Available online at **www.joac.info**

ISSN: 2278-1862

Journal of Applicable Chemistry, 2012, 1 (2):167-173

(International Peer Reviewed Journal)

DOCKING-A Review

Sushma B[1*], Ch. V. Suresh[1]

1. St. Mary's College of Pharmacy, Surampalem, E.G.Dt. AP- 533437.

E-mail: sushmabondada@gmail.com

ABSTRACT

*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. Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules for example scoring functions. **Molecular docking** tries to predict the structure of the intermolecular complex formed between two or more constituent molecules.*
The associations between biologically relevant molecules such as proteins, nucleic acids, carbohydrates, and lipids play a central role in signal transduction. Furthermore, the relative orientation of the two interacting partners may affect the type of signal produced (e.g., agonist vs. antagonism). Therefore docking is useful for predicting both the strength and type of signal produced. 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] Given the biological and pharmaceutical significance of molecular docking, considerable efforts have been directed towards improving the methods used to predict docking.

Keywords: Docking, Molecular docking, Protein- Ligand

INTRODUCTION

Molecular docking is a well established computational technique[1] which predicts the interaction energy between two molecules. This technique mainly incorporates algorithms like molecular dynamics, Monte Carlo stimulation, fragment based search methods.

Molecular docking studies are used to determine the interaction of two molecules and to find the best orientation of ligand which would form a complex with overall minimum energy. The small molecule, known as ligand usually fits within protein's cavity which is predicted by the search algorithm. This protein cavity becomes active when comes in contact with any external compounds and are thus called as active sites.
The results are analyzed by a statistical scoring function which converts interacting energy into numerical values called as the docking score; and also the interacting energy is calculated. The 3D pose of the bound ligand can be visualized using different visualizing tools like Pymol, Rasmol etc which could help in inference of the best fit of ligand. Predicting the mode of protein-ligand interaction can assume the active site of the protein molecule and further help in protein annotation.

Different types of Interactions

Interactions between particles can be defined as a consequence of forces between the molecules contained by the particles. These forces are divided into four categories:

• **Electrostatic forces** - Forces with electrostatic origin due to the charges residing in the matter. The most common interactions are charge-charge, charge-dipole and dipole-dipole.
• **Electrodynamics forces**-The most widely known is the Van der Waals interactions.
• **Steric forces** - Steric forces are generated when atoms in different molecules come into very close contact with one another and start affecting the reactivity of each other. The resulting forces can affect chemical reactions and the free energy of a system.
• **Solvent-related forces** - These are forces generated due to chemical reactions between the solvent and the protein or ligand. Examples are Hydrogen bonds (hydrophilic interactions) and hydrophobic interactions.
• A common characteristic of all these forces is their **electromagnetic** nature.
• Other physical factors - **Conformational changes** in the protein and the ligand are often necessary for successful docking.

Protein - Ligand docking

● The final goal uses to predict the biological activity of a given ligand.

Two different problems:
POSING

The process of determining whether a given conformation and orientation of a ligand fits the active site. This is usually a fuzzy procedure that returns many alternative results.

SCORING

The pose score is a measure of the fit of a ligand into the active site. Scoring during the posing phase usually involves simple energy calculations (electrostatic, van der Waals, ligand strain). Further re-scoring might attempt to estimate more accurately the free energy of binding (G, and therefore K_A) perhaps including properties such as entropy and solvation.

