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Review Article

Molecular Docking: A Structure-Based Drug Designing Approach

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Abstract

With the advancement of novel techniques in drug discovery, various approaches have been used in the structure based drug designing. One of the most important strategies is molecular docking. The study of molecular docking and simulation deals with the intermolecular interaction of drug targets i.e. proteins, nucleic acids, lipids and ligands. The aim of molecular docking is to achieve an optimized conformation for both the protein and ligand and relative orientation between protein and ligand such that the free energy of the overall system is minimized. The aim of this review article is to focus on various aspects of molecular docking including basic steps of docking, types of interactions, software tools with their algorithms and applications. Molecular docking study is highly relevant in order to predict potential targets of diseases as well as in designing effective drugs for pharmaceutical industry.

INTRODUCTION

Over the last couple of decades, many experimental and high-throughput screening methods have been used in drug designing. Traditional approaches were highly expensive, more time consuming and less efficient to discover novel therapeutic drugs. To overcome drawback of traditional methods, more effective and rational methods have been introduced which rely on virtual screening. Based on the availability of structural information, the method of virtual screening can be classified as structure-based and ligand-based drug designing method. The structure-based drug designing approach describes molecular docking whereas ligand-based methods are dealing with quantitative structure activity relationship and pharmacophore modeling. A wide range of therapeutically important molecular targets are known due to availability of structural information of proteins and protein-ligand complexes through techniques of chemical synthesis, purification, X-ray crystallography and Nuclear Magnetic Resonance Spectroscopy (NMR) [1]. The molecular docking method determines interaction between ligand and target molecule. It predicts binding affinity of ligand to form a stable complex with protein by finding preferred orientation of minimum free binding energy [2]. This interaction involves many types of non-covalent interactions such as hydrogen bond, ionic bond, hydrophobic and van der Waals. Molecular docking study can be possible in between protein-protein, protein-ligand and protein-nucleotide [3]. Multiple steps of molecular docking method consist of preparation of 3-D structure of proteins, preparation of ligands, estimation of binding energy of protein-ligand complex and analysis of results as shown in Figure 1 [4].

BASIC STRATEGIES IN MOLECULAR DOCKING

Shape complementarity

Geometric Complementarity between protein and ligand using search algorithm. Mostly search algorithms such as Monte Carlo, Genetic algorithm and Exhaustive methods are used to predict different conformations of ligand.

Simulation

The simulation of the docking process as such is a much more complicated process in this approach, the protein and the ligand are separated by some physical distance, and the ligand finds its position into the protein's active site after a certain number of "moves" in its conformational space. The moves incorporate rigid body transformations such as translations and rotations, as well as internal changes to the ligand's structure including torsion angle rotations. Each of these moves in the conformation space of the ligand induces a total energetic cost of the system, and hence after every move the total energy of the system is calculated. The interaction between ligand and receptor is usually measured in terms of minimal binding free energy with different scoring functions like force-field based functions, empirical scoring functions, knowledge-based scoring functions, Consensus scoring and descriptor based scoring functions [5].

The advantage of the Simulation method is that it is more amenable to incorporate ligand flexibility into its modeling whereas shape complementarity techniques have to use some ingenious methods to incorporate flexibility in ligands. Another advantage is that the process is physically closer to what happens

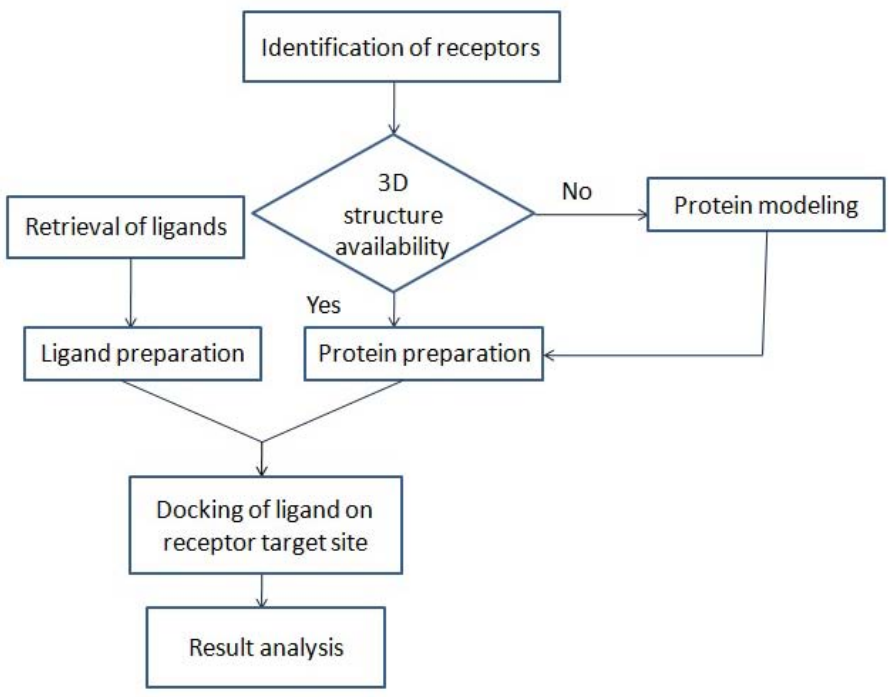

Figure 1 Basic steps of molecular docking.

