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Review Article

A Review on Molecular Docking: Novel Tool for Drug Discovery

Kamal Kumar Chaudhary and Nidhi Mishra*

Department of Bioinformatics, Indian Institute of Information Technology, India

***Corresponding author**

Nidhi Mishra, Department of Bioinformatics, Indian Institute of Information Technology- Allahabad, Deoghat, Jhalwa, Allahabad, Uttar Pradesh- 211012, India, Tel: 91-0532-2922540; Email: nidhimishra@iiita.ac.in

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Abstract

The field of computer aided drug design and discovery (CADDD) is a rapidly growing area that has seen many successes in the last few years. Many giant pharmaceutical companies, in addition to academia, adopt CADDD ford rug lead discovery. The explosion of structural informatics, genomics and proteomic plays a major role in leading the efforts towards modern era drug discovery and development. Enormous research from last two decades has been pursued to study various docking algorithms and predicting the active site of the molecule. Various docking programs were developed to visualize the3D structure of the molecule and docking score can also be analyzed with the aid of different computational methods. Molecular Docking is a structure-based virtual screening (SBVS) that is used to place the computer-generated three-dimensional Structures of small molecules into a target structure in a variety of positions, conformations and orientations. Protein-ligand docking is a new concept with a variety of applications. It acts as a vivacious explore domain because of its significance to structure-based drug design (SBDD), Lead Optimization, Evaluation of Biochemical pathways, in De Novo drug design. In this Review whole description on Molecular Docking are mentioned here. Through Molecular Docking the Binding mode and affinity of the complex so formed is estimated and thus helps in the Molecular Recognition Process docking towards discovery of new drug leads.

ABBREVIATIONS

ADMET: Absorption, Distribution, Metabolism, Excretion and Toxicity; PDB: Protein Data Bank; 3D: Three Dimensional; SBDD: Structure-Based Drug Design; SBVS: Structure-Based Virtual Screening

INTRODUCTION

Molecular Docking is a method which anticipates the favored orientation of ligand against receptor (Protein) to make a stable complex [1]. Favored orientation possibly utilized to predict the strength of connection or binding affinity among ligand and protein by utilizing scoring functions. Docking is often applied to anticipate the binding orientation of drug candidates against protein targets in order to predict the affinity and activity of the drug (Figure 1). Therefore docking plays a pivotal role in the drug design and discovery process [2]. The main aim of molecular docking is to computationally simulate the molecular identification process and accomplish an optimized conformation so that the free energy of overall system is minimized. The process of discovery of a new drug is a very difficult task. Modern drug discovery is mainly based In-silico–chemico biological approach. Use of computer aided techniques in drug discovery and development process is rapidly gaining popularity, implementation and appreciation.

CADD (COMPUTER AIDED DRUG DISCOVERY) ENTAILS

a. Use of computational ability to streamline drug discovery and development process.

b. Advantage of chemical and biological information about ligands and/or targets to discover and optimize novel drugs.

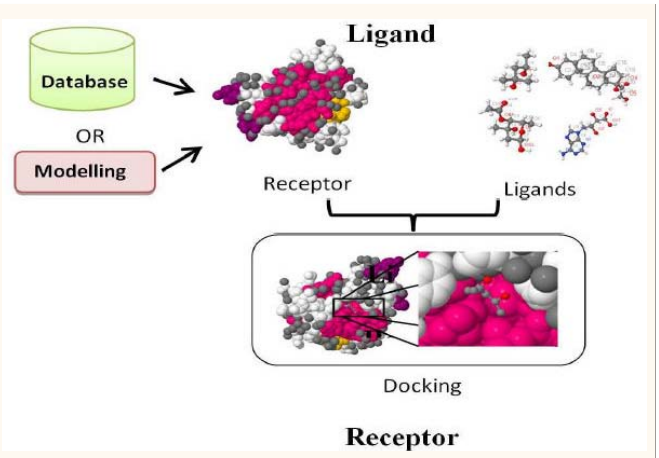

Figure 1 Molecular docking flow chart.

c. Designing of in-silico filters to get rid of chemical compound with unwanted properties (poor activity and/or poor Absorption, Distribution, Metabolism, Excretion and Toxicity, (ADMET)) and select the most promising candidates.

d. Identification of novel drug targets and retrieval through database of target protein structures like the protein data bank (PDB) www.pdb.org. CADD (Figure 2) is being used to discover hits (drug candidates).

e. Virtual screening is applied to find out novel drug candidates from various chemical scaffolds by exploring databases [3-4].

DIFFERENT TYPES OF INTERACTIONS

Interaction forces are generally separated into four classes:

(1) Electrostatic forces - dipole-dipole, charge-dipole and charge-charge.

(2) Electrodynamics forces- Van der Waals interaction.

