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An Overview of Molecular Docking - A Novel Technique for Drug Discovery

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ABSTRACT

Computer-aided drug design and discovery (CADDD) is a fast developing discipline that has experienced several achievements in recent years. In addition to academics, several large drug manufacturers use CADDD for lead development. The emergence of molecular informatics, genomics, and proteomics is driving efforts toward modern-era drug discovery and development. Over the last two decades, enormous research has been conducted to investigate alternative docking methods and predict the active site of the molecule. Several docking tools have been created to show the 3D structure of the molecule, and docking score may also be assessed using various computational approaches. Molecular Docking is a type of structure-based virtual screening (SBVS) that employs computer-generated three-dimensional structures containing biomolecules to incorporate them in a target structure together in number of locations, conformations, and orientations. Protein-ligand docking is a novel idea with several applications. It serves as an active research domain due to its importance in structure-based drug design (SBDD), lead optimization, biochemical pathway evaluation, and De Novo drug design. The entire explanation of Molecular Docking is mentioned in this Review. The binding mechanism and affinity of the complex generated are evaluated via Molecular Docking, which aids in the Molecular Recognition Process docking towards the development of novel drug leads.

Keywords: Drug discovery; Molecular docking; ADMET; Binding; Conformations

I. INTRODUCTION

Molecular Docking is a tool for predicting the preferred orientation of a ligand towards a receptor (Protein) in order to form a stable compound (Lengauer et al 1996). Using scoring functions, preferred orientation might be used to estimate the strength of the link or binding affinity between ligand and protein. Docking is frequently used to predict the binding orientation of drug candidates against protein targets in order to predict the medication's affinity and activity (Figure 1). As a result, docking is critical in the drug design and discovery process (Kitchen et al 2004). The primary goal of molecular docking is to computationally mimic the molecular identification process and achieve an optimal conformation such that the total system's free energy is reduced. The process of discovering a new medicine is quite complex. The modern drug discovery process is mostly focused on an in-silico–chemico biological approach. The use of computer-aided approaches in the drug design and development process rapidly successful strategies, acceptance, and adoption.

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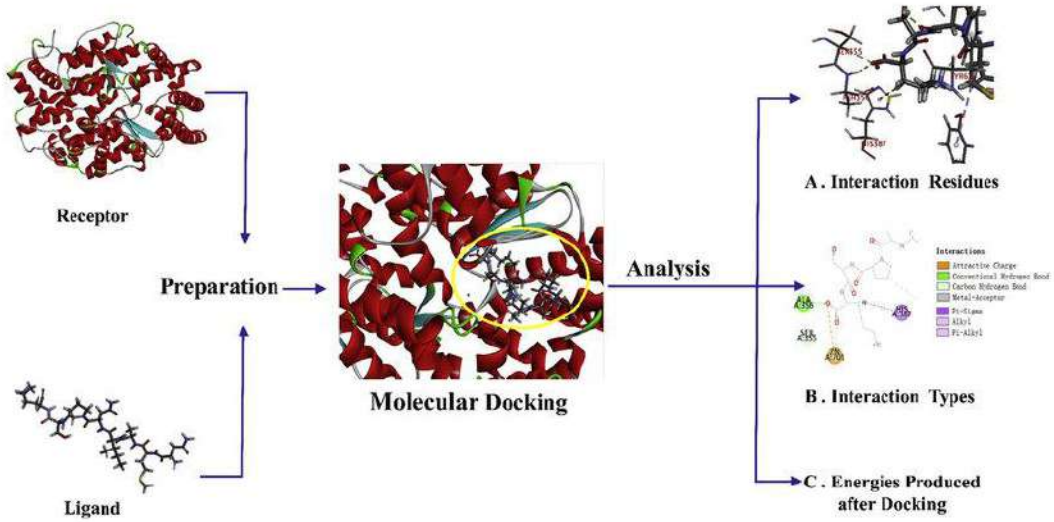

