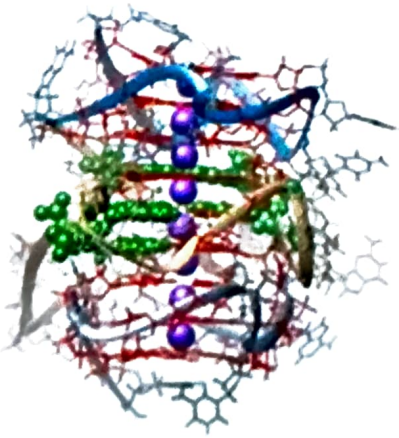
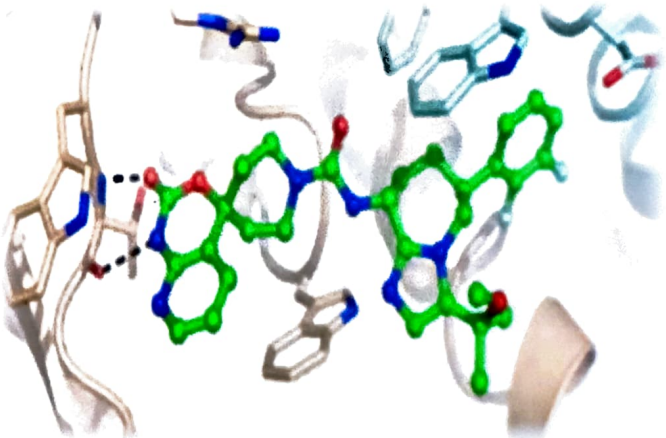
UNIT-V

Molecular modeling

Points to be covered in this topic

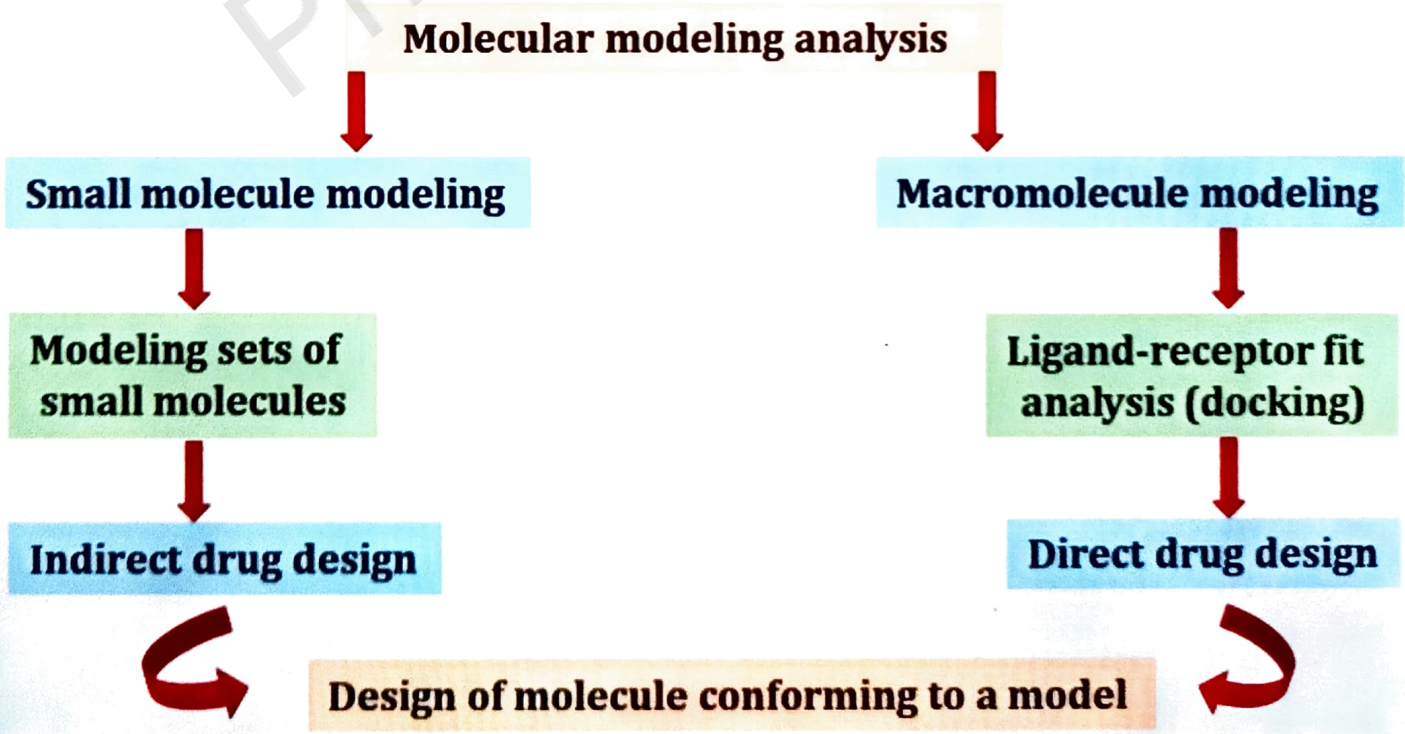
- ❑ INTRODUCTION
- ❑ MOLECULAR MECHANICS
- ❑ QUANTUM MECHANICS
- ❑ ENERGY MINIMIZATION
- ❑ CONFORMATIONAL ANALYSIS
- ❑ GLOBAL CONFORMATIONAL MINIMA DETERMINATION





