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Review Article

A REVIEW ON MOLECULAR DOCKING – Novel tool in drug design and analysis

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Abstract:
Tremendous research from last twenty years has been pursued to study various docking algorithms and predicting the active site of the molecule. 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. Protein-DNA docking is a very challenging problem in structural bioinformatics and has important implications in a number of applications, such as structure-based prediction of transcription factor binding sites and rational drug design. Protein-DNA docking is very computational demanding due to the high cost of energy calculation and the statistical nature of conformational sampling algorithms. More importantly, experiments show that the docking quality depends on the coverage of the conformational sampling space. It is therefore desirable to accelerate the computation of the docking algorithm, not only to reduce computing time, but also to improve docking quality.

Keywords: Docking, Auto dock, Ligand, Docking score, Algorithm

Introduction

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[1]. Knowledge of the preferred orientation in turn may be used be predict the strength of association or binding affinity between two molecules using for example scoring functions. Docking is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets in order to in turn predict the affinity and activity of the small molecule. Hence docking plays an important role in the rational design of drugs[2].

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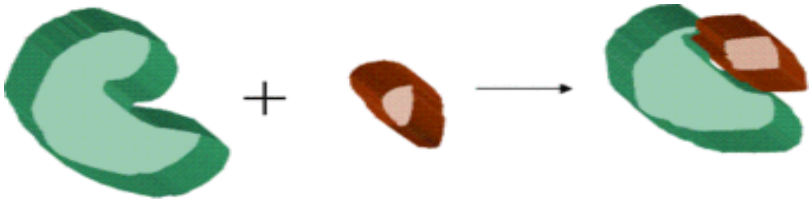

Figure1 illustrating the docking of a small molecule ligand (brown) to a protein receptor (green) to produce a complex.

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". 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. However, since both the ligand and the protein are flexible, a "hand-in-glove" analogy is more appropriate than "lock-and-key". 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". The focus of molecular docking is to computationally simulate the molecular recognition process. 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.

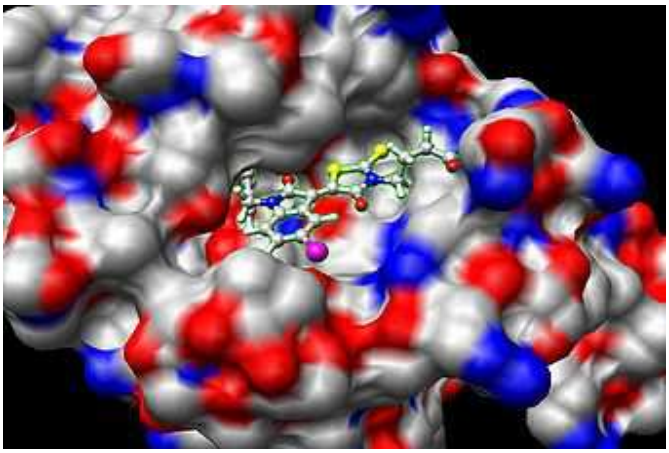

Figure 2 depicting a small molecule docked to a protein

Docking programs

AutoDock

Auto dock 4 is a suite of automated docking tools. It is designed to predict how small molecules, such as substrates or drug candidates, bind to a receptor of known 3D structure

Auto dock 4 comprises three major improvements:

- The docking results are more accurate and reliable.

- It can optionally model flexibility in the target macromolecule.
- It enables Auto dock's use in evaluating protein – protein interactions.

DOCK

DOCK is one of the oldest and best known ligand-protein docking programs. It is a fragment-based method using shape and chemical complementary methods for creating possible orientations of the ligand. This program seems to handle well with apolar binding sites and is useful for fast docking process.

FlexX

FlexX is another fragment based method using flexible ligands and rigid proteins.It has a bit lower hit rate than DOCK but provides better estimates of Root Mean Square Distance for compounds with correctly predicted binding mode. There is an extension of FlexX called FlexE with flexible receptors which has shown to produce better results with significantly lower running times.

GOLD (Genetic Optimization for Ligand Docking):

It has a good hit rate overall, however it somewhat suffers when dealing with hydrophobic binding pockets. Gold uses genetic algorithm to provide docking of flexible ligand and protein with flexible hydroxyl groups. Otherwise the protein is considered to be rigid. This makes it a good choice when the binding pocket contains amino acids that form hydrogen bonds with the ligand.

Ligand-Protein Binding Studies Using Docking:-

The docking process involves the prediction of ligand conformation and orientation within a targeted binding site.

Objectives of docking:-

1. Accurate structural modeling
2. Correct prediction of activity**.**

Theoretical aspect of docking:-

For an enzyme and inhibitor docking aims at correct prediction of the structure of the complex (E+I) =(EI) under equilibrium conditions