Figure 1: Shows Flow chart for molecular docking

II. CADD (COMPUTER-AIDED DRUG DISCOVERY)

a) Enhancing use of computational capabilities to intensify the drug research and development process.

b) To find and improve therapeutic approaches, take use of biological and chemical knowledge about the importance of ligands and/or targets.

c) Establishing in-silico screening to exclude active ingredients with undesirable features (low activity and/or poor Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET)) and identifying among most potential candidates.

d) Insight into potential therapeutic targets and acquisition of target protein structures from databases such as the Protein Data Bank (PDB) www.pdb.org. CADD (Figure 2) is utilised towards locate hits (drug candidates) (Pozzan 2006, Green 1990).

Different types of interactions

Interaction forces were classified into four types:

1. Electrostatic forces include dipole-dipole, charge-dipole, and charge-charge interactions.
2. Van der Waals interaction involves electrodynamic forces
3. Entropy promotes steric forces.
4. Hydrogen bonding and hydrophobic interactions under Solvent related forces (Goodsell et al 1990, Kuntz et al 1982).

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III. MOLECULAR DOCKING

Molecular docking is divided into two categories.

I) SEARCH ALGORITHM

The programme would generate the maximum number of configurations that enables binding modes to be determined using the experimental technique. Point complementary, Monte Carlo, Fragment-based, Genetic algorithms, Systematic searches, Distance geometry, and other algorithms have been used for docking analysis (Rarey et al 1997, Schulz-Gasch et al 2003).

II) SCORING FUNCTION

The scoring function provides a way to rate ligand placement proportionate to another. The score should ideally match to the ligand's binding affinity for the protein, such that the best scoring ligands are also the best binders.

Either empirical, knowledge-based, or molecular mechanics-based scoring functions can be used. The scoring system is made up of three distinct expressions that are used in docking and drug design:

(1) The docking search ranks the generated configurations.

(2) Virtual screening of several ligands against protein.

(3) The binding affinity of one or more ligands against various proteins (selectivity and specificity) (Friesner 2004, Jones et al 1997, Venkatachalam et al 2003, Abagyan et al 1994).

DIFFERENT METHODS OF DOCKING

The following are the most often used docking methods:

Rigid docking: It mainly involves keeping both the receptor as well as the ligand stable while docking takes place.

Fit induced docking: It mainly involves both the ligand and the receptor are conformational flexible in an induced fit docking. The surface cell occupancy and energy are computed for each rotation, and the most optimal position is then chosen (Trosset et al 1999).

IV. DOCKING MECHANICS

THE FOLLOWING ARE THE MAJOR STEPS IN MOLECULAR DOCKING MECHANICS:

In-silico study of the intermolecular interaction between two molecules is known as Molecular Docking. The protein receptor is the macromolecule in this process. The Ligand molecule is a tiny molecule that can serve as an inhibitor. As a result, the docking procedure entails the following steps:

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Step I – PROTEIN PREPARATION:

The three-dimensional structure of the protein should be downloaded from the Protein Data Bank (PDB), and then the structure should be pre-processed. According to the parameters supplied, this should allow for the removal of water molecules from the cavity, charge stabilisation, filling of missing residues, creation of side chains, and so on.

Step 2 - ACTIVE SITE PREDICTION

Once the protein has been prepared, the active site should be predicted. Although the receptor may have several active sites, just the one that is of concern should be chosen. If water molecules and hetero atoms have become present, they are mostly eliminated (McMartin et al 1997, Schnecke et al 2000).

Step 3 - LIGAND PREPARATION

Ligands could be acquired either from variety of sources, including ZINC and Pub Chem, or drawn using the Chem sketch tool. The LIPINSKY'S RULE OF 5 should be used while selecting the ligand. The Lipinski rule of five can help distinguish between non-druglike and druglike candidates. It indicates good possibility of success or failure owing to pharmacological similarity for compounds that follow two or more of the rules.