in reality, when the protein and ligand approach each other after molecular recognition. A clear disadvantage of this technique is that it takes longer time to evaluate the optimal pose of binding since they have to explore a rather large energy landscape. However grid-based techniques as well as fast optimization methods have significantly ameliorated these problems Figure 1.

Types of molecular docking

The basic methodology of molecular docking can be categorized into three ways:

I. **Induced fit docking:** Both ligand and receptor are flexible. The ligand binds flexibly at the active site of receptor to maximize bonding forces between them. It implements the concept of complementarity between protein and ligand.

II. **Lock and key docking:** On the basis of Lock and key theory, both ligand and receptor are rigid and show tight binding [6]. It defines the basic concept of three-dimensional complementarity.

III. **Ensemble docking:** This approach explains flexibility and complexity of conformational states of proteins. Multiple protein structures utilized as an ensemble for docking with ligand [7,8].

Recent studies have reported covalent docking of irreversible inhibitors on a target receptor. Covalent docking provides chemical probes with high level of potency and selectivity due to formation of strong linkage between electrophile (ligand) and nucleophile (protein). It has been found that many FDA approved drugs show covalent bonding such as Aspirin, Warfarin, Azacytidin, Isoniazid and so on. The concept of covalent bonding can be used for virtual screening, lead optimization, QSAR studies and molecular dynamics simulation [9,10].

Molecular docking can be manual or automated. In manual docking binding groups on the ligand and binding site are known, ligand is paired with its complementary group in the binding site. Bonding distance for each potential interaction is defined. Program moves the molecule around within the binding site to try and get the best fit as defined by the operator. The paired groups are not directly overlaid but fitted such that groups are within preferred bonding distances of each other. Automatic docking can be carried out where the software itself decides how it will dock the ligand. The task for docking program is twofold,

I. It has to place the ligand within the active site in different orientations or binding modes.

II. It has to score the different binding modes to identify the best ones.

The order of complexity may be (a) both ligand and target as rigid body; (b)target as rigid body but ligand as flexible body and (c)both target and ligand as flexible body.

TOOLS FOR DOCKING STUDY

There are many software tools available for docking study. Table 1 summarizes the list of docking tools with their algorithms, scoring functions and advantages. Based on hierarchical docking strategy, Glide generates top hits by passing through four main steps. First step is site-point search in the active site of receptor. Second step involves rough scores assignment using diameter test, subset test and greedy scoring. Third step deals with energy minimization with OPLA-AA vdW and electrostatic grids. Fourth step assigns final scores based on Glide Score function [11]. In

AutoDock, the conformational search is usually carried out with Lamarkian genetic algorithm to evaluate interaction of ligands against a particular protein [12]. GOLD implements Chemscore function using two docking protocols. Goldscore-CS protocol performs docking with Goldscore function and ranks with Chemscore function whereas Chemscore-GS protocol produces dockings with ChemScore and ranks with Goldscore function [13]. In Surflex flexible molecular docking method, the search component of docking can be exploited on the basis of force field of small molecules that extends Cartesian coordinates with internal ligand energetics as well as knowledge of strong intermolecular interaction between ligands and protein [14]. Flex X incorporates physico-chemical properties of ligand molecules with efficient sampling methods that explore different conformations of ligand to predict most potential binding mode [15]. The methodology of Molegro Virtual Docker (MVD) is based on iterative evaluations of ligands binding mode to find their interaction energy with target molecule. It identifies binding site on target molecule using cavity detection algorithm [16]. The use of energy function in terms of continuously differentiable empirical potential and composition of search space by internal coordinates of ligands with distinctive properties of rigid target molecule, two peculiar features of GlamDock methodology [17]. Various servers are also available for molecular docking such as Swiss Dock, PatchDock, UCSF-DOCK, ClusPro, 3D- Garden, 1-Click Docking and Hex [18], Table 1.

SIGNIFICANT ROLE OF MOLECULAR DOCKING IN DRUG DESIGNING

Molecular docking study is extremely significant in a wide range of applications in computer aided drug designing. A binding interaction between a small molecule ligand and an enzyme protein may result in activation or inhibition of the enzyme. If the protein is a receptor, ligand binding may result in agonism or antagonism. Docking is most commonly used in the field of drug design - most drugs are small organic molecules, and docking may be applied to:

Hit identification

Docking combined with a scoring function can be used to quickly screen large databases of potential drugs in silico to

Table 1: List of software tools for docking and their algorithms.

