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COMPUTATIONAL APPROACH IN DRUG DISCOVERY: MOLECULAR DOCKING USING HEX 4.5

MR. CHETAN R. DUDHAGARA,

*N.V.Patel College of Pure And Applied Sciences-Vallabh Vidyanagar, Gujarat, India.
Chetan_dudh@hotmail.com*

MR. ASHISH P. JOSHI,

*V. P. & R.P.T.P. Science College – Vallabh Vidyanagar, Gujarat, India
India.ashu.josh@yahoo.com*

MR. BINOD KUMAR

ISTAR, MCA Department – Vallabh Vidyanagar, Gujarat, India

Abstract

This article reviews achievements in the field of cheminformatics, bioinformatics and their impact on modern drug discovery processes. The application of computational methods to study the formation of intermolecular complexes has been the subject of intensive research during the last decade. It is widely accepted that drug activity is obtained through the molecular binding of one molecule i.e. ligand, to the pocket of another, usually larger, molecule i.e. receptor, which is commonly a protein.

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 using for example scoring functions.

Keyword: Cheminformatics, Bioinformatics, Drug Discovery, Molecular Docking, Computational Method

1. COMPUTATIONAL METHODS:

Computational methods can be used to predict or simulate how a particular compound interacts with a given protein target. They can be used to assist in building hypotheses about desirable chemical properties when designing the drug and they can be used to refine and modify drug candidates.

Computational Methods can also be used to automate repetitive tasks such as searching large compound databases. **Virtual Screening** (VS) is a general term for computational methods that use computers to screen a database of virtual drug candidates (called **compounds**) to identify promising candidates (**leads**). This can be seen as an alternative to perform laboratory experiments.

The main advantages of computational methods compared to laboratory (wet-lab) experiments are:

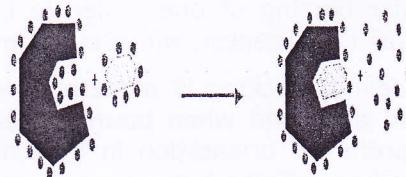
- Low costs, no compounds have to be purchased externally or synthesized by a chemist.
- It is possible to investigate compounds that have not been synthesized yet.
- Conducting HTS experiments is expensive and VS can be used to reduce the initial number of compounds before using HTS methods.
- Huge chemical search space. The number of possible virtual molecules available for VS is much higher than the number of compounds presently available for HTS.

Molecular Docking is used in drug design. Most drugs are small molecules, and molecular docking allows the screening of large databases of potential drugs against protein targets

2. MOLECULAR DOCKING:

The drug activity obtained through the molecular binding of one molecule i.e. the ligand, to the pocket of another, usually larger, molecule i.e. the receptor, which is commonly a protein. In their binding conformations, the molecules exhibit geometric and chemical complementarity, both of which are essential for successful drug activity. The computational process of searching for a ligand that is able to fit both geometrically and energetically the binding site of a protein is called molecular docking.

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**".

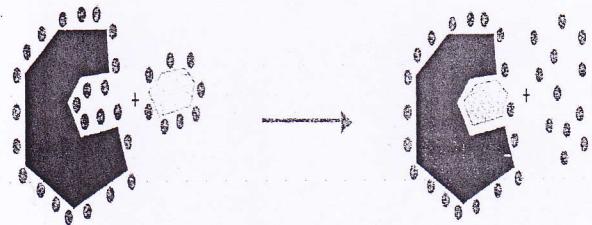


The focus of molecular docking is to computationally simulate the molecular recognition process. The aim of molecular docking is to achieve an optimized conformation for both the protein and ligand and relative orientation between protein and ligand such that the free energy of the overall system is minimized. Molecular docking software consists of two core components :

- **A search algorithm / optimization :** The search algorithm is responsible for finding the best conformations of the ligand and protein system. A conformation is the position and orientation of the ligand relative to the protein. In *flexible* docking a conformation also contains information about the internal flexible structure of the ligand and in some cases about the internal flexible structure of the protein. Since the number of possible conformations is extremely large, it is not possible to test all of them, therefore sophisticated search techniques have to be applied. Examples of some commonly used methods are Genetic Algorithms and Monte Carlo simulations.
- **An evaluation function / score function:** This is a function providing a measure of how strongly a given ligand will interact with a particular protein. *Energy force fields* are often used as evaluation functions. These force fields calculate the energy contribution from different terms such as the known electrostatic forces between the atoms in the ligand and in the protein, forces arising from deformation of the ligand, pure electron-shell repulsion between atoms and effect from the solvent in which the interaction takes place. It is not possible to guarantee that the search algorithm will find the same solution as the true natural process, but more efficient search algorithms will be more likely to find the true solution

