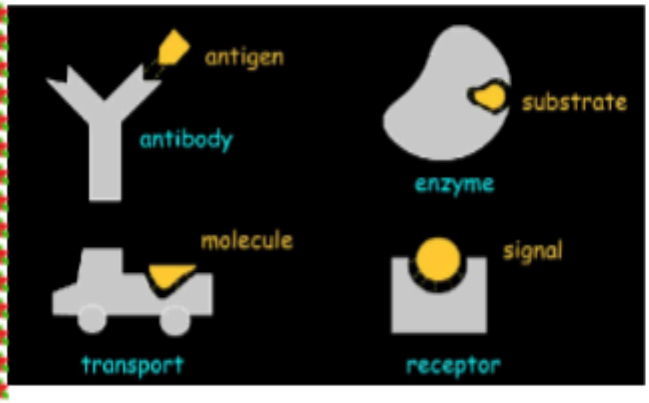
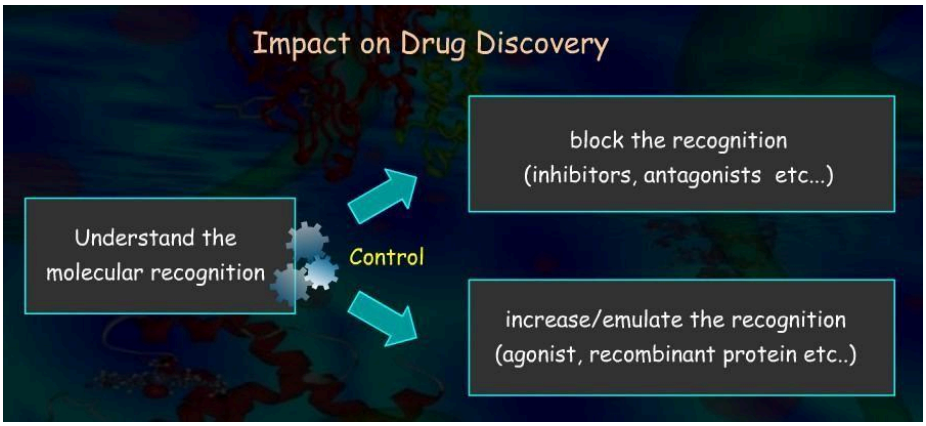
DOCKING TECHNIQUES

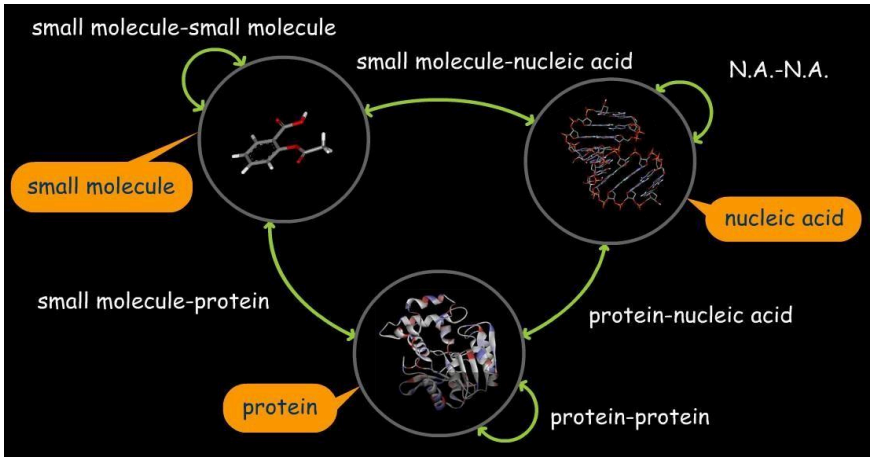


Molecular docking is the process that involves placing molecules in appropriate configurations to interact with a receptor. Molecular docking is a natural process which occurs within seconds in a cell. **In molecular modeling the term "molecular docking" refers to the study of how two or more molecular structures fit together.** Thus, Docking may be defined as the computational simulation of a candidate ligand binding a receptor.Understanding the principles of molecular recognition at the molecular level is essential to a good understanding of molecular function and biological process. Knowledge of the mechanical features of a biological signal can be used to design novel therapeutic agents.



DOCKING CLASSIFICATION

- Molecular docking classifies biomolecules into three categories: small molecules (also called 'ligands'), proteins, and nucleic acids.
- The most important types of docking systems are: protein - ligand, protein - protein and nucleic acid- protein.
- The interactions between a small molecule and a protein are by far much better understood than those between a protein and a nucleic acid.



