International Research Journal of Pure & Applied Chemistry

22(3): 60-68, 2021; Article no.IRJPAC.58789
ISSN: 2231-3443, NLM ID: 101647669

A Review on Molecular Docking

Khemnar Manisha Dnyandev[1*], Galave Vishal Babasaheb[1], Kulkarni Vaishali Chandrashekhar[1], Menkudale Amruta Chandrakant[1] and Otari Kishor Vasant[1]

[1]Department of Chemistry, Navsahyadri Institute of Pharmacy, Pune, Maharashtra, India.

Authors' contributions

This work was carried out in collaboration among all authors. Author KMD designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors GVB and KVC managed the analyses of the study. Authors MAC and OKV managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IRJPAC/2021/v22i330396
Editor(s):
(1) Dr. Wolfgang Linert, Vienna University of Technology, Austria.
Reviewers:
(1) Ahmed N. Ayyash, University of Fallujah, Iraq.
(2) C. V. Vidhya, Ethiraj College for Women, India.
(3) Nadeem A. Kizilbash, Applied Medical Sciences Northern Border University, Saudi Arabia.
Complete Peer review History: http://www.sdiarticle4.com/review-history/58789

Review Article

Received 19 May 2020
Accepted 24 July 2020
Published 20 May 2021

ABSTRACT

Molecular docking is computational modeling of structure complexes formed by two or more interacting molecule. The goal of molecular docking is prediction of three dimensional structure of interest. Molecular docking software mostly used in drug improvement. Molecules and effortless entrance to structural databases has befallen essential mechanism. Molecular Docking provide a collection of expensive tools for drug design and analysis. Simple prophecy of molecules and easy way in to structural databases has become essential components on the desktop of the medicinal chemist. The most important application of molecular docking is virtual screening. A variety of docking programs were residential to imagine the three dimensional structure of the molecule and docking gain can also be analyze with the assist of dissimilar computational methods. Molecular docking is a key tool in structural molecular biology and computer-assist drug design. Docking can be worn to execute virtual screening on large libraries of compounds, rank the results, and suggest structural hypotheses of how the ligands reduce the target, which is precious in lead optimization.

**Corresponding author: E-mail: Manishakhemnar5258@gmail.com;*

Keywords: Molecular docking; types of molecular docking; mechanism of docking; docking assessment; application.

1. INTRODUCTION

In the meadow of molecular modeling, docking is a technique which predict the prefer direction of one molecule to a second when jump to each other to form a steady compound [1]. Information of the chosen direction in rotate may be worn to expect the strength of involvement or binding affinity linking two molecules with each, for example, score function.

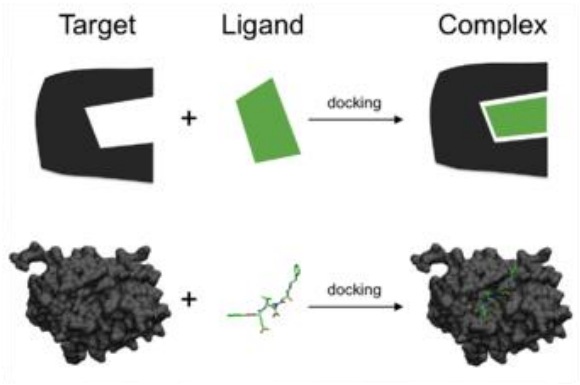

Fig. 1. Schematic diagram of docking a undersized molecule ligand (green) to a protein target (black) produce a steady compound

The relations between physically appropriate molecules such as proteins, peptides, nucleic acids, carbohydrates, and lipids play a central role in signal transduction. Furthermore, the relative orientation of the two interact associates may involve the type of signal formed (e.g., agonist vs antagonism). Therefore, docking is helpful for predict both the potency and type of signal produced. Molecular docking is one of the majority generally used technique in structure-based drug design, due to its capability to forecast the binding-conformation of small molecule ligands to the suitable target binding site. Characterization of the binding performance plays a significant role in rational plan of drugs as well as to explain fundamental biochemical process [2].