❑ INTRODUCTION

- Molecular modeling allow scientists to use computers **to visualize molecules means representing molecular structures numerically** and simulating their behaviour with the equations of quantum and classical physics, to discover new lead compounds for drugs or to refine existing drugs in silico.
- The term **"Molecular modeling "**expanded over the last decades from **a tool to visualize three-dimensional structures and to simulate, predict and analyse the properties and the behaviour of the molecules** on an atomic level to data mining and platform to organize many compounds and their properties into database and to perform virtual drug screening via 3D database screening for novel drug compounds.
- There are two major modeling strategies currently used in the conception of new drugs that is **"Direct" and "indirect" design**.
- In the first approach the three- dimensional features of **a known receptor site are directly considered.**
- The design is based on the **comparative analysis of the structural features of known active and inactive molecules** that are interpreted in terms of complementarity with a hypothetical receptor site model.

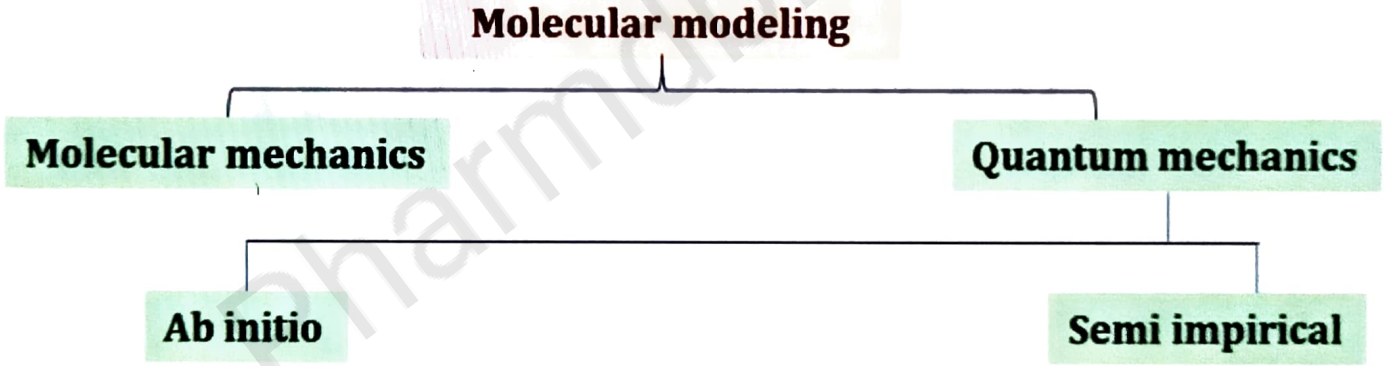


Direct drug design:-

- The three dimensional features of the known receptor site are **determined from X-ray crystallography to design a lead molecule.**
- The receptor site geometry is known, the problem is to find a molecule **that satisfies some geometry constraints** 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:-

- It 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 design on the other ligand molecules that bind well to the site.**



❑ MOLECULAR MECHANICS:-

- Molecular mechanics describes the energy of a molecule in terms of a simple function which accounts for distortion from **"ideal" bond distances and angles, as well as for non bonded, van der Waals and Coulombic interactions.**
- Molecular mechanics is a mathematical 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.

