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Journal of Advanced Scientific Research

J. Adv. Sci. Res, 2010, 1(1); 67-72
Published on 10th Aug 2010

Review Article

Molecular Docking: An overview

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ABSTRACT

Molecular docking provides useful information about drug receptor interactions and 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. Generally, classical mechanics based force field methods are used in the molecular docking. Monte Carlo and molecular dynamics methods have also been employed to predict the best structural fit between protein and ligand molecules. Most docking algorithms are able to generate a large number of possible structures and hence there is a need to score each structure to identify which are of most important. Thus docking problem is concerned with generation and evaluation of possible structures of protein ligand complexes.

Keywords: Molecular Docking, Search Algorithm, Scoring Functions, Optimization

INTRODUCTION

In recent years the search for novel drugs has evolved from a process of trial and error into a sophisticated procedure including several computer-based approaches. In structure-based design the structures of known target proteins are used to discover new compounds of therapeutical relevance. The approaches can be classified roughly into two categories: *de novo* design and docking. The former method designs new ligands to fit the protein target, whereas the latter is used to decide whether existing compounds possess good steric and chemical complementarities to the given protein[1].

In the field of molecular modeling, 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[2]. Docking methods provide useful tool for drug receptor interaction and serve better results for other molecular docking studies. Molecular models of drug compounds can reveal intricate, atomic scale binding properties that are difficult to envision in any other way. When we show researchers new molecular models of their putative drug compounds, their protein targets and how the two bind together, they often come up with new ideas on how to modify the drug compounds for improved fit. This is an intangible benefit that can help design research programmers[3].

DEFINITION

Molecular docking may be defined as an optimization problem, which would describe the "best-fit" orientation of a ligand that binds to a particular protein of interest and is used to predict the structure of the intermolecular complex formed between two or more molecules. The most interesting case is the protein ligand interaction, because of its applications in medicines. Ligand is a small molecule, which interacts with protein's binding sites. Binding sites are areas of protein known to be active in forming of compounds. There are several possible mutual conformations in which binding may occur. These are commonly called binding modes [4].

Molecular docking can be thought of as a problem of "lock-and-key", where one is interested in finding the correct relative orientation of the "key" which will open up the "lock" (where on the surface of the lock is the key hole, which direction to turn the key after it is inserted, etc.). Here, the protein can be thought of as the "lock" and the ligand can be thought of as a "key". However since both the ligand and the protein are flexible, a "hand-in-glove" analogy is more appropriate than "lock-and-key"[5]. During the course of the process, the ligand and the protein adjust their conformation to achieve an overall "best-fit" and this kind of conformational adjustments resulting in the overall binding is referred to as "induced-fit"[6].

BINDING INTERACTIONS

Modeling the interaction of a drug with its receptor is a complex problem. Many forces are involved in the intermolecular association: hydrophobic, dispersion, or van der walls, hydrogen bonding, and electrostatic. The major force for binding appears to be hydrophobic interactions, but the specificity of the binding appears to be controlled by hydrogen bonding and electrostatic interactions. Modeling the intermolecular interactions in a ligand-protein complex is difficult because there are so many degrees of freedom and insufficient knowledge of the effect of solvent on the binding association[7] .The process of docking a ligand to a binding site tries to mimic the natural course of interaction of the ligand and its receptor via a lowest energy pathway.

In order to use computational methods for structure- based design, several assumptions have to be made. There are simple methods for docking rigid ligands with rigid receptors and flexible ligands with rigid receptors, but general methods of docking conformationally flexible ligands and receptors are problematic. Early docking tools treated both the ligand and the protein as rigid structures for efficiency reasons. At present, standard applications of current docking tools like DOCK[8], GOLD[9], and FLEXX[10] use flexible ligands, but keep the protein structure essentially rigid, except for a few terminal H-bond donors and acceptors, and assume one single protein conformation even for complexes with different ligands. Therefore, ligands requiring larger conformational changes within the protein upon binding cannot be placed correctly by these methods.

