IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
August 2020 Vol.:19, Issue:1

Molecular Docking: A Novel Appliance for Structure Based Drug Discovery

IJPPR
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An official Publication of Human Journals
ISSN 2349-7203
HUMAN

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Submission: 24 July 2020
Accepted: 30 July 2020
Published: 30 August 2020

HUMAN JOURNALS
www.ijppr.humanjournals.com

Keywords: Molecular docking, drug discovery, CADDD, LMMC, Docking methods

ABSTRACT

Molecular docking has become an increasingly significant tool for drug discovery. In this review paper, we present a short-term introduction of the available molecular docking methods, their development, and applications in drug discovery. The relevant basic theories, including sampling algorithms and scoring functions, are potted. Flexible receptors molecular docking approaches, especially those as well as backbone flexibility in receptors, are a challenge for obtainable docking methods. A newly developed Local Move Monte Carlo (LMMC) based approach is presented as a potential solution to flexible receptor docking problems. Molecular docking provides new approaches for drug discovery. Computer-Aided Drug Design and Discovery (CADDD) is a speedily rising area that has seen many successes in a very short period. Many massive pharmaceutical companies, in addition to the academe, adopt CADDD for drug lead discovery. Through Molecular Docking, the binding mode as well as the affinity of the complex formed is estimated and thus helpful in the Molecular Recognition Process docking on the way to the discovery of new drug leads.

INTRODUCTION

In current drug designing, molecular docking is regularly used for considerate drug-receptor interaction. Molecular docking is defined as an optimization problem, which would designate the ‘‘best-fit’’ orientation of a ligand that binds to a specific protein of interest as well as it is used to predict the structure of the intermolecular complex designed between two or more molecules.[1] In modern drug designing, molecular docking is routinely used for understanding drug-receptor interaction. Molecular docking offers useful information about drug-receptor interactions also, frequently used to predict the binding orientation of small molecule drug candidates to their protein targets to expect the affinity and activity of the small molecule.[2] Molecular Docking is a method which antedates the preferred orientation of ligand against receptor (Protein) to make a stable complex [3]. Favored orientation possibly utilized to predict the strength of the connection or binding affinity among ligand and protein by utilizing scoring functions. Docking is frequently applied to anticipate the binding orientation of drug members against protein targets to predict the affinity and activity of the drug (Figure 1). Therefore docking plays a central role in the drug design and discovery process [4]. The main purpose of molecular docking is to computationally pretend the molecular identification process and accomplish an optimized conformation so that the free energy of the general system is minimized. The procedure of discovery of a new drug is a very difficult task. The use of computer-aided methods in drug discovery and development process is rapidly gaining popularity, execution, and appreciation.

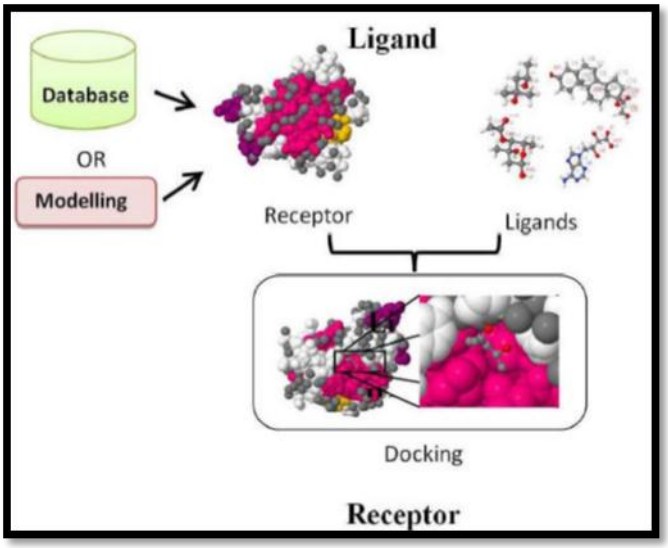

Figure No. 1: Molecular docking flow chart

The molecular docking approach can be used to model the interaction between a small molecule and a protein at the atomic level, which permit us to illustrate the behavior of minor molecules in the binding site of target proteins as well as to elucidate fundamental biochemical processes [5]. The docking process involves two basic steps: prediction of the ligand conformation and its position and orientation inside these sites (usually referred to as *pose*) and assessment of the binding affinity. These two steps are related to sampling procedures and scoring schemes, respectively which will be discussed in the theory section.

