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# Molecular Modeling: A Dominant Technique for Drug Design and Molecular Docking

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***ABSTRACT***

*Molecular modeling permits us teach chemistry better by providing best tools for scrutinizing, understanding, explaining and discovering phenomena. The computational chemistry programmes agree to scientists to produce and present molecular data. Interaction of macromolecular receptors and small drug molecules is a necessary step in regulatory mechanisms, pharmacological actions of drugs, toxic side effects, etc. The process of docking a ligand to a binding site tries to copycat the natural course of interaction of the ligand and its receptor via a lowest energy pathway.*

**Keywords:** computational chemistry, drug design, molecular modeling, molecular docking, molecular visualization.

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## INTRODUCTION

Molecular modeling has become a valuable and essential tool to medicinal chemists in the drug design process. Molecular modeling describes the generation, manipulation or representation of three-dimensional structures of molecules and associated physico-chemical properties. It involves a range of computerized techniques based on theoretical chemistry methods and experimental data to predict molecular and biological properties. Depending on the context and the rigor, the subject is often referred to as 'molecular graphics', 'molecular visualizations', 'computational chemistry', or 'computational quantum chemistry'. The molecular modeling techniques are derived from the concepts of molecular orbitals of Huckel, Mullikan and 'classical mechanical programs' of Westheimer, Wiberg and Boyd. Molecular modelling allows scientists to use computers to visualize molecules means representing molecular structures numerically and simulating their behavior with the equations of quantum and classical physics, to discover new lead compounds for drugs or to refine existing drugs in silico. The goal is to develop a sufficient accurate model of the system so that physical experiment may not be necessary. The term “Molecular modeling” expanded over the last decades from a tool to visualize three-dimensional structures and to simulate, predict and analyze the properties and the behavior of the molecules on anatomic level to data mining and platform to organize many compounds and their properties into database and to perform virtual drug screening via 3D data base screening for novel drug compounds. Molecular modeling starts from structure determination. Selection of calculation methods in computational chemistry Starting geometry from standard geometry, X-ray, *etc*. (Figure 1).

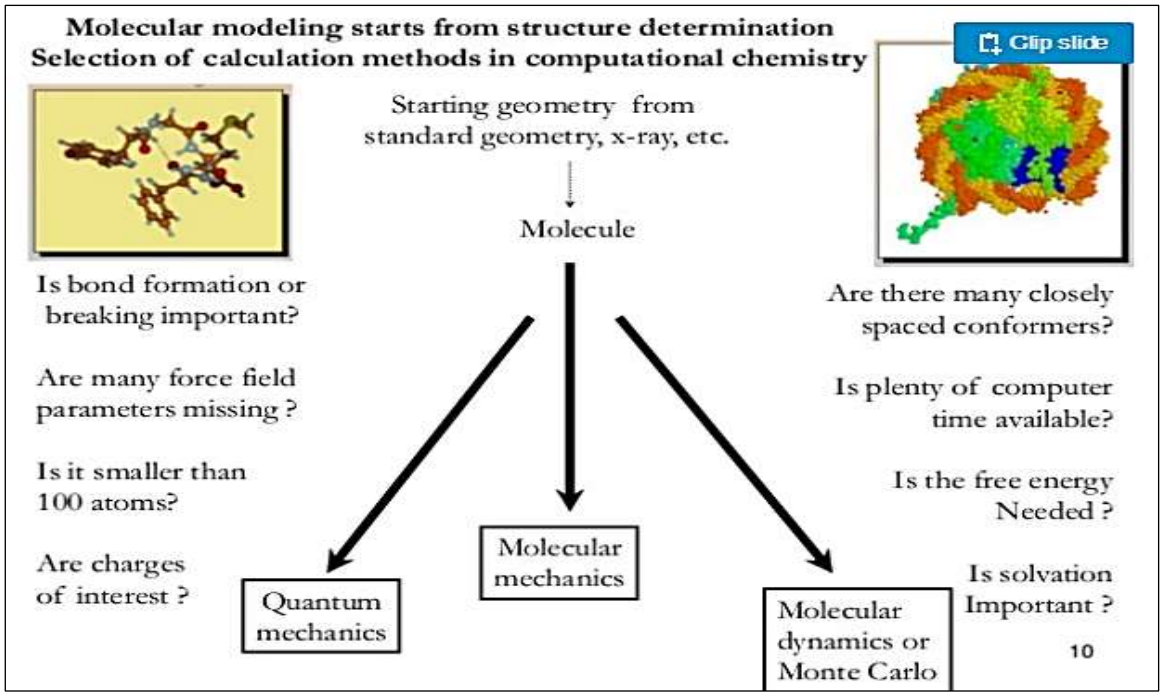


***Fig. 1.*** *Molecular modeling starts from structure determination and selection of calculation methods in computational chemistry.*

**Computational Chemistry Approaches**

- Molecular modelling or more generally computational chemistry is the scientific field of simulation of molecular systems.
- Basically, in the computational chemistry, the free energy of the system can be used to assess many interesting aspects of the system.
- In the drug design, the free energy may be used to assess whether a modification to a drug increases or decrease target binding.
- The energy of the system is a function of the type and number of atoms and their positions.
- Molecular modelling softwares are designed to calculate this efficiently.