- Molecular mechanics breaks down **pair wise interaction into Bonded interaction** (internal coordination) **i.e. Atoms** that are connected via one to three bonds and **Non bonded interaction i.e. Electrostatic and Van der waals component.**
- $E_{Total} = E_{Bonded} + E_{Nonbonded}$

Bonded interactions

- Used for better approximate the **interaction of the adjacent atoms.**
- Calculations in the molecular mechanics is **similar to the Newtonians law of classical mechanics and geometry** as a function of steric energy. it will calculate
- **f=kx, Hooke's law is applied here**
- **F = force on the spring needed to stretch an ideal spring is proportional to its elongation x**, and where **k is the force constant or spring constant of the spring.**
- $E_{Bonded} = E_{Bond} + E_{Angle} + E_{Dihedral}$

Non bonded interaction

- Nearly applied to all pairs of atoms
- The nonbonded interaction terms usually include **electrostatic interactions and van der waals interaction**, which are expressed as coloumbic interaction as well as Lennard-Jones type potentials, respectively.
- $E_{nonbounded} = E_{electrostatic} + E_{vander\ waals}$

Force Fields

- A force field refers to the functional form and parameter sets **used to describe the potential energy of a system of particles.**
- The molecular mechanics energy expression consists of a simple algebraic equation for the energy of the compound.
- A set of the equations with their associated constants which are the energy expression is **called a force field.**
- Such equations describes the various aspects of the equation like **stretching, bending, torsions, electronic interactions van der waals forces and hydrogen bonding.**

➢ Importance of Force field:

- Analysis of the energy contributions **at the level of individual** or classes of interactions.
- Energy expression is the equation **that describes the potential energy surface** of a particular model as a function of its atomic coordinates.

➢ Applications

- **To Calculate the Geometries and Energies**
- **Computing Enthalpies of Bond Formation or Breaking**
- **To Monitor Reaction Path**
- **To Calculate Frequencies**

❑ QUANTUM MECHANICS:-

- Quantum Mechanics defines the **behaviour of nuclei and electrons and it also explains the molecular interactions** in terms of distribution and motion.
- It is necessary to describe **the quantized energy levels** and to understand the bonding electronic orbitals of atoms and molecules.
- Quantum methods utilize the principles of particle physics **to examine structure as a function of electron distribution.**
- Geometries and properties **for transition state and excited state** can only be calculated with Quantum mechanics.
- Their use can be extended to the **analysis of molecules** as yet unsynthesized and chemical species which are difficult to isolate.
- It is based on the realisation that electrons and all material particles exhibit wave-like properties.
- Mathematics of wave motions are applied to **electrons, atomic and molecular structure.**
- The basis of these calculations is the **Schrodinger wave equation:**
- $H\Psi = E\Psi$
- Ψ = time dependent wave function, which **defines the state of a system.**

- **E Ψ=** represents the total potential and kinetic energy of all the particles (nuclei and electrons) in the structure.
- **H =** Hamiltonium operator acting on the wave function.

❖ Applications:

- For calculating the values of ionisation **potentials, electron affinities, heats of formation, dipole moments** and other physical properties of atoms and molecules.
- To calculate the **relative probabilities of finding electrons** (the electron density) in a structure.
- This makes it possible to determine the most likely points at which a **structure will react with electrophiles and nucleophiles.**
- To assess the nature of the **binding of a possible drug to a target site.**

❖ Ab initio methods:-

- The term **Ab initio is Latin for "from the beginning"** premises of quantum theory.
- This is an approximate quantum mechanical **calculation for a function or finding an approximate solution to a differential equation.**
- In its purest form, quantum theory uses well known physical constants such as the velocity of light, values for the masses and charges of nuclear particles and differential equations **to directly calculate molecular properties and geometries.**
- This formalism is referred to as **Ab initio (from first principles) quantum mechanics.**