The aim of molecular docking is to accomplish an optimized conformation for both the protein and ligand and fundamental direction between protein and ligand so that the free energy of the generally method is minimized [3]. Molecular recognition plays a key role in promote elementary bimolecular proceedings such as enzyme substrate, drug-protein and drug-nucleic acid interactions [4]. Detailed appreciative of the universal principles that administrate the nature of the connections (van der Waals, hydrogen bonding, electrostatic) involving the ligands and their protein or nucleic acid targets may afford a framework for designing the most wanted potency and specificity of potential drug leads for a given therapeutic target [5]. Practical application of this information requires structural data for the goal of significance and a progression for evaluating candidate ligand [6]. A variety of computational docking methods are accessible [7].

2. TYPES OF DOCKING

There are 2 types of docking;

1. Rigid docking
2. Flexible docking

2.1 Rigid Docking

If we think that the molecules are rigid, then we are looking for a conversion in 3D space of one of the molecules which bring it to an most favorable fit with the other molecules in provisions of a scoring function. Conformation of the ligand may be generating in the absence of receptor or in the occurrence of receptor binding activity.

2.2 Flexible Docking

We think molecule flexibility then in adding to transformation, our aspire to locate the confirmations of the receptor and the ligand molecules, as they emerge in complex [9].

3. MOLECULAR DOCKING APPROACHES

There are number of approach survive for docking as follows –

3.1 Monte Carlo Approach

i. It generates a preliminary Configuration of a ligand in an energetic site consisting of Random conformation, conversion & rotation.

ii. It score initial configuration. Then it generates new arrangement & score it.

iii. It employ Metropolis criterion to decide whether the new configuration is retain.

3.2 Metropolis Criterion

If new solution score improved than the preceding one, it is immediately accepted. If the configuration is not new one, a Boltzmann-based prospect function is useful. If the solution passes the possibility function test, it is established; if not the configuration is unwanted [10].

3.3 Fragment Based Method

Fragment base method can be described as separating the ligand into divide protons or fragments, docking the fragments & finally connecting these fragments together.

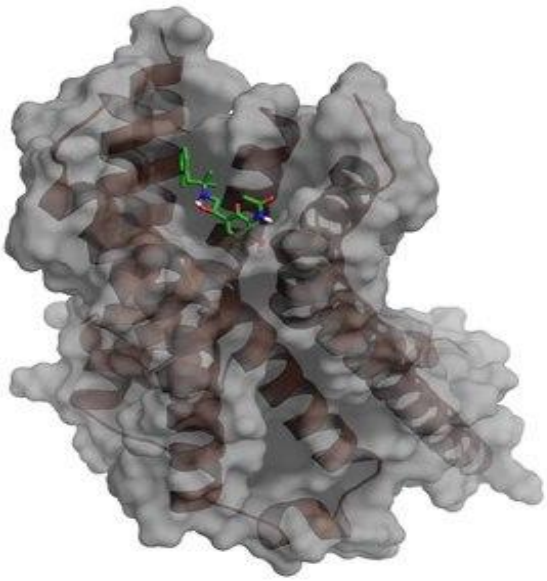

Fig. 2. Docking of a little molecule (green) into the crystal composition of the beta-2 adrenergic g-protein coupled receptor (PDB: 3SN6)