The need for Computer-Aided Drug Discovery [6-7]

- Use of computational ability to streamline drug discovery and development process.
- The benefit of chemical and biological information about ligands and/or targets to determine and optimize innovative drugs.
- Designing of *in-silico* filters to dispose of chemical compounds with unwanted goods (less activity and/ or less Absorption, Distribution, Metabolism, Excretion, and Toxicity, (ADMET)) and select the most promising candidates.
- Proof of identity of novel drug targets and retrieval through a database of target protein structures like the protein data bank (PDB) www.pdb.org. CADD (Figure 2) is used to discover hits (drug candidates).
- Virtual screening is applied to discover novel drug candidates from several chemical scaffolds by exploring databases.

Different types of interactions

Interaction forces are generally separated into four classes:

- Electrostatic forces - dipole-dipole, charge-dipole and charge-charge.
- Electrodynamics forces- Van der Waals interaction.
- Stearic forces - Caused by entropy.
- Solvent-related forces - Hydrogen bond and hydrophobic interactions [8-9].

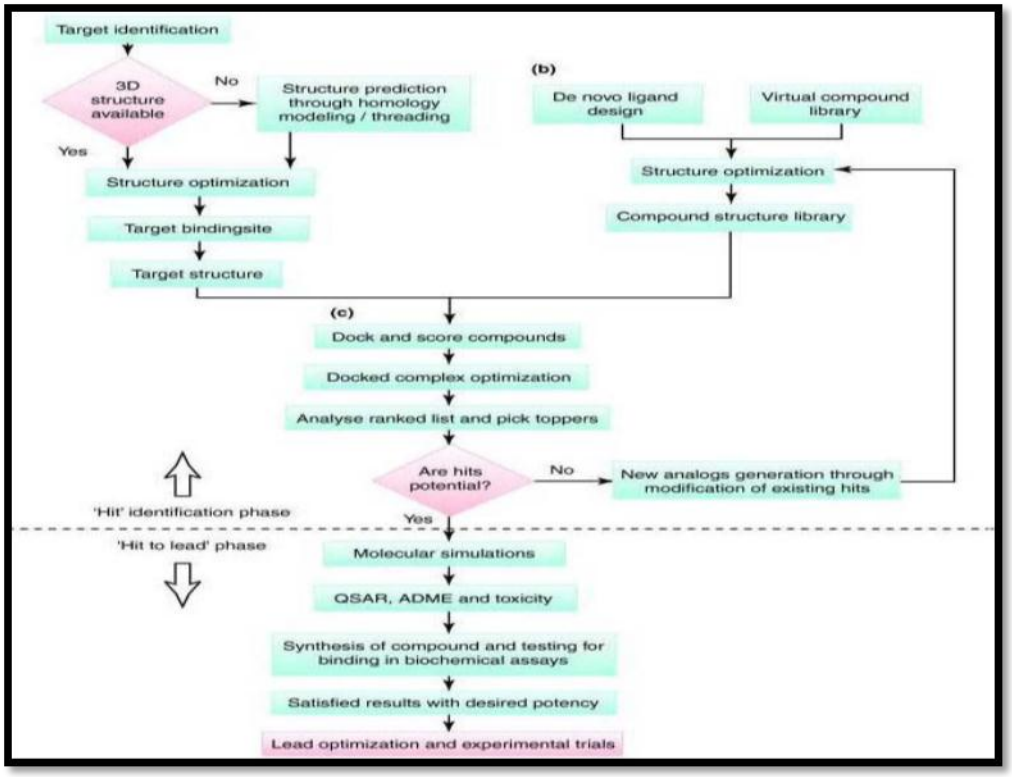

Figure No. 2: The computer-aided drug design and discovery (CADDD) procedure.

Theory of docking

Essentially, the purpose of molecular docking is to give a guess of the ligand-receptor complex assembly using computation procedures. Docking can be completed through two inter-connected steps: first by sampling conformations of the ligand in the active site of the protein; then after ranking these conformations via a scoring function. Preferably, sampling algorithms should be capable to replicate the experimental binding mode, as well as the scoring function, should also rank it highest among all generated conformations. From these two perspectives, we give a brief overview of elementary docking theory.