❖ Semi-empirical methods:-

- Semi-empirical quantum methods, represents a middle road **between the mostly qualitative results** available from molecular mechanics and the high computationally demanding quantitative results from Ab initio methods.
- Semi empirical methods use **experimental data to parameterize equations.**

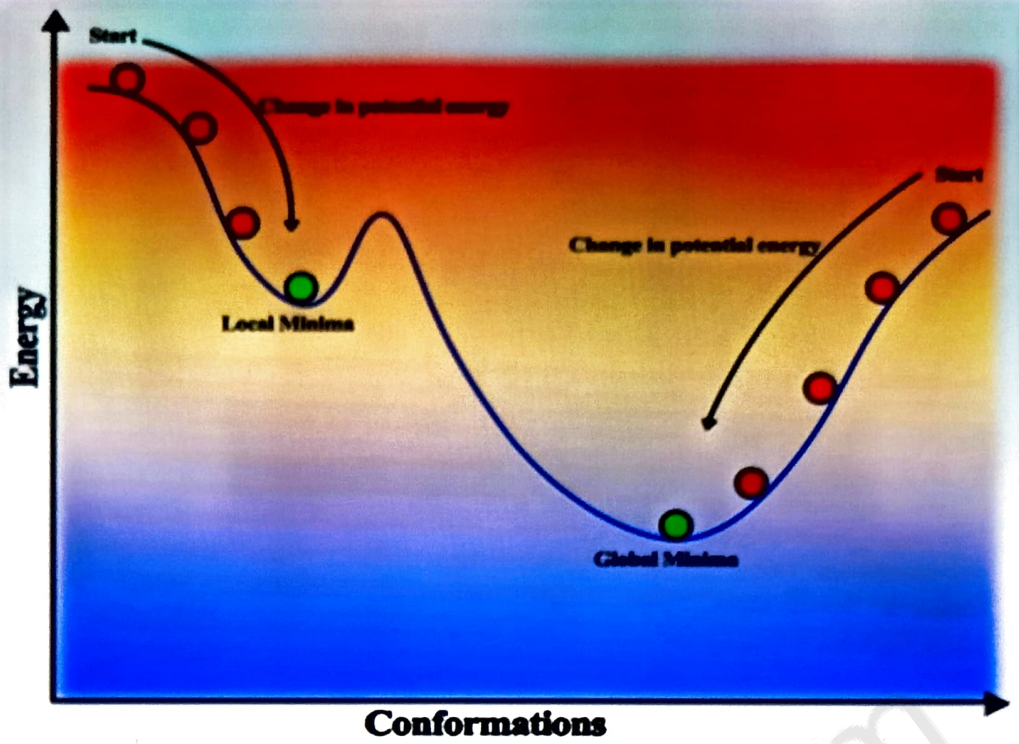
- Like the **Ab initio methods, Hamiltonian and wave function** are used.
- Less accurate than Ab initio methods but also **much faster.**
- Capable of **calculating transition states and excited state**.

✓ **Quantum mechanical methods are suitable for calculating the following:**

- Molecular orbital energies and coefficients
- Heat of formation for specific conformations
- Partial atomic charges calculated **from molecular orbital coefficients**
- Electrostatic potentials
- Dipole moments
- Transition-geometries and energies
- Bond dissociation energies.

❑ ENERGY MINIMIZATION

- Process of converting 2D structure in to 3D structure using quantum mechanics or molecular mechanics or other advanced methods.
- **Optimized (lowest energy) structures** are required to calculate various properties.
- Under typical experimental conditions, **a molecule will be in its lowest energy conformation.**
- To directly compare computed and experimental properties, **our virtual molecules must have the correct geometry.**
- Always optimize the geometry **before calculating some molecular property.**
- Efficient way of **"polishing and shining"** your protein model.
- **Removes atomic overlaps and unnatural strains** in the structure.
- Stabilizes or reinforces **strong hydrogen bonds, breaks weak ones.**
- Brings protein to lowest energy in about 1- 2 minutes CPU time.
- Select an appropriate energy function and derive conformations that yield minimal energies based on the function selected, **Involves local minima and global minima conformations.**



