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A OVER VIEW ON MOLECULAR DOCKING

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ABSTRACT

Molecular docking software mainly used in drug development. 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. The most important application of molecular docking is virtual screening. Various docking programs were developed to visualize the three dimensional structure of the molecule and docking score can also be analyzed with the aid of different computational methods. This article has basic information on molecular docking, molecular modeling, types of docking, molecular docking models, basic requirements of molecular docking, molecular approach, applications, evaluation and software available for molecular docking.

INTRODUCTION

Docking is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets in order to predict the affinity and activity of the small molecule. Hence docking plays an important role in the rational drug design as shown in figure 1.

Given the biological and pharmaceutical significance of molecular docking, considerable efforts have been directed towards improving the methods used to predict docking. Docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. Knowledge of the preferred orientation is used to predict the strength of association or binding affinity between two molecules using scoring functions. The associations between biologically relevant molecules such as proteins, nucleic acids carbohydrates, and lipids play central role in signal transduction. Therefore docking is useful for predicting both the strength and type of signal produced. Docking is frequently used to predict the binding orientation of drug candidates to their protein targets in order to predict the affinity and activity of the small molecule. Hence docking plays an important role in the rational design of drugs. The aim of molecular docking is to achieve an optimized conformation for both the protein and ligand and relative orientation between protein and ligand so that the free energy of the overall system is minimized.

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Molecular docking

Molecular docking is the process that involves placing molecules in appropriate configurations to interact with a receptor. Molecular docking is a natural process which occurs within seconds in a cell when bound to each other to form a stable complex in figure 1.

Molecular Modelling

Molecular modelling is a technique for deriving, representing and manipulating the structures and reactions of molecules, and those properties that are dependent on these three dimensional structures in molecular modelling[1].

TYPES OF DOCKING

There are 2 types of docking

1. Rigid docking
2. Flexible docking

1.Rigid Docking

If we assume that the molecules are rigid, then we are looking for a transformation in 3D space of one of the molecules which brings it to an optimal fit with the other molecules in terms of a scoring function. Conformation of the ligand may be generated in the absence of receptor or in the presence of receptor binding activity.

2. Flexible Docking

We consider molecule flexibility then in addition to transformation, our aim to find the confirmations of the receptor and the ligand molecules, as they appear in complex in figure 3.

MOLECULAR DOCKING MODELS

1. The Lock and Key Theory

As far back as 1890 Emil Fischer proposed a model called the "lock-and-key model" as shown in figure 4 states that explained how biological systems function. A substrate fits into the active site of a macromolecule, just like a key fits into a lock. Biological locks have unique stereochemical features that are necessary to their function in figure 4.

The Induced-Fit Theory

In 1958 Daniel Koshland introduced the "induced-fit theory". The basic idea is that in the recognition process, both ligand and target as shown in figure 5 mutually adapt to each other through small conformational changes, until an optimal fit is achieved in figure 5.

The Conformation Ensemble Model

In addition to small induced-fit adaptation, it has been observed that proteins can undergo much larger conformational changes. A recent model describes proteins as a pre-existing ensemble of conformational states. The plasticity of the protein allows it to switch from one state to another [2].

MOLECULAR DOCKING APPROACHES

There are number of approaches exist for docking as follows

Monte Carlo Approach: It generates an initial configuration of a ligand in an active site consisting of random conformation, translation & rotation. It scores initial configuration. Then it generates new configuration & score it. It use Metropolis criterion to determine whether the new configuration is retained. (Metropolis criterion- If new solution scores better than the previous one, it is immediately accepted. If the configuration is not new one, a Boltzmann-based probability function is applied. If the solution passes the probability function test, it is accepted; if not the configuration is rejected).

Fragment based method: Fragment based methods can be described as dividing the ligand into separate protons or fragments, docking the fragments & finally linking these fragments together.

