Molecular Docking in Drug Discovery

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Authors' contributions

Article Information

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ABSTRACT

In last few years the Computer Aided Drug Design and Discovery is many success rates. In academics and many pharmaceutical industries for drug lead discovery they adopt the Computational Drug Design. The modern era of drug discovery and development structural information play an important role. For visualization of 3D-structure of molecule different docking program are developed. The docking score is analysed by using computer-based drug design software. It is structure based virtual screening method for the orientation, conformation, position into a structure of target molecule. Ligand and Protein docking is new concept. Molecular docking method complication is optimization of lead molecule, biological pathway evaluation and de Novo drug design.

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1. INTRODUCTION

The Suitable orientation of ligand molecule overs the receptor molecule to build a stable complex is called as molecular docking [1-7]. This orientation utilized for the binding affinity prediction and strength of connection of ligand and protein by using scoring function. The drug receptor interaction predicts the affinity and activity of molecule [8-17]. It plays vital role in drug design and drug discovery. It is minimized overall free energy of system. New drug discovery and development is very challenging task. With the help of In-Silico method new drug discovery occurs [18-27]. For the rapid gaining of drug discovery process the computer-based drug design should be used. It is useful in structural biology of molecule and computational drug design [28-35]. It is used to anticipate the 3-Dimensional structure of molecule. With the help of scoring function currently rank candidates docking for large libraries compound perform the virtual screening [36-42].

2. COMPUTER AIDED DRUG DESIGN

It is computer-based technique used in the computational chemistry to discover, enhance or study of drug and related biologically active molecule is called as (CADD) Computer Aided Drug Design.

1. It is most useful in new drug design.
2. It provides knowledge about the chemical and biological properties of ligands and targets.
3. It is used to find and improve novel drug.

4. Discovery of in-silico filters for prediction of undesirable properties like poor activity and poor Pharmacokinetic and Toxicity of drug molecule.
5. It is used for the optimization of novel drug targets. CADD is being used to find hits
6. By using chemical scaffolds to find out novel Virtual screening is applied for new drug molecules.

