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Molecular Docking

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ABSTRACT

Molecular docking refers to the use of computational modeling for creating structure complexes that are formed by two or more interacting molecules. The primary goal of molecular docking is to predict the three-dimensional structure of interest. Molecular docking software is mostly used in drug improvement. The easy access to structural databases and molecules has become an essential mechanism for drug design and analysis. Simple prediction of molecules and easy access to structural databases have become essential components on the desktops of medicinal chemists. The primary application of molecular docking is virtual screening, which is a crucial tool in structural molecular biology and computer-aided drug design. Various docking programs have been developed to imagine the three-dimensional structure of the molecule and docking gain can also be analyzed with the assistance of different computational methods. Docking can be used to perform virtual screening on large libraries of compounds, rank the results, and suggest structural hypotheses of how the ligands reduce the target, which is valuable in lead optimization.

INTRODUCTION: -

Molecular Docking is a technique that predicts how a ligand will orient itself against a receptor (protein) to form a stable complex. This predicted orientation is used to estimate the strength of the bond or binding affinity between the ligand and protein using scoring functions. Docking is commonly used to predict the binding orientation of potential drug candidates against protein targets to determine the drug's affinity and activity. Therefore, molecular docking plays a crucial role in the drug design and discovery process. The main goal of molecular docking is to simulate the molecular identification process computationally and achieve an optimized conformation that minimizes the free energy of the overall system. Discovering a new drug is a challenging task. The modern drug discovery process primarily relies on the in-silico-chemical biological approach, which involves using computer-aided techniques that are gaining popularity, recognition, and implementation.

CADD (Computer Aided Drug Discovery): -

Objectives: -

Use of computational ability to streamline drug discovery.

a. Advantages of chemical and natural information about ligands and targets to discover and optimize new medicines.
b. Designing of In-silico pollutants to get relief of chemical emulsion with unwanted parcels (poor exertion and/ or poor immersion, Distribution, Metabolism, Excretion, and toxin, (ADMET) and elect the most promising campaigners.
c. Identification of new medicine targets and reclamation through a database of target protein structures like the protein data bank (PDB). CADD is being used to discover successes (medicine campaigners).
d. Virtual screening is used to uncover new drug candidates from different chemical scaffolds.

Molecular Docking:

Docking is the process of arranging molecules in the most advantageous positions for interaction with a receptor. It is a phenomenon observed in cells when molecules bond to form a stable complex (As shown in fig.no.1).

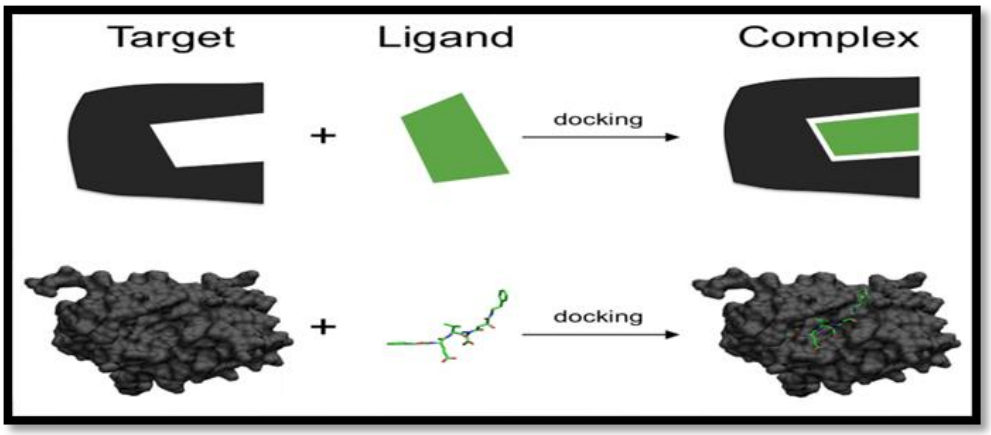

Figure No. 1: Molecular Docking

Molecular Modelling:

A technique for creating, characterizing, and altering the configurations and interactions of compounds as well as the properties of these molecules that depend on their three-dimensional geometries is molecular modelling.

Types of Docking:

1. Rigid Docking
2. Flexible Docking

1. Rigid Docking:

If we assume that the molecules are inflexible, we aim to transform one of the molecules in 3D space to achieve the best possible fit with the other molecules according to a scoring function. The ligand's conformation can be generated either in the absence or presence of receptor-binding activity.