S.No.	Software tools	Algorithm	Scoring term	Advantages	Reference
1.	Glide (Grid-based Ligand Docking with Energetics)	Monte Carlo	Glide score	Lead discovery and lead optimization	[11]
2.	AutoDock	Lamarkian genetic algorithm	Empirical free energy function	Adaptability to user defined input	[12]
3.	GOLD (Genetic Optimization for Ligand Docking)	Genetic algorithm	GoldScore, ChemScore, 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 helixes	[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]

identify molecules that are likely to bind to protein target of interest

Lead optimization

Docking can be used to predict in where and in which relative orientation a ligand binds to a protein (also referred to as the binding mode or pose). This information may in turn be used to design more potent and selective analogs.

Bioremediation

Protein ligand docking can also be used to predict pollutants that can be degraded by enzymes

Molecular docking leads to discovery of therapeutic drugs through multiple ways that include:

I. Identification of potential target

II. Screening of potent drugs as activators/inhibitors against certain diseases

III. Designing of novel drugs by lead optimization

IV. Prediction of binding mode and nature of active site

V. Synthesis of chemical compounds with less time consumption.

Molecular docking is considered as a highly efficient method for the designing, synthesis and discovery of therapeutically important drugs. It can be implemented in medicinal chemistry, protein engineering, chemo informatics, bioremediation and many other biological and medicinal fields. The efficacy of molecular docking method has been highlighted to find the role of Human Leukocyte Antigen (HLA) variants in idiosyncratic adverse drug reactions through HLA-drug interaction analysis. Among HLA variants, HLA-B*57:01 variant was found to be most potent that exerts HLA-linked adverse reaction like abacavir hypersensitivity syndrome. The analysis of HLA-abacavir complex interaction plays significant role in virtual drug screening of HLA variants [25]. Recently, the functionality of G protein-coupled receptors (GPCRs) has been predicted using molecular docking [26]. Molecular docking method has been used to predict potent drug molecules in order to inhibit growth of cancer stem cells. Many derivatives of naturally occurring compounds against breast cancer stem cells have been designed to reduce relapse of cancer growth [27,28]. In drug discovery, molecular docking method has many advantages over other techniques like High-Throughput Screening (HTS). The method of molecular docking is much faster for evaluating binding affinity of ligands from large chemical library with minimum cost. It reduces processing time to analyze complexity of protein-ligand interaction [29]. Despite the improved features and wider utility, there are several drawbacks of molecular docking methods. The impact of water molecules at the active site and solvation effect on binding affinity is considered as a challenging task in docking [30]. Molecular recognition is a function of solvent. Ability of receptor to discriminate between different ligands Δ, in addition to their free energies of association (Δ G4), also depend on the relative free energies of solvation of ligands (Δ G3) higher is the free energy of desolvation of a ligand, weaker is its association with the receptor. Calculating Δ Δ Gbind and Δ G3 theoretically and their experimental values have been found to be in good agreement which gives mechanistic insight into these processes.

DISCUSSION & CONCLUSION

In the present review, the essentiality of molecular docking and simulation study has been highlighted. There are a large number of structures from X-ray crystallography for complexes between proteins and high affinity ligands, but comparatively fewer for low affinity ligands as the later complexes tend to be less stable and therefore more difficult to crystallize. Scoring functions trained with this data can dock high affinity ligands correctly, but they will also give plausible docked conformations for ligands that do not bind. This gives a large number of false positive hits, i.e., ligands predicted to bind to the protein that actually doesn't when placed together in a test tube. One way to reduce the number of false positives is to recalculate the energy of the top scoring poses using potentially more accurate but computationally more intensive techniques such as Generalized Born or Poisson-Boltzmann methods. Molecular recognition is a function of solvent. Ability of receptor to discriminate between different ligands Δ, in addition to their free energies of association (Δ G4), also depend on the relative free energies of solvation of ligands (Δ G3). Higher is the free energy of desolvation of a ligand, weaker is its association with the receptor. Calculating Δ Δ Gbind and Δ G3 theoretically and their experimental values have been found to be in good agreement which gives mechanistic insight into these processes.

Various software tools have been described that explore binding affinity of ligand against multiple receptors. However, further improvements are needed to include thermodynamic parameters like desolvation energies, real time change in energies due to conformational transformations in both the receptor as well as ligand i.e. dynamic simulations. Implementation of molecular docking methods facilitates synthesis, designing and development of novel therapeutic drugs as well as understanding the molecular interactions of diverse enzymatic reactions. This approach can be used to treat variety of chronic diseases through designing and discovery of novel drugs.

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