Distance Geometry: Many types of structural information can be expressed as intra or intermolecular distances. The distance geometry formalism allows these distance to be assembled & 3 dimentional structures consistent with them to be calculated.

Matching approach: These approach focus on complimentarity. Ligand atom is placed at the 'best' position in the site, generating a ligand receptor configuration that may require optimization

Ligand fit approach: Ligand fit term provide a rapid accurate protocol for docking small molecules ligand into protein active sites for considering shape complimentarity8 between ligand & protein active sites

Point Complimentarity approach: These methods are based on evaluating a shape & /or chemical complimentarity between interacting molecules.

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

Inverse Docking: In this use of a computer method for finding toxicity & side effect protein targets of a small molecule. Knowledge of these targets combined with that of proteomics pharmacokinetic profile can facilitates the assessment of potential toxicities side effect of drug candidate. One of these protocols is selected for docking studies of particular ligand [3].

BASIC REQUIREMENTS FOR MOLECULAR DOCKING

The setup for a ligand docking approach requires components a target protein structure, the molecules of interest or a database containing existing o components a target protein structure, the molecules virtual compounds for the docking process, and a computational framework that allows the implementation of the desired docking and scoring procedures. Most docking algorithms assume protein to be rigid; the ligand is mostly regarded flexible. Beside the conformational degree of freedom the binding pose in proteins binding pocket must be taken in to consideration .docking can be performed by rigid molecules or fragments in to protein active site using different approaches like the clique-search, geometric hashing ,pose clustering.

Ligand Representation

Typically, the structure most likely to be dominant further adjusted by adding or removing hydrogens provided approximate pKa values. It is important to make sure that accurate atom typing occurs.

Receptor Representation

The quality of receptor structure employed plays central role in determining the success of docking calculations. In general, the higher the resolution of the employed crystal structure better will be the observed docking results. A recent review for accuracy, limitations and pitfalls of the structure refinement protocols of protein ligand complexes in general provided a critical assessment of the available structures.

MECHANISM OF DOCKING

To perform a docking screen, the first requirement is a structure of the protein of interest. Usually the structure has been determined using a biophysical technique such as x-ray crystallography, or less often, NMR spectroscopy. This protein structure and a database of ligands serve as inputs to a docking program. The success of a docking program depends on two components such as search algorithm and scoring function. Searching Conformational Space The search space consists of all possible orientations and conformations of the protein paired with ligand. With present computing resources, it is impossible to exhaustively explore the search space this would enumerating all possible distortions of each molecule and all possible rotational and translational orientations of the ligand relative to the protein at a given level of granularity. Most docking programs in use account for flexible ligand, and several are attempting to model a flexible protein receptor in figure 7 [4].

APPLICATIONS OF MOLECULAR DOCKING

Applications of molecular docking in drug development

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 silco to 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 sorientation 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.

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

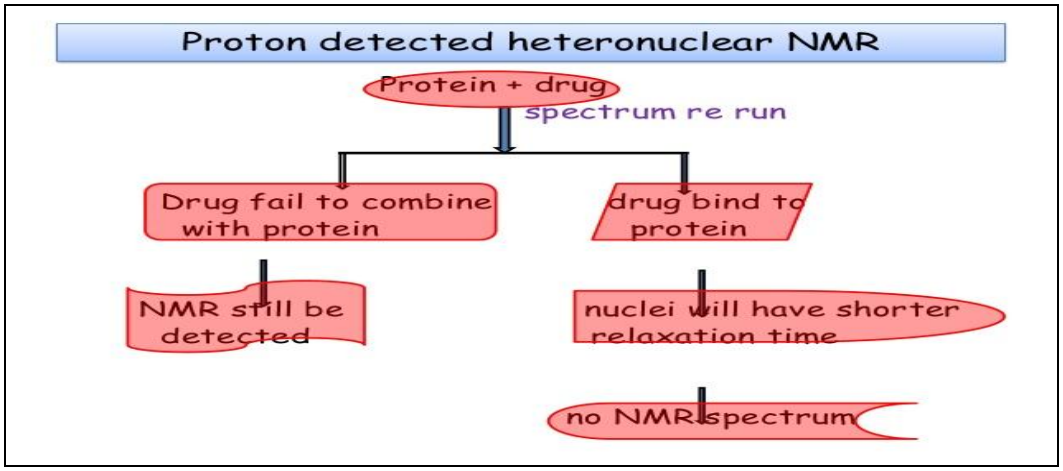
- Identification of target site.
- Selection of best drug (based on scoring function).
- Enzymes and its mechanisms
- Protein interactions
- Virtual Screening of compounds.