TYPES OF DOCKING

The two main types of docking techniques used in the drug designing process are:

a) **RIGID DOCKING:** In this type of docking technique, both the internal geometry of the receptor and ligand is kept fixed and then the docking is done. First the stearic constraints are applied to a particular limit in the search space and then it is examined for energetic of possible binding conformations.

b) **FLEXIBLE DOCKING:** An enumeration on the rotation of one of the molecule (usually smaller one) is performed. In every rotation the surface cell occupancy and energy is calculated and later the most optimum pose is then selected. A "pose" is a term widely adopted for describing the geometry of a particular complex (also called "binding mode"). It refers to a precise configuration

which is characterized not only by the relative orientation of the docked molecules but also their respective conformations.In this type of docking, usually the ligand remains flexible, while the receptor remains rigid.

DOCKING METHODS

Docking algorithms are used to treat ligand flexibility, and to some extent protein flexibility. Treatment of ligand flexibility can be divided into three basic categories:

A) **Systematic search:** These algorithms try to explore all the degree of freedom in a molecule. It is performed by varying systematically each of the tension angle of the molecule in order to generate all possible conformations. Most popular systematic approach is incremental construction method.

B) **Random search:** These algorithms operate by making random changes to either a single ligand or a population of ligands. A newly obtained ligand is evaluated on the basis of pre-defined probability function.

C) **Simulation methods:** Molecular dynamics is currently the most popular simulation approach. However, the molecular dynamics is unable to cross high energy barriers with in the feasible simulation time periods, therefore might only accommodate ligands in the local minima in energy surface.

Search Algorithms

The following approaches are used in computational docking:

- Exhaustive search (for small systems only)
- Monte Carlo
- Genetic Algorithms
- Simulated Annealing
- Tabu searches
- Tabu search (TS) is a stochastic searching algorithm that maintains a list of previously visited poses. These poses are forbidden and cannot be revisited (they are "taboo"). TS effectively guides the search process into unvisited areas of the space.

Molecular Flexibility in Protein-Ligand Docking

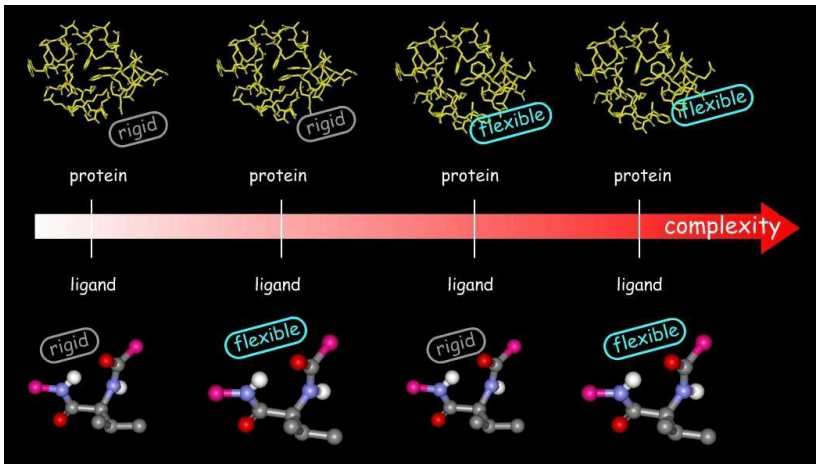
The mutual adaptation of a ligand with its receptor is crucial to understanding ligand binding and protein function. One of the major challenges in molecular docking is how to account for this adaptation in docking calculations.

The docking problem can be classified according to the way flexibility is modeled. In ascending order of complexity:

1. Rigid body docking ignores the flexibility of the molecules and treats them like rigid objects.

2. Rigid receptor – flexible ligand docking: only the ligand is treated as flexible, receptor is rigid.

3. Flexible receptor – flexible ligand docking: both protein and ligand are treated as flexible.



Two Components of Docking Software

Docking software can be categorized based on the following criteria:

(I) **Molecular representation** - a way to represent structures and properties (atomic, surface, grid representation). There are three representations commonly used in docking programs:

- the atomic representation (the most common)
- the surface representation
- the grid representation

The choice of representation dictates the way the docking problem will be tackled.