2. Flexible Docking:

In order to identify conformations for the receptor and ligand molecules as they exist in the complex, we evaluate molecular flexibility alongside transformation.

Models of Molecular Docking: -

1. The Lock and Key Model:

In 1890, Emil Fischer created the "lock-and-key model" to illustrate the workings of biological processes. This model compares the way a key fits into a lock to how a substrate fits into the active site of a macromolecule. The active site of biological locks has specific stereochemical features that are essential for their function (As shown in fig.no.2).

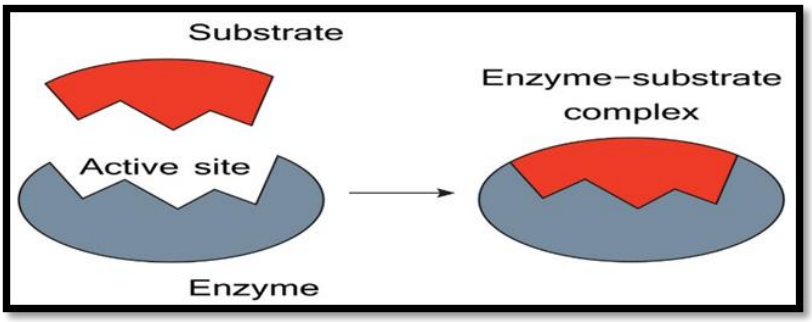

Figure No.2: The Lock and Key Model

2. The Induced Fit Theory:

Daniel Koshland proposed the "induced fit theory" in 1958. According to this theory, both the ligand and target undergo conformational changes during character recognition until they reach an ideal match (As shown in fig.no.3).

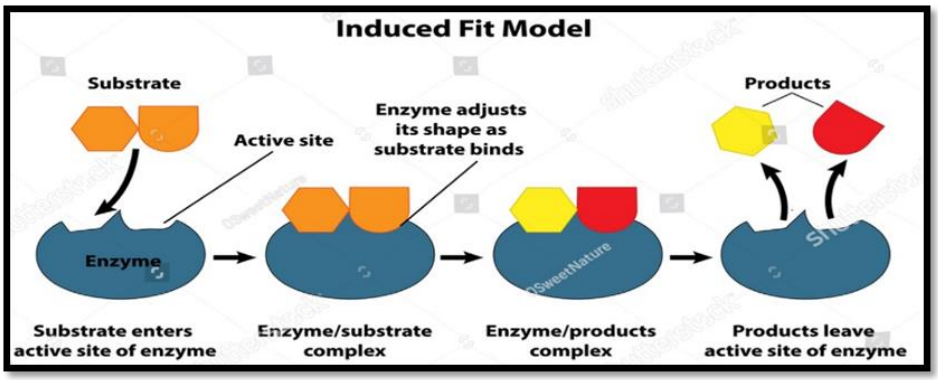

Figure No.3: Induced Fit Model

3. The conformation ensemble model:

Recent research suggests that proteins undergo a significant number of conformational changes beyond just induced-fit modifications. A new theory proposes that a protein's conformational states already exist in an ensemble. The flexibility of the protein allows it to transition between different states.

Mechanism of Molecular Docking: -

The first step in conducting a docking screen is to have the sequence of the specific protein. This structure is usually discovered by using a biophysical approach such as X-ray crystallography or, less commonly, NMR spectroscopy. The process involves using a docking tool that takes the protein function and a database of compounds as inputs. The success of a docking program depends on three main aspects: the search algorithm, the scoring mechanism, and the conformational space of the protein bound to a ligand.

The search space includes all possible directions and conformations of the protein, but with current processing resources, it's difficult to exhaustively explore the search space. This would entail listing all potential molecular distortions and all likely translational and rotational configurations of the ligand relative to the protein at a moderate criterion of resolution. Most docking systems in use account for flexible ligands, while others attempt to represent a dynamic protein receptor.

Major Steps Involved in Mechanics of Molecular Docking: - (As shown in fig.no.4)

Step I – preparation of protein:

In order to properly prepare a protein, it is essential to obtain its three-dimensional structure from the Protein Data Bank (PDB). This structure must then undergo pre-processing, which includes the removal of any water molecules present within the cavity and the stabilization of charges. Additionally, any missing residues must be filled in and side chains adjusted as necessary based on available parameters. By completing these steps, the protein can be effectively prepared for further use in a variety of applications.