Application of molecular modelling in modern drug development

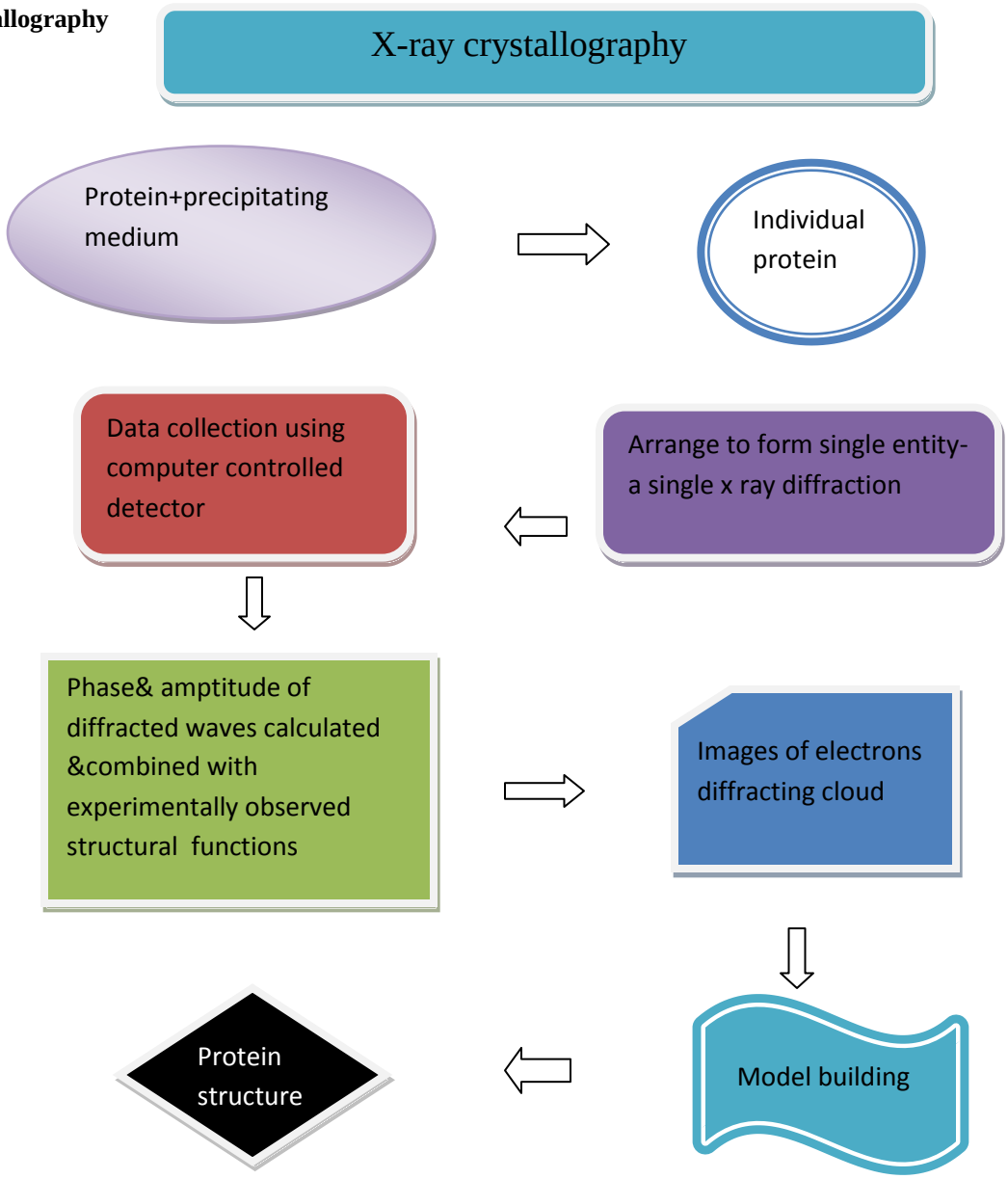
- It is used to screening for the side effects that can be caused by the interactions with other proteins, like proteases, Cytochrome P450 and others can be done.
- It is also possible to check the specificity of the potential drug against homologous proteins through docking.
- Docking is also a widely used tool in predicting protein-protein interactions.
- Knowledge of the molecular associations aids in understanding a variety of pathways taking place in the living and in revealing of the possible pharmacological targets.