- The energy minimization process is usually carried out by a molecular mechanics program, which calculates the energy of the starting molecule, then varies the **bond length, bond angles and torsion angles** to create a new structure.
- The energy of the new structure is **calculated to see whether it is energetically more stable or not.**

❑ CONFORMATIONAL ANALYSIS

- It involves the **determination or analysis of the spatial arrangement** of the functional group of the respective molecule.
- It is different from molecular dynamics because **it is purely a space move and does not involves an analysis of the movement, velocity, or acceleration of the atoms.**

➢ Following strategies used to study the conformational analysis

- Rigid geometry approximation
- Rigid body rotation
- Conformational clustering
- Conformational restriction strategies

➢ Electronic properties

- Electronic properties are **used to predict the chemical behaviour** of the compound.
- These properties include **molecular orbitals, electron densities, electrostatic potentials and electric fields.**
- Electrostatic potentials can be **determined experimentally by X-rays diffraction or electron diffraction techniques.**

✓ **Various ways of representation of electrostatic potential on computer include:**

1) Contour level in selected planes.
2) Coloured area maps where areas **between successive contour levels in a plane** are coloured as a function of the electrostatic potential.
3) Colour coded dots on the **molecular surface.**
4) **Mapping of electrostatic potential value into solid models.**

➢ Limitations

- Each energy term has **no absolute meaning** only the sum of energy terms could be used.
- Force fields are best used within the class of compounds.
- Parameters in the force field are not transferable to others.
- **Properties related to the electronic structures (electrical conductivity, optical rotation, magnetic)** are not accessible.

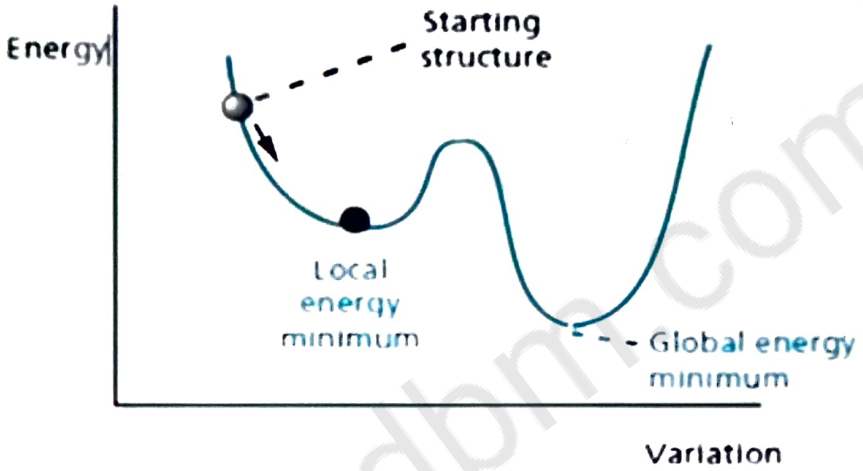
❑ GLOBAL CONFORMATIONAL MINIMA DETERMINATION:-

➢ Local and global energy minima

- If the 3D structure created initially is on the energy curve at the position energy minimization will stop when **it reaches the first stable conformation** it encounters a local energy minimum.