SEARCH ALGORITHM

Molecular docking can be divided into two separate problems. The search algorithm should create an optimum number of configurations that include the experimentally determined binding modes. These configurations are evaluated using scoring functions to distinguish the experimental binding modes from all other modes explored through the searching algorithm[4]. A rigorous searching algorithm would go through all possible binding modes between the two molecules. However, this is impractical due to the size of the search space. Consider a simple system comprised of a ligand with four rotable bonds and six rigid-body alignment parameters and a cubic active site measuring 10^3 Å^3.

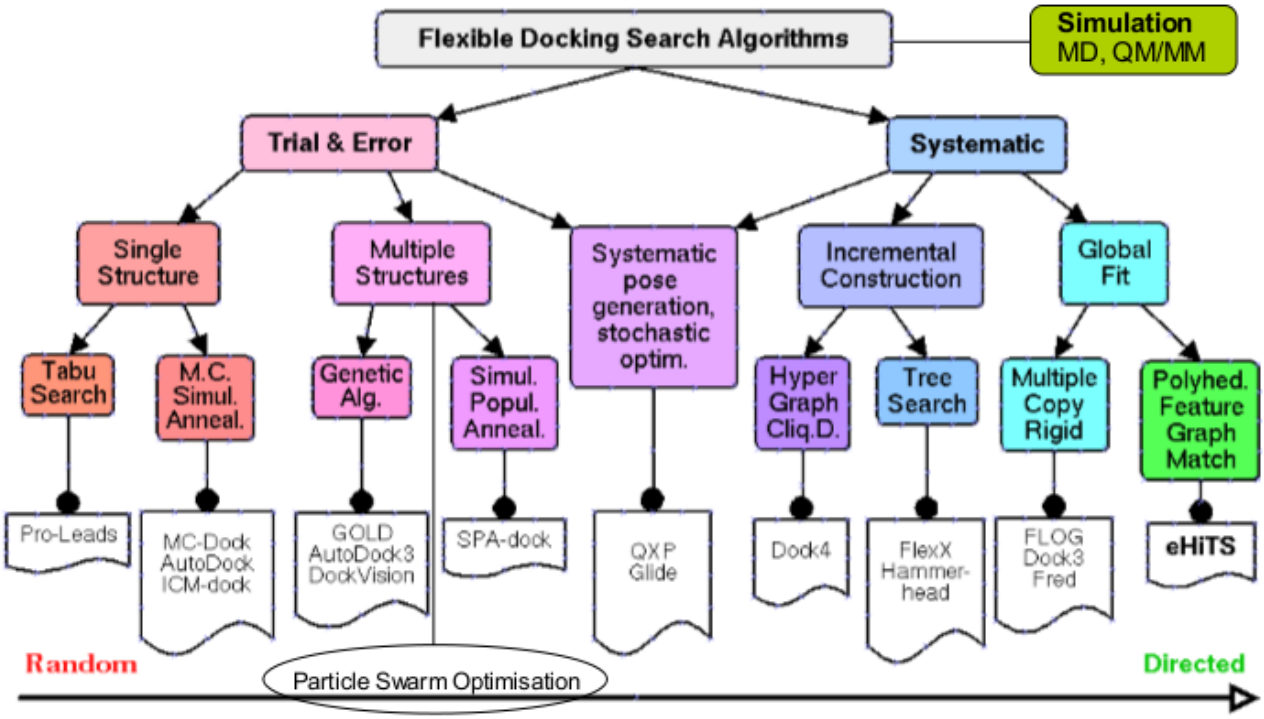

Fig.1: Molecular Docking Search Algorithm[11]

The translational and rotational properties add up to six degrees of freedom. If the angles are considered in 10 degree increments and translational parameters on a 0.5 Å grids there are approximately 4 x 108 rigid body degrees of freedom to sample, corresponding to 6 x 1014 configurations to be searched. This would require approximately 2000000 years of computational time at a rate of 10 configurations per second. As a consequence only a small amount of the total conformational space can be sampled, and so a balance must be reached between the computational expense and the amount of the search space examined.