EVALUATION OF STRUCTURES

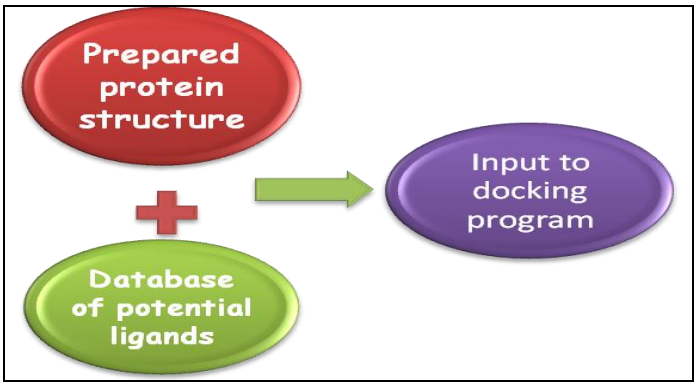
NMR

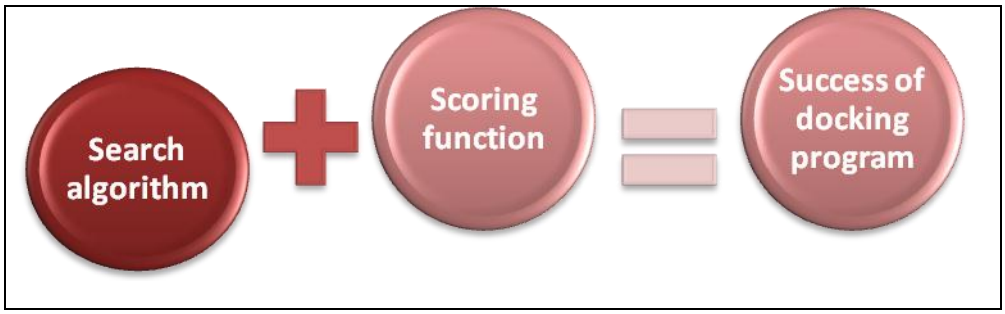


X-ray crystallography



Homology modeling





Receptor Preparation

- Dependent on docking program used
- Structure selection
- Site selection
- Often have to add hydrogens, some programs more sensitive to positions than other
- Remove/include waters, cofactors, metals
- Pre-docking remember to consider missing residues or atoms.

Ligand preparation

- Generate isomers if chiral centers
- Calculate charges – Predict pKa's for each potential charged atom – Generate a structure for each charge combination for a given pH range (e. .g., 5-9)
- Minimize structures – Generally using a molecular mechanics forcefield [5].

