Lecture
12

Organic Pharm. Chemistry for Pharmacy Students

By

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Molecular docking system

الالتحام الجزيئي

Basic technique to predict drug-receptor interactions

- **Introduction**
- Molecular docking analysis has been one of the most basic and important strategy for *drug discovery*. It allows prediction of molecular interactions that hold together a protein and a ligand in the bound state
- Molecular docking is an attractive way to understand drug biomolecular interactions for the rational drug design and discovery, as well as in the mechanistic study by placing a molecule (ligand) into the preferred binding site of the target specific region of the DNA/protein (receptor) mainly in a non-covalent fashion to form a stable complex of potential efficacy and more specificity.
- The information obtained from the docking technique can be used to suggest the binding energy, free energy and stability of complexes.

- Based on the types of ligand, docking can be classified as:
- Protein–small molecule (ligand) docking
- Protein–nucleic acid docking
- Protein–protein docking
- **Protein–small molecule** (ligand) docking represents a simpler end of the complexity spectrum, and there are many available programs that perform particularly well in predicting molecules that may potentially inhibit proteins.
- **Protein–protein** docking is typically much more complex. The reason is that proteins are flexible and their conformational space is quite vast.شاسع

- **The performance of docking** depends on the search algorithm [e.g., MC methods, genetic algorithms (GAs), fragment-based methods, Tabu searches, distance geometry methods, and the scoring functions like force field (FF) methods and empirical free energy scoring functions].
- The first step of docking is the generation of composition of all possible conformations and orientations of the protein paired with the ligand.
- The second step is that the scoring function takes input and returns a number indicating favorable interaction .

- At present, **docking technique** is utilized to predict the tentative binding parameters of ligand-receptor complex beforehand.
- The main **objective** of molecular docking is to attain ligand-receptor complex with optimized conformation and with the intention of possessing less binding free energy.
- Practical application of molecular docking requires data bank.