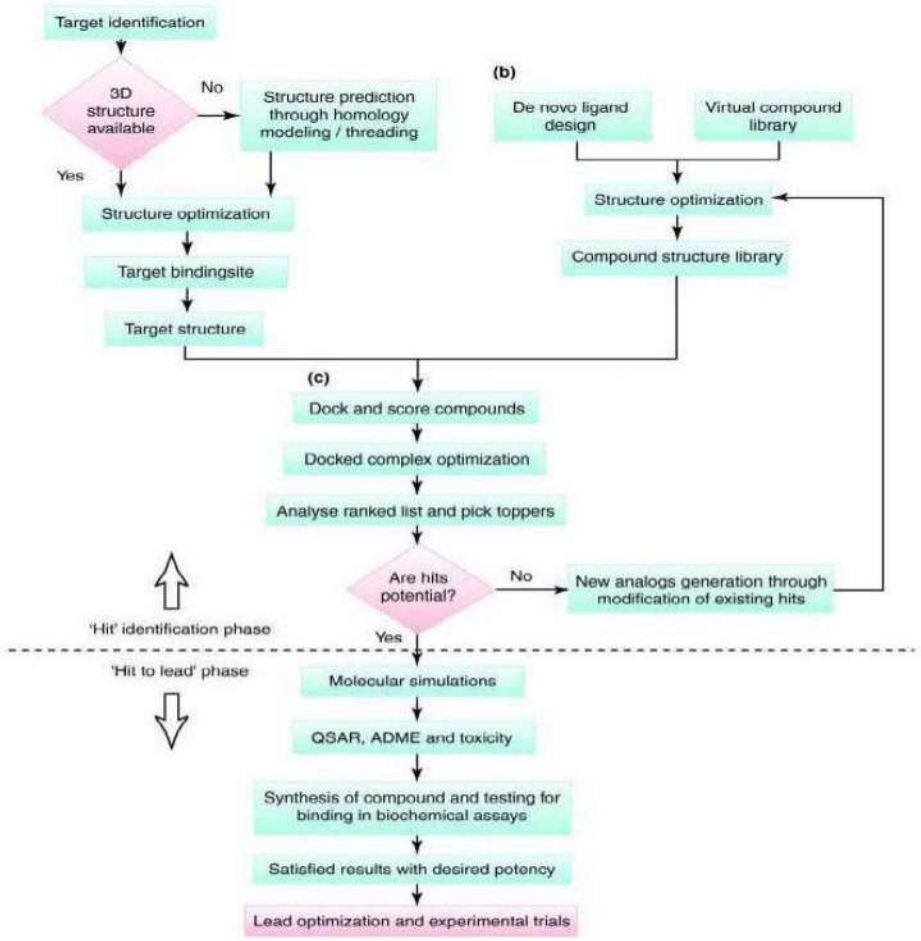

Figure 2: Shows Flow chart for Computer-aided Drug Design.

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LIPINSKY'S RULE:

It allows for the selection of a ligand.

(1) Less than five hydrogen bond donors
(2) Less than ten hydrogen bond acceptors
(3) Molecular mass less than 500 Da
(4) High lipophilicity (expressed as LogP not over 5)
(5) Molar refractivity should be between 40-130

Step 4 - DOCKING

The ligand is docked against the protein and the interactions are evaluated in step IV. The scoring function assigns a score based on the best docked ligand complex selected.

V. DOCKING SOFTWARE

Various docking programs were developed during the previous two decades. Table (1) outlines the main elements of currently available docking technologies, such as approved platforms, licence requirements, algorithms, and scoring methods. Table (2) lists the advantages and disadvantages of existing protein ligand docking technologies based on their codes (Kellenberger et al 2004).