**Modeling and Molecular Modeling**

Modeling is a tool for carrying out the work of chemistry. Models are central for understanding of chemistry. Molecular modeling allows us to do and teach chemistry better by providing better tools for examining, understanding, explaining and determining innovative phenomena. Like experimental chemistry, it is a skill-demanding science and must be learnt by doing and not just reading. Molecular modeling is easy to perform with presently available software.

**Molecular Modeling Tools**

The tools of the trade have gradually evolved from physical models and calculators, including the use of programmable calculators, computers as visualization aids, computers running commercially written analysis packages such as Sybyl and most recently integration using internet based tools and work benches based on HTML, Java Script, *etc*. The following tools are required for modeling of a drug using computers

***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.

***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 softwares that are available for commercial and academic molecular modeling are given below.

- 3D molecular graphics
- Interactive model building
- Quantum chemistry for small molecules
- Force field development
- Biomolecular dynamic simulations
- GPU accelerated molecular modeling

The computational chemistry programmes allow scientists to generate and present molecular data including geometries (bond lengths, bond angles, and torsion angles), energies (heat of formation, activation energy, *etc*.) and properties (volumes, surface areas, diffusion, viscosity, *etc*.).

## MOLECULAR MODELING STRATEGIES

Presently, two chief modeling strategies are used for the outset of new drugs. They are:

**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.

**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, as is often the case, the designer must base the design on other ligand molecules that bind well to the site (Figure 2).

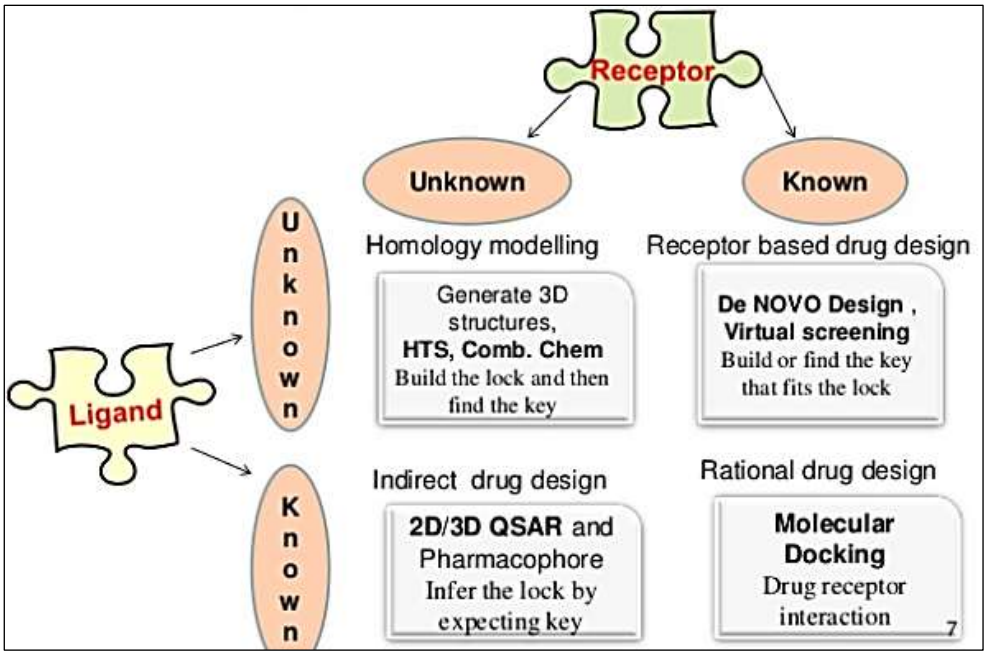


***Fig. 2.*** *Modeling strategies.*

**Molecular Modeling Applications**

The starting point for many computer assisted molecular modeling studies is generally a two-dimensional drawing of a required molecule. These diagrams can range from note-book sketches to electronically stored connection tables in which one defines the types of atoms in the molecule, their hybridization and how they are bonded to each other. Then the two-dimensional structures are transformed into three-dimensional representations to study chemical properties. However, more accurate molecular structures may be available from the Cambridge X-ray crystallographic database (about 50,000 structures). Various applications of computer assisted molecular modeling techniques are reviewed here.

***Generation of Chemical Structures***

- Molecular structures may be generated by a variety of software. The 3D structures of molecules may be created by several common building functions like make-bond, break-bond, fuse rings,
- Delete-atom, add-atom-hydrogens, invest chiral center, *etc*. Computer modeling allows chemists to build dynamic models of compounds which in turn allow them to visualize molecular geometry and demonstrate chemical principles.

