Molecular Modeling and virtual screening techniques

Molecular Modeling



Definition:

- Molecular modeling is a method used in computer-aided drug design (CADD) to represent and predict the structure, shape, behavior, and interactions of molecules, especially drugs and biological targets (like proteins or enzymes), using computer software.

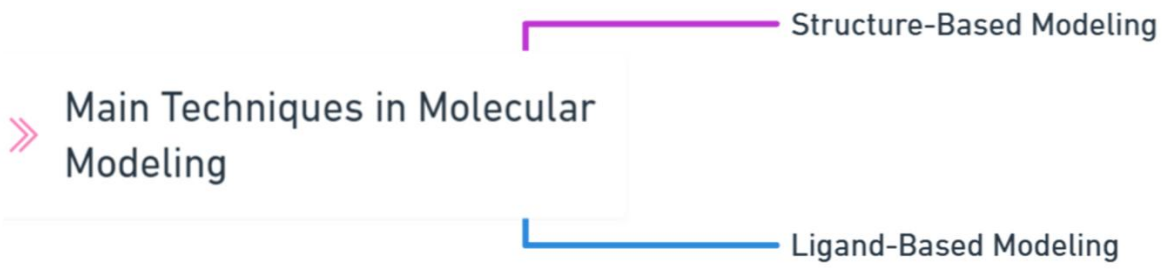
Purpose:

- The goal of molecular modeling is to understand how a drug molecule interacts with a biological target so that scientists can design better and more effective drugs.

Basic Idea:

- Every molecule, including drugs and proteins, is made up of atoms.
- These atoms are arranged in 3D space.
- Molecular modeling tries to create a 3D model of these molecules and then uses physics and chemistry rules to study how they behave.

Main Techniques in Molecular Modeling:



1. **Structure-Based Modeling:**
   - This method needs the 3D structure of the biological target (like a protein).
   - Used to design drugs that can bind well to the target.
   - Examples: Molecular docking, molecular dynamics.
2. **Ligand-Based Modeling:**
   - This method is used when the 3D structure of the target is **not known**.
   - It depends on the knowledge of other molecules (ligands) that bind to the target.
   - From these known ligands, common chemical features are extracted to design new drug-like molecules.

Tools Used:

- Software like PyMOL, AutoDock, Schrödinger, MOE, Discovery Studio.
- These tools help scientists visualize the molecule, rotate it, zoom in on specific parts, and even simulate interactions.

Applications:

- Designing new drugs.
- Understanding how existing drugs work.
- Predicting side effects by studying binding to unintended targets.
- Finding which part of a molecule is important for activity.

Energy Calculations:

- Molecular modeling calculates the energy of a molecule.
- Molecules with lower energy are more stable.
- Energy minimization techniques help find the most stable shape (conformation) of a molecule.

Types of Models:

1. **Wireframe model** – shows atoms connected by lines (bonds).
2. **Ball and stick model** – shows atoms as balls and bonds as sticks.
3. **Space-filling model** – shows the actual volume occupied by atoms.
4. **Surface model** – shows the surface where interactions happen.

Virtual Screening Techniques

What is Virtual Screening?

- Virtual screening is a computational technique used to search large libraries of molecules to find potential drug candidates.
- It mimics the process of real laboratory screening but on a computer.

Why is it used?

- Screening millions of compounds in a wet lab is expensive and time-consuming.
- Virtual screening helps reduce the number of compounds that need to be tested experimentally.

Types of Virtual Screening:



1. Structure-Based Virtual Screening (SBVS):

- Used when the 3D structure of the target protein is known.
- The software simulates how each molecule from a library fits into the protein's active site (this process is called *docking*).
- The molecules are ranked based on how well they fit (called *binding affinity*).

2. Ligand-Based Virtual Screening (LBVS):

- Used when the structure of the protein is not known.
- It relies on known active compounds to search for other molecules with similar shapes or chemical properties.

Workflow of Virtual Screening:

1. **Target Identification:** Understand what part of the body the drug will act on.
2. **Selection of compound library**: Choose a large set of potential drug molecules.
3. **Preparation of molecules:** Optimize structures of both target and compounds.
4. **Screening process:** Use software to dock or compare molecules.
5. **Scoring and ranking:** Evaluate how well each molecule fits or behaves.
6. **Selection of hits:** Choose top molecules for further testing.

Common Tools and Databases:

- **ZINC:** Database of commercially available compounds.
- **PubChem:** Database of chemical molecules.
- **AutoDock**, **GOLD**, **MOE:** Software for docking and scoring.
- **ROCS**, **Schrodinger Phase:** Used in ligand-based screening.

Advantages of Virtual Screening:

- Saves time and money
- Reduces the number of compounds to test
- Can identify novel (new) drug-like molecules

Drug-likeness Screening

What is Drug-likeness?

- Drug-likeness is a concept used to decide whether a chemical compound (a potential drug) has properties that would make it a good **oral** drug in humans.
- It's like a checklist to see if a molecule is "drug-like."
- It helps scientists decide early whether a compound is worth testing further.

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