Some common searching algorithms include:

- Molecular dynamics
- Monte Carlo methods
- Genetic algorithms
- Fragment-based methods
- Point complementary methods
- Distance geometry methods
- Tabu searches
- Systematic searches

SCORING FUNCTIONS

Docking plays an important role in the rational design of drugs[12]. Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules using for example scoring functions.

Current docking methods utilize the scoring functions in one of two ways. The first approach uses the full scoring function to rank a protein-ligand conformation. The system is then modified by the search algorithm, and the same scoring function is again applied to rank the new structure. In the alternative approach a two stage scoring function is used. A reduced function is used in directing the search and a more rigorous one is then used to rank the resulting structures.

Some common scoring functions are:

- Force-field methods
- Empirical free energy scoring functions
- Knowledge-based potential of mean force [4].

APPLICATIONS

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 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[13].

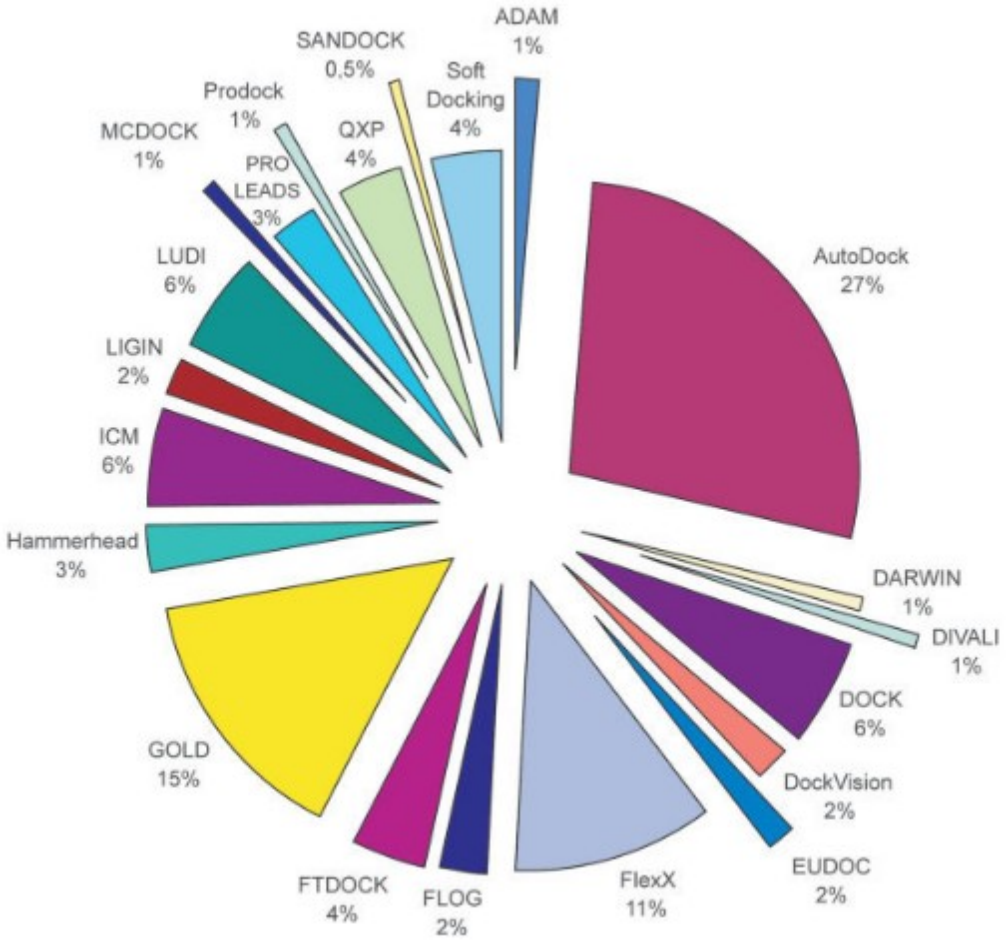

Fig.2: Various docking softwares and their exercise percentage[14]

CONCLUSIONS

From the above discussions it can be clearly understood that various docking tools by their scoring functions are quite useful for determining the binding sites and various binding modes for a given type of ligands to a rigid protein. The focus of molecular docking is to computationally simulate the molecular recognition process and 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.

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