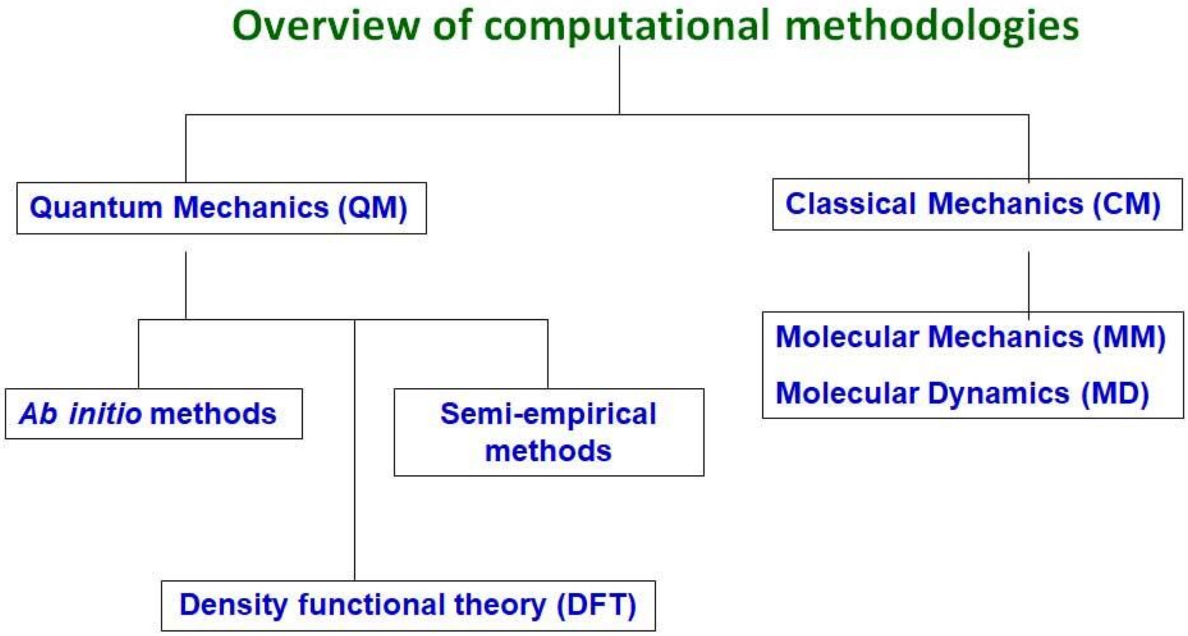
Overview of Computational Methodologies:

Computational chemistry is primarily concerned with the numerical computation of molecular electronic structures and molecular interactions. Computational chemistry is the application of chemical, mathematical and computing skills to the solution of interesting chemical problems. It uses computing algorithms to generate information such as properties of molecules or simulated experimental results. Large number of software packages and codes has made innumerable contributions to the understanding of molecular phenomena that underlie and control chemical processes. Computational chemistry has become one of the significant ways to investigate molecules of interest that are too difficult to be synthesized/handled or too expensive for laboratory experimental investigations. It also helps chemists to make predictions before running the actual experiments so that they can be better prepared for making observations.

The quantum and classical mechanics forms the backbone for most of the computational chemistry tools and programs. Using computational chemistry software one can perform:
Electronic structure predictions
Geometry optimizations or energy minimizations
Conformational analysis and potential energy surfaces (PES)
Frequency calculations
Finding transition structures and reaction pathways
Molecular docking: Protein – Protein and Protein-Ligand interactions
Electron and charge distribution calculations
Calculations of rate constants for chemical reactions: Chemical kinetics
Thermochemistry - heat of reactions, energy of activation, etc.
Calculation of many other molecular and physical and chemical properties

The most important computational methods are as follows:



