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MOLECULAR DOCKING: AN ADVANCED TOOL FOR DECISION MAKING IN DRUG DISCOVERY AND DEVELOPMENT

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Abstract

Molecular in-silico docking of the influenza virus protein using docking software with various drugs aims to study drug-target interactions. This approach identifies drug molecules through virtual screening via molecular docking. Recognized as a fast and cost-effective technique, molecular docking analyses the conformation and orientation of atoms or molecules within the binding site of a macromolecular target. Biochemists have developed various models over the years to identify key elements of the molecular process. Docking methods are categorized based on the degrees of flexibility of the molecules being investigated. Interactions between small molecules, such as ligands, and proteins (which may be enzymes) can predict the activation or inhibition of the target enzyme. This review follows the main theories of lock and key, induced-fit, and conformational ensemble. There are three primary types of scoring functions used in molecular docking: force-field-based scoring functions, empirical scoring functions, and knowledge-based scoring functions. By expanding pharmacodynamic information such as strength, viability, selectivity, pharmacokinetic properties, absorption, distribution, metabolism, excretion, and toxicity (ADMET) docking software can enhance drug design. This review will explore how molecular docking optimizes drug design by identifying the best target site of the protein for the ligand, ultimately enhancing ligand-receptor binding before developing the drug.

Key words: Molecular docking, influenza virus, force-field, ligand, receptor, lock and key, conformation ensemble, induced-fit

Introduction:

Molecular Docking

Molecular docking is a technique used to model interactions between small molecules and proteins at the atomic or molecular level, helping to characterize the behavior of small molecules in the binding sites of target proteins. The docking process includes predicting the conformation and orientation of ligands within a binding site. Molecular docking studies aim for accurate structural modeling and correct prediction of activity[1].

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In-silico docking of the influenza virus protein using docking software with various antiviral herbal drugs is used to study drug-target interactions. The discovery of effective antiviral drugs is crucial for controlling the spread of flu. With the emergence of new viral strains, there is an urgent need for novel antivirals with fewer side effects. Computational molecular docking enhances drug-target interactions, leading to the development of new antiviral drugs with high efficacy against the virus[2].

Virtual screening via molecular docking is an encouraging approach to identifying potential drug molecules. Recognized as a fast and inexpensive technique, molecular docking analyzes the conformation and orientation of atoms or molecules within the binding site of a macromolecular target[3]. The primary goals of molecular docking studies are accurate structural modeling and correct prediction of activity. In-silico docking of the influenza virus protein with antiviral herbal drugs using docking software aims to study these drug-target interactions

Knowing the location of the binding site before initiating the docking process significantly enhances docking efficacy. Typically, the binding site is identified prior to docking ligands. The lock and key theory, proposed by Fischer, explains the early mechanism of ligand-receptor binding by illustrating how the ligand fits into the receptor like a key into a lock, treating both as rigid bodies[4].

The induced-fit theory, proposed by Koshland, builds on the lock and key theory by suggesting that the active site of the protein continuously reshapes itself through interactions with the ligand. This theory treats both the ligand and receptor as flexible during docking[5].

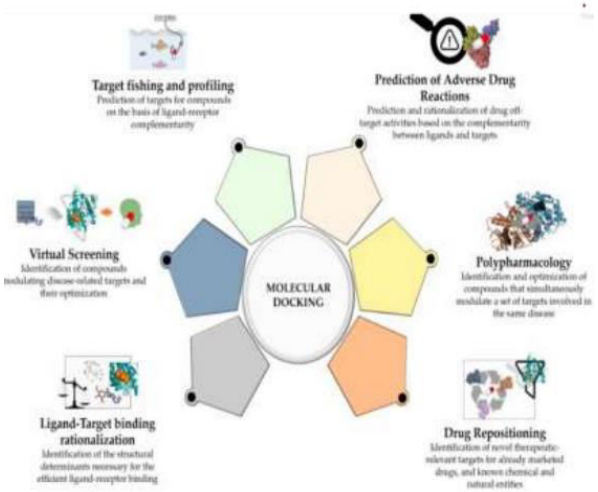

Fig 1: Various Applications of Molecular Docking in Current Drug Discovery

Molecular docking aids in understanding ligand activity towards a target of interest and facilitates structure-based virtual screening. It can identify a series of targets where ligands show good complementarity[6]. Docking is employed to pinpoint ligands that bind effectively to selected targets. Successful docking methods efficiently search high-dimensional spaces and utilize a scoring function that accurately ranks candidate dockings. Docking can be used to conduct virtual screening on large compound libraries, rank the