AVAILABLE SOFTWARES FOR DOCKING

- DOCK (1982,2001)
- FleX (1996)
- Hammerhead (1996)
- Surflex (2003)
- SLIDE (2002)
- AutoDock (1990,1998)
- ICM (1994)
- MCDock (1999)
- GOLD (1997)
- GemDock (2004)
- Glide (2004)
- Yucca (2005)

GOLD

- Genetic Optimisation and Ligand Docking, uses multiple subpopulations of ligand
- Force-field based scoring function, includes three terms: H-bonding term, intermolecular dispersion potential, intra molecular potential
- 71% success in identifying experimental binding mode in 100 protein complexes

AUTODOCK

- Grid for each atom type (e.g. C, H, O, N)
- Consists of 3D lattice of regularly spaced points, surrounding and centered on region of interest in the macromolecule
- Typical spacing is 0.375
- Probe atom placed at each

FLEX-X

- Base fragment is picked up and docked using "pose-clustering" algorithm
- Clustering algorithm is implemented to merge similar ligand transformations into active site Flexible fragments are added incrementally using MIMUMBA and evaluated using overlap function, followed by energy calculations till the ligand is completely built
- Final evaluation through Böhm's scoring function that includes H-bonds, ionic, aromatic and lipophilic terms [6, 7].