Step II – active site prediction:

After preparing a protein, it is necessary to predict its active site. The receptor strength contains multiple active sites, but only the relevant one should be selected. Typically, water molecules and hetero atoms can be disregarded if they are present.

Step III – preparation of ligand:

To prepare the ligand, you can obtain it from various databases like ZINC or Pub Chem or create it using a Chem sketch tool. When selecting the ligand, it is important to use Lipinski's Rule of 5. This rule helps distinguish between drug-like and non-drug-like compounds. The CAD method, which uses computer aid for drug design and detection, has a high potential for success or failure depending on how well the molecules comply with two or more of the Lipinski rules.

Lipinsky's rule -

The following criteria should be met by the molecule:

(1) No more than five hydrogen bond donors

(2) No more than ten hydrogen bond acceptors

(3) Molecular mass below 500 Daltons

(4) High lipophilicity, expressed as Log not exceeding 5

(5) Molar refractivity within the range of 40-130.

Step IV Docking:

Docking is a method used in molecular modeling to determine the binding affinity between a ligand and a protein. The process involves the careful positioning of the ligand in close proximity to the protein in order to observe the resulting interactions. This allows researchers to gain insight into the potential effectiveness of the ligand as a therapeutic agent or drug target.

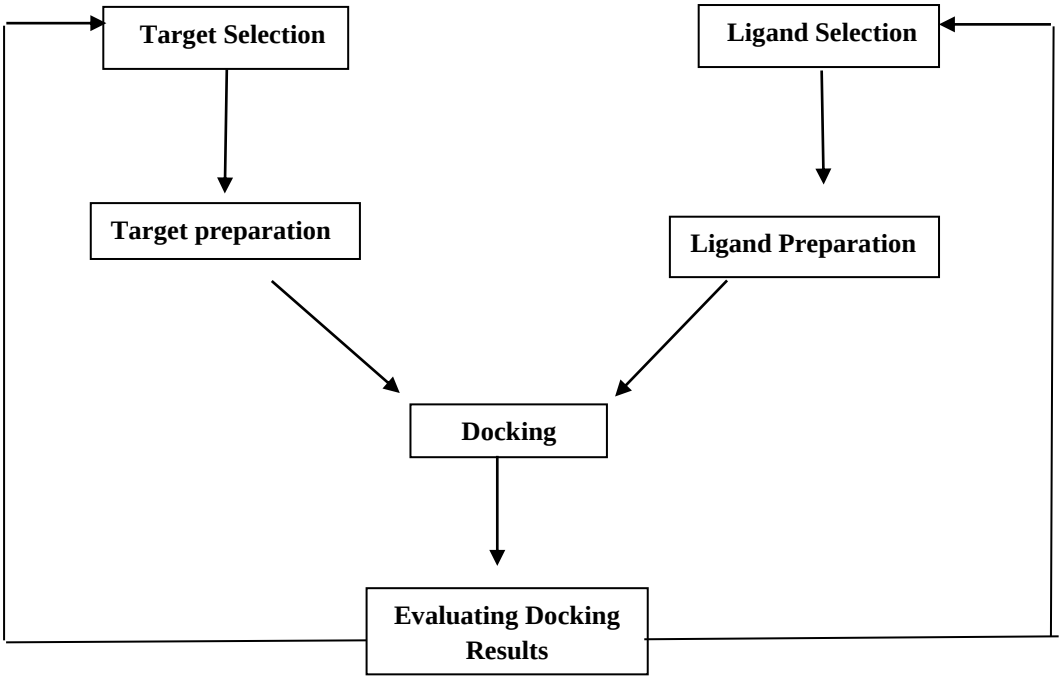

Figure No.4: Steps Involved in Mechanics of Molecular Docking

Molecular docking approaches: -

- **Monte Carlo approach:**

  In this process, a molecule called a ligand is placed in a specific location within a larger molecule, and then its shape and position are randomly adjusted. A standard configuration is assigned to it, and then a new configuration is created and evaluated based on a scoring system. The Metropolis criterion is used to determine whether the new configuration should be kept.

  This criterion states that if the new configuration performs better than the old one, it is immediately accepted. However, if the new configuration is not substantially different from the old one, Boltzmann's law will be used to evaluate it. If the probability of the new configuration is too low, it will be rejected.

- **Matching approach:**

  This approach emphasizes redundancy, determines the best place for the ligand atom in the site, and produces a ligand-receptor configuration that might also benefit from optimization. This approach emphasizes redundancy, determines the optimal position

of the ligand atom in the binding site, and generates a ligand-receptor configuration that can be further optimized.