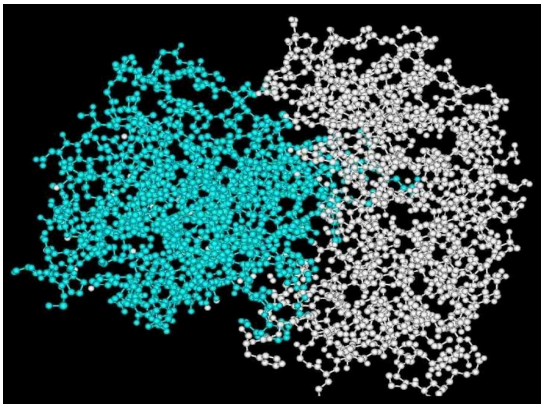


Fig. Atomic Representation

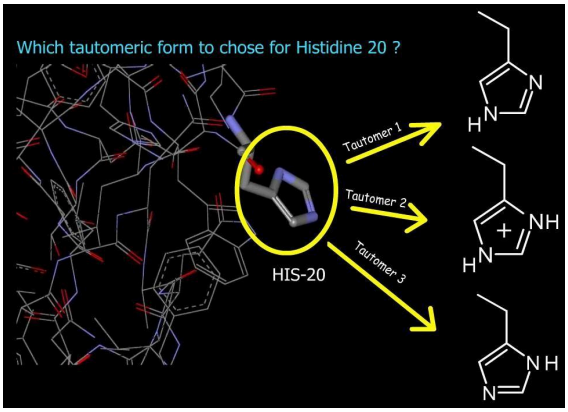
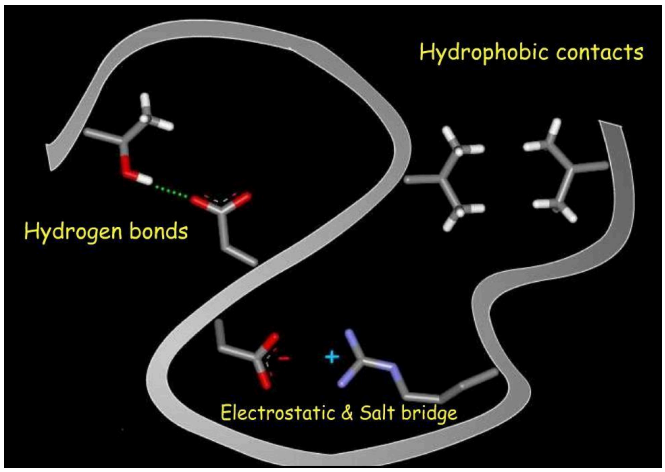


Fig. Protein Preparation

(II) **Scoring method** – It aims at assessing the quality of docked complexes and guiding the docking algorithm. The binding process that leads to the formation of a complex between a ligand and its receptor is controlled by several factors including:

1. The interaction energies between the two molecules. The interaction forces between two molecules can be divided into:

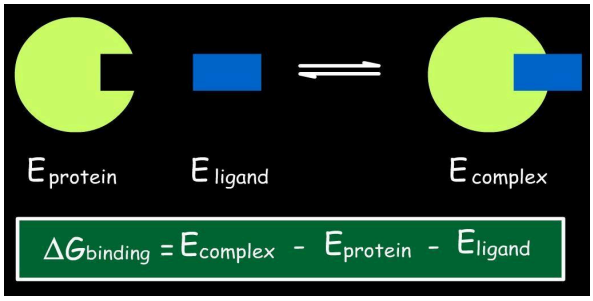


- Electrostatic interactions
- Hydrogen bond interactions
- Van der Waals interactions
- Hydrophobic forces

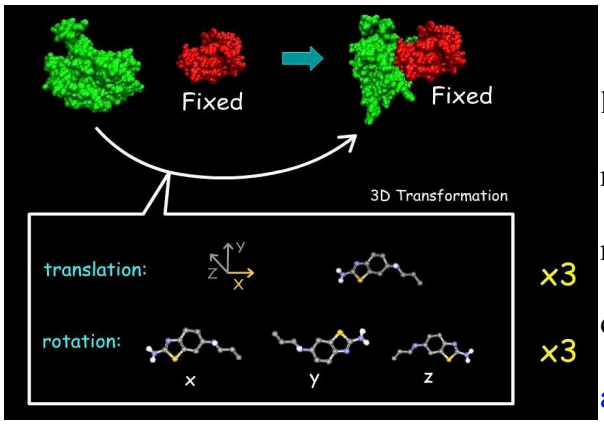
2. The desolvation and solvation energies associated with the interacting molecules. The binding of a ligand to a protein is a complex process influenced by desolvation and solvation phenomena where the interacting entities become partially desolvated.