Molecular Docking

Molecular docking can be separated into two sections.

Search algorithm

The algorithm should generate an optimal number of configurations that admit by experimentation method determining binding modes. The following are the many algorithms

applied for docking analysis such as Point corresponding, Monte Carlo, Fragment-based, Genetic algorithms, Systematic searches, Distance geometry, etc. [10,11].

Scoring Function

The scoring function provides a mode to rank the positioning of ligands proportional to some other. Preferably, the score should resemble directly to the binding kinship of the ligand for the protein, so that the finest scoring ligands are the best binders. Scoring functions can be practical, knowledge base dor molecular mechanics based. Scoring is essentially compiled of three various expressions valid to docking and drug design:

- Created configurations ranking by the docking search.
- Ranking several ligands against the protein (virtual screening).
- One or more ligands ranking in contrast to different proteins by their binding affinity (selectivity and specificity) [12-15].

DOCKING METHODOLOGIES

Rigid ligand and rigid receptor docking

When the ligand and receptor are both preserved as rigid bodies, the pursuit space is very limited, considering only three translational and three rotational degrees of freedom. In this case, ligand flexibility could be addressed using a pre-computed set of ligand conformations, or by permitting for a degree of atom-atom intersection between the protein and ligand. The initial versions of DOCK [16, 17, 18, 19], FLOG [20], and some protein-protein docking programs, such as FTDOCK [21], accepted such a method that kept the ligand and receptor rigid during the procedure of the docking. DOCK is the first automated procedure for docking a molecule into a receptor site. It exemplifies the ligand and receptor assets of spheres which could be covered using a discovery process [22]. Geometrical, as well as chemical matching algorithms, are used; also the ligand-receptor complexes can be scored by accounting for stearic fit, chemical complementation, or pharmacophore resemblance. Within its improved versions, incremental creation method and exhaustive search are added to consider the ligand flexibility. The complete search randomly generates a user-defined number of conformers as many of the number of rotatable bonds in the ligand. Concerning scoring, the latest variety DOCK 6.4 has included both an AMBER-derived force field

scoring with implied solvent [23] and GB/SA, PB/SA solvation scoring [24, 25]. FLOG creates ligand conformations based on detachment geometry and uses a clique finding algorithm to calculate the sets of distances. Up to 25 explicit conformations of the ligand could be used to dock for some flexibility. FLOG permits users to define essential points that must be paired with a ligand atom. This approach is useful if a significant interaction is previously known before docking. Conformations are scored with a function given van der Waals, electrostatic, hydrogen bonding, and hydrophobic interactions.

Flexible ligand and rigid receptor docking

For systems whose behavior tracks the tempted fit paradigm [26,27], it is of vital reputation to consider the flexibilities of both the ligand and receptor since in that case both the ligand and receptor alteration their conformations to form a minimum energy perfect-fit complex. Though, the cost is very high when the receptor is also flexible. Thus the mutual approach, also a trade-off between accuracy and computational time, is treating the ligand as flexible while the receptor is kept rigid during docking. Nearly all the docking programs have accepted this methodology, such as AutoDock [28], FlexX [29]. AutoDock 3.0 incorporates Monte Carlo simulated annealing, evolutionary, genetic, and Lamarckian genetic algorithm methods to classical the ligand flexibility while keeping the receptor inflexible. The scoring function is founded on the AMBER force field, as well as van der Waals, hydrogen bonding, electrostatic interactions, conformational entropy, and de-solvation terms. Each term is weighted using an empirical scaling aspect obtained from investigational data. AutoDock 4.0 is capable to model receptor flexibility by permitting side-chains to move.

Moreover, the interaction of protein-protein docking could be estimated in this version of AutoDock. AutoDock Vina was newly released as the newest version for molecular docking and virtual screening [30]. By re-docking the 190 receptor-ligand complexes that had been used as a training set for the AutoDock 4, AutoDock Vina simultaneously presented approximately a two commands exponential enhancement of magnitude in speed and expressively better accuracy of the binding mode prediction. FlexX uses an incremental creation algorithm to sample ligand conformations. The base fragment is first docked into the active site by identical hydrogen bond pairs and metal and aromatic ring interactions between the ligand and protein. Then the residual component incrementally built-up in accord with a set of pre-defined rotatable torsion angles to account for ligand flexibility. The FlexX scoring function is based on Bohm's work [31]. Its current version includes terms of electrostatic

interactions, directional hydrogen bonds, rotational entropy, and aromatic and lipophilic interactions. The interactions between functional groups are also taken into account by assigning the type and geometry for groups.