- **Ligand fit approaches:**

  A rapid and accurate method for docking small molecule ligands into protein active sites while taking form complementarity into consideration is referred to as "ligand fit."

- **Fragment-Based Method:**

  In the process of fragment-based drug design, the ligand is broken down into smaller components or fragments. Each of these fragments is then docked onto the target protein to analyze its binding affinity. Finally, the fragments are connected together to form the complete ligand. This approach enables the identification of potential drug candidates with higher accuracy and efficiency.

- **Point complimentarily approach:**

  These complementary approaches involve comparing the shapes and chemical properties of various molecules. Blind docking, a technique designed to scan the entire interface of target molecules, was created to identify potential peptide ligand binding sites and mechanisms of action.

- **Inverse docking:**

  In this approach, computer technology is utilized to determine the toxicity and side effects of protein targets caused by a small molecule. By combining the information about these targets with the knowledge of proteomics pharmacokinetic profile, it becomes easier to evaluate the possible toxicities and side effects of a drug candidate. A specific ligand is chosen for docking studies using one of these protocols.

Applications of Molecular Docking: -

Molecular docking is a useful technique that is commonly used in drug development. This technique can be used in various ways: -

- Hit Identification (Virtual Screening)

- Lead Optimization (Drug discovery)
- Bioremediation
- Receptor preparation
- Ligand Preparation
- Drug-DNA interaction
- Application of molecular modeling in modern drug development

➢ **Hit Identification (Virtual Screening): -**

Hit identification involves using docking in combination with a score function to screen large databases of potential drugs in silico. This way, compounds that can bind to a specific target of interest can be quickly identified (As shown in fig no.5).

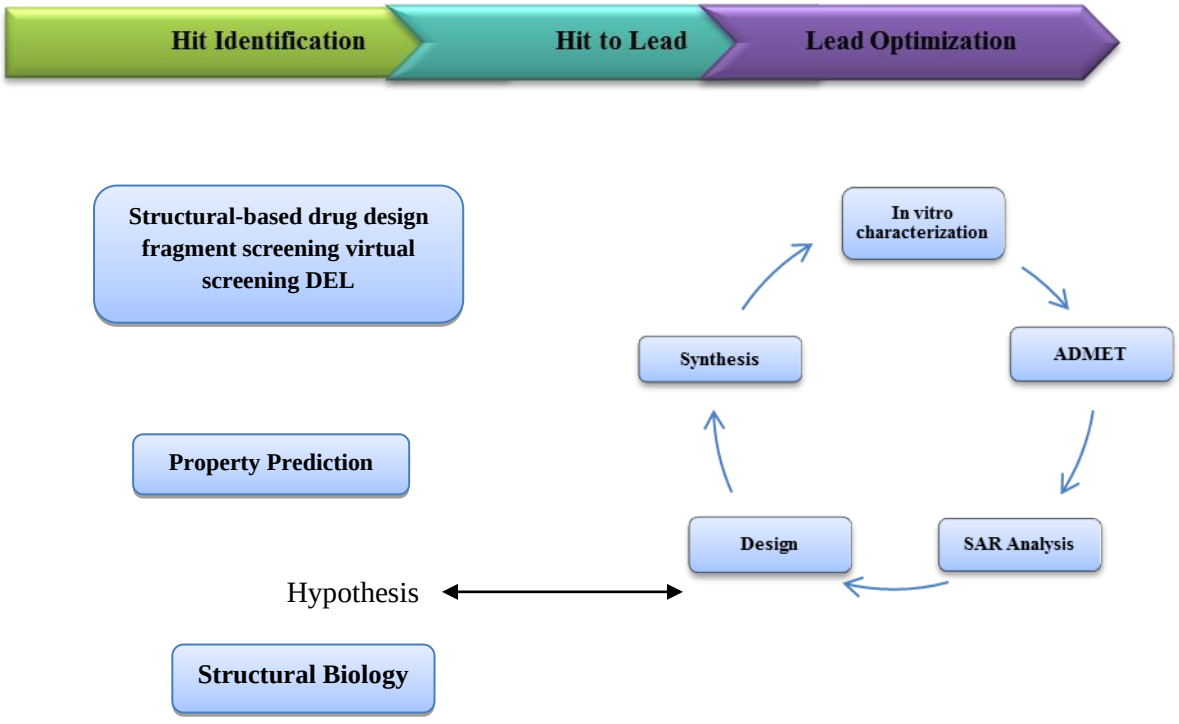

Figure No.5: Mechanism of Hit Identification

- **Lead Optimization (Drug discovery):**

Lead optimization can be done by using docking to anticipate the position and relative location of the interaction between a ligand and a protein. This information can be used to develop more potent and selective analogs.

