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REVIEW ARTICLE

An Overview of Molecular Docking

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ABSTRACT:

The computational modeling of structural complexes formed by two or more interacting molecules is known as molecular docking. Prediction of an interesting three-dimensional structure is the primary goal of molecular docking. Software for molecular docking is mostly employed in the development of drugs. Molecules and the simple use of structural databases caused damage to an important mechanism. Several expensive tools for drug design and research are provided by molecular docking. Simple molecular prediction as well as rapid access to structural databases have become important components on the medicinal chemist's desktop. Virtual screening is the most important contribution of molecular docking. Numerous docking programs were used to visualize the three-dimensional structure of the molecule, and different computational techniques can be used to analyze docking gain. In structural molecular biology and computer-aided drug design, molecular docking is a key tool. Docking is useful for lead optimization because it can be used to do virtual screening on huge collections of compounds, rate the results, and provide structural ideas for how the ligands affect the target.

KEYWORDS: Molecular; Docking; receptor; ligand; binding; CADD; rigid; flexible.

INTRODUCTION:

Molecular docking is the process of arranging a ligand or receptor molecule to create a stable complex¹. By using a scoring function, this orientation is used to predict binding affinity and the strength of the bond between a ligand and a protein. The affinity and activity of a chemical are predicted by the drug-receptor interaction². It is important for both drug discovery and drug design. Finding and developing new drugs is an extremely difficult process. New drugs are discovered using the in-silico approach³. Computer-based drug design should be employed to speed up the drug discovery process. It is helpful for computational drug design and the structural biology of molecules³.

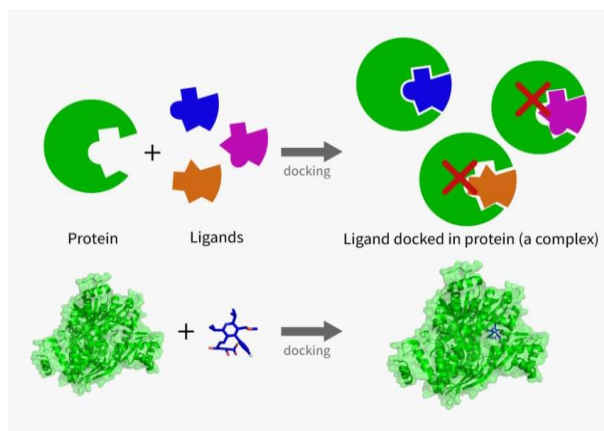


Fig.1. Schematic diagram of Docking ⁴

Docking is a method that predicts the preferred direction that two molecules will take when they jump to one another to form a stable compound in the area of molecular modeling⁵. It is possible to predict the degree of involvement or binding affinity between two molecules using the rotational direction that is chosen in signal transduction, the interactions between chemically similar components, such as proteins, peptides, nucleic

acids, carbohydrates, and lipids, are important. In addition, the type of signal created (such as agonist vs. antagonism) may affect the positioning of the two interactive associates⁶.

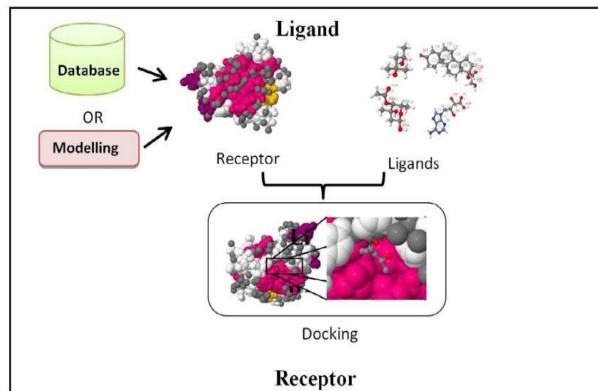


Fig.2. Molecular Docking⁷.