Fig 1. Molecular Docking

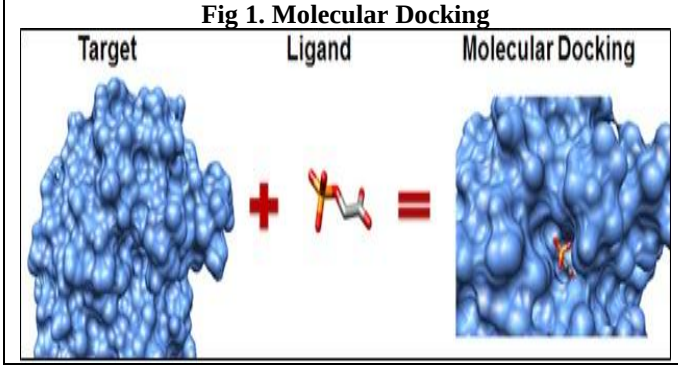


Fig 2. Molecular Modelling

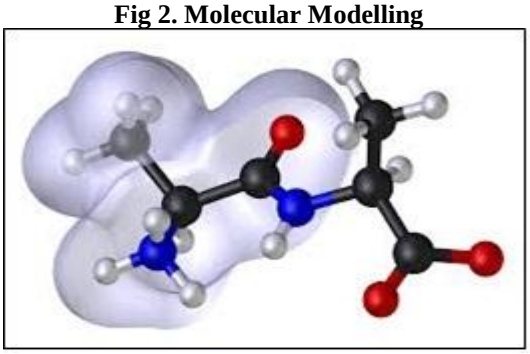


Fig 3. Rigid and Flexible Docking

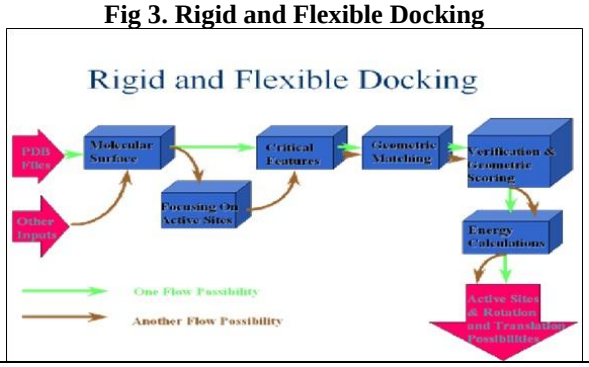


Fig 4. The lock and key model

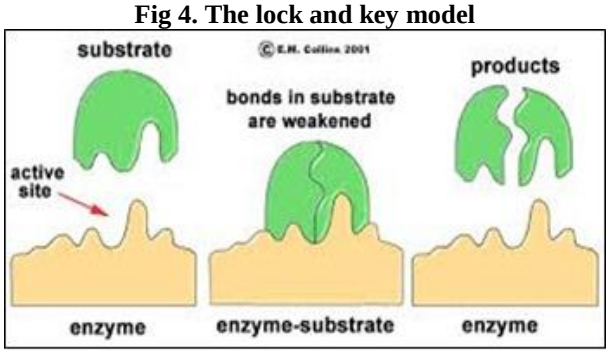


Fig 5. The induced -Fit theory

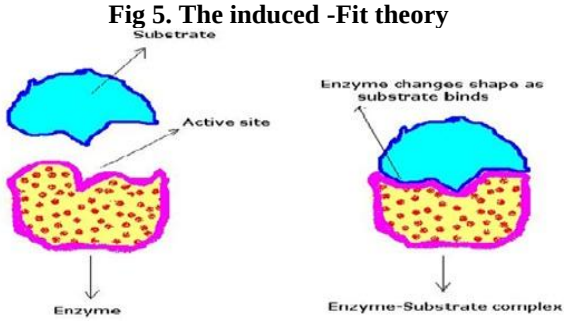


Fig 6. Molecular Docking Approach

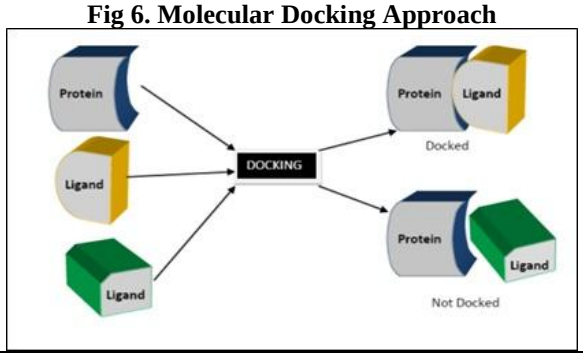


Fig 7. Mechanisms of Docking

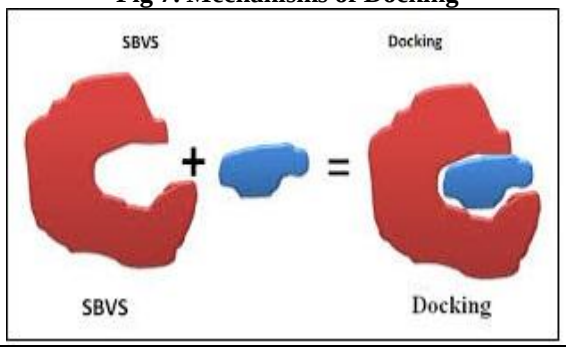
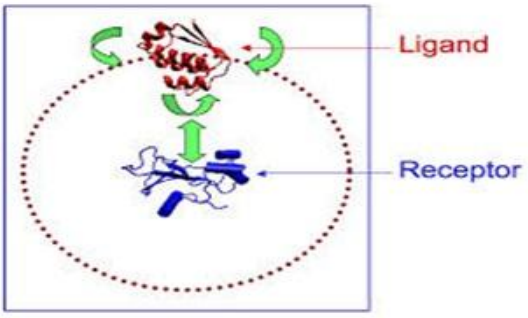


Fig 8. Preparation of ligand and receptor



CONCLUSION

Molecular docking is an inexpensive, safe and easy to use tool, helps in investigating, interpreting, explaining and identification of molecular properties using three-dimensional structures. Since different models yield different results, it is necessary to have a small number of standard models which are applicable to very large systems. Molecular docking used to predict the structural inter molecular complexes formed between two or more constitution molecules. The technique are used in the field of computational chemistry, computerised biology material used for molecular system ranging from small molecules to large biological molecules and material assemblies .Most of the docking presently being studied the binding of a flexible ligand to a biological receptor.

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CONFLICT OF INTEREST:
The authors declare that they have no conflict of interest.

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