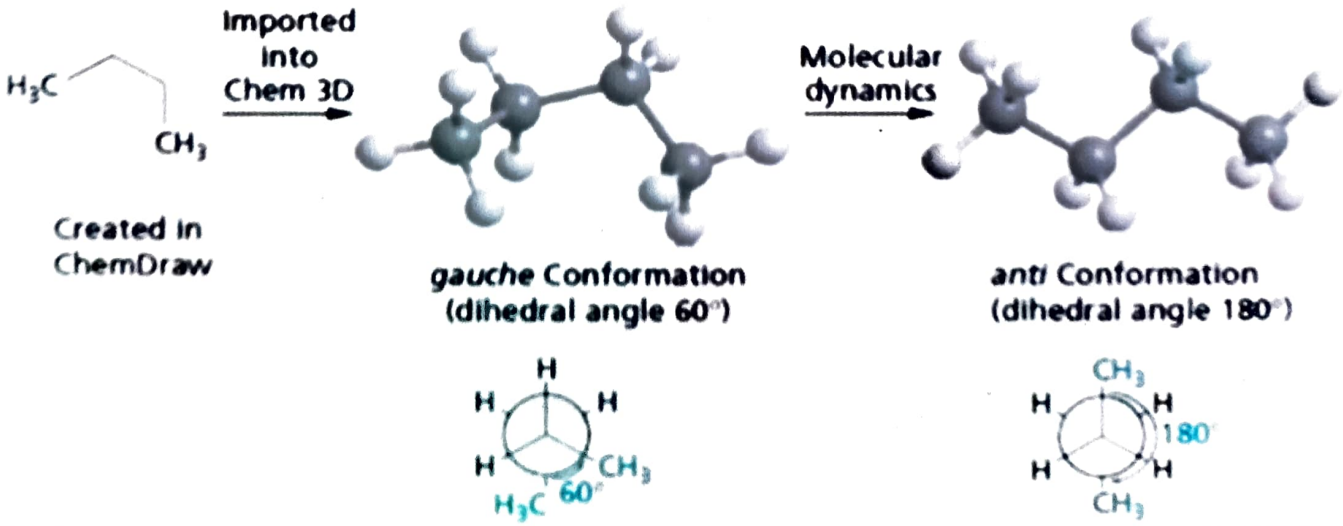
➢ Physical properties

- Theoretical calculation can provide a **number of indices** that may not so the minimization will stop.
- In order to the saddle **to the more stable conformation,** structural variations would have be carried out which increase the strain energy of the structure and these will rejected by the program.
- The minimization program has no way of knowing **there is a more stable conformation** (a global energy minimum) beyond the energy saddle.



➢ Molecular dynamics

- Molecular dynamics is a molecular mechanics program **designed to mimic the movement of atoms** within a molecule.
- The force acting on each atom are then calculated by considering **bond lengths, bond angles, torsinol term and non bonded interaction with surrounding atoms.**



Stepwise bond rotation

- It is to **generate different conformations** by automatically rotating every single bond by a set number of degrees. **For example, 12 different conformations of butane were generated by automatically rotating the central bond in 30° steps.**
- The steric energy of each conformation was calculated and graphed, **revealing that the most stable conformation** was the fully staggered one, whereas the least stable conformation was the eclipsed one.
- In this operation, energy minimization is not carried out on each structure because the aim is to identify both stable and unstable conformations.
- The number of conformations generated will **depend on the number of rotatable bonds present and the set amount of rotation. For example,** a with three rotatable bonds could be analyzed for conformations resulting from **10° increments at each bond to generate 46,656 conformations.** With four rotatable bonds, 30° increments would generate 20,736 conformations.
- **The number of shapes and conformations are calculated by following equation:**

No. of conformation=(360°/angle increment)× No. of rotated bond

Monte Carlo and the Metropolis method

- The Monte Carlo method of conformational analysis introduces a **bias towards stable, conformations** such that more processing time is spent on these process known as importance sampling.
- Different conformations are generated by carrying out **random bond rotations.**
- **This is quite different from molecular dynamics, where atoms are shifted in space. As each conformation is generated, it is energy minimized to give a stable conformation, and its steric energy is calculated and compared with the previous structure.**
- If the **steric energy of the new conformation is lower (more stable),** it is accepted used as the starting structure for the next conformation.

- If the steric energy is higher, **it may be accepted or rejected depending on a probability formula** which takes into account both the energy of the new conformation and the 'temperature' of the system.

The Metropolis method (also known as simulated annealing)

- It is an approach which can be **used to increase finding the global minimum.**
- It involves a number of cycles where the Monte Carlo algorithm is **run at different temperatures.**
- In the first cycle, a high temperature is set (T_1) and **a set of structurally diverse conformations is generated.**
- The most stable conformation is then used as the starting structure for the next run **where the temperature is set at a lower value.**
- This process is repeated several times with the probability equation becoming more **'choosy'** about which structures are accepted.
- This slowly 'focuses' the search on a particular area of conformational space **which can be searched more rigorously.**
- In this way, there is **more chance of finding the global minimum, but there is still no guarantee of success.**