Flexible ligand and flexible receptor docking

The central flexibility of proteins has been demonstrated to be closely linked to ligand binding behavior and it has been studied by Teague [32]. Integrating receptor flexibility is an important challenge in the area of docking. Ideally, by using MD simulations could model all the grades of freedom in the ligand-receptor complex. But MD has the problem of insufficient sampling that we stated earlier. Another hurdle is its high computational expenditure, which avoids this method from being used in the screening of bulky chemical database. In addition to the notable induced-fit several theoretical models, conformer collection as well as conformational induction, have been planned to demonstrate the flexible ligand-protein binding procedure. According to the definition given by Teague [32], conformer selection denotes to a procedure when a ligand selectively binds to a favorable conformation from several protein conformations; conformational initiation defines a process in which the ligand renovates the protein into a conformation that it would not naturally adopt in its liberated state. In some cases, this conformational conversion can be associated with a partial refolding of the protein.

Utilizing rotamer libraries [33, 34] is another method of displaying receptor flexibility. Rotamer libraries include a set of side-chain conformations which are usually determined from statistical analysis of organizational experimental data. The advantage of using rotamers is the relative speed in sampling and the ducking of minimization barriers. ICM i.e. Internal Coordinates Mechanics [35] is a program using rotamer libraries with the biased prospect methodology [36], coupled with Monte Carlo search of the ligand conformation. Auto-Dock 4 [37] approves a simultaneous sample method to deal with side-chain flexibility. Some side chains of the receptor can be selected by users and simultaneously sampled with a ligand using similar methods. Other portions of the receptor are preserved rigidly with a grid energy map through sampling. The grid energy map presented by Good ford [38] is used to store energy information of the receptor and make a simpler interaction energy design between ligand and receptor. Still another way to deal with the protein flexibility is to use an ensemble of protein conformations, which corresponds to the theory of conformer selection [39, 40]. A ligand is separately docked into a set of rigid protein conformations rather than a single one,

and the results are merged depending on the method of choice [41]. This method was originally implemented in the DOCK, which generates an average potential energy grid of the ensemble [39] and is extended in many programs in different ways. For example, FlexE [42] collects multiple crystal structures of a certain protein, merging similar parts while marking the dissimilar areas as different alternatives. During the incremental construction of a ligand discrete protein conformations are sampled in a combinatorial fashion. The maximum scoring protein structure is nominated based on a comparison amongst the ligand and each substitute.

The hybrid method is an additional practical strategy to model receptor flexibility. One example is Glide [43], a very popular program in the field of docking. Glide designs a series of hierarchical filters to search the possible poses and orientations of the ligand within the binding site of the receptor. Ligand flexibility is handled by an exhaustive search of the ligand torsion angle space. Early ligand conformations are selected based on torsion energies and docked into receptor binding sites with soft potentials. Then a rotamer exploration is used to further model receptor flexibility [44]. IFREDA [41] utilizes a hybrid method that combines soft potential and multiple receptor conformations, accounting for receptor flexibility. Other programs, like QXP [45] and Affinity [46], perform a Monte-Carlo search of ligand conformations followed by a minimization step. Throughout minimization, the user-defined parts of the protein are permitted to move to sidestep atom clashes between the ligand as well as the receptor. SLIDE [47] is designed to incorporate flexibility with the ability to remove clashes by directed, single bond rotation of either the ligand or the side chains of the protein. An optimization approach based on the mean-field theory is applied to model induced-fit complementarities between the ligand and protein. Methods stated above either include only side-chain flexibility or full flexibility of the receptor. We have identified that loops forming active sites play a significant role in ligand binding. In some cases, the loop may undergo dramatic conformational change whereas in other portions of the receptor there is little change upon ligand binding. For this state, side-chain flexibility approaches fail to sample the accurate protein conformation as well as full flexibility seems to be a computational waste. (Figure.3) shows superimposed crystal structures of triosephosphate isomerase as an example. The active site of triosephosphate isomerase has an 11-residue loop which moves 7Å upon ligand binding [48]. However, the rest of the enzyme has no movement in comparison to their apo and hole structures. Some enzyme families also involve loop rearrangement inside the active site answerable for ligand binding, such as Bromodomain, a wide family related to acetyl-lysine binding, or Dihydrofolate reductase,

responsible for the preservation of the cellular pools of tetrahydrofolate, as well as other kinds of kinases [49, 50]. In the next section, we present the Local Move Monte Carlo (LMMC) loop sampling method, an innovative approach that emphases sampling ligand conformation inside loop-containing active sites.