3. STRUCTURE-BASED DRUG DESIGN

Structure-based computer aided drug design depend on the knowledge of the target protein structure to calculate interaction energies for all tested compounds [43-46]. In structural data-base is crystalized target proteins are available. structure- based is to design compounds that bind with minimal energy by specifically and tightly to the target [47-57]. A broader terminology, Virtual high-throughput screening, is a computer-based screening tool that allows screening of a large library of similar chemical compounds for a particular biological activity [58-65]. Virtual high-throughput screening comes in many forms, including: chemical similarity search, selecting compounds by predicted biologic activity through quantitative structure-activity relationship (QSAR) models or pharmacophore mapping, and virtual docking of compounds against protein target of interest [66-74]. By using computational tools in the lead optimization phase of drug development is significant and cost benefit. Application of computational tools in hit-to-lead optimization while reducing the number of compounds that must be synthesized and tested *In vitro* [75-79].
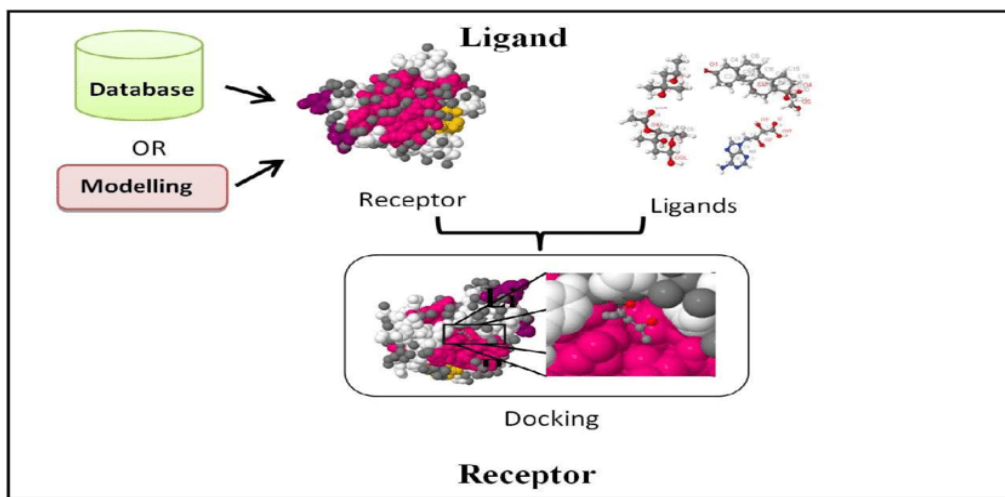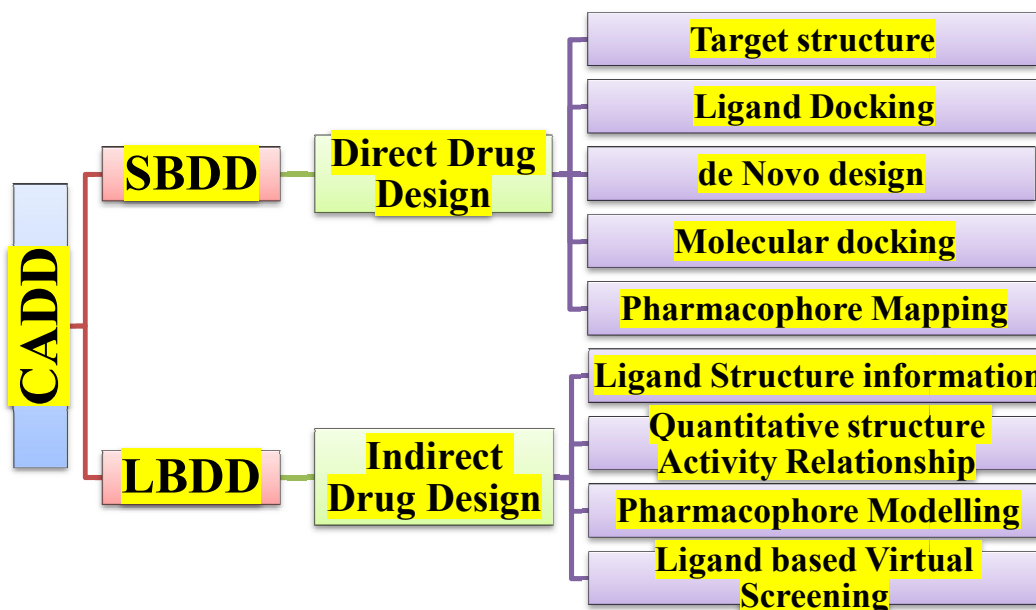
Fig. 1. Commuter aided drug design model

Fig. 2. Drug design structure

4. LIGAND-BASED DRUG DESIGN

Ligand-based exploits the knowledge of known active and inactive molecules for chemical similarity searches or quantitative structure-activity relation (QSAR). Ligand-based, is ideal where the 3D structure of the target proteins are not available.

Structural-Based Computer Aided Drug Design:

Steps includes:

(1) For docking Preparation of the target protein and compound library,
(2) Determining a Proper binding pose for each compound, and
(3) Ranking the docked structures of molecules.

To predicts the orientations or conformations of a receptor-ligand complex by using the Molecular docking and it is a structural based computer simulation procedure and used to predict the binding affinity between the molecules in the complex.