- ***Ab-initio***, (Latin form of "from the beginning or first principles") a group of methods in which molecular structures can be calculated using the Schrödinger equation. Computations of this type are derived directly from theoretical principles, with no inclusion of experimental data. Mathematical approximations are usually a simple functional form for an approximate solution to a wave equation.
- **Semi-empirical methods** use approximations from empirical (experimental) data to provide the input into the quantum chemical models.
- With **DFT** it is possible to get information about energy, structure and molecular properties in computational cost effective manner. It goes with electron density rather than wave function and the accuracy of this method varies with selected functionals; however, no systematical way of improving the accuracy is available.
- **Molecular mechanics** uses classical physics and empirical or semi-empirical (predetermined) force fields to explain and interpret the behavior of atoms and molecules.
- **Molecular dynamics** is a computer simulation technique that allows one to predict the dynamic properties of a system of interacting particles (atoms, molecules, etc.).

Energy Minimization or Geometry Optimization

- Energy minimization helps attaining chemically favorable conformations of a given molecular structure, the so called local or global minimum.
- The minimization process provides energy for each conformation.
- Structure of a molecule in general is how atoms are arranged in the molecule in a three dimensional space.
- Evidences are available from the spectroscopic measurements of simple diatomic molecule on the observed changes in energy with variations in bond length.
- This variation is represented as a plot of bond length against the observed energy - the potential energy curve.
- Similarly in case of polyatomic molecules, since many atoms are present it might require many coordinates.
- Potential energy surface is a plot of energy with respect to various internal coordinates of a molecule such as bond length, bond angle etc.
- Geometry optimization or energy minimization is a process of obtaining the three dimensional spatial arrangement of atoms in a molecule which has the lowest energy at zero absolute temperature.
- In other words, finding the coordinates of atoms in a molecule with minimum energy is known as geometry optimization.
- The obtained geometry at zero absolute temperature is called as global minimum which has the lowest energy in the potential energy surface.
- The optimization can be performed either by molecular mechanics by employing force field functions or by quantum mechanics with optimized wave functions of Schrödinger equation.
- The function has many variables, and all the commonly used methods assume that at least the first derivative of the function with respect to all variables, the gradient **g**, can be calculated analytically.
- Steepest Descent and Conjugate Gradient are the two commonly used methods for geometry optimization.

Steepest Descent method:

The gradient vector **g** points in the direction where the function increases rapidly. The values of the function can always be lowered by stepping in the opposite direction of the gradient vector **g**. In the *Steepest Descent* (SD) method, a series of function are evaluated in the negative gradient direction, that is along a search direction defined as $\mathbf{d} = -\mathbf{g}$. From the point at which the gradient changes its sign, an approximate minimum can be determined by interpolating between the calculated points. At this interpolated point, a new gradient is calculated and used for the next line search. If the line minimization is carried out sufficiently accurately, it will *always* lower the function value and is therefore *guaranteed* towards approaching a minimum.

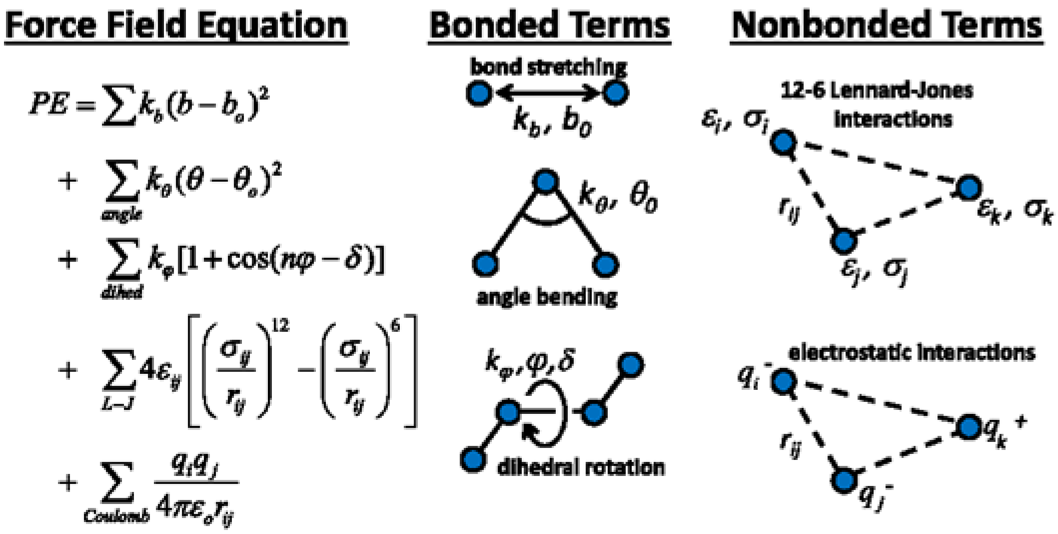
Conjugate gradient method:

The *Conjugate Gradient* (CG) method performs line search not along the current gradient but along a line that is constructed such that it is “conjugate” to the previous search direction(s). If the surface is purely quadratic, the conjugate direction criterion guarantees that each successive minimization will not generate gradient components along any of the previous directions and the minimum is reached after N_{var} steps. The first step is equivalent to a steepest descent step, but subsequent searches are performed along a line formed as a mixture of the current negative gradient and the previous search direction.

Geometry optimization using force field:

The force field is a collection of equations and associated constants designed to reproduce geometry and selected properties of tested structures.

$E= E_{str} + E_{bend} + E_{tor} + E_{vdw} + E_{elc}$



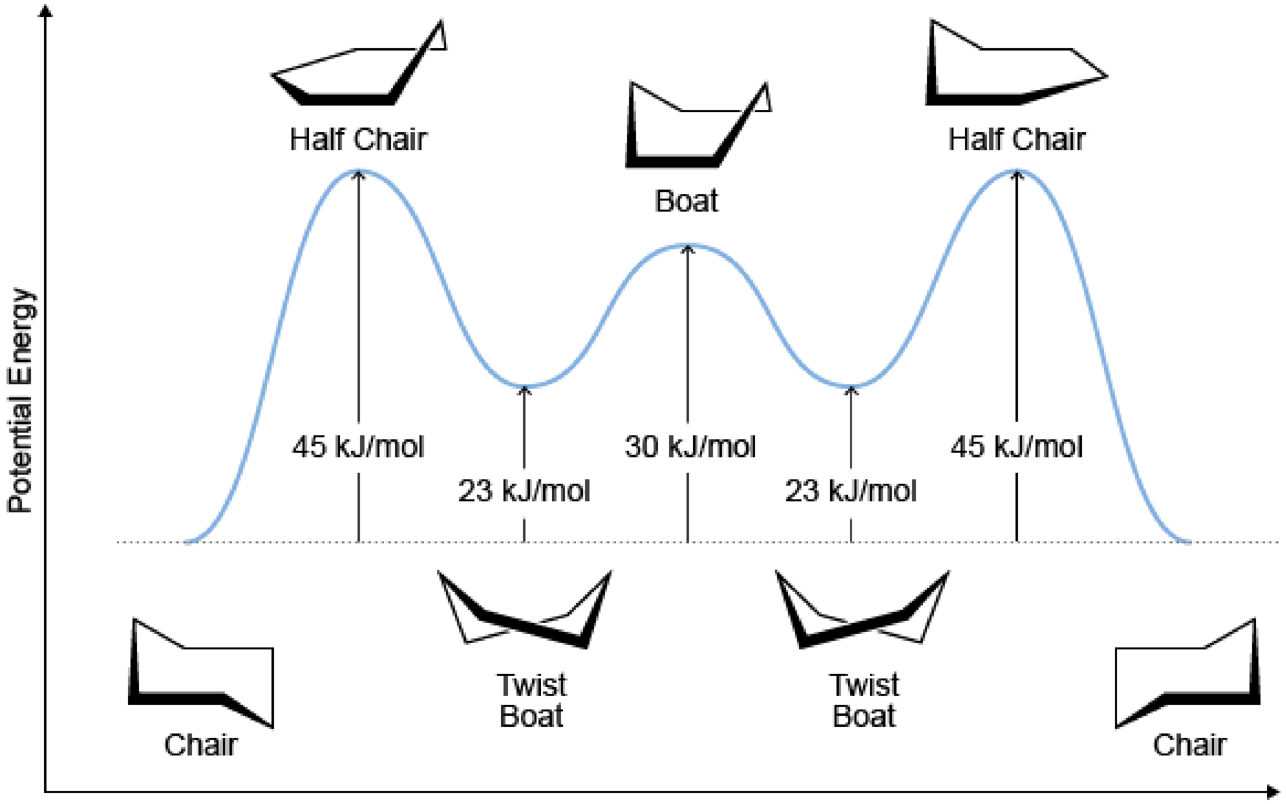
$$PE = \sum k_b(b-b_o)^2 + \sum_{angle} k_\theta(\theta-\theta_o)^2 + \sum_{dihed} k_\varphi[1+\cos(n\varphi-\delta)] + \sum_{L-J} 4\varepsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] + \sum_{Coulomb} \frac{q_i q_j}{4\pi\varepsilon_o r_{ij}}$$