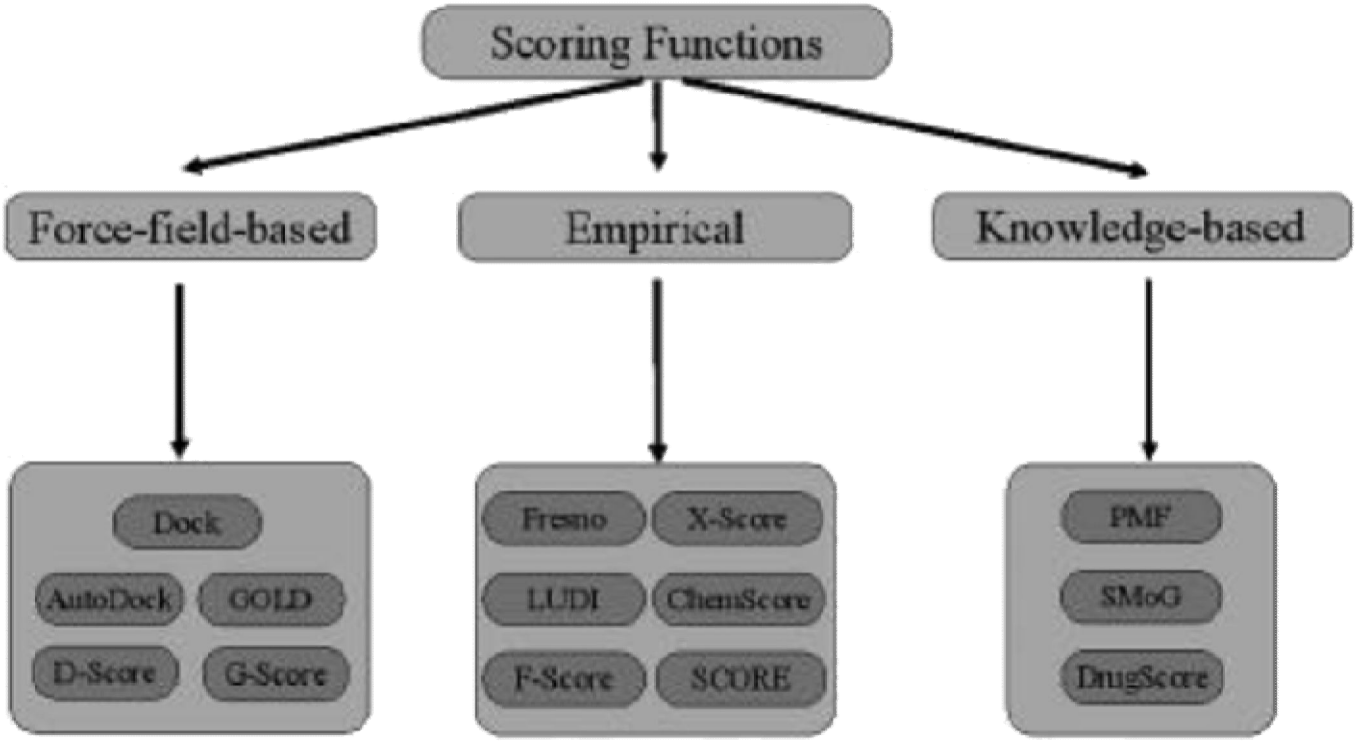


Fig.1 Scoring Functions

Molecular docking

Molecular docking can be divided into two separate sections.

1) **Search algorithm** – These algorithms determine all possible optimal conformations for a given complex (protein-protein, protein-ligand) in a environment i.e. the position and orientation of both molecules relative to each other. They can also calculate the energy of the resulting complex and of each individual interaction.

The different types of algorithms that can be used for docking analysis are-

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

2) **Scoring function** –These are mathematical methods used to predict the strength of the non-covalent interaction called as binding affinity, between two molecules after they have been docked. Scoring functions have also been developed to predict the strength of other types of intermolecular interactions, for example between two proteins or between protein and DNA or

protein and drug. These configurations are evaluated using scoring functions to distinguish the experimental binding modes from all other modes explored through the searching algorithm.
For example:

- Empirical scoring function of Igemdock
  Fitness = vdW + Hbond + Elec

- Binding Energy
  $\Delta G_{bind} = \Delta G_{vdw} + \Delta G_{hbond} + \Delta G_{elect} + \Delta G_{conform} + \Delta G_{tor} + \Delta G_{sol}$

General concept of the algorithm:
1) A 'negative' image of the binding site is made - a collection of spheres of varying radii, each touching the molecular surface at just 2 points.
2) Ligand atoms are then matched to sphere centers where at least four distances between ligand atoms are matched to sphere center distances.
3) Proper orientation is achieved by a least squares fit of ligand atoms to the sphere centers.
4) Orientation is checked for any steric clashes between ligand and receptor.
5) If acceptable, then interaction energy is computed as a 'score' for that binding mode.
6) New orientations are obtained by matching different sets of atoms and sphere centers.
7) Top-scoring orientations are retained for subsequent analysis.