Table 1. Difference between rational drug design and computer aided drug design

| Rational Drug Design	Computer Aided Drug Design
1. It is Time consuming Method.	1. It is Time saving Method
2. It is very slow Process and less Accuracy.	2. It is very Rapid Process and More Accuracy.
3. It is costly process.	3. It is cost effective process.
4. It required More manpower.	4. It Required Less manpower
5. In this Finding New medication Based On knowledge of Biological Target.	5. In this Finding New Medication Based on Structure and Ligand based.
6. It is not used for Drug repurposing.	6. It is Useful for Drug Repurposing.
7. Ligand Receptor Interaction is not evaluated.	7. Ligand receptor Interaction is Evaluated.
8. It is not helpful for the Rapid designing and discovery of New Therapeutic Entity.	8. It is helpful for the Rapid designing and discovery of New Therapeutic Entity.
9. In this Do not need to know the Biological target structure.	9. In this need to know the Biological target structure.
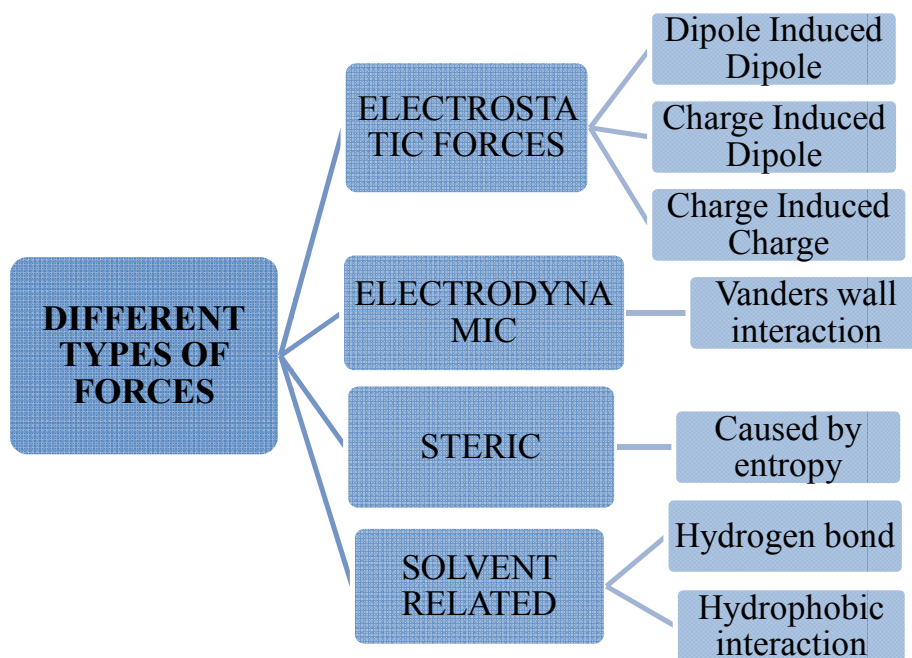
Fig. 3. Interactions different types

5. TYPES OF MOLECULAR DOCKING

1 Search Algorithm: The experimentation method determines the binding modes and number of configurations creates. For docking analysis, the Monte Carlo method, fragment and genetic based, systemic searches is applied.

- **a.** Rigid Docking
- **b.** Flexible Docking

2. Rigid Docking: In this docking the receptor and ligand molecule both are fixed. Docking is performed.

3. Flexible Docking: In this docking the ligand and the receptor both are movable. It is conformationally flexible. Each rotation the energy is calculated. Each conformation surface cell occupancy is calculated. After that the most optimum binding pose is selected.

4. Scoring Function: The binding affinity is directly corresponding to the binding score. The best binders are best scoring ligands. It can be experimental, knowledge and molecular mechanics based. Docking Scoring is play important role in designing of drug:

a) Knowledge-based and
b) Energy component methods

a) **Knowledge-based scoring function** uses the statistics of the observed inter-atomic contact frequencies in a large database of the crystal structure of protein-ligand complexes. Molecular interactions close to the maximum frequency of interactions in the data-base will have a high binding affinity [80-85]. A molecular interaction with a low binding affinity in data base will have a low frequency of interaction.

b) **Energy component scoring method** is based on the mathematical assumption that change in free energy upon binding of a ligand to a protein target (DG bind) is the sum of the free energy for ligand-protein interaction, ligand-protein and solvent interaction, conformational changes in the ligand and protein and the motion in the ligand and protein target during complex formation [86-90].

6. MOLECULAR DOCKING MECHANICS STEPS

In In-Silico method studied the intermolecular interaction between 2 drug molecules. The protein receptor is Macromolecule. It acted as an inhibitor. The following steps involved in docking process are as.

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Step I – Preparation of protein and Ligand: From Research Collaboratory Structural Bioinformatics Protein data bank (PDB) downloading the 3D-structure of the Protein. After that downloaded structure should be pre-processed. From the cavity removal of the water molecules, the charges stabilization, missing residues filling, add hydrogen atom side chains generation.

Step II –Ligand Preparation: By using different databases such as ZINC, Pub Chem Ligands molecule can be downloaded. It can be draw in Chem sketch tool in mol file. Then utilized LIPINSKY'S RULE OF 5 for this ligand molecule. It is used for the drug like and unlike molecules. It increases the high chance of success rate and decrease the failure due to drug likeness properties for molecules.

Step III- Grid Generation: In this all factors like site, rotatable group, excluded volumes, constraints kept constant. The number of genetic operations performed (crossover, migration, mutation) is the key parameter in determining. Binding Cavity Prediction are to be done.