Applications of molecular docking

Molecular docking interactions can cause the protein to be activated or inhibited, whereas ligand binding can cause agonise or antagonism. Molecular docking might be used to:

1. Hit Recognition (Virtual Screening)
2. Lead Improvement (Drug discovery)
3. Biological remediation
4. KA (Biological Activity?) Prediction
5. Prediction of the binding location (Blind docking)
6. Protein de-orphaning
7. Protein-protein and nucleic acid interactions
8. Looking for protein target lead structures
9. Structure-function studies
10. Enzymatic Reaction Mechanisms
11. Protein synthesis

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Table 1: Shows Basic Characteristics for Current Protein-Ligand Docking Tools

Entry	Program Ref**	Designer / Company	Licence terms	Supported platforms	Docking Approach	Scoring Function
1	Auto Dock[5]	D. S. Good sell and A. J. Olson The Scripps Research Institute	Free for Academic use	Unix, Mac OSX, Linux, SGI	Genetic algorithm Lamarckian genetic algorithm Simulated Annealing	Auto Dock (force-field methods)
2	DOCK[6]	I. Kuntz University of California, San Francisco	Free for academic use	Unix, Linux, Sun, IBM AIX, Mac OSX, Windows	Shape fitting (sphere sets)	Chem Score, GB/SA solvation scoring, other
3	Flex X[7]	T. Lengauer and M. Rarey Bio SolveIT	Commercial Free evaluation (6 weeks)	Unix, Linux, SGI, Sun Windows	Incremental Construction	FlexXScore, PLP, Screen Score, Drug Score
4	FRED[8]	Open Eye Scientific Software	Free for academic use	Unix, Linux, SGI, Mac OSX, IBM AIX, Windows	Shape fitting (Gaussian)	Screen Score, PLP, Gaussian shape score, user defined
5	Glide[9]	Schrödinger Inc.	Commercial	Unix, Linux, SGI, IBM AIX	Monte Carlo Sampling	Glide Score, Glide Comp
6	GOLD[10]	Cambridge Crystallographic Data Centre	Commercial Free evaluation (2 months)	Linux, SGI, Sun, IBM, Windows	Genetic Algorithm	Gold Score, Chem Score user defined
7	LigandFit[11]	Accelrys Inc.	Commercial	Linux, SGI, IBM AIX	Monte Carlo Sampling	Lig Score, PLP, PMF

*Other current docking tools are: ICM [12], Pro Dock [13], QXP [14], Slide [15], Surflex [16].
**Internet addresses of selected home pages are given [17].

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Table 2: Shows Pros And Cons Of Docking Tools (Kellenberger Et Al., Proteins (2004), 57, 224-242)

Program	Pros	Cons
DOCK	Small binding sites Opened cavities Small hydrophobic ligands	Flexible ligands Highly polar ligands
FLEXX	Small binding sites Small hydrophobic ligands	Very flexible ligands
FRED	Large binding sites Flexible ligands Small hydrophobic ligands High speed	Small polar buried ligands
GLIDE	Flexible ligands Small hydrophobic ligands	Ranking very polar ligand Slow speed
GOLD	Small binding sites Small hydrophobic ligands	Ranking very polar ligands Ranking ligands in large Cavities
SLIDE	Side chain flexibility	Sensitivity to input Coordinates
SURFLEX	Large and opened cavities Small binding sites Very flexible ligands	Low speed for large ligands
QXP	Optimizing known binding Modes	Sensitivity to input coordinates

VI. DISCUSSION & CONCLUSION

For pharmaceutical design and analysis, Molecular Docking offers a variety of useful tools. Simple molecular visualisation and quick access to structural databases have become crucial components of the medicinal chemist's workstation. The primary user interface of commercial software packages continues to evolve. Commercial and academic strategies are frequently incorporated into high-end products. Public domain software is becoming more stable, with functionality that rivals that of commercial software. Every year and a half, computer speeds double, and visual displays get more complex and intuitive. All of these factors combine to make molecular docking an important feature of drug development. Its importance in cutting-edge approaches like computational enzymology, genomics, and proteomic search engines continues to grow.

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