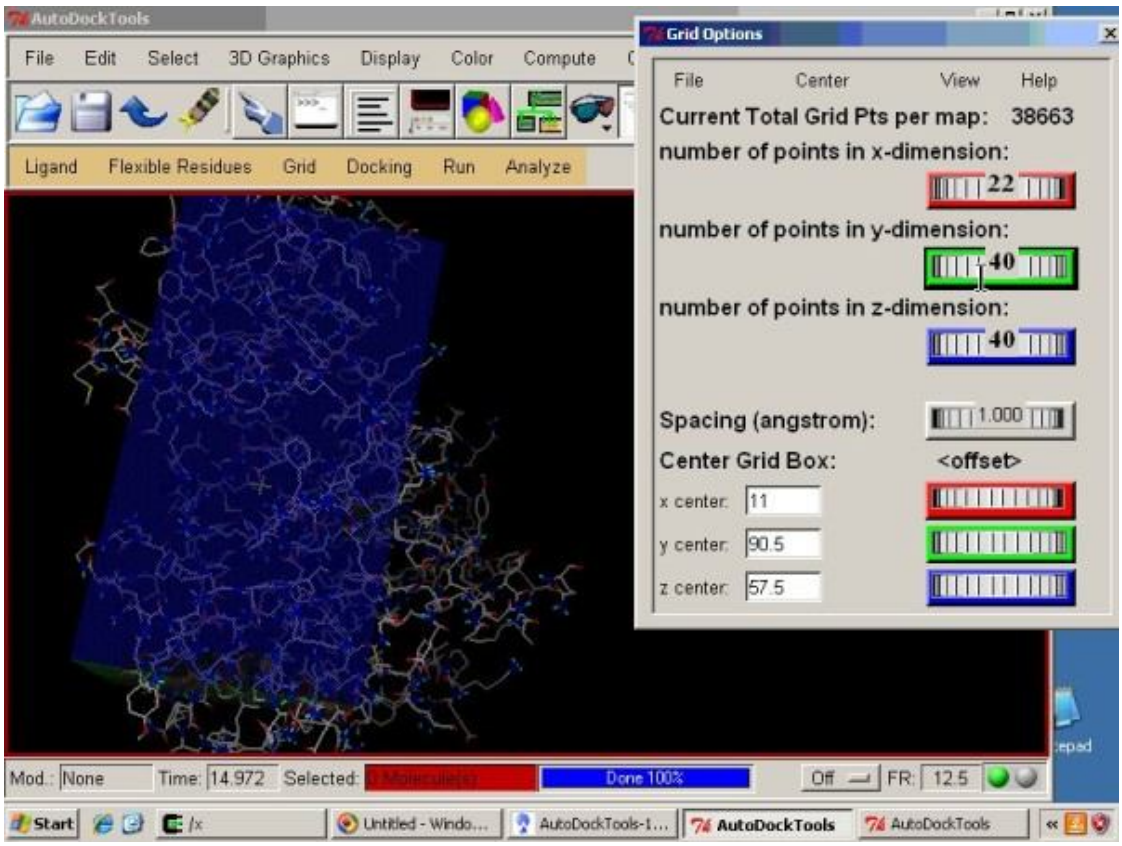


Fig.2 AutoDock view for Docked Ligand-Protein

Types of Docking -

The following are majorly used type of docking are-

• **Lock and Key or Rigid Docking** – In rigid docking, both the internal geometry of the receptor and ligand is kept fixed during docking.

