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An overview of Molecular Docking

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Abstract

Molecular docking is a kind of computational modeling of the complexes, which is formed from the interaction of two or more molecules. It predicts the three-dimensional structure of adducts, based upon binding properties of participating ligand and target molecules. Molecular docking generates different possible candidate structures, which are ranked and grouped together using scoring function in the software of molecular docking tool. Docking simulations predict optimized docked conformer based upon total energy of the system. Various computational aspects of molecular docking with respect to its approaches and types are presented in this article.

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Submitted: 18 April 2016

Accepted: 19 May 2016

Published: 23 May 2016

ISSN: 2333-6633

Keywords

- Molecular docking
- Scoring function
- Shape complementarity
- Computer simulations

INTRODUCTION

Molecular docking is a kind of computational modeling, which facilitates the prediction of preferred binding orientation of one molecule (eg. ligand) to another (eg. Receptor), when both interact each other in order to form a stable complex [1]. Information gained from the preferred orientation of bound molecules may be employed to predict the energy profiling (such as binding free energy), strength and stability (like binding affinity and binding constant) of complexes. This can be done using scoring function of molecular docking. Now days, molecular docking is often utilized to forecast the binding orientation of small molecules (drug candidates) to their biomolecular target (such as protein, carbohydrate and nucleic acid) with the aim to determine their tentative binding parameters. This establishes raw data for the rational drug designing (structure-based-drug development) of new agents with better efficacy and more specificity [2].

The main objective of molecular docking is to attain an optimized docked conformer of both the interacting molecules in furtherance of achieving lessen free energy of the whole system. Final predicted binding free energy (ΔG_{bind}) is modeled in terms of dispersion & repulsion (ΔG_{vdw}), hydrogen bond (ΔG_{hbond}), desolvation (ΔG_{desolv}), electrostatic (ΔG_{elec}), torsional free energy (ΔG_{tor}), final total internal energy (ΔG_{total}) and unbound system's energy (ΔG_{unb}). Therefore, detailed understanding of the general principles that govern predicted binding free energy (ΔG_{bind}) provides auxiliary information about the nature of various kinds of interactions driving the docking of molecules [3].

Practical application of molecular docking requires structural data bank for the search of target of interest and a methodology to evaluate ligand. To accomplish this, there are various molecular docking tools and methodologies are available. These computational tools provide the hierarchy to potential ligands based upon their ability to interact with given target candidates. Molecular docking of small molecules to a biological target includes animaginative sampling of possible poses of the ligand in the specified groove or pocket of target candidate in an order to establish the optimal binding geometry. This can be performed using user defined fitness or scoring function of docking software [1,4]. However, X-ray crystallography and Nuclear Magnetic Resonance (NMR) spectroscopy are the primary techniques for the investigation and establishment of three dimensional structure data for biomolecular targets. Nevertheless, homology modeling facilitates the determination of tentative structure of those proteins (of unknown structure) having high sequence homology to known structure. This presents a substitute approach for target structure establishment, which forms an initiation point for *in silico* discovery of high affinity drug candidates. There are various databases available, which offer information on small ligand molecules such as CSD (Cambridge Structural Database), ACD (Available Chemical Directory), MDDR (MDL Drug Data Report) and NCI (National Cancer Institute Database). While performing molecular docking, different docked conformers (poses) are generated, scored and compared with each other. One of the poses is either accepted or rejected based upon the scoring function of docking software. In the condition of rejection, new poses are generated and again search procedure iterates to its endpoint of one pose acceptance. In molecular docking, searching and scoring are tightly coupled with each other. However, ranking of docked conformers according to their experimental binding affinities and binding free energies seems to be more difficult than the searching of their binding orientation. To overcome this challenge, different scoring functions are employed such as consensus scoring; appliance of number of score functions to the same docked pose in order to eliminate false positives [1,2,4,5].