3. The entropic factors that occur upon binding. The flexibility of the molecules and the consequences in terms of entropy can have a significant impact on the binding energy of a ligand. The binding

energy $\Delta G_{binding}$ is the energy required to separate a complex into separate parts (protein and ligand). It is defined as the difference between the energy of the associated(bound) form ($E_{complex}$) and that of the separated (unbound) molecules ($E_{protein}$ and E_{ligand}).



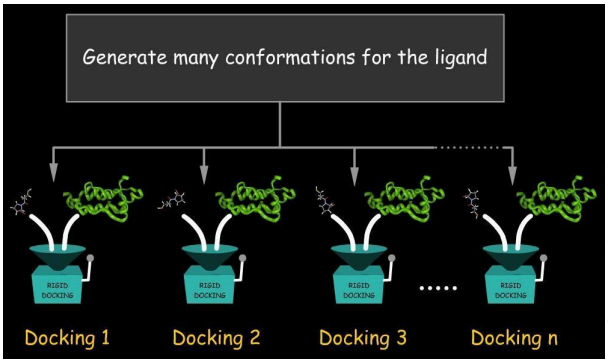
Rigid Docking Methods



If we assume that the molecules are rigid, we are then looking for a transformation in 3D space of one of the molecules which brings it into optimal fit with the other molecule in terms of a scoring function. In rigid-body docking, the search space is restricted to three rotational and three translational degrees of freedom.

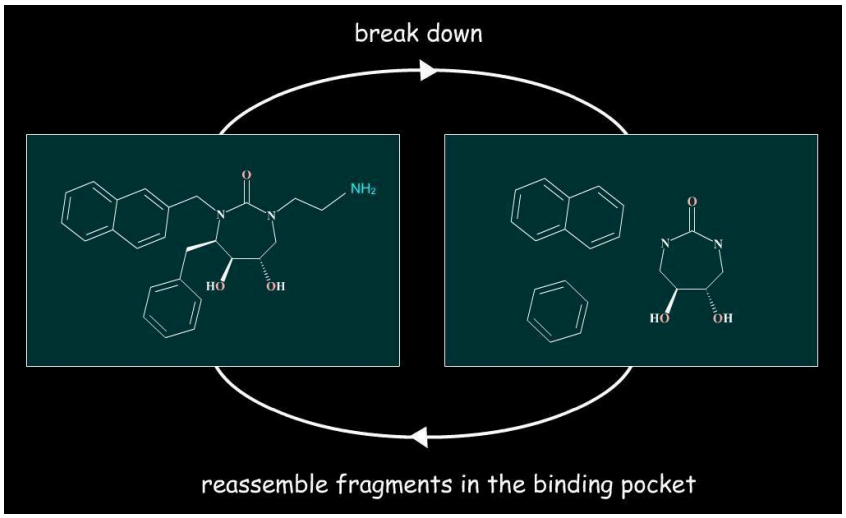
Methods for Handling Ligand Flexibility

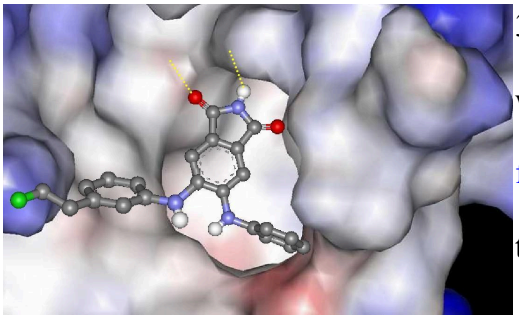
Many methods have been developed for incorporating flexible small molecules into docking software; they include:



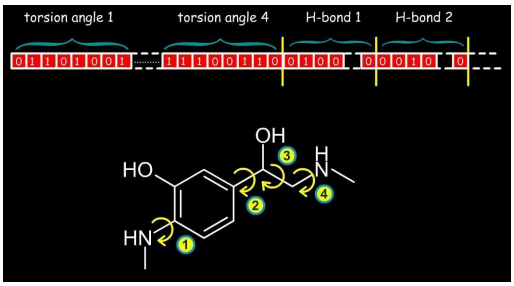
1. **Ligand-ensemble docking method** - The simplest method to account for small molecule flexibility is to consider it as an "ensemble" of rigid and independent ligand conformations. In the first step low energy conformers of ligand are generated by conformational analysis. In the second step, rigid docking is applied for each conformer independently in order to find the most favorable small molecule-protein complex.