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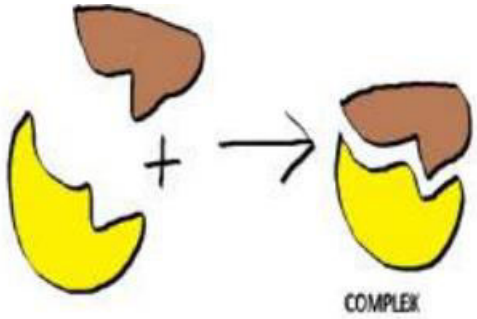
results, and propose structural hypotheses on how ligands inhibit the target, which is invaluable for lead optimization.

Molecular Docking Models

Over the years, biochemists have developed various models to identify key elements of molecular processes. Despite their simplicity, these models have proven highly useful to the scientific community. Numerous authors have introduced different models at various times, each contributing to the field's advancement[7].

Lock and Key Theory

In 1894, Emil Fischer proposed the "lock and key" theory, suggesting that an enzyme's specificity for its substrate is based on the complementary geometric shapes of the two components, fitting together perfectly like a key in a lock. In this analogy, the lock represents the enzyme, and the key represents the substrate or ligand. For the substrate to fit into the active site of the enzyme (the keyhole of the lock), it must have the correct shape. Keys that are too small, too large, or incorrectly shaped will not fit into the lock[8].



Induced-fit

The induced-fit model accurately predicts ligand binding modes and the resulting structural changes in the receptor. A Python script automates the Induced Fit Design (IFD) protocol, specifying receptor and ligand structures. Standard virtual docking studies typically assume a rigid receptor, but in reality, many receptors adjust their binding sites to conform to the shape and binding mode of the ligand[9]. This phenomenon, known as induced fit, is a major complicating factor in structure-based drug design. The ability to model induced-fit docking has two main applications:

1. It provides more accurate predictions of ligand binding.
2. It allows for the design of more effective drugs by accounting for receptor flexibility.

Generation of Accurate Complex Structures

The induced-fit docking (IFD) protocol allows for the generation of accurate complex structures for ligands known to be active but unable to dock in an existing rigid receptor structure. This method can also rescue false negatives (poorly scored true binders) in virtual screening experiments by screening against multiple receptor conformations obtained from the IFD protocol, rather than a single conformation[10].

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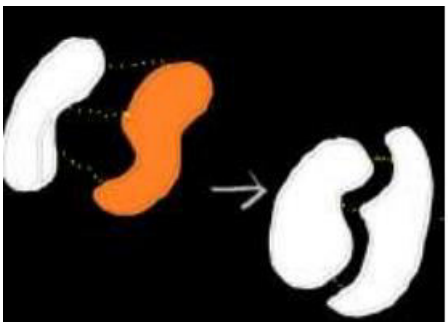


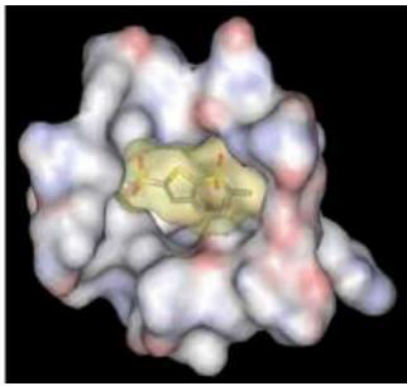
Conformation Ensemble Model

Beyond small induced-fit adaptations, it has been observed that proteins can undergo much larger conformational changes. A recent model describes proteins as a pre-existing ensemble of conformational states, allowing them to switch from one state to another due to their plasticity. These three models are not contradictory, as each focuses on a particular aspect of the recognition process:

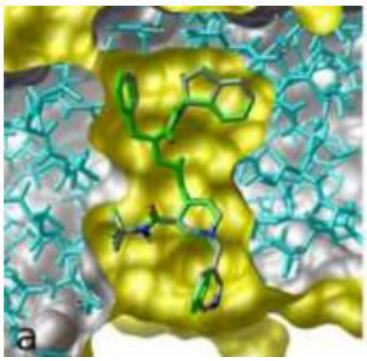
- The lock-and-key model introduces the "principle of 3D complementarity."
- The induced-fit model explains "how complementarity is achieved."
- The ensemble model depicts the "conformational complexity of proteins."

