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Chapter

# Introductory Chapter: Molecular Docking and Molecular Dynamics Techniques to Achieve Rational Drug Design

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Molecular docking and molecular mechanics simulations are important approaches to achieve a rational drug design or a chemical process modeling. It goes to deep molecular insights as structures and mechanisms helping researchers to characterize various conformations and molecular interactions in terms of energy and binding affinities, giving the possibility to search among dozens, hundreds of real or imaginary compounds, the most suitable for a precise, well-defined purpose. The biochemical purpose derives from the chosen macromolecular target, protein, or enzyme. Starting from a known substance with a known mechanism of action and biological activity, we can imagine other related compounds as drug candidates with better efficacy and fewer side effects. These in silico methods help us to identify and select among large compound libraries the most suitable therapeutic agent before even starting its chemical synthesis. That can be called virtual chemistry before reaction tube. It is very convenient, reducing the consumption of chemical reagents, preclinical, clinical trials, and time.

The purpose of this book project is to clearly explain the principles of molecular docking and molecular dynamics, with examples of algorithms and procedures proposed by different software programs for small molecule-protein or protein-protein complexes of medical or materials sciences interest.

Molecular docking studies provide us an overview of type of interactions occurring in ligand (small molecule)-protein or protein-protein complexes and rank the candidate poses by their affinity scoring function.

The concept of molecular recognition of ligand at the protein/enzyme active site, classically named "lock and key," has been extended at "hand and glove," considering the protein flexibility and reciprocal adaptability between the receptor and ligand [1].

Molecular dynamics simulations explore extrinsic surface and bulk properties of various forms of pharmaceutically active molecules to aid the selection of a successful candidate. It involves accurate evaluation of binding pathways, kinetics, and thermodynamics of ligands in different solvents.

Both these computer-aided drug design (CADD) methods lead to ligand identification and optimization, favoring rapid development of pharmaceutical compounds.

## 1. Molecular docking approaches and challenges

Different software algorithms use various approaches such as rigid protein or flexible protein, rigid receptor, soft receptor, flexible side chains, induced fit, or multiple structure algorithms [2].

The steps for conducting molecular docking studies are:

- Ligand preparation consists in generation, optimization, and analysis of its 3D structure. Among multiple conformers, the most stable, as lowest energy, can be used for docking simulations. An aspect to be considered is the fact that in physiological media, the ligand appears ionized. The effect of solvation due to the surrounded water molecules must be solved. The presence of active site water molecules influences the docking pose of the ligand and makes questionable the accuracy of the method [2]. Three-dimensional structures of small ligand molecules are available in virtual databases such as Cambridge Structural Database (CSD), Available Chemical Directory (ACD), MDL Drug Data Report (MDDR), or National Cancer Institute Database (NCI).

- Receptor preparation. The use of a rigid target protein will conduct a single conformation of the receptor. Flexible protein involves different conformations to bind the ligand. Often the site water molecules are removed before performing a docking simulation.

Protein Data Bank (https://www.rcsb.org/) provides various solved 3D structures of protein, protein fragments, nucleic acids, and protein-ligand complexes. The assemblies are characterized by X-ray crystallography, nuclear magnetic resonance (NMR), infrared spectroscopy, and or/electron density and are available as PDB files format. This online tool allows us to explore and analyze the structures or to compare any protein in the PDB archive, including support for rigid-body and flexible alignments.

Also, for simulation the optimized ligand structure must be imported and used in the docking software as *.pdb or compatible file.

- Identify the binding site: This step plays a key role in structure-based drug design. It can be determined experimentally or computationally. Some software are created to identifying and analyzing binding sites and predicting receptor druggability [3].

- Dock ligands: Different algorithms are used, fragment-based algorithms, genetic algorithm, Monte Carlo algorithms, and molecular dynamics protocols.

- Docking validation and results analysis: For validation, the software must reproduce the real binding site that was founded and characterized by X-ray crystallography or NMR techniques. To dock ligand similar derivative structures, the same binding site is used, and different conformation dues to rotations around flexible bond are performed for each new structure. The results conduct to predicting preferential binding orientation and the strength of binding affinity, interactions (type, strength, bond length); the conformations are ranked by mean of scoring functions [or root-mean-score deviation (RMSD)]. Furthermore, the stability of receptor-ligand complexes is assessed, and ligand/pharmaceutical small compound druggability is evaluated.

Pharmaceutical applications

- Exploring DNA binding properties of some malignant tumor chemotherapeutic agents [4–7] (to identify the DNA binding site, to predict interactions between potential therapeutic compound and DNA, to assess the stability of DNA-complexes, and to establish correlations between structure and cytotoxicity).

- In silico modeling as attempts to find new efficient therapeutic compounds against pathogens, causative agents of infectious disorders, antitubercular drugs [8–11], antibiotics agents against Escherichia coli [12–14], Pseudomonas aeruginosa [14–16], Staphylococcus aureus [13, 14, 16–19], Bacillus cereus [13, 16], Klebsiella pneumoniae [13], or others.

The computational findings must be completed and confirmed by biological assays to determine in vitro activity, by measuring minimum inhibitory concentration against tested microorganisms.

Molecular dynamics (MD) simulations are useful approaches when analysis of thermodynamic and kinetic properties of ligand-binding events is required to consider. Besides, MD has become effective tools used to modeling chemical processes and to evaluating different parameters of materials in different media (water or gas): velocity direction of removal of material electrical discharge machining (EDM) [20], indentation [21], wear and friction [22], nano-cutting [23], and laser machining [24].

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