Docking is therefore useful for predicting both the signal's potency and nature. Due to its capacity to predict how small molecule ligands would attach to the ideal target binding site, molecular docking is one of the most frequently utilized techniques in structure-based drug design. Identifying binding performance serves as essential for medicine planning and for understanding the meaning of basic biochemical processes⁸.

COMPUTER-AIDED DRUG DESIGN:

Computational chemistry uses this computer-based method to discover, identify, or enhance the study of drugs and related biologically active molecules is the computer-Aided Design of Molecules (CADD) Design of drugs.

1. It is especially helpful when creating novel drugs.
2. It offers information regarding the chemical and ligand biological characteristics, and targets.
3. It is used to discover and enhance novel medicines.
4. Development of in-silico filters for predicting unwanted characteristics like poor performance poor Pharmacokinetics, as well as the toxicity of drug substances.
5. It is utilized to improve new drug targets. CADD is used for detecting hits.
6. By utilizing chemical scaffolds to identify novel virtual screening is used for chemical molecules⁹.

STRUCTURE-BASED DRUG DESIGN:

Knowing the structure of the target protein is essential for structure-based drug design to identify the interaction energies of each molecular structure⁹.

LIGAND-BASED DRUG DESIGN:

Ligand-based searches for chemical similarity or quantitative structure-activity relation (QSAR) take advantage of the knowledge of known active and inactive molecules. When the target proteins' 3-D

structures are unavailable, ligand-based methodologies are ideal⁹.

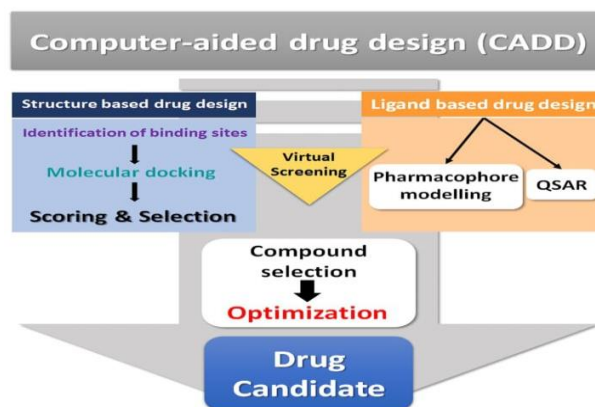


Fig.3. Drug Design Structure¹⁰

TYPES OF MOLECULAR DOCKING:

Search Algorithm:

The experimentation method determines the binding modes and number of configurations created. For docking analysis, the Monte Carlo method, fragment and genetic-based, systemic searches are applied¹¹.

- a. Rigid Docking
- b. Flexible Docking

Rigid Docking:

In this docking, the receptor and ligand molecule both are fixed. Docking is performed¹².

Flexible Docking:

In this docking the ligand and the receptor both are movable. It is conformationally flexible. For each rotation, the energy is calculated. Each conformation surface cell occupancy is calculated. After that, the most optimum binding pose is selected¹³.

Scoring Function:

The binding affinity directly corresponds to the binding score. The best binders are the best-scoring ligands. It can be experimental, knowledge, and molecular mechanics-based. Docking Scoring plays an important role in designing drugs¹⁴:

- a) Knowledge-based and
- b) Energy component method

a) Knowledge-based scoring function:

The statistics of the observed inter-contact frequencies in an extensive database of the protein complex crystal structure are evaluated using a knowledge-based method. High binding affinity is expected for molecular interactions that are near the maximum frequency of interactions in the database [80-85]. Low-binding affinity molecules will interact less frequently, according to database information¹⁵.

b) Energy component scoring method:

The free energy for ligand interaction, ligand-protein and solvent interaction, conformational changes in the ligand and protein, and motion in the ligand and protein target during complex formation have been added together in the energy component scoring method based on the mathematical assumption that the change in free energy upon binding of a ligand to a protein target (DG bind) is the sum of these four factors ¹⁶.