Step IV –Prediction of Active site: The active site of protein molecule should be predicted. after that Preparation of protein, the water molecules and hetero atoms if present they are removed from cavity.

Step V- Docking: Ligand and protein interactions are analyzed. Best docking score should be selected.
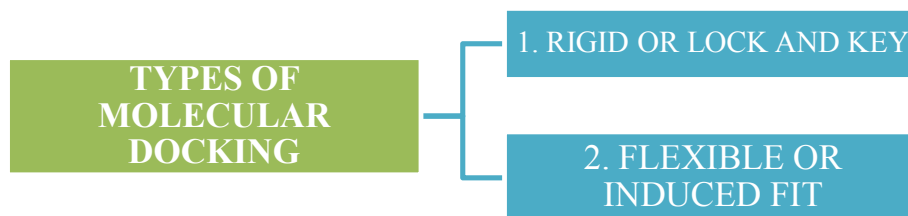
Fig. 4. Types of molecular docking
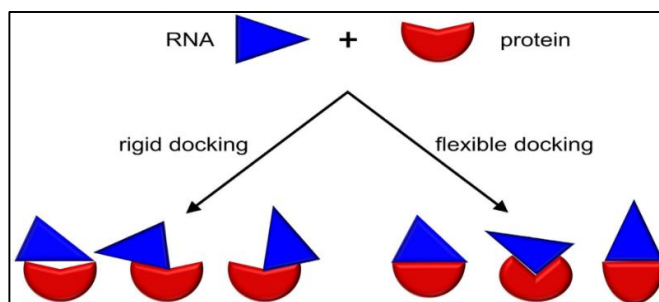
Fig. 5. Flexible Docking
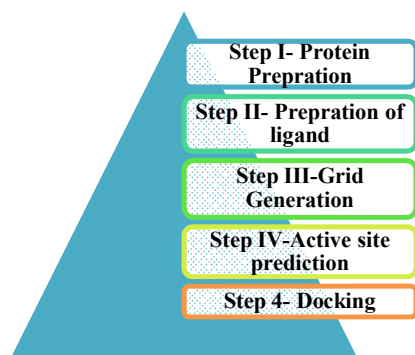
Fig. 6. Molecular docking mechanics steps

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Table 2. Difference between lipinsky's rule and muegge rule

Properties	Lipinsky's rule of 5	Muegge RULE
Molecular weight	< 500 g/mol	780.94 g/mol
Log P	< 5	3.92
H- bond donor	< 5	6
H- bond acceptor	< 10	14
Polar surface area	< 140 A^0	203.06 A^0