***Molecular Structure Visualization***

- The most important area of the molecular modeling concept is visualization of molecular structures and interactions. The molecules are visualized in three dimensions by various representations like connected sticks, ball and stick models, space filling representations and surface displays.

***Generation of Conformations***

The most active area of theoretical research using molecular orbital theory has been in the prediction of the preferred conformation of molecules. Most molecules exist in multiple conformations. The preferred conformation of a molecule is a structural characteristic feature that arises as a response to the force of attraction and repulsion. The shape should be considered primarily in determining the interaction of the molecule with the receptor. The minimization energy is a function of bond angles, bond lengths, torsion angles and non-covalent interactions. By varying these parameters in a systematic way and calculating the total energy as a sum of orbital energies, one can determine a minimum energy structure for example, by using conjugated gradient algorithm working under universal force field.

***Modeling of Drug Receptor Interactions***

The 3D structures of many ligands (drug molecules) that interact with the receptors may be known but the structures of most receptors are not known. The interaction of macromolecular receptors and of small drug molecules is an essential step in many biological processes: regulatory mechanisms, pharmacological actions of drugs, the toxic effect of certain chemicals, etc. The receptor cavity mode is constructed by using programmes like RECEPS and AUTO FIT. The receptor model provides 3D information on the physical and chemical properties of the receptor cavity, size, and shape of the cavity, H-bond expectability and electrostatic potential.

***Docking (Molecular Interactions)***

Modeling the interaction of a drug with its receptor is a complex problem. Many forces are involved in the intermolecular association: hydrophobic, dispersion, or van der Waals, hydrogen bonding, and electrostatic. The major force for binding appears to be hydrophobic interactions, but the specificity of the binding appears to be controlled by hydrogen bonding and electrostatic interactions. Modeling the

intermolecular interactions in a ligand-protein complex is difficult because there are so many degrees of freedom and insufficient knowledge of the effect of solvent on the binding association. The process of docking a ligand to a binding site tries to mimic the natural course of interaction of the ligand and its receptor via a lowest energy pathway. There are simple methods for docking rigid ligands with rigid receptors and flexible ligands with rigid receptors, but general methods of docking conformationally flexible ligands and receptors are problematic.

***Determination of Molecular Properties***

Molecular properties are important indicators of various chemical molecules including pharmaceuticals. Molecular properties are normally categorized as physical, chemical and biological. The three major computational methods used for calculation of properties of molecules are:

*Empirical (Molecular Mechanics)*

Molecular mechanics methods are less complicated, fast, and are able to handle very large systems including enzymes. Molecular mechanics is a formalism which attempts to reproduce molecular geometries, energies and other features by adjusting bond lengths, bond angles and torsion angles to equilibrium values that are dependent on the hybridization of an atom and its bonding scheme. A force field is used to calculate the energy and geometry of a molecule. It is a collection of atom types, parameters and equations.

*Molecular Dynamics*

Molecular dynamics simulations have been used in a variety of bimolecular applications. The technique, when combined with data derived from NMR studies, has been used to derive 3D structures for peptides and small proteins in cases where X-ray crystallography was not practical. Additionally, structural, dynamic and thermodynamic data from molecular dynamics has provided insights into the structure function relationships, binding affinities, mobility and stability of proteins, nucleic acids and other macromolecules that cannot
be obtained from static models.

*Quantum Mechanics*

Quantum mechanics is one of the oldest mathematical formalisms of theoretical chemistry. In its purest form, quantum theory uses well-known physical constants such as velocity of light, values for the masses and charges of nuclear particles and differential equations to directly calculate molecular properties and geometrics. This formalism is referred to as *ab initio* (from first principles) quantum mechanics.

**Lead Generation**

A lead is any chemical compound which shows biological activity. It is not the same as a drug molecule, but its generation is an important step in drug discovery process. It is the process of identifying potential drug compounds or leads that interact with a target with sufficient potency and selectivity. Lead generation is a complex process, which involves two basic steps:

(i) Lead finding: Here, the task is to find a chemical compound, which has a desired biological activity.
(ii) Lead optimization: Lead optimization involves elaborating around the basic lead structure to build in all the desirable properties, such as safety, solubility, etc.

**Determination of Properties of Pharmacophoric Pattern**

A phartnacophoric pattern may be defined as geometrically arranged functionality possessed by a set of active compounds having some mechanism of action. Identification of pharmacophores is especially useful for designing receptor

agonists and antagonists, enzyme inhibitors, *etc*. Molecular modeling approach has been particularly rewarding in dopamine agonists, antagonists and for drugs acting on histamine and morphine receptors.

## CONCLUSIONS

Molecular modeling is an economical, nontoxic and easy to use technique, helps in examining, understanding, elucidating and identification of molecular properties using three-dimensional structures. Subsequently several models yield diverse outcomes, it is required to have a small number of standard models which are relevant to very large systems.

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