Triggering the Computational Docking

Challenges in obtaining structural data of macromolecular complexes have spurred the development of computational predictive procedures. Computational molecular docking aims to predict the optimal binding orientation and conformation of interacting molecules in space, helping to estimate the stability of their complex. Molecular docking predicts whether two molecules will interact, the binding affinity, and the 3D structure of the complex.



AutoDock Vina



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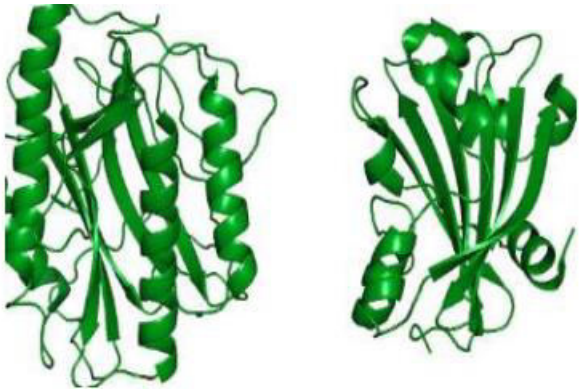
AutoDock Vina: A Molecular Docking Program

AutoDock Vina, designed and implemented by Dr. Oleg Trott at the Scripps Research Institute, is a program for molecular docking. It improves the average accuracy of binding mode predictions compared to its predecessor, AutoDock 4. AutoDock Vina has been rigorously tested against the Directory of Useful Decoys virtual screening benchmark and proven to be a strong competitor among other software programs.

Compatibility: AutoDock Vina uses the same PDBQT molecular structure file format for both input and output, which is also used by AutoDock. PDBQT files can be generated and viewed using MGLTools.

Molecular Docking Approaches: Monte Carlo

The Monte Carlo approach involves creating randomized conformations by performing translations and rotations of the ligand within the active site. It develops and scores new configurations using random or pseudo-random modifications of bond rotations. This technique determines whether a new configuration is accepted based on the Metropolis criterion, where Boltzmann's law is employed to assess the probability of the configuration; if the criteria are satisfied, the arrangement is accepted; otherwise, it is rejected.



Molecular Docking Techniques:

Matching: Determines the optimal location of the ligand in the binding site, ensuring accurate placement of ligand atoms to achieve a ligand-receptor arrangement, which may require further refinement.

Point Complementarity: Focuses on comparing the shapes and/or chemical properties of different molecules. Blind Docking is a technique developed to identify potential peptide ligand binding sites and understand the mode of action of target molecules.

Distance Geometry: Represents various features in terms of intramolecular or intermolecular dimensions. The distance geometry framework facilitates the assembly of these distances and the calculation of 3D structures that are compatible with them.

Inverse Docking: Pairs targets with pharmacokinetic properties to evaluate a drug's potential for toxicities and side effects.

Conclusion

Molecular docking, developed in the 1980s, has become a fundamental strategy in drug discovery. It enables the prediction of molecular interactions that bind a protein and a ligand

in their bound state, making it a crucial tool in pharmaceutical research. Given its significance, practical exercises with detailed protocols are essential for understanding its application. Molecular dynamics methods, integrating quantum chemistry, statistical mechanics, and force field features, further enhance its utility.

Various molecular docking tools like AutoDock, AutoDock Vina, Gilde, DOCK, GOLD, FlexX, and Surflex, along with docking servers such as ZDOCK, HDOCK, ClusPro, and SwissDock, are available for diverse docking purposes. Molecular docking facilitates virtual screening, binding affinity calculations, and determination of binding free energies. It also aids in visualizing different types of bonded and nonbonded interactions between ligands and amino acid residues of proteins.

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