In addition, protein-ligand docking can be used to predict which contaminants can be degraded by enzymes. It can also identify enzymes and their mode of action, as well as determine relationships between proteins. The remediation method is used to screen molecules (As shown in fig. no. 5).

- **Bioremediation:**

Protein-ligand docking is a computational method that allows the prediction of how small molecules (ligands) bind to proteins. This technique is not only useful in drug discovery but also in environmental science. Enzymes can utilize protein-ligand docking to identify pollutants and forecast how they can be broken down into less harmful substances. This has great potential for designing new bioremediation strategies to clean up polluted environments (As shown in fig no.6).

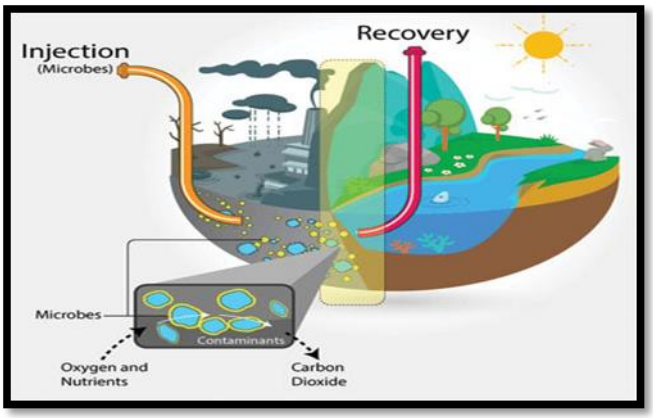

Figure No.6: Schematic diagram of the bioremediation process

- **Receptor Preparation:**

Receptor preparation, which involves selecting a structure and binding sites, depends on the specific docking software used. Hydrogens may need to be added, with some programs being more position-sensitive than others.

- **Ligand Preparation:**

  Ligand preparation involves predicting the Pka values for each charged atom and implementing programs for each possible charge arrangement within a specified pH range, such as 5-9. The use of a quantum mechanical force field can also help reduce the chemical structure.

- **Drug-DNA interaction:**

  Molecular docking is commonly used to study drug-DNA interaction and predict the binding properties of drugs and nucleic acids. Medicinal chemists use computer simulations to predict whether a compound/drug will interact with a protein/DNA.

- **Application of molecular modeling in modern drug development:**

  Molecular modeling is an important tool in modern drug development. It is used to assess potential harms caused by interactions with other proteins such as proteases, cytochrome P450, and others. Additionally, docking can be used to determine the specificity of a proposed medication against homologous proteins. It is also frequently utilized in identifying protein-protein interactions. Understanding cellular connections helps in comprehending various processes occurring in live organisms and identifying potential pharmaceutical targets.

Representative Software for Molecular Docking: -

SR. No	Name	Search algorithm	Evaluation method	Speed	Features & Application areas
1	Flex X [33]	Fragmentation algorithm	Semi-empirical calculation on free energy	Fast	Flexible-rigid docking.
2	Gold [34]	GA (genetic algorithm)	Semi-empirical calculation on free energy	Fast	Flexible docking.
3	Glide [35]	Exhaustive systematic search	Semi-empirical calculation on free energy	Medium	Flexible docking.
4	AutoDock [36]	GA (genetic algorithm) LGA (Lamarckian genetic algorithm)	Semi-empirical calculation on free energy	Medium	Flexible-rigid docking.
5	ZDOCK [37]	Geometric complement-arity and molecular dynamics	Molecular force field	Medium	Rigid docking.
6	RDOCK [39]	GA (genetic algorithm) MC (Monte Carlo) MIN (Simplex minimization)	Molecular force field	Medium	Rigid docking.
7	LeDOCK [40]	Simulated annealing (SA) Genetic algorithm (GA)	Molecular force field	Fast	Flexible docking.
8	Dock [42]	Fragmentation algorithm	Molecular force field	Fast	Flexible docking.
9	Autodock Vina [6]	GA (genetic algorithm)	Semi-empirical calculation on free energy	Fast	Flexible-rigid docking.

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