• **Induced fit or Flexible Docking -** In this model, the ligand is kept flexible and the energy for different conformations of the ligand fitting into the protein is calculated. Though more time consuming, this method can evaluate many different possible conformations which make it more reliable.

Major steps in molecular docking:

Step I – Building the Receptor

In this step the 3D structure of the receptor should be downloaded from PDB; and modified. This should include removal of the water molecules from the cavity, stabilizing charges, filling in the missing residues, generation the side chains etc according to the parameters available. After modification the receptor should be biological active and stable.

Step II – Identification of the Active Site

After the receptor is built, the active site within the receptor should be identified. The receptor may have many active sites but the one of the interest should be selected. Most of the water molecules and heteroatoms if present should be removed.

Step III – Ligand Preparation

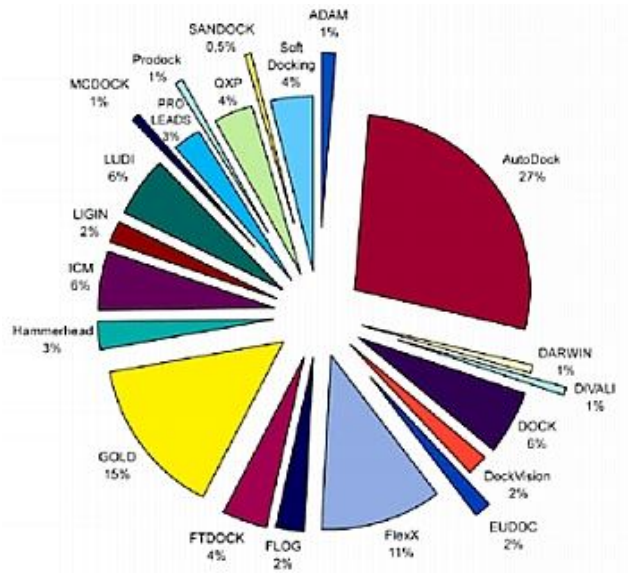
Ligands can be obtained from various databases like ZINC, PubChem or can be sketched using tools like Chemsketch. While selecting the ligand, the LIPINSKY'S RULE OF 5 should be applied. The rule is important for drug development where a pharmacologically active lead structure is optimized stepwise for increased activity and selectivity, as well as drug-like properties, as described.

For the selection of a ligand using LIPINSKY'S RULE:

- Not more than 5 –H bond donors.
- Molecular Weight NOT more than 500 Da.
- Log P not over 5 for octanol water partition coefficient.
- NOT more than 10 H bond acceptors.

Step IV- Docking

This is the last step, where the ligand is docked onto the receptor and the interactions are checked. The scoring function generates scores depending on which the ligand with the best fit is selected.



Software available for Molecular Docking:

1) SCHRODINGER
2) DOCK
3) AUTOLOCK TOOLS [2].
4) DISCOVERY STUDIO.
5) iGemDock

APPLICATIONS

- Virtual screening (hit identification) [3]
  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
- Drug Discovery (lead optimisation)
  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.
- Prediction of K_A (biological activity)
- Drug design
- Binding-site identification (blind docking)
- De-orphaning of a receptor
- Protein – Protein (or Protein – Nucleic Acid) interactions
- Structure-function studies
- Enzymatic reactions mechanisms
- Protein engineering

- Bioremediation [4] – Protein ligand docking can also be used to predict pollutants that can be degraded by enzymes.

REFERENCES

[1] Lengauer T, Rarey M (**1996**). "Computational methods for biomolecular docking". *Curr. Opin. Struct. Biol.* 6 (3): 402–6.
[2] http://autodock.scripps.edu
[3] Kitchen DB, Decornez H, Furr JR, Bajorath J (**2004**). "Docking and scoring in virtual screening for drug discovery: methods and applications". *Nature reviews. Drug discovery* 3 (11): 935–49.
[4] Suresh PS, Kumar A, Kumar R, Singh VP (January **2008**). "An in silico [correction of insilico] approach to bioremediation: laccase as a case study". *J. Mol. Graph. Model.* 26 (5): 845–9.