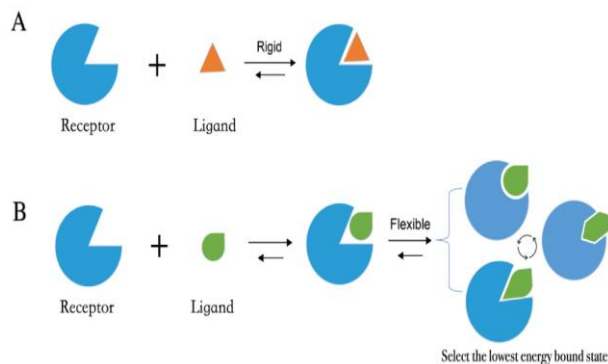


Fig.4. Type of Molecular Docking

MAJOR STEP INVOLVED IN MOLECULAR DOCKING MECHANISM:

The docking procedure includes the following steps:

Step 1- Protein preparation:

The Protein Data Bank (PDB) must be used to retrieve the three-dimensional structure of the Protein; the structure must then be pre-processed. According to the given parameters, this should permit amputation of the water molecules from the cavity, stability of charges, substantial of the missing residue, formation of side chains, etc ¹⁷.

Step 2- Ligand preparation:

Pub Chem Ligands molecules can be obtained utilizing several databases, such as ZINC. It can be drawn using the Mol file's Chem sketch tool. used LIPINSKY'S RULE OF 5 for this ligand molecule after that. The drug's like and unlike compounds are used with it. Due to the molecule's drug-like characteristics, it raises the success rate and decreases failure rates ¹⁸.

Lipinsky's rule states that;

- 1) Molecules must have a molecular mass of less than 500 Da.
- 2) A lesser number of 10 hydrogen bond acceptors.
- 3) A lesser number of five hydrogen bond donors. (4)
- High lipophilicity (defined as a Log not exceeding.
- (5) The ideal range for molar refractivity is 40–130 ¹⁹.

Step 3- Grid generation:

The site, rotatable group, excluded volumes, and limitations were all constant in this. The most important factor in determining how many genetic operations

(crossover, migration, and mutation) are to be conducted is binding cavity prediction ²⁰.

Step 4- Prediction of Active site:

The active site of the protein molecule should be predicted in this step. Following protein preparation, water molecules, and any heteroatoms are removed from the cavity ²¹.

Step 5- Docking:

In this step, we study the interactions between ligands and proteins. You should choose the best docking score ²².

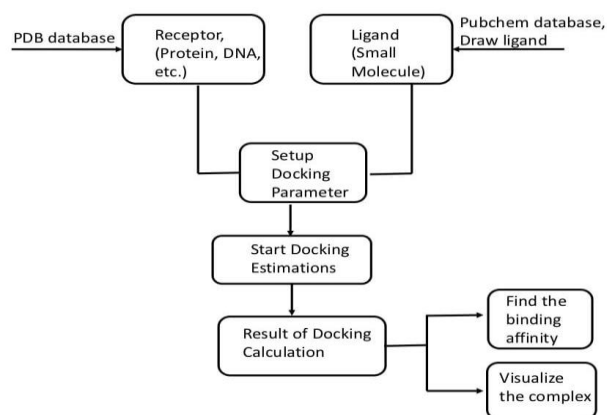


Fig.5.Flow chart of Molecular Docking Mechanism Steps ²³

APPLICATION OF MOLECULAR DOCKING:

An enzyme may be activated or inhibited by a binding interaction between a small molecule ligand and an enzyme protein. If the protein is a receptor, the binding of a ligand can produce either agonistic or antagonistic effects. Docking is mainly used in the development of drugs. Since tiny chemical compounds make up the majority of pharmaceuticals, docking may be used for Hits identification, Lead optimization, Bioremediation, Prediction of the binding site, etc ²⁴.