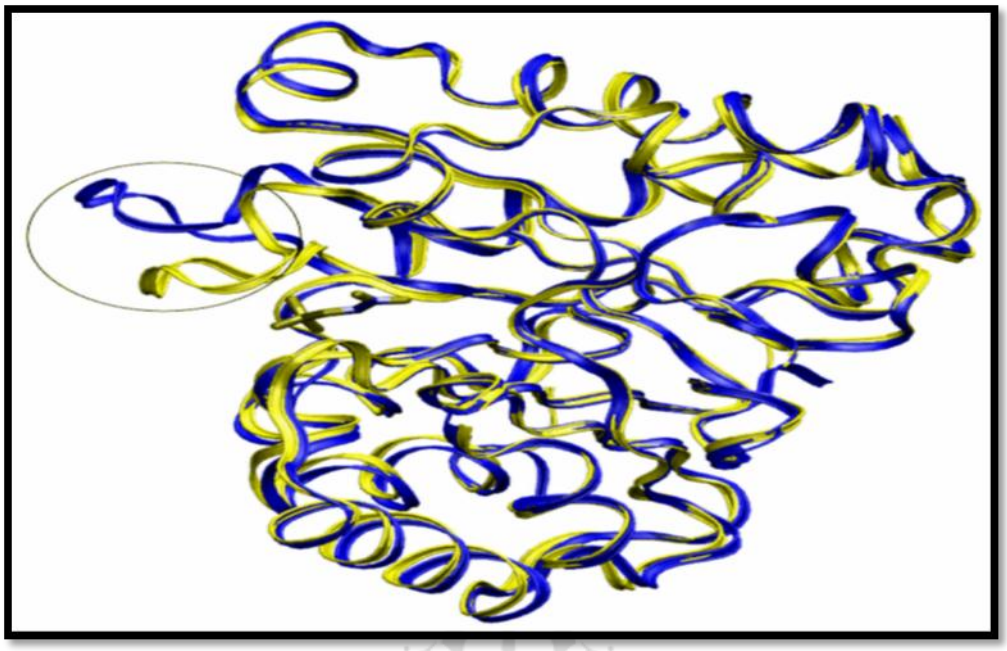

Figure No. 3: Superimposed apo- (in yellow) and holo- (in blue) crystal assemblies of *triosephosphate isomerase*. PDB code 1YPI and 2YPI, respectively [48]. The 11 residue-loop collected of The binding site is the individual region that has bulky motion upon ligand binding (in the circle).

Local Move Monte Carlo [LLMC] sampling for flexible receptor docking

A local move (also referred to as 'window move') starts with changing one torsion angle (called the driver torsion) followed by the adjustment of the six subsequent torsions to allow the rest of the chain to remain in its original position while preserving all bond lengths and bond angles (Figure 4). The pioneering work on the local move was done by Go and Schrage[51], who developed a solution for the system of equations defining the values of the six torsion angles that preserve the backbone bond lengths and angles. Hoffmann and Knapp first applied the local move method in an MC simulation of polyalanine folding that includes suitable Jacobian [52], required for maintaining detailed balance. They demonstrated that this method samples the conformational space more efficiently than a single move [53]. The method has been further tested on proline-containing peptides [54], proteins, and nucleic

