully embedded within automated workflows for the screening of large libraries of compounds and targets.Of course, the recent advancements in the field

of high-performance computing played a key role in this respect. For example, they enabled the in silico screening of millions of compounds in an affordable time.Moreover, the recent advancements on Graphics Processing Units (GPUs) have also provided remarkable improvements, both in data-driven drug discovery and in molecular dynamics simulations.Indeed, GPU calculations enabled a large exploration of the conformational landscape potentially accessible to proteins, in shorter times with respect to CPUs.Finally, GPU computing made big data-driven computation tasks accessible to a larger public and it is expected to play a prominent role, not only in docking but in future in silico drug design in general.

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