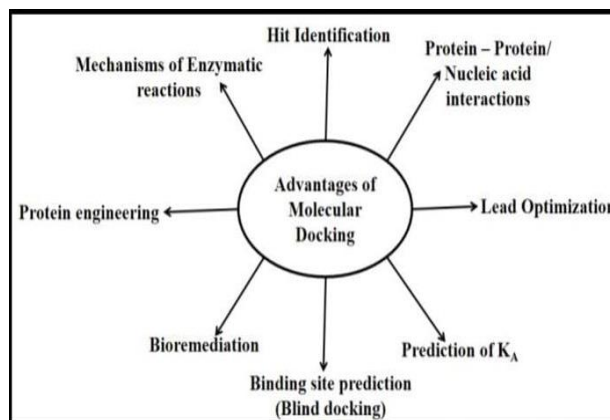


Fig.6.Application of Molecular Docking ²⁵

DOCKING SOFTWARE²⁶

S. No	Software tools	Algorithm	Scoring term	Advantages	Ref
1	Glide (Grid-based Ligand Docking with Energetics)	Monte Carlo	Glide score	Lead discovery and lead optimization	[11]
2	AutoDock	Lamarckian genetic algorithm	Empirical free energy function	Adaptability to user defined input	[12]
3	GOLD (Genetic Optimization for Ligand Docking)	Genetic algorithm	Gold Score, Chem Score, ASP (Astex Statistical Potential), CHEMPLP (Piecewise Linear Potential), User defined	Allows atomic overlapping between protein and ligand	[13]
4	Surflex	Surflex-Dock search algorithm	Bohm's scoring function	High accuracy level by extending force- fields	[14]
5	FlexX	Incremental reconstruction	Modified Bohm scoring function	Provides large number of conformations	[15]
6	ICM (Internal Coordinate Modelling)	Monte Carlo minimization	Virtual library screening scoring function	Allows side chain flexibility to find parallel arrangement of two rigid helices	[19]
7	MVD (Molegro Virtual Docker)	Evolutionary algorithm	MolDock score	High accuracy level of predicting binding mode	[16]
8	Fred (Fast Rigid Exhaustive Docking)	Exhaustive search algorithm	Gaussian scoring function	Nonstochastic approach to examine all possible poses within protein active site	[20]
9	LigandFit	Monte Carlo method	LigScore, Piecewise Linear Potential (PLP), Potential of Mean Force (PMF)	Generates good hit rates based on LigScore	[21]
10	FITTED (Flexibility Induced Through Targeted Evolutionary Description)	Genetic algorithm	Potential of Mean Force (PMF), Drug Score	Analyzes effect of water molecules on protein-ligand complexes	[22]
11	GlamDock	Monte Carlo method	ChillScore	Provides provision of two-dimensional analysis to screen ligands by targeting protein	[17]
12	vLifeDock	Genetic algorithm	PLP score, XCScore	Facilitates batch docking	[23]
14	iGEMDOCK	Genetic algorithm	Empirical scoring function	Highly significant in post-screening analysis	[24]

CONCLUSION:

Molecular Docking offers a variety of methods for drug discovery and design. The representation of molecular structure databases is simple for medicinal chemistry researchers. It accurately predicts how ligands will attach to receptors. These drugs use the molecular docking method in their medicinal development. It is both time and money-effective. It is employed in the creation of new drugs. Future medicinal chemists would benefit greatly from learning about the novel drug design and novel drug development process. The lead molecule's optimization, the assessment of biological pathways, and de novo drug design are challenges of the molecular docking process. Mention all relevant information on molecular docking in this review. Due to the rise of drug resistance strains, infectious diseases such as malaria, heart failure, cancer, and others create a risk to the public's health in the majority of nations, requiring the development of novel, efficient treatment using a newly discovered medicine to treat an illness after identifying a new indication from an existing drug. The validated and reliable alternative to the expensive and time-consuming traditional method of drug discovery is computational drug design, which is a cost-effective and less time-consuming approach. With the use of computer-aided drug design (CADD), it has

become a potent alternative technique to find and develop innovative medications from current drugs.

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