acids [55]. Mazie introduced the 'reverse proximity criterion' for filtering all possible loop closure solutions to select the most structurally conservative one and tested it on a solvated lipid bilayer [56]. We have advanced an improved local move Monte Carlo (LMMC) loop sampling method for loop predictions. The method generates loop conformations based on simple moves of the torsion angles of side chains also local moves of the backbones of loops. To reduce the computational charges for energy evaluations, we established a grid-based force field to characterize the protein environment and solvation result. Simulated annealing has been used to improve the efficacy of the LMMC loop sampling and recognize low-energy loop conformations. The forecast quality was assessed on a set of protein loops with an identified crystal structure that has been before used by others to test different loop prediction methods. The results show that this approach can reproduce the experimental results with root mean square deviation (RMSD) within 1.8 Å for all the test cases [57]. (Figure 5) shows the loop structures of 2act (198-205) sampled by the LMMC method. This LMMC loop forecast style could be suitable for flexible receptor docking. In our future studies, we will advance our LMMC based molecular docking approach, which samples not only the side chains but also the backbone loops in the binding site of proteins and flexible ligands. A flowchart of the LMMC based molecular docking approach is given in (Figure 6).

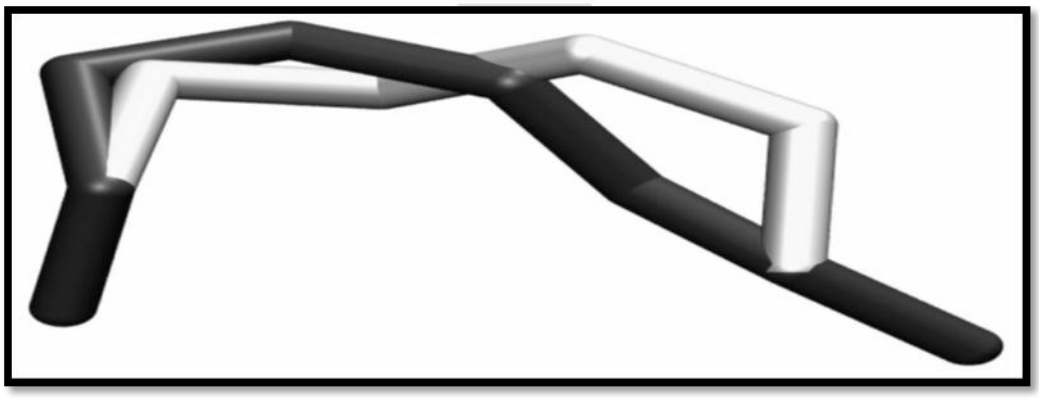

Figure No. 4: Local moves of a lipid tail. Six subsequent torsions change while keeping the rest of the chain to remain in its unique position.

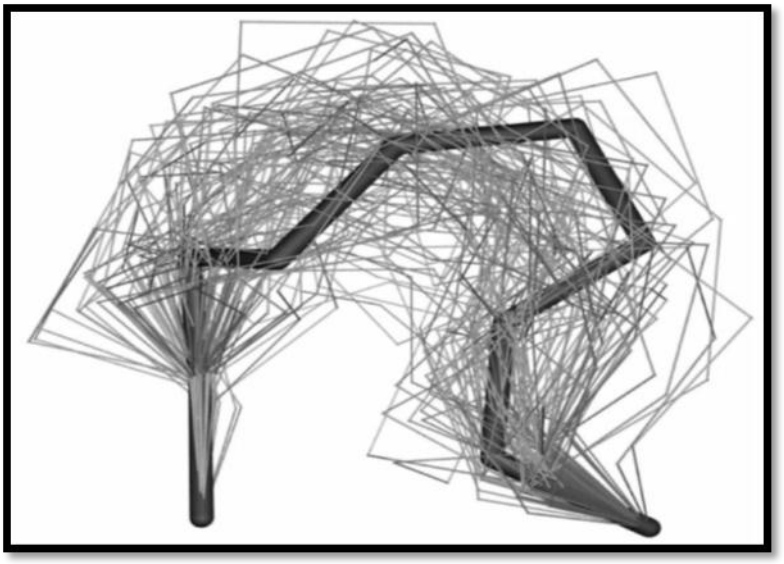

Figure No. 5: Flowchart of local move Monte Carlo (LMMC) loop sampling method for protein-ligand docking. Abbreviate: MC, Monte Carlo. ESC, Exponential Coolong Scheme. LCS, Linear Cooling Scheme.