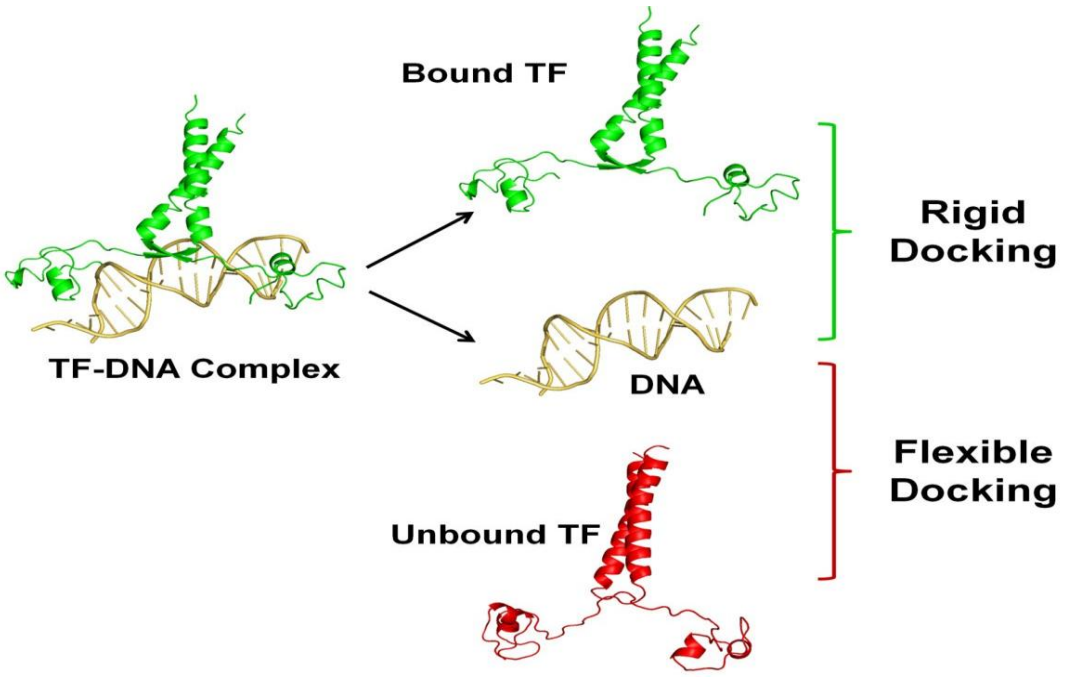

Fig. 3. Structural images of rigid docking and flexible docking [8]

3.4 Distance Geometry

Many types of structural in sequence can be articulated as intra or intermolecular distances. The distance geometry formalism allows these detachment to be assembled & 3 dimensional structures dependable with them to be considered.

3.5 Matching Approach

These approach focus on complimentarily. Ligand atom is located at the “best‟ position in the site, generate a ligand receptor Configuration that may involve optimization.

3.6 Ligand Fit Approach

Ligand robust term afford a rapid accurate protocol for docking small molecules ligand into protein vigorous sites for consider shape complimentarity8 between ligand & protein active sites.

3.7 Point Complimentarily Approach

These method are Based on evaluate a shape & /or chemical complimentarily between interact molecules.

3.8 Blind Docking

It was introduced for detection of possible binding sites & modes of peptide ligand by scanning the entire surface of protein targets.

3.9 Inverse Docking

I. In this use of a computer technique for decision toxicity & side effect protein targets of a small molecule.

II. Knowledge of these targets combined with that of proteomics pharmacokinetic profile can facilitates the assessment of potential toxicities side effect of drug candidate.

III. One of these protocols is selected for docking studies of particular ligand [10].

4. MECHANISM OF DOCKING

1. To achieve a docking screen, the first obligation is an organization of the protein of attention. Typically the structure has been unwavering using a biophysical method such as x-ray crystallography, or less often, NMR spectroscopy. This protein organization and a folder of ligands serve as input to a docking agenda [11].

2. The Success of a docking program depends on two mechanisms such as search algorithm and scoring function. The investigate space consists of all Possible orientations and conformations of the protein Paired with ligand [12]. With near computing possessions, it is Impossible to comprehensively discover the investigate space this would enumerate all potential distortion of each molecule and all probable rotational and translational Orientations of the ligand relation to the protein at an agreed level of granularity.