The equation on the left represents the potential energy (PE) as a function of the conformation of a molecule, with the overall PE represented as the summation of contributions from covalent bond stretching, angle bending, dihedral rotation and a summation of non-bonded contributions from atom-atom overlap repulsion and *van der* Waals dispersion interactions represented by a Lennard–Jones (L–J) potential, respectively, and electrostatic interactions represented by Coulomb's law. Force field parameters are adjusted to represent the behavior of a designated molecular system and environment. Parameters k_b and k_θ represent the force constants for covalent bond stretching and bending as a function of the deviation in bond length (b) and angle (θ) from a defined minimum energy position (b_o and θo), respectively, and $\mathbf{k_\phi}$ represents the force constant from dihedral rotation as a function of rotation parameters **φ** and **δ**. Parameter **ε** is the well depth and a measure of how strongly the two atoms attract each other and the σ is the distance at which the intermolecular potential between the two atoms is zero. The σ gives a measurement of how close two nonbonding atoms can get and is thus referred to as the *van der Waals* radius. The r_{ij} is the distance of separation between both atoms. Each atom is then assigned a partial charge value (q_i) with ε_o being the permittivity of free space.

In the 8th experiment of the engineering chemistry lab, you will be performing geometry optimization using Avogadro software which optimizes the geometry using force fields.

Conformational Analysis

- The determination of molecular structure is essential as the structure of the molecule dictates the physical, chemical, and biological properties of the molecule of our interest.
- Identification of all possible minimum energy structures (conformations) of a molecule is called conformational analysis.
- Conformational analysis is an important step in computational chemistry as it is necessary to reduce time spent on screening of compounds for properties and activities.
- The major objective of the conformational analysis is to gain insight into the conformational characteristic of molecules and also to identify the relation between the role of conformational flexibility and their activity.
- Conformational analysis will be a difficult problem when simple molecules have large number of conformational isomers, for example, cyclohexane (shown in figure below).
- Molecules containing freely rotatable bonds can adopt many different conformations.
- The usual strategy in the conformational analysis is to use a search algorithm to generate a series of initial conformations.
- Each of the above conformations will then be subjected to energy minimization in order to derive the associated minimum energy structures.
- The identified conformation could be the local minimum, global minimum, or any transition state between the minima.
- Out of the several local minima on the potential energy surface of a molecule, the lowest energy conformation is known as the global minimum.
- Manual conformational search is one method where the chemical intuition of the chemist plays a major role in performing conformational analysis.
- Various automated methods of conformational analysis include systematic search, random search, Monte Carlo simulations, molecular dynamics and genetic algorithms.


Half Chair
Boat
Half Chair
Potential Energy
45 kJ/mol
23 kJ/mol
30 kJ/mol
23 kJ/mol
45 kJ/mol
Chair
Twist Boat
Twist Boat
Chair