Computational approaches (*In Silico* methods) should be quick and robust, so that it can create foremost impact on target recognition. For it, the capability of different docking

methods is evaluated using docking-based virtual screening protocols to prioritize known active candidates out of several inactive molecules from a database [1,2,4]. Keeping this in view, a huge amount of attempts has been made for the development and establishment of efficient scoring and docking protocols. Nevertheless, significant progress has been accomplished in the computational prediction of receptor-ligand docking modes. There are number of research and review articles, which demarcate various emerging information in this area. This mini review article dedicated to recent computational docking approaches, its types and its applications.

Approaches of Molecular Docking

For performing molecular docking, primarily two types of approaches are used. One of the approaches employs computer simulations, in which energy profiling is estimated for ligand-target docked conformer. Whereas, second approach utilizes a technique that calculates surfaces complementarity between ligand and target [1]. Both approaches are described below; in brief and their main properties are also summarized in (Table 1).

Simulation Approach

In this approach, ligand and target molecules are separated by some physical distance and then, ligand is allowed to bind into groove/pocket of target molecule after a "definite times of moves" in its conformational space. The moves involve variations to the ligand structure either internally (torsional angle rotations) or externally (rigid body transformations such as rotations and translations). Every move in the conformational limits of ligand generates energy, which is calculated as "Total Energy of the System". This approach is more advantageous over shape complementarity one as it is morecompatible to accept ligand flexibility in to molecular modeling tool. An additional benefit of this approach is that, it is more real to assess the molecular recognition between ligand and target molecule. However, molecular docking using this approach takes longer duration to appraise optimal docked conformer, since large energy landscapes need to be calculated for each pose. Nevertheless, fast optimization method and grid-based tools have appreciably revolutionized this drawback to make computer simulation approach more user-friendly [1,6].

Shape Complementarity Approach

This approach employs ligand and target as a set of surface structural features that facilitate their molecular docking. In order to achieve molecular docking, molecular surface of target is elucidated with respect to its solvent-accessible surface area, whereas; ligand's molecular surface is described in terms of matching surface illustration. The complementarity between two molecular surfaces is evaluated based on shape matching illustration, which assist in searching the complementary groove/pocket for ligand docking on target molecular surface. In particular, for protein target molecules, hydrophobicity is also estimated employing number of turns in the main-chain atoms. Shape complementarity approach is rather quick and robust, which involves the rapid scanning of numerous thousands of ligand in a few seconds to find out the possible binding properties of ligand on target molecular surface [1,6].

Types of Docking

Comprehensively utilized docking tools employ search algorithms such as genetic algorithm, fragment-based algorithms, Monte Carlo algorithms and molecular dynamics algorithms. Besides this, there are some tools such as DOCK, GOLD, FlexX and ICM, which are mainly used for high throughput docking simulations. There are various kinds of molecular docking procedures involving either ligand/target flexible or rigid based upon the objectives of docking simulations [2,5,7]. Specifically these may be-

Table 1: Molecular Docking Approaches.

Simulation Approach	Shape Complementarity Approach
In this approach, interaction energy as per ligand-receptor pair are calculated	This approach implies the estimation of complementarity between ligand and receptor surface
To achieve the best docked conformer of ligand and receptor, ligand is allowed to fit into receptor's groove based upon minimum energy consideration.	To attain the docked conformer *via* this approach, solvent accessible topographic features of ligand and receptor in terms of matching surface is described. This is followed by the estimation of shape complementarity between interacting molecules for finding out optimal groove/pocket for ligand binding on its target.
Every move of ligand into receptor's pocket for best fitting generates an energy as Total Energy of System, which is compared to find out best docked conformer with minimum energy	This method consists of surface representation of receptor and ligand (i.e. surface construction and smoothing), features/curvature calculation followed by docking and scoring contingent to geometric complementary criteria.
This approach is more compatible to accept ligand flexibility in molecular modeling tool, which facilitates real assessment of molecular perception and interaction between ligand and receptor molecules.	Shape complementarity approach allows both types of docking; flexible docking and rigid docking. In case of flexible or soft docking conformational changes may take place among bound and free interacting molecules. This is accompanied with the penetration and overlapping of both interacting molecules on each other. However, rigid docking does not let spatial alteration into shape of interacting molecules during molecular modeling
Performing the molecular modeling, through this approach, requires much longer time as large energy profiling needs to be estimated. However, grid-based tools and fast optimization methods have significantly transfigured this downside.	This method encompasses the rapid scanning of large number of ligands for the binding on its target in a few seconds and hence, provides quick and robust outcomes