3. Most docking program in use account for bendable ligand, and numerous are attempting to model a flexible protein receptor [13].

4. Molecular Docking is the procedure in which the intermolecular announcement between 2 molecules was studied in In-silica. In this improvement, the Macromolecule is the protein receptor. The small particle is the Ligand

5. Molecule which can be acted as an inhibitor [14].

4.1 Major Steps Involved in Mechanics of Molecular Docking

So, the Docking process involves the following steps:

4.1.1 Step I – preparation of protein

Three dimensional structure of the Protein must be retrieve from Protein data bank (PDB); later the retrieve structure should be pre-processed. This should admit amputation of the water molecules from the cavity, stabilize the charges, substantial the missing residue, production the side chains etc. according to the parameter available.

4.1.2 Step II – active site prediction

After the preparation of protein, the active site of protein must be predicted. The receptor strength possesses lots of active sites merely the one of the concern should be chosen out. Generally the water molecules and hetero atoms are unconcerned if present [15,16].

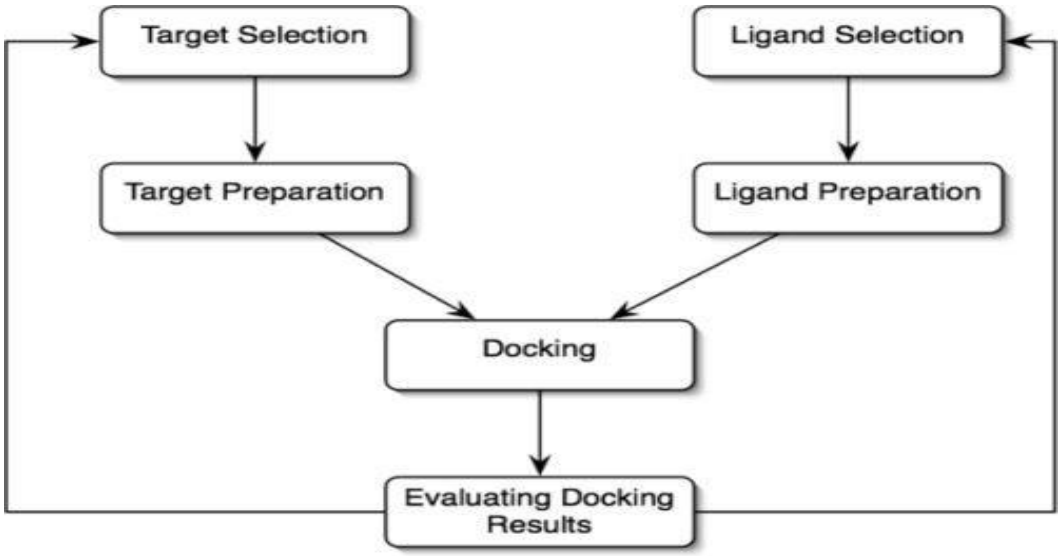

Fig. 4. Flow chart for evaluating docking [12]

4.1.3 Step III – preparation of ligand

Ligand can be retrieve from numerous databases such as ZINC, Pub Chem. or can be sketched apply Chem. sketch tool. While picking out the ligand, the LIPINSKY'S RULE OF 5 should be utilizing. Lipinski rule of 5 assist in discriminating among non-drug like and drug like. The computer aided drug design and detection (CADDD) method. It promises high possibility of achievement or failure due to drug likeness for molecules remaining by with 2 or more than of the complying rules. For choice of a ligand allow to the

4.1.3.1 Lipinsky's rule

(1) A lesser amount of five hydrogen bond donors
(2) A lesser amount of ten hydrogen bond acceptors
(3) Molecular mass less than 500 Da
(4) High lipophilicity (expressed as Log not over 5)
(5) Molar refractivity should be between 40-130 [17].

4.1.4 Step IV

Docking: Ligand is docked alongside the protein and the interactions are analyzed [11].