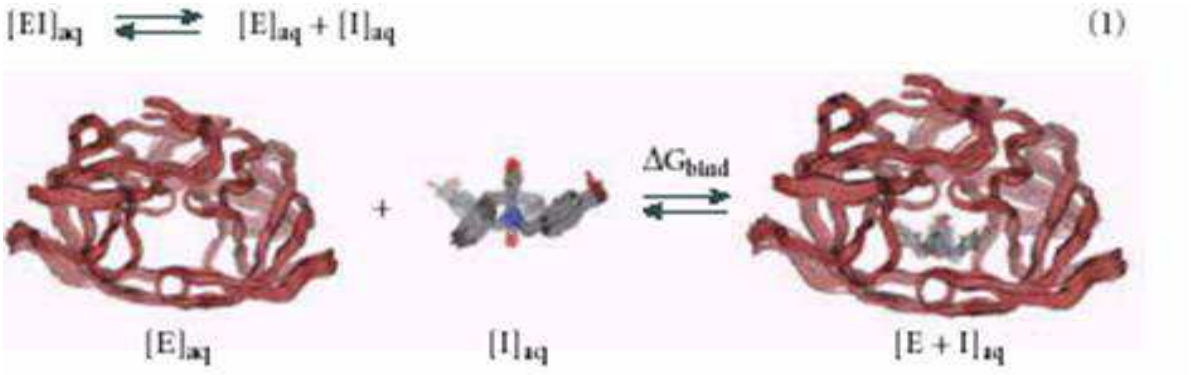

Figure 3 illustrates the binding of inhibitor Dmp323 to HIV protease.

When considering the term (EI), the following factors are important:-

1. Steric
2. Electrostatic
3. Hydrogen Bonding
4. Inhibitor Strain
5. Enzyme Strain

When considering the equilibrium the following factors are important:-

1. Desolvation
2. Rational entropy
3. Translational entropy

Steps involved in ligand-protein binding studies using computer aided Drug Design:

1. Molecular modeling of Ligand:

a. First step involved in CADD is drawing of the two dimensional (2D) structure of the ligand.

b.Then the conversion of 2D structure to three dimensional (3D) structure of ligand

c. 3D structure binds to the enzyme or receptor.

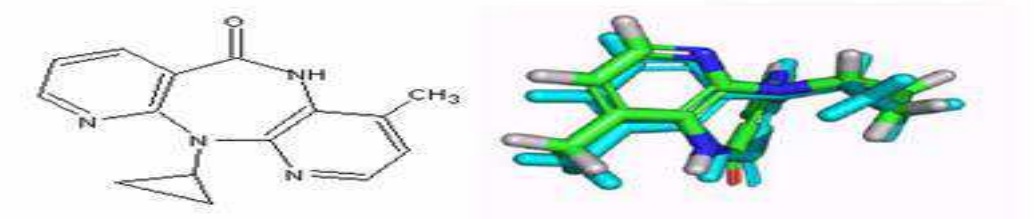

Figure 4 depicting 2D and 3D structure of nevirapine

2. Energy Minimization:

Energy minimization studies are carried out for ligand. Ligand can exist in different conformations. The conformation, which has lower energy, will be the most stable conformation of the ligand. There are two types of energies.

a) Electrostatic Potential Energy:

It is Electrostatic Potential Energy a pair wise summation of columbic interactions as described in equilibrium.

$$E_{coul}(r) = \sum_{i=1}^{N_A} \sum_{j=1}^{N_B} \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}}$$

In Equation N= the number of atoms in molecules A & B respectively q = charge on each atom.

b) Vander Waals Potential Energy:

For general treatment of non-bonded interactions is often modeled by a Lennard-Jones 12-6 function as in equilibrium In equation

$$E_{vdW}(r) = \sum_{j=1}^{N} \sum_{i=1}^{N} 4\varepsilon\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right]$$

S = is the well depth of the potential

s = is the collision diameter of respective atoms i & j

3. Validation of Docking Software Packages

There are number of software packages available for docking in the market. To know the best software package which predicts the closest match to the crystallographic data on protein-ligand complex, the following comparative evaluation is carried out.

a. Take a known standard ligand e.g. Nevirapine.

b. From X-ray crystallography co –ordinates of binding position of Nevirapine and co-

ordinates of active site amino acids are already known experimentally.

c. Take a ligand dock it into the active site of different enzyme software packages carry out

translation and rotation of ligand as a whole. Then determine final binding or clocking

energy and grade them.

d. Best fit of ligand will be compared with the X-ray crystallographic binding co-ordinates.

From this comparison we can know the best software package for docking studies.

4. Different Protocols or Approaches for docking[5,6,7]:

There are number of approaches exist for docking as follows:-

a. 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).

b. 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.

c. 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.

d. 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

e. Ligand fit approach:-

Ligand fit term provide a rapid accurate protocol for docking small molecules ligand into protein active sites for considering shape complimentarity[8] between ligand & protein active sites

f. Point Complimentarity approach:-

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

g. Blind Docking:-

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

h. 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.

5. Binding or Docking Energy Calculation:

After formation of the complex of ligand with protein there will be calculation of binding energy or docking energy. If there is no. of proposed compounds then binding energy will be different for all of them. The grading of these energies is done. After grading we will come to know best-fit ligand complex[9-12].

Applications of docking studies:

A binding interaction between a small molecule ligand and a enzyme protein may result in activation or inhibition of the

enzyme. If the protein is a receptor, ligand binding may results 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 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 protein. This information may in turn be used to design more potent and selective analogs.
- **Bioremediation**[13] – Protein ligand docking can also be used to predict pollutants that can be degraded by enzymes

Conclusions:

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 programs continue to expand upon the core user interface. New algorithms from industry and academia are quickly incorporated into the high end packages. Public domain packages are becoming more stable and offering functionality that rivals some of the commercial offerings computers continue to double in speed every year and a half while graphic displays became more sophisticated and intuitive. All of these elements make molecular docking an integral part of drug design. It continues to extend its role in exciting new techniques such as computational enzymology, genomics, and proteomic search engines.

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