(3) Steric forces - Caused by entropy.

(4) Solvent-related forces - Hydrogen bond and hydrophobic interactions [5,6].

MOLECULAR DOCKING

Molecular docking can be separated into two sections.

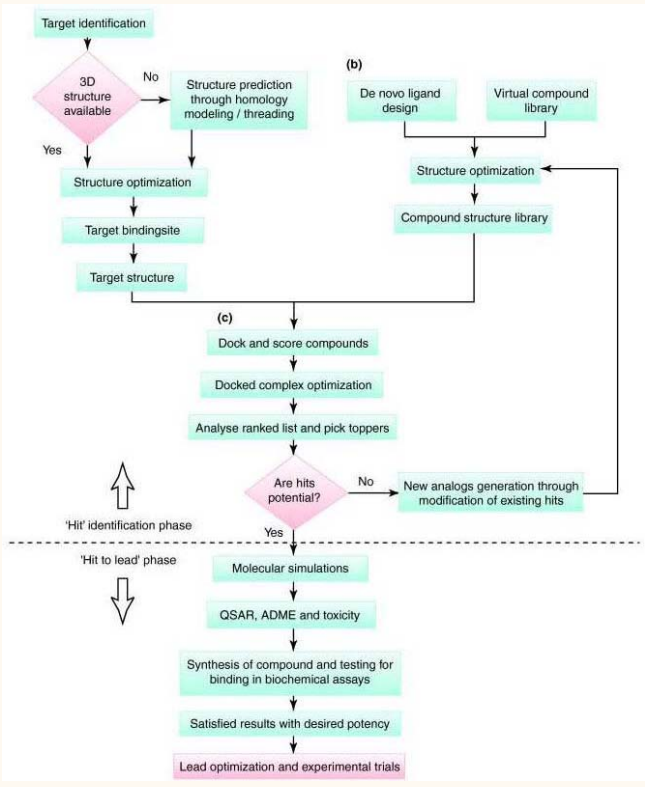

Figure 2 The computer aided drug design and discovery (CADDD) procedure.

Search algorithm

The algorithm should create an optimum number of configurations that admit by experimentation method determining binding modes. The following are the various algorithms applied for docking analysis such as Point complementary, Monte Carlo, Fragment-based, Genetic algorithms, Systematic searches, Distance geometry etc [7,8].

Scoring Function

The scoring function furnishes a mode to rank positioning of ligands proportional to some other. Ideally, the score should correspond directly to the binding affinity of the ligand for the protein, so that the best scoring ligands are the best binders. Scoring functions can be empirical, knowledge based, or molecular mechanics based. Scoring is actually compiled of three different expressions applicable to docking and drug design:

(1) Generated configurations ranking by the docking search.

(2) Ranking different ligands against protein (virtual screening).

(3) One or more ligands ranking against different proteins by their binding affinity (selectivity and specificity) [9-12].

Various types of docking

The following are primarily applied method for docking

(1) Lock and Key\Rigid Docking-Both the receptor and ligand is maintained fixed and docking is executed.

(2) Induced fit\Flexible Docking-In induced fit docking both the ligand and the receptor are conformationally flexible. Every rotation the surface cell occupancy and energy is calculated; later the most optimum pose is selected [13].

Major steps involved in mechanics of molecular docking

Molecular Docking is the process in which the intermolecular interaction between 2 molecules was studied in In-silico. In this process, the Macromolecule is the protein receptor. The micro molecule is the Ligand molecule which can be acted as an inhibitor. So, the Docking process involves the following steps:

Step I – preparation of protein: Three dimensional structure of the Protein should be retrieved from Protein data bank (PDB); afterward the retrieved structure should be pre-processed. This should admit removal of the water molecules from the cavity, stabilizing the charges, filling the missing residues, generation the side chains etc. according to the parameters available.

Step II – active site prediction: After the preparation of protein, the active site of protein should be predicted. The receptor might possess lots of active sites merely the one of the concern should be picked out. Mostly the water molecules and hetero atoms are removed if present [14-15].

Step III – preparation of ligand: Ligands can be retrieved from several databases such as ZINC, Pub Chem or can be sketched applying Chem sketch tool. While picking out the ligand, the LIPINSKY'S RULE OF 5 should be utilized. Lipinski rule of 5 assists in discerning amongst non-drug like and drug like

candidates. It promises high chance of success or failure due to drug likeness for molecules abiding by with 2 or more than of the complying rules. For choice of a ligand allowing to the LIPINSKY'S RULE:

(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 IV- docking: Ligand is docked against the protein and the interactions are analyzed. The scoring function gives score on the basis of best docked ligand complex is picked out.