4.2 Docking Assessment

The interdependence between sampling and scoring function affect the docking capacity in predict possible poses or binding affinities for novel compounds. Thus, an evaluation of a docking protocol is normally essential (when experimental data is available) to determine its analytical capability. Docking measurement can be performing using different strategy, such as:

I. Docking accuracy (DA) calculation.

II. The correlation between a docking score and the experimental response or determination of the fortification factor (EF).

III. The distance between an ion-binding moiety and the ion in the active site;

IV. The presence of induce-fit models [18].

4.2.1 Docking accuracy

Docking accuracy represent one decide to quantify the situation of a docking program by rationalizing the ability to guess the right pose of a ligand with respect to that experimentally observed [19,20,21].

4.2.2 Enrichment factor

i. Docking screens can also be evaluated by the enrichment of annotate ligands of known binders from between a large database of recognized non-binding, "entice" molecules [22]. In this way, the achievement of a docking screen is evaluate by its capacity to improve the small number of known active compound

in the top ranks of a screen from between a much greater number of decoy molecules in the database.

ii. The area under the recipient in commission characteristic (ROC) curve is widely used to estimate its presentation.

4.2.3 Prospective

i. Resultant hits from docking screens are subjected to pharmacological validation (e.g. IC50, similarity or strength measurements).

ii. Only prospective study comprises convincing proof of the fitness of a performance for a meticulous target [23].

4.2.4 Benchmarking

i. The potential of docking program to replicate binding modes as unwavering by X-ray crystallography can be assess by a range of docking benchmark sets.

ii. For small molecules, numerous standard data sets for docking and virtual transmission exist e.g. Astex Diverse Set consisting of high quality protein−ligand X-ray crystal structure or the register of Useful Decoys (DUD) for evaluation of virtual screening presentation [24].

iii. An assessment of docking program for their possible to replicate peptide binding modes can be assess by Lessons for Efficiency evaluation of Docking and Scoring (LEADS-PEP) [25].

5. APPLICATION

A binding communication 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 agonist or antagonism. Docking is mainly used in the field of drug design. Most drugs are small organic molecules, and docking may be applied to:

5.1 Hit Identification

Docking collective with a scoring function can be used to rapidly screen large databases of potential drugs in silico to recognize molecules that are likely to bind to protein are set of attention [26].

5.2 Lead Optimization

Docking can be used to calculate in where and in which relation direction a ligand binds to a protein (also referred to as the binding mode or pose). This turn may in turn be used to design more potent and selective analogs [27].

5.3 Bioremediation

Protein ligand docking can also be used to forecast pollutants that can be despoiled by enzymes [28].

