

## Course 6: Introduction to Modeling

### 1. Introduction

An introduction to molecular modeling involves using computer tools and techniques to study and represent the three-dimensional structure of molecules. This approach allows researchers and scientists to visualize, analyze, and predict molecular behavior, which is essential in fields such as chemistry, biochemistry, pharmacology, and pharmaceutical chemistry.

### 2. Objective of Molecular Modeling:

Molecular modeling aims to understand the structure and properties of molecules at an atomic level. This can include the study of molecular conformation, intermolecular interactions, chemical reactivity, etc.

- **Why molecular modeling?**

Molecular modeling is a tool for researchers concerned with the structure and reactivity of molecules. A molecule is accurately described by its geometry and thermodynamic properties. Visualization must capture all of these characteristics. The essential challenge is to represent a molecule on the screen as closely as possible to its "real" state. The use of computers has enabled the development of a powerful tool: molecular modeling.

**Modeling:** Transformation of the largest possible set of experimental observations into the smallest possible set of parameters.

**Model:** The set of parameters and mathematical functions that allow for a simplified representation of reality. The ideal model (M) would be: **Accurate, General, and Real.**

*Note : " Molecular modeling: Development and application of a mathematical model that allows molecules to be represented at the microscopic scale."*

### 3. Principle of molecular modeling:

Modeling a molecule involves determining, through calculations, the position of its constituent atoms in space and calculating the energy of the resulting structure. A representation "as close as possible to reality" will correspond to a structure with the lowest energy.

- **Calculations**

Users of molecular modeling fall into two groups:

- Those who perform relatively precise calculations on small molecules (approximately 100 atoms)
- Those who seek to determine the structure of macromolecules using more approximate methods.

### 4. Molecular modeling calculation methods

Molecular modeling aims to predict the structure and reactivity of molecules or systems of molecules. Molecular modeling methods can be grouped into three categories:

- Quantum methods.
- Molecular mechanics.
- Molecular dynamics.

#### 4.1. Molecular Mechanics

This technique calculates the energy of atoms (rather than electrons) using classical approximations. It is based on classical approximations where atoms are treated as point particles connected by springs. Newton's classical equations of motion are used to simulate the behavior of molecules.

- **Advantage :**

1. Large molecules (macromolecules, proteins, ...)
2. Calculation of vibration modes

### 3. Thermodynamic properties

### 4. Molecular Dynamics, Docking

➤ Disadvantages:

**1. Treatment of non-covalent interactions:** Non-covalent interactions, such as hydrogen bonds, can be difficult to model accurately; impossible to break bonds therefore no reactivity.

**2. Dependence on initial conditions:** The results of the simulations may depend on the initial conditions, which may make some predictions less reliable.

#### 4.2. Molecular Dynamics

This technique aims to calculate the movements of molecules over time, most often using molecular mechanics energies. It therefore allows the calculation of kinetic energy by simulating the movement of atoms and molecules over time, numerically solving the equations of motion.

#### 4.3. Quantum methods

These methods provide a more accurate description of the electronic properties of molecular systems compared to classical methods such as molecular mechanics. They are based on solving the Schrödinger equation and calculating molecular orbitals (MOs). Their complexity increases rapidly with the number of electrons. Here are some of the main quantum methods used in molecular modeling:

1. **initio calculations :** These calculations aim to solve the Schrödinger equations without making significant approximations. They provide an exact quantum description of electronic systems, but they are generally more computationally expensive. Methods such as the Hartree- Fock method and the correlation - consistent wavefunction method are examples of ab initio calculations .
2. **Density Functional Theory (DFT):** DFT is an approach that uses electron density rather than the wave function to describe the electronic state of a system. It is less expensive than ab initio calculations and offers a good compromise between accuracy and efficiency.

3. **Semi-empirical methods:** These methods combine elements of ab initio calculations with empirically adjusted parameters to reduce computational costs. Examples include MNDO ( Modified MNDO) methods. Neglect of Differential Overlap ) and PM3 ( Parametric Method 3).
4. **Perturbation theory calculations:** Quantum perturbation theory is used to improve results obtained by simpler methods by introducing systematic corrections.
5. **Full electronic configuration (FCE) calculations:** These methods consider all possible electronic configurations and are particularly important for describing excited states or chemical reactions.
6. **Multireference calculations :** These methods, such as multireference complete configuration theory (MR-CI) and multireference complete correlated wavefunction method (MR-CC), allow for a more precise consideration of electronic correlations.
7. **renormalization group theory (RGF):** These methods include renormalization group theory (RGF) and allow for the treatment of strong interactions in electronic systems.
8. **Relativistic quantum chemistry calculations:** For systems where relativistic effects are important, especially heavy elements, relativistic quantum chemistry methods are used, such as the self-consistent general field relativity theory (SAC-CI) and the relativistic generic component theory (GCR).

## 5. Molecular Modeling Software

Molecular modeling software generally includes the following modules:

- 1 - Construction, visualization and manipulation of molecules.
- 2 - Calculations
- 3 - Backup of structures and file management
- 4 - Study of molecular properties.

Numerous molecular modeling software packages are available, each offering specific features for simulating and analyzing molecular systems. Here are some popular molecular modeling software packages:

1. **Gaussian** : Gaussian is a widely used software for ab initio and DFT calculations . It is primarily used for predicting molecular structures, simulating electronic spectra, and other molecular properties.
2. **GAMESS (General Atomic and Molecular Electronic Structure System):** GAMESS is a suite of quantum chemistry programs that offers various electronic calculation methods, including ab initio calculations , DFT, and perturbation calculations.
3. **NWChem** : NWChem is an open-source quantum chemistry package that offers a variety of computational methods, including ab initio calculations , DFT, and molecular dynamics simulations.
4. **AMBER ( Assisted Model Building with Energy Refinement ):** AMBER is a suite of programs for molecular dynamics simulation, force field modeling, and molecular structure analysis. It is widely used in biomolecular simulation.
5. **CHARMM ( Chemistry) at Harvard Macromolecular Mechanics ):** CHARMM is a molecular modeling software used for molecular dynamics simulation, force field modeling, and the study of biomolecule structures.
6. **Schrodinger Suite:** The Schrodinger suite offers a range of software for molecular modeling, including tools for molecular docking , drug design, and molecular dynamics simulation.
7. **AutoDock** : AutoDock is a molecular docking software widely used for predicting the structures of molecular complexes.
8. **VMD (Visual Molecular Dynamics):** VMD is a molecular visualization software that is often used in conjunction with molecular dynamics simulation programs to analyze and visualize results.
9. **Open Babel:** Open Babel is an open-source chemical library that offers tools to convert between different file formats of molecular structures.
10. **Avogadro:** Avogadro is an open-source molecular modeling software that allows 3D visualization, editing of molecular structures, and creation of quantum chemistry calculations.

These software programs serve different purposes depending on the specific needs of the research or application. Some are better suited for ab initio calculations , others for molecular dynamics simulation, molecular docking , or molecular visualization. The choice of software often depends on the nature of the research and the user's preferences.

## 6. Applications of Molecular Modeling:

- **Drug Design:** Predicting drug-target interaction and optimizing drug structure.
- **Structural Biology:** Study of the three-dimensional structure of biological macromolecules.
- **Organic Chemistry:** Prediction of chemical reactions and study of reaction mechanisms.

## 7. Limitations of Molecular Modeling:

- a. Models are approximations based on simplifications.
- b. Accuracy depends on the methods used and the force parameters chosen.
- c. Modeling cannot completely replace real-world experiences.

Molecular modeling is a powerful technique that complements laboratory experiments, offering unique perspectives for understanding and predicting the behavior of molecules in various scientific contexts.