Above figure shows a two-dimensional sketch of the docking between a protein target (black color) and a drug candidate (grey color). The cave-like structure in the target is the active site (also called the binding pocket) upon which the drug attaches.

Metaphorically, the active site of the protein can be viewed as a lock, and the ligand can be thought of as a key. In this picture, molecular docking is the process of testing whether a given key fits a particular lock. This picture is slightly oversimplified due to the fact that neither the ligand nor the protein are completely rigid structures. Their shapes are somewhat flexible and may adapt to each other.



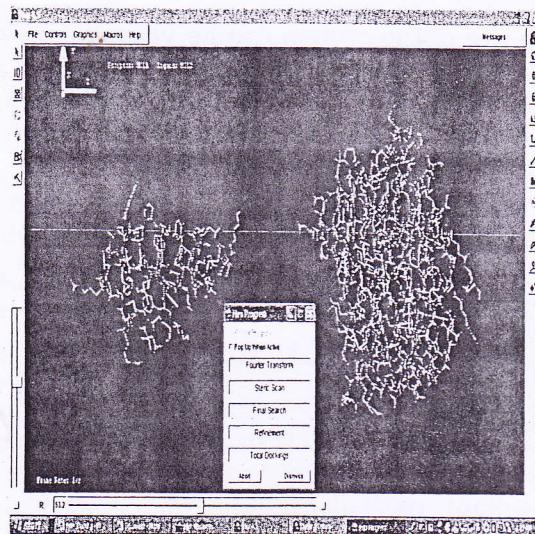
3. Experimental Work:

3.1 Search Modes :-

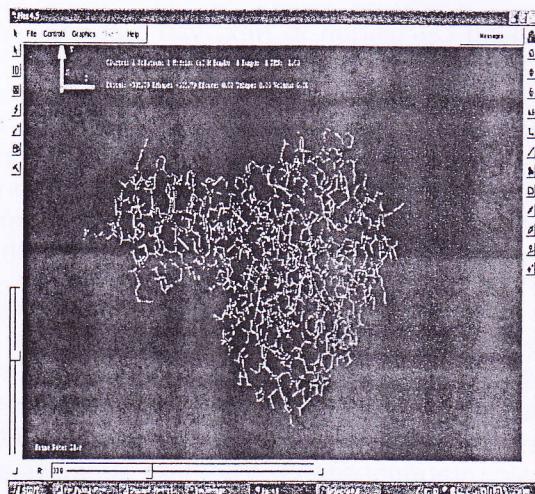
- In order to run a docking calculation in Hex, you will need to load a *receptor* and a *ligand* PDB structure using the *File* pull-down menu.
- Hex currently supports *three* docking search modes, which may be selected using the *Search Mode* selection box in the *Docking Control* panel. Most docking problems require only the default *Full Rotation* mode, in which the receptor and ligand are effectively rotated about their own centroids, and the ligand is twisted about the intermolecular axis at each of a range of intermolecular distances.
- There are several controls which specify the resolution, and in particular the *order*, *N*, of the docking correlation. The default settings are for the program to perform an initial *Steric Scan* at *N*=16, followed by a *Final Search* at *N*=25, using just the steric contribution to the docking energy.
- In this mode, about all but the top 20,000 orientations are discarded after the *Steric Scan*. The *Steric Scan* may be toggled off, in which case every orientation is evaluated using a steric correlation to order *N*, as given the *Final Search* slider.
- In addition to the basic rotational search, Hex also supports a *Ligand Translation* and a *Ligand Orbit* search mode.
- In *Ligand Translation* mode, the receptor is held fixed and the ligand is translated about the receptor using the *Ligand Range* and *Samples* angular parameters and the *Distance Range* and *Step* parameters to generate different ligand poses about the receptor. A pure translation is achieved if the *twist angle* is set to zero.
- In *Ligand Orbit* mode, the ligand is translated as above, but it is now also rotated about its own principle axis. A "wobble" may be added to the search by setting a small range for the *twist angle*. These search modes are largely experimental, but may be useful if the relative orientation of a pair of molecules in a complex is known but the exact binding mode is not.
- These modes are less efficient than the default rotational search mode since they can't exploit the fast (FFT) twist angle search on the innermost loop of a rotational docking search. If in doubt, use the default *Full Rotational* search mode.