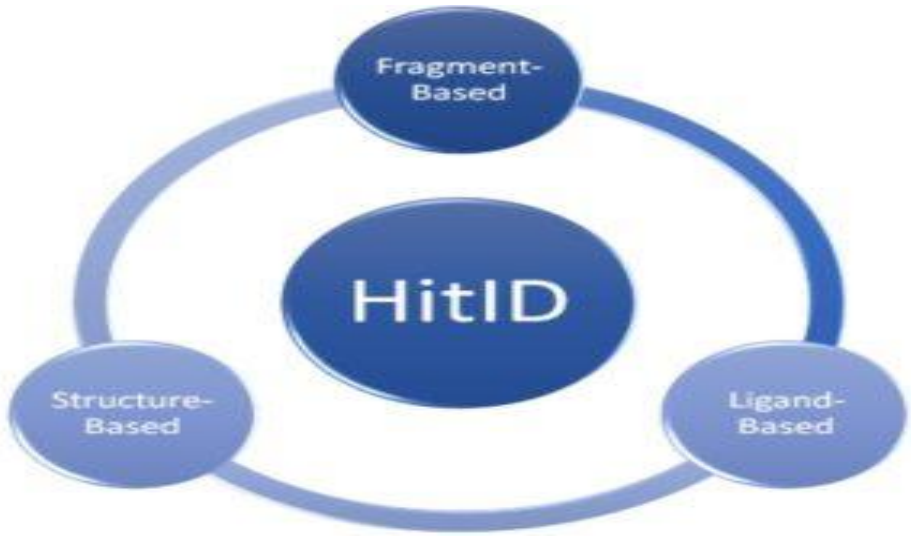

Fig. 5. Hit identification

Fig. 6. Lead optimization

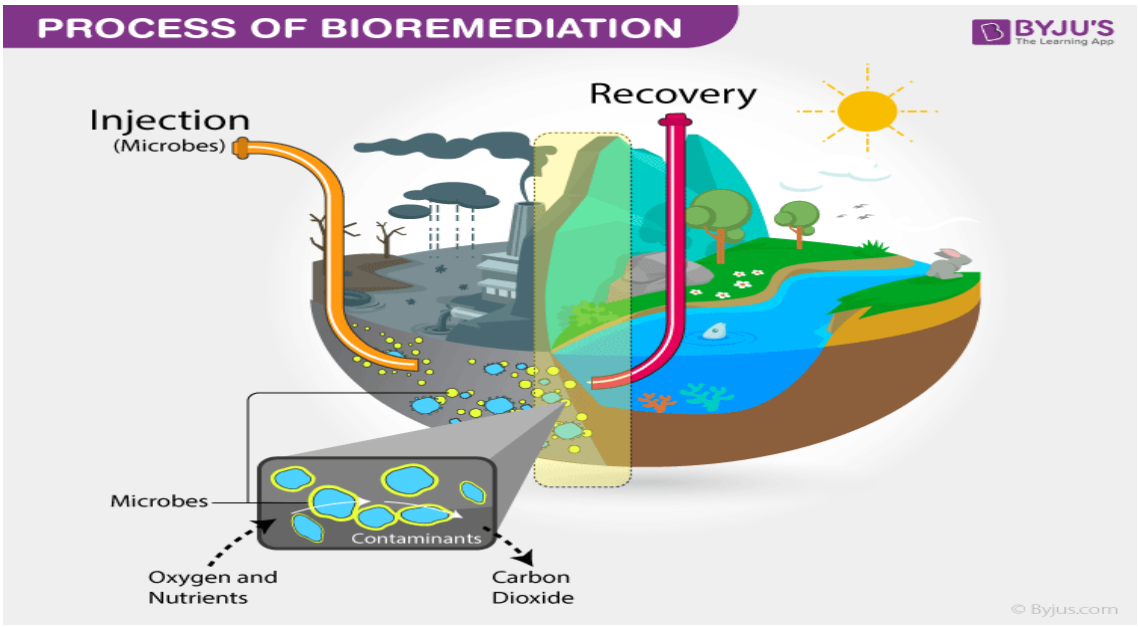

Fig. 7. Schematic diagram of bioremediation process

6. 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 program continue to expand upon core user interface. The probable docking method is done after systematically screening of the target, ligand and docking technique presentation. The ligand flexibility though is almost determined and does not generate much difficulty however protein suppleness needs to be enhanced. Water molecules should be incorporated to think the hydrogen bonding with non-aqueous residue. It is apparent from docking prose that it has attain a good amount of adulthood and in this short review, we have focused on types, approaches, applications of molecular docking in concise but secretarial for flexibility and thriving scoring remain significant challenge. Scoring function is a fundamental component worth being further improved upon in docking. Successful application examples show that computational approaches have the power to screen hits from a huge database and design novel small molecules. However, the realistic interactions between small molecules and receptors are still relied on experimental technology. Accurate as well as low computational cost scoring functions may bring docking application to a new stage. New algorithm from industry and academia are quickly incorporated into the high end packages. It continues to extend role in exciting new techniques such as computational enzymology, genomics and proteomics search engines.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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