2. **Fragmentation method** - Fragmentation methods break down the molecule into small rigid fragments, the fragments are then reassembled in the binding pocket. Two different approaches are used for reassembling the disconnected moieties: the place-and-join and the incremental approach.





3. **Incremental based approach** – This approach starts with an initial core docked in the active site, and new fragments are progressively added and minimized; the treatment is terminated when the entire molecule is formed.



4. **Stochastic Conformational search method** - Stochastic search methods modify the conformation of the small molecule in the receptor site and assess it on the fly .In the case of genetic algorithms, the torsion angles are added on the

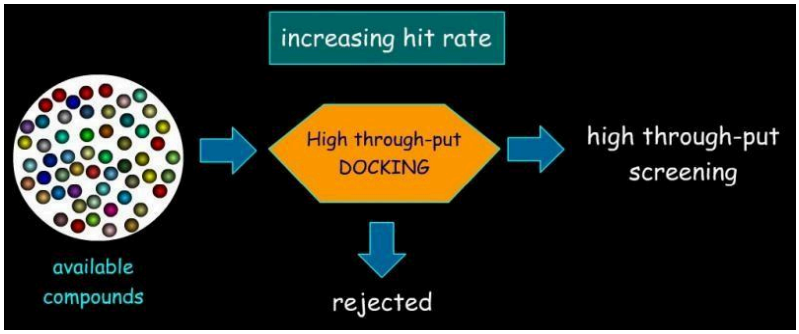
chromosomes; in Monte Carlo based methods they are set as parameters for optimization.

DOCKING SOFTWARES

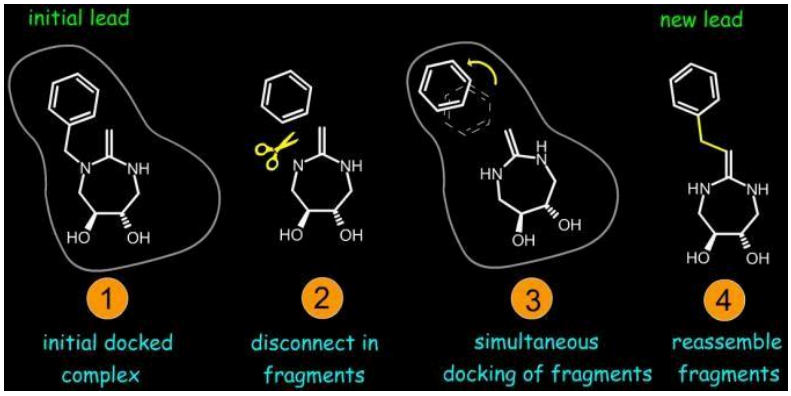
S.NO.	DOCKING PROGRAM	DOCKING METHOD	DEVELOPER	YEAR PUBLISHED IN
1	Dock Dock 4.0	Point complementary method Incremental method	Kuntz et al Ewing and kuntz et al	1982 2001
2	AutoDock	Lemarckian genetic algorithm and Monte Carlo method	Morris et al	1998
3	GOLD	Genetic algorithm	Jones et al	1997
4	FlexX	Incremental Construction method	Rarey et al	1996
5	Hammerhead	Incremental Construction method	Welch et al	1996
6	ICM	Monte Carlo method	Abagyan et al	1994
7	MC Dock	Monte Carlo method	Liu and Wang	1994
8	SLIDE	Incremental method	Schnecke et al	2002
9	Glide	Simulation method	Frienser et al	2004

APPLICATIONS OF DOCKING

1) **VIRTUAL SCREENING (Hit identification):** Docking with a scoring function can be used to predict where and in which relative orientation a ligand binds to a protein. This information may then be used to design more potent and selective analogues.



2) **DRUG DISCOVERY (Lead Optimization):** Docking with a scoring function can be used to quickly screen the large databases of potential drugs in silico to identify molecules that are likely to bind to the protein target of interest.



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3) **BIOREMEDIATION:** Protein ligand docking can be efficiently used to predict pollutants thta can be degraded by enzymes.

Limitations in Computational Docking

Computational docking has emerged recently as a new discipline. Despite the important achievements that have been obtained, substantial progress remains to be made to exploit the full potential of this approach. Current challenges of docking methods are:

- Trade off between efficiency and accuracy
- More effective scoring functions
- Better model of flexibility