Molecular Modeling: Necessary tool for drug designing

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Abstract

Molecular modeling covers a wide range of molecular graphics and computational chemistry techniques used to build, display, manipulate, simulate, and analyze molecular structures, and to calculate properties of these structures. Molecular modeling is used in a number of different research areas, and therefore the term does not have a rigid definition. To a chemical physicist, molecular modeling might imply performing a high quality quantum mechanical calculation using a supercomputer on a structure with 4 or 5 atoms; to an organic chemist, molecular modeling might mean displaying and modifying a candidate drug molecule on a desktop computer. The criterion for a successful modeling experiment should not be how accurately the calculations are performed, but whether they are useful in rationalizing the behavior of the molecule, or in enhancing the creativity of the chemist in the design of novel compounds.

Key Words : *Molecular modelling, computational chemistry techniques, applications*

Introduction

Molecular modeling is the general term used to describe the use of computers to construct molecules and perform a variety of calculations on these molecules in order to predict their chemical characteristics and behavior. The term molecular modeling is often used synonymously with the term computational chemistry.[1-5]Molecular modeling allows the user to determine three fundamental items of interest of a molecule or system of molecules[6-7]:

• the structure, or geometry of the molecule (number and type of atoms, bonds, bond lengths, angles, and dihedral angles);

• the property or properties of a molecule or system of molecules (basic characteristics of the molecule, such as its molecular energy, enthalpy, and vibrational frequencies)

• the activity, or reactivity, of a molecule or system of molecule (how the molecule behaves in the presence of other molecules, such as its nucleophilicity, electrophilicity, and electrostatic potentials).

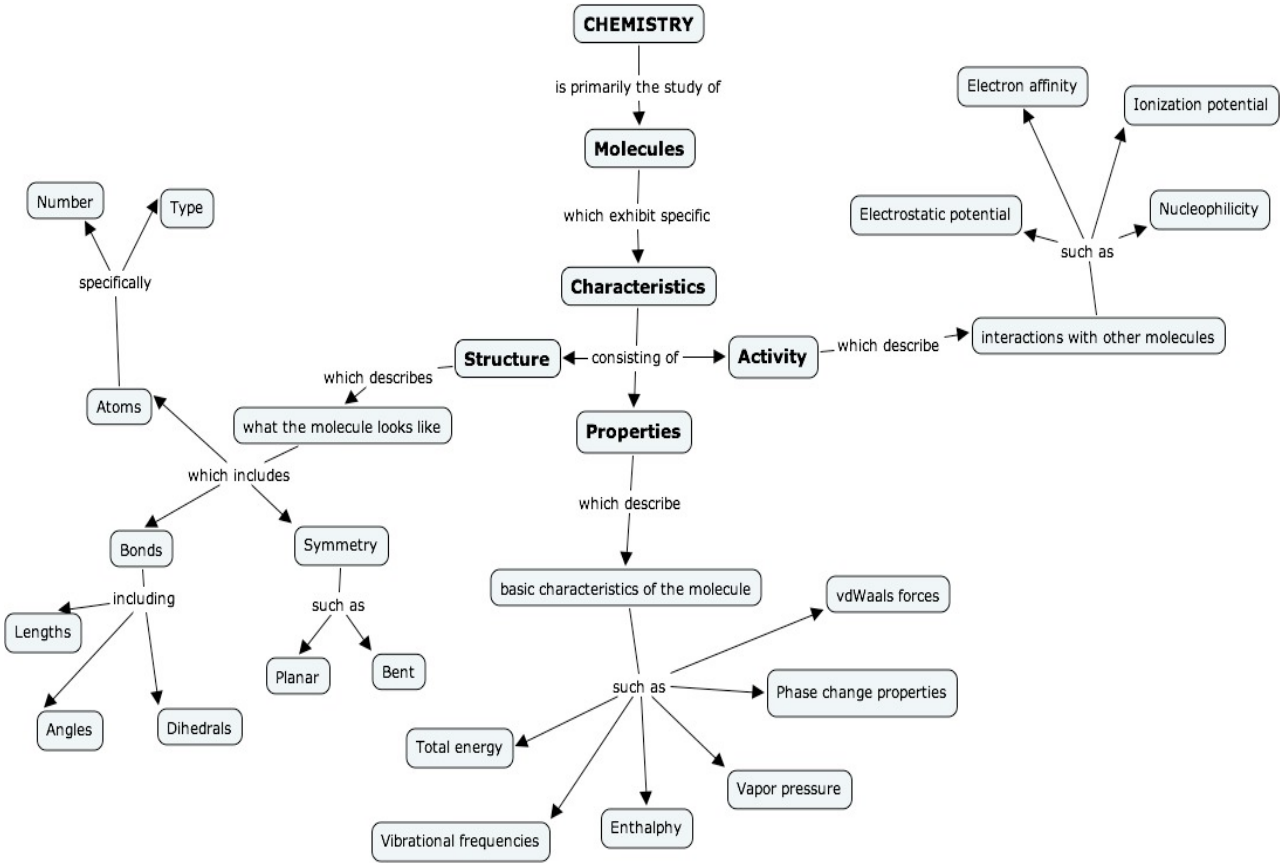
In using molecular modeling techniques and tools, modelers can calculate structure, properties, and/or activities [10-14].