Fig. 7. Drug receptor response

Fig. 8. Application of molecular docking

Table 3. Docking software

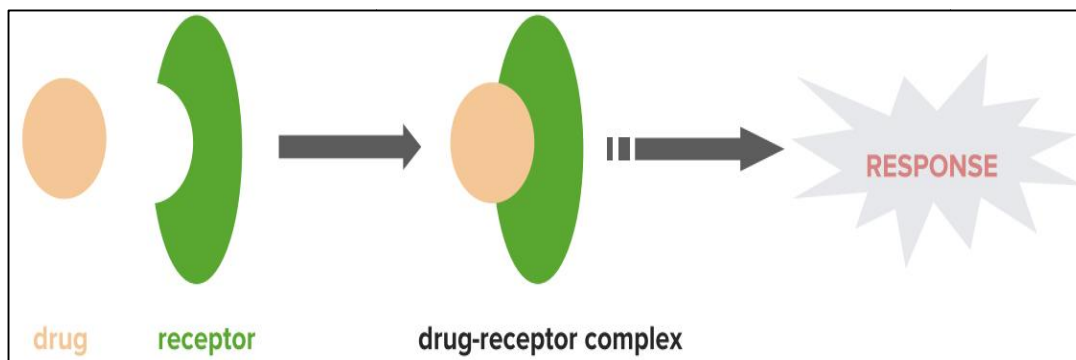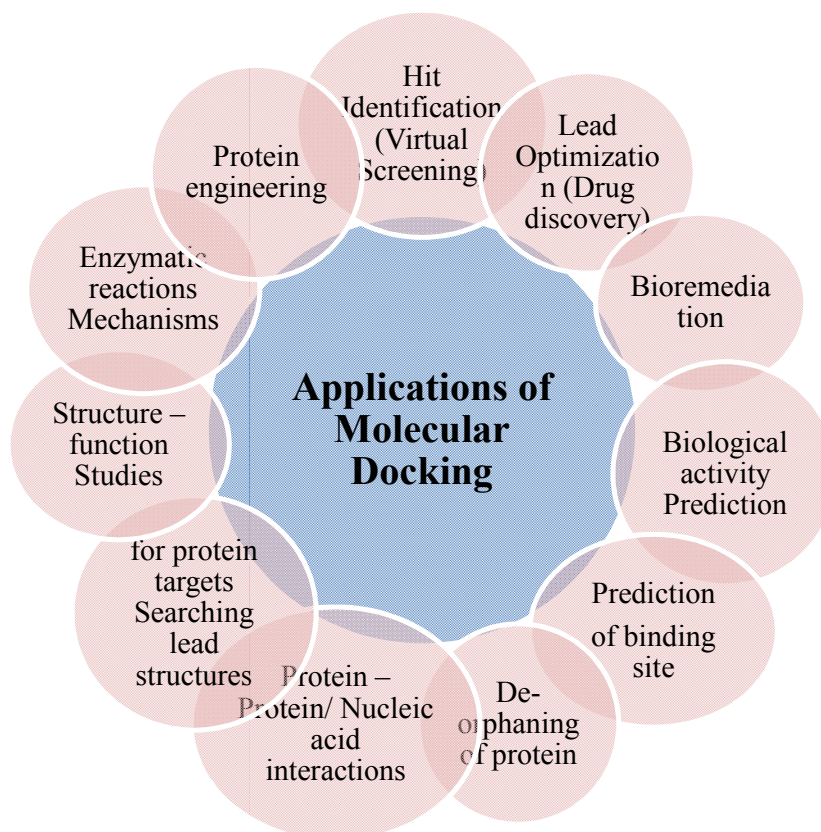| Sr No.	Program	Docking Approach	Scoring Function	Advantages	Disadvantages	Licence Term
1.	Auto Dock	Genetic algorithm and Simulated Annealing	force-field methods	Small cavities opened for hydrophobic ligands	Polar flexible ligand	Free for Academic Use
2.	Dock	fitting of Shape	Chem Score	Known binding site	Slow speed	Free for Academic Use
3.	Flex X	Construction Increment	Flex X Score,	Small cavities opened for hydrophobic ligands	More flexible ligands	Commercial Free evaluation (6week)
4.	FRED	fitting of Shape	Piece wise Linear Potential,	High speed, large binding site	Polar ligands	Free for Academic Use
5.	Glide	Sampling of Monte Carlo	Glide Score, Glide Comp	Flexible Hydrophobic ligands	Ranking very slow	Commercial
6.	GOLD	GA searching	Gold and Chem Score	Small Hydrophobic ligands	Large cavity ligand ranking	Commercial
7.	Ligand Fit	Sampling Monte Carlo	Ligand Score	Known binding site	Slow speed	Commercial

7. DISCUSSION AND CONCLUSION

Molecular Docking provides different tools used for drug design and discovery. The medicinal chemist easy to visualization of molecules structural databases. It successfully predicts the binding of ligands within receptor. These drugs make molecular docking process in drug design. It is time-saving, cost-effective. It is used for the novel drug development [91-95]. It Is Very Useful for Future Medicinal Chemist to Discover the Novel Drug Design and Novel Drug Development Process. Molecular docking method complication is optimization of lead molecule, biological pathway evaluation and de Novo drug design. In this review mention all information regarding molecular docking. Malaria, Heart failure, Cancer and other infectious diseases are public health challenges in most countries due to the emergence of drug resistance strains, thus necessitating the need for novel effective remedies [96-100]. Identification of new indication from existing drug and application newly identified drug to treatment of disease. Computational drug design, a cost- effective and less time-consuming approach, is a validated and reliable alternative to the cost expensive and time-consuming conventional method of drug discovery. Malaria, Heart failure, Cancer and other infectious diseases are public health challenges in most countries due to the emergence of drug resistance strains, thus necessitating the need for novel effective remedies. Identification of new indication from existing drug and application newly identified drug to treatment of disease. Computational drug design, a cost- effective and less time-consuming approach, is a validated and reliable alternative to the cost expensive and time-consuming conventional method of drug discovery. It is become powerful alternative strategy to discover and develop novel drugs from existing drug with the help of Computer Aided Drug Design (CADD).

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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