Docking software

Various docking programs have been formulated throughout the last twenty years. Table (1) summarizes basic features such as endorsed platforms, license conditions, algorithms and scoring functions of currently available docking tools. While Table (2) summarizes pros and cons of existing protein ligand docking tools based on their codes [16-18].

Applications of molecular docking

Molecular docking interactions may lead in activation or inhibition of the protein, whereas ligand binding may lead in agonism or antagonism. Molecular Docking possibly employed to:

1. Hit Identification (Virtual Screening)
2. Lead Optimization (Drug discovery)
3. Bioremediation
4. Prediction of K_A (Biological activity?)
5. Binding site prediction (Blind docking)
6. De-orphaning of protein
7. Protein – Protein/ Nucleic acid interactions
8. Searching for lead structures for protein targets
9. Studies of Structure – function
10. Mechanisms of Enzymatic reactions
11. Protein engineering

DISCUSSION & CONCLUSION

Molecular Docking provides an array of valuable tools for drug design and analysis. Simple visualization of molecules and easy access to structural databases has become essential components on the desktop of the medicinal chemist. Commercial software programs continue to expand upon the core user interface.

Table 1: 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].

Table 2: 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

New algorithms from industry and academia are quickly incorporated into the high end packages. Public domain packages are becoming more stable and offering functionality that rivals some of the commercial offerings computers continue to double in speed every year and a half while graphic displays became more sophisticated and intuitive. All of these elements make molecular docking an integral part of drug design. It continues to extend its role in exciting new techniques such as computational enzymology, genomics, and proteomic search engines.

REFERENCES

1. Lengauer T, Rarey M. Computational methods for bimolecular docking. Curr Opin Struct Biol. 1996; 6: 402-406.
2. Kitchen DB, Decornez H, Furr JR, Bajorath J. Docking and scoring in virtual screening for drug discovery: methods and applications. Nat Rev Drug Discov. 2004; 3: 935-949.
3. Pozzan A. Molecular descriptors and methods for ligand based virtual high throughput screening in drug discovery. Curr Pharm Des. 2006; 12: 2099-2110.
4. Green DV. Virtual screening of virtual libraries. Prog Med Chem. 2003; 41: 61-97.
5. Goodsell DS, Olson AJ. Automated Docking of Substrates to Proteins by Simulated Annealing, Proteins. 1990; 8: 195-202.
6. Kuntz ID, Blaney JM, Oatley SJ, Langridge R, Ferrin TE. A geometric approach to macromolecule-ligand interactions. J Mol Biol. 1982; 161: 269-288.
7. Rarey M, Kramer B, Lengauer T. Multiple Automatic Base Selection: Protein-ligand Docking Based on Incremental Construction without Manual Intervention. J Comput Aided Mol Des. 1997; 11: 369-384.
8. Schulz-Gasch T, Stahl M. Binding Site Characteristics in Structure-based Virtual Screening: Evaluation of Current Docking Tools. J Mol Model. 2003; 9: 47-57.
9. Friesner RA, Banks JL, Murphy RB, Halgren TA, Klicic JJ, Mainz DT, et al. Glide: A New Approach for Rapid, Accurate Docking and Scoring. 1. Method and Assessment of Docking acuracy. J Med Chem. 2004; 47: 1739-1749.
10. Jones G, Wilett P, Glein RC, Leach AR, Taylor R. Development and Validation of Genetic Algorithm and an Empirical Binding Free Energy Function. J Mol Biol. 1997; 267: 727-748.
11. Venkatachalam CM, Jiang X, Oldfield T, Waldman M. LigandFit: A Novel Method for the Shape-directed Rapid Docking of Ligands to Protein Active Sites. J Mol Graphics Modell. 2003; 21: 289-307.
12. Abagyan RA, Totrov MM, Kuznetsov DA. ICM: A New Method For Protein Modeling and Design: Applications to Docking and Structure Prediction from the Distorted Native Conformation. J Comp Chem. 1994; 15: 488-506.
13. Trosset JY, Scheraga HA. PRODOCK: Software Package for Protein Modeling and Docking. J Comput Chem. 1999; 20: 412-427.
14. McMartin C, Bohacek RS. QXP: Powerful, Rapid Computer Algorithms for Structure-based Drug Design. J Comput Aid Mol Des. 1997; 11: 333-344.
15. Schnecke V, Kuhn LA. Virtual Screening with Solvation and Ligand-induced Complementarity, Perspect. Drug Discov. 2000; 20: 171-190.
16. Jain AN. Surflex: Fully Automatic Flexible Molecular Docking Using a Molecular Similarity-Based Search Engine. J Med Chem. 2003; 46: 499-511.
17. Internet addresses of selected docking tools:
AutoDock.
DOCK.
FlexX.
FRED.
Glide.
GOLD.
ICM.
LigandFit.
18. Kellenberger et al. Proteins. 2004; 57: 224-242.

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