Flexible ligand docking, which incorporates target as rigid molecule. This is the most commonly used in docking.

Rigid body docking, where both the target and ligand molecules are kept as rigid molecules.

Flexible docking that involves both interacting molecules as flexible

APPLICATIONS OF MOLECULAR DOCKING

Molecular docking is the need of today's research. It can demonstrate the feasibility of any task, if it carried out before experimental part of any investigation. There are some areas, where molecular docking has revolutionized the findings. In particular, interaction investigations between small molecules (ligand) and protein target (may be an enzyme) may predict the activation or inhibition of enzyme. Such type of information may provide a raw material for the rational drug designing. Some of the major applications of molecular docking are described below-

Lead optimization

Molecular docking can predict an optimized orientation of small molecule or ligand on its target. It can predict different binding modes of ligand in the groove of target molecule. Knowledge gained from such type of investigations may be employed to develop more potent, selective and efficient analogs [5,7].

Hit Identifications

Molecular docking in combination with scoring function can be used to screen huge databases for finding out potent drug candidates *in silico*, which can target the molecule of interest [8].

Drug-DNA Interactions Studies

In recent times, majority of regimens and approaches, leading to cancer treatment, involve the utilization of chemotherapy. Despite inexorably significant role of chemotherapy in cancer cure and control, cytotoxic mechanisms of several chemotherapeutic agents are not well characterized. Many of these anticancer chemotherapeutic drugs possess nucleic acid and auxiliary processes as their main cellular target. Keeping this in view, researchers are constantly putting their efforts to elucidate the underlying anticancer mechanism of drugs at molecular level by investigating the interaction mode between nucleic acid and drugs [9-13]. Here, molecular docking plays a significant role in the preliminary prediction of drug's binding properties to nucleic acid. The information gathered from the outcome of such investigations is helpful in the establishment of a correlation between drug's molecular structure and its cytotoxicity. Furthermore, this knowledge would be instrumental in the detection of those structural modifications in a drug that could result in sequence/structure specific binding to their target (nucleic acid). This comprehension can be exploited in the rational designing and synthesis of new drugs, possessing better efficacy and reduced side effects, since; non-specific binding restricts drug dose and regularity in cancer treatment [7,8,14].

CONCLUSION

In this mini review, we have focused on types and approaches of molecular docking in brief. The main objective of molecular docking simulations is to identify new lead candidates. In order to achieve its aim with better efficacy, robust and reliable scoring function appears to be one of the challenges, which should be addressed in near future. To conquer the limitations of currently established scoring function, novel algorithm needs to be developed. In particular, for protein-ligand docking, induced-fit-motions and flexibility of the protein will be implicated in coming years in an order to discover and design new chemotherapeutic agents. In pharmaceutical industries, the impact of molecular docking is well recognized and established. Now a day's computational docking simulations are routinely employed at different stages of the drug discovery and rational drug designing procedures. As the area of molecular docking-based virtual screening will grow, its recognition will be significantly enhanced. Widely accepted and validated test data should be established to facilitate the comparisons needed to explain the new frontiers of research in this field.

ACKNOWLEDGMENT

The authors thank Director, CSIR-National Physical Laboratory, New Delhi, India, for granting the permission for publication of the work.

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Cite this article

Agarwal S, Mehrotra R (2016) An overview of Molecular Docking. JSM Chem 4(2): 1024.