3.2 Docking Example :-

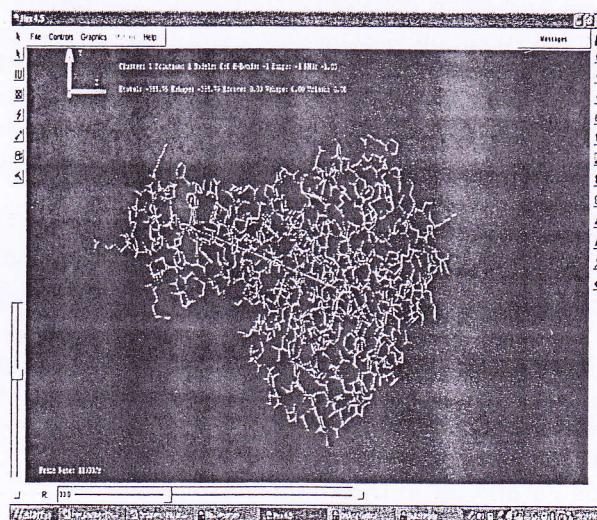
- Open Receptor and Ligand :
- Select Controls and Docking :
- Set Various Parameter in Docking Control :
- Perform Fourier Transformation Process, Steric Scan Process, Final Search, Refinement, Total Dockings Process:



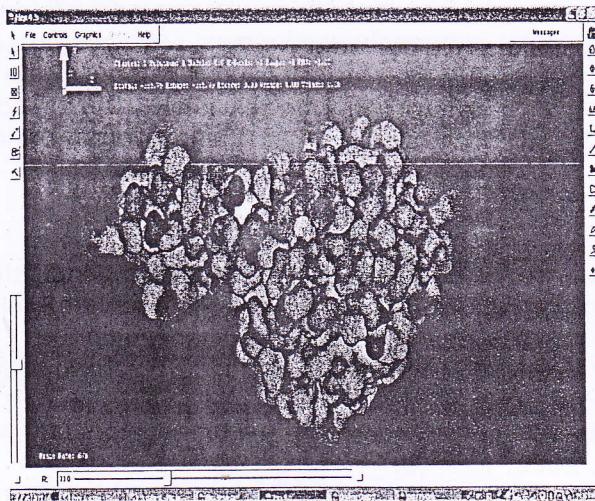
➤ Docking Result :



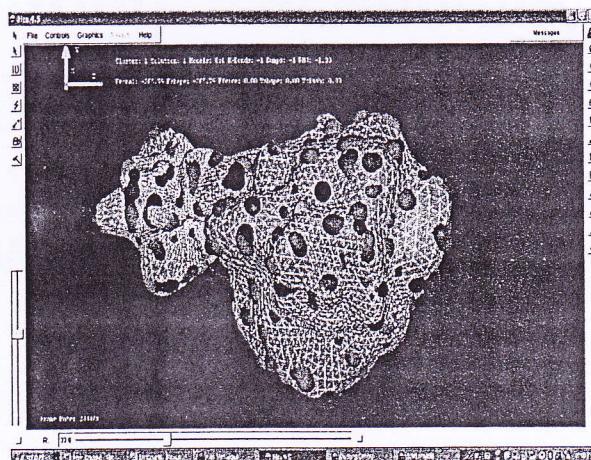
➤ Intermolecular axis :



➤ Representation of Solid Surface :



➤ Representation of Harmonic Surface :



3.2 Docking Result :-

4. CONCLUSION:

When the structure of the target is known (available), usually from X-ray crystallography, the most commonly used virtual screening method is molecular docking. Molecular docking can also be used to test possible hypotheses before conducting costly laboratory experiments. Molecular docking programs try to predict how a drug candidate binds to a protein target without performing a laboratory experiment.

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