Application examples of molecular docking for drug discovery

- Molecular docking has been the most widely employed method. Though the key application lies in structure-based virtual screening for identification of modern active compounds towards specific target protein, in which it has produced many of success stories [58], it is not a stand-alone technique but is normally embedded in a workflow of different in silico as well as experimental techniques [59]. Various research groups focus on evaluating the performance of various docking methods or on making improvements to the scoring functions when experimental testing has already been done. Such efforts could give meaningful guidance to choose the methodology for a particular target system. Docking, combined with other computational techniques and experimental data, also could be involved in analyzing drug metabolism to obtain some useful information from the cytochrome P450 system [60-62], for example. In the following, three examples of successful applications of docking are presented.

- *DNA gyrase* is a bacterial enzyme that presents negative supercoils into bacterial DNA and unwinds of DNA, thus being considered as an antibacterial target. HTS unsuccessful to find new inhibitors of DNA gyrase. Boehm et. al. used de novo design for this enzyme and effectively obtained several innovative inhibitors [63]. Firstly, 3D complex structures of

DNA gyrase with identified inhibitors, ciprofloxacin as well as novobiocin, were carefully analyzed to get a mutual binding pattern, in which both inhibitors donate one hydrogen bond to Asp73 and accept one hydrogen bond from a preserved water molecule. Also, some lipophilic fragments should be involved in the molecule to have lipophilic interaction with the receptor. Based on this information, LUDI and CATALYST were working to search the Accessible Chemicals Directory (ACD) and a part of the Roche compound inventory (RIC), respectively, and collected about 600 compounds. Close analogs of these compounds were also regarded, thus in total 3000 compounds were nextley tested using biased screening. Consequently, 150 hits were selected and clustered into 14 classes of which 7 classes were proven to be the true and novel inhibitors. Subsequent hit optimization relied strongly on the information of 3D structures of the binding site and eventually produced a series of highly potent DNA gyrase inhibitors.

- Another example is focused on the validation of docking and scoring practical in cytochromesP450 and other heme-containing proteins [64]. Docking against heme-containing complexes seems to be tough because certain ligands co-ordinate directly to the hemeiron atom and the precise energetics of this interaction for different chelating groups needs to be correctly balanced with other energetic terms, and in the case of the P450s, the environment above the heme group is very hydrophobic associated to other enzymes and some scoring functions and docking methods perform poorly on interactions driven entirely by Lipophilic contacts. In this study, 45 complexes from the PDB database comprising heme-containing proteins and ligands were selected. The native ligands were removed and then docked into the defined active cavities using the GOLD [65] software which employs genetic algorithms to produce ligand conformations. The scoring functions used to rank the docking poses were Gold-score [66] and Chem-score [65]. The results show that the success rates are 64% and57% for Chem-score and Gold-score respectively, which is significantly lower than the value of 79% observed with both scoring functions for the full GOLD validation set. Additionally, it is apparent from the data that the search algorithm was very unlikely to be responsible for the failure in docking. Further study designated that re-parameterization of metal-accept printer actions and lipophilicity of planar nitrogen atoms in the scoring functions resulted in a substantial increase in the percentage of effective docking poses against the heme-binding proteins (Chem-score 73%, Gold-score 65%), which might be useful in docking application son P450 enzymes and other heme-binding proteins.

CONCLUSION

Molecular Docking makes available an array of valuable tools for drug design and analysis. Simple visualization of molecules, as well as easy access to structural databases, has become required components on the desktop of the medicinal chemist. Marketable software programs continue to expand upon the core user interface. Receptor flexibility, especially backbone flexibility and movement of several important secondary elements of the receptor involving ligand binding and the catalyst, is still a major hurdle in docking studies. Some methods to deal with side-chain flexibility have been confirmed effective and adequate in certain cases. Concerning global flexibility, an ensemble of proteins is a common solution which accords with the lookout of conformer selection. It entails an effectual way to obtain and select reliable protein structures used for docking, which means structures that the ligand can fit in should be included in the ensembles. Besides, the computational cost is another restriction for this method. LMMC could be an appropriate method for sampling a ligand within loop-containing active sites since the loop tends to be extra flexible as well as hard to model using existing methods especially due to their possibly affected movements. Another benefit is the adjustment of the extent of flexibility. Also, the side chain or full movement of the loop can be straight controlled by users. The scoring function is a key program worth being further improved upon in docking. Successful application examples show that computational approaches have the power to screen hits from a large database and design unique small molecules. However, the realistic interactions amongst small molecules and receptors have still relied on experimental technology. Accurate as well as low computational price scoring functions may bring docking application to a new stage.

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