- This can be made possible using scoring function of software , using the infrared spectroscopy (IR), X-ray crystallography and Nuclear Magnetic Resonance (NMR) spectroscopy for the investigation and establishment of three dimensional structures of any organic molecule/ biomolecular receptor.
- There are various **databases** available, which offer information on small ligand molecules such as **CSD** (Cambridge Structural Database), **ACD** (Available Chemical Directory), **DDR** (Drug Data Report) and **NCI** (National Cancer Institute Database).
- A huge number of attempts has been made for the development of efficient docking protocols.
- No doubt, significant progress has been made in the computational prediction of docking modes.
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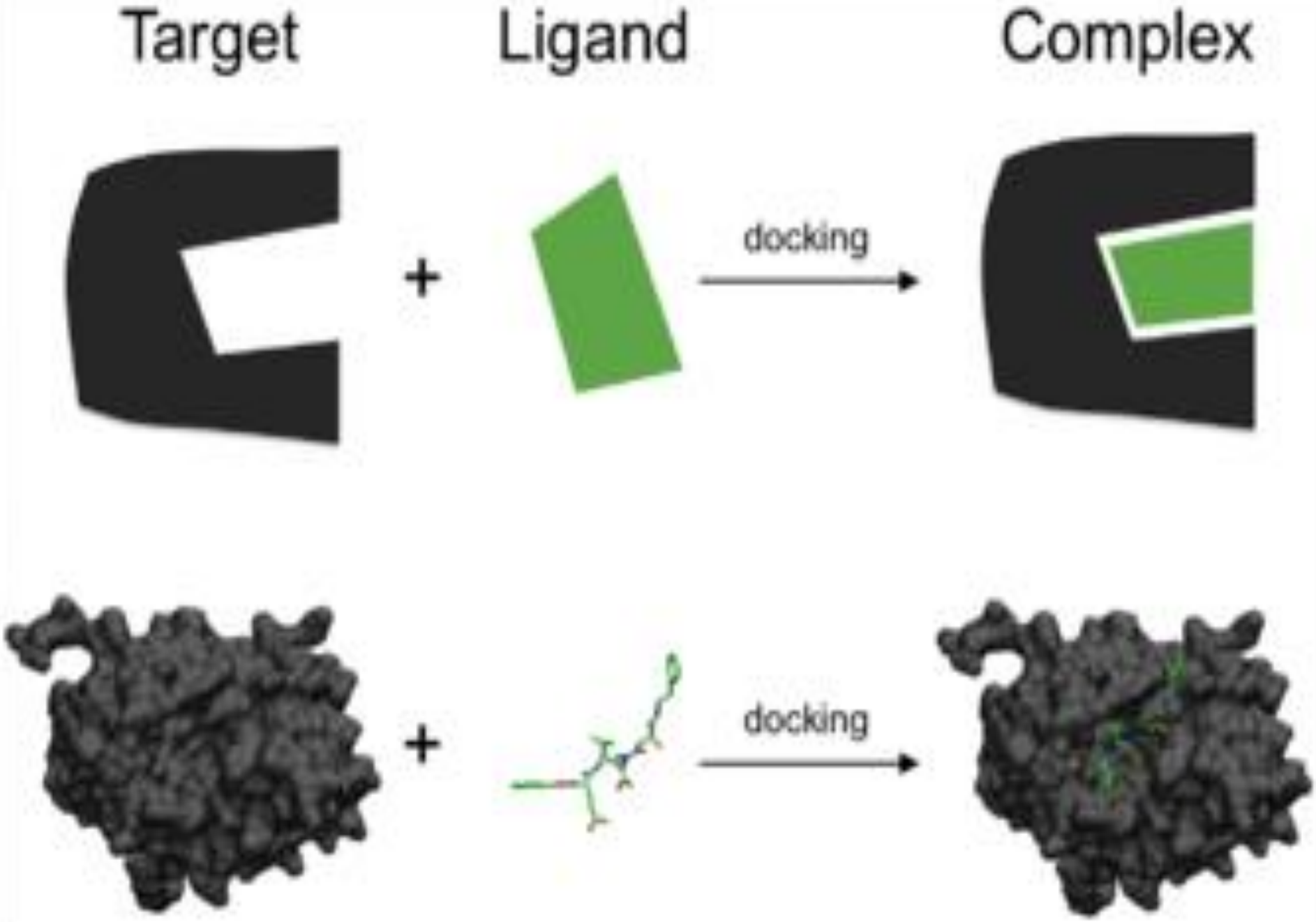
- Depending upon binding properties of ligand and target, it predicts the three-dimensional structure of any complex.
- Molecular docking is one of the most frequently used methods in structure-based drug design, due to its ability to predict the binding-conformation of small molecule ligands to the appropriate target binding site.
- Characterisation of the binding behaviour plays an important role in rational design of drugs as well as to elucidate fundamental biochemical processes.
- 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.


Target
Ligand
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docking
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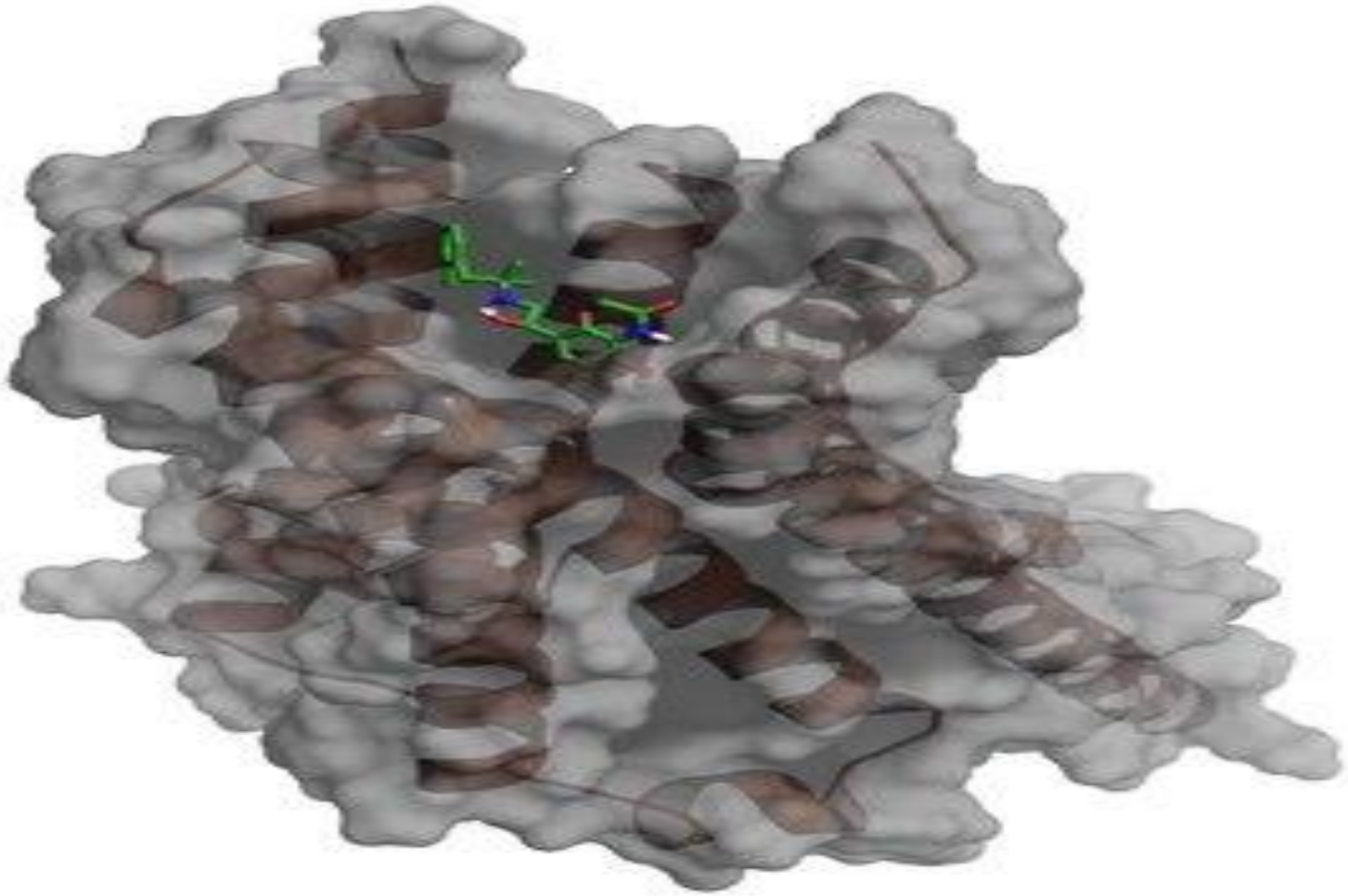


Docking of a small molecule (green) into the crystal structure of the beta-2 adrenergic G-protein coupled receptor (PDB: 3SN6)

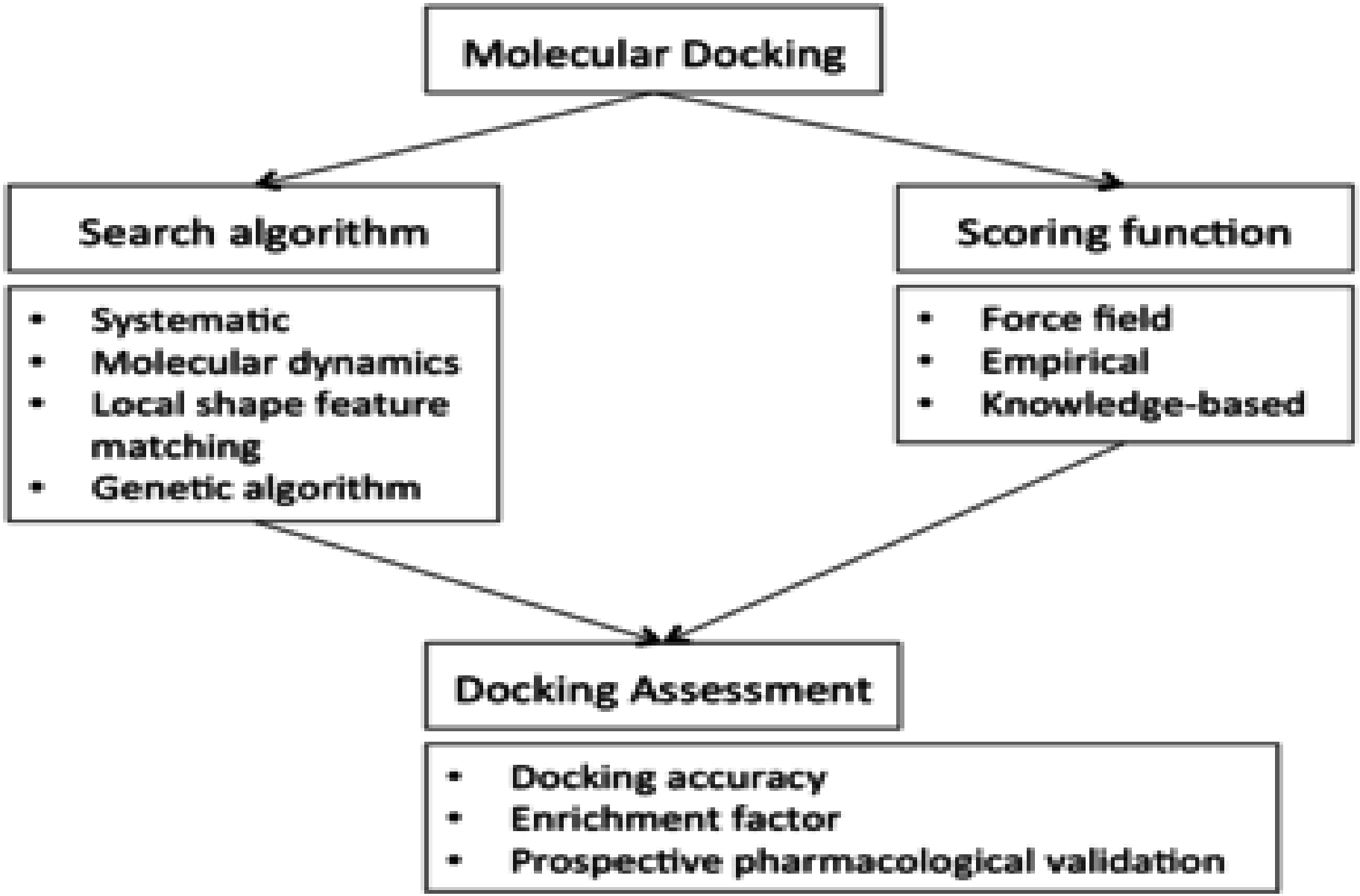
- The associations between biologically relevant molecules متشابه - ذات صلة such as proteins, peptides, nucleic acids, carbohydrates, and lipids play a central role in signal transduction.
- Furthermore, the relative orientation of the two interacting partners may affect the type of signal produced (e.g., agonism vs antagonism).
- **Therefore, docking is useful for predicting both the strength and type of signal produced.**

- **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.**
- One can think of molecular docking as a problem of ***"lock-and-key",*** in which one wants to find the correct relative orientation of the *"key"* which will open up the *"lock"*
- However, since both the ligand and the protein are flexible, a ***"hand-in-glove"*** analogy is more appropriate than *"lock-and-key"*

- Molecular docking research focuses on computationally simulating the molecular recognition process.
- It aims 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 generates different possible adduct structures that are ranked and grouped together using scoring function in the software.

Docking approaches.

- Two approaches are particularly popular within the molecular docking community.
- **One approach** uses a matching technique that describes the protein and the ligand as complementary surfaces.
- **The second approach** simulates the actual docking process in which the ligand-protein pairwise interaction energies are calculated
- Both approaches have significant advantages as well as some limitations.



Docking flow-chart overview

(Algorithm : - خوارزمية – حلول حسابية scoring function :وظيفة التهديف)

خوارزمية:خطوات رياضية متسلسلة لحل مشكلة ما.

- To perform a docking screen, the first requirement is a **structure of the protein** of interest.
- Usually the structure has been determined using a biophysical technique such as x-ray crystallography, NMR spectroscopy or cryo electron microscopy (cryo-EM), but can also derive from homology modeling construction.
- This protein structure and a database of potential ligands serve as inputs to a **docking program**.
- The success of a docking program depends on two components: the search algorithm and the scoring function

Search algorithm.

Searching the conformational space for docking

- The search space in theory consists of all possible orientations and conformations of the protein paired with the ligand.
- Most docking programs in use account for the whole conformational space of the ligand (flexible ligand),), and several attempt to model a flexible protein receptor.

Ligand flexibility

- Conformations of the ligand may be generated in the absence of the receptor and subsequently docked or conformations may be generated on-the-fly in the presence of the receptor binding cavity or with full rotational flexibility of every dihedral angle using fragment based docking.
- Peptides are both highly flexible and relatively large-sized molecules, which makes modeling their flexibility a challenging task.

Receptor flexibility

- Computational capacity has increased dramatically over the last decade making possible the use of more sophisticated and computationally intensive methods in computer-assisted drug design. However, dealing with receptor flexibility in docking methodologies is still a thorny شائك issue

Scoring function

- *Scoring functions for docking*
- Docking programs generate a large number of potential ligand poses. توليد عدد كبير من اشكال الترابط المحتمله
- Most scoring functions are physics-based molecular mechanics force fields that estimate the energy of the pose within the binding site.
- The various contributions to binding can be written as an additive equation:
- The components consist of solvent effects, conformational changes in the protein and ligand, free energy due to protein-ligand interactions, internal rotations, association energy of ligand and receptor to form a single complex and free energy due to changes in vibrational modes.

- A low (negative) energy indicates a stable system and thus a likely binding interaction.
- Alternative approaches use protein-ligand interactions,
- or knowledge-based potentials derived from interactions observed in large databases of protein-ligand structures (e.g. the Protein Data Bank).
- There are a large number of structures from X-ray crystallography for complexes between proteins and high affinity ligands,

Docking assessment

Critical Assessment of Prediction of Interactions

- An assessment of a docking protocol is generally required (when experimental data is available) to determine its predictive capability). Docking assessment can be performed using different strategies, such as:
- docking accuracy (DA) calculation;
- the correlation between a docking score and the experimental response or determination of the enrichment factor (EF);
- the distance between an ion-binding moiety and the ion in the active site;
- the presence of induce-fit models.

- **Docking accuracy**
- Docking accuracy represents one measure to quantify the fitness of a docking program by rationalizing the ability to predict the right pose of a ligand with respect to that experimentally observed
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Prospective المستهدف او المأمول

- Resulting hits from docking screens are subjected to pharmacological validation (e.g. IC„ affinity or potency measurements).
- Only prospective studies constitute conclusive proof of the suitability of a technique for a particular target.

Benchmarking المرجعية

- The potential of docking programs to reproduce binding modes as determined by X-ray crystallography can be assessed by a range of docking benchmark sets.
- **several benchmark data sets** for docking and virtual screening exist e.g. *Astex Diverse Set* consisting of high quality protein–ligand X-ray crystal structures ,
- or the *Directory of Useful Decoys* (DUD) for evaluation of virtual screening performance.

Applications

- Docking is most commonly used in the field of drug design .
- A binding interaction between a small molecule ligand and an enzyme protein may result in activation or inhibition of the enzyme. If the protein is a receptor, ligand binding may result in agonism or antagonism.
- Most drugs are small organic molecules, and docking may be applied to:
- i.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** .
- ii.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**.
- iii.Bioremediation :– Protein ligand docking can also be used to **predict pollutants that can be degraded by enzymes**.

Docking glossary

- **Receptor or host or lock**
- The "receiving" molecule, most commonly a protein or other biopolymer.
- **Ligand or guest or key**
- The complementary partner molecule which binds to the receptor. Ligands are most often small molecules but could also be another biopolymer.
- **Docking** الالتحام الجزيئي
- Computational simulation محاكاة of a candidate **ligand binding to a receptor.**
- **Binding mode**
- The orientation of the ligand relative to the receptor as well as the conformation of the ligand and receptor when bound to each other

- **Pose**
- A candidate binding mode. اشكال الترابط
- **Scoring**
- The process of **evaluating** a particular pose by counting the number of favorable intermolecular interactions such as hydrogen bonds and hydrophobic contacts.
- **Ranking**
- The process of classifying which ligands are most likely to interact favorably to a particular receptor based on the predicted free-energy of binding.
- **Docking assessment (DA)** Procedure
  تقييم الالتحام الجزيئي
  to quantify the predictive capability of a
- docking protocol.