There are four different molecular modeling methods: one that uses classical physics (i.e. mechanics) to study the behavior and interactions of molecules, and three electronic/quantum mechanical areas [18-21].

1. Molecular mechanics: this method uses traditional classical mechanics. In essence, atoms are considered to be spheres that are connected to other atoms by a spring. Various properties of the molecule can be calculated by measuring the motion of the atoms and the changing energies of the springs [25].

2. Ab initio quantum mechanics: In ab initio methods, Schrödinger mathematics are used to calculate a wide variety of quantum chemical properties. The main calculation is the wave

function determination. Based on the results of calculating the wave function, other chemistry properties and activities can be determined. In this method, 100% of the final determination is done mathematically[26].



3. Semi-empirical quantum methods: in semi-empirical methods, a portion of the calculation comes from experimental data, and the rest comes from mathematics. The major advantage of the semi-empirical method is that it is faster and able to perform calculations on larger molecules[27].

4. Density Functional Theory (DFT): DFT is the newest computational method, and is increasing in popularity among computational chemists. Rather than calculate molecular properties based on the determination of the wave function, the DFT method determines

properties from calculating the electron density. It uses functional (a function of a function) to determine the electron density, and by extension, the quantum properties of a molecule[28].

1. The following tools are required for modeling of a drug using computers.

a) Hardware: Various classes of computers are required for molecular modeling. For chemical information systems the choice of a computer is generally larger, and many packages run on VAX, IBM, or PRIME machines. Currently, the molecular modeling community is using equipment from manufacturers such as Digital, IBM, Sun, Hewlett-Packard and Silicon Graphics running with the UNIX operating system.

b) Software components: A variety of commercial packages are available for PC-based systems as well as supercomputer based systems. Currently, some of the molecular modeling software that are available for commercial and academic molecular modelling functions are given in Table 1.

2. Molecular Modeling Strategies[29]

Currently, two major modeling strategies are used for the conception of new drugs. They are:

a) Direct drug design: In the direct approach, the three-dimensional features of the known receptor site are determined from X-ray crystallography to design a lead molecule. In direct design, the receptor site geometry is known; the problem is to find a molecule that satisfies some geometric constraints and is also a good chemical match. After finding good candidates according to these criteria, a docking step with energy minimization can be used to predict binding strength.

b) Indirect drug design: The indirect drug design approach involves comparative analysis of structural features of known active and inactive molecules that are complementary with a hypothetical receptor site. If the site geometry is not known, asIn the field of molecular

modeling, docking[31] is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex.

Table- 1. Molecular modeling software [30]

Software Program	Function
1. MOE	G,S,M,CA,MM,MD,MO
2. ACD/Chemsketch	- do –
3. MDLS	- do –
4. AMBER	M,MM,MD,FE
5. Chem – X	G,S,M,CA,MM,STAT
6. Disgeo	DG
7. Disman	DG
8. ChemSw	-do-
9. Cerices 2	-do-
10. Catalyst	-do-
11. Embed	DG
12. Grid	PR
13. Gromos	M,MM,MD,FE
14. Macromodel	-do-
15. IDAS	GM
16.MOGLI	G,S,M
17.Tripos G,S,M,CA,MM,DM,STA,MO	
18. VMD	-do-
19. G & W	-do-
20. Cosmoplayer	-do-
G = Graphics and manipulation; S = Small molecule structure building; M = Molecular structure building; CA = conformational analysis facilities; MM = Molecular Mechanics; Stat = Statistical tool; PR = Probe interaction energies; FE = Free energy perturbation methods; MD= Molecular dynamics.	

Docking is frequently used to predict the binding orientation of small moleculedrug candidates to their protein targets in order to in turn predict the affinity and activity of the small molecule. Hence docking plays an important role in the rational design of drugs. 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".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, or less often, NMR spectroscopy. This protein structure and a database of potential ligands serve as inputs to a docking program.

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.

Application of docking

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. Docking is most commonly used in the field of drug design — most drugs are small organic molecules, and docking may be applied to:

- 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 (see virtual screening).
- 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.
- Bioremediation – Protein ligand docking can also be used to predict pollutants that can be degraded by enzymes

Conclusion:

The use of molecular modeling/computational chemistry is not restricted to researchers and students who are solely interested in studying traditional chemistry topics, such as molecular structure,kinetics, reaction mechanisms, and thermodynamics. To a large extent, molecular modeling is becoming an increasingly important tool to researchers in other scientific disciplines, such as materials